Alfred Bader

Aldrich

[Selections from the Aldrichimica Acta 1968-1982]

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Selections from the Aldrichimica Acta

Fifteen Years

1968 through 1982

About Our Cover

Almost everyone who first looks at this *trompe l'oeil* thinks that someone has thrown a curtain over the scene depicting the marriage of King Alexander of Macedonia with Princess Roxana of Persia. It is a wonderfully imaginative painting by a late seventeenth-century Bolognese artist which at one time belonged to the great collection of the King of Saxony in Dresden. While our chemist-collector generally prefers Dutch to Italian paintings, he bought this because it is such an extraordinary work which he thought would make a perfect cover for any book of great interest. Just lift the cover and see.

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Preface

Selections from the *Aldrichimica Acta*

When we started the *Aldrichimica Acta* in 1968 we didn't envisage that it would grow into an international journal, just as we did not dream that Aldrich, which began in 1951 as a part-time operation run by one chemist making one compound in a garage, would become a world-wide supplier of 40,000 products.

The first issues of the *Acta*, sent to 10,000 customers, were just glorified advertisements, and since most were promptly thrown away, the early issues have become collectors' items. Many of our customers ask, "Where can I obtain a complete set?" Even Aldrich has just a few of the early issues, and we have had to photocopy many thousands of pages to satisfy the demand for the most interesting articles.

At the beginning it took courage (or was it nerve?) to ask scientists to write papers, and only our best friends did. Today chemists know that the *Acta* goes to 170,000 readers all over the world, the papers are abstracted by *Chemical Abstracts,* and are often cited. Among our authors are some of the world's most eminent chemists, and two issues were dedicated to two of America's greatest teachers, Robert Burns Woodward and Gilbert Stork.

For the *Selections* we have chosen those articles which we believe are still of interest to many of our readers, and for the cover we chose the painting which was on the *Acta* dedicated to Professor Woodward.

It is with great pleasure and pride that we serve chemists throughout the world, and count them as our friends.

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The Evolution of Totally Synthetic, Strong Analgesics

Everette L. May: Chief, Section on Medicinal Chemistry, National Institutes of Health, Bethesda, Maryland

The use of opium for the relief of pain and distress dates from antiquity. Until the invention of the hypodermic syringe by Christopher Wren (about 1850) opium was either smoked or eaten. This invention, the isolation of morphine from Opium by Sertürner (1803), and the synthesis and clinical use of diacetylmorphine (heroin) in the late 1890's presaged the modern age of potent pain-relieving agents with all its advantages and problems, medical and social.

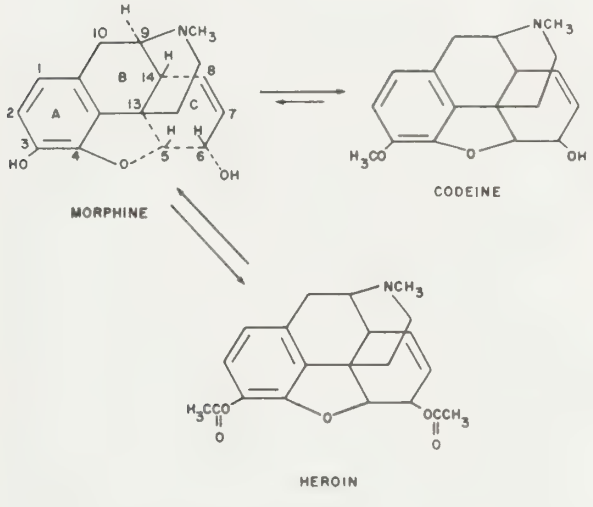


Fig. 1. Chemical structure of morphine, codeine, and heroin.

Thus, for well over a half century, especially since the chemical architecture of morphine became known and the interrelations of morphine, codeine and heroin (Fig. 1) were fairly well understood, scientists of various disciplines have toiled diligently to develop substances with morphine-like, pain-relieving efficacy and negligible adverse effects particularly abuse liability. Early attempts consisted principally of modifications of morphine and codeine or of the toxic, medically useless thebaine which occurs in opium along with morphine and codeine and is closely related chemically. Of the hundreds of congeners made (some of which are shown in Fig. 2) none has attained more than limited medical use, usually in restricted clinical situations.

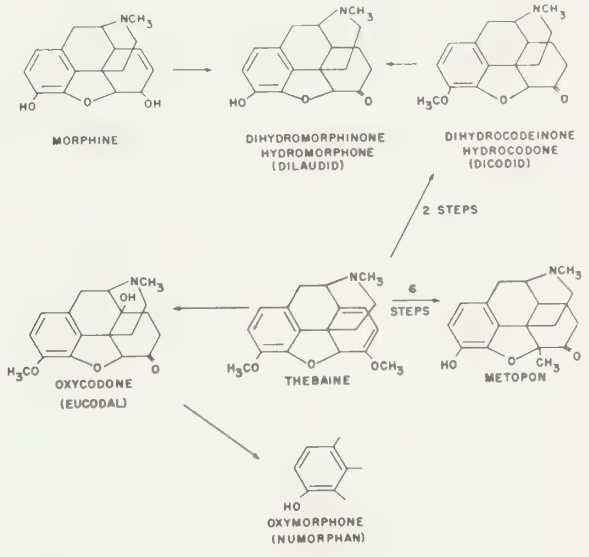


Fig. 2. Chemical structure of congeners of morphine.

And, with the possible exception of metopon (5-methyldihydromorphinone) prepared in the systematic studies of Small, Eddy, and Mosettig (1929-1939), any change in analgesic potency has been paralleled in general, by changes in deleterious effects including those of dependence liability, a term now preferred to addiction liability.

Equally discouraging were efforts directed toward the total synthesis of structures simulating various portions of morphine. In these efforts, morphine was considered as a phenanthrene, a dibenzofuran, an isoquinoline, a piperidine, etc. with phenanthrene the most frequently used fundamental structure again by the Small-Eddy-Mosettig group. However, the serendipitous discovery of pethidine (Demerol, meperidine) by two astute German investigators, Eisleb and Schaumann, a chemist and a pharmacologist, provided a breakthrough in 1939 which added a new dimension and direction to the search for totally synthetic analgesics. After it was found that pethidine, which was really modeled after cocaine as a spasmolytic agent, was a morphine-like analgesic agent, albeit of lesser potency than morphine, these investigators discerned that pethidine represented a substantial fragment of morphine as shown in Fig. 3.

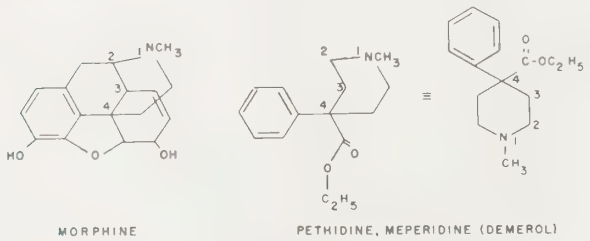


Fig. 3. Chemical structure of pethidine.

Pethidine has become a popular and valuable analgesic but possesses the same general drawbacks as morphine and a shorter duration of action. Perhaps more importantly, its advent stimulated the synthesis of hundreds of analogs, the more prominent of which are shown in Fig. 4, and more divergent structures such as methadone which was developed in World War II, also in Germany (Bockmühl and Ehrhart). The pharmacologic profile of methadone, whose structural resemblance to morphine is depicted in Fig. 5, is similar to that of morphine, although it is much more effective orally and longer acting. It is presently under investigation (Dole, Nyswander) in maintenance and rehabilitation therapy for heroin and morphine addicts, apparently with marked success. *d*-Propoxyphene (Darvon), discovered by Pohland, *et al.* and dextromoramide (Janssen) are practical developments arising from methadone (see Fig. 6).

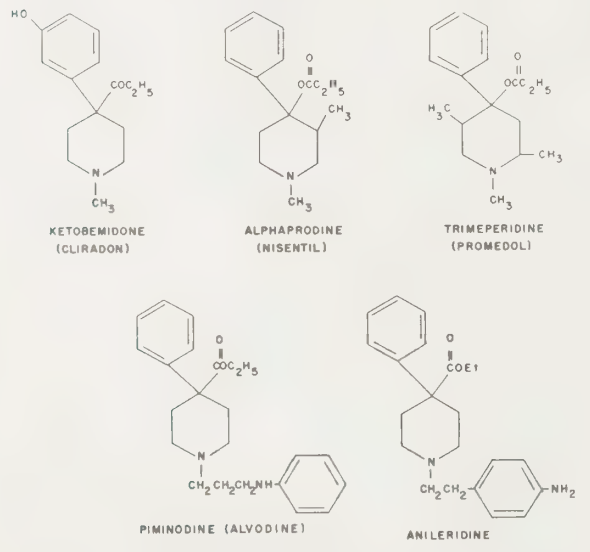


Fig. 4. Chemical structure of analgesic compounds related to pethidine.

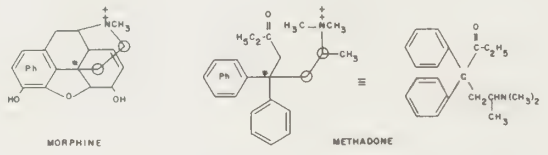
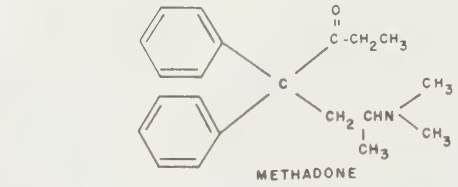


Fig. 5. Structure of methadone.



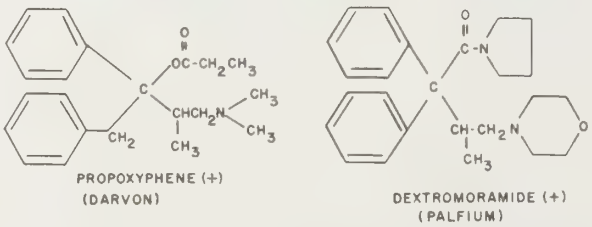
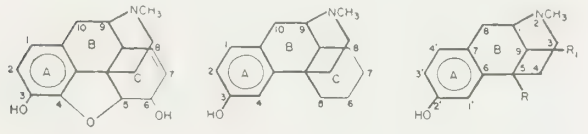


Fig. 6. Structure of d-propoxyphene and dextromoramide.

Almost simultaneously with the emergence of methadone came another important advance in synthesis, the morphinans which resulted indirectly from one of the early attempts at the total synthesis of morphine, again by a German chemist, Rudolph Grewe. The best- known analgesic of this series (-)-3-hydroxy-N-methylmorphinan (levorphanol Fig. 7), contains the complete carbon-nitrogen framework of morphine but lacks several of morphine's peripheral functional groups. It is, nevertheless, four times as potent as morphine on a dosage basis with good oral effectiveness. A tangential development and fringe benefit of the morphinan research was the discovery of an effective, non-narcotic antitussive, (+)-3-methoxy-N-methylmorphinan (dextromethorphan), the methyl ether of the enantiomorph of levorphanol. Levorphanol and dextromethorphan are due to Schnider, *et al.*

Still further alteration and simplification of the molecule (deletion of part of the terminal hydroaromatic ring C, Fig. 8) has provided 6,7-benzomorphans (National Institutes of Health) with the intact iminoethano system and other structural features of morphine believed essential for strong, central analgesic action. These compounds as racemates have shown a consistent separation of morphine-like analgesia (referred to the mouse and rat) and physical

dependence properties (tests in monkeys). Never before has any substantial divorcement of these advantages and disadvantages been demonstrated for a class of compounds even in animal species. This separation is not entirely species related but is shown to apply partially to man in the few compounds so tested. One N-substituted derivative, (±)-5, 9-dimethyl-2-hydroxy-2-phenethyl-6, 7-benzomorphan (Fig. 8) has been marketed in the United States as Prinadol and in England as Narphen. It has a broad pain-relief spectrum, 3-5 times the milligram potency of morphine, oral effectiveness and less abuse liability than morphine.



I Morphine (-) II Levorphanol (-) III 6,7-Benzomorphans

Fig. 7

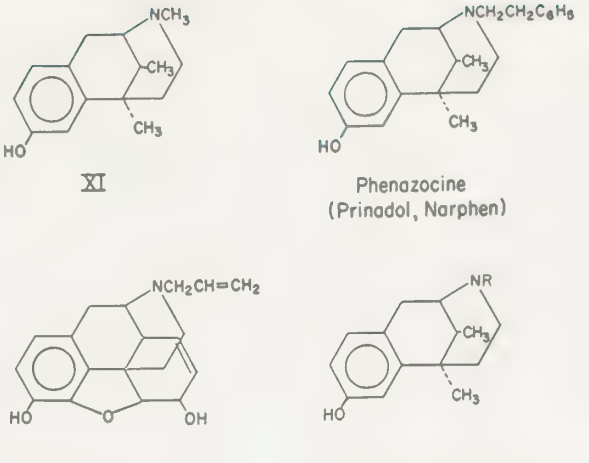
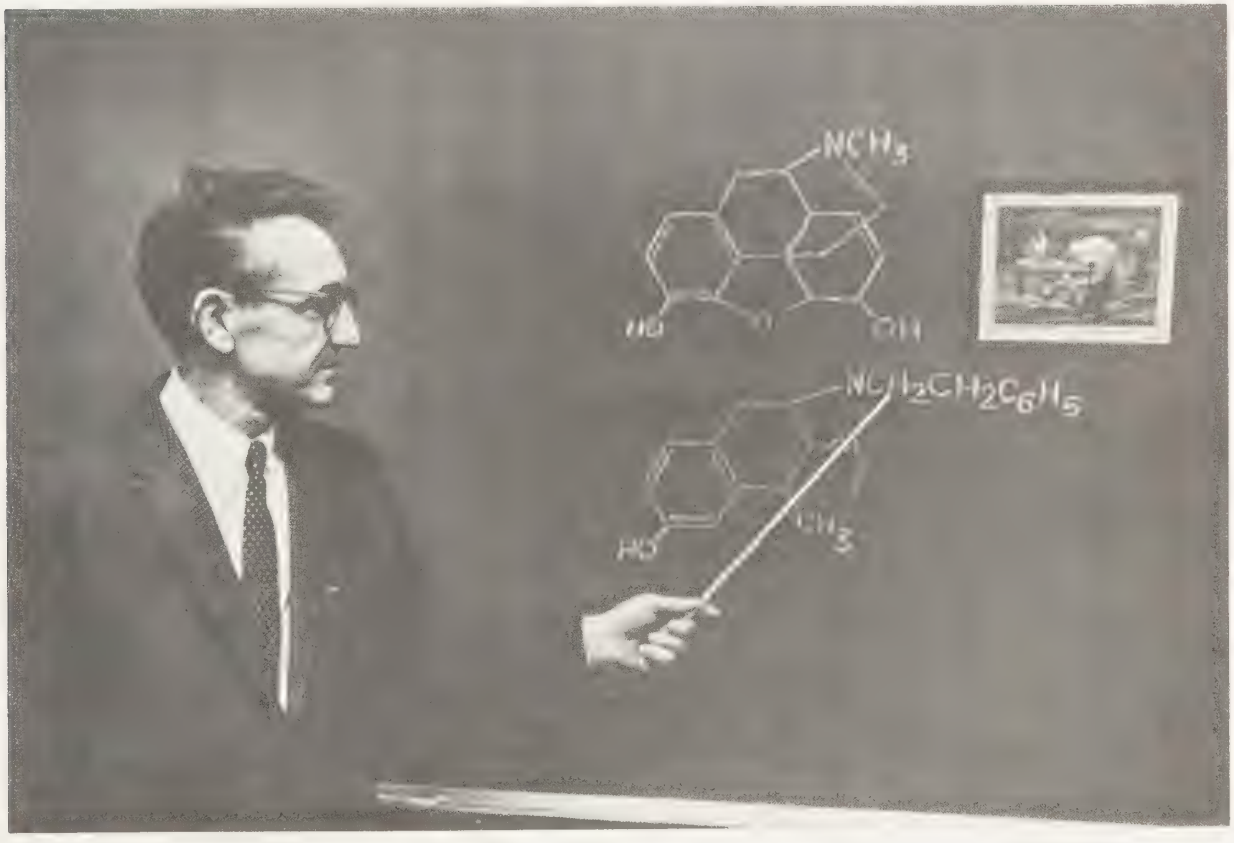
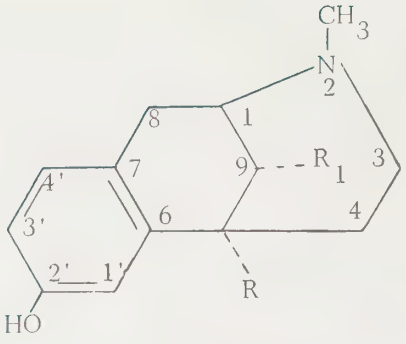


Fig. 8

Based on these findings and on the discovery of strong analgesic activity for the non-dependence producing, narcotic antagonist, nalorphine, Archer Harris, *et al.* have synthesized a series of antagonists of varying degrees of potency by substituting other hydrophobic groups for the methyl of 2′-hydroxy-2,5, 9-trimethyl-6, 7-benzomorphan (Fig. 8). The 2-(N)-cyclopropylmethyl analog (cyclazocine) is not only a strong narcotic antagonist but is also



Dr. May discussing structural differences and similarities of morphine and phenazocine.



Ia R = R_1 = Me

b R = R_1 = Et

c R = Me, R_1 = H

d R = Et, R_1 = H

e R = Pr, R_1 = Me

Fig. 9

a powerful, orally effective analgesic in man without substantial abuse liability. It appears to be useful (Freedman) as a deterrent and rehabilitation agent in heroin and morphine abuse. Pentazocine, the dimethylallyl congener (Fig. 8) is marketed as a non-narcotic analgesic, Talwin, 20-40 mg. being as efficacious, it is claimed, as 10 mg. of morphine in most types of pain.

Finally, optical resolution of several of the racemates of the benzomorphan group containing methyl on the nitrogen (Fig. 9) has resulted in further separation of morphine-like effects. Thus, the *levo*-isomers (in some instances twice as potent as morphine) contain almost all the activity elicited by the racemates, yet have no capacity to substitute for morphine in an established physical dependence in rhesus monkeys. In fact, these *levo*-antipodes will actually precipitate or exacerbate abstinence signs, being nalorphine-like in this respect. Apparently, they will also antagonize some of the (undesired) effects of their weakly analgesically effective *dextro*-counterparts which, surprisingly, have from low to high physical dependence capacity in monkeys; in all cases, the racemates from which these *levo*- and *dextro*-isomers are derived have *very low* or no physical dependence capacity. It is already known that the *levo*-isomers are excellent pain-relieving agents in man, so that if the results obtained in monkeys are also quantitatively transferred to man, the near-ideal strong analgesic may be at hand.

In any event, with the plethora of efficacious, totally synthetic analgesics and antitussives now extant, several of which are much less likely to be abused than morphine and heroin, mankind would not be handicapped without opium. It is possible even probable that if opium, the only ready source of morphine, codeine and heroin, were to be extinguished, the problem of drug dependence of the morphine type (narcotic addiction) would be greatly alleviated.

For a detailed treatment of Morphine-like and peripherally acting analgesics, see "Analgetics", G. deStevens, Ed., Academic Press, Inc., New York, N. Y. 1965.

Organothallium Chemistry-New Horizons in Synthesis

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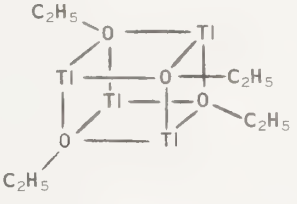
The last two decades have seen a tremendous upsurge of interest and activity in organometallic chemistry, with the result that there are now few metals the organochemistry of which has not been investigated in some detail. Prior to the initiation of our studies on organothallium chemistry in 1966, however, little was known of the organic chemistry of this group IIIB metal. This situation must be regarded as surprising, as not only is thallium abundant, inexpensive and readily available in a high state of purity, but sporadic reports during the past half century have clearly indicated that in certain reactions thallium derivatives are effective chemical intermediates. In this article we summarize the remarkable utility of thallium compounds in organic synthesis. We believe that the reactions discovered thus far presage a bright future for this versatile metal.

Our initial interest in thallium chemistry stemmed from curiosity about a statement made some years ago by Menzies and Wilkins[1] that the thallium(I) salt of ethyl acetonedicarboxylate was "readily soluble in cold ethyl or methyl iodide, thallous iodide being deposited on standing or heating". This startling statement about the apparent solubility of a β-dicarbonyl chelate in ethyl iodide (not a popular solvent for ionic compounds!) prompted the rash conclusion on our part that thallium(I) salts might be unusually covalent in character, thus raising exciting prospects of a wide spectrum of possible base-catalyzed reactions in homogeneous solution. A later report by Fear and Menzies[2] that reaction of the thallium(I) salt of ethyl acetoacetate with ethyl iodide resulted in apparent C-ethylation stimulated us to prepare some representative thallium(I) salts of β-dicarbonyl compounds and to investigate their physical and chemical properties.

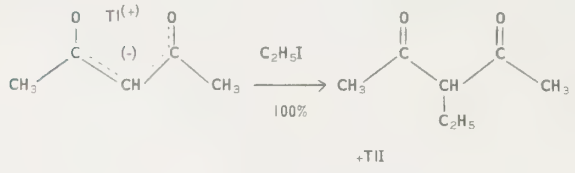
We found that the most effective reagent for the formation of thallium(I) salts of β-dicarbonyl compounds was thallium(I) ethoxide. This remarkable compound is a covalent tetramer[3] which is soluble in most organic solvents (including heptane and benzene) and thus possesses considerable advantages over sodium ethoxide and other alkali metal alkoxides in that homogeneous base-catalyzed reactions can be carried out in non-polar solvents. Treatment of a benzene or petroleum ether solution of a β-dicarbonyl



compound (e.g., acetylacetone, (eq. 1)) with 1 equivalent of thallium(I) ethoxide resulted in the instantaneous separation in quantitative yield of its thallium(I) salt.

(*eq. 1*)

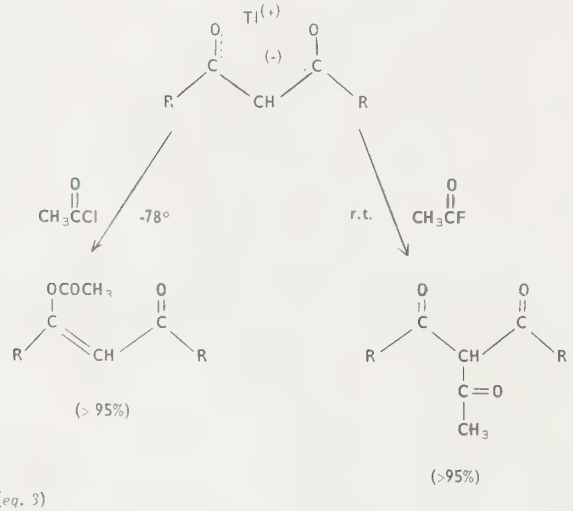
To our great surprise, and contrary to the previous report,[1] these salts were completely *insoluble* in cold ethyl iodide. Heating the suspension, however, resulted in the formation, *in quantitative yield,* of pure mono-C-ethylated product



(*eq. 2*)

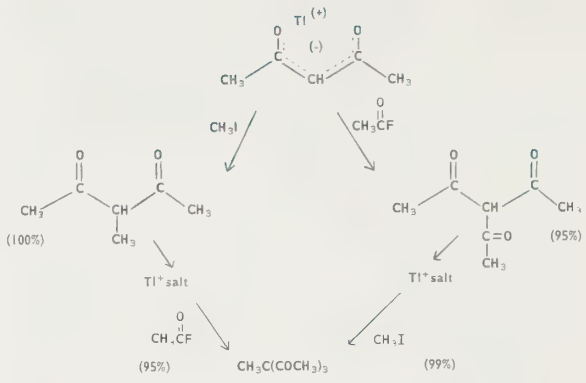
(eq. 2).[4] Ironically, the extreme insolubility of these thallium salts in alkyl iodides appears to be the key to the remarkable specificity of alkylation (and acylation) which we have observed upon treatment of these thallium(I) salts, in suspension, with alkylating and acylating agents.[4] It appears that reaction occurs at the crystal surface, literally "peeling away" the crystal until complete reaction has been achieved; retention of the geometry of the thallium(I) chelate in the transition state leads to regiospecificity rivalling that of an enzymatic reaction.

Not only are thallium(I) salts of β-dicarbonyl compounds alkylated regiospecifically, but they may also be acylated selectively on oxygen or on carbon, depending upon reaction conditions.[4] Thus, reaction with acid chlorides in ether suspension at −78° leads to exclusive O-acylation, while treatment with acetyl fluoride in ether suspension at room temperature leads to exclusive C-acylation (eq. 3).



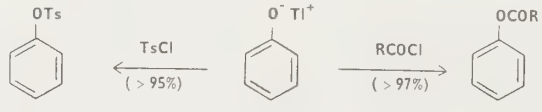
(*eq. 3*)

The remarkable effectiveness of this combination of regiospecific acylation and alkylation reactions is illustrated in eq. 4, which describes the synthesis of 1,1,1-triacetylethane.



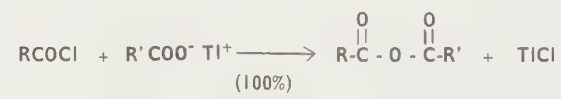
(*eq. 4*)

Thallium(I) ethoxide forms thallium(I) salts with a wide spectrum of acidic organic substrates, and the properties of the resulting thallium(I) salts resemble those of the above β-dicarbonyl salts: they are all highly crystalline, colorless, sharp-melting, light-insensitive and readily recrystallizable solids. They are also exceptionally useful intermediates in a wide diversity of synthetic reactions. Thus, treatment of an ether suspension of thallium(I) salts of phenols with an equimolar quantity of an acyl or aroyl halide at room temperature affords pure phenol esters in yields seldom lower than 97%. Phenol tosylates are prepared similarly (eq. 5).[5]



(*eq. 5*)

Treatment of thallium(I) carboxylates with a stoichiometric amount of an acyl or aroyl halide in ether suspension, followed by removal of thallium(I) chloride by filtration and evaporation of the ether, affords symmetrical or unsymmetrical carboxylic anhydrides (according to the choice of the acid chloride) in quantitative yield (eq. 6).[5]

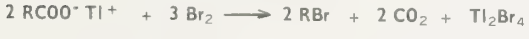


(*eq. 6*)

Symmetrical anhydrides are alternatively prepared by treatment of thallium(I) carboxylates with thionyl chloride in ether suspension at room temperature; the intermediate diacyl or diaroyl sulfites spontaneously lose sulfur dioxide (eq. 7).[5]

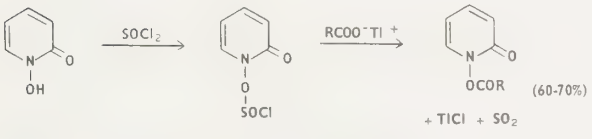
(eq. 7)

Thallium(I) carboxylates of *n*-alkanoic acids readily yield *n*-alkyl bromides upon treatment with bromine and carbon tetrachloride in a modification of the classical Hunsdiecker reaction (eq. 8).[6]



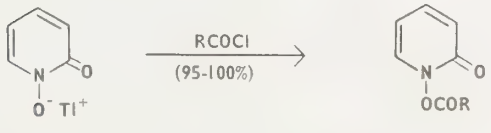
(eq. 8)

The utility of thallium(I) carboxylates in organic synthesis can be further illustrated by an improved preparation of Paquette's "active esters"[7] (eq. 9); this procedure



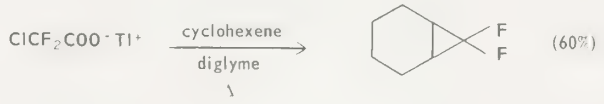
(eq. 9)

permits the direct conversion of an amino acid to a peptide without the necessity of intermediate formation of an acid chloride.[8] However, an even better route to these "active esters" involves treatment of the thallium(I) salt of 1-hydroxy-2(1*H*)-pyridone with acid chlorides; the reaction proceeds instantaneously at room temperature to give quantitative yields of products (eq. 10).[8]



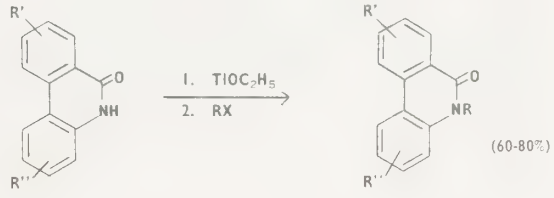
(eq. 10)

A common feature of all of the above metathetical reactions is the avidity of thallium for halide ion and the consequent separation of an insoluble thallium(I) halide from the organic reaction medium. As a result, facilitation of *intra*molecular halide abstraction by thallium(I) was to be anticipated. Thus, difluorocarbene is conveniently prepared by thermolysis of thallium(I) chlorodifluoroacetate (eq. 11).[9]



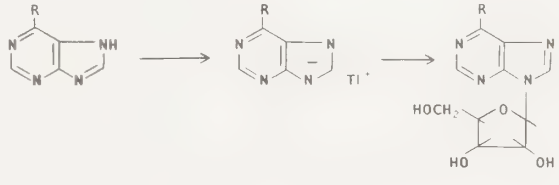
(eq. 11)

The physical properties of thallium(I) salts (solubility, crystallinity, stability) can also be used to advantage in the alkylation and acylation of a variety of heterocyclic compounds. For example, phenanthridones can be alkylated smoothly at room temperature via their thallium salts (eq. 12)[10]; previous procedures required formation of the



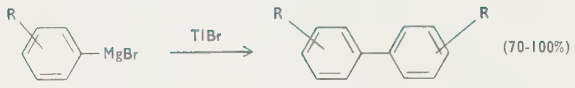
(eq. 12)

potassium salt by fusion with solid potassium hydroxide, followed by alkylation in a sealed tube at elevated temperatures.[11] A variety of purines readily form thallium(I) salts upon treatment in ethanol or DMF solution with thallium(I) ethoxide; in contrast to sodium or chloromercuri salts, these thallium(I) salts alkylate exclusively at position 9, and this reaction has been exploited for the preparation of nucleosides (eq. 13).[12]



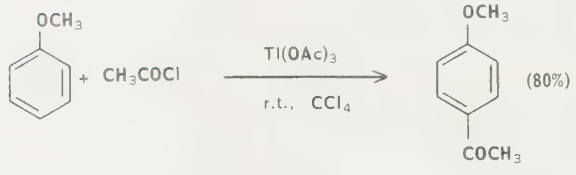
(eq. 13)

By-products of many of the above reactions are thallium(I) halides, and it is interesting to note that thallium(I) bromide is an extremely effective reagent for the synthesis of biaryls from aromatic Grignard reagents (eq. 14).[13]



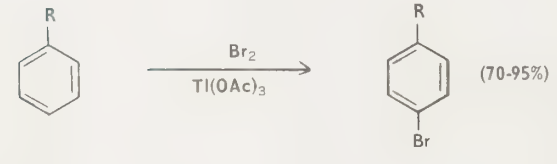
(eq. 14)

This superficially prosaic process has been shown to proceed via a complex series of redox reactions involving all three of the valence states of thallium (0, I and III). Facile interplay among these valence states is, in fact, a characteristic feature of much of thallium chemistry. It is somewhat surprising that the chemistry of thallium(III) has been generally neglected in view of the well-known position of its reduction potential between that of mercury (II) and lead (IV). Furthermore, thallium(III) compounds would be expected to be strong Lewis acids, and may be considered coordinatively unsaturated if the associated anion is considered as a monodentate ligand. We have found, for example, that thallium(III) acetate is an extremely effective Friedel-Crafts catalyst (eq. 15).[14] Fur-



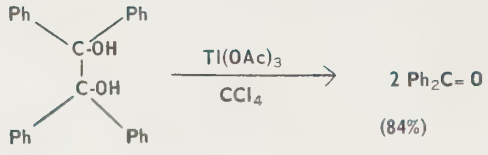
(eq. 15)

thermore, a combination of thallium(III) acetate and bromine has been found to effect exclusive *para* bromination; an ordered bromine-thallium(III) acetate-aromatic substrate complex appears to be involved in this highly specific electrophilic reaction (eq. 16).[15]



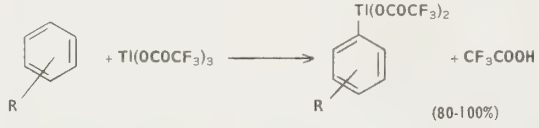
(eq. 16)

The mild, selective and non-radical oxidizing properties of thallium(III) acetate are illustrated by its utility in the cleavage of α-glycols (eq. 17).[16]



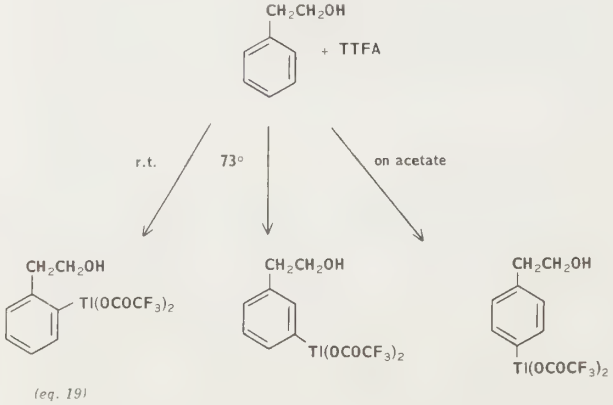
(eq. 17)

One of the most interesting and versatile thallium(III) reagents which we have discovered thus far is thallium(III) trifluoroacetate ($Tl(OCOCF_3)_3$,TTFA). Its extraordinary reactivity as an electrophilic metallating reagent is illustrated by its reaction with aromatic substrates, often at room temperature, to give arylthallium ditrifluoroacetates (eq. 18).[17] Kinetic investigations[18] have shown that thal-



(eq. 18)

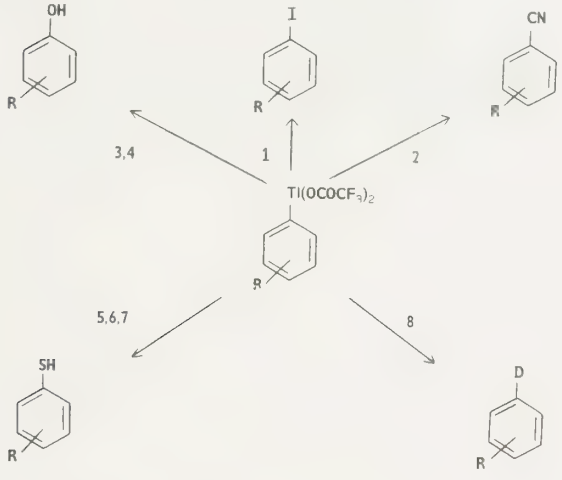
lation, like aromatic mercuration,[19] is one of the few examples of a freely reversible electrophilic substitution reaction. Thallation with TTFA of phenylethanol at room temperature (kinetic control) leads to *ortho* substitution, while thallation at 73° (thermodynamic control) gives predominant *meta* substitution. *Ortho* substitution, we believe, results from intramolecular delivery of the thallium electrophile from an intermediate Lewis acid-Lewis base complex between the TTFA and the side-chain hydroxyl group, and is thus subject to control by appropriate modification in the structure and size of the intermediate chelate. This is dramatically illustrated by the observation that thallation at room temperature (kinetic control) of the *acetate* of phenylethanol results in *para* substitution (eq. 19).[20]



(eq. 19)

These arylthallium ditrifluoroacetates are versatile intermediates for the synthesis of a wide spectrum of substituted aromatic compounds. For example, treatment with aqueous potassium iodide at room temperature yields aromatic iodides.[21] Phenols are readily prepared by treatment with lead tetraacetate followed by triphenylphosphine.[22] It should be noted that it is not necessary to isolate the intermediate arylthallium ditrifluoroacetates in either of the above reactions: thallation can be carried out in trifluoroacetic acid solution and the appropriate reagents added directly to the reaction mixture.

Arylthallium ditrifluoroacetates may also be utilized as intermediates for the synthesis of aromatic nitriles[22] and thiophenols,[23] while reductive cleavage with lithium aluminum deuteride or aluminum amalgam in D_2O leads to specific deuteration of aromatic substrates.[24] These reactions are summarized in Scheme 1.

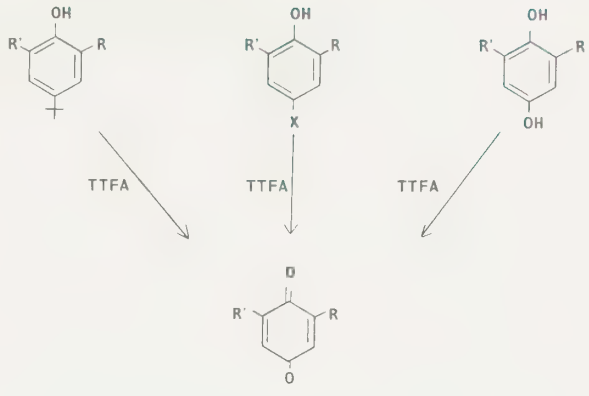


Reagents: 1. aq. KI 2. aq. KCN, $h\nu$ 3. $Pb(OAc)_4$ 4. PPh_3
5. $K^{+-}SCSN(CH_3)_2 \longrightarrow ArTl(SCSN(CH_3)_2)_2$
6. $h\nu$ in acetone gives mixture of ArSSAr and $ArSCSN(CH_3)_2$
7. (H) or H_3O^+ 8. $LiAlD_4$

SCHEME 1

It should be noted that control over the orientation of thallation, as illustrated above (eq. 19) with phenylethanol, has as its consequence control over isomer orientation in the above syntheses of iodides, phenols, nitriles, thiophenols, and deuterated aromatics.

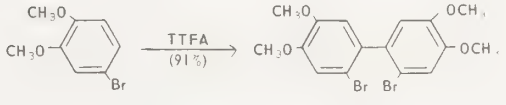
Just as lead tetratrifluoroacetate is a more powerful oxidizing agent then lead tetraacetate,[25] so TTFA is a more effective and versatile oxidizing agent than thallium(III) acetate. For example, we have found that a wide variety of *p*-*t*-butyl phenols are smoothly transformed into *p*-quinones upon treatment with TTFA in either TFA or carbon tetrachloride solution.[26] A variety of other *p*-substituted phenols are likewise converted to *p*-quinones upon treatment with TTFA. Hydroquinones can literally be titrated with TTFA and this reaction constitutes an extremely convenient procedure for their oxidation to *p*-quinones (eq. 20).[26]



R = R' = alkyl, halogen, etc
X = halogen, OAc, NR_2, etc.

(eq. 20)

Finally, the reactivity and selectivity of TTFA as an oxidizing or metallating agent can apparently be extensively modified by the addition of appropriate co-reagents. For example, treatment of 4-bromoveratrole with TTFA and boron trifluoride etherate results in a smooth Scholl reaction (eq. 21)[27] in which oxidative coupling rather than



(eq. 21)

thallation has taken place.

It is widely recognized that organometallic chemistry offers some of the greatest challenges and promises some of the richest rewards in synthetic organic chemistry. We suggest that thallium may well be regarded in the future as one of the indispensable metals in synthetic organic chemical methodology.

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Batrachotoxin, a Novel Steroidal Alkaloid with Selective Effects on Biomembrane Permeability

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Bernhard Witkop, Chief, Laboratory of Chemistry, National Institutes of Health, Bethesda, Maryland 20014

During their evolution, amphibians developed an amazing variety of pharmacologically active compounds, which play a role in defending the frog, toad, newt or salamander, against predators. These defensive principles are remarkable for both their chemical and pharmacological diversity. They include biogenic amines, peptides, proteins, steroids, steroidal alkaloids and a variety of other compounds. Their pharmacological activities encompass cardio-, myo- and neuro-toxins, cholinomimetics, sympathomimetics, vasoconstrictors, hypotensive agents and hallucinogens. Among these compounds are some of the most powerful venoms known. A few examples are give in Fig. 1.

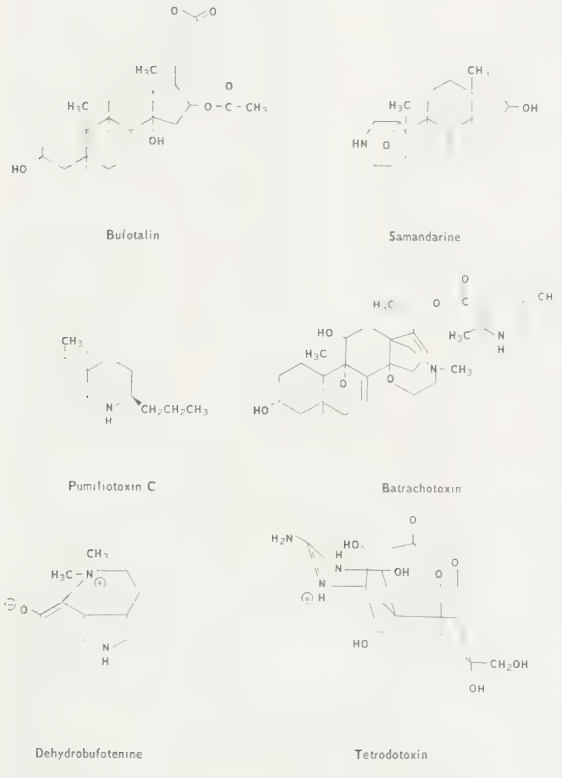

Fig. 1. Pharmacologically Active Substances Isolated from Various Amphibians

Among these venoms, perhaps the most interesting, from both the chemical and pharmacological standpoint, is the steroidal alkaloid, batrachotoxin, which is found in the skin of a small, brightly colored, Colombian frog of the genus *Phyllobates* (Fig. 2). The poisonous character of skin

Fig. 2. The Colombian Poison Arrow Frog, *Phyllobates aurotaenia*

secretions of this frog was recognized long ago by the Indians of the Pacific rain forests in Colombia and they developed methods for obtaining the venom and using it on their blowdarts for hunting birds and small game. The use of blowguns and darts poisoned with the milky secretion from this small frog persists even to this day in the upper reaches of the Rio San Juan in the Choco jungle of western Colombia. The first scientific report on this venom appeared in 1871. Subsequently, the gross toxicological effects of the crude extracts have been published, but it remained for our own studies initiated in 1961 to demonstrate that the active ingredient from extracts of this frog was one of the most toxic substances known so far (Table I). Only certain bacterial toxins, such as the one from

Table I Toxic Substances with Their LD_{50} for Subcutaneous Administration in Mice

Substance	LD_{50} $\mu g/kg$
Batrachotoxin	2
Tetrodotoxin	8
Bufotalin	400
Curare	500
Strychnine	500
Sodium Cyanide	10,000

Botulinus, surpass it in toxicity. The structure and mechanism of action of such a potent venom were indeed of great interest.

Investigation of batrachotoxin was handicapped by the paucity of material and by its lability. The skin of an adult frog, approximately 3 cm in length, contains only 80 micrograms of toxic congeners consisting mainly of batrachotoxin, homobatrachotoxin, pseudobatrachotoxin and batrachotoxinin A. The frog which occurs in a rather inaccessible region of Colombia was difficult to obtain in large numbers, but in the course of four expeditions, approximately 7000 frogs were collected. Methods for the isolation and separation of the active principles were developed, which minimized losses resulting from their great lability.

Preliminary investigation indicated that these compounds were weak bases with a pk of approximately 7.5. High resolution mass spectrometry indicated that batrachotoxin and homobatrachotoxin were steroidal alkaloids with the empirical formula $C_{24}H_{33}NO_4$. The much less toxic batrachotoxinin A, on the basis of mass spectral data, was closely related in structure, but contained the additional elements of water in its molecular ion of $C_{24}H_{35}NO_5$. Since the compounds were weakly basic and since the mass spectra indicated only one nitrogen, it was quite surprising when, in the course of microchemical investigation, it was discovered that batrachotoxin and homobatrachotoxin gave a strong positive Ehrlich's test indicative of the presence of a pyrrole moiety. In view of the evidence, the conclusion was inevitable that the basic nitrogen in (homo)batrachotoxin was part of a potential pyrrole ring which converted to a pyrrole under the strongly acid conditions of the Ehrlich's reaction.

A crystalline derivative suitable for X-ray analysis was finally obtained in 1967, when Dr. Tokuyama succeeded in preparing a crystalline *p*-bromobenzoate derivative of batrachotoxinin A, the least toxic of the congeners. X-ray analysis of a tiny crystal of this derivative by the "symbolic addition procedure" of Jerome and Isabella Karle established its structure as the 20-α-*p*-bromobenzoate of batrachotoxinin A (Fig. 3).

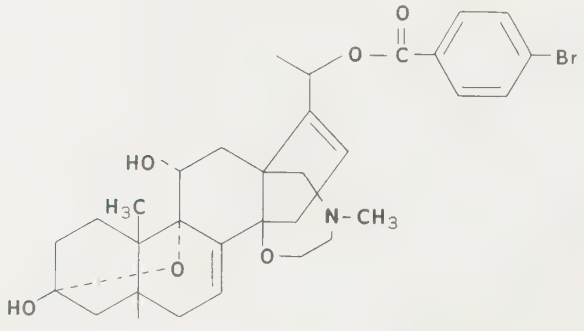

Fig. 3. Batrachotoxinin A 20α-*p*-bromobenzoate

With the structure of one of the bases now known, reexamination and reinterpretation of the physical and spectral properties of batrachotoxin and homobatrachotoxin led to the elucidation of the actual venom. Thus, when the mass and n.m.r. spectra of bactrachotoxinin A were compared with those of (homo) batrachotoxin, the presence of a common steroid moiety in all of these bases became apparent. Batrachotoxin and homobatrachotoxin, however, exhibited ultraviolet spectra with λmax at 234 and 264 mμ, indicative of a conjugated system, infrared absorption bands at 1690 cm^{-1}, typical of a carbonyl group or perhaps a vinyl ether, and, of course, the positive Ehrlich reaction due to a (potential) pyrrole system. In addition, the n.m.r. spectra showed that batrachotoxin contained two additional methyl groups and homobatrachotoxin, an additional methyl and ethyl group not present in the n.m.r. spectrum of batrachotoxinin A. It was impossible to rationalize structures for (homo)batrachotoxin in terms of solely a C_{24} steroid structure closely related to batrachotoxinin A. The inescapable conclusion was that the true molecular ion *had so far escaped detection* in the mass spectra of (homo)batrachotoxin and that these compounds contained the steroid system of batrachotoxinin A plus an additional moiety responsible for the ultraviolet chromophore, the carbonyl band, the pyrrole reactions and the additional methyl and ethyl groups. It was postulated that this moiety consisted of a dimethylpyrrole-carboxylate ester in the case of batrachotoxin and an ethylmethylpyrrole-carboxylate in the case of homobatrachotoxin. The mass spectra of batrachotoxin and homobatrachotoxin *did contain* additional low-mass nitrogen-containing fragments not present in the spectra of batrachotoxinin A. These fragments, for example, $C_8H_{11}NO_2$ in homobatrachotoxin and $C_7H_9NO_2$ in batrachotoxin, could well have arisen from an ethylmethylpyrrole-carboxylic ester or a dimethylpyrrole-carboxylic ester, respectively. It now remained to prove that batrachotoxin and homobatrachotoxin were, indeed, dialkylpyrrole-carboxylates of batrachotoxinin A.

The mass spectrum of batrachotoxin was reexamined and great attention was given to detecting the true molecular ion. As predicted for a dimethylpyrrole-carboxylate of batrachotoxinin A, a very weak molecular ion was found at m/e 538. Batrachotoxin was then hydrolyzed in base. A low yield of a compound identical with batrachotoxinin A was obtained.

The next task was to establish the position of esterification and nature of the dialkylpyrrole-carboxylate moiety. Comparison of the n.m.r. and mass spectra of (homo)-batrachotoxin and batrachotoxinin A and its 20α-*p*-bromobenzoate clearly established that the position of esterification in (homo)batrachotoxin was the 20α-hydroxyl group. Thus, the resonance peak for the 20β-hydrogen in batrachotoxin A appeared at 4.58 δ, while in (homo)batrachotoxin and the 20α-*p*-bromobenzoate of batrachotoxinin A, it is shifted downfield, approximately 1.3 ppm, a change compatible with esterification of the 20α-hydroxyl group.

The ring substitution pattern of the dialkylpyrrole-carboxylate moiety was now investigated. A comparison of ultraviolet spectra of ethylpyrrole carboxylates with those of (homo)batrachotoxin demonstrated the presence of a pyrrole-3-carboxylate in these alkaloids. The position of the two alkyl substituents was determined by n.m.r. spectroscopy using two different solvents and observing the shifts in position of methyl resonance in (homo)batrachotoxin and ethyl-dimethylpyrrole-3-carboxylates. **Batrachotoxin was shown to be batrachotoxinin A 20α-2,4-dimethylpyrrole-3-carboxylate and homobatrachotoxin to be batrachotoxinin A 20α-2-ethyl-4-methyl-pyrrole-3-carboxylate.**

This assignment of structure was confirmed by the partial synthesis of batrachotoxin, *viz*, by acylation of the allylic 20α-hydroxyl of batrachotoxin with the mixed anhydride prepared from 2,4-dimethylpyrrole-3-carboxylic acid and ethyl chloroformate (Fig. 4). The synthetic material was identical in all respects with natural batrachotoxin.

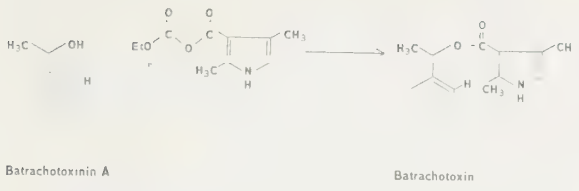

Fig. 4. Partial Synthesis of Batrachotoxin from Batrachotoxinin A

A variety of other synthetic analogs of batrachotoxin were prepared in a similar manner. The effect of different ester moieties on the toxicity of batrachotoxinin A is shown in Table II.

Table II Effect of the Ester Moiety on the Toxicity of Batrachotoxinin A Esters on Subcutaneous Administration in Mice

20-α-Ester Moiety	LD_{50} (μg/kg)
None (batrachotoxinin A)	1000
2,4-Dimethylpyrrole-3-carboxylate (batrachotoxin)	2
2-Ethyl-4-methylpyrrole-3-carboxylate (homobatrachotoxin)	3
2,5-Dimethylpyrrole-3-carboxylate	2.5
4,5-Dimethylpyrrole-3-carboxylate	260
2,4,5-Trimethylpyrrole-3-carboxylate	1
2,4-Dimethyl-5-ethylpyrrole-3-carboxylate	8
2,4-Dimethyl-5-acetylpyrrole-3-carboxylate	250
N,2,4,5-Tetramethylpyrrole-3-carboxylate	> 1000
Pyrrole-2-carboxylate	> 1000

The many unusual structural features in batrachotoxin, such as the 3α,-9α-hemiketal bridge, the 7-membered 14β,18β-heterocyclic ring, the Δ^{16} double bond, and the unique 20β-(2,4-dialkylpyrrole-3-carboxylate) pose many interesting biogenetic questions and, in addition, a major challenge to the synthetic organic chemist.

The pharmacology of batrachotoxin has proven no less interesting than its history and chemistry. When administered subcutaneously to mice, approximately 0.2 μg of batrachotoxin causes partial paralysis of the limbs. This state is soon interrupted by violent convulsions, dyspnea and death within a course of eight minutes. Cardiac effects and neuromuscular blockade both appear to play a role in the toxicology of the venom. The mechanism of action of batrachotoxin in eliciting neuromuscular blockade has now been the subject of elegant investigations by Dr. E. X. Albuquerque and his collaborators, who have used pharmacological, biochemical and ultrastructural techniques. Their results demonstrate that batrachotoxin is an extremely important tool for the study of events in nerve, synapse and muscle.

These events are summarized schematically in Fig. 5 and are currently thought to consist of: 1. Generation of an action potential in nerve; *i.e.*, depolarization of the nerve membrane with *passive* diffusion of sodium ions into the axon (increase in sodium permeability), followed by repolarization due to passive diffusion of potassium ions out of the axon (increase in potassium permeability). The membrane potential with excess sodium ions outside and excess potassium inside the cell is maintained by the action of the sodium pump (Na-K^+ activated ATPase) which transports sodium ions out of, and potassium ions into, the cytoplasm; 2. a calcium-dependent quantal release of acetylcholine as a result of depolarization of the membrane of the presynaptic terminal; 3. interaction of acetylcholine with receptors in the muscle endplate resulting in depolarization of the muscle membrane, generation of a muscle action potential and a concomitant liberation of calcium ions from the sarcoplasmic reticulum into muscle cytoplasm; 4. combination of calcium ions with troponin which thereby permits the interaction of actin and myosin, the basic process of muscle contracture; 5. sequestration of calcium ions, followed by inhibition of actinmyosin interaction by troponin and muscle relaxation.

This complex series of events has been elucidated in large measure through the use of compounds which specifically interact at one of these molecular steps. A few examples are given in Fig. 5.

Batrachotoxin blocks neuromuscular transmission and then evokes a powerful muscle contracture in isolated nerve-muscle preparations. The work of Dr. Albuquerque and collaborators has now demonstrated that batrachotoxin does not affect the action potential-generating system of either nerve or muscle and that the acetylcholine sensitivity

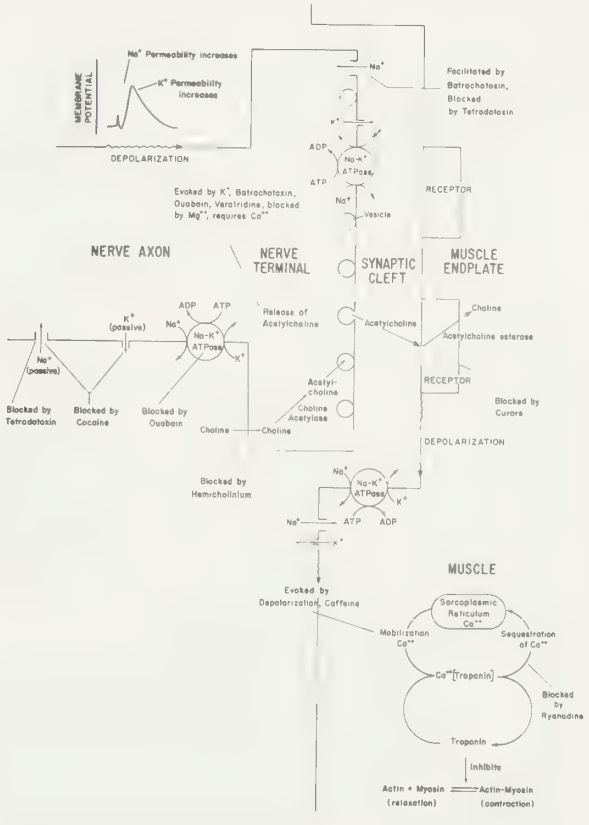

Fig. 5. A Schematic Diagram of Neuromuscular Transmission and Probable Interactions of Various Drugs with This System

of the muscle endplate is unaffected, suggestive of blockade of transmission in the presynaptic terminal. Batrachotoxin does not inhibit Na^+-K^+-ATPase as does ouabain. Instead, it appears to cause a specific increase in the permeability of excitable membranes, especially the presynaptic terminal, to sodium ions. This increase in sodium permeability results in depolarization of the presynaptic terminal and a concomitant calcium-dependent increase in acetylcholine release. The subsequent block in transmitter release appears due to complete depolarization of the nerve terminal. **The effects of batrachotoxin can be prevented by tetrodotoxin** which blocks *passive* diffusion of sodium ions through excitable membranes. The muscle contracture caused by batrachotoxin appears to be due to muscle depolarization elicited by an increase in sodium permeability in the muscle membranes. The extreme toxicity of batrachotoxin has been related to effects on cardiac conduction which result in extra systoles and ventricular fibrillation. These toxicological effects seem to have their molecular origin in the selective action of batrachotoxin on the permeability of the cardiac membrane to sodium. Such an agent with selective effects on membrane permeability should find wide application in studies of nerve, muscle and synapse. Indeed, studies on the interrelation of nervous activity, biogenic amines and cyclic AMP formation in brain slices (Shimizu *et al.*, 1970) have already made use of batrachotoxin, as a potent and selective depolarizing agent, and have confirmed the fact that tetrodotoxin is a specific antagonist.

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Doctors Witkop, Daly and Tokuyama

Macrocyclic Polyethers for Complexing Metals

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Discovery of "Crown"

Certain macrocyclic polyethers, nicknamed crown compounds, have aroused considerable interest in several branches of chemistry in recent years because they are the first neutral synthetic compounds to form stable complexes with the alkali metal ions. It is my purpose in this short article to tell you about the preparation and properties of these compounds and their complexes. To start with, this is how I discovered the crown compounds.

For years, I had studied the autoxidation of petroleum products and rubber, and its retardation by antioxidants. Autoxidation is greatly catalyzed by trace-metals, such as copper and vanadium, which also accelerate the destructive oxidation of antioxidants. Hence, I had developed compounds known as "metal deactivators" which suppress the catalytic activity of the metal salts by converting them into inactive, multidentate complexes.[1] For example, N,N'-(1,2-propylenebis) (salicylideneimine) is an excellent deactivator for copper and has been used industrially for this purpose for many years. (See Figure 1.)

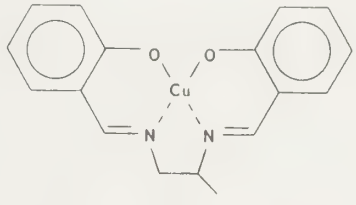


Figure 1. Copper Complex of N,N'-(1,2-Propylenebis)(Salicylideneimine)

When I transferred my interest to vanadium catalysts for the polymerization of olefins, I decided to study the effects of uni- and multidentate phenolic ligands on the catalytic properties of the vanadyl group, VO. The quinquedentate ligand I selected was bis [2-(o-hydroxyphenoxy)ethyl] ether whose synthesis is depicted in Figure 2.

The partially protected catechol[2] (see Figure 2, I) was contaminated with about 10% unreacted catechol but I decided to use this mixture for the second step, since purification would be required anyway at the end. The reactions were carried out as outlined and gave a product mixture in the form of an unattractive goo. Initial attempts at purification gave a small quantity (0.4% yield) of white crystals which drew attention by their silky, fibrous structure and apparent insolubility in hydroxylic solvents.

It was fortunate that I used an ultraviolet spectrophotometer to follow the reactions of the phenols. These compounds and their ethers, in neutral methanol solutions, absorb in the region of 275 mμ. On treatment with alkali, the absorption curve is not significantly altered if all the hydroxyl groups are covered, but it is shifted to longer wavelengths and higher absorption if one or more hydroxyl groups are still free.

The unknown product was very little soluble in methanol and the neutral solution gave an absorption curve characteristic for a phenolic compound. The solution was made alkaline with sodium hydroxide with the expectation that the curve would either be unaffected or shifted to longer wavelengths. The resulting spectrum, however, showed neither effect but the one shown in Figure 3. At the same time, I noticed that the fibrous crystals were freely soluble in methanol in the presence of sodium hydroxide. This seemed strange since the compound did not contain a free phenolic group, a fact confirmed by its infrared and NMR spectra. I then found that the compound was soluble in methanol containing any soluble sodium salt. Thus, the increased solubility was not due to alkalinity but to sodium ions, but there was no obvious explanation for this property of the compound because its elementary analysis corresponded with that for 2,3-benzo-1,4,7-trioxacyclononane,

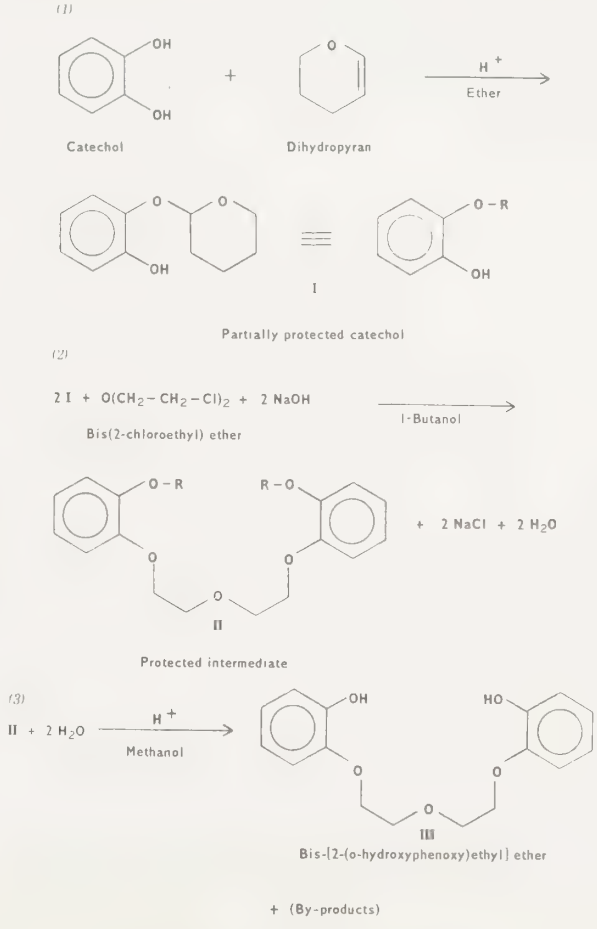
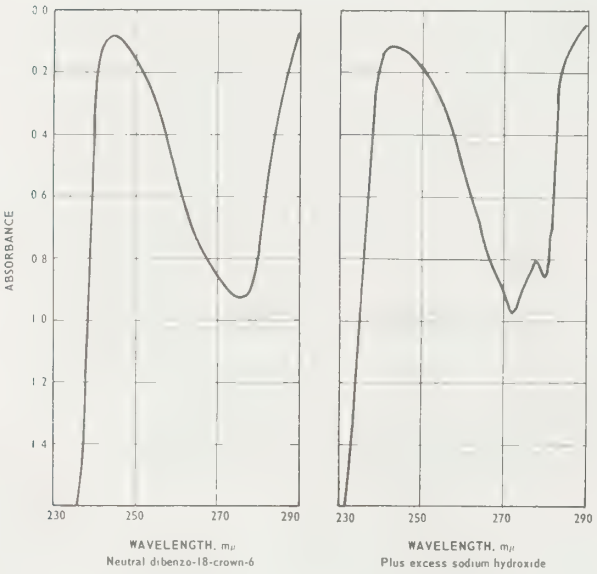


Figure 2. Synthesis of Bis[2-(o-Hydroxyphenoxy) Ethyl] Ether

(see Figure 4) a plausible product from the reaction of catechol and bis(2-chloroethyl) ether in the presence of sodium hydroxide. Its molecular weight, however, was exactly twice that of the above compound and revealed the true structure of dibenzo-18-crown-6, the first and most versatile of the aromatic crown compounds. (see Figure 5)

It seemed clear to me now that the sodium ion had fallen into the hole in the center of the molecule, and was held there by the electrostatic attraction between its positive charge and the negative dipolar charge on the six oxygen atoms symmetrically arranged around it in the polyether ring. Tests showed that other alkali metal ions and ammonium ion behaved like the sodium ion so that, at long last, a neutral compound had been synthesized which formed stable complexes with alkali metal ions. My excitement, which had been rising during this investigation, now reached its peak and ideas swarmed in my brain. I applied the epithet "crown" to the first member of this class of macrocyclic polyethers because its molecular model looked like one and, with it, cations could be crowned and uncrowned without physical damage to either, just as the heads of royalty.

Another aspect of this discovery filled me with wonder. A ring of eighteen atoms had been formed in a single operation by the reaction of two molecules of catechol, which was present as a minor impurity, with two molecules of bis(2-chloroethyl) ether. Further experiments revealed that dibenzo-18-crown-6 can be synthesized from these intermediates in a 45% yield without resorting to high dilution techniques. This was most unexpected and some good reason must exist for such an unusual result. I concluded that the ring-closing step, either by a second molecule of catechol or a second molecule of bis(2-chloroethyl) ether, was facilitated by the sodium ion which, by ion-dipole interaction, "wrapped" the three-molecule intermediates around itself in a three-quarter circle and disposed them to ring closure. Later experiments appear to support this hypothesis. The yields of dibenzo-18-crown-6 are higher when it is prepared with sodium or potassium hydroxide than when lithium or tetramethylammonium hydroxide is used. Lithium and the quaternary ammonium ions are not strongly complexed by the polyether. The best complexers, rings of 15 to 24 atoms including 5 to 8 oxygen atoms, are formed in higher yields than smaller or larger rings, or rings of equal sizes with only 4 oxygen atoms. Finally, open-chain polyethers such as 3,4,12,13-dibenzo-2,5,8,11,14-pentaoxapentadeca-3,12-diene, (see Figure 6) were found to form complexes with sodium and potassium ions.[3]



Concentration of polyether: 0.000183 mole/liter Cell path: 1 cm.

Figure 3. Effect of Sodium Hydroxide on the Ultraviolet Spectrum of Dibenzo-18-Crown-6 in Methanol

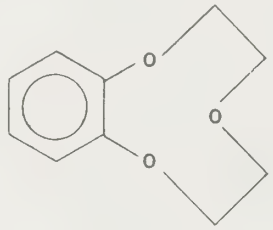


Figure 4. 2,3-Benzo-1,4,7-Trioxacyclononane

Preparation and Properties of Macrocyclic Polyethers

Spurred by curiosity regarding the factors involved in the stability of the salt complexes, such as the relative sizes of the hole and the cation, and the number and symmetrical arrangement of the oxygen atoms in the polyether ring, I initiated an extensive program of syntheses. Ultimately, about 60 macroyclic polyethers were prepared containing 12 to 60 atoms in the polyether ring including 4 to 20 oxygen atoms.[4,5] Many of these compounds were found to be useless as complexing agents but they served to define the effective ones which are compounds containing 5 to 10 oxygen atoms in the ring each separated from the next by 2 carbon atoms.

Since the official names of the macrocylic polyethers is too cumbersome for convenient use, a system of abbreviated names has been devised solely for their ready identification.[4] The examples in Figure 7 illustrate how the name is made up of the side-ring substituents, the total number of atoms in the polyether ring, the word "crown", and the number of oxygen atoms in the main ring.

The aromatic macrocyclic polyethers are neutral, colorless compounds with sharp melting points, and are little soluble in water and alcohols, fairly soluble in aromatic solvents, and very soluble in methylene chloride and chloroform. They undergo substitution reactions characteristic for aromatic ethers (halogenation, nitration, etc.), and form formaldehyde resins when treated with paraformaldehyde under acid conditions. They are decomposed by reactions which cause the scission of aromatic ethers.

The saturated macrocyclic polyethers are obtained most simply by catalytically hydrogenating the aromatic compounds using ruthenium catalyst. Bridge-bond isomers are obtained from compounds containing two or more aromatic side-ring substituents. For example, dibenzo-18-crown-6 gives two isomers of dicyclohexyl-18-crown-6. The saturated polyethers are colorless, viscous liquids or solids of low melting points. They are thermally stable but, like the aromatic compounds, must be protected from oxygen at high temperatures. They are, as a group, very much more soluble than the aromatic compounds in all solvents, and

most of them are even soluble in petroleum ether. They cannot be easily substituted but certain substituted compounds can be obtained by hydrogenating the appropriate aromatic precursors.

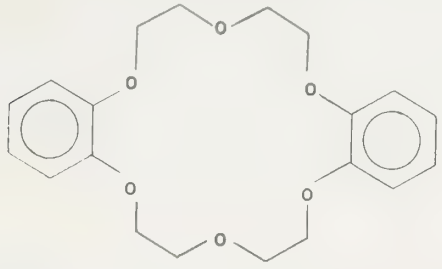


Figure 5. 2,3,11,12-Dibenzo-1,4,7,10,13,16-Hexaoxacyclooctadeca-2,11-Diene (Dibenzo-18-Crown-6)

Salt Complexes of Macrocylic Polyethers

The importance of macrocyclic polyethers as complexing agents is due to their preference for alkali metal ions which do not form complexes with many of the numerous ligands for the transition metal ions. The crown compounds form stable crystalline complexes and solutions of the complexes with some or all of the cations of Li, Na, K, Rb, Cs, NH_4, RNH_3, Ag(I), Au(I), Ca, Sr, Ba, Ra, Zn, Cd, Hg(I & II), La(III), Tl(I), Ce(III), and Pb(II).[4] Some of them, e.g., dicyclohexyl-18-crown-6, also form complexes with Co(II) and some other transition metal ions.[6] The saturated compounds are better complexing agents than the corresponding aromatic compounds.

Three criteria have been used for the formation of complexes between macrocyclic polyethers and salts: (a) isolation of the complexes as crystals; (b) characteristic changes in the ultraviolet spectra of the aromatic compounds; and (c) changes in the solubilities of the polyethers and salts in different solvents.

As is evident from the diagrams in Figure 7, these compounds have holes of different diameters in the center of the polyether rings. The uncomplexed cations also differ in size: sodium 1.90A, potassium 2.66A, ammonium 2.84A, rubidium 2.96A, and cesium 3.34A. Depending, therefore, on the relative sizes of the hole and the cation, crystalline complexes with polyether/cation ratios of 1:1, 3:2, and 2:1 have been prepared.[7] For example, benzo-15-crown-5 forms 1:1 with sodium, 2:1 with potassium, ammonium and cesium; dibenzo-18-crown-6 forms 1:1 with potassium, ammonium and rubidium, 3:2 with cesium, 2:1 with rubidium and cesium; dibenzo-21-crown-7 forms 2:1 with cesium; and dibenzo-24-crown-8 forms 2:1 with cesium.[6] The aromatic macrocyclic polyethers tend to give high melting complexes which are not readily soluble in aprotic solvents, while the saturated compounds give lower melting complexes which are more soluble. Most of the pure complexes are decomposed by water, the rate and extent of decomposition depending on the proportion of water and the temperature.

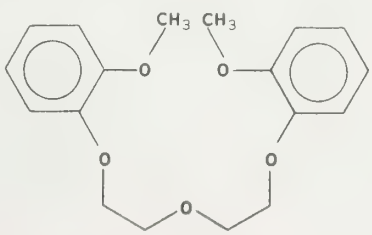
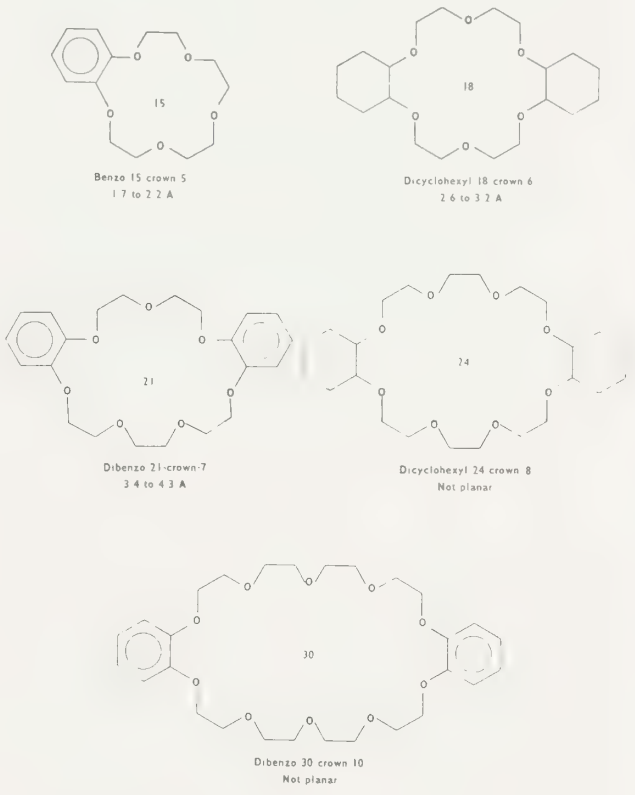


Figure 6. 3,4,12,13-Dibenzo-2,5,8,11,14-Pentaoxapentadeca-3,12-Diene

It was postulated from the beginning that complexes of macrocyclic polyethers containing less than 7 oxygen atoms consisted of a cation surrounded by the oxygen atoms arranged symmetrically in a single plane.[4] The essential correctness of this view of the structure has been confirmed by Professor M. R. Truter and her collaborators who have been the first to determine the structures of a number of crystalline salt complexes of crown compounds.[8,9]

All macrocyclic polyethers containing one or more benzo groups have a characteristic absorption maximum at 275 mμ in methanol, and the shapes of the curves are altered by the addition of complexable salts as shown in Figure 3. The spectral evidence is nearly always confirmed by the other two criteria. This is a convenient test but it cannot be applied to the saturated polyethers which do not absorb in a useful range.

Macrocyclic polyethers and complexable salts mutually increase their solubilities in solvents wherein the complexes are soluble. Sometimes these effects are spectacular, for instance, the solubility of dibenzo-18-crown-6 in methanol is 0.001 mole per liter, but the solubility of the potassium thiocyanate complex is 0.107 moles per liter, a 100-fold increase. Many other examples are given in the original publication.[4] Some of the saturated polyethers, such as dicyclohexyl-18-crown-6, have the useful property of solubilizing alkali metal salts, particularly those of potassium,



The numbers within the diagrams are the numbers of atoms in the polyether rings.

The numbers under the names are the estimated diameters of the holes in A.

Figure 7. Some Macrocyclic Polyethers

in aprotic solvents. Crystals of potassium permanganate, potassium *tertiary*-butoxide, and potassium palladous tetrachloride ($PdCl_2 + 2\ KCl$) can be made to dissolve in liquid aromatic hydrocarbons merely by adding dicyclohexyl-18-crown-6. Benzylpotassium is rendered soluble in n-heptane by this polyether, but the polyether ring is gradually decomposed by this organometallic compound. A strongly alkaline (ca. 0.3 normal) solution is obtained by dissolving an equimolar mixture of potassium hydroxide and dicyclohexyl-18-crown-6 in methanol, and replacing as much as possible of the methanol with benzene or toluene.[4] This solution will readily saponify the hindered esters of 2,4,6-trimethylbenzoic acid which are resistant to ordinary saponifying agents. The solution also is a powerful anionic catalyst and induces the polymerization of anhydrous formaldehyde and the trimerization of aromatic isocyanates. The solubilizing power of the saturated macrocyclic polyethers permit ionic reactions to occur in aprotic media. It is expected that this property will find practical use in catalysis, enhancement of chemical reactivity, separation and recovery of salts, electrochemistry, and in analytical chemistry.

When a large quantity of a salt solubilized with dicyclohexyl-18-crown-6 is used in stoichiometric rather than catalytic proportion, it is frequently possible to recover the polyether for further use after the desired reaction has been completed. If the reaction mixture is warmed in a large amount of water, the polyether will separate and can be extracted by a solvent, such as toluene.

When an aqueous solution of an alkali metal hydroxide or salt containing a very low concentration of the picrate of the same cation is mixed with an equal volume of an immiscible organic solvent, such as methylene chloride or toluene, nearly all the picrate is present in the yellow aqueous phase and the organic phase remains substantially colorless. If a cyclic polyether is added to the system, the complexed picrate transfers to the organic phase, the extent depending on the effectiveness of the polyether as a complexing agent for the cation. If the polyether is ineffective, the organic phase will be colorless; if the polyether is very powerful, most of the color will be in the organic phase. The efficiencies of the polyethers will lie between these two limits, and can be expressed as percentage extracted. This method is simple, it can be applied to saturated compounds, and it makes it possible to numerically rank the efficiencies of complexation.[10]

Dr. H. K. Fresdorff has determined the stability constants for 1:1 complexes of many macrocyclic polyethers with alkali metal ions by potentiometry with cation-selective electrodes.[11] Selectivity toward the different cations varies with polyether ring size, the optimum ring size being such that the cation just fits into the hole, i. e., 15–18 for sodium ion, 18 for potassium ion, and 18–21 for cesium ion.

The structures of macrocyclic polyethers are similar to those of certain naturally-occurring macrocyclic antibiotics, such as valinomycin, which affect cation transport across biological and artificial membranes. The polyethers, therefore, have created great interest among biologists for studying the mechanism of transport of sodium and potassium ions across cell membranes, one of the fundamental processes in both animal and vegetable kingdoms.

Limitations and Toxicity

Although salts with high lattice energy, such as fluorides, nitrates, sulfates and carbonates, form complexes with macrocyclic polyethers in alcoholic solvents, they cannot be isolated in the solid state because one or the other uncomplexed component precipitates on concentrating the solutions. For the same reason, these salts cannot be rendered soluble in aprotic solvents by the polyethers.

Dicyclohexyl-18-crown-6 possesses unusual physiological properties which require care in handling. It is likely that other cyclic polyethers with similar complexing power are also toxic, and should be handled with equal care. The approximate lethal dose for ingestion by rats was 300 mg./kg. It should be mentioned, however, that no difficulty whatever was encountered with this compound during seven years of handling in the laboratory.

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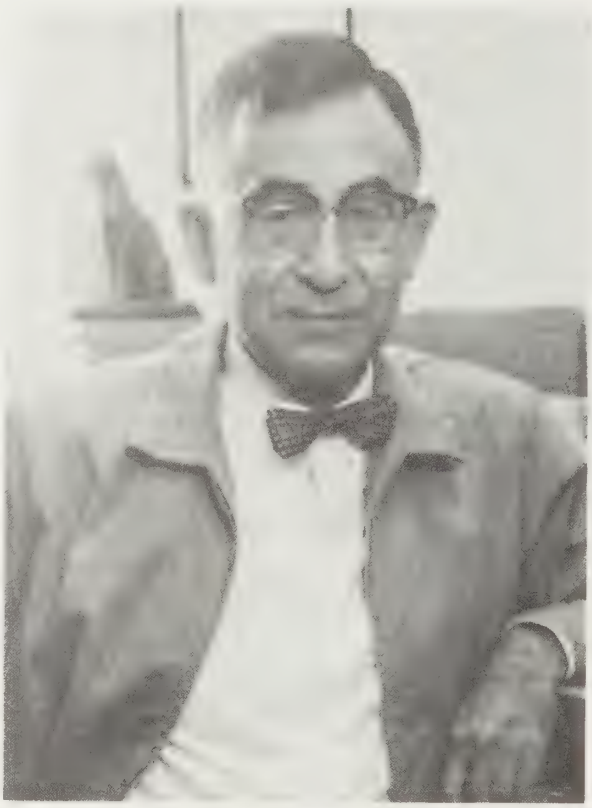

Dr. Charles J. Pedersen

Cornelis Bega's Alchemist

A Problem in Art History

Alfred Bader

One of the best known works in the collection of alchemical paintings of the Fisher Scientific Company in Pittsburgh, is a painting by Cornelis Bega called *The Chemyst* (fig. 1), familiar to most chemists through more than 9000 reproductions distributed by Fisher Scientific.[1]

Fisher describes this painting as "the gem of all alchemist paintings because of its modern rendition of highlights, the meticulous attention to all details, the flesh-tones of the alchemist, and the unusual heliotrope tint of the entire picture. In fact, the former director of fine arts of Carnegie Institute, Pittsburgh, stated that this picture would do justice to any collection in America for its artistic merit alone—without even considering its scientific interest."

Figure 1

"This particular painting was the favorite picture of the late Sir William Jackson Pope, professor of chemistry at the University of Cambridge in England, who attained just about all the honors available to a chemist, including an honorary membership in the American Chemical Society, for his contributions to the winning of World War I."

Figure 2

Certainly it is one of the two best paintings in the Fisher Collection. Unfortunately, the greatest artists—Rembrandt, Titian, Vermeer, Velasquez, for instance—did not paint alchemical subjects, and so most alchemical paintings are of greater historical than artistic interest. The Fisher Collection's other really fine alchemical painting is a study by Adriaen van der Venne (fig. 2) which unfortunately has never been reproduced.

Two years ago there appeared at Christie's a small canvas (fig. 3) which of course must be related to the Fisher painting.

The painting in London came from the collection of one of England's greatest 19th century collectors, John Sheepshanks, is signed and, except for a yellowed varnish which was easily removed, is in a fine state of preservation.

1 I would like to thank Mr. John C. Pavlik, the Director of Public Relations at the Fisher Scientific Company for allowing me to reproduce the cover of *The Laboratory* and the Fisher paintings, and for his generous help in comparing the paintings.

The great English auction houses have a simple way of indicating their opinion of a painting's authenticity. If it is called "Cornelis Pietersz Bega" they believe it to be a work by the artist. If called "C. P. Bega" they believe it to be a work of the period, which *may* be the work of the artist. If just called "Bega," they don't think that it could possibly be a work by Bega, but the owner says it is. The Sheepshanks painting was called Cornelis Pietersz Bega, and because of its beauty and provenance brought an auction record for a work by Bega, and perhaps also for an alchemical painting.

Professor Pope had purchased the Fisher painting from the collection of J. C. W. Sawbridge–Earle–Drax which was auctioned also at Christie's, on May 10, 1935, was then described as a work by C. P. Bega and brought the rather unsubstantial price of 50 guineas.

Figure 3

Knowing that, it seemed possible that the Fisher painting was a copy after the Sheepshanks original. A direct comparison of the paintings side by side in Pittsburgh made it clear however that both paintings are of such fine quality, and there are so many variations of details that one cannot think of one being someone else's copy of the other, no matter how skillfully done. The Fisher painting is somewhat smaller (14½ x 13⅛ inches against 16¼ x 15 inches), on panel and signed and indistinctly dated. The Sheepshanks painting is on canvas and signed on the lower right.

Some years ago, Fisher's publication, The Laboratory (Vol. 23, Number 1; fig. 4), featured on its front cover one of the world's foremost authorities on the conservation of paintings, The Mellon Institute's Dr. Robert L. Feller, examining the Fisher painting.

When asked about the signature of the Fisher painting, he said that he had not really cleaned the painting, but only posed for the photograph; Dr. Eric C. Holmer, the restorer who really did clean the painting, is certain that the signature in the Fisher painting sits firmly on the letter in the center of the painting. Similarly, the signature on the painting on canvas was immovable by acetone during cleaning, and is certainly contemporary with the painting.

Thus the logical conclusion is that both paintings are by Cornelis Bega. It is surely conceivable that a customer had greatly admired the first work and had commissioned the artist to paint a work much like it.

But which is the first and which the second version? There certainty is much harder to attain. Comparing details, there are some in each painting better than the corresponding detail in the other. This is subjective and elusive. But I believe that there are some changes which only an artist would make when 'improving' a second version after a first. Take the pestle, for instance, at the foot of the step. In the Sheepshanks painting it is small (fig. 5) and the spatial delineation of the steps is not quite clear. In the Fisher

Figure 4

Figure 5

Figure 6

painting, the pestle (fig. 6) is much larger and serves to give spatial clarity to the steps. The larger pestle is, I believe, the sort of 'improvement' an artist would make when working on a replica of his own work. This is, of course, a double edged argument: if I thought the Sheepshanks painting to be a copy after the Fisher painting, I would argue that the copyist simply did not understand the purpose of the large pestle—to aid in delineating the steps. Clearly, art historical analysis is not as straightforward as chemical analysis. Perhaps the most convincing argument for the priority of the Sheepshanks painting lies in the comparison of size and support. When Bega painted these around 1660, canvas was relatively inexpensive and can, of course, be cut to any size. Panels were much more expensive, were planed towards the edges and hence of fixed size. If Bega had painted the panel painting first, he could easily have cut the canvas to the same size as the panel. The painting on canvas contains some beautiful details which are partly or fully missing in the panel painting: presumably Bega only had a panel smaller than the canvas, and so had to leave them out.

I think that Bega would be amused and intrigued if he could know that his two alchemical paintings after 300 years are in the collections of chemical companies and enjoyed by thousands of chemists.

The Methadone Story

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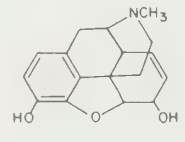
Abstract -

Methadone, a synthetic analgesic, topologically similar to morphine and with a similar pharmacologic profile was confiscated from Germany in the spring of 1945. Craving for methadone does not match that experienced for morphine or heroin and withdrawal symptoms, although prolonged, are much milder than with morphine or heroin. Consequently its principal use in the United States to 1965 was for the alleviation of heroin withdrawal sickness. Since that time, it has been used as a substitute for heroin in so-called maintenance programs begun by Dole and Nyswander of New York City. Its virtues are high oral effectiveness, long duration of action and blocking of the thrill normally given by heroin. At present 45 - 50 thousand former heroin addicts are participating in the programs. Many are now useful members of society. Longer-acting methadone derivatives (e.g., acetylmethadols) hold promise of being superior to methadone.

In the spring of 1945, a team of scientists headed by Dr. Ervin C. Kleiderer of Eli Lilly and Company was sent by the United States government to study the pharmaceutical activities at the I. G. Farbenindustrie plant, Hochst am Main, Germany. Among the interesting products disclosed in the so-called Kleiderer Report that followed[1] was 6-dimethylamino-4,4-diphenyl-3-heptanone (amidone, methadone, II), a potent analgesic initially synthesized by Bockmuhl and Ehrhart[2] of Germany and first tested for spasmolytic properties. Since that time, methadone researches have been numerous, and a plethora of papers have been published on the chemistry and pharmacology of this drug and on literally thousands of analogs and derivatives.[3,4]

Although on casual examination, methadone's structural resemblance to morphine (I) appears remote, an inspection of molecular models reveals striking similarities in rigidity and topology.[5,6] More recently, Beckett[7] suggested that interaction of the free electron pair of the nitrogen and the slightly positive carbonyl carbon of methadone might assist in the formation of a favorable conformation (III) for a biological receptor that would also accommodate morphine and pethidine. One might consider, too, a conformation (IV) which would result from intramolecular bonding between the (protonated) nitrogen (at physiological pH)and the oxygen function.[4b] In any event, methadone and morphine do have in common, chemically, a quaternary carbon, a phenyl group attached to this carbon, and a tertiary amino group two carbons removed.



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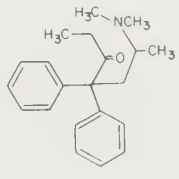
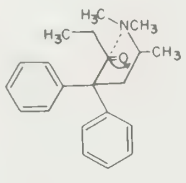
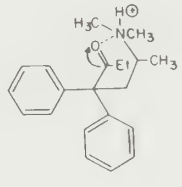


METHADONE, II



III



IV

Fig. 1

The synthesis of methadone (Fig. 2) is readily achieved in two steps by condensation of diphenylacetonitrile (V) and 2-chloro-N,N-dimethylpropylamine (VI) ($NaNH_2$[2,4] or KOH[8] as carbanion-forming reagent) followed by reaction of one (VII) of the two isomeric nitriles thus formed with ethylmagnesium bromide. The other nitrile (VIII) leads to isomethadone (IX), also an effective pain-relieving compound.

It has been amply demonstrated that the pharmacologic profile of methadone closely parallels that of morphine with some *important* time-action differences and *clearly superior oral*

effectiveness for methadone.[9,10] In an individual dependent on large daily doses of morphine, methadone can be substituted and the dose rapidly reduced with days elapsing before the patient is aware that either has taken place. Impending abstinence phenomena can be avoided by administration of small *oral* doses of methadone. Given a choice, some former addicts prefer methadone (for its prolonged effect) to morphine or heroin, but some reverse this choice later because of the greater peak thrill which morphine and heroin provide.[9,10,11]

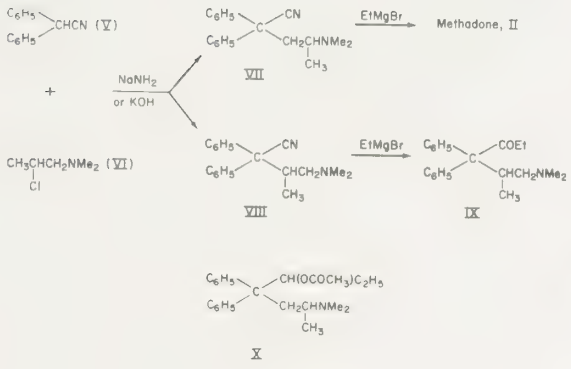


Fig. 2

Chronic administration of methadone causes rapid development of tolerance and cross-tolerance to heroin, morphine and other morphine-like agents (but not to barbiturates and stimulants [9,10,11]) and of a physical dependence of the morphine type. On abrupt withdrawal, abstinence signs are not evident for about 48 hours. These signs never reach severe intensity and disappear more slowly than with a morphine dependence. Thus, orally administered methadone has long been used to minimize withdrawal sickness in narcotics addiction.

About 1964, Drs. Vincent Dole and Marie Nyswander, a husband-wife medical team of New York City, recognizing the inadequacies of narcotics-addiction treatment and cognizant of the differences in pharmacologic properties of the large battery of 'narcotic' drugs at a physician's disposal, conceived and began a program of 'maintenance* therapy' with a few *selected* heroin addicts. Their philosophy[12] was based on the belief that *rehabilitation* of a drug-dependent individual should be given priority over *elimination* of drugs. Their choice of methadone was out of consideration not only for the published pharmacologic properties of available agents, but also for actual clinical trial of some of these agents in a small group of patients during a two-year period.[10,12]

*For a statement on the concept of maintenance, see Wld. Hlth. Org. Techn. Rep. Ser., 1970, No.460, p. 20, ff. and references therein.

The original protocols and rationale[13] emphasized the importance of having available a long-acting orally effective drug (methadone) and plausible reasons for failure of the limited trial with 'maintenance' [with relatively short-acting, parenterally (sometimes self-) administered morphine] from 1919-1923. Using methadone,[13] patients can be stabilized by a single, daily, oral dose. Maintaining patients on methadone was said to be [13] 'no more difficult than maintaining diabetics with oral hypoglycemic agents.' It was further stated[13] that methadone 'appears to relieve narcotic hunger and thus free the patient for other interests as well as protect him against readdiction to heroin by establishing a pharmacological block.'

The program was developed in three phases.[13] 1. Stabilization of addict patients with methadone hydrochloride, administered orally, in an unlocked hospital ward during a period of about six weeks. The patients are given a complete medical workup, psychiatric evaluation, review of family and housing problems and job-placement study. 2. Discharge of patients to outpatient care, these patients returning every day for methadone medication. 3. Return of the patients to society. These patients still receive methadone medication (cf. references 10, 13 for details of these three phases).

Dr. Everette L. May

During the approximately eight years since its inception in New York City, the methadone program has proliferated throughout the United States and Canada. It is estimated that in the United States alone, 300 Investigational New Drug (IND) licenses have been issued by the Food and Drug Administration (which jointly with the Bureau of Narcotics and Dangerous Drugs exercise controls over the program) for this modality of treatment of narcotics addiction[14]; there are presently about 50,000 patients in the program.* No reliable figures are available on what percentage of this restricted group of patient addicts have been returned as useful members to society or what has been the impact of the methadone program on crime and economics. The consensus seems to be that overall, the results are favorable. Also, not yet known is what will happen if and when the 'rehabilitated', methadone-dependent individual is deprived of this 'crutch'. Will there be recidivism to the same extent as with other treatment methods or is the methadone-treated patient truly cured?

As for the future, it is likely that methadone maintenance programs will continue to grow; political leaders have called for rapid expansion in New York City alone to a caseload of 25,000. Better drugs for this type of treatment are being sought. Already, a methadone derivative, alpha-(+)-3-acetoxy-6-dimethylamino-4,4-diphenylheptane (alpha-acetylmethadol),[15] a longer-acting, also orally effective drug has been tried with marked success.[16] More recently[17] the *levo* isomer has been under study. Others are no doubt in the chemical and pharmacologic 'pipelines'.

*For a current medical report *cf.* Medical World News (a McGraw-Hill publication) March 17, 1972, p. 53.

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CHEMICAL INFORMATION MANAGEMENT FOR THE 21ST CENTURY

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The 20th century is characterized by the profound change from flowery words and phrases to severely compressed identifications that more efficiently accomodate the information "explosion" of this era. Thus if people in ACS, EPA, FDA, ISI, NBS, NCI, NIH, NLM, and related organizations talked about ESR, GC, GLC, IR, LD50, MAC or TLV, NMR, and UV records, they would be dealing with the central problem in chemical information management--the "cosmic" addresses for the basic substances of these records. By the 21st century, such people also would have annually updated "chemical almanacs" about the size of the 1972 edition of *The Aldrich Handbook of Organic Chemicals* that would explain the meanings of these organizational and technical abbreviations, as well as very many other frequently used chemical terms such as "the Q1 equivalent" of antifreezes,"the Q2 concentration" of cocktails, "the QH content" of foods, "the QR coefficient" of germicides, and some 10,000 easily indexed structural identifications of the commonly met lab and shop environmental chemicals. Such "cosmic" identifications will be as commonplace to chemists as "Mr, Mrs, and Ms" now are to their secretaries. In the relentless competitions of "mass action" usage, these SHORTEST NECESSARY AND SUFFICIENT DESCRIPTIONS will survive like many work-horse Anglo-Saxon words have-- because they minimize the reading, writing and remembering effort for the users[1], and minimize the storage, retrieval and processing costs for the computers.

This seems an appropriate year to make these predictions, because our proposed solution to the chemical indexing problem was summarized in *C&EN* 20 years ago, and its key value for high-speed structure display was realized 10 years ago (demonstrated with a UNIVAC "dot-plot" program in February 1964). The first fundamental inspiration for our notation proposal was documented **thirty-five** years ago, in these 1938 notes on "Systematic Names," prepared for an invited discussion with Dr. A. M. Patterson at the National Meeting of the American Chemical Society at Baltimore in April 1939:

> "... The Geneva principle is to name the open-chain derivatives according to the **number of atoms** in the principal chain. It would seem desirable that closed-chain structures be named the same way--by the total number of atoms in the basic ring frame. Since the very same chain of atoms can, through ring closure, give rise to alicyclic and aromatic compounds, this geometrical connectedness can be profitably implied in the root name."

The tragic theme of history is that the young ignore its lessons and thereby are condemned to repeat its mistakes. After this encouraging 1939 meeting with Dr. Patterson, ten years passed before the revealing history on the origin and development of line-formula notations was gathered and reported at the 118th National Meeting of ACS at Chicago in 1950. This historic research was updated in 1961 for the hundredth anniversary of line-formula notations, and again in 1968 for a symposium on chemical notations[2]. Youthful ignorance of origins and developments in science and technology should not continue if humans are to enjoy the 21st century as a freedom-tolerating world community.

DEVELOPMENT OF LINE-FORMULA APPROACH

Computer identifications for chemicals in the 21st century will use the same short and simplified descriptions that the users will have learned in their first courses in general chemistry, because this directness and familiarity is overall "least effort." For example, the first chapters in their chemistries should explain how the science started in the 17th and 18th centuries through systematic examinations of naturally separated MINERALS (crystallized in deep layers from evaporated inland seas and lakes, or from colossal pools of lava) and METAL-BEARING ORES (studied with obvious enterprising motivations).

Mineral examples such as these--with short names that will survive for another century--were cited in Josiah P. Cooke's Harvard textbook of 1871, a full hundred years ago[3]; these selections indeed had name and synonym identifications in Martin Klaproth's "Chemischen Kenntniss der MINERALKORPER"[4] in 1807:

.AG	.AG3.SB	.BA..C-03
.AU	.AG5.BI	.BA..S-04
.BI	.AL2.03	.CA..C-03
.CU	.AS2.03	.CA..S-04
.FE	.AS4.S4	.CO..AS-S
.NI	.AS4.S6	.FE..AS-S
.PB	.AU2.BI	.FE..C-03
.SN	.BI2.S3	..H3.B-03
.TE	.CA..F2	.MG..C-03
.AS4	.FE..S2	.MN..C-03
.AG..G	.FE2.03	.PB..C-03
.AG2.S	.FE3.04	.PB..S-04
.CU..S	.MN..02	.SB2.0.S2
.CU2.O	.MN3.04	.SR..C-03
.CU2.S	.SB2.03	.SR..S-04
.HG..S	.SB2.S3	.ZN..C-03
.MN..S	.SI..02	.AG..AS.S3
.NI..S	.SN..02	.AG3.SB.S3
.PB..S	.TI..02	.AG5.SB.S4
.ZN..S	.UR3.08	.AL2.BE-04

No chemist should need help in understanding these identifications, thanks mainly to the notational concerns of Jons Jacob Berzelius (1779-1848), "the organizer of chemistry." At a time when the tools of the chemist were the same primitive ones of the alchemist, he proved to be a master craftsman in chemistry: he analyzed over 2000 minerals and compounds, discovered more elements than any other individual (deter-

mining the atomic weights of 55 of them), made his own special glassware, introduced rubber tubing, the water bath, desiccator, wash bottle, filter paper, test tube, and separatory funnel. As a pioneering editor and abstractor, this "respected professor of chemistry of the Karolinska Medical Institute at Stockholm, Secretary of the Swedish Academy of Science, and uncrowned ruler of chemistry" insisted that "the chemical signs ought to be letters, for the greater facility of writing, and not to disfigure a printed book"[5]. He was indeed the "Rembrandt" of the chemical world, creating "a work of art--a thing of beauty that is a joy forever." Our chemical contribution is very modest by comparison. All we have done is standardize his symbol set and the "line-formula" citing method that first appeared in 1861 (13 years after his death), then combine these with a mathematically basic analysis of ring systems.

STANDARDIZATION OF ATOMIC SYMBOLS

The first and simplest step in this standardization is to implement his intent to distinguish at a glance the few commonplace NONMETALS from the many less frequently cited METALS. Cooke's Harvard text contained appended tables with **Ur** (like **Cr**) for uranium, **Va** (like **Ta**) for vanadium, and **Wo** (like **Mo**) for tungsten, 100 years ago. This grand oversight is matched by a much later one--in the 1921 M.I.T. Textbook by Norris[6] and in other Periodic Tables of the early 1920's) showing **Yt** (like **Yb**, both from the Swedish Ytterby sands) for yttrium. Since Berzelius started with **Po** and **So** for potassium and sodium, all that is needed to complete the standardization of two-letter symbols for ALL metals is to maintain the parallel with **Ka** for *kalium,* like **Na** for *natrium.*

CHLORINE NOTATION

Berzelius had proposed single-letter symbols for the commonly met but small number of NONMETALS--reserving the letters B, C, F, H, I, N, O, P and S (initially also *M* for the "muriatic" radical) for these most frequently cited elements. Now students occasionally slur the symbol of chlorine into a fusion that looks like G, and they might even misspell it as "GLORINE" with subconscious association of that 7th letter of the alphabet (which also appears in the word HALOGEN) for the element that "glorifies" the 7th Periodic Group. So the symbol **G** replaces the ambiguous symbol **Cl**.

BROMINE NOTATION

Bromine today is extracted in ton-a-day quantities from the sea, so when we suggested "extracting" from **Br** a letter in the alphabetically closed set covering E, F, G, H and I, a Syracuse University student many years ago very aptly showed how to extract the desired letter by proudly writing "SEA" on the blackboard and then rubbing out the two end letters! It also appears in the word haloGEn, right next to its companion letter **G**.

HYDROXYL NOTATION

Astronauts marvel at the beautiful blue color of our planet, caused by the bountiful abundance of that thermodynamically unusual vapor and liquid sea of AQUA. Surely the letter **Q** from this aqueous medium best describes its characteristic group--as an O-atom with a tiny H-tail.

AMINES AND THE IMINO NOTATION

Nitrogen parallels oxygen with a corresponding IMINO or IMIDE group, so this important NH-group is best denoted with the mid-letter M, pictured as a tilted N with a slender H-prop. When nitrogen appears as a doubly hydrogenated primary AMINO or AMINE (inorganic AMIDE or NH_2 anion) group, an end selection ends the inorganic A, B, C's of the symbolism with the letter Z--literally and figuratively an N on end (rotated 90°)!

COMPACT LISTING OF MINERALS

Now with a frequently useful Q for OH, M for NH, E for Br, G for Cl, and Z for NH_2, additional minerals identified by Klaproth in 1807 can be lucidly explained by the cation-anion formulations that first appeared with "ferrIC *vs* ferrOUS" types of names just about 100 years ago:

```
.AG..G          .CU2.C-O3.Q2
.MG..G          .CU3.P-O4.Q3
.MA..G          .PB2.C-O3.G2
.Z&..G          .CA..S-O4.QM2
.CU2.Q3         .CO..S-O4.QH7
.MG..Q2         .CU..S-O4.QH5
.MN..O.Q        .FE..S-O4.QH7
.FE2.O.Q4       .MG..S-O4.QH7
.FE4.O3.Q6      .MG3.B7-O13.G
.CU2.AS-O4.Q    .PB5.P-O4*3.G
```

In these examples of a computer-generated "compacted listing," Mitscherlich and Berzelius would have been delighted to see how the intercrystallizing or isomorphous (very closely related) minerals are automatically associated by simple alphabetization within each fixed-length set of records. Periods "fill" the separating blank spaces for simple cations and anions--with a reserved place for the first multiplier to guarantee simple scanning of the anionic descriptions. Compound anions are recognized at a glance by the bonding hyphen mark, and when necessary, these are multiplied with the Fortran mark and multiplier in a manner that does not mess up the sorting advantages. No artificial "connection-table" gyrations are needed to create these notations, because MINERALS AND INORGANIC SALTS are **aggregates of ions**; and here these descriptive units are cited one after another in an ordered manner, directly reporting the experimentally found compositions of these "aggregates."

CITING ORDER

Structural chemistry could not begin with this description of component parts like marbles in a bag, freely slipping and sliding around. Modern structural chemistry, as A. M. Butlerov first visualized in his 1861 paper on "The Chemical Structure of Compounds," is concerned with the connecting **arrangements of atoms** in molecules. For more than a century now chemists have speculated (sometimes wildly) on imaginary "stick-like" connections between atoms in molecules such as these:

```
NN    OCO    CNNC    NCSCN    NCOCCCN    OCCCCCO
OO    ONN    NCCN    OCCCO    NNNCCCN    SCCCCCO
OC    OSO    NCNC    SCCCO    OCNCCCN    SCCCCCS
ON    SCO    ONCN    SCCCS    SCNCCCN
SO    SCS    ONNO    SNSNS    SCNCCNC
```

These are linear chains of atoms connected to form molecules by a cementing cloud of electrons that has elongated spherical harmonic spatial patterns[7]. But why should the computer records be labored with these speculations? Moreover, the "chemical bondage" cannot explain why intermediate cases like OCCO, SCCO, SCCS or OCCCCO, SCCCCO, and SCCCCS do not exist! If the only experimentally confirmed details are the locations of the atomic groups (by beams scattering from those sharply defined centers), why force in more than we truly know? These end-to-end descriptions of unbranched molecules are the **simplest** necessary and sufficient descriptions, hence the preferred "cosmic" identifications and self-determined computer addresses. For the asymmetric cases, and for all "otherwise equal" citing alternatives in more complicated structures, a "highest first" resolving rule based on anciently familiar **alphabetic** order suffices. Indexing emphasis thus is automated as in arabic numeration, by first citing the highest-valued and most important mark on the left.

ALKYL CHAINS

Paraffin chains are so named because they have *par affinis*–least chemical affinity and therefore least indexing value; the FUNCTIONAL GROUPS attached to them determine the properties which determine the uses and values. So ALKYL CHAINS are denoted with ARABIC NUMERALS for the number of C-atoms in them, and the citing values ascend with 1,2,3,....A,B,C,... to X,Y,Z. The FUNCTION comes first, then the paraffinic or alkyl "tail."

UNSATURATION MARK

Unsaturations classically relate to dehydrogenations between **carbon** atoms, for E. Erlenmeyer was referring to **olefinic** double bonds and **acetylenic** bonds when he introduced the multiple bond marks in 1866. Thus when **carbon**-chain terminals are dehydrogenated, a single U-mark logically denotes the "single" unsaturation or dehydrogenation, and a UU-mark (logically and quantum-mechanically) denotes the "double" unsaturation or dehydrogenation (two **plus** the single bond line).

CARBONYL NOTATION

A **V**ery commonly met di**V**alent connecti**V**e that appears with the *paraffinis* groups (and causes frustrating nomenclatural gyrations in its great variety of combinations) is the ALDO- or KETO- or CARBONYL group. Within it is a classical C-to-O "unsaturation," so the etymologically related letter V (a Latin variant for "least effort" chiseling of U-marks in granitic monuments) is most appropriate for this -CO.- connective. When this V-mark is used (as VH) to signal ALDO- as well as KETO-groups (without H-mark), programmers should be cautioned that the aldo-V is two-connected like the keto-V only if the cited H is counted as a valid connection. When the H-details are ignored (traditionally giving "primary, secondary, ternary and quaternary" connecting differences among alkane carbons), the aldo-C is only 2-connected (to O and C) whereas the keto-C is 3-connected (to O, C and C).

DI-OXYGEN TERMINAL

DIOXO or DIOXYGEN branches with N- or S-atoms in nitro- and sulfonyl- and like groups classically have a **doubly unsaturated** hypothetical bonding pattern, so this logically and etymologically leads to a selection of the W-mark for **branched** dioxygen groups, because the medieval letter truly whispers this "double-U" meaning.

SIMPLE UNBRANCHED EXAMPLES

Now with single digits for the ever-present alkyl(ene) chains, single letters for five commonly met groups that first appeared as anions (E, G, M, Q, Z), and these last three (U, V, W) for unbranched aliphatic additions, chemists and computers have a powerfully efficient set of tools: **one** mark for each commonly met variable leads to an ultimate of simplicity and conciseness for thousands of linear combinations that show their connections with pictorial directness. Here is a "compacted listing" of items that were available 20 years ago.

WLN DESCRIPTIONS OF UNBRANCHED MOLECULES COMMERCIALLY AVAILABLE IN 1953

5H	G3	I8	Z3	2ØH	3V3	6M6	E1E	G1E	GV6
6H	G4	IG	Z4	28H	4M4	606	E2E	G1G	GV7
7H	G5	IH	Z5	2M2	402	6S6	E3E	G2E	GV8
8H	G6	Q1	Z6	202	404	6V1	E4E	G2G	I1Ø
E1	G7	Q2	Z7	2S1	4S1	7M7	E5E	G3E	I12
E2	G8	Q3	ZZ	2S2	4S2	7S7	EV1	G3G	I16
E3	I1	Q4	1ØH	2V1	4S4	7U1	EV2	G4G	I1I
E5	I2	Q5	12H	2V2	4U1	9V1	EV3	G5G	I3I
E6	I3	Q6	14H	32H	4V2	E1Ø	EV4	GV1	I5I
E7	I4	Q7	16H	3M3	4V4	E12	G1Ø	GV2	NC1
E8	I5	Q8	1M1	303	5M5	E14	G12	GV3	NC2
EH	I6	Z1	1S1	3S3	505	E16	G16	GV4	NC3
G2	I7	Z2	1V1	3V1	5V1	E18	G18	GV5	etc.

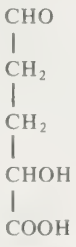
This "simplistic" listing, ordered by the lengths or "Hollerith numbers" of the records, automatically displays the simplest (2- and 3-mark) structure descriptions first, and provides easy visual scanning of both ends of the descriptions. No other kind of display can compress so much chemical information into such a small amount of line-printing space, so this method should enjoy a long-enduring profitable usage in the 21st century. Perhaps these simplest commercially available chemical descriptions are uninteresting, but for the same reason they should be very inexpensive: processed in huge quantities for the benefits of all chemists at **trifling** costs per entry!

BRANCHED CHAINS

Branching points are topologically unique features (nodes), so these deserve distinct single-letter marks for the most important or most frequently cited cases: Y-marks for the ternary or Y-branched CH-groups (with U if unsaturated), X-marks for the quaternary or X-branched C-atoms, and K-marks for the analogous quaternary N-atoms. These complete the eleven new aliphatic letters, with the five and three noted above.

Branched line-formula descriptions incorporate a subtle and tacitly understood **rightward**-unfolding polarization that has been followed ever since shrewd Josef Loschmidt published the first line-formula examples in his 1861 booklet on

Chemische Studien. Thus inorganic examples like FBFF and GPGG never are garbled into FFBF or GGGP citing sequences. This rightward polarization came naturally as a mechanical scanning of the earliest diagrams, in which the carbon skeleton extended vertically, like the human skeleton. Substituted groups were cited **after** the chain atom (like its associated H-atoms). The inset diagram (figure 1 in our 1952 *C&EN* report[8]) shows the "Origin of the Line-Formula delineation (*circa* 1861) as a television-like scanning of the vertical chain diagram, top to bottom and left to right, giving this delineation: $CHO.CH_2.CH_2.CHOH.COOH$ (with a period marking the **end** of each scanned line)."

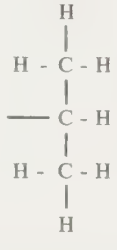


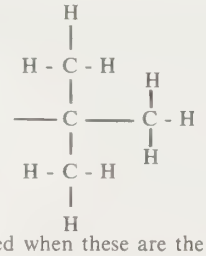
Selection of the letter Y for a Y-branched or 3-connected CH-group, as noted above, leads to YU or UY for the corresponding keto-like dehydrogenated acyclic C-branch, and to the letter X for the corresponding acyclic quaternary or 4-connected C-atom. Then all simple secondary alcohols are automatically indexed under the QY... marks, and simple tertiary alcohols under the QX...marks, with similar automated benefits for the corresponding halides and all other terminal functional groups. The letter X in turn suggests selection of its graphically related letter K for the corresponding quaternary N-atom.

METHYL CONTRACTION

Now Y, X and K are new and distinct branching symbols, so they can be defined as **methyl-branched unless otherwise specified**. This expressive conciseness for the ubiquitous "unit" alkyl group reflects the century-old custom of omitting the cluttering "unit" marks in chemical formulas: not H_2O_1 and $H_1N_1O_3$ and $H_1C_1N_1$ or the like, but simply H_2O and HNO_3 and HCN.

A terminating ...Y expresses the nine connections among the three C-atoms and seven H-atoms in the **isopropyl group** with maximum economy (see inset). The terminating ...X likewise is a "least effort" ultimate for the four C-atoms, nine H-atoms, and their twelve connections in the tertiary butyl group (2nd inset). This is the meaningful kind of symbol economy that is mandatory if the six million presently reported structures in the chemical world are to be widely available and **searchable** at low cost by the 21st century.





Contractions, like linguistic abbreviations, should not disturb the indexing first parts of any descriptions, so the corresponding methyl-branched groups are written as 1Y..., 1X..., and 1K... (for quaternary trimethylammonium) when they initiate a notation. No branch-ending punctuation is needed when these are the only branches in the description, and no additional explanations should be needed for the following simple isoalkyl and neoalkyl examples found in *The Aldrich Handbook of Organic Chemicals*:

```
2X  4Y  GX  QY   E1Y  NCX  Q2Y  SHY  Z3Y
2Y  5Y  GY  ZX   E2Y  NCY  Q3Y  VHY  ZVY
3X  6Y  IX  ZY   G2X  Q1X  QVX  WNY  (and others
3Y  EX  IY  2VY  GVX  Q1Y  QVY  Z1Y   among the
4X  EY  QX  3VX  GVY  Q2X  SHX  Z2Y   10,000 rarer
                                      chemicals)
```

These "curt, clear and complete" descriptions have enjoyed more stability during the past 20 years than the corresponding names, and the contrast in long-enduring usefulness seems likely to intensify much sooner than the 21st century!

BENZENE

BENZENE is a **R**esonating, **R**egular-hexagonal, a**R**omatic **R**ing, so the R-mark for this unit provides the greatest symbol economy of all, because in large collections this ring occurs **more frequently than all other rings combined**. It is subordinated to all other atomic group symbols because of this superprominence and its consequent negligible indexing value (nearly **two million** of the six million reported structures contain benzene rings without any other rings). A terminal ...R denotes the three double bonds, eleven single bonds, six C-atoms and five H-atoms in the **phenyl group** (often written with least effort as the Greek *phi* or ϕ mark). Here are a few examples:

```
2R  8R  QR  1SR  2VR  5VR  G1R  Q1R  R1R  RVR  Z2R
3R  ER  RR  1VR  2XR  E1R  G2R  Q2R  R2R  SHR  Z3R
4R  FR  ZR  1XR  2YR  E2R  GVR  QVR  RMR  VHR  ZMR
5R  GR  1MR 1YR  3VR  E3R  NCR  QXR  ROR  WNR  ZVR
6R  IR  1OR 2MR  4OR  EVR  ONR  QYR  RSR  Z1R  ZYR
```

REVIEW OF SYMBOLS

Chemists in the 21st century will be able to read these descriptions as easily as our children today read words like ace, ape, ark, art, asp, bad, bag, bar, bat, bay, bib, cab, car, cat, cog, cow, and so on. By that time the international professional competition will have convinced chemistry teachers and practicing chemists that they have an information-managing bargain with hundreds of such descriptions per printed page--at pennies per page (or less with reading equipment for microfilm cartridges or microfiche packets). Here is the learning requirement for the examples given thus far:

Letter:	E	G	K	M	Q	R
Meaning:	Br	Cl		NH	OH	
Letter:	**U**	**V**	**W**	**X**	**Y**	**Z**
Meaning:	=		O_2			NH_2

ARABIC NUMERALS denote ALKYL CHAIN lengths (carbon count). K, X and Y are methyl-branched unless otherwise specified. ZERO is slashed as ϕ, leaving the far more frequently cited O unmarked.

BRANCHING TERMINATION

The **ampersand** here is the "end mark" for punctuating alkyl side groups and any others that do not end with the strictly terminal E, F, G, H, I, Q, W or Z groups. When some of these in turn--like iodine--are not terminal, they are set off

with **hyphens**, like all organometallic two-letter symbols. The ampersand is retained whenever a methyl-contracted Y, X or K group is **not** the last branch in the notation (or in a clearly "spaced" cyclic side group), simply to keep things clear when descriptions get complicated. The Aldrich *Handbook* again has many simple examples of notations with punctuated side groups, and others with the "understood" punctuation for E, F, G, H, I, Q, W and Z marks:

```
1Y&X    1N1&1   4N4&4   OSR&R   QY4&2
1Y&Y    1N1&R   4P4&4   Q1YGG   QY4&3
2Y&Y    1X&&X   8N8&8   QVYER   QY4&4
EYEE    1Y&1Y   EXEEE   QVYFF   QY4&R
EYER    1Y&2X   EYR&R   QVYGG   QY5&4
GPGR    1Y&2Y   FXFFR   QX&&Y   QY5&Y
GXGG    1Y&3Y   GPR&R   QX2&2   QY6&3
GYGE    1Y&MY   GX&&X   QX3&2   QY7&2
GYGG    1Y&SY   GXGGE   QX3&3   QYR&R
GYGR    1Y&UY   GXGGG   QX4&2   RNR&R
IYII    1Y&VY   GY&YG   QY&1Y   RPR&R
QBQR    2N2&1   GYG1G   QY&Y2   SPGGR
QY&X    2N2&2   GYGO1   QY&YQ   SUYGG
QY&Y    2N2&R   GYGVG   QY2&2   WS3&3
WSG1    2Y&1Y   GYGVR   QY2&R   WS4&4
WSGR    2Y&UY   GYR&R   QY2&X   WSR&R
WSQ1    2Y&Y2   OPGGR   QY2&Y   Z1YQR
WSQR    2Y2&2   OS1&1   QY3&2   ZMSWR
ZSWR    3N3&3   OS3&3   QY3&3   ZN1&1
ZY&X    3N3&R   OS4&4   QY3&R   etc.!
```

Of course there is no very simple way to describe very complicated structures, but there are far more 2- to 5-mark notations in the chemical world than equally short words in the English language. Yet while "apathy is our deadliest danger," chemists may have to wait until the 21st century before the **simplest** million reported chemical descriptions are widely and cheaply available for their "professional enhancement." There are over 1000 notations with **five or less** places in a file of 30,000 biologically screened compounds, so this same first fraction is more than a hundred thousand in the six million world total! Most of the high-volume, high interest, high-hazard chemicals are in this simplest fraction: must we wait another 25 years to structurally identify and reference the first few thousand in a $2 chemical almanac?

RING LOCANTS

LOwer **CA**se let**TE**rs were used to LOCATE ring positions in 1866 when Kekule[9] presented his historic discussion of benzene ring isomerism. These letters are more logical than numbers for such information, because positions are relative rather than absolute values, and in modern chemistry these citations frequently go past the single digit range, but seldom go past the alphabetic range. Lower-case meaning is indicated in computer applications without a penny of special hardware cost by prefixing such (upper case) letters with a blank **space**. This nonprinting signal serves as a shift key to denote lower-case meaning for the letter that follows; like the familiar space bar, this is the most frequently used keyboard signal. Spaces also serve handsomely to break up the units of information, just as words are clarified by putting spaces between them (a great discovery of the Middle Ages). Thus the notation logically shows a locant **between** the ring description and the substituent symbols, saying in effect, "and at this position there is a so-and-so group."

Phenylene (C_6H_4) segments of chains are distinguished by assuming the a-position for the first-cited substituent, thus giving ...R B... for *ortho*-, ...R C... for *meta*-, and ...R D... for the *para*- isomers. Kekule's student, William Körner, established these cleverly distinctive names just 99 years ago (1874), and the corresponding "computerized" O@-, M@- and P@- prefix marks deserve continuing usage with two-connected phenylene root names.

Locant marks, like atomic Y, X and K branches, can be defined as methyl-"filled" when not otherwise specified. Aldrich *Handbook* selections again show frequent usage of this contraction along with other locant-specifying short notations:

```
1R C    1OR B   FR DF   Q1R D   QR DG
1R D    1R CR   FR DR   QR B2   QR DI
2R B    1R DR   G1R B   QR B3   QR DQ
2R C    1VR C   G1R D   QR BE   QR DR
2R D    1VR D   GR BE   QR BF   QR DX
ER B    1XR D   GR BG   QR BQ   QVR B
ER D    1YR D   GR CE   QR BR   QVR C
FR B    2MR B   GR CG   QR BX   QVR D
FR D    2MR C   GR DE   QR BY   QYR D
GR B    2R B2   GR DF   QR C3   RR BR
GR C    2R C2   GR DG   QR CE   RR DR
GR D    2R D2   GR DR   QR CF   SHR B
IR B    E1R B   GVR B   QR CG   SHR C
IR C    E1R C   GVR C   QR CQ   SHR D
QR B    E1R D   GVR D   QR CX   VHR B
QR C    ER BE   IR DG   QR CY   VHR C
QR D    ER DE   NCR B   QR D2   VHR D
ZR C    FR BE   NCR C   QR D3   WNR B
ZR D    FR CF   NCR D   QR DE   WNR C
        FR DE   ONR B   QR DF   etc.
```

An important complementing pair of resolving rules should be emphasized here: **outside** the ring, the **highest** of otherwise equal marks are cited first (to put front emphasis on functions); **inside** the ring, the **lowest** sets of locants, etc., are chosen (to follow this well-justified tradition).

OTHER RINGS

The simplest features of aliphatic and benzenoid notations now have been illustrated with several hundred Aldrich *Handbook* selections, none of which required more than five typing columns. Distinctly longer notations will be needed to illustrate the simplest types of other cyclic compounds, because the rings themselves have many independent variables: carbocyclic or heterocyclic, aromatic or having a lone saturated C-atom, and saturated or having localized unsaturations. Each feature will be explained very briefly--with examples.

Beyond benzene, the **cyclic** part of a structure is traditionally and topologically the main feature and most useful indexing part, so the notations in this largest class all begin with a "ring-closing or ring-starting" mark, followed by the traditional ring number(s), heterogroup symbols, then the saturation character and finally the "ring-finishing" mark. The carbocyclic or "a**L**icyclic ring-closing L...J marks were inspired by Emil Erlenmeyer's historic (but contorted) 1866 diagram[10] for his postulated structure of naphthalene. In the inset diagram, his vertically extended ring has been swung up from his original lower position to more clearly display

```
      HC - CH
      ‖   ‖
      HC  CH
      |   |
HC = C - C = C - C = CH
L                    J
```

his subtle "L- and J-shaped" angle-brackets that Erlenmeyer used to imply the ring closure. Beilstein's separation of a "he**T**erocyclic" kingdom justified the corresponding T...J marks, first used with the L...J in a 1951 demonstration deck of IBM cards. These punched-card substitutes for parentheses are still the users' choices, even though non-distinguishing parentheses (as in the 1954 manual) are more logical to set off this first part of the cyclic **connecting** specifications.

RING SATURATION

After the ring numbers and heterogroup symbols are cited, four distinct types of rings are denoted as combinations of two binary variables: minimum-maximum **hydrogenation**, and minimum-maximum notation marks. The minimum **marks** logically apply to the most frequently met extremes in hydrogenation: the aromatic, understood with no mark; and the fully saturated, distinguished with a "sa**T**uration" mark. In the 1954 manual, this mark was a "slash" or virgule ("capitalized letter symbols to denote atoms or atomic groups" and "punctuation marks to denote modes of connection or disconnection" or the like), but today it is a T-mark just before the ring-closing J-mark. This double usage of the T for a kind of "punctuation" was necessary with the primitive 1950 equipment, but the make-shift obviously would not be necessary today.

Aromatic monocyclic descriptions (with no lone saturated C-atoms) perhaps are most easily explained by citing many examples from the Aldrich *Handbook* (the parent ring is the catalog item in most cases, but some appear only as substituted derivatives).

```
L8J     T6NJ    T5NSJ    T5VMVJ    T5MNNNJ    T6MVMVMVJ
L7VJ    L4VVJ   T6MVJ    T5OVOJ    T6MVMVJ    T6MVMVVVJ
T5MJ    L6VVJ   T6NNJ    T5VOVJ    T6VMMVJ    L6VVVVVVJ
T5OJ    T5MNJ   T6OVJ    T6MVNJ    T5MMVMVJ   T6BHMBHMBHMJ
T5SJ    T5NOJ   T5NONJ   L6VVVVJ   T6NMVMVJ   T6BHOBHOBHOJ
```

Here adjacent heterogroups appear exactly as they would in an open-chain segment, but with the traditional "lowest first" choice inside the ring. If aromatic C-atoms separate the heterogroups, **spaced** letters locate them:

```
L6V DVJ    T6N CNJ    T5NN DSJ
T5M CNJ    T6N DNJ    T6NN DNJ
T5N CSJ    T6O DVJ    T6VM DNJ
T6M DVJ    T5MN DNJ   T6N CN ENJ
```

Connecting **positions** are considered before the symbols at those positions, so T6VM DNJ by this rule is correct and "lower on first counts" than T6MV ENJ.

"Extra hydrogen" citations (always with a locant, to avoid ambiguity with heterocyclic H-attachment) characterize those structures that are dehydrogenated to the aromatic limit and have just **one** remaining saturated C-atom:

```
L5 AHJ          T5NMV DHJ
L7 AHJ          T5NOV EHJ
L4V BHJ         T5MVMV EHJ
L6V BHJ         T5SVMV EHJ
T6M DHJ         T6MV DV CHJ
T5MM CHJ        T6MVMVV FHJ
T5OV CHJ        T6OV DV CHJ
T5OV EHJ        T6VMVMV FHJ
```

Fully saturated structures provide the greatest number of **mono**cyclic examples (parent ring systems) in the Aldrich *Handbook*. All end with ...TJ marks; all have **more than one** saturated C-atom, and none have any C-to-C unsaturations:

```
L5TJ    T5STJ    T9MVTJ    T6M CVTJ
L4TJ    T6MTJ    T5MVMTJ   T6M DMTJ
L5TJ    T6OTJ    T5MVOTJ   T6M DOTJ
L6TJ    T6STJ    T5OMVTJ   T6M DVTJ
L7TJ    T7MTJ    T5OSOTJ   T6O COTJ
L8TJ    T7OTJ    T5OSWTJ   T6O DOTJ
L4VTJ   T8MTJ    T5VMVTJ   T6O DSTJ
L5VTJ   T9MTJ    T5VOVTJ   T6S CSTJ
L6VTJ   L6VVTJ   T6MVMTJ   T6S DSTJ
L7VTJ   L7VVTJ   T6OSWTJ   T6S DVTJ
L8VTJ   T4OVTJ   T6VMVTJ   T7M DMTJ
L9VTJ   T5MVTJ   T6VOVTJ   T6M DSWTJ
T3MTJ   T5OVTJ   T5OPHOTJ  T6MV DOTJ
T3OTJ   T5SVTJ   T6OBHOTJ  T6MV DSTJ
T3STJ   T5SWTJ   L5V CVTJ   T6OV DOTJ
T4MTJ   T6MVTJ   L6V CVTJ   T6MV DMVTJ
T4OTJ   T6OVTJ   L6V DVTJ   T6VOV EOTJ
T5MTJ   T7MVTJ   T5M CSTJ   T6M CM EMTJ
T5OTJ   T8MVTJ   T5O COTJ   T6O CO EOTJ
                            T6S CS ESTJ
                            T8OSWO EOSWOTJ
```

The dioxygen symbol W, like H, is defined as a strictly terminal symbol and is cited **immediately after** the symbol of the atom to which it is attached, inside as well as outside the "ring-enclosing" marks.

UNSATURATED RINGS

Localized unsaturations characterize the fourth class of ring notations--those with maximum hydrogenation and maximum citing marks; the cited U-mark appears without a locant only in the special case of simple cycloalkenes, cycloalkynes, and their combinations that have no heterogroup:

```
L5UTJ    L7U CUTJ    T6O BUTJ
L6UTJ    L8U CUTJ    T7N AUTJ
L7UTJ    L8U EUTJ    T5SW CUTJ
L8UTJ    T5M BUTJ    T6NMV FUTJ
L5V BUTJ T5M CUTJ    T5N CO AUTJ
L6U CUTJ T5O BUTJ    T5N CS AUTJ
L6U DUTJ T5O CUTJ    T6M CN BUTJ
L6V BUTJ T6M CUTJ    T6O DO BUTJ
```

Benzyne is an exceptional structural type, justifying a **single** U **without** a T when this dehydrogenation is superimposed on an aromatic one: L6UJ. In all cases, localized unsaturations (like "extra" or indicated hydrogen) are cited as subordinated details that do not change the other "lowest locant," etc., measures within the ring-enclosing marks. This is equally true of any substituents; beyond the special case of benzene rings, **substituents** are cited in ascending order of locants, then "highest first" when locants are equal.

Thio- or imino- or methylene-type substituents on cyclic keto-groups provide a fifth type of ring, with a **cyclic** Y-mark here replacing the V-mark, and the necessary U-mark appearing outside the ring description:

```
L5YTJ AU1      L6V DYJ DUM       T6MVMVYVJ EUM
L5YTJ AUM      T5MYMTJ BUS       L6YYTJ AUM BUM
L6YTJ AU1      T5NMYSJ CUM       T5MYMV EHJ BUS
L6YTJ AUM      T5NYVOJ BU1       T5OYMV EHJ BUS
L7YTJ AUM      T5SYSTJ BUS       T5SYMV EHJ BUM
T6MYJ BUS      T6MYMVJ BUS       T5SYMV EHJ BUS
T6MYTJ BUM     T5MVMVYJ EUM      T5VOVY EHJ DU1
T6MYTJ BUS     T4VOY DHJ CU1     L6Y DYJ AU1 DU1
T7MYTJ BUS     T5MY DMTJ BUS     L6YVYTJ AUM CUM
```

Some of these are keto-like tautomers of enolic or mercapto-groups.

MACRO RINGS

Macro-rings stand out in this notation because two-digit ring sizes are set off with hyphens (avoiding ambiguity with sizes 33 and higher *vs* bicyclics). Again the Aldrich *Handbook* contains a good number of examples:

```
L-1Ø-TJ          L-13-VTJ
L-11-TJ          L-15-VTJ
L-12-TJ          T-13-MVTJ
L-1Ø-VTJ         L-11-UTJ
L-11-VTJ         L-12-UTJ
L-12-VTJ         L-12-U EUTJ
                 L-12-U EU IUTJ
```

Substituents, as previously mentioned, are cited in ascending alphabetic order for all rings beyond the special case of benzene rings.

POLYCYCLIC RINGS

Chemical notation and nomenclature systems eventually "meet their Waterloo" in the polycyclic region, where seemingly endless complications keep compounding to a climax of frustrations. The strength of the WLN in this area was sensed in 1952:[8] "The most outstanding feature of this notation is that a single position-determining rule suffices for all kinds of polycyclic structures." This central advantage is based on a traditionally familiar aim--to seek a lowest possible set of ring measures, one that subordinates heterogroup variations. Each measure has a sharply defined priority, as stated by E. G. Smith in the official manual[11] of the Chemical Notation Association.

DETERMINING LOCANT PATH

The first requirement is that the locant path must be a continuous one through the largest possible number of ring positions (generally it is a peripheral loop or spiral through all of them). This aim maximizes the number of automatically defined connections--i to j to k...--and thus minimizes the necessary specifications of all other (nonconsecutive) links. For example, the elaborate tetracyclic steroid connecting pattern of 17 positions and 20 connections is compacted into a record of just four pairs of locants, each indicating a ring-closing link: (ei bj am aq). Chemists prefer to see the ring sizes directly, so this becomes (e5 b6 a6 a6) or simply (e5 b666) after omitting the understood **a**-locants.

The pathfinding rule was stated as follows in 1952: "All polycyclic ring positions are determined by starting the longest possible chain of ring positions at the point which gives the lowest sum for the **fusion** locants," "the name given here for the lowest position in each ring, relative to (this path)." In the above example, **e, b, a, a** are the fusion points, and their sum is 5 + 2 + 1 + 1 or 9.

All bicyclic fused and bridged ring paths thus start at one of the atoms common to both rings, for then the fusion locants are **a,a** (the same lowest position in each ring). In perifused systems where one "triple point" is common to three rings, this singular multicyclic junction or focal point is the starting point, and from here the locant chain proceeds through the shortest possible path to the furthermost ring. Some well-known examples that were included in the 1951 demonstration deck of IBM cards had these name identifications:

```
L57J      azulene          T56 BMJ D   skatole
L66J      naphthalene      T56 BMVVJ   isatin
T56 BMJ   indole           L B666J     phenanthrene
T66 BNJ   quinoline        L C666J     anthracene
T66 CNJ   isoquinoline     L B656 HVJ  fluorenone
T56 BNOJ  anthranil        L C666J BQ  anthranol
T66 BMVJ  carbostyril      L E6 B666J  chrysene
T66 BOVJ  coumarin
```

Many additional examples are provided in "Educator" decks of IBM cards.

Free radicals are freely and easily described with the 1964 "dot-plot" extension of the carbyl C (for an unbranched C-atom); D for the diatomic, dehydrogenated, unbranched CH-group (pictured as a C-image and H-bar); L for the a**L**iphatic CH_2 **L**ink; and T for the 3-connected or T-branched C-atom. With these the writer also urged the use of J for a **J**unction N-atom, the very frequently cited 3-connected nitrogen of tertiary amines, N-nitrosamines, and the like (rather than wasting this valuable atomic-symbol letter on a rarely cited "Jeneric haloJen"). But nine years have passed, and the other users still strangely oppose any change in "the sacred symbol set."

THE CHEMICAL NOTATION ASSOCIATION

The most bizarre aspect about this notation is that its designer no longer "owns and controls" it: that sensitive responsibility has been put in the hands of the Chemical Notation Association, an international association of more than 100 members. At the time of this writing, a "NATO/CNA Advanced Study Institute (ASI) on Computer Representation and Manipulation of Chemical Information" is planned to be held in Noordwijkerhout, near Amsterdam, from June 4 to 15, 1973, cosponsored by the North Atlantic Treaty Organization and the Chemical Notation Association.

Elbert G. Smith, more than any other individual, extended the spirit that this notation "was designed to be shared" with the chemical world. He started encoding the organic tables in the Hodgman and Lange Handbooks with the rudimentary instructions in the 1952 reports, helped edit the 1954 manual, wrote a faculty report demonstrating the notation's value in a table of phenylhydrazones (identification derivatives), built an experimental file of over 80,000 WLN descriptions--with other identification and reference data, wrote an attention-commanding report on substructure searching (with his set of 48 bit screens) when this file was 50,000-items strong, established the rule-controlling Chemical Notation Association, helped by his personal visits to establish the United Kingdom and Japanese chapters of CNA, and encoded the 15,000 *Ring Index* structures as part of his most time-consuming undertaking--to write a comprehensive WLN manual[11]. The royalties from this 6-year effort he turned over to the Chemical Notation Association. Smith's "Tutorial Lessons" provide 21 pages of the best kind of introduction to the WLN--learning by doing the stepwise decoding and encoding exercises[12].

Graham Palmer provided an excellent introduction to the WLN in 1970[13], which Usdin and Efron noted in 1972 with their own lucid summary[14]. Gibson and Granito also published a well-composed tutorial introduction to "Wiswesser chemical line-notation" in 1972[15]. Computer applications of

the WLN were summarized in 1969[16] and 1970[17], but so many advances have occurred since then that these reports now are regarded as obsolete.

UTILIZATION OF WLN BY ORGANIZATIONS

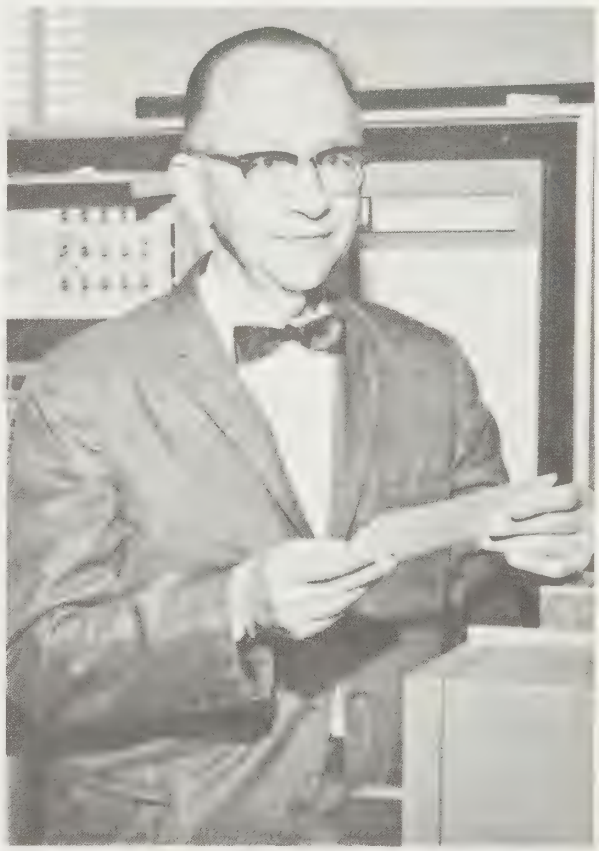
In the final analysis, the best "proof by test" of this information-managing tool is the extent to which others have published on their encouraging **uses** of it. The letter-symbol set was "finalized" at mid-century, in 1950. Only twelve reference citations on the notation appeared in the first ten years (1950-1959), then ten in the next five years (to 1964), followed by twelve in two years (1965-66), seven in 1967, and now there are some 150 citations from the organizations listed in Table I.

TABLE I.

ORGANIZATIONS THAT HAVE PUBLISHED OR PRESENTED PAPERS ON WLN

(An author index, keyed to these organizations and including the titles with journal or meeting citations, is given in a special report of the Committee on Chemical Information Management, Lehigh Valley Section of ACS.[18])

Aldrich Chemical Company
Althouse Chemical Division (C&K Corp.)
American Society for Testing & Materials
J. T. Baker Chemical Company
Biological Abstracts (BIOSIS)
Chemical Abstracts Service
Chemical Rubber Company
Ciba-Geigy Corporation
College of Charleston
Columbia University (Biological Sciences)
Diamond Shamrock Chemical Company
Dow Chemical Company
Drexel University
Excerpta Medica Foundation
Food and Drug Administration
GAF Corporation
Goodyear Tire & Rubber Company
Hebrew University (Israel)
Hoffmann-La Roche, Inc.
Horner Associates
Imperial Chemical Industries
Indian Institute of Science (India)
Institute for Scientific Information
Lehigh Valley Section of the ACS
Eli Lilly and Company
McCormick & Company, Inc.
Meta Information Applications, Inc.
Mills College (E.G. Smith)
Ministry of Defense of Israel
Monsanto Company
Moravian College (Bethlehem, Pa.)
National Bureau of Standards
National Cancer Institute
National Council of R & D (Israel)
National Institute of Mental Health
National Institute for Occupational Safety & Health
National Institutes of Health, DCRT
National Library of Medicine
Oesterr. Kunststoffinst. (Austria)
Ohio State University
Olin Corporation
Reading Chemists' Club (Reading, Pa.)
Remington-Rand Corporation (Norwalk, Ct.)
Sankyo Company (Tokyo, Japan)
G. D. Searle & Company, Inc.
Shippensburg (Pa.) State College
Simpson College (Indianola, Iowa)
Stanford Research Institute
State University of N. Y., Stony Brook
Tanabe Seiyaku Co. (Saitama, Japan)
Texas A&M University, TRC-API
United Kingdom Atomic Energy Authority
University of Sheffield (UK)
University of Pennsylvania
U.S. Army, CIDS Program (Edgewood Arsenal)
U.S. Army, Fort Detrick, VCD
U.S. Army, Industry Liaison Office (E.A.)
Wildlife Research Center, USDI (Denver)
Willson Products (Division of ESB Corp.)
Winthrop Laboratories (A. Addelston)



William J. Wiswesser

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THE APPLICATION OF ELECTRON SPIN RESONANCE AND SPIN-LABELING IN BIOCHEMISTRY AND PHARMACOLOGY

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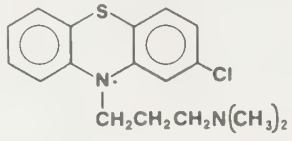
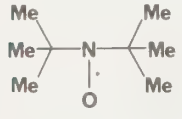
Spin-labeling is a spectroscopic technique that employs stable organic radicals as probes or reporter groups for biological macromolecules.[1–5] The first free radical to be used as a spin label was the cation radical of the phenothiazine drug chlorpromazine (I). Ohnishi and McConnell studied the binding of

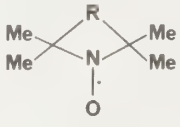


I

this radical to shear-oriented DNA and found that the aromatic plane of the drug was perpendicular to the helix axis of the nucleic acid.[6] Since the chlorpromazine free radical was stable over a rather limited pH range, McConnell and coworkers sought other spin labels. In 1961, Hoffmann and Henderson had reported the synthesis of di-*t*-butyl nitroxide (DTBN) (II), a free radical that was stable in aqueous solution over a wide range of temperatures and pH values.[7] Subsequently, Rozantsev[8] in Russia and Rassat[9] in France had synthesized a large number of free radicals in which the nitroxide group was part of a heterocyclic ring system (III).



II



III

These nitroxides provided McConnell and his coworkers with the starting materials from which they prepared more specific spin labels. A wide variety of compounds containing the nitroxide free radical have now been synthesized.[1–5, 8, 9]

THE ELECTRON SPIN RESONANCE SPECTROSCOPY OF THE NITROXIDE RADICAL

When an unpaired electron is placed in a magnetic field, it may exist in one of two energy states in which its magnetic moment is aligned either parallel or antiparallel to the direction of the applied field. Transitions between these two energy states can be induced by the application of electromagnetic radiation of the appropriate energy. The relationship between the magnetic field strength *(H)* and the required frequency (ν) is given by

$$h\nu = g\beta H \qquad (1)$$

where h is Planck's constant, g is the so-called g-value for the electron, and β is the Bohr magneton, a fundamental constant for the electron. Equation (1) indicates that at resonance, the applied frequency (ν) is directly proportional to the magnetic field *(H)*, so that electron spin resonance (ESR) can be observed when either H or ν is varied. For experimental convenience, it is usual to keep ν constant while H is changed. Most commercial ESR spectrometers operate in the microwave frequency range of 9 x 10^9 Hz (or 9 GHz) so that H is approximately 3300 gauss (G).

When the nitroxide radical is present at low concentration in a non-viscous solvent, its ESR spectrum consists of three equally spaced lines of about the same height (Fig. 1). This

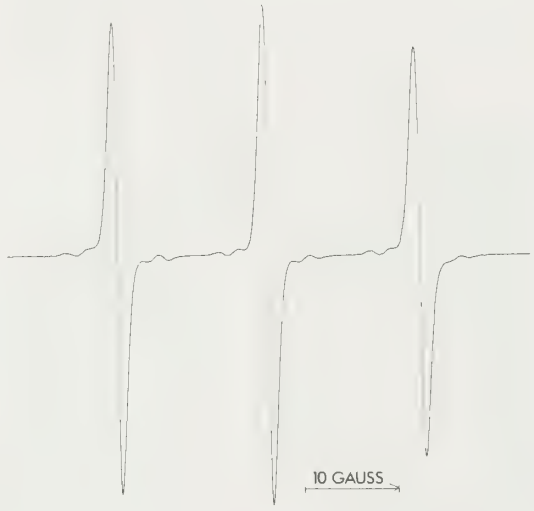


Fig. 1. The ESR spectrum of a nitroxide radical in aqueous solution.

triplet results from an interaction between the magnetic moment of the unpaired electron and the magnetic moment of the ^{14}N nucleus. In qualitative terms, the magnetic moment of the nitrogen nucleus can be aligned parallel, anti-parallel or perpendicular to the applied magnetic field. Since the magnetic field experienced by the electron is the sum of the external magnetic field and the local contribution provided by the ^{14}N nucleus, it follows that the electron experiences three different magnetic field values each of which gives rise to an absorption line in the spectrum (Fig. 1). For technical reasons, the commercially available ESR instruments display the spectrum as its first derivative instead of the simple absorption spectrum familiar to optical spectroscopists. The spectrum is characterized by three parameters: (1) the hyperfine splitting (A_o), *i.e.*, the distance (G) between adjacent lines, (2) the so-called g-factor (g_o), *i.e.*, the position of the center line in the magnetic field and (3) the peak-to-peak linewidth (G).

When a nitroxide spin label is incorporated into a host crystal, the ESR spectrum of the free radical is dependent upon its orientation with respect to the magnetic field (Fig. 2). The largest hyperfine splitting (A_{zz}) is observed when the magnetic field is parallel to the nitrogen π-orbital (z-axis) (Fig. 3). The g-values are also dependent on the orientation of

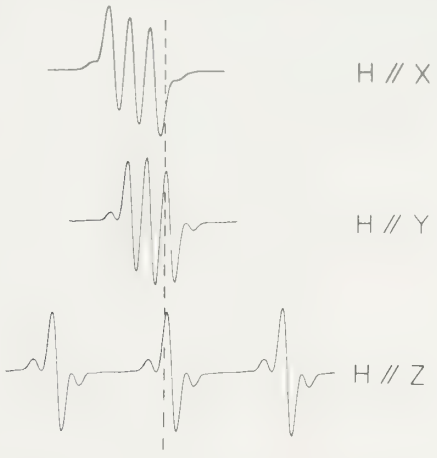


Fig. 2. The ESR spectra of 4',4'-dimethyloxazolidine-*N*-oxyl derivative of acetone oriented in the crystal 2,2,4,4-tetramethyl-1,3-cyclobutanedione (adapted from reference 26)

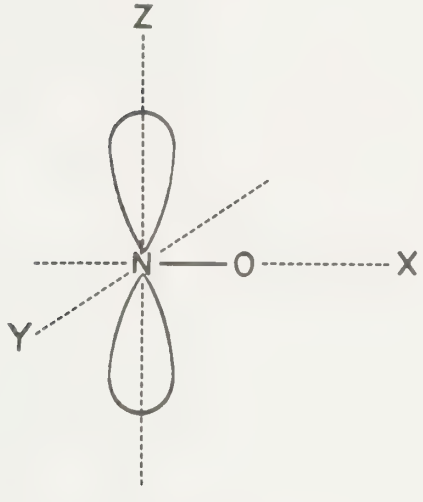


Fig. 3. The molecular coordinate system of the nitroxide group

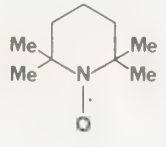
the nitroxide group (Fig. 2). At angles that lie between the three principal axes, the ESR spectra are intermediate between those shown in Fig. 2. When the crystal of nitroxide is dissolved in a solvent of low viscosity, the motion of the free radical is so rapid that its ESR spectrum appears as a triplet (Fig. 1) in which the hyperfine splitting (A_o) and g-value (g_o) are the average of the values seen in Fig. 2.

The ESR spectrum of the nitroxide radical is sensitive to changes in (1) the **polarity** of the environment of the radical, (2) the **molecular motion** of the radical and (3) the **orientation** of the radical with respect to the applied magnetic field. The ESR spectrum of the nitroxide group is modified by the presence of other paramagnetic species. Furthermore, the nitroxide group can be chemically reduced by a variety of agents with the concomitant loss of its ESR signal. While these properties make the nitroxide radical an almost ideal reporter group, it should be borne in mind that the bulkiness of the nitroxide radical may cause a large steric perturbation of its local environment.

THE NITROXIDE GROUP AS A PROBE FOR BINDING SITE POLARITY

Solvent effects on the ESR spectrum of the nitroxide radical are characterized by changes in both A_o and g_o parameters. DTBN in water yields A_o = 16.7 G and g_o = 2.0056 while DTBN in hexane is characterized by A_o = 14.8 G and g_o = 2.0061. An extensive study by Dodd *et al.* has shown that A_o decreases while g_o increases as the solvent polarity is decreased.[10] In line shape studies of moderately immobilized spin labels, the solvent dependence can be troublesome because it is difficult to estimate the effects on the principal values of A and g. However, when small, rapidly tumbling spin labels are used, the solvent effects can be useful.

Hubbell and McConnell have reported that when IV is dif-



IV

fused into an aqueous phospholipid dispersion or a rabbit vagus nerve in Ringer solution, the high field line is replaced by two lines.[11] Similar observations have been made by Jost and Griffith with the DTBN-myelin system.[12] The relative intensities of the two high field lines provide a measure of the amount of spin label in hydrocarbon and aqueous environments. McConnell and coworkers have made use of this fact to develop a method for the estimation of the fraction of lipid in a biological membrane that is in a fluid state.[13]

THE NITROXIDE GROUP AS AN INDICATOR OF MOLECULAR MOTION

When the molecular motion of a nitroxide radical in dilute solution is decreased by increasing solvent viscosity, the ESR lines of the free radical appear to broaden and the spectrum becomes asymmetric (Fig. 4). The limiting line shape is known as the rigid glass, powder or polycrystalline spectrum of the nitroxide radical. This spectrum can be thought of as a simple sum of all the spectra shown in Fig. 2 together with the spectra of all possible intermediate orientations. As a result, the splitting between the outermost peaks of the rigid glass spectrum is $2A_{zz}$, corresponding to the bottom spectrum of Fig. 2. The rigid glass spectrum is encountered whenever the spin label is randomly oriented and molecular motion is either absent or very slow on the ESR time scale, *i. e.*, when $\tau^{-1} << |A_{zz} - A_{xx}| \sim 7 \times 10^7$ sec^{-1} and $\tau^{-1} << |g_{xx} - g_{zz}| \beta Hh^{-1} \sim 3 \times 10^7$ sec^{-1} (at 9.5 *GHz*), where τ is the rotational correlation time.

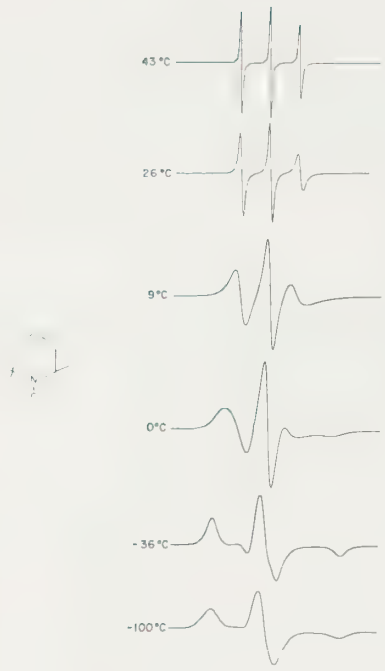
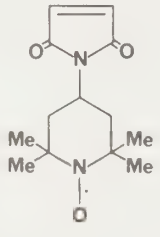


Fig. 4. The effect of solvent viscosity on the ESR spectrum of 2,2,6,6-tetramethylpiperidine-1-oxyl (5×10^{-4} M) dissolved in glycerol (adapted from reference 26)

The ESR spectrum of the nitroxide group can often provide useful information on the mobility of the spin label probe. For example, the ESR spectrum of human erythrocyte ghost membranes labeled with V reveals the presence of at least two



V

populations of spin labels that differ in their relative mobilities. The spectrum of one group resembles the rigid glass spectrum of the nitroxide group (*cf.* Fig. 4) with a splitting of 59 G between the low and high field extrema (Fig. 5, lines a and e). These spin labels are highly immobilized. In

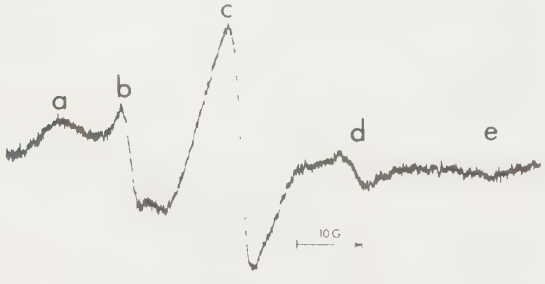
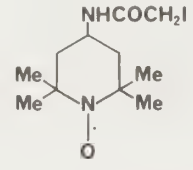


Fig. 5. The ESR spectrum of human erythrocyte ghost membranes spin-labeled with V

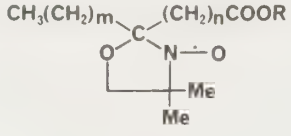
contrast, a second group has a fairly sharp three line spectrum (Fig. 5, lines b and d) that is characteristic of mobile nitroxide groups. The center line in Fig. 5 (line c) contains contributions from all of the spin labels. Holmes and Piette[14] have suggested that the highly immobilized spin labels are attached to sulfhydryl groups which are buried deep within the membrane where their motion is restricted. The more mobile spin labels are probably attached to surface sulfhydryl groups. In contrast to the maleimide spin label (V), the iodoacetamide analog (VI) labels only the surface sulfhydryl groups.[14]



VI

Holmes and Piette have found that when erythrocyte ghosts labeled with VI are treated with chlorpromazine, a highly immobilized population of spin labels appears in the spectrum. They have suggested that the drug induces a change in the conformation of the erythrocyte membranes so that spin labels which are on the outside of the membrane are moved into the interior.[14]

Spin-labeled analogs of stearic acid (VII) have proved to be very useful probes for both natural and artificial membranes.



VII

For example, when VII (m=12, n=3, R=H) is incorporated into erythrocyte ghost membranes, its ESR spectrum resembles the rigid glass spectrum of the nitroxide group with a splitting of 57 G between the low and high field extrema (Fig. 6). In contrast, when VII (m=1, n=14, R=H) is incorporated into the ghost membranes, its ESR spectrum (Fig. 6) indicates a high degree of motional freedom. Since it seems most likely that both labels are oriented with their ionized

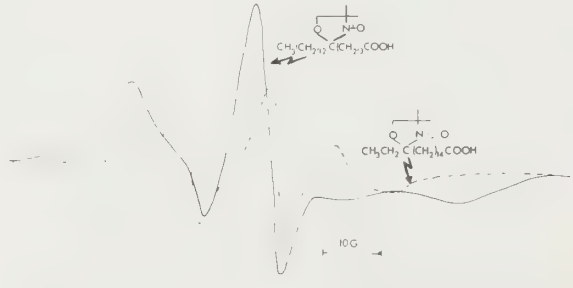


Fig. 6. The ESR spectra of two stearic acid spin labels bound to human erythrocyte ghost membranes

carboxyl groups at the membrane interface, these observations suggest that near its surface, the membrane has a highly ordered rigid structure, whereas the interior of the membrane is fairly fluid in nature. Similar results have been observed for other membrane systems both natural and artificial.[15–17]

Spin labels have been employed to study the effect of various perturbants on membrane systems. For example, Hubbell and coworkers have made use of nitroxide analogs of methyl stearate (VII, m=5, n=10, R=CH_3) and 17β-hydroxy-5α-androstane to study the interaction of the local anesthetics benzyl alcohol and lidocaine with erythrocyte ghost membranes.[18] ESR measurements indicated that at low concentrations, benzyl alcohol produced a fluidizing effect on the membrane. However, at high (lytic) benzyl alcohol concentrations, the spin labels became highly immobilized. Hubbell and coworkers have suggested that at lytic concentrations, benzyl alcohol uncovered protein spin label binding sites that were covert in the unperturbed membrane.[18] These results were in good agreement with the previously reported nuclear magnetic resonance studies of Metcalfe and coworkers.[19]

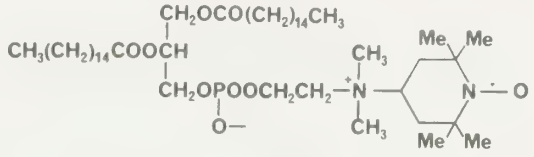
THE NITROXIDE GROUP AS A PROBE FOR MOLECULAR ORIENTATION

The ESR spectrum of the nitroxide radical is sensitive to the orientation of the radical with respect to the applied magnetic field (Fig. 2). The z-axis of the stearic acid spin label VII (m=5, n=10, R=H) is parallel to the long hydrocarbon chain. Hubbell and McConnell have shown that when this spin label is incorporated into shear-oriented canine erythrocytes, there is a larger splitting when the magnetic field is oriented perpendicular to the surface of the red cells.[11] This suggests that the preferred orientation of VII (m=5, n=10, R=H) is one in which its long hydrocarbon chain is perpendicular to the membrane surface. Similar observations have been made with artificial membrane systems such as oriented phospholipid multilayers. In their experiments with phosphatidylcholine multilayers, Griffith and coworkers [20] have reported that as the nitroxide group is moved farther and farther away from the carboxyl head group of stearic acid, the difference between spectra recorded with the field parallel and perpendicular to the plane of the multilayers decreases until with VII (m=1, n=14, R=H), there is little difference between the two orientations. These observations indicate that while an ordered multilamellar arrangement of hydrocarbon chains exists at the surface, the interior of the multilayer is quite fluid. Other experiments by Hsia and coworkers [21–23] employing both a cholestane spin label and VII (m=10, n=5, R=H) have shown that cholesterol causes an increase in the rigidity of egg lecithin multilayers. Similar results have been reported by Kroes *et al.* for erythrocyte membranes isolated from cholesterol-fed guinea pigs.[24] In contrast to cholesterol, general anesthetics such as chloroform and butane decrease the organization of lecithin or brain lipid multilayers at very low concentrations.[25] Local anesthetics such as procaine or tetracaine increase order at low concentrations but decrease order at high concentrations.[25]

OTHER APPLICATIONS INVOLVING NITROXIDE SPIN LABELS

Membranes

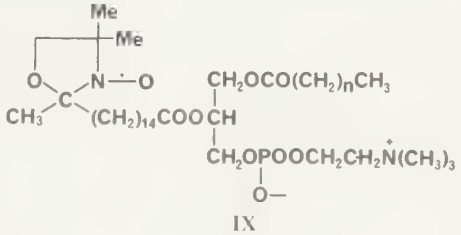
It is obvious from the foregoing discussion that spin labels have played an important role in determining the structure of membranes (see also refs. 26 and 27). More recently, McConnell and coworkers have used spin-labeled phosphatidylcholine analogs to measure some of the dynamic properties of membranes. For example, Kornberg and McConnell have estimated the rate of inside-outside transitions occurring in egg lecithin vesicles with the aid of spin label VIII.[28] In their



VIII

experiments, vesicles labeled with VIII were treated with ascorbic acid at 0°. The ascorbic acid quickly reduced the spin labels present in the external monolayer thereby abolishing their paramagnetism. Since ascorbic acid is a highly polar molecule, it cannot penetrate the vesicles and reduce the spin labels present in the internal monolayer. However, when the internally oriented labels reoriented toward the outside, they were reduced with a half time of 6.5 hrs. From this experiment, Kornberg and McConnell were able to measure the rate of phospholipid flip-flop across the artificial membrane.

Scandella and coworkers have estimated the rate of phospholipid lateral diffusion in rabbit sarcoplasmic reticulum using spin labels VIII and IX.[29] When vesicles were prepared from

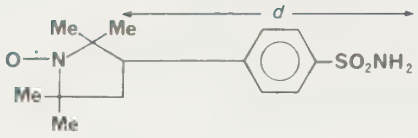


IX

either VIII or IX, nitroxide-nitroxide interactions reduced the ESR spectrum to a single line.[5] When such vesicles were added to a sarcoplasmic reticulum preparation, patches of the spin label were incorporated into the membrane. As the spin labels diffused into the membrane, their ESR spectra changed until eventually the three-line pattern reappeared. From an analysis of the line shapes and their rate of change with time, Scandella and coworkers were able to estimate that the diffusion constant D of the spin labels was 6×10^{-8} cm^2/sec at 37°.[29] Grant and McConnell have used this same approach to examine phospholipid diffusion in the membrane of *Acholeplasma laidlawii*.[30]

Topographical Studies of Binding Sites

Chignell and coworkers have studied the topographies of the active sites of several mammalian erythrocyte carbonic anhydrases by means of a series of spin-labeled aromatic sulfonamide (X) inhibitors.[31–34] The active site of carbonic anhydrase is a deep crevice at the bottom of which is a single zinc

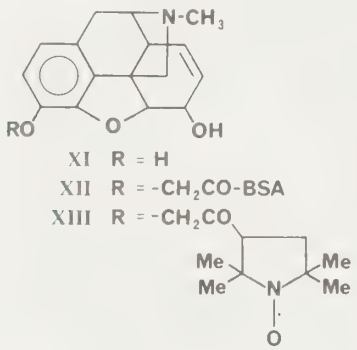


X

atom. When an aromatic sulfonamide inhibitor binds to the active site, the sulfonamide group is directly coordinated to the zinc atom. Chignell and coworkers prepared a series of spin-labeled sulfonamides in which the distance *d*, between the sulfonamide group and the pyrrolidine ring of the spin label, was varied. It was found that when *d* was small, the spin label was highly immobilized when the inhibitor bound to the enzyme active site. As *d* increased, the mobility of the spin label also increased until eventually the free radical demonstrated little or no interaction with the active site. Using this technique, it was possible to determine that the active site of human erythrocyte carbonic anhydrase C was funnel-shaped and about 14 A deep. Similar studies with the human B isozyme and bovine carbonic anhydrase B suggested that the active sites of these enzymes were the same shape as human carbonic anhydrase C but somewhat deeper. This "molecular dipstick" approach was originally devised by Hsia and Piette who used the technique to study the topography of hapten binding sites on rabbit anti-2,4-dinitrophenyl immunoglobulins.[35]

Free Radical Assay Technique

Leute and coworkers have used spin labeling in conjunction with the immunoassay technique for the rapid determination of morphine (XI) and other drugs in urine, saliva and other



biological fluids.[36] These workers prepared an antigen (XII) by coupling morphine to bovine serum albumin (BSA). Antibodies were then raised against the antigen in rabbits. When the spin-labeled morphine analog XIII bound to the antibodies, the ESR spectrum of the nitroxide group became broad and asymmetric, indicating a high degree of immobilization at the immunoglobulin binding site. When morphine was added to the spin label-immunoglobulin complex, the spin label was displaced and its ESR spectrum reverted to the sharp three-line pattern. Leute and coworkers were able to estimate the concentration of free spin label by measuring the amplitude of the low field peak. When this amplitude was plotted as a function of added morphine, a calibration curve was obtained from which it was possible to estimate the concentration of morphine in any biological sample. Morphine substitutes such as methadone and propoxyphene and unrelated drugs such as barbiturates and amphetamines were not recognized by the antibody. Thus, the technique is well suited for use in heroin treatment programs. Chignell and Starkweather[37] have recently shown that this same approach can also be used when other drug-binding proteins such as enzymes are available.

PROGNOSIS

Spin-labeling is a versatile spectroscopic technique that can be used to probe the structure of biologically important macromolecules. The future should see increasing application of spin-labeling to biological problems, particularly those that involve the various receptor proteins. Finally, when used in conjunction with immunoassay procedures, spin labels provide a rapid method for the detection and quantitation of drugs and other small molecules present in biological fluids.

Dr. Colin F. Chignell

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Hexachlorocyclopentadiene Adducts of Aromatic Compounds and their Reaction Products

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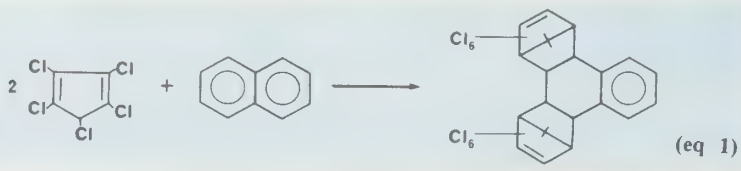
HISTORY AND BACKGROUND

In 1953, Hyman and Danish[1] disclosed that hexachlorocyclopentadiene forms an adduct with naphthalene (eq 1).

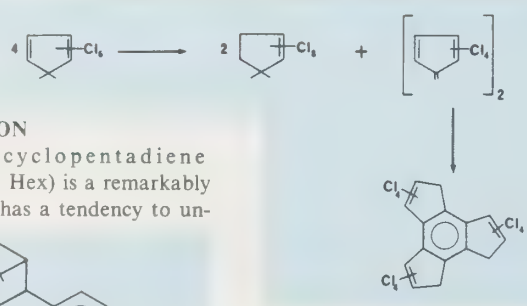


(eq 1)

The adduct thus formed undergoes normal aromatic substitution reactions (preferably in the β-position), exclusively in the unadducted ring of naphthalene. Moreover, the substituted adduct can undergo a reverse Diels-Alder reaction when heated, yielding naphthalene compounds which are otherwise difficult to synthesize.[2] These reactions were developed further in the Florida Hyman Laboratories.[3] Efforts to develop these studies into commercial processes were conducted by the Berkeley Hyman Laboratories in 1958 to 1964. This report covers the work of this latter period. Much of the research is unpublished or has never been reported to the scientific community. It is hoped that the vast amount of new and specific reactions available to the organic chemist may broaden the horizon of these naphthalene and related polynuclear aromatic compounds.

THE ADDUCTION

Hexachlorocyclopentadiene (henceforth called Hex) is a remarkably active diene that has a tendency to undergo Diels-Alder reactions.[4] Under normal conditions the reaction with polynuclear aromatic hydrocarbons is slow. Extensive studies in Berkeley showed a conversion of 25-35% to the adduct when a reaction mixture of naphthalene and Hex (1 to 3 mole ratio) was heated at 150-160° for one week (less than 1/4% per hour).[5] Petroleum-derived naphthalene consistently gave a purer product than coal tar naphthalene. Commercial grade Hex (purity 95%) was used. Glass vessels gave the cleanest material; however, Monel™ vessels were found to be feasible at plant scales. Usually, the adduct of naphthalene [1,2,3,4,5,6,7,8,13,13,14,14-dodecachloro-1,4,4a,4b,5,8,8a,12b-octahydro-1,4,5,8-dimethanotriphenylene — henceforth called Di-Hex-Adduct (DHA)] can be filtered off, the mother liquor reconstituted with fresh starting materials to the original 1:3 naphthalene-Hex mixture, and readducted. Generally 3 to 5 recycles can be made without a high accumulation of impurities. Runs up to 200 gallons have been conducted successfully in Berkeley.

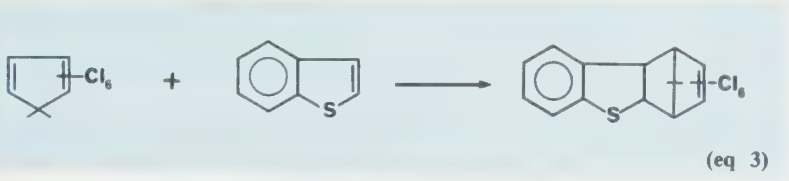


(eq 2)

Among the by-products formed during the adduction is an unusual tetracyclic compound formed by the disproportionation of Hex (eq 2).
The structure of the tetracyclic compound was determined simultaneously by Mark[6] and by our group in Berkeley. The reaction is minimal at 150-160° (less than 1% in one week). A serious impurity formed when coal tar naphthalene is used is a mono-Hex adduct of thianaphthene,

a common coal tar impurity (eq 3). This adduct is more active to substitution than DHA and causes the formation of tars when reactions are conducted on DHA.

Very little is known about the orientation and physical structure of the DHA molecule. The nature of the hindrance to substitution in the α-position is unknown.



(eq 3)

The adduction reaction was extended to other β-substituted naphthalenes (eq 4),[7] yielding, for instance, the very useful 2-methyl-DHA with 2-methylnaphthalene. Adduction attempts with α-substituted naphthalenes were nonproductive, and in some cases their very presence as impurities in β-substituted naphthalenes gave rise to impure and tarry DHA products. Other polynuclear aromatics form adducts (mono- and di-Hex), the notable exception being phenanthrene (eq 4).

REACTIONS OF DHA'S (eq 5)

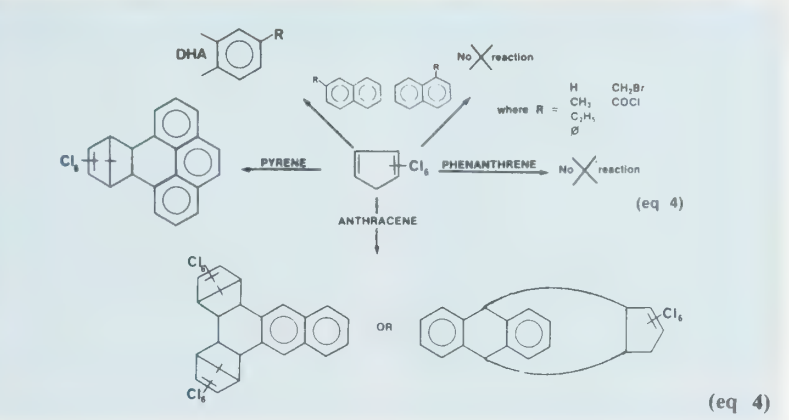
1) Nitration

Nitration of DHA does not form β-nitro-DHA exclusively as previously believed[3] but a mixture of 13% α-nitro-DHA and 87% β-nitro-DHA. Instead of the strenuous conditions formerly used,[2] we found that anhydrous nitric acid in either sulfuryl chloride or methylene chloride at reflux gave quantitative yields of nitro-DHA.[11] The isomers are separable by recrystallization from aqueous acetone. The ultraviolet spectrum of α-nitro-DHA is similar to that of 6-nitrotetralin, while the spectrum of β-nitro-DHA is similar to that of 7-nitrotetralin. The ratio of nitro isomers did not deviate greatly under varying nitrating methods and conditions, *e.g.*, nitrogen pentoxide in chloroform at 0°, 70% nitric acid at reflux, and anhydrous nitric acid in solvent. The possibility of two forms of DHA is disproved by the following experiments: Pure β-nitro-DHA was reduced to β-amino-DHA which was diazotized and reduced to DHA. Renitration of this DHA gave the normal α- and β-nitro-DHA mixture (eq 6).[12] α-Amino-DHA cannot be diazotized, probably because of stearic reasons.

Under slightly more stringent nitrating conditions, α-nitro-DHA is quantitatively converted to 1,3-dinitro-DHA.[13] Still more stringent nitration gives 2,3-dinitro-DHA from β-nitro-DHA.[14] The α-nitro-DHA is completely nitrated to 1,3-dinitro-DHA before β-nitro-DHA is formed. Nitration of 2-methyl-DHA gives a quantitative yield of 2-methyl-3-nitro-DHA (eq 7).

2) Halogenation

Chlorination of DHA gives 1,2,3,4-tetrachloro-DHA.[3] Depending on conditions, bromination or iodination with 3*N* nitric acid in methylene chloride solution gives 2-bromo-, 2,3-dibromo-, 2-iodo- or 2,3-diiodo-DHA. No noticeable amount of nitration is encountered if nitric acid remains at or below 3*N*.[15] No work was conducted on fluorination. Chlorination of 2-nitro-DHA gives 3,4-dichloro-2-nitro-DHA.[16] 3-Bromo-2-nitro-DHA is synthesized by nitrating 2-bromo-DHA.[16]



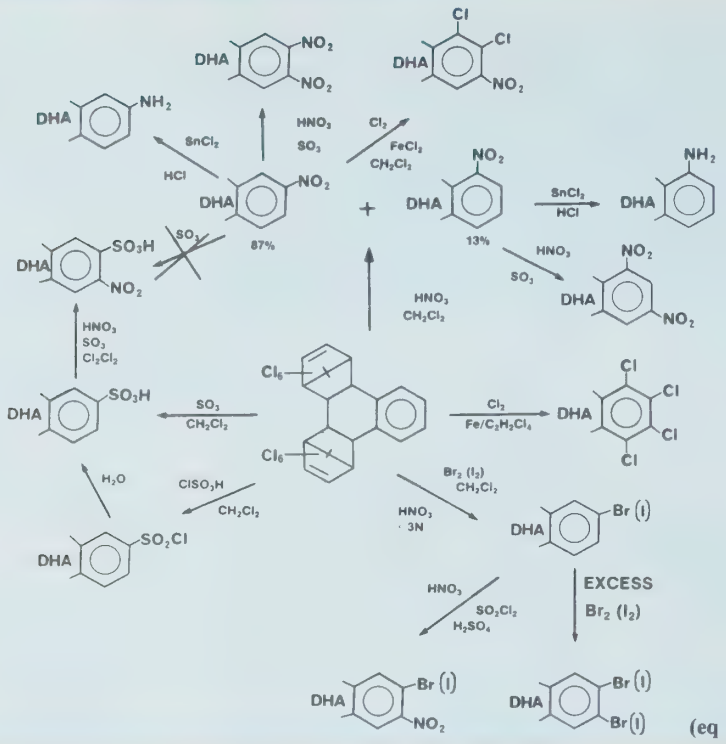
(eq 4)

(eq 4)

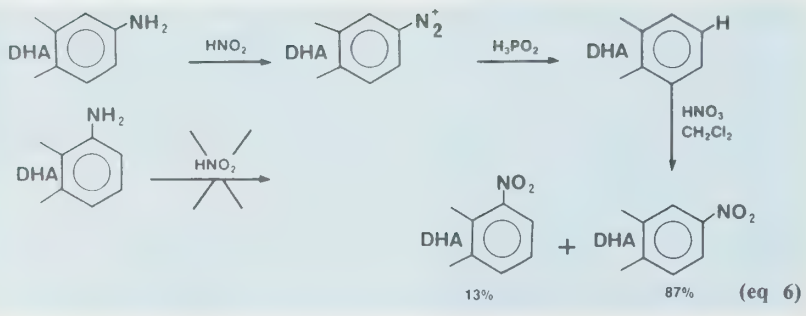
One of the major difficulties to commercialization of the adduct process was the extremely slow rate of the reaction. Since a considerable decrease in volume results from the formation of the diadduct, the age-old Le Chatelier principle in adduction was studied. Preliminary studies at 7000 psi and 150-160° showed a three-fold increase in rate. With specialized equipment,[8] our studies eventually culminated at a pressure of 100,000 psi and 300° where yields were quantitative in 3 minutes (Table 1).[9] One of the main advantages of high pressure adductions is that higher temperatures can be used, without formation of the undesirable by-products encountered in atmospheric reactions. The only comparable studies of the Diels-Alder reactions at high pressures are those of Plieninger.[10]

TABLE 1

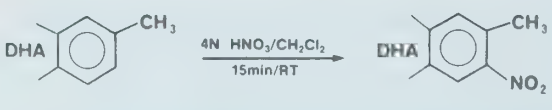
Dienophile	Temp.	PSI	Time/hr.	Yield	Yield/hr.
Naphthalene	150-160	(Atmos)	200	44%	0.25%
	160	6-7000	18	13.1	0.73
	160	15,000	18	22.9	1.23
	160	35,000	18	45.9	2.55
	200	35,000	4	75	18.75
	230	35,000	1	55.6	55.6
	235	100,000	1/120	1	(100)
	260	100,000	1/20	31	(100)
	160	100,000	2.75	12.1	4.4
2-Methylnaphthalene	160	(Atmos)	168	55	0.33
	160	35,000	18	27.9	1.55
	180	35,000	18	64.3	3.57
Pyrene	150	(Atmos)	168	0	0
	150	35,000	5	40	8



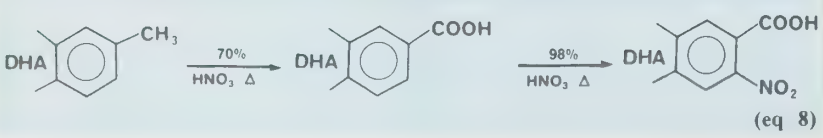
(eq 5)



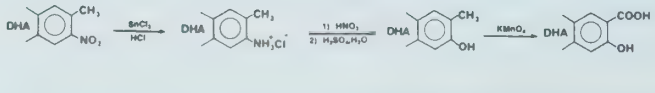
(eq 6)



(eq 7)



(eq 8)



(eq 9)

3) Sulfonation

Sulfonation of DHA's is accomplished with 30% oleum[3] or, preferably, with sulfur trioxide in methylene chloride.[17] We were never able to synthesize DHA-2,3-disulfonic acid. Chlorosulfonation of DHA is done in methylene chloride with chlorosulfonic acid.[18]

4) Multiple Reactions

Many of the common reactions on aromatic compounds have been carried out on the DHA compounds. A few examples include the oxidation of 2-methyl-DHA with concentrated nitric acid to DHA-2-carboxylic acid[18] which can be nitrated with white fuming (98%) nitric acid to 3-nitro-DHA-2-carboxylic acid (eq 8).

2-Methyl-3-nitro-DHA is reduced with stannous chloride to 2-amino-3-methyl-DHA. Hydrolysis of the diazonium salt of the amino-DHA gives 2-hydroxy-3-methyl-DHA. The latter can be oxidized to 2-carboxy-3-hydroxy-DHA (eq 9).[18]

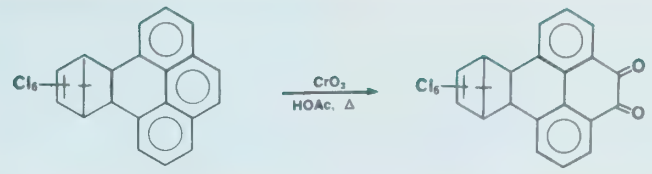
Preparation of 2-nitro-DHA-3-sulfonic acid may be effected by the nitration of DHA-sulfonic acid but not by the reverse sequence (eq 5).[15]

5) Other Reactions (and Non-Reactions)

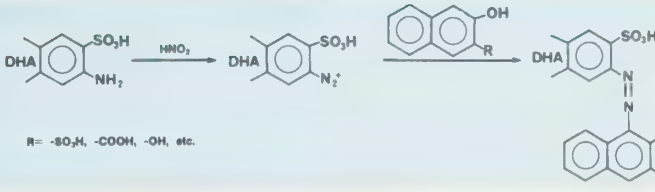
We have never been able to perform a Friedel-Crafts reaction or a chloromethylation on DHA or its derivatives. DHA is unaffected by chromic oxide-acetic acid at reflux; oxidation of the pyrene adduct by this method gives the 1,2-pyrenequinone adduct (eq 10).[19]

2-Amino-DHA-3-sulfonic acid can be diazotized and coupled to phenols and naphthols to give dyes and pigments with probable flame retarding properties (eq 11).

(eq 10)



(eq 11)



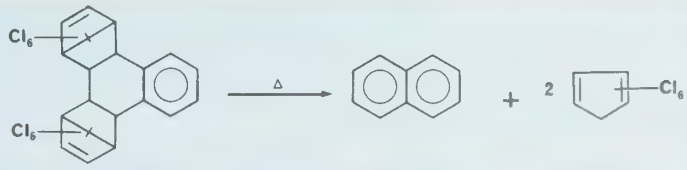
REVERSE DIELS-ALDER REACTIONS

All of the mentioned Hex adducts undergo reverse Diels-Alder reactions at 250-400° to regenerate Hex and the dienophile or substituted dienophile if the latter is stable to heat and does not readily react with Hex at these conditions (eq 12). Small quantities (0.5 to 2 gms) can be pyrolyzed in a test tube; the products tend to collect on the cooler part of the tube. Larger quantities are usually cracked in rotary flask equipment designed for solvent evaporation, using a nitrate-nitrite salt bath as a source of heat. Ideally, pyrolysis of larger quantities is carried out in a wipe-film still such as the ASCO molecular Rota-Film™ still. In the latter case, the DHA's are fed into the still as a slurry in Hex. In each case, a vacuum corresponding to the vapor pressures of the products at the temperature of pyrolysis is necessary. DHA derivatives were pyrolyzed continuously in hundreds-of-pounds scale in our plant using wipe-film pyrolyzers. DHA-acids are pyrolyzed as their salts, in which case the residue is the product (eq 13).

Mono-adducts are similarly pyrolyzed (eq 14).

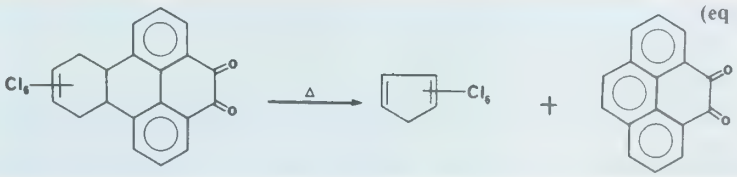
The products are usually separated from Hex by hexane extractions. The products are usually insoluble in hexane, whereas Hex is completely miscible with aliphatic hydrocarbons.

(eq 12)

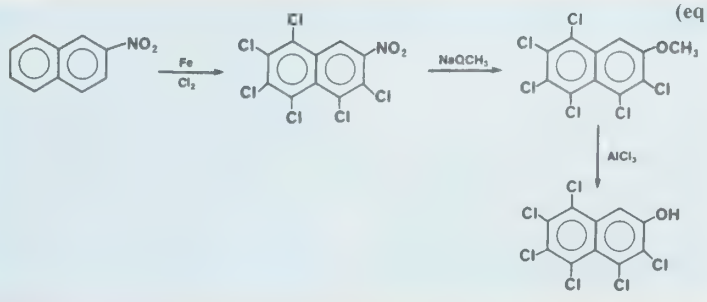


(eq 13)

(eq 14)



(eq 15)



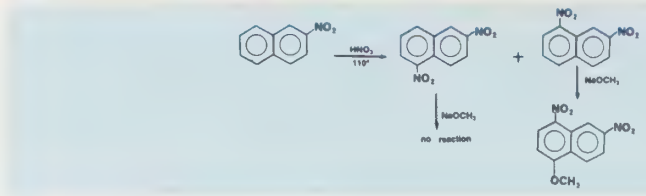
REACTIONS OF PYROLYZED PRODUCTS

Because the products made *via* the Hex adduction method were rare and otherwise difficult to synthesize by other processes, many of the reactions we studied were new. Only a few representative examples will be described for it will be impossible to discuss the hundreds of polynuclear aromatic compounds that were synthesized in Berkeley by direct or indirect use of our processes. Readers who are interested in the details of earlier naphthalene compounds should consult either of two references available.[20]

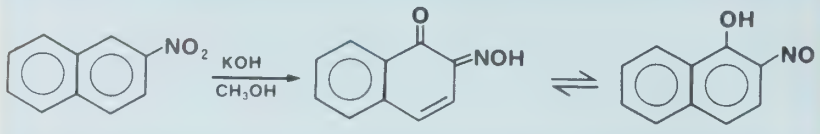
β-NITRONAPHTHALENE

This compound is prepared from 2-nitro-DHA by thermal decomposition at 250-375° at 12mm pressure in yields greater than 95%. β-Nitronaphthalene is chlorinated to form 1,2,3,4,5,6-hexachloro-7-nitronaphthalene.[21] The nitro-group of this compound is displaced with sodium methoxide to form the 7-methoxychloronaphthalene which can be cleaved to the naphthol (eq 15).

β-Nitronaphthalene is nitrated with concentrated nitric acid to form an equal mixture of 1,6- and 1,7-dinitronaphthalene.[22] The more valuable 1,6-dinitronaphthalene can be separated from the 1,7-isomer by reaction with sodium methoxide. The 1,6-dinitronaphthalene remains insoluble, while the 1,7-isomer is solubilized by the reaction (eq 16).[23]

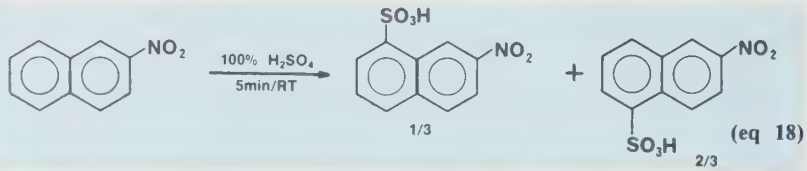


(eq 16)



(eq 17)

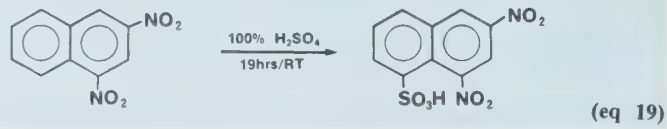
β-Nitronaphthalene is reduced to β-naphthylamine by several methods. The amine is well known for its carcinogenic properties.[24] Though β-nitronaphthalene was once implicated in studies as being carcinogenic,[25] our cooperative studies show that the nitro compound is not carcinogenic.[26] It is of interest to note that 3-methyl-2-naphthylamine prepared from the corresponding nitro compound is a highly potent intestinal carcinogen.[27] No DHA's tested have been found to be carcinogenic.



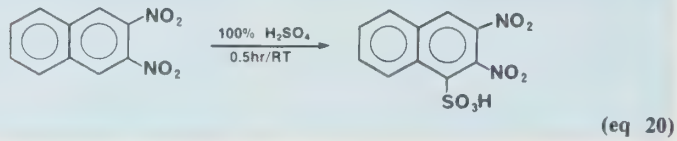
(eq 18)

β-Nitronaphthalene undergoes the Meisenheimer reaction to give a quinone oxime (eq 17). Mononitrated naphthalenes are usually sulfonated with anhydrous sulfuric acid (concd sulfuric acid boosted to 100% with oleum) at room temperatures (eq 18).

Dinitronaphthalenes require more strenuous sulfonating conditions (eq 19, 20).

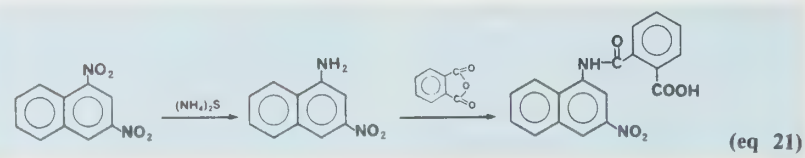


(eq 19)



(eq 20)

1,3-Dinitronaphthalene can be partially reduced to 3-nitro-1-naphthylamine under a variety of conditions.[20] The phthalamic acid of the amine shows growth regulatory properties in bean plants (eq 21).[28]

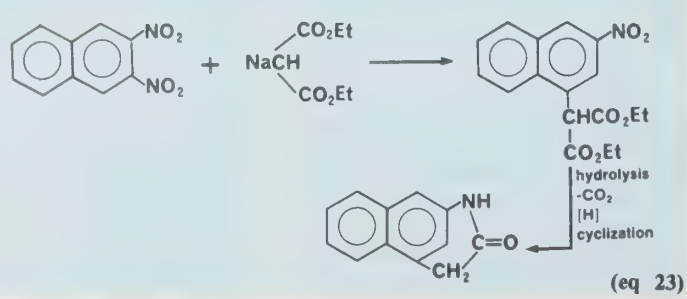


(eq 21)

2,3-Dinitronaphthalene undergoes many unusual reactions not attributed to other dinitro aromatic compounds. Reactions of the compound with numerous carbanions result in products where the 2-nitro group is removed as the carbanions enter the 1-position (eq 22).[29]

(eq 22)

Numerous biologically active compounds were synthesized by this method.[28] This type of reaction may offer an alternative route to the benzomorphan analgesic-type compounds described by May (eq 23).[30]



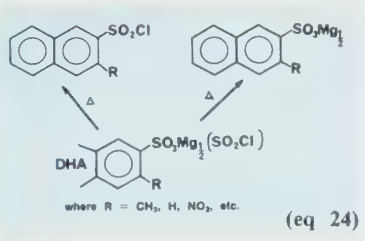
(eq 23)

HALOGENATED NAPHTHALENES

By the use of the DHA-nitric acid halogenation method and other methods, numerous rare halogenated naphthalenes were made available for experimental purposes (Figure 1). No mixed halogenated naphthalenes were synthesized, but there appears to be no reason why they cannot be made using our methods. Typical reactions of these compounds were described in one of our publications.[16]

SULFONATED NAPHTHALENES

The chemistry of sulfonated naphthalenes is well documented, particularly in dye chemistry.[31] Sulfonated naphthalenes, if prepared from DHA's, are synthesized as their salts or acid chlorides (eq 24). Sulfonated 2-methyl-DHA is the



(eq 24)

basis of a new process for synthesizing BON acid (3-hydroxy-2-naphthoic acid), an important dye intermediate (eq 25).[18]

2-Nitronaphthalene-3-sulfonic acid, magnesium salt, pyrolyzed from its DHA derivative is the basis of a process for another dye intermediate, 2,3-naphthalenediol (eq 26).[17]

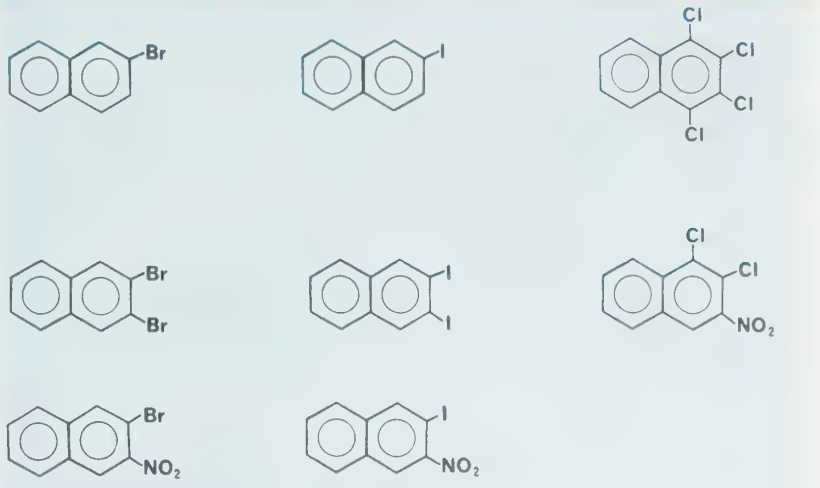
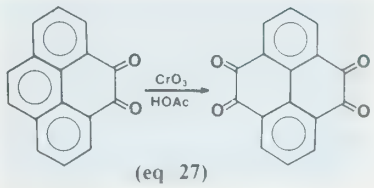


Figure 1

POLYNUCLEAR AROMATICS OTHER THAN NAPHTHALENE

Little work was done by the Berkeley group on the higher polynuclear aromatics and their adducts. The 1,2-pyrenequinone can be oxidized to 1,2,6,7-pyrenediquinone with chromic anhydride (eq 27).[19]

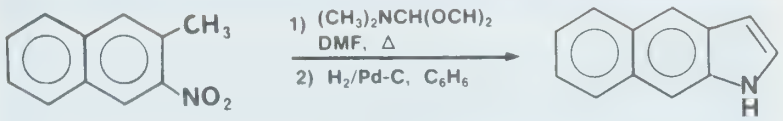
Although the anthracene adducts have been studied, most of the work in this area is still unfinished.



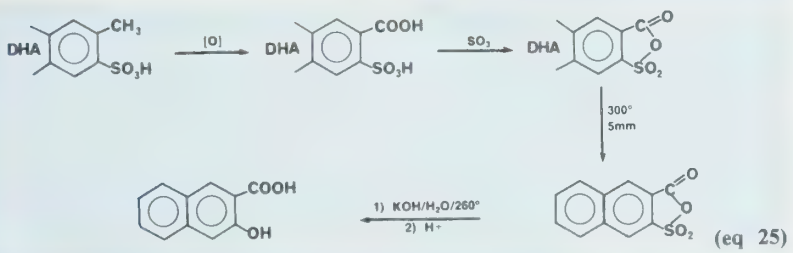
(eq 27)

SIGNIFICANCE OF COMMERCIAL AND ACADEMIC POTENTIALS

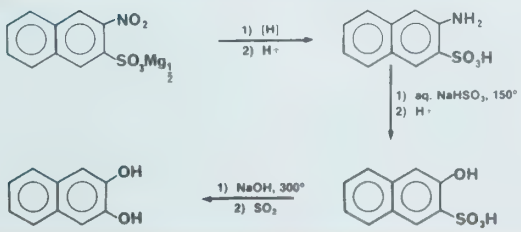
A vast amount of work remains to be done on DHA's and their derivatives. Studies on the use of high pressures in



(eq 28)



(eq 25)



(eq 26)

Diels-Alder reactions are still in their infancy. The work in Berkeley shows that one can avoid the use of the dangerous β-naphthylamine intermediate for the preparation of dyestuffs. Naphthalene compounds made available by the Berkeley group have led to many potentially interesting commercial products and biologically active products, some of which were discussed in this article. Many newly discovered reactions were never pursued; *e.g.*, 2-methyl-3-nitronaphthalene can be utilized in the new indole synthetic reactions described by Leimgruber and Batcho[32] (eq 28) to produce benzoindole. There is an open challenge in DHA technology to all chemists.

ACKNOWLEDGEMENT

The author wishes to acknowledge the work of chemists, J. Fenyes, D. Morrison and H. Lee; engineers, J. McLaughlin and W. Hoffman; research director, M. Padgett; and the President of Hyman Laboratories, Dr. J. Hyman and assistants. Their combined talents at the Berkeley laboratory resulted in the work which is only partially reported here.

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The Aldrich First System of Information Retrieval

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Aldrich Chemical Company, Inc.

Since the Aldrich **FIRST** (Fragment Information Retrieval of STructures) system was introduced more than six years ago,[1] we have processed thousands of inquiries for computer-generated lists of structurally similar compounds. Hopefully, this article will acquaint our readers with many of the advantages of using the Aldrich FIRST system. Lists of compounds for consideration as reagents in various research projects may be obtained at no cost to the inquirer.

One immediate advantage of using the Aldrich FIRST system is that the more than 20,000 compounds being surveyed represent the most current listing of products available from Aldrich and its Alfred Bader Chemicals Division. At present, there are approximately 800 Aldrich items and 2,000 Alfred Bader items in the Aldrich FIRST computer file that do not appear in "The Aldrich Handbook of Organic Chemicals". This gap will be reduced with the release of our newest catalog. However, because of the rate at which new compounds are added to our product line, a gap between catalog items and all available compounds will always exist. The Aldrich FIRST system helps to keep this gap at a minimum.

The Aldrich FIRST system of information retrieval is based on the various structure fragments which an individual molecule contains rather than on its chemical characteristics. More than 250 structure fragments have arbitrarily been assigned a two-character code designation. By means of these code designations, one can request a listing of substances having a particular structure fragment or a combination of fragments, while at the same time excluding other coded fragments.

CODING OF RING SYSTEMS

A significant structure fragment in any ring compound is the ring system itself. Unlike the arbitrary code designations given to other structure fragments, ring systems are coded according to a definite set of rules:

1) A number is used to indicate the total number of atoms in a ring.

2) Hetero atoms in a ring system are represented by the element symbol which is placed directly ahead of the ring size number.

3) If more than one hetero atom is present in a ring, the element symbols are listed in alphabetical order.

4) If more than one non-fused ring is present in a molecule, the rings are listed in increasing order of size.

5) If a molecule contains at least two non-fused rings of the same size, the rings are listed in increasing order of hetero complexity. If the degree of hetero complexity is the same, alphabetical order becomes the determining factor.

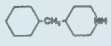
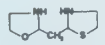
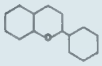
6) Fused ring systems are coded by applying the rules for non-fused rings just given.

7) If a molecule contains both a fused and a non-fused ring system, the non-fused ring is listed first.

8) An asterisk (*) is placed before the ring designation for a non-fused ring and the letter R before that of a fused ring system.

Examples of ring designations in the Aldrich FIRST system are given in Table I.

Table I. Ring Designations

Ring System	Ring Code	Rule	Ring System	Ring Code	Rule
	*6	1		R66	6
	*N5	2		RN56	6
	*NS5	3		RNN5NN6	5
	*56	4		R566	6
	*6N6	5		R66NO6	6
	*NO5NS5	5		*6R6O6	7
	R46	6			

The value of these systematic ring designations will become apparent as the utility of the Aldrich FIRST system is discussed.

RETRIEVAL OF BENZENE DERIVATIVES

It is possible to produce lists of a wide variety of benzene derivatives by means of the Aldrich FIRST system. The benzene ring itself can be retrieved from our computer file by means of its ring designation, the number 6. However, since cyclohexane, cyclohexene and cyclohexadiene all have the same ring designation as benzene, these rings are normally excluded from any request for benzene derivatives. This is done simply by excluding the arbitrary structure fragment codes which were assigned to the three cyclohexane ring systems.

The significant structure fragments in benzoic acid derivatives (in addition to the benzene ring) are the carboxyl and conjugated carbonyl groups. These fragments may be requested in order to obtain a listing of all of our benzoic acids. For other benzoyl derivatives, the carboxyl group code is replaced by the code for the carbonyl derivative being sought. In this manner, one can obtain lists of benzoyl halides, benzamides, benzaldehydes, phenyl ketones, benzoate esters and benzoic acid hydrazides (see Table II).

Cinnamic acid derivatives contain an additional structure feature which allows them to be distinguished from benzoic acid derivatives by the Aldrich FIRST system. That feature is the double bond which is in conjugation with both the carbonyl group and the benzene ring. By requesting this structure fragment along with the benzene ring and the carboxyl and conjugated carbonyl groups, a listing of all of our cinnamic acids may be obtained. If the carboxyl group code is replaced by other carbonyl derivative codes, lists of cinnamoyl halides, cinnamamides, cinnamaldehydes and cinnamate esters may be obtained (see Table III).

Although substituent orientation has not been encoded for all polysubstituted benzene derivatives, it is possible to specify orientation for certain nitrogen-containing compounds by means of coded structure fragments such as N-C-C-N, N-C-C-C-N, N-C-C-C-C-N, N-C-C-O and N-C-C-S. A listing of *o*-phenylenediamines can be produced by requesting benzene derivatives which contain an amino function together with the structure fragment N-C-C-N. Similarly, *m*-phenylenediamines and *p*-phenylenediamines can be located by replacing the N-C-C-N fragment code with those for the N-C-C-C-N and N-C-C-C-C-N fragments, respectively. The means by which lists of these and other nitrogen-containing benzene derivatives can be requested are summarized in Table IV.

Table II. Retrieval of Benzoyl Derivatives

Class of Compound	Structure Fragments Required (other than benzene ring)
benzoic acids	-C(=O)-O-, -C(=O)-C=C-
benzoyl halides	-C(=O)-X, -C(=O)-C=C-
benzamides	-C(=O)-N, -C(=O)-C=C-
benzaldehydes	-C(=O)-H, -C(=O)-C=C-
phenyl ketones	-C-C(=O)-C-, -C(=O)-C=C-
benzoate esters	-C(=O)-O-C-, -C(=O)-C=C-
benzoic acid hydrazides	-C(=O)-N-N, -C(=O)-C=C-

Table III. Retrieval of Cinnamoyl Derivatives

Class of Compound	Structure Fragments Required (other than benzene ring)
cinnamic acids	-C(=O)-O, -C(=O)-C=C-, -C=C-C=C-
cinnamoyl halides	-C(=O)-X, -C(=O)-C=C-, -C=C-C=C-
cinnamamides	-C(=O)-N, -C(=O)-C=C-, -C=C-C=C-
cinnamaldehydes	-C(=O)-H, -C(=O)-C=C-, -C=C-C=C-
cinnamate esters	-C(=O)-O-C, -C(=O)-C=C-, -C=C-C=C-

Table IV. Retrieval of Specifically Oriented Benzene Derivatives

Class of Compound	Structure Fragments Required (other than benzene ring)
o-phenylenediamines	$-NH_2$, N-C-C-N
m-phenylenediamines	$-NH_2$, N-C-C-C-N
p-phenylenediamines	$-NH_2$, N-C-C-C-C-N
o-aminophenols	$-NH_2$, -OH, N-C-C-O
o-aminobenzenethiols	$-NH_2$, -SH, N-C-C-S
o-nitroanilines	$-NH_2$, $-NO_2$, N-C-C-N
m-nitroanilines	$-NH_2$, $-NO_2$, N-C-C-C-N
p-nitroanilines	$-NH_2$, $-NO_2$, N-C-C-C-C-N
picrylamines (2,4,6-trinitroanilines)	$-NH_2$, $-NO_2$, N-C-C-N, N-C-C-C-N, N-C-C-C-C-N

Additional structure fragments of particular utility in the retrieval of benzene derivatives are the phenethylamine (C_6H_5-C-C-N) and benzhydryl (C_6H_5-C-C_6H_5) groupings. With these fragments, it is possible to produce lists of phenylacetamides (which contain both amide and phenethylamine fragments), phenylacetonitriles (nitrile and phenethylamine fragments) and benzophenones (ketone, conjugated carbonyl and benzhydryl fragments). The phenethylamine grouping is also present in many physiologically active benzene derivatives such as ephedrine and norepinephrine. A listing of these and related compounds can be obtained by requesting the phenethylamine, hydroxy and N-C-C-O fragments.

RETRIEVAL OF HETEROCYCLIC COMPOUNDS

The Aldrich FIRST system is also useful in the retrieval of heterocyclic compounds. As discussed previously, heterocyclic ring systems have been assigned specific ring designations which can be used to retrieve systems of interest. Most of the common monocyclics, as well as certain bicyclics such as indole, purine, quinoline and isoquinoline, also have been given arbitrary two-character code designations. This is necessary in order to distinguish between heterocyclic ring systems like pyridazine, pyrimidine and pyrazine, all of which have the ring designation *NN6. It is possible to produce lists of specifically substituted heterocycles by requesting a specific heterocyclic ring system and certain other structure fragments as summarized in Table V.

Certain heterocyclic alkaloids have characteristic structures which allow for their ready retrieval by the Aldrich FIRST system structure fragment approach. Compounds such as papaverine and laudanosine contain isoquinoline and phenethylamine fragments, which can be requested and subsequently retrieved. Harman alkaloids have a polycyclic fused ring system which includes an indole ring system, a pyridine (or piperidine) nucleus and the N-C-C-N fragment. These three fragments can be requested to produce a listing of harman alkaloids.

Some fused ring heterocycles which have not been assigned arbitrary two-character code designations can be retrieved by requesting a coded heterocyclic fragment and the specific ring code designation for the fused ring system as shown in Table VI.

Table V. Retrieval of Specifically Substituted Heterocycles

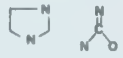
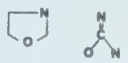
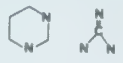
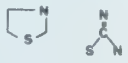
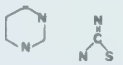
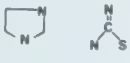
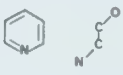
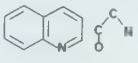
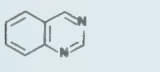
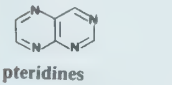
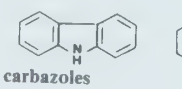
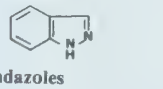
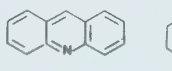
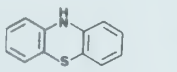
Class of Compound	Structure Fragments Required	Class of Compound	Structure Fragments Required
2-aminoimidazoles		2-hydroxyimidazoles	
2-aminooxazoles		2-aminopyrimidines	
2-aminothiazoles		2-pyrimidinethiols	
2-imidazolethiols		3-hydroxypyridines	
2-thiazolethiols		8-hydroxyquinolines	

Table VI. Retrieval of Fused Ring Heterocycles

Class of Compound	Structure Fragments Required	Class of Compound	Structure Fragments Required
quinazolines	 R6NN6	benzoxazoles	 RNO56
pteridines	 RNN6NN6	carbazoles	 RN566
indazoles	 RNN56	acridines	 R66N6
benzimidazoles	 RNN56	phenothiazines	 R66NS6

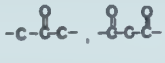
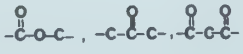
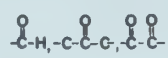
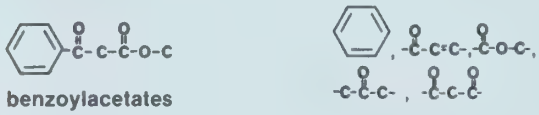
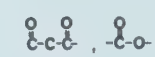
MISCELLANEOUS RETRIEVALS

Many types of amino acid derivatives can be retrieved by the Aldrich FIRST system because they contain other characteristic structure fragments in addition to the amino acid fragment. For example, phenylalanines contain the phenethylamine grouping; serines and threonines contain the N-C-C-O fragment; cysteines, including penicillamines, contain the N-C-C-S fragment; and N-carbobenzyloxy amino acids contain the carbamate ester grouping.

A wide variety of α- and β-dicarbonyl compounds can also be retrieved. Some examples are shown in Table VII.

Special mention should be made of a device used by the Aldrich FIRST system to insure that some listings of structurally similar compounds do not contain a large number of invalid items. When looking for malonic acids, one might request a listing of all compounds containing the carboxyl and β-dicarbonyl fragments (see Table VII). However, such a listing would also contain many β-keto carboxylic acids. In order to avoid this type of problem, the Aldrich FIRST system has been programmed so that either an exact or a minimum number of atoms of a particular element can be specified. Thus, in addition to structure fragment codes, a request for malonic acids will require that each valid compound contains a minimum of four oxygen atoms per molecule. This procedure can be used because the FIRST file contains both structure fragment codes and the molecular formula for each item listed. This also makes it possible to provide lists of compounds containing a particular element such as a listing of all of our organoboron compounds. Similarly, various elements may be excluded from a request.

Table VII. Retrieval of Dicarbonyl Compounds

Class of Compound	Structure Fragments Required
α-diketones	
β-diketones	
β-keto esters	
pyruvaldehydes	
oxamates	
benzoylacetates	
malonic acids	

GUIDELINES TO USERS OF THE FIRST SYSTEM

Some guidelines are given below for those who might wish to submit a computer search request:

1. Make your request as specific as possible. This is especially important when requesting such categories as benzene derivatives and chlorinated compounds. We list several thousand compounds in each of these categories, making a total listing useless to the inquirer as well as costly for us to provide. To avoid producing such listings, we often make assumptions based on the structure of interest which may have been included with the request. For example, if the structure does not contain any ring systems, we will exclude them unless given instructions to the contrary.

2. Try to keep the number of variables in your request at a minimum. A seemingly simple request for trisubstituted benzene derivatives can lead to an imposing number of individual requests if, for example, each of the three substituents could be three different functional groups. We try to overcome this problem by providing a more general listing than that requested if in our opinion such a listing would not be too large to diminish its usefulness. However, it would always contain compounds having the desired structure fragments.

3. When requesting nitrogen-containing compounds such as amines and amides, it is helpful to indicate the degree of substitution. Primary, secondary and tertiary amines as well as primary, secondary and tertiary amides are each considered to be a separate structure fragment in the Aldrich FIRST system.

4. If you are interested only in the specific compound included with your request, please indicate this. Such a request can be answered immediately upon inspection of our molecular formula file. This will also avoid the nuisance of receiving a listing of our products which contain all the structure fragments of the particular compound of interest but not the compound itself (if it should be unavailable).

5. If you receive a listing of our products which does not appear to be related to your request, please write to us concerning the problem. We will explain the particular structure fragment approach used on your request. Often, we are able to use a modified approach based on your additional comments which will allow us to provide you with a more useful list of products.

Although many examples have been given, these should not be considered to represent all the possibilities. They have been presented primarily to show the general utility of the Aldrich FIRST system of generating lists of structurally similar compounds. It is hoped that many of our readers will avail themselves of this free service.

REFERENCE

W.F. Buth, *Aldrichimica Acta,* **1**, No. 1, 3 (1968).

New Reagents for Hydroboration and for Synthesis Via Boranes*

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*An address presented before "The Robert A. Welch Foundation Conferences on Chemical Research. XVII. Organic-Inorganic Reagents in Synthetic Chemistry," which was held in Houston, Texas, November 5-7, 1973. The Aldrich Chemical Company expresses thanks to Dr. W. O. Milligan, Director of Research of the Robert A. Welch Foundation for permission to publish this paper.

1. INTRODUCTION

The original studies of the hydroboration reaction emphasized the application of the parent reagent, borane-tetrahydrofuran or other ether complexes.[1] Consequently, it was natural that the subsequent studies of the applicability of boron intermediates in organic synthesis emphasized the utilization of the trialkylboranes,[2] the usual products of such hydroborations.

Instances arose where it was desirable to achieve hydroboration with better regioselectivity than could be achieved with borane itself. This led to the development of a number of substituted boranes for hydroboration with improved regioselectivity.

Some reactions of organoboranes, such as oxidation with alkaline peroxide, carbonylation to tertiary alcohols, and brominolysis to alkyl bromides, utilize all three groups of the trialkylborane, R_3B. However, other reactions utilize only one or two groups. This made it desirable to utilize substituted boranes in these reactions to minimize loss of valuable R groups.

We have had considerable success in overcoming these difficulties with the new reagents. Consequently, it appeared that this symposium would provide an exceptional opportunity to review our work exploring these reagents.

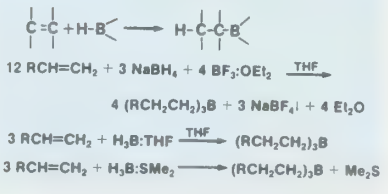
Developments in this area have been exceptionally rapid. Moreover, experience in working with organoboranes is not generally available. Consequently, we are faced with the major hurdle of teaching the chemistry to organic chemists interested in synthesis and of transmitting sufficient know-how to help create the confidence required to utilize this chemistry. To assist in this objective, I have prepared the manuscript for a new book, "Organic Syntheses *via* Boranes." I have also encouraged the Aldrich Chemical Company to set up a subsidiary, "Aldrich-Boranes, Inc." to make available the various intermediates we have found to be valuable in utilizing the fascinating chemistry of the organoboranes, and to participate in transmitting the techniques for work in this field. The time appeared particularly appropriate, therefore, to discuss these new reagents and their interesting possibilities.

2. HYDROBORATION WITH BORANE[1]

Let us first take a few minutes to review. Hydroboration is broadly defined as the addition of an H-B< bond to multiple bonds of carbon with oxygen, nitrogen, and carbon. In this discussion we shall be concerned primarily with hydroboration involving the addition of the H-B< bond to carbon-carbon double and triple bonds.

Hydroboration can be carried out very simply by starting with sodium borohydride (Fig. 1).

Figure 1
Hydroboration Procedures



For many purposes it is desirable to avoid the presence of the salt, sodium fluoroborate. This is now easily accomplished by using borane-tetrahydrofuran complex or borane-methyl sulfide complex, both available from Aldrich Chemical Co., Inc. (Fig. 1). The use of borane-methyl sulfide complex makes it possible to synthesize the desired organoboranes readily in hydrocarbon media, ethyl ether and other solvents, so one is no longer restricted to tetrahydrofuran as the operating medium.

The reaction is essentially quantitative and instantaneous. It proceeds in an anti-Markovnikov manner, and involves a clean cis-addition (Fig. 2).

The addition takes place preferentially from the less hindered side of the double bond. No rearrangements of the carbon skeleton have been observed, even in molecules as labile as α-pinene (Fig. 3).

Figure 2
Hydroboration Characteristics

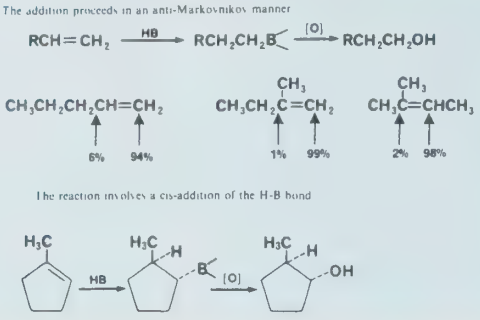


Figure 3
Hydroboration Characteristics

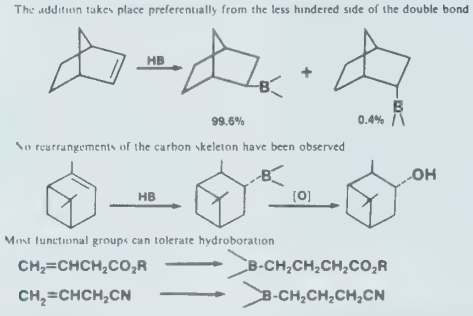


Figure 4
Partially Alkylated Boranes

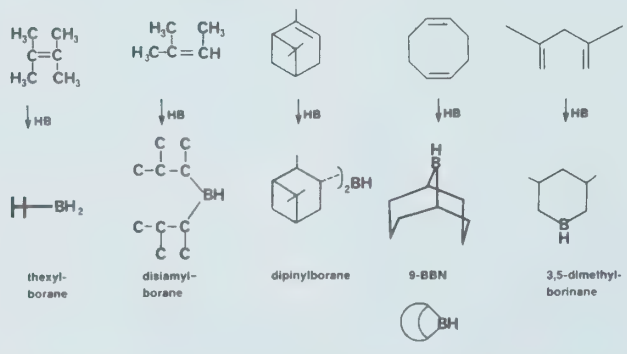
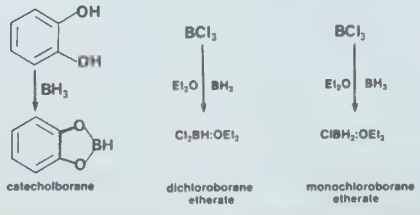


Figure 5
Partially Substituted Boranes



Finally, but perhaps most important is the fact that olefins containing functional groups can be hydroborated (Fig. 3). Thus, for the first time we are in position to synthesize reactive organometallic intermediates containing such functional groups. (Some people may object to considering the organoboranes as organometallics; however, they have many similar characteristics and fill many of the same applications.)

3. HYDROBORATION WITH BORANE DERIVATIVES[2-4]

In an earlier work we converted the unsaturated organic compound to the R_3B derivative by treatment with borane and then utilized the organoborane in subsequent reactions. In many cases we observed that in such subsequent reactions only two of the three R groups were being utilized. Sometimes only one of these groups would be utilized. Clearly, this could be a serious handicap if R was derived from a valuable intermediate. Consequently, we began to explore the possibility of synthesizing hydroborating agents that had only one or two reactive centers by achieving the partial alkylation of borane (Fig. 4).

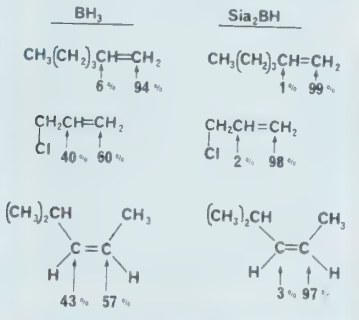
Thexylborane is the most readily available monoalkylborane.[10] Disiamylborane is perhaps the most readily available dialkylborane.[10] Dipinylborane (diisopinocampheylborane) is an asymmetric dialkylborane.[1,4] 9-BBN[2,4] is the first dialkylborane which is sufficiently stable to the atmosphere to permit handling in air with precautions comparable to those used with lithium aluminum hydride and sodium borohydride. It is now commercially available from Aldrich Chemical Co., Inc. Finally, 3,5-dimethylborinane[2,4] has found application in synthesizing the corresponding B-R derivatives for transfer of the R group in free radical reactions.

An alternative approach would be the introduction of alternative substituents into the borane molecule. Dimethoxyborane is readily synthesized. Unfortunately, it is not satisfactory for hydroboration. Presumably the resonance of the oxygen atoms with the boron atom so stabilizes the boron atom that it will not add to the carbon-carbon double bond. Such resonance should be less favorable in a phenol derivative. Indeed, catecholborane[2,4] proves to be a valuable hydroborating agent (Fig. 5).

The reaction of boron trichloride with borane in the presence of an ether can be controlled to yield either the dichloroborane etherates or the monochloroborane etherates,[2,4] which have valuable applications (Fig. 5).

