Alfred Bader

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Aldrichimica ACTA

VOL. 33, NO. 1 • 2000

The Chemical Vapor Deposition of Metal Nitride Films Using Modern Metalorganic Precursors

Synthetic Applications of Indium Trichloride Catalyzed Reactions

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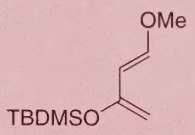
New Products

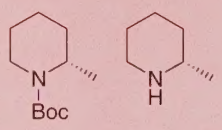
The *tert*-butyldimethylsilyl analog of Danishefsky's diene is now available. It has been used to prepare a variety of bicyclic enones and 2,3-dihydro-4*H*-pyran-4-ones.[1-3]



(1) Uchida, H. et al. *Tetrahedron Lett.* **1999**, *40*, 113. (2) Pudukulathan, Z. et al. *J. Am. Chem. Soc.* **1998**, *120*, 11953. (3) Annunziata, R. et al. *J. Org. Chem.* **1992**, *57*, 3605.

51,536-1 ***trans*-3-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1,3-butadiene**, 95% **5g $53.00**

Building blocks for *trans*-2-methyl-6-substituted piperidines via deprotonation with *sec*-butyllithium followed by reaction with an electrophile.[1-3]



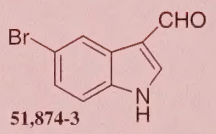
52,288-0 **52,290-2**

(1) Chackalamannil, S. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9812. (2) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. (3) Idem *ibid.* **1990**, *55*, 2578.

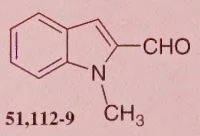
52,288-0 **(*S*)-(+)-*N*-(*tert*-Butoxycarbonyl)-2-methylpiperidine**, 98% **1g $31.50**

52,290-2 **(*S*)-(+)-2-Methylpiperidine**, 97% **1g $68.00**

Precursors for a wide variety of substituted indoles.[1-3]

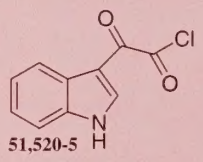


51,874-3



51,112-9

(1) Battaglia, S. et al. *Eur. J. Med. Chem.* **1999**, *34*, 93. (2) Joseph, B. et al. *J. Heterocycl. Chem.* **1997**, *34*, 525. (3) Le Borgne, M. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 333.



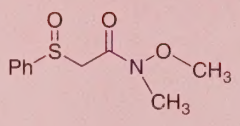
51,520-5

51,874-3 **5-Bromoindole-3-carboxaldehyde**, 98% **5g $26.40**

51,112-9 **1-Methylindole-2-carboxaldehyde**, 97% **5g $45.70**

51,520-5 **3-Indoleglyoxylyl chloride**, 98% **5g $40.60**

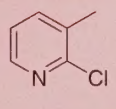
α,β-Unsaturated *N*-methoxy-*N*-methylamides are prepared from this reagent through deprotonation with sodium hydride, reaction with an alkyl halide, and in situ heating.



Beney, C. et al. *Tetrahedron Lett.* **1998**, *39*, 5779.

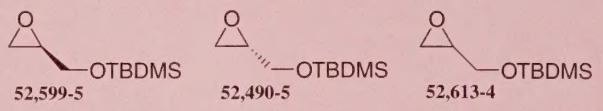
51,139-0 ***N*-Methoxy-*N*-methyl-2-(phenylsulfinyl)acetamide**, 96% **1g $30.00; 5g $100.00**

2-Substituted picolines have been prepared from this compound. Examples include (2-pyridyl)indoles and endothelin receptors.[1,2]



(1) Amat, M. et al. *J. Org. Chem.* **1997**, *62*, 3158. (2) Kourounakis, A. et al. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2223.

51,894-8 **2-Chloro-3-methylpyridine**, 97% **5mL $35.40; 25mL $117.90**



52,599-5 **52,490-5** **52,613-4**

A variety of nucleophiles have been used to open the oxirane ring of these compounds. Examples include lithium acetylides[1,2] and lithium dithianes.[3]

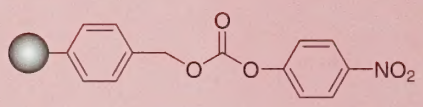
(1) Arista, L. et al. *Heterocycles* **1998**, *48*, 1325. (2) Maguire, R. J. et al. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853. (3) Smith, A. B., III; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925.

52,599-5 ***tert*-Butyldimethylsilyl (*R*)-(+)-glycidyl ether**, 98% **5g $65.00**

52,490-5 ***tert*-Butyldimethylsilyl (*S*)-(−)-glycidyl ether**, 98% **5g $65.00**

52,613-4 ***tert*-Butyldimethylsilyl glycidyl ether**, 98% **10g $42.00**

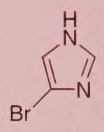
This carbonate resin is used to bind amines or amino acids as urethanes. Dipeptides and hydantoins have been prepared from these polymer-bound urethanes.[1-3]



(1) Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc., Chem. Commun.* **1977**, 798. (2) Dressman, B. A. et al. *Tetrahedron Lett.* **1996**, *37*, 937. (3) Gouilleux, L. et al. *ibid.* **1996**, *37*, 7031.

51,529-9 **4-Nitrophenyl carbonate, polymer-bound on Wang Resin 1g $35.60; 10g $199.00**

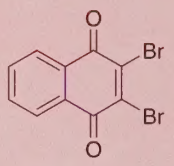
Starting material for the preparation of 4-substituted imidazoles.[1,2]



(1) Lange, J. H. M. et al. *Tetrahedron* **1995**, *51*, 13447. (2) Singh, B. et al. *J. Med. Chem.* **1992**, *35*, 4858.

47,869-5 **4-Bromo-1*H*-imidazole**, 97% **1g $31.50**

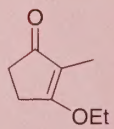
Naphthoquinones are prepared from this compound via palladium-catalyzed coupling reactions with tributylstannyl-heteroaromatics or by nucleophilic displacement of one or both bromides.[1,2]



(1) Yoshida, S. et al. *Chem. Lett.* **1996**, 139. (2) Falling, S. N.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 1260.

52,342-9 **2,3-Dibromo-1,4-naphthoquinone**, 97% **25g $58.00**

Precursor for 3-substituted-2-methyl-2-cyclopenten-1-ones.[1,2]



(1) Cossy, J. et al. *Tetrahedron Lett.* **1997**, *38*, 4069. (2) Junga, H.; Blechert, S. *ibid.* **1993**, *34*, 3731.

51,440-3 **3-Ethoxy-2-methyl-2-cyclopenten-1-one**, 97% **5g $36.00**

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Our first cover of 2000 is a montage of various art works that have graced some of our past publications. The top three and number 6 are part of the extensive personal art collection of Dr. Alfred Bader, founder of Aldrich Chemical Co. and formerly the *Acta's* "Chemist Collector". These are *The Farm Scale* by John Whalley [no. 1], *King David* by Govaert Flinck [no. 2], *Trompe L'oeil* [no. 3], and *Lady in Black* [no. 6].

The other two are *The Dreamer* by Pierre Auguste Renoir [no. 4] and *The Column* by Hubert Robert [no. 5]. Both of these paintings are in the permanent collection of the Saint Louis Art Museum, Saint Louis, MO.

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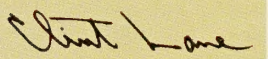


Clint Lane, President

Dear Fellow Chemists:

It is a great pleasure for me to again provide a contribution to our *Aldrichimica Acta*, this time as President of Aldrich. During the years 1973–1977, I contributed nine reviews to this publication. Now, 23 years later, I am back on these pages. Much has changed over the years, but we never stopped publishing what we here at Aldrich simply call "the ACTA".

Year 2000 was viewed as a perfect time to roll out a new look for our classic. However, we have not deleted any of the features that you have come to expect. Art on the cover (reprints available), excellent and timely reviews, lab notes, featured new products, etc. are all here for you to enjoy. Our goal is to continue to be *Chemists Helping Chemists* as we move into the new millennium. We know you will continue to find new ideas and information to help you in your research efforts.

Thank you for staying with us over all these years. This is the first issue in the year 2000. We are up to Volume 33 (33 years) and still counting. As always, "Please Bother Us" with comments or contributions.

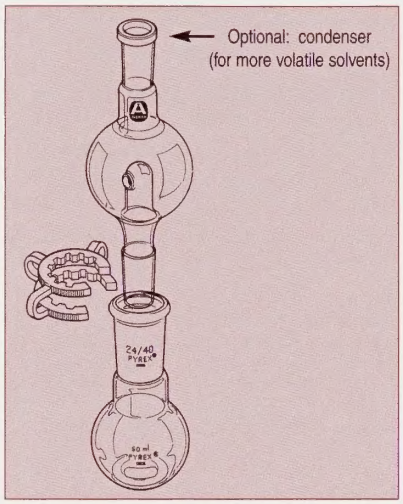
Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Lab Notes

Aldrich Rotary Evaporator Antisplash Adapters as Solvent Traps in Recrystallizations

For practicing synthetic chemists, recrystallization of reaction intermediates is routine. For maximal product recovery, it is important to prepare a saturated solution of the compound. In many instances, this is difficult to judge, since excess solvent is sometimes needed to completely dissolve the solute, or since filtration subsequent to charcoal treatment is followed by washing of the residue with hot solvent. These steps result in dilution of the crystallizing solution, and, therefore, concentration of such a solution has to be performed. This is usually accomplished by simply heating the solution to evaporate some of the solvent. However, this leads to two problems: (a) how much solvent is actually left in the flask cannot be accurately estimated, and (b) solvent vapors are discharged into the hood and are not collected for recycling or disposal. We have devised a simple solution to these two problems that uses the Aldrich rotary evaporator antisplash adapter (without return holes, Cat. No. Z17,604-4 to Z20,329-7).

The rotary evaporator antisplash adapter doubles as a solvent trap for the recovery of the crystallization solvent. The compound is placed in a round-bottom flask, and heated while the solvent is gradually added until the compound



dissolves completely. The antisplash adapter is then attached to the flask and heating is continued. The solvent that evaporates at this stage condenses and collects in the antisplash adapter. A couple of modifications of this setup are possible. For larger-scale operations, the solutions can be magnetically stirred and heated. Also, for better recoveries of volatile solvents, a reflux condenser can be attached to the top of the antisplash adapter. After the solvent has collected in the adapter, the adapter is disconnected, and the solvent is removed and its volume measured. Besides effecting the desired concentration of the crystallization solution, this procedure allows one to calculate the amount of solvent left in the crystallization flask, and to recycle or properly dispose of the condensed solvent.

We routinely use this setup and find it very convenient. We hope that other researchers will find it equally helpful.

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Please turn to page 12 for more Lab Notes.

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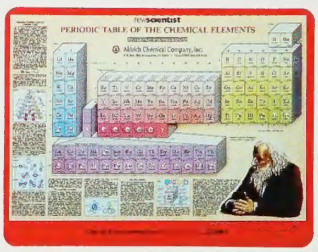

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Aldrichimica ACTA

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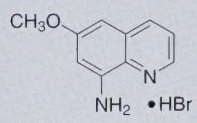
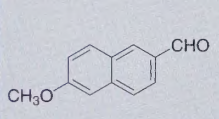


Quinoline building block.[1] Used as an amino component in a novel series of bladder-selective diaminocyclobutenedione potassium channel openers.[2]

(1) Armer, R.E. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2430. (2) Butera, J.A. *J. Med. Chem.* **2000**, *43*, 1187.

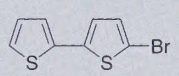
52,809-9 **8-Amino-6-methoxyquinoline hydrobromide**, 97% **1g $57.10; 10g $317.00**



Employed in the synthesis of biologically active naphthalenes.[1] The aldehyde moiety has been elaborated into an oxetane in a photocyclization[2] and to a butanone in the preparation of the NSAID nabumetone.[3]

(1) Bosca, F. et al. *Photochem. Photobiol.* **2000**, *71*, 173. (2) Abe, M. et al. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3261. (3) Prabhakar, C. et al. *Org. Process Res. Dev.* **1999**, *3*, 121.

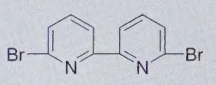
53,308-4 **6-Methoxy-2-naphthaldehyde**, 98% **5g $138.00**



Used recently in the synthesis of oligothiophenes [1,2] and oligothienylferrocene complexes.[3]

(1) Jiang, B. et al. *J. Am. Chem. Soc.* **1999**, *121*, 9744. (2) Ibrahim, M. A. et al. *Synth. Met.* **1999**, *105*, 35. (3) Zhu, Y.; Wolf, M. O. *Chem. Mater.* **1999**, *11*, 2995.

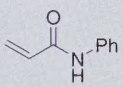
52,285-6 **5-Bromo-2,2′-bithiophene**, 96% **1g $40.90; 5g $171.20**



Direct copper catalyzed substitution of the bromines with nitrogen led to chiral bipyridine ligands based on camphor sultam or a prolinol ether.[1] The bis(3-pyrazolyl) derivative was studied as a tetradentate chelating ligand.[2]

(1) Kandzia, C. et al. *Tetrahedron: Asymmetry* **1993**, *4*, 39. (2) Couchman, S. M. et al. *Polyhedron* **1999**, *18*, 2633.

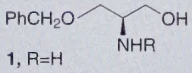
51,388-1 **6,6'-Dibromo-2,2'-dipyridyl**, 90% **500mg $45.70**



The BPO initiated graft polymerizations of this *N*-substituted acrylamide and *N*-isopropylacrylamide (41,532-4) onto ethylene-propylene-diene terpolymer were conducted. Thermal and mechanical properties were studied along with changes in morphology upon irradiation.

Park, K-G et al. *J. Appl. Polym. Sci.* **1999**, *74*, 3259.

53,004-2 ***N*-Phenylacrylamide**, 99% **10g $84.60**



1, R=H
2, R=BOC

Used for preparing the enantiopode of Garner's aldehyde,[1] peptide nucleic acid (PNA) analogs,[2] and chiral gadolinium complexes that are employed as MRI contrasting agents.[3]

(1) Avenoza, A. et al. *Synthesis* **1997**, 1146. (2) Ramasamy, K. S.; Seifert, W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1799. (3) Sajiki, H. et al. *Synth. Commun.* **1996**, *26*, 2511.

47,375-8 **(*R*)-(+)-2-Amino-3-benzyloxy-1-propanol**, 97% (99% ee/GLC) (1) **1g $38.60**

47,376-6 **(*R*)-(+)-3-Benzyloxy-2-(*tert*-butoxycarbonyl-amino)-1-propanol**, 98% (2) **5g $169.60**

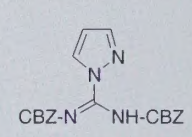
1, R=CBZ
2, R=BOC

Used to prepare fluoro-substituted pyrrolidinyl-2-pyridinones as antibacterial agents[1] and in the study of Protein Kinase C (PKC) inhibitors.[2,3]

(1) Li, Q. et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1953. (2) Jagdmann, G.E. et al. *ibid.* **1995**, *5*, 2015. (3) Lai, Y. et al. *ibid.* **1995**, *5*, 2151.

49,412-7 **Benzyl 3-pyrroline-1-carboxylate**, 90% (1) **1g $16.50; 5g $54.90**

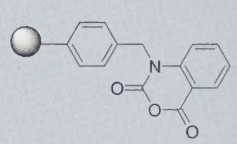
47,751-6 ***tert*-Butyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate**, 97% (2) **1g $67.60**



Bis-protected guanylating agent used in the preparation of guanidinonaphthyl amino acid esters, "inverse" substrates for trypsin and trypsin-like enzymes.[1,2]

(1) Tanizawa, K. et al. *Chem. Pharm. Bull.* **1999**, *47*, 104. (2) Sekizaki, H. et al. *Tetrahedron Lett.* **1997**, *38*, 1777.

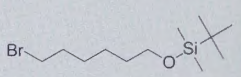
43,942-8 ***N,N'*-Bis(benzyloxycarbonyl)-1*H*-pyrazole-1-carboxamidine**, 97% **1g $24.60; 5g $81.90**



The highly reactive anhydride moiety makes this a commonly used scavenger resin to remove primary and secondary aliphatic amines from solution-phase reactions.

Coppola, G.M. *Tetrahedron Lett.* **1998**, *39*, 8233.

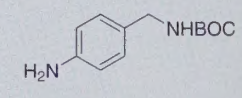
51,437-3 **Isatoic anhydride, polymer-bound**, 2.0-2.5 mmol N/g **5g $88.40**



A pheromone intermediate was prepared by displacement of the bromide with an acetylene followed by selective deprotection of the silyl group with neutral alumina in the presence of a THP ether.

Capdevila, A. et al. *Org. Lett.* **1999**, *1*, 845.

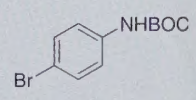
51,314-8 **(6-Bromohexyloxy)-*tert*-butyldimethylsilane**, 99% **5mL $38.40; 25mL $127.90**



Pharma building block used in the preparation of topomerase inhibitors,[1] neuroprotective agents,[2] and novel antagonists for vascular $5HT_{1B}$-like receptors.[3]

(1) Dudouit, F. et al. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 553. (2) Di Fabio, R. et al. *J. Med. Chem.* **1999**, *42*, 3486. (3) Moloney, G.P. et al. *ibid.* **1999**, *42*, 2504.

52,562-6 **4-[(*N*-BOC)aminomethyl]aniline**, 97% **1g $22.00**



BOC protection makes this aniline a good substrate for Suzuki coupling. Two examples are the biaryls from reaction with pyridine[1] or 3-benzaldehyde[2] boronic acids.

(1) Iamothe, M. et al. *J. Med. Chem.* **1997**, *40*, 3542. (2) Coutts, I.G.C. et al. *Tetrahedron Lett.* **1997**, *38*, 5563.

52,724-6 ***N*-(*tert*-Butoxycarbonyl)-4-bromoaniline**, 97% **10g $40.00**

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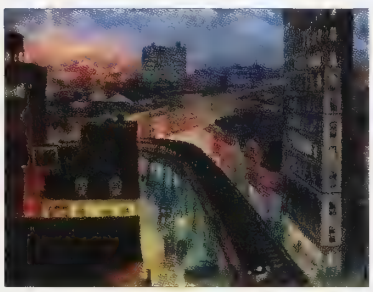

The City from Greenwich Village (oil on canvas, 26 in. x 33¾ in.) was painted in 1922 by the American artist John Sloan, one of a number of artists who came to be called the "Ash Can School" because of their use of busy city streets, tenements, and back alleys as subjects. Sloan, who was born in 1871 in Lock Haven, Pennsylvania, worked during the 1890s as a newspaper illustrator in Philadelphia, where he came in contact with the artist Robert Henri. Henri had returned from several years' study in Paris determined to lead a revolt against academic art and with a strong belief that works of art should reflect the reality of contemporary life.

After 1904, Sloan settled permanently in New York, and though he continued to work as an illustrator, he devoted himself increasingly to the pursuit of subjects of human interest and the depiction of scenes of everyday life among ordinary people in the city. He was one of the original members of a group of artists called The Eight, who were not united by a common style but by a rejection of academic aestheticism. This group came into being in 1907, when the National Academy of Design rejected the work of Sloan, George Luks, and William Glackens, and Henri withdrew his own paintings in protest from the Academy's annual exhibition.

The City from Greenwich Village shows the view from the artist's Washington Place studio out over the street on a rainy winter evening. Automobiles and figures bearing umbrellas make their way under the elevated trains, which ran then along Sixth Avenue. Electric lights reflect from the rainy streets and cast a glow between the buildings, and the lights of the skyscrapers at the far left are like a celestial vision in the distance. A much more romantic image than is commonly found in Sloan's earlier works, it is a celebration of the energy and excitement of a great modern city.

This painting is a gift of Helen Farr Sloan to the National Gallery of Art, Washington, D.C.

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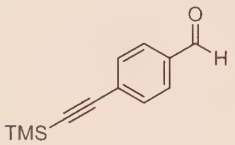
Clint Lane, President



Professor Jonathan S. Lindsey (NCSU, Raleigh) kindly suggested that we make 4-(trimethylsilylethynyl)benzaldehyde. This protected arylacetylene is a useful precursor to porphyrin building blocks, and, subsequently, porphyrin-based molecular devices.

Ravikanth, M.; Strachan, J.-P.; Li, F.; Lindsey, J.S. *Tetrahedron* **1998**, *54*, 7721.

52,338-0
4-(Trimethylsilylethynyl)-benzaldehyde, 97%
5g $57.00

Naturally, we made this useful building block. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

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Lab Notes

Analysis of Volatile Compounds in Resins by GC/MS

A convenient and simple way to analyze volatile compounds in resins used in polymerization processes is by GC/MS. The power of GC/MS as an analytical tool is well developed and most laboratories are now equipped with bench-top GC/MS units. Therefore, it is quite convenient to use GC/MS to analyze the amount of monomers present in a resin, the volatile products from polymerization (condensation), or the impurities in a resin. The difficulty in analyzing a resin arises from the fact that it is usually a thick and viscous liquid. The normal procedure of using a solvent to dissolve the resin is tedious and difficult and requires the judicious choice of solvent. In addition, the solvent peak in GC/MS often obscures the small amount of volatile compounds to be analyzed. The use of fixed-volume micro syringes allows simple, direct analysis of the sample without contamination. The micro syringe (Dynatech Mini-injector, from 0.01 to 0.10 microliters, Aldrich Cat. No. Z17,096-8 and Z17,099-2) is dipped directly into the resin sample. Normal injection is made into a GC/MS. The injection port is kept at the appropriate temperature, and the needle is left in the injection port for sufficient time to allow the vaporization of volatile compounds from the needle (about one minute). The needle can be cleaned with appropriate solvents and any residue burned off using a burner. We have used this method successfully to analyze the amount of allyl alcohol (a potent irritant) in a Vibrin resin.

Ambrose Leong, Ph.D.
Billy Sue Hurst Professor of Chemistry
Department of Chemistry
Emory & Henry College
Emory, VA 24327-0947
E-mail: aleong@ehc.edu

Preventing Cross-Contamination in Solvent Stills Connected in Series to the Same Inert Gas Manifold

We have always had the problem of solvents getting contaminated with other solvents, when several stills were connected to a common inert gas source. The flow of the inert gas was designed to entrain the solvent vapors by entering the still with the low-vapor-pressure solvent and ending in a bubbler next to the high-vapor-pressure solvent. But, often, solvents were contaminating each other during the distillation due to changes in the rate of inert gas flow, water flow cutoff, or power failure.

To minimize this contamination, we have designed a new piece of glassware called a Protecting Head, as shown in **Figure 1**. Since the solvent vapors are carried deep inside the side arm, they condense, allowing only the inert gas to escape. In a typical setup, each still is fitted with a protecting head and connected to the common inert gas manifold through T-connectors. Any contaminated solvent accumulated in the side arm is periodically removed through the bottom stopcock, making sure that the accumulated solvent does not reach the bottom of the inner tube.

We have successfully used this setup in the distillation of such solvents as diethyl ether, dichloromethane, hexane, toluene, acetonitrile, and THF. We hope that chemists the world over will find it equally useful.

Maravanji S. Balakrishna, Assistant Professor
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Powai, Mumbai 400 076, INDIA
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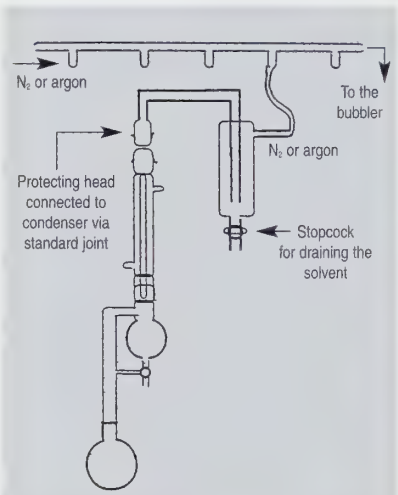

Figure 1
Solvent Still with a Still Protecting Head.

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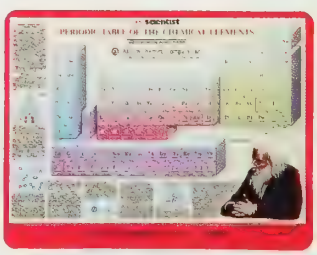

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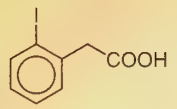
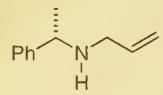


Used in the synthesis of nitrogen-containing heterocycles via vinylogous Pummerer reactions of amido sulfoxides.

Padwa, A.; Kuethe, J.T. *J. Org. Chem.* **1998**, *63*, 4256.

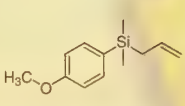
53,147-2 2-Iodophenylacetic acid, 97%



Nitrogen-containing heterocycles have recently been prepared from this chiral amine in a tandem aminocarbonylation/Pauson–Khand reaction.

Balsells, J. et al. *Org. Lett.* **1999**, *1*, 1981.

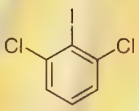
52,554-5 (*S*)-*N*-Allyl-α-methylbenzylamine, 97%



This silane is a key intermediate in the synthesis of a silicon linker, useful for the traceless synthesis of pyridine-based tricyclics.

Woolard, F.X. et al. *J. Org. Chem.* **1997**, *62*, 6102.

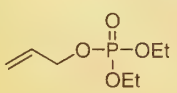
51,104-8 Allyl(4-methoxyphenyl)dimethylsilane, 98%



Useful for the synthesis of *m*-terphenyls, and, subsequently, novel cyclophanes.[1,2]

(1) Rajakumar, P.; Srisailas, M. *Tetrahedron Lett.* **1997**, *38*, 5323. (2) Kannan, A. et al. *J. Org. Chem.* **1996**, *61*, 5090.

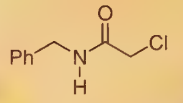
51,045-9 1,3-Dichloro-2-iodobenzene, 98%



A simple, one-step reaction employing this reagent leads to the direct regioselective dehydrogenation of aldehydes and cyclic ketones.

Shvo, Y.; Arisha, A.H.I. *J. Org. Chem.* **1998**, *63*, 5640.

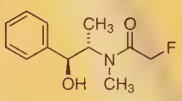
52,585-5 Diethyl allyl phosphate, 98%



Employed in the synthesis of novel tetrazoles via tetrazolylbenzyl radicals.

Biadatti, T. et al. *Tetrahedron Lett.* **1998**, *39*, 19.

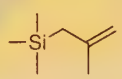
53,199-5 2-Chloro-*N*-benzylacetamide, 97%



This chiral auxiliary provides practical access to a wide range of α-fluoro-carboxylic acids in high enantiomeric excess.

Myers, A.G. et al. *Tetrahedron Lett.* **1998**, *39*, 1335.

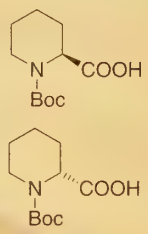
52,561-8 (1*S*,2*S*)-Pseudoephedrine α-fluoroacetamide, 98%



Utilized in the catalytic synthesis of optically active allyl α-amino acids.

Fang, X. et al. *J. Org. Chem.* **1999**, *64*, 4844.

51,026-2 Methallyltrimethylsilane, 97%



Synthons for the synthesis of the immunosuppressive agent FK506[1] and the thrombin inhibitor inogatran,[2] and for preparing new cyclosporin derivatives.[3]

(1) Baker, R.K. et al. *Tetrahedron Lett.* **1998**, *39*, 229. (2) Preville, P. et al. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1563. (3) Eberle, M.K. et al. *J. Med. Chem.* **1995**, *38*, 1853.

51,636-8 (*S*)-(–)-1-(*tert*-Butoxycarbonyl)-2-piperidine-carboxylic acid, 98% (98% ee/GLC)

51,634-1 (*R*)-(+)-1-(*tert*-Butoxycarbonyl)-2-piperidine-carboxylic acid, 98% (98% ee/GLC)

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About Our Cover

Street in Venice (oil on wood panel, 17¾ in. x 21¼ in.) was painted by the American artist John Singer Sargent. Sargent was born in Florence in 1856 to affluent expatriate American parents and spent most of his life in Europe. He lived mainly in Paris until 1884, and then in London, where he died in 1925. His formal instruction in art was in Rome, Florence, and Paris, and, from 1877, he exhibited at the official salons in the French capital. Sargent traveled extensively, copying Velázquez at the Prado in Madrid and Frans Hals in Belgium and Holland, and developing a style that combines close observation with a fluent and painterly technique derived at least partly from these earlier masters. In 1881, he met James McNeill Whistler in Venice, where he painted this picture, probably in the fall of 1882. By the end of the nineteenth century, he had become the most celebrated international society portrait painter of his time, with a wealthy, aristocratic, and fashionable clientele; but he sought every chance he could to escape the constraints of formal portraiture for genre subjects.

Sargent does not paint the colorful, idealized views of scenes like the Piazza San Marco or the Grand Canal, commonly portrayed by many of his contemporaries, but captures a casual moment in one of the back streets of a working class district of Venice. Observed by two men standing near a doorway, a young woman hurries along, her expression preoccupied and aloof, her shawl drawn about her against the chill. The limited range of color, the deep perspective view of the narrow street, and the dark silhouettes of the men, one of whom glances at the woman, create a mood that is almost sinister, and certainly ambiguous. Who is this young woman? Who are the two men? Do they know her? We cannot be sure, but this mystery is one reason that Sargent's painting is so compelling and so memorable.

This painting is a gift of the Avalon Foundation to the National Gallery of Art, Washington, D.C.

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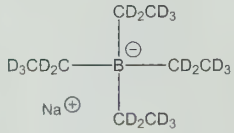
Clint Lane, President



Professor Janusz Pawliszyn of the University of Waterloo, Waterloo, Canada, kindly suggested that we make sodium tetraethylborate-d_{20}, which is used as a derivatization reagent for the determination of alkyllead and inorganic lead in aqueous samples. Dr. Pawliszyn's method can be adapted for field measurements, and has the potential of becoming a general method for the speciation of inorganic and organometallic compounds.

Yu, X.; Pawliszyn, J. *Anal. Chem.* **2000**, *72*, 1788.

49,504-2
Sodium tetraethylborate-d_{20},
98 atom % D

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Lab Notes

Effective Cooling System in Bulb-to-Bulb Distillation

Bulb-to-bulb distillation is a useful laboratory technique for the small-scale purification of liquid substances. In this microscale, short-path technique, a small quantity of material is redistilled using several glass bulbs connected in line. In some Kugelrohr models, heating is carried out by a built-in oven, and control of both temperature and stirring speed is performed by an integrated electronic controller. The flask containing the product to be distilled and the collecting bulbs are connected to a rotary device (**Figure 1**).

Traditionally, cooling of the collecting bulbs has been carried out with dry ice in acetone (-78°C), especially when working with low-boiling substances or when distilling under vacuum. This cooling technique has several drawbacks:

a) Acetone is usually applied by a piece of cotton held with tweezers and may accidentally drip on the Kugelrohr apparatus and attack the plastic cover. It may also drip inside the housing, through the control buttons, and damage the electronic circuit boards. Acetone can also dissolve the plastic parts of the front panel and lead to the fusion of the buttons to the housing.

b) Acetone, because of its low flash point (-18 °C), could ignite if it contacts the electrical system since the rotor can generate sparks.

c) From an operational point of view, the ground joints, which connect the glass bulbs, usually are not lubricated with vacuum grease to avoid contaminating the final distillate during its recovery. As a result, and even though the bulb-to-bulb seal is usually good, a reabsorption of acetone through the joints could happen principally when the distillation is carried out under vacuum. In this case, contamination of the distillate with acetone could become a problem, especially when dealing with low-boiling substances.

To avoid these problems, we have designed and used extensively a new, safe, and simple cooling system. In this system, the distillation bulbs are cooled with dry ice without the use of acetone. As containers of solid dry ice (coolers), we use cheap and readily available plastic or cardboard cylindrical tubs of 4 to 5 cm in diameter and 10 cm in length (**Figure 2a**).

To adapt the cylindrical container to the shape of the cooling bulb and to increase the cooling surface, it is recommended that two circular cuts be made on opposite sides of the bottom of the cylinder (**Figure 2b**).

Ángel M. Montaña, Ph.D., and **Pedro M. Grima**
Departamento de Química Orgánica, Universidad de Barcelona
Martí i Franquès 1-11, 08028-Barcelona, Spain
E-mail: ammontana@qo.ub.es

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? See the inside back cover for details.

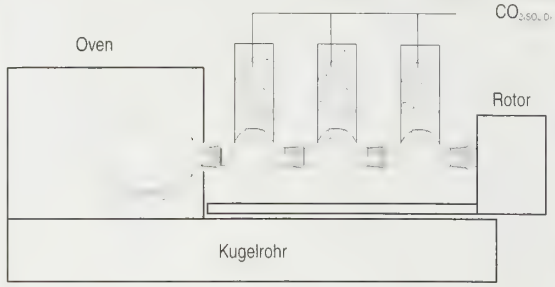


Figure 1: Bulb-to-bulb distillation apparatus with a cooling system of open cylinders filled with dry ice.

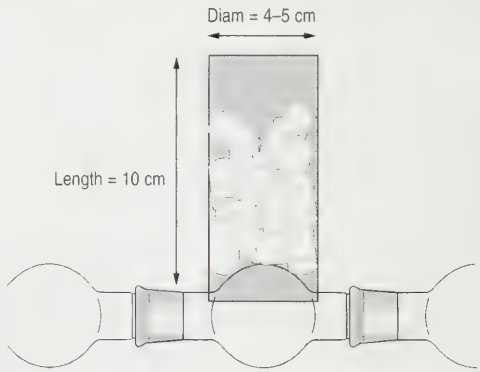


Figure 2(a): Detail of the cylindrical dry-ice container of the cooling system.

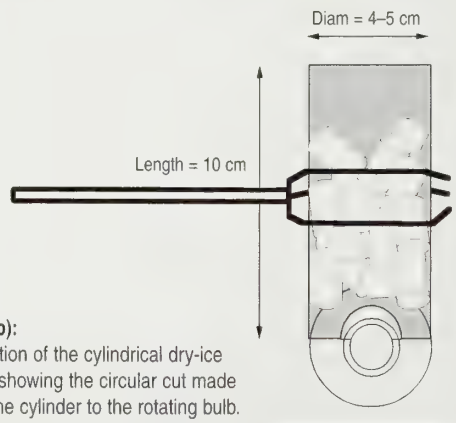


Figure 2(b):
Cross section of the cylindrical dry-ice container showing the circular cut made to adapt the cylinder to the rotating bulb.

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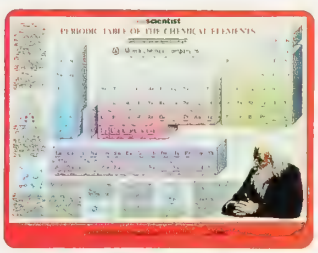

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53,182-0 ***N,N'*-Di-(*tert*-butoxycarbonyl)thiourea**, 97%

This diprotected thiourea is widely used in the synthesis of heterocycles, including a pentacyclic guanidine system as an intermediate to ptilomycalin A,[1] and, recently, in the preparation of *p*-*N,N'*-bis-Boc-guanidophenol, a key intermediate for the preparation of a series of aryl *o*-aroylbenzoates as serine protease inhibitors.[2]

(1) Nagasawa, K. et al. *Tetrahedron* **2000**, *56*, 187. (2) Jones, P.B.; Porter, N.A. *J. Am. Chem. Soc.* **1999**, *121*, 2753.

54,036-6 **1,1-Diethoxy-3-methyl-2-butene**, 97%

This acetal has been utilized in the synthesis of the related 1-alkoxy-3-phenylselenoalkenes and 3-phenylselenoalkanals,[1] and in the preparation of 2,2-dimethylchromenes from electron-deficient phenols.[2]

(1) Nishiyama, Y. et al. *Tetrahedron Lett.* **1998**, *39*, 8685 (2) North, J.T. et al. *J. Org. Chem.* **1995**, *60*, 3397.

16,345-7 **Dimethyl L-tartrate**, 99% (99+% ee/GLC)

Recent citations for this versatile chiral building block include the enantioselective synthesis of α-bromo carbonyl and carboxylic acid derivatives,[1] and the synthesis of enantiomerically pure spirane porphyrazines.[2]

(1) Boyes, S.A.; Hewson, A.T. *J. Chem. Soc., Perkin Trans.1* **2000**, 2759. (2) Hachiya, S.-i. et al. *Tetrahedron* **2000**, *56*, 6565.

46,944-0 **(*R*)-(+)-1-(*tert*-Butoxycarbonyl)-2-pyrrolidinemethanol**, 97%

This protected pyrrolidinemethanol was used in a recent study of 3-substituted indoles as potential antimigraine drugs.[1] It was also utilized in the preparation of a novel, potent, and selective 5-HT_1 antagonist via elongation of the side chain followed by transformation into the protected piperidinylethylpyrrolidine, subsequent deprotection and arylsulfonylation.[2]

(1) Sternfeld, F. et al. *J. Med. Chem.* **1999**, *42*, 677. (2) Lovell, P.J. et al. *ibid.* **2000**, *43*, 342.

53,673-3 **2-Fluoro-6-methoxybenzaldehyde**, 98%

On conversion to a dinitro ester, the aryl fluorine acts as a useful leaving group early in the synthesis of the macrolactam portion of the ansamycin antibiotic (+)-thiazinotrienomycin E.

Smith, A.B., III; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738.

54,331-4 **2-Fluoro-5-iodobenzaldehyde**, 97%

The related iodobenzo[b]thiophenecarboxylate ester has been synthesized in moderate yield from this dihalo aldehyde.

Bridges, A.J. et al. *Tetrahedron Lett.* **1992**, *33*, 7499.

54,540-1 **(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol**, 98%

54,897-9 **(1*S*,2*R*)-1-Phenyl-2-(1-pyrrolidinyl)-1-propanol**, 98%

These norephedrine derivatives are useful chiral mediators and have applications in the enantioselective addition of acetylides to carbonyl compounds. Examples include the synthesis of the HIV-1 reverse transcriptase inhibitor DMP 266[1] and the enantioselective addition of diethylzinc to aldehydes.[2]

(1) Pierce, M.E. et al. *J. Org. Chem.* **1998**, *63*, 8536. (2) Soai, K. et al. *ibid.* **1991**, *56*, 4264.

54,174-5 **Tri-*O*-acetyl-β-D-arabinosylbromide**, 95%

Among the many applications for this protected bromosugar, the solid-state reaction to make glycopyranosyl pyrimidine nucleosides,[1] the novel synthesis of thioglycosides,[2] and the high-yield preparation of pyranoid glycals[3] are some of the ones that have been cited.

(1) Im, J. et al. *Tetrahedron Lett.* **1997**, *38*, 451. (2) Pakulski, Z. et al. *Tetrahedron* **1994**, *50*, 2975. (3) Kovács, G. et al. *ibid.* **1999**, *55*, 5253.

52,869-2 **2-(6-Bromohexyloxy)tetrahydro-2*H*-pyran**, 97%

This THP-protected bromoalcohol is an important building block used in the synthesis of alkaloids,[1] symmetrical olefins,[2] and 14-membered macrocyclic ethers.[3]

(1) Kaiser, A. et al. *J. Org. Chem.* **1999**, *64*, 3778. (2) Poulain, S. et al. *Tetrahedron Lett.* **1996**, *37*, 7703. (3) Clyne, D.S.; Weiler, L. *Tetrahedron* **1999**, *55*, 13659.

51,587-6 **Imidazole, trifluoromethanesulfonate salt**, 97%

This triflate has been used as a coupling agent for oligonucleotide synthesis[1] and as a reagent for the synthesis of aryl triflates.[2]

(1) Hayakawa, Y.; Kataoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12395. (2) Effenberger, F.; Mack, K.E. *Tetrahedron Lett.* **1970**, 3947.

54,039-0 **(3,4-Dihydro-1-naphthyloxy)trimethylsilane**, 97%

The titanium tetrachloride promoted reaction of this trimethylsilyl enol ether with ethylene oxide affords the homoaldol-type product in moderate yield.[1] In other studies, C_2-symmetric copper complexes have been shown to catalyze the enantioselective amination of,[2] or ketomalonate addition to,[3] this enol silane.

(1) Lalic, G. et al. *Tetrahedron Lett.* **2000**, *41*, 763. (2) Evans, D.A.; Johnson, D.S. *Org. Lett.* **1999**, *1*, 595. (3) Reichel, F. et al. *J. Chem. Soc., Chem. Commun.* **1999**, 1505

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About Our Cover

Edgar Degas's *Ballet Scene* (pastel on cardboard, 30¼ in. x 43¾ in.) was executed ca. 1907 when the artist was in his seventies, and not long before his career was cut short by his growing blindness. The subject of the picture is one indelibly identified with Degas who, unlike his impressionist friends, more often chose to represent urban scenes than the country landscapes they preferred. Life in the cafés, at the racetrack, in the theatre, at the opera, and in particular at the ballet, was what most attracted him.

However, it was not the glamour, the drama, and the sumptuous spectacle of a ballet performance that interested him, but the behind-the-scenes work that goes on before the dancers go on stage. His goal was to distill from the constantly changing movements and postures of the dancers a single moment which would capture the essence of motion, and it was the exercises, the rehearsals, the minutes before a performance that gave him the opportunity to do this.

This goes some way towards explaining the medium he used for this work, which is not an oil painting on canvas but a picture executed in pastel chalks, a dry medium similar to the charcoal he often used to sketch quickly the varied life of the city of Paris all around him. Through his depiction of varied postures and gestures, Degas leads the eye along a curving line from the lower right corner of the picture to the left, contrasting the more static attitudes of the three figures in the right foreground with the animated movements of the dancers further back on the left, to capture in an essentially motionless work of art a sense of the dynamic actions of a group of dancers at work.

This painting is in the Chester Dale Collection at the National Gallery of Art, Washington, D.C.

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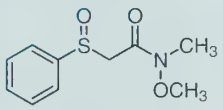


Professor Ahcène Boumendjel of the Université Joseph Fourier (La Tronche, France) kindly suggested that we make *N*-methoxy-*N*-methyl-2-(phenylsulfinyl)-acetamide.[1] This amide is useful for the homologation of alkyl halides to α,β-unsaturated *N*-methoxy-*N*-methyl-amides, which are valuable intermediates in the synthesis of natural products and therapeutics.[2]

(1) Beney, C.; Boumendjel, A.; Mariotte, A.-M. *Tetrahedron Lett.* **1998**, *39*, 5779. (2) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.

51,139-0
***N*-Methoxy-*N*-methyl-2-(phenylsulfinyl)acetamide**, 96%

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Lab Notes

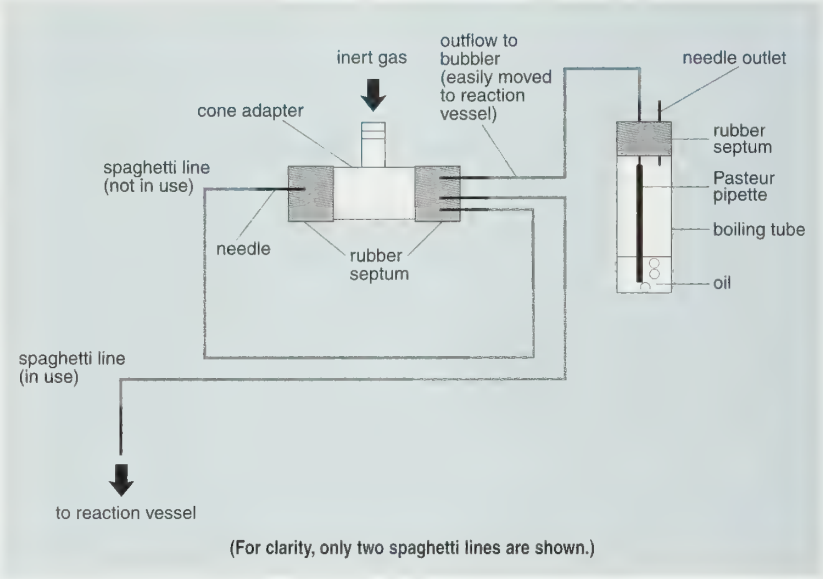
Inexpensive and Easily Constructed Space-Saving "Spaghetti Tubing Apparatus" for Creating Inert Atmospheres within a Large Number of Reaction Vessels

I read a recent Lab Notes article,[1] which prompted me to share another innovative method for creating and maintaining inert atmospheres within a large number of reaction vessels or reagent bottles. The setup is easily constructed from inexpensive equipment generally found in a laboratory, and occupies less space than a conventional manifold line.

The system has been used in our laboratories for several years with great success, supplying inert atmospheres to multiple reactions and easily coping with the higher pressures required for cannulation. Based on the "spaghetti tubing" manifold described by Casey et al.,[2] this apparatus consists of a single source of inert gas connected to the side-arm of a B29/32 cone adapter, which has been fitted at each end with rubber septa. The single source of inert gas is split into multiple supplies (comfortably up to six) by needle-tipped, 3-mm (o.d.) spaghetti lines piercing the septa. A positive pressure of inert gas in the apparatus is maintained by means of an outflow passing through a bubbler assembled from a boiling tube, an inverted Pasteur pipette, a needle and a rubber septum. The various outflow supply lines are easily moved to individual reaction vessels allowing each reaction to be individually purged with inert gas.

The present trend toward the efficient synthesis of compounds via parallel synthesis should make this apparatus invaluable for the pharmaceutical chemist. In addition, its cost effectiveness and small size make it ideal for university chemistry departments, where restricted space within fume cupboards and tight budgetary constraints may exist.

References: (1) Flemer, S., Jr. *Aldrichimica Acta* **1998**, *31*, 34. (2) Casey, M.; Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*; Blackie & Son: London, UK, 1990; pp 108-109.



(For clarity, only two spaghetti lines are shown.)

Materials for Constructing the Spaghetti Line and Bubbler:

- B29/32 socket/cone adapter with "T" connection (equivalent to Aldrich cat. no. **Z41,580-4**) (fitted with detachable plastic connector for easy coupling of tubing)
- Suba•Seal® No. 45 (Aldrich cat. no. **Z16,732-0**)
- Suba•Seal® No. 57 (Aldrich cat. no. **Z16,735-5**)
- Silicone tubing (Versilic) (o.d. 3 mm; bore x wall, 1x1 mm)
- Pasteur pipette (9.0 in. long) (Aldrich cat. no. **Z19,061-6**)
- Disposable needles (16 ga. x 1 in.). Using grips to hold the metal needle, pliers are used to remove the purple plastic sheath. The blunt end of the needle is then pushed into the spaghetti tubing) (Aldrich cat. no. **Z19,256-2**).

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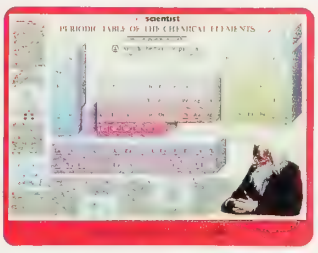

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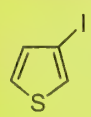
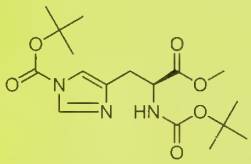


Has been used recently in the stereoselective synthesis of (*E*)-(3-thienyl)vinylgermanes via a Stille coupling reaction,[1] and in the preparation and study of 3-(diacetoxyiodo)thiophene.[2]

(1) David-Quillot, F. et al. *Tetrahedron Lett.* **2000,** *41,* 9981. (2) Togo, H. et al. *J. Org. Chem.* **2000,** *65,* 8391.

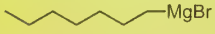
55,075-2 Nα,*N*-(im)-Di-Boc-L-histidine methyl ester, 97%
1g $14.00; 5g $49.60



Was employed in the preparation of the corresponding imidazole-2-thione during the development of the first synthesis of L-(+)-ergothioneine.

Xu, J.; Yadan, J.C. *J. Org. Chem.* **1995,** *60,* 6296.

55,065-5 Heptylmagnesium bromide, 1.0*M* solution in diethyl ether
100mL $115.20; 1L $640.00



In situ generation of the corresponding organozinc compound was a key step in the recent use of this Grignard reagent in the stereoselective synthesis of protected alkylhydroxypyrrolidinones.[1] In another report, this reagent was used in the enantioselective opening of an epoxide en route to (*S*)-(+)-8-hydroxyhexadecanoic acid.[2]

(1) Huang, P.Q. et al. *Synth. Commun.* **2000,** *30,* 2259. (2) Shimojo, M. et al. *Tetrahedron* **2000,** *56,* 9281.

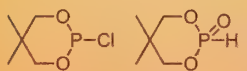
54,330-6 2,7-Di-*tert*-butylfluorene, 98% **25g $131.00**

Two recent examples of the use of this building block include the preparation of new group 4 metal complexes containing aminofluorenyl ligands,[1] and a novel, soluble analog of the Fmoc group.[2]

(1) Miller, S.A.; Bercaw, J.E. *Organometallics* **2000,** *19,* 5608. (2) Stigers, K.D. et al. *J. Org. Chem.* **2000,** *65,* 3858.

54,151-6 2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane, 97%
25g $74.00

54,152-4 5,5-Dimethyl-1,3,2-dioxaphosphorinan-2-one, 96%
1g $9.10; 5g $30.30

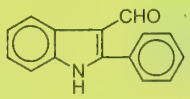


54,151-6 **54,152-4**

Reaction of the chlorophosphorinane with Cp_2NbH_3 proceeds via a carbene-like insertion mechanism to give a derived cationic diphosphite complex in high yield.[1] Other workers have prepared tungsten (*Z*)-1,2-diphosphite–alkene tetracarbonyl and (*E*)-vinyl–phosphite pentacarbonyl complexes from this reagent via phosphite Fischer carbene complexes.[2]

(1) Nikonov, G.I. et al. *J. Organomet. Chem.* **1997,** *547,* 183. (2) Barluenga, J. et al. *Organometallics* **1997,** *16,* 3732.

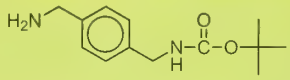
54,332-2 2-Phenylindole-3-carboxaldehyde, 97%
1g $14.60; 5g $48.50



Has been employed in a study of the inhibition of tubulin polymerization and the growth of breast cancer cells.

Gastpar, R. et al. *J. Med. Chem.* **1998,** *41,* 4965.

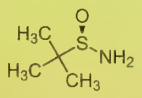
53,944-9 1-(*N*-Boc-aminomethyl)-4-(aminomethyl)benzene, 97%
1g $31.50; 5g $105.10



Has been utilized for the solid- and solution-phase syntheses of oligomeric thioureas,[1] the preparation of a bipyrrole-based [2]catenane,[2] and, very recently, for the synthesis of model receptors for dicarboxylates and monosaccharides.[3]

(1) Smith, J. et al. *J. Org. Chem.* **1996,** *61,* 8811. (2) Andrievsky, A. et al. *J. Am. Chem. Soc.* **1998,** *120,* 9712. (3) Benito, J.M. et al. *J. Org. Chem.* **2001,** *66,* 1366.

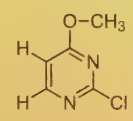
49,740-1 (*R*)-(+)-2-Methyl-2-propanesulfinamide, 98%
1g $123.35



Developed by Ellman, this chiral sulfinamide has found widespread use in diastereoselective enolate alkylations,[1] the synthesis of protected chiral amines,[2] the Strecker synthesis of α-alkyl α-amino acids,[3] and the preparation of novel ligands for asymmetric Lewis acid catalysis.[4]

(1) Backes, B.J. et al. *J. Org. Chem.* **1999,** *64,* 5472. (2) Borg, G. et al. *Tetrahedron Lett.* **1999,** *40,* 6709. (3) Davis, F.A. et al. *J. Org. Chem.* **2000,** *65,* 8704. (4) Owens, T.D. et al. *J. Am. Chem. Soc.* **2001,** *123,* 1539.

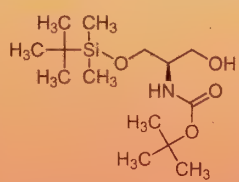
53,645-8 2-Chloro-4-methoxypyrimidine, 98%
1g $24.85; 5g $82.80



The introduction of the 2-pyrimidinyl functionality, in the synthesis of methylene phosphonate analogs of thymidine 3′-phosphate, was achieved via a nucleophilic substitution reaction by an intermediate thioglycoside on this chloropyrimidine.[1] A number of related pyrazolylpyrimidines were prepared for study as potential cytoprotective antiulcer agents.[2]

(1) Yokomatsu, T. et al. *Heterocycles* **1999,** *50,* 21. (2) Ikeda, M. et al. *Chem. Pharm. Bull.* **1996,** *44,* 1700.

52,007-1 (*R*)-(+)-*N*-(Boc)-*O*-(TBDMS)serinol, 97%
1g $32.40; 5g $108.00



The TEMPO oxidation of this protected serinol yields the α-amino aldehyde in good yield and without racemization.[1] This amino alcohol has also been employed in the diastereoselective synthesis of 1,2-diamines.[2]

(1) Jurczak, J. et al. *Tetrahedron* **1998,** *54,* 6051. (2) Gonda, J. et al. *Synthesis* **1993,** 729.

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Aldrichimica ACTA

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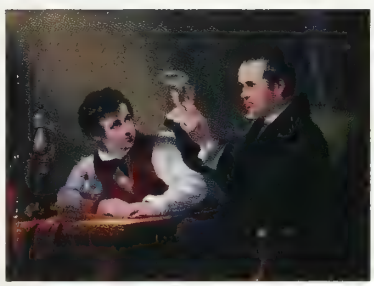

Paintings of all kinds have graced the covers of our *Aldrichimica Acta* over the years. Most were old masters, a few (like the one on the cover of Vol. 1, No. 1) were alchemical, and a few others were modern. Perhaps, none has a more direct connection to chemistry than the one reproduced on the cover of this issue. It (oil on canvas, 40 in. x 50 in.) was painted by Thomas Phillips in London in 1816, and depicts a 24-year-old Michael Faraday watching his teacher, Professor W. T. Brande, make **Prussian Blue**. At the time, Faraday was not yet the great chemist and physicist he later became—arguably the ablest British scientist of the 19th century.

What a fitting cover for the *Acta* issue celebrating Aldrich's 50th birthday!

The interested reader can learn more about this painting in: (a) Bader, A. End of the Mystery. *Chem. Br.*, July 2001, in press. (b) Bader, A. Out of the Blue. *Chem. Br.*, November 1997, p 24.

This painting is in the collection of Alfred Bader Fine Arts, Milwaukee, WI.

Full-color reproductions (11 in. x 14 in.) of this painting are available for a nominal fee to cover postage and handling. Please call 800-558-9160 (USA) and specify the Prussian Blue painting (Z52,866-8) from the cover of Aldrichimica Acta, *Volume 34, Number 2.*

Table of Contents

Lab Notes

1-Chlorobutane—A Useful Solvent for Recrystallizations

When carrying out a recrystallization, there are sometimes problems with the choice of solvent and recourse is made to mixed solvents. Of these, the combination ethyl acetate–petroleum ether is perhaps the most common pairing. Usually, one obtains a hot solution by addition of the more polar solvent to a hot suspension of the would-be solute in the less polar solvent. However, on cooling there is frequently development of two phases followed by precipitation of the solute as a solid mass rather than as crystals of good texture.

After some experiences as outlined above, we sought an alternative approach. What we were seeking was a solvent of low but definite polarity, with a convenient boiling point. We chose 1-chlorobutane, bp 77–78 °C, and we have found this to be a convenient solvent for the recrystallization of oxime ethers;[1] nitrogen ylides, such as $Me_3N^+–N^-–CN$ (with no butylation of the ylide);[2] and 3-pyrrolylpentanoic acid.[3] In unpublished work, we have used 1-chlorobutane to advantage in the recrystallization of the nitrogen ylide $Me_3N^+–N^-–C(=O)Me$ (again without butylation), and the bicyclic compounds 1-nitrocamphene and camphor-4-carboxylic acid.

Although the bulk dielectric constant does not tell the whole story about a solvent, 1-chlorobutane, interestingly, has a higher dielectric constant (7.28) than ethyl acetate (6.08); that of *n*-hexane is 1.89.[4] Specific solute–solvent interactions also need to be taken into account.

We recommend that 1-chlorobutane be considered as a solvent for recrystallization in appropriate cases subject to a couple of caveats: (a) manipulations with the solvent be carried out in a fume cupboard, and (b) one is mindful that 1-chlorobutane may be attacked by nucleophiles, though its reactivity is, at best, sluggish.

For recrystallizations that require a higher temperature, 1-chloropentane is worth consideration.

References: (1) Bradley, G. W.; Morris, D. G. *J. Chem. Res. (S)* **1993**, 220. (2) Chardin, A.; Berthelot, M.; Laurence, C.; Morris, D. G. *J. Phys. Org. Chem.* **1995**, *8*, 626. (3) Ryder, K. S.; Morris, D. G.; Cooper, J. M. *Langmuir* **1996**, *12*, 5681. (4) *CRC Handbook of Chemistry and Physics*, 79th ed.; Lide, D. R., Ed.; CRC Press LLC: Boca Raton, FL, 1998–1999; Section 6, pp 139–161.

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Making Optimal Use of Peristaltic Pumps

Laboratories involved in process development (e.g., fermentation research) frequently need to pump liquids at constant rates for specified periods of time. These liquids may be culture media, acids, alkalis, or special feed supplements. Peristaltic pumping is the chief means by which this is achieved. However, it may occasionally happen that the rate at which a liquid needs to be delivered is much lower than what can be achieved with the available pump head and tubing. This is especially the case if the pump head cannot accommodate tubings of different diameters. One simple and inexpensive solution is to pass a tubing of a smaller diameter through a short length of the pump head tubing and fix this tube-in-a-tube arrangement into the pump head. The pressure that is applied to the outer tubing by the pump rollers is transferred to the outer walls of the inner tubing, facilitating peristaltic action. Sometimes, the inner tubing may slip out of the pump head tubing when the pump is operating. To prevent this, the inner tubing may be fastened to physical supports using rubber bands or pieces of string near the two points where it emerges from the pump head.

If it is found difficult to pass the thinner tubing through the pump head tubing, smearing its outer walls with a lubricant (an oil, for instance) may help. Furthermore, the thinner tubing may be easily passed through the thicker one if twisting motions are used. If suction of liquid does not occur, a slight adjustment of the gap between the rollers and the wall of the pump head may be required.

We have successfully used this arrangement in our laboratory. It does not appear to have any drawbacks, either with regard to the pump or the tubing. In fact, it has a distinct advantage: the wear on the inner tubing is reduced, since it is shielded by the thicker pump head tubing.

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Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? See the inside back cover for details.

A Half Century of Chemists Helping Chemists

Aldrich from 1951 to 2001

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E-mail: sfirsan@sial.com

Outline

1. Introduction

This August, Aldrich Chemical Company turns fifty. What a remarkable fifty-year period this has been! While it is today a "household" name among chemical scientists and practitioners worldwide, it is hard to imagine that Aldrich is only a half century old. On the following pages, I will take a brief look back at the past fifty years. While the story of Aldrich has been told and retold in one form or another many times,[1,2,3] it is my sincere hope that the fresh approach I am using will prove to be of most interest to our *Aldrichimica Acta* readers. This approach traces the development of Aldrich through the key chemical products and business ventures that played a crucial role in the uninterrupted success that the company has enjoyed over the past fifty years. Since the success of any great enterprise is dependent immensely on the contributions of a legion of dedicated individuals who believe in its mission, the roles that key people played in the development of Aldrich will also be highlighted.[4]

2. What's in a Name?

2.1. Alfred R. Bader

Alfred Robert Bader, a young Austrian immigrant and a chemistry graduate student at Harvard University, first entertained the idea of starting a company to sell research chemicals in 1949—on the suggestion of Warren Stockwood, the storeroom supervisor at Harvard's Department of Chemistry[5]—after being disappointed with the service he received from the leading supplier of research chemicals at the time. Acting on the premise that chemists needed a wider array of research chemicals and better service, he and Jack Nathan Eisendrath, a Milwaukee attorney, founded Aldrich Chemical Company, Inc. on August 17, 1951. Jack became the company's first president.[6] In a curious twist of fate, the company was named following a coin toss, not after either of the founders, but after Eisendrath's fiancée, Bettie Mae Aldrich.[7] Had Bader won the coin toss, the company would have been named Daniels Chemical Company, after Helen Ann Daniels, Bader's fiancée and future wife.[2]

2.2. Aldrich Chemical Company, Inc.

In 1951, the company operated first from Eisendrath's office on 161 W. Wisconsin Avenue and, later that year, from a rented garage located on N. Farwell Avenue in Milwaukee's East Side. It had three part-time employees: Alfred, Jack, and Lorraine Worby (née Neau). Lorraine first worked for Aldrich part-time, 4–5 hours on Wednesday nights, then became the first full-time Aldrich employee in August of 1954.[8] From 1951 to 1954, Alfred sowed the seeds of what later became very important collaborations and acquisitions through visits to small chemical producers in Continental Europe and the United Kingdom. Noteworthy are two visits in 1952 to Fluka AG Chemische Fabrik in St. Gallen, Switzerland, and Heidenheimer Chemisches Laboratorium (HCL) in Heidenheim, Germany. These two companies as well as many others served as

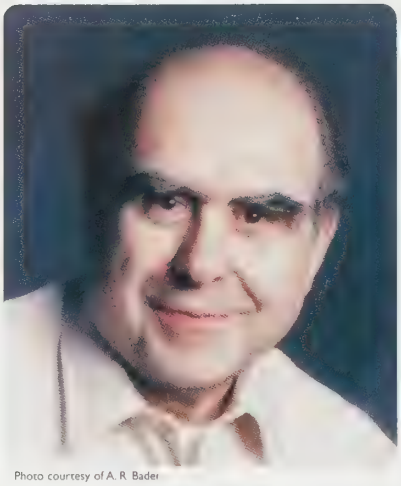


Photo courtesy of A. R. Bader

Alfred R. Bader, cofounder of Aldrich (mid-1980s).

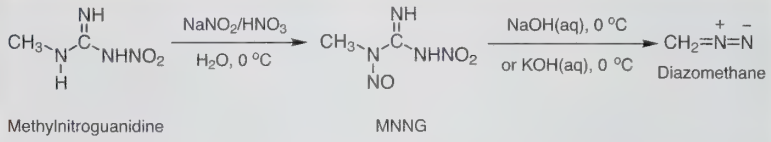
Photo courtesy of Bette Aldrich Eisendrath

Jack N. Eisendrath, cofounder and first president of Aldrich (1951).

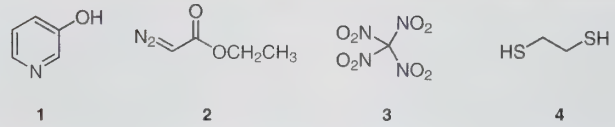
Table 1. Aldrich's Vital Statistics for the First Four Years

Year	Sales	Products Offered	Catalog Number	Catalog Pages	Employees[a]
1951	$1,705	1	1	1	Alfred, Jack, Lorraine
1952	$5,400	12	2	1	Alfred, Jack, Lorraine
1953	$15,000	>100	3 & 4[b]	4	Alfred, Jack, Lorraine
1954	$45,000	>1,200	5	32	Alfred, Jack, Lorraine, Anthony

[a] All part-time employees except for Anthony D. Kontowicz. In August 1954, Alfred and Lorraine became full-time employees; Lorraine was the first non-owner employee. [b] Two catalogs were produced for 1953, one came out in October 1952 (No. 3) and the other in May 1953 (No. 4). Each consisted of 4 pages and listed over 100 products. Sources: references 1 and 8 and company catalogs.



Scheme 1. Preparation of MNNG and Generation of Diazomethane.



1 **2** **3** **4**

Figure 1. Some of the Interesting Products Offered in the Early Fifties.

important suppliers to Aldrich in this period and for years thereafter. **Table 1** summarizes the fledgling company's vital statistics for this period.

2.3. MNNG and Other Products

Aldrich offered 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) as its first product. MNNG is a convenient, small-scale precursor to diazomethane, a widely used methylating reagent (**Scheme 1**).[9,10] Perhaps foretelling of the vital role that suppliers would subsequently play in helping Aldrich grow and prosper, Aldrich did not at the time produce MNNG but sourced it from two companies, one in Milwaukee and the other in Canada.

Some of the other interesting products offered in the early fifties include 3-hydroxypyridine (**1**), which later became one of the company's best-selling products; ethyl diazoacetate (**2**); tetranitromethane (**3**); and ethanedithiol (**4**) (**Figure 1**). The addition of new products was guided by the beliefs that production should be combined with resale and that the company should not offer products that were also sold by its main competitor, Eastman Kodak's Fine Chemicals Division, which dominated the fine chemicals market at that time. In addition, Aldrich recognized very early on the vital role of suppliers in its growth and worked diligently to establish mutually beneficial relationships with them. Suppliers continue to be important to the growth of the company to the present day.

3. Critical Years: 1954 and 1955

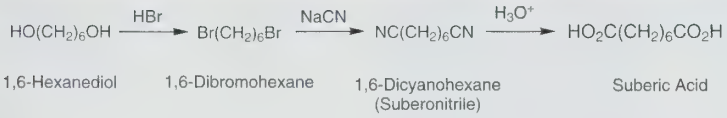
3.1. A Crucial Decision

First, Alfred Bader elected not to relocate to the Pittsburgh area, where The Pittsburgh Plate Glass Co. (PPG), his employer at the time, was relocating the research laboratories of its Milwaukee paint division. Alfred had been working for PPG-Milwaukee since January 1950. Instead, he left PPG in August 1954 to dedicate his time and energy fully to the fledgling company, which he had cofounded only three years earlier. He also became convinced that products should not only be sourced but also sold overseas, e.g., in Western Europe, in spite of the potential stiff competition from well-established fine chemicals companies. This conviction would later have important consequences for the future of Aldrich.

Second, William Kesselman, a Milwaukee businessman, bought one-third of Aldrich for $25,000, but bowed out seven months later, with the company owing him $12,000.[11] In August 1954, after Kesselman bought into the company, Aldrich moved out of the N. Farwell Avenue garage into a 1,000-sq ft, rented laboratory at 3747 N. Booth Street, one block south of Capitol Drive, still in Milwaukee.

Third, Aldrich hired a second full-time employee, Anthony D. Kontowicz, a former laboratory technician at PPG. Anthony was thus the first full-time laboratory technician hired; however, he worked at Aldrich for only a short period of time (ca. 1 year).[8a,12,13]

1955 was no less critical for Aldrich. The Eisendraths sold their 50% stake in the company for $15,000.[14,15,16] Alfred and Helen Bader became the sole and equal owners of the company,[17] and Alfred became the second president of Aldrich in May 1955.[18] In August 1955, Alfred met Marvin E. Klitsner, a Milwaukee attorney, at a religious retreat.



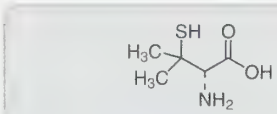
Scheme 2. Large-Scale Preparation of Suberic Acid.

Later on, Marvin was instrumental in guiding the growth of Aldrich, both as legal counsel and director of Aldrich and of Sigma-Aldrich. As Alfred put it, Marvin "was the moving spirit in the growth of Aldrich".[19] Marvin also played a key role in the negotiations leading up to the merger of Aldrich Chemical Company, Inc. and Sigma International, Ltd. in 1975; but more on that later! Beginning in January 1955, Helen Bader, Alfred's wife since July 1952, began working full-time for Aldrich.[20,21] On September 01, 1955, George Skeff, also a former PPG laboratory technician, was hired as a full-time laboratory technician, following the departure of Anthony D. Kontowicz. George retired from Aldrich on April 14, 1989, after close to 34 years of employment!

3.2. *Suberic Acid and D-Penicillamine*

More importantly, Aldrich delivered its first bulk order, 500 lb of suberic acid, to Du Pont toward the end of 1955 (**Scheme 2**).[3a]

Furthermore, one of the important products that Aldrich began to offer that same year was D-penicillamine or 3-mercapto-D-valine (**5**), an antirheumatic α-amino acid and, at the time, a promising orphan drug, which chelates and removes the copper accumulated in the liver of patients suffering from the rare disorder known as Wilson's Disease.[22]



D-Penicillamine (**5**)

4. The Remainder of the 1950s

4.1. *Rapid Growth*

The remainder of the 1950s was characterized by rapid growth in sales and the number of products offered. This growth in sales led to the expansion of the physical facilities and the hiring of additional staff. In February 1956, Beverly Horick, the fourth non-owner employee, was hired on a part-time basis.[23] The next employee hired was Stella Ward. By 1958, Aldrich had about a dozen employees. In the same year, Aldrich purchased and moved to a three-story, 27,000-sq ft building at 2369 N. 29th Street in Milwaukee's inner city. Two years later (1960), a larger, 70,000-sq ft building was purchased nearby at 2371 N. 30th Street. The 29th Street building housed the R&D and Production departments, while the 30th Street building had administrative offices and the QC, Packaging, and Warehousing departments.[24] The 29th and 30th Street buildings remained Aldrich's headquarters until 1969, when they were condemned by the Milwaukee County Expressway and Transportation Commission in preparation for building the east–west Park Freeway (which was never built). In 1969, Aldrich relocated to 940 W. St. Paul Avenue into an eight-story building that previously belonged to General Electric Company.[25]

The 7th edition of the Aldrich catalog (December 1955) and its supplements featured over 1,600 products.[26] Some of the products offered in the late fifties became success stories. Among the most interesting ones are dicyclohexylcarbodiimide (DCC, **6**), a useful reagent in peptide coupling reactions; *p*-tolylsulfonylmethylnitrosamide (Diazald®, **7**), a diazomethane precursor that is safer than MNNG; and *p*-phenylazomaleinanil (**8**), a reagent employed for the characterization of conjugated dienes (**Figure 2**). Other interesting products from this period include lithium borohydride ($LiBH_4$), sodium tetraphenyl boron ($NaBPh_4$), diketene ($C_4H_4O_2$), and triallylamine ($C_9H_{15}N$).

The births of several important company entities, as well as other significant developments, also took place in the late fifties.

4.2. *The Rare Chemical Library*

The Rare Chemical Library (RCL) grew out of the collecting and salvaging of valuable research samples of retiring or deceased academic researchers and from other sources. While the RCL was initially part of a separate company, the Alfred Bader Chemical Corporation, it was sold to Aldrich Chemical Co. on December 20, 1965, just prior to a public offering of 100,000 Aldrich shares.[2] Over the years, large-scale contributions of samples to the library came from, among others, the personal collection of Joe Karabinos (who founded Carbolabs,

Photo courtesy of the Helen Bader Foundation

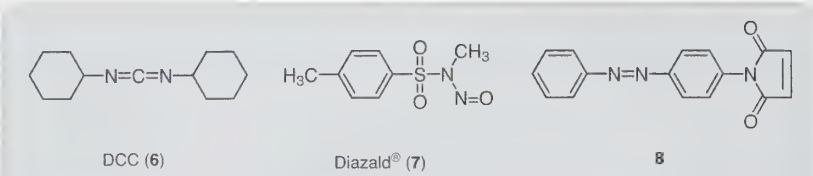
Helen A. Bader (née Daniels), 1982.

Photo courtesy of Bettie Aldrich Eisendrath

Bettie Aldrich Eisendrath (née Aldrich), 1951.

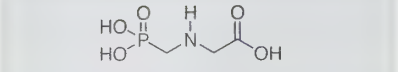
Photo courtesy of A.R. Bader

Left to right: Lorraine, George, Stella, and Beverly—1st, 3rd, 5th, and 4th Aldrich employee, respectively (1978).



DCC (**6**) Diazald® (**7**) **8**

Figure 2. Best-Selling Products from the Period 1955–1959.



N-(Phosphonomethyl)glycine
(*Active Ingredient in Roundup®*)

Sigma-Aldrich facility in Gillingham, Dorset, United Kingdom.

Sigma-Aldrich facility in Steinheim am Albuch, Germany.

Inc.) and from the laboratories of such chemical luminaries as Henry Gilman, George Wittig, Robert Woodward, and Louis and Mary Fieser. The RCL currently boasts over 90,000 listings of hard-to-find chemicals. Over the years, the RCL has been invaluable to researchers in the chemical sciences and has led to the discovery and commercialization, by others, of some very valuable chemical commodities, e.g., Roundup® (Monsanto Co.), based on lead compounds obtained from the RCL.

4.3. Aldrich Chemical Co Ltd

In 1959, Aldrich's British subsidiary formally began as Ralph N. Emanuel, Ltd., and was equally owned by the Emanuel and Bader families. It had less than $1,000 in sales in its first year,[28] but sales grew briskly leading to a rapid expansion of the physical facilities and the number of employees. Between 1969 and 1973, Aldrich began gradually acquiring Ralph N. Emanuel, Ltd., and turning it into a wholly owned subsidiary. It was then renamed Aldrich Chemical Co. Ltd. Ralph Emanuel became an Aldrich and, afterwards, a Sigma-Aldrich director. Business growth led to the company moving to the current site in Gillingham, Dorset, U.K., where a distribution center and a new cGMP manufacturing facility are presently located. In 1986, Sigma-Aldrich purchased Bristol Organics, a small manufacturer and long-time Aldrich supplier of fluoro-aromatics, and shortly thereafter integrated its operations with those of the larger British subsidiary. Three years after the acquisition of Fluka Chemie by Sigma-Aldrich Corp., the operation of Fluka's subsidiary in Glossop, Derbyshire, was transferred to the Gillingham facility in September 1992. The British subsidiary has a special significance to the corporation, not only because it has become Britain's largest supplier of research chemicals, but also because it has been a source of a number of individuals in corporate leadership positions. Moreover, success of the British subsidiary encouraged the company to open other branches in Continental Europe, where strong competition from well-established fine chemicals companies had been a concern.

4.4. Aldrich Chemie KG

The story of Aldrich's subsidiary in Germany is somewhat different. It starts out with Heidenheimer Chemisches Laboratorium (HCL) in Heidenheim, Germany, acting as Aldrich's best supplier for most of the 50s. HCL was then operated by Dr. Ernst Reif, a chemist, and Gerhard Keppler, a businessman. Following, an industrial accident at HCL and a legal setback for the company, Aldrich became involved in the restructuring and refinancing of its operations. It was renamed EGA-Chemie KG[29] and moved to Steinheim am Albuch—with Aldrich owning about 80% of it. Later (1971),[30] Aldrich bought the remaining 20% of EGA and renamed it Aldrich-Chemie GmbH & Co. KG. Like its British counterpart, the German subsidiary has been a tremendous success story, and has grown steadily in capabilities, personnel, and facilities. It now manufactures a range of products [e.g., 2,4-dimethylbenzaldehyde (**9**), 6-hydroxydihydrotheaspirane (**10**), and 6-acetoxydihydrotheaspirane (**11**)—all three are important flavoring raw materials for the food industry (**Figure 3**).] and serves a corporate warehousing function for all markets in Continental Europe from warehouses in three German towns: Schnelldorf, Steinheim, and Seelze. In 1975, it started producing a full German language edition of the Aldrich catalog concurrently with the English language editions. Two decades later, the activities of all Sigma-Aldrich brands in Germany were combined in one legal entity, Sigma-Aldrich Chemie GmbH, in order to streamline their operations. Perhaps one name stands out more than any other and is credited for most of the early success of Aldrich Chemie—that of Dr. Alfred Griesinger. Dr. Griesinger joined the company in March 1963, owned an interest in EGA-Chemie (1965–1970), and served in various important capacities. He later became a director of Aldrich-Chemie KG, and remained with the company until his untimely death in August 1997.[31]

4.5. Custom Synthesis

The late fifties and early sixties also witnessed the growing importance of custom synthesis and bulk sales. In these early days, custom synthesis was formally one of the business activities of the separate corporation, Alfred Bader Chemical Corp., which was sold to Aldrich on December 20, 1965.[27] Over the years, custom synthesis became an important function within the Aldrich Production department, and, together with bulk sales, evolved into Sigma-Aldrich Fine Chemicals (SAFC), currently one of four strategic business units within Sigma-Aldrich Corporation. SAFC concentrates on worldwide large-scale manufacturing and sales. Past and present custom synthesis customers are some of the best-known chemical and pharmaceutical companies in the world. Perhaps some of the more interesting custom synthesis projects that Aldrich worked on in the sixties involved the preparation of *tert*-butoxycarbonyl azide (**12**), BSA (**13**), and acryloyl chloride (**14**).[32] Some of the hard-to-find products offered in bulk (100–1,000 lb) in the late fifties included several dimethylphenols (**15**),

trimethylphenols (**16**), 2-methylresorcinol (**17**), and dihydroxybenzoic acids (**18**) (**Figure 4**). Along with the R&D group, the custom synthesis team routinely carries out significant process improvement and scale-up projects as well as the manufacture of newly introduced products.

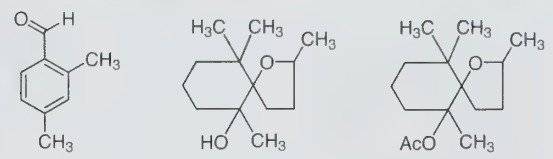
5. The 1960s: A Decade of Transformation

Firstly, Aldrich went from being a privately owned company to being a publicly traded one. Secondly, the growth in sales began to occur, not only as a result of the addition of new products, but also as a result of joint ventures and acquisitions. Finally, important developments took place within the company, such as the birth of this magazine (1967) and the transformation of the Aldrich catalog from a simple list of products and prices into a "handbook", as a consequence of the inclusion of useful factual information about the compounds being offered.

5.1. Early to Mid-1960s

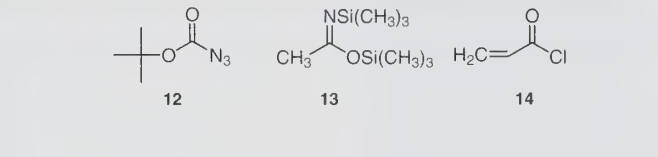
1962 was, in many respects, a watershed year for the young company. Annual sales reached the $1 million mark for the first time, and the Aldrich catalog grew to 303 pages, as the number of products offered swelled to 10,000. Aldrich became Janssen Pharmaceutica's sales agent in the US, and started ALFA Inorganics, a joint venture with Metal Hydrides, Inc. Dr. John Biel joined the company as Director of Research, replacing Edmund (Pete) J. Eisenbraun, Harvey B. Hopps was hired as an R&D group leader, and Bernard (Bernie) E. Edelstein joined as a chemist. Bernie went on to become one of the company's directors, its secretary, and then its first Executive Vice President (1974). In 1962, William Buth was Aldrich's General Manager; he later became the first Aldrich Vice President. In the same year (1962), J. T. Baker Chemical Co. attempted to buy Aldrich for $1.5 million, but was rebuffed.[33]

In the mid-sixties, the prior practice of listing only products that were not offered by Eastman Kodak's Fine Chemicals division was abandoned in favor of listing products based on their usefulness and marketability. An interesting offering from this period is 9-amino-1,2,3,4-tetrahydroacridine hydrochloride hydrate (Tacrine hydrocloride; **19**), which was first introduced as an Aldrich product in 1963, and is now sold by Warner–Lambert, a division of Pfizer Inc., under the trade name COGNEX® for the treatment of mild to moderate dementia of the Alzheimer's type.[34,35]



9 **10** **11**

Figure 3. Important Flavoring Raw Materials Manufactured by the German Subsidiary.



12 **13** **14** **15** **16** **17** **18**

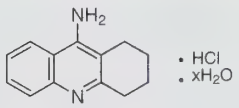
Figure 4. Custom Synthesis (**12–14**) and Hard-to-Find Products Offered in Bulk (**15–18**) in the Late Fifties.

5.2. Business, Art, and Chemistry

In 1965 and then in 1966, the Bader family sold some of their shares in the company first to a select group of chemists and friends and then to the public at large. By 1965, sales had almost doubled to about $1.8 million, from $1 million in 1962, and the number of employees had grown to over 100, of which 15 were chemists (7 with a Ph.D.).[33] The Aldrich Catalog/Handbook took on its now familiar name and look, as the 1967/1968 edition was the first to have a painting, *The Quill Cutter* by Paulus de Lesire, on its cover. Contrary to popular belief, the idea for placing a painting on the cover of the catalog came, not from Bader—the art lover and collector—but from Bernie Edelstein, an Aldrich employee.[36]

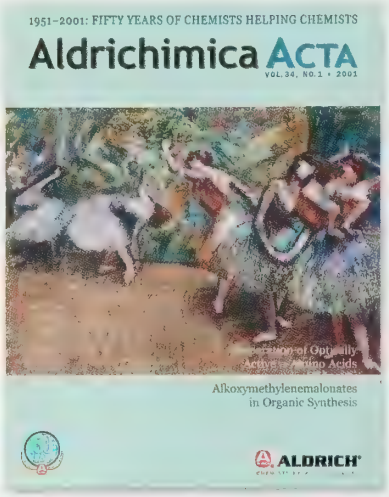
Following the public offerings, sales and the share price rose steadily as Aldrich grew by expanding into new lines of business and entering into (exclusive) distributorship agreements with a number of commodity chemical producers and other companies. Aldrich also acquired stakes in a number of U.S. based, small chemical producers, such as Hexagon and Kaplop Laboratories, but later divested itself of these stocks after the companies ran into business difficulties.

The *Aldrichimica Acta* evolved from the *Kardindex Sheets* that Aldrich used to mail to its best customers to keep them informed of its newest product offerings.[37] A preview issue was printed in the fall of 1967, and then



Tacrine Hydrochloride (**19**)

publication on a regular basis started in 1968. Richard K. Vitek, Aldrich's Director of Marketing at the time, became its first editor—albeit for a very short period of time. A classical alchemical Dutch painting by



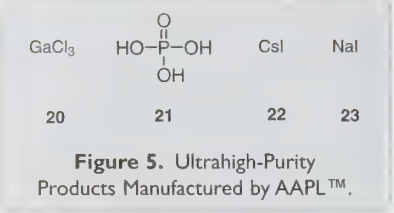


Figure 5. Ultrahigh-Purity Products Manufactured by AAPL™.

Aldrich's manufacturing site near Sheboygan, Wisconsin.

Thomas Wyck (17th century) from the Alfred Bader art collection was reproduced on the cover of the first issue of 1968. Of this very same issue, 10,000 copies were printed, whereas, today, over 130,000 copies of each issue are distributed worldwide free of charge. Alfred Bader, who coined the name *Aldrichimica Acta*, came up with the idea of placing a painting on its cover,[17] following the precedent-setting reproduction of a painting on the cover of the 1967/1968 edition of the Aldrich Catalog/Handbook (vide supra).

5.3. Joint Ventures

5.3.1. ALFA Inorganics, Inc.

This 50/50 joint venture with Metal Hydrides, Inc. (later became Ventron, Inc. and then a part of Thiokol Corp.) began in 1962 and ended in 1967. It was created to market inorganics, organometallics, and others such as organoboron and organoarsenic reagents.[38] Even though the joint venture lasted only five years, it helped Aldrich learn a great deal about inorganics and set the stage for Aldrich to expand into this market sector in the 1970s.

5.3.2. Aldrich-Europe

In the late fifties and early sixties, Janssen Pharmaceutica (JP) of Beerse, Belgium, had become one of Aldrich's better suppliers. It was no surprise then that, in 1962, Aldrich became JP's sales agent in the United States. Thus started the good relationship between the two companies. It led in May of 1970 to the creation of Aldrich-Europe, a wholly owned division of JP, charged with distributing Aldrich products in Continental Europe. The joint venture lasted until June 1982. Its dissolution opened the way for Sigma-Aldrich to start subsidiaries and sales offices in many countries in Continental Europe. Today, these number 18.

5.3.3. Riedel-deHaën® Laboratory Chemicals

Fast-forwarding to the present, Sigma-Aldrich first formed a joint venture, Riedel-deHaën® Laborchemikalien GmbH & Co. KG, with Allied Signal in 1997 to market and sell mainly analytical reagents and solvents carrying the Riedel-deHaën® brand name. Three years later, the joint venture became a wholly owned subsidiary of Sigma-Aldrich Corporation and is currently offering close to 4,000 products belonging to three general types: Karl Fischer reagents for water determination, standards for environmental analysis, and high-purity solvents.

5.3.4. Aldrich-APL, L.L.C. (AAPL™)

Also in the present, Aldrich has a majority stake in a joint venture with APL Engineered Materials to produce select inorganics of extremely high purity and low moisture content (ultradry) intended for the high-tech market. This collaboration began in September 1995 and presently operates from a manufacturing facility in Urbana, Illinois. Dr. John Long, who had been hired by Aldrich in the 1970s to head the inorganics production laboratories in Milwaukee, was initially charged with managing the Urbana facility. Some of the more popular, ultrahigh-purity products that are presently manufactured by AAPL™ include anhydrous gallium(III) chloride (**20**), phosphoric acid (**21**), anhydrous cesium iodide (**22**), and anhydrous sodium iodide (**23**) (**Figure 5**).

6. Great Opportunities and Profound Changes (1970s)

6.1. Aldrich-Boranes, Inc.

The greatest opportunity came when Professor H. C. Brown of Purdue University convinced Aldrich to further develop and commercialize the hydroboration technology and organoborane chemistry that he had developed and patented. This led, in May 1972, to the establishment of Aldrich-Boranes, Inc., a wholly owned Aldrich subsidiary, created to manufacture, among others, hydroboration reagents and products. Aldrich-Boranes, Inc. began operation in September 1972, with Dr. Harvey B. Hopps as its manager, Professor Brown as one of its directors, and a small development group of chemists headed by Clinton F. Lane, an enthusiastic young Ph.D., who had trained with Professor Brown at Purdue. Some of the first compounds manufactured by Aldrich-Boranes were borane–THF (**24**), 9-BBN (**25**), borane–methyl sulfide (**26**), and compounds **27–30** (**Figure 6**).[39] A multitude of others followed in rapid succession. The early development of this chemistry has been described in several reviews by Lane.[40] In the early 80s, Aldrich-Boranes, Inc. was integrated into Aldrich.

In the first five years, Aldrich-Boranes, Inc. operated from the production laboratories on West St. Paul Avenue in Milwaukee's city center. Following the purchase, in December 1977, of a laboratory building and a property in the town of Wilson, Sheboygan County, Wisconsin, its operations were moved to this site in March 1978.[41] This became the nucleus of Sigma-Aldrich's current 513-acre manufacturing site at 5485 County Road V. The range of products manufactured at the site has long expanded to include pharmaceutical intermediates, air-sensitive reagents, various organometallics, cGMP products, high-purity solvents, and many other compound types.

6.2. Stable Isotopes

Also in 1972, Aldrich acquired Diaprep, an Atlanta based manufacturer of deuterated solvents, and with it two experienced chemists—Tom Wickersham and Bob Askins. Tom remained with Aldrich until his retirement in 1999; he spent most of his career in the Stains & Dyes division, which he helped grow into an important part of the business (vide infra). With the acquisition of Diaprep, Aldrich started the production of

deuterated solvents; this production has expanded rapidly and considerably to the point that Aldrich is presently perhaps the world's largest producer of deuterated solvents. Moreover, through special agreements with companies such as Isotec Inc., Aldrich has also been able to significantly expand its offerings of products labeled with other stable isotopes, such as ^{6}Li, ^{7}Li, ^{10}B, ^{11}B, ^{12}C, ^{13}C, ^{15}N, and ^{18}O. In February 2001, Sigma-Aldrich purchased Isotec, Inc., thus becoming the leader in the stable isotopes market.

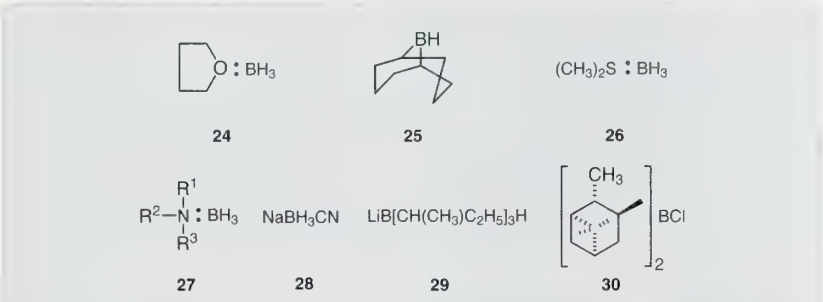


Figure 6. Some of the Early, and Still Popular, Organoboranes.

6.3. Sigma-Aldrich Corporation

The other profound event occurred three years later, in August 1975, when Aldrich Chemical Co. merged with Sigma International, Ltd. of St. Louis, Missouri, to form Sigma-Aldrich Corporation. At the time, both companies were publicly owned, with Aldrich the leading supplier of organic research chemicals and Sigma the leading supplier of research biochemicals. Having dodged several takeover attempts, Aldrich had, in 1967, approached Sigma—then a privately owned company—with an offer to merge, but was rebuffed. By 1975, however, changing trends in chemical research and the synergy to be realized from their complementary business practices and product offerings convinced the two companies to finally merge.

Dan Broida, Sigma's president at the time of the merger, became chairman of the board, while Alfred Bader, Aldrich's president, became president of Sigma-Aldrich Corp. At the time, the new company did not have a CEO. As anticipated, the merged companies drew on each other's strengths—Sigma's emphasis on quality and service and Aldrich's emphasis on introducing new products and maintaining good relationships with suppliers.

A little over a year prior to the merger (April 23, 1974), four Aldrich departmental managers—Robert Gorzek, Irwin (Ike) Klundt, Charles (Chuck) Pouchert, and Edward Segrin—were promoted to vice presidents. On the same date, Vice President Bernard Edelstein was promoted to Executive Vice President.[42] The first and second Aldrich vice presidents, William Buth and John Biel, had left the company in 1973 and 1968, respectively.[43] Also in 1974, David R. Harvey (see Section 7.1) became Aldrich's Vice President of European Operations.[44]

6.4. Floyd Green's Stains and Dyes

In 1973, Dr. Floyd J. Green, a widely respected authority on biological stains and dyes, founded Aristo Custom Chemicals, Inc. in Cincinnati, Ohio, to manufacture biological stains. He sold Aristo to Sigma-Aldrich in 1977 and moved to Milwaukee to become an Aldrich vice president in charge of the company's newly created Stains and Dyes division. This division currently boasts ca. 1,300 products, and offers an attractive handbook on stains, dyes, and indicators that was originally prepared by Dr. Green.[45] Two of the early dyes sold by the division were pararosaniline chloride and acetate. Presently, the Stains and Dyes division operates from a 110,000-sq ft facility, at 230 S. Emmber Lane in Milwaukee, that was purchased in the early seventies.

6.5. Nonchemical Products

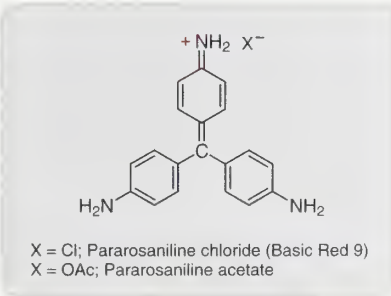
6.5.1. Laboratory Equipment (Techware)

Charles J. Pouchert, a long-time Aldrich employee and Manager of its Quality Control department in the early 70s, promoted the idea that Aldrich should sell books that are useful to chemists. Not surprisingly, the first nonchemical item that Aldrich offered (cat. no. Z10,000-5)[46] was the first edition (1970) of *The Aldrich Library of Infrared Spectra*, that Pouchert edited. The idea of offering a laboratory equipment item was advanced by Dr. Harvey B. Hopps, at the time Aldrich's Manager of Technical Services. This first laboratory equipment item was a Diazald® kit (cat. no. Z10,025-2) and was listed for sale for the first time in the very early 70s.[24] Thus started the Techware division of Aldrich—with much input and encouragement from Edward J. Segrin, Aldrich's Sales Manager at the time. This division expanded rapidly over the years into such product areas as books, electronic media products, and glassware. It currently offers over 13,000 nonchemical items[47]—everything the practicing chemist needs in addition to chemicals.

6.5.2. The Aldrich Glass Shop

The Aldrich glass shop grew simply enough from the need to repair laboratory glassware in-house. In the early 70s, and by arrangement with Daytime Vacuum Products, a glass shop was set up on the 4th floor of the 940 W. St. Paul Avenue building. When the lone glass blower retired, Aldrich purchased the shop and looked to hire a glass blower to operate it. An early hire in 1974 left after a few months.[48] However, in 1975, an able

2001 edition of the Aldrich Stable Isotopes catalog.



X = Cl; Pararosaniline chloride (Basic Red 9)
X = OAc; Pararosaniline acetate

Techware CD-ROM product.

Sophisticated piece of glassware manufactured by the Aldrich Glass Shop.

Company logo from the early days.

glass blower, Dieter Damrow, was hired to operate the glass shop. Dieter stayed with the shop until his retirement in 1999, and has had a greater impact on the growth and development of the shop than anyone else. During Dieter's tenure, the glass shop grew steadily and its mission expanded to include the manufacture of new glass apparatus and custom glassware, and the taking on of outside repair jobs. Back in 1985, the glass shop was relocated to newer quarters in the 2905 W. Hope Avenue facility.

6.6. New Lines of Business

As is clearly evident from the preceding discussion, the 70s were an exciting period for Aldrich. In addition to those mentioned in the previous sections, Aldrich availed itself of other business opportunities. Thus, in 1971, Aldrich launched its line of biochemical products with Irwin Klundt as its technical manager.[42] However, this line of products had a brief, independent existence up until Aldrich's merger with Sigma in 1975. In 1978—free from the restrictions of the separation agreement that led to the dissolution of the Aldrich–Ventron joint venture (see Section 5.3.1)—Aldrich hired Dr. John Long, a promising young inorganic chemist, to spearhead its development and production of inorganic products. It wasn't long before Aldrich was competing successfully with ALFA Inorganics, Inc. The inorganic line of products is thriving today, enhanced by the establishment of the joint venture with APL Engineered Materials in 1995 (see Section 5.3.4). Together with the line of organometallics, it offers close to 10,000 products for, among others, the high-technology markets.

6.7. Craftsmen in Chemistry?

Just as many other companies have had to, Aldrich also had to change with the times. The "Craftsmen in Chemistry" slogan, which was in use in the late 60s, was abandoned a few years later (1975), since it was deemed politically incorrect. It wasn't until early 1978 that a new slogan, "chemists helping chemists in research and industry", began appearing in company literature. Presently, this motto is slowly being phased out in favor of its shorter version, "chemists helping chemists". Aldrich's logo also underwent a face-lift; an earlier version is depicted here. Fortunately, and unlike many other prominent chemical companies, Aldrich did not succumb to the pressure of dropping the word "chemical" from its name, during a period of time when this word had become a public relations liability.

7. Post-Merger Era

7.1. The Succession

With Aldrich now a company within Sigma-Aldrich Corporation, Alfred Bader became President of the merged company and remained President of Aldrich until early 1981. He was succeeded as President of Aldrich by Dr. David R. Harvey (1981–1986), Dr. Jai P. Nagarkatti (1987–1999), and Dr. Clinton F. Lane (1999–Present).[49]

David R. Harvey, an Oxford University graduate, started out in Aldrich-UK in August 1974 as Vice President of European Operations. As president of Aldrich, he oversaw, among others, the relocation of the distribution center to the Hope Avenue facility and the construction of the laboratory building at the Sheboygan County site. He is also credited with starting the company's Flavors & Fragrances division. David went on to become President of Sigma-Aldrich Corp. and then, in 2000, its Chairman, President, and CEO.

A graduate of East Texas State University, Jai P. Nagarkatti started his career at Aldrich in 1976 as a Process Development Chemist in the Production Laboratory. He progressed through the ranks to become Vice President of Production in 1985 and President of Aldrich in 1987. Late in 1999, he was promoted to President of Sigma-Aldrich Fine Chemicals, one of four strategic business units of Sigma-Aldrich Corp. During his tenure as president, Aldrich experienced a substantial growth in business. He oversaw a major expansion of the manufacturing plant (Pro II) at the Sheboygan County site, and worked tirelessly to integrate Aldrich more closely into Sigma-Aldrich Corp.

Clinton F. Lane, the current president, is a Purdue University graduate who was the first chemist hired for the Aldrich-Boranes, Inc. venture back in September 1972. After working as a bench chemist in Milwaukee, he moved, along with Aldrich-Boranes, Inc. to the Sheboygan County site soon after its purchase in 1977. After 13 years as Plant Manager of the Sheboygan County site, he was promoted to Vice President, Executive Vice President, and then President of Aldrich in 1999. Clint is credited with the substantial growth that both the Sheboygan County site and the line of boron-containing products have experienced. The interested reader should review Section 6.1 for more details.