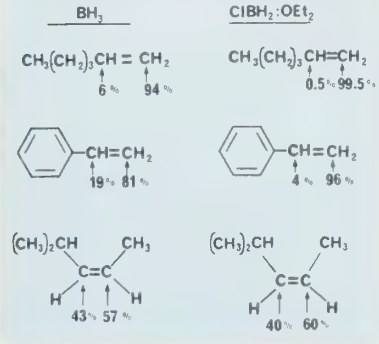
It is helpful to be familiar with these various reagents and their similarities and differences in directive effects. Some of the advantages of disiamylborane over borane are indicated in Fig. 6.

Figure 6
Directive Effects (Disiamylborane)



Chloroborane etherate exhibits a high directive influence for the hydroboration of terminal olefins (Fig. 7). However, it does not exhibit the large steric factor that makes disiamylborane so useful in the hydroboration of internal olefins, such as 4-methyl-2-pentene (Fig. 7).

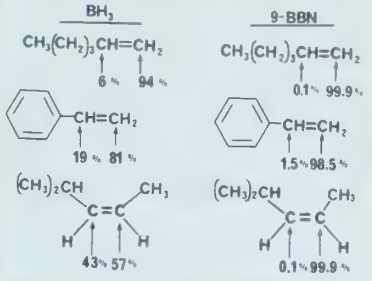
Figure 7
Directive Effects (Chloroborane)



9-BBN exhibits a remarkable directive influence, both for terminal and many internal olefins (Fig. 8).

Obviously, the availability of these reagents facilitates the task of doing selective hydroborations at a particular double-bond or of doing regioselective hydroboration of many double-bonds.

Figure 8
Directive Effects (9-BBN)

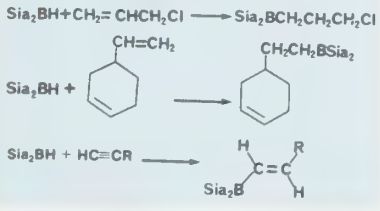


4. SYNTHESIS OF BORON INTERMEDIATES[2,4]

These reagents can be utilized to synthesize specific organoboranes (Fig. 9).

It is interesting that only a few years ago it was thought that mixed organoboranes (organoboranes with two or three different groups attached to boron) could not be synthesized and, if synthesized, would undergo spontaneous conversion into the corresponding symmetrical molecules. However, hydroboration makes these "mixed" organoboranes readily available and they can be converted into other products without loss of the original structure.

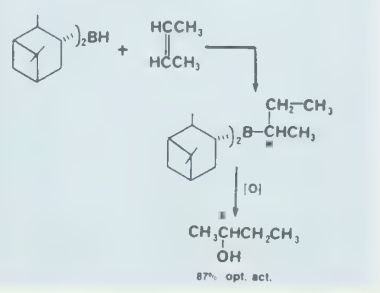
Figure 9
Synthesis of Boron Intermediates (Disiamylborane)



Optically active dipinylborane can be utilized to achieve asymmetric syntheses (Fig. 10).

Since the α-pinene utilized was only 90% optically active, hydroboration achieves an asymmetric synthesis almost as good as that induced by enzymes.

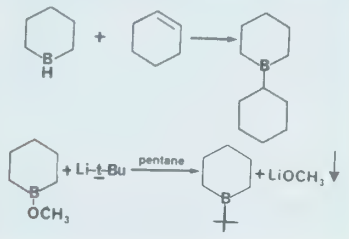
Figure 10
Synthesis of Boron Intermediates (Dipinylborane)



There are many promising reactions of dipinylborane. We used it to separate 3-methylcyclopentene into its antipodes. It has been used to obtain optically active allenes. Finally, it has been used recently to prepare optically active prostaglandin intermediates.

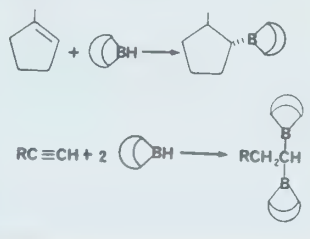
Boracyclanes, such as 3,5-dimethylborinane (Fig. 5) or borinane itself, can be used to hydroborate olefins to obtain the corresponding derivatives. (Fig. 11).

Figure 11
Synthesis of Boron Intermediates (Borinane)



Various derivatives of 9-BBN are readily synthesized (Fig. 12). These derivatives find valuable applications, to be described later.

Figure 12
Synthesis of Boron Intermediates (9-BBN)



Catecholborane reacts more sluggishly than borane itself. In tetrahydrofuran at 0° the borane reaction is often over in less than one minute. However, the reaction of catecholborane with representative olefins requires a temperature of 100° and reaction time of approximately one hour. Acetylenes are somewhat more reactive, so that one hour at 67° is usually adequate (Fig. 13). An advantage of this reagent is that the products can be readily hydrolyzed to the corresponding borinic acids.

Figure 13
Synthesis of Boron Intermediates (Catecholborane)

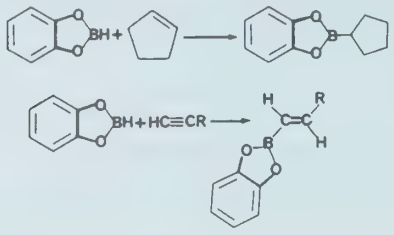


Figure 14
Synthesis of Boron Intermediates (Dichloroborane Etherate)

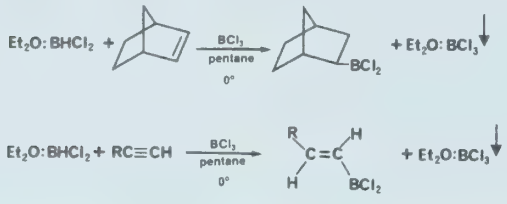


Figure 15
Synthesis of Boron Intermediates (Thexylborane)

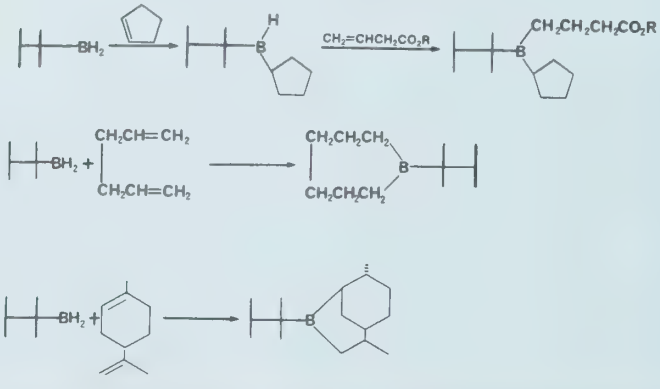
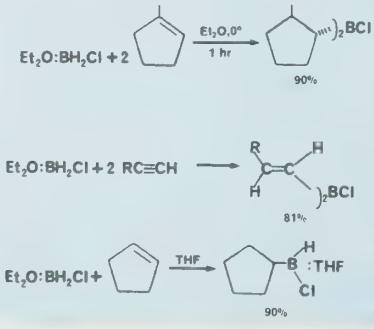


Figure 16
Synthesis of Boron Intermediates (Monochloroborane Etherate)



In the case of dichloroborane etherate, the complex is so stable that hydroboration does not occur at any convenient rate. Unfortunately, a higher reaction temperature or a long reaction time does not solve the difficulty, since the products obtained are no longer the pure monoalkyldichloroboranes desired. Fortunately, the addition of the reagent to a mixture of the olefin and boron trichloride in pentane at 0° solves the problem and provides the desired $RBCl_2$ derivatives (Fig. 14). The synthesis is readily extended to acetylenes.

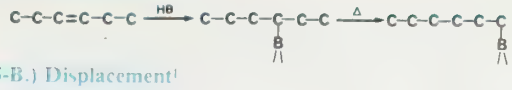
Thexylborane is the most readily available monoalkylborane. In the early days we used it empirically and often encountered phenomena we could not understand. More recently, we undertook a systematic study of thexylborane as a hydroborating agent and established the conditions which provide first, the monoalkylthexylborane and then the dialkylthexylborane[10] (Fig. 15).

One of the valuable applications of thexylborane as a bifunctional hydroborating agent, is the cyclic hydroboration of dienes. For example, the cyclic hydroboration of limonene controls the stereochemistry at three centers (Fig. 15) and provides a simple route to (-)-carvomenthol.

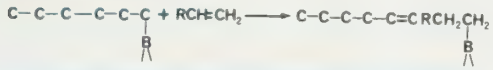
In contrast to the behavior of dichloroborane etherate (Fig. 14), monochloroborane etherate hydroborates olefins and acetylenes readily at 0°. This provides a simple new route to dialkylchloroboranes and their corresponding borinic acids and esters (Fig. 16). In the presence of one mole of tetrahydrofuran, the reaction can be controlled to yield the monoalkylchloroborane species (Fig. 16).

These developments make readily available a large number of borane derivatives. Consequently, we have been exploring the chemistry of these derivatives with emphasis on their utilization to facilitate organic synthesis.

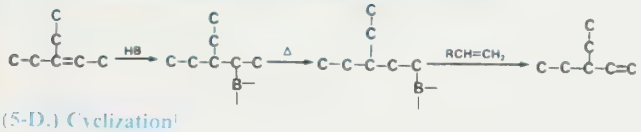
(5-A.) Isomerization[1]



(5-B.) Displacement[1]

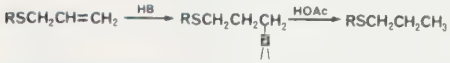


(5-C.) Contrathermodynamic isomerization of olefins[1]

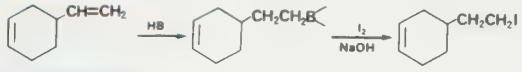


(5-D.) Cyclization[1]

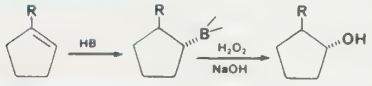
(5-E.) Protonolysis[1]



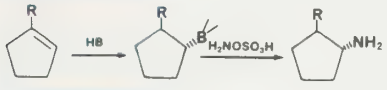
(5-F.) Halogenolysis[2-4]



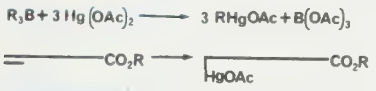
(5-G.) Oxidation[2-4]



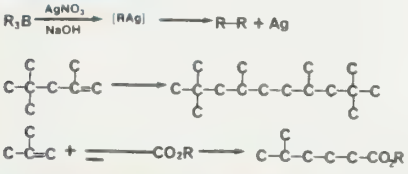
(5-H.) Amination[2-4]



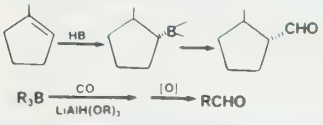
(5-I.) Metallation[2-4]



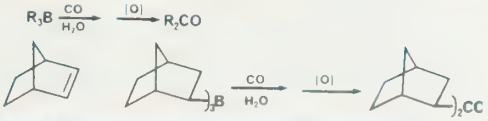
(5-J.) Coupling[1]



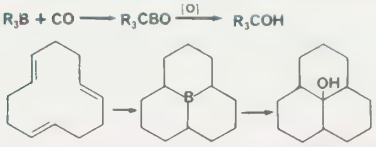
(5-K.) Carbonylation to aldehydes[4]



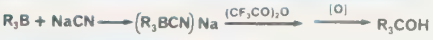
(5-L.) Carbonylation to ketones



(5-M.) Carbonylation to tertiary alcohols

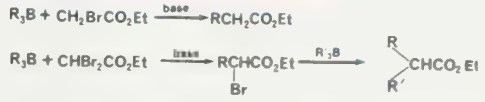


(5-N.) Cyanoboration to tertiary alcohols



(5-O.) The DCME reaction

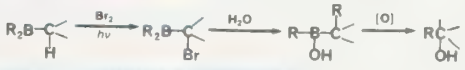
(5-P.) Alkylations and arylations



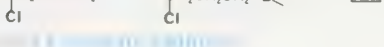
Also $RCOCH_2Br$, CH_2ClCN, $CHCl_2CN$, $CHCl(CN)_2$, etc.

Also N_2CHCOR, N_2CHCHO, N_2CHCN, etc.

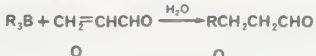
(5-Q.) α-Bromination



(5-R.) Cyclopropanation



(5-S.) Homologation



(5-T.) Alkynylboration

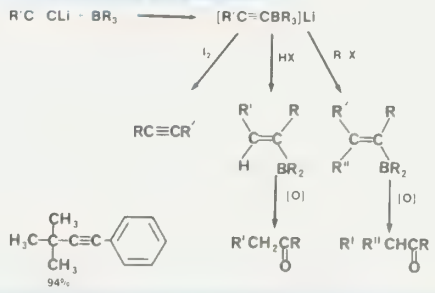


Figure 17
Synthesis of Boron Intermediates (Trialkylborohydrides)

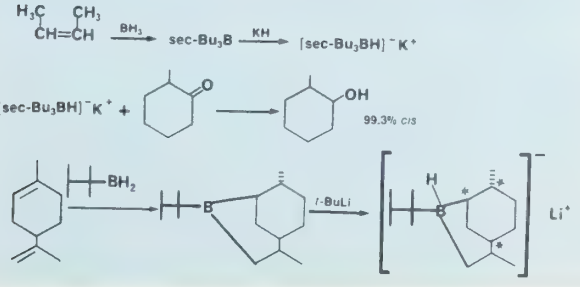
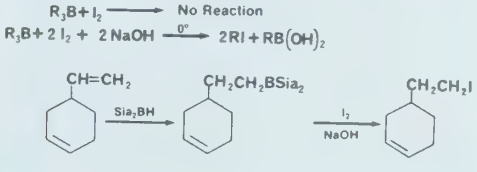


Figure 18
Application of Disiamylborane (Halogenolysis)



For example, triethylborane reacts with lithium hydride to produce lithium triethylborohydride, apparently the most active nucleophile known. The corresponding derivative from tri-*sec*-butylborane cannot be synthesized by direct reaction with lithium hydride, but can be made by reaction with lithium trimethoxyaluminohydride or potassium hydride. It exhibits remarkable selectivity for the reduction of ketones (Fig. 17). Both of these reagents are now commercially available from Aldrich Chemical Co., Inc., (Super Hydride® and Selectride®). The related derivative from thexylborane and limonene has been reported to be uniquely effective for the reduction of a prostaglandin intermediate.

It is important to realize the power of these new methods. At one time it was a major task to prepare pure isomeric alcohols, such as *cis*- and *trans*-2-methylcyclohexanol. However, hydroboration-oxidation of 1-methylcyclohexene yields *trans*-2-methylcyclohexanol. Oxidation to the ketone followed by reduction with Selectride® yields essentially pure *cis*-2-methylcyclohexanol (99.3%). Consequently, it is no longer a problem to provide these derivatives in quantity.

5. THE VERSATILE ORGANOBORANES[2-4,6,9]

The ready availability of the trialkylboranes via the hydroboration reaction prompted research to explore the chemistry of these derivatives. This exploration has been exceptionally fruitful. Time will not permit a detailed discussion of the developments in this area.[2-4] However, it may be helpful to outline the main features (A-T).

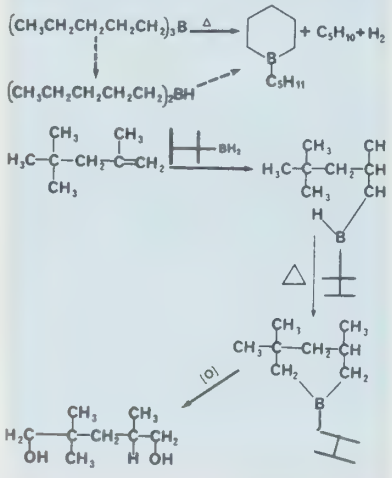
6. APPLICATIONS OF BORON INTERMEDIATES[2-4]

It was not feasible here to attempt a detailed discussion of the remarkable chemistry of the versatile organoboranes, summarized in the previous section. It seems more appropriate, for the special objectives of the present treatment, to consider some of the advantages of the new boron intermediates in some of these reactions.

The reaction of iodine with organoboranes is greatly facilitated by alkali. Unfortunately, only one or two of the alkyl groups of the R_3B intermediate react readily. Since primary alkyl groups react far more readily than secondary, it is possible to utilize disiamylborane[1] to achieve high yields of the desired iodide (Fig. 18).

The cyclization reaction (5-D) apparently proceeds through the formation of a dialkylborane intermediate formed in the thermal decomposition of the trialkylborane. Utilization of thexylborane[10] provides the thexylmonoalkylborane directly for cyclization (Fig. 19).

Figure 19
Application of Thexylborane (Cyclization)

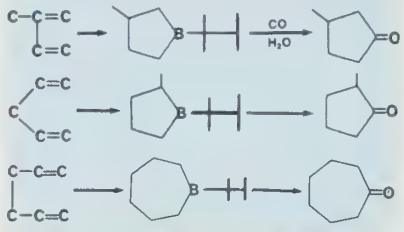


A disadvantage in applying the carbonylation reaction[5] to simple trialkylboranes (5-L) is the loss of one of the three alkyl groups. The use of thexylborane avoids this difficulty and makes possible the synthesis of ketones containing two different groups (Fig. 20).

The Pelter reaction (5-N), treatment with an alkali metal cyanide, followed by trifluoroacetic acid anhydride, provides an alternative route.

Cyclic hydroboration of appropriate dienes with thexylborane, followed by carbonylation or cyanidation, provides a simple route from such dienes to the corresponding ring ketones (Fig. 21).

Figure 21
Application of Thexylborane (Ring Ketones via Carbonylation or Cyanidation)



These reactions provide a new annelation reaction of wide applicability[10] (Fig. 22).

α-Bromination[2,4] in the presence of water provides an alternative means of converting organoboranes into carbon structures (5-Q). Thus, the same cyclic hydroboration intermediate (Fig. 22) is converted through this reaction into a different carbon structure (Fig. 23).

It is possible to utilize α-bromination[2,4] to achieve the synthesis of tertiary alcohols, many of them not readily available by classical methods (Fig. 24).

The Zweifel trans olefin synthesis provides a simple valuable route to the trans olefins.[2-4] However, it suffers from the disadvantage of requiring dialkylboranes as intermediates, and many of these are not readily available. Moreover, only one of the two alkyl groups in the dialkylborane is utilized. Use of the thexylmonoalkylborane circumvents these difficulties[4,10] (Fig. 25).

The thexylmonoalkylboranes also provide a convenient new route to the monoalkylboranes, making these derivatives readily available for the first time.[4,10] Treatment of the borane with a tertiary amine of low steric requirements, such as pyridine, results in the formation of a simple addition compound. However, a base of larger steric requirements such as triethylamine, results in the displacement of 2,3-dimethyl-2-butene and the formation of the aminate of the monoalkylborane (Fig. 26).

Figure 20
Application of Thexylborane (General Ketone Synthesis *via* Carbonylation)

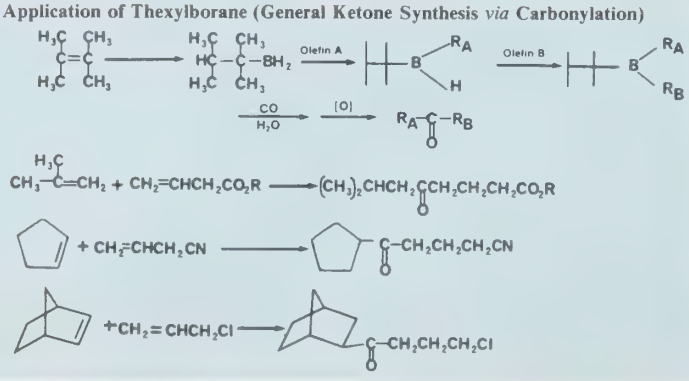


Figure 22
Application of Thexylborane (New Annelation Reaction *via* Carbonylation or Cyanidation)

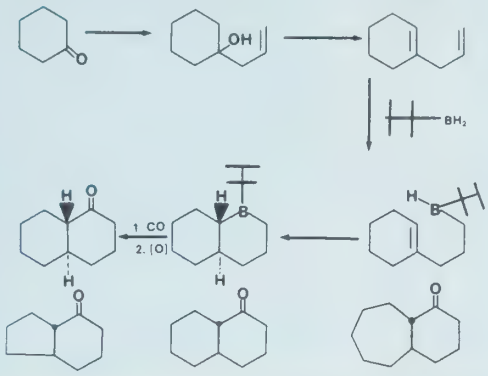


Figure 23
Application of Thexylborane (α-Bromination)

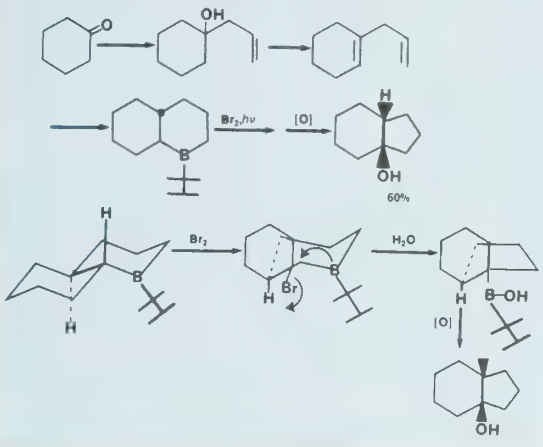


Figure 24
Application of Thexylborane (α-Bromination)

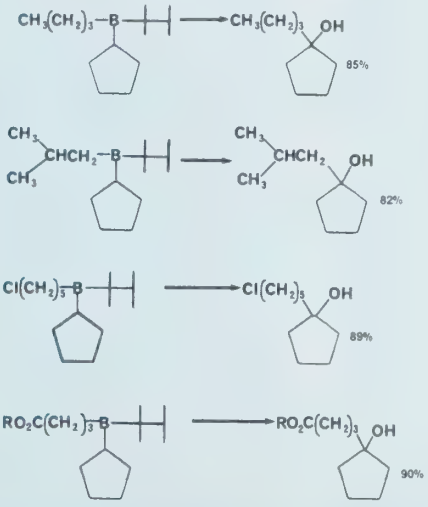
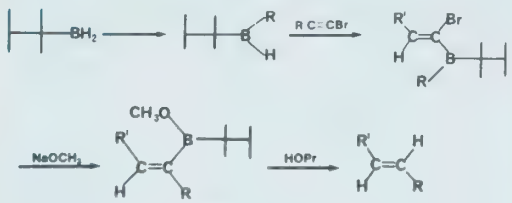


Figure 25
Application of Thexylborane (Zweifel *trans* Olefin Synthesis)



See also E.J. Corey, T. Ravindranathan, *J. Amer. Chem. Soc.*, 94, 4013 (1972)

R'	R	Yield %
n-Bu	2-methyl-1-pentyl	94
	3-hexyl	93
	2-methyl-2-butyl	86
	cyclohexyl	85
	trans-2-methylcyclopentyl	94

Figure 26
Application of Thexylborane (Synthesis of Monoalkylboranes)

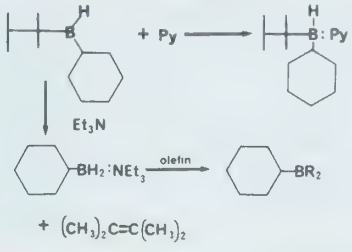


Figure 27
Application of 9-BBN (Cyclopropane Synthesis)

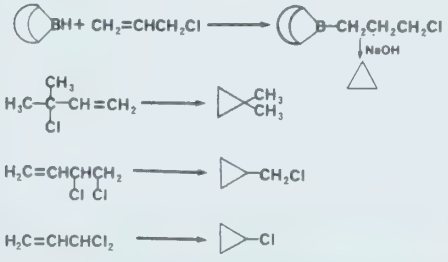
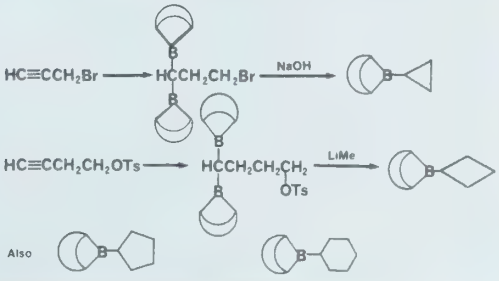


Figure 28
Application of 9-BBN (Synthesis of Cyclic Derivatives)



The boron derivatives realized from allylic halides provide a simple route to cyclopropanes (Fig. 27). 9-BBN possesses advantages in this application because its high regiospecificity for the terminal carbon atom overcomes the unfavorable directive influence of the allylic halogen.[2-4] The relative openness of the 9-BBN boron atom facilitates addition of the hydroxide ion leading to closure.

A similar cyclization reaction of di-9-BBN derivatives provides routes to the corresponding B-cycloalkyl-9-BBN compounds (Fig. 28). Oxidation of the B-cyclopropyl derivative yields cyclopropanol in excellent yield. The parent 9-BBN derivatives are also valuable to transfer the B-R group to the α-position of ketones, esters, nitriles, etc. (5-P).[7]

A highly useful reaction which should be in the repertoire of every chemist engaged in organic synthesis is the conversion of the B-R-9-BBN derivatives into the corresponding aldehydes[2,4,5] (Fig. 29).

It should be recalled that in this reaction, as in many others which have been mentioned, many functional groups can be accommodated (Fig. 30).

The B-alkyl- and B-aryl-9-BBN transfer selectively the B-R group to the α-position of α-halo ketones, esters, nitriles, etc. (5-P).[2,4,7] Moreover, this reaction, as do practically all which have been studied, proceeds with retention at the migrating center (Fig. 31).

In free radical reactions involving organoborations, such as the conjugate addition (5-S), secondary and tertiary alkyl groups participate in preference to primary.[2,4,8] Therefore, in such reactions, the B-R-9-BBN derivatives are unsatisfactory. Fortunately, the borinane derivatives are entirely satisfactory for many of these free radical reactions[4] (Fig. 32).

The B-alkylcatecholborane derivatives are readily reduced to the corresponding boranes.[2,3] This provides an alternative route for the synthesis of monoalkylboranes (Fig. 33).

The B-vinylcatecholborane derivatives react rapidly at 0° with mercuric acetate to produce the corresponding mercurials with complete stereospecificity[2,4] (Fig. 34). This approach has been utilized in the Pappo prostaglandin synthesis.[4]

Figure 29
Application of 9-BBN (Aldehyde Synthesis *via* Carbonylation)

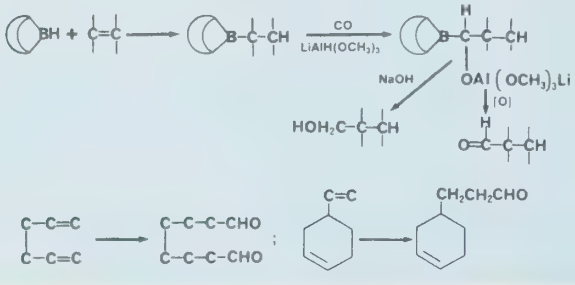


Figure 30
Application of 9-BBN (Aldehyde Synthesis *via* Carbonylation)

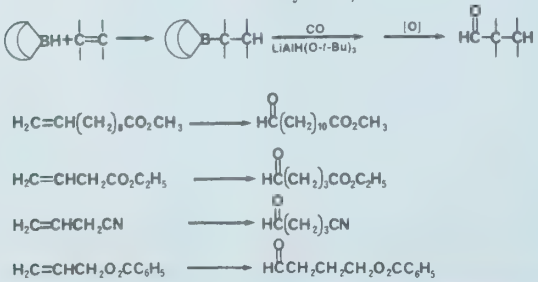


Figure 31
Application of 9-BBN (Alkylation and Arylation)

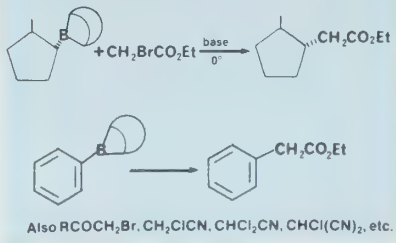


Figure 32
Application of Borinane (Free Radical Reactions)

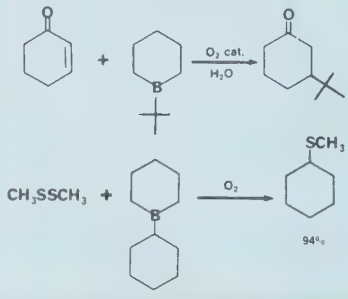


Figure 33
Application of Catecholborane (Synthesis of Monoalkylboranes)

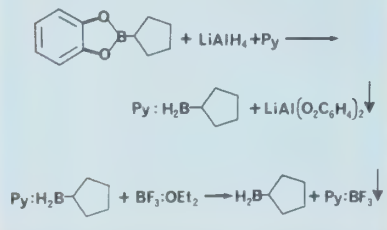
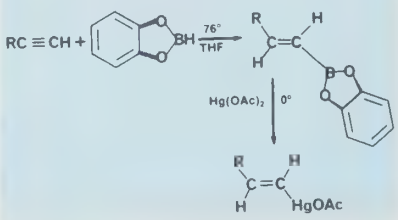
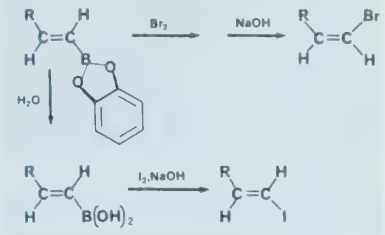


Figure 34
Application of Catecholborane (Vinyl Mercurials)



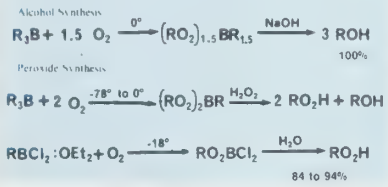
The B-vinylcatecholborane derivatives are readily transformed into the corresponding vinyl halides. The reactions can be directed to achieve the replacement of the boronic acid grouping either with inversion or with retention[4] (Fig. 35). This reaction has also been utilized in a prostaglandin synthesis.[4]

Figure 35
Application of Catecholborane (Vinyl Halides)



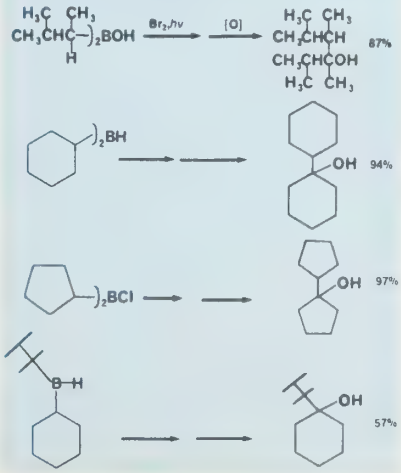
The synthesis of peroxides from organoboranes can be improved by utilizing the alkyldichloroborane etherate (Fig. 36). This avoids loss of one of the three alkyl groups and the need to separate the peroxide from the accompanying alcohol.[2,4]

Figure 36
Application of Dichloroborane (Synthesis of Peroxides)



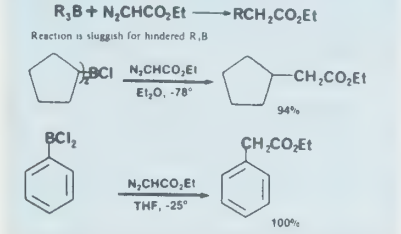
Dialkylborinic acids are especially valuable as intermediates in the α-bromination reaction (5-Q). While a few dialkylboranes (*e.g.*, disiamylborane, dicyclohexylborane) are readily available through hydroboration, many others are not. Fortunately, chloroborane provides a simple route to such borinic acids, as illustrated for the synthesis of dicyclopentylchloroborane and its conversion to 1-cyclopentylcyclopentanol in 97% yield[2,4] (Fig. 37).

Figure 37
Application of Chloroborane (α-Bromination)



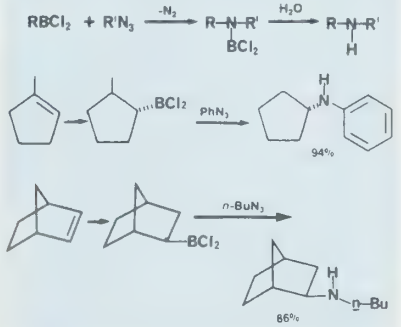
The greater acid strength of the R_2BCl and $RBCl_2$ derivatives over the parent R_3B compounds greatly facilitates the reactions with diazo derivatives and makes it possible both to extend the reaction to hindered groups and to achieve a higher utilization of the groups[2-4] (Fig. 38).

Figure 38
Application of Chloroborane (Hooz Reaction)



The related reaction with alkyl or aryl azides provides a stereospecific route to secondary amines (Fig. 39).

Figure 39
Application of Chloroborane (Reaction with Organic Azides)



The hydroboration of acetylenes with chloroborane provides a direct route to the dialkenylborinic acids and greatly facilitates the Zweifel synthesis of cis,trans-dienes[4] (Fig. 40).

The power of these new methods is illustrated by their utilization for the stereospecific synthesis of aziridines[4] (Fig. 41). In this synthesis the stereochemistry of the two centers of the ethylenimine ring can be controlled as well as that of the R′ group attached to the nitrogen atom.

The ready availability of the borinic acid derivatives through selective hydroboration to the dialkylborane or through reaction with chloroborane can be combined with the base-induced reaction with dichloromethyl methyl ether (DCME) (5-O) to provide a versatile, new synthetic route to ketones (Fig. 42).

7. CONCLUSION

The facile hydroboration of olefins was discovered in 1956. For the next decade we were engaged primarily in the study of this fascinating new reaction. This reaction made the organoboranes readily available. Consequently, we then began to shift our emphasis from the study of hydroboration to a study of the chemistry of organoboranes.

This proved to be an extraordinarily rich, albeit largely virgin, unexplored area.

Figure 40
Application of Chloroborane (Zweifel Diene Synthesis)

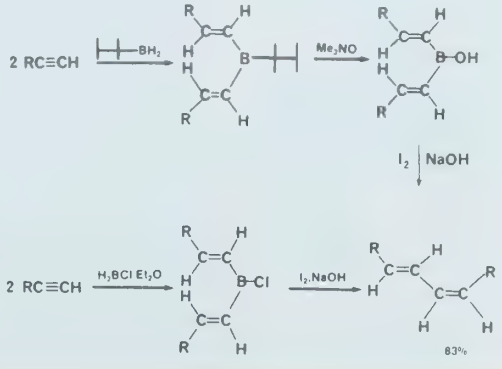


Figure 41
Application of Chloroborane (Stereospecific Synthesis of Aziridines)

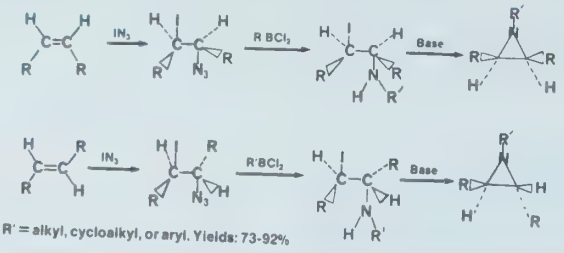
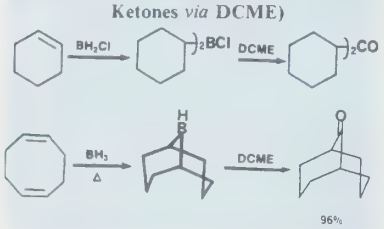


Figure 42
Application of Chloroborane (Synthesis of Ketones *via* DCME)



In this lecture I could present only a part of the remarkable chemistry of the organoboranes that we and others have uncovered. Clearly, these developments will have a major impact on synthetic organic chemistry. The problem is how to transmit this information to the workers in the field who hesitate to utilize organoboranes because of their inexperience with them.

One approach I have taken is to write a book, "Organic Syntheses *via* Boranes," which will give a) reviews of the chemistry, b) detailed procedures for the various syntheses, and c) a detailed description of the laboratory techniques. A second approach has been to persuade Dr. Alfred R. Bader of the Aldrich Chemical Company to set up a subsidiary, Aldrich-Boranes, Inc., to make readily available the basic chemicals and intermediates and certain specialized pieces of apparatus to facilitate application of these new methods by chemists.

Before us lies the utilization of these methods for the synthesis of complex molecules, such as natural products and pharmaceuticals. Before us lies the exploration of the applicability of this chemistry for the synthesis of fine chemicals. Before us lies the exploration of the utility of this chemistry in the petrochemical area.

But this is only the beginning. Before us also lies the exploration of the reaction mechanisms involved in the remarkably clean reactions of the organoboranes. The spectroscopy of organoboranes is in its infancy. Structural effects have yet to be explored systematically.

Clearly it will require another generation of chemists to conquer fully this new continent.

References*

*It appears impractical to give the individual references for the many items covered in this lecture. The books and reviews referred to provide a ready means for obtaining more detailed information and literature references.

1) H.C. Brown, "Hydroboration," W.A. Benjamin, Inc., New York, N.Y., 1962.
2) H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972.
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6) H.C. Brown, *Chem. Brit.*, 7, 458 (1971).
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Trialkylborohydrides as New Versatile Reducing Agents in Organic Synthesis

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INTRODUCTION

Addition compounds of lithium hydride and sodium hydride with trialkylboranes were first discovered in the course of War Research in the period of 1942-45 at the University of Chicago by Professor H.C. Brown, the late Professor H.I. Schlesinger with their coworkers[1] (eq 1 and 2).

$$LiH + B(CH_3)_3 \longrightarrow Li(CH_3)_3BH \quad \text{(eq 1)}$$

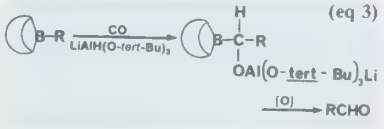
$$NaH + B(C_2H_5)_3 \longrightarrow Na(C_2H_5)_3BH \quad \text{(eq 2)}$$

However, relatively little research was devoted to these derivatives. A brief study indicated that lithium triethylborohydride is a stronger reducing agent than the parent compound, lithium borohydride.[2] There was no reason to anticipate that these compounds would possess highly useful properties. However, developments within the past two years at Purdue University have altered this situation. This review summarizes the discovery of the exceptional properties of trialkylborohydrides, the various methods that have been developed for the synthesis of trialkylborohydrides and their utility in organic synthesis.

THE DISCOVERY OF EXCEPTIONAL PROPERTIES OF LITHIUM TRIETHYLBOROHYDRIDE (SUPER HYDRIDE®)[3]

The author may be permitted to describe how an unusual experimental observation, noticed in the exploratory program dealing with the carbonylation of organoboranes led to the discovery of exceptional characteristics of lithium triethylborohydride.

Lithium tri-*tert*-butoxyaluminohydride is a very mild reducing agent, stable indefinitely in tetrahydrofuran at 25°. However, we observed a puzzling feature in applying this reagent to the carbonylation of B-alkyl-9-BBN derivatives (to give the corresponding homologated aldehydes)[4] (eq 3).



(eq 3)

To obtain a good yield, it was important that the reagent be added concurrently with the uptake of carbon monoxide. If the reagent was added to the organoborane prior to the introduction of carbon monoxide, the yield of the aldehyde decreased sharply.

Investigation soon revealed that the addition of an equimolar amount of triethylborane to a 0.5 *M* solution of lithium tri-*tert*-butoxyaluminohydride (LTBA) resulted in a very rapid loss of hydride, 72% of the active hydride disappearing in 5 min.[3] Upon hydrolyzing the reaction mixture, an equivalent quantity of 1-butanol was found. A catalytic quantity of triethylborane was also effective. The reactions were essentially complete in 3 hr (Figure 1). Thus, triethylborane induces a rapid, essentially quantitative reductive opening of the tetrahydrofuran ring at 25° (eq 4).

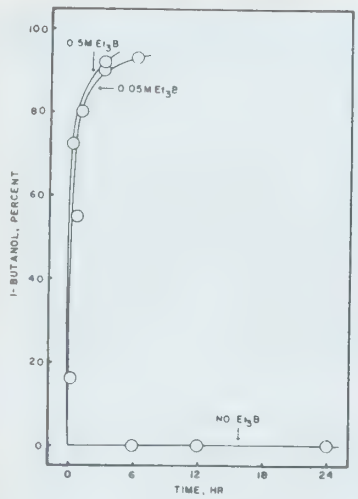
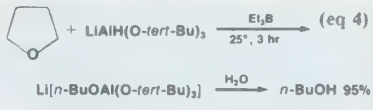


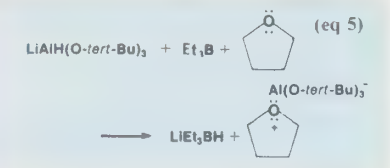
Figure 1. Reductive cleavage of tetrahydrofuran at 25° by lithium tri-*tert*-butoxyaluminohydride (0.5 *M*) in the absence and presence of triethylborane.



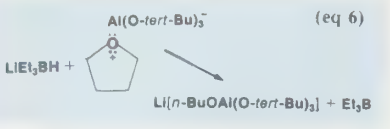
(eq 4)

Surprisingly, triethylborane fails to induce a similar reductive cleavage of THF by the otherwise more powerful reducing agent, lithium trimethoxyaluminohydride. The significance of this will be discussed later.

How could even trace quantities of triethylborane cause the mild reducing agent LTBA to open THF, impervious to the most powerful reducing agents previously known? Further research in this area indicated that the reaction proceeds through the formation of a new type of hydride, lithium triethylborohydride ($LiEt_3BH$), and possibly the hitherto unknown monomeric aluminum-*tert*-butoxide, an exceptionally powerful Lewis acid capable of coordinating with the oxygen atom of THF[5] (eq 5).



The highly active hydride reagent $LiEt_3BH$ then reacts (by displacement) with the polarized carbon-oxygen bond to open the ring and to regenerate triethylborane (eq 6).

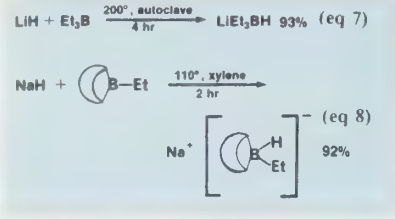


These investigations led us to believe that lithium triethylborohydride should possess enormous hydride transfer ability. Accordingly, we undertook a major new program to synthesize a variety of lithium trialkylborohydrides with different alkyl substituents and to study their chemistry. Because of their superior hydridic property, these are named "super-hydrides", a term truly representative of their activity.

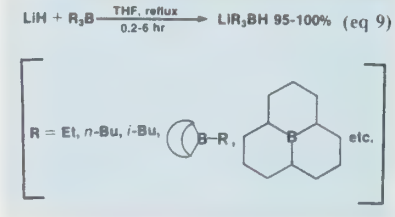
APPROACHES TO THE SYNTHESIS OF SIMPLE AND STERICALLY HINDERED TRIALKYLBOROHYDRIDES

As mentioned earlier, trialkylborohydrides were first prepared by Professor Brown and the late Professor Schlesinger at the University of Chicago.[1] In the period 1956-60, Dr. A. Khuri of our laboratory (a graduate student of Professor Brown) carried out a detailed study of the reactions of alkali metal hydrides (LiH and NaH) with trimethyl- and triethylboranes in a variety of ethereal solvents in vacuum lines.[2]

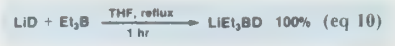
In 1968 Professor Köster and coworkers reported the synthesis of a variety of trialkylborohydrides and some of their properties.[6] Unfortunately, the majority of their reactions have been carried out neat or in aromatic hydrocarbon solvents requiring rather drastic reaction conditions (eq 7 and 8).



However, a systematic research directed towards the synthesis of various trialkylborohydrides in our laboratory, revealed that in tetrahydrofuran solvent lithium hydride reacts with a variety of simple organoboranes under mild conditions to give lithium trialkylborohydrides in quantitative yield[7] (eq 9).



Lithium hydride reacts quantitatively with triethylborane even at room temperature (24 hr). The corresponding deuterium derivatives are readily synthesized from lithium deuteride (eq 10).



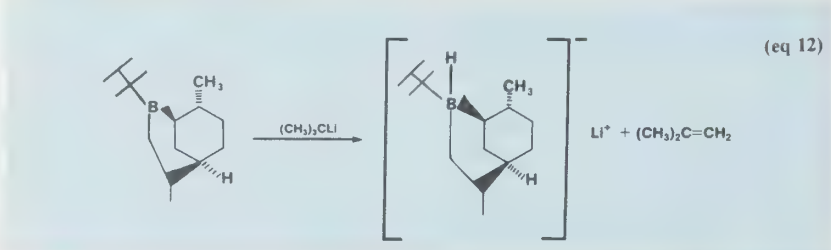
Unfortunately, with the hindered trialkylboranes such as tri-*s*-butylborane, we encountered a major synthetic difficulty. The reaction is very sluggish and incomplete (eq 11).

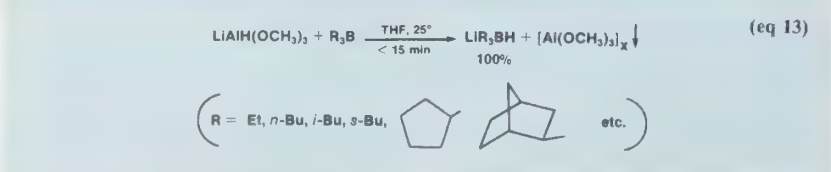
However, the preliminary experiments soon made it clear that the stereoselectivity achieved in the reduction of ketones with trialkylborohydrides increases remarkably with the steric bulk of the trialkylborane. Consequently, synthesis of highly hindered trialkylborohydrides was a necessity.

Professor Corey and coworkers also found that thexyllimonylborane[8a] (a hindered trialkylborane derived from limonene and thexylborane) fails to react with lithium hydride in THF.[8b] They circumvented the difficulty by using *tert*-butyllithium, which yields the corresponding trialkylborohydride (eq 12).

We were also actively exploring the methods for the synthesis of hindered trialkylborohydrides. Finally, after extensive research, we discovered that the addition of one mole equivalent of any trialkylborane (simple or hindered) to a THF solution of lithium trimethoxyaluminohydride (LTMA) at room temperature results in a facile and rapid displacement of aluminum methoxide to produce the corresponding lithium trialkylborohydride in quantitative yield[9] (eq 13). The reaction is highly general and aluminum methoxide does not interfere in the further reactions of LiR_3BH.

At that time Professor Charles A. Brown at Cornell University was uncovering many remarkable and unique characteristics of potassium hydride. For example, potassium hydride exhibits unprecedented reactivity toward weak organic acids, such as amines, sterically hindered alcohols, etc.[10] Further, he found that unlike lithium hydride and sodium hydride, potassium hydride

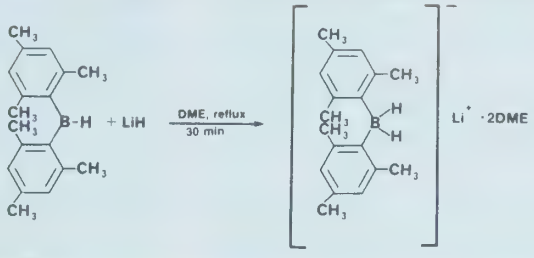




reacts rapidly and quantitatively with the hindered trialkylboranes, such as tri-*s*-butylborane, yielding the corresponding potassium trialkylborohydride under mild conditions[11] (eq 14).

$$KH + s\text{-}Bu_3B \xrightarrow[1\ hr]{THF,\ 25^\circ} K\ s\text{-}Bu_3BH \quad 100\% \quad \text{(eq 14)}$$

Recently Professor Hooz and coworkers have reported the synthesis of lithium dimesitylborohydride bis(dimethoxyethane)[12] (eq 15).

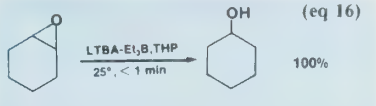


(eq 15)

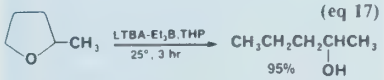
The discovery of the hydroboration reaction in 1956 has made possible the synthesis of organoboranes with a wide variety of structures.[13] These can now be readily converted to the corresponding trialkylborohydrides and dialkylborohydrides.

REDUCTIVE CLEAVAGE OF CYCLIC ETHERS[3]

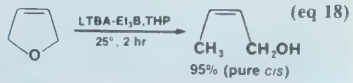
The lithium tri-*tert*-butoxyaluminohydride-triethylborane system, discussed earlier, has been found to be one of the most active reagents currently available for the reductive cleavage of cyclic ethers. To our knowledge, no reducing system currently available is capable of achieving the reductive cleavage of THF so rapidly and cleanly. Both monoglyme (MG) and tetrahydropyran (THP) dissolve the LTBA-Et_3B system. At 25° monoglyme yields 47% 2-methoxyethanol. However, the reductive cleavage of THP is very slow as we observed only 17% of 1-pentanol after 24 hr. Consequently, we used this as the solvent for the following interesting synthetic transformations (eqs 16-19).



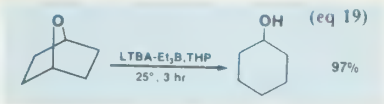
(eq 16)



(eq 17)



(eq 18)



(eq 19)

LITHIUM TRIETHYLBOROHYDRIDE AS A SUPERNUCLEOPHILE. FACILE DEHALOGENATION OF ALKYL HALIDES[14]

Lithium triethylborohydride has been found to be an extraordinarily powerful reducing agent, far more powerful than lithium aluminum hydride and lithium borohydride, as revealed by the rates of reduction of *n*-octyl chloride represented graphically in Figure 2. Further, kinetic studies reveal that the reagent is considerably more powerful than nucleophiles such as thiophenoxide and alkyl mercaptides, previously considered to be the most powerful simple nucleophiles available for S_N2 displacements (eq 20).

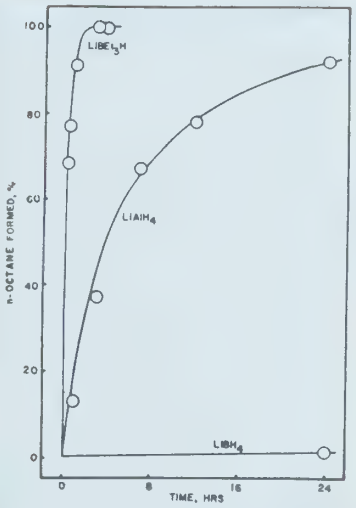


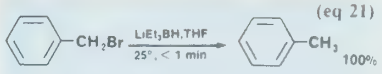
Figure 2. Rates of reduction of *n*-octyl chloride (0.25 *M*) with representative complex metal hydrides (0.5 *M*) in tetrahydrofuran at 25°.

$$\frac{k_{(Et_3BH)^-}}{k_{(C_6H_5S)^-}} = 20 \qquad \text{(eq 20)}$$

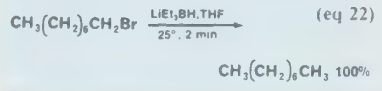
$$\frac{k_{(Et_3BH)^-}}{k_{(NO_3)^-}} = 10^7$$

$$\frac{k_{(Et_3BH)^-}}{k_{(BH_4)^-}} = 10^4$$

The reaction exhibits typical characteristics of a nucleophilic displacement of the S_N2 type. Simple primary alkyl bromides and allylic and benzylic bromides are reduced almost instantly (eq 21 and 22).

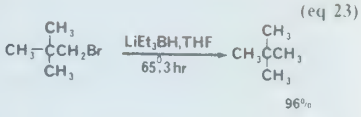


(eq 21)

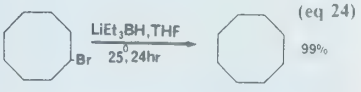


(eq 22)

Super Hydride® reduces cleanly and with remarkable ease, even neopentyl bromide and cycloalkyl bromides which are highly resistant to S_N2 displacement reactions (eqs 23 and 24).



(eq 23)



(eq 24)

Lithium triethylborodeuteride provides a simple means of introducing deuterium with clean stereochemical inversion at the substitution center (eq 25).

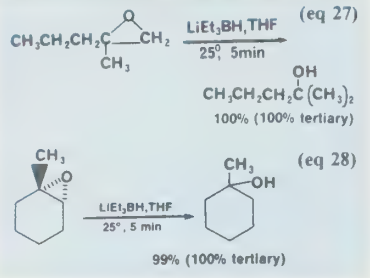
(eq 25)

Unlike lithium aluminum hydride,[15] Super Hydride® is inert toward aryl halides and should therefore be valuable for the reduction of alkyl halides without simultaneous attack on aromatic halogen (eq 26).

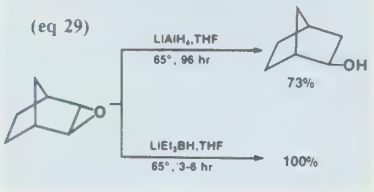
$$ArX \xrightarrow{LiEt_3BH,THF} \text{no reaction} \qquad \text{(eq 26)}$$

REGIOSPECIFIC AND STEREOSPECIFIC REDUCTION OF HINDERED AND BICYCLIC EPOXIDES[16]

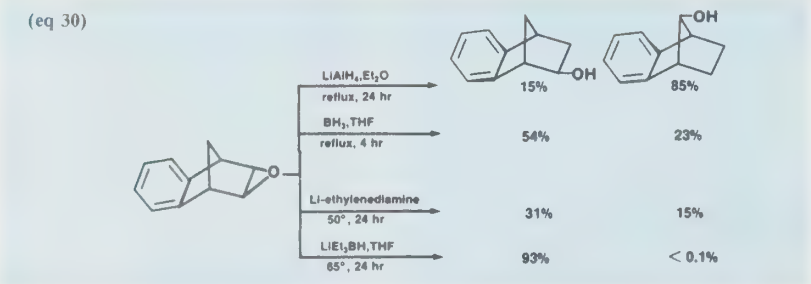
Lithium triethylborohydride in THF possesses remarkable ability for the facile, regiospecific and stereospecific reductive opening of epoxides to give the Markovnikov alcohol in excellent isomeric purity. The reaction is very general, applicable to epoxides with a wide range of structural features. Simple mono-, di- and trisubstituted epoxides are completely reduced in 2-5 min with this reagent, yielding the more substituted of the two possible isomeric alcohols in 100% isomeric purity (eq 27 and 28).



Such reactions are far faster and cleaner than those involving lithium aluminum hydride, Li-ethylenediamine, etc. (eq 29).



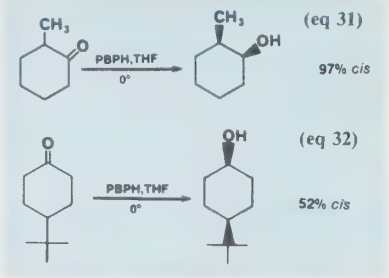
The advantage of Super Hydride® is especially evident in the reduction of labile bicyclic epoxides. Thus, benzonorbornadiene oxide which invariably gives rearranged products with conventional reducing agents undergoes facile reduction with Super Hydride® yielding 93% of *exo*-benzonorbornenol in > 99.9% isomeric purity (eq 30).



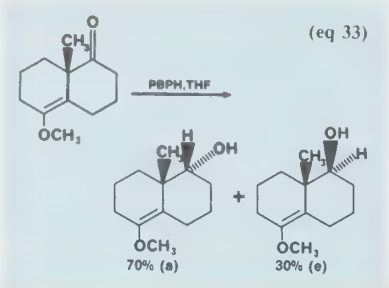
The high regio- and stereospecificity of the reaction, especially with the labile epoxides, enable us to use this reaction as a chemical tool to determine precisely the stereochemistry of epoxidation of such labile bicyclic olefins.[17]

ENZYME-LIKE STEREOSELECTIVE REDUCTION OF KETONES

One of the remarkable features of the trialkylborohydrides is their unusual ability to introduce steric control into the reduction of cyclic ketones. This ability was first recognized in our laboratory with lithium perhydro-9b-boraphenalyl hydride (PBPH).[18] Reduction of ketones with trisubstituted borohydride proceeds rapidly even at -78° and the yields of the corresponding alcohols are quantitative[19] (eq 31 and 32).



The discovery was quite timely as demonstrated by its immediate application in one of the stereoselective syntheses by Professor Ireland[20] (eq 33).

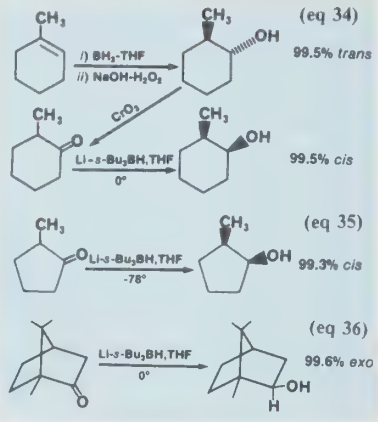


Conventional reducing agents gave only the more stable equatorial isomer.

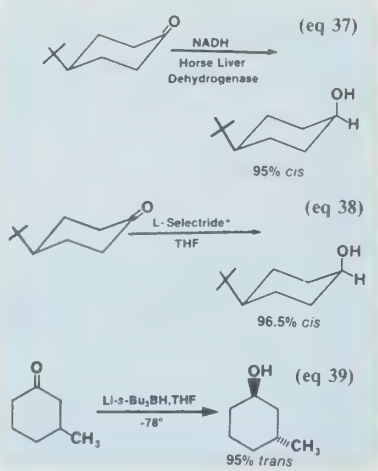
These results stimulated our further interest in this area. Consequently, we undertook examination of the influence of the steric bulk of the trialkylborohydride on the stereoselectivity of the ketone reduction.[21] For example, examination of $LiEt_3BH$, Li-*n*-Bu_3BH and Li-*i*-Bu_3BH clearly revealed that, unlike lithium trialkoxyaluminohydrides, increasing the size of the alkyl substitution on boron enhances the stereoselectivity (towards the less stable isomer). It appeared that a more hindered trialkylborohydride might improve the stereoselectivity.

Indeed our prediction became a reality when we first synthesized lithium tri-*s*-butylborohydride (L-Selectride®), the first simple and highly hindered trialkylborohydride.[9] It exhibits essentially an enzyme-like stereoselectivity in the reduction of cyclic and bicyclic ketones, unequalled by any other previously known reducing agents.

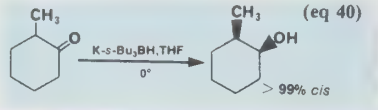
Hindered ketones, such as 2-methylcyclohexanone, 2-methylcyclopentanone, camphor, etc., are reduced rapidly and quantitatively with this new reagent, with over 99.5% stereoselectivity to the corresponding less stable epimers. The new reagent coupled with hydroboration-oxidation provides the synthesis of both the isomeric alcohols in high stereochemical purity (eqs 34-36).



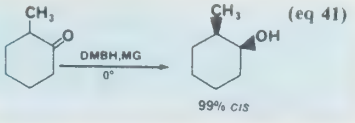
Even ketones with an alkyl group relatively remote from the reaction center, such as 3- and 4-alkylcyclohexanones, are predominantly (>90%) reduced from the equatorial side. The remarkable effectiveness of this reagent is demonstrated by the higher selectivity observed with L-Selectride® than with an enzyme in the reduction of 4-*tert*-butylcyclohexanone[22] (eqs 37-39).



The corresponding potassium derivative (K-Selectride®) prepared by Professor Charles A. Brown is equally effective for stereoselective reductions[11] (eq 40).



Recently, Professor Hooz and coworkers have reported that lithium dimesitylborohydride bis(dimethoxyethane) complex (DMBH) also reduces cyclic ketones with exceptionally high stereoselectivity comparable to that of the Selectrides®[12] (eq 41).

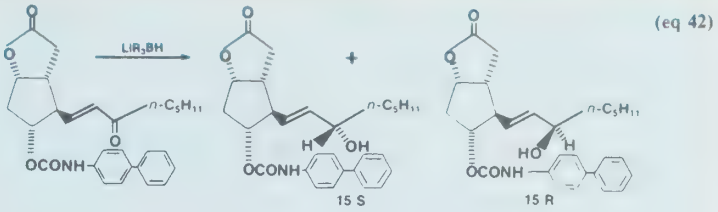


(eq 41)

Interestingly, unlike the trialkylborohydrides, this reagent reacts very sluggishly with hindered ketones such as camphor.

APPLICATIONS OF HINDERED TRIALKYLBOROHYDRIDES IN PROSTAGLANDIN SYNTHESIS

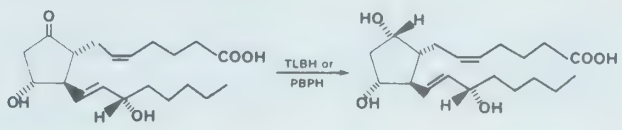
Many of these hindered trialkylborohydrides are finding attractive applications in the stereoselective synthesis of prostaglandins, where the use of other known reducing agents has failed. Professor Corey and coworkers first initiated work in this area by their elegant application of lithium thexyllimonylborohydride (TLBH) to the stereoselective reduction of the C_{15} carbonyl group;[8b] later this was remarkably improved by utilizing an exogenous directing group[23] (eq 42). It should be noted that the use of $NaBH_4$ or $Zn(BH_4)_2$ leads to a 1:1 mixture of 15S and 15R alcohols.



(eq 42)

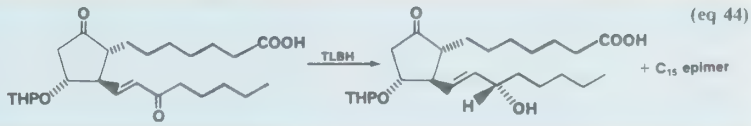
LiR_3BH	15S/15R
TLBH	92/8
L-Selectride®	89/11

Further, the stereoselective conversion of prostaglandin E_2 to $F_{2\alpha}$ has been achieved using TLBH and PBPH. No $F_{2\beta}$ could be detected[24] (eq 43).



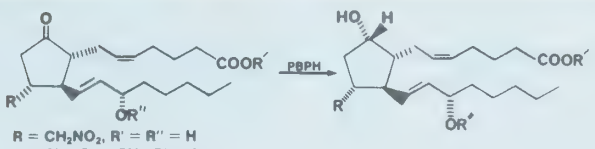
(eq 43)

Drs. Miyano and Stealey have selectively reduced C_{15} carbonyl without affecting the C_9 carbonyl group in the total synthesis of prostaglandin E_1[25] (eq 44).



(eq 44)

Dr. Weiss and coworkers have extensively utilized PBPH for stereoselective synthesis of various prostaglandin intermediates, especially 11-substituted derivatives of 11-deoxyprostaglandin $F_{2\alpha}$[26,27] (eq 45).

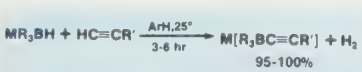


(eq 45)

R = CH_2NO_2, R' = R'' = H
R = CH_3, R' = CH_3, R'' = Ac
R = $CH{=}CH_2$, R' = R'' = H
R = H, R' = R'' = H
R = $CONH_2$, R' = CH_3, R'' = Ac

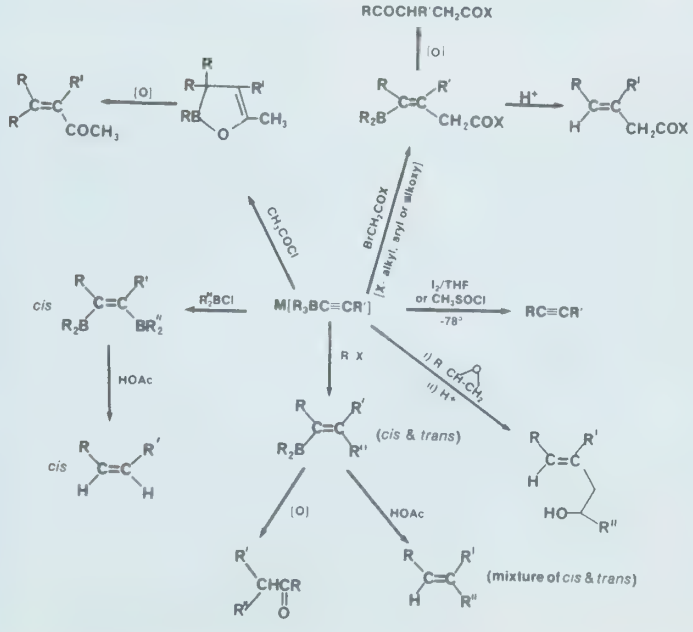
TRIALKYLALKYNYLBORANATES. VERSATILE INTERMEDIATES FOR THE SYNTHESIS OF CARBON STRUCTURES

Alkali metal trialkylborohydrides react rapidly and quantitatively with terminal acetylenes to yield the alkali metal trialkylalkynylboranates[28] (eq 46).



M = Li, Na, R' = alkyl or aryl
M = K, R' = H, alkyl or aryl (eq 46)

SCHEME I



These are highly versatile intermediates for the synthesis of carbon structures (Scheme I). Preliminary experiments indicate that it should be possible to synthesize functionalized alkynyl-"ate" complexes.[29]

CONCLUSION

In 1971 we first recognized the exceptional characteristics of trialkylborohydrides, especially lithium triethylborohydride.[30] Since then, further research in our laboratory and elsewhere has led to the synthesis of a number of trialkylborohydrides with different structural features and their application to organic synthesis. All prove to be highly active nucleophilic selective reducing agents. Many of these derivatives possess extremely attractive properties, such as the reduction of cyclic ketones with enzyme-like stereoselectivity. Research underway in our laboratory is leading to the discovery of many more attractive uses for these new reagents in organic synthesis.[31] In addition to their reducing properties, we are discovering certain new aspects of these reagents, useful for the regio- and stereoselective synthesis of carbon structures.[32] These new, exciting developments will be reviewed later. Finally, it should be pointed out that we are only in the beginning of the exploration of a vast new area of synthetic and theoretical interest. Continued research in this area together with the understanding of the structure-reactivity relationship should facilitate the development of highly specific reducing agents, similar to the enzymes developed by Nature, to achieve highly specific biological transformations.

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation and profound gratitude to Professor Herbert C. Brown of Purdue University for his advice, guidance and encouragement, under whose supervision most of this work was accomplished. The author also wishes to express his appreciation and thanks to Professor Charles A. Brown and Mr. S.C. Kim for stimulating and helpful discussions. The generous financial support of the U.S. Army Research Office (Durham) North Carolina (Grant Nos. DA-ARO-D-31-124-73-G1 and DA-ARO-D-31-121-73-G148) is gratefully acknowledged.

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Sodium Cyanoborohydride: A Highly Selective Reducing Agent

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The synthetic organic chemist, faced with the need to prepare compounds of ever-increasing complexity, has had the problems confronting him greatly simplified by the development of numerous selective reducing agents.[1,2] Reagents that are capable of reducing a given functional group in the presence of various other sensitive functional groups have been prepared by modifying the reducing power of complex metal hydrides. For example, substituted borohydrides are a particularly successful modification. The steric and electronic effects of the substituents greatly influence the reactivity of the borohydride ion.[3] Thus, sodium cyanoborohydride with its strongly electron-withdrawing cyano group is a milder and more selective reducing agent than sodium borohydride.

The initial exploratory work on the utility of an alkali metal cyanoborohydride as a reducing agent resulted in almost totally negative results. Of all the functional groups studied, only aldehydes were reported to have been reduced.[4] Fortunately, the reagent was not forgotten and recent investigations have shown that, under the proper conditions, sodium cyanoborohydride is an extremely useful reagent for the selective reduction of organic functional groups.

PHYSICAL PROPERTIES

Sodium cyanoborohydride is highly soluble in a variety of solvents including water, alcohols, amines, and tetrahydrofuran (THF) but is insoluble in hydrocarbons. Complete solubility data are summarized in Table I.

The $NaBH_3CN$ available from the Aldrich Chemical Company is of sufficient purity for most applications. However, if ultra-pure material is required, one of the following purification procedures should be used. The $NaBH_3CN$ is dissolved in THF (20%w/v), filtered and reprecipitated by a four-fold volume of methylene chloride.[5] The $NaBH_3CN$ is then collected and dried *in vacuo*. Alternatively, the $NaBH_3CN$ is dissolved in dry nitromethane and filtered, and the filtrate is poured into a ten-fold volume of carbon tetrachloride with vigorous stirring.[6] The white precipitate of $NaBH_3CN$ is filtered, washed several times with carbon tetrachloride and dried *in vacuo*. A third method for the purification of $NaBH_3CN$ involving precipitation and recrystallization of the dioxane complex has been reported in detail by Borch and coworkers.[7]

Solvent-free $NaBH_3CN$ is a white amorphous powder, m.p. 240-242° (dec.). Contact with air should be kept to a minimum because $NaBH_3CN$ is very hygroscopic.

CHEMICAL PROPERTIES

1. Hydrolysis

The utility of $NaBH_3CN$ as a reducing agent is greatly enhanced by its stability in acid to pH 3.[8] The hydrolysis of $NaBH_3CN$ is acid-catalyzed. However, its rate of hydrolysis is 10^{-8} times that of $NaBH_4$.[9] The

$$BH_3CN^- + 3H_2O \xrightarrow{12N\ HCl} B(OH)_3 + CN^- + 3H_2 \qquad (1)$$

decomposition of $NaBH_3CN$ in water at pH 7 as measured by hydrogen evolution at concentrations from 10^{-3} to $0.3M$ is less than 0.5 mole % after 24 hr.[6] In $12N$ hydrochloric acid, relatively rapid hydrolysis occurs (eq 1).[6]

Table I. Solubility of $NaBH_3CN$[a]

Solvent	Temp., °C	Solubility, g/100g solvent
THF	28	37.2
	46	41.0
	62	42.2
Water	29	212
	52	181
	88	121
Methanol	25	Very soluble
Ethanol	25	Slightly soluble
Diglyme	25	17.6
Isopropylamine	25	Slightly soluble
Diethyl ether	25	Insoluble
Benzene	25	Insoluble
Hexane	25	Insoluble

[a]Data taken from Ref. 5.

The acid stability of $NaBH_3CN$ has resulted in numerous applications of this reagent that would not be possible with $NaBH_4$ (*vide infra*). For example, $NaBH_4$ can be used to trap carbonium ions formed in the ionization of readily ionizable organic halides in an aqueous diglyme solution.[10] The rate of solvolysis would, of course, be enhanced by the presence of acid, but this would also rapidly destroy the $NaBH_4$. This serious limitation is not present with $NaBH_3CN$, which has been used to trap carbonium ions generated with hydrogen chloride in aqueous THF.[11]

The addition of one equivalent of hydrogen chloride to a solution of $NaBH_3CN$ in THF results in incomplete hydrolysis with the formation of cyanoborane, which was postulated to exist in THF as the $BH_2CN{\cdot}THF$ complex (eq 2).[12] The addition of amines to this solution has been used for the preparation of various amine-cyanoborane adducts.[13,14] This procedure appears generally useful for the synthesis of donor-cyanoborane complexes. If diethyl ether is used as the solvent instead of THF, then various polymeric forms of cyanoborane are formed.[15]

$$NaBH_3CN + HCl \xrightarrow{THF} BH_2CN{\cdot}THF + NaCl + H_2 \quad (2)$$

Measurement of the volume of hydrogen evolved upon complete hydrolysis in aqueous acid can be used for the quantitative analysis of sodium borohydride.[16] However, this procedure cannot be used conveniently to analyze $NaBH_3CN$ due to its slow rate of hydrolysis even in aqueous acid. Iodometric titration has been used to determine the purity of $NaBH_4$[17] and $NaBH_3CN$.[7,9] The half-reaction for this redox reaction is as shown (eq 3).[6]

$$BH_3CN^- + 3H_2O \longrightarrow B(OH)_3 + CN^- + 6H^+ + 6e^- \quad (3)$$

2. Exchange

At pH 3, the hydrogens of BH_3CN^- can be readily exchanged for either deuterium or tritium,[8] thus permitting the direct synthesis of $NaBD_3CN$ and $NaBH_3CN$-*t*.[7] When D_2O is used, the rate of exchange is about 15 times as fast as the rate of hydrolysis.[9] In the case of $NaBH_4$, hydrolysis competes with exchange so that exchange is barely detectable.

Recent experimental results have shown that as the solvent becomes more basic, the ratio of the exchange rate to the hydrolysis rate becomes greater.[18] For example, the ratio k_{ex}/k_{hy} is equal to 34 in pure water while in 4:1 DMSO-water, the ratio is equal to 374.

3. Industrial Applications

The reducing properties of alkali metal cyanoborohydrides have led to a number of interesting industrial applications. Lithium cyanoborohydride has been used to cure a liquid nitrile polymer[19] and a polymer made from an aliphatic mercaptan and a conjugated diene.[20] Cyanoborohydrides have been used for the reductive bleaching of groundwood pulp, sulfate pulp and chemigroundwood pulp without corrosion of the equipment.[21] Finally, chemical metal plating baths have been described where a cyanoborohydride is used as the reducing agent[22] or as an additive to improve the stability and efficiency of the chemical plating solution.[23]

4. Transition Metal Complexes

The cyanoborohydride ion can act as a ligand for transition metal complexes, and the preparation, structure, physical properties and spectra of a number of these complexes have been described. Complexes have been reported where the transition metal is copper,[24-30] silver,[24,26] nickel,[24,27,30] cobalt,[27,30] ruthenium,[31] rhodium,[27,32,33] or iridium.[27,32]

The synthesis of these complexes is quite simple. For example, a copper complex is readily prepared by adding an ethanol solution of $NaBH_3CN$ to a chloroform solution of $(Ph_3P)_3CuCl$.[24] On standing, this solution develops colorless crystals of $(Ph_3P)_3Cu(NCBH_3)$.

A systematic investigation of the chemical properties of these transition metal cyanoborohydride complexes has not been undertaken. These complexes may show interesting and useful characteristics for the reduction of organic functional groups. For example, aromatic nitro groups are normally inert to $NaBH_4$ but are readily reduced to amines in the presence of $(Ph_3P)_3NiCl_2$.[34] This process may be more complicated but it could involve an intermediate nickel borohydride complex.[35]

SELECTIVE REDUCING PROPERTIES

Sodium cyanoborohydride is a versatile reagent that will reduce a variety of organic functional groups with remarkable selectivity. For example, many selective reductions have resulted from the observation that an imminium ion (**I**) is reduced much faster than a carbonyl group (eq 4).[7,8]

$$>C{=}O + HN< \rightleftharpoons >C{=}\overset{+}{N}< \xrightarrow[\text{fast}]{NaBH_3CN} HC{-}N<$$

I

$$\xrightarrow[\text{very slow}]{NaBH_3CN} HC{-}O{-}B \quad (4)$$

Also, the stability of $NaBH_3CN$ in protic solvents at low pH has allowed reductions under conditions that would rapidly hydrolyze $NaBH_4$. Finally, the solubility of $NaBH_3CN$ in polar aprotic solvents has further enhanced its utility as a reducing agent.

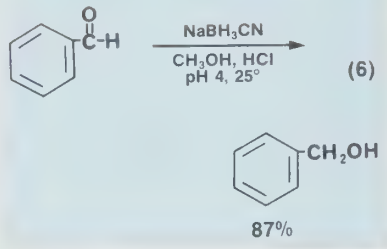
Sodium cyanoborohydride is a very selective reducing agent because, even under the diverse reaction conditions employed, many sensitive functional groups are not reduced. For example, amides, esters, lactones, nitriles, nitro compounds and epoxides are inert toward this reagent.

The various selective reductions will now be discussed in detail.

1. Reduction of Aldehydes and Ketones

Under neutral conditions in water or methanol, there is negligible reduction of aldehydes and ketones. However, at pH 3-4, the rate of reduction is sufficiently rapid to be synthetically useful.[7,36] Since the reduction consumes hydrogen ions (eq 5), a buffered system is required or acid must be added to maintain the necessary low pH.[7] Some specific examples are illustrated below (eq 6,7).[7]

$$3\dot{C}{=}O + BH_3CN^- + 3ROH + H^+ \longrightarrow 3H\dot{C}OH + B(OR)_3 + HCN \quad (5)$$



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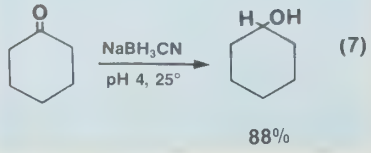
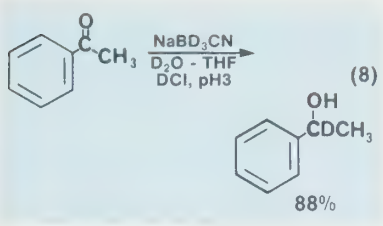


(7)

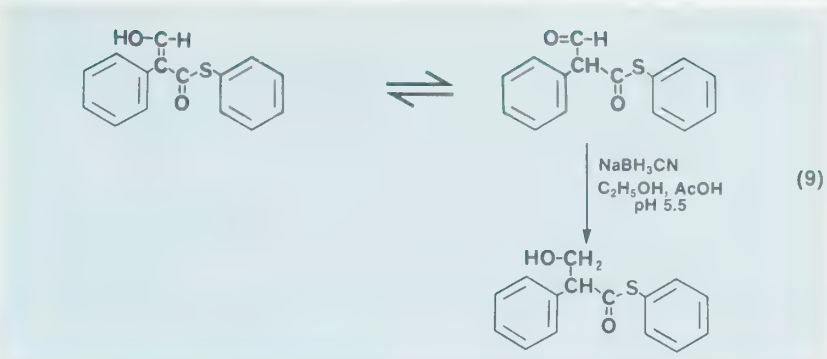
The reduction of cyclopentenone with $NaBH_3CN$ gives mainly cyclopentanol.[7] However, this may not be a general result for α,β-unsaturated systems. Recently, it was shown that, in the reduction of a series of conjugated ketones of the cholestenone type with $NaBH_3CN$ in THF, the major product was usually the corresponding allylic alcohol.[16]

For $NaBD_3CN$ reductions, the recommended solvent is THF-D_2O and the pH is maintained by adding a solution of DCl-AcOD in THF-D_2O.[7] High yields of deuterated alcohols are possible as shown in equation 8.



(8)

The mild conditions employed for these reductions with $NaBH_3CN$ should result in many applications for the selective reduction of aldehydes and ketones. Recently, a specific example was reported which showed that an aldehyde group can be selectively reduced with $NaBH_3CN$ in the presence of a thiol ester group (eq 9).[38]



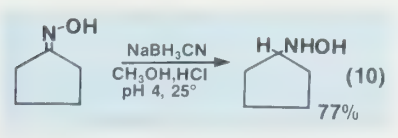
(9)

By changing the cation and solvent, it is possible to carry out an even more selective reduction. Thus, tetrabutylammonium cyanoborohydride in acidified hexamethylphosphoramide (HMPA) selectively reduces aldehydes in the presence of almost all other functional groups including cyano, ester, amido, nitro, and even the keto group.[39]

A recent patent disclosed that a new class of reducing agents can be prepared by the reaction of sodium cyanide with dialkylboranes in THF.[40] The resulting Na-[R_2BHCN] reagent was claimed to be useful for carbonyl reductions.

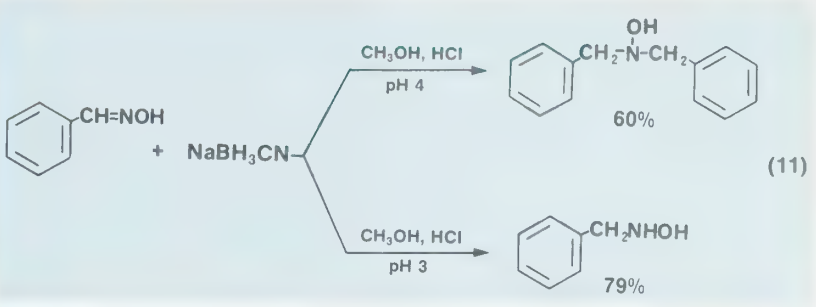
2. Reduction of Oximes

Under acid conditions, the reduction of a ketoxime proceeds smoothly to the corresponding *N*-alkylhydroxylamine with no trace of the amine which would result from overreduction (eq 10).[7]



(10)

The reduction of aldoximes is extremely pH-dependent. When the reduction is carried out at pH 4, the major product is the dialkylhydroxylamine, while at pH 3, the major product is the monoalkylhydroxylamine (eq 11).[7]



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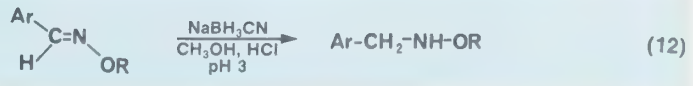

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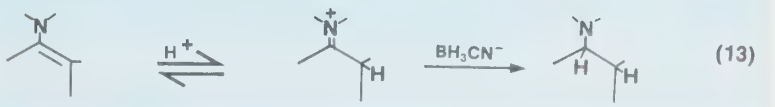

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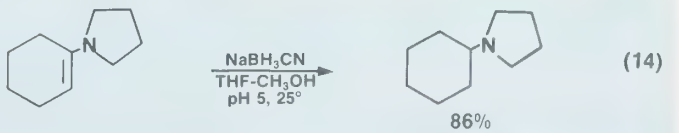


(14)

Reduction with $NaBH_3CN$ provides what is apparently the only known method for the conversion of *O*-alkylbenzaldoximes to the corresponding *N,O*-dialkylhydroxylamines (eq 12).[41]

The reduction of oximes with borane-THF provides an alternative method for the preparation of *N*-alkylhydroxylamines.[42] However, this procedure cannot be used to prepare *N,O*-dialkylhydroxylamines because reduction of oxime ethers[43] and oxime esters[43,44] with borane-THF proceeds readily to give the corresponding amines in excellent yields. Also, catalytic hydrogenation of arylketoximes gives amines,[45] while aldoximes afford *N,N*-disubstituted hydroxylamines[45] and *O*-alkylbenzaldoximes give benzyl and dibenzylamines.[46]

3. Reduction of Enamines

Although the enamine group should be resistant to reduction by $NaBH_3CN$, rapid and reversible protonation of the β-carbon generates a readily reducible imminium salt (eq 13).

Simple enamines are rapidly reduced by $NaBH_3CN$ at an initial pH of 5 in a 15:1 THF-methanol solvent mixture (eq 14).[7]

If the enamine is conjugated with a carbonyl group, the reduction becomes more difficult and acid must be added to maintain a pH of 4 (eq 15).[7]

4. Reductive Amination of Aldehydes and Ketones

Since the imminium ion is reduced much faster than a carbonyl group, it is possible to reductively aminate an aldehyde or ketone by simply reacting the carbonyl compound with an amine at pH 6-8 in the presence of $NaBH_3CN$ (eq 16).[7]

The reaction is general for ammonia, primary and secondary amines, all aldehydes, and unhindered ketones. Hindered and diaryl ketones fail to react and aromatic amines react somewhat sluggishly. Some interesting examples of reductive amination are given below along with isolated yields (eq 17-20).

The reductive amination process is not limited to the simple amines. The reaction of a ketone with hydroxylamine has been used to prepare the *N*-alkylhydroxylamines **II** and **III**.[7]

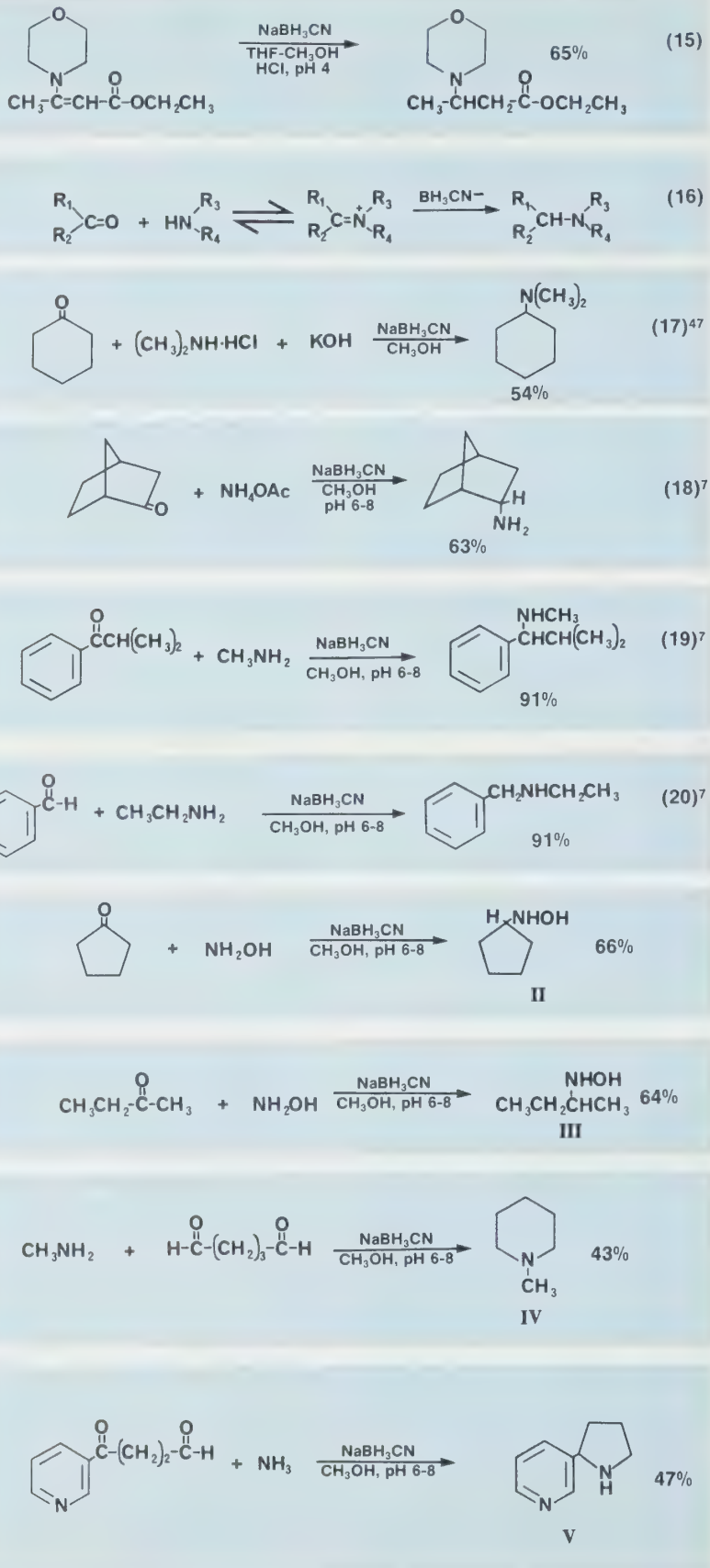
The reaction of a dicarbonyl compound with an amine in the presence of $NaBH_3CN$ provides an interesting new synthesis of nitrogen heterocycles, as illustrated in the preparation of compounds **IV**,[7] **V**,[7] **VI**,[48] and **VII**.[49]

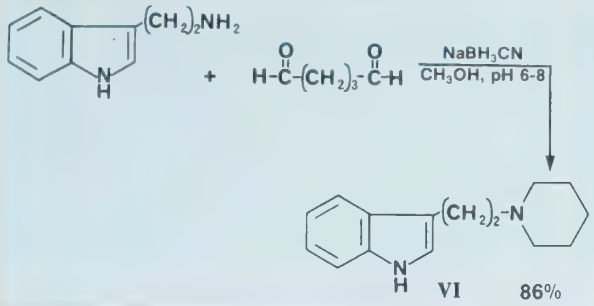
The mild conditions employed for these reductive aminations obviously indicate that numerous highly selective reductions should be possible. Recently, it has been shown that reductive amination with $NaBH_3CN$ can be used to prepare each of the following functionally substituted amines: aminoester (**VIII**),[7] aminoepoxide (**IX**),[50] and aminonitroxide free radical (**X**).[51] An unhindered ketone can be selectively aminated in the presence of a relatively hindered ketone to give the aminoketone (**XI**).[52] Finally, a selective amination of a formyllactone gave the aminolactone (**XII**).[53] This was then used as the key step in a convenient and high yield synthesis of the plant antifungal agent, tulipalin A (**XIII**).[54]

The reductive amination of substituted pyruvic acids provides a useful new synthesis of *dl*-α-amino acids (eq 21,22).[7] This procedure is apparently the most efficient and economical route for preparing ^{15}N-labelled amino acids (eq 23).[7]

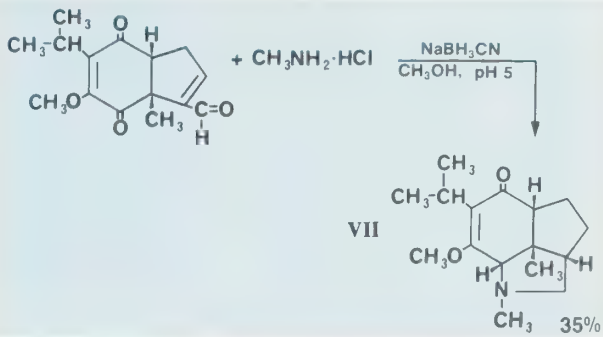
5. Reductive Alkylation of Amines and Hydrazines

A mild and efficient method for the synthesis of tertiary methylated amines has been developed that involves simply the reductive amination of formaldehyde.[55] The reaction of an aliphatic or aromatic amine with aqueous formaldehyde and $NaBH_3CN$ in acetonitrile results in excellent isolated yields of methylated amines (eq 24-27).

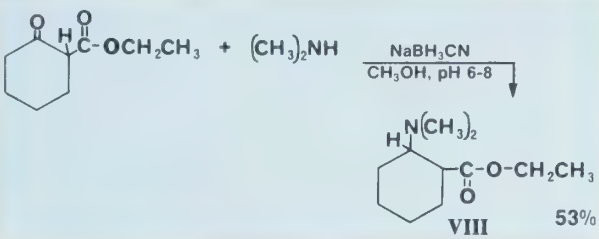




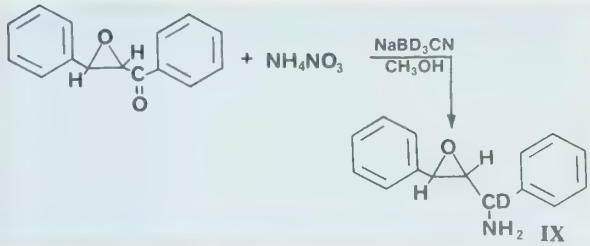
VI 86%



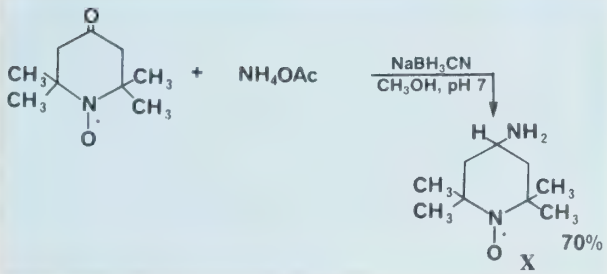
VII 35%



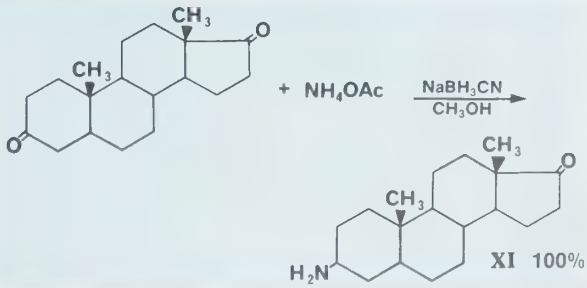
VIII 53%



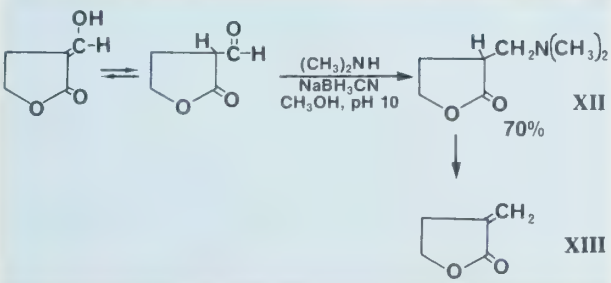
IX



X 70%

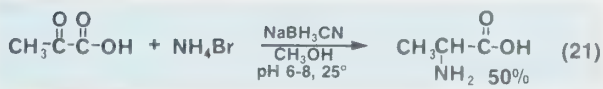


XI 100%



XII 70%

XIII



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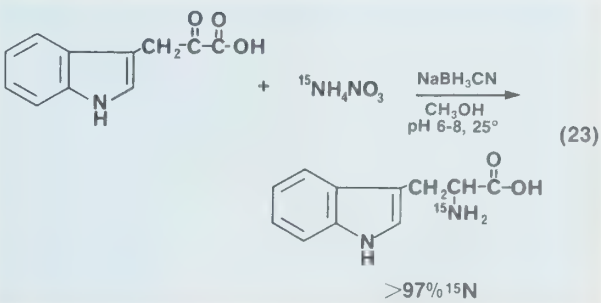
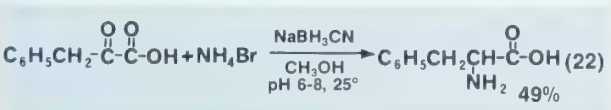


(23)

>97% ^{15}N



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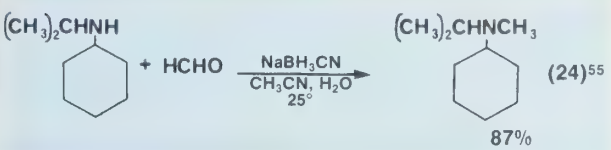

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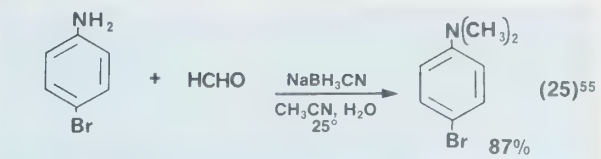

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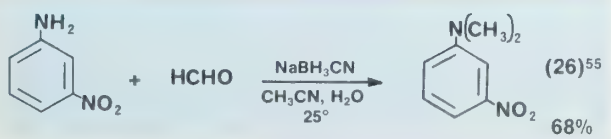

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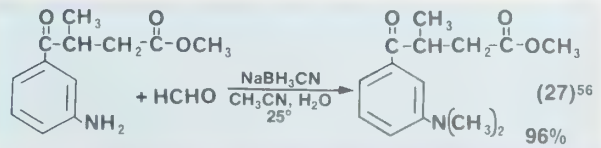
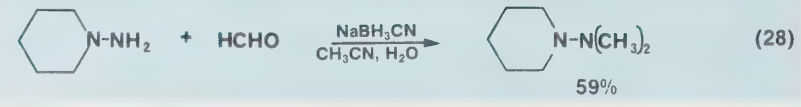


96% (27)[56]

The mild conditions, ease of experimental manipulation and the high yield of pure product appear to make this the method of choice for the reductive methylation of amines.

Hydrazines can also be reductively alkylated using $NaBH_3CN$ to provide a simple synthesis of some interesting tetraalkylhydrazines (eq 28-30).[57]



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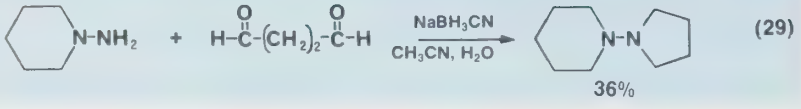

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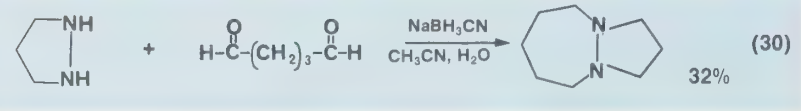
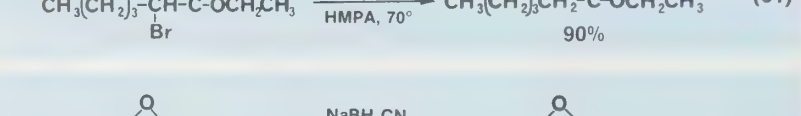


(30)

6. Reductive Displacement of Halides and Tosylates

Sodium cyanoborohydride in HMPA provides a rapid, convenient, and exceedingly selective system for the reductive removal of iodo, bromo and tosyloxy groups.[58,59] The following examples give an indication of the scope of this reductive displacement procedure (eq 31-33).

Primary alcohols may be converted by a simple two-step-in-one process to the corresponding hydrocarbons. The process involves conversion of the alcohol to the iodide with methyltriphenoxyphosphonium iodide in HMPA at room temperature followed by addition of $NaBH_3CN$ and stirring at 70°. Equations 34 and 35 illustrate this procedure.



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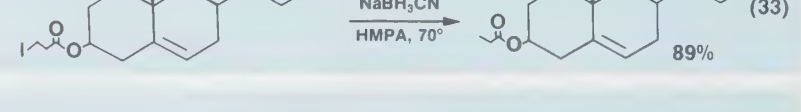

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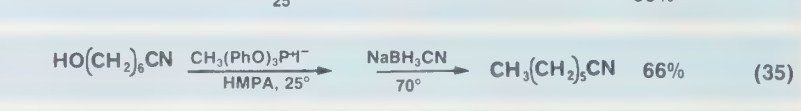

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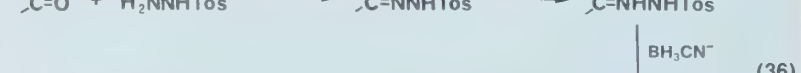


(35)

The superior selective feature of this reductive displacement reaction is demonstrated by its inertness toward almost all other functional groups including ester, amide, nitro, chloro, cyano, alkene and even such sensitive groups as epoxide, ketone, and aldehyde.[58] This selectivity becomes even more pronounced when tetrabutylammonium cyanoborohydride is used.[39]

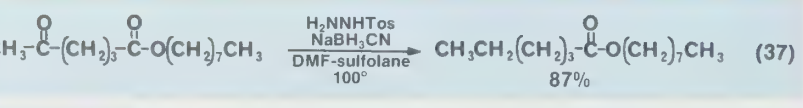
7. Deoxygenation of Aldehydes and Ketones

The propensity for $NaBH_3CN$ to reduce imminium ions has resulted in the development of still another useful synthetic reaction. The reduction of aliphatic ketone and aldehyde tosylhydrazones with $NaBH_3CN$ in acidic 1:1 DMF-sulfolane provides a mild, selective, convenient, and high-yield alternative to the Wolff-Kishner and Clemmensen reductions (eq 36).[60-62]

(36)

The prior preparation of the tosylhydrazone is unnecessary in many cases since the slow rate of carbonyl reduction permits the *in situ* generation from tosylhydrazine and the carbonyl compound.

A number of general deoxygenation procedures have been developed depending on the structure of the carbonyl compound. The original investigation, in which over 60 different carbonyl compounds were studied, should be consulted for experimental details,[61] but the following examples should indicate the utility and selectivity of this method for the deoxy-



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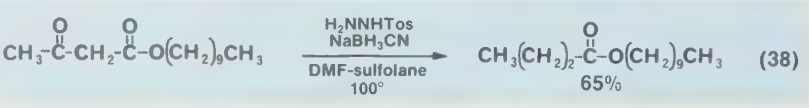

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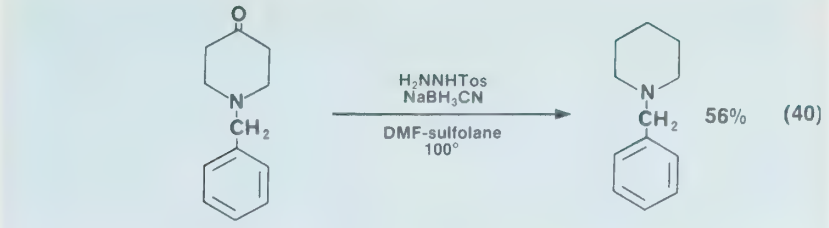
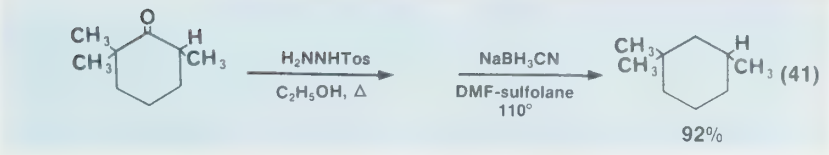
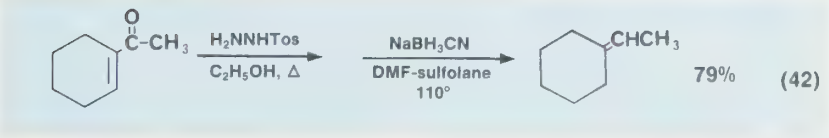
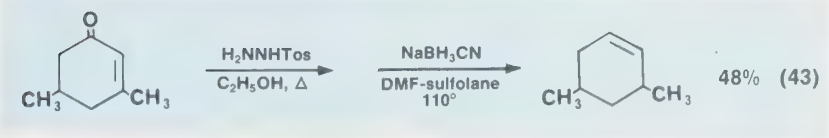
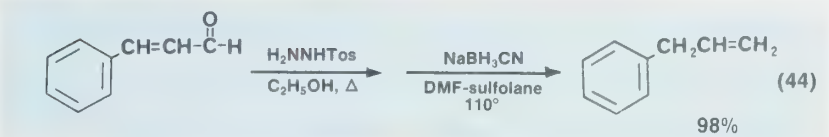
(39)

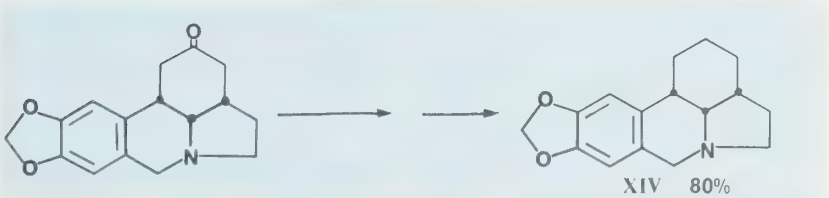


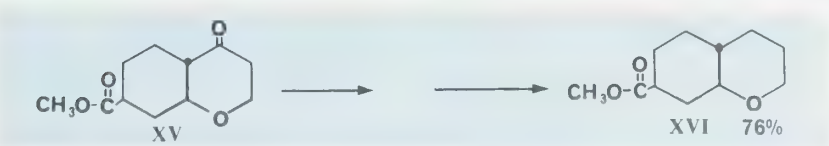


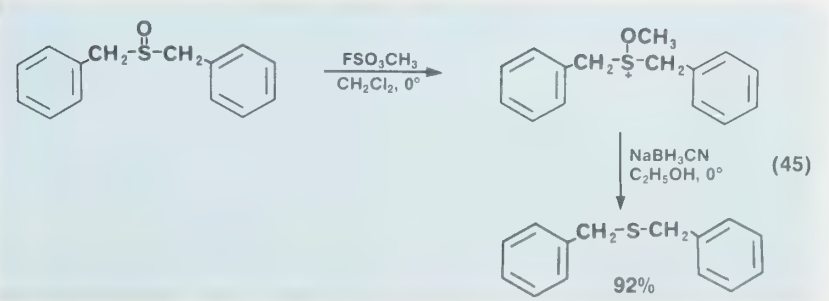












genation of carbonyl compounds (eq 37-44).

Aryl carbonyl compounds proved to be quite resistant to reduction by this method regardless of the procedure used.[61] However, this might prove to be useful because aliphatic ketones and aldehydes could probably be selectively removed in the presence of an aryl carbonyl group.

The mild conditions required for this modified Wolff-Kishner process should result in numerous applications in synthetic organic chemistry. For example, this deoxygenation procedure was recently used as a key step in the stereoselective synthesis of the ring skeleton of the alkaloid lycorine.[63] An 80% isolated yield of γ-lycorane **(XIV)** was obtained. Deoxygenation of **XV** also occurred without bridgehead epimerization giving a 76% conversion to the desired *trans*-1-oxadecalin structure **XVI**.[64]

A procedure has also been developed for the deoxygenation of sulfoxides using $NaBH_3CN$ which involves the prior formation of an alkoxysulfonium salt using methyl fluorosulfonate (eq 45).[65]

In conclusion, the stability and reactivity of the cyanoborohydride ion in aqueous systems at pH 6-8 indicate the potential for carrying out imine reductions and carbonyl aminations on complex biological systems. Recently, such an application has been reported where the imino linkage between 11-*cis*-retinal and the lipoprotein, opsin, has been reduced under mild conditions (aqueous, pH 5, 3°) using $NaBH_3CN$.[66] Also, the observed deactivation by $NaBH_3CN$ in aqueous acid medium was used in a recent characterization of an aldolase enzyme.[67]

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2) For a listing of the various selective reducing agents available from Aldrich and for a summary of their uses, please consult the technical bulletin "Reducing Agents" which is available upon request from the Aldrich Chemical Company, Inc.

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15,615-9
Sodium cyanoborohydride

11,008-6
Acetonitrile

D6,510-0
Dichloromethane

D15,855-0
***N,N*-Dimethylformamide**
(DMF)

H1,160-2
Hexamethylphosphoramide
(HMPA)

17,995-7
Methyl alcohol

18,656-2
Tetrahydrofuran,
anhydrous

T2,220-9
Tetramethylene sulfone
(sulfolane)

13,200-4
***p*-Toluenesulfonhydrazide**
(*p*-$TsNHNH_2$)

Organic Synthesis via Organoboranes. IV.[1]

Reduction of Organic Functional Groups with Borane-Methyl Sulfide

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Borane•methyl sulfide (BMS) is a concentrated, reactive, and stable source of BH_3, and we have reported its utility in the hydroboration of alkenes[2] and in the reduction of aromatic carboxylic acids.[3]

Borane•tetrahydrofuran (BH_3•THF) is the most commonly used hydroboration reagent and its use was recently reviewed by Professor Herbert C. Brown.[4] However, this reagent possesses certain characteristics which limit its preparation, storage, and use as a commercial source of borane, namely: (1) BH_3•THF can only be sold as a dilute solution (*1M*) in THF (1.5 wt % BH_3), (2) THF is slowly cleaved by BH_3 at room temperature, (3) sodium borohydride (5 mole %) must be added to BH_3•THF to inhibit the cleavage of THF, and (4) THF is relatively expensive and at times has been in short supply.

BMS has been found to overcome all of these disadvantages. BMS has a molar concentration of BH_3 *ten times* that of the BH_3•THF reagent. It can be stored for months at room temperature without loss of hydride activity and is apparently stable indefinitely when refrigerated. Also, BMS is soluble in and unreactive toward a wide variety of aprotic solvents.

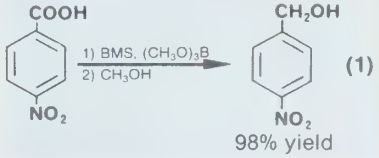
The BMS available from the Aldrich Chemical Company is a clear, colorless liquid with a BH_3 concentration of one mole per 100ml (*ca.* 10*M*). The reagent contains only BMS and *ca.* 5% excess methyl sulfide.

BMS is very soluble in ethyl ether, tetrahydrofuran, hexane, heptane, toluene, xylene, methylene chloride, monoglyme, diglyme, and numerous other aprotic solvents. BMS dissolves readily in alcohols with the quantitative evolution of hydrogen. However, BMS is insoluble in water and only very slow hydrolysis occurs. The addition of water to ether solutions of BMS results in rapid hydrolysis.

We recently reported that quantitative hydroborations with BMS are possible under mild conditions in a variety of aprotic solvents such as ethyl ether, THF, hexane, toluene, and methylene chloride.[2] The vastly improved air stability and ease of handling of this reagent have resulted in its use as a hydroboration reagent in an undergraduate laboratory.[5] The successful hydroboration of olefins with BMS in a variety of solvents prompted a similar study with BMS as a reducing agent.

The reduction of organic functional groups with BMS has been under active investigation for the past two years in the laboratories of Aldrich-Boranes, Inc. The results of this study seem to indicate that the reactivity of BMS parallels that of BH_3•THF.[6] However, BMS reductions usually require somewhat higher temperatures, *i.e.*, with BH_3•THF many reactions occur readily at 0-5° while the analogous reactions with BMS occur readily only at 20-25°. Consequently, it is strongly recommended that the addition of BMS to a reactive molecule be carried out at 20-25° or higher. Addition of BMS at 0° or lower may result in a very slow reaction; upon subsequent warming a vigorous exothermic reaction may then occur.

The reduction of carboxylic acids with BH_3•THF was found to yield the corresponding alcohols rapidly and quantitatively under remarkably mild conditions. A detailed study of the scope of this reduction has been reported.[7] We have investigated the use of BMS for the reduction of carboxylic acids.[3] *n*-Hexanoic acid and benzoic acid were initially studied as representative carboxylic acids. The reduction of *n*-hexanoic acid was found to occur rapidly and quantitatively in THF while the reduction of benzoic acid was appreciably slower, giving a low yield of benzyl alcohol. Fortunately, this difficulty was easily overcome by carrying out the reduction in the presence of trimethyl borate. This improved procedure was then used to reduce a number of functionally substituted benzoic acids on a preparative scale. Equation 1 gives a specific example.



(1)

98% yield

Although THF was used as the solvent in this study, reductions with BMS can be carried out in various aprotic solvents as shown in Table 1.

A wide range of functional groups can be reduced with BMS and, to illustrate this, representative procedures have been developed for the reduction of carboxylic acids, esters, oximes, nitriles, and amides. The selectivity of the reagent is also illustrated by the complete absence of reduction of halides and nitro groups.

An important feature of the following experimental procedures is the ease of product isolation. In the reduction of carboxylic acids and esters, it is only necessary to add an excess of methanol and then remove all volatiles *in vacuo* to give an alcohol residue that is boron-free and of satisfactory purity for most applications. In the reduction of oximes, nitriles, and

Table 1. Reduction of *n*-Hexanoic Acid with BMS Solvent Study[a]

Solvent	Time, hr	1-Hexanol, % yield[b]
Ethyl ether	1	100
THF	4(0.5)[c]	100
Hexane	0.5	100
Toluene	2	99
Triglyme	4	91
Trimethyl borate	0.5	100

[a]*n*-Hexanoic acid (30mmol) added dropwise to BMS (33mmol) in 30ml of solvent at 20-25°. [b]Yield by gc analysis after hydrolysis using an internal standard. [c]BMS added to *n*-Hexanoic acid in 30ml of THF.

amides, it is necessary to add anhydrous hydrogen chloride to hydrolyze the boron-nitrogen intermediates to trimethyl borate and the amine hydrochloride salt. Again, simple removal of all volatiles *in vacuo* on a rotary evaporator or similar apparatus gives the amine hydrochloride which is boron-free and of satisfactory purity for most applications.

The key step in the isolation procedures is the removal of solvent and trimethyl borate *in vacuo*. Although the residue obtained may be reasonably pure, it is usually necessary to carry out a distillation, recrystallization, or a related purification process to obtain a product of high purity. The procedure below for the preparation of 11-bromo-1-undecanol describes the use of the Aldrich Kugelrohr distillation apparatus while that of 2-chloro-4-nitrobenzyl alcohol illustrates another approach to the purification of an alcohol product.

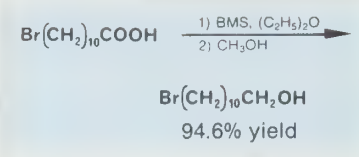
The procedures describing the reduction of an oxime, nitrile, and amide illustrate three different methods that we have found particularly useful for the purification of amine products. The preparation of *N*-cyclohexylhydroxylamine hydrochloride has as its purification step a straightforward recrystallization of the amine hydrochloride salt. The preparation of 2-(2,6-dichlorophenyl)ethylamine illustrates the conversion of the amine hydrochloride salt to the free amine followed by distillation. Finally, the preparation of 4-nitrobenzylamine hydrochloride describes a special technique where only the stoichiometric amount of methanol is added followed by treatment with hydrogen chloride gas which results in the precipitation of the amine hydrochloride salt. Simple removal of the supernate then eliminates the majority of the impurities.

The isolation procedures given are not limited to these specific examples or these specific functional groups. For a given reduction it is usually necessary to proceed with a trial-and-error approach to the best isolation procedure. The following procedures are given for illustrative purposes only and may, in fact, not be the best procedure for the isolation and purification of specific products.

It is hoped that the following examples will make it apparent that BMS is a very useful reagent for the reduction of organic functional groups. The stability, commercial availability in pure form, solubility in a wide variety of solvents, and ease of experimental work-up should make BMS the reagent of choice for many borane reductions.

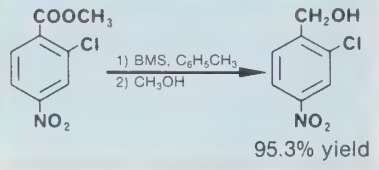
Preparation of 11-bromo-1-undecanol

A one-liter, three-necked, round-bottomed flask equipped with a magnetic stirring bar, pressure-equalizing addition funnel, thermometer well, and reflux condenser is flushed thoroughly with dry, high-purity nitrogen and maintained under a slight positive nitrogen pressure by use of a mercury or mineral oil bubbler attached to the condenser. The flask is opened and quickly charged with 100g (377 mmol) of 11-bromoundecanoic acid. After reflushing the apparatus with nitrogen, anhydrous ethyl ether (500 ml) is added using the double-tipped needle transfer technique (note 1). The resulting clear solution is stirred at room temperature with no external heating or cooling as the BMS (42



ml, 420 mmol, note 2) is added dropwise. Vigorous gas evolution occurs during the addition of the first 12-13 ml of BMS (time of addition 0.5-1hr) and the reaction does not appear to be exothermic. When the gas evolution is complete, the BMS addition is stopped and the reaction is heated to a gentle reflux using a warm water bath. The BMS addition is then continued at a rate sufficient to maintain a gentle reflux . The reaction mixture remains clear throughout the BMS addition which takes a total of 1-1.5hr. Following the BMS addition, the reaction mixture is maintained at reflux for an additional hour (note 3), then cooled to 20° in a cold water bath and poured into 1 liter of ice-cold methanol with gentle swirling (note 4). The resulting clear solution is loosely covered with aluminum foil, allowed to stand overnight in a hood, and concentrated to an oil (note 5) on a rotary evaporator (note 6). Short-path distillation of this oily solid on the Aldrich Kugelrohr[8] gives 89.6g (94.6% yield) of a colorless, crystalline solid, b.p. 140-145° (air bath temp.) at 0.08mm, m.p. 45-47° (uncorrected) (Lit.[9] m.p. 46-49°), with ir and nmr spectra in accordance with assigned structure. The solid product is conveniently removed from the Kugelrohr receiver by melting with a hot-air gun and pouring into an open dish for crystallization.

Preparation of 2-chloro-4-nitrobenzyl alcohol

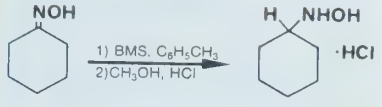


The reaction apparatus is assembled as described in the foregoing experiment and charged with 87.9g (408 mmol) of methyl 2-chloro-4-nitrobenzoate and 400ml of toluene (note 7). The addition funnel is charged with 43ml (430 mmol) of BMS (note 2). The reaction mixture is then stirred in a 20-25° water bath as the BMS is added dropwise over a 0.5 hr period. The reaction is not exothermic and only a minor amount of gas evolution occurs. Following the BMS addition, the resulting clear solution is stirred for an additional 0.5hr at 20-25°, heated slowly to a gentle reflux and maintained at reflux for 4 hr (note 3), cooled to 20°, and then slowly poured into 400ml of ice-cold methanol with gentle swirling (note 4). The resulting clear solution is loosely covered with aluminum foil, allowed to stand overnight in a hood, and then concentrated to 76.5g of a boron-free (note 6), orange, crystalline solid on a rotary evaporator. This solid shows no carbonyl absorption in its ir spectrum but does contain a small amount of ether-insoluble material. The solid is slurried in ethyl ether (1.5l) and THF (0.5l), heated to reflux, cooled to 20°, filtered, extracted with 25% aqueous potassium carbonate (2 x 250ml) and saturated aqueous sodium chloride (1 x 250ml), dried over anhydrous potassium carbonate, filtered, and concentrated to dryness on a rotary evaporator. The resulting yellow, crystalline solid is further dried *in vacuo* giving 73.0g (95.3% yield) of 2-chloro-4-nitrobenzyl alcohol, m.p. 78-80°, with nmr spectrum identical to that reported for the authentic material.[10] Recrystallization from toluene gives light-yellow needles, m.p. 79-80° (uncorrected).

Preparation of *N*-cyclohexylhydroxylamine hydrochloride

A two-liter, three-necked, round-bottomed flask is equipped and assembled as previously described and charged with

134g (1.18mol) of cyclohexanone oxime and 1 liter of toluene (note 7). The addition funnel is charged with 130ml (1.3mol) of BMS (note 2). After heating the clear reaction mixture to a gentle reflux, the BMS is added dropwise with the heat turned off and at a rate sufficient to maintain a gentle reflux. Vigorous gas evolution and moderate foaming occur during the addition of the first 50ml of BMS (addition time: 0.5-1hr). The remaining 80ml of BMS is then added at an increased rate due to decreased gas evolution. Total time for BMS addition is 1-1.5hr. Following the BMS addition, the clear reaction mixture is heated at reflux with stirring for an additional 3hr period (note 3). After cooling to 20° in a cold water bath, methanol (300ml) is added dropwise (note 4) over a 1hr period. During the methanol addition, a white solid forms in the reaction mixture. This slurry is stirred for an additional hour

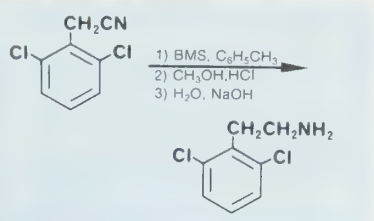


64.8% yield

at 20-25°, and then in an ice-water bath as anhydrous hydrogen chloride is bubbled (note 4) into the reaction mixture until a pH of <2 is reached. During the HCl addition, the reaction temperature is maintained <15° and the solid dissolves giving a clear solution at pH 7. The mixture becomes cloudy as more HCl is added. When stirring is stopped, the cloudy reaction mixture separates into two clear, colorless, liquid layers. This two-phase reaction mixture is stirred overnight at 20-25° and then concentrated to a solid on a rotary evaporator (note 6). The solid (note 8) is dried to constant weight at 20-25°/0.01mm giving 167g (93.4% yield) of a white, crystalline solid, m.p. 125-130°. A trace of boron was indicated by flame test. Recrystallization from methanol-ethyl ether gave 115.9g (64.8% yield) of *N*-cyclohexylhydroxylamine hydrochloride as colorless needles, m.p. 139-141°, with ir and nmr spectra in accordance with assigned structure. Percent Cl calculated for $C_6H_{14}ClNO$: 23.38; found: 24.12. Purity by perchloric acid titration: 99.4%.

Preparation of 2-(2,6-dichlorophenyl)-ethylamine

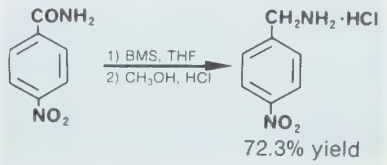
The reaction apparatus is assembled as previously described and charged with 82.0g (441 mmol) of 2,6-dichlorophenylacetonitrile and 0.5l of toluene (note 7). The addition funnel is charged with 48.5ml (485 mmol) of BMS (note 2). The clear reaction mixture is heated to a gentle reflux as the BMS is added dropwise over a 1hr period. The heat is shut off whenever the refluxing becomes too vigorous. Following the BMS addition, the reaction mixture is maintained at a gentle reflux for 24hr (note 3). After cooling to 20° in a water bath, methanol (0.5l) is added dropwise. Gas evolution occurs during the addition of the initial 50ml of methanol which is added



63.7% yield

slowly over 0.5-1hr. The remaining 450ml of methanol is then added rapidly over 0.5hr. After cooling to <10° with stirring in an ice-water bath, anhydrous hydrogen chloride is bubbled into the clear solution until a pH of <2 is reached. The resulting clear, light-yellow solution is heated to reflux, maintained at reflux for 1hr, cooled to 20°, and concentrated to a yellow solid on a rotary evaporator. This solid is redissolved in 0.5l of methanol and again concentrated to a solid on a rotary evaporator. Further drying *in vacuo* at 20-25°/0.01mm gives 102g (100% yield) of a light-yellow crystalline solid. A flame test showed that a trace of boron was present. Percent total chlorine calculated for $C_8H_{10}Cl_3N$: 46.95; found: 43.68. Purity by perchloric acid titration: 92.5%. This solid is dissolved in 250ml of water with gentle heating and the solution is then cooled in an ice-water bath as solid sodium hydroxide pellets are added slowly with swirling until a pH of >10 is reached. The aqueous layer is saturated with solid sodium chloride, extracted with ethyl ether (400ml), and discarded. The ether extract is dried over anhydrous potassium carbonate, filtered, and concentrated to an oil on a rotary evaporator. Short-path distillation of this oil from a few pellets of potassium hydroxide on the Aldrich Kugelrohr[8] gives 53.4g (63.7% yield) of 2-(2,6-dichlorophenyl)ethylamine as a clear, colorless oil, b.p. 68-72° (air bath temp.) at 0.07mm, n_D^{20} 1.5705, with ir and nmr spectra in accordance with assigned structure. Purity by gc analysis: 96%. Sample contains 4% of a single lower boiling impurity.

Preparation of 4-nitrobenzylamine hydrochloride



72.3% yield

The reaction apparatus is assembled as previously described and charged with 50.0g (301 mmol) of *p*-nitrobenzamide and 0.6l of THF. The addition funnel is charged with 73.7ml (737 mmol, note 9) of BMS (note 2). The BMS is then added dropwise with stirring to the amide-THF slurry at 20-25° over a 1hr period. Gas evolution occurs during the BMS addition and the amide dissolves giving a clear solution. This solution is stirred for an additional 0.5hr at 20-25° and is then heated to reflux and maintained at reflux for 5hr (note 3). After cooling to 20-25°, methanol (100ml, 2.43 mol) is added dropwise over a 1hr period at a rate such that the reaction temperature does not exceed 30° (note 4). The resulting clear solution is allowed to stand overnight at room temperature. After cooling to <10° in an ice-water bath, anhydrous hydrogen chloride is bubbled slowly into the solution with stirring while maintaining a temperature <15° (note 4). A white precipitate immediately forms and the HCl addition is stopped when the solution reaches a pH of <2. The resulting white slurry is heated to reflux, maintained at reflux for 1hr and then cooled in an ice-water bath. The solid settles giving a white, crystalline precipitate and a clear, yellow supernate. This supernate is removed *via* a double-tipped needle using nitrogen pressure (note 8) and the solid is dissolved in 1 liter of methanol with gentle heating. Concentration of this solution on a rotary evaporator followed by drying to constant weight *in vacuo* gives 41.0g (72.3% yield) of 4-nitrobenzylamine hydrochloride, m.p. >260° (dec.), with ir and nmr spectra in accordance with assigned structure. Percent Cl calculated for $C_7H_9ClN_2O_2$: 18.79; found: 19.63. Purity by perchloric acid titration: 99.2%.

Notes

1) For a description of syringe and double-tipped needle transfers, please consult the bulletin "Handling Air-Sensitive Solutions," which is available upon request from the Aldrich Chemical Company, Inc.

2) For best results, BMS should be handled using syringe and double-tipped needle techniques (note 1). A few chemists, who have never handled BMS, have expressed concern about a possible odor problem in working with BMS. Naturally, BMS should be handled in a hood, but whether an odor is offensive or otherwise is a highly individual judgment. To the author, working with BMS has never caused any odor problems. In fact, in dilute concentrations he finds the odor reminiscent of tomatoes, and a laboratory aide has expressed the same observation.

3) Depending upon the compound being reduced and the presence of other substituents, it may be necessary to increase or decrease the time and temperature required for complete reduction.
4) Caution: vigorous gas evolution along with foaming may occur.
5) A solid if temperature of water bath on the rotary evaporator is below *ca.* 45°.
6) The presence of boron in the product is indicated by a green flame. Dissolving the product in methanol followed by concentration to dryness removes the boron as the volatile trimethyl borate. This procedure may be repeated until a negative flame test is observed.
7) Commercial, bulk-solvent grade toluene is dried over a small amount of calcium hydride prior to use.
8) Exposure of the hydrochloride salt to air must be kept at a minimum until purified and dried because the crude salt is usually very hygroscopic.
9) For complete reduction, one equivalent of primary amide requires $^{7}/_{3}$ equivalents of BMS, one equivalent of secondary amide requires $^{6}/_{3}$ equivalents of BMS, and one equivalent of tertiary amide requires $^{5}/_{3}$ equivalents of BMS.

References

1) For Part III of this series, see C.F. Lane, *Aldrichimica Acta,* **7,** 32 (1974).
2) C.F. Lane, *J. Org. Chem.,* **39,** 1437 (1974).
3) C.F. Lane, H.L. Myatt, J. Daniels, and H.B. Hopps, *ibid.,* **39,** 3052 (1974).
4) H.C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972; H.C. Brown, G.W. Kramer, A.B. Levy, and M.M. Midland, "Organic Syntheses *via* Boranes," John Wiley and Sons, New York, N.Y., 1975.
5) G. W. Kabalka, University of Tennessee, Knoxville; private communication, 1974; manuscript has been submitted to *J. Chem. Educ.*
6) For the results of a detailed study on the reaction of BH_3·THF with various organic functional groups, see H.C. Brown, P. Heim, and N.M. Yoon, *J. Amer. Chem. Soc.,* **92,** 1637 (1970).
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8) Aldrich Kugelrohr Distillation Apparatus, Catalog No. Z10,046-3,
9) *Beil.,* **1,** (4), 1837.
10) C.J. Pouchert and J.R. Campbell, "The Aldrich Library of NMR Spectra," Aldrich Chemical Company, Inc., Milwaukee, Wisconsin, 1974, Vol. V, p 161C.

Crown Ether Chemistry: Principles and Applications

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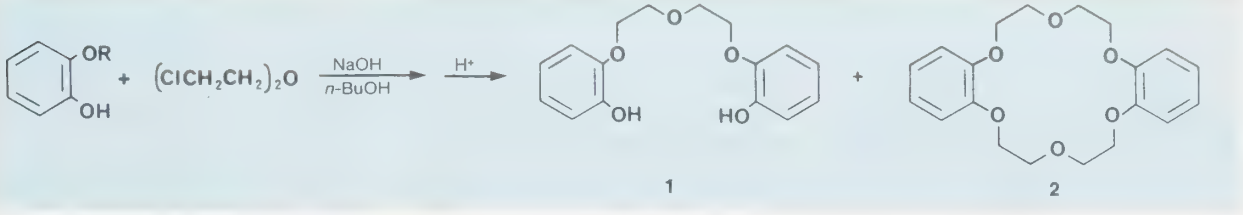
Background

The importance of macrocyclic polyethers and the field bearing the cognomen "crown ether chemistry" can be attributed largely to the work of Charles J. Pedersen of the DuPont Company, who reported many of these compounds and considerable complexation data in 1967.[1] Compounds of this type, *viz.*, glymes[2] and cyclic polyethers[3] were known, but no alkali metal complexes had been reported. Many such complexes are now known and have been catalogued.[4]

Pedersen's discovery of these compounds is interesting and the details are available in an earlier issue of this journal.[1b] Pedersen was attempting a synthesis of bis-phenol **1** by the sequence illustrated below. Apparently, some of the incompletely protected mono-THP-catechol reacted with 2,2′-dichlorodiethyl ether to yield dibenzo-18-crown-6 (**2**). Although ir analysis showed that compound **2** had no hydroxyl group, it exhibited a base-induced shift in the UV. This shift is now understood and is attributed to complex formation.[5]

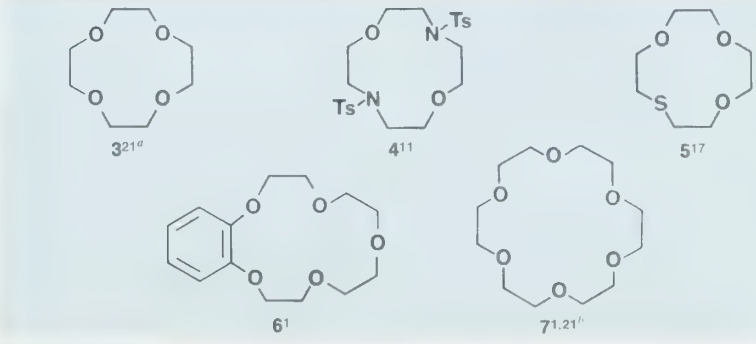


1 **2**

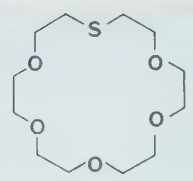
The macrocyclic polyethers are generally defined as being cycles containing repeating $(-X-CH_2-CH_2-)_n$ units. For the cases where X=O, the repeating unit is ethyleneoxy. If the carbon portion were one carbon shorter (methyleneoxy) the repeating unit would be an acetal function and would exhibit hydrolytic instability. If longer carbon chains were involved, the CH-CH interactions would exert an effect on the overall conformation of the macroring. The generic name "crown" was evidently suggested to Pedersen by the similarity of the (CPK) molecular models to a regal crown, and by the ability of these compounds to "crown" cations by complexation. The smallest value of n which fits the above definition is 2, *i.e.*, 1,4-dioxane. No smaller molecule satisfies the "repeating" requirement of the definition. The name for **2** is derived as follows: dibenzo— describes the non-ethyleneoxy substituents, 18— the total number of atoms in the ring, crown is the class name, and 6 is the total number of heteroatoms in the ring portion of the macrocycle. Compound **7** would simply be called 18-crown-6.[1a]

Structural Variation

The principal variation in X has been to substitute NH or NR for O.[6-16] Sulfur has also been substituted for oxygen and the efforts in this area have recently been reviewed.[17] Other variations include replacement of O by P[18] or CH_2.[10,11,19,20] The structural variation is illustrated in formulas **3-17**. These are representative examples of the variety possible and are only a small fraction of the structures which have been reported. For more complete listings, the reader is directed to the extensive reviews which have appeared in the last five years.[4,17,30-34]



3[21a] **4**[11] **5**[17] **6**[1] **7**[1,21b]



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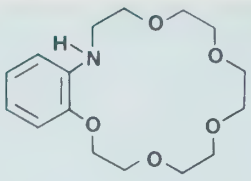

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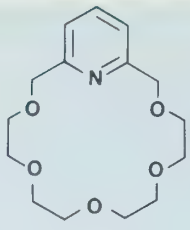

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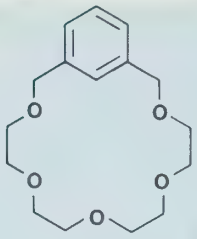

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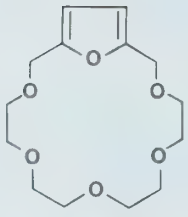

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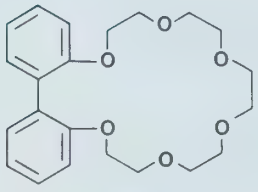
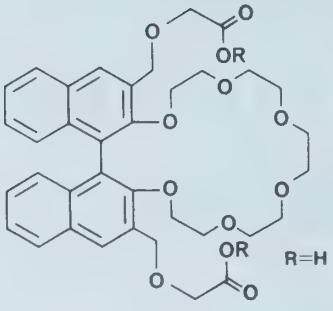


13[26]



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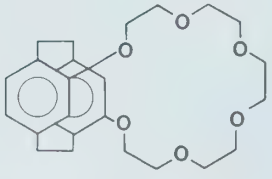

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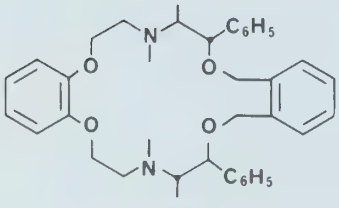
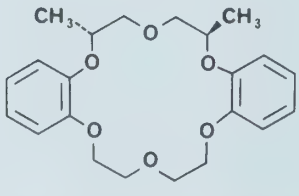
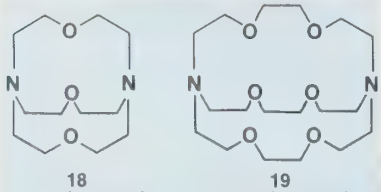


16[28]



17[29]

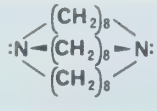
A cursory examination of the structures formulated above will indicate that a feature common to all of them is an effective two-dimensionality. The polyheteroatom macrocycles may be made three-dimensional by adding a third (-X-CH_2-CH_2-) strand. Lehn and his collaborators have designed numerous three-dimensional polyheteroatom macrocycles which he has named "cryptates."[7,33,35-39] The molecules which Lehn has designated the 1.1.1- and 2.2.2-cryptates are represented by structures **18** and **19**. The conceptually



18 (1.1.1 Cryptate)

19 (2.2.2 Cryptate)

related but independently developed "in-out" bicyclic amines which were developed by Simmons and Park,[40] are represented by structure **20**. The molecule represented by



20

structure **21** is similar to a cryptate but the pentaerythritol unit replaces the bridgehead nitrogen.[41] The elegant cryptate

21

chemistry developed by Lehn is closely related to that of the simpler crown ethers and it serves admirably for many of the applications discussed in later sections. Because of the greater cost of these bicyclic materials and their consequent relative unavailability, we will largely restrict further discussion of applications to the monocyclic crowns.

Complexes and the Template Effect

Despite the multiplicity of structural variation, the macroheterocycles would be little more than an interesting chemical curiosity were it not for the ability of these cycles to complex a wide variety of substrates. Pedersen, in his early papers,[1] demonstrated this property. He reported that crown ethers complex alkali and alkaline earth cations, transition metal cations, and ammonium cations. The binding constants for metal ions generally are largest for the most similar relationships of cation diameter to hole size. Pedersen and Frensdorff[31] have reported stability constants (K) for polyether-cation complexes with dicyclohexyl-18-crown-6 in water at 25°C (see Table 1). The hole size of 18-crown-6 has been estimated to be 2.6-3.2Å.[42] The available evidence suggests that the appropriately sized metal ion is lodged in the hole of the crown, coplanar with and equidistant from each oxygen atom.[33]

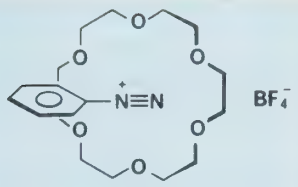
Table I[31]

Stability Constants K (in water) for Equation 1

Cation	Ionic diam. (Å)	K(l/mol)
Li^+	1.28	0.6
Na^+	1.93	1.7
K^+	2.66	2.2
Rb^+	2.96	1.5
Cs^+	3.66	1.2
NH_4^+	3.6*	1.4
Ag^+	2.39	2.3

*Authors' estimate based on CPK scale model examination. Note that the ammonium ion complex involves H-bonding to the face of the crown and not insertion. Its effective size is similar to K^+ ion.

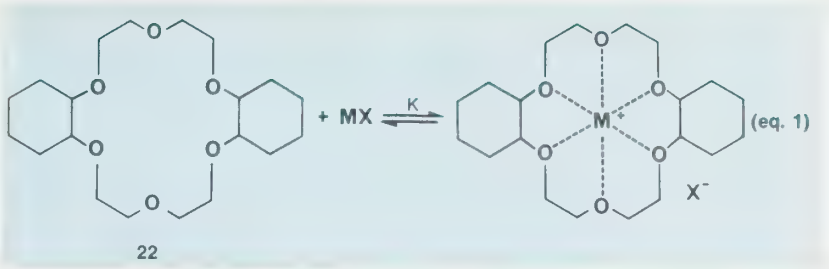
A number of other substrates have also been shown to form either solid or transient complexes. Examples include solid complexes of crown ethers with hydronium ion[43] and a complex of benzo-27-crown-9 with guanidinium ion.[44] In addition, evidence has been developed for a complex between benzene diazonium ion and crown ethers in a non-polar solution.[45] The presumed structure is formulated as **23**. Other



23

solid materials which may be complexes, solvates or clathrates between crown ethers and acetonitrile,[21] thiourea,[40] THF[22] and dimethyl acetylenedicarboxylate[47] have been reported.

The complexation of the Lewis acid is also crucial to the formation of these rings. Apparently, the final step in the Williamson ether synthesis of these compounds involves a wrapping of the polyheteroatom chain about the metal ion, bringing the alkoxide and the carbon bearing the leaving group into proximity (see eq. 2). Because of this, the crown ethers can be prepared in relatively concentrated solution, while most large ring syntheses require high dilution. Pedersen's dibenzo-18-crown-6 is routinely prepared in 39-48% yield working at a concentration of *ca.* 0.75 molar.[48] Compound **7**, 18-crown-6, is prepared in about 1 molar solution.[21b]



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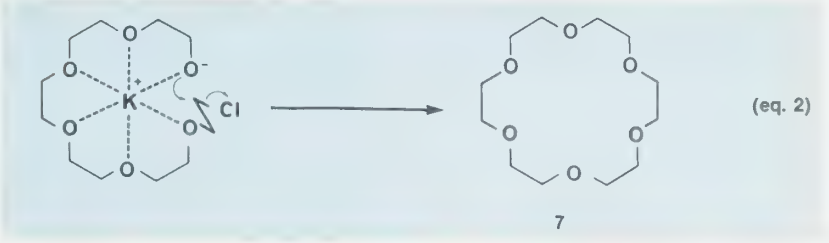

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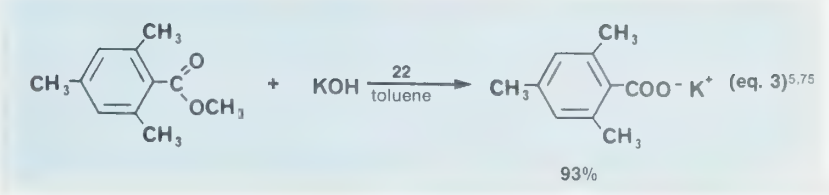
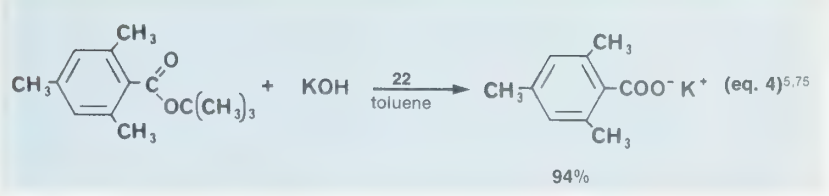


93%



94%

Application in Synthesis

The synthetic utility of crown ethers is derived from their ability to solvate cations in a non-polar environment. A large body of work has developed over the last ten years on phase-transfer (PT) chemistry[49] using quaternary ammonium cations to transfer otherwise insoluble anions into non-polar media. The development of synthetic reactions using crown ethers clearly parallels the development of the quaternary ammonium (or phosphonium) catalysts. The synergistic power of crown ethers was first pointed out by Pedersen[1,48] who showed that potassium hydroxide could be solubilized in toluene and that the crown-complexed potassium hydroxide was a powerful base. Pedersen found that esters of mesitoic acid (2,4,6-trimethylbenzoic acid) could be hydrolyzed using the crown-complexed potassium hydroxide salt (eq. 3). Not only was the methyl ester hydrolyzed (no reaction was observed in the absence of a crown ether) but the *t*-butyl ester was also cleaved in high yield (eq. 4). Pedersen also reported that this reagent may be used for the anionic polymerization of anhydrous formaldehyde and the trimerization of aromatic isocyanates.

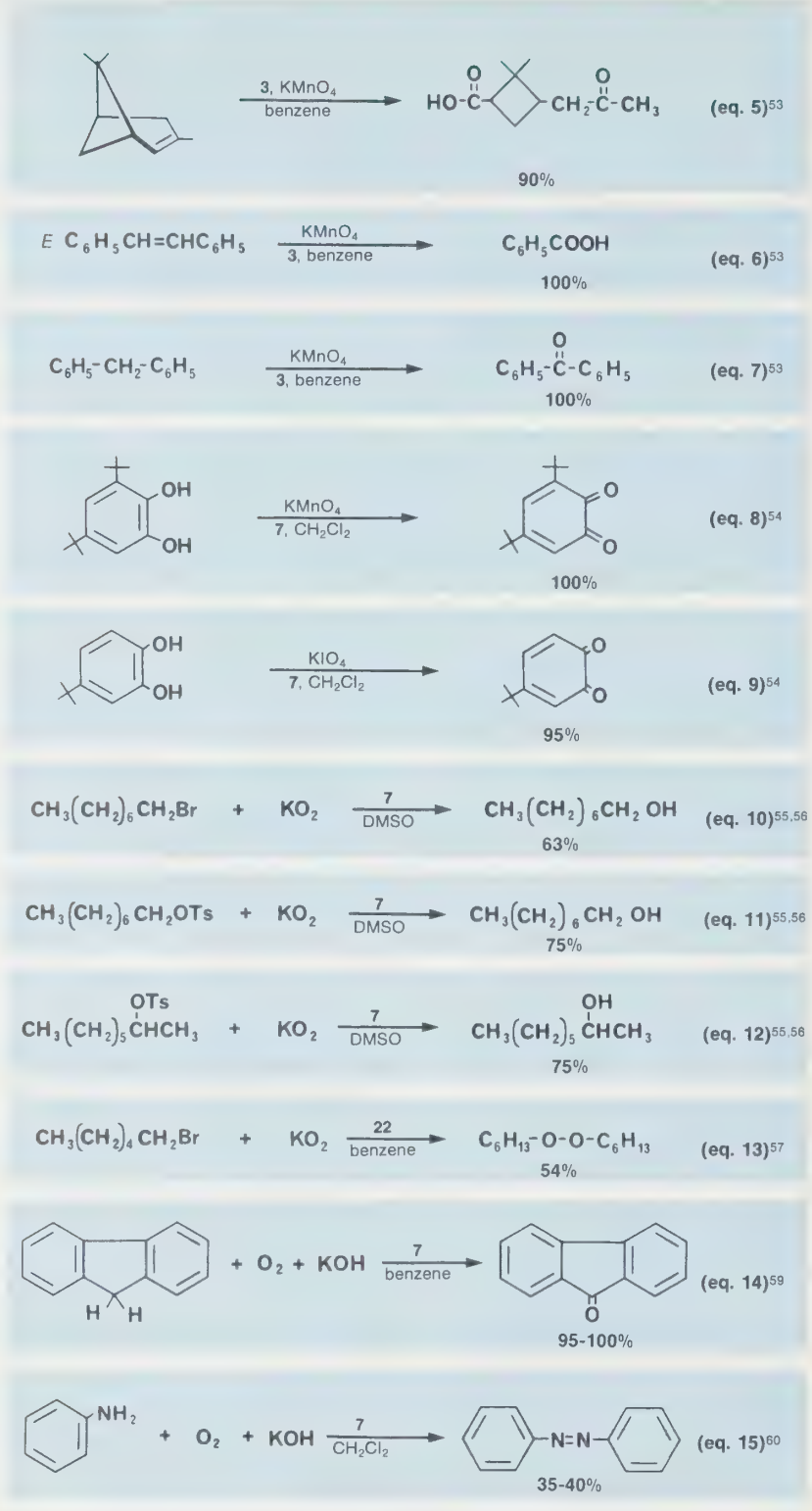
The major difference between crown-catalyzed reactions and the quaternary ammonium catalysts is that crown ethers may catalyze a direct solid/liquid phase-transfer of salts into non-polar solvents whereas most quaternary ammonium-catalyzed reactions are done from a liquid (aqueous) phase into non-polar solvents. The success of crown ethers as reagents for solid-liquid PT can likely be attributed to two properties of these systems. The first is that crown ethers are multidimensional flexible molecules with a number of polar sites. When the crown ether interacts with the crystal lattice of a salt, it may assume the approximate geometry of the complex on the crystal surface and the subsequent transfer of the cation from its lattice site to the crown cavity is energetically favorable. The anion simply accompanies the cation complex. In case of quaternary salts, the positive nitrogen is sterically shielded and therefore cannot achieve proximity to the lattice-bound cation. The second important property is the intrinsic difference between crown ethers and quaternary salts, namely that crown ethers are neutral ligands. Whereas the quaternary ion is always associated with an anionic species, the crown ether can be neutral both as a crown-cation-anion complex or as the free ligand. The efficiency of crown ethers as solid-liquid PT reagents may well be attributable to the fact that the complexed product salt can be deposited in a crystal lattice and the ligand freed to complex more reactant salt.

After Pedersen's initial observations, the first major interest in crown-complexed salts was in their ability to generate separated ion pairs.[50] Maskornick[51] observed that potassium *t*-butoxide in DMSO initiated E-2 type reactions in the presence of 18-crown-6 (**7**) with great facility. Maskornick also observed that the reaction, in the presence of the crown ether, gave pseudo first order rates even in con-

centrated (≅0.5 *M*) solution. In the absence of the crown ether, the reaction showed pseudo first order kinetics only at low (≅10^{-3} *M*) concentrations. The crown-complexed base apparently inhibits aggregate formation, even at high concentration, dramatically increasing the reactivity of potassium *t*-butoxide. Bartsch,[52] and others,[53] have studied the effect of the crown ether complexation in numerous nucleophilic substitution and β-elimination reactions. As a general observation, these reactions are substantially affected by the presence of the appropriately sized crown ether, especially in non-polar solvents. A comprehensive review of this reactivity has recently appeared.[52]

In the initial work by Pedersen, the potassium hydroxide complex with dicyclohexyl-18-crown-6 **(22)** had to be preformed in methanol then used in toluene (or benzene) after the methanol was removed. Sam and Simmons,[53] also at DuPont, observed that direct solid-liquid phase transfer of potassium permanganate could be effected with **22**. This hydrocarbon-solubilized permanganate (commonly known as purple benzene) is a very mild, yet effective, oxidizing reagent. Under these conditions, α-pinene is oxidized to pinonic acid (eq. 5), stilbene to benzoic acid (eq. 6), and diphenylmethane to benzophenone (eq. 7). Solubilization of potassium permanganate with 18-crown-6 **(7)** in CH_2Cl_2 has been observed[54] to transform substituted catechols to *o*-quinones in high yields (eq. 8). The same solubilization of potassium periodate and potassium iodate was also observed to transform catechols to *o*-quinones in high yields[54] in a solid-liquid process (eq. 9). In all cases, only one equivalent of the oxidizing reagent is required. No evidence of over-oxidation to open ring products was observed under these conditions.

Recent work at Rutgers[55] and Upjohn[57] has shown that potassium superoxide may be solubilized by **7** and **22** in both DMSO and benzene. Once in solution, this reagent may be used as a very nucleophilic oxygen anion which reacts with alkyl halides and tosylates (eq. 10-13). The products seem to be solvent-dependent, *i.e.*, in DMSO,[56] the alcohol is produced as the major product (by a mechanism which remains obscure at present) whereas in benzene,[57] the major product is the dialkyl peroxide. A hydroperoxide[58] has been isolated in at least one case as an intermediate. Recent work[58] has also shown that dialkyl peroxides may be reduced to alcohols with potassium superoxide. Stereochemical studies[56,57] indicate that the displacement occurs with virtually complete inversion of configuration at the asymmetric carbon.



Crown ether **7** catalyzes the air oxidation of fluorene[59] to fluorenone in the presence of solid potassium hydroxide (eq. 14) in quantitative yields. Similarly, aniline[60] undergoes oxidative condensation to azobenzene (eq. 15), although in somewhat lower conversion. In the former case, the oxidation rate is enhanced by rapid stirring which presumably increases both interfacial contact and oxygen absorption. Boden[61] has shown that the potassium salt

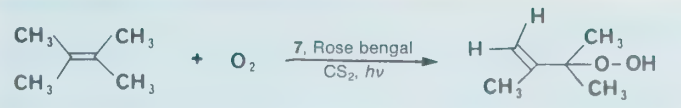
of rose bengal is solubilized by 7 in non-polar solvents. This crown-dye complex sensitizes the photoaddition of singlet oxygen to either tetramethylethylene (eq. 16) or anthracene (eq. 17). The reaction conditions are very mild and may be conducted conveniently in several aprotic solvents. An additional advantage is that singlet oxygen generated in aprotic solvents (such as CS_2) has a longer lifetime than singlet oxygen generated in protic solvents (such as methanol).

The remarkable ability of the macrocyclic polyethers to draw salts into non-polar solution has been utilized in reactions involving fluoride ion. 18-Crown-6 (7) assists the solubilization of KF in either acetonitrile or benzene and the poorly solvated fluoride anion exhibits potent nucleophilic properties.[62] Two examples of fluoride substitution are illustrated in eqs. 18-21. In cases where elimination is more favorable than substitution, it becomes a major side reaction. Bromocyclohexane under these conditions yields only cyclohexene. In cases where elimination is unlikely, the substitution reaction works extremely well giving high yields of product (eqs. 22 and 23). The substitution reaction can also be aplied to vinyl chloride, yielding vinyl fluorides (see eqs. 24 and 25).[63] This reaction proceeds *via* addition-elimination.

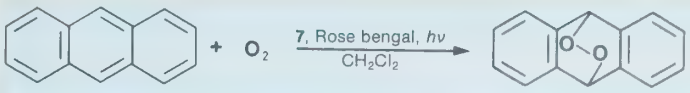
Other halides[64,65] also exhibit reasonable nucleophilic behavior. In a liquid-liquid phase-transfer system,[65] the 1- and 2-octyl mesylates were converted to the iodide (eq. 26) and the bromide (eq. 27) respectively, by the appropriate nucleophiles. The lower yield reported in the latter case is presumably due to loss of product by elimination. The crown-mediated reaction of KBr in acetone yields the alkyl bromide in quantitative yield from the corresponding brosylate (eq. 28).[64] Methoxide ion also gives a net substitution reaction where halide is the leaving group.[64] This is illustrated for *o*- and *m*-dichlorobenzene in equations 29 and 30.

The pseudohalide cyanide ion exhibits similar behavior in S_N2 reactions, and a variety of nitriles have been prepared in good yield using PT techniques (eq. 31-33).[65b,66,67] A particularly interesting case[66] is illustrated in eq. 34. To our knowledge, the preparation of trimethylsilyl cyanide has not yet been effected under quaternary ion-catalyzed phase-transfer conditions.

The carboxylate ion is not generally considered a good nucleophile; its Swain-Scott constant is near 3. In non-polar media, however, it is quite nucleophilic. 18-Crown-6-complexed potassium acetate

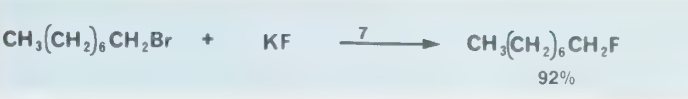


(eq. 16)[61]



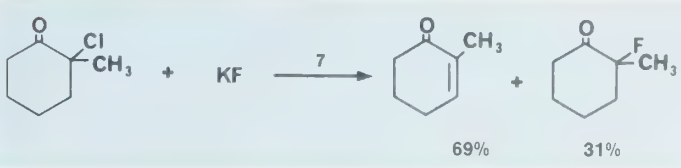
(eq. 17)[61]

(eq. 18)[62]

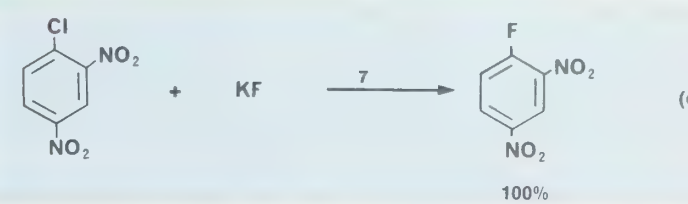


(eq. 19)[62]

(eq. 20)[62]



(eq. 21)[62]

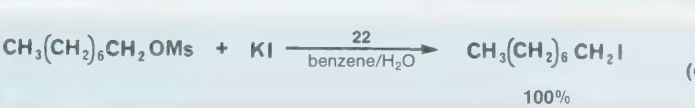


(eq. 22)[62]

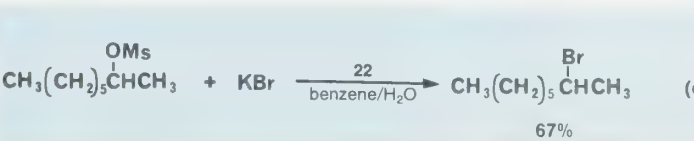
(eq. 23)[62]

(eq. 24)[63]

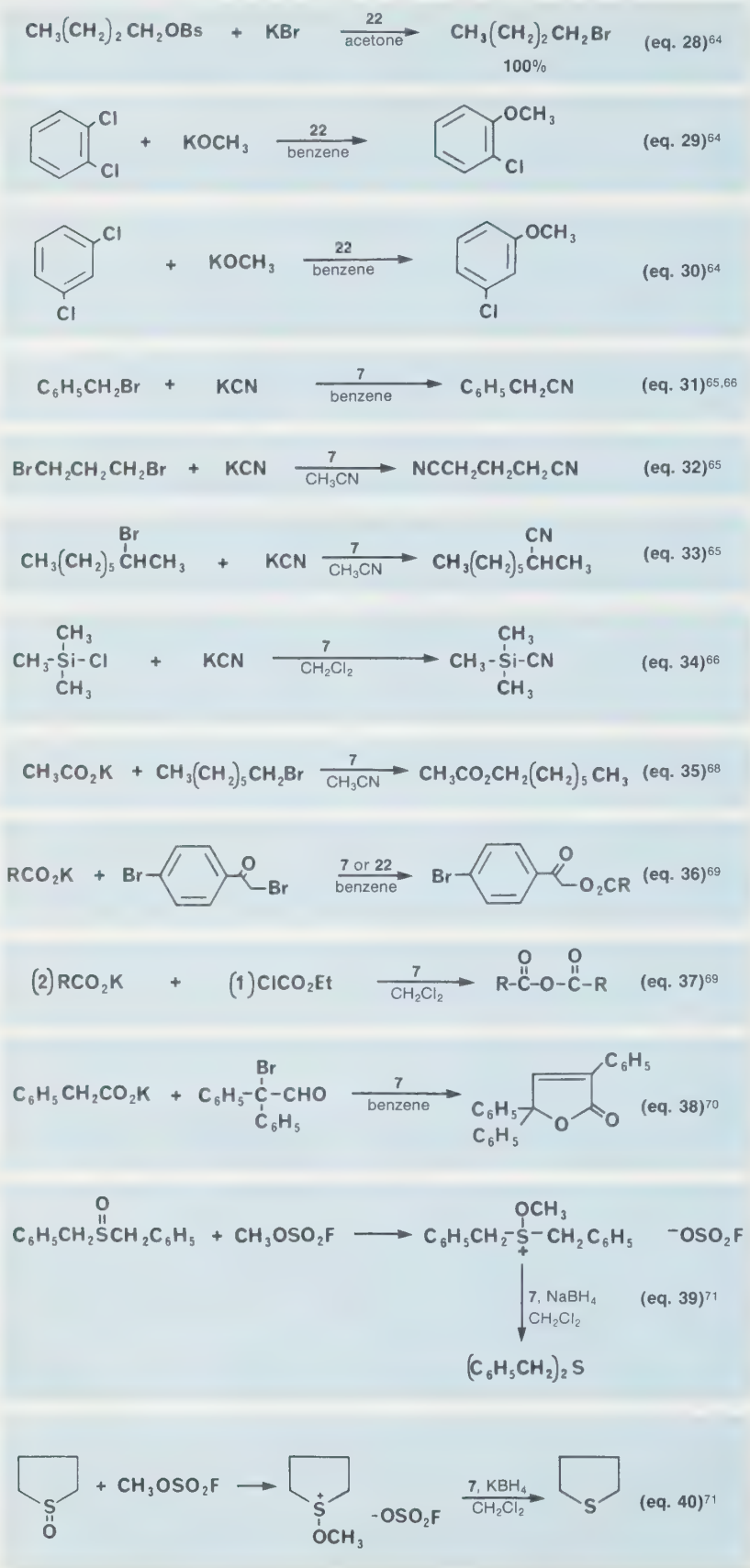
(eq. 25)[63]



(eq. 26)[65]



(eq. 27)[65]



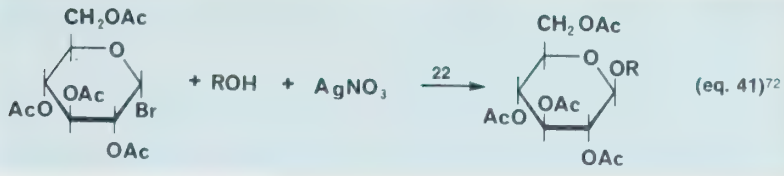
(sometimes called "bare acetate") reacts readily with *n*-heptyl bromide in acetonitrile to yield *n*-heptyl acetate (eq. 35).[68] Considerable utility has been demonstrated in the corresponding reaction of other carboxylate ions.[69] They have been used in the preparation of phenacyl ester derivatives (eq. 36), anhydrides (eq. 37), and some otherwise inaccessible lactone precursors (eq. 38).[70]

Several other crown-assisted nucleophilic substitution reactions have been reported. The sequence of reactions formulated in eqs. 39 and 40 provides a mild and general method for the reduction of sulfoxides using crown solubilization in the reduction step.[71] The Koenigs-Knorr alcoholysis of bromosugars (eq. 41) is also assisted by the presence of the crown ether.[72]

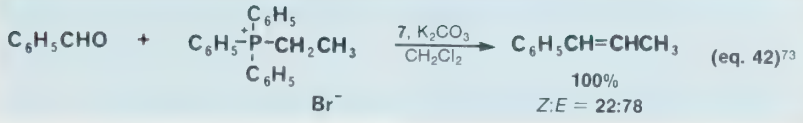
The presence of crown ether has also been shown to influence product geometry in the Wittig reaction. The olefins formed from benzaldehyde and two phosphonium ylides are illustrated in eqs. 42 and 43. Note that the products exhibit predominant *trans* geometry.

Addition of polyethers to solutions containing configurationally mobile salts has yielded interesting results. Noe and Raban[74] have noted that the crown ether **7** causes a change in the preferred conformation of sodium acetoacetonate. Gokel and coworkers[75a] have developed evidence for crown ether-cation interaction in the Cannizzaro reaction. In other systems, crown ether-solvation of potassium-containing ion pairs evidently enhances reaction to a considerable extent. In the two reactions formulated, a rate acceleration of approximately 10^5 was observed. The fact that both a decarboxylation (eq. 44)[76] and an oxy-Cope rearrangement (eq. 45)[77] exhibit similar rate enhancements is probably not coincidental: the Williamson reaction of potassium *t*-butoxide with benzyl chloride in THF is dramatically accelerated by addition of **7**.[75b]

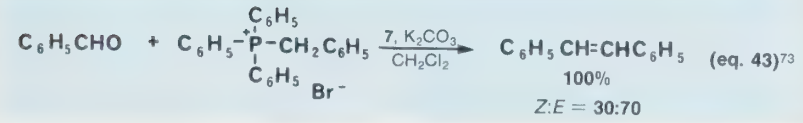
The generation of carbenes or carbenoid intermediates has been reported by several groups. Weber and coworkers[78] have shown that diazomethane may be generated from aqueous potassium hydroxide, chloroform, hydrazine hydrate, and 18-crown-6 (**7**) in 48% yield (eq. 46). In Weber's procedure only 0.004 mole % of **7** is used. The advantages of this procedure over the classical methods of generating diazomethane are manifest. Markosza[79] also reports the generation of dichlorocarbene under the influence of **22** by a liquid-liquid (PT) process (eq. 47). The selectivity and reactivity of crown-catalyzed di-



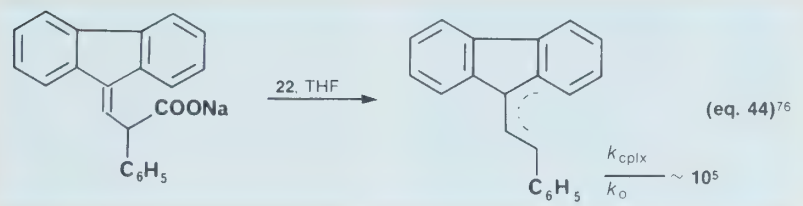
(eq. 41)[72]



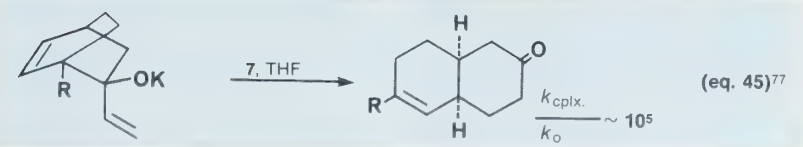
(eq. 42)[73]



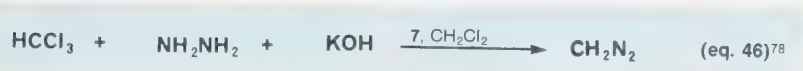
(eq. 43)[73]



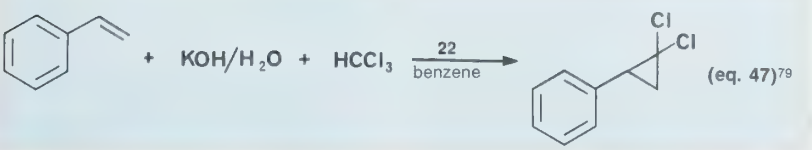
(eq. 44)[76]



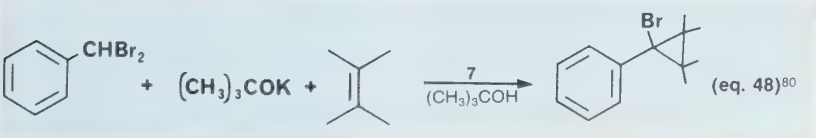
(eq. 45)[77]



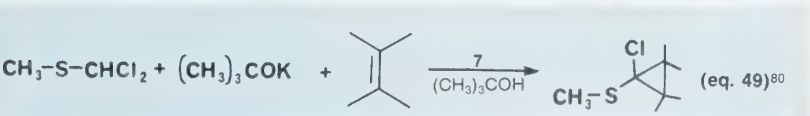
(eq. 46)[78]



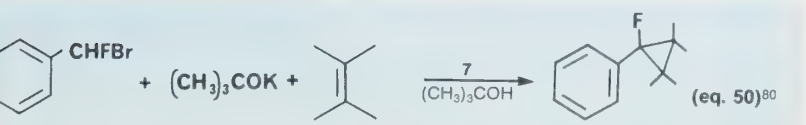
(eq. 47)[79]



(eq. 48)[80]



(eq. 49)[80]



(eq. 50)[80]

chlorocarbenes mimic the quaternary ammonium PT dichlorocarbene formation.

Moss and Pilkiewicz[80] reported the reaction of activated dihalides (*i.e.*, benzal halides, thiomethyl dihalides) with the 18-crown-6 (**7**) complex of potassium *t*-butoxide. The rate of reaction, product yields, and selectivity are similar to those observed for carbenoid intermediates generated by the photolysis of diazirines (eqs. 48-50). Since the halides are generally more readily available than diazirines, this synthetic procedure makes this route to halophenyl carbenes quite attractive.

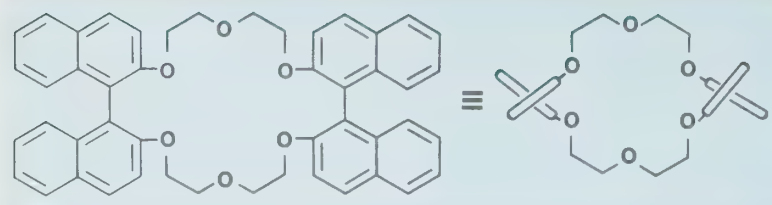
In a somewhat different application of the complexation of crown ethers, Cram and coworkers[27,81] have designed optically active crown ethers, such as the dibinaphthyl crown ether (**24**), which extract alkyl ammonium salts (such as phenethylammonium hexafluorophosphate) from water into chloroform. The optically pure *S,S* crown ether was found to prefer the *R*-enantiomer of phenethylamine over the *S* enantiomer by a ratio of *ca.* 2:1. Because of this chiral recognition, effective partial resolutions of amines can be achieved on a preparative scale in separatory funnels.

Cram also reports that the related optically active diacid binaphthyl-20-crown-6 (**25**) has a great specificity for Sr^{++} ions, even in the presence of a large excess of Ba^{++} ions. For example, hydrolysis of the diester of **25** with barium hydroxide containing 0.8% Sr^{++} as an impurity gives a complex (**26**) where the Sr^{++} had been scavenged from the $Ba(OH)_2$ solution.

Optically pure diacid crown *S*-**25** was found to preferentially complex *S*-valine from a racemic mixture by a ratio of 1:3.

This same chiral recognition approach has recently been extended by Stoddart and coworkers[82] who synthesized a series of chiral 18-crown-6 ligands based on optically active diols. Selective extraction-complexation with the 18-crown-6 ligand (**27**) was observed with enantiomeric amines (as their salts).

The "chiral recognition" achieved by formation of diastereomeric complexes apparently depends largely on complementary steric relationships. Where the "fit" between a chiral ammonium salt and a chiral crown ether is good for one amine enantiomer and poor for its antipode, the selectivity of the crown ether will be high and so will the chiral recognition. As might be expected, a broad range of enantiomer selectivities has been reported. This procedure for partial resolution may be coupled with liquid chromatography to multiply the advantages of enantiomer



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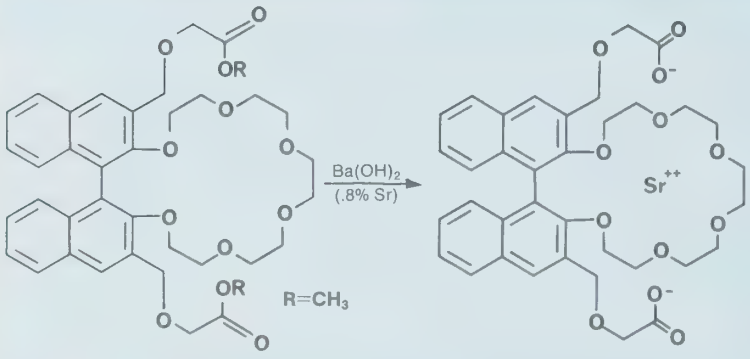

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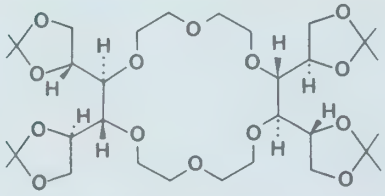

27

selectivity. In this way, Cram and coworkers have achieved total resolution of several amines.

Toxicology

Relatively little toxicity data is available on the crown ethers despite the many structures which have been prepared. This is particularly surprising in light of the cation binding properties of these systems and the biological implications thereof. Pedersen[48] reports that dicyclohexyl-18-crown-6 exhibits an approximate lethal dose (ALD) by ingestion (in rats) of 300 mg/kg. The compound is both a skin and eye irritant and exhibits a somewhat higher toxicity (ALD 130 mg/kg) by skin absorption. Sublethal doses appeared to be non-cumulative.

The cyclic tetramer of ethylene oxide (EO-4, 12-crown-4) has been found by Leong and coworkers[83] to exhibit considerable biological activity. This molecule exhibited deleterious effects on inhalation by rats, and higher homologs showed CNS activity. *It is clear that these and all new crown ethers should be handled with all due caution and respect.*

Conclusion and Prognosis

The report by Pedersen in 1967 that macrocyclic polyethers are effective complexing agents for numerous substrates and his preparation of many of these "crown" molecules has engendered considerable scientific activity during the last eight years. The complexation phenomenon is intrinsically linked to the template effect which allows these large ring com-

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pounds to be prepared in good yields at extraordinarily high concentration.

The crown ethers now seem to be firmly entrenched as phase-transfer catalysts and reagents to influence ionic reactions. They allow for enhanced rates, reactivity, economy, and convenience. For these and as yet unreported reasons, crown ether chemistry will continue to be important in the foreseeable future.

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18,883-2 15-Crown-5
18,665-1 18-Crown-6
15,839-9 Dibenzo-18-crown-6
15,840-2 Dicyclohexyl-18-crown-6

Applications of Phase-Transfer Catalysis in Organic Synthesis

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Organic chemists are frequently faced with synthetic routes which involve the reaction between water-soluble reagents and water-insoluble organic compounds. Traditionally, this problem has been resolved by the use of an appropriate mutual solvent, such as dimethylformamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, or hexamethylphosphoric triamide.[1] There are disadvantages, however, in the use of these dipolar aprotic solvents, especially in their application on an industrial scale, as they are both expensive and difficult to recover. Their use at elevated temperatures may also give rise to complicated side reactions. Alternatively, a water-miscible cosolvent, such as ethanol or dioxane, may be added to the organic phase in order to promote the solubility of the organic compound, but such procedures are not universally applicable. The rate of the heterogeneous two-phase reaction may also be increased by rapid agitation, which increases interfacial contact between the two phases. Such a procedure is not always successful, however, as illustrated by the failure of 1-bromooctane to react with aqueous sodium cyanide under vigorous stirring at 100° for two weeks, the only reaction being the hydrolysis of the cyanide to give sodium formate. The rate of the interfacial reaction may be enhanced by the use of surfactants which disperse the organic compound in the aqueous phase through micellar formation. Such reactions are characterized by the linear dependence of the reaction rate upon the rate of stirring and discontinuity behavior in the dependence of the reaction rate upon the surfactant concentration, due to changes in the micelle size.[2]

During the past few years, due largely to the pioneering work of Brändström, Starks and Makosza,* increasing interest has been centered upon phase-transfer catalysis, also sometimes referred to as "ion-pair partition" or "extractive methylation," as a solution to the problem posed by heterogeneous systems.[4] An increase in the reaction rate for such heterogeneous systems is brought about by the addition of catalytic amounts of an agent which transfers the water-soluble reactant across the interface into the organic phase where a homogeneous reaction can take place rapidly. Thus, in the reaction involving the water-soluble nucleophile, A^- (eq. 1), the addition of the phase-transfer catalyst, Q^+X^-, causes the transfer of the nucleophile as an ion-pair $[Q^+A^-]$ into the organic phase where it reacts with the organic reagent, BX. Migration of the cationic catalyst back to the aqueous phase completes the cycle, which continues until equilibrium has been reached or until all of either the nucleophile, A^-, or the organic compound, BX, has been consumed.

The success of the catalytic effect depends to a large extent upon the high partition coefficient of the ion-pair $[Q^+A^-]$ between the aqueous and organic phases, compared with the corresponding value for the ion-pair $[Q^+X^-]$. Where the leaving group, *e.g.*, Y^-, from the organic compound is not the same as the anion associated with the phase-transfer catalyst, a third partition coefficient for the ion-pair $[Q^+Y^-]$ is significant.[5] As the reaction rate is directly dependent upon the partition coefficient for the ion-pairs between the two phases, it is solvent-dependent. The most commonly used organic solvents are methylene chloride, chloroform and *o*-dichlorobenzene and it has been generally observed that the reaction rate enhancement is greater with the more polar solvents. Quaternary ammonium and phosphonium salts are excellent phase-transfer catalysts and it has been found that salts having the larger and more symmetrical cations, *e.g.*, tetrabutylammonium, methyltrioctylammonium, and tetra-

aqueous phase $Q^+X^- + A^- \rightleftharpoons [Q^+A^-] + X^-$

organic phase $[Q^+X^-] + AB \longleftarrow [Q^+A^-] + BX$ (eq. 1)

* The technique is by no means new, however, and examples of the procedure were reported as long ago as 1926.[3]

butylphosphonium salts, are the most effective.[6,7] Early suggestions that these reagents behave as surfactants have been discounted,[6,7] although the more linear ammonium salts, *e.g.*, cetyltrimethylammonium salts, are known to be micellar catalysts. Crown ethers also serve as efficient phase-transfer catalysts and their activity has been reviewed in earlier issues of *Aldrichimica Acta*.[8]

The versatility, simplicity and speed of phase-transfer-catalyzed reactions make them particularly attractive synthetic procedures. Relatively few kinetic data are available but it appears that reactions induced by phase-transfer catalysis proceed to completion more rapidly than do the corresponding "classical" reactions conducted in a homogeneous medium, while the addition of a phase-transfer catalyst to a heterogeneous system has been observed to produce reaction rate increases of the order of 10^4 to 10^9. In addition, many reactions which hitherto required anhydrous solvents may now be carried out in the presence of water.

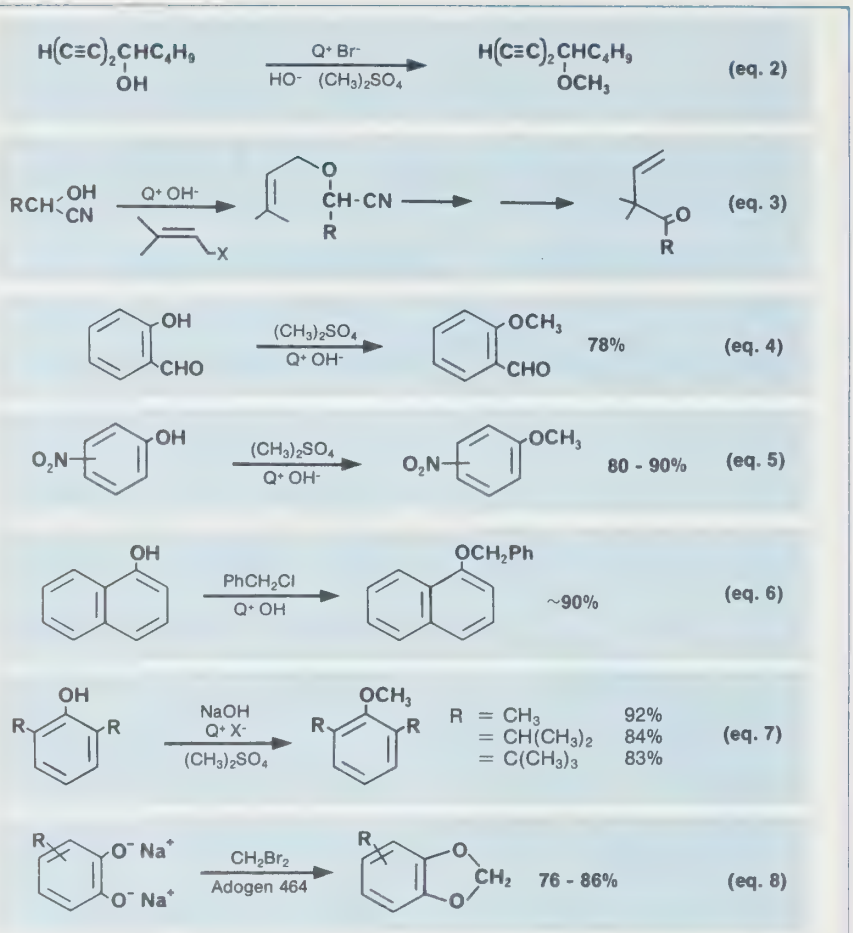
Experimentally, the reactions are very easy to perform. The reagents, appropriately dissolved in water or an organic solvent, are shaken or stirred in the presence of a catalytic amount of, for example, tetrabutylammonium hydrogen sulfate, at room temperature or, if necessary, under reflux conditions. The course of the reactions, which may be complete within a matter of several minutes, may be followed easily by TLC or GLC analysis of the organic layer and the product is readily isolated by separation of the organic phase and evaporation. In many instances the yields are in excess of 90% and, if considered expedient for economic reasons, the catalyst may be recovered and recycled.

NUCLEOPHILIC SUBSTITUTION REACTIONS:

Using phase-transfer catalysis, *SN2* reactions become perfectly simple and straightforward. Examples have been cited in the literature for reactions of alkyl chlorides and bromides with the

$$RX + Y^- \xrightarrow{Q^+} RY + X^-$$

nucleophiles Y = F,[9] Cl,[6a] Br,[6a,10] CN,[6, 11-14] NCO,[6a] HO,[6a] alkyl-O,[15,16] aryl-O,[3,17,18] aryl-S and alkyl-S,[7,19,20] RCO_2,[6a,21-26] and NO_2.[6a] In the majority of cases the reaction times are short when 1-10% catalyst is used and the yields are frequently almost quantitative. Nucleophilic substitution of alkyl iodides, however, requires the use of greater-than-catalytic amounts of the quaternary ammonium salts, due to the high solubility of the quaternary ammonium iodides in organic solvents. Similarly, quaternary ammonium tosylates and mesylates are extremely soluble in organic solvents and, although examples of the nucleophilic displacement of tosyloxy and mesyloxy groups have been reported,[27-29] almost equimolar quantities of the catalyst and substrates must be used. Kinetic studies[30] have suggested that the nucleophilicity of the non-solvated halide ions, produced upon dissolution of the quaternary ammonium salts in organic solvents, follows the order F > Cl > Br > I. However, the conversion of chloroalkanes into the corresponding fluoro compounds requires high temperatures and prolonged reaction times and may be accompanied by elimination reactions.[9] The method of choice for the preparation of fluoroalkanes appears to be by the displacement of an alkyl or aryl sulfonyloxy group.[27-29] It is obvious that reactions which normally require anhydrous conditions or the use of strong bases, such as alkoxides, amides or carbanions, can now be accomplished in the presence of water. In addition to the Williamson-type synthesis of alkyl ethers from alkyl halides, the phase-transfer-catalyzed methylation of alcohols with dimethyl sulfate has been reported.[31] Among the examples cited is the O-methylation of acetylenic alcohols, which occurs without alkylation of the terminal acetylenic group (eq. 2).



The alkylation of cyanohydrins under phase-transfer-catalyzed conditions has been utilized in the synthesis of unsaturated ketones (eq. 3).[32]

The phase-transfer-catalyzed O-alkylation of phenols generally proceeds in yields in excess of 80% and the procedure is particularly attractive for cases where the classical methods give trouble as, for example, in the alkylation of resonance-stabilized phenoxide anions (eq. 4, 5, 6). Moreover, it has been noted that the reaction is virtually insensitive to steric effects (eq. 7).[18]

Although dichloromethane is frequently used as the organic solvent, it has been found that it will react with phenols in the presence of benzyltriethylammonium salts and solid potassium hydroxide to form di(aryloxy)methanes.[33] Similarly, methylenedioxy derivatives, which are usually difficult to prepare by conventional methods, have been obtained in good yield *via* the reaction of the disodium salts of catechols with dibromomethane in the presence of Adogen 464 [$CH_3(C_8\text{-}C_{10})_3N^+Cl^-$] (eq. 8).[34]

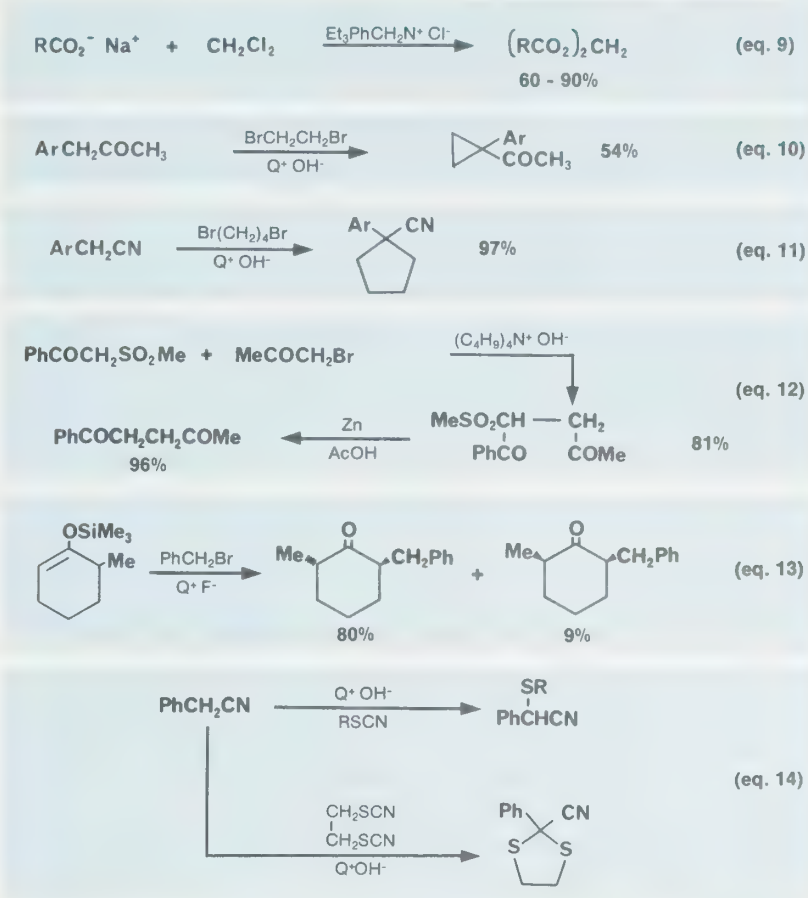
Thiols also react with dichloromethane to give the corresponding dithioethers.[19] The reactions of the dihalogenomethanes are, however, generally slower than the corresponding reactions involving monohalogenoalkanes.

Esterification of carboxylic acids proceeds rapidly under phase-transfer conditions and may be applied to the synthesis of sterically hindered esters.[35] In the absence of other alkylating agents, carboxylic acids react slowly with dichloromethane to give methylene diesters (eq. 9).[26]

Sulfones have been synthesized by the alkylation of sodium arylsulfinates in the presence of tetrabutylammonium bromide[36] and mixed dialkyl phosphates by the reaction of bis(tetraalkylammonium) monoalkyl phosphates with alkyl halides.[37] Phosphorylation of alcohols has also been carried out by means of the phase-transfer-catalyzed reaction with dialkyl phosphites in the presence of either tetrabutylammonium bromide or benzyltriethylammonium chloride.[38] The phase-transfer-catalyzed two-phase system has also been applied to the corresponding Atherton-Todd phosphorylation of amines,[39] and di-*tert*-butyl phosphorochloridate and the analogous bromine derivative have been synthesized by the reaction of the phosphite with the appropriate tetrahalogenomethane under basic conditions in the presence of benzyltriethylammonium chloride.[40] Attempts to prepare other dialkyl phosphorobromidates failed. The heterogeneous reaction of bromoalkanes with silver nitrate to yield alkyl nitrates is accelerated by the presence of tetraethylammonium salts.[41]

An important application of phase-transfer-catalyzed two-phase reactions is the formation of carbanions in the presence of water. The reaction of compounds containing acidic C-H groups with quaternary ammonium hydroxides, generated from the ammonium salts with sodium hydroxide, yields the corresponding quaternary ammonium salts of the carbanion, which, in certain instances, have been isolated.[42,43] The salts are soluble in dichloromethane and react readily with alkylating agents.[6d,42-75] Reaction with an excess of the alkylating agent frequently yields the dialkylated product,[43,49-51,55,60] while dihalogenoalkanes react with the quaternary ammonium salts to give cycloalkanes (eq. 10, 11).[51,56,62,63,67,76]

The phase-transfer-catalyzed reaction of β-keto sulfones with bromoacetone provides a convenient route to γ-dicarbonyl compounds (eq. 12).[77]



In virtually all cases where there are alternative sites for alkylation of the carbanion as, for example, in the reactions of β-dicarbonyl compounds, the C-alkylated products predominate. Only in reactions in which there is a possibility of steric hindrance between the alkylating agent and the carbanionic system is there any evidence of O-alkylation. In such reactions the rate of alkylation is extremely slow and yields of the O-alkylated product are small.[55,63,68] The C-arylation of the quaternary ammonium salts of the carbanions by activated halogenobenzenes has also been reported to proceed in good yields.[78] In contrast, acylation of β-dicarbonyl compounds under phase-transfer conditions has been found to produce the O-acylated derivatives in yields in excess of 75%.[75]

An interesting variation of the alkylation of quaternary ammonium enolates, generated by proton extraction from the ketone, is the displacement of a trimethylsilyl group from silyl enol ethers by quaternary ammonium fluorides in the presence of an alkylating agent (eq. 13).[72] Such reactions have been shown to be regiospecific, monoalkylation occurring at the least substituted α-C atom. (The cleavage of silyl enol ethers by quaternary ammonium fluorides[79] appears to be superior to procedures using potassium fluoride.)

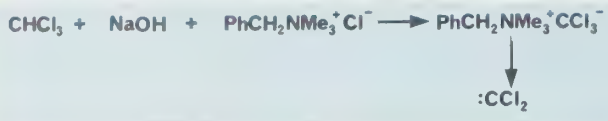
The asymmetric alkylation of ketones using chiral quaternary ammonium salts has met with only limited success.[80]

Carbanions, generated under phase-transfer conditions, react with organic thiocyanates to give thioethers.[81] Thioketals have been synthesized by a similar route (eq. 14).[81]

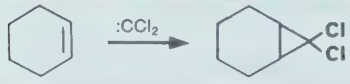
Reissert compounds, derived from isoquinoline, have been alkylated at the 1-position under the influence of quaternary ammonium bases.[82]

FORMATION OF CARBENES:

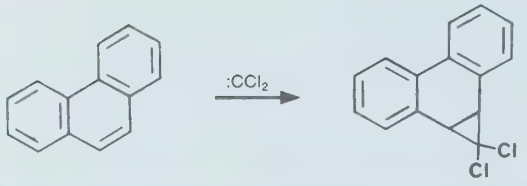
Perhaps the most impressive use so far made of phase-transfer catalysts is in the generation of carbenes. The dihalogenocarbenes can be generated readily under very mild conditions and can be utilized as standard reagents.[6d,81,83-132] Thus, a very wide range of dichlorocyclopropane derivatives have been synthesized from dichlorocarbenes, generated from the reaction of chloroform and aqueous sodium hydroxide in the presence of a quaternary ammonium salt (usually benzyltriethylammonium chloride) (eq. 15, 16, 17).



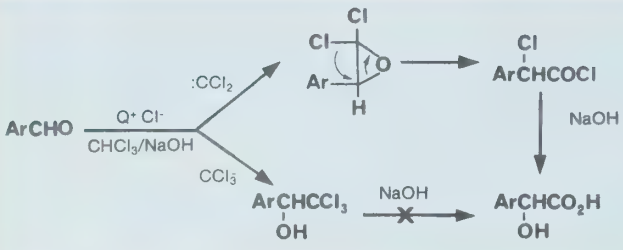
(eq. 15)



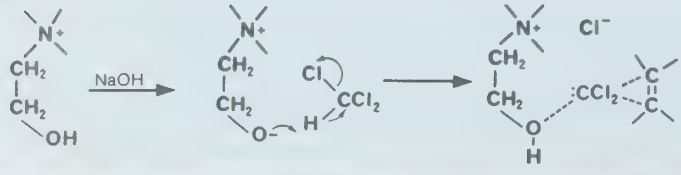
98% (eq. 16)



79% (eq. 17)



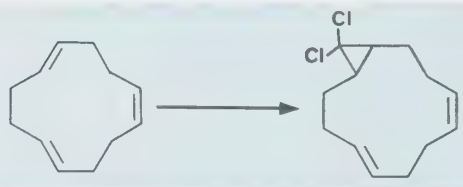
(eq. 18)



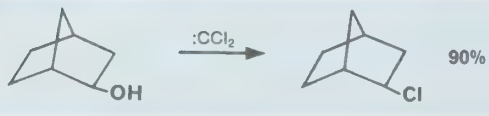
(eq. 19)

62% (eq. 20)

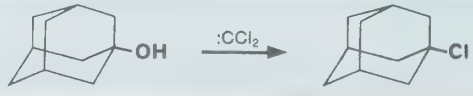
93% (eq. 21)



72% (eq. 22)



90% (eq. 23)



94% (eq. 24)

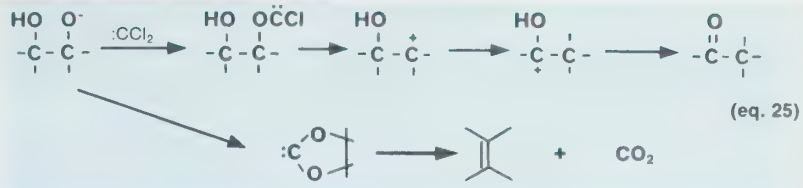
The corresponding production of dibromocarbene from bromoform is generally poor and good yields of the dibromocyclopropanes are obtained only by the use of an excess of bromoform and prolonged reaction time.[85,101,102,107,123,124,126-128] Bromofluorocarbene,[129] chlorofluorocarbene,[129,131] and fluoroiodocarbene[130] have been generated by similar procedures and the method appears to be particularly effective for the production of diiodocarbene.[132] It has been shown, however, that monohalogenocarbenes cannot be generated in the two-phase system.[4] The stronger electron-withdrawing effect of a cyano group, however, allows the formation of monocyanocarbene under the mildly basic conditions.[133,134]

As indicated above, the dihalogenocarbenes are generated in the organic phase *via* the trihalogenomethyl anion. It has been assumed that the reaction of carbenes with alkenes produces the cyclopropane derivatives, whereas reactions involving the trihalogenomethyl anion generally yield open-chain products. The mechanism of the phase-transfer-catalyzed addition reactions, however, appears to depend upon the electronic character of the unsaturated system.[96,135,136] The conversion of aryl aldehydes into mandelic acids has been shown to proceed *via* the carbene and not through nucleophilic attack by the anion upon the carbonyl group (eq. 18).[125]

Dichlorocarbene, when generated in the presence of tetraalkylammonium salts, generally reacts at all available unsaturated sites of a polyalkene.[89] However, when β-hydroxyethylammonium salts are used to generate the carbene, selective addition of the carbene to only one site occurs.[119] It has been suggested that a complex (eq. 19) is formed between the hydroxyalkylammonium ion and the carbene and, although it has been shown that β-hydroxyethylammonium salts greatly enhance the rate of *SN2* reactions,[137,138] the formation of the complex presumably reduces the reactivity of the carbene. The addition reactions appear to occur invariably at the more reactive highly substituted unsaturated sites (eq. 20,21), but it is not immediately obvious why the *trans* alkenic bond is more readily attacked than the *cis* bond in the cyclododeca-1,5,9-triene system (eq. 22). The use of a chiral β-hydroxyethylammonium salt appears to result in some asymmetric induction in the reaction.

When dichlorocarbenes are generated in the presence of an alcohol, the normal deoxygenation reaction occurs with the formation of the corresponding chloroalkane *via* the carbonium ion intermediate (eq. 23, 24).[87,96]

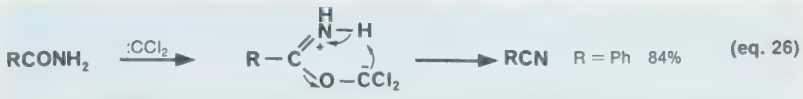
1,2-Diols react with dichlorocarbene, generated under phase-transfer conditions, to yield ketones and alkenes, possibly by the mechanisms shown in eq. 25.[110]



(eq. 25)

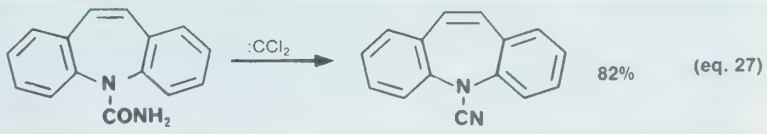
Amides are dehydrated efficiently to give nitriles in a two-phase system (eq. 26, 27). Yields vary from *ca.* 10 to 90%.[104,109]

The use of a phase-transfer catalyst represents a major improvement upon the classical Hofmann carbylamine reaction for the synthesis of isonitriles (eq. 28).[90,91]



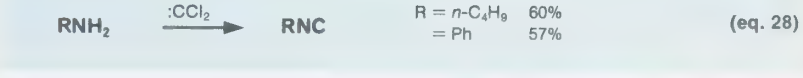
(eq. 26)

Under similar conditions secondary amines yield formamido derivatives (eq. 29)[115] and tertiary amines react with C-N cleavage (eq. 30).[105]



(eq. 27)

The aziridines, produced from the reaction of imines with dichlorocarbene, rearrange under the basic phase-transfer conditions to yield α-chloroacetamides (eq. 31).[118]

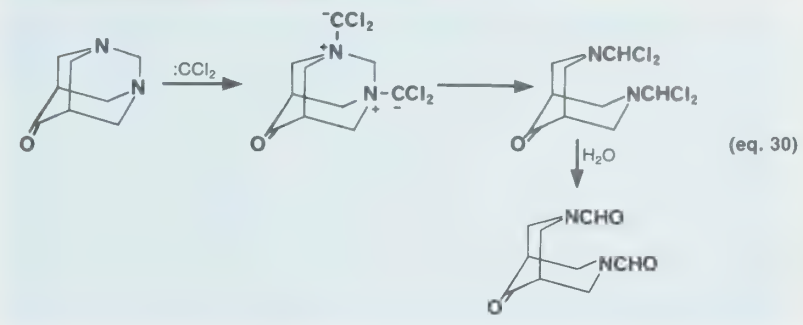


(eq. 28)

The ring expansion of indoles into 3-halogenoquinolines proceeds cleanly and in moderate yields under phase-transfer-catalyzed conditions.[139]

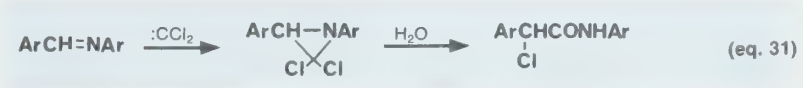
(eq. 29)

Phase-transfer catalysts have also been used to prepare vinylidene carbenes from 3-chloroprop-1-ynes and from 1-chloroprop-1-ynes.[140–143] 1-Halogenoallenes react in a similar manner.[140] In the presence of alkenes the expected reaction to give vinylidenecyclopropanes occurs (eq. 32),[140–142] but in an interesting rearrangement reaction which involves N-N cleavage, dimethylvinylidene carbene reacts with azobenzene to give a benzimidazole derivative (eq. 33).[143]



(eq. 30)

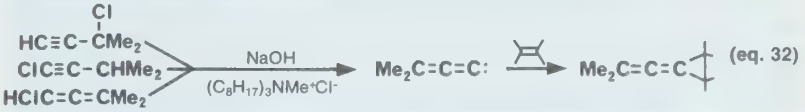
N-β-Hydroxyethyl-N-nitrosoacetamides yield vinylidene carbenes under basic conditions in the presence of quaternary ammonium salts (eq. 34).[144–146]



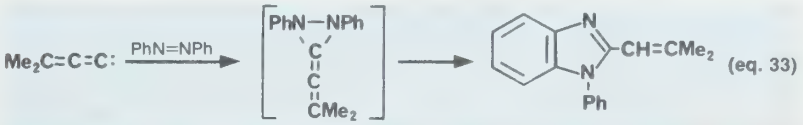
(eq. 31)

N-ALKYLATION REACTIONS:

The phase-transfer-catalyzed alkylation of acidic NH-compounds proceeds cleanly and, in the majority of cases, in excellent yield. The alkylation of acetanilide and of phthalimide generally requires reaction temperatures of between 60 and 100°,[147,148] while pyrroles and indoles react exothermically with primary and secondary alkyl halides.[149–151] Alkylation with tertiary alkyl halides fails,[150] presumably due to a preferential elimination reaction.

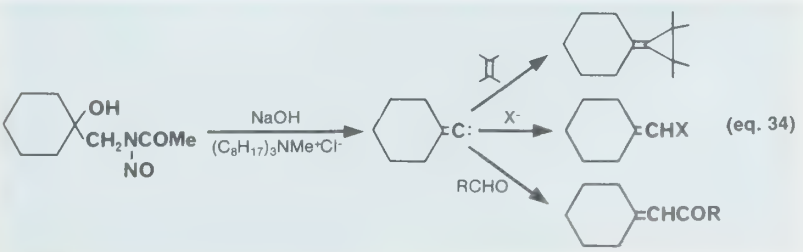


(eq. 32)



(eq. 33)

The alkylation of 1,4-dihydropyridines under phase-transfer conditions has also been reported.[152]



(eq. 34)

OXIDATION REACTIONS:

In the presence of quaternary ammonium and phosphonium salts, permanganate ions are transferred efficiently into benzene ("purple benzene") and they

oxidize terminal alkenes in the organic phase to give carboxylic acids having one carbon atom less than the alkene.[6a,153,154] Non-terminal alkenes are oxidized to 1,2-diols under strongly alkaline conditions in dichloromethane.[155] Diols, which are highly soluble in water, are oxidized with C-C cleavage to dicarboxylic acids in the aqueous phase of the two-phase system. Benzonitrile, benzyl alcohol and stilbene are oxidized by tetrabutylammonium permanganate in benzene to give benzoic acid[155] in yields in excess of 90%.

Quaternary ammonium perchlorates have been prepared and used as oxidizing agents in chloroform.[156]

REDUCTION REACTIONS:

The rate of reduction of ketones to the corresponding alcohols with sodium borohydride is greatly enhanced in a two-phase system by the addition of quaternary ammonium salts.[6a,157,158] Tetraalkylammonium borohydrides can be extracted almost quantitatively into dichloromethane from an aqueous sodium hydroxide solution of sodium borohydride upon the addition of the tetraalkylammonium salt. Evaporation of the organic phase yields the solid ammonium borohydride,[5,159,160] which, in spite of its low reactivity, has been used extensively for reductions in organic solvents.

The reagent has been used, for example, in the synthesis of 1,3-dioxolanes from 2-methoxyethyl carboxylates (eq. 35).[161]

Attempts to induce asymmetric reduction of ketones by the use of chiral quaternary ammonium salts have met with varied success.[157,158] The degree of asymmetric induction depends upon the structure of the ketone and is enhanced by a high concentration of catalyst.

In general it has been assumed that diborane can be generated and used only in ethers. It is possible, however, to produce diborane in dichloromethane through the reaction of tetrabutylammonium borohydride with alkyl halides (eq. 36). The diborane so produced is as versatile and, in many respects, more reactive than that generated by classical procedures. Thus, in addition to the normal reduction of nitriles, aldehydes and ketones to amines, primary and secondary alcohols respectively, it has been found that esters are also reduced to give alcohols. Hydroboration of alkenes in dichloromethane and the subsequent almost quantitative conversion into alkyl alcohols by the addition of sodium hydroxide and hydrogen peroxide is extremely simple.

Tetrabutylammonium cyanoborohydride has been prepared and used for the reduction of alkyl iodides and bromides at room temperature.[162]

Dialkyl disulfides are reduced to thiols in high yield by formamidinesulfinic acid in the presence of cetyltributylammonium bromide and aqueous sodium hydroxide (eq. 37).[163]

ELIMINATION REACTIONS:

The rate of elimination of halogen acids from halogenoalkanes is dramatically increased by the addition of a phase-transfer reagent, particularly when the products are conjugated (eq. 38).[4] A phase-transfer catalyst has also been used in the preparation of dichloroacetylene from tetrachloroethylene.[164]

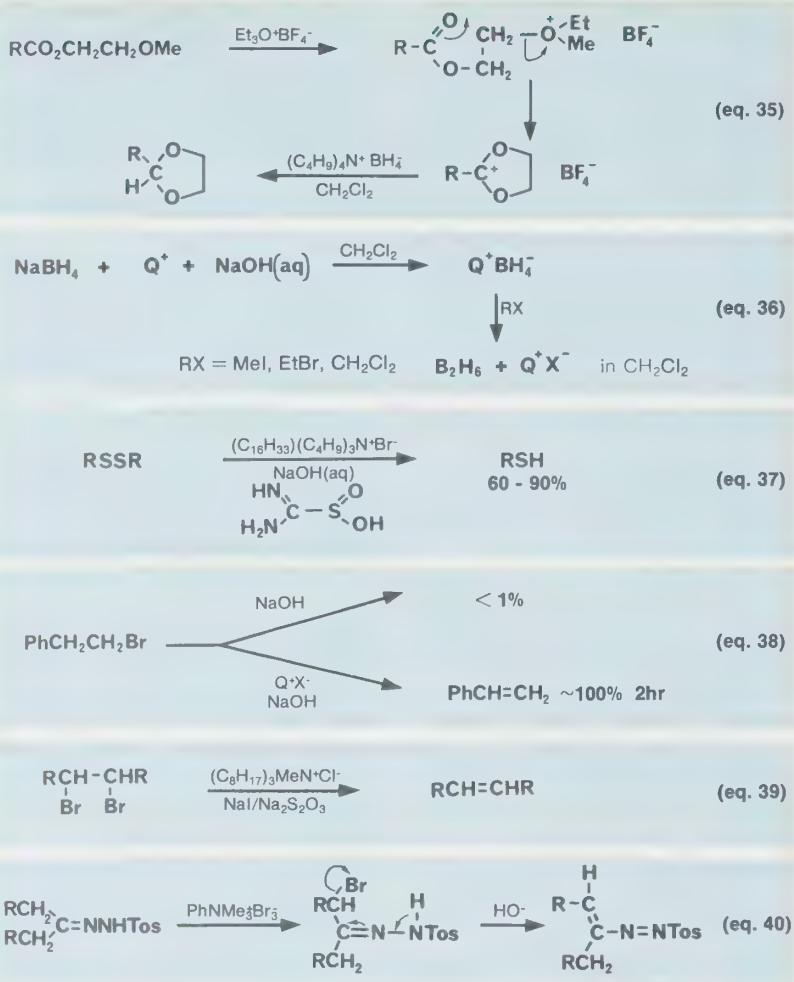
The reaction of 1,2-dibromoalkanes with sodium iodide in the presence of sodium thiosulfate and methyltrioctylammonium chloride proceeds easily to give the alkenes in 85-95% yield (eq. 39).[165]

Trimethyl(phenyl)ammonium perbromide brominates tosylhydrazones which, under basic conditions, eliminate HBr with the formation of tosylazo derivatives (eq. 40).[166]

The elimination of triphenylsilane from 2-triphenylsilylalk-1-enes to give allenes has been found to be catalyzed by quaternary ammonium fluorides.[167]

ADDITION REACTIONS:

Tetraethylammonium bromide catalyzes the addition of ethylene oxide to aldehydes and ketones to form 1,3-dioxolanes.[168] It has been postulated that tetraethylammonium β-bromoethoxide is formed, which acts as a nucleophile in the initial step of the reactions. The same intermediate is involved in the phase-transfer-catalyzed reaction of ethylene oxide with alkyl halides in the formation of β-halogenoethyl ethers.[169] Highly reactive sulfur ylides have been formed in the presence of water and have been employed in the synthesis of oxiranes through their reaction with aldehydes and ketones (eq. 41).[170,171] Both trimethylsulfonium iodide and trimethyloxosulfonium iodide are converted into the sulfur ylides in dichloromethane by aqueous sodium hydroxide in



the presence of tetrabutylammonium salts. A six-membered ring by-product is produced in the reaction of benzaldehyde with trimethyloxosulfonium iodide (eq. 42) and a similar 2:1 cyclized adduct results from the base-catalyzed reaction of benzaldehyde with dimethyl sulfone (eq. 43).[172] In none of the reactions is there any evidence of a Cannizzaro reaction in the case of benzaldehyde, or of aldol condensation products from other aldehydes.

α,β-Unsaturated ketones yield cyclopropyl ketones in high yield in their reaction with the ylide derived from trimethyloxosulfonium iodide under the phase-transfer conditions (eq. 44).[170]

Utilization of chiral β-hydroxyethyl quaternary ammonium salts results in the enantioselective ring closure in the formation of the oxiranes from aldehydes and the ylide derived from trimethylsulfonium iodide.[171]

Oxiranes have also been prepared *via* the phase-transfer-catalyzed reaction of chloromethylsulfones and aldehydes or ketones.[173] It was assumed that a carbanionic intermediate is involved in the reaction, but it is possible that a carbene is generated. The sulfonyloxiranes, which hitherto had been assumed to be of limited stability, may be isolated under the mild phase-transfer conditions (eq. 45).

The Michael addition reaction to α,β-unsaturated ketones and esters is catalyzed by tetrabutylammonium cyanide (eq. 46).[12] In the carbohydrate field, it has been observed that the use of phase-transfer catalysis favors the formation of the thermodynamically less stable isomer in the addition of carbanions to nitroalkenes (eq. 47).[174]

The catalyzed addition of phenylacetonitrile to acetylenes under basic conditions has also been reported (eq. 48).[175,176]

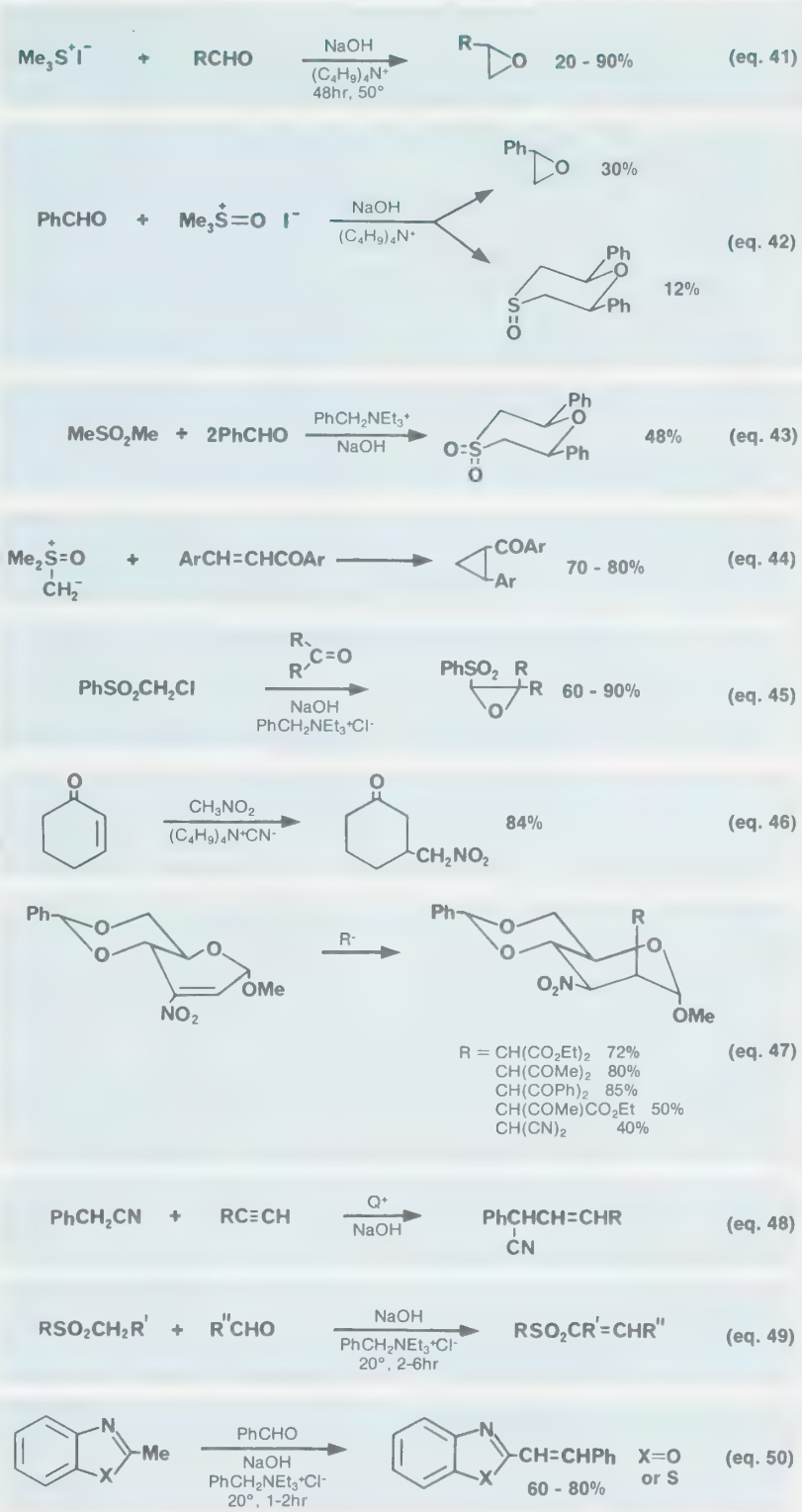
CONDENSATION REACTIONS:

The benzoin condensation of benzaldehyde may be effected by tetrabutylammonium cyanide under considerably milder conditions than those used in the classical procedures.[12,177] The reaction may be carried out in water in the absence of an organic phase.

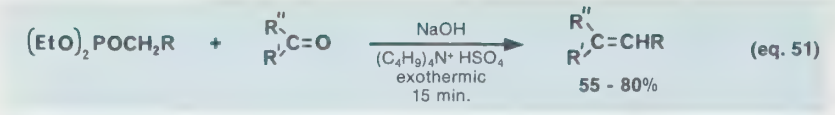
The base-catalyzed condensation of aldehydes with sulfones to give α,β-unsaturated sulfones (eq. 49)[178] and the synthesis of 2-styrylbenzazoles (eq. 50)[179] have been shown to be catalyzed by benzyltriethylammonium chloride.

WITTIG AND WITTIG-HORNER REACTIONS:

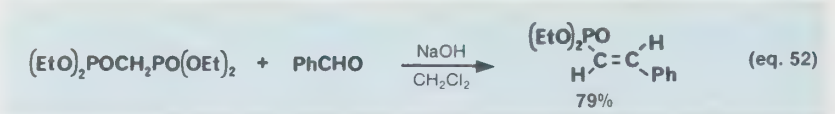
Application of phase-transfer catalysis permits the generation of phosphoranes and phosphonate anions by aqueous sodium hydroxide without recourse to strong bases or anhydrous solvents. Quaternary ammonium salts have been used[52,180–182] but, as phosphonates and, in particular, phosphonium salts are excellent phase-transfer catalysts, it is possible to conduct both the Wittig and the Wittig-Horner reactions in two-phase systems without the addition of a catalyst.[183–187] Although the yields obtained with and without a quaternary ammonium salt are comparable, the rates of the reactions at room temperature are invariably slower when a catalyst is not used.



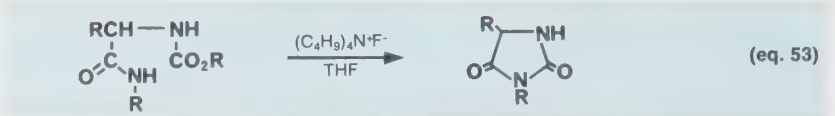
In the preparation of α,β-unsaturated sulfides (R = SPh, R′ = Ph, R″ = H) it has been noted that the *E* : *Z* isomer ratio depends upon the catalyst used, being higher with the more efficient catalysts (eq. 51).[52,181] In the absence of an added catalyst the tetraethyl bis-phosphonate reacts with benzaldehyde to give exclusively the *E*-isomer (eq. 52).[187]



(eq. 51)



(eq. 52)



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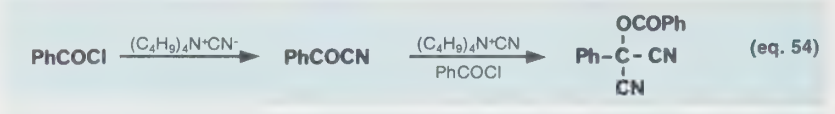
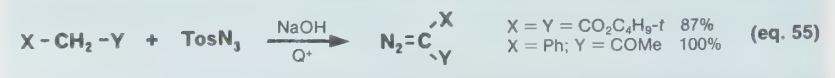


(eq. 54)



(eq. 55)

MISCELLANEOUS REACTIONS:

The hydrolysis of carboxylic esters by aqueous sodium hydroxide is aided by the addition of quaternary ammonium salts.[6a,188,189] The rate enhancement is most significant in the hydrolysis of low molecular weight esters. Thus, for example, although dimethyl adipate is inert to 50% aqueous sodium hydroxide at room temperature over a period of several hours, the addition of a catalytic amount of tri(hexadecyl)methylammonium chloride produces an exothermic reaction and hydrolysis is complete in 30 min.[6a] The catalytic effect is less powerful in the hydrolysis of long-chain carboxylic esters, due possibly to the formation of strong ion-pairs between the quaternary ammonium ion and the carboxylate anion, which are highly soluble in the organic phase. Hydrolysis tends to stop after 35% reaction, but further addition of catalyst does not produce any appreciable continuation of the reaction.[6a] It is apparent that quaternary ammonium hydroxides are stronger bases than they are nucleophiles in organic solvents, as they rapidly generate the carbanion from ethyl acetoacetate without any significant hydrolysis of the ester group. Use is made of the reactivity of the non-solvated fluoride ion in the catalytic effect of tetrabutylammonium fluoride in the synthesis of hydantoins (eq. 53).[190]

Tetrabutylammonium azide has been employed in the Curtius rearrangement reaction for the preparation of acyl azides in toluene[191] and, in a similar reaction, the moisture-sensitive aroyl cyanides have been synthesized in *ca.* 60% yield from aroyl chlorides and tetrabutylammonium cyanide in dichloromethane.[192] A further reaction can occur between the aroyl cyanide and the reactive cyanide ion to yield a higher molecular weight by-product (eq. 54).