7.2. The 80s and 90s

Following the merger of Aldrich and Sigma, business expectations for the merged company were soon realized. Annual double-digit growth has since been the norm, and other companies[50,51]—Floyd Green's Aristo Custom Chemicals (USA, 1977), Makor Chemicals (Israel, 1978), Pathfinder (USA, 1984), Bio Yeda (Israel, 1986), Bristol Organics (UK, 1986), Fluka Chemie AG (Switzerland, 1989), Supelco (USA, 1993), LabKemi AB (Sweden, 1994), Research

David R. Harvey, Aldrich President (1981–1986).

Jai P. Nagarkatti, Aldrich President (1987–1999).

Clinton F. Lane, Aldrich President (1999–Present).

Biochemicals International (USA, 1997), Carbolabs (USA, 1997), Genosys Biotechnologies, Inc. (USA, 1998), Riedel-deHaën® Laborchemikalien GmbH & Co. KG (Germany, 1999), ARK Scientific GmbH (Germany, 2000), First Medical, Inc. (USA, 2000), Amelung GmbH (Germany, 2000), Isotec, Inc. (USA, 2001)—have also become part of Sigma-Aldrich Corp. In 2000, Sigma-Aldrich corporate sales were over one billion dollars![52] The brands that make up Sigma-Aldrich Corp. are now well-known and trusted worldwide. The total number of products they offer is about 85,000 of which about 40,000 are poduced.

Aldrich continued its spectacular growth in these two decades as evidenced by the purchase of several large buildings in the mid-1980s: 2905 W. Hope Avenue (currently holds the RCL collection), 1101 W. St. Paul Avenue (contains the Flavors & Fragrances products), and 1001 W. St. Paul Avenue (houses administrative offices and support departments). In 1986, Aldrich added 284 acres to the Sheboygan County site, and, in the early 90s, purchased and then added to a site at 6000 N. Teutonia Avenue in Milwaukee. In the 1990s, groupings of products, that Aldrich had offered since its early days, evolved into distinct product lines with their own technical managers, e.g., chiral, nonracemic products (~2,400 listings) and monomers & polymers (~3,100 products).

7.3. The Present and its Future

Today, Aldrich continues to thrive within Sigma-Aldrich Corp. and has expanded into new market sectors—such as combinatorial chemistry, active high-purity metals and inorganics, and high-purity gases—and new overseas markets. In the past decade, it has also upgraded and enlarged its Milwaukee and East Coast distribution centers to enable the company to become even more responsive to its customers.

What does the future hold for Aldrich? Aldrich's future is intimately tied to that of Sigma-Aldrich. In December 2000, Sigma-Aldrich launched a new strategic plan clearly focusing the company on "leadership in Life Science and High Technology". In fact, 75% of the company's current sales are for Life Science applications, while the remaining 25% are in a variety of High Technology areas. The other key initiatives undertaken focus on service and process improvements.[53] The strategic plan made Aldrich a part of the Scientific Research business unit of Sigma-Aldrich Corp. The startup of a state-of-the-art, $25 million production plant (Pro I) near Sheboygan Falls, WI, a combinatorial chemistry product line, a wide array of active and high-purity metals, and a strong Internet presence are but a few of the ways in which Aldrich is implementing this strategy and is continuing to evolve.

Aldrich's Teutonia Avenue site.

Pro I building at Aldrich's Sheboygan County site.

Sigma-Aldrich's corporate vision is embodied in its motto: "We Are Committed to the Success of Our Customers, Employees and Shareholders through Leadership in Life Science, High Technology and Service."

7.4. Internet Presence

Over the past five years, Sigma-Aldrich Corp. has been implementing its strategic plan for a strong, independent presence on the Internet with the goal of eventually transacting at least 50% of sales via the Internet. In 2000, corporate Internet sales represented over 10% of sales in the USA and about 5% of sales worldwide.[52] Ongoing updates and a vast array of useful information, coupled with a focus on ease of use and visual appeal, have characterized the corporation's Web site.

Aldrich has vigorously participated in this effort by making available free of charge not only its catalog/handbook and various specialty catalogs and promotional materials,

Photo courtesy of H.C. Brown

Professor Herbert C. Brown (1999).

Photo courtesy of B.J. Horick

Beverly J. Horick (2001), recently retired Aldrich employee with the most years of service (February 17, 1956 to February 28, 2001).

but also its vast store of MSDSs, CofAs, and product technical data. One of its goals for the near future is to make available, free of charge, its IR, UV, and NMR spectral libraries on its Web site.

8. The Role of Science and Scientists

This is a topic that is so dear to the "heart" of the company that it merits a separate treatment.

8.1. Scientists' Contributions

Aldrich is a science-based company. It was cofounded by a Ph.D. chemist, currently employs several dozen Ph.D. chemists and many hundreds of college-educated chemistry professionals. Most of its customers are scientists of all walks of life. Early on, Aldrich recognized the importance of scientists to the growth and health of the company: Scientists were the originators of many of the successful Aldrich products, as well as the main consumers of its products. As discussed in Section 4.2, a large portion of the company's collection of hard-to-find research samples, known as the Rare Chemical Library, comes from the laboratories of these scientists.

Aldrich has been fortunate to have had long-standing professional collaborations with many of the leading chemists of the second half of the twentieth century. These relationships proved advantageous not only to the company, but also to the community of chemists by making available reagents that are now indispensable for chemistry research: $Me_2S{\bullet}BH_3$, $NaBH_3CN$, and the family of Selectride® reducing agents, to name a few. In the early days, it was natural for Alfred Bader to turn to Louis Fieser, his Ph.D. advisor at Harvard, or Martin Ettlinger, his graduate school contemporary, for ideas on what compounds would be of interest to researchers. Subsequently, Aldrich has had significant collaborations with many other leading chemists. What follows is only a partial list (in alphabetical order):[54] E. J. Corey, Henry Gilman (deceased), Eric N. Jacobsen, Kim D. Janda, Richard Lerner, Andrew G. Myers, K. C. Nicolaou, Martin J. O'Donnell, David O'Hagan, Siegfried Pickholz (deceased), Reuben Rieke, Ian P. Rothwell, I. Herbert Scheinberg, Barry K. Sharpless, John C. Sheehan (deceased), Gilbert Stork, and Robert B. Woodward (deceased).

Perhaps more than any other factor, it was the development of ideas and technologies, invented by researchers and developed or commercialized by Aldrich, that propelled Aldrich (and later Sigma-Aldrich) to the prominent position that it is presently in. It is unquestionably the vigorous pursuit of these contacts and collaborations that will keep Sigma-Aldrich a leading technology company.

8.2. Herbert C. Brown

Aside from Alfred Bader, perhaps no other single chemist has had a greater impact on the success of Aldrich than Professor Herbert C. Brown of Purdue University. A Nobel laureate and a towering figure in chemistry, Brown not only was the catalyst and a driving force for Aldrich–Boranes, Inc., as explained in Section 6.1, but he also served on the Aldrich Board of Directors (1972–1975) and the Sigma–Aldrich Board of Directors (1975–1979). In recognition of his lasting contributions, Aldrich not only pays royalties to the Purdue Research Foundation, but also co-sponsors the *Herbert C. Brown Award for Creative Research in Synthetic Methods* that is administered by the American Chemical Society.

8.3. Rewarding Excellence

Aldrich has also had a tradition of rewarding excellence in chemistry research by sponsoring or co-sponsoring prestigious professional awards, symposia, and student fellowships. A few examples come to mind: *ACS Award for Creative Work in Synthetic Organic Chemistry*, *ACS Award in Inorganic Chemistry*, *Herbert C. Brown Award for Creative Research in Synthetic Methods*, Project SEED, 32nd Organosilicon Symposium (Milwaukee, 1999), Asymmetric Synthesis Symposium (Milwaukee, 1998), Boron–USA meetings, and various Gordon Conferences. Moreover, Alfred Bader, Aldrich's cofounder, personally sponsors the *Alfred Bader Award in Bioinorganic or Bioorganic Chemistry*, and has helped over the years many deserving academic chemists by underwriting some of their research.[2]

9. Valued Customers, Dedicated Employees

Aldrich recognized very early on the importance of establishing strong relationships with its customers, and the necessity to provide them with valuable information related to the products that they were purchasing. Thus, it was no surprise that the Aldrich catalog was transformed from a listing of available products and prices to a "handbook" containing a wealth of information, which has made it an indispensable desk reference in many academic and industrial laboratories and libraries. Chemists active in research were not only customers, but also partners in the chemical enterprise, who were also invited to share their insights with others through such widely circulated and *free* Aldrich publications as the *Aldrichimica Acta* (which has been in existence for 34 years). It is also no secret that ideas for new products often

Table 2. Present and Former Aldrich Employees with 25 or More Years of Continuous Service [a,b]

Adler, Wayne J.	Gorzek, Robert J.	Leitner, Lorraine	Rochwerger, Leonard L.
Ahmed, Waheeduddin	Griesinger, Alfred	Lenga, Robert E.	Roper, Mattie D.
Bader, Alfred R.	Griffiths, David W.	Lent, Mary A.	Saladin, Barbara L.
Benson, Christine F.	Gunther, Patricia A.	Lewis, Robert J.	Schreiber, Peter L.
Borenstein, Mark	Harvey, David R.	Lisztwan, Emilia M.	Settingsgaard, Jacqueline L.
Bourgeois, Shirley R.	Helmin, William T.	Malone, Rosie L.	Shortridge, Nelgene
Branski, Robert A.	Holm, Phillip L.	Mehta, Milan N.	Shuder, Diane L.
Brien, Diana M.	Horick, Beverly J.	Metz, Marian E.	Siegel, Brian S.
Brien, James J.	Jenkins, Dolores H.	Mititch, Jacqueline	Skeff, George
Bruesewitz, Richard J.	Kasprzak, Russell J.	Nagarkatti, Jai P.	Smith, Andrew P.
Creighton, Anthony J.	Kett, Jeffrey A.	Napiorkowski, Anna M.	Smith, Robert W.
Daniels, John J.	Koppel, Henry C.	Podd, Rodney L.	Stanton, Genevieve L.
Edelstein, Sara	Kopperud, Cynthia A.	Poth, Donna L.	Wallace, Kenneth J.
Farrell, Richard T.	Korthoff, Kristine L.	Pouchert, Charles J.	Ward, Stella L.
Feustel, Barbara L.	Kratzer, Phyllis C.	Pruss, Judith R.	Weber, Roger O.
Fox, Lyle G.	Kreinus, Timothy M.	Pykett, Jonathan R.	Wells, Sheila E.
Freeman, Roland P.	Kurzynski, Alice J.	Rebarchik, Joseph A.	Wickersham, Thomas W.
Gallaspy, Barbara A.	Lane, Clinton F.	Riedmaier, John E.	Wondra, Carl T.

[a] As of June 2001. [b] Admittedly, length of service is an imperfect measure of an employee's contribution to the company; however, this author was at a loss to come up with a fair, objective way of recognizing those employees who have given so much to the company, but may not be mentioned in the text. I offer my apologies to those employees, whose names belong in the table, but were inadvertently left out.

came from customers. To appreciate this fact more fully, it is sufficient to consult the "Please Bother Us." section of any recent *Aldrichimica Acta* issue.

Aldrich's phenomenal success is a tribute to the vision and determination of its cofounder, Dr. Alfred R. Bader, and the dedication and hard work of thousands of former and present employees. **Table 2** is only a modest attempt at acknowledging their contributions.

10. Acknowledgments

In addition to the sources cited, I wish to acknowledge the specific assistance of (in alphabetical order): (i) Bettie Aldrich Eisendrath, Gerd Backes, Alfred Bader, Jim Brien, Tom Gandia, David Harvey, Don Hobbs, Harvey Hopps, Beverly Horick, Peter Hyland, Linda Kehren, Clinton Lane, Lorraine Leitner, Edward Niemiec, Judith Pruss, Robert Smith, Joan Suda, Robert Wandler, Tom Wickersham, and LaShannon Wilson, who provided me with valuable information and recollections either via personal communications or via source materials that they supplied to me; (ii) Brian Case, Robert Gorzek, David Harvey, Chris Hewitt, Harvey Hopps, Peter Hyland, Anthony J. La Loggia, Clinton Lane, Jai Nagarkatti, and Craig Recatto, who proofread the manuscript or sections thereof, and offered helpful comments; (iii) Jennifer L. Botic, who laid out the manuscript and this issue of the *Acta*, and who assisted me in locating some of the photographs used; and (iv) Rebecca Zelenka, who helped with contacting former Aldrich employees. Finally, I would like to thank my wife for her patience and understanding while I was preparing the manuscript.

11. References and Notes

(1) This brief tour of the past fifty years cannot possibly do justice to the topic. For more details and anecdotes, the interested reader is directed to the very readable book by one of the founders of Aldrich: Bader, A. *Adventures of a Chemist Collector*; Weidenfeld and Nicolson: London, U.K., 1995.

(2) Cori, T.; Emanuel, R. N.; Harvey, D.; Klitsner, M. E. *Aldrichimica Acta* **1984**, *17*, 3.

(3) (a) Bader, Alfred. The Building of Aldrich. My Advice to Entrepreneurs. *The Chemist*, November/December 1997, pp 1–5. (b) Buchan, P. Bruce. Three Boards and "A Bet Against the Company". *The Chemical Intelligencer*, October 1996, pp 24–29 and 41. (c) Edward, J. T. *Can. Chem. News* **1992**, *44*(6), 23. (d) Bohning, James J. Crystallizing Hamburger: Alfred Bader and the Aldrich Chemical Company, Part I. *Beckman Center News*, Spring 1991, pp 1 and 8–9. (e) Bohning, James J. Crystallizing Hamburger: Alfred Bader and the Aldrich Chemical Company, Part II. *Beckman Center News*, Fall 1991, pp 3–4. (f) Bader, A. R. *CHEMTECH* **1990** (March), 138. (g) A Chemical Company in Your Garage. An Interview with Dr. Alfred Bader. *The DEL–CHEM BULLETIN*, May 1974, pp 5–10.

(4) While it is unquestionably the contributions of a great many dedicated employees that have made Aldrich what it is today, it is not possible in such a short overview to mention them all. The author regrets any inadvertent or necessary omissions.

(5) Reference 1, pp 70, 101, and 185.

(6) (a) The 500 shares of stock issued were owned 50% by Alfred R. Bader and 50% by Jack N., Frank N., and Bettie Mae Eisendrath. Professor A. F. McKay of the University of Toronto, Canada, owned only one share of stock: Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, April 09, 2001. (b) Prior to cofounding Aldrich, Jack Eisendrath had attempted to start and run a number of mail order/catalog businesses (e.g., selling moccasins): Eisendrath, B. A. Washington, DC. Personal communication, April 03, 2001.

(7) (a) Reference 1, p 70. (b) Up until the Eisendraths sold their 50% stake in the company, Bettie acted as the company's (unpaid) secretary. As of the writing of this review, Bettie was still a remarkably energetic and socially active octogenarian living in Washington, DC.

(8) (a) Leitner, L. (née Neau; retired) Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, March 16, 2001. (b) Horick, B. J. (retired) Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, February 01, 2001.

(9) (a) McKay, A. F.; Wright, G. F. *J. Am. Chem. Soc.* **1947**, *69*, 3028. (b) McKay, A. F. *J. Am. Chem. Soc.* **1948**, *70*, 1974. (c) McKay, A. F.; Ott, W. L.; Taylor, G. W.; Buchanan, M. N.; Crooker, J. F. *Can. J. Res., Sec. B* **1950**, *28*, 683.

(10) Aldrich Chemical Co., Inc. *Diazald®, MNNG, and Diazomethane Generators*. Aldrich Technical Information Bulletin No. AL-180; Milwaukee, WI, 1993.
(11) Reference 1, pp 71–72.
(12) Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, March 19, 2001.
(13) While at PPG, Anthony co-authored a paper with Alfred Bader on the easy preparation of phenyl esters of carboxylic acids by heating the acid and phenol in the presence of PPA: Bader, A. R.; Kontowicz, A. D. *J. Am. Chem. Soc.* **1953**, *75*, 5416.
(14) Reference 1, p 74.
(15) Jack Eisendrath continued his practice of general, family, and consumer law in Milwaukee for about 40 years. He died on November 06, 1997 at the age of 85: Knoche, Eldon. Consumers Had Advocate in Attorney Eisendrath. *The Milwaukee Journal Sentinel* [Online], November 9, 1997, main page (www.jsonline.com).
(16) For a glimpse of Eisendrath's perspective of these events, see: (a) Lank, Avrum D. Chemist Mixes Knowledge, Savvy. *The Milwaukee Sentinel*, October 01, 1985, Part 4, pp 1–2. (b) Gillespie, Scott. Alfred Bader's Diverse Talents Led Firm to International Role. *The Business Journal Special Report* (Milwaukee), Week of September 22, 1986, p 9.
(17) Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, March 09 and April 09, 2001.
(18) Kenney, Ray. Aldrich Firing Up All Burners. *The Milwaukee Sentinel*, September 02, 1974, Part 2, p 9.
(19) Reference 1, p 77.
(20) Bader, A. R. Alfred Bader Fine Arts, Milwaukee, WI. Personal communication, March 23, 2001.
(21) Helen Bader (née Daniels) worked for Aldrich in various capacities on and off for over twenty years, whenever her family obligations permitted her to. In addition to being one of the owners of Aldrich, she was also a company director and treasurer for several years and the third company president for a very short period of time (1964). Following her death in 1989, her family established the Helen Bader Foundation, Inc. to honor her memory and continue the charitable work that she had started. The interested reader can find out more by accessing the Foundation's Web site at *www.hbf.org*.
(22) Reference 1, pp 80–81.
(23) Horick, Beverly J. Then & Now. *The Aldrich Reporter*, January 2001, p 10. When Beverly J. Horick retired from Aldrich on February 28, 2001 (after a little over 45 years of continuous service!) she set a record as the employee with the longest service to the company.
(24) Hopps, H. B. Amarillo College, Amarillo, TX. Personal communication, February 21, 2001.
(25) (a) Aldrich Chemical Co., Inc. The Aldrich Annual Report; Milwaukee, WI, September 03, 1969. (b) Aldrich Chemical Co., Inc. Annual Report; Milwaukee, WI, September 30, 1970.
(26) Reference 1, p 98.
(27) Aldrich Chemical Co., Inc. Prospectus; Milwaukee, WI, December 30, 1965; p 2.
(28) Reference 1, p 79.
(29) EGA from the names Ernst, Gerhard, and Alfred.
(30) Aldrich Chemical Co., Inc. Annual Report 1971; Milwaukee, WI, March 24, 1972.
(31) (a) Mack, H. Sigma-Aldrich Chemie GmbH, Steinheim, Germany. Personal communication, March 06, 2001. (b) Backes, G. Sigma-Aldrich Chemie GmbH, Steinheim, Germany. Personal communication, March 09, 2001.
(32) Koppel, H. *Aldrichimica Acta* **1968**, *1*, 3.
(33) Reference 1, p 88.
(34) Medical Economics Company, Inc. *Physicians' Desk Reference*, 52nd ed.; Montvale, NJ, 1998; pp 2082–2086.
(35) The statements in this paragraph should not be construed to imply that COGNEX® is formulated with a material obtained from Aldrich. Aldrich brand products are sold mainly for research or industrial applications and are not intended for drug or household use, unless specifically designated for that purpose.
(36) Reference 1, pp 82–83.
(37) Aldrich Chemical Co., Inc. *Aldrichimica Acta* (Preview Issue); Milwaukee, WI, Fall 1967.
(38) Reference 1, p 133.
(39) Lane, Clinton F. Greetings from the Future Leaders in Organoborane Chemicals! *Aldrich-Boranes, Inc. Newsletter*, February 1973, p 2.
(40) For some examples, see: (a) Lane, C. F. *Aldrichimica Acta* **1973**, *6*, 21. (b) Lane, C. F. *Aldrichimica Acta* **1973**, *6*, 51. (c) Lane, C. F. *Aldrichimica Acta* **1974**, *7*, 7. (d) Lane, C. F. *Aldrichimica Acta* **1974**, *7*, 32. (e) Lane, C. F. *Synthesis* **1975**, 135. (f) Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 3. (g) Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 20. (h) Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981. (i) Lane, C. F. *Chem. Rev.* **1976**, *76*, 773. (j) Lane, C. F. *Aldrichimica Acta* **1976**, *9*, 31. (k) Lane, C. F.; Kramer, G. W. *Aldrichimica Acta* **1977**, *10*, 11. (l) Brown, H. C.; Lane, C. F. *Heterocycles* **1977**, *7*, 453. (m) Lane, C. F. *Aldrichimica Acta* **1977**, *10*, 41.
(41) Aldrich Chemical Co., Inc. *Welcome to Aldrich Sheboygan Site*. Aldrich Informational Bulletin; Sheboygan Falls, WI, 1999.
(42) Aldrich Chemical Co., Inc. The Aldrich Semimonthly Newsletter (Extra); Milwaukee, WI, April 25, 1974.
(43) (a) Aldrich Chemical Co., Inc. Annual Report 1973; Milwaukee, WI, February 15, 1974. (b) Reference 1, p 167.
(44) Aldrich Chemical Co., Inc. Annual Report 1974; Milwaukee, WI, February 21, 1975.
(45) Green, F. J. *The Sigma-Aldrich Handbook of Stains, Dyes and Indicators*; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1990.
(46) Has since been replaced by the third edition, cat. no. Z10,750-6: Pouchert, C. J. *The Aldrich Library of Infrared Spectra*, 3rd ed.; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1981.
(47) Brien, J. J. Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, March 08, 2001.
(48) Damrow, D. (retired) Aldrich Chemical Co., Inc., Milwaukee, WI. Personal communication, February 22, 2001.
(49) For the record, Aldrich has had the following presidents in the following order: Jack Eisendrath, Alfred Bader, Helen Bader, Alfred Bader, David Harvey, Jai Nagarkatti, and Clinton Lane.
(50) Suda, Joan. *The Sigma-Aldrich Story. Overview of a Multinational Family of Companies*. Sigma-Aldrich Bulletin; Sigma-Aldrich Corp.: St. Louis, MO, 2001.
(51) Sigma-Aldrich Corp. *Sigma-Aldrich Acquires Isotec to Enhance Life Science Capabilities*. Press Release; St. Louis, MO, February 16, 2001.
(52) Suda, Joan. *An Interview with David R. Harvey*. Sigma-Aldrich Bulletin; Sigma-Aldrich Corp.: St. Louis, MO, January 2001; p 1.
(53) Harvey, D. R. Sigma-Aldrich Corp., St. Louis, MO. Personal communication, May 05, 2001.
(54) Many more scientists have had fruitful collaborations or a significant impact on the growth of Aldrich. The author regrets not being able to acknowledge all of them.

Monsanto Company: Roundup®; **Riedel-deHaën GmbH**: Riedel-deHaën®; **Rieke Metals**: Rieke®; **Sigma-Aldrich Co.**: AAPL™, ALDRICH®, Diazald®, FLUKA®, Selectride®, SIGMA®; **Warner-Lambert Co.**: COGNEX®.

Happy 50th Anniversary Aldrich!

About the Author

Sharbil J. Firsan was born and raised in Lebanon. He completed his undergraduate studies at the American University of Beirut and his graduate work on acyclic imidate and thioimidate *N*-oxides with Professor Robert M. Coates at the University of Illinois in Urbana-Champaign (Ph.D., 1986). He did postdoctoral work at the University of Oregon in Eugene, OR, and then moved to Oklahoma State University in Stillwater, OK, to become a Research Associate and then a Visiting Assistant Professor. In 1996, he joined Aldrich Chemical Co., Milwaukee, WI, as a Promotions and Publications Specialist. He is currently a Senior Promotions and Publications Specialist and Editor of the *Aldrichimica Acta*. With his wife, Leah (Leila), Sharbil enjoys outdoor activities, gardening, and travel.

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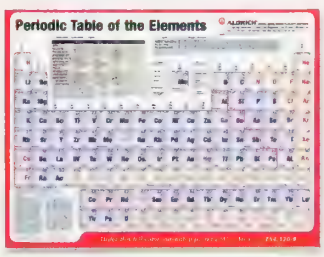

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(Last issue in 2001)

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[Hydroxy(tosyloxy)-iodo]benzene

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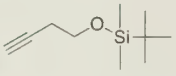
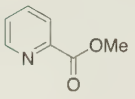
54,167-2 4-(*tert*-Butyldimethylsilyloxy)-1-butyne, 97%
5mL $22.50; 25mL $75.00



Has been utilized for a transition-metal-catalyzed regioselective cyclotrimerization with enones[1] and as a starting material in the synthesis of (±)-asteriscanolide.[2]

(1) Ikeda, S.-I. et al. *Chem. Commun.* **2000**, 815. (2) Krafft, M. E. et al. *Synthesis* **2000**, 1020.

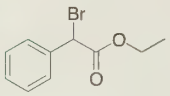
55,628-9 Methyl picolinate, 99%
25g $63.00; 100g $175.00



Useful as a ligand for the formation of metal complexes[1] and as a starting material for the synthesis of biologically active aza-anthraquinones.[2]

(1) Britovsek, G. et al. *J. Mol. Catal. A: Chem.* **1996**, *110*, 77. (2) Epsztajn, J. et al. *Tetrahedron* **1996**, *52*, 11025.

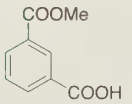
55,406-5 Ethyl α-bromophenylacetate, 97%
25g $78.00; 100g $235.00



This versatile alkylating reagent has been utilized in the preparation of multifunctional phosphonates,[1] oxazinones,[2] and α-alkoxycarbonyl compounds.[3]

(1) Prager, R. H. et al. *Aust. J. Chem.* **1997**, *50*, 813. (2) Remuzon, P. et al. *Tetrahedron* **1997**, *53*, 17711. (3) Berglund, P. et al. *Tetrahedron: Asymmetry* **1999**, *10*, 4191.

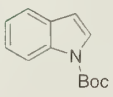
55,540-1 Monomethyl isophthalate, 97%
1g $21.90; 5g $72.90



Was recently used to introduce structural variations in benzazepines,[1] and to synthesize a monomer for the preparation of an authentic H–T poly(amide–ester).[2]

(1) Murakami, Y. et al. *J. Med. Chem.* **1999**, *42*, 2621. (2) Li, L. et al. *Macromolecules* **1999**, *32*, 3851.

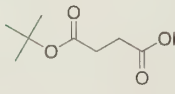
51,810-7 *tert*-Butyl 1-indolecarboxylate, 97%
25mL $59.00



Allows the easy preparation of indole-2-boronic acid[1] and the corresponding 3-nitroindole.[2]

(1) de Koning, C. B. et al. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1705. (2) Pelkey, E. T.; Gribble, G. W. *Synthesis* **1999**, 1117.

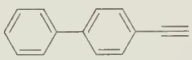
54,735-2 Mono-*tert*-butyl succinate, 97%
1g $12.75; 5g $42.45



Key building block for the construction of a chiral lactone that is a versatile intermediate for possible HIV-1 protease inhibitors,[1] and for the construction of the carbacephem β-lactam framework.[2]

(1) Solladié-Cavallo, A. et al. *Tetrahedron: Asymmetry* **1996**, *7*, 1797. (2) Guzzo, P.R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4862.

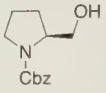
52,117-5 4-Ethynylbiphenyl, 97% **5g $68.00**



This terminal acetylene has been converted to enamines with resin-bound 2° amines.[1] It is also suitable for Pd(0)-mediated coupling on solid supports.[2]

(1) Aznar, F. et al. *Tetrahedron Lett.* **2000**, *41*, 5683. (2) Berteina, S. et al. *Synlett* **1998**, 676.

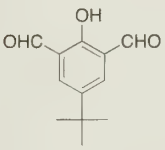
51,296-6 Z-L-prolinol, 97% **1g $48.80**



Useful for synthesizing peptidomimetics. A relatively recent application is in the synthesis of an ester mimic for the generation of catalytic antibodies.

Anderson, G. T. et al. *J. Org. Chem.* **1996**, *61*, 125.

55,415-4 4-*tert*-Butyl-2,6-diformylphenol, 96%
1g $15.00; 5g $48.90



Reported applications for this diformylphenol include the synthesis of binucleating macrocyclic ligands[1] and homooxocalix[*n*]arenes.[2]

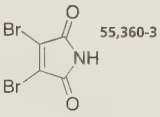
(1) Lindoy, L. F. et al. *Synthesis* **1998**, 1029. (2) Komatsu, N. *Tetrahedron Lett.* **2001**, *42*, 1733.

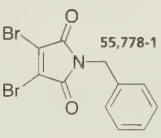
55,587-8 Chloromethyl(dimethyl)silane, 97%
5mL $47.05; 25mL $156.75

Hydrosilylation of olefins using this reagent provides the corresponding chloromethyl(dimethyl)silyl (CMDMS) derivatives.[1,2] This method was employed to introduce CMDMS groups on the terminal branches of carbosilane dendrimers.[2]

(1) Thibon, J. et al. *J. Org. Chem.* **1997**, *62*, 4635. (2) Krska, S. W.; Seyferth, D. *J. Am. Chem. Soc.* **1998**, *120*, 3604.

55,360-3 2,3-Dibromomaleimide, 97%
1g $12.00; 5g $40.00
55,778-1 *N*-Benzyl-2,3-dibromomaleimide, 97%
1g $13.50; 5g $45.00





Dihalogenated maleimides have applications in a broad spectrum of synthetic transformations, such as mono- or disubstitutions, Suzuki-type couplings, Grignard reactions, and Diels–Alder cyclizations. They are key intermediates in the synthesis of arcyriarubin,[1] staurosporine,[2] and pyrroloquinoxaline systems.[3]

(1) Mahboobi, S. et al. *Pharmazie* **1999**, *54*, 820. (2) Joyce, R. P. et al. *J. Org. Chem.* **1987**, *52*, 1177. (3) Hanaineh-Abdelnour, L. et al. *Tetrahedron* **1999**, *55*, 11859.

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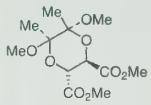
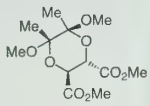


55,692-0



55,693-9

Professor Steven V. Ley of the University of Cambridge, U.K., kindly suggested that we offer these enantiomeric 2,3-butanediacetal-protected dimethyl tartrates. These compounds have been used in the synthesis of protected chiral tetrol derivatives[1] and for the transfer of chirality in enantioselective reactions.[2]

(1) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1635. (2) Barlow, J. S.; Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1627.

55,692-0
(2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2,3-dicarboxylic acid dimethyl ester, 98% **25g $56.85**

55,693-9
(2*S*,3*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxane-2,3-dicarboxylic dimethyl ester
1g $10.45; 5g $34.80

Naturally, we made these useful reagents. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

About Our Cover

Edouard Manet's *Masked Ball at the Opera* (oil on canvas, 23¼ in. x 28½ in.), signed and dated 1873, is a reminder of one of the many sophisticated entertainment forms available to Parisians in the third quarter of the nineteenth century: the balls held at the opera on Saturday nights in March during Lent. The foyer of the old Opera House in the Rue Le Peletier is shown crowded with figures. The flowing line of the silk hats of a large group of elegantly dressed gentlemen creates a graceful rhythm across the center of the scene, helping to unify an otherwise somewhat fragmented composition. The informality and great variety of poses of the figures and the seemingly random cropping on either side and across the top of the image give a sense of immediacy and realism to the scene. The figures of Polichinelle on the left, of the gentleman on the right edge of the canvas, and of those on the balcony are all cut off by the frame, suggesting that only a small part of what is going on is visible in the picture. Manet included portraits of himself and several of his friends in the painting, which is remarkable for the absence of color. Manet saw the men's silk hats and evening clothes as a unique opportunity to depict every variation of ebony.

This painting is a gift of Mrs. Horace Havemeyer to the National Gallery of Art in Washington, D.C.

Table of Contents

Lab Notes

Rapid-Dry TLC Spotter

Flash chromatography can very quickly generate a lot of samples that may require spotting on a TLC plate for analysis. If you want to get small spots at the origin you have to add the solvent slowly while blowing on the spot to evaporate the solvent. This can lead to hyperventilation or solvent inhalation and, depending on the number of fractions, can take longer than running the column.

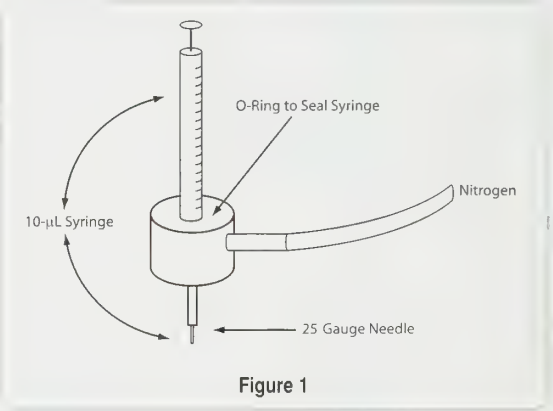


Figure 1

To simplify this operation and speed up the process, I devised a simple apparatus (**Figure 1**) to facilitate spotting of the TLC plate. The device is made from a cylinder of polymer in which the top is bored out to receive a flat-nosed, 10-microliter syringe, which is held in place by an O-ring (a trace of silicone grease on the O-ring facilitates the insertion and removal of the syringe barrel). A hose connector is attached to the side of the cylinder and used as an inlet for nitrogen. A hole in the bottom of the cylinder is fitted with a 25-gauge needle through which the tip of the 10-microliter syringe just emerges when inserted through the top. Nitrogen flows into the body of the device, down through the 25-gauge annulus and around the syringe needle, where it evenly and quickly evaporates the solvent as it is applied by depression of the syringe plunger.

This device has saved me countless hours while spotting TLC plates with flash chromatography fractions, especially those in higher boiling solvents. You also get narrower spots and thus achieve better resolution upon development of the TLC plate.

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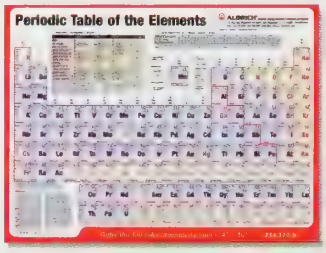

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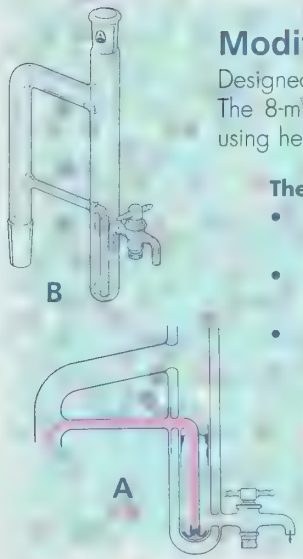

Modified Dean-Stark Apparatus

Designed specifically for azeotropic distillation using solvents heavier than water (e.g., chloroform). The 8-mL reservoir is specifically designed for small-scale azeotropic distillation of valuable solvents using heavy water. 2mm bore PTFE stopcock, 300mm overall height.

The modified Dean-Stark technique

- Solvent vapors condense and collect in the receiver.
- The modified Dean-Stark trap separates the two components.
- The heavier-than-water layer sinks to the bottom of the trap leaving the water on top.
- The solvent is forced back through the inside tube and returned to the boiling flask.
- The upper water layer is drained out through the 2mm PTFE stopcock.

Reservoir Cap.	₹ 24/40 Cat. No.	₹ 29/32 Cat. No.	Each
A. 8mL	Z51,617-1	Z51,629-5	$256.55
B. 35mL	Z24,959-9	Z51,630-9	263.25

DEDICATED TO PROFESSOR H. C. BROWN ON HIS 90TH BIRTHDAY

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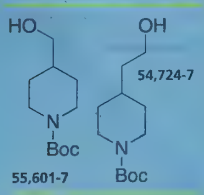
Pinane-Based
"Allyl"boranes

NEW Products

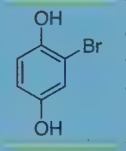


These Boc-protected piperidines have been utilized extensively in the drug discovery arena. Recent applications include their use in the synthesis of several types of GPIIb/IIIa antagonists[1-4] and of potent and selective inhibitors of acetylcholineesterase.[5]

(1) Hoekstra, W. J. et al. *J. Med. Chem.* **1999**, *42*, 5254. (2) Fisher, M. J. et al. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 835. (3) Egbertson, M. S. et al. *J. Med. Chem.* **1999**, *42*, 2409. (4) Xue, C.-B. et al. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3499. (5) Villalobos, A. et al. *J. Med. Chem.* **1994**, *37*, 2721.

55,601-7
***N*-Boc-4-piperidinemethanol**, 97% **1g $20.20; 5g $67.25**

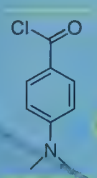
54,724-7
***N*-Boc-4-piperidineethanol**, 97% **1g $22.80; 5g $76.00**



This versatile hydroquinone has been employed as a building block for the synthesis of biologically active marine metabolites such as *ent*-chromazonarol,[1] 9,11-drimen-8α-ol,[2] and fulvanin.[2] It has also found applications in nonlinear optics as a monomer for phenylene–ethynylene oligomers.[3]

(1) Barrero, A. F. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2325. (2) Barrero, A. F. et al. *Synlett* **2000**, *11*, 1561. (3) Wautelet, P. et al. *Macromolecules* **1996**, *29*, 446.

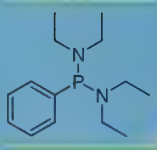
16,713-4
2-Bromohydroquinone, 97% **1g $17.10; 10g $95.00**



This convenient building block allows the facile preparation of 4-(dimethylamino)benzoyl-substituted compounds.

Purchase, T. S. et al. *Bioorg. Med. Chem.* **1997**, *5*, 739.

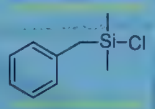
52,611-8
4-(Dimethylamino)benzoyl chloride, 97%
1g $6.00; 5g $19.00



Utilized as a milder alternative to dichlorophenylphosphine (Aldrich catalog number D7,198-4).

(1) Nettekoven, U. *J. Org. Chem.* **1999**, *64*, 3996. (2) Tollefson, M. B. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9052.

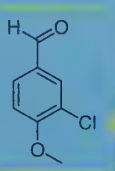
55,470-7
Bis(diethylamino)phenylphosphine, 97%
1g $8.00; 5g $25.50



Employed in the synthesis of amino-substituted vinylsilanes, which were smoothly cyclized to the corresponding pyrrolidines.

Miura, K. et al. *Org. Lett.* **2000**, *2*, 385.

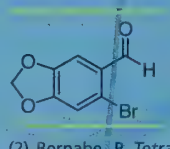
56,237-8
Benzylchlorodimethylsilane, 97% **1mL $15.00; 5mL $50.00**



Has been used in the synthesis of lycorine-type alkaloids[1] and substituted phthalazines.[2]

(1) Lida, H. et al. *J. Chem. Soc., Perkin Trans. I* **1975**, 2502. (2) Watanabe, N. et al. *J. Med. Chem.* **1998**, *41*, 3367.

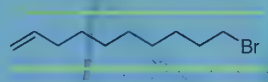
56,504-0
3-Chloro-4-methoxybenzaldehyde, 97%
1g $27.55; 5g $91.75



This bromo aldehyde was employed in total syntheses of (–)-lycoricidine,[1] benzo[*c*]phenanthridines,[2] and the diaza analog of ellagic acid.[3]

(1) Keck, G. E. *J. Am. Chem. Soc.* **1999**, *121*, 5176. (2) Bernabe, P. *Tetrahedron Lett.* **1998**, *39*, 9785. (3) Kanojia, R. M. *ibid.* **1995**, *36*, 8553.

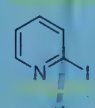
56,301-3
6-Bromopiperonal, 97% **50g $17.80**



Important intermediate for the preparation of macrocyclic ketones, such as (*R*)-(–)-muscone,[1] and biologically active macrocyclic lactones.[2]

(1) Kamat, V. P. et al. *Tetrahedron* **2000**, *56*, 4397. (2) Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65*, 612.

56,085-5
10-Bromo-1-decene, 97% **1g $19.25; 5g $64.05**



This versatile reagent has been used in Sonogashira[1] and Suzuki coupling reactions in the presence of carbon monoxide to produce α-pyridyl ketones,[2] as well as in coupling reactions with aryl thiols to produce heteroaromatic thioethers.[3]

(1) Koseki, Y. et al. *Tetrahedron Lett.* **2000**, *41*, 2377. (2) Couve-Bonnaire, S. et al. *ibid.* **2001**, *42*, 3689. (3) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069.

55,876-1
2-Iodopyridine, 98% **1g $16.00; 5g $59.55**

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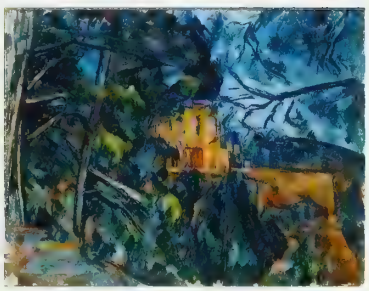


Le Château Noir (oil on canvas, 73.7 cm x 96.6 cm) was painted by Paul Cézanne between 1900 and 1904. At the center of the painting stands the chateau, with its Gothic windows, red door, and terra cotta and ochre walls contrasted with the deep green of the surrounding vegetation and the intense blue of the Provençal sky. The title, *The Black Chateau*, comes from the fact that the original owner, a manufacturer of lampblack (a pigment made from soot), had the house's interior walls painted black.

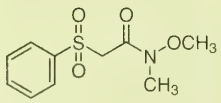
Cézanne was born in nearby Aix-en-Provence, and as a youth took long walks to the chateau and the surrounding estate. His father wanted him to study law, but in 1861 he abandoned his legal studies and went to Paris to devote himself to painting. There, he met the artist Camille Pissarro and became acquainted with the impressionists. He exhibited with these artists in 1874 and 1877, but his artistic aims were never entirely compatible with impressionism, which sought to capture through the analysis of color and light the effect of transitory visual sensation. The impressionist technique tends to dissolve any sense of solid form, but Cézanne declared that he wished "to make of impressionism something solid and durable, like the art of the museums". He wanted to "do Poussin over again, after nature", which is to say that he wanted to reconcile two seeming opposites, the immediacy of observed nature and the timeless order of the compositions of his seventeenth-century predecessor. He increasingly thought in terms of simple planes and volumes modeled in color, which he understood as the embodiment of the underlying forms of visible objects.

In *Le Château Noir*, the walls of the house, the path, the tree trunks and leafy branches, even the sky, are painted in planes of rich color. Cézanne had no interest in specific or picturesque details, but believed that a painting must succeed both as an illusion of depth and as a textural surface of heavy and vibrant pigments. The result of this approach was an ever-greater abstraction, and his influence on artists like Picasso and Braque, who in time almost completely abandoned any connection to the illusionism of traditional representation, was incalculable.

This painting is a gift of Eugene and Agnes Meyer to the National Gallery of Art, Washington, D.C.

"Please Bother Us."

Clint Lane, President



Dr. Indrapal Singh Aidhen and his research group at the Indian Institute of Technology Madras (Chennai, India) have developed *N*-methoxy-*N*-methyl-2-phenylsulfonyl-acetamide as a versatile reagent for the two-carbon homologation of alkyl halides under mild conditions (K_2CO_3 in DMF). Dr. Aidhen kindly suggested that we offer this valuable amide to our customers.

Satyamurthi, N.; Singh, J.; Aidhen, I. S. *Synthesis* **2000**, 375.
Satyamurthi, N.; Aidhen, I. S. *Carbohydr. Lett.* **1999**, *3*, 355.

56,108-8
***N*-Methoxy-*N*-methyl-2-phenylsulfonyl-acetamide**, 97% **1g $13.00; 5g $42.90**

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Herbert C. Brown and Aldrich

There is hardly any chemist today, who is not aware of Professor Brown's accomplishments in, and impact on, the field of chemistry. Perhaps no one is more keenly aware of his lasting contributions than we are at Aldrich Chemical Company.

When Professor Brown finally convinced a small chemical company (Aldrich) of the merits of commercializing his hydroboration technology,[1] a 30-year, highly successful collaboration began between Dr. Brown and Aldrich Chemical Company. Thus, the Aldrich-Boranes "acorn" was planted just over 30 years ago and has now grown into a tall, sturdy "oak". Some of the fruits of this collaboration have been the wide array of boron compounds that Aldrich has made available to chemists worldwide, and the financial rewards that the Purdue Research Foundation[2] and the recipients of the annual Herbert C. Brown Award[3] have reaped.

Photo courtesy of H.C. Brown

Sarah and Herbert Brown in front of the new building devoted to the production of air-sensitive compounds at the Aldrich plant near Sheboygan Falls, WI (October 14, 1999).

Brown served on the Aldrich Board of Directors (1972–1975), the Sigma-Aldrich Board of Directors (1975–1979), and has been retained as a consultant by Aldrich (1972–Present). A few of Brown's students came to work for Aldrich and made important contributions to the growth of the business, perhaps none more so than Clint Lane, Aldrich's current president.

No write-up about Professor Brown, however brief, would be complete without mentioning his lifelong passion for *chemistry*.[4] As attendees of professional meetings such as the ACS or the Boron Americas meetings can attest to, Nobel Laureate Brown still attends as many talks as he possibly can and unassumingly walks around the exhibition halls checking out exhibits, visiting vendors, and picking up chemical literature—just as an eager, young graduate student would do, except that Brown is nearly 90 years old! Professor Brown's other lifelong love is *Sarah Baylen Brown*, his wife of 65 years. As Brown put it "I take care of the chemistry, and Sarah takes care of the money and everything else". Brown relates a pertinent story that is dear to his heart: not long ago both of them were attending a professional function and were observed to treat each other affectionately. This prompted a couple, who didn't know them well, to ask them if they were newlyweds! After family and chemistry in general, Brown is perhaps most fond of *boron* and its compounds; he was particularly thrilled when he bought a laser pointer that emitted a green light—the color associated with the combustion of boron compounds. In fact, those very close to him know that just about the only way to get him off the subject of boron chemistry is to ask him about his two granddaughters.

In writing this piece about Professor Brown, we were hard-pressed to learn about any interests he might have outside of chemistry. The only one we could identify is photography. Of the few things he dislikes, doing chores that require physical exertion appears to be foremost.[5]

Professor Brown,

Your friends and admirers at Aldrich thank you for your lasting contributions to chemistry and to the success of Aldrich, and wish you a happy ninetieth birthday.[6] Many of us look forward to celebrating your birthday—with you, Sarah, your son Charles, your two granddaughters, Tamar and Ronni, and many of the more than 500 former Brown students—at a special symposium to be held on May 23–25, 2002 at Purdue University.

References and Notes: (1) Firsan, S. J. *Aldrichimica Acta* **2001**, *34*, 35. (2) Reference 1, p 44. (3) *The Herbert C. Brown Award for Creative Research in Synthetic Methods*, administered by the American Chemical Society (ACS) and co-sponsored by Aldrich Chemical Company. More information on this award is found on the ACS Web site at www.chemistry.org. (4) (a) Many anecdotes and fascinating information, particularly about Brown's early years, have been compiled in a book celebrating Brown's 66th birthday and retirement: *Remembering HCB: Memoirs of Colleagues and Students of Herbert C. Brown*; Bank, S., Ed.; Purdue University: West Lafayette, IN, 1978. (b) An essay honoring Professor Brown on the occasion of his 75th birthday has appeared in an earlier issue of this magazine: Brewster, J. H. *Aldrichimica Acta* **1987**, *20*, 3. (5) Reference 4a, p 5. (6) Herbert C. Brown's ninetieth birthday falls on May 22, 2002.

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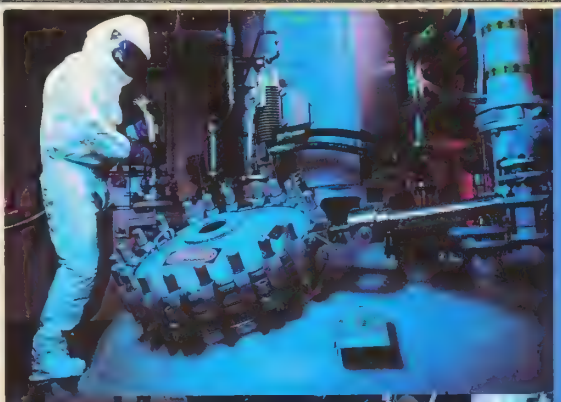

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Borane–Amine Complexes for Hydroboration

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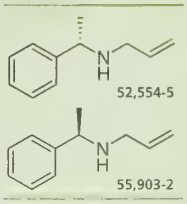
Was employed in the synthesis of nonlinear optical polymers,[1] and served as a starting material for the construction of complex organometallics.[2]

(1) Buchmeiser, M.; Schrock, R.R. *Macromolecules* **1995**, *28*, 6642. (2) Buchmeiser, M.; Schottenberger, H. *J. Organomet. Chem.* **1992**, *441*, 457.

44,265-8

Ethynylferrocene, 97% **1g $59.00**



These chiral amines have been utilized in the asymmetric synthesis of β-lactams[1] and β-amino acids.[2]

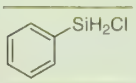
(1) Bull, S. D. et al. *J. Chem. Soc., Perkin Trans. I* **2001**, 3106. (2) Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1999**, *40*, 9313.

52,554-5

(*S*)-(–)-*N*-Allyl-α-methylbenzylamine, 97% **1mL $9.90; 10mL $55.00**

55,903-2

(*R*)-(+)-*N*-Allyl-α-methylbenzylamine, 97% **1g $58.15; 5g $193.80**

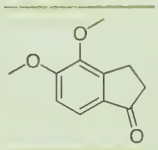


Utilized in the platinum-catalyzed hydrosilylation of olefins for the generation of dendrons with a chlorosilyl functional group.

Cuadrado, I. et al. *J. Am. Chem. Soc.* **1997**, *119*, 7613.

56,923-2

Chlorophenylsilane, 97% **1g $16.95; 5g $56.40**

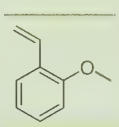


Employed in the synthesis of cyclopentano-1,2,3,4-tetrahydroisoquinolines[1] and a novel 5-HT_{2c} receptor agonist.[2]

(1) Mathison, I. W. et al. *J. Org. Chem.* **1974**, *39*, 2852. (2) Adams, D. R.; Duncton, M. A. J. *Synth. Commun.* **2001**, *31*, 2029.

56,825-2

4,5-Dimethoxy-1-indanone, 97% **1g $28.80; 5g $96.00**

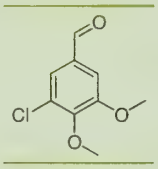


Has been employed to produce isoxazolidines through 1,3-dipolar cycloaddition reactions.

Chiacchio, U. et al. *Tetrahedron* **1994**, *50*, 6671.

56,306-4

2-Vinylanisole, 98% **1g $22.60; 5g $75.30**

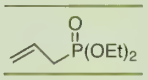


Basic building block for the synthesis of 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines.[1,2]

(1) Weinstock, J. et al. *J. Med. Chem.* **1986**, *29*, 2315. (2) Gallagher, G., Jr. et al. Ger. Patent 2,802,087, Jul 1978; *Chem. Abstr.* **1978**, *89*, 163433v.

56,939-9

3-Chloro-4,5-dimethoxybenzaldehyde, 97% **1g $25.60; 5g $100.00**

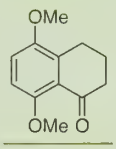


Used in the preparation of 1,3-dienes with high *E*-isomer selectivity through the Horner–Wadsworth–Emmons reaction.[1,2]

(1) West, F.G.; Wang, Y. *Synthesis* **2002**, 99. (2) Maryanoff, B.E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

56,541-5

Diethyl allyl phosphonate, 98% **1g $13.35; 5g $44.40**

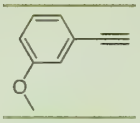


Tetralones have proven their synthetic versatility in the development of numerous biologically active compounds. 5,8-Dimethoxy-1-tetralone, for example, is a key intermediate in the synthesis of the antifungal and anticancer natural product (±)-diepoxin σ and related isomers.

Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319.

56,965-8

5,8-Dimethoxy-1-tetralone, 99% **1g $42.55; 5g $141.80**

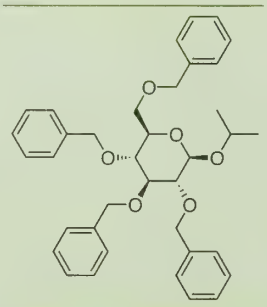


Utilized in palladium-catalyzed coupling reactions that lead to vinylsilanes stereoselectively.

Chatani, N. et al. *J. Org. Chem.* **1995**, *60*, 1834.

51,941-3

3-Ethynylanisole, 96% **5g $74.00**



An excellent glycoside for the stereoselective synthesis of complex oligosaccharides and glycoconjugates.[1,2]

(1) Mereyala, H.B.; Reddy, G.V. *Tetrahedron* **1991**, *47*, 6435. (2) Garcia, B.A.; Gin, D.Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

57,004-4

Isopropyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside, 98% **1g $32.35; 5g $107.70**

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About Our Cover

Photograph © Board of Trustees, National Gallery of Art, Washington

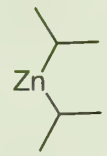
Baby at Play (oil on canvas, 81.9 x 122.9 cm) was painted by Thomas Eakins in 1876. Eakins was born and grew up in Philadelphia. After taking courses at the Pennsylvania Academy of the Fine Arts, and studying anatomy there and at the Jefferson Medical College, he went in 1866 to Paris, where he attended the École des Beaux-Arts and studied independently with several artists, including Jean-Léon Gérôme. During the five or six years after his return to Philadelphia three years later, Eakins painted a number of both individual and group portraits of members of his family and that of his sister Frances, who married Eakins's boyhood friend, William J. Crowell. The subject of *Baby at Play* is Eakins's two-year-old niece, Ella Crowell. The low vantage point from which we see the figure, which is life-size, helps to draw attention to the child's almost solemn concentration on what she is doing. The painting is a good example of what the artist called "genre portraits", i.e., representations of people shown engaged in typical activities in their usual settings. It is probable that it is more than that, however.

The picture was painted just at the time that educational reformers in Europe, especially the English social philosopher Herbert Spencer, whose *Education: Intellectual, Moral, and Physical* was published in New York in 1866, were having a great effect on educational thought and practice in America. Eakins, who was well-known for his serious dedication to the disciplined teaching of art, mentioned Spencer in a letter to his father just two years later. It is quite likely that this painting reflects Spencer's statement that "men are at last seeing that the spontaneous activity of the observing faculties in children has a meaning and a use. What was once thought mere purposeless action, or play, or mischief, as the case might be, is now recognized as the process of acquiring a knowledge upon which all after-knowledge is based." Eakins's acquaintance with Spencer's ideas means that this painting probably should not be considered as simply a representation of light-hearted childish play, but as a depiction of a more serious endeavor, the learning a child gains through experience and observation.

This painting is in the John Hay Whitney Collection at the National Gallery of Art, Washington, D.C.

"Please Bother Us."

Clint Lane, President



Professor Matthew H. Todd of the Department of Chemistry at Queen Mary, University of London, kindly suggested that we offer diisopropylzinc. This organometallic reagent undergoes an asymmetric autocatalytic reaction with substituted pyrimidines and a chiral initiator.

Shibata, T. et al. *J. Am. Chem. Soc.* **1998**, *120*, 12157

56,811-2
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5mL $66.00; 25mL $222.00

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

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Lab Notes

A Simple Procedure for Polishing Circular and Rectangular Infrared Crystal Windows[1]

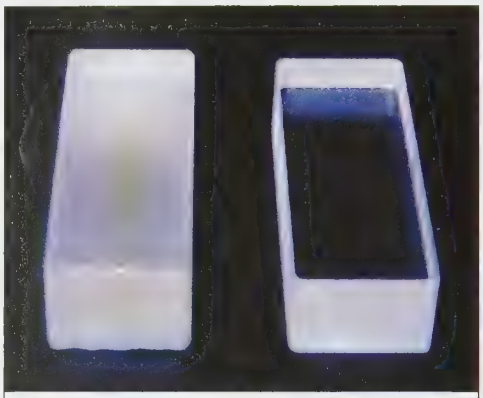

Figure 1. IR Crystal Window Before and After Polishing with the Current Procedure.

Polished crystal windows intended for use in infrared (IR) spectroscopy tend to fog even when not heavily used. The fogging is due primarily to ambient humidity and/or to trace amounts of water in the samples being analyzed.

In addition to the obvious cost saving on replacing windows (a pair of NaCl windows, the cheapest of all such windows, now costs about $20), the main reason for polishing IR windows is to improve the evenness of the crystal surface and thus the sample film or mull, resulting in an enhancement of the overall quality of the spectrum.

Assuming that the IR user does not have access to a crystal-polishing kit,[2] the materials needed to carry out the procedure described below are: (1) a flat, hard surface such as a bench top; (2) a laboratory paper towel (e.g., KIMTOWELS® wipers; Aldrich cat. no. Z23,678-0); (3) an ordinary piece of harsh, tan paper towels (the kind found in many bathrooms); (4) polishing compound (ferric oxide powder, Fe_2O_3; e.g., Aldrich cat. no. 31,005-0); and (5) a polishing solution (*i*-PrOH/H_2O 9:1).

Lay the laboratory and tan paper towels side by side on the lab bench. Place a small amount of the polishing compound on the tan paper towel and saturate the towel with the polishing solution. Using a spatula or spoon, smear the polishing compound over the soaked towel in such a way as to create a smooth, even layer of polishing compound. Grip the sample-free window firmly between the thumb and index finger, and rub its bottom side on the polishing compound using light pressure and tracing a figure 8. The number of times a figure 8 is traced will depend on how bad the window surface is. Lift the window off of the paper towel and trace figure 8's with it on the laboratory towel in order to dry it and rid it of excess ferric oxide.

Inspect the polished surface. If it looks transparent enough, repeat the above procedure with the opposite face of the window. When both surfaces are done, and only if needed, they can be rinsed with an anhydrous solvent such as anhydrous acetone. When not in use, the polished windows should be stored in a desiccator over a drying agent such as Drierite®.

This polishing procedure is routinely used in our laboratories, and is recommended mainly for NaCl or KBr windows—which are the most widely used types.

Notes: (1) If the IR crystal window is badly scratched or pitted, or if its surfaces are no longer flat from uneven polishing, the damaged window can be reclaimed as follows: It is first lapped on an ultrafine 600 grit sandpaper (e.g., 3M's TRI-M-ITE™ silicon carbide 600 TN4) to remove surface damage or flatten the entire window face. The window is then polished as described above. (2) For example, Aldrich cat. no. Z11,186-4.

KIMTOWELS and Drierite are registered trademarks of Kimberly-Clark Corp. and W. A. Hammond Drierite Co., respectively. TRI-M-ITE is a trademark of 3M Co.

Editor's Notes: (1) Other, less detailed or related procedures for polishing cloudy infrared crystal windows have been reported: (a) Winston, A. *J. Chem. Educ.* **1991**, *68*, A124 (NaCl). (b) Gallego G., J. M. *J. Chem. Educ.* **1978**, *55*, 681 (NaCl, KCl). (c) Nemo, T. E. *Aldrichimica Acta* **1977**, *10*, 22 (AgCl). (d) Feairheller, W. R., Jr.; DuFour, H. *Appl. Spectrosc.* **1967**, *21*, 45 (CsI, CsBr). (e) Levine, M. A. *Appl. Opt.* **1966**, *5*, 1957 (CsI). (2) Customary lab safety precautions, such as the donning of suitable gloves, should be taken when using this polishing procedure.

James J. Brien
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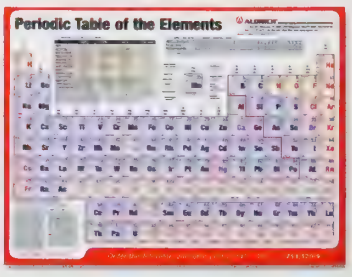

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(Last issue in 2002)

Applications of Ionic Liquids in Organic Synthesis

Novel Methods of Resolving Racemic Diols and Amino Alcohols

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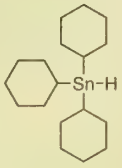
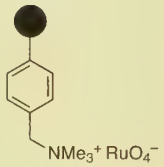


Utilized in the hydrostannation of a variety of functionalized alkenes in good yields.

Jousseaume, B. et al. *Organometallics* **1995**, *14*, 685.

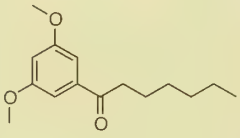
51,158-7 Perruthenate, polymer-bound
5g $82.00; 25g $340.00



Has been used in the oxidation of pyridylcarbinols,[1] hydroxylamines,[2] benzylic alcohols,[3] and primary alcohols to their corresponding aldehydes.

(1) Habermann, J. et al. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253. (2) Hinzen, B.; Ley, S.V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1. (3) Haunert, F. et al. *ibid.* **1998**, 2235.

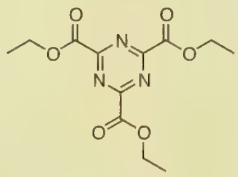
57,553-4 1-(3,5-Dimethoxyphenyl)heptan-1-one, 96%
1g $25.75; 5g $85.75



An intermediate in the synthesis of functionalized cannabinoids.[1,2]

(1) Papahatjis, D. P. et al. *J. Med. Chem.* **1998**, *41*, 1195. (2) Harrington, P. E. et al. *J. Org. Chem.* **2000**, *65*, 6576.

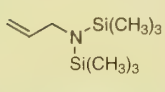
57,669-7 Triethyl 1,3,5-triazine-2,4,6-tricarboxylate, 97%
1g $24.30; 5g $81.00



A reactive azadiene that is very useful in inverse-electron-demand Diels–Alder reactions for the efficient synthesis of highly functionalized pyrimidines.[1] Also utilized in the synthesis of purines and purine analogs via Diels–Alder reactions with aromatic dienophiles.[2]

(1) Dang, Q. et al. *J. Org. Chem.* **1996**, *61*, 5204. (2) Dang, Q. et al. *J. Am. Chem. Soc.* **1999**, *121*, 5833.

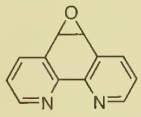
57,893-2 2-Allyl-1,1,1,3,3,3-hexamethyldisilazane, 97%
5g $18.80; 25g $62.50



Was utilized to generate aminoalkylboronic acids.

Goeller, B. et al. *Main Group Metal Chemistry* **1997**, *20*, 795.

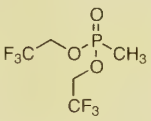
57,878-9 5,6-Epoxy-5,6-dihydro[1,10]phenanthroline, 98%
1g $28.00; 5g $100.00



Versatile reagent that has been employed in syntheses of 5-substituted 1,10-phenanthrolines[1] and in the preparation of the marine alkaloid ascididemin.[2]

(1) Riklin, M. et al. *J. Chem. Soc., Dalton Trans.* **2001**, 1813. (2) Moody, C. J. et al. *Tetrahedron* **1992**, *48*, 3589.

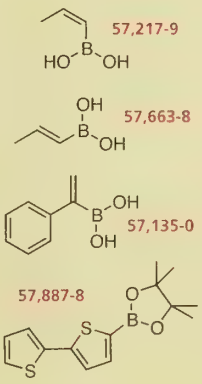
57,944-0 Bis(trifluoroethyl) methylphosphonate, 99%
5g $25.00; 25g $85.00



An excellent starting material for the stereoselective synthesis of Z α,β-unsaturated esters[1] and ketones.[2]

(1) Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (2) Yu, Y. et al. *ibid.* **1999**, *40*, 6725.

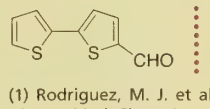
57,217-9 *cis*-Propenylboronic acid 1g $31.30; 5g $104.20
57,663-8 *trans*-Propenylboronic acid 1g $59.00; 5g $188.00
57,135-0 α-Phenylvinylboronic acid 1g $25.75; 5g $85.75
57,887-8 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2′-bithiophene 1g $30.00; 5g $88.00



Vinyl boronic acids, like arylboronic acids, undergo facile Suzuki–Miyaura coupling with aromatic halides in the presence of palladium catalysts.[1] Several years ago, Miyaura and co-workers demonstrated the utility of cyclic pinacol esters of arylboronic acids in Suzuki–Miyaura coupling reactions.[2,3] Very recently, α-phenylvinylboronic acid was used for the preparation of the corresponding nonracemic alcohols via asymmetric hydrogenation, in the presence of a chiral rhodium catalyst, followed by oxidative cleavage.[4]

(1) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (2) Ishiyama, T. et al. *J. Org. Chem.* **1995**, *60*, 7508. (3) Ishiyama, T. et al. *Tetrahedron Lett.* **1997**, *38*, 3447. (4) Ueda, U. et al. *J. Organomet. Chem.* **2002**, *642*, 145.

57,670-0 2,2′-Bithiophene-5-carbaldehyde, 98%
1g $22.00; 5g $80.00



Useful in medicinal chemistry[1,2] and materials science.[3,4]

(1) Rodriguez, M. J. et al. *J. Antibiot.* **1998**, *51*, 560. (2) Xu, W.-C. et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2279. (3) Kamal, M. R. et al. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *126*, 65. (4) Soudan, P. et al. *J. Mater. Chem.* **2001**, *11*, 773.

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About Our Cover

Photograph © Board of Trustees, National Gallery of Art, Washington

Cattleya Orchid and Three Brazilian Hummingbirds (oil on wood panel, 34.8 x 45.6 cm), signed and dated 1871, was painted by the American artist Martin Johnson Heade. Heade's earliest works were portraits, but by the early 1860s he had turned to landscape, a subject more attuned to his artistic personality. Using a limited number of pictorial elements: sky, clouds, water, perhaps some trees or rocks in an essentially flat landscape, Heade created an art of varied and shifting moods. Often his portrayal of natural phenomena such as shifting sunlight, approaching rain, lightning, dark clouds, and fog gives his paintings a dramatic and even disquieting character.

During the 1860s, Heade turned to painting objects at close range, and produced a series of remarkably sensuous still life paintings of flowers. In 1863, he sailed to Rio de Janeiro to study and paint the major species of tropical hummingbirds for a book. The book was never published, but he made two other trips to Central and South America in 1866 and 1870, fascinated by the wildlife and the landscape. His approach was different from that of his friend Frederick Edwin Church, who also traveled to Latin America, but who sought to capture the grandeur of vast tropical landscapes, and it was different from that of naturalists like John James Audubon, whose purpose was to create an objective record of the birds and plants he saw. In *Cattleya Orchid and Three Brazilian Hummingbirds*, Heade carefully represents a specific kind of pink orchid and two particular species of hummingbird, one Sappho Comet, green with a yellow throat and red tail feathers, and two green-and-pink Brazilian Amethysts, but he sets these subjects in an evocative and mysterious tropical setting full of mist and diffuse light, combining the two kinds of painting at which he excelled, still life and landscape.

This painting is a gift of the Morris and Gwendolyn Cafritz Foundation to the National Gallery of Art, Washington, DC.

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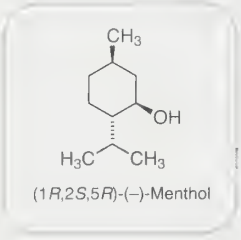
Lab Notes

(1*R*,2*S*,5*R*)-(–)-Menthol: Proposed Calibration Standard for Polarimetry

Since its discovery in the early part of the nineteenth century,[1] polarimetry has been employed extensively in the sugar[2] and pharmaceutical industries,[3] and for the analysis of chiral compounds[4] and asymmetric synthesis products[5] and catalysts.[6] Polarimetry is also used in the teaching laboratory.[7,8]

While glucose and sucrose solutions are the most commonly utilized international standards for calibrating polarimeters,[9] their use suffers from the following disadvantages:



(1*R*,2*S*,5*R*)-(–)-Menthol

- Their solutions can become easily contaminated with bacteria or fungi.
- Sucrose can hydrolyze to a mixture of glucose and fructose, with a resulting reversal of the optical rotation.[10]
- Mutarotation is observed for solutions of glucose, which give constant rotations only after some hours.[11]

Thus, we thought it desirable to search for a new polarimetry standard, which ought to be stable, inexpensive, and easy to prepare and purify. We conducted preliminary tests on several candidates [(+)-tartaric acid, quinine sulfate, ephedrine, and *l*-menthol] and compared the results with those obtained with glucose and sucrose:

- Aqueous solutions of (+)-tartaric acid[12] and quinine sulfate racemized slowly and did not give stable readings.
- Aqueous solutions of ephedrine hydrochloride[13] (generated in situ from the free base and hydrochloric acid) gave stable readings, but, after three months, these readings changed due to racemization.

In contrast, we obtained good results with (1*R*,2*S*,5*R*)-(–)-menthol,[14] which may be obtained by resolving racemic synthetic menthol,[8] by asymmetric synthesis,[15] or, more commonly, from the essential oils of several species of mint, e.g., *Mentha piperita* or *Mentha herbensis*.[16] It is also commercially available,[17] inexpensive (much less so than ephedrine or quinine sulfate), and easy to purify by recrystallization or sublimation[14]—even easier than sucrose or glucose. We found ethanolic solutions of (–)-menthol to be stable for years.

We used samples of enantiomerically pure natural (–)-menthol[18] of constant melting point (41–42 °C), and checked their chemical purity by the method of Ligor and Buszewski.[19,20] The purities obtained fell in the range of >99.9 to 100%. We then measured the absolute optical rotation of a 10% solution of (–)-menthol in absolute ethanol on a JASCO DIP 370 digital polarimeter. 27 measurements were carried out at 25 °C over a period of 72 days. The average of these measurements, $[\alpha]_D^{25}$ = -50.40 ± 0.01 (c = 10, C_2H_5OH), compares very favorably with the reported value of $[\alpha]_D^{25}$ = -50 (c = 10, C_2H_5OH).[8,14,17]

We have been routinely using such an ethanolic solution of natural menthol (stored in a tightly closed vial) as a polarimeter calibration standard for over three years. We have obtained very stable readings during this period, and found no evidence of decomposition or loss by evaporation.

References and Notes

(1) (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994; pp 2–3. (b) The first practical polarimeter was constructed in 1840. Biot, J. B. *Ann. Chim. Phys.* **1840**, *74*, 401; http://museum.nist.gov/panels/bates/intro.htm (accessed May 14, 2002). (2) Ulber, R.; Faurie, R.; Sosnitza, P.; Fischer, L.; Stärk, E.; Arbeck, C.; Scheper, T. *J. Chromatogr., A* **2000**, *882*, 329. (3) Maier, N. M.; Pilar, F.; Lindner, W. *J. Chromatogr., A* **2001**, *906*, 3. (4) Goodall, D. M. *Trac-Trend Anal. Chem.* **1993**, *12*, 177; *Chem. Abstr.* **1993**, *119*, 155032m. (5) Huerta, F. F.; Minidis, A. B. E; Backvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 221. (6) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (7) Mosher, M. D.; Kelly, C. O.; Mosher, M. W. *J. Chem. Educ.* **1996**, *73*, 567. (8) Poiré, C.; Rabiller, C.; Chon, C.; Hudhomme, P. *J. Chem. Educ.* **1996**, *73*, 93. (9) National Institute of Standards and Technology (NIST). *Standard Reference Materials*; SRM No. 17e and 917b. http//www.srmcatalog.nist.gov/srmcatalog/tables/204-6.htm (accessed May 8, 2002). (10) Eggleston, G.; Vercelotti, J. R. *J. Carbohydr. Chem.* **2000**, *19*, 1305. (11) Yamabe, S.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 4519. (12) Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. *J. Chem. Soc.* **1959**, 2492. (13) Goss, C. A.; Wilson, D. C.; Welser, W. E. *Anal. Chem.* **1994**, *66*, 3093. (14) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, U.K., 1988; p 215. (15) Milone, C.; Gangemi, C.; Neri, G.; Pistone, A.; Galvagno, S. *Appl. Catal. A, Gen.* **2000**, *199*, 239. (16) Veronese, P.; Li, X.; Niu, X. M.; Weller, S. C.; Bressan, R. A.; Hasegawa, P. M. *Plant Cell. Tiss. Organ Cult.* **2001**, *64*, 133. (17) For example, Aldrich Chemical Company. *Handbook of Fine Chemicals and Laboratory Equipment*, U.S. ed.; Milwaukee, WI, 2003–2004; p 1161, cat. no. M278-0. Also available at www.sigma-aldrich.com. (18) Brazilian standard pharmaceutical grade, which is equivalent to USP grade. The samples were obtained from Drogasil or Henrifarma). (19) Ligor, M.; Buszewski, B. *J. Chromatogr., A* **1999**, *847*, 161. (20) HP 5890 II gas chromatograph; HP5, cross-linked 5% methyl silicone capillary glass column (30 m x 0.32 mm x 0.25 μm); nitrogen carrier gas; the injector temperature (200 °C), the FID temperature (250 °C), and the heating program were the same as those reported by Ligor and Buszewski.

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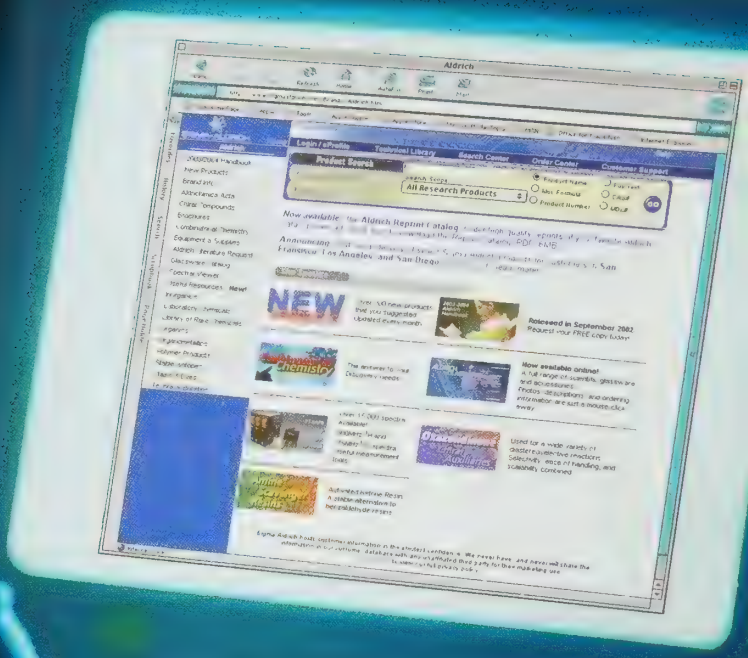

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VOL. 36, NO. 1 • 2003

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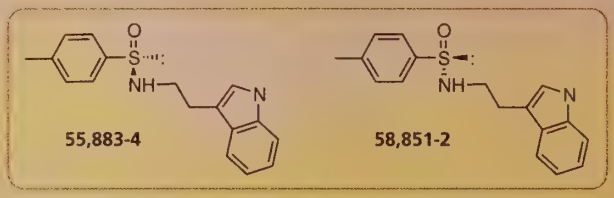


55,883-4 (*R*)-(+)-*N*-*p*-Tolylsulfinyltryptamine, 97%
1g $32.00; 5g $106.65

58,851-2 (*S*)-(–)-*N*-*p*-Tolylsulfinyltryptamine, 97%
1g $32.00; 5g $106.65

These chiral tryptamine-derived sulfinamines can be condensed with aldehydes to form *N*-sulfinyliminium ions with high diastereomeric ratios. These ions undergo Picket–Spengler cyclization to generate biologically active tetrahydro-β-carbolines.

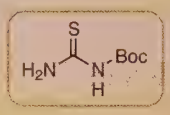
Gremmen, C. et al. *Org. Lett.* **2000**, 2, 1955.

57,926-2 3,5-Dimethoxyphenol trifluoromethanesulfonate, 97%
5g $44.40; 25g $148.00

This triflate-activated dimethoxyphenol readily undergoes Suzuki cross-couplings under mild conditions. It has been utilized in the synthesis of naturally occurring 5-alkylresorcinols[1] and Δ^8-tetrahydrocannabinol analogs.[2]

(1) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332. (2) Crocker, P. J. et al. *Tetrahedron* **1999**, *55*, 13907.

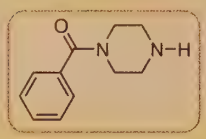
59,276-5 *N*-Boc-thiourea **1g $45.90; 5g $153.00**



This monoprotected thiourea has been used in the synthesis of 2-aminothiazole intermediates for the study of marine metabolites.

Schiavi, B. et al. *Synth. Commun.* **2002**, *32*, 1671.

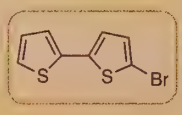
57,108-3 1-Benzoylpiperazine, 97% **1g $22.15; 5g $73.80**



Employed in the synthesis of various biologically active compounds such as nitric oxide donors,[1] pyruvate dehydrogenase kinase inhibitors,[2] and serine protease factor Xa inhibitors.[3]

(1) Mu, L. et al. *Chem. Pharm. Bull.* **2000**, *48*, 808. (2) Aicher, T. D. et al. *J. Med. Chem.* **2000**, *43*, 236. (3) Jones, S. D. et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 733.

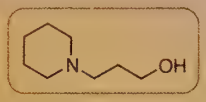
52,285-6 5-Bromo-2,2′-bithiophene, 96%
1g $40.90; 5g $171.20



Building block for the synthesis of soluble thiophene oligomers possessing electronic and electro-optical properties.

Sotgiu, G. et al. *Tetrahedron* **2002**, *58*, 2245.

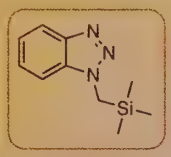
15,293-5, 1-Piperidinepropanol, 97% **1g $11.00; 5g $38.00**



Employed in the preparation of new nonimidazole histamine H_3 receptor ligands designed to increase histaminergic neurotransmission.

Apelt, J. et al. *J. Med. Chem.* **2002**, *45*, 1128.

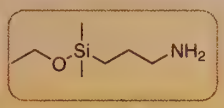
58,928-4 1-[(Trimethylsilyl)methyl]benzotriazole, 99%
1g $16.65; 5g $55.50



Reagent for the one-carbon homologation of acyl chlorides to the corresponding acids or esters.

Katritzky, A. R. et al. *J. Org. Chem.* **2001**, *66*, 5606. Katritzky, A. R. et al. *ibid.* **2002**, *67*, 7526.

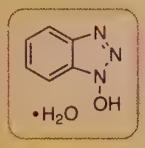
58,885-7 3-(Ethoxydimethylsilyl)propylamine, 97%
1g $39.75; 5g $132.40



Was utilized to develop surface tension arrays for the synthesis of oligonucleotide arrays on glass surfaces.

Butler, J. H. et al. *J. Am. Chem. Soc.* **2001**, *123*, 8887.

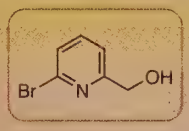
57,896-7 1-Hydroxybenzotriazole hydrate, 15 wt. % solution in dimethylfomamide
25g $28.75; 100g $79.80



A key reagent for peptide[1] and polyamide[2] synthesis.

(1) *Encyclopedia of Reagents for Organic Synthesis;* Paquette, L. A., Ed.; Wiley: West Sussex, U.K., 1995; pp 2752–2755. (2) Xiao, J. et al. *J. Org. Chem.* **2000**, *65*, 5506.

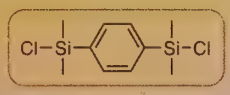
55,414-6 (6-Bromopyridin-2-yl)methanol, 96%
1g $38.25; 5g $127.40



Has been used in the synthesis of oligopyridine-functionalized aza-crown ethers[1] and 4-pyridyl-1,4-dihydropyridines.[2]

(1) Tsukube, H. et al. *J. Org. Chem.* **1993**, *58*, 4389. (2) Ashimori, A. et al. *Chem. Pharm. Bull.* **1990**, *38*, 2446.

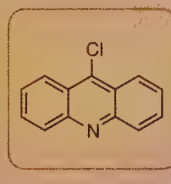
54,944-5 1,4-Phenylenebis(chlorodimethylsilane), 95%
1g $13.90; 5g $46.25



This organosilane was utilized in the synthesis of zirconocene polymers and macrocycles.

Mao, S. S. H. et al. *J. Am. Chem. Soc.* **1998**, *120*, 1193.

15,942-5 9-Chloroacridine **1g $35.00; 5g $120.00**



A main building block for many biologically active compounds such as anti-inflammatory,[1] antibacterial,[1] and antimalarial[2] substances.

(1) Yeh-Long, C. et al. *J. Med. Chem.* **2002**, *45*, 4689. (2) Kimura, M.; Okabayashi, I. *J. Heterocycl. Chem.* **1986**, *23*, 965.

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About Our Cover

Photograph © Board of Trustees, National Gallery of Art, Washington.

Landscape at Vétheuil (oil on canvas, 115 x 165 cm) was painted by the French impressionist painter Auguste Renoir around 1890. Vétheuil, on the river Seine northwest of Paris, was chosen by Renoir's fellow impressionist Claude Monet as a location sufficiently distant from Paris to avoid urban distractions and allow concentration on painting. The landscape around Vétheuil, like that near Argenteuil and other popular boating and picnicking spots along the Seine, was an important source of inspiration for a number of these artists.

The impressionists were not actually a homogeneous group united by clearly defined principles. Some can be called impressionists only at certain times during their careers, and among the group there is considerable ideological and stylistic variety. Generally speaking, however, they were unhappy with academic training, rejected the notion central to romanticism that a work of art should convey emotional content, and were uninterested in the message of social realism. They felt that the proper purpose of a work of art is not to be a vehicle for the artist's imagination or to represent historical or literary subjects, but to record dispassionately the actuality of nature and contemporary life.

Renoir's *Landscape at Vétheuil* is characteristic of impressionist paintings in the artist's rejection of a balanced and contrived composition in favor of what might be called a snapshot view, and in his use of a loose technique of small strokes of paint to convey the immediacy of visual experience. The irony is that this quasiscientific approach is often misinterpreted by modern viewers, who see in impressionism a romantic and idealized vision of the world, rather than the direct record of experience it was meant to be.

This painting is in the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

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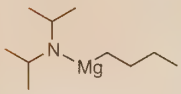
Joe Porwoll

Joe Porwoll, President



Professor Philip Eaton of the Department of Chemistry at The University of Chicago kindly suggested that we market a solution of butylmagnesium diisopropylamide. This thermally stable reagent deprotonates cyclopropane carboxamides and weak CH acids stoichiometrically and regioselectively.

Zhang, M.-X.; Eaton, P. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2169

59,045-2
Butylmagnesium diisopropylamide, 1.0*M* solution in tetrahydrofuran
25mL $21.10; 100mL $58.50

Naturally, we made this valuable reagent. It was no bother at all, just a pleasure to be able to help.

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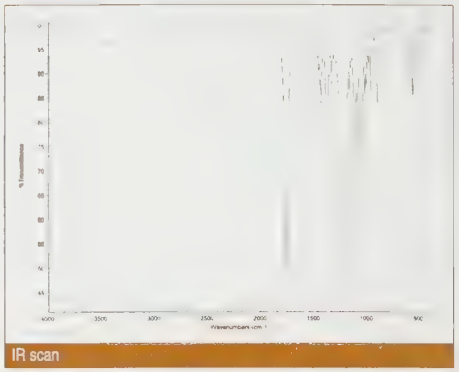
Lab Notes

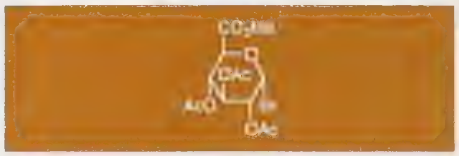
Purification of 1α-Bromotriacetylglucuronate Methyl Ester

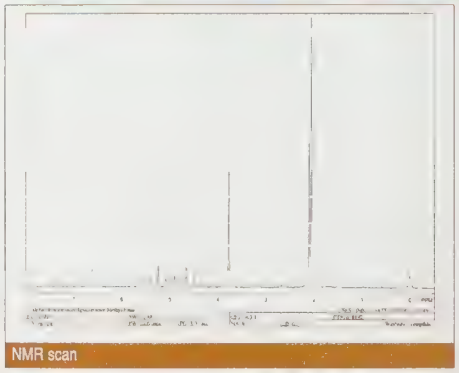
Glycoside linkages are most commonly synthesized by the Koenigs–Knorr reaction,[1] through coupling of an acetylated 1-bromosugar with an alcohol or phenol group in the presence of a salt such as silver carbonate. The key to the success of this reaction is the purity of the bromosugar, which is prepared by reacting the fully acetylated and esterified sugar with an acetic acid solution of hydrobromic acid. The original method for preparing 1α-bromotriacetylglucuronate methyl ester recommended recrystallizing the product from absolute alcohol.[2] Over the years, observations in our labs have led us to the realization that residual alcohol in the purified bromosugar generates hydrobromic acid and causes the rapid degradation of the crystals.[3] In fact, after just a few hours at room temperature, the material rapidly turns brown. After 1–3 days, the material is definitely degraded, turning an oily black, and must be recrystallized before it can be used. This degradation is so rapid that the material is not widely available commercially.[4] Even when stored under anhydrous conditions in the freezer, the material has a relatively short life span.

Difficulties with maintaining large quantities of the pure bromosugar have led us to search for a better recrystallization solvent. The requisite solvent(s) must be anhydrous and not contain reactive groups such as hydroxyls. We found that benzene–hexane or, preferably, toluene–hexane meets these requirements. The crude bromosugar is dissolved in warm (not boiling) toluene and briefly treated with decolorizing charcoal. The solution is filtered while warm through a sintered glass funnel (do not use filter paper) containing a Celite® pad, and hexane is added with stirring to the colorless filtrate until it begins to turn cloudy. The white crystals, which form after refrigeration overnight, are collected on a sintered glass funnel and thoroughly dried under high vacuum at room temperature. Material prepared in this fashion may be stored under anhydrous conditions in the freezer for an indefinite period, and is even stable at room temperature under anhydrous conditions or under vacuum for several days.

Purity can be readily determined visually (white to off-white) or by odor, since HBr can be easily detected in the decomposed material. The melting point must be carefully determined. When rapidly heated, the material melts at 82–83 °C, but, if allowed to cool and resolidify and is then heated slowly, the sample melts with decomposition at 102–104 °C. A slowly heated sample also melts with decomposition at 102–104 °C. Infrared and NMR analyses are also useful for purity determination. The IR (KBr) spectrum has two sharp carbonyl absorptions at 1767 and 1748 cm^{-1} and a set of C–O absorptions centered at 1229 cm^{-1}. The ^1H NMR ($CDCl_3$, 60 MHz) spectrum consists of overlapping acetate methyls centered at 2.05 ppm (9 H), the ester methoxy at 3.77 ppm (3 H), the C-2, C-3, C-4, and C-5 ring hydrogens between 4.5 and 5.8 ppm (4 H), and the C-1 hydrogen centered at 6.65 ppm (1 H, doublet).[5]


IR scan




NMR scan

References and Notes: (1) Conrow, R. B.; Bernstein, S. *J. Org. Chem.* **1971**, *36*, 863. (2) Bollenback, G. N.; Long, J. W.; Benjamin, D. G.; Lindquist, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 3310. (3) Hadd, H. E.; Slikker, W., Jr.; Helton, E. D. *J. Steroid Biochem.* **1980**, *13*, 1107. (4) 1α-Bromotriacetylglucuronate methyl ester (CAS Registry Number℠ 21085-72-3) is currently available from a very small number of companies, including the Sigma (cat. no. A8292) and Fluka (cat. no. 00533F) brands of Sigma-Aldrich Corp., and is shipped in dry ice. (5) The resonances at 7.27 and 7.37 ppm arise from a trace of $CHCl_3$ (from $CDCl_3$) and benzene (recrystallization solvent), respectively. While it is difficult to pump off all of the aromatic solvent, it should not affect further use of the material in the Koenigs–Knorr reaction, since this reaction is most often carried out in benzene or toluene.

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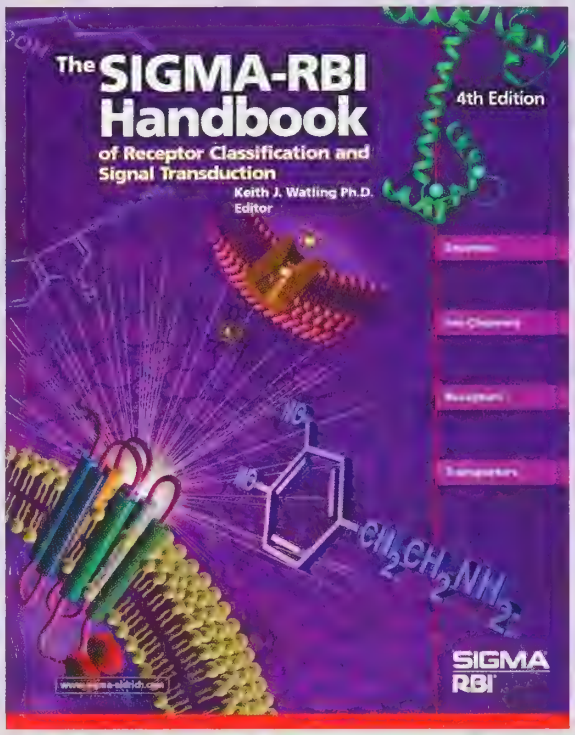

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(**2002**, *45*, 992–993)

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SPECIAL FOCUS ON NONRACEMIC AZIRIDINES AND OXAZOLINES

Aldrichimica ACTA

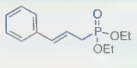
VOL. 36, NO. 2 • 2003

Aziridines and Oxazolines: Valuable Intermediates in the Synthesis of Unusual Amino Acids

Highlights of the Chemistry of Enantiomerically Pure Aziridine-2-carboxylates

New Products from Aldrich R&D

Diethyl *trans*-cinnamylphosphonate, 98%

59,438-5  5g, 25g

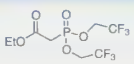
Diethyl (2-methylallyl)phosphonate, 97%

59,309-5  1g

These phosphonates were utilized in the Horner–Wadsworth–Emmons reaction to form conjugated carbon–carbon double bonds.[1] They were also employed as starting materials in an efficient and regiospecific synthesis of 4-oxo-2-alkenylphosphonates, which can serve as building blocks for the construction of polyethylenic chains.[2]

(1) Oestreich, M.; Hoppe, D. *Tetrahedron Lett.* **1999**, *40*, 1881. (2) Lee, B. S. et al. *J. Org. Chem.* **2000**, *65*, 4175.

Ethyl [Bis(2,2,2-trifluoroethoxy)phosphinyl]acetate

59,557-8  5g, 10g

This compound was exploited in the Horner–Wadsworth–Emmons reaction to synthesize α,β-unsaturated esters derived from 6-methoxytetrahydropyran-3-one.

López Tudanca, P. L. et al. *J. Chem. Soc., Perkin Trans. 1* **1992**, 533.

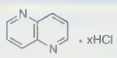
2,6-Dichloropyridine-1-oxide, 99%

59,405-9  1g, 5g

It oxidizes alkenes to epoxides[1] and alkanes to alcohols[2] in the presence of ruthenium catalysts.

(1) Zhang, J.-L.; Che, C.-M. *Org. Lett.* **2002**, *4*, 1911. (2) Yamaguchi, M. et al. *Chem. Lett.* **2002**, 434.

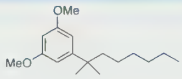
1,5-Naphthyridine hydrochloride

59,416-4  1g, 5g

Serves as a precursor of diaza-*cis*-decalins, a structurally novel class of diamine ligands.[1] Has also been used in the synthesis of one member of a series of antimicrobial parenteral 3′-quaternary ammonium cephalosporins.[2]

(1) Li, X. et al. *Org. Lett.* **2000**, *2*, 875. (2) Brown, R. F. et al. *J. Med. Chem.* **1990**, *33*, 2114.

1-(1,1-Dimethylheptyl)-3,5-dimethoxybenzene, 97%

59,522-5  1g, 5g

Employed as a starting material in the synthesis of a number of THC analogs that were evaluated for their binding affinity towards cannabinoid receptors.

Gareau, Y. et al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 189.

2,3-Dibromo-*N*-methylmaleimide

59,593-4  1g, 5g

2,3-Dibromomaleimide, 97%

55,360-3  1g, 5g

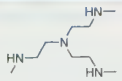
N-Benzyl-2,3-dibromomaleimide, 97%

55,778-1  1g, 5g

Dihalogenated maleimides can be used either as dieneophiles or as electrophiles. 2,3-Dibromo-*N*-methylmaleimide is a key starting material in the synthesis of rebeccamycin[1] and 7-azarebeccamycin analogs.[2] These analogs were then evaluated for their antitumor activities.

Marminon, C. et al. *Bioorg. Med. Chem.* **2003**, *11*, 679. (2) Marminon, C. et al. *J. Med. Chem.* **2003**, *46*, 609.

Tris[(methylamino)ethyl]amine, 97%

46,353-1  5g, 10g, 25g

A tripodal metal chelating agent that has been employed in the preparation of *N*-methyl superbase (Aldrich Cat. No. **46,355-8**),[1] and its stilbene and bismuth azaatrane analogs:[2] *N,N′,N″*-trimethylazastibatrane and *N,N′,N″*-trimethylazabismatrane.

(1) Tang, J.-s.; Verkade, J. G. *Tetrahedron Lett.* **1993**, *34*, 2903. (2) Shutov, P. L. et al. *Inorg. Chem.* **2002**, *41*, 6147.

N,N-Diethyl-1,1-dimethylsilylamine, 97%

58,624-2  1g, 5g

Complements $NaBH_3CN$, and has been used in the Lewis acid catalyzed reductive amination of carbonyl compounds.

Miura, K. et al. *Synlett* **2001**, 1617.

Please see pages 54–55 for additional new products.

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About Our Cover

The Railway (oil on canvas, 93.3 x 111.5 cm) was painted in 1873 by the French painter Edouard Manet. When it was exhibited in the following year, it was severely criticized by both the critics and the public, who were greatly puzzled by the subject of the picture, or rather by the fact that it seemed to have no real subject. In late 19th-century France, the most highly valued subjects in art were religious, mythological, historical, or literary. At the same time, a contrary naturalistic movement, paralleled in literature by the writings of reformist authors such as Émile Zola, favored subjects that portrayed the lower classes, like scenes of peasants working in the fields.

Photograph © Board of Trustees, National Gallery of Art, Washington

Manet's picture, however, does not represent an imaginary literary subject or a glorious historical event, nor does it portray the travails of the poor or idealize the dignity of manual labor. It simply shows a young woman, who is neither rich nor poor, pausing to rest on a bench with a puppy in her lap, accompanied by a little girl with her back to us who grasps the bars of an iron fence. It does not even seem to show what is indicated by the title of the painting, and the only clue to this is the steam rising in the background.

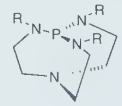
The clear outdoor light and bright color and the broad brushstrokes of his technique seem to link Manet with the impressionists, and indeed, a year after he painted *The Railway*, he was at Argenteuil painting in the open air alongside Renoir and Monet. Manet is not truly an impressionist painter, however. This is not a quickly executed representation of a chance moment, captured by the painter as a photographer makes a snapshot, but a carefully planned work. Manet sketched in the basic composition before carrying the canvas outdoors to work directly from the models. Such details as the placement of one figure facing out and the other into the picture, and the color scheme of the dresses, one white on blue and the other blue on white, show the calculation that underlies his representation of *The Railway*, a phenomenon common to modern life.

This painting is a gift of Horace Havemeyer to the National Gallery of Art, Washington, DC, in memory of his mother, Louisine W. Havemeyer.

"Please Bother Us."

Joe Porwoll

Joe Porwoll, President



R = Me, *i*-Pr, *i*-Bu

Professor John G. Verkade of the Department of Chemistry at Iowa State University kindly suggested that we provide the following three proazaphosphatrane nonionic bases. This family of superbases has broad applications[1] including recently as ligands in the Pd-catalyzed amination of aryl bromides and iodides.[2]

(1) Wroblewski, A. E.; Bansal, V.; Kisanga, P.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 561. (2) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452

46,355-8
2,8,9-Trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

55,695-5
2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

56,588-1
2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

Naturally, we made these valuable superbases. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Lab Notes

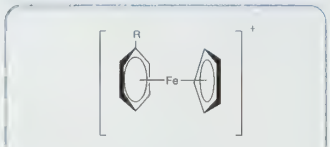
Use of the Microwave Oven for Sublimation: Flash Sublimation

Sublimation is a useful technique for the purification[1-3] or isolation[2-4] of some organic, inorganic, or organometallic compounds. Generally, if a compound can be sublimed, sublimation can be a good alternative to recrystallization or distillation. Sublimation has been known since alchemical times and, in the past, was carried out by simply heating the compound in a porcelain dish covered with a common filter paper.[5] Nowadays, a sublimation apparatus or, sometimes, a Kugelrohr oven[3,4] is used under ambient or reduced pressure.

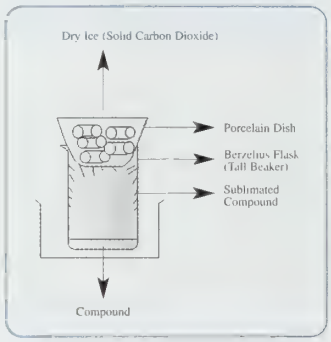
We have recently developed an improved method for the synthesis of arenocenium salts using a simple assembly for reactions under microwave conditions.[6a] It consists of a crystallizing dish and a 250-mL, tall beaker (Berzelius flask) that is covered with a porcelain dish containing dry ice. Dry ice does not absorb microwaves and, therefore, does not vaporize under microwave irradiation conditions.[6b] We found that this simple device may also be used for sublimations. Microwave sublimation has been utilized to manufacture and isolate carbon nanotubes and essential powders from fresh animal, plant, or microbial matter.[7]

We have carried out the sublimation, under microwave heating, of some representative inorganic, organometallic, and organic compounds in the apparatus shown here. The sublimations were fast and easy to carry out. Collection of the sublimate with a spatula was also straightforward. The compounds tested and the "yields" of the corresponding sublimates are presented in **Table 1**. Even certain slightly air-sensitive compounds (Table 1, entries 7, 8, and 10), that are generally purified by sublimation under reduced pressure, may be purified by this method.

Acetyl ferrocene,[9] decadeuteroferrocene,[4] and (cyclopentadienyl)manganese tricarbonyl[3] were prepared by published procedures. Bromopentacarbonylmanganese was prepared by reaction of dimanganese decacarbonyl (Aldrich Cat. No. 24,526-7) and bromine. We tested all the recommended solvents for this reaction: CS_2,[10] dichloromethane,[10] carbon tetrachloride,[11] and hexane (used for the rhenium analog[12]), but found that benzene[13] was the best solvent. $Mn(CO)_5Br$ was obtained in 96% yield, in practically pure form, without formation of manganese(II) bromide as side product.[11] All other compounds in Table 1 were obtained from commercial sources.



(η^6-Arene)(η^5-cyclopentadienyl)iron(II) salts
(arenocenium salts)



References: (1) *Purification of Laboratory Chemicals*, 4th ed.; Perrin, D. D., Armarego, W. L., Eds.; Butterworth Publishers: New York, 1996. (2) Verberne, M. C.; Brouwer, N.; Delbianco, F.; Linthorst, H. J. M.; Bol, J. F.; Verpoorte, R. *Phytochem. Anal.* **2002**, *13*, 45. (3) Federman Neto, A.; Borges, A. D. L.; Miller, J.; Darin, V. A. *Synth. React. Inorg. Met.-Org. Chem.* **1997**, *27*, 1299. (4) Federman Neto, A.; Borges, A. D. L.; de Arruda Campos, I. P.; Miller, J. *Synth. React. Inorg. Met.-Org. Chem.* **1997**, *27*, 1543 (5) (a) Engel, R. *Traité Elémentaire de Chimie*; Librairie J.-B. Baillière et Fils (Publisher): Paris, France, 1896; p 13. (b) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: Harlow, U.K., 1989; pp 153–155. (6) (a) Federman Neto, A. *An. Acad. Bras. Cienc.* **2003**, in press. (b) Dabirmanesh, Q.; Fernando, S. I. S.; Roberts, R. M. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 743. (7) Mochizuki, T.; Yoshizawa, H. Jpn. Patent 2000 272,913, October 3, 2000; *Chem. Abstr.* **2000**, *133*, 254543z. (8) Maghami, P. Fr. Patent 2,618,450, January 27, 1989; *Chem. Abstr.* **1989**, *111*, 150119v. (9) Darin, V. A.; Federman Neto, A.; Miller, J.; de Freitas Afonso, M. M.; Fonsatti, H. C.; Borges, A. D. L. *J. Prakt. Chem.* **1999**, *341*, 588. (10) Quick, M. H.; Angelici, R. J. *Inorg. Synth.* **1979**, *19*, 160. (11) Abel, E. W.; Wilkinson, G. *J. Chem. Soc.* **1959**, 1501. (12) Schmidt, S. P.; Trogler, W. C.; Basolo, F.; Urbancic, M. A.; Shapley, J. R. *Inorg. Synth.* **1985**, *23*, 41. (13) Federman Neto, A.; Oliveira, W. J. S.; Borges, A. D. L. University of São Paulo, Ribeirão Preto, Brazil. Unpublished work, 2003.

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Editor's Note: *Caution*. Sigma-Aldrich scientists have not tested this procedure in-house and do not have any experience with it. Its publication in this magazine should not be construed as being endorsed or recommended by Sigma-Aldrich. The user should base his/her decision to use this technique solely on the claims made by the authors.

Table 1. Sublimation Using a Microwave Oven[a]

Entry	Compound Sublimed: Formula or Name	Amount (g)	Microwave Setting (%)[b]	Heating Time (s)	"Yield" of Sublimate (%)
1	I_2	1.0	60	360	>99
2	$AlCl_3$	0.5	60	180	64
3	Hg_2Cl_2	0.5	60 and 80	360	–[c]
4	$(C_{10}H_{10})Fe$	0.5	30	60	92
5	$(C_{10}D_{10})Fe$	0.1	30	45	96
6	Acetyl ferrocene	0.5	60	60	15[d]
7	$Mn_2(CO)_{10}$	0.1	40	40	58
8	$Mn(CO)_5Br$	0.1	30	40	33[e]
9	$Mo(CO)_6$	0.3	30	60	81
10	$(C_5H_5)Mn(CO)_3$	0.1	30	30	72[e]
11	(–)-Menthol	0.5	30	180	98
12	(±)-Camphor	0.5	20	60	84
13	Vanillin	0.5	10	30	–[f]
14	Piperonal	0.5	80	20	66
15	Biphenyl	0.5	40	150	78
16	Naphthalene	0.5	40	120	96
17	Anthracene	0.5	40	360	89
18	Salicylic acid	0.5	40	120	97
19	Benzophenone	0.5	80	90	71
20	Benzoic acid	0.5	60	60	89

[a] Sharp microwave oven, model Carousel III; manufactured by SANYO®: Manaus, Amazonas State, AM, Brazil. Of all the conditions tested, the best ones are shown in this table. [b] Setting as a percent of maximum power of 800 W. [c] Hg_2Cl_2 appears to sublime only at higher temperatures. [d] With extensive decomposition. [e] With some decomposition. [f] The material sublimed easily, but the vapors were lost without good condensation, even when low power was used.

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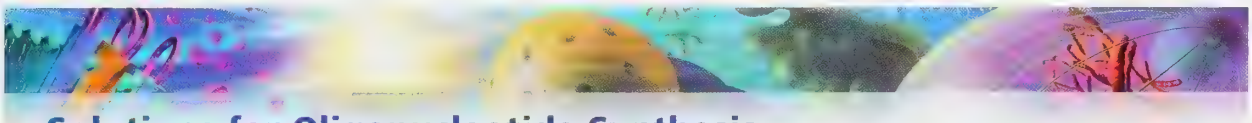

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55,533-9	**Cap Mix A, with pyridine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine)	1L 2L
55,532-0	**Cap Mix B** (Contains 84% tetrahydrofuran: 16% 1-methylimidazole)	1L 2L

Catalog No.	Product Name	Unit
55,535-5	**Cap Mix B, with pyridine** (Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole)	1L 2L
56,193-2	**Deblock** (Contains 3% trichloroacetic acid in dichloromethane)	1L 2L
55,404-9	**Activator** (1-*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1L 2L

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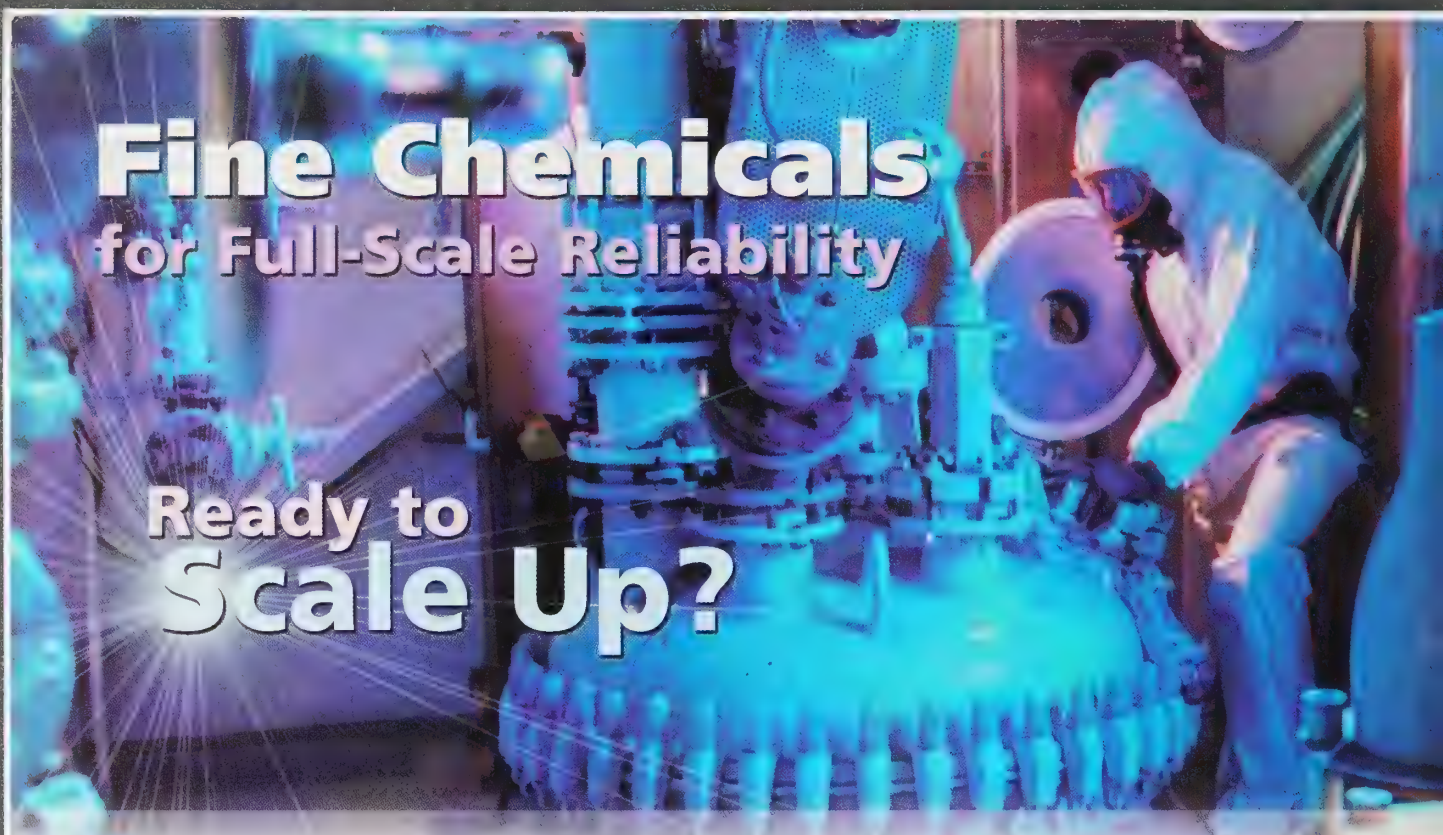

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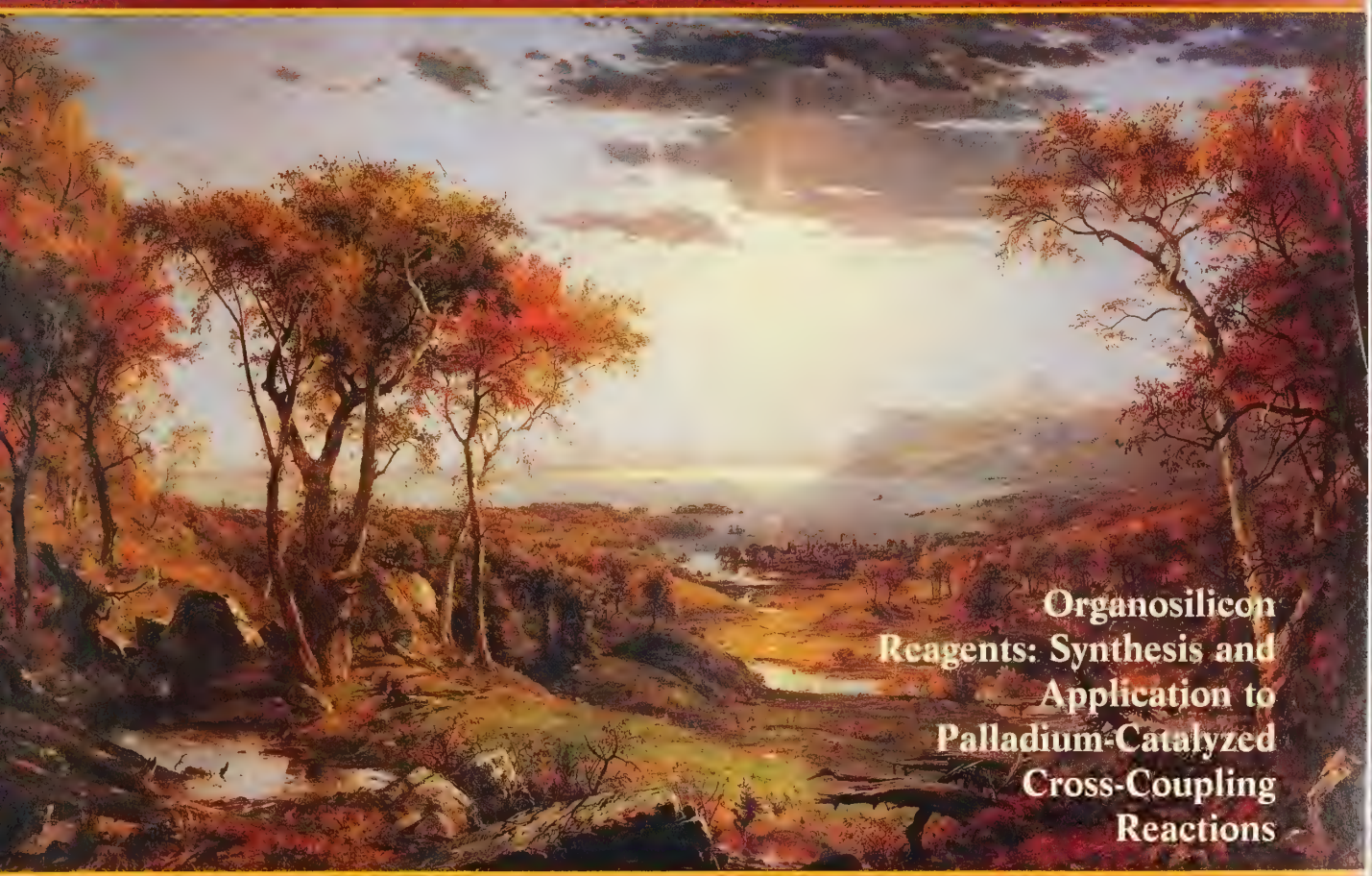


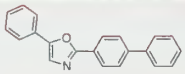
Organosilicon Reagents: Synthesis and Application to Palladium-Catalyzed Cross-Coupling Reactions

Cross Metathesis of Nitrogen-Containing Systems

New Products from Aldrich R&D

2-(4-Biphenylyl)-5-phenyloxazole, 98%

21,698-4



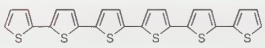
1g $13.80
5g 45.90

Widely used as an activator in C_6F_6-based scintillators for the study of α-particles,[1] γ-rays,[2] and solar neutrinos from β-decay.[3]

(1) Britvich, G.I. et al. *Nucl. Instrum. Methods Phys. Res., Sect. A* **1993**, *A326*, 483; *Chem. Abstr.* **1993**, *118*, 200826r. (2) Barabanov, I.R. et al. *Prib. Tekh. Eksp.* **1995**, 75; *Chem. Abstr.* **1995**, *123*, 125307v. (3) Barabanov, I.R. et al. *ibid.* **1996**, 41; *Chem. Abstr.* **1996**, *125*, 98054t.

α-Sexithiophene

59,468-7



1g $80.00

This thiophene oligomer is known for its semiconducting, electrochemical, and photoelectric properties.

Bungs, M.; Tributsch, H. *J. Appl. Electrochem.* **2002**, *32*, 91.

1,10-Phenanthrolin-5-ylamine, 97%

63,150-7

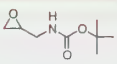
5g $195.00

Employed in the formation of luminophores and metal–ligand complexes for the detection of chemical and biochemical materials.[1,2]

(1) Lecomte, J.-P. et al. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 3261. (2) Meggers, E. et al. *Helv. Chim. Acta* **1997**, *80*, 640.

tert-Butyl *N*-(2-oxiranylmethyl)carbamate

63,066-7



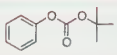
1g $58.00

This functionalized epoxide can undergo hydrolytic kinetic resolution.[1] It has also been used as a building block for the construction of HIV proteinase inhibitors.[2,3]

(1) Schaus, S.E. et al. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (2) Rocheblave, L. et al. *J. Med. Chem.* **2002**, *45*, 3321. (3) Kitchin, J. et al. *J. Med. Chem.* **1994**, *37*, 3707.

tert-Butyl phenyl carbonate, 98%

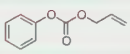
12,430-3



25g $37.40
100g 106.40

Allyl phenyl carbonate, 97%

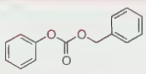
63,065-9



1g $11.00
5g 36.40

Benzyl phenyl carbonate, 97%

63,064-0



5g $29.90

These carbonates provide a practical and versatile method for selective Boc, Alloc, and Cbz protection of primary amines in simple symmetrical aliphatic diamines, and can selectively protect primary amines in the presence of secondary amines.

Pittelkow, M. et al. *Synthesis* **2002**, 2195.

2,4,6-Trichloropyridine, 97%

63,353-4

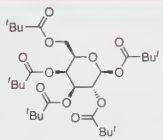
1g $35.00
5g 120.00

Building block for a variety of biologically active compounds such as some cephalosporins,[1] anticancer agents,[2] and herbicides.[3]

(1) D'Andrea, S.V. et al. *Tetrahedron* **2000**, *56*, 5687. (2) Kyoji, T. et al. Int. Patent Appl. WO 9534,559, Dec 21, 1995; *Chem. Abstr.* **1996**, *124*, 289559a. (3) Hisashi, K. et al. Eur. Patent Appl. EP 693,490, Jan 24, 1996; *Chem. Abstr.* **1996**, *124*, 289242s.

β-D-Galactose pentapivalate, 98%

63,247-3



1g $18.00
5g 55.00

This fully protected carbohydrate is a convenient precursor for 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine, a useful chiral auxiliary for chiral α-amino nitrile preparation via the Strecker synthesis.

Kunz, H. et al. *Tetrahedron Lett.* **1988**, *29*, 4397

6-Chloropyran-2-one, 97%

63,299-6

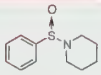
1g $24.50
5g 84.50

Has been used as a starting material for alkynylpyranones,[1] and for a wide spectrum of biologically active substrates including pretetramides.[2]

(1) Biagetti, M. et al. *Tetrahedron Lett.* **2003**, *44*, 607. (2) Gilbreath, G. S. et al. *J. Am. Chem. Soc.* **1988**, *110*, 6172.

1-Benzenesulfinylpiperidine, 97%

63,023-3



1g $13.80
5g 45.90

Novel reagent for the synthesis of glycosides from thioglycoside donors in high yields and excellent stereoselectivities.

Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640.

4-(Trimethylsilylethynyl)morpholine, 97%

63,277-5

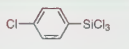
1g $10.00
10g 29.90

Employed in the Lewis acid mediated ring opening of terminal epoxides leading to the corresponding γ-butanolides.

Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456.

Trichloro(4-chlorophenyl)silane, 97%

63,045-4



1g $18.50
5g 61.65

Employed as a starting material in the synthesis of tripod-shaped oligophenylenes designed for thin-film applications.

Deng, X.; Cai, C. *Tetrahedron Lett.* **2003**, *44*, 815.

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About Our Cover

Photograph © Board of Trustees, National Gallery of Art, Washington

Autumn—On the Hudson River (oil on canvas, 151.8 x 274.9 cm) was signed and dated by the American painter Jasper Francis Cropsey in 1860. This enormous painting represents a panoramic view of the Hudson River valley about 60 miles north of New York City near West Point and Storm King Mountain.

At first glance, this landscape, painted in brilliant autumnal colors under a magnificent sunlit sky, may appear to show nature in a completely wild state. Mankind is not entirely absent, however. In the foreground and left of center, three hunters and their dogs have stopped to rest; a log cabin sits among the trees in the middle distance on the right; a town can be seen along the bank of the river; and a number of boats, including a steamer, are on the river itself. The setting is neither completely untouched by man nor overly domesticated. Man may at first seem dwarfed by nature, but is shown here to take his place harmoniously in the natural world.

More than simply a visual record of a certain time and place, however, this painting embodies certain ideas that were current in nineteenth-century America. The natural world was thought to be the most profound manifestation of the Divine order. Moreover, the magnificence of the American landscape came to signify the expansionist ideal and the opportunities and potential greatness of this new country. The critics praised the picture extravagantly when it was exhibited in London, where it was painted from memory and from sketches brought from America during the second of two study trips the artist made to Europe. Viewers, however, questioned the brilliant colors of the foliage represented in the painting, which were more intense than anything they had ever seen. Cropsey, however, had thought to bring from America samples of brightly colored autumn leaves pasted on cardboard to demonstrate that his painting was not an exaggeration, but was quite true to nature, at least in America.

This painting is a gift of the Avalon Foundation to the National Gallery of Art, Washington, DC.

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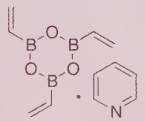
Joe Porwoll

Joe Porwoll, President



Professor Donal F. O'Shea of the Department of Chemistry at University College Dublin kindly suggested that we offer 2,4,6-trivinylcyclotriboroxane-pyridine complex. This stable vinylboronic acid equivalent undergoes facile Suzuki cross-coupling with aryl halides to provide valuable functionalized styrene derivatives.

Kenns, F.; O'Shea, D. F. *J. Org. Chem* **2002**, *67*, 4968

63,799-8
Vinyl boronic anhydride-pyridine complex
1g $21.00; 5g $73.50

56,814-7
Vinylboronic acid dibutyl ester, 97%
1g $25.70; 5g $85.40

63,334-8
Vinylboronic acid pinacol ester, 95%
1g $20.40; 10g $112.50

Naturally, we made not only this reagent but also two other stable vinylboronic acid esters—vinylboronic acid dibutyl ester and vinylboronic acid pinacol ester—which are useful for the Suzuki coupling, Heck coupling, and Grubb's olefin cross-metathesis reactions. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Lab Notes

A Funnel Assembly for the Safe Disposal of Nitrogen Discharged from an NMR Magnet during Cryogen Refilling

In NMR laboratories, where large volumes of cryogens are routinely dispensed, a condition of displacement or deprivation of atmospheric oxygen may occur if the released gases are not efficiently removed. There is at least one reported case of displacement of oxygen by nitrogen during the installation of a magnetic resonance imaging system causing the death of a worker by asphyxiation.[1] In addition, similar incidents of asphyxiation resulting from unsafe handling of liquid nitrogen have been reported in other laboratory settings.[2,3] In setting up a Bruker 400 MHz NMR instrument in our laboratory, we were constrained to install the magnet as well as the ancillary LC-NMR components in a 6 ½'-deep well and the computers at the main level of the room. The well and the main level of the room were equipped with ZoneGuard sensors (Biosystems Inc., Middletown, CT) for a constant monitoring of the well and room oxygen levels. The monitoring systems were set to activate an audible alarm if the oxygen level dropped to 19.5% from the normal reading of 20.9%. During refilling of the magnet with liquid nitrogen, the oxygen level in the well dropped below the danger level of 18.0% and the alarm rang continuously.[4] To minimize the risk of oxygen displacement, we explored the possibility of diverting the flow of cold nitrogen gas exiting the magnet into an area outside the NMR room. To accomplish this goal, we have fabricated a funnel assembly (**Figure 1**) for efficiently capturing and disposing of nitrogen gas and for maintaining safe oxygen levels in the room.

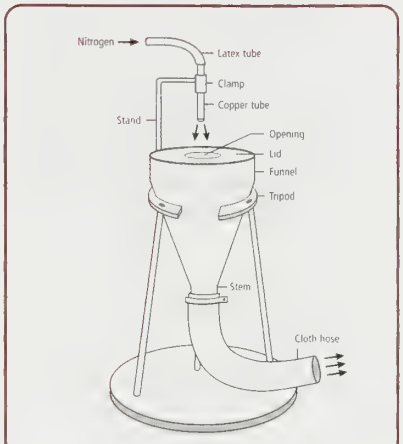


Figure 1. Schematic Diagram of the Funnel Assembly.

The assembly consists of a funnel mounted on a tripod, a clamp supported by the funnel, and a flexible hose attached to the stem of the funnel—as shown in the figure.[5] The mouth of the funnel is sealed with a lid that has a circular opening (3" diam) at its center, and through which the nitrogen stream enters the funnel's chamber. The internal diameter of the funnel at the lid is 9" and that of the stem 2¾" and, at 2" into its depth, the funnel's body gradually begins to narrow along the 8"-long curvature. The length of the funnel, including the two-inch-long stem, is 12" and its capacity is adequate to capture the nitrogen gas emitted from the NMR magnet during refilling. The clamp (4" long x ¼" thick) is supported by a stand (7" high x ¼" thick) welded to the rim of the funnel. A copper tube (7" long x ⅜" i.d.) is clamped in an upright position to deliver the nitrogen gas at the center of the funnel. The tip of the copper tube is positioned approximately 3" above the opening in the funnel lid, and its top end is attached to a latex tube (5' long x ⅜" i.d.) that receives nitrogen gas from the magnet. The supporting tripod consists of a partial O-ring (7" i.d.) mounted on top of 3 legs (16" high), which are fastened to a heavy circular base (14" diam). The O-ring has a 3½"-wide slit through which the funnel along with its attached stand can be readily dismounted from the tripod whenever needed. The material used for the fabrication of the funnel is nonmagnetic stainless steel, whereas that of the tripod is aluminum. The stem of the funnel is connected to a cloth hose (14' long x 3" i.d.) for carrying nitrogen gas into an exhaust line. The figure shows a segment of the latex tubing carrying nitrogen into the funnel and of the cloth hose discharging the gas.

Before liquid-nitrogen refilling, the funnel assembly is placed near the magnet and the funnel's latex tubing is connected to the left-hand-side turret. During refilling of the magnet, the funnel collects the gas discharge with no significant diffusion into the air. As it is denser than air, cold nitrogen gas settles well in the funnel and flows through the hose without applying suction. It also appears that the force of nitrogen streaming through the circular opening prevents back diffusion and exerts pressure sufficient to cause expulsion of the gas from the funnel through the hose. The gas is discharged near an exhaust line located in the well. When the magnet is full, liquid nitrogen spraying into the funnel is clearly visible from several feet away. There is practically no drop in the oxygen level in the well or in the rest of the room during the refilling procedure, suggesting efficient trapping and disposal of nitrogen by this device. Occasionally, water condenses in the first two-foot segment (from the stem of the funnel) of the exterior of the cloth hose carrying the cold gas; placing an absorbent pad underneath the hose takes care of this problem.

The funnel assembly helps in maintaining the room oxygen level during refilling of the NMR magnet with liquid nitrogen, especially if the room is not spacious or not adequately ventilated. In addition, it minimizes the chances of spillage of the cryogen and thus accidental freezing of the O-rings in the base plate and top flange of the magnet cryostat. (If freezing occurs, the sealing O-rings will be hardened leading to loss of vacuum between the casings of the magnet cryostat.) Certain modifications of the funnel assembly may be needed depending on the room's configuration or on whether added efficiency in the removal of nitrogen gas is warranted. For instance, if an exhaust line is not accessible, the delivery end of the hose may be placed outside the room for safe disposal of the gas. If improved gas flow is needed, a suction fan may be attached at the delivery end of the hose.

References and Notes: (1) Gill, J.R.; Ely, S.F.; Hua, Z. Environmental gas displacement: three accidental deaths in the workplace. *Am. J. Forensic Med. Pathol.* **2002**, *23*, 26; abstract available at the National Library of Medicine website at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi (accessed March 2003). (2) Kernbach-Wighton, G.; Kijewski, H.; Schwanke, P.; Saur, P.; Sprung, R. Clinical and morphological aspects of death due to liquid nitrogen. *Int. J. Legal Med.* **1998**, *111*, 191. (3) Tabata, N.; Funayama, M.; Ikeda, T.; Azumi, J.-i.; Morita, M. On an accident by liquid nitrogen—histological changes of skin in cold. *Forensic Sci. Int.* **1995**, *76*, 61. (4) Aside from recommending the installation of oxygen sensors, the manufacturer does not provide any device or recommend any procedure for handling the nitrogen discharged from the magnet during cryogen refilling. (5) The funnel, stand, and clamp were fabricated by Atlantic Sheet Metal Manufacturing (Essex, MD). The tripod was fabricated at the Division of Engineering Services, National Institutes of Health (Bethesda, MD). The entire assembly can be readily fabricated in any workshop using nonmagnetic metal sheets and rods (e.g., aluminum, copper, or nonmagnetic stainless steel) and cloth hose.

H. Umesha Shetty (Ph.D.),* **Jinsoo Hong**, and **Victor W. Pike**
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Editor's Note: *Caution.* The potential user of this note should carefully evaluate its suitability for a particular application, as well as familiarize himself/herself with any potential hazards associated with the construction and use of this assembly. The procedure described in this note has not been tested by Sigma-Aldrich scientists. Its publication in this magazine should not be construed as being endorsed or recommended by Sigma-Aldrich

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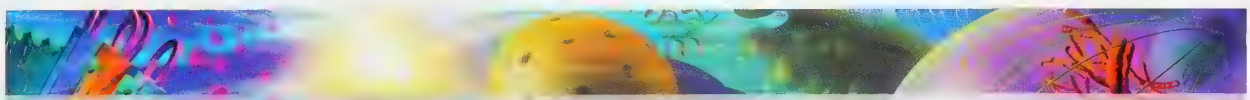

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55,531-2	**Cap Mix A, with 2,6-lutidine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% 2,6-lutidine)	1L 2L	98.60 157.60
55,533-9	**Cap Mix A, with pyridine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine)	1L 2L	78.90 124.10
55,532-0	**Cap Mix B** (Contains 84% tetrahydrofuran: 16% 1-methylimidazole)	1L 2L	108.40 174.30

Catalog No.	Product Name	Unit	Price
55,535-5	**Cap Mix B, with pyridine** (Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole)	1L 2L	$105.00 168.40
56,193-2	**Deblock** (Contains 3% trichloroacetic acid in dichloromethane)	1L 2L	82.60 130.30
55,404-9	**Activator** (1*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1L 2L	221.30 344.20

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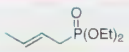
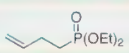
59,759-7



1g	$14.65
5g	48.75

Diethyl 3-butenylphosphonate

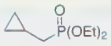
64,052-2



1g	$23.50
10g	130.00

Diethyl cyclopropylmethylphosphonate, 97%

63,582-0



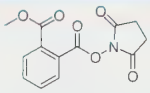
1g	$47.00
5g	163.00

Phosphonates have been utilized extensively in the Horner–Wadsworth–Emmons reaction for the construction of carbon–carbon double bonds These phosphonates have been employed in the preparation of 3-acetoxy-1-alkenyl phosphonates.[1] They were also exploited in an efficient and regiospecific synthesis of 4-oxo-2-alkenylphosphonates.[2]

(1) Principato, B. et al. *Tetrahedron* **1996**, *52*, 2087. (2) Lee, B.S et al. *J. Org. Chem* **2000**, *65*, 4175

Methyl 2-((succinimidooxy)carbonyl)benzoate, 97%

63,392-5



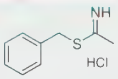
5g $32.50

This reagent efficiently undergoes N-phthaloylation with α-amino acids, α-amino alcohols, α-amino carboxamides, α-amino esters, and dipeptides in high yields without racemization

Casimir, J. et al. *J. Org. Chem* **2002**, *67*, 3764

Benzyl thioacetimidate hydrochloride, 96%

63,711-4



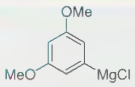
1g	$14.50
5g	51.00

This functionalized thioimidate is a useful reagent for the conversion of anilines to N-substituted acetamidines.[1,2]

(1) Doise, M. et al. *Tetrahedron Lett* **1990**, *31*, 1155 (2) Collins, J. L. et al. *J. Med. Chem* **1998**, *41*, 2858

3,5-Dimethoxyphenylmagnesium chloride

63,762-9



50mL $69.50

This Grignard reagent was used recently to make materials for studies in crystal engineering.

Tanaka, T. et al. *J. Am. Chem Soc.* **2002**, *124*, 12453

2-Bromo-3-thiophenecarboxylic acid, 97%

63,812-9

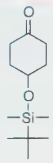
1g	$39.00
5g	135.00

This bifunctional building block was recently utilized in the preparation of oligothiophenes for materials science applications.[1,2]

(1) Zhang, O. T.; Tour, J. M. *J. Am. Chem. Soc* **1997**, *119*, 9624. (2) Pomerantz, M. et al. *J. Org Chem* **2002**, *67*, 6931

4-(*tert*-Butyldimethylsilyloxy)cyclohexanone

63,815-3



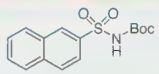
1g	$11.50
5g	39.00

As a protected 4-hydroxycylclohexanone, this compound has been exploited in the synthesis of butenolides,[1] (±)-cocculolidine,[2] and the enyne A-ring synthon of 1α-hydroxy vitamin D_3.[3]

(1) Majewski, M. et al. *Tetrahedron: Asymmetry* **1995**, *6*, 1837. (2) Kawasaki, T. et al *Tetrahedron Lett* **2001**, *42*, 8003. (3) Parker, K. A.; Dermatakis, A. *J. Org. Chem* **1997**, *62*, 6692

N-Boc-2-naphthalenesulfonamide, 97%

63,921-4



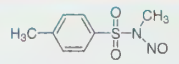
1g	$21.00
5g	72.00

This novel reagent allows the stepwise synthesis of secondary aliphatic amines, such as selectively protected derivatives of spermidine. Cleavage of the sulfonylcarbamate group can be achieved with catalytic amounts of $Mg(ClO_4)_2$ without affecting other Boc-protected amines.

Grehn, L.; Ragnarsson, U. *J. Org Chem.* **2002**, *67*, 6557

Diazald®, 20 wt. % mixture with sodium sulfate

64,053-0



20 wt. % mixture with sodium sulfate

25g $22.00

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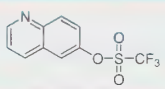
6-Quinolyl trifluoromethanesulfonate, 97%

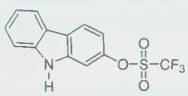
63,344-5



1g	$12.00
5g	39.50

9*H*-Carbazol-2-yl trifluoromethanesulfonate, 97%

63,920-6



1g	$17.00
5g	58.50

These heterocyclic triflates are convenient building blocks for the synthesis of the corresponding halides,[1] thiols,[2] and alkenes.[1] They have also been exploited in cross-coupling reactions with Grignard reagents.

(1) Ritter, K. *Synthesis* **1993**, 735. (2) Arnould, J. C. et al. *Tetrahedron Lett* **1996**, *37*, 4523 (3) Furstner, A. *J. Am. Chem. Soc* **2002**, *124*, 13856

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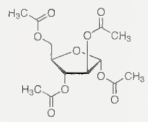
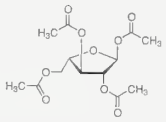
Professor Masaru Kobayashi of Hokkaido University, Japan, kindly suggested we offer 1,2,3,5-tetra-*O*-acetyl-α-D-arabinofuranose and 1,2,3,5-tetra-*O*-acetyl-α-L-arabinofuranose. These fully protected carbohydrates are convenient reagents for determining the absolute configuration of secondary alcohols by ^{13}C NMR spectroscopy.

Kobayashi, M. *Tetrahedron* **2002**, *58*, 9365.



63,480-8



63,744-0

63,480-8	**1,2,3,5-Tetra-*O*-acetyl-α-D-arabinofuranose**	**1g $34.50; 5g $125.00**
63,744-0	**1,2,3,5-Tetra-*O*-acetyl-α-L-arabinofuranose**	**1g $34.50; 5g $125.00**

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Photograph © Board of Trustees, National Gallery of Art, Washington

Flower Beds in Holland (oil on canvas, 48.9 x 66.0 cm) was painted by Vincent van Gogh, probably in 1883. Born in 1853, he left school at the age of sixteen to work for the Goupil art firm in The Hague. This was followed by a period of wandering and spiritual anguish that took him to London (1873), Paris (1875), and Belgium (1878), after which he returned to Holland determined to become an artist.

Van Gogh studied at the Antwerp Academy, but was impatient with formal training and, in 1886, left for Paris. His earliest works portray sympathetically the lives of peasants and workmen, but after he met Pissarro, Degas, Gauguin, Seurat, and Toulouse-Lautrec, he developed an obsessive interest in the symbolic and expressive possibilities of colors. In a frenzy of creation during the last years of his life, he produced over 800 paintings and 850 drawings.

Although its date makes it one of Van Gogh's earliest known works, one can already see in *Flower Beds in Holland* the interest in surface texture and expressive color so prominent in his later works. The bright stripes of color of the flower beds in the foreground contrast strongly with the relatively flat outlines of the tree branches against the gray sky. The low horizon follows the tradition of Dutch landscape painting, which reflects the natural geography of the country. Van Gogh's handling of paint and use of color, however, show the influence of his contacts with contemporary French artists, and point the way to the ever more impassioned and brilliantly colored works of his later career.

This painting is in the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

Lab Notes

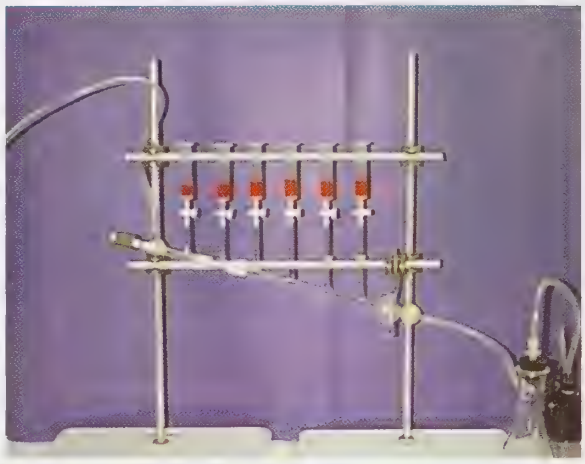
An Inexpensive, Manually Operated, Solid-Phase, Parallel Synthesizer

Solid-phase synthesis is routinely used for the preparation of peptides and small molecules.[1-6] Because solid-phase synthesis involves sequential mixing and draining steps, it is frequently performed in automated solid-phase synthesizers. Although solid-phase synthesis offers many advantages over its solution-phase counterpart, the cost of instrumentation is a limiting factor that prevents many laboratories from venturing into this methodology.[7] Reaction vessels for manual synthesis are commercially available, but each usually requires its own setup for mixing and draining. This makes it more complicated to run multiple reactions at a time. To address this shortcoming, we have designed an inexpensive, manually operated, solid-phase, multiple synthesizer ("CHOIR")[8] that is easy to use and maintain, and that should be affordable (~$250 for glassware) to a wide variety of researchers and educators, especially in cost-conscious academic laboratories.

CHOIR, in its current design, permits up to six syntheses to be performed simultaneously and independently. It consists of a modified vacuum manifold (Chemglass custom Cat. No. UM-2008-301D) with 8 outlets (see figure). The left end of the manifold serves as an inlet for the inert gas, which is bubbled through the reaction vessels in order to mix the reactants and resins. A regulator controls the gas flow and maintains enough gas pressure through the reaction vessels to prevent premature drainage of the solvents. The right end has a three-way stopcock that is opened only when the solvents are being drained. Solvents are drained into a solvent trap with the aid of a vacuum pump or aspirator. The remaining six outlets have LUER® connectors, which are used to attach the reaction vessels via two-way stopcocks. Solid-phase extraction tubes with polyethylene frits, available in a variety of sizes (e.g., Supelco Cat. No. 57176), are used as reaction vessels. These tubes are inexpensive and can be discarded after each synthesis. The inert gas, the solvent trap, and the vacuum pump are connected to CHOIR by means of chemically resistant tubing (e.g., Aldrich Cat. No. Z27,986-2). CHOIR is very easy to operate, since each reaction vessel can be controlled separately by closing and opening the individual stopcock attached to it. Once the parallel syntheses are completed, the reaction vessels are removed from CHOIR, and the peptides individually cleaved from the resins in the same reaction vessels.

We have used CHOIR for the synthesis, partial or complete, of a large number (100–150) of linear and cyclic peptides of various sizes (5–11 residues) in high yields and purities, or for the optimization of the reaction conditions leading to these peptides. Examples of peptides synthesized include cyclic and linear analogs of the opioid peptide dynorphin A:[5,6,9-11]

- *cyclo*[D-Asp^2,Xxx^3,Dap^5]Dyn A-(1–11)NH_2 and linear [D-Asp^2,Xxx^3,Dap^5]Dyn A-(1–11)NH_2, where Xxx = Gly, Ala, D-Ala, Trp, D-Trp, or Pro.
- *cyclo*[D-Asp^2,Xxx^4,Dap^5]Dyn A-(1–11)NH_2 and linear [D-Asp^2,Xxx^4,Dap^5]Dyn A-(1–11)NH_2, where Xxx = Phe, D-Phe, HomoPhe, or D-HomoPhe.
- *cyclo*^{N,5}[Trp^3,Trp^4,Glu^5]Dyn A-(1–11)NH_2 and its cyclic and linear analogs.
- *cyclo*^{N,5}[$COCH_2$Tyr^1,Lys^5]Dyn A-(1–11)NH_2 and analogs.
- *cyclo*^{N,5}[$COCH_2$Tyr^1,Lys^3]Dyn A-(1–11)NH_2 and analogs.



References and Notes: (1) For a review, see *Solid-Phase Synthesis, A Practical Guide*; Kates, S. A., Albericio, F., Eds.; Marcel Dekker, Inc.: New York, 2000. (2) Gorman, J. J. *Anal. Biochem.* **1984**, *136*, 397. (3) Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*, 2nd ed.; Pierce Chemical Co.: Rockford, IL, 1984. (4) Knapp, D. R.; Oatis, J. E., Jr.; Papac, D. I. *Int. J. Pept. Protein Res.* **1993**, *42*, 259. This report describes a similar albeit less practical synthesizer, and gives a brief history of systems devised to carry out parallel syntheses of peptides. (5) Bennett, M. A.; Murray, T. F.; Aldrich, J. V. *J. Med. Chem.* **2002**, *45*, 5617. (6) Vig, B. S.; Murray, T. F.; Aldrich, J. V. *J. Med. Chem.* **2003**, *46*, 1279. (7) For example, the Bohdan MiniBlock® system, which is convenient to use, is roughly 14 times more expensive than the system described here ($3,500 vs $250). (8) CHOIR = Cheap Homemade Organic Inline Reactor. (9) Vig, B. S.; Aldrich, J. V. Strategies for the Synthesis of Novel Head-to-Side Chain Cyclic Peptides: Application to Dynorphin A Analogs. In *Peptides: The Wave of the Future*; Lebl, M., Houghten, R. A., Eds.; American Peptide Society: San Diego, CA, 2001; pp 144–145. (10) Vig, B. S.; Murray, T. F.; Aldrich, J. V. *J. Med. Chem.* **2004**, *47*, 446. (11) Vig, B. S.; Murray, T. F.; Aldrich, J. V. *Biopolymers* **2004**, in press.

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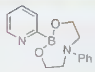
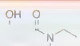


A stable 2-pyridinylboronate that is suitable for Suzuki–Miyaura coupling reactions.[1] This air-stable solid is a practical alternative to unstable 2-pyridinylboronic acids or esters

(1) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685. (2) Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21. (3) Thompson, W. J. et al. *J. Org. Chem.* **1988**, *53*, 2052.

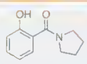
N,N-Diethylsalicylamide, 97%

64,423-4 — 5g $27.50; 25g 95.50



N-(2-Hydroxybenzoyl)pyrrolidine, 97%

64,293-2 — 5g $19.00; 25g 65.00

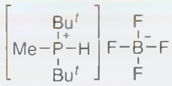


These ligands have recently been utilized in copper-catalyzed aminations of aryl bromides with primary alkylamines under mild, solvent-free conditions and are compatible with a variety of functional groups. High yields have been obtained regardless of the ortho-, meta-, or para- substitution pattern on the aryl bromide

Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793.

Di-*tert*-butylmethylphosphine tetrafluoroborate

64,377-7 — 1g $28.00; 5g 98.50

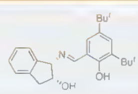


This reagent is a convenient substitute for the air-sensitive di-*tert*-butylmethylphosphine (Aldrich Cat. No. **64,262-9**), and displays a remarkable reactivity in palladium-catalyzed Suzuki cross-coupling reactions.

Kirchhoff, J. H. et al. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

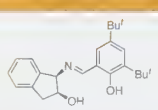
(1*R*,2*S*)-1-[(2-Hydroxy-3,5-di-*tert*-butylbenzylidene)]-aminoindan-2-ol

64,295-9 — 1g $16.50; 5g 58.00



[illegible]-1-[(2-Hydroxy-3,5-di-*tert*-butylbenzylidene)]-aminoindan-2-ol

64,414-5 — 1g $16.50; 5g 58.00

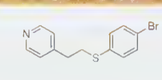


These chiral ligands have recently been used in the vanadium-catalyzed oxidation of sulfides in conjunction with hydrogen peroxide. Optically active sulfoxides are obtained in high yields and selectivities.

Pelotier, B. et al. *Synlett* **2002**, 1055.

4-[2-(4-Bromophenylsulfanyl)ethyl]pyridine, 97%

64,223-1 — 1g $16.50; 5g 58.00

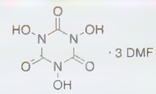


The pyridinylethyl group protects the phenylthio group for subsequent modification. The later-freed thio group in phenylethynyl oligomers was used to anchor self-assembled monolayers (SAMs)[1] and molecular wires.[2]

(1) Collman, J. P. et al. *Synthesis* **2001**, 367. (2) YU, C. J. et al. *J. Org. Chem.* **1999**, *64*, 2070.

N,N',N''-Trihydroxyisocyanuric acid dimethylformamide complex, 97%

64,341-6 — 1g $35.00; 5g 119.50

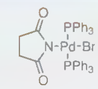


An efficient catalyst for the aerobic oxidation of alkylbenzenes

Hirai, N. et al. *J. Org. Chem.* **2003**, *68*, 6587.

Bromobis(triphenylphosphine)(*N*-succinimide)palladium(II)

64,374-2 — 250mg $39.00; 1g 97.50

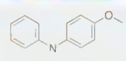


This bromosuccinimide-based palladium catalyst is used for Stille cross-coupling of allylic and benzylic halides

Crawforth, C. M. et al. *Chem. Commun.* **2003**, 2194.

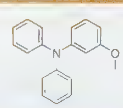
4-Methoxy-*N,N*-diphenylaniline

64,612-1 — 1g $14.00; 10g 77.50



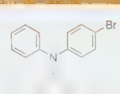
3-Methoxy-*N,N*-diphenylaniline, 97%

64,054-9 — 1g $12.00; 5g 37.50



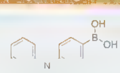
4-Bromo-*N,N*-diphenylaniline, 97%

64,383-1 — 5g $34.50; 25g 115.50



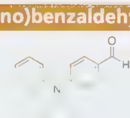
4-(*N,N*-Diphenylamino)phenylboronic acid, 95%

64,729-2 — 1g $52.00; 5g 205.00



4-(*N,N*-Diphenylamino)benzaldehyde

64,720-9 — 1g $22.00; 5g 76.50



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(1) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10*, 1471. (2) Miller, J. S.; Epstein, A. J. *MRS Bull.* **2000**, November, 21. (3) Veciana, J.; Iwamura, H. *MRS Bull.* **2000**, November, 41.

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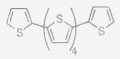
(1) Garnier, F. et al. *Adv. Mater.* **1990**, *2*, 592. (2) Dodabalapur, A. et al. *Science* **1995**, *268*, 270. (3) Garnier, F. *Acc. Chem. Res.* **1999**, *32*, 209. (4) Sakamoto, Y. et al. *J. Am. Chem. Soc.* **2001**, *123*, 4643. (5) Locklin, J. et al. *Langmuir* **2002**, *18*, 877. (6) Garnier, F. et al. *J. Am. Chem. Soc.* **1993**, *115*, 8716.



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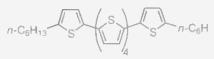

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The Harbor at Lorient (oil on canvas, 43.5 × 73.0 cm) was painted by the French artist Berthe Morisot in 1869. In the right foreground of the picture, a young woman holding a parasol is shown seated on a low stone wall bordering the waters of the harbor, in which ships and boats of various sizes are anchored. The strong diagonal of the wall leads our eye straight to the figure of the woman, making her the obvious focal point of the painting. In the background can be seen the buildings of Lorient, a busy port on the south coast of Brittany on the estuary of the river Blavet. Morisot came to visit the town in 1869 to stay with her sister Edma, whose husband was a naval officer stationed there, and it is Edma who posed for the painting.

Morisot had studied with the painter Camille Corot, whose influence can be seen in the delicate palette and soft, atmospheric effects of this painting. In 1868, she began to study with the painter Édouard Manet. She came to know the impressionist painters, with whom she shared a preference for subjects from everyday life and for painting directly from nature to capture as much as possible the immediacy of visual experience. Beginning with the first group exhibition of these artists in 1874, she exhibited in all but one of the eight impressionist exhibitions held between that date and the last, in 1886. She married Manet's younger brother Eugène in 1874, but despite this close family tie, Morisot never convinced Manet to exhibit with the impressionist group. She had a uniquely important effect on the art of her brother-in-law, however, as it was under her influence that Manet abandoned the use of black, and adopted a lighter and more colorful impressionist palette.

This painting is in the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

Queen's University Honors

Alfred Bader on His 80th Birthday

Alfred Bader—chemist, art collector, philanthropist, and cofounder of Aldrich Chemical Company—has had a long association with Queen's University (Kingston, Ontario). He was a student there from 1941 to 1947, and has since been one of its most loyal supporters and generous benefactors.

It was no surprise, therefore, that Queen's University invited a group of distinguished guests and longtime friends of Alfred to participate in a celebration of his 80th birthday. The two-day gala, on May 12 and 13 of this year, combined festive social events with scholarly lectures organized by the chemistry and art departments at the university, as well as a public lecture by Dr. Bader (*The Aldrich Chemical Company Story*) and a student awards luncheon. Nobel Laureate Barry Sharpless and Columbia Professor Emeritus Gilbert Stork were speakers at the chemistry symposium. In addition, the university renamed Queen's Crescent, a street running through the center of campus, Bader Lane in gratitude to Alfred and his family's many contributions to the university over the years.

Left to right: Barry Sharpless, Alfred Bader, Gilbert Stork, and Victor Snieckus at the chemistry symposium

Alfred Bader with mementos of the event

Left to right: Henry van Oudenaren (Sigma-Aldrich), Gilbert Stork, and Alfred Bader

Alfred, his wife Isabel, and his two sons, Daniel and David, attended the celebrations. Sigma-Aldrich was represented by Henry van Oudenaren (Country Manager, Canada). Some highlights of these events are captured in the accompanying photographs.

Alfred Bader at the student awards luncheon

Alfred, Your Sigma-Aldrich Family Wishes You a Happy 80th Birthday.

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All four photographs are courtesy of Linda Raber, Assistant Managing Editor, *Chemical & Engineering News*

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(Last issue in 2004)

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64,930-9

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45,770-1

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64,931-7

1 g	$38.00
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45,769-8

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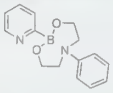
Excellent catalysts for the asymmetric reduction of prochiral ketones.[1] Reduction of aralkyl ketones with borane sources such as BH_3–THF, BMS, amine-boranes, catecholborane, in the presence of these catalysts (0.02 to 0.1 mol %), provides the corresponding secondary alcohols in high (>95% ee) enantiomeric excesses.[2-5] These reagents are also effective for kinetic resolutions.[6]

(1) Corey, E. J., Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (2) Corey, E. J. et al. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (3) Corey, E. J. et al. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (4) Cho, B. T.; Kim, D. J. *Tetrahedron: Asymmetry* **2001**, *12*, 2043. (5) Cho, B. T. et al. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1204. (6) Lebsack, A. D. et al. *J. Am. Chem. Soc.* **2001**, *123*, 4851.

2-Pyridineboronic acid *N*-phenyldiethanolamine ester

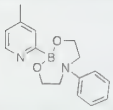
64,728-4



1 g	$18.00
5 g	71.30
10 g	128.60

6-Methyl-2-pyridineboronic acid *N*-phenyldiethanolamine ester

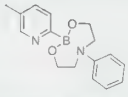
64,884-1



5 g	$63.00

5-Methoxy-2-pyridineboronic acid *N*-phenyldiethanolamine ester

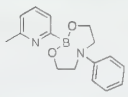
64,882-5



500 mg	$27.50
1 g	46.00
5 g	181.00

3-Pyridineboronic acid *N*-phenyldiethanolamine ester

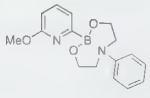
64,881-7



1 g	$16.50
5 g	66.00

4-Methoxy-2-pyridineboronic acid *N*-phenyldiethanolamine ester

64,915-5



1 g	$43.50
5 g	172.00

Novel 2-pyridineboronic acid derivatives that are stable for storage and suitable for Suzuki–Miyaura cross-coupling.

(1) Fischer, F. C., Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21. (2) Bouillon, A. et al. *Tetrahedron* **2003**, *59*, 10043. (3) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685.

2-Chloro-6-(methylamino)purine, 97%

64,459-5

5 g	$59.50

Has been employed in the preparation of selective $P2Y_1$ receptor agonists and antagonists as pharmacological probes.[1-3]

(1) Kim, Y.-C. et al. *J. Med. Chem.* **2000**, *43*, 746. (2) Nandanan, E. et al. *J. Med. Chem.* **2000**, *43*, 829. (3) Kim, H. S. et al. *J. Med. Chem.* **2001**, *44*, 3092.

Benzofurazan, 97%

65,013-7

1 g	$17.50
10 g	95.00

Modifications around this key heterocyclic nucleus have led to the preparation of fluorescence probes[1] and inhibitors of nucleic acid and protein biosyntheses.[2,3]

(1) Uchiyama, S. et al. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2525. (2) Crampton, M. R. et al. *J. Chem. Soc., Perkin Trans. 2* **2002**, 257. (3) Ghosh, P. B. et al. *J. Med. Chem.* **1972**, *15*, 255.

2,3-Dibromobenzo[*b*]thiophene, 97%

64,737-3

1 g	$29.50
5 g	97.50

Served as a basic starting material for the synthesis of novel, chiral benzothiophene ligands via Pd-catalyzed allylation.[1] Selective displacement of each bromine makes this compound a very useful building block in Suzuki and Stille coupling reactions.[2,3]

(1) Tietze, L. F.; Lohmann, J. K. *Synlett* **2002**, 2083. (2) Heynderickx, A. et al. *Synthesis* **2002**, 213. (3) Yamamura, K. et al. *Org. Biomol. Chem.* **2004**, *2*, 1413.

2-Chloro-1,1,1-triethoxyethane, 97%

64,975-9

1 g	$13.50
10 g	75.00

An effective reagent for the large-scale preparation of 2-chloromethylbenzothiazoles and benzoxazoles.[1] Used also in the synthesis of 21-desoxy-21-chlorocorticosteroids with functionalized 17α-ester groups.[2]

(1) Mylari, B. L. et al. *Synth. Commun.* **1989**, *19*, 2921. (2) Ueno, H. et al. *J. Med. Chem.* **1991**, *34*, 2468.

(Chloromethyl)dimethylvinylsilane, 97%

64,911-2

1 g	$17.30
10 g	95.00

Utilized in the synthesis of silylated β-lactams possessing antibacterial properties.

Altamura, M. et al. *J. Org. Chem.* **1995**, *60*, 8403.

2-(Trimethylsilyl)pyridine, 98%

64,985-6

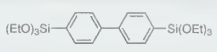
1 g	$25.50
10 g	140.00

Utilized in the preparation of a novel hydroxymethylating reagent, which was then used in the stereoselective synthesis of vinylsilanes.

Itami, K. et al. *Tetrahedron* **2001**, *57*, 5045.

4,4'-Bis(triethoxysilyl)biphenyl, 95%

63,810-2



1 g	$23.50
10 g	128.50

Employed in the preparation of arylene-bridged polysilsesquioxanes.[1,2]

(1) Kapoor, M. P. et al. *Chem. Lett.* **2003**, *32*, 914. (2) Schaefer, D. W. et al. *Chem. Mater.* **2004**, *16*, 1402.

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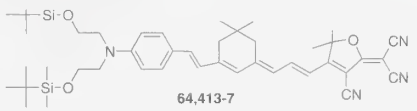
1) Zhang, C.; Todorova, G.; Wang, C.; Londergan, T.; Dalton, L. R. *Proc. SPIE* **2000**, *4114*, 77. (2) Oh, M.-C.; Zhang, H.; Zhang, [illegible] Erlig, H.; Chang, Y.; Tsap, Y.; Chang, D.; Szep, A.; Steier, W. H.; Fetterman, H. R.; Dalton, L. R. *IEEE J. Sel. Top. Quantum Electron.* **2001** [illegible]



64,413-7

65,158-3 **CLD-1–APC polymer**, 10 wt. % solution in dichloroethane **5 mL $385.00**
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Photograph © Board of Trustees, National Gallery of Art, Washington

The Race Track (oil on canvas, 80.5 × 114.9 cm) was painted about 1891 by the French artist Jean-Louis Forain. Just to the right of center in the foreground of the painting, two men and a woman converse intently. A little further back and near the left edge of the picture, several figures appear to be rushing towards the horses and riders. The relative position and differing size—some larger, some smaller—of these groups of figures help to create a sense of space in the picture, which otherwise is dominated by large relatively flat areas of brilliant color, the light green of the grass, the white of the clouds, and the intense blue of the sky

At first glance, one might identify the artist of this painting as Degas, an artist well known for horseracing subjects. Not only the subject, however, but also the style of the painting may remind us of Degas, as it exhibits the same casual, seemingly unplanned composition that is usual in the work of the more famous artist. It is as if the figures in the painting were caught unawares in a snapshot shortly before the beginning of the race. Indeed, Forain had a chameleon-like tendency to imitate other artists he admired. Not only did he paint racehorses and ballet dancers in a manner that reminds one of Degas, but his wily lawyers and scheming politicians can also be easily mistaken for those of Daumier. And like Daumier, he was a graphic artist as well as a painter. In fact, it was his etchings that brought Forain his greatest fame. He was what we now might call a political cartoonist. Fine as his graphic technique was, however, his paintings almost always remind us of other, better-known artists. All his life, he remained something of a follower, rather than an inventive and original creator of his own unique style

This painting is in the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

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56,193-2	**Deblock** (Contains 3% trichloroacetic acid in dichloromethane)	1 L 2 L	90.20 142.50
55,404-9	**Activator** (1*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1 L 2 L	249.00 387.00
63,457-3	**Activator** (5-Ethylthio-1*H*-tetrazole, 0.25*M* in acetonitrile)	1 L 2 L	241.50 365.00

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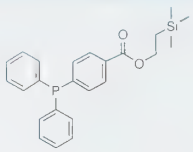
63,801-3



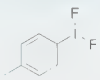
5 mL $28.50
25 mL 99.50

This reagent was developed to replace triphenylphosphine in the Mitsunobu reaction The resulting phosphine oxide is easily removed from the reaction during workup

Yoakim, C. et al *Synlett* **2003**, 473

4-Iodotoluene difluoride

65,111-7



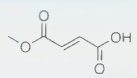
1 g $31.50
5 g 108.00

A new and efficient fluorinating reagent that is recommended for the fluorination of the α carbon of sulfanyl amides under mild conditions

Motherwell, W. B. et al. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2816

mono-Methyl fumarate, 97%

65,141-9



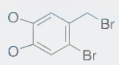
1 g $10.50
10 g 55.00

Employed in the design of affinity labels for opioid receptors[1] and in a highly stereoselective synthesis of optically active furfuryl fumarates

(1) Chang, A.-C. et al. *J. Med. Chem.* **1994**, *37*, 4490. (2) Butz, T.; Sauer, J. *Tetrahedron Asymmetry* **1997**, *8*, 703

5-Bromo-6-bromomethylbenzo[1,3]dioxole

65,374-8



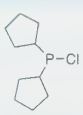
5 g $29.50
25 g 105.00

Has been utilized in the preparation of toddaquinoline, an unusual medicinal alkaloid,[1] and lignans, which are known for their biological activity and effectiveness as antineoplastic agents

(1) Harrowven, D. C. et al. *Tetrahedron* **2001**, *57*, 4447 (2) Cochran, J. E.; Padwa, A *J. Org. Chem.* **1995**, *60*, 3938

Chlorodicyclopentylphosphine

64,906-6

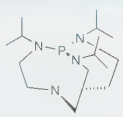


1 g $24.50
5 g 95.00
25 g 375.00

A phosphine precursor for ligand preparation in Negishi and Suzuki coupling reactions

2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undecane, 1 M in toluene

65,435-3



10 mL $159.00

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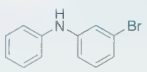
Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37*, 3

N-(3-Bromophenyl)aniline, 97%

65,424-8



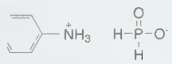
1 g $13.50
10 g 74.50

A useful building block in the preparation of triarylamines, which have been extensively employed in electroluminescent materials as hole-transport materials and hole-transport emitters,[1] and in the development of organic-based magnets.[2,3]

(1) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10*, 1471. (2) Miller, J. S.; Epstein, A J. *MRS Bull.* **2000**, *25*, 21. (3) Veciana, J.; Iwamura, H. *MRS Bull.* **2000**, *25*, 41

Anilinium hypophosphite

65,411-6



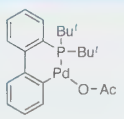
25 g $19.50

An easy-to-handle and relatively nonhygroscopic reagent that has been used in the preparation of monosubstituted phosphinic acids via Pd-catalyzed reaction with aryl halides or triflates.[1] A practical triethylborane-initiated radical addition of anilinium hypophosphite to olefins has been reported.[2]

(1) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510. (2) Deprele, S.; Montchamp, J.-L. *J. Org. Chem* **2001**, *66*, 6745

2-(2′-Di-*tert*-butylphosphine)biphenylpalladium(II) acetate

65,541-4



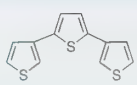
250 mg $28.50
1 g 75.00

A novel, air- and moisture-stable pre-catalyst for the amination of aryl chlorides

Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413

3,2′:5′,3″-Terthiophene

65,138-9



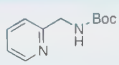
1 g $105.00

An efficient singlet-oxygen sensitizer. This compound is also associated with photoantibiotic and phototoxic properties.[1,2]

(1) Beny, J.-P. et al. *J. Org. Chem.* **1982**, *47*, 2201 (2) Moriarty, R. M. et al. *Synth Commun.* **1985**, *15*, 789

N-Boc-2-aminomethylpyridine, 97%

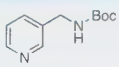
65,157-5



5 g $25.00
25 g 87.50

N-Boc-3-aminomethylpyridine, 97%

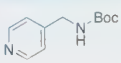
63,444-1



1 g $21.00
5 g 73.50

N-Boc-4-aminomethylpyridine, 96%

64,976-7



1 g $20.50
10 g 111.50

These Boc-protected pyridines can be used as pharmaceutical building blocks in thrombin[1] and PKC inhibitor[2] research, and can be readily hydrogenated to the protected piperidines

(1) Hilpert, K. et al. *J. Med. Chem.* **1994**, *37*, 3889. (2) Shearer, B. G. et al. *J. Med Chem.* **1991**, *34*, 2928

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Professor Ei-ichi Negishi of Purdue University kindly suggested that we offer *trans*-1-bromo-2-iodoethene, a useful synthon in Pd-catalyzed cross-coupling reactions. Its utility has recently been demonstrated in the synthesis of xerulin, an inhibitor of cholesterol biosynthesis,[1] *cis*- and *trans*-bupleurynol,[2] in the preparation of 1-halo-1,3-dienes,[3] and in coupling reactions with alkynylzinc reagents.[4]

(1) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65. (2) Ghasemi, H.; Antunes, L. M.; Organ, M. G. *Org. Lett.* **2004**, *6*, 2913. (3) Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531. (4) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597.

57,780-4	***trans*-1-Bromo-2-iodoethene, 97%**	5 g	$36.70
		25 g	122.50

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Photograph © Board of Trustees, National Gallery of Art, Washington

The Fence (oil on canvas, 37.8 × 45.7 cm) was signed and dated by the French painter Camille Jacob Pissarro in 1872. During the 1860s, Pissarro moved his family from Paris to various small villages in the French countryside. He was committed to the principles of socialism, and felt a strong affinity for the peasant farmers who worked the land. Like the other impressionists, Pissarro chose to represent subjects from modern life; but, while they often painted the pleasures of the urban bourgeoisie, scenes from the theatre, the opera, the ballet, or the racetrack, Pissarro was more likely to portray the rustic life of farmers working in the fields with whom he identified.

The warm colors of the trees and shrubbery in the picture show that it is the fall of the year. At the left in the foreground is a large bent and broken tree, whose almost leafless branches are silhouetted against the light sky. Near the lower right corner of the painting, a peasant couple chat together on either side of a rustic fence. In the distance, one can make out the buildings of the local village, towards which a woman moves along the path near the right edge of the picture. As in a snapshot, nothing in nature has been rearranged to create a more pleasing, harmonious, or picturesque effect. The rapidly executed brushwork is variegated to suggest the different textures of diverse objects in the painting, which was almost certainly painted in a single session on the site. One might say, in fact, that a central purpose of all the impressionist artists was not to create an invented world on canvas, but to capture the immediacy of the unique conditions of a specific moment in time in a particular place.

This painting is a part of the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

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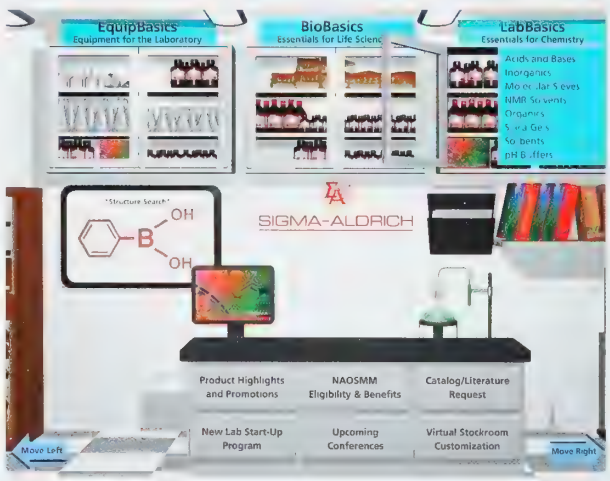

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Aldrichimica ACTA

VOL. 38, NO. 2 • 2005

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Organotrifluoroborates: Expanding Organoboron Chemistry

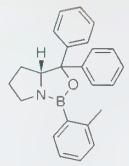
Recent Advances in the Chemistry of Lithium Aminoborohydrides

New Products from Aldrich R&D

REAGENTS FOR ASYMMETRIC SYNTHESIS

lidine solution, 0.5 M in toluene

65,429-9

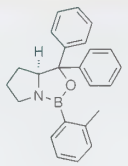


5 mL	$31.50
25 mL	109.00

Excellent reagents for catalytic asymmetric transformations such as the Diels–Alder reaction[1] and the cyanosilylation of aldehydes.[1,2] Chiral cationic oxazaborolidines, prepared from *o*-tolyloxazaborolidine and triflic acid, catalyze Diels–Alder reactions to provide high ee's.[3] Recently, Corey and co-workers used these catalysts to synthesize several chiral natural products, otherwise synthesized in racemic form.[4]

0.5 M in toluene

65,430-2

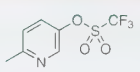


5 mL	$31.50
25 mL	109.00

(1) Corey, E. J. et al. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (2) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106. (3) Ryu, D. H. et al. *J. Am Chem. Soc.* **2002**, *124*, 9992. (4) Hu, Q.-Y. et al. *J. Am. Chem. Soc.* **2004**, *126*, 13708.

REAGENTS FOR CROSS-COUPLING REACTIONS

64,848-5

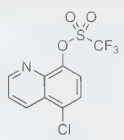


1 g	$25.00
5 g	78.00

Activated triflates of this type have served as alternatives to aryl halides in a variety of palladium-catalyzed coupling reactions

5-Chloroquinolin-8-yl trifluoromethanesulfonate, 9

64,850-7



1 g	$42.00
5 g	124.00

(1) Matthews, D. P. et al. *Tetrahedron Lett.* **1994**, *35*, 5177. (2) Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386. (3) Ellingboe, J. W. et al. *J. Med Chem.* **1994**, *37*, 542.

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65,532-5

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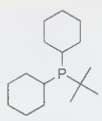
tert-Butyldicyclohexylphosphine, 97%

65,160-5



1 g	$49.00
5 g	172.00

This novel phosphine was used to prepare catalysts for the ring-opening metathesis polymerization of cyclooctene.

Jan, D. et al. *J. Organomet. Chem.* **2000**, *606*, 55.

REAGENT FOR C–X BOND FORMATION

65,531-7

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5 g	216.00

Reacts with imines under mild conditions and without demethylation to form α-aminophosphonothionates.

Tongcharoensirikul, P. et al. *J. Org. Chem.* **2004**, *69*, 2322.

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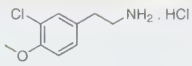
65,632-1



5 g $80.00

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(1) Charifson, P. S. et al. *J. Med. Chem.* **1988**, *31*, 1941. (2) Chumpradit, S. et al. *J. Med. Chem.* **1991**, *34*, 877.

Please see pages 56, 58, and 59 for additional new products.

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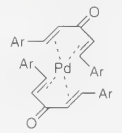
Dr. Ian J. S. Fairlamb of the University of York, U.K., kindly suggested that we offer this Suzuki–Miyaura cross-coupling palladium catalyst in our catalog. Palladium-catalyzed cross-coupling reactions constitute some of the most important and applied transformations for the synthesis of natural products, pharmaceutical targets, and conjugated materials.[1] This palladium catalyst has shown a higher activity over $Pd_2(dba)_3$ in the Suzuki–Miyaura cross-coupling of organic halides with arylboronic acids.[2]

(1) *Handbook of Organopalladium Chemistry for Organic Synthesis*, Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002.
(2) Fairlamb, I. J. S., Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435.



Ar = 3,5-dimethoxyphenyl

65,693-3	**Bis(3,5,3′,5′-dimethoxydibenzylideneacetone)-palladium(0)** [$Pd(dm\text{-}dba)_2$]	1 g 5 g	$19.65 65.50

Naturally, we made this useful catalyst. It was no bother at all, just a pleasure to be able to help.

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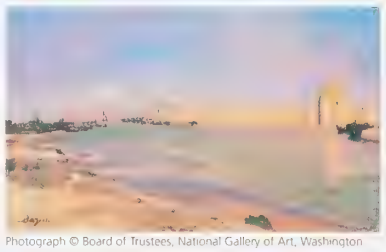

Photograph © Board of Trustees, National Gallery of Art, Washington

The Ramparts at Aigues-Mortes (oil on canvas, 60 × 100 cm) was painted and signed by the artist Frédéric Bazille in 1867. Probably few tourists who visit the famous classical ruins at Nîmes and Arles in southern France are aware that nearby is the best-preserved medieval fortress in Europe, the subject of this painting. In 1246, King Louis IX began the tower seen just to the left of the center of this picture and had a five-mile channel dug through the estuary of the Rhone river to the Mediterranean for ships embarking on the Seventh and Eighth Crusades. His son, Philippe III, started the enormous adjoining battlements in 1272, but, within less than a century, silting closed the passage to the sea and the structure was abandoned.

Bazille was born not far away at Montpellier to a well-to-do family and was expected to become a doctor. While still in medical school, however, he convinced his father to subsidize his artistic education in Paris. He soon became fast friends with Alfred Sisley, Auguste Renoir, and Claude Monet, who suggested to Bazille and the others that they paint out-of-doors directly in front of their subjects, thus initiating the essential aspect of impressionist painting. When in the spring of 1867 Bazille went to paint *The Ramparts at Aigues-Mortes*, he wrote to his mother that he intended to paint "a very simple painting" of "the walls of the city reflected in a pond at sunset". The composition of the picture is indeed very simple, defined by the diagonal of the sandbar in the foreground and the almost equal areas of water and sky on either side of the long horizontal of the ramparts. The view is to the east, with the late afternoon sun striking the walls of the fortress. A tower near the right edge of the painting is reflected in the water, and the pink tinge of the clouds suggests the coming sunset.

This painting is a part of the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

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(1) (a) Chandrasekharan, J. et al. *J. Org. Chem.* **1985**, *50*, 5446. (b) Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9

(2) Drury, W. J., III et al. *Angew. Chem., Int. Ed* **2004**, *43*, 70

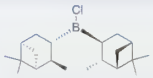
(3) Beardsley, D. A. et al. *Tetrahedron Lett.* **1994**, *35*, 1511

(4) Felpin, F.-X.; Lebreton, J. *J. Org. Chem* **2002**, *67*, 9192

(5) Stocker, B. L. et al. *Eur. J. Org. Chem.* **2004**, 330

(6) Dhar, R. K. *Aldrichimica Acta* **1994**, *27*, 43

(+)-DIP-Chloride™

31,701-2		5 g	$33.50
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		100 g	300.50
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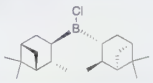
31,702-0		5 g	$35.00
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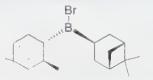
41,427-1		5 g	$74.10
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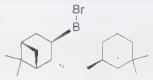
41,099-3		5 g	$177.00
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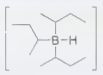
17,849-7		100 mL	$37.40
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		8 L	931.00
		18 L	1865.00

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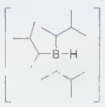
22,592-4		100 mL	$105.50

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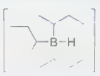
22,076-0		100 mL	$83.30
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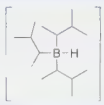
22,077-9		100 mL	$77.40

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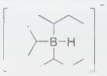
21,340-3		100 mL	$48.00
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(7) Some recent examples: (a) Bahia, P. S.; Snaith, J. S. *J. Org. Chem.* **2004**, *69*, 3226. (b) Thede, K. et al. *Org. Lett.* **2004**, *6*, 4595. (c) Banwell, M. G. et al. *Org. Lett.* **2004**, *6*, 2737. (d) Lichtenthaler, F. W. et al. *Tetrahedron: Asymmetry* **2003**, *14*, 727. (e) Nelson, T. D. et al. *Tetrahedron Lett.* **2004**, *45*, 8917

(8) (a) Hanessian, S.; Machaalani, R. *Tetrahedron Lett.* **2003**, *44*, 8321. (b) Navarre, J.-M. et al. *Tetrahedron Lett* **2003**, *44*, 2199

(9) Nagaoka, Y. et al. *Tetrahedron Lett.* **2002**, *43*, 4355

(10) (a) Chen, W. et al. *J. Org. Chem.* **2003**, *68*, 1929. (b) Appendino, G. et al. *Eur. J. Org. Chem* **2003**, 4422

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THE NEGISHI COUPLING: AN UPDATE

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Palladium-Catalyzed Alkenylation by the Negishi Coupling

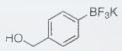
Enantiopure Sulfoxides and Sulfinamides

New Products from Aldrich R&D

TRIFLUOROBORATES

Potassium 4-(hydroxymethyl)phenyltrifluoroborate

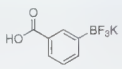
659762



1 g	$24.00
5 g	80.00

Potassium 3-carboxyphenyltrifluoroborate

659789



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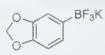
5 g	80.00

Potassium 3,4-(methylenedioxy)phenyltrifluoroborate

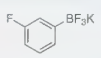
659754



1 g	$24.00
5 g	80.00

Potassium 3-fluorophenyltrifluoroborate

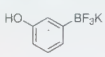
659770



1 g	$24.00
5 g	80.00

Potassium 3-hydroxyphenyltrifluoroborate

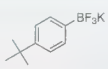
659746



1 g	$24.00
5 g	80.00

Potassium 4-*tert*-butylphenyltrifluoroborate, 95%

654728



1 g	$14.50
10 g	81.00

Potassium 2-methoxyphenyltrifluoroborate

654930

1 g	$24.00
5 g	80.00

Potassium vinyltrifluoroborate, 95%

655228

1 g	$24.00
5 g	80.00

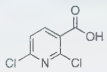
Trifluoroborates are air-stable alternatives to boronic acids in the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[1–3] They are more robust, easier to handle, and less prone to protodeboronation.[1] They display a remarkably uniform behavior.[2]

(1) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (2) Molander, G. A. et al. *J Org. Chem.* **2003**, *68*, 5534. (3) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49

BUILDING BLOCKS

2,6-Dichloronicotinic acid, 97%

658219



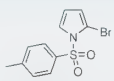
1 g	$33.00
5 g	115.00

This pharmaceutical research[1,2] key building block is now available in 97% purity. See **479586** for a technical grade (90%) of this material.

(1) Kelly, T. P. et al. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 451. (2) Laeckmann, D. et al. *Bioorg Med. Chem.* **2002**, *10*, 1793

2-Bromo-1-(*p*-toluenesulfonyl)pyrrole, 90%

650900



1 g	$33.00
5 g	115.00

This product is a stable and easily handled alternative for the labile bromopyrrole, and is an excellent substrate for the Suzuki coupling reaction. The tosyl group is readily cleaved under basic conditions to generate the 2-arylpyrrole coupling product.

Knight, L. W. et al. *Synlett* **2003**, 1993

N-Boc-piperidine, 98%

655872

5 g	$30.00
25 g	105.00

A wide variety of substituted piperidines can be synthesized from this Boc-protected building block. Lithiation with BuLi leads to substitution at the 2 position with aryl, vinyl, and alkynyl halides.[1] Its use in the stereoselective synthesis of D-*threo*-methylphenidate (Ritalin®) and similar substrates has been reported.[2,3]

(1) Dieter, R. K.; Li, S. J. *J. Org. Chem.* **1997**, *62*, 7726. (2) Axten, J. M. et al. *J. Am. Chem. Soc.* **1999**, *121*, 6511. (3) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109

BENZOFURAZANS

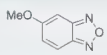
Benzofurazan, 97%

650137

1 g	$17.50
10 g	95.00

5-Methoxybenzofurazan, 97%

656925



1 g	$26.50
5 g	92.50

5-Chlorobenzofurazan

659118

1 g	$24.00
5 g	80.00

Benzofurazans have been utilized as effective fluorescence probe motifs[1] and as medicinal building blocks in the synthesis of antileukemic agents.[2,3]

(1) Uchiyama, S. et al. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2525. (2) Ghosh, P. B.; Whitehouse, M. W *J. Med. Chem.* **1968**, *11*, 305. (3) Ghosh, P. B.; Whitehouse, M. W. *J. Med. Chem.* **1969**, *12*, 505

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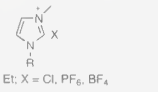
Joe Porwoll, President

Dr. Annegret Stark of the University of Jena (Friedrich-Schiller-Universität Jena), Germany, kindly suggested that we add high-purity ionic liquids (HPIL) to our existing extensive list of ionic liquids. Dr. Stark stated, "In our laboratories, HPILs serve as a benchmark in investigating impurity-dependent effects on reactions." The low water and halogen content of HPILs renders them more effective as solvents in transition-metal-catalyzed reactions.

(1) Seddon, K. R.; Stark, A. *Green Chem.* **2002**, *4*, 119. (2) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun.* **1999**, 25. (3) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH, 2003; p 26. (4) Stark, A.; Ajam, M.; Green, M.; Raubenheimer, H. G.; Ranwell, A.; Ondruschka, B. *Adv. Synth. Catal.*, submitted for publication, 2005.



R = Bu, Et; X = Cl, PF_6, BF_4

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55509	**1-Butyl-3-methylimidazolium chloride**, dry, ≥99.0% (AT)	5 g 25 g	57.40 229.30
18122	**1-Butyl-3-methylimidazolium hexafluorophosphate**, for catalysis, ≥98.5% (T)	5 g 50 g	114.80 820.00
39931	**1-Butyl-3-methylimidazolium tetrafluoroborate**, for catalysis, ≥98.5% (T)	5 g 50 g	105.00 315.00
39736	**1-Ethyl-3-methylimidazolium tetrafluoroborate**, for catalysis, ≥98.5% (T)	5 mL 50 mL	262.00 720.50

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Photograph © Board of Trustees, National Gallery of Art, Washington

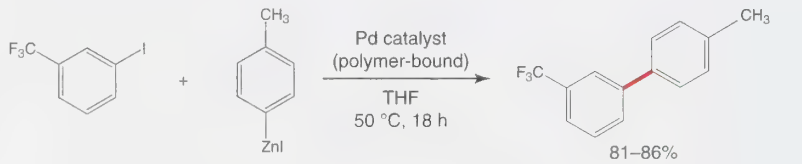
Valdemosa, Majorca: Thistles and Herbage on a Hillside (oil on canvas, 55.8 × 71.1 cm) was painted by the artist John Singer Sargent in 1908. Sargent was born in 1856 in Florence, Italy, to expatriate American parents. His first artistic training was in Rome, but he later attended the Accademia delle Belle Arti in Florence, and studied drawing at the École des Beaux-Arts and painting in the studio of the portrait painter Charles Carolus-Duran in Paris. In 1877, he began to exhibit in the Salons, the French government sanctioned art exhibitions. Sargent copied works by Diego Velázquez on a trip to Spain in 1879 and by Frans Hals in Belgium and Holland in 1880, an experience that had a great impact on his artistic development.

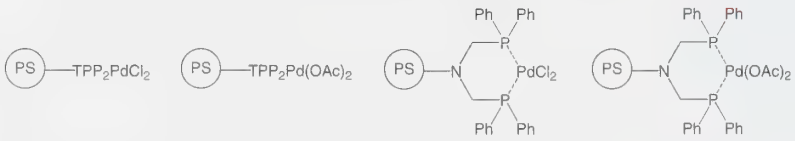
By the end of the nineteenth century, Sargent had become the most sought-after portrait painter of his time, but he always felt constrained by the limitations of portrait painting. By the early twentieth century, his success finally allowed him to free himself almost completely from the painting of formal portraits. He made annual trips to Spain, Italy, Austria, and Switzerland, and it was on a trip to the Balearic island of Majorca that he painted this small picture. He had no interest in what he called "enormous views and huge skies", and chose to concentrate on a small patch of vegetation growing in the earth of a hillside. This painting is not strictly a realistic image, but one which, with its strong formal contrasts, bright colors, and seemingly spontaneous execution, achieves an extraordinary intensity of expression. Confronted with such an immediate response to nature that seems almost spiritual in its intensity, it is easy to understand Sargent's disdain for the artificiality of the academic portrait painting that had dominated his career for most of his life.

This painting was acquired by the National Gallery of Art, Washington, DC, through the Avalon Fund and by Gift of Virginia Bailey Brown.

The Negishi Coupling Catalyzed by Palladium on Polymer Supports

Supported palladium catalysts are widely used in the Suzuki, Heck, and Sonogashira cross-coupling reactions. However, no examples of their use in the Negishi coupling have been reported in the literature. There are several advantages to using supported catalysts in organic synthesis. These include reagent stability, suitability for automation, ease of workup, recyclability, and lower Pd contamination in the final product. Herein, we describe the application of four commercially available polymer-supported palladium reagents as catalysts in the Negishi coupling.





596930 654167 646555 654159

Typical Experimental Procedure

The palladium catalyst (0.01 mmol Pd) is charged into the reaction vessel. 3-Iodobenzotrifluoride (144 µL, 1 mmol) is then introduced, followed by addition of a THF solution of 4-methylphenylzinc iodide (0.5 M, 3 mL, 1.5 mmol). The resulting mixture is stirred at 50 °C for 18 h, cooled, and then filtered. The resin is washed with THF (2 × 3 mL), the THF filtrates combined and evaporated. The evaporation residue is dissolved in a minimum amount of THF and filtered through a silica gel pad to remove any residual zinc compounds. The pad is rinsed with ether, and the combined ether filtrates evaporated. The crude product thus obtained is purified by flash chromatography on silica gel (column size 1.5 × 2.5 cm) using hexane as eluent. The purified product, 4-methyl-3′-trifluoromethylbiphenyl, is isolated as a colorless oil. (See the table below for yields.)

Cat. No.	Catalyst Name	Price	Product Yield	Byproduct Yield[a]
596930-1G **596930-5G**	Dichlorobis(triphenylphosphine)palladium(II), polymer-bound	$29.00 147.50	83%	4%
654167-5G **654167-25G**	Diacetoxybis(triphenylphosphine)palladium(II), polymer-bound	280.00 800.00	84%	5%
646555-1G **646555-5G**	Bis[(diphenylphosphanyl)methyl]aminepalladium(II) dichloride, polymer-bound	23.50 110.00	86%	4%
654159-1G **654159-5G**	Bis[(diphenylphosphanyl)methyl]aminepalladium(II) diacetate, polymer-bound	187.50 700.00	81%	5%

[a] 4,4′-Dimethylbiphenyl.

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Organic Synthesis with Light-Fluorous Reagents, Reactants, Catalysts, and Scavengers

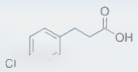
Synthetic Applications of Buchwald's Phosphines in Palladium-Catalyzed Aromatic-Bond-Forming Reactions

New Products from Aldrich R&D

Phenylpropionic Acid Derivatives

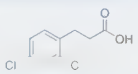
3-(4-Chlorophenyl)propionic acid, 97%

656151 1 g $20.80
[*2019-34-3*] 5 g 52.00
$C_9H_9ClO_2$



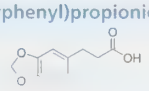
3-(2,4-Dichlorophenyl)propionic acid, 97%

656186 1 g $18.70
[*55144-92-8*] 5 g 62.40
$C_9H_8Cl_2O_2$



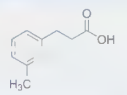
3-(3,4-Methylenedioxyphenyl)propionic acid, 97%

657565 1 g $24.50
[*2815-95-4*] 5 g 85.00
$C_{10}H_{10}O_4$



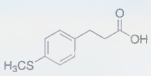
3-(3-Methylphenyl)propionic acid, 97%

656178 1 g $22.90
[*3751-48-2*] 5 g 62.40
$C_{10}H_{12}O_2$



3-(4-Methylthiophenyl)propionic acid, 97%

656135 1 g $20.80
$C_{10}H_{12}O_2S$ 5 g 52.00



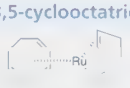
Versatile building blocks employed in the synthesis of several biologically active compounds, including γ-secretase inhibitors[1,2] and antagonists of human vanilloid receptor 1,[3,4] adenosine A_1 receptor,[5] and dopamine D_4 receptor.[6]

(1) Owens, A. P. et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4143. (2) Churcher, I. *Bioorg Med. Chem. Lett.* **2003**, *13*, 179. (3) Jetter, M. C. et al. *Bioorg. Med. Chem. Lett* **2004**, *14*, 3053. (4) McDonnell, M. E. et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 531. (5) Van Calenbergh, S. et al. *J. Med. Chem.* **2002**, *45*, 1845. (6) Unangst, P. C. et al. *J. Med Chem.* **1997**, *40*, 4026

Organometallic Reagents

(1,5-Cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium, Ru(cod)(cot)

654418 1 g $165.00
[*127382-91-6*]
$C_{16}H_{20}Ru$



Highly selective catalyst for amine alkylations, [2+2] cycloadditions, and enyne generation;[1] and key precursor for the preparation of stabilized Ru nanoparticles.[2]

(1) (a) Mitsudo, T. et al. *J. Am. Chem. Soc* **1999**, *121*, 1839. (b) Watanabe, Y. et al. *J Org. Chem.* **1996**, *61*, 4214. (2) (a) Pelzer, K. et al. *Chem. Mater* **2004**, *16*, 4937. (b) Pan, C. et al. *J. Am. Chem. Soc.* **2001**, *123*, 7584

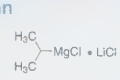
Dicyclohexyl(2-methylphenyl)phosphine, 95%

651885 1 g $26.50
[*173593-25-4*] 10 g 145.00
$C_{19}H_{29}P$

Bulky ligand in catalyst systems utilized in coupling reactions.

Isopropylmagnesium chloride–lithium chloride complex solution, 1.0 M in tetrahydrofuran

656984 10 mL $18.00
[*807329-97-1*] 100 mL 60.00
$C_3H_7Cl_2LiMg$



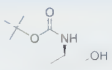
Performs halogen–magnesium exchange better than its counterparts, isopropylmagnesium chloride and diisopropylmagnesium

Ren, H. et al. *Org. Lett.* **2004**, *6*, 4215

1,2-Amino Alcohols

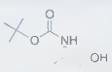
N-Boc-(*R*)-(+)-2-amino-1-butanol, 96%

660108 1 g $24.00
$C_9H_{19}NO_3$ 5 g 80.00



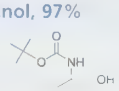
N-Boc-(*S*)-(–)-2-amino-1-butanol, 96%

660116 1 g $24.00
$C_9H_{19}NO_3$ 5 g 80.00



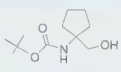
N-Boc-DL-2-amino-1-butanol, 97%

657786 1 g $18.70
[*138373-86-1*] 5 g 62.40
$C_9H_{19}NO_3$



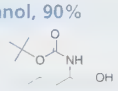
N-Boc-1-amino-1-cyclopentanemethanol, 97%

657689 1 g $65.50
$C_{11}H_{21}NO_3$ 5 g 218.50



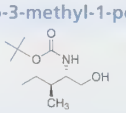
N-Boc-DL-2-amino-1-hexanol, 90%

657794 1 g $40.00
$C_{11}H_{23}NO_3$ 10 g 275.00



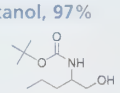
N-Boc-(2*S*,3*S*)-(–)-2-amino-3-methyl-1-pentanol, 96%

660205 2 g $46.00
$C_{11}H_{23}NO_3$ 10 g 152.00



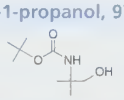
N-Boc-DL-2-amino-1-pentanol, 97%

657808 1 g $31.20
[*179684-02-7*] 5 g 104.00
$C_{10}H_{21}NO_3$



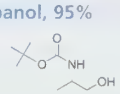
N-Boc-2-amino-2-methyl-1-propanol, 97%

657778 1 g $23.40
[*102520-97-8*] 5 g 78.00
$C_9H_{19}NO_3$



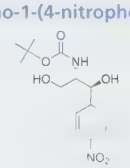
N-Boc-DL-2-amino-1-propanol, 95%

657816 1 g $26.50
[*147252-84-4*] 5 g 88.40
$C_8H_{17}NO_3$



N-Boc-(1*R*,2*R*)-(–)-2-amino-1-(4-nitrophenyl)-1,3-propanediol

660213 1 g $24.00
$C_{14}H_{20}N_2O_6$ 5 g 80.00



Versatile building blocks for the synthesis of aldehydes,[1] carboxylic acids,[2] aziridines,[3] azides,[4] and oxathiazolidines.[5]

(1) Tietze, L. F.; Burkhardt, O. *Synthesis* **1994**, 1331. (2) (a) Kokotos, G. et al. *J. Med Chem.* **2004**, *47*, 3615. (b) Sasaki, N. A. *Tetrahedron Lett.* **1987**, *28*, 6069. (3) (a) Wessig, P.; Schwarz, J. *Synlett* **1997**, 893. (b) Braga, A. L. et al. *Org. Lett.* **2003**, *5*, 2635. (4) Benalil, A. et al. *Tetrahedron* **1991**, *47*, 8177. (5) Posakony, J. J. et al. *J. Org Chem.* **2002**, *67*, 5164

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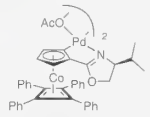
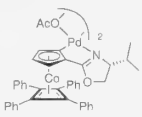
Joe Porwoll, President
Aldrich Chemical Co., Inc

Professor Larry Overman of the University of California, Irvine, kindly suggested that we offer these cobalt(I) oxazoline palladacycle enantiomers. These acetate-bridged dimers (COP-OAc) effectively promote the asymmetric rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides.[1] This grants ready access to valuable allylic amines of high enantiomeric purity, following the removal of the trichloroacetyl group under basic, acidic, or reductive conditions

(1) Krsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101



661716



661708

661716	(*S*)-(+)-COP-OAc Catalyst, 95%	250 mg	$75.00
		1 g	215.00
661708	(*R*)-(–)-COP-OAc Catalyst, 95%	250 mg	$35.00
		1 g	120.00

Naturally, we made these useful catalysts. It was no bother at all, just a pleasure to be able to help

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

Family Group (oil on canvas, 182.8 × 213.3 cm) was painted by the American painter William Glackens in 1910–1911. Glackens was one of a number of artists whose works reflected the rapid changes that were occurring in America in the early years of the twentieth century. America was evolving from a predominantly agricultural society into an industrial power, people were moving from the country to the cities, and massive immigration was rapidly increasing the population. These artists strove to document the realism of everyday life, painting scenes in fashionable cafés and restaurants, immigrant life on New York City's Lower East Side, theatergoers emerging from popular shows on Broadway, and views in Central Park and the city's streets. Rejecting any self-conscious aestheticism or romanticism, eight of them joined together in 1908 to stage their own independent exhibition, repudiating the prevailing academicism of the time. The culmination of this movement occurred in 1913 with The Armory Show, a huge exhibition of modern American and European art in New York, in which Glackens's *Family Group* was first shown.

The painting records a visit to the artist's Fifth Avenue apartment by Grace Morgan, a family friend who had recently returned to New York from France. Mrs. Edith Glackens leans on her sister Irene's chair, while Ira Glackens, the artist's son, stands between his mother and a table on which their visitor rests her elbow. The light streaming in from the window in the background illuminates the diverse colors and patterns in the room, and the casual arrangement of the figures and their closeness to the viewer underscore the naturalness of the artist's approach. Even the fact that the bottom edge of the picture cuts off the diagonal of the carpet implies that the carpet extends into the space occupied by the viewer, further enhancing the immediacy and realism of Glackens's representation of a singular, but otherwise ordinary event in the life of his family

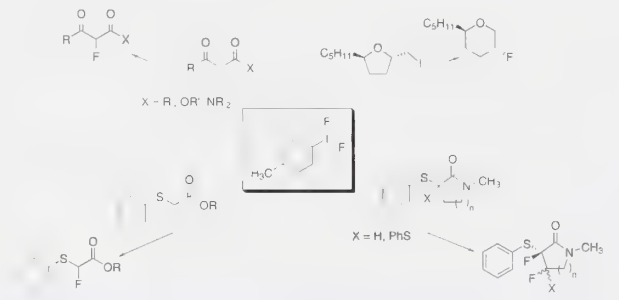
This painting is a gift of Mr. and Mrs. Ira Glackens to the National Gallery of Art, Washington, DC.