The synthesis of α-diazoalkanes is improved by the addition of quaternary ammonium salts (eq. 55).[193]

Quaternary ammonium salts have also been utilized in D/H exchange reactions[6a] and, in place of ion-exchange resins, in the conversion of iodides into chlorides.[194]

EVALUATION OF CATALYSTS:

In early studies, Makosza examined the catalytic activity of different quaternary ammonium salts in the ethylation of benzyl cyanide.[4] It is evident that the benzyltriethylammonium ion is more effective than the more symmetrical tetraethylammonium ion.[cf195] Similarly, the efficiency of alkyltriethylammonium ions, [$Me(CH_2)_n$-NEt_3^+] in the catalytic elimination of hydrogen bromide from 2-phenylethyl bromide increases to a maximum when n = 5, but falls off only slightly through to n = 11,[4] while the maximum activity with alkyltrimethylammonium ions was found with the butyl derivative.[196]

As indicated in the Introduction, the rate of reaction depends to a great extent upon the ability of the quaternary ammonium ion to transfer the reactive anionic species into the organic phase as an ion-pair and is therefore dependent, not only upon the structure of the ammonium ion, but also upon the anion. Consequently, no one catalyst can be said to be universally the most effective. Thus, for example, the activities of different catalysts upon the generation of carbenes,[122] *SN2* reactions,[7] and the transfer of the permanganate anion into organic solvents[155] have been examined. It is generally accepted that benzyltriethylammonium chloride is the catalyst of choice for carbene reactions, whereas methyltrioctylammonium chloride and tetrabutylammonium hydrogen sulfate are the most effective for the other two reactions, respectively. These three salts are the most commonly employed phase-transfer catalysts and they are commercially available. Other quaternary ammonium salts are frequently used, however, as are phosphonium salts. Although the selected kinetic data presented in the Table show phosphonium salts to be as efficient as many ammonium salts in *SN2* reactions, they are less frequently used, due to their susceptibility to decomposition, particularly under basic conditions, and to their proneness to side reactions.

Second-Order Rate Constants for the Reaction of Thiophenoxide with 1-Bromooctane in Benzene:Water[7]

Catalyst (0.00137 mol)	k x 10^3 $M^{-1}sec^{-1}$
$Me_4N^+Br^-$	<0.0016
$PhCH_2NEt_3^+Br^-$	<0.0016
$C_{16}H_{33}NMe_3^+Br^-$	0.15
$C_{16}H_{33}NEt_3^+Br^-$	0.48
$(C_4H_9)_4N^+Br^-$	5.2
$(C_8H_{17})_3NMe^+Cl^-$	31.0
$Ph_3PMe^+Br^-$	1.7
$C_{16}H_{33}PEt_3^+Br^-$	1.8
$Ph_4P^+Br^-$	2.5
$(C_4H_9)_4P^+Cl^-$	37.0
$(C_8H_{17})_3PEt^+Br^-$	37.0

Recently, renewed interest has been shown in the catalytic effect of tertiary amines as catalysts for two-phase systems but, in general, they are less effective than the quaternary ammonium salts.[15,113,197,198]

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Recent Advances in Synthetic Pyrethroids

Alfred Bader

How is great research achieved?

Perhaps a systematic study of how research is carried out in various countries is just not possible, as it would require intimate knowledge of so many research groups. Even today, when great research is being done so openly by many academic research teams, often in the same or adjacent buildings — R.B. Woodward's or E.J. Corey's groups at Harvard, for example — there has not been a systematic study of how this differs from country to country, from industrial to academic laboratories, or even from one professor's laboratory in the same building to the next. One can come close to understanding how academic research was done fifty to a hundred years ago by reading those wonderfully informative obituaries of great chemists that appeared in the Berichte. Also, some autobiographies, such as "Aus meinem Leben" by Richard Willstätter, are most informative. Today, however, chemists write much less personally: too many heed that most foolish of sayings that time is money. Time is the one commodity that money cannot buy, and we are so busy "doing" chemistry that we seldom reflect how it could be done best.

Naturally, as a supplier of building blocks for organic chemical research, we are most interested in how research is being done, and most suggestions for our new compounds have come from great research laboratories around the world. Thus, we were very interested in meeting, and discussing research in general and his research in particular, with Dr. Michael Elliott of the Rothamsted Experimental Station in Harpenden, Hertfordshire, England, whose work is likely to change the world's agriculture as fundamentally and more lastingly than the chlorinated hydrocarbons such as DDT have done earlier.

Dr. Elliott, born in London in 1924, educated at University College at Southampton and King's College, University of London (Ph.D. and D. Sc.), is a most approachable chemist, and when I called him from London recently, he readily invited me to his laboratories in Harpenden, and he subsequently visited Aldrich for a day to discuss our interest in providing building blocks for synthetic pyrethroids. (Fig. 1 shows Dr. Elliott with Dr. Irwin Klundt and Mr. Charles Pouchert of Aldrich.)

Dr. Elliott's interest in the chemistry of pyrethrins started when he was a student with Professor Stanley Harper, with whom he moved from Southampton to London. From London, Dr. Elliott went directly to the Rothamsted Experimental Station where work on pyrethrins had been guided by Dr. Frederick Tattersfield and Dr. Charles Potter, who had realized the great importance of a stable supply of insects to the studies of structure-activity relationships, and who had built a multidisciplinary team at the Experimental Station. Today the team associated with Dr. Elliott includes organic chemists Dr. Norman F. Janes (Fig. 2) and Dr. David A. Pulman (Fig. 3), an electrophysiologist, Mr. Paul Burt, and entomologists Dr. Andrew W. Farnham and Mr. Paul H. Needham. This team works in modest, cluttered laboratories, much like university laboratories built in the thirties, and one gets no inkling

Fig. 1. From left to right, Mr. Pouchert, Dr. Elliott and Dr. Klundt.

from discussions with these modest scientists that they are doing fundamental work on which the giants of the world's chemical industry — ICI, Roussel-Uclaf, FMC, Sumitomo and others — are spending millions in efforts to commercialize these inventions.

Naturally, my first question to Dr. Elliott was how he believed his research differs in method from that in the laboratories of the industrial giants. The Rothamsted research on pyrethroids has been supported by the National Research Development Corporation which has patented the active compounds and has licensed these to the companies mentioned, and so Dr. Elliott has been able to compare their research efforts with those of his own team. In some of the laboratories of the chemical giants, one group of chemists makes the new compounds. These are then computer-coded and eventually — often months later — fed to insects by scientists

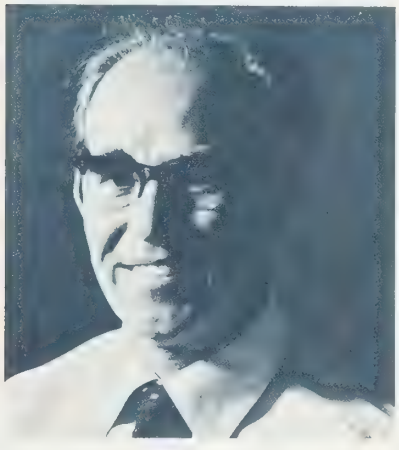
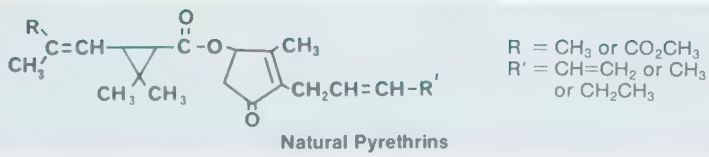


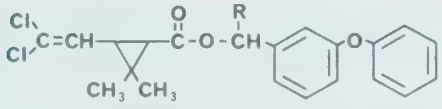
Fig. 2. Dr. Norman F. Janes

who may not even know the chemists who made the chemicals, and it may be months later before the synthetic chemists get the neatly tabulated test results. All this is often impersonal and always time-consuming. At Rothamsted, a compound synthesized in the morning is sometimes tested for its insecticidal activity the same afternoon, by scientists working in proximity. They know and talk to each other, and have only one aim — to produce quickly the most active, least toxic compound of the series being studied to establish fundamental structure-activity relationships. Clearly it is easier to find active compounds in such an environment.

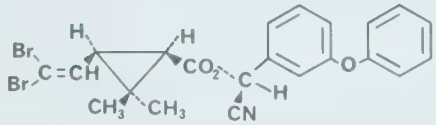
The natural pyrethrins are the active insecticidal ingredients of pyrethrum flowers. Their chemistry has been carefully reviewed;[1a-d] they are esters of cyclopropanecarboxylic acids and alkenylcyclopentenolones.



Natural Pyrethrins



NRDC 143 (R=H)
NRDC 149 (R=CN)



NRDC 161

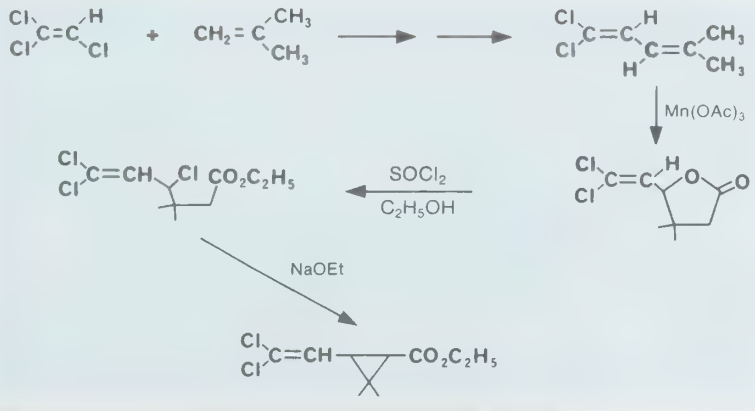
Until relatively recently, the interest in the pyrethrins as insecticides was greatly overshadowed by the interest in the chlorinated hydrocarbons, phosphates and carbamates, because these are generally much more easily made and more stable than the pyrethrins. The pyrethrins, however, have the great advantages of being biodegradable, much less volatile, and harmless to mammals, and so the environmentalists' concern about DDT, Aldrin, Dieldrin, etc., has shifted interest to the synthetic pyrethroids which have been studied by Dr. Elliott and his coworkers since the sixties. Many hundreds of analogs of the natural pyrethrins have been made, and the relationship between structure and activity has been studied in detail.[2]

To date, the three most promising compounds are NRDC 143, NRDC 149 and NRDC 161.

All three compounds appear very difficult to prepare, and their facile preparations are the result of work by some of the ablest chemists in the world's giant chemical companies.

The acid moiety was the more difficult to synthesize, and Professor Ralph A. Raphael of Cambridge University electrified this September's symposium on synthetic pyrethroids in San Francisco when he described the as yet unpublished preparation from trichloroethylene and isobutylene, developed by Dr. Peter Cleare at ICI. Trichloroethylene and isobutylene are condensed to 1,1-dichloro-4-methyl-1,3-pentadiene which is then converted to a lactone with manganic acetate. When this is treated with thionyl chloride and ethanol, it yields an ester which can be cyclized to the key cyclopropanecarboxylic ester required for NRDC 143.

FMC chemists reported a parallel synthesis of this ester at the same symposium. It proceeds *via* the same dichloromethylpentadiene, which is converted to the ester with ethyl diazoacetate. FMC reported raw materials cost by this route to be low, only about $2.50/lb, but the cost of a plant to handle ethyl diazoacetate safely is likely to be much higher than that for the ICI process.



m-Phenoxybenzyl alcohol and *m*-phenoxybenzaldehyde are much more easily made, but how best to do this on the hundreds-of-tons scale that may be needed? We understand that an air-oxidation process from *m*-phenoxytoluene, which is readily available from phenol and *m*-cresol, has been developed. Also *m*-phenoxytoluene can be halogenated and hydrolyzed to *m*-phenoxybenzyl alcohol which can be easily oxidized to the aldehyde. Alternately, the benzal halide can be converted to the aldehyde directly. These methods, however, involve a raw material cost estimated at $5-6 per lb of alcohol or aldehyde, which may be too high for economic feasibility.

Aldrich became interested in *m*-phenoxybenzyl alcohol when we were asked to study the reduction by hydroboration of *m*-phenoxybenzoic acid, easily made by the oxidation of *m*-phenoxytoluene. We had no problem scaling up the hydroboration and made several hundred pounds of the alcohol. However, it became clear that this process could not compete economically with the alternate routes.

Fig. 3. Dr. David A. Pulman

Shortly after completion of this work, we found a much better synthesis of *m*-phenoxybenzyl alcohol *via* the aldehyde. This uses neither *m*-phenoxytoluene nor the acid, and has an intrinsically lower raw material cost than the syntheses from *m*-phenoxytoluene. Just at that time, attention focused on NRDC 161, the ester of the cyanohydrin of the aldehyde, so the aldehyde itself became important. We believe that we have a more economical synthesis of the aldehyde than any involving the oxidation of *m*-phenoxybenzyl alcohol and, in fact, the most economical preparation of the alcohol may be *via* the reduction of the aldehyde made by our method.

We at Aldrich do not have any large-scale equipment and certainly could not make many tons ourselves. However, some time ago I discussed the industrial production of the aldehyde with one of my best friends, Bert Van Deun, at Janssen Pharmaceutica in Belgium. The Janssen engineers then scaled up the process using specific technology developed within the company, and so we have licensed Janssen to prepare the aldehyde, and hope that they will be able to fill much of the demand.

Naturally, we were most interested to learn what the contributions of the NRDC licensees have been. As we understand the situation, it is as follows: ICI may have made the greatest synthetic efforts, particularly towards NRDC 143, culminating in Dr. Cleare's work discussed. Shell appears to have concentrated on new structures, and FMC with ICI (U.S.), the licensees in the Western Hemisphere, have emphasized studies of biological activity. Roussel-Uclaf has developed elegant syntheses of chrysanthemic acid, either *via* a sulfone[3] derived from isoprene, and β,β-dimethylacrylic acid (which may explain why we have sold many tons of this recently) or *via* addition of this sulfone to an isopropylidenemalonate ester.[4] All the most active compounds are resolved, optically active isomers; for example, the (+)-*trans*-chrysanthemates and analogs are active while the (-)-*trans*-isomers are virtually inactive. Thus, resolution is very important, and the best methods appear to have been developed by chemists at Roussel-Uclaf.[5] Sumitomo's contributions have been both in synthetic innovations and of new structures. They have prepared the esters *via* the triethylamine salt of *m*-phenoxybenzyl bromide without isolation of the alcohol. Also, they have shown[6] that the cyclopropane moiety is not essential to activity: 'Sumicidin,' S5602, is the *p*-chloro-α-isopropylphenylacetate of the cyanohydrin of *m*-phenoxybenzaldehyde.

Just how active these synthetic pyrethroids are in comparison with the older insecticides can be seen from this table.[7]

	Relative toxicity to	
	house flies	mustard beetles
Parathion	37	7
DDT	4-15	11
Dieldrin	35	4-10
NRDC 161	2300	1600

This much greater insecticidal activity, coupled with their low mammalian toxicity and biodegradability, makes it appear likely that these pyrethroids will become important insecticides in the future.[8]

Because of my interest in art, I am often asked how I believe motivation between great artists and great chemists differs. The great chemists often achieve greatness because they want to be the first to reach a difficult goal: R.B. Woodward must have known that if he did not synthesize quinine or strychnine and Vitamin B_{12}, *someone else would*. A great artist paints because he knows that if he does not create this great work, no one else will. If Rembrandt had not painted that marvellous "Return of the Prodigal Son" now in the Hermitage, *no one else would have*. This rather pat answer falters when considering Dr. Elliott's work: would NRDC 161 really have been made without him and his team? Probably not, or at least not for a very long time: in the case of men like Elliott, the motivation of scientists and that of artists overlap.

Please contact Aldrich for quotations on bulk quantities of:

19,175-2 m-Phenoxybenzaldehyde

19,028-4 m-Phenoxybenzyl alcohol

References:

1) a) L. Crombie and M. Elliott, *Fortschr. Chem. Org. Naturst.*, **19**, 120 (1961).
   b) M. Elliott, *Chem. Ind. (London)*, 776 (1969).
   c) M. Matsui and I. Yamamoto in "Naturally Occuring Insecticides," M. Jacobson and D.G. Crosby, Eds., Marcel Dekker, New York, N.Y., 1971, Chapter 1.
   d) M. Elliott and N.F. Janes in "Pyrethrum, The Natural Insecticide," J.E. Casida, Ed., Academic Press, New York and London, 1973, Chapter 4.
2) M. Elliott, *Bull. W.H.O.*, **44**, 315 (1971).
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4) M. Julia and A. Guy-Rouault, *ibid.*, 1411 (1967).
5) B. Goffinet and A. Locatelli, French Patent 1,536,458 [C.A. **71**, 90923w (1969)].
6) N. Ohno *et al., Agric. Biol. Chem.*, **38** (4), 881 (1974).
7) Abstracted from M. Elliott *et al., Nature*, **248**, 710 (1974).
8) For the most recent work on pyrethroids, see the abstracts of the symposium on synthetic pyrethroids held at the San Francisco ACS Convention, September 1976, and M. Elliott, "Properties and Applications of Pyrethroids," *Environmental Health Perspectives*, **14**, 3 (1976).

Robert Burns Woodward: Three Score Years and Then?

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Synthetic organic chemistry began 150 years ago when, in 1828, Wöhler[1] prepared urea from ammonium cyanate. "The unexpected result," reported Wöhler, "is also a remarkable fact inasmuch as it presents an example of the artificial production of an organic, and so-called animal, substance from an inorganic substance." Liebig, who at this time was working in similar areas, initially doubted Wöhler's work but was soon convinced, however, of its correctness, and the two young chemists became close and lifelong friends. Only a decade after Wöhler's original discovery, he and Liebig, writing jointly on uric acid, asserted that, "The philosophy of chemistry will draw the conclusion that the synthesis of all organic compounds, as long as they are not a part of an organism, must be seen as not merely probable but certain."[2] No one has more completely fulfilled this prophecy than R.B. Woodward, who in 1965 was awarded the Nobel Prize for art in organic synthesis. Some of his most notable achievements are the synthesis of vitamin B_{12}, the most complex non-polymeric naturally occurring substance, as well as a series of other synthetic triumphs which have each in their turn established standards of elegance and creativity for which most other organic chemists can only hope to strive.

How does one tell the chemical community anything about Woodward which either they do not already know, or which they cannot readily learn by consulting any of the numerous collections of biographical data? I could list here the more than 30 honorary degrees which have been bestowed on him, and which are recorded in a closet in Cambridge as an array of multi-

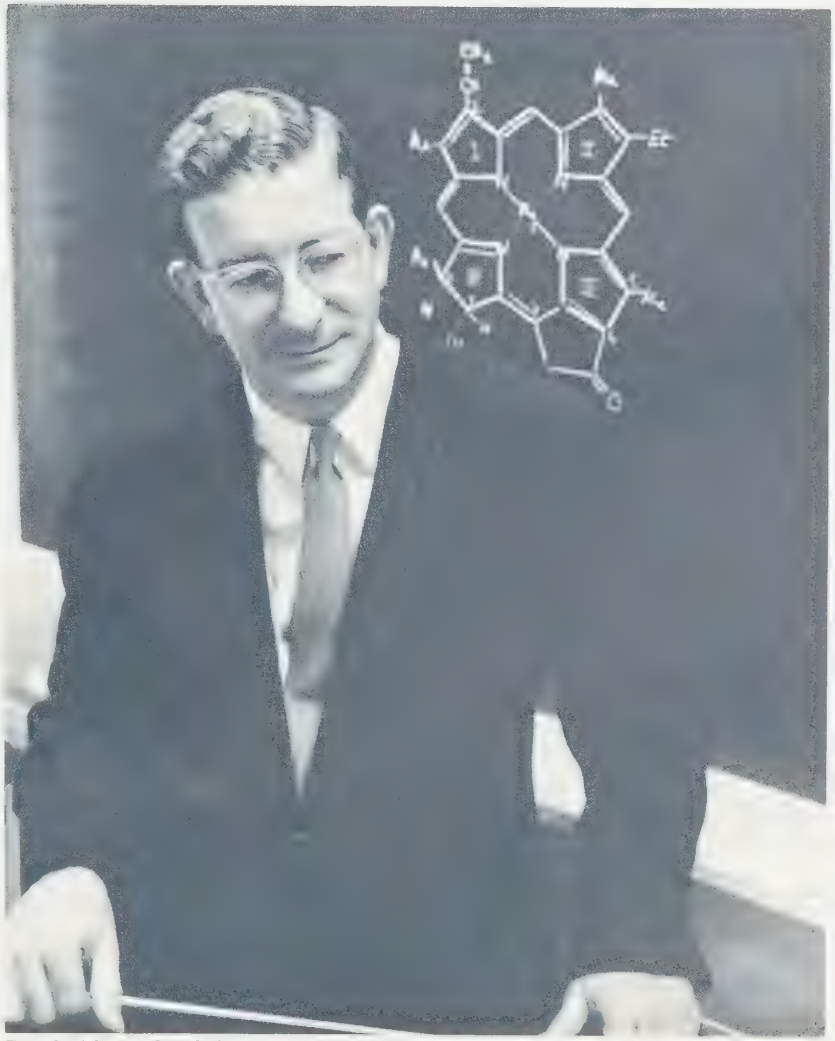


Fig. 1. Plan in detail, then carry it out (printed with permission of the American Chemical Society, from Chemical and Engineering News, Nov. 1965, p. 38).

hued academic robes (with the exception of one from a Scottish University, which shall remain unnamed, which insisted that if Woodward wanted the gown, he would have to buy it!). And I could follow this by a list of awards which would include the Theodore William Richards Medal, the Roger Adams Award, the Willard Gibbs Medal, the Pius XI Gold Medal, the National Medal of Science, the Nobel Prize in Chemistry, the Lavoisier Medal, the Decorated Order of the Rising Sun (Japan), and on into a list which would require more space for its completion than the *Aldrichimica Acta* has available. Rather than pursue this typical approach, I have decided to take a light-hearted look at the man as well as his chemistry.[3]

Neither teacher nor student of chemistry can have failed to have come across many of the contributions that R.B. Woodward has made to science in the past four decades. This was certainly true for me as an undergraduate, as well as a graduate of chemistry at the University of Nottingham where I worked with Alan Johnson in the early 60's. When it became clear that I would probably obtain my Ph.D., I asked my mentor what he would suggest I do after I was through at Nottingham, and he advised me that it might be good for my soul to go somewhere where I would be expected to work a little harder than I had been used to, and that I might think about trying to work with Woodward at Harvard. After some considerable agonizing I came to the conclusion that surely all of the rumors I had heard about this man, his work habits and those of his collaborators, could not possibly be true, and that I should indeed see if Woodward would give me a postdoctoral appointment in his laboratories. Having prepared a carefully worded letter I took it along to Alan Johnson to see if it met with his approval, and I was told I would be wasting my time if I sent it since Woodward never replied to letters. I have since learned that this was a slight exaggeration; nonetheless, the letter was never sent. Instead, however, when a few days later I was present at a half-day symposium on Vitamin B_{12} in London at the Royal Society, during one of the traditional tea breaks I was approached by an individual whom I knew, by the tell-tale cigarette and blue tie, could be none other than Woodward. Within ten seconds he ascertained that I did indeed wish to work with him, and suggested that I should write to his secretary and say that I would be arriving the following September.

Having made plans to cross the Atlantic in search of fame and fortune, I thought it advisable to familiarize myself in a general way with some of Woodward's work, and

Fig. 2. RBW working with fibrous proteins (from the Boston Herald, Wednesday, June 18, 1947).

am sure that you will be as interested as I was to note that his first two papers were:

> Precipitation of barium in the coppertin group of qualitative analysis, W.J. Hall and R.B. Woodward, *Ind. Eng. Chem., Anal. Ed.*, **6**, 478 (1934).
>
> The staling of coffee II, S.C. Prescott, R.L. Emerson, R.B. Woodward, and R. Heggie, *Food Research*, **2**, 165 (1937).

But a glimpse of the greatness to come was evident in his third contribution to science:

> A pressure regulator for vacuum distillation, R.L. Emerson and R.B. Woodward, *Ind. Eng. Chem., Anal. Ed.*, **9**, 347 (1937).

Arriving in Boston in the fall of 1965, I was met by his secretary, Dodie Dyer, and told if I would like to wait in the library Dr. Woodward would soon see me. And indeed, two weeks later, I was shown into his office, where we discussed what I might do during my stay at Harvard and agreed that I would participate in the synthesis of B_{12}. Having established my scientific program for the period of my stay I turned my attention to more important matters such as the length of any holidays that I could expect. After a brief pause Woodward shrugged his shoulders and said, "Well, I take Christmas Day off."

During this first discussion I had been seated at the side of his desk. Convinced, as I am now, that Bob Woodward does nothing which he has not carefully thought out I have realized since that the small quotation I saw then in front of him was as much for the benefit of his colleagues as for him, and after slowly moving my position so that I was able to read it, at the conclusion of the interview I saw the words that were to encourage me in my work for the next year: "Let sleeping dogs lie."

That year I spent in Woodward's laboratories was an especially exciting one and was highlighted early one morning when, as I walked into the laboratories, I heard the clinking of champagne glasses, and realized that although I had missed the news, the inevitable had obviously happened. The speed at which the champagne appeared in Bob's office surprised me, but I soon found out that, in fact, the champagne had been laid down by the department some time earlier in anticipation of the Nobel Prize. As the party progressed it was generally felt that signed champagne bottles would make a suitable memento of the occasion; however, it transpired that there were more drinkers than bottles. Woodward soon remedied this problem by holding sufficient parties until enough bottles had been accumulated. A few days later the Swedish television company came into Bob's laboratories and said how disappointed they were that they had missed the party, since they felt that scenes of a less formal nature might be suitable for a program they were preparing on that year's Nobel Laureate. Not wishing to disappoint his visitors from Sweden, Bob threw another round of parties which were received by his group with no less enthusiasm

than the initial ones.

Since he obtained the highest accolade in his field it might be of interest to see how Woodward's career had developed up to the time of the Nobel Prize. Born on April 10, 1917 in Boston, Woodward spent his childhood in a suburb of that city, Quincy. To give you a brief glimpse of his childhood I quote from an article in the Boston Daily Globe of June 8, 1937. "As a boy in short pants in Quincy Grammar School, he consistently brought home report cards dimmed with a pair of D's for conduct and effort. The Woodward youngster, who was always playing in the cellar with a chemistry set, received three double promotions hurdling the fourth, seventh and tenth grades, all the while whispering in classes, chewing bubble gum, being the last one in after recess and pulling little girls' long curls." I can assure you, after ten years of close association with Bob Woodward, that things have certainly changed since his earlier days — I don't think I have seen him blowing bubble gum in a long while.

In addition, it would appear that the passing years have also instilled a little caution. Recently, at an MIT fraternity house Pat[4] introduced RBW to a striking young redhead who was interested in meeting him. Amid the din and accompanying revelry the two remained locked in an animated conversation. After some time RB, looking a little disillusioned, came over and said: "I find this young lady quite interesting. However, she has just made a strategic mistake." "What could she have done?" Pat queried. "Well," said RB, "she just told me that she had been engaged to a professional wrestler. And, Pat, that is a very hard act to follow."

Robert B. Woodward and William E. Doering, first to synthesize quinine

Fig. 3. Printed with permission of the American Chemical Society, from Chemical and Engineering News, 1944, p. 730.

Returning to the report from the Boston Globe we find that "in 1933, a sixteen year-old lad from Quincy with a very distinguished scholastic record appeared at MIT where professors, being only human, formed a quick but wrong impression of him. The savants at this institute solemnly soliloquized, 'Woodward as a freshman had much to learn. He was in no position to think the world his oyster in or out of season, so happy-go-lucky, not at all the grim and studious type.' " One professsor had remarked, "Well, the Institute, young man, is a different place than a public school." It would appear then, as now, that MIT professors can be mistaken, for in four years Woodward had obtained his Ph.D. from MIT — not, however, without some difficulties. His transcript which shows a 4.9 out of a possible 5 was highlighted by a double F in gym.

Clearly Woodward's career at MIT was atypical in that he obtained both his Bachelor's and Doctorate degrees by the age of 20. Again quoting from the Boston Globe, "The achievement was the more remarkable in that Woodward obtained his goal after only four years of study against the seven usually required; when during this period much of his time had been devoted to outside work to finance his collegiate career."

"I never heard of it being done by any young man before, either at Tech or anywhere in the world," was the commendation of James Flack Norris, Professor of Organic Chemistry and Director of the Tech Research Laboratory in the field in which young Woodward took his degree.

While taking the regular freshman courses, during the first semester at the Institute, Woodward applied for a seat in the laboratory. The Organic Department told him that only graduate students, men who possess degrees, are allowed that privilege; but his appeal interested the Department and he was told that if he could supply a list of the experiments he was planning, he might be given some consideration. A few days later he produced a list of experiments that showed such outstanding originality and scope that he was granted a seat.

Toward the end of the second semester of his freshman year Woodward walked into the examination room where third-year students were being tested in organic chemistry. He inserted a note in his examination book, asking the professor to correct it, and if possible, to give him credit.

At the beginning of his second year he was given his own laboratory in which to experiment. In that year he happened to attend an organic chemistry lecture in which the professor told about the difficulty of synthesizing the female sex hormone from carbon. At the end of the lecture Woodward came to the professsor and showed him a way which might lead to such a synthesis.

The professor was amazed; the entire organic chemistry department became excited. For Woodward had hit on something that might prove to be revolutionary in the field of organic chemistry.

During his third year Woodward took as many as 15 courses in one semester so that he might receive his Ph.D. sooner. The faculty permitted him to spend as little time as he wished in classes. Instead he studied the required subject matter independently and simply presented himself at the examinations. Again and again he walked off with honors in organic chemistry courses. At the end of his third year Woodward was notified that he was to be granted a bachelor's degree.

His last and fourth year at Tech, Woodward describes as his happiest, for he was able to spend his time in the research laboratory where he could resume his experiments, which he had begun in his second year at the Institute, on the female hormone. He did this work independently and wrote his thesis on it.

In explaining Tech's attitude toward Woodward, during that period of time, Professor Norris says, "We saw that we had in our midst a person who possessed a very unusual mind. We wanted to let it function at its best. If red tape, which was necessary for other less brilliant students, had to go, we cut it. We did for Woodward what we have done for no other student in our department, for we have had no student like him in our department. And we think he will make a name for himself in the scientific world." Norris further said, "But unlike some scholars, he will not burn out suddenly." It was not to be long before these prophesies were to be fulfilled.

Upon graduating from MIT Woodward spent the summer of 1937 at the University of Illinois but, with the approach of winter, migrated to warmer climes and moved back to Cambridge, where he became an assistant to Professor Elmer Peter Kohler at Harvard. The following year he was elected to the Harvard Society of Fellows, and by 1941 had published a series of papers on ultraviolet spectral structure correlations which are still used to this day. In 1944 Woodward (as a consultant for the Polaroid Corp.) and Bill Doering achieved

the total synthesis of quinine in only 14 months (Fig. 3). In 1947 he was to elucidate the structure of strychnine, to be followed in 1954 by total synthesis of strychnine and lysergic acid. The synthesis of strychnine was not without its difficulties, however, and after several months of trying to close the 6th ring, and after the most recent experiments had failed, Bob is recorded as saying, "If we can't make strychnine, we'll take strychnine!"

Prior to the total synthesis of strychnine both cholesterol and cortisone were synthesized, and in 1952 Woodward proposed the sandwich structure for ferrocene.

Few personal accounts of the major discoveries in chemistry are documented. An exception to this is the dream of August Kekulé[5] which led to the suggestion that benzene contained a cyclic structure. "There I sat and wrote my Lehrbuch," reported Kekulé, "but it did not proceed well, my mind was elsewhere. I turned my chair to the fireplace and fell half asleep. Again the atoms gamboled before my eyes. Smaller groups this time kept modestly to the background. My mind's eye, trained by repeated visions of a similar kind, now distinguished larger formations of various shapes. Long rows, in many ways more densely joined; everything in movement, winding and turning like snakes. And look, what was that? One snake grabbed its own tail, and mockingly the shape whirled before my eyes. As if struck by lightning I woke; this time I again spent the rest of the night to work out the consequences."

This dream of 1865, occurred 35 years before Sigmund Freud's theories were published in 1900,[6] and one can but wonder about Freud's reaction to snakes' biting their own tails! If, however, this led to the elucidation of the structure of benzene, what thoughts led Woodward to the sandwich structure of ferrocene would, I am certain, prove fascinating.

While the suggested structure for ferrocene initiated an era of organometallic chemistry, it also aided in the demise of Woodward's continuing practice at the bench. About 3 a.m. one day the group was gathered in the laboratory suggesting ways to try and oxidize or reduce the then-new ferrocene. RB put a lump of $FeSO_4$ into a separatory funnel and shook it with a solution of ferrocinium ion to reduce it. On being shaken, the funnel was broken by the lump, and the solution poured out onto RB's trousers (where it had the audacity to remain oxidized).

In 1960 Woodward announced the total synthesis of chlorophyll (Fig. 1), having already synthesized lanosterol and reserpine, and followed these successively with

Fig. 4. A telegram from Sweden!

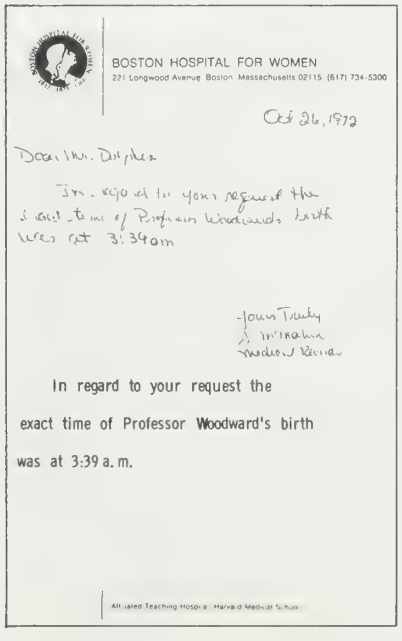
syntheses of tetracycline, cortisone and cephalosporin during the period in which he was awarded the Nobel Prize (Fig. 4).

While I have chosen only a few of the highlights in the above list of achievements in synthesis, it must be remembered that the theoretical aspects of organic chemistry are areas to which Woodward has also turned his talents. The latest of these is the conservation of orbital symmetry developed by Woodward and Hoffmann in the late 60's, and so elegantly summed up by them in their *Angewandte Chemie* article in 1968 where, in considering violations to the rules, they concluded "there are none!" Oosterhoff had suggested that orbital symmetry might play a role in electrocyclic reactions, and, while introducing Roald Hoffmann to an audience, made the observation that throughout the history of organic chemistry a number of significant contributions had been made by various distinguished Hoffmanns, among them being August Wilhelm von Hoffmann, and Friedrich Hoffmann. However, Oosterhoff noted, "of all the Hoffmanns the most famous is undoubtedly the Hoffmann whose first name is Woodward."

The greatest of all of Woodward's synthetic achievements is that of Vitamin B_{12}, which, in collaboration with Albert Eschenmoser, was completed in the early 70's. As colloquia chairman at Harvard I persuaded Woodward to present a talk on the synthesis of B_{12}. Our colloquia at Harvard were normally of an hour duration, and at first Bob was reluctant to lecture, since he assured me that there would be no way he could say his piece in an hour. If we were to schedule the talk at 5 p.m. as normal, we might break into the dinner hour and upset the audience. We easily overcame these objections by starting the talk at 8 p.m. which of course left us the rest of the evening, and if necessary the following morning, for the remainder of the presentation. It had not gone unnoticed, on earlier occasions, that Woodward's talks had occupied several hours, and since I had no reason to expect that this occasion would be any different I felt it might be appropriate to give a more detailed than usual introduction of our speaker.

A few weeks earlier Duilio Arigoni had presented the Tishler lectureship to the department, and had been introduced by Woodward who took some delight in giving a detailed discussion of a horoscope that had been prepared for Arigoni. I remembered, too, that Woodward had told me several years earlier that one should use all available avenues to gain information about a subject. In particular I remember that Woodward was trying to repeat some of Thorpe's earlier work in which he had claimed to have synthesized some derivatives of tetrahedrane. By the time Woodward was attempting to repeat this work Thorpe had died and parts of the experimental details were no longer available. Woodward knew, however, that Lady Thorpe was a clairvoyant who claimed to be in touch quite regularly with her husband, so Bob thought that this might indeed be a unique way of obtaining information and would certainly constitute a novel footnote. It thus seemed appropriate to me that, in the absence of a clairvoyant, possibly a detailed analysis of a horoscope prepared for Woodward might be included in my own introduction. At the time of the

preparation of Arigoni's horoscope, it had been suggested by the young lady preparing the horoscope, that perhaps Bob himself might like to have a horoscope prepared, but that in order to do this she would need the exact time, to the minute, of Woodward's birth. Woodward suggested that rather than use that time, which he didn't know anyway, and doubted that it could now be found, the young lady should prepare a horoscope for every minute of the day of his birth, and then by looking at the various comments decide what time he was born. Since I had neither the time nor the resources to undertake this obvious scientific but rather lengthy procedure, I determined to try and establish the exact time of Woodward's birth. A trip to the Massachusetts State House told me that Woodward was born on April 10, 1917 in the Boston Lying In Hospital for Women, but unfortunately no time had been recorded. However, the Boston Lying In Hospital for Women is an old established hospital and they informed me that for a small research fee they would check their records and find the information I needed, and behold a few days later a letter (Fig. 5) appeared recording Woodward's time of birth as 3:39 a.m. This is an especially significant time I feel, for I remember, one morning toward the end of a party in Bob's apartment, we saw the sun rise over the river Charles at about four in the morning. Woodward commented that yes, indeed he observed this every morning. Somewhat to our amazement he told us that he slept only three hours a day and had done so for as long as he could remember, and that he usually went to bed about 1 a.m. and got up



BOSTON HOSPITAL FOR WOMEN
221 Longwood Avenue Boston Massachusetts 02115 (617) 734-5300

Oct 26, 1972

Dear Mrs. Dreyfus

In regard to your request the exact time of Professor Woodward's birth was at 3:39 a.m.

Yours Truly
J. Miranda
Medical Records

In regard to your request the

exact time of Professor Woodward's birth

was at 3:39 a.m.

Affiliated Teaching Hospital, Harvard Medical School

Fig. 5.

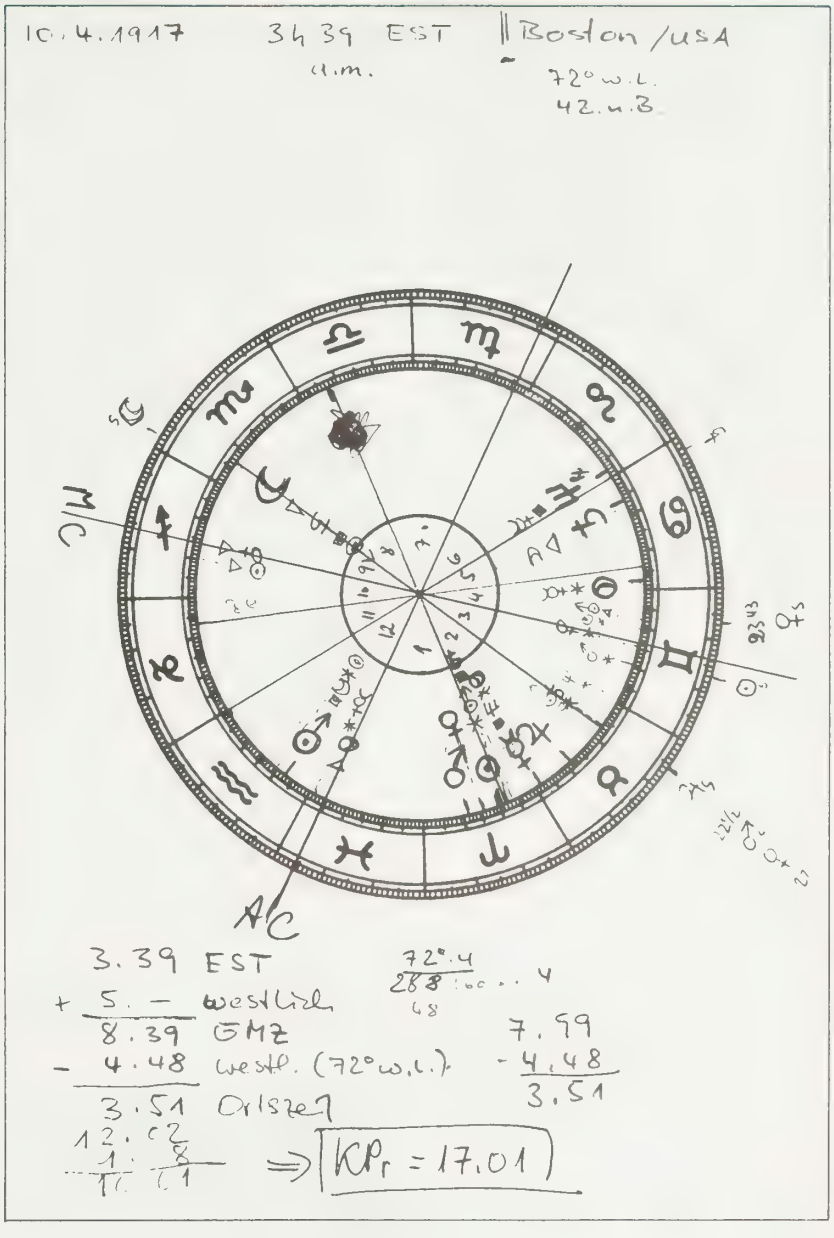


Fig. 6. Horoscope prepared for Woodward.

around 4 a.m. It would appear that he acquired this habit at a very young age then, and hasn't changed it since.

Having determined the exact time of Woodward's birth, I transmitted this information to Zürich and on the day of Woodward's lecture at Harvard, Arigoni flew in with the appropriate document and a somewhat detailed analysis of the horoscope. You will appreciate that it would be ignoble of me to outline here details of many of the comments that were made, but I reproduce in Fig. 6 the horoscope, so that those of you who are trained in the art of interpreting such documents can come to your own conclusions. I must make it clear right from the beginning that up until that time I had little faith in horoscopes, but many of the interpretations were indeed accurate in many respects; we knew we were on to a good thing with the first comment Woodward's favorite color was red! It was noted, however, that his career had begun at 22, an accurate deduction, and that the man for whom this horoscope had been prepared should be a scientist. And not only that, that he should be a chemist, too. I must admit that to this day I do not know how much of this information came from the horoscope and how much came via Arigoni. The analysis went on to point out the subject was a user of nicotine and liquor, but was such a strong individual that

these had no effect on his health. Woodward ran true to form to show us, that night, how accurate the statement was by consuming his usual number of packages of Benson & Hedges and by finishing the two pints of Daiquiri that had been prepared for him as part of my introduction. Despite what non-smokers believe, among them such crusaders as James the First, who had this to say

> Smoking is a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fumes thereof nearest resembling the Stygian smoke of the pit that is bottomless.

the habit has been a tradition amongst synthetic chemists since the time of Wöhler and Liebig, both of whom were heavy smokers, especially Wöhler, who once made this comforting comment to a non-smoking colleague: "there are examples of non-smokers who became bearable chemists; however, this occurs only rarely."[7]

The horoscope indicated that the individual was forceful, energetic, had a good practical sense but was by no means diplomatic, and that he impressed others with his own personal viewpoint. And the individual was possessed with a phenomenal memory. To this I can personally attest. In late 1973 just before I left Harvard to move to the University of British Columbia, I was discussing the oxidizing power of oxaziridines with Woodward, who said that he recalled a paper from the Redstone Arsenal which he had read a while ago, where oxaziridines were titrated with iodide and hence oxidants. As a measure of Woodward's memory it transpires that the paper he referred to had been written about twenty years earlier, and that the iodide titrations were described in a footnote to the experimental section.

But let me return to Woodward's latest accomplishment. Although the total synthesis of B_{12}, in the form of cobyrinic acid, formally represented a total synthesis of the vitamin itself, it was only a year ago that the complete synthesis was achieved, when the nucleotide loop was attached to the cobyrinic acid. (Fig. 7)

My latest count of the people involved in this undertaking, in both Cambridge and Zürich, totalled about 100 postdoctoral fellows. It is, of course, apparent that during the past 40 years Woodward's achievements must also be gauged in reference to Woodward as a teacher. During these past four decades nearly 400 students have been associated with him. It is said that a man can be judged by the company he keeps, and it is certainly true that a chemist can be measured by the men he has trained. It would be inappropriate to list here all 400 colleagues; other ventures being planned to celebrate Woodward's 60th birthday will better measure the magnitude of this group.[8] I have however gone through the list of Woodward's collaborators and randomly selected about ten percent of the names:

> Bill Ayer, Jerry Berson, Ray Bonnett, Rich Borch, Axsel Bothner-By, Ron Breslow, Bill Chan, Malcolm Clark, Gerhard Closs, Pat Confalone, Pierre Deslongchamps, Bill Doering, Paul Dowd, Ian Fleming, Chris Foote, David Ginsburg, Jacques Gosteli, Hans Gschwend, James Hendrickson, Kenichi Hiroi, Ken Houk, Shô Itô, Bill Jencks, Tom Katz, Andy Kende, Yoshi Kishi, Hoshiro Kobayashi, Jean-Marie Lehn, Willy Leimgruber, David Lemal, Paul de Mayo, Jerry Meinwald, David Ollis, Roy Olofson, Avram Patchornik, Subramania Ranganathan, Myron Rosenblum, Dick Schlessinger, Franz Sondheimer, Bal Dattaraya Tilak, Denny Valenta, Harry Wasserman, Larry Weiler, Ernie Wenkert, Emil White, Mark Whiting, Alex Wick, Charles Wiesner, Reuven Wolovsky, Peter Yates, Alexander Gregoryevitch Yurlchenko, Howie Zimmerman.

It is inevitable, in preparing a list of this type, that some of the more famous colleagues should have been left out. These names I have added below.[9]

In May of 1944 *The Tech* (The MIT newspaper) made the following comment. "Professors who have known him well have stated that Woodward was excellent not only in *chemical* subjects but in *academic* studies as well." Those same professors would now have to admit that through the efforts of Robert Burns Woodward chemistry can at last be acclaimed a scholarly and academic pursuit.

And what of the future? You might imagine that the best answer to this question would come from the oracle himself. However, such pilgrimages are usually destined to failure. For example, I remember a press conference that was held on the morning that Bob won the Nobel Prize. A reporter from one of the local newspapers asked if he thought that he now would begin to synthesize life in the test tube. After a moment's reflection he looked up and said, "No, I am quite happy with the way it is done now."

After all of Woodward's scientific achievements one might imagine that there is nothing that he can do to exceed, for instance, the elegance or complexity of the B_{12} synthesis. I am certain that this is not so, and that we shall see even greater triumphs in the future. If you doubt this statement I leave you with the words of Lewis Carroll:

> "There is no use trying," she said; "one can't believe impossible things." "I dare say you haven't had much practice," said the Queen. "When I was your age, I always did it for half an hour a day. Why, sometimes I believed as many as six impossible things before breakfast."

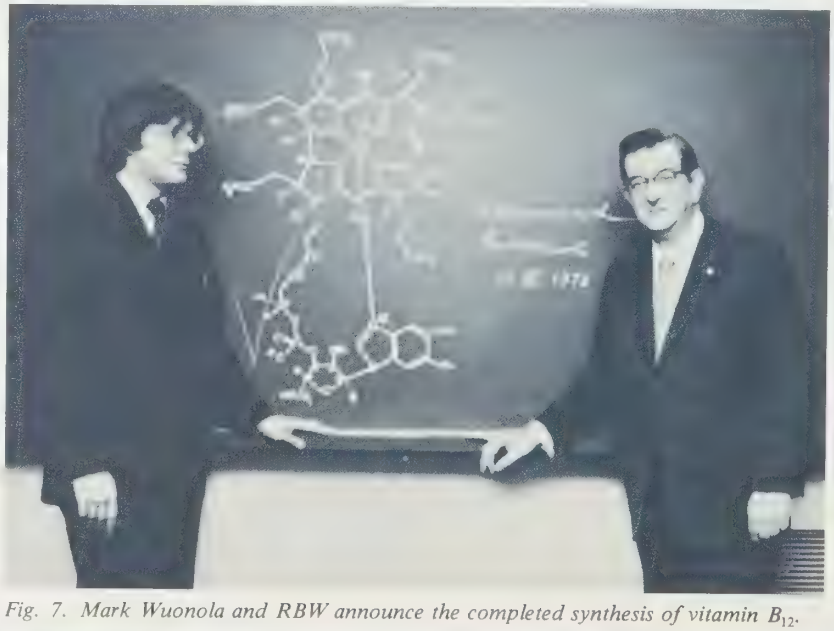
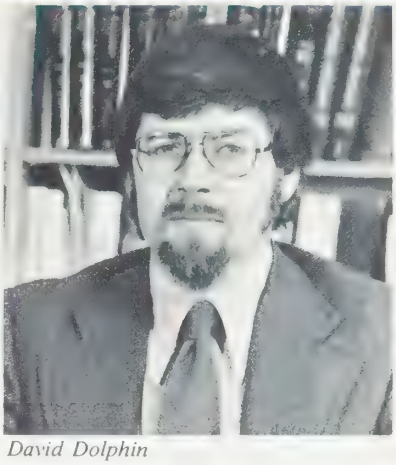


Fig. 7. Mark Wuonola and RBW announce the completed synthesis of vitamin B_{12}.

Footnotes:

1) F. Wöhler, *Ann. d Physik*, **12**, 253 (1828).
2) F. Wöhler and J.v. Liebig, *Justus Liebigs Ann. Chem.*, **26**, 254 (1838).
3) This article is written as an appreciation of all that Woodward has done for chemistry in general and for me in particular, and is dedicated to him on the anniversary of his sixtieth birthday. If at any stage the reader should feel that my personal account transgresses the bounds of gentlemanly behavior, then I would refer them to the first piece of advice that Woodward ever gave me: "David, there is not time enough to worry over what others think about you."
4) I thought of changing your name, Pat, but I know, and you know, and he knows where the story comes from, so what's the point?
5) R. Anschütz, "August Kekulé 1829-1896" in *Great Chemists*, ed. E. Farber, *Interscience*, New York, 1961, p. 697.
6) Sigmund Freud, *The Interpretation of Dreams*, trans. A.A. Brill, completely revised edition (London: George Allen and Unwin, Ltd., 1937).
7) F. Haber, "Justus von Liebig 1803-1873" in *Great Chemists*, ed. E. Farber, *Interscience*, New York, 1961, p. 535.
8) In addition to papers, dedicated to Woodward on the occasion of his sixtieth birthday, which will be published throughout the scientific literature, *Heterocycles*, under the editorship of Tetsuji Kametani, will publish an issue containing papers dedicated to Woodward.
   This year's Leermakers Symposium, to be held at Wesleyan University three weeks after Woodward's birthday, is to be built around the impact Woodward has made on total synthesis. Additional information on the symposium, of which Woodward is the Honorary Chairman, can be obtained from Professor Max Tishler, Department of Chemistry, Wesleyan Univesity, Middletown, CT 06457.
9) David Dolphin.



David Dolphin

About the Author

After obtaining his Ph.D. with Alan Johnson in 1965 David Dolphin spent a year's postdoctoral fellowship with Woodward, and he then joined the faculty of the chemistry department at Harvard where he stayed for eight years, moving in 1974 to his present location at the University of British Columbia.

Handling Air-Sensitive Reagents

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A large variety of air-sensitive reagents is available from Aldrich. Specific examples include solutions of borane complexes, organoboranes, borohydrides, Grignard reagents, organoaluminums, organolithiums, and organozincs. Since all of these reagents react with water or oxygen or both, they must never be exposed to the atmosphere.

Most modern synthetic chemists are familiar with the utility of these versatile organometallic reagents. However, because the compounds are air-sensitive or pyrophoric, some workers hesitate to make use of the remarkable chemistry of these reagents. Some chemists still believe that very specialized equipment and complicated techniques are required for handling air-sensitive reagents. This is often not the case.

Air-sensitive materials can be separated into two categories: those which react catalytically with air and/or water and those which react stoichiometrically. In the latter case, which fortunately includes most of the synthetically useful reagents, the reagents can be handled easily on a laboratory scale using syringe and syringe-related techniques. The catalytically sensitive materials often require the use of more sophisticated apparatus such as vacuum lines, Schlenk-apparatus, or inert-atmosphere glove boxes.

Brown and coworkers have recently described simple, convenient bench-top methods for handling stoichiometrically sensitive compounds on a laboratory scale.[1] Shriver has presented an excellent description of the more sophisticated techniques used to manipulate catalytically sensitive materials.[2]

The present discussion is limited to those techniques necessary for handling air-sensitive reagents on a preparative scale. In addition, several pieces of specialized equipment which greatly facilitate the safe and effective handling of these reagents will be described. The book by Brown and coworkers should be consulted for more detailed descriptions of simple techniques for working with air-sensitive materials.

Air-sensitive reagents available from Aldrich are packaged in special bottles. The Aldrich Sure/Seal packaging system (Fig. 1) provides a convenient new method for storing and dispensing research quantities of air-sensitive reagents. With this new bottle, reactive materials can be handled and stored without exposure to atmospheric moisture or oxygen. The reagent comes in contact only with glass and Teflon®, yet it can be readily transferred using standard syringe techniques.

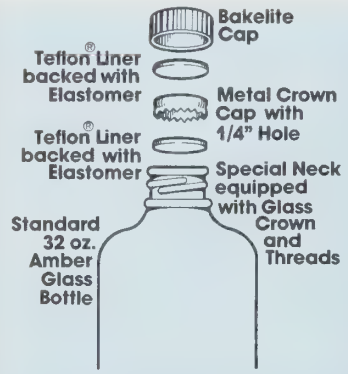


Fig. 1. The Aldrich Sure/Seal packaging system.

Syringe transfer techniques will be described in more detail later, but a short discussion at this point will illustrate the convenience of the new Sure/Seal packaging system.

The Bakelite cap on a Sure/Seal bottle can be safely removed because the crown cap, with its Teflon/elastomer liner, is already crimped in place. The reagent can then be dispensed using a syringe or double-tipped needle inserted through the hole in the metal crown cap. After the needle has been withdrawn from the bottle, a small hole will remain in the Teflon/-elastomer liner. Under normal circumstances, the hole in the liner will self-seal and the reagent will not deteriorate. However, the possibility exists that once an elastomer liner is punctured, it may leak on long-term storage. This possibility is virtually eliminated with the Sure/Seal system because when the Bakelite cap is replaced, the Teflon/elastomer liner in the cap forms a seal against the top of the metal crown. Thus, the contents are effectively protected from moisture and oxygen in the atmosphere.

Reactions involving our air-sensitive reagents may be carried out in common ground-glass apparatus. The only additional equipment required is a source of inert gas, a septum inlet, a bubbler, and syringes fitted with suitable needles. Aldrich offers a variety of septums, syringes and syringe-related hardware, several pieces of septum-inlet-equipped glassware, and a bubbler.

Laboratory glassware contains a thin film of adsorbed moisture which can be easily removed by heating in an oven (125°/overnight or 140°/4 hrs). The hot glassware should be cooled in an inert atmosphere by assembling the glassware

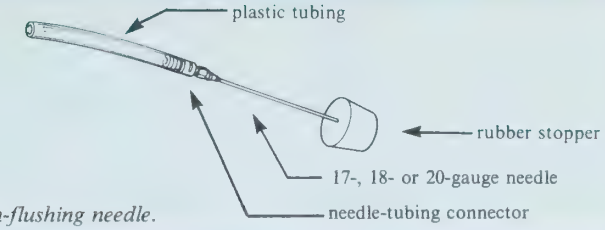


Fig.2. Nitrogen-flushing needle.

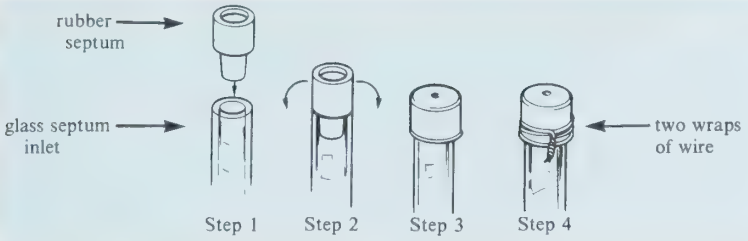


Fig. 3. Procedure for utilization of rubber septum.

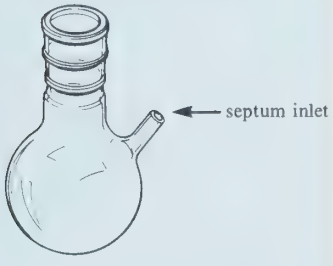


Fig. 4. Flask equipped with septum inlet.

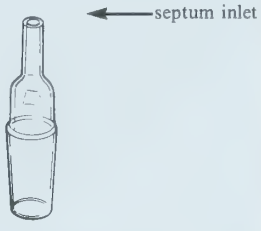


Fig. 5. Septum inlet adapter.

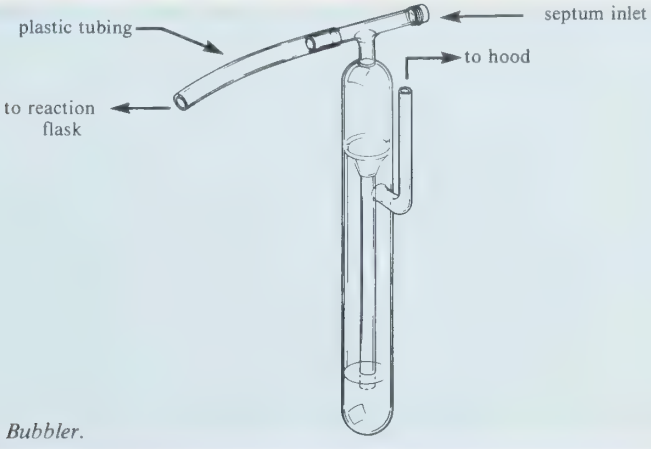


Fig. 6. Bubbler.

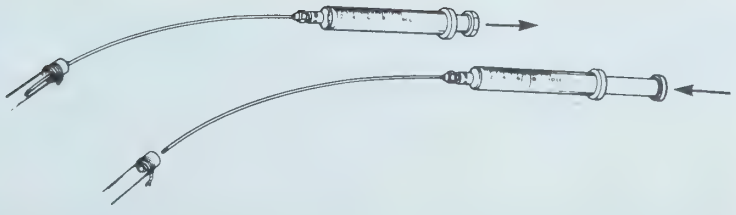


Fig. 7. Flushing a syringe with nitrogen.

while hot and flushing with a stream of dry nitrogen or argon. A thin film of silicone or hydrocarbon grease must be used on all standard taper joints to prevent seizure upon cooling. Alternatively, the apparatus may be assembled cold and then flamed with a Bunsen burner while flushing with dry nitrogen.

The oven drying procedure is more efficient than flaming with a burner because it removes moisture from inner surfaces of condensers and from other intricate parts. Spring clips or rubber bands are required to secure joints during the flushing since the nitrogen pressure may open the seals of unsecured standard taper joints, especially when the joints are hot.

Only high-purity, dry nitrogen from a cylinder with a pressure regulator (adjusted to 3-5 psi) should be used for flushing. Plastic tubing (Aldrich Catalog No. Z10,119-2) can be used to connect the nitrogen line to a tube connector adapter (equipped with a stopcock) on the reaction apparatus. Nitrogen may also be introduced through a rubber septum *via* a hypodermic needle connected to the end of the flexible tubing on the nitrogen line. The needle-tubing connector (Aldrich Catalog No. Z10,116-8) provides a simple method for attaching the needle to the tubing. When not in use, this nitrogen-flushing needle (Fig. 2) should be closed by inserting the needle into a solid rubber stopper to prevent diffusion of air into the needle when the nitrogen supply is turned off.

Large rubber septums may be used to cap female joints. However, the use of 6-mm septums and 8-mm o.d. standard wall or 9-mm o.d. medium wall (6-mm i.d.) glass septum inlets is preferred. The small rubber septum (Aldrich Catalog No. Z10,072-2) provides a more positive reseal after puncture and allows less rubber to be in contact with organic vapors in the reaction vessel. The use of 9-mm o.d. medium wall tubing, instead of the more common 8-mm o.d. standard wall, with 6-mm septums is preferred. With the medium wall tubing, the 6-mm septum not only fits the inside diameter of the glass tube but also fits snugly over the outside when the top is folded over (Fig. 3). The glass septum inlet can be built into the reaction flask (Fig. 4) or placed on an adapter (Fig. 5) for use with unmodified glassware.

The rubber septum may be wired in place as shown in Figure 3. However, if the 6-mm septum is properly fitted to 9-mm medium wall tubing, the wiring step may be omitted unless high pressures (>10 psi) are expected.

To maintain an air-tight system the reaction vessel must be vented through a mer-

cury or mineral oil bubbler. Obviously, simple drying tubes will *not* prevent oxygen from entering the system. At all times during the reaction, the system should be under a slight positive pressure of nitrogen as visually indicated by the bubbler. Figure 6 illustrates a suitable bubbler (Aldrich Catalog No. Z10,121-4).

A pressure reversal in the reaction vessel may cause the liquid in the bubbler to be sucked back. The enlarged head space in the bubbler will minimize the danger of the bubbler liquid being sucked back *into the reaction vessel*. However, if a large pressure reversal occurs, *air will be admitted* into the reaction vessel. The T-tube bubbler shown can be used to prevent this problem because nitrogen pressure can be introduced intermittently through the septum inlet. The problem can be completely eliminated by a slow and continuous nitrogen flow.

When the assembled (nitrogen-flushed) glassware has cooled, air-stable solids may be introduced through an entry port under a blanket of nitrogen. The entry port is closed and the system is flushed with nitrogen.

Small quantities (up to 50ml) of air-sensitive reagents and dry solvents may be transferred with a syringe equipped with a needle (length 1-2ft). The long needles are used to avoid having to tip reagent bottles and storage flasks. Tipping often causes the liquid to come in contact with the septum. Contact of rubber septums with many organic liquids causes swelling and deterioration of the septums, and should therefore be avoided.

A rubber septum in contact with organic vapors provides a positive seal for only a limited number of punctures, depending upon the needle size. The lifetime of the septum may be extended by always reinserting the needle through an existing hole. It is also advantageous to put a layer of silicone or hydrocarbon grease on a rubber septum to facilitate passage of the needle through the rubber and to minimize the size of the hole in the septum. Ideally, the syringe and needle should be dried in an oven prior to use. Naturally, the syringe body and plunger should *not* be assembled before being placed in the oven. The syringe should be flushed with nitrogen during the cooling. A syringe may also be flushed 10 or more times with dry nitrogen as illustrated in Figure 7 to remove the air and most of the water adsorbed on the glass. A dry syringe may be closed to the atmosphere by inserting the tip of the needle into a rubber stopper.

The syringe-needle assembly should be tested for leaks prior to use. The syringe is half filled with nitrogen and the needle tip is inserted in a rubber stopper. It should be possible to compress the gas to half its original volume without any evidence of a leak. A *small* amount of stopcock grease or a drop of silicone oil placed on the Luer lock tip will help insure tightness.

The syringe transfer of liquid reagents is readily accomplished by first pressurizing the Sure/Seal reagent bottle with dry, high-purity nitrogen followed by filling the syringe as illustrated in Figure 8. The nitrogen pressure is used to slowly fill the syringe with the desired volume plus a slight excess (to compensate for gas bubbles) of the reagent. Note that the nitrogen pressure pushes the plunger back as the reagent enters the syringe. The plunger should not be pulled back since this tends to cause leaks and creates gas bubbles. The excess reagent along with any gas bubbles is forced back into the reagent bottle as illustrated in Figure 9. The accurately measured volume of reagent in the syringe is quickly transferred to the reaction apparatus by puncturing a rubber septum on the reaction flask or addition funnel, as shown in Figure 10. Syringes with capacities up to 100ml are available. However, the large syringes become

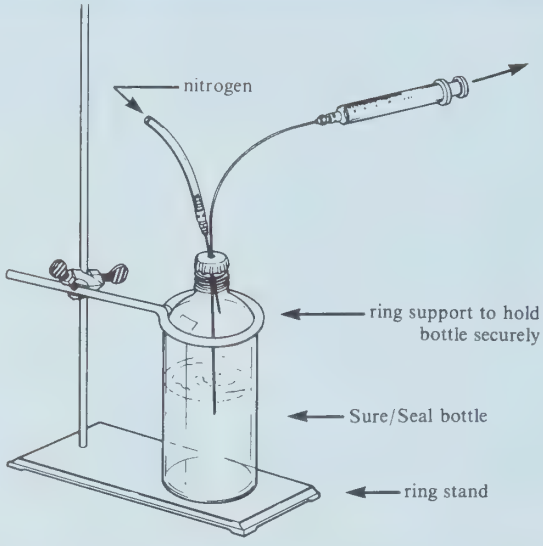


Fig. 8. Filling syringe using nitrogen pressure.

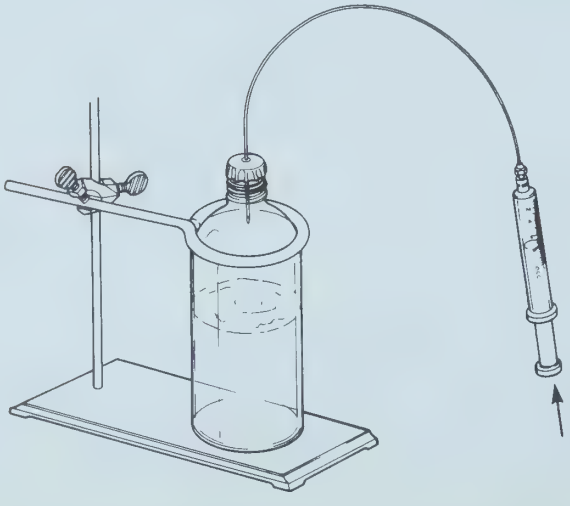


Fig. 9. Removing gas bubbles and returning excess reagent to the Sure/Seal bottle.

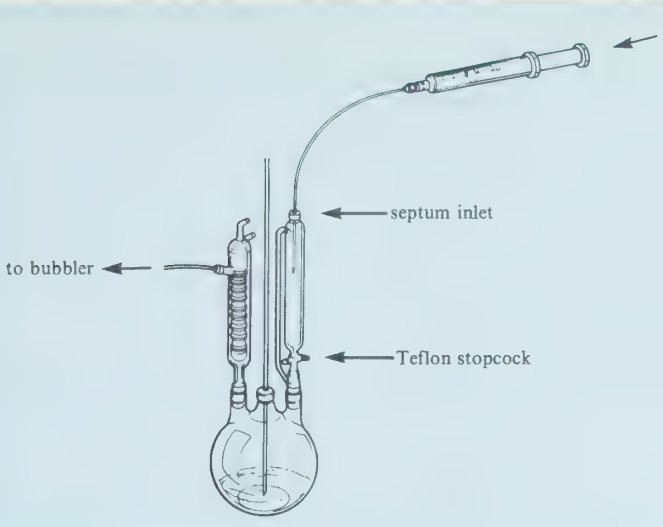
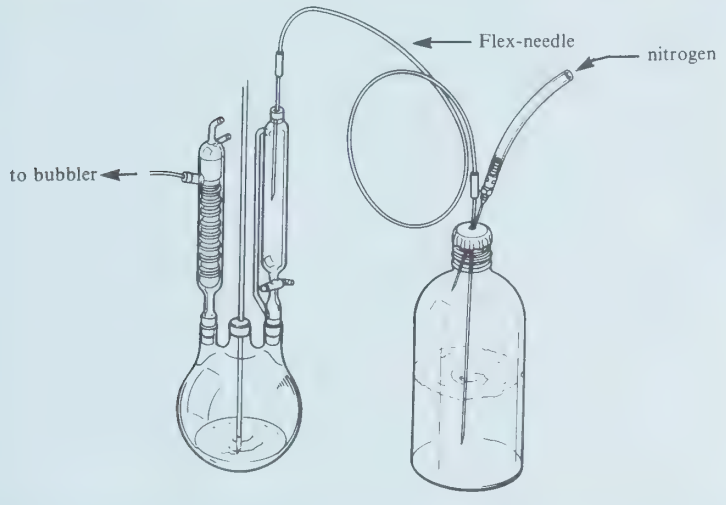


Fig. 10. Syringe transfer of reagent to reaction vessel.



awkward to handle when completely full.

When the transfer of more than 50ml of solvent or liquid reagent is required, it is generally much more convenient to use the double-tipped needle technique. Figure 11 illustrates liquid–reagent transfer under nitrogen pressure using this technique.

To accomplish the double-tipped needle transfer, the needle is first flushed with nitrogen. The Sure/Seal bottle is pressurized with nitrogen using the nitrogen flushing needle. The double-tipped needle is then inserted through the septum on the reagent bottle into the head space above the reagent. Nitrogen immediately passes through the needle. Finally, the other end of the double-tipped needle is inserted through the septum on the reaction apparatus, and the end of the needle in the reagent bottle is pushed down into the liquid. The volume of liquid reagent transferred is measured by using a calibrated flask or addition funnel. When the desired volume has been transferred, the needle is immediately withdrawn to the head space above the liquid, flushed slightly with nitrogen, and removed. The needle is first removed from the reaction apparatus and then from the reagent bottle.

An alternative method for transferring measured amounts of reagents is shown in Figure 12. The reagent is first transferred *via* a double-ended needle from the Sure/-Seal bottle to a dry, nitrogen-flushed graduated cylinder equipped with a female ⅋ joint and a double inlet adapter (glassware G as illustrated in equipment section). Only the desired amount of reagent is transferred to the cylinder. The needle is then removed from the Sure/Seal bottle and inserted through the septum on the reaction apparatus. By applying nitrogen presssure as before, the reagent is added to the reaction apparatus. If it is necessary to add the reagent slowly, a modified double-tipped needle can be used. This useful transfer needle is constructed from two long standard needles and a male Luer lock to male Luer lock syringe valve (accessory O as illustrated in equipment section). The valve may be opened slightly allowing only a very slow flow of reagent. Thus, the addition funnel is not needed and many reactions can be carried out in single-necked flasks as shown in Figure 13.

The 12-gauge stainless steel needles on the Flex-needle provide a rapid means of transferring air-sensitive reagents under nitrogen pressure. However, the needles are so large that once the crown cap liner on the Sure/Seal bottle is punctured, the liner will not self-seal. If only a portion of the contents is to be used up, a needle no larger than 16-gauge should be utilized. By using small needles and by always tightly replacing the Bakelite cap, the reagent in a Sure/Seal bottle will not deteriorate even after numerous septum punctures. However, if the reagent is to be used repeatedly for small-scale reactions or if an unused portion is to be stored for an extended length of time, the material should be transferred from the Sure/Seal bottle to a suitable storage bottle. One type of container (Aldrich Catalog No. Z10,248-2) for air-sensitive reagents is shown in Figure 14. Alternatively, an appropriate adapter (Fig. 15) can be used to convert a round-bottomed flask into a storage vessel.

The Teflon stopcock on the storage bottle keeps solvent vapors away from the septum, thereby minimizing swelling and deterioration of the septum. Furthermore, the stopcock allows for replacement of the septums. A change of septums is sometimes necessary because they tend to deteriorate on prolonged standing in a laboratory atmosphere.

Naturally, this storage bottle must be oven-dried and flushed with nitrogen before use. A clean and dry Flex-needle should be used to transfer the contents of the Sure/Seal bottle to the storage bottle, using the standard double-tipped needle technique.

Clean-up of equipment that has been used to transfer air-sensitive reagents must not be taken lightly. Since many of these reagents react violently with water, fires are a potential hazard. The crown cap and liner of an "empty" Sure/Seal bottle should be removed and the open bottle placed in a hood to allow the last *traces* of reactive

reagent to slowly air-hydrolyze and oxidize. After at least a day, the inorganic residue can be rinsed out with water. Empty storage bottles and storage flasks should be treated similarly. Air-hydrolysis in a hood is appropriate only for the last *traces* of material that remain after a Sure/Seal bottle has been emptied as completely as possible *via* syringe or double-ended needle transfer. The Aldrich Catalog/Handbook should be consulted for the recommended disposal procedures for larger amounts of reactive chemicals.

All syringes and needles that have been used to transfer air-sensitive materials must be cleaned *immediately* following use. Also, in general, a syringe should only be used for a single transfer. Failure to follow this practice will invariably result in plugged needles and "frozen" syringes due to hydrolysis or oxidation of the reagents. The double-tipped needles are flushed free of reagent with nitrogen in the transfer system, and then immediately removed and placed in a clean sink. With water running in the sink and in the complete absence of flammable solvents and vapors, the double-tipped needles or Flex-needle can be rinsed with water. When activity in the rinse water is no longer observed, acetone from a squeeze bottle can be flushed through the needle. Depending on the reagent transferred, it may be necessary to use dilute aqueous acid or base from a squeeze bottle to remove inorganic residue that is not water-soluble.

Following its use, a syringe contains a larger residual amount of reagent. It is advisable to rinse out the reactive reagent by first placing a few milliliters of the *same* solvent that was used for the reagent in a small Erlenmeyer flask in the hood. Keeping the needle tip under the solvent at all times, no more than half the solvent is then sucked into the syringe until the syringe is at least half-full. The solvent plus dissolved residual reagent is ejected from the syringe back into the same Erlenmeyer flask. This rinsing treatment is repeated at least three times. The wash solution can be safely combined with other waste solvents for eventual burning, and the syringe may be further cleaned with water and acetone in the sink. Again, treatment with dilute aqueous acid or base may be necessary.

Once the syringe needles and double-tipped needles have been rinsed in a sink, they can be further cleaned and dried using a device similar to that shown in Figure 16. Needles are cleaned by inserting them through the septum. Vacuum from a water aspirator is used to pull solvents from squeeze bottles through the needles. After pulling air through the system for a few minutes, the syringe plus needle or the

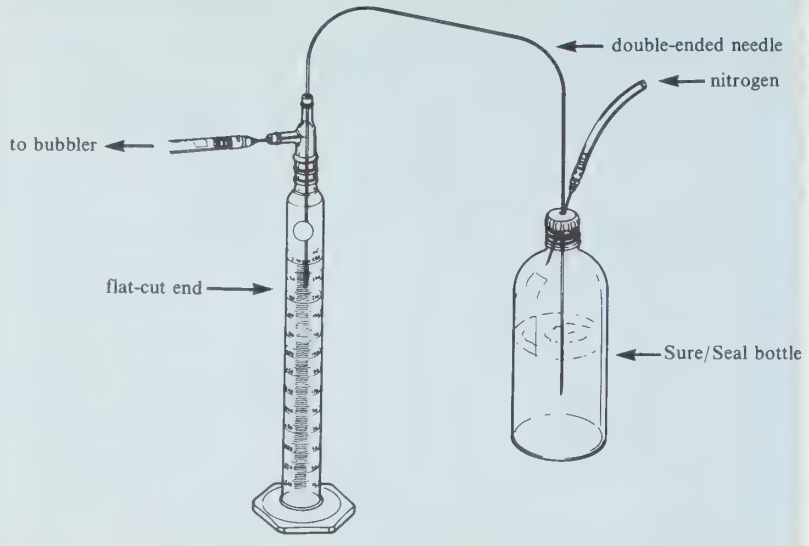


Fig. 12. Double-ended needle transfer to graduated cylinder.

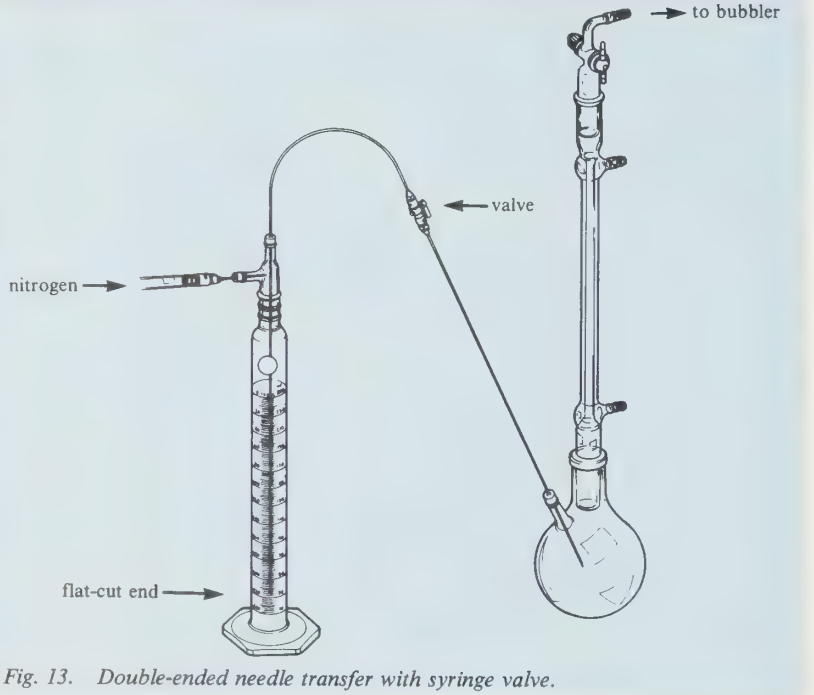


Fig. 13. Double-ended needle transfer with syringe valve.

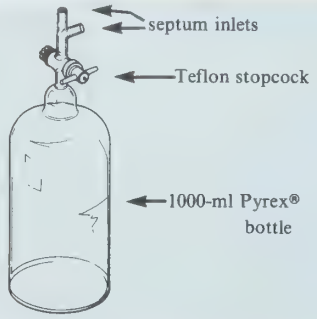


Fig. 14. Storage bottle equipped with Teflon stopcock.

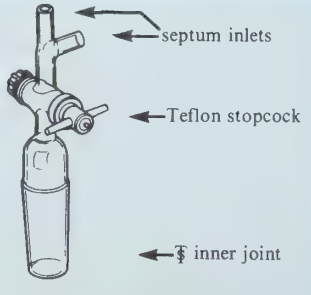


Fig. 15. Septum inlet adapter for storage flask.

double-tipped needle will be dry. The syringe plunger should be replaced in the barrel for storage. If a syringe plunger and barrel are not assembled for storage, dust can settle on the plunger and in the barrel. Upon reassembly, these fine particles will occasionally scratch the barrel or cause seizure of the plunger in the barrel. However, the plunger and barrel must be disassembled before oven drying.

Most of the above techniques were developed for handling various organoborane reagents. However, these methods are applicable to other air-sensitive materials.

When handling air-sensitive materials, it is important that the user be thoroughly familiar with the basic chemistry of the reagent. Also, the user should be prepared for unexpected problems. For example, at least one extra set of clean, dry syringes and needles or double-tipped needles should always be available in case the first set of equipment becomes plugged.

As in all laboratory practices, simple "common sense" is required. It is impossible to describe in detail the techniques required for all possible situations. As a rule-of-thumb, the chemist working with these air-sensitive reagents should always keep in mind that, if at all possible, these solutions should never be allowed to come in contact with the atmosphere.

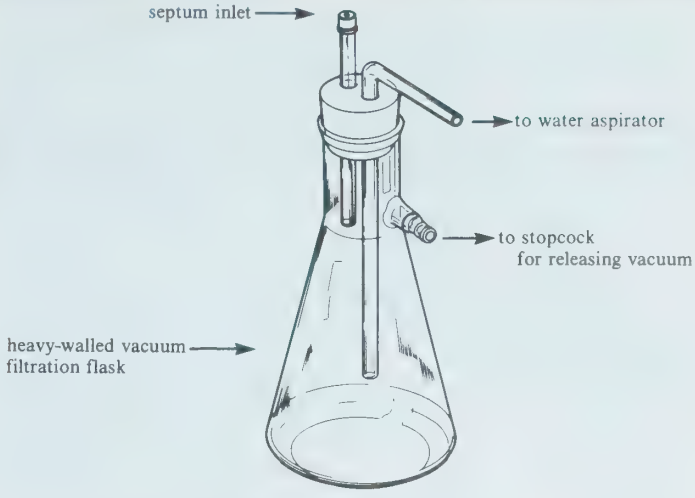


Fig. 16. Needle cleaning and drying apparatus.

Finally, it is our sincere hope that with the convenience of our new Sure/Seal packaging system, coupled with simple, convenient syringe techniques, no technically qualified chemist will ever again hesitate to use air-sensitive reagents.

References:

1) G.W. Kramer, A.B. Levy, and M.M. Midland in H.C. Brown, "Organic Syntheses *via* Boranes," John Wiley and Sons, Inc., New York, N.Y., 1975 (Aldrich Catalog No. Z10,144-3, $17.50).

2) D.F. Shriver, "The Manipulation of Air-sensitive Compounds," McGraw-Hill Book Company, New York, N.Y., 1969.

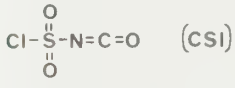
Chlorosulfonyl Isocyanate

Silver Anniversary of a Lively Heterocumulene

William A. Szabo
Aldrich Chemical Company, Inc.
Milwaukee, Wisconsin 53233

Introduction

Chlorosulfonyl isocyanate (CSI) is probably the most chemically reactive isocyanate known. It was discovered by Graf[1] 25 years ago and has been the subject



(CSI)

of several reviews.[2] The present survey will emphasize the synthetic applications of this extremely versatile reagent.

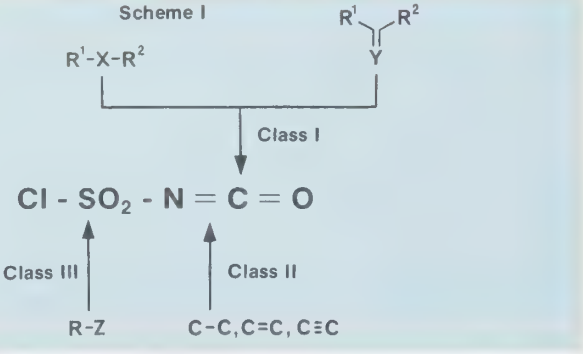
Chlorosulfonyl isocyanate is a clear, colorless, mobile liquid which freezes at -43°C and boils at 107-108° / 760mm (38° / 50mm).[2b] It shows no sign of thermal decomposition up to 300°. CSI fumes slightly on exposure to humid air, but reacts *violently* with water. Solvents which are generally inert to CSI include aliphatic, aromatic, and chlorinated hydrocarbons, diethyl ether (but not tetrahydrofuran), and acetonitrile. The high reactivity of CSI precludes the use of protic solvents.

Chlorosulfonyl isocyanate has enabled a wide variety of useful and often novel synthetic transformations. For clarity, reactions will be classified according to the probable site of initial attack on the CSI molecule by a given nucleophile, as depicted in Scheme I. Accordingly, Class I reactions will involve initial attack on the isocyanate carbon atom; Class II reactions will include formal [2+2] cycloadditions of carbon-carbon bonds across the isocyanate C=N bond; and Class III reactions of CSI will include the relatively few reported examples of nucleophilic additions to the sulfur atom. These are, of course, somewhat arbitrary classifications intended to facilitate an organized presentation of chlorosulfonyl isocyanate chemistry.

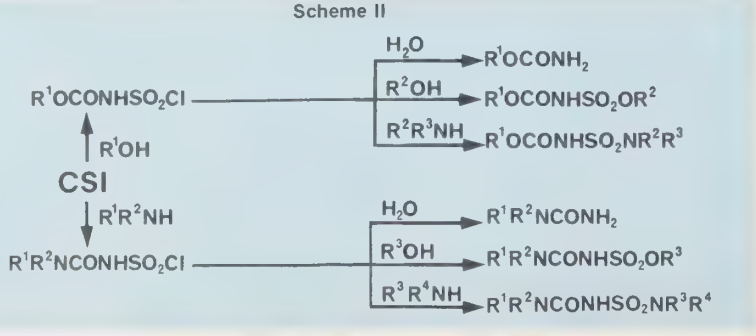
Class I: Nucleophilic Addition to the Isocyanate Carbonyl

CSI undergoes the expected nucleophilic additions by **alcohols, phenols,** and **amines.**[2] The resulting *N*-chlorosulfonyl derivatives may be subsequently functionalized, as shown in Scheme II. The use of CSI thus enables the formal insertion of the -$CONHSO_2$- linkage between alcohol and/or amine functional groups. The reac-

Scheme I



Scheme II



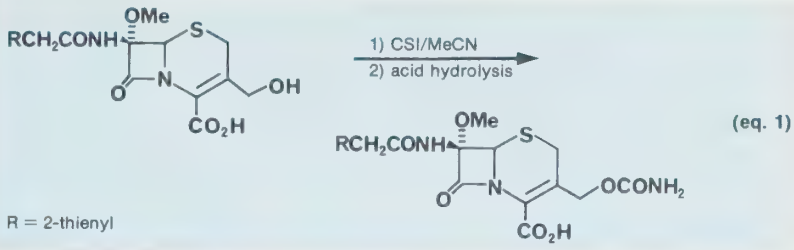
tivity of CSI with **alcohols** is so great that primary alcohols can be derivatized in the presence of other functionalities. In addition, reaction with CSI generally does not alter the stereochemistry at other centers, even of complex molecules. The examples shown in equations 1[3] and 2[4] illustrate this selectivity. A synthesis of the oxazolones **2** depends on the facile reaction of CSI with the alcoholic function of **α-hydroxy ketones** (equation 3).[5] Ring closure of the resulting carbamates (**1**) was accomplished by heating at 175-250°.

The novel reagent **4**[6] (Scheme III), prepared by the reaction of CSI with methanol followed by treatment of the resulting (in 92% yield) carbamate **3** with triethylamine, has been used by Burgess[6] to synthesize carbamates from primary alcohols and to dehydrate secondary alcohols. Intermediate **3**, itself a useful reagent,[7] has been used for the preparation of heterocycles **5**,[7a] **6**, and **7**. The ratio of **6** to **7** is both temperature and solvent dependent.[7b] Compounds such as **3** which are derived from certain **phenols** (*e.g.*, 2,4,6-trichlorophenol) are claimed to be useful bactericides and fungicides.[8] They may be further functionalized by treatment with alcohols, as shown in equation 4. Heating the resulting carbamates **8** above 100° produces alkoxysulfonyl isocyanates **9** in 47-77% overall yields.[9]

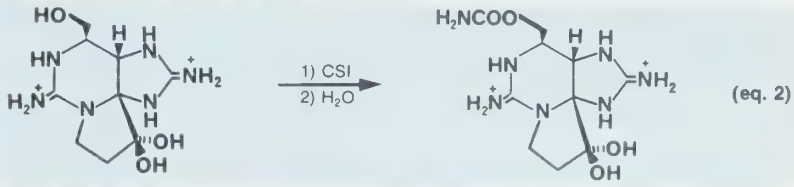
The reaction of CSI with **mercaptans** affords *thio*carbamates **10**, intermediates for the synthesis of potential herbicides (*e.g.*, **11**, equation 5[10]).

The reaction of CSI with **ketals** results in the insertion of the -*CON*(*SO*$_2$*Cl*)- linkage between oxygen and carbon atoms of the ketal functional group.[11] This transformation has been used by Hall *et al.*[11b] for the net conversion of the isopropylidene-protected sugar **12** (equation 6) to its corresponding 1,2-carbonate (**13**).

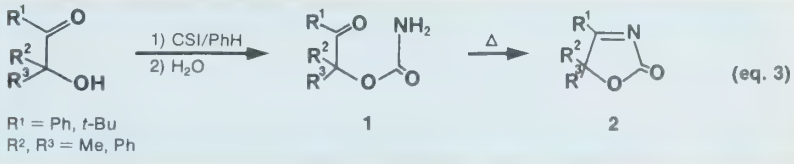
Aromatic compounds that readily undergo electrophilic substitution react with chlorosulfonyl isocyanate to produce the corresponding *N*-chlorosulfonyl carboxamides **14** (equation 7). Lohaus[12] has demonstrated that these intermediates can be converted *in situ* to nitriles in good overall yields by treatment with dimethylformamide. The method is characterized by mild reaction conditions (15-20°) and facile workup (quenching with ice and extraction). A related sequence converts enolizable **ketones** (equation 8[13]), certain cyclic **enamides** (*e.g.*, **15** in equation 9[14]), and **carboxylic acids** (equation 10[15]) to the corresponding nitriles. In the case of the latter the intermediate **16** is often stable enough to be isolated, depending on the nature of the starting acid.[15] Faubl[16] has



(eq. 1)

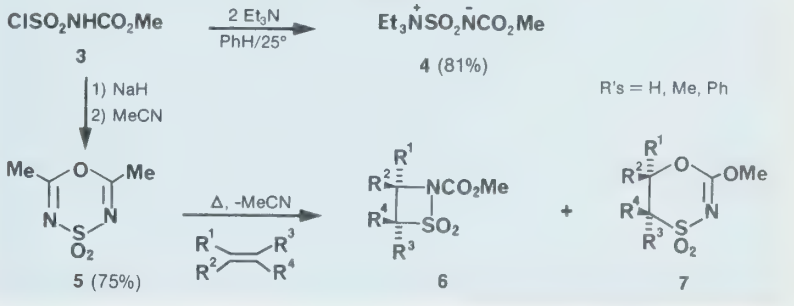


(eq. 2)

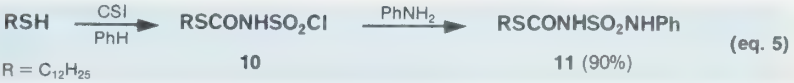


(eq. 3)

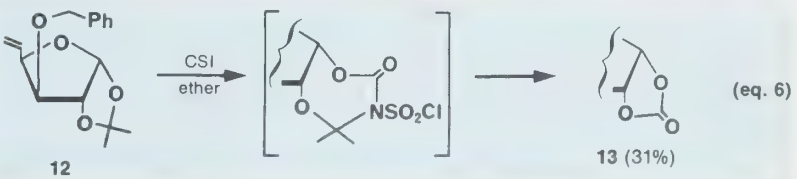
Scheme III



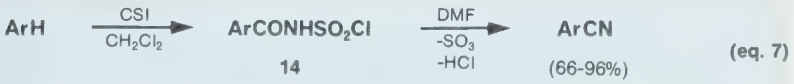
(eq. 4)



(eq. 5)

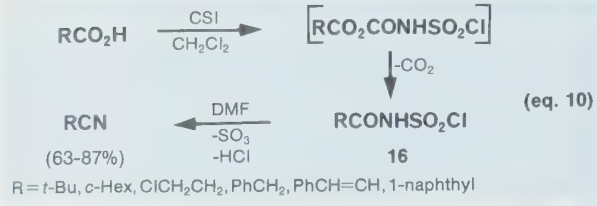


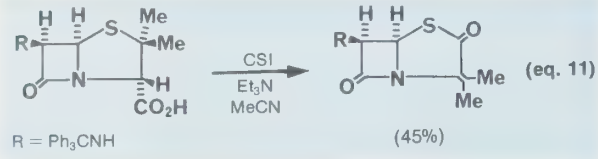
(eq. 6)

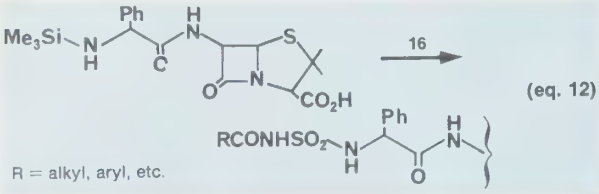


(eq. 7)

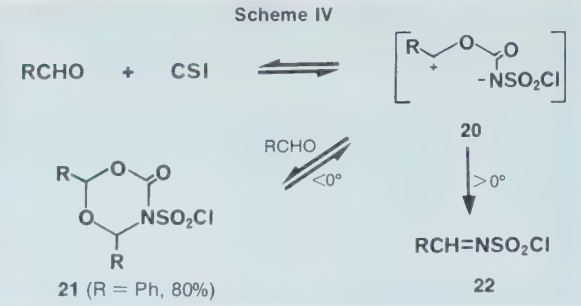
(eq. 8)

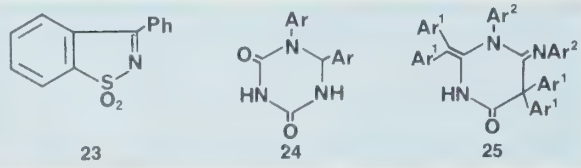


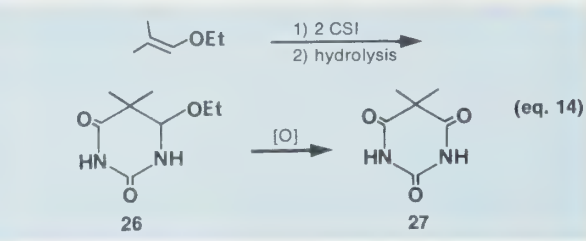


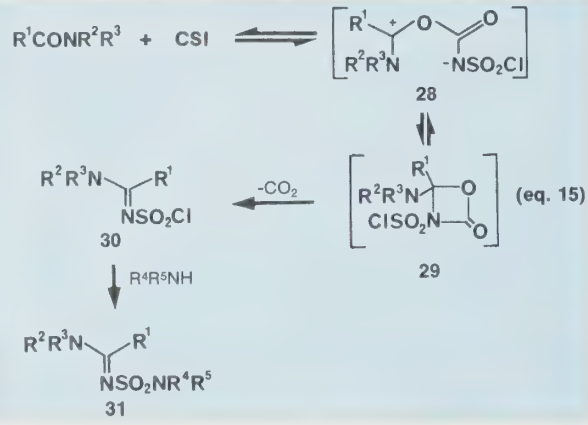


Scheme IV









recently reported an anhydropenicillin rearrangement (equation 11) induced by chlorosulfonyl isocyanate, which is thought to proceed *via* an intermediate of type **16**. As an interesting aside, intermediates such as **16** can also displace *N*-trimethylsilyl groups under mild conditions. An example is given in equation 12.[17]

A variation of equation 8 provides either the potential "third-generation" sweeteners[18] **17** or substituted uracils **19** (derived from products **18**), as outlined in equation 13.[19] The ratio of **17** to **18** is dependent on the nature of the substituents on the starting ketone and on the solvent. This work by Hassner and Rasmussen is a particularly striking example of the versatility of chlorosulfonyl isocyanate for the synthesis of useful intermediates from readily accessible starting materials.

The reaction of CSI with certain **aldehydes**[20] can also be included in Class I, since evidence recently published by Clauss *et al.*[11a] suggests that products **21** and **22** (Scheme IV) are derived from 1,4-dipolar intermediates **20,** the apparent result of nucleophilic attack by the aldehydic carbonyl on the isocyanate carbon atom. The reaction of benzophenone with CSI in nitrobenzene at 130° produces benzoisothiazole **23**,[11] probably *via* cyclization of the diphenyl *ket*imine corresponding to **22**. Such species can be isolated from the reaction of CSI (and other activated isocyanates) with **γ-pyrones**.[21] *N*-Aryl **imines** and **ketenimines** afford (after removal of the *N*-chlorosulfonyl group) heterocycles of types **24**[22] and **25**,[23] respectively. A similar cyclization takes place with ethyl isobutenyl ether to produce, after oxidation of intermediate **26** (equation 14), dimethylbarbituric acid (**27**).[2b] This is an interesting, but atypical (*vide infra*), mode of addition of an olefin to CSI. Products which are analogous to **26** have also been obtained from certain *sulfur*-substituted olefins.[24]

Dipolar intermediates have been postulated for the reaction of CSI with ***N,N*-dialkylamides**.[25] As shown in equation 15, collapse of dipole **28** to form the unstable **29**, followed by loss of carbon dioxide, produces the observed amidines, **30**. The amidines can be further functionalized to prepare derivatives of type **31**, which have been claimed to exhibit insecticidal and acaricidal activity.[26]

Class II: Net [2+2] Cycloaddition of Carbon-Carbon Bonds to the Isocyanate C=N

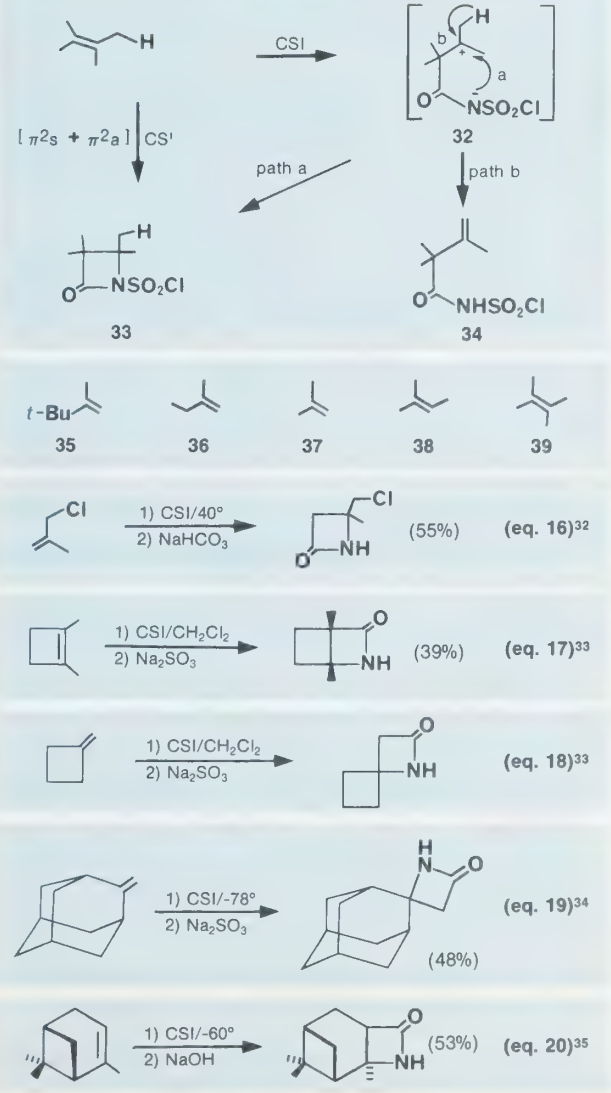
The ability of chlorosulfonyl isocyanate to undergo cycloaddition to carbon-carbon bonds adds another dimension to its usefulness. The most studied case to date is the net [2+2] cycloaddition of CSI to a wide variety of **olefins** to produce β-lactams (**33**, Scheme V).[27] Adducts of type **34** are common by-products. Their proportion in the product mixture appears to be a function of the pattern and type of substitution on the olefin. For example, the ratio of **33** to **34** has been determined by Graf[2b] for the following olefins: **35**, 50:50; **36**, 65:35; **37**, 70:30; **38**, 80:20; and **39**, *ca.* 100% β-lactam.

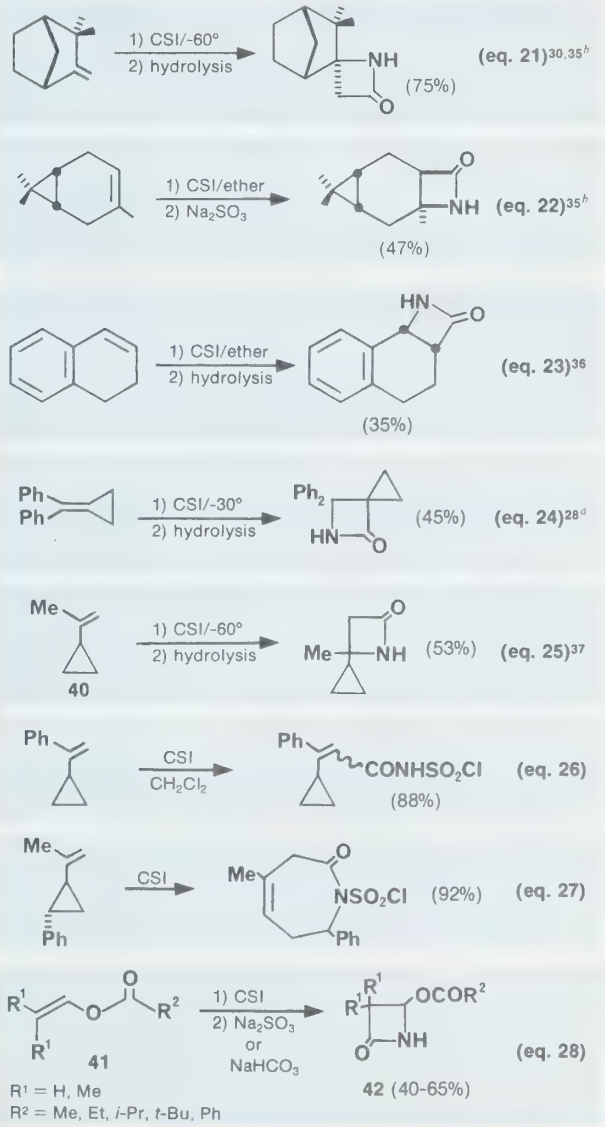
Both concerted[28] (involving orthogonal approach of the CSI and olefin π orbitals[29]) and nonconcerted, 1,4-dipolar[20,30] (*via* **32**) mechanisms have been proposed for these reactions. It seems likely that either or both mechanisms may be operative, depending on the substitution (and, hence, charge stabilization) of the olefin.[31] The cycloadditions are highly stereo- and regiospecific: the *cis* adduct is always formed, and addition takes place in such a way that the most stable carbonium ion would be generated.[2] The examples cited in equations 16 through 25[32-37] illustrate the utility and high specificity of Class II reactions of chlorosulfonyl isocyanate. Note that reductive hydrolysis of the initial cycloadduct to the corresponding N-unsubstituted β-lactam can be accomplished by employing a two-phase system consisting of organic solvent and aqueous sodium sulfite, the latter being kept slightly basic by the addition of KOH.[38] Note, too, that the low temperatures indicated in several of the examples are necessary to preclude Wagner-Meerwein rearrangement of the intermediate *N*-chlorosulfonyl β-lactams. **Vinylcyclopropanes** (including **40**) are particularly prone to rearrangement, especially when the reaction with CSI is conducted at or above room temperature (see, for example, equations 26 and 27[39]).

Heterosubstituted β-lactams, which comprise the fundamental nucleus of the penicillin and cephalosporin antibiotics, may be prepared by the reaction of CSI with a variety of **vinyl esters** (**41**, equation 28).[40] The acyloxy substituent of the resulting β-lactams (**42**) may be selectively replaced by a variety of nucleophiles (*e.g.*, RCO_2^-, RSO_2^-, N_3^-, RO^-, and RS^-) in good to excellent yields, leaving the four-membered ring intact.

In view of the stereospecific cis addition of chlorosulfonyl isocyanate to olefins and

Scheme V





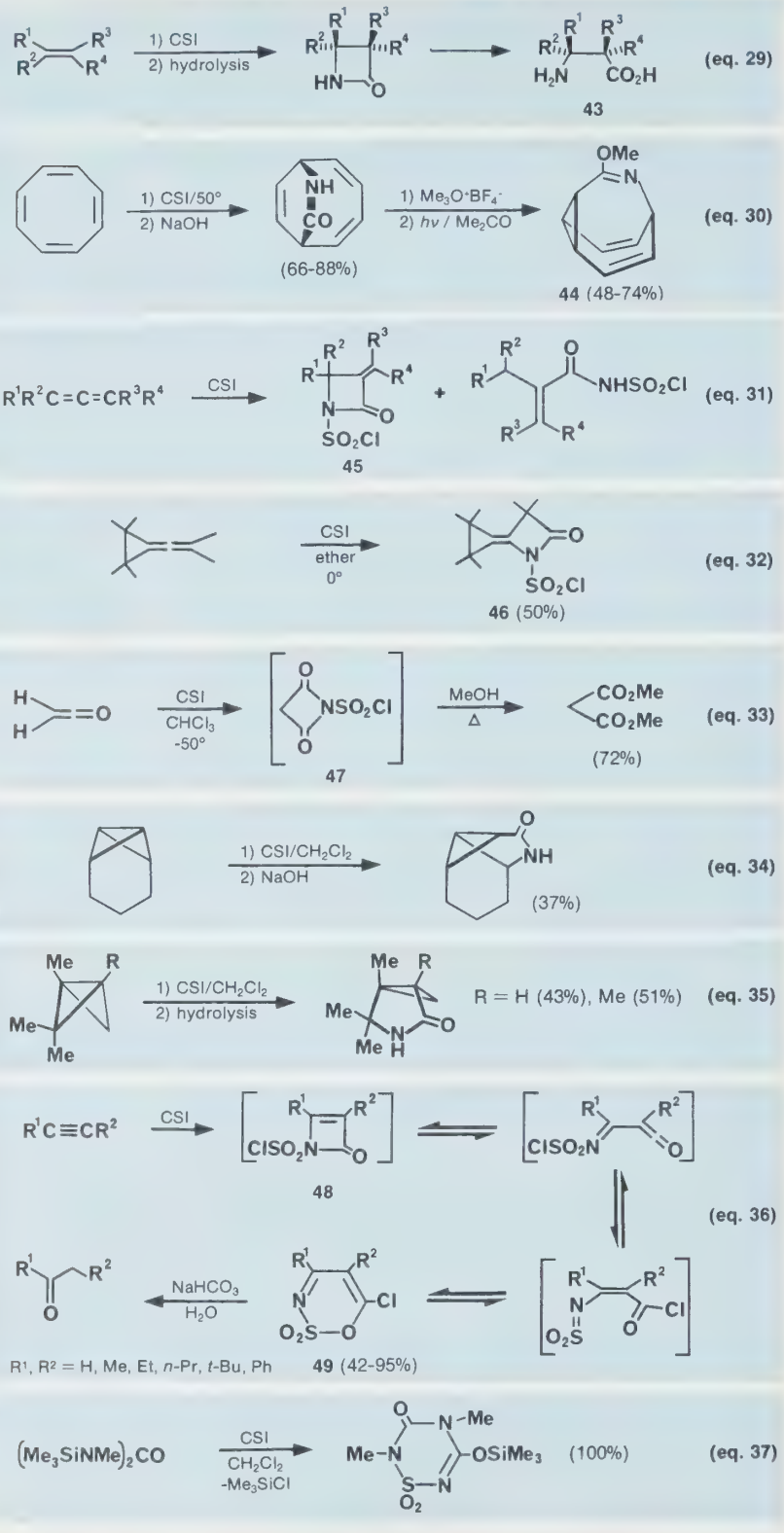
the facile cleavage of the resulting β-lactams, this versatile reagent provides a convenient route to *erythro*- and *threo*-β-amino acids (**43**, equation 29).[41]

The uniparticulate electrophile CSI can be an extremely useful reagent for the generation and intramolecular trapping of carbonium ions in **polyenes**. Paquette[42] has amply demonstrated this use of CSI as a *mechanistic probe* in his studies of molecules such as bullvalene,[42a] barrelene,[42b] and homobarrelene.[42c] A practical synthesis of methoxyazabullvalene **44** (equation 30) has emerged from this research on fluxional systems.[43]

Reaction of CSI with residual olefinic bonds in certain **polymers**, followed by cleavage of the chlorosulfonyl groups from the resulting β-lactam units, has been claimed to enhance the resistance of some natural and synthetic rubbers to thermal and physical stress.[44] In addition, chlorosulfonyl isocyanate has been used as a probe for the study of polymer microstructure in certain rubbers.[45] Recently, CSI has figured in the preparation of desalination membranes from a variety of polyisoprenes.[46]

CSI reacts with *cumulated* double bonds to produce a multitude of interesting compounds. For example, simple **allenes** react quickly at room temperature to afford mixtures of β-lactams (**45**) and α,β-unsaturated amides, as shown in equation 31.[47] The lactams generally predominate. Cyclopropylidene derivatives are exceptions[48] in that they react with CSI to produce "reversed" regioisomers such as **46** (equation 32[48b]), the apparent result of electrophilic attack by CSI at a *terminal* allenic carbon atom. Mundlos and Graf[49] have suggested that the reaction of **ketene** with CSI at low temperature produces the unstable imide **47**,[50] which is readily transformed into malonic acid derivatives, as shown in equation 33.

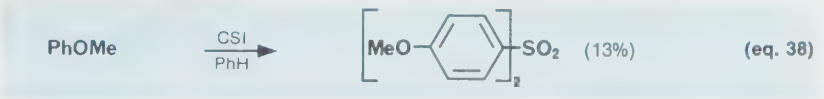
Strained, carbon-carbon single bonds of certain **bicyclic hydrocarbons** undergo formal cycloaddition reactions with chlorosulfonyl isocyanate as a consequence of their high degree of p character.[51] The products obtained are often novel heterocycles which might be difficult to prepare by other methods. Examples taken from Paquette's work[51b] are given in equations 34 and 35 (the major products are indicated).

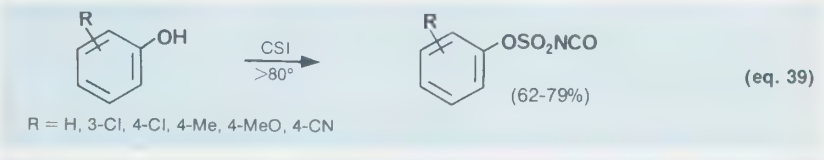


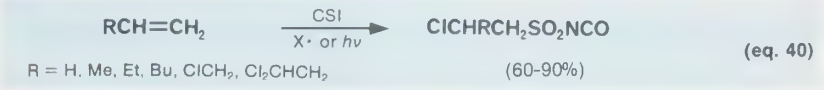
CSI reacts with most **acetylenes** to produce good yields of 1:1 adducts **49**, probably *via* the intermediates shown in equation 36.[52] Although it was claimed[53] that intermediates of type **48** could be isolated from the reaction mixture, the species isolated were shown by Moriconi and Shimakawa[52] to be products **49**. The hydrolysis of such products affords ketones, as indicated in equation 36. Interestingly, CSI reacts only with the *acetylenic* function of 1-octen-4-yne: an equimolar mixture of these two materials in CH_2Cl_2 produced only **49**, R^1 = *n*-Pr, R^2 = $CH_2CH{=}CH_2$.[52]

Class III: Nucleophilic Addition to Sulfur

Compounds that are unreactive toward the isocyanate moiety of CSI may react with the chlorosulfonyl group. Equations 37[54] and 38[55] depict reactions whose products are probably derived from this mode of addition. Certain experimental conditions also promote Class III reactions. Equations 39[56] and 40[57] illustrate such additions to CSI under the influence of high temperature and free-radical conditions, respectively.







Conclusion

Considering the rich chemistry of chlorosulfonyl isocyanate, and now its inexpensive and ready commercial availability from Aldrich, it is safe to predict that CSI will enjoy many more "anniversaries" as one of the most useful reagents in synthetic organic chemistry.

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14,266-2
Chlorosulfonyl isocyanate (CSI)

About the Author

William A. Szabo received his Ph.D. degree in organic chemistry from the University of Florida in 1974. He did postdoctoral work at Wesleyan University with Professor Max Tishler before joining Aldrich. Dr. Szabo's interests span synthetic and medicinal organic chemistry, in particular, new reagents, synthetic strategy, and drug design.

It is easy to exaggerate the dangers of new inventions and to forget that we have learned to live with the hazards of familiar materials. In Newsletter 70 I reprinted an article which assumed that coal had just been discovered but that nuclear energy had been in use for a long time. In the following, we assume that water, in the pure form, has been unknown — there are no seas, no rivers, no lakes — and has just been discovered.

NEW FIRE-FIGHTING AGENT MEETS OPPOSITION
"COULD KILL MEN AS WELL AS FIRES"

T. A. Kletz
Division Safety Adviser
Imperial Chemical Industries Limited

ICI has announced the discovery of a new fire-fighting agent to add to their existing range. Known as WATER (Wonderful And Total Extinguishing Resource), it augments, rather than replaces, existing agents such as dry powder and BCF which have been in use from time immemorial. It is particularly suitable for dealing with fires in buildings, timber yards and warehouses. Though required in large quantities, it is fairly cheap to produce and it is intended that quantities of about a million gallons should be stored in urban areas and near other installations of high risk ready for immediate use. BCF and powder are usually stored under pressure, but WATER will be stored in open ponds or reservoirs and conveyed to the scene of the fire by hoses and portable pumps.

ICI's new proposals are already encountering strong opposition from safety and environmental groups. Professor Connie Barrinner has pointed out that, if anyone immersed their head in a bucket of WATER, it would prove fatal in as little as 3 minutes. Each of ICI's proposed reservoirs will contain enough WATER to fill half a million two-gallon buckets. Each bucket-full could be used a hundred times so there is enough WATER in *one* reservoir to kill the entire population of the UK. Risks of this size, said Professor Barrinner, should not be allowed, whatever the gain. If the WATER were to get out of control the results of Flixborough or Seveso would pale into insignificance by comparison. What use was a fire-fighting agent that could kill men as well as fires?

A Local Authority spokesman said that he would strongly oppose planning permission for construction of a WATER reservoir in this area unless the most stringent precautions were followed. Open ponds were certainly not acceptable. What would prevent people falling in them? What would prevent the contents from leaking out? At the very least the WATER would need to be contained in a steel pressure vessel surrounded by a leak-proof concrete wall.

A spokesman from the Fire Brigades said he did not see the need for the new agent. Dry powder and BCF could cope with most fires. The new agent would bring with it risks, particularly to firemen, greater than any possible gain. Did we know what would happen to this new medium when it was exposed to intense heat? It had been reported that WATER was a constituent of beer. Did this mean that firemen would be intoxicated by the fumes?

The Friends of the World said that they had obtained a sample of WATER and found it caused clothes to shrink. If it did this to cotton, what would it do to men?

In the House of Commons yesterday, the Home Secretary was asked if he would prohibit the manufacture and storage of this lethal new material. The Home Secretary replied that, as it was clearly a major hazard, Local Authorities would have to take advice from the Health and Safety Executive before giving planning permission. A full investigation was needed and the Major Hazards Group would be asked to report.

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Selective Reductions Using Borane Complexes*

Clinton F. Lane
Aldrich - Boranes, Inc.
Milwaukee, Wisconsin 53233

Boron hydride reducing agents are becoming increasingly important in synthetic organic chemistry. Sodium borohydride, sodium cyanoborohydride,[1] the Selectride® reagents,[2] and Super-Hydride®[2,3] are all widely utilized for selective reductions. These borohydride reagents react principally by nucleophilic attack on an electron-deficient center. Conversely, borane, which is electron-deficient, is believed to function through attack on an electron-rich center.[4] Thus, borane complexes are acidic-type reducing agents which exhibit markedly different selectivity from the basic-type reducing agent, sodium borohydride.[5] This interesting difference in the reducing activity of diborane and sodium borohydride prompted an extensive study of the reduction of organic compounds with borane-ether complexes.[6,7]

In addition to the Lewis acid character of borane, other important chemical properties have enhanced the utility of borane complexes as reducing agents. Many reactions involving borane complexes have unusually low activation energies. Consequently, most reactions occur readily at or below room temperature. These low temperatures favor clean reaction mixtures. Because of the solubility of borane complexes, the reactions are usually homogeneous, proceed without induction periods, and are easily controlled. Finally, the inorganic by-product of a borane reduction is usually an inert, water-soluble borate salt, which can be washed away over a broad pH range. All of these chemical and physical properties combine to make borane one of the most chemically versatile compounds known.

*For a more comprehensive treatment of this topic, see C.F. Lane, *Chem. Rev.*, **76**, 773 (1976).

THE REAGENTS

The high reactivity of diborane is presumably due to its ready dissociation into borane (BH_3).[8] The borane molecule behaves as a strong electron-pair acceptor (Lewis acid) forming coordination complexes with suitable electron donors (Lewis bases). Of the various known complexes, the borane-amine, borane-ether, and borane-alkyl sulfide complexes are all particularly interesting because of their wide range of physical and chemical properties. More importantly, these borane-Lewis base complexes provide a convenient source of borane for use as a reducing agent.

1) BH_3·Amine Complexes

The borane-amine complexes are very useful reagents which have many important laboratory and industrial applications.[9]

The first borane-amine complex was reported in 1937 and was prepared by the direct reaction of diborane with trimethylamine (eq. 1).[10] Since then almost all structural types of amines have been used to

$$2\ (CH_3)_3N + B_2H_6 \longrightarrow 2\ (CH_3)_3N{:}BH_3 \qquad \text{(eq. 1)}$$

prepare borane-amine complexes. A wide variety of these complexes is now available from Aldrich.

An important feature of the borane-amine complexes is their broad range of physical properties. Liquid, low-melting solid, and high-melting solid borane-amines are known. The borane-amines also have low vapor pressures and can be purified by distillation and/or recrystallization. They are also soluble in a wide variety of solvents.[9,11]

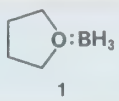
Most borane-amines are stable indefinitely at room temperature and are unaffected by dry air. The borane-amines prepared from primary and secondary amines are surprisingly resistant to loss of hydrogen.

Only the borane complexes with *N*-arylamines (*N*-phenylmorpholine and *N*,*N*-diethylaniline) are hydrolyzed by water (atmospheric moisture) and alcohols.[11] However, by careful and rapid handling, they may be transferred in air with only minimal loss of hydride activity. All of the other borane-amines are stable in hydrolytic solvents at neutral pH for a minimum of 12hr at 25°.[11]

The most important chemical property of the borane-amine complexes is their ability to act as reducing agents.[9] The use of borane-amines for the reduction of organic functional groups will be discussed in later sections of this review.

2) BH_3·THF

A Raman spectroscopic investigation of the liquid systems diborane-THF, diborane-dimethyl ether, and diborane-diethyl ether, provides evidence for the formation of a $R_2O{:}BH_3$ addition complex in each system.[12] Also, a study of the solid-liquid equilibrium for diborane-THF clearly indicates the formation of the compound tetrahydrofuran-borane (**1**).[13] On



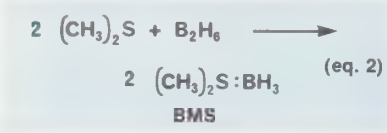
1

the basis of these two studies, the stability of borane-ether complexes is believed to decrease in the order: **1** > $Me_2O{:}BH_3$ >> $Et_2O{:}BH_3$. Additional evidence is available for the existence of **1** in a THF solution of diborane. In THF the solubility of

diborane is much greater than perfect-solution predictions, *i.e.*, the solubility increases as the square root of diborane pressure increases.[14] Also, a phase diagram study[15] and two ^{11}B plus ^{1}H nmr studies[16] provide convincing evidence for the existence of **1** in excess THF. It is apparent that diborane must be present in THF solution as the complex **1**. The stability of **1** is quite unique and is mainly responsible for the interest in and utility of BH_3-THF as a convenient reducing agent.

3) $BH_3 \cdot Me_2S$

The first reported preparation of a borane-alkyl sulfide complex was by Burg and Wagner.[17] Condensation of dimethyl sulfide and diborane on a vacuum line produced a stable, liquid adduct of borane-methyl sulfide (BMS) (eq. 2).



(eq. 2)

The surprising stability of BMS at room temperature prompted a more detailed study of borane-alkyl sulfide complexes by Stone and coworkers.[18]

The physical and chemical properties of BMS make this reagent an attractive source of BH_3, and its numerous advantages over BH_3-THF as a storable reagent were first discussed by Adams and coworkers.[19] The BH_3-THF reagent possesses certain characteristics which limit its preparation, storage, and use as a commercial source of BH_3, namely: (1) BH_3-THF can only be sold as a dilute solution (1 *M*) in THF (1.5 wt % BH_3), (2) THF is slowly cleaved by BH_3 at room temperature, and (3) sodium borohydride (<5 mole %) must be added to BH_3-THF to inhibit the cleavage of THF.

Fortunately, BMS has been found to overcome all of these disadvantages. BMS has a molar concentration of BH_3 *ten times* that of the BH_3-THF reagent. It can be stored for months at room temperature without loss of hydride activity and is apparently stable indefinitely when refrigerated. Also, BMS is soluble in, and unreactive toward, a wide variety of aprotic solvents including ethyl ether, THF, hexane, heptane, toluene, xylene, methylene chloride, glyme, and diglyme. BMS dissolves readily in alcohols with the quantitative evolution of hydrogen. However, it is insoluble in water and only very slow hydrolysis occurs. The addition of water to ether solutions of BMS results in rapid hydrolysis.

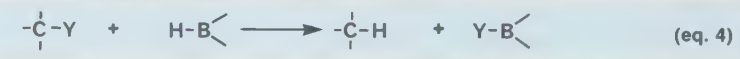
Quantitative hydroborations with BMS are possible under mild conditions in a variety of aprotic solvents such as ethyl ether, THF, hexane, toluene, and methylene chloride.[20] The air-stability and ease of handling of this reagent have permitted its use in an undergraduate laboratory.[21] The successful hydroboration of alkenes with BMS prompted similar studies with BMS as a reducing agent.[22] The results of these investigations make it apparent that BMS is a very useful reagent for the reduction of organic functional groups.

REACTION WITH ACIDIC HYDROGENS

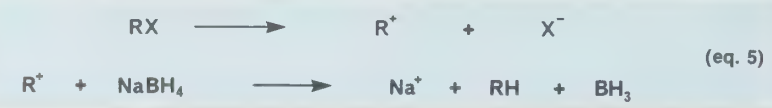
BMS and BH_3-THF react rapidly and quantitatively with various acidic hydrogens (H-Y), liberating one mole of hydrogen per equivalent of boron hydride (eq. 3). The acidity of the hydrogen and the ability of the donor atom Y to share a pair of electrons influence the rate of these reactions.[7]

The direct measurement of the volume of hydrogen gas produced upon hydrolysis of a boron hydride provides a convenient and accurate method for the determination of either the purity of a boron hydride or the concentration of a boron hydride solution.[23]

(eq. 3)



(eq. 4)



(eq. 5)

In reactions of borane complexes with compounds containing acidic hydrogens, hydrogenolysis of the C-Y bond is usually not observed. Upon hydrolysis the alcohol, amine, thiol, or related functional group is regenerated. However, in a few specialized cases, those alcohols which can readily form carbonium ions are transformed by diborane into the corresponding hydrocarbons (*vide infra*). Even though the alcohol, thiol, and amine groups are normally recovered, their presence and reactivity must by considered when carrying out a borane reaction, *i.e.*, sufficient borane reagent must be added to compensate for loss of hydride activity upon reaction with acidic hydrogens.

Other functional groups which contain acidic hydrogens such as carboxylic acids and primary and secondary amides, react with borane with evolution of hydrogen. However, since these groups react further with borane, they will be discussed in later sections dealing with the reduction of such functional groups.

REDUCTIVE CLEAVAGE

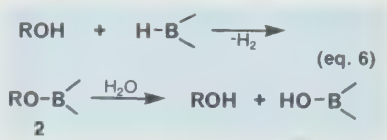
In general, this section deals with those reactions which involve the reductive cleavage of a C-Y single bond (eq. 4). The reduction of organic functional groups containing carbon-sulfur, carbon-nitrogen, or carbon-oxygen multiple bonds will be discussed in later sections. Naturally, some overlap is inevitable; but by subdividing the sections into discussions of specific functional groups, the retrieval of information about the reducing characteristics of borane complexes should be simplified.

1) Organic Halides

Primary, secondary, and tertiary alkyl and aryl fluorides, chlorides, bromides, and iodides are all inert toward the various borane-Lewis base complexes.[7] Even under vigorous conditions (1hr at reflux), the more reactive primary alkyl bromides and iodides are stable to BH_3-THF.[24] Under similar conditions, lithium aluminum hydride (LAH) is extremely reactive.[25] Under solvolytic conditions, sodium borohydride reacts with readily ionizable secondary and tertiary organic halides to give good yields of the corresponding hydrocarbons (eq. 5).[26] Obviously, the presence of sodium borohydride as a stabilizer in commercial BH_3-THF must be considered when using this reagent for the reduction of an organic compound containing a readily ionizable halide since a small amount of a side reaction involving the $NaBH_4$ can occur as shown above.

2) Alcohols

Alcohols normally react rapidly with diborane to give alkoxyboranes (**2**). Hydrogenolysis of the carbon-oxygen bond usually does not occur. Thus, the alcohol is regenerated upon hydrolytic work-up (eq. 6). However, this does not



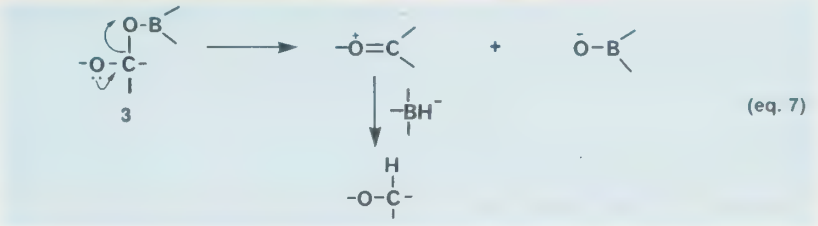
(eq. 6)

mean that reductive cleavage of the carbon-oxygen σ bond is unimportant in borane reductions. When the intermediate alkoxyboron compound is of the correct structural type, cleavage of the carbon-

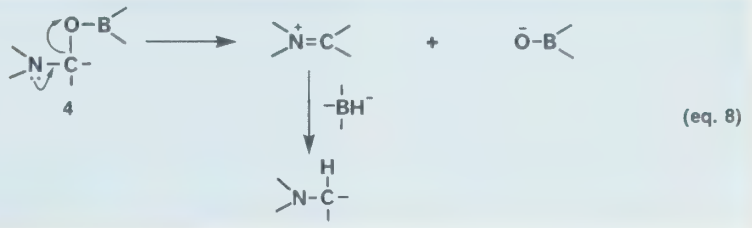
oxygen bond becomes the major reaction pathway. Equations 7-10 illustrate a variety of known carbon-oxygen bond cleavage reactions.

Although the mechanism may be more complex, the presence of an *electron-donating* atom is required before cleavage of the C-O bond is observed in a C-O-B type of intermediate. Other examples are known and will appear later, but intermediates **3-6** illustrate the generality of this *electron-donation-induced cleavage*.

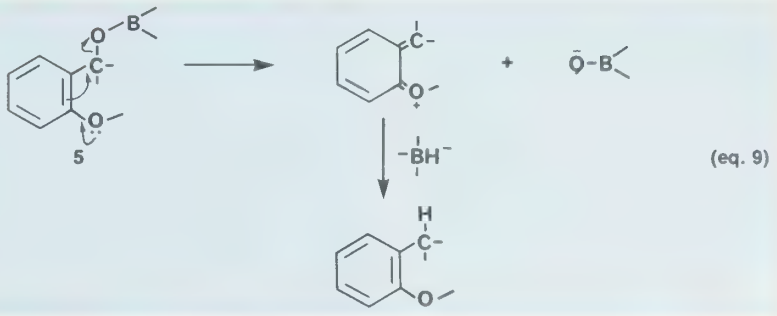
Obviously, intermediate **3** is formed during the reaction of esters and lactones with borane and the importance of this reductive cleavage will be discussed in a later section. Also, the fragmentation of intermediate **4** constitutes the reaction pathway observed in the facile reduction of amides with borane reagents. Intermediates of the type illustrated by **6** can be formed by reduction of the corresponding aldehyde or ketone. Finally, intermediates similar to **5** are formed not only during the reduction of certain aldehydes and ketones but can also arise directly from an appropriate alcohol. Reductive cleavage of the alcohol then results. A specific example is illustrated by equation 11.[27]



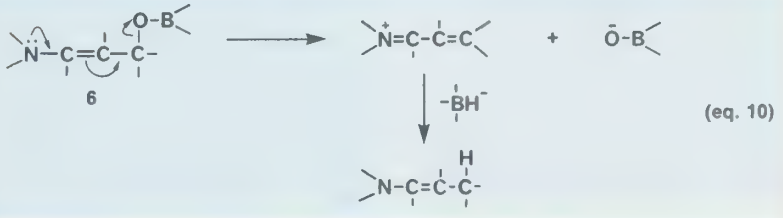
(eq. 7)



(eq. 8)



(eq. 9)



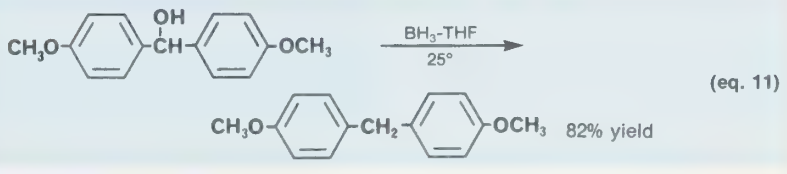
(eq. 10)

3) Ethers

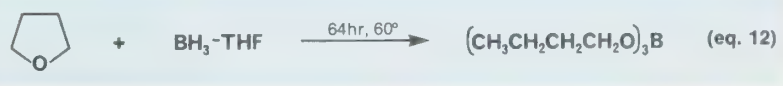
The formation of borane-ether complexes is known to occur, but more crucial is the fact that reductive cleavage of ether linkages by borane is also known. Fortunately, reductive cleavage is a relatively slow reaction under normal conditions.[28,29] With BH_3-THF, heating for an extended period of time in a sealed tube is necessary to obtain a reasonable yield of tri-*n*-butyl borate (eq. 12).[28,30]

The reductive cleavage of THF by BH_3-THF is negligible for the laboratory use of this reagent. The BH_3-THF reagent is stable for several months when prepared and stored at 0° under nitrogen.[31] The reagent loses 1-3% of the available BH_3 per day when stored at ordinary temperatures (25-30°).[29] This becomes a major problem during the manufacture, storage, and shipment of the commercial material. Fortunately, Brown discovered that a small amount of dissolved sodium borohydride stabilizes the BH_3-THF reagent and effectively eliminates the loss of hydride due to reductive cleavage.[29] The commercial availability of the reagent is a result of this observation. The stabilized BH_3-THF reagent shows no loss in active hydride after 2 weeks at 25°.[29] Even so, whenever possible, the reagent should be stored at 0° to maintain maximum hydride activity.

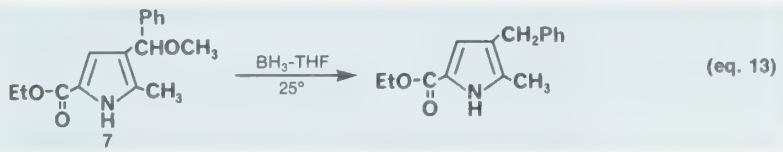
Brown also disclosed that solutions of diborane in THF are stabilized against decomposition for at least 8 weeks by the presence of an organic sulfide.[32]



(eq. 11)



(eq. 12)



(eq. 13)

As was observed for the hydrogenolysis of alcohols, the presence of electron-donating groups greatly enhances the ease of reductive cleavage. The reductive cleavage of the benzylic ether **7** is a specific example (eq. 13).[33] This reaction presumably involves an intermediate analogous to **6**.

Acetals and ketals are reductively cleaved with borane reagents under milder conditions (2-3hr at 25-30°) than are required for simple ethers.[34,35] A probable reaction pathway is illustrated in equation 14. This mechanism is a straightforward extension of the idea of electron-donation-induced cleavage. Two specific examples are illustrated in equations 15 and 16.[35] Although it

has not been shown in these equations and will generally be omitted in later equations, a hydrolysis step is usually necessary in the borane reductions.

4) Epoxides

Brown and Yoon have demonstrated the pronounced catalytic action of both $NaBH_4$ and BF_3 on the reduction of epoxides with BH_3-THF.[36,37] For example, in the presence of a catalytic quantity of boron trifluoride, styrene oxide undergoes a quantitative, regioselective, reductive, ring-opening reaction (eq. 17).[36]

REDUCTION OF ORGANIC SULFUR COMPOUNDS

Dimethyl sulfoxide is reduced to dimethyl sulfide with BH_3-THF at a moderate rate at 0°.[7] Such a deoxygenation reaction was recently used as the final step in the first reported preparation of 1,3-dithietane (eq. 18).[38]

All other compounds containing sulfur-oxygen double bonds, including aromatic and aliphatic sulfones and cyclohexyl tosylate, are inert to BH_3-THF under standard conditions.[7]

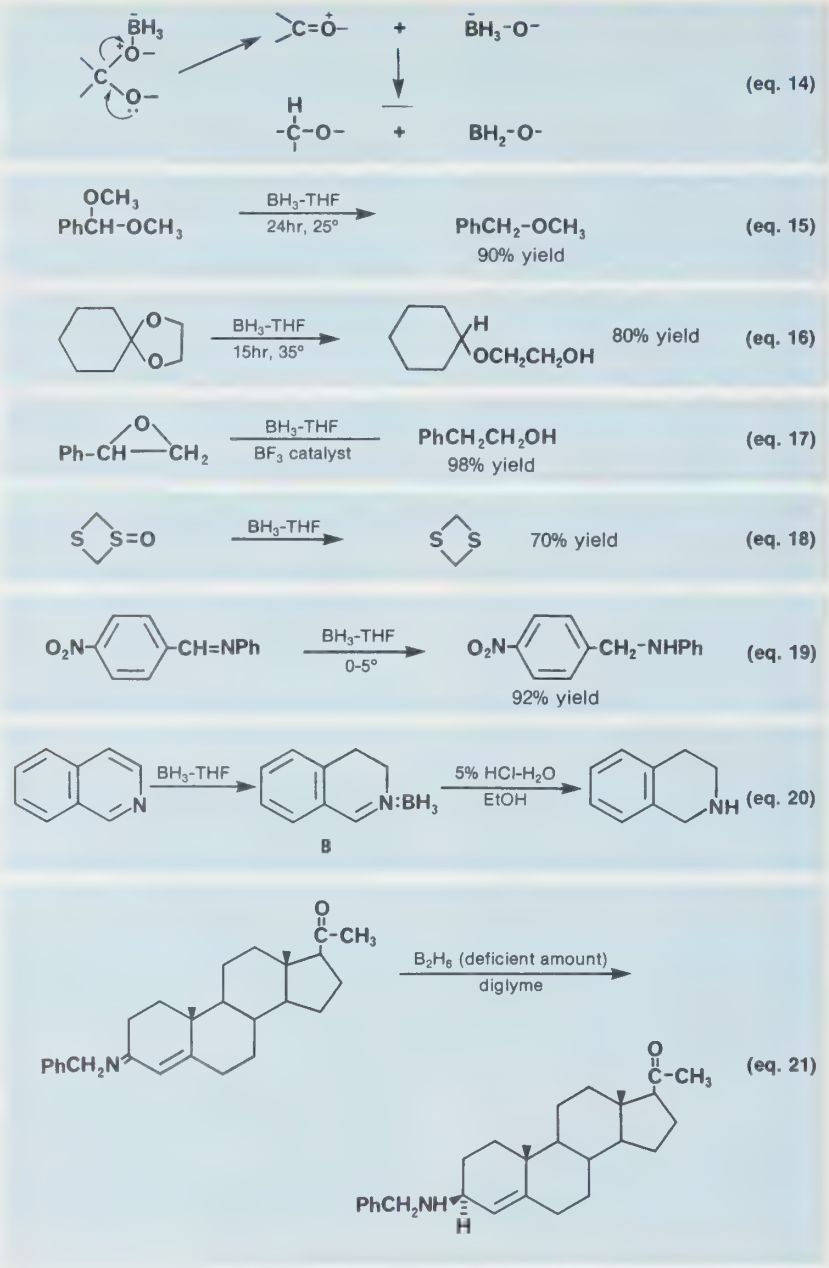
REDUCTION OF ORGANIC NITROGEN COMPOUNDS

A variety of organic functional groups containing a multiple-bonded nitrogen is reduced with borane reagents. Most of the effort has been directed towards the reduction of imines, oximes, nitro derivatives, and nitriles. The reaction of borane reagents with these functional groups will be discussed in detail in individual sections. However, a number of other nitrogen-containing groups undergo reaction with borane.

Diazomethane reacts readily with BH_3-THF giving an almost quantitative yield of a highly crystalline, boron-containing polymethylene.[39] Diborane reacts with organic isocyanates and isothiocyanates to give thermally unstable diadducts at low temperatures.[40] At higher temperatures decomposition leads to complex mixtures which include aminoboranes and boron-nitrogen cyclic trimers. Finally, pyridine *N*-oxide is reduced at a moderate rate, but hydride uptake and examination of the ir spectrum of the product indicate attack on the aromatic ring.[7]

1) Imines

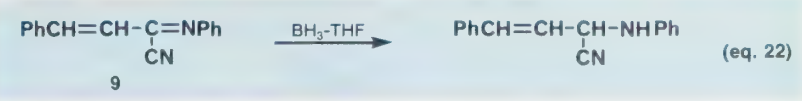
The reduction of Schiff bases with BH_3-THF proceeds under very mild conditions giving excellent yields of the corresponding amines.[41] A specific example is shown in equation 19, but this reduction and similar reductions of Schiff bases can also be carried out with the milder reducing agent, sodium borohydride. Consequently, the borane reagents would appear to be of limited utility for imine reductions.

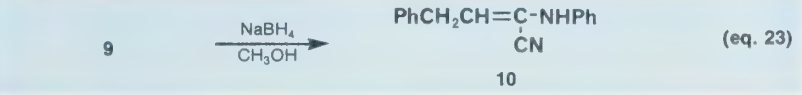


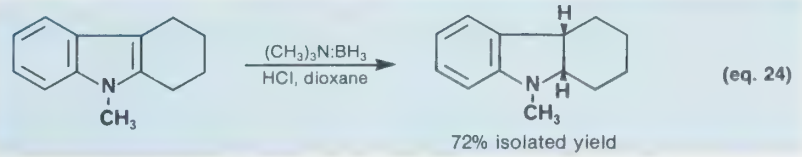
With a number of specific systems, borane either exhibits superior selectivity or gives a product that is not possible using sodium borohydride as the reducing agent. For example, isoquinoline reacts with BH_3-THF giving an intermediate dihydroisoquinoline-borane adduct **8** which is reduced further to tetrahydroisoquinoline upon treatment with dilute, aqueous hydrochloric acid in ethanol (eq. 20).[42] The selectivity of borane is illustrated by the reported reduction of an imine group in the presence of a ketone (eq. 21).[43] When sodium borohydride in methanol was used as the reducing agent, both the imine and ketone were readily reduced.

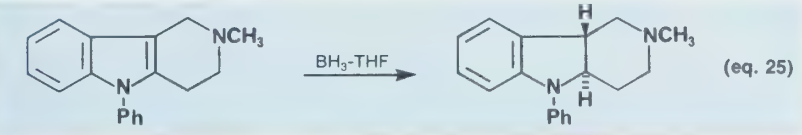
The selective reduction of the cyano-substituted imine **9** is possible using BH_3-THF (eq. 22).[44] When sodium borohydride in methanol at room temperature is used, a rearranged nitrile (**10**) is obtained (eq. 23).[44]

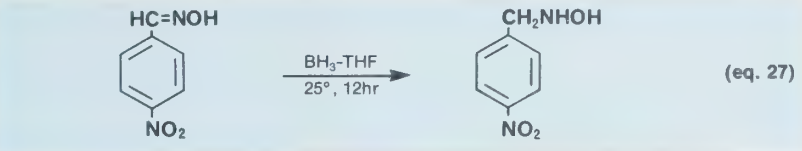
For alkyl-substituted imines, an equilibrium may exist between the imine and the corresponding enamine. Evidence for this equilibrium was provided by the observation that hydroboration-oxidation of some cyclohexanone imines gave both the corresponding amine and the 2-hydroxycyclohexylamine.[45]

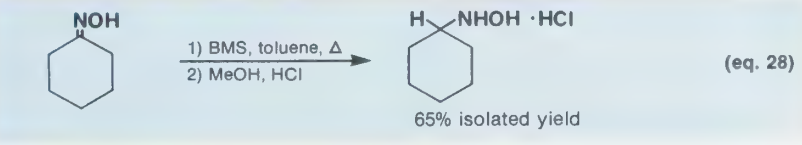


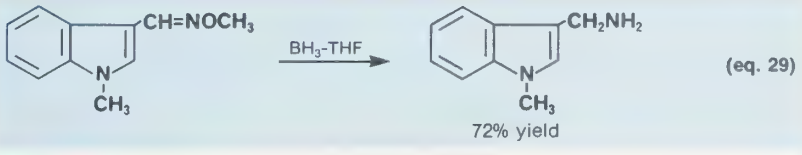


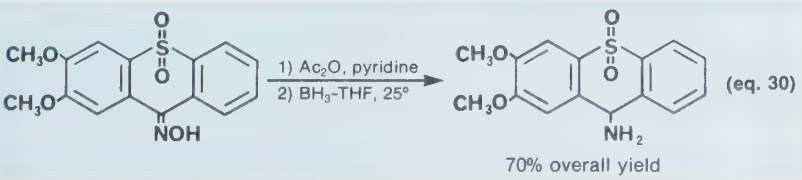




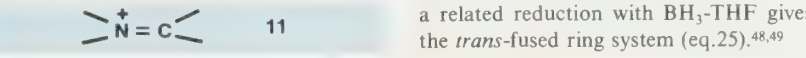








The reaction of N-unsubstituted indoles with excess BH_3-THF results in an initial, rapid evolution of hydrogen gas.[46] Addition of excess acetone or slow inverse addition to a large excess of methanol gives the starting indole. However, if the reaction mixture is treated with methanol under neutral, acidic, or basic conditions, reduction to an indoline is observed.[46] The mechanism probably involves an intermediate iminium ion (**11**).



Recently, Berger found that various indoles can be reduced *via* their indolinium salts by borane-trimethylamine in generally good yields.[47] The success of Berger's method is a result of the fact that borane-trimethylamine is a hydridic species which is remarkably stable under the highly acidic conditions required to generate indolinium ions. The reduction of a tetrahydrocarbazole provides a specific example (eq. 24).[47] Surprisingly, in certain specific cases, a related reduction with BH_3-THF gives the *trans*-fused ring system (eq.25).[48,49]

An intermediate iminium ion must also be involved when borane-amines are used for the reductive amination of ketones. Reduction of ketones with a borane-amine in the presence of an excess of ammonia, methylamine, or dimethylamine (pH ~9-10) at room temperature gives reasonable yields of the corresponding amines.[50] An interesting modification of this reaction was used to prepare α-amino acids. Thus, several substituted pyruvic acids were reduced at room temperature with a borane-amine complex in the presence of a 5-fold excess of ammonia to give the corresponding α-amino acid in 66-72% yield.[50]

Borane-amines can also be used for the reduction of imines. Borane-dimethylamine selectively reduces the imino linkage in the presence of the chloro, nitro, alkoxy, hydroxy, carboxy, carbethoxy, and sulfonamido groups.[51] This reduction proceeds rapidly and smoothly in glacial acetic acid to give excellent yields of secondary amines.

When the reduction of imines is carried out under more vigorous conditions using an excess of borane-trimethylamine, reductive acylation is observed.[52]

2) Oximes

The reduction of readily available aldoximes and ketoximes with BH_3-THF provides a facile and convenient synthesis of N-monosubstituted hydroxylamines (eqs. 26,27).[53] BMS can also be used as the reducing agent and offers the advantage of a much simpler isolation procedure (eq. 28).[22]

Heating the intermediate from the BH_3-THF reduction of an aliphatic oxime to 105-110° in a diglyme-THF solvent system gives complete reduction to the corresponding amine.[54] On the other hand, oxime ethers and oxime esters are reduced readily at 25°.[54,55] Hydrolysis then gives excellent yields of the corresponding amines (eqs. 29, 30).

3) Nitro Compounds and Related Derivatives

Nitrobenzene and 1-nitropropane fail to react with BH_3-THF in any reasonable time under normal conditions.[7] Also, the aryl nitro group fails to react with BMS even under somewhat more vigorous conditions.[22] Azoxybenzene is unreactive, but azobenzene is reduced at a moderate rate, utilizing two hydrides with hydrogen evolution and giving aniline upon hydrolysis.[7]

Even though the nitro group is inert, salts of nitroalkanes are readily reduced to hydroxylamines with BH_3-THF.[56] Presumably, the anion provides a point of attack for the electrophilic borane species.

The reduction of aromatic nitroso compounds with BH_3-THF at 25° affords the corresponding amines in good yields.[57]

4) Nitriles

The BH_3-THF reagent reacts slowly at 0° with both aliphatic and aromatic nitriles.[7] However, by using an excess of borane reagent and a higher temperature, reasonable isolated yields of amines are possible upon acid hydrolysis of the intermediate borazines (eqs. 31-33).

BMS is also a useful reagent for the preparation of amines *via* reduction of nitriles (eq. 34).[22]

An interesting nitrile reduction step has been used for the preparation of ^{11}C-labeled norepinephrine hydrochloride (eq. 35).[59] It should be possible to use the same procedure to reduce other cyanohydrins. Indeed, recently, various substituted benzaldehyde cyanohydrins were reduced with BH_3-THF to give 70-80% isolated yields of the corresponding β-amino alcohols.[60]

REDUCTION OF ORGANIC OXYGEN COMPOUNDS

1) Aldehydes and Ketones

Excess diborane reacts readily at room temperature with aldehydes and ketones to yield the corresponding dialkoxyboranes (eq. 36).[4] All attempts to isolate the monoalkoxy derivative have been unsuccessful.[4,61] When an excess of aldehyde or ketone is used, the trialkyl borate is formed (eq. 37).[4]

BH_3-THF reacts similarly. For example, the reaction of two equivalents of acetone with one equivalent of BH_3-THF gives a 95% yield of diisopropoxyborane.[62] Aliphatic and aromatic aldehydes and dialiphatic, monoaromatic, and alicyclic ketones all react rapidly with BH_3-THF at 0°.[7] Only with benzophenone is the rate considerably slower, probably a consequence of the combined steric and electronic effects of the phenyl groups.[7]

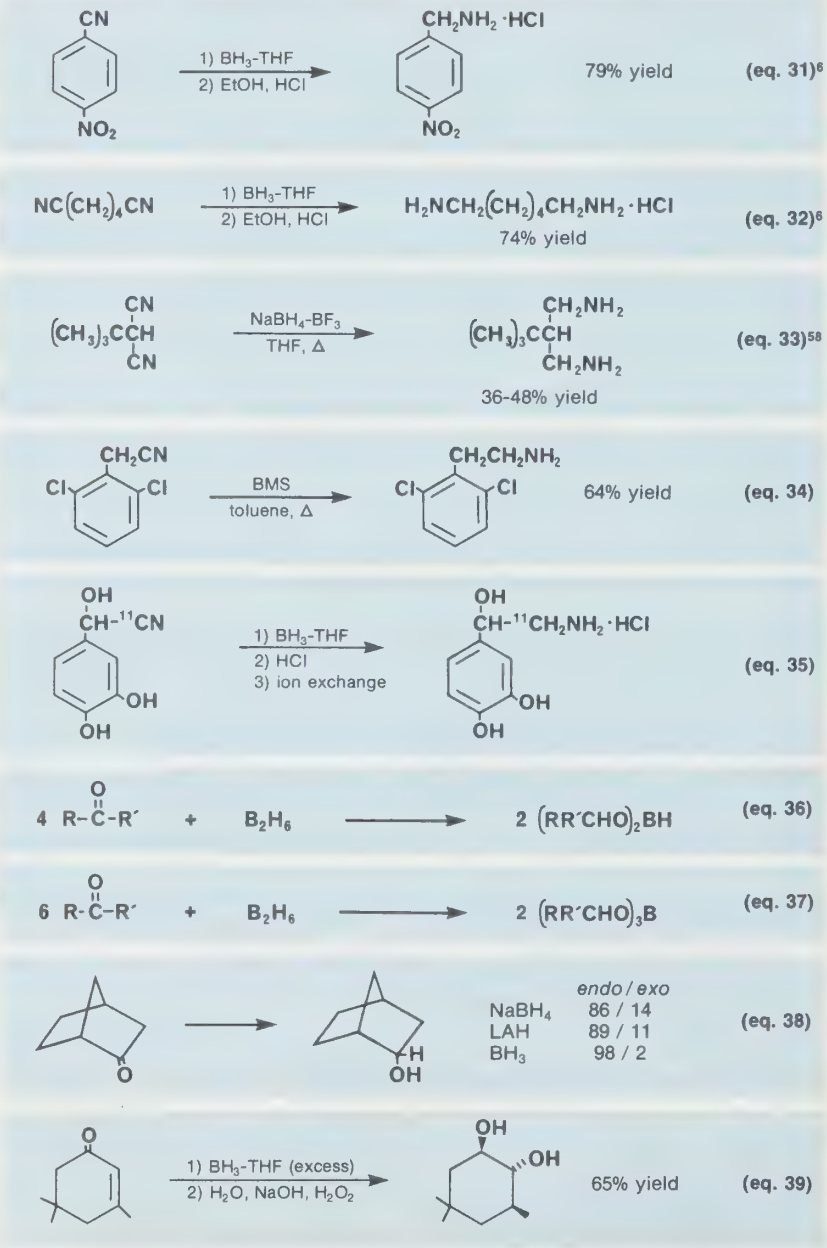
Borane-*N*-arylamine complexes reduce cyclohexanone in less than 3hr at 25° in THF.[11] However, again only two of three hydrides on boron are available for reaction, *i.e.*, the intermediate $(RO)_2BH$ must fail to react with ketones as observed for BH_3-THF reductions. Borane-pyridine and borane-trimethylamine in THF give no detectable reduction of a carbonyl compound after 38hr at 25°.[11] Under more vigorous conditions (benzene or toluene at reflux), borane-pyridine reduces aldehydes and ketones to the corresponding alcohols.[63,64]

Interestingly, the borane-amines are much more effective reducing agents in strong aqueous acid. The rate of reaction with carbonyl compounds actually increases with increasing acidity of the medium.[65] A tremendous increase in rate occurs upon addition of either a mineral acid[11] or a Lewis acid.[66] The effect of added boron trifluoride etherate is very striking.[66] It has been used for the reduction of ketones with borane-d_3-trimethylamine to give α-deuterio alcohols.[67]

Sodium borohydride is a much milder reducing agent than BH_3-THF and is normally the reagent of choice for the preparation of alcohols *via* reduction of aldehydes and ketones. However, with a number of systems, reduction with a borane reagent gives a selectivity or a product that is not possible using sodium borohydride. For example, the reduction of norcamphor with BH_3-THF is unusually stereoselective (eq. 38).[7]

The borane reduction of α,β-unsaturated carbonyl systems does not provide a general synthetic procedure for the preparation of allylic alcohols.[68] Hydroboration of the carbon-carbon double bond competes as a side reaction and proceeds to completion when sufficient borane reagent is used.

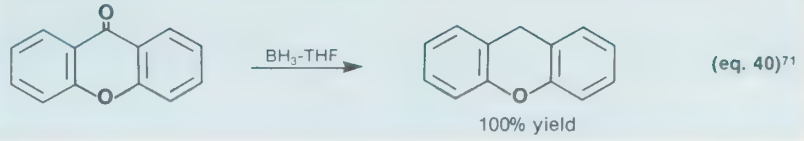
The double bond may undergo hydroboration directly, or a 1,4-addition of boron hydride may occur. Reduction of isophorone with excess BH_3-THF probably involves a direct hydroboration



of the carbon-carbon double bond. The 1,2-diol is obtained upon alkaline peroxide oxidation (eq. 39).[69]

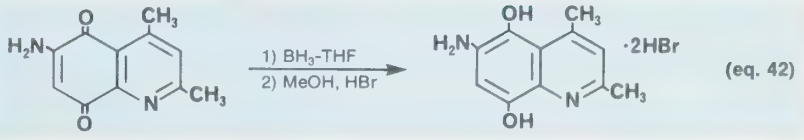
The electron-donation-induced reductive cleavage of carbon-oxygen bonds is of fundamental importance in the reduction of aldehydes and ketones with borane reagents. Intermediates corresponding to **5** and **6** are formed during the reduction of many functionally substituted carbonyl compounds. The reductive cleavage is known to be catalyzed by trace amounts of both BF_3[70] and $NaBH_4$.[27] The exact mechanism is unknown, but in all cases an intermediate closely related to **5** or **6** is probably involved. For the reduction of certain systems, this process is an unfortunate and undesirable side reaction. However, if the product of choice is the alcohol, then sodium borohydride should be used for the reduction.

In many cases the methylene derivative is the product of choice. Consequently, the reduction of these appropriately substituted carbonyl compounds with a borane reagent provides a mild, synthetically useful deoxygenation procedure. The borane deoxygenation of xanthone and pyrrole derivatives is particularly important and has been widely utilized (eqs. 40, 41).

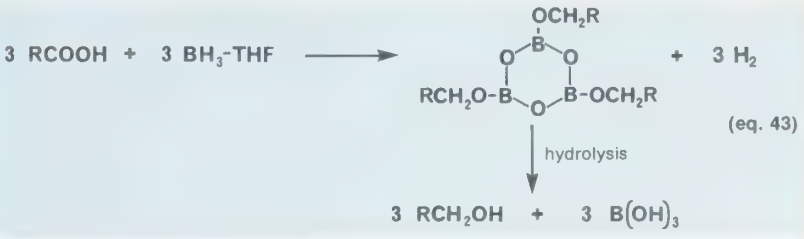


(eq. 40)[71]

(eq. 41)[33]

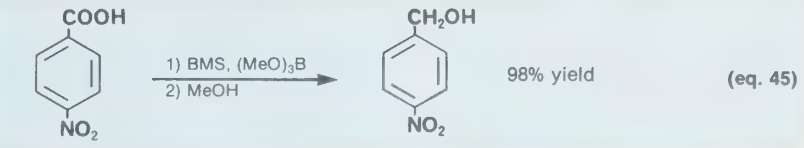


(eq. 42)

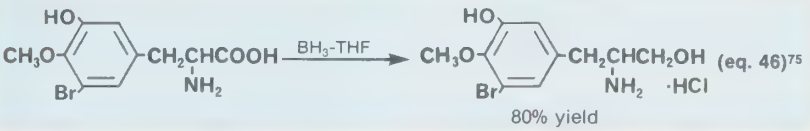


(eq. 43)

(eq. 44)



(eq. 45)



(eq. 46)[75]

(eq. 47)[73]

2) Quinones

p-Benzoquinone reacts slowly with BH_3-THF utilizing two hydrides, one for reduction and one for hydrogen evolution.[7] This stoichiometry corresponds to reduction to hydroquinone. In fact, Brown and coworkers obtained a quantitative yield of hydroquinone following methanolysis.[7]

An interesting application of this reduction involves the conversion of a 5,8-quinolinedione to a 5,8-dihydroxyquinoline in an 86% isolated yield (eq. 42).[72]

3) Carboxylic acids

Both aliphatic and aromatic carboxylic acids are reduced by BH_3-THF to the corresponding primary alcohols rapidly and quantitatively under remarkably mild conditions (eq. 43).[7] The obvious potential of this reaction for selective reductions in multifunctional molecules prompted a detailed study of the scope of this reduction.[73] This investigation by Brown and coworkers summarizes the reactivity and selectivity observed for the reaction of BH_3-THF with carboxylic acids. Also, some mechanistic possibilities are given.[73]

Aliphatic carboxylic acids react readily at 25° with BMS in a variety of solvents.[22] This reaction has been developed into a useful synthetic procedure for the preparation of 11-bromo-1-undecanol (eq. 44).[22] Aromatic carboxylic acids react very slowly with BMS, but reduction occurs rapidly in the presence of trimethyl borate.[74] The reduction of *p*-nitrobenzoic acid provides an example of the synthetic utility (eq. 45).[74]

The use of borane reagents provides a highly convenient synthetic procedure for the selective reduction of the carboxylic acid group in the presence of other potentially reactive functional groups. Numerous examples could be cited, but equations 46-51 should be sufficient to indicate the selectivity that is possible. For simplicity the hydrolysis step has been omitted, and the yield given is for isolated, purified product.

As illustrated by the examples, the reduction of carboxylic acid groups is possible in the presence of nitro, amino, nitrile, keto, ester, lactone, and amide groups. Even in cases where a selective reduction is not required, the BH_3-THF reagent is often used to reduce carboxylic acid groups because of the mild reaction conditions and ease of product isolation.

The mild conditions and selectivity indicate the potential for carrying out carboxylic acid reductions on complex biological systems. For example, a series of dipeptides (as *N*-trifluoroacyls) was treated with BH_3-THF to give 62-100% reduction of the C-terminal amino acid.[80] This pro-

cedure was later applied to a series of polypeptides and naturally occurring proteins and specific reduction of the free carboxyl groups was achieved in these complex systems.[81] Interestingly, if *N*-acylamino acids are used instead of *N*-trifluoroacyl, a substantial amount of amide reduction is also observed.[82]

Obviously, in most, if not all, of the above examples, the BH_3-THF reagent is superior to LAH. In a specific case, the LAH reduction of polysiloxanes containing terminal carboxyl groups results in extensive reductive cleavage of silicon-oxygen bonds whereas with BH_3-THF, the terminal carboxyl groups are reduced cleanly.[83]

When appropriate electron-donating groups are present, complete reduction to a methyl group is possible (eqs. 52, 53).

4) Carboxylic Anhydrides

n-Hexanoic anhydride and benzoic anhydride are satisfactorily reduced with BH_3-THF giving a 94% isolated yield of 1-hexanol and an 82% isolated yield of benzyl alcohol.[86]

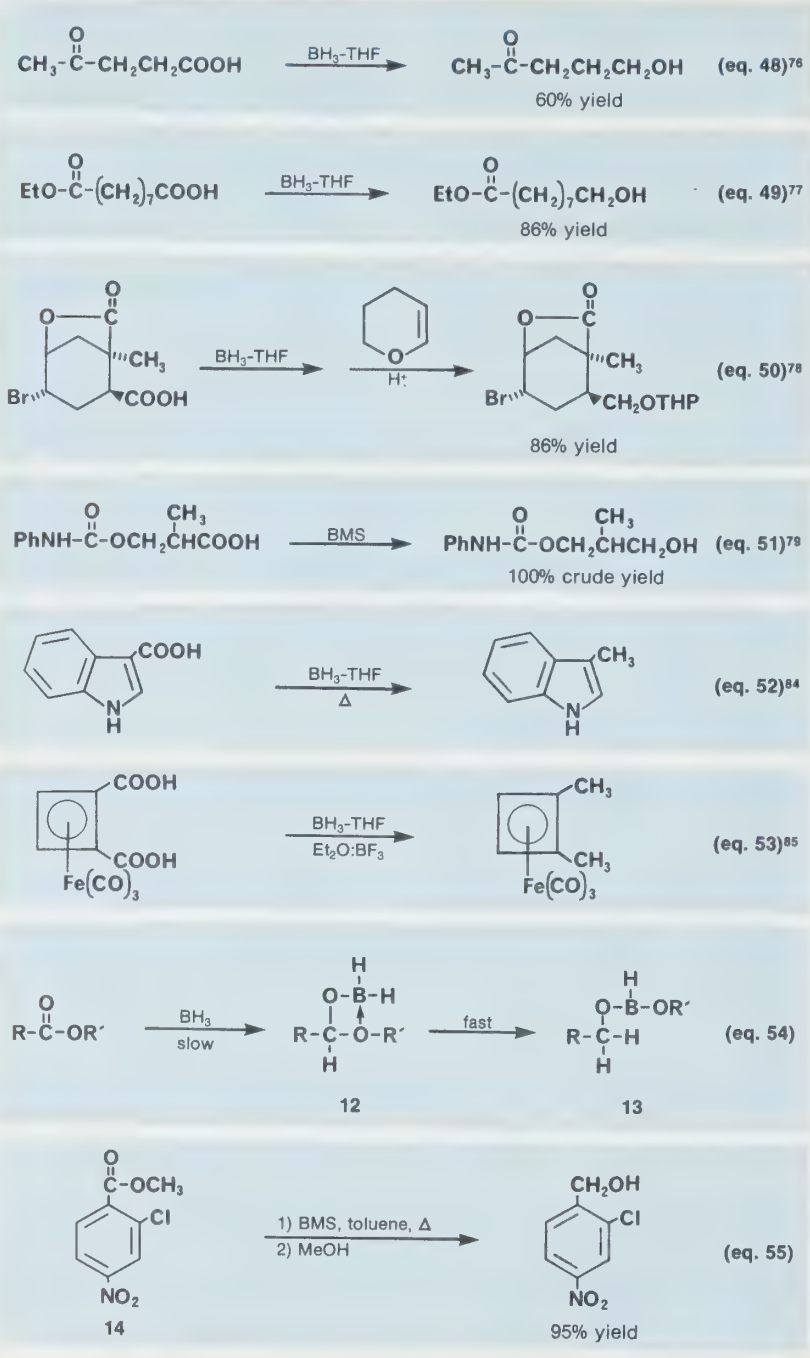
5) Esters and Lactones

Aliphatic esters and lactones are reduced relatively slowly with BH_3-THF at 0°.[7] A 12-24hr period is required for complete conversion to the corresponding alcohol. Phenyl acetate is reduced somewhat more slowly, but the aromatic esters and lactones are almost completely unreactive at 0°, exhibiting only 4-6% uptake of hydride after 24hr.[7] Apparently, resonance of the aromatic ring with the carbonyl group renders the group less susceptible to electrophilic attack by the borane species.

In general, the lower reactivity of the ester group is probably a result of the electron-withdrawing inductive effect of oxygen on the carbonyl group. For example, carbonate esters[24] and polycarbonates[87] are stable to BH_3-THF at room temperature.[88] Steric hindrance can also lower the reactivity of esters. Thus, pivalate esters are stable toward BH_3-THF at room temperature.[24] During reduction of esters to alcohols, there is no detectable aldehyde formation, indicating that no stable intermediate is formed.[7] A probable mechanism which explains all of the above results is shown in equation 54.

Intermediate **12** is probably very unstable, and a rapid intra- or intermolecular hydride transfer occurs to give the stable intermediate **13**. This hydride transfer could be promoted by an intramolecular coordination of boron and oxygen in **12**.

BMS can be used to reduce a variety of functional groups and is particularly useful for the high-temperature reduction of normally unreactive esters. The reduction of **14** illustrates a specific example in which



the relatively high temperature found necessary to reduce the ester function still did not result in reduction of the nitro group (eq. 55).[22]

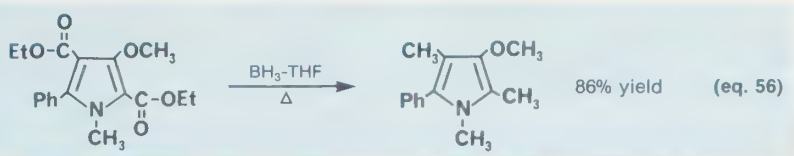
During the selective reduction of a more reactive group with BH_3-THF, the slow reduction of an ester group is sometimes a problem. However, Jackson and coworkers found that the reduction of an aliphatic ester group is inhibited by the presence of ethyl acetate.[89]

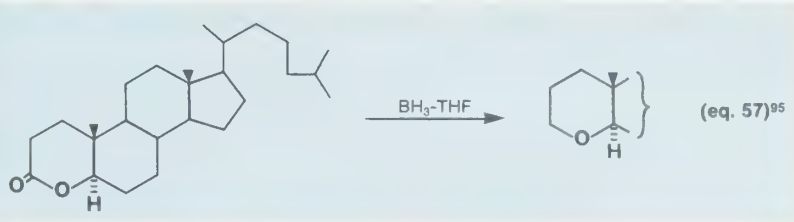
Electron-donation-induced reductive cleavage *via* an intermediate analogous to **6** can also occur during borane reduction of an ester group resulting in complete reduction to a methyl group. Again many examples are found in derivatives of pyrrole, equation 56 being representative.[90]

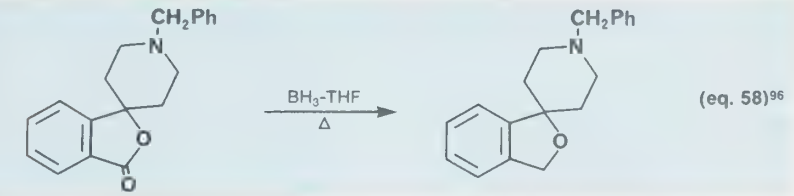
Reduction of an appropriately substituted lactone with a borane reagent can result in complete deoxygenation of the carbonyl group to give an ether. Steroidal δ-lactones were examined in the most detail and experimental conditions were developed for the conversion of these lactones to cyclic ethers. This is another exam-

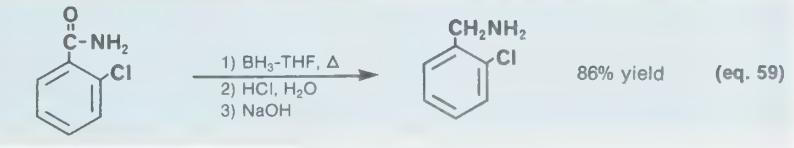
ple of an electron-donation-induced reductive cleavage which probably involves an intermediate similar to **3**.[91] The original procedure used by Pettit consisted of treating the lactone with diborane in the presence of a large excess of boron trifluoride.[92] He later found that the ester to ether conversion was favored if the ester or lactone was derived from a tertiary, hindered alcohol,[93] but branching next to the carbonyl had little influence on the yield of ether and only decreased the rate of reduction.[94]

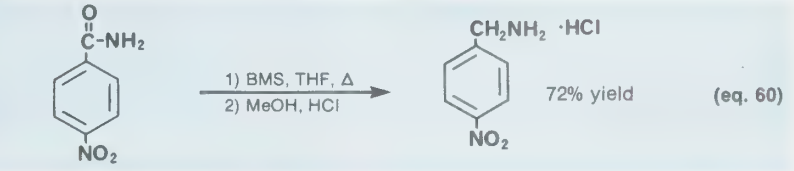
Recently, Pettit found that the large excess of BF_3 is not necessary in many cases, *i.e.*, a large excess of BH_3-THF gives essentially analogous results.[91] A large number of cyclic ethers has been prepared using these procedures. Equations 57 and 58 provide specific examples.

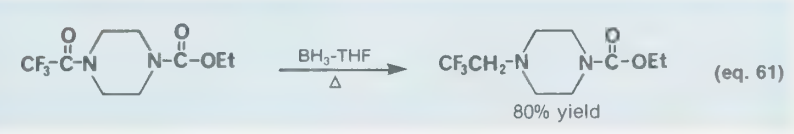


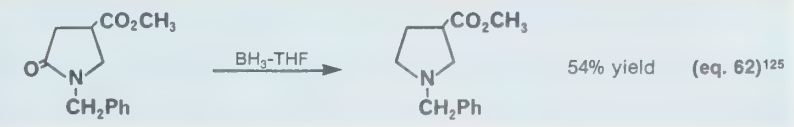












6) Amides

Primary, secondary and tertiary amides derived from both aliphatic and aromatic carboxylic acids are reduced rapidly with BH_3-THF in THF at reflux. Acidic or basic hydrolysis then provides the corresponding amine in excellent yield. The reduction of amides with diborane was originally investigated by Brown and Heim[97] and a full report of their detailed study has been published.[98]

Commercial BH_3-THF (eq. 59)[99] and BMS (eq. 60)[22] have both been used for selective amide reductions. In general, this reaction provides a convenient synthetic procedure and has been used extensively over the past 12 years, since the appearance of Brown's original communication.[97]

The syntheses of natural products and new pharmaceuticals are two important areas where many applications and advances have been made using this reduction. For example, the reduction of an amide functional group with BH_3-THF provided one of the key steps in the synthesis of the naturally occurring polyamine, *sym*-homospermidine.[100] An amide reduction was involved in an interesting synthesis of the eburnamine alkaloid ring system.[101] Also, amide reductions with borane reagents have been used for the preparation of catecholamines,[102] dehydrobufotenine,[103] tetrahydrocarbolines,[104] desoxypithecolobines,[105] and derivatives of ephedrine.[106]

Numerous chemicals of interest and importance in medicinal chemistry have been prepared through an amide reduction with a borane reagent. A few specific examples include derivatives of 2-fluoroethylamine[107] (potential carcinolytic agents), derivatives of *N*-(2-haloethyl)benzylamine[108] (antineoplastic agents), 1-deaza-1-thiareserpine[109] (antihypertensive), 6-(*N*-alkyl-*N*-arylamino)pyrimidines[110] (potential antimetabolites), various derivatives of 1,4-benzodiazepine[111] (antianxiety drugs), derivatives of 2-oxa-5-azabicyclo[2.2.1]heptane[112] (anticholinergic agents), 1,2-dihydro-3*H*-imidazo[1,5-*a*]-indol-3-ones[113] (CNS-active agents), and 4,4′-diaminodiphenyl sulfone derivatives[114] (antileprotic agents).

Various other metal hydride reagents are known to reduce amides to amines, but LAH is probably the most widely used alternative to the borane reagents. However, LAH is an extremely powerful reducing agent which will attack a large variety of sensitive functional groups. Thus, the utility of LAH as a selective reducing agent is rather limited. Examples of groups attacked by LAH during attempted amide reduction include α-fluoro,[110,115] α-bromo,[116] *N*-cyclopropyl,[117] (trifluoromethyl)aryl,[84,117,118] and sulfonyl.[119] Also, LAH reductions of trifluoroacetamides are extremely violent[120] and other trifluoromethyl groups are known to undergo complete hydrogenolysis with LAH.[121] Finally, reductive cleavage of the *N*-benzyl group is usually a serious problem during LAH reduction of benzamide derivatives.[112,122] Fortunately, amides which contain the above substituents or structural features are readily and cleanly reduced to amines using one of the borane reagents.[123]

In addition to the selective reductions mentioned above, the BH_3-THF reagent also reduces an amide substituent in the presence of either a carbamate (eq. 61)[124] or an ester (eq. 62).[125,126]

The preceding discussion and examples should indicate that BH_3-THF is usually the reducing agent of choice for the conversion of amides to the corresponding amines.

CONCLUSION

Brown and Korytnyk established the relative rates of reduction by BH_3-THF for a number of representative classes of organic compounds.[127] The results of these experiments indicate that the rate of reaction decreases in the order: carboxylic acids > alkenes > ketones > nitriles > epoxides > esters > acid chlorides. However, the reactivity of a given functional group can be greatly modified by the structure of the molecule. It is important to recognize that these relative reactivities must be considered approximate values for simple, representative groups, and may be altered or even inverted by modifications in the molecular structure. Hopefully, this review will help to further define the reactivity of the borane reducing agents and will assist organic chemists in deciding when it would be advantageous to utilize a borane reduction to solve a synthetic problem.

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Chemical Reactions of 2,3-Cycloalkenopyridines

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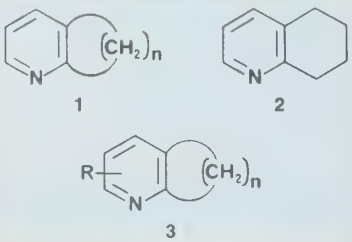
Degussa

INTRODUCTION

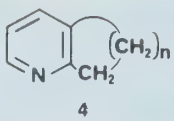
In the last decades pyridine derivatives have gained importance, particularly in the production of herbicides and medicinals. The only 2,3-cycloalkenopyridines (**1**, n = 3-13) of any importance have been 5,6,7,8-tetrahydroquinoline (**2**) and its alkyl derivatives. The syntheses known for **1** did not enable the technical utilization of these compounds, although derivatives of **2** are accessible through hydrogenation of the corresponding quinolines.[1] A new synthesis of 2,3-cycloalkenopyridines (**3**, n = 3-13; R = H, CH_3) involving a heterocatalytic gas-phase reaction of cycloalkanones with alkenones and ammonia,[2] makes such pyridines accessible. From acrolein and the ketones cyclohexanone, cyclopentanone, cycloheptanone and cyclododecanone, one obtains 5,6,7,8-tetrahydroquinoline, 2,3-cyclopentenopyridine, 2,3-cycloheptenopyridine and 2,3-cyclododecenopyridine respectively in yields of 60-90%. Methyl vinyl ketone yields 2-methyl derivatives, whereas methacrolein and crotonaldehydes lead to 3-methyl- and 4-methyl derivatives. Since these compounds can now be made so easily, their applications have become of special interest. The purpose of this review is to summarize the reactions of these 2,3-cycloalkenopyridines.



CHEMICAL TRANSFORMATIONS WITH 2,3-CYCLOALKENOPYRIDINES

Chemical reactions of 2,3-cycloalkenopyridines can be most easily classified according to the initial chemical reaction of the cycloalkenopyridine, *i.e.*, N-oxidation, hydrogenation of the pyridine ring, dehydrogenation of the aliphatic ring, metallation of the reactive CH_2 group attached to the α-position of the pyridine ring, and the reaction of this reactive group with carbonyl compounds.

As this reactive methylene group is especially important in many reactions, these 2,3-cycloalkenopyridines will be depicted as **4**.



Most of the reactions in the literature involve 5,6,7,8-tetrahydroquinoline (**4**, n = 3) or its methyl derivatives, 2,3-cyclopentenopyridine (**4**, n = 2) and 2,3-cycloheptenopyridine (**4**, n = 4). Methyl substitution, particularly common in the 3-position of 5,6,7,8-tetrahydroquinoline, will not be referred to specifically, because it does not affect the reaction schemes.

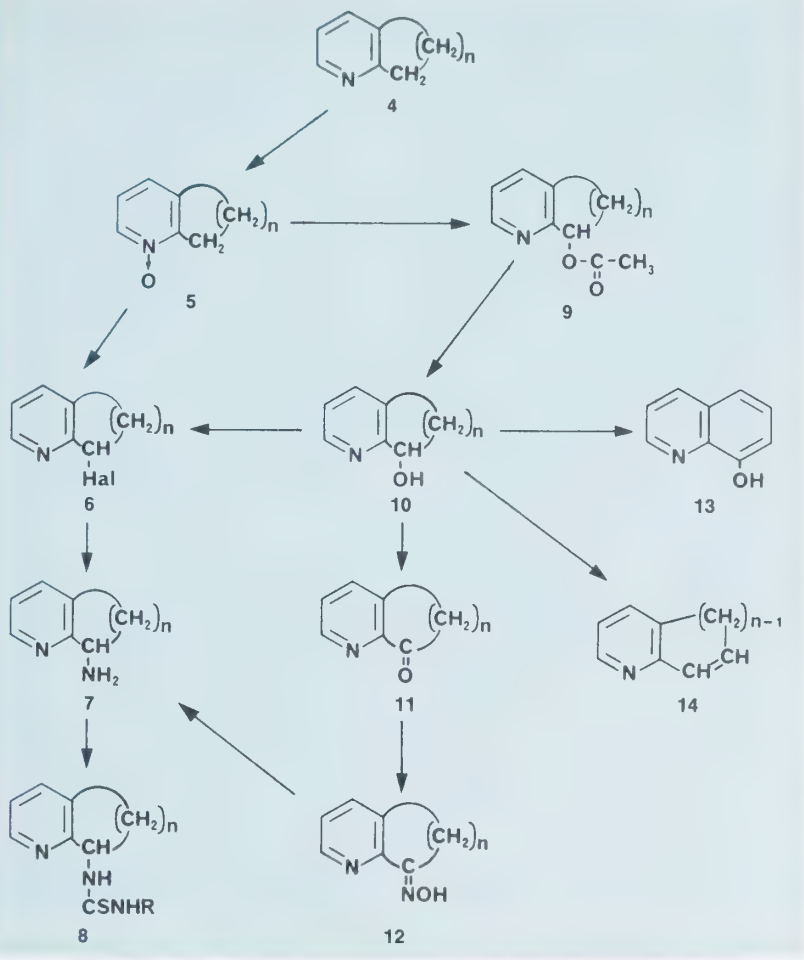
N-Oxidation and Subsequent Reactions (Scheme I)

The N-oxidation of various 2,3-cycloalkenopyridines with H_2O_2 in acetic acid has been described.[3-7] Reaction of the *N*-oxide **5** with methanesulfonyl chloride yields the α-chloro compound **6**,[5,6] which is transformed to the α-amino compound **7** by treatment with methanolic ammonia at 80° for 24 hours.[5,6] Reaction with isothiocyanates affords the corresponding 8-thiocarbamoylamino derivative **8**,[5] *e.g.*, **7** reacts with methyl isothiocyanate in acetonitrile to yield the 8-methylthiocarbamoylamino compound, and with benzoyl isothiocyanate in acetone to give the 8-benzoylthiocarbamoylamino compound. The latter is hydrolyzed with alkali to the 8-thiocarbamoylamino compound.[5]

The Boekelheide rearrangement converts the *N*-oxide **5** (with acetic anhydride) to the acetate **9**, which undergoes saponification with alkali or hydrochloric acid to the carbinol **10**.[9]

8-Hydroxy-5,6,7,8-tetrahydroquinoline (**10**, n = 3) was dehydrogenated with palladium on charcoal in diisopropylbenzene to 8-hydroxyquinoline **13**[9] and it was dehydrated (by heating with polyphosphoric acid) to 5,6-dihydroquinoline (**14**, n = 3).[10] The analogous dehydration of 7-hydroxypyrindan to 5,6-dihydropyrin-

Scheme I



Scheme II

a: $R_1 = R_2 = R_3 = R_4 = H$
b: $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$ (α, β)
c: $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$ (α, β)
d: $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$ (only α)
e: $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$ (α, β)

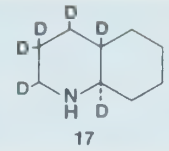
dan (**14**, n = 2) has also been described.[10]

The carbinol **10** can be oxidized with manganese dioxide in methylene chloride[5,7] or with chromium trioxide in dilute sulfuric acid[9] to the ketone **11** which has been converted to the oxime **12**[5,7] followed by hydrogenation with Raney nickel to the amine **7**.[5] Finally, **10** has been converted to the chloro compound **6** with thionyl chloride[5,6] and to the corresponding bromide with PBr_3.[11] The preparation of various guanidines from the amine **7** has also been described.[12]

Hydrogenation of the Pyridine Ring (Scheme II)

The hydrogenation of 5,6,7,8-tetrahydroquinoline and its methyl derivatives **15a-e** with sodium in ethanol leads to the corresponding *trans*-decahydroquinolines **16** in better than 90% yields.[13] The methyl derivatives **15b, c** and **e** yield two diastereoisomers, α and β, whereas **15d** yields only the α-isomer in which the methyl group is equatorial.

Hydrogenation of 5,6,7,8-tetrahydroquinoline in ethan(ol-*d*) yields predominantly the *trans*-decahydroquinoline-2,3,3,4,9,10-d_6, **17**.[13]



The synthesis of the corresponding *trans*-diastereoisomers by reduction with sodium in ethanol has been described for cycloheptano-2,3-piperidine[14] and cyclopentadecano-2,3-piperidine.[15] In contrast, the hydrogenation with platinum and acetic acid yields the *cis*-diastereoisomers, *e.g.*, *cis*-cyclopentadecano-2,3-piperidine.[15]

Dehydrogenation of the Aliphatic Ring

The dehydrogenation of the aliphatic ring of 2,3-cycloalkenopyridines succeeds only in the case of 5,6,7,8-tetrahydroquinolines: by heating with palladium at 300°C, the expected quinoline is formed.[16] This dehydrogenation fails with compounds such as 2,3-cyclopentenopyridine in which no aromatic ring can be formed, and which are unchanged by palladium or selenium at elevated temperatures.[16]

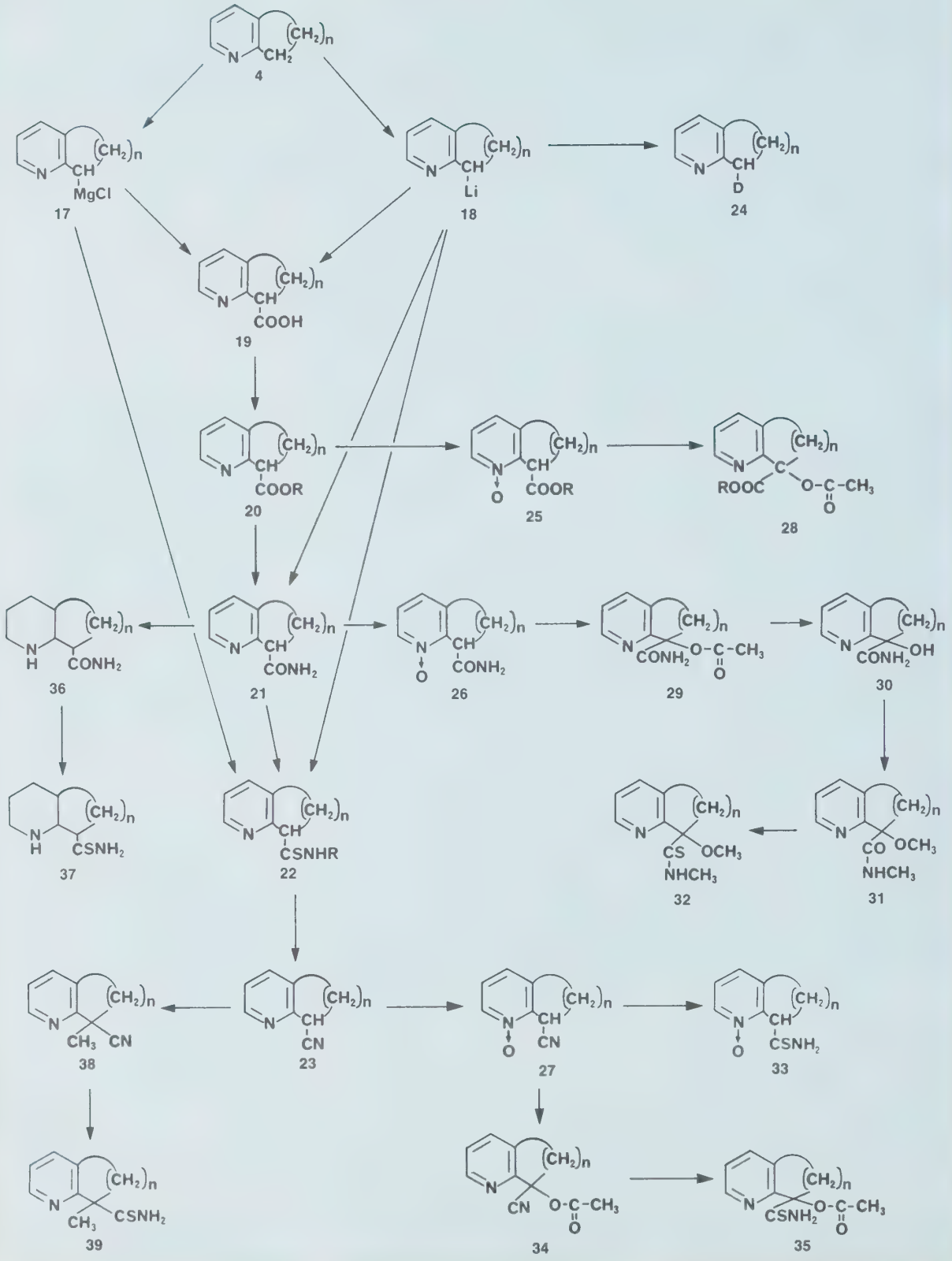
Metallation of the Reactive CH_2 Group (Scheme III)

Numerous compounds can be synthesized from 2,3-cycloalkenopyridines *via* the metallation of the reactive CH_2 group. These compounds can undergo further reaction, *e.g.*, N-oxidation or hydrogenation. It is even possible for the N-oxides to rearrange with acetic anhydride to form acyloxy compounds, yielding cycloalkenopyridines with two different substituents on the α-methylene carbon atom.

Metallation can be effected with either Grignard reagents to form **17**[17,18,20] or, better, with organolithium compounds to yield **18**.[17,18,21,22] As expected, the carboxylic acids **19**,[20–22] esters **20**,[20–22] amides **21**,[18–20,22] thioamides **22**,[17,18,21,22] and nitriles **23**[18] were formed. The deuterated derivative **24** has also been made.[21]

The *N*-oxides **25**, **26** and **27** made from the esters, amides and nitriles have been described.[23,24] Rearrangement of the ester *N*-oxide **25** yields the acetoxy ester **28**.[23] The corresponding amide **26** was converted in four steps *via* the acetoxycarboxamide **29**, the hydroxycarboxamide **30** and the methoxy-*N*-methylcarboxamide **31**, into the methoxy-*N*-methylthiocarboxamide **32**.[23,24] The cyano-*N*-oxide **27** was converted to the thiocarboxamide-*N*-oxide **33**, and also, by rearrangement to the acetoxycarbonitrile **34**, to the acetoxycarbothioamide **35**.[23]

Scheme III


4
17
MgCl
18
Li
24
D
19
COOH
20
COOR
25
28
ROOC
21
CONH2
26
29
30
OH
36
37
CSNH2
22
CSNHR
32
CS
OCH3
NHCH3
31
CO
38
CH3
CN
23
27
33
39
34
35
O-C-CH3

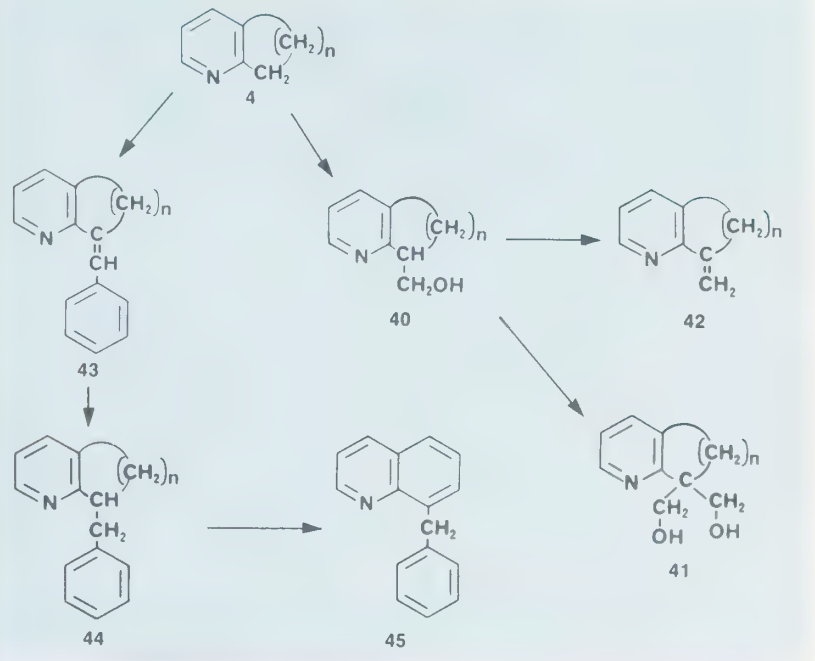
As already mentioned, one can hydrogenate substituted 2,3-cycloalkenopyridines to the corresponding piperidines. For example, the carboxamide **21** can be reduced to the decahydro-3-methylquinoline-8-carboxamide **36**, which can then be converted to the thioamide **37**.[24]

The 8-cyano-5,6,7,8-tetrahydro-3-methylquinoline, **23**, was metallated further and reacted with methyl iodide to produce the compound with a methyl group on the reactive carbon atom. The product, 8-cyano-5,6,7,8-tetrahydro-3,8-dimethylquinoline, **38**, was then converted to the corresponding thioamide **39** with H_2S.[24]

Reactions with Carbonyl Compounds (Scheme IV)

2,3-Cycloalkenopyridines **4** react with formaldehyde to yield the hydroxymethyl derivatives **40** at 110-120° and the bis(hydroxymethyl) derivatives **41** at 150-160°.[3] The hydroxymethyl derivatives can be dehydrated to the "styrenes" **42** with polyphosphoric acid.[11] Reaction with benzaldehyde,[25,26] methoxybenzaldehydes[25] and *m*-nitrobenzaldehyde[26] yields the benzylidene derivatives **43**. Some of these were hydrogenated to the benzyl derivatives **44**[25] and, where n = 3, the 8-benzylquinoline **45** was obtained by dehydrogenation.

Scheme IV



CONCLUSION

It is surprising that many compounds have been made from the relatively few 2,3-cycloalkenopyridines that were known prior to Degussa's work.[2] About half of the published work came from one group [12,24] that has been interested in antiulcer therapeutic agents. Considering the ease and specificity with which one can chemically modify the 2,3-cycloalkenopyridines, these versatile intermediates offer the synthetic and medicinal chemist a fresh area for exploration, bounded only by the imagination.

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7) John Wyeth and Brother, Ltd., British Patent 1463584 (1974).
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21) John Wyeth and Brother, Ltd., British Patent 1463670 (1973).
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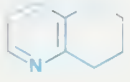
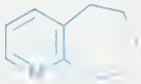
About the Author

Helmut Beschke, born in 1919 in Unseburg near Magdeburg, began his chemical studies in Jena in 1941. He joined Degussa in 1955 working in medicinal chemistry. He has been involved in the synthesis of pyridine derivatives since 1970.

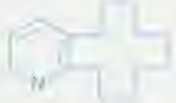
19,749-1 2,3-Cyclopentenopyridine



19,748-3 2,3-Cyclohexenopyridine



19,751-3 2,3-Cycloheptenopyridine



19,750-5 2,3-Cyclododecenopyridine

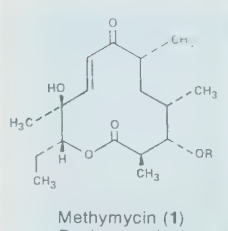
Recent Progress in Macrolide Synthesis

Award Address
presented by
Professor Satoru Masamune
Department of Chemistry
University of Alberta
Edmonton, Canada
at the
ACS Award Symposium
held on March 14, 1978
in Anaheim, California

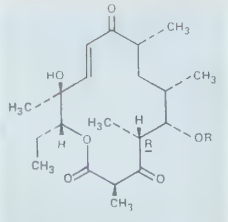
The recent history of organic chemistry is adorned with an impressive list of synthetic achievements of numerous complex molecules. Most of these compounds, however, incorporate 5- and 6-membered-ring systems where conformational analysis displays its power. In contrast, the synthesis of acyclic systems has received less attention in the past and there remains much to be explored in order to enhance synthetic expertise in this area. The structures of macrolides are basically acyclic, uniquely and regularly oxygenated, and rich in chirality. Thus, the synthesis of macrolides obviously demands new methodologies fundamentally important to organic chemistry, and further, there is good reason to believe that a deeper understanding of several basic reactions may enrich our knowledge of biochemical processes involved in the early stages of lipid synthesis. We are now witnessing a surge of effort underway in many laboratories, directed toward these objectives. It is my pleasure to present some of our contributions in this lecture.

The macrolide family includes more than one hundred physiologically active metabolites,[1] and approximately a half of these compounds are subgrouped as polyoxo macrolides, represented by the five antibiotics shown below [methymycin (**1**), pikromycin (**2**), erythromycin (**3**), leucomycin A_1 (**4**), and tylosin (**5**)]. They are twelve-, fourteen-, and sixteen-membered lactones with numerous substituents on the ring, and one or more hydroxy groups are glycosidated with sugars. It is clear from the structures that these compounds are biosynthesized from acetate and propionate, and in the case of 16-membered macrolides such as **4** and **5**, one butyrate unit is incorporated. This lecture concerns mainly the progress that has been made in this area since our methymycin synthesis, and particular emphasis is placed on pikromycin, the first macrolide antibiotic discovered.[2] The arrangement of substituents attached to the lactone framework is remarkably systematic and all follow what is now called Celmer's model (**6**),[3] expressed by the Fischer projection formula (Figure 1), and the antibiotics differ mainly in the degree of oxidation. The conformation of macrolides has received much attention and indeed there have appeared numerous papers concerning this subject.[4] In short, the majority of 14-membered macrolides, represented by erythronolide B (**7**), prefer a conformation similar to that shown by the bold line indicated in the diamond model I. Conformer **7a** is further modified in order to eliminate *syn*-periplanar interactions between the two methyl groups indicated by the arrow and also in order to enhance

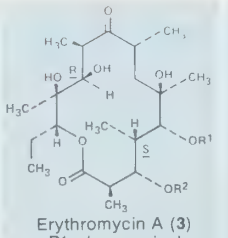
Professor Satoru Masamune (right) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.



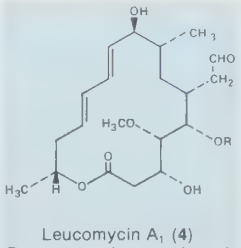
Methymycin (**1**)
R=desosaminyl



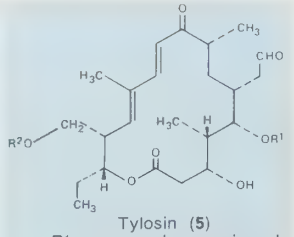
Pikromycin (**2**)
R=desosaminyl



Erythromycin A (**3**)
R^1=desosaminyl
R^2=cladinosyl



Leucomycin A_1 (**4**)
R=mycarosyl-mycaminosyl



Tylosin (**5**)
R^1=mycarosyl-mycaminosyl
R^2=mycinosyl

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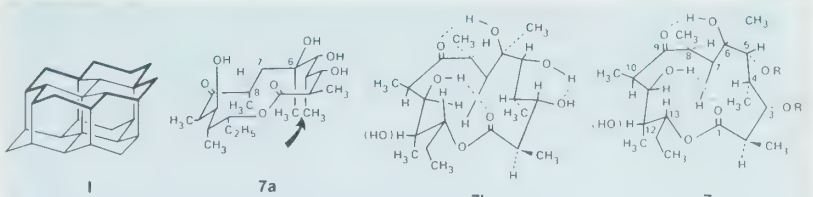
the hydrogen bonding interaction in the molecule. This provides what we now call Perrin's conformer **7b** or **7c**, which turned out to be almost the same as that of the crystal structure elucidated by X-ray analysis.[5] Two comments are in order. First, it is clear that the molecule does not have much conformational freedom even in solution; thus, the molecule is very rigid. This rigidity can be clearly indicated by space-filling models such as CPK models, and one is led to believe that even the seco-acid derived from the macrolide may possess a high degree of rigidity except for one or two freely rotating carbon-carbon single bonds. This consideration was important in selecting a synthetic scheme for a macrolide, and we were led to believe that the seco-acid might cyclize under proper conditions much more readily than one would normally expect. Another interesting feature of the molecule is that virtually all of the hydroxy groups are oriented on one side and most of the methyl groups lie below the ring framework, a structural feature likely having an important bearing on the microbial activity of the antibiotic.

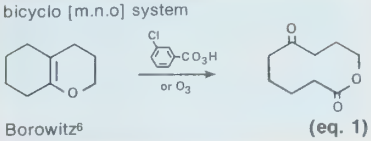
Let me review briefly two major, obvious problems associated with the macrolide synthesis. The first one is the construction of a medium- or large-sized lactone and the second involves the incorporation of the substituents in a stereochemically controlled manner. It is natural to devise a methodology for lactone formation first, and then to test its applicability to more complex molecules. This has been the practice in many recent cases. Some representative approaches are illustrated by equations 1-3. Borowitz disclosed a clever idea of the fused bond rupture of a bicyclo[m.n.o] system to obtain the corresponding keto-lactone,[6] and Vedejs



Conformation of Erythronolide B

utilized a 2,3-sigmatropic rearrangement by which the original ring system was expanded by three carbon atoms.[7] This ring-growing reaction is repeatable; therefore, consecutive applications of this sequence would lead, in principle, to the construction of a desired ring system. The approaches represented by these two examples, however, must solve difficult stereochemical problems of a medium-sized ring system at each step. Several cyclizations of acyclic precursors have been reported, and one of the most recent involves the aldol condensation of an aldehydic bromo ester.[8]

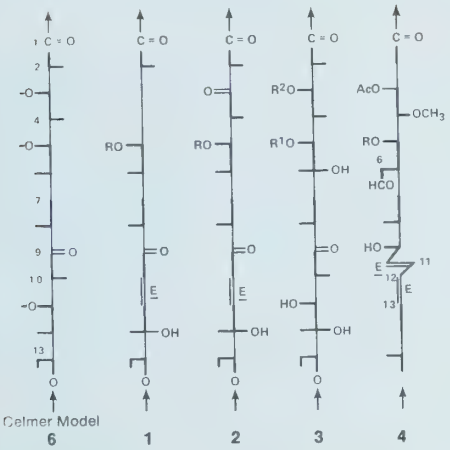
The fused bond rupture of a bicyclo [m.n.o] system



Borowitz[6] **(eq. 1)**

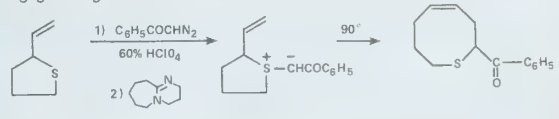
It is appropriate at this point to consider the feasibility of the direct lactonization of the seco-acid corresponding to a natural macrolide. This is obviously a most naive way to analyze the synthesis of a macrolide, and it is rather surprising that this method has not been utilized until recently. There was one reason for it. Stoll's classical work on the acid-catalyzed lactonization of ω-hydroxycarboxylic acids (eq. 4) was indeed discouraging for the purpose of preparing the corresponding monolactone, and even the use of a dilute solution of the carboxylic acid (**8**) led to none of compound **9** and the majority of the product consisted of the dimer **10** or oligomer.[9] This reaction, in essence, is the competition between the first order versus second order reaction; therefore, in an infinitely dilute solution of **8** the lactone **9** should be the sole product. This high dilution technique can be effected in practice, if one can devise an efficient method for the reaction. Suppose you add slowly a solution of compound **11** (eq. 5) to dimethyl sulfoxide containing potassium carbonate.[10] Since the lactonization proceeds very rapidly, the first drop of compound **11** completes its reaction before the second drop is added to the solution; thus, at any given time the concentration of **11** is extremely small. Galli and Mandolini report that the ratio of **9** to **12** is 89:9.[10] Another important consideration in this connection is concerned with the conformational rigidity of the seco-acid which may favor the lactonization rather than intermolecular ester formation. These two encouraging, nonetheless very risky predictions led us to examine direct lactonization of the seco-acid for the synthesis of methymycin, and fortunately we were able to complete the first synthesis of this polyoxo macrolide.[11] Since then the lactonization of seco-acids has become the standard ap-

Figure 1



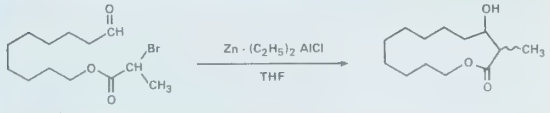
1: Methymycin
2: Pikromycin
3: Erythromycin A
4: Leucomycin

Ring-growing reaction

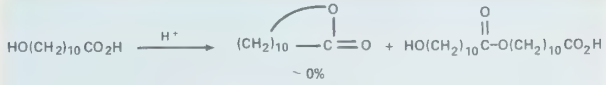


Vedejs[7] **(eq. 2)**

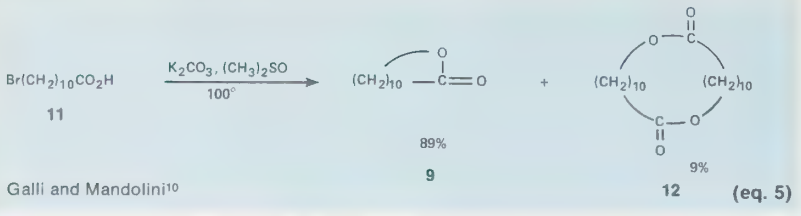
Cyclization of an acyclic precursor



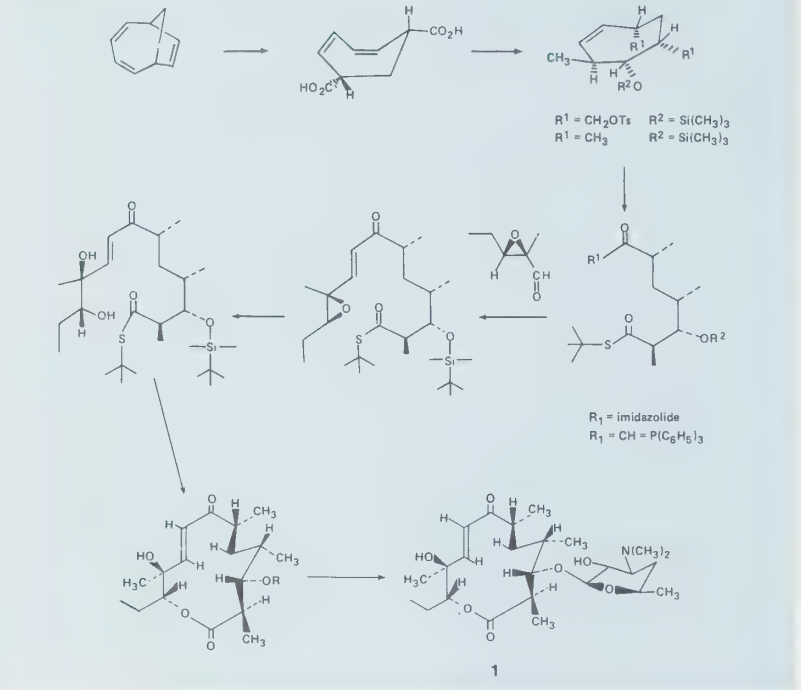
Nozaki[8] **(eq. 3)**



Stoll[9] **(eq. 4)**



Scheme I



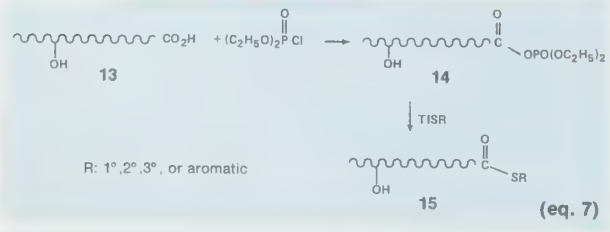
proach to the synthesis of macrolide molecules.

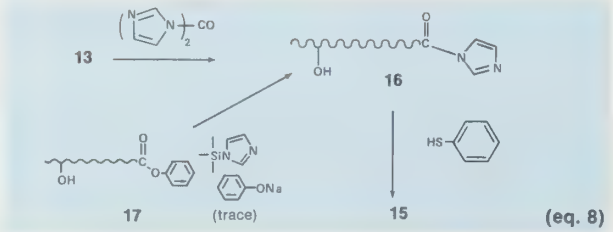
Scheme I outlines the synthesis of methymycin (**1**)[11] which appears to represent a major part of the citation for the Award. I am not going into details of each step but wish to draw your attention to the process of lactonization. The use of thiol esters for this purpose is obviously hinted at by a similar process likely taking place in the biological system, and a considerable effort has been made since the completion of the methymycin synthesis in order to widen the scope and define the limitations.

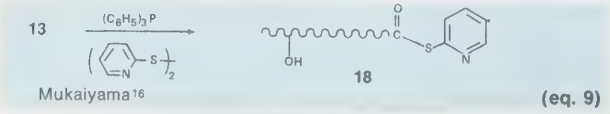
In view of the enormous amount of sulfur chemistry accumulated over a century, I was surprised to find at the outset of this work that there had not been much chemistry done which was useful and applicable to our case. The synthesis of thiol esters was one of them. Thus, our work began with this apparently simple preparative method. The standard method to prepare thiol esters using an acid chloride and sodium thiolate does not proceed well when both R and R^1 are bulky and this problem was quickly solved by replacing sodium with thallium (eq. 6).[12] Another problem which one faces very often in the macrolide synthesis is selective functionalization of the carboxylic acid in the presence of hydroxy groups in the same molecule. The examination of the behavior of diethyl chlorophosphate has suggested that it might distinguish between the two groups. Indeed, use of this reagent converted compound **13** into the anhydride (**14**) of compound **13** and phosphoric acid which in turn produced the desired thiol ester (**15**) upon treatment with thallium thiolate (eq. 7). This reaction is quite general and R can be primary, secondary, tertiary aliphatic, or aromatic.[13] A similar selectivity was also attained with carbonyldiimidazole and the intervening acid imidazolide (**16**) was converted into its benzenethiol ester (**15**) (eq. 8).[14] This last reaction appears to require protonation of imidazole; therefore, a less acidic alkanethiol does not react readily with this intermediate. Very often the direct conversion of an ester into the corresponding thiol ester is desirable, and this has been achieved by reacting a phenyl ester (**17**) with trimethylsilylimidazole in the presence of trace amounts of sodium phenoxide.[15] Reactive thiol esters such as pyridinethiol esters (**18**) can be prepared by Mukaiyama's procedure[16] using triphenylphosphine and the corresponding disulfide (eq. 9).

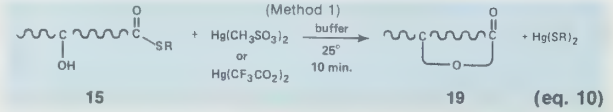
Several satisfactory procedures are now available for the preparation of thiol esters, and the next step involves conversion of the thiol esters to the corresponding lactones or O-esters through thiol activation. Three efficient techniques for this conversion were disclosed almost simultaneously by three research groups and became available for use three years ago. Our method utilizes thiophilic mercury(II) salts to activate alkanethiol esters (eq. 10).[17] The reaction proceeds, in general, almost instantaneously at room temperature or below to provide a near-quantitative yield of compound **19**. Corey's procedure is patterned after Mukaiyama's peptide synthesis using pyri-

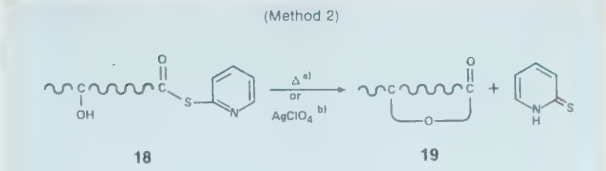
RCOCl + $TISR^1$ ⟶ $RCOSR^1$ (eq. 6)
(R,R^1: Bulky)





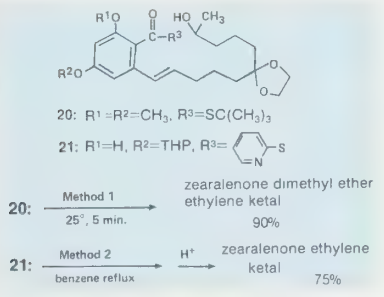






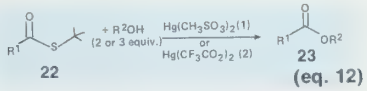
(eq. 11)

dinethiol esters (**18**) for the S→O conversion (eq. 11).[18] Since the hydroxy group is not a particularly good nucleophile toward thiol esters as compared with the amino group, this conversion requires refluxing of a xylene or toluene solution of compound **18** for a prolonged period of time (eq. 11a). Gerlach found that the same reaction was enormously accelerated by the addition of silver perchlorate and was completed within one hour at room temperature (eq. 11b).[19] The superiority of the newer methods as compared with the earlier,



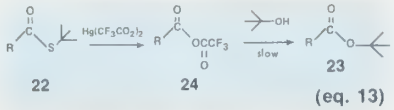
classical techniques was evident. For instance, the lactonization of a zearalenone seco-acid derivative (**20** with R³=OH) by means of the mixed anhydride method published in 1968, proceeded in low yield,[20] whereas use of the thiol esters (**20** and **21**) with or without a catalyst brought about quite acceptable results.

The application of equation 10 to macrolides other than methymycin and zearalenone requires modification of the

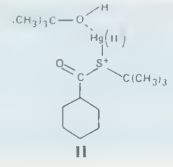


(eq. 12)

original procedure and progress has been made to this end.[21] First, it should be pointed out that 2-methylpropane-2-thiol esters (**22**) are as stable toward acid and base as O-esters and survive many synthetic operations. Second, the S→O conversion (eq. 12) proceeds smoothly even if both R¹ and R² are very bulky (Table 1). The pivalic thiol ester provides a 90% yield of its O-*tert*-butyl ester (**23**) upon this treatment (entry 2). The double bond conjugation does not suppress the efficiency of this reaction (entry 3). This result almost excludes the intermediacy of the ketene during this reaction and the retention of the α-deuterium during the same reaction (entry 4) further corroborates this conclusion. Expectedly, in the absence of an alcohol, Hg(II) trifluoroacetate converts thiol esters (**22**) into the mixed anhydride (**24**) which only slowly reacts with *tert*-butyl alcohol, approximately ten times more slowly than the above S→O conversion (eq. 13). Therefore, we conclude that the major course of the direct conversion involves an intermediate complex similar to that shown as II. In this intermediate, the soft-

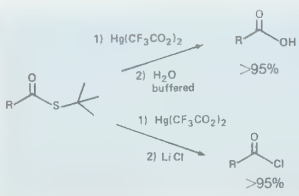


(eq. 13)



soft interaction between the sulfur and Hg(II) and the hard-hard combination of the hydroxy and acyl groups ideally satisfy Saville's rule[22] and effect the desired reaction smoothly. There arises no problem in the hydrolysis of thiol esters and their conversion into the acid chlorides also proceeds without difficulty (eqs. 14 and 15).[23] These two operations are executed under neutral or near neutral conditions, so that sensitive functional and protective groups remain intact.

Needless to say, this Hg(II)-assisted activation of thiol esters is not free from disadvantageous side reactions, which are mainly caused by the soft-soft interaction of Hg(II) with other functional groups. Thus, the metal cation reacts with an electron-rich double bond to bring about the well known hydroxymercuration although α,β-unsaturated ketones and esters very



(eq. 14)

(eq. 15)

Table 1

Entry	R¹	R²	Reagent	Buffer	Yield(%)
1			1 or 2	Na_2HSO_4 (or none)	100%
2			1		90%
3			1 or 2		85%
4				Na_2HPO_4	

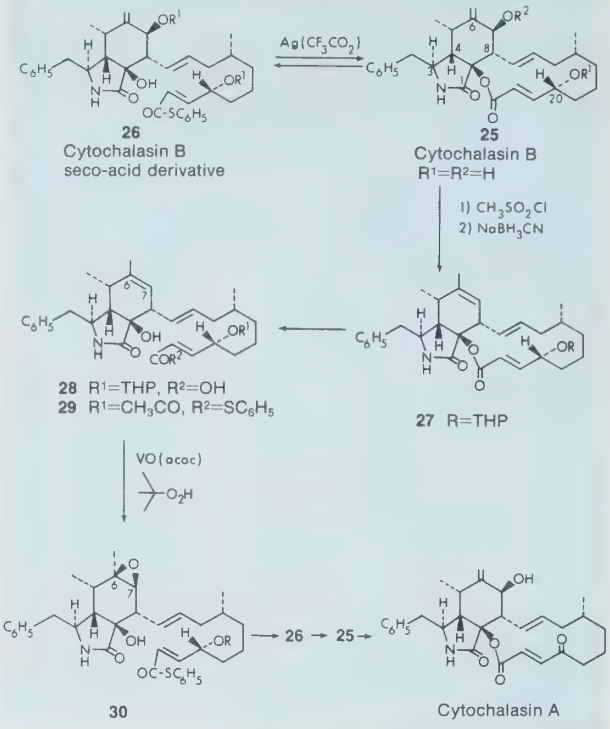
often found in macrolides are inert to this reagent. How can we overcome this difficulty when a reactive double bond is present in the substrate? Note that in the S→O conversion reaction there are four variables to manipulate: S, R², M, and X (eq. 16). All that has to be done is to find a combination of reactivity-matching pairs for the reaction. Since selenol esters are found to offer no obvious advantages and indeed suffer from several other serious side reactions, we decided to concentrate our investigation on the behavior of thiol esters. Known soft or thiophilic cations other than Hg(II), and chemically inert to ordinary double bonds are Ag(I), Cu(I), and Cu(II), and the reactivity of these cations toward thiol esters was first tested. Interestingly, *S-tert*-butyl cyclohexylmethanethioate was completely inert to $Ag(I)CF_3CO_2$ and $Ag(I)CF_3SO_3$ even if a tetrahydrofuran reaction mixture was refluxed for a prolonged period of time (entry 1 in Table 2). This result suggested a need for modification of R² in order to match the reactivity of S with Ag(I). Thus, replacement of the *tert*-butyl group with the phenyl or benzothiazole group brought about very rewarding results (entries 2 and 3). The three entries (4, 5, and 6) deal with the model experiment for a synthesis of cytochalasin, and the last three examples (entries 7, 8, and 9) provide some assurance that pikromycin seco-acid which has a β-keto moiety would cyclize with the combination of the 2-methylpropane-2-thiol ester and $Cu(I)CF_3CO_2$ or the benzenethiol ester and $Ag(I)CF_3CO_2$.