Fluorinating Reagents from Sigma-Aldrich

The importance of selectively fluorinating compounds in medicinal chemistry, biology, and organic synthesis is well appreciated and provides a major impetus to the discovery of new and mild fluorinating agents that can operate safely and efficiently. Elemental fluorine and many electrophilic fluorinating agents have been used in synthesis; however, most of these fluorinating agents are highly aggressive, unstable, and require special equipment and care for safe handling. Sigma-Aldrich is pleased to offer the following alternatives, which lack these drawbacks

NEW 4-Iodotoluene Difluoride (Tol-IF_2)

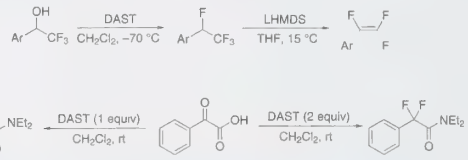
4-Iodotoluene difluoride (Tol-IF_2) is easy to handle and less toxic than many fluorinating agents. Selective monofluorination of β-keto esters, β-keto amides, and β-diketones takes place under mild conditions without the use of HF–amine complexes.[1] A new methodology for the synthesis of fluorinated cyclic ethers was recently reported, which utilized Tol-IF_2 to achieve a fluorinative ring-expansion of four-, five-, and six-membered rings.[2] When one equivalent of Tol-IF_2 is reacted with phenylsulfanylated esters, the α-fluoro sulfide results through a fluoro-Pummerer reaction.[3] When phenylsulfanylated lactams were treated with two equivalents of Tol-IF_2, the lactams were fluorinated in the α and β positions, resulting in diastereomeric difluorides.[4]



Diethylaminosulfur Trifluoride (DAST)

DAST has been regularly employed in selective fluorinations of alcohols, alkenols, carbohydrates, ketones, sulfides, epoxides, thioethers, and cyanohydrins. In addition, some novel organic cyclizations are possible when DAST is employed as a reagent.[5] 1,2,2-Trifluorostyrenes can be synthesized by fluorination of the parent α-(trifluoromethyl)phenylethanol with DAST, followed by dehydrohalogenation with lithium bis(trimethylsilyl)amide (LHMDS). This method leads to the trifluorostyrene without requiring a palladium-catalyzed coupling.[6]

The one-pot synthesis of α,α-difluoroamides via direct fluorination was recently reported using DAST as the fluorinating reagent. Decreasing the molar ratio of DAST to substrate resulted in the formation of the corresponding α-keto amide.[7]

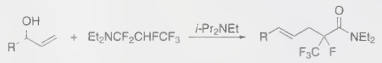


Selectfluor™ Fluorinating Reagent (F-TEDA)

Selectfluor™ fluorinating reagent [(1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), or F-TEDA)] is a user friendly, mild, air- and moisture-stable, non-volatile reagent for electrophilic fluorination. Selectfluor™ is capable of introducing fluorine into organic substrates in one step, with a remarkably broad scope of reactivity, often with excellent regioselectivity.[8] For example, allylic fluorides can be prepared using Selectfluor™ via a sequential cross-metathesis–electrophilic fluorodesilylation route. This route avoids the formation of byproducts that result from allylic transposition, which is observed when nucleophilic displacement or ring-opening reaction with DAST is attempted.[9]

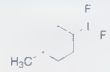
Ishikawa's Reagent

Ishikawa's reagent [(*N*,*N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine) has also demonstrated its utility in fluorination reactions. In a recent example, Ishikawa's reagent has been used in a clean and reproducible fluorination protocol on an intermediate in the total synthesis of 26-fluoroepothilone B.[10] Ishikawa's reagent also displays the ability to insert a fluoro(trifluoromethyl)methylene moiety into unsaturated alcohols.[11]



References: (1) Yoshida, M. et al. *Arkivoc* [Online] **2003**(vi), 36. (2) Inagaki, T. et al. *Tetrahedron Lett* **2003**, *44*, 4117. (3) Motherwell, W. B. et al. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2809. (4) Greaney, M. F. et al. *Tetrahedron Lett* **2001**, *42*, 8523. (5) For a review, see Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561. (6) Anilkumar, R.; Burton, D. J. *Tetrahedron Lett* **2003**, *44*, 6661. (7) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063. (8) For a review, see Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res* **2004**, *37*, 31. (9) Thibaudeau, S.; Gouverneur, V. *Org. Lett* **2003**, *5*, 4891. (10) Koch, G. et al. *Synlett* **2004**, 693. (11) Ogu, K.-i. et al. *Tetrahedron Lett* **1998**, *39*, 305

4-Iodotoluene difluoride



p-Tolyliododifluoride
[*371-11-9*] $CH_3C_6H_4IF_2$ FW 256.03
mp . . . . . 102–106 °C
R: 34 S: 26-36/37/39-45

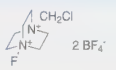
651117-1G	1 g	$32.80
651117-5G	5 g	112.50

(Diethylamino)sulfur trifluoride

DAST
[*38078-09-0*] $(C_2H_5)_2NSF_3$ FW 161.19
Feiser **6**, 183; **10**, 142; **12**, 183; **13**, 110; **16**, 128
bp. . . . . .30–32 °C/ 3 mm Hg
density . . . . . 1.22 g/mL at 25 °C
R: 11-14-20/21/22-34 S: 16-26-36/37/39-45

235253-1G	1 g	$20.30
235253-5G	5 g	62.90
235253-25G	25 g	194.50
235253-125G	125 g	606.00
235253-250G	250 g	936.00

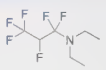
Selectfluor™ fluorinating reagent



F-TEDA
[*140681-55-6*] $C_7H_{14}B_2ClF_9N_2$ FW 354.26
>95% in F+ active
mp . . . . . 260 °C
R: 22-36/37/38-41 S: 26-36/37/39

439479-5G	5 g	$20.50
439479-25G	25 g	70.80

Ishikawa's Reagent



N,*N*-Diethyl-1,1,2,3,3,3-hexafluoropropylamine
[*309-88-6*] $CF_3CF_2CHFN(C_2H_5)_2$ FW 223.16
bp. . . . . 56–57 °C n_D^{20} 1.3460
density . . . . . 1.230 g/mL at 25 °C
R: 10-34 S: 16-26-36/37/39-45

564990-25G	25 g	$63.70
564990-100G	100 g	217.00

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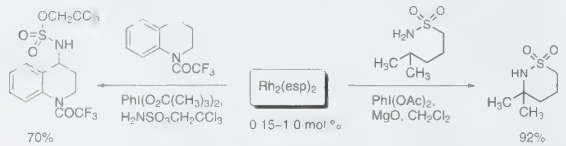
Du Bois C–H Amination Catalyst

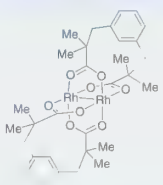
The Du Bois group at Stanford University has utilized $Rh_2(esp)_2$ to facilitate both inter- and intramolecular N-insertion in a range of benzylic, secondary, and tertiary C–H bonds, giving the corresponding aminated products in high yields.[1,2]



(1) (a) Espino, C. G. et al. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (b) Fiori, K. W. et al *Angew. Chem., Int. Ed.* **2004**, *43*, 4349. (2) (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (b) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (c) Diaz-Requejo, M. M. et al. *J. Am. Chem. Soc* **2003**, *125*, 12078

Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)], 96%

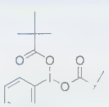
$Rh_2(esp)_2$
662623
[*819050-89-0*]
$C_{32}H_{40}O_8Rh_2$
FW: 758.47



100 mg	$35.00
500 mg	125.00

Bis(*tert*-butylcarbonyloxy)iodobenzene, 97%

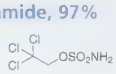
662283
[*57357-20-7*]
$C_{16}H_{23}IO_4$
FW: 406.26



5 g	$15.00
25 g	40.00
100 g	110.00

2,2,2-Trichloroethoxysulfonamide, 97%

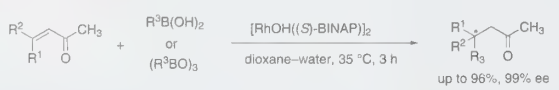
663727
[*69226-51-3*]
$C_2H_4Cl_3NO_3S$
FW: 228.48



1 g	$25.00
10 g	154.00

Hayashi Asymmetric Conjugate-Addition Catalyst and Precursors

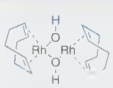
The dimeric catalysts and catalyst precursors developed by Hayashi demonstrate impressive levels of enantiocontrol in the conjugate-addition reactions of both acyclic and cyclic enones of varying electronic character.[1–5]



(1) Hayashi, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (2) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (3) Takaya, Y. et al. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (4) Takaya, Y. et al. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (5) Takaya, Y. et al. *Tetrahedron Lett.* **1999**, *40*, 6957

Hydroxy(cyclooctadiene)rhodium(I) dimer, 95%

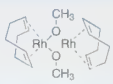
661023
[*73468-85-6*]
$C_{16}H_{26}O_2Rh_2$
FW: 456.19



250 mg	$28.00
1 g	80.00

Methoxy(cyclooctadiene)rhodium(I) dimer

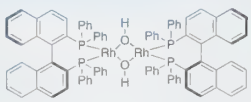
661058
[*12148-72-0*]
$C_{18}H_{30}O_2Rh_2$
FW: 484.24



250 mg	$28.00
1 g	80.00

Hydroxy[(*S*)-BINAP]rhodium(I) dimer, 90%

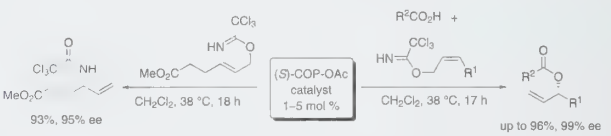
661007
[*434314-10-0*]
$C_{88}H_{66}O_2P_4Rh_2$
FW: 1485.17



1 g	$75.00

Overman Asymmetric Allylic Rearrangement Catalysts

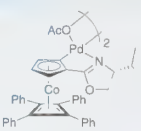
Overman and others have successfully utilized Co-based COP catalysts in the preparation of chiral amides and esters via cyclic rearrangement of allylic trichloroacetimidates. These rearrangements occur in high yield with excellent enantiocontrol.[1,2]



(1) (a) Kirsch, S. F. et al. *J. Org. Chem.* **2004**, *69*, 8101. (b) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412. (c) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866. (2) Kwon, T. W. et al. *J. Org. Chem.* **1992**, *57*, 6169.

(*R*)-(–)-COP-OAc Catalyst, 95%

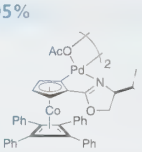
661708
[*849592-74-1*]
$C_{82}H_{72}O_6N_2Co_2Pd_2$
FW: 1512.17



250 mg	$35.00
1 g	120.00

(*S*)-(+)-COP-OAc Catalyst, 95%

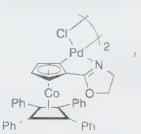
661716
[*222400-03-5*]
$C_{82}H_{72}O_6N_2Co_2Pd_2$
FW: 1512.17



250 mg	$35.00
1 g	120.00

(*R*)-(–)-COP-Cl Catalyst

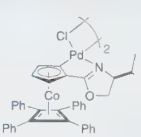
661791
[*612065-00-6*]
$C_{78}H_{66}Cl_2Co_2N_2O_2Pd_2$
FW: 1464.98



100 mg	$45.00
500 mg	245.00

(*S*)-(+)-COP-Cl Catalyst

646636
[*612065-01-7*]
$C_{78}H_{66}Cl_2Co_2N_2O_2Pd_2$
FW: 1464.98



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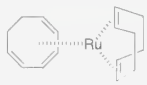
Professor John G. Ekerdt of the University of Texas at Austin and his student, Wyatt Winkenwerder, kindly suggested that we offer (1,5-cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium, or Ru(cod)(cot). This complex is used in the preparation of monodisperse ruthenium nanoparticles for catalysis,[1,2] as well as a highly selective catalyst for amine alkylations, [2+2] cycloadditions,[3] and enyne generation

(1) Pelzer, K.; Philippot, K.; Chaudret, B. *Z. Phys. Chem* **2003**, *217*, 1539. (2) Hulea, V.; Brunel, D., Galarneau, A.; Philippot, K.; Chaudret, B.; Kooyman, P. J.; Fajula, F. *Microporous Mesoporous Mater.* **2005**, *79*, 185. (3) Mitsudo, T.; Suzuki, T.; Zhang, S.-W.; Imai, D.; Fujita, K.; Manabe, T.; Shiotsuki, M.; Watanabe, Y.; Wada, K.; Kondo, T. *J. Am. Chem. Soc.* **1999**, *121*, 1839



654418-1G **(1,5-Cyclooctadiene)(1,3,5-cyclooctatriene)-ruthenium**, Ru(cod)(cot) 1 g $165.00

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Photograph © Board of Trustees, National Gallery of Art, Washington

View from Vaekero near Christiania (oil on canvas, 60.5 × 96.5 cm) was painted by the Norwegian romantic painter Johan Christian Dahl in 1827. Dahl studied in Dresden and was directly influenced by his teacher and friend, the German painter Casper David Friedrich. Dahl's paintings also show his strong interest in the work of seventeenth century Dutch landscape painters such as Jacob van Ruisdael.

Dahl visited Christiania, present-day Oslo, in the summer of 1826. The following winter in Dresden, Dahl painted *View from Vaekero near Christiania* from memory for the Hamburger Kunstverein artists' cooperative. In this moody and melancholy nocturne, Dahl invites the viewer to imagine a romantic moonlit evening complete with sand, sea, and sky. His use of successive bands of light and dark clouds against a pink-and-blue backdrop shows an alluring distance, possibly unattainable. Harmoniously cascading hills, which meld into an illuminated sea, may also suggest adventure. Ethereal light and drying fishnets seem to envelop the mysterious, solitary couple, who stand in the center foreground contemplating the quixotic setting. True to his romantic spirit, Dahl presents a thought-provoking and poignant scene, allowing us to do what paintings should make us do—dream.

This painting was purchased for the National Gallery of Art by the Patrons' Permanent Fund.

NEW Shibasaki Catalysts: La, Y, Gd, and Sm Trisisopropoxides

Rare-Earth Metals Used in Diversity-Oriented Organic Transformations

Product Highlights

- Dramatically enhance selectivities by varying the nature of the rare-earth (RE) metal and the ratio of catalyst to reaction partners.
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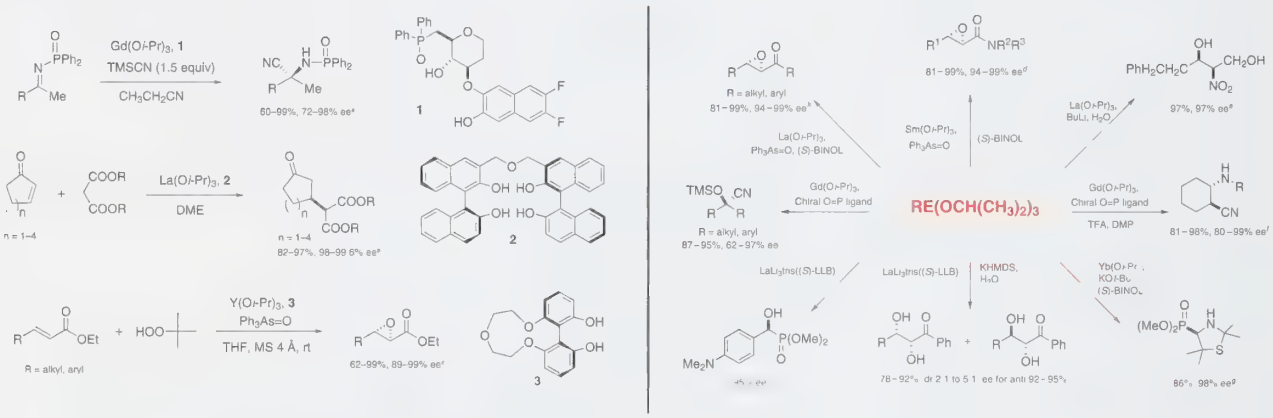
- RE catalyst systems can effectively facilitate a broad range of organic reactions.

Shibasaki and co-workers have developed rare-earth (RE) metal catalysts, utilized in conjunction with a variety of chiral ligands, to effect asymmetric transformations ranging from the formation of quaternary chiral centers to the epoxidation of unsaturated substrates. The Shibasaki research group has published extensively in the field of RE-metal catalysis and has optimized reaction conditions to afford high selectivities in C–C and C–O bond-forming reactions. Sigma-Aldrich is pleased to offer an array of RE-metal pre-catalysts that can be paired with our growing line of chiral ligands to accelerate your research discoveries.



References: (a) Masumoto, S. et al. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (b) Kim, Y. S. et al. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (c) Kakei, H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8962. (d) Nemoto, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 14544. (e) Sasai, H. et al. *J. Am. Chem. Soc.* **1993**, *115*, 10372. (f) Mita, T. et al. *J. Am. Chem. Soc.* **2005**, *127*, 11252 (g) Gröger, H. et al. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (h) Yoshikawa, N. et al. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (i) Shibasaki, M. et al. *Chem. Rev.* **2002**, *102*, 2187. (j) Yabu, K. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (k) Nemoto, T. et al. *J. Am. Chem. Soc.* **2001**, *123*, 2725

Lanthanum(III) isopropoxide NEW
[*19446-52-7*]
$C_9H_{21}LaO_3$
FW: 316.17

665193-500MG	500 mg	$45.00
665193-3G	3 g	185.00

Yttrium(III) isopropoxide NEW
[*2172-12-5*]
$C_9H_{21}YO_3$
FW: 266.17

665916-500MG	500 mg	$45.00
665916-3G	3 g	199.00

Gadolinium(III) isopropoxide NEW
[*14532-05-9*]
$C_9H_{21}GdO_3$
FW: 334.51

663948-500MG	500 mg	$75.00
663948-3G	3 g	365.00

Samarium(III) isopropoxide
[*3504-40-3*]
$C_9H_{21}SmO_3$
FW: 327.62

410136-1G	1 g	$26.70

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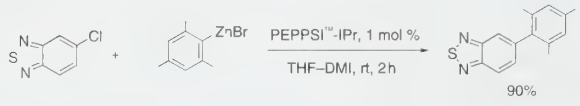
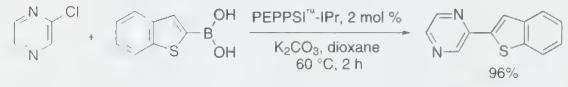
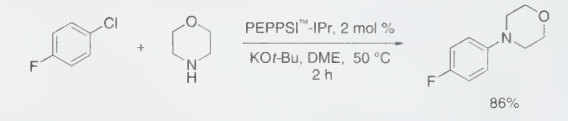


Suzuki Coupling



Kumada Coupling

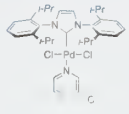
Buchwald–Hartwig Amination



(1) (a) O' Brien, C. J. et al. *Eur. J. Org. Chem.* **2006**, in press. (b) O' Brien, C. J. et al *Eur. J. Org. Chem.* **2006**, in press. (c) O'Brien, C. J. et al. *Manuscript in preparation* (d) O'Brien, C. J. et al. *Manuscript in preparation*

[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl) palladium(II) dichloride, 98%

PEPPSI™-IPr Catalyst
669032
$C_{32}H_{40}Cl_3N_3Pd$
FW: 679.46



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5 g 270.00

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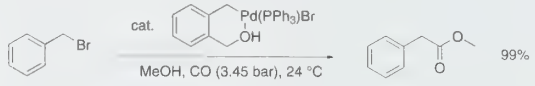
Heriot-Watt Carbonylation Catalysts

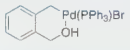
These palladium catalysts, sold under exclusive license from Heriot-Watt University (Scotland),[1] efficiently carbonylate benzyl halides in methanol under low pressures and temperatures.[2]



(1) Manufactured by Aldrich under exclusive license from Heriot-Watt University, PCT/GB2005/002738 patent pending. (2) (a) Jones, R. V. H. et al. *Tetrahedron Lett.* **2005**, *46*, 8695. (b) Lindsell, W. E. et al. *Organometallics* **2005**, *24*, 1119.

Bromo[[2-(hydroxy-κO)methyl]phenylmethyl-κC](triphenylphosphine)palladium(II)

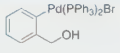
666327
[*849417-33-0*]
$C_{25}H_{23}BrOPPd$
FW: 569.77



250 mg $30.00
1 g 95.00

2-[Bis(triphenylphosphine)palladium(II) bromide]benzyl alcohol, 96%

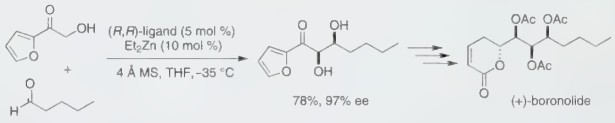
665932
$C_{43}H_{37}BrOP_2Pd$
FW: 818.02



250 mg $30.00
1 g 95.00

Trost Bis-ProPhenol Ligands

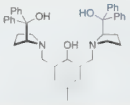
The combination of these phenolic ligands and diethylzinc generates catalyst systems that are capable of effecting a variety of asymmetric reactions. This methodology has been applied to asymmetric aldol condensations,[1] Mannich-type reactions,[2] and Henry reactions.[3]



(1) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513. (2) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (3) Trost, B. M. et al. *Org. Lett.* **2002**, *4*, 2621.

(*R,R*)-(-)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinylmethyl]-4-methylphenol, 95%

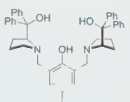
Trost (*R,R*)-Bis-ProPhenol Ligand
667625
$C_{43}H_{46}N_2O_3$
FW: 638.84



1 g $20.50
5 g 81.20

(*S,S*)-(+)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinylmethyl]-4-methylphenol, 95%

Trost (*S,S*)-Bis-ProPhenol Ligand
668370
$C_{43}H_{46}N_2O_3$
FW: 638.84



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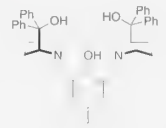
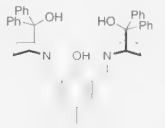
"PLEASE BOTHER US."

Professor Barry Trost of Stanford University kindly suggested that we offer these enantiomeric Bis-ProPhenol ligands. Upon treatment of a Bis-ProPhenol ligand with diethylzinc, a versatile catalyst is formed, which is capable of performing a variety of reactions in an asymmetric fashion. Aldol, imine-aldol, and nitro-aldol condensations all proceed with impressive levels of stereocontrol.[1] Additionally, the catalyst system promotes the asymmetric alkynylation of unsaturated aldehydes.[2]

(1) See the references on the facing page. (2) Trost, B. M. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8



667625



668370

667625	**(*R*,*R*)-(–)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinyl-methyl]-4-methylphenol,** 95% Trost (*R*,*R*)-Bis-ProPhenol Ligand	1 g 5 g	$20.50 81.20
668370	**(*S*,*S*)-(+)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinyl-methyl]-4-methylphenol,** 95% Trost (*S*,*S*)-Bis-ProPhenol Ligand	1 g 5 g	$20.50 81.20

Naturally, we made these useful ligands. It was no bother at all, just a pleasure to be able to help.

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Photograph © Board of Trustees, National Gallery of Art, Washington

View of the Tiber near Perugia (oil on canvas, 98.0 × 161.5 cm) was painted in Italy between 1872 and 1874 by George Inness, the American landscape artist. Inness was born in 1825 in Newburgh, New York, and was raised in New York City and New Jersey. Although he had little formal artistic training, he developed his painting style through his association with artists from the American Hudson River School and his frequent visits to Europe, where 17th-century old masters and French Barbizon School landscape painters influenced him. Emanuel Swedenborg, the 18th-century Swedish scientist and theologian who stressed that the spiritual world was as much a reality as the material world, also inspired Inness to express his personal vision of spiritual harmonies in nature

Subtle, yet dramatic atmospheric effects of harmonious color, light and shade, and mood and meaning are displayed in this painting. The dynamic diagonal created by the middle ground landscape reinforces the suggestion of depth and recession and separates the foreground from the background. A sense of the human proportion is understood by looking at the figures in the near ground. This poetic and spiritual view of the Perugia area is remarkably rendered with a sense of peace and calm

Purchased for the National Gallery of Art, Washington, DC, through the Ailsa Mellon Bruce Fund.

Biocatalytic Aldol Reactions in Organic Synthesis

The construction of C–C bonds with complete stereochemical control of the reaction course is a key goal in organic synthesis. The desired relative and absolute configurations of the newly formed stereogenic centers can be achieved by using chiral starting materials and chiral auxiliaries. Catalytic approaches towards asymmetric aldol reactions have been a special focus in recent years.[1] Aldolases and catalytic Aldolase antibodies represent valuable tools for the biocatalytic asymmetric C–C-bond formation.

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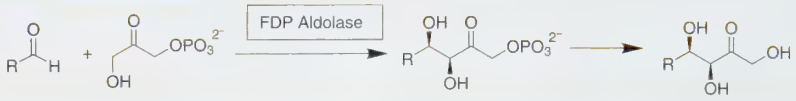
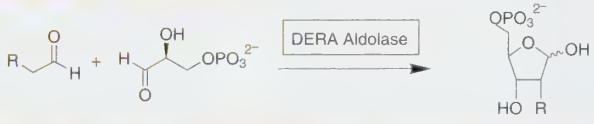
(1) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352.

FDP Aldolase E.C. 4.1.2.13



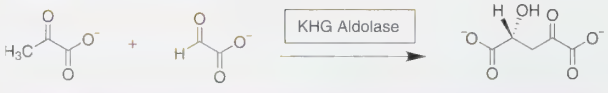
Cat. No.	Name	Pack Sizes
94864	Fructose-1,6-bisphosphate Aldolase from *Staphylococcus carnosus*	5 mg
05518	Aldolase from rabbit muscle	10 mg 50 mg
A2714	Aldolase from rabbit muscle	100 units 200 units 500 units
A9329	Aldolase from spinach	25 units

DERA Aldolase E.C. 4.1.2.4



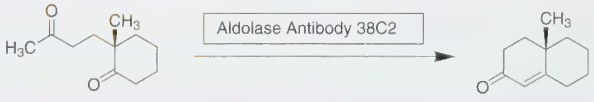
Cat. No.	Name	Pack Sizes
91252	2-Deoxy-D-ribose 5-phosphate Aldolase, E. coli K12, recombinant from *Escherichia coli*	25 mg 100 mg
41228	2-Deoxyribose-5-phosphate Aldolase from *Lactobacillus plantarum*	10 mg

KHG Aldolase E.C. 4.1.3.16



Cat. No.	Name	Pack Sizes
59892	4-Hydroxy-2-oxoglutarate Aldolase from *Escherichia coli*	10 mg

Aldolase Antibody 38C2



Cat. No	Name	Pack Sizes
479950	Aldolase Antibody 38C2, murine catalytic monoclonal antibody, contains phosphate buffer salts (pbs)	10 mg
481572	Aldolase Antibody 38C2, murine catalytic monoclonal antibody	10 mg

Other Aldol Reaction Biocatalysts

Cat. No.	Name	E.C. Number	Pack Sizes
47153	*N*-Acetylneuraminic acid Aldolase from *Escherichia coli*	4.1.3.3	25 mg 100 mg
A6680	*N*-Acetylneuraminic acid Aldolase from *Escherichia coli*	4.1.3.3	25 units
96586	L-Threonine Aldolase from *Pseudomonas putida*	4.1.2.5	10 mg 50 mg
67891	3-Deoxy-D-manno-octulosonate Aldolase from *Escherichia coli*	4.1.2.23	10 mg
527858	Aldolase Antibody 84G3, murine catalytic monoclonal antibody		10 mg

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VOL. 39, NO. 4 • 2006

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for Cross-Coupling Reactions

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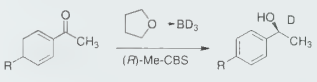
BD_3–THF Solution Stabilized with NIMBA and Me-CBS Solutions in THF

The asymmetric borane reduction of prochiral ketones catalyzed by (*R*)- or (*S*)-Me-CBS provides a facile method for accessing chiral secondary alcohols.[1] We are pleased to introduce *N*-isopropyl-*N*-methyl-*tert*-butylamine (NIMBA) stabilized BD_3–THF solutions for the preparation of isotopically labeled alcohols.[2] Amine-stabilized borane–THF solutions exhibit enhanced shelf-life over those containing other stabilizers, and additionally, higher levels of enantiomeric excess are obtained.[3] Deuterium-labeled alcohols may also be synthesized through the sequence of hydroboration–oxidation of olefins. Either method of alcohol preparation gives high levels of deuterium incorporation into the substrate molecule. We are also pleased to now offer (*R*)- and (*S*)-Me-CBS as solutions in THF, in addition to our toluene solutions of the same catalysts.[4]

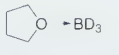


R	Yield (%)	ee (%)	D atom %
H	100 (GC)	96.6	97.0
CH_3	100 (GC)	94.5	96.4
NO_2	91 (isolated)	97.8	98.1
OCH_3	100 (GC)	94.2	96.1

(1) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (2) Sigma-Aldrich, patent pending. (3) (a) Nettles, S. M. et al. *J. Org. Chem.* **2002**, *67*, 2970. (b) Aldrich Technical Bulletin, AL-218. (4) Sold under license. US4943635 and foreign equivalents apply. End user is granted on purchase a label license to use without scale limitation.

Borane-d_3–THF complex solution, 1.0 M in THF, stabilized with 0.005 M *N*-isopropyl-*N*-methyl-*tert*-butylamine, 97.5 atom % D NEW

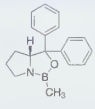
667714
$C_4H_6BD_3O$
FW: 88.96



1 mL	$28.50
5 x 1 mL	100.00

(*R*)-2-Methyl-CBS-oxazaborolidine solution, 1 M in THF NEW

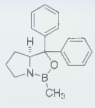
674656
[*112022-81-83*]
$C_{18}H_{20}BNO$
FW: 277.17



5 mL	$91.70
25 mL	312.00

(*S*)-2-Methyl-CBS-oxazaborolidine solution, 1 M in THF NEW

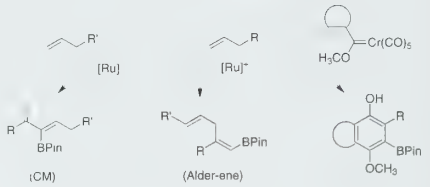
674648
[*112022-81-8*]
$C_{18}H_{20}BNO$
FW: 277.17



5 mL	$91.70
25 mL	312.00

Alkynylboronates

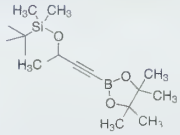
Alkynylboronates participate in a variety of regio- and stereoselective carbon–carbon bond-forming reactions including enyne cross metathesis (CM),[1] Alder-ene,[2] and Dötz annulation reactions.[3] Products obtained from these reactions are either alkenyl or arylboronates, which are active coupling partners in Suzuki and Heck reactions.



(1) Kim, M.; Lee, D. *Org. Lett.* **2005**, *7*, 1865. (2) (a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 3252. (b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 8142. (3) Davies, M. W. et al. *J. Org. Chem.* **2001**, *66*, 3525.

3-(*tert*-Butyldimethylsilyloxy)-1-butyn-1-ylboronic acid pinacol ester, 96% NEW

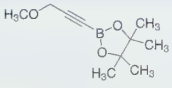
674729
$C_{16}H_{31}BO_3S$
FW: 310.31



1 g	$55.20
5 g	193.50

3-Methoxy-1-propyn-1-ylboronic acid pinacol ester, 96% NEW

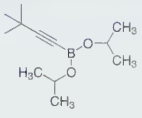
674710
$C_{10}H_{17}BO_3$
FW: 196.05



1 g	$45.00
5 g	179.00

3,3-Dimethylbutynylboronic acid diisopropyl ester, 97% NEW

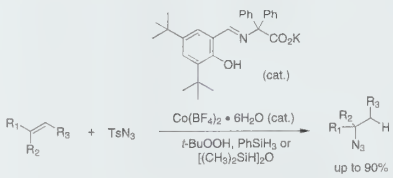
639192
[*121021-24-7*]
$C_{12}H_{23}BO_2$
FW: 210.12



1 g	$29.80
5 g	85.80

Cobalt-Catalyzed Hydroazidation

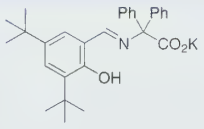
Organoazides have gained considerable interest recently because of their use in click chemistry and as masked amines. Erick Carreira (ETH Hönggerberg) and co-workers have developed a convenient method for preparing these useful intermediates by Markovnikov hydroazidation of olefins.[1] The method utilizes a cobalt catalyst prepared in situ from a Schiff base and $Co(BF_4)_2{\cdot}6H_2O$ in the presence of a silane to give secondary and tertiary alkyl azides in good yields.



(1) Waser, J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8294.

Potassium 2-(3,5-di-*tert*-butyl-2-hydroxybenzyl-ideneamino)-2,2-diphenylacetate, 95% NEW

676551
$C_{29}H_{32}KNO_3$
FW: 481.68



250 mg	$38.25
1 g	114.75

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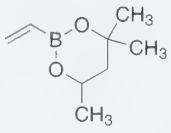
"PLEASE BOTHER US."

Professor Andrew Whiting of the University of Durham, U.K., kindly suggested that we offer vinylboronic acid 2-methyl-2,4-pentanediol ester. This reagent functions as a vinyl dianion equivalent, since it can react at either end of the double bond under Suzuki–Miyaura or Heck coupling conditions. This compound also exhibits enhanced stability and lower volatility than related vinylboronate esters. [1–3]

(1) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S. J. R.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7645 (2) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Org. Biomol. Chem.* **2005**, *3*, 3167. (3) Lightfoot, A P.; Twiddle, S. J. R.; Whiting, A. *Synlett* **2005**, 529



673641 **Vinylboronic acid 2-methyl-2,4-pentanediol ester,** 95% (4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane) — 1 g $30.20; 10 g 211.50

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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Photograph © Board of Trustees, National Gallery of Art, Washington

No one will be surprised to read that the painting on our cover, ***Ships Riding on the Seine at Rouen*** (1872/1873, oil on canvas, 37.8 × 46.6 cm), was painted by the archetypal Impressionist, Claude Monet (French, 1840–1926) His distinctive style is recognizable, fresh, and still sought after over 130 years after his radical and expressive brushwork shocked the art world in Paris in the 1860s and 1870s.

Monet's devotion to the ideals of Impressionism lasted throughout his long and prolific life. It is fitting that the word Impressionism, which defines the movement and style, was coined by an art critic reviewing Monet's painting *Impression: Sunrise*, 1872 (Musée Marmottan, Paris).

This delightful, small painting displays large and small sailboats comfortably resting on the river Seine on a sunny, warm, and idyllic day. Monet's choice of primarily soft blues and greens creates an alluring calm and relaxed atmosphere. He characteristically captures the illusion of moving water by suggesting with broad brushstrokes that the landscape, sky, clouds, and boats are reflected in the gently rolling water

This painting is in the Ailsa Mellon Bruce Collection of Small French Paintings at the National Gallery of Art, Washington, DC.

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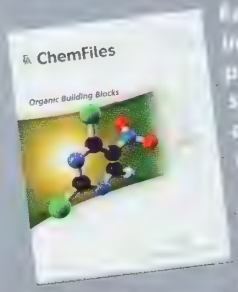

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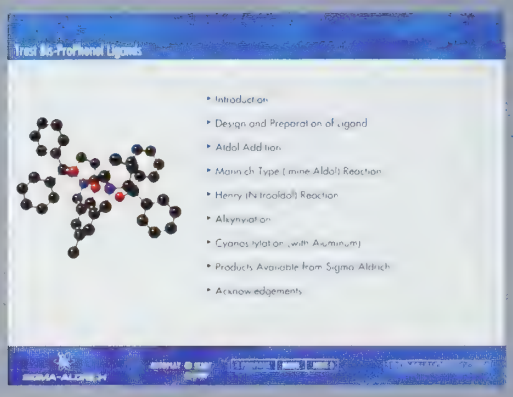

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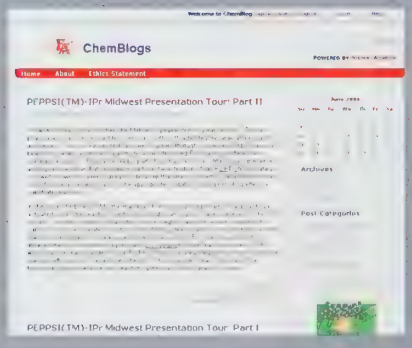

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Aldrichimica ACTA

VOL. 40, NO. 1 • 2007

Catalytic Azide–Alkyne Cycloaddition

Selecting and Driving Monolayer Structures

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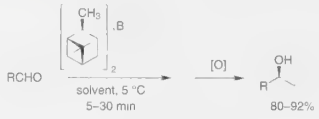
Aldrich Is Pleased to Offer the Latest Asymmetric Allylation Reagents

Stable Ipc$_2$B(allyl) Solutions

The asymmetric allylboration of aldehydes is an extremely important method for the preparation of homoallylic alcohols, as demonstrated in numerous complex natural product syntheses.[1] Although a variety of reagents have been developed to execute this reaction, the most broadly adopted have been Brown's α-pinene-derived (–)- and (+)-*B*-allyldiisopinocampheylboranes.[2] Typically, the allylboration reagents are generated in situ and used immediately at –78 to –100 °C. We recently developed new, salt-free, Ipc$_2$B(allyl) reagents as stable solutions in pentane or dioxane.[3] Under refrigerator storage, no appreciable decreases in selectivity are observed after several months. They exhibit superb reactivity, and reactions can be performed at 5 °C, *even in water*.[4] We are excited to introduce these convenient allylboration reagents to the research community.



Enantiomeric excess, ee (%)

R	Pentane	Dioxane	Water
Ph	94*	92	90
2-BrC$_6$H$_4$	92	90	89
Et	92	90	

*96% ee at –78 °C

(1) (a) Fürstner, A. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 5506. (b) Smith, A. B., III et al. *J. Am. Chem. Soc.* **2003**, *125*, 350. (2) For a review of allylborane reagents, see Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23. (3) Patent pending. (4) Josyula, K. V. B. et al., 2006 National ACS meeting, San Francisco, MEDI 545.

(+)-Ipc$_2$B(allyl) solution, 1 M in pentane
((+)-*B*-Allyldiisopinocampheylborane)

678503 5 mL $36.50
[*106356-53-0*] 25 mL 128.00
$C_{23}H_{39}B$
FW: 326.37

(–)-Ipc$_2$B(allyl) solution, 1 M in pentane
((–)-*B*-Allyldiisopinocampheylborane)

678538 5 mL $41.60
[*85116-38-7*] 25 mL 145.50
$C_{23}H_{39}B$
FW: 326.37

(+)-Ipc$_2$B(allyl) solution, 1 M in dioxane

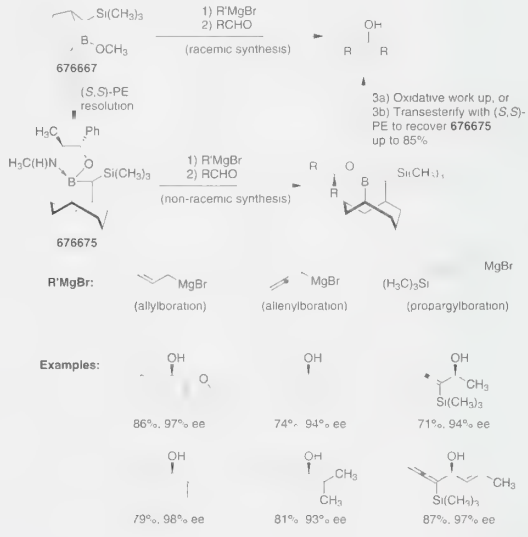
678511 5 mL $57.30
[*106356-53-0*] 25 mL 199.50
C H B
FW: 326.37

(–)-Ipc$_2$B(allyl) solution, 1 M in dioxane

678546 5 mL $55.00
[*85116-38-7*] 25 mL 192.50
$C_{23}H_{39}B$
FW: 326.37

Soderquist Borabicyclodecanes

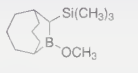
Treatment of these air-stable crystalline pseudoephedrine (PE) borinic acid complexes with the appropriate Grignard reagent is an excellent method for accessing non-racemic homoallylic or homopropargylic alcohols and α-allenyl carbinols via asymmetric allyl-, propargyl-, and allenylboration reactions.[1–3] Allylboration reactions occur rapidly (<3 h), can be performed in the presence of Mg salts, and the degree of asymmetric induction is only minimally affected by temperature. Moreover, the reagent is easily recycled in good yield. The reagents also perform well in asymmetric crotylborations,[1] allylborations of imines,[4] and the alkynylboration of *N*-acylimines to give chiral *N*-propargylamides.[5]



(1) Burgos, C. H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (2) Lai, C.; Soderquist, J. A *Org. Lett.* **2005**, *7*, 799. (3) Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397 (4) Hernandez, E. et al. *Pure Appl. Chem.* **2006**, *78*, 1389. (5) Gonzales, A. Z. et al. *Org Lett.* **2006**, *8*, 3331.

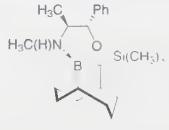
***B*-Methoxy-10-trimethylsilyl-9-borabicyclo[3.3.2]decane, 95%**

676667 5 g $84.00
$C_{13}H_{27}BOSi$ 25 g 336.50
FW: 238.25



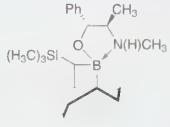
(+)-9-(1*S*,2*S*-Pseudoephedrinyl)-(10*R*)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane

676675 1 g $48.00
[*848618-13-3*] 5 g 168.50
C H BNOSi
FW: 371.44



(–)-9-(1*R*,2*R*-Pseudoephedrinyl)-(10*S*)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane

676683 1 g $55.70
$C_{22}H_{38}BNOSi$ 5 g 195.00
FW: 371.44



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"PLEASE BOTHER US."

Christopher P. Johnson, III, of the process development department at Boehringer Ingelheim Chemicals, Inc., kindly suggested that we offer boron trichloride as a solution in toluene, in addition to our other solutions of this reagent. Boron trichloride is a versatile Lewis acid and has been used extensively in the selective cleavage of alkyl aryl ethers[1] as well as a variety of C–C and C–O bond-forming reactions.[2]

(1) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (2) For recent examples, see: (a) Zhang, L.; Zhang, J. Y. *J. Comb. Chem.* **2006**, *8*, 361. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S. *J. Am. Chem. Soc.* **2006** *128*, 11320. (c) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 3819

678732 Boron trichloride solution, 1.0 M in toluene 100 mL $30.75
800 mL 138.25

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington

Winter in the Country (oil on canvas, 66.7 × 92.1 cm) was painted by the American landscape artist, George Henry Durrie (1820–1863), in Connecticut in the winter of 1859. Durrie, the son of a stationer, married a choirmaster's daughter and lived in New Haven, Connecticut, most of his short life. Although he studied painting with a portraitist, landscapes, which first appeared as backgrounds for his portraits, became his primary focus. Durrie did many snow scapes and advertised them in New Haven newspapers, noting, "no collection … is complete without … [a] winter scene." After his death, he was immortalized when the lithographic firm of Currier and Ives successfully reproduced ten of his scenes.

In *Winter in the Country*, Durrie illustrates a number of his most famous compositional conventions. Snow blankets the cold, shadowy landscape, while the ominous sky, reminiscent of Dutch landscapes, covers most of the background. The composition is at eye level, balanced by the centered barn and complementary dark leaf-less trees. Farm workers and animals in the barnyard bring a sense of scale and reality and suggest a waning day. The viewer is invited to explore this everyday 19th-century New England winter scene, pleased to find curling smoke from the farmhouse in the left middle ground, signifying a welcome and warm refuge from the cold, hard day

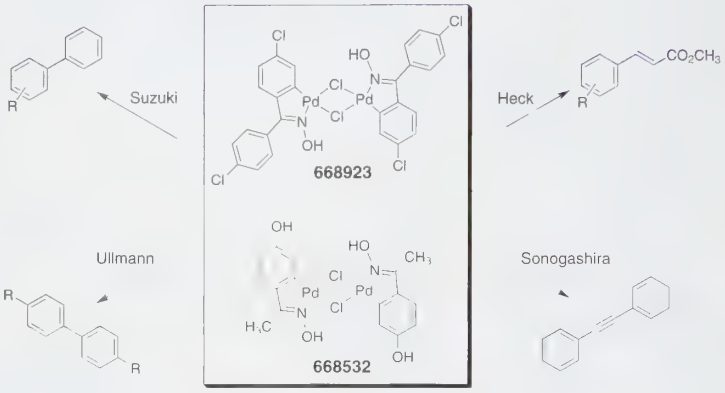
This painting was acquired by the National Gallery of Art, Washington, DC, through the Avalon Fund.

New Products for Cross-Coupling

Highly Robust Oxime Palladacycles

The air- and water-stable palladium complexes shown here are extremely active catalysts for C–C and C–X bond-forming processes, ranging from the Heck to the Sonogashira to the Suzuki reaction.[1] These oxime palladacycles represent novel and powerful tools to mediate an array of industrially useful transformations. Furthermore, the versatility of this family of Pd compounds and their electronic and steric features should ensure their wide application in research and manufacturing.

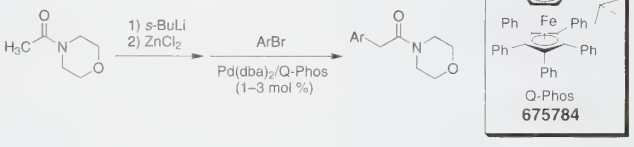
(1) (a) Botella, L.; Najera, C. *J. Org. Chem.* **2005**, *70*, 4360. (b) Alonso, D. A. et al. *Org. Lett.* **2000**, *2*, 1823.



Hindered Ferrocenyl(Dialkyl)phosphine Ligand (Q-Phos)

Developed by the Hartwig group, Q-Phos is a sterically hindered ferrocenylphosphine ligand that has demonstrated broad applicability in a variety of Pd-catalyzed C–C, C–N, and C–O bond-forming reactions including: amination and etherification of aryl chlorides, Suzuki coupling and, most recently, the α arylation of zinc amide enolates.[1]

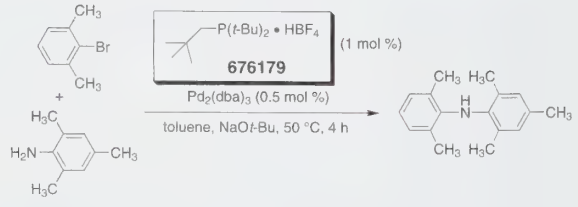
(1) (a) Hama, T. et al. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (b) Kataoka, N. et al *J. Org. Chem.* **2002**, *67*, 5553



Bulky Alkylphosphine Ligand for Amination Reactions

Shaughnessy and co-workers have utilized this neopentyl-substituted phosphine with a palladium source to form a highly active catalyst for the amination of a diverse set of aryl halides.[1] The increased steric bulk of this ligand, when compared to tri(*tert*-butyl)phosphine, enhances the effectiveness of this system and allows for the formation of the tetra-*ortho*-substituted product shown here.

(1) Hill, L. L. et al. *J. Org. Chem.* **2006**, *71*, 5117.



For more information on these and other new products from Sigma-Aldrich, visit sigma-aldrich.com/synthesis.

What a Journey It Has Been!

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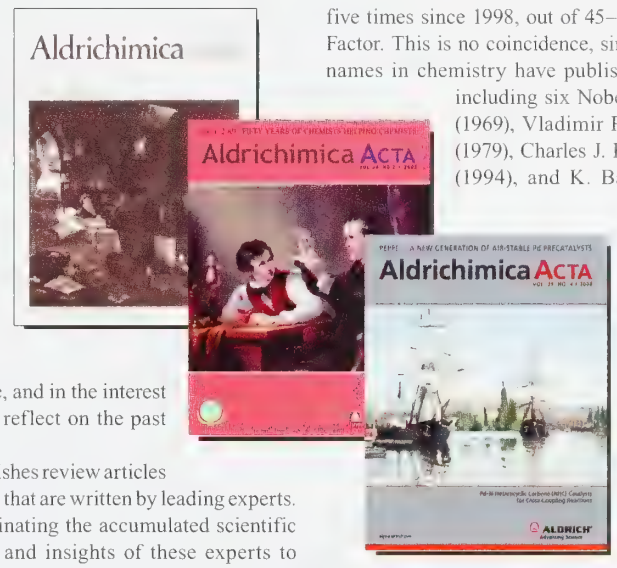
This January, the *Aldrichimica Acta* begins its 40th year of uninterrupted publication. Reaching this milestone is a genuine measure of the high regard in which chemists worldwide have held it for four decades. Their enduring interest has been sustained by the high-quality scientific information they find within its pages—information contributed by their peers from around the world. Without the loyalty and commitment of these two pillars of the *Acta*, its authors and readers, I would not be sharing this significant anniversary with you today. Thank you both! Your interest and support over the years have fostered stimulating scientific exchanges, provided many answers, and inspired further quests. I am enthusiastic about the prospect of continuing this journey with a new generation of *Aldrichimica Acta* authors and readers.



While some readers may be quite familiar with the *Acta*, others have only recently been introduced to it. As we celebrate reaching this milestone, and in the interest of these readers, let me briefly reflect on the past four decades of the *Acta*.

The *Aldrichimica Acta* publishes review articles on innovative chemistry research that are written by leading experts. It is an ideal vehicle for disseminating the accumulated scientific knowledge, research findings, and insights of these experts to chemistry practitioners in academic, industrial, governmental, and nonprofit laboratories around the globe. In this regard, it serves an important function for both our readers and our company. The key to its popularity and longevity has been its unique format and look, which successfully combine high-quality scientific and technical information with an eye-catching cover featuring a beautiful painting and accompanying commentary, and with the latest useful product offerings from the publisher, Sigma-Aldrich Corporation. All of this at no cost to over 130,000 readers worldwide! While its appearance has undergone several modifications over the years, the premise the *Acta* was based on has not changed.

Now for a bit of history. The *Aldrichimica Acta* evolved from the *Kardindex Sheets* that Aldrich used to distribute to its best customers in the 1960s. Dr. Alfred R. Bader, the President of Aldrich Chemical Company at the time, came up with the name, in analogy to the names of such well-known chemistry journals as *Helvetica Chimica Acta* and *Inorganica Chimica Acta*. The name, of course, is a great choice because it combines in its first half the name of the company ("Aldri" from Aldrich) with the type of business it is in ("chimica" for chemical). The second half of the name, *Acta*, is derived from the Latin "Ācta", which means "Proceedings", and was intended to convey the idea that it is a record of scientific proceedings both at Aldrich and the chemistry community at large. The name *Aldrichimica Acta* has been in use since 1967, and is currently highly recognized worldwide.

The *Aldrichimica Acta* is treated on a par with other popular chemistry journals and its content is covered by such prominent chemical-abstract publishers as Chemical Abstracts Service® and Thomson ISI®. Collections of *Acta* issues are in practically every academic and industrial science library in the U.S. and many others abroad. In the field of organic chemistry, the Science Edition of Thomson ISI®'s *Journal Citation Reports*® has ranked the *Acta* #1 five times since 1998, out of 45–58 journals compared by Impact Factor. This is no coincidence, since some of the most prestigious names in chemistry have published in the *Acta* over the years, including six Nobel laureates: Derek H. R. Barton (1969), Vladimir Prelog (1975), Herbert C. Brown (1979), Charles J. Pedersen (1987), George A. Olah (1994), and K. Barry Sharpless (2001). On this occasion, I would like to state unequivocally that we owe them, as well as all the authors that have published in the *Acta* since 1967 (cf. table), a debt of gratitude for their outstanding contributions. Without these contributions, we would not be marking this significant milestone today.

I would be remiss if I didn't also acknowledge my debt and gratitude to all the editors that have preceded me, to the dedicated staff past and present, and to the members of Sigma-Aldrich management, past and present, who have believed in the vital role that the *Acta* plays and have shown unwavering support for it through the ups and downs of the often-turbulent world of modern business. I would also like to thank Sean Battles of Sigma-Aldrich for his stimulating questions and comments relating to this write-up.

Mindful of the great legacy of the past 40 years, we strive everyday not only to keep the *Acta* changing with the times, but also to maintain and enhance its appeal, relevance, and usefulness to our readers and to our company.

Here is to another 40 magnificent years of the Aldrichimica Acta!

All Contributors to the *Aldrichimica Acta* from 1967 to the Present[a]

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University of Illinois

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Aldrichimica ACTA

VOL. 40, NO. 2 • 2007

Recent Advances in Intermolecular Direct Arylation Reactions

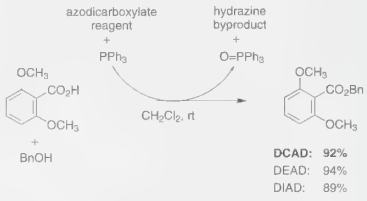
Evolution and Applications of Second-Generation Ruthenium Olefin Metathesis Catalysts

New Products from Aldrich R&D

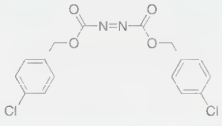
Aldrich is pleased to offer cutting edge tools for organic synthesis

Optimized Mitsunobu Reagent

The Mitsunobu reaction is one of the most extensively used coupling reactions in organic synthesis and typically employs azodicarboxylate reagents such as DEAD or DIAD. However, these reagents have drawbacks such as low room-temperature stability and difficulty in removing the hydrazine byproducts. Professor Bruce Lipshutz and co-workers have developed an attractive alternative to the existing reagents: di(4-chlorobenzyl) azodicarboxylate (DCAD). DCAD is a stable solid that has an activity comparable to those of DEAD and DIAD in typical Mitsunobu reactions such as substitutions, esterifications, and etherifications. However, unlike the standard reagents, the hydrazine byproduct can be removed by simple precipitation directly from the reaction mixture, and is easily recycled in high yield to regenerate DCAD.

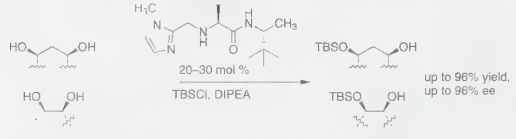


Lipshutz, B. H. et al. *Org. Lett.* **2006**, *8*, 5069.

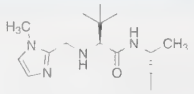
680850		1 g	$24.00
$C_{16}H_{12}Cl_2N_2O_4$		10 g	99.50
FW: 367.18			

Asymmetric Silylation Reagent

Because of the ease of preparation of *meso*-diols, synthetic methods that can desymmetrize these substrates are critically important. Professors Marc Snapper and Amir Hoveyda at Boston College have reported the first practical enantioselective silylation of *meso*-1,2- and 1,3-diols relying on an amino acid derived organocatalyst. The reactions do not require the rigorous exclusion of air or moisture, and the catalyst can be nearly quantitatively recovered by an aqueous wash. This catalyst greatly increases the efficiency with which optically enriched molecules can be prepared.

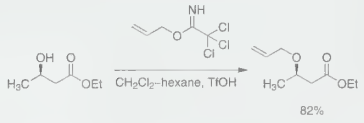


Zhao, Y. et al. *Nature* **2006**, *443*, 67

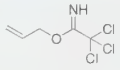
680826		1 g	$90.00
$C_{17}H_{33}N_4O$			
FW: 308.46			

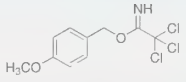
Trichloroacetimidate Reagent

Trichloroacetimidates are useful reagents for protection of alcohols as their allyl and benzyl ethers. We are delighted to offer two new reagents, allyl 2,2,2-trichloroacetimidate and 4-methoxybenzyl 2,2,2-trichloroacetimidate, that have been extensively employed in organic synthesis. These reagents are particularly attractive in applications where base-sensitive functional groups are present that would not tolerate the standard alkoxide alkylation method of alcohol protection.



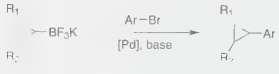
Clark, J. S. et al. *Tetrahedron* **2006**, *62*, 73.

678414		5 g	$75.00
$C_5H_6Cl_3NO$			
FW: 202.47			

679585		5 g	$50.00
$C_{10}H_{10}Cl_3NO_2$		25 g	198.00
FW: 282.55			

Cyclopropyltrifluoroborate

Cyclopropyl groups are found in a variety of natural products and are increasingly incorporated into pharmaceuticals such as the broad-spectrum antibiotic ciprofloxacin. Both the Charette[1] and Deng[2] groups have reported success in the cross-coupling of potassium cyclopropyltrifluoroborates with aryl bromides in the presence of common palladium catalysts. The trifluoroborate salts exhibit enhanced stability and more certain stoichiometry relative to their boronic acid counterparts. However, like boronic acids, post-reaction byproducts are easily removed. We are pleased to add this useful reagent to our ever-growing arsenal of organoboron compounds.



(1) Charette, A. B. et al. *Synlett* **2005**, *11*, 1779. (2) Fang, G.-H. et al. *Org. Lett.* **2004**, *6*, 357

662984		1 g	$54.00
$C_3H_6BF_3K$		5 g	216.00
FW: 147.98			

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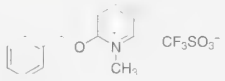
Professor Gregory B. Dudley of Florida State University kindly suggested that we make 2-benzyloxy-1-methylpyridinium triflate. This crystalline, neutral, and stable organic salt is an excellent reagent for the protection of an alcohol as a benzyl ether under mild conditions. Reaction with this reagent can be performed under near-neutral pH, unlike other benzylation protocols, which require strongly acidic or basic reaction media (e.g., the use of benzyl trichloroacetimidate or benzyl halides).[1]

(1) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923. (2) Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett* **2005**, 3142.



679674 2-Benzyloxy-1-methylpyridinium triflate 1 g $75.00
5 g 250.00

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

Photograph © Alfred Bader

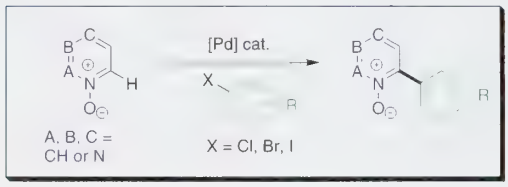
Panoramic Landscape with Hunters (oil on canvas, 105 × 135 cm) was painted in the mid-1660s by Philips Koninck (1619–1688), one of the great Baroque landscape artists of the Golden Age of Dutch Art (ca. 1600–1680). Although a contemporary of Rembrandt, Koninck is not believed to have studied with him. However, Koninck knew the master and some of his pupils and was certainly familiar with Rembrandt's paintings, which had some influence on him.

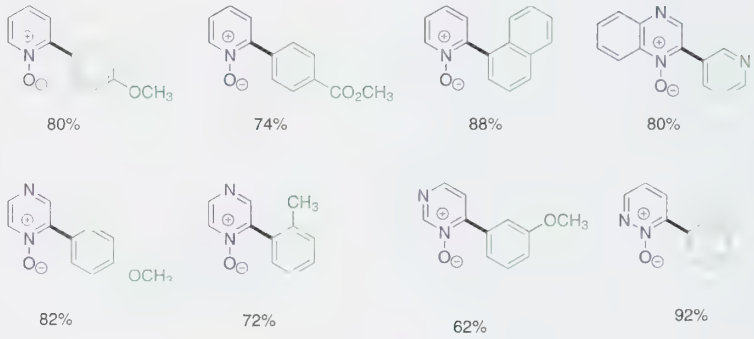
This painting illustrates Koninck's method of bringing together details of real-life scenes to create fictional but convincing sweeping landscapes featuring streams, fields, abundant flora, and rural dwellings. The translucent colors of the sky, the receding diagonal lines, and the horizontal striations denoting successive planes that recede into the distance add to the great allure of this landscape.

This painting is in the private collection of Isabel and Alfred Bader. Dr. Bader is a perennial "chemist collector" and a former Aldrich and Sigma-Aldrich president.

Reagents for Direct Arylation

Pd-catalyzed cross-coupling of organometallic nucleophiles with aryl halides has become the most commonly used method for biaryl synthesis. However, the range of biaryls that can be prepared is limited to those organometallic reagents that are commercially available or easily made. Nitrogen-containing heterocyclic organometallic reagents are often difficult to prepare and success of their coupling reactions can be sporadic. Professor Keith Fagnou and co-workers at the University of Ottawa have developed a novel method for biaryl synthesis by the direct arylation of heterocyclic *N*-oxides.[1–3] Yields are typically very good, and the oxide residue is easily reduced to give the free azine or diazine.





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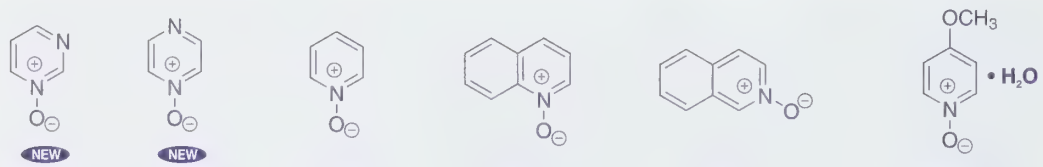
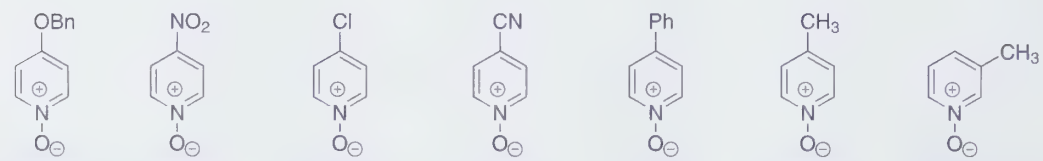
(1) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (2) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (3) Campeau, L.-C.; Stuart, D.R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35.





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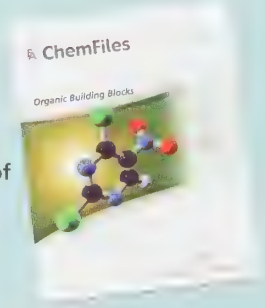

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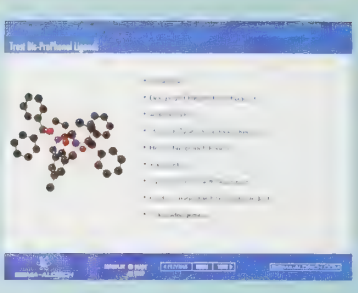

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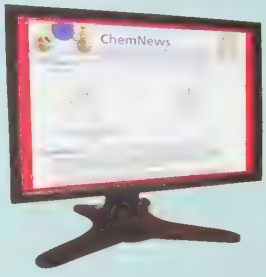

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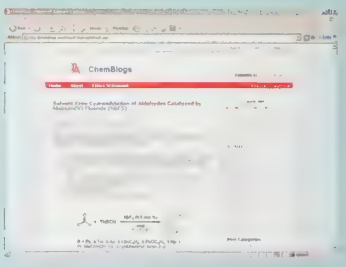

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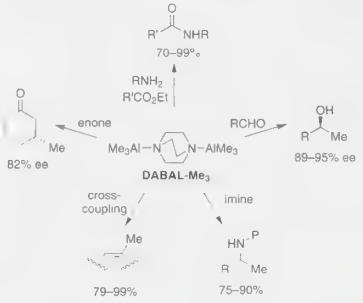
DABAL-Me$_3$

Trimethylaluminum is a versatile methylation reagent in organic synthesis. However, because of its pyrophoric nature, it cannot be handled in open air. Developed by the Woodward group (University of Nottingham, U.K.), DABAL-Me$_3$ is a free-flowing solid adduct of trimethylaluminum and DABCO® that can be manipulated without the need for an inert atmosphere.[1] This bench-stable reagent has been employed in numerous reactions including methylations of aldehydes and imines,[1,2] methylation of aryl and vinyl halides,[3] conjugate additions to enones,[4] and amide-bond formation.[5] In the presence of the appropriate chiral ligand and catalyst, many of these reactions can be performed asymmetrically



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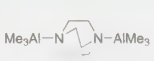
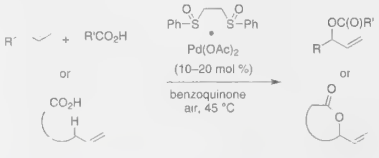
Bis(trimethylaluminum)–1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me$_3$)

682101 1 g $20.90
[*137203-34-0*] 5 g 71.60
$C_{12}H_{26}Al_2N_2$
FW: 256.34



White Catalyst for Allylic C–H Oxidation

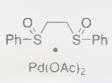
Professor Christina White's group (University of Illinois) recently reported selective allylic C–H oxidation reactions catalyzed by a Pd(II)–bis-sulfoxide system that furnishes branched allylic esters from α-olefins and carboxylic acids.[1] These reactions can be performed in an inter- or intramolecular fashion, the latter being capable of yielding highly functionalized, large-ring macrolactone products.[2] Finally, the catalyst system allows for a one-pot sequential allylic oxidation–C–H arylation to afford the *E* arylated allylic ester from the corresponding olefin, carboxylic acid, and arylboronic acid.[3]



(1) Chen, M. S. et al. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (2) Fraunhoffer, K. J. et al. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (3) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc* **2006**, *128*, 15076

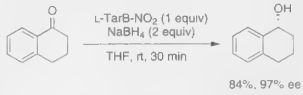
White Catalyst

684821 250 mg $27.50
[*858971-43-4*] 1 g 90.00
$C_{16}H_{14}O_6PdS_2$
FW: 502.90



TarB-NO$_2$ Reducing Reagents

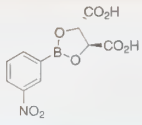
In conjunction with $NaBH_4$, Singaram's chiral TarB-NO_2 boronic esters rapidly reduce prochiral ketones to optically active secondary alcohols with enantiomeric excesses as high as 99%.[1-3] The reagents cleanly reduce aromatic ketones with high enantioselectivity and, in many cases, aliphatic ketones can be reduced with a similar degree of selectivity. Typically, TarB-NO_2 reagents perform as well as, or better than, existing hydridic asymmetric reduction methods such as those employing DIP-Chloride™ or the CBS reagents.



(1) Kim, J.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 3901. (2) Kim, J. et al. *Org. Process Res. Dev.* **2006**, *10*, 949. (3) Cordes, D. B. et al. *Eur. J. Org. Chem.* **2005**, 5289.

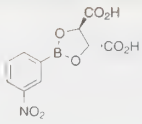
3-Nitrophenylboronic acid D-tartaric acid ester, 1 M in THF (D-TarB-NO_2)

682748 5 mL $54.30
$C_{10}H_8BNO_8$ 25 mL 187.50
FW: 280.98



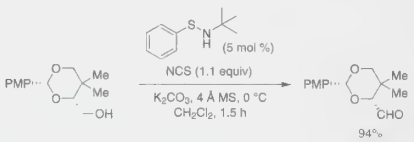
3-Nitrophenylboronic acid L-tartaric acid ester, 1 M in THF (L-TarB-NO_2)

682713 5 mL $54.30
[*467443-01-2*] 25 mL 187.50
$C_{10}H_8BNO_8$
FW: 280.98



N-tert-Butylbenzenesulfenamide

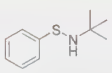
In the presence of NCS, *N-tert*-butylbenzenesulfenamide catalyzes the selective oxidation of a variety of primary and secondary alcohols to the corresponding aldehydes and ketones in high yield and under mild conditions.[1,2] The catalytic oxidation tolerates various functional groups including silyl ethers, epoxides, urethanes, esters, and olefins. The reaction is particularly useful for the preparation of labile or easily epimerized aldehydes.



(1) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590. (2) Matsuo, J.-i. et al. *Tetrahedron* **2003**, *59*, 6739

***N-tert*-Butylbenzenesulfenamide, 97%**

681792 1 g $65.90
[*19117-31-8*] 5 g 263.50
$C_{10}H_{15}NS$
FW: 181.30



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Joe Porwoll, President
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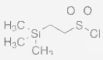
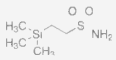
Professor Carsten Bolm of RWTH Aachen University, kindly suggested that we make 2-(trimethylsilyl)ethanesulfonyl chloride (SES-Cl). This reagent is employed to protect an amine in the form of its sulfonamide. In contrast to the harsh conditions sometimes needed to deprotect tosyl-protected amines, the SES group is readily cleaved under mild conditions using a fluoride ion source, regenerating the parent amine along with volatile byproducts. We have also prepared SES-NH_2, a useful reagent for the introduction of a protected nitrogen atom into a substrate.[1,2]

(1) Weinreb, S. M. et al. *Tetrahedron Lett.* **1986**, *27*, 2099. (2) Ribière, P. et al. *Chem. Rev.* **2006**, *106*, 2249





681334	**2-(Trimethylsilyl)ethanesulfonyl chloride** (SES-Cl)	1 g 5 g	$89.40 330.50
681326	**2-(Trimethylsilyl)ethanesulfonamide** (SES-NH_2)	1 g	$95.60

Naturally, we made these useful reagents. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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Photograph © Board of Trustees, National Gallery of Art, Washington

Oarsmen at Chatou (oil on canvas, 81.2 × 100.2 cm) was painted in 1879 by the French impressionist painter, Pierre Auguste Renoir (1841–1919), on the river Seine west of Paris. His use of light fresh colors in this painting and throughout his career was the result of his love of paintings from the Rococo period and of his training in a porcelain factory as a young man

Rowing was the foremost attraction at Chatou. The man in this boat—wearing the typical costume of a short jacket and a straw hat—may be the artist's brother, Edmond. The man standing on the bank, similarly attired, is probably the painter Gustave Caillebotte, a devoted rowing enthusiast and a friend of Renoir. The woman is most likely Aline Charigot, who was his favorite model and later became his wife

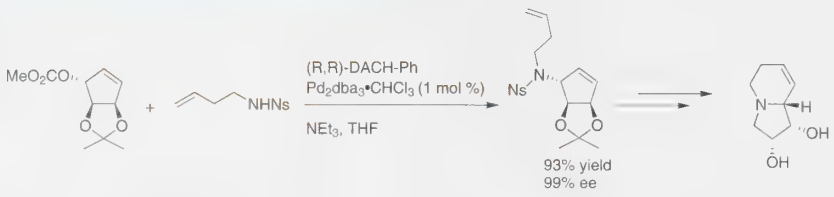
The painting captures the brilliance of sun and water, summer and youth. In the water, strong blues and white alternate. Their shimmering intensity is enhanced by the equally strong presence of orange in the boat's reflection and the scarlet accent of Aline's bow. Renoir has put into practice the principle of simultaneous contrast: colors are perceived stronger when juxtaposed with their opposites—orange with blue, for example, or green with red. The silky texture of Renoir's feathery brushstrokes mirrors the languid and leisurely scene

This painting is a gift of Sam A. Lewisohn to the National Gallery of Art, Washington, DC.

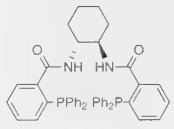
Trost Ligands for Asymmetric Allylic Alkylation

Asymmetric allylic alkylation is a versatile catalytic reaction allowing access to a diversity of chiral molecules. This transformation converts both enantiomers of the substrate into the same enantiomer of the product, allowing theoretical yields of 100% of one enantiomer. Professor Trost developed a series of ligands based on diphenylphosphinobenzoic acid (DPPBA) and used them with a variety of palladium complexes for the asymmetric allylic alkylation. These ligands perform with a high degree of enantioselectivity and high yields.

DACH-Phenyl Trost Ligands



Ovaa, H. et al. *Chem. Commun.* **2000**, 1501

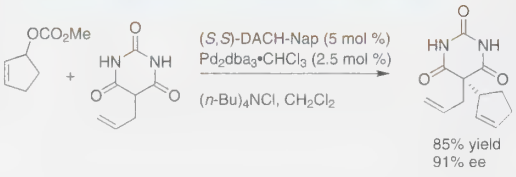


692808

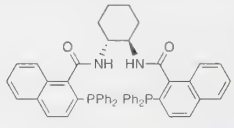
(*R,R*)-DACH-Phenyl Trost Ligand
692808

(*S,S*)-DACH-Phenyl Trost Ligand
692794

DACH-Naphthyl Trost Ligands



Trost, B. M.; Schroeder, G. M. *J. Org. Chem.* **2000**, *65*, 1569

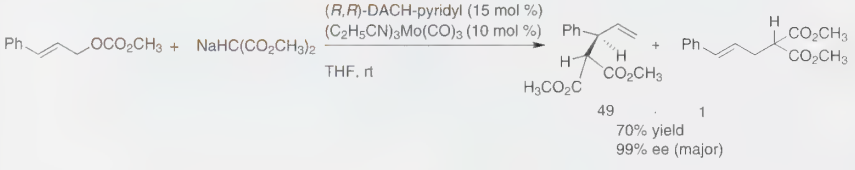


692778

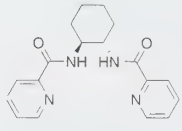
(*R,R*)-DACH-Naphthyl Trost Ligand
692778

(*S,S*)-DACH-Naphthyl Trost Ligand
692786

DACH-Pyridyl Trost Ligands



Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.



692743

(*R,R*)-DACH-Pyridyl Trost Ligand
692751

(*S,S*)-DACH-Pyridyl Trost Ligand
692743

For more information, see Professor Trost's review in this issue.

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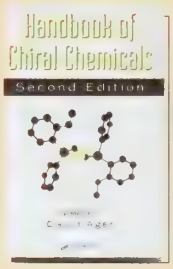
Palladium in Heterocyclic Chemistry A Guide for the Synthetic Chemist, 2nd Edition
J. J. Li and G. W. Gribble, Elsevier, 2007, 658 pp. Softcover



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Handbook of Chiral Chemicals, 2nd Edition
D. Ager, Ed., CRC Press, 2006, 664 pp. Hardcover.

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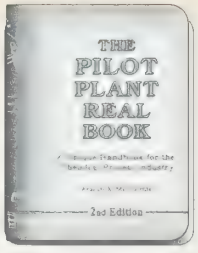
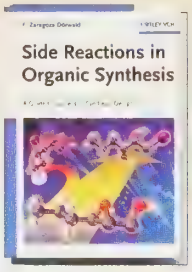
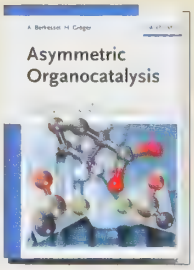
Chiral Analysis
K. W. Busch and M. A. Busch, Eds., Elsevier, 2006, 720 pp. Hardcover.



Z730181 - $115.00
The Pilot Plant Real Book, 2nd Edition
F. X. McConville, FXM Engineering, 2006, 320 pp. Softcover



Z703354 - $110.00
Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design
F. Z. Dörwald, Wiley-VCH, 2005, 389 pp. Softcover



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Asymmetric Organocatalysis – From Biomimetic Concepts to Applications in Asymmetric Synthesis
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ALLENES AND IONIC LIQUIDS IN ASYMMETRIC SYNTHESIS

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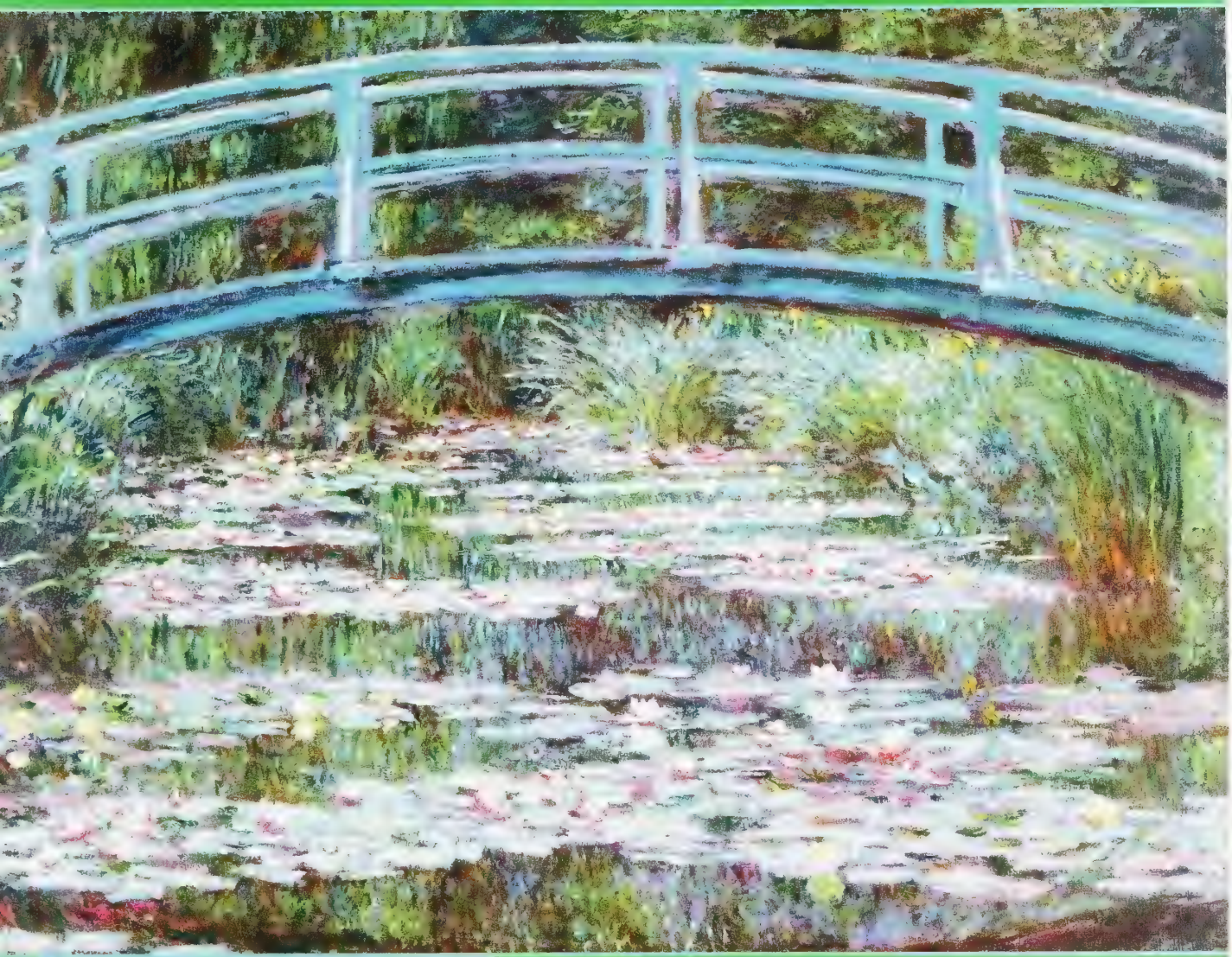

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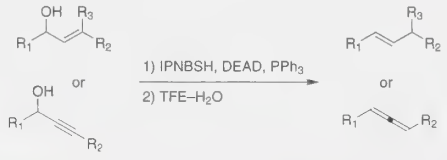
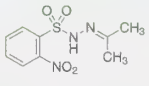
Deoxygenation Reagent

Developed by the Movassaghi group at MIT, *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine (IPNBSH) is a useful reagent for the mild deoxygenation of allylic and propargylic alcohols to give allylically transposed alkenes and allenes, respectively.[1] This reagent exhibits excellent reactivity in difficult reductive fragmentations, as demonstrated in the total syntheses of (–)-acylfulvene and (–)-irofulven.[2]



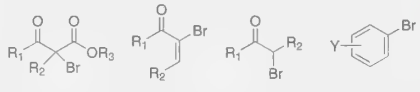
(1) Movassaghi, M.; Ahmad, O. K. *J. Org. Chem.* **2007**, *72*, 1838. (2) Movassaghi, M. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 5859.

N-Isopropylidene-N′-2-nitrobenzenesulfonyl hydrazine, 97%
IPNBSH

687855		1 g	$52.50
[*6655-27-2*]		5 g	175.00
$C_9H_{11}N_3O_4S$			
FW: 257.27			

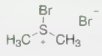
Bromination Reagent

Bromodimethylsulfonium bromide (BDMS) is an easy-to-handle and highly effective bromination reagent as well as a catalyst for various organic transformations.[1] BDMS has been employed in numerous reactions including the preparation of α-bromo-β-keto esters and α-bromo enones, from their corresponding keto esters and enones, respectively;[2] the conversion of epoxides and enamines to α-bromoketones;[3] and electrophilic aromatic bromination.[4] BDMS has also been employed in the synthesis of α-aminonitriles and homoallylic amines, and in Michael additions of amines to electron-deficient olefins.[5]



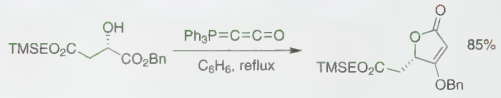
(1) Choudhury, L. H. *Synlett* **2006**, 1619. (2) (a) Khan, A. T. et al. *J. Org. Chem.* **2006**, *71*, 8961. (b) Chow, Y. L.; Bakker, B. H. *Can. J. Chem.* **1982**, *60*, 2268. (3) Olah, G. A. et al. *Tetrahedron Lett.* **1979**, *20*, 3653. (4) (a) Majetich, G. et al. *J. Org. Chem.* **1997**, *62*, 4321. (b) Megyeri, G.; Keve. T. *Synth. Commun.* **1989**, *19*, 3415. (5) (a) Das, B. et al. *Synthesis* **2006**, 1419. (b) Das, B. et al. *Tetrahedron Lett.* **2006**, *47*, 5041. (c) Khan, A. T. *Tetrahedron Lett.* **2007**, *48*, 3805

Bromodimethylsulfonium bromide, 95%
BDMS

694142		5 g	$60.00
[*50450-21-0*]		25 g	217.50
$C_2H_6Br_2S$			

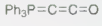
Cumulated Ylide

The cumulated ylide (triphenylphosphoranylidene)ketene is a versatile two-carbon building block useful in preparing numerous classes of oxygen- and nitrogen-containing heterocycles. While typically not Wittig-active itself, this reagent reacts with a host of electrophiles to yield Wittig-active products that can participate in subsequent intra- or intermolecular olefination reactions.



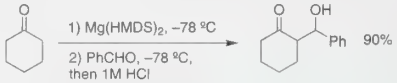
(1) Schobert, R.; Jagusch, C. *Synthesis* **2005**, 2421. (2) Schobert, R. et al. *Synthesis* **2006**, 3902. (3) Boeckman, R. K., Jr. et al. *J. Am. Chem. Soc.* **2006**, *128*, 11032.

(Triphenylphosphoranylidene)ketene
Bestmann ylide

688185		1 g	$55.00
[*15596-07-3*]			
$C_{20}H_{15}OP$			
FW: 302.31			

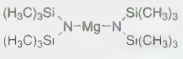
$Mg(HMDS)_2$

While lithium amides, such as LDA and LiHMDS, are the predominant bases of choice for the selective generation of enolates, magnesium amide bases have garnered recent attention due to their enhanced thermal stabilities and selectivity characteristics.[1] Magnesium bis(hexamethyldisilazide), $Mg(HMDS)_2$, has demonstrated efficacy in ketone–aldehyde aldol addition reactions[2] and in the regio- and stereoselective synthesis of silyl enol ethers.[3]



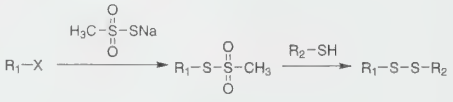
(1) He, X. et al. *J. Am. Chem. Soc.* **2006**, *128*, 13599. (2) Allan, J. F. et al. *Chem. Commun.* **1999**, 1325. (3) Bonafoux, D. et al. *J. Org. Chem.* **1996**, *61*, 5532.

Magnesium bis(hexamethyldisilazide)
$Mg(HMDS)_2$

692352		5 g	$36.00
[*857367-60-3*]		25 g	120.00
$C_{12}H_{36}MgN_2Si_4$			
FW: 345.07			

Reagent for Disulfide Synthesis

The reaction of alkyl halides or pseudohalides with the sulfur-based nucleophile sodium methanethiosulfonate (NaMTS) yields organic methanethiosulfonates, intermediates that are highly reactive towards sulfhydryl groups, yielding unsymmetrical disulfides. NaMTS has been extensively used in glycosylations, spin-labeling, and photoprobe chemistry.[1–3]



(1) Grayson, E. J. et al. *J. Org. Chem.* **2005**, *70*, 9740. (2) Kálai, T. et al. *Synthesis* **2006**, 439. (3) Guo, L.-W. et al. *Bioconjugate Chem.* **2005**, *16*, 685.

Sodium methanethiosulfonate, 95%
NaMTS

684538		1 g	$39.50
[*1950-85-2*]			
$CH_3O_2NaS_2$			
FW: 134.15			

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Joe Porwoll, President
Aldrich Chemical

Professor Keith Fagnou of the University of Ottawa (Canada) kindly suggested that we make cesium pivalate. This versatile base has been used by several research groups in transition-metal-catalyzed direct arylations of indoles.[1] Cesium pivalate has also been employed as a base in the study of aryl-to-aryl palladium migration in Heck and Suzuki couplings of *o*-halobiaryls.[2]

(1) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Campeau, L.-C. et al. *Aldrichimica Acta* **2007**, *40*, 35. (c) Wang, X. et al. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (2) Campo, M. A. et al. *J. Am. Chem. Soc.* **2007**, *129*, 6298

694037 Cesium pivalate, 98% 5 g $40.00
25 g 134.00

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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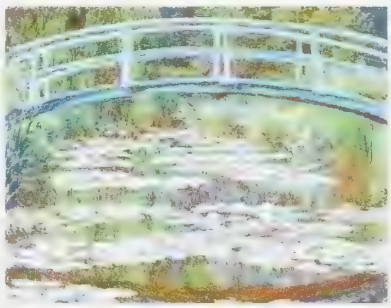


Photograph © Board of Trustees, National Gallery of Art, W

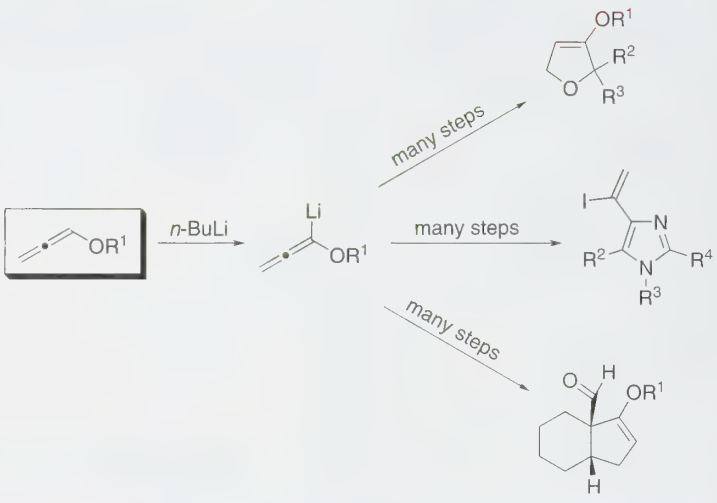
In the last decades of Monet's life, his prized water garden became his most important—and eventually his only—subject. Monet began to paint his lily pond and our cover, *The Japanese Footbridge* (oil on canvas, 81.3 × 101.6 cm), in his garden at Giverny in 1899. He constructed the water garden soon after he moved to Giverny with his family in 1893, petitioning local authorities to divert water from the nearby river. Monet remade the landscape with the same artifice he applied to his paintings—and then he used it, in turn, as his creative focus. When Monet exhibited his lily ponds, a number of critics mentioned his debt to Japanese art and the idea of the *hortus conclusus* (closed garden) of medieval images

Monet painted his garden from the same vantage point as our cover twelve times, focusing on the arching blue-green bridge and a microcosm of the water. He gave equal emphasis to the physical qualities of his painting materials and to the landscape motif he depicted. In this painting, the sky has already disappeared; the lush foliage rises all the way to the horizon; and the decorative arch of the bridge flattens the space. Floating lily pads and mirrored reflections assume equal stature, blurring distinctions between solid objects and transitory effects of light. Monet had always been interested in reflections, seeing their fragmented forms as the natural equivalence for his own broken brushwork. The artist—who, as a leader of the impressionists, had espoused the spontaneity of directly observed works that capture the fleeting effects of light and color—had in these later paintings subjected a nature he re-created to sustained, meditated scrutiny

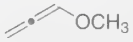
This painting is a gift to the National Gallery of Art from Victoria Nebeker Coberly, in memory of her son, John W. Mudd, and Walter H. and Leonore Annenberg.

New Reactive Allenes

Allenes are becoming highly sought building blocks for their ability to react with many different classes of substrates. In addition, the allene moiety itself is present in many bioactive natural products and pharmaceutical agents. Recent work by Reissig[1] and Zhang[2] demonstrates the utility of lithiated allenyl ethers in the synthesis of various carbocycles and heterocycles. Other work by Suginome and co-workers reports the use of cyclohexylallene in a palladium-catalyzed asymmetric silaboration.[3] Sigma-Aldrich is pleased to add these and other allenes to our expanding portfolio of reactive building blocks.



New Allenes



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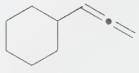

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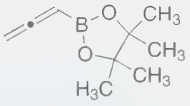

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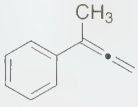

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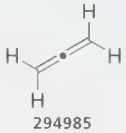
Other Allenes



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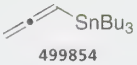

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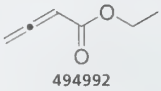

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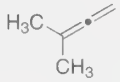

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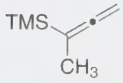

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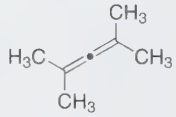

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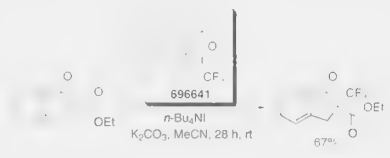


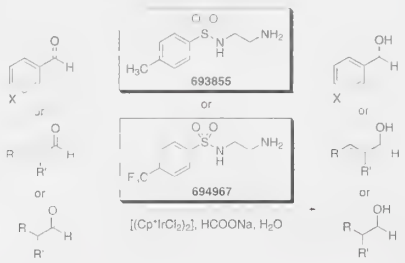
Eisenberger, P. et al. *Chem.—Eur. J.* **2006**, *12*, 2579

3,3-Dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, 97%

696641		250 mg	$71.50
[887144-97-0]		1 g	199.00
$C_{10}H_8F_3IO$			
FW: 330.09			

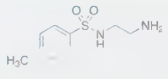
Ligands for Aqueous Transfer Hydrogenation

When used in conjunction with $[(Cp^*IrCl_2)_2]$, the ligands *N*-tosylethylenediamine (Ts(en)) and *N*-(2-aminoethyl)-4-(trifluoromethyl)-benzenesulfonamide (CF_3-Ts(en)) enable the facile and selective transfer hydrogenation of aldehydes with TOFs as high as 1.3×10^5 h^{-1}. Furthermore, the reactions are carried out in aqueous media and exhibit very good chemoselectivity and functional-group tolerance. In cases where α,β-unsaturated aldehydes are employed, reduction occurs selectively on the formyl group. Aliphatic aldehydes are also readily converted when the substrate is added portionwise over the course of the reaction.

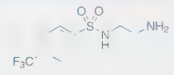


Wu, X. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 6718

N-Tosylethylenediamine, 97%

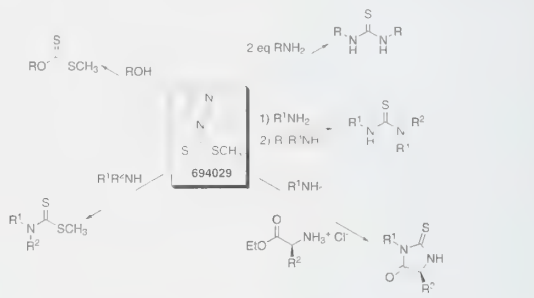
693855		5 g	$57.50
[14316-16-6]			
$C_9H_{14}N_2O_2S$			
FW: 214.28			

N-(2-Aminoethyl)-4-(trifluoromethyl)benzenesulfonamide, 97%

694967		500 mg	$49.00
$C_9H_{11}F_3N_2O_2S$			
FW: 268.26			

Thiocarbonyl Transfer Agent

1-(Methyldithiocarbonyl)imidazole is a stable, non-hazardous reagent that can replace thiophosgene, isothiocyanates, chlorothioformates, and other high-hazard reagents as a thiocarbonyl-transfer agent for the synthesis of dithiocarbonates,[1] dithiocarbamates, symmetrical and unsymmetrical thioureas,[2] and 2-thiohydantoins.[3]



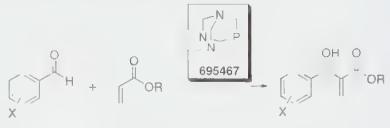
(1) Sun, W. Y. et al. *Synlett* **1997**, 1279. (2) Mohanta, P. K. et al. *Tetrahedron* **2000**, *56*, 629. (3) Sundaram, G. S. M. et al. *Synlett* **2007**, 251

1-(Methyldithiocarbonyl)imidazole, 97%

694029		5 g	$74.50
[74734-11-5]			
$C_5H_6N_2S_2$			
FW: 158.24			

Air-Stable, Nucleophilic Alkylphosphine

1,3,5,-Triaza-7-phosphaadamantane (PTA) is a convenient, efficient, and air-stable nucleophilic trialkylphosphine organocatalyst for the Baylis–Hillman reaction. Both aromatic and aliphatic aldehydes react with activated alkenes in the presence of 15–20 mol % of PTA to afford the corresponding adducts in fair-to-excellent yields. Furthermore, PTA displays activity that is superior to that of the structurally similar hexamethylenetetramine.



He, Z. et al. *Adv. Synth. Catal.* **2006**, *348*, 413

1,3,5-Triaza-7-phosphaadamantane

695467		500 mg	$25.00
[53597-69-6]		2 g	90.00
$C_6H_{12}N_3P$			
FW: 157.15			

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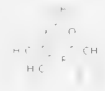
Professor Matthew Clarke of the University of St. Andrews (U.K.) kindly suggested that we make 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane. This phosphine is very stable to air and moisture and has the stereoelectronic properties of bulky phosphonites. When employed with rhodium complexes, this ligand shows high catalytic activity in the hydroformylation of various alkenes. High selectivities and conversions as high as 99% have been reported.

Clarke, M. L.; Roff, G. J. *Chem.—Eur. J.* **2006**, *12*, 7978.



695459	**1,3,5,7-Tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane, 97%**	500 mg 2 g	$52.00 170.00

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Photograph © Alfred Bader

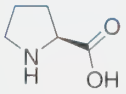
Landscape with Tobias and the Angel, with a View of Antwerp in the Background (oil on copper, 20.5 × 26.0 cm) was painted possibly around 1665 by Gillis Neyts, an enigmatic Flemish painter and engraver. Neyts (1623–1687) was born in Ghent, and spent a good part of his life in the city of Antwerp. He specialized in small, imaginary landscape scenes, which sometimes incorporated historical material or views of Flemish towns. His style approaches that of Lucas van Uden (1595–1672; Antwerp), who may have been his teacher.

This small painting, with its soft and delicate handling, which was typical for Neyts, shows on the left just below the horizon a part of the skyline of the city of Antwerp. The spectacular form of the arching tree in the center frames the figures of two travelers (with walking sticks) in the foreground on the right. One of them appears to waive at the viewer, while the other—dressed in red and white and with wings rising from his shoulders—is identified as the Archangel Raphael accompanying young Tobias on his journey.

Neyts has painted here a fantasy landscape in which he transposes the ancient story of Tobias and the angel onto a contemporary setting, the outskirts of the 17th-century city of Antwerp. It would appear that Neyts's purpose is to help the viewer of that period identify more closely with the story.

This painting is in the private collection of Isabel and Alfred Bader.

Explore Organocatalysis



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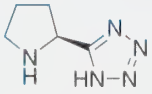

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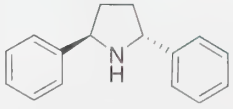

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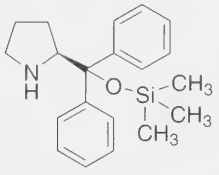

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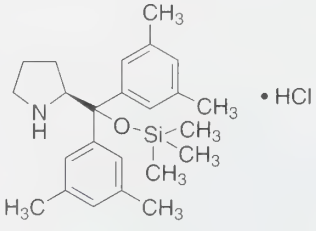

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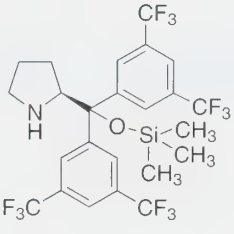

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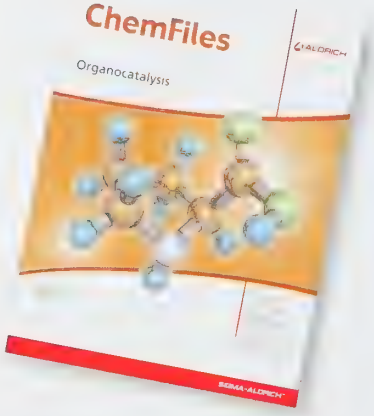

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Practical Organocatalysis with (*S*)- and (*R*)-5-Pyrrolidin-2-yl-1*H*-tetrazoles

From left to right: Dr. Deborah A. Longbottom, Dr. Veit Wascholowski, Mr. Vilius Franckevičius, Prof. Steven V. Ley, Mr. Alexander J. Oelke, and Ms. Sirirat Kumarn.