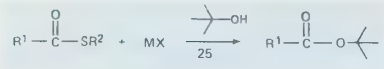
Cytochalasins have attracted much attention in recent years because of their unique cytostatic activity (see Scheme II). The structure of the B species (**25**) shows, in a rather straightforward manner, that a simple retrosynthesis dissects the molecule into three sub-units because of the stereochemistry of the ring juncture and also the presence of functional groups, providing the seco-acid can be lactonized at a late stage of the synthesis. This assumption is rather "shaky" because of the tertiary nature of the hydroxy group and the extreme crowdedness of the reaction center as well as the presence of some sensitive functional groups in its neighborhood. Therefore the

Table 2

Entry	R^1	R^2	MX	Solvent	Time	Yield
1			$Ag(CF_3CO_2)$ $Ag(CF_3SO_3)$	THF THF	18 hr. 18 hr.	0 0
2			$Ag(CF_3CO_2)$	C_6H_6/THF	3 hr.	95%
3			$Ag(CF_3CO_2)$	C_6H_6	10 min.	100%
4			$Cu(CF_3SO_3)$	C_6H_6/THF	5 hr	80%
5			$Cu(CF_3SO_3)_2$ $Ag(CF_3CO_2)$ $AgBF_4$ $Ag(CF_3SO_3)$	CH_3CN C_6H_6 (Δ) C_6H_6 (Δ) C_6H_6 (Δ)	1.5 hr. 1.5 hr. 1 hr. 1 hr.	24% 100% < 5% < 5%
6			$Ag(CF_3CO_2)$ $Cu(CF_3SO_3)$ $Cu(CF_3SO_3)_2$	C_6H_6 (Δ) C_6H_6/THF CH_3CN	1.5 hr. 5 hr. 30 min.	100% 90% 100%
7			$Hg(CF_3CO_2)_2$ $Ag(CF_3CO_2)$ $Cu(CF_3SO_3)$	CH_3CN THF C_6H_6	0.5 hr. 18 hr. 2 hr.	0 recover 100%
8			$Cu(CF_3CO_2)$	CH_2Cl_2	2 hr.	100%
9			$Hg(CF_3CO_2)_2$ $Ag(CF_3CO_2)$	CH_3CN THF	0.5 hr 2 hr	0 95%

Scheme II



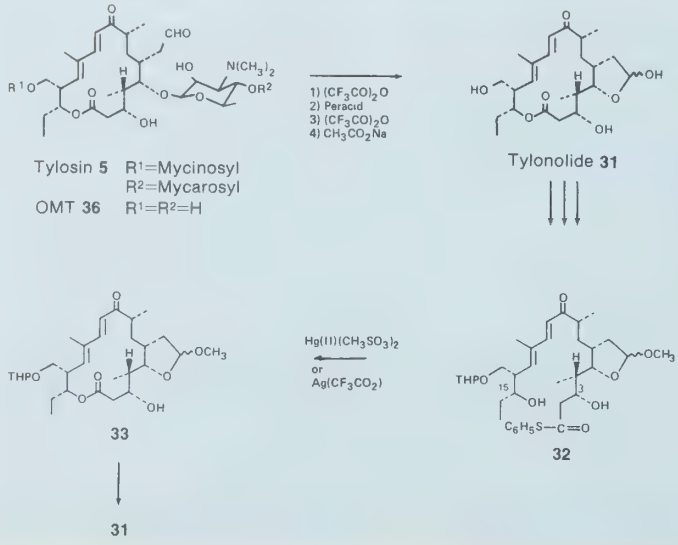


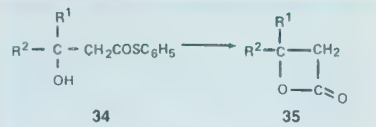
(eq. 16)

feasibility of the lactonization should be examined before attempting the construction of the seco-acid. None of the then existing methods was applicable to this lactonization and the Hg(II) activation simply destroyed cytochalasin B very readily. Indeed it was this failure that had motivated us to modify the original procedure and broaden the scope of the S→O conversion reaction that has been discussed. Ag(I) forms a complex with cytochalasin but is inert chemically, and eventually turned out to be a reagent of choice. The benzenethiol ester (**26**) of the diacetylcytochalasin seco-acid derived from the natural metabolite underwent smooth cyclization in the desired manner,[21] and therefore the presumed last step of the synthesis is now secured. Additional conversions of **25** have been made.[21] Reductive isomerization of the allylic system *via* the mesylate (**25**→**27**) followed by lactone opening provided **28** which was converted to **29** and then epoxidized by Sharpless' procedure. The acid treatment of **30** afforded cytochalasin B seco-acid **26**. The utility of compound **28** as a relay compound is thus evident. The stereochemistry of this ring juncture is such that the Diels-Alder reaction of two appropriate components (diene and ene) does lead to the correct stereochemistry as shown by Weinreb,[24] and substantial progress toward the synthesis of **28** has already been made.

Another interesting observation is worth mentioning. Tylonolide (**31**), the aglycone of a 16-membered macrolide antibiotic, tylosin (**5**), has been converted into the corresponding seco-acid derivative (**32**) through three steps (Scheme III). Treatment of the compound with Hg(II)-$(CH_3SO_3)_2$ or better with Ag(I)CF_3CO_2 effected formation of the 16-membered lactone system.[25] It is rather surprising to note that the 15-hydroxy group had to compete with the hydroxy group located at the 3-position for lactonization, yet the macrocyclic ring (**33**) has formed. We were aware that the benzenethiol ester of a β-hydroxycarboxylic acid (**34**) produces, under the same conditions, the corresponding β-lactone (**35**) in good yield (eq. 17) and that the β-lactone corresponding to **32** is not an intermediate of the lactonization of **32** to **33**. There must be some strong conformational preference as is suggested

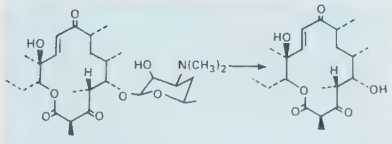
Scheme III





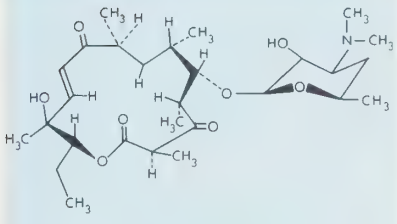
34 35

(eq. 17)



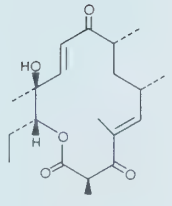
Pikromycin Pikronolide (37)

(eq. 18)



2a
Pikromycin

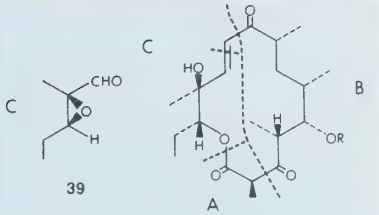
pH 6.5
100°



38

Kromycin

(eq. 19)



39 37
Pikronolide (R=H)

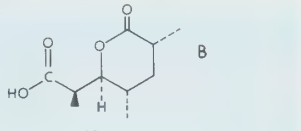
(+)-C + rac.B + A → (+)-C—(+)-B—A + (+)-C—(-)-B—A

from the CPK atomic model. No appreciable non-bonded interaction is expected to be present inside the ring system in contrast to the situation of 12-membered methymycin. Tylosin also provided us with the unique opportunity to devise a procedure to remove an acid-resistant amino sugar from an antibiotic under mild conditions in order to secure an intact aglycone — a general problem inherent to macrolide antibiotics that required a solution. Obviously, direct acid hydrolysis of the glycoside linkage present in tylosin leads to partial or total destruction of the aglycone tylonolide. Application of the Polonovski reaction to OMT (**36**) involving the conversion of the amine to its amine oxide and ensuing acylation offered a smooth pathway to tylonolide. This technique is also found to be applicable to pikromycin (**2**) (eq. 18), which is unusually prone to eliminate water as is evident from its structure.

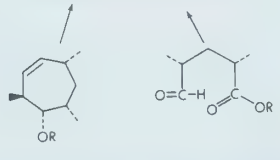
The rest of this lecture describes our effort directed toward the synthesis of pikromycin. We are no longer worried about the success of lactonization, but our main attention has been directed toward two unique aspects of this molecule: the presence of the β-keto ester moiety which has indeed caused many problems during the synthesis, and facile elimination of water from the β-hydroxy ketone fragment. Brockmann, as early as 1950, noted this elimination and his attempt at preparing pikronolide (**37**), the intact aglycone, invariably led to the formation of kromycin (**38**) (eq. 19). The correct structure and a likely conformation of this antibiotic are now known, and the facile elimination which occurs even at pH 6.5 (an observation by Brockmann) is explained by the *anti*-periplanar disposition of the hydroxy and glycosidic linkages as shown in **2a**. The retrosynthetic dissection of the molecule was patterned after our earlier synthesis of methymycin and consists of three fragments A, B, and C.

The enolate or its equivalent derived from propionic thiol ester (propanethioate) serves as fragment A and the aldehyde **39** which has already been available in optically pure form can be utilized to construct the C unit. Fragment B is a modified representation of the so-called Prelog-Djerassi lactonic acid (**40**), which was prepared from the cycloheptene derivative (**41**) as described in the methymycin synthesis.[11] Recently lactonic acid **40** has been more conveniently obtained from aldehyde **42** using Heathcock's procedure (eq. 20).[26] Reaction of this readily obtainable aldehyde (**42**) with enolate **43** afforded the aldol product **44** in as high as 50% yield (eq. 21). This result is rather surprising because Cram's rule does not apply to this case. A tentative explanation may be offered by invoking some weak interaction of the rather remote carbomethoxy group with the aldehydic group. The β-side approach of the enolate as shown in III is thus disfavored and the now preferred conformation similar to IV leads to the formation of **44**. Recent studies in our laboratory demonstrate that boron enolates also undergo stereoselective aldol condensations and appear to solve several fundamental problems exemplified here by the conversion of **42** into **44**. Hopefully the progress of this investigation will soon reach a stage that the results may be disclosed.

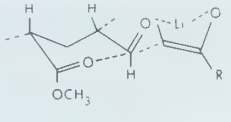
We planned to combine the optically pure C fragment with racemic B+A to give a diastereoisomeric mixture of (+)-C-(+)-B-A and (+)-C-(-)-B-A. Our expectation was that the wrong isomer might fail to cyclize as judged from inspection of CPK



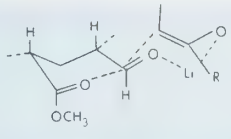
40
Prelog-Djerassi lactonic acid



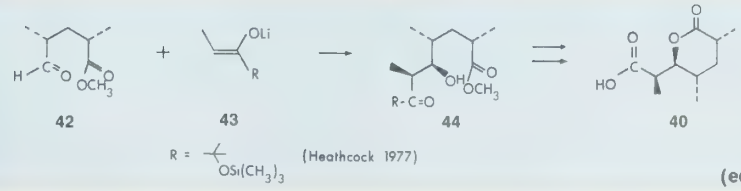
41 42 (eq. 20)



III



IV



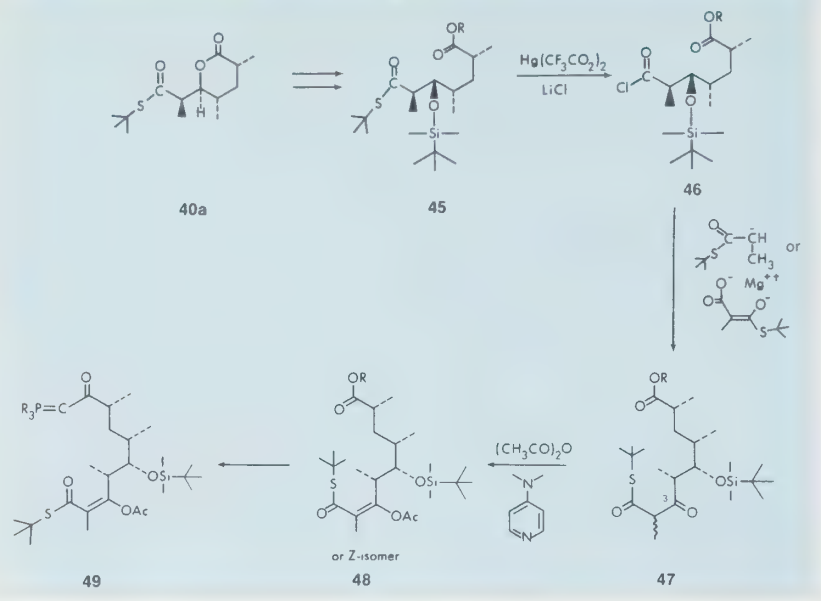
42 43 44 40

R = $-O-Si(CH_3)_3$ (Heathcock 1977)

(eq. 21)

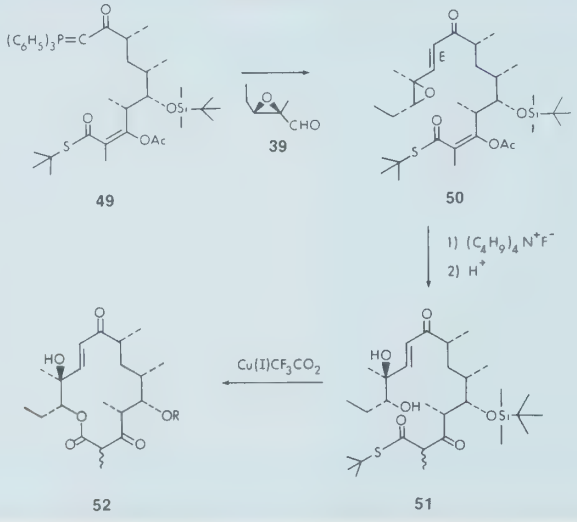
models, and thus, separation would be facilitated after the lactonization. There are two sequences for combination of the three fragments: A+B+C (counter clockwise) and C+B+A (clockwise). The A+B+C sequence was examined first and is briefly summarized in Scheme IV. The facile ring opening of the δ-lactone **40a** which proceeds *ca.* 100 times as fast as the alkaline hydrolysis of normal esters leads to the hydroxy acid salt which is then converted *via* two steps to the silyl ether (**45**) with R = C_6H_5 or Cl_3C-CH_2. The acid chloride **46** is now readily obtainable from the thiol ester and treated at -70° C with a standard acylating reagent without causing epimerization of the chiral centers to provide compound **47**. In order to suppress the facile dehydration of **47**, there was a need for deactivation of the 3-keto group which was attained by means of acetylation. Conversion of **48** into the (neutral) Wittig reagent (**49**) followed the procedure previously utilized for the methymycin synthesis.

Scheme IV



The Wittig reagent **49** with the aldehyde **39** proceeded in the expected manner to afford **50** with an *E* double bond and the next operation involved the removal of an O-protecting group (Scheme V). The two protecting groups were originally chosen because the generation of the O^- anion at the 5-position by means of the F^- anion should induce the acyl migration from the C-3 enol position. What actually occurred in the system was that the silyl group brought in its vicinity the F^- anion which subsequently attacked the C-3 acetyl group rather than the C-5 silyl protecting group. We realized the seriousness of this result, nonetheless proceeded with the next cyclization which provided the 14-membered lactone **52** in acceptable yield. Compound **52** turned out to be, as we were afraid, a dead-end product and all the attempts at removing the silyl group resulted in either recovery of **52** or destruction of the system. For example, the F^- anion, a specific reagent for cleavage of the O-Si bond, in this case caused enolate formation at C-2,3 and the silyl ether remained intact. This unusual stability of the O-Si$(CH_3)_2$(*tert*-C_4H_9) group toward the F^- anion may be due to the presence of the electronegative O^- group in the vicinity of the silyl group repelling the approach of a second anion of F^-. Also mild acid treatment of **52** led to complete recovery of starting material under conditions normally used to liberate the hydroxy group of a silyl ether. This result may be due to the extremely crowded environment of the silyl ether at C-5.

Scheme V



Clearly there was a need for the invention of a new OH-protecting group or reexamination of older ones to replace the *tert*-butyldimethylsilyl group. We have also considered the alternative C+B+A, clockwise approach rather than the A+B+C that has just been presented. While the latter approach requires two protecting groups, the former needs only one for the 5-OH group, but demands a mild acylation technique, disallowing the use of the normal, basic conditions generally used for this reaction. Thus, if one adopts the C+B+A approach, there are two problems: (1) use of a proper OH-protecting group which satisfies several conditions and (2) realization of non-basic acylation.

The requirement for the OH-protecting groups in the present case is described as follows. The same group must be attached to both the hydroxy and carboxy group and be selectively removed to regenerate the latter. Because the hydroxycarboxylic acid (**45** without Si protection) derived from Prelog-Djerassi's lactone (**40a**) relactonizes with extreme ease, the attachment of the protective group to OH must proceed with high efficiency. The protected hydroxy group then should survive a variety of conditions tabulated below and be removed selectively under mild conditions. Our choice, after many trials, has turned out to be the old methoxymethyl group, which has not enjoyed popularity in the

Stability of R-OCH_2OCH_3

survive:

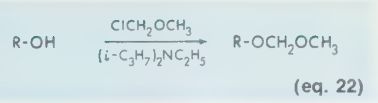
- 1N H_2SO_4 in THF, 16 hr
- $ZnBr_2$, $MgBr_2$
- $(CH_3)_3C$-S^- in DMF or THF
- Hg(II), Cu(I)
- $(n$-$C_4H_9)_4N^+F^-$

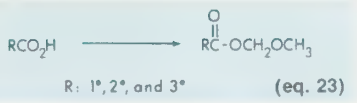
past, partly because the removal requires somewhat drastic conditions or hydride abstraction.[27] The deficiencies have now been remedied. First, primary, secondary, and tertiary hydroxy groups as well as carboxylic acids are protected efficiently (eqs. 22 and 23). The stability of R-OCH_2OCH_3 appeared quite adequate for its use in the sequence and provided a promising outlook.

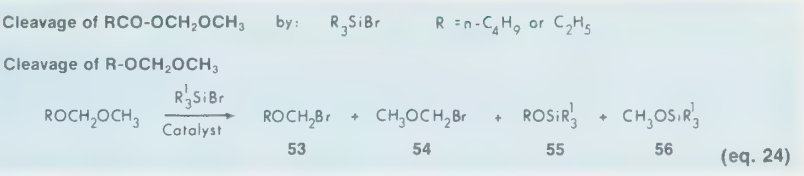
Selective cleavage of methoxymethyl esters in the presence of methoxymethyl ethers can easily be effected by bromotributylsilane and a trace amount of methanol,[28] followed by near-neutral hydrolysis. In contrast, cleavage of methoxymethyl ethers is somewhat complex. Some phosphorus impurities which had fortuitously been introduced into the silyl reagents in our earlier preparations, and whose exact composition is still unknown to us, were found to catalyze the reaction (eq. 24). With small R^1, the reaction of a methoxymethyl ether with bromosilanes leads initially to a kinetically controlled distribution of four possible products (**53**, **54**, **55** and **56**) which equilibrate to a thermodynamically controlled mixture. However, when both R and R^1 are bulky (*e.g.*, *i*-C_4H_9) as in the present case, there is no equilibration and the formation of $ROCH_2Br$ proceeds in excellent yields. Thus, removal of the methoxymethyl protecting group or its conversion into other protecting groups appropriate for the ensuing operation has become feasible as shown (Scheme VI).

The methoxymethyl protecting group having met the requirements, our attention was focused on the development of a facile non-basic acyl-transfer reaction. A brief description of the acetoacetic acid biosynthesis is an appropriate introduction to this subject.[29] One molecule of acetyl CoA (**57**) is transformed, with the aid of biotin, into malonyl CoA (**58**) which is properly attached to an acyl carrier protein (ACP) through a so-called central SH, as indicated in **59** (eq. 25). Another molecule of acetyl CoA, after being linked with a peripheral SH in ACP, moves into the active site of an enzyme and acts as an acceptor of malonyl CoA (eq. 26), and then the condensation takes place with concurrent evolution of CO_2 (eq. 27). Probably organic chemists can conceive several reaction systems that mimic this biosynthetic process and bring about a non-enzymatic, efficient acetoacetic acid condensation. Four such reaction systems are: (1) intramolecular acylation, using malonyl thiol half-ester as an enolate source (V), (2) neutral generation of an acyl cation in the presence of a ketene hemithioacetal (VI), (3) use of a thiophilic metal [*e.g.*, Cu(I)] to activate a thiol ester and at the same time to induce decarboxylation (VII), and (4) use of a relatively hard metal to bring two reactants together and also to simultaneously activate the methylene group of the malonyl half-ester (VIII).

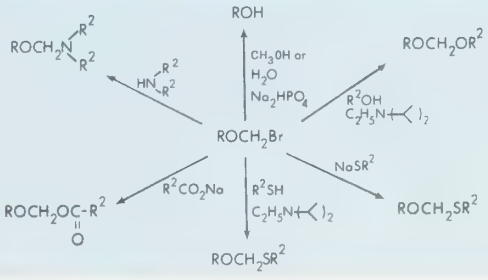
We indeed spent a great deal of effort to explore all of these possibilities, each of which met with a varying degree of success in both model studies and the preparation of an intermediate for the synthesis of pikromycin. Summarized below is the use of the magnesium salt of a malonic thiol half-ester which has provided by far the most encouraging result. Reagent I consists of an equimolar mixture of magnesium pivalate **61** and malonic or methylmalonic thiol half-ester **62** with $R^1 = C_2H_5$ or *tert*-C_4H_9. Treatment of an unhindered carboxylic acid with carbonyldiimidazole followed by Reagent I provides an excellent yield of the corresponding acetoacetic thiol ester (eq. 28). While this reaction proceeds very effectively with primary carboxylic acids, the yields decrease substantially with secondary carboxylic acids

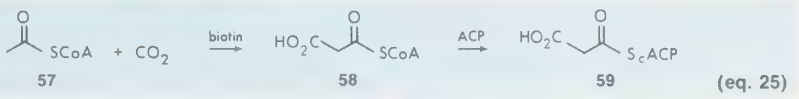


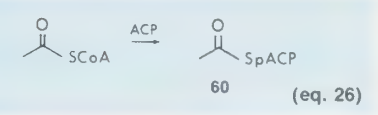


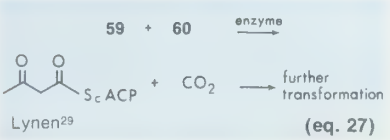


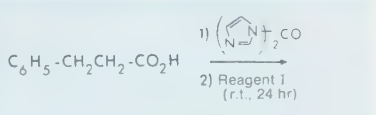
Scheme VI

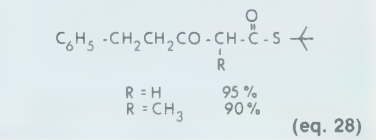


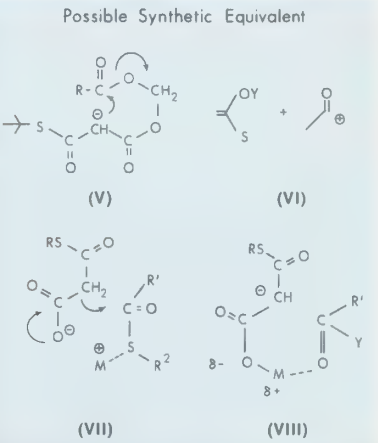


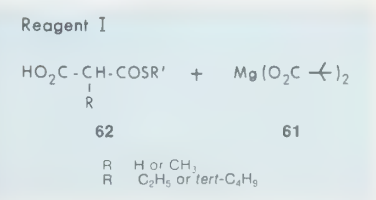


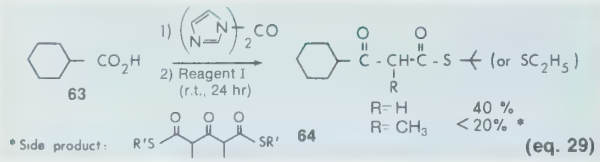


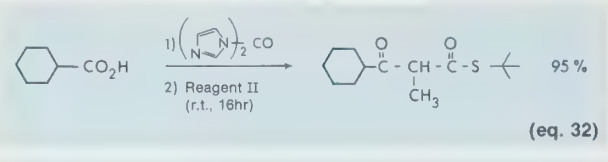


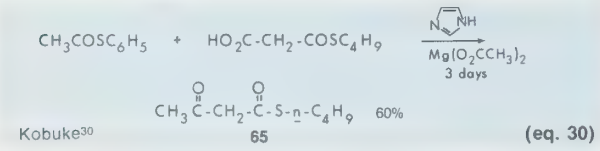


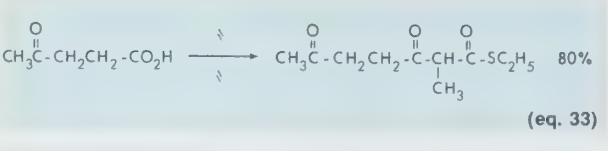


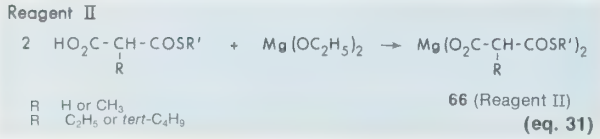


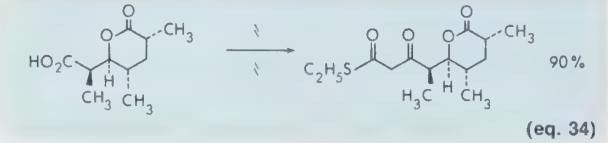












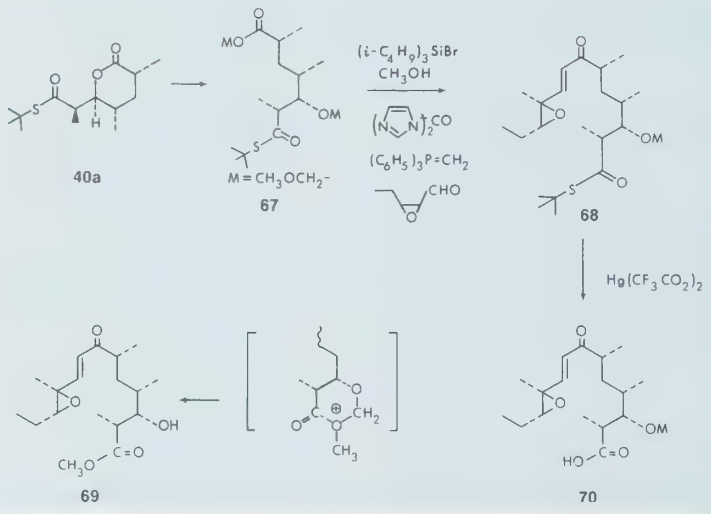
such as cyclohexanecarboxylic acid **63** and the formation of dimethylacetonedicarboxylic thiol ester **64** becomes a major reaction course (eq. 29). Other salts thus far tested include Zn(II), Cu(II), Co(II), $Ag(I)CF_3CO_2$, $Mg(II)(CF_3CO_2)_2$, and these were found to be less effective than Mg(II) pivalate **61**. Before a newer version (Reagent II) of Reagent I is discussed, a recent report by Kobuke and Yoshida should be mentioned, which describes the formation of an acetoacetic thiol ester **65** from the benzenethiol ester of acetic acid and a malonic half-thiol ester in the presence of imidazole and magnesium acetate (eq. 30).[30]

Reagent II, the magnesium salt of malonic or alkylmalonic thiol half-ester **66** (eq. 31), is much more effective than Reagent I and provides a wide scope of this reaction. Note that Reagent II is a neutral, crystalline salt, and that the acylation proceeds under *near-neutral conditions with sensitive functional groups being kept intact*, an achievement significant to organic synthesis. Three selected examples clearly demonstrate the superiority of this reaction (eqs. 32-34).

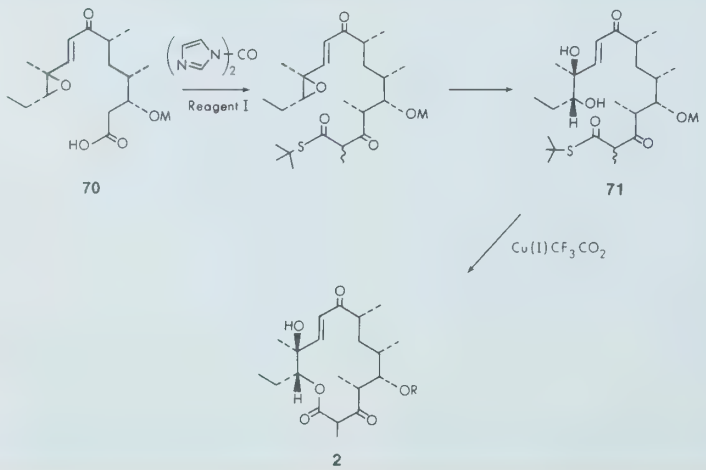
We were now ready to utilize the new acylation reaction for the synthesis of pikromycin **2**. The thiol ester (**40a**) of the Prelog-Djerassi lactone was converted to its open form with the methoxymethyl protective group as shown in **67** (Scheme VII) and then was connected with the left-hand fragment C to provide **68** in a manner similar to that described earlier. The reaction of **68** with $Hg(CF_3CO_2)_2$ under the standard conditions took a rather abnormal course to give **69** because of the unexpected participation of the methoxymethyl group in the reaction, but this difficulty was soon overcome by a modified procedure.

The next crucial step, acylation of **70**, (Scheme VIII) proceeded rather ironically even with Reagent I, which is normally less efficient than Reagent II, despite the steric congestion around the carboxylic acid. As was noted earlier in the Hg(II) treatment of **68**, this anomalous behavior appears to be again attributable to the methoxymethyl participation which leads to the activation of the acid imidazolide intermediate which reacts with Reagent I. We now have the pikronolide seco-acid precursor **70** with the

Scheme VII



Scheme VIII



properly protected functional groups, and from previous experience we do not anticipate any major problem in executing the lactonization of **71**.

I have outlined the current status of our work in this area. I may conclude that the problems associated with the formation of medium- and large-sized lactones have found satisfactory solutions. This completes phase I of macrolide syntheses and we and others have now entered the second stage of the project that concerns the acyl and aldol condensations. I am pleased to learn at this meeting that some important progress has been made and am sure that the next few years will witness the major breakthrough in this challenging problem.

No account of this work would be complete without mention of the devotion and expertise of my co-workers. I wish to express my particular appreciation to Dr. G.S. Bates and Mr. D.W. Brooks who have made the progress in the pikromycin synthesis, and also to Drs. Y. Hayase and W.-K. Chan who have executed numerous delicate experiments on cytochalasin and tylosin.

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ABOUT THE AUTHOR

Professor Satoru Masamune, the recipient of the 1978 ACS Award for Creative Work in Synthetic Organic Chemistry, currently holds a joint appointment with the University of Alberta and the Massachusetts Institute of Technology.

Professor Masamune was born in Fukuoka, Japan, and received his undergraduate training at Tohoku University, an A.B. being conferred in 1952. In 1953, he came to the United States as one of the first Fulbright exchange students at the University of California at Berkeley and obtained his Ph.D. in 1957. From 1956 until 1961 he held a research appointment with the University of Wisconsin, first as a postdoctoral fellow, then as lecturer. For the next three years, he was a Fellow of the Mellon Institute in Pittsburgh before joining the staff of the University of Alberta in 1964. He was promoted to full professor in 1967. His appointment with MIT was initiated on July 1, 1978. In 1975, he was elected a Fellow of the Royal Society of Canada and has been on the editorial board of Organic Syntheses since 1970, and of Chemical Intermediates since 1976. He is in demand as a seminar speaker and recent major lectureships include the 2nd IUPAC meeting on Non-benzenoid Aromatic Compounds held in Lindau, West Germany in 1974, the 4th International Symposium on Syntheses in Organic Chemistry at Cambridge, England in 1975, the 1975-76 Purves lectureship at McGill University, the 1976-77 distinguished visiting professorship at the University of Texas, Austin, the Karl Pfister visiting professorship at MIT in 1977, and the 10th National Symposium on Non-benzenoid Aromatic Chemistry sponsored by the Chemical Society of Japan in 1977.

Professor Masamune has made many significant contributions to two broad areas of organic chemistry, the synthesis of natural products and the chemistry of small ring systems. His well known synthetic achievements which have resulted in international acclaim are the diterpene alkaloids, the indole alkaloids, ajmaline, and the macrolide antibiotic, methymycin. The first successful synthesis of the polyoxomacrolide was indeed remarkable in that it required solution of two formidable problems, 1) the construction of a medium-sized lactone ring and 2) the introduction of chiral centers into a straight-chain aliphatic acid. His work on small ring systems has included both cyclic π-electron and strained systems. Important results which have enriched the knowledge of the cyclic π-electron system have emerged from his work on cyclobutadiene and cyclodecapentaene. His contributions to the chemistry of strained systems have opened a new dimension in carbocation chemistry and have provided invaluable experimental evidence to evaluate recent theoretical treatments of organic molecules.

Aldrich offers these reagents cited by Prof. Masamune.

14,304-9	Aldrithiol-2 (2,2′-dipyridyl disulfide)
19,050-0	*tert.*-Butyldimethylsilyl chloride
11,553-3	1,1′-Carbonyldiimidazole
C6,270-0	*m*-Chloroperoxybenzoic acid
13,900-9	1,5-Diazabicyclo[5.4.0]undec-5-ene
D9,163-2	Diethyl chlorophosphate
10,770-0	4-Dimethylaminopyridine
E105-5	Epichlorohydrin
15,648-5	Mercuric trifluoroacetate
10,920-7	2-Methyl-2-propanethiol
17,643-5	Silver trifluoromethanesulfonate
15,615-9	Sodium cyanoborohydride
19,568-5	Tetrabutylammonium fluoride, 1*M* solution in tetrahydrofuran
T6,240-5	Trifluoroacetic acid, silver salt
15,358-3	*N*-(Trimethylsilyl)imidazole,

Selenium Reagents for Organic Synthesis

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During the last few years the rapid development of selenium chemistry has provided organic synthesis with a number of very useful procedures.[1] Selenium metal is, of course, the starting point for all of these developments but it is convenient to summarize the new work by describing the main transformations that can be done with commercially available reagents or with materials easily made from them.

1. Preparation of α,β-unsaturated carbonyl compounds

One of the major applications of organoselenium chemistry is based on the fact[2] that phenyl alkyl selenides can be converted into olefins under very mild conditions (eq. 1).

The intermediate selenoxide fragments by a *syn*[2d] elimination as shown and the process is usually both rapid and efficient at room temperature. It constitutes a standard method for making α,β-unsaturated carbonyl compounds (eq. 2) and is carried out *formally* in three steps: (a) introduction of a benzeneseleno group (PhSe-) *alpha* to the carbonyl, (b) oxidation of the resulting selenide to the selenoxide level and (c) fragmentation of the selenoxide.

The usual method for introducing the PhSe- group is by way of a lithium enolate generated at a low temperature in tetrahydrofuran and then allowed to react with PhSe-SePh, PhSeCl, or PhSeBr* (eq. 3). This method has not been used with *aldehydes* but it works for ketones,[3] esters,[4] lactones,[3,4',5] nitriles[6] and lactams.[7]

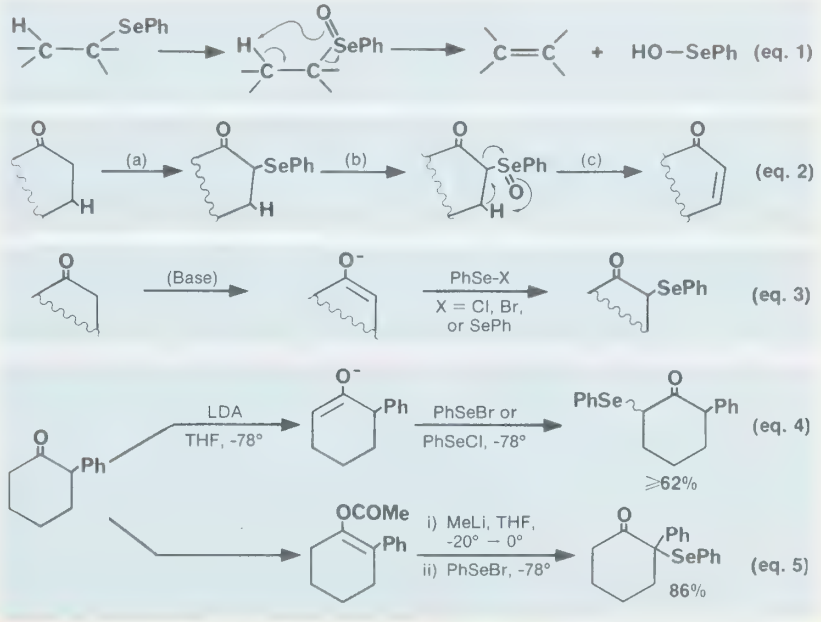
In the case of unsymmetrical ketones (eqs. 4 and 5) the kinetic enolate can be generated using LDA while the isomeric enolate is accessible *via* the enol acetate.[8] These enolates react very rapidly[3] with PhSeCl and PhSeBr, but PhSe-SePh is not suitable as a selenenylating agent for ketones.[3] It can be used, however, with the enolates of esters, lactones, and nitriles. Lactams have been studied only with PhSeCl.[7] Equations 6 – 9 are representative examples and two special points should be noted. First, the selenenylation of enolates sometimes requires the presence of HMPA to proceed well, and, secondly, *two* equivalents of base are needed for the monoselenenylation of nitriles and lactams. PhSeCl and PhSeBr can probably be used interchangeably.

The enolates of multifunctional compounds such as β-keto-esters, β-keto-sulfoxides, and β-diketones are also selenenylated by treatment with PhSeCl or PhSeBr.[3]

The selenenylation of aldehydes[4c] (and ketones) may be carried out by direct treatment with PhSeCl (*not* PhSeBr) (eq. 10). The process is accelerated by addition of a little concentrated hydrochloric acid but all mineral acid — both that added deliberately and that generated in the reaction must be removed before oxidation of the selenide.

Finally, it is possible to introduce the PhSe- group in the absence of a strong base by using certain enol derivatives (eqs. 11 and 12).

With the α-selenenylated carbonyl compound in hand, the next stage involves oxidation followed by fragmentation of the resulting selenoxide. A variety of methods is available for these processes. Sodium periodate, peracids (usually *m*-chloroper-



*Of these, only PhSeBr is not commercially available. It is made by adding Br_2 (1 equiv.) in dry CCl_4 to a solution of PhSe-SePh in the same solvent. Removal of CCl_4 after 30 minutes leaves a maroon, crystalline residue of PhSeBr.

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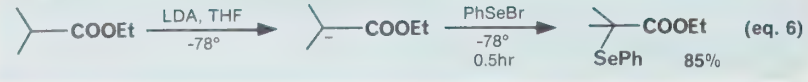
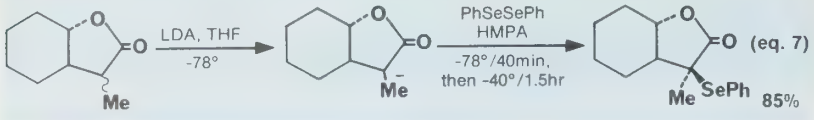
Esters:[4a]



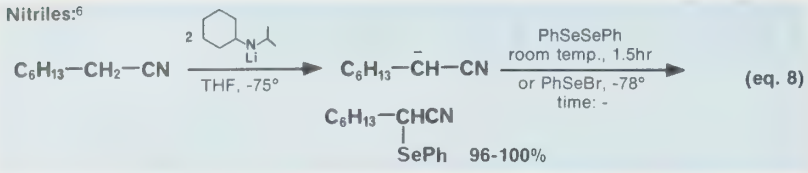
(eq. 6)

Lactones:[5]



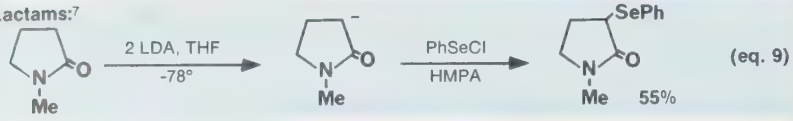
(eq. 7)

Nitriles:[6]

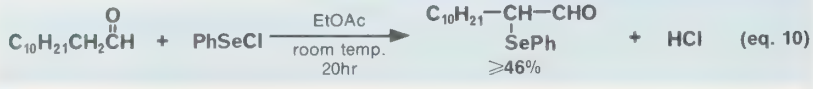


(eq. 8)

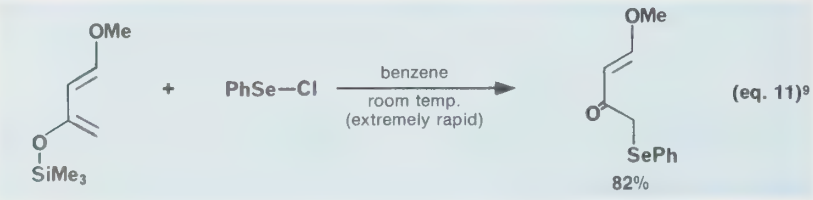
Lactams:[7]



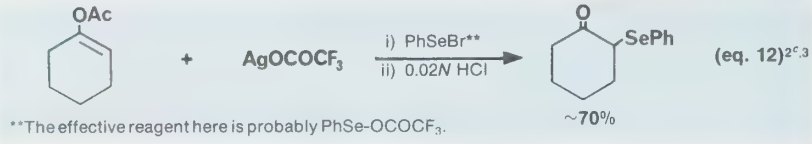
(eq. 9)



(eq. 10)

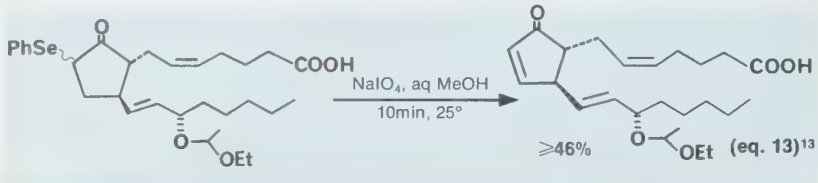


(eq. 11)[9]

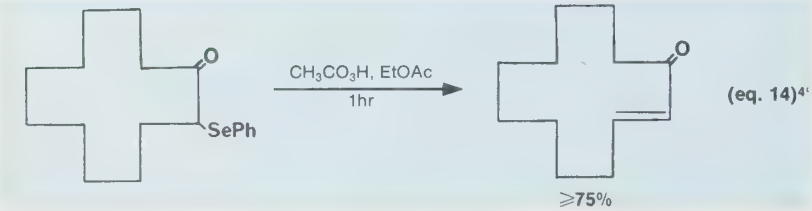


(eq. 12)[2c,3]

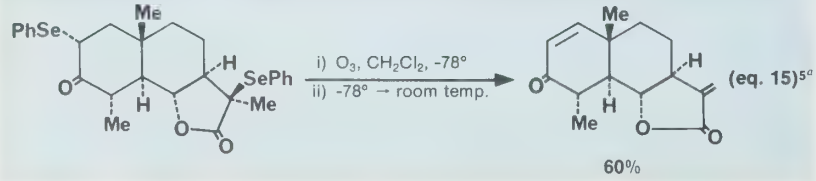
**The effective reagent here is probably PhSe-OCOCF$_3$.



(eq. 13)[13]



(eq. 14)[4c]



(eq. 15)[5a]

benzoic acid), ozone, and hydrogen peroxide are the most common reagents and it is often advisable to purify the α-selenenylated carbonyl compound — especially to free it of unselenenylated material.

The choice of reagent is guided[10] by several factors. Other functionalities in the molecule must, of course, be inert and, where an excess of oxidant is used, the sensitivity of the fragmentation product is a factor to be considered. One of the products of selenoxide fragmentation is PhSe-OH, which can disproportionate to PhSe-SePh, PhSe(O)OH, and H_2O.[3] Sometimes, however, unless special precautions are taken, the PhSe-OH is oxidized by residual selenoxide so that the eventual yield of unsaturated compound is lowered.[11]

With $NaIO_4$ general practice calls for an aqueous organic solvent and at least sufficient oxidant to react with the selenide and the PhSeOH. Under these conditions oxidation and fragmentation are complete at room temperature. Occasionally, it is an advantage to buffer the reaction mixture with sodium bicarbonate.

Peracids are generally used in an organic solvent and are employed in stoichiometric amounts (1 mole per mole of selenide) at low temperature. If the fragmentation product is inert to peracid, a sufficient amount is used to oxidize the PhSeOH formed, and the reaction is run in the temperature range of 0° to 25°.

It is usual to employ ozone at -78° (if possible) in CH_2Cl_2, Et_2O, or CCl_4. (The reagent attacks THF.)

The selenoxide (from peracid or ozone treatment) can be allowed to fragment by warming the cold selenoxide solution to room temperature. (Occasionally, pyridine is added to suppress certain side reactions.[3]) Alternatively, the cold (-78°) selenoxide solution is added to refluxing CH_2Cl_2 or CCl_4 and a useful variation of this procedure is to mix *i*-Pr_2NH with the selenoxide initially. The presence of the amine again results in improved yields.

Hydrogen peroxide (typically 30-50% w/w) is one of the most frequently used oxidants and a sufficient quantity is employed to quench the PhSeOH resulting from the fragmentation. THF is the usual solvent and careful temperature control (0° to room temperature) is necessary because the oxidation is strongly exothermic. Hydrogen peroxide converts[12] PhSe(O)OH into PhSe(O)OOH, and this compound has sometimes caused problems by epoxidizing double bonds or causing ketones to undergo the Baeyer-Villiger reaction.[12] Products sensitive to basic H_2O_2 can be protected by addition of a trace of acetic

acid.

Often, best results with H_2O_2 are obtained with the following two-phase system: a CH_2Cl_2 solution of the selenide and, usually, two equivalents of pyridine are stirred with an excess of H_2O_2. Oxidation and fragmentation are usually complete within about 15 minutes.[3]

The selenium method for making α,β-unsaturated carbonyl compounds has proved very effective in natural-product synthesis. A few of many[10] published examples of the method are shown below (eqs. 13 → 16).

2. Preparation of olefins by using aryl selenide anions and aryl selenocyanates

Aryl selenide anions ($ArSe^-$) are strong nucleophiles and this property can be used to attach the arylseleno group to a carbon skeleton and then by selenoxide fragmentation, to introduce a carbon-carbon double bond under mild conditions.

$PhSe^-Na^+$ is generated[14] (as a BH_3 complex) by addition of $NaBH_4$ to an ethanol solution of PhSe-SePh. The selenium ion attacks epoxides, halides and sulfonates (eqs. 17 → 19). Aryl-substituted selenide anions have been used with halides and sulfonates (eq. 20). The anion shown (see eq. 20) is generated by treating the selenocyanate with $NaBH_4$. (Both EtOH and DMF[16] have been used as solvents for this reduction.)

Selenide anions are also involved, mechanistically, in an efficient method (eqs. 21 and 22) for converting primary alcohols and aldehydes into selenides.

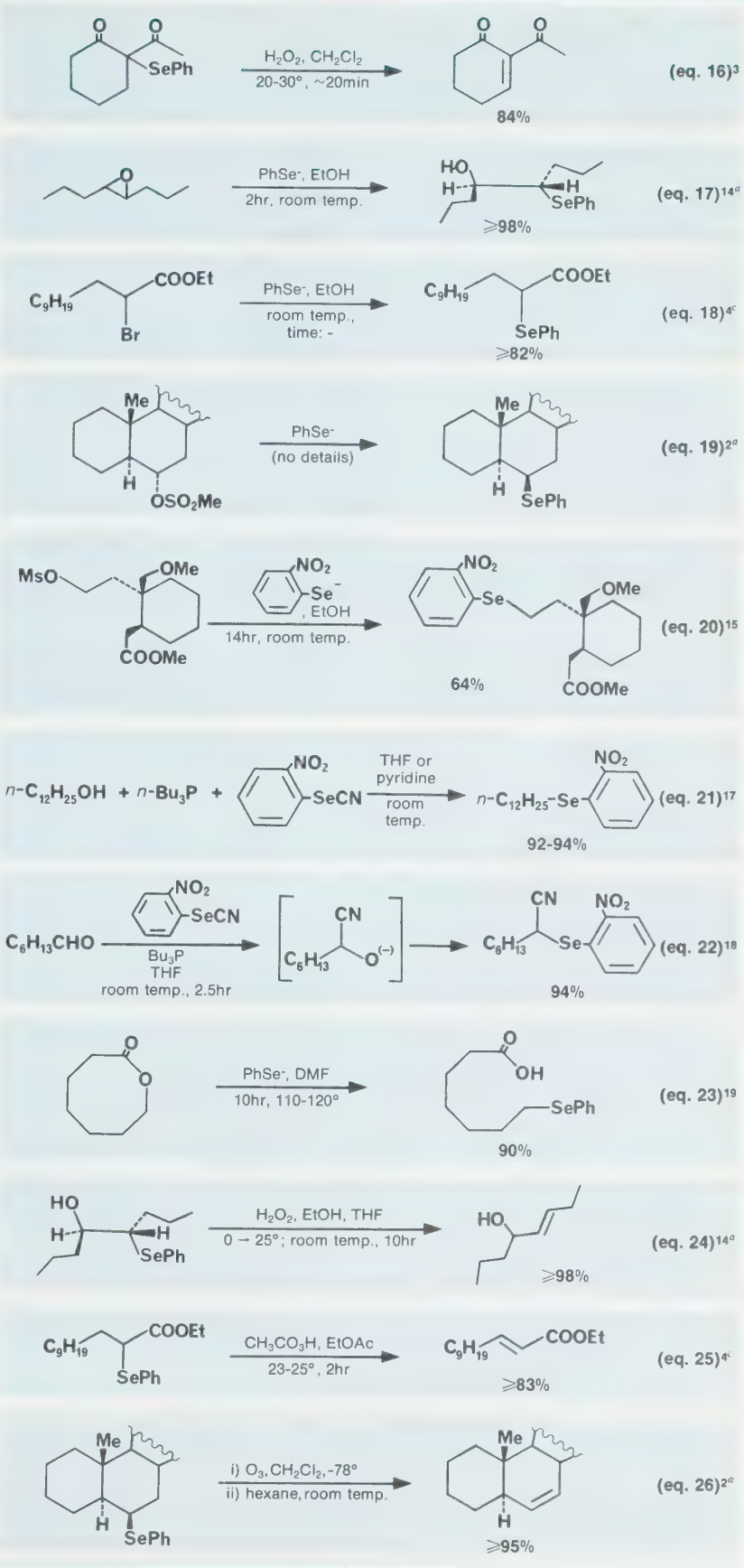
A phenyl selenide anion with enhanced nucleophilic properties can be generated by heating sodium with PhSe-SePh in THF.[14b] The uncomplexed salt, $PhSe^-Na^+$, formed in this way, and solubilized by addition of HMPA or 18-crown-6, opens lactones. $PhSe^-Na^+$ generated in DMF by $NaBH_4$ reduction of PhSe-SePh[19] reacts similarly at 110-120° (eq. 23).

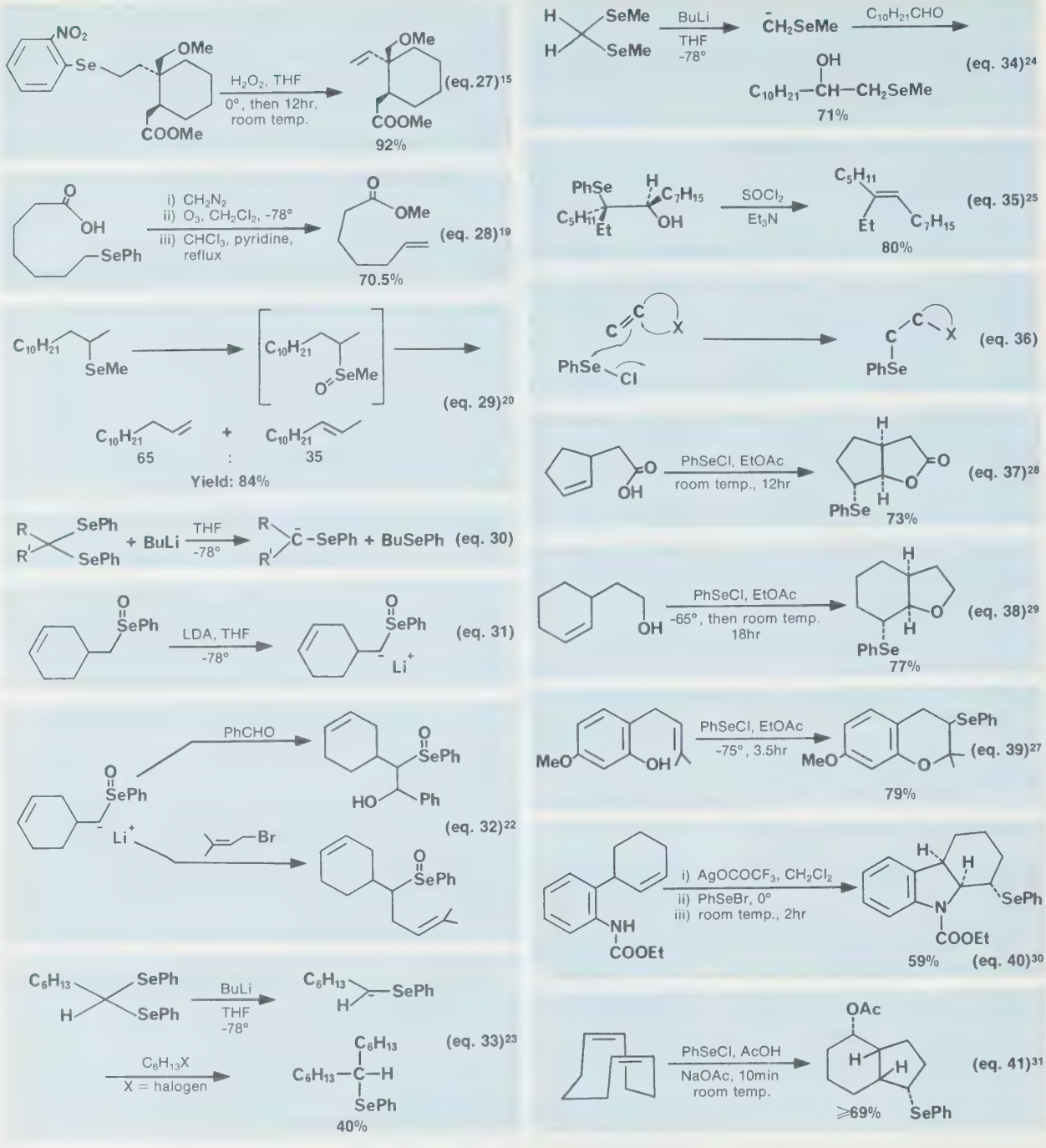
Each of the selenides (see eqs. 17 → 23) can be converted into an olefin by oxidation under appropriate conditions (*e.g.*, eqs. 24 → 28).

Several points emerge from these and many other related experiments:

(i) Conformational freedom permitting, disubstituted olefins are formed with *trans* stereochemistry, except in the case of α,β-unsaturated nitriles which give both *cis* and *trans* isomers.

(ii) When adjacent oxygen substituents are present (see eq. 24) elimination is strictly away from the oxygen-bearing carbon to give an allylic alcohol.





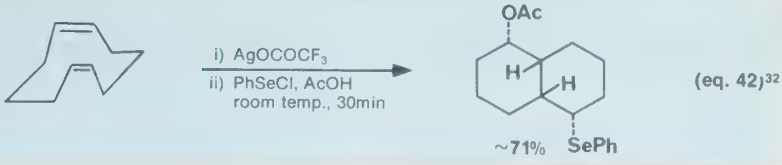
(iii) The preparation of terminal olefins — using the oxidation-fragmentation methods already described — often proceeds poorly unless (a) specially substituted aryl selenides are used (eq. 27) or (b) the selenoxide is made to collapse by heating[3] in the presence of a base (eq. 28). However, a very promising alternative procedure is being developed. The selenide is warmed (55°) in THF containing suspended alumina and an excess of *t*-BuOOH. Under these conditions terminal (unsubstituted) phenyl selenoxides and even methyl alkyl selenoxides[10] fragment readily (eq. 29).

3. Formation of carbon-carbon double bonds by using selenium-containing synthons

A methodology more advanced than the attachment of the benzeneseleno group to an existing carbon framework is one that uses synthons already containing this group. Such procedures are made possible in part by the fact that selenoacetals can be converted[21] into carbanions (eq. 30) and in part by the fact that selenoxides (kept at a low temperature) can be deprotonated[22] (eq. 31). Both selenium-stabilized and selenoxide-stabilized anions react with alkyl halides and with carbonyl compounds. The following are typical examples (eqs. 32 → 34).

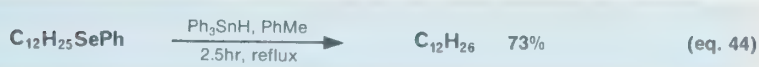
The products of these reactions are suitable for a variety of transformations:

(i) Selenides (*e.g.*, from the process of eq. 33) can be oxidized and allowed to fragment, or the resulting selenoxide can be deprotonated and treated with an alkyl

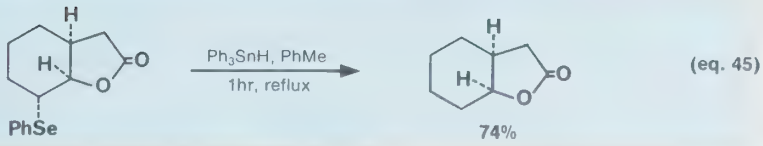


(eq. 42)[32]

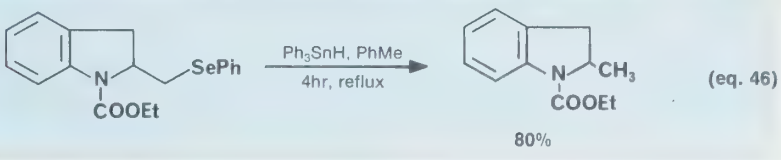
(eq. 43)



(eq. 44)



(eq. 45)



(eq. 46)

(eq. 47)

(eq. 48)

halide or a carbonyl compound.

(ii) Selenoxides (*e.g.*, from the process of eq. 32) can be permitted to fragment or they can be reduced ($NaHSO_3$ or KI) to the Se(II) level. In the case of β-hydroxyselenides, conversion of the -OH to a good leaving group affords an olefin (eq. 35).

Several reagents are available for this purpose[24,25,26] [$(CF_3CO)_2O + Et_3N$; TsOH; $HClO_4$; $SOCl_2 + Et_3N$; $MeSO_2Cl + Et_3N$] and β-hydroxyselenides, which are usually made by processes of the type shown in eq. 34, are useful precursors to olefins. Removal of the $PhSe^-$ and OH^- groups occurs in a *trans* fashion.

4. Cyclofunctionalization with selenenyl reagents

Cyclofunctionalization[27] is an intramolecular ring-forming process in which one end of the double bond involved in the cyclization becomes attached to a group — such as PhSe — that allows further transformations at that site (eq. 36). Typical examples are shown in eqs. 37 → 42. The reactions, which occur under the conditions indicated, proceed in a clearly defined stereochemical fashion and the utility of these processes has been demonstrated in natural-products work.[33]

Olefins not properly constituted for cyclofunctionalizations react with selenenyl reagents as shown in eq. 43, where Y can be Cl, Br, $OCOCH_3$, $OCOCF_3$, OMe, OEt, O-*i*-Pr depending on the reaction conditions.[34]

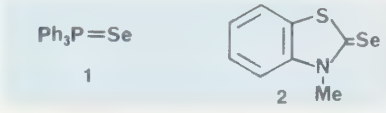
5. Deoxygenation reactions using selenium chemistry

Raney nickel can be used to hydrogenolize monoselenides and selenoacetals[23] but both compound classes are reduced smoothly by tin hydrides[35] (eqs. 44 → 48).

This tin hydride reduction, which works in the presence of a range of functionality is, of course, suitable for making labelled compounds by use of Ph_3SnD.

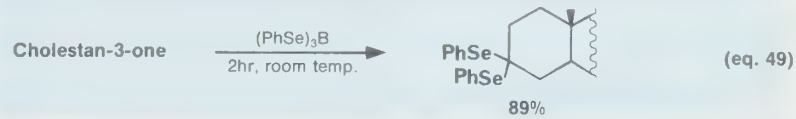
The selenoacetals needed for the reduction can be generated from aldehydes and ketones by treatment with PhSeH in the presence of sulfuric acid or zinc chloride.[36] Selenoacetals are also formed by treating carbonyl compounds with $(PhSe)_3B$ (eqs. 49 and 50). This reagent is a crystalline carrier for the very air-sensitive PhSeH. In using the boron reagent[37] it is sometimes advantageous or necessary to add to the reaction mixture a small amount (~10 mole %) of trifluoroacetic acid. Some preliminary results are given in the equations.

A second type of deoxygenation is the conversion of epoxides into olefins (eq. 51) by Reagents **1**[38] and **2**.[39] Both react with epoxides in the presence of one equivalent of trifluoroacetic acid and the olefin is generated without disturbing the relative stereochemistry about the carbon-carbon bond of the epoxide.

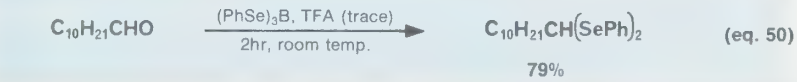


6. Catalytic uses of selenium

Metallic selenium can be used — frequently in a catalytic manner — to generate carbonyl selenide, which reacts with nucleophiles to give species of the type

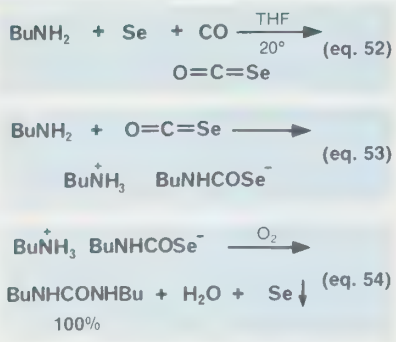


(eq. 49)



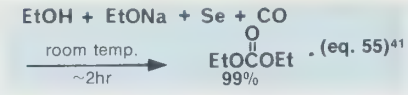
(eq. 50)

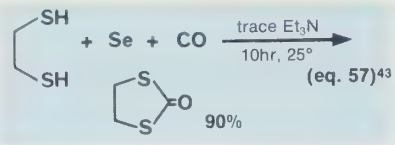
(eq. 51)

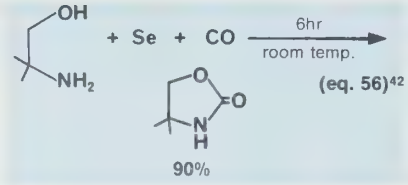


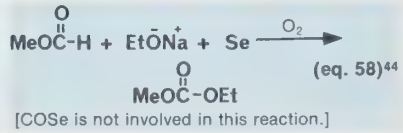
X-C(=O)-Y where X and Y are heteroatoms.

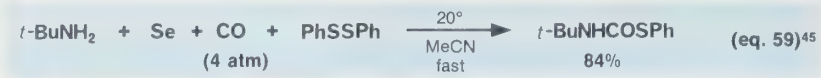
For example, when CO is passed into a THF solution of $BuNH_2$ containing a small portion of selenium, the metal dissolves as it is converted into COSe (eq. 52). The latter reacts with the amine (eq. 53) and, if a controlled amount of oxygen is now added to the CO stream, the salt (see eq. 53) is converted into a urea (eq. 54). The selenium metal generated in the latter process is recycled. Therefore, production of the urea is catalytic in selenium.[40] Equations 55 → 59 summarize analogous processes that have been reported.

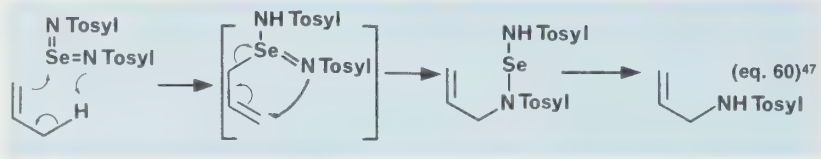


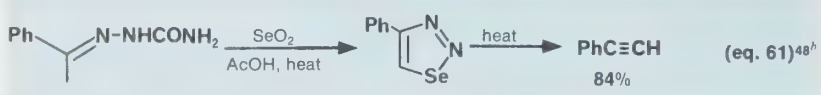


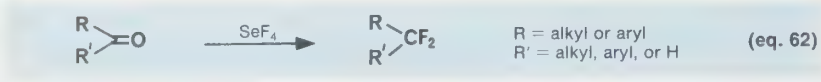


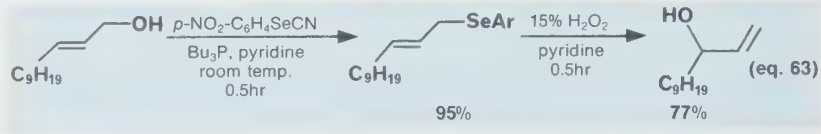


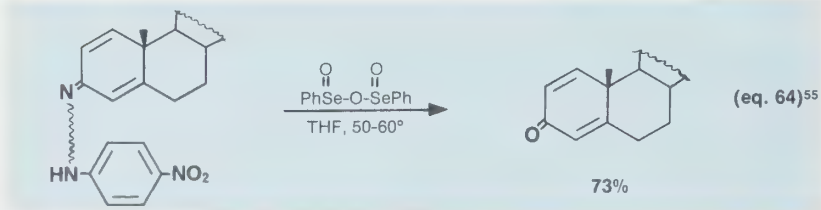


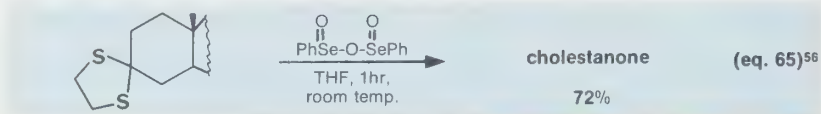












These species aminate olefins (eq. 60).

Selenium dioxide can also be used to convert semicarbazones into 1,2,3-selenadiazoles[48] (eq. 61).

These heterocycles decompose — usually between 160 and 220° — to afford acetylenes. Although thermally severe conditions are needed the yields of simple acetylenes are frequently excellent.

Selenium dioxide

Substantial insight has been obtained into the mechanism of action of SeO_2[46] and a few aza-analogs, *e.g.*, 3, are now available.

R-N=Se=N-R

3

R = *p*-Me-$C_6H_4SO_2$-; *t*-Bu-

8. Preparation of fluoro-compounds

Dissolution of selenium pellets in ClF_3 affords SeF_4 which converts ketones and aldehydes into *gem*-difluorides[49] at, or below, room temperature (eq. 62) in yields of 65-100%. Alcohols are converted into alkyl fluorides and carboxylic acids (as well as their anhydrides) into acyl fluorides.[49] Reactions with hydroxylic substrates are best done in the presence of an equivalent of pyridine to quench the HF that is evolved.

9. 1,3-Transposition of allylic alcohols

1,3-Transposition of primary allylic alcohols can be achieved[50] by the sequence summarized in eq. 63. The intermediate allylic selenoxide rearranges and the resulting selenenic ester is hydrolyzed *in situ*. Both of these stages occur spontaneously in the reaction medium.[51]

10. Applications of benzeneseleninic anhydride

Benzeneseleninic anhydride oxidizes certain amines to the ketone level[52] and can be used to hydroxylate[53] or aminate[54] phenols. The reagent has a general application in synthesis for releasing carbonyl compounds from hydrazones, oximes, semicarbazones, and thioacetals (eqs. 64 and 65).

11. Miscellaneous reactions

(i) Benzeneselenol reduces diazonium salts to arylhydrazines.[57]

(ii) $PhCH_2Se^-Na^+$, in refluxing DMF, demethylates phenolic ethers.[58]

(iii) Selenoxides can be used as weak oxidizing agents.[59]

12. Acknowledgements

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University of Alberta selenium chemists (left to right): seated, Dr. D. Clive, Dr. Gim Chittattu; standing, Dr. Wong, Neville Curtis, William Kiel, Steve Menchen.

About the Author

Dr. Clive was educated at Imperial College, London and received his Ph.D. from that Institute for research work in Sir Derek Barton's group. Postdoctoral studies followed, under the supervision of Professor Woodward at Harvard. Dr. Clive then became an I.C.I. fellow at Imperial College and is now on the staff of the Chemistry Department at the University of Alberta.

The purpose of the experimental work in Clive's laboratory is the invention of new reagents and methods that can be applied in the synthesis of natural products and pharmaceuticals. His group has found that organic selenium and tellurium chemistry is a very fertile area in this respect.

Aldrich offers these reagents cited by Professor Clive:

21,300-4	Benzeneseleninic acid
21,301-2	Benzeneseleninic anhydride
18,617-1	*n*-Butyllithium, solution in hexane
85,731-9	Chloramine-T trihydrate
18,062-9	Diphenyl diselenide
H1,160-2	Hexamethylphosphoramide
16,197-7	*N*-Isopropylcyclohexylamine
18,334-2	Phenylselenenyl chloride
20,430-7	Selenium, pellets, 99.9999%
20,431-5	Selenium(IV) oxide, 99.999%
20,010-7	Selenium(IV) oxide, 99.9+%
21,004-8	Sodium periodate
T6,240-5	Trifluoroacetic acid, silver salt
18,013-0	Triphenylphosphine selenide

Organic Sulfur Compounds in Organic Synthesis: Some Recent Advances

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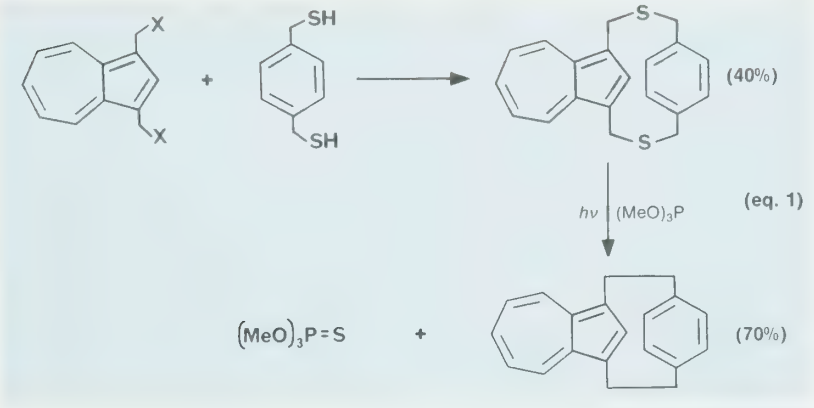
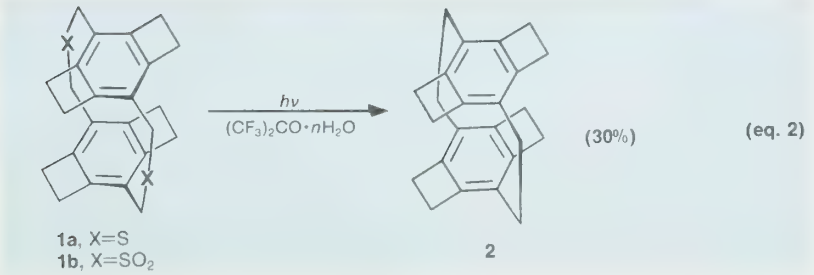
"We may judge, with great accuracy, of the commercial prosperity of a country from the amount of sulfuric acid it consumes." This often repeated observation by the great German chemist Justus von Liebig[1] is as true today as it was in 1851, for sulfuric acid annually tops the list, in tonnage, of all synthetic chemicals. Since most sulfuric acid is made from elemental sulfur it is fair to say that sulfur is the chemical industry's most widely used raw material. While dwarfed in importance by their inorganic counterparts, organic sulfur compounds have nonetheless become increasingly useful and important in organic synthesis. This essay will briefly outline some of the transformations which can be effected with sulfur-containing reagents, using examples selected from the recent literature. More detailed consideration of the reactions described herein and of the basic chemistry of organosulfur compounds is to be found in a recently published book by this author.[2]

The range of reactions available for organosulfur compounds is aptly illustrated by examples chosen from syntheses of cyclophanes, strained molecules with interesting properties due to transannular π-electron interaction between the facing aromatic rings. An important synthetic approach to these structures involves coupling a bis-thiol with a bis-halide (or related derivative) under high dilution conditions and then extruding the sulfur with concomitant carbon-carbon bond formation. In eq. 1,[3] carbon-carbon bond formation is achieved by photodesulfurization in trimethyl phosphite, a procedure discovered by Corey and Block.[4] Photodesulfonylation of sulfone **1b**, prepared in quantitative yield by *m*-chloroperbenzoic acid (MCPBA) oxidation of sulfide **1a**, has been employed in the synthesis of novel cyclophane **2**.[5] Pyrolytic methods are also very useful in cleanly removing sulfur. For example, [2.2](3,3′)biphenylophane, **5**, may be synthesized in good yield by pyrolysis (at 500°) of sulfone **4**.[6] Sulfur dioxide is, of course, an excellent leaving group in pyrolysis reactions. Sulfenic acids (RSOH) are also readily produced, efficient leaving groups as illustrated by the conversion of dithiacyclophane **3** to [2.2](3,3′)biphenylophane-1,15-diene, **8**, through a sequence involving methylation of **3** with dimethoxycarbonium tetrafluoroborate, double Stevens rearrangement of the bis-sulfonium salt **6**, oxidation of bis-sulfide **7a** to the bis-sulfoxide **7b** with MCPBA at 0°, and finally elimination of CH_3SOH at 320°C. Bis-sulfoxide **7b** may also be desulfurized to **5** with Raney nickel in refluxing ethanol.





Several additional points should be made regarding the reactions in eq. 3. The ability to oxidize sulfide sulfur to the sulfoxide or sulfone level selectively, often in the presence of other sensitive functionalities, is critical in realizing the full synthetic potential of sulfur. Generally, the oxidation can be stopped at the sulfoxide stage as the second oxidation (to sulfone) is slower than the first. Reagents are available, however, which will transform sulfoxides to sulfones in the presence of sulfides without affecting the latter.[7] Pyrolysis of sulfoxides represents a very useful means of introducing unsaturation. Often the elimination reaction is combined with an alkylation sequence involving α-sulfinyl or α-sulfenyl carbanions as will be discussed below. Pyrolysis of sulfoxides also represents a useful means of synthesizing sulfenic acids which themselves are interesting compounds whose basic structure has been only recently determined.[8] An alternative to the Stevens/sulfenic acid

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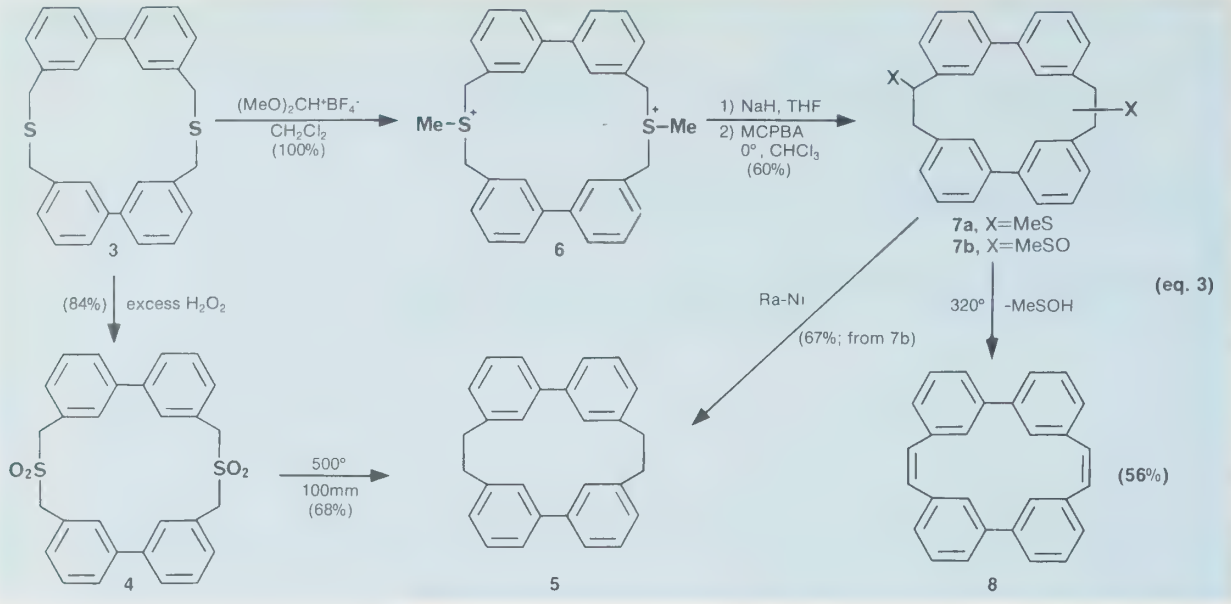
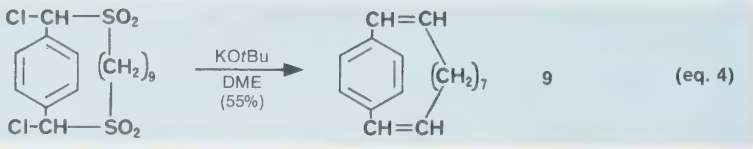
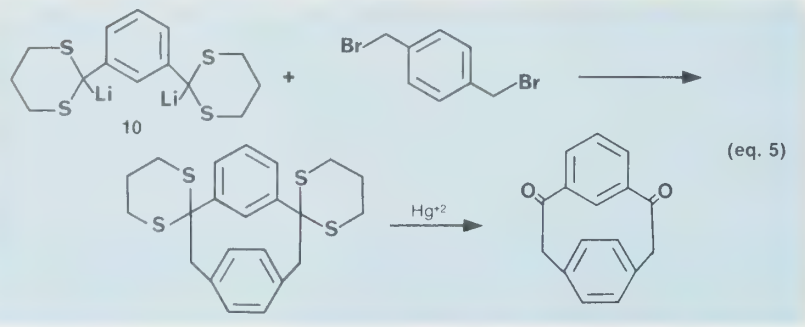


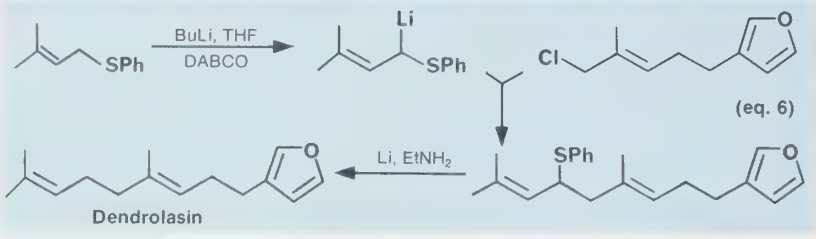
elimination route to unsaturated cyclophanes is the Ramberg-Bäcklund reaction, illustrated by the preparation of **9**.[9] Cyclophanediones may be generated by a sequence employing alkylation of bis-dithianyl derivative **10**.[10] Both of these latter routes will be discussed further.

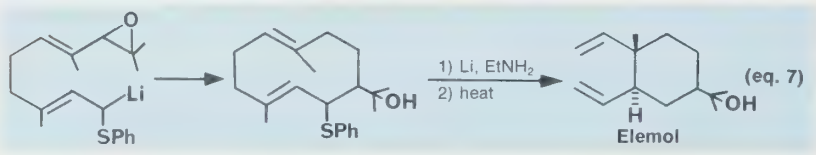


C - C from C - X

The controlled formation of C - C bonds is often a critical step in organic syntheses. Organosulfur carbanions have proven to be extremely useful in this process. In eq. 5, carbon-carbon bond formation is achieved by displacement on an alkyl halide by a lithio dithiane. Allylic groups can be coupled *via* allylic thiocarbanions in a process termed **Biellmann alkylation.**[11] In the dendrolasin synthesis (eq. 6),[12] the thiophenyl group is removed with lithium-ethylamine.[7] Elemol has been synthesized by an intramolecular variant of the Biellmann alkylation process (eq. 7).[13] Alkylation of **α-sulfinyl carbanions** followed by sulfenic acid elimination has been employed in a triene synthesis (eq. 8)[14] and in the synthesis of muscone (eq. 9).[15] (±)-Nuciferal has been prepared by alkylation of an α-sulfonyl carbanion followed by elimination of sulfinate anion (eq. 10).[16]

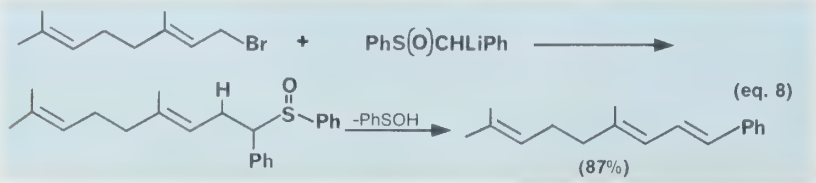


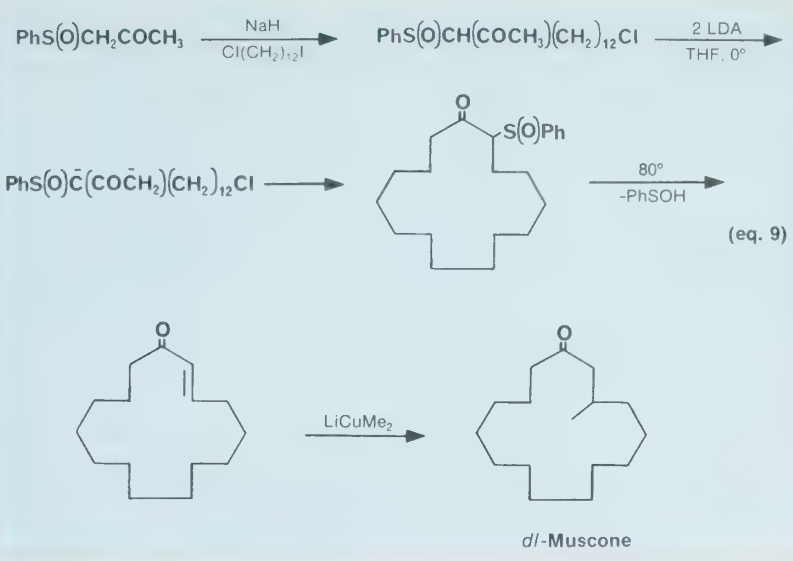


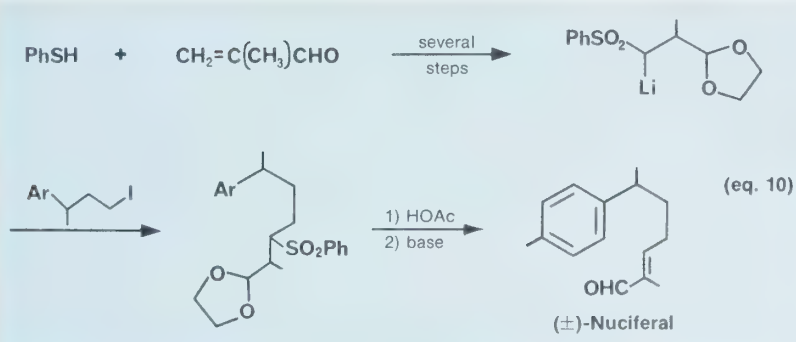


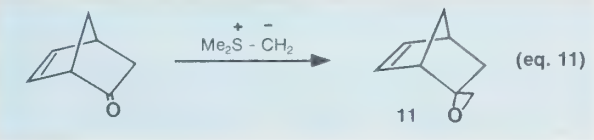
C - C from C = O
\ /
O

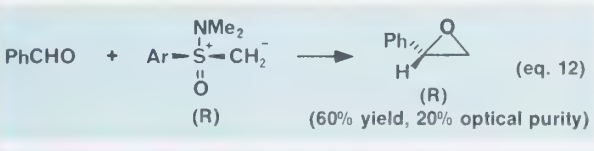
While phosphorus ylides react with carbonyl compounds giving olefins *via* the well known Wittig reaction, sulfur ylides afford epoxides under analogous conditions, *e.g.*, **11** (eq. 11).[17] In view of the importance of epoxides as synthetic intermediates and the ready availability of

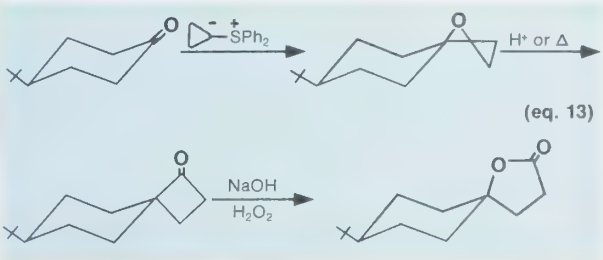


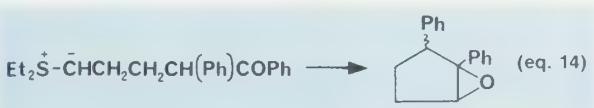












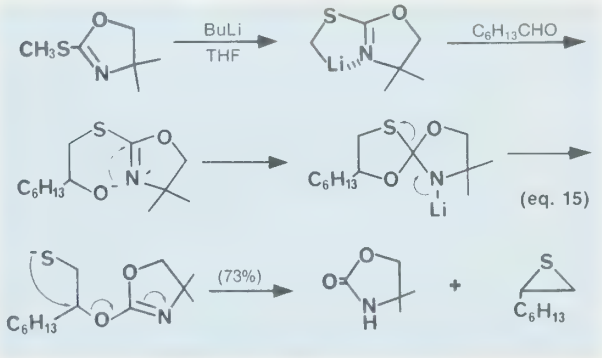
carbonyl compounds, epoxide formation using sulfur ylides is a very useful procedure that has been studied in great detail both from a mechanistic and a preparative standpoint. The generality of the reaction is demonstrated by the lack of interference from enol ethers, acetals, amides, nitriles, divalent sulfur, and in some cases, esters, hydroxyl groups and amino groups.[18] Asymmetric syntheses of epoxides may be realized using optically active sulfur ylides (eq. 12).[19] The use of cyclopropyl sulfur ylides is the basis for the novel process of "spiroannelation" (eq.13).[18] An instance of intramolecular epoxide formation has been published recently (eq. 14).[20]

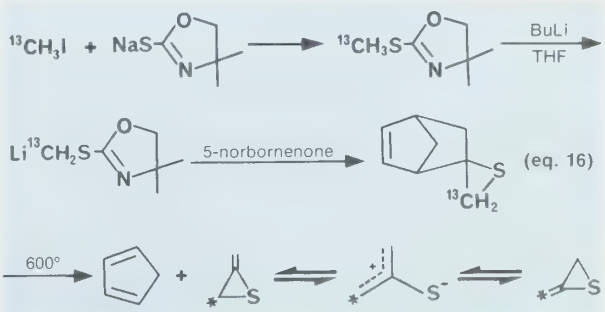
C - C from C = O

Ketones and aldehydes may be converted into thiiranes using lithio derivatives of 2-(thiomethyl)-Δ^2-oxazolines as shown in eq. 15.[21] Through the use of ^{13}C-labeled methyl iodide, ^{13}C-labeled thiiranes may be prepared. These compounds have been employed in mechanistic studies of the thermal rearrangement of allene episulfide (eq. 16).[22]

C - C from C = C

Sulfonium and sulfoxonium ylides readily add to such Michael acceptors as α,β-unsaturated ketones, esters, nitriles, isonitriles, sulfones, sulfoxides, sulfonamides, sulfonates, and nitro compounds to afford cyclopropanes,[18] *e.g.*, eq.



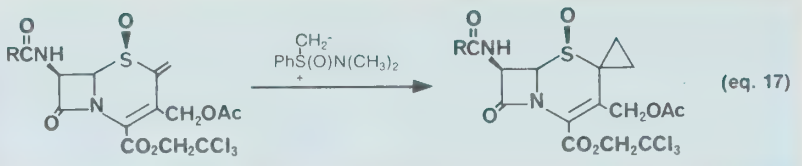


17.[23] These reactions are all nucleophilic cyclopropanations which proceed best with electron deficient olefins. While sulfonium ylides such as diphenyl sulfonium methylide are normally unreactive toward olefins such as *cis*- and *trans*-2-octene, it has been discovered that cyclopropanation does occur in the presence of copper salts and that these reactions are stereospecific with retention (eq. 18).[24]

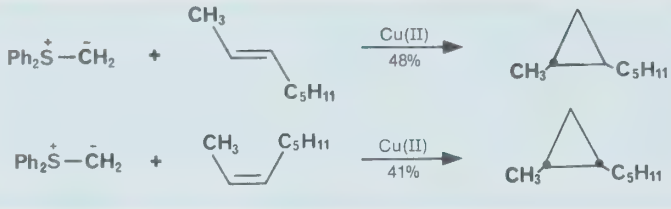
C = O from CHOH

A useful procedure for the selective oxidation of alcohols to aldehydes or ketones involves treatment of the alcohols with dimethyl sulfoxide (DMSO) and a coreagent such as dicyclohexylcarbodiimide (DCC)-pyridinium trifluoroacetate (Pfitzner-Moffatt oxidations, eq. 19),[25] acetic anhydride, methanesulfonic anhydride, trifluoroacetic anhydride, oxalyl chloride or pyridine-sulfur trioxide (the latter three coreagents are compared in eq. 20).[26] All of these reactions involve α,β'-elimination of an intermediate oxysulfonium ylide.[2] A number of sulfonium and sulfoxonium reagents of the type $R_2\overset{+}{S}X$ and $R_2\overset{+}{S}(O)X$ have also proven useful in alcohol oxidations as indicated by the reactions in eqs. 21[27] and 22.[28] The latter reaction is significant in that a vicinal diol is oxidized without complications from C - C bond cleavage (the case with most other oxidants!).

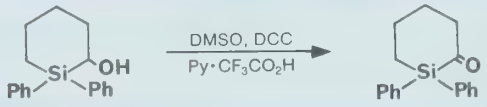
A variety of organosulfur compounds that have the same level of oxidation as aldehydes and ketones (*e.g.*, **12-15**) or carboxylic acids (*e.g.*, **16**) and which are readily converted into the carbonyl equivalents by hydrolysis is known. Thioacetals and thioketals, of course, have long been used as protecting groups for the carbonyl function. By taking advantage of the carbanion-forming capacity of these organosulfur carbonyl equivalents, it becomes possible to achieve *nucleophilic acylation,* as illustrated for the 1,3-dithianyl group in eq. 23. In effect, the normal direction of polarity of the carbonyl group has been temporarily reversed, transforming the normally electrophilic carbonyl carbon into a nucleophilic center (termed *Umpolung* or *dipole inversion*). This procedure is of obvious great synthetic importance since the whole range of reactions characteristic of carbanions can now be conducted with these nucleophilic carbonyl equivalents. Following the original publications by Corey and Seebach, reports of other useful organosulfur (and sulfur-free) nucleophilic acylating agents have appeared frequently in the chemical literature. Certain of these newer methods are claimed to offer advantages over the dithiane method because of



(eq. 17)



(eq. 18)

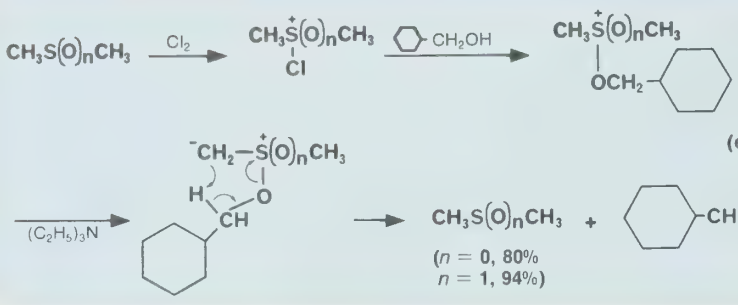


(eq. 19)

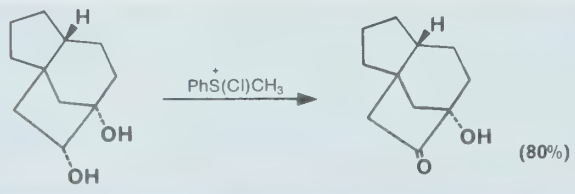
$C_{13}H_{27}CH_2OH \longrightarrow C_{13}H_{27}CHO$

System	Yield
DMSO, $(COCl)_2$	97%
DMSO, TFAA, *i*-Pr_2NEt	85%
DMSO, Py-SO_3	42%

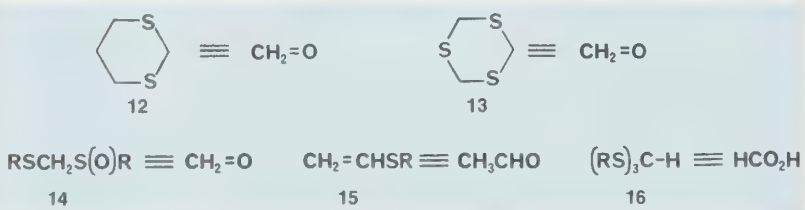
(eq. 20)

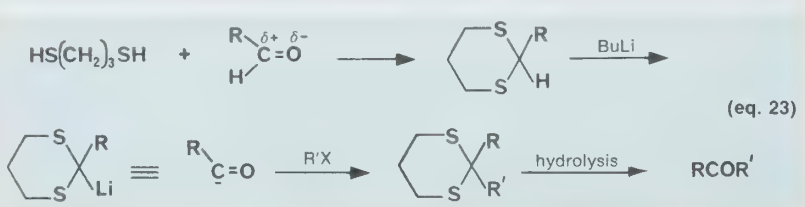


(eq. 21)



(eq. 22)





(eq. 23)

greater ease of hydrolysis to carbonyl compounds or greater availability of starting materials. One example of the use of a dithianyl reagent has already been given (eq. 5); other examples are the preparation of L-streptose (eq. 24),[29] alnusone dimethyl ether (eq. 25),[30] and the Δ^1-cannabinoid derivative **17** (eq. 26).[31] Examples of other nucleophilic acylating agents are given in eqs. 27[32] and 28.[33] Extensive reviews of nucleophilic acylation and *Umpolung* employing organosulfur reagents have been published.[34]

E / C - NH_2 from RCH - NH_2 / R

A method has recently been reported for the *Umpolung* of reactivity of amino carbons. As illustrated in eq. 29,[35] transformation of primary amines to *N*-sulfinylamines followed by treatment with base affords the equivalent of α-amino carbanions which may then be converted into α-alkylated amines.

ortho-Alkylation of aromatic amines can be realized through application of the Sommelet-Hauser rearrangement of ylides (a [2,3]-sigmatropic process) derived from azasulfonium salts as shown in eq. 30 and Scheme I.[36]

O - C - C_n - C = O from HO - C - C_n - COOH

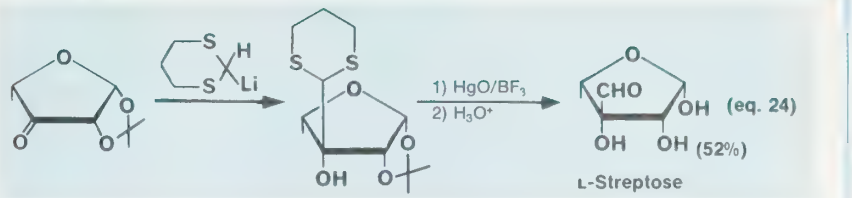
A valuable method for lactonization consists of the treatment of ω-hydroxy-*S*-2-pyridyl carbothioates with silver perchlorate as illustrated by the conversion of ricinoleic acid, **18**, to ricinoleic acid lactone, **19** (eq. 31).[37] An additional feature of this synthesis is the *cis* to *trans* isomerization of **18** through irradiation in the presence of diphenyl disulfide. The lactonization process is thought to be promoted by coordination of the silver ion.[38] In some instances, cyclization can be achieved without the silver salt although higher temperatures are required.[39]

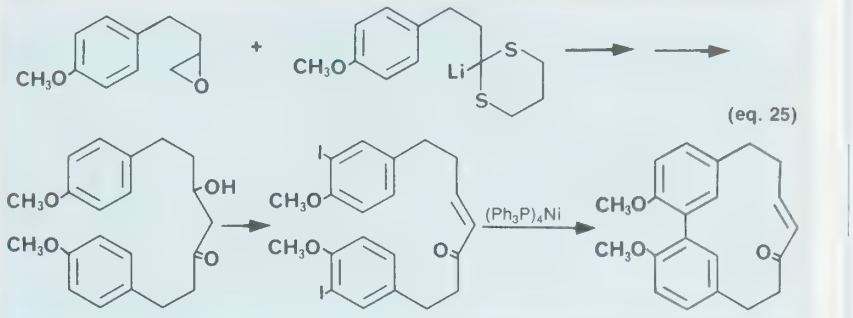
C - Hal from C - O

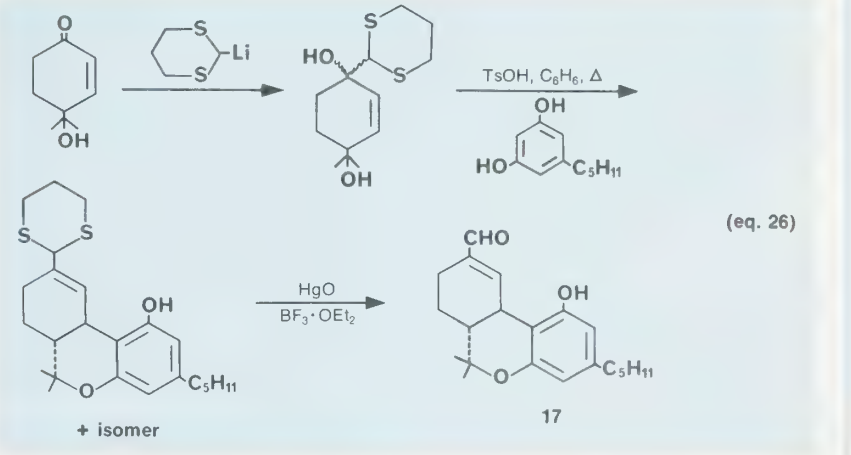
Allylic hydroxyl functions can be selectively replaced by chloride in the presence on nonallylic alcohol units. (eq. 32.).[40]

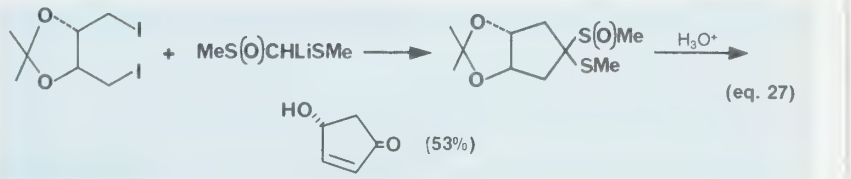
C - CH_2I from C - I

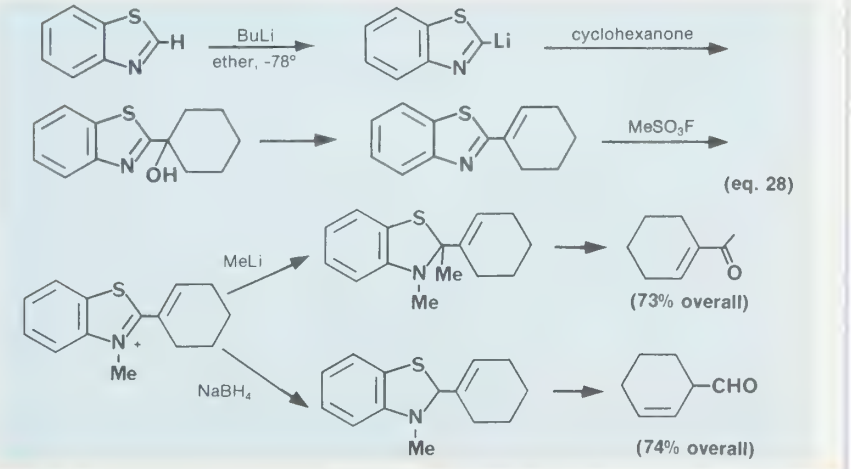
Polymeric phenylthiomethyllithium is a reusable reagent for homologation of alkyl iodides (eq. 33).[41]

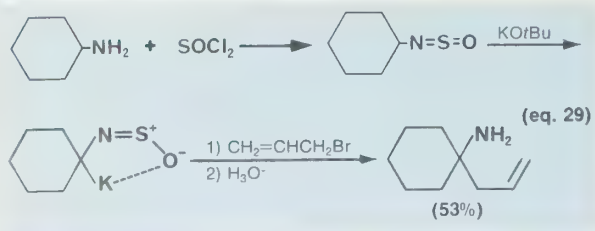


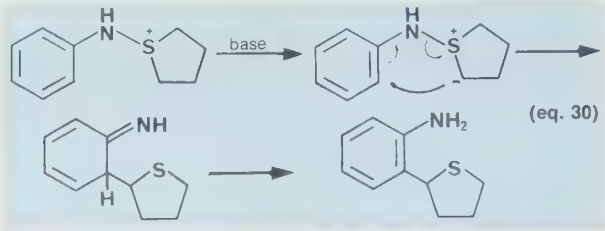




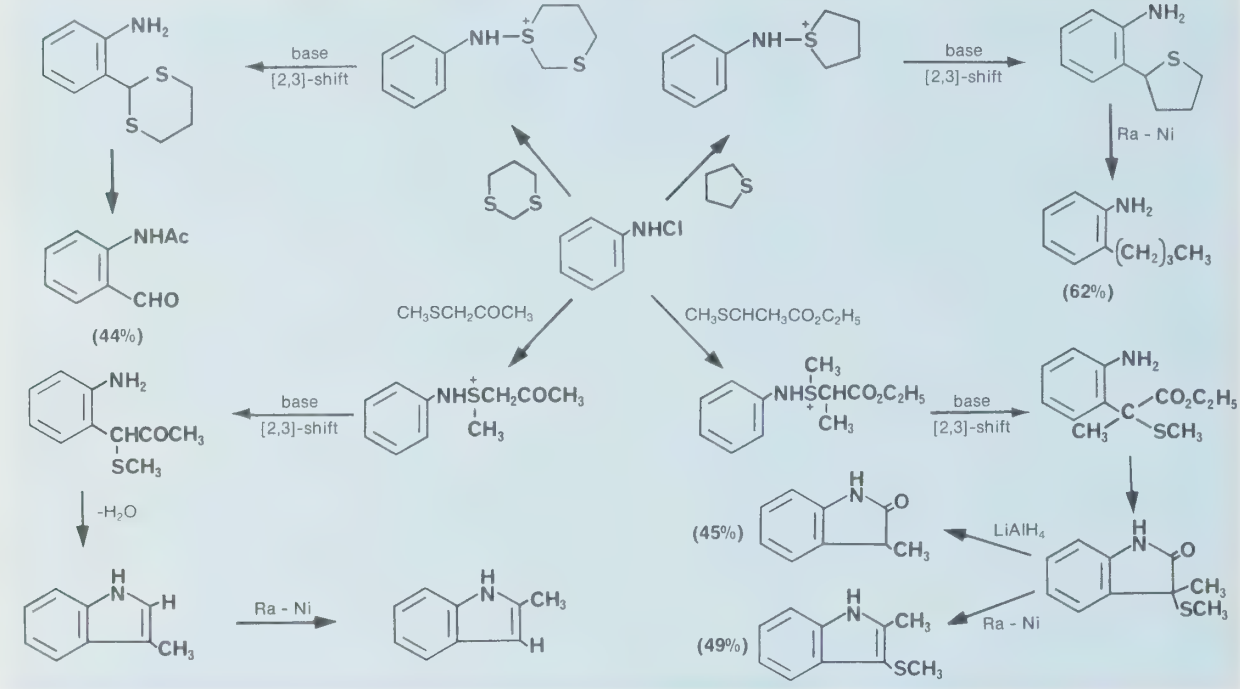


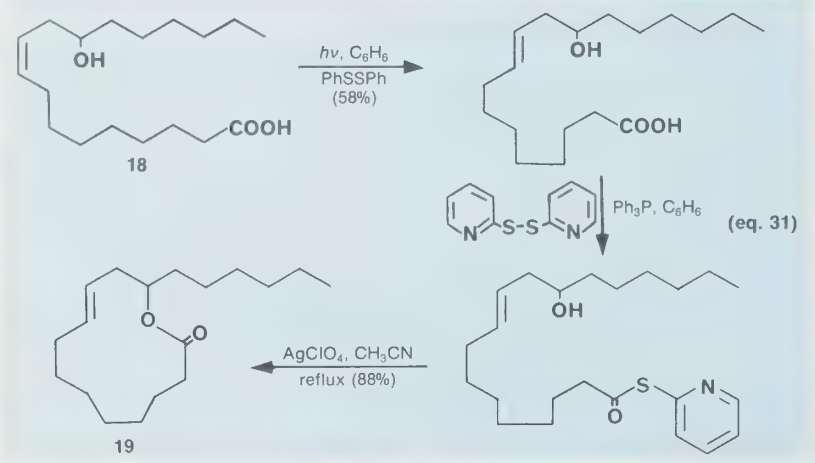


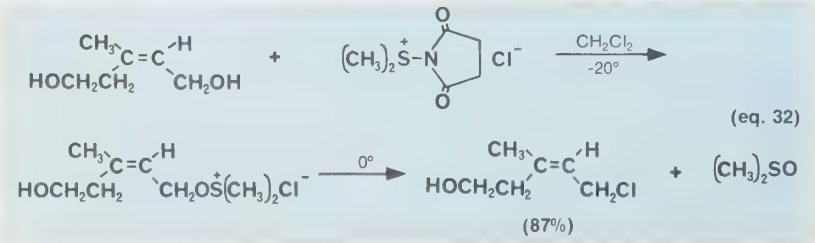




Scheme I. Azasulfonium Route to Substituted Anilines and N-Heterocycles







O⁻ from C - O

The high nucleophilicity of RS^- is exploited in the splitting of *O*-methyl bonds in esters (eq. 34)[42] and ethers (eq. 35).[43]

C - NH_2 from C - OH

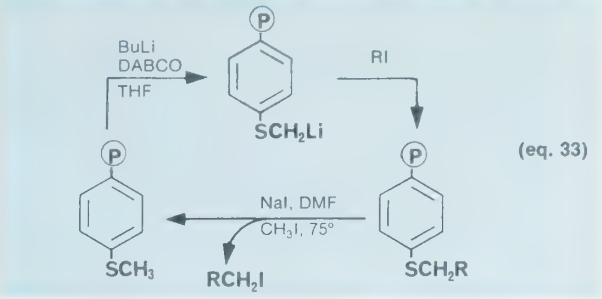
Lithium bisbenzenesulfenimide is employed in a variant of the Gabriel synthesis of primary amines. The N-S bonds are easily cleaved with acid (eq. 36).[44]

C - H from C - NH_2

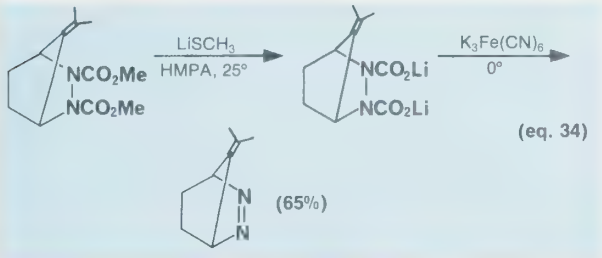
Reductive deamination of primary amines is achieved *via* borohydride reduction of *N,N*-disulfonamides (eq.37).[45]

C - H from C - OH

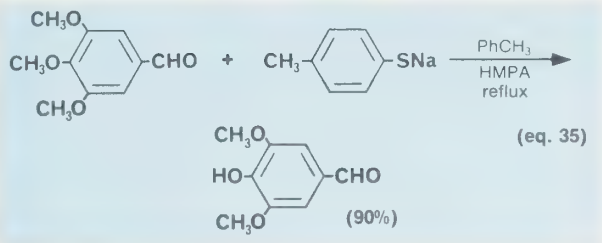
Barton has devised a new method for the replacement of a hydroxyl function by hydrogen involving conversion of the hydroxyl group to a xanthate ester followed by treatment with tributyltin hydride (eq. 38).[46a] Using tributyltin deuteride, stereoselective synthesis of certain deoxydeuterio systems is possible.[46b]



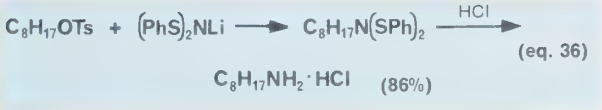
(eq. 33)



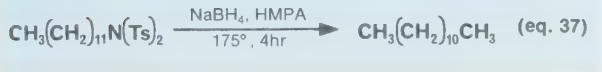
(eq. 34)



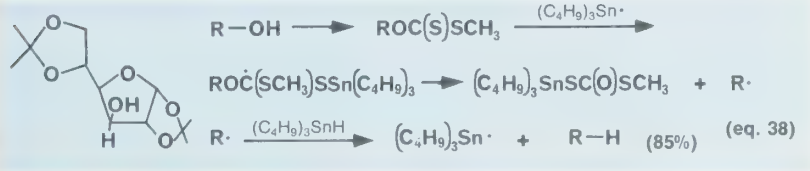
(eq. 35)



(eq. 36)



(eq. 37)



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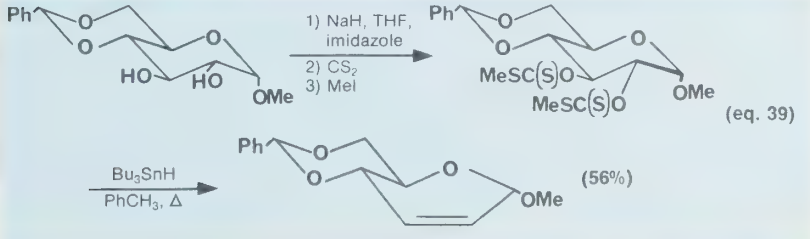
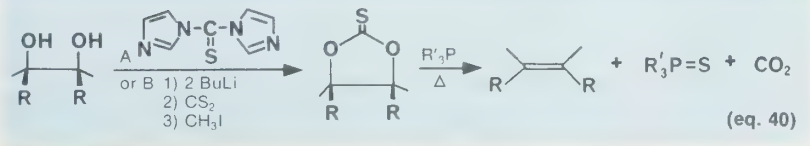


(eq. 39)



(eq. 40)

Table I. The Corey-Winter Olefin Synthesis

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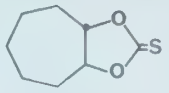
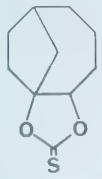
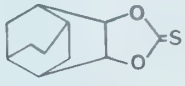
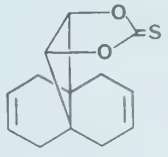
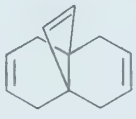
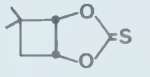
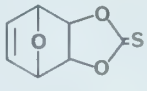
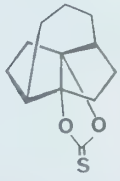
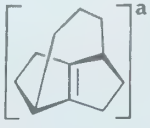
1		 [a]	—	48a
2		 [a]	62	48b
3			50	48c
4			54	48d
5			71	48e
6			60	48f
7		 [a]	85	48g

[a] As 2,5-diphenyl-3,4-isobenzofuran adduct

C = C from C(OH)C(OH)

A procedure related to that shown in eq. 38 enables the conversion of vicinal diols to olefins (eq. 39).[47] This same type of conversion can be accomplished stereospecifically through the Corey-Winter olefin synthesis which involves conversion of the diol to a cyclic thiocarbonate followed by heating with a tervalent phosphorus compound (eq. 40).[2] Applications of the Corey-Winter olefin synthesis are summarized in Table I.[2]

C = C from 2 C = O

Barton (and independently, Kellogg) has developed a "two-fold extrusion" approach to olefin synthesis which involves pyrolysis of Δ^3-1,3,4-thiadiazolines (available in good yields from ketones or thioketones as shown in eq. 41) in the presence of phosphines, reagents known to extrude sulfur from episulfides.[49] Applications of this reaction appear in Table II.

C = C from 2 C - X

The Ramberg-Bäcklund reaction, the sulfur analog of the Favorskii rearrangement, is general for molecules containing the structural elements of a sulfonyl group, an α-halogen (or other suitable leaving group), and at least one α′-hydrogen atom and, with few exceptions, enables the clean replacement of a sulfonyl group by a double bond (see eq. 42)[2,51] The required α-halogen atom may be introduced by treatment of the corresponding α-sulfonyl carbanion with a source of X^+ ($BrCN$, I_2 and Cl_3CSO_2Cl are convenient sources of Br^+, I^+, and Cl^+, respectively).[52] A particularly useful modification of the Ramberg-Bäcklund reaction has been developed by Meyers[53] whereby sulfones may be taken directly to olefin without the isolation of α-halosulfones (carbon tetrachloride serves as the halogen source). A variety of synthetic applications of the Ramberg-Bäcklund reaction and the Meyers modification of this reaction is listed in Table III (also see eq. 4). An additional related reaction sequence in which an episulfone is produced by oxidation of an α,α′-sulfonyl dicarbanion is shown in eq. 43.[55]

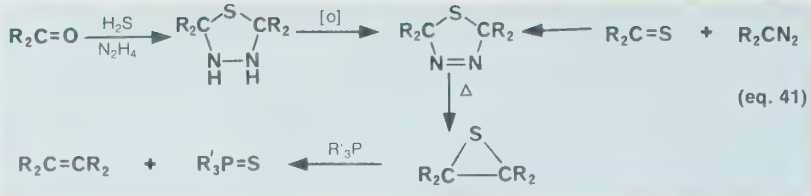
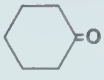
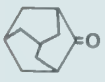
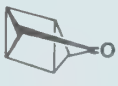
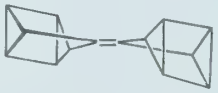
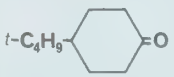
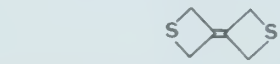
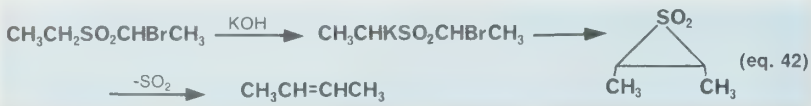
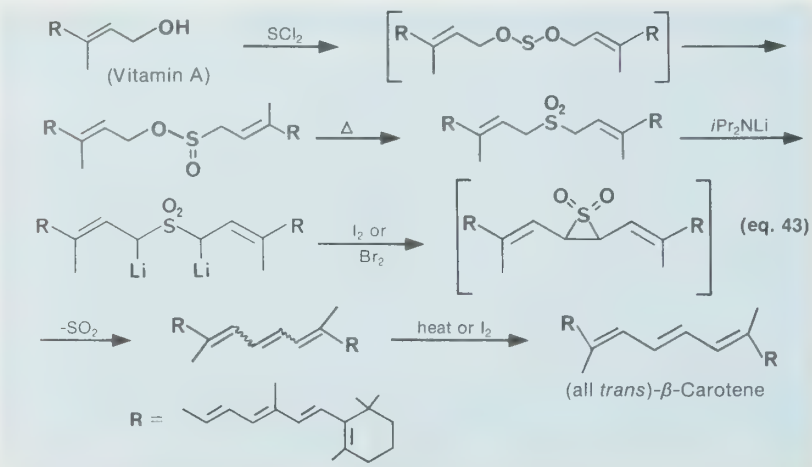


Table II. Olefin Synthesis *via* Two-fold Extrusion

Ketone (or thioketone)	Olefin product	Overall yield (%)	Reference
		42	49
		69	50a
		65	50b
		20	50c
$(t\text{-}C_4H_9)_2C{=}S$[a]	$(t\text{-}C_4H_9)_2C{=}CPh_2$	68	49
		90	50d
		50	50e

[a] Coreactant is diphenyldiazomethane.
[b] From *cis*-Δ³-1,3,4-thiadiazoline.





ACKNOWLEDGMENT

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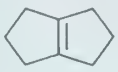
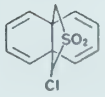
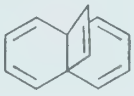
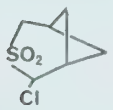
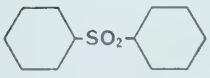
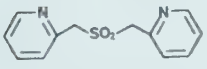
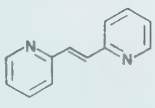
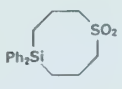
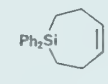
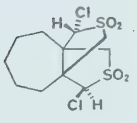
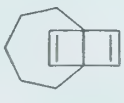
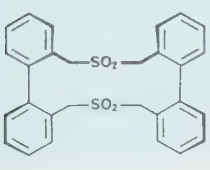
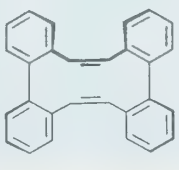
Table III. Some Synthetic Applications of the Ramberg-Bäcklund Reaction

Sulfone	Product	Yield (%)	Reference
		81	52
		14	54a
		68	54b
		32	53
		—	54c
		40	54d
		12	54e
		65	54f

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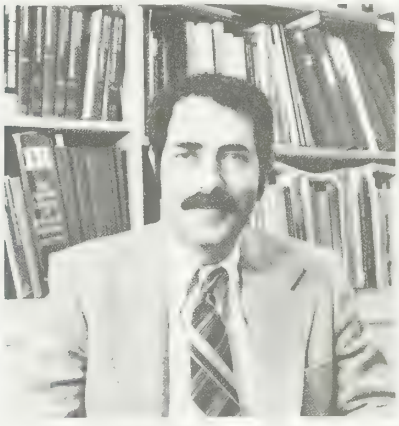

About the Author

Dr. Eric Block is Associate Professor of Chemistry at the University of Missouri-St. Louis. He received his B.S. degree from Queens College of the City University of New York (1962) and his M.S. (1965) and Ph.D. (1967) from Harvard University. He has served as visiting professor at the University of Illinois (summer 1973) and Harvard University (1974), and, under the NATO Research Grants Programme, at the University of Frankfurt (1978). Professor Block is a Reporter for the British Chemical Society's Specialist Periodical Reports on "Organic Compounds of Sulphur, Selenium, and Tellurium" and is the author of the recent monograph "Reactions of Organosulfur Compounds" (Academic Press, 1978) and over 30 other publications in the areas of organic sulfur chemistry, flash-vacuum pyrolysis, applications of microwave spectroscopy in organic chemistry, small-ring chemistry and mechanistic organic chemistry.

Aldrich offers these reagents cited by Professor Block:

14,304-9	Aldrithiol-2
10,133-8	Benzothiazole
17,550-1	Boron trifluoride etherate
18,617-1	*n*-Butyllithium, 1.6*M* solution in hexane
C6,270-0	*m*-Chloroperoxybenzoic acid
D2,780-2	1,4-Diazabicyclo[2.2.2]octane
12,591-1	α,α'-Dibromo-*m*-xylene
D4,480-4	α,α'-Dibromo-*p*-xylene
D12,580-6	*N,N*-Diisopropylethylamine
15,787-2	1,3-Dithiane
E2,740-8	Ethylene glycol dimethyl ether
13,923-8	Hexafluoroacetone sesquihydrate
H1,160-2	Hexamethylphosphoramide
20,794-2	Hydrazine hydrate
19,987-7	Lithium aluminum hydride
16,048-2	Magic Methyl® (methyl fluorosulfonate)
17,610-9	Mercuric acetate
17,895-0	Methanesulfonyl fluoride
18,620-1	Methyllithium-lithium bromide complex
17,795-4	Methyl methylsulfinylmethyl sulfide
O-880-1	Oxalyl chloride
15,667-1	Potassium *tert*-butoxide
20,801-9	Potassium ferricyanide
P5,060-9	1,3-Propanedithiol
19,807-2	Sodium borohydride
19,923-0	Sodium hydride
S755-6	Sulfur trioxide pyridine complex
T1,560-1	Tetrahydrothiophene
15,605-1	1,1′-Thiocarbonyldiimidazole
T7,970-7	Trimethyl phosphite
T8,048-9	Trimethylsulfonium iodide
T8,840-4	*s*-Trithiane

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Reactions of Organosulfur Compounds

by
Eric Block

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Boranes For Organic Reductions – A Forty-Year Odyssey[1]

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West Lafayette, Indiana 47907

I. INTRODUCTION

In 1939 there appeared a publication in the March issue of the *Journal of the American Chemical Society*, "Hydrides of Boron. XI. The Reaction of Diborane with Organic Compounds Containing a Carbonyl Group," by H.C. Brown, H.I. Schlesinger, and A.B. Burg.[2] This is the first report of the application of a hydride for the reduction of organic functional groups.

Forty years have elapsed since this original report. This observation initiated rapid progress in the development of new boron hydride reducing agents and in the exploration of their scope and applications in organic synthesis. These developments have revolutionized the procedures for the regio-, stereo-, and chemoselective reduction of various organic functional groups.[3,4] It appears appropriate at this time to summarize the progress of these forty years in the application of borane and borohydride reducing agents.

Before the discovery of hydrides as reducing agents for the reduction of organic functional groups, there were available a number of nonhydridic reduction procedures to achieve such transformations. Thus, the reduction of aldehydes to the corresponding alcohols was achieved by a variety of metal-acid (zinc dust + acetic acid, sodium amalgam + acetic acid, iron + acetic acid, etc.) procedures (eq. 1).[5]

$$CH_3(CH_2)_5CHO \xrightarrow[6hr,\ 100°]{Fe,\ HOAc} CH_3(CH_2)_5CH_2OH \quad 80\% \qquad \text{(eq. 1)}$$

The corresponding reduction of ketone to alcohol was achieved by sodium in ethanol or zinc-sodium hydroxide in ethanol.[6,7]

The discovery of the Meerwein-Ponndorf-Verley reduction introduced a more general, improved procedure for the reduction of aldehydes and ketones to the corresponding carbinols.[8-12] Similarly, the Bouveault-Blanc method enabled the reduction of carboxylic acid esters to the corresponding alcohols.[13]

The nonhydridic reduction procedures for the reduction of carbonyl groups often required elevated temperatures and long reaction times and resulted in low yields of the desired products. However, the discovery of boron hydride reducing agents has dramatically changed the situation, not only for the reduction of carbonyl groups, but for reduction of a wide variety of other organic functional groups.

II. THE DISCOVERY OF BORON HYDRIDES AS REDUCING AGENTS. HISTORICAL DEVELOPMENTS

In 1936 there was considerable discussion about the structure of borane-carbonyl, then recently synthesized by Professor H.I. Schlesinger and Dr. A.B. Burg at the University of Chicago (eq. 2).[14]

$$\tfrac{1}{2}\,(BH_3)_2 + CO \rightleftharpoons H_3B:CO \qquad \text{(eq. 2)}$$

It was suggested that the senior author, then a new graduate student at the University of Chicago, undertake a study of the reaction of diborane with aldehydes and ketones in the hope that the results would contribute to the better understanding of the structure of borane-carbonyl. Soon it was discovered that aldehydes and ketones react rapidly with diborane at 0° (or even at -78°); hydrolysis of the resulting dialkoxyborane yielded the corresponding alcohol (eqs. 3 and 4).[2]

$$2\,R_2CO + \tfrac{1}{2}\,(BH_3)_2 \longrightarrow (R_2CHO)_2BH \qquad \text{(eq. 3)}$$

$$(R_2CHO)_2BH + 3\,H_2O \longrightarrow 2\,R_2CHOH + H_2 + B(OH)_3 \qquad \text{(eq. 4)}$$

However, interest in this new development among organic chemists was minimal because diborane was a chemical rarity, available only in milligram quantities through complex preparative procedures.[15-17]

The situation was soon altered by pressures of World War II. The National Defense Agency was interested in new volatile uranium compounds with as low molecular weights as possible. Uranium(IV) borohydride appeared to be a suitable candidate in meeting these requirements. Accordingly, it was decided to undertake the preparation of uranium borohydride from aluminum borohydride.[18-20] Indeed, this was successful and the chemical proved to be volatile (eq. 5).[21]

$$UF_4 + 2\,Al(BH_4)_3 \longrightarrow U(BH_4)_4\uparrow + 2\,AlF_2(BH_4)\downarrow \quad \text{(eq. 5)}$$

This development led to the need for considerable quantities of uranium borohydride for large-scale testing.

The development of practical procedures for the synthesis of diborane (ingredient in the synthesis of aluminum borohydride) was stimulated by this requirement. Indeed, such routes to diborane[22] and lithium borohydride[23] were developed from lithium hydride and boron trifluoride. These intermediates could be readily utilized for the synthesis of uranium borohydride (eqs. 6-9).[24]

$$6\,LiH + 8\,BF_3:OEt_2 \xrightarrow{Et_2O} (BH_3)_2\uparrow + 6\,LiBF_4 \quad \text{(eq. 6)}$$

$$LiH + \tfrac{1}{2}\,(BH_3)_2 \xrightarrow{Et_2O} LiBH_4 \quad \text{(eq. 7)}$$

$$AlCl_3 + 3\,LiBH_4 \xrightarrow{\Delta} Al(BH_4)_3\uparrow + 3\,LiCl \quad \text{(eq. 8)}$$

$$UF_4 + 2\,Al(BH_4)_3 \longrightarrow U(BH_4)_4\uparrow + 2\,AlF_2(BH_4)\downarrow \quad \text{(eq. 9)}$$

Unfortunately, lithium hydride was in very short supply and could not be spared for the synthesis of uranium borohydride on a commercial scale. The supply of sodium hydride was ample.

Although sodium hydride could not be utilized in the same way, a new sodium hydride derivative, sodium trimethoxyborohydride,[25] solved the problem and achieved the desired transformations (eqs. 10-13).[22,23]

$$NaH + B(OCH_3)_3 \longrightarrow NaBH(OCH_3)_3 \quad \text{(eq. 10)}$$

$$6\,NaBH(OCH_3)_3 + 8\,BF_3:OEt_2 \longrightarrow (BH_3)_2\uparrow + 6\,B(OCH_3)_3\uparrow + 6\,NaBF_4 + 8\,Et_2O \quad \text{(eq. 11)}$$

$$NaBH(OCH_3)_3 + \tfrac{1}{2}\,(BH_3)_2 \longrightarrow NaBH_4 + B(OCH_3)_3 \quad \text{(eq. 12)}$$

$$AlCl_3 + 3\,NaBH_4 \longrightarrow Al(BH_4)_3\uparrow + 3\,NaCl \quad \text{(eq. 13)}$$

At this point (1943), the Signal Corps became interested in the new compound, sodium borohydride (eq. 12), for the field generation of hydrogen. Further research under their sponsorship led to an improved method for the synthesis of sodium borohydride, the basis of the present U.S. industrial process for this chemical (eq. 14).[26]

$$4\,NaH + B(OCH_3)_3 \xrightarrow{250^\circ} NaBH_4 + 3\,NaOCH_3 \quad \text{(eq. 14)}$$

The reaction provides a mixture of two solids, sodium borohydride and sodium methoxide. Acetone was among the solvents tested for the separation of these two components. With acetone, a vigorous reaction was observed. Hydrolysis of the reaction mixture indicated the absence of any active hydrogen and the presence of four moles of isopropyl alcohol per mole of sodium borohydride. In this way it was discovered that sodium borohydride was a valuable new reagent for the hydrogenation of organic molecules (eq. 15).

$$NaBH_4 + 4\,(CH_3)_2C{=}O \longrightarrow NaB[OCH(CH_3)_2]_4 \xrightarrow{H_2O} NaB(OH)_4 + 4\,(CH_3)_2CHOH \quad \text{(eq. 15)}$$

The alkali metal hydride route was later successfully extended to the synthesis of lithium aluminum hydride (eqs. 16-18).[27]

$$4\,LiH + AlCl_3 \xrightarrow{Et_2O} LiAlH_4 + 3\,LiCl \quad \text{(eq. 16)}$$

$$3\,LiAlH_4 + AlCl_3 \longrightarrow 4\,AlH_3 + 3\,LiCl \quad \text{(eq. 17)}$$

$$4\,AlH_3 + 4\,LiH \longrightarrow 4\,LiAlH_4 \quad \text{(eq. 18)}$$

III. MODIFICATION OF BOROHYDRIDES

The discovery of sodium borohydride[23] in 1942 and of lithium aluminum hydride[27] in 1945 brought about a revolutionary change in procedures for the reduction of functional groups in organic molecules.[4,28] Indeed, numerous major applications have appeared for both the reagents and more are still appearing. Lithium aluminum hydride is an exceptionally powerful reducing agent capable of reducing almost all organic functional groups.[29] Sodium borohydride is an exceptionally mild reducing agent, which readily reduces only aldehydes, ketones, and acid chlorides (Table 1). The mildness of sodium borohydride limits its applicability to selective reductions involving relatively reactive groups. Consequently, it appeared desirable to develop various boron hydride reagents with markedly different reactivities towards various organic functional groups, reagents possessing a high degree of selectivity. Accordingly, we undertook a program of research on "Selective Reductions" to explore these possibilities. The reducing characteristics of the parent hydride, sodium borohydride, could be modified by various means, such as varying the cation in the complex hydride, introduction of substituents (alkyl or alkoxy) in the complex ion that would exert marked steric and electronic influences upon the reactivity of the parent ion, etc. Yet another approach would be the development of acidic reducing agents such as borane and its substituted derivatives (alkylboranes, alkoxyboranes, haloboranes, etc.). In the following section we shall discuss the evolution of various new boron hydrides as selective reducing agents and their utility in organic synthetic transformations.

IV. EVOLUTION OF VARIOUS BORON HYDRIDE REAGENTS AND THEIR APPLICABILITY

1. Sodium borohydride

Sodium borohydride is a very mild reducing agent, insoluble in ethyl ether, only slightly soluble in tetrahydrofuran, but readily soluble in diglyme and triglyme.[30] In hydroxylic solvents, it reduces aldehydes and ketones rapidly at 25°, but is essentially inert to the other organic functional groups. The reductions can be carried out in aqueous solutions (basic), ethanol, or 2-propanol (eq. 19).

$$4\,R_2CO + NaBH_4 \longrightarrow Na[B(OCHR_2)_4] \xrightarrow{H_2O} NaB(OH)_4 + 4\,R_2CHOH \quad \text{(eq. 19)}$$

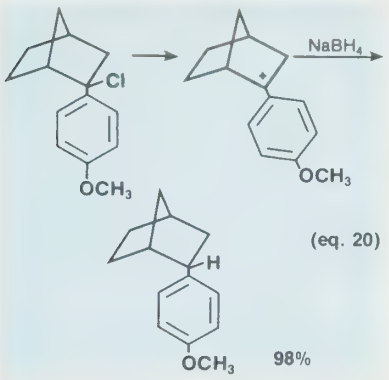
In aqueous solvents, sodium borohydride reacts with ionizable alkyl halides to

Table I. Comparison of sodium borohydride with lithium aluminum hydride

	$NaBH_4$ in EtOH	$LiAlH_4$ in THF
Aldehyde	+	+
Ketone	+	+
Acid chloride	R	+
Lactone	—	+
Epoxide	—	+
Ester	—	+
Acid	—	+
Acid salt	—	+
tert-Amide	—	+
Nitrile	—	+
Nitro	—	+
Olefin	—	—

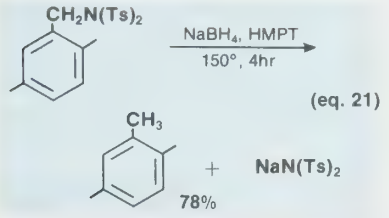
(+) = Rapid reaction
(—) = Insignificant reaction
R = Reaction with solvent

give the corresponding hydrocarbons, proceeding through the intermediacy of carbonium ions (eq. 20).[31]



(eq. 20)

Recently, sodium borohydride has been successfully employed for the reductive deamination of primary amines through their sulfonimide derivatives (eq. 21).[32]



(eq. 21)

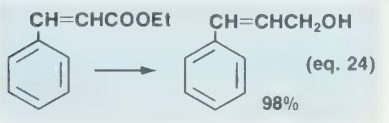
2. Lithium Borohydride

Preliminary exploratory studies on the reduction characteristics of lithium and sodium borohydrides indicated a marked difference in their reactivity.[33,34] Lithium borohydride is a more powerful reducing agent. The reagent can be synthesized conveniently *in situ* by the addition of an equivalent quantity of lithium halide to a solution of sodium borohydride in diglyme or monoglyme (reflux, eq. 22).

$$NaBH_4 + LiBr \longrightarrow LiBH_4 + NaBr\downarrow \quad \text{(eq. 22)}$$

Lithium borohydride reduces a number of representative esters to the corresponding carbinols quantitatively in 1-3 hr at 100° in diglyme.[35] Under these conditions, sodium borohydride alone brings only slight reduction of such esters (eqs. 23 and 24).

$$CH_3(CH_2)_{16}COOEt \xrightarrow[\text{diglyme, } 100°]{NaBH_4\text{-}LiBr} CH_3(CH_2)_{16}CH_2OH \quad 98\% \quad \text{(eq. 23)}$$

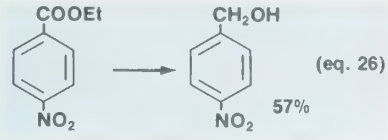


(eq. 24)

3. Borohydrides Containing Polyvalent Metal Ions

Ions of higher ionic potential would be expected to be even more effective. Thus, magnesium borohydride synthesized by the addition of an equivalent amount of solid magnesium chloride to a diglyme solution of sodium borohydride, brings about the facile reduction of esters (eqs. 25 and 26).[35]

$$CH_3(CH_2)_{16}COOEt \xrightarrow[\text{diglyme, } 100°]{NaBH_4\text{-}MgCl_2} CH_3(CH_2)_{16}CH_2OH \quad 74\% \quad \text{(eq. 25)}$$



(eq. 26)

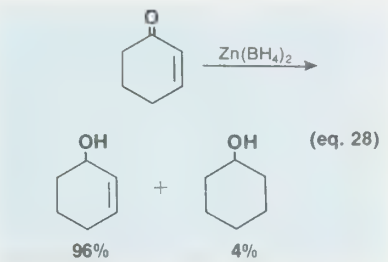
Kollonitsch and coworkers have achieved rapid reduction of esters by sodium borohydride in the presence of magnesium, calcium, barium and strontium salts.[36,37]

Aluminum borohydride is synthesized by the addition of one equivalent of aluminum chloride to three equivalents of sodium borohydride solution in diglyme. The reaction mixture remains clear; no precipitation of sodium chloride is observed, indicating an equilibrium[38] which must favor the reverse reaction (eq. 27).

$$AlCl_3 + 3\ NaBH_4 \rightleftharpoons Al(BH_4)_3 + 3\ NaCl \quad \text{(eq. 27)}$$

Nevertheless, the resulting solutions exhibit markedly enhanced reducing power approaching that of lithium aluminum hydride itself, capable of reducing lactone, epoxide, carboxylic acid, *tert*-amide, nitrile, etc. The mixture is capable of hydroborating olefins to the corresponding organoboranes.[38,39]

Zinc borohydride, synthesized from zinc chloride and sodium borohydride in ethyl ether, is useful for the selective reduction of α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols (eq. 28).[39]



(eq. 28)

4. Sodium and Potassium Triisopropoxyborohydrides

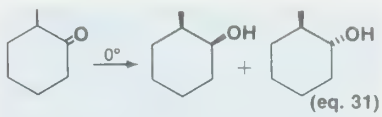
Sodium and potassium triisopropoxyborohydrides are synthesized from triisopropyl borate and sodium or potassium hydride (eqs. 29 and 30).[40,41]

$$NaH + (i\text{-}PrO)_3B \xrightarrow[170hr]{THF,\ 67°} Na(i\text{-}PrO)_3BH \quad \text{(eq. 29)}$$

$$KH + (i\text{-}PrO)_3B \xrightarrow[1hr]{THF,\ 25°} K(i\text{-}PrO)_3BH \quad \text{(eq. 30)}$$

Fortunately, unlike the less hindered derivatives[40] (such as sodium trimethoxyborohydride), triisopropoxyborohydride solutions in THF are quite stable and do not undergo disproportionation.

Potassium triisopropoxyborohydride in tetrahydrofuran behaves as an exceptionally mild reducing agent similar to sodium borohydride and lithium tri-*tert*-butoxyaluminohydride.[42] It reduces only aldehydes and ketones, being essentially inert to almost all other organic functional groups. In contrast to the other two mild reagents, the new reagent has the ability to introduce major steric control into the reduction of cyclic ketones (eq. 31).



(eq. 31)

$NaBH_4$	31%	69%
$Li(t\text{-}BuO)_3AlH$	27%	73%
$K(i\text{-}PrO)_3BH$	92%	8%

5. Alkali Metal Trialkylborohydrides[43]

In recent years, a number of alkali metal trialkylborohydrides have emerged as highly attractive reducing agents capable of achieving stereo- and regioselective synthetic transformations, unequalled by any other reagent currently available. These reagents are soluble in a variety of organic solvents (ethyl ether, tetrahydrofuran, diglyme, benzene, pentane, etc.) and are stable indefinitely when stored under nitrogen.

i) *Lithium Triethylborohydride (Super-Hydride®)*

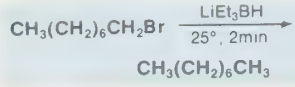
Lithium hydride reacts rapidly and quantitatively with triethylborane in refluxing tetrahydrofuran to give lithium triethylborohydride in quantitative yield. The corresponding deuterium derivative is synthesized from lithium deuteride (eqs. 32 and 33).[44]

$$LiH + Et_3B \xrightarrow[0.25hr]{THF,\ 65°} LiEt_3BH \quad 100\% \quad \text{(eq. 32)}$$

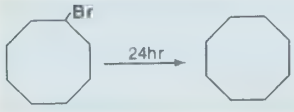
$$LiD + Et_3B \xrightarrow[1hr]{THF,\ 65°} LiEt_3BD \quad 100\% \quad \text{(eq. 33)}$$

Lithium triethylborohydride (Super-Hydride) is an extraordinarily powerful reducing agent, far more powerful than lithium aluminum hydride and lithium borohydride.[45] Lithium triethylborohydride is the most powerful nucleophile available to organic chemists, considerably more powerful than nucleophiles such as thiophenoxide.

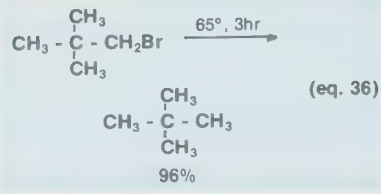
The reagent is exceptionally useful for the facile reductive dehalogenation of alkyl halides. The reaction involves a clean inversion at the reaction site (S_N2, eqs. 34-37).[45]



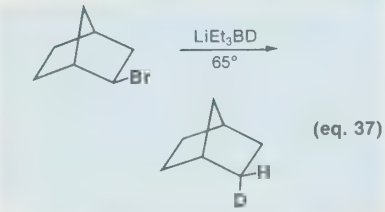
(eq. 34)



(eq. 35)

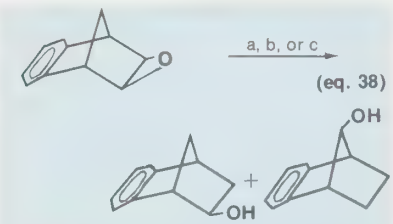


(eq. 36)



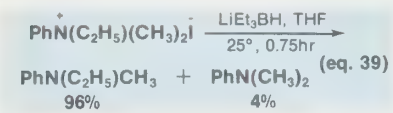
(eq. 37)

Lithium triethylborohydride reduces epoxides rapidly with remarkable regio- and stereospecificity to give the Markovnikov alcohol. The advantage is especially evident for the reduction of labile bicyclic epoxides (eq. 38).[46]



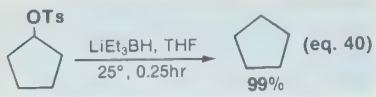
(eq. 38)

Super-Hydride reduces quaternary ammonium salts rapidly and cleanly to the corresponding amines in quantitative yield. The reagent is remarkable in discriminating between methyl and ethyl groups (eq. 39).[47]

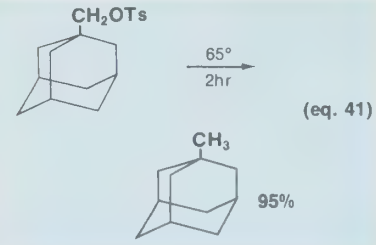


(eq. 39)

Super-Hydride provides an advantageous procedure for the deoxygenation of acyclic, cyclic and hindered alcohols through the reduction of their *p*-toluenesulfonate esters (eqs. 40 and 41).[48,49]

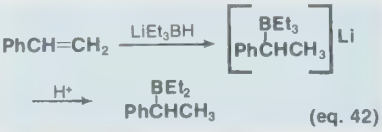


(eq. 40)



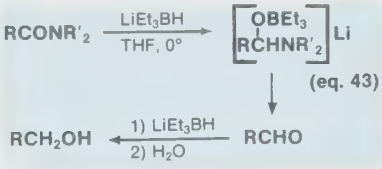
(eq. 41)

Lithium triethylborohydride adds to substituted styrenes providing a convenient entry into Markovnikov trialkylboranes (eq. 42).[50]



(eq. 42)

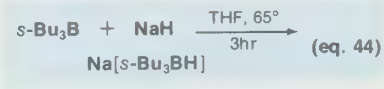
Reduction of tertiary amides with lithium triethylborohydride proceeds with carbon-nitrogen fission producing the corresponding alcohol (eq. 43).[51]



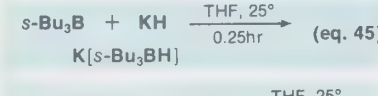
(eq. 43)

ii) *Lithium and Potassium Tri-sec-butylborohydrides (L- and K-Selectrides®)*

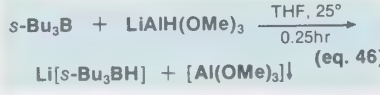
A number of methods have been developed for the quantitative synthesis of alkali metal trialkylborohydrides carrying hindered alkyl substituents (eqs. 44-47).[41,44,52-55]



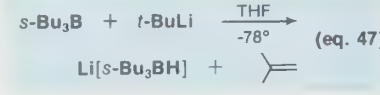
(eq. 44)



(eq. 45)

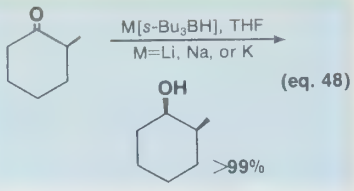


(eq. 46)

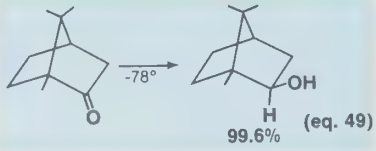


(eq. 47)

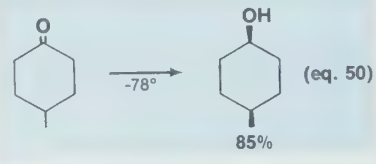
Aldehydes and ketones are reduced by alkali metal trialkylborohydrides rapidly and quantitatively to the corresponding alcohols even at -78°. One of the remarkable features of hindered trialkylborohydrides is their unusual ability to introduce major steric control into the reduction of cyclic ketones (eqs. 48-50).[56,57]



(eq. 48)

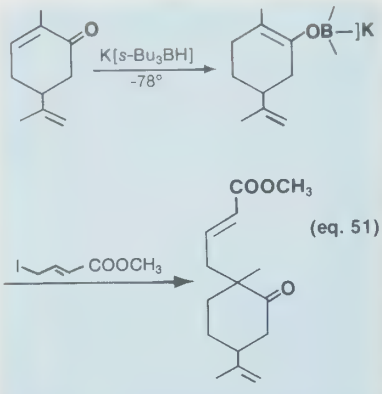


(eq. 49)



(eq. 50)

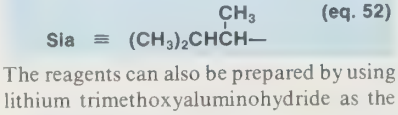
L- and K-Selectrides reduce α,β-enones and α,β-enoates in a conjugate fashion (1,4-reduction). This provides a convenient method for the generation of enolates which are trapped with a variety of electrophiles (eq. 51).[58,59]



(eq. 51)

iii) *Lithium and Potassium Trisiamylborohydrides (LS- and KS-Selectrides™)*

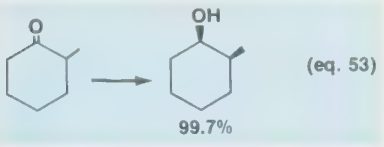
It was desirable to achieve the synthesis of a reagent that would reduce even 3- and 4-alkylcyclohexanones to the corresponding alcohols in a stereoselectivity of 99% or better. Recently, we have synthesized two highly hindered trialkylborohydrides — lithium tris(*trans*-2-methylcyclopentyl)-borohydride and lithium trisiamylborohydride — both of them containing secondary alkyl groups substituted by β-methyl (eq. 52).[60]



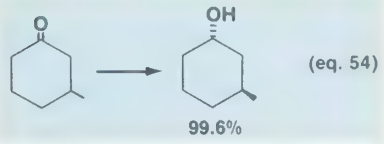
(eq. 52)

The reagents can also be prepared by using lithium trimethoxyaluminohydride as the hydride source.[55]

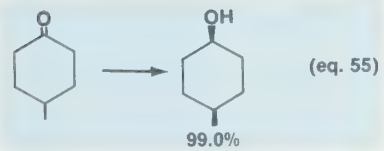
Lithium trisiamylborohydride reduces cyclic ketones with super stereoselectivity. Thus, 2-, 3-, and 4-alkylcyclohexanones are all reduced with lithium trisiamylborohydride at -78°C in ⩾99% stereoselectivity (eqs. 53-55).



(eq. 53)



(eq. 54)

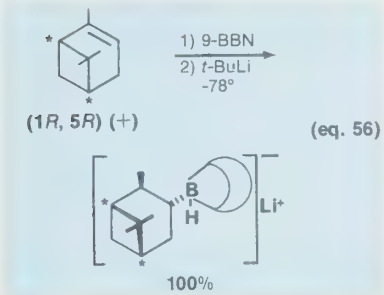


(eq. 55)

The corresponding potassium derivative synthesized recently by a catalytic process is equally effective.[61]

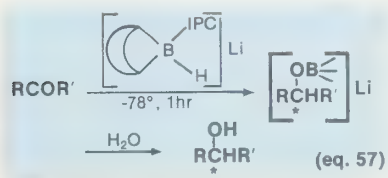
iv) *Lithium B-Isopinocampheyl-9-borabicyclo[3.3.1]nonyl Hydride. An Asymmetric Reducing Agent*[62]

A trialkylborohydride containing an asymmetric alkyl group, lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride, has been synthesized (eq. 56).



(eq. 56)

The reagent, prepared from (+)-α-pinene, rapidly and quantitatively reduces a wide variety of ketones to the corresponding alcohols. The alcohols produced are optically active (3-36% *e.e.*) and are consistently enriched in the *R* enantiomer (eq. 57).



(eq. 57)

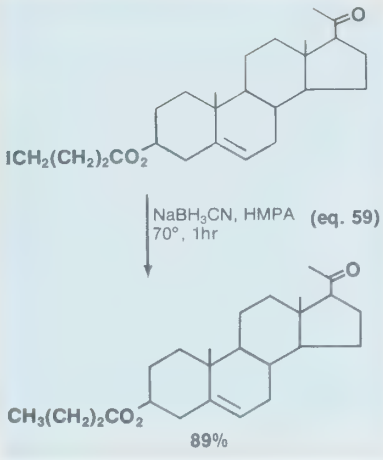
6. Sodium Cyanoborohydride

Sodium cyanoborohydride, synthesized from sodium borohydride and hydrogen cyanide, is a white crystalline solid, mp 240° (eq. 58).[63]

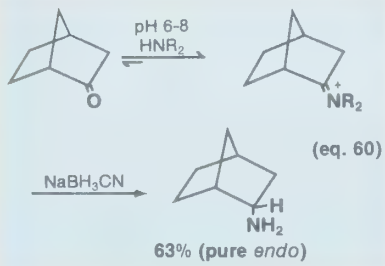
$$NaBH_4 + HCN \xrightarrow{THF} NaBH_3CN + H_2 \quad \text{(eq. 58)}$$

Unlike other hydride reagents, it is stable in acid solutions down to pH 3. It is soluble in tetrahydrofuran, methanol, water and in dipolar aprotic solvents (HMPA, DMF, sulfolane). It possesses a remarkable functional-group selectivity.

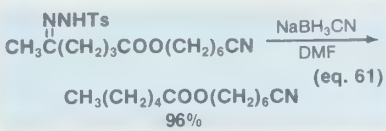
Sodium cyanoborohydride efficiently and selectively reduces alkyl halides to alkanes,[64] imines to amines,[65] and tosylhydrazones derived from aldehydes and ketones to the corresponding alkanes,[66] all in excellent yields (eqs. 59-61).



(eq. 59)



(eq. 60)



(eq. 61)

7. Borane

Reductions involving complex borohydrides and their substituted derivatives discussed in the earlier sections (1-6) appear to involve transfer of the hydride moiety from the complex anion to an electron-deficient center of the functional group. Consequently, these are called nucleophilic or basic reducing agents.

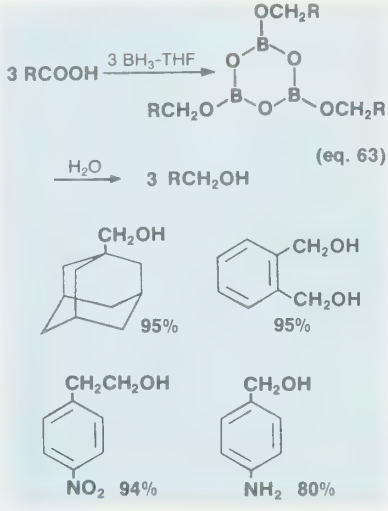
The reactions involving borane, a strong Lewis acid, are expected to involve a preferential electrophilic attack at the centers of highest electron density. Hence, it is an electrophilic or acidic reducing agent.

Diborane is sparingly soluble in ethyl ether and diglyme. It readily dissolves in tetrahydrofuran in which it exists as the borane-tetrahydrofuran addition compound. A standard solution of borane-THF in tetrahydrofuran can be prepared conveniently by treating sodium borohydride in diglyme with boron trifluoride etherate and passing the gas as generated into tetrahydrofuran (eq. 62).[67]

$$3\ NaBH_4 + 4\ BF_3 : OEt_2 \longrightarrow 2\ (BH_3)_2\uparrow + 3\ NaBF_4 \quad \text{(eq. 62)}$$

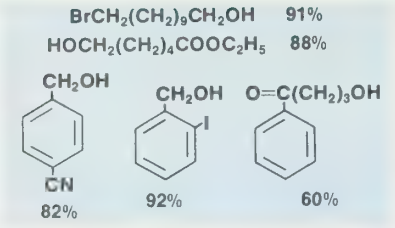
The exploration of the reducing characteristics of borane in THF has revealed a number of interesting features of this acidic reducing agent, quite different from those of the basic borohydride anion.[68-70]

Aliphatic and aromatic carboxylic acids are reduced rapidly and quantitatively to the corresponding alcohols by borane in tetrahydrofuran, either at 0° or 25° (or even at -78°). (In view of the usual inertness of carboxylic acids toward many reducing agents, this high reactivity toward borane must be considered exceptional.) The reaction is applicable to a variety of structures such as sterically hindered acids, di- and polycarboxylic acids, phenolic acids, amino acids, etc. (eq. 63).[71]

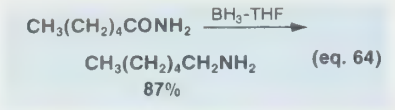


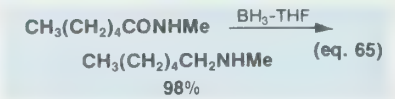
(eq. 63)

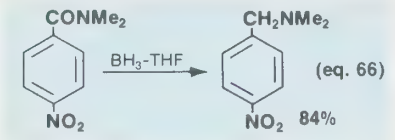
Borane-THF can tolerate a variety of functional groups and a number of functionalized alcohols have been prepared from the corresponding carboxylic acids in excellent isolated yields.



Another major application of borane-THF is the facile reduction of primary, secondary, and tertiary amides to the corresponding amines. Here again the reaction can tolerate many functional groups (eqs. 64-66).[72]



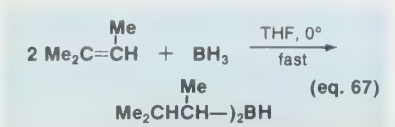


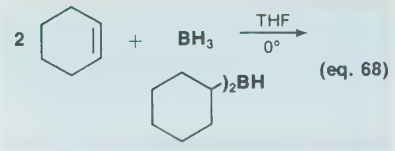


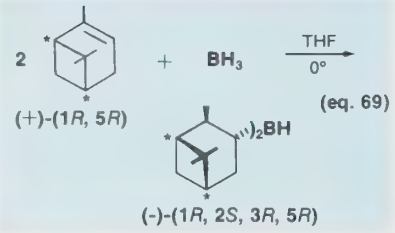
Until recently, the majority of borane reductions were carried out in tetrahydrofuran as the solvent. The recently introduced borane-methyl sulfide complex[73] has several advantages over borane-THF. It is exceptionally stable and is soluble in a variety of aprotic solvents such as ethyl ether, tetrahydrofuran, hexane, toluene, methylene chloride, diglyme, etc. Further, the reactivity of borane-methyl sulfide towards organic functional groups parallels that of borane-THF. Consequently, it is an advantageous reagent for the reduction of many organic functional groups.[74]

8. Dialkylboranes

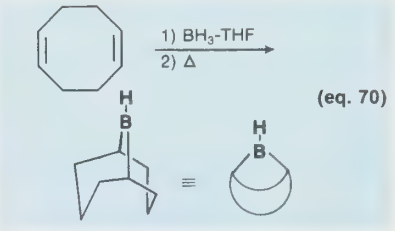
Hydroboration of certain hindered olefins or structurally suited dienes yields dialkylboranes preferentially. Thus, hydroboration of 2-methyl-2-butene rapidly forms the dialkylborane, disiamylborane (Sia_2BH).[75] The addition of the third mole of olefin is very sluggish. Similarly, dicyclohexylborane ($CHex_2BH$) and diisopinocampheylborane (IPC_2BH) (an asymmetric dialkylborane) can be prepared by the hydroboration of the corresponding olefins.[76] More recently, diisopinocampheylborane has been synthesized in very high purity (chemical as well as optical, eqs. 67-69).[77]



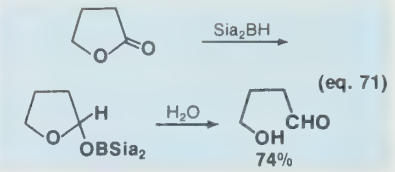




Cyclic hydroboration of 1,5-cyclooctadiene yields a bicyclic dialkylborane, 9-borabicyclo[3.3.1]nonane (9-BBN).[78] It exhibits certain unique physical and chemical characteristics. It is a white crystalline solid (mp 154-155°), thermally stable, relatively insensitive to air and soluble in a variety of organic solvents (eq. 70).

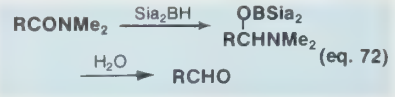


A systematic examination of the reducing characteristics of these dialkylboranes (disiamylborane and 9-BBN) towards representative organic functional groups has revealed a number of possible applications for these reagents in selective reductions.[79] One of the major applications of disiamylborane is the selective reduction of lactone to hydroxyaldehyde (eq. 71).[80]

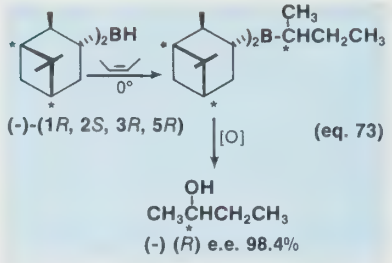


The reaction appears to be general. A number of interesting applications of this reagent for this type of transformation have been reported.[79a]

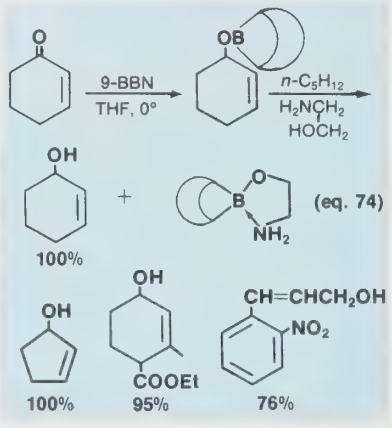
Preliminary investigations indicate that disiamylborane exhibits promise for the selective reduction of tertiary amides to the corresponding aldehydes (eq. 72).[79a]



Recently, diisopinocampheylborane of high optical purity has been examined for the asymmetric reduction of a representative series of alkyl methyl ketones. Asymmetric induction in the alcohol products in the range of 9 to 37% was observed.[81] Even more important, this new reagent achieves the asymmetric hydroboration of *cis*-2-butene to give, after oxidation, 2-butanol of optical purity as high as 98.4% (eq. 73).[77]



9-Borabicyclo[3.3.1]nonane reduces α,β-unsaturated aldehydes and ketones rapidly and quantitatively to the corresponding allylic alcohols. The development of a unique nonaqueous work-up procedure renders possible the isolation of the alcohols in excellent yields. Unlike conventional reagents, the mildness of 9-BBN permits the presence of almost any other functional group, such as ester, amide, carboxylic acid, nitro, halogen, and nitrile (eq. 74).[82]

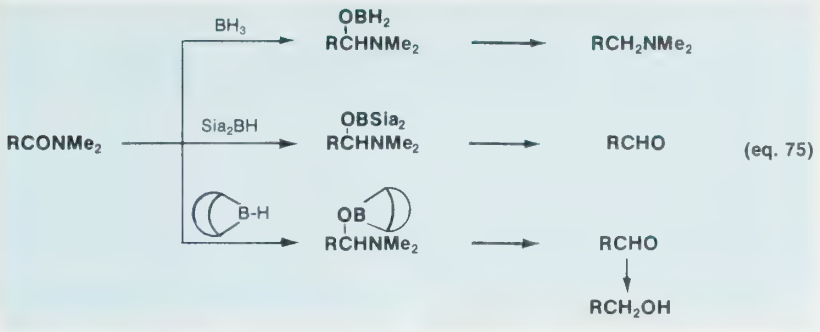


Reduction of tertiary amides to alcohols represents another promising area of application for 9-BBN yet to be explored in detail. It should be pointed out that we are now in a position to control the course of this reaction to get three different products by using various reagents (eq. 75).

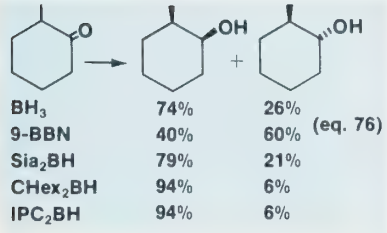
Dialkylboranes are consistent reagents for introducing steric control in the reduction of cyclic ketones. Increasing the size of the alkyl substituent(s) on boron enhances the stereoselectivity dramatically (eq. 76).[83]

9. Catecholborane and Chloroborane

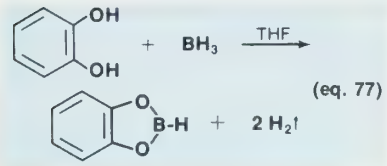
Several heterosubstituted boranes also exhibit valuable properties as reducing agents. Thus, catechol reacts with borane to produce a new useful reducing agent, catecholborane (CB) (eq. 77).[84,85]



(eq. 75)

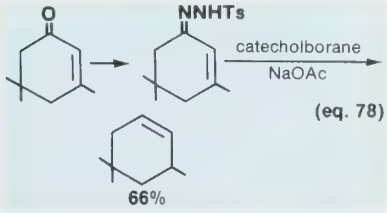


BH_3	74%	26%	(eq. 76)
9-BBN	40%	60%	
Sia_2BH	79%	21%	
$CHex_2BH$	94%	6%	
IPC_2BH	94%	6%	



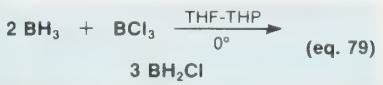
(eq. 77)

The reducing characteristics of this new reagent have been explored in detail.[86] The reagent is quite useful for the deoxygenation of α,β-unsaturated aldehydes and ketones through the reduction of their tosylhydrazones (eq. 78).[87]

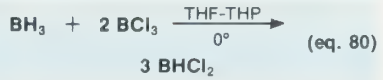


(eq. 78)

Procedures have been developed for the convenient synthesis of mono- and dichloroboranes (eqs. 79 and 80).[88]

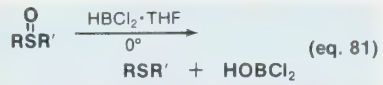


(eq. 79)



(eq. 80)

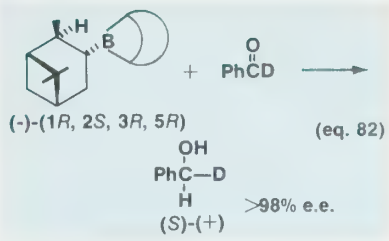
Aliphatic sulfoxides are rapidly deoxygenated to the corresponding sulfides in excellent yields by dichloroborane in tetrahydrofuran at 0° in a matter of minutes. The reaction can tolerate a variety of other reactive functional groups such as ketone, ester and amide (eq. 81).[89]



(eq. 81)

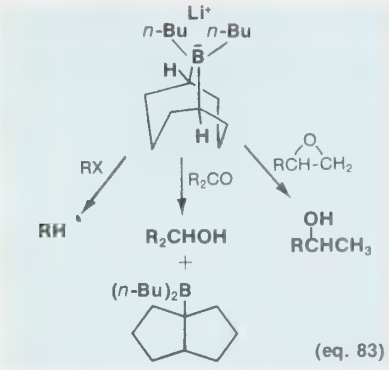
10. Trialkylboranes and "Ate" Complexes

Recently, certain trialkylboranes have been found to be effective reagents for the reduction of aldehydes to the corresponding alcohols. Especially interesting is the asymmetric reduction of benzaldehyde-α-*d* to benzyl-α-*d* alcohol by chiral *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (eq. 82).[90]



(eq. 82)

Certain "ate" complexes derived from *B*-alkyl-9-BBN derivatives, such as lithium di-*n*-butyl-9-borabicyclo[3.3.1]nonane "ate" complex, have been discovered to be efficient reducing agents (eq. 83).[91]



(eq. 83)

V. SUMMARY

The systematic exploration of the reducing characteristics of various hydride reagents that have evolved during the course of forty years (1939-1979) has led to better understanding and appreciation of the scope and applicability of each reagent. The reactivities of hydride reagents toward various organic functional groups at 0-25° under standard conditions are summarized in Table 2. Symbol (+) indicates rapid reaction; symbol (-) indicates very slow or insignificant reaction; symbol (±) indicates a borderline case, the reactivity being sen-

Table II. Summary of behavior of various functional groups toward the hydride reagents

	$NaBH_4$ in ethanol	$Li(O\text{-}t\text{-}Bu)_3AlH$	$NaBH_4+LiCl$ in diglyme	$NaBH_4+AlCl_3$ in diglyme	BH_3 in THF	Sia_2BH in THF	9-BBN in THF	AlH_3 in THF	$Li(OMe)_3AlH$ in THF	$LiAlH_4$ in THF	$LiEt_3BH$ in THF
Aldehyde	+	+	+	+	+	+	+	+	+	+	+
Ketone	+	+	+	+	+	+	+	+	+	+	+
Acid chloride	R	+	+	+	—	—	+	+	+	+	+
Lactone	—	±	+	+	+	+	+	+	+	+	+
Epoxide	—	±	+	+	+	±	±	+	+	+	+
Ester	—	±	+	+	±	—	±	+	+	+	+
Acid	—	—	—	+	+	—	±	+	+	+	—
Acid salt	—	—	—	—	—	—	—	+	+	+	—
tert-Amide	—	—	—	—	+	+	+	+	+	+	+
Nitrile	—	—	—	—	+	—	±	+	+	+	+
Nitro	—	—	—	—	—	—	—	—	+	+	+
Olefin	—	—	—	—	+	+	+	—	—	—	—

R = Reacts with solvent; reduced in nonhydroxylic solvent

sitive to the structure of the functional group (both steric and electronic effects). A quick inspection of Table 2 reveals that by judicious choice of reducing agent it should be possible to reduce one group selectively in the presence of a second or to carry out the reverse operation. A word of caution is in order. The reactivities of the various functional groups can be greatly altered by the structures containing them. Consequently, these generalizations must be used with caution in predicting the behavior of greatly modified systems.

VI. CONCLUSIONS

Forty years ago it was first discovered that diborane reduces aldehydes and ketones rapidly. Unfortunately, the chemical rarity of diborane at the time prevented organic chemists from utilizing this reagent as a reducing agent. Subsequently, the development of practical synthetic routes to diborane, the discovery of sodium borohydride and, later, lithium aluminum hydride made such hydride reducing agents readily available. There then resulted rapid progress in the development of new reducing agents and in the exploration of their scope and applicability in organic synthesis. Still, we are in constant search of new selective reducing agents that are capable of reacting with a specific functional group. Today an organic chemist has a choice of specific hydride reagents for achieving specific synthetic transformations. Even more important, the majority of these reagents are now commercially available to facilitate their application by chemists.[92]

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$$AlCl_3 + NaBH_4 \underset{\text{diglyme}}{\rightleftharpoons} NaCl_3Al \cdot BH_4$$

$$NaCl_3Al \cdot BH_4 + NaBH_4 \rightarrow NaAlCl_3H + NaB_2H_7$$

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92) Available from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin 53233

Aldrich offers these reagents cited by Professor Brown and Dr. Krishnamurthy:

20,691-1 Aluminum chloride, anhydrous

15,107-6 9-BBN, 0.5*M* solution in THF

17,619-2 Borane-tetrahydrofuran complex, 1*M* solution in THF

17,550-1 Boron trifluoride etherate

18,891-3 Catecholborane

18,525-6 Disiamylborane Preparation Kit, (1 mole)

E2,740-8 Ethylene glycol dimethyl ether (monoglyme)

18,014-9 K-Selectride®, 0.5*M* solution in THF

20,934-1 KS-Selectride™, 0.5*M* solution in THF

19,987-7 Lithium aluminum hydride

20,104-9 Lithium hydride

L290-4 Lithium tri-*tert*-butoxyaluminohydride

17,849-7 L-Selectride®, 1*M* solution in THF

M1,410-2 2-Methoxyethyl ether (diglyme)

P4,568-0 (+)-α-Pinene $[\alpha]^{22}$ +47.1°

19,789-0 Potassium triisopropoxyborohydride, 1*M* solution in THF

19,807-2 Sodium borohydride

20,097-2 Sodium borohydride, 0.5*M* solution in diglyme

15,615-9 Sodium cyanoborohydride

19,923-0 Sodium hydride, 50% dispersion in mineral oil

18,086-6 Super-Deuteride®, 1*M* solution in THF

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T5,980-3 Triethylene glycol dimethyl ether (triglyme)

19,733-5 Triisopropyl borate

T7565-5 Trimethyl borate

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Trialkylborohydrides in Organometallic Syntheses

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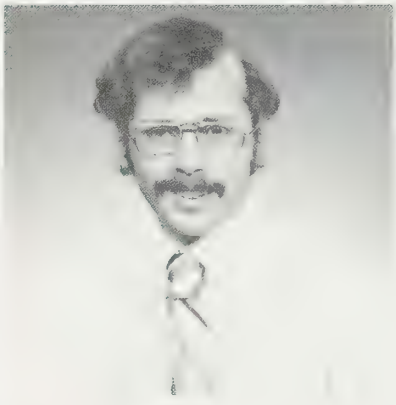


Trialkylborohydrides have been well established as potent hydride donors toward a variety of organic electrophiles.[1] Lithium triethylborohydride (Super-Hydride®) has been shown to be an exceptionally clean reagent for the reductive displacement of alkyl halides[2] and tosylates[3] and reductive ring opening of epoxides.[4] Hindered trialkylborohydrides such as lithium trisiamylborohydride (siamyl = 3-methyl-2-butyl) can reduce ketones such as 3-methylcyclohexanone with ≥99.6% stereoselectivity.[5] Other applications include the use of K(*sec*-$C_4H_9)_3BH$ (K-Selectride®) for the 1,4-reduction of enones[6] and chiral trialkylborohydrides for executing asymmetric reductions.[7]

A somewhat different line of research involving trialkylborohydride reagents has been under investigation in our laboratory. We have been interested in their reactivity toward inorganic and organometallic electrophiles. With substrates containing metal-metal or heteroatom-heteroatom bonds, rapid and high-yield cleavage to two nucleophilic anionic species occurs in many cases. Since transition metal anions, main-group metal anions, and metalloid anions are key intermediates in organometallic syntheses, our studies impact upon a broad front of synthetic chemistry.

It was our interest in nucleophilic attack upon coordinated CO that first led us to study the reactions of trialkylborohydrides with metal carbonyl complexes. A variety of reactions had been observed previously between $NaBH_4$ and metal carbonyl complexes.[8] We thought that a hydride source which was soluble in organic solvents and contained only one transferable hydride per mole would yield better defined chemistry.

One of the first useful reactions observed was the cleavage of metal carbonyl dimers to metal carbonyl anions (eqs. 1-4).[9,10] Transition metal anions play a pivotal role in the construction of metal-carbon and metal-metal bonds. They are highly nucleophilic species which may be readily alkylated, acylated, or metalated by reaction with an appropriate electrophile.

Conventionally, 1% Na/Hg amalgam or other heterogeneous metal reductants have been employed for the conversion of metal carbonyl dimers to metal carbonyl anions.[11] The problems involved are mainly ones of manipulation and handling. When Na/Hg is utilized, mercury-containing by-products are sometimes produced.[12] The use of $Li(C_2H_5)_3BH$, however, enables the rapid, room-temperature, one-flask synthesis of anions $Li[Co(CO)_4]$, $Li[(C_5H_5)Mo(CO)_3]$, and $Li[Mn(CO)_5]$ in near-quantitative yield under homogeneous conditions. Only the volatile by-products H_2 and $(C_2H_5)_3B$ are produced (eqs. 1-3).

Many elegant and useful synthetic transformations utilizing organometallics prepared from $[(C_5H_5)Fe(CO)_2]^-$ have been described in the literature.[13] The generation of $Li[(C_5H_5)Fe(CO)_2]$ *via* $Li(C_2H_5)_3BH$ or Li(*sec*-$C_4H_9)_3BH$ (L-Selectride®), however, requires longer reaction times (2hr) and ≥50% HMPA cosolvent (eq. 4). This is likely a consequence of the higher reduction potential of $[(C_5H_5)Fe(CO)_2]_2$ relative to the other metal carbonyl dimers. However, potassium trialkylborohydrides are stronger hydride donors, and K(*sec*-$C_4H_9)_3BH$ and $K(C_2H_5)_3BH$ were found to effect the synthesis of $K[(C_5H_5)Fe(CO)_2]$ in THF (eq. 5). Reaction times were 3hr at room temperature or 0.5hr at 45-65°C.

$$(CO)_4Co\text{-}Co(CO)_4 + 2\,Li(C_2H_5)_3BH \longrightarrow 2\,Li[Co(CO)_4] + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 1)}$$

$$(CO)_5Mn\text{-}Mn(CO)_5 + 2\,Li(C_2H_5)_3BH \longrightarrow 2\,Li[Mn(CO)_5] + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 2)}$$

$$(C_5H_5)(CO)_3Mo\text{-}Mo(CO)_3(C_5H_5) + 2\,Li(C_2H_5)_3BH \longrightarrow 2\,Li[(C_5H_5)Mo(CO)_3] + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 3)}$$

$$(C_5H_5)(CO)_2Fe\text{-}Fe(CO)_2(C_5H_5) + 2\,Li(C_2H_5)_3BH \xrightarrow{HMPA} 2\,Li[(C_5H_5)Fe(CO)_2] + 2\,(C_2H_5)_3B + H_2 \qquad \text{(eq. 4)}$$

$$(C_5H_5)(CO)_2Fe\text{-}Fe(CO)_2(C_5H_5) + 2\,K(sec\text{-}C_4H_9)_3BH \xrightarrow{3hr} 2\,K[(C_5H_5)Fe(CO)_2] + 2\,(sec\text{-}C_4H_9)_3B + H_2 \qquad \text{(eq. 5)}$$

Potassium salts of other metal carbonyl anions, (*e.g.*, $K[(C_5H_5)Mo(CO)_3]$, $K[Mn(CO)_5]$; eqs. 6 and 7) can also be prepared with $K(sec\text{-}C_4H_9)_3BH$ and $K(C_2H_5)_3BH$. Sodium trialkylborohydrides are readily synthesized[14] and can be used similarly. Thus, transition metal anions can be prepared with a number of different counter-ions by the trialkylborohydride method. Triethylborohydrides are preferable to tri-*sec*-butylborohydrides because of the greater volatility of the borane by-product.

To demonstrate the preparative utility of these metal anion solutions, we have synthesized a number of derivatives.[9,10] These are compiled in Table I; full experimental details have been published.[10] Entries 1 and 10 depict the actual isolation of two anions as their air-stable "PPN⁺", or $[(C_6H_5)_3P]_2N^+$, salts. Acylation reactions are illustrated in entries 4,5,7,9,13, and 14. Alkylation reactions and the formation of tin and silicon derivatives are also tabulated. Isolated yields are uniformly good.

We have investigated the *in situ* preparation of other metal carbonyl anion derivatives. Protonation of $Li[Mn(CO)_5]$ and $Li[(C_5H_5)Mo(CO)_3]$ with the nonaqueous, nonoxidizing acid CF_3SO_3H affords quantitative spectroscopic yields of $H[Mn(CO)_5]$ and $H[(C_5H_5)Mo(CO)_3]$, respectively (eqs. 8 and 9).[15]

Transition metal hydrides are key intermediates in numerous stoichiometric and catalytic reactions, and have been the object of a variety of structural, spectroscopic, and theoretical studies.[8] Since the conventional preparation of anhydrous $H[Mn(CO)_5]$ requires extensive vacuum-line manipulations,[16] our *in situ* synthesis offers obvious advantages. We have used it to study several $H[Mn(CO)_5]$ reactions.[15]

Trialkylborohydrides also enable the preparation of metal carbonyl anions from other organometallic precursors.[10] Eqs. 10 and 11 provide two such examples.

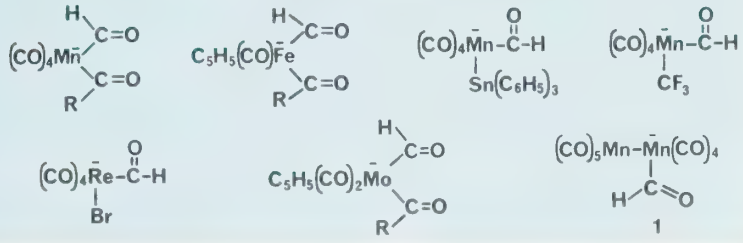
We anticipate that such reactions may prove of occasional synthetic utility. For instance, $[Mn(CO)_5]Br$ undergoes much more rapid exchange with ^{13}CO than $[Mn(CO)_5]_2$. Thus, the preparation of ^{13}CO-labeled $[Mn(CO)_5]R$ species would be most readily accomplished *via* initial conversion of $[Mn(CO)_5]_2$ to $[Mn(CO)_5]Br$. After ^{13}CO exchange, the desired product could be obtained in a one-flask operation from labeled $[Mn(CO)_5]Br$.

A major focus of research in our laboratory has been the preparation and characterization of reactive ligand types believed to be present on the reaction coordinate between CO/H_2 and alkanes and alcohols in Fischer-Tropsch-type processes.[17] There has been a great deal of attention focused upon formyl ligands as the probable initially formed catalyst-bound species.[17]

Trialkylborohydrides provide an excellent means of generating anionic formyl complexes according to the generalized eq. 12. Because most anionic formyl complexes rapidly decompose at room temperature, reactions must be carried out below 0°C and the products characterized by low temperature spectroscopy. Figure 1 illustrates the variety of unstable metal formyl complexes prepared by this method.[18-20] Not surprisingly, we believe anionic formyl complexes are intermediates in many of our metal carbonyl anion syntheses. Species **1** is formed in 99% yield when $[Mn(CO)_5]_2$ is treated with one equivalent of $Li(C_2H_5)_3BH$ at -20°C; warming to room temperature and the addition of a second equivalent of $Li(C_2H_5)_3BH$ affords two equivalents of $Li[Mn(CO)_5]$ quantitatively.[9]

Figure 1

UNSTABLE ANIONIC FORMYL COMPLEXES PREPARED WITH $Li(C_2H_5)_3BH$



1

The metal carbonyl dimer $[Re(CO)_5]_2$ did not cleave upon reaction with $Li(C_2H_5)_3BH$. Instead, a thermally stable binuclear rhenium formyl complex was obtained, which proved *isolable* (eq. 13).[21] Rhenium is known to form stronger metal-metal and metal-ligand bonds than manganese.

Anionic formyl complexes can undergo further reduction by trialkylborohydrides. Organic products, presumably derived from the formyl ligand, include formaldehyde and methanol.[21] When $Fe(CO)_5$ was treated with 2 equivalents of $K(sec\text{-}C_4H_9)_3BH$, the formyl complex $K[(CO)_4Fe(COH)]$ (**2**) was rapidly formed;[22] refluxing the reaction mixture for 3hr in THF afforded $K_2[Fe(CO)_4]$ in quantitative yield as an analytically pure precipitate (eq. 14).[23] The highly nucleophilic tetracarbonylferrate dianion, $[Fe(CO)_4]^=$ has been proven to be of considerable value in organic and inorganic syntheses.[11,24] A number of useful organic transformations employing $Na_2[Fe(CO)_4]$ or $Na_2[Fe(CO)_4]$·dioxane have been developed by Collman and coworkers.[24] Although $K_2[Fe(CO)_4]$ has not been as extensively utilized, its preparation is distinctly easier and it is not pyrophoric. To provide additional characterization, we carried out the homologation reaction depicted in eq. 15 and the derivatization with $AuCl[P(C_6H_5)_3]$ depicted in eq. 16.[23]

Trialkylborohydrides may prove useful in the synthesis of other transition metal dianions. Following an initial report by Shore,[25] we were able to prepare the cluster dianion $K_2[H_2Ru_4(CO)_{12}]$ according to eq.

$$(C_5H_5)(CO)_3Mo\text{-}Mo(CO)_3(C_5H_5) + 2\,K(sec\text{-}C_4H_9)_3BH \longrightarrow 2\,K[(C_5H_5)Mo(CO)_3] + 2\,(sec\text{-}C_4H_9)_3B + H_2 \quad \text{(eq. 6)}$$

$$(CO)_5Mn\text{-}Mn(CO)_5 + 2\,K(sec\text{-}C_4H_9)_3BH \longrightarrow 2\,K[Mn(CO)_5] + 2\,(sec\text{-}C_4H_9)_3B + H_2 \quad \text{(eq. 7)}$$

$$Li[Mn(CO)_5] + CF_3SO_3H \longrightarrow H[Mn(CO)_5] + CF_3SO_3Li \quad \text{(eq. 8)}$$

$$Li[(C_5H_5)Mo(CO)_3] + CF_3SO_3H \longrightarrow H[(C_5H_5)Mo(CO)_3] + CF_3SO_3Li \quad \text{(eq. 9)}$$

$$[Mn(CO)_5]Br + 2\,Li(C_2H_5)_3BH \longrightarrow Li[Mn(CO)_5] + LiBr + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 10)}$$

$$[(C_5H_5)Mo(CO)_3]Cl + 2\,Li(C_2H_5)_3BH \longrightarrow Li[(C_5H_5)Mo(CO)_3] + LiCl + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 11)}$$

17.[26] Exploratory reactions indicate that trialkylborohydrides are not sufficiently strong reductants to produce metal carbonyl trianions and tetraanions of the type reported by Ellis.[27]

Recently, we have found that trialkylborohydrides can also be used to form *neutral* formyl complexes from metal carbonyl cations according to the generalized eq. 18.[28] These reactions, and the properties of the products, are under active investigation. The neutral formyl $(C_5H_5)Re(CO)(NO)(COH)$ (**3**), whose preparation is depicted in Scheme I, has a half-life of *ca.* 3hr at room temperature. The addition of a second equivalent of $Li(C_2H_5)_3BH$ affords **4**, the first bis(formyl) complex prepared. Reaction of **3** with $BH_3 \cdot THF$ reduces the formyl ligand to a methyl ligand (Scheme I).

In only one instance have we observed a trialkylborohydride to cleanly attack a metal carbonyl complex at a site other than coordinated CO. The reaction of **5** with $Li(C_2H_5)_3BH$ afforded the novel metallocycle **6**, presumably *via* intermediate **7** (eq. 19).[29] We undertook an X-ray crystal-structure determination of the PPN^+ salt of **6** to confirm its structure. Metallocycle **6** is not merely a curiosity; it serves as a pivotal intermediate in our recently described approach to α-silyloxyalkyl and α-hydroxyalkyl metal complexes.[29] α-Hydroxyalkyl ligands are believed to be key mechanistic branch points in Fischer-Tropsch-type processes.[17]

Having established that trialkylborohydrides can effect the net cleavage of metal-metal bonds, we decided to see if metalloid-metalloid bonds could be broken as well. Gray, elemental selenium consists of polymeric, unbranched helical chains.

$$L_nM\text{-}C{=}O + Li(C_2H_5)_3BH \longrightarrow Li^+ L_nM^-\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + (C_2H_5)_3B \quad \text{(eq. 12)}$$

$$(CO)_5Re\text{-}Re(CO)_5 \xrightarrow{Li(C_2H_5)_3BH} Li^+(CO)_5Re\text{-}\underset{\underset{H\text{-}C=O}{|}}{Re}(CO)_4 \cdot THF \quad \text{(eq. 13)}$$

$$Fe(CO)_5 \xrightarrow[3hr,\ THF,\ \Delta]{2\ K(sec\text{-}C_4H_9)_3BH} \underline{K_2[Fe(CO)_4]}\downarrow \quad 100\% \quad \text{(eq. 14)}$$

$$K_2[Fe(CO)_4] \xrightarrow[3)\ CH_3COOH]{1)\ n\text{-}C_8H_{17}Br,\ 2)\ P(C_6H_5)_3} \text{1-nonanal} \quad 100\% \quad \text{(eq. 15)}$$

$$K_2[Fe(CO)_4] \xrightarrow{2\ AuCl[P(C_6H_5)_3]} [Fe(CO)_4][AuP(C_6H_5)_3]_2 \quad 82\% \quad \text{(eq. 16)}$$

$$H_4Ru_4(CO)_{14} + 2\ K(sec\text{-}C_4H_9)_3BH \longrightarrow \underline{K_2[H_2Ru_4(CO)_{12}]} + 2\ (sec\text{-}C_4H_9)_3B + 2\ H_2 \quad \text{(eq. 17)}$$

$$[L_nM\text{-}C{=}O]^+ + Li(C_2H_5)_3BH \longrightarrow \overset{O}{\overset{\|}{L_nM\text{-}C}}\text{-}H + (C_2H_5)_3B + Li^+ \quad \text{(eq. 18)}$$

Scheme I. Formation and Further Reductions of Neutral Formyl 3

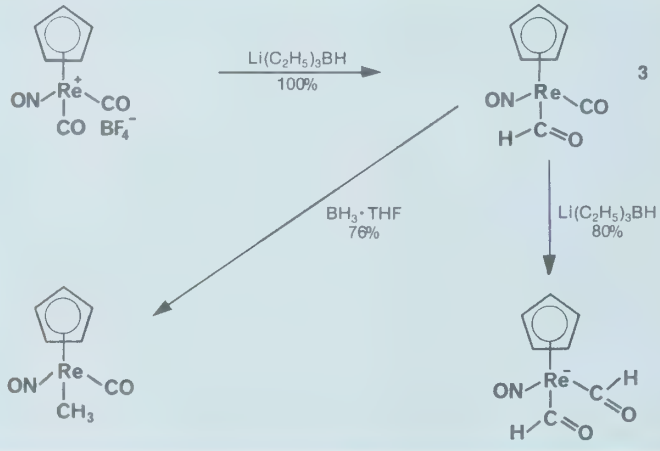


TABLE I. SUMMARY OF TRANSITION METAL MONOANION DERIVATIVES PREPARED

Entry	Starting Carbonyl	Hydride Reagent	Monoanion Produced	Electrophile Added	Product Formed	Isolated Yield (%)
1	$[Co(CO)_4]_2$	$Li(C_2H_5)_3BH$	$Li[Co(CO)_4]$	$[(C_6H_5)_3P]_2N^+Cl^-$	$[(C_6H_5)_3P]_2N^+[Co(CO)_4]^-$	79
2	$[Co(CO)_4]_2$	$Li(C_2H_5)_3BH$	$Li[Co(CO)_4]$	$(C_6H_5)_3SnCl$	$[Co(CO)_4]Sn(C_6H_5)_3$	83
3	$[(C_5H_5)Mo(CO)_3]_2$	$Li(C_2H_5)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	CH_3I	$[(C_5H_5)Mo(CO)_3]CH_3$	77
4	$[(C_5H_5)Mo(CO)_3]_2$	$Li(C_2H_5)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	$(CH_3O)COCOCl$	$[(C_5H_5)Mo(CO)_3]COCO_2CH_3$	77
5	$[(C_5H_5)Mo(CO)_3]_2$	$Li(sec\text{-}C_4H_9)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	$(CH_3O)COCOCl$	$[(C_5H_5)Mo(CO)_3]COCO_2CH_3$	77
6	$[(C_5H_5)Mo(CO)_3]_2$	$Li(C_2H_5)_3BH$	$Li[(C_5H_5)Mo(CO)_3]$	$(C_6H_5)_3SnCl$	$[(C_5H_5)Mo(CO)_3]Sn(C_6H_5)_3$	76
7	$[Mn(CO)_5]_2$	$Li(C_2H_5)_3BH$	$Li[Mn(CO)_5]$	$C_6H_5COCOCl$	$[Mn(CO)_5]COCOC_6H_5$	92
8	$[Mn(CO)_5]_2$	$Li(C_2H_5)_3BH$	$Li[Mn(CO)_5]$	$(C_6H_5)_3SnCl$	$[Mn(CO)_5]Sn(C_6H_5)_3$	88
9	$[Mn(CO)_5]_2$	$Li(C_2H_5)_3BH$	$Li[Mn(CO)_5]$	$(CH_3O)COCOCl$	$[Mn(CO)_5]COCO_2CH_3$	81
10	$[Mn(CO)_5]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[Mn(CO)_5]$	$[(C_6H_5)_3P]N^+Cl^-$	$[(C_6H_5)_3P]_2N^+[Mn(CO)_5]^-$	78
11	$[Mn(CO)_5]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[Mn(CO)_5]$	$(CH_3)_3SiBr$	$[Mn(CO)_5]Si(CH_3)_3$	60-80
12	$[(C_5H_5)Fe(CO)_2]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	$(C_6H_5)_3SnCl$	$[(C_5H_5)Fe(CO)_2]Sn(C_6H_5)_3$	93
13	$[(C_5H_5)Fe(CO)_2]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	$C_6H_5CH{=}CHCOCl$	$[(C_5H_5)Fe(CO)_2]COCH{=}CHC_6H_5$	72
14	$[(C_5H_5)Fe(CO)_2]_2$	$K(sec\text{-}C_4H_9)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	C_6H_5COCl	$[(C_5H_5)Fe(CO)_2]COC_6H_5$	67
15	$[(C_5H_5)Fe(CO)_2]_2$	$K(C_2H_5)_3BH$	$K[(C_5H_5)Fe(CO)_2]$	CH_3I	$[(C_5H_5)Fe(CO)_2]CH_3$	56

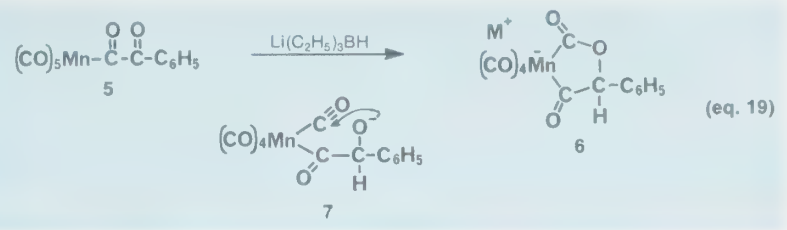
While it is only partially reduced by $NaBH_4$,[30] $Li(C_2H_5)_3BH$ rapidly converts Se_x to Li_2Se or Li_2Se_2 (depending upon stoichiometry) according to eqs. 20 and 22.[31] Alkyl halides could then be added to the heterogeneous suspensions (optimally in the presence of *t*-butyl alcohol cosolvent) and dialkyl selenides and dialkyl diselenides obtained in 50-90% yields (eqs. 21 and 23).[31]

This one-flask preparation of R_2Se and R_2Se_2 compounds offers distinct advantages over many previous methods. Alkali metal-ammonia reduction converts Se_x to $Se^=$ or $Se_2^=$, but is obviously a more cumbersome procedure. Sodium formaldehyde sulfoxylate ("Rongalite") can also reduce selenium but requires an aqueous solvent system.[31]

We have undertaken a more extensive investigation of the reaction of sulfur (S_8) with trialkylborohydrides.[32,33] Although there exists a variety of means for the introduction of sulfur into organic molecules, research continues on the development of new sulfur transfer reagents and methods. When $Li(C_2H_5)_3BH$ is simply syringed onto sulfur or a sulfur/THF suspension, Li_2S or Li_2S_2 formation occurs over a two-minute period as depicted in eqs. 24 and 25. Significantly, these reaction mixtures are homogeneous, whereas commercial anhydrous Li_2S is insoluble in THF. While there may be some association between the sulfur anions and the by-product $(C_2H_5)_3B$, experiments[33] indicate that the homogeneity is primarily due to supersaturation.

A variety of electrophiles have been added to these reaction mixtures. Some of the organosulfur compounds thus prepared are tabulated in Table II.[32,33] Although the synthesis of simple dialkyl sulfides is adequately served by inexpensive $Na_2S \cdot 9H_2O$, this reagent is, of course, incompatible with electrophiles requiring strictly anhydrous conditions. Notably, our Li_2S preparation undergoes facile acylation (entries 5 and 6), providing a distinct improvement over existing synthetic methods for diacyl sulfides.[34] While anhydrous alkali metal sulfides are commercially available, they are exceedingly hygroscopic, and thus, our one-flask *in situ* synthesis offers obvious advantages.

Alkali metal disulfides are not commercially available. Methods for their preparation (*e.g.*, Li/NH_3) are cumbersome and sometimes afford mixtures of polysulfide salts. Hence, alkylation of Na_2S_2 has been reported to proceed only in fair yield.[33] As is evident from Table IIB, our disulfide yields are uniformly high. Thus, disulfides may be readily prepared from nonsulfur-containing precursors. Particularly for the diacyl disulfides (entries 13 and 14) are the literature procedures markedly simplified.[35]



(eq. 19)

$$Se + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2Se} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 20)}$$

$$Li_2Se + 2\,RX \longrightarrow \underline{R_2Se} + 2\,LiX \quad \text{(eq. 21)}$$

$$2\,Se + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2Se_2} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 22)}$$

$$Li_2Se_2 + 2\,RX \longrightarrow \underline{R_2Se_2} + 2\,LiX \quad \text{(eq. 23)}$$

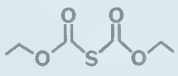
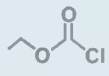
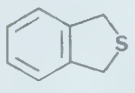
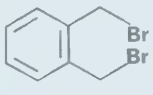
$$S + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2S} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 24)}$$

$$2\,S + 2\,Li(C_2H_5)_3BH \longrightarrow \underline{Li_2S_2} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 25)}$$

$$RSSR + 2\,Li(C_2H_5)_3BH \longrightarrow 2\,\underline{RSLi} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 26)}$$

$$RSeSeR + 2\,Li(C_2H_5)_3BH \longrightarrow 2\,\underline{RSeLi} + 2\,(C_2H_5)_3B + H_2 \quad \text{(eq. 27)}$$

TABLE II. REPRESENTATIVE ORGANOSULFUR COMPOUNDS PREPARED

Entry	Product	Electrophile	Yield (%)[a]	Reaction Conditions[b]
		A. Sulfides		
1	$(C_6H_5CH_2)_2S$	$C_6H_5CH_2Cl$	[94]	3hr
2	$(n\text{-}C_4H_9)_2S$	$n\text{-}C_4H_9I$	71	5hr
3	$(n\text{-}C_5H_{11})_2S$	$n\text{-}C_5H_{11}Br$	71	5hr
4	$(sec\text{-}C_4H_9)_2S$	$sec\text{-}C_4H_9I$	63	12hr reflux
5	$(CH_3CO)_2S$	CH_3COCl	87	2hr
6			51	2.5hr
7			[63]	1.5hr
		B. Disulfides		
8	$(C_6H_5CH_2)_2S_2$	$C_6H_5CH_2Br$	[89] 85	5hr
9	$(H_2C{=}CHCH_2)_2S_2$	$H_2C{=}CHCH_2Br$	[93]	2hr reflux
10	$(n\text{-}C_4H_9)_2S_2$	$n\text{-}C_4H_9I$	[87] 78	1hr
11	$(n\text{-}C_5H_{11})_2S_2$	$n\text{-}C_5H_{11}Br$	99	2hr reflux
12	$(sec\text{-}C_4H_9)_2S_2$	$sec\text{-}C_4H_9I$	[73]	2hr reflux
13	$(C_6H_5CO)_2S_2$	C_6H_5COCl	85	1hr reflux
14	$(CH_3CO)_2S_2$	CH_3COCl	[82]	0.5hr

[a]Yields are based upon starting sulfur and are not optimized. Bracketed values are ^1H NMR yields; others are isolated yields.

[b]Room temperature unless noted.

Disulfides and diselenides are rapidly cleaved by $Li(C_2H_5)_3BH$ to thiolates and selenolates, respectively (eqs. 26 and 27).[31-33] These reactions enable facile syn-

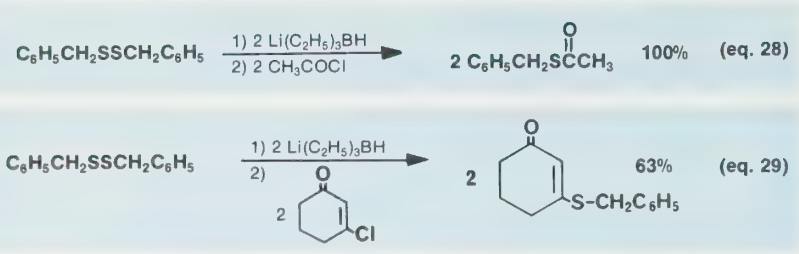
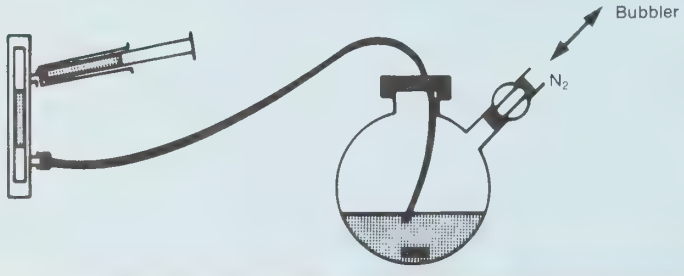


Figure II

APPARATUS FOR IR MONITORING OF REACTIONS



theses of unsymmetrical sulfides and selenides. Thus, the sequential treatment of dibenzyl disulfide with $Li(C_2H_5)_3BH$ and CH_3I gave benzyl methyl sulfide in 75% yield. Benzyl acetyl sulfide was obtained in 100% yield by the reaction of dibenzyl disulfide with $Li(C_2H_5)_3BH$ and acetyl chloride (eq. 28).[32,33] Eq. 29 depicts the formation of a vinyl sulfide *via* an addition-elimination reaction.[33]

APPARATUS

Metal carbonyl compounds have strong and characteristic IR bands in the 1800-2100 cm^{-1} region. Although the reactions we describe can be run in good yield in the absence of spectroscopic monitoring, the simple apparatus detailed in Figure II enables reactions to be titrated to 100% yields. Solutions of the metal carbonyl reactant are placed in a Schlenk flask which is fitted with a septum and a Teflon needle. A standard 0.1-mm-cavity NaCl IR cell is mated to the other end of the needle with a machined Teflon plug. To the other IR cell inlet is attached a (gas-tight) syringe. A slight positive nitrogen pressure is maintained *via* the side arm of the Schlenk flask. Reagents and reactants are added as needed through the septum. By pumping the syringe, the reaction mixture can be spectroscopically sampled at any time.

Such an apparatus might also see use in purely organic transformations. For instance, it should be as (or more) effective as TLC in monitoring the disappearance of a carbonyl-containing compound.

CONCLUSION AND PROGNOSIS

A number of rapid, high-yield, multi-step, single-flask synthetic sequences utilizing trialkylborohydrides have been described. Most of the transformations detailed result in the formation of a metal-carbon or heteroatom-carbon bond. Other applications include the synthesis of metal hydrides, mixed metal compounds, and formyl complexes.

We anticipate that trialkylborohydrides may also be of use in the generation of phosphorus- and silicon-based anions. Our own efforts are focused on the applications of some of the organometallic species described herein to organic synthesis. Although the potential of metal carbonyl reagents has long been recognized by organic chemists, their inaccessibility by standard bench-top techniques has often discouraged their use. In light of the studies summarized in this article, we hope this will no longer be the case.

ACKNOWLEDGEMENTS

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About the Author

John A. Gladysz is a native of Galesburg, Michigan. He earned his B.S. degree at the University of Michigan and his Ph.D. at Stanford University. In 1974, he joined the UCLA Faculty as an Assistant Professor. His research interests encompass a wide area of synthetic chemistry, emphasizing organometallic compounds and new preparative methods (high pressure chemistry, metal atom chemistry).

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Spin Trapping

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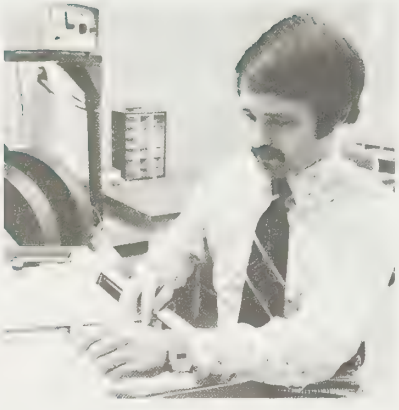


Since its discovery some thirty-four years ago electron spin resonance (ESR) has proven to be a useful tool for studies in chemical, physical, and biological systems.[1] The ability of ESR to detect low concentrations of free radicals and its sensitivity to their environment and molecular motions have contributed greatly to its popularity. A limitation in the application of ESR to solution studies has been the difficulty in producing sufficient quantities of reactive free radicals to make possible direct ESR detection. Various methods have been employed to overcome this problem including high-energy *in situ* radiolyses,[2] high-intensity photolyses,[3] and rapid-flow techniques.[4] However, these techniques are rather expensive or cumbersome and do not appear to be generally applicable. Until recently, therefore, most research in ESR in the solution phase was limited to that involving relatively stable free-radical systems.

In 1968 the technique of spin trapping was introduced by Professor Edward Janzen's group at the University of Georgia as well as by other groups around the world, either simultaneously or a short time afterwards.[5] Since that time publications in this area have proliferated[6] with applications appearing in the fields of polymerization,[7] radiation chemistry,[8] biology,[9] and general solution chemistry.[10]

Interest in biological applications of spin trapping is picking up, with several laboratories presently devoting a significant portion of their research effort to the detection of free-radical processes in biological systems. Because of this increased interest and because existing general reviews of the technique are now some eight years old,[11] it seems appropriate to discuss some of the recent work that has been done using the spin-trapping technique. Particular attention will be given to the spin traps that have been used. Biological applications will be discussed in some detail and a cautionary note is given to help in avoiding potential pitfalls in the application of the technique.

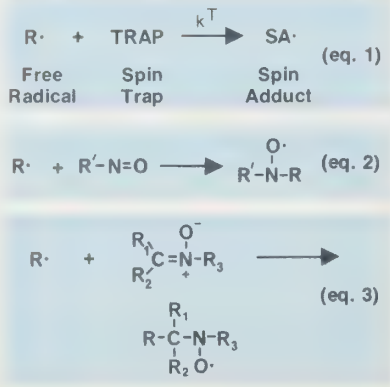
THE TECHNIQUE

The technique of spin trapping makes use of a diamagnetic compound (the spin trap) which reacts with a free radical (the spin) giving rise to a relatively stable, ESR-observable free radical (the spin adduct, eq. 1). In favorable cases the free radical, R•, can be identified from the ESR parameters [*e.g.*, hyperfine coupling constants (hfsc), g-factor] of SA•. Thus spin trapping extends the capabilities of ESR in that previously unobservable free radicals (or, at least, radicals observable only with difficulty) can now be studied as their respective spin adducts in a somewhat more leisurely fashion.

The spin traps that have been most commonly employed are those designed so that on reaction with a free radical a nitroxide is produced. Typically, spin traps are either nitroso compounds[11a] (eq. 2) or nitrones[11b] (eq. 3).

The actual experimental procedure employed in spin-trapping experiments depends on a number of factors such as the manner of radical production, the inertness of the solvent and reagents with respect to the spin trap, the lifetime of the spin adducts, how much or what kind of deoxygenation (if any) is required. Usually deoxygenation by bubbling purified nitrogen or argon gas through the solution is sufficient for spin-trapping purposes. In some cases degassing by the freeze-pump-thaw vacuum technique is necessary if a very low oxygen level is required or if volatile reagents are involved.

An apparatus that has proven rather generally useful for us in spin trapping and other organic applications of electron spin



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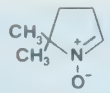
resonance is shown in figure 1.[12] This consists of a "U"-tube (a) which connects *via* a 7/25 tapered ground-glass joint to a Varian "flat cell" [Fig. 1 (b)] for aqueous or high dielectric solvents, or to a standard ESR round cell [Fig. 1 (c)] if a low dielectric (nonlossy) solvent is used. In a typical experiment one positions the "U"-tube vertically and a solution of the spin trap is placed in one chamber of the "U"-tube and the radical producer in the other. The chambers are stoppered with rubber septa through which long (#18 or #20) syringe needles are inserted. A stream of purified nitrogen or argon gas is then passed through the solutions for 15-30 minutes. If a flat cell is used it may be attached during the outgassing procedure since the gas can escape through the opposite end of the cell. Since the round cell has no secondary opening it must be flushed with nitrogen or argon gas just prior to attachment to the "U"-tube. When outgassing is complete the system is stoppered and the contents of the "U"-tube and sample cell are thoroughly mixed and shaken down into the ESR cell, which is inserted into the microwave cavity of the ESR spectrometer. Relatively simple modifications of this basic experimental design allow the use of vacuum degassing, three- (or more) component mixing, etc.

SPIN TRAPS

As mentioned earlier spin traps are usually either nitroso compounds or nitrones. By far the most popular nitroso compound has been 2-methyl-2-nitrosopropane or, trivially, nitroso-*tert*-butane (NtB). Nitroso compounds have an inherent advantage over nitrones for radical identification in that the added group lies immediately adjacent to the nitroxide center and therefore can easily give rise to additional hyperfine splitting. For example, reaction of ethyl radical with NtB gives the ethyl adduct of NtB (NtB-Et) (eq. 4). The ESR spectrum of this nitroxide [Fig. 2 (a)] shows the unpaired electron resonance split first into three lines of equal intensity by interaction with the nitrogen (nuclear spin = 1) and then into three lines of a 1:2:1 intensity ratio by interaction with the two equivalent methylene hydrogens of the ethyl group. A long-range splitting from the methyl hydrogens shows up as a 1:3:3:1 pattern superimposed on the nine major lines and helps to identify the radical trapped.

The nitrone which has been used most in spin-trapping studies is phenyl *N-tert*-butyl nitrone (PBN). This is probably due to the fact that it has a good shelf stability, has been commercially available for a long time, and was the first nitrone to be used in this manner. However, PBN does not distinguish between alkyl radicals particularly well, its spin adducts generally consisting of triplet of doublets with a relatively small variation in the doublet splitting as a function of trapped radical. An example of a typical ESR spectrum is shown in Fig. 2 (b) for the ethyl adduct of PBN (PBN-Et) (eq. 5).

A nitrone which has shown more sensitivity to the structure of the radical is 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO),



DMPO

introduced by Janzen in 1972.[13] Examples of the spectra obtained on trapping different types of radicals with DMPO are shown in Fig. 3.

It is interesting to consider the origin of the variation in the proton hyperfine splitting observed as a function of structure of the trapped free radical. The magnitude of this interaction is governed by the Heller-McConnell equation (eq. 6),[14] where B_0 and B_2 are constants ($B_0 \cong 0$ and $B_2 \cong 26$ Gauss for nitroxides) and θ is the dihedral angle formed by the C-N *p*-orbital and the N-C βH planes (Fig. 4). Thus, each group *R* added to the spin trap will have different stereoelectronic characteristics and will therefore give rise to a different value for θ.

The spin trap DMPO is structured so that the conformation of its adducts places the β-hydrogen in a nearly eclipsing relationship with the nitrogen *p*-orbital (*i.e.*, θ is small and $A_{H\beta}$ is large). As a result, small changes in the bulk of R• give rise to relatively large variations in $A_{H\beta}$. This is illustrated in the "scatter plot" of A_N *vs.*

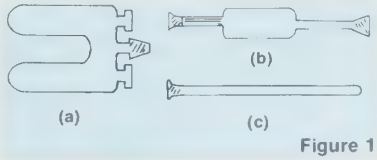
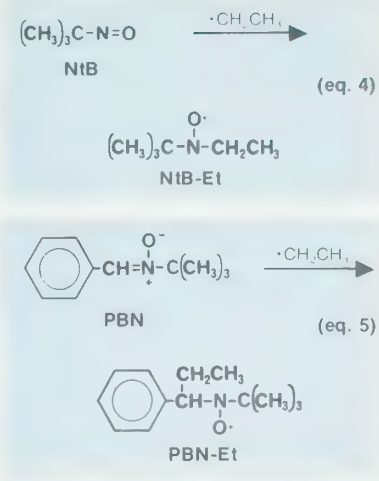


Figure 1



$$A_{H\beta} = B_0 + B_2 \cos^2\theta \quad \text{(eq. 6)}$$

$A_{H\beta}$ for a number of adducts to DMPO (Fig. 5). In this kind of plot, the better the scatter the better is the spin trap for purposes of identification of the trapped radical. The range of hfsc's for the same adducts to PBN is indicated on the plot.

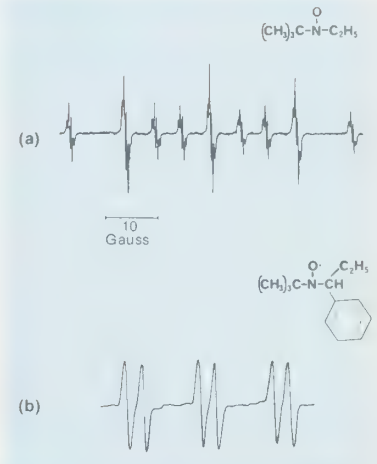


Figure 2

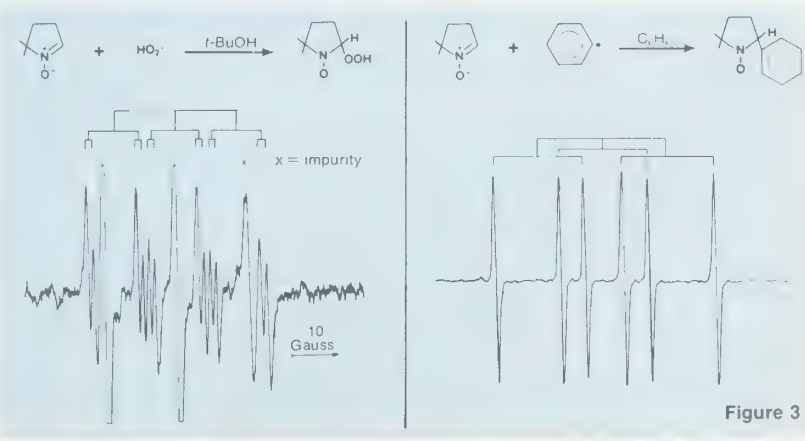
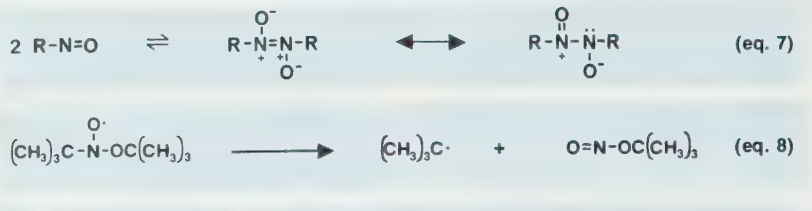


Figure 3



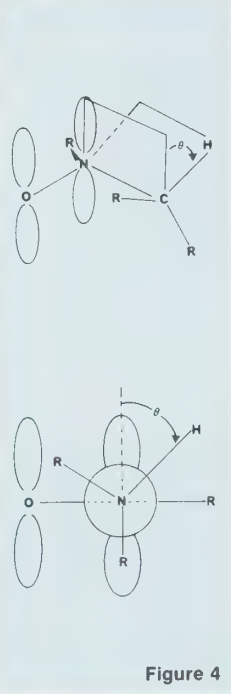


Figure 4

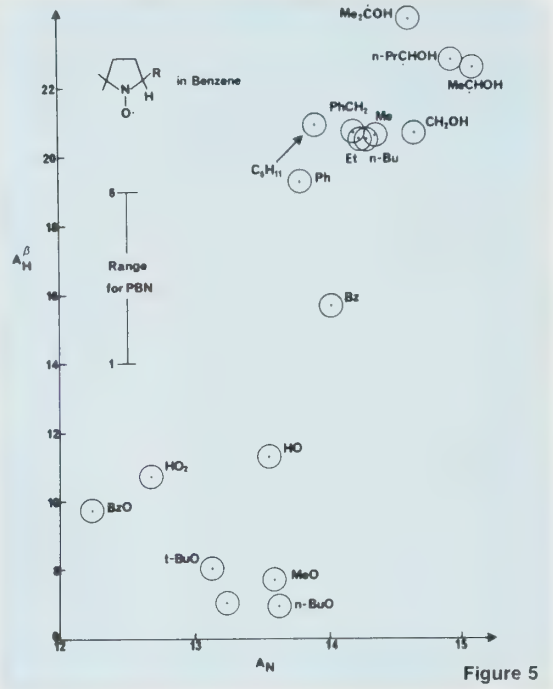


Figure 5

OTHER SPIN TRAPS

The three spin traps discussed above have been the ones most utilized by researchers up to this point. Although a great deal of tailored synthesis has been done for the technique of spin labelling,[15] very little has been done to configure spin traps to suit the exact problem under investigation. With the advent of investigational activity in the biological area, it is likely that this situation will be changing over the next few years.

A number of other traps have been used in problems investigated by spin trapping, particularly in the early days of the development of the technique.[5,16] These will not be discussed specifically, but the structures of some of these traps are shown in Figure 6.

Janzen has recently published the preparations of a number of traps which seem to be quite good for trapping hydroxyl radicals.[17]

RELATIVE MERITS OF NITROSO VERSUS NITRONE SPIN TRAPS

Earlier it was mentioned that nitroso compounds are generally more capable than nitrones of providing a "fingerprint" of the trapped radical because the added group lies closer to the unpaired electron center. However nitroso compounds have the disadvantage of being both thermally and photochemically unstable.[11b,16b,18] In addition they possess a low-energy visible absorption band which makes it nearly impossible to use them for photochemical studies. One of the consequences of this instability is that the ESR spectra of spin adducts of nitroso compounds invariably show the presence of impurity nitroxides which may obscure certain regions of the spectra and hinder interpretations. It should be noted that aromatic nitroso compounds show much more desirable properties in this regard.[16b]

There are other problems associated with the use of nitroso compounds in spin-trapping applications. Nitroso compounds have a tendency to form dimers which are inert towards radical trapping (eq. 7).[16b] Thus, in any quantitative applications it is necessary to take this equilibrium into account. Nitroso compounds seem somewhat unreliable in spin-trapping applications involving oxygen-centered radicals. For example, it has been shown[18] that the *tert*-butoxy adduct of NtB is unstable, decomposing to give a *tert*-butyl radical and *tert*-butyl nitrite (eq. 8).

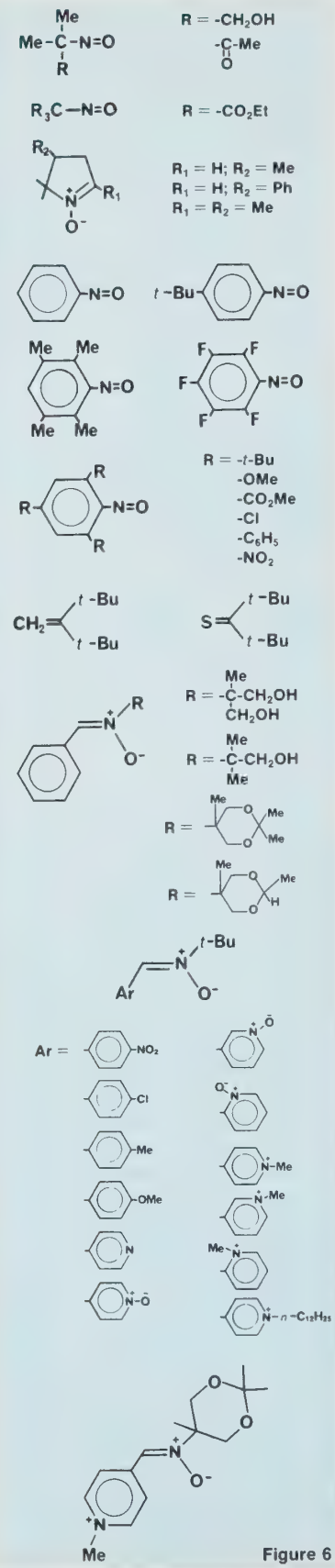


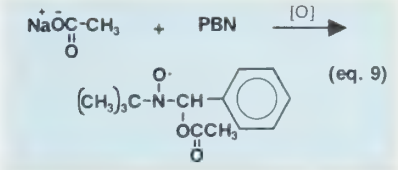
Figure 6

In contrast to nitroso compounds, nitrones have absorption bands firmly in the ultraviolet which render them suitable for a number of photochemical studies. In general, use of wavelengths longer than 300nm completely avoids direct photolysis of the spin trap. Indeed, photolysis of benzene solutions of PBN for over two hours with a low-pressure mercury lamp gives no detectable ESR signal.[19] Nitrones are monomeric and, to my knowledge, show no tendency to dimerize. Many of the spin adducts produced from nitrones are stable for long periods (the phenyl spin adduct of PBN has a half-life of several weeks; the dodecyl adduct, several years[19]). The most serious disadvantage of nitrones is their tendency to undergo reactions with nucleophiles. A weak signal of the acetoxyl adduct of PBN can be detected from reaction of sodium acetate with PBN.[20] This probably arises from nucleophilic addition of acetate to PBN with subsequent oxidation of the anion produced (eq. 9).

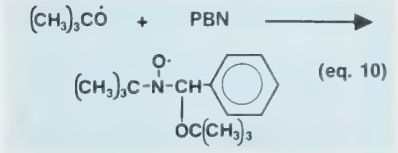
One concludes from this discussion that there is no such thing as the ideal spin trap. One trap will be good for a given application and another will be good for a different application. It seems, therefore, that it would be good to have a kit of spin traps from which a researcher could select the trap appropriate for his experimental needs. This is one of the reasons that I hope the custom design of spin traps will accelerate in order that a larger number of spin traps will become available.

SPIN ADDUCTS

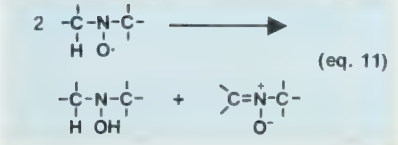
The spin-trapping reaction has been studied extensively within Janzen's group and a review of this aspect of spin trapping has appeared.[21] A large number of rate constants have now been determined for the formation reaction (eq. 1) principally by Janzen, Evans, *et al.*[22] and by Schmid and Ingold.[23] A limited amount of data has been made available by other workers in the field[24]. This rate constant data is summarized in Table I.



(eq. 9)



(eq. 10)



(eq. 11)

All rate constants for the spin-trapping reaction have been measured either by direct competition or by determining a rate constant ratio in which some other rate constant is a "known" quantity. Thus, it is doubtful that any spin-trapping rate constant is correct to better than a factor of 2 and a safer margin of error would be to say that the listed quantities are correct to within an order of magnitude. All values so far fall in the extremes of 1×10^5 to 5×10^8 M^{-1} sec^{-1}.

It is appropriate to remark that preliminary flash photolysis-ESR results[25] on the system *tert*-butoxy-PBN (eq. 10) indicate a $k^T \cong 2 \times 10^6$ M^{-1} sec^{-1} at 25°, in good agreement with the earlier work of Janzen and Evans.[22b]

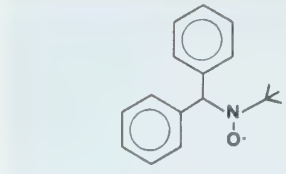
Very little information on activation parameters has been obtained for the spin-trapping reaction, but it appears that energies of activation will fall in the range of 1-5 kcal/mole.[23b]

DECAY OF SPIN ADDUCTS

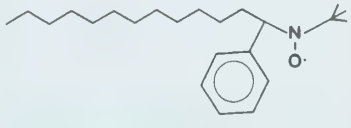
A number of decay routes are possible for spin adducts. In the following discussion, some reference will be made to nitroxides which are not spin adducts, *per se*. However, it is felt that data which is available for these nitroxides has a bearing on the decay of spin adducts.

Spin adducts which have a hydrogen attached to the α-carbon can decay by disproportionation (eq. 11). The mechanism for this decay pathway has been worked out by Ingold and co-workers.[26] For diethyl nitroxide, the decay involves the initial formation of a dimer which decomposes to products. The decay is rather fast ($k = 1 \times 10^4$ M^{-1} sec^{-1} at 25° in benzene). For more substituted nitroxides, the decay is slower (*n*-hexyl *tert*-butyl nitroxide: $k \leqslant 100$ M^{-1} sec^{-1} at 40° in benzene)[23a] and is probably "a straightforward disproportionation not involving the formation of an intermediate dimer."[26c] Indeed, the decrease in decay rate seems to continue as the degree of substitution and size of attached groups increase.[19,27] In fact some spin adducts are so stable they are at least partially isolable.[19,27]

In preliminary work aimed at studying the effect of the size of the added radical on spin adduct lifetime, I have compared the relative persistence of the phenyl adduct of PBN (I) and the dodecyl adduct of PBN (II). The phenyl adduct has a half-life of several months in benzene whereas the



I



II

dodecyl adduct evidently has a half-life of several years.[19] Similar results were obtained for the phenyl and dodecyl adducts of DMPO, although these adducts were much less stable.[19]

TABLE I. RATE CONSTANTS FOR THE SPIN-TRAPPING REACTION

$$R\cdot + TRAP \xrightarrow{k^T} SA\cdot$$

Spin Trap	Radical	T (°C)	k^T ($M^{-1}sec^{-1}$)	Reference
PBN	*t*-BuO·	25	5×10^6	22,44
	Ph·	25	2×10^7	22,44
	BzO·	40	3×10^7	22,44
	CH_3·	25	4×10^6	22,44
	RCH_2·	40	1.3×10^5	23
DMPO	*t*-BuO·	25	4×10^8	22,44
	Ph·	25	7×10^7	22,44
	BzO·	40	8×10^7	22,44
	$PhCH_2$·	25	2×10^7	22,44
	RCH_2·	40	2.5×10^6	23
NtB	*t*-BuO·	25	2×10^6	22,44
	CH_3O·	-45	1.3×10^8	24e
	$(CH_3)_3OC$·=O	40	1×10^6	24a
	RCH_2·	40	9×10^6	23

It may not be too obvious to remark that the stable nitroxides used for spin labels are almost exclusively those in which all of the hydrogens on the α-carbons have been substituted.

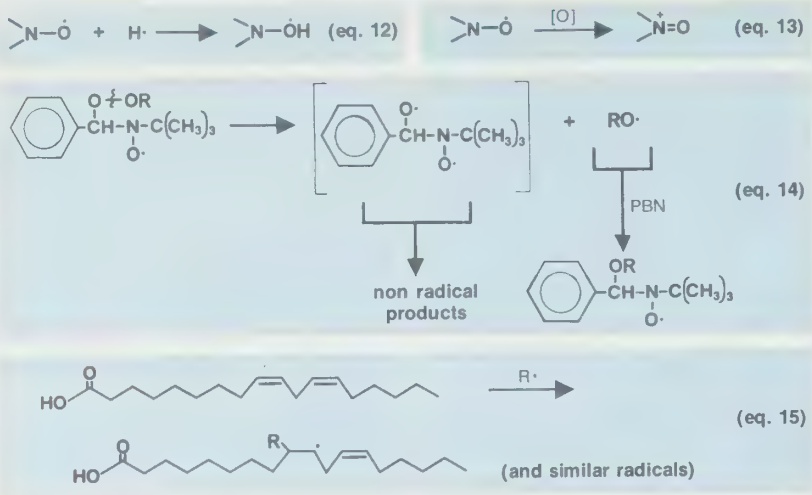
There are some other ways in which the spin adduct can decay. One of the most common is by means of a reduction of the spin adduct (shown formally in equation 12 as reaction of the nitroxide with a hydrogen atom). The observation of this reaction is becoming more common now that the use of spin traps in biological systems is increasing. This is, of course, because of the endogenous reducing agents present in many biological preparations. The most common reductant is ascorbate, but there may be others (such as dithionite) which are not naturally occurring, but may have been added in the preparative procedure. One positive aspect of the disappearance of spin adduct due to reduction is that the skeletal structure of the adduct is generally preserved. Therefore, it may be possible to regenerate the ESR spectrum by means of an appropriately chosen oxidative procedure. It might even be possible to isolate the reduced adduct and to study it by other techniques such as NMR.

It is, of course, possible to oxidize nitroxides[28] (eq. 13), but this appears to be less common than reduction, particularly in biological systems. It may well be that nitroxides which have been one-electron oxidized are more prone to undergo cleavage than are the reduced species. If this is the case, skeletal integrity will not be preserved and it will be difficult to regenerate the original nitroxide.

Spin adducts may decay by means of cleavage of a portion of the nitroxide as a free radical. This was mentioned earlier for the *tert*-butoxy adduct of NtB (eq. 8). This may also be a problem when certain groups which add to the spin trap contain weak chemical bonds (*e.g.*, -O-O-, -N=N-). For example, alkylperoxy radical adducts of PBN are difficult to observe except at low temperatures.[29] One exception was the adduct derived from n-$C_{18}H_{37}O_2$· and PBN, which was observed at room temperature. The decay pathway for these adducts may well involve breaking of the O-O bond. At room temperature, alkoxy radical adducts are observed instead of alkylperoxy adducts (eq. 14).

SELECTED APPLICATIONS OF SPIN TRAPPING TO BIOLOGY

The presence of free radicals in biological systems has been postulated for some time. Conventional ESR has not been heavily utilized to study these radical processes because of the short lifetime and consequent low concentrations of the free

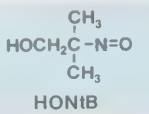


radicals involved. In recent years spin trapping has spurred interest in the application of ESR to biological problems and several successful studies have been reported. One of the more common kinds of studies concerns free radicals produced by high-energy radiation of aqueous solutions of peptides,[30] amino acids,[31] nucleic acids,[32] etc., in the presence of a spin trap. These have been discussed in some detail in a recent review.[33]

In this article I will briefly discuss the application of spin trapping to the study of lipid peroxidation and to the detection of superoxide (O_2^{-}·) and hydroxyl radicals. This is in no way intended to be a comprehensive review. These papers and others are discussed in considerably greater detail in the review by Janzen.[33]

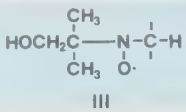
LIPID PEROXIDATION

In one of the earliest applications of spin trapping to a problem of biological interest, de Groot *et al.* examined the production of radicals in the anaerobic reaction of lipoxygenase with linoleic acid using 2-methyl-2-nitrosopropanol (HONtB)



as spin trap.[34] The nitroso alcohol (HONtB) was chosen as spin trap because of its greater solubility in water over NtB.

The reaction of interest in this work was the formation of dimeric linoleic acid which was shown to require hydroperoxy-linoleic acid. Garssen *et al.*[35] had proposed a mechanism for this dimerization involving a linoleic acid radical. When linoleic acid was incubated aerobically with lipoxygenase and HONtB an ESR spectrum consisting of a triplet of doublets was observed. The ESR spectrum indicated an interaction of the unpaired electron with a nitrogen (A_N 16.0 Gauss) and a proton (A_N 2.0 Gauss), consistent with the basic structure III. The reaction could also be

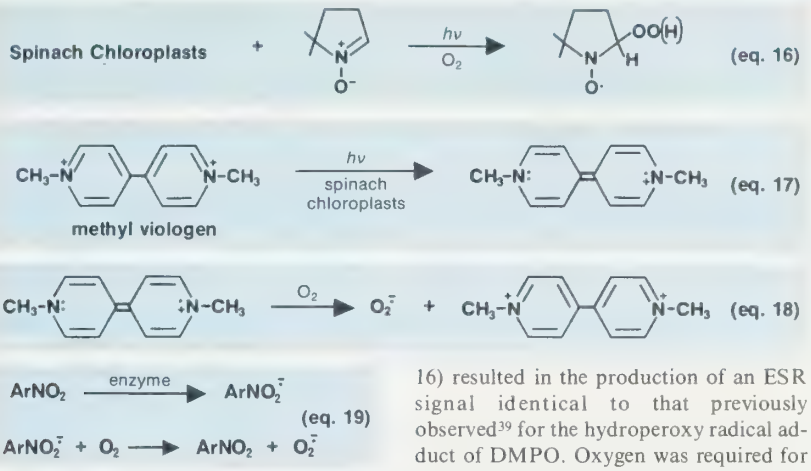


carried out anaerobically without the enzyme. In this experiment, a degassed solution of linoleic acid and spin trap was prepared and mixed with a degassed solution of hydroperoxylinoleic acid. An ESR spectrum identical with the one described above was obtained.

The workers were able to assign a more precise structure to the radical giving rise to the ESR spectrum by means of experiments using deuterated linoleic acids. When 11,11-d_2-linoleic acid was used in place of linoleic acid the ESR spectrum was unchanged. However, when either 9,10,11,11,12,13,-d_6- or 9,10,12,13-d_4-linoleic acids were used, the doublet splitting disappeared and the ESR spectrum consisted of three lines. The authors concluded that a linoleic acid radical at either C-13 or C-9 appeared to have been trapped. Of course, there is no *a priori* reason to exclude trapping at C-10 or C-12. Radicals derived from addition reactions to the double bond (eq. 15) are consistent with the above experiments whereas radicals derived from hydrogen abstraction at C-11 are not.

Other experiments carried out with deuterated compounds established that the radical was derived from linoleic acid and not from the hydroperoxide.

It should be reemphasized at this point that nitroso compounds are notoriously unreliable as traps of oxygen-centered radicals. It would perhaps be advisable to reinvestigate this system using nitrone spin traps to see if other radicals present in the



reaction could be detected. This system was reexamined recently, but again, only a nitroso trap was used.[36]

Perhaps the most powerful application of spin trapping to the lipid peroxidation area has been due to Piette and coworkers.[37] These workers have explored radical production in rat liver microsomes using both PBN and DMPO as spin traps. The liver microsomal NADPH-dependent lipid peroxidation system was shown to produce free radicals from a variety of substrates, *viz.*, methanol, ethanol, propanol, acetone, acetonitrile, DMSO, linoleic acid and the well known carcinogens, dimethylnitrosamine and diethylnitrosamine.[37a] The authors also showed that a good signal could be obtained when the common buffering agent, Tris, was used. This latter result further demonstrates that all components of the system must be checked in order that the true source of radicals giving rise to a particular spin adduct be identified.

Lai and Piette[37b] have also demonstrated hydroxyl radical production in the microsomal system.

SUPEROXIDE DETECTION

Singly-reduced oxygen, superoxide ($O_2^{\bullet-}$), has been postulated as an intermediate in a host of biochemical redox reactions. Because of its importance, a great deal of attention is being paid to the detection of superoxide anion by spin trapping.[33]

The first paper in this area was the paper by Harbour and Bolton,[38] who studied superoxide production in spinach chloroplasts. Indeed, it now appears that this paper was the one which triggered much of the current interest in spin-trapping applications to biological problems.

Harbour and Bolton found that red light ($\lambda > 600$nm) illumination of spinach chloroplasts in the presence of DMPO (eq. 16) resulted in the production of an ESR signal identical to that previously observed[39] for the hydroperoxy radical adduct of DMPO. Oxygen was required for the reaction and the observed signal was much larger in the presence of methyl viologen, a species known to accept electrons from the primary acceptor of photosystem I. The methyl viologen functions by taking the electron from the photosynthetic chain and forming the methyl viologen radical cation (eq. 17). This radical in turn reduces molecular oxygen to form the superoxide radical (eq. 18).

A recent work from the National Biomedical ESR Center describes the detection of superoxide during the aerobic liver microsomal reduction of nitro compounds[40] (eq. 19). Both DMPO and PBN were used as spin traps. The mechanism for production of superoxide is very similar to that given above for methyl viologen.

Buettner and Oberley have published a paper in which lifetimes of the $O_2^{\bullet-}$ (or $HO_2^{\bullet}$) adduct of DMPO were measured under a variety of conditions.[41] A method for quickly purifying the commercially available DMPO is presented. This paper should prove to be valuable since it aids in defining the limits of observation of superoxide by spin trapping.

HYDROXYL RADICAL DETECTION

Hydroxyl radical is one of the most powerful oxidizing radicals occurring in biological systems. DMPO and PBN have been shown[39] to be effective traps for this radical.

One of the more intriguing observations of hydroxyl has been in the Fe^{+2}-bleomycin-DMPO system.[42] Bleomycin[43] is a multifunctional anticancer antibiotic known to induce strand breakage in DNA. The efficiency of strand breakage is markedly increased when reducing agents are added.

When a solution of $FeSO_4$, bleomycin and DMPO is placed in the cavity of an ESR spectrometer the characteristic signal of the hydroxyl radical adduct to DMPO is observed. Control experiments verify that the entire system is necessary to produce the signal, *i.e.*, Fe^{+2} or bleomycin alone with DMPO does not give rise to the ESR spectrum. The authors propose that the hydroxyl radical is the actual toxic species giving rise to the DNA strand breaks. These strand breaks are somewhat "site-specific" because bleomycin is bound to DNA and the hydroxyl radical is released in the vicinity of the site of strand breakage.

SOME CAUTIONARY NOTES TO PRACTITIONERS OF SPIN TRAPPING

It seems to be somewhat of a law of nature that the easier a technique is to perform, the more subject to abuse are the interpretations of the results. Spin trapping is in most cases rather easy to do experimentally and, accordingly, may well fall under the jurisdiction of the above law. It seems appropriate, therefore, to lay out some guidelines which may be helpful in avoiding some of the more common pitfalls.

> 1. The observation of an ESR signal in a spin-trapping experiment is not *prima facie* evidence that one has trapped the radical of greatest interest to the researcher.

Thus, *the highest priority in any spin-trapping experiment is assignment of the ESR signal(s).*

> 2. The observation of a spin adduct corresponding to the radical of greatest interest to the researcher does not necessarily mean that the ESR signal arose by means of the pathway of greatest interest to the observer.

Considerable testing needs to be done to assure that the spin adduct did indeed get there by the proposed mechanism. One simple test is to vary the concentration of the spin trap to determine the kinetic order of the reaction in spin trap. It should be quite general that the *overall reaction should tend toward zeroth order in spin trap as the concentration of spin trap is increased.*[44] It may not be too obvious to remark that observation of zero order dependence of spin trap is not 100% assurance of the radical nature of the adduct formation. It is, however, a step in the right direction.

> 3. Corollary to #1. The lack of observation of an ESR signal does not mean that the radical of interest is not present.

It may be that the spin adduct is unstable, the trapping rate is too slow relative to other pathways for the radical, or there might be a number of other reasons for the

failure to observe the adduct of interest. Some ideas for dealing with this and the other problems above are discussed in Janzen's review.[33]

To summarize, spin trapping is a powerful technique for the indirect ESR observation of many reactive free radicals. As with all techniques, some care should be taken to cross-check results whenever possible.

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About the Author

C. Anderson Evans received his Ph.D. degree from the University of Georgia in 1974. He received his post doctoral training at the Centre D'Études Nucléaire, Grenoble, France under a Fulbright-Hays Fellowship, 1973-1974 and at the University of Western Ontario, London, Ontario, 1974-1976. His current interests include magnetic resonance, spin trapping, NMR/ESR applications to biological problems and computer applications to instrumentation.

New Synthetic Reagents and Reactions*

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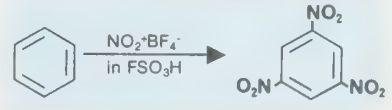
I. INTRODUCTION

Synthetic organic chemistry encompasses, besides multistep synthesis of complex target molecules (frequently natural products with specific stereochemistry), the development of simple, basic reactions and new methods for carrying out individual steps or preparing products.

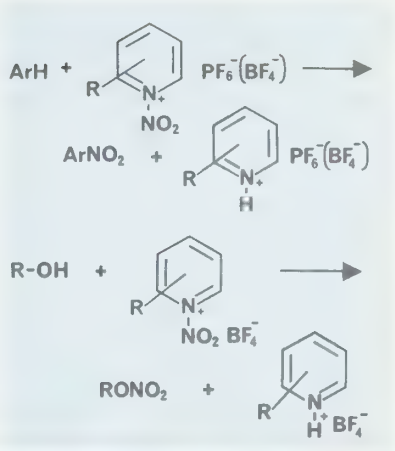
It is in this latter area that our synthetic investigations are centered, encompassing the study of basic (unit) reactions as well as development of new reagents.

II. NITRATION

Conventional nitration[1] of aromatic compounds uses mixed acid (mixture of nitric and sulfuric acid). In the reaction the water formed dilutes the acid; further, due to its strong oxidizing ability, mixed acid is ill-suited to nitrate many sensitive compounds. It also presents serious problems in spent-acid disposal. We have developed a series of efficient new nitrating agents and methods to overcome these difficulties. Readily prepared and isolated stable **nitronium salts**, such as $NO_2^+BF_4^-$ and $NO_2^+PF_6^-$, nitrate aromatics[2] in organic solvents generally in close-to-quantitative yields. **Alkyl nitrates**, such as $MeONO_2$,[3] $BuONO_2$ or acetone cyanohydrin nitrate, $Me_2C(CN)ONO_2$,[4] with BF_3 as catalyst are similarly effective and more selective nitrating agents. The powerful nature of nitronium salts as nitrating agents enables, for example, even trinitration[5] of benzene to trinitrobenzene.



Nitro-onium ions, such as $C_5H_5N^+NO_2$, readily prepared[6a,b] from suitable donors and nitronium salts, act as convenient **transfer nitrating reagents** in generally selective, clean reactions. Transfer nitrations are equally applicable to C- as well as to O-nitrations allowing, for example, safe, acid-free preparation of alkyl nitrates and polynitrates from alcohols (polyols).[6c]



$$ArH + \overset{+}{N}O_2\bar{P}F_6 \longrightarrow ArNO_2 + HPF_6$$

$$ArH + CH_3ONO_2 \xrightarrow{BF_3} ArNO_2$$

or

$$(CH_3)_2C(CN)ONO_2$$

Professor George A. Olah (right) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

*Based on Lecture given upon receipt of the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, 1979, sponsored by the Aldrich Chemical Company, delivered at the ACS/CSJ Chemical Congress in Honolulu, Hawaii, April 4, 1979 (Paper ORGN 236).

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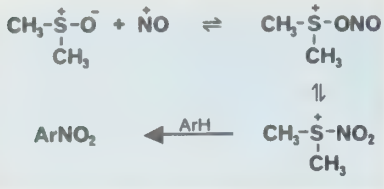
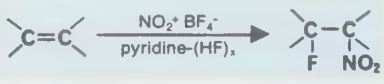
A new nitration system in the form of nitrosonium $(NO)^+$ salts in DMSO was developed.[7] The S-nitro ⇌ S-nitrito equilibrium was also directly observed by ^{13}C and ^{15}N NMR spectroscopy.



Solid superacid catalysts, comparable to or stronger than sulfuric acid, play a significant role in replacing conventional liquid acid (protic and Friedel-Crafts-type Lewis) catalysts in developing novel, clean, heterogeneous reactions. In the case of nitration, not only were alkyl nitrate nitrations carried out in this way, but also the **azeotropic nitration** of aromatic compounds with nitric acid was developed[4,5] over solid perfluorinated sulfonic acid catalysts (Nafion-H).

Water formed is continuously azeotroped off by excess of aromatics, thus preventing dilution of acid and allowing its extensive utilization.

Electrophilic nitration of olefins is also readily carried out[8a] with nitronium salts in pyridinium polyhydrogen fluoride as solvent. The reaction gives high yields of nitrofluorinated alkanes which subsequently can be dehydrofluorinated to nitroolefin.



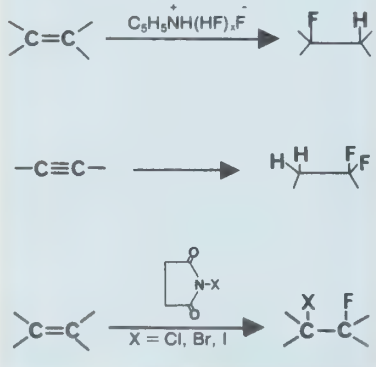
Some of the characteristic reactions of NO_2^+ and NO^+ salts are depicted in Figures I and II, respectively.

III. HALOGENATION

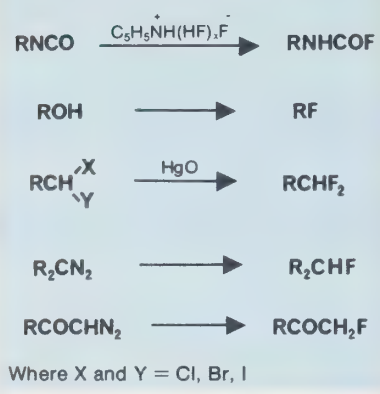
Fluorination of organic compounds still requires special techniques not generally feasible in the average laboratory. Reactions with the industrially most generally used and inexpensive fluorinating agent, anhydrous hydrogen fluoride, must be carried out under pressure in special equipment due to its relatively low boiling point (20° C) and corrosive nature.

We have found a simple way to enable carrying out anhydrous hydrogen fluoride reactions at atmospheric pressure in ordinary laboratory equipment (polyolefin or even glass) — by using the remarkably stable complex formed between pyridine and excess hydrogen fluoride. HF (70% w/w) and pyridine (30%) form a liquid complex, $C_5H_5NH^+(HF)_xF^-$, showing little vapor pressure at temperatures up to 60° C.[8b] The reagent (pyridinium polyhydrogen fluoride) thus enables[8(b-j)] one to carry out a wide variety of synthetically very useful fluorination reactions at atmospheric pressure under very simple experimental conditions. Examples of the usually high-yield reactions are:

Hydro- and Halofluorination of Olefins and Acetylenes

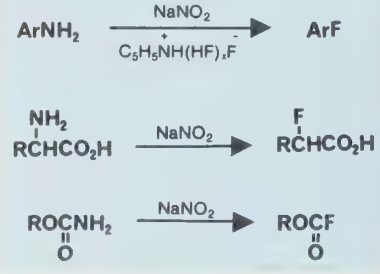


Fluorinations with Pyridinium Polyhydrogen Fluoride

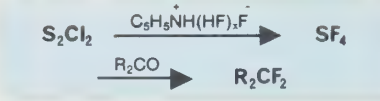


Where X and Y = Cl, Br, I

Deaminative Fluorination Reactions in Pyridinium Polyhydrogen Fluoride Solution



The pyridinium polyhydrogen fluoride reagent is also very convenient for the *in situ* preparation of inorganic fluorides such as SF_4.[9] Due to the good solvent properties



of pyridinium polyhydrogen fluoride, SF_4 fluorinations can be carried out *in situ* at atmospheric pressure.

Figure I.

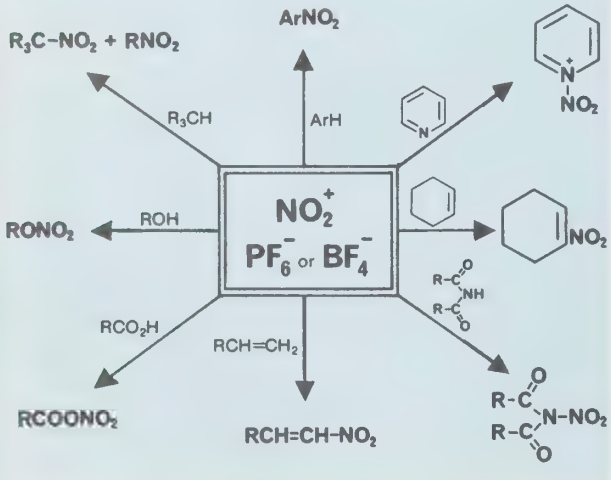
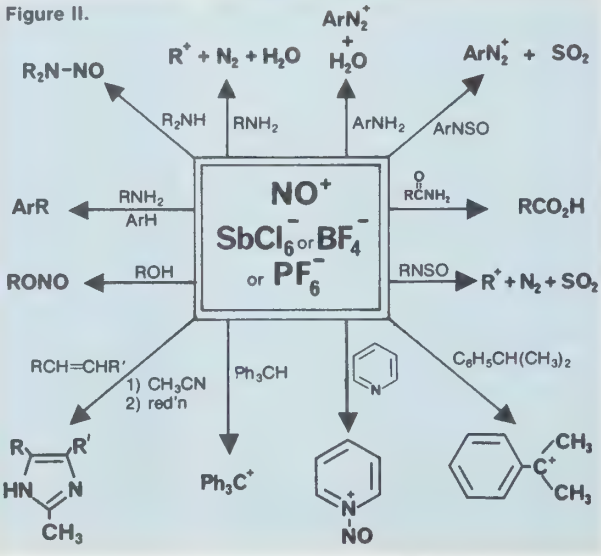
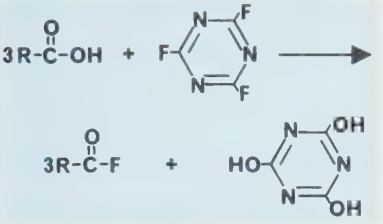


Figure II.

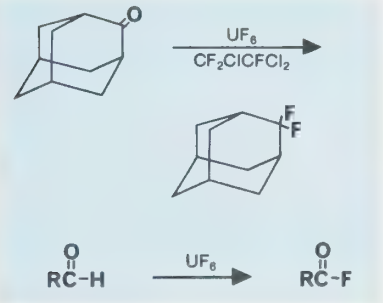


An alternative reagent, **selenium tetrafluoride** (SeF_4), which has an atmospheric boiling point of 106°, was also developed.[10] Fluorination of ketones, aldehydes, etc., proceeds in high yield. Since selenium compounds are generally toxic, the reagent must be handled with great care.

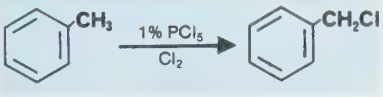
Cyanuric fluoride, another easily prepared fluorinating agent, is particularly advantageous in the preparation of acyl fluorides, including formyl fluoride.[11]



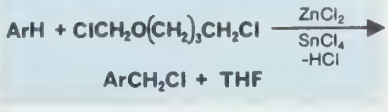
Uranium hexafluoride depleted of U^{235} is an abundant by-product of enrichment plants. It was found[12] to be highly soluble in fluorocarbons and halofluorocarbons, thus allowing its convenient use in atmospheric-pressure fluorination reactions (as well as in oxidations, *vide infra*).



Due to the high carcinogenic activity of chloromethyl ethers,[13] **chloromethylation** reactions have presented significant problems in recent years. A simple substitute for the preparation of chloromethylarenes is the selective side-chain chlorination of methylarenes. Whereas many radical chlorinations are known, an exceedingly simple and efficient PCl_5-catalyzed side-chain chlorination of alkylbenzenes (and alkanes) was found.[14]



An alternative chloromethylating agent, 1-chloro-4-chloromethoxybutane, reacting *via* oxygen participation to give tetrahydrofuran as the by-product, is also very effective.[15]

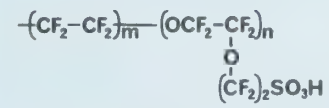


IV. ALKYLATION

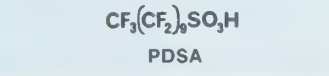
In the Friedel-Crafts alkylation method using aluminum chloride or related metal halide catalysts, complex mixtures of products are generally formed due to consecutive and concurrent polyalkylation and isomerization-disproportionation processes. They are promoted by extensive carbocationic complex formation with the catalyst.[16]

In order to avoid much of the side reactions and complex formation that necessitate aqueous acid/caustic workup (generally accompanied by loss of the catalytic halide), high-acidity solid acid catalysts which allow clean heterogeneous reactions without workup problems have been used increasingly. My group[17] has found of particular utility, solid perfluorinated sulfonic acids such as the acid form of DuPont's ion-membrane Nafion resin (Nafion-H) or longer-chain perfluorinated alkanesulfonic acids such as perfluorodecanesulfonic acid (PDSA). If needed, the

Solid Superacid Catalysts



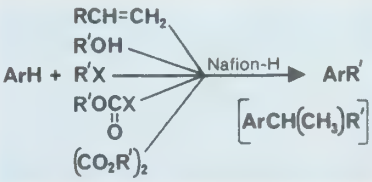
Nafion-H



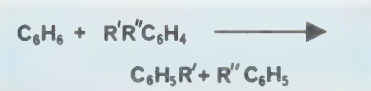
PDSA

acidity of these acids, which is similar to that of liquid Magic Acid® (FSO_3H-SbF_5), can be further increased by complexing with higher-valency fluorides such as SbF_5, TaF_5, and NbF_5.[18]

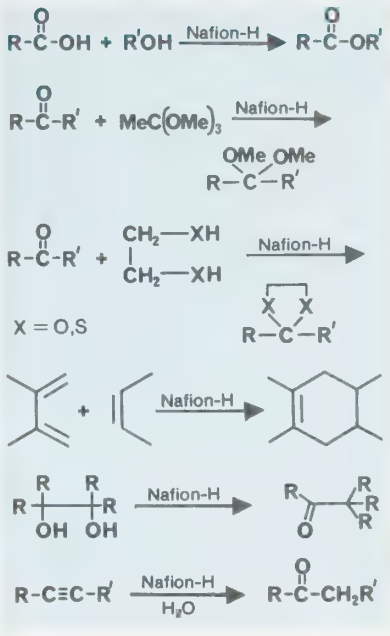
Alkylation of aromatics with olefins, alkyl halides, alcohols (including methyl alcohol), esters and the like takes place with ease over these catalysts.[19]



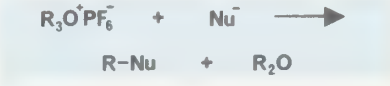
Transalkylation of aromatics with di- or polyalkylbenzenes can be carried out with equal ease.[20]



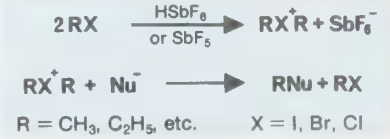
Solid superacid catalysts of the Nafion-H type also efficiently catalyze various reactions such as esterification, ketal (acetal) formation, Diels-Alder reactions, pinacol-pinacolone rearrangement and hydration of alkynes.[21]



For selective laboratory alkylations, we have also developed a series of ionic alkylating agents. Although Meerwein's[22] trialkyloxonium and dialkoxycarbenium tetrafluoroborate and hexachloroantimonate salts (as well as the conveniently soluble hexafluorophosphate salts used in our work[23]) are widely used as transfer alkylating agents, they lack selectivity and generally are incapable of C-alkylation.



Dialkylhalonium salts such as dimethylbromonium and dimethyliodonium fluoroantimonate, prepared from excess alkyl halide with antimony pentafluoride or fluoroantimonic acid and isolated as stable salts, as well as the less stable chloronium salts obtainable in solution,

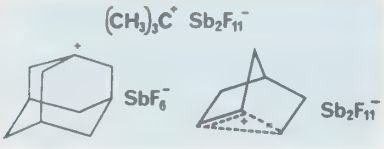


are very effective alkylating agents for heteroatom compounds (Nu = R_2O, R_2S, R_3N, R_3P, etc.), and for C-alkylation (arenes, alkenes). As the nature of the halogen atom can be varied, these salts provide useful selectivity in their alkylation reactions.[24]

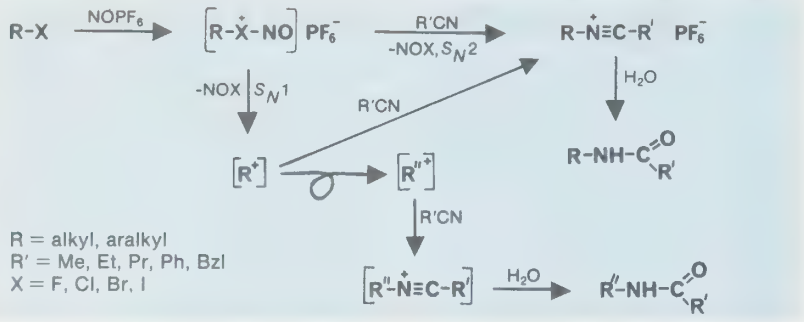
A great variety of other halonium ions was also prepared, including the following:

Their alkylating abilities were also studied.[24c,25]

Not only onium ions, but also **carbocation salts,** can be prepared and used as highly reactive alkylating agents. The remarkably stable triphenylcarbenium salts are widely used as hydride-abstracting agents and as initiators for cationic polymerizations. Using methods developed for preparing stable carbocations in superacidic media and isolating the salts generally by addition of Freon-type solvents or by evaporation of solvent SO_2, SO_2ClF or SO_2F_2, we have isolated a series of stable salts.[26] Typical carbocation salts, generally isolated as the fluoroantimonates, include such simple tertiary ions as the *tert*-butyl and adamantyl cations,[27] as well as stabilized secondary ions, such as the norbornyl cation.

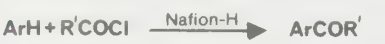


A particularly advantageous new technique is to carry out alkylation reactions with alkyl halides by initiation with nitrosonium salts. Using this reaction, a very mild form of the Ritter reaction was developed.[28]



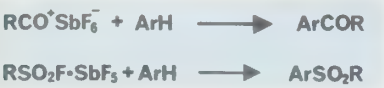
V. ACYLATION, SULFONYLATION

Solid superacidic catalysts of the Nafion-H type are also effective in bringing about Friedel-Crafts-type acylations with aroyl halides.[29] Interestingly, acetyl

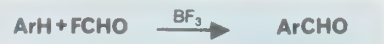


chloride gives predominantly ketene under the reaction conditions.

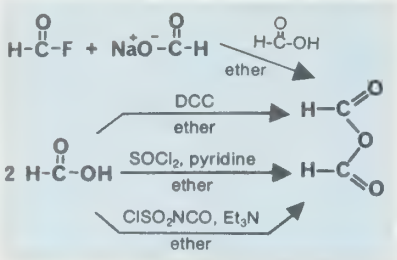
Isolated acyl salts, such as acetyl, propionyl and benzoyl salts, as well as similarly isolated sulfonyl halide-antimony pentafluoride complexes, are effective acylating (sulfonylating) agents.[30]



Acylation[31a] with acyl fluorides, generally catalyzed by boron trifluoride, also allows formylation, as formyl fluoride is a stable acyl halide of formic acid.



Formic anhydride was also prepared, characterized (by NMR and IR spectroscopy), and used as a new formylating agent.[32]

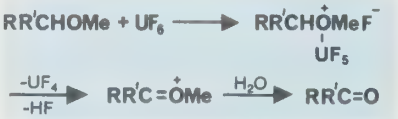


VI. OXIDATION AND OXYGENATION

During investigations of oxidation reactions, including electrophilic oxygenation of hydrocarbons, we have studied new oxidations with higher-valency fluorides (UF_6, WF_6, MoF_5, IF_5 and CoF_3),[12,33] peroxy compounds ($UO_4 \cdot 2H_2O$),[34] superacid-catalyzed hydrogen peroxide[35] and ozone reactions[36] (*i.e.*, with $H_3O_2^+$ and O_3H^+), as well as oxidations with NO_2^+.[7,37]

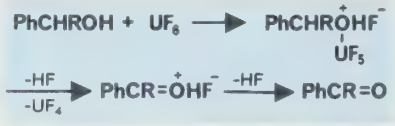
In spite of the availability of uranium hexafluoride depleted of fissionable ^{235}U and its remarkable properties, the study of the reactions of UF_6 with organic compounds remained virtually unexplored. The highly covalent nature of UF_6 makes it particularly suitable for reaction in nonaqueous solvents. Stable solutions of UF_6 in chlorofluorocarbons (Freons) or chlorohydrocarbons (methylene chloride or chloroform) can be used conveniently as they do not attack glass and are generally easy to handle.

Ethers undergo oxidative cleavage to form carbonyl compounds and alcohols. Furthermore, the direction of cleavage is predictable, thus the utility of ethers (such as benzyl or benzhydryl ethers) as protecting groups for alcohols is broadened. The oxidation of methyl ethers is of high yield and regiospecific. Trapping experiments with phenyllithium suggest the intermediacy of methoxycarbenium ions in the reaction.

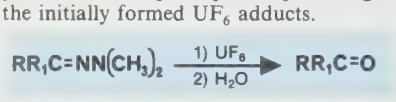


Benzyl and benzhydryl ethers are cleaved to the corresponding alcohols and benzaldehyde or benzophenone, respectively.

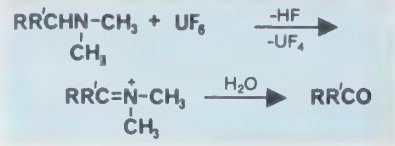
Benzyl alcohols are further readily oxidized to the corresponding carbonyl compounds.



Oxidative cleavage of protected carbonyl compounds such as tosylhydrazones and *N,N*-dimethylhydrazones also takes place with ease upon aqueous quenching of the initially formed UF_6 adducts.



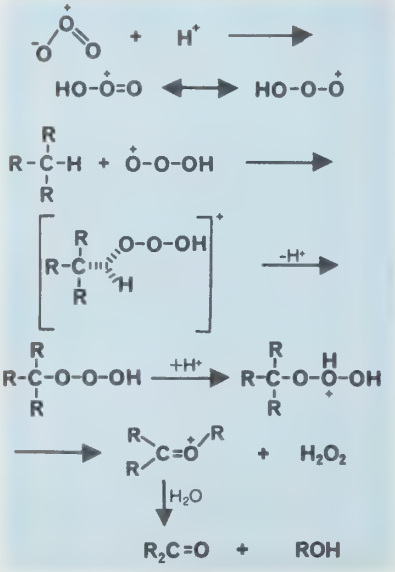
N,N-Dimethylalkyl(cycloalkyl)amines are also oxidized by UF_6 yielding, upon aqueous quenching, the corresponding carbonyl compounds.



WF_6, MoF_5, IF_5, and CoF_3 are capable of oxidations similar to those with UF_6 but are considerably less easily available and also tend to give more fluorination side reactions.

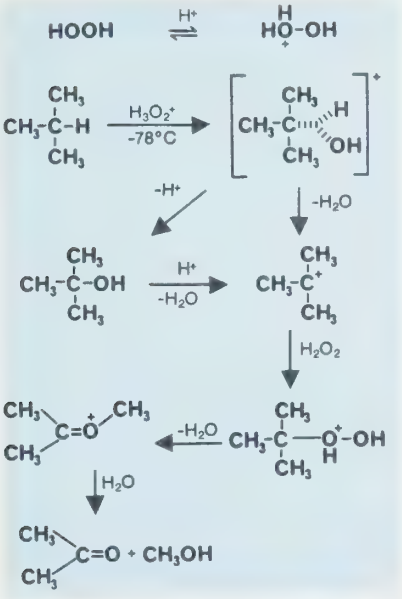
Both hydrogen peroxide and ozone readily protonate in superacids, giving the reactive electrophilic oxygenating agents H_2O^+-OH and $O=O^+$-OH, respectively.

Protonated ozone, upon reaction with a tertiary alkane *via* front-side insertion into the C-H bond, gives a very unstable trioxide which immediately undergoes acid-catalyzed cleavage rearrangement leading to the corresponding ketone and alcohol.



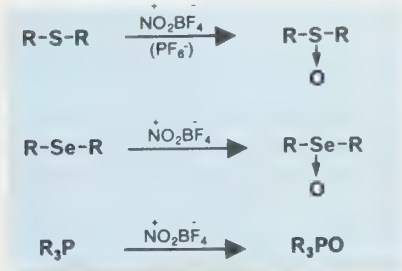
The reaction can be considered as the aliphatic equivalent of the well known cumene hydroperoxide reaction giving phenol and acetone.

Protonated hydrogen peroxide similarly acts as an electrophilic hydroxylating agent, forming alcohols which can react further with hydrogen peroxide giving hydroperoxides and thus, acid-catalyzed cleavage rearrangement products.

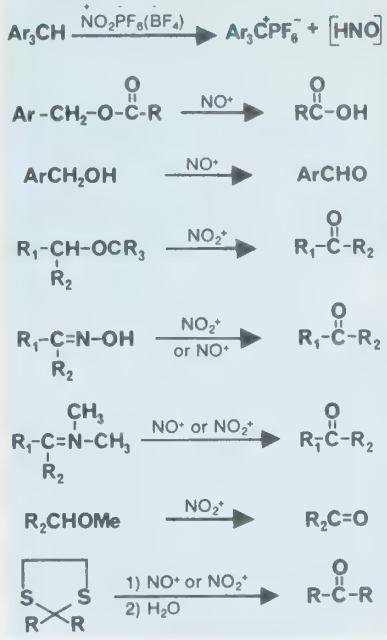


Benzene and alkylbenzenes are hydroxylated to phenols with high selectivity as the products are protonated in the acidic media and thus, are protected from further oxidation.

The nitronium ion, NO_2^+, is generally considered to function only as a nitrating agent. It was found,[7] however, that it possesses significant ambident reactivity and acts as an oxidizing agent. Dialkyl (aryl) sulfides and selenides, as well as trialkyl(aryl)phosphines, react with nitronium salts to give the corresponding oxides.

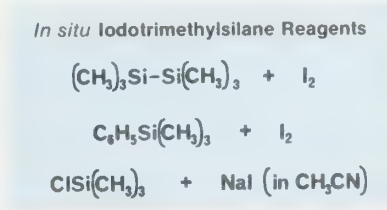


Another interesting aspect of our work relates to the utilization of stable nitronium (NO_2^+) and nitrosonium (NO^+) salts, particularly the PF_6^- and BF_4^- salts, as mild and selective hydride-abstraction and oxidative cleavage agents.[37] Representative examples are:

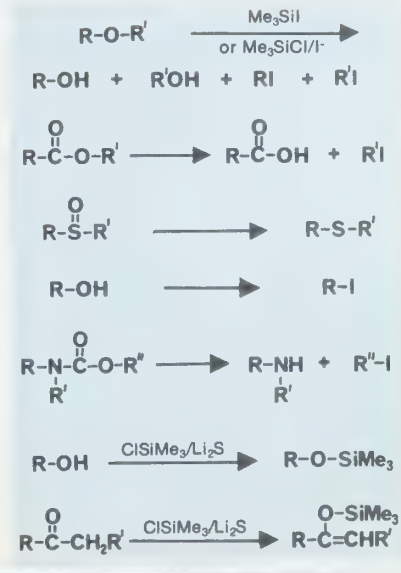


VII. MISCELLANEOUS REAGENTS

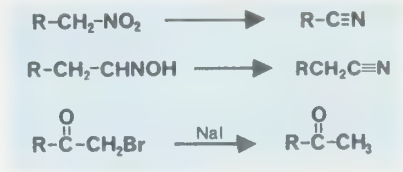
The utilization of **iodotrimethylsilane, $(CH_3)_3SiI$**,[38] (also studied independently by M. Jung[39]) and its simplified *in situ* analogs



offer excellent preparative possibilities for mild, neutral, nonaqueous cleavage-hydrolysis reactions, deoxygenations, oxidations, halogenations, and the like. Some examples are:



Other recently[40] developed reagents from our laboratory include the solid, stable and quite soluble **trimethyl(ethyl)-aminesulfur dioxide complexes** $R_3N \cdot SO_2$. These "solid forms" of SO_2 make many dehydrogenation, reduction, and halogenation reactions readily available, avoiding the use of inconvenient, low-boiling, and difficult-to-handle sulfur dioxide. Examples are:



Acknowledgment

Support of our research by the National Science Foundation, the National Institutes of Health and the U.S. Army Office of Research is gratefully acknowledged.

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3) a) G.A. Olah and H.C. Lin, *Synthesis*, 489 (1973).
b) G.A. Olah and H.C. Lin, *J. Am. Chem. Soc.*, **96**, 2892 (1974).
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b) G.A. Olah, R. Malhotra, and S.C. Narang, *J. Org. Chem.*, **43**, 4628 (1978).
c) S.C. Narang and M.J. Thompson, *Aust. J. Chem.*, **31**, 1839 (1978).
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7) G.A. Olah, B.G.B. Gupta, and S.C. Narang, *J. Am. Chem. Soc.*, in press.
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George Olah is Professor of Chemistry at the University of Southern California, Los Angeles, and Co-director of the Hydrocarbon Research Institute. His work was honored by such previous recognitions as the American Chemical Society Award in Petroleum Chemistry, the Leo Hendrick Baekeland Award and the Morley Medal. He belongs to a number of scientific societies and is a member of the National Academy of Sciences.

Professor Olah's research interests range from basic studies in hydrocarbon and petroleum chemistry to the study of new synthetic methods and reactions including investigation of reaction mechanisms and intermediates, most notably carbocations. He pioneered, *inter alia*, the field of superacid chemistry, *i.e.*, acid systems millions of times stronger than sulfuric acid, allowing observation and even isolation of many previously considered unstable species such as carbocations, halonium ions, and various other onium and carboxonium ions. A new field of chemistry is rapidly evolving using both liquid and solid superacidic catalysts developed in his studies.

Choosing and Using Noble Metal Hydrogenation Catalysts

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Catalytic hydrogenation at its best cannot be topped as a means of achieving controlled transformations of organic compounds. Yields are often very high and the products are obtained free of reagents by simply filtering off the catalyst. Appropriate conditions and catalysts usually can be chosen quickly, and satisfactory results obtained with very little experimentation.

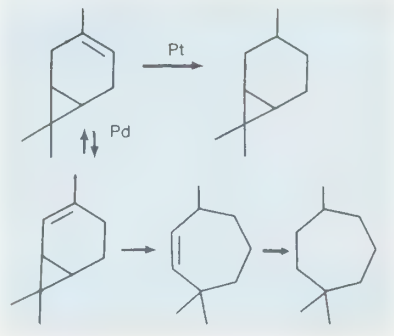
It is the aim of this paper to explore some of the factors that enter into the choice of catalysts and conditions and to set down general guidelines to facilitate suitable choices. Emphasis will be placed on noble-metal catalysts. These catalysts can be exceedingly active and can reduce most functions even at ambient conditions.

Choosing a Catalyst

The main catalytic properties of a catalyst are determined by the major metal present. In choosing a metal it is convenient to treat the metal as if it were a reagent with characteristic properties toward each type of function. This is done with the realization that these characteristic properties are modified by the reaction environment and by the overall electronic and steric structure of the molecule. All organic chemists are familiar with this type of thinking. Most noble metals will reduce most functions, but the activities vary tremendously. Metals can be chosen most easily by recourse to one of several books that list metals effective for hydrogenation of various functions.[1-4] A first-choice guide is appended herewith.

Suitable metals are chosen from these lists on two counts: they should be good for what one wants to do, and poor for what one does not want to do. For instance, palladium is excellent for the hydrogenation of aromatic nitro compounds and is widely used for this purpose, but it would not be the preferred catalyst for the hydrogenation of halonitroaromatics to chloroanilines, as palladium is also an excellent catalyst for dehydrohalogenation. Platinum is much better for halonitroaromatics, having excellent activity for nitro-group reduction, but relatively poor activity for dehydrohalogenation. This reduction can also be done quantitatively by use of a sulfided platinum-on-carbon catalyst; the sulfur present completely prevents dehalogenation.

Sometimes a combination of properties renders a metal unsuitable. The point is illustrated by hydrogenation of car-3-ene. This compound is reduced over platinum to *cis*-carane in very high yield, but over palladium the major product is trimethylcycloheptane. The latter compound results from three properties of palladium: it is excellent for double-bond migration, for hydrogenolysis of conjugated cyclopropyl systems, and for olefin saturation. Platinum, on the other hand, is relatively active only for olefin saturation, hence the excellent yield of carane.[5]



Choosing a Support

More effective use of a metal is made if it is supported. Hundreds of supports have been used, but for most purposes a good carbon or alumina support will be adequate for the majority of reactions. Indeed these supports account for most catalyst usage. Sometimes in reactions of the type A → B → C, a support such as calcium carbonate or barium sulfate may give slightly better yields of B, presumably because B is less strongly adsorbed. Hydrogenation of acetylenes to *cis*-olefins is an example.

Carbon seems more effective than alumina in promoting intermolecular reductions such as reductive alkylations and the formation of dicyclohexylamines in the reduction of anilines.[6] Alumina is a better support than carbon for the rhodium-catalyzed hydrogenation of acetophenone to cyclohexylethanol; in various solvents the yields with alumina are 15-25% higher than with carbon.[7]

Concentration of Metal on a Support

Metal concentration on commercial hydrogenation catalysts varies from a fraction of a percent to 30% or more. High

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metal concentrations decrease the volume of catalyst to be handled, low metal concentrations increase the activity on a *weight of metal* basis. Some change in selectivity may also occur as concentration changes, as will be discussed later. In general, unless there are special demands, 5% metal-on-support is a convenient catalyst for most applications.

Concentration of Catalyst in the System

Commercial hydrogenations have been run with catalyst concentrations from a fraction of a percent of catalyst to equal weights of substrate and catalyst. In general, for easily hydrogenated functions a 0.5 to 2% catalyst on support loading is probably more than enough; more resistant functions and sterically impeded functions may require higher loadings for convenient rates. It is much less frustrating to use an unnecessarily large amount initially, than too little. The amount of catalyst can always be cut down once the reaction has been shown to go. Easily hydrogenated functions may produce marked exotherms and due allowance should be made for this.

Temperature and Pressure

Temperature and pressure ranges over which successful hydrogenations can be carried out are often very large, fortunately. In general, activity increases with increasing temperature and pressure, but obvious and not-so-obvious exceptions exist. In practice the conditions are often set by the equipment available, and lack of activity is compensated for by use of more catalyst and by patience.

Agitation

Heterogeneous liquid-phase hydrogenations are three-phase systems. For a reaction to proceed, hydrogen must leave the gas phase, cross a gas-liquid interface, cross a liquid-solid interface, and be adsorbed on the catalyst surface. There are surprisingly high resistances to these processes and the rates of many hydrogenations, especially over the very active noble metal catalysts, are controlled largely by these and other diffusional resistances. Vigorous agitation is important to achieve maximal activity of the catalyst.

Hydrogen Availability

When the rate is limited in large part by the rate of hydrogen transport to the catalyst surface, as it often is, the catalyst can be said to be operating in a "hydrogen-poor" condition. That is, the reduction would go faster if more hydrogen were available at the catalyst sites. On the other hand, when the rate is controlled largely by the intrinsic rate of the chemical reaction, the catalyst can be said to be operating in a "hydrogen-rich" mode. That is, the rate would not increase substantially if more hydrogen were available at the catalyst. It is easy to determine experimentally these different modes of operation.

Reactions operating in a "hydrogen-poor" mode increase in rate when the agitation is increased. Also, in reactions rate-limited by gas-liquid hydrogen transport, the rate will not increase linearly with an increase in the amount of catalyst. Reactions operating in a "hydrogen-poor" mode clearly are not using the catalyst efficiently, a consequence of some importance in industrial operations.

Effect of Hydrogen Availability on Selectivity

The concept of "hydrogen-poor" and "hydrogen-rich" catalysts can be used to predict the direction of change that changing pressure, temperature, metal concentration, catalyst loading and agitation will have on the selectivity of a reaction. Consider that hydrogenation of a substrate A can afford products B and C either by the parallel reactions A → B and C or the series reaction A → B → C. If the rate equations leading to B and to C contain hydrogen terms raised to different powers then the two reactions will be affected differently by changes in hydrogen availability at the catalyst surface.

Whether this condition exists can be easily determined experimentally. For instance, in going from a reaction with poor agitation to one with good agitation the ratio of B to C increases, then the assumption can be made that B is favored by a "hydrogen-rich" catalyst. Under this circumstance the product B is favored by a higher hydrogen pressure, a lower operating temperature (in that it decreases the rate of reaction relative to the rate of mass transport), a lower concentration of metal on the support, and less catalyst in the system. Deliberate deactivation of the catalyst may be in order. Solvents tend to increase hydrogen availability by lowering the surface tension and viscosity of the system. However, solvents have more complex effects as well, as will be discussed. On the other hand, if B is favored by a condition of low hydrogen availability, the reverse actions are taken.

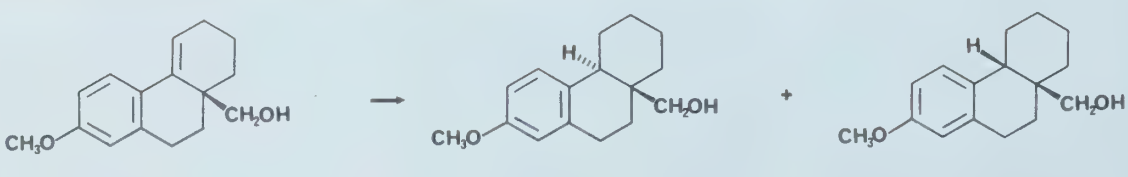
Two types of reactions that are favored by "hydrogen-poor" catalysts are the isomerization of a double bond relative to its hydrogenation and, in general, hydrogenolysis relative to hydrogenation.

Solvents

Solvents can have profound effects on both rate and selectivity of hydrogenation.[8] Rates can be influenced markedly both by an intrinsic property of the solvent and by its contained impurities. The number of active sites in a catalyst is usually only a small fraction of the catalyst present, and the amount of total catalyst used, a small fraction of the amount of solvent. Very small percentages of certain impurities can thus exert large influences on the rate. On the other hand, gross amounts of impurities can easily be tolerated if they happen not to affect the catalyst adversely. The best method for ascertaining suitability of a particular batch of solvent is by actual test. In general, impurities apart, more polar solvents tend to give faster rates than less polar ones.

Selectivity of hydrogenation sometimes can be drastically altered by the solvent and, fortunately, in ways that are largely predictable. Solvent is often a most important variable, but it is one whose potential for selectivity control is often overlooked. Some idea of the extent of influence by solvent is illustrated in the following examples concerning stereochemistry. From these data and others not presented here, some working generalities for choice of solvent will be given.

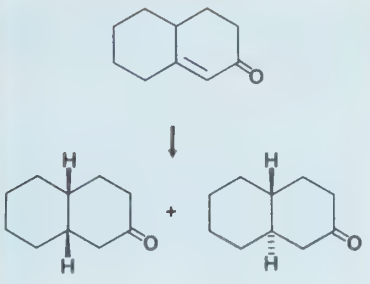
Stereochemistry: Solvents offer an important means of influencing stereochemistry, as illustrated by the following abstracted data:[9]



Solvent	Dielectric Constant	Relative Amounts in Product	
Hexane	1.9	39	61
DMF	36.7	94	6

In this case the influence of solvent was thought to arise from competition for catalyst sites by solvent and the hydroxymethyl function, which anchors the olefin in an orientation such that hydrogen adds from the same side of the molecule. Only extremes are shown here and the correlation between dielectric constant of the solvent and stereochemistry holds for a variety of solvents. From these data the generality was derived that to the extent this type of anchoring (haptophilic effect) is operative, the extremes of stereospecificity are likely to be found at the extremes of the dielectric constant of the solvent.

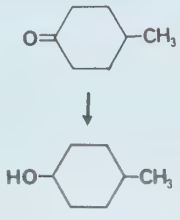
Augustine[10] found it necessary, in making a correlation between dielectric constant and stereospecificity, to group solvents as protic and aprotic. When this is done the extremes of stereospecificity are again found at the extremes of dielectric constant, but the direction of change is opposite in the two groups. The extremes of the two series are shown in the data below.



Solvent	Dielectric Constant	Percent *cis*-β-Decalone
MeOH	33.6	41
t-BuOH	10.9	91
DMF	38.0	79
n-Hexane	1.9	48

The data illustrate also how easily one can be misled in deriving generalities about solvents from limited experiments. If, for instance, only methanol and hexane had been compared, the conclusion would have been reached that large differences in dielectric constant cause only small changes in stereospecificity, whereas a comparison of methanol and dimethylformamide would suggest that relatively small differences in dielectric constant cause large differences in stereoselectivity. Perhaps the safest way of ascertaining whether a stereochemical (or other) sensitivity to dielectric constant exists, without extensive testing, is to compare two solvents of widely differing dielectric constant with both solvents being either protic or aprotic. Presumably the protic solvents should require separate treatment only with those substrates that would readily hydrogen-bond.

Stereochemistry of ketone hydrogenation also can be profoundly altered by solvent and catalyst. For example, hydrogenation of 5α-cholestan-3-one over platinum in *t*-butyl alcohol gives mainly the equatorial alcohol 5α-cholestan-3β-ol, whereas the axial alcohol 5α-cholestan-3α-ol is obtained in high yield over rhodium in isopropyl alcohol-hydrogen chloride.[11] The latter system, rhodium in isopropyl alcohol-hydrogen chloride or in tetrahydrofuran-hydrogen chloride, has been claimed to be one of the best means of producing axial alcohols from unhindered ketones by hydrogenation.[12]



Catalyst	Solvent	*cis*/*trans*
Platinum black	*t*-BuOH	3.5
Rhodium black	*i*-PrOH-HCl	11

Useful Working Generalities Regarding Solvents

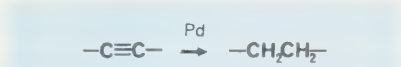
1) The extremes of selectivity of any kind will be found at the extremes of the dielectric constants of the solvents used, with the following provisos:
   a) protic and aprotic solvents may have to be considered separately as noted above
   b) the species actually undergoing hydrogenation must not change, as for example, a neutral species being changed by solvent into either an anionic or cationic one.
2) Hydrogenolysis relative to hydrogenation is favored by solvents of higher dielectric constant. The generality is applicable to a variety of competitive situations, and presumably holds because the transition state in the hydrogenolysis reaction always has the greatest charge separation.

GUIDE TO CATALYST SELECTION

Acetylenes → *cis*-Olefins

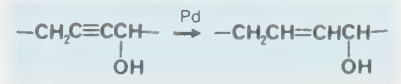
Palladium usually gives excellent results if the reduction is arrested at one mole of hydrogen absorption. Some *trans* olefin may form even in the earliest stages of reduction, but the amount increases rapidly as absorption of one mole of hydrogen is approached and exceeded. Subambient temperatures (-20°C) and/or inhibitors such as Pb or Cd may be used, if needed, to maximize the yield.

Acetylene → Paraffin



Palladium gives excellent results. Platinum is better, if isomerization of the intermediate olefin prior to its saturation is likely to affect selectivity.

Propargyl Alcohols → Allylic Alcohols



Hydrogenolysis of the allylic function is usually not a troublesome side reaction and palladium gives excellent results. Acetylenic glycols are more difficult. Rhodium, especially in the presence of alkali, may be suitable if palladium fails.

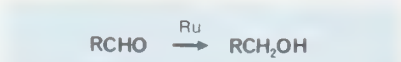
Acids → Alcohols

The reduction is difficult and requires high pressures. Ruthenium has been used at pressures of 15,000 psig. Rhenium heptoxide has given good results at 4,000 psig.

Acid Chlorides → Aldehydes

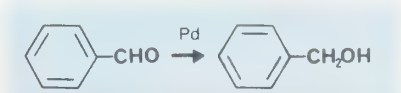
Palladium is the preferred catalyst. Reduction goes easily but the problem is to prevent reduction to the alcohol. Inhibitors are often used. Excellent yields have been obtained with one mole of added base or reduction at reduced pressures.

Aliphatic Aldehydes → Alcohols



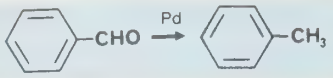
Ruthenium is excellent. Water acts as cocatalyst. Maximal yields are obtained at high pressures and low temperatures (which minimize noncatalytic condensations).

Aromatic Aldehydes → Alcohols



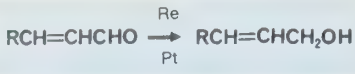
Palladium is excellent. If the yield of alcohol is less than quantitative, the problem can be corrected usually by the use of nonpolar, nonacidic solvents with perhaps a trace of base. Hydrogen absorption should be limited to one mole.

Aromatic Aldehydes → Hydrocarbons



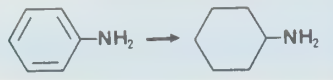
Palladium is excellent. Hydrogenolysis is promoted by traces of acids and by polar solvents. The reduction proceeds largely in a stepwise fashion through the benzyl alcohol.

Unsaturated Aldehydes → Unsaturated Alcohols



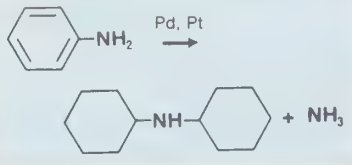
The reduction is difficult. Rhenium (modified), ruthenium (modified), and platinum (modified) have all been used successfully. The reaction depends critically on the metal, catalyst preparation and the presence of various modifiers. Most catalysts exhibit the reverse selectivity.

Anilines → Cyclohexylamines



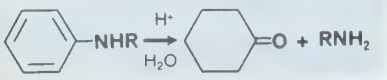
Rhodium and ruthenium are excellent. They are active and give little dicyclohexylamine. Slightly more coupling is obtained over carbon support than over alumina. Coupling may be decreased by the presence of ammonia, increased pressure, and decreased temperature.

Anilines → Dicyclohexylamines



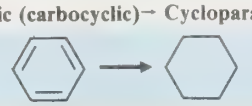
Palladium and platinum give moderate yields which increase with increasing temperature. Coupling is decreased by increasing pressure.

Anilines → Cyclohexanones



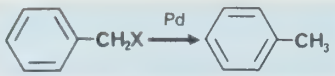
Palladium is quite effective, probably due to its excellence for double-bond migration in partially hydrogenated rings and relative ineffectiveness for imine saturation. Yields increase with increasing substitution on the nitrogen atom.

Aromatic (carbocyclic)→ Cycloparaffin



Rhodium, platinum, ruthenium and palladium are all used industrially. Choice depends on other functions present and on the operating conditions available. Palladium and ruthenium require more vigorous operating conditions than rhodium or platinum.

Benzyl Compounds → Aromatic Hydrocarbons



Palladium is excellent for hydrogenolysis of benzyl functions. The reaction is accelerated by polar solvents and by acids. Ring saturation is nil.

Dehydrohalogenation

Palladium is excellent and is widely used. The reaction is frequently carried out in the presence of a mole of base. In complex molecules the base chosen may make a difference in yields. Polyhalo compounds can usually be dehalogenated in a stepwise manner.

Epoxides → Alcohols

Palladium is usually used. It mainly opens the ring with inversion. Direction of the ring opening depends on the substrate and often on the pH. Deoxygenation is rarely a problem.

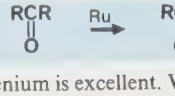
Hydrazones → Hydrazines

Platinum is usually used in this reduction. Hydrogenolysis of the nitrogen-nitrogen bond is rarely a problem.

Imines → Amines

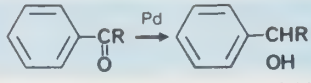
Platinum is widely used for this reaction and for reductive alkylation, which gives an imine intermediate. Palladium can be effectively used when there is little steric hindrance around the bond.

Ketones (aliphatic) → Alcohols



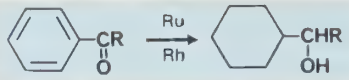
Ruthenium is excellent. Water functions as cocatalyst. Hydrogenolysis is nil, as is ketal formation in lower alcohols.

Aromatic Ketones → Aromatic Alcohols



Palladium is excellent and yields approach 100%. Hydrogenolysis can be prevented by use of nonacidic, nonpolar solvents with traces of base if necessary.

Aromatic Ketones → Saturated Carbinols



Rhodium and ruthenium have given excellent yields. Hydrogenolysis decreases as pressure is increased. Acidic solvents should be avoided although traces of acid have proved beneficial.

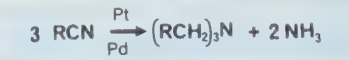
Aliphatic Nitriles → Primary Amines

Palladium, platinum and rhodium have been used in this reduction, but little primary amine will result unless the nitrile is hindered or the reaction is carried out in a reactive solvent, such as ammonia, acid, or acetic anhydride.

Aliphatic Nitriles → Secondary Amines

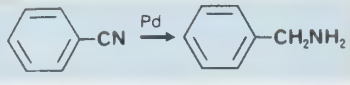
Rhodium is uniquely effective in this reduction and gives high yields of secondary amines. It is also useful in making unsymmetrical secondary amines by nitrile reduction in the presence of an amine.

Aliphatic Nitriles → Tertiary Amines



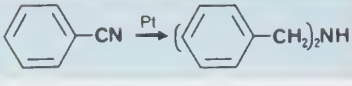
High yields of tertiary amines are obtained from low-molecular-weight nitriles in nonreactive solvents over either palladium or platinum.

Aromatic Nitriles → Benzylamines



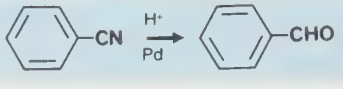
Using palladium, yields approach theoretical if small amounts of an aliphatic secondary amine are present. Otherwise a mixture of benzyl and dibenzylamine results. The yield is also solvent dependent.

Aromatic Nitriles → Dibenzylamines



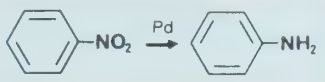
Nearly quantitative yields of dibenzylamines are obtained over platinum, preferably with one-half mole of water present to minimize catalyst inhibition.

Aromatic Nitriles → Aldehydes



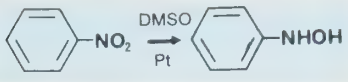
Good yields of aldehydes can be obtained over palladium in acidic media. Conditions should be arranged so that hydrolysis of the intermediate imine is faster than its hydrogenation. Hydrogen absorption should be limited.

Nitroaromatic Compounds → Anilines



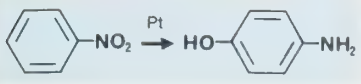
The reduction goes very easily over a number of catalysts. Palladium is usually preferred for economic reasons and for minimal ring reduction.

Nitroaromatic Compounds → Aromatic Hydroxylamines



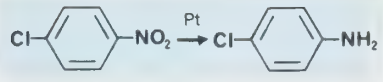
High yields of aromatic hydroxylamines can be obtained by hydrogenation over platinum in lower alcohols containing 1-2% of dimethyl sulfoxide.

Nitroaromatic Compounds → Aminophenols



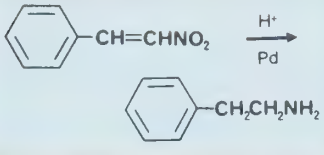
Production of aminophenol depends on successful competition between hydrogenation of the intermediate hydroxylamine and its acid-catalyzed rearrangement. Platinum is the preferred metal. The yield is sensitive to reaction variables.

Halonitroaromatics → Haloanilines



The product can be obtained in excellent yield over inhibited palladium or platinum, or over platinum or rhodium (sulfided).

Nitroolefins → Saturated Amines

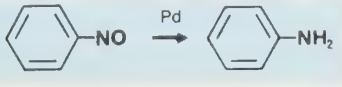


Good yields of saturated amine can be obtained over palladium in acidic media. In neutral media dimeric butane derivatives result.

***N*-Nitrosoamines → Hydrazines**

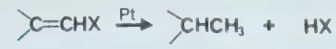
Over palladium, hydrogenolysis of the nitrogen-nitrogen bond can be kept to low levels. Excellent yields can be expected.

Nitrosoaromatic Compounds → Anilines



The reaction proceeds easily and in excellent yield over palladium.

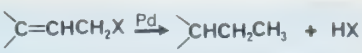
Hydrogenolysis of Vinyl Compounds



X = Cl, Br, OR, OCOR, etc.

The result is sensitive to structure. Hydrogenolysis should precede hydrogenation. Platinum seems generally preferred over palladium.

Hydrogenolysis of Allylic Compounds



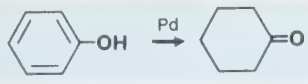
X = Cl, Br, OR, OCOR, etc.

The result is sensitive to the steric requirements of the molecule. Palladium seems generally more effective than platinum. Hydrogenolysis should precede saturation.

Oximes → Primary Amines

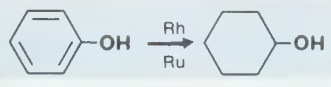
Excellent yields have been obtained by reduction over rhodium in alcoholic ammonia. Yields may be sensitive to substrate concentration due to hydrolysis of oxime by water formed in the reduction.

Phenols → Cyclohexanones



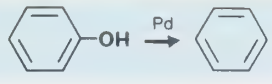
Palladium is excellent due to low activity for ketone reduction and high double-bond isomerization. Rhodium is perhaps better with polyhydric compounds. High yields can be expected.

Phenols → Cyclohexanols



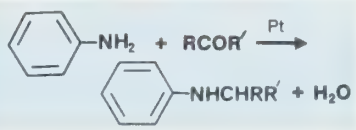
High yields are expected over rhodium or ruthenium. Hydrogenolysis is minimized by neutral, nonpolar solvents, low temperature, and high pressure.

Phenols → Benzenes



This reduction is easily achieved if the phenol is first converted to a suitable ether derivative as by reaction with 2-chlorobenzoxazole or 5-chloro-1-phenyltetrazole.

Reductive Alkylation



Platinum is used usually, affording high yields of alkylated product. Palladium is effective with aldehydes or low-molecular-weight ketones. Precursors of anilines such as nitrobenzenes or nitrosobenzenes may be used directly in the reductive alkylation without prior conversion to anilines.

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7) P.N. Rylander and L. Hasbrouck, *Engelhard Ind. Tech. Bull.*, **8**, 148 (1968).
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9) H.W. Thompson, E. McPherson, and B.L. Lences, *J. Org. Chem.*, **41**, 2903 (1976).
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12) S. Nishimura, M. Ishige, and M. Shiota, *ibid.*, 963 (1977).

About the Author

Dr. Rylander received the B.Ch.E. degree from Johns Hopkins University in 1942 and his Ph.D. from Indiana University in 1948. After postdoctoral studies at the University of Rochester and at Harvard, he joined Standard Oil Co. of Indiana in 1951. For the past 23 years; Dr. Rylander has been associated with Engelhard Industries where he has pursued research in the field of his main interest: application of catalysis to organic syntheses.

Dr. Rylander is the author of three books and numerous papers on catalysis. He has edited two other books and holds quite a number of patents in the areas of hydrogenation, dehydrogenation, dehydration, oxidation, alkylation and polymerization.

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Catalytic Hydrogenation in Organic Syntheses

by

Paul N. Rylander

Published in 1979 by Academic Press

Z10,430-2

Aldrich offers an extensive collection of noble metal catalysts and salts; the following may be especially pertinent to the chemical processes discussed by Dr. Rylander.

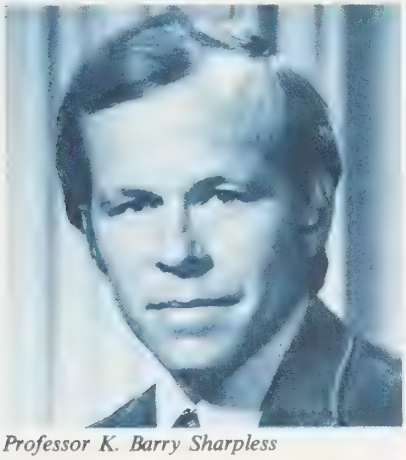
20,867-1	Bis(triphenylphosphine)-palladium(II) chloride
20,901-5	Palladium(II) acetylacetonate
20,583-4	Palladium black
21,291-1	20% Palladium hydroxide on carbon
20,567-2	1% Palladium on activated carbon
20,568-0	5% Palladium on activated carbon
20,569-9	10% Palladium on activated carbon
20,570-2	1% Palladium on alumina
20,571-0	5% Palladium on alumina
20,574-5	0.5% Palladium on $^1/_8$-inch alumina pellets
20,572-9	5% Palladium on barium sulfate
21,435-3	5% Palladium on calcium carbonate
20,573-7	5% Palladium on calcium carbonate, poisoned with lead
20,575-3	1% Palladium on 4- to 8-mesh carbon
20,591-5	Platinum black
20,592-3	1% Platinum on activated carbon
20,593-1	5% Platinum on activated carbon
20,595-8	10% Platinum on activated carbon
20,596-6	1% Platinum on alumina
20,597-4	5% Platinum on alumina
20,601-6	0.5% Platinum on $^1/_8$-inch alumina pellets
20,598-2	1% Platinum on calcium carbonate
20,599-0	5% Platinum on calcium carbonate
20,602-4	0.5% Platinum on 4-to 8-mesh carbon
20,600-8	5% Platinum on sulfide carbon
20,603-2	Platinum(IV) oxide
20,614-8	0.5% Rhenium on $^1/_8$-inch alumina pellets
20,615-6	5% Rhenium on carbon
20,617-2	0.5% Rhodium on $^1/_8$-inch alumina pellets
21,285-7	5% Rhodium on alumina powder
20,616-4	5% Rhodium on carbon
20,619-9	0.5% Ruthenium on $^1/_8$-inch alumina pellets
20,618-0	5% Ruthenium on carbon
21,666-6	Tetrakis(triphenylphosphine)-palladium(0), 99%

Metal-Catalyzed, Highly Selective Oxygenations of Olefins and Acetylenes with *tert*-Butyl Hydroperoxide. Practical Considerations and Mechanisms.

K. Barry Sharpless
and Thomas R. Verhoeven
Department of Chemistry
Stanford University
Stanford, California 94305

I. Introduction

The purpose of this review is to call attention to recent advances in the use of *tert*-butyl hydroperoxide (TBHP) in organic synthesis. The emphasis here will be on the nonradical, metal-catalyzed oxygenations shown in Scheme I.

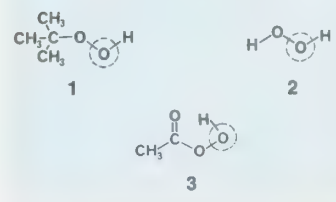


Professor K. Barry Sharpless

Dr. Thomas R. Verhoeven

When one considers the combined features of economics, selectivity, and safety, TBHP emerges as one of the best sources of oxygen atoms for a variety of organic oxygenations. Some of the factors which make TBHP (**1**) superior to better known sources of oxygen atoms such as hydrogen peroxide (**2**) and peracetic acid (**3**) are worth discussing. Perhaps the key advantage of TBHP is its selectivity. In contrast to hydrogen peroxide and peracetic acid, TBHP is unreactive toward most organic compounds **in the absence of catalysts.** TBHP is less sensitive to contamination by metals than either peracetic acid or H_2O_2, and on this basis is safer to handle. In dilute organic solution TBHP has high thermal stability (its half-life is 36 days at 115°C as a 0.2*M* solution in benzene).[1] Hydrogen peroxide is, in principle, also very stable thermally, but it is more sensitive to decomposition catalyzed by trace metallic impurities than is TBHP.[2]

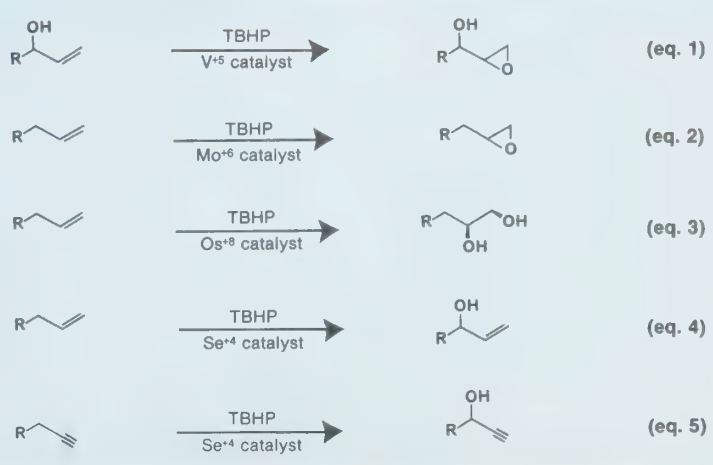
Scheme II. Oxygen Atom Sources



1 **2** **3**

Peracetic acid is on every count less stable than TBHP. The 40% solution of peracetic acid in acetic acid sold by FMC can only be shipped by truck, and even then only in minidrums or smaller containers, whereas solutions which are (by weight) 70% TBHP and 30% H_2O may be shipped in tank car quantities. This does not mean there are no hazards associated with using TBHP (potentially hazardous situations to be avoided in handling TBHP will be discuss-

Scheme I.



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ed later). What it does mean is that peracetic acid is more dangerous in almost every situation than is TBHP. High-strength hydrogen peroxide solutions also tend to be less stable than TBHP solutions of comparable peroxide content.

After six years of working on metal-catalyzed reactions of TBHP (somtimes as much as five moles in one reaction) we have not yet had a single explosion. On the other hand, we have had a few small explosions while working with small amounts of hydrogen peroxide and also with peracetic acid. The above mentioned explosions only occurred when some metal-catalyzed process was being attempted. In our opinion, these explosions were due to accelerated decomposition of H_2O_2 or of peracetic acid catalyzed by the metal.

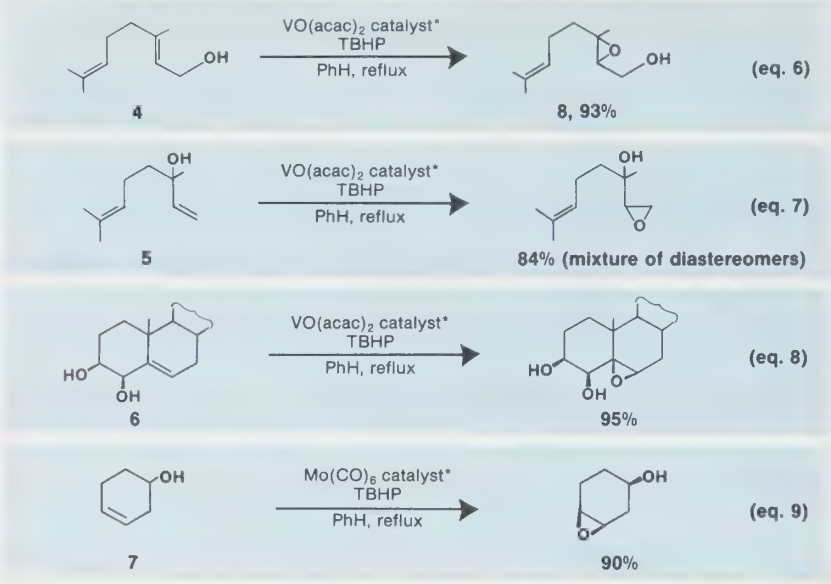
We have made safety comparisons of TBHP with the two most common peroxidic oxidants, H_2O_2 and peracids, because it is our experience that most chemists regard these latter reagents as less dangerous than *tert*-butyl hydroperoxide (TBHP). The origin of this phobia toward organic peroxides (*e.g.*, TBHP) almost certainly is derived from two factors, the more important being that common organic ethers (diethyl ether, tetrahydrofuran and, especially, diisopropyl ether) form dangerously explosive hydroperoxides by autoxidation upon exposure to the atmosphere. Chemists are justifiably afraid of ether hydroperoxides, and tend to associate *tert*-butyl hydroperoxide with this deadly class of compounds. Thus, any substance whose name includes the word peroxide is regarded as very dangerous to work with. Some peroxides are indeed extremely unstable and can only be stored at low temperature; but the range of stability is wide, and TBHP is one of the most stable organic peroxides known.

The other important factor in the TBHP phobia is lack of familiarity. This is largely due to the fact that TBHP is a rather new compound, being first prepared in 1938 by Milas.[3] This has led to the curious situation where chemists, who have long been comfortable with the idea of using peracids[4] (*e.g.*, for epoxidation of olefins), have less respect for the explosive possibilities with peracids than they do with the tamer substance TBHP. All of this has begun to change due to the discovery, almost simultaneously (*ca.* 1965) in several industrial laboratories,[5-7] that propylene could be epoxidized by TBHP in the presence of a molybdenum catalyst. This process (Oxirane Process) is now yielding two billion pounds of propylene oxide each year. Our interest in metal-catalyzed reactions of TBHP began in 1972 and was aroused by the remarkable effectiveness of the industrial epoxidation process.[8]

II. Epoxidation of Olefins

1. Selective Epoxidation of Olefinic Alcohols (Scheme I, eq. 1)

From reports by Sheng and Zajacek[9] and by List and Kuhnen[10] one could see that simple allylic alcohols were especially reactive toward epoxidation by TBHP in the presence of vanadium catalysts. We decided to have a look at more complex allylic alcohols in order to determine the regioselectivity and/or stereoselectivity available with these systems. The results were unexpectedly dramatic in that the selectivities were much greater than those discovered by Henbest[11] for the epoxidation of olefinic alcohols by carboxylic peracids. As shown in equations 6 through 9, geraniol (**4**), linalool (**5**), 4β-hydroxycholesterol (**6**) and 3-cyclohexen-1-ol (**7**) all gave excellent yields of only one of the possible isomeric epoxy alcohols.[12a] Both allylic and homoallylic (*e.g.*, **7**) alcohols showed the effects. In the case of vanadium catalysis even a bishomoallylic alcohol [1-hydroxy-(*E*)-4-nonene] exhibited a substantial (13.4 times) rate acceleration over an analogous olefin [(*E*)-5-decene).[12a]



The different, and often superior, stereoselectivity of these metal-catalyzed epoxidations is also observed with acyclic olefinic alcohols (Table I). The examples in Table I are taken from our recent publication[13] in which we correct the errors in our earlier work[14,15] on this same subject.

The experimental details for these epoxidations are contained in our original publications[12a,14] although two important modifications of those procedures merit discussion: (1) Heating (reflux in benzene) was employed for both the vanadium- and molybdenum-catalyzed epoxidations (eq. 6-9). **Although heating is often necessary to achieve reasonable rates for the molybdenum-catalyzed process, most vanadium-catalyzed epoxidations of olefinic alcohols proceed readily at, or below, room temperature.**[12b] (2) We originally used aqueous bisulfite (HSO_3^-) to reduce excess TBHP. We have found that the use of bisulfite makes it difficult, and often impossible, to distill the products without extensive polymerization occurring. These problems became especially severe when large-scale (>1 mole) distillations were attempted (after bisulfite work-up) with simple epoxides as well as with epoxy alcohols and even allylic alcohol products. **The use of aqueous sulfite (*e.g.*, Na_2SO_3, pH of aqueous solution is *ca.* 9)[17] or dimethyl sulfide (with or without a catalytic amount of acetic acid)[18] provide preferable alternatives[19] for reduction of excess TBHP.**

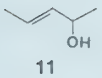
During the past five years these molybdenum- and vanadium-catalyzed epoxidations of olefinic alcohols have been utilized often in complex synthetic sequences. Space does not allow enumeration of all the applications. Consequently, only some of the more interesting examples are presented here (eq. 10 → eq. 31). The examples are arranged in the order of allylic alcohols, then homoallylic alcohols, and finally bishomoallylic alcohols.

Allylic alcohols have been the substrates most often epoxidized by these reagents (*e.g.*, eqs. 10-26). Although molybdenum catalysts are much (*ca.* 100 times) more reactive for epoxidation of isolated olefins, vanadium catalysts are usually preferred for allylic alcohols. With vanadium catalysts the rate acceleration for epoxidation of allylic alcohols is so great (on the order of 10^3 faster than the parent olefin) that the absolute rates, and usually also the selectivities, surpass those realized with molybdenum catalysis.[12b]

Reasonable selectivities are also achieved with some homoallylic (*e.g.*, eqs. 27-30) and bishomoallylic (eq. 31) alcohols. In

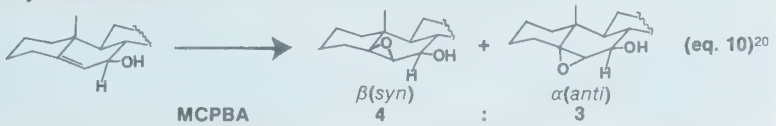
*We usually add the vanadium and molybdenum catalysts in these lower valent forms [*i.e.*, $VO(acac)_2$ and $Mo(CO)_6$]. However, these species are oxidized by TBHP to the catalytically active V^{+5} and Mo^{+6} complexes.

Table I. Stereochemistry of Epoxidation of Acyclic Allylic Alcohols.[a]

Allylic alcohol		*threo*	*erythro*
 9	V^{+5}, TBHP	20	80
	MCPBA	60	40
 10	V^{+5}, TBHP	5	95
	MCPBA	45	55
 11	V^{+5}, TBHP	29	71
	MCPBA	64	36
 12	V^{+5}, TBHP	71	29
	MCPBA	95	5

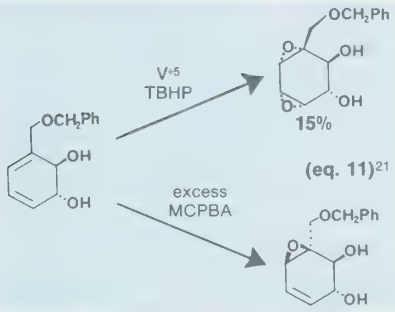
[a]For the reaction conditions and for additional examples see ref. 13.

(a) Allylic Alcohols

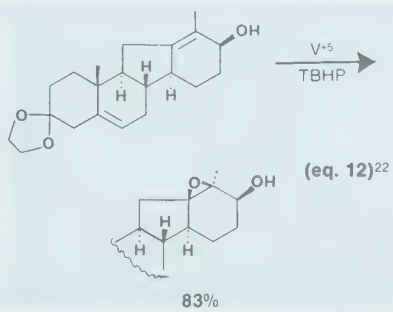


(eq. 10)[20]

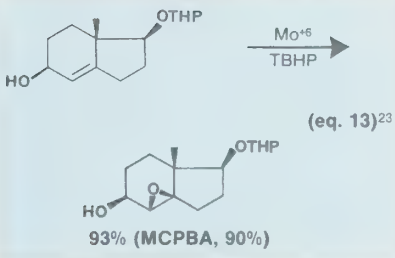
	β(*syn*)		α(*anti*)
MCPBA	4	:	3
V^{+5}, TBHP	100	:	~0



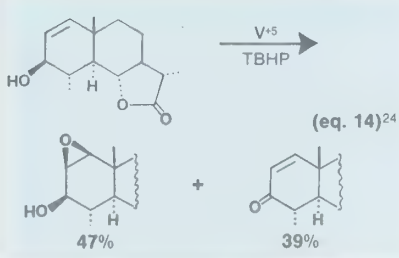
(eq. 11)[21]



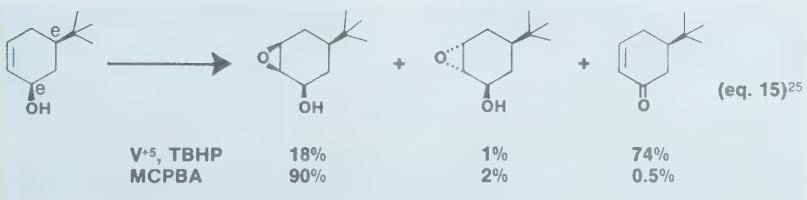
(eq. 12)[22]



(eq. 13)[23]



(eq. 14)[24]



(eq. 15)[25]

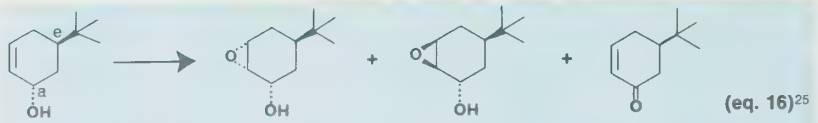
these cases peracids usually exhibit poor or no selectivity. Kishi's use of NaOAc as a buffer (eq. 31) to prevent premature cyclization of the epoxy alcohols to the tetrahydrofurans is a noteworthy modification[39] which should prove useful in other cases where acid-sensitive epoxides are produced.

In spite of the remarkable selectivity exhibited in these new metal-catalyzed epoxidations, they do have limitations. The most common problem occurs with certain rigid cyclic allylic alcohols (eqs. 14-16). In these cases there can be competition from a dehydrogenation process leading to the α,β-unsaturated ketone.[24,25] This side reaction seems to intrude principally in six-membered rings having an equatorial hydroxyl group. However, eqs. 10, 12 and 13 reveal that even this structural feature does not necessarily mean there will be trouble. From existing results,[24,25,40] the factors leading to unsaturated ketone formation are not altogether clear; however, this side reaction is likely if the face of the molecule *syn* to the equatorial hydroxyl is substantially hindered in the vicinity of the olefinic linkage. Severe steric shielding of the double bond can lead to unsaturated ketone formation even when the allylic hydroxyl moiety has an axial orientation.[85]

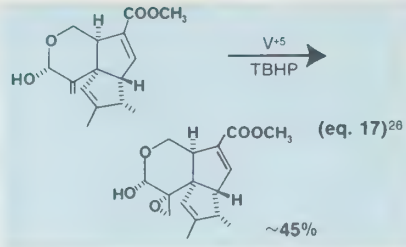
One of the more attractive features of these metal-catalyzed epoxidations is that they look appealing for the purpose of accomplishing asymmetric epoxidations. The first successes in this area were achieved independently by Yamada's group[41] and by our group.[42] Yamada used a molybdenum catalyst with chiral ligands derived from ephedrine. We employed vanadium catalysts bearing chiral hydroxamic acids as ligands. Since our initial publication we have found[43] more effective chiral hydroxamate ligands. The best asymmetric induction we ever achieved is shown in eq. 32.

Breslow and Maresca have reported that these metal-catalyzed epoxidations can be directed over a remarkably long distance using their template-directed strategies (eq. 33).[44]

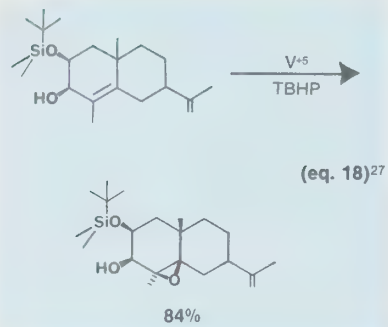
There has been recent interest in assigning optimum O—C—C=C dihedral angles for epoxidation of allylic alcohols by both peroxy acids[45,46] and by vanadium catalysts.[25,40] The conclusions reached in earlier studies were based on epoxidation of cyclohexenols and suggested optimum dihedral angles of *ca.* 150° (peroxy-acid epoxidations)[25,40,45] and *ca.* 90° (V^{+5}-catalyzed epoxidations).[25] We feel that the different steric environments between equatorial and axial positions in cyclohexenols as well as the rapid half-chair/half-boat interconversion could cloud the interpretation of epoxidation results based on such models. We feel a careful consideration of the stereoelectronic requirements of the epoxidation process might provide a more fruitful approach.



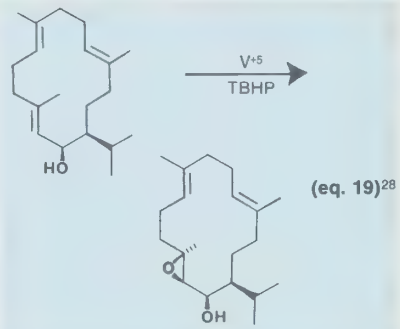
(eq. 16)[25]



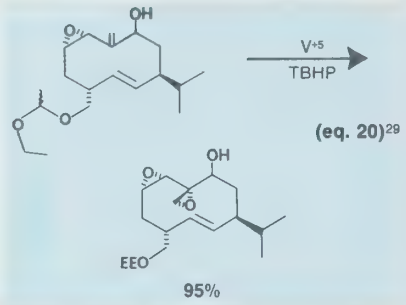
(eq. 17)[26]



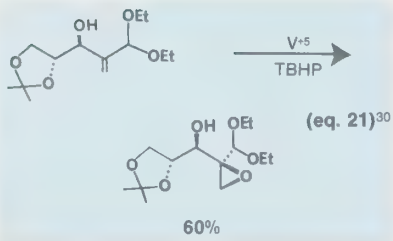
(eq. 18)[27]



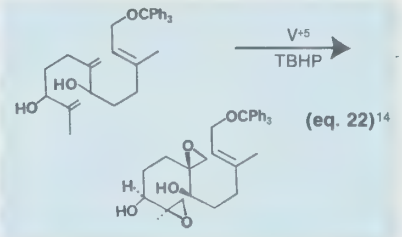
(eq. 19)[28]



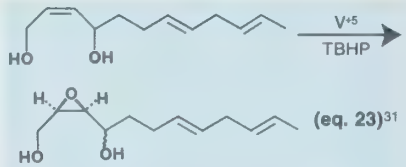
(eq. 20)[29]



(eq. 21)[30]

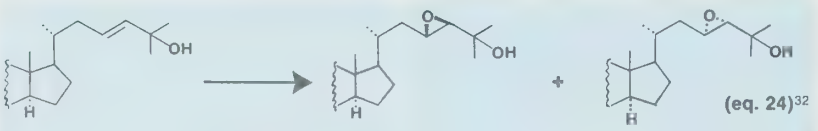


(eq. 22)[14]

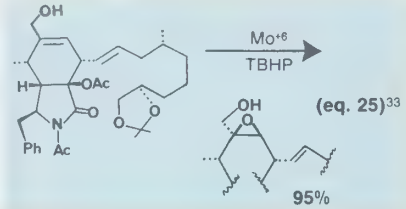


(eq. 23)[31]

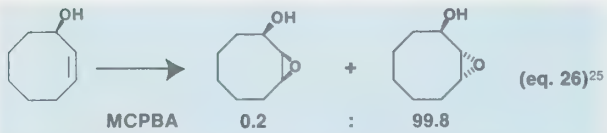
7:1 mixture of diastereomers, peracids attack only the isolated double bonds



(eq. 24)[32]

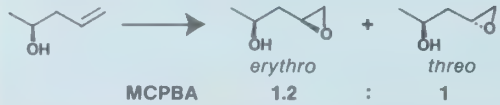


(eq. 25)[33]

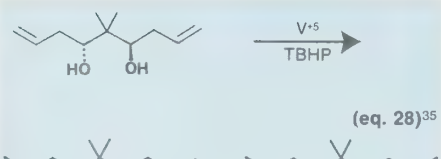


(eq. 26)[25]

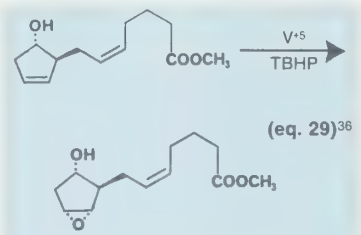
(b) Homoallylic Alcohols



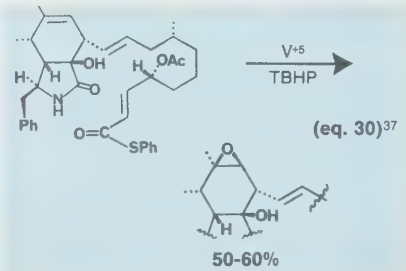
(eq. 27)[34]



(eq. 28)[35]

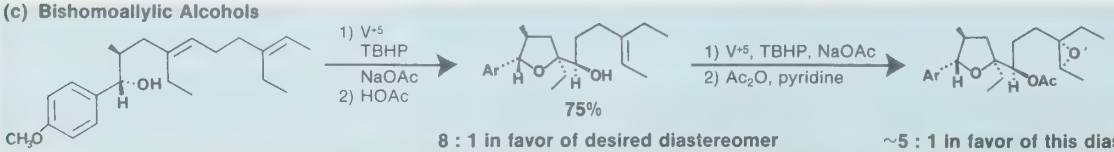


(eq. 29)[36]



(eq. 30)[37]

(c) Bishomoallylic Alcohols



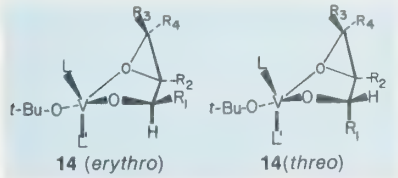
(eq. 31)[38,39]

8 : 1 in favor of desired diastereomer

~5 : 1 in favor of this diastereomer

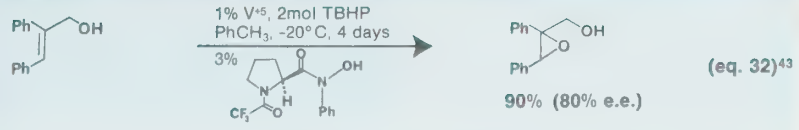
Our detailed mechanistic picture for the vanadium-catalyzed epoxidations is shown in Scheme III. The exchange reactions depicted are well precedented for similar vanadium(+5) alkoxide complexes.[47] The key intermediates are **13** and **14**, both being neutral, roughly trigonal bipyramidal complexes. The slow step in the catalytic cycle is thought to be the oxygen-transfer step (*i.e.*, **13**→**14** in Scheme III). Of course, this is also the step in which the stereoselectivity is determined. A crucial variable associated with the transformation of **13** to **14** is the orientation of the olefinic linkage with respect to the peroxide bond being broken in the oxygen-atom-transfer process. It is our opinion that all epoxidation processes involving attack of olefins on peroxide reagents will be subject to fairly rigid stereoelectronic requirements. (Surprisingly, this point has often been ignored even in the well studied epoxidations of olefins by organic peroxy acids.) In particular, displacement on the peroxide bond should occur from the backside and along the axis of the O—O bond being broken.[48] Thus, in **13** the conformation of the allyloxy group which best allows linear backside displacement on the O^1—O^2 bond produces a boat-like folding resulting in an O—C—C=C angle near 50°. The predicted conformations for the vanadium(+5)-catalyzed epoxidation are illustrated in Scheme IV (**15** and **16**). Thus, the stereoselectivities for the vanadium-catalyzed epoxidations of alcohols **10** (R_1 and R_2=alkyl) and **12** (R_1 and R_3= alkyl) are readily rationalized in terms of the stereoelectronically predicted conformations (either **15** or **16**) of the allyoxy moiety.

To adequately deal with allylic alcohols **9** and **11** however, the interactions between substituents on the allylic alcohol and the ligands on vanadium need to be considered (these interactions are ignored in the simplified analysis of Scheme IV). To the extent that the coordinated epoxy alcohol product **14** resembles the transition state, one can rationalize the stereoselectivity by analyzing the interactions for various substitution patterns in **14**. When R_1 is α (*threo*

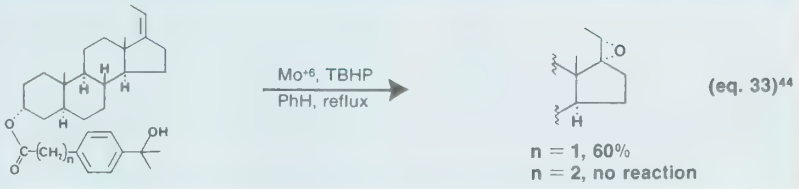


14 (*erythro*) **14**(*threo*)

product) it experiences a 1,3-diaxial-like interaction with the L′ ligand (L′ is either O or OR). At present we have no way of predicting the relative positions of the O and OR ligands in **14**. When R_1 is β (*erythro* product) there is no obvious interaction with the metal ligands. R_3 experiences a weak 1,3-diaxial-like interaction with the L ligand in **14** (L is either O or OR) in both the *erythro* and *threo* cases; therefore its effect on the product ratios should be negligible. R_2 and R_4 are not in a position to interact with the vanadium

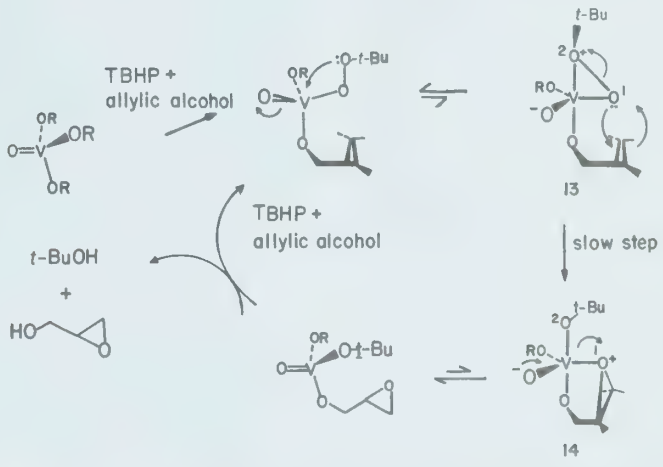


(eq. 32)[43]



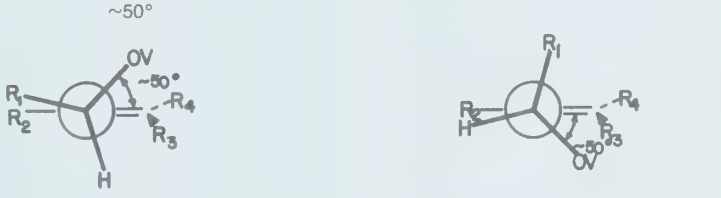
(eq. 33)[44]

Scheme III. Possible Mechanism for the Vanadium-Catalyzed Epoxidations.



Scheme IV. Predicted O-C-C=C Dihedral Angles

for V^{+5}, TBHP epoxidations:



15, leads to *threo* product

16, leads to *erythro* product

for peroxy acid (MCPBA) epoxidations:

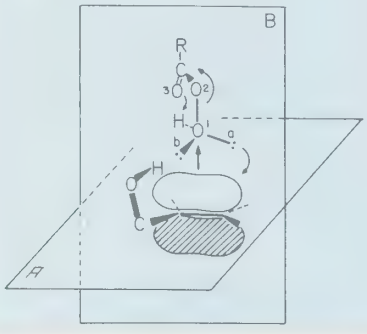
17, leads to *threo* product

18, leads to *erythro* product

ligands. Thus, it appears that other things being equal these interactions add up to a slight disadvantage for the *threo* transition state. This effect provides an appealing rationale for the weak *erythro* selectivity with substrates **9** and **11** (Table I).

The application of similar stereoelectronic considerations to the peroxy-acid epoxidations leads us to propose the orientation of the reactants illustrated in Scheme V. The plane defined by the peracid molecule is oriented (about 60° to plane B) so that one of the nonbonding pairs on oxygen (pair a) lies in plane B and is nicely oriented to begin bonding with the olefinic carbon; it may also be able to interact favorably with the antibonding π orbital of the olefin. The nonbonding pair b is favorably oriented (in front of plane B) to hydrogen-bond with an allylic hydroxyl group. It should be noted that the selectivity effects seen in the peracid epoxidations of allylic alcohols have previously been explained by hydrogen bonding to either oxygen-2 or oxygen-3 of the peracid,[45] never to oxygen-1 as is suggested in Scheme V. However, if one invokes

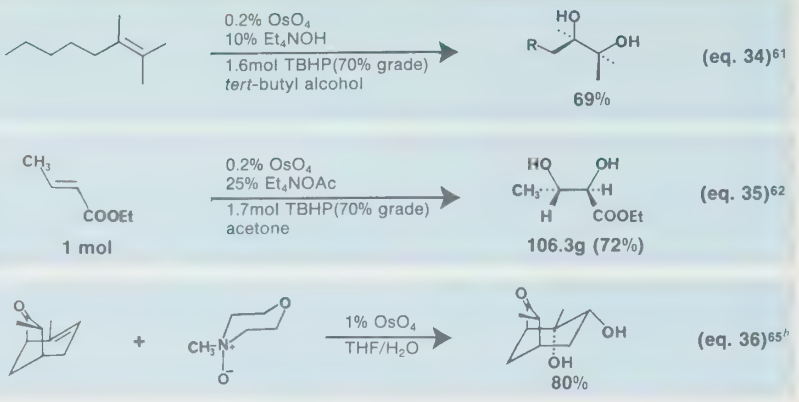
Scheme V. Consideration of Stereoelectronic Effects in Peracid Epoxidations of Allylic Alcohols.



backside displacement on the peroxide bond,[48] it is impossible to form a hydrogen bond between the allylic hydroxyl and either oxygen-2 or oxygen-3. A hydrogen bond to oxygen-1 in Scheme V appears feasible for O—C—C=C dihedral angles ranging from ~50° to ~130°. The observed stereoselectivities in Table I seem best accommodated by a dihedral angle near 120° (see **17** and **18** in Scheme IV).[49]

2. Epoxidation of Isolated Olefins (Scheme I, eq. 2)

If one wishes to epoxidize an isolated olefin, peracids are the first reagents which come to mind. Several years ago we wondered whether the industrially important Oxirane Process (TBHP and Mo^{+6} catalyst) could be adapted to laboratory-scale (*e.g.*, 1-5 mole) epoxidations. We immediately encountered two problems. The commercially available forms of TBHP contained varying amounts of water. Water is deleterious to the reaction, for it not only inhibits the epoxidations, but also gives rise to epoxide opening which produces diols as byproducts.[50,51] We have since found that the epoxidation of isolated



olefins can be carried out efficiently by operating in nonreactive solvents (*e.g.*, benzene, dichloromethane, dichloroethane) under moderately anhydrous conditions. The use of small amounts of anhydrous disodium hydrogen phosphate (Na_2HPO_4) powder as an additive in these reactions further reduces the formation of byproducts.[52] Since this work has not been published yet[51] the complete experimental details for the epoxidation of 1-decene are presented below. Monosubstituted olefins such as 1-decene are among the most difficult to epoxidize. Therefore, the conditions now given for 1-decene will epoxidize all simple di-, tri- and tetrasubstituted olefins much more rapidly[51] than the *ca.* 10 hrs at reflux required for complete conversion of 1-decene. With more reactive olefins we recommend that the course of oxidation be followed so that it can be stopped soon after completion. The more reactive olefins also give rise to more reactive epoxides, and there is no sense in heating such epoxides in the presence of Mo^{+6} (a weak Lewis acid) any longer than necessary.

Epoxidation of 1-Decene (1-mole scale)

a) General procedure for azeotropic drying of "Aqueous TBHP-70" (or the equivalent Aldrich 18,471-3): "Aqueous TBHP-70" (500ml, 3.6 mol) and 850ml of reagent-grade 1,2-dichloroethane [53] are combined in a 2-liter separatory funnel, which is then swirled (vigorous shaking can lead to emulsions) for about one minute. Two phases form, and the upper, aqueous layer (*ca.* 125ml) contains only about 2.7% (0.10mol) of the TBHP originally added. The lower organic layer (1225ml, containing *ca.* 2.35mmol of TBHP per ml and, therefore a total of 3.5mol of TBHP) is drained into a 2-liter, one-necked, round-bottomed flask. **[Thus, by simple phase separation one obtains this TBHP solution which is similar in water content to solutions which we used[12,14,54] to prepare by adding commercial Lucidol-90 or Aldrich's 21,312-8 to the appropriate organic solvent (*e.g.*, CH_2Cl_2, benzene or $ClCH_2CH_2Cl$). We now recommend TBHP solutions prepared in this way for the SeO_2-catalyzed oxidations[54,55] (CH_2Cl_2 or $ClCH_2CH_2Cl$ as solvent) and for the vanadium-catalyzed epoxidation of allylic alcohols (benzene or CH_2Cl_2 as solvent). However, for the molybdenum-catalyzed epoxidations of isolated olefins removal of even this last bit (estimated to be *ca.* 5-7%) of water is important, and is easily accomplished as described below.]** A few boiling stones are added and the flask is fitted with a distillation head. Distillation ($ClCH_2CH_2Cl/H_2O$ azeotrope, bp 72° C) commences a few minutes after heat is applied with a steam bath. The distillate is cloudy and separates in the collection vessel into organic and aqueous layers. After *ca.* 450ml of solvent is removed the distillate becomes clear and homogeneous. A total of *ca.* 575ml of distillate[56] is collected, and this leaves about 650ml of an anhydrous,[57] *ca.* 4.1*M* solution of TBHP (*ca.* 2.67moles) in dichloroethane.* [The precise TBHP concentration can be very easily determined by iodometric titration; the exact details for these titrations are given in Note 58a below. The TBHP concentration can also be estimated (± 10%) by NMR integration; a convenient equation for calculating the molarity of such solutions when using dichloroethane as solvent is given in Note 58b below.] The anhydrous TBHP solution is allowed to cool and can be stored[59] or used immediately.

b) Molybdenum-catalyzed epoxidation: A 2-liter, 3-necked round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar, a reflux condenser, a 500-ml dropping funnel, and a nitrogen inlet. All glassware was dried in an oven, and the system flushed with nitrogen. The flask is charged with 1 liter of reagent-grade 1,2-dichloroethane, 146.14g (1.00mol, corrected for purity) of Aldrich 1-decene (95% purity), 0.668g (0.0025mol, 0.25mol %) of $Mo(CO)_6$, and 1.0g (0.007mol) of anhydrous disodium hydrogen phosphate (Na_2HPO_4, AR grade, freshly ground into a powder). The dropping funnel is charged with 490ml (*ca.* 2mol) of the previously prepared solution of anhydrous TBHP in dichloroethane. The stirrer is started, and the reaction mixture is brought to a gentle reflux. Dropwise addition of the TBHP solution is started and then the source of heat is removed from the reaction vessel.[60] The TBHP solution is added to the stirred mixture at a rate which is sufficient to maintain reflux. The addition requires ~0.5hr. (With unreactive olefins such as 1-decene it may be necessary to reapply the heat source before the addition is complete in order to sustain reflux.) When the addition is complete heat is reapplied and refluxing is continued until the olefin is completely consumed (monitor by GLC, TLC or other appropriate method). In the present experiment with 1-decene this required *ca.* 10 hours at reflux (GLC revealed <1% olefin). If for some reason olefin still remains, one can simply add more of the anhydrous TBHP solution to the refluxing reaction mixture.

The reaction vessel is then cooled in an ice bath and 300ml (*ca.* 0.24mol) of a freshly prepared 10% solution of sodium sulfite (Na_2SO_3) is added dropwise with stirring. When addition is complete the ice bath is removed and stirring is continued for 3 hours at autogenous temperature. At this point the organic phase should give a negative peroxide test using acidified starch-iodide test paper.[80] If the test is positive additional aqueous sulfite solution should be added and stirring continued until the test is negative. The aqueous and organic phases are separated, and the milky white organic layer is washed twice with 250-ml portions of water, once with 250ml of brine, dried ($MgSO_4$) and concentrated to afford a colorless but somewhat cloudy oil. Distillation of this oil afforded 137.4g (center cut, bp 52-4° C/1mm) of 1-decene oxide which was 98% pure by GLC analysis (therefore 86% yield).

Other isolated olefins which have been epoxidized following the above procedure in 85-95% distilled yield include cyclohex-

***Warning:** It is important not to allow the distillation to proceed too long, for this would eventually produce high-strength TBHP solutions.

ene, methyl oleate, 1-methylcyclohexene, 1-phenylcyclohexene, (*E*)-2-decene and methyl 10-undecenoate. Other solvents (*e.g.*, benzene,[53] CH_2Cl_2 and CCl_4) also work well in this epoxidation procedure (*i.e.*, in both the azeotropic drying and epoxidation stages of the process). The use of methylene chloride, due to the less favorable composition of its azeotrope with water, requires about twice the initial volume of solvent needed for the other solvents mentioned above. Furthermore, the epoxidation step takes longer in methylene chloride due to its lower boiling point. In fact, 1-decene cannot be epoxidized in CH_2Cl_2, but more reactive olefins can be epoxidized in excellent yield in 5-24 hours at reflux.[51]

In summary, we feel that even with isolated olefins these metal-catalyzed epoxidations may sometimes have advantages over the more traditional peracid methods. This would seem especially true for larger-scale (1-5mol) epoxidations where cost and safety become important considerations.

III. Vicinal Dihydroxylation of Olefins (Scheme I, eq. 3)

Our experience with vanadium- and molybdenum-catalyzed epoxidations encouraged us to think of TBHP as a possible oxygen-atom source for other metal-catalyzed oxidations of olefins. This has led to the discovery of very effective procedures[61,62] for the osmium-catalyzed vicinal hydroxylation of olefins (eq. 3, Scheme I), and for selenium-catalyzed allylic oxygenations of olefins[54] and acetylenes[55] (eqs. 4 and 5, Scheme I).

These new TBHP-based osmium-catalyzed procedures for *cis*-vicinal dihydroxylation of olefins are much more reliable than the earlier ClO_3^- (Hofmann[63])- and H_2O_2 (Milas[64])- based osmium-catalyzed procedures for this transformation. The key to the success of the new methods appears to be the presence of a nucleophile (either Et_4N^+OH[61] or Et_4N^+OAc[62]). It seems likely that the role of the nucleophile is to increase the turnover rate of the catalytic cycle by facilitating removal of the glycol product from the coordination sphere of the osmium. Thus, it has been possible to hydroxylate even some tetrasubstituted olefins using the Et_4NOH modification (eq. 34). The Et_4NOAc modification fails with tetrasubstituted olefins, but, being much less basic than the Et_4NOH method, it can be used with base-sensitive olefinic substrates (eq. 35).

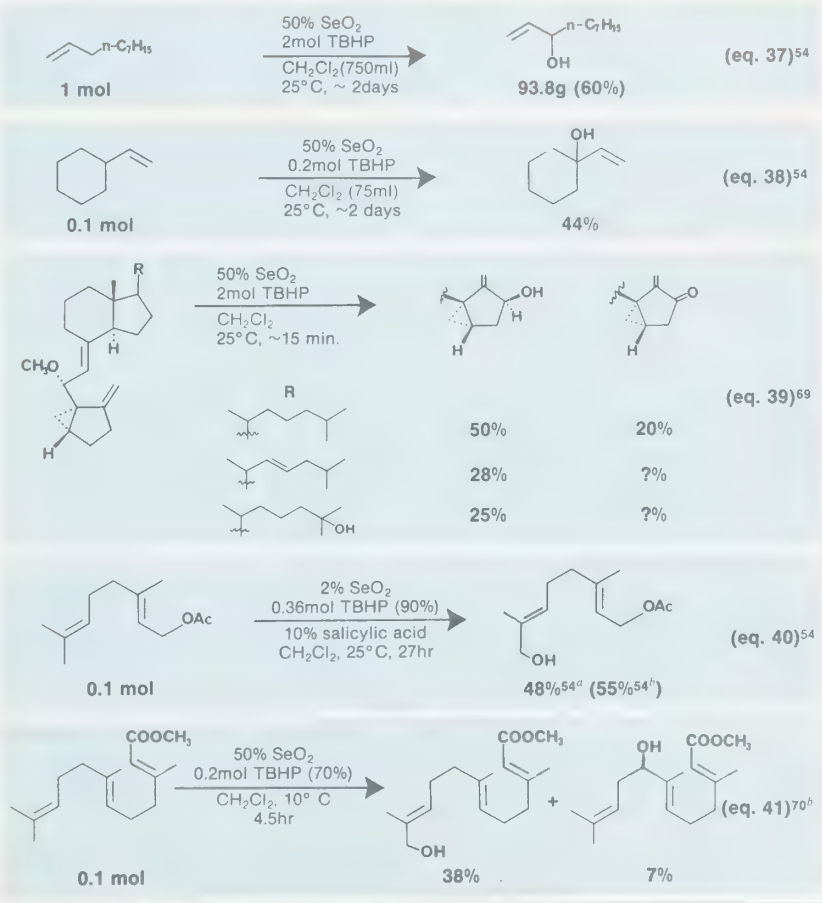
Upjohn chemists have also recently reported a very effective new osmium-catalyzed procedure for *cis*-vicinal dihydroxylation of olefins.[65a] The oxidant in their process is *N*-methylmorpholine-*N*-oxide. In the short time since its discovery it has been used many times with great success (*e.g.*, eq. 36). In comparing this method with our TBHP-based procedures we noted that the Upjohn procedure failed in our hands with the tetrasubstituted olefin shown in eq. 34. We also suggested that it might not be very useful with trisubstituted olefins. **We now wish to retract and apologize for that inference, because enough examples are now known to make it clear that the *N*-methylmorpholine-*N*-oxide method is marvelously effective with many trisubstituted olefins (*e.g.*, eq. 36).**

There have been only two applications[66,67] of our method so it has not really been adequately tested. At present it would appear to have only two possible advantages over the Upjohn procedure. Our procedure does work with some tetrasubstituted olefins, and TBHP is about 20 times less expensive than *N*-methylmorpholine-*N*-oxide (NMO) even at fine chemical prices (and TBHP is available at much lower prices in bulk quantities). Another minor point is that we always use 0.2% OsO_4 catalyst, whereas the NMO procedure has been reported with from 0.2 to 5% OsO_4 catalyst. If the TBHP and NMO routes gave comparable yields of diol in a given case, considerations of cost would favor the TBHP process, especially on larger-than-mmole scales.

In summary, these two new catalytic methods (TBHP-based[61,62] and NMO-based[65a]) have greatly increased the reliability of the olefin to *cis*-vicinal diol transformation. Of equal importance, the reaction can now be carried out on a one-mole scale at a reasonable cost; this should allow the use of such a step early in a synthetic sequence.

IV. Allylic Oxidation of Olefins and Acetylenes (Scheme I, eqs. 4 and 5)

Selenium dioxide is the most reliable and predictable reagent for direct insertion of oxygen into an allylic carbon-hydrogen bond.[68] A serious complication in this reaction is the inevitable production of reduced forms of selenium. The frequent difficulty of removing colloidal selenium from the products is well known. Another drawback of these oxidations is the formation of organoselenium by-products. We reasoned that an oxidant which would rapidly and selectively reoxidize the reduced selenium species to SeO_2 would circumvent these problems, and furthermore might enable the reaction to proceed with catalytic amounts of SeO_2. Indeed, we found that TBHP is an excellent oxidant for this purpose.[54] Allylic oxidation proceeds in CH_2Cl_2 at room temperature with catalytic (2-50%) amounts of SeO_2. Examples from our work[54] (eqs. 37, 38, 40) and from other laboratories (eqs. 39, 41, 42) are shown below. The transformation shown in eq. 42 by Cook and Campos[70a] is interesting in that the substrate contains both indole and

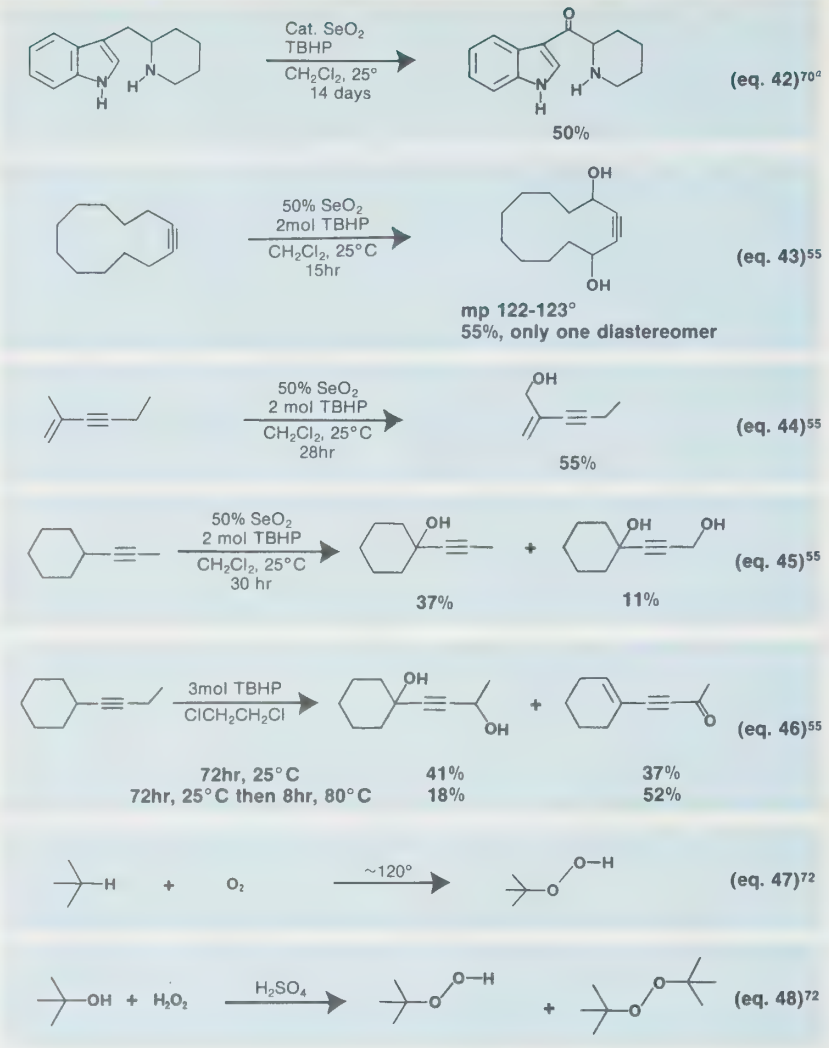


piperidine moieties. Stoichiometric SeO_2 oxidation of the same substrate required more vigorous conditions, and gave only the product of complete dehydrogenation (*i.e.*, piperidine ring → pyridine ring).[70a]

In our first publication on this subject,[54] we mentioned that cyclohexene was a poor substrate for the SeO_2/TBHP allylic oxidation procedure. The allylic alcohol is a minor product and the two major products are the allylic *tert*-butyl ether and the allylic *tert*-butyl perether. We have since found that this is a general problem when the olefinic linkage is in a ring (*i.e.*, endocyclic).[71] Smaller-ring olefins (*e.g.*, 5- and 6-membered) are worse than larger-ring olefins (*e.g.*, 8- and 12-membered), but even in the case of cyclododecene the ether and perether by-products are still apparent. For cyclododecene the ratio of allylic alcohol to by-products (*i.e.*, allylic ether and perether) is 7:3; the ratio for cyclohexene is 1:4. **Thus, it is important that one be wary of applying our procedure to endocyclic olefins which are in small- and medium-sized rings,** especially if the C—H bond to be oxidized lies within the same ring. However, exocyclic olefins work well (eq. 39), and it also appears that the reaction proceeds normally with endocyclic olefins if the allylic C—H bond which is oxidized lies outside the ring.[71]

We have recently found that, unlike olefins, acetylenes show a strong tendency to undergo α,α'-dioxygenation upon reaction with the SeO_2/TBHP system (eq. 43).[55] The oxidation of ten different acetylenes allowed assignment of the relative reactivity sequence as $CH_2 \cong CH > CH_3$, thus allowing selective monooxygenation in the case of CH_2 *vs.* CH_3 or of CH *vs.* CH_3 (eq. 45). Alkynes bearing one methylene and one methine substituent afford the enynone as the major product (eq. 46).

Both the olefin[54] and the acetylene[55] SeO_2/TBHP α-oxygenation procedures have been performed on a one-mole scale with no difficulty. One advantage of these procedures is that they can be run quite concentrated (at least 1 *M* in olefin or acetylene), and hence are conveniently scaled-up. **However, the key advantage of the SeO_2/TBHP/CH_2Cl_2 system is that it is more reactive and also more selective than any known[68] stoichiometric SeO_2 oxidation procedures.** With the exception of the endocyclic olefins mentioned above, it is clearly the method of choice for obtaining synthetically useful yields of unrearranged allylic alcohols from a greatly broadened spectrum of olefins. The positional selectivity, which has been the chief attraction of SeO_2 oxidations, is retained. The milder conditions avoid the rearrangements and dehydrations which can occur under the standard stoichiometric conditions. Finally, the dramatic reduction in the amount of colored, malodorous organoselenium by-products formed, and the elimination of precipitated selenium metal should help to overcome the selenophobia which currently afflicts many synthetic organic chemists.



V. Practical Considerations in Handling TBHP

1. Commercial Sources. There are two commercial routes to TBHP. The most important is the autoxidation[72] of isobutane (eq. 47). The older route involves acid-catalyzed alkylation[72] of hydrogen peroxide with *tert*-butyl alcohol (eq. 48). This latter route leads to coproduction of di-*tert*-butyl peroxide (DTBP). Lucidol offers two grades of TBHP: (1) Lucidol-TBHP-70 contains (by wt.) 70% TBHP, ~19% DTBP, and 11% of TBA and water;[73] (2) Lucidol-TBHP-90 contains 90% TBHP, ~6% TBA, ~4% H_2O, and <1% DTBP.

The 90% grade of TBHP is also available from Aldrich, but it must now be sent by truck according to a recent ruling of the DOT.

Oxirane Corporation produces TBHP by the autoxidation route. Almost all of this TBHP is used on-site for the molybdenum-catalyzed epoxidation of propylene. However, they do sell some of it for use outside their plant. This material is almost pure TBHP except for 30% water which is added as a stabilizer to permit shipment in tankcar and tanktruck quantities. Oxirane calls this material "Aqueous TBHP-70".[74] The vital statistics for the Oxirane "Aqueous TBHP-70", Lucidol TBHP-90 and pure TBHP are given in Table II. Please note that the data for pure TBHP are given only for the sake of comparison with the commercial grades. Pure TBHP is not commercially available nor should it, in our opinion, ever be prepared and used except on a very small scale. The 70% TBHP is available from Aldrich and can be shipped by UPS making it an ideal form in which to receive TBHP for laboratory-scale operations.

2. Purification. Of the three[75] commercial grades of TBHP only the two shown in Table II are suitable for use in the metal-catalyzed oxidations described here. Since the 90% grade is inherently more expensive, and is made even more so because it must travel by truck, we have adapted to

using the 70% grade (70% TBHP/30% H_2O) for all our needs. This approach is actually much more attractive than one might at first think.

The aqueous 70% TBHP is ideal for direct use in the osmium-catalyzed vicinal dihydroxylation of olefins (eq. 3, Scheme I).[61,62] This process requires the presence of water and there is absolutely no virtue in using drier grades of TBHP. In fact, anhydrous solutions of TBHP do **not** work for this application.

The vanadium- and selenium-catalyzed oxidations (eq. 1,4 and 5, Scheme I) were all initially developed[12,14,54,55] using the commercial 90% grade (~4-5% H_2O) of TBHP. The vanadium-catalyzed processes are definitely slowed by the presence of water, but the 90% grade is dry enough to give reasonable rates and good yields. However, the rates and sometimes the yields can be increased if one prepares anhydrous solutions of TBHP in organic solvents. The selenium-catalyzed processes show a more complicated dependence on the water content of the TBHP. When using 50% SeO_2 catalyst the reactions are rather insensitive to water content. Thus, Sum and Weiler were able to use 70% TBHP directly for oxidation of methyl farnesoate (eq. 41),[70b] whereas we have found that 90% TBHP was optimum when using only 2% SeO_2 catalyst for oxidation of the similar olefin, geranyl acetate (eq. 40).[54] Both less water (anhydrous TBHP) and more water (70% TBHP or phase-separated TBHP in CH_2Cl_2) resulted in substantially slower oxidations under otherwise identical conditions.[76a] However, even in this case the phase-separated TBHP/CH_2Cl_2 solutions were adequate for use.

The only process in Scheme I which actually requires anhydrous conditions for good yields is the molybdenum-catalyzed epoxidation of isolated olefins (eq. 2). Fortunately, we have found that it is relatively easy to obtain anhydrous solutions of TBHP in organic solvents, even when starting with the wettest grade of TBHP, namely "Aqueous TBHP-70" (70% TBHP/30% H_2O, w/w) by employing the phase-separation and azeotropic-distillation techniques which are described above for the epoxidation of 1-decene.

Note that the easy phase-separation procedure for removing most of the water from the 70% TBHP means that the less convenient (more expensive and less stable) 90% commercial grade of TBHP is no longer really essential. Recall that 90% TBHP was the grade we used to recommend for the vanadium- and selenium-catalyzed oxidations (eqs. 1, 4 and 5, Scheme I). **We have also found that the TBHP solutions one gets by the simple phase-separation procedure have nearly the same reactivity as solutions generated by dissolving commercial 90% TBHP in the same solvent.**[76] This is as it should be since both methods yield TBHP solutions which contain similar (based on TBHP content) amounts of water (*i.e.*, 4-5% H_2O for Lucidol TBHP-90 and 6-7% H_2O for the TBHP solutions we prepare by phase separation).

3. Dangers. We have so far emphasized the relative safety of working with TBHP as compared to working with other peroxidic substances. **Now we must point out that TBHP, like almost all substances having O—O bonds, has to be regarded with respect. However, provided one avoids certain situations, this state of respect need not degenerate into a state of fear.**

There are three main situations to avoid. The first rule is never add a strong acid (even just a drop) to high-strength TBHP solutions. The second rule is never add transition metal salts known to be good autoxidation catalysts (*e.g.* Mn, Fe and Co are particularly bad) to high-strength TBHP solutions. Alkyl hydroperoxides are sensitive to metal-catalyzed radical-chain decomposition.[8,72,77] Among other things this produces a lot of oxygen gas. **The third rule** (which, if followed, will ameliorate any problems arising from violations of the first two rules) **is never work with pure TBHP and avoid using high-strength solutions of it whenever possible.**

The literature contains a number of examples of violations of this last rule.[78] Most of these involve distillation of TBHP to purities of 98% or greater. These are performed at reduced pressure and, if done carefully in clean glassware, are probably quite safe. However, many people use heating mantles for distillations and one wonders what would happen if the flask broke or had a crack in it. But the real problem here is that one might produce really pure (>99%) TBHP which has to be regarded as too dangerous to work with, especially on a preparative scale. In the past, perhaps the main reason for distilling TBHP was the desire to obtain anhydrous material for further reactions (*e.g.*, to form *tert*-butyl peresters from the corresponding acid chlorides[78]). **Our new azeotropic procedure for generating anhydrous solutions of pure TBHP in aprotic organic solvents should in many cases obviate the need to distill pure TBHP.**

Since much of this review is concerned with removing water from TBHP, one might naturally wonder about the effectiveness of molecular sieves for this purpose. For this reason we quote the following account of a small accident which occurred at Shell Development Company in Houston: "We had been routinely drying 90% TBHP (typically containing 6% H_2O, 3% TBA and 1% Di-*t*-butyl peroxide) on a small scale using 4A molecular sieves. A technician inadvertently used Linde 13X mol sieves. After pouring one or two liters on the packed bed the technician was sufficiently alarmed at the unusual exothermic reaction taking place that he quickly closed the fume hood. Within one or two minutes the hydroperoxide ignited. The ensuing fire was contained within the fume hood. We surmise that the heat of adsorption of TBHP on 13X sieves (pore size ~9Å) was sufficient to raise the temperature to the autoignition point. Note that, in contrast, penetration of TBHP into the pores of a 4A sieve is not possible)."[79]

Perhaps this behavior is specific for the 13X sieves, but at present we would not be too sanguine about pouring high-strength (*e.g.*, 90%) TBHP over molecular sieves of any kind.

One can remove some of the remaining (~6-7%) water from the organic solutions of TBHP (obtained from 70% TBHP by the phase-separation technique) by swirling them with anhydrous $MgSO_4$. The $MgSO_4$ should be removed by filtration through a plug of glasswool placed in the stem of a regular funnel; a sintered-glass funnel should not be used for it may be contaminated with metals. However, TBHP solutions dried in this way are less effective (presumably because they are wetter) in the molybdenum-catalyzed epoxidations of isolated olefins than are TBHP solutions dried by the azeotropic technique.[51]

If one contemplates larger-scale (0.1 mole and greater) reactions of the type shown in Scheme I, then the following advice is of special importance. **Whenever possible add the TBHP slowly to the reaction mixture under conditions where it is being consumed as it is added.** We have run the molybdenum-catalyzed epoxidation of isolated olefins (eq. 2, Scheme I) on a 2.5-mole scale; this involves at least 5 moles of TBHP. However, the TBHP is added at a rate which maintains a gentle reflux and therefore does not build up in the reaction mixture. The larger-scale reactions also tend to need less catalyst. We have used as

Table II. Properties of Commercial Grades of TBHP

Properties	Aqueous TBHP-70	Lucidol TBHP-90	Pure TBHP*
diluents	30% H_2O	~6% TBA ~4% H_2O <1% DTBP	
bp(°C/mm)	96/760		133/760
mp(°C)	-2.8	-10	4.2
density (25°C)	0.935	0.90	0.8960
ca. mmol TBHP/ml	7.2	9.0	9.94
shipping	UPS	Truck only	

*Not commercially available, only included in table for comparison with the two commercial grades.

little as 0.1% $Mo(CO)_6$ catalyst in the 2.5-mole scale epoxidations. **A situation to be avoided at all costs is that where one places large quantities of TBHP and the substrate (olefin or acetylene) together and then adds the catalyst.** This can sometimes be done, but only after one has very carefully established that the substrate is so unreactive that the reaction cannot get out of control. Finally, if you really must risk mixing everything together at once it is always safer to be in a lower boiling solvent than a higher boiling one.

Dr. E.S. Shanley has pointed out that there is a common ambiguity in the use of the term "stability". We have used it in this review to mean low decomposition rate during storage. Another meaning of "stability" is lack of potential for spontaneous change. TBHP is certainly not stable in this latter sense. **It is therefore important to be sure that most all peroxidic substances are reduced before engaging in distillation of reaction mixtures in which TBHP was used as oxidant.** The Na_2SO_3[17] and dimethyl sulfide[18] procedures for reducing excess TBHP are reliable, and the absence of TBHP can, and should, be established with acidified starch-iodide test paper.[80] **However, of greater concern is the possibility that the TBHP has become bound into the molecule in some more-stable form.** This is especially true in those reactions in Scheme I which involve mildly acidic conditions (*viz.*, eqs. 1, 2, 4 and 5). **If the molecule contains a ketone or aldehyde function in addition to the olefinic unit one should be aware of the possibility of peroxyketal or peroxyacetal formation.**[81] An NMR spectrum of the crude reaction mixture should reveal contamination by *tert*-butyl peroxyacetals or ketals.

Above all, we prefer steam baths for heating TBHP reaction mixtures (especially on a large scale). Oil baths are also acceptable, but messy on a large scale, and heating mantles involve obvious dangers. We have used heating mantles for heating TBHP solutions, but are **careful to use low power settings, and to see that the level of solvent in the flask is always above the top of the mantle.**

A lot more information about safety and handling of TBHP as well as other peroxides is available in various bulletins from the companies which sell it (*e.g.*, Lucidol,[82] Oxirane,[83] and Witco[1]). E.S. Shanley has written a chapter on "Organic Peroxides: Evaluation and Management of Hazards" in Swern's series on "Organic Peroxides".[84]

4. Storage. The maximum recommended storage temperature for TBHP is 38°C (100°F).[82] It is stable essentially indefinitely at room temperature (25°C) and, thus, does not need refrigeration. In fact, it is important that the "aqueous 70% TBHP" not be stored much below room temperature. It is essentially saturated with water at 25°C, and at lower temperatures an aqueous phase separates which is visible on the bottom of the storage container. This circumstance would cause the concentration of the supernatant TBHP solution to vary. TBHP containers should best be stored in the dark or at least out of bright light, and should be kept in an area free of accelerators, corrosives and other inherently hazardous materials. **To avoid contamination while sampling always pour TBHP out of the container, never stick sampling devices into the container, and never return unused TBHP to the container.**

Like all strong oxidants TBHP is an eye and skin irritant. It is especially bad in the eyes. Should it get in your eyes flush them immediately with copious amounts of water and contact a physician. Eye protection and rubber gloves should be worn when handling these materials.

"Aqueous 70% TBHP" will burn vigorously if ignited but will not explode unless it is contained. This is one of the advantages of shipping peroxides in plastic containers. Should things get hot the containers melt down and prevent containment. Should a fire arise copious amounts of water, coolants and foam extinguishers should be employed.

VI. Conclusion

Because TBHP is a **selective,** inexpensive, and relatively safe oxidant, its applications in organic synthesis should continue to increase. Few reactions have caught on as rapidly among synthetic chemists as the vanadium-catalyzed epoxidation of olefinic alcohols (eq. 1, Scheme I). This gives some insight into the importance of being able to stereoselectively introduce new asymmetric centers into a molecule under the direct control of a preexisting chiral center. The fact that this particular reaction also exhibits good stereoselectivity on acyclic molecules, and even over fair distances, makes it all the more valuable. As synthetic chemists become more familiar with TBHP, they may find that some of the other metal-catalyzed oxygenations discussed here (Scheme I) are also useful for the construction of complex molecules.

Acknowledgement

We are grateful to Lucidol, Oxirane and Witco Chemical Companies for having provided us with generous samples of various hydroperoxides and peroxides. We especially wish to thank Dr. Chester Sheppard of Lucidol for many helpful discussions over the past six years in which he taught us a lot about peroxide chemistry. Most of our TBHP-related research described here was carried out in the Chemistry Department of the Massachusetts Institute of Technology. This research was, and still is, supported by grants from the National Science Foundation and from the National Institutes of Health. We are also very grateful to Bryant E. Rossiter, Doris J. Scheffel and Dr. Per H.J. Carlsen for their help with many last-minute details needed to get this manuscript ready. Finally, we are indebted to Drs. Orville L. Mageli, Edward S. Shanley, Chester S. Sheppard and Jeff White for reading and providing important criticisms of the manuscript, and to Prof. Julius Rebek for many insightful discussions on the mechanism of peracid epoxidations (see his student's Ph.D. thesis[48d]).

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53) Most of our early development work on this problem was done using benzene as the solvent. Benzene is an ideal solvent for these epoxidations, but for obvious reasons we decided to move away from it. We have found that dichloroethane, with its similar boiling point and its similar ability to remove water azeotropically, is a good alternative to benzene. However, it must be pointed out that benzene is the best solvent we have ever found for these epoxidations. Anhydrous solutions of TBHP in benzene are more stable than those in dichloroethane, and the Mo^{+6}-catalyzed radical decomposition of TBHP is more serious competition for the desired epoxidation pathway in dichloroethane than it is in benzene. However, given the toxicity problem with benzene, dichloroethane is the best alternative solvent we have found to date
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55) B. Chabaud and K.B. Sharpless, *J. Org. Chem.*, **44** 4202 (1979)
56) This distillate (aqueous phase = 20ml, organic phase = 555ml) contains *ca.* 0.9 mole of TBHP which co-distills along with the dichloroethane and the water (90% of this TBHP is in the organic phase of the distillate). Co-distillation of TBHP also occurs when benzene is used as the azeotropic solvent, but occurs only to a very slight extent when CH_2Cl_2 is the azeotropic solvent
57) We have no proof that these solutions are truly anhydrous. The important fact is that they are highly effective for the Mo^{+6}-catalyzed epoxidations of isolated olefins
58) a) This procedure was adapted from that described in the October, 1971 technical bulletin available from the Oxirane Corporation. Place 2ml of glacial acetic acid and 25ml of isopropanol in a 250ml Erlenmeyer flask. Mix the contents and add 10ml of a freshly prepared sodium iodide-isopropanol solution prepared by refluxing a mixture of 22g of NaI in 100ml of isopropanol, followed by cooling to room temperature and filtering. Add an accurately measured sample of the TBHP solution (containing no more than 2.5mmoles of active oxygen) and gently reflux for 30 sec. After dilution with 100ml of distilled water, immediately titrate the solution with 0.1*N* sodium thiosulfate (E.M., "Titrasol") to the disappearance of the yellow iodine color. Starch indicator solution may be used toward the end of the titration to enhance the endpoint. The concentration is calculated according to the equation: [S x N]/[2 x (ml of sample)] = molarity of TBHP solution, where S = ml of thiosulfate for titration and N = normality of thiosulfate. b) Molarity $\cong A/[(0.10A) + (0.18B)]$ where A = integration of *tert*-butyl resonance ($\sim$ 1.25 δ) and B = integration of dichloroethane resonance ($\sim$ 3.70 δ)
59) We have prepared, by this azeotropic technique, anhydrous solutions of TBHP in a variety of organic solvents. We have stored these solutions for at least 6 months at room temperature with no significant loss of titer. However, such solutions prepared from chlorinated solvents (*e.g.*, CH_2Cl_2, $ClCH_2CH_2Cl$, $CHCl_3$, and CCl_4) all seem to very gradually release a gas (presumably oxygen); if the container is opened every few weeks, one notices a hissing sound. This has never caused us any trouble, but we would not recommend that large quantities of such solutions be stored in sealed vessels for long periods of time. In contrast to this behavior, we have found that azeotropically dried solutions of TBHP in benzene, toluene, cyclohexane, ethyl acetate and *tert*-butyl alcohol seem to be completely stable (no out-gassing) when stored in sealed containers at room temperature
60) **It is especially important to remove the heat source, during TBHP addition, in large-scale epoxidations. The reaction is exothermic and refluxing will be sustained by gradual addition of the TBHP solution.** In small-scale epoxidations, especially with less reactive olefins (*e.g.*, 1-decene), it may be necessary to maintain heating to sustain reflux
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74) This is equivalent to Aldrich's 18,471-3, Lucidol-TBHP-70X, and Witco Chemical's USP-800
75) Oxirane Aqueous TBHP-70, Lucidol-TBHP-90, and Lucidol-TBHP-70
76) a) B. Chabaud, L.E. Khoo, B.E. Rossiter, D.J. Scheffel, and K.B. Sharpless, unpublished results b) The TBHP solutions generated by phase separation are slightly less reactive, presumably because they contain a little more (*ca.* 1-3% more) water than the solutions made from commercial 90% TBHP
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81) We have observed peroxyketal and peroxyacetal formation with TBHP and ketones and aldehydes in CH_2Cl_2 in the presence of catalytic amounts of SeO_2: I. Takagi, B. Chabaud, and K.B. Sharpless, unpublished results,
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Dr. Sharpless received a B.A. degree from Dartmouth College in 1963 and his Ph.D. from Stanford University in 1968. He was a professor at the Massachusetts Institute of Technology from 1970-1977 and has been Professor of Chemistry at Stanford University since 1977. He received an A.P. Sloan Fellowship and a Dreyfus Teacher-Scholar Award in 1973.

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Dr. Verhoeven obtained his Ph.D. from the University of Wisconsin in 1979 and is currently a postdoctoral fellow with Dr. Sharpless at Stanford.

Aldrich offers these compounds cited by Drs. Sharpless and Verhoeven:

18,471-3 *tert*-Butyl hydroperoxide, 70%, remainder water

21,312-8 *tert*-Butyl hydroperoxide, 90%, contains 5% water and 5% *tert*-butyl alcohol

11,019-1 Acetic acid, sodium salt, anhydrous, 99%

C6,270-0 *m*-Chloroperoxybenzoic acid, tech., 80-90%

D180-7 1-Decene

20,809-4 Magnesium sulfate, anhydrous, tech.

M8,163-2 Methyl sulfide

19,995-8 Molybdenum hexacarbonyl

20,103-0 Osmium tetroxide, 99.8%

20,886-8 Osmium tetroxide, 2.5% w/v solution in *tert*-butyl alcohol

10,591-0 Salicylic acid, 99+%

21,336-5 Selenium(IV) oxide, 99.8%

20,010-7 Selenium(IV) oxide, 99.9+%

20,431-5 Selenium(IV) oxide, 99.999%

21,988-6 Sodium hydrogen phosphate, anhydrous, A.C.S. reagent

21,763-8 Sodium iodide, anhydrous

20,784-5 Sodium sulfite, anhydrous

21,726-3 Sodium thiosulfate, anhydrous

21,724-7 Sodium thiosulfate, pentahydrate, A.C.S. reagent

17,993-0 Starch, soluble, A.C.S. reagent

20,558-3 Tetraethylammonium acetate tetrahydrate, 99%

17,780-6 Tetraethylammonium hydroxide, 20% solution in water

21,287-3 Vanadyl acetylacetonate

Hydroxylamine-*O*-sulfonic acid — a versatile synthetic reagent

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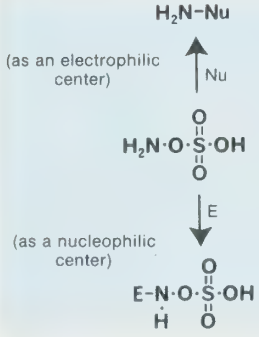
Synopsis

Hydroxylamine-*O*-sulfonic acid (HOSA) has only recently become widely commercially available despite the fact that it has proved to be a valuable synthetic reagent in preparative organic chemistry. Unfortunately, however, information regarding the use of HOSA in organic synthesis has remained scattered in the literature, and it is to focus attention on the versatility and potential of this reagent that this information has been brought together now in the form of a short review article.

Important among the areas of application of HOSA are amination and reductive deamination reactions, nitrile and oxime formation, and the preparation of amides and diazo compounds. These and other reactions, including the use of HOSA for the synthesis of heterocycles such as oxaziridines, diaziridines, pyrroles, isothiazoles, benzisoxazoles, benzodiazepines, isothiazolo- and pyrazolopyridines, and imidazolinones and related derivatives are discussed in the review. Many of these preparations can be carried out in high yield.

Hydroxylamine-*O*-sulfonic acid, $NH_2 \cdot OSO_3H$ (abbreviated to HOSA in this article) has become in recent years commercially available. Although much fruitful chemistry has been carried out using HOSA, to this author's knowledge, there has been no systematic review in English* of its use as a synthetic reagent. It is a chemically interesting compound because of the ability of the nitrogen center to act in the role of both nucleophile and electrophile, dependent on circumstances, and thus it has proved to be a reagent of great synthetic versatility.



Besides being directly involved in reactions, it may serve as an *in situ* source of other chemical entities (*e.g.*, imene) which then undergo reaction with a given substrate. Reference will be made from time to time to these various modes of reaction. The uses of HOSA as a reagent are organized below according to the different synthetic transformations that it can bring about.

Probably by far the most well known and explored reactions of HOSA are amination reactions, illustrating electrophilic attack by HOSA, with amination on nitrogen being the most important, although a significant number of aminations on both carbon and sulfur have been reported. Amination on phosphorus also occurs.

AMINATION

(a) At a nitrogen atom

(i) Preparation of mono- and disubstituted hydrazines and trisubstituted hydrazinium salts

Monosubstituted hydrazines can be prepared in yields of the order of 50% by treatment of a primary amine with HOSA in aqueous solution in the presence of base (eq. 1).[2-5] Similarly, secondary amines react to give 1,1-disubstituted hydrazines (eq. 2).[4,5]

An alternative route for mono- or disubstituted hydrazines uses an aqueous solution of the amine and a ketone, or the

*For a short review in Japanese see ref. 1.

†On secondment from the Cancer Research Campaign's Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

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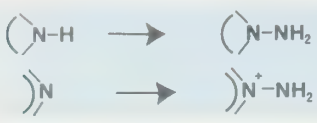
corresponding Schiff's base, instead of the amine alone and involves diaziridine ring formation (*vide infra*) which avoids the use of a considerable excess of amine to suppress further reaction of the hydrazine product and has additional advantages (for a discussion see reference 6 and references cited therein).

1,1,1-Trisubstituted hydrazinium salts are formed when tertiary amines are treated with HOSA under basic conditions in aqueous or alcoholic media (eqs. 3,4).[4,5,7]

(ii) Masked hydrazines - amination on the nitrogen heteroatom of nitrogen heterocycles



Many nitrogen heterocycles can be aminated on nitrogen using HOSA. These include azetidine,[8] pyridine,[4,5] quinoline,[4,5] pyridazine,[9] pyrimidine,[7] pyrazine,[9] tetrazole,[10] indole,[11,12] benzimidazole,[12,13] triazine,[14] benzoxazole,[15] and purine[12,16] ring systems (eqs. 5-16). (The pyrimidine ring system, however, will often undergo ring opening and rearrangement reactions as alternative reaction pathways:[9] a specific example of this is given under miscellaneous reactions.) Here, as in the synthesis of the simple hydrazines, the nitrogen of the HOSA acts as an electrophilic center in the reaction.

In the case of the 1-aminopyridinium cation,[4,5] 1-aminoindole,[11] and 1,2-diaminobenzimidazole[13] especially, the method constitutes an important preparative procedure since the reaction either fails with other reagents (pyridine) or the HOSA synthesis provides a more straightforward route to the compounds in question (indole, benzimidazole). 1-Aminobenzotriazole[14] forms a convenient benzyne precursor.

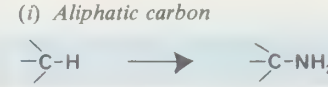
(iii) Preparation of 2-tetrazenes

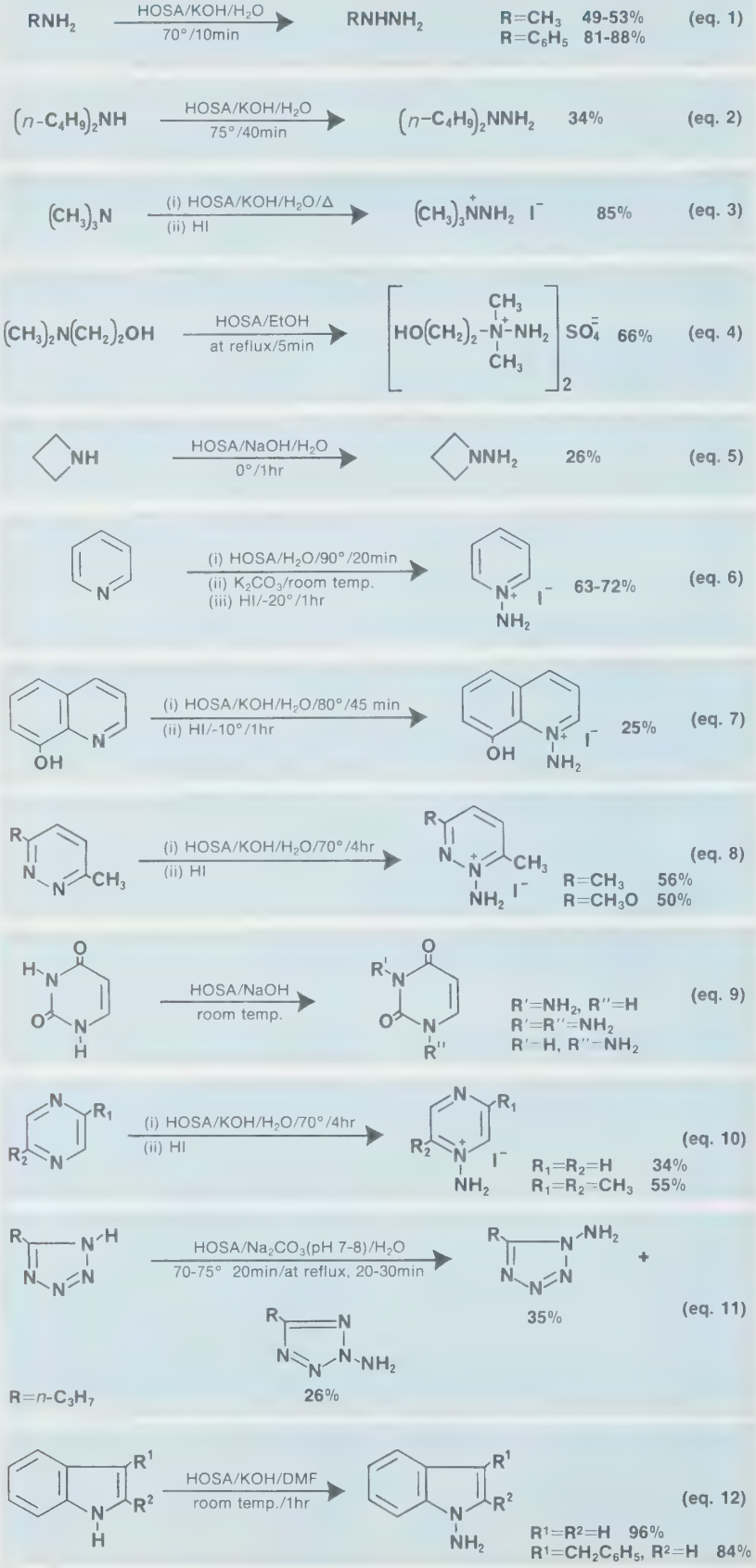
Piperidine and pipe colines react with HOSA in aqueous solution, in the presence of sodium hydroxide, to give 1,1,4,4-tetrasubstituted 2-tetrazenes (eq. 17).[17] Presumably, the simple hydrazine is initially formed and is subsequently oxidized to the tetrazene.

(b) At a carbon atom

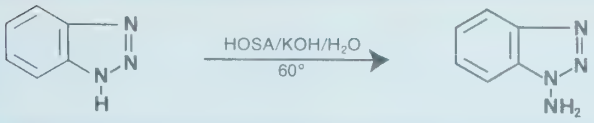
HOSA will aminate on aliphatic, aromatic and heterocyclic carbon atoms under a variety of conditions.

(i) Aliphatic carbon

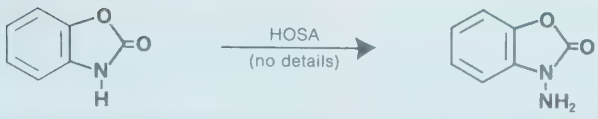




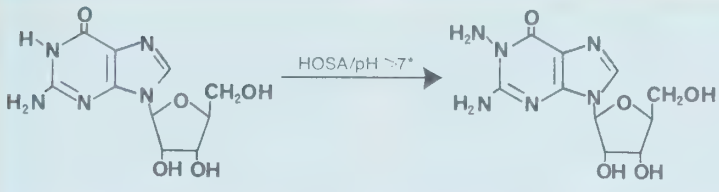
$R_1=R_2=H$ 76% (eq. 13)



(eq. 14)

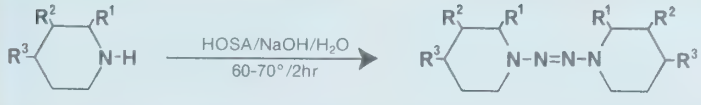


(eq. 15)

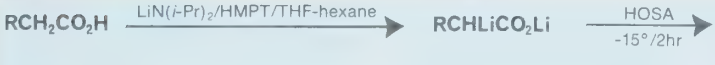


almost quantitative (eq. 16)

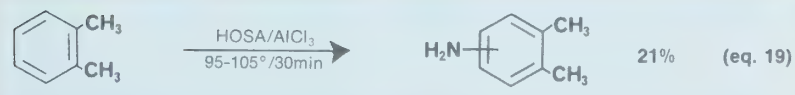
*Note: pH 2-4 gives C-8 amination



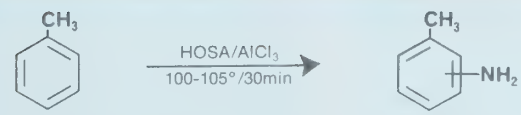
$R^1=R^2=R^3=H$ 18% (eq. 17)



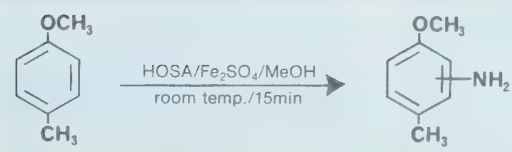
$RCH(NH_2)CO_2H$ $R=C_6H_5$ 83% (eq. 18)



21% (eq. 19)



50% (eq. 20)



34% (with respect to HOSA) (eq. 21)

$C_6H_5NH_2$ 35% (eq. 22)

One of the most successful of these procedures is the elegant one-step synthesis of α-amino acids from carboxylic acids. The acid is lithiated in a mixed solvent system and afterwards treated with HOSA (eq. 18)[18] to give the α-amino acid. HOSA will also aminate active methylene compounds as is demonstrated in the synthesis of substituted pyrroles[19] from β-keto esters and β-diketones.

(ii) Aromatic carbon

Two main methods have been employed to bring about direct amination in aromatic systems using HOSA. In both cases the yields tend to be on the low side.

The first employs aluminum chloride as a catalyst and has been fairly extensively investigated by Keller[20] and Kovacic.[21] There appears to be a number of points of variance between the work of the two authors. The precise aminating species is not known. Examples from both authors' work are given below (eqs. 19,20).[20,21]

The second method is a homolytic amination procedure developed by Minisci and his co-workers,[22] whereby what is thought to be a protonated amino radical is generated in a redox system (H_2N-$\cdot OSO_3H$/Fe^{++}) at room temperature and this then attacks an aromatic substrate. Yields of between 10 and 40% of monoaminated product are reported (eq. 21). (In many instances the yields are quantitative with respect to the aromatic substrate actually consumed.) In certain cases the reaction shows a degree of stereospecificity.

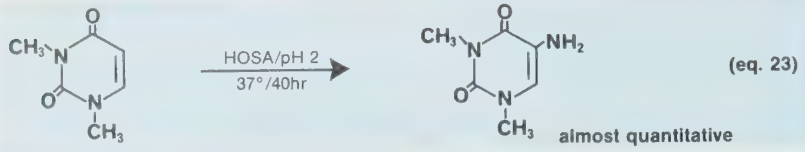
A third method,[23] from the very recent literature, is based on H.C. Brown's procedure for the conversion of alkenes *via* the organoborane to aliphatic amines (*vide infra*). If an aryl organoborane is substituted for the alkyl borane in the reaction (the paper gives triphenylborane as an example – prepared from phenylmagnesium bromide and boron trifluoride) an arylamine is produced (eq. 22). The disadvantage of the method is that, unlike trialkyl boranes, which utilize two of the three alkyl groups in amine formation, triphenylborane uses only one phenyl group and thus the overall yield with regard to amination on the aromatic ring is not high.

(iii) Heterocyclic carbon

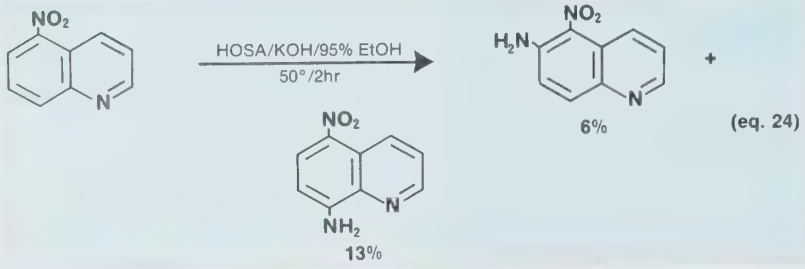
Certain heterocycles will react with HOSA to give a C-substituted amino derivative. For instance, 1,3-dimethyl-

uracil reacts with HOSA at pH 2 over 40 hours to give the C-amino product in almost quantitative yield (eq. 23).[24] Guanosine (eq. 16) aminates at the 8-position[16] at pH 2-4 (70°) and 5-nitroquinoline (*cf.* 8-hydroxyquinoline) aminates at the 6- and 8-positions under basic conditions (eq. 24).[25]

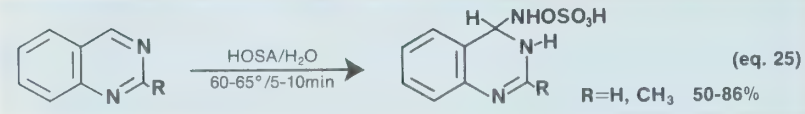
That the mechanism of some of these reactions may be one of addition followed by elimination is suggested by the fact that quinazolines, unsubstituted in the 4-position, react with HOSA at 60-65° over 5-10 minutes to give *N*-(3,4-dihydro-4-quinazolinyl)hydroxylamine-*O*-sulfonic acids, which can be isolated in good yield (eq. 25).[26] However, prolonged treatment with HOSA (70°, 4 hours) gives principally the 4-aminoquinazoline and no dihydro compound. (Interestingly, benzimidazoles and *ortho*-disubstituted benzenes are also products of the reaction under these conditions).[25]



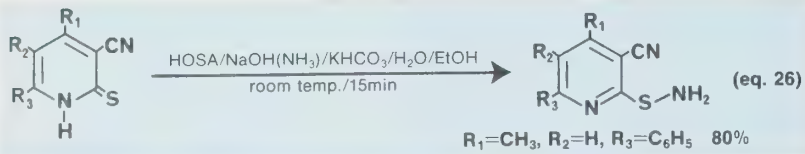
(eq. 23)



(eq. 24)



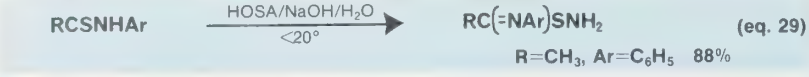
(eq. 25)



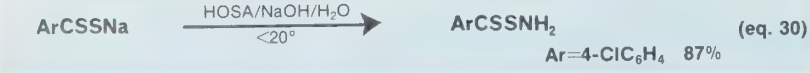
(eq. 26)

(eq. 27)

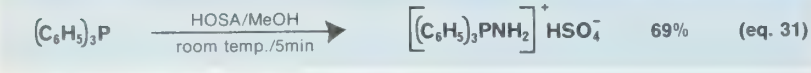
(eq. 28)



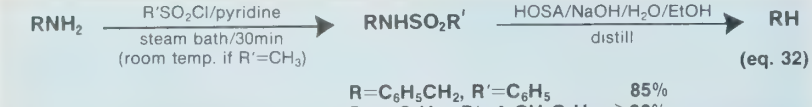
(eq. 29)



(eq. 30)



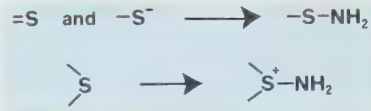
(eq. 31)



(eq. 32)

(eq. 33)

(c) At a sulfur atom



Amination of sulfur in a variety of organic situations can be carried out using HOSA. Thus thiols(ones),[27] thioacids,[28] thioamides,[28,29] dithioacids[28] and thioethers[30] undergo amination to give the corresponding hydrosulfamines and hydrosulfonium salts (eqs. 26-30). The yields for the reactions are generally good and, as with most HOSA transformations, the experimental procedure is relatively simple.

Sulfilimines, in particular, have proved to be very useful intermediates in organic synthesis.[31]

(d) At a phosphorus atom

Triphenylphosphine, when treated with HOSA in methanol, gives triphenylphosphiminium hydrogen sulfate (eq. 31) in 69% yield.[32]

REDUCTIVE DEAMINATION

Two methods of bringing about the transformation $RNH_2 \rightarrow RH$ using HOSA are available: an indirect method *via* the sulfonamide[33] and a direct route[34] which has appeared in the literature only recently.

Reductive deamination refers to the transformation of an amine to a product of lower oxidation level (in the sense proposed by Robinson) and involves the net replacement of an amino group by hydrogen.

In the indirect route,[33] a primary aliphatic or aromatic amine is treated with sulfonyl chloride (typically benzene-, *p*-toluene- or methanesulfonyl chloride) in dry pyridine and the mixture warmed on a steam bath. The sulfonamide, which is isolated, is dissolved in NaOH and then treated with HOSA and the reaction mixture distilled to give the alkane or arene. Yields of product are usually high (eq. 32).

Doldouras and Kollonitsch[34] have shown that there is no need to proceed *via* the sulfonamide, since the primary amine will react directly with 2-3 molar equivalents of HOSA, in the presence of

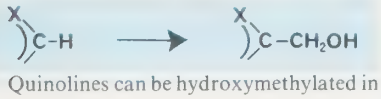
base, at 0°, to give the deaminated product in yields in excess of 50% (eq. 33). The authors have shown that the reaction works for a variety of structural types including amines containing other functionalities, and claim that it is a selective and general method. They have coined the name 'hydrodeamination' for the process and furthermore have illustrated how it may be extended to the conversions $RNH_2 \rightarrow RD$ and RT.

In both methods a common monosubstituted diimide (RN=NH) is proposed as an intermediate (their mode of formation differing) which readily decomposes to RH and nitrogen.

REDUCTION

HOSA alone, or in conjunction with other reagents, provides under basic conditions a source of diimide which will reduce double bonds. Thus, HOSA with cyclohexanone gives 1,1-dihydroxyazocyclohexane, an unstable substance, which, if allowed to decompose at room temperature (which it does rapidly by way of diimide) in the presence of quinone or of azobenzene, yields hydroquinone and hydrazobenzene respectively.[35] HOSA and hydroxylamine sulfate together form an *in situ* source of diimide capable of selectively hydrogenating conjugated multiple bonds (eqs. 34, 35).[36] Using HOSA alone, Appel and Büchner[37] give examples of the reduction of both conjugated and nonconjugated multiple bonds but the yields tend to be lower (eq. 36).

HYDROXYMETHYLATION

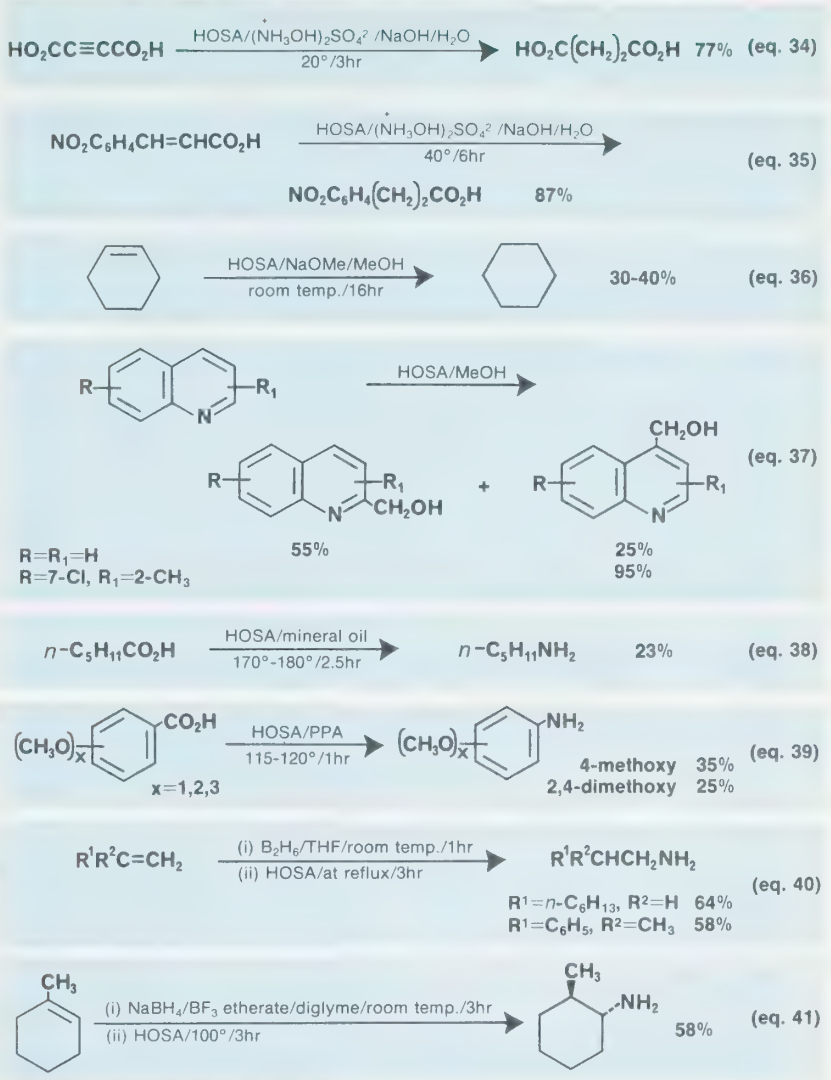


Quinolines can be hydroxymethylated in the 2- and/or 4-position using HOSA in methanol (eq. 37).[38] The discovery arose when a desired amination on nitrogen using the standard HOSA method could not be achieved owing to insolubility of some quinolines in the aqueous medium and, as a result, the solvent was changed to methanol. The reaction has been found to be general for quinolines substituted in the carbocyclic ring and having either a 2- or 4-position (or both) vacant.

FUNCTIONAL GROUP TRANSFORMATIONS:

Loss of carbon

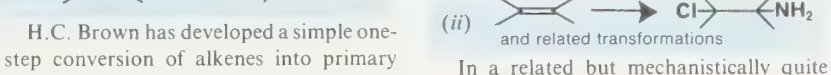
Numerous attempts have been made[39,40] to prepare amines in high yield by the reaction of carboxylic acids or their derivatives with HOSA. The best results to date have been yields of the order of 20-30% and have been obtained by heating the acid (or its anhydride) with HOSA in mineral oil at 160-180° (eq. 38)[39] or polyphosphoric acid at 115-125° (eq. 39).[40] However, the conditions for this transformation clearly still need to be optimized.



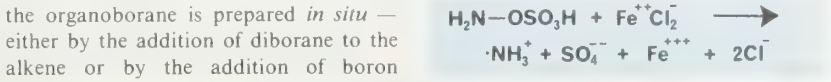
Addition to double bonds

Alkenes

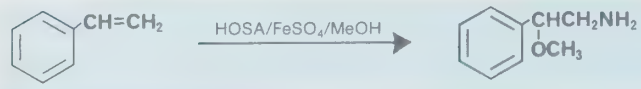
H.C. Brown has developed a simple one-step conversion of alkenes into primary amines *via* the corresponding organoborane using HOSA (eq. 40).[41] The method is applicable to a wide variety of alkenes, and in a later paper,[42] he has shown that it can be applied to relatively hindered alkenes with equal success by conducting the reaction in diglyme, in which HOSA is soluble, rather than in tetrahydrofuran as in the earlier work (eq. 41). In both cases the organoborane is prepared *in situ* — either by the addition of diborane to the alkene or by the addition of boron trifluoride etherate to the alkene and sodium borohydride in diglyme. The reaction is highly stereospecific as is demonstrated in the conversion of norbornene and α-pinene to the isomerically pure *exo*-norbornylamine and isopinocampheylamine, respectively.[42] Occasionally a rearranged amination product is observed.[43]



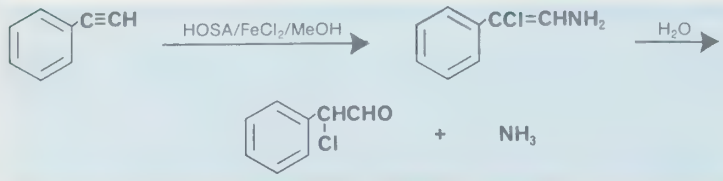
In a related but mechanistically quite different process, the metal salt redox system of Minisci (*cf.* amination on aromatic carbon — method two) is used to bring about the addition of the elements NH_2 and Cl across a double bond.[44,45] The addition occurs when HOSA is decomposed by $FeCl_2$ in the presence of the alkene:



$RCH{=}CH_2 \xrightarrow[0°]{HOSA/FeCl_2/MeOH} RCHClCH_2NH_2$ $R{=}n\text{-}C_4H_9$ 8%, $R{=}C_6H_5$ 13% (eq. 42)



(eq. 43)



(eq. 44)

$R_1R_2C{=}O \xrightarrow[0°/1min]{HOSA/K_2CO_3 \text{ or } KOAc} R_1R_2C{=}NOSO_3K$ $R_1{=}n\text{-}C_4H_9, R_2{=}CH_3$ 55%; $R_1{=}CH_2CO_2CH_3, R_2{=}CH_3$ 55% (eq. 45)

$ArCHO \xrightarrow[room\ temp.]{HOSA/H_2O} ArCH{=}NOSO_3H$ Ar=subst. benzene, pyridine or imidazole* (eq. 46)

*R.G. Wallace, unpublished observations.

Examples are given in eq. 42. It would appear that the amino group attaches itself to the least-substituted carbon atom. The addition differs from the organoborane method in not being stereospecific.

If addition is carried out in methanolic solution with $FeSO_4$ instead of $FeCl_2$, an amino ether is produced (eq. 43)[44] and if sodium azide is also present an azido amine is formed.[45]

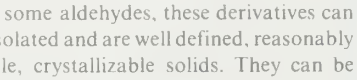
Phenylacetylene with $FeCl_2$ yields α-chlorophenylacetaldehyde by hydrolysis of the corresponding intermediate enamine (eq. 44).[44]

Carbonyl compounds

(*i*) 

Both ketones and aldehydes react with HOSA to give oxime-*O*-sulfonic acids and salts (eqs. 45, 46).[46,47] In the case of ketones and some aldehydes, these derivatives can be isolated and are well defined, reasonably stable, crystallizable solids. They can be prepared in good yield and undergo a variety of further reactions. This transformation illustrates the alternative role of the HOSA nitrogen as nucleophile.

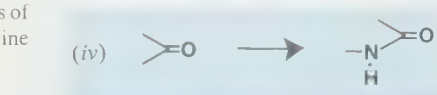
The condensation reaction to give the oxime-*O*-sulfonic acid or salt forms a common first stage in a number of related and synthetically very useful transformations.

(*ii*) 

Aldehydes, in aqueous solution/suspension, can be smoothly converted in high yield into nitriles (of the same carbon number) with HOSA.[26,47] The precise conditions depend on the nature of the aldehyde (details are given in eqs. 47-49), the important factor being for them to be sufficiently rigorous to bring about the elimination of sulfuric acid from the intermediate oxime-*O*-sulfonate.

(*iii*) 

Aliphatic ketones react exothermically when warmed together with HOSA in a water bath to give the corresponding oxime in very good yield (eq. 50).[48] The reaction is accompanied by the loss of nitrogen.

(*iv*) 

Aryl alkyl ketones, under the above conditions (eq. 51), yield N-aryl aliphatic amides, again in good yields.[48]

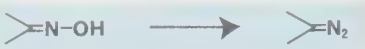
According to Sherk *et al.*,[48] diaryl ketones do not react under these conditions, but Ho[49] has reported the formation of amides in tetrahydrofuran. Schmidt- and Beckmann-type mechanisms are proposed for these rearrangement reactions, the precise details of which have not been resolved.[48,49]

In a very recent extension of this synthetic transformation, Olah and Fung[50] have shown that alicyclic ketones can be converted to their corresponding lactams, in high yield, by heating the ketone and HOSA under reflux in formic acid for several hours (eq. 52). Benzophenone, under similar conditons, gives benzanilide in 68% yield.[50]

Enamines

An additional nitrile synthesis using HOSA has recently been reported.[51] This time the precursor is an enamine. The method is extremely useful since enamines can be prepared readily from a variety of active methylene compounds and ketones. The enamine and HOSA are stirred together for 1 hour at room temperature, whereby the nitrile is obtained in good yield (eq. 53).

Forster reaction



Oximes react with HOSA in aqueous base to give diazo compounds.[52] Thus,

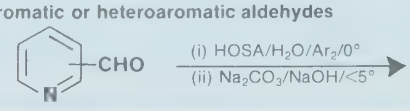
Aliphatic aldehydes

$RCHO \xrightarrow[20\text{-}40°/20min]{HOSA/H_2O} RCN$ $R{=}n\text{-}C_6H_{13}$ 87%, $R{=}HOCH_2$ 71% (eq. 47)

Aromatic or heteroaromatic aldehydes

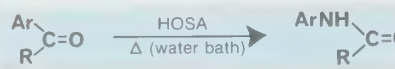
$ArCHO \xrightarrow[(ii)\ 65°/30min]{(i)\ HOSA/H_2O/room\ temp.} ArCN$ $Ar{=}4\text{-}CH_3C_6H_4$ 85%; $Ar{=}3\text{-}CH_3O, 4\text{-}CH_3C_6H_3$ 89% (eq. 48)

Aromatic or heteroaromatic aldehydes

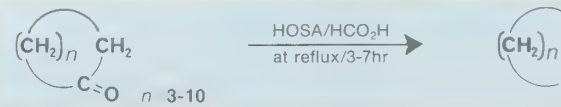


(eq. 49)

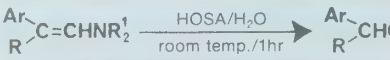
$RR^1C{=}O \xrightarrow[\Delta\ (water\ bath)]{HOSA} RR^1C{=}NOH$ $R{=}R^1{=}CH_3$ 90%; $R{=}CH_3, R^1{=}C(CH_3)_3$ 85% (eq. 50)



$Ar{=}C_6H_5, R{=}CH_3$ 90%; $Ar{=}4\text{-}CH_3OC_6H_4, R{=}CH_3$ 90% (eq. 51)

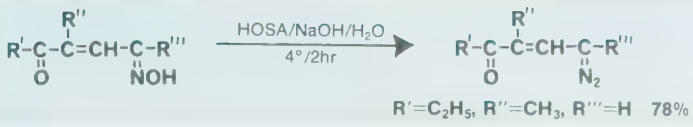


(eq. 52)



$Ar{=}4\text{-}NO_2C_6H_4, R^1{=}CH_3$ 78%; $Ar{=}4\text{-pyridyl}, R^1{=}CH_3$ 68% (eq. 53)

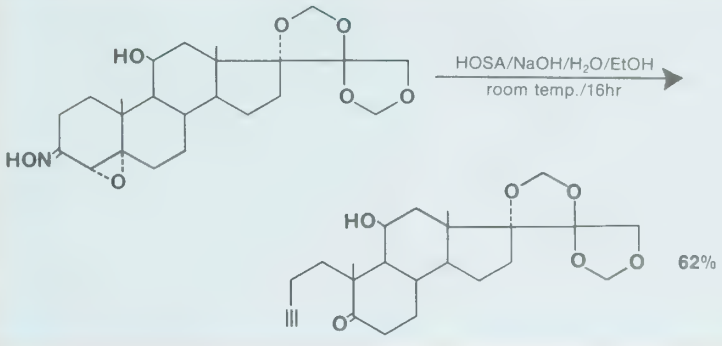
fluorenone oxime gives diazofluorene in 60% yield and benzophenone oxime gives diphenyldiazomethane (30%). The reaction also works well for fully conjugated α,β-unsaturated 1,4-ketoximes (eq. 54).[53]



(eq. 54)

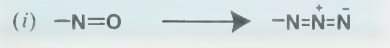
Fragmentation reactions

In a sagacious extension of the diazo functionality formation reaction just described, Wieland, Kaufmann and Eschenmoser[54] have demonstrated in the field of steroidal chemistry the facile conversion of an α,β-oxido oxime to an alkynone (eq. 55). A further example and a discussion of the mechanism of the reaction is given in a later paper.[55]



(eq. 55)

Miscellaneous

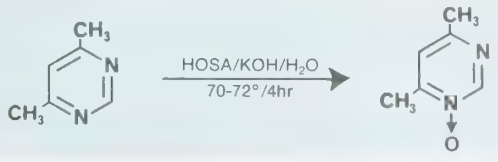


Nitrosobenzene will react with HOSA in tetrahydrofuran in the presence of base to give phenyl azide (*cf.* Forster reaction) (eq. 56).[56]

(eq. 56)

(ii) N-Oxide formation

Certain 4-substituted pyrimidines[9] and condensed pyrimidines (quinazolines)[26] react with HOSA to give N-oxides. For example, 4,6-dimethylpyrimidine, with the potassium salt of HOSA in aqueous methanol over 4 hours at 70°-72°, gives 4,6-dimethylpyrimidine-1-oxide (eq. 57).[9] A mechanism involving addition of HOSA, followed by ring opening and then recyclization and, finally, loss of sulfur trioxide and ammonia is proposed for the reaction.[9]



(eq. 57)

(eq. 58)

(eq. 59)

HETEROCYCLE FORMATION

(a) Cyclization reactions

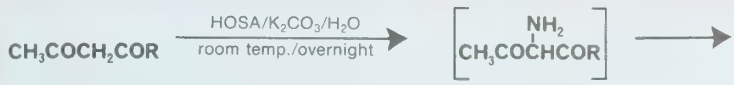
Oxaziridines

The oxaziridine ring system can be prepared by the reaction of HOSA with an aliphatic ketone[57,58] or benzaldehyde[59] in 2*N* NaOH at 6-8°. Thus, 3-ethyl-3-methyloxaziridine is obtained in 96% yield (eq. 58)[57] from 2-butanone. The oxaziridine is stable only at very low temperature. More stable oxaziridines are generally obtained by acylating the unsubstituted oxaziridine *in situ*.[59]

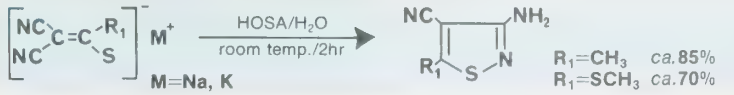
Diaziridines

Related to the preparation of oxaziridines and probably another of the most widely explored areas of HOSA chemistry has been the synthesis of diaziridines. Both simple[60] and complex diaziridines such as those with steroidal[61] and multifused[62] ring structures have been described. Principal references are given in reviews by Schmitz[63,64] who notes that by 1964, fifty or so diaziridines had been prepared by the HOSA method.

The diaziridine is formed by reaction of HOSA with ketone/ammonia mixtures. Schiff's bases or a mixture of a carbonyl compound and a primary amine. A typical synthetic procedure, described in *Organic Syntheses*,[65] is illustrated in eq. 59. The diaziridines may easily be oxidized to diazirines.



(eq. 60)



(eq. 61)

The pyrrole system

Tamura *et al.*[19] have described a simple one-step method for the preparation of tetrasubstituted pyrroles. A β-diketo compound is treated with HOSA in aqueous potassium carbonate solution overnight to give a symmetrically substituted pyrrole (yields 28-34%, eq. 60). Pyrroline is formed in low yield when HOSA is treated with NaOMe in methanol in the presence of 1,3-butadiene.[66] The 1,4-addition of imene ($\bar{N}H$) to the diene is invoked in this reaction.

Isothiazoles

Dicyanothioalkene salts* (eq. 61, these

*The yields from monocyano compounds are very low

can easily be prepared in yields of over 70% by the thioacylation of malononitrile by esters of dithiocarboxylic, thionocarboxylic, xanthic or trithiocarbonic acids at room temperature) react with HOSA in aqueous solution to give 3-aminoisothiazoles.[67,68] The yield of crude reaction product is generally good but isolation of the pure isothiazole may in some cases present technical difficulties.

Benzisoxazoles

Kemp and Woodward[69] have described how benzisoxazole can be prepared in 95% yield when salicylaldehyde is combined with HOSA in water, followed by treatment with sodium bicarbonate for 1 hour at room temperature (eq. 62). A similar preparation was reported eleven years after the publication of Kemp and Woodward's paper, by Suwinski,[70] who seems to have been unaware of the former authors' work. The reaction involves nucleophilic attack by the HOSA nitrogen. The preparation of Kemp and Woodward is suited to large-scale reaction.

Benzodihydro-[1,2]-diazepines

δ-Amino aromatic aldehydes (see eq. 63) can be cyclized in low yield using HOSA to give diazepines.[71] The major product of the reaction, however, is the aromatic nitrile (*vide ante*). The yields of diazepines, nevertheless, can be increased by increasing the nucleophilicity of the nitrogen atom of the aniline function (see eq. 63) and/or by employing mesitylsulfonylhydroxylamine in place of HOSA in the reaction (yields up to 76%).

The proposed mechanism for the cyclization involves a ring expansion step; an additional benzodiazepine ring synthesis, which is a direct ring expansion of a preformed starting material, is described a little later.

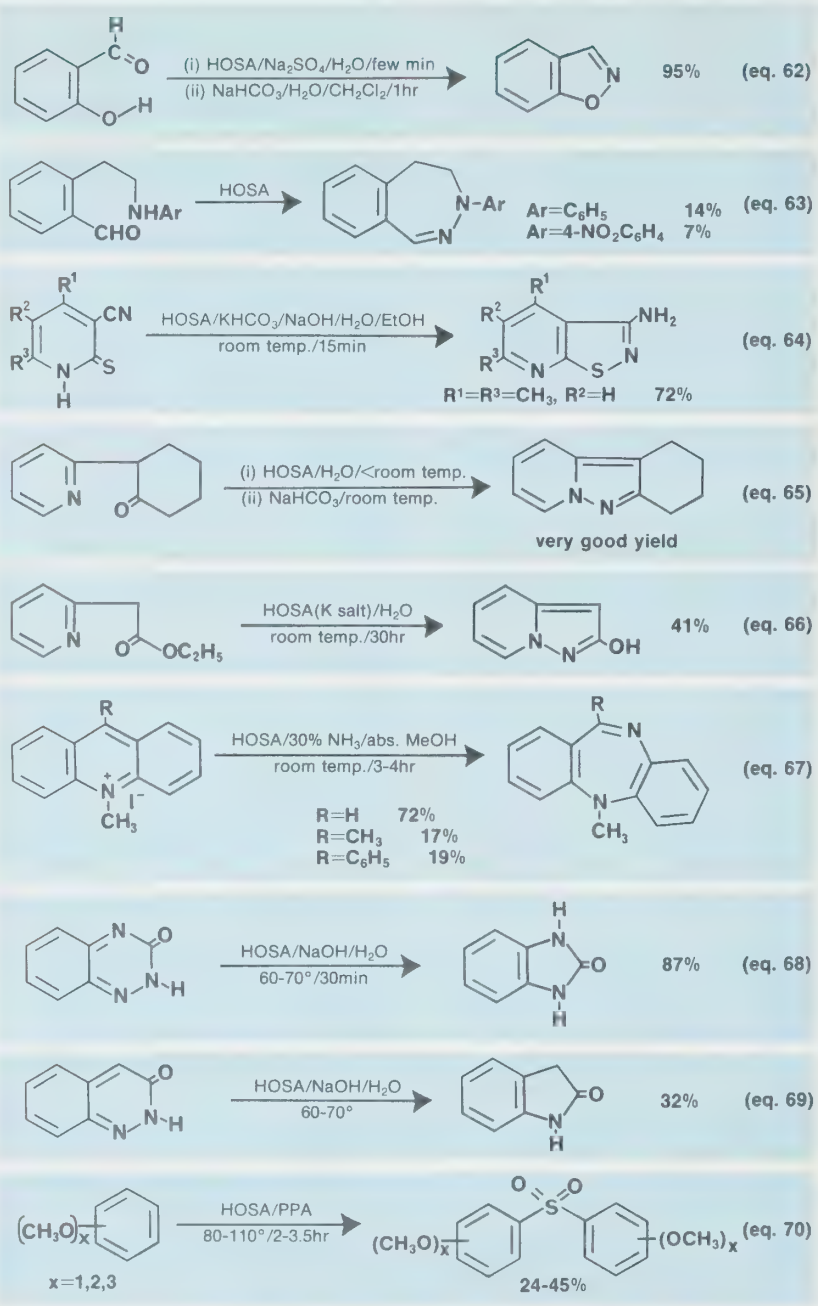
Isothiazolopyridines

In an extension of the isothiazole synthesis described above, 3-cyanopyridine-2-thiones are found to cyclize on treatment with HOSA in the presence of base to give 3-aminoisothiazolo[5,4-*b*]pyridines (eq. 64).[27] The yields in this reaction are good.

Pyrazolopyridines

Pyridines with a β-carbonyl functionality in the 2-position undergo ring closure with HOSA to give pyrazolo[1,5-*a*]-pyridines (eqs. 65,66)[70,72] in good yield. The reaction would seem to occur by electrophilic attack of the HOSA on the carbonyl function to give a derived oxime-*O*-sulfonate, with subsequent electrophilic attack of the oxime nitrogen on the nitrogen of the pyridine ring.

(b) Ring expansion



Dibenzo-[1,4]-diazepines

Treatment of *N*-methylacridinium derivatives with HOSA in absolute methanol containing 30% ammonia for 3-4 hours at room temperature results in an expansion of the heterocyclic ring. The resulting 5-methyldibenzo[*b*,*e*]-(1,4)-diazepines[73] are obtained in variable yield (eq. 67).

(c) Ring contraction

Imidazolin-2-ones and their benzo derivatives

1,2,4-Triazin-3-ones, when treated with HOSA in aqueous alkali at 70°, undergo a ring contraction reaction to give imidazolin-2-ones in high yield.[74] Thus, 5,6-diphenyl-1,2,4-triazin-3-one gives 4,5-diphenylimidazolin-2-one (68%), 1,2,4-benzotriazin-3-one gives benzimidazolin-2-one (87%, eq. 68) and phenanthro[9,10-*e*]-[1,2,4]triazin-3-one (requiring aqueous/ethanolic NaOH) gives 1,3-dihydrophenanthro[9,10-*d*]imidazol-2-one (74%). *N*-Aminotriazines are considered to be intermediates in these ring contractions.

Oxindole

Cinnolin-3-one, under similar conditions to those above, reacts with HOSA

to give oxindole in 32% yield (eq. 69).[74]

MISCELLANEOUS

Most of the preceding reactions described have involved the incorporation of the nitrogen of the HOSA in the reaction product. One reaction which differs from all of these is that between aromatic ethers and HOSA in polyphosphoric acid. Here, sulfur is incorporated and the product is a diaryl sulfone (eq. 70).[75] It is suggested that HOSA is cleaved to give H_2SO_4 and it is further reaction of this that gives rise to the sulfone.

CONCLUSIONS

HOSA has proved to be a reagent of diverse synthetic utility, its multifarious uses having been amply illustrated in the foregoing paragraphs. Such versatility is a consequence of the inherent ability of HOSA to act as both a nucleophile and electrophile and also to provide an *in situ* source of other chemical entities, factors referred to at the beginning of this article. These properties have led to its exploitation in such a variety of situations.

Clearly there is scope for its application in further organic transformations, and in particular, it must have a further part to play in new heterocyclic syntheses.

ACKNOWLEDGMENT

I wish to thank the Cancer Research Campaign for financial support.

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About the Author

Dr. Wallace is a research scientist working for the Cancer Research Campaign. He obtained his B.Sc. degree from Southampton University in 1968 and subsequently carried out his Ph.D. research at the School of Pharmacy, Portsmouth Polytechnic. His main interests lie in the area of heterocyclic chemistry and in particular he is concerned with the synthesis of hypoxic cell radiosensitizers for use in cancer therapy. He holds a Visiting Research Fellowship at Brunel University.

Aldrich offers HOSA and many of the reagents cited by Dr. Wallace:

21,313-6 Hydroxylamine-*O*-sulfonic acid

Chiral Starting Materials and Reagents

An Outline of Recent Synthetic Applications

William A. Szabo
and
Helen T. Lee
Aldrich Chemical Company, Inc.
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Format and Scope

In recent years the chemical literature has reflected the growing popularity of chiral starting materials and reagents for the construction of optically active organic molecules.[1] We present below a broad overview of some of this literature in outline form, arranged according to an arbitrary system of chemical classes. It is hoped that this format will provide the reader with an appreciation for the wide variety of readily available, optically active compounds which have been successfully employed in contemporary organic synthesis.

Space limitations require that we confine our examples to those starting materials and reagents (used in stoichiometric[2] quantities) whose chirality is incorporated intact into the product molecule and/or is used to direct the stereochemical outcome of a synthetic step. We must apologize to the many authors whose work could not be accommodated in a survey of this length.

Categories of Synthetically Useful, Optically Active Starting Materials and Reagents

I. Natural Products
  A. Containing Nitrogen
    1. Alkaloids
    2. α-Amino Acids
  B. Non-nitrogenous
    1. Sugars
    2. Terpenes
    3. α-Hydroxy Acids

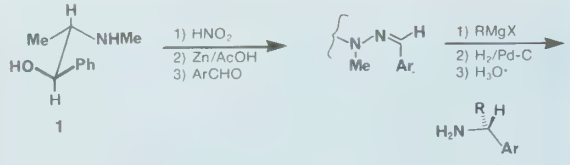
II. Synthetic Products
  A. Primary Amines
  B. Alcohols
  C. Miscellaneous

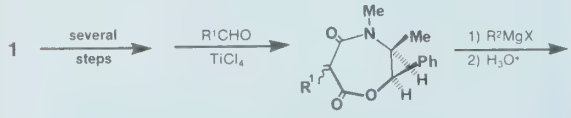
Chiral[3] Starting Materials and Reagents: Recent Synthetic Applications

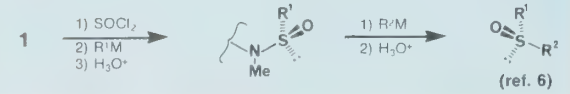
I. Natural Products
  A. Containing Nitrogen

1. Alkaloids

(-)-Ephedrine (**1**):

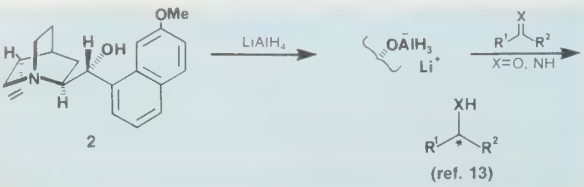






Also: preparation of chiral, isotope-labeled ATP,[7] α-substituted ketones and carboxylic acids,[8] *O,S*-dialkyl phosphoramidothioates,[9] and a carbonyl masking group.[10] The enantiomeric (+)-ephedrine has recently been used for the synthesis of (*S*)-(+)-4-methyl-3-heptanone, an alarm pheromone.[11,12]

Quinine (**2**):



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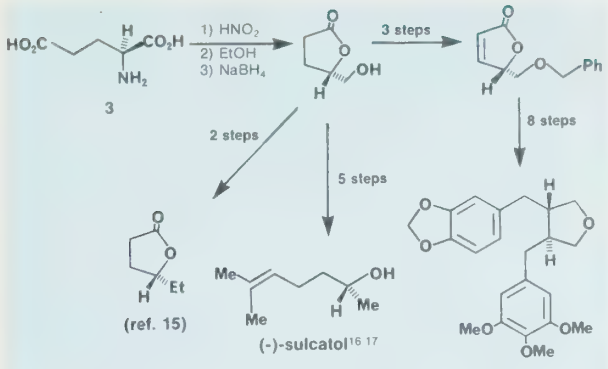
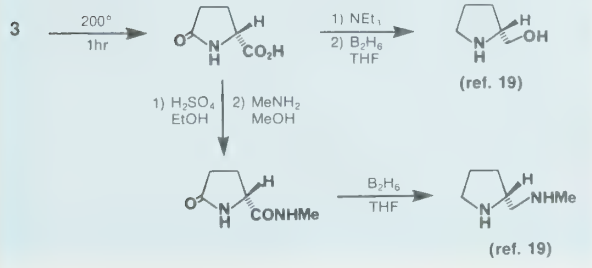
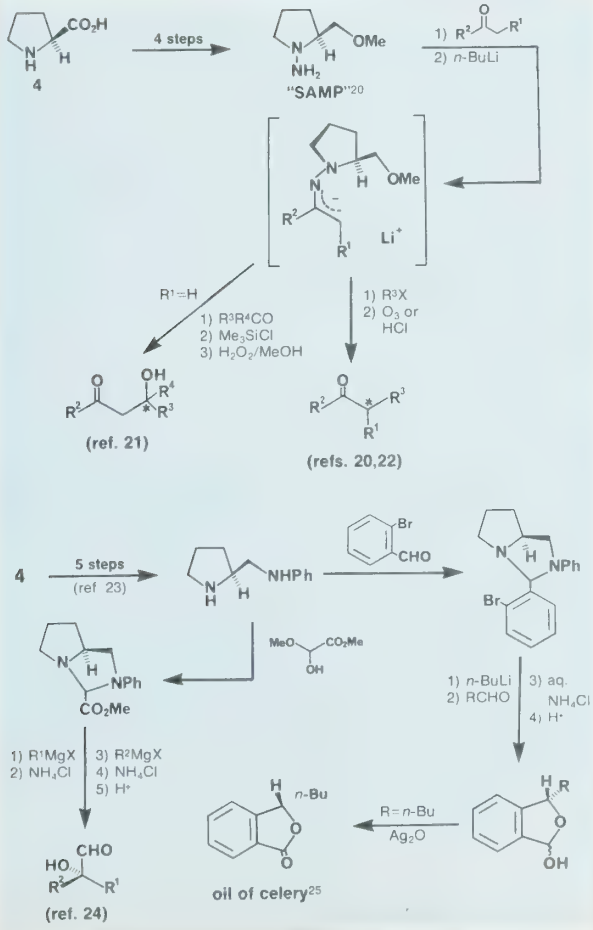
2. α-Amino Acids

L-(+)-Glutamic acid (3):[14]



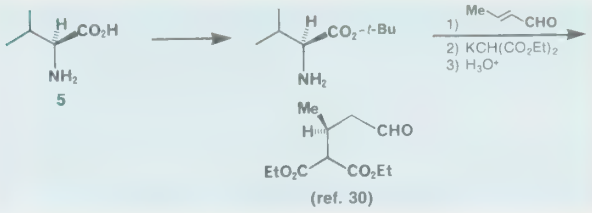


L-(-)-Proline (4):



Also: preparation of chiral α-hydroxy acids,[26] α-amino acids,[27] alkyl methylphenylphosphinates,[28] and prolyl dipeptides.[29]

L-(+)-Valine (5):



D-(+)- and L-(-)-Cystine: studies on the total synthesis of streptogramin antibiotics.[31]

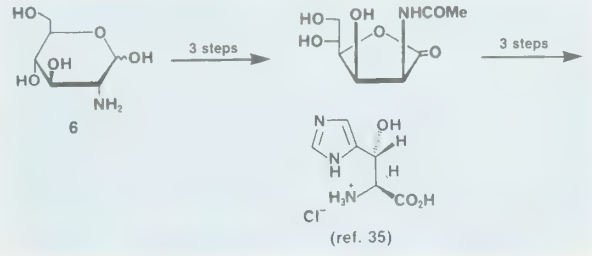
L-(+)-Leucine: preparation of (-)-ipsenol, an active component of a bark beetle aggregation pheromone.[32]

L-(+)-Serine: synthesis of (-)-deoxoprosopinine and (-)-deoxoprosophylline, the unnatural enantiomers of two *Prosopsis* alkaloids.[33]

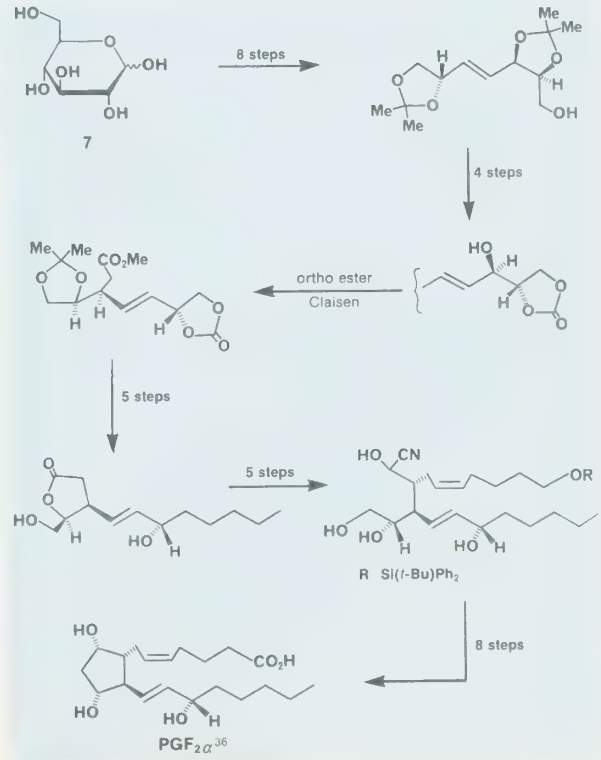
B. Non-nitrogenous (*parent systems*)

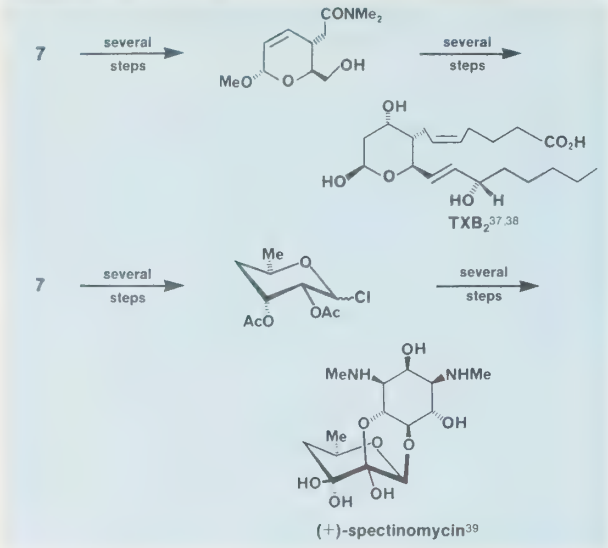
1. Sugars[34]

D-(+)-Glucosamine (6):



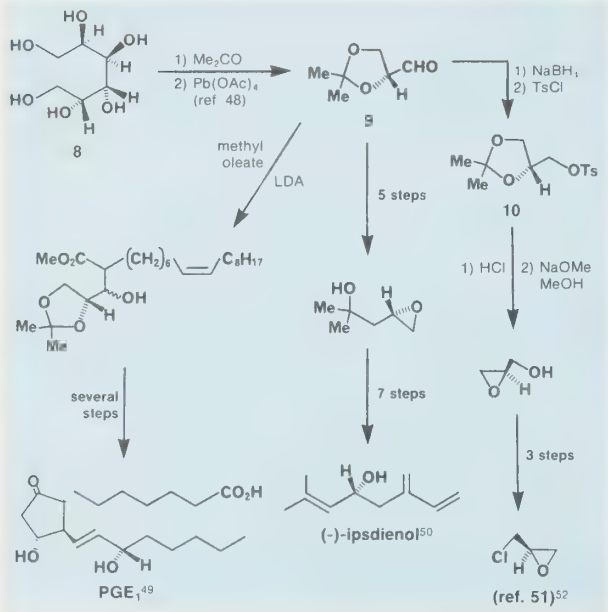
D-(+)-Glucose (7):





Also: recent total synthesis of anisomycin,[40] (+)-furanomycin,[41] pentenomycin,[40] canadensolide,[42] cerulenin,[43] tetrahydrocerulenin,[44] and (-)-α-multistriatin;[45] and synthesis of macrolide fragments[46] and a variety of chiral pyranones.[47]

D-Mannitol (**8**):



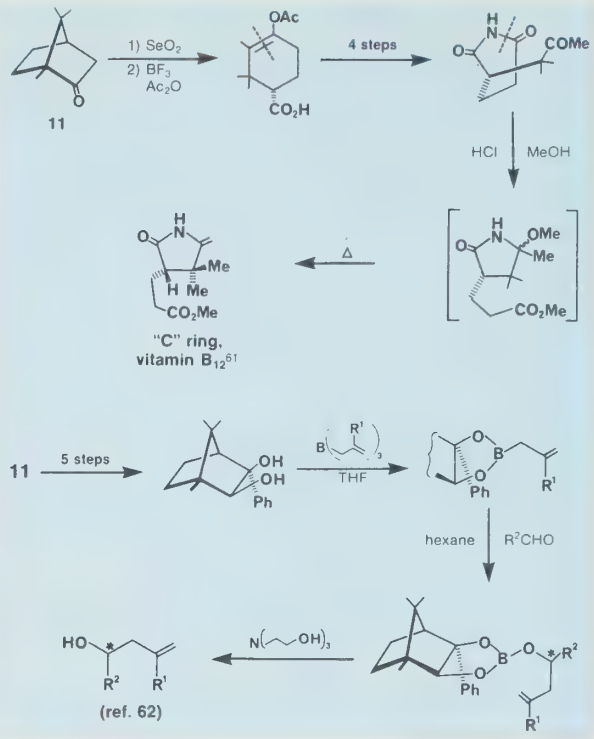
Also: preparation of chiral cryptands,[53] (-)-α-multistriatin,[54] and a variety of chiral epoxides,[55] amino alcohols,[56] and benzodioxans[57] of medicinal interest.

General: preparation of optically active macrocyclic polyethers (*e.g.*, from D-altrose, D-galactose, D-glucose, L-iditol, D-mannitol, D-mannose, and L-threitol)[58] and reducing agents (prepared from a variety of O-protected sugars and $LiAlH_4$[59] or $NaBH_4$[60]).