*Deborah A. Longbottom, Vilius Franckevičius, Sirirat Kumarn, Alexander J. Oelke, Veit Wascholowski, and Steven V. Ley**
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Professor Ley (center) receiving the Sigma-Aldrich sponsored *2007 ACS Award for Creative Work in Synthetic Organic Chemistry*. Pictured with Professor Ley are Dr. John Chan (left), Sigma-Aldrich Market Segment Manager, and Dr. Catherine T. Hunt (right), 2007 ACS President. Photo © Peter Cutts Photography, LLC.

Outline

1. Introduction

The phenomenal renaissance of interest in organocatalysis has been fuelled by the ever-increasing repertoire of organocatalytic reactions of utility to the synthetic organic chemist. Innovative reactions appear weekly in research publications throughout the world, and these developments have spawned a search for newer and more effective catalysts to bring about a myriad of important chemical transformations.[1,2]

As with any evolving scientific (sub)discipline, there exists a need to provide a range of tools to solve particular problems and stimulate the creation of new concepts. The properties, function, and mechanisms of action of the individual organocatalysts are of prime importance for they must tolerate a wide range of chemistries, functional groups, and reaction conditions and, ideally, be of broad synthetic utility.

The simple amino acids L- and D-proline (**1** and **2**, **Figure 1**) have been widely utilized in many organocatalytic reactions and are often considered the benchmark with respect to which other catalysts are evaluated. Nevertheless, their lack of solubility in certain solvents and sometimes slow turnover rates have caused concern and, therefore, led to the discovery of other related catalytic systems that overcome some of these drawbacks.

For example, (*S*)- and (*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**3** and **4**) are isosteres of proline with similar pK_a's but anticipated greater solubility and, hence, reactivity in more lipophilic organic solvents. They were originally synthesized for organocatalytic applications almost simultaneously by three groups, Yamamoto's,[3] Arvidsson's,[4] and ours,[5] and have since proven very useful in a wide range of reactions.

Herein, we discuss the practical synthetic opportunities that have arisen through the development of these new catalytic species, which are shelf- and thermally stable, crystalline, and readily prepared on scale.[6-8] Emphasis is given to reaction type, rather than to detailed mechanistic discussion, as this is still the subject of much study and debate. In each reaction table, several examples have been selected from the original publication(s) to represent the breadth in substrate substitution, electronic character, and general compatibility of functional groups.

2. The Aldol Reaction

The aldol reaction is one of the most important carbon–carbon-bond-forming reactions and, therefore, the widespread interest in developing asymmetric variants of this transformation is not surprising. The direct asymmetric addition of unmodified ketones to aldehydes has been developed by Shibasaki's and Trost's groups by using heterobimetallic catalysts,[9] whereas others have used more nature-inspired catalytic systems

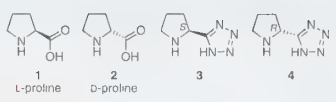
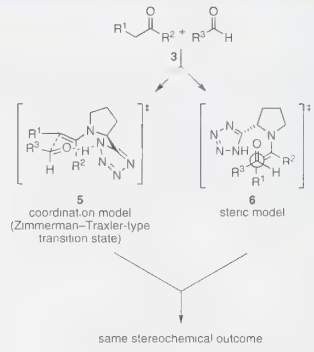
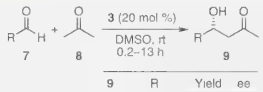


Figure 1. L- and D-Proline and (*S*)- and (*R*)-5-Pyrrolidin-2-yl-1*H*-tetrazole.



Ref. 7

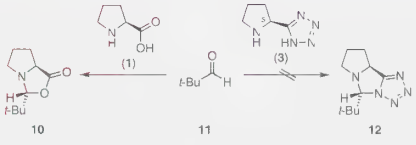
Scheme 1. Transition States in the Pyrrolidinyltetrazole **3** Mediated Aldol Reaction.



9	R	Yield	ee
a	Ph	69%	65%
b	4-$MeOC_6H_4$	65%	62%
c	4-BrC_6H_4	67%	66%
d	4-$O_2NC_6H_4$	82%	79%
e	*i*-Pr	79%	99%

Ref. 1

eq 1



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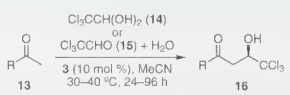
Scheme 2. Parasitic Consumption of the Catalyst in the Case of L-Proline (**1**), but not in the Case of Pyrrolidinyltetrazole **3**.



16	R	Yield	ee
a	*i*-Pr	79%	97%
b	EtO_2C	55%	86%
c	$Me_2C{=}CH(CH_2)_2$	93%	82%
d	Ph	75%	92%
e	2-Np	83%	91%

Ref. 3

eq 2

consisting of aldolase enzymes and catalytic antibodies.[10] An organocatalytic approach that uses L-proline (**1**) as catalyst for an intramolecular aldol cyclization, known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction, was reported around 35 years ago.[11] More recently, following List's important work,[2] a number of groups have confirmed that L-proline (**1**) can also mediate the analogous intermolecular aldol reaction of unmodified ketones and aldehydes.[12]

To date, there have been three publications that focus fully on the ability of pyrrolidinyltetrazole **3** to facilitate the intermolecular aldol reaction,[3,4,7] and its usefulness has now been further demonstrated in an aldol reaction applied to natural product synthesis.[13]

As alluded to previously, the details of the mechanism of these reactions are generally the subject of much debate and discussion. However, two widely accepted transition state models for the aldol reaction catalyzed by **3** produce the same stereochemical outcome and involve an enamine intermediate reacting either via a coordinated Zimmerman–Traxler-type transition state, **5**, or via transition state **6** (**Scheme 1**).[7]

Hartikka and Arvidsson have shown that aliphatic aldehydes are generally less reactive than aromatic ones in the direct asymmetric aldol reaction between acetone (**8**) and a variety of aldehydes leading to β-hydroxy ketones **9** (**eq 1**).[4,7] Nevertheless, the high catalytic activity of pyrrolidinyltetrazole **3** allowed even aliphatic aldehydes to be transformed into the corresponding chiral β-hydroxy ketones **9** with high enantioselectivities and fair yields in thirteen hours or less. The authors additionally proved that even a catalyst loading of 5% was still effective, though a longer reaction time was required.

It is interesting to note at this point that parasitic catalyst consumption[14] is observed with L-proline (**1**) but not with **3**. Arvidsson carried out NMR studies using a mixture of **1** or **3** and 2,2-dimethylpropionaldehyde (**11**) and proved that, while L-proline (**1**) easily engages in parasitic formation of bicyclic oxazolidinone **10**, pyrrolidinyltetrazole **3** does not (**Scheme 2**).[7] Consequently, in theory, this results in more of **3** being available to form the postulated enamine intermediate in the aldol reaction. The authors suggested that this could be the main reason for the increased reactivity of **3** compared to that of L-proline (**1**) in DMSO.[15] However, this does not rule out the possibility that factors relating either to the increased solubility of **3** in DMSO or to alternative mechanistic pathways operating in other solvent systems may also be contributing to the observed enhancement in reactivity of **3**.

Yamamoto's work has focused on the formation of optically active 1,1,1-trichloro-2-alkanols (**eq 2**),[3] previously demonstrated as being versatile tools for the preparation of variously functionalized compounds such as α-hydroxy and α-amino acids.[16] The formation of 1,1,1-trichloro-2-alkanols by the asymmetric aldol reaction is challenging due to the propensity of the starting aldehydes to form hydrates. However, in Yamamoto's report, **3** displayed excellent catalytic efficiency and activity in the reaction of either chloral monohydrate (**14**) or chloral (**15**) and water with a variety of aliphatic and aromatic ketones.

Ward then proved that pyrrolidinyltetrazole **3** was also useful in a total synthesis program:[13] serricornin (**21**), a sex pheromone produced by the female cigarette beetle *Lasioderma serricorne F.*, was elegantly prepared in just seven steps and overall 31% yield from the readily available *racemic* aldehyde **18** (**Scheme 3**).[13] The enantioselective direct aldol reaction of **17** with **18**, catalyzed by **3**, was the key step in the synthesis

and occurred with dynamic kinetic resolution to give adduct **19** with >98% ee. Aldol product **19** was then smoothly converted into diol **20** with excellent yield and diastereoselectivity. Because diastereomeric diols **22**, **23**, and **24** (**Figure 2**) are also readily prepared from **19**,[17] it was proposed that this powerful strategy could be extended to afford stereoisomers of **21**, which could then be tested for biological activity.

3. The Mannich Reaction

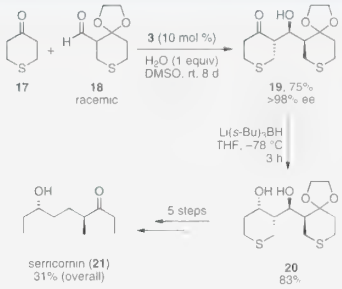
The development of syntheses that provide enantiomerically pure α-amino acids has been the subject of generations of research by organic chemists. This has engendered an array of methodologies,[18] which, not only allow for the stereoselective construction of naturally occurring amino acids, but also permit the rational design of optically active nonproteinogenic ones. These unnatural amino acids in particular have enjoyed increased popularity, mainly due to their incorporation into nonscissile peptide mimetics and peptide isosteres, known to exhibit reduced susceptibility to catabolism and thus increased bioavailability.[19]

In a similar way, chiral diamines are important building blocks for pharmaceuticals and are features that are frequently found in natural products.[20,21] As synthetic tools, chiral diamines are also used extensively as chiral auxiliaries and catalysts.[22] However, despite their significance, their asymmetric synthesis is not straightforward: they are most frequently synthesized from diols or aziridines[21] or by addition of glycine ester enolates to imines.[23] The direct reductive coupling of imines has also been reported, but this approach is limited to the preparation of symmetrical vicinal diamines and results in relatively low stereoselectivity.[24]

Thus, the organocatalytic synthesis of enantiomerically pure α-amino acids and diamines had so far represented a worthwhile challenge to organic chemists. Gratifyingly, pyrrolidinyltetrazole **3** has now been used to great effect in the synthesis of both classes of compound by employing the Mannich reaction as the key carbon–carbon-bond-forming step. In the synthesis of α-amino acid derivatives—which serves as an excellent comparison with previous work by Barbas (where L-proline (**1**) is the catalytic species)[25]—our group has showed that **3** also effectively catalyzes this reaction (**eq 3**).[5,26] Indeed, our method represents a very attractive alternative to Barbas's as the yields and stereoselectivities are comparable to those obtained with L-proline (**1**),[25] yet the reaction is carried out in solvents such as dichloromethane (avoiding dimethyl sulfoxide) and with catalyst loadings as low as 1%.[27]

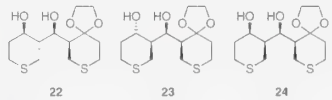
Following this report, Barbas showed that the organocatalytic asymmetric Mannich reaction of protected amino ketones with imines in the presence of **3** affords diamines with excellent yields and enantioselectivities of up to 99%.[28] The amino ketone protecting group controlled the regioselectivity of the reaction, providing access to chiral 1,2- and 1,4-diamines from azido and phthalimido ketones, respectively. Under optimized conditions, the three-component Mannich reaction of various combinations of azido ketones and aldehydes was investigated (**eq 4**).[28] All products were obtained regioselectively and with good diastereo- (syn:anti = 70:30 to 91:9) and enantioselectivities (82–99% ee, syn). A one-pot reduction–Boc-protection of Mannich product **31b** provided differentially protected 1,2-diamine **32** (**eq 5**), illustrating the potential utility of these compounds in further synthetic steps. The scope of this reaction seems very broad, and the azido ketones products, **31**, are in themselves interesting substrates for potential "click chemistry" based diversification.[29]

The Mannich reaction of phthalimidoacetone (**33**), a phthaloyl-protected amino ketone, in *N*-methyl-2-pyrrolidone (NMP) as



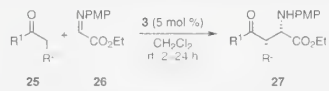
Ref. 13

Scheme 3. Enantioselective Total Synthesis of Sericornin (**21**) from Racemic Aldehyde **18**.



Ref. 17

Figure 2. **19**-Derived Diastereomeric Diols for the Synthesis of Sericornin Analogues.



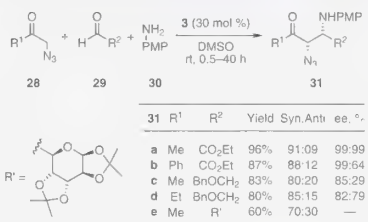
PMP = *p*-methoxyphenyl

27	R^1,R^2	Yield	Syn:Anti	ee
a	$-(CH_2)_4-$	65%	>19:1	>99%
b	$-(CH_2)_5-$	59%	>19:1	>99%
c	$-(CH_2)_7-$	74%	>19:1	94%
d	Me,H	99%	—	>99%
e	Me,Et	72%	>19:1	>99%

[a] Reaction carried out in acetone

Ref. 5,26

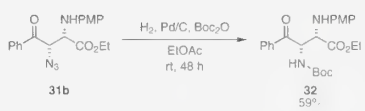
eq 3



31	R^1	R^2	Yield	Syn:Anti	ee, %
a	Me	CO_2Et	96%	91:09	99:99
b	Ph	CO_2Et	87%	88:12	99:64
c	Me	$BnOCH_2$	83%	80:20	85:29
d	Et	$BnOCH_2$	80%	85:15	82:79
e	Me	R'	60%	70:30	—

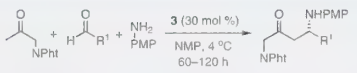
Ref. 28

eq 4



Ref. 29

eq 5



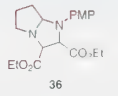
33 34 30 35

NMP = *N*-methyl-2-pyrrolidone
Pht = phthalimido

35	R^1	Yield	ee
a	CO Et	88%	91%
b	4-$O_2NC_6H_4$	68%	97%
c	4-NCC_6H_4	56%	95%
d	Ph	71%	77%

Ref. 28

eq 6



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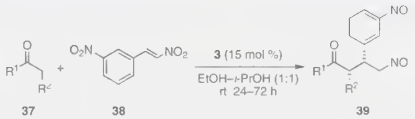
Ref. 28

Figure 3. Major Product of the Mannich Reaction of Phthalimidoacetone in the Presence of L-Proline (**1**).

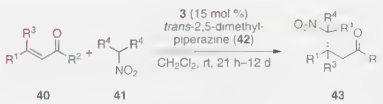


37 38 39

39	R^1,R^2	Yield	Syn:Anti	ee
a	$-(CH_2)_2SCH_2-$	62%	10:1	70%
b	$-(CH_2)_2OCH_2-$	94%	6:1	54%
c	Me,Me	71%	10:1	32%
d	Me,H	72%	-	33%
e	Et,Me	68%	>19:1	65%

Ref. 26,30

eq 7

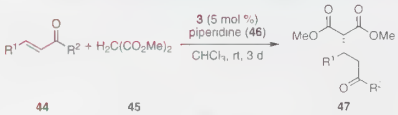


40 41 43

43	R^1,R^2	R^3	R^4	Yield	ee
a	$-(CH_2)_3-$	Me	H	64%	91%
b	$-(CH_2)_2-$	H	Me	62%	80%
c	Ph,Et	H	Me	78%	78%
d	thien-2-yl,Me	H	Me	61%	72%
e	CO_2Me,Me	H	Me	96%	82%
f	*n*-Pent,Me	H	Me	44%	58%

Ref. 32

eq 8



44 45 47

47	R^1,R^2	Yield	ee
a	$-(CH_2)_5-$	87%	83%
b	Ph,Me	89%	84%
c	4-$F_3CC_6H_4$,Me	84%	78%
d	4-HOC_6H_4,Me	70%	64%
e	furan-2-yl,Me	69%	81%
f	thien-2-yl,Me	82%	84%

Ref. 33

eq 9

solvent exhibited excellent regioselectivity: Enamine formation was favored at the less hindered side of the carbonyl group and generated protected 1,4-diamines **35** in good yields and enantioselectivities (**eq 6**).[28] Interestingly, when the formation of **35a** was attempted using L-proline (**1**) as catalyst in NMP at room temperature, phthalimidoacetone (**33**) provided Mannich product **35a** only in trace amounts accompanying the formation of cycloadduct **36** (**Figure 3**) as the major product in 59% yield. It would thus appear that L-proline (**1**) is not a useful catalyst in this reaction.

To summarize, the pyrrolidinyltetrazole **3** mediated Mannich reaction provides efficient access to several highly important product types, namely chiral α-amino acids and diamines. It can be performed under environmentally favorable conditions without the requirement for inert atmosphere or dry solvents, and provides good-to-excellent yields and regio- and stereoselectivities.

4. Conjugate Additions

The organocatalytic conjugate addition of nucleophiles to nitroolefins[26,30] and enones[31–33] can also be mediated by **3** and leads to useful adducts such as γ-nitro ketones and 1,5-dicarbonyl compounds (**eq 7–9**).

In the former case (see eq 7),[26,30] ketone-derived enamines add to electrophilic nitroalkenes to form Michael adducts **39**, which are useful synthetic precursors to other functionalities that are derived from the nitro group.[34] Interestingly, when compared to the results obtained with L-proline (**1**),[35] pyrrolidinyltetrazole **3** far outperformed it in terms of yield, enantioselectivity, reaction times, and stoichiometry. However, despite the fact that the results published were the best in the literature at that time, they still left some room for improvement, and it was only when the homoproline tetrazole derivative **50** (**eq 10**) was used that the yields and enantioselectivities moved to practically useful levels.[36,37]

In the addition of nitroalkanes to enones, the same type of γ-nitro ketone adduct is formed but, due to the nature of the reaction, products with alternative structural features are obtained (see eq 8).[31,32] In this case, pyrrolidinyltetrazole **3** proved to be a versatile catalyst for the asymmetric 1,4 addition of a variety of nitroalkanes to cyclic and acyclic enones, using *trans*-2,5-dimethylpiperazine (**42**) as a stoichiometric base additive. Using **3**, the reaction was also scalable, providing enantiomeric excesses of up to 98% in relatively short reaction times (1–3 days) and employing just two equivalents of the coupling nitroalkane.[38] Kinetic investigations, combined with the observed sensitivity of certain substrates to water, support the iminium catalysis mechanism.[32]

The addition of malonates to enones (see eq 9)[33] leads to a variety of useful 1,5-dicarbonyl compounds. In the case of **3**,[39] only 1.5 equivalents of malonate is needed, and the reaction is readily scaled and practical to operate,[33] rendering the process potentially useful in a synthesis program. The utility of such addition products in synthesis has now been further proved by carrying out the decarboxylation of **47a** to the corresponding monomethyl ester (**53**, **eq 11**). While a loss in enantiomeric excess had been observed under various Krapcho conditions,[40,41] it has now been shown that sodium hydroxide or porcine liver esterase (PLE) smoothly mediates the monohydrolysis of **47a**; subsequent decarboxylation provides the corresponding methyl ester, **53**, in excellent yield, with neither step resulting in any reduction in enantiomeric purity.[41]

Finally, it was thought that an extension of these conjugate addition methods might be useful in a new organocatalytic

asymmetric nitrocyclopropanation reaction. Cyclopropane-containing structures are compounds of interest within organic chemistry as they display a relatively large amount of stereochemical information over a small, rigid framework of just three carbon atoms. They serve as versatile synthetic intermediates in a variety of reactions[42] and are widely distributed in a range of naturally occurring compounds[43] and peptidomimetics.[44] Consequently, their stereoselective preparation is a valuable goal and, to date, several methods have been developed towards this aim.[45]

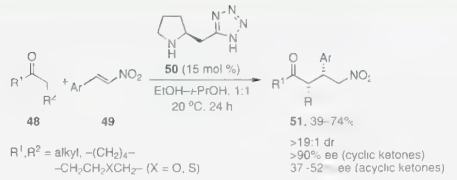
In particular, nitrocyclopropanes may be converted into a wide range of functional groups[34,46] and can be prepared by a variety of methods.[47] Therefore, it was surprising that there were only two synthetic approaches,[48] prior to the one described below,[49] that detailed their enantioselective formation. Indeed, the novel organocatalytic method developed by our group provides a higher yield and enantioselection than is found in either: following optimization studies, 7-nitrobicyclo[4.1.0]-heptanone **56** (**eq 12**) was provided in 80% yield and 77% ee, which was then easily improved to >98% ee upon a single recrystallization.[49] More recent experiments have indicated that, under further optimized reaction conditions, not only can this result be improved (87% yield, 90% ee),[50] but that the reaction is now generally applicable to a wider range of substrates such as aliphatic and aromatic enones, providing useful products in good yields and enantiomeric excesses.[50]

Thus, these conjugate addition procedures can be extremely powerful, providing, not only the products of conjugate addition, but also of tandem reactions such as the nitrocyclopropane example given above. Many further applications of this concept can be envisaged and are currently being investigated in our laboratory.

5. α-Aminoxylation, α-Hydroxyamination, and α-Amination

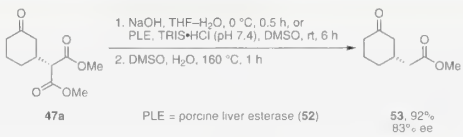
The regio- and stereoselective replacement of hydrogen by oxygen or nitrogen results in a rapid increase in molecular complexity,[51] and one can see that, with a nitrosobenzene electrophile[52] under enamine catalysis, either the oxygen- (α-aminoxylation) or nitrogen-substituted (α-hydroxyamination) product might be observed. This can give rise to optically active α,α'-disubstituted oxy- or amino aldehydes.[53]

The two major independent studies that have been carried out by Yamamoto and Kim, respectively, have shown that a reactivity pattern exists.[6,54] When ketones and aldehydes with no branching at the α position are employed (**eq 13**),[6] generally the preference is for α-aminoxylation; whereas if the substrate is α-branched, α-hydroxyamination is also observed, at least in the case of aldehydes (**eq 14**).[54] A plausible explanation for this inherent difference in reactivity is found when the reaction transition state is examined (**Figure 4**): if α branching is present, the clash between the α substituent and the phenyl group of nitrosobenzene in the usual transition state, **63**, will push the phenyl group into the pseudoequatorial position, **64**. This results in hydrogen bonding of the oxygen rather than the nitrogen atom with the tetrazole portion, thus changing the regiochemical outcome of the reaction. However, although the contrasting regioselectivity of this reaction is usually predictable, the selective formation of α-hydroxyamination products is not yet general: in order to introduce an α-nitrogen substituent, α-branched aldehydes must be utilized, and mixtures of O- and N-substituted products are usually observed.



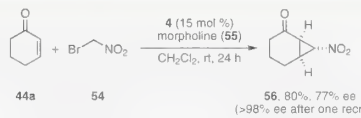
Ref. 36

eq 10



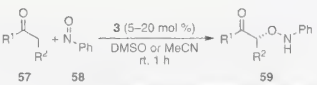
Ref. 41

eq 11



Ref. 49

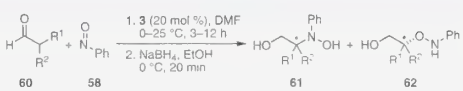
eq 12



59	R^1,R^2	Yield	ee
a	$-(CH_2)_4-$	94%	>99%
b	$-CH_2O(CH_2)_2-$	87%	>99%
c	$-CH_2C(OCH_2)_2(CH_2)_2-$	97%	99%
d	$CH_3Ni(BnCO)_2(CH_2)_2-$	95%	>99%
e	H,Bn	67%	98%
f	H,*i*-Pr	65%	98%
g	H,*n*-Bu	69%	98%

Ref. 6

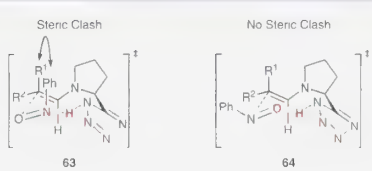
eq 13



No.	R^1	R^2	Yield	61:62	ee, 61	ee, 62
a	Bn	Me	96%	1.0:1	81%	37%
b	4-$MeOC_6H_4CH_2$	Me	75%	1.7:1	90%	35%
c	4-$BrC_6H_4CH_2$	Me	98%	1.4:1	86%	45%
d	$BnOCH_2$	Me	89%	0.8:1	79%	5%
e	allyl	Me	91%	0.7:1	62%	27%
f	*n*-Bu	Et	55%	0.6:1	5%	2%

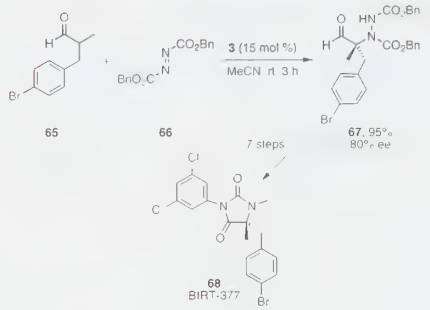
Ref. 54

eq 14



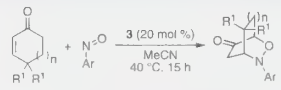
Ref. 6

Figure 4. Postulated Transition States Leading to α-Aminoxylation or α-Hydroxyamination.



Ref. 55

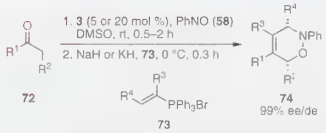
Scheme 4. α-Amination of Aldehydes as a Step in the Total Synthesis of BIRT-377 (**68**).



71	n	R^1	Ar	Yield	ee
a	1	Me	Ph	64%	99%
b	1	Ph	Ph	56%	99%
c	1	Me	*p*-Tol	47%	98%
d	1	Me	*m*-Xyl	52%	98%
e	1	Me	*p*-Br	50%	99%
f	2	H	H	14%	99

Ref. 58a

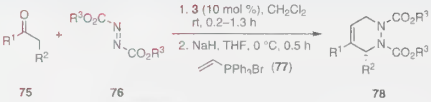
eq 15



74	R^1,R^2	R^3	R^4	Yield
a	$-(CH_2)_4-$	H	H	60%
b	$-(CH_2)_4-$	Me	H	39%
c	$-(CH_2)_4-$	H	Me	65%
d	$-(CH_2)_2SCH_2-$	H	H	51%
e	$-(CH_2)_2C(OCH_2CH_2O)CH_2-$	H	H	50%
f	H,*i*-Pr	H	H	71%
g	H,*t*-Bu	H	H	82%
h	H,$(CH_2)_3CO_2Me$	H	H	50%

Ref. 59a,b

eq 16



78	R^1,R^2	R^3	Yield	ee
a	H,*i*-Pr	Et	89%	94%
b	H,*i*-Pr	*t*-Bu	81%	99%
c	H,*i*-Pr	Bn	63%	89%
d	H,*t*-Bu	Et	84%	99%
e	H,allyl	Et	69%	90%
f	H,$(CH_2)_3CO_2Me$	Et	67%	69%
g	$-(CH_2)_4-$	Et	52%	76%
h	$-(CH_2)_2SCH_2-$	Et	40%	83%
i	$-(CH_2)_2C(OCH_2CH_2O)CH_2-$	Et	50%	76%

Ref. 59c,60

eq 17

In their total synthesis of BIRT-377 (**68**),[55] Chowdari and Barbas have shown that, as a related reaction, pyrrolidinyltetrazole **3** mediated α-amination is possible with dibenzyl azodicarboxylate (**66**) as the nitrogen source, and that even a quaternary stereocenter can be formed (**Scheme 4**). The synthesis of quaternary amino acids through organocatalytic amination reactions is challenging, since the cis and trans enamines derived from α-branched aldehydes are energetically less distinct, as compared with their linear counterparts, and this can lead to low enantioselectivities.[55] The higher reactivity and enantioselectivity obtained with **3** relative to L-proline (**1**), in the reaction leading to **67**, was ascribed to the lower pK_a and increased steric bulk of the tetrazole relative to proline's carboxylic acid moiety. Indeed, the desired key intermediate **67** was formed in an excellent 95% yield and 80% ee (compared with those observed with L-proline (**1**): 5-day reaction time, 90% yield, and 44% ee). It was suggested that analogues of **67** could be accessed by simply changing the α,α'-disubstituted aldehyde and catalyst stereochemistry. This means much scope remains for investigations into this unexploited area of research.

6. One-Pot Reaction Processes[56]

Presently, organic synthesis can be hampered by time-consuming and costly protecting-group strategies and (lengthy) purification procedures after each synthetic step. In order to circumvent these difficulties, the synthetic potential of multicomponent domino reactions has now been exploited in the efficient and stereoselective construction of complex molecules from simple precursors in a single process. These domino reactions often proceed with excellent stereoselectivities and are generally environmentally more appropriate. The efficiency of asymmetric domino reactions can easily be seen in the number of newly formed bonds, the number of new stereocenters, and the concomitant rapid increase in molecular complexity. In particular, domino reactions mediated by organocatalysts are of great utility as they are characterized by high efficiencies and are in a way biomimetic in origin: the same governing principles are often found in the biosynthesis of natural products.[57]

This field has grown over the last few years and, often, the advantage of employing organocatalysts is their ability to promote several types of reactions through different activation modes. Pyrrolidinyltetrazole **3** has so far been useful in two major tandem reaction types, namely the enantioselective α-aminoxylation–Michael reaction (**eq 15**),[58] and the formation of chiral 1,2-oxazines (**eq 16**)[59] and their 3,6-dihydropyridazine congeners (**eq 17**).[59c,60] In the former example (see eq 15), pyrrolidinyltetrazole **3** mediated a highly enantioselective synthesis of Diels–Alder nitroso adducts **71**,[58] and the results disclosed revealed opposite regioselectivities and increased stereochemical control over the more common and complementary Diels–Alder procedures used to make the same structural motif. In the latter tandem reaction type (see eq 16), a new method was developed for the synthesis of enantiomerically pure 1,2-oxazines **74** from achiral starting materials.[59] This procedure relies on initial α-aminoxylation of an enamine intermediate with nitrosobenzene (**58**), followed by nucleophilic attack on a vinylphosphonium salt **73**, and subsequent intramolecular Wittig reaction. This tandem process is a useful addition to the toolbox of the organic chemist: it is quite general and reliable, and methods for preparing this unit in an optically pure fashion are scarce.

In addition, an analogous method was published for the synthesis of a related heterocycle, the 3,6-dihydropyridazine unit

(**78**), from aldehydes and ketones.[59c,60] In the case of aldehydes,[60] products were formed in generally good-to-excellent yields and enantioselectivities with a variety of nitrogen protecting groups. This method has now been extended to ketones,[59c] greatly increasing its scope. Furthermore, the selective α amination of aldehydes with differentially protected azodicarboxylates (e.g., BocN=NTroc) has also been developed recently, serving as a useful platform for further selective derivatization of these products.[61]

Thus, it can be seen that early results on these one-pot reaction processes show that they can be very powerful, generating molecular complexity extremely quickly. We look forward with great excitement to further publications in this area.

7. Conclusions

In this short review, the variety of practical synthetic opportunities offered by the (*S*)- and (*R*)-pyrrolidinyltetrazole catalysts **3** and **4** has been illustrated. Their utility has been demonstrated beyond doubt: they are indeed worthy catalysts of a number of asymmetric organocatalytic processes and are undeniably useful additions to the rapidly developing armory of shelf-stable catalysts available to the synthetic organic chemist.

8. References and Notes

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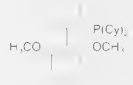
Veit Wascholowski was born in 1975 in Braunschweig, Germany. He studied chemistry at the University of Karlsruhe, Germany, and completed his Diploma in 2000. He received his Ph.D. degree in 2006 from the University of Leipzig, Germany, where he worked under the guidance of Professor Athanassios Giannis in the field of chemical biology, which involved the synthesis and biological evaluation of natural products and their analogues. In 2006, he joined Professor Ley's research group at the University of Cambridge as a postdoctoral research associate, where he is currently working on the development of new organocatalytic reactions and their application in the total synthesis of natural products.

Steven V. Ley received his Ph.D. degree from Loughborough University in 1972, after which he carried out postdoctoral research with Professor Leo Paquette at Ohio State University, and then with Professor Derek Barton at Imperial College, London. In 1975, he joined that Department as a lecturer and became Head of Department in 1989. In 1992, he moved to take up the 1702 BP Chair of Organic Chemistry at the University of Cambridge, and became a Fellow of Trinity College. He was elected to the Royal Society in 1990 and, between 2000 and 2002, was President of the Royal Society of Chemistry (RSC). In addition, Steve was made a Commander of the British Empire (CBE) early in 2002, and has been the recipient of many prizes and awards for his creative work and innovative solutions in the art of organic synthesis. Among the most recent of these are the Yamada–Koga Prize (2005), the Nagoya Gold Medal (2006), the ACS Award for Creative Work in Synthetic Organic Chemistry (2007), and the Paul Karrer Medal (2007).

Accelerate Catalysis

Buchwald Ligands

The Pd-catalyzed C–N-bond formation has become an important synthetic reaction in the past 20 years. Buchwald and co-workers have been very active in synthesizing and developing a portfolio of phosphine ligands for this transformation and other cross-coupling reactions. The ligands chosen are based on a biaryl skeleton with a phosphorus moiety at the 2 position of one aromatic ring and another moiety on the other aromatic ring. These ligands are very stable and active in a variety of cross-coupling reactions such as carbon–carbon, carbon–nitrogen, and carbon–oxygen coupling. Sigma-Aldrich is pleased to offer the following portfolio of Buchwald ligands.



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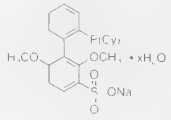

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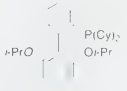

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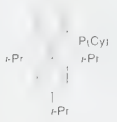

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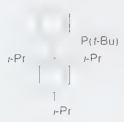

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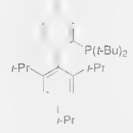

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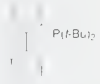

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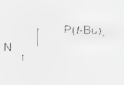

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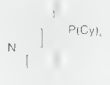


(DavePhos)
638021

Buchwald Ligands Kit I **659932**
The kit contains:

638021	638072	638099
638064	638080	638439

Buchwald Ligands Kit II **687243**
The kit contains:

638439	638080	638021
638099	663131	638064
675938	638072	677280

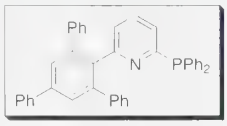
Buchwald Ligands Kit III **698903**
The kit contains:

638072	675938	695882
677280	695262	695874
663131	695211	638021
638064	638439	
638080	638099	

HydraPhos Ligands

Hintermann and coworkers introduced a new set of ligands based on a pyridylphosphane backbone for the anti-Markovnikov hydration of terminal alkynes. When used with a ruthenium complex, high yields were reported for a variety of terminal alkynes.

Labonne, A. et al. *Org. Lett.* **2006**, *8*, 5853



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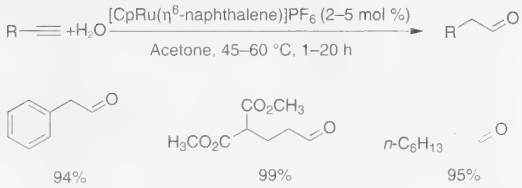

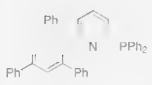

(ARPYPhos)
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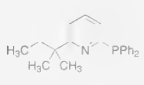

(ALPYPhos)
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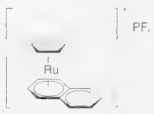
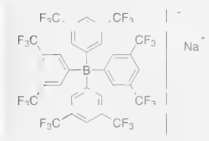


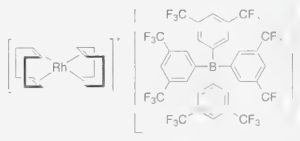
685054

New Metal Precursors for Asymmetric Catalysis

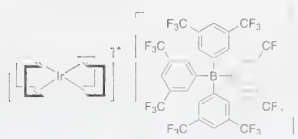
Sigma-Aldrich is pleased to offer a comprehensive portfolio of rhodium and iridium BARF complexes for asymmetric transformations.



(NaBARF)
692360



(Rh(cod)$_2$BARF)
692573

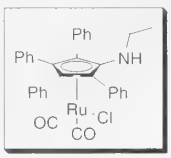


(Ir(cod)$_2$BARF)
693774

Dynamic Kinetic Resolution Catalysts

Dynamic Kinetic Resolution (DKR) catalysis is an essential methodology for the conversion of racemic substrates into single enantiomers. Kim et al. reported the (*S*)-selective DKR of a variety of alcohols by utilizing a combination of substilisin and an aminocyclopentadienylruthenium complex. High yields and selectivities were observed for a variety of secondary alcohols.

Kim, M.-J. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11494



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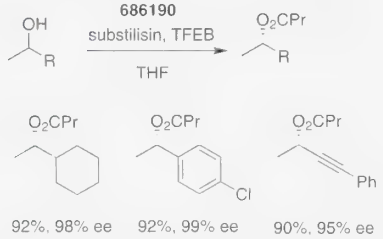

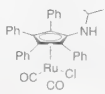

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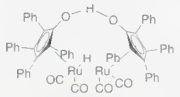
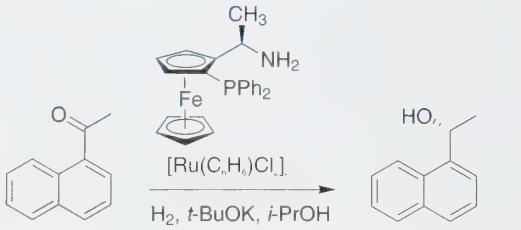


668281

686441

Aminophosphine Ligands

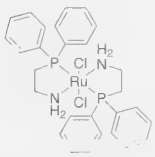
Recently, there has been a growing interest in aminophosphine ligands for asymmetric synthesis. Researchers at Kanata Chemical Technologies, Inc., have synthesized several sets of aminophosphine ligands that show high reactivity and selectivity in a wide array of enantioselective reactions.



100%, 66.7% ee

A growing area of application for aminophosphine ligands in asymmetric synthesis is in ruthenium-catalyzed hydrogenations. Chen et al. have described the use of ferrocenylaminophosphines in the ruthenium-catalyzed asymmetric hydrogenation of acetonaphthone. Using the precatalyst $[Ru(C_6H_6)Cl_2]_2$ and the ferrocenyl-based aminophosphine ligand, these researchers found that the hydrogenation proceeded efficiently with reasonable enantioselectivity. Aldrich is pleased to offer a portfolio of aminophosphine ligands and complexes.

Chen, W.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Tetrahedron: Asymmetry* **2006**, *17*,1161.



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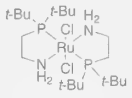

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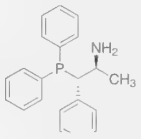

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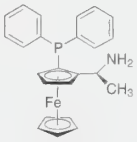

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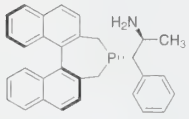

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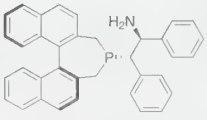

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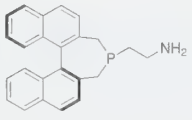

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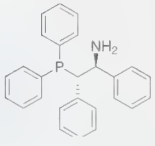

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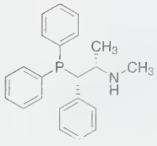

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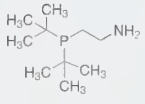

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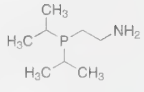

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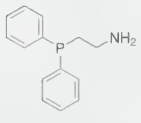

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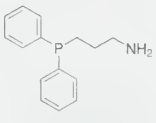

43163

Aminophosphine Catalysts in Modern Asymmetric Synthesis


Dr. Dino Amoroso


Dr. Todd W. Graham


Dr. Rongwei Guo


Dr. Chi-Wing Tsang


Dr. K. Abdur-Rashid

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Outline

1. Introduction

The importance of ligand composition and structure in transition-metal-catalyzed asymmetric synthesis cannot be overstated. From the simplest lock-and-key model to the most complex transition state, the interaction between catalyst and substrate can be completely dictated by the chemical composition and spatial orientation of the supporting ligands. An excellent example of this is in the direct hydrogenation of ketones, aldehydes, and imines catalyzed by ruthenium complexes supported by phosphine or amine ligands.[1] In this process, the unsaturated substrate does not bind directly to the metal center, but rather interacts simultaneously with the Ru–H and N–H bonds of an amine-containing ligand (**Figure 1, Part A**). Often generically described as metal–ligand bifunctional catalysis, the importance of the ligand composition (e.g., incorporation of an N–H bond) and structure (e.g., the spatial orientation of the N–H bond and the other spectator ligands that direct the approach of substrate and often govern stereochemistry) in this reaction manifold is clear.

A particular class of ligand, which is often involved in such ligand-dependent interactions, is chelating aminophosphines (**Figure 1, Part B**). The nature of the substituents at nitrogen, and the stereochemistry at phosphorus and in the ligand backbone, render this motif particularly versatile in catalysis. Because of the highly modular nature of this ligand type, it has found application in a broad range of asymmetric transformations and has become an invaluable tool for the preparation of chiral molecules. In this review, a subset of this ligand class, defined by restricting at least R^1 or R^2 to H, is considered. This class is of particular interest owing to the potential involvement of this functionality in catalysis. A further restriction that excludes ligands incorporating a direct P–N bond has also been imposed. However, in select instances—such as in the Rh-catalyzed hydrogenation where the direct P–N bond motif is almost exclusively employed, or in cases where ligands are readily derived from those which *are* included in the preceding subset –both restrictions have been overlooked. The synthesis of the group of chelating aminophosphine ligands that results from imposing these two restrictions, and their application in asymmetric synthesis over the last 10 years, are reviewed.

2. Ligand Synthesis

The growth in popularity of aminophosphine ligands in asymmetric synthesis is due in part to the increasing number of convenient synthetic pathways leading to useful ligand sets. In recent years, several general routes have been described, which allow access to a broad range of versatile aminophosphines.

Amino acids constitute a convenient class of precursors to chiral aminophosphine ligands.[2,3] Morimoto and Achiwa have described the use of L-valine (**1a**, **Scheme 1**) and other amino acids in the preparation of aminophosphine ligands of type **2**. These ligands have widespread applications in catalysis, particularly in hydrogenation, while other derivatives of L-valine have been exploited in palladium-catalyzed allylic transformations (vide infra).

Another common route to chiral aminophosphine ligands is through commercially available chiral amino alcohols such as ephedrine, norephedrine, and pseudoephedrine. Dahlenburg and Götz have reported the synthesis of chiral aminophosphines by the aziridination of amino alcohols.[4] Ring-opening of the aziridines by nucleophilic attack with diphenylphosphine affords chiral ligands **3**–**5** (**Figure 2**). The appeal of this route is in its ability to dictate the stereochemistry of the ring-opened aminophosphine by controlling that of the aziridine (via a judicious choice of the aziridination protocol). Indeed the ring opening of aziridines is a convenient route to a range of chiral aminophosphines (**eq 1**).[5] Yudin and co-workers employed secondary phosphines as nucleophiles to ring-open cyclohexene aziridines to cyclohexylaminophosphines, which were optically resolved with D-tartaric acid. It is worth noting that pyrazole derivatives were also prepared from the cyclohexylaminophosphines.

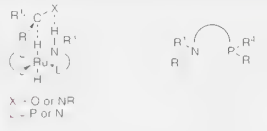
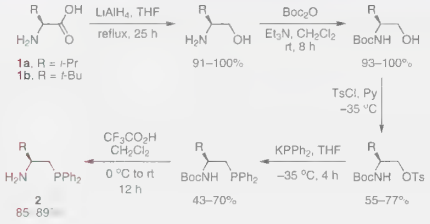
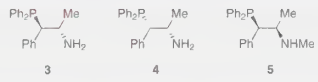


Figure 1. (A) Interaction Between Ligands and Substrate in the Ruthenium-Catalyzed Hydrogenation of Ketones, Aldehydes, and Imines. (B) General Structure of a Chelating Aminophosphine Ligand.



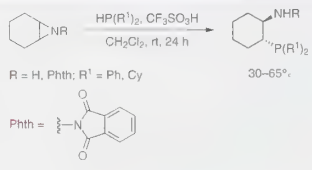
Ref. 2a,d

Scheme 1. The Synthesis of Aminophosphines from Amino Acids.



Ref. 4

Figure 2. Aminophosphines Derived from Commercially Available Amino Alcohols.



Ref. 5

eq 1

An alternate route employing amino alcohols has been disclosed by our group (**Scheme 2**)[6] and others.[7] The route involves the formation of cyclic sulfamidates from the corresponding N-protected sulfamidites. Treatment of the sulfamidate with a metal phosphide, followed by removal of sulfate with dilute acid and N-deprotection, yield the chiral or achiral aminophosphine. The route described by Hilmersson and co-workers differs in that they include an N-alkylation step prior to sulfamidite formation. This allows them to proceed without protecting the amine. Some representative examples of the ligands prepared by our method are shown in **Figure 3**.

We have also described a simple route to aminophosphines via haloalkylammonium salts (**Scheme 3**).[6] Many haloalkylammonium salts are commercially available, although they can also be readily prepared from amino alcohols. The procedure involves neutralization of the salt and protection of the amine, followed by halide substitution with a metal phosphide. Hydrolysis then leads to the desired aminophosphine ligand. Representative examples are depicted in **Figure 4**.

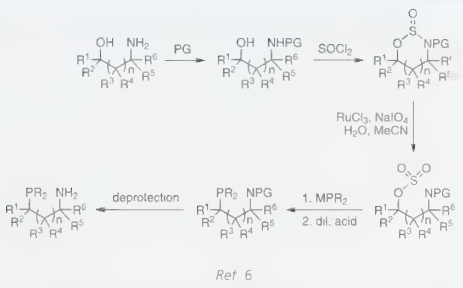
While chiral amino alcohols and acids represent a convenient source of chirality for ligand construction, so too does the 1-ferrocenylalkyl fragment that has been exploited for the development of chiral ferrocenylaminophosphines by Boaz[8] and Chen.[9] Boaz prepared chiral ferrocenylaminophosphines of type **6**, which were subsequently derivatized into phosphinoferrocenyl-aminophosphines and extensively studied in asymmetric synthesis (**Scheme 4**).[8] Chen synthesized similar compounds by a modified procedure, which provides entry into a range of P-chiral ligands with nonidentical substituents on phosphorus. An attractive feature of all such ferrocenylaminophosphines is their remarkable stability toward air oxidation, as samples of material exposed to air for up to 3 years showed no loss in enantioselectivity or activity in Rh-catalyzed hydrogenations.[8d]

A library of compounds aimed at elucidating ligand structural effects in the asymmetric transfer hydrogenation of prochiral ketones was described by Jubault and co-workers.[10] This group employed two different routes to arrive at intermediate amides that were subsequently reduced and deprotected (**Scheme 5**). Both the coupling and reduction of the amides proceeded in moderate-to-high yields, while the removal of borane took place quantitatively.

A simple route to enantiopure β-aminophosphines through vinylphosphine oxides (**Scheme 6**) was employed by Maj et al.[11] While these workers described several variants of aminophosphine oxides and their use as ligands in transfer hydrogenation,[11a] aminophosphines **7b** and **8b** were also prepared and tested vis-à-vis their oxidized precursors.[11b]

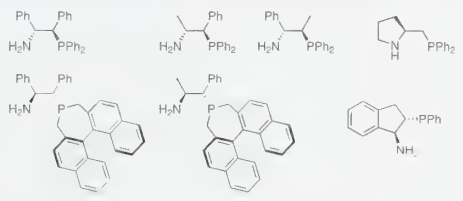
Hii and co-workers have employed a similar methodology to prepare other *N*-alkylaminophosphine (and aminodiphosphine) ligands from vinylphosphine oxides, and reported on their use in ruthenium-catalyzed transfer hydrogenation.[12] These workers also described the development of a range of chiral aminophosphine ligands (**Figure 5**)[12c,d] subsequent to their initial disclosure of several achiral variants.[12a,b]

A strong base containing a guanidine functional group was utilized by Fu et al. to catalyze the phospha-Michael reaction between a number of diarylphosphine oxides and various aryl-substituted nitroalkenes. Subsequent reduction of the nitro and phosphine oxide groups led to the corresponding aminophosphines in good yields and >99% ee's (**Scheme 7**).[13]



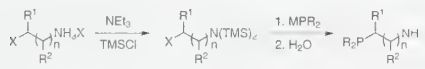
Ref. 6

Scheme 2. The Sulfamidate Route to Aminophosphines.



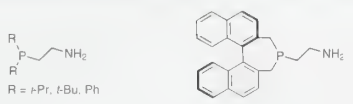
Ref. 6

Figure 3. Representative Chiral Aminophosphines Prepared by the Sulfamidate Route.



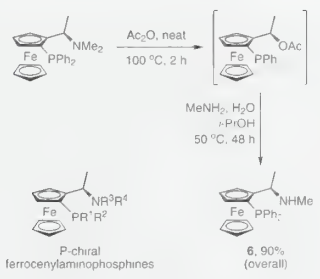
Ref. 6

Scheme 3. The Haloalkylammonium Route to Aminophosphines.



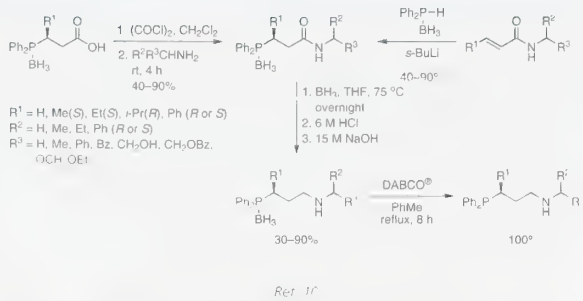
Ref. 6

Figure 4. Representative Aminophosphines Prepared from Haloalkylammonium Salts.



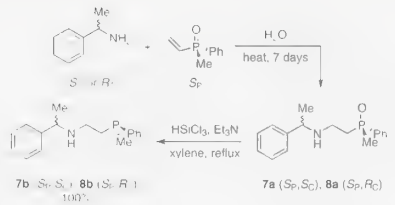
Ref. 8c

Scheme 4. Aminophosphines Prepared from Ferrocene Derivatives.



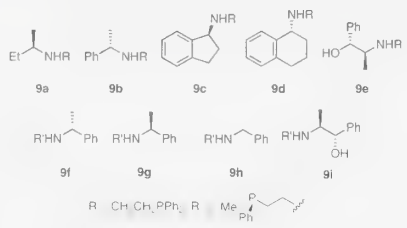
Ref. 11c

Scheme 5. Aminophosphines Derived from Amides.



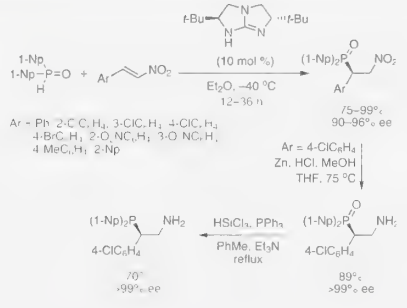
Ref. 11b

Scheme 6. β-Aminophosphines Derived from Vinylphosphine Oxides.



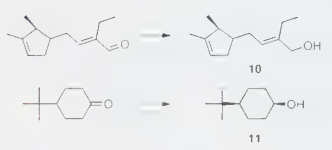
Ref. 12a,f

Figure 5. Chiral Aminophosphines Derived from Vinylphosphine Oxides.



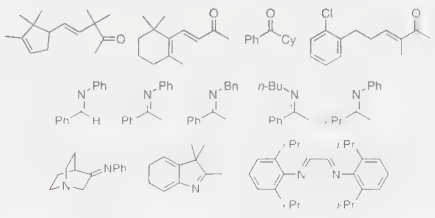
Ref. 13

Scheme 7. Synthesis of Aminophosphines Catalyzed by the Guanidine Functional Group.



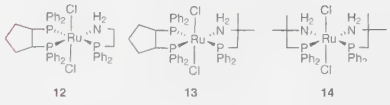
Ref. 17

Scheme 8. Industrially Significant Alcohols Prepared by the Ruthenium–Aminophosphine-Catalyzed Hydrogenation.



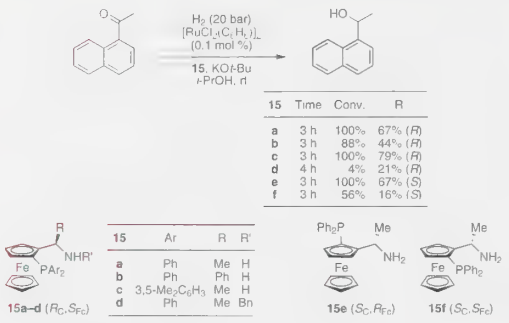
Ref. 17

Figure 6. Representative Ketones and Imines that Have Been Reduced to the Corresponding Alcohols and Amines by the Ruthenium–Aminophosphine-Catalyzed Hydrogenation.



Ref. 18

Figure 7. Ruthenium–Aminophosphine Complexes Employed in the Hydrogenation and Transfer Hydrogenation of Ketones.



15	Time	Conv.	R
a	3 h	100%	67% (*R*)
b	3 h	88%	44% (*R*)
c	3 h	100%	79% (*R*)
d	4 h	4%	21% (*R*)
e	3 h	100%	67% (*S*)
f	3 h	56%	16% (*S*)

15	Ar	R	R'
a	Ph	Me	H
b	Ph	Ph	H
c	3,5-$Me_2C_6H_3$	Me	H
d	Ph	Me	Bn

Ref. 9b

eq 2

3. Hydrogenation

3.1. Ruthenium Catalysts

A heavily exploited application area for aminophosphine ligands in asymmetric synthesis is the ruthenium-catalyzed hydrogenation. This process is integral to the preparation of alcohols and amines that are useful in the flavor and fragrance, pharmaceutical, agrochemical, materials, and fine chemicals industries.[14] Our group and others have reported extensively on the use of ruthenium aminophosphine complexes, and has studied the relationship between catalyst structure and enantioselectivity.[3,15,16,17] The industrially relevant compounds (*E*)-2-ethyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl) but-2-en-1-ol (**10**) and *cis*-4-*tert*-butylcyclohexanol (**11**) are two examples of the type of product that can be very efficiently produced from the corresponding aldehyde or ketone by using ruthenium aminophosphine catalysts (**Scheme 8**).[17] With precatalysts of the type $RuCl_2$(aminophosphine)$_2$ or $RuCl_2$(diphosphine)(aminophosphine), substrate:catalyst ratios of 100,000:1 or greater are typical in the direct hydrogenation. This approach was applied to a broad range of ketones, aldehydes, and imines (**Figure 6**).[17] The advantage of a ruthenium-catalyzed hydrogenation over a conventional stoichiometric reduction with a hydride-transfer reagent (e.g., alkali metal borohydrides or aluminum hydrides) is quite apparent: avoid the use of large quantities of expensive and difficult-to-handle materials that produce inorganic hydroxides in favor of utilizing catalytic amounts of robust materials. It should also be pointed out that these ruthenium catalysts selectively reduce only the ketone, aldehyde, or imine while leaving carbon–carbon double bonds intact.

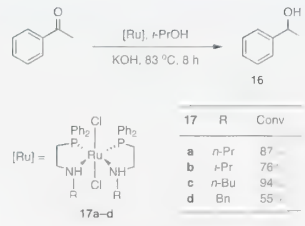
Dahlenburg and Kühnlein have described the use of ruthenium–aminophosphine complexes **12**–**14** (**Figure 7**) in the transfer hydrogenation and, in the case of **14**, the direct hydrogenation of acetophenone.[18] They observed an induction period in the transfer-hydrogenation experiments corresponding to the time needed for the active catalyst to arise from the precatalyst complexes. Variations in induction times were observed and found to correlate directly to the extent of steric shielding of the amino group. Catalyst **14** was effective in the direct hydrogenation of acetophenone to 1-phenylethanol as well. It was shown, through the use of isotopically labeled solvent, that, under the direct hydrogenation conditions, the source of hydrogen atoms in the alcohol product was indeed hydrogen gas.

Chen and co-workers have described the use of ferrocenylaminophosphines in the ruthenium-catalyzed asymmetric (direct) hydrogenation of 1-acetonaphthone (**eq 2**).[9b] In the presence of precatalysts of type $RuCl_2$(**15**)$_2$, derived from the reaction of $[RuCl_2(C_6H_6)]_2$ and **15**, the hydrogenation proceeded rapidly and with reasonable enantioselectivity when ligands **15a**, **15c**, and **15e** were used. When the steric bulk of the phosphine aryl substituent was largest (**15c**), enantioselectivity was highest. In contrast, increasing the steric bulk at or near nitrogen resulted in significantly diminished activity and selectivity (e.g., **15d** and **15f**). This was anticipated as increased steric bulk at nitrogen should limit the ability of the substrate to interact with the N–H bond. The carbon-centered chirality was found to dictate the sense of induction in the product.

Using aminophosphines derived from vinylphosphine oxides (see Scheme 6), a comparison of the catalytic activities between reduced and oxidized β-aminophosphines has been reported.[11] In the transfer hydrogenation of various aromatic ketones, the reduced aminophosphine ligands had activities comparable to those of the corresponding aminophosphine oxide ligands, but gave rise to consistently higher ee's. Hii and co-workers have also used similarly derived β-aminophosphines (and their oxides) in the

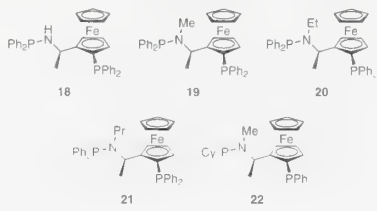
transfer hydrogenation of ketones (**eq 3**).[12] They initially described the use of achiral ligands (**17a–d**) and reported that increasing the steric bulk of the N-substituent led to diminished activity. Upon examination of chiral ligands **9a–e** (see Figure 5), they found that incorporation of the alcohol functionality in the ligand resulted in dramatically improved enantioselectivity. They obtained a 79% ee (*R* form) in the hydrogenation of acetophenone using ligand **9e**, compared to 39% ee (*R* form) with **9b** as the next best of the five chiral ligands tested in this transformation. It is worth noting that Hii's group also discovered that the optimal metal-to-ligand ratio (when $[RuCl_2(p\text{-cymene})]_2$ was used as the Ru source) was 1:1, in contrast to the 2:1 ratio traditionally employed in Ru-catalyzed transfer hydrogenations.

The library of aminophosphines developed by Jubault and co-workers (see Scheme 5) was tested in the transfer hydrogenation of acetophenone, propiophenone, and isobutyrophenone.[10] These researchers found that acetophenone and propiophenone were most effectively reduced when R^1 = Et (*S*), R^2 = Ph (*S*), and R^3 = Me. For isobutyrophenone, the best results were obtained when R^1 = H, R^2 = Ph, and R^3 = CH_2OBz. Jubault's group was also able to glean the impact of the nature and position of the substituents on this particular class of ligands. For instance, the introduction of a chiral center adjacent to phosphorus has a dramatic effect on enantioselectivity, while the sense of induction is most strongly governed by the chiral center adjacent to the amine.



Ref. 12b

eq 3



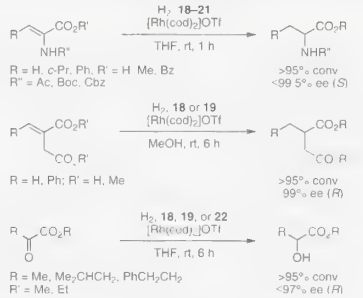
Ref. 8c

Figure 8. BoPhoz Ligands Derived from Phosphinoferrocenylethylamine.

3.2. Rhodium Catalysts

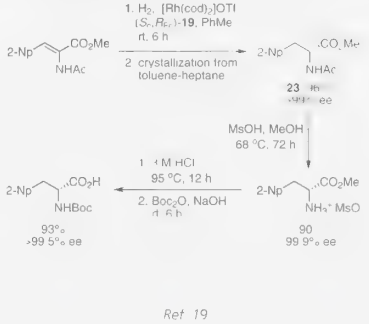
When combined with rhodium, the versatile chiral phosphine–aminophosphine and phosphine–phosphoramidite ligands, derived by combining phosphorus and nitrogen functional groups in one molecular structure, represent a particularly important class of catalyst.

In 2002, Boaz first introduced the hybrid phosphine-aminophosphine ligands **18–22** (**Figure 8**), based on a chiral ferrocenylethylamine backbone, for the rhodium-catalyzed asymmetric hydrogenation of olefins.[8] Ligands **18** and **19** showed excellent enantioselectivities in the hydrogenation of dehydro-α-amino acid and itaconic acid derivatives, while **22** showed very good enantioselectivity in the hydrogenation of α-keto esters (**Scheme 9**).[8c] Ligand (S_C,R_{Fc})-**19** was successfully utilized for the preparation of single-enantiomer 2-naphthylalanine derivatives on multikilogram scale by Eastman Chemical Company (**Scheme 10**).[19] The catalyst system Rh–(S_C,R_{Fc})-**19** showed high activity and enantioselectivity, as the hydrogenation product **23** was obtained in 96% isolated yield and >99% ee after one crystallization from toluene–heptane. Further elaboration of **23** led to the final product in high yield and >99.5% ee.[19]



Ref. 8c

Scheme 9. Hydrogenations with Rh–BoPhoz Ligands.

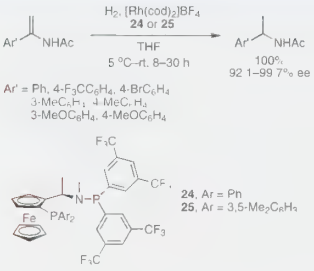


Ref. 19

Scheme 10. Multikilogram Hydrogenation Process with the Rh–(S_C,R_{Fc})-**19** Catalyst System.

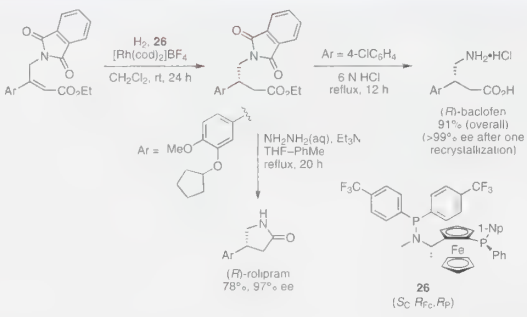
While Rh–BoPhoz catalysts show high activity and enantioselectivity in the hydrogenation of dehydro-α-amino acid derivatives, they result in only moderate enantioselectivity in the hydrogenation of α-aryl enamides (~80% ee). Chan introduced fluorinated phosphinoferrocenylaminophosphine ligands **24** and **25**, which showed excellent enantioselectivities in the hydrogenation of dehydro-α-amino acid derivatives (≤99.7% ee) and α-aryl enamide substrates (≤99.7% ee) (**eq 4**).[20] A significant feature of this catalyst system is that the rhodium complexes are exceptionally air- and moisture-stable, even when dissolved in an organic solvent.[20]

Hu, Zheng, and co-workers recently introduced a modified BoPhoz ligand with three chiral centers, **26**, for the highly enantioselective (≤97% ee) rhodium-catalyzed hydrogenation of γ-phthalimido-substituted α,β-unsaturated carboxylic acid esters (**Scheme 11**).[21] The catalyst system Rh–**26** was successfully applied to the synthesis of the optically active pharmaceuticals (*R*)-baclofen,



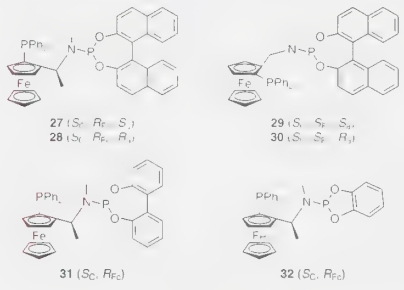
Ref. 20

eq 4



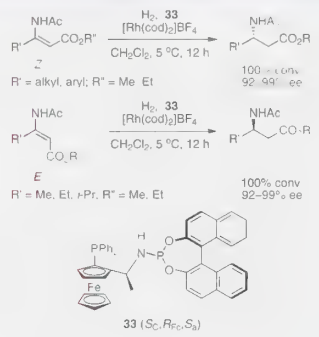
Ref. 21

Scheme 11. Application of Rh–**26** Catalyst System to the Preparation of (*R*)-Baclofen and (*R*)-Rolipram.



Ref. 22

Figure 9. Phosphine–Phosphoramidite Ligands.



Ref. 23

Scheme 12. Rhodium–**33** Hydrogenation of Dehydro-β-amino Acid Derivatives.

which is widely used as an antispasmodic agent, and (*R*)-rolipram, which is employed as an antidepressant and anti-inflammatory agent.

In 2004, Hu and Zheng employed a new set of phosphine–phosphoramidite ligands, **27–32** (**Figure 9**), as alternatives to BoPhoz ligands for the Rh-catalyzed hydrogenation of olefins.[22] The enantioselectivity with the Rh–**27** catalyst system in the hydrogenation of *N*-(1-phenylethenyl)acetamide was greater than 99% ee (S/C = 5,000/1). Rh–**27** also led to >99% ee for the hydrogenation of dimethyl itaconate and (*Z*)-acetamidocinnamate at low catalyst loadings (S/C = 10,000). The rhodium-catalyzed hydrogenation reactions employing these ligands were carried out under ambient conditions, taking no precautions to exclude air or moisture, with no loss in activity or enantioselectivity.[22]

While **27** showed high enantioselectivities in the rhodium-catalyzed hydrogenation of enamides, itaconates, and dehydro-α-amino acid derivatives, very low enantioselectivities were observed for the rhodium-catalyzed hydrogenation of the *Z* and *E* isomers of dehydro-β-amino acid derivatives (20–60% ee's). After expanding the ligand scope, Zheng's group found that **33**, bearing a proton instead of a methyl group on nitrogen, showed excellent enantioselectivity in the rhodium-catalyzed hydrogenation of *Z* and *E* β-aryl- or β-alkyl-β-(acylamino)acrylates, leading to the two products with opposite configurations (**Scheme 12**).[23]

Leitner, Faraone, and co-workers introduced chiral phosphine–phosphoramidite ligands **34** and **35** (*n*-Bu-QuinaPhos) for the rhodium-catalyzed hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate (**eq 5**).[24] Excellent activity and enantioselectivity were observed for the reaction. Moreover, the rhodium-catalyzed hydroformylation of styrene with *n*-Bu-QuinaPhos gave rise to high regioselectivity and moderate enantioselectivity.[24]

Me-AnilaPhos (**36**) and IndolPhos ligands **37** and **38** were recently reported by the groups of Kostas and Reek (**Figure 10**).[25,26] These chiral phosphine–phosphoramidite ligands, derived from achiral aminophosphine ligands, also show high enantioselectivity in the rhodium-catalyzed hydrogenation of enamides and itaconate derivatives (≤97% ee for enamides and 98% ee for itaconates). Owing to the simple structure and the wide range of available aminophosphine precursors, **36–38** represent a highly versatile ligand class.

The novel phosphine–phosphoramidite ligands **39–42** (PEAPhos), derived from chiral α-phenylethylamine, and **43**, derived from 1,2,3,4-tetrahydro-1-naphthylamine, were disclosed by Zheng and co-workers.[27] The Rh–**39** catalyst system showed excellent enantioselectivity (>99% ee) in the hydrogenation of olefins (**Scheme 13**).[27] Ligand **43** was also successfully applied to the synthesis of α-hydroxyphosphoric acid derivatives by the rhodium-catalyzed hydrogenation (a significant achievement) of β-substituted α-acyloxyphosphonates. A greater than 99% ee was achieved for a range of substrates bearing β-aryl, β-alkoxy, and β-alkyl substitutents (**eq 6**).[27]

3.3. Iridium Catalysts

The class of aminophosphine ligands discussed so far has found only limited application in iridium-catalyzed hydrogenations. Dahlenburg and collaborators have employed aminophosphine ligands in the iridium-catalyzed hydrogenation of unsaturated substrates.[4,28] They described a series of chiral and achiral aminophosphine-chelated iridium(I) complexes prepared by treating $[Ir(cod)_2]BF_4$ with the β-aminophosphine or by treating $Ph_2PCH_2CMe_2N(Li)H$ and 2-$(Ph_2P)C_6H_4N(Li)Me$ with $[Ir(cod)(\mu\text{-}Cl)]_2$ to give the neutral alkyl and aryl amido compounds. When

combined with an alkali or amine base in methanol, all of the iridium complexes acted as catalysts for the direct hydrogenation of alkyl aryl ketones to the corresponding 1-phenylalkanols. The reactions, carried out at 25–50 °C and 10–50 bar of hydrogen, occurred with modest-to-good enantioselectivities (20–75% ee).

4. Allylic Alkylation

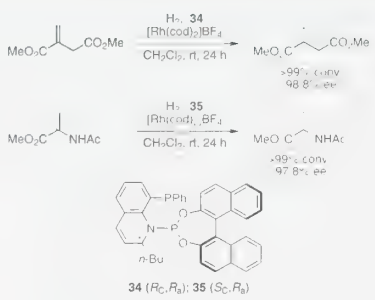
The palladium-catalyzed allylic alkylation has emerged as a powerful carbon–carbon-bond-forming reaction, and is now widely used in organic synthesis. The reaction is believed to proceed by nucleophilic addition to either C-1 or C-3 of a coordinated η^3-allyl ligand (**Scheme 14**).[2,29] The asymmetric version of this reaction has become quite popular, and aminophosphine ligands may provide a distinct advantage over symmetrical analogues as alkylation tends to occur at the position that is trans to the more strongly π-acidic PR_2 group.[2,29] The enantioselective C–C-bond-formation step occurs via the major diastereomer of the equilibrating diastereomeric π-allyl intermediates.

Achiwa and co-workers have reported the synthesis of the chiral amidine ligand VALAP (**44**) from L-valine by condensation of aminophosphine **2a** with $Me_2NCH(OMe)_2$ (**eq 7**).[2a] VALAP has been utilized in the Pd-catalyzed asymmetric allylation of 1,3-diphenyl-2-propenyl acetate and pivalate (**eq 8**) with dimethyl malonate in the presence of BSA and LiOAc, affording excellent yields and up to 95% ee's. Loadings of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as low as 0.01 mol % still allowed for reasonable reaction times.

Morimoto modified the VALAP ligand (and the *tert*-butyl leucine analogue) via reaction of **44** with pyrrolidine and piperidine, or reaction of **2a** with para-substituted aromatic aldehydes (**Scheme 15**).[2d] An examination of the effect of ligands **45c–h** on the allylic alkylation reaction showed a clear electronic effect wherein electron-donating substituents in the para position resulted in higher yields and ee's (**eq 9**).[2d,30] This effect is most dramatic when comparing R = CF_3 (entry 3) and CH_3 (entry 4) which have a similar steric profile, yet the presence of the CH_3 group resulted in a marked improvement in both yield and ee. With the strongly electron-donating substituent, NMe_2, both the catalytic activity and enantioselectivity are higher still than those obtained with the less electron-donating substituents. Indeed, use of this substituent allowed the $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ loading to be reduced to 0.005 mol % while still retaining excellent reactivity and leading to only a slight decrease in selectivity.

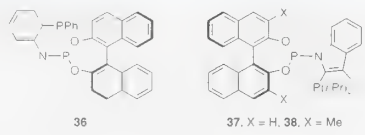
Saitoh et al. have also investigated the allylation reaction with silyl acetals and ketals **46a–d** and found that $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–VALAP and related systems exhibit low-to-moderate activities with moderate-to-high enantioselectivities: ≤93% ee using ligand **44** with acetal **46d** (**eq 10**).[2d] When the analogous reaction with RR′C=C(OMe)(OM) (M = Li, NR_4) as the nucleophile was examined, a low enantioselective induction was observed.

Yudin's group has employed iminophosphine ligands of type **47** (**eq 11**) in the palladium-catalyzed allylation.[31] The $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ -**47** catalyzed allylation of 1,3-diphenyl-2-propenyl acetate in the presence of BSA and diethyl malonate was explored in order to determine the efficiency of the new chiral ligands for asymmetric induction. In the presence of aminocyclohexylphosphines, the precursors to ligands **47**, the reaction resulted in low yields and low enantioselectivities. When the catalytic reaction was carried out in the presence of the iminophosphine ligands, more favorable results were obtained. The yield and asymmetric induction for **47a** and **47b** were similar (≤89% yield and 87% ee), indicating that the ortho-methoxy fragment had little effect, whereas an electron-withdrawing



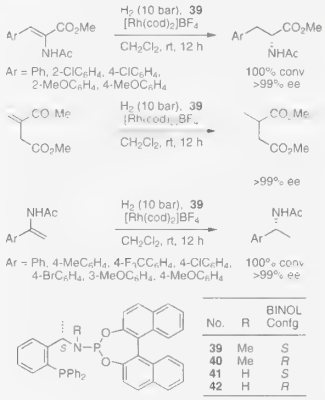
Ref. 24a

eq 5



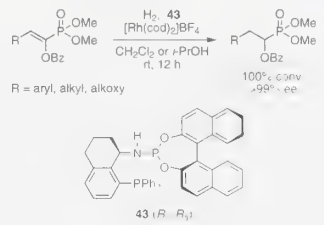
Ref. 25,26

Figure 10. Me-AnilaPhos and IndolPhos.



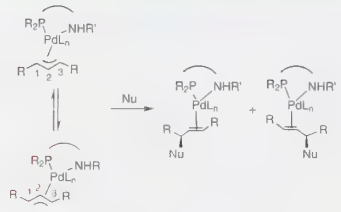
Ref. 27a

Scheme 13. Hydrogenation of Olefins with Rh–PEAPhos.



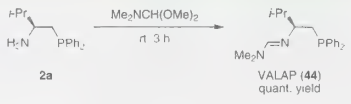
Ref. 27b

eq 6



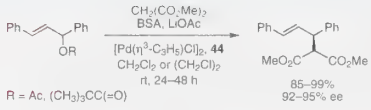
Ref 2a,29

Scheme 14. Palladium-Catalyzed Allylic Alkylation.



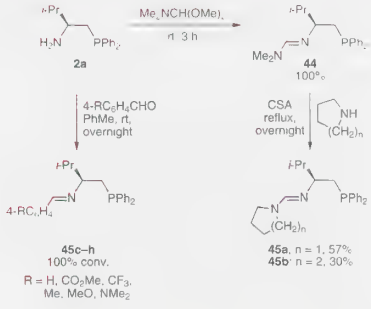
Ref 2a

eq 7



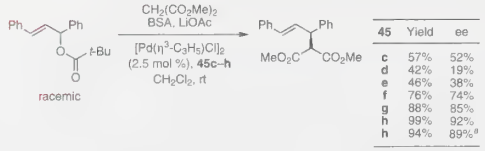
Ref 2a

eq 8



Ref 2d

Scheme 15. Modified VALAP and Leucine Ligands.



45	Yield	ee
c	57%	52%
d	42%	19%
e	46%	38%
f	76%	74%
g	88%	85%
h	99%	92%
h	94%	89%[a]

[a] 0.5 mol % of the Pd catalyst was used

Ref 2d

eq 9

substituent in this position, as in **47d**, had a deleterious effect on the reaction (60% yield and 51% ee). The bulky anthryl group, **47e**, greatly enhanced the reaction rate (complete in ca. 5 min), but resulted in a large decrease in enantioselectivity (21% ee).

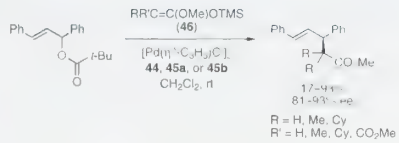
Zheng and co-workers have recently reported on ferrocenylaminophosphine ligands that are capable of producing high yields and excellent asymmetric induction in the catalytic alkylation of 1,3-diphenyl-2-propenyl pivalate with dimethyl malonate.[32] The ligands are prepared in one step from aminophosphines or phosphinoacetates and chloropyrimidines, chlorotriazines, or aminopyridines (**Scheme 16**). Their report indicates that increasing the number of nitrogen atoms in the ligand dramatically increases both the catalytic activity and enantioselectivity. For example, substituting the NMe_2 group with MeN(2-Py) results in an increase in enantioselectivity from 48% to 81% ee. When the pyrimidine-substituted ligand **51b** is used, an ee of 93% is obtained. The triazine-substituted ligand **50b** results in an enantioselectivity of 98% ee.

Gong, Mi, and co-workers have disclosed a series of aminophosphinite ligands, **53–54** (**Figure 11**), that give good-to-excellent asymmetric induction in the Pd-catalyzed allylation of 1,3-diphenyl-2-propenyl acetate with dimethyl acetate.[33] The chiral ligands were prepared in one step by the reaction of aminoethanols with chlorodiphenylphosphine. These workers found that ligands with an NHR fragment (**54a–c**) gave higher ee's than ligands with an NMeR group (**53a–d**). The authors indicated that the N–H group was essential for optimal catalyst activity and selectivity, and proposed that the selectivity was a result of substrate interaction with the NH group.

5. Hydroformylation

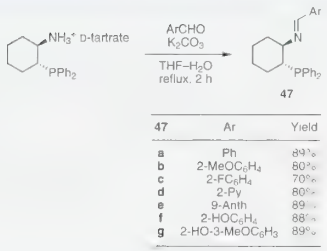
While the hydroformylation of olefins employing rhodium catalysts represents an area of significant interest,[34] few recent reports have focused on the use of aminophosphine ligands bearing an NH group. Despite the relative scarcity of information, much is understood about the role and efficacy of such ligands in this process.

In a report by Andrieu and co-workers, diastereomeric trifunctional diaminophosphine ligands were derived from bidentate aminophosphine ligands by nucleophilic addition of a phosphinoalkyl carbanion (generated by lithiation) onto an imine (**Scheme 17**).[35] Both the bifunctional precursors and the derived trifunctional ligands were tested in the hydroformylation of styrene. Andrieu's group found that, while there was no impact on the isomer ratio, a substantial increase in activity was observed as a result of variation in the ligand set. An approximate threefold increase in activity using **55** or **56** relative to its precursor ligand suggested a dependence on the proximity and/or basicity of the dangling amine functionality. In subsequent studies,[36] it was determined that under catalytically relevant conditions, the aminophosphine ligand binds in a monodentate fashion through phosphorus while the amine functionality remains uncoordinated. The role of Brønsted base was proposed for the uncoordinated amine, which could assist in either the heterolytic splitting of dihydrogen or in the reductive elimination of HCl. Either scenario leads to an ammonium functionality in the dangling ligand. Based on a series of experiments designed to elucidate the mechanism, the authors proposed that a key step in rhodium-catalyzed hydroformylations employing aminophosphine ligands involves Rh–acyl racemization. This occurs via interaction of the acyl intermediate with the ammonium functionality of the dangling ligand (**eq 12**).



Ref. 2d

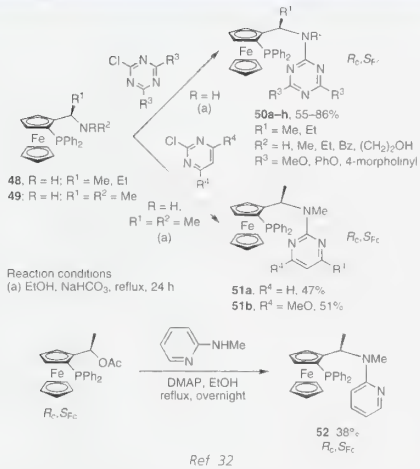
eq 10



47	Ar	Yield
a	Ph	89%
b	2-MeOC6H4	80%
c	2-FC6H4	70%
d	2-Py	80%
e	9-Anth	89%
f	2-HOC6H4	88%
g	2-HO-3-MeOC6H3	89%

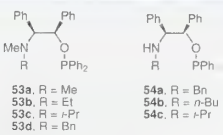
Ref. 31

eq 11



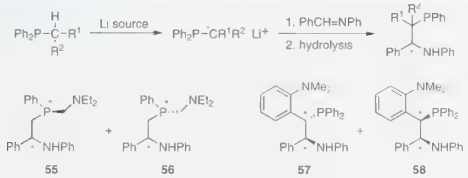
Ref. 32

Scheme 16. Ferrocenylaminophosphine Ligands for Allylation Reactions.



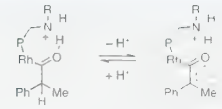
Ref. 33

Figure 11. Aminophosphinite Ligands Used in Allylation Reactions.



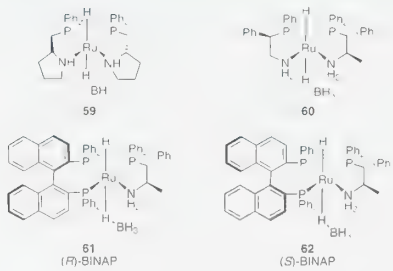
Ref. 35

Scheme 17. Preparation of Trifunctional Diaminophosphine Ligands via Nucleophilic Addition of Phosphinoalkyl Carbanions onto Imines.



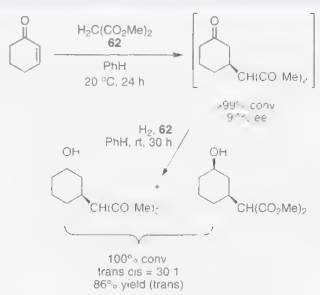
Ref. 36b

eq 12



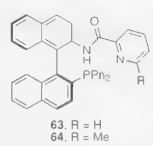
Ref. 15b

Figure 12. Ruthenium–Aminophosphine Complexes as Catalysts in the Asymmetric Michael Addition.



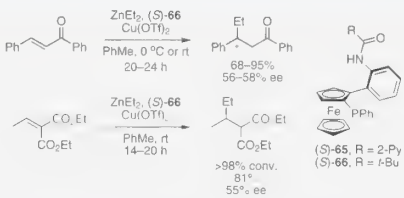
Ref. 15b

Scheme 18. Tandem Michael Addition–Hydrogenation Catalyzed by Ruthenium–Aminophosphine Complexes.



Ref. 37

Figure 13. Binaphthyl Aminophosphines for the Copper-Catalyzed Conjugate Addition to Enones.



Ref. 38

Scheme 19. Amidoarylferrocenyldiphenylphosphine Ligands in the Copper-Catalyzed Addition of Diethylzinc to Enones.

6. Conjugate Additions

6.1. Asymmetric Michael Addition to Enones

Ruthenium complexes of aminophosphines catalyze the asymmetric Michael addition reaction.[15b] A range of such complexes (**Figure 12**) containing borohydride ligands were employed in the addition of dimethylmalonate to 2-cyclohexenone and, in a tandem process, were subsequently used in the asymmetric hydrogenation of the Michael adduct to the alcohol (**Scheme 18**).

The results of the Michael addition reaction clearly showed that catalyst activity and enantioselectivity were sensitive to solvent and ligand structure, respectively. While the activity of all of the catalysts employed in the Michael addition was insensitive to ligand structure, their sensitivity to solvent was pronounced. Enantioselectivity also displayed a strong dependence on solvent as a clear preference for aprotic solvents emerged (strongly coordinating acetonitrile also displayed deleterious effects on enantioselectivity). A pronounced favorable effect of ligand rigidity on enantioselectivity was observed, with the more rigid BINAP-supported catalysts (**61** and **62**) affording the highest enantiomeric excess (≤97%). Furthermore, while (*R*)-BINAP (**61**) provided the *R* product, (*S*)-BINAP (**62**) gave the *S* isomer and the highest ee. In the subsequent hydrogenation, excellent diastereoselectivity was observed as a 30:1 trans:cis ratio was achieved for the alcohol product.

Zhang and co-workers reported on the use of larger-bite-angle aminophosphines in the copper-catalyzed addition of diethylzinc to enones.[37] The performance of the chiral binaphthyl ligands **63** and **64** (**Figure 13**) was evaluated in the conjugate addition of diethylzinc to 2-cyclohexenone and several acyclic enones, including chalcone and substituted chalcones, as well as an entirely aliphatic acyclic enone. In the case of 2-cyclohexenone, Zhang's group found that nonpolar solvents favored higher conversions and enantioselectivities over coordinating solvents. Mixtures of solvents such as toluene–dichloroethane were also effective. Removal of dissociated CH_3CN from the copper precursor $[Cu(CH_3CN)_4]BF_4$ was important in realizing higher conversions and ee's and improved enantioselectivity was also gained from decreasing the temperature. $[Cu(OTf)]_2 \cdot C_6H_6$ was the preferred copper precursor, as it allowed for room-temperature reactions albeit with diminished selectivity. Enantioselectivity was dependent on the ligand:metal ratio and was highest with a ligand:metal ratio of 5:1, but only slightly better than with a ratio of 2.5:1. The methyl-substituted ligand, **64**, gave modest improvements in ee over the unsubstituted analogue **63**. Ligand **64** provided much higher ee's in the alkylation of acyclic enones. The mixed solvent system toluene–dichloroethane was optimal with respect to yield and enantioselection, likely owing to the improved solubility of the substrates. This system proved to be competent in the asymmetric addition of diethylzinc to the entirely aliphatic acyclic enone as well.

A pair of amidoarylferrocenyldiphenylphosphines have also found application in the copper-catalyzed asymmetric addition of diethylzinc to enones (**Scheme 19**).[38] Johannsen and co-workers reported that the alkylated product from the addition of diethylzinc to *trans*-chalcone was obtained in reasonable yields and modest enantioselectivities. A strong dependence on solvent was observed as the highest yield (95%) and ee (58%) were realized in toluene, whereas halogenated solvents resulted in a dramatic reduction in both yield and ee. The better performance by ligand (*S*)-**66** in this alkylation prompted the authors to investigate the asymmetric addition of diethylzinc to the more challenging substrate diethyl ethylidenemalonate. In this case, a conversion of >98% was obtained with moderate enantioselectivity (55%). No dependence on the ligand–metal ratio was observed in either of the enone addition reactions.

Adding to the diversity of scaffolds of aminophosphine ligands for conjugate additions, a series of carbohydrate-based aminophosphines were tested by Diéguez and his team in the copper-catalyzed addition of diethylzinc to 2-cyclohexenone.[39] The furanoside-supported aminophosphines (**Figure 14**) showed good activity, with phosphoramidite **70** being best in this regard (TOF >1200). In these systems, dichloromethane was the preferred solvent giving the highest conversions and enantiomeric excesses (≤63%). The optimal temperature was 0 °C, as either increasing or decreasing the temperature resulted in diminished selectivity. Replacing the *tert*-butyl group at the para position of the biphenyl moiety with a methoxy group resulted in a decreased enantioselectivity. The aminomethyl substituent that gave both the greatest enantioselectivity and TOF was the phenylaminomethyl group. The sense of enantioselectivity was also influenced by the aminomethyl substituent. The more sterically demanding *tert*-butylamino group of ligand **67** gave preferentially the *R* product, while the less demanding isopropylamino and phenylamino substituents of **68** and **69**, respectively, provided the *S* isomer. Ligand **72**, having the opposite configuration at C-3 of the furanoside ring to that of ligand **69**, showed similar activity to **69**, however the enantioselectivity was dramatically reduced (only 8% ee). As mentioned above, phosphoramidite **70** gave the highest reaction rate, but the corresponding enantioselectivity was lower than that of **68** and **69**.

6.2. Asymmetric Addition of Organolithiums to Aldehydes

The asymmetric addition of organolithium reagents to aldehydes is a recent entry into the repertoire of transformations in which aminophosphine ligands play an important role.[7] A series of aminophosphine ligands have been employed in the addition of *n*-butyllithium to benzaldehyde (**eq 13**).[40] A comparison of the aminophosphines with the corresponding ether and thioether ligands showed that the aminophosphines gave comparable high yields of the alcohol in consistently (and sometimes substantially) higher enantiomeric excess (≤98% ee).

7. Cycloaddition Reactions

While a broad range of both metals and ligand scaffolds have been employed in selective cycloaddition reactions,[41] only recently has the potential utility of aminophosphines bearing NH groups come to light. The enantioselective addition of dimethyl maleate to iminoester **73a** is efficiently catalyzed by silver acetate in the presence of ferrocenyl-based aminophosphines (**eq 14**).[42] The significance of this account lies in the fact that incorporation of H, rather than alkyl or aryl substituents, on nitrogen leads to the opposite absolute configuration of the product pyrrolidine **74a** (compare **75a** with **75b**). The ability of the H substituent to participate in substrate–ligand hydrogen bonding is implicated in the observed results. Increasing the steric bulk at phosphorus leads to improved enantioselectivity and the same reversal of configuration (**75c** vs **75d**). The mixed, NHMe-containing ligand, **75e**, gives dramatically reduced enantioselectivity (19%). Lowering the temperature to –25 °C results in greater selectivity than when the temperature is equal to 0 °C. A broad range of iminoesters and dipolarophiles were tested, and successful reversal of absolute configuration was maintained (**eq 15**).[42]

8. Conclusions

Aminophosphines are a highly versatile class of ligands for asymmetric synthesis. While their applications in metal-catalyzed hydrogenations predominate, involvement of these ligands in other

asymmetric processes continues to gather interest. Simplicity and diversity in structure and preparation, coupled with a unique ability to become an integral component in chiral syntheses, guarantee continued development. With the current level of understanding of the role that these ligands assume in catalysis, researchers can apply them in catalytic transformations based on the nature of the substrate of interest. That is, in catalytic transformations where hydrogen-bonding interactions may play a role, aminophosphine ligands should be leading candidates in the ligand selection process.

9. Acknowledgment

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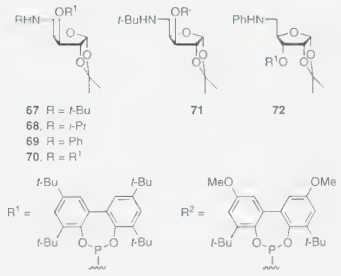
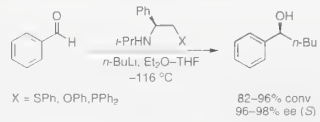


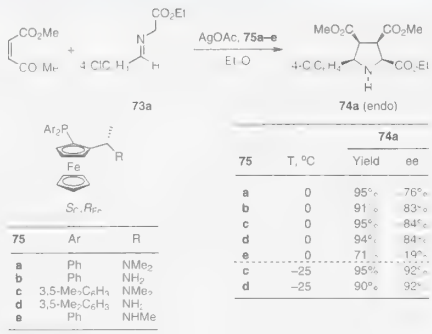
Ref. 39

Figure 14. Furanoside-Supported Aminophosphines for Conjugate Additions.



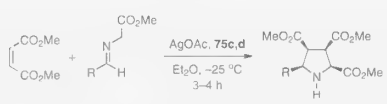
Ref. 40

eq 13



Ref. 42

eq 14



Ref. 42

eq 15

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About the Authors

Dino Amoroso received his B.Sc. degree in chemistry in 1997 from McMaster University. In 2002, he received his Ph.D. degree from the University of Ottawa under the supervision of Professor Deryn Fogg. His graduate studies focused on diversifying ligand scaffolds employed in ruthenium-catalyzed olefin metathesis reactions to affect stereochemical control. After graduation, he moved to industry where he has developed transition-metal catalysts for a range of transformations including olefin polymerization, C–X bond formation, and hydrogenation. He is currently a Senior Research Scientist with Kanata Chemical Technologies (KCT) in Toronto.

Todd W. Graham received his Ph.D. degree in 1999 from the University of Alberta under the supervision of Professor Martin Cowie, studying the synthesis and reactivity of early–late heterobimetallic transition-metal complexes incorporating bifunctional cyclopentadienylalkyldiphenylphosphine ligands. He then joined the group headed by Peter Maitlis and Michael Turner at the University of Sheffield, studying C–C bond forming reactions related to Fischer–Tropsch chemistry. Next, he joined Professor Douglas Stephan's group at the University of Windsor, where he prepared and studied the reactivity of low-valent titanium phosphinimide ($R_3P{=}N$) complexes. He then moved to Professor Arthur Carty's group at the National Research Council of Canada in Ottawa, where he examined the chemistry of electrophilic aminophosphinidene complexes ($L_nM{=}PNR_2$), which are phosphorus analogues of Fischer carbenes. He is currently a Research Scientist at KCT in Toronto, Canada.

Rongwei Guo received his Ph.D. degree in 2002 from Hong Kong's Polytechnic University under the supervision of Professor Albert S. C. Chan. His thesis research focused on the synthesis of novel chiral ligands and their applications in asymmetric catalysis. In 2003, he joined Professor Morris's group at the University of Toronto, where he worked on the enantioselective hydrogenation of C=O and C=N double bonds and the formation of C–C bonds. Since 2005, he has been employed by KCT in Toronto, Canada, where he is currently a Senior Research Scientist.

Chi-Wing Tsang received his Ph.D. degree in 2000 in the field of inorganic clusters from the Chinese University of Hong Kong under the direction of Professor Zuowei Xie. He then joined the research group of Professor Derek Gates at the University of British Columbia as a postdoctoral fellow studying inorganic polymers. He later moved to Ottawa to take up the position of Visiting Fellow at the National Research Council of Canada in the field of metal-containing biodegradable polymers. He is currently a Research Scientist at KCT in Toronto.

Kamaluddin Abdur-Rashid received his Ph.D. degree in 1994 at the University of the West Indies, Mona Campus, Jamaica, under the supervision of Professor Tara Dasgupta. He was a research associate from 1998 to 2002 in Professor Bob Morris's group at the University of Toronto, where he spearheaded the group's quest into pure and applied catalysis research. His discoveries led to the development of new classes of organometallic catalysts and their applications in organic synthesis, including industrial use. In 2004, he founded Kanata Chemical Technologies, Inc., an R&D company that is dedicated to the development and application of innovative catalyst technologies and processes.

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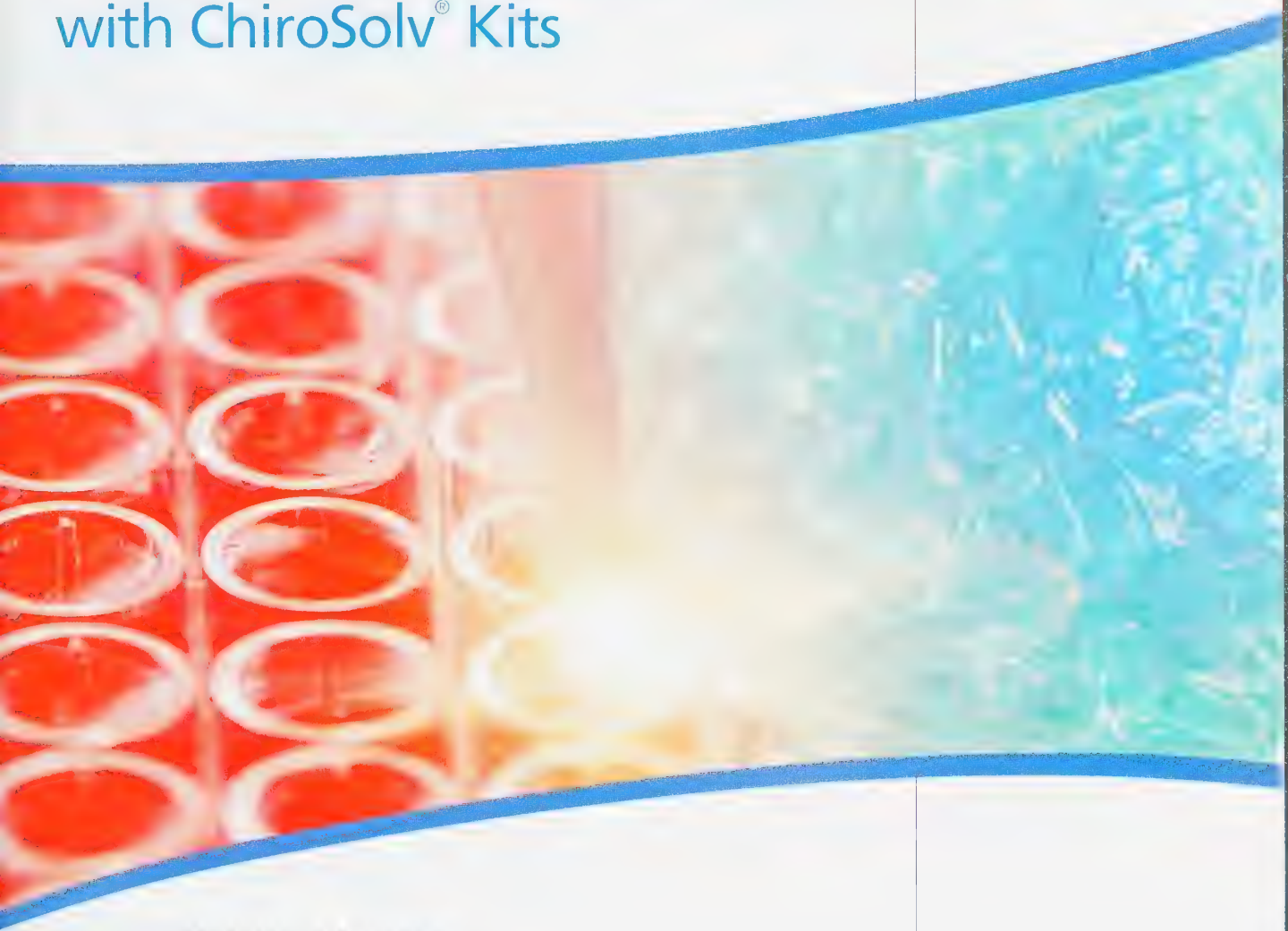

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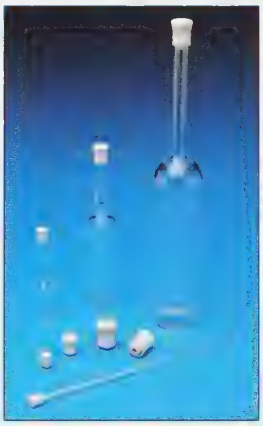

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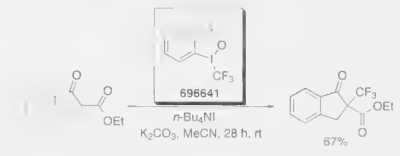


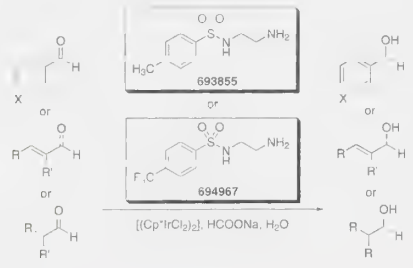
Eisenberger, P. et al. *Chem.—Eur. J.* **2006**, *12*, 2579

3,3-Dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, 97%

696641		250 mg	$71.50
[*887144-97-0*]		1 g	199.00
$C_{10}H_{10}F_3IO$			
FW: 330.09			

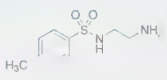
Ligands for Aqueous Transfer Hydrogenation

When used in conjunction with $[(Cp^*IrCl_2)_2]$, the ligands *N*-tosylethylenediamine (Ts(en)) and *N*-(2-aminoethyl)-4-(trifluoromethyl)-benzenesulfonamide (CF_3-Ts(en)) enable the facile and selective transfer hydrogenation of aldehydes with TOFs as high as 1.3×10^5 h^{-1}. Furthermore, the reactions are carried out in aqueous media and exhibit very good chemoselectivity and functional-group tolerance. In cases where α,β-unsaturated aldehydes are employed, reduction occurs selectively on the formyl group. Aliphatic aldehydes are also readily converted when the substrate is added portionwise over the course of the reaction

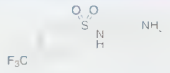


Wu, X. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 6718

***N*-Tosylethylenediamine, 97%**

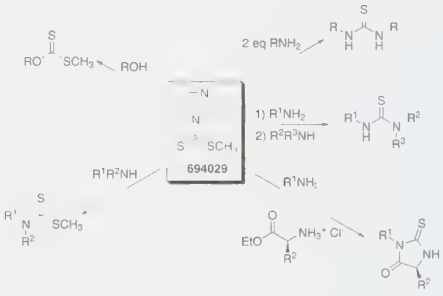
693855		5 g	$57.50
[*14316-16-6*]			
$C_9H_{14}N_2O_2S$			
FW: 214.28			

***N*-(2-Aminoethyl)-4-(trifluoromethyl)benzenesulfonamide, 97%**

694967		500 mg	$49.00
$C_9H_{11}F_3N_2O_2S$			
FW: 268.26			

Thiocarbonyl Transfer Agent

1-(Methyldithiocarbonyl)imidazole is a stable, non-hazardous reagent that can replace thiophosgene, isothiocyanates, chlorothioformates, and other high-hazard reagents as a thiocarbonyl-transfer agent for the synthesis of dithiocarbonates,[1] dithiocarbamates, symmetrical and unsymmetrical thioureas,[2] and 2-thiohydantoins.[3]



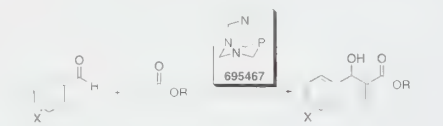
(1) Sun, W. Y. et al. *Synlett* **1997**, 1279. (2) Mohanta, P. K. et al. *Tetrahedron* **2000**, *56*, 629. (3) Sundaram, G. S. M. et al. *Synlett* **2007**, 251

1-(Methyldithiocarbonyl)imidazole, 97%

694029		5 g	$74.50
[*74734-11-5*]			
$C_5H_6N_2S_2$			
FW: 158.24			

Air-Stable, Nucleophilic Alkylphosphine

1,3,5,-Triaza-7-phosphaadamantane (PTA) is a convenient, efficient, and air-stable nucleophilic trialkylphosphine organocatalyst for the Baylis–Hillman reaction. Both aromatic and aliphatic aldehydes react with activated alkenes in the presence of 15–20 mol % of PTA to afford the corresponding adducts in fair-to-excellent yields. Furthermore, PTA displays activity that is superior to that of the structurally similar hexamethylenetetramine.



He, Z. et al. *Adv. Synth. Catal.* **2006**, *348*, 413

1,3,5-Triaza-7-phosphaadamantane

695467		500 mg	$25.00
[*53597-69-6*]		2 g	90.00
$C_6H_{11}N_3P$			
FW: 157.15			

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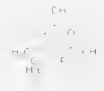
Professor Matthew Clarke of the University of St. Andrews (U.K.) kindly suggested that we make 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane. This phosphine is very stable to air and moisture and has the stereoelectronic properties of bulky phosphonites. When employed with rhodium complexes, this ligand shows high catalytic activity in the hydroformylation of various alkenes. High selectivities and conversions as high as 99% have been reported.

Clarke, M. L.; Roff, G. J. *Chem.—Eur. J.* **2006**, *12*, 7978.



695459	**1,3,5,7-Tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane, 97%**	500 mg 2 g	$52.00 170.00

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

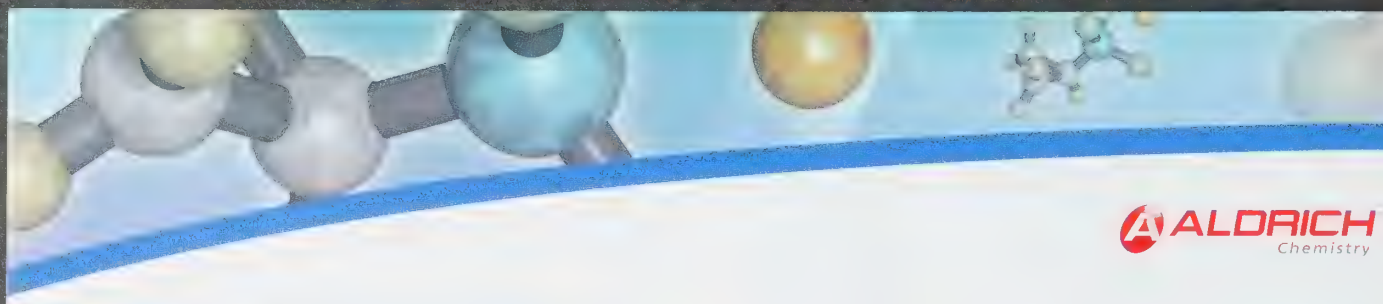
Photograph © Alfred Bader

Landscape with Tobias and the Angel, with a View of Antwerp in the Background (oil on copper, 20.5 × 26.0 cm) was painted possibly around 1665 by Gillis Neyts, an enigmatic Flemish painter and engraver. Neyts (1623–1687) was born in Ghent, and spent a good part of his life in the city of Antwerp. He specialized in small, imaginary landscape scenes, which sometimes incorporated historical material or views of Flemish towns. His style approaches that of Lucas van Uden (1595–1672; Antwerp), who may have been his teacher.

This small painting, with its soft and delicate handling, which was typical for Neyts, shows on the left just below the horizon a part of the skyline of the city of Antwerp. The spectacular form of the arching tree in the center frames the figures of two travelers (with walking sticks) in the foreground on the right. One of them appears to waive at the viewer, while the other—dressed in red and white and with wings rising from his shoulders—is identified as the Archangel Raphael accompanying young Tobias on his journey.

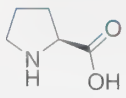
Neyts has painted here a fantasy landscape in which he transposes the ancient story of Tobias and the angel onto a contemporary setting, the outskirts of the 17th-century city of Antwerp. It would appear that Neyts's purpose is to help the viewer of that period identify more closely with the story.

This painting is in the private collection of Isabel and Alfred Bader.



ALDRICH Chemistry

Explore Organocatalysis



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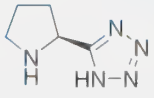

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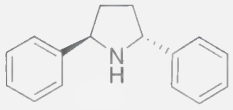

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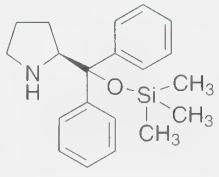

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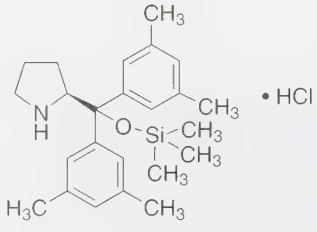
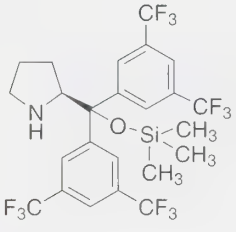


671428



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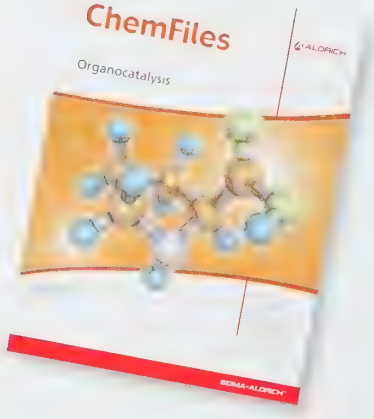

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ASYMMETRIC CATALYSIS WITH TRIP AND NHC–Cu(I)

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ALDRICH Chemistry

TRIP—A Powerful Brønsted Acid Catalyst for Asymmetric Synthesis

N-Heterocyclic Carbene–Copper Complexes: Synthesis and Applications in Catalysis

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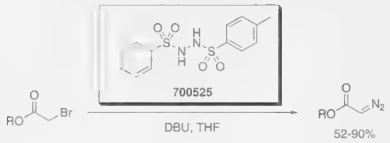
Aldrich Is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Reagent for the Synthesis of Diazoacetates

Diazoacetates are extremely useful reagents for a variety of reactions, such as cyclopropanations and C–H insertions. *N,N'*-Bis-(*p*-toluenesulfonyl)hydrazine is a stable, crystalline reagent that offers a useful alternative to tosyl azide for the production of diazoacetates. A variety of diazoacetates can be synthesized from the corresponding bromoacetates by treatment with *N,N'*-bis(*p*-toluenesulfonyl)-hydrazine in moderate-to-high yields in relatively short reaction times.



Toma, T. et al. *Org. Lett.* **2007**, *9*, 3195

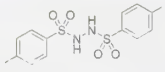
N,N'-Bis(*p*-toluenesulfonyl)hydrazine

700525 1 g $39.50

[*14062-05-6*]

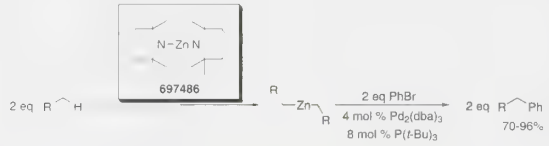
$C_{14}H_{16}N_2O_4S_2$

FW: 340.42



Zn(tmp)$_2$ for the Selective Functionalization of C–H bonds

The selective functionalization of C–H bonds by neutral organozincs has typically been limited to fairly acidic carbon acids due to the slow kinetics of most dialkyl- and diarylzinc reagents. Bis(2,2,6,6-tetramethylpiperidinyl)zinc, Zn(tmp)$_2$, is an effective and versatile base for the mild, selective deprotonation of a broad range of substrates. The resultant organozincs can be conveniently coupled with aryl bromides using typical Pd-catalyzed cross-coupling methods



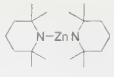
Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105.

Bis(2,2,6,6-tetramethylpiperidinyl)zinc, 0.5 M in toluene

697486 50 mL $165.00

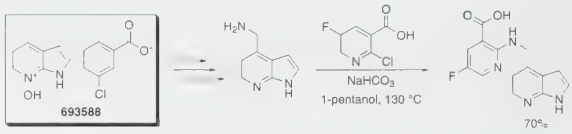
$C_{18}H_{36}N_2Zn$

FW: 345.88



7-Azaindoles

The derivatives of 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) have emerged as an important and promising class of compounds in agrochemistry and medicinal chemistry. Recent years have seen an exponential increase in reports about pharmaceutically active 7-azaindole derivatives in the medicinal chemistry literature. One recent report details the practical synthesis of the key pharmaceutical intermediate 2-[(7-azaindol-4-yl)methylamino]-5-fluoronicotinic acid from the 7-azaindole *N*-oxide MCBA salt, **693588**.



Wang, X. et al. *J. Org. Chem.* **2006**, *71*, 4021.

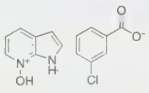
7-Azaindole *N*-oxide 3-chlorobenzoate, 95%

693588 1 g $50.00

[*611197-49-0*]

$C_{14}H_{11}ClN_2O_3$

FW: 290.71



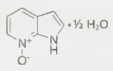
7-Azaindole *N*-oxide hemihydrate, 97%

696838 1 g $62.50

[*55052-24-9*]

$C_7H_6N_2O$

FW: 134.14



4-Chloro-7-azaindole, 97%

696218 250 mg $49.00

1 g 136.00

[*55052-28-3*]

$C_7H_5ClN_2$

FW: 152.58

3-Nitro-7-azaindole

699268 1 g $49.50

[*23709-47-9*]

$C_7H_5N_3O_2$

FW: 163.13

1-Boc-7-azaindole-3-carboxaldehyde

696811 1 g $76.50

[*144657-66-9*]

$C_{13}H_{14}N_2O_3$

FW: 246.26

3-(Dimethylaminomethyl)-7-azaindole, 97%

696846 1 g $64.00

[*5654-92-2*] 5 g 212.50

$C_{10}H_{13}N_3$

FW: 175.23

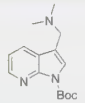
1-Boc-3-[(dimethylamino)methyl]-7-azaindole, 97%

699209 1 g $87.50

[*144657-65-8*]

$C_{15}H_{21}N_3O_2$

FW: 275.35



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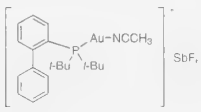
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc

Professor Antonio M. Echavarren from the Institute of Chemical Research of Catalonia (ICIQ) (Tarragona, Spain) kindly suggested that we make (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate. This crystalline gold complex is air-stable and can be handled under ordinary bench-top conditions. The cationic complex is capable of catalyzing various unique intramolecular cyclization reactions.[1–3]

(1) Nieto-Oberhuber, C. et al. *J. Am. Chem. Soc.* **2008**, *130*, 269. (2) Jiménez-Núñez, E. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (3) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105



697575 **(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate** 250 mg $65.00
1 g 235.00

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER


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Camille Pissarro (1830–1903), one of the creators of the impressionist style, painted our cover, *Orchard in Bloom, Louveciennes* (oil on canvas, 45.1 × 54.9 cm) in 1872. Early in his career, Pissarro designated himself a pupil of Corot and, in this painting, Pissarro's broad method of composing and choice of a tranquil rural setting inhabited by a few small peasant figures still recall the older artist

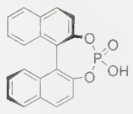
Pissarro completed this work shortly after he had returned to his home in Louveciennes after fleeing France during the Franco-Prussian War and Paris Commune. (Born in the Virgin Islands, then a possession of Denmark, Pissarro was a Danish citizen.) During the war, his house had been used by Prussian troops, and many of the canvases he left there were destroyed. He must have viewed the freshly plowed earth, like the spring blossoms that bring life to the dormant landscape, as a signal of renewed hope for his adopted country and for his career

When the idea arose for a group exhibition of work by the artists who would come to be called impressionists, Pissarro was among the earliest and most enthusiastic supporters Pissarro drafted the group's written statement of purpose and was the only artist to participate in all eight impressionist exhibitions. This painting was one of five he showed at the first exhibition in 1874

This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

ALDRICH Chemistry

Chiral Phosphoric Acids



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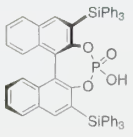

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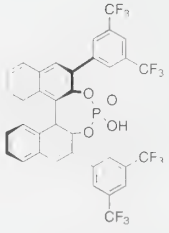

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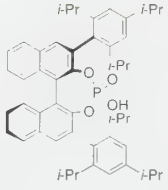

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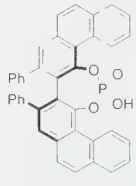

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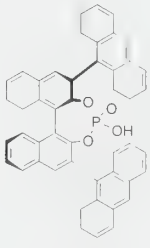

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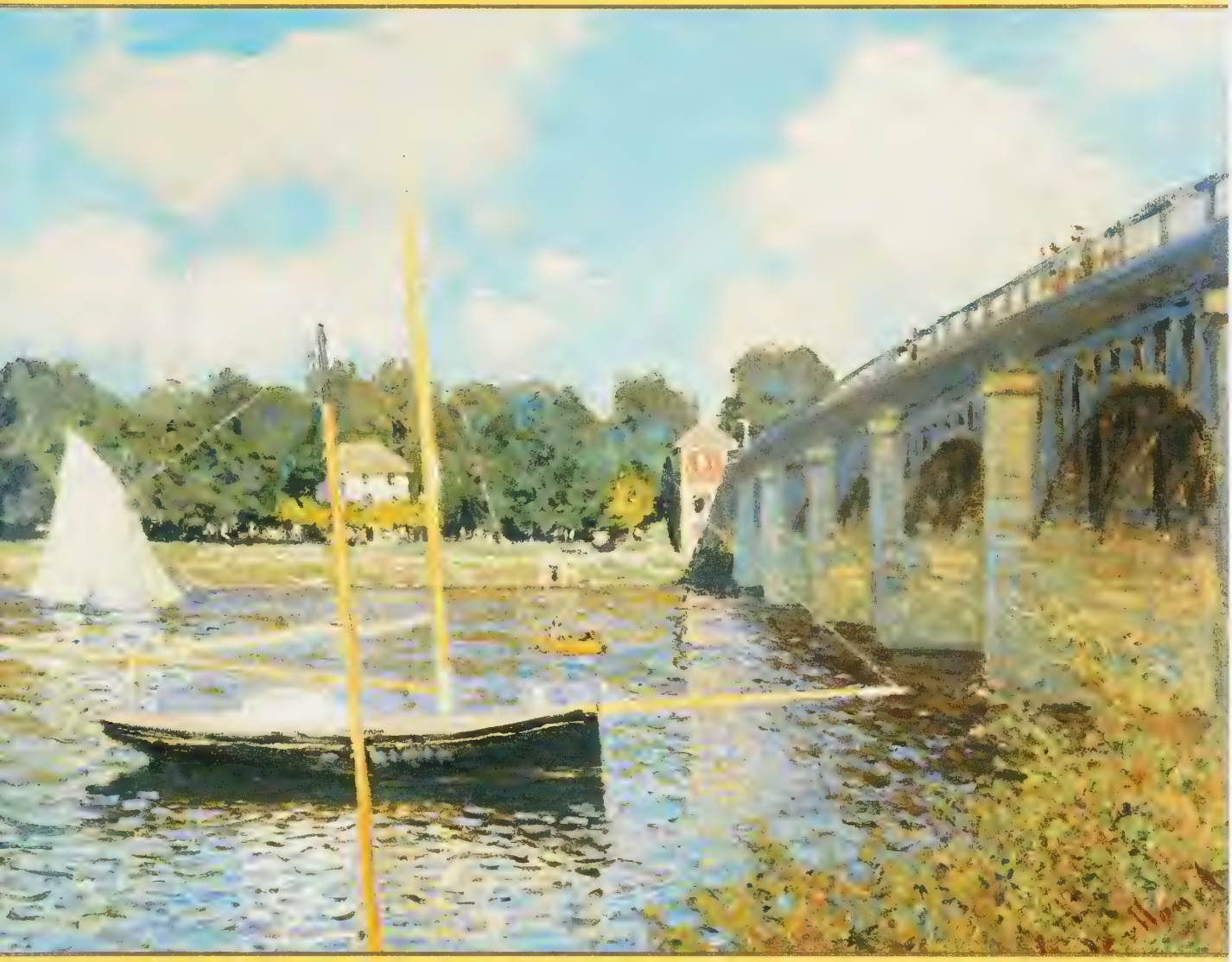
ALDRICH Chemistry



Transition-Metal-Catalyzed Cross-Couplings Going Green: in *Water* at Room Temperature

Preparation of Chiral Diamines by the Diaza-Cope Rearrangement (DCR)

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ALDRICH Chemistry

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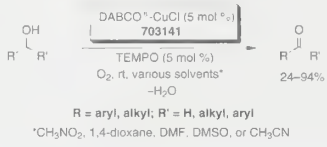


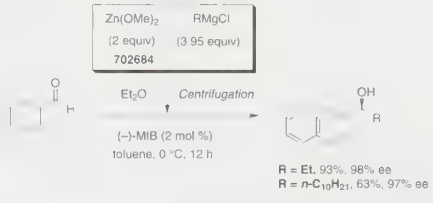
Mannam, S. et al. *Adv. Synth. Catal.* **2007**, *349*, 2253

DABCO®-CuCl Complex

703141	1 g	$49.00
$C_7H_{11}ClCuN_2$		
FW: 211.17		

Reagent for the Preparation of Organozincs

$Zn(OMe)_2$ is an exceptional precursor for the formation of reactive and selective organozinc reagents under salt-free conditions. Historically, the difficulty in preparing organozinc reagents that has prevented their widespread use is due to their highly pyrophoric nature as well as the generation of byproducts. The use of additives, which remove these byproducts, presents other limitations. Therefore, a method to control the solubility of the byproducts so that they can be removed by simple filtration or centrifugation has been developed, and relies on the use of $Zn(OMe)_2$ as a precursor to the organozinc reagent to be formed in solution. Following formation of the active organozinc compound, filtration or centrifugation is followed by the desired organic transformation. Examples of such a transformation include the catalytic enantioselective addition of organozincs to imines, conjugate addition, addition to aldehydes (example below), and addition to β-nitrostyrene.



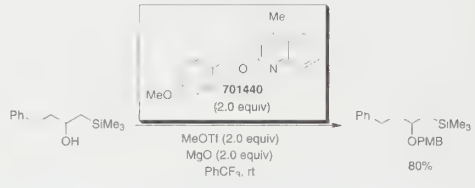
Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771

Zinc Methoxide

702684	1 g	$75.00
$C_2H_6O_2Zn$	5 g	249.00
FW: 127.46		

Reagent for the PMB-protection of Alcohols

Protection with the *para*-methoxybenzyl protecting group (PMB) has been an ongoing challenge in organic chemistry due to the limitations with regard to the reagents that can be used. Common reagents typically require acidic or basic reaction media and present problems that relate to their long-term storage. The lepidine ether below (2-(4-methoxybenzyloxy)-4-methylquinoline) was developed to address some of these limitations and, in combination with MeOTf, affords an active reagent *in situ*. A plethora of alcohols are readily protected under neutral reaction conditions. Additionally, 2-(4-methoxybenzyloxy)-4-methylquinoline is stable, and byproducts generated by its use are easily removed through aqueous workup or chromatography.



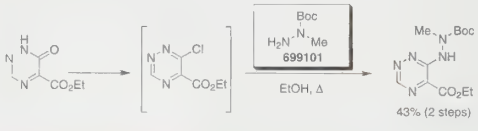
Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436

2-(4-Methoxybenzyloxy)-4-methylquinoline

701440	1 g	$39.00
[*937184-70-8*]	5 g	130.00
$C_{18}H_{17}NO_2$		
FW: 279.33		

Reagent for Selective Methylhydrazine Addition

N-Boc-*N*-methylhydrazine is a useful reagent that can be employed when reaction at the less nucleophilic nitrogen of methylhydrazine is desired. Without protection of the methylated nitrogen with a Boc group, reaction would occur also at the methylated nitrogen. As demonstrated below, reaction of the chlorotriazine provides the corresponding, properly hydrazine-functionalized arene.



Kelly, T. R. et al. *J. Am Chem. Soc.* **2006**, *128*, 5646

1-Boc-1-methylhydrazine

699101	5 g	$56.50
[*21075-83-2*]	25 g	187.50
$C_6H_{12}N_2O_2$		
FW: 146.19		

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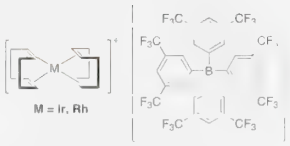

(1) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 280. (2) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063

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Looking at ***The Bridge at Argenteuil*** (oil on canvas, 60 × 79.7 cm) from a distance of ten feet or so, Claude Monet's brushstrokes blend to yield a convincing view of the river Seine and the pleasure boats that drew tourists to Argenteuil. Up close, however, each dab of paint is distinct, and the scene dissolves into a mosaic of paint—brilliant, unblended tones of blue, red, green, and yellow. In the water, quick, fluid skips of the brush mimic the lapping surface. In the trees, thicker paint is applied with denser, stubbier strokes. The figure in the sailboat is only a ghostly wash of dusty blue, and the women rowing nearby are indicated by mere shorthand

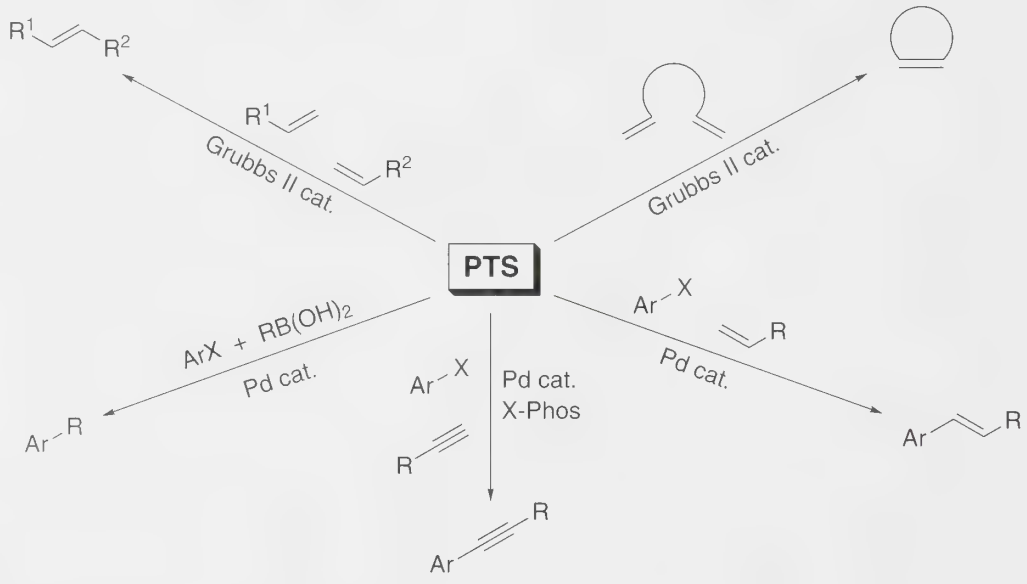
In the early years of impressionism, Monet, Renoir, and others strove to capture the fleeting effects of light and atmosphere on the landscape and to transcribe directly and quickly their sensory experience of it. Monet advised his students, "When you go out to paint, try to forget what objects you have before you, a tree, a house, a field or whatever. Merely think here is a little square of blue, here an oblong of pink, here a streak of yellow, and paint it just as it looks to you, the exact color and shape, until it gives your own naive impression of the scene before you."

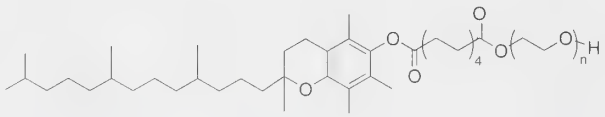
In this early work (1874), Monet (1840–1926) captures a warm, sunny, idyllic day—a motif he used often and for which he became famous. Today, Monet's characteristic style and distinctive brushstroke are still fresh, recognizable, and most popular

This painting is part of the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

PTS—New Amphiphile for Metathesis and Cross-Coupling in Water

Recently introduced by Professor Bruce Lipshutz of UC, Santa Barbara, polyoxyethanyl α-tocopheryl sebacate (PTS) is a nonionic amphiphile that is proving to be a versatile "solubilizer" for organic molecules in water.[1] Lipophilic substrates and catalysts can efficiently enter micelles formed by PTS in water, leading to cross-coupling reactions at room temperature without the need for a co-solvent.[2]





PTS (n = ca. 13)

Polyoxyethanyl α-tocopheryl sebacate, 15 wt. % in H_2O

698717	10 mL	$47.50

(1) Sold under license from Zymes, LLC. (2) (a) Lipshutz, B. H. et al. *Org. Lett.* **2008**, *10*, 1325. (b) Lipshutz, B. H. et al. *Adv. Synth. Catal.* **2008**, *350*, 953. (c) Lipshutz, B. H. et al. *Org. Lett.* **2008**, *10*, 1333. (d) Lipshutz, B. H.; Taft, B. R. *Org. Lett.* **2008**, *10*, 1329. (e) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, in press. (f) Lipshutz, B. H. et al. *Org. Lett.* **2008**, *10*, ASAP.

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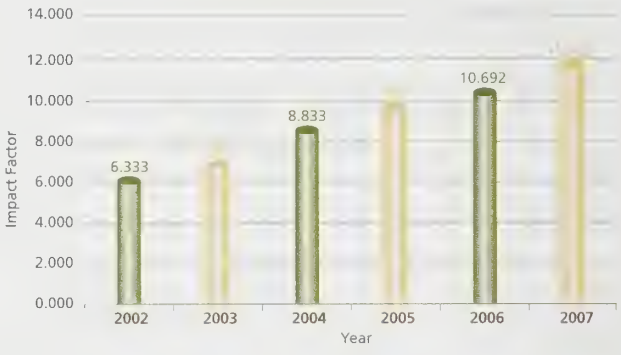

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CARBONYL COMPOUNDS: STILL CENTRAL TO ORGANIC SYNTHESIS

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VOL. 41, NO. 4 • 2008

ALDRICH Chemistry

Formation of C–C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation: Vinylation, Allylation, and Enolate Addition

Amino Carbonyl Compounds in Organic Synthesis

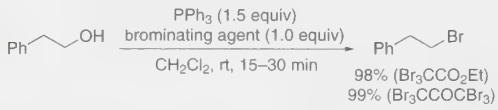
SIGMA-ALDRICH

New Products from Aldrich R&D

Aldrich Is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Reagents for the Bromination of Alcohols

There are various methods for the conversion of alcohols to bromides; however, commonly employed methods either use or generate toxic HBr gas. The use of hexabromoacetone ($Br_3CCOCBr_3$) and ethyl tribromoacetate (Br_3CCO_2Et) as less toxic, milder bromination reagents has recently been reported. Both reagents provide the desired alkyl bromide in excellent yield.



Tongkate, P. et al. *Tetrahedron Lett.* **2008**, *49*, 1146

Ethyl tribromoacetate, 97%

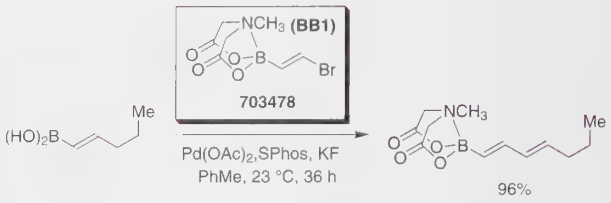
704679	1 g	$34.50
[599-99-5]	5 g	114.50
$C_4H_5Br_3O_2$		
FW: 324.79		

1,1,1,3,3,3-Hexabromoacetone, 97%

702404	5 g	$61.50
[23162-64-3]	25 g	205.00
C_3Br_6O		
FW: 531.46		

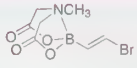
New Boronic Acid Surrogates for Iterative Cross-Coupling

Professor Martin Burke and co-workers at the University of Illinois (Urbana-Champaign) have recently disclosed a technology employing boronic acid surrogates (termed "MIDA boronates") for use in iterative Suzuki cross-coupling reactions. The air-stable, chromatography-compatible, and easily deprotected boron building blocks permit difficult couplings through the attenuation of transmetallation via pyramidalization of the boron atom. The chemistry has been applied to the preparation of polyenyl MIDA boronates, for which the boronic acid counterpart is unstable. This subsequently led to the efficient synthesis of the left half of amphotericin B.



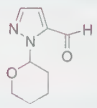
Lee, S. J. et al. *J. Am. Chem. Soc.* **2008**, *130*, 466

trans-2-Bromovinylboronic acid MIDA ester

703478		500 mg	$120.00
$C_7H_9BBrNO_4$		1 g	200.00
FW: 261.87			

New Aldehydes from Aldrich R&D

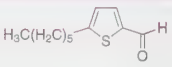
1-(2-Tetrahydropyranyl)-1*H*-pyrazole-5-carboxaldehyde

699365		1 g	$89.50
[957483-88-4]			
$C_9H_{12}N_2O_2$			
FW: 180.20			

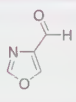
3-Methylpyridine-2-carboxaldehyde, 97%

699071		1 g	$82.00
[55589-47-4]			
C_7H_7NO			
FW: 121.14			

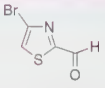
5-Hexylthiophene-2-carboxaldehyde, 97%

699187		1 g	$89.50
[100943-46-2]			
$C_{11}H_{16}OS$			
FW: 196.31			

4-Oxazolecarboxaldehyde, 97%

697915		250 mg	$84.40
[118994-84-6]		1 g	237.50
$C_4H_3NO_2$			
FW: 97.07			

4-Bromothiazole-2-carboxaldehyde, 96%

699284		1 g	$47.50
[167366-05-4]			
C_4H_2BrNOS			
FW: 192.03			

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Joe Porwoll, President
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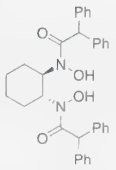
Professor Hisashi Yamamoto of The University of Chicago kindly suggested that we make bis(hydroxamic acid) based ligands, which, in combination with $VO(Oi\text{-}Pr)_3$, generate highly active catalysts for the asymmetric epoxidation of allylic alcohols. Good-to-excellent yields and enantioselectivities of up to 97% ee have been reported.



Zhang, W. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389.

700592 (1*R*,2*R*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(diphenylacetyl)-1,2-cyclohexanediamine, 97% 50 mg $115.00
(*R*)-CBHA-DPA

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(*S*)-CBHA-DPA

Naturally, we made these useful ligands. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington

Pont Neuf, Paris (oil on canvas, 75.3 × 93.7 cm), was painted by the French Impressionist painter, Pierre Auguste Renoir (1841–1919), on a gloriously sunny and warm summer's day in 1872. While Renoir's paintings of women and children are better known, his landscapes resonate with a vigor and freshness new to the art scene at the time

In this painting, Renoir uses a bright, light palette to emphasize an intense midday sun, but he deliberately suppresses incidental detail and clarity, displaying the basic tenets central to the development of Impressionism Although Renoir presents us with an impressionistic view of the scene, the bridge and buildings in the background are accurate enough to be identifiable, then and now

Renoir occupied an upper floor of a café on the left bank of the Seine to depict this famous view of the ninth bridge. Pont Neuf connects the Île de la Cité with the rest of Paris. Edmond Renoir, the artist's younger brother and novice journalist in 1872, later recounted in an interview that he helped his brother by periodically delaying a Parisian on the bridge long enough for the artist to record their appearance. Renoir captures Edmond, walking stick in hand, wearing a light-colored straw hat and slacks and a dark jacket in at least two locations. Can you find him?

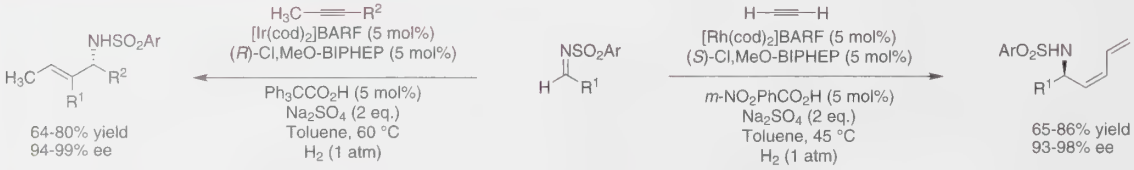
This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

ALDRICH Chemistry

Metal Complexes and Ligands for Enantioselective Reductive Coupling

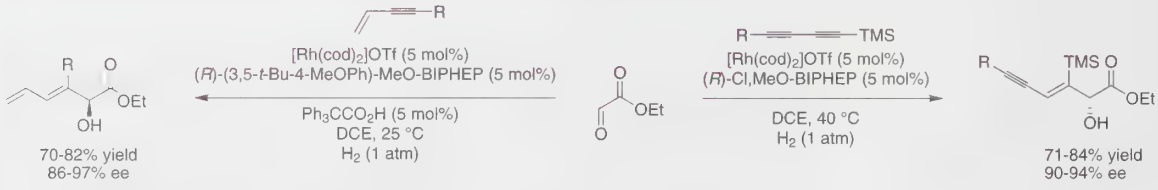
Asymmetric hydrogenation is one of the most utilized reactions to induce chirality in a molecule. It is currently widely used in industry. Krische and co-workers have developed a new type of transformation based on the enantioselective reductive C–C bond formation mediated by hydrogen. Utilizing a rhodium-, iridium-, or ruthenium-based complex with a variety of ligands, Krische and co-workers demonstrated the potency of this reaction for the reductive coupling of conjugated enones, dienes, imines, enynes, and carbonyls. Aldrich is offering a series of complexes and ligands for enantioselective reductive coupling.

Enantioselective Imine Vinylation



Ngai, M.-Y. et al. *J. Am. Chem. Soc.* **2007**, *129*, 12644. Skucas, E. et al. *J. Am. Chem. Soc.* **2007**, *129*, 7242.

Enantioselective Reductive Coupling of Alkynes with Glyoxalates



Hong, Y.-T. et al. *Org. Lett.* **2007**, *9*, 3745. Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873

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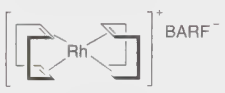

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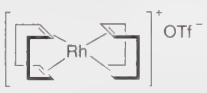

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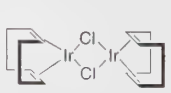

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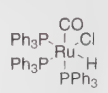

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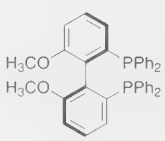

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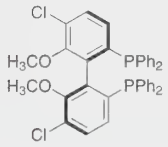
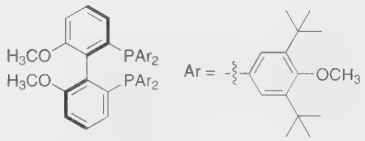
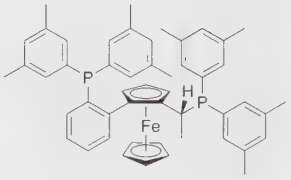
(S)-(–)-MeO-BIPHEP **29511**



(R)-(–)-Cl,MeO-BIPHEP **76854**
(S)-(+)-Cl,MeO-BIPHEP **96738**



(R)-(3,5-*t*-Bu-4-MeOPh)-MeO-BIPHEP **29512**
(S)-(3,5-*t*-Bu-4-MeOPh)-MeO-BIPHEP **29513**



(R)-Xylyl-WALPHOS **65683**
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Aldrichimica ACTA

VOL. 42, NO. 1 • 2009

ALDRICH Chemistry

The Super Silyl Group in Diastereoselective Aldol and Cascade Reactions

Iterative Cross-Coupling with MIDA Boronates: towards a General Strategy for Small-Molecule Synthesis

SIGMA-ALDRICH

Editorial

"Please Call Me Alfred"

On April 28 of this year, Dr. Alfred Bader, undeniably the world's best-known Chemist Collector, celebrated his 85th birthday. Alfred's amazing life story has been covered extensively in books, magazines, and lectures, by Alfred himself and by others, and need not be repeated here. Furthermore, most of our readers are undoubtedly aware of Alfred's strong connections, past and present, not only to Sigma-Aldrich, but also to the *Aldrichimica Acta*, which he has showered with his attention for many years. Many of Alfred's paintings have graced the covers of the *Acta*, including this issue, which is featuring one of Alfred's favorite paintings.

We honor and thank Alfred for his outstanding contributions to Sigma-Aldrich and to the worlds of chemistry, business, and art. To what he calls the "ABC" (Art, Bible, Chemistry) of his life, one should add a "D" for Donating. Alfred's philanthropic activities are considerable and ongoing, and cover a wide range of causes that are near and dear to Alfred's heart.

The magnitude of Alfred's philanthropic efforts was made possible by the considerable financial rewards that he has reaped from two of his lifelong passions. The first is a spectacularly successful chemical business (Aldrich and Sigma-Aldrich) that he helped found and successfully managed for years. The second is his passion for collecting art works, particularly of Dutch and Flemish Masters, as well as rare stamps. His collection of about two hundred such paintings has been donated by Alfred to the Agnes Etherington Art Centre of Queen's University in Kingston, Ontario (Canada). This gift is one of several sizeable ones that he has made to Queen's in gratitude for the education he received there in the 1940s.

Photo Courtesy of Alfred Bader

Dr. Alfred Bader in 2005

Lesser known, but not less important to Alfred, is his Bible scholarship, particularly of Old Testament themes, which he has studied all his life and taught for a good many years. Another lesser known trait of Alfred is his modesty and unassuming lifestyle, which used to lead many a new employee of Aldrich, in the days when Alfred was company president, to think, when running into him for the first time, that he was just another employee. After meeting Alfred for the first time and calling him Dr. Bader, the editor of this publication was gently chided for calling him Dr. Bader, rather than Alfred, which is what he insists on being called even by people who don't know him that well.

On behalf of all Sigma-Aldrich employees, past and present, we wish Alfred a very happy 85th birthday and many more in years to come.

SAFC® Launches New Vendor Audit Services

On March 19, 2009, SAFC® announced details of its new Vendor Audit Services, designed to extend audit reach for customers that need to secure global supply chain integrity through enhanced traceability and quality confirmation for critical raw materials and key intermediates. SAFC's Vendor Audit Services are an extension of in-house auditing programs, and provide pharmaceutical and biotechnology firms with a team of highly trained auditors that have extensive regulatory compliance expertise and are on the ground in local regions, including China

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- ICH Q7A
- GAMP 5
- GLP
- 21CFR58

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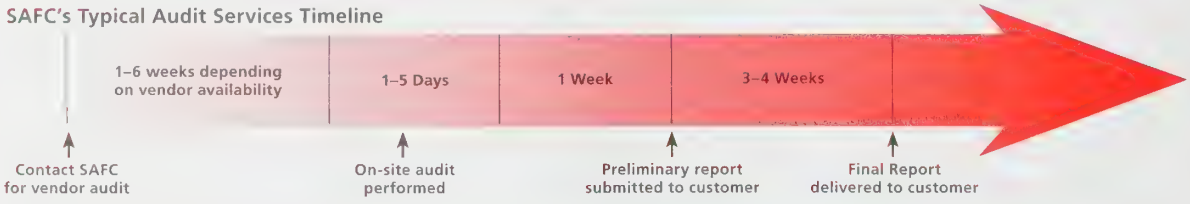

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Aldrichimica Acta

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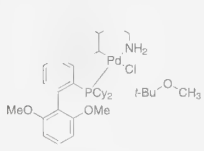
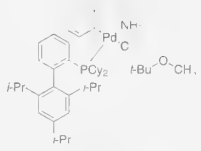
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Stephen Buchwald of the Massachusetts Institute of Technology kindly suggested that we make the single-component palladacycle precatalysts of SPhos and XPhos. These complexes simplify the use of these Buchwald ligands in a pre-defined metal-to-ligand ratio. The precatalysts are air- and moisture-stable, and can achieve high yields in C–N cross-coupling reactions using catalyst loadings as low as 0.1 mol % and 10-minute reaction times.



704946



704954

Biscoe, M. R. et al. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

704946 SPhos-palladium(II)phenethylamine chloride (1:1 MTBE solvate)

250 mg	$45.00
1 g	150.00

704954 XPhos-palladium(II)phenethylamine chloride (1:1 MTBE solvate)

250 mg	$69.00
1 g	190.00

Naturally, we made these useful catalyst precursors. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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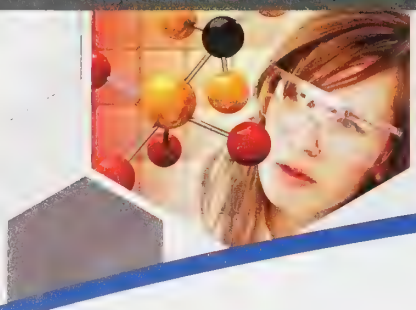
ABOUT OUR COVER

Detail from ***Two Squirrels*** Photograph © Alfred Bader

Two Squirrels (oil on panel, 33.0 × 40.6 cm) was painted around 1616 and is attributed to the Flemish painter Jan Brueghel (or Bruegel) the Elder (1568–1625), also known as "Velvet" Brueghel and "Flower" Brueghel. He was the second son of Pieter Brueghel the Elder and trained with his older brother, Pieter Brueghel the Younger, in the family workshop in Antwerp.

The painting, which reflects the painter's focus later on in life on painting flowers and animals, depicts two sprightly squirrels clutching a gnarly, twisting branch set against an empty sky. This simple, engaging, and humorous depiction of a pair of lively small animals parallels the practice, at that time, of hanging portraits of husband and wife. Its high level of finish suggests that it probably was executed on commission or for sale in the market. The luminous effect created by the thin pigment layers and the fine detail are reminiscent of the style of the Brueghel family.

This painting is part of the Bader Collection of Dutch and Flemish Paintings at the Agnes Etherington Art Centre of Queen's University, Kingston, ON, Canada.



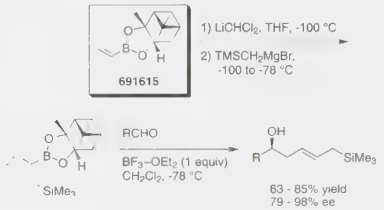
ALDRICH Chemistry

New Products from Aldrich R&D

Aldrich is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Double-Allylation Reagents

Reagents bearing multifunctional handles are of interest for the preparation of complex molecules. Professor Hall and coworkers developed a new multifunctional reagent that provides high diastereo- and enantiocontrol in a number of reactions, such as in the nucleophilic addition to aldehydes.



Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070

(+)-Allylboronic acid pinanediol ester, 97%

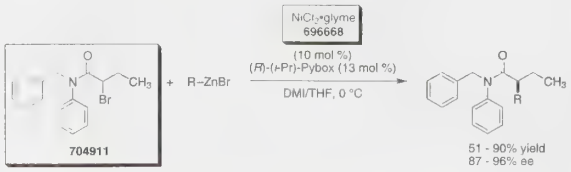
694584		1 g	$34.60
$C_{13}H_{21}BO_2$		5 g	112.00
FW: 220.12			

(+)-Vinylboronic acid pinanediol ester, 95%

691615		1 g	$66.00
$C_{12}H_{19}BO_2$		5 g	218.50
FW: 206.09			

Substrate for Nickel-Catalyzed Negishi Coupling

Chiral building blocks are of the utmost importance in the synthesis of more complex molecules. Professor Fu and coworkers devised the first catalytic enantioselective cross-coupling of secondary α-bromo amides with organozinc reagents. This new method proved to be highly selective for the coupling of unfunctionalized and functionalized organozincs with good yields



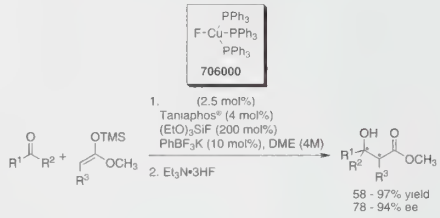
Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594

N-Benzyl-2-bromo-N-phenylbutanamide, 97%

704911		5 g	$65.00
[*851073-30-8*]			
$C_{17}H_{18}BrNO$			
FW: 332.23			

Copper(I) Fluoride Complex for Aldol Reaction

Chiral tertiary alcohols are important building blocks for the synthesis of more complex molecules such as biologically active compounds or potential drugs. Shibasaki and coworkers developed a new copper fluoride catalyzed aldol reaction of ketones using ketene silyl acetals. Various aromatic ketones were screened and led to the desired aldol products in good yields and high selectivity.



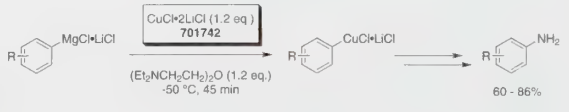
Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164. Taniaphos is a registered trademark of OMG AG and Co.

Fluorotris(triphenylphosphine)copper(I), 95% by HMR

706000		250 mg	$39.00
$C_{54}H_{45}CuFP_3$		1 g	95.00
FW: 869.40			

Copper Chloride–Bis(lithium chloride) Solution for Transmetallation

Cross-coupling reactions are essential tools for chemists. In particular, the amination of aromatic halides has become a method highly relied upon to prepare aryl amines. Knochel and coworkers developed a new general amination procedure using amidocuprates. This method proved to be very versatile resulting in good yields of the amine products. This new method is a good complement to the Pd-catalyzed amination reactions.



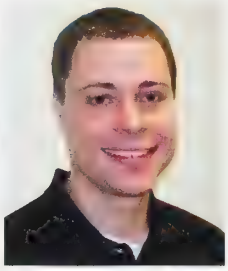
Del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7838.

Copper(I) chloride–bis(lithium chloride) complex, 1 M in tetrahydrofuran

701742		50 mL	$95.00
CuCl•2(LiCl)	CuCl•2(LiCl)		
FW: 183.79			

The Super Silyl Group in Diastereoselective Aldol and Cascade Reactions

Dr. Matthew B. Boxer



Dr. Brian J. Albert

*Matthew B. Boxer, Brian J. Albert, and Hisashi Yamamoto**
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ACS Photo © Peter Cutts Photography, LLC

Professor Hisashi Yamamoto (second from right) receiving the Sigma-Aldrich sponsored *2009 ACS Award for Creative Work in Synthetic Organic Chemistry*. Pictured with Professor Yamamoto are Dr. Thomas H. Lane (right), 2009 ACS President, and Dr. Joseph S. Francisco (left), 2009 ACS President-Elect. Presenting the award on behalf of Sigma-Aldrich is Dr. Mark Redlich (second from left), Product Line Manager, Chemical Synthesis.

Outline

1. Introduction

Silyl groups constitute a very important and distinct class of protective groups and serve as active participants in many thermal, and acid- and base-catalyzed reactions,[1] such as the Mukaiyama aldol, Mannich, Hosomi–Sakurai, and many cyclization reactions.[2] Their unique and important reactivity profile is manifested in several ways: (i) The silyl ethers, silyl enol ethers (SEEs), and allylsilanes of a large variety of substrates can be prepared under mild conditions.[1,3] (ii) A wide stability range exists for the many commercially available silyl-group-containing reagents.[1] Specifically, smaller silyl groups, such as TMS and TBS, can be cleaved under certain acidic or basic conditions, while larger silyl groups, like TIPS and TPS, are stable to those same conditions, This difference in reactivity allows for the development of selective protection–deprotection strategies. (iii) The particularly low electronegativity of silicon (1.8 vs 2.5 for carbon on the Pauling electronegativity scale) permits the stabilization of positive charges on silicon, while its large size (compared to carbon) stabilizes negative charges through polarization.[2,4] These properties, combined with their aforementioned thermal and chemical stabilities, have made silyl groups remarkably useful in many synthetic reactions. Lastly, one of the most distinct features of silyl groups is their facile and selective cleavage by the fluoride ion—conditions that generally do not affect the rest of the organic molecule.[1]

One silyl group that has been occasionally employed as a protective group, but rarely outside of radical reactions, is tris(trimethylsilyl)silyl {$[(CH_3)_3Si]_3Si$; TTMSS}, which is also known in the literature as the hypersilyl, sisyl, or super silyl group. In this review, we will use the term super silyl that was coined by Hans Bock in 1993.[5] Our group has found that the super silyl group exhibits peerless reactivity in a variety of diastereoselective C–C-bond-forming reactions,[6] which is the main topic of this article, as it has not been reviewed to date.

While many literature reports of the application of the super silyl group in chemistry have been published, the majority (61%) of these reports involve its use in radical reactions (**Figure 1**).[7] Tris(trimethylsilyl)silane (TTMSSH) won Fluka's Reagent of the Year Prize in 1990 for its use in radical reactions as an alternative to the toxic $(n\text{-Bu})_3SnH$. By substituting the three alkyl groups of a silane with three TMS groups, a Si H bond weakening of 11 kcal/mol is observed ($\Delta_f H^\circ$: TESH = 90 kcal/mol vs TTMSSH = 79 kcal/mol).[8] TTMSSH has been employed in hydrosilations of alkenes and alkynes,[9–11] radical cyclization reactions,[9] the reduction of acid chlorides,[9e] the hydrosilation of carbonyl groups,[9a,12] and the reduction of carbon–halogen bonds.[9b]

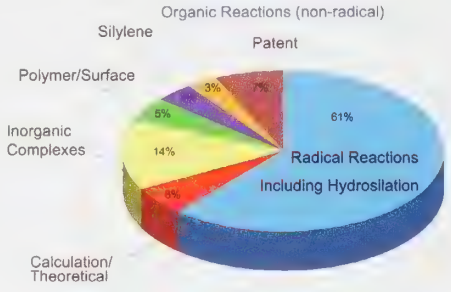
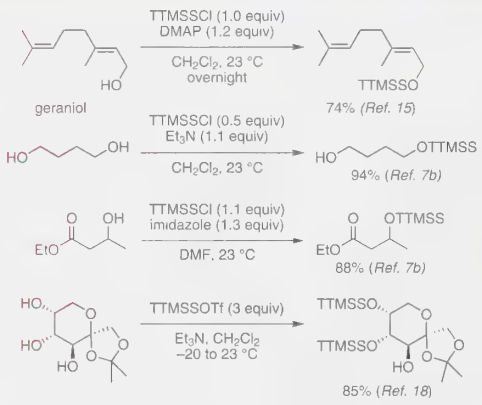
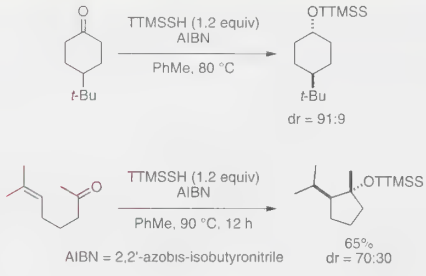


Figure 1. Pie Chart Showing the Breakdown by Application of Literature References Citing the Tris(trimethylsilyl)silyl (TTMSS) Group. *(Ref. 7)*



Scheme 1. Synthesis of Super Silyl Ethers under Standard Conditions.



Scheme 2. Radical Hydrosilylation Reactions. *(Ref. 12)*

The second most commonly reported application of the super silyl group deals with its complexation with transition metals and main group elements (14%).[13] Its extremely bulky size and electron-donating ability stabilize metals and main group elements in various oxidation states. In 2004, Kornev published a review on the tris(trimethylsilyl)silyl group, with emphasis on its complexation with transition metals and main group elements and on its application in radical reactions.[13c]

Surprisingly, the employment of the super silyl group in nonradical, standard acid–base, catalytic, and thermal reactions comprises only around 3% of the total literature.[13c,14,15] Much of this 3% is devoted to papers describing its photochemical and strong-acid- or strong-base-induced rearrangements, which are rarely accompanied by C–C-bond formation. A small portion of the 3% is devoted to its application as an alcohol protecting group.[15] Recently, the super silyl group has been incorporated into organic catalysts to increase their steric requirement and selectivity.[16]

The major structural difference between the super silyl group and the more typical silyl groups, which all contain only Si–C and Si–O bonds, is the presence of the Si–Si bonds. A number of experimental and theoretical calculations attribute many of the unique properties of this silyl group to its Si–Si bonds,[17] which render it UV active (allowing for straightforward TLC analysis) and impart other distinct electronic properties. These unique characteristics are demonstrated in the thoroughly studied polysilanes and oligosilanes, where the electrons are actually delocalized along the Si–Si σ bonds.[17] In these cases, photolysis reactions arise by promoting an electron from a σ orbital to the σ* orbital, which often takes place with remarkably low excitation energy (320 nm).

Recently, the unique reactivity of the super silyl group has led to its successful application in a variety of C–C-bond-forming reactions: [2 + 2] cyclizations, Mukaiyama aldol synthesis, and various sequential reactions.[6]

2. Installation of the Super Silyl Group

The protection of alcohols with the super silyl group can be easily achieved under standard conditions (**Scheme 1**).[7b,15,18] Brook and co-workers have demonstrated that protection of various primary and secondary alcohols can be accomplished using 1 equivalent of the alcohol, 1 equivalent of super silyl chloride, and 1.2 equivalents of DMAP.[15] We have found that unhindered primary alcohols can be efficiently protected by employing super silyl chloride and triethylamine in either THF or CH_2Cl_2.[7b] We have also been able to protect β-hydroxy esters using super silyl chloride and imidazole in DMF.[7b] Super silyl triflate has also been utilized in conjunction with triethylamine to selectively protect carbohydrates.[18]

Because of the ability of TTMSSH to participate in hydrosilation reactions, the radical reaction conditions shown in **Scheme 2** have been utilized to prepare super silyl ethers in one step from carbonyl compounds.[12]

The initial synthesis of the first super silyl enol ether (super SEE) utilized an *n*-BuLi induced THF fragmentation to generate the lithium enolate of acetaldehyde (**Scheme 3**).[19] The synthesis of super SEEs evolved over time to use a metal–halogen exchange of AgOTf and TTMSSCl to generate the silyl triflate, which was then employed under soft enolization conditions to form **1**. The synthesis of TTMSSOTf was further modified

and took advantage of a triflic acid–super silane reaction that liberated H_2 gas and generated the silyl triflate in situ, which was again utilized to prepare **1**.[6a-c]

3. [2 + 2] Cyclizations

The cyclobutane ring is found in various natural and unnatural bioactive molecules, and is commonly found in synthetic intermediates as well.[20] There is only a limited number of reports of efficient syntheses of this 4-membered ring by non-photochemical [2 + 2] cycloadditions,[20–22] in large part because one of the synthetic routes, the concerted cyclization, is disallowed by the Woodward–Hoffmann rules.[23] Thus, both thermal and ground-state catalytic reactions must proceed stepwise, which forms the basis for the proposed Michael aldol mechanism (**Scheme 4**).[6a,22a] This mechanism invokes a zwitterionic Michael addition intermediate, **A**, which may be present long enough to give rise to undesirable side-products. The use of aldehyde enol equivalents for this type of reaction had been previously unattainable, presumably due to this fact.

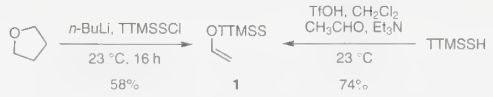
Takasu, Ihara, and co-workers have published numerous reports on formal [2 + 2] cyclizations of SEEs derived from ketones.[22] Their original report took advantage of in situ SEE formation with a TMSI–HMDS system and the use of a chiral auxilliary (8-phenylmenthyl ester).[22a] They later employed preformed TBS and TIPS enol ethers in cyclizations with hexafluoroisopropyl acrylate catalyzed by $EtAlCl_2$,[22e,d] which worked well for forming cyclobutane-containing products including 5,4-, 6,4-, 7,4-, and 8,4-fused bicyclic compounds. A few years later, they reported the use of a strong Brønsted acid, Tf_2NH, to effect the [2 + 2] cyclization of SEEs and methyl acrylate.[22c]

The same research group also investigated formal [2 + 2] cyclizations of α,β-unsaturated esters with acetaldehyde-derived SEEs, and reported that TBS[22d] and TIPS SEEs[22c] failed to give any desired products (**eq 1**). To prevent side reactions potentially stemming from high-energy intermediates such as **A**, it was envisaged that a bulky super silyl group, such as **1**, could stabilize and "shield" **A** from undesired reactions and decomposition. Fortunately, using **1**, hexafluoroisopropyl acrylate, and $EtAlCl_2$ as catalyst gave the desired cyclobutane in 45% yield with low diastereoselectivity.[6a] Interestingly, the use of the pentamethyldisilyl (PMDS) derived enol ether **2**, containing one Si–Si bond, also afforded the cyclobutane adduct, albeit in 7% yield. The effect of the R group of the ester was investigated next: aliphatic esters gave no product, whereas phenyl acrylate gave the best yield and diastereoselectivity.

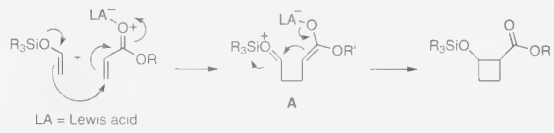
Various Lewis acids were screened, but only the $EtAlCl_2$-based catalyst gave acceptable results, while $TiCl_4$, $GaCl_3$, $SnCl_4$, $AgNTf_2$, TMSOTf, and $HNTf_2$ all gave <10% of the desired product. It has been observed that unwanted transfer of silyl groups during attempted asymmetric aldol synthesis could be prevented by using a bulky Lewis acid with the triflimide counteranion.[24] The use of bulky catalysts based on the methylaluminum bis(2,6-diphenylphenoxide) (MAPH)[25] scaffold were also investigated. The best result was obtained with bis(2,6-diphenylphenoxide) aluminum triflimide (BDAT).

Both aldehyde- and ketone-derived super SEEs were shown to succeed in this system. The reaction proceeded smoothly in all cases at –40 °C with a 3 mol % catalyst loading and gave high yields with high trans:cis ratios (**eq 2**).[6a] Acetaldehyde SEE afforded cyclobutane **4** with a >99:1:0:0 dr by use of the chiral *trans*-(1*R*,2*S*)-2-phenylcyclohexanol derived ester (entry 2). SEE **5** led to *gem*-dimethylcyclobutane **6**, with excellent stereoselectivity (entry 3), while super SEE **7** gave cyclobutane **8**, which contains a chiral quaternary carbon (entry 4). Interestingly, the highest yield (94%) and excellent selectivity were observed for cyclohexanecarboxaldehyde SEE **9** (entry 5). Three contiguous stereocenters were formed with excellent diastereoselectivity from the reaction of *E*-**11** with phenyl acrylate (entry 6).

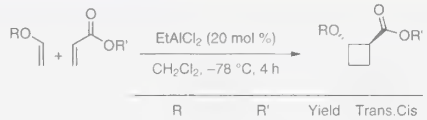
The significance of these super SEEs was clearly demonstrated by their success in the [2 + 2] cyclizations. That is, these examples represented the first formal [2 + 2] condensations between an acetaldehyde SEE and an acrylic



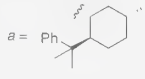
Scheme 3. Evolution of the Synthesis of Super Silyl Enol Ether **1**. *(Ref. 6a-c, 19b)*



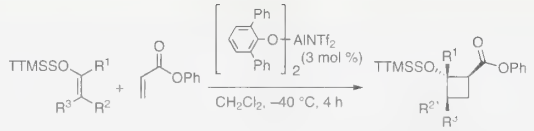
Scheme 4. Proposed Michael Aldol Mechanism for the Formal [2 + 2] Cyclization. *(Ref. 6a, 22d)*



R	R'	Yield	Trans:Cis
TBS	*a*	0%	-----
TIPS	$(CF_3)_2CH$	0%	-----
PMDS (**2**)	$(CF_3)_2CH$	7%	1.5:1
TTMSS (**1**)	$(CF_3)_2CH$	45%	2.0:1
TTMSS (**1**)	Et	0%	-----
TTMSS (**1**)	Ph	58%	5.0:1

a = 

eq 1 *(Ref. 6a, 7b, 22d)*



1, 5, 7, 9, 11 **3, 4, 6, 8, 10, 12**

No	R^1	R^2,R^3	Yield	Trans:Cis
3	H	H,H	84%	10:1
4	H	H,H[a]	81%	>99:1:0:0
6	H	Me,Me	91%	>99:1
8	Me	H,H	81%	25:1
10	H	$(CH_2)_5$	94%	>99:1
12	H	Me,H[b]	93%	>99:1

[a] *trans*-(1*R*,2*S*)-2-Phenylcyclohexyl acrylate was used. [b] *E*:*Z* (of starting silyl enol ether **11**) = 92:8

eq 2 *(Ref. 6a)*

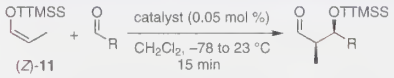
ester. The necessity of the Si–Si bonds for these reactions was a first indication of the distinctiveness of the super silyl group in Lewis acid catalyzed reactions.

4. The Mukaiyama Aldol Reaction

The aldol reaction has emerged as a regular method for forming β-hydroxy carbonyl and/or 1,3-diol motifs typically seen in polyketides.[26] Of the various examples, a great deal utilize an ester, thioester, or ketone enolate (or enolate equivalent) as the nucleophile to circumvent problems associated with the aldehyde crossed aldol reaction. Frequently, the resulting products are reduced to the desired hydroxy-protected aldehydes through an additional one- or two-step procedure. Since Mukaiyama's seminal report on the titanium-catalyzed reaction of SEEs with aldehydes and ketones,[27] the Mukaiyama aldol reaction has developed into one of the most powerful and best-known synthetic reactions.[28] With a large number of reviews and books published in this area, this section will focus mainly on the aldehyde crossed aldol reaction.

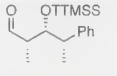
4.1. α-Substituted Enol Ethers

Although the Mukaiyama aldol synthesis is one of the most powerful variants of the aldol reaction, the aldehyde crossed aldol reaction has only been realized in a few cases, many of which are limited in scope.[29–31] In 1974, Mukaiyama followed his archetypal report with two examples of the isobutyraldehyde SEE crossed aldol reaction.[29b] This system took advantage of the fact that neopentyl aldehydes were formed after the first aldol reaction and, thus, further aldol reactions were retarded.

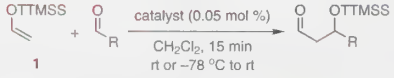


(*Z*)-**11**

R	Catalyst	Yield	Syn:Anti
n-Hep	$HNTf_2$	82%	80:20
n-Hep	$TTMSSNTf_2$	85%	79:21
Cy	$HNTf_2$	72%	85:15
Cy	$TTMSSNTf_2$	71%	82:18
t-Bu	$HNTf_2$	78%	95:5
t-Bu	$TTMSSNTf_2$	79%	95:5
(*S*)-PhCH(Me)	$HNTf_2$	84%	>95:5:0:0[a]
(*S*)-PhCH(Me)	$TTMSSNTf_2$	87%	>95:5:0:0[a]

[a] Ratio for 

eq 3 *(Ref. 6b)*



1

R	Catalyst	Yield	Syn:Anti
n-Hep	$HNTf_2$	87%	----
n-Hep	$TTMSSNTf_2$	85%	----
Cy	$HNTf_2$	89%	----
Cy	$TTMSSNTf_2$	86%	----
t-Bu	$HNTf_2$	90%	----
t-Bu	$TTMSSNTf_2$	91%	----
(*E*,*E*)-MeCH=CHCH=CH	$HNTf_2$	78%	----
(*E*,*E*)-MeCH=CHCH=CH	$TTMSSNTf_2$	75%	----
Ph	$HNTf_2$	83%	----
Ph	$TTMSSNTf_2$	87%	----
(*S*)-PhCH(Me)	$HNTf_2$	86%	>95:5
(*S*)-PhCH(Me)	$TTMSSNTf_2$	85%	>95:5
(2*R*)-EtCH(Me)	$HNTf_2$	93%	86:14
(2*R*)-EtCH(Me)	$TTMSSNTf_2$	90%	85:15
(2*S*)-MeCH(OTIPS)CH_2	$HNTf_2$	88%	85:15
(2*S*)-MeCH(OTIPS)CH_2	$TTMSSNTf_2$	89%	88:12

eq 4 *(Ref. 6b,7b)*

In 2001, Denmark reported that trichloro SEEs of propanal and heptanal successfully reacted with aromatic and aliphatic aldehydes in an enantioselective fashion catalyzed by a chiral phosphoramide base.[30g] The diastereoselectivity was controlled by the enol geometry, with the *Z* enols giving high syn selectivity and the *E* enols giving high anti selectivity.

Later use of α-substituted aldehydes took advantage of in situ enolate formation. In 1980, Heathcock reported the use of the in situ formed lithium enolate of propanal, which gave low selectivity when reacted with benzaldehyde.[30a] In 1983, Kato and Mukaiyama reacted an in situ generated tin enolate of isobutyraldehyde with a variety of aryl and alkyl aldehydes.[29c] Mahrwald's[30b,d] and Oshima's[30e,f] groups utilized in situ formed titanium enolates for reaction with a variety of aldehydes.

After MacMillan's seminal report on the enantioselective proline-catalyzed aldehyde crossed aldol reaction,[31a] an explosion of variants of this reaction emerged. Publications from Jørgensen, Córdova, and Barbas all employed proline-based catalysts to effect the direct aldehyde crossed aldol reaction of α-alkyl-substituted aldehydes.[31]

In 2006, our group published a diastereoselective reaction that worked very well with propionaldehyde-derived super SEE (*Z*)-**11**.[6b] High yields and good syn:anti ratios were obtained using $HNTf_2$ as the precatalyst. This Brønsted acid is termed the precatalyst due to the fact that the use of $(TTMSS)NTf_2$ (0.05 mol %) as the catalyst in all reactions shown in equations 3 and 4 led to results identical to those obtained using $HNTf_2$, implying that the silyl triflimide is likely the true catalyst (see Section 7 for the proposed protodesilylation mechanism). Aliphatic and branched aldehydes successfully underwent this reaction, generating aldolates in moderate-to-high diastereoselectivities (**eq 3**).[6b] The use of (*S*)-2-phenylpropanal exhibited high Felkin control in conjunction with syn selectivity, providing three adjacent stereocenters. Importantly, this provides a complementary method to the anti selectivity obtained by MacMillan.[31a]

4.2. Acetaldehyde-Derived Enol Ethers

Interestingly, the direct installation of acetaldehyde had not been described in any *broad* sense before 2006. In 1958, Leech and co-workers reported the condensation of an alkyl vinyl ether with an aldehyde catalyzed by BF_3.[29a] Paterson et al. later utilized the TBS enol ether of acetaldehyde in a reaction with a highly electrophilic oxonium ion in the presence of super stoichiometric $Cl_2Ti(O\textit{i}\text{-}Pr)_2$.[32] There are a few reports on the use of the enzyme 2-deoxyribose-5-phosphate aldolase (DERA) for the aldol reaction of acetaldehyde with various aldehydes; however, the observed yields are rather low.[33]

Denmark and Bui have reported a chiral-phosphoramide-catalyzed enantioselective aldol reaction of the TMS-SEE of acetaldehyde with aldehydes.[30b] High enantioselectivities and good yields were obtained for a variety of aryl aldehydes, but the products were isolated as the dimethyl acetals after addition of MeOH followed by $NaHCO_3$ to the reaction mixture.

In 2006, our group reported a broad, highly diastereoselective, aldehyde crossed aldol reaction of acetaldehyde super SEEs (**eq 4**).[6b,7b] The use of $HNTf_2$ as the precatalyst gave consistently high yields of the aldol products with aliphatic, branched, aryl, and even α,β-γ,δ-unsaturated aldehydes. Moreover, (*S*)-2-phenylpropanal was tested and showed extremely high Felkin selectivity. Somewhat amazingly, good selectivity was

obtained in the reaction with 2-methylbutanal, demonstrating the ability of this reaction to differentiate between methyl and ethyl groups. Syn selectivity was observed for the reaction of **1** with a β-siloxy aldehyde, in contrast to previous studies by Evans and co-workers, wherein anti selectivity was observed for the open-transition-state Mukaiyama aldol additions to β-alkoxy aldehydes.[34] The syn selectivity observed in our system is proposed to arise from the size of the TIPS and super silyl groups, whereas the study reported by Evans dealt with much smaller β-alkoxy aldehydes. A more detailed discussion of these observations, including DFT calculations, is presented in Section 8.

Recently, acetaldehyde has been introduced through the Mannich reaction. A singular example was given in the $Yb(OTf)_3$ catalyzed reaction of vinyloxytrimethylsilane.[35] List later published a paper on the direct use of acetaldehyde under proline catalysis.[36] While yields were relatively low, enantiomer ratios were very high for a range of substrates.

4.3. Ketone-Derived Super Silyl Enol Ethers (SEEs)

Ketone-derived super SEEs were also examined in simple Mukaiyama aldol reactions.[6f] The acetone-derived super SEE gave exceedingly high Felkin selectivity with 2-methylbutanal and 2-phenylpropionaldehyde (**Scheme 5**). The reaction of cyclohexanone super SEE with isobutyraldehyde gave the aldol product in high yield and unprecedented high anti selectivity for this type of Mukaiyama aldol reaction. This is in stark contrast to the TBS and TMS SEEs of cyclohexanone, which have been reported to give little-to-no selectivity in aldol reactions with a variety of catalysts.[37]

5. Sequential Aldol–Aldol Reactions

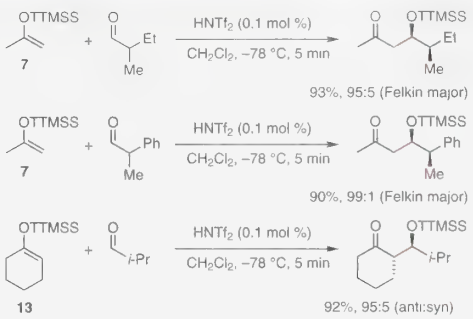
For many obvious and necessary reasons, there is considerable interest in economical and environmentally friendly reactions.[38,39] In this vein, one-pot, sequential and multicomponent reactions have emerged as an important means for accomplishing some of these goals. As Tietze and Beifuss wrote in a review on sequential reactions,[39] "if we compare our synthetic performance to date with that of Nature, then we must recognize that Nature is not just highly selective, but also very efficient, often employing sequential transformations. By this we understand a series of reactions steps in which several bonds are formed or broken, without the isolation of any intermediates". They later go on to say, "the quantity of solvents and eluents required in comparison with stepwise processes is considerably reduced. Sequential reactions should, therefore, be more frequently included in future synthetic planning". The use of sequential reactions not only saves bulk materials, but also time and labor.

Aldol–aldol reactions that incorporate more than three equivalents of starting aldehyde in the product have been described in discussions of aldolase-catalyzed reactions.[33,40] As previously mentioned, these systems suffer from low yields and limited applicability. MacMillan expanded his proline-catalyzed aldehyde crossed aldol reaction to include a two-step synthesis of enantiopure hexoses.[41,42] This elegantly designed system took advantage of the enantioselective aldol dimerization of α-siloxy- and α-benzyloxy aldehydes under proline catalysis. Various α-heteroatom-substituted TMS enol ethers were then added under $TiCl_4$ catalysis to give the cyclized hexoses in diastereo- and enantiomerically enriched forms, thereby providing an excellent means for protective-group control in ^{13}C-labelling experiments. Leighton and co-workers later used strained silacycles for a one-pot, ketone enol, aldol–aldol reaction, which provided hemiketal products containing two chiral quaternary carbon stereocenters.[43]

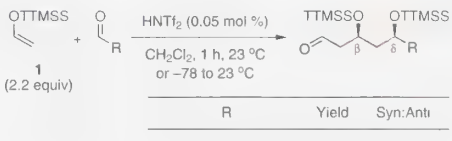
5.1. Cascade Reactions of Aldehyde-Derived SEEs

Our group described a cascade aldol reaction, later termed sequential aldol–aldol (SAA) reaction.[6b] Interestingly, this reaction stops at the 2:1 adduct (SEE:starting aldehyde) stage even when an excess of super SEE is employed. It is believed that after the first addition and silyl transfer, the steric encumbrance of the super silyl group kinetically slows down the addition of a second equivalent of SEE to a rate that does not compete with the rate of the first addition. When all of the aldehyde starting material has been consumed, a second addition occurs giving the 2:1 adducts with high diastereoselectivity. After the second aldol reaction, the substrate has two super siloxy groups (at the β and δ positions), and a third aldol reaction would require the coordination of a third super silyl group (as the catalyst), which should significantly slow the third aldol reaction due to steric hindrance.

The SAA reaction succeeded in generating a variety of protected β,δ-dihydroxy aldehydes in good yields and selectivities (**eq 5**).[6b] Pival- and cyclohexyl aldehydes showed comparable selectivities. Octyl aldehyde led to a slightly lower selectivity, while (*S*)-2-phenylpropanal resulted in high selectivity for the all-syn isomer. The β-TIPSoxy aldehyde afforded the all-syn protected β,δ,ζ-tris-siloxy aldehyde, and



Scheme 5. Mukaiyama Aldol Reactions of Ketone-Derived Super SEEs. *(Ref. 6f)*



R	Yield	Syn:Anti
t-Bu	75%	>99:1
Cy	72%	95:5
n-Hep	68%	90:10
(*S*)-PhCH(Me)[a]	74%	86:13:<1:<1
(*S*)-MeCH(OTIPS)CH_2	64%	----
rac-BnOCH(Me)	61%	----

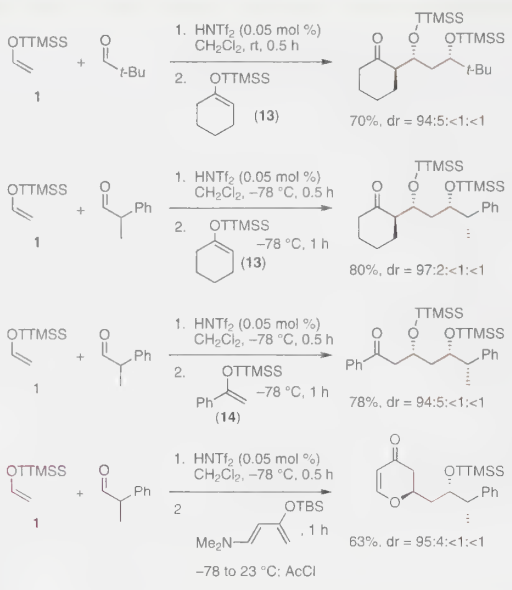
[a] Major product has the opposite configuration at the β and δ carbons

eq 5 *(Ref. 6b)*

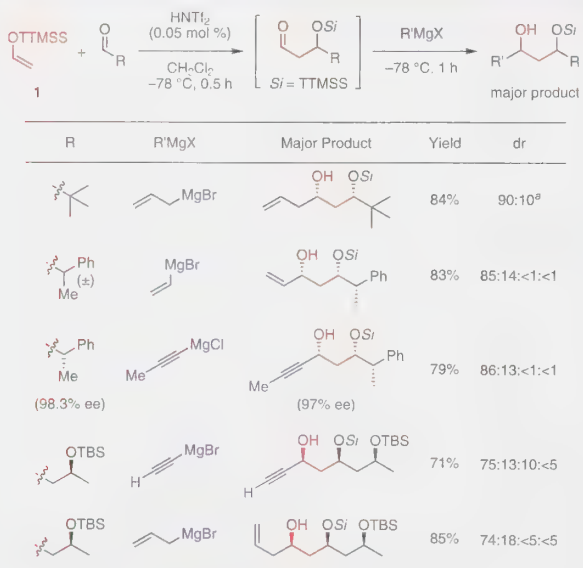
α-benzyloxypropanal formed a β,δ,ε-trihydroxy aldehyde adduct—consistent with a mechanism involving chelation-controlled first aldol addition followed by a syn-selective second aldol addition.

5.2. Cascade Reactions of Ketone- and Aldehyde-Derived SEEs

The SAA reaction was extended to ketone- and aldehyde-derived super SEEs (**Scheme 6**),[6d] which requires, in this case, the addition of first the aldehyde and then the ketone SEEs due to their competitive reactivity with the initial aldehyde. Following the standard aldol reaction of **1** with pivalaldehyde, addition of the super SEE of cyclohexanone (**13**) to the reaction mixture gave the SAA adduct in excellent diastereoselectivity. A similar reaction sequence employing 2-phenylpropionaldehyde in the first step generated a product with three new stereocenters highly stereoselectively. Substituting acetophenone super SEE (**14**) in the second step of the same reaction cascade similarly yielded the product with high diastereoselectivity. Using a hetero-Diels–Alder reaction with a siloxy-diene, developed by Kozmin and Rawal,[44] as the second step in the cascade formed a dihydropyranone with comparable diastereoselectivity.



Scheme 6. SAA and SA–Hetero-Diels–Alder Reactions of Super SEEs. *(Ref. 6d)*



Scheme 7. Sequential Aldol–Grignard Addition with Super SEE **1**. *(Ref. 6d)*

6. Other Sequential Reactions of SEEs

The 1,3-diol substructure is very common in many important medicinal compounds.[28] The majority of syntheses of molecules containing this motif require a multistep protocol to access the stereodefined diol. Significant contributions by Leighton's group and ours have employed SEEs in tandem and sequential reactions to access the 1,3-diol motif in one step.[6b-f,43,45]

6.1. Silyl Dinucleophile Reagents

In 1999, Berrisford's group published a very interesting report of a silicon-tethered dinucleophile reagent that undergoes a sequential aldol–allylation reaction.[46] When this unique reagent was reacted with dimethyl acetals in the presence of BF_3•OEt_2, the aldol–allylation product was obtained in reasonable yield, but with rather low diastereoselectivity.

Leighton and co-workers later developed a number of strained silacycles that are very efficient at tandem aldol–allylation, aldol–crotylation, and aldol–aldol reactions.[43,45] These reagents rely on an increase in Lewis acidity of the silicon center that arises from the strained 5-membered ring, thus enabling the aldol -allylation and aldol–crotylation to proceed without the need for a catalyst. Moderate yields and reasonable selectivities were obtained for various combinations of enol and allyl or crotyl moieties. The strained silacycle approach was also extended to include the use of ketone enol equivalents for the synthesis of tertiary carbinols.[43] In this latter case, the sequential aldol–allylation, aldol–methallylation, aldol–crotylation, and aldol–aldol reactions proceeded in good yields and selectivities producing a variety of relatively complex polyketide-like products in one pot.

6.2. Sequential Aldol–Carbanion Addition Reactions

Due to the very low catalyst loading (0.05–0.10 mol % of $HNTf_2$) utilized in the aldol reactions and the high diastereoselectivity obtained in the SAA reactions, it was anticipated that the addition of Grignards would be tolerated and would proceed with high stereoselectivity in generating secondary and tertiary carbinols, which still remains a challenging task in organic chemistry.[47] Following the aldol reaction of pivalaldehyde and **1**, allylmagnesium bromide was added to give the aldol–allylation product in 90:10 syn:anti selectivity in one pot (**Scheme 7**).[6d] Chiral starting aldehydes 2-phenylpropionaldehyde and 3-TBSoxybutanal also led to good selectivities for the corresponding sequential SA–Grignard reaction product. The use of vinyl-, alkynyl-, and allylmagnesium halides generated synthetically useful allylic, propargylic, and homoallylic alcohols with high selectivity. Worthy of note is that enantioenriched (*S*)-2-phenylpropanal (98.3% ee) led to the major diastereomeric product in 97% ee, indicating no racemization during the acid-catalyzed aldol step.[6d]

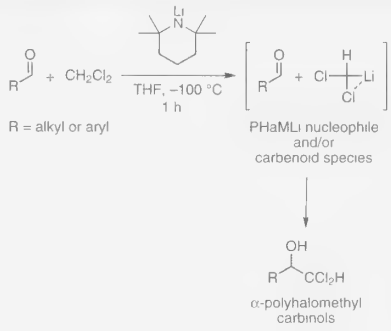
Polyhalomethanes (PHaMs) are small inexpensive molecules that are typically used as solvents (i.e., CH_2Cl_2 and $CHCl_3$). Halogens, of course, have a diverse reactivity profile and can render compounds electrophilic or nucleophilic.[48] Medicinal chemistry has revealed that fluorine- and chlorine-containing compounds have enhanced properties in biological settings as well as in crop management.[49] Despite considerable evidence of the importance of halogen-containing compounds, the stereocontrolled introduction of the polyhalomethyl group is not widely achievable.[50] To our knowledge, there exist only a few examples of the diastereoselective introduction of such groups.[50c,e,h]

One of the most straightforward pathways to these PHaMs is the nucleophilic addition of polyhalomethyllithiums (PHaMLi's) to aldehydes (**Scheme 8**).[6e] PHaMLi's are best generated by deprotonation of PHaMs with bulky lithium amides such as LiTMP (TMP = 2,2,6,6-tetramethylpiperidinyl). A potential difficulty with this approach is dealing with the instability of such carbenoid-type species even at low temperatures.[50,51] However, it has been shown that when a solution of an aldehyde or ketone, in the presence of excess PHaMs, is treated with a bulky lithium amide, the kinetically generated lithium carbenoid species reacts with the aldehyde or ketone before side reactions and decomposition occur.[50a]

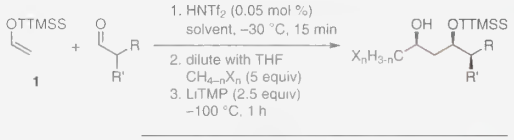
Thus, this reaction is a natural fit for our SA–nucleophile addition reaction sequence, since the requisite acid catalyst for the first step is present at only 0.05 mol % and the reaction proceeds in nonprotic solvents. Using our standard aldol reaction of **1** and 2-phenylpropionaldehyde, a variety of solvents and temperatures were screened for the diastereoselective sequential addition of dibromomethyllithium (**Scheme 9**).[6e] 1,2-Dichloroethane was utilized as solvent for the aldol reaction since CH_2Cl_2 is competitively deprotonated under the subsequent PHaMLi-generating reaction conditions. For PHaMLi generation and addition reactions, employing THF as solvent at –100 °C was optimal for producing the syn diols. The aldol solvent could also be utilized as the PHaMLi precursor. The highest selectivity was obtained with the largest such anion, tribromomethide, giving the product in high yield and high syn selectivity. Diiodomethane is also successfully deprotonated under these conditions and adds with high selectivity to give α-diiodomethylcarbinols in good yields.

A mixed α-polyhalomethylcarbinol has also been synthesized by Kuroboshi's group using a slightly different protocol.[52] Following the standard aldol reaction, $CFBr_3$ was added, the solution diluted with 2:1 THF–Et_2O, cooled to –130 °C, and Br_2FCLi prepared in situ by lithium–bromine exchange with *n*-BuLi (**Scheme 10**).[6e] The α-dibromofluorocarbinol was produced in 55% yield with good selectivity, and was converted into the *Z* α-haloenol ester by treatment with acetic anhydride and then $CrCl_2$ in refluxing THF.[53] Moreover, a disubsituted *Z* fluoroalkene was prepared by an SA–Wittig-type olefination sequence.[6e] This sequential reaction succeeded when the aldol reaction was followed by addition of the in situ prepared $(n\text{-Bu})_3$P-CF-P$(n\text{-Bu})_3$Cl.[54] After stirring for 12 h, 10% NaOH was added and stirred for an additional 12 h, inducing hydrolysis of the vinylphosphonium salt, thereby generating the *Z* fluoroalkene, in moderate yield and high selectivity.

With a clear indication that ketone-derived super SEEs were satisfactory in the basic Mukaiyama aldol reaction, their use in SA–Grignard addition reactions was also demonstrated.[6i] While a plethora of literature reports have been published on the diastereoselectivity of additions to β-oxygenated aldehydes,[34,55] significantly fewer reports can be found for the corresponding simple β-oxygenated ketones (not including hydrogenation–reduction reactions).[47b,e,56] The majority of the reports that do exist, involve a β-hydroxy ketone and are proposed to undergo cyclic, 6-membered-ring transition states involving a Lewis acid catalyst or a metal from the organometallic species. While there is a report concerning syn selectivity for the methyl and butyl additions to β-TBSoxy-protected ketones,[47b] few examples of this type of diastereoselective reaction exist. This likely arises from



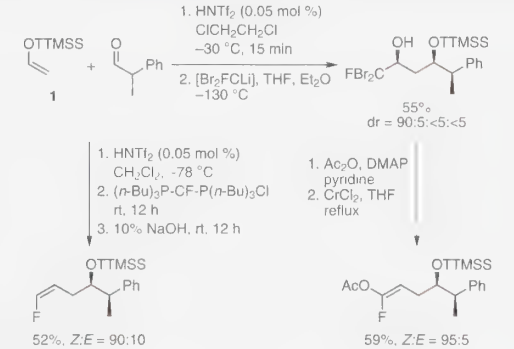
Scheme 8. PHaMLi Generation and in Situ Reaction with Aldehydes. *(Ref 6e)*



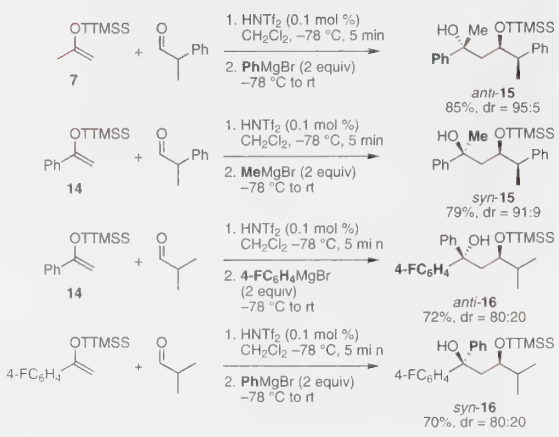
R	R'	Solvent	$CH_{4-n}X_n$	Yield	dr
Ph	Me	$ClCH_2CH_2Cl$	CH_2Br_2	72%	85:5:5:5
Et	Me	CH_2Cl_2[a]	CH_2Cl_2	72%	70:18:10:2
Bn	H	$CHCl_3$	$CHCl_3$	70%	90:10
Ph	Me	$ClCH_2CH_2Cl$	$CHBr_3$	70%	90:7:<2:<2
b	Me	$ClCH_2CH_2Cl$	CH_2I_2	76%	82:15:<2:<2
Ph	Me	$ClCH_2CH_2Cl$	CH_2I_2	76%	82:15:<2:<2

[a] At –78 °C. [b] R =

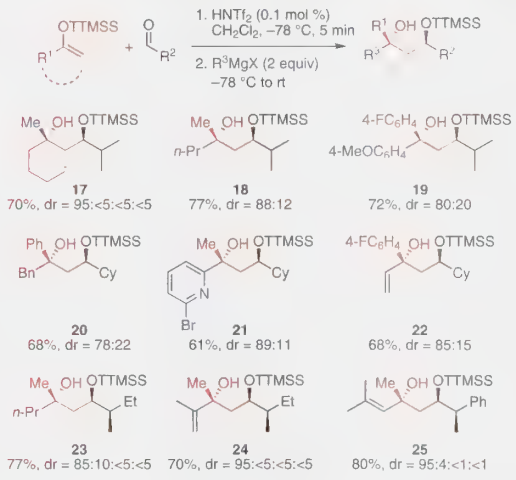
Scheme 9. Sequential Aldol–Polyhalomethyllithium Addition Reactions. *(Ref 6e)*



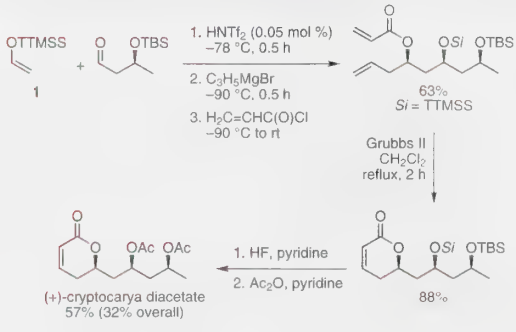
Scheme 10. Synthesis of Mixed α-Polyhalomethyl Carbinols and Fluoroalkenes. *(Ref 6e)*



Scheme 11. Distinct Diastereomer Formation by Simple Substrate Choice. *(Ref. 6f)*



eq 6 *(Ref. 6f)*



Scheme 12. Total Synthesis of (+)-Cryptocarya Diacetate. *(Ref. 6d)*

two main factors: (i) ketones typically show lower selectivity and reactivity than aldehydes in many stereoselective reactions, and (ii) stereoselectivity induced by chirality at the β carbon is often lower than that induced by chirality at the α carbon.

Using the previously established, simple, one-pot SA–Grignard addition reaction protocol, acetone super SEE and 2-phenylpropionaldehyde underwent the aldol reaction initiated by 0.1 mol % of $HNTf_2$. PhMgBr was subsequently added leading to *anti*-**15** in good yield and excellent diastereoselectivity (**Scheme 11**).[6f] Interestingly, the anti product was the major diastereomer, and this sense of stereoinduction results from nucleophilic attack on the π face of the carbonyl *opposite* to that which is seen for SAA and SA–Grignard additions utilizing **1**. DFT calculations were carried out to investigate the nature of the transition state (TS) in these reactions; the results will be discussed in Section 8. Aware that the choice of substrate could lead to predictable, distinct diastereomer formation, *syn*-**15** was prepared with high selectivity by simply employing acetophenone super SEE in the first (SA) step, and adding MeMgBr in the second step. Extending this idea to generate a tertiary carbinol with similarly sized substituents, *anti*-**16** was obtained from acetophenone super SEE and *p*-fluorophenylmagnesium bromide in a similar reaction sequence. Next, using 4'-fluoroacetophenone super SEE and phenylmagnesium bromide sequentially led to the expected isomer *syn*-**16**. These examples clearly demonstrate the TS control exhibited by the super siloxy substituent in these open-chain β-super-siloxy ketone intermediates, as well as the ability to generate the desired diastereomers by the judicious choice of the SEE and the Grignard reagent.[6f]

The generality of this one-pot sequence was demonstrated by the success of a variety of ketone super SEEs, aldehydes, and Grignard reagents (**eq 6**).[6f] The reaction scope was quite broad, giving products such as **17**, which contains three contiguous stereocenters. The use of vinyl and alkyl Grignards worked quite well, giving products **18–25** with good selectivity. The formation of **24** and **23** again showcases the super silyl group's powerful control of diastereoselection by first differentiating methyl and ethyl groups to give a large excess of the Felkin isomer, and then by stereoselectively controlling the Grignard addition via its presence in the β position. Product **21**, containing the valuable pyridine moiety, was generated by the in situ preparation of the heteroaryl Grignard through Knochel's powerful *i*-PrMgCl–2,6-dibromopyridine exchange reaction.[57]

6.3. The Super Silyl Group in Four-Component Reactions

A four-component, one-pot reaction sequence was employed for the extremely concise synthesis of cryptocarya diacetate.[6d] This compound is isolated from the bark of the South African plant, *Cryptocarya latifolia*, which is used for medicinal purposes.[58,59] The synthesis was initiated with a one-pot, SA–Grignard addition–acylation sequence, which generated a diene in 63% yield along with a 24% yield of minor diastereomers (**Scheme 12**).[6d] The use of Grubbs's second-generation catalyst in the ring-closing metathesis step gave a dihydropyranone, which was treated with HF–pyridine and then excess Ac_2O–pyridine to furnish cryptocarya diacetate. This total synthesis was accomplished in only three laboratory steps and 32% overall yield.