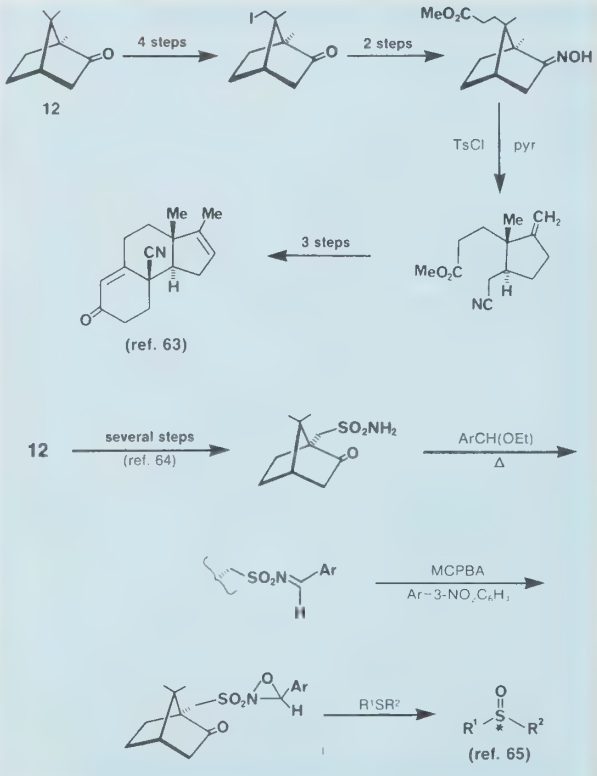
2. Terpenes

a. Type 

(+)-Camphor (**11**):



(-)-Camphor (**12**):

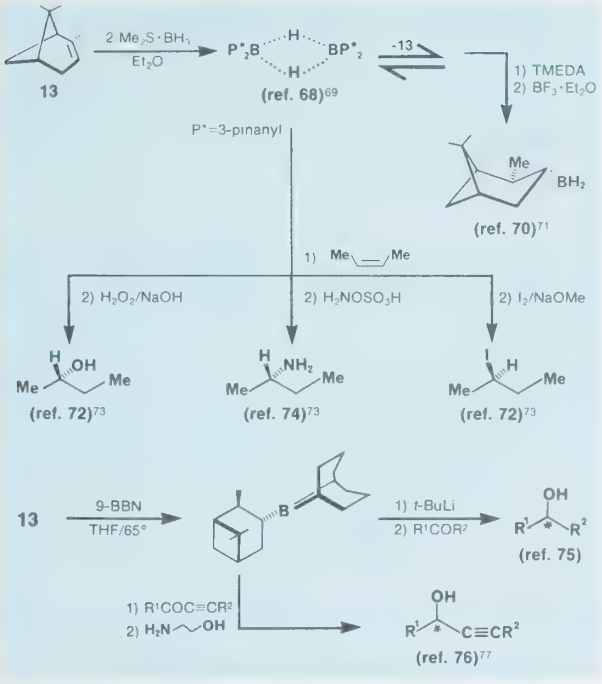


(-)-Borneol: synthesis of cyclopropanes *via* chiral carbenoids.[66]

(-)-Camphene: synthesis of nojigiku, an alcohol found in Japanese chrysanthemum.[67]

b. Type 

(+)-α-Pinene (**13**):

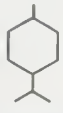


Also: synthesis of chrysanthemic acid derivatives[78] and (+)-*trans*-verbenol, a component of bark beetle pheromone.[79]

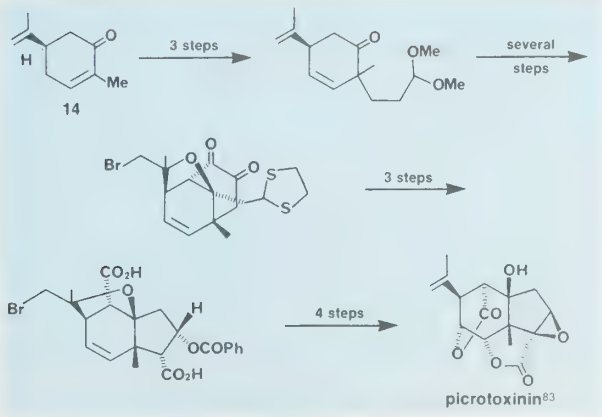
(-)-Nopol: preparation of structural analogs of thromboxane A_2.[80]

(-)-3-Pinanecarboxylic acid: preparation of a chiral oxidizing agent.[81]

(-)-β-Pinene: synthesis of (+)-grandisol, the major component of a male boll weevil pheromone.[82]

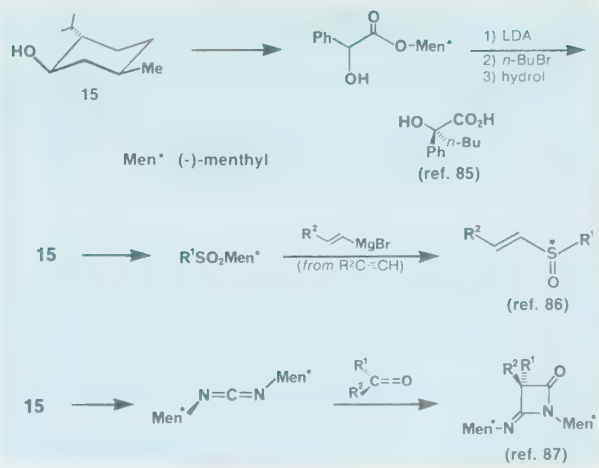
c. Type 

(-)-Carvone (**14**):



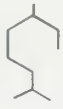
Also: synthesis of (-)-4,11-epoxy-*cis*-eudesmane, the major component of a termite defense secretion.[84]

(-)-Menthol (**15**):

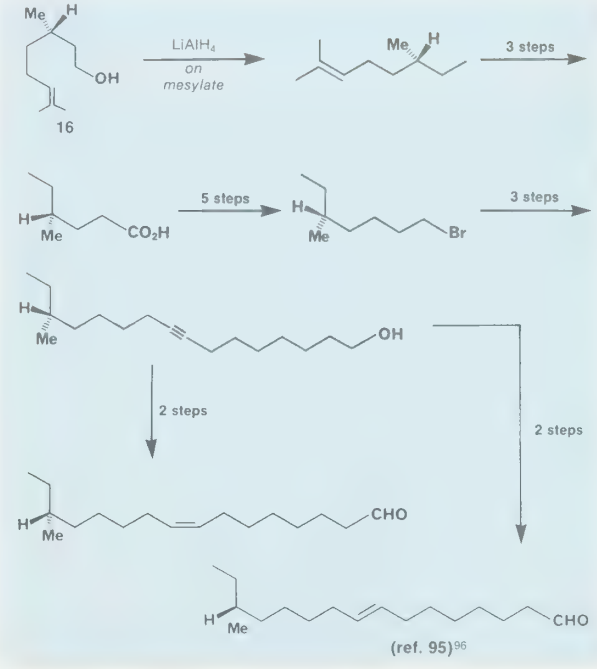


Also: use of menthyl *esters* for the synthesis of optically active β-sulfonyl sulfoxides,[88] sulfoximines,[89] chrysanthemic acids (*via* chiral carbenoids),[90] and (+)-disparlure;[91] asymmetric crossed aldol reactions;[92] and photocycloadditions to produce optically active oxetanes.[93]

(*R*)-(+)-Limonene: synthesis of (*R*)- and (*S*)-*p*-mentha-1,8-dien-4-ol, one of which (not disclosed) is a component of several essential oils and an insect attractant.[94]

d. Type 

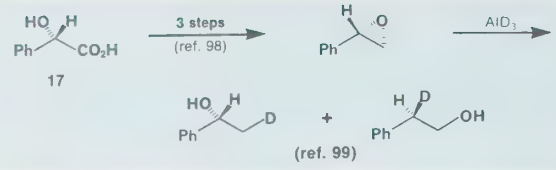
(-)-Citronellol (**16**):



(+)-Citronellol: synthesis of (-)-α-multistriatin.[97]

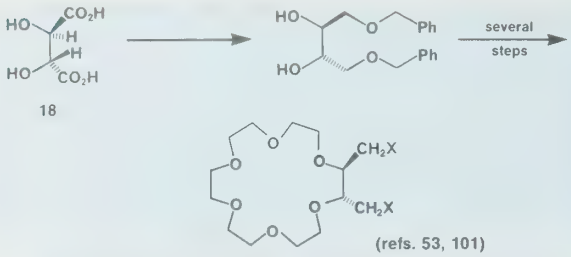
3. α-Hydroxy Acids

(+)-Mandelic acid (**17**):



Also: preparation of deuterated, optically active 2-phenylethanols and phenylethanes.[100]

(+)-Tartaric acid (**18**):

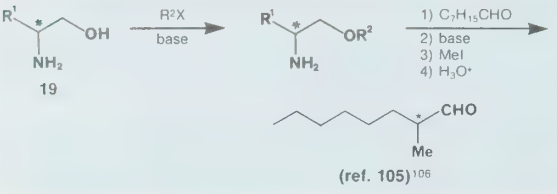


Also: synthesis of prostaglandin intermediates,[102] (+)-disparlure,[103] and optically active 1-benzyloxy-3,4-epoxy-2-butanol, a useful synthon for the preparation of a variety of asymmetric molecules.[104]

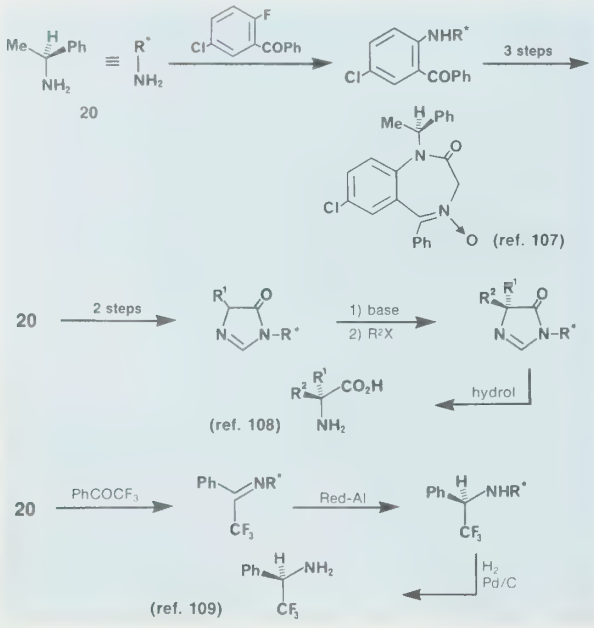
II. Synthetic Products

A. Primary Amines

Ethanolamines (**19**):



(-)-α-Methylbenzylamine (**20**):



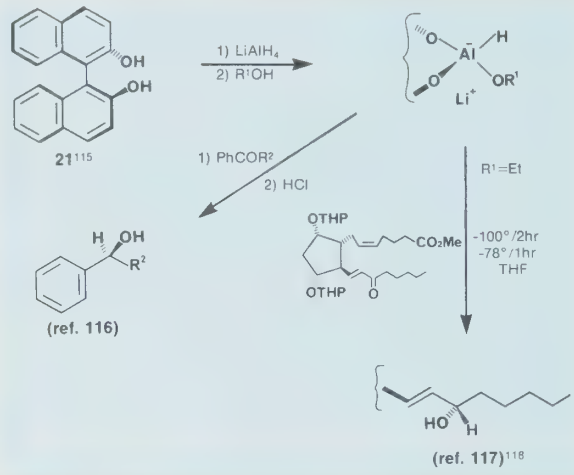
Also: synthesis of stereoisomers of 4-methylcyclophosphamide,[110] optically active aspartic acid[111] and serine[112] (*via* chiral aziridines), and a complex (with $LiAlH_4$) for the asymmetric reduction of ketones.[113] Note that many of the transformations described above have also been effected with the (*R*)-(+)-enantiomer of **20**.

(*R*)-(-)-2-Amino-1-butanol: asymmetric alkylation of cyclohexanone.[114]

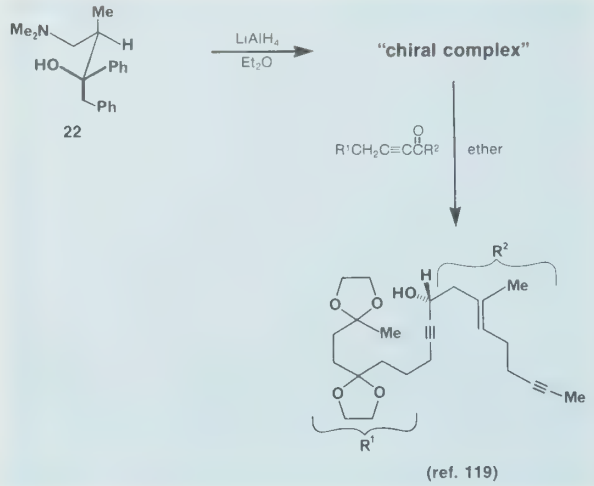
(+)-2-Amino-1-phenyl-1,3-propanediol: preparation of (-)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline [see Section IIC].

B. Alcohols

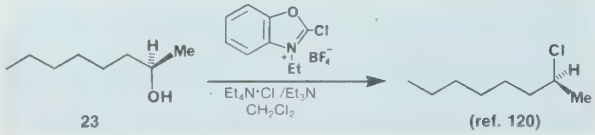
(-)-2,2′-Dihydroxy-1,1′-binaphthyl (**21**):



(+)-4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol (**22**):



(-)-2-Octanol (**23**):



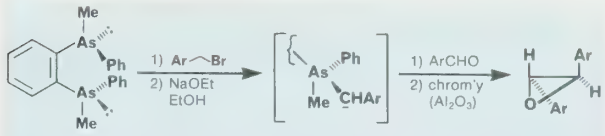
(*S*)-(+)-3-Hydroxy-2-methylpropanoic acid: synthesis of the ionophore antibiotic calcimycin,[121] (*R*)- and (*S*)-muscone,[122] and α-tocopherol.[123]

(*S*)-(-)-2-Methyl-1-butanol: synthesis of *S*-enantiomers of several *Trogoderma* sex pheromone components.[124]

Chiral benzyl alcohols: preparation of optically active β-phenylpropionic acids.[125]

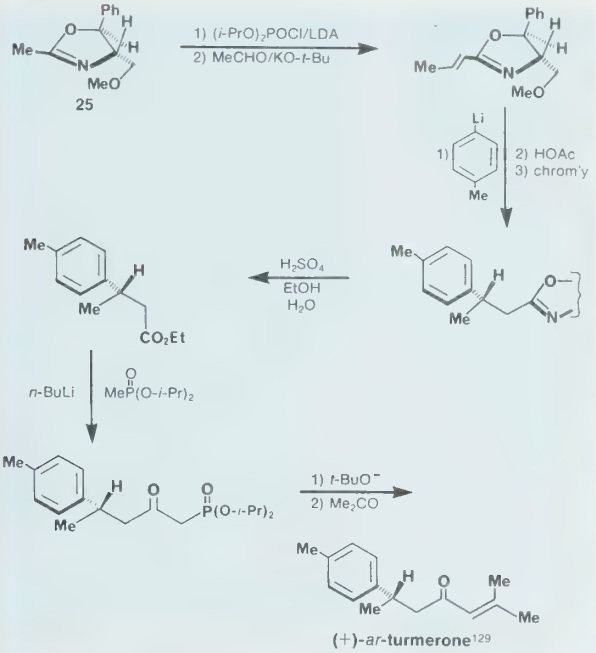
C. Miscellaneous

Arsonium ylides (**24**):



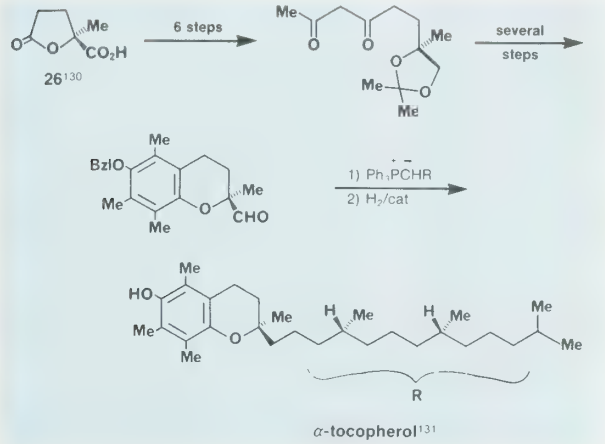
24 (ref. 126)

(-)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline (**25**):[127,128]



(+)-*ar*-turmerone[129]

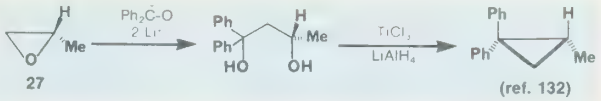
(-)-2-Methyl-5-oxotetrahydro-2-furoic acid (**26**):



α-tocopherol[131]

Also: synthesis of (*S*)-(-)-frontalin, an aggregation pheromone component.[130]

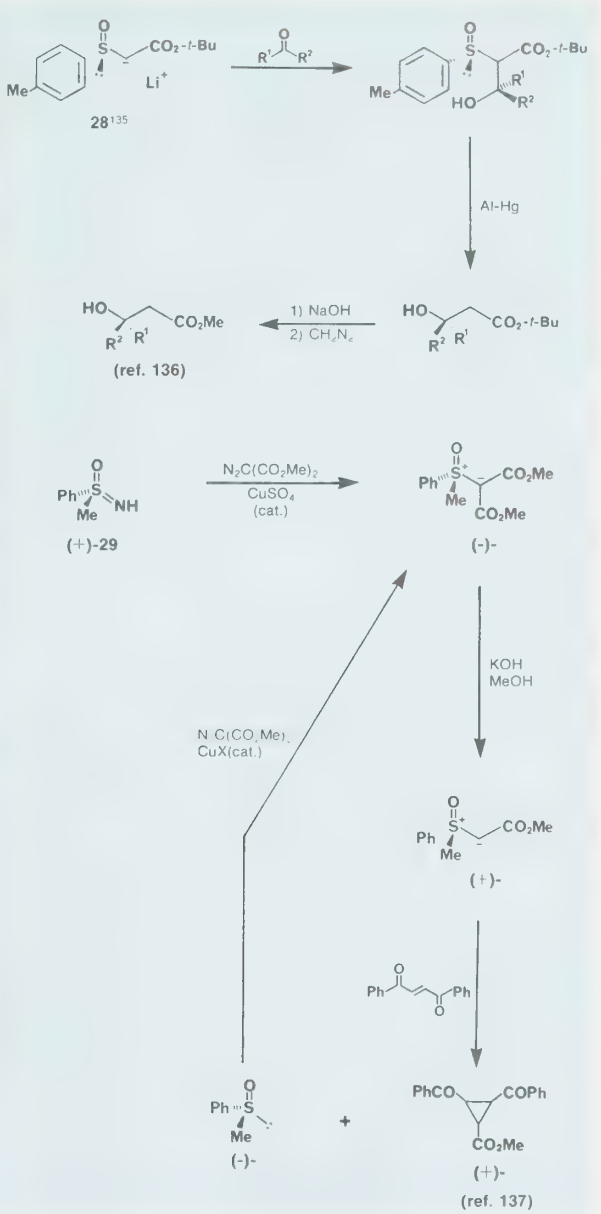
(-)-Propylene oxide (**27**):



27 (ref. 132)

(+)-Propylene oxide: synthesis of (*R*)-(+)-recifeiolide, a fungal macrolide.[133]

Sulfur reagents (**28,29**):[134]



References and Notes:

1) See, for example, the following general reviews and discussions on asymmetric synthesis: (*a*) T.D. Inch, *Synthesis*, 466 (1970); (*b*) J. D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1971; (*c*) J.W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974); (*d*) A. Fischli, *Nachr. Chem., Tech. Lab.*, **25**, 390 (1977); *Chem. Abstr.*, **87**, 151153z (1977); (*e*) Y. Izumi and A. Tai, "Stereo-Differentiating Reactions," Kodansha Ltd., Tokyo, Japan, 1977, and Academic Press, Inc., New York, N.Y.; (*f*) H.B. Kagan and J.C. Fiaud in "Topics in Stereochemistry," Vol. 10, E.L.Eliel and N.L. Allinger, Eds., John Wiley and Sons, Inc., 1978, pp 175-285; (*g*) T. Mukaiyama and T. Sato, *Kagaku (Kyoto)*, **33**, 324 (1978); *Chem. Abstr.*, **90**, 21696e (1979); and (*h*) D. Valentine, Jr., and J.W. Scott, *Synthesis*, 329 (1978). Discussions on the uses of specific classes of chiral compounds are cited at the appropriate sections of this survey

2) Unfortunately these restrictions preclude coverage of the very interesting and useful synthetic applications of, for example, chiral solvents, catalysts, polymers, supporting electrolytes, sensitizers, agents for optical resolution and spectroscopic assay, and physical forces

3) Structures represented in three-dimension indicate absolute stereochemistry

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5) T. Mukaiyama, T. Takeda, and K. Fujimoto, *Bull. Chem. Soc. Jpn.*, **51**, 3368 (1978).
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11) M. Larcheveque, E. Ignatova, and T. Cuvigny, *J. Organomet. Chem.*, **177**, 5 (1979)
12) For a review on the synthesis of chiral components of insect pheromones, see R. Rossi, *Synthesis*, 413 (1978).
13) This and other uses of chiral reducing agents derived from alkaloids are discussed, for example, in reference 1*b*, pp 204-210.
14) For a review on the uses of glutamic acid as a chiral pool for the synthesis of pheromones, see L.R. Smith and H.J. Williams, *J. Chem. Ed.*, **56**, 696 (1979)
15) U. Ravid and R.M. Silverstein, *Tetrahedron Lett.*, 423 (1977)
16) K. Mori, *Tetrahedron*, **31**, 3011 (1975)
17) Note that the enantiomer depicted is actually the minor of the two which comprise the aggregation pheromone *sulcatol*. The major antipode was prepared in the same fashion from D-glutamic acid (see reference 16)
18) K. Tomioka, T. Ishiguro, and K. Koga, *Chem. Commun.*, 652 (1979); K. Tomioka and K. Koga, *Tetrahedron Lett.*, 3315 (1979).
19) U. Schmidt and R. Schölm, *Synthesis*, 752 (1978); the absolute configurations of the products are drawn as presented in this reference
20) D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, **15**, 549 (1976); D. Enders and H Eichenauer, *Chem. Ber.*, **112**, 2933 (1979).
21) H. Eichenauer, E. Friedrich, W. Lutz, and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **17**, 206 (1978)
22) D. Enders and H. Eichenauer, *Tetrahedron Lett.*, 191 (1977); for the recent application of this method to the synthesis of the alarm pheromone (*S*)-(+)-4-methyl-3-heptanone, see D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, **18**, 397 (1979).
23) T. Mukaiyama, M. Asami, J. Hanna, and S. Kobayashi, *Chem. Lett.*, 783 (1977)
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35) S.M. Hecht, K.M. Rupprecht, and P.M. Jacobs, *J. Am. Chem. Soc.*, **101**, 3982 (1979)
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37) E.J. Corey, M. Shibasaki, and J. Knolle, *Tetrahedron Lett.*, 1625 (1977)
38) For another (earlier) synthesis of thromboxane B_2 from D-glucose, see S. Hanessian and P. Lavallee, *Can. J. Chem.*, **55**, 562 (1977)
39) S. Hanessian and R. Roy, *J. Am. Chem. Soc.*, **101**, 5839 (1979).
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46) See, for example, S. Hanessian, G. Rancourt, and Y. Guindon, *ibid.*, **56**, 1843 (1978), and references cited therein.
47) F.W. Lichtenthaler, S. Nishiyama, and P. Jarglis, *Angew. Chem., Int. Ed. Engl.*, **18**, 936 (1979).
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51) J.J. Baldwin, A.W. Raab, K. Mensler, B.H. Arison, and D.E. McClure, *J. Org. Chem.*, **43**, 4876 (1978).
52) The enantiomer (*S*)-(+)-epichlorohydrin is also available from **10** (in 3 steps); see reference 51.
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19,341-0 (-)-3-Pinanecarboxylic acid

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11,208-9 (-)-β-Pinene

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11,556-8 (-)-α-Methylbenzylamine (α-phenylethylamine)

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Recent Developments in the Chemistry of Natural Products[1]

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For the past ten years we have been studying the total synthesis of various natural products. We have emphasized particularly polyfunctional, complex, rather unstable natural products such as tetrodotoxin,[2] sporidesmins,[3] gliotoxin,[4] saxitoxin,[5] and mitomycins.[6] However, about five years ago we decided to add a new topic to our research program; namely, the study of acyclic chemistry. More specifically, we were interested in synthesizing polyketide-derived natural products from acyclic precursors. There are various polyketide-derived natural products which await the synthetic chemist's quest; for example, macrolide antibiotics, ansamycin antibiotics, polyether antibiotics, and so on. We decided to consider polyether antibiotics[7] as our primary synthetic target for the following reasons. First, at the time this project was started, we had never heard of any synthetic studies on polyether antibiotics. Second, polyether antibiotics present a formidable challenge to the synthetic chemist. Four representative polyether antibiotics are listed in Table 1.[7] There are 17 asymmetric centers present in monensin, for example, which means that in principle 131,072 stereoisomers exist for this antibiotic. In the case of lonomycin, the number of possible stereoisomers exceeds 8 million! The total number of isomers for these antibiotics will be infinite if constitutional isomers are counted. Thus, to achieve the total synthesis of one of these antibiotics, it is very important to have a high degree of stereo-, regio-, and chemoselectivity for each step of the synthesis. Third, polyether antibiotics present almost perfect cases for testing principles or synthetic methods for controlling stereo-, regio-, and chemoselectivity in acyclic systems.

In order to propose a sensible and workable scheme for a synthesis, we need to know the answers to three questions:

1) What might be the expected major product for each step of the proposed synthesis?
2) What might be the expected degree of stereo-, regio-, or chemoselectivity?
3) In cases where the selectivity is found not satisfactorily high, what might be the method to improve it?

Judging from experience gained over the past five years, we are now convinced that these three questions can be answered reasonably well even in acyclic systems, and hence syntheses using acyclic compounds can be executed in a stereo- and regiocontrolled manner effectively.

Going back to the synthesis of polyether antibiotics, we did not hesitate in choosing lasalocid A as our first target molecule. At the time this project was begun, we did not have enough confidence to propose the synthesis of complex molecules from a con-

Dr. Yoshito Kishi (left) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

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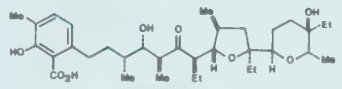
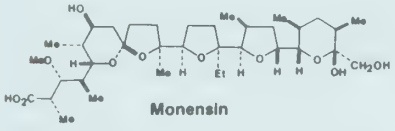
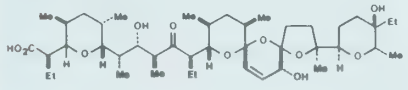
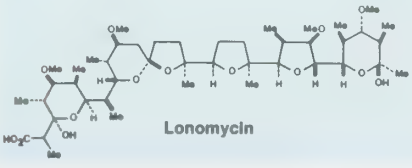
formationally flexible acyclic precursor. Therefore, we decided to start with a relatively simple molecule. Lasalocid A is one of the simplest polyether antibiotics in terms of the number of asymmetric centers — *only* 10 asymmetric centers exist — yet it has three important functional groups, β-hydroxy ketone, tetrahydrofuran, and tetrahydropyran, commonly found in other naturally occurring polyether antibiotics. Therefore, the synthesis of lasalocid A will be the cornerstone for the synthesis of polyether antibiotics in general. Fortunately the total synthesis of lasalocid A was successfully carried out:[8] the key intermediate isolasalocid ketone was synthesized by three different routes.[9] We were particularly pleased with the route starting with the vinyl ketone, shown in the lower half of Scheme 1. In this synthesis, the isolasalocid ketone was synthesized in 11 steps, including protecting and deprotecting steps, from the vinyl ketone in about 20% overall yield by using only acyclic precursors. The most remarkable aspect of this synthesis is that in terms of stereo-, regio- and chemoselectivity, even the worst step had a product ratio of 10:1.

Encouraged by the successful synthesis of lasalocid A, we then moved to monensin. Again, a very successful conclusion[10] certainly provided more confidence toward this type of approach in organic synthesis. More important, however, during studies for the synthesis of the left half of monensin, we felt able, at least to some extent, to answer the three questions raised previously.

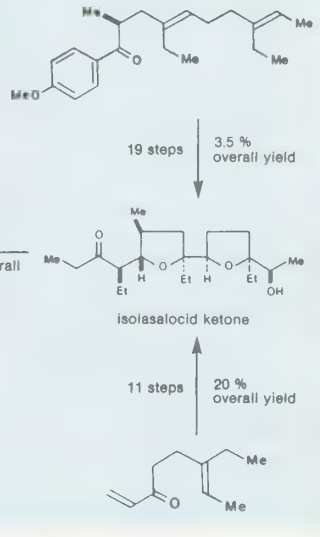
Based on Professor Heathcock's[11] and also our own[8] studies on crossed aldol reactions, we originally considered that the left half of monensin might be synthesized by two crossed aldol reactions as indicated in Scheme 2. Indeed, this was the way we had first synthesized the left half of the antibiotic. However, we were not satisfied since the stereoselectivity of the second crossed

Table 1

Polyether Antibiotics	Number of Asymmetric Centers	Number of Possible Stereoisomers
 Lasalocid A	10	1,024
 Monensin	17	131,072
 Narasin	19	524,288
 Lonomycin	23	8,388,608

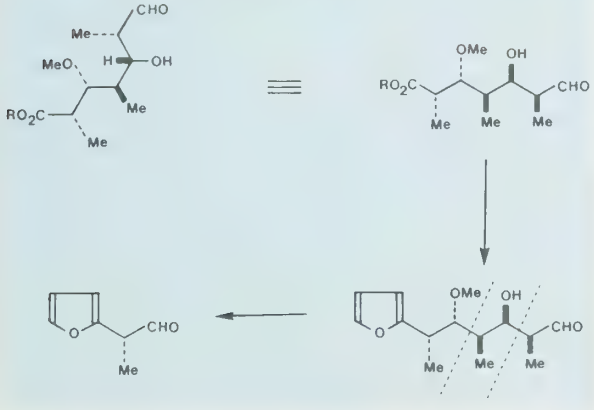
Scheme 1

T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978)

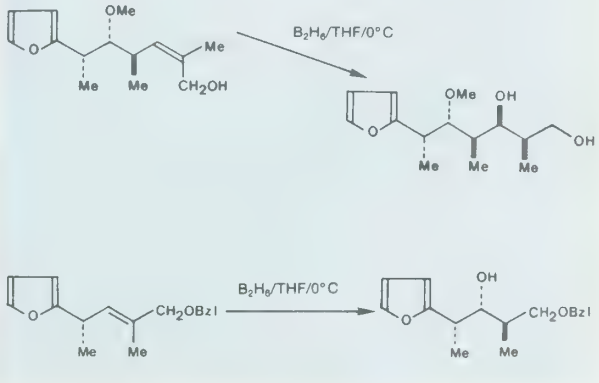


T. Nakata and Y. Kishi, *Tetrahedron Lett.*, 2745 (1978)

Scheme 2

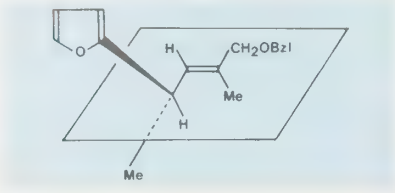


Scheme 3



aldol reaction was only a ratio of 1.8:1 at best. After numerous unsuccessful experiments, we finally discovered a satisfactory method. That was the hydroboration shown in Scheme 3, the stereoselectivity of which was a ratio of 8:1 and 12:1, respectively.

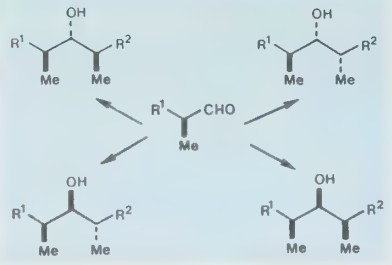
The origin of the remarkable stereoselectivity observed might be related to the conformational preference at the sp^3 and sp^2 centers of the allylic alcohols. According to the pioneering investigations by Wilson,[12] Herschbach,[13] Bothner-By,[14] and others, the preferred conformation of this type of compound is assumed to be eclipsed. Among the three possible eclipsed conformations, the one shown below is assumed most preferred because of the least steric



crowding. Hydroboration is expected to take place from the less hindered side to yield the observed product. The observed phenomena are similar, in a very broad sense, to examples where Cram's rule is applied. Indeed, based on a consideration of the preferred conformation of the carbonyl compounds, some efforts toward the rationalization of Cram's rule have been made by Karabatsos.[15] However, the situation with carbonyl compounds is complicated by the fact that the stability difference among the three eclipsed conformations is relatively small and also that the carbonyl groups are strongly polarized. On the other hand, the situation of the olefinic compounds is simpler, and hence a straightforward analysis based on this picture is possible. We would like to demonstrate the usefulness of this concept with the following example.

The partial structural unit, R^1-CH(Me)CH(OH)CH(Me)-R^2, is often found in important natural products. The three asymmetric centers of this unit give rise to four possible diastereomers[16] as shown in Scheme 4, all of which are known to be partial structures of polyether, ansamycin, or macrolide antibiotics. We have been interested in developing stereo- and regioselective methods for synthesizing these four structural units from the indicated aldehyde, which is readily available in optically active and racemic forms. Through the studies of the monensin synthesis, it has already been shown that the two diastereomers shown in the lower half of Scheme 4 can be synthesized by hydroboration or crossed aldol reactions.

Scheme 4



A proposal for controlling the stereochemistry of the two remaining diastereomers is shown in Scheme 5. Considering the preferred, eclipsed conformation discussed previously, it might be possible to invert the stereochemical outcome of hydroboration by using a polar functional group on group R^1. Thus, the diastereomer shown on the upper left of Scheme 4 would be produced. By changing the stereochemistry of the olefinic bond of the starting material, the diastereomer shown on the upper right of Scheme 4 should be formed. To this end, it should be mentioned that a highly stereoselective synthesis of *cis*-allylic alcohols necessary for these studies, from the indicated aldehydes, has been developed in our laboratories.[10]

In order to examine the aforementioned possibility, we synthesized *trans*- and *cis*-allylic alcohols with R^1=CH_2OH, CH_2OMe, CH_2SMe, or CH_2NMe_2 and studied the stereochemical outcome of hydroboration, using borane complex with tetrahydrofuran, dimethylamine or dimethyl sulfide in various solvents. We uniformly observed that the major product is the one belonging to the diastereomer shown on the lower left of Scheme 4. Under these circumstances, we decided to study the epoxidation reaction, the results of which are summarized in Table 2.[17] The high stereoselectivity observed for the two

Scheme 5

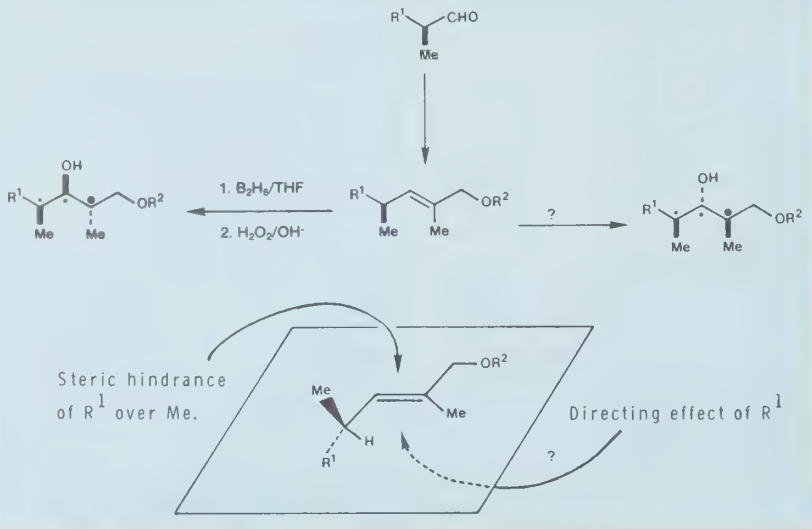
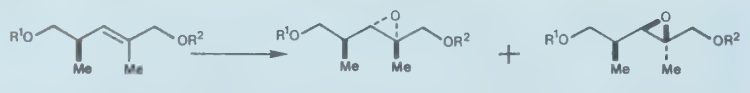
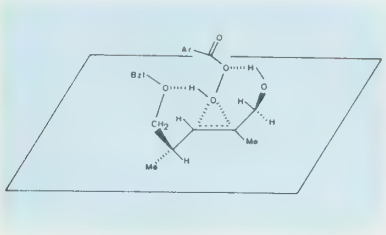


Table 2



R^1	R^2	Ratio (A : B) MCPBA/CH_2Cl_2/0°C	Ratio (A : B) t-BuO_2H/$VO(acac)_2$/C_6H_6/RT
H	H	> 25 : 1	> 25 : 1
H	$C_6H_5CH_2$	6 : 1	> 25 : 1
$C_6H_5CH_2$	H	> 25 : 1	4 : 3
$C_6H_5CH_2$	$C_6H_5CH_2$	1 : 1 (RT)	too slow to measure

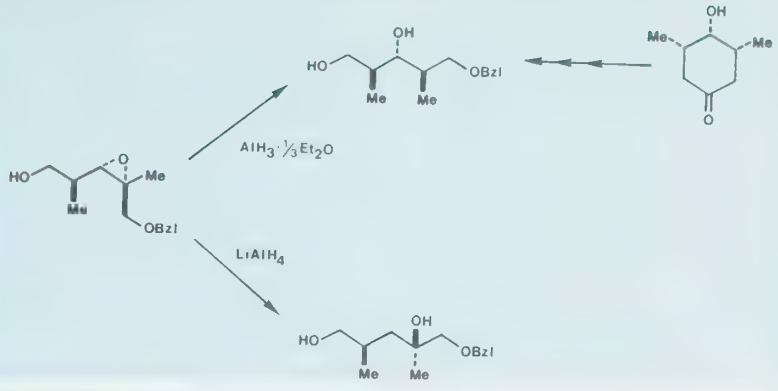
compounds listed on the top two lines is well explained by applying the directing effects recognized by Henbest[17] and Sharpless[18] to the aforementioned preferred, eclipsed conformation of the substrates (*cf.* Scheme 5). The high stereoselectivity observed for the compound listed on the third line, under the conditions indicated by an arrow, was explained by a cooperative effect depicted below. Very similar results were observed for the



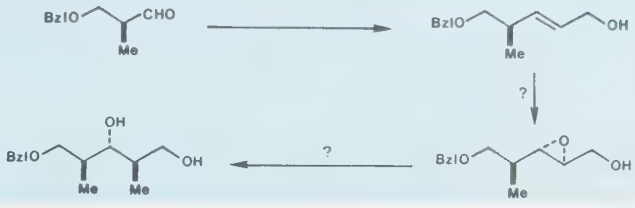
cis-allylic alcohol as well. The stereochemistry assignment of the epoxides was made mainly by chemical methods. For example, the stereochemistry of the major epoxide derived from the *cis*-allylic alcohol was determined by chemical correlation with the cyclohexanone derivative as shown in Scheme 6. Although the aluminum hydride reduction of the epoxide gave the alcohol corresponding to the upper left diastereomer in Scheme 4 as the major product, this procedure was not satisfactory in terms of regio- and stereoselectivity. To overcome this problem, we considered the possibility depicted in Scheme 7. Namely, we hoped that the ring-opening reaction of the epoxide might take place more regio- and stereoselectively. As expected, we could realize a complete regio- and stereospecific ring-opening reaction of the epoxide with lithium dimethylcuprate. The major reason for the observed regiospecificity seems due to the steric hindrance toward the incoming reagent, since the ring-opening reaction of the epoxide shown in the lower half of Scheme 8 gave a mixture of two possible products.

Let us now turn our attention to the stereoselectivity of the epoxidation reaction of the nor- series. The degree of the stereoselectivity of the nor-allylic alcohol shown in Scheme 9 was very low compared with the example discussed before, which is shown again in the lower half of Scheme 9 for comparison purposes. At first glance, the results were very surprising, but we soon realized that they could be explained in terms of the stability difference among the three eclipsed conformations shown in Scheme 10. In the case of R=Me, the conformation **A** is expected to be the most preferred by far, because of considerable steric compression due to the R and methyl

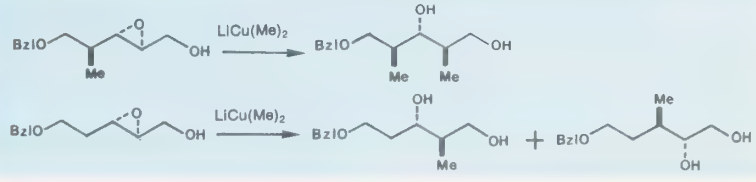
Scheme 6



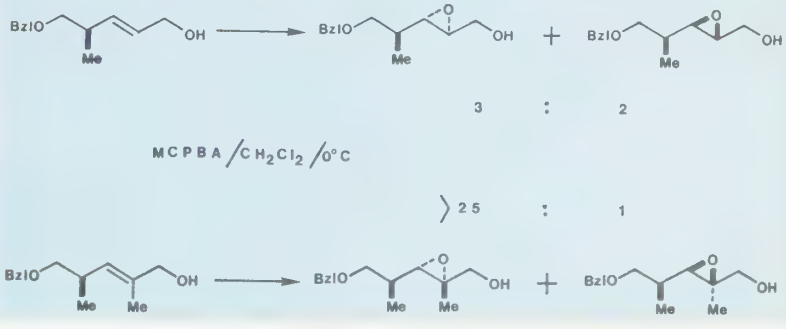
Scheme 7



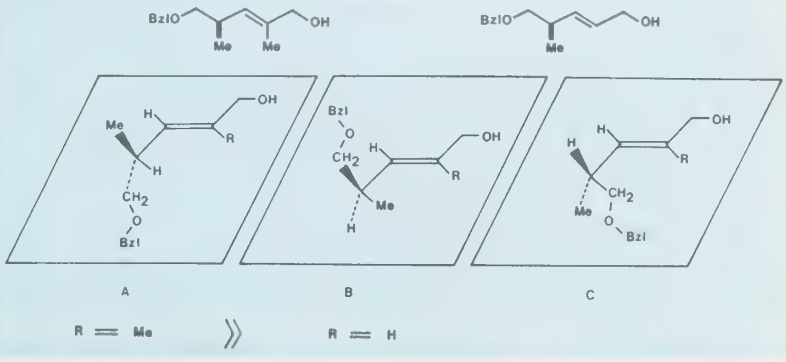
Scheme 8



Scheme 9



Scheme 10



or benzyloxymethyl groups in the conformations **B** or **C**. On the other hand, in the case of R=H, the steric compression due to the R and methyl or benzyloxymethyl groups will be small, hence the stability difference among the three conformations will be small. This could be reflected in the poor stereoselectivity.

Given the explanation above, there are two very obvious methods to be considered to improve this poor stereoselectivity. One is the epoxidation reaction of the nor-*cis*-allylic alcohol shown in Scheme 11. As expected, the alcohol gave a single epoxide, based on NMR analysis of the crude product. In Scheme 12, a complete regio- and stereospecific transformation of the epoxide to the upper right and left diastereomers in Scheme 4, respectively, is summarized.[19]

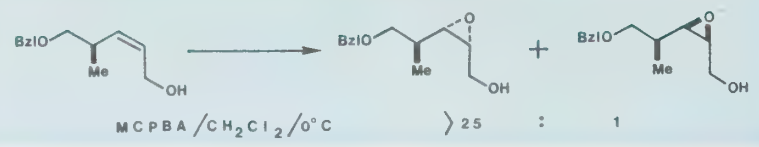
The second possible method to improve the poor stereoselectivity is depicted in Scheme 13. In this scheme, the substituted X, desirably bulky, will make one eclipsed conformation preferred over the other two, hence we can expect a highly stereoselective epoxidation. After epoxidation, the C-X bond should be replaced by the C-H bond with retention of its stereochemistry. A current literature search made the choice of X=$SiMe_3$ seem obvious. To test this possibility, the allylic alcohol with the trimethylsilyl group was stereospecifically synthesized (see Scheme 14). As expected, epoxidation did take place cleanly, and then the carbon-silicon bond was replaced by the carbon-hydrogen bond on treatment with fluoride anion. The overall stereospecificity was excellent; no signals due to other diastereomers were detected in the NMR spectra of the crude product.[20] Thus, it was now possible to synthesize the four diastereomers shown in Scheme 4 in a stereo- and regiocontrolled manner.

Now let us examine the application of the methods we have just discussed.

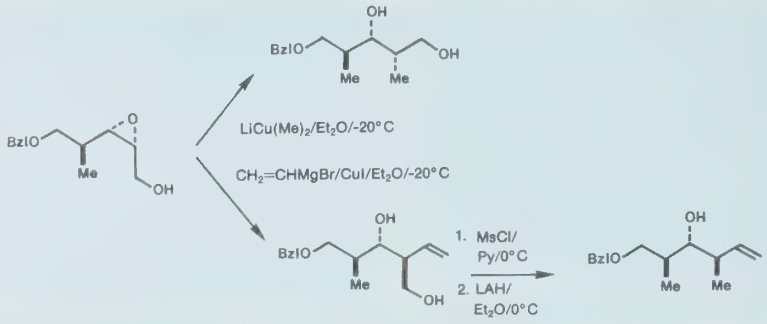
One specific example we would like to discuss briefly is the total synthesis of the polyether antibiotic narasin.[7] In narasin, there are 19 asymmetric centers in addition to one *cis*-olefinic bond. This means that control of more than 1 million stereoisomers is necessary, in principle, to synthesize the antibiotic from acyclic precursors. The first step of our retrosynthesis was the crossed aldol reaction shown in Scheme 16. The feasibility of this type of crossed aldol reaction was well demonstrated in our lasalocid A and monensin syntheses.

The retrosynthesis of the right half from its open form is shown in Scheme 17. Stereocontrolled intramolecular ketaliza-

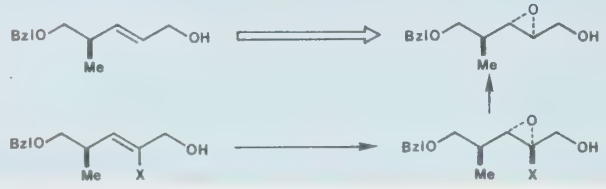
Scheme 11



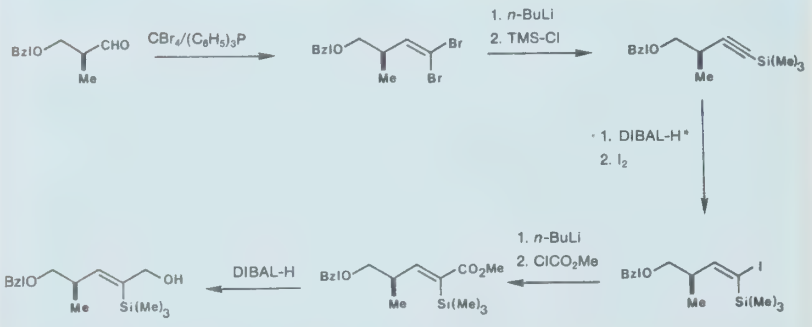
Scheme 12



Scheme 13

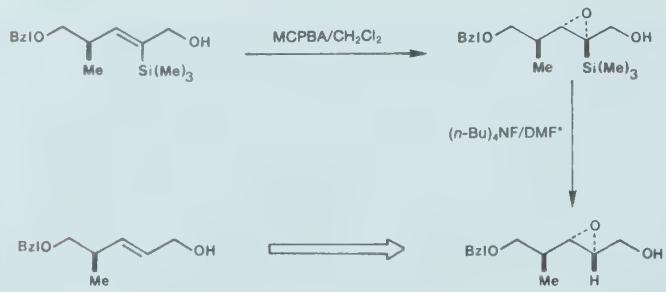


Scheme 14



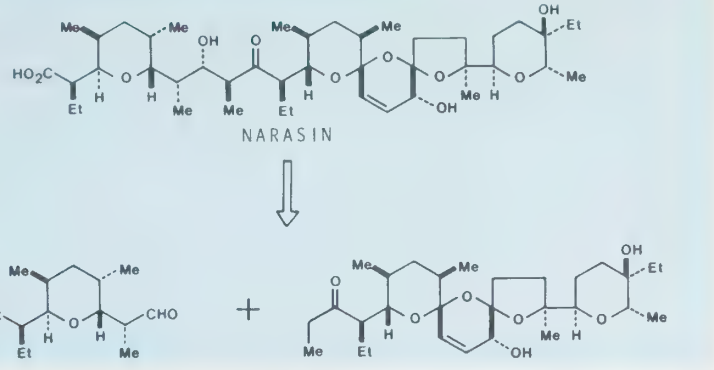
* *cf.* K. Uchida, K. Utimoto, and H. Nozaki, *J. Org. Chem.*, **41**, 2215 (1976)

Scheme 15

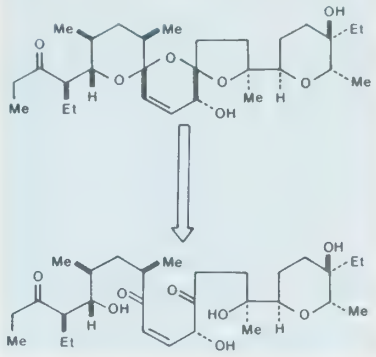


* *cf.* T. H. Chan, P. W. K. Lau, and M. P. Li, *Tetrahedron Lett.*, 2667 (1976)

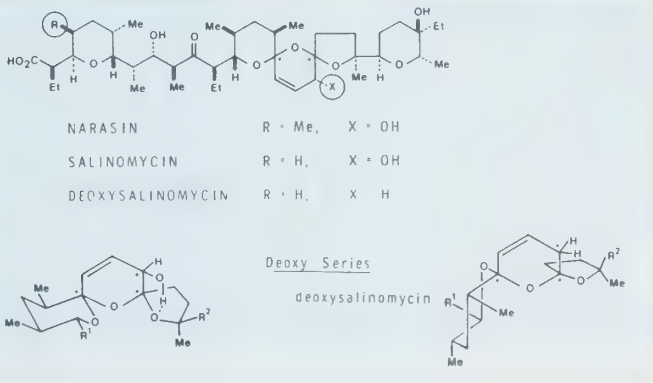
Scheme 16



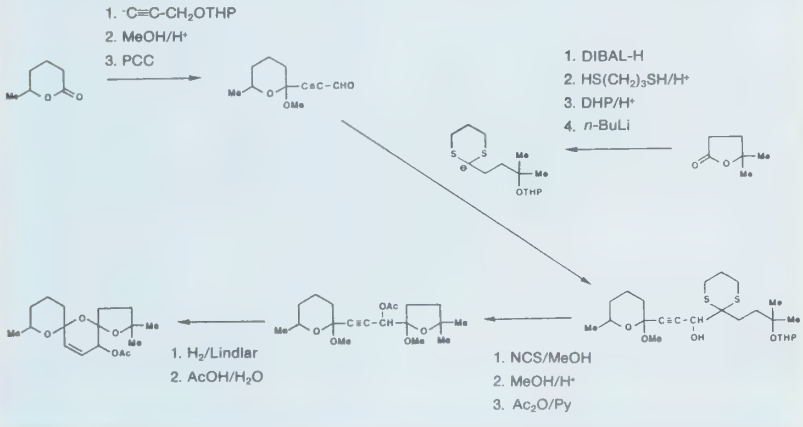
Scheme 17



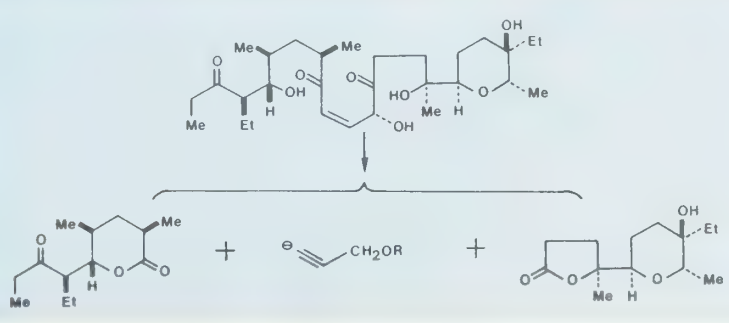
tion under thermodynamically controlled conditions, somewhat similar to the proposed retrosynthesis, was one of the key steps of our monensin synthesis. However, the present case is more complicated than the monensin case, since the relative stability of the desired and undesired stereoisomers with respect to two spiro ketal centers is obscure. In relation to this problem, it is important to mention the relative stereochemistry at the two spiro ketal centers of narasin, salinomycin, and deoxysalinomycin; namely, it is known that narasin and salinomycin have the same relative stereochemistry, while that of deoxysalinomycin is different. The dipole-dipole interaction of the two carbon-oxygen bonds in the narasin and salinomycin series seems to be thermodynamically unfavorable. Nonetheless, a review of the extraction procedure of these antibiotics makes it hard to believe that narasin or salinomycin would have thermodynamically unfavorable relative stereochemistry. We believed that the indicated hydrogen bond stabilization would override a seemingly unfavorable dipole-dipole interaction at the bisspiro center of the narasin and salinomycin series. Indeed, we could recently demonstrate that this was the case. Analysis of the stereoview of the bisspiro center of narasin clearly indicated the possibility that the allylic alcohol group could stereoselectively be introduced by kinetically controlled reduction of the corresponding α,β-unsaturated ketone.



Scheme 18



Scheme 19



Regarding the possible synthetic route of the open form and its cyclization to the bisspiro ketal, an efficient method shown in Scheme 18 was developed by using the model system.[21] It is important to protect the allylic alcoholic group to avoid the aromatization to a furan.

Supported by successful results in the model system, the open form of the right half can now be disconnected into three segments as seen in Scheme 19. The lactone of the right side is structurally very similar

to lasalocid A ketone, which has already been synthesized in our laboratory (see Scheme 20).[8] Indeed, the synthesis of this lactone was straightforward.

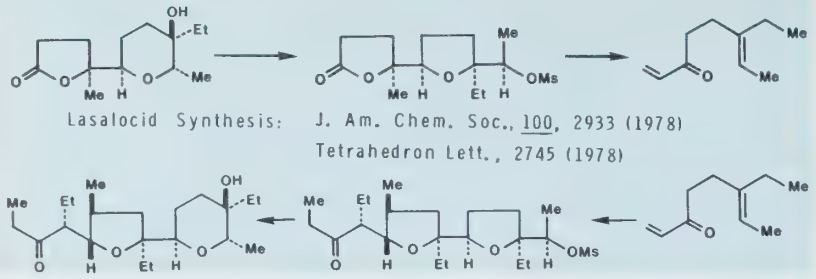
It seemed that the tetrahydropyran ring of the left half of narasin might be constructed from the properly functionalized 1,5-diol system as depicted in Scheme 21. There are two options available for this disconnection, but we chose the one shown at the left. The reason for this decision should be obvious when one recognizes the structural similarity between the left and middle segments; these segments share the same five carbon atoms indicated by asterisks in the following structures.

Relying on the methods discussed previously, a straightforward retrosynthesis of these segments can be envisioned. In the upper half of Scheme 22, a retrosynthesis of the left segment is summarized. The first disconnection utilized the hydroboration method. To continue the disconnection along this line, a hydroxyl group must be put temporarily at the methylene carbon. In the actual synthesis, this type of hydroxyl group used as a handle can smoothly be removed by mesylation, followed by hydride reduction, in excellent overall yield. There are two options available for this purpose, but we chose the diastereomer shown in the right hand corner of the second line for the following reason. The stereoselectivity of method B — epoxidation followed by cuprate reaction — is extremely high, while the stereoselectivity of method A — hydroboration — is a range of 12~4:1, depending on substrates. In the lower half of Scheme 22, a retrosynthesis of the middle segment — note the structural similarity between the middle segment Prelog-Djerassi lactonic acid — is summarized, which is nearly identical to the one shown for the left segment.

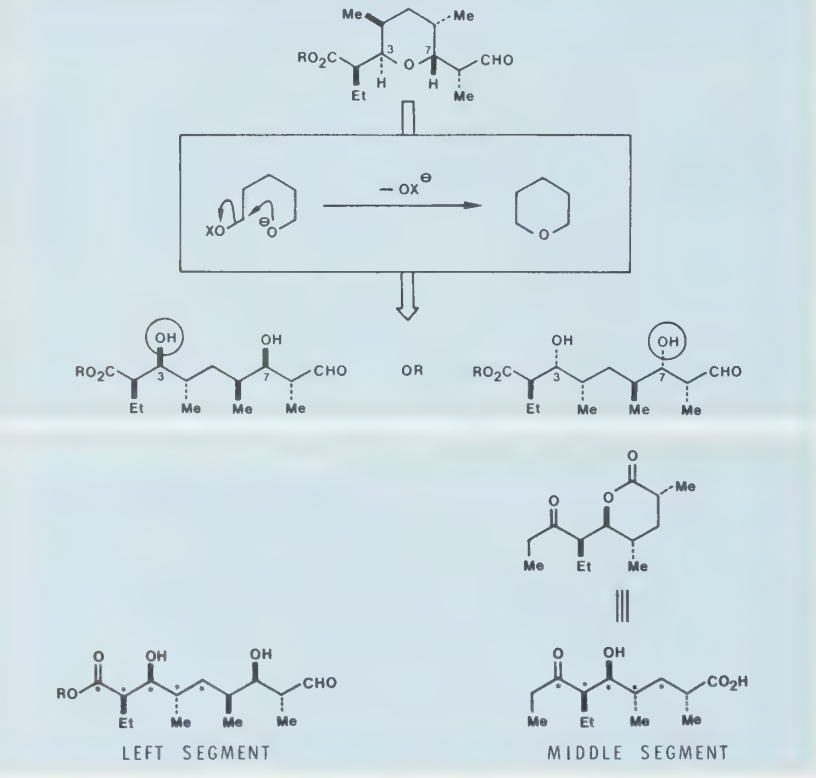
Following the proposed schemes, we have recently completed a stereocontrolled total synthesis of narasin,[22] although improvements on some steps are still needed. For example, at the present moment, the cyclization reaction to construct the tetrahydropyran ring is not satisfactorily effective enough, but we are very optimistic about improving this step.

In closing, I would like to take this opportunity to express my sincere appreciation to all of my former and present group members. Needless to say, it would be impossible to carry out any single synthesis to its successful completion without their commitment, enthusiasm, and devotion to chemistry. Financial support from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 7806296) is gratefully acknowledged.

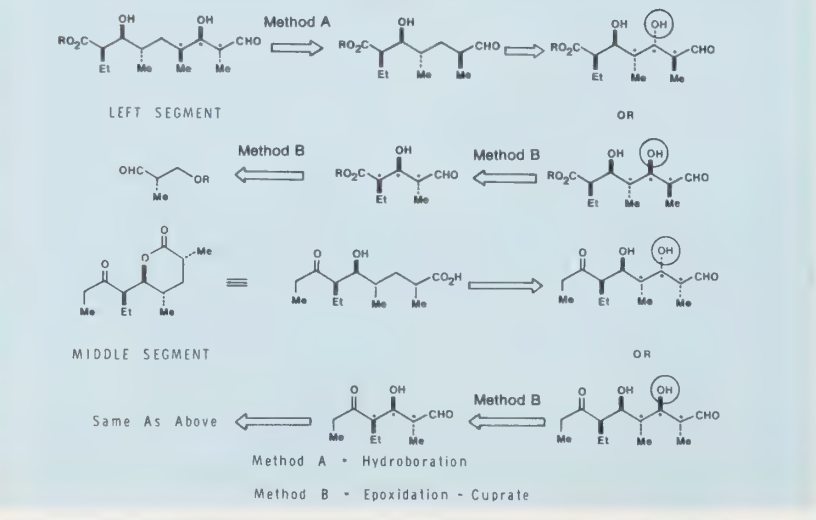
Scheme 20



Scheme 21



Scheme 22



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1) This work was presented as the Award Address for the ACS Award for Creative Work in Synthetic Organic Chemistry at the 179th ACS National Meeting in Houston on March 25, 1980.
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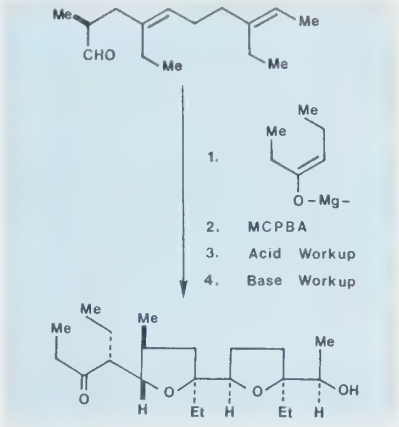
9) At the early stage of the lasalocid study, we examined the following sequence of reactions to the isolasalocid ketone. Not surprisingly, the sequence was completely nonstereoselective, but the isolasalocid ketone was isolated in about 1.5% overall yield by preparative layer chromatography; unpublished results, B. Vranesic and Y. Kishi.



10) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979); T. Fukuyama, C.-L.J. Wang, and Y. Kishi, *ibid.*, **101**, 260 (1979); T. Fukuyama, K. Akasaka, D.S. Karanewsky, C.-L.J. Wang, G. Schmid, and Y. Kishi, *ibid.*, **101**, 262 (1979); Y. Kishi, *Lectures in Heterocyclic Chemistry, Vol. 5*, HeteroCorporation, Provo, Utah, 1980.
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20) This work was done by Dr. I. Hasan.
21) This work was done by Dr. R.W. Freerksen
22) The total synthesis of narasin was achieved by Dr S. Hatakeyama and Mr. M.D. Lewis.

About the Author

Yoshito Kishi was born on April 13, 1937, in Nagoya, Japan. He received the B.S. degree from Nagoya University in 1961, and the Ph.D. degree (Professors Yoshimasa Hirata and Toshio Goto) from the same institution in March 1966. During the period from 1966 through 1969 when he was an Instructor in the Department of Chemistry at Nagoya University, he took a leave of absence to conduct research at Harvard University as a Postdoctoral Fellow with Professor Robert B. Woodward (1966-1968). Upon returning to Nagoya, he was promoted to the position of Associate Professor in the Department of Agricultural Chemistry which he held from 1969 through 1974. Since July 1974, he has been a Professor of Chemistry at Harvard University.

Dr. Kishi has achieved the total synthesis of numerous complex natural products including *Cypridina* luciferin, *Latia* luciferin, echinulin and neoechinulin, tetrodotoxin, sporidesmins, gliotoxins, penam and cephem, octahydrohistrionicotoxin, saxitoxin, mitomycins, lasalocid A, monensin, austamide, gephyrotoxin, narasin and rifamycin S.

His awards include the 1967 Award of the Chemical Society of Japan, the 1972 Asahi Press Award, the 1973 Chunichi Press Award, and the 1980 ACS Award for Creative Work in Synthetic Organic Chemistry. Dr. Kishi has been invited to deliver plenary lectures in his field at numerous U.S. and international conferences. He is a member of the American Chemical Society, the Chemical Society of Japan, The Chemical Society (London) and the Swiss Chemical Society. He has been awarded a Guggenheim Fellowship for 1980.

Aldrich offers these compounds cited by Dr. Kishi.

18,023-8	Borane-dimethylamine complex
17,982-5	Borane-methyl sulfide complex
19,211-2	Borane-methyl sulfide complex, 2*M* in ether
19,212-0	Borane-methyl sulfide complex, 2*M* in THF
19,303-8	Borane-methyl sulfide complex, 1*M* in methylene chloride
19,482-4	Borane-methyl sulfide complex, 2*M* in toluene
17,619-2	Borane-THF complex, 1*M* in THF
21,312-8	*tert*-Butyl hydroperoxide, 90%
18,471-3	*tert*-Butyl hydroperoxide, 70%
18,617-1	*n*-Butyllithium, 1.6*M* in hexane
C1108-1	Carbon tetrabromide
C6270-0	*m*-Chloroperoxybenzoic acid, tech
10,968-1	*N*-Chlorosuccinimide, 98+%
C7285-4	Chlorotrimethylsilane, 98%
20,554-4	Copper(I) iodide, 98%
21,555-0	Copper(I) iodide, 99.99+%
21,494-9	DIBAL-H, 1*M* in cyclohexane
21,495-7	DIBAL-H, 1*M* in diethyl ether
21,496-5	DIBAL-H, 1*M* in heptane
19,030-6	DIBAL-H. 1*M* in hexane
21,497-3	DIBAL-H, 1*M* in methylene chloride
21,498-1	DIBAL-H, 1*M* in THF
21,500-7	DIBAL-H, 1*M* in toluene
19,272-4	DIBAL-H, 25 wt. % solution in toluene
D10,620-8	Dihydropyran
21,676-3	Hydrogen peroxide, 30%
20,777-2	Iodine, resublimed
21,111-7	Lasalocid, sodium salt
19,987-7	Lithium aluminum hydride
21,279-2	Lithium aluminum hydride, 1*M* in diethyl ether
21,277-6	Lithium aluminum hydride, 1*M* in THF
M880-0	Methanesulfonyl chloride
M3530-4	Methyl chloroformate
P5060-9	1,3-Propanedithiol
19,014-4	Pyridinium chlorochromate
21,614-3	Tetrabutylammonium fluoride, 1*M* in THF
T8440-9	Triphenylphosphine
21,287-3	Vanadyl acetylacetonate
22,558-4	Vinylmagnesium bromide, 1*M* in THF

Organosilicon Reagents for Carbon-Carbon Bond-Forming Reactions

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The development of new synthetic methods for use in organic synthesis is one of the areas of organic chemistry that has experienced a major renaissance during the past fifteen years or so. More recently there has been an extremely large number of publications describing the use of organosilicon chemistry in synthesis. Nearly every journal that synthetic organic chemists read contains papers devoted to the use of silicon-based chemistry for the construction of organic molecules. Since the carbon-carbon bond is a focal point of organic synthesis it is important to have many and varied ways to construct this bond in a predictable fashion. The intention of this article is to describe how certain organosilicon-based reagents, some of which are commercially available, can be used to make carbon-carbon bonds in a controlled and predictable way that is useful to the practicing synthetic organic chemist.

α-SILYL CARBANIONS

The first reported α-metallosilane was prepared by Whitmore and Sommer in 1946.[1] Treatment of α-chloromethyltrimethylsilane (**1**) with magnesium in ether gave the stable Grignard reagent **2** (eq. 1). Surprisingly, the reagent did not

$$\underset{\mathbf{1}}{Me_3SiCH_2Cl} \xrightarrow{Mg} \underset{\mathbf{2}}{Me_3SiCH_2MgCl} \qquad \text{(eq. 1)}$$

reappear until 1968 when Peterson developed an alkene synthesis based on this Grignard reagent.[2] Treatment of aldehydes or ketones with **2** gave, after mild hydrolysis, the β-hydroxysilanes **3** (eq. 2). Frequently, when R^1 and R^2 are alkyl

$$\underset{\mathbf{3}}{R^1R^2C(OH)CH_2SiMe_3} \xrightarrow[\text{or base}]{H_3O^+} R^1R^2C{=}CH_2 \qquad \text{(eq. 2)}$$

groups or part of a carbocyclic ring the adducts **3** are not stable, and eliminate trimethylsilanol to give an alkene. When the adducts **3** are isolable they may be converted into an alkene under either acidic or basic conditions. When the elimination of trimethylsilanol is conducted with sodium or potassium hydride in tetrahydrofuran the process is a *syn*-elimination. Treatment of the adducts **3** with acid (5% H_2SO_4 or HCO_2H) results in an *anti*-elimination, leading to an alkene of opposite geometrical configuration.[3]

Tetramethylsilane can be deprotonated using *n*-butyllithium in tetrahydrofuran containing tetramethylethylenediamine (eq. 3) to give the α-lithiomethyltrimethyl-

$$Me_4Si \xrightarrow[\text{TMEDA}]{n\text{-BuLi}} \underset{\mathbf{4}}{Me_3SiCH_2Li} \xrightarrow{ClSiMe_3} \underset{\mathbf{5}}{Me_3SiCH_2SiMe_3} \qquad \text{(eq. 3)}$$

silane (**4**), as evidenced by treatment with chlorotrimethylsilane to give bis(trimethylsilyl)methane (**5**).[4] This type of hydrogen-metal exchange is by far the

Back row — left to right: D. Quagliato, J. Venit, G. Roy, J. Schwindeman, T. Sarkar
Front row: S. Djuric, P. Magnus, D. Gange

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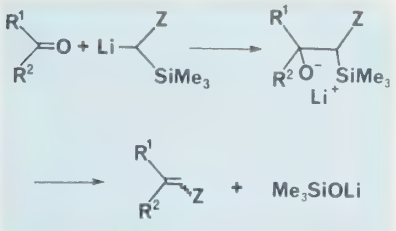
most convenient way of preparing α-metallosilanes, since α-halosilanes are not so readily available. Table I lists a number of α-metallosilanes that have usually been prepared by hydrogen-metal exchange.

Other anions that are made by halogen-metal exchange or *trans*-metallation include $(Me_3SiCCl{=}CHCH_2)Li$,[32] Me_3SiCCl_2Li, $(Me_3Si)_2CClLi$, Me_3SiCBr_2Li and $Me_3SiCHBrLi$.[33]

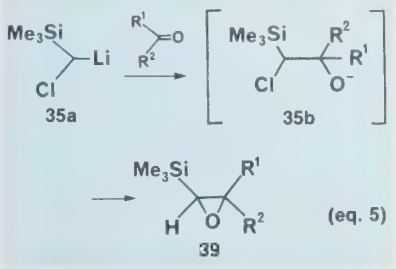
The reagents **6-38** are largely used for the so-called Peterson olefination reaction, which may be classified, in its most general sense, as follows (eq. 4):



(eq. 4)

The wide variations in the nature of Z give this synthetic method its useful versatility. It should be noted that apart from the cases described below, the elements of trimethylsilanoxide are lost in a *syn*-elimination even when Z is an excellent leaving group, to give an olefin. As such, the main advantage of the Peterson reactions over the conventional Wittig reaction is their greater flexibility for the synthesis of heterosubstituted alkenes, and perhaps more importantly, the carbanions listed (particularly **29**, **35**, and **37**) are more nucleophilic than their phosphonate counterparts.

α-Chloromethyltrimethylsilane (**35**) is deprotonated by treatment with *s*-butyllithium in tetrahydrofuran at -78° C to give **35a**. It is essential to use *s*-butyllithium to obtain good yields of **35a**; *n*-BuLi, *t*-BuLi, alkoxides and amides give unsatisfactory results. Treatment of **35a** with aldehydes or ketones leads to α,β-epoxysilanes **39** *via* the intermediacy of the chlorohydrin (eq. 5). This is a surprising result since the intermediate chlorohydrin (**35b**), by analogy with the examples described above (Z=Cl), would have been expected to eliminate the



(eq. 5)

Table I

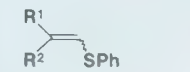
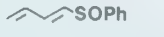
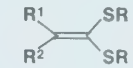
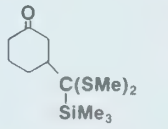
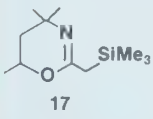
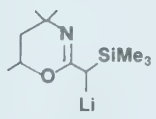
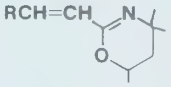
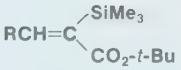
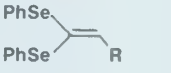
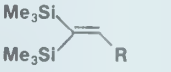
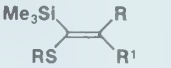
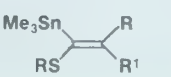
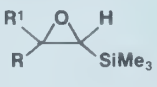
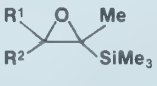
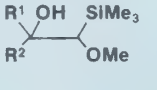
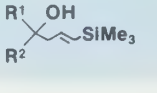
Substrate	Reagent	α-Lithiospecies	Electrophile	Product	Ref.
Me_3SiCH_2Ph **5**	*n*-BuLi/-HMPA	$Me_3SiCHPh$ | Li	PhCHO	PhCH=CHPh	5
$Me_3SiCH_2SiMe_3$ **7**	*t*-BuLi/-HMPA	$Me_3SiCHSiMe_3$ | Li	PhCHO	PhCH=CHSiMe$_3$	6
$Me_3SiCH(SiMe_3)_2$ **8**	*n*-BuLi	$Me_3SiC(SiMe_3)_2$ | Li	CH_2O	$CH_2=C(SiMe_3)_2$	6
$Me_3SiCH_2PPh_2$ **9**	*n*-BuLi	$Me_3SiCHPPh_2$ | Li	Ph_2CO	$Ph_2C=CHPPh_2$	7
$Me_3SiCH_2P(S)Ph_2$ **10**	*n*-BuLi	$Me_3SiCHP(S)Ph_2$ | Li	Ph_2CO	$Ph_2C=CHP(S)Ph_2$	7
Me_3SiCH_2SMe **11**	*n*-BuLi	$Me_3SiCHSMe$ | Li	Ph_2CO	$Ph_2C=CHSMe$	7
$Me_3SiCH_2P(O)(OEt)_2$ **12**	*n*-BuLi	$Me_3SiCHP(O)(OEt)_2$ | Li			8
Me_3SiCH_2SPh **13**	*n*-BuLi	$Me_3SiCHSPh$ | Li			8,9
Me_3SiCH_2SOPh **14**	*n*-BuLi	$Me_3SiCHSOPh$ | Li			10
$Me_3SiCH(SR)_2$ **15**	*n*-BuLi	$Me_3SiC(SR)_2$ | Li			11
$Me_3SiCH(SMe)_2$ **16**	*n*-BuLi	$Me_3SiC(SMe)_2$ | Li			12
 **17**	*n*-BuLi		RCHO		13
$(Me_3Si)_2CHCO_2$-*t*-Bu **18**	LDA	$(Me_3Si)_2CCO_2$-*t*-Bu | Li	RCHO		14
$PhSeCHSiMe_3$ | Ph **19**	$LiNEt_2$	Li | $PhSe{-}C{-}SiMe_3$ | Ph	MeI	Me | $PhSe{-}C{-}SiMe_3$ | Ph	15
$PhSeCH_2SiMe_3$ **20**	LDA	$PhSeCHSiMe_3$ | Li	RCH_2I	$PhSeCHSiMe_3$ | CH_2R	16
$(PhSe)_2CHSiMe_3$ **21**	LDA	$(PhSe)_2CSiMe_3$ | Li	RCHO		17
$(Me_3Si)_3CH$ **22**	MeLi	$(Me_3Si)_3CLi$	RCHO		17
$(Me_3Si)_2CHSR$ **23**	*n*-BuLi	$(Me_3Si)_2CSR$ | Li	$RCOR^1$		17
Me_3SiCH | SnMe$_3$ | SR **24**	LDA	$Me_3SiC{-}Li$ | SnMe$_3$ | SR	$RCOR^1$		17

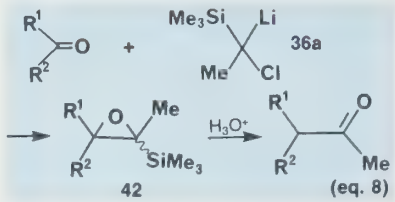
Table I (cont'd.)

Substrate	Reagent	α-Lithiospecies	Electrophile	Product	Ref.
$ArSO_2CH(OMe)SiMe_3$ **25**	*n*-BuLi	$ArSO_2C(OMe)(Li)SiMe_3$	$RCOR^1$	$ArSO_2C(OMe)=CRR^1$	18
$Me_3SiCH_2CH=NR$ **26**	LDA	$Me_3SiCH(Li)-CH=NR$	R^1CHO	$R^1CH=CH-CH=NR$	19
Me_3SiCH_2CN **27**	LDA	$Me_3SiCH(Li)CN$	RCHO	$RCH=CHCN$	20
$Me_3SiCH_2CO_2H$ **28**	LDA	$Me_3SiCH(Li)CO_2Li$	RCHO	$RCH=CHCO_2H$	21
$Me_3SiCH_2CO_2Et$ **29**	LDA	$Me_3SiCH(Li)CO_2Et$	RCHO	$RCH=CHCO_2Et$	22
Me_3SiCHN_2 **30**	*n*-BuLi	$Me_3SiC(Li)N_2$	RCHO	$RCH(O)CHSiMe_3$ or $RC\equiv CR$	23
$PhMe_2SiCH(Me)CN$ **31**	LDA	$PhMe_2SiC(Me)(Li)CN$	$R_2C=O$	$R_2C=C(CN)Me$	24
$(Me_3Si)_2CHBr$ **32**	*n*-BuLi	$(Me_3Si)_2CBr(Li)$	RCHO	$Me_3SiC(Br)=CHR$	25
$Me_3SiCH_2N(NO)$-*t*-Bu **33**	LDA	$Me_3SiCH(Li)N(NO)$-*t*-Bu	RCHO	*t*-BuN(NOH)=CHCR	26
Me_3Si-Cl **34**	*t*-BuLi	Me_2SiCH_2Li Cl	Me_3SiCl	$Me_3SiCH_2SiMe_2Cl$	27
Me_3SiCH_2Cl **35**	*s*-BuLi	$Me_3SiCH(Li)Cl$ **35a**	$RCOR^1$		28
$Me_3SiCH(Cl)$-Me **36**	*s*-BuLi	$Me_3SiC(Li)(Cl)$-Me **36a**	$R^1R^2C=O$		29
Me_3SiCH_2OMe **37**	*s*-BuLi	$Me_3SiCH(Li)OMe$ **37a**	$R^1R^2C=O$		30
$Me_3SiCH_2CH=CH_2$ **38**	*s*-BuLi	$(Me_3SiCH=CHCH_2)Li$ **38a**	$R^1R^2C=O$		31

elements of trimethylsilanoxide to give a vinyl chloride rather than an α,β-epoxysilane. This useful result can be exploited in synthesis (eq. 6) since α,β-epoxysilanes are precursors to carbonyl compounds.[34]

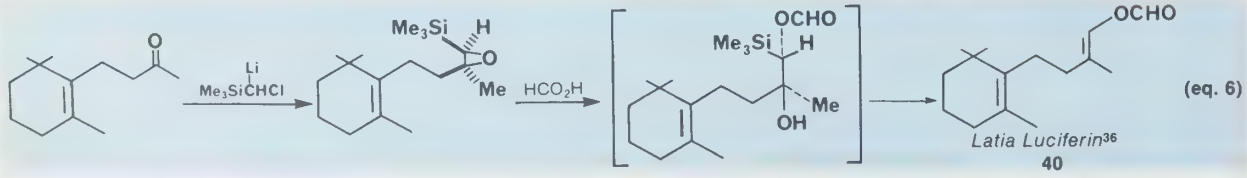
The addition of CTC (abbreviation for **35a**) to estrone *O*-methyl ether (eq. 7) is particularly noteworthy since 17-keto-steroids are hindered, readily enolizable carbonyl compounds. Merely dissolving the α,β-epoxysilane **41** in 90% formic acid gave the 20-aldehyde in excellent yield. The overall transformation of a carbonyl group to the homologous aldehyde, where the original electrophilic carbonyl group has been reduced, is termed REDUCTIVE NUCLEOPHILIC ACYLATION.[35]

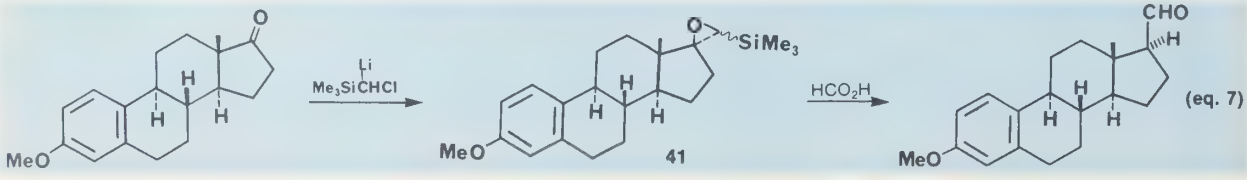
The methyl analog of CTC, namely MCTC (**36a**), is made from **36** by deprotonation with *s*-butyllithium in tetrahydrofuran at -78°C. Treatment of **36a** with ketones or aldehydes (eq. 8) gives



α,β-epoxysilanes **42**. This new methodology has been used in a short synthesis of (*R*)-(+)-frontalin **43**,[35,36] the aggregation pheromone of the Southern Pine beetle, *Dendroctonus frontalis* (Scheme 1).

Another silicon-based reagent that can be used for reductive nucleophilic acylation reactions is methoxymethyltrimethylsilane (**37**). It can be deprotonated selectively using *s*-butyllithium in tetrahydrofuran (Scheme 2) to give the lithio species **37a**. The use of *s*-butyllithium is vital to the success of this reaction. *n*-Butyllithium reacts with **37** to give products that appear to result from nucleophilic attack at silicon and subsequent cleavage of the $-CH_2OMe$ group; *t*-butyllithium gave the lithio species **44**.[30]





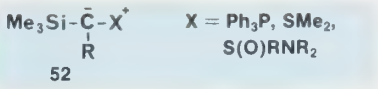
The lithio species **37a** reacts with carbonyl compounds to give adducts such as **56**. Treatment of these adducts with potassium hydride results in the elimination of potassium trimethylsilanoxide to give enol ethers. When the adduct **45** is treated with cesium fluoride in dimethyl sulfoxide, disilylation takes place to give the compound **46** (Scheme 3).[30] Surprisingly no elimination takes place, giving enol ethers.

Synthetic equivalents of the β-acyl anion equivalent (homoenolate) have been widely investigated. A solution to this problem utilizing allyltrimethylsilane is forthcoming.

The allyltrimethylsilyl anion (**38a**) is readily prepared from allyltrimethylsilane (**38**) by treatment with *s*-butyllithium in tetrahydrofuran. As an illustration of the use of **38a** in synthesis, and its high nucleophilicity, the synthesis of the 17-spirolactone steroid is described (Scheme 4).[37] 3-Methoxyandrosta-3,5-dien-17-one (**47**) reacts with allyltrimethylsilylzinc chloride (**38a** plus $ZnCl_2$) to give the adduct **48** after acidic workup. The vinylsilane side chain present in **48** was epoxidized with $VO(acac)_2$/*t*-BuOOH to give **49**. Methanolysis of **49** gave **50** which, on Jones oxidation, yielded the lactone **51**. The yield of **48** exceeded 90%, demonstrating that even in the case of hindered and readily enolizable 17-ketosteroids, the allyltrimethylsilyl anion is sufficiently nucleophilic to give excellent yields of addition products, namely **48**.

SILICON-STABILIZED YLIDES FOR CARBON-CARBON BOND FORMATION

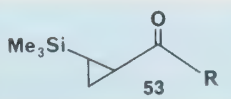
We can represent a silicon-stabilized ylide by the general formula **52**. Such com-



52

pounds have been known for a considerable time; notably, the works of Gilman,[38] Schmidbaur[39] and Miller[40] described how to make these ylides, but these reagents have not been used in synthesis.

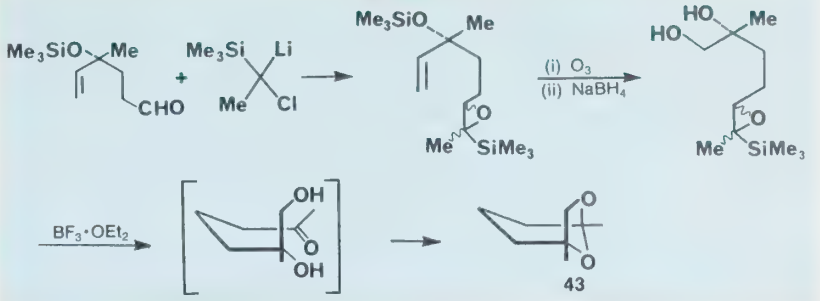
We were concerned with developing a reagent that would convert α,β-unsaturated carbonyl systems into silylcyclopropyl ketones **53**. Methylthio-



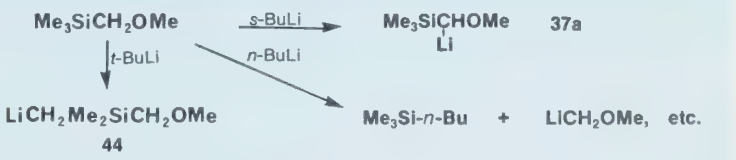
53

methyltrimethylsilane was converted into the methiodide **54** (Scheme 5), and deprotonated[41] using *s*-butyllithium in tetrahydrofuran to give the ylide **55**.[41]

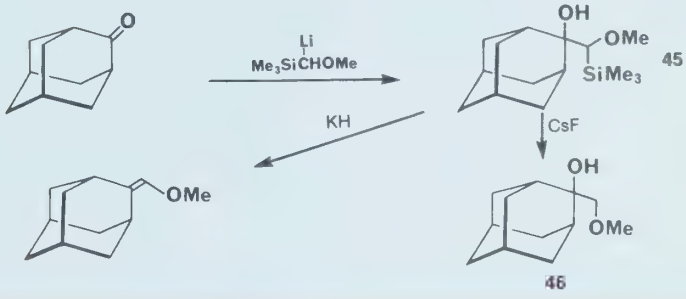
Scheme 1



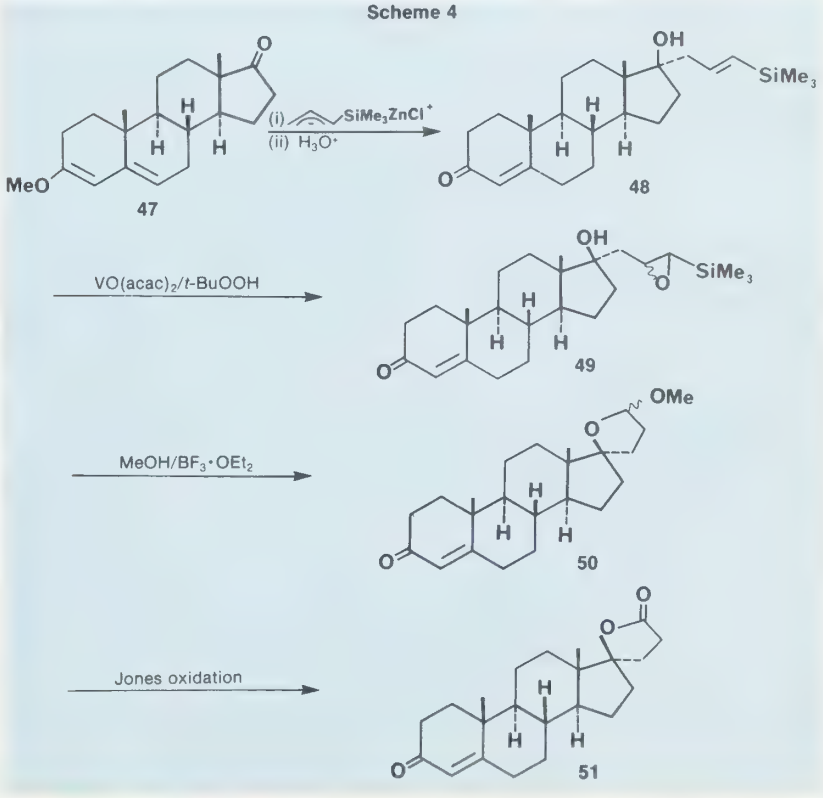
Scheme 2



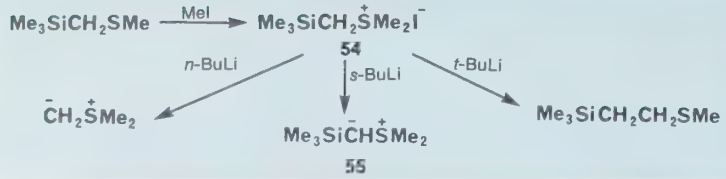
Scheme 3



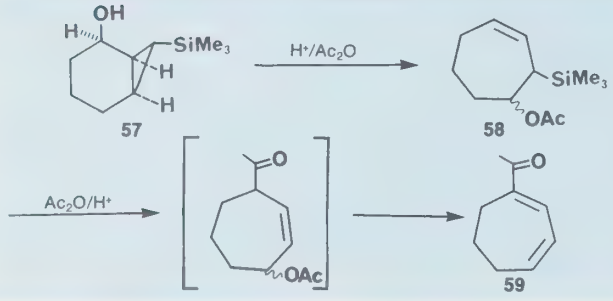
Scheme 4



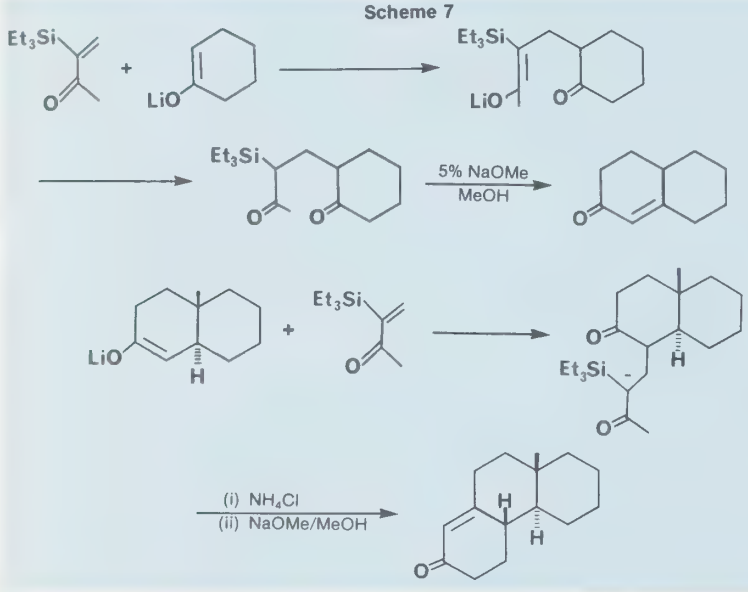
Scheme 5

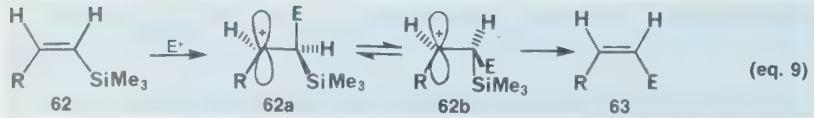


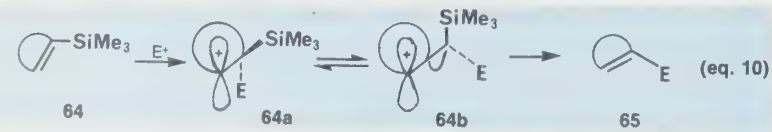
Scheme 6



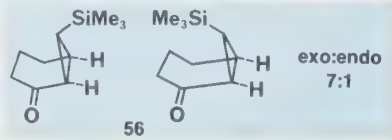
Scheme 7



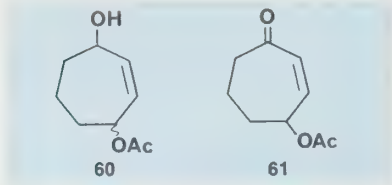




This new class of compounds offers the opportunity to conduct some useful synthetic transformations by exploiting the ability of the silicon atom to stabilize a β-carbonium ion. Treatment of **56** with sodium borohydride gave the alcohol **57**. When this alcohol was treated with acetic anhydride in the presence of a catalytic amount of perchloric acid (Scheme 6) the compound **58** was formed. Further exposure of **58** to the above conditions gave the dienone **59**. The allylsilane has been acylated under these mild conditions.



Another variation on this sequence is to treat **57** with AcOH/AcOOH/H^+ to oxidize the intermediate allylsilane **58** to the allylic alcohol **60**. Oxidation with pyridinium chlorochromate gave the ring-expanded γ-acetoxyenone **61**.[42]



VINYLSILANES FOR CARBON-CARBON BOND FORMATION

While this section will concentrate on the addition of carbon electrophiles to vinylsilanes mention is made of an important advance in annulation reactions. The conjugate addition of enolate anions to activated vinylsilanes (Scheme 7) has solved a long-standing problem in organic synthesis, namely the trapping of regiospecifically generated enolates in aprotic solvents with a methyl vinyl ketone equivalent, and subsequent reactions to produce an annulated product.[43]

The addition of an electrophile to a vinylsilane (**62**) results in the build-up of electrophilic character β to the carbon-silicon bond (eq. 9).[44] Such a species (**62a**) is said to be stabilized either by bridging,[45] or by so-called vertical stabilization (hyperconjugation).[46] The addition has the geometrical requirement that the electrophilic character of the β-position can only enjoy stabilization if the developing positive charge is contained in a $2p_z$ orbital that is in the same plane as the C-Si α-bond. This geometrical condition imposes a severe limitation upon the use of the β-effect for stabilizing electrophilic additions to vinylsilanes. In acyclic systems there is usually no problem; as the incoming electrophile approaches the vinylsilane π-system, rotation about the central carbon-carbon bond can take place to bring the β-carbonium ion into the same plane as the carbon-silicon bond,[47] **62**→**62a**⇌**62b**→**63**.

For cyclic vinylsilanes, particularly in conformationally rigid systems, it may be difficult, and in certain cases impossible, (eq. 10) for the carbon-silicon bond to move into the same plane as the $2p_z$ orbital carrying the positive charge, **64**→**64a**⇌**64b**→**65**.

As can be seen from the above mechanistic consideration, electrophilic substitution of vinylsilanes takes place with retention of geometrical configuration, and with the incoming electrophile replacing the trimethylsilyl group.

Treatment of the cyclic vinylsilane **66**

with acetyl chloride-aluminum trichloride at 0° (eq. 11) gave the enone **67** uncontaminated by other regioisomers.[48] It should be noted that the same electrophilic substitution when carried out on 4,4-dimethylcyclohexene gave a mixture of **67** and **68**. Several other examples of the electrophilic substitution of vinylsilanes with carbon-carbon bond formation are shown below (eq. 12-16).

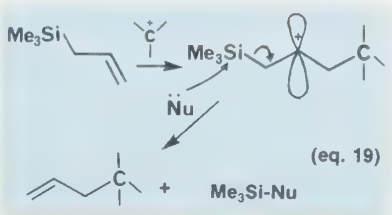
Vinyltrimethylsilane can act as an ethylene equivalent in Friedel-Crafts reactions to synthesize fused cyclopentenones. For example, treatment of the α,β-unsaturated acid chloride **69** with vinyltrimethylsilane (eq. 17) in the presence of stannic tetrachloride gave bicyclo[3.3.0]-Δ^7-octen-1-one **70** (52%).[54]

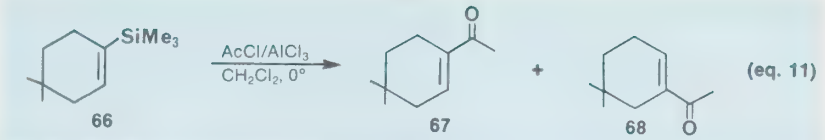
The roles of reagent and substrate in this annulation reaction may be reversed; treatment of the vinylsilane **71** with 3,3-dimethylacryloyl chloride in the presence of aluminum trichloride (eq. 18) gave **72**, which was cyclized with stannic tetrachloride to a mixture of isomers **73**. Treatment of this mixture with rhodium trichloride in ethanol at reflux converted unwanted isomers into **74**.[55]

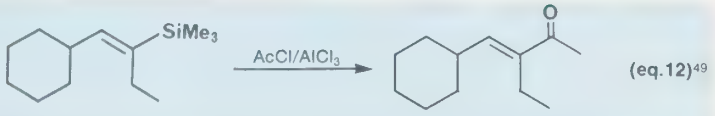
Another annulation reaction that utilizes a new vinylsilane reagent has been developed in our laboratories (Scheme 8). Treatment of vinyltrimethylsilane with phenylsulfenyl chloride in dichloromethane at -70° gave the adduct **75** in excellent yield. Dehydrohalogenation of the adduct **75** with DBU or DBN provided the substituted vinylsilane **76**.[56] When **76** was treated with α,β-unsaturated acid chlorides in nitromethane followed by silver tetrafluoroborate, the 3-thiophenylcyclopentenones **77** were produced.[57]

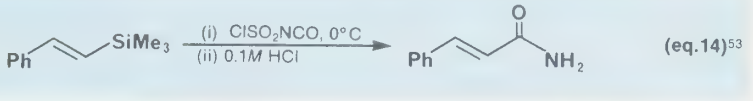
ALLYLSILANES FOR CARBON-CARBON BOND FORMATION

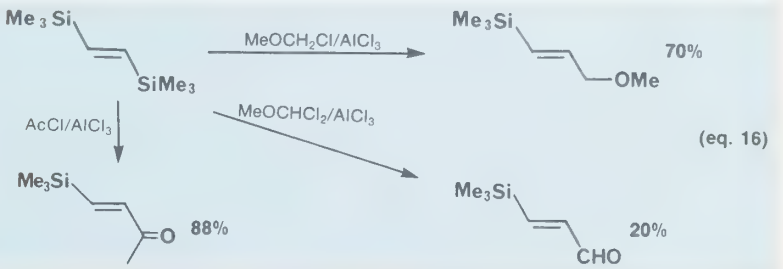
Without doubt allylsilanes have found the premier place in organosilicon chemistry, as applied to synthesis. This is primarily because allylsilanes are stable compared with other allylmetal species. As a result they usually give regiospecific reactions with electrophilic species. The general representation, in mechanistic terms, of the reaction of allylsilanes with carbon electrophiles is illustrated in eq. 19.

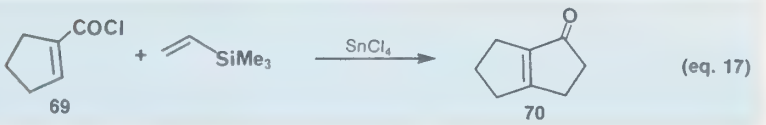


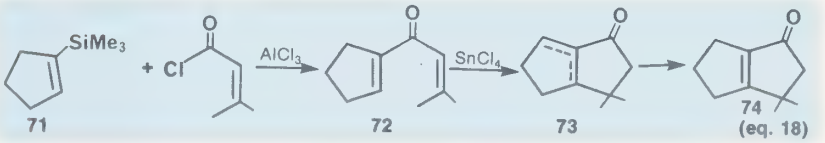












Scheme 8

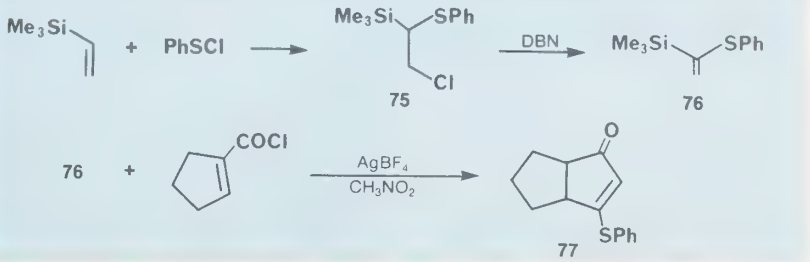
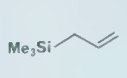
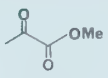
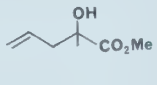
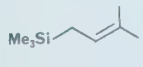
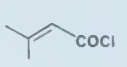
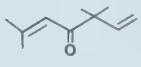
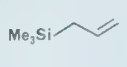
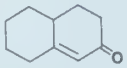
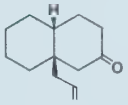
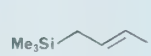
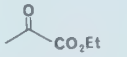
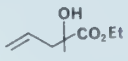
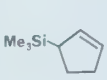
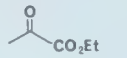
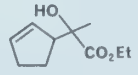
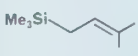
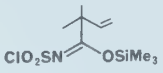
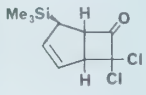
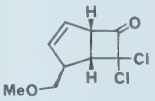
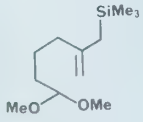
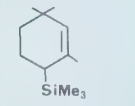
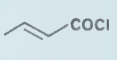
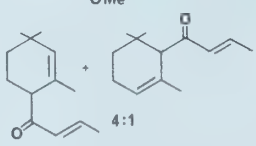
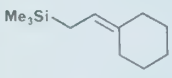
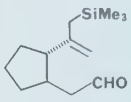
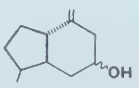
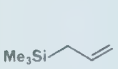
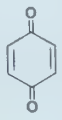
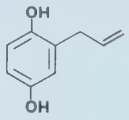
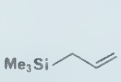
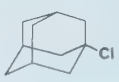
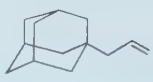
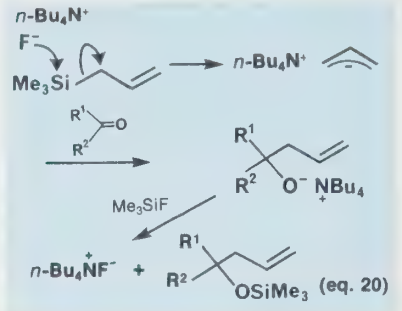


Table II

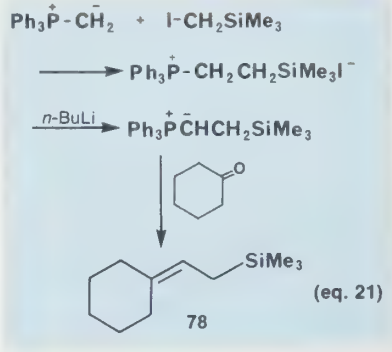
Substrate	Electrophile	Catalyst	Product	Ref.
				58
		$AlCl_3$/-60°		59
		$TiCl_4$/-30°		60
		$TiCl_4$/RT		61
		$TiCl_4$/-15°		62
	$ClSO_2NCO$	no catalyst, 0°		63
	$MeOCH_2Cl$	$SnCl_4$		64
	—	$SnCl_4$		65
		$SnCl_4$/0°		66
	*t*-BuCl	$TiCl_4$		67
	—	$BF_3 \cdot OEt_2$		68
		$TiCl_4$		69
				70

The cleavage of the C-Si bond may be concerted with the build-up of electrophilic character β to the Si atom. The most important feature of this reaction is that the electrophile enters on the terminus of the allyl system, and the π-system is relocated adjacent to its original position. Because of this predictability, and the high nucleophilicity of allylsilanes, they have found many imaginative uses in synthesis. Table II provides a number of specific examples of this chemistry for carbon-carbon bond formation.

The silicon-fluorine bond is remarkably strong, *ca.* 140 kcal/mole. This can be applied in allylsilane chemistry by treating allyltrimethylsilane with tetra-*n*-butylammonium fluoride in the presence of an electrophile to generate the allyl anion.[71] The reaction is catalytic in fluoride ion, and explained by the mechanistic rationale in eq. 20.



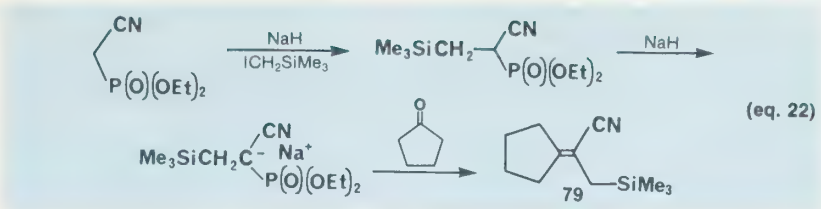
One of the major limitations of allylsilane chemistry is that there are no really versatile methods for preparing allylsilanes. It is not intended to discuss preparative methods for allylsilanes here[72] but to indicate the current trend. If allylsilane chemistry is to find a really useful place in organic synthesis then one must have ways of introducing this functional group into a relatively complex molecule in a predictable fashion. The Wittig reaction can be used to prepare allylsilanes by the sequence shown in eq. 21.[73]



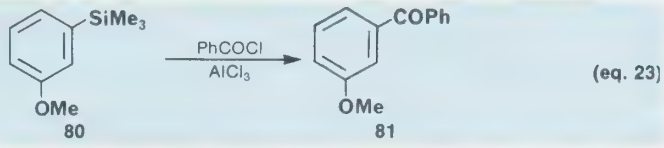
This sequence is adequate for aldehydes and reactive ketones, but unfortunately with cyclopentanone and acyclic ketones the yields of allylsilanes are extremely low.[74] A modification of the Wadsworth-Emmons-Wittig reaction allows the synthesis of functionalized allylsilanes.[75] The yield of **79** is 75% (eq. 22) and the reaction works with a wide range of ketones. As might be expected, since **79a** is an electron-deficient allylsilane it is relatively unreactive towards electrophiles.

ARYLSILANES FOR CARBON-CARBON BOND FORMATION

The use of arylsilanes for carbon-carbon bond-forming reactions is limited by the availability of the arylsilane, but it does

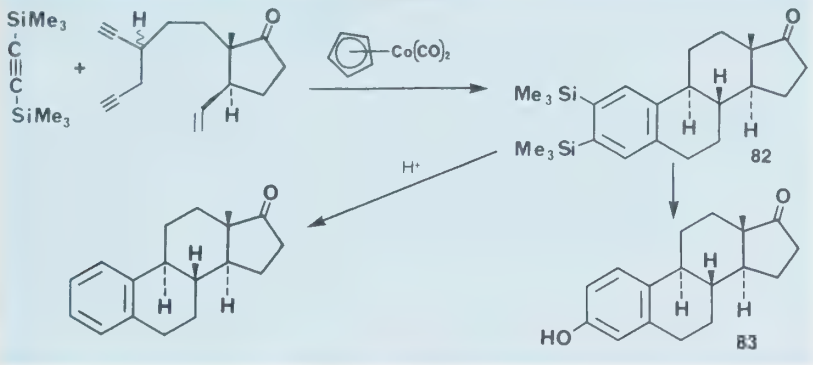


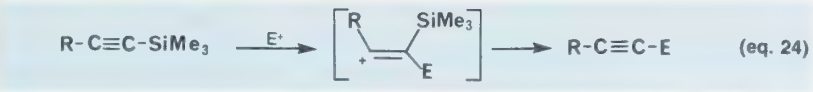
(eq. 22)



(eq. 23)

Scheme 9

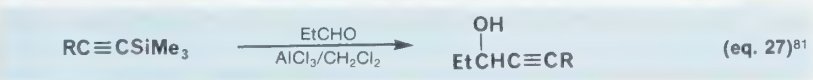




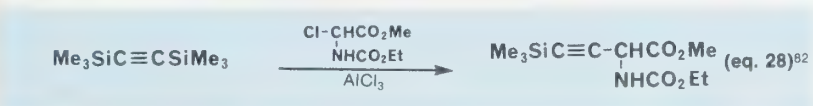
(eq. 24)

(eq. 25)[79]

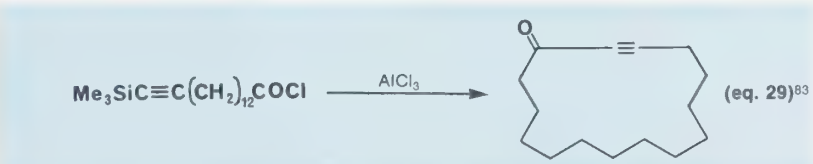
(eq. 26)[80]



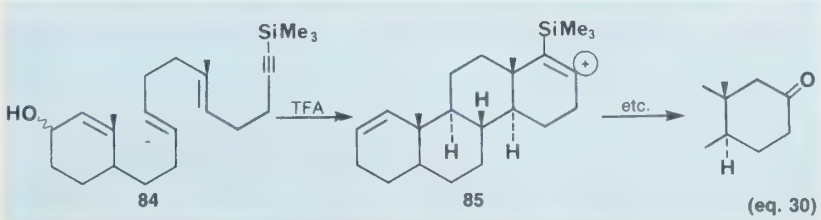
(eq. 27)[81]



(eq. 28)[82]



(eq. 29)[83]



(eq. 30)

have interesting and useful orientation value. It was shown by Eaborn that arylsilanes such as **80** (eq. 23) on treatment with benzoyl chloride in the presence of aluminum trichloride underwent electrophilic aromatic substitution (*ipso facto*) to give the *meta*-substituted anisole **81**.[76] The most dramatic example of the use of arylsilanes[77] in steroid synthesis is the total synthesis of estra(10)-trien-17-one by Vollhardt (Scheme 9).[78]

This sequence can be modified by the appropriate use of different electrophiles to convert **82** into estrone **83** itself.[78]

ALKYNYLSILANES FOR CARBON-CARBON BOND FORMATION

Alkynylsilanes react with electrophiles in much the same way as vinylsilanes; the electrophile attaches itself to the carbon atom bearing silicon, with the corresponding build-up of electrophilic character β to silicon (eq. 24).

Equations 25-29 are examples of this electrophilic substitution.

An excellent illustration of a polyene cyclization directed by a trimethylsilyl group is the conversion of the trienyne **84** into the D-homosteroid **85** (eq. 30). If the $-SiMe_3$ group is replaced by a methyl group then cyclization leads to the normal five-membered D-ring.[84]

CONCLUSION

The large number of examples of carbon-carbon bond-forming reactions shown in this review is by no means exhaustive, but illustrates the leading features that have brought organosilicon chemistry to its prominent position during the last several years.

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Dr. Magnus was awarded the Corday-Morgan medal and prize for organic chemistry by the British Chemical Society in 1978. He is also the recipient of the Akron ACS Award in 1980.

Among the many compounds mentioned by Dr. Magnus offered by Aldrich are the following:

14,604-8 2-Adamantanone

20,826-4 Allyltrimethylsilane

18,743-7 Bis(trimethylsilyl)acetylene

21,312-8 *tert*-Butyl hydroperoxide, 90%

18,617-1 *n*-Butyllithium, solution in hexane

19,559-6 *sec*-Butyllithium, solution in cyclohexane

18,619-8 *tert*-Butyllithium, solution in pentane

19,832-3 Cesium fluoride

10,033-1 Chloromethyl methyl ether

20,535-4 Chloromethyltrimethylsilane

C7,285-4 Chlorotrimethylsilane

12,778-7 Crotonyl chloride

C10,281-4 2-Cyclohexen-1-one

13,658-1 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)

13,900-9 1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU)

D6,565-8 α,α-Dichloromethyl methyl ether

D9,170-5 Diethyl cyanomethylphosphonate

18,366-0 3,3-Dimethylacryloyl chloride

E4,780-8 Ethyl pyruvate

20,912-0 Ethyl (trimethylsilyl)acetate

I-850-7 Iodomethane

22,030-2 Iodomethyltrimethylsilane

19,734-3 Methyllithium, 1.4*M* in diethyl ether

M7,980-8 Methyl pyruvate

21,581-3 Potassium hydride, 35 % dispersion in mineral oil

P5,145-1 Propionaldehyde

19,014-4 Pyridinium chlorochromate

20,626-1 Rhodium(III) chloride trihydrate

20,836-1 Silver tetrafluoroborate

21,346-2 Sodium borohydride, 99+%

22,344-1 Sodium hydride, dry

15,625-6 Sodium methoxide, 25 wt. % solution in methanol

21,614-3 Tetrabutylammonium fluoride, 1*M* solution in THF

T2,250-0 *N,N,N'N'*-Tetramethylethylenediamine

T2,400-7 Tetramethylsilane

20,856-6 Titanium(IV) chloride

21,287-3 Vanadyl acetylacetonate

21,395-0 Vinyltrimethylsilane

PTC in PracTiCe

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During the last few years articles and books on phase-transfer catalysis — PTC — have appeared in a steadily increasing stream.[1] The stream is likely to continue increasing and will change conventional chemical syntheses and processes greatly as many areas have been touched upon only briefly.

The transfer of hydrophilic ions into a lipophilic organic medium seems strange at first, but in practice the technique is remarkably simple.

For this article I have abstracted PTC information that has been valuable in our own process development work. Some ideas are taken directly from the literature while others have been developed further through our daily use. Areas focused upon are:

- replacement of sodium or sodium hydride by 50% NaOH in alkylation reactions
- extended uses of inorganic salts in organic reactions
- C- *vs.* O-alkylations
- transfer of "nonionic" species like H_2O_2 and HCl
- extractive separations.

I will also discuss catalyst cost and advantages of catalyst recovery. A simple quantitative analytical method for quaternary ammonium ions, the most common PTC catalysts, is described.

The reader who has had only brief contact with PTC techniques will find background information in the literature given in reference 1.

Use of 50% NaOH instead of sodium in alkylations

PTC sometimes allows strong bases like sodium hydride or sodium amide to be replaced by 50% aqueous sodium hydroxide[2] or, better still, a mixture of solid sodium hydroxide and sodium carbonate.[3] Zwierzak has shown that benzamides and formamides can be N-alkylated in good yields in such a solid base-organic liquid two-phase system.[4a] He uses about 10 mole % of $TBAHSO_4$, but this figure can probably be lowered under optimized industrial conditions. However, at a conventional PTC catalyst level of 1 mole % the yield is halved. One of Brändström's coworkers, Ulf Junggren, in his thesis of 1972, showed that benzamide could not be alkylated using 50% sodium hydroxide in the "Extractive Alkylation Procedure."[4b] Junggren states that "the limit for the practical application of this procedure is for compounds with a p*Ka* of about 15." For the alkylations of weaker acids he gives sodium hydride as the alternative. Using Zwierzak's modification, however, this limit moves to a p*Ka* of 22-25.

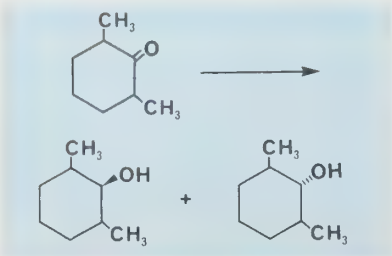
Alkylation of *N*-alkylformamides, general procedure

The mixture of the *N*-alkylformamide (0.1mol), finely powdered sodium hydroxide (14.0g), potassium carbonate (8.0g), tetra-*n*-butylammonium hydrogen sulfate (3.4g, 0.01mol), and benzene (60ml) is stirred vigorously at 35-40°C for 30 min. The resultant slurry of the sodium salt of the amide is heated to 60° and a solution of the alkylating agent (0.2mol of dimethyl sulfate or 0.11mol of alkyl halide) in benzene (40ml) is then added at this temperature over a period of 1h. Stirring is continued at 60-70° for 4h. The mixture is then cooled to room temperature, diluted with benzene (50ml) and filtered. The precipitate is washed with benzene (2 x 30ml) and the washings are combined with the filtrate. The benzene solution is washed with water (2 x 20ml), dried with anhydrous magnesium sulfate and evaporated. The oily residue is kept at 30-40°/0.2 torr for 1h to remove volatile impurities. Crude products are analytically pure.

Uses of "new" inorganic anions

TBA salts of a number of common inorganic ions which have not been found to have extensive organic chemical use earlier are now being reported. The high solubility of inorganic anions as their TBA salts in nonpolar organic solvents never ceases to surprise traditional chemists. Try 40% TBAOH in water with an equal amount of petroleum ether!

Quaternary ammonium dithionite has already been used in reductions of ketones to alcohols.[5] It may become a cheap alternative to established reducing agents.



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To our knowledge the anion of sodium carbonate peroxyhydrate ("solid H_2O_2") has not yet been tried with the PTC technique. This salt has been put on the market recently by Interox America and might find use as an oxidizing or epoxidizing agent using the PTC technique.[6]

$TBABF_4$ is reported as a useful electrolyte in electrochemical synthesis.[7]

$TBAClO_4$ has interesting solubility properties. It is almost insoluble in water.

$TBAMnO_4$ is frequently used in oxidations.[8] However, it is unstable and thus dangerous to use as an isolated salt.[9]

Although borohydrides are well established in organic synthesis, an extra advantage of using $TBABH_4$ deserves attention. In an earlier survey on "Applications of Phase-Transfer Catalysis in Organic Synthesis," reduction with $TBABH_4$ was reported.[1a] $TBABH_4$ is readily obtained from $TBAHSO_4$. Applications of this lipophilic BH_4^- salt are presently arousing interest.

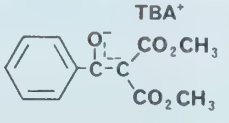
Not only can solid $TBABH_4$ be isolated, its solution in a non-ethereal solvent can be obtained.[10] The replacement of ether or THF by dichloromethane is a contribution to laboratory and industrial safety. Diborane is easily obtained from a dry solution of $TBABH_4$ in dichloromethane by treatment with an alkyl halide such as methyl iodide or 1,2-dichloroethane. The diborane solution thus obtained can be used for all the common reductions and hydroboration reactions.

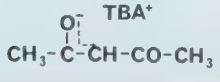
C- *vs.* O-alkylation

Solvents have a well-known effect on C- *vs.* O-alkylation. Similarly, application of the PTC technique can change the C/O ratio.

Brändström and Junggren have studied factors influencing C- *vs.* O-alkylation of ambident anions such as those of methyl acetoacetate and dimethyl benzoylmalonate. The expected importance of the alkylating agent is verified.[11,12,13]

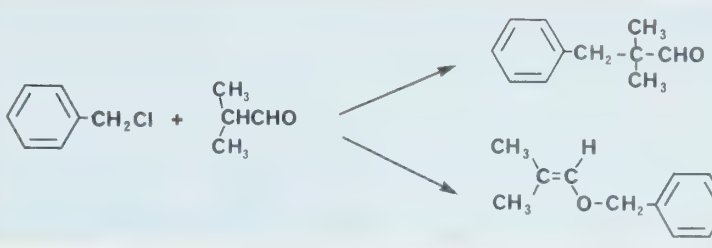
These three papers introduce the concept of "extractive alkylation." The authors have isolated the crystalline TBA salts of dimethyl benzoylmalonate and acetylacetone.





C- *vs.* O-alkylation of aldehydes

We have studied the alkylation of isobutyraldehyde in our laboratories.[14] In the manufacture of 1-butanol by the OXO-process between 10 and 25% of isobutyraldehyde is formed as a by-product. This compound is available worldwide in quantities of 500 million lbs/year and premium outlets are sought. After treating isobutyraldehyde with benzyl chloride, we have isolated, not only the C-alkylated product, but also the O-alkylated one which has not been previously reported.



The highest C/O ratio (10.9) is obtained using tetrapropylammonium iodide. The bigger tetrabutylammonium ion gives a smaller C/O ratio. TBA counterions less lipophilic than iodide, *viz.*, bromide, chloride and sulfate all give smaller C/O ratios (see Table 1).

Most surprising is the higher yield obtained when iodide is the counterion. The known poisoning effect of iodide in PTC reactions seems not to apply to this reaction. A yield of 80% is obtained although only 1 mole % of catalyst is used. Furthermore, the reaction is faster when iodide is the counterion.

Transfer of neutral molecules

Transfer of hydrogen peroxide **anions** from an alkaline aqueous phase is not practically possible.[15] Hydrogen peroxide anions remain mainly in the aqueous phase. However, in neutral or acidic media hydrogen peroxide **molecules** are indeed transferred, probably solvated, by TBA bromide. Dehmlow has demonstrated that the more lipophilic the ion pair, the better it transfers H_2O_2.[15] $TBAHSO_4$ transfers only 10% of the equivalent amount of H_2O_2, whereas TBABr transfers 68%. The still more lipophilic tetrahexylammonium bromide transfers H_2O_2 equivalently. Similarly, hydrogen chloride can be transferred into benzene.

Recovery of TBA ions

Catalysts are expensive and are normally used over and over again. In industrial processes, recovery and regeneration of ineffective catalysts are standard procedures.[3] The cost of these operations plus make-up catalyst is included as catalyst cost in the process cost calculation. The price/lb of the catalyst itself is seldom representative of catalyst cost in a process.

Table 1

Alkylation of isobutyraldehyde with benzyl chloride in 50% sodium hydroxide/toluene at 70° C for 4 hours

No.	Catalyst (1.25 mole %)	C/O ratio	Benzyl chloride reacted (%)
1	TBA iodide	7.6	82.7
2	TBA hydrogen sulfate	4.3	71.0
3	TBA bromide	3.7	74.0
4	Tetrapropylammonium iodide	10.9	79.3
5	Methyltrioctylammonium chloride	5.8	68.5
6	TBA chloride	4.3	69.2

Let us examine the figure used as catalyst cost in the PTC field. A PTC catalyst is recovered by an extractive procedure. Regeneration (*i.e.*, requaternization of a tertiary amine) is probably not of interest.

We have made a catalyst-cost calculation on the propylation of phenylacetonitrile by 1-chloropropane.[16] We use $TBAHSO_4$ as a catalyst at $8/lb and 50% NaOH as a base. At the laboratory scale it was possible to recover 87% of the catalyst as TBACl after the reaction. This puts the figure for catalyst cost, including recovery cost, at about $2 per pound of $TBAHSO_4$ charged in an industrial scale.

Recovery at such a high percentage is only possible for quaternary ammonium ions with a balanced hydrophilicity/lipophilicity. The TBA ion outstandingly combines the lipophilicity necessary for an efficient PTC catalyst with the hydrophilicity necessary for efficient recovery.

How is this recovery achieved?

There are three different ways to recover a quaternary ammonium ion.

1) Salt it out from an aqueous phase with sodium hydroxide.[17]
2) Transfer it selectively into the desired phase using a suitable counterion.[18]
3) Transfer it selectively into the aqueous phase by cooling.[19]

Recovery according to method 1 is accomplished as follows. The solubility of tetrabutylammonium bromide in sodium hydroxide solutions varies markedly with the concentration. A solution of 1% NaOH can dissolve 27% TBABr, whereas a 15% NaOH solution only dissolves 0.07% of TBABr. This spectacular difference in solubility can be utilized in synthetic work as well as in process design. The factor to keep in mind is that hydroxide ions often are consumed during the course of the reaction. If NaOH is not in excess during the latter part of the reaction, the availability of the PTC catalyst will drop, thus changing the reaction conditions.

An example of method 2 is the addition of a lipophilic sulfonate, such as sodium naphthalenesulfonate, or a lipophilic carbonic acid to an aqueous solution containing a quaternary ammonium compound.[18] By this procedure TBA^+ is transferred into an organic phase. If TBA^+ is to be moved into an aqueous phase, the system should be acidified with sulfuric acid. The naphthalenesulfonic acid will remain in the organic layer and TBA^+ as the hydrogen sulfate will move into the water. Unfortunately, this simple procedure does not work for all quaternary ions. The more lipophilic they are, the less easy it is to transfer them into water.

Walters has demonstrated the third method of recovery by showing that the distribution of TBA salts between an aqueous and an organic phase is strongly temperature-dependent.[19] In the hydrodimerization of acrylonitrile to adiponitrile TBA salts are used as electrolytes. When the adiponitrile is purified there is the problem of removing TBA salts dissolved in the product. This has been done effectively by cooling the product emulsion from 25°C to 0°C.

$$K = \frac{\text{wt \% of TBA in the organic phase}}{\text{wt \% of TBA in the aqueous phase}}$$

$K_{25°C} = 1.4$; $K_{0°C} = 0.01$

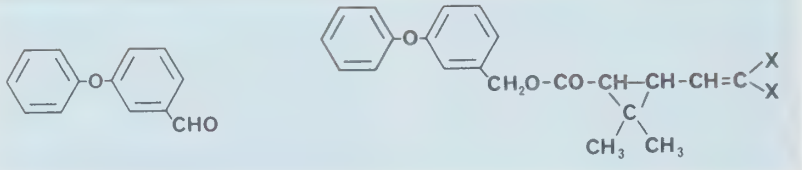
The distribution of the organic products is not affected by the change in temperature.

In the recovery of quaternary ammonium ions the best results are obtained with TBA ions. Generally, methyltrioctyl ions are too lipophilic to reenter an aqueous phase to a practical degree.

Extractive separations

Quaternary ammonium salts may also be used in purifications. Harmful ions like cyanides or phenolates can be transferred from an aqueous waste stream into an organic phase. Valuable compounds like penicillins can be separated as TBA salts and thus recovered.

Aldehydes are purified as bisulfite complexes. $TBAHSO_3$ is easily transferred into the organic phase and the formation of bisulfite complexes of lipophilic aldehydes is rapid. Mizutani and co-workers report the purification of 3-phenoxybenzaldehyde in this manner. The impure aldehyde itself serves as the organic phase and the crystalline bisulfite adduct is easily separated from the impurities. Again TBA salts give the best results and purities of more than 99% are obtained. The purity of the aldehyde is important in the manufacture of chrysanthemic esters, well-known insecticides.[20]



In the subsequent esterification of chrysanthemic acid with 3-phenoxybenzyl chloride, PTC is also favorably used.

Environmental aspects

In earlier days the LD_{50} value of a compound gave sufficient information about its toxicity. Today additional information, such as fish toxicity (LC_{50}), plays an important environmental role. A comparison of the LD_{50} and LC_{50} values of the two TBA salts seems to show a practical PTC example. The LD_{50} values on $TBAHSO_4$ and TBABr are both between 500 and 600mg per kilo of body weight. In the case where the salt is administered into the test animal, the impact of the counterion is low.

A look at the LC_{50} values gives a very different picture of the two salts. A zebrafish, generally accepted as a representative test fish, tolerates a 2.5 times higher concentration of $TBAHSO_4$. This can be attributed to the more lipophilic nature of TBABr. The values are:

$TBAHSO_4$	3370mg/l, 96 hours
TBABr	1380mg/l, 96 hours

Titration of TBA ions

An important method of titration of lipophilic cations like TBA ions is well-hidden in Brändström's "Preparative Ion-Pair Extraction".[18] The method is important because it is a simple quantitative analytical technique for quaternary ammonium ions. Other methods used to determine quaternary ammonium ions, *e.g.*, ion-exchange to the quaternary ammonium iodide, then transfer of the iodide to an organic phase followed by treatment with mercuric acetate and titration of acetate ions with perchloric acid, gives the amount of the counterion from which the figure for TBA ions can be calculated indirectly only.

Brändström titrates in a two-phase system, water and methylene chloride. Thus, the titration itself is a practical application of PTC (what else!). The titrant is a sulfonate, potassium 3,5-di-*tert*-butyl-2-hydroxybenzenesulfonate, that is very lipophilic. At the beginning of the titration the amount of TBA ions in the sample is distributed between the aqueous and the organic phase. During the titration all TBA ions present in the aqueous phase move as ion pairs with the sulfonate into the organic phase. The TBA ions already present in the organic phase at the beginning of the titration, owing to the distribution, pull an equivalent amount of sulfonate ions into the organic phase. When all TBA ions are present in the organic phase, an indication that the titration end point is reached is necessary. The sulfonate with an *o*-hydroxy function also acts as a chelating agent for ferric ions. The chelate is greenish blue. The addition of ferric chloride to the aqueous phase gives the indication.

Experimental part

1) Titration of crystalline TBA salts

Dissolve an accurately weighed sample of about 320mg TBABr or 340mg $TBAHSO_4$ in 20ml of dichloromethane. Add 20ml of indicator solution B (see below).

Titrate under stirring with solution A (see below) until the lower dichloromethane layer gets a faint blue color. The upper aqueous layer, at this stage, will have changed from yellow to blue-green.

Calculations:

$$\text{TBABr \%} = \frac{A(322.4)(M)}{100(\text{mg TBABr})}$$

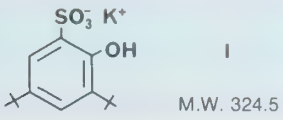
$$\text{TBAHSO}_4\text{ \%} = \frac{A(339.5)(M)}{100(\text{mg TBAHSO}_4)}$$

A = ml of solution A
M = molarity of solution A

2. Titration of TBA salts in solution

A solution containing about 0.3g of TBABr or $TBAHSO_4$ is made alkaline and extracted twice with ether if contaminated with organic compounds other than the TBA ion (such as amines) and then acidified. To the sample is then added 20ml of dichloromethane and 10ml of solution B. The mixture is then titrated as in procedure 1.

Solution A: A 0.1*M* solution of potassium 3,5-di-*tert*-butyl-2-hydroxybenzenesulfonate (I) is prepared by dissolving 32.4g of **I** in water containing 10% acetone to a total volume of 1 liter.



I

M.W. 324.5

Solution B (indicator): A 0.1*M* solution of $FeCl_3 \cdot 6H_2O$ in 0.1*M* HCl is prepared by dissolving 27g of $FeCl_3 \cdot 6H_2O$ (M.W. = 270.3) in 1 liter of 0.1*M* HCl.

Procedures:

Solution A is standardized prior to use with a reference sample of TBABr or $TBAHSO_4$. See titration procedure 1.

Calculations:

$$\text{Molarity Solution A} = \frac{\text{mg TBABr}}{(322.4)(\text{A})} = \frac{\text{mg TBAHSO}_4}{339.5\ (\text{A})}$$

Accuracy of the method:

Titration of 20ml of a 0.01*M* solution of a TBA salt will give a breakpoint within 0.03ml of the sulfonate solution.

At lower concentrations of TBA (0.001*M*) there is no color in the organic phase, but the aqueous phase will change from light green to light blue. The change interval is now larger.

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About the Author

Dr. Kjell Sjöberg studied organic chemistry at the University of Stockholm, Sweden and obtained his doctorate in 1971 for a thesis on synthetic penicillins. In the course of the work he spent a year at the University of Munich and concluded at the Royal Institute of Technology in Stockholm. He had also spent a year at Harvard University (1967) working on organometallic chemistry.

In 1968 he joined the Swedish chemical company KemaNobel, and in 1975 returned to the Royal Institute of Technology as a Professor of Chemical Technology. At present he is on a half-time appointment at Bofors Nobel Kemi AB, which recently took over a company he had founded, Synecon Chemicals AB.

Among the many compounds mentioned by Dr. Sjöberg offered by Aldrich are:

20,561-3 Aliquat® 336

19,175-2 *m*-Phenoxybenzaldehyde

22,344-1 Sodium hydride, dry

19,923-0 Sodium hydride, 60 % dispersion in mineral oil

19,311-9 Tetrabutylammonium bromide

17,242-1 Tetrabutylammonium chloride

15,583-7 Tetrabutylammonium hydrogen sulfate

17,878-0 Tetrabutylammonium hydroxide, 40 wt. % solution in water

14,077-5 Tetrabutylammonium iodide

21,796-4 Tetrabutylammonium tetrafluoroborate

Synthesis and Applications of Vinylic Organoboranes*

Herbert C. Brown
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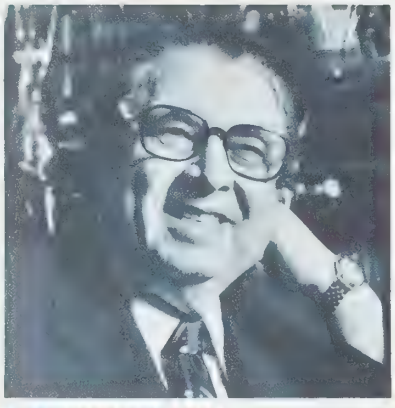
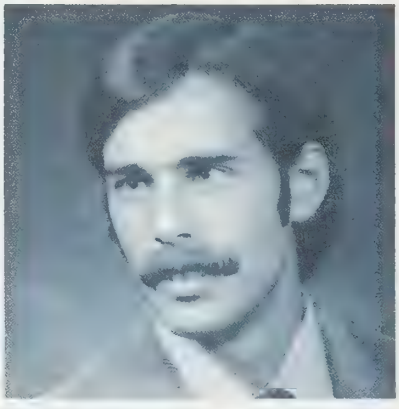
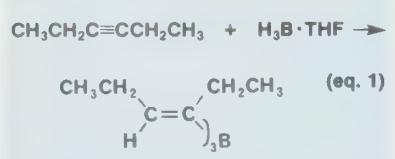


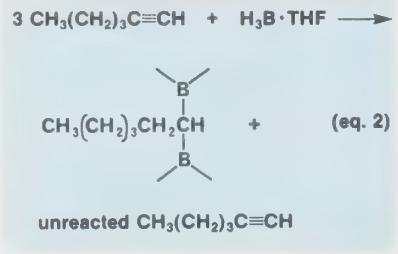


I. INTRODUCTION

The hydroboration of olefins with diborane in ether solvents provides a convenient synthesis of aliphatic and alicyclic organoboranes.[1] The resulting organoboranes have proven to be exceptionally useful synthetic reagents.[2]

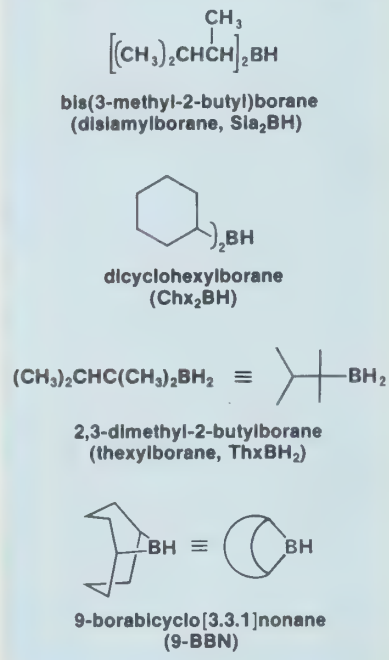
Early work which attempted to extend hydroboration with borane to alkynes as a route to the vinylic organoboranes, met with limited success. While the reaction of internal alkynes with diborane provides the trialkenylboranes in moderate yields (eq. 1), terminal alkynes yield little or none of the desired alkenylborane.[3] Apparently dihydroboration competes with monohydroboration in the case of internal acetylenes, becoming the predominant reaction in the case of terminal acetylenes (eq. 2).





The large steric requirements of certain olefins apparently hinder reaction with $H_3B \cdot THF$ beyond the formation of the corresponding mono- or dialkylboranes.[2a,d] This feature makes possible the convenient synthesis of several mono- and dialkylboranes and their utilization as desirable hydroborating reagents. Many of these reagents exhibit highly selective behavior in the hydroboration of olefins. Consequently, they appeared attractive as precursors for the controlled monohydroboration of acetylenes for the synthesis of the desired vinylic boranes. In fact, all of the mono- and dialkylborane reagents indicated in Fig. 1 have demonstrated utility for such monohydroboration of alkynes. The later introduction of several other heterosubstituted boranes as hydroborating reagents further expanded the availability of reagents for preparing vinylic boranes from acetylenes (Fig. 2).

FIGURE 1. MONO- AND DIALKYLBORANE HYDROBORATING AGENTS



All the reagents illustrated permit the controlled monohydroboration of both terminal and internal alkynes to provide the corresponding vinylic boranes. The mildness of the reagents tolerates the

*Based in part upon lectures presented at the Symposium on Synthesis and Chemistry of Acetylenic Compounds, Division of Petroleum Chemistry, Meeting of the American Chemical Society, Honolulu, Hawaii, April 1-6, 1979, and the International Symposium on Metallo-Organics in Organic Synthesis, Perkin Division, The Royal Society of Chemistry, University College, Swansea, Wales, UK, July 14-17, 1980.

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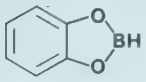
FIGURE 2. HETEROSUBSTITUTED BORANES AS HYDROBORATING AGENTS



1,3,2-dioxabenzoborole
(catecholborane, CtO_2BH)

$H_2BCl \cdot OEt_2$
monochloroborane-ethyl etherate

$HBCl_2 \cdot OEt_2$
dichloroborane-ethyl etherate

$H_2BCl \cdot SMe_2$
monochloroborane-methyl sulfide

$HBBr_2 \cdot SMe_2$
dibromoborane-methyl sulfide

presence of a wide variety of functional groups, such as ester, ether, halogen, and nitrile. The stereospecific *cis* nature of hydroboration gives exclusively the *trans*-alkenylboranes, often also in high regioisomeric purity. Subsequent reactions of the alkenylboranes usually proceed by stereodefined pathways, thus allowing highly stereo- and regiospecific syntheses.

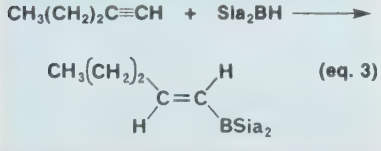
Many of the mono- and difunctional hydroborating reagents exhibit diverse reactivity characteristics toward different unsaturated substrates. Thus, the availability of an array of hydroborating reagents to convert alkynes to the alkenylboron compounds expands the synthetic capability immensely. A wide spectrum of possible selective transformations of an alkyne in the presence of various functional groups, alkenes, or even structurally different alkynes may then be conducted *via* hydroboration.

With the evolution of each new reagent came an advance in the capability of performing selective transformations of alkynes by hydroboration. Thus, each new reagent will be discussed in a more or less chronological perspective. A separate section will examine directive effects in the hydroboration of several unsymmetrically substituted alkynes. Finally, representative transformations of the vinylic boranes or the diboraalkanes, readily available now *via* the hydroboration of alkynes, will be presented.

II. HYDROBORATION OF ALKYNES WITH BORANE DERIVATIVES

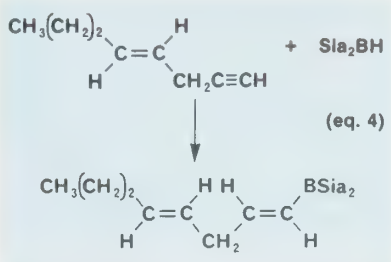
A. Disiamylborane

Reaction of either terminal or internal alkynes with disiamylborane at 0° proceeds rapidly to form the alkenyldisiamylboranes[3] (eq. 3). Competing dihydroboration is insignificant even with an excess of the borane present, thus overcoming the difficulties associated with $H_3B \cdot THF$ as the hydroborating agent. Apparently the high steric requirements of disiamylborane minimize further reaction with the alkenylborane.



(eq. 3)

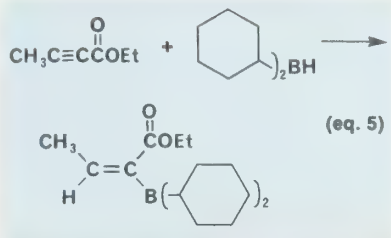
While diborane in THF is fairly nondiscriminating among unsaturated substrates, disiamylborane reveals a far more selective reactivity. In fact, an internal or terminal alkyne can be selectively hydroborated with disiamylborane in the presence of all but unhindered terminal olefins[4,5a] (eq. 4).



(eq. 4)

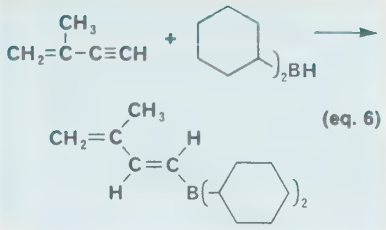
B. Dicyclohexylborane

In many cases, dicyclohexylborane may be substituted for disiamylborane. However, the slightly lower steric requirements of dicyclohexylborane may allow dihydroboration of the alkyne,[6] but careful control of the reaction conditions affords the corresponding alkenyldicyclohexylboranes in excellent yields[7] (eq. 5).



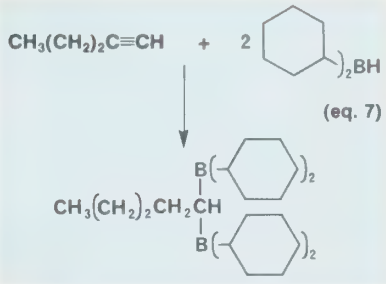
(eq. 5)

Although the relative reactivity of olefinic and acetylenic substrates toward dicyclohexylborane has not been quantitatively established, selective hydroborations are also achievable[8] (eq. 6).



(eq. 6)

Hydroboration of 1-alkynes with two equivalents of dicyclohexylborane results in exclusive formation of the 1,1-diboraalkanes[6] (eq. 7). Thus, direct access to such

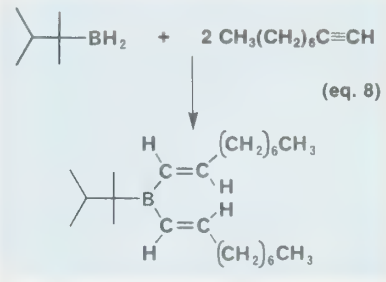


(eq. 7)

geminal organometallics can be accomplished virtually quantitatively from any 1-alkyne and dicyclohexylborane.

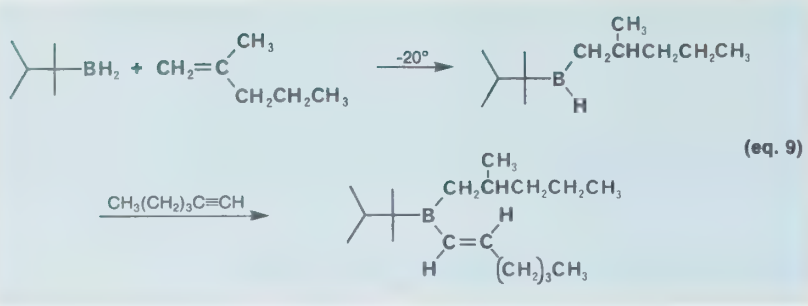
C. Thexylborane and Thexylmonoalkylboranes

Thexylborane is unique among the available alkylborane hydroborating reagents because of its difunctional nature.[5a] Reaction of two equivalents of a 1-alkyne with thexylborane cleanly produces the thexyldialkenylborane[9] (eq. 8). With the exception of simple terminal

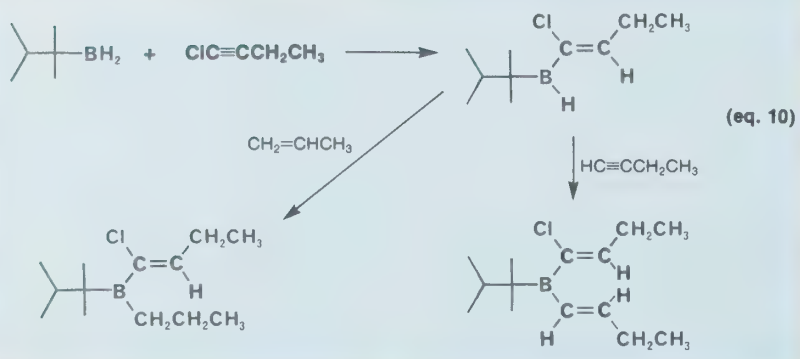


(eq. 8)

olefins, the controlled low-temperature hydroboration of all other olefins with thexylborane provides the corresponding thexylmonoalkylboranes in nearly quantitative yield. Subsequent addition of an alkyne gives the mixed thexyldialkenylborane[10] (eq. 9). Although reaction of thexylborane with one equivalent of a 1-alkyne does not cleanly afford the thexylmonoalkenylborane, reaction with either a 1-chloro- or 1-bromoalkyne does provide the thexyl-1-halo-1-alkenylborane[11] (eq. 10). This monofunctional alkenylborane may then be used to prepare either mixed thexyldialkenyl- or thexylalkylalkenylboranes.



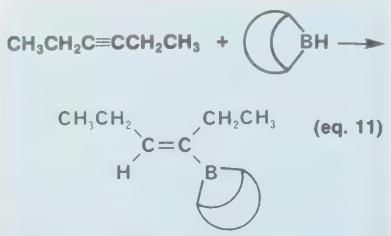
(eq. 9)



(eq. 10)

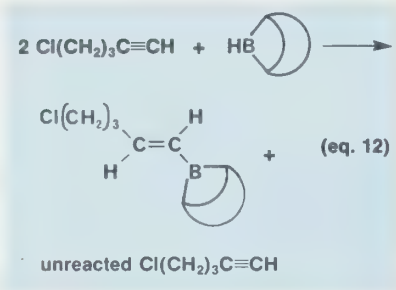
D. 9-BBN

Of the alkyl-substituted hydroboration reagents, 9-BBN possesses by far the greatest thermal and oxidative stability.[12] The reagent, a crystalline solid, may be stored for long periods of time under nitrogen and is in fact commercially available.[5b] Reaction of 9-BBN with internal alkynes affords the *B*-alkenyl-9-BBN derivatives in good yields[13] (eq. 11).



(eq. 11)

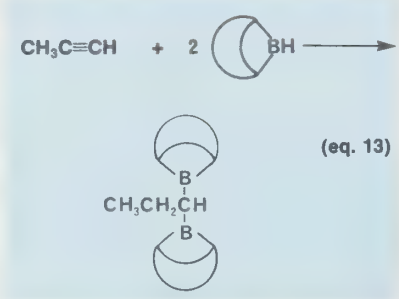
However, addition of 9-BBN to a 1-alkyne in stoichiometric quantities leads to the formation of substantial amounts of the dihydroboration product along with the desired alkenylborane. Presumably the openness of the boron atom in the 9-BBN moiety permits further reaction with the intermediate alkenylborane to give the 1,1-diboraalkane. However, use of a considerable excess of 1-alkyne, usually 100%, suppresses dihydroboration, yielding the desired alkenylborane in excellent yield[13] (eq. 12). The excess alkyne is generally easily recovered. The resulting *B*-alkenyl-9-BBN derivative is stable and can be isolated by vacuum distillation, if desired, to obtain the pure alkenylborane.



(eq. 12)

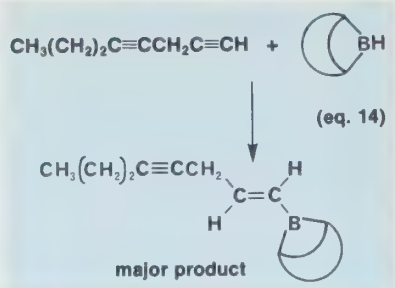
unreacted $Cl(CH_2)_3C{\equiv}CH$

Addition of two equivalents of 9-BBN to the 1-alkyne readily produces the 1,1-diboraalkane in nearly quantitative yield (eq. 13), providing an alternative route to such derivatives.[14]



(eq. 13)

Unlike many of the other dialkylborane hydroborating reagents, 9-BBN demonstrates a significantly different reactivity toward unsaturated substrates. In general, unhindered terminal olefins react more readily than terminal and internal alkynes, while terminal alkynes react more readily than internal alkynes[15] (eq. 14).

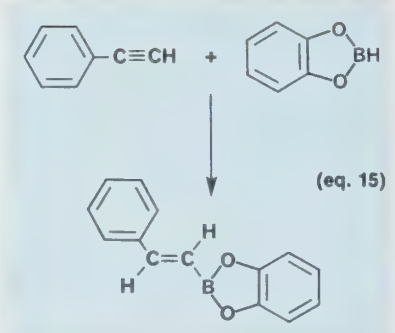


(eq. 14)

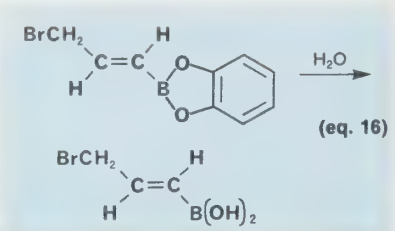
major product

E. Catecholborane

Addition of one equivalent of catechol to an equivalent of borane in THF gives the monofunctional reagent, catecholborane.[16,5b] The reaction of alkynes with catecholborane proceeds quite sluggishly at room temperature. However, at elevated temperatures, in refluxing tetrahydrofuran, the reaction proceeds smoothly to give the alkenylcatecholboranes in excellent yields[17] (eq. 15). These alkenylboranes are quite stable to air and can be isolated by simple distillation or recrystallization. Such access to the alkenylcatecholboranes also allows direct entry into the class of stereodefined alkenylboronic acids and esters *via* hydroboration (eq. 16).



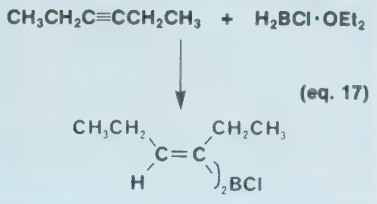
(eq. 15)



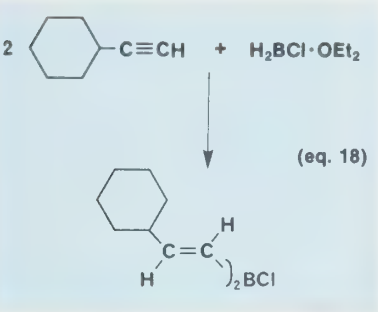
(eq. 16)

F. Mono- and Dichloroborane-Ethyl Etherates

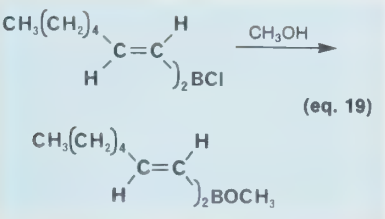
The preparation of mono- and dichloroborane-ethyl etherates and their use as hydroborating reagents for olefins subsequently led to their development as precursors to the alkenylchloroboranes. Reaction of monochloroborane-etherate[18] with two equivalents of an internal alkyne cleanly affords the dialkenylchloroboranes in excellent yields[19] (eq. 17). Attempts to



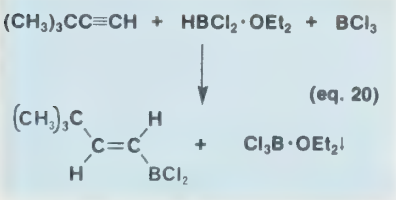
extend the reaction to 1-alkynes incur complications due to competing dihydroboration. However, use of an excess (~40%) of the 1-alkyne gives quantitative yields of the desired bis(1-alkenyl)chloroboranes[19] (eq. 18). Hydrolysis or alcohol-



ysis of these boranes then provides a simple, direct synthesis of dialkylborinic acids or esters of known stereochemistry (eq. 19).



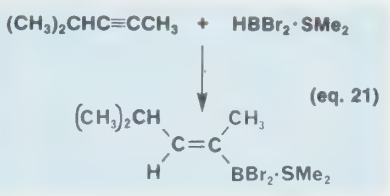
The reaction of dichloroborane-ethyl etherate with alkynes proceeds slowly. Apparently the strong bond between the ether and the Lewis acid, dichloroborane, impedes the reaction. However, addition of one equivalent of boron trichloride to a mixture of dichloroborane-etherate and alkyne results in rapid hydroboration with deposition of the $Cl_3B \cdot OEt_2$ adduct[20] (eq. 20). Presumably, the stronger Lewis acid,[21]



BCl_3, effectively removes the complexing ethyl ether, permitting the liberated dichloroborane to undergo immediate reaction. Hydrolysis or alcoholysis of the resultant alkenyldichloroborane then provides a simple preparation of the desired alkenylboronic acid or esters *via* hydroboration.

G. Dibromoborane-Methyl Sulfide

Quite recently, dibromoborane-methyl sulfide was prepared[22] and demonstrated to react directly with olefins without addition of a stronger Lewis acid.[23] This is puzzling since one would expect dibromoborane to form an especially strong adduct which should exhibit a diminished reactivity. Nevertheless, reaction of dibromoborane-methyl sulfide with alkynes cleanly affords the corresponding alkenyldibromoboranes in excellent yields[24] (eq. 21). For-



tunately, with 1-alkynes, the reaction proceeds readily to the alkenylborane stage, with no significant complications arising from competitive dihydroboration.

Moreover, dibromoborane-methyl sulfide exhibits an unusually rapid reaction with internal alkynes, far faster than the reaction of the reagent with terminal double or triple bonds. This offers considerable promise. The relative reactivity data suggest that selective hydroboration of internal alkynes in the presence of 1-alkynes or any olefin should be feasible. The markedly different selectivity of 9-BBN[15] and $HBBr_2 \cdot SMe_2$[24] should be noted (eq. 22).

III. DIRECTIVE EFFECTS

Availability of the considerable number of different hydroborating reagents for the preparation of alkenyl- and dialkenylboranes permits various valuable selective hydroborations. For example, 9-BBN permits the selective hydroboration of a terminal alkene in the presence of an internal alkyne[15] (eq. 22). On the other hand, dibromoborane-methyl sulfide selectively hydroborates an internal alkyne in the presence of a terminal alkene[24] (eq. 22).

The various hydroborating reagents also provide a regioselectivity spectrum in the hydroboration of unsymmetrically substituted alkynes. Nearly all of the reagents place boron exclusively at the terminal position in 1-alkynes. However, many internal alkynes involve a balance between steric and electronic effects in the placement of the boron.

In Table I, the directive effects encountered in the hydroboration of 2-hexyne and 4-methyl-2-pentyne are summarized for the hydroborating reagents discussed. Clearly, all of the reagents show some sensitivity to steric effects, placing boron predominantly at the least hindered position. Both 9-BBN and $HBBr_2 \cdot SMe_2$ appear to be even more selective than the highly hindered reagents, disiamylborane and dicyclohexylborane.

The effect of a phenyl group, which alters the electronic requirements of the triple bond, is significant, as is evidenced by a comparison of the data for 1-phenyl-1-propyne with those for 1-cyclohexyl-1-propyne (Table II).

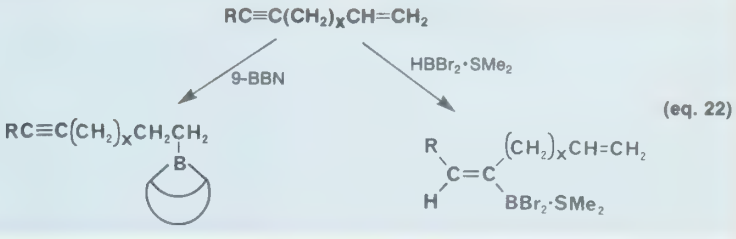
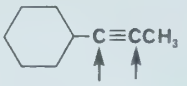
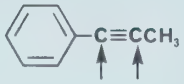


TABLE I. DIRECTIVE EFFECTS IN THE HYDROBORATION OF 1-SUBSTITUTED PROPYNES[a]

Hydroborating Reagent	$CH_3(CH_2)_2C{\equiv}CCH_3$		$(CH_3)_2CHC{\equiv}CCH_3$	
Diborane	40	60	25	75
Thexylborane[b]	39	61	19	81
Disiamylborane[b]	39	61	7	93
Dicyclohexylborane[b]	33	67	8	92
$HBBr_2 \cdot SMe_2$[c]	25	75	4	96
9-BBN[d]	22	78	4	96

[a] Determined by oxidation of the alkenylboranes to the carbonyls.
[b] Data from reference 8.
[c] Data from reference 24.
[d] Data from reference 13.

TABLE II. DIRECTIVE EFFECTS IN 1-CYCLOHEXYL- AND 1-PHENYL-1-PROPYNE[a]

Hydroborating Reagent				
Disiamylborane[b]	9	91	19	81
Dicyclohexylborane[b]	8	92	29	71
$HBBr_2 \cdot SMe_2$[c]	9	91	64	36
9-BBN[d]	4	96	65	35

[a,b,c,d] Same as in Table I

In 1-cyclohexyl-1-propyne, all of the reagents show a marked tendency to place boron at the least hindered position. However, the presence of the phenyl group directs both 9-BBN and $HBBr_2 \cdot SMe_2$ primarily to the position adjacent to the ring. Contrariwise, both dicyclohexylborane and disiamylborane still show a large preference to locate next to the smaller methyl group. Both 9-BBN and $HBBr_2 \cdot SMe_2$ appear to be sensitive to electronic and steric effects, and can be strongly influenced by electronic effects. On the other hand, disiamylborane and dicyclohexylborane apparently are controlled mainly by steric effects, with considerably smaller sensitivity to electronic factors.

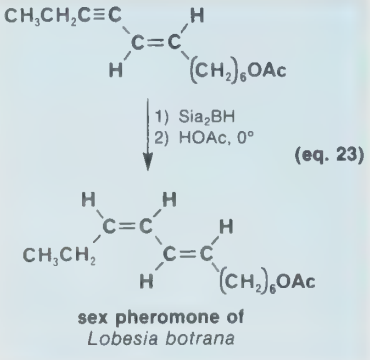
The diverse regioselectivity exhibited by the several hydroborating reagents has important implications for the regioselective transformations of alkynes. Based upon the steric and electronic environment of an alkyne, the appropriate choice of hydroborating reagent could provide a range of regiospecific hydroborations.

IV. REPRESENTATIVE APPLICATIONS OF VINYLIC BORANES

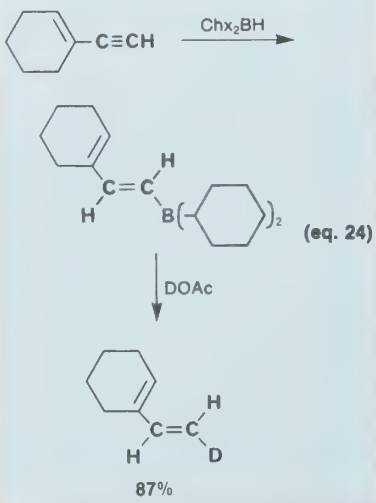
All of the resulting classes of vinylic boranes prepared by the hydroboration of alkynes have demonstrated considerable utility in organic synthesis.[2] Many of the reactions are, in fact, extensions of known alkylborane chemistry. However, the vinylic boranes also exhibit their own unique characteristics in many cases. Moreover, since the hydroboration of an alkyne produces the *trans*-alkenylborane solely, the stereodefined nature of many of the subsequent reactions often permits the precise prediction of the stereochemistry of the product. Representative transformations of vinylic organoboranes are reviewed below.

A. Protonolysis

Addition of acetic acid to an alkenylborane results in mild protonolysis of the boron-carbon bond to yield the corresponding alkenes.[3] The reaction proceeds stereospecifically with retention of configuration[25] (eq. 23). Thus, hydroboration-

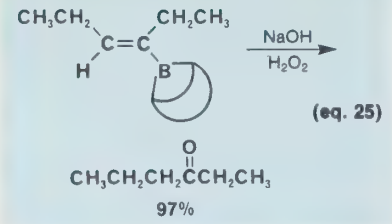


protonolysis of an alkyne provides a noncatalytic hydrogenation of triple to double bonds. In the case of internal alkynes, this procedure provides a valuable route to the pure *cis*-alkenes. The mildness and selectivity allow the presence of many functional groups and ready adaptability to the synthesis of many natural products. Deuterioacetic acid provides a simple, stereospecific preparation of deuterated olefins[8] (eq. 24).

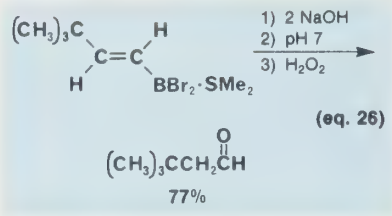


B. Oxidation

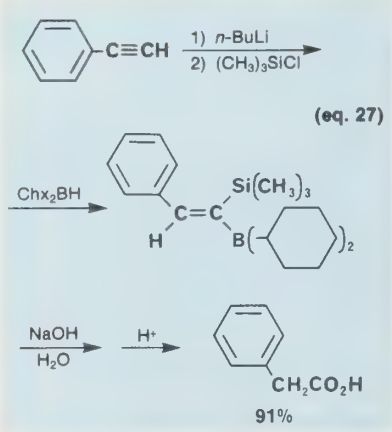
Oxidation of alkenylboranes can be easily achieved with alkaline hydrogen peroxide to produce the corresponding carbonyl compounds[3,13] (eq. 25). For oxidation of 1-



alkenylboranes, the addition of a pH 7 buffer is desirable to minimize base-promoted condensations of the resulting aldehydes[3,24] (eq. 26). Hydroboration of 1-



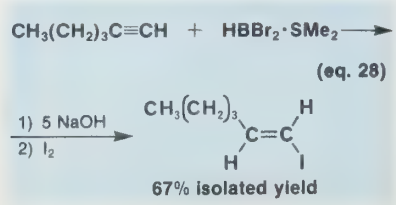
trimethylsilylacetylenes, followed by oxidation, provides a method of converting 1-alkynes to the corresponding carboxylic acids[26] (eq. 27). The 1-trimethylsilylacetyl-



enes may be prepared and used directly *in situ* to prepare the carboxylic acids.

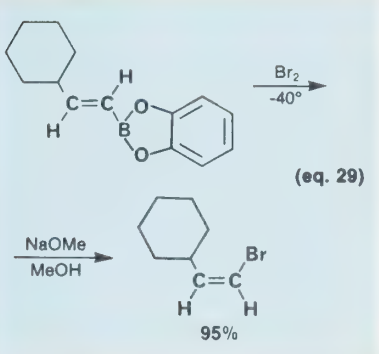
C. Halogenation

A variety of stereochemically pure alkenyl halides may be prepared from alkenylborane precursors. Iodination of an alkenylboronic acid in the presence of base gives excellent yields of the *trans*-1-alkenyl iodide.[27a] Use of $HBBr_2 \cdot SMe_2$ permits a simple one-pot conversion of 1-alkynes to stereodefined alkenyl iodides without isolation of any intermediates[24] (eq. 28).



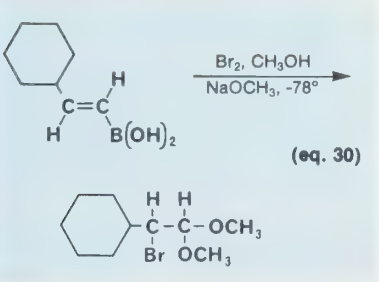
The corresponding *cis*-alkenyl iodide may be prepared by first treating the alkenylboronic acid with excess iodine, allowing sufficient time to form the diiodo derivative, followed by the addition of base.[27b]

The faster addition of bromine to the double bond makes the preparation of *cis*-1-bromoalkenes easier by a process involving the reaction of bromine with the alkenylcatecholborane, followed by addition of sodium methoxide[28] (eq. 29).



(eq. 29)

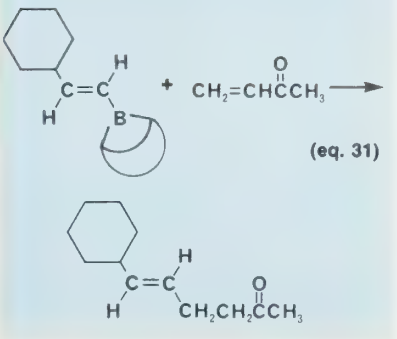
The reaction of such alkenylboronic acids with bromine in methanol at -78°, in the presence of sodium methoxide, provides a convenient synthesis of α-bromo acetals[29] (eq. 30).



(eq. 30)

D. Conjugate Addition

B-Alkenyl-9-BBN derivatives undergo 1,4-addition of the alkenyl group to acyclic enones, yielding γ,δ-unsaturated ketones[30] (eq. 31). The addition occurs with strict

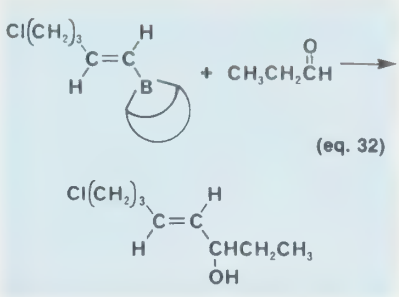


(eq. 31)

retention of configuration in the initial vinylic borane. The reaction evidently proceeds through a cyclic transition state, so that transoid enones, such as 2-cyclohexenone, cannot be utilized. On the other hand, cisoid enones, including very sensitive and easily polymerized derivatives, such as methyl vinyl ketone, react without difficulty.

E. 1,2-Addition to Aldehydes

Unlike alkylboranes, *B*-alkenyl-9-BBN derivatives add across the carbonyl group of aldehydes to produce stereochemically pure allylic alcohols[31] (eq. 32). Since many

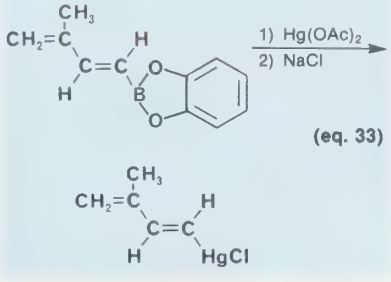


(eq. 32)

functional groups, such as ester, halogen, and nitrile, are tolerated by hydroboration, a "Grignard-like" synthesis of such allylic alcohols with reactive substituents present in the organometallics is now possible.

F. Mercuration

The mercuration of alkenylboranes provides easy access to stereochemically defined alkenylmercurials.[32] Addition of mercuric acetate to an alkenylcatecholborane results in clean formation of the alkenylmercuric compound in excellent yields[32b] (eq. 33). The resulting organo-

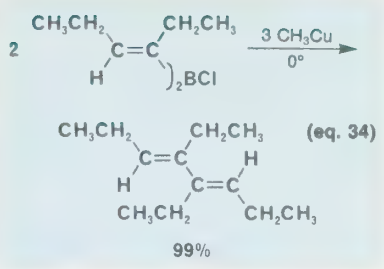


(eq. 33)

mercurials have since been shown to be exceptionally useful synthetic reagents, undergoing a variety of carbon-carbon bond-forming reactions.[33]

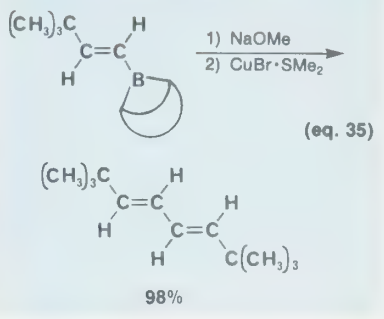
G. Transmetallation to Copper

Recently, dialkenylchloroboranes were reported to undergo methylcopper-induced coupling to give *trans,trans*-1,3-dienes in excellent yields and high stereochemical purity[34] (eq. 34). The reaction presumably involves initial formation of an alkenylcopper reagent which undergoes thermal dimerization with retention of configuration to give the 1,3-diene. An



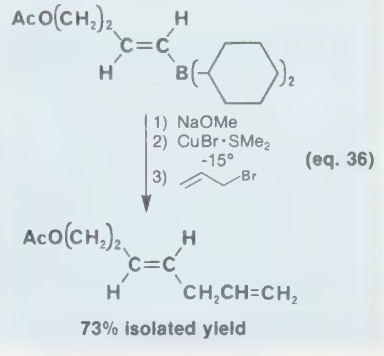
(eq. 34)

alternative procedure employing milder conditions proceeds *via* the sodium methoxide addition compound of an alkenyldialkylborane[35a] (eq. 35). The



(eq. 35)

stability of the vinylic copper intermediate should be greater at lower temperatures. Indeed, by working at -15°, the decomposition of the copper intermediate is retarded and it can be trapped by allylic halides to afford a stereochemically defined synthesis of 1,4-dienes[35b] (eq. 36).

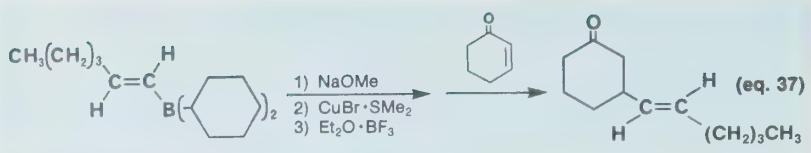


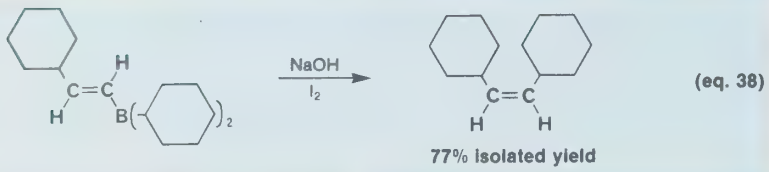
(eq. 36)

Again, the mildness of the reaction allows a wide variety of functional groups to be tolerated. Finally, conjugate addition of the copper reagent to cyclic enones can be effected,[35c] supplementing the 1,4-addition reaction of *B*-alkenyl-9-BBN derivatives (Section D) (eq. 37).

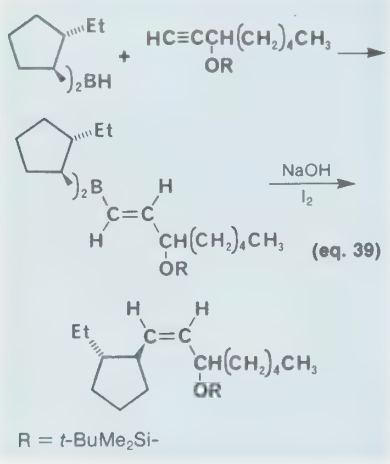
H. *cis*-Olefin Synthesis

Addition of iodine to an alkenyldialkylborane in the presence of base results in the exclusive formation of a *cis*-olefin derived from transfer of an alkyl group from boron to the adjacent carbon[36] (eq. 38). Migration of the alkyl group from boron occurs with strict retention of configuration,



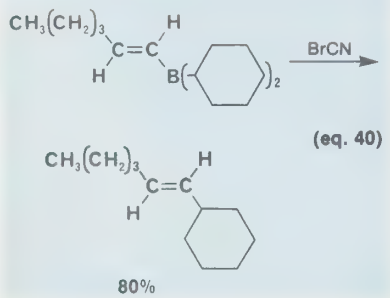


defined in the hydroboration step. Because of the known stereochemical outcome, the reaction has proven to be of value in the preparation of prostaglandin analogs[37] (eq. 39).

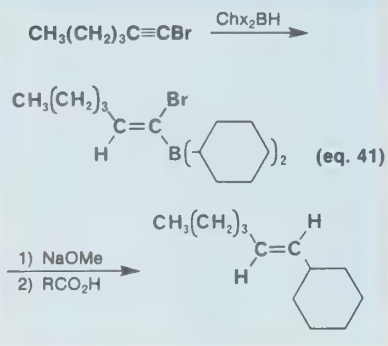


I. *trans*-Olefin Synthesis

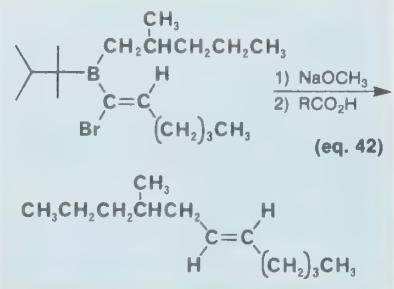
Reaction of an alkenyldialkylborane with cyanogen bromide produces the *trans*-olefin, again derived from alkyl-group transfer from boron[38] (eq. 40).



Alternatively, hydroboration of 1-halo-1-alkynes with a dialkylborane followed by treatment with sodium methoxide provides *trans*-olefins[39] (eq. 41). Unfortunately, these reactions are limited by the availability of dialkylborane hydroborating reagents. Also, only one of the two available groups on boron transfers.



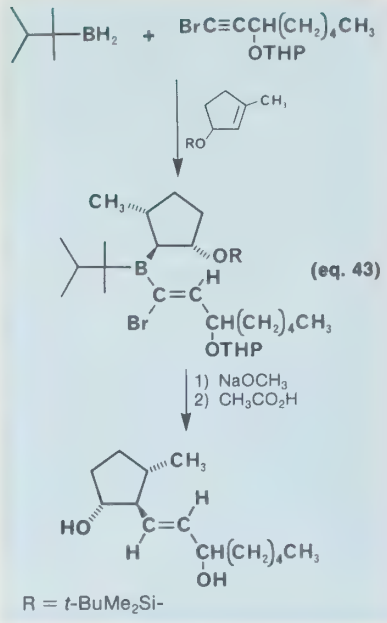
Use of the thexylmonoalkylboranes, readily synthesized from thexylborane, overcomes these difficulties, allowing the introduction of many alkyl groups. An alkyl-1-haloalkenylthexylborane[10] is perfectly set up for an alkyl group migration, and indeed, treatment with sodium methoxide, followed by protonolysis, releases the desired *trans*-olefin (eq. 42).

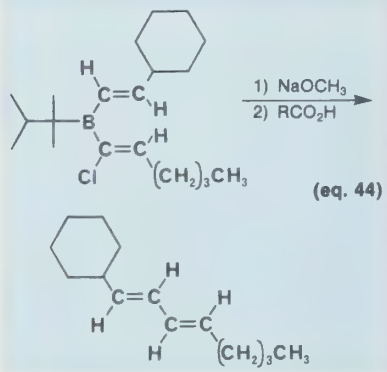


The application of such a stereodefined reaction to the synthesis of natural products is again illustrated by the preparation of a prostaglandin model[40] (eq. 43).

J. Synthesis of Conjugated *trans,trans*-Dienes

Reaction of thexylborane, first with a 1-haloalkyne followed by addition of a second alkyne, gives the mixed dialkenylthexylborane.[11] Treatment first with sodium methoxide followed by protonolysis provides the conjugated *trans,trans*-diene in good yields[11] (eq. 44). This

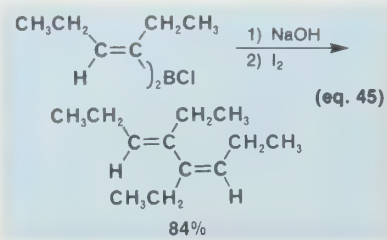




procedure also permits the synthesis of unsymmetrical *trans,trans*-dienes. An alternative preparation of symmetrical *trans,trans*-dienes has been discussed earlier (Section G).

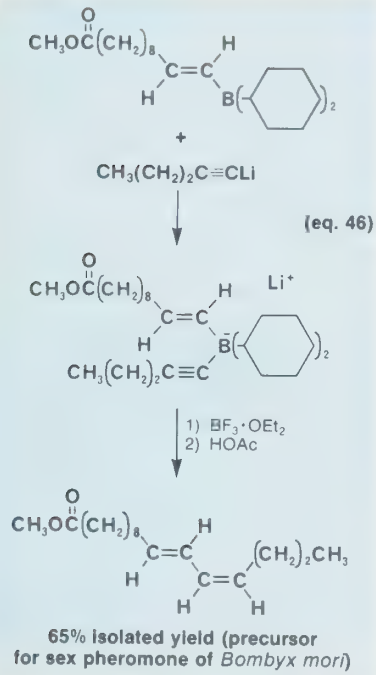
K. Synthesis of Conjugated *cis,trans*-Dienes

Preparation of symmetrical *cis,trans*-dienes may be performed by iodination of dialkenylboronic acids in the presence of base, a procedure analogous to that described for the synthesis of *cis*-olefins[41] (eq. 38). The requisite dialkenylborinic acids are most conveniently formed by basic hydrolysis of the dialkenylchloroboranes (eq. 45), readily produced by



hydroboration of alkynes with chloroborane etherate.[42] Thus, hydroboration of alkynes with $H_2BCl \cdot OEt_2$, followed by sequential treatment with base and iodine, provides a direct route to such dienes.

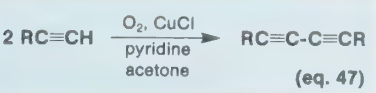
Another more general procedure for preparing *cis,trans*-dienes, which can be utilized for the synthesis of unsymmetrical derivatives, involves stepwise treatment of an alkenyldialkylborane with a lithium alkynylide, followed by boron trifluoride etherate[43] (eq. 46). Protonolysis of the intermediate releases the isomerically pure unsymmetrical *cis,trans*-diene in good yield.



(eq. 46)

L. Synthesis of Conjugated *cis,cis*-Dienes

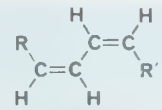
The oxidative coupling of 1-alkynes in the presence of copper salts provides a convenient route to the symmetrical conjugated diynes[44] (eq. 47). Hydroboration-protonolysis of such diynes makes readily available the symmetrical conjugated *cis,cis*-dienes[45] (eq. 48).



(eq. 47)

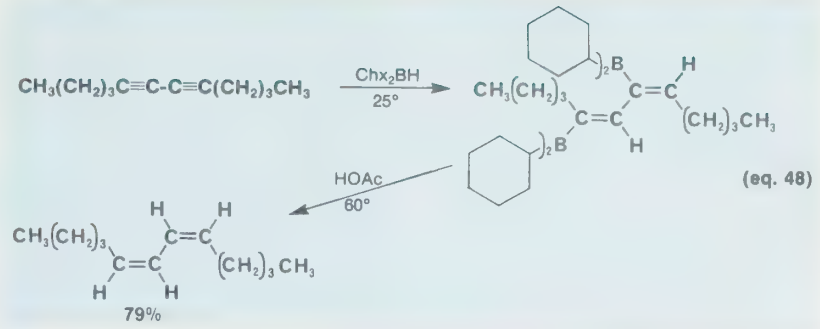
Borane chemistry now provides two synthetic routes to the synthesis of unsymmetrical conjugated diynes, one proceeding through dicyclohexylmethylthioborane[46] and the other proceeding through disiamylmethoxyborane.[47] The latter will be illustrated here (eq. 49), although both appear equally satisfactory.

Hydroboration-protonolysis of this unsymmetrical conjugated diyne by the Zweifel-Polston procedure[45] should provide the corresponding conjugated *cis,cis*-diene.

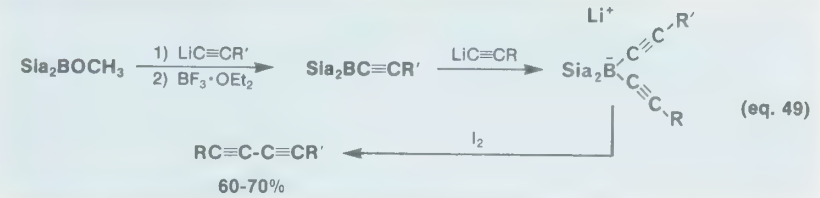


M. 1,1-Dibora Compounds

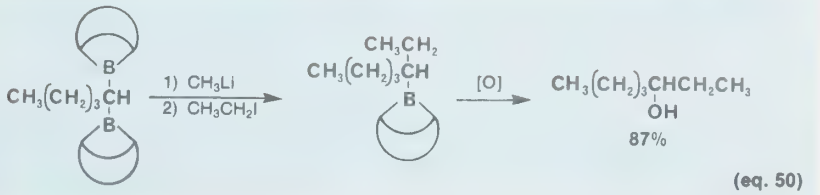
The often troublesome 1,1-dibora compounds accompanying the hydroboration of alkynes have themselves, in fact, revealed some interesting synthetic potential. Treatment of a 1,1-diboraalkane with one equivalent of CH_3Li,[48] followed by excess of an alkyl halide, gives a substituted secondary alcohol upon oxidation[14] (eq. 50). Additions of the organometallic reagent derived from 1,1-diboraalkanes and methyllithium to carbonyl compounds give a "Wittig-like" olefination[49] (eq. 51).



(eq. 48)



(eq. 49)

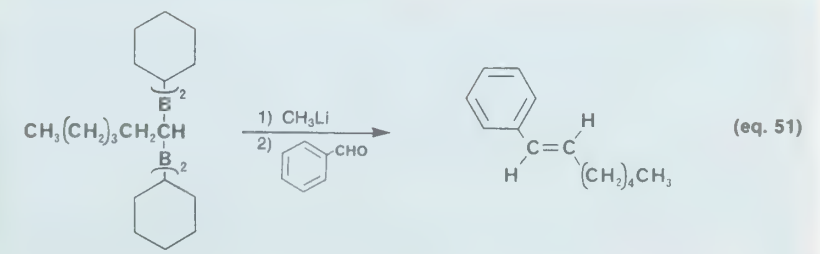


(eq. 50)

V. CONCLUSION

The controlled monohydroboration of both internal and terminal alkynes provides a stereospecific synthesis of vinylic organoboranes. In some cases the reaction can be directed to the formation of 1,1-diboraalkanes. Highly selective and regiochemically distinct transformations of alkynes are possible depending upon the proper choice of hydroborating reagent. The alkenylboranes thus produced can undergo a variety of stereoselective reactions with defined stereochemical results.

Undoubtedly, the chemistries of alkenylboranes and 1,1-diboraalkanes are still in their infancy, awaiting further exploitation of the remarkably versatile derivatives made available by the hydroboration of acetylenes. Further development of novel hydroborating reagents and of convenient synthetic routes to the *cis*-vinylic organo-



(eq. 51)

boranes will greatly expand the horizons, allowing many more selective transformations of acetylenes.

VI. ACKNOWLEDGEMENT

The support of the National Science Foundation (Grants CHE 76-20846 and CHE 79-18881) is gratefully acknowledged.

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Aldrich offers the following borane reagents cited by Prof. Brown and Dr. Campbell:

17,871-3	9-BBN, dimer, crystalline
19,385-2	9-BBN, 0.5*M* in hexane
15,107-6	9-BBN, 0.5*M* in THF
17,982-5	Borane-methyl sulfide complex
17,619-2	Borane-tetrahydrofuran complex, 1*M* in THF
20,220-7	Boron tribromide
21,123-0	Boron tribromide, 1*M* in hexane
21,122-2	Boron tribromide, 1*M* in methylene chloride
21,124-9	Boron trichloride, 1*M* in hexane
17,893-4	Boron trichloride, 1*M* in methylene chloride
21,660-7	Boron trifluoride etherate
18,891-3	Catecholborane
22,078-7	Disiamylborane preparation kit (0.1 mole of 0.5*M* disiamylborane in THF)
22,079-5	Thexylborane preparation kit (0.1 mole of 0.5*M* thexylborane in THF)

Chemical Reactions of Newly Available Pyridines

Helmut Beschke
Degussa

INTRODUCTION

During the last few decades pyridine derivatives have become steadily more important in the fields of medicinal and herbicide chemistry. The structures of the pyridine derivatives on the market are as varied as their fields of application. A few structural derivatives of importance are: quaternary, dimeric, halogenated, and vinyl compounds, as well as carbinols, ketones, mercaptans, carboxylic acids, and polycyclics. Research and development teams are seeking new variants steadily and often the feasibility of an economic synthesis of an intermediate determines the commercial viability of the end product.

In this connection a new method of synthesis of substituted pyridines is of interest.[1] Substituted aldehydes or ketones are reacted with acrolein or formaldehyde and ammonia in heterocatalytic gas-phase reactions to yield products which, until now, could be made only by multi-step syntheses. Many of these newly available pyridine derivatives are offered by Aldrich (Scheme 1). To show the many possibilities offered by these 12 selected compounds, we have summarized their reactions in this essay.

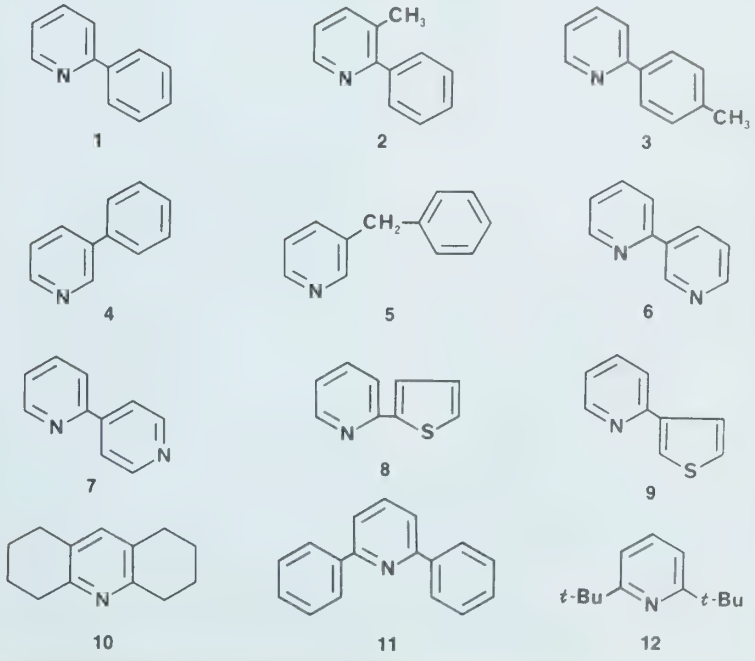
CHEMICAL TRANSFORMATIONS OF PYRIDINES

Among the newly offered compounds are five aryl pyridines, two bipyridines, two thienylpyridines and three symmetrically substituted pyridines. The known reactions of these products will be enumerated in the same order. In each case, the first reaction determined the order of the ensuing conversions.

CHEMICAL TRANSFORMATIONS OF ARYLPYRIDINES 1 - 5

2-Phenylpyridine (1) has been the starting material in a great many reactions (Scheme 2). Quaternization with chloro-

Scheme 1
Pyridine Derivatives



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acetaldoxime leads to oxime **13** (X = NOH, R = H) which is transformed with HBr and perchloric acid into benzo[*a*]quinolizinium perchlorate **(14)**.[2] Analogously, reaction with methyl δ-bromolevulinate yields ketoester **13** (X = O, R = $CH_2CH_2COOCH_3$) and from that, the corresponding substituted compound **14**.[3]

N-Oxidation of 2-phenylpyridine yields the N-oxide **15** from which one obtains the *m*-nitrophenyl derivative **16**, and by reduction, 2-(*m*-nitrophenyl)pyridine **(17)**.[4-6]

Hydrogenation with nickel yields 2-phenylpiperidine **(18)**,[7] and with platinum, 2-cyclohexylpiperidine (**19**, R = H).[8] 2-Cyclohexylpiperidine has been used for the preparation of various antiinflammatories (**19**, R as shown).[9-11]

Amination of 2-phenylpyridine, employing Tschitschibabin reaction with sodium amide, leads to 2-amino-6-phenylpyridine (**20**, X = NH_2) from which one obtains, in the usual manner, 2-bromo-6-phenylpyridine (**20**, X = Br), the 2-cyano derivative as well as 6-phenylpyridine-2-carboxylic acid.[12-14]

Reaction with *p*-methoxyphenyllithium yields the diphenyl derivative **21** which can be hydrogenated with sodium in ethanol to a *cis*/*trans* mixture of piperidine **22**. Both isomers can be converted to the *N*-nitroso compound **23**; the *cis* isomer is then reduced to the hydrazine derivative **24** and converted with mercuric oxide to a mixture of the conjugated olefins **25** and **26**.[15]

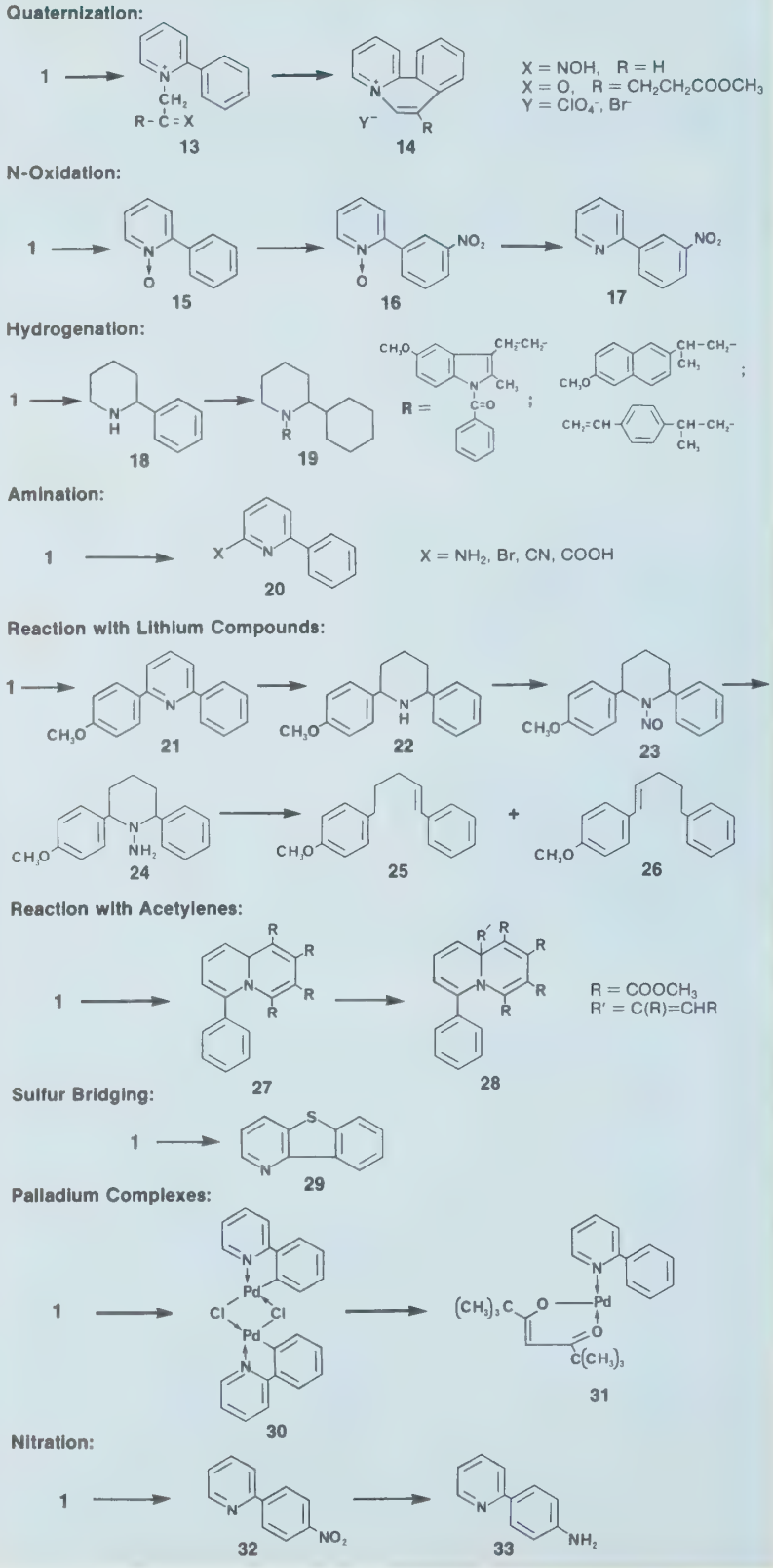
Addition of dimethyl acetylenedicarboxylate to 2-phenylpyridine yields the quinolizine derivative **27** and, after further reaction with the acetylene derivative, compound **28**.[16]

Reaction of 2-phenylpyridine with hydrogen sulfide/alumina at 630°C yields the ring-closed product, thienopyridine **(29)**.[17]

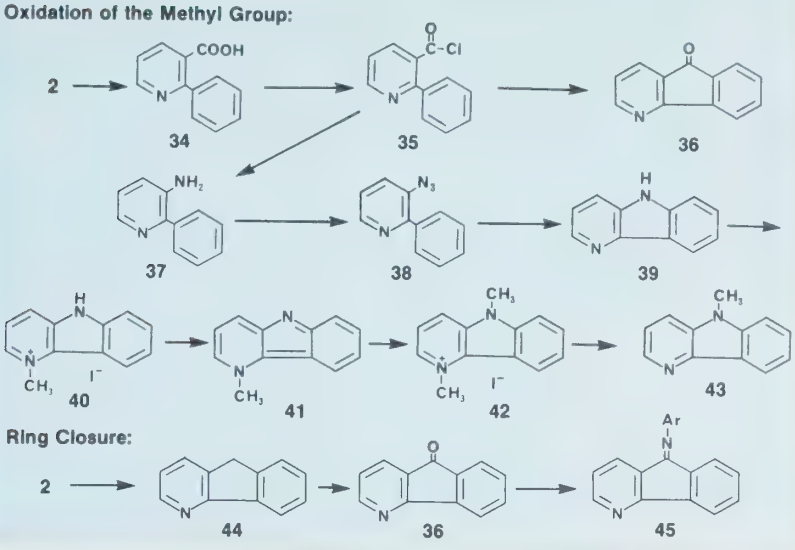
Palladium complexes are obtained by reaction with $PdCl_2$. Thus was formed the dimeric 2-(2-pyridyl)phenylpalladium(II) chloride **(30)** which, upon treatment with 2,2,6,6-tetramethyl-3,5-heptanedione, yielded 2,2,6,6-tetramethyl-3,5-heptanedionato-2-(2-pyridyl)phenylpalladium(II) **(31)**. These complexes are useful in the production of palladium coatings on glass or ceramics.[18]

The only reaction which has been described that involves the benzene ring is nitration. In contrast to the nitration of N-oxide **15** in which the main product is the *m*-nitro derivative **16**, nitration of 2-phenylpyridine results in substantial quantities of 2-(*p*-nitrophenyl)pyridine **(32)** as well as the *m*-derivative **17**.[4]

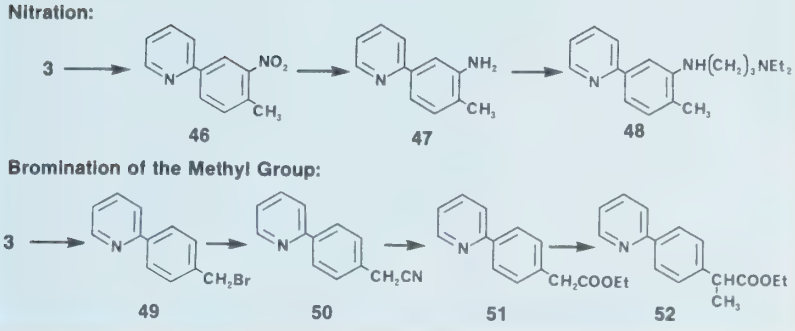
Scheme 2
Reactions of 2-Phenylpyridine (1)



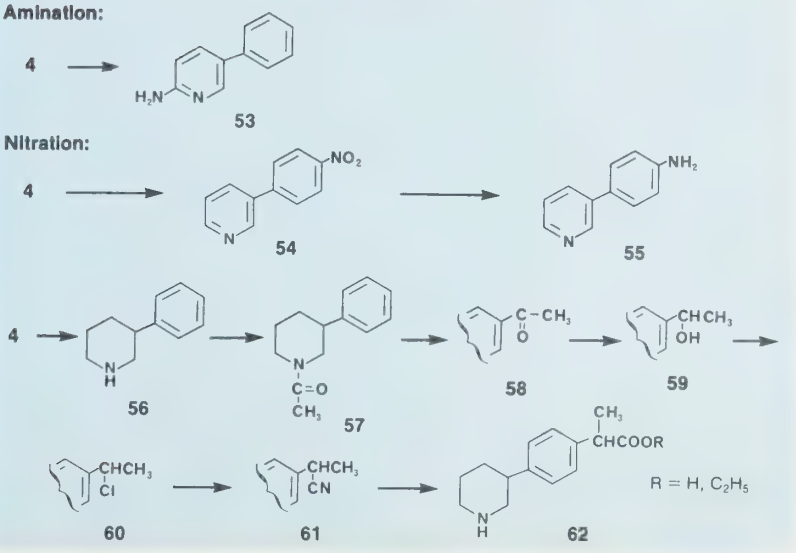
Scheme 3
Reactions of 3-Methyl-2-phenylpyridine (2)



Scheme 4
Reactions of 2-(*p*-Tolyl)pyridine (3)



Scheme 5
Reactions of 3-Phenylpyridine (4)



3-Methyl-2-phenylpyridine (2) has been used to make the polycyclics 4-azafluorene and δ-carboline (Scheme 3).

Oxidation affords carboxylic acid **34** which leads to 4-azafluorenone **(36)** *via* the acid chloride **35**.[19] Curtius degradation through the azide converts **35** to 3-amino-2-phenylpyridine **(37)**, from which one obtains the δ-carboline **39** *via* 3-azido-2-phenylpyridine **(38)**. The quaternary salt **40**, the anhydro base **41**, the quaternary dimethyl derivative **42** and *N*-methylcarboline **(43)** have been described.[20]

With a catalyst, direct ring closure of **2** to 4-azafluorene **(44)** can be effected. Oxidation yields 4-azafluorenone **(36)**, which reacts with aniline to yield the imine **45**.[21]

With **2-(*p*-tolyl)pyridine (3)** only reactions with the phenyl moiety have been described (Scheme 4).

Nitration of **3** yields the *m*-nitro compound **46**, which has been converted to the 3-diethylaminopropylamino derivative **48** *via* the amine **47**.[22] These compounds were made in a search for new antimalarials.

The bromo derivative **49**, obtained by bromination of the methyl group, can be converted to the nitrile **50** and the esters **51** and **52**. The ester **52** possesses analgesic and antiinflammatory properties.[23]

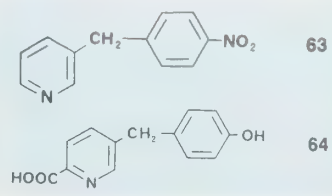
3-Phenylpyridine (4) (Scheme 5) has been described as an antimicrobial,[24] as well as an anti-corrosion agent for steel, zinc and aluminum.[25]

Amination of **4** using the Tschitschibabin reaction yields 2-amino-5-phenylpyridine **(53)**.[26]

Nitration yields the *p*-nitrophenyl derivative **54** which upon hydrogenation affords 3-(*p*-aminophenyl)pyridine **(55)**.[27]

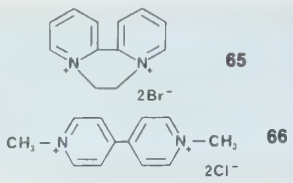
Hydrogenation of **4** yields 3-phenylpiperidine **(56)**, from which the acetyl derivative **57**, and thence the diacetyl compound **58**, the carbinol **59**, the chloride **60**, the cyanide **61** and the anti-inflammatory α-[*p*-(3-piperidyl)phenyl]propionic acid **(62)** and its ethyl ester were prepared.[28]

3-Benzylpyridine (5) has been nitrated to the *p*-nitro derivative **63**.[29] Further transformations have not been described. It should be noted that 3-benzylpyridine is structurally related to the anti-hypertensive phenopicolinic acid **(64)**.[30]



REACTIONS OF BIPYRIDINES 6 AND 7

Thus far, only two of the six bipyridines, namely 2,2′-bipyridine and 4,4′-bipyridine, have found technical applications. From these two, the herbicides Diquat (**65**) and Paraquat (**66**) have been made on a large scale.[31]



2,3′-Bipyridine and 2,4′-bipyridine, inaccessible up to now, can be made by our new pyridine synthesis.

2,3′-Bipyridine (6) (Scheme 6) can be quaternized preferentially in the pyridine ring which is substituted in the 3-position. With methyl bromide the quaternary bipyridine **67** is obtained, which has been hydrogenated to the piperidine **68**.[32]

N-Oxidation with peracetic acid yields the di-N-oxide **69**, from which the nitro dioxide **70**, the ethoxy dioxide **71** (by exchange), and the ethoxybipyridine **72** (by reduction with phosphorus trichloride) have been made.[33] The dioxide **69** can be converted to the bromobipyridine **78**.[34] With hydrochloric acid the nitro dioxide **70** can be converted to the chloro dioxide **73** from which 4-chloro-2,3′-bipyridine (**74**) can be obtained by reduction with phosphorus trichloride. This can be converted to the quaternary product **75**.[35]

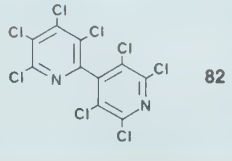
Amination of 2,3′-bipyridine yields a mixture of **76** and **77**.[36]

Bromination yields 5′-bromo-2,3′-bipyridine (**78**) which can be hydrolyzed with potassium hydroxide under pressure to the hydroxybipyridine **79**.[37]

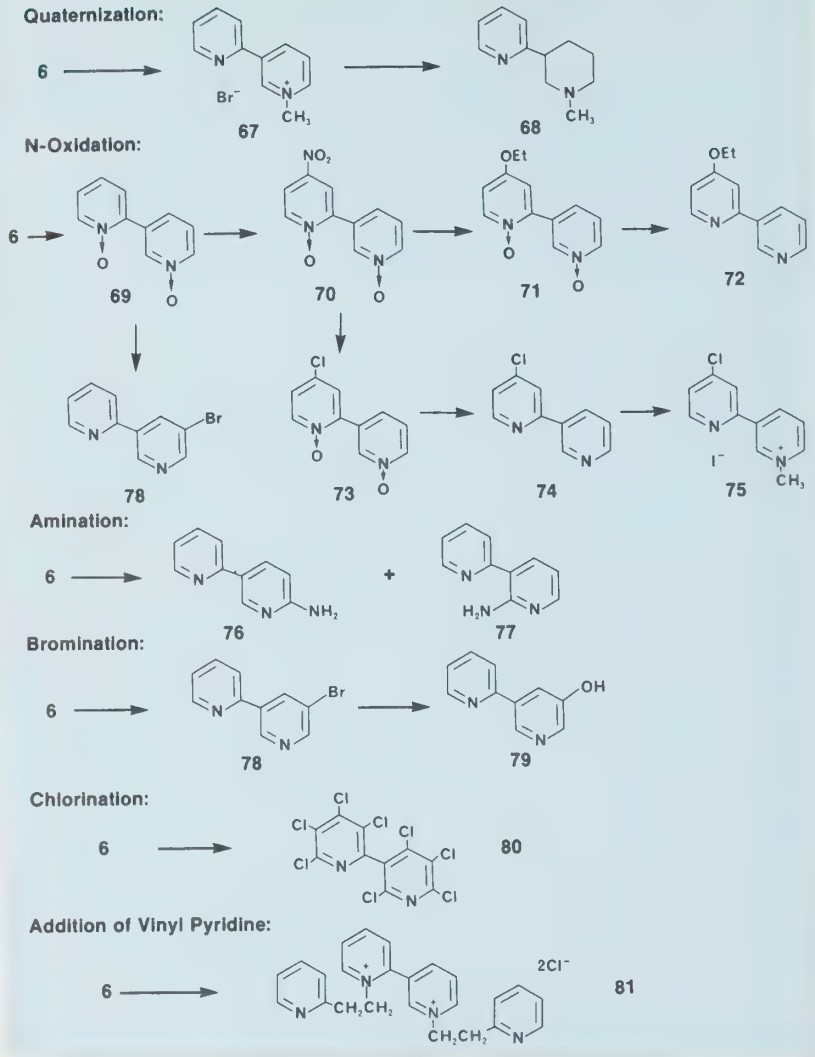
Chlorination in the gas phase yields the herbicide octachloro-2,3′-bipyridine (**80**).[38]

Addition of 2-vinylpyridine to 2,3′-bipyridine dihydrochloride yields the diquaternary chloride **81** which has been reported to have fungicidal, insecticidal, herbicidal and germicidal activity; it is also a corrosion inhibitor.[39]

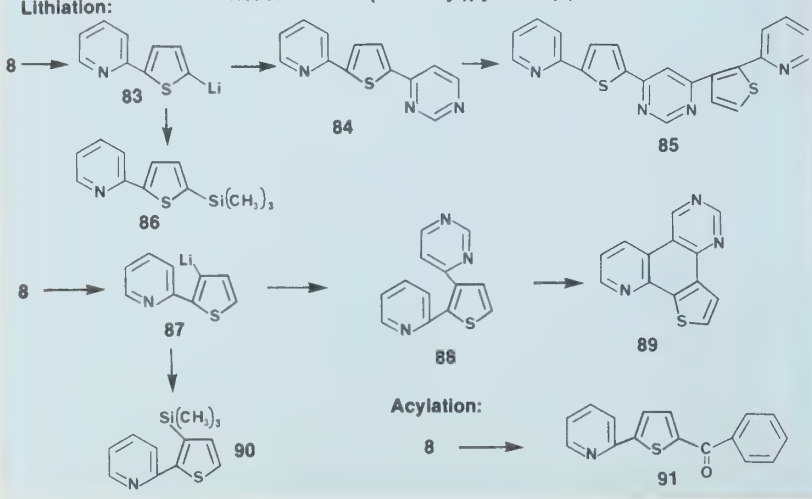
2,4′-Bipyridine (7) can be chlorinated to octachloro-2,4′-bipyridine (**82**).[38]



Scheme 6
Reactions of 2,3′-Bipyridine (6)



Scheme 7
Reactions of 2-(2-Thienyl)pyridine (8)



CHEMICAL REACTIONS OF THIENYLPYRIDINES 8 AND 9

Because of the reactivity of the thiophene ring, interesting polyheterocyclics have been made from thienylpyridines.

2-(2-Thienyl)pyridine (8) (Scheme 7), on treatment with butyllithium, yields preferentially either the lithium derivative **83** or **87** depending on the solvent. With chlorotrimethylsilane either **86** or **90** is obtained. Reaction with pyrimidine affords either the triheterocyclic **84** or **88**.[40] The 2-isomer **84** can react with the lithium derivative **87** to yield the pentaheterocyclic **85**. Irradiation of **88** leads to the interesting thieno[3,2-*e*]pyrido[2,3-*g*]quinazoline **(89)**.[41]

Acylation of 2-(2-thienyl)pyridine with benzoyl chloride yields the benzoyl derivative **91**.[42]

Heavy metal complexes of 2-(2-thienyl)-pyridine with Ni^{++}, Cu^{++} and Zn^{++} have been described.[43-45]

2-(3-Thienyl)pyridine (9) (Scheme 8) reacts with butyllithium to form the lithium derivative **92** which has been converted with pyrimidine to the triheterocyclic **93**, and to thieno[2,3-*e*]pyrido[2,3-*g*]quinazoline **(94)** by irradiation. The tetraheterocyclic **95** was made from **92** by treatment with $CuCl_2$.[41]

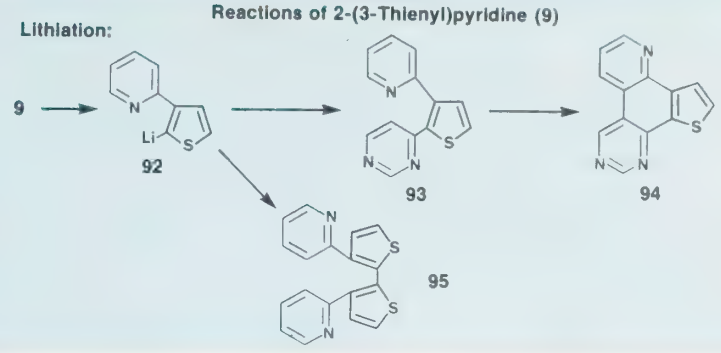
REACTIONS OF SYMMETRICALLY SUBSTITUTED PYRIDINES 10 - 12

1,2,3,4,5,6,7,8-Octahydroacridine (10) (Scheme 9) can be hydrogenated with nickel to perhydroacridine **(96)**, the configuration of which has not been determined.[46] Reduction with sodium in ethanol gives *trans-syn-trans*-perhydroacridine **(96a)** in high yield.[47,48] Electrochemical reduction yields a mixture of products with stereoselectivity dependent on the cathode potential.[49]

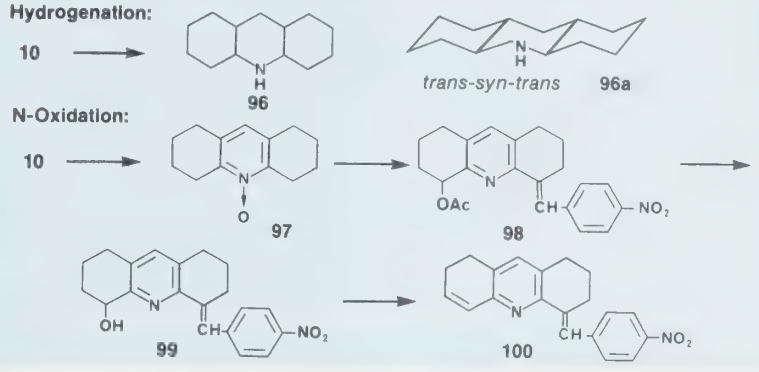
N-Oxidation of **10** yields the N-oxide **97** which has been converted and rearranged with *p*-nitrobenzaldehyde and acetic anhydride to the benzylidene acetic ester **98**. Acid hydrolysis yields the carbinol **99**, and dehydration with polyphosphoric acid yields the vinyl derivative **100**.[50]

2,6-Diphenylpyridine (11) (Scheme 10) can be reduced with sodium in ethanol to a mixture of *cis*- and *trans*-2,6-diphenylpiperidine **(101)** which, because of differences in their physical properties, can be separated then converted to the *cis*- and *trans*-nitrosopiperidines **(102)** and to the *cis*- and *trans*-hydrazines **(103)**. Oxidative degradation of these hydrazines leads to a mixture of *cis*- and *trans*-1,2-diphenylcyclopropane and 1,5-diphenyl-1-pentene respectively.[51]

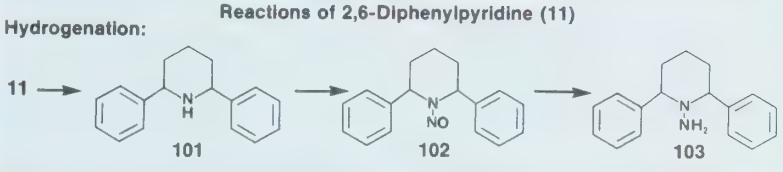
Scheme 8
Reactions of 2-(3-Thienyl)pyridine (9)



Scheme 9
Reactions of 1,2,3,4,5,6,7,8-Octahydroacridine (10)



Scheme 10
Reactions of 2,6-Diphenylpyridine (11)

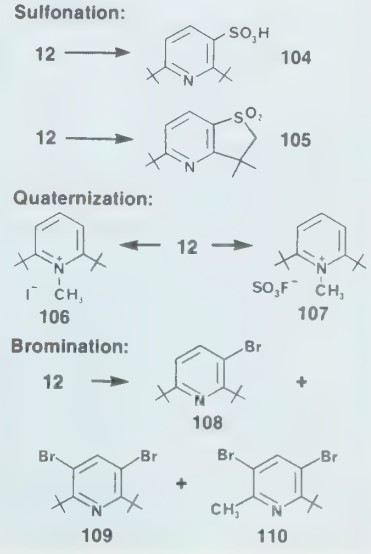


2,6-Diphenylpyridine acts as a catalyst in the side-chain chlorination of ring-chlorinated toluenes.[52]

2,6-Di-*t*-butylpyridine (12) (Scheme 11) has been investigated particularly because of its extraordinary properties as a sterically hindered base. It is a weaker base than pyridine; it reacts with proton acids, but not with electrophilic compounds such as methyl iodide or boron trifluoride under the usual conditions. Also, 2,6-di-*t*-butylpyridine displays a different reactivity than most pyridines. Thus, it can be sulfonated with sulfur trioxide at low temperature to obtain 2,6-di-*t*-butylpyridine-3-sulfonic acid **(104)**,[53] while at high temperature 2,3-dihydro-3,3-dimethyl-5-*t*-butylthieno-[3,2-*b*]pyridine 1,1-dioxide **(105)** is obtained.[54]

The quaternization of **12** with methyl iodide and with methyl fluorosulfonate has been accomplished recently to yield the quaternary compounds **106** and **107**. A pressure of 5,000-6,000 bars over a period

Scheme 11
Reactions of 2,6-Di-*t*-Butylpyridine (12)



of 10-15 hours at 90° was required.[55] Reaction occurs only when the pressure is higher than 4,000 bars.[56]

Bromination of **12** with bromine and sulfuric acid yields a mixture of the bromine derivatives **108**, **109** and **110**.[57]

SUMMARY

This overview demonstrates the interesting chemistry of twelve pyridine derivatives. Since it is now possible to produce these compounds by heterocatalytic gas-phase syntheses, they have become commercially available, and this is likely to lead to much new research. The important aim of this review is to challenge the reader's imagination for new derivatives that he can make from these pyridines.

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The twelve pyridine starting materials in the reactions outlined by Mr. Beschke are available from Aldrich as follows:

P3,340-2	2-Phenylpyridine (**1**)
19,886-2	3-Methyl-2-phenylpyridine (**2**)
19,887-0	2-(*p*-Tolyl)pyridine (**3**)
20,973-2	3-Phenylpyridine (**4**)
20,974-0	3-Benzylpyridine (**5**)
19,888-9	2,3′-Dipyridyl (**6**)
19,889-7	2,4′-Dipyridyl (**7**)
19,890-0	2-(2-Thienyl)pyridine (**8**)
19,894-3	2-(3-Thienyl)pyridine (**9**)
19,891-9	1,2,3,4,5,6,7,8-Octahydroacridine (**10**)
19,892-7	2,6-Diphenylpyridine (**11**)
21,958-4	2,6-Di-*tert*-butylpyridine (**12**)

Bromotrimethylsilane and Iodotrimethylsilane — Versatile Reagents for Organic Synthesis[1]

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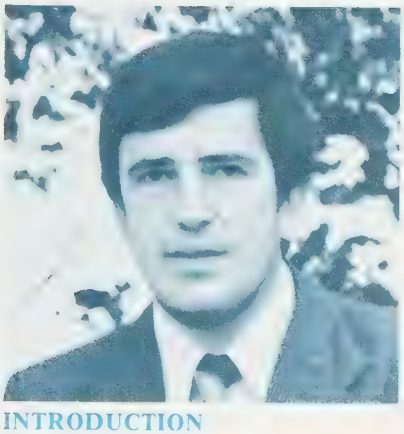


INTRODUCTION

In the mid-seventies several research groups independently started investigations on the synthetic use of bromotrimethylsilane and iodotrimethylsilane. Within a short period of time it became evident that the reactivity of both reagents differed dramatically from that of chlorotrimethylsilane and that numerous standard procedures of organic synthesis may be effected by bromo- and iodotrimethylsilane under extremely mild conditions. Furthermore, it became clear that bromo- and iodotrimethylsilane should offer a variety of novel functional group transformations. Thus, both compounds have rapidly become important reagents for the organic chemist.

PREPARATION

The methods for the generation of bromo- and iodotrimethylsilane on a preparative scale are based on the cleavage of a Si-Y bond by means of bromine or iodine, respectively, or by a halogenation reagent MX_n. Thus, bromotrimethylsilane was prepared in 73% yield by the treatment of hexamethyldisiloxane with phosphorus tribromide in the presence of a catalytic amount of ferric chloride hexahydrate (eq. 1).[2] The yield of bromotrimethylsilane was improved to 81% by using a mixture of phosphorus tribromide/bromine,[3] to 87% by the use of catechyl phosphorus tribromide,[3] and to 86% by the treatment of hexamethyldisiloxane with aluminum tribromide.[4] The following physical data[2] have been reported: clear, colorless liquid; bp 79.9°C/754 torr; d_4^{20} 1.188; air- and moisture-sensitive. Analogously, iodotrimethylsilane is prepared by treatment of hexamethyldisiloxane with aluminum triiodide, generated *in situ* from the elements (eq. 2).[5-7] According to Voronkov[5] iodotrimethylsilane is thus obtained in 93% yield as a colorless liquid; bp 107°C/760 torr; d_4^{20} 1.422;[4] 1.470.[5] The compound is extremely sensitive to light, moisture, and air.

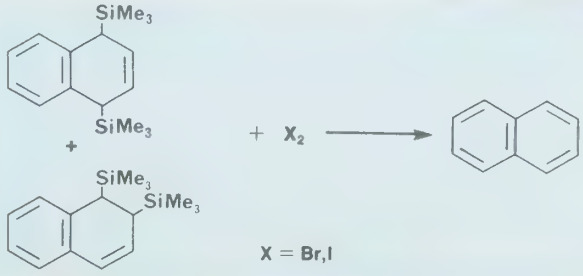
An excellent alternative procedure[8] for the preparation of bromo- and iodotrimethylsilane consists of the treatment of a mixture of 1,4-bis(trimethylsilyl)-1,4-dihydronaphthalene and the 1,2-isomer[9] with bromine and iodine, respectively (eq. 3). This preparation procedure was recently optimized by us,[10] affording bromotrimethylsilane and iodotrimethylsilane in 94% and 92% yield, respectively.

IN SITU GENERATION

Despite the ready availability of iodotrimethylsilane, routine application in organic synthesis may be difficult due to its marked instability toward hydrolysis. This has prompted several groups to devise suitable methods for the *in situ* generation of iodotrimethylsilane. Though bromotrimethylsilane is less sensitive several of these procedures have also been extended to its *in situ* preparation. Table 1 gives a summary of these methods.