The success achieved with SAA and SA–Grignard addition sequences, led our group to combine these methods in a four-component, SAA–Grignard addition protocol.[6f] The aldol reaction of **1** and cyclohexanecarboxaldehyde was followed by reaction

with a second ketone SEE and subsequent addition of MeMgCl, which gave the four-component product in moderate yield and high diastereoselectivity (**Scheme 13**).[6f] The same protocol was employed with **1**, isobutyraldehyde, 4'-fluoroacetophenone super SEE, and PhMgBr to give the product in moderate yield and selectivity. These four-component, one-pot reaction sequences truly showcase the power of this approach by producing relatively complex chiral architecture from simple starting materials.

7. Protodesilylation–Self-Repair Mechanism

Due to the prevalence of protodesilylation reactions of allyl silanes and SEEs under Brønsted acid conditions, we postulated that the reaction of super SEEs and aldehydes might be proceeding via this protodesilylation mechanism (**Scheme 14**).[6b,60] In this case, $HNTf_2$ would actually be the precatalyst and $(TTMSS)NTf_2$ the true catalyst. This was supported by the use of $(TTMSS)NTf_2$ (generated from the exchange reaction of TTMSS–Cl and $AgNTf_2$) as the catalyst, which led to essentially identical results to those obtained using triflimide (see eq 3 and 4). This fact, in combination with the tolerance of an extremely low catalyst loading (S:C = 2000:1), led us to propose a self-repairing catalyst system, wherein the silyltriflimide can be generated and regenerated even in the presence of water or other protic Lewis bases.[6b]

8. Transition-State Calculations

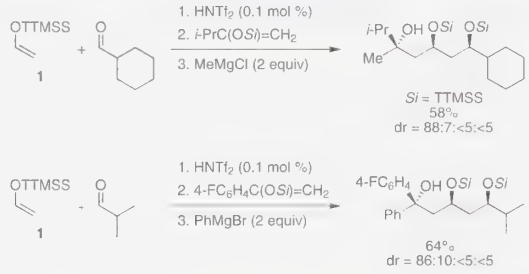
Much of the exceptional diastereoselectivity and control associated with the TTMSS group can likely be traced to its large steric size.[2,61] The super silyl group is extraordinarily bulky, and has been stated to shield molecular skeletons with a "H_3C-skin."[2] It has been reported that this group has a local steric influence comparable to that of the *t*-Bu group,[61a] and is among the strongest electron donors to π systems, lone-pair centers, and molecular cations.[61b] The important work done by Evans's group on the selectivity of additions to β-oxygenated aldehydes, led us to initially propose TS **B** as the reason for the syn selectivity. This TS does not suffer the unfavorable steric interaction that is present in conformation **C** between the Lewis acid coordinated oxygen and the R group (**Figure 2**).[6b,34]

This proposal was corroborated through DFT calculations at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level, which led to a TS structure particularly similar to **B**.[6f] Informative results were also gleaned regarding the reversal of selectivity observed for nucleophilic addition to β-super siloxy aldehydes versus that to β-super siloxy ketones. The calculations showed that the vinyl Grignard addition to the β-super siloxy aldehyde favored the syn pathway by 0.3 kcal/mol in the TS leading to the experimentally observed syn isomer. The calculations for the β-super siloxy methyl ketone gave a 2.6 kcal/mol preference in the TS for formation of the observed anti isomer. Significant steric repulsion between the methyl group of the ketone and the β-*iso*propyl group in the syn TS is a major reason for the divergence of TS energies. Akin to the work by Evans, the ketone and aldehyde transition states indicate a conformational preference that minimizes destabilizing electrostatic β-C–O and C=O dipole interactions.[34] In the case of the β-super siloxy aldehyde, the methyl group is replaced with a hydrogen, resulting in the oxygen being the larger atom (hydrogen vs oxygen in aldehyde and methyl vs oxygen in ketone). This leads to a preferable passing through the syn TS. A key feature that is revealed in these calculations is that the super silyl group creates a large "umbrella"-like structure under which the rest of the molecule aligns, and which restricts the conformational freedom of the remaining portion of the molecule.

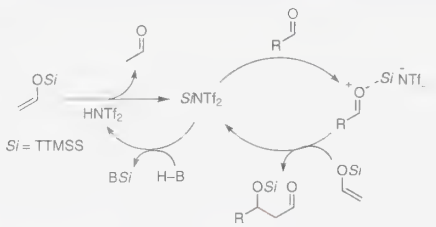
The stereochemical outcome is then largely determined by the interaction of the carbonyl and its substituent (Me for ketone and H for aldehyde) with the medium-sized β-group (*i*-Pr). This is in contrast to typical open-chain ketones and aldehydes, which have much more freedom of rotation due to the absence of the "umbrella" effect, which is why we believe we see such high selectivities for these β-super siloxy carbonyl addition reactions.

9. Stability and Cleavage of Super Silyl Ethers

As mentioned in the introduction, silyl groups occupy a distinct place in protective-group chemistry.[1] Their ease of preparation, combined with the range of stabilities associated with the various commercially available silyl-group-containing reagents, allow for tailor-made syntheses, in which a distinct deprotection step can be planned well in advance. Significant work by Brook's group has shown that the super silyl group is a unique, photolabile protecting group that is stable to a range of typical synthetic conditions, such as Grignards, Wittig reagents, and oxidation conditions (Jones reagent).[15] Through our research, we additionally found



Scheme 13. Four-Component SAA–Grignard Addition Reactions. *(Ref. 6f)*



Scheme 14. Proposed Protodesilylation–Self-Repair Mechanism. *(Ref. 6b)*

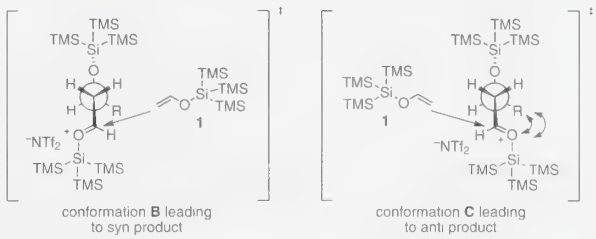


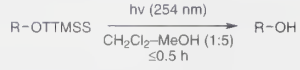
Figure 2. Original Transition-State Proposal for an Aldol Addition of **1** to a β-Super Siloxy Aldehyde. *(Ref. 6b)*

that super silyl ethers are stable to (i) reducing agents ($NaBH_4$, DIBAL-H, and L-Selectride®); (ii) oxidizing reagents (SO_3–pyridine–DMSO, OsO_4, and Dess–Martin periodinane); and (iii) the Tebbe reagent and organometallic reagents derived from Ce, Mn, and Cu. Interestingly, the super silyl group is also stable towards CsF and KF–18-crown-6, but is cleaved with $(n\text{-Bu})_4NF$ in under 1 min. Super silyl ethers show limited stability in the presence of *n*-BuLi or LAH for prolonged periods of time.

Perhaps the most appealing aspect of the reactivity of the super silyl group is its photochemical lability. In 1997, Brook reported that the super silyl group could be cleaved in methanolic dichloromethane upon irradiation with UV light (**eq 7**).[7b,15a] The absorption of super silane and the related super silyl ether derivatives at 254 nm was exploited to effect this deprotection. Moreover, the typical silyl group, TBS, wasn't deprotected under these conditions (254 nm irradiation in quartz cell). We decided to further explore this reactivity profile by irradiation of substrates containing both the super silyl group and other typical silyl groups.[7b] 1,4-Butanediol was used as the starting material for the preparation of various disilylated compounds. The experimental setup was designed to test an extremely simple and practical application of this selective photochemical deprotection. While the use of a quartz round-bottom flask was necessary, the deprotection was carried out by irradiation with a common UV lamp designed for analysis of typical fluoroescent TLC plates. All substrates tested gave high yields for the selective deprotection of the super silyl group.

10. Conclusions and Outlook

The super silyl group is superior in achieving many of the promises of one-pot sequential and multicomponent reactions. The reactivity profile of the super silyl group in a variety of C–C-bond-forming reactions is quite broad and useful. The super silyl group imposes significant steric bulk and possesses unique electronic properties that have enabled it to outperform commonly employed silyl groups in typical as well as atypical reactions. In particular, its use in sequential reactions has assigned the super silyl group a distinctive place in efficient one-pot transformations. Thus far, super SEEs have succeeded in [2 + 2] cyclization reactions, Mukaiyama aldehyde crossed aldol reactions, SAA reactions, SA–hetero-Diels–Alder reactions, SA–Grignard addition reactions, and SAA–Grignard addition reactions. While a number of SEEs have succeeded in these cases, we believe that an array of sequentially added acidic and/or basic reagents and substrates can be combined with the SA system to generate complex chiral architecture in simple and efficient one-pot protocols. We intend to include these sequential reactions in future synthetic planning whenever we encounter the 1,3-diol- and 1,3,5-triol motifs (**Figure 3**).



R	Yield
Cl_3CCH_2	89%
$Me(CH_2)_5CH(Me)$	95%
$(E)\text{-}Me_2C{=}CH(CH_2)_2C(Me){=}CHCH_2$	90%
$TESO(CH_2)_4$	90%
$TBSO(CH_2)_4$	88%
$TIPSO(CH_2)_4$	95%

eq 7 *(Ref. 7b,15a)*

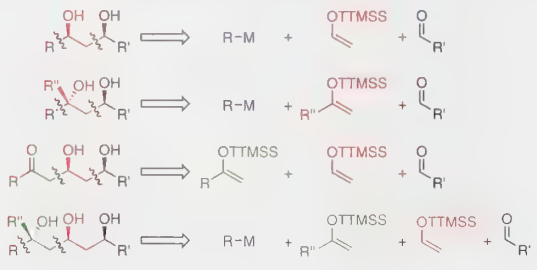


Figure 3. Anticipated Retrosynthetic Disconnections (All Would Be One-Pot Reactions).

11. Acknowledgements

We thank the University of Chicago and Merck Co. for their generous financial support of this work.

12. References and Notes

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Keywords: super silyl group; silyl enol ethers; aldol reaction; sequential reactions; stereoselective reactions.

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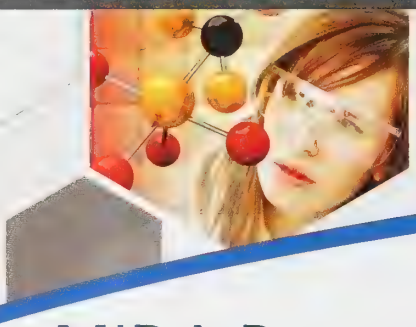

ALDRICH Chemistry

MIDA Boronates

For Suzuki–Miyaura Cross-Couplings

The Suzuki–Miyaura cross-coupling reaction is one of the most important and highly utilized reactions in organic chemistry, with applications in polymer science as well as in the fine chemicals and pharmaceutical industries. However, some classes of boronic acids are exceptionally unstable and susceptible to decomposition, which renders them inefficient in coupling reactions or makes long-term storage difficult. These limitations also make iterative cross-couplings challenging. Recently, Burke and coworkers have developed a method to allow such iterative couplings under mild conditions by attenuating the reactivity of boronic acids through complexation with *N*-methyliminodiacetic acid (**MIDA**). The MIDA ligand can be cleaved under mild conditions to liberate the corresponding boronic acid. MIDA boronates are easily handled, indefinitely bench-top stable under air, compatible with chromatography, unreactive under standard anhydrous cross-coupling conditions, even at temperatures up to 80 °C, and are stable to harsh reagents such as triflic acid and Jones reagent.

Palladium-catalyzed cross-coupling reactions are ideal methods for the synthesis of polyenes because of their stereospecificity and mildness. However, polyenylboronic acids are very unstable and therefore difficult to employ in the synthesis of polyenes by the Suzuki–Miyaura cross-coupling. In an exemplary demonstration of the stability and efficiency of MIDA boronates in iterative cross-couplings, Burke and coworkers utilized a common alkenyl, *trans*-2-bromovinylboronic acid MIDA ester (BB1, **703478**), to create a series of polyenyl building blocks. The MIDA boronate terminus is inert to Suzuki, Stille, and Heck couplings, yielding butadienyl MIDA boronates. Sonogashira and Negishi couplings, as well as Miyaura borylations also proved effective and yielded versatile bis-metallated lynchpin-type reagents.

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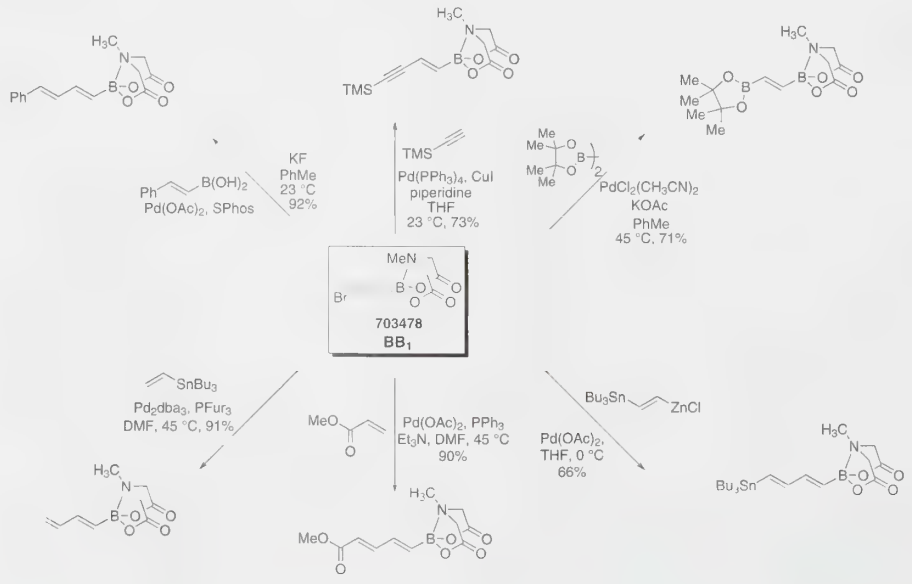

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Iterative Cross-Coupling with MIDA Boronates: towards a General Strategy for Small-Molecule Synthesis

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Outline

1. Introduction

Many organic molecules are inherently modular in their constitution. With respect to the molecules found in living systems, this modularity is a direct consequence of the fact that nearly all biosynthetic systems are based on the iterative coupling of bifunctional building blocks. For example, polypeptides are built from amino acids, oligonucleotides are derived from nucleotide monomers, and oligosaccharides are stitched together from individual sugar units. Interestingly, most *small-molecule* natural products are similarly constructed by the iterative coupling of bifunctional building blocks: e.g., polyketides from malonyl-CoA or methylmalonyl-CoA units, nonribosomal peptides from amino acids, polyterpenes from isopentenyl pyrophosphate or dimethylallyl pyrophosphate, and fatty acids from malonyl-CoA.[1] Similarly, many man-made pharmaceuticals are also highly modular because they are constructed by using different reactions to assemble collections of small building blocks, typically cyclic and heterocyclic fragments and their associated appendages. Thus, modularity is a remarkably general feature of many of the molecules that are targeted for synthesis in the laboratory.

Despite this common modularity, the strategies utilized for making polypeptides, oligonucleotides, and oligosaccharides are very different from those typically used to prepare small molecules. Specifically, all of the former classes of compounds are almost always constructed via iterative coupling of suitably protected forms of their constituent monomers.[2] Organic polymers can be similarly prepared.[3] Due to the powerfully simple nature of this iterative coupling approach, these processes are now increasingly performed in a fully automated fashion.[2,3] With peptides and oligonucleotides, the advanced development of such automation has made it possible for even nonchemists to routinely prepare these types of compound for a wide range of applications.

In stark contrast, it is typical for a synthetic chemist to develop a unique, customized strategy for each small molecule that is targeted for preparation in the laboratory. As a result, the synthesis of small molecules remains a relatively complex, unsystematized, and inflexible process that is practiced almost exclusively by highly trained specialists. Driven by the hypothesis that the inherent modularity in small molecules remains largely underutilized, we have established a research program that aims to develop a unified strategy for the construction of these compounds by the iterative coupling of bifunctional building blocks.[4–7] Specifically, we have targeted the development of building blocks representing substructures that appear frequently in natural products and man-made pharmaceuticals and the chemistry that will enable their precise union via iterative, metal-mediated, cross-coupling reactions. In the idealized form of this "Iterative Cross-Coupling" (ICC) approach, building blocks having all of the required functional groups preinstalled in the correct oxidation state and with the desired stereochemical relationships are iteratively united using only stereospecific cross-coupling reactions (**Figure 1**). In addition to being simple, efficient, and potentially amenable to automation, the modularity of this approach makes it inherently well-suited for generating diverse collections of compounds simply by substituting modified building blocks into the same synthesis pathway. It is anticipated that the advanced development of this ICC strategy will substantially enable the laboratory synthesis of a wide range of natural products, pharmaceuticals, and organic materials, and may even extend the power of small-molecule synthesis to the nonchemist.

As described in this review, *N*-methyliminodiacetic acid (MIDA) boronates[8,9] represent a highly promising platform for this type of synthesis strategy. These building blocks are remarkably convenient to prepare, analyze, purify, and store, and many are now commercially available. The MIDA boronate functional

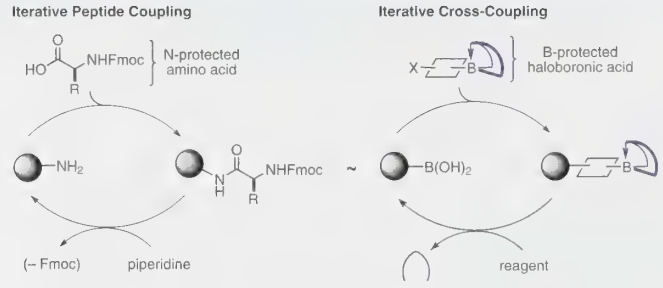
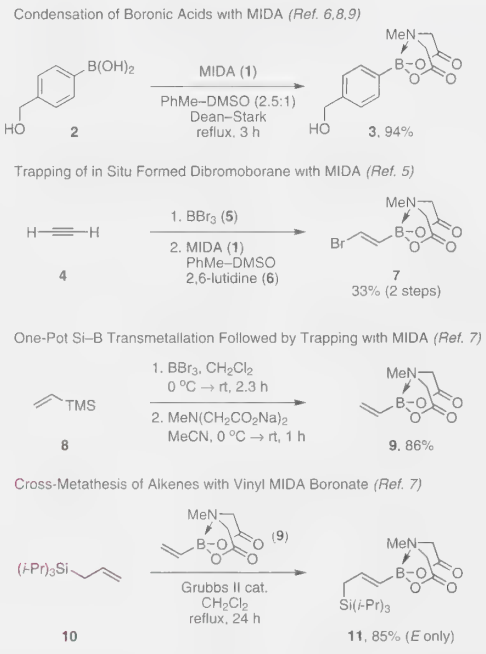


Figure 1. Analogous Strategies for the Synthesis of Peptides and Small Molecules.



Scheme 1. Examples of Known Methods for the Synthesis of MIDA Boronates.

group is also stable to anhydrous cross-coupling conditions, but is easily hydrolyzed with mild aqueous base, thereby enabling the controlled ICC of B-protected "haloboronic acids".[4–6] In addition, MIDA boronates are remarkably stable to a wide range of common reaction conditions and chromatography, which makes possible the facile preparation of complex borane building blocks from simple MIDA boronates via multistep synthesis.[6,7] This review aims to enable the effective utilization of this platform and the ICC strategy to promote the simple, efficient, and flexible construction of small molecules.

2. Synthesis of MIDA Boronates

N-Methyliminodiacetic acid, $MeN(CH_2CO_2H)_2$ (MIDA, **1**),[10] is nontoxic, biodegradable,[11] and commercially available. It can also be conveniently, efficiently, and inexpensively synthesized on a large scale[12] from the commodity chemical iminodiacetic acid.[13]

Presently, four different methods for the synthesis of MIDA boronates are known (**Scheme 1**).[4–9] Many boronic acids can be easily transformed into the corresponding MIDA boronates simply by condensation with MIDA under Dean–Stark conditions (Scheme 1, reaction 1).[4,6,8,9,12] The removal of water by a variety of alternative techniques (e.g., molecular sieves, azeotropic drying with CH_3CN, etc.) can also promote full conversion to the MIDA boronate product. Typically, this condensation process requires heating to at least 40 °C, and the use of DMSO as a co-solvent is required to partially dissolve the MIDA ligand.

We have also developed several methods that enable the preparation of MIDA boronates without the intermediacy of a boronic acid. Alkenyl MIDA boronates can be synthesized via bromoboration of an alkyne to form the corresponding dibromoborane followed by trapping with MIDA in the presence of 2,6-lutidine (Scheme 1, reaction 2).[5] Alternatively, a one-pot procedure has been developed in which organotrimethylsilanes can be converted directly into MIDA boronates via transmetallation with BBr_3, followed by trapping with the disodium salt of MIDA (Na_2MIDA, Scheme 1, reaction 3).[7] This approach was employed in the efficient synthesis of vinyl MIDA boronate (**9**), for which condensation of MIDA with the related vinylboronic acid or vinylboronate species failed. Lastly, a variety of olefins can be transformed directly into alkenyl MIDA boronates via cross-metathesis with **9** (Scheme 1, reaction 4).[7] This approach is notable for its generality, efficiency, and mildness. Moreover, in contrast to previous reports involving the use of vinyl or propenyl pinacol boronic esters,[14,15] cross-metathesis with vinyl MIDA boronate yields only the *E* isomer, and the products are uniformly compatible with silica gel chromatography (vide infra).

3. Physical Properties of MIDA Boronates

MIDA boronates possess a number of highly enabling physical properties that make them useful as a platform for ICC and as convenient alternatives to boronic acids for a wide range of other applications. These properties are remarkably general, i.e., aryl, heteroaryl, alkenyl, and alkyl MIDA boronates all behave similarly. Specifically, MIDA boronates are monomeric, free-flowing, crystalline solids which are stable to storage on the bench top in closed containers under air. MIDA boronates are also universally compatible with silica gel chromatography, allowing convenient reaction monitoring by TLC and facile product isolation and purification.[4–7] If the goal is to separate different MIDA boronates of similar polarity, a ternary eluent of hexanes,

ethyl acetate, and up to 10% methanol is most effective. We have found that under these conditions even diastereomeric mixtures of MIDA boronates can be resolved. For the purification of nonpolar MIDA boronates, hexanes–ethyl acetate is an effective eluent. Additionally, acetic acid is generally compatible as a co-eluent in most solvent mixtures. Dichloromethane–methanol is a useful eluent for TLC analysis, but some decomposition of the MIDA boronates can occur if this eluent is used for preparative chromatography. Similarly, MIDA boronates should not be left to stand in solutions containing alcohols for more than an hour.

This compatibility with silica gel chromatography and the facility with which MIDA boronates can be formed from the corresponding boronic acids make it possible to utilize MIDA boronate formation and purification as a powerful tool to isolate high-purity boronic acids from crude mixtures that contain many nonboronic acid byproducts. Specifically, we have found that adding a small excess of MIDA to a crude mixture containing a boronic acid and performing a Dean–Stark complexation lead to the formation of the corresponding MIDA boronate while the other impurities remain largely unchanged. If the boronic acid is desired, a simple hydrolysis of the purified MIDA boronate with 1 M aqueous NaOH, followed by extraction of the boronic acid into an organic solvent, typically yields the pure boronic acid.

MIDA boronates are also easily purified by crystallization. A generally effective strategy is to dissolve the crude MIDA boronate in a minimum volume of acetone at 23 °C and then slowly add Et_2O to promote crystallization. The crystallization is complete when the addition of Et_2O no longer clouds the solution. Alternative crystallization solvents include MeCN–Et_2O and EtOAc–Et_2O. X-ray quality crystals are conveniently prepared via vapor diffusion of petroleum ether into an acetone solution of the MIDA boronate: The acetone solution of the MIDA boronate is placed in a small vial (7 mL or 15 mL; the solution is 2–5 mm in height), and this vial is placed in a closed jar containing petroleum ether (about 1 cm in height). Crystals form upon standing at room temperature overnight.

Another important property of MIDA boronates is their solubility in many organic solvents. Reactions are typically performed using THF, dioxane, dichloromethane, DMF, toluene, DMSO, acetonitrile, acetone, or 1,2-dichloroethane. Prolonged exposure of MIDA boronates to aqueous conditions or alcoholic solvents leads eventually to hydrolysis of the MIDA ligand, and this effect is accelerated with heating or in the presence of base. However, water or alcoholic solvents have been successfully employed as co-solvents in some reactions with MIDA boronates.[6] Furthermore, MIDA boronates are generally compatible with aqueous extractions employing water, brine, aqueous acids (e.g., aq HCl or NH_4Cl), and even some oxidative or reductive aqueous solutions (e.g., aq H_2O_2 at pH < 6, or aq $Na_2S_2O_3$). Remarkably, even saturated aqueous $NaHCO_3$ is tolerated in the absence of alcoholic solvents. Aqueous extractions are typically performed using EtOAc or CH_2Cl_2 as the organic phase. For highly polar MIDA boronates, solvent mixtures of EtOAc–acetone (1:1) or THF–Et_2O (1:1) are convenient. As described below, despite this widespread stability, MIDA boronates are easily hydrolyzed to yield the corresponding boronic acids using very mild aqueous basic reagents at 23 °C.

Interestingly, in contrast to MIDA boronates such as **3**, similarly pyramidalized *N*-methyldiethanolamine adducts such as **12** **(Figure 2)** are not stable to silica gel. As described below, again in contrast to the MIDA boronates, *N*-methyldiethanolamine adducts are also reactive under cross-coupling and many other common reaction conditions.[4,6,16] The remarkable (and in many cases unique) stability of MIDA boronates to storage under air, chromatography, aqueous workups, as well as cross-coupling and many other reaction conditions is tentatively attributed to the unique conformational rigidity of the fused bicyclic [*N*-methyliminodiacetate-*O,O',N*] borane framework. Specifically, as shown in Figure 2, variable-temperature NMR experiments with a DMSO-d_6 solution of **3** reveal no coalescence of the diastereotopic methylene protons of the MIDA backbone, even at 150 °C.[6,17] In contrast, the same experiment with **12** reveals coalescence of the diastereotopic methylene protons of the diethanolamine backbone over a temperature range of 23 to 60 °C, suggesting that this complex is highly dynamic.[6,17] Although the fundamental underpinnings of these striking differences in conformational rigidity remain to be elucidated, these studies suggest that, uniquely in MIDA boronates, the potentially reactive boron p orbital and nitrogen lone pair are kinetically inaccessible, even at elevated temperatures. This kinetic stability may be responsible for many of the unique physical properties of MIDA boronates.

4. Iterative Cross-Coupling (ICC) with Halogenated MIDA Boronates

The now routinely automated process of iterative peptide coupling[2a] represents an inspiring benchmark for a potentially general strategy for making small molecules in the laboratory. It is interesting to note that peptides are quite complex in structure, having many different functional groups with varied oxidation states and a large number of stereogenic centers. However, the synthesis of many peptides is now very simple, involving the use of a single reaction to iteratively assemble a collection of amino acid building blocks having all of the required functional groups and stereochemistry preinstalled.

With the goal of developing an analogous process for the laboratory construction of small molecules, we decided to focus on the Suzuki–Miyaura reaction and the ICC of bifunctional "haloboronic acids" (see Figure 1).[6] To avoid random oligomerization of a haloboronic acid under cross-coupling

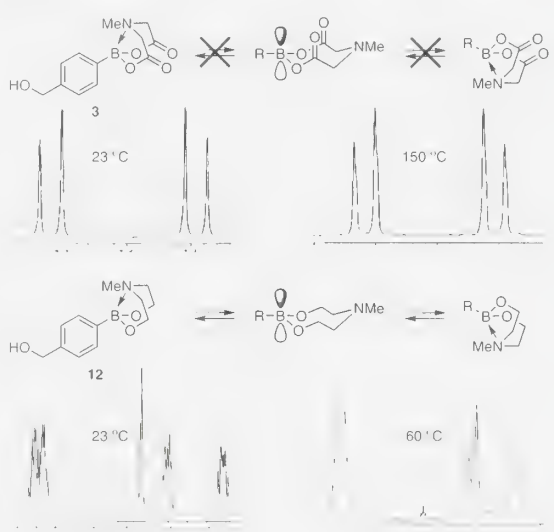


Figure 2. Variable-Temperature NMR Studies in DMSO-d_6 with MIDA Boronate and *N*-Methyldiethanolamine Adducts That Demonstrate the Unique and Remarkable Conformational Rigidity of the MIDA Boronate Framework. *(Ref. 6)*

conditions, it is necessary to reversibly attenuate the reactivity of one end of this type of bifunctional reagent, in analogy to the use of a protective group to control the reactivity of the amine terminus of an amino acid.[18] Toward this goal, we chose to focus on controlling the reactivity of the boronic acid functional group.

It is hypothesized that a vacant and Lewis acidic boron p orbital is required for transmetallation of a boronic acid under Suzuki–Miyaura cross-coupling conditions (**Figure 3a**).[19] Consistent with this, complexation with electron-donating, Lewis basic ligands is known to attenuate the reactivity of boronic acids towards cross-coupling (**Figure 3b**).[19a] For example, pinacol boronic esters can be less reactive towards cross-coupling than the corresponding boronic acids.[20] This reactivity attenuation can be attributed to the decreased Lewis acidity of the boron p orbital as a result of conjugation with the lone pairs of the ligand heteroatoms.[19a] This same approach has been utilized with a variety of other divalent heteroatomic ligands.[21] There is an inherent limitation, however, that precludes the general utilization of this approach for complex small-molecule synthesis. Specifically, conjugation between the heteroatom lone pairs and the boron p orbital produces relatively strong boron–heteroatom bonds, creating a high energy barrier for bond cleavage. Moreover, the equilibrium between the boronic acid and the corresponding boronic ester typically lies strongly towards the latter, thereby disfavoring hydrolysis. As a result, cleaving this type of ligand to regenerate the boronic acid typically requires harsh conditions[19–21] and/or additional reagents to destroy the divalent ligand after it has been cleaved.[22] These types of conditions can be problematic in the context of complex small-molecule synthesis.

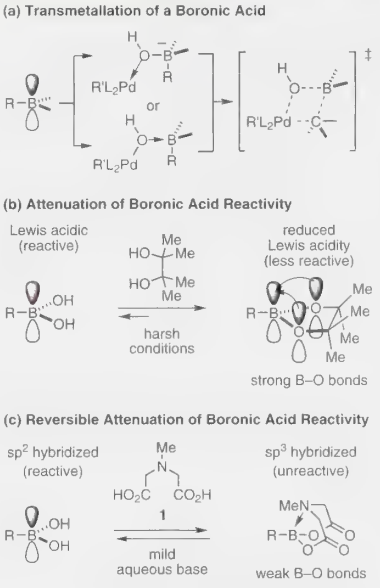
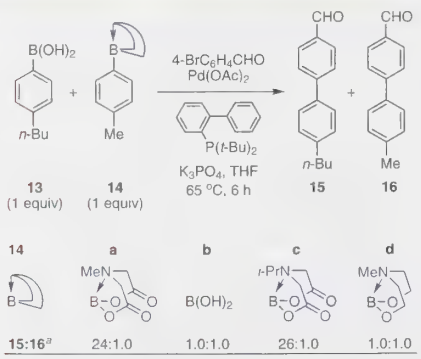


Figure 3. Under Suzuki–Miyaura Cross-Coupling Reaction Conditions: (a) Transmetallation Requires a Vacant and Lewis Acidic Boron p Orbital. (b) Strongly Electron-Donating Divalent Ligands Can Attenuate Boronic Acid Reactivity, but Typically Require Relatively Harsh Conditions for Cleavage. (c) The Reactivity of a Boronic Acid Can Be Reversibly Attenuated via Pyramidalization with a Trivalent Heteroatomic Ligand. *(Ref. 4)*



eq 1 *(Ref. 4)*

Recognizing the inherent limitations of this approach, we focused on an alternative strategy (**Figure 3c**).[4] Specifically, given that the boron p orbital is predicted to be critical for the transmetallation of a boronic acid, we hypothesized that removing this p orbital through rehybridization of the boron atom from sp^2 to sp^3 via complexation with a trivalent heteroatomic ligand would eliminate its reactivity towards cross-coupling. Further increasing our interest in this approach, it is known that boron–heteroatom bonds in tetrahedral adducts are weaker than those in their tricoordinate counterparts.[23] For example, the pyramidalization of trimethyl borate via complexation with ammonia weakens the boron–oxygen bonds by about 10–12 kcal/mol.[24] Thus, we felt that it might be possible to find relatively mild conditions that could hydrolyze this type of pyramidalized boronate and regenerate the reactive boronic acid. After surveying a series of trivalent heteroatomic ligands, we discovered that MIDA boronates embody all of these expectations and represent a powerful platform for ICC chemistry.

In a competition experiment between *p*-(*n*-butyl)phenylboronic acid (**13**) and *p*-tolyl MIDA boronate (**14a**) under Buchwald-type[25] anhydrous Suzuki–Miyaura cross-coupling conditions with *p*-bromoanisaldehyde, we observed a 24:1 ratio of products **15** and **16** (**eq 1**), consistent with a strong preference for cross-coupling of the sp^2-hybridized boronic acid.[4] Interestingly, a wide range of non-aryl substituents were tolerated on the nitrogen atom. The diethanolamine adduct, **14d**, lacking the carbonyl units of MIDA, was as reactive as boronic acid **13**. As described above, this difference in reactivity between **14a** and **14d** is attributed to differences in the conformational rigidity of these two complexes.

Encouraged by these results, we set out to prepare a series of bifunctional B-protected haloboronic acids and explore their capacity to undergo selective cross-coupling at the halide terminus. The efficient synthesis of aryl, heteroaryl, alkenyl, and alkyl derivatives was achieved via simple condensation of the corresponding boronic acids with MIDA under Dean–Stark conditions (**eq 2**).[4]

As shown in **Scheme 2**,[4] this B-protection strategy is remarkably general, with the same ligand similarly protecting aryl, heteroaryl, alkenyl, and alkyl haloboronic acids, thereby enabling the highly selective coupling of the halide terminus of building blocks **18a–f**. Moreover, consistent with our initial hypothesis, the MIDA boronate products **19a–f** can all be hydrolyzed under mild aqueous basic conditions (1 N NaOH(aq), THF, 23 °C, 10 min) to generate the corresponding free boronic acids **20a–f**.

Polyenes are especially challenging synthetic targets because of the sensitivity of this framework to light, oxygen, and acid. It is also critical to control the stereochemistry of each double bond. The ICC approach is particularly well-suited to preparing these types of compound due to the mild and stereospecific nature of the

metal-mediated cross-couplings. Given the prevalence of alkenyl and polyenyl subunits in both natural products and pharmaceutical targets, we developed a collection of bifunctional building blocks specifically designed to enable polyene synthesis via ICC.[5]

As described in Scheme 1, *trans*-(2-bromovinyl) MIDA boronate (**7**) can be prepared via bromoboration of acetylene[26] followed by complexation with MIDA in the presence of 2,6-lutidine. An alternative and more convenient procedure involves transmetallation of 1-bromo-2-(trimethylsilyl)ethylene with BBr_3[27] followed by trapping with Na_2MIDA.[7] Bifunctional olefin **7** is a remarkably versatile cross-coupling partner (**Scheme 3**).[5] Specifically, Suzuki–Miyaura, Stille, and Heck couplings are all achieved at the bromide terminus without perturbing the MIDA boronate. A series of bismetallated lynchpin-type reagents are also created via Sonagashira coupling with trimethylsilylacetylene, Miyaura borylation with pinacolatodiborane (**25**), or a triply metal-selective (Zn vs Sn and B) Negishi coupling with bismetallated olefin **27**.

A generally useful strategy involves the boron-selective coupling of differentially ligated diboron reagents.[5,28] In the first example of such a reaction, **26** was selectively coupled with *trans*-1-chloro-2-iodoethylene at the sp^2-hybridized pinacol boronic ester terminus to generate chlorodienyl MIDA boronate **29** (**Scheme 4**).[5] A better-precedented Sn vs B coupling[29] between bismetallated diene **28** and *trans*-1-chloro-2-iodoethylene generated chlorotrienyl MIDA boronate **30**.[5]

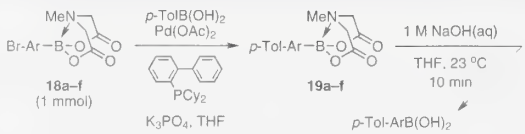
The olefin cross-metathesis route to MIDA boronates is remarkably tolerant of a wide range of functional groups, including halogens. Thus, this method is also well-suited for preparing various haloalkenyl MIDA boronates, as shown for a series of bromostyrene derivatives (**eq 3**).[7]

The capacity to prepare and selectively couple bifunctional halo MIDA boronates enables one to envision the synthesis of natural products or pharmaceuticals by using only a single reaction iteratively to bring together a collection of pre-assembled building blocks. This strategy was first realized with the total synthesis of ratanhine,[4] a complex neolignan isolated from the *Ratanhiae radix* by Arnone and co-workers in 1990.[30] This natural product was retrosynthetically fragmented using recursive Suzuki–Miyaura transforms to generate four simpler building blocks, **35**–**38** (**Figure 4**). There were several challenges associated with this plan that were expected to test the limits of the MIDA-based

18	R	Yield[a]
a	4-BrC_6H_4	98%
b	3-BrC_6H_4	93%
c	2-BrC_6H_4	97%
d	5-Br-thien-2-yl	99%
e	*trans*-3-Br-styryl	99%
f	2-(3-BrC_6H_4)-*c*-Pr	88%

[a] Yields refer to *analytically pure* materials obtained conveniently via silica gel chromatography

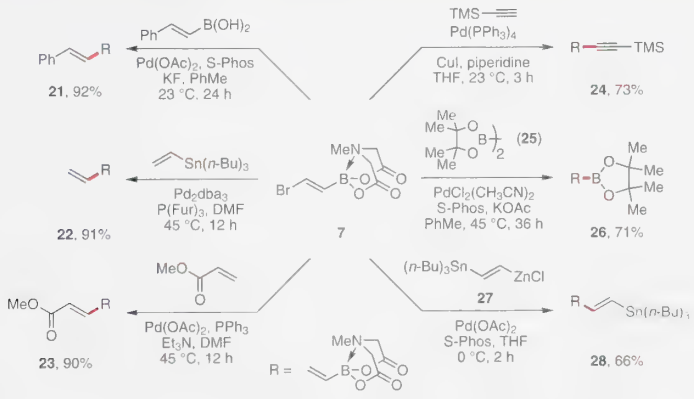
eq 2 *(Ref. 4)*



No.	*p*-TolAr	19	20
a	4-(*p*-Tol)C_6H_4	87%	86%
b	3-(*p*-Tol)C_6H_4	85%	92%
c	2-(*p*-Tol)C_6H_4	80%	97%[a]
d	5-(*p*-Tol)thien-2-yl	81%	88%[b]
e	*trans*-3-(*p*-Tol)styryl	82%	83%
f	2-[3-(*p*-Tol)C_6H_4]-*c*-Pr	94%	91%

[a] B-Deprotection was also achieved by treatment with saturated aq. $NaHCO_3$–MeOH, 23 °C, 6 h (85%). [b] X-Phos was used as the phosphine ligand

Scheme 2. Selective Coupling and Mild Deprotection of Halogenated Aryl, Heteroaryl, Alkenyl, and Alkyl MIDA Boronates. *(Ref. 4)*

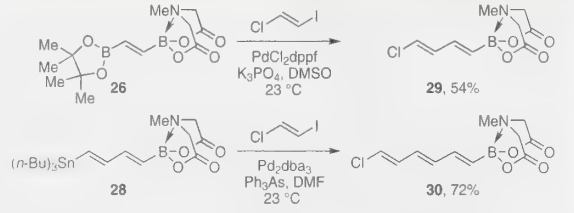


Scheme 3. Bifunctional Halogenated MIDA Boronate Building Blocks Such as **7** Can Be Rapidly and Selectively Elaborated at the Halogen Terminus. *(Ref. 5)*

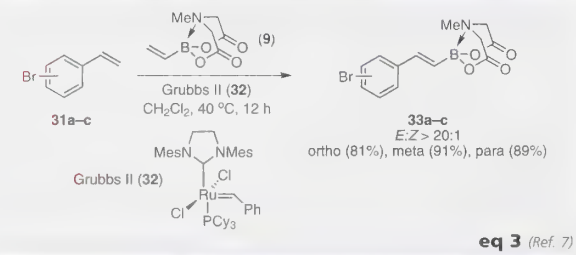
ICC methodology. First, couplings of alkenylboronic acids tend to be less efficient than those of their aryl counterparts, making the selective coupling between **35** and aryl MIDA boronate **36** unsecured. In addition, 2-substituted heterocyclic boronic acids such as **36** are notoriously unstable and difficult to purify, store, and cross-couple.[31] Finally, the coupling of highly deactivated bromoaryl MIDA boronate **37** was expected to demand more forcing reaction conditions that would test the limits of stability of the MIDA boronate functionality.

Despite these challenges, the total synthesis of ratanhine was achieved via ICC as shown in **Scheme 5**.[4] Specifically, selective coupling between propenylboronic acid (**35**) and 5-bromobenzofuran-2-yl MIDA boronate (**36**) proceeded smoothly to generate substituted benzofuranyl MIDA boronate **39**. Remarkably, while the corresponding benzofuranylboronic acid decomposed over the course of several days, MIDA boronate **39** was stored on the bench top under air without noticeable decomposition for more than 6 months. This MIDA boronate was hydrolyzed under mild conditions, and the resulting boronic acid was immediately utilized in a cross-coupling reaction with bromoaryl MIDA boronate **37**. As expected, this coupling required increased temperature (80 °C in a sealed tube) and an extended reaction time (28 h). Remarkably, the MIDA boronate functional group was stable to these forcing conditions, yielding the highly conjugated MIDA boronate product **40**. A final sequence of boronic acid deprotection and coupling with alkenyl bromide **38** and MOM-ether deprotection completed the first total synthesis of ratanhine. More importantly, to the best of our knowledge, this represents the first total synthesis of any natural product in which a single reaction was utilized iteratively to assemble all of the required building blocks.

This ICC strategy is also highly effective in the synthesis of polyene natural products.[5] Specifically, *all-trans*-retinal[32] was prepared simply via ICC of boronic acid **42**, bromoalkenyl MIDA boronate **7**, and alkenyl bromide **44** (**Scheme 6**).[5] In a similar vein, β-parinaric acid[33] was prepared by ICC of butenylboronic acid (**46**), chlorodienyl MIDA boronate **29**, and alkenyl iodide **48** (**Scheme 7**).[5] Finally, despite the fact that



Scheme 4. The Preparation of Bifunctional Halogenated MIDA Boronates for Use in Polyene Synthesis. *(Ref. 5)*



eq 3 *(Ref. 7)*

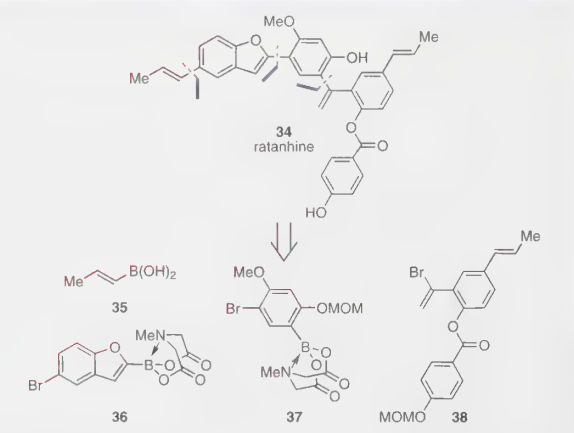
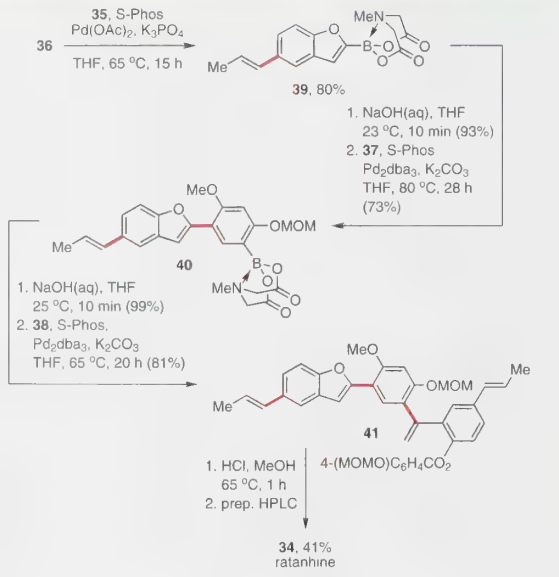
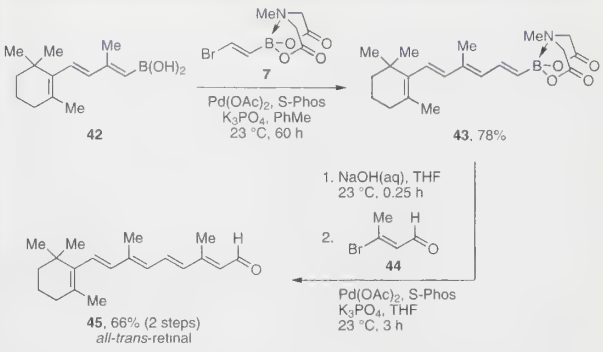


Figure 4. Retrosynthetic Analysis of the Natural Product Ratanhine Using ICC Identified Four Building Blocks, of Which **36** and **37** Are Bifunctional Halogenated MIDA Boronates. *(Ref. 4)*



Scheme 5. Application of ICC in the First Total Synthesis of Ratanhine. *(Ref. 4)*



Scheme 6. Application of ICC in the Synthesis of *All-trans*-Retinal. *(Ref. 5)*

polyenylboronic acids can be very unstable,[34] the notoriously challenging heptaene framework of the polyene natural product amphotericin B was prepared using only the Suzuki–Miyaura reaction to assemble a collection of bifunctional haloalkenyl MIDA boronates (**Scheme 8**).[5]

As demonstrated by these examples, the ICC approach has significant potential to enable the simple, efficient, and flexible construction of small molecules.

5. Multistep Synthesis of Complex Boronic Acids from Simple MIDA Boronates

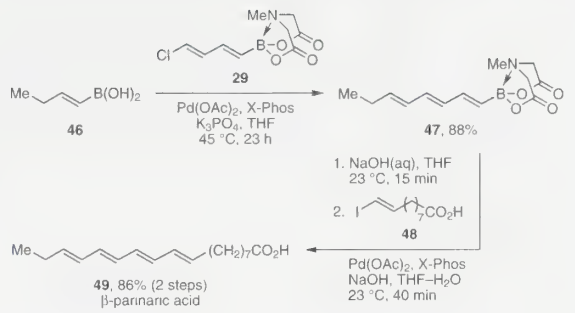
To avoid a general incompatibility with synthetic reagents, it is typically necessary to introduce the boronic acid functional group just prior to its utilization in a cross-coupling or other type of reaction. However, most of the methods that are available for achieving this have poor functional-group tolerance. Collectively, these limitations can render the synthesis of complex boronic acids very challenging. This can sometimes preclude the use of boronic acids in complex-molecule synthesis, and represents a potential bottleneck for the development of a truly general ICC-based approach.

Some sterically bulky boronic esters are known to be more tolerant of synthetic reagents;[35] however, removing these ligands to generate a targeted boronic acid usually requires harsh conditions that are generally incompatible with sensitive building blocks. Trifluoroborate salts represent very useful surrogates for boronic acids,[36] and Molander and co-workers have powerfully demonstrated that the trifluoroborate functional group is compatible with many synthetic reagents.[37] These features have provided novel access to many new organoborane building blocks. However, the incompatibility of trifluoroborate salts with chromatography can limit the utilization of these reagents in multistep synthesis, which is often necessary for accessing structurally and/or stereochemically complex building blocks.

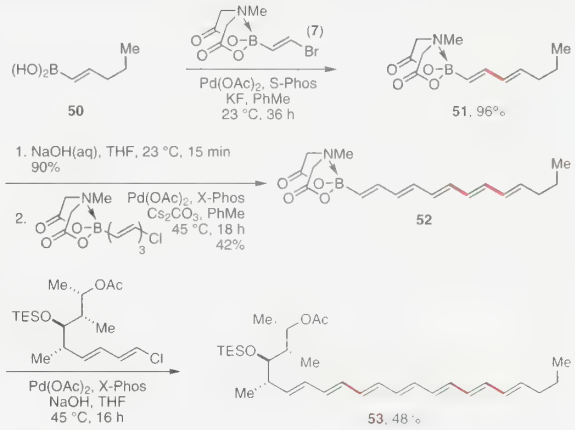
Overcoming these limitations, we have recently found that the MIDA boronate functional group is stable to a wide range of common synthetic reagents, presumably due to the lack of a reactive boron p orbital.[6] Combined with the general compatibility of MIDA boronates with chromatography and the capacity to release the corresponding boronic acids under very mild conditions, this stability enables the first reliable approach for the multistep synthesis of complex boronic acids from simple organoborane starting materials.

Specifically, *p*-(hydroxymethyl)phenyl MIDA boronate (**3**) can be smoothly oxidized under Swern conditions to generate the corresponding benzaldehyde (**Scheme 9**).[6] Remarkably, this MIDA boronate is also stable to the very strongly acidic and oxidizing Jones conditions (H_2SO_4–CrO_3). This latter stability is highly unique; i.e., under these same conditions, the corresponding boronic acid (**56a**), pinacolboronic ester (**56b**), 1,8-diaminonaphthalene adduct (**56c**), trifluoroborate salt (**56d**), and *N*-methyldiethanolamine boronate[16b,38] (**56e**) all decomposed. Similar to that which we observed under cross-coupling conditions, the remarkable difference in reactivity between the MIDA and diethanolamine boronates is likely related to the differences in conformational flexibility of the two complexes (see Figure 2).

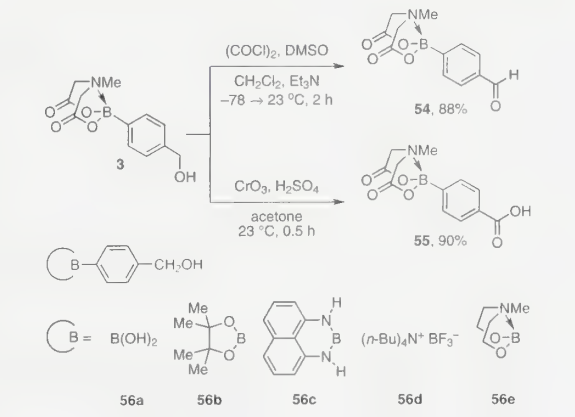
This unique compatibility with strong acid and oxidants suggested that MIDA boronates could be stable to a wide range of reaction conditions. In fact, even triflic acid (pK_a –14) was tolerated, enabling the *p*-methoxybenzylation of **3** and the reversal of this transformation with DDQ (**Scheme 10**).[6]



Scheme 7. Application of ICC in the Synthesis of β-Parinaric Acid. *(Ref. 5)*



Scheme 8. Application of ICC in the Synthesis of the Heptaene Framework of Amphotericin B. *(Ref. 5)*



Scheme 9. MIDA Boronates, Such as **3**, Are Uniquely Stable to the Strongly Acidic and Oxidizing Jones Conditions, Whereas Boronic Acids and Boronates, Such as **56a–e**, Are Not. *(Ref. 6)*

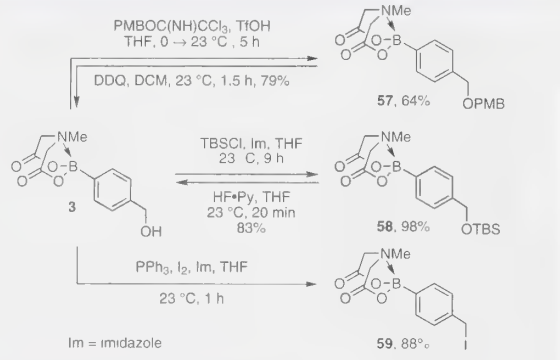
Similarly, silation and desilation were well-tolerated, as was the transformation into the corresponding benzyl iodide **59** with PPh_3–I_2.

This latter reaction suggested compatibility with soft nucleophiles. In this vein, benzaldehyde **54** was successfully utilized in a series of carbon–carbon-bond-forming reactions including the Evans aldol, Horner–Wadsworth–Emmons, and Takai olefination reactions. Reductive amination and aldehyde reduction were also well-tolerated (**Scheme 11**).[6]

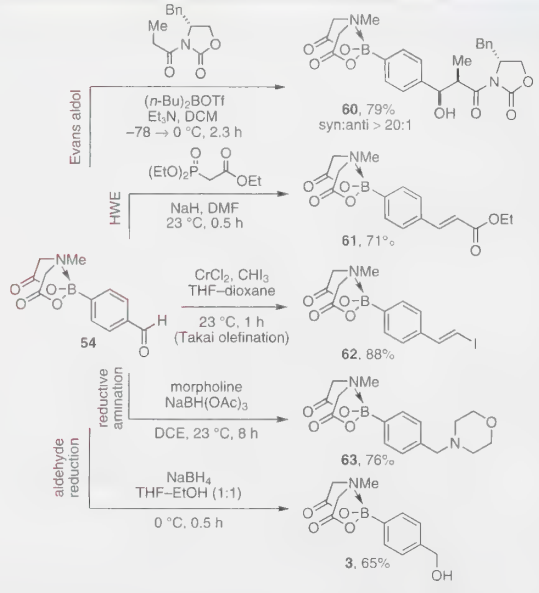
Whereas cyclopropanation of vinyl boranes[39,40] and epoxidation of 1,2-disubstituted alkenyltrifluoroborate salts[37b] are known, the versatility and broad compatibility of vinyl MIDA boronate (**9**) as a starting material has also been demonstrated (**Scheme 12**).[7] Specifically, cyclopropanation of **9** produced cyclopropyl MIDA boronate (**64**) in excellent yield. Remarkably, epoxidation of this olefin with *m*CPBA was also well-tolerated, and even this epoxide, **65**, was stable to column chromatography and bench top storage under air. Boronate **9** was successfully engaged in the Heck reaction[41] to yield styrenyl derivative **66**. Similarly, the White catalyst[42] promoted an efficient oxidative Heck-type[43] reaction[44] to yield **67**. As described previously (see eq 3), **9** is also an excellent substrate for olefin cross-metathesis[14,15] (analogous to *tert*-butylethylene), yielding (*E*)-octenyl MIDA boronate (**68**) as a chromatographically and air-stable crystalline solid and a single stereoisomer (see Scheme 12). Fortunately, this approach has proven to be quite general, and represents a very useful method for preparing a range of (*E*)-alkenyl MIDA boronates (**eq 4**).[7]

This broad compatibility of the MIDA boronate functional group with a wide range of reagents can enable the transformation of simple MIDA boronates into otherwise difficult-to-access complex boronic acids for use in a variety of synthesis applications. These include structurally complex B-protected haloboronic acids for use in ICC.

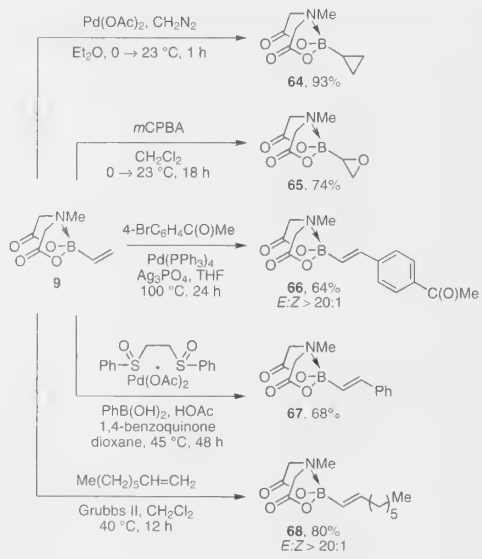
To explore the enabling potential of this approach, we targeted the total synthesis of the natural product crocacin C.[6,45] As shown in **Figure 5**, this molecule was retrosynthetically



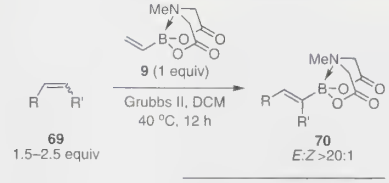
Scheme 10. MIDA Boronates Are Stable to a Number of Useful Reagents in Organic Synthesis. *(Ref. 6)*



Scheme 11. MIDA Boronate Building Blocks Can Be Elaborated Through a Number of Common Organic Reactions. *(Ref. 6)*



Scheme 12. Vinyl MIDA Boronate (**9**) Is an Exceptionally Versatile Building Block. *(Ref. 7)*



R	R'	Yield
$TIPSCH_2$	H	85%
$AcOCH_2$	$AcOCH_2$	84%
$BzOCH_2$	$BzOCH_2$	98%
Cy	H	96%
$Me_2C(OH)$	H	94%
Ph	H	93%

eq 4 *(Ref. 7)*

fragmented via recursive cross-coupling transforms into known building blocks **72** and **74** as well as the novel, complex iodoalkenyl MIDA boronate **73**. The preparation of the latter represented a significant challenge that we hypothesized could be overcome via multistep synthesis starting with simple MIDA boronate **75** (**Scheme 13**).[6]

In practice, a Paterson aldol reaction between **75** and **76** followed by diastereoselective reduction of the resulting β-hydroxy ketone yielded diol **77**. Importantly, the small amounts of diastereomeric byproducts that are typically generated in these types of transformations were readily removed by taking advantage of the compatibility of the MIDA boronate functional group with silica gel chromatography. A subsequent sequence of permethylation with Meerwein's salt, oxidative cleavage of the PMB ether, oxidation of the resulting primary alcohol, and Takai olefination yielded the targeted, complex halogenated MIDA boronate **73**. Importantly, **73**, **75**, and all intermediates were compatible with chromatography and storage on the bench top under air. With B-protected haloboronic acid **73** in hand, the synthesis of (+)-crocacin C was readily achieved via ICC.[6]

6. Conclusions and Prospects

As described herein, the inherent modularity found in many of the small molecules targeted for synthesis in the laboratory stands to be more effectively harnessed via the ICC approach. Analogous to the synthesis of peptides, oligonucleotides, and oligosaccharides, this strategy has the potential to enable the preparation of a wide range of small molecules by the simple, iterative union of pre-assembled, bifunctional building blocks. Due to their ease of synthesis, purification, characterization, and storage; their capacity for reversibly attenuated reactivity under cross-coupling conditions; and their compatibility with a wide range of common synthetic reagents; MIDA boronates represent a powerful platform for the development of this type of synthesis strategy. Moreover, it was recently discovered that, under novel "slow-release cross-coupling" conditions, MIDA boronates can serve as highly effective surrogates for even notoriously unstable boronic acids, such as 2-heterocyclic (including 2-pyridyl), vinyl, and cyclopropyl derivatives.[46] This remarkably general approach has transformed a wide range of unstable boronic acids into air-stable and highly effective cross-coupling partners.

Looking forward, the ever-expanding scope of the Suzuki–Miyaura coupling suggests that the potential generality of this ICC approach could be substantial. Particularly critical to realizing this potential will be finding a way to form Csp^3–Csp^3 and even Csp^3–Csp^3 bonds with the same efficiency that is now routinely achieved stereospecifically with Csp^2–Csp^2 linkages. The discovery of additional methods to prepare MIDA boronates that do not proceed through the intermediacy of a difficult-to-access and/or unstable boronic acid will also be vital. Moreover, to realize the ultimate goal of developing a machine with the capacity for fully automated ICC, it will be important to further develop cross-coupling conditions that are maximally general[25] (to avoid the requirement for ad hoc optimization of conditions for each combination of coupling partners) and amenable to translation into the solid phase or some other form of iterative-synthesis-enabling technology. While these challenges are admittedly considerable, we are convinced that they each can be solved. Achieving these goals could have a substantial impact on the synthesis of small molecules in the laboratory, and may ultimately even extend the power of this discovery engine to the nonchemist.

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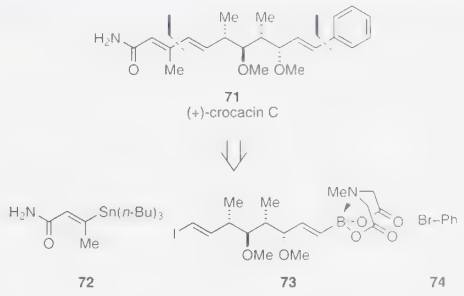
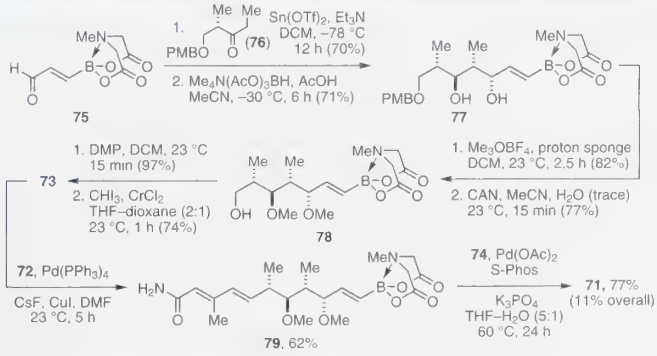


Figure 5. Retrosynthetic Analysis of the Natural Product (+)-Crocacin C Identified the Relatively Complex Halogenated MIDA Boronate Building Block **73**. *(Ref 6)*



Scheme 13. The Broad Chemical Stability of the MIDA Boronate Functional Group Is Taken Advantage of in the Synthesis of (+)-Crocacin C. *(Ref 6)*

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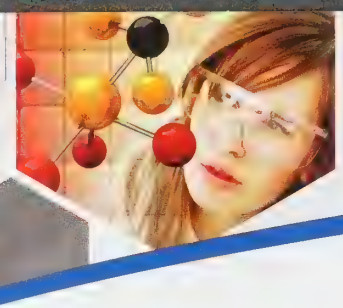
Keywords: MIDA boronate; iterative cross-coupling; automated synthesis; *N*-methyliminodiacetic acid; bifunctional molecules.

About the Authors

Eric Gillis grew up in Portland, ME, and received his undergraduate education at Grinnell College in Grinnell, IA. While at Grinnell, he worked with Professor T. Andrew Mobley on the synthesis and characterization of tungsten–tin complexes. In 2005, he began his doctoral studies under the direction of Professor Martin Burke at the University of Illinois at Urbana-Champaign. His current research focuses on the development of MIDA boronate esters as a platform to enable the automated synthesis of small molecules.

Marty Burke grew up in Manchester, MD, and graduated in 1998 with a B.A. degree in chemistry from Johns Hopkins University. He then moved to Harvard Medical School as a Ph.D. and M.D. student in the Health Sciences and Technology program. From 1999 to 2003, Marty completed his thesis research in organic synthesis under the direction of Professor Stuart Schreiber, and graduated from medical school in 2005. That same year, Marty began his independent career as an assistant professor in the Department of Chemistry at the University of Illinois at Urbana-Champaign. His research focuses on the synthesis and study of small molecules that perform protein-like functions. To enable these studies, Marty's group is pioneering a new synthesis strategy, dubbed *Iterative Cross-Coupling (ICC)*, that aims to make the process of complex-small-molecule synthesis as simple, efficient, and flexible as possible. The group is now harnessing the power of this new chemistry to systematically dissect the structure–function relationships that underlie the protein-like activities of a variety of prototypical small molecules, including the channel-forming polyene natural product amphotericin B.



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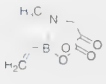
MIDA Boronates from Sigma-Aldrich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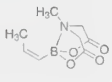
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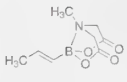
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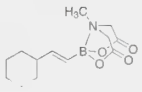
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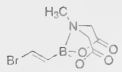
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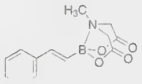
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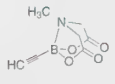
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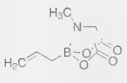
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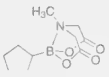
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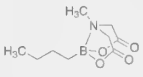
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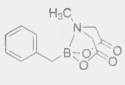
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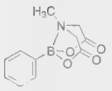
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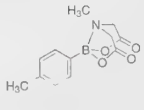
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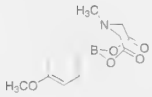
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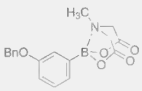
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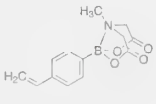
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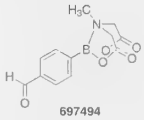
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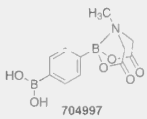
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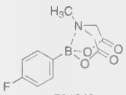
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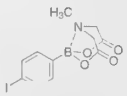
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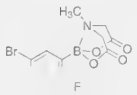
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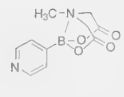
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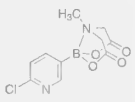
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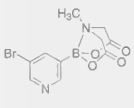
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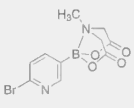
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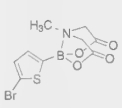
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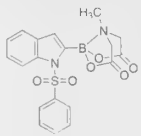
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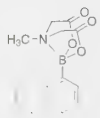
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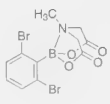
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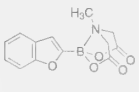
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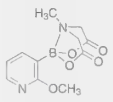
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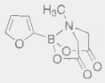
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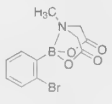
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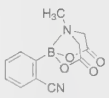
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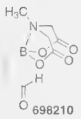
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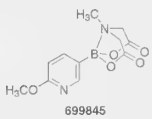
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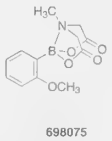
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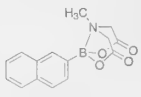
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Aldrichimica ACTA

VOL. 42, NO. 1 • 2009

ALDRICH Chemistry

The Super Silyl Group in Diastereoselective Aldol and Cascade Reactions

Iterative Cross-Coupling with MIDA Boronates: towards a General Strategy for Small-Molecule Synthesis

SIGMA-ALDRICH

Editorial

"Please Call Me Alfred"

On April 28 of this year, Dr. Alfred Bader, undeniably the world's best-known Chemist Collector, celebrated his 85th birthday. Alfred's amazing life story has been covered extensively in books, magazines, and lectures, by Alfred himself and by others, and need not be repeated here. Furthermore, most of our readers are undoubtedly aware of Alfred's strong connections, past and present, not only to Sigma-Aldrich, but also to the *Aldrichimica Acta*, which he has showered with his attention for many years. Many of Alfred's paintings have graced the covers of the *Acta*, including this issue, which is featuring one of Alfred's favorite paintings.

We honor and thank Alfred for his outstanding contributions to Sigma-Aldrich and to the worlds of chemistry, business, and art. To what he calls the "ABC" (Art, Bible, Chemistry) of his life, one should add a "D" for Donating. Alfred's philanthropic activities are considerable and ongoing, and cover a wide range of causes that are near and dear to Alfred's heart.

The magnitude of Alfred's philanthropic efforts was made possible by the considerable financial rewards that he has reaped from two of his lifelong passions. The first is a spectacularly successful chemical business (Aldrich and Sigma-Aldrich) that he helped found and successfully managed for years. The second is his passion for collecting art works, particularly of Dutch and Flemish Masters, as well as rare stamps. His collection of about two hundred such paintings has been donated by Alfred to the Agnes Etherington Art Centre of Queen's University in Kingston, Ontario (Canada). This gift is one of several sizeable ones that he has made to Queen's in gratitude for the education he received there in the 1940s.

Photo Courtesy of Alfred Bader

Dr. Alfred Bader in 2005

Lesser known, but not less important to Alfred, is his Bible scholarship, particularly of Old Testament themes, which he has studied all his life and taught for a good many years. Another lesser known trait of Alfred is his modesty and unassuming lifestyle, which used to lead many a new employee of Aldrich, in the days when Alfred was company president, to think, when running into him for the first time, that he was just another employee. After meeting Alfred for the first time and calling him Dr. Bader, the editor of this publication was gently chided for calling him Dr. Bader, rather than Alfred, which is what he insists on being called even by people who don't know him that well.

On behalf of all Sigma-Aldrich employees, past and present, we wish Alfred a very happy 85th birthday and many more in years to come.

SAFC® Launches New Vendor Audit Services

On March 19, 2009, SAFC® announced details of its new Vendor Audit Services, designed to extend audit reach for customers that need to secure global supply chain integrity through enhanced traceability and quality confirmation for critical raw materials and key intermediates. SAFC's Vendor Audit Services are an extension of in-house auditing programs, and provide pharmaceutical and biotechnology firms with a team of highly trained auditors that have extensive regulatory compliance expertise and are on the ground in local regions, including China.

Standard audits available include:

- ISO 9001:2008 (previously ISO 9001:2000)
- ISO 13485:2003
- 21 CFR 211
- 21 CFR 820
- ICH Q7A
- GAMP 5
- GLP
- 21CFR58

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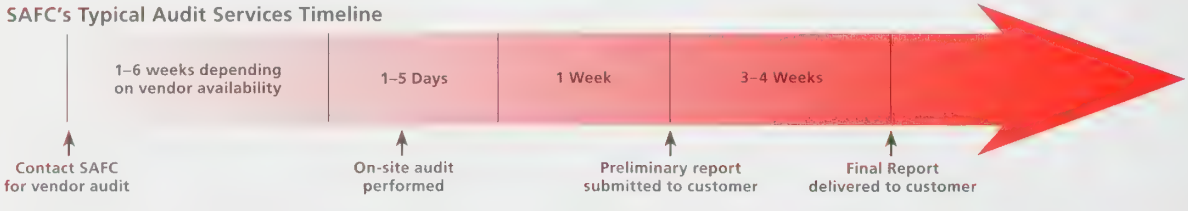
SAFC's Typical Audit Services Timeline



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Aldrichimica Acta

VOL. 42, NO. 1 • 2009

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The *Aldrichimica Acta* is also available on the Internet at **sigma-aldrich.com/acta**.

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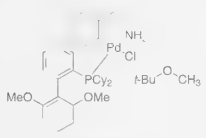
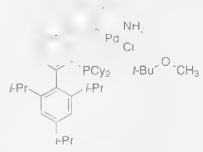
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Stephen Buchwald of the Massachusetts Institute of Technology kindly suggested that we make the single-component palladacycle precatalysts of SPhos and XPhos. These complexes simplify the use of these Buchwald ligands in a pre-defined metal-to-ligand ratio. The precatalysts are air- and moisture-stable, and can achieve high yields in C–N cross-coupling reactions using catalyst loadings as low as 0.1 mol % and 10-minute reaction times.



704946



704954

Biscoe, M. R. et al. *J. Am. Chem. Soc.* **2008**, *130*, 6686

704946 SPhos-palladium(II)phenethylamine chloride (1:1 MTBE solvate)

250 mg	$45.00
1 g	150.00

704954 XPhos-palladium(II)phenethylamine chloride (1:1 MTBE solvate)

250 mg	$69.00
1 g	190.00

Naturally, we made these useful catalyst precursors. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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ABOUT OUR COVER

Detail from ***Two Squirrels*** Photograph © Alfred Bader

Two Squirrels (oil on panel, 33.0 × 40.6 cm) was painted around 1616 and is attributed to the Flemish painter Jan Brueghel (or Bruegel) the Elder (1568–1625), also known as "Velvet" Brueghel and "Flower" Brueghel. He was the second son of Pieter Brueghel the Elder and trained with his older brother, Pieter Brueghel the Younger, in the family workshop in Antwerp.

The painting, which reflects the painter's focus later on in life on painting flowers and animals, depicts two sprightly squirrels clutching a gnarly, twisting branch set against an empty sky. This simple, engaging, and humorous depiction of a pair of lively small animals parallels the practice, at that time, of hanging portraits of husband and wife. Its high level of finish suggests that it probably was executed on commission or for sale in the market. The luminous effect created by the thin pigment layers and the fine detail are reminiscent of the style of the Brueghel family.

This painting is part of the Bader Collection of Dutch and Flemish Paintings at the Agnes Etherington Art Centre of Queen's University, Kingston, ON, Canada.

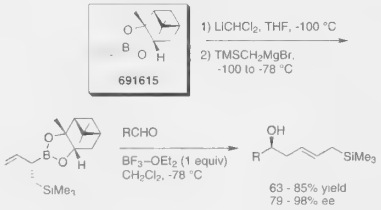
ALDRICH Chemistry

New Products from Aldrich R&D

Aldrich is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Double-Allylation Reagents

Reagents bearing multifunctional handles are of interest for the preparation of complex molecules. Professor Hall and coworkers developed a new multifunctional reagent that provides high diastereo- and enantiocontrol in a number of reactions, such as in the nucleophilic addition to aldehydes.



Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.

(+)-Allylboronic acid pinanediol ester, 97%

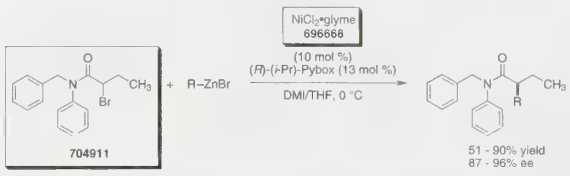
694584		1 g	$34.60
$C_{13}H_{21}BO_2$		5 g	112.00
FW: 220.12			

(+)-Vinylboronic acid pinanediol ester, 95%

691615		1 g	$66.00
$C_{12}H_{19}BO_2$		5 g	218.50
FW: 206.09			

Substrate for Nickel-Catalyzed Negishi Coupling

Chiral building blocks are of the utmost importance in the synthesis of more complex molecules. Professor Fu and coworkers devised the first catalytic enantioselective cross-coupling of secondary α-bromo amides with organozinc reagents. This new method proved to be highly selective for the coupling of unfunctionalized and functionalized organozincs with good yields.



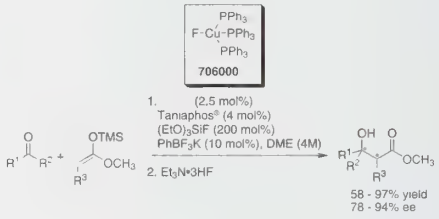
Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594

***N*-Benzyl-2-bromo-*N*-phenylbutanamide, 97%**

704911		5 g	$65.00
[*851073-30-8*]			
$C_{17}H_{18}BrNO$			
FW: 332.23			

Copper(I) Fluoride Complex for Aldol Reaction

Chiral tertiary alcohols are important building blocks for the synthesis of more complex molecules such as biologically active compounds or potential drugs. Shibasaki and coworkers developed a new copper fluoride catalyzed aldol reaction of ketones using ketene silyl acetals. Various aromatic ketones were screened and led to the desired aldol products in good yields and high selectivity.



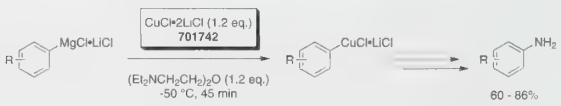
Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.
Taniaphos is a registered trademark of OMG AG and Co.

Fluorotris(triphenylphosphine)copper(I), 95% by HMR

706000		250 mg	$39.00
$C_{54}H_{45}CuFP_3$		1 g	95.00
FW: 869.40			

Copper Chloride–Bis(lithium chloride) Solution for Transmetallation

Cross-coupling reactions are essential tools for chemists. In particular, the amination of aromatic halides has become a method highly relied upon to prepare aryl amines. Knochel and coworkers developed a new general amination procedure using amidocuprates. This method proved to be very versatile resulting in good yields of the amine products. This new method is a good complement to the Pd-catalyzed amination reactions.



Del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7838

Copper(I) chloride–bis(lithium chloride) complex, 1 M in tetrahydrofuran

701742		50 mL	$95.00
CuCl•2(LiCl)	CuCl•2(LiCl)		
FW: 183.79			

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CHIRAL DIENE AND NHC LIGANDS FOR ASYMMETRIC CATALYSIS

Aldrichimica ACTA

VOL. 42, NO. 2 • 2009

ALDRICH Chemistry

Chiral Diene Ligands for Asymmetric Catalysis

Chiral, Chelating, Hydroxyalkyl and Hydroxyaryl N-Heterocyclic Carbenes: Design, Synthesis, and Application in Copper-Catalyzed Asymmetric Conjugate Addition (Cu-ACA)

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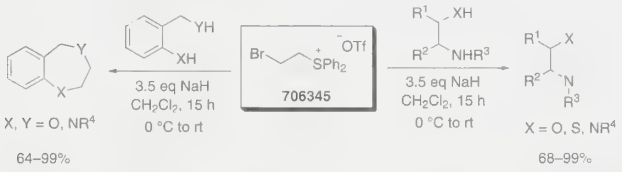
ALDRICH Chemistry

New Products from Aldrich R&D

Aldrich is Pleased to Offer Cutting-edge Tools for Organic Synthesis

Annulation Agent for Heterocyclic Synthesis

Professor Varinder Aggarwal recently reported an efficient annulation reaction to prepare a variety of 1,4-heterocyclic products in good-to-excellent yields. The mild reaction employs a bromoethylsulfonium salt in the presence of 1,2- and 1,3-amino alcohols, amino thiols, or diamines to give access to pharmacologically important morpholines, piperazines, thiomorpholines, benzoxazepines, and benzodiazepines



Yar, M. et al. *Org. Lett.* **2009**, *11*, 257.

(2-Bromoethyl)diphenylsulfonium trifluoromethanesulfonate

706345
$C_{15}H_{14}BrF_3O_3S_2$
FW: 443.30

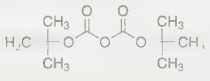
1 g $38.50
5 g 130.00

NEW Solutions of Common Reagents

Every researcher has experienced the frustration of using some lab reagent on a regular basis that is annoying to handle: it might be difficult to weigh out, is sticky, prone to static, or normally comes in a large size. Sigma-Aldrich has launched a series of solutions intended to make many of these common reagents easier to use. Each solution is prepared

Di-*tert*-butyl dicarbonate, 1 M in THF

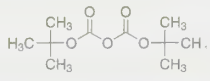
436267
[24424-99-5]
$C_{10}H_{18}O_5$
FW: 218.25



100 mL
800 mL

Di-*tert*-butyl dicarbonate, 2 M in THF

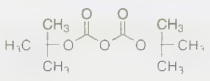
703753
[24424-99-5]
$C_{10}H_{18}O_5$
FW: 218.25



100 mL $51.50

Di-*tert*-butyl dicarbonate, 2 M in dichloromethane

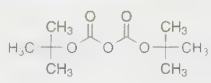
703737
[24424-99-5]
$C_{10}H_{18}O_5$
FW: 218.25



100 mL $51.50

Di-*tert*-butyl dicarbonate, 2 M in ethyl acetate

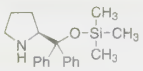
703745
[24424-99-5]
$C_{10}H_{18}O_5$
FW: 218.25



100 mL $51.50

(*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether, 0.05 M in toluene

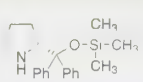
706442
[848821-58-9]
$C_{21}H_{31}NOSi$
FW: 325.52



25 mL $49.50

(*R*)-(+)- α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether, 0.05 M in toluene

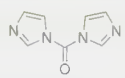
706450
$C_{21}H_{31}NOSi$
FW: 325.52



25 mL $49.50

1,1′-Carbonyldiimidazole, 0.4 M in dichloromethane

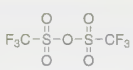
705284
[530-62-1]
$C_7H_6N_4O$
FW: 162.15



100 mL $30.70

Triflic anhydride, 1 M in dichloromethane

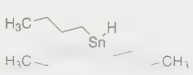
704083
[358-23-6]
$C_2F_6O_5S_2$
FW: 282.14



25 mL $53.00
100 mL 145.50

Tributyltin hydride 1 M in cyclohexane

704091
[688-73-3]
$C_{12}H_{28}Sn$
FW: 291.06



10 mL $28.50
50 mL 95.00

Iodine monochloride, 1 M in dichloromethane

291048
[7790-99-0]
ICl
FW: 162.36

100 mL $41.80
800 mL 195.50

Acetyl chloride, 1 M in dichloromethane

708496
[75-36-5]
C_2H_3ClO
FW: 78.50

100 mL $23.10
500 mL 77.00

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"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Mark Jensen of SCYNEXIS, Inc., kindly suggested that we make 5-chloro-1-aza-5-stanna bicyclo[3.3.3]undecane. The derivatives formed from this stannatrane are typically air stable and unusually reactive in various Stille couplings.[1] Furthermore, the byprod the coupling reaction can easily be recovered and recycled to afford the stannatran quantitative yield

707562

(1) Vedejs, E. et al. *J. Am. Chem. Soc.* **1992**, *114*, 6556. (2) Jensen, M. S. et al. *Org. Lett.* **2000**, *2*, 1081. (3) Sebahar, P. R. et al. *J. Org. Chem.* **2002**, *67*, 3788.

707562 5-Chloro-1-aza-5-stannabicyclo[3.3.3]undecane, 97%

Naturally, we made this useful alkyl-transfer reagent. It was no bother at all, just a pleasure to be able to help.

consideration. You can contact us in any one of the ways shown on this page and

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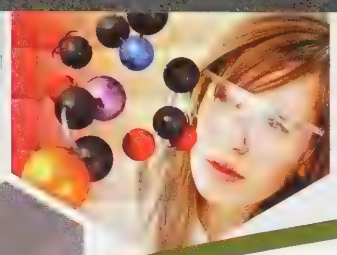
ABOUT OUR COVER

Camille Pissarro (1830–1903) painted ***The Artist's Garden at Éragny*** (oil on canvas, 73.4 × 92.1 cm) in 1898 in a small village (Eragny-sur-Oise) about 16 miles northwest of Paris. As seen in this painting and many of his other works, Pissarro was strongly attached to the land and to those who worked it. Critics complained about Pissarro's ability to find beauty in the rural way of life, but they never criticized the way he portrayed that beauty. As an originator of the [illegible]ement, Pissarro remained committed t[illegible] Impressionism's "fresh sensation throughout most of his life. A bit older than the other impressionists and, by all accounts, a generous and sympathetic man, Pissarro was an important influence on many younger artists, including Cézanne and Van Gogh.

In the artist's garden, a woman is working amidst vegetables and blooming flo[illegible] winds. A fresh breeze gently stirs the foliage and the puffy white clouds above. Nestled behind the garden wall is a charming chateau, no doubt where the vegetables being harv[illegible] made part of a sumptuous summer dinner later in the day.

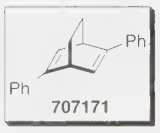
This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.



ALDRICH Chemistry

Chiral Diene Technology

In the past 5 years, a number of chiral diene ligands have emerged for a variety of asymmetric transformations. Hayashi[1] and Carreira[2] pioneered this field by synthesizing chiral diene ligands that formed stable complexes with metals and exerted high catalytic activities as well as high enantioselectivities. To demonstrate the potency of these new ligands, Hayashi and co-workers synthesized tolterodine, an antimuscarinic drug used to treat urinary incontinence, in a five-step sequence with an overall yield of 61%.[3] The first step of the sequence is an asymmetric 1,4 addition of phenylboronic acid, using a chiral diene ligand with a rhodium complex, to give the corresponding phenylated product in 96% yield.



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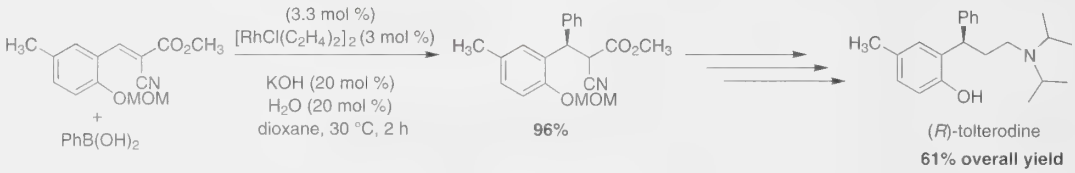

References:

(1) Hayashi, T. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11508.

(2) Fischer, C. et al. *J. Am. Chem. Soc.* **2004**, [illegible].

(3) [illegible] *Org. Lett.* **2008**, *10*, 589.

679941

707406

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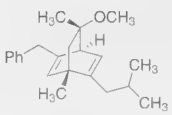
707171



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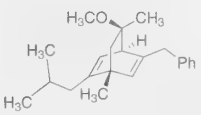

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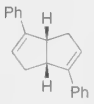

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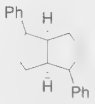
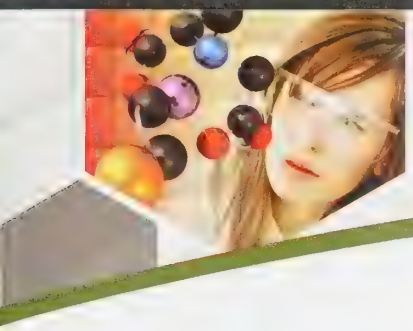


698733

Aldrich is pleased to offer these chiral diene ligands for use in a variety of applications. For additional information, please visit *sigma-aldrich.com/cpc*



ALDRICH Chemistry

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- Assured solvent quality
- No electrical power
- Low-pressure operation
- Safe, nonsparking design

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OPENING NEW FRONTIERS IN SYNTHESIS AND CATALYSIS

Aldrichimica ACTA

VOL. 42, NO. 3 • 2009

ALDRICH Chemistry

Discovering New Reactions with N-Heterocyclic Carbene Catalysis

Synthesis and Applications of Diorganozinc Reagents: Beyond Diethylzinc

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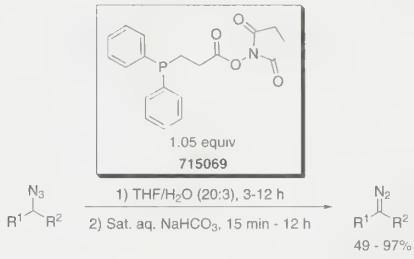
ALDRICH Chemistry

New Products from Aldrich R&D

Aldrich Is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Phosphine for the Conversion of Azides into Diazo Compounds

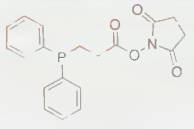
Due to difficulties with their preparation, especially when sensitive functional groups are present, diazo compounds are often overlooked in synthesis despite their synthetic versatility. Myers and Raines have developed a mild method to convert an azido group with delicate functional groups into a diazo compound by using the phosphine reagent shown below. Formally, this reaction is a reductive fragmentation of the azide, like the venerable Staudinger reaction, and is highly selective in most chemical environments



Myers, E. L; Raines, R. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2359

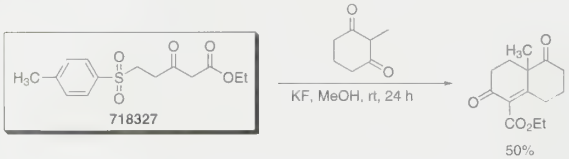
N-Succinimidyl 3-(diphenylphosphino)propionate, 95%

715069 1 g $27.50
[170278-50-9] 5 g 91.50
$C_{19}H_{18}NO_4P$
FW: 355.32



Stable Precursor for Nazarov's Reagent

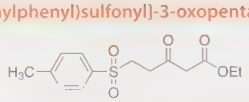
Nazarov's reagent is a commonly used annulating agent, but its synthesis is often fraught with poor yields or difficulties isolating the material. De Risi and coworkers recently reported a bench-stable powder that can be demasked under various conditions to generate Nazarov's reagent in situ



Benetti, S. et al. *Synlett* **2008**, 2609

Ethyl 5-[(4-methylphenyl)sulfonyl]-3-oxopentanoate, 95%

718327 1 g $77.50
$C_{14}H_{18}O_5S$
FW: 298.35

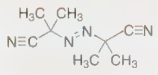


More NEW Solutions of Common Reagents

Every researcher has experienced the frustration of using on a regular basis some lab reagent that is annoying to handle: It might be difficult to weigh out, extremely volatile, prone to static, or noxious. Sigma-Aldrich has designed a series of solutions intended to make many of these common reagents easier to measure, handle, and dispense

2,2'-Azobis(2-methylpropionitrile) solution, 0.2 M in toluene

714887 100 mL $36.40
[78-67-1]
$C_8H_{12}N_4$
FW: 164.21

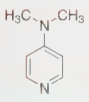


Iodine monochloride, 1 M in acetic acid

714836 100 mL $44.20
[7790-99-0]
ICl
FW: 162.36

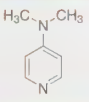
4-(Dimethylamino)pyridine solution, 0.5 M in ethyl acetate

714720 100 mL $41.00
[1122-58-3]
$C_7H_{10}N_2$
FW: 122.17



4-(Dimethylamino)pyridine solution, 0.5 M in THF

714844 100 mL $42.60
[1122-58-3]
$C_7H_{10}N_2$
FW: 122.17



1,8-Diazabicyclo[5.4.0]undec-7-ene solution, 1 M in ethyl acetate

714860 100 mL $41.10
[6674-22-2]
$C_9H_{16}N_2$
FW: 152.24

1,8-Diazabicyclo[5.4.0]undec-7-ene solution, 1 M in THF

714852 100 mL $41.10
[6674-22-2]
$C_9H_{16}N_2$
FW: 152.24

Acetaldehyde solution, 5 M in THF

719099 50 mL $45.00
[75-07-0]
C_2H_4O
FW: 44.05

Carbon disulfide, 5 M in THF

721476 50 mL $51.50
[75-15-0]
CS_2
FW: 76.14

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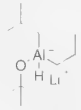
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc

Dr. Biagetti Matteo from GlaxoSmithKline kindly suggested that we make lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA). LDBBA is an effective reducing agent for the conversion of esters into aldehydes without the problematic over-reduction or the inconvenience of requiring lower temperatures.

Kim, M. S.; Choi, Y. M.; An, D. K. *Tetrahedron Lett.* **2007**, *48*, 5061.



718386

718386 Lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), 0.5 M in THF-hexanes 25 mL $73.00; 100 mL 201.00

Naturally, we made this useful reducing agent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help your research by saving you time and money? If so, please send us your suggestion. We promise to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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ABOUT OUR COVER

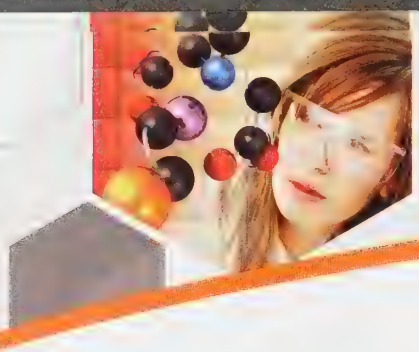
Photograph © Board of Trustees, National Gallery of Art, Washington

Paul Cézanne (1839–1906), who painted ***Landscape near Paris*** (oil on canvas, 50.2 × 60 cm) around 1876, was born in Aix en-Provence in 1839. His father, a prosperous businessman, decided that his only son should become a lawyer. Cézanne attended the Aix law school, but preferred classes at the Musée d'Aix (now the Musée Granet) and decided on a life as an artist instead.

In 1861, Cézanne, encouraged by his boyhood friend, the novelist Emile Zola, traveled to Paris. There, he frequented the Salon, studied the old masters, and copied Delacroix at the Louvre. He also forged friendships with many important artists, one of whom, Camille Pissarro, became a pivotal, lifelong influence on Cézanne.

Cézanne exhibited with the impressionists in 1874 and 1877. Our cover possibly painted in the company of Pissarro in Auvers-sur-Oise, a northwestern suburb of Paris, was completed sometime between the two exhibitions. The work clearly denotes Cézanne's departure from his early romantic and realist influences, and displays his enduring interest in *plein-air* painting. In this work, Cézanne placed an emphasis on the observation of nature and the rendering of light and atmospheric effects. He achieved structure by applying paint directly to the canvas, recording his response to the sensation of color.

This painting is part of the Chester Dale Collection at the National Gallery of Art, Washington, DC.



ALDRICH Chemistry

N-Heterocyclic Carbene Organocatalysts

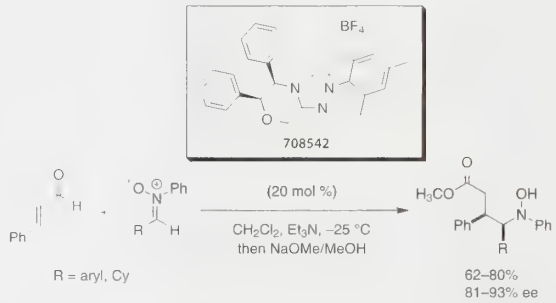
Organocatalysis has been an active field of research with over 2,000 publications in the past 10 years. Interest in this relatively new field derives from the many advantages of organocatalysis such as easy experimental procedures, reduction of chemical waste, avoidance of metal contamination in the product, and cost saving from not using expensive metals for the catalysis.

Scheidt and coworkers have developed a series of N-heterocyclic carbene organocatalysts for various reactions. These catalysts are efficient, and the chiral ones have given rise to good enantioselectivities.

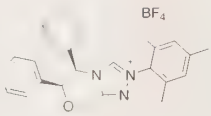
In 2005, Audrey Chan and Karl A. Scheidt reported the transformation of unsaturated aldehydes into saturated esters in good yields by using as low as 5 mol % of an N-heterocyclic carbene catalyst.

Reference:
Chan, A. and Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905

Recently, Phillips et al. reported the utilization of a chiral triazole for the enantioselective addition of homoenolates to nitrones affording γ-amino esters. This reaction is very versatile and tolerates electron-rich and electron-poor groups on the aldehyde. Using 20 mol % of the chiral triazole at –25 °C affords the desired products in good yields and selectivities.



Reference:
Phillips, E. M. et al. *J. Am. Chem. Soc.* **2008**, *130*, 2416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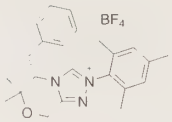
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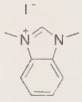
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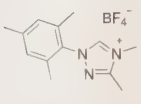
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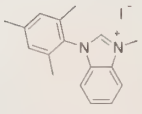
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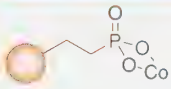
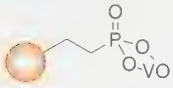
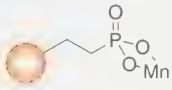
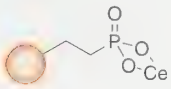
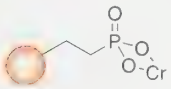
	Allylic/Benzylic CH_2 Allylic alcohols	Ketones Enones	*t*-BuOOH
	Allylic alcohols Sulfides	Epoxides Sulfoxides	*t*-BuOOH or NaBrO or H_2O
	Allylic CH_2 or Benzylic CH	Ketones	*t*-BuOOH
	1° alcohols 2° alcohols Sulfides	Acids Ketones Sulfoxides	NaBrO or *t*-BuOOH
	Sulfides	Sulfoxides	$NaBrO_3$ or *t*-BuOOH

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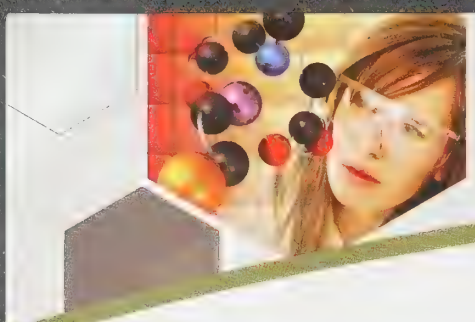
ALDRICH Chemistry

Powerful and Versatile Silicon Lewis Acids for Asymmetric Chemical Synthesis

Copper-Free Click Chemistry: Bioorthogonal Reagents for Tagging Azides

SIGMA-ALDRICH



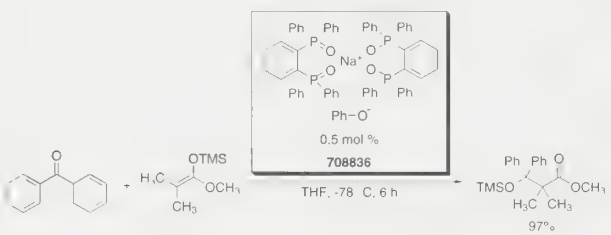
ALDRICH Chemistry

New Products from Aldrich R&D

Aldrich is Pleased to Offer Cutting Edge Tools for Organic Synthesis

Efficient Lewis Base for Mukaiyama Aldol Reaction with Ketones

There have been few reported methods for the synthesis of tertiary aldols, due to the low reactivity of the starting ketones and the rapid retro-aldol reaction, even at low temperatures. Ishihara and coworkers recently reported the Lewis base catalyzed Mukaiyama aldol reaction using a simple, mixed sodium phenoxide--phosphine oxide catalyst. The catalyst was effective with a wide variety of TMS enolates and ketones, providing the aldol adducts in generally good-to-excellent yields. Additionally, the catalyst was also effective in Mannich-type reactions when benzyl-, Boc-, or Cbz-protected aldimines were used as substrates



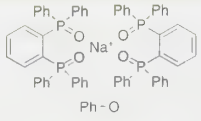
Hatano, M. et al. *Org. Lett.* **2007**, *9*, 4527

Bis[1,2-bis(diphenylphosphine oxide)benzene] sodium phenoxide, 95%

708836 1 g

$C_{54}H_{44}NaO_5P_4$

FW: 1073.01



Indoles and Azaindoles

The indole subunit is a near-ubiquitous component of biologically active natural products, and the study of indoles has been a major focus of research for generations. Substituted indoles have frequently been referred to as privileged structures,[1] since they are capable of binding to multiple receptors with high affinity, and thus have applications across a wide range of therapeutic areas. Due to this activity, it is not surprising that the indole ring system has become an important structural motif in many pharmaceutical agents.