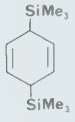
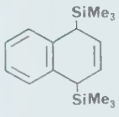
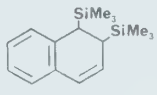
$$Me_3SiOSiMe_3 + PBr_3 \xrightarrow{FeCl_3 \cdot 6H_2O} 2\ Me_3SiBr + (POBr) \qquad \text{(eq. 1)}^2$$

$$Me_3SiOSiMe_3 + AlI_3 \longrightarrow 2\ Me_3SiI + (AlOI) \qquad \text{(eq. 2)}^{5-7}$$

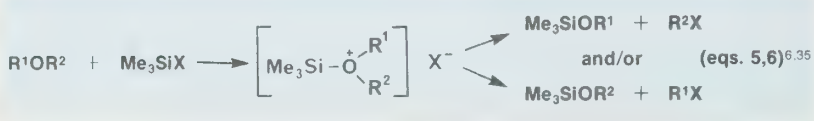


(eq. 3)[8,10]

Table 1. Methods for the *in situ* Generation of Bromotrimethylsilane and Iodotrimethylsilane

Reagents	Products	Solvent	Ref.
$2\ Me_3SiCl + MgBr_2$	$2\ Me_3SiBr + MgCl_2$	diethyl ether (as solvate)	11
$2\ Me_3SiCl + MgI_2$	$2\ Me_3SiI + MgCl_2$	xylene	11
$Me_3SiCl + NaI$	$Me_3SiI + NaCl$	a) neat or excess substrate	12,13,14
		b) CH_2Cl_2	12
		c) MeCN	12,15
$Me_3SiCl + LiI$	$Me_3SiI + LiCl$	a) CH_2Cl_2	12,14
		b) CCl_4	16
$Me_3SiCl + NaBr$	$Me_3SiBr + NaCl$	a) MeCN	17,18,19
		b) neat or excess substrate	19
$Me_3SiPh + I_2$	$Me_3SiI + PhI$	a) neat	20
		b) nitromethane	21
$Me_3SiCH_2CH{=}CH_2 + I_2$	$Me_3SiI + CH_2{=}CHCH_2I$	aprotic solvents	22
 $+ I_2$	$2\ Me_3SiI + PhH$	aprotic solvents	22
mixture of $+ 2\ X_2$	$4\ Me_3SiX$ a) X = Br; b) X = I	a) neat or excess substrate	23
 		b) MeCN	24
		c) CCl_4	25
$Me_3SiSiMe_3 + I_2$	$2\ Me_3SiI$	a) neat	26
		b) CCl_4	26,27
		c) $CHCl_3$	28
$Me_3SiSiMe_3 + Br_2$	$2Me_3SiBr$	neat or PhH	45

(eq. 4)[34]



(eqs. 5,6)[6,35]

Table 2. Cleavage of Ethers by Means of Iodotrimethylsilane

R^1	R^2	Solvent	Temp./Time	Yield[a]	Ref.
Ph	Me	neat	*ca.* 130°/21h	99%	34
2-MePh	Me	neat	*ca.* 130°/30h	97%	34
4-MePh	Me	neat	*ca.* 130°/18h	99%	34
4-BrPh	Me	neat	*ca.* 130°/36h	98%	34
Hexyl	Me	$CDCl_3$	25°/6h	95%	6
Hexyl	Et	$CDCl_3$	25°/12h	48.7%	6
Hexyl	*t*-Bu	CCl_4	25°/0.1h	100%	6
Ph	Me	$CDCl_3$	25°/48h	100%	6
4-BrPh	Me	$CDCl_3$	25°/120h	100%	6

[a]The yields refer to the trimethylsilyl ethers R^1OSiMe_3

USE IN ORGANIC SYNTHESIS

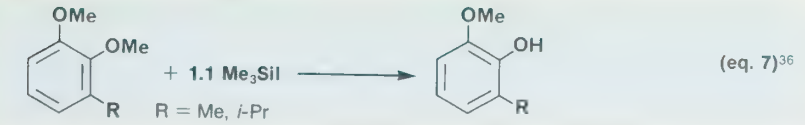
Ether Cleavage

Several early investigations have dealt with the cleavage of various ethers by means of bromo- and iodotrimethylsilane.[11,29-33] However, the great preparative value of this method and its general applicability were not clearly realized for a long time. In 1976 Voronkov[34] demonstrated that the heating of 16 differently substituted aryl methyl ethers with iodotrimethylsilane to 120-130°C for 20-50hrs afforded the corresponding aryloxytrimethylsilanes in practically quantitative yields (eq. 4). Investigations on the same topic were independently carried out by others.[6,35] The experimental results summarized by Jung indicated the possibility of cleaving ethers selectively in the presence of structurally different ethers and of other compounds with various functional groups under surprisingly mild conditions (eqs. 5 and 6, Table 2).

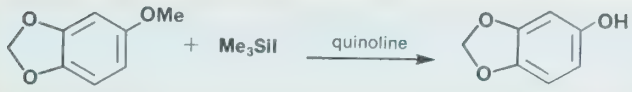
Numerous examples have been reported on the dealkylation of ethers with iodotrimethylsilane, demonstrating the tremendous preparative value of this method. Furthermore, several variations of the standard procedure have been found useful and have been proposed for the dealkylation of specific ethers. Such examples are:

The regiospecific mono-O-demethylation of substituted catechol methyl ethers (eq. 7),[36] the selective O-demethylation of the methyl ether function leaving the methylenedioxy group intact as in the cases of sesamol methyl ether (eq. 8)[37] and 1,2-methylenedioxy-3-methoxybenzene (eq. 9).[37] To effect these demethylations it was necessary to use quinoline as the solvent. The methoxy group in the isoquinoline alkaloid hydrocotarnine was cleaved selectively with iodotrimethylsilane in boiling *o*-dichlorobenzene in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) affording hydrocotarnoline (eq. 10).[38] An interesting reaction sequence was observed when the demethylation of 1,4-dimethoxyphenanthrene with iodotrimethylsilane was attempted. Heating of the reactants in CCl_4 for 48hrs effected demethylation and subsequently oxidation to 1,4-phenanthroquinone (eq. 11).[39] Furthermore, iodotrimethylsilane smoothly dealkylates 2,4-dialkoxypyrimidines to give uracils in high yield (eq. 12, $R^1{=}CH_3$, $R^2{=}SO_3H$, 40-45°C in sulfolane, 15 min., quantitative yield).[40] Dealkylation of alkoxyalkynes with iodotrimethylsilane, prepared *in situ* from hexamethyldisilane and iodine, afforded trimethylsilylketenes in moderate yield (eq. 13).[26]

Removal of the urethane and the benzyl ether blocking groups from peptides is



(eq. 7)[36]

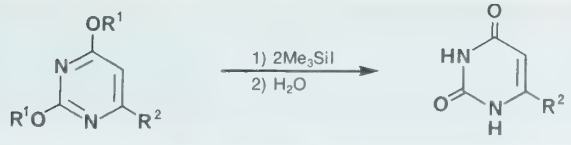


(eq. 8)[37]

(eq. 9)[37]

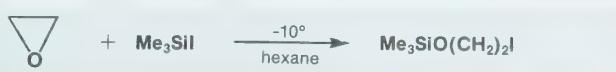
(eq. 10)[38]

(eq. 11)[39]

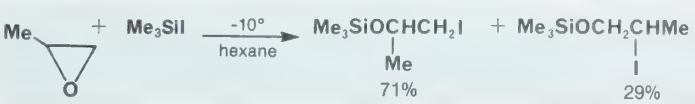


(eq. 12)[40]

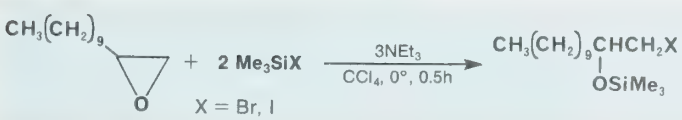
(eq. 13)[26]



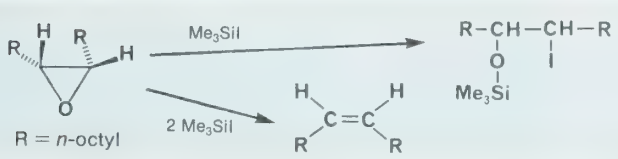
(eq. 14)[42]



(eq. 15)[42]



(eq. 16)[43]



(eq. 17)[43]

(eq. 18)[43]

(eq. 19)[44]

readily accomplished by treatment with iodotrimethylsilane. The method seems to be particularly useful for the debenzylation of *O*-benzyltyrosine peptides since no troublesome side products are formed in this reaction.[41]

Some of the results obtained so far from studies of the reactions of epoxides with bromo- and iodotrimethylsilane are shown in eqs. 14-16.[42,43]

Simple epoxide ring opening was also observed on adding an equimolar amount of iodotrimethylsilane to *cis*-9,10-oxidooctadecene (eq. 17). The reverse addition of this epoxide to a twofold equimolar amount of iodotrimethylsilane, however, effects deoxygenation and affords 9-*Z*-octadecene in 83% yield (eq. 18).[43]

The generation of allylic alcohols from epoxides by treatment with iodotrimethylsilane and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[44] or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)[45] has been reported recently (eqs. 19, 20).

Dealkylation of Acetals, Ketals and Related Compounds

Dealkylation of acetals and ketals to the corresponding carbonyl compounds is one of the most useful transformations in organic chemistry. This reaction is usually carried out under aqueous, acidic conditions. Jung's group[46] discovered that treatment of acetals and ketals with iodotrimethylsilane (CH_2Cl_2, 25°C, 15 min.) afforded the corresponding carbonyl compounds (eq. 21). It is particularly noteworthy that this transformation proceeds under extremely mild, neutral, and nonaqueous conditions and that the products are obtained in very high yield (Table 3). Surprisingly, treatment of ethylene ketals with iodotrimethylsilane results in the formation of a mixture of products (eq. 22).[46]

In the context of deacetalization and deketalization two further examples of the synthetic applicability of iodotrimethylsilane need be mentioned. Treatment of trialkyl orthoformates with an equimolar amount of iodotrimethylsilane[46] or bromotrimethylsilane[19,47] affords the corresponding alkyl formates in high yield (eq. 23). The formation of Mannich salts from the reaction of tetraalkylaminals with iodotrimethylsilane (eq. 24)[48] is of great preparative value and awaits further investigation with respect to its scope and limitations.

Various α-iodoethers and α-iodothioethers have been made easily accessible by means of iodotrimethylsilane. Thus, iodomethyl methyl ether is generated conveniently by reacting dimethoxymethane

(eq. 20)[45]

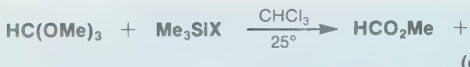
(eq. 21)[46]

Table 3. Conversion of Ketals to Ketones by Means of Iodotrimethylsilane[46]

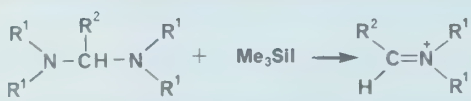
R^1	R^2	R^3	Solvent[a]	Yield[b]
- $(CH_2)_4$ -		Me	$CHCl_3$/propene	87%
- $(CH_2)_5$ -		Me	$CHCl_3$/propene	90%
C_6H_{13}	Me	Me	CH_2Cl_2	87%
C_5H_{11}	H	Me	$CHCl_3$/propene	85%
- $(CH_2)_5$ -		Et	$CHCl_3$/propene	84%

[a]Conditions: 25°C/15 min.
[b]Yields refer to isolated product

(eq. 22)[46]



(eq. 23)[19,46,47]

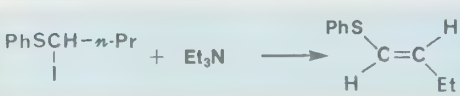


(eq. 24)[48]

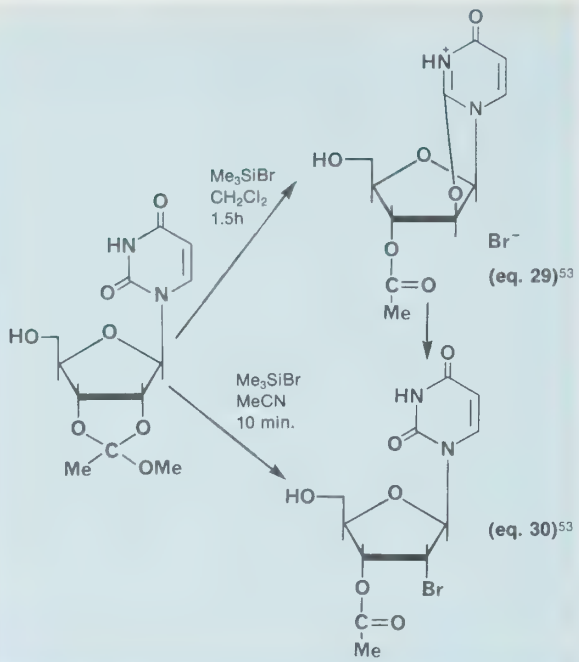
(eq. 25)[49]

(eq. 26)[50,51]

(eq. 27)[52]

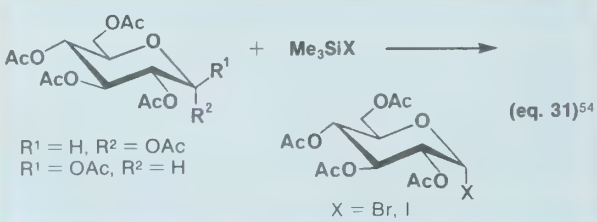


(eq. 28)[52]

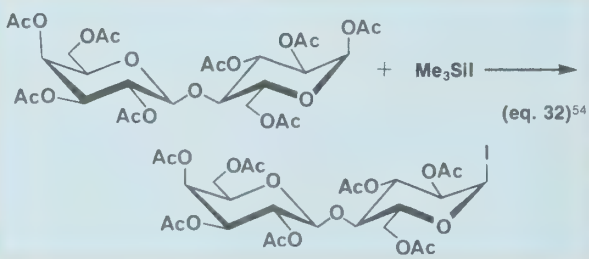


(eq. 29)[53]

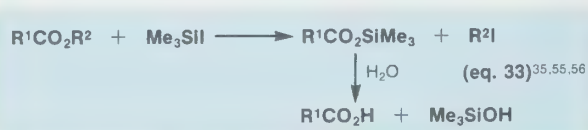
(eq. 30)[53]



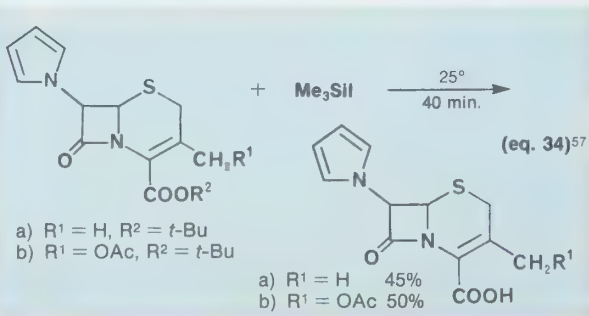
(eq. 31)[54]



(eq. 32)[54]



(eq. 33)[35,55,56]



(eq. 34)[57]

(methylal) with iodotrimethylsilane at room temperature (eq. 25).[49] This method is amenable to large-scale synthesis, and yields as high as 93% have been realized. Another important advantage of this procedure is that it does not produce the potentially carcinogenic bis(iodomethyl) ether. Iodomethyl methyl ether has been found useful for the methoxymethylation and iodomethylation of various organic substrates.

The α-iodoethers and the α-iodothioether obtained from the reaction of iodotrimethylsilane with 1,3-dioxolanes and 1,3-oxathiolane respectively (eq. 26) are highly reactive species and have been used successively for the alkylation of purines and pyrimidines.[50,51]

Other α-iodothioethers were obtained by the reaction of *O*-(trimethylsilyl)hemithioacetals with iodotrimethylsilane (eq. 27).[52] Treatment of these α-iodothioethers with an appropriate base (*e.g.*, triethylamine) provided an easy access to vinyl sulfides. In cases where geometric isomers were possible, the products with *E* geometry were obtained (eq. 28).

The first synthetic applications of bromo- and iodotrimethylsilane in the nucleoside and saccharide fields have been reported. On treatment of a (methoxyethylidene)uridine with bromotrimethylsilane, the 2,2′-anhydrouridine (eq. 29) or the 2′-bromouridine (eq. 30) is obtained, depending on the solvent and the reaction time.[53] Both compounds are useful for further modification of the nucleoside sugar moiety. Primary and secondary acetoxy-substituted saccharides react with bromo- and iodotrimethylsilane to effect exclusive formation of glycosyl iodides. Accordingly, pentaacetyl hexapyranoses afford the corresponding glycosyl halides in high yield (eq. 31).[54] In the disaccharide series, α-octaacetyllactose was treated with iodotrimethylsilane. The product was found to be α-heptaacetyllactosyl iodide; no monosaccharide formation was observed (eq. 32).[54]

Transesterification and Cleavage of Carboxylic Esters

In 1976 Olah[35,55] reported the cleavage of methyl, ethyl, and benzyl carboxylic esters by treatment with iodotrimethylsilane (100°C, 2-4 hrs) and subsequent hydrolysis of the trimethylsilyl esters (eq. 33). The yields of free carboxylic acids were found to be in the range of 55-90%. Independently, Jung[56] demonstrated that for the ester cleavage much milder conditions were sufficient. The reaction was carried out in CCl_4 or $CHCl_3$. In the case of methyl, ethyl, and isopropyl carboxylic esters, temperatures of 50°C were found to be adequate. The dealkylation of *tert*-butyl and benzyl carboxylic esters proceeded rapidly at 25°C. A survey is given in Table 4.

The preparative value of this method has been demonstrated by the dealkylation of a *tert*-butyl ester in the 7-pyrrolocephalosporin series to the corresponding acid (eq. 34a).[57] The great selectivity of this method was shown by the removal of the *tert*-butyl group leaving an acetate group intact (eq. 34b).[57]

It was found recently that ester cleavage by introduction of iodotrimethylsilane is strongly catalyzed by free iodine.[58]

Treatment of carboxylic esters with bromotrimethylsilane under similar conditions effected the desired dealkylation only in low yields.[20,47] Consistent with this, ring opening of lactones by iodotrimethylsilane is an easy process (eq. 35)[59,60] while the analogous process with bromotrimethylsilane requires drastic reaction conditions.[17,19,60]

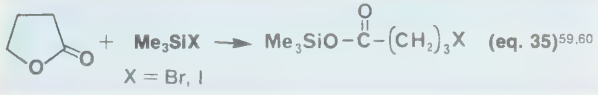
In a similar fashion, the treatment of 5-methyl-1,3-dioxolan-4-one with iodotrimethylsilane afforded a trimethylsilyl ester (eq. 36).[61] In contrast, the reaction of ethylene carbonate with bromo- or iodotrimethylsilane proceeded with decarboxylation to give the β-bromoethyl trimethylsilyl ether (eq. 37) or 1,2-diiodoethane (eq. 38).[60] Decarboxylation in connection with ester dealkylation has also been observed in the treatment of β-ketocarboxylic esters and *gem*-dicarboxylic esters such as dialkylmalonates with iodotrimethylsilane (eq. 39).[62] A new method for the construction of the α-methylene-γ-butyrolactone moiety consists of the treatment of 1-(2-dimethylaminoethyl)cyclopropanecarboxylates with iodotrimethylsilane (eq. 40).[63]

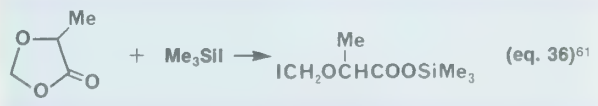
In this context the conversion of carbamates to amines by means of iodotrimethylsilane (60°C, 1-2.5 hrs) deserves special mention (eq. 41).[64] This procedure has been applied successfully in the removal of the benzyloxycarbonyl and the *tert*-butyloxycarbonyl group in N-protected peptides[28,41] as well as in the synthesis of spectroscopically pure azepine (eq. 42).[65]

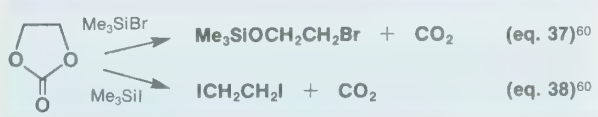
Table 4. Cleavage of Carboxylic Esters with Iodotrimethylsilane

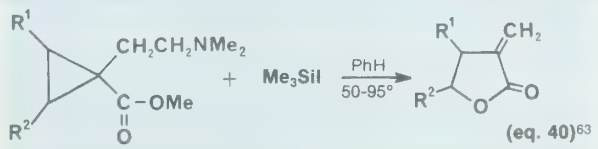
R^1	R^2	Solvent	Time/Temp.	Yield[a]	Ref.
n-Octyl	Me	CCl_4	35h/50°	85[b]	56
Ph	Me	CCl_4	6h/50°	b	56
Ph	Me	- - -	2h/100°	80[c]	35
2-BrPh	Me	- - -	2h/100°	81[c]	35
Ph	Et	CCl_4	48h/50°	b	56
Ph	Et	- - -	4h/100°	72[c]	35
Me	*i*-Pr	CCl_4	10.5h/50°	b	56
Me	*t*-Bu	CCl_4	1/6h/25°	b	56
Ph	*t*-Bu	CCl_4	0.5h/25°	90[b]	56
Ph	Bz	CCl_4	1.5h/25°	b	56
Ph	Bz	- - -	2h/100°	86[c]	35
c-Hexyl	Bz	- - -	2h/100°	85[c]	35

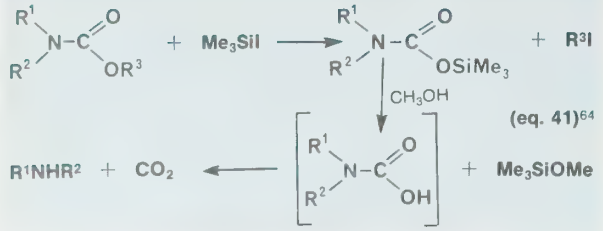
[a]The numbers refer to yields of isolated product.
[b]Product: trimethylsilyl ester of the carboxylic acid. Yields determined by ^1H NMR are *ca.* 100%.
[c]Product: carboxylic acid.



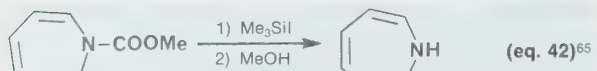




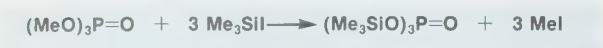




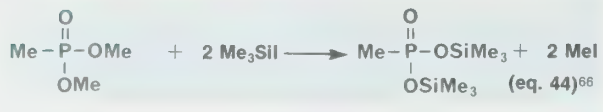
(eq. 41)[64]



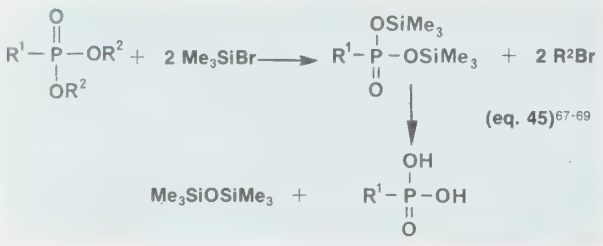
(eq. 42)[65]



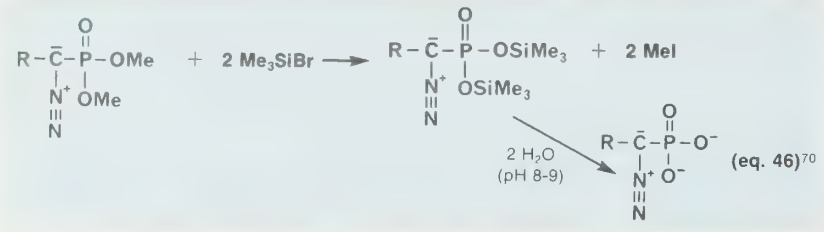
(eq. 43)[66]



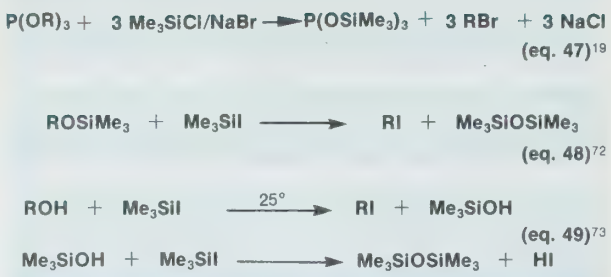
(eq. 44)[66]



(eq. 45)[67-69]



(eq. 46)[70]



(eq. 47)[19]

(eq. 48)[72]

(eq. 49)[73]

Table 5. Conversion of Alcohols to Alkyl Iodides and Alkyl Bromides by Means of Iodo- and Bromotrimethylsilane

R	Time/Temp.	Alkyl Iodide	Alkyl Bromide	Ref.
Me	0.5h/25°	100%[a]		73
	19h/25°		95%[a]	47
Et	5h/25°	99%[a]		73
	307h/25°		100%[a]	47
i-Pr	24h/25°	96%[a]		73
	46h/50°		100%[a]	47
t-Bu	0.2h/25°	100%[a]		73
	<1/6h/25°		100%[a]	47
Bz	24h/25°	85%[b]		73
	<1/6h/25°		95%[b]	47
c-Hexyl	24h/25°	81%[b]		73
	14h/50°		90%[b]	47

[a]Yields were determined by ^{1}H NMR.
[b]Yields refer to isolated product.

Transesterification and Ester Cleavage of Trialkyl Phosphates, Phosphonic Acid Dialkyl Esters, and Trialkyl Phosphites

One of the most valuable applications of bromo- and iodotrimethylsilane is the mild and selective dealkylation of trialkyl phosphates and dialkyl phosphonates. On addition of iodotrimethylsilane to a solution of trimethyl phosphate or dimethyl methylphosphonate Schmidbaur[66] obtained, after 1hr at 25°C, a 98% yield of tris(trimethylsilyl) phosphate (eq. 43) and bis(trimethylsilyl) methylphosphonate (eq. 44), respectively. Only a little later the groups of Rudinskas[67] and Mc Kenna[68] reported the dealkylation of dialkyl phosphonates by means of bromotrimethylsilane and were the first to clearly recognize the synthetic potential of this deesterification procedure. The general applicability of the method has been demonstrated, in the meantime, using a large number of phosphonic esters (eq. 45).[69]

Two interesting applications of this procedure have been reported: the synthesis of α-diazophosphonic acids[70] (eq. 46) and the synthesis of enol phosphates.[71]

The treatment of trialkyl phosphites with chlorotrimethylsilane/NaBr afforded tris(trimethylsilyl) phosphite in 67% yield (eq. 47).[19]

Synthesis of Alkyl Bromides and Alkyl Iodides

In the early experiments on the reaction of ethers with bromo- and iodotrimethylsilane, alkyl halides were usually obtained as side or main products. These results suggested the formation of trimethylsilyl ethers as intermediates, which reacted with more halotrimethylsilane to give alkyl halides. In agreement with this Voronkov[72] showed that the treatment of trimethylsilyl ethers with iodotrimethylsilane afforded alkyl iodides in practically quantitative yields (eq.48). Further investigation showed that alkyl iodides are easily obtained in good yields by the direct treatment of alcohols with iodotrimethylsilane (eq. 49).[73] The silicon-containing byproducts are a mixture of trimethylsilanol and hexamethyldisiloxane. A drawback of the method is the formation of free hydrogen iodide. Similarly, treatment of alcohols with 1.5-4.0 equivalents of bromotrimethylsilane afforded the expected bromides (Table 5).[47]

Reaction with Carbonyl Compounds

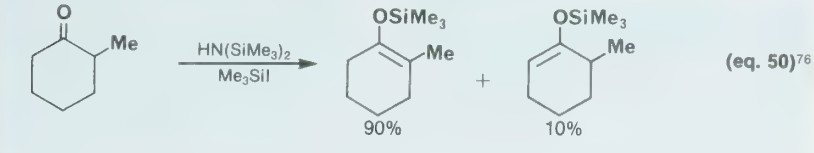
The reaction of aldehydes and ketones with halotrimethylsilanes has been examined in depth with respect to the formation of trimethylsilyl enol ethers.[74,75] Recently the use of the hexamethyldisilazane/iodotrimethylsilane system was proposed as a highly effective silylating reagent.[76] The reactions are carried out at room temperature and usually afford a very good yield of the thermodynamically more stable product (eq. 50).

Since 1975 we have been exploring the reactions of carbonyl compounds with halotrimethylsilanes in the absence of a base. On the addition of iodotrimethylsilane to acetone, or on the addition of chlorotrimethylsilane to a suspension of NaI in excess acetone, we observed an ex-

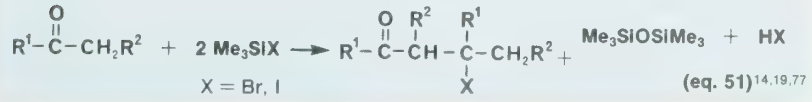
othermic reaction which afforded 4-iodo-4-methylpentan-2-one.[14] The corresponding β-bromoketone was obtained in a similar way.[14,19] This aldol-like reaction has been observed in the meantime for numerous other carbonyl compounds (eq. 51).[77,78] During the course of these investigations the iodotrimethylsilane/zinc system was introduced by us.[77,79]

It has been proposed[80] that the formation of the β-haloketones may proceed through an α-halotrimethylsilyl ether. The formation of such a species was suggested by the formation of α,α-diiodotoluene when excess iodotrimethylsilane was added to benzaldehyde.[81]

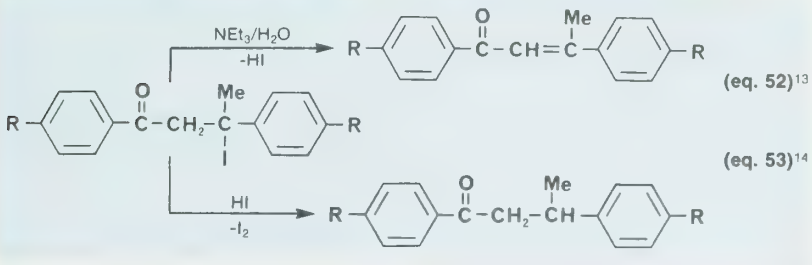
Depending upon the work-up conditions the reaction of aryl methyl ketones with iodotrimethylsilane afforded α,β-unsaturated ketones (eq. 52) or the corresponding saturated ketones (eq. 53).[13,14] The generation of both types of products may be explained by the intermediacy of β-iodoketones.



(eq. 50)[76]

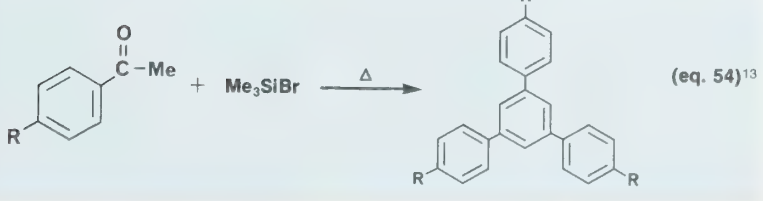


(eq. 51)[14,19,77]



(eq. 52)[13]

(eq. 53)[14]



(eq. 54)[13]

In addition to the results shown in eq. 53 the conversion of α-hydroxyketones to ketones by means of iodotrimethylsilane needs to be mentioned.[82]

When aryl methyl ketones or cyclopentanone were heated with bromotrimethylsilane three molecules of ketone were condensed to form a benzene nucleus (eq. 54).[13]

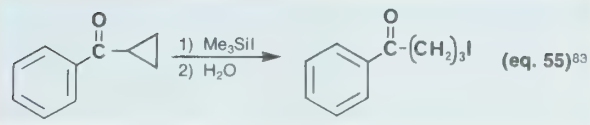
The reactions of bromo- and iodotrimethylsilane with unsaturated ketones, quinones, and several specially substituted ketones are summarized in eqs. 55-58.[83-85]

Miscellaneous Reactions

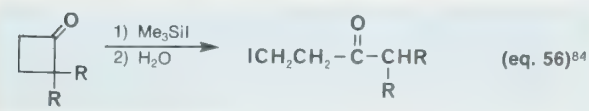
Several reports are available dealing with the addition of bromo- and iodotrimethylsilane to various pentavalent phosphorus compounds.(eq. 59, 60).[66,86,87]

The deoxygenation of sulfoxides to sulfides may be accomplished easily by means of iodotrimethylsilane[21] and bromotrimethylsilane (eq. 61).[21] For this purpose both reagents may also be generated *in situ*.[19,21,88] The procedure has been found useful in the selective deoxygenation of an α,β-unsaturated sulfoxide.[89] Similarly, sulfonyl halides can be deoxygenated with iodotrimethylsilane to yield disulfides.[90]

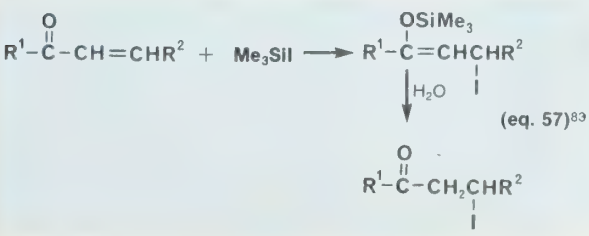
Recently bromo- and iodotrimethylsilane have been found useful in halogen-exchange reactions. Thus, acid chlorides were easily converted under very mild conditions to acid bromides and acid iodides (eq. 62).[1,91] Furthermore, chlorophosphines and chlorophosphoranes have been converted to the corresponding iodides by means of iodotrimethylsilane (eq. 63).[92] Surprisingly, iodotrimethylsilane also brings about chlorine or bromine/iodine exchange in bis- and tris(halomethyl)-phosphine oxides. In the same way the tosyloxy group may be exchanged (eq. 64).[92]



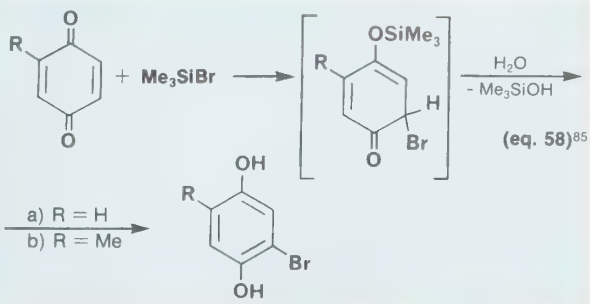
(eq. 55)[83]



(eq. 56)[84]



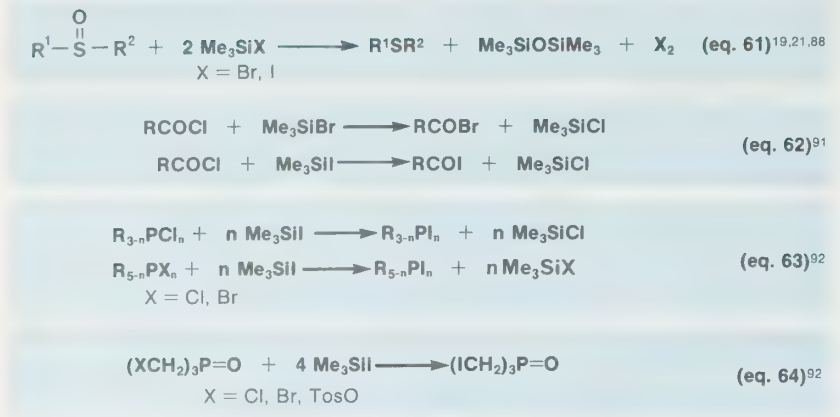
(eq. 57)[83]



(eq. 58)[85]

(eq. 59)[86]

(eq. 60)[66,87]



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Dr. Arthur H. Schmidt was educated at the University of Frankfurt/Main, West Germany, where he received his Ph.D. (Dr. phil. nat.) in 1970. After postdoctoral studies at the University of Frankfurt/Main, at Columbia University, New York, and at the Université de Paris-Sud, Orsay, France, he joined Bayer AG at Leverkusen. Since 1975 he has been on the staff of the Fachhochschule Fresenius at Wiesbaden, West Germany. His research interests encompass organometallic compounds, heterocyclic compounds, and small-ring chemistry.

Transition-Metal Templates for Selectivity in Organic Synthesis

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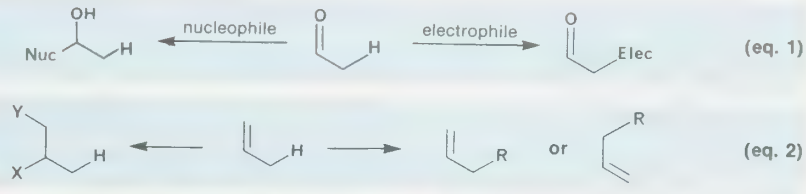
A key aspect of synthetic design is efficiency — the ability to transform readily available starting materials into target compounds *via* the shortest possible routes. Synonymous with efficiency is selectivity, which may be divided into three major classes: (1) chemoselectivity — functional group differentiation, (2) regioselectivity — orientational control in the reaction of an unsymmetrical functional group and/or an unsymmetrical reagent, and (3) stereocontrol — control of relative stereochemistry (diastereoselectivity) and/or control of absolute stereochemistry (enantioselectivity).

The unique position of the carbonyl group in synthetic design stems from the selective formation of bonds at the carbonyl carbon atom or the alpha carbon atom according to eq. 1. The corresponding reactions of the π-isoelectronic olefin, especially with respect to allylic functionalization, has proven much less useful because low selectivity frequently plagues such processes (eq. 2). In our search for chemoselective allylic alkylation procedures, we focused on the ability of palladium salts to achieve activation of the allylic system and to permit subsequent alkylation in the presence of other functional groups — especially the carbonyl group. In the course of these studies, we delved into the palladium-catalyzed alkylation of allylic systems in which palladium templates exercise an extraordinary degree of control over the behavior of organic molecules.[1] In this report, I wish to consider the application of these concepts in four different problems, but first to outline the basic principles.

GENERAL CONSIDERATIONS

As a general introduction of the basic process, we can consider the alkylation of 2-methylcyclopentane-1,3-dione. Such systems are notorious for their tendency to suffer O- *vs.* C-alkylation. Allylation of 2-methylcyclopentane-1,3-dione with allyl bromide proceeded in only 30% yield; however, with allyl acetate and a palladium(0) catalyst, the yield of **2** (R = H) jumped dramatically to 94%.[2] Use of **1** (R = OC_2H_5) gave **2** (R = OC_2H_5) which permitted development of a cyclopentenone annulation as illustrated in eq. 3. The bicyclic ketone **3**, a bis-nor analog of the Wieland-Miescher ketone, can prove pivotal as a general intermediate towards polycondensed cyclopentanoid natural products — such as coriolin and hirsutic



Professor Barry M. Trost (right) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

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acid C — in a fashion similar to the pivotal role the Wieland-Miescher ketone has played in cyclohexanoid natural products. A total synthesis of coriolin using this strategy nears completion.[3]

Eq. 4 illustrates the reordering of reactivity of two functional groups.[4] In the absence of the transition-metal catalyst, only the bromide would be expected to react, as is observed. However, addition of a Pd(0) catalyst allows selective alkylation of the allylic acetate without any attack at the bromide.

Normally, displacement reactions in organic chemistry are accompanied by inversion of configuration. As shown in eq. 5, this alkylation involves displacement with retention of configuration.[4]

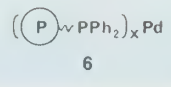
Eq. 6 represents a convenient working hypothesis. When coordination of the Pd(0) catalyst occurs on the face of the double bond opposite the acetate, it induces ionization of the acetate to give a π-allylpalladium intermediate. The position identity of the acetate, *i.e.*, whether it was originally located at C(a) or C(b), is lost at this stage. Thus, the choice of substrate with acetate at either C(a) or C(b) can depend only on synthetic expediency — a real benefit of this methodology. The regioselectivity depends upon: (1) the nature of the nucleophile, (2) the nature of the substitution on the allyl unit, and (3) the nature of the ligands on Pd.

CATALYSTS

Pd(0) is required as a catalyst for these reactions. Soluble palladium catalysts which are sensitive to oxygen normally bear phosphine ligands. The most common catalysts are **4**[5] and **5**.[6,7] In some cases, to

preserve catalyst lifetime and increase turnover, 1-2 equivalents of additional phosphines are added. Rate retardation normally accompanies such a modification. To avoid handling such oxygen-sensitive materials, the catalyst can be generated *in situ* from Pd(II) salts by reduction with DIBAL or, in the case of $Pd(OAc)_2$, with an olefin (typically the substrate) in the presence of phosphine ligands. For small-scale reactions, 1-10 mol % of catalyst has been employed. The amount of catalyst decreases as the scale of the reaction increases; as little as 0.01 mol % has been employed.

An insolubilized version of the catalyst has been produced.[8,9] Either silica gel or crosslinked polystyrene can be phosphinylated and the modified support exchanged with **4** to give **6**. Besides facilitating



recovery and recycling of the catalyst, such insolubilized versions do show modified selectivities as a result of the modified ligands.

STEREO-RELAY

In Fig. 1, we consider the question of control of stereochemistry at a reaction site relative to a remote chiral center. In a conformationally well defined system, such as a six-membered ring, this problem is minimized. The presence of substituents on the ring normally fixes the conformation in one of the two possible chair forms as shown in **7**. Thus, the two faces of the carbonyl group are quite distinct and reaction is expected to occur preferentially on one of the two faces — most frequently from the equatorial direction as shown. Cleavage of bond "a" in **7** creates **8** where the interconnecting chain between the chiral

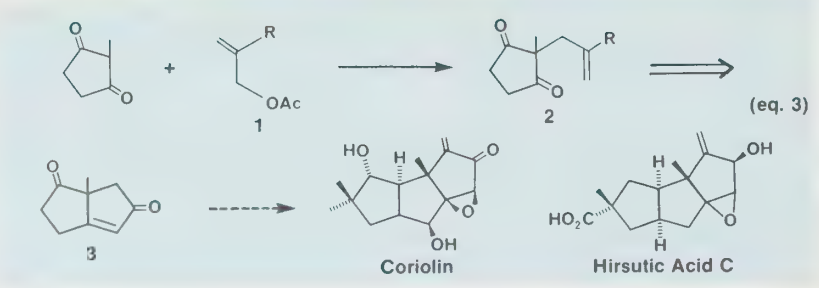
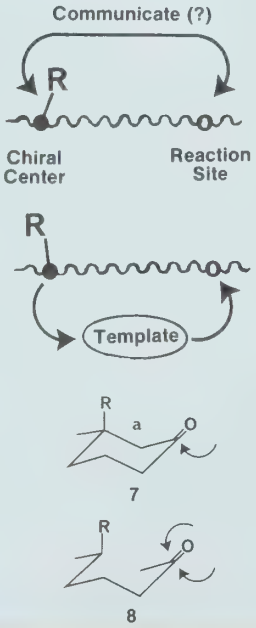
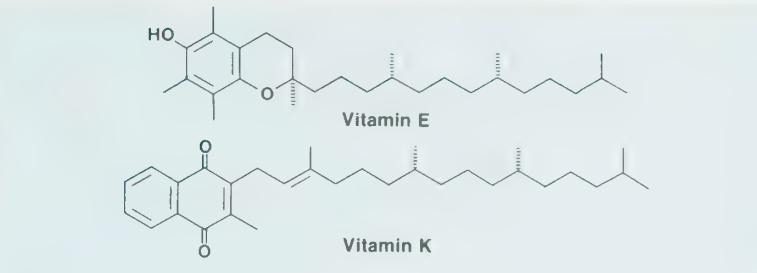
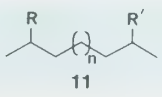


Figure 1



center and the reaction site no longer exhibits a conformational bias. Here reaction on the two faces of the carbonyl group occurs with equal probability. Thus, in conformationally non-rigid systems — acyclic or macrocyclic ones — a mechanism to communicate between these two sites needs to be found. One approach is to design a substrate that permits temporary complexation of a normally non-rigid chain onto a template, thereby inducing conformational rigidity. We chose to examine this question in terms of the creation of the side chains of Vitamins E and K for which **9**, which possesses the two chiral centers, provides a logical target.[10] In terms of allylic alkylation, **9** translates into **10** in which bond "a" creates the second chiral center relative to the existing one.[11,12]



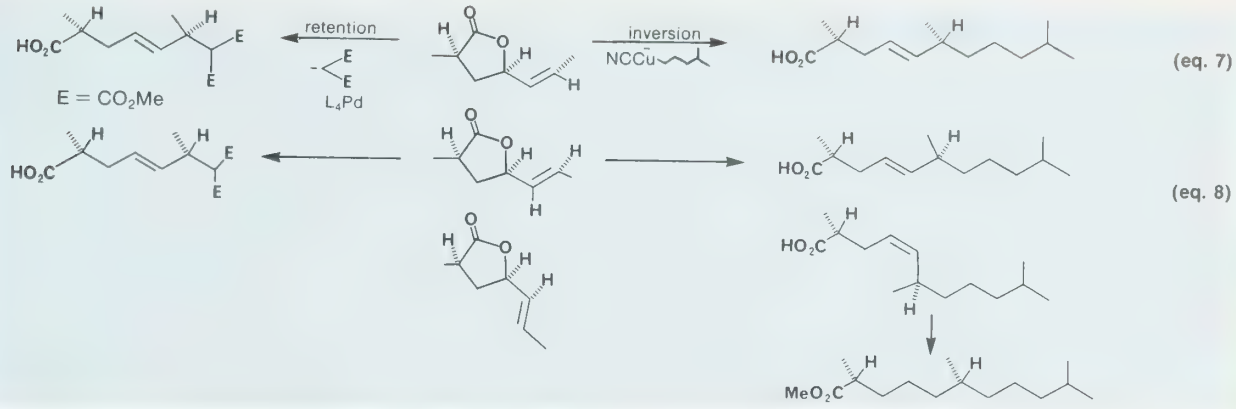


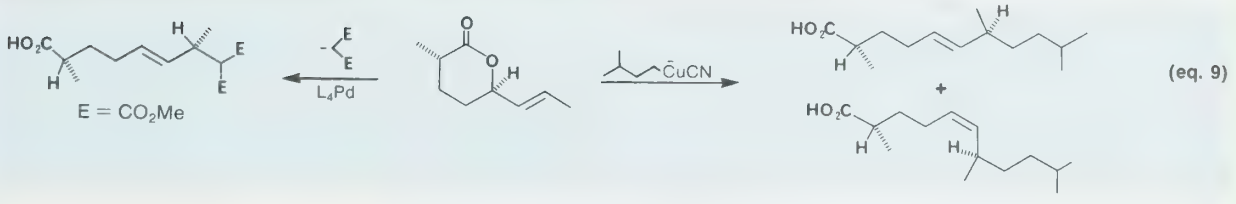
Vinyl lactones represent ideal choices for this stereo-relay process in which the ring geometry will be transmitted down the chain. Eqs. 7 and 8 illustrate the success of this approach where Pd(0)-catalyzed alkylation leads to S_N2' reaction with clean **retention** of configuration regardless of the olefin geometry.[11] This reaction varying the size of the lactone ring.[13] Here, too, the higher degree of control exhibited by the palladium template is obvious.

While the products of the reactions illustrated in eqs. 7 and 8 have been converted to the target for the vitamin side chains, this approach only controls relative stereochemistry. One reason for choosing such substrates is the use of carbohydrates as potential optically pure raw materials. Indeed, glucose is converted to lactone **12** (eq. 10) by straightforward chemistry and the latter smoothly participates in the palladium-initiated reaction (95% yield) to give a single homogeneous product which is converted to the side-chain fragment where both relative and absolute stereochemistry have been fully controlled.[14]

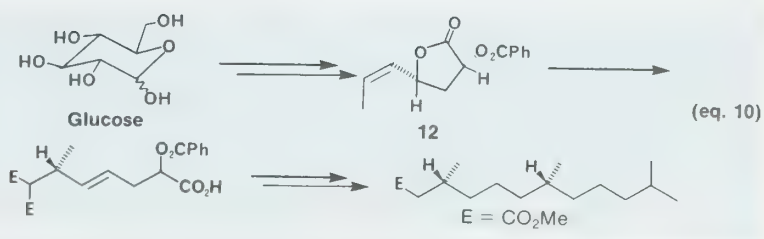
[1,3] REARRANGEMENT

The chemistry of allyl vinyl ethers in-

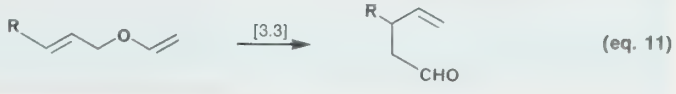




complements cuprate chemistry, shown in eqs. 7 and 8, which also proceeds with allyl transposition but with **inversion** of configuration.[12] Unfortunately, the cuprate chemistry does not exhibit as high a degree of stereochemical control with the *E* olefin series (eq. 8) as do the palladium templates, demonstrating the superiority of the palladium reaction in this case.



Variation of the separation between the chiral centers as in **11** can be achieved by varying the position of the substituents on the vinyl lactone or, as shown in eq. 9, by



variably becomes integrated with [3.3] sigmatropic rearrangements (eq. 11). In cases such as **13**, the cycloheptenone **14** is produced (eq. 12). For many natural products, an alternative pathway, a [1.3] rearrangement, to produce a 3-vinylcyclopentanone would be the desired course. Indeed, a reordering of the "expected" reactivity profile of **13** is available using a palladium template in which the exclusive product is indeed the cyclopentanone **15**.[6]

This process takes on added importance due to the cyclization proclivity of β-ketoesters such as **16** (eq. 13) for O- rather than C-alkylation. Indeed, all attempts to cyclize **16** lead only to the alkylidenevinyltetrahydrofuran **17**. However, this tendency no longer presents a problem since **17** smoothly isomerizes to the desired cyclopentanone with a Pd(0) catalyst; in this case, an approach to prostaglandin analogs.

The utility of this cyclopentanone synthesis depends upon the availability of the requisite alkylidenetetrahydrofurans. Eq. 13 illustrates their accessibility from ketones through use of the new conjunctive reagent 1-(2,6-dimethoxyphenylthio)-cyclopropanecarboxaldehyde.[15] Especially valuable are vinyl lactones such as **18** (eq. 14) and **19** (eq. 15) which are, in turn, available from carbohydrates.[16] Ynamines smoothly effect olefination of a lactone (87% yield) and the product rearranges to the cyclopentanone in 93% yield with complete regio- and stereocontrol upon subjection to **5** as the palladium template. Alternatively, **19** reacts with *t*-butyl lithioacetate followed by dehydration to give **20** in 91% yield. In this case, rearrangement can be controlled to give either the cycloheptenone **22** or the cyclopentanone **23** by judicious choice of catalyst. The regioselectivity depends upon the rate of *syn-anti* interconversion in the intermediate **21**. With the sterically demanding polymeric catalyst, such interconversion is inhibited and only the normal [1.3] product is seen. With a sterically small ligand, such interconversion is fast and only the seven-membered ring is observed. Such rational control of reactivity is a decided advantage of transition-metal-catalyzed reactions.

An alternative approach employs methyl 6-oxo-2-pentynoate as a conjunctive reagent for cyclopentanone synthesis.[17] Chemoselective addition of vinyl organometallics produces the alcohol **24** (eq. 16). Surprisingly, conjugate addition of the alcohol proved particularly troublesome. An efficient solution to this perplexing problem evolved from organosulfur chemistry. Addition of sodium benzenesulfinate to a warm alcoholic solution of **24** smoothly triggered cyclization to the desired alkylidenevinyltetrahydrofuran. Isomerization with the palladium catalyst completed an additional entry into the family of prostanoids. Thus, the availability of alkylidenevinyltetrahydrofurans of type **25** from many different types of substrates suggests great versatility for this cyclopentanone synthesis (eq. 17).

CYCLOPENTANE ANNULATION

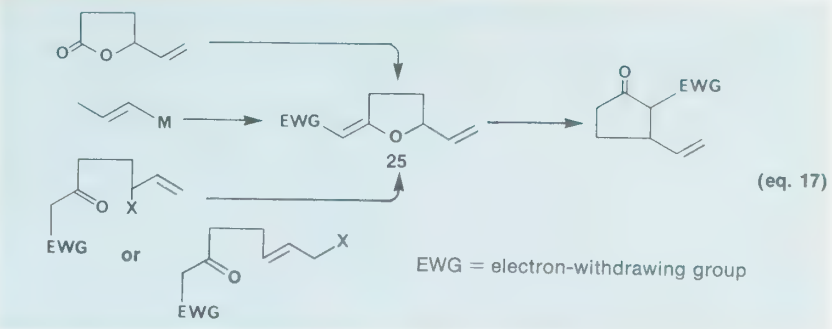
The increasing importance of cyclopentanoid natural products heightens the demand for increased flexibility in synthetic approaches to them. The [1.3] isomerization of alkylidenevinyltetrahydrofurans contributes to that flexibility. In cyclohexanoid chemistry, the Diels-Alder reaction (eq. 18) holds a special position. The virtues of such a cycloaddition approach are lacking for the case of five-membered carbon rings for which the analog might be a 1,3-dipolar cycloaddition as illustrated in eq. 19. Initiating an investigation into such an area draws our attention to trimethylenemethane, shown in a dipolar form in **26**, a reactive in-

termediate which has been studied from a physical point of view but whose use in synthesis is precluded because of very low yields.

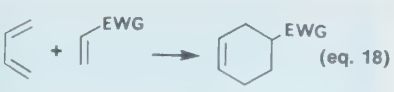
Combining the virtues of organosilicon chemistry with palladium templates led us to propose that a bifunctional conjunctive reagent such as **27** (eq. 20) would be ideal since the π-allylpalladium intermediate **28** could suffer desilylation by acetate to generate not trimethylenemethane itself, but its palladium complex **29** where the only by-product is trimethylsilyl acetate.[18-20] Of course, the reactivity of an intermediate such as **29** was not known.[21] For example, iron complexes of trimethylenemethane are notorious for their lack of reactivity.[22] Hoping that cycloaddition would occur, we employed traps such as **30** and **31** (eqs. 21 and 22) which contain both electron-rich and electron-poor olefins. Both reacted smoothly and chemoselectively with **27** in the presence of a Pd(0) catalyst to give cycloaddition-like products with the electron-poor olefin. The cycloaddition to dimethyl *E,E*-muconate produces a methylenecyclopentane (eq. 23) which possesses structural features that naturally lead to application of this methodology to a total synthesis of brefeldin A, **32**. The chemistry as well as Fenske-Hall calculations[20,23,24] lead to the conclusion that this complex indeed behaves as a zwitterion as represented in structure **29** (eq. 20). Thus, the cycloaddition can be generalized as in eq. 24, in which the trap must bear at least one electron-withdrawing group (EWG).

The utility of such a cycloaddition approach depends upon the accessibility of the requisite bifunctional reagents such as **27** and the extension to substituted analogs. Such an extension is not trivial. Consider the case of the methyl derivative **33** where, at every stage, proton transfer can compete with the desired process as illustrated (eq. 25).

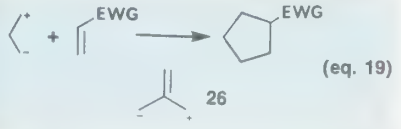
Scheme I outlines three of the four approaches we have developed to the requisite substrates.[25] The direct metallation (path A) is very general for methallyl alcohols. 2-Trimethylsilylmethylpropenal, available from methylallyl alcohol by the metallation-silylation procedure of path A followed by oxidation, represents an acceptor conjunctive reagent where organometallics serve as the source of the R group (path B). Alternatively, the lithium or magnesium derivative of 2-bromoallyltrimethylsilane, available from 2,3-dibromopropene, represents a donor conjunctive reagent where electrophiles such as aldehydes serve as the source of the R group (path C).



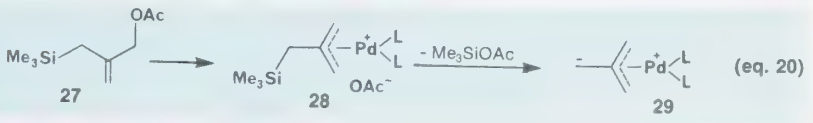
(eq. 17)



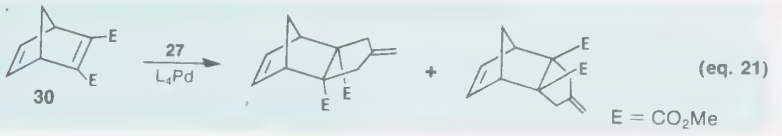
(eq. 18)



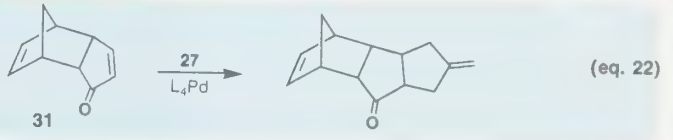
(eq. 19)



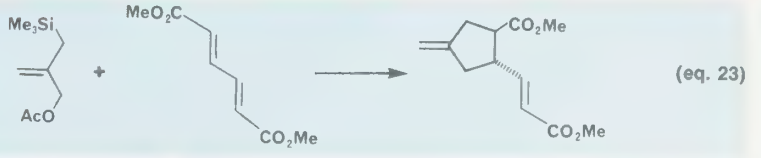
(eq. 20)



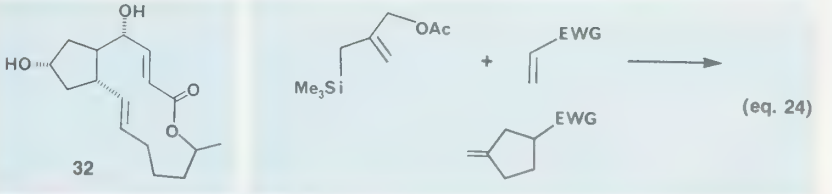
(eq. 21)



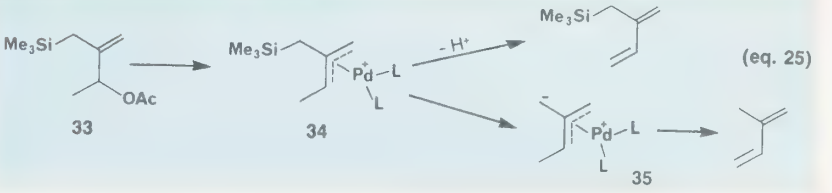
(eq. 22)



(eq. 23)



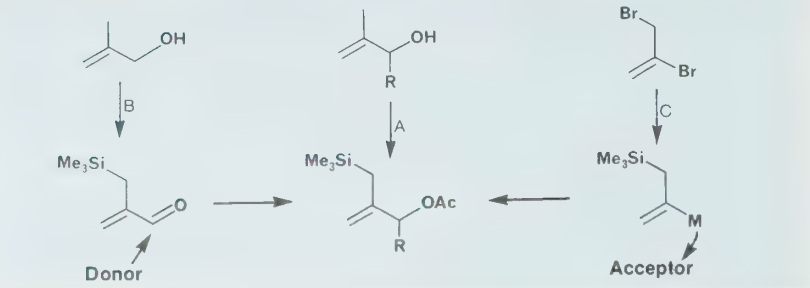
(eq. 24)

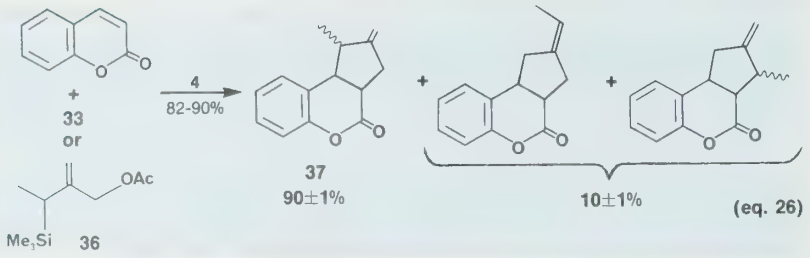


(eq. 25)

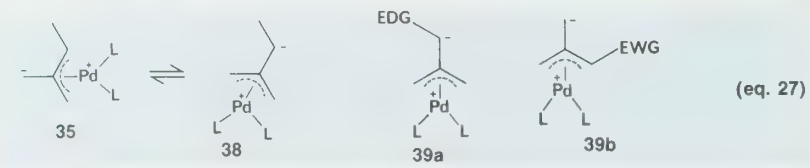
The aspirations for the generality of this cycloaddition were fulfilled. Using coumarin as a trap (eq. 26), a single major product resulted. Thus, an extraordinary event occurred. Desilylation of **34** to give reactive intermediate **35** competes favorably with simple proton loss to give a stable molecule (eq. 24)! Whereas use of **33** initially generates **35**, the regioisomer **36** generates **38**. Yet, the same product mixture emerges. Using the simple notion that the reaction is initiated by nucleophilic at-

Scheme 1. Synthetic Approaches to Bifunctional Conjunctive Reagents for Cycloaddition

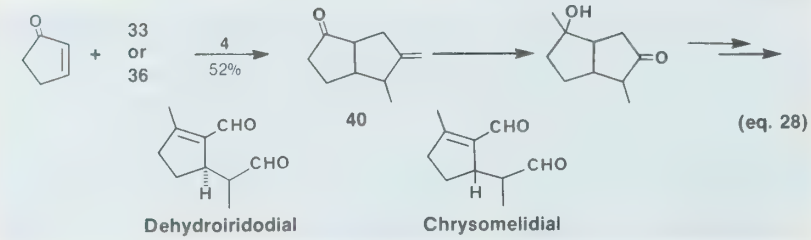




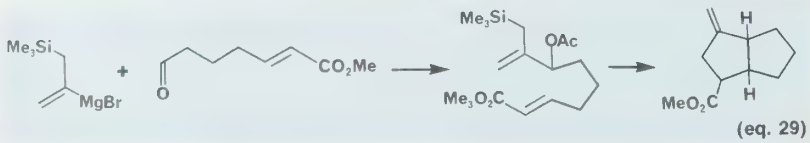
(eq. 26)



(eq. 27)

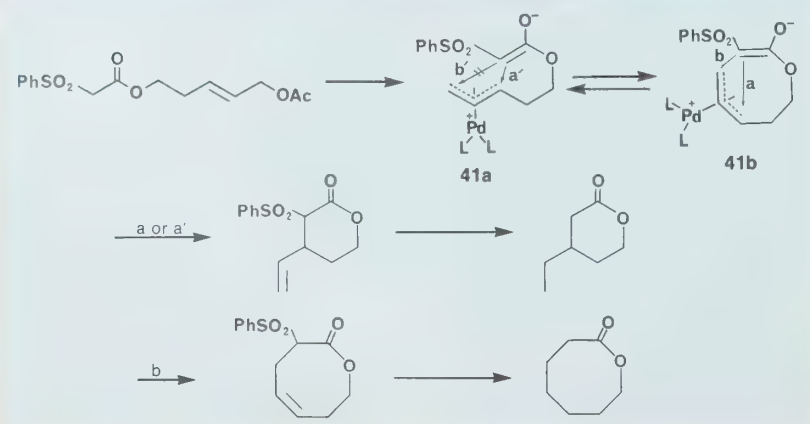


(eq. 28)



(eq. 29)

Scheme 2. Formation of 7-Heptanolide

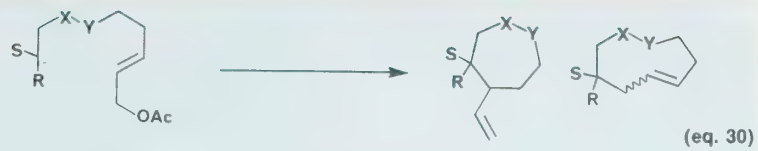


tack of the most anionic carbon of the complex, the predominant cycloadduct **37** is derived from **38**. Indeed, calculations predict **38** to be more stable than **35**. The electron-releasing methyl group prefers to be on the most electron-rich carbon — the antithesis of normal behavior in organic chemistry! Thus, the transition-metal template imposes a level of control that leads to new selectivity. The factors that lead to placing the electron-donating group (EDG) on the most electron-rich carbon of the TMM system (*i.e.*, **39**) can suggest that the EWG be placed on the least electron-rich carbon as in **39b**.

Cyclopentanone reacts smoothly with either **33** or **36** to give **40** virtually exclusively (>20:1 in regioisomers) — an intermediate towards loganin[26] as well as the insect pheromones dehydroiridodial and chrysomelidial[27] as shown in eq. 28. The availability of a donor reagent to create the requisite structural unit particularly facilitates the synthesis of a substrate for an intramolecular reaction as shown in eq. 29. The promise of a family of reagents for cycloaddition-like approaches to cyclopentanoid natural products appears fulfilled.

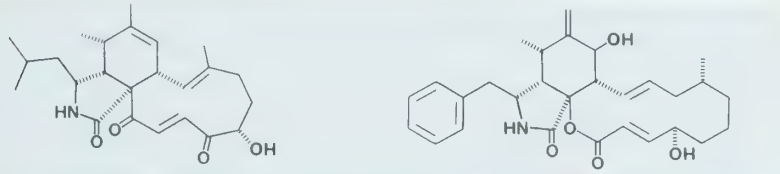
MACROCYCLIZATION

Thus far, the utility of these templates for ring formation dealt only with the more normal ring sizes — five-, six- and seven-membered rings. Macrolides and all carbon macrocycles represent major synthetic challenges. Techniques that focus on formation of such rings by C-C bond formation represent the most flexible methods. Our initial attention[28] focused on macrolides where palladium-initiated cyclization to rings of ten or more members culminated in syntheses of phoracantholides I and J,[28,29] recifeiolide,[28,30] and exaltolide.[28,31] Most striking is the regioselectivity in formation of medium-size rings. For example, cyclization of the substrate shown in Scheme 2 can proceed to either a six- or an eight-membered ring. In addition to the 10^5 kinetic preference for formation of six-membered rings, the higher stability of *syn* complexes such as **41a** should reinforce the preference for six-membered ring formation. In spite of all this, eight-membered ring formation dominates (93%). As shown in eq. 30, nine-membered ring formation dominates over seven. Once again the normal rules for reactivity are violated — the normally difficultly available eight- and nine-membered rings are now preferred! As eq. 30 summarizes, variation of the nature of the nucleophiles, of the substitution in the chain, and of the ligands on the palladium permit complete control of regiochemistry and thus, ring size — truly a remarkable



(eq. 30)

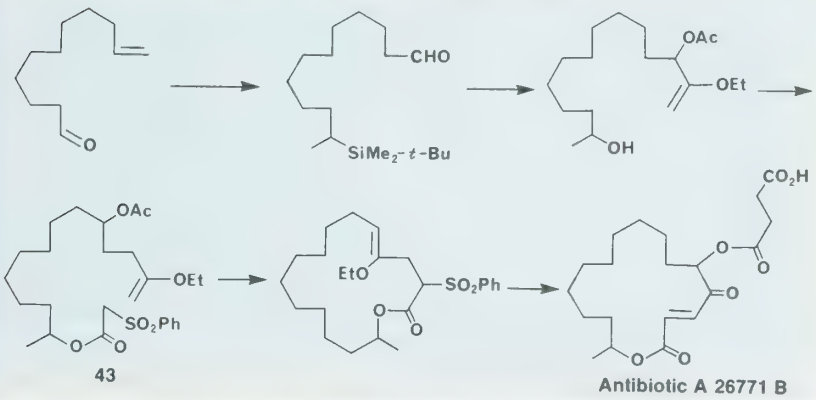
S	R	X	Y	Catalyst		
$PhSO_2$	CO_2Me	C=O	O	$(Ph_3P)_4Pd$	-----	only
$PhSO_2$	CO_2Me	CH_2	CH_2	$(Ph_3P)_4Pd$	only	-----
$PhSO_2$	$PhSO_2$	CH_2	CH_2	$(Ph_2PCH_2CH_2PPh_2)_2Pd$	-----	only



Aspochalasin B

Cytochalasin B

Scheme 3. Synthesis of Antibiotic A 26771 B



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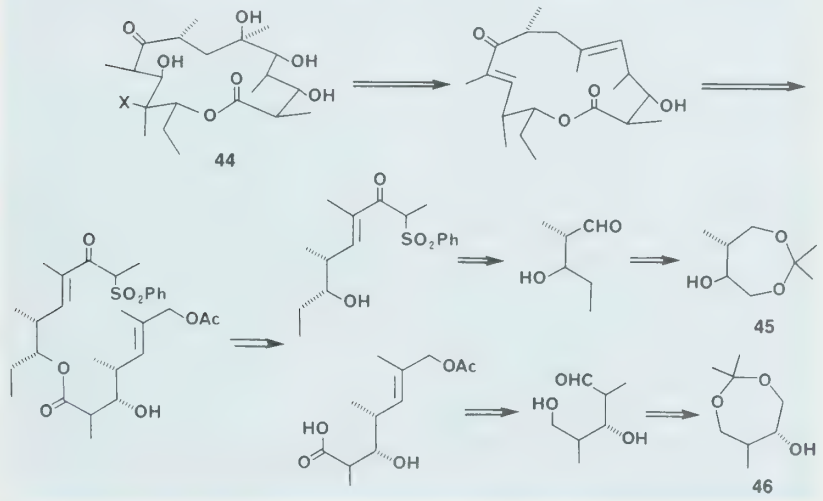
Antibiotic A 26771 B

Scheme 4. Retrosynthetic Analysis of Erythrynolide Synthesis



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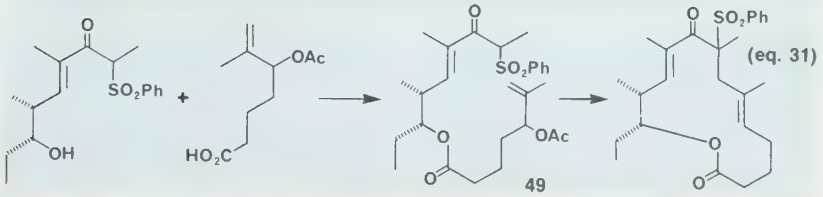
45

46

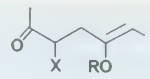


(eq. 31)

49

level of control of reactivity.[32]

The challenge of the synthesis of complex natural products offers an ideal testing ground for this method. The cytochalasin family of natural products consists of a highly substituted cyclohexyl ring fused to a macrolide as in cytochalasin B or to an all-carbon macrocycle as in aspochalasin B. A common feature of both is the highly oxygenated pattern in the macrocycle, a type of pattern found in other natural products such as antibiotic A 26771 B (see Scheme 3). An ideal precursor to all of these is the fragment shown in structure **42**,

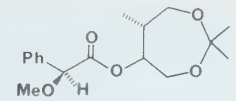


42

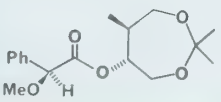
where the enol ether can serve as an easy entry into the simple alcohol as in cytochalasin B or an α-hydroxy ketone as in aspochalasin B and antibiotic A 26771 B. This fragment becomes an obvious target of allylic alkylation.

Scheme 3 illustrates the ready availability of the requisite substrate **43** from 10-undecenal. Treatment of **43** with a Pd(0) catalyst and *N,O*-bis(trimethylsilyl)acetamide in refluxing THF gave the requisite macrocycle in 55-61% yield, a much higher yield than obtained by any lactonization approach.[33] Hydroxylation using a catalytic amount of osmium tetroxide followed by esterification with succinic anhydride completes the sequence. The soundness of this strategy for cytochalasin synthesis is established.

Equally challenging targets are the erythrynolides A (**44**, X=OH) and B (**44**, X=H) as shown in Scheme 4. The retrosynthetic analysis utilizing this macrocyclization principle converges to **45** and **46** — a pair of enantiomers! Thus, the problem of control of absolute as well as relative stereochemistry is resolved as long as both enantiomers are available in a simple operation. A simple solution emerged. The *O*-methylmandelate esters **47** and **48** revealed two well-resolved peaks by HPLC and permitted large-scale separation on a Waters Prep 500 instrument.[34] A second advantage of this approach is the ability to assign stereochemistry. Using the Mosher model, the stereochemistry depicted in **47**



47



48

and **48** corresponds to the less and more polar isomers, respectively. Further correlation was provided by comparison of the regenerated optically pure **45** and **46** whose absolute configurations were established by Horeau's method.

With the strategy developed, the elaboration of **45** into the desired alcohol is complete, and the corresponding elaboration of **46** into the carboxylic acid is nearing completion. However, establishment of the critical ring closure remains to be accomplished. Comfortingly, subjection of a model **49** (eq. 26), which possesses a fully elaborated alcohol half and a stripped version of the carboxylic acid portion, to the normal cyclization conditions creates the correct fourteen-membered macrolide ring of the erythrynolides.

CONCLUSION

An appreciation of the intricacies of transition-metal chemistry in the design and application of new reactions is emerging. The fact that insight based upon traditional thinking is challenged offers an unprecedented opportunity to expand the rules of selectivity. Indeed, such an expansion is critical if we are to mount a successful campaign to have chemistry better serve the needs of man by instilling efficiency and bringing to application more sophisticated materials. We hope the above will contribute to this task.

ACKNOWLEDGMENTS

Our work on the use of transition-metal templates in organic synthesis represents the collaborative effort of an enthusiastic group of graduate and postdoctoral students. The four thrusts which have been the focus of this report were derived principally from the efforts of Mr. Thomas P. Klun (stereo-relay), Dr. Thomas A. Runge (1,3-rearrangement), Mr. Dominic M.T. Chan (cyclopentane annulation), and Dr. Thomas R. Verhoeven, Dr. Steven J. Brickner and Dr. John L. Belletire (macrocyclization). To them and to the rest of the group I am most indebted. We are especially grateful for the continuing financial support of the National Science Foundation, the General Medical Sciences Institute and the National Cancer Institute of the National Institutes of Health, and the University of Wisconsin.

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About the Author

Professor Barry M. Trost was born on June 13, 1941. He received the B.A. degree from the University of Pennsylvania in 1962 and the Ph.D. degree (Professor H.O. House) from the Massachusetts Institute of Technology in 1965. He was appointed Assistant Professor of Chemistry at the University of Wisconsin in 1965 and was promoted to Associate Professor, Professor, and Evan P. and Marion Helfaer Professor in 1968, 1969 and 1976, respectively.

Dr. Trost has developed transition-metal-assisted synthetic methodologies including allylic alkylation, cyclopentanone annulation, and medium-to-large ring cyclization reactions. Natural-product chemistry to his credit include the total syntheses of juvenile hormone, grandisol, methyldesoxypodocarpate, juvabione, ibogamine, recifeiolide, exaltolide, and phoracantholides I and J.

Among his many awards and distinctions are the 1977 ACS Award in Pure Chemistry, the 1981 Baekeland Award, and election to the National Academy of Sciences in 1980. Dr. Trost has delivered 50 plenary lectures in the U.S. and abroad, has served as editor of numerous books and journals, and is the author of over 200 scientific papers. He is a member of the American Chemical Society, the Chemical Society (London), and is a Fellow of the American Association for the Advancement of Science.

The following compounds useful in Trost Chemistry are offered by Aldrich:

22,086-8	1-Acetoxy-1,3-butadiene
12,357-9	Benzenesulfinic acid, sodium salt
23,027-8	Bis[ethylenebis(diphenylphosphine)]palladium(0) [$Pd(DIPHOS)_2$]
12,891-0	Bis(trimethylsilyl)acetamide (BSA)
B8,820-9	*tert*-Butyl acetate
C6,270-0	*m*-Chloroperoxybenzoic acid, tech., 80-85%
18,665-1	18-Crown-6
22,724-2	Cyclopropyl phenyl sulfide
13,900-9	1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)
10,649-6	Ethylenebis(diphenylphosphine) (DIPHOS)
18,987-1	Ethylmagnesium bromide, 3*M* solution in diethyl ether
18,519-1	Lead tetraacetate
11,702-1	2-Methyl-1,3-cyclopentanedione
18,620-1	Methyllithium-lithium bromide complex, 2*M* solution in diethyl ether
23,418-4	Methyl phenylsulfonylacetate
22,803-6	*OXONE*® monopersulfate compound (potassium hydrogen persulfate
16,902-1	Phenyl disulfide
21,581-3	Potassium hydride, 35 wt. % dispersion in mineral oil
22,344-1	Sodium hydride, dry
21,614-3	Tetra-*n*-butylammonium fluoride, 1*M* solution in THF
21,666-6	Tetrakis(triphenylphosphine)-palladium(0)

Isobenzofuran and Related o-Quinonoid Systems

A New Group of Synthetic Intermediates

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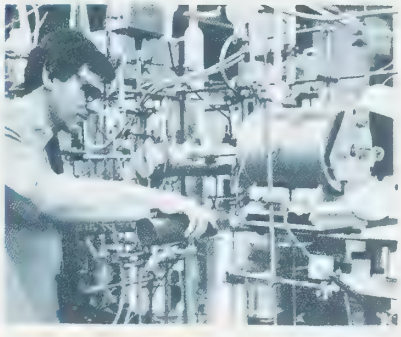
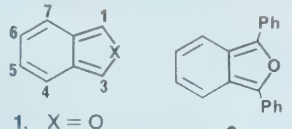


INTRODUCTION

Isobenzofuran (IBF) or benzo[*c*]furan (**1**) has long been an elusive species[1,2] and, until very recently, its chemistry has been underdeveloped. Only 1,3-diphenylisobenzofuran (**2**) is well known[3] as a standard trapping agent for olefins.[4]



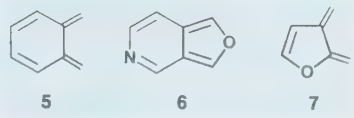
1, X = O
3, X = S
4, X = NH

2

The fundamental question, whether isobenzofuran and the related isothianaphthene (**3**, benzo[*c*]thiophene) and isoindole (**4**, benzo[*c*]pyrrole) are aromatic or *o*-quinonoid systems, makes these compounds naturally attractive to organic chemists. Theoretical studies have been published in recent years.[5-7]

Despite their relatively recent isolation, the chemistry of the parent isothianaphthene **3**[8,9] and isoindole **4**[10,11] was developed[12,13] earlier than that of isobenzofuran. Isobenzofuran is only very briefly treated in heterocyclic textbooks. In 1978, Haddadin wrote an excellent review on isobenzofuran and related isoannelated heteroaromatics.[14] Recently a comprehensive review covering the literature up to mid-1978 was published by Friedrichsen.[15] However, since these reviews, new methods for the generation of isobenzofurans have been found. Their application in the Diels-Alder synthesis of polycyclic systems, including natural products, has become recognized.

This development is paralleled by the use of other *o*-quinonoid systems, *e.g.*, *o*-quinodimethane (**5**),[16] furo[3,4-*c*]pyridine (**6**),[17] or 2,3-dimethylene-2,3-dihydrofuran (**7**).[18] Like isobenzofuran, these systems are conveniently prepared by flash-vacuum thermolysis (FVT).[19]



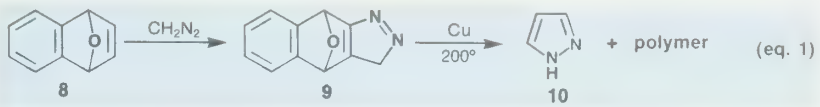
5 **6** **7**

The aim of this review is to present the title compounds as a complementary set of synthetic intermediates, which also have potential application in the natural-product area.

ISOBENZOFURAN, GENERATION AND REACTIONS

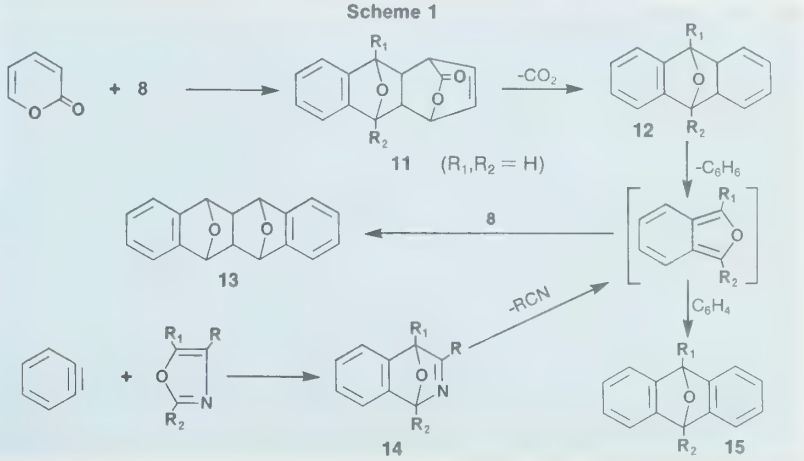
In 1956, Wittig and Pohmer,[20] while developing the chemistry of benzyne, prepared 1,4-epoxy-1,4-dihydronaphthalene (**8**). The double bond in **8**, like in norbornene, is quite reactive as a dienophile.[21] With diazomethane the pyrazoline **9** (eq. 1) was formed which, on thermal decomposition, yielded pyrazole **10** and a polymer indicated as polyisobenzofuran.[20]

Isobenzofuran was first demonstrated to exist as a transient intermediate by Fieser and Haddadin.[22] They reacted **8** with α-pyrone to form Diels-Alder adduct **11** (Scheme 1), which spontaneously loses car-



8 **9** **10**

Scheme 1



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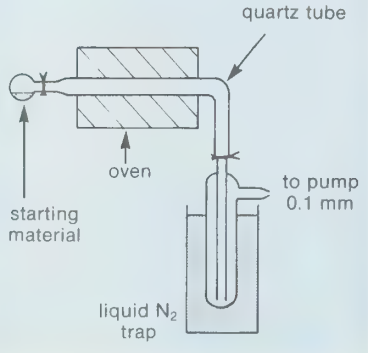
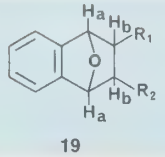
bon dioxide to give product **12**, the formal Diels-Alder adduct of isobenzofuran and benzene, decomposing above 60°C. Isobenzofuran is trapped *in situ* by dienophiles added to the reaction mixture, or by an excess of **8** to give an *exo-endo* mixture of diepoxide **13**. Isobenzofurans are also transient intermediates in the reaction of benzyne with oxazoles.[23] The initial adduct **14** decomposes into isobenzofuran and a nitrile.[24] Another molecule of benzyne traps the isobenzofuran to give adduct **15**.

Isobenzofuran was isolated simultaneously by three different groups, *via* retro-Diels-Alder reaction with derivatives of **8**. Warrener[25] applied 3,6-di(2′-pyridyl)-*s*-tetrazine (Scheme 2) as the diene component with **8** to prepare adduct **16**, which loses nitrogen to form **17**. By decomposing **17** under reduced pressure at 120°C, **1** and dipyridylpyridazine were trapped on a cold finger. Wege[26] isolated isobenzofuran in a similar experiment with lactone **11**. The simplest and most rapid route to relatively large quantities of **1** involved flash-vacuum thermolysis (FVT) of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene (**18**).[1] When this compound is evaporated at 0.1mm Hg into an unpacked quartz tube (25cm long, 0.8in. diam) heated at 650°C, ethylene is expelled and a quantitative amount of colorless crystals of pure **1** is collected in a cold trap connected to the tube (see Figure 1), at a

Figure 1

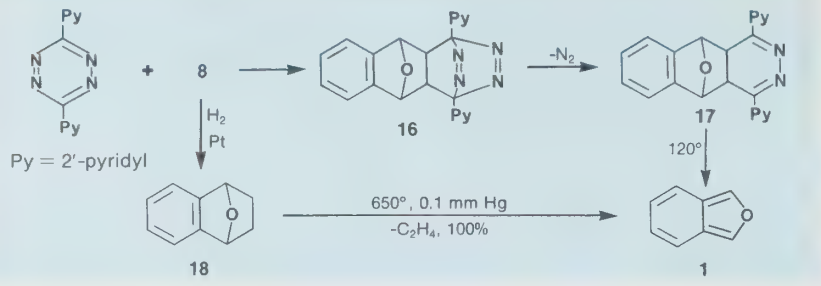


rate of 5-10g/h. In organic solvents, **1** homopolymerizes at room temperature but it can be stored in the refrigerator for longer periods. These solutions react instantaneously and quantitatively with dienophiles such as maleic anhydride and methyl vinyl ketone to produce mixtures of *exo-* and *endo*-adducts **19**.[1,15] With less



19

Scheme 2



reactive olefins such as styrene or cyclohexene, homopolymerization of **1** starts to compete with the Diels-Alder addition.[1] The *exo-* and *endo*-isomers **19** are nicely distinguishable by NMR:[21] the bridgehead methine protons H_a in the *exo*-isomers show no coupling with the H_b protons, while in the *endo*-isomers, J_{ab} is about 5Hz.[27] In most of the adducts, the 1,4-oxygen bridge can be easily eliminated under mildly acidic conditions to naphthalene derivatives, or to naphthols with adducts of acetylenic dienophiles.[2,20,28]

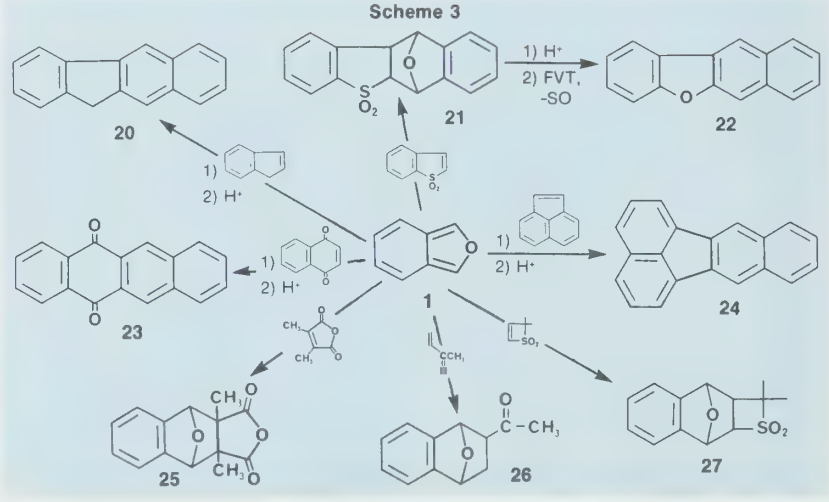
Several condensed aromatic compounds are rapidly prepared *via* isobenzofuran (Scheme 3), *e.g.* 2,3-benzofluorene (**20**), benzonaphthofuran (**22**), 5,12-naphthacenedione (**23**), and benzo[*k*]fluoranthene (**24**).[29] 3,4-Dimethylmaleic anhydride does not react with furan to give the Spanish fly component cantharidin;[30] however, its benzo analog **25** is rapidly formed with **1**.[29] Some adducts could not be dehydrated to the corresponding naphthalenes, *e.g.*, those of methyl vinyl ketone[29] and benzothiete-1,1-dioxide[31] gave deviant reactions.[32]

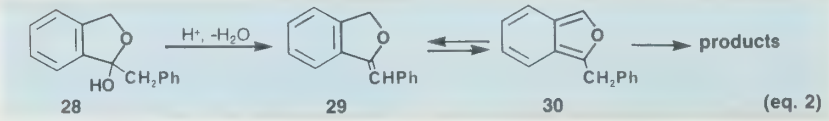
The reactivity of the isobenzofuran moiety in Diels-Alder reactions and its versatility as a synthetic intermediate are also illustrated with numerous reactions of 1,3-diphenylisobenzofuran (**2**).[14,15,33] A new synthesis[34] and new reactions[35] of **2** were very recently reported. The photochemistry and the reaction of **2** with singlet oxygen have also been well studied.[15]

1,3-Dialkylisobenzofurans and some 4-, 5-, 6-, or 7-substituted isobenzofurans are prepared by the FVT method of Wiersum and Mijs.[1] This method was developed independently by Heaney and coworkers,[36] who prepared 4,5,6,7-tetrafluoro- and 4,5,6,7-tetrachloroisobenzofuran which, as their isoindole analogs, [37] are considerably more stable than the parent systems.

The FVT method was also applied to the preparation of 1-benzylisobenzofuran (**30**).[38] It was demonstrated[39] earlier that **30** shows an interesting tautomerism with benzalphthalan (**29**), formed *via* dehydration of hemiketal **28** (eq. 2). In the presence of dienophiles, the equilibrium shifts towards **30** and the Diels-Alder adducts are

Scheme 3





formed. Several adducts of **30** and their conversion to naphthalenes have been reported.[28]

Isobenzofuran synthesis *via* a hemiketal precursor goes back to the formation of 1-benzoyl-3-phenylisobenzofuran[40] and 1,3-diphenylisobenzofuran (**2**).[41] The linearly annelated 1,3-diphenylnaphtho[2,3-*c*]-furan (**32**), less stable and more reactive than **2**, was also prepared[42] *via* the corresponding hemiketal **31** (eq. 3). Nevertheless, isobenzofuran generation at ambient temperatures from hydroxy- or alkoxyphthalan derivatives was only recognized as general in 1980.[2,28,43] Methoxyphthalan (**34**), rapidly prepared from phthalyl alcohol (**33**), gives the parent isobenzofuran (**1**) in quantitative yield by treatment with lithium diisopropylamide or by refluxing in toluene (eq. 4).[2]

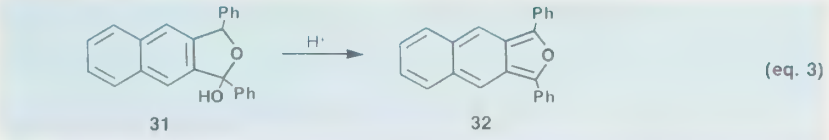
Essentially similar in the final step is the generation of 5,6-dimethoxyisobenzofuran (**37**).[43] 6-Bromoveratraldehyde (**35**) is converted in a number of steps to 1,5,6-trimethoxyphthalan (**36**) which spontaneously yields **37** *in situ* which, in turn, is trapped by dienophiles to yield adducts **38** (Scheme 4).

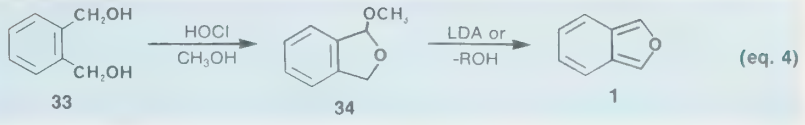
Methoxy- or alkoxy-substituted isobenzofurans are of special interest for application in natural-product synthesis. An ingenious route (Scheme 5) to 1-arylnaphthalide ligands **40** was reported by Plaumann, Smith and Rodrigo.[44] Piperonal and **35** provide the ketal **39**, the precursor to the isobenzofuran derivative that is reacted with dimethyl acetylenedicarboxylate to give the Diels-Alder adduct which is hydrolyzed to the naphthol and then reduced to **40**.

In another application, Kende and coworkers[45] generated 4-methoxyisobenzofuran (**41**) *via* the α-pyrone method,[22] as an intermediate in the construction of the tetracyclic skeleton of the aglycone part (**42**) of daunorubicin, used in cancer chemotherapy (eq. 5).

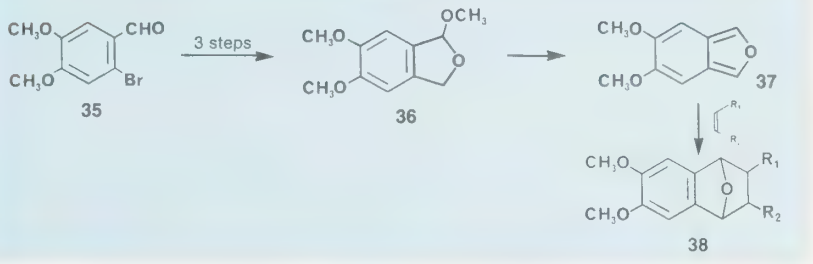
1-Phenylisobenzofuran (**44**) is generated from 2-methylbenzophenone *via* photobromination to **43**, and subsequent elimination of hydrogen bromide by boiling in carbon tetrachloride (eq. 6). **44** is trapped by dienophiles and the adducts **45** are, under the acidic reaction conditions, converted directly to naphthalenes **46**.[46] With methyl vinyl ketone as dienophile, only 1-phenyl-2-acetylnaphthalene was formed in this sequence.

o-Carbonylated phenylcarbenes yield isobenzofurans; for example, the photolysis of 1,4-diphenylphthalazine-*N*-oxide to 1,3-diphenylisobenzofuran is thought to proceed *via* *o*-benzoyldiphenylcarbene.[47] 1-methoxyisobenzofurans **49**[2] are

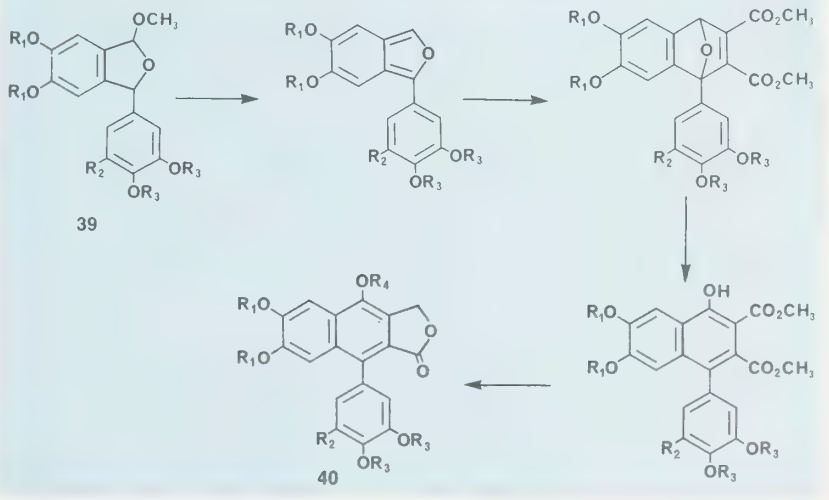


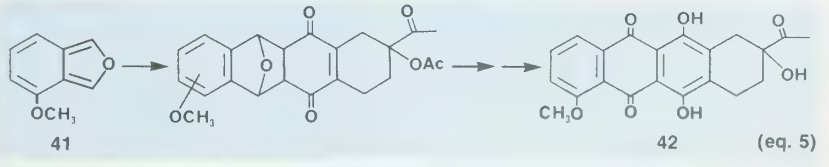


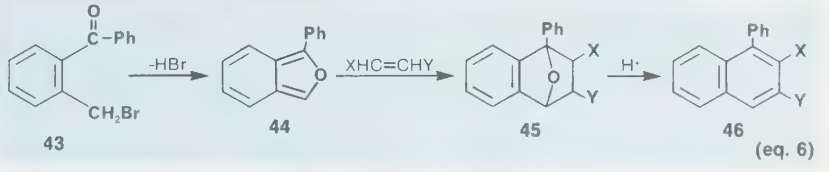
Scheme 4

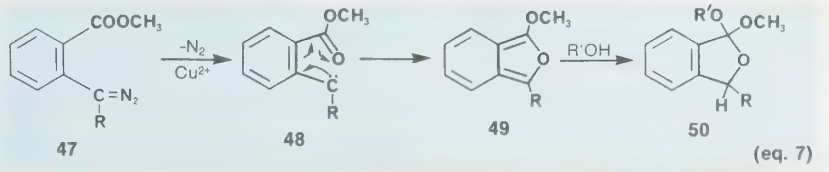


Scheme 5



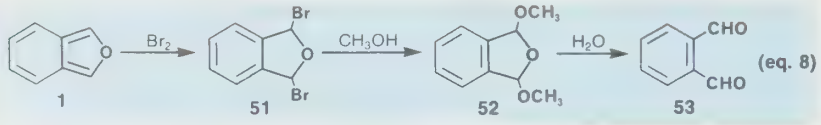






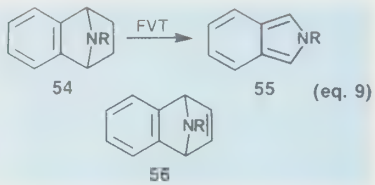
generated and trapped[48,49] in the copper-catalyzed decomposition of *o*-diazomethylbenzoates **47**, *via* the carbene **48** (eq. 7). In the absence of a trapping dienophile, the cyclic orthoester **50** was formed by the addition of alcohols. It was not discussed if this ester reversibly forms **49**. The question of whether the addition of alcohols to isobenzofurans is reversible and the possible existence of equilibria like **1** ⇌ **34** or **36** ⇌ **37** remain to be further investigated.[2]

Bromine reacts instantaneously with isobenzofuran (eq. 8).[50] Work-up in the presence of methanol gives phthalaldehyde (**53**), presumably *via* intermediates **51** and **52**.[50] 1-Hydroxyphthalan can be prepared *via* autooxidation of phthalan.[41] The free-radical chemistry of 1-methoxyphthalan (**34**) has been studied.[51]



GENERATION OF RELATED *o*-QUINONOIDS BY FLASH-VACUUM THERMOLYSIS

Several reactive *o*-quinonoid intermediates have been generated and characterized by FVT procedures. FVT has expanded the scope of the retro-Diels-Alder reaction enormously.[52] Expulsion of ethylene from tetrahydronaphthalenes, analogous to the procedure for isobenzofuran,[1] is rather general. Isoindoles **55** (eq. 9) are obtained from 1,4-imino-1,2,3,4-tetrahydronaphthalenes **54**.[11,36,37] The iminodihydronaphthalenes **56** are good dienophiles.[53,54] Isoindole chemistry continues to grow.[55]



1,4-Methano-1,2,3,4-tetrahydronaphthalene (**57**) yields indene (**59**) quantitatively (eq. 10).[1] The intermediacy of isoindene (**58**) as a discrete species in this reaction could not be firmly established with photoelectron spectroscopy.[56] This method,[57] in addition to matrix isolation,[58] is a good tool for the characterization of reactive intermediates. Indenes thermally equilibrate to isoindenes[59] and can be trapped with olefins.[60]

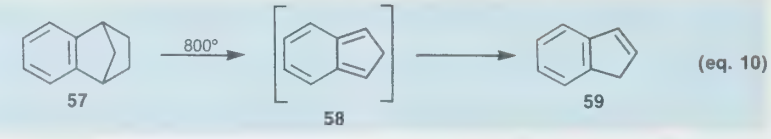
Methylene-methanotetrahydronaphthalenes **60** show a deviant reaction (Scheme 6) to form cyclopentaindenes **61**,[36] which ultimately form benzo[*a*]fulvene (**62**) in good yield.[61] No isobenzofulvene (**63**) was found.

Tetralin (**64**) itself was intensively studied as a hydrogen donor in coal technology.[62] Laser-induced decomposition experiments (eq. 11) indicate that benzocyclobutene (**65**) is the primary product,[63] but under FVT conditions, styrene, indene and naphthalene are major products.[50,63] Benzocyclobutene (**65**) undergoes thermal ring opening (eq. 12) to *o*-quinodimethane (**5**). *o*-Quinodimethanes are highly reactive dienes that enable a similar annelation approach, as *via* isobenzofurans. The field, opened by Cava[64] who trapped **5** in the pyrolysis of 1,3-dihydroisothianaphthene-2,2-dioxide (**66**), has been extensively reviewed.[16,65,66] A large number of preparative approaches to benzocyclobutenes, including many FVT procedures, have been found.[16,59]

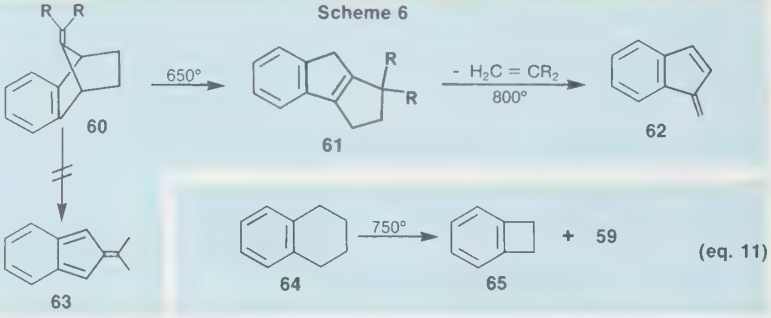
Intramolecular Diels-Alder cyclization, *via* benzocyclobutene ⇌ *o*-quinodimethane intermediates, has been applied to natural-product synthesis by Oppolzer[66] and Kametani.[67] Cava prepared 4-demethoxydaunomycinone[68] (**42**) similarly. His method for the generation of benzocyclobutenes from sulfones of type **66** (eq. 12) was recently applied to the total synthesis of steroids,[69] an alternative to the cobalt-catalysis method of Vollhardt.[69]

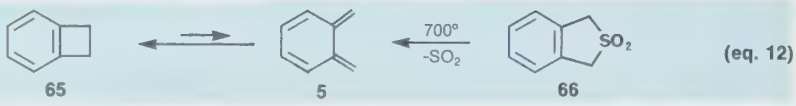
FVT of *o*-methylbenzyl chloride (**67**) is an excellent method of preparation of **65** (eq. 13).[70] Cyclobutapyridines **68** and **69** are prepared in a similar way.[71]

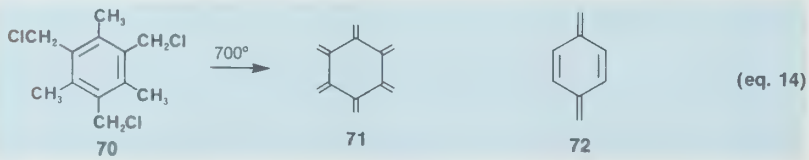
The mechanism of the pyrolysis of **67** was studied by deuterium labeling.[72] FVT of 2,4,6-tris(chloromethyl)mesitylene (**70**, eq. 14) gives hexamethylenecyclohexane (**71**, hexaradialene) in good yield.[16,73,74] *p*-Quinodimethane (**72**) can be isolated by FVT of [2.2]paracyclophane.[75] Boekelheide[74] applied benzocyclobutene pyrolysis to the preparation of multibridged

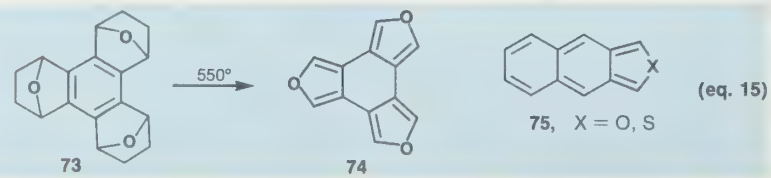


Scheme 6



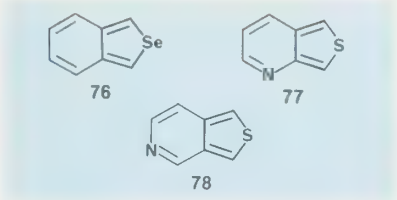






cyclophanes. Hexaradialene (**71**) is structurally related to triphenylene and its heterocyclic analogs, *e.g.*, benzo[1,2-*c*:3,4-*c'*:5,6-*c''*]trifuran (**74**). Several isoannelated furans, including **74**, have been prepared (eq. 15) from the corresponding epoxy precursors[76] such as **73**, *via* retro-Diels-Alder FVT reaction. Non-linear annelation stabilizes the isobenzofuran structural system.[76]

Naphtho[2,3-*c*]furan (**75**, X = O) is expected to be much more unstable and is still unknown. However, the thiophene analog (**75**, X = S), much less stable than **3**,[77] was isolated *via* FVT of the corresponding 1,3-dihydrosulfoxide,[78] according to Cava's dehydration method.[9] This route was also successful for the synthesis of benzo[*c*]-selenophene (**76**),[79] thieno[3,4-*b*]pyridine (**77**), and thieno[3,4-*c*]pyridine (**78**).[80,81]

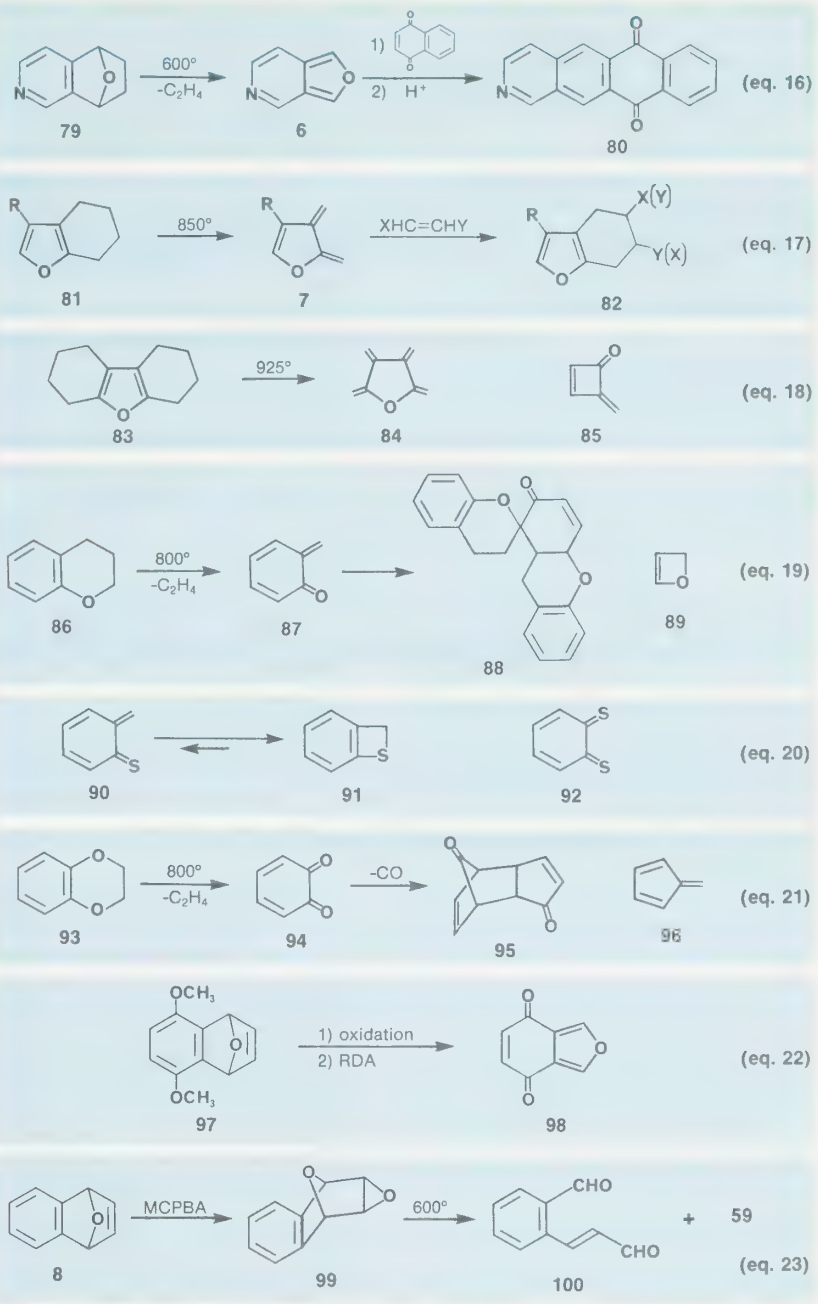


Furo[3,4-*c*]pyridine (**6**) was prepared (eq. 16) by FVT of 5,8-epoxy-5,6,7,8-tetrahydroisoquinoline (**79**).[17] **6** has synthetic potential similar to isobenzofuran, as illustrated by the preparation of 8-aza-5,12-naphthacenedione (**80**).[17]

Tetrahydrobenzofurans **81** produce 2,3-dimethylene-2,3-dihydrofurans **7**, which form a mixture of Diels-Alder adducts (**82**) with activated olefins (eq. 17).[18] **7** is also obtained by FVT of 2-methyl-3-acetoxymethylfurans.[82] Hexaradialene (**71**) has a heterocyclic counterpart in furanoradialene (**84**), formed in a two-step retro-Diels-Alder reaction (eq. 18) of octahydrodibenzofuran (**83**).[83] Another interesting FVT preparation of a furan is the formation of methylenecyclobutenone (**85**) from furfuryl benzoate.[84]

Heteroanalogs of *o*-quinodimethane (**5**) have also been characterized and are expected to have good synthetic potential as well.[74] *o*-Quinonemethide (**87**), usually isolated as the trimer **88**,[85] can be generated from various precursors.[58] FVT of chroman (**86**)[50] gives trimer **88** above 800° (eq. 19), but other fragmentations occur at lower temperatures.[86] In contrast to the *o*-quinodimethane series, *o*-quinonemethides definitely exist in the open form (**87**). The parent oxetene (**89**), however, was isolated at low temperature *via* FVT, although it rearranges rapidly to acrolein at room temperature.[87]

In the sulfur series, benzo[*b*]thiete (**91**) is obtained in good yield as a relatively stable



compound,[88] but it dimerizes and undergoes Diels-Alder reaction[74] *via* the open thio-*o*-quinonemethide **90** (eq. 20). The formation of **91** in the high-temperature pyrolysis of thianaphthene-1,1-dioxide[89] is mechanistically interesting, in comparison to the SO extrusion[90] in the conversion **21** → **22**.[29] Dithio-*o*-benzoquinone (**92**) is reported as an FVT intermediate.[91] Preparatively interesting is the FVT reaction (eq. 21) of benzodioxane (**93**) which shows a genuine retro-Diels-Alder reaction.[92] The primary product *o*-benzoquinone (**94**) is unstable at the applied temperature, and, contrary to *p*-benzoquinone,[93] loses one molecule of CO to yield cyclopentadienone, ultimately isolated as its dimer (**95**) in good yield. At temperatures above 800°, *o*-quinonemethide (**87**) also begins to decarbonylate, thus representing a simple preparation of fulvene (**96**).[94]

Many more FVT reactions, as summarized here, can be run with the simple apparatus shown in Figure 1.[95] In connection with isobenzofuran chemistry, the preparation of isobenzofuran-4,7-quinone (**98**, eq. 22) *via* 1,4-epoxy-5,8-dimethoxy-1,4-dihydronaphthalene (**97**) must be recalled.[96] Diepoxide **99** (eq. 23) is the major metabolite of **8** in rats.[97] It is rapidly

prepared from **8** by *m*-chloroperoxybenzoic acid oxidation and yields *o*-formylcinnamaldehyde (**100**) and indene (**59**) in equal amounts,[98] when subjected to FVT.

CONCLUSION

Isobenzofurans have become readily available synthetic intermediates which can add two rings at an olefinic bond in one step. The presence of the oxygen bridge in the adducts implies aromatization to naphthalene derivatives or hydroxyl functionalization as further strategic possibilities. In the complementary case of benzocyclobutene addition, a tetralin unit is constructed. Heterocyclic analogs of isobenzofuran such as furopyridines, thia-*o*-quinonemethides and dimethylenedihydrofurans allow, in a similar way, the construction of, for example, isoquinoline, thiachroman, or benzofuran units.

The recent abundance of data on the generation of a great variety of the title intermediates certainly enables new approaches in natural-product synthesis. The FVT method is a synthetic means of great value for the title compounds.

Another important conclusion is that FVT is a synthetic method of general utility[95] which encompasses many areas of organic chemistry.[19,99] Isotope labeling of the starting materials in FVT experiments makes these unimolecular, clean, gas-phase reactions likewise suited for mechanistic studies.

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At the AKZO Corporate Research Department, Dr. Wiersum did pioneering work in the area of flash-vacuum thermolysis, with special emphasis on synthetic utility. His research activities include studies in polymer-degradation mechanisms in relation to polymer additives as flame retardants, polymerization initiators and antioxidants.

The Role of Silver Salts in Organic Processes

John R. Long
Aldrich Chemical Company, Inc.

INTRODUCTION

In the early 1970's, topical reviews[1-6] and resources such as the Fiesers' *Reagents for Organic Synthesis* highlighted many uses of silver compounds in organic synthesis. This article extends that perspective by supplementing earlier citations with reports of recent applications such as rearrangements and isomerizations, cycloadditions and ring expansions, oxidative cleavages and couplings, and alkylations.

Despite its wide range of applications, silver chemistry has remained rather specialized, an inference readily drawn from literature of the mid-seventies. Ozin[2] described some rather selective silver chemistry (including the use of silver supported on silica in the catalytic oxidation of ethylene) in his account of metal-ion-matrix chemistry; however, Kozikowski and Wetter[3] reviewed transition metals in organic synthesis with great emphasis on first-row (Group B) elements and platinum-group metals but made no mention of silver.

SILVER CARBONATES AND CARBOXYLATES

McKillop and Young[4] recently reviewed the use of supported reagents in organic preparations and highlighted numerous applications of the Fetizon reagent (silver carbonate on Celite) including: 1) general, selective and unusual oxidations; 2) fragmentation reactions; 3) rearrangements of bromohydrins; and 4) oxidations of nitrogen compounds (see Fig. 1).

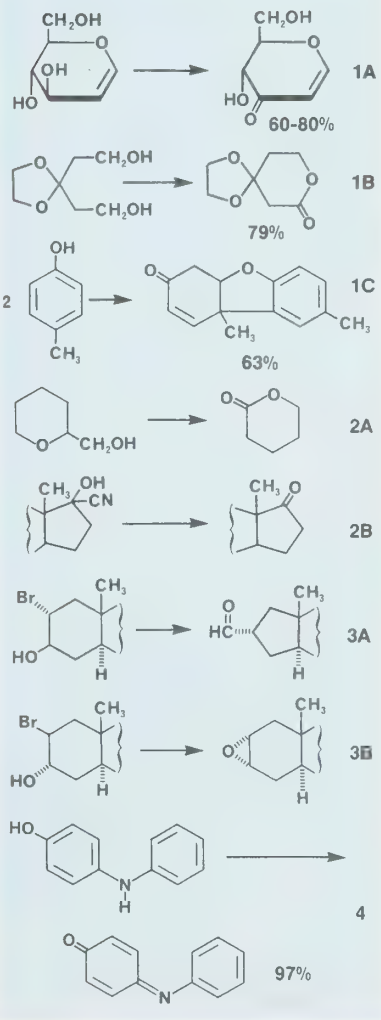
The Fetizon reagent is most effective when prepared immediately before use; the Fiesers described its role in the oxidative coupling of phenols and anilines (eq. 1)[5] and in the oxidation of 1,4-diols to lactones.[6]

In the course of the recent synthesis of (±)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol, **2**, an intermediate in the synthesis of anthracyclinones, the Fetizon reagent was the only suitable means of oxidizing **1** to **2** (eq. 2).[7] Attempts to effect the conversion with Collins reagent, pyridinium chlorochromate, pyridinium dichromate, or $NCS/Me_2S/Et_3N$ were unsuccessful.

Examination of some reactions characteristic of unsupported silver carbonate shows that the elimination of silver halide, the driving force for a large number of silver-induced transformations, is frequently utilized; eq. 3 is an example.

Work on glycoside synthesis showed that, relative to the Konigs-Knorr synthesis, improvements in reaction conditions and yield could be achieved by treating gluco-

Figure 1



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pyranosyl bromides with appropriate silver salts of dicarboxylic acids or hydrocarboxylic acids.[8] Extended to alcohols of various types, the reaction sequence seems to follow a trimolecular synchronous mechanism (eq.4).

A variety of tertiary alkyl chlorides have been converted to di-*t*-alkyl ethers by a slight excess of silver carbonate in pentane at 20°C (eq. 5).[9] The yield of the hindered ether decreased as the alkyl groups became bulkier. Silver oxide was not as effective in promoting the conversion as shown by comparative data (Table 1). It was suggested that calcium hydride suppressed the formation of the alcohol by reacting with a postulated silver hydroxide intermediate. Preparations of these hindered ethers using HgO, ZnO, $ZnCO_3$, PbO_2 and Tl_2O_3 were not satisfactory.

Silver carbonate was found to be the most effective of a variety of silver salts used as catalysts in novel syntheses of enol esters from carboxylic acids and acetylenic compounds (eq. 6).[10]

Another transformation attributed to the chemists who popularized the reagent is the Prévost-Woodward[1b] reaction which utilized silver acetate and iodine in tandem. In wet acetic acid, the reagent converted the olefinic diketone **3** (eq. 7) to the diacetate **4** as part of a stereocontrolled total synthesis[11] of the triacetate precursor of 20-hydroxyecdysone, a highly oxidized crustacean molting hormone.

The Prévost reagent is also commonly known as the silver benzoate-iodine combination; Gunstone[12] described this reagent and its variations in conjunction with trans-hydroxylation of olefins as a function of reaction stoichiometry (eq. 8).

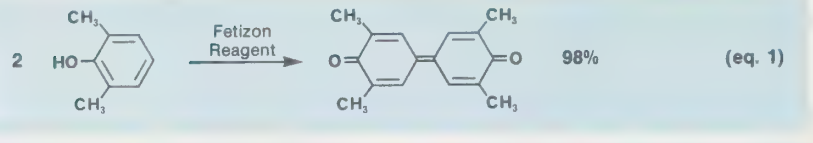
The reagent also cleaves α-glycols to carbonyls[13] and may be effective in transformations where complications from free iodine are negligible.

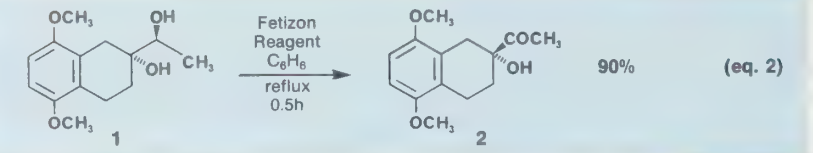
A recent report on the synthesis of α-acyloxy carbonyl compounds featured a study of the oxidation of enol silyl ethers by seven different silver carboxylate-iodine combinations.[14]

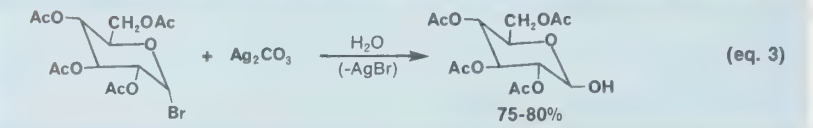
PRINCIPAL ACTIVE AREAS

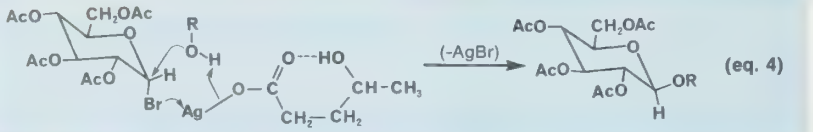
A few selected topics which represent areas of most active research involving silver salts in organic processes are:

1) general synthetic procedures which are "silver-assisted"
2) oxidative processes, also frequently described as "silver-assisted"
3) rearrangements and ring contractions
4) cycloadditions and ring expansions
5) alkylations and dealkylations
6) protecting-group removal and other specialized uses.









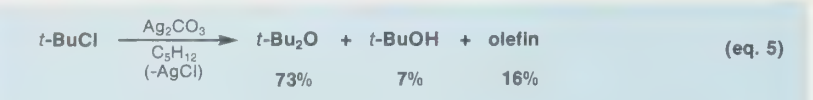
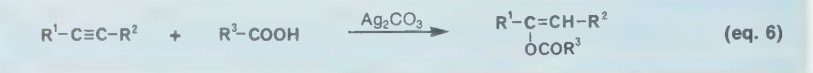
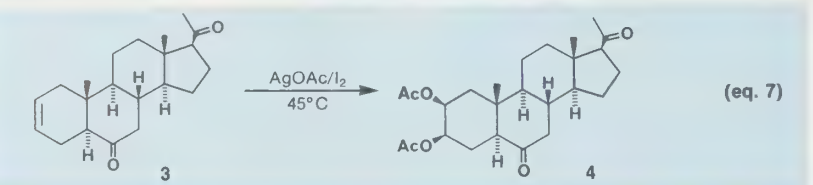
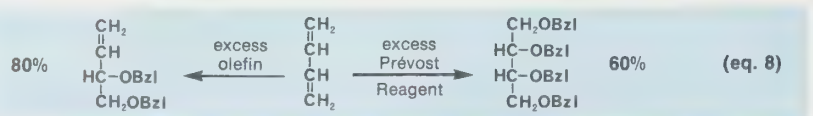


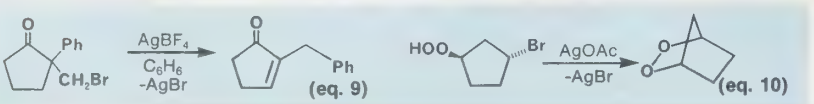
TABLE 1

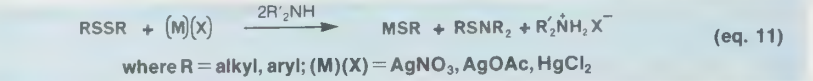
SUBSTRATES	CONDITIONS	YIELD (%) $[Et(Me)_2C]_2O$	$Et(Me)_2COH$	olefin
$Et(Me)_2CCl$; Ag_2CO_3	hexane/20°/20h	47	21	32
$Et(Me)_2CCl$; Ag_2O	hexane/35°/20h	34	27	39
$Et(Me)_2CCl$; Ag_2O/CaH_2	hexane/35°/40h	16	1	83











Silver-Assisted Transformations

There are many ways in which the silver ion assists in organic transformations to yield unique products. Its solubility property is exploited in eqs. 9[15] and 10.[16]

Equation 11 depicts the synthesis of sulfenamides, important intermediates in organic synthesis. Their preparation is greatly simplified in a one-pot synthesis[17] in which, compared to eqs. 9 and 10, more direct interaction of the silver ion with substrate occurs. Mercuric chloride is preferred where silver nitrate reacts with the amine; however, somewhat lower yields and diminished product stability are obtained with the mercury salt.

A formidable synthetic problem involving Diels-Alder routes to potential trichothecene precursors was solved by the use of silver acetate as shown in eq. 12.[18]

Silver cyanide has a catalytic effect in the reaction between acid chlorides and alcohols to form hindered esters. The data appear to rule out acyl cyanide intermediates although precise definition of the mechanism is complicated by the fact that silver trifluoroacetate or carbonate as well as copper cyanide are ineffective for this transformation.[19]

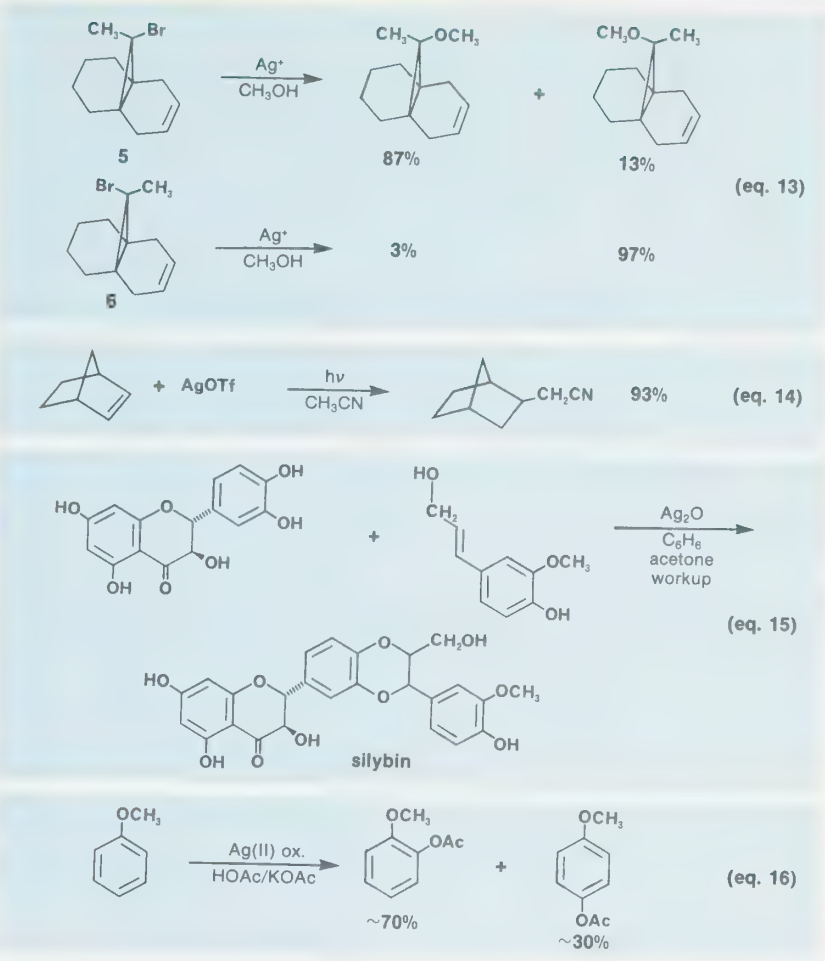
Silver ion can be used to activate 2-pyridylthiol esters by complexation to promote lactonization.[20]

The silver-assisted methanolyses of **5** and **6** (eq. 13) are particularly interesting because in **5** the silver ion is subject to a concerted interaction involving both π-complexation with the double bond and the attraction leading to bromide displacement. Ensuing rearrangement results in an unexpectedly great proportion of secondary product (13%) in comparison with methanolysis of **6** which favors the halide displacement with minimal competition from the Ag-π interaction.[21]

Irradiation of an acetonitrile solution of norbornene and silver trifluoromethanesulfonate (AgOTf, silver triflate) effects a conversion (eq. 14) involving a surprisingly complex mechanism.[22]

Mechanisms have been proposed for a number of silver-assisted transformations. The reaction of terminal alkynes with iodine in methanol may produce diiodoalkenes *via* a molecule-induced homolytic radical mechanism, but in the presence of silver ion, diiodoketones and substitution products are also formed in considerable yield, presumably *via* an ionic mechanism.[23]

A mechanistic study of the reactions of methylallyl chlorides with silver nitrate in acetonitrile has been reported,[24] and the stereoelectronic control in the S_N1 mechanism of the silver(I) ion-catalyzed acetolysis of



various bromo-4-en-3-oxo steroids was recently discussed.[25]

The determination of mechanisms in transformations involving natural product derivatives is a complex exercise. The oxidative coupling of substituted catechols with isoeugenol or coniferyl alcohol in the presence of Ag_2O is highly regioselective when the catechol bears an alkyl substituent.[26] While a free-radical coupling mechanism has been proposed similar to that suggested for the biosynthesis of silybin,[27] the possibility that a π-silver complex is assisting the reaction warrants further investigation. Evaluation of the system is made more interesting in that the best route to a simple biomimetic synthesis of silybin involved oxidation with equimolar amounts of silver(I) oxide (eq. 15).[26] The reaction seemed to be fairly general in scope.

The coupling of selectively blocked bromosaccharides can be effected with either silver triflate or $Ag_2CO_3/AgClO_4$.[28]

Selected Oxidations

As part of a series on metal-ion oxidations, Nyberg and Wistrand[29] discussed the oxidative acetoxylation of aromatic compounds in acetic acid by silver(II) complexes with nitrogen-containing ligands. Such high-yield catalytic reactions can be initiated either by presynthesized $Ag(bpy)_2S_2O_8$ or by a AgOAc/2,2'-bipyridine/$K_2S_2O_8$ mixture. The procedure may be useful for the preparation of alkoxy- and hydroxy-substituted derivatives of aromatic acetates (eq. 16).

Comparative studies were carried out with Ag(II) complexes having non-oxidizing counterions, *viz.* silver(II) dipicolinate and $Ag(bpy)_2(OTf)_2$. The reaction proceeded independently of the anion *via* a mechanism involving removal by Ag(II) of one electron from the aromatic substrate to form a radical cation. Previous studies have shown that the primary oxidant is indeed Ag(II), formed by the action of $S_2O_8^{2-}$(or $SO_4^{\cdot}$) on Ag(I).[30] The authors also reported catalyst efficiencies of between 1,500 and almost 10,000%.

Silver dipicolinate has also been shown to act as a highly selective oxidant in the synthesis of novel quinones (eq. 17).[31]

Persulfate-silver ion oxidations of numerous substrates have been reported recently, along with much discussion on the

mechanism. The development of this area bears considerable potential for new selective synthetic procedures.

In order to better define the role of the silver ion, Caronna *et al.* used protonated quinoline to trap nucleophilic free-radical intermediates formed during the oxidation of various alcohols.[32] The authors concluded that alkoxy radicals were formed in all cases (eq. 18).

Drawing similar conclusions, Walling and Camaioni emphasized that both the oxidants $SO_4^{\cdot}$ and Ag(II) are present in such systems and may show different selectivity patterns yielding very different products.[33]

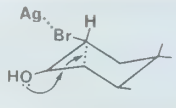
Clerici[34] reported new types of selective homolytic aromatic substitutions involving protonated heteroaromatic bases. The reaction shown in eq. 19 occurs in lower yield in the absence of Ag^+.

Clerici and Porta[35] showed that unsaturated aliphatic and arylalkyl alcohols were oxidized by $S_2O_8^{2-}/Ag^+$ to cyclic ethers through different pathways. Contributing factors included chain length and heteroatom influence; the primary step is the formation of the alkoxy radical and hydrogen abstraction.

Silver ion has also assisted pyridinium chlorochromate in the oxidation of tertiary 2-alkylcyclopropylcarbinols to corresponding β,γ-unsaturated ketones (eq. 20),[36] a synthetically useful method for 1,4-carbonyl transposition.

Rearrangements/ Ring Contractions

Silver-ion-induced ring contraction of steroidal bromohydrins is both stereospecific and highly dependent upon the conformation of the bromine atom.[37] As in eq. 3A (Figure 1), ring contraction occurs if the



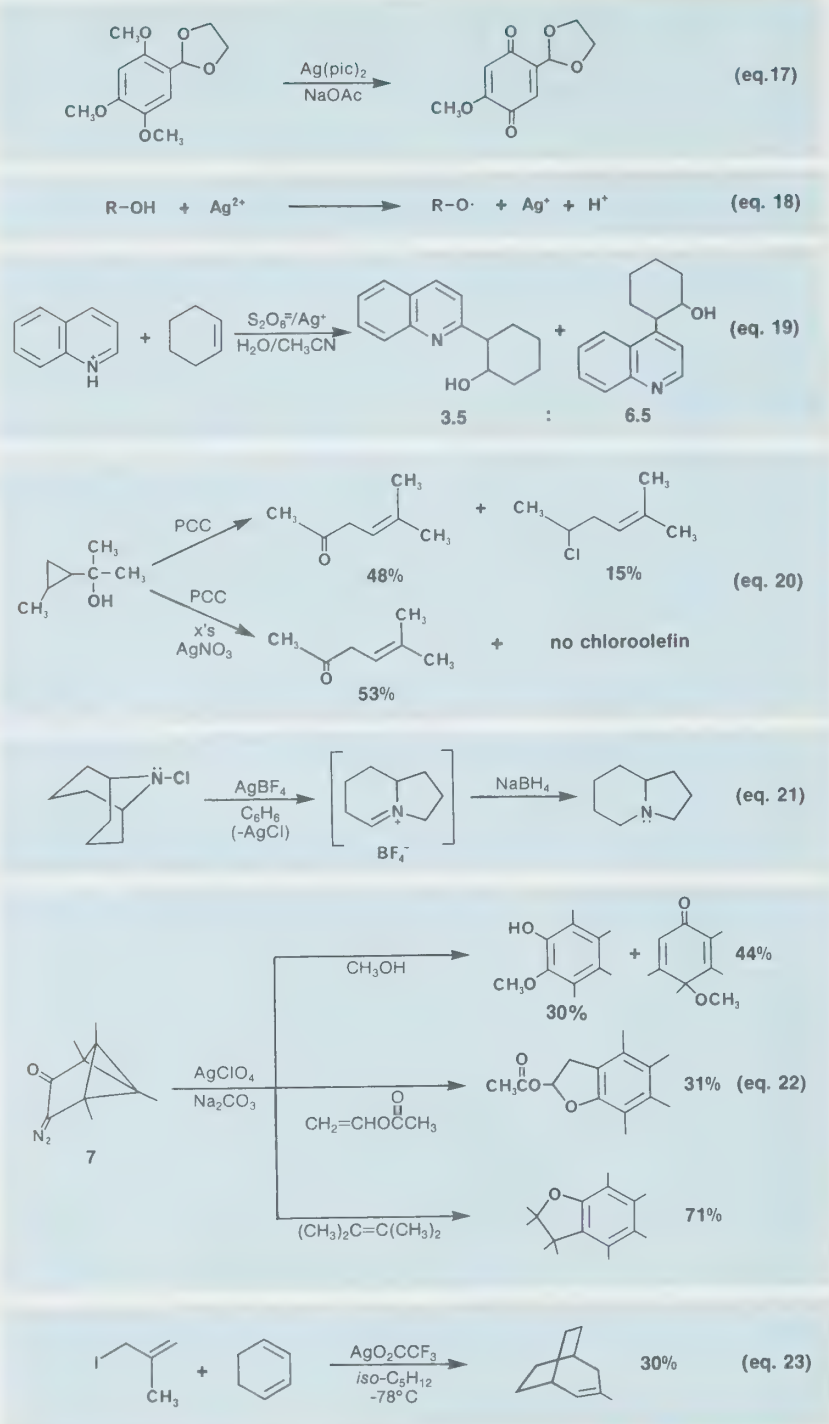
bromine atom is equatorial; if the bromine is axial, oxide or ketone formation (*via* hydride shift) occurs.

Schell[38] recently reported the first ionic rearrangement product isolated from a silver-ion-induced reaction of a chloramine (eq. 21) as part of a continuing model study for the synthesis of alkaloids containing a bridgehead nitrogen.

The procedure allows the isolation of primary products in good yield by preventing oxidation of immonium-ion-rearrangement products and minimizing production of secondary amines.

Silver perchlorate catalyzes loss of nitrogen from the strained-ring diazoketone **7** to yield an α-ketocarbene which undergoes further rearrangement (eq. 22).[39] Sodium carbonate prevented possible acid catalysis, but its presence raised the possibility that silver carbonate might have been a participating entity.

A similar study has shown that only appropriate substitution of the benzotricycloheptene framework with labilizing substituents permits silver-ion-induced skeletal rearrangement.[40]



Cycloadditions/Ring Expansions

Several studies by Hoffmann and coworkers[41] on cycloadditions of allyl cations to conjugated dienes have provided data pertaining to both reaction conditions and the role of various silver counterions in the process. The authors stated that the most important factor in optimizing the yield of a reaction such as shown in eq. 23 is the nature of the silver counterion.

The authors were also able to initiate the first cycloaddition of an open-chain diene (eq. 24).

If silver tetrafluoroborate is used in the reaction, the BF_4^- ion is not effective in stabilizing postulated intermediates, and can cause the untimely production of HBF_4 which promotes the polymerization of reactants and products. Electrophilic catalysts such as silver benzoate or silver acetate give only allylic esters, even with the reactive cyclopentadiene.

Silver trifluoroacetate seemed to be even more effective than the trichloroacetate because it is soluble in both ether and water, it bears considerable thermal and photochemical stability, and it liberates little if any trifluoroacetic acid. Silver trifluoroacetate supported on diatomite resulted in little change in product yield or distribution, indicating that the reaction can proceed in either a homogeneous or heterogeneous mode.

Silver trifluoroacetate has been used more recently to promote the reaction of allenyl cations with dienes (eq. 25).[42]

Jendralla[43] has been able to isolate thermally stable, moderately light-sensitive *trans*-cycloheptene derivatives with $AgClO_4$ and $AgOSO_2CF_3$, and carry out cycloadditions with several dienes (eq. 26).

Both $AgBF_4$ and $AgPF_6$ have been applied to the cycloaddition of vinyl bromides to various olefins in methylene chloride.[44] The method gives high yields and appears to be widely applicable.

Loozen[45,46] has investigated the silver-ion-assisted ring expansion of geminal dibromobicycloalkanes, and has discussed the application of silver perchlorate, silver tosylate and silver nitrate to complex transformations such as shown in eq. 27. The method enables the stereospecific synthesis of medium-sized rings apparently *via* a free cationic intermediate.

Alkylations/Dealkylations

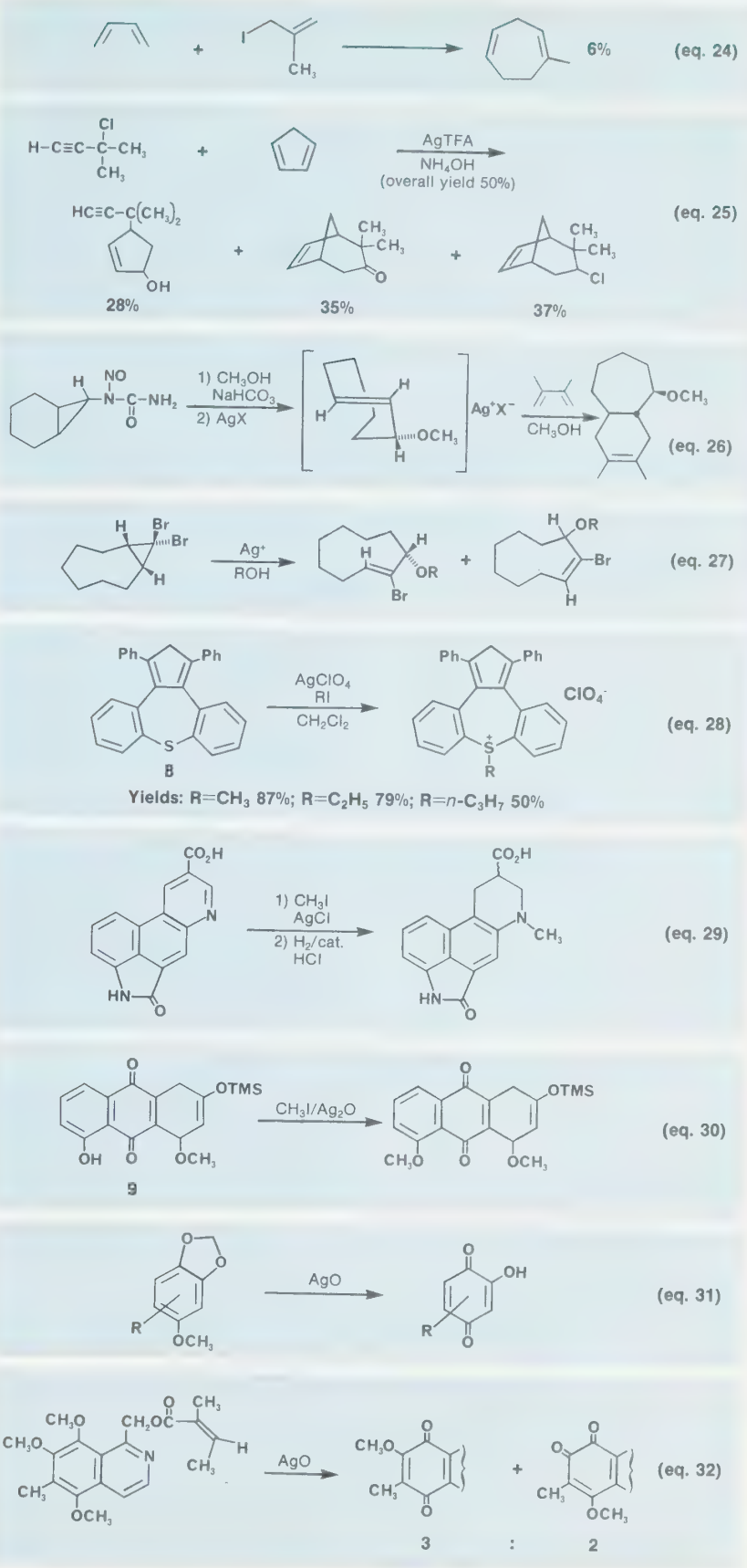
Silver perchlorate promotes the reaction of alkyl iodides with the thiazulene **8** to give thiazulenium salts in various yields (eq. 28).[47]

Silver chloride/methyl iodide was used recently to methylate at nitrogen in the ergoline ring system of ergot alkaloids (eq. 29).[48]

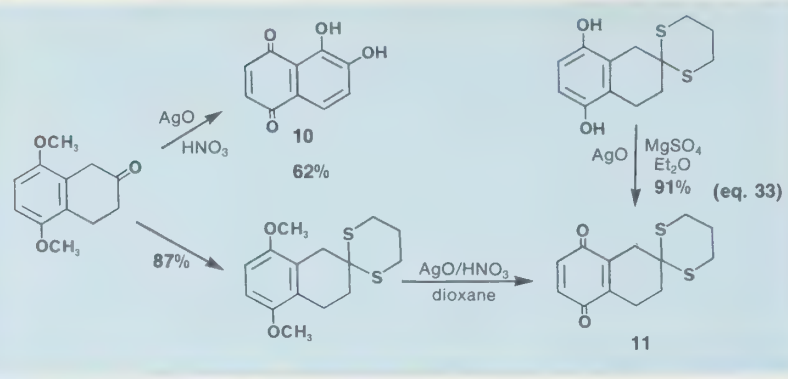
A silver(I) oxide/CH_3I methylation of a hydroxyl group of the anthraquinone **9** was carried out in chloroform (eq. 30).[49]

Oxidative demethylations[50-52] are commonly carried out with AgO (eqs. 31 and 32).

Both Ag_2O and AgO have been used by Farina and Torres[53] in the synthesis of naph-

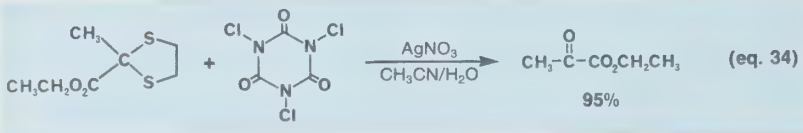


thoquinone derivatives which are valuable intermediates in the preparation of antitumor anthracyclines. An unexpectedly convenient synthesis of *o*-naphthazarin (5,6-dihydroxy-1,4-naphthoquinone), **10**, arose from an attempt to prepare the thioacetal **11** from 5,8-dimethoxy-2-tetralone (eq. 33).

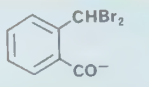


Specialized Applications

Olah[54] has used the industrial chemical trichloroisocyanuric acid in place of *N*-chlorosuccinimide in the cleavage of ethanediyl S,S-acetals, a reaction which can be carried out quickly at room temperature in the presence of silver nitrate (eq. 34).

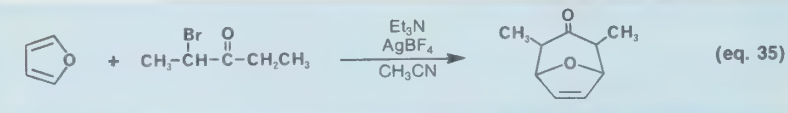


Removal of the protecting group DBMB from 2-dibromomethylbenzoate esters has

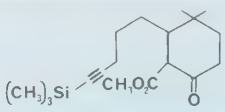


DBMB

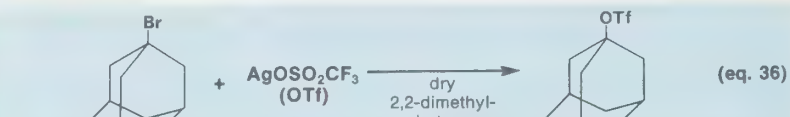
been carried out under exceptionally mild conditions with silver perchlorate/lithium bromide.[55] This technique should be useful in transformations involving sensitive compounds such as oligonucleotides; its application in the synthesis of adenylyl-(2′→5′)-adenylyl-(2′→5′)-adenosine has been described.[56]

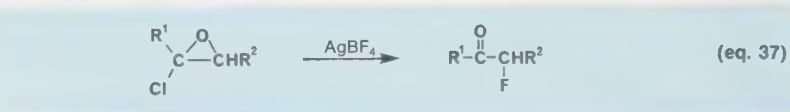


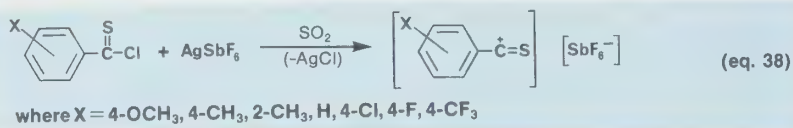
Deprotection of the acetylenic intermediate



was carried out with $AgNO_3$-KCN because KF/DMF/H_2O led to aldol condensation products.[57]

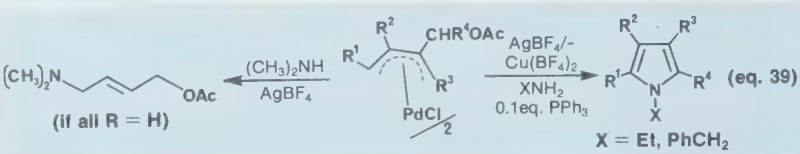






where X = 4-OCH_3, 4-CH_3, 2-CH_3, H, 4-Cl, 4-F, 4-CF_3

A new method for generating oxyallyls from α-bromoketones uses silver tetrafluoroborate/NEt_3 to promote the reaction in the presence of various furans.[58] This produces cycloadducts useful in the synthesis of biologically active analogs of α-multistriatin (eq. 35).



Studies on the thermal decomposition of silver salts of aryldinitromethanes in the presence of unsaturated systems[59] and of arenesulfinates[60] have shed additional light on a relatively unexploited area of silver chemistry.

The specialized reactions of other simple and complex fluoride salts of silver merit discussion. Zweig[61] and co-workers described a new method for selective monofluorination of aromatics using silver difluoride as a strong oxidant and fluoride source. Oxidative fluorination of diaryl diselenides has also been reported.[62]

Silver ion catalysis of fluoroxysulfate oxidations has demonstrated surprising selectivity toward certain inorganic substrates, and the system may bear considerable potential as a chemical reagent in organic processes.[63]

Silver(I) fluoride was required to induce fluorine exchange with di-, tri-, and tetrabromoadamantanes, providing the respective fluoroadamantanes in about 70% yield.[64]

Recently, the first reported preparation of 1-adamantyl triflate using silver triflate was described (eq. 36).[65]

Silver triflate[66] and silver methanesulfonate[67] are also convenient precursors to a number of alkylmethanesulfonate derivatives useful as alkylating agents for aromatic compounds.

Silver tetrafluoroborate reacts with chlorinated oxiranes to produce α-fluorinated carbonyl compounds (eq. 37).[68]

Olah has shown that silver hexafluoroantimonate, $AgSbF_6$, is an electrophilic bromination catalyst[69] and is useful in promoting chlorination of reactive alkanes.[70] A later report has shown the salt useful in the generation of thiobenzoyl cations (eq. 38).[71]

There seems to be great potential in the area of silver-assisted transformations of complexes stabilized by other metals. For example, $AgBF_4$ plays an important role in

the palladium-promoted 1,4-cycloamination of 1,3-dienes to pyrroles (eq. 39),[72] a significant class of compounds to which simple synthetic approaches are lacking.

Vermeer *et al.* have extended the chemistry of lithium bromide-stabilized alkyl silver complexes ($RAg \cdot 3LiBr$)[73] to include the synthesis of alkylated butatrienes, RCH_2-$C(R')=C=C=CR^2R^3$, from the enynylmethanesulfinates $H_2C=C(R')C\equiv C$-CR^2-R^3OSOCH_3.[74]

Such transformations may follow mechanisms which utilize the silver ion in both σ and π bonding modes; they are also interesting because of the parallels and contrasts that can be drawn with organocopper chemistry.

A similar magnesium-stabilized complex was recently reported for the *trans*-addition shown in eq. 40.[75]

A brief examination of the use of silver compounds in some recent preparations of organometallic and coordination compounds is also instructive because such studies may pertain to complex catalytic processes.

The preparation of the first structurally characterized alkoxyplatinum compound employed silver ion (as $AgNO_3$) to effect chloride displacement from $Pt(COD)Cl_2$ and provide an intermediate susceptible to the base-induced methoxidation shown in eq. 41.[76]

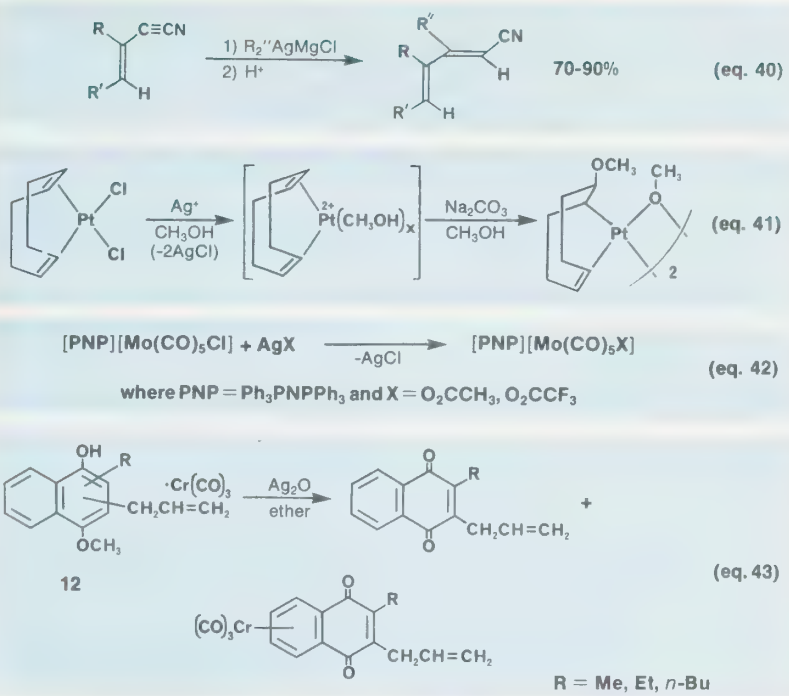
Alkoxy and hydroxy complexes of Pt(II) may be intermediates in the preparation of hydridoplatinum complexes[77,78] and in catalytic processes such as the hydration of nitriles.[79]

Salts such as $AgBF_4$, $AgPF_6$, $AgOSO_2$-CF_3 and $AgOSO_2C_6H_4CH_3$ have the capacity to serve a dual function in some synthetic procedures: the introduction of a complex anion to assist in the stabilization of the desired product, and the generation of unique intermediates by chloride displacement.

Silver hexafluorophosphate has been used in preparations of adducts formed with neutral diamagnetic organometallics; these derivatives can function as controlled sources of highly reactive radical cations.[80] An example is $Ag[Rh(CO)PPh_3(C_5H_5)]_2$-$[PF_6]$ which contains Ag-Rh bonds and is a stable source of the reactive radical cation $[Rh(CO)PPh_3(C_5H_5)]^{\bullet +}$.

Cotton *et al.*[81] found both silver acetate and silver trifluoroacetate useful in the synthesis of novel aceto complexes of molybdenum and chromium which exhibit a monodentate acetate group which may be a strongly labilizing ligand (eq. 42).

Some interesting chemistry has been demonstrated by Doetz and Pruskil[82] in complex reactions between silver(I) oxide and **12**, the condensation product of pentacarbonyl(methoxyphenylcarbene)chromium(0) and selected enynes (eq. 43).



Yields are low, the reaction likely complicated by the fluxional interaction between the tricarbonylchromium moiety and the delocalized aromatic groups.

While we acknowledge the omission of the specifics of numerous traditional applications of silver salts to organic processes (such as Lewis acid-catalyzed nitrations using $AgNO_3$),[83] we are interested in keeping new applications in a high profile for our readership. Please feel free to submit any new, unusual, or overlooked reports of such usage to our editor for future updated reviews.

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About the Author

Dr. John Long received the B.S. degree from the University of Toledo in 1967 and the Ph.D. degree in 1973 from the Ohio State University where he worked with Professor Sheldon Shore in the area of boron hydride chemistry. Postdoctoral appointments at the Ames Laboratory (Iowa State University) and the National Bureau of Standards afforded him the opportunity to investigate the chemistry of rare-earth water-splitting cycles and the synthetic potential of laser-induced chemistry, respectively. Dr. Long's arrival at Aldrich coincided with the company's expansion of the Inorganics Division into a highly successful product line.

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18,453-5	Silver cyanide
D9,350-3	Silver diethyldithiocarbamate, 99%
20,092-1	Silver difluoride
22,687-4	Silver dipicolinate
22,686-6	Silver fluoride*
22,773-0	Silver hexafluoroantimonate
22,772-2	Silver hexafluorophosphate
22,682-3	Silver iodide*
M870-3	Silver methanesulfonate
20,913-9	Silver nitrate,* 99.9+%, A.C.S. reagent
22,718-8	Silver nitrite
22,116-3	Silver(I) oxide*
22,363-8	Silver(II) oxide
22,654-8	Silver perchlorate hydrate
22,567-3	Silver sulfate*
20,836-1	Silver tetrafluoroborate
17,642-7	Silver *p*-toluenesulfonate
T6,240-5	Silver trifluoroacetate
17,643-5	Silver trifluoromethanesulfonate

*Ultrapure grades of these items are also available; please consult your catalog or call for prices.

A Compilation of References on Formyl and Acyl Anion Synthons

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Dr. Koskimies

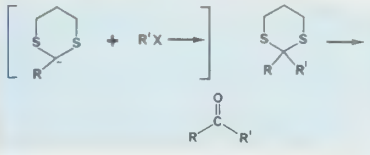
This compilation is intended to include acyl synthons which yield carbonyl compounds by direct alkylation

$$RCO^- + R'-X \longrightarrow R-CO-R'$$

or addition

$$RCO^- + R'-CHO \longrightarrow RCO-CHOH-R'$$

requiring the unmasking of the carbonyl group only, *e.g.*,

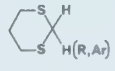
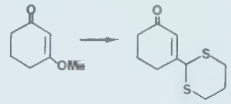
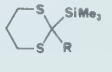


Thus, the various homologative reactions, *e.g.*,

$$R-CHO \longrightarrow RCH_2-CHO$$

(such as use of $Ph_3P{=}CH-OR$) are excluded although these are often somewhat loosely cited as examples of nucleophilic acylation.

Note that RCHO (or RCDO) will be obtained on quenching a RCO^- synthon with water (or D_2O). This trivial solution is omitted from the Table, but other electrophiles are given as originally reported. Expressions such as C=C–C=O are used to cover both aldehydes and ketones, and imply generality in regard to double-bond substitution. A direct or Michael addition to such species is indicated by "1,2-" or "1,4-", respectively, in parentheses. Individual compounds (*e.g.*, $CH_2{=}CHCH_2OAc$) are only shown when generality is lacking or was not reported. Although many of the acyl anion reagents listed can accommodate functionality in R (or Ar) such as unsaturation, ether groups, etc., it is intended that a compilation of R-functional RCO^- synthons be presented later. Similarly, synthons such as ^-COOH and derivatives, ^-C-OH, $^+C-C{=}O$, etc., fall outside the scope of the present tabulation.

Equivalence	Reagent	Electrophile	Ref.
HCO^- (RCO^-, $ArCO^-$)		RX, ROTs (cyclic or tertiary unreactive), aldehydes, ketones	1
		$ROSO_2Ph$ (primary only)	2
		oxiranes, oxetanes	1,3,4
		RCOCl, RCOOR', ArCN	1
		$HCOOEt$, $(COOEt)_2$ for aryl dithianes	5
		C=C–C=O (1,2- *vs.* 1,4-addition)	6-10
		$C{=}C-CONR_2$ (1,4-)	11
		$C{=}C-NO_2$ (1,4-)	12
		$C{=}N^+R_2$	13
		$ArC{\equiv}N \rightarrow O$ (→ α-oximinodithiane)	14
		RSSR	15
		Me_3SiCl, Me_3GeBr, Ph_3SnCl	16-18
		allylic alcohol (S_N2')	19,20
			21
			18
		 C-anion generation with F^-; for cyclization [R = $(CH_2)_nCHO$ or enal]	22
		 (*i.e.*, overall 1,4-addition to enones)	23,24

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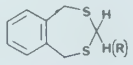
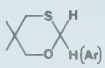
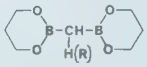
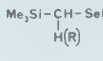
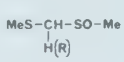
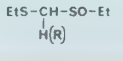
Equivalence	Reagent	Electrophile	Ref.
		selective reaction with ArCHO *vs.* ketones	25
		stereochemistry of the anion	26
		stereoselective addition to cyclohexanones	27
HCO^- (RCO^-)		primary RBr, RI, ketones, oxiranes, ClCOOEt	28
HCO^-		RBr, RI, ketones	29
HCO^- (RCO^-)		oxiranes	30
HCO^-		primary RX, ketones, oxiranes, enones (1,2-)	31
RCO^-	$(R'S)_2CHR$	RCl	32
		Me_3SiCl	16
		oxiranes	33,34
		ketones, CO_2, ClCOOEt	35
		enones (1,4-)	10,35,36
RCO^-	$(PhS)_2CHR$	RBr, RI	37,38
		Me_3SiCl	16
		ketones	39-41
		enones, enoic esters (1,2- and 1,4-)	10,42,43
HCO^-	$(R_2NCS\text{-}S)_2CH_2$	RI (primary)	43,44
HCO^-	$MeS\text{-}CH_2\text{-}S\text{-}CSNMe_2$	RBr, RI (primary)	45
HCO^-	$PhS\text{-}CH_2OMe$	RBr, ketones, lactones	46,47
HCO^-		RBr, RI (primary)	48
HCO^- ($ArCO^-$)		MeI, ketones, ArCOOEt chiral anion	49-51
HCO^-	$PhS\text{-}CH_2SiMe_3$	RBr, RI, oxiranes	52-54
HCO^- (RCO^-)		RBr, RI, ROTs; PhCHO ⟶ $PhCH_2COR$ and PhCOOMe ⟶ $PhCOCH_2R$	55
HCO^- (RCO^-)		RBr, RI (primary)	56,57
		ketones	57,58
RCO^-	$(PhSe)_2CHR$	RX, Me_3SiCl, oxiranes, ketones	59
		enones, enoic esters (poor 1,2- *vs.* 1,4-selectivity)	10
RCO^-		intramolecular rearrangement of the ylid	60,61
HCO^- (RCO^-)		RX, ketones, RCOOR′	62,63
HCO^- (RCO^-)		RBr, RI, ROTs	64-66
		dialkylation with RX	67
		with α,ω-dihalide	68-70
		2-Br-pyridine	64
		$C{=}N^+R_2$	13
		ketones	71
		RCOOR′	72
		PhCHO, RCN⟶abnormal products	73-75
		Cyclopentenone 1,4- but cyclohexenone unselective	76
		rearrangement	66
HCO^- (RCO^-)		RBr, RI (primary), ketones, RCOOR′, RCOCl, C=C-COOR (1,4-) unselective for enones	77-80

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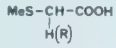
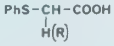
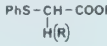
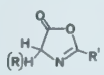
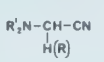
Equivalence	Reagent	Electrophile	Ref.
HCO^-	*p*-tolyl-S-CH_2-SO-*p*-tolyl	chiral products from RCHO, cyclopentenone (1,4-)	81-82
HCO^-	Me_3SiCH_2-SO-Ph	MeI	83-84
		PhCOOEt	85
		ketones (→R_2C=CH-SO-Ph)	85
HCO^-		RBr, RI, Me_3SiCl, ketones	86
HCO^-	$TsCH_2$-pyridinium	maleic anhydride (1,4-)	87
HCO^-	$PhSO_2$-CH_2NO_2	RX (primary), CH_2=$CHCH_2OAc$(Pd)	88
HCO^-	$PhSO_2$-CH_2O-CHMe-OEt	RX, ketones	89
HCO^- (RCO^-)		RBr, RI	90-93
		MeSSMe	91
HCO^- (RCO^-)		RX, ketones, enones (1,2-)	94-96
HCO^- (RCO^-)		ketones; enones and enoic esters (1,4-)	95
HCO^-	NC-CH_2S-CS-NMe_2	RX (primary), α,ω-dihalides	97
HCO^- (RCO^-)		RX	98-100
		CH_2=CHCN, HC≡CCOOMe (1,4-)	101,102
RCO^-	PhCH=N-CHR-COOEt	RX; enones and enoic esters (1,4-)	103
HCO^- (RCO^-)		RX (primary, secondary)	104-106
		ketones, oxiranes	104,107
		enones (1,4-)	104
		enoic esters (1,4-)	108
$ArCO^-$	Ar-CH(NR'_2)CN	RX	109,110
		C=C-CN (1,4-)	111-113
		enoic esters (1,4-)	111
RCO^-	R-CH(OR')-CN	RCl, RBr, RI, ROTs (primary, secondary)	114-117
		ketones	115-119
		enones (1,4-)	118,119
		preparation	120-126
$ArCO^-$	Ar-CH(OR')-CN	RX, R_2SO_4, ROTs	127,128
		ketones	129,130
		cyclohexenone (1,2- or 1,4- selectively)	131
		acyclic enones (dependence on substituents in Ar)	132
		quinoline N→O (attack at C-2)	133
$ArCO^-$	PhCH = N-CH_2-Ar	RBr (primary), RI, ClCOOEt	134
HCO^-	N-(phthalimide)-CH_2NO_2	enones, enoic esters (1,4-)	135
RCO^- ($ArCO^-$)	X_2PO-CH($OSiMe_3$)-R (-Ar)	RBr, RI (primary)	136-138
		ketones	139-140
		PhSSPh	136
RCO^-	RCH_2COOH	RX (and decarboxylation)	141
HCO^-	*p*-tolyl-CH_2NC	ketones	142
RCO^-	RCH_2CN	RX	143
$ArCO^-$	$ArCH_2CN$	enoic esters (1,4-)	144
RCO^-	RCH_2NO_2	ClCOOEt, $(RO)_2CO$, PhCHO, ketones, esters, anhydrides	145-154

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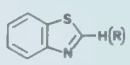
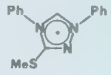
Equivalence	Reagent	Electrophile	Ref.
HCO^- (RCO^-)	$(EtOOC)_2CH\text{-}H$ (-R)	RX, ROTs	155
RCO^- ($ArCO^-$)	$TsCH_2\text{-}R$ (-Ar)	RBr, RI	156,157
HCO^- (RCO^-)		PhCN, PhCOCl	158-160
HCO^-		RX (primary)	161
RCO^-	RCHO	thiazolium salt-catalyzed addition: R'CHO enones, enoic esters (1,4)	 162-165 166-170
$MeCO^-$	$CH_2{=}CH\text{-}SiMe_3$	RX, ketones, PhCOBr enones (1,4- with Cu^+)	171-172 173-174
$MeCO^-$	$CH_2{=}CH\text{-}OR'$	RBr, ketones, esters enones (1,4- with Cu^+)	175-180 174,177, 180
R_2CHCO^-	$R_2C{=}CH\text{-}SR'$	RI (primary) Me_3SiCl, PhSeBr, Bu_3SnCl, RSSR, PhCOBr ketones, CO_2, oxiranes vinyl cuprates→cumulenes	172,181-184 172,185, 186 181,183, 185,187 188
$PhCH_2CO^-$	$PhCH{=}CH\text{-}SePh$	PhCOBr	172
$MeCO^-$	$Bu_3Sn\text{-}CH{=}CH_2$	enones (1,4-)	189
R_2CHCO^-	$R_2C{=}CH\text{-}NC$	MeI, Me_3SiCl, Me_2CO	190
RCO^-	R'NC+RLi	RX, Me_3SiCl, aldehydes, oxiranes, CO_2, ClCOOEt	191,192
HCO^-	CH_2Cl_2	ketones	193-197
HCO^-	CH_2Br_2	RX, ketones, CO_2, RCOOR'	198
HCO^- (RCO^-)	$Na_2Fe(CO)_4$	RCl, RBr, RI, ROTs (primary), RCOCl (esters unreactive)	199-205
RCO^-	$NaRFe(CO)_4$	RX, ketones, RCOCl enones, enoic esters (1,4-)	200,201, 206-208 208
HCO^-	$NaCo(CO)_4$	RX (primary)	209
RCO^-	$Me_3SiO\text{-}CR{=}CR\text{-}OSiMe_3$	RX (primary, secondary)	210
RCO^- ($ArCO^-$)	R'CO-CHOH-R (Ar'CO-CHOH-Ar)	RX (but allylic halides give acyl oxiranes), enoic esters and amides (1,4-)	211
$ArCO^-$	ArCO-CHOH-Ar	RX (allylic, benzylic only)	212
$ArCO^-$	$ArCOCH{=}CH\text{-}Me$	MeI, PhSeBr	213
$ArCO^-$	$ArCOSiMe_3$	RBr, RI (primary)	214
$MeCO^-$	MeCOCN	ketones	215

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About the Authors

Dr. Hase was born in Helsinki in 1937. He received the M.Sc. degree from the Helsinki University of Technology in 1962, and obtained the Ph.D. in 1969 from Imperial College (London) where he worked under Prof. D.H.R. Barton. In 1974-1975 he visited Harvard University as a research fellow, working in Prof. E.J. Corey's group. Dr. Hase is now an Associate Professor at the University of Helsinki, with research interests in synthetic organic chemistry.

Jorma Koskimies was born in Finland in 1946. He received his candidate in philosophy from the University of Helsinki and his Ph.D. degree from the University of North Carolina in 1976 where he studied with E.L. Eliel. He then returned to the University of Helsinki where he is currently a lecturer in organic chemistry.

Among the many compounds cited by Drs. Hase and Koskimies and offered by Aldrich are the following:

B868-1 DL-Benzoin

B895-9 Benzonitrile

10,133-8 Benzothiazole
13,972-6 Benzoyl bromide

B1,269-5 Benzoyl chloride

18,572-8 Benzyl cyanide

B8,010-0 2-Bromopyridine

19,440-9 Bromotrimethylsilane

C7,285-4 Chlorotrimethylsilane

D9,775-4 Diethyl malonate

13,536-4 Diethyl oxalate

22,549-5 Disodium tetracarbonylferrate compound with 1,4-dioxane (1 to 1.5)

15,787-2 1,3-Dithiane

18,589-2 Ethyl chloroformate

E5,125-2 Ethyl vinyl ether

19,552-9 Iodotrimethylsilane

M18-8 Maleic anhydride

11,214-3 2-Methylbenzothiazole

17,185-9 Methyl propiolate

M8,163-2 Methyl sulfide

16,334-1 *o*-Nitrophenylacetonitrile

15,157-2 *p*-Nitrophenylacetonitrile

N2,285-1 1-Nitropropane
16,902-1 Phenyl disulfide

18,820-4 Tosylmethyl isocyanide

T5,020-2 Tri-*n*-butyltin chloride

14,649-8 Trimethyltin chloride

T8,840-4 *s*-Trithiane

21,395-0 Vinyltrimethylsilane

Gilbert Stork
A Celebration of 35 Years in Research & Teaching

Frances Hoffman
Director of Chemical Laboratories
Columbia University
New York, NY 10027

Thirty-five years spent in research and teaching is not a special milestone, but for friends of Gilbert Stork, it provides a welcome focus to think back on our happy associations with him as well as to look forward to the continued sharing in this creative life. One of Gilbert's most remarkable qualities is his willingness to share time and energy with those who seek his counsel. His involvement could range from an in-depth discussion of the enamine reaction with a starting graduate student to whether a distinguished colleague should accept a position as president of a major academic institution or an industrial concern. In every situation, not only does he project complete attention, he gives it. At the end of a discussion with Gilbert, one certainly knows a lot more about chemistry and life, and, equally important, one's self-confidence grows as a result of his generous encouragement and recognition. He always gives more than he receives. Although he is one of chemistry's superstars, he is a warm human being.

It is no surprise that the graduate students and postdoctoral research fellows who have been associated with Gilbert are among the most productive and influential academic and industrial chemists in the world today. The deep loyalty felt by this group prompted the creation of an informal organization known as "The Stork Group." In Gilbert's Cope Award address in 1980, he presented, as his last slide, a list of the members of the Stork Group who presently hold positions in academia throughout the world. The slide listed over 110 names, an impressive number — indeed a possible world record for a single research professor. The names on the slide belong to distinguished chemists and Gilbert must feel proud of this remarkable list — a superb testimony to him.

Gilbert Stork's birthday is celebrated by everyone throughout the world, for he was born on New Year's Eve in 1921 in Brussels, Belgium. Shortly afterward, his parents, Jacques and Simone Weil Stork, moved to Paris where he spent his childhood.

Certain of Gilbert's well recognized characteristics were evident in his youth. For example, his rigorous testing of reality began at an early age. One day his nurse took him to the park and carefully explained that he should under no circumstances go near a pond which was completely covered with water lilies. Since he found it difficult to believe that there could be any danger with what appeared to be a solid flower garden, he ran over to test the nurse's story. When he was pulled out of the pool with his felt hat still firmly fastened under his chin, he believed her; but the poor nurse lost her job.

Gilbert's qualities for leadership were evident quite early, for as a Boy Scout he was elected head of the choir in spite of being completely tone-deaf. This small group, under his command, was propelled to greater feats than music. With visions of Napoleon at Austerlitz, he conceived an adventure which would have taken his group into the woods of St. Cloud to emerge proudly from the wilderness by marching smartly down the main street in full view of the proud citizenry of Garches, a small suburb of Paris. Unfortunately, his leadership ran afoul with his lack of sense of direction and the group became completely lost in the woods. The adventure ended with a "Waterloo-like atmosphere" consisting of bedraggled Boy Scouts and hysterical parents.

His creative solutions to difficult problems also surfaced early. Gilbert's favorite occupation during his summers at Ostend was going for pony rides on the beach. Unfortunately, he often had to wait fifteen to twenty minutes because of the long lines. One weekend, Gilbert was left in the care of his favorite Uncle Alex. Gilbert explained his problem to his uncle and proposed that the way to solve it was to have a pony of his own. His uncle found this to be a good solution, but when the pony appeared on the grounds of his home, considerable rumblings from the neighbors mounted to a volcanic eruption when Gilbert's parents returned.

Gilbert's interest in chemistry was sparked by an excellent teacher at the Lycée Janson de Sailly (other graduates we know are Jacques Barzun and Giscard d'Estaing). By the time his family came to the United States at the beginning of World War II, his course had been set. But Gilbert was in

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a new country, did not speak English and was familiar only with the French educational system where, if one wished to attend a university, one simply showed up on the first day of classes. Consequently, there was a slight detour in his path toward the study of chemistry. He decided that the best way to select a university was to read everything published by the Office of Higher Education available in the New York Public Library. After two weeks of study, he concluded that the University of North Carolina was the best school for chemistry so he immediately boarded a bus for Chapel Hill. Unfortunately, the University did not expect him, was on a quarter system and furthermore, it was very cold in North Carolina at that time. After a brief and unsatisfactory interview, he got back on the bus, headed further south to St. Petersburg, Florida, still speaking no English and still not realizing that one had to apply for admission to a university. The details were sorted out eventually, and he was admitted to the University of Florida at Gainesville, in those days an all-male school with an enrollment of 3,000 students.

During the six weeks Gilbert had to wait for the semester to start, he enrolled in English and Speech courses in St. Petersburg. It was in those classes that he met Winifred Stewart whom he later married. Winifred has been his life's partner and they now have four grown children. It is difficult to imagine that Gilbert could be the person he is today, had he not married Winifred.

Problems of American procedures continued to plague Gilbert at Gainesville. For example, he thought it unnecessary to attend chemistry laboratory classes if he knew the answers to the questions in the laboratory notebook. Instead, he spent his time in the chemistry library where he read an extraordinary paper by Paul Rabe published in the 1930's on the synthesis of dihydroquinine. Quinine had become an important national problem, and after reading Rabe's paper, Gilbert devised a synthesis of quinine. On the basis of this synthesis, he was given his own laboratory. The grumble on his non-attendance of laboratory courses lowered considerably. The starting material for his synthesis was bis(2-chloroethyl)methylamine which he prepared in large quantities. During the preparation, his left hand became a red, swollen glob with fingers no longer visible. Some time later, it was learned that this compound was a lethal nerve gas - we are lucky to have Gilbert to write about today. He graduated in two-and-a-half years from the University of Florida, in part, because of the many credits he received for having taken Greek in France, and obviously, because he was a rather special student.

His chemical interests had been aroused by pyridine and piperidine compounds, so Gilbert decided to do graduate work with either Professor Roger Adams at the University of Illinois or Professor S.L. McElvain at Wisconsin. Again, he boarded a bus, this time for Urbana, Illinois, but he was told that Professor Adams could not see him that day. Gilbert therefore continued his bus trip to Madison, Wisconsin. He saw Professor McElvain and gave him his projected synthesis of quinine to think about overnight. Professor McElvain was so impressed with the synthesis that Gilbert started working in the laboratory the following day. This work on *cis*-3,4-disubstituted piperidines inspired his life-long interest in the stereochemical control of reactions. In 1946 he devised a synthesis of 6-methoxy-α-tetralone, which he probably wishes he had patented, for it is still the method used to make starting material for aromatic steroids such as estrone.

The Three Musketeers.

It was at Wisconsin that Gilbert had his first experience with formal teaching. At first, he supported himself by analyzing for nitrogen and phosphorus in fertilizer but he was later promoted to the lofty position of teaching assistant. His section was composed of Army recruits who had the lowest grade-point averages in chemistry and were less than competent in the laboratory. Remembering how he had learned English by the use of flash cards, Gilbert devised a set of chemistry cards. He went to the barracks where his students copied them and studied from them. On the next examination, his group received the highest grades on the exam and, instead of being praised, Gilbert was accused of giving his students the answers to the questions on the examination. The *coup de grace* came, however, when some of his students climbed out a laboratory window to beat the lunch crowd at the student union. This heinous crime was discovered by the major domo of the laboratory and Gilbert was asked to give the students' names. He refused in the name of honor. The fact is that he had not remembered their names and did not know who had skipped out. As a result of this incident, he was summarily fired as a teaching assistant and was told that he was an incompetent teacher and should plan on doing something else with his life. The dark cloud had a silver lining, for the next day he received a university fellowship which permitted him to devote full time to research.

Two of his closest life-long friendships developed while he was at Wisconsin. Carl Djerassi was a fellow graduate student and William S. Johnson was a member of the staff. Gilbert's friendship with Carl was cemented by such episodes as sharing living quarters in Mexico City for three days during a complete shut-off of the city's water supply.

After receiving his degree from Wisconsin, he joined Lakeside Laboratories in Milwaukee as the only senior research chemist in the company. By day he worked as a medicinal chemist; by night he worked on his own ideas.

Bill Johnson was responsible for encouraging Gilbert to apply for an independent fellowship at Harvard. Part of the application was an original research proposal

on the synthesis of estrone. Professor Paul Bartlett, then Chairman of the Department, called and offered him an instructorship at Harvard. Gilbert promptly accepted.

Harvard was an incredibly exciting and fun place to be when Gilbert was there. Many still remember the colloquia he presented during those years, especially one on the stereochemistry of polyene cyclization in which he proposed what is now known as the "Stork-Eschenmoser Hypothesis." Notable achievements during the Harvard years include the total synthesis of cantharidin, a significant accomplishment since no entirely stereospecific synthesis of a natural product had yet been reported. The synthesis was completed at 4:00 a.m. on July 4, 1951 while Albert Burgstahler, the graduate student working on the problem, alternated between working-up the last step and singing Gregorian chants on the roof of the chemistry building. The determination of the structure of cedrene was also completed during the Harvard period. At the same time, Carl Djerassi arranged for Gilbert to be a consultant at Syntex. His contribution to the introduction of an 11-oxygen function into sterols unsubstituted in ring C led not only to an important industrial method, but also to Gilbert's and Carl's appearance in a *Life* magazine photograph.

A novel aspect of chemistry.

At the urging of Professor Louis Hammett, Gilbert joined the Department of Chemistry of Columbia University in 1953 as an Associate Professor. Columbia was a far cry from what it is today, both physically and academically. I remember the alchemical nature of the laboratories, heightened by the dimness of the light, the effort it took to pull open the cast-iron laboratory drawers while trying desperately not to break the glass contents, the thick white line painted across the sixth-floor corridor which was meant to keep organic chemists from crossing into Professor Victor K. La Mer's territory, and Gilbert's office, which would have made a rather spacious closet. This closet had had a distinguished history since it had served as the office of Professor Arthur C. Cope and Professor William E. von Doering.

The inner sanctum at Columbia, 1953.

A distinguished event occurred there when Linus Pauling came to discuss the possibility of Gilbert's moving to Cal Tech. At that time, the Columbia Chemistry Department had a regular table at the Faculty Club and Gilbert remembers, with mischievous pleasure, that he took Pauling to lunch making certain that he and Pauling could be seen from the Chemistry table. The physical chemists, not knowing of the Cal Tech offer, could not understand why the great physical chemist, Pauling, would choose to discuss scientific matters with Gilbert rather than with them.

Gilbert has had a distinct elegance and style in all his endeavors — from playing table tennis to working in the laboratory where he resembles a Grand Prix racing driver. An example is the synthesis of bicyclo[4.1.0]octanone from *m*-hydroxybenzoic acid. It was calculated to take eight steps and Gilbert asserted that it would

How many of these "distinguished looking" chemists can you identify? See page 10.

take only two days to prepare. The rest of us roared with laughter at this unrealistic suggestion and the substantial bet of $100 was made that he could not do it in two days. The race began on Saturday morning and by 7:00 on Sunday evening, the compound was ready to be sent for analysis. I will always remember paying off part of the bet.

There is one aspect of Gilbert's life that has bewildered me. How can such an intelligent man insist on buying cars which, without fail, are incapacitated at least fifty percent of the time? One of these "treasures" was a sporty, white Simca with red, leather seats. After spending a good amount of money transporting it from France, a small fortune to adapt it to New Jersey requirements and further fortunes to keep it running, the engine blew up as he was driving to Yale to present the Treat B. Johnson lectures. With the usual Storkian luck, the car was on an incline which terminated in front of a gas station. Gilbert arranged for the car to be fixed and took a train to New Haven. He retrieved the car on the way back after contributing Yale's honorarium to the garage mechanic. While on the Merritt Parkway, the engine exploded again. This was the end of Gilbert's endurance and he decided to abandon the car then and there. While he was removing the license plates, a state trooper stopped to check on the strange situation. With characteristic aplomb, Gilbert struck a bargain — the state trooper could have the car in exchange for a ride to the nearest railway station. I have often wondered who made out best on that one.

Then, there was the elegant, British-racing-green Jaguar with its impeccable styling. It was nursed through frequent nervous breakdowns by a mechanic complete with French beret and eyes which projected megabucks. The demise of this thoroughbred was spectacular. One wet evening Gilbert was crossing the George Washington Bridge when the car lurched to a stop. Concurrently, a series of collisions occurred on the opposite side of the bridge. The bridge patrol was baffled by the number of simultaneous accidents until a wheel was spotted careening back and forth, between and over the cars like a volley ball. This was Gilbert's wheel which eventually plunged into the Hudson River. Shaken by these six accidents, Gilbert and the Jaguar parted company the next day.

At present, his "true love" is a 1957, silver, two-seater Thunderbird. What marvelous shape! But don't step too firmly on the floorboards or your feet will hit the pavement.

An unpublished Stork original construction.

Stork has been the master architect of Columbia's organic group. The emergence of this faculty from relative obscurity in 1952 to its present position of eminence would not have taken place without his remarkable intuition and judgment. Because of his ability to recognize young people of outstanding talent and to persuade them to join Columbia, the building of the organic group was accomplished (with one exception) with appointments at the non-tenure level. Perhaps one of the most striking attributes of the Columbia organic faculty is its ability to combine a passionate involvement in chemistry with a relaxed and friendly attitude. Gilbert has had much to do with this feeling which extends to the graduate students of all the organic research groups.

The core of Gilbert Stork's life has been his creative research in organic chemistry. Since I do not have the expertise to give a summary of his glittering scientific achievements, I wish to express my thanks to those who have contributed the material for this section.

Stork's achievements fall into three "naturally occurring" areas: the total synthesis of complex natural products; the creation of new synthetic methods; and, finally, the investigation of reaction mech-

On the occasion of a reunion at Aldrich.

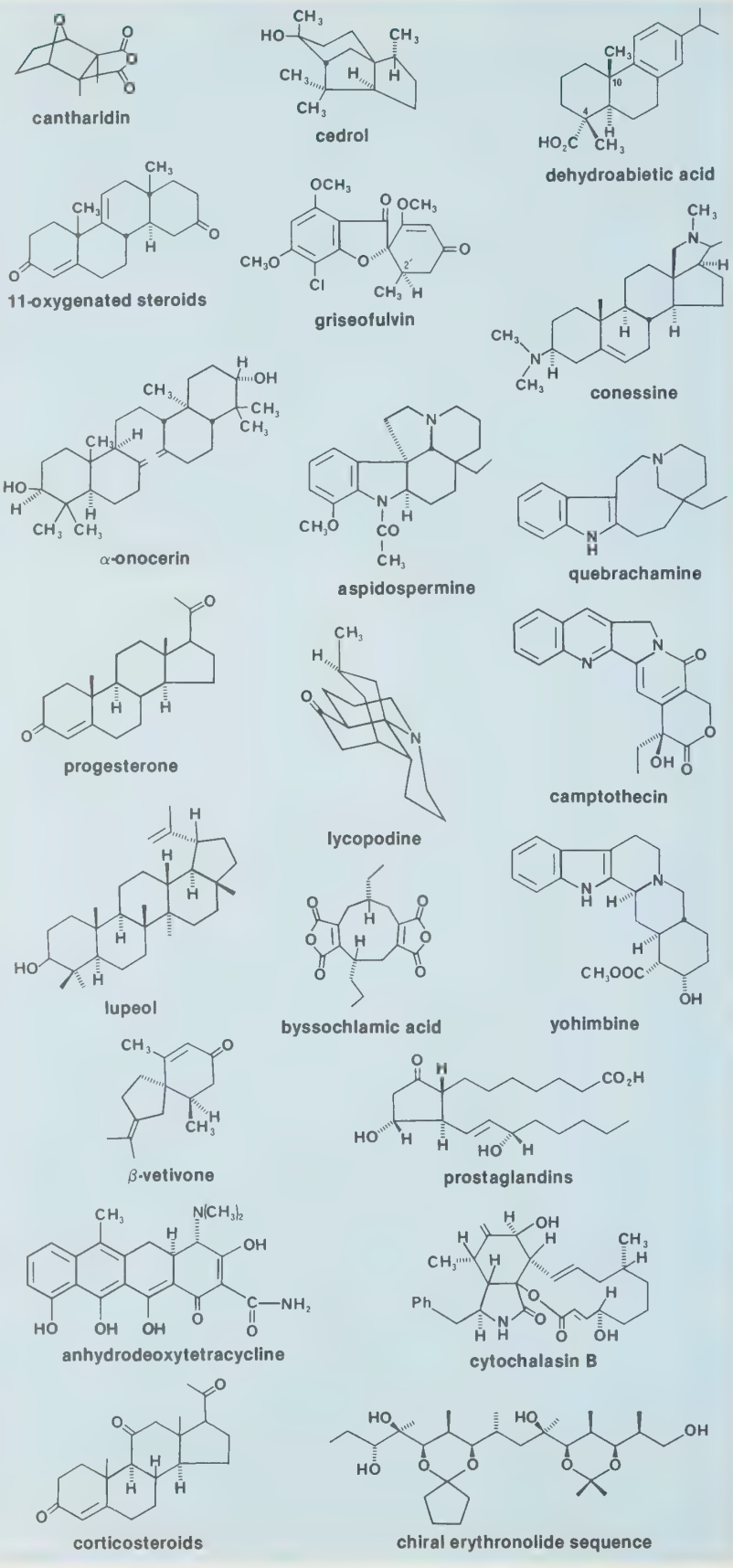
anisms. To separate synthesis from the creation of new reactions is totally arbitrary because of the strong interplay between these two areas. It has been Stork's philosophy that the purpose of a total synthesis must be more than a demonstration of the brilliance of the molecular architect in the clever orchestration of known synthetic methods. In his search for new reactions he has concentrated his efforts in seeking new and controlled methods of forming carbon-carbon bonds, the foundation of organic synthesis.

A. TOTAL SYNTHESIS

From the very first, Stork's syntheses were designed to be stereospecific. The importance of achieving a stereoselective synthesis had not been considered or recognized before Stork. This principle, now universally appreciated and used, was already a factor in his design of the synthesis of cincholoipon (1946), a *cis*-3,4-disubstituted piperidine related to hydroquinine; and in the totally stereospecific synthesis of cantharidin in 1951. It is of historical interest, with respect to the development of stereocontrolled syntheses, that his very first paper (1945), a communication (of which he is sole author), reported the synthesis of a 3,4-diaminofuran, the starting material for a planned stereospecific synthesis of biotin. The correct stereochemistry was to follow from catalytic hydrogenation of a 2,3,4-trisubstituted furan followed by further stereo-controlled transformation of oxabiotin to biotin itself.

Many of these total syntheses served as the focus for the development of new reactions. The stereospecific synthesis of the pentacyclic triterpene lupeol is a showcase of the power of the regiospecific formation and trapping of enolates. In this molecule a system of ten asymmetric centers was put in place with complete stereochemical control. Regiospecific formation and trapping of enolates was also used to simplify markedly the building of such diverse molecules as the prostaglandins, lycopodine and some of the steroids.

It would be surprising if enamines had not found an important use in a variety of these total syntheses: it will suffice to mention the construction of yohimbine and aspidospermine. Even seemingly small synthetic contributions have had considerable impact: the synthesis of 6-methoxy-α-tetralone, the previously mentioned starting material for the aromatic steroids, was based on Stork's discovery that the catalytic hydrogenation of substituted naphthalenes could be made to take place in the unsubstituted ring.

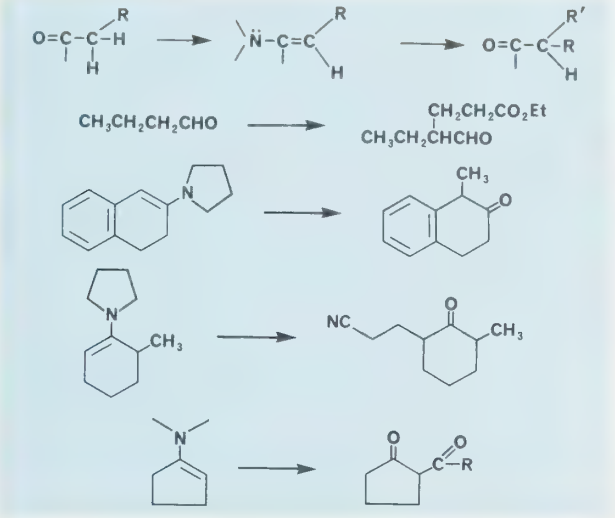


B. SELECTED SYNTHETIC METHODS

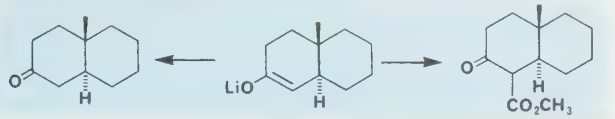
It is the creation of new synthetic methods rather than the area of total synthesis which Stork believes will be his most valuable contribution to organic chemistry. These methods can be divided conveniently into three parts.

The first, and perhaps foremost, concerns the regiospecific formation of carbon-carbon bonds *alpha* to a carbonyl group. To understand what impact this has had on modern chemistry, it must be recalled that, prior to this work, it was impossible to achieve such a fundamental operation as the alkylation of an *aldehyde* with an alkyl halide or with an electrophilic olefin, or the *regiospecific* (the word did not even exist) formation of a carbon-carbon bond on one or the other side of a ketone carbonyl. Gilbert Stork created many important synthetic transformations which contributed greatly to the explosive development of organic synthesis. His creative brilliance can be judged by the following work:

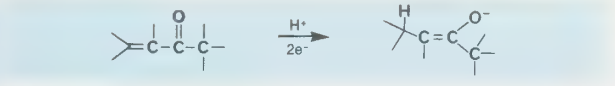
1) Formation of carbon-carbon bonds by the monoalkylation of ketones and aldehydes with alkyl halides, aldehydes, acylating agents and electrophilic olefins: "The Enamine Alkylation and Acylation" (1954, 1956, 1959, 1961, 1963).



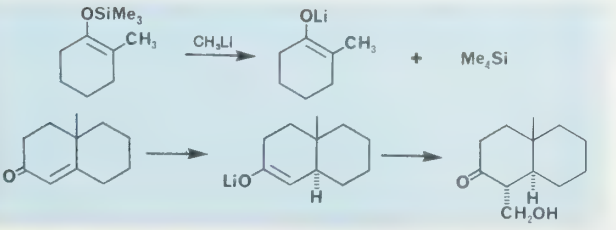
2) Demonstration that *lithium* enolates can be alkylated and carbonated without loss of any built-in regiospecificity (1961; 1965).



3) First and most widely used method for the specific formation of a *lithium* anion on either side of a ketone carbonyl (1961; 1965).

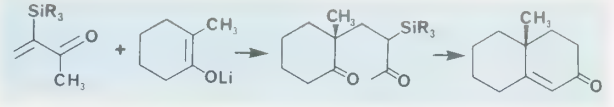


4) Generation of specific lithium enolates by cleavage of silyl enol ethers with lithium alkyls (1968).

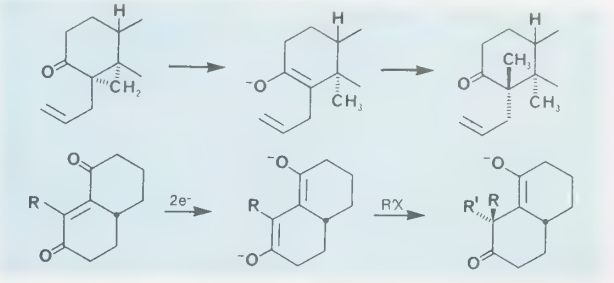


Two friends in search of a treasure on the sixth floor of Chandler.

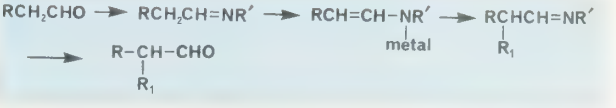
5) Extension of the regiospecific lithium enolate alkylation reaction to aldol condensations (1974), and to the first general solution to the problem of trapping these enolates with Michael acceptors (*via* α-silylated vinyl ketones, esters . . .) (1973, 1974).



6) Extension of the regiocontrolled enolate processes to cyclopropyl ketones (1971) and to enediones (1980).

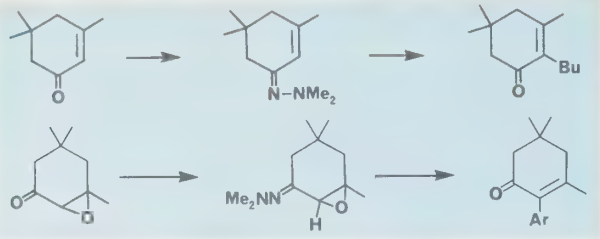


7) First demonstration that imines can be deprotonated to imine anions ("metalloenamines") thus leading to a general method for the monoalkylation of ketones (saturated and conjugated) and aldehydes with a wide variety of halides (1963).



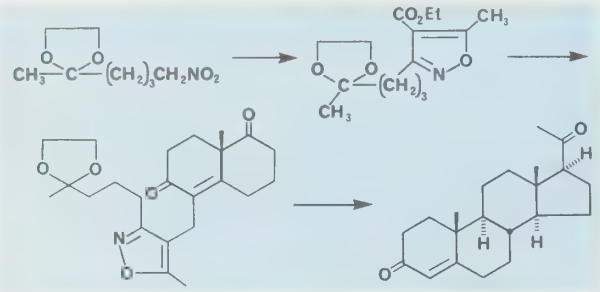
8) First extension of the process to *N,N*-dimethylhydrazones (1971). Further extension to regiospecific arylation *via* the *N,N*-dimethylhydrazones of epoxyketones (1978). These processes have seen numerous applications by many groups in recent years,

especially in the area of asymmetric induction using chiral imines and related substances.

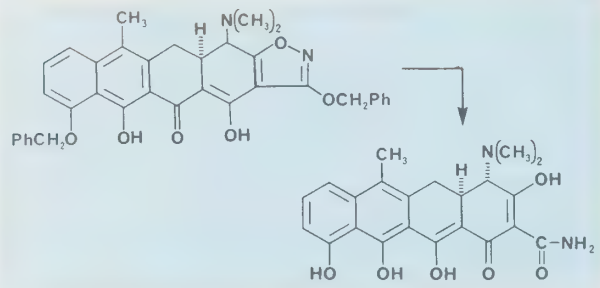


A variety of novel systems have been designed which allow the storage of reactive carbonyl systems in relatively stable forms until needed (*cf.* 9-13):

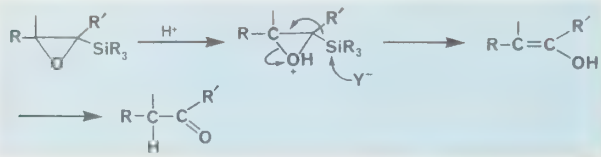
9) The isoxazole annelation, as illustrated in a total synthesis of progesterone (1967).



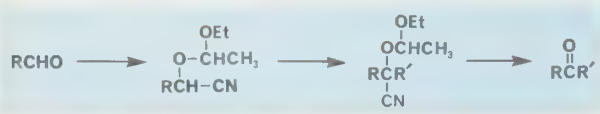
10) Another form of isoxazole annelation as exemplified by the construction of the most characteristic ring of the tetracyclines (1979).



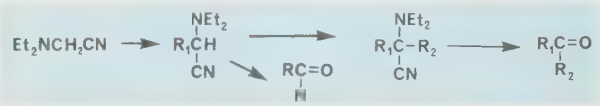
11) Introduction of the vinylsilane moiety as an enol (*i.e.*, latent ketone or aldehyde) precursor (1971).



12) Protected cyanohydrins (1971, 1974, 1975) as acyl carbanion equivalents in the formation of cyclic and acyclic ketones.

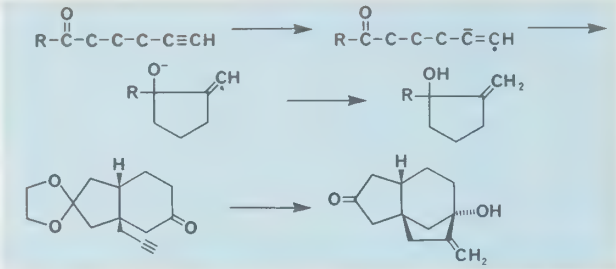


13) The α-dialkylaminoacetonitrile system as a carbonyl dianion equivalent (1978, 1979).



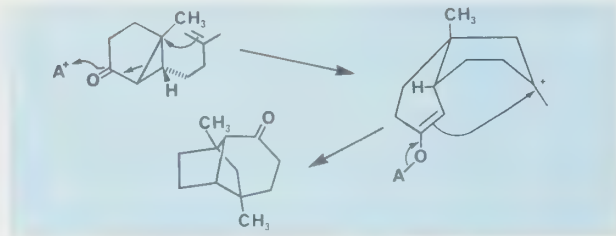
14) Cyclization of unsaturated α-diazoketones (1961).

15) Reductive cyclization of unsaturated (*e.g.*, acetylenic) ketones (1965).

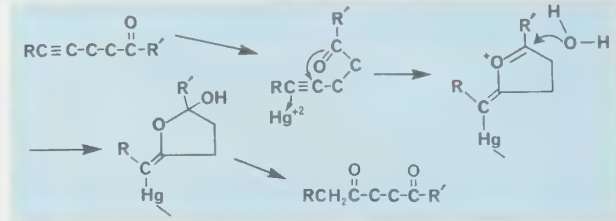


16) Formation of various-size rings by intramolecular opening of epoxynitriles. This leads, *inter alia*, to one of the few non-photochemical syntheses of functionally substituted cyclobutanes (1974).

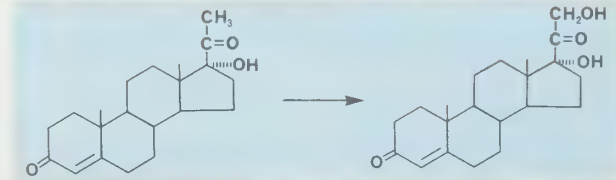
17) Generation of polycyclic and bridged systems from olefinic acylcyclopropanes (1969, 1971).



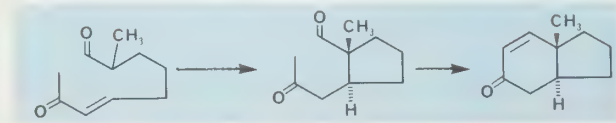
18) General synthesis of 1,4- and 1,5-diketones by carbonyl-assisted hydration of acetylenes (1964).



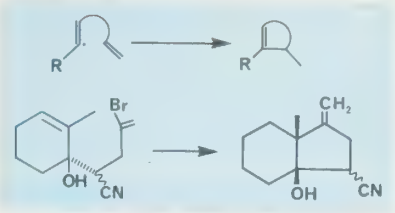
19) Direct C-21 hydroxylation in the construction of the dihydroxyacetone side chain of corticoids (1957).



20) Stereocontrol in vicinally substituted rings and *trans* hydrindanes by internal Michael addition (1982).



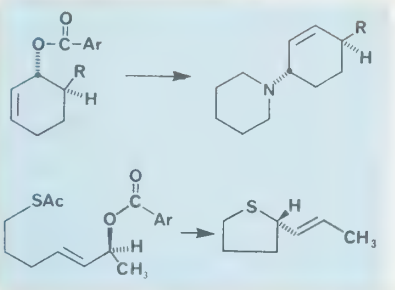
21) Functionally substituted rings *via* the cyclization of olefinic vinyl radicals (1982).



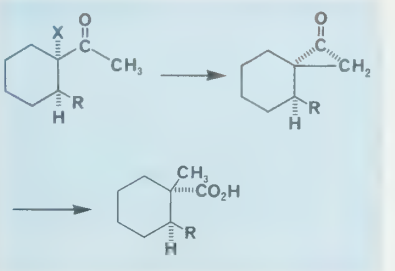
C. MECHANISTIC AND STEREOCHEMICAL STUDIES

These studies were conducted not so much for their own sake as for their potential in leading to controlled synthetic processes.

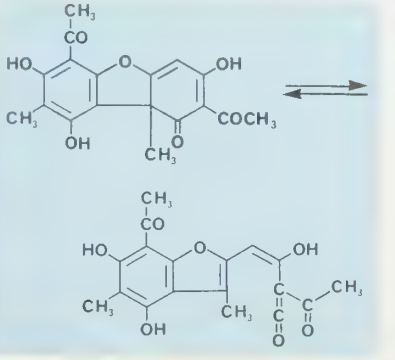
1) Investigation of the stereochemistry of the S_N2' reaction (1956, 1977).



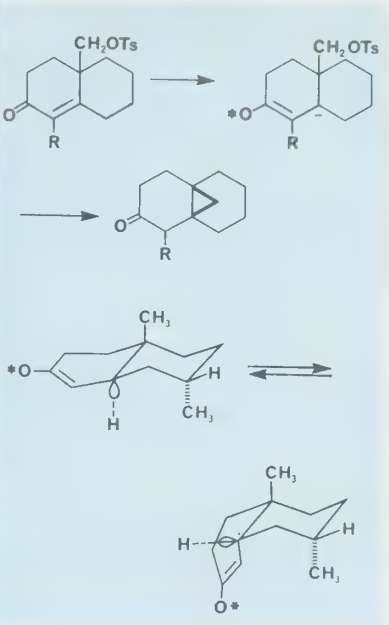
2) Stereochemistry of the Favorskii rearrangement of α-haloketones (1960).



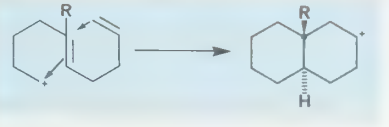
3) The mechanism of the racemization of usnic acid. This problem had long baffled the chemical community and was explained as a reversible electrocyclic reaction (1955).



4) Intermediates and stereochemistry in the metal-ammonia reduction of enones (1960, 1961, 1964).



5) We end by referring to the Stork-Eschenmoser hypothesis. The conclusion that the stereochemistry of a bicyclic cation made by a *concerted* reaction from an acyclic triene must be a *trans* bicyclic system was advanced in 1950. The possibility was then raised that this theoretical conclusion might well be the explanation of the *trans-anti-trans* arrangement so prevalent in polyterpenes and steroids. This has been amply confirmed, biogenetically as well as by the superb synthetic work of W. S. Johnson.



Not many people have had greater impact on modern organic chemistry than Gilbert Stork. He certainly has left his imprint on those who have had the good fortune to be associated with him.

HONORS AND AWARDS

Award in Pure Chemistry of the American Chemical Society (1957)
Baekeland Medal (1961)
D.Sc. (Hon.) Lawrence University (1961)
Elected to the National Academy of Sciences (1961)
Elected to the American Academy of Arts and Sciences (1962)
Harrison Howe Award (1962)
Edward Curtis Franklin Memorial Award, Stanford University (1966)
American Chemical Society Award for Creative Work in Synthetic Organic Chemistry (1967)
SOCMA Gold Medal (1973)
Roussel Prize, Paris (1978)
D.Sc., Honoris Causa, Université Pierre et Marie Curie of Paris, (1979)
Nichols Medal (1980)
Arthur C. Cope Award (1980)
Edgar Falis Smith Award (1982)
Willard Gibbs Medal (1982)
National Academy of Sciences Award in Chemical Sciences (1982)

Note: The picture of the "distinguished looking" chemists was taken in the mid '50's at a conference in the Grand Manan Island, Nova Scotia. Back row, left to right: H. Conroy, K. Wiesner, E. Wasserman, Z. Valenta, G. Stork, P. Belleau, D.H.R. Barton, and B. Witkop. Front row: J. Fried, C. Djerassi, F. Anet, F. Toole, M. Kupchan, and H.G. Khorana.

About the Author

Frances Hoffman has been a friend of Gilbert Stork for over thirty years.

After graduating from Mount Holyoke College, she obtained a position with Carl Djerassi at Ciba. When he left to join Syntex in Mexico, she went to work with Gilbert in the Department of Chemistry at Harvard and in 1953 moved to Columbia's Department of Chemistry with the Stork group.

From 1954 to 1961 she was a member of Lewis H. Sarett's research department at Merck and Company where she did research in the field of steroid chemistry.

In 1961 she returned to the Department of Chemistry of Columbia University as Director of Chemical Laboratories. For the past twenty years she has contributed to the growth and development of that department. At present, she is deeply involved in the development of plans for a new chemistry building.

Recent Applications of Homogeneous Catalysis to Organic Synthesis

T. Howard Black
Aldrich Chemical Company

INTRODUCTION

Transition metal-assisted organic synthesis has enjoyed explosive growth and exploitation in the past decade.[1] One of the most exciting advances is the adaptation of stoichiometric homogeneous reactions to catalytic reactions, largely decreasing the amount of noble metal needed.

Nearly everyone is familiar with heterogeneous catalysis, usually as applied to hydrogenations. Actually, these catalysts can be used in the synthetic applications to be discussed, but are extremely inefficient compared to their solubilized counterparts. Homogeneous catalysis embodies several important advantages:

1) Each expensive metal atom is an "active site", as opposed to just those on a surface.
2) Each atom is in an identical environment, increasing reaction specificity.
3) Selectivity can be "fined-tuned" by the judicious choice of ligands, solvents, and other variables.
4) Heat is more efficiently dissipated, and reaction conditions are generally milder.
5) Mechanistic studies are easier, allowing better understanding and thus greater control of reactions.

The sheer vastness of this expanding field precludes in-depth treatment of any particular aspect in this survey. The aim is, rather, to provide the reader with an overview of the very diverse, useful, and intriguing reactions made possible by homogeneous catalysis. Specifically omitted are hydrogenation reactions[2] and those employing chiral ligands.[3]

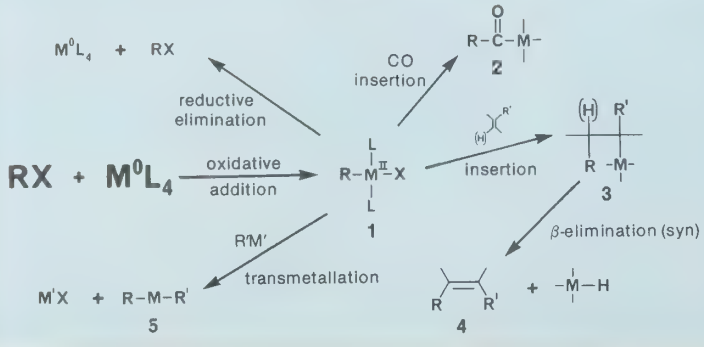
MECHANISTIC CONSIDERATIONS[4]

Transition metals undergo reaction pathways impossible for organic molecules, thus, complexation of a functional group to a metal usually drastically alters its normal chemistry. In order to aid in the planning and execution of a catalytic reaction, a short summary of pertinent organometallic reactions will be presented. In this review, the term "metal" (M) will always refer to a Group VIII metal.

Both σ- and π-organometallic complexes are involved in catalysis. σ-Complexes usually arise from the oxidative addition of a metal to an organic halide. Since the metal loses two electrons in the process, ligands which increase electron density facilitate the reaction while electron-withdrawing ligands impede it. Thus, phosphines (strong σ-donors) aid oxidative addition while carbonyls (strong π-acceptors) retard it.

σ-Complexes (*e.g.*, **1**) undergo five major reactions, summarized in Scheme I. Reductive elimination is the reverse of oxidative addition, and often constitutes the last step of a catalytic reaction. Insertion of carbon monoxide affords a metallated acyl species (**2**), while alkenes insert to give complexes such as **3**. If a β-hydrogen is present, (*syn*) β-elimination of metal hydride yields an alkene, **4** (of course, this can also

Scheme I



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occur in **1** if R contains a β-hydrogen). Finally, transmetallation with another organometallic species affords σ-complex **5**.

Electrophilic attack by metal on an alkene can result in the formation of either a π-olefin (**6**) or a π-allyl (**7**) complex. The most important consequence of such interaction is activation of the involved carbon atoms toward nucleophilic attack.

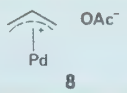
6 **7**

LIGAND ABBREVIATIONS

A great many ligands are employed in transition-metal chemistry. Throughout this survey standard abbreviations are employed: acac = acetylacetonate; DIPHOS = 1,2-bis(diphenylphosphino)ethane; dba = dibenzylideneacetone; COD = 1,5-cyclooctadiene; NBD = norbornadiene; dppf = 1,1′-bis(diphenylphosphino)ferrocene.

ALLYLIC ALKYLATION[1d,5,6]

The nucleophilic alkylation of allylic systems constitutes one of the most thoroughly studied aspects of transition-metal-catalyzed reactions. Basically, a metal (usually Pd) induces ionization of an allylic unit (often an acetate) which is then attacked by a nucleophile. Studies on the racemization of optically active allylic lactones implicate a symmetrical π-allylpalladium intermediate (*e.g.*, **8**),[7] although recent evidence[8] indicates that other species may be involved.

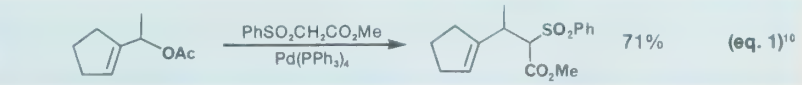


8

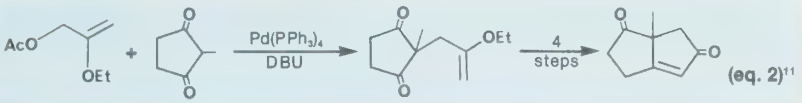
Many nucleophiles participate in this reaction. The regiochemical outcome is highly dependent upon the nature of the nucleophile, the allylic substituents, and the ligands on the metal.[9]

1,3-Diketones are favorite alkylating agents, although alkyl α-sulfonylacetates are often more synthetically useful due to the variety of possible further manipulations. The nucleophile can be used directly (eqs. 1,2) or is sometimes first deprotonated (eqs. 3,4). Since the leaving group departs and the nucleophile enters *trans* to the metal, retention of configuration is observed (eq. 3). Scheme II outlines a short synthesis of phoracantholide J,[14] in which the penultimate step involves an intramolecular alkylation. (±)-Recifeiolide has also been prepared *via* this approach.[15]

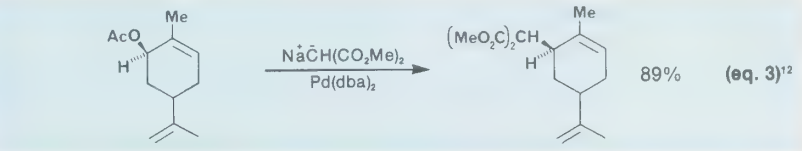
Other nucleophiles recently applied to this reaction include enamines (eq. 5), alcohols (eq. 6), and amines (eq. 7). The latter



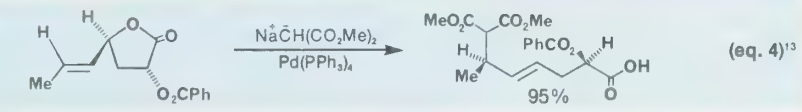
(eq. 1)[10]



(eq. 2)[11]

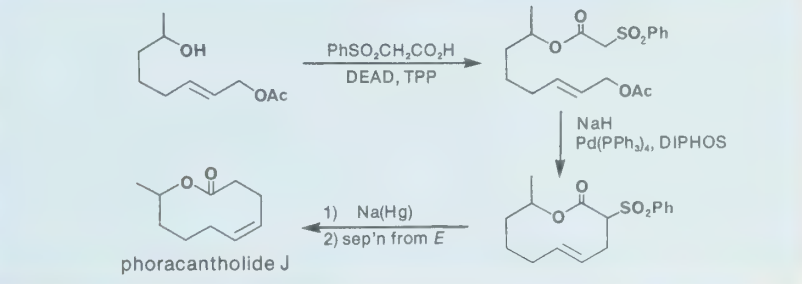


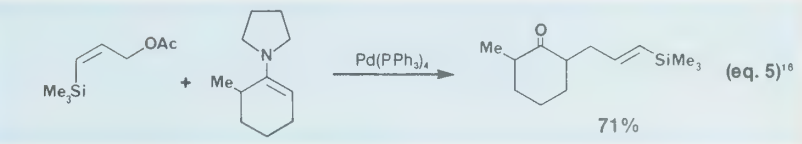
(eq. 3)[12]



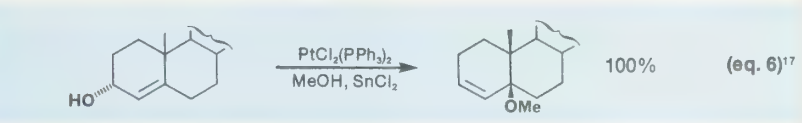
(eq. 4)[13]

Scheme II

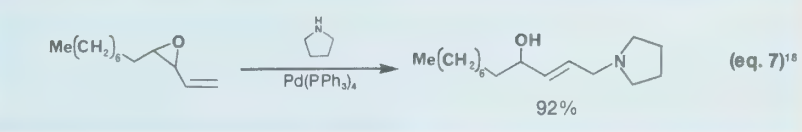




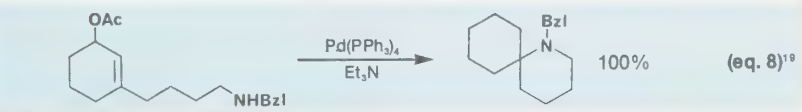
(eq. 5)[16]



(eq. 6)[17]

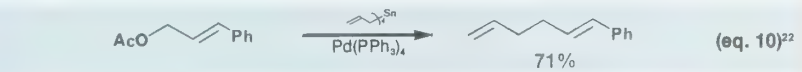


(eq. 7)[18]

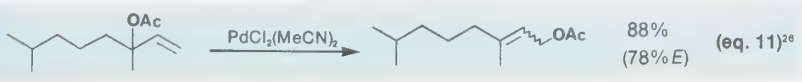


(eq. 8)[19]

(eq. 9)[21]



(eq. 10)[22]



(eq. 11)[26]

are particularly useful intramolecularly (eq. 8) and have enabled the facile construction of N-heterocycles (*e.g.*, isoquinuclidine).[20]

Organometallic species also serve well; compounds of magnesium (eq. 9), tin (eq. 10, or tin enolates[23]), zirconium,[24] aluminum,[25] and others have been employed successfully.

ALLYLIC TRANSPOSITIONS; REARRANGEMENTS

In the absence of added nucleophiles, allylic acetates can undergo 1,3-transposition, usually toward the less hindered allylic terminus. The *E* isomer generally predominates (eqs. 11 and 12). Since the acetate departs and enters *trans* to palladium (as noted previously), efficient transfer of chirality is possible (eq. 13).

A general furan synthesis involves rearrangement of an acetylated cyanohydrin followed by ester saponification, nitrile reduction, and acid-catalyzed cyclization (eq. 14).

Various Pd species also catalyze sigmatropic rearrangements, usually of the [3,3] variety involving heteroatoms. Of particular note is the propensity for S→N migration (eqs. 15 and 16). A potentially very useful reaction employs a Pd(0)-catalyzed allyl vinyl ether shift to construct prostaglandin precursors (eq. 17).

ISOMERIZATIONS

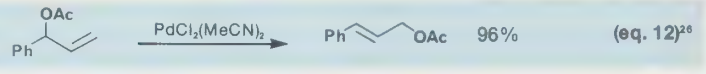
Although valence isomerizations have been observed (*e.g.*, eq. 18), positional isomerization of alkenes is most often the purpose of metal catalysis. Usually the thermodynamically more stable isomer is produced, as noted in a new synthesis of hydroquinones (eq. 19).

A useful facet of ruthenium catalysis is the tendency for isomerization of allyl to vinyl ethers, allowing the preparation of enol ethers from allylic alcohols (eq. 20). A short, general tetrahydrofurancarboxaldehyde synthesis exploits this phenomenon (Scheme III).[35]

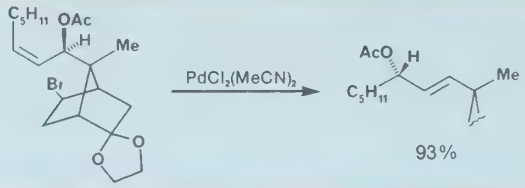
Enol ethers also result from rearrangement of alkoxycyclopropanes (eq. 21).

OLEFIN DIMERIZATIONS; ADDITIONS

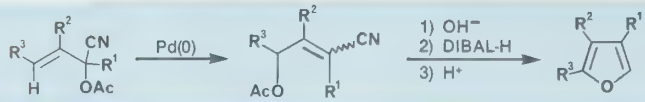
Metal-catalyzed oligomerization of butadienes has been known for many years.[37] Often, dimerization of the olefin is followed by attack of a nucleophile, resulting in the net attachment of a 2,7-octadiene fragment (eq. 22). Additionally, methylenecyclopropane codimerizes with CO_2 or certain olefins to afford some interesting products; $Pd(dba)_2$ is used for these transformations (Scheme IV).



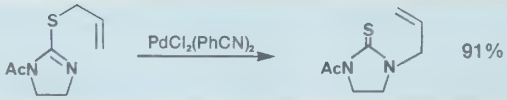
(eq. 12)[26]



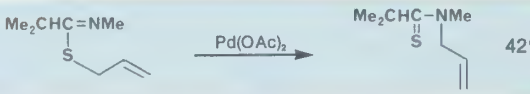
(eq. 13)[27]



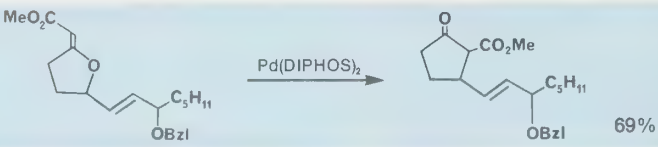
(eq. 14)[28]



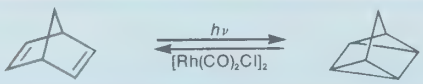
(eq. 15)[29]



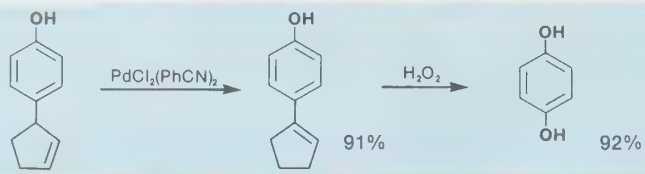
(eq. 16)[30]



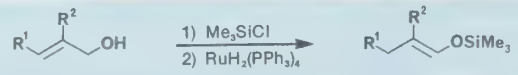
(eq. 17)[31]



(eq. 18)[32]



(eq. 19)[33]

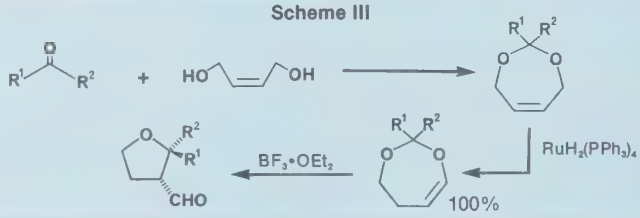


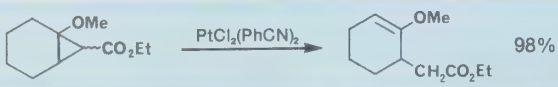
R^1, R^2 = H, Me

>90% (mainly Z)

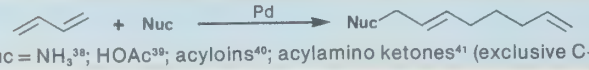
(eq. 20)[34]

Scheme III





(eq. 21)[36]



(eq. 22)

Nuc = NH_3[38]; HOAc[39]; acyloins[40]; acylamino ketones[41] (exclusive C-allylation)

Olefins also undergo electrophilic addition of halogenated compounds,[45] as seen in a novel, one-step γ-lactone synthesis (eq. 23). If the olefin possesses two allylic hydrogens, elimination to form 4-alkylidenebut-2-enolides is possible (eq. 24). The reaction also works well with silyl carboxylates.[47]

Trimethylenemethane, a Diels-Alder diene equivalent,[49] can be generated *in situ* to react with a variety of dienophiles in a unique three-carbon annulation technique (eq. 25).

CYCLIZATIONS

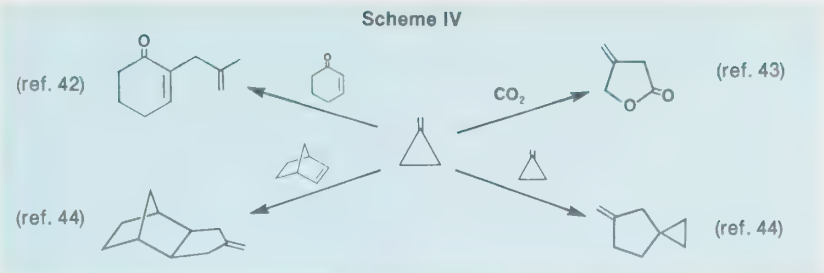
Many 1,5- and 1,6-dienes are cyclized in the presence of palladium. Although ring size can be governed by the oxidation state of the catalyst (eq. 26), five-membered rings usually are formed. Functionalized cyclopentenes[52] and γ-methylenebutyrolactones[53] have been constructed in this way.

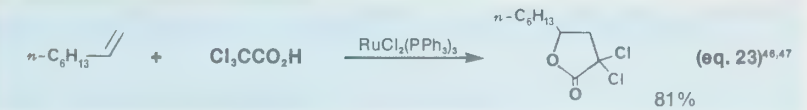
Miscellaneous cyclizations which have appeared recently include the formation of N-heterocycles from α,ω-diamines (related to the disproportionation of primary amines),[54] and the one-step synthesis of quinolines[55] and chromans[56] from monocyclic precursors.

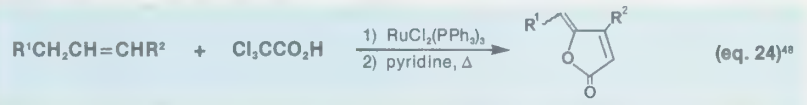
THE HECK REACTION[57]

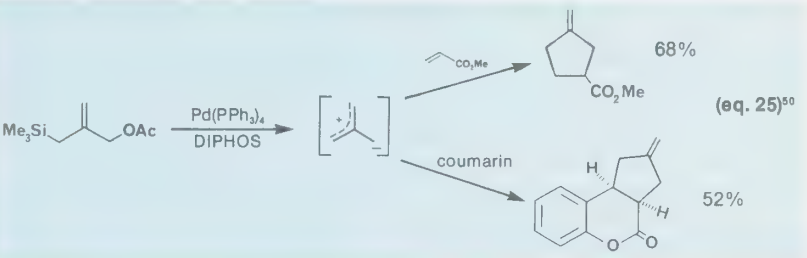
One of the most general and useful applications of homogeneous catalysis is the Heck reaction, in which organic halides are coupled with olefins under palladium catalysis (eq. 27). The reaction is remarkably selective, and almost any functional group can be present in either reactant. Generally, the halide prefers the less-substituted carbon of the olefin, whose stereochemistry is *retained* consistent with the *syn* addition of an RPdX species followed by *syn* β-elimination of palladium hydride. Typically, $Pd(OAc)_2$ is used in conjunction with tri-*o*-tolylphosphine; triethylamine is added to scavenge the HX produced. Scheme V outlines some representative examples with aromatic bromides.[57a,58] Note that allylic alcohols (or their trimethylsilyl ethers[59]) afford carbonyls; these arise from vinylic alcohols created in the elimination step. A recent synthesis of curcumone makes use of this transformation.[60]

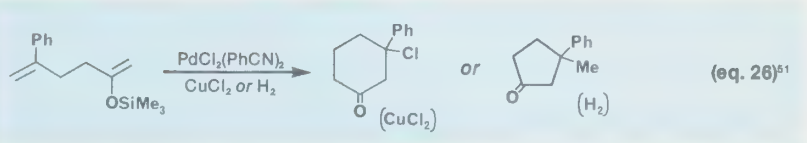
Aryl iodide-palladium complexes require no phosphines for stabilization; thus, selective reactions (*e.g.*, eq. 28) are possible. *o*-Iodoanilines are cyclized with dimethyl maleate to 2-quinolines in one step.[62] The aryl component can also be organometallic (*e.g.*, boron[63] and mercury[64]) or a diazonium salt.[65] Very recently, N-substituted anilines have been shown to be equally effective,[66] affording β-amino enones.

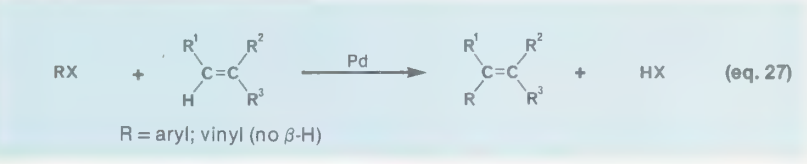


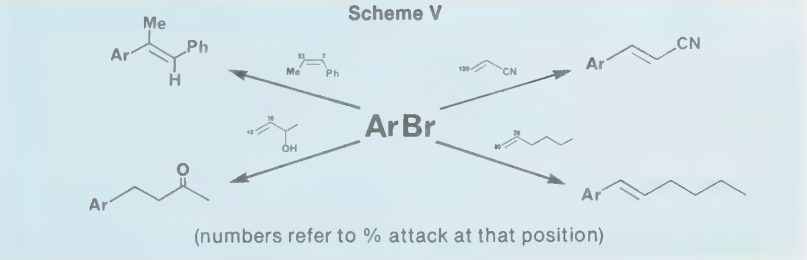


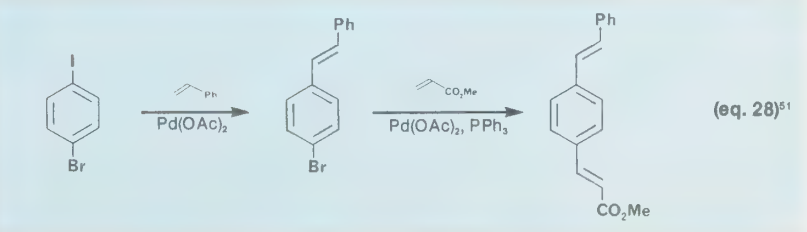












Vinyl halides also couple smoothly, exhibiting the same high stereoselectivity and generality, as indicated in eqs. 29 and 30.

CONJUGATE ADDITIONS

Many 1,4-additions are expedited by metal catalysis. The nucleophilic species is usually organometallic, although amines can often be effective.[69] Arylmercurials are commonly employed (eq. 31), although tin and many other metals also add; the choice is mainly one of synthetic convenience.

Alkenylzirconiums, easily prepared from alkynes, smoothly add to both enones and dienones (eq. 32) under Ni(0) catalysis; prostaglandin precursors have been prepared *via* this route.[73] Alkynylalanes also pose no problem (eq. 33).

COUPLING REACTIONS

A species such as **5** (Scheme I), formed *via* transmetallation, often undergoes reductive elimination to complete a very useful coupling reaction. A host of metals and halides can participate; as before, their choice is usually one of synthetic expediency. Thus, magnesium[76] (eq. 34) and boron[77] (eq. 35) compounds are commonly used, although tin,[79] silicon,[80] zirconium,[81] zinc,[82] aluminum,[83] lithium,[84] and others[85] are effective. The halides involved include aromatic, alkenyl, benzyl, propargyl, and allenyl derivatives. The major asset of this method is the retention of olefin geometry resulting in products of exceptional isomeric purity.

Acyl halides can couple with organometallics to afford ketones in high yield. Benzoyl chloride has been coupled with vinyl,[86] trimethylsilyl,[87] benzyl,[88] aryl,[86] and alkyl[89] groups.

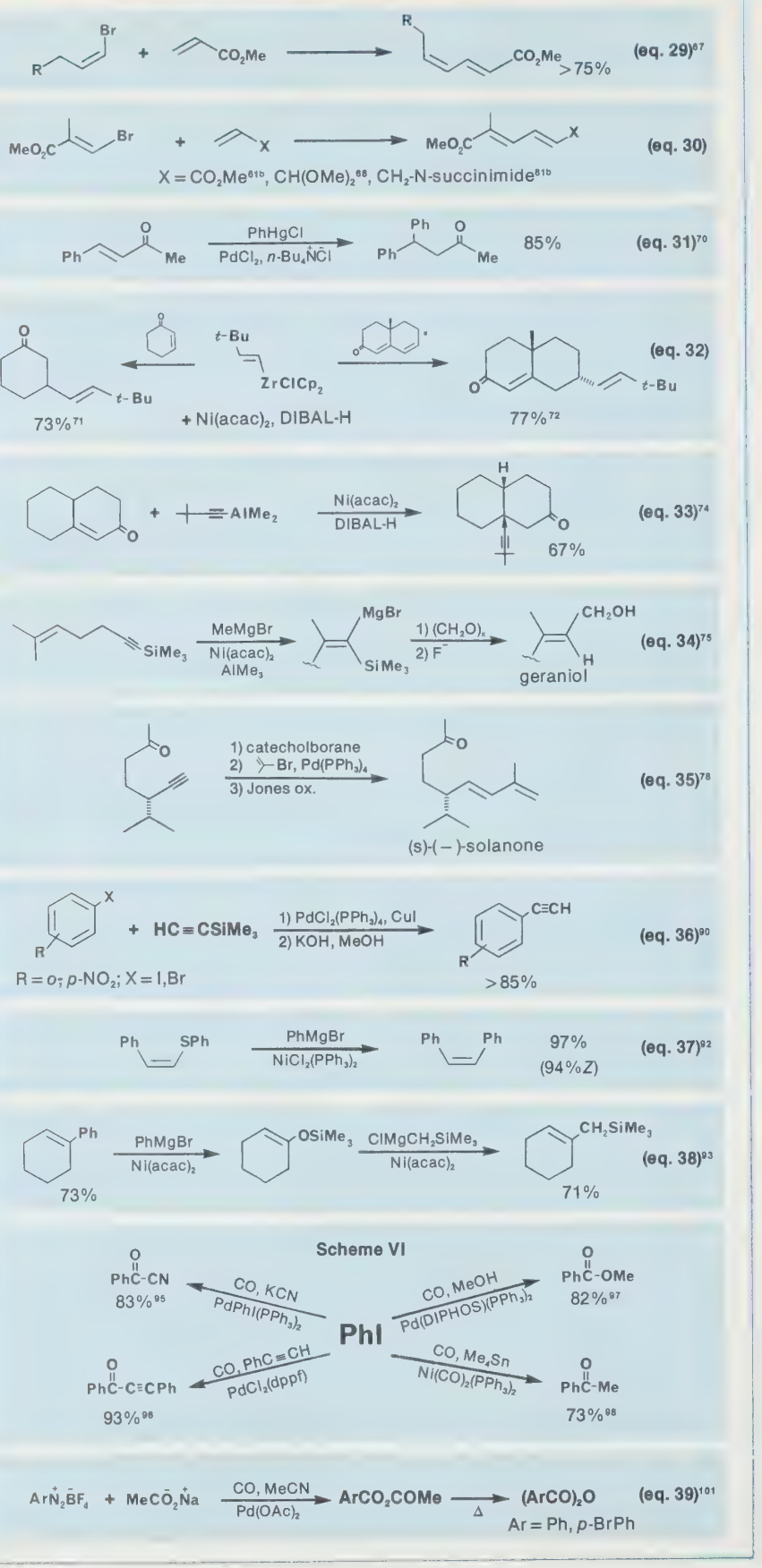
Aryl and vinyl halides couple with acetylenes in the presence of Pd(II) and Cu(I) (eq. 36); even sensitive iodouracils are compatible.[91]

A related reaction allows the displacement of enol ethers by Grignard reagents to afford alkenes (eqs. 37 and 38). Interestingly, enol phosphates are displaced preferentially to enol thioethers.[94]

CARBONYLATION

Metallated carbonyls (*e.g.*, **2**, Scheme I) which arise from CO insertion react with an array of nucleophiles to afford ketones. Scheme VI illustrates the diversity of this reaction. Intramolecular transformations include the synthesis of lactones from *o*-iodobenzyl alcohols,[97] indolines from *o*-allyl amines,[99] and berbines from papaverines.[100]

When carbonylated in the presence of carboxylates, aryldiazonium species afford mixed anhydrides which thermally



rearrange into symmetrical aryl anhydrides (eq. 39).

Alkenylboranes readily carbonylate in methanol to give α,β-unsaturated esters.[102] In the absence of added nucleophiles, alkenylmercury compounds dimerize onto CO to produce divinyl ketones (eq. 40), previously very difficult to prepare. Intramolecular alkene carbonylations have enabled the one-step construction of substituted 2(5*H*)-furanones[104] and α-methylene-γ-lactones.[105]

Small-ring heterocycles also insert CO, as in the preparation of α-phenylpropiolactone from styrene oxide[106] or of fused β-lactams from aziridines (eq. 41). The latter process would appear to have great potential for antibiotic synthesis.

In the presence of allyl or benzyl chlorides and a palladium catalyst, cyclic ethers open to form ω-chloro ethers (eq. 42).

DECARBOXYLATION

In the presence of base, allylic acetates can be oxidatively eliminated to afford olefins. The reaction is most facile when an aromatic (*e.g.*, eq. 43) or conjugated system results; the latter was exploited in a recent homoazulene synthesis.[110] α-Carboxylic acids depart as easily as protons (*e.g.*, eq. 44); a vitamin A precursor was constructed in this manner.[112]

Allyl esters decarboxylate in a new carbon-carbon bond-forming reaction (eq. 45) which also allows the preparation of ethers from carbonates.[114]

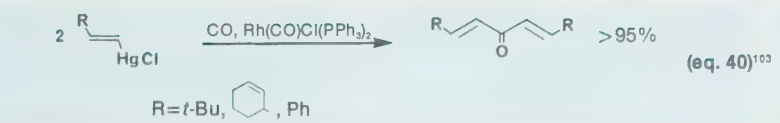
OXIDATIONS

Transition-metal catalysis enables mild, selective oxidations under neutral or basic conditions. Under Ru catalysis, alcohols are oxidized to either aldehydes or acids depending on the oxidant [PhIO *vs.* $PhI(OAc)_2$].[115] Other oxidants include CCl_4,[116] aryl bromides,[117] and oxygen (specific for allylic alcohols, eq. 46). Such methods offer an attractive alternative to the acidic chromium systems.

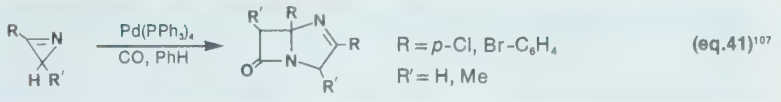
Terminal olefins are oxidized to methyl ketones under Pd(II) catalysis in an extension of the industrially important Wacker process.[119] The transformation involves a formal addition of H_2O; the added oxidant (even air![120]) serves to re-oxidize extruded Pd(0). Eq. 47 illustrates a two-step cyclopentenone synthesis based on this conversion, which has recently been shown to apply to enone systems (eq. 48).

REDUCTIONS

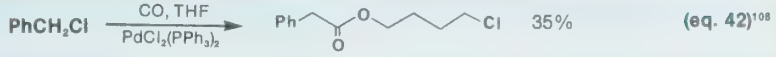
Metals catalyze many useful reductions besides hydrogenations. In the presence of Ru complexes, ketones are reduced to alcohols in high yield by formic acid[123] or



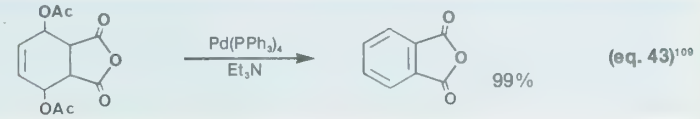
(eq. 40)[103]



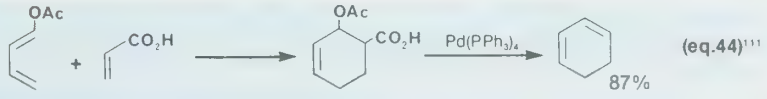
(eq.41)[107]



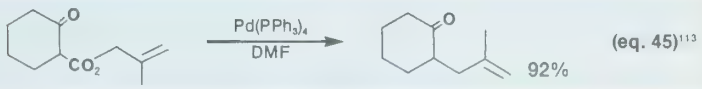
(eq. 42)[108]



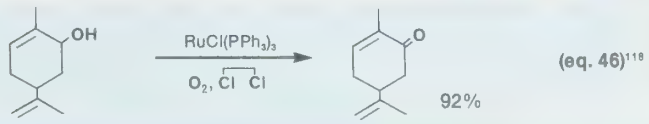
(eq. 43)[109]



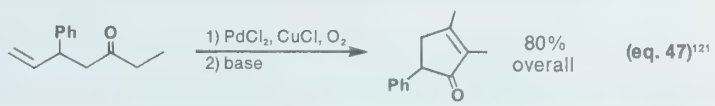
(eq.44)[111]



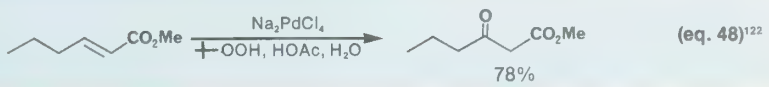
(eq. 45)[113]



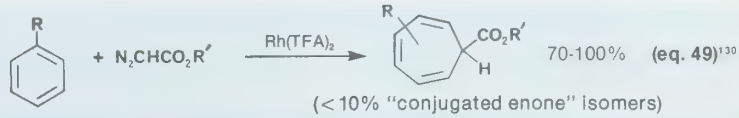
(eq. 46)[118]



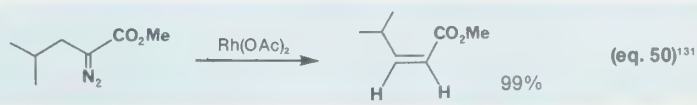
(eq. 47)[121]



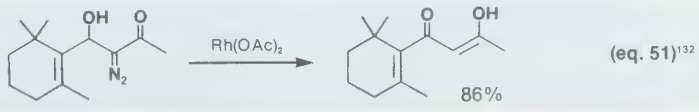
(eq. 48)[122]



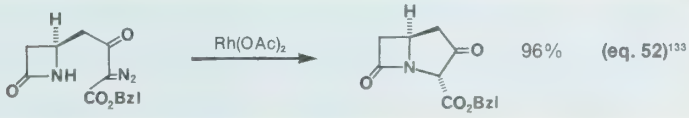
(eq. 49)[130]



(eq. 50)[131]



(eq. 51)[132]



(eq. 52)[133]

trialkoxysilanes.[124] Interestingly, the former effects the 1,4-reduction of chalcone to yield the saturated ketone.[125]

Aryl ketones are smoothly reduced to methylenes by a $NaBH_4/PdCl_2$ system in a mild, neutral alternative to Wolff-Kishner or Clemmensen chemistry.[126] Imines are easily reduced to amines by isopropanol under rhodium catalysis.[127] Finally, $Li(t\text{-}BuO)_3AlH$ can be replaced by $n\text{-}Bu_3SnH/Pd(0)$ for the preparation of aldehydes from acid chlorides.[128]

DIAZO CHEMISTRY

α-Diazoketones are valuable precursors to reactive carbenoid species.[129] Classically effected by copper, the decomposition of α-diazoketones proceeds in high yield in the presence of Rh(II) carboxylates (commonly acetate). Cycloheptatrienes can be prepared from substituted benzenes in high chemical and stereochemical yield using alkyl diazoacetates (eq. 49).

Z-α,β-Unsaturated esters result from treating α-diazoesters with $Rh(OAc)_2$ (eq. 50). The key step in an elegant synthesis of α-damascone involved the conversion shown in eq. 51; this mild oxidation avoids the partial retro-aldol reaction which always accompanies the acid treatment of α-diazo-β-hydroxy ketones.[132]

A recently developed intramolecular carbene addition allows easy entry into the 1-carbapenam ring system from diazo precursors (eq. 52). Yields are high, and rarely is more than one isomer produced. The generality of this method is indicated by its recent application in the syntheses of Antibiotic PS-5[134] and epithienamycin.[135]

CONCLUSION

Space limitations have prohibited the coverage of many useful miscellaneous reactions mediated by homogeneous catalysts, among them N-[136] and C-alkylations,[137] epoxide openings,[138] desulfurizations,[139] and Wittig-type olefinations.[140] It is hoped, however, that this short survey has instilled in the reader an appreciation of homogeneous catalysis as a rich and diverse methodology not to be neglected in planning a synthetic strategy. Many of the transformations covered in this review simply have no one-step synthetic alternative. Hopefully, broader awareness of this exciting field and its tremendous potential will result in greater application in organic synthesis.

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About the Author

After undergraduate work at Ohio Wesleyan University, Dr. Howard Black received the M.S. degree in 1977 from Central Michigan University, where he worked in the area of organic photochemistry. He obtained the Ph.D. degree in 1980 from Northwestern University, where he prepared and studied strained bicyclic alkenes under the direction of Professor James A. Marshall. Dr. Black is currently the Principal Investigator of Aldrich's preparative contract with the National Cancer Institute; his interests include the chemistry of strained and/or optically active hydrocarbons, synthetic applications of photochemistry, and homogeneous catalysis as applied to organic synthesis.

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21,666-6	Tetrakis(triphenylphosphine)-palladium(0)
20,586-9	Palladium(II) acetate
20,588-5	Palladium(II) chloride
20,901-5	Palladium(II) acetylacetonate
22,238-0	Allylpalladium chloride dimer
20,867-1	Bis(triphenylphosphine)palladium(II) chloride
22,545-2	Bis(triphenylphosphine)palladium(II) acetate
22,565-7	Bis(acetonitrile)palladium(II) chloride
22,368-9	Bis(benzonitrile)palladium(II) chloride
20,581-8	Sodium tetrachloropalladate
23,716-7	Lithium tetrachloropalladate(II) hydrate
23,027-8	Bis[bis(1,2-diphenylphosphino)ethane]palladium(0)
22,799-4	Palladium(0) bis(dibenzylideneacetone)
19,998-2	Tris(triphenylphosphine)-rhodium(I) chloride
20,503-6	Tris(triphenylphosphine)-rhodium(I) chloride, ultrapure
21,464-7	Carbonylbis(triphenylphosphine)rhodium(I) chloride
20,424-2	Carbonylbis(triphenylphosphine)rhodium(I) chloride, 99.99%
20,902-3	μ-Dichlorotetraethylene-dirhodium(I)
20,903-1	μ-Dichlorotetracarbonyl-dirhodium(I)
20,905-8	Rhodium(II) acetate dimer
22,566-5	Carbonyltris(triphenylphosphine)rhodium(I) hydride
22,795-1	Chloro(1,5-cyclooctadiene)-rhodium(I) dimer
N750-8	Nickel acetylacetonate hydrate
23,711-6	Bis(triphenylphosphine)-nickel(II) chloride
22,338-7	Nickel(II) chloride hexahydrate
21,393-4	Bis(triphenylphosphine)dicarbonyl nickel(0)
24,406-6	Nickel(II) acetate tetrahydrate
22,366-2	Tris(triphenylphosphine)-ruthenium(II) chloride
24,496-1	Tetrakis(triphenylphosphine) platinum(0)

Studies in Asymmetric Synthesis. The Development of Practical Chiral Enolate Synthons.[1]

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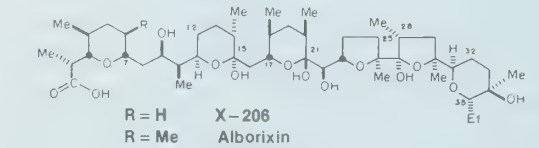
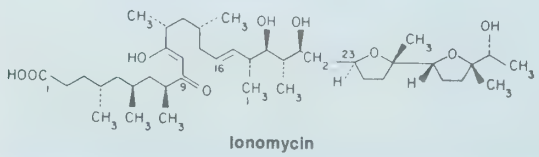
During the last decade, impressive progress has been made by organic chemists in further advancing the science of chemical synthesis. Within this discipline, one of the major ongoing objectives has been associated with the discovery and development of highly stereoselective bond construction reactions. With the recognition of macrolide and polyether antibiotics as potentially viable targets for total synthesis came the realization that "state-of-the-art" reaction methodology left much to be desired when applied to these architecturally complex molecules. One need only survey the stereochemical complexity of the ionophores, such as ionomycin (14 asymmetric centers) and alborixin (23 asymmetric centers), or the macrocyclic antibiotics, such as erythronolide or tylosin, to realize that highly stereoselective chemical reactions are an absolute necessity for such synthesis ventures (Scheme I). By inspection, one can readily perceive an acyclic carbon backbone in each of the illustrated target molecules which contains a center of asymmetry at nearly every carbon. Conventional wisdom has dictated that such acyclic stereochemical exercises may be addressed by interlocking sets of asymmetric centers

Professor David A. Evans (right) receiving the A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

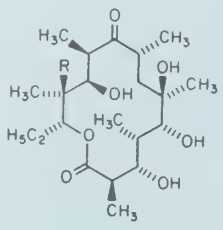
Scheme I



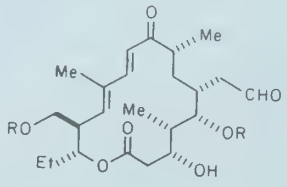
R = H X–206
R = Me Alborixin



Ionomycin



R = OH, Erythronolide A
R = H, Erythronolide B



Tylosin

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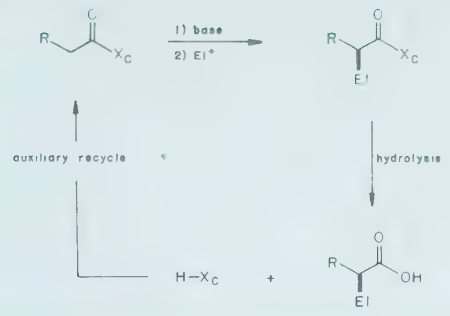
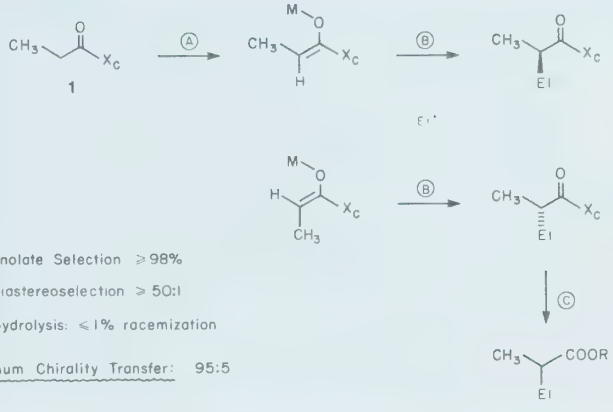
via the agency of temporarily formed rings wherein remote asymmetric induction from one center to another may be achieved in a predictable fashion with the aid of ring conformational analysis. Two elegant syntheses of erythromycin employing this "cycle strategy" for chirality transfer have been reported in recent years.[2,3]

Our own approach to the architectural problems presented by these classes of molecules has been to focus on the development of efficient asymmetric C—C bond constructions which are relevant to the synthesis of polyketide-derived natural products. Our first objectives in this area have been directed toward the development of chiral enolate-derived reactions such as alkylations, aldol additions and acylations wherein the chiral auxiliary (X_C) is both readily obtained and easily recoverable after the desired bond construction has been achieved (Scheme II). The major obstacles presented by this overall objective are threefold in nature (Scheme III): Given the carbonyl derivative **1**, the chiral auxiliary X_C must provide a strong bias for a highly selective enolization process (A); it must also provide a strong topological bias for enolate diastereoface selection in the bond construction (B); and finally its nondestructive removal (C) must be carried out with minimal racemization under mild conditions. For the reasons outlined in a previous review, we have chosen to develop chiral amide and imide enolates.[4] Several important aspects associated with these systems are illustrated below. With respect to the question of enolization stereoselectivity, we reasoned that *Z*-enolates should be strongly preferred if one considers transition state allylic strain conformational control elements (Scheme IV). This same conformational control element in the enolization process also assumes an important role in preventing product racemization (*via* enolization) in the bond-construction process. This important point will become strikingly evident later in this discussion (*vide infra*). Given the assumption that *Z*-enolates will be produced during the enolization process, the derived chiral amide enolates (Scheme V) require an additional organizational feature which locks the chiral auxiliary, X_C, in either the W- or U-conformation to ensure a pronounced enolate diastereofacial bias during the bond construction (Scheme V). Early in our studies, chiral amide enolates possessing fixed chirality disposition in both the W- and U-geometries were explored. The prolinol-derived amide enolates **2** and the imide enolates **3** developed in this laboratory have both proven to be exceptionally versatile chiral nucleophiles. In numerous instances, the two systems have been quite complementary in nature. The general utility of these systems in both alkylation and aldol addition reactions becomes apparent from the following data. The alkylation studies summarized in Scheme VI for the highly nucleophilic prolinol amide enolate **2** lead to the conclusion that excellent si-face enolate diastereoface

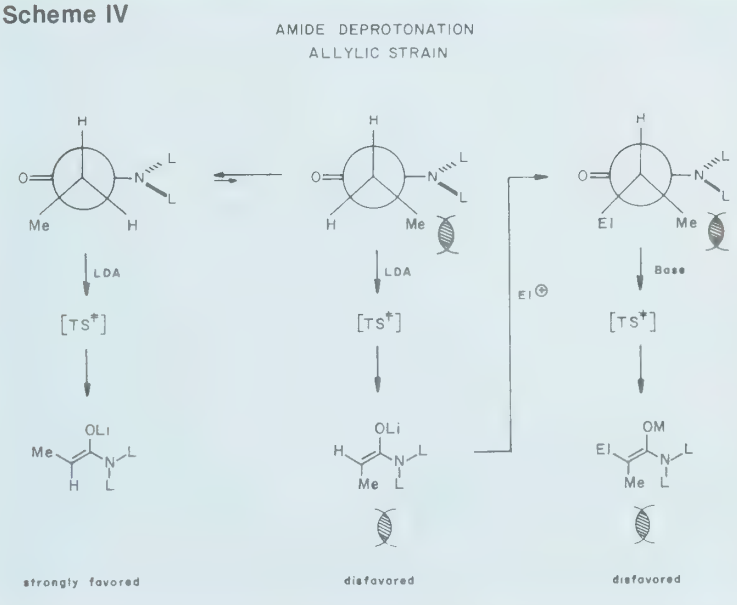
Scheme II



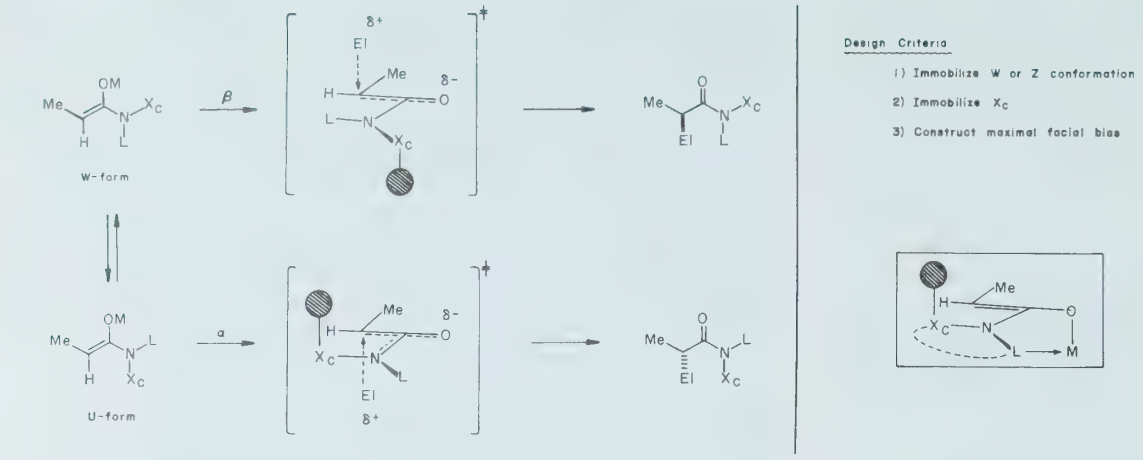
Scheme III



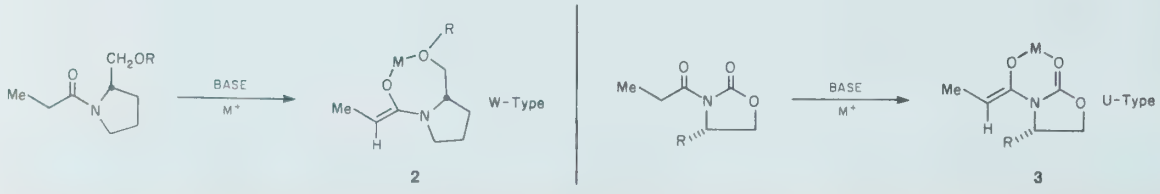
Scheme IV



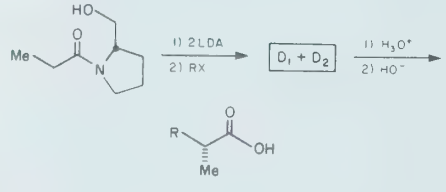
Scheme V

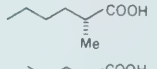
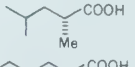
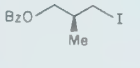
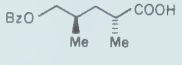
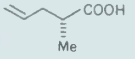
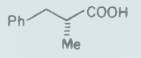


CHELATED CHIRAL ENOLATES



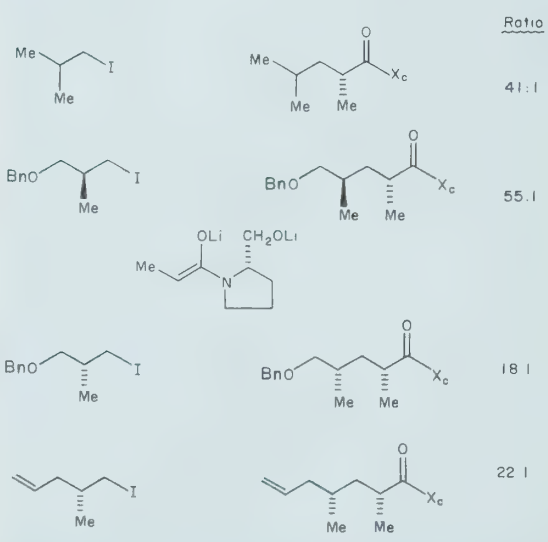
Scheme VI



Electrophile	$D_1 : D_2$	Carboxylic Acid	
$n\text{-}C_4H_9\text{-}I$	94 : 6		82%
	97 : 3		85%
	97 : 3		54%
	96 : 4		81%
$PhCH_2Br$	88 : 12		69%

Scheme VII

DOUBLE DIASTEREODIFFERENTIATION



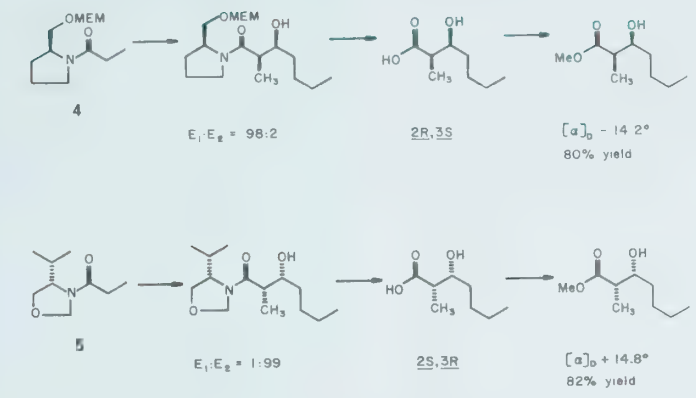
selection is observed for a range of alkyl halides.[5] We have also studied the influence of chirality in the alkylating agent with this enolate (Scheme VII). Under individually optimized reaction conditions, the illustrated chiral alkyl iodides were found to exhibit alkylation diastereoselection ranging from 18 to 55:1.[6]

Not surprisingly, the aldol addition reactions of the lithium enolates derived from these systems proved to be unsatisfactory; however, the derived zirconium enolates in these and related systems have proven to be exceptional.[7,8] Several examples which illustrate the utility of the zirconium metal center in providing stereoregulation in amide enolate aldol additions are illustrated in Scheme VIII. The amides

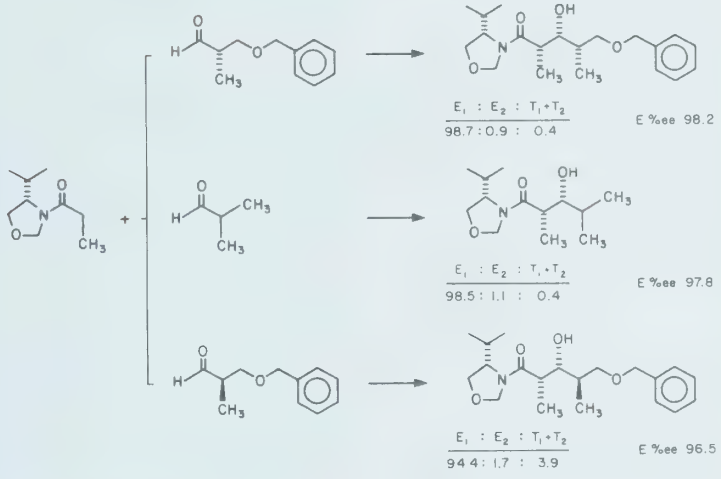
4 and **5**, each of which is readily derived from *S*-proline and *S*-valine respectively, exhibit good *erythro* diastereoface selection with a range of aldehydes. The major limitation that we have noted with these systems to date has been associated with the acidic conditions that are required to hydrolyze these chiral amides to their derived carboxylic acids. While this is not a problem in simple systems, in more complex cases where acid-labile functionality (*e.g.*, protecting groups) is present, these hydrolytic conditions have proven to greatly limit the utility of these enolate systems.

Due to the limitations noted above, several years ago we turned our attention to the exploration of the imide-derived enolates **3**. Our initial expectations for these systems were that good enolate diastereoface selection would be possible and that the derived imides might be readily hydrolyzed or reduced under mild conditions required for the construction of architecturally complex systems. The two chiral 2-oxazolidones chosen for study and their respective syntheses are shown in Scheme IX. As illustrated, the *S*-valine-derived heterocycle **6** (X_V) and the 1*S*,2*R*-norephedrine-derived heterocycle **7** (X_N) are readily prepared from inexpensive commercially available chiral precursors whose optical purities exceed 99%. The preparation of the derived imides and their respective alkylation reactions are summarized in Schemes X and XI.[9] As is evident from these data, excellent diastereoface selection was observed for both the valine-derived auxiliary (X_V) and the corresponding norephedrine counterpart (X_N). In full accord with our expectations, the sense of asymmetric induction noted in these alkylation studies was that predicted from the chelated *Z*-enolate **3** (*c.f.* Scheme V). The major limitation associated with these imides is that they are not particularly potent nucleophiles. For example, no reaction was observed with isobutyl bromide. In general, these reactions must be run at temperatures $\leqslant 0\,^{\circ}C$ to avoid enolate decomposition. The counterpoint to this restriction is the superb alkylation selectivity noted with these systems in numerous instances. When questions of reactivity have become an issue for us, the highly nucleophilic prolinol amide enolates **2** (Schemes VI, VII) serve admirably. One of the real, but unanticipated, benefits associated with the oxazolidone auxiliaries is in the area of diastereomer resolution. Invariably, we have found that the diastereomeric alkylation products (*c.f.* Scheme X, XI) are easily separated by either column chromatography or recrystallization. It should be noted that the iso-

Scheme VIII

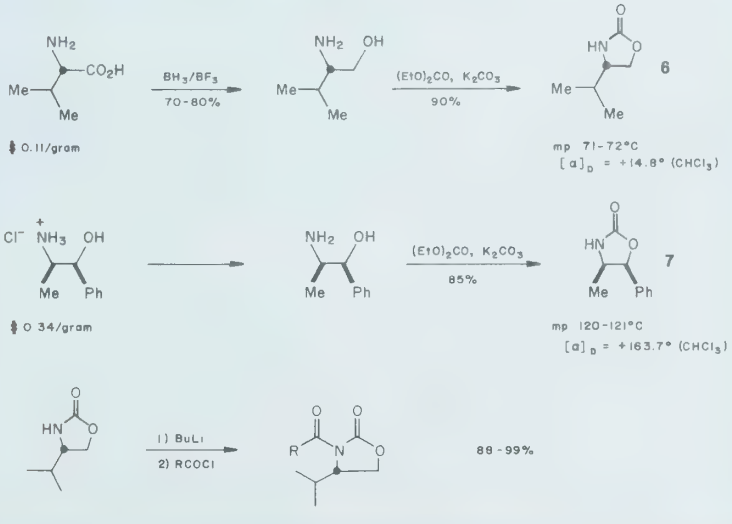


DOUBLE DIASTEREOSELECTION
via Zirconium Enolates



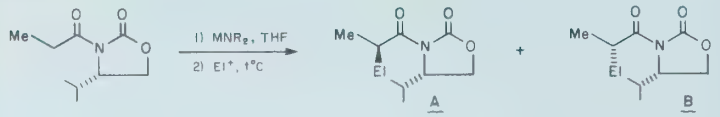
Scheme IX

CHIRAL AUXILIARY SYNTHESIS



lated yields cited in these alkylation studies refer to diastereomerically "pure" (A:B ≥ 99:1) adducts. With regard to the influence of chiral auxiliary structure versus enolate diastereoselection, we have carried out a series of enolate methylations on a variety of substituted N-acyl-2-oxazolidones (Scheme XII).[10] As anticipated from the presumed chelated *Z*-enolate structure **8**, the C_5-substituent (R_2) is not involved in the creation of the enolate diastereofacial bias. More surprisingly, our own preconception that the "size" of the C_4-substituent (R_1) would be an important consideration in asymmetric induction is strikingly refuted. The data in Scheme XII indicate that a broad range of β-amino alcohol-derived oxazolidone auxiliaries can be employed with nearly equal success. This being the case, other factors such as product crystallinity can become the major criteria associated with the selection of a specific chiral oxazolidone for a given application.

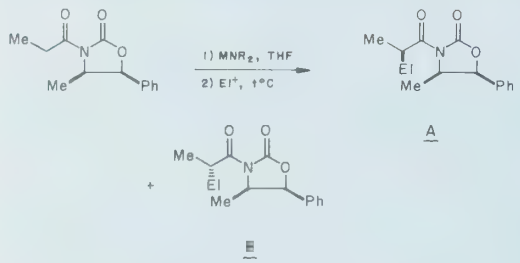
Scheme X



Electrophile	Metal	Temp	Ratio	Yield*
$PhCH_2Br$	Li	0°C	120:1	75%
	Li	0°C	98:2	62%
	Li	0°C	98:2	71%
	Na	-78°C	99:1	
CH_3CH_2I	Li	0°C	96:4	36%
$PhCH_2OCH_2Br$	Li	-30°C	98:2	77%
	No reaction			

*A:B ≥ 99:1

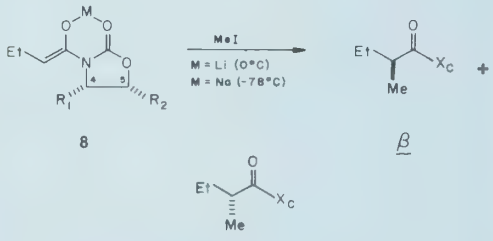
Scheme XI



Electrophile	Metal	Temp	Ratio	Yield*
$PhCH_2Br$	Li	0°	2:98	75%
	Li	0°	3:97	73%
	Li	0°	2:98	75%
CH_3CH_2I	Li	-78°	6:94	
$PhCH_2OCH_2Br$	Li	-30°	2:98	70%

*B:A ≥ 99:1

Scheme XII



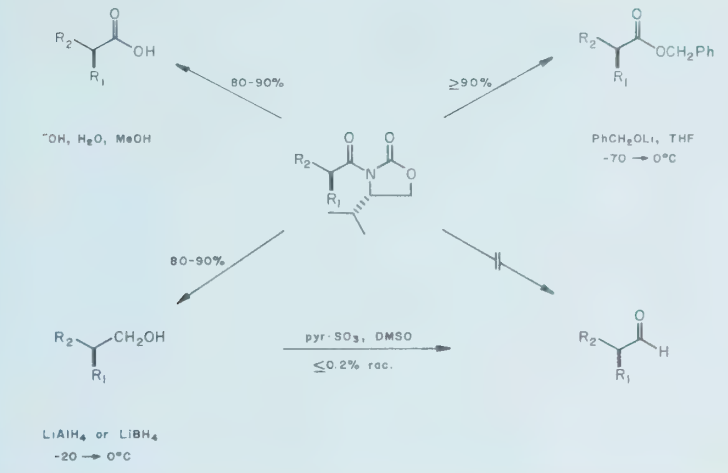
R_1	R_2	β:α Ratio (Li)	β:α Ratio (Na)
$i\text{-}C_3H_7$	H	90:10	91:9
C_6H_5	H	81:19	87:13
CH_3	H	86:14	92:8
CH_3	Ph	87:13	93:7

Conclusion: R_2-substituent plays no role dictating degree of diastereoface selectivity

To date, we have examined a series of transformations that result in the mild, nondestructive removal of the oxazolidone auxiliaries (Scheme XIII).[9] Basic hydrolysis, transesterification and reduction are all viable chemical operations in these systems; however, some system dependence associated with the success of these reactions has been noted. Specifically, the major side reaction, which becomes significant as the steric requirements of R_1 and R_2 increase, is competitive nucleophile attack at the oxazolidone carbonyl center. Surprisingly, the noted transesterification process has been the most system-independent transformation yet discovered. Overall, these chiral imide enolates have provided us with an exceptionally useful class of optically pure, dioxygenated synthons (Scheme XIV) in either enantiomeric series which are currently being employed in a range of ongoing projects. One particularly relevant example is shown in Scheme XV. The chiral alcohol **11**[11] has proven to be exceptionally valuable in the synthesis of polyether antibiotics.[12] We routinely prepare optically pure *R*- or *S*-**11** in good overall yield from the diastereomerically pure precursor imides **10** or **9** respectively.

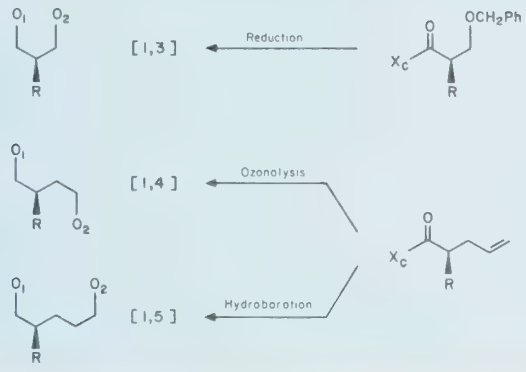
To date, the full range of electrophiles has not yet been explored with these imide enolate systems; nevertheless, we have already made a number of striking observations which should considerably extend the general utility of these reagents. One such case is the acylation reaction illustrated in

Scheme XIII SELECTED TRANSFORMATIONS

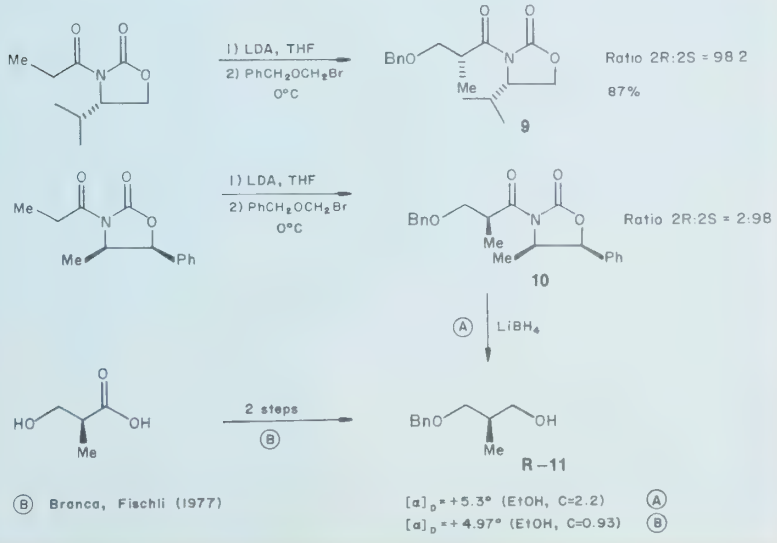


Scheme XIV

CHIRAL DI-OXYGENATED SYNTHONS



Scheme XV

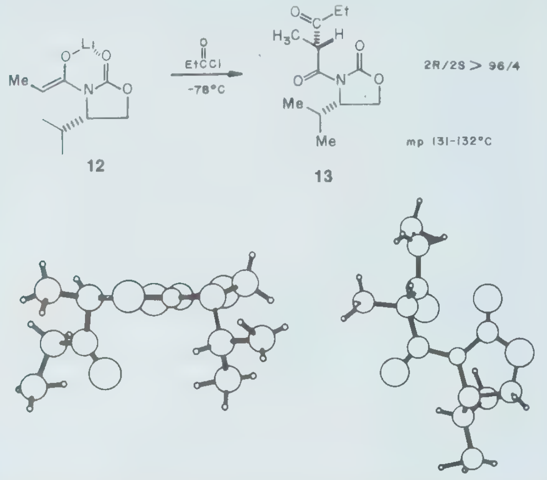


Scheme XVI.[13] Acylation of enolate **12** with propionyl chloride afforded the chiral β-keto imide **13** (95% yield) which was found to be remarkably resistant to racemization *via* enolization. An examination of its X-ray structure reveals that the allylic strain concepts earlier delineated (*c.f.* Scheme IV) destabilize that conformation of the molecule wherein both carbonyl π-systems are co-planar with the C_2-hydrogen. This unprecedented observation provides an entry into an exceptionally interesting class of chiral substances. The full details of these reactions await a more detailed examination.

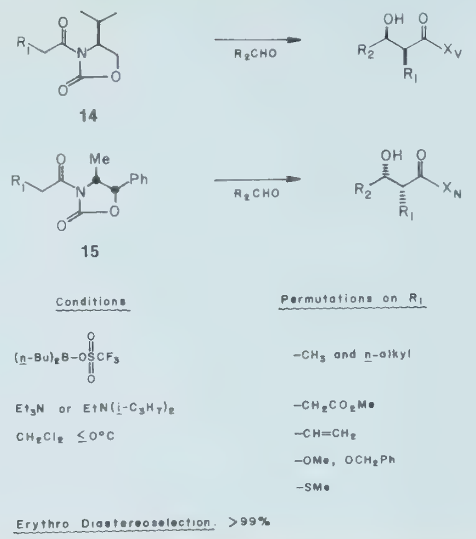
The aldol process has occupied a great deal of our attention over the last few years.[7,8,14] This reaction is of paramount importance in devising efficient approaches to the synthesis of polyketide natural products. Understandably, a number of research groups have addressed this problem over the last five-year period, and remarkable strides have been made in this area,[15] particularly from the laboratories of Professors Heathcock[16] (University of California, Berkeley) and Masamune[17] (Massachusetts Institute of Technology). In our own studies, we concluded that metal-centered steric effects play a dominant role in aldol stereoregulation from enolates of defined structures. The subsequent exploitation of dialkylboryl enolates by us,[14] and simultaneously by the Masamune research group,[17] are now a matter of record, and the application of this technology to the aldol addition reactions of the previously developed chiral imides has led to some of the most stereoselective bond constructions yet revealed (Scheme XVII). From the illustrated valinol and norephedrine imides **14** and **15**, the derived dibutylboryl enolates undergo condensation with a broad range of aldehydes in greater than 99% asymmetric induction for both newly formed asymmetric centers. We have found that a wide range of enolate substituents, R_1, may be tolerated without loss of reaction stereoselectivity.[18] With regard to condensations with chiral α-substituted aldehydes, the chiral propionimides illustrated in Scheme XVIII perform with equal facility.[19] In these cases, resident enolate chirality strongly overrides chirality in the aldehyde condensation partner. This point is further emphasized in the addition reactions of enolate **18** (R = OMe, Me) with the optically pure aldehydes **16** and **17** (Scheme XIX). In both examples the illustrated adducts were obtained in good yield and in high diastereomeric purity.[20]

One additional set of aldol addition reactions which we have not yet reported is illustrated in Scheme XX.[21] We have found

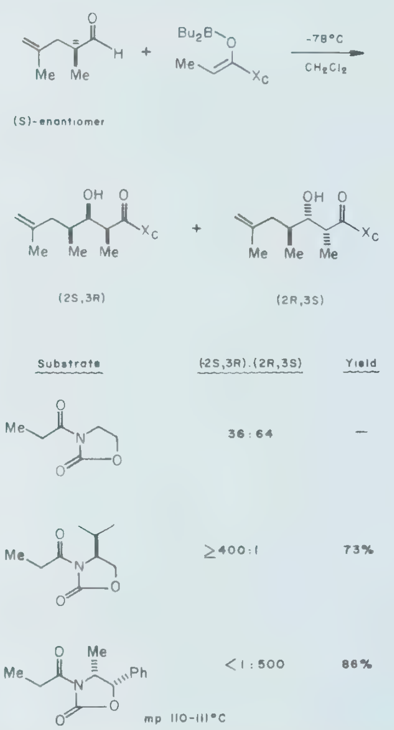
Scheme XVI



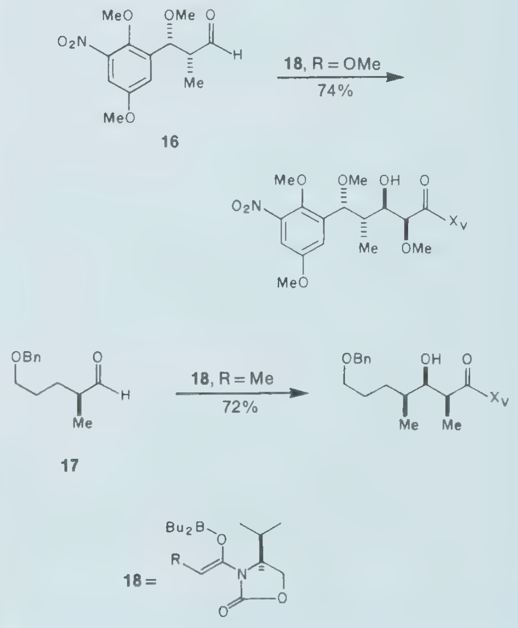
Scheme XVII



Scheme XVIII



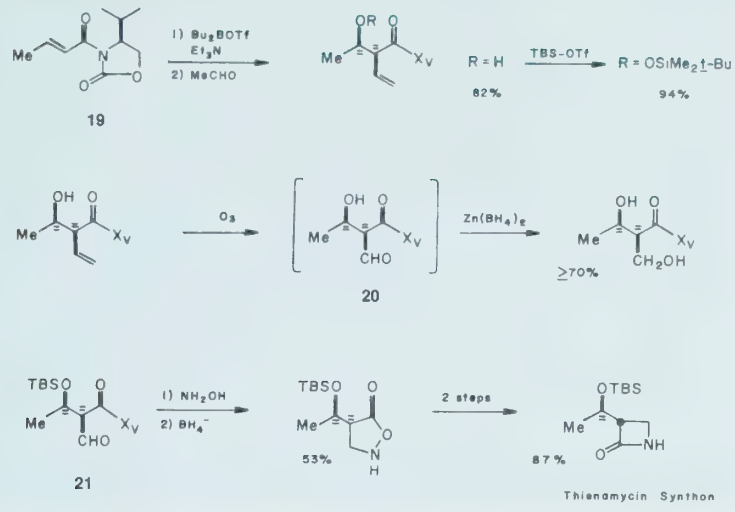
Scheme XIX



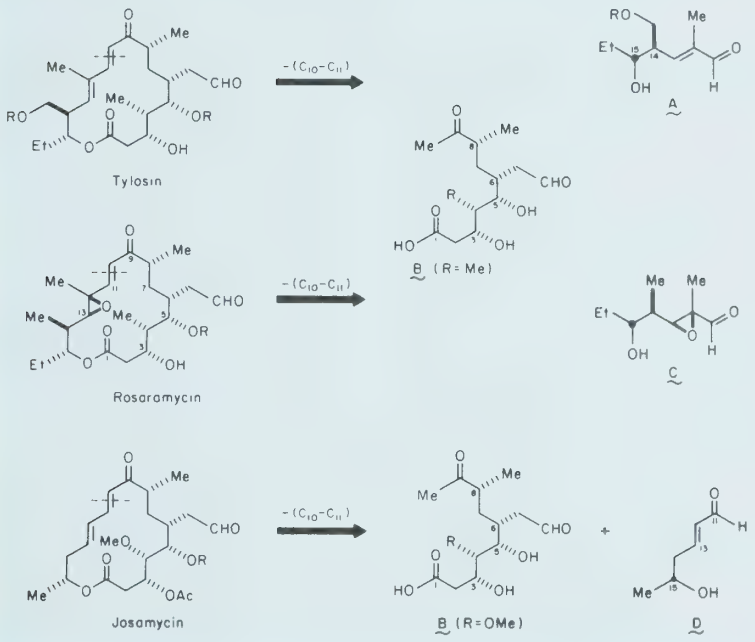
that chiral crotonate imides such as **19** also undergo the analogous aldol condensations with equal facility. The diastereomerically pure adducts provide a facile entry to the chiral α-formyl imides **20** and **21** *via* ozonolysis. Based upon our earlier discussion on the low kinetic acidity of the dipropionyl imide **13** (*c.f.* Scheme XVI), it is no longer quite so surprising that both **20** and **21** can be chemically manipulated *via* either reduction or oxime formation without racemizing the potentially labile center of asymmetry.

From the preceding discussion, one may now begin to address a number of architectural exercises wherein chiral enolate-derived bond constructions may be effectively exploited. One such project area currently under study here at Caltech is a general approach to the macrolides tylosin, rosaramycin, and josamycin. The derived aglycones for these three structures may be disconnected into a C_1-C_{10} synthon **B** (R = Me, R = OMe) and three smaller fragments containing the C_{11}-C_{15} moieties of the individual macrocycles. In approaching the construction of the C_1-C_{10} synthon, it is apparent from the previous studies that all of the asymmetry in this fragment may be derived from a single source, the (1*S*,2*R*)-

Scheme XX



Scheme XXI



norephedrine-derived 2-oxazolidone chiral auxiliary, X_N (Scheme XXII). In recently completed studies, we have demonstrated that the C_6-stereocenter may be constructed with 50:1 diastereoselection *via* the illustrated alkylation process while the C_4 (R = Me)- and C_5-asymmetric centers are efficiently established *via* the previously developed boron enolate aldol technology.[22] The C_3-asymmetric center was also established *via* the same aldol process wherein the chiral thiomethyl acetate **24** is required as a chiral acetate enolate synthon.[18] The C_8-asymmetric center in the C_1-C_{10} macrolide synthon may be stereoselectively introduced at a variety of points in the synthesis *via* hydroboration. Prior studies from our laboratory have revealed that the 1,3-asymmetric induction noted for this hydroboration process is rather general in nature (Scheme XXIII), and an example of this process was noted in our recently published Prelog-Djerassi lactonic acid synthesis (*c.f.* Scheme XXIV).[19] Consequently, we have observed that the required C_8-asymmetric center for tylosin and related macrolides may be introduced *via* the hydroboration of either **23** or **25** but not **22** (Scheme XXII). Nicolaou and coworkers have recently noted related observations in their own successful approach to the synthesis of the tylosin aglycone.[23]

The remaining C_{11}-C_{15} subunit required for the tylosin aglycone and our basic approach for its construction is illustrated in Scheme XXV. The establishment of the desired C_{14}- and C_{15}-stereocenters for this synthon has been accomplished *via* the illustrated aldol process. The five-step synthesis of this molecule (Scheme XXVI), which has been executed in an overall yield of 64%, is noteworthy for its brevity.

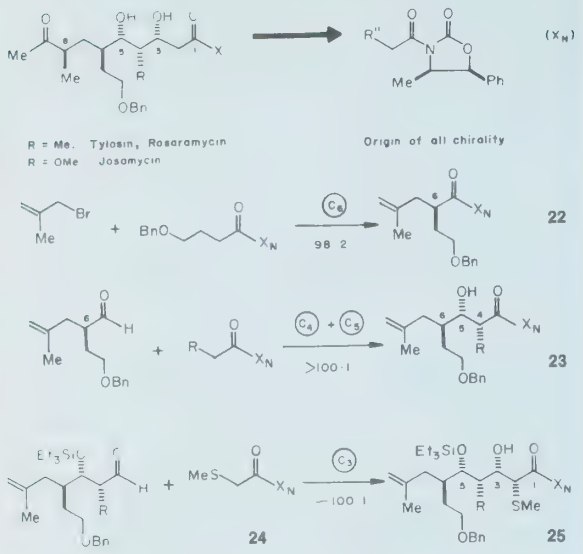
The chiral enolate technology described in this review is currently being applied to architectural exercises in the polyether antibiotics field as well. One such project, which is nearing completion, is the synthesis of the calcium-selective ionophore ionomycin (Scheme XXVII).[24] The basic approach being followed has focused on the synthesis of the four illustrated subunits (**A** → **D**). The basic protocol for absolute stereochemical control in this project is identical to that previously described for the tylosin synthesis. All asymmetry is being derived from the chiral oxazolidone auxiliaries highlighted in this review. At the present time we have already accomplished the synthesis of all four of the illustrated ionomycin synthons (**A-D**) in optically pure form.[25]

In summary, there are several well recognized approaches that are currently being followed for the production of chiral substances. These include chemical resolution, the chemical modification of chiral natural products (*e.g.*, carbohydrates), and asymmetric synthesis. Until recently, organic chemists have not enjoyed a great deal of success in this latter venture. This has been particularly true in the area of asymmetric carbon-carbon bond construction. It is my firm conviction that we will witness spectacular advances in this field over the next few years.

I feel exceptionally fortunate to have been associated with a number of outstanding colleagues, both graduate students and postdoctoral associates, who have contributed the experimental expertise and a great deal of the intellectual input contained in this research effort. Finally, I wish to acknowledge financial support from the National Science Foundation (CHE-81-01742), the National Institutes of Health (CA-29187-02, GM-27111-07) and the Eli Lilly Company.

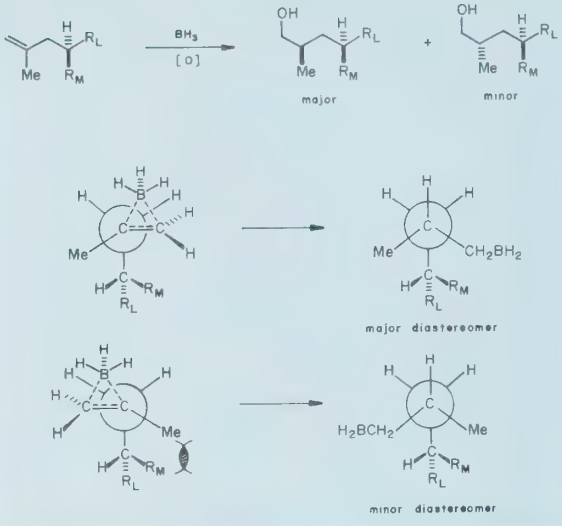
Scheme XXII

C_1–C_{10} Macrolide Synthons



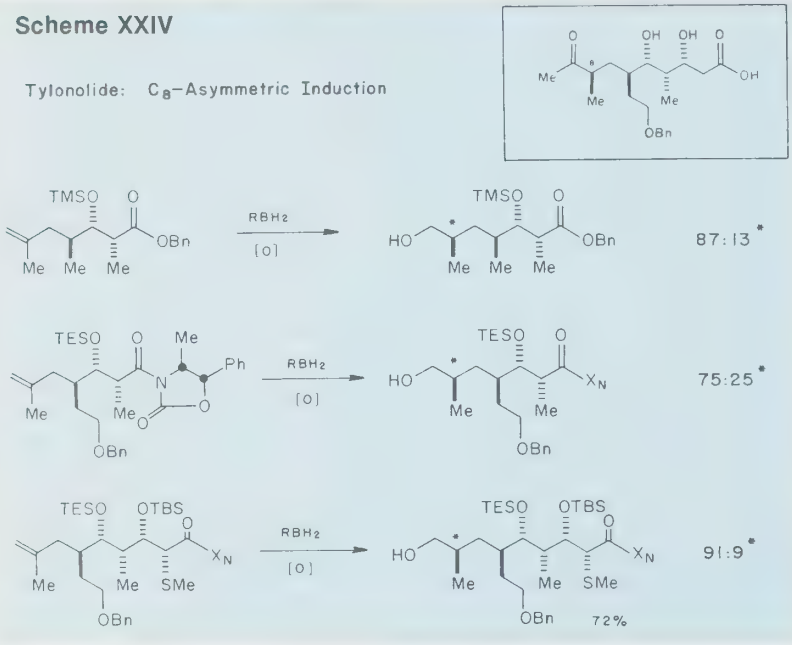
Scheme XXIII

HYDROBORATION CONTROL ELEMENTS



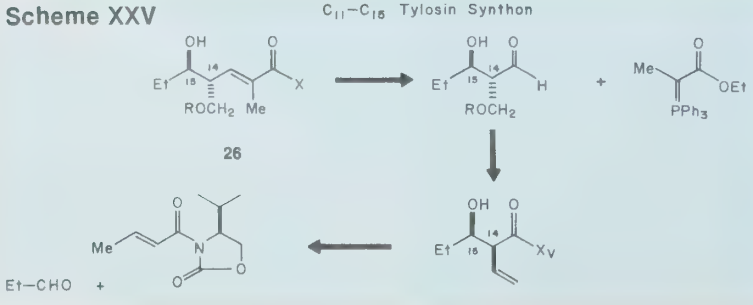
Scheme XXIV

Tylonolide: C_8–Asymmetric Induction



Scheme XXV

C_{11}–C_{15} Tylosin Synthon



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14) For a full account of our studies on aldol stereoregulation *via* boron enolates, see: Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* **1981**, *103*, 3099 and earlier references cited therein.
15) For a recent review of the aldol process see: Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* **1982**, *13*, 1.
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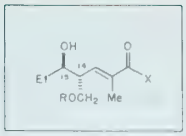
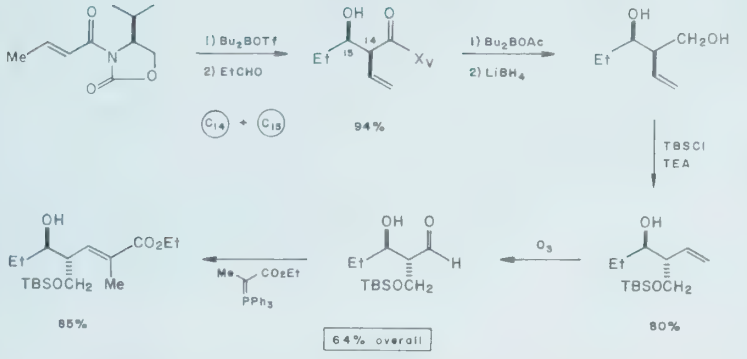
Scheme XXVI

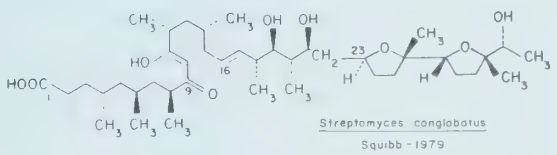
C_{11}–C_{15} Tylosin Sython Construction

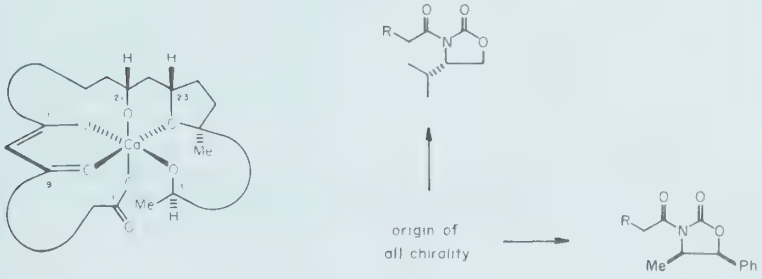




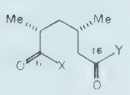
Scheme XXVII

Ionomycin Total Synthesis

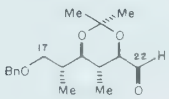




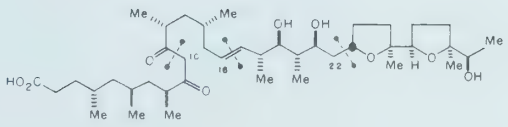
Subgoals

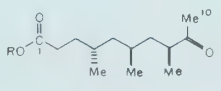


B C_{11}-C_{16}

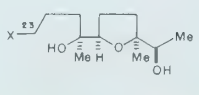


C C_{17}-C_{22}





A C_1-C_{10}



D C_{23}-C_{32}

19) Evans, D.A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807.
20) Evans, D.A.; Ennis, M.D.; Shih, T.L., unpublished observation.
21) Evans, D.A.; Sjogren, E., unpublished observation.
22) Evans, D.A.; Godel, T.; Bartroli, J., unpublished observations.
23) Nicolaou, K.C.; Pavia, M.R.; Seitz, S.P. *J. Am Chem. Soc.* **1982**, *104*, 2027, 2030.
24) Toeplitz, B.K.; Cohen, A.I.; Funke, P.T.; Parker, W.L.; Gougoutas, J. *ibid.* **1979**, *101*, 3344.
25) Evans, D.A.; Zahler, R.; Dow, R.; Shih, T.L., unpublished observation.

About the Author

Professor David A. Evans was born on January 11, 1941. He received the A.B. degree from Oberlin College in 1963, and the Ph.D. degree (under Professor Robert Ireland) from the California Institute of Technology in 1967. He was appointed Assistant Professor of Chemistry at UCLA in 1967 and was promoted to Associate Professor and Professor in 1972 and 1974, respectively. Since 1974, he has been Professor of Chemistry at Cal Tech and a consultant for Eli Lilly Co.

Dr. Evans has developed diverse and valuable synthetic methodologies ranging from the anionic oxy-Cope rearrangement to blocked quinones in total synthesis. Recently, his efforts have culminated in the successful application of boron and zirconium enolates to highly diastereo- and enantioselective aldol condensations allowing construction of complex carbon skeletons in optically pure form. Among the natural products synthesized by Professor Evans' group are hasubanan, luciduline, bakkenolide-A, β-dolabrin, colchicine, histrionicotoxin, and calcimycin.

Previous awards and distinctions include the Camille and Henry Dreyfus Teacher-Scholar Award, an Alfred P. Sloan Foundation Fellowship, and the UCLA Alumni Association Distinguished Teaching Award. Professor Evans serves on two National Research Council committees as well as on the Honorary Editorial Advisory Board of *Tetrahedron* and *Tetrahedron Letters*.

A Compilation of References on R-Functional Acyl Anion Synthons, RCO^-

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R-Functional RCO^- Synthons

Functionality in R:

1) C=C Unsaturation
   a) Protected β,γ-unsaturated cyanohydrins and analogs
   b) Allylic or ketene dithioacetals
   c) Allenic ethers, thioethers, and analogs
2) Carbonyl
3) Carboxylic acid, ester, nitrile, etc.
4) Hydroxyalkyl, alkoxyalkyl, aminoalkyl, etc.
5) C-Cationic or additional C-anionic center elsewhere in chain

Note that many of the acyl anion synthons (RCO^-, $ArCO^-$) listed previously (*Aldrichimica Acta* **1981**, *14*, 73) presumably can accommodate functionality (*e.g.*, unsaturation, ether groups, etc.) in R (or Ar), although the original papers may not have given specific examples of such cases. Within the present group, conjugated enone acyl anion synthons (Subgroup 1) constitute a special case as they may react at the α- ($C{=}C{-}\dot{C}O^-$) and/or the γ-site ($^-\dot{C}{-}C{-}COOH$) irrespective of the original location of the double bond. This is especially true of Subgroup 1b synthons (allylic or ketene dithioacetals). Synthons in which the γ-reactivity mode is dominant will be presented in a forthcoming installment. For studies on the effect of solvent, temperature, counterion, etc. on the α/γ reactivity of ketene dithioacetal anions, see references 1-7. In view of the importance of allylic or ketene dithioacetal anions in this context, we include here a concise survey of some of the more recent routes to such compounds (for references to earlier work, see ref. 8). "Trivial" routes involving the γ-alkylation of ketene dithioacetals belong to the group of $^-C{-}C{-}COOH$ synthons. Also, the obvious route to allylic dithioacetals from 2-enals is omitted here.

Again, expressions such as C=C–CO are used to imply generality in regard to double-bond substitution. A direct carbonyl as opposed to Michael addition to such species is indicated by "1,2-" or "1,4-", respectively, in parentheses. Individual substitution patterns (*e.g.*, CH_3-$COCO^-$) are only shown when generality is lacking or was not reported. In Subgroup 5, the electrophiles and/or nucleophiles which are known to react at the sites shown are indicated separately.

1a) Protected β,γ-unsaturated cyanohydrins and analogs.

Equivalence	Reagent	Electrophile	Ref.
$C{=}C{-}CO^-$	$C{=}C{-}CH(CN)(O\{SiMe_3$ or $-CH(OEt)-Me\})$	RBr, RI, ROTs	9-11
		aldehydes, ketones → $R_2C(OSiMe_3)(CO-C{=}C)$ (directly)	12,13
		C=C–COR (1,2-)	12
$RCH{=}CHCO^-$	$RCH{=}CH{-}CH(CN)(NR'_2)$	ketones	14

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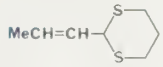
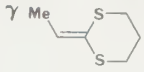
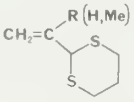
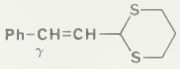
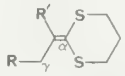
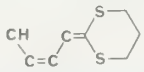
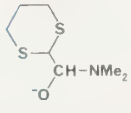
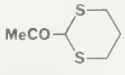
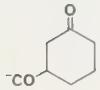
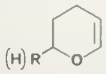
1b) Allylic or ketene dithioacetals

Equivalence	Reagent	Electrophile	Ref.
$MeCH{=}CH{-}CO^-$ (*E*)		$ArCH_2Br$	2
$CH_2{=}CH{-}CO^-$		cyclobutanone and cyclopentanone only; aldehydes and other ketones give γ products	1
$CH_2{=}C(R\,(H, Me))CO^-$		cyclic C=C–COR (1,4-)	3
$PhCH{=}CH{-}CO^-$ (*E*)		RX, Me_2SO_4, Me_3SiCl ($PhCH_2Br$ gives γ product)	2
$RCH{=}CR'{-}CO^-$		RX; aldehydes and ketones give α/γ mixtures RCH_2I, allylic and benzylic Br, Me_2S_2	15 16
$C{=}C{-}C{=}C{-}CO^-$		MeI	15

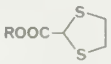
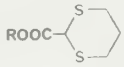
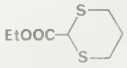
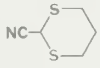
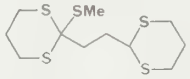
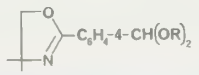
1c) Allenic ethers, thioethers and related compounds

$CH_2{=}CH{-}CO^-$	$(RO)_2PO{-}NMe{-}CH{=}C{=}CH_2$	MeI, $PhCH_2Br$	17
$MeCH{=}CH{-}CO^-$ (*E*)	$CH_2{=}CH{-}CH{=}CH{-}OMe$	PhCHO	18
$CH_2{=}CH{-}CO^-$	$BuOCH{=}CH{-}CH_2OBu$	RBr, RI	19
$RCH{=}CH{-}CO^-$	$RCH{=}C{=}CH{-}SR'$	aldehydes, ketones	20
$RCH{=}CH{-}CO^-$	$RCH_2C{\equiv}C{-}SEt$	RBr	21
$CH_2{=}CH{-}CO^-$	$CH_2{=}C{=}CH{-}OR$ (or $HC{\equiv}C{-}CH_2OR$)	aldehydes, ketones, Me_2S_2 RX (primary only)	22 23

2) Aldehyde or ketone functionality in R

Equivalence	Reagent	Electrophile	Ref.
$OHC{-}CO^-$	 (from 2-lithio-1,3-dithiane + DMF; *in situ* alkylation)	allylic Br	24
$OHC{-}CO^-$	$(EtO)_2CH{-}CHO$	thiazolium salt-catalyzed addition to C=C–CO (1,4-)	25
$MeCOCO^-$ [and $CH_2{=}C(OMe){-}CO^-$]	$CH_2{=}C(OMe)CH(CN){-}OSiMe_3$	RI, $PhCH_2Br$	11
$MeCOCO^-$ ($MeOCOCH_2CH_2CH_2CO{-}CO^-$ similarly)		RI, allyl Br, $PhCH_2Br$	26
$RCOCO^-$ (or $ArCOCO^-$)	$RCOCH_2SEt$ (or $ArCOCH_2SEt$)	RI, $PhCH_2Br$, ArCHO, oxiranes	27
$OHC{-}CH_2{-}CO^-$	$MeSC{\equiv}C{-}CH_2OMe$	RX	28
$RCO{-}CH_2{-}CO^-$	$MeS{-}CR{=}C{=}CH{-}OMe$ (from $MeSC{\equiv}C{-}CH_2OMe$)	ketones	28
$RCOCH_2CH_2CO^-$		RCH_2Br aldehydes, ketones, esters	29 30
	$(MeS)_2CH{-}SnR_3$ + 2-cyclohexenone	MeI	31
$(H^-)\,R{-}CO(CH_2)_3CO^-$		RCH_2I, allylic Br, ketones	32

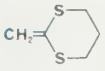
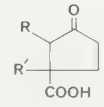
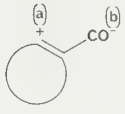
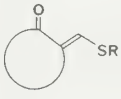
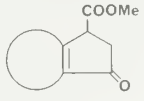
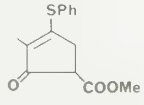
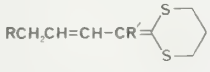
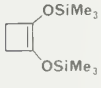
3) Carboxylic acid or derived functionality in R

Equivalence	Reagent	Electrophile	Ref.
(H) ROOC–CO⁻ [and ROOC–C⁻(OMe)₂]	(H) ROOCCH₂SEt	RI, PhCH₂Br, ArCHO, oxiranes	27
ROOC–CO⁻	ROOC–CHCl₂	RBr, aldehydes	33
ROOC–CO⁻ [and ROOC–C⁻(OR')₂]	ROOC–CH(OR')₂	RI (primary, secondary), RBr (primary, allylic, benzylic), MeOCH₂Cl	34
		aldehydes, ketones; 2-cyclohexenone (1,2-)	35
		butenolides (1,4-)	36
HOOC–CO⁻	HOOC–CH(SR)₂	RI, RBr, PhCH₂Cl, ROTs, oxiranes, N-Ts-aziridine	37,38
ROOC–CO⁻	ROOC–CH(SEt)₂	C=C–CO{R, OR (1,4-)	39
ROOC–CO⁻		C=C–CO{R, OR (1,4-)	40
ROOC–CO⁻		RBr (primary, secondary), PhCH₂Cl	41
EtOOC–CO⁻	 (Li or Mg enolate)	aldehydes (using Mg enolate), 2-enals (1,2- with Mg enolate but 1,4- with Li enolate)	42
NC–CO⁻		RBr, PhCOCH₂Br	43
HOOC–CH₂CO⁻	HOOC–C≡CH	oxiranes	44
EtOOC–CH₂CO⁻	(EtO)₂CH–C≡C–SMe	RCH₂X	45
R₂NCO–CH₂CO⁻	R₂NCO–CH=CH–NR'₂	RI, ArCOOR''	46
MeOOC–CHMe–CO⁻	MeOOC–CMe=CH–SPh	aldehydes, acyl Cl; 2-enoic esters (1,4-); 2-enals (can be made to react either 1,2- or 1,4-)	47
R'OOC–CHR–CH₂CO⁻	R'OOC–CHR–CH₂CH(SMe)–SOMe [from R'OOC–C⁻HR + CH₂=C(SMe)–SOMe]	MeI, allylic Br	48
ROOC–CH₂CH₂CO⁻		RX	49
p-HOOC–C₆H₄CO⁻		RI, allylic X, acyl Cl, aldehydes	50

4) Hydroxyalkyl, alkoxyalkyl, aminoalkyl or similar functionality in R

Equivalence	Reagent	Electrophile	Ref.
HOCH₂CO⁻	CH₂=CHOMe	ketones	51
RSCH₂CO⁻	RS–CH=CH–SR (*Z*)	FSO_3Me, aldehydes, Me_2S_2	52
HOCH₂(CH₂)ₙCO⁻ (n = 2 or 3)		RCH₂I, allylic Br, ketones	32
Ph₃C– / RCO– / BOC– } NH(CH₂)ₙ-CHRCO⁻	BOC–NH(CH₂)ₙCHR–CONH–CH(*i*-Pr)–COOH (n = 0, 1 or 9)	CH₂=CHCOOEt, CH₂=CHCN (1,4-)	53
RCO⁻; R = ROCH₂-, 2- or 3-THP-yl, or 2-(Δ³ or Δ⁴-DHP)yl	RCHO	thiazolium salt-catalyzed addition to 2-enones (1,4-)	54

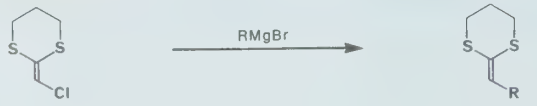
5) C-cationic or additional C-anionic center elsewhere in chain

Equivalence	Reagent	Electrophile	Ref.
$^{(a)}{}^{+}CH_2CO^{-}{}^{(b)}$		(a) RLi (b) MeI	55
$^{(a)}{}^{+}CH_2CO^{-}{}^{(b)}$	$CH_2=C(SR)-SOR$	(a) ester enolate (b) MeI, allyl Br	56
$^{(a)}{}^{+}CH_2CO^{-}{}^{(b)}$	$CH_2=C(Y)-SiMe_3$; Y = SMe or $SiMe_3$	(a) RLi (excl. MeLi, PhLi, RMgX) (b) RCHO (~ RCH_2^{+})	55
$^{(a)}{}^{+}CH_2CO^{-}{}^{(b)}$	$CH_2=C(CN)-NMe-Ph$	(a) *t*-BuLi, allyl Li, ArLi (b) RI, $PhCH_2Br$	57
$RC^{(a)}{}^{+}H-CO^{-}{}^{(b)}$	$RCH=C(SMe)-SOMe$	(a) imine α-anion (b) MeI	58
$^{(a)}{}^{+}CH_2CH_2CO^{-}{}^{(b)}$		(a) + (b) β-keto ester enolate, → 	59
		(a) + (b) $CH_2=CHCOOMe$, → 	60
$^{(a)}{}^{+}CO-CHMe-CO^{-}{}^{(b)}$	$PhS-CLi=CMe-COOMe$	(a) + (b) $CH_2=CHCOOMe$, → 	61
$RC^{(a)}{}^{+}HCH=CR'-CO^{-}{}^{(b)}$		(a) RLi (b) MeI	55
$^{(a)}{}^{+}COCH_2CH_2CO^{-}{}^{(b)}$		(a) MeMgI (b) acetals, then oxidation, → $MeCOCH_2CH_2CO-CRR'-OMe$	62
$^{(a)}{}^{-}CH_2CO^{-}{}^{(b)}$	$Me-CSSEt$	(a) aldehydes (b) CO_2, aldehydes, 2-enals (1,2-), R_2NCHO	63
$^{(a)}{}^{-}COCH_2CO^{-}{}^{(b)}$	$MeS-C\equiv C-CH_2OMe$	(a) RX (b) ketones	28
$^{(a)}{}^{-}CH=CH-CO^{-}{}^{(b)}$	$(RO)_2PO-NMe-CH=C=CH_2$	(a) MeI, $PhCH_2Br$ (b) $PhCH_2Br$	17
$R-C^{(a)}{}^{-}=CH-CO^{-}{}^{(b)}$	$RC\equiv C-CH_2OMe$	(a) R_2SO_4, Me_3SiCl (b) RBr, R_2SO_4, Me_3SiCl	64
$Ph-C^{(a)}{}^{-}=CH-CO^{-}{}^{(b)}$	$PhC\equiv C-CH_2OMe$	(a), (b) RCH_2Br, Me_2SO_4, Me_3SiCl	65
$Me_3SiC^{(a)}{}^{-}=CH-CO^{-}{}^{(b)}$	$Me_3SiC\equiv C-CH_2OBu$	(a) MeI, Me_3SiCl (b) MeI, Me_3SiCl, ketones	66
$^{(a)}{}^{-}CH=C(SePh)-CO^{-}{}^{(b)}$	$PhSeCH_2C\equiv CH$	(a) RCH_2Br, RI (secondary) (b) MeI, Me_3SiCl, aldehydes, ketones	67,68
$^{(a)}{}^{-}CH=CH-CH=CH-CO^{-}{}^{(b)}$ (*E*,*E*)	$CH_2=CHCH_2CH_2-CSSR$	(a) aldehydes, ketones (b) RI	69

Routes to allylic or ketene dithioacetals

1) By chain extension of ketene dithioacetals, excluding alkylation of γ-anion
2) Dehydrogenation of saturated dithioacetals
3) *Via* alkanethionocarboxylic acids and related compounds
4) Wittig- or Peterson-type olefinations
5) Other

1) Chain extension of ketene dithioacetals

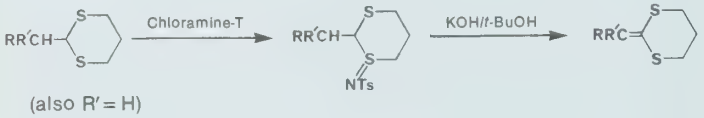


Ref. 70

$RCO-CR=C(SMe)_2 \xrightarrow{Ph_3P=CH_2} CH_2=CR-CR'=C(SMe)_2$ 71

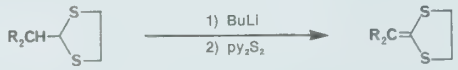
$RCH_2CO-CR'=C(SMe)_2 \xrightarrow[ZnCl_2]{Me_3SiCl/Et_3N} RCH=C(OSiMe_3)-CR'=C(SMe)_2$ 71

2) Dehydrogenation of saturated dithioacetals



72

(also R′ = H)



73

(or dithiane)

3) From alkanethionocarboxylic acids and related compounds

$RR'CH-CSSMe \xrightarrow[2)\ Me_3SiCl]{1)\ LDA} RR'C=C(SMe)-SSiMe_3$ 74

(also R′ = H)

$MeSCS-NHNHTs + RCH=CR'-CH_2X \longrightarrow TsNHN=C(SMe)-SCH_2CR'=CHR$ 75

$\xrightarrow[2)\ [2,3]\text{- rearr.}\ 3)\ MeI]{1)\ NaH} (MeS)_2C=CR-CR'=CH_2$

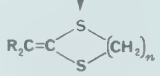
$CH_2=CHCH_2CH_2CSS\text{-}i\text{-}Pr \xrightarrow[2)\ RCOR\ 3)\ MeI]{1)\ base} R_2C(OH)CH_2CH=CH-CH=C(SMe)-S\text{-}i\text{-}Pr$ 69

$RR'CH-CSSH \xrightarrow[2)\ R''X]{1)\ LDA} RR'C=C(SR'')_2$ 76

(R, R′ = H or alkyl)

$RCH_2-CSSR' \xrightarrow{-OH/MeI} RCH=C(SMe)-SR'$ (also monoxide) 58

$R_2CHMgX + CS_2 + Cl(CH_2)_nBr \longrightarrow R_2CH-CSS(CH_2)_nCl$ 77



n = 1-4 (not for n = 1 when $R_2 = H_2$ or H + Me)

$MeMgCl \xrightarrow[3)\ Me_2SO_4]{1)\ CS_2\ \ 2)\ LDA} CH_2=C(SMe)_2$ (also monoxide) 78

$RCH_2MgX \xrightarrow[3)\ R'X]{1)\ CS_2\ \ 2)\ LDA} RCH=C(SR')_2$ $[R_2C=C(SR')_2]$ similarly 79

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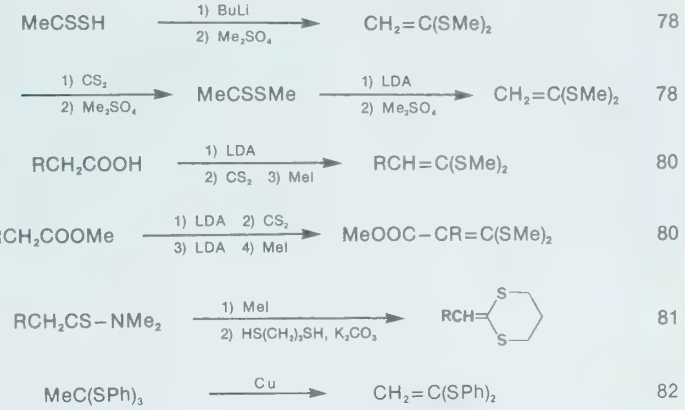
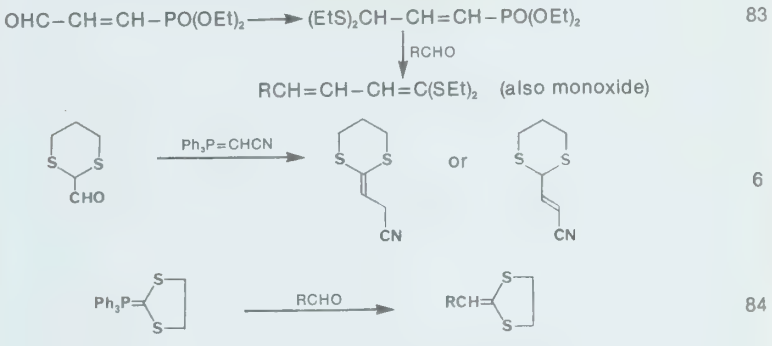
3) From alkanethionocarboxylic acids and related compounds (continued)

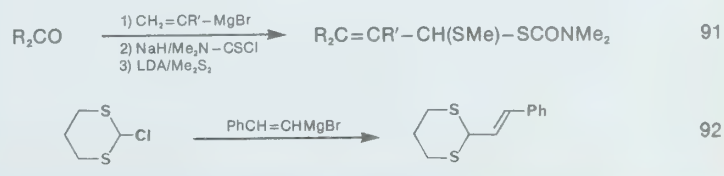
Ref.



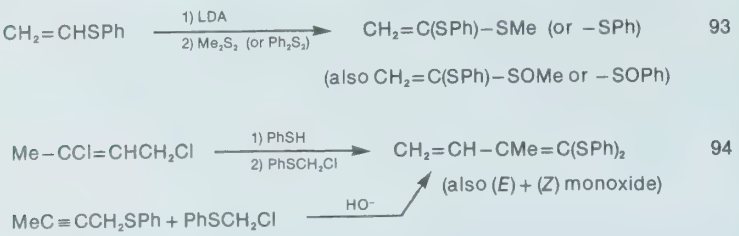
4) Wittig- or Peterson-type olefinations



5) Other methods



5) Other methods (continued)



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Among the many compounds cited by Drs. Hase and Koskimies and offered by Aldrich are the following:

15,787-2 1,3-Dithiane

22,081-7 2-Trimethylsilyl-1,3-dithiane

21,284-9 Trimethylsilyl cyanide

A1,625-4 2-Acetylfuran

F1,957-4 2-Furanacrylonitrile

M4,684-5 2-Methylfuran

18,592-2 Furan, 99+%

C7,285-4 Chlorotrimethylsilane

22,724-2 Cyclopropyl phenyl sulfide

C11,240-2 Cyclopentanone

C9,600-1 Cyclobutanone

24,131-8 Methyl disulfide, GOLD LABEL

D10,620-8 Dihydropyran

P5,140-0 Propiolic acid

M2,730-1 Methyl acrylate

13,007-9 (Methyl)triphenylphosphonium bromide

23,275-0 1-Bromo-2-chloroethane

23,644-6 1-Bromo-3-chloropropane

B6,080-0 1-Bromo-4-chlorobutane

24,166-0 1-Bromo-5-chloropentane

24,165-2 1-Bromo-6-chlorohexane

P5,060-9 1,3-Propanedithiol

85,731-9 Chloramine-T hydrate

16,902-1 Phenyl disulfide

23,071-5 *n*-Butyllithium, 10.5*M* solution in hexane

23,070-7 *n*-Butyllithium, 2.5*M* solution in hexanes

18,617-1 *n*-Butyllithium, 1.6*M* solution in hexane

19,559-6 *sec*-Butyllithium, 1.3*M* solution in cyclohexane

18,619-8 *tert*-Butyllithium, 1.7*M* solution in pentane

19,734-3 Methyllithium, 1.4*M* solution in diethyl ether

18,620-1 Methyllithium-lithium bromide complex, 2*M* solution in diethyl ether

22,102-3 Phenyllithium, 2*M* solution in cyclohexane-ether, 70 to 30

22,575-4 Allylmagnesium bromide, 1*M* solution in diethyl ether

22,590-8 Allylmagnesium chloride, 2*M* solution in tetrahydrofuran

22,591-6 Benzylmagnesium chloride, 2*M* solution in tetrahydrofuran

22,437-5 Butylmagnesium chloride, 2*M* solution in diethyl ether

22,442-1 *sec*-Butylmagnesium chloride, 2*M* solution in diethyl ether

22,382-4 *tert*-Butylmagnesium chloride 2*M* solution in tetrahydrofuran

22,441-3 Cyclohexylmagnesium chloride, 2*M* solution in diethyl ether

22,440-5 Cyclopentylmagnesium chloride, 2*M* solution in diethyl ether

18,987-1 Ethylmagnesium bromide, 3*M* solution in diethyl ether

22,688-2 Ethylmagnesium bromide, 2*M* solution in tetrahydrofuran

22,438-3 Isopropylmagnesium chloride, 2*M* solution in diethyl ether

18,989-8 Methylmagnesium bromide, 3*M* solution in diethyl ether

18,990-1 Methylmagnesium chloride, 3*M* solution in tetrahydrofuran

17,156-5 Phenylmagnesium bromide, 3*M* solution in diethyl ether

22,444-8 Phenylmagnesium chloride, 2*M* solution in tetrahydrofuran

22,439-1 Propylmagnesium chloride, 2*M* solution in diethyl ether

22,558-4 Vinylmagnesium bromide, 1*M* solution in tetrahydrofuran

22,723-4 2-Mesitylmagnesium bromide, 1*M* solution in tetrahydrofuran

23,011-1 Isopropylmagnesium chloride, 2*M* solution in tetrahydrofuran

22,449-9 *tert*-Butylmagnesium chloride, 2*M* solution in diethyl ether

22,574-6 Isobutylmagnesium chloride, 2*M* solution in diethyl ether

Advances in Stereochemical Control: The 1,2- and 1,3-Diol Systems[1]

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1. Introduction and Background

In recent years natural-product synthesis has placed heavy emphasis on asymmetric synthesis.[2] This trend has been brought about not only for the elucidation of fundamental processes involved in asymmetric synthesis, but by the structural requirement of some target molecules. The pre-1970 literature records many elegant total syntheses of steroids, alkaloids, terpenes, and others in **racemic** form. In addition to those polycyclic compounds, numerous other natural products are of a different structural type, **basically acyclic** in nature, as exemplified by macrolide and ionophore antibiotics. Structural analysis of this last group of compounds readily reveals that coupling of two chiral fragments A and B be incorporated as a logical step in their syntheses.[3] With *d*-A—*d*-B representing the structure of a natural product, this assembly can be executed in three ways: (1) connection of the optically pure fragments both in *d*-form (eq. 1), (2) reaction of *d*-A with the racemate of B (eq. 2) normally leading to a mixture of two compounds *d*-A—*d*-B and *d*-A—*l*-B, which are diastereomeric and hence potentially separable, and (3) pairing of the two racemates (eq. 3) usually resulting in the formation of two A-B racemates in nearly equal quantities,

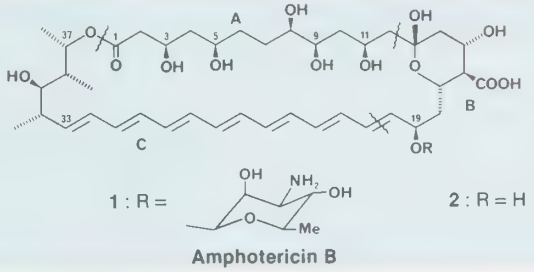
$$d\text{-A} + d\text{-B} \longrightarrow d\text{-A—}d\text{-B} \qquad \text{(eq. 1)}$$

$$d\text{-A} + dl\text{-B} \longrightarrow d\text{-A—}d\text{-B} + d\text{-A—}l\text{-B} \qquad \text{(eq. 2)}$$

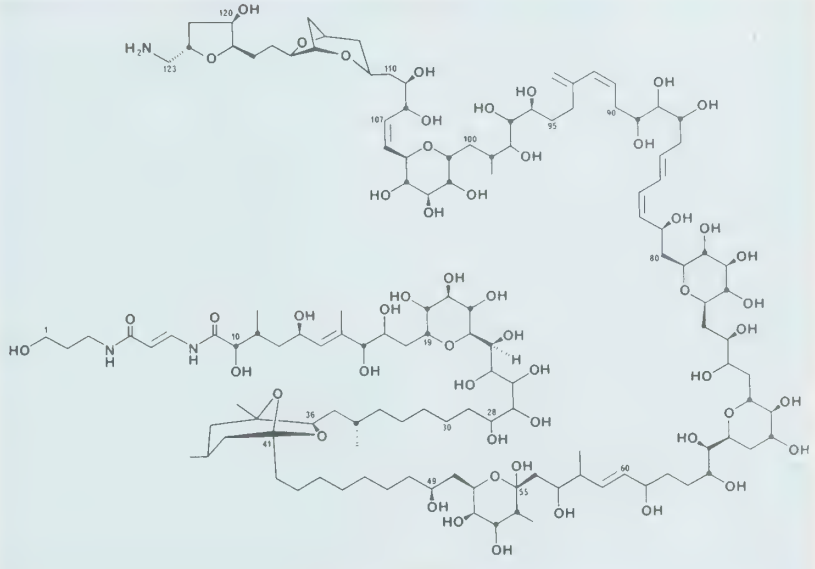
$$dl\text{-A} + dl\text{-B} \longrightarrow d\text{-A—}d\text{-B} + l\text{-A—}l\text{-B} + (d\text{-A—}l\text{-B} + l\text{-A—}d\text{-B}) \qquad \text{(eq. 3)}$$

unless, on rare occasions, the reaction is carried out under ideal conditions of kinetic resolution. While reactions 2 and 3 must be followed by separation of the diastereoisomers, a normally tedious process of optical resolution is further required in the latter case in order to complete the synthesis of the target molecule *d*-A—*d*-B. Thus, the method of choice is obviously reaction 1, for which *enantiomerically pure A and B fragments are required*. The role of asymmetric synthesis is self-evident and will become even more significant as this Account unfolds.

As an illustration, let us examine the structure of amphotericin B (**1**)[4] which represents the large family of macrolides of acetate and propionate origin.[3] One logical retrosynthesis of its aglycone (**2**) (the non-sugar portion of **1**) dissects, as indicated by the wavy lines in **2**, the 38-membered lactone into chiral fragments A, B, and C which feature the presence of one 1,2-diol and several 1,3-diol structural units. In fact, these dihydroxyl units are ubiquitous in numerous polyketide natural products of biological significance, as exemplified in a dramatic manner by palytoxin (**3**), a potent toxin of marine origin having a molecular formula of $C_{129}H_{223}N_3O_{54}$, 64 asymmetric centers, and eight double



Amphotericin B



3 Palytoxin

$C_{129}H_{223}N_3O_{54}$, 64 asymmetric centers, 8 double bonds

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bonds.[5] Thus, an approach or approaches to the construction of these basic diol units become a necessity. Once efficient methodologies are established, one can contemplate a logical synthetic scheme even for palytoxin, although in this particular instance, one will be inevitably bogged down with repetitious operations as well as technical problems associated with the handling of large molecules such as peptides.

Approximately three years ago at M.I.T., we launched a project aimed at the efficient synthesis of several representative macrolide antibiotics of medium complexity, with the prime objective of establishing the methodology for the sequential construction of the 1,3- and 1,2-diol systems. Although seemingly severe at the time, our requirements for a successful methodology were (a) a stereoselection of, at minimum, 15:1, (b) a chemical yield of greater than 80%, and (c) functional groups in the product so chosen that they can be easily and mildly transformed into a substrate for the next stereoselective reaction of the sequence. For these objectives, two synthetic transformations were selected: (1) the asymmetric aldol reaction for the 1,3-diols (eq. 4) and (2) a sequence of reactions involving Wittig reaction, asymmetric epoxidation, and ring opening for the 1,2-diols (eq. 5).

Five or fewer consecutive applications of eqs. 4 and 5 together with additional functional-group transformations will be adequate for the construction of a molecule with ten or fewer chiral centers, the degree of stereochemical complexity possessed by the target molecules. If the conditions set above are met, the overall stereoselection for all the reactions will still exceed a gratifying 72%.

In this article we outline the mainstream of our own research developments, and deliberately limit the citation of other contributors to only those pertinent to the discussion. Emphasis is placed on the analysis of the stereochemical problems and the conceptual development in solving the problems that have emerged. There is a wealth of new findings in the fields of asymmetric aldol reaction and asymmetric epoxidation and excellent review articles already exist.[6]

2. Aldol Reaction

2.1. Stereochemical Descriptors. Before we unfold a rather complicated account of aldol chemistry, the nomenclature to be used throughout this article must be unambiguously defined. The aldol reaction (eq. 6) is a carbon-carbon bond-forming reaction which involves an aldehyde (**4**) and an enolate (**5**) and, in general, creates two chiral centers in the product (**6**). Thus, if **4** is an enantiomerically pure 2-methyl-substituted aldehyde and **5** is an enolate derived from an ethyl ketone, the reaction products that may result from this reaction are four diastereoisomers, **6a-6d**. For the reasons detailed elsewhere,[7] the stereochemistry of these isomers is now expressed in this article by the zigzag main-chain formula, and the descriptors "*syn*" and "*anti*" are used, as shown in eq. 6, to describe two (non-hydrogen) substituents on the same side and those on the opposite sides of the plane defined by this chain, respectively. The proposal of an additional set of descriptors also appears to be appropriate. The two lithium enolates **7a** and **7b** are designated *Z* and *E*. Since very often we are concerned with the relative disposition of the OLi and methyl groups with respect to the double bond, and in fact both enolates **7a** and **7b** induce the same stereochemical consequence, it is preferred to assign the same descriptors to both of them. We propose the use of *Z*(O), indicating that top priority is conferred on the element in the bracket in this special case.[7] *E*(O) is defined in the same manner. These two sets of stereochemical descriptors eliminate the ambiguity that unfortunately has appeared in the recent aldol literature, and this proposed nomenclature hopefully will receive universal acceptance in the future.

2.2. Models for the Aldol Reaction. Any condensed-phase reaction which involves an organometallic reagent (including metal enolates) takes an extremely complicated course, and our understanding of it is still at the infant stage. Even in cases where the degree of aggregation of the reagent in solution was known, *e.g.*, a lithium enolate[8] and cuprate,[9] the actual species reacting with a substrate had not been determined. Moreover, reactions of the same type have been performed under a variety of experimental conditions, *i.e.*, the aldol condensation may have been effected with various Lewis acids or bases, and thus, the conformation of the transition state has varied from case to case.[6a–d] For these reasons we are concerned only with aldol reactions (eq. 7) using a cation M^+ (M in **8**: a Group I, II, or III metal) and the model of our selection is one which best rationalizes the experimental results.

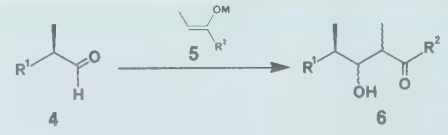
Some time ago Zimmerman and Traxler proposed, for the Ivanov reaction, the chair-type pericyclic intermediate[10] (al-

Asymmetric Aldol Reaction

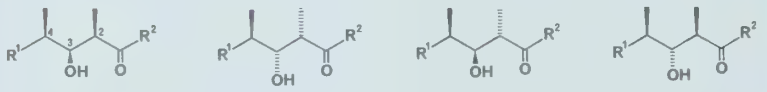
$$^{*}R\text{-}CHO \longrightarrow {}^{*}R\text{-}{}^{*}CH(OH)\text{-}{}^{*}CH(Me)\text{-}CHO \qquad \text{(eq. 4)}$$

Asymmetric Epoxidation and Ring Opening

$$^{*}R\text{-}CH{=}CH\text{-}CH_2OH \longrightarrow {}^{*}R\text{-}{}^{*}CH\text{-}{}^{*}CH\text{-}CH_2OH \longrightarrow {}^{*}R\text{-}{}^{*}CH(OR)\text{-}{}^{*}CH(OR)\text{-}CHO \qquad \text{(eq. 5)}$$



(eq. 6)



6a: 2,3-*syn* 3,4-*syn* | 6b: 2,3-*syn* 3,4-*anti* | 6c: 2,3-*anti* 3,4-*syn* | 6d: 2,3-*anti* 3,4-*anti*

Z-enolate | *E*-enolate = *Z*(O)-enolate

7a | 7b

(eq. 7)

8 : *Z*(O)-enolate α(re)-face attack

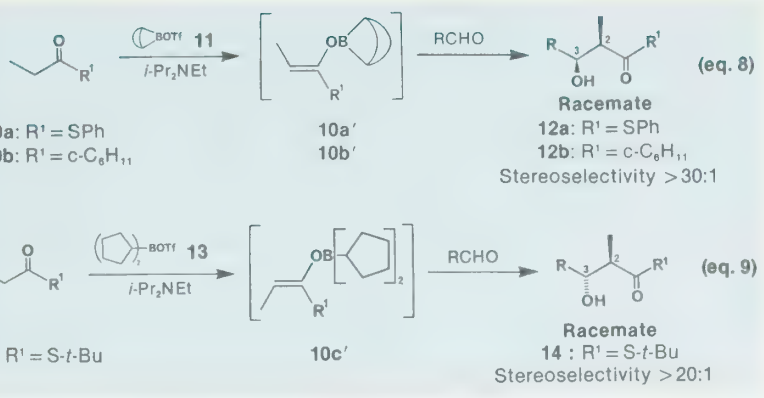
Z(O), α: 2,3-*syn* 3,4-*syn* | *E*(O), α: 2,3-*anti* 3,4-*syn* | *Z*(O), β: 2,3-*syn* 3,4-*anti* | *E*(O), β: 2,3-*anti* 3,4-*anti*

most the same as shown in **8**) which, prior to our initiation of this project, had already proven useful in explaining the stereochemical course of several aldol-type reactions.[6a–d]

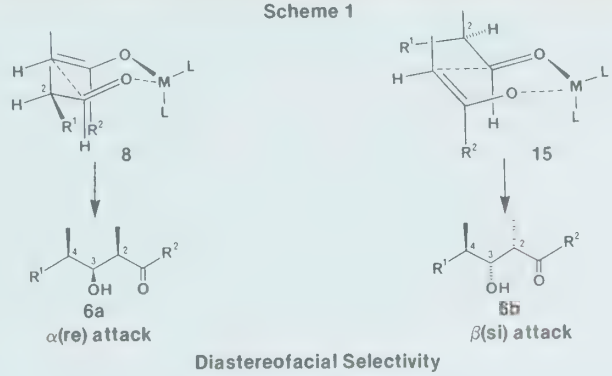
The outcome of the reaction proceeding through **8** which delineates the case of the *Z*(O) enolate approaching the α(re)-face of the aldehyde is straightforward: the aldol product **9** should have the 2,3-*syn*, 3,4-*syn* stereochemistry. The other combinations for the assembly of the enolate and aldehyde are: *E*(O) enolate approaching the α-face of the aldehyde; *Z*(O) enolate, β(si)-face, and lastly *E*(O) enolate, β-face. The stereochemistry of the product in each case is tabulated. It is clear that (1) the *Z*(O) and *E*(O) geometries of the enolate are translated into the 2,3-*syn* and 2,3-*anti* stereochemistry of the aldol product, respectively and (2) the enolate's approach to the aldehyde (from the α- or β-face) determines the absolute configuration of the C-3 hydroxyl group created in the reaction. (The α- and β-face selections correspond to the β- and α-absolute configurations of the C-3 hydroxyl group of the product, respectively.) Since the β-absolute configuration of the C-4 methyl group in **9** is "handed over" from the aldehyde, the 3,4-stereochemistry of **9** is *syn* in this case. Therefore, the stereochemical problem in the aldol reaction consists of two parts: how to control the 2,3- and 3,4-stereochemistry.

2.3. **2,3-Stereochemistry.**[11] One simplistic conformational analysis of the transition state **8** (coupled with some serendipity) has led to an expeditious solution of this problem. The relatively short O—B and C—B bondlengths as well as the strong affinity of boron toward an oxygen lone pair would "tighten" the transition state; at the same time a bulky ligand attached to the boron atom would exert a steric demand in the lower space of the chair ring. These factors would thus force the orientation of the aldehyde in the manner shown in **8**. This prediction has indeed been realized and, in a way, validates the Zimmerman-Traxler model, particularly in the case of the boron-mediated aldol condensation.[12]

The experimental results are briefly summarized in eqs. 8 and 9.[11] Treatment of *S*-phenyl propionate (**10a**) and ethyl cyclohexyl ketone (**10b**) with **9-borabicyclo-[3.3.1]nonyl** trifluoromethanesulfonate (triflate) (**11**) effects the stereoselective formation of the corresponding *Z*(O) boron enolates **10a′** and **10b′**, respectively, which react with many aldehydes of various structural types to provide the racemic 2,3-*syn*-3-hydroxy-2-methylcarbonyl compounds **12a** and **12b** with a stereoselection of at least 30:1. On the other hand, **dicyclopentylborinyl** triflate (**13**) converts ***S*-tert-butyl** propionate (**10c**) to its *E*(O) enolate **10c′**, which is capable of producing 2,3-*anti* aldol products (**14**), again with excellent stereoselection (>20:1). The majority of the above results have been confirmed independently by Evans and coworkers.[13] Although a number of methods for the stereoselective synthesis of **racemic** 2,3-*syn*- and *anti*-3-hydroxy-2-methylcarbonyl compounds are now available, the boron-enolate aldol reaction remains the method of choice in terms of overall selectivity, yield, and operational simplicity.



Scheme 1

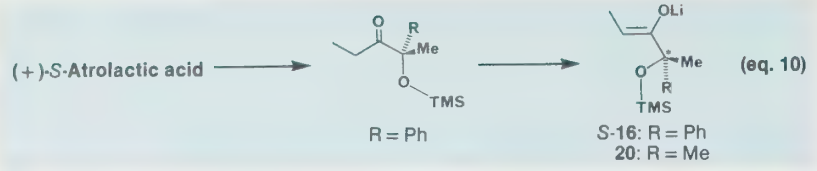


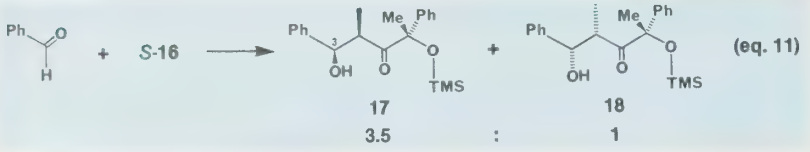
Diastereofacial Selectivity
(1) The chirality of an aldehyde
(2) The chirality of an enolate

2.4. **3,4-Stereochemistry.** While the 2,3-problem quickly came to a successful end, the 3,4-problem consumed a great deal of our effort. The issue in question was this: how to force the enolate into either the α (see **8**) or the β (see **15**) side of an aldehyde.

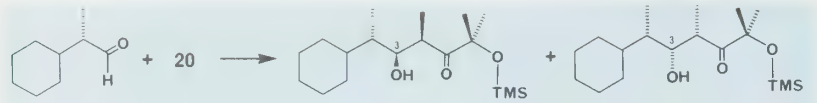
The aldehyde (with a trigonal carbon) has two faces: re and si (α and β, respectively) as shown in Scheme 1. These faces (or environments) are equivalent when the aldehyde is achiral, *i.e.*, R′ = H or Me. In the case of R′ ≠ H or Me, these faces are diastereotopic.[14] Thus, when an **achiral** reagent (a nucleophile in the aldol reaction) approaches the aldehyde, the reagent, in principle, exhibits a varying degree of preference for one face over the other. The degree of this preference normally shown in the product ratio is defined as **diastereofacial selectivity**.[15] The same argument also applies to the reagent. Thus, an **achiral** aldehyde approaching a **chiral** enolate "senses" the difference between the two faces of the enolate, and the latter becomes diastereoface-selective. Furthermore, the chirality of the ligands (L) attached to the metal (M) will also contribute to choosing between **8** and **15**. Although in actual synthesis the aldehyde is normally preselected, the enolate, metal, and its ligands can be varied, providing a means of controlling the 3,4-stereochemistry. Diastereofacial selectivity of the aldehyde has been extensively investigated both experimentally[2,16] and theoretically[17] and is often referred to as the Cram/anti-Cram selectivity.

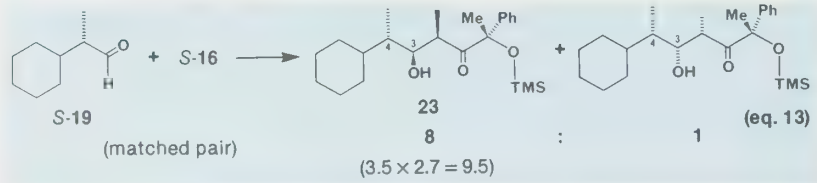
The concept of diastereofacial selection is not new.[14] However, our appreciation of the concept, which was clearly recognized in the process of solving the entire 2-, 3-, and 4-stereochemical problem, justifies a somewhat elaborate illustration.[7a] The chiral lithium enolate ***S*-16** has been readily prepared from (+)-*S*-atrolactic acid (eq. 10). The reaction of benzaldehyde with ***S*-16** leads to the formation of two aldol products, **17** and **18**, in a 3.5:1 ratio (eq. 11) which can be equated to the diastereofacial selectivity of ***S*-16**. As indicated by the β absolute configuration of the C-3 hydroxyl

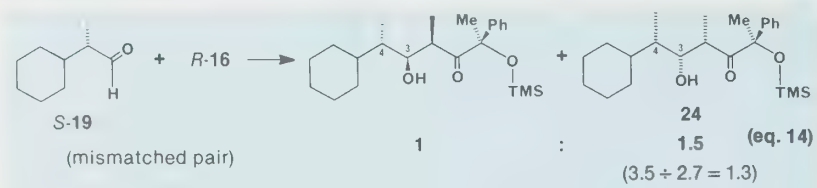


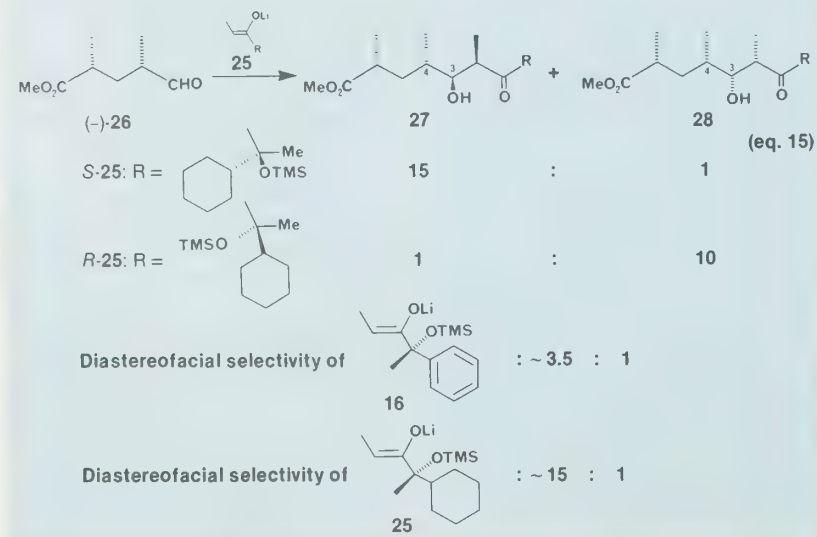


group of the major product **17** (section 2.2), the transition state of type **8** is more stable than that of type **15**, and thus *S*-**16** enolate exhibits a slight preference for the α-face of the aldehyde in the reaction. The diastereofacial selectivity of an aldehyde has also been evaluated. Thus, *S*-2-cyclohexylpropionaldehyde (*S*-**19**) provides, upon treatment with achiral lithium enolate **20** (R = Me), a 2.7:1 ratio of aldol products **21** and **22** (eq. 12), favoring its α-diastereoface for the approach of the external nucleophile **20**.[18a] Then, upon combination of *S*-**19** and *S*-**16** (a matched pair), both the aldehyde and enolate favor the α-face of the aldehyde in the reaction which would result in the enhancement of the 3,4-stereoselection (eq. 13). On the other hand, the reaction of *S*-**19** with *R*-**16** (a mismatched pair) would lead to inferior stereoselection (eq. 14). These predictions are confirmed by the results shown (8:1 in favor of **23** for the matched pair, and 1.5:1 in favor of **24** for the mismatched counterparts).[7a,19] Note that the absolute configuration of the hydroxyl groups in **23** and **24** are β and α, respectively.









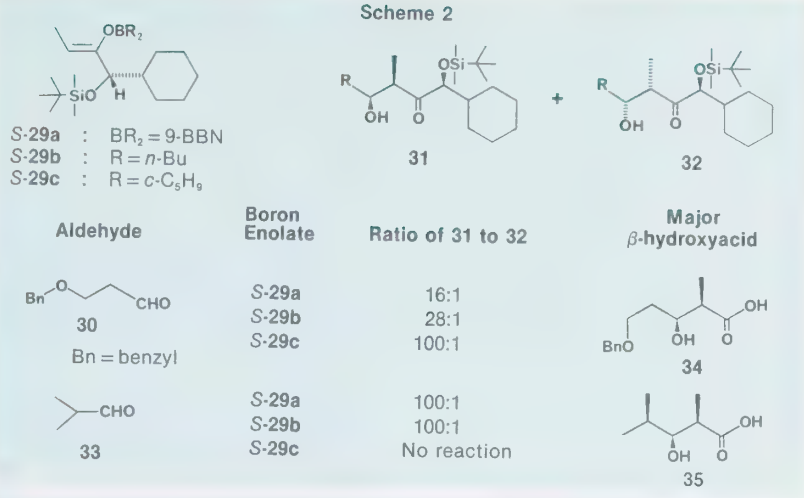
A judicious choice of a pair, reagent and substrate, may succeed in achieving the highly selective construction of 3,4-stereochemistry of *one kind* (*e.g.*, 3,4-*anti* as in **23**). Unfortunately, this methodology is bound to fail in preparing the other 3,4-stereoisomer (*e.g.* , **24**) in an equally selective manner. Therefore, stereochemical **control** has not been achieved. However, there emerges an important corollary: if one can prepare a chiral enolate reagent which possesses sufficiently high diastereofacial selectivity (*i.e.*, > 100:1), the normally small (Cram/anti-Cram) selectivity of aldehydes (ranging 1:1 to 4:1)[11] can be easily outweighed to the extent that either the 3,4-*syn* or the 3,4-*anti* isomer can be prepared as the (nearly) exclusive product. The first step we took toward this aim was the use of reagent **25** (eq. 15), the hexahydro derivative of **16**, which was found to have a diastereofacial selectivity of approximately 15:1.

The reaction of semi-aldehyde (−)-**26** with the chiral lithium enolate reagent *S*-**25** provides a 15:1 ratio of **27** (3,4-*anti*) and **28** (3,4-*syn*). Use of the *R*-reagent reverses the ratio to 1:10.[7a] This was the **first important demonstration of 3,4-control** in aldol chemistry, although admittedly, the ratios are marginally acceptable and the diastereofacial selectivity of **26** is only in the neighborhood of 3:2.

2.4.1. **Chiral *Z*(O) Boron Enolate Reagent (2,3-*syn*-Selective).**[20] An immediate goal was clear at this stage: we must prepare a chiral enolate reagent with a diastereofacial selectivity of 100:1 or greater. Eliminating the details of the long road leading to this goal as well as abbreviating a mechanistic rationale for its high selectivity, we show in Scheme 2 the structure of the reagent(s) which are now used routinely for the synthesis of complex molecules (see Section 3). The *S*(or *R*)-boron enolates [*S*(*R*)-**29a,b,c**] are prepared from optically active mandelic acids through routine operations (see Experimental Part). The reactivity and selectivity of **29** in the aldol reaction can be adjusted with the selection of a proper boron substituent as shown (a-c). For instance, aldehyde **30**, a primary aldehyde chosen from many examples tested, undergoes aldol reaction with *S*-**29c**, the most stereoselective (but least reactive) to

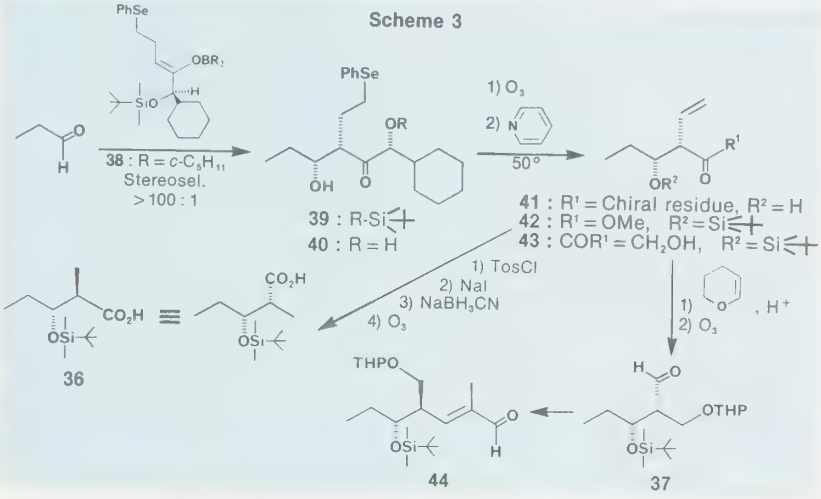
provide a 100:1 mixture of two diastereoisomers **31** and **32** (R = $PhCH_2O-CH_2-CH_2$-). In the case of **33**, an α-branched aldehyde, the stereoselectivity of the reaction is very high [>100:1 of **31** to **32** (R = Me_2CH-)] even with the least selective (but most reactive) *S*-**29a**.[21] Successive treatments of a mixture of **31** and **32** with hydrogen fluoride (or fluoride anion) followed by sodium metaperiodate provide the corresponding 2,3-*syn*-3-hydroxy-2-methylcarboxylic acid (**34** or **35**) with an enantiomeric excess higher than 98%! These results meet the standards set for the project. The capability of these reagents to control the 3,4-stereochemistry in the reaction with chiral aldehydes will be examined in the total syntheses that are described in Section 3.

Scheme 2



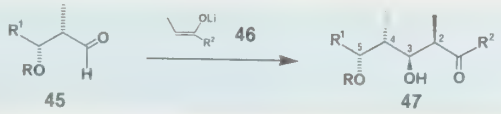
2.4.2. **Enantioselective Synthesis of the 2,3-*anti*-3-Hydroxy-2-methylcarbonyl Compounds *via* an Indirect Route.**[7b] Since the aldol reaction with the *Z*(O) boron enolate **29a-c** provides a means of synthesizing 2,3-*syn* compounds enantioselectively, this general approach should be extended to the use of chiral *E*(O) enolates. From the above discussions, these *E*(O) enolates are expected to give rise to optically active 2,3-*anti* isomers (*e.g.*, **36**). Unfortunately, many attempts made thus far by us and others at devising such *E*(O) reagents (with diastereofacial selection comparable to that of **29a-c**) have met with only partial success.[22] Enolate precursors (Et-COR) which have a bulky chiral auxiliary (R) are prone to form the corresponding *Z*(O) enolate even with reagents normally used to generate *E*(O)-isomers (Section 2.3). This tendency is mainly responsible for the lack of a highly diastereofaceselective *E*(O) reagent at present. An indirect and somewhat circuitous solution which we have found for this 2,3-*anti* problem is outlined below. This tentative solution also happens to provide a route to the systems having two hydroxyl groups at the β and β′ positions to a carbonyl group (*e.g.*, **37**), another structural unit commonly found in natural products (Sections 3.3 and 5), but difficult to construct otherwise.

Scheme 3



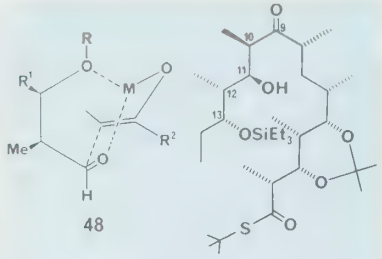
Syntheses of the optically pure 2,3-*anti*-3-*tert*-butyldimethylsilyloxy-2-methylpentanoic acid (**36**, Scheme 3) and the corresponding 2-hydroxymethyl aldehyde **37** illustrate the case. The reaction of propionaldehyde with the new chiral selenium-containing reagent **38**, modified slightly in structure from **29c**, proceeds in the expected manner (diastereoselection >100:1) to provide **39** which, after removal of the silyloxy protecting group (see **40**), is subjected to standard conditions for the elimination of the PhSeOH group (O_3 and then warming at 50° with pyridine). Successive treatments of the resulting vinyl compound **41** with sodium metaperiodate, diazomethane, and *tert*-butyldimethylsilyl triflate provide a key intermediate (**42**), which possesses two different functional groups, an olefin and an ester. Both groups can be readily modified to reach **36** and **37**. First, diisobutylaluminum hydride (DIBAL-H) reduction converts **42** into **43**. Transformations of **43** into **36** and **37** are straightforward (see Scheme 3). Compound **37** has been used to prepare the right-hand portion (**44**) of tylonolide (Section 3.3) through a Wittig reaction with ethoxycarbonylethylidenetriphenylphosphorane, DIBAL-H reduction, and Collins oxidation. Another application of this methodology appears in Section 5. It is apparent that the right-hand end of the main chain and the 2-substituent of the key intermediate **42** are interchanged in **36** and **37** in order to construct the 2,3-*anti* stereochemistry. Thus, overall, a chiral *Z*(O) enolate provides a highly selective synthesis of an optically active 2,3-*anti* aldol product as well.

2.4.3. **Coordination of the Lithium Cation with an Alkoxy Substituent: Construction of the 2,3-*syn*-3,4-*anti*-4,5-*syn*-3,5-Dihydroxy-2,4-dimethylcarbonyl System.**[23] Lithium and magnesium enolates used in aldol reactions, in contrast to boron enolates, exhibit distinct propensity for coordination with oxygenated functional groups present in either the enolate itself or the reacting aldehyde. The stereochemical consequence resulting from this coordination has been delineated by Cram's cyclic (coordination) model,[24] as illustrated by the reaction of a 2,3-*syn*-3-alkoxy-2-methylcarboxaldehyde (**45**) with a lithium *Z*(O) enolate (**46**, eq. 16).



(eq. 16)

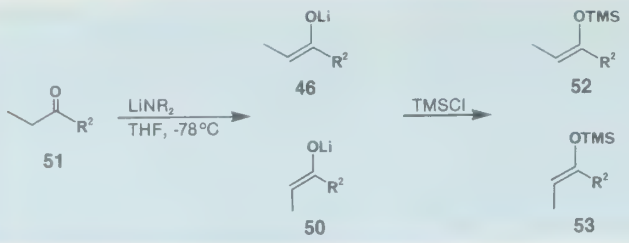
In a Cram-type transition state (**48**) the lithium cation is coordinated with three oxygen atoms including one of the 3-alkoxy group. The enolate **46** is assumed to approach the aldehyde **45** from the α (re) face of **45** in order to minimize the interaction between **46** (carrying the substituent R^2) and the two substituents at the 3- and 2-positions of **45**. Transition state **48** should



48

49

lead to the formation of the 2,3-*syn*-3,4-*anti*-4,5-*syn*-3,5-dihydroxy-2,4-dimethylcarbonyl derivative **47**, a structural feature in several natural products such as C-9—C-13 fragment (**49**) of 6-deoxyerythronolide B. Obviously, the difference between the two transition states [emerging from the re (shown in **48**) and si (not shown) approaches] is likely to depend in part on the size of both R^1 in **45** and R^2 in **46**. Also prerequisite for the construction of the stereochemistry embedded in **47** is the exclusive generation of the lithium *Z*(O)-enolate **46** from the corresponding ethyl ketone, a task that has demanded an extensive survey of lithium bases. [Compare with the generation of *Z*(O) boron enolate which is under nearly perfect control (Section 2.3).] In general the *Z*:*E* ratio of the two geometrically differing enolates **46** and **50** (eq. 17) derived from an ethyl ketone **51** with a lithium amide depends largely on the size of the R^2 group in **51** as well as the basicity and steric bulk of the base used. Thus, while treatment of a 2,2-dimethylpentan-3-one (**51** with a bulky R^2) with lithium diisopropylamide provides its *Z*-enolate (**46**:$R^2 = t$-Bu) quantitatively, the **direct**, exclusive generation of the *Z*-lithium enolate from a ketone with a less bulky R^2 such as ethyl had not been realized prior to our investigation. Table 1 summarizes some selected results. Pentan-3-one (**51a**) and ethyl cyclohexyl ketone (**51b**), chosen as representative ethyl ketones having a small and a medium R^2 group, respectively, provide varying *Z*:*E* ratios (**46** versus **50**), as analyzed by the corresponding trimethylsilyl ethers (**52** and **53**) obtained from their lithium enolates. Clearly, in both cases, the ratio is significantly enhanced as the size of the substituents of the disilazide increases; in particular, the use of lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide (**54**) leads



51 46 50 52 53 (eq. 17)

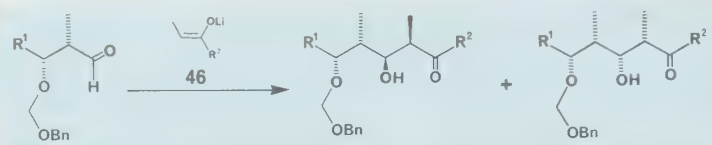
Table 1

The *Z*:*E* Ratio of the Enolates derived from Ethyl Ketones.

R^2 in 51	Base	Z:E Ratio
Et (**51a**)	*i*-Pr_2NLi	30:70
Et (**51a**)	$(Me_3Si)_2NLi$	70:30
Et (**51a**)	$(Me_2PhSi)_2NLi$ (**54**)	>100:1
Et (**51a**)	$(Et_3Si)_2NLi$	99:1
Cyclohexyl (**51b**)	*i*-Pr_2NLi	61:39
Cyclohexyl (**51b**)	$(Me_3Si)_2NLi$	85:15
Cyclohexyl (**51b**)	$(Me_2PhSi)_2NLi$ (**54**)	99:1
Cyclohexyl (**51b**)	$(Et_3Si)_2NLi$	94:6

to the exclusive formation of *Z*-enolates. This finding is general for a variety of simple ketones and obviously has great synthetic utility.

With the geometrically pure *Z*-enolates now readily available from ethyl ketones **51a** and **51b**, the factors that influence the stereoselectivity in the construction of the 2,3-*syn*-3,4-*anti*-4,5-*syn*-3,5-dihydroxy-2,4-dimethylcarbonyl system (see **55** or **47**) may be defined. The aldol reaction of **45a** with **46** (eq. 18) proceeds efficiently at -78 °C to provide two major products **55** and **56** (see Table 2), in addition to minor amounts of the 2,3-*anti*-stereoisomers corresponding to **55** and **56**. (Amounts of these 2,3-*anti*-3,4-*syn*-isomers are significantly smaller than those observed in the aldol reaction with an aldehyde carrying no β-alkoxyl substituent.) This is consistent with the view that the reaction of **45a** proceeds through the transition state **48**. The β-alkoxyl substituent organizes, in **48**, a rigid framework with the lithium cation which steers the reaction to create the 2,3-*syn* stereochemistry. The interaction between the enolate with R^2 and the two groups of the aldehyde, methyl and in particular R^1, are indeed important, as anticipated. With a small interaction (entries 1-3, Table 2) the ratio ranges between 3.5:1 to 5:1 and increases to approximately 10:1 when R^1 is primary or secondary alkyl and R^2 is secondary alkyl (entries 4, 6, 8). Most significantly, when R^1 carries an additional ethereal substituent, and thus creating yet



45a 55 56 (eq. 18)

Table 2

Entry	R^1 in 45a	R^2 in 46	Ratio of 55 : 56	Combined Yield (%) of 55 and 56
1	H	Et	4:1	87
2	H	Cyclohexyl	3.6:1	79
3	Et	Et	5:1	81
4	Et	Cyclohexyl	9:1	79
5	$PhCD_2$-	Et	5.5:1	71
6	$PhCD_2$-	Cyclohexyl	9:1	70
7	*i*-Pr	Et	6.9:1	75
8	*i*-Pr	Cyclohexyl	11.5:1	68
9	*t*-$BuMe_2SiOCH_2CH_2$-	Et	13:1	82
10	*t*-$BuMe_2SiOCH_2CH_2$-	Cyclohexyl	19:1	79

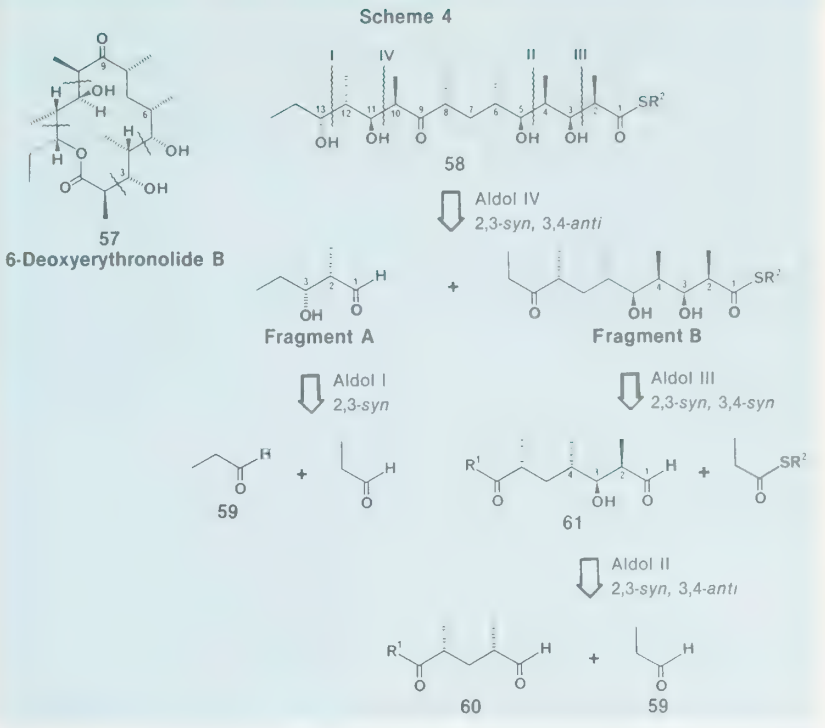
another ligand to coordinate the lithium cation, the observed selectivities (entries 9, 10) now exceed 10:1.

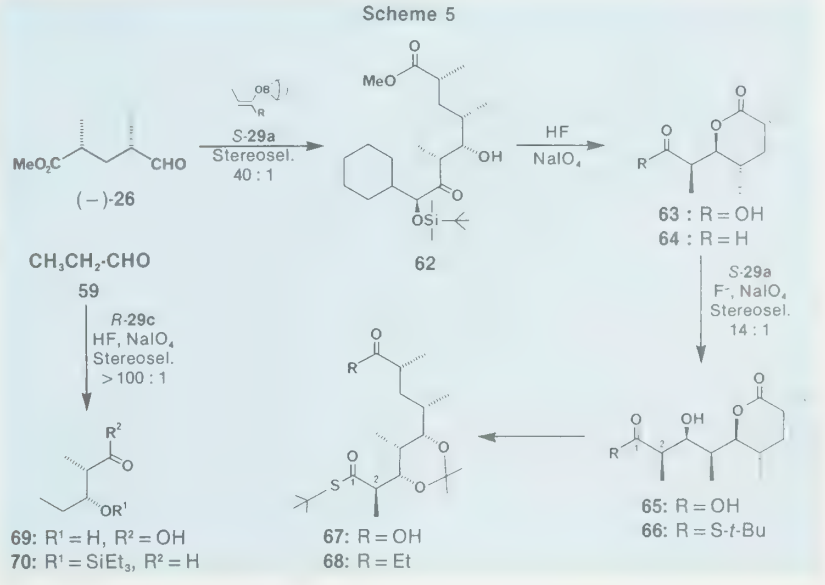
3. Macrolide Synthesis *via* Aldol-Type Reactions

Stereocontrol described in the preceding sections is sufficient for most of the crucial synthetic transformations in the total syntheses of the selected macrolides: 6-deoxyerythronolide B, rifamycin S, and tylonolide. All the synthetic designs follow the simple and now established "seco-acid aldol approach" (in which a seco-acid is, in a final stage, lactonized to the corresponding macrolide).[3] The central issue is the creation of the chiral centers embedded in the carbon skeleton, and this challenge has been resolved by means of the aldol methodology with remarkable overall efficiency in terms of both yield and stereoselection.

3.1. **6-Deoxyerythronolide B.**[25] This metabolite **57** is biosynthesized exclusively from propionates (one propionyl CoA and six methylmalonyl CoA's) and leads to all the erythromycins presently known. Once the seco-acid aldol approach is adopted, designing a synthetic scheme is straightforward. Splitting the seco-acid derivative (**58**), drawn in a zigzag fashion, into fragments A and B immediately suggests the order of the aldol reactions to be utilized in the synthesis (Scheme 4). Aldol I (involving propanal **59** and its equivalent) produces fragment A, while aldols II (**59** and **60**) and III (**61** and an equivalent of **59**) complete a synthesis of fragment B. Finally, both fragments are combined *via* aldol IV. Note that aldols I, II, and III all concern the creation of 2,3-*syn* stereochemistry, the task that can be readily achieved with the chiral boron enolates **29a,b,c** described earlier (Section 2.4.1).

3.1.1. **Seco-Acid.** The reaction of (−)-aldehyde **26** with the *S*-chiral reagent **29a** (Scheme 5) proceeds smoothly (stereoselection 40:1) to provide an aldol product **62**[18] which, after removal of the chiral auxiliary (HF and then $NaIO_4$), is converted quantitatively into the Prelog-Djerassi lactonic acid **63**. A key intermediate in the syntheses of several natural products such as methymycin[26] and narbonolide,[27] **63** is readily available in multigram quantities and in optically pure form (>98% e.e.). Addition of the C-1, C-2 fragment to **63** again uses the *S*-chiral reagent **29a**. Aldol reaction of the aldehyde **64** derived from **63** provides (with 14:1 stereoselection) the major product which, upon standard treatment (*e.g.*, **62** to **63**), is transformed to the carboxylic acid **65** and then to its thiol ester **66**. After modification of the functional groups of **66** through a series of routine reactions, the resulting carboxylic acid **67** is further converted to the corresponding ethyl ketone **68**, which is an equivalent of fragment B.





The enantioselective synthesis (selectivity >100:1) of the hydroxy acid **69** corresponding to fragment A (Scheme 5) is readily achieved using propionaldehyde (**59**) and the *R*-chiral reagent **29c**. A sequence of standard operations converts **69** into aldehyde **70** which is ready for coupling with **68**.

The final aldol coupling of **70** and **68** (eq. 19) is different from those described above in that both the aldehyde and enolate (ethyl ketone) are set and a diastereofacial-selective reagent (such as **29**) cannot be used to advantage. What is displayed in this final carbon-carbon bond formation is the strong coordinating power of the lithium cation with the ethereal oxygen atom attached to the β-carbon of aldehyde **70**, as already outlined in Section 2.4.3. Treatment of **68** with lithium hexamethyldisilazide* at -78 °C followed by addition of **70**

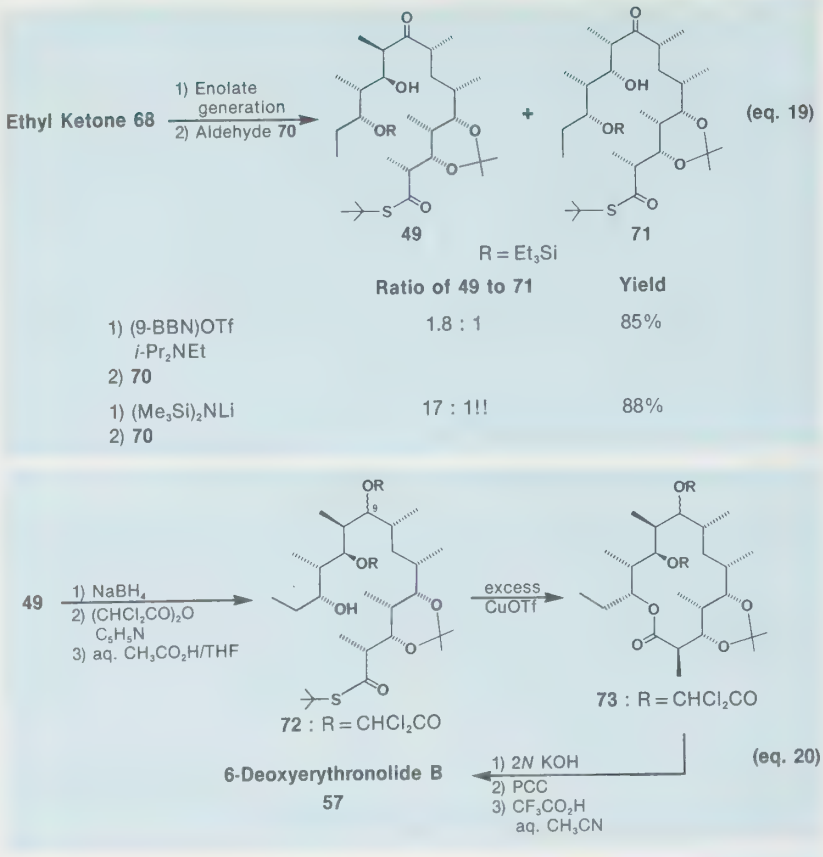
*The use of **54** is unnecessary to achieve the exclusive formation of the *Z*-enolate in this case because the effective bulk of the C-8—C-1 fragment of this ethyl ketone **68** is considerably larger than that of **51a** or **51b**.

gives rise to the desired **49** and its diastereoisomer **71** at a diastereoselection of 17:1, a highly gratifying result in view of the low selectivity (1.8:1) observed in the boron-mediated aldol reaction. The synthesis of the seco-acid **49** containing 10 chiral centers thus proceeds in 11% overall yield based on (–)-aldehyde **26** and propanal **59** used and an overall stereoselection of 85% for the four aldol reactions.

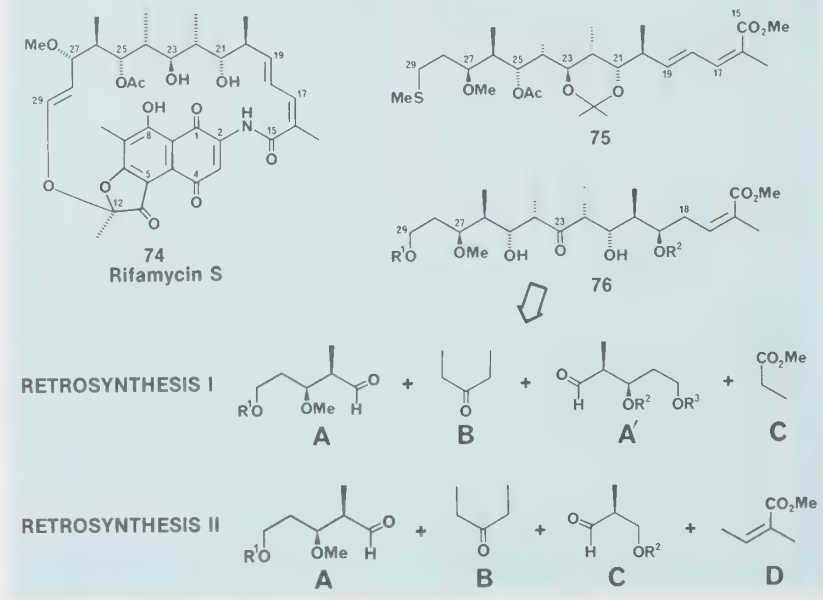
3.1.2. **Lactonization.** The conclusion of the 6-deoxyerythronolide B synthesis is briefly summarized below, as this is not the main subject of this article. A sequence of reactions (eq. 20), (1) reduction of **49** with $NaBH_4$, (2) bisdichloroacetylation of the resulting dihydroxyl compounds, and (3) desilylation, provides epimeric (9α and 9β) 13-hydroxy thiol ester **72** which is lactonized with excess copper(I) trifluoromethanesulfonate[25] in benzene containing 2 equiv. of diisopropylethylamine. After the successful execution of this crucial lactonization step, the subsequent transformation of **73** proceeds in a straightforward manner. Removal of the dichloroacetate protecting group, followed by selective oxidation of the C-9 hydroxyl group and finally hydrolysis of the acetonide group with mild acid completes the synthesis of the target molecule **57**.

3.2. **The Ansa Chain of Rifamycin S.**[28] Rifamycin S (**74**) is a well known antibiotic belonging to the ansamycin family (see Scheme 6).[28] The structure of this compound is uniquely characterized by the naphthoquinone moiety bridged at the 2 and 12 positions by the "ansa" chain (**75**). The symmetry element which is present in **75** becomes all the more evident with two retrosynthetic operations: (1) oxidation of the C-23 hydroxyl group to the ketone, and (2) hydration of the double bond as indicated in **76**. The C-18—C-28 fragment incorporating all the chiral centers in **76** now has C_s symmetry (if R^2 = Me). Dissection of **76** leads to a set of four units, A, B, A′, C (retrosynthesis I) or another set, A, B, C, D (retrosynthesis II), the former (I) being more symmetrical than the latter. Note that (1) units A and A′ are enantiomeric and are readily available in >98% optical purity (see Section 2.4.1) and that (2) each half (C-18—C-23 and C-23—C-28) of **76** constitutes a 2,3-*syn*-3,4-*anti*-4,5-*syn*-2,4-dihydroxy-3,5-dimethylcarbonyl system (numbering starts with the carbonyl group), whose stereoselective construction can be achieved by a single aldol reaction (see Section 2.4.3). The aldol approach to the synthesis of **75** is, thus, extremely attractive. The synthesis described below is based on retrosynthesis II rather than I, as II offers the advantage of confirming the stereochemistry of a synthetic intermediate halfway in the entire sequence. Even with this less symmetrical design, the 18-step synthesis proceeds in 30% overall yield and with 80% overall stereoselectivity.[29]

3.2.1. **The C-19—C-29 Fragment.** The synthesis (Scheme 7) starts with (–)-3-hydroxy-2-methylcarboxylic acid (**34**) which is readily prepared enantioselectively (99% e.e.) from **30** (see Section 2.4.1). A sequence of standard reactions converts **34** into **77** which is ready for the aldol reaction with the *Z*-enolate generated from pentan-3-one with lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide (Section 2.4.3). The reaction proceeds smoothly to provide the



Scheme 6

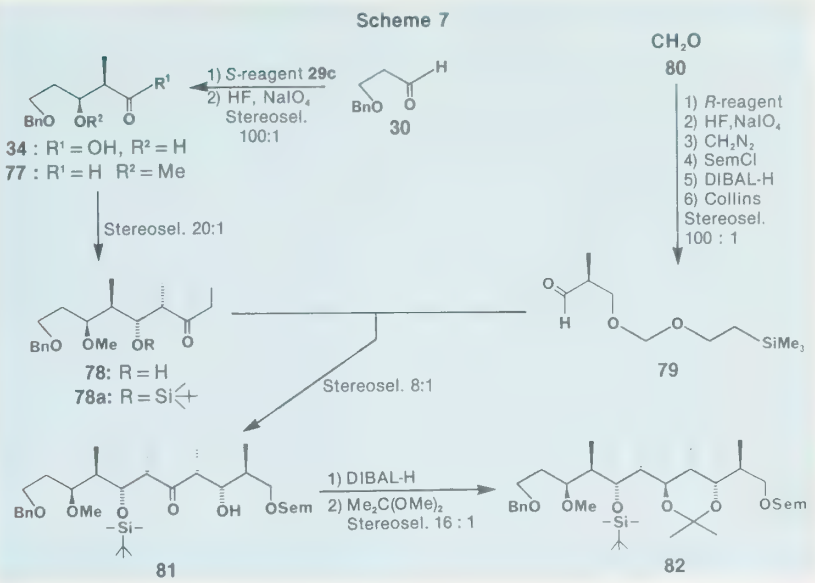


ethyl ketone **78** in >95% yield and with 20:1 stereoselection. The C-25 hydroxyl group of **78** is then protected with a *bulky* group (*t*-BuMe$_2$Si). The silylated ketone (**78a**) is converted to the corresponding lithium *Z*-enolate for the final aldol reaction with aldehyde **79**, prepared from formaldehyde (**80**)[30a] or, directly, from enzymatically derived *S*-3-hydroxyisobutyric acid.[30b] With the bulky substituent at the C-25 position of the enolate (derived from **78a**), the **intramolecular** coordination of the lithium cation is suppressed and the intermolecular coordination with the ethereal oxygen of **79** is maximized.[31] Yet, as expected from the structure of **79**, having the primary Sem-O substituent (Section 2.4.3), the diastereoselectivity of this aldol reaction is only modest (3:1) and is enhanced to 8:1 only with the addition of bis(cyclopentadienyl)-zirconium dichloride to the lithium enolate[32] prior to the reaction with **79**. This ratio is expected to be further enhanced if the synthesis is based on the symmetrical retrosynthesis I (see Section 2.4.3).

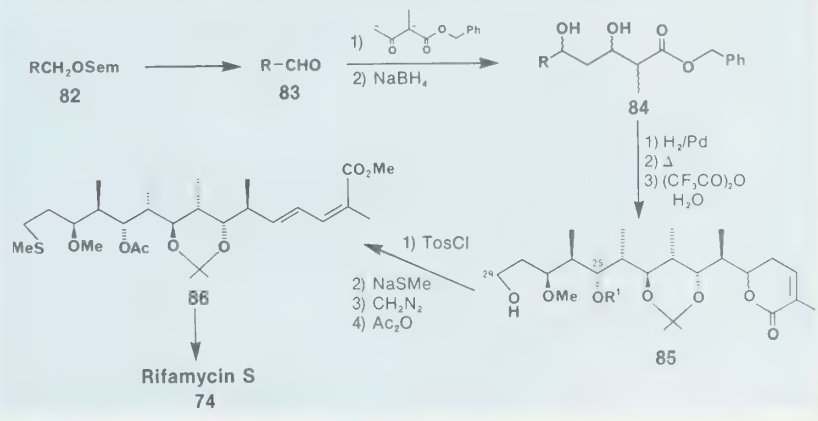
The reduction of **81** with DIBAL-H proceeds with a stereoselection of 16:1 as expected, and the resulting diol is converted to its acetonide **82**, which is correlated with a degradation product of the antibiotic **74** to confirm its stereochemistry. Thus, **the seven-step sequence** converts **34** into **82** which incorporates all the 8 chiral centers present in the ansa chain.

3.2.2. **Ansa Chain.** The addition of a five-carbon (C-15—C-18) unit to the C-19—C-29 fragment to construct a *Z*:*E*-dienoic acid system is patterned after the methodology originally developed for the synthesis of monomethyl *Z*,*E*-muconate by Linstead and coworkers.[33] Thus, aldehyde **83** (derived from **82**, Scheme 8) is treated with the lithium dianion of benzyl 2-methylacetoacetate to yield the expected β-keto ester which is reduced with NaBH$_4$ to yield the diol isomers **84**. The number of diastereoisomers (eight) is irrelevant, since all will be converted to a single final product. Hydrogenolysis followed by heating causes complete lactonization; treatment with trifluoroacetic anhydride and then water provides the α,β-unsaturated δ-lactones **85** (R^1 = CF$_3$CO). The C-29 primary hydroxyl group of **85** is then tosylated. The ensuing step is efficient; reaction of the tosylate of **85** with excess sodium methanethiolate effects three transformations: (1) substitution of the tosyl group, (2) liberation of the C-25 hydroxyl group, and (3) the desired lactone ring opening to yield the *Z*,*E*-dienoic acid (80%) without double-bond isomerization. Esterification and acetylation completes the synthesis of **86**, which was earlier converted to rifamycin S.[29]

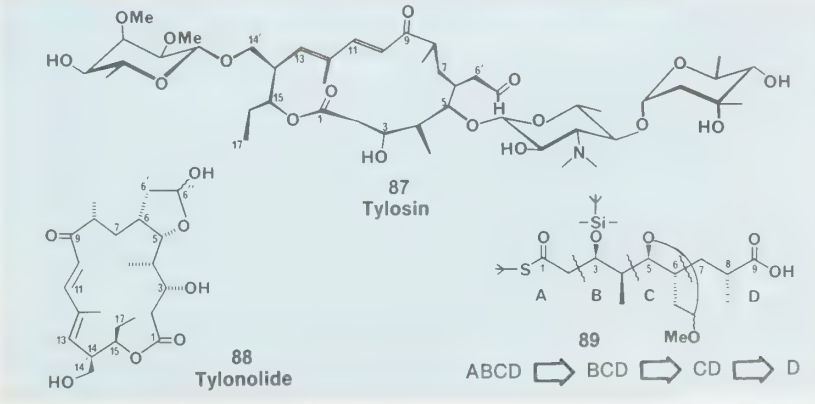
Scheme 7



Scheme 8



3.3. **Tylonolide, the Aglycone of Tylosin.**[15] The antibiotic tylosin (**87**) represents the well known family of 16-membered polyoxomacrolide antibiotics.[15] The structure of its aglycone, tylonolide (**88**), reveals the unique C-13—C-15 unit with an *anti*-14-hydroxymethyl-15-acyloxy stereochemistry, a structural and stereochemical feature absent in 6-deoxyerythronolide B (**57**) and rifamycin S (**74**). With the methodology developed for the construction of this unit (Section 2.4.2), the seco-acid aldol approach to the synthesis of **88** is now feasible. A retrosynthetic analysis of **88** which is similar to that applied to **57** dissects the 16-membered ring into three fragments: the left-hand (C-11—C-17, **44**), C-10, and the right-hand (C-1—C-9, **89**). The last



fragment is further split into four subunits in the manner, ABCD→BCD→CD→D.[34] The synthesis of **89** features the asymmetric aldol reaction and asymmetric hydroboration. In addition there emerges a new problem of constructing the 3-hydroxycarbonyl (*CHOH-CH_2-CO-) system (in contrast with 3-hydroxy-2-methyl system discussed repeatedly above).

3.3.1. **Preparation of Subunit BCD (C-3—C-9) in 89.** Reaction of the lithium dianion derived from 4-benzyloxybutyric acid (**90**) with methallyl chloride (Scheme 9) provides the racemic monoalkylated carboxylic acid **91**, which is converted into the corresponding aldehyde **93** through the hydroxyl compound **92**. The *S*-enantiomer of **93**, which is of no avail in the synthesis, is most conveniently removed in the subsequent step.

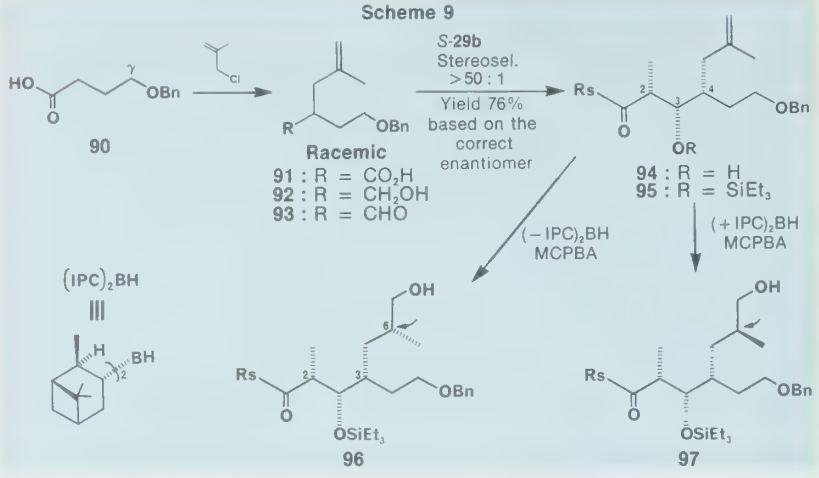
The construction of three chiral centers (C-2, C-3, and C-6 in **96** corresponding to C-4, C-5, and C-8 in **88** or **89**) is achieved with an excellent overall stereoselection of >25:1. Thus, aldol reaction of **93** with 1.7 equiv. of the *S*-boron enolate reagent (**29b**) proceeds with the dominating diastereofacial selectivity inherent in the reagent, converting the *R*-enantiomer of **93** exclusively to **94** and the *S*-enantiomer of **93** (see above) to the C-4 epimer of **94**. The two diastereomeric products are separated (Section 1). Hydroboration of **95**, the triethylsilylated derivative of **94**, with (−)- and (+)-bis(isopinocampheyl)borane [$(IPC)_2$-BH] results in the exclusive formation of **96** and **97**, respectively. This remarkably high stereoselectivity (>50:1) is normally not expected for the reaction of the methallyl system with these reagents.[35] Compound **95** behaves in a unique manner and, apparently, the chirality existing in **95** hardly influences the overall steric course of the reaction.

3.3.2. **Preparation of the Right-Hand Fragment 86: Problems Concerning the Acetate Addition.** The dihydroxyl compound **98** (Scheme 10) that results from selective deprotection of the C-3 hydroxyl group of **96** is oxidized with Fetizon's reagent to provide directly the lactone **99**, which, after desilylation, borane-ammonia reduction, and sodium metaperiodate oxidation, is converted to aldehyde **100**. Thus, we arrive at the last stage of the sequence leading to **89**, which involves a stereoselective addition of an acetate unit to aldehyde **100**. This two-carbon extension is indeed a fundamental process in the synthesis of acetate-derived natural products for which a general method has been sought.

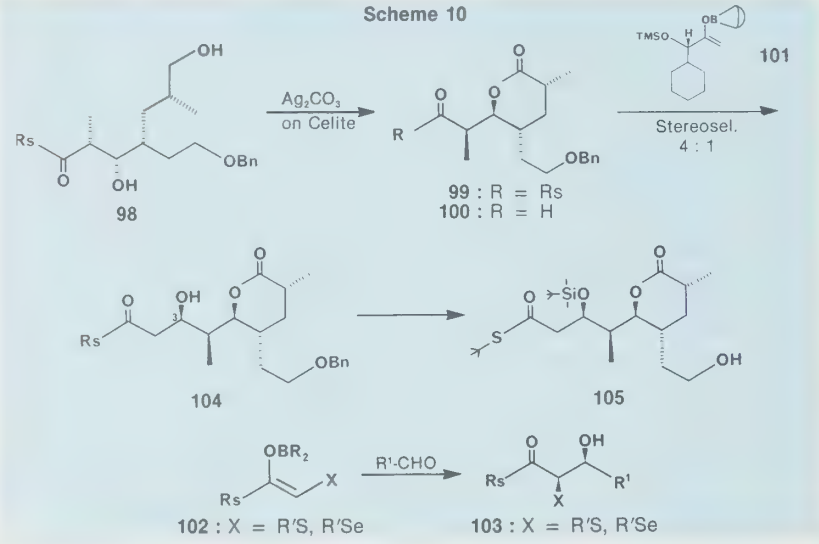
Many examples have already been quoted above to demonstrate the large diastereofacial selectivity of boron enolates derived from the corresponding *ethyl* ketones, *e.g.*, **29a,b,c**. In contrast, an aldol reaction using an analogous enolate [*e.g.*, **101a** (TBDMS instead of TMS in **101**)] prepared from the *methyl* ketone and an achiral aldehyde proceeds virtually nonselectively. Although the sulfur reagent (**102** with X = SMe or SPh) similar to that described by Evans *et al.*[21] regenerates the high selectivity, experiments in our laboratories have shown that removal of the thiol group from aldol products (**103** with X = RS) involves rather serious problems [such as low yields (35-40%)]. Extensive investigation has been carried out to explore the reaction involving selenium reagents in combination with a variety of hindered bases (including 2,6-di-*tert*-butyl-4-methylpyridine) to generate the corresponding enolates (**102** with X = MeSe, *c*-C_6H_{11}Se, *i*-PrSe, PhSe) in high yield.[36] After the completion of an aldol reaction, the selenyl group is readily and quantitatively eliminated from **103** (X = R′Se) by washing with a K_2HPO_4-buffered solution containing benzenethiol.[37] The overall selectivity of the aldol reaction with primary aldehydes, followed by removal of the selenyl group, ranges between 20-50:1 with a 50-80% yield. However, the reaction with secondary aldehydes (which are model substrates pertinent to the present case) is extremely sluggish and results in an unacceptable yield of the product.[36]

After all this, we concluded that at the time, the aldol reaction of **100** with **101** served as the best available solution in terms of yield, stereoselectivity, and operational simplicity. Using the chiral boron enolate **101** in the standard boron-mediated aldol reaction with 9-BBN(OTf), **100** provides a 4:1 mixture of aldol products, **104** and its C-3 epimer, in 88% yield. While both **100** and **101** exhibit small but apparently "matched" diastereofacial selectivities, thus bringing about the above modest ratio, this selectivity certainly falls short of the standards originally set for the project.

Scheme 9



Scheme 10



Indeed, this result catalyzed our exploration of eq. 5 involving asymmetric epoxidation, mentioned at the beginning of this article and to be elaborated in Sections 4 and 5.

Compound **104** is converted to **105** *via* a sequence of six reactions: (1) removal of the chiral auxiliary, (2) catalytic hydrogenolysis, (3) silylation, (4) hydrolysis of the silyl ester, (5) conversion into the thiol ester, and finally, (6) selective hydrolysis of the primary silyl ether.

3.3.3. **Preparation of the Seco-acid Derivatives and Their Lactonization.** With all of the chiral centers embedded in tylonolide **88** having been constructed, the remaining tasks were to join the right- and left-hand fragments and then to lactonize the resulting seco-acid derivative whose functional groups were properly protected. These transformations have been achieved in a manner similar to that of the narbonolide synthesis.[27]

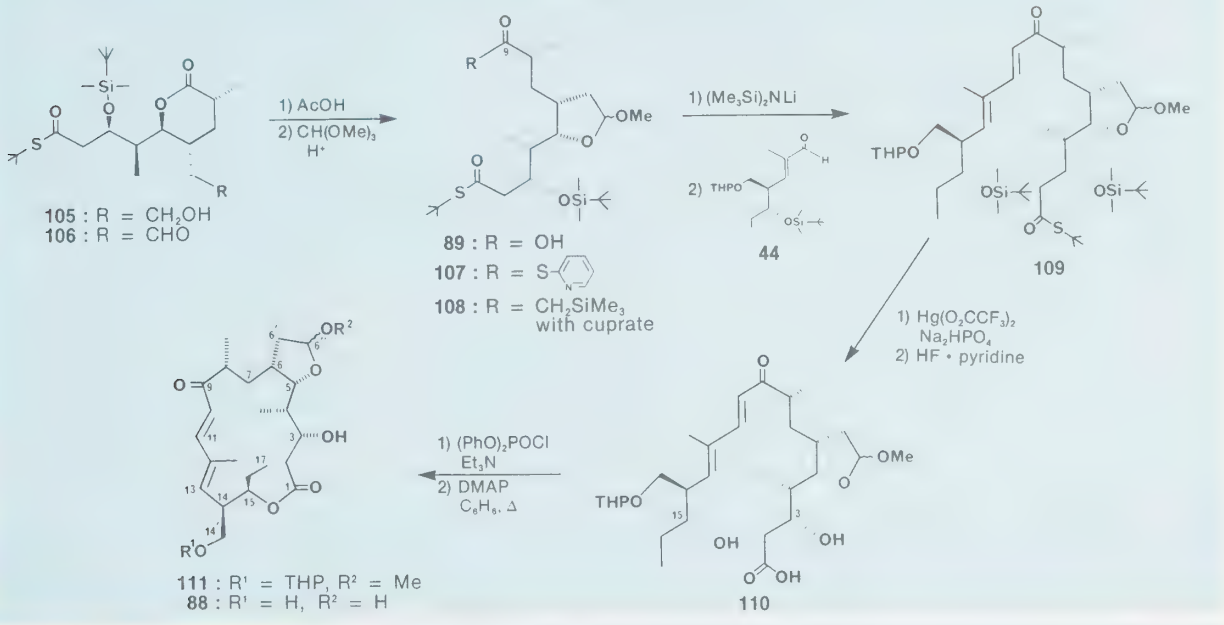
The aldehyde **106** derived from **105** (Scheme 11) undergoes an acid-catalyzed rearrangement of the δ-lactone into the γ-lactol, which is protected to give **89**. This C-9 carboxylic acid is converted through **107** to the corresponding trimethylsilylmethyl ketone (**108**), the lithium anion of which is condensed with the left-hand aldehyde **44** to complete the construction of the seco-acid skeleton (**109**). Partial deprotection of the functional groups attached to **109** leads to seco-acid **110**, which is then macrolactonized through a phosphate intermediate. Acid treatment of the resulting lactone **111** produces tylonolide **88**.

4. **Asymmetric Epoxidation — Ring Opening Sequences**[61,a]

As shown in the preceding sections, the excellent stereoselective addition of a propionate unit to an aldehyde (**A**) can be applied effectively in the preparation of any of the stereoisomerically possible 3-hydroxy-2-methylaldehydes (**B**, reaction 4, Scheme 12), whereas the aldol reaction for transforming **A** to **C**, formally an addition of an acetate unit, proceeds with only marginal stereoselection. For the latter transformation, a route involving epoxidation and reductive ring opening was considered highly promising. Thanks to Sharpless' discovery, the versatile epoxide functionality can be introduced into the allylic system of various structural types with his titanium reagent which possesses an impressively high diastereofacial selectivity (50-100:1).[38] It soon became apparent that this general route, with some modification, would bring about another important transformation, **A** to **D** (reaction sequence 5), thus creating two chiral hydroxymethylene (-*CHOH-) centers in one sequence.

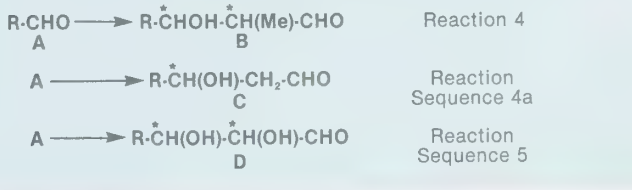
Reaction sequences 4a and 5 (Scheme 13)

Scheme 11

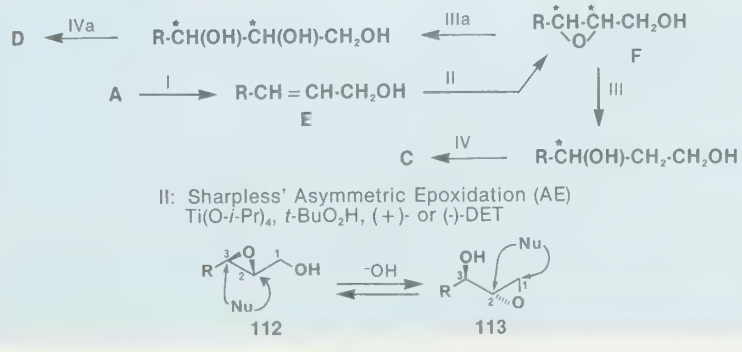


Scheme 12

Work in collaboration with Professor Sharpless' group.



Scheme 13



II: Sharpless' Asymmetric Epoxidation (AE)
Ti(O-*i*-Pr)$_4$, *t*-BuO$_2$H, (+)- or (-)-DET

are formulated as follows: The first step (I) consists of the construction of an *E*- or *Z*-allylic alcohol (**E** or its precursor) *via* a Wittig reaction. In the next step (II) the asymmetric epoxidation (AE) using titanium tetraisopropoxide and *tert*-butyl hydroperoxide with (−)- and (+)-diethyl tartrate (DET) or diisopropyl tartrate (DIPT) plays a key role. While these first two steps are obvious choices for the overall conversions of **A** to **C** and **A** to **D**, the subsequent steps, III and IV, and IIIa and IVa involve little known transformations of epoxy alcohols **F**; *e.g.*, **112** which are rearranged to the isomeric alcohols **113** with base (Payne rearrangement).[39] Thus, all of the C-1, C-2, and C-3 positions of **F** can be sites for nucleophilic attack.

The approach outlined above is best illustrated by the exploratory work which has been most effectively carried out through collaboration with Professor Sharpless' research group.

4.1. **Reaction Sequence 5.**[40] The scope and limitations of reaction sequence 5, **A** to **D**, (Scheme 12) can be evaluated through the synthesis of model compounds, tetritols and pentitols, which may lead to the establishment of a general, iterative approach to a wide variety of higher and more complicated saccharides and other polyhydroxylated natural products.

4.1.1. **Tetritols.**[40] Because of the ready availability of the monobenzyl ether **114** (Scheme 14), this series omits step I. The asymmetric epoxidation proceeds satisfactorily to yield **115**. The exposure of **115** to sodium benzenethiolate and sodium hydroxide in a protic solvent leads, through the Payne rearrangement of the epoxy alcohol moiety, to exclusive attack of benzenethiolate at the C-1 position, yielding *threo* diol **117** (the stereochemical descriptors in Section 4 conform to the convention of sugar chemistry). This mode of epoxide opening is discussed in some depth at the end of Section 4.1.2. Compound **117** provides for protection of the two newly generated hydroxyl groups and sets the stage for a facile Pummerer rearrangement. Thus, **117** is converted *via* **118** to the corresponding alcohol **119**; its conversion to L-threitol tetraacetate **120** proceeds in a conventional manner.

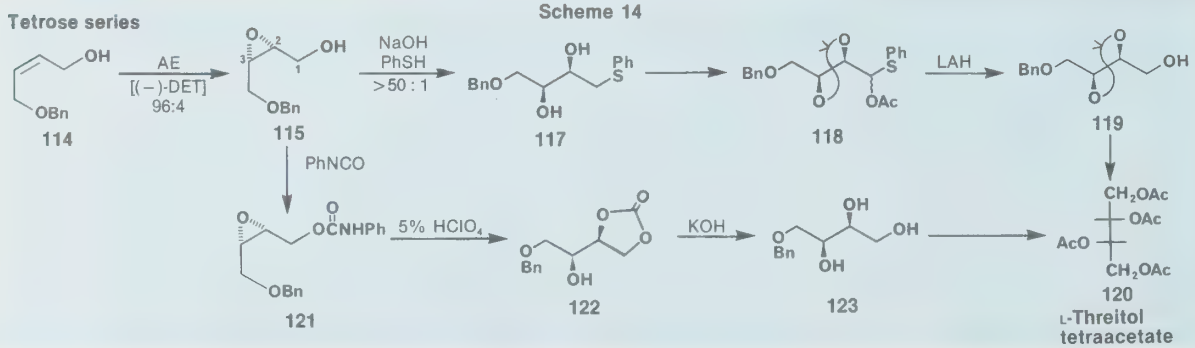
Another stereoselective epoxide opening employs attack by an intramolecular oxygen nucleophile at the C-2 center of **115**. The phenylurethane **121** undergoes smooth ring opening with the aid of an acid catalyst,[41] and the resulting carbonate **122** is converted to **123** with potassium hydroxide and then to the tetraacetate **120**.

All the transformations in the above sequence apply equally well to the *E*-allylic alcohol **124** (Scheme 15). The epoxy alcohol **125**, obtained from **124**, is transformed through two sets of intermediates **126-128** and **130-132** to the final tetraacetate **129** of erythritol.

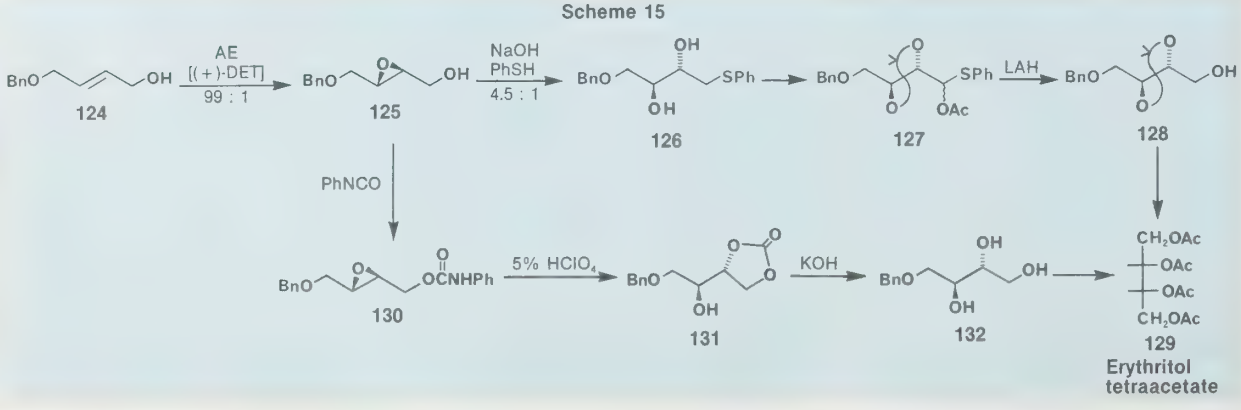
4.1.2. **Pentitols.**[40] The Wittig reaction of the known D-glyceraldehyde acetonide **133** with triphenylformylmethylenephosphorane followed by DIBAL-H reduction yields the *E*-allylic alcohol **134** (Scheme 16). The asymmetric epoxidation of **134** proceeds in the normal fashion with both (+)- and (−)-DET to epoxy alcohols **135** and **136**, respectively. The hydroxide ion attack provides both **135** and **136** exclusively, which constitutes yet a third variation on the stereo- and regioselective epoxide-ring-opening theme. The resulting triols **137** and **138** are correlated with the pentaacetates **139** and **140** derived from D-lyxitol (= D-arabinitol) and ribitol, respectively.

So far, so good. However, the *Z*-allylic alcohol **141** (Scheme 17) is found to react with Sharpless' reagent very slowly: with (+)-DET the epoxidation reaches only 55% completion in 14 days at -20 °C. The stereoselectivity is excellent however, favoring the formation of **142** in a 30:1 ratio. With (−)-DET, the reaction is too slow to be practical and the desired epoxy alcohol **143** is prepared with *m*-chloroperoxybenzoic acid in a virtually non-selective manner. The epoxide rings of **142** and **143** are opened in the same manner as that for **135** and **136** to provide triols **144** and **145**, res-

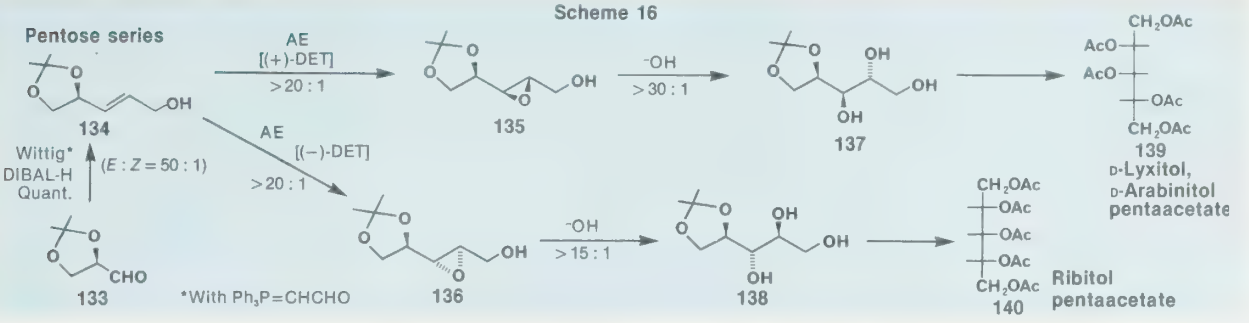
Scheme 14



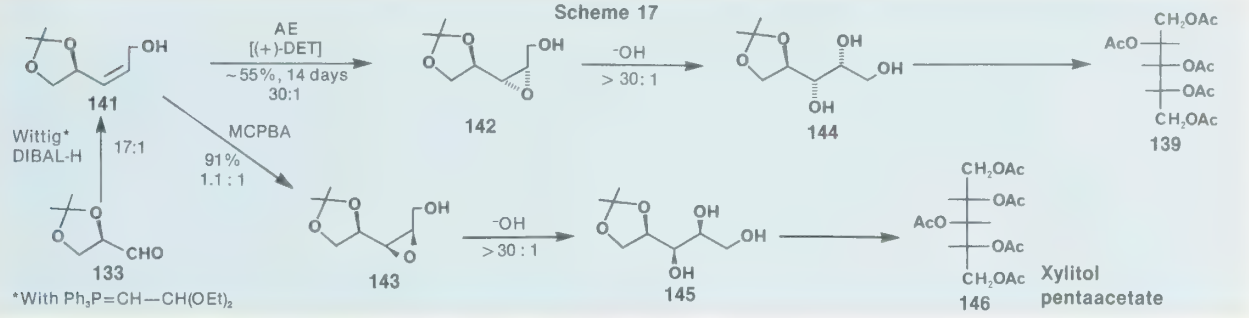
Scheme 15



Scheme 16



Scheme 17



pectively, which are further converted to D-arabitol pentaacetate (**139**) and xylitol pentaacetate (**146**).

The above preliminary examination of the reaction sequence 5 as applied to the synthesis of the pentitols and other similar compounds reveals that (1) in all cases examined, the sequence (Scheme 18) leading to the 2,3-*erythro* products **149** (such as **137** and **138**) *via* the *E*-isomer **147** (such as **134**) is satisfactory, and (2) in contrast, the AE of the *Z*-isomer **147** (such as **141**) in the 2,3-*threo* series **150** (such as **144** and **145**), when R is chiral, often proceeds intolerably slowly and/or with low stereoselection. This latter deficiency is now remedied by a simple but highly effective modification, and the overall transformation is now executed in a unified manner as summarized below.[42]

Scheme 18

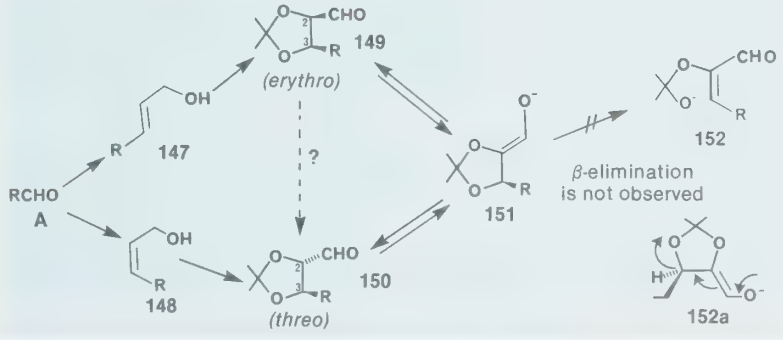
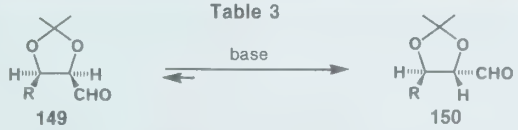
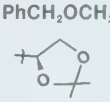
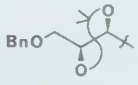


Table 3



BASE-CATALYZED EPIMERIZATION OF ERYTHRO (149) TO THREO (150) ACETONIDES

ERYTHRO ISOMER	THREO ISOMER	R IN 149 AND 150	EQUILIBRIUM RATIO OF 150:149
149a	150a	$PhCH_2OCH_2$	97:3
149b	150b		98:2
149c	150c		95:5

In compounds **149** and **150** the proton at C-2 is α to the aldehyde group and thus epimerizable. From the expected stability of **150** relative to **149**, the latter which is readily obtainable, can be equilibrated to give a mixture enriched in **150**, which has been up to now of limited access (see above). The acetonide chosen as a protecting group apparently suppresses the potential complication of a β-elimination (**151** to **152**) as the acetonide group helps maintain orthogonality between the enolate π system and the β-alkoxy substituent (see **152a**). Thus, treatment of **149a-c** with potassium carbonate in methanol at 25 °C effects smooth isomerization (>20:1) as summarized in Table 3. These examples represent the tetrose, pentose, and hexose series. Incorporation of this critical epimerization technique in our general approach leads to the satisfactory synthesis of all possible stereoisomers derived through reaction sequence 5.

Our final version is shown in Scheme 19, using the pentoses as illustration (**A** = **133**). The epoxy alcohol **136** undergoes ring opening to provide **153** which is converted to the acetonide **154** through kinetically

controlled acetonation followed by oxidation and acetylation. Reaction of **154** with DIBAL-H provides, virtually without epimerization, a product (**155**) which proves to be a ribose derivative. Compound **154** can also be converted to the C-2 epimer of **155**. Thus, treatment of **154** with potassium carbonate in methanol (see above) causes hydrolysis of the acetoxythioacetal group and epimerization at the C-2 center to give a mixture of **156** and **155** in a 98:2 ratio. Compound **156** has the arabinose configuration. The acetonides (**159** and **160**) of xylose and lyxose are prepared in exactly the same manner. The key intermediate **158** obtained from **135** *via* **157** provides **159** and **160** in a manner indicated in the scheme. In this way a highly efficient route from the same intermediate **134** to either the *erythro*- or the *threo*-2,3-dihydroxy aldehydes has been established.

It is obvious that the success of the above scheme depends heavily upon high asymmetric induction realized by the titanium-catalyzed epoxidation with (+)- or (−)-tartrates. The diastereofacial selectivity of this reagent outweighs the influence of the pre-existing chirality in the allylic alcohol. Now that **efficient, practical** routes from a chiral or achiral aldehyde to all the four possible bishomologated aldehydes have been established, these final products are ready for a second two-carbon extension. Indeed, the synthesis of all the possible hexoses has now been completed,[43] although a detailed discussion of the synthesis is abbreviated in this article.

A brief comment appears appropriate at this point on the ring opening of epoxy alcohols which have been proven to be extremely versatile synthetic intermediates. As described earlier, the known, facile base-catalyzed equilibration of 2,3- and 1,2-epoxy alcohols (*i.e.*, **112** and **113**) has been exploited to draw out a subtle mode of reactivity, and both epoxides possess two potential sites for nucleophilic attack. It is now evident that in the carbohydrate context, C-1 of compound **135** (Scheme 20), for instance, is by far the most reactive electrophilic site for a range of nucleophiles including the thiolate and hydroxide ions. Thus, the attack at C-1 of **161** leads to **162**, as exemplified by the predominant formation of **137** and **157**. Under proper conditions it is also possible to direct nucleophiles selectively to either C-2 or C-3. For example, reaction of **135** with the azide ion provides compound **163** as the major product.[44] The most interesting example by far is reduction at C-2 with metal hydrides, in particular, sodium bis(methoxyethoxy)-aluminum hydride (Red-Al®). The regiospecificity of this reduction plays a major role in developing the reaction sequence 4a, which would achieve the stereospecific addition of an acetate unit to aldehydes described earlier and is now discussed in the following section.

4.2. **Reaction Sequence 4a, Construction of the 3-Hydroxycarbonyl System.**[45] Table 4 lists two examples of many in which Red-Al reduction of epoxy alcohols proceeds smoothly under normal conditions (THF solvent) to provide a single

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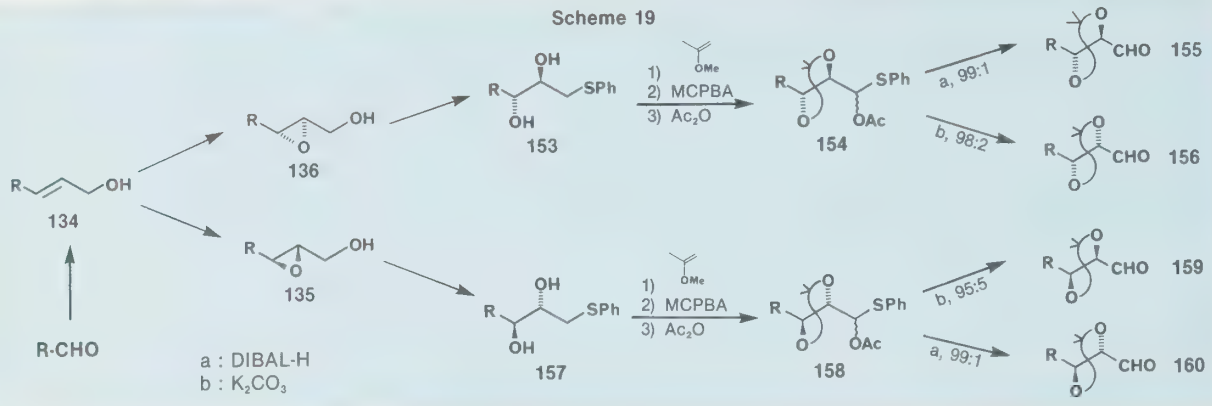
Scheme 19



Scheme 20

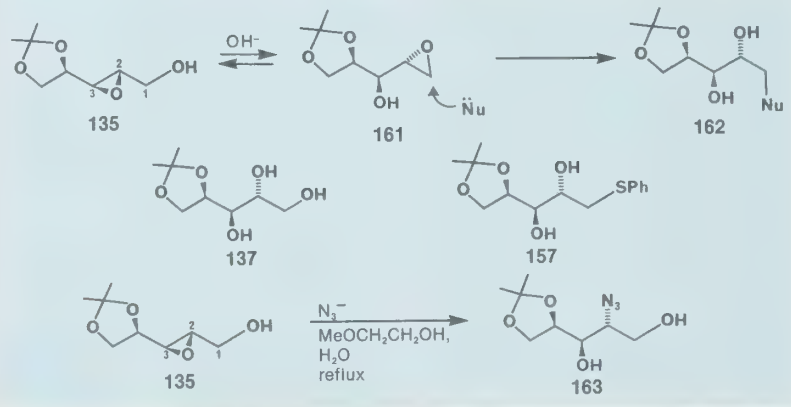
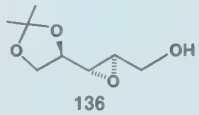
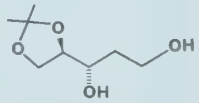
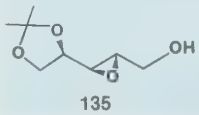
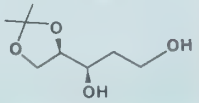


Table 4

Epoxyalcohol	Reductant (Reaction temperature, °C)	Ratio	Yield (%)	Structure of the major diol
 136	Red-Al (0)	> 100 : 1	78	 164
 135	Red-Al (0)	> 100 : 1	82	 165

product, a 1,3-diol. The regioselectivity is uniformly high and in many cases no traces of the corresponding 1,2-diols are found. A more impressive demonstration of this selectivity includes the reduction of 2,3:4,5-diepoxy alcohol with the same reductant. Thus, compound **166** (prepared from **167** through AE) undergoes clean double-ring opening to provide only one product, 1,3,5-triol **168** with the indicated stereochemistry (Scheme 21). Similarly, Red-Al reduction of **169** (obtained from **170**) provides **171** exclusively. These findings, in particular the simultaneous creation of two new hydroxylated chiral centers of 1,3-relationship, are important and bring us to the synthesis of amphotericin B (1), the polyenemacrolide described in the introduction of this article.

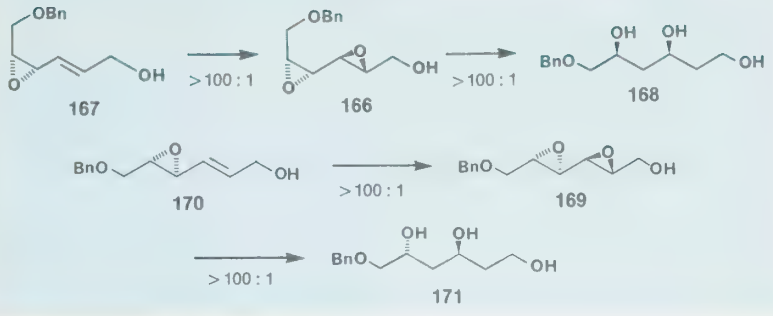
5. Studies Toward the Synthesis of Amphotericin B

As indicated earlier, the retrosynthetic dissection of **2**, the aglycone of the antibiotic, leads to fragments A, B, and C (Scheme 22), two of which may be further split into smaller sub-fragments: A into A-1 and A-2 and C into C-1 and C-2. Both A-1 and A-2 can be readily derived from **30** and the enantiomer of **168**, respectively, and have indeed been prepared in substantial quantities. The construction of the polyene (C-1) and the propionate (C-2) moieties should not present serious problems. As we are equipped with adequate methodologies (Section **2**), these two fragments are also in our hands. The only fragment that remained to be prepared was B. The methodology for the synthesis of **43** discussed in Section 2.4.2 is now applied in this instance. The 2-vinylcarboxylic acid ester **174** (Scheme 23) obtained from **30** (see Sections 2.4.1 and 2.4.2) is reduced with DIBAL-H. The resulting hydroxy compound is oxidized with Collins' reagent to yield (without isomerization of the double bond or epimerization of the C-2 center of **174**) the corresponding aldehyde, which is then treated with a Wittig reagent followed by DIBAL-H reduction to provide **175**. A sequence of four now standard reactions indicated in the Scheme converts **175** into the carboxylic acid **176**, which, after methylation and hydrolysis of the primary silyloxy ether leads to **177**, an immediate precursor of fragment B. The assembly of all these fragments to synthesize **2** is in progress and will hopefully be completed shortly.

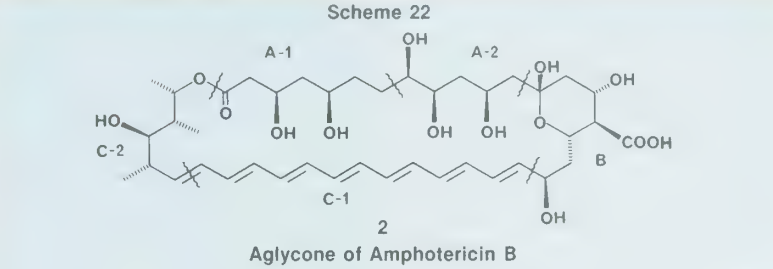
6. Concluding Remarks. The authors must apologize for the deletion in the above discussion of numerous contributions made by other groups — in particular, those led by Professors Heathcock (Berkeley) and Evans (Pasadena) — mainly because of space limitations. This article attempts to present the chronological and conceptual development of our research in this area.

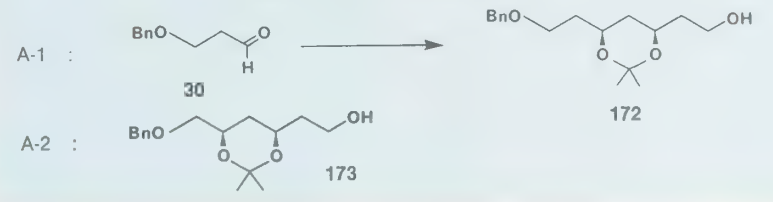
The initial investigation dealt mainly with the control of the 2,3-stereochemistry of aldol products. It soon entered the second generation through the modest but important demonstration of the 3,4-stereochemical control using chiral enolate reagents derived from the enantiomers of atrolactic acid. With the advent of highly diastereoselective enolate reagents, as well as a clearer understanding of the influence of metal coordination, one can now draw efficient and reasonably short synthetic schemes for most of the macrolide antibiotics of **polypropionate** origin. The aldol methodology offers one distinct advantage: stereoselective creation of two new chiral centers *in one step*. Moreover, the chiral auxiliaries contained in our reagents (*e.g.*, **29**), after the aldol reaction, can be removed **quantitatively** and **under virtually neutral conditions** to provide intermediates ready for the next sequence or a final product, a technical aspect which is extremely important in executing the synthe-

Scheme 21

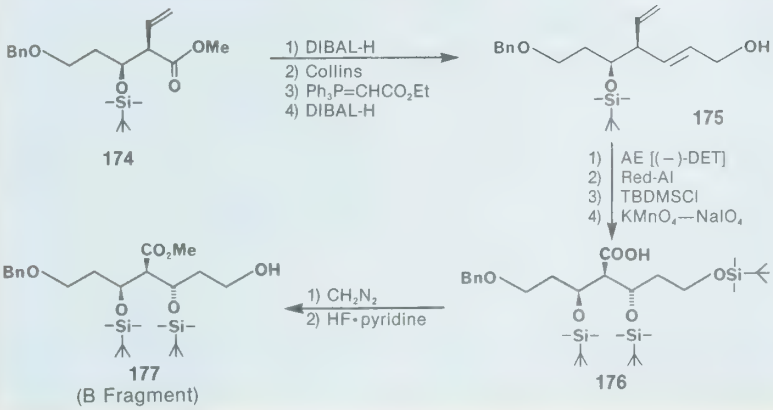


Scheme 22





Scheme 23



sis of the acid- and base-sensitive polyhydroxyl compounds.

Natural products or their fragments which are of **polyacetate** origin are also amenable to synthesis. In the asymmetric epoxidation process developed by Sharpless, the diastereofacial selectivity of the reagent is, at least, as high as that of **29** and thus overrides, in many cases, the stereochemical complications arising from a chiral substrate used in the reaction. With these two asymmetric reactions, aldol and epoxidation, we can now achieve many synthetic tasks which were regarded as unattainable even as recently as three years ago.

What has been learned about organic synthesis? Previously, stereochemical control in the synthesis of (poly)cyclic compounds, as witnessed in numerous classical examples, usually took advantage of the **large** diastereofacial selectivity of reacting substrates through the ingenious design of synthetic intermediates which were cyclic. This advantage no longer exists in **acyclic** stereoselection, as the Cram/anti-Cram selectivity is small and either does or does not favor the construction of a desired stereoisomer (Section 2.4). However, with the invention of highly diastereoface-selective chiral reagents, as well as a better understanding of the stereochemical interaction between reagent and substrate, we can now create any new required chiral center or centers (C_n^*) in a highly diastereoselective manner as shown in equation 1′: *d*-**A** + *d*-**B** → *d*-**A**′-(C_n^*)-*d*-**B**′ . Normally this can be achieved only with a combination of enantiomerically pure **A** and **B**. The clear recognition of this last precept underlying asymmetric synthesis is perhaps the most important outcome of the entire work.

Acknowledgments. With great pleasure we thank our major contributors in several areas of the chemistry discussed herein: exploration of the aldol strategy, Mr. J. Ellingboe; 6-deoxyerythronolide B, Drs. M. Hirama, S. Mori, Sk.A. Ali, and D.S. Garvey; rifamycin S, Ms. B. Imperiali; tylosin, Drs. W. Jackson, L. Lu, T. Toyoda, and Mr. T. Kaiho; amphotericin B, Messrs. P. Ma and T. Sakai. It has also been a memorable and gratifying experience for us to have collaborated with Professor K.B. Sharpless in the carbohydrate research which involved Drs. T. Katsuki, A. Lee, V. Martin, D. Tuddenham, and F. Walker, and Messrs. P. Ma and S. Viti. The work and this writing have been supported by grants from the National Institutes of Health, the National Science Foundation, as well as Hoffmann-La Roche (Nutley, N.J.) and Yoshitomi Pharmaceutical Industries (Japan).

Experimental Part:

The preparation of *R*- or *S*-1-cyclohexyl-1-*tert*-butyldimethylsilyloxybutan-2-one, the precursor for the *R*- or *S*-chiral enolate

(A) *R*- or *S*-Hexahydromandelic Acid. A 500-ml Parr hydrogenator bottle is charged with 19.78g of either *R*-or *S*-mandelic acid (130mmol), 115ml of methanol, 1.25ml of acetic acid, and 5g of 5% rhodium on alumina. The bottle is connected to a Parr pressure hydrogenation apparatus and charged to a pressure of 45psi. The bottle is shaken until absorption of hydrogen ceases. After disconnection from the apparatus the reaction mixture is filtered through a 2.5-cm pad of Celite. The solid residue is washed with a further 150ml of methanol. The combined filtrates are evaporated (rotary evaporator) to afford a white solid which is then powdered and further dried under high vacuum. Recrystallization from 50ml of acetone at -20°C affords 13.4-14.2g (65-69%) of optically pure hexahydromandelic acid, m.p. 128-129°. Optically pure *R*-hexahydromandelic acid should have $[\alpha]_D^{25} = -22.8°$ (c = 1.10, CH_3CO_2H); the *S*-enantiomer should have $[\alpha]_D^{22} = +23.0°$ (c = 1.065, CH_3CO_2H). NMR: δ[$(CD_3)_2CO$] 1.10-2.10 (11 H, m), 3.95 (1 H, d, J = 3Hz), and 6.57 (2 H, br s, D_2O ex).

(B) *R*- or *S*-1-Cyclohexyl-1-hydroxybutan-2-one. A dry 1-liter three-neck round-bottom flask fitted with a magnetic stirring bar, a jacketed dropping funnel (Fig. 1), an argon inlet, and a condenser is charged with 12.66g of *R*- or *S*-hexahydromandelic acid (80mmol) and 200ml of diethyl ether. The dropping funnel which has been precooled to -23°C (carbon tetrachloride/dry-ice) is charged with 276ml of 1.1*M* ethyllithium and the reaction vessel is cooled to -78°. The ethyllithium is added dropwise over two hours to the stirred reaction mixture. The mixture is then allowed to stir for 3 hours at 0°C and then overnight (15 hours) at room temperature. The reaction mixture is *carefully* poured onto 1 liter of 1*N* HCl in a 3-liter beaker, which is moderately stirred with a stirring bar. The mixture is transferred to a 2-liter separatory funnel and the aqueous phase is extracted twice with 200ml of diethyl ether. The combined ether extracts are washed with 500ml of a saturated sodium bicarbonate solution followed by 500ml of distilled water. After drying over anhydrous sodium sulfate the solvent is removed by rotary evaporation to afford an oil which is distilled to give 9.4-11.4g (69-84%) of *R*- or *S*-1-cyclohexyl-1-hydroxybutan-2-one, b.p. 63-64° (0.3 mm). The crude ethyl ketone should be distilled soon after removing the solvent. The ketone becomes yellow on exposure to light and cannot be fully purified by distillation. Similarly, the distilled material should be used in the next reaction as soon as possible to avoid the same problem. For the *R*-enantiomer, $[\alpha]_D^{22} = -128.0°$ (c = 1.45, $CHCl_3$) and for the *S*-enantiomer, $[\alpha]_D^{22} = +128.5°$ (c = 1.26, $CHCl_3$). NMR: δ($CDCl_3$) 1.10 (3 H, t, J = 7Hz), 1.30-2.10 (11 H, m), 2.52 (2 H, q, J = 7Hz), 3.53 (1H, s), and 4.05 (1 H, d, J = 2Hz).

Fig. 1
Jacketed Dropping Funnel, 250ml, ₹24/40
(Aldrich Catalog No. Z11,742-0, $189.00)

(C) *R*- or *S*-1-Cyclohexyl-1-*tert*-butyldimethylsilyloxybutan-2-one. A 250-ml round-bottom flask, fitted with a magnetic stirring bar, a condenser, and an argon inlet is charged with 6.12g of *R*- or *S*-1-cyclohexyl-1-hydroxybutan-2-one (36mmol), 10.9g of *tert*-butyldimethylsilyl chloride (72mmol), 9.8g of imidazole (140mmol), 0.1g of 4-dimethylaminopyridine, and 150ml of tetrahydrofuran. The mixture is stirred at reflux for 18 hours. After cooling to room temperature, the mixture is poured into 1 liter of distilled water and the products are extracted three times with 200ml of petroleum ether (b.p. 30-60°). The combined petroleum ether extracts are washed with 200ml of 1*N* hydrochloric acid followed by 200ml of distilled water. The solution is dried over anhydrous sodium sulfate, filtered, and the solvent removed by rotary evaporation. The resulting oil is warmed (50°C, water bath) under high vacuum until the weight is about 10.5g. The residue is distilled to give 8.5-9.5g (83-95%) of *R*- or *S*-1-cyclohexyl-1-*tert*-butyldimethylsilyloxybutan-2-one, b.p. 112-114° (1.5mm). For the *R*-enantiomer, $[\alpha]_D^{25} = +59.8°$ (c = 1.24, $CHCl_3$); for the *S*-enantiomer, $[\alpha]_D^{25} = -61.0°$ (c = 1.14, $CHCl_3$). NMR: δ($CDCl_3$) 0.04 (3 H, s), 0.06 (3 H, s), 1.10 (9 H, s), 1.17 (3 H, t, J = 7Hz), 1.30-2.00 (11 H, m), 2.33 (2 H, m), and 3.73 (1 H, d, J = 5Hz).

Preparation of ethyllithium.
A 2-liter three-neck, round bottom flask, fitted with a mechanical stirrer, a 250-ml pressure-equalized dropping funnel and a condenser with an argon inlet is charged with 17g of chopped lithium wire (2.45mol) and 200ml of diethyl ether. A solution of 134g of ethyl bromide (1.23mol) (distilled from phosphorus pentoxide immediately before use) in 260ml of diethyl ether is added to the cooled (-30 ± 5°C, CH_3CN/dry ice), stirred mixture over a period of 3 hours. The volume of solution requires that the addition funnel be charged twice. After the addition is complete, 340ml of diethyl ether is added to dilute the mixture and the temperature is raised to 0°C, with an ice bath (under argon and with the aid of a cannula). The mixture is filtered through a Schlenck frit containing 1cm of Celite, and the receiver is cooled in a bath of acetone/dry ice. The product should be stored in a freezer (-25 to -30°C) and used within one week after preparation. The concentration of ethyllithium is determined by titration. The amount of the reagent is sufficient for at least two reactions on the scale described. All solvents used in this and experiments B and C must be dried in the usual manner prior to use.

References and Notes:

1) This article is based mainly on the 24th Bachmann Memorial lecture presented by S. Masamune at the University of Michigan on April 15 and 16, 1982.
2) This phrase is used in the article in the sense originally defined by (a) W. Marckwald (*Ber.* **1904**, *37*, 1368): "those reactions which produce *optically active* substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes." For a broader definition, see (b) Morrison, J.D.; Mosher, H.S. "Asymmetric Organic Reactions"; American Chemical Society: Washington D.C., 1976; p 4.
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6) For the aldol reaction (eq. 4), see (a) Evans, D.A.; Nelson, J.V.; Taber, T.R. In "Topics in Stereochemistry"; Allinger, N.L.; Eliel, E.L.; Wilen, S.H. Eds.; John Wiley & Sons: New York, 1982; Vol. 13, p 1. (b) Heathcock, C.H. *Science* **1981**, *214*, 395. (c) Hajos, Z.G. in "Carbon-Carbon

Bond Formation"; Augustine, R.L. Ed.; Marcel Dekker: New York, 1979; Vol. 1, Chapter 1. (d) Mukaiyama, T. *Organic Reactions* **1982**, *28*, 203. (e) For related work see: Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. For the Wittig reaction/asymmetric epoxidation-ring opening (eq. 5), see (f) Sharpless, K.B.; Behrens, C.H.; Katsuki, T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodward, S.S. *Pure and Applied Chemistry*, in press. (g) Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* **1979**, *12*, 63. For general discussion of acyclic stereoselection, see (h) Bartlett, P.A. *Tetrahedron* **1980**, *36*, 3.

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12) The Zimmerman-Traxler model is effective only under non-equilibrating conditions. Under equilibration the 2,3-selection is often less than 10:1. However, normal reactions involving boron enolates lead to kinetic products. See references 6a-d.
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14) For instance, see Kagan, H.B. In "Organic Stereochemistry"; Halstead Press: New York, 1979; Chapter 4.
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18) (a) Note that the major product is the anti-Cram product. [For the description of Cram's *acyclic* model, see Cram, D.J.; Abd Elhafez, F.A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.] (b) The major product from the "mismatched" reaction of (−)-**26** and R-**29a** is a Cram product in 15:1 selection (reference 25).
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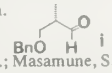

i

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Among the many compounds cited by Prof. Masamune and Dr. Choy and offered by Aldrich are the following:

11,004-3 Acetic anhydride, 99+%

24,284-5 Acetic anhydride, A.C.S. reagent

17,871-3 9-BBN, dimer, crystalline

19,385-2 9-BBN, 0.5*M* in hexane

15,107-6 9-BBN, 0.5*M* in THF

19,621-5 Bis(cyclopentadienyl)zirconium dichloride, 98+%

23,960-7 Bromoethane, 99+%, GOLD LABEL

12,405-2 Bromoethane, 98%

19,050-0 *tert*-Butyldimethylsilyl chloride

21,312-8 *tert*-Butyl hydroperoxide, 90%

18,471-3 *tert*-Butyl hydroperoxide, 70%

16,743-6 Celite, high-purity, analytical grade

22,179-1 Celite 521

10,803-0 3-Chloro-2-methylpropene, tech., 90%

C6,270-0 *m*-Chloroperoxybenzoic acid, tech., approx. 80-85%

23,265-3 Chromium(VI) oxide, 99.9%

20,782-9 Chromium(VI) oxide, 99+%

24,950-5 2,6-Di-*tert*-butyl-4-methylpyridine, 98%

14,926-8 Dichloroacetic anhydride, 98%

21,396-9 (−)-Diethyl D-tartrate

15,684-1 (+)-Diethyl L-tartrate, 98%

D10,620-8 Dihydropyran, 97%

21,500-7 Diisobutylaluminum hydride, 1.0*M* in toluene (DIBAL-H)

Solutions of DIBAL-H in other solvents are also available; see pp 446-447 of the 1982-1983 Aldrich Catalog/Handbook.

D12,580-6 *N,N*-Diisopropylethylamine, 98%

22,780-3 (−)-Diisopropyl D-tartrate

22,918-0 (+)-Diisopropyl L-tartrate, 99%

10,770-0 4-Dimethylaminopyridine, 99%

D20,655-5 Diphenyl chlorophosphate, 98%

24,427-9 Hydrofluoric acid, A.C.S. reagent

18,422-5 Hydrogen fluoride - pyridine

I-20-2 Imidazole, 99%

24,078-8 Isobutyraldehyde, 99+%, GOLD LABEL

I-1,550-5 Isobutyraldehyde, 98%

22,091-4 Lithium, 98%, wire

19,987-7 Lithium aluminum hydride, 95+%

Solutions of $LiAlH_4$ in various solvents are also available; see page 720 of the 1982-1983 Aldrich Catalog/Handbook.

22,436-7 Lithium bis(trimethylsilyl)-amide, 1*M* in hexane

22,577-0 Lithium bis(trimethylsilyl)-amide, 1*M* in THF

M200-4 *d*-Mandelic acid, 99+%, GOLD LABEL

15,421-0 *l*-Mandelic acid, 99+%, GOLD LABEL

M220-9 *l*-Mandelic acid, 98%

15,648-5 Mercuric trifluoroacetate, 98%

17,464-5 2-Methoxypropene, 99+%

24,304-3 3-Pentanone, 99%, spectrophotometric grade, GOLD LABEL

12,760-4 3-Pentanone, 98%

24,425-2 Perchloric acid, A.C.S. reagent

20,961-9 Potassium carbonate, anhydrous, 99+%

24,355-8 Potassium carbonate sesquihydrate, 99%

24,084-2 Propionaldehyde, 99+%, GOLD LABEL

P5,145-1 Propionaldehyde, 97%

19,014-4 Pyridinium chlorochromate, 98%

19,619-3 Red-Al®, 3.4*M* in toluene

21,285-7 Rhodium on alumina powder, 5%

17,964-7 Silver carbonate, 99%

19,807-2 Sodium borohydride, powder, 98+%

$NaBH_4$ in pellet form, in solution, and on solid supports are also available; see pp 1042-1043 of the 1982-1983 Aldrich Catalog/Handbook.

15,615-9 Sodium cyanoborohydride, 95+%

21,763-8 Sodium iodide, anhydrous, 99+%

21,730-1 Sodium iodide dihydrate, 99+%

21,004-8 Sodium periodate, 99%

21,988-6 Sodium phosphate, dibasic, anhydrous, 98+%, A.C.S. reagent

22,199-6 Sodium phosphate, dibasic, heptahydrate, A.C.S. reagent

24,024-9 Thiophenol, 99+%, GOLD LABEL

T3,280-8 Thiophenol, 97%

20,527-3 Titanium(IV) isopropoxide

24,087-7 *p*-Toluenesulfonyl chloride, 99+%, GOLD LABEL

T3,595-5 *p*-Toluenesulfonyl chloride, 98%

23,962-3 Triethylamine, 99+%, GOLD LABEL

13,206-3 Triethylamine, 99%

T6,220-0 Trifluoroacetic acid, 99%

10,623-2 Trifluoroacetic anhydride, 99+%, GOLD LABEL

15,853-4 Trifluoromethanesulfonic acid

24,092-3 Trimethyl orthoformate, 99+%, GOLD LABEL

10,845-6 Trimethyl orthoformate, 98%

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