The azaindole moiety differs only by the presence of an additional ring nitrogen and, thus, it exhibits excellent potential as a bioisostere of the indole ring system. Although considerably more rare in nature, azaindoles still constitute essential subunits in many pharmaceutically important compounds, and have been very valuable to synthetic and medicinal chemists. 7-Azaindoles are of particular interest because of their ability to mimic purine in its role as a hydrogen-bonding partner

(1) Horton, D. A. et al. *Chem. Rev.* **2003**, *103*, 893 and references therein. (2) (a) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 1031. (b) Popowycz, F. et al. *Tetrahedron* **2007**, [illegible] c) Song, J. J. et al. *Chem. Soc. Rev.* **2007**, *36*, 1120

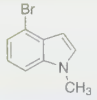
4-Bromo-1-methylindole, 95%

720860 500 mg

[590417-55-3]

C_9H_8BrN

FW: 210.07



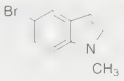
5-Bromo-1-methylindole, 97%

718300 5 g

[10075-52-2]

C_9H_8BrN

FW: 210.07

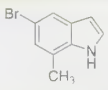


5-Bromo-7-methylindole, 97%

710822 1 g

C_9H_8BrN

FW: 210.07

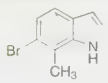


6-Bromo-7-methylindole, 97%

707155 250 mg

C_9H_8BrN

FW: 210.07



6-Fluoro-7-methylindole, 97%

707147 250 mg

[57817-10-4]

C_9H_8FN

FW: 149.16

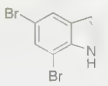
5,7-Dibromoindole, 97%

708798 1 g

[36132-08-8]

$C_8H_5Br_2N$

FW: 274.94



7-Fluoro-5-iodoindole, 97%

707058 500 mg

C_8H_5FIN

FW: 261.03

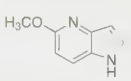
5-Methoxy-4-azaindole, 95%

707953 250 mg

[17288-40-3]

$C_8H_8N_2O$

FW: 148.16



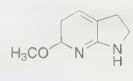
6-Methoxy-7-azaindole, 97%

702838 250 mg

[896722-53-5]

$C_8H_8N_2O$

FW: 148.16



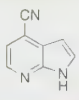
7-Azaindole-4-carbonitrile, 97%

706426 250 mg

[344327-11-3]

$C_8H_5N_3$

FW: 143.15



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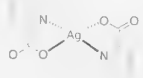
Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Phil Baran of The Scripps Research Institute kindly suggested that we make silver picolinate. Baran and coworkers recently utilized silver picolinate to effect a chemoselective oxidation of the guanidine ring en route to their notable total synthesis of palau'amine.[1] This approach avoids overoxidation and laborious protecting group chemistry. Silver picolinate was also employed in the total synthesis of (±)-axinellamines A and B.

(1) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095. (2) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581. (3) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.



718157

718157 Silver(II) picolinate, 97% 5 g
25 g

Naturally, we made this useful oxidation reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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ABOUT OUR COVER

The Grand Canal (oil on canvas, 23.0 × 33.0 cm) is one of twenty works of art by the British artist Richard Parkes Bonington (1802–1828) in the collection of the National Gallery of Art, and was painted c.1825/1827. At the age of 16, Bonington moved to Paris with his parents and studied there at the French National Art School, the Ecole des Beaux-Arts. During his brief career as an artist, he adopted the ideals of the Romantic Movement, and was influenced by the French artists Antoine-Jean Gros and Eugène Delacroix and by his fellow Englishman, John Constable.

Bonington was greatly admired for his exceptional ability to capture the effects of daylight and atmosphere with unerring assurance. In this work, the lovely play of sunlight on the building facades, the delicate reflections on the water, and the sweep of the clouds across the sky entice the eye and can be appreciated independently of the subject and its imitative appeal.

In the nineteenth century, painted scenes of Venice were very popular with the "Grand Tour" set, as post cards or photographs are today. Bonington produced many studies of this most beautiful city on the Adriatic while visiting Italy in 1826. He turned his sketches into some of his finest paintings, like the one seen here, which further enhanced his flourishing reputation as a landscape painter in London and Paris.

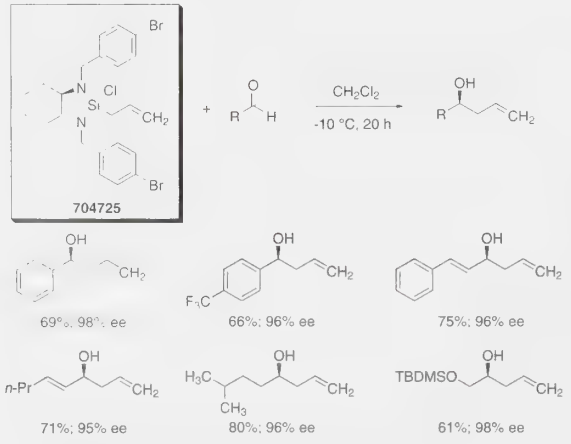
This painting is a gift of Roger and Victoria Sant to the National Gallery of Art, Washington, DC.

ALDRICH Chemistry

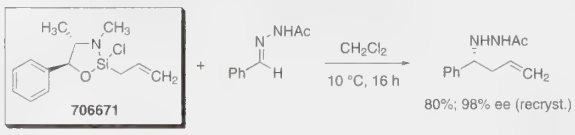
Leighton's Chiral Silane Reagents

The asymmetric allylation of carbonyl compounds remains one of the most important and fundamental addition reactions for the synthesis of optically active chiral building blocks.

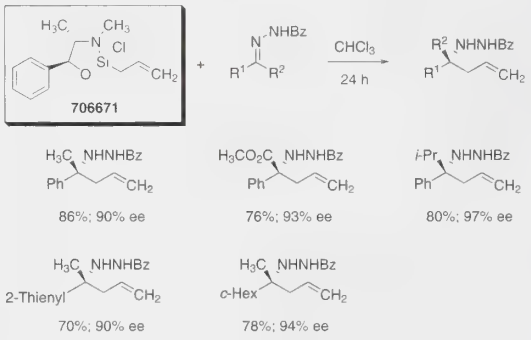
In 2002, Leighton and co-workers developed strained silacycle compounds as versatile reagents for the practical enantioselective allylation of aldehydes.[1] A newly developed chiral auxiliary based on the cyclohexane-1,2-diamine scaffold successfully allylated a broad range of aldehydes highly enantioselectively.[2]



The development of practical enantioselective syntheses of chiral amines is of great importance to synthetic organic and medicinal chemists. In 2003, Leighton and co-workers successfully used a pseudoephedrine-derived, five-membered-ring, strained silacycle reagent for the enantioselective allylation of acylhydrazones.[3]



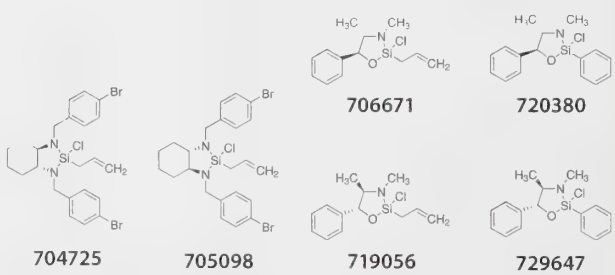
The reaction scope of these silacycles was extended to a practical method for the enantioselective synthesis of tertiary carbinamines based on the addition of this chiral allylsilane reagent to a structurally diverse array of ketone-derived benzoylhydrazones.[4] While many methods for the synthesis of quaternary α-amino acids have been published, far fewer reports have dealt with the synthesis of tertiary carbinamines. The free amines are easily accessed in good yields by treating the product hydrazides with SmI_2.



The reagents are effective with other types of imine electrophiles, and may be derivatized efficiently using cross-metathesis reactions. In addition, the corresponding phenylsilanes are effective general Lewis acids for a variety of enantioselective (nonallylation) nucleophilic addition reactions with acylhydrazones and other imine electrophiles.

References:

(1) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (2) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946. (3) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (4) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686



For more information on the applications of the Leighton silacycle reagents, please see Professor Leighton's review in this issue or visit *sigma-aldrich.com*

of soluble tetraazido star polymers (red) and biscyclooctyne-containing cross-linkers (blue) causes the formation of a 3D gel network (triazole linkages are shown in purple). The use of different star polymers and cross-linkers enables the modulation of gel properties (e.g., solubility, ability to be degraded by UV light, ability to be further functionalized post-gelation with imaging agents, drugs, or other probes). Incorporation of different cyclooctynes into the cross-linker (e.g., MOFO vs DIFO) allows for the tuning of gelation kinetics. See also reference 48.

(48) DeForest, C. A.; Polizzotti, B. D.; Anseth, K. S. *Nat. Mater.* **2009**, *8*, 659.

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(50) Blackman, M. L.; Royzen, M.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 13518.

(51) Devaraj, N. K.; Weissleder, R.; Hilderbrand, S. A. *Bioconjugate Chem.* **2008**, *19*, 2297.

(52) Pipkorn, R.; Waldeck, W.; Didinger, B.; Koch, M.; Mueller, G.; Wiessler, M.; Braun, K. *J. Pept. Sci.* **2009**, *15*, 235.

(53) Devaraj, N. K.; Upadhyay, R.; Haun, J. B.; Hilderbrand, S. A.; Weissleder, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 7013.

(54) Gutsmiedl, K.; Wirges, C. T.; Ehmke, V.; Carell, T. *Org. Lett.* **2009**, *11*, 2405.

(55) Dondoni, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8995.

(56) Song, W.; Wang, Y.; Qu, J.; Madden, M. M.; Lin, Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 2832.

(57) Song, W.; Wang, Y.; Qu, J.; Lin, Q. *J. Am. Chem. Soc.* **2008**, *130*, 9654.

(58) Wang, Y.; Song, W.; Hu, W. J.; Lin, Q. *Angew. Chem., Int. Ed* **2009**, *48*, 5330.

Trademarks: **ALEXA FLUOR**® (Molecular Probes, Inc.), **Hoechst** (Hoechst GmbH Corp.).

Keywords: click chemistry; [3 + 2] cycloaddition; bioorthogonal reagent; cyclooctynes; azides.

About the Authors

Jeremy M. Baskin was born in Montreal, Canada. He received his B.S. degree in chemistry in 2004 from the Massachusetts Institute of Technology (M.I.T.), with minors in biology and music. While at M.I.T., he performed research in the laboratories of Professor Stephen L. Buchwald and Professor Alice Y. Ting. In 2004, Jeremy began graduate studies in the laboratory of Professor Carolyn R. Bertozzi at the University of California, Berkeley. As a graduate student, Jeremy's research focused on the development of fluorinated cyclooctyne reagents for copper-free click chemistry and their application to imaging glycans in vivo. He earned his Ph.D. degree in 2009 and is currently conducting postdoctoral research under the guidance of Professor Pietro De Camilli at the Yale School of Medicine.

Carolyn R. Bertozzi is the T. Z. and Irmgard Chu Distinguished Professor of Chemistry and Professor of Molecular and Cell Biology at UC Berkeley; an Investigator of the Howard Hughes Medical Institute; and Director of the Molecular Foundry, a DOE Nanoscale Science and Research Center at the Lawrence Berkeley National Laboratory. She received her undergraduate degree in chemistry from Harvard University in 1988 and her Ph.D. degree in chemistry from UC Berkeley in 1993. After postdoctoral work at UC San Francisco in the field of cellular immunology, she joined the UC Berkeley faculty in 1996.

Professor Bertozzi's research interests span the disciplines of chemistry and biology with an emphasis on studies of cell surface glycosylation pertinent to disease states. Her lab focuses on profiling changes in cell surface glycosylation associated with cancer, inflammation, and bacterial infection, and on exploiting this information for the development of diagnostic and therapeutic approaches. In addition, her group develops nanoscience-based technologies for probing cell function and for medical diagnostics.

Professor Bertozzi has been recognized with many honors and awards for both her research and teaching accomplishments. She is an elected member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the German Academy of Sciences Leopoldina. She has been awarded the Whistler Award, the Ernst Schering Prize, a MacArthur Foundation Fellowship, the ACS Award in Pure Chemistry, a Presidential Early Career Award in Science and Engineering, and the Irving Sigal Young Investigator Award of the Protein Society, among many others. Her efforts in undergraduate education have earned her a UC Berkeley Distinguished Teaching Award and the Donald Sterling Noyce Prize for Excellence in Undergraduate Teaching. Professor Bertozzi participates in high-school outreach programs such as the Catalyst Program sponsored by the Camille and Henry Dreyfus Foundation, as well as programs that promote the participation of women in science. She was recently presented with the Li Ka Shing Award for Women in Science in recognition of these efforts.

New Catalysis Products from Aldrich R&D

Palladium(II) Acetate, Recrystallized

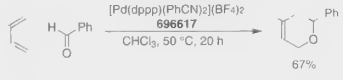
It has been shown that in some applications recrystallized palladium(II) acetate, $Pd(OAc)_2$, performs better than typical grades. White and Overman have both independently demonstrated that in some applications a particular grade of $Pd(OAc)_2$ is necessary. In particular, the preparation of the White catalyst as well as the preparation of the COP catalysts-$[COP\text{-}OAc]_2$ and $[COP\text{-}Cl]_2$ by Overman successfully employ and require recrystallized $Pd(OAc)_2$.

720070

References: Anderson, C. E.; Kirsch, S. F.; Overman, L. E.; Richards, C. J.; Watson, M. P *Tra. Synth.* **2007**, *84*, 148

Cationic Palladium Complexes, $[Pd(dppp)(PhCN)_2](BF_4)_2$

Cationic palladium(II) complexes are utilized in a variety of reactions. $[Pd(dppp)(PhCN)_2](BF_4)_2$ catalyzes the hetero-Diels–Alder reaction of dienes with aldehydes. The reaction yields substituted 5,6-dihydro-2*H*-pyrans without the use of Lewis acids and is believed to proceed through a stepwise mechanism.



References: (1) Oi, S.; Kashiwagi, K.; Terada, E.; Ohuhi, K.; Inoue, Y. *Tetrahedron Lett* **1996**, *37*, 6351. (2) Davies, J. A.; Hartley, F. R.; Murray, S. G. *J. Chem. Soc., Dalton Trans* **1980**, 2246

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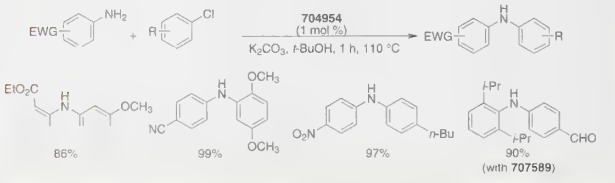
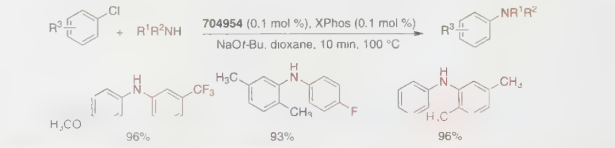
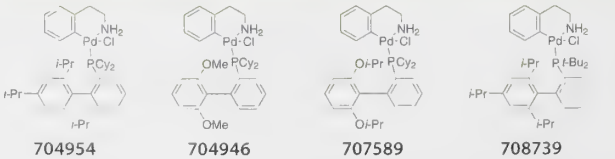
Air-Stable Precatalysts for Amination

C–N-bond-forming cross-coupling reactions typically require a palladium source along with associated ligands. Most Pd(0) sources are not air-stable, while the commonly employed air-stable Pd(0) source, $Pd_2(dba)_3$, contains associated ligands which could impede the reaction in some cases. Stable Pd(II) precursors require reduction under the reaction conditions. In either case, a ligand must be added to the reaction in order to lead to the active Pd species. Buchwald and coworkers recently reported the use of highly active air- and moisture-stable precatalysts, which, under the standard reaction conditions, form the active monoligated Pd species. These precatalysts are exceptionally efficient even under challenging conditions, such as coupling electron-poor anilines with deactivated aryl chlorides. The catalyst precursors also offer other advantages including low catalyst loadings and short reaction times.







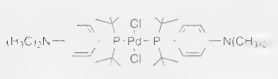
704954 (from XPhos) **704946** (from SPhos) **707589** (from RuPhos) **708739** (from *t*-BuXphos)

Reference: Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686

For more information on our Buchwald catalysts and ligands, visit ***aldrich.com/buchwald***

Nonproprietary Catalysts for Cross-Coupling Reactions

The cross-coupling reaction of heteroaryl halides is of particular interest to the pharmaceutical industry since many biologically active compounds are accessed through use of the Suzuki–Miyaura reaction. However, the efficient coupling of boronic acids with five-membered-ring heteroaryl halides or six-membered-ring heteroaryl chlorides bearing heteroatom substituents has not been well-developed. Catalysts are thought to form inactive complexes with many of these types of substrates, and thus, they typically require high catalyst loadings in order to achieve good yields. Guram's group at Amgen has recently reported the development of an air-stable palladium complex, $(A^{ta}Phos)_2PdCl_2$, for Suzuki–Miyaura cross-coupling reactions. The catalyst is very effective at coupling a wide range of substrates with arylboronic acids, including amino-substituted 2-chloropyridines and five-membered-ring heteroaryl halides. The products are obtained in excellent yields and high turnover numbers (up to 10,000 TON) are typically achieved. A series of new $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ catalysts were developed with various reactivities.



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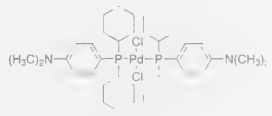

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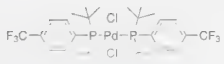

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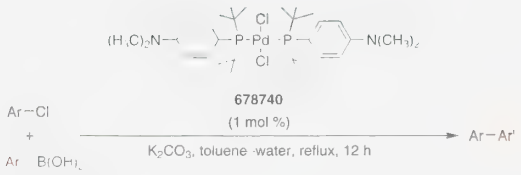

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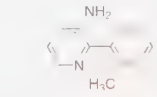
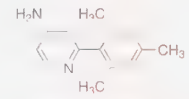
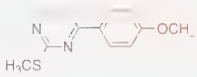
1		93
2		98
3		95

References: (1) Singer, R. A. et al. *Tetrahedron Lett.* **2006**, *47*, 3727. (2) Singer, R. A. et al. *Synthesis* **2003**, 1727. (3) Guram, A. S. et al. *Org. Lett.* **2006**, *8*, 1787

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Palladium(II) [1,3-bis(diphenylphosphino)propane]bis(benzonitrile) bis(tetrafluoroborate)
696617 250 mg
[175079-12-6]
FW: 898.71

(XPhos) palladium(II) phenethylamine chloride
704954 250 mg
$C_{41}H_{50}ClNPPd$ 1 g
FW: 738.76

(SPhos) palladium(II) phenethylamine chloride (1:1 MTBE solvate)
704946 250 mg
1 g
FW: 760.72

RuPhos palladium(II) phenethylamine chloride
707589 250 mg

t-BuXPhos palladium(II) phenethylamine chloride
708739 250 mg
FW: 686.69

Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine) dichloropalladium(II)
678740 1 g
[887919-35-9] 5 g
FW: 708.07

Bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine]palladium(II) chloride
692913 250 mg
$C_{40}H_{64}Cl_2N_2P_2Pd$ 1 g
FW: 812.22

chloride
692921 250 mg
$C_{36}H_{44}Cl_2F_6P_2Pd$ 1 g
FW: 757.93

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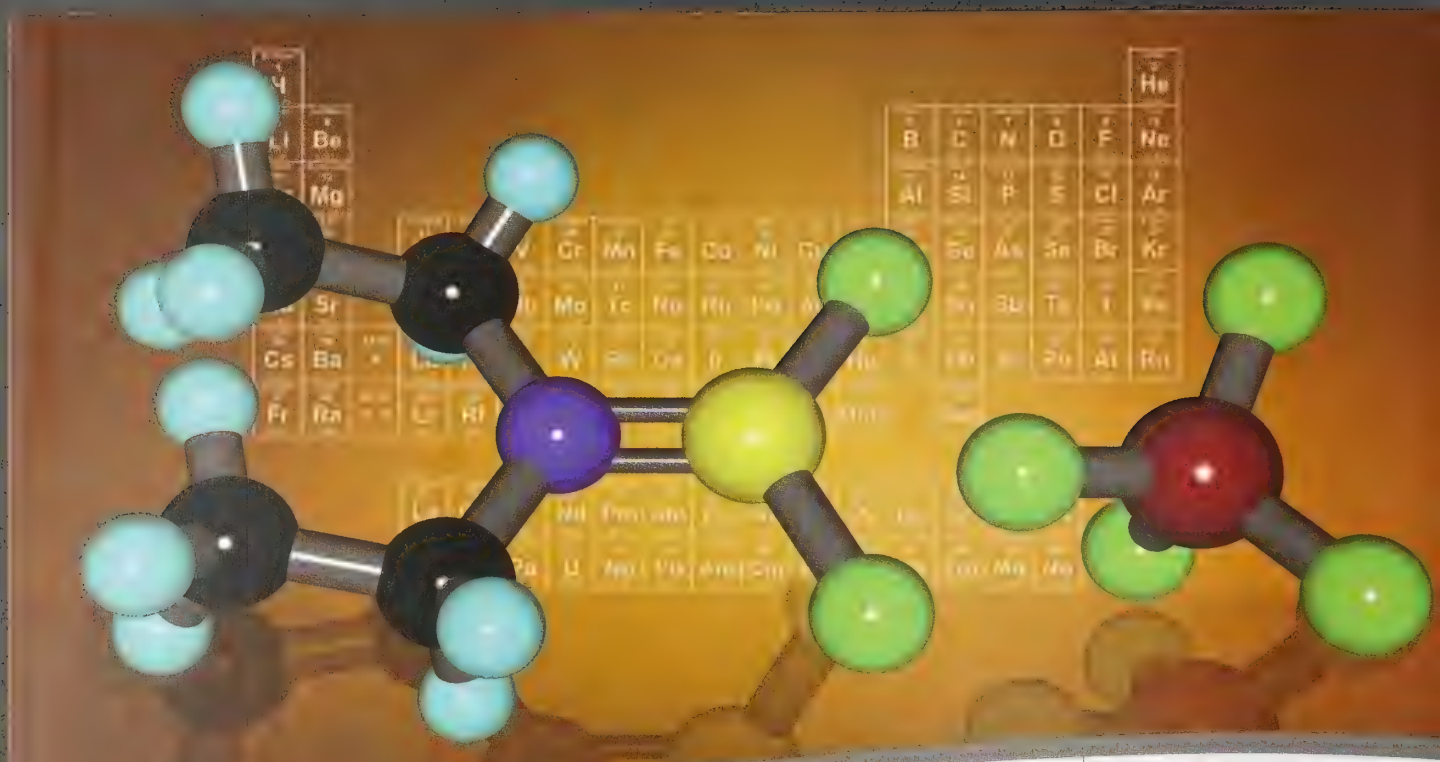

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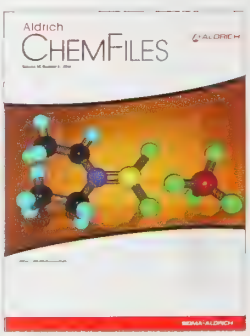

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Joe Porwoll, President
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Professor Bruce Lipshutz from the University of California, Santa Barbara, kindly suggested that we make copper-in-charcoal. This useful heterogeneous catalyst promotes a variety of catalytic transformations such as asymmetric hydrosilylations, click reactions, and is also used in the preparation of diaryl ethers

(1) Lipshutz, B. H.; Frieman, B. A.; Tomaso, A. E., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 1259 (2) Lipshutz, B. H.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235. (3) Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, *9*, 1089

Cu/C
709107

709107 Copper-in-charcoal, 3 wt. % 5 g $71.80

Naturally, we made this useful heterogeneous catalyst. It was no bother at all, just a pleasure to be able to help

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion. We would be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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Detail from ***Travellers near the Edge of a Wood*** (oil on panel, 51.5 × 67.2 cm) was painted ca. 1638 by Jacob van Geel (ca.1585–1638), the seventeenth-century Dutch painter. Born in Middelburg, Zeeland Province, he became a member of the guild of St. Luke (Middelburg) at about age 30, and later joined the painters' guilds of Delft and Dordrecht, and seems to have led a private life dominated by debt and conflict.

Having been influenced by the painting styles of Jan Brueghel the Elder (1568–1625) and Hercules Seghers (ca. 1589–1638), he specialized in painting fantasy landscapes often dominated by a large cluster of trees, as is the case here. In this complex composition, the viewer is drawn to at least three scenes featuring travellers at various stages of their journey. The bright daylight penetrates from the left side and illuminates the twisted and bulging trees that fill the composition and attract the viewer's eyes to the center of this work.

This painting is part of the Bader Collection of Dutch and Flemish Paintings, whose future home will be the Agnes Etherington Art Centre of Queen's University, Kingston, ON, Canada.

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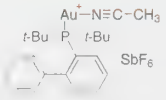
Gold Catalysts



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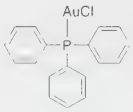

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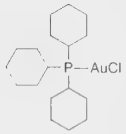

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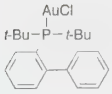

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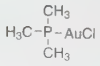

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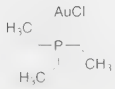

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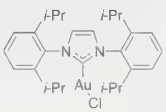

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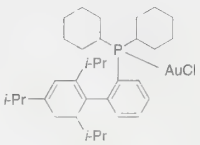

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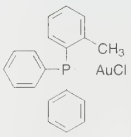

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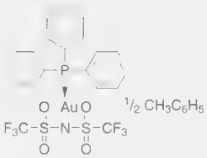


677922

$NaAuCl_4 \cdot 2H_2O$

298174

$AuBr_3$

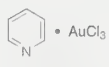
398470

AuCl

481130

$AuCl_3$

334049



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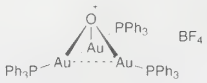

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Silver Salt Additives

$AgNTf_2$	AgOTs	$AgSbF_6$	$AgBF_4$	$AgPF_6$	AgOTf
668001	176427	227730	208361	227722	176435

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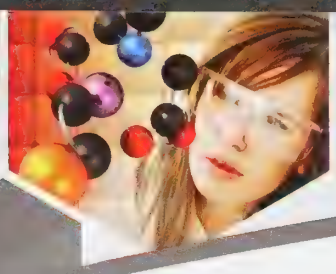


ALDRICH Chemistry

Heterocyclic MIDA Boronates from Aldrich

Aldrich has prepared a series of 2-, 3-, and 4-heterocyclic MIDA boronates, including the notoriously unstable 2-pyridyl boron anion equivalent 2-pyridinylboronic acid MIDA ester (**719390**).

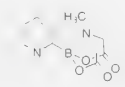
(1) Gillis, E.P.; Burke, M.D. *Aldrichimica Acta* **2009**, *42*, 17. (2) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

Figure 1. 2-Pyridinylboronic acid MIDA boronate, stable 2-pyridyl boron anion equivalent.

Benefits of MIDA Boronates:

- Bench- and air-stable
- Stable to anhydrous cross-couplings conditions
- Good solubility properties
- Monomeric composition
- Silica gel compatible
- Controlled release for in situ cross-coupling
- Straightforward surrogate to unstable boronates
- Simple, IP-included model

Aldrich has prepared a growing series of heterocyclic MIDA boronates, many of which are shown below.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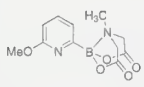
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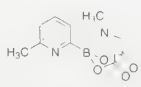
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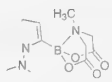
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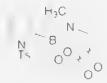
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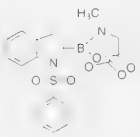
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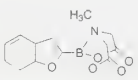
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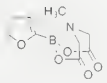
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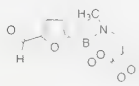
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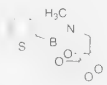
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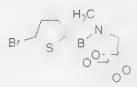
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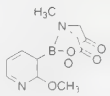
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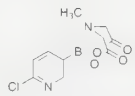
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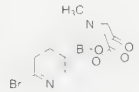
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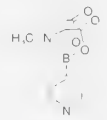
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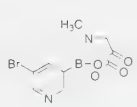
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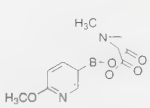
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For more information on MIDA boronates, please visit *aldrich.com/mida*

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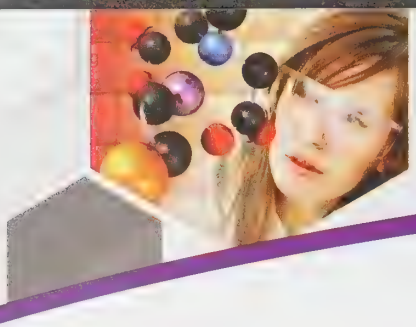
ALDRICH Chemistry

SIGMA-ALDRICH



ALDRICH Chemistry

Aldrich Congratulates the 2010 Winners of the Nobel Prize in Chemistry

Professors **Ei-ichi Negishi**, **Akira Suzuki**, and **Richard F. Heck** have been awarded the 2010 Nobel Prize in Chemistry by The Royal Swedish Academy of Sciences for their trailblazing contributions to the area of "palladium-catalyzed cross couplings in organic synthesis".

Photo courtesy of Purdue U./ Andrew Hancock

Distinguished Professor
Ei-ichi Negishi
Purdue University, U.S.A.

Photo courtesy of Hokkaido U

Distinguished Professor Emeritus
Akira Suzuki
Hokkaido University, Japan

Photo courtesy of U of Delaware

Professor Emeritus
Richard F. Heck
University of Delaware, U.S.A

Aldrich congratulates these distinguished chemistry pioneers on this achievement and thanks them for their lasting contributions to organic synthesis. Our company is proud to have had close collaborations with Professors Negishi and Suzuki, two former associates of another Nobel laureate and longtime Aldrich collaborator and member of the Board of Directors, the late Professor H. C. Brown.

The *Aldrichimica Acta* has had the distinct privilege of publishing high-impact review articles by a number of chemistry Nobel laureates, such as Professors Derek H. R. Barton, Herbert C. Brown, Elias James Corey, Ei-ichi Negishi, George A. Olah, Charles J. Pedersen, Vladimir Prelog, and K. Barry Sharpless.

The tradition of supporting future scientific leaders is strong at Sigma-Aldrich. Throughout our history, we have acknowledged scientific excellence through sponsorship of awards, symposia, and graduate-level research in the fields of chemistry, life science, and materials science. A number of previous winners of Sigma-Aldrich sponsored American Chemical Society awards (e.g., Professors George A. Olah, K. Barry Sharpless, and Ei-ichi Negishi) have gone on to receive the ultimate recognition, the Nobel Prize in Chemistry.

To access highly informative *Aldrichimica Acta* reviews written by Nobel laureates and other chemistry luminaries, visit ***aldrich.com/acta***

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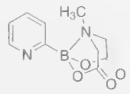
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

A number of customers have suggested that we produce 2-pyridinylboronic acid MIDA ester. This isolable, chromatographically and benchtop-stable reagent serves as a viable 2-pyridylboron anion equivalent, and is used as a versatile cross-coupling partner.

(1) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961



719390

719390 2-Pyridinylboronic acid MIDA ester 1 g, 5 g

Naturally, we made this useful boronic acid surrogate. It was no bother at all, just a pleasure to be able to help

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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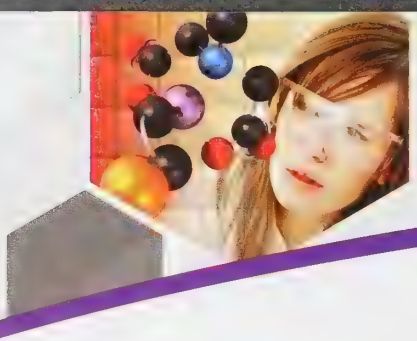
ABOUT OUR COVER

Photograph © Rosie Sandifer

Taos Pueblo Snow (oil on canvas, 40.6 × 70.0 cm) was painted in 2009 by the American painter and sculptor Rosie Sandifer (b. 1946) following a visit to the Pueblo. It depicts the centuries-old, Native American village with the same name. Taos Pueblo is located about two miles north of the town of Taos, New Mexico, and is one of the longest continually inhabited places in the U.S.A. It has been designated a World Heritage Site by UNESCO and a National Historic Landmark by the U.S. Government.

Equally gifted at painting and sculpting, Sandifer paints her impressions of what she observes in nature by simplifying to the essentials the effects of fleeting light on the subject, as evidenced by the white, brown, and turquoise that dominate in this painting. While her subject matter has included landscapes, figures, and animals, she has tended to focus on Western landscapes. She has participated in numerous solo, group, and juried exhibitions, and her paintings and sculptures are on display in a number of museums and public places in the U.S. Currently a resident of Santa Fe, NM, Sandifer received her extensive art education and training most notably at the Froman Painting School in Cloudcroft, NM, and the Art Students League in Stowe, VT, where she was influenced by Frank Mason, a classical realist painter and one of the most acclaimed modern American painters and teachers.

This painting is provided courtesy of the artist and is in her private collection.



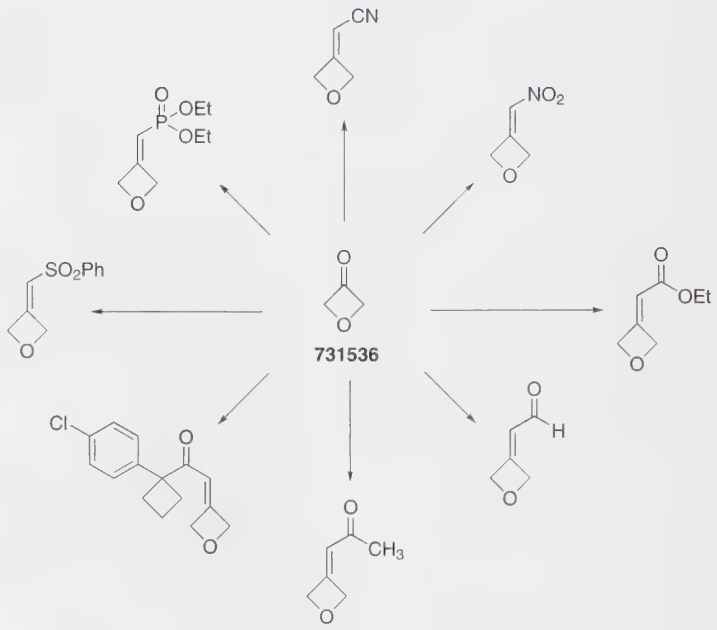
ALDRICH Chemistry

New Oxetane Building Blocks

Oxetanes have historically been of modest interest to synthetic and medicinal chemists, perhaps with the natural product paclitaxel or TAXOL® being the best known example of an oxetane-containing substance. Presently, oxetanes are receiving greater attention as attractive modules for drug discovery, largely due to a series of reports from Rogers-Evans, Carreira, and coworkers. These reports have demonstrated the improved physico- and biochemical properties of a molecular scaffold when an oxetane unit replaces a *gem*-dimethyl unit[1] and the ability for an oxetane ring to function as a surrogate for a carbonyl group.[2,1b] Another recent report has disclosed the use of 1,6-substituted azaspiro[3.3]heptanes containing an oxetane ring as alternatives to unstable 1,3-heteroatom-substituted cyclohexanes.[3] In most cases, 3-oxetanone, **731536**, was the principal building block employed by the authors to install the oxetane unit (**Scheme 1**).

References: (1) (a) Wuitschik, G. et al. *Angew. Chem., Int Ed.* **2006**, *45*, 7736. (b) Wuitschik, G. et al. *J. Med. Chem.* **2010**, *53*, 3227. (2) Wuitschik, G. et al. *Angew. Chem., Int Ed.* **2008**, *47*, 4512. (3) Burkhard, J. A. et al. *Org. Lett.* **2010**, *12*, 1944.

For a complete list of available oxetanes, please visit *aldrich.com/oxetane*



Scheme 1. Oxetane Derivatives Synthesized from 3-Oxetanone.

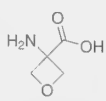
We are pleased to offer a wide selection of new oxetane building blocks for a variety of applications in synthetic and medicinal chemistry.


731536

733296

731560

731579



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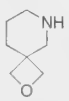

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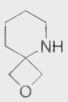

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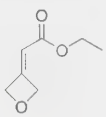
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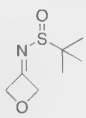

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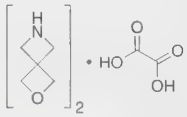

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Remembering Dr. Jai P. Nagarkatti (1947–2010)

Dr. Sharbil J. Firsan[1]
Editor, Aldrichimica Acta
Sigma-Aldrich Corp.

The *Aldrichimica Acta* has lost a dear friend, a lifelong staunch supporter, and a strong believer in its value and mission, both to the company and to the chemistry community. Dr. Jai P. Nagarkatti—the company's Chairman, CEO, and President—died suddenly on Saturday, November 13, 2010.[2–4] While his Sigma-Aldrich "family" has been devastated by his unexpected departure and mourn his loss, this editorial will not be about the facts and figures of Jai's career and accomplishments, nor about Sigma-Aldrich's growth under his tenure. Suffice it to say that he gave over 34 years of dedicated service to Aldrich and Sigma-Aldrich, the only employer he ever worked for after receiving his Ph.D. degree from Texas A&M University, Commerce, TX. Not that facts and figures are not important, but the intention here is to offer fond recollections that shed some light on the kind of man Jai really was.

It was during my first interview with the company that I met Jai. He was the president of Aldrich at the time, and came across as energetic, eager, engaged, and passionate about Aldrich and the business and science of chemistry. He was keen to find out from me what new ideas I was bringing in and what I, as a customer, thought of Aldrich. He took notes during our meeting. During the interview, I could tell he was very proud of working for Aldrich.

After joining the company, I became well acquainted with Jai, who consistently showed strong interest in the *Acta*: He eagerly anticipated each issue, kept copies in his office, and took a strong interest in what was published and what was advertised in it. He recommended authors, emailed thank-you letters to them, and never missed a chance to offer this editor sincere words of appreciation and encouragement. In fact, one little story sums him up in this regard: I sometimes would be crossing St. Paul Avenue in Milwaukee going from one Aldrich building to another, while Jai would be crossing the same street in the opposite direction. He, invariably, would stop me in the middle of the street to ask me about the *Acta*—totally oblivious to fast-moving traffic and the fact that both of us could be run over by an inattentive driver.

I wholeheartedly concur with one of Jai's longtime associates who related to me that he was always amazed at how eminently reachable Jai was, even after becoming the Chairman, President, and CEO of Sigma-Aldrich, a $2+ billion company, considering how incredibly busy and in demand he was. While he had administrative assistants, Jai never walled himself off; one could walk into his office anytime. He also did not hesitate to answer a phone call or an email himself, or walk into any area of the company and chat with anyone. When he wanted to talk to a subordinate, he preferred to walk over to his/her cube or office, rather than call him/her to come to his office. He did not hesitate, as this editor can attest to, to pick up the phone and call someone in the company to thank them for their efforts and offer words of encouragement. He was incredibly humble and had a knack for conversing with equal ease with a custodian at Sigma-Aldrich, a Wall Street analyst, or a highly regarded university professor. He made sure to attend and serve at as many of the company functions for employees as he could. He almost was a fixture at our Company's annual picnic and other events. That was his way of staying connected to the employees. As Dr. Alfred Bader put it, "[Jai] was inspirational for employees who appreciated his dedication and warmth. Jai was so very human...."

Jai P. Nagarkatti in 2007 at Sigma-Aldrich's Headquarters in St. Louis, MO.

By keeping a full schedule and working hard to the point of being a workaholic, Jai led by example and brought an excitement, and a depth of perception, to projects and tasks that went beyond the customary business reasons and logic: If you met with him to discuss a project, you learned not only about the project, but also about the deeper significance of the project to the company, to customers, and even to society. This, of course, meant that you also left his office with a lot more work to do than when you walked in.

Being focused on his work and responsibilities did not mean that he lacked a sense of humor. In fact, it wasn't unusual to overhear him being lighthearted. One noteworthy moment that I remember occurred at an Aldrich employee award dinner in Milwaukee, when he was introducing a longtime, distinguished associate, who was well-known for being outspoken. Jai said that, "when [name omitted] reported to me, I was never sure who reported to whom." Being as humble as he was, Jai was not afraid of making fun of his weaknesses, as when he picked up a set of golf clubs at a company outing and played a round of golf, never having swung a golf club before! Jai just wanted employees to see that he wasn't good at everything.

Farewell my friend, Jai. Your enthusiasm, dedication, thoughtfulness, humility, and kindness will be forever missed.

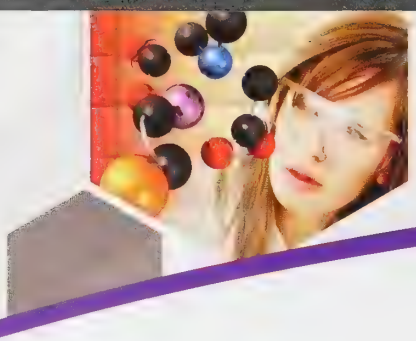
Notes

(1) I thank John Radke, Joe Porwoll, and Ali Ataei for sharing their recollections of Jai. Some of these recollections have been weaved into this article. I am also grateful to Ms. Melissa Jacobs of Sigma-Aldrich for reviewing this article and offering helpful suggestions.

(2) A summary of Jai's career at Sigma-Aldrich is part of a press release issued by the company on November 14, 2010, announcing Jai's sudden death and the appointment of a successor. It can be accessed at *http://investor.sigmaaldrich.com/releasedetail.cfm?ReleaseID=530331.*

(3) The obituary released by Jai's family was published in the St. Louis Post-Dispatch of Monday, November 15, 2010, which can be accessed at *http://www.legacy.com/obituaries/stltoday/obituary.aspx?n=jai-nagarkatti&pid=146642609.*

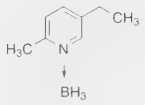
(4) The St. Louis Post-Dispatch ran a story on Jai by Jim Doyle on Tuesday, November 16, 2010, which can be accessed at http://*www.stltoday.com/business/article_46d399bc-61e2-521a-9ff8-b7048bf6ab3b.html.*



ALDRICH Chemistry

New Reductive Amination Reagent

PEMB: A Stable, Liquid Pyridine Borane Complex

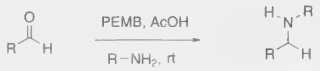


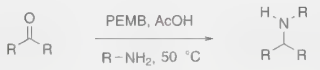
5-Ethyl-2-methylpyridine borane (PEMB)
725080

Advantageous Properties of PEMB:

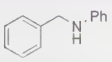
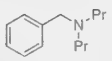
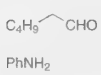
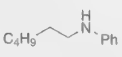
- Excellent for reductive aminations
- Mild reducing agent for imines and oximes
- Reaction with protic solvents is very slow
- Soluble in aromatic hydrocarbons, alcohols, and ether solvents
- Can be used solvent-free for reductive aminations
- Chemically efficient: two of three hydrides are utilized

Select Substrate Scope





Examples

Aldehyde and Amine	Conditions	Product	% Yield in MeOH (% Yield Neat)
	PEMB, AcOH, MeOH, 25 °C		72 (80)
	PEMB, AcOH, MeOH, 25 °C		0 (96)
	PEMB, MeOH, 25 °C		92 (94)
	PEMB, AcOH, MeOH, 25 °C		92 (93)
	PEMB, AcOH, MeOH, 50 °C		74 (94)

For more examples and experimental details, please see: Burkhardt, E. R.; Coleridge, B. M. *Tetrahedron Lett.* **2008**, *49*, 5152

For more information, please visit ***aldrich.com/pemb***
For research quantities under 500 grams, please contact Aldrich Chemistry.
For quantities over 500 grams, please contact BASF.

Recent Advances in the Application of α-Phenylethylamine (α-PEA) in the Preparation of Enantiopure Compounds

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Outline

1. Introduction

Mostly as a consequence of the increased interest in the production of enantiomerically pure compounds by the pharmaceutical and agrochemical industries, the chemistry community has intensified its efforts to develop more efficient ways to obtain chiral products with the desired configuration. In this regard, α-phenylethylamine (α-PEA, 1-phenylethylamine, 1-phenylethanamine, α-methylbenzenemethanamine, α-methylbenzylamine, α-aminoethylbenzene, $CH_3CH(Ph)NH_2$) has emerged as an important chiral reagent principally because of its low price, accessibility in both enantiomeric forms, and facile introduction and removal in most asymmetric syntheses. Two reviews appeared in the late 1990s on the use of α-PEA in the preparation of enantioenriched compounds.[1] However, a significant number of new developments have been reported in the last decade, which warrants an update on the more significant advances in the area that were reported between 2000 and early 2010. This review focuses on the applications of α-PEA as a chiral ligand for asymmetric catalysis, as a chiral auxiliary in the resolution of racemates, and as a chiral reagent in the stereodifferentiation of prochiral substrates, as well as on its incorporation into novel organocatalysts.

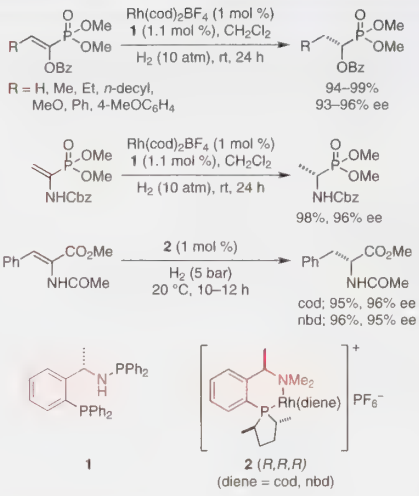
2. Incorporation of α-Phenylethylamine (α-PEA) in Chiral Ligands for Asymmetric Catalysis

A central development in asymmetric catalysis has been the design and preparation of enantiopure catalysts containing an active metal and a regulating chiral organic ligand and their application in the synthesis of enantioenriched building blocks from prochiral substrates. Following the great success of complexes of chiral phosphine ligands and transition metals in asymmetric synthesis,[2] intense research activity has been directed towards the development of comparable ligands containing nonracemic amines. In particular, catalysts incorporating ligands with the α-PEA moiety have been quite effective in several asymmetric transformations.

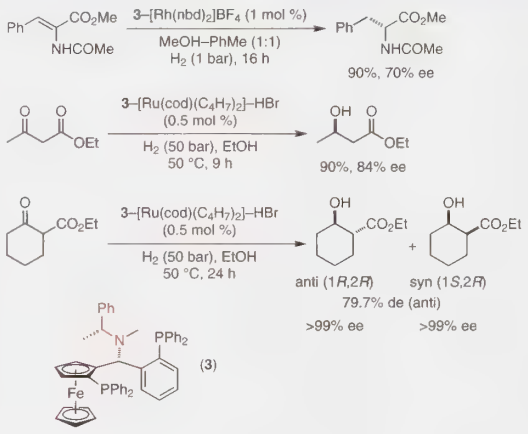
2.1. Enantioselective Reduction of Prochiral Unsaturated Double Bonds

Hu, Zheng, and co-workers[3] have described the use of chiral phosphine–aminophosphine ligand **1** (easily synthesized from (*S*)-α-PEA, *n*-BuLi, and Ph_2PCl), in combination with $Rh(cod)_2BF_4$, for the enantioselective hydrogenation of the C–C double bond in various α-enol ester phosphonates and α-enamido phosphonates. In particular, ligand **1** was utilized in the successful preparation of biologically important α-hydroxy and α-amino phosphonates in 94–99% yields and 93–97% ee's (**Scheme 1**). In the same way, optically active ligand **2** was developed by Brauer et al.[4] for the enantioselective hydrogenation of methyl acetamidocinnamate to the corresponding amido ester with 95% ee (see Scheme 1).

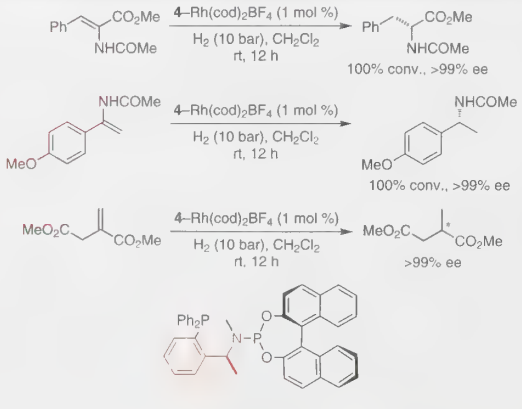
In a related development, Knochel and collaborators reported on the effectiveness of the nonracemic, ferrocene-based ligand **3** in



Scheme 1. Highly Enantioselective Hydrogenations of C–C Double Bonds in the Presence of Chiral Ligands Incorporating α-PEA.



Scheme 2. Chiral Ferrocene Derivative **3** in the Ru- and Rh-Catalyzed Hydrogenation of C=C and C=O Bonds. *(Ref. 5)*



Scheme 3. Highly Enantioselective Hydrogenations Catalyzed by **4**–Rh(I) Complexes. *(Ref. 6)*

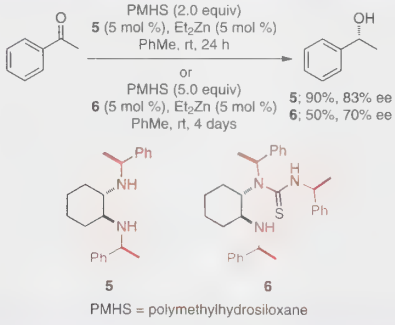
the enantioselective ruthenium- and rhodium-catalyzed hydrogen addition to prochiral substrates containing C=C or C=O bonds (**Scheme 2**).[5]

Similarly, Huang et al. prepared an interesting phosphine–phosphoramidite ligand, **4**, starting from (*S*)-α-PEA. Together with Rh(I), **4** efficiently catalyzes the reduction of α-dehydroamino esters, enamines, and dimethyl itaconate to afford the reduced products in ≥99% ee's. These results show that the central chirality of the α-phenylethylamine moiety in **4** dictates the absolute configuration of the hydrogenation product, regardless of the axial chirality of the binaphthyl moiety (**Scheme 3**).[6]

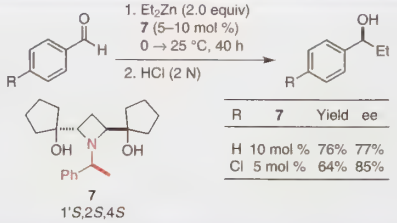
The asymmetric transfer hydrogenation of prochiral ketones can be carried out successfully by employing α-PEA derivatives. For example, the enantioselective hydrosilylation and reduction of prochiral ketones to alcohols has been effected by using polymethylhydrosiloxane (PMHS) as the hydride source and a set of *all-S*, α-PEA-containing, chiral diamines, **5**, and thioureas, **6**. This procedure afforded the respective secondary *R* alcohol (**eq 1**).[7] Along similar lines, Adolfsson and co-workers showed that the use of α-amino-acid-containing chiral thioamide ligands, *i*-PrOH as a hydride source, and Ru(II)- or Rh(III)-based catalyst complexes, led to several secondary alcohols derived from acetophenones in high yields and good enantioselectivities.[8]

2.2. Enantioselective Addition of Diethylzinc to Aromatic Aldehydes

Asymmetric organozinc addition to prochiral aldehydes and ketones allows the synthesis of chiral alcohols, which are ubiquitous features in the structures of natural products and pharmaceuticals. The reaction between diethylzinc (Et_2Zn) and benzaldehyde has become a benchmark reaction for testing newly designed ligands for catalytic enantioselective synthesis.[9] In this context, Wilken et al. have reported the use of several nonracemic tridentate azetidines in the enantiocontrolled catalytic addition of diethylzinc to several aromatic aldehydes, and demonstrated that the *all-S* chiral ligand, **7**, efficiently catalyzes this reaction in good yields and ee's (**eq 2**).[10] In a related development, Guofu Zi and collaborators prepared



eq 1 *(Ref. 7)*



eq 2 *(Ref. 10)*

various chiral azetidines by reaction of (*R*)- or (*S*)-α-PEA, benzaldehyde, and acetoxyacetyl chloride. These researchers observed that the resulting *R,R,R* azetidine ligand led to the *S* alcohols, while the *R,S,S* diastereomer gave rise to the *R* alcohols in 73–94% yields and 57–95% ee's.[11]

Moreover, Wang's group[12] has described the application of optically active ligand **8**—prepared by a one-pot condensation of the corresponding aldehyde with 2-naphthol and (*S*)-α-PEA—in the enantioselective addition of diethylzinc to aldehydes. Most interesting are the high ee values obtained at room temperature (>99% ee's for the *R* alcohols). Furthermore, Mikami and collaborators[13] have demonstrated that ligand **9** efficiently catalyzes diethylzinc addition to several aromatic aldehydes in good yields and high ee's (**eq 3**).

Based on the efficient opening of cyclohexene oxide by α-PEA,[14] Mastranzo et al. prepared a series of chiral ligands derived from *trans*-β-aminocyclohexanol. The versatility of this approach resulted in the preparation of a large number of optically active ligands that were successfully tested in the benchmark reaction of Et_2Zn with benzaldehyde (**eq 4**).[15]

2.3. α-PEA Derivatives as Ligands in Miscellaneous Enantioselective Reactions

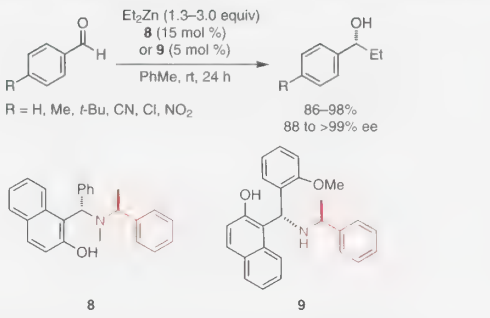
Recently, Isleyen and Dogan described the use of chiral ferrocenyl aziridinylmethanol **14**, which is prepared in three steps from an acryloylferrocene precursor and (*S*)-α-PEA. In particular, these authors showed that **14** can be employed in the catalytic, enantioselective conjugate addition of diethylzinc to enones to give β-ethylated ketones in up to 80% ee's, with the *R* enantiomer being favored in the majority of cases (**eq 5**).[16]

Another case of successful application of α-PEA derivatives as ligands in asymmetric synthesis is the palladium-catalyzed enantioselective allylic alkylation with dimethyl malonate in the presence of chiral ligands **15** and **16**. Ding and co-workers prepared chiral ligand **15** by the asymmetric aminoalkylation of 2-naphthol with (*R*)-α-PEA and benzaldehyde. Ligand **15** efficiently catalyzes the asymmetric substitution of the acetate group in 1,3-diphenylprop-2-en-1-yl substrates in 41–96% yields and with ee's as high as 70% in favor of the *S* product (**Scheme 4**).[17a] A few years later, Huang et al. employed a non-racemic imine, **16**, synthesized from (*S*)-α-PEA, to catalyze a similar reaction, achieving better yields and enantioselectivities (see Scheme 4).[17b] Furthermore, Tsogoeva and collaborators have recently obtained modest enantioselectivities in the allylation of aldimines and the reduction of ketimines with trichlorosilane by utilizing chiral proline–formamide derivatives.[18]

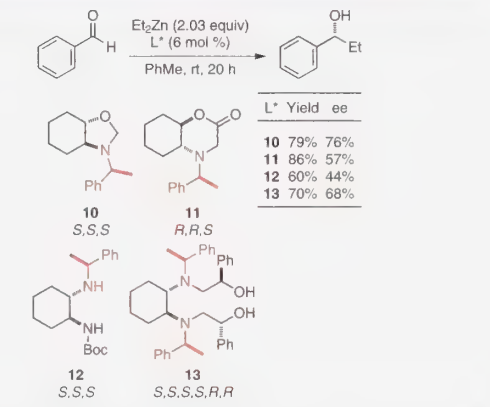
In a very recent elegant work, Alonso et al. examined a set of chiral phosphoramidite–gold(I) complexes, incorporating the bis(α-PEA) moiety, as catalysts in the intramolecular, enantioselective [4 + 2] cycloaddition reaction of allenes and dienes. In one example, Au–phosphoramidite complex **17** catalyzed the enantioselective allene and diene [4 + 2] cycloaddition over the [4 + 3] cycloaddition, giving rise to enantiomeric ratios greater than 95:5 (**eq 6**).[19]

Chiral, cyclic hydroxynaphthylphosphonodiamide **18**—synthesized from (*S*)-α-PEA, 1,2-dibromoethane, and *O*-aryl phosphorodichloridates—has been employed as a chiral ligand in the asymmetric cyanation of aromatic aldehydes catalyzed by $Ti(i\text{-}PrO)_4$. The corresponding cyanohydrins were obtained in good yields and ee's (**eq 7**).[20]

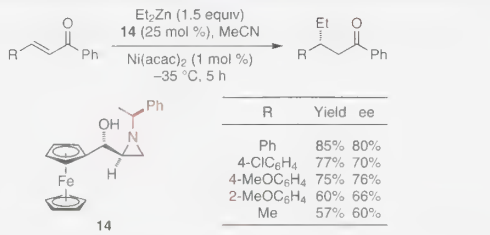
A remarkable application of a chiral ligand containing α-PEA was reported by Mikami's group, who prepared nonracemic ligand **19** from bis((*S*)-α-PEA), PCl_3, and 2,2'-methylenebis(4-



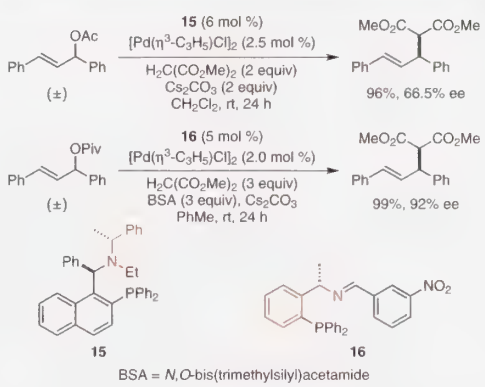
eq 3



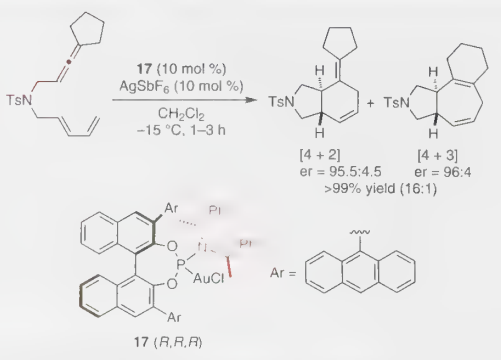
eq 4 *(Ref 14)*



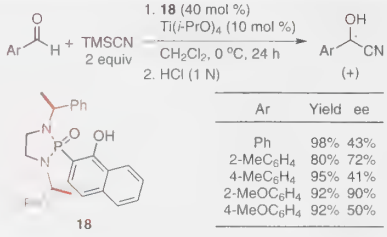
eq 5



Scheme 4. Enantioselective Palladium-Catalyzed Allylic Alkylation of Allyl Acetates with Dimethyl Malonate in the Presence of **15** and **16**. *(Ref 17)*

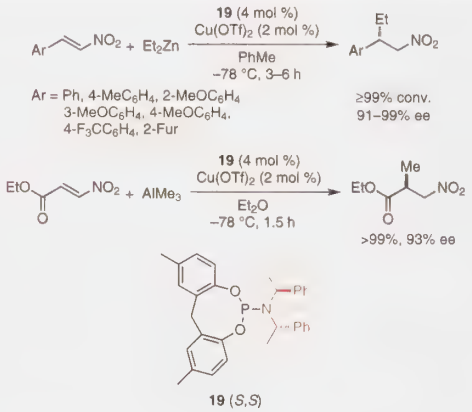


eq 6 *(Ref. 19)*

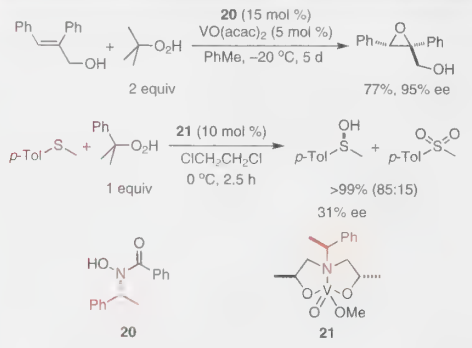


Ar	Yield	ee
Ph	98%	43%
2-MeC$_6$H$_4$	80%	72%
4-MeC$_6$H$_4$	95%	41%
2-MeOC$_6$H$_4$	92%	90%
4-MeOC$_6$H$_4$	92%	50%

eq 7 *(Ref. 20)*



Scheme 5. Asymmetric Cu-Catalyzed Conjugate Additions to Nitroalkenes and Nitroacrylates. *(Ref. 21)*



Scheme 6. Asymmetric Oxidations Catalyzed by Complexes of Vanadium and Chiral Ligands Incorporating α-PEA. *(Ref*

methylphenol) for use in copper-catalyzed conjugate additions of organometallics to nitroalkenes and nitroacrylates. In the case of copper-catalyzed addition of diethylzinc to nitroalkenes, metal complexes containing ligand **19** showed high catalytic activity and very good enantioinduction (>99%, 91–99% ee). Similarly, the conjugate addition of trimethylaluminum to nitroacrylate proceeded in high yield (>99%) and enantioselectivity (93% ee) (**Scheme 5**).[21] The product of this latter reaction was hydrogenated with palladium-on-charcoal to give the corresponding β^2-alanine ethyl ester.[21]

On the other hand, the asymmetric oxidation of prochiral olefins and thioethers, catalyzed by chiral vanadium complexes, has emerged as an important alternative to other standard oxidation procedures. Traber et al.[22] have described the application of a series of chiral hydroxamic acids as ligands for the vanadium-catalyzed asymmetric epoxidation of allylic alcohols. A noteworthy example is the preparation of the *S,S* epoxy alcohol in 77% yield and 95% ee by the asymmetric epoxidation of 2,3-diphenylallyl alcohol catalyzed by a vanadium complex with chiral ligand **20** (**Scheme 6**). In the same context, Rehder and co-workers[23] evaluated the catalytic properties of a series of chiral oxovanadium(V) complexes containing a chiral tridentate amino-bis(alcoholate) in the asymmetric oxidation of prochiral sulfides by organic hydroperoxides. (*S*)-Methyl *p*-tolyl sulfoxide was obtained with modest ee in the presence of catalyst **21** and cumyl hydroperoxide (CHP) as the oxidant (see Scheme 6).

Millward et al.[24] employed an optically active cyclopentadienylamido titanocene complex in the enantioselective ethylalumination of allylbenzene and styrene, which proceeded with modest yields and enantioselectivities. Bianchini and Lee[25] carried out the cyclopropanation of styrene with ethyl diazoacetate catalyzed by a chiral ruthenium 2,6-bis(imino)pyridyl complex in good yield but modest enantioselectivity.

3. α-Phenylethylamine as a Resolving Agent

The resolution of racemates through the formation of ionic or covalent diastereomeric derivatives is widely used in academic research as well as in industry, in particular for the manufacture of pharmaceuticals on an industrial scale.

3.1. Resolution via Diastereomeric Salt Formation

A variety of chiral racemic acids—mandelic,[26] organophosphorus,[27] acetic and benzoic acid derivatives,[28,29] and others[30]—have been resolved by separation of the diastereomeric salts that they form with α-PEA. Ma and co-workers[31] developed an elegant synthesis of enantiopure β-halobutenolides (*R*)- and (*S*)-**24** that relies on the resolution of racemic 2-methyl-4-phenyl-2,3-butadienoic acid with (*R*)- or (*S*)-α-PEA (**Scheme 7**).

Similarly, Kato and collaborators employed (*S*)-*N*-benzyl-α-PEA, ((*S*)-**26**) to form a mixture of diastereomeric salts with the key chiral carboxylic acid precursor to the cardioprotective drug (*S*)-**27** (**Scheme 8**).[32] Fractional crystallization of the diastereomeric salts and further elaboration of the precursor led to enantiopure (*S*)-**27**.

Another successful application of α-PEA as resolving agent in the pharmaceuticals area was disclosed by Trung et al.[33] In this work, fractional crystallization of the diastereomeric salts, prepared from (*R*)-α-PEA and racemic ibuprofen, was a key step in the preparation of (*R*)-ibuprofen, an effective analgesic and anti-inflammatory agent.

3.2. Resolution via Covalent Attachment of α-PEA to Racemic Substrates

Very recently, Aitken's group[34] carried out the preparation of the four possible stereoisomers of 2-aminocyclobutanecarboxylic acid starting with the condensation of the cis racemate with (*R*)-α-PEA to give a mixture of the corresponding diastereoisomeric amides. The amides were separated by column chromatography, (*R*)-α-PEA cleaved, and a controlled epimerization to the more stable trans isomers carried out, leading to the isolation of all four stereoisomers in enantiomerically pure form.

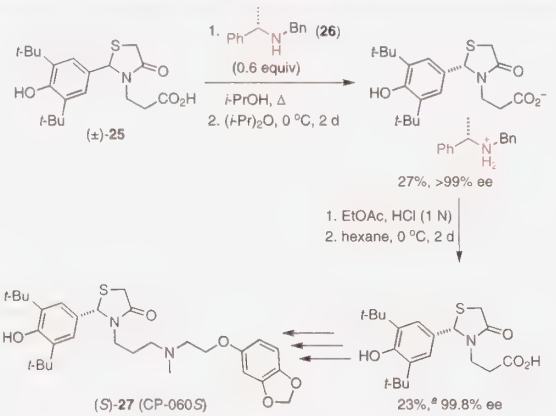
The 1,3-dipolar cycloaddition of a proline-derived, cyclic nitrone with acrylamide, followed by a reductive cleavage–cyclization domino process, afforded the racemic trans hydroxy ester **28**. Reaction of **28** with (*R*)-α-PEA led to two diastereomeric intermediates, which were separated and subjected to reductive cleavage of the α-PEA moiety to give enantiomerically pure, bicyclic pyrrolizidinones **30** (**Scheme 9**).[35] Pyrrolizidinones **30** were subsequently coupled to α-amino acids to give pseudotripeptides that induce β-turn peptidomimetic foldamers.

Recently, Morales-Ríos and co-workers further confirmed the efficiency of α-PEA in the enantioselective synthesis of natural products, by carrying out the preparation of debromoflustramine B (**31**). This approach involved reacting the racemic γ-lactone precursor with (*S*)-α-PEA and chromatographic separation of the resulting diastereomeric *N*-(α-phenylethyl)lactam intermediates, Subsequent hydrolytic cleavage of the α-PEA moiety regenerated the lactone; this was followed by formation of the *N*-methyllactam with $MeNH_2$ in methanol and reduction of the amide carbonyl to afford both enantiomers of **31** (**Scheme 10**).[36]

An efficient resolution of chiral, C_2-symmetric biphenols, e.g., **32**, was described by Delogu et al., who employed the α-PEA-containing reagent (*S*)-**33** to derivatize **32** into diastereomeric phosphorothioamidates **34**. Separation of the phosphorothioamidate intermediates by fractional crystallization and reductive cleavage with $LiAlH_4$ afforded biphenols (*M*)-**32** and (*P*)-**32** (**Scheme 11**).[37] A similar approach was employed by Rozenberg and collaborators in the resolution of 15-hydroxy[2.2]paracyclophane-4-carbaldehyde.[38] In another interesting development, Zakrzewski and co-workers reported the resolution of a racemic diphosphaferrocenecarboxylic acid by chromatographic separation of the corresponding diastereomeric amides formed by reaction of the acid with (*S*)-α-PEA.[39]

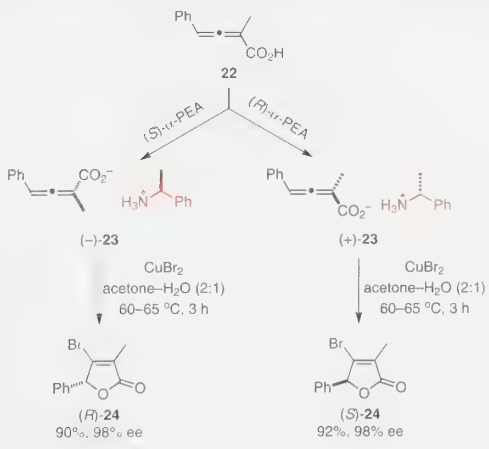
3.3. Chiral Solvating Agents Containing the α-PEA Fragment

One advantage of chiral recognition is that it can be easily evaluated spectroscopically, for example by NMR using chiral discriminating reagents. A variety of chiral solvating agents based on α-PEA are known; they efficiently differentiate the enantiomers of several types of molecules such as chiral Kemp's acid derivatives,[40] iminoboronate derivatives of chiral alcohols,[41] chiral phospholene oxides,[42] chiral unsaturated ethers,[41b,43] and chiral carboxylates.[44] In a relevant example, our group[44a] has demonstrated that simple chiral thiourea (*S,S*)-**35** (**Scheme 12**) is an efficient receptor for chiral carboxylates, such as α-amino

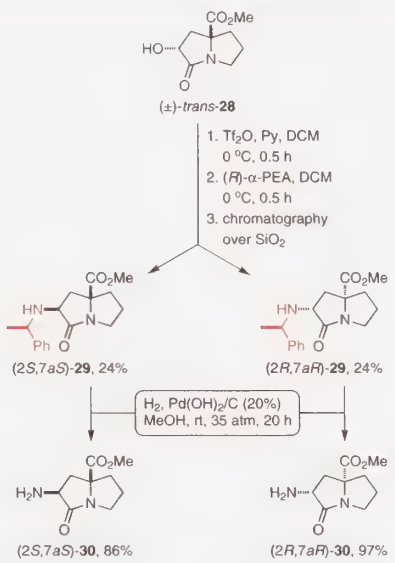


[a] The yield of the desired *S* acid was improved to ~70% after recovering the undesirable *R* isomer, racemizing it, and subjecting it to the resolution steps outlined here.

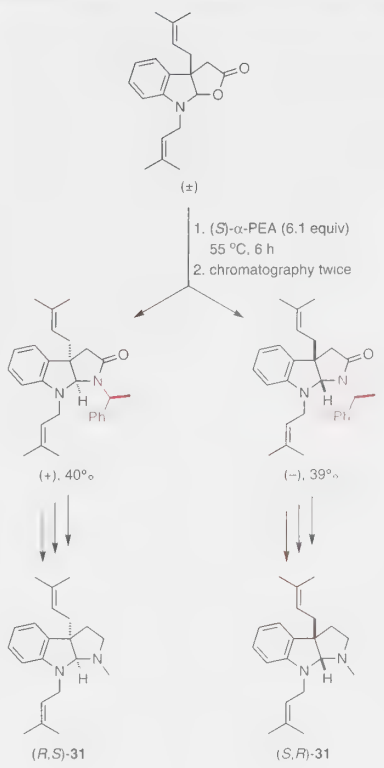
Scheme 8. Key Enantiomeric Separation in the Synthesis of the Cardioprotective Drug (*S*)-**27**.



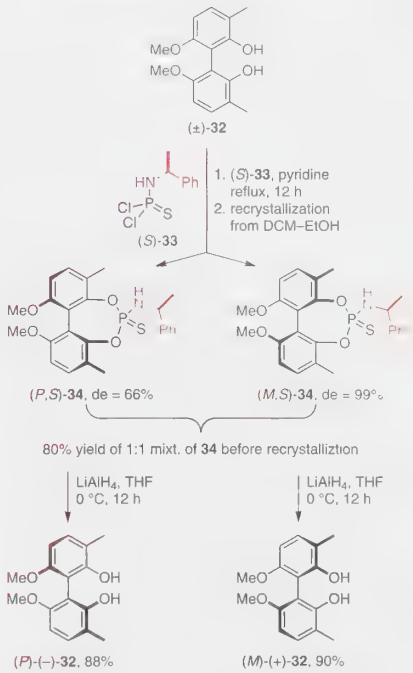
Scheme 7. Resolution of *rac*-2-Methyl-4-phenyl-2,3-butadienoic Acid (*rac*-**22**), and Subsequent Formation of Enantioenriched β-Halobutenolides. *(Ref. 31a)*



Scheme 9. Synthesis of Enantiopure **30** by Covalent Attachment of Enantiopure α-PEA to Racemic Substrates. *(Ref. 35a)*



Scheme 10. Synthesis of Enantiopure Debromoflustramine B, (*R,S*)- and (*S,R*)-**31**. *(Ref. 36a)*



Scheme 11. Resolution of C_2-Symmetric Biphenols **32**. *(Ref. 37a)*

and α-hydroxy acids. The diastereomeric complexes obtained from such complexation give rise to distinguishable signals in ^{1}H NMR spectra, which can be used for determining the optical purity. Furthermore, thiourea (*S,S*)-**35** has proved useful for assigning the absolute configuration of the carboxylic acids; indeed, it was observed that the *R* enantiomer of the carboxylate exhibits a C_α–H chemical shift at higher frequency.

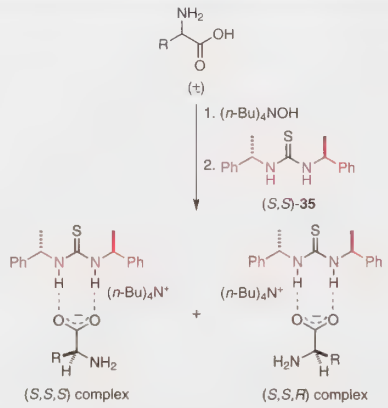
4. α-Phenylethylamine as Chiral Auxiliary

The ready availability of α-PEA and its facile incorporation in, and removal from, organic molecules have contributed to making α-PEA into an excellent auxiliary in asymmetric synthesis. Thus, α-PEA-controlled reactions have become an important tool in the preparation of enantioenriched products.

4.1. Diastereoselective Reactions of Chiral Imines Incorporating the α-Phenylethyl Moiety

The condensation of aldehydes and ketones with α-PEA provides the corresponding chiral imines, in which the difference in size between substituents at the stereogenic center helps to differentiate the diastereotopic faces at the prochiral C=N bond, especially in those cases where one conformation of the chiral auxiliary predominates in the transition state. This working hypothesis has been exploited in several methods, which are described below.

The apparent addition of hydride from the side of the less bulky group in the reduction of α-PEA imines has allowed the synthesis of several types of enantioenriched product such as ferrocenes,[45] amines,[46] glycosyl amino acids,[47] amino esters,[48] and spiro compounds.[49] Indeed, an excellent procedure for the preparation of chiral primary amines from both cyclic and acyclic dialkyl or aryl–alkyl prochiral ketones was described by Nugent and co-workers.[46e] The key step in this reaction consists of the asymmetric reductive amination of the ketone with (*R*)- or (*S*)-α-PEA in the presence of a Lewis acid and a conventional hydrogenation catalyst. The correct combination of hydrogenation catalyst, solvent, and temperature is essential for achieving high reaction yields and high diastereomeric excesses. In one example, the reduction of ethyl or hexyl methyl ketone afforded the corresponding amines in good yields and diastereoselectivities (**Scheme 13**, Part (a)). When Raney® Ni was employed as the hydrogenation catalyst in the reduction of ethyl methyl ketone, the product was formed with a 74% de, whereas the use of rhodium-on-charcoal led to a significantly



Scheme 12. Thiourea (*S,S*)-**35** and its Proposed Coordination in the Stereodifferentiation of Chiral α-Amino Carboxylates. *(Ref. 44a)*

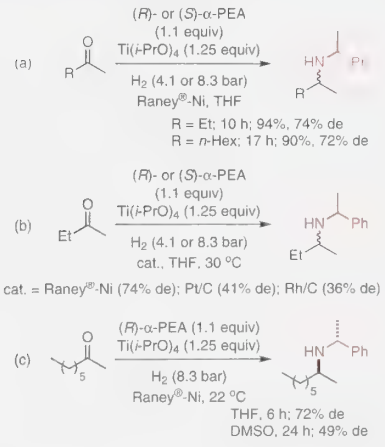
lower diastereoselectivity (de = 36%, **Scheme 13**, Part (b)). Finally, the α-phenylethylimine derivative of hexyl methyl ketone was reduced with 72% diastereomeric excess in THF as solvent, and 49% de in DMSO (**Scheme 13**, Part (c)).

A variety of nucleophiles also add stereoselectively to α-PEA-containing imines. When the nucleophile is cyanide, this leads to enantioenriched non-natural amino acids (**Figure 1**).[50] An illustrative procedure for the enantioselective preparation of carbocyclic α-amino acids was described by Frahm's group.[51] Chiral ketimines were obtained by condensation of racemic 2-alkylcyclopentanones and (*S*)-α-PEA as chiral auxiliary. In the key stereodifferentiating step, cyanide addition provided diastereomeric mixtures of nitriles, whose composition is dramatically influenced by the nature of the solvent, the temperature, and the size of the substituents. Hydrolysis of the nitriles with conc. H_2SO_4 yielded diastereomeric mixtures of carboxamides, which were separated, hydrogenolyzed, and hydrolyzed to yield the pure stereoisomers of 1-amino-2-methoxycyclopentanecarboxylic acid.

In a similar fashion, the addition of allylmetal nucleophiles to imines provides a valuable route to homoallylic amines, which can undergo any number of transformations at the C=C bond of the allylic fragment.[52] Gálvez and co-workers[53] reported a good application of this approach in the synthesis of non-natural α-amino acid **37**. Thus, chiral *N*-phenylethylimines were prepared from (*R*)-2,3-di-*O*-benzylglyceraldehyde and (*S*)- or (*R*)-α-PEA and treated with allylmagnesium bromide or allyl-9-borabicyclo[3.3.1]nonane (allyl-9-BBN). Conversion of the resulting homoallylic amine into the corresponding syn or anti *N*-Boc-aminodiol was conveniently performed by hydrogenolysis with $Pd(OH)_2$ on charcoal in the presence of $(Boc)_2O$. Subsequent treatment with an excess of sodium periodate in the presence of ruthenium trichloride followed by acid hydrolysis, gave α-amino acid (*R*)- or (*S*)-**37**, depending on the nature of the starting material (**Scheme 14**).

4.2. Diastereoselective Reactions of Optically Active Enamines

The enantioselective reduction of enamines, is a useful tool for the synthesis of biologically important molecules such as β-amino acids, as demonstrated by Wright and collaborators.[54] These workers prepared diverse cyclic β-amino acids by amination of cyclic β-keto esters with (*R*)-α-PEA in the presence of acetic acid. The enamines were reduced with $NaBH_3CN$ in acetic acid, the resulting mixtures of diastereomers purified by chromatography, separated by recrystallization, and the chiral auxiliary cleaved by hydrogenation over Pd/C. Final saponification of the methyl ester and Fmoc protection of the amino group provided cyclic β-amino acids, e.g. (*S*,*S*)-**38**, that are suitable for peptide synthesis (**Scheme 15**).[54] Other remarkable examples that follow this strategy were reported by Lhommet's group[55] and by Jona



Scheme 13. The Asymmetric Reductive Amination of Prochiral Ketones Evaluated under a Variety of Conditions. *(Ref. 46e,h)*

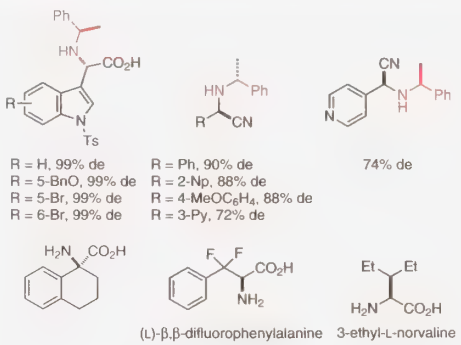
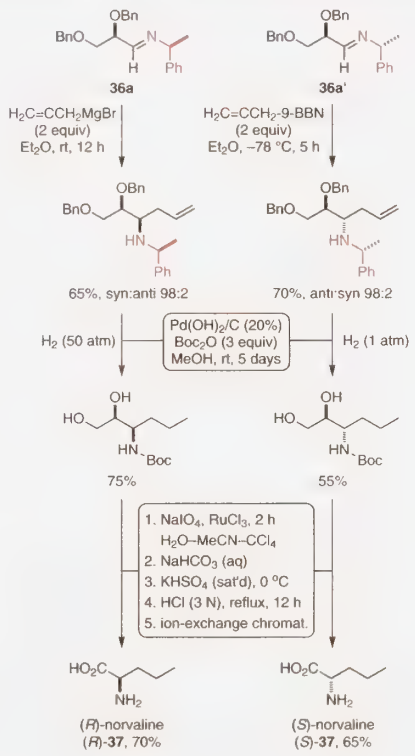
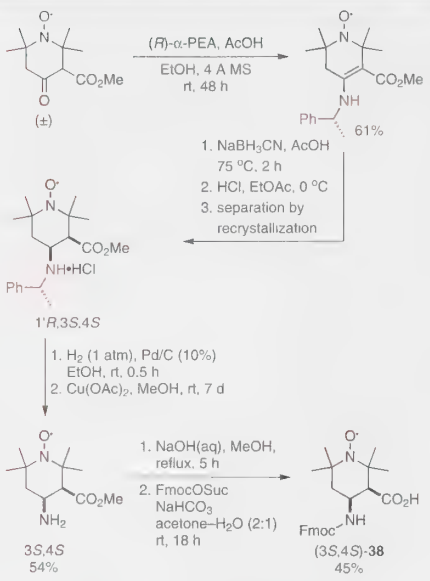


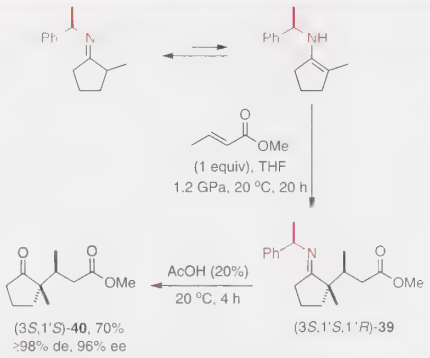
Figure 1. Select Intermediates and α-Amino Acids Obtained by the Diastereoselective Addition of Cyanide to Chiral Imines Containing the α-PEA Moiety.



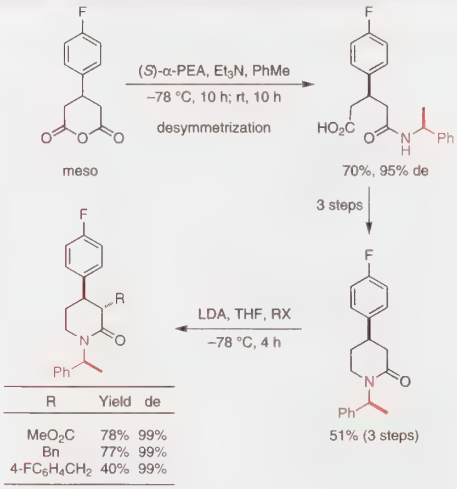
Scheme 14. The Diastereoselective Allylation of *N*-(α-Phenylethyl)imines in the Enantioselective Preparation of α-Amino Acids.



Scheme 15. Preparation of Cyclic β-Amino Acids (*S,S*)-**38** by Reduction of Enamines. (Ref. ..)



Scheme 16. Michael Addition to Methyl Crotonate of Chiral Imines Derived from 2-Methylcyclopentanone and α-PEA. ..



Scheme 17. α-PEA as Chiral Auxiliary in the Desymmetrization and Alkylation or Acylation of an α-PEA-Containing 2-Piperidinone Enolate. (Ref. 59)

and co-workers[56] in the synthesis of chiral enamino lactones and dihydrobenzimidazolepiperidine-1,3-dicarboxylate, respectively, in good yields and ee's.

On the other hand, Michael addition of enamines to electron-deficient olefins has emerged as a simple and efficient tool for the stereocontrolled synthesis of quaternary stereocenters, as demonstrated in several recent reports.[57] A relevant example is the report by Dumas and co-workers[58] of the stereoselective addition to methyl crotonate of chiral imines derived from 2-methylcyclopentanone and enantiopure α-PEA to give, in the case of the *R* imine, product **39**. Hydrolysis of **39** afforded keto ester **40** in 70% yield, ≥98% de, and 96% ee (**Scheme 16**).

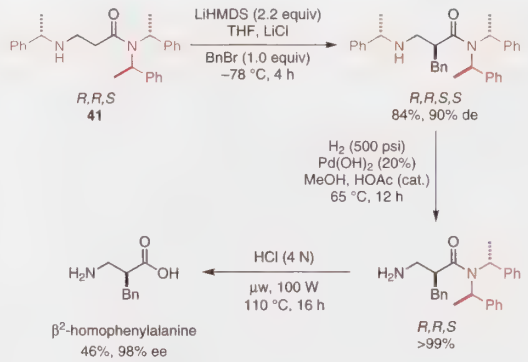
4.3. Diastereoselective Alkylation of α-PEA-Containing Enolates

The diastereoselective alkylation of enolates containing the α-phenylethylamino moiety has been employed in the synthesis of open-chain or cyclic enantioenriched compounds, notably piperidinones,[59] β-amino acids,[60] diamino dicarboxylic acids,[61] disubstituted phosphonopropanamides[62] or alkylcyclobutanones.[63] An illustrative example was described by Liu and co-workers, who prepared nonracemic disubstituted piperidinones and piperidines by alkylation or acylation of the enolate derived from α-PEA-containing 2-piperidinone (**Scheme 17**).[59]

Our group has successfully employed C_2-symmetric bis(α-PEA) and Evans-type hexahydrobenzoxazolidinone chiral auxiliaries in the asymmetric synthesis of β²-amino acids, such as (*R*)-β²-homoDopa, (*S*)-β²-homophenylalanine, (*S*)-β²-homovaline, (*S*)-β²-homoleucine, and (*S*)-β²-homotryptophan.[60] Thus, chiral amide **41** is conveniently metallated with lithium hexamethyldisilazide (LiHMDS) whose diastereotopic faces in the resulting enolate allow the stereoselective addition of benzyl bromide in 90% de. In this instance, hydrogenolysis of the benzylated product and hydrolysis under microwave (μw) irradiation result in the formation of (*S*)-β²-homophenylalanine with 98% ee (**Scheme 18**).[60b]

4.4. α-PEA in Diastereoselective Cyclization Reactions

Piperidine, pyrrolidine, and morpholine derivatives have received considerable attention because of their applications in organic, materials, and pharmaceutical chemistry. The use of α-PEA has permitted the preparation of several promising molecules in this class, such as tetrahydroisoquinolines (used in the treatment of Parkinson's disease);[64] benzodiazepines (sedatives);[65] oxazolidines,



Scheme 18. Enantioselective Synthesis of β²-Homophenylalanine.

oxazolidinones, and lactams (antibiotics);[66] piperidine and pyrrolidine derivatives;[67] phthalides (enzyme inhibitors);[68] noranabasamine alkaloids (anti-inflammatory); and others.[69]

In this regard, Yamaguchi and collaborators[70] reported an interesting N-heterocyclization of primary amines with diols catalyzed by an iridium complex. When the reaction of (*R*)-α-PEA and 1-phenyl-1,5-pentanediol was carried out in the presence of a catalytic amount of $[Cp^*IrCl_2]_2$, a diastereoisomeric mixture of phenylpiperidines formed in 76% yield, 92% de, and good enantiomeric excess. Reduction of this mixture with Pd/C gave (*S*)-2-phenylpiperidine **42** in 96% yield and 78% ee (**Scheme 19**).

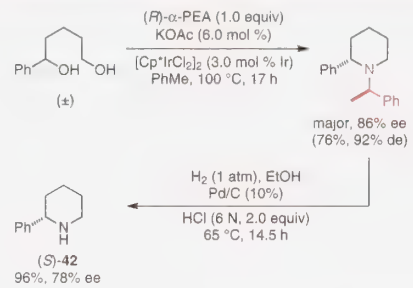
The potential of α-PEA as chiral auxiliary in diastereoselective Diels–Alder reactions was successfully demonstrated in recent years.[71] In a relevant example, Badorrey et al.[71a] employed a chiral imine dienophile prepared from (*S*)-2,3-di-*O*-benzylglyceraldehyde and (*R*)-α-PEA. In the presence of Danishefsky's diene and ZnI_2, this chiral imine underwent a hetero-Diels–Alder reaction leading to **43** (**Scheme 20**), which is a valuable intermediate in the synthesis of palinavir—a potent inhibitor of the human immunodeficiency virus (HIV-1 and HIV-2).

4.5. α-PEA as Chiral Auxiliary in Miscellaneous Procedures

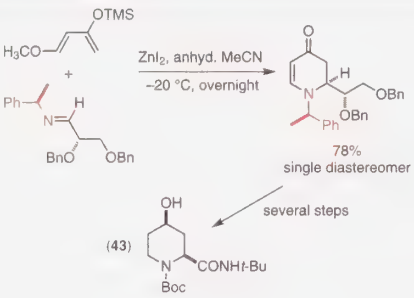
In addition to the processes described above, the applications of α-PEA as chiral auxiliary include several other kinds of reactions such as diastereoselective carbozincation of propargylic amines,[72] aldimine coupling of imines with methoxyketene methyltrimethylsilyl acetal in the synthesis of β-amino-α-hydroxy acids,[73] preparation of α,β-unsaturated amides from 2-phosphonamides via the Horner–Wadsworth–Emmons reaction,[74] preparation of imidazole derivatives by the thio-Ugi reaction,[75] synthesis of azabicyclooctane carboxylic acids,[76] α-pyridylation of amines through urea coupling, stereoselective lithiation and rearrangement,[77] development of amino vinyl cyclohexenes,[78] and synthesis of therapeutic agents such as DPC 961 (HIV non-nucleoside reverse transcriptase inhibitor).[79]

5. α-Phenylethylamine as Chiral Reagent in the Stereodifferentiation of Prochiral Substrates

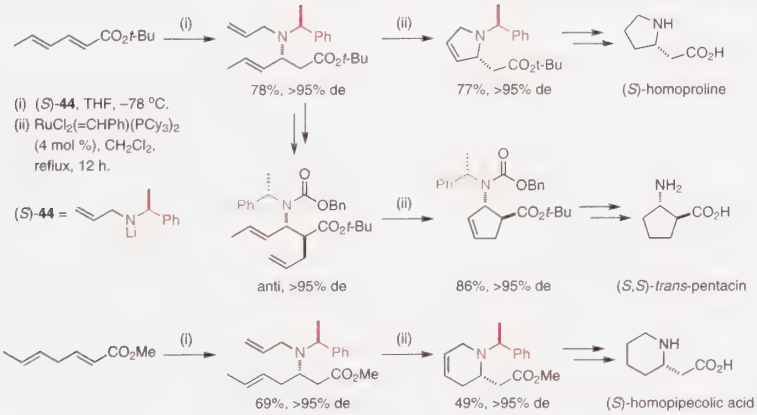
Conjugate addition of a nitrogen nucleophile to α,β-unsaturated carboxylic acid derivatives is one of the most useful and simplest methods for the formation of N–C bonds.[80] In particular, addition of "chiral ammonia" nucleophiles to the acceptor unsaturated carbonyl group produces a new stereogenic center at the β position. The diastereoselectivity of this reaction depends on the nature of the starting ester, the "chiral ammonia" equivalent, and on the particular reaction conditions. Davies, the recognized pioneer and leader of this methodology, has demonstrated the versatility of this approach in the synthesis of a large number of chiral β-amino acids.[81] In a striking example, Davies and co-workers[82] achieved the diastereoselective conjugate addition of lithium *N*-allyl-(*S*)-α-PEA, (*S*)-**44**, to a wide range of α,β-unsaturated esters (**Scheme 21**). Subsequent ring-closing metathesis (RCM) afforded a variety of substituted cyclic β-amino esters in high de's. Final reduction and



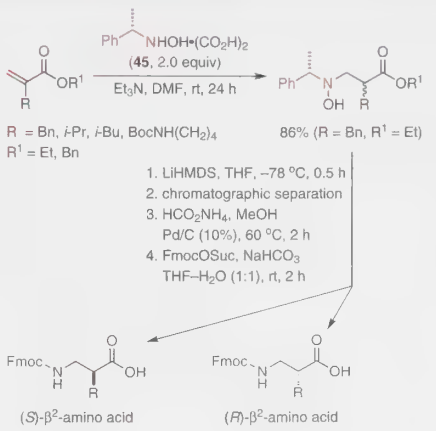
Scheme 19. Diastereoselective Cyclization in the Enantioselective Synthesis of (*S*)-2-Phenylpiperidine, (*S*)-**42**.



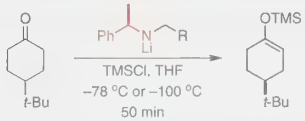
Scheme 20. Hetero-Diels–Alder Reaction in the Synthesis of **43**, an Intermediate in the Synthesis of Palinavir. *(Ref*



Scheme 21. The Synthesis of β-Amino Acids by Addition of "Chiral Ammonia" Equivalent (*S*)-**44** to α,β-Unsaturated Esters Followed by RCM. *(Ref. 82)*

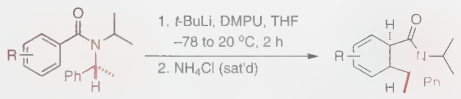


Scheme 22. Formation of β²-Amino Acids by Diastereoselective Michael Addition. *(Ref 86)*



R	Yield	ee
Me	55%	41%
t-Bu	94%	32%
FCH_2	61%	43%
F_2CH	66%	59%
F_3C	**86%**	**92%**
CF_3CF_2	**92%**	**83%**
Me_2NCH_2	92%	18%

eq 8



R[a]	Yield	ee
2-MeO	74%	>99%
3-MeO	66%	>99%
4-MeO	80%	>99%

[a] Position numbers are with respect to starting material

eq 9 *(Ref. 92)*

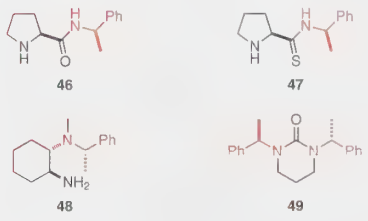


Figure 2. Chiral, α-PEA-Containing Organocatalysts Employed in Asymmetric Aldol Reactions. *(Ref. 94–97)*

hydrolysis generated the corresponding cyclic β-amino acids; i.e., (*S*)-homoproline, (*S*)-homopipecolic acid, and carbocyclic (*S*,*S*)-*trans*-pentacin.

A vast number of important molecules have been synthesized by applying this methodology. For example, Michael's group[83] prepared the optically active bicyclic compound (−)-indolizidine; Coleman and collaborators[84] synthesized nonracemic dihydrobenzofuran β-amino acids, which are aspartic acid mimetic that are structurally related to benzodioxole systems; and Podlech[85] reported the preparation of enantiomerically pure β-amino acids. Moreover, Gellman and co-workers described the enantioselective Michael addition of chiral hydroxylamine (*S*)-**45** to α-alkylacrylates followed by cyclization to give a diastereomeric mixture of α-substituted isoxazolidinones. A set of α-substituted β²-amino acids were obtained after separation, hydrogenation, and final Fmoc protection (**Scheme 22**).[86] Furthermore, Herrera et al.[87] reported the preparation of chiral α-hydroxy-β-amino acid derivatives based on the diastereoselective addition of (*R*)-α-PEA to representative captodative olefins, a strategy that Blanchet and co-workers[88] used later in the enantioselective synthesis of (*S*)-β-proline. Lhommet and collaborators[89] carried out a similar intramolecular Michael addition of (*S*)-α-PEA to chloroacetylenic esters in acetonitrile to form chiral piperidine enamino esters.

Several examples have been described in which α-PEA-lithium amide has been employed for the selective removal of one enantiotopic proton in symmetrical carbonyl compounds.[90] In a particularly interesting example, Aoki and Koga[91] reported an efficient procedure for the enantioselective deprotonation of 4-*tert*-butylcyclohexanone. These researchers utilized α-PEA-derived chiral lithium amides containing alkyl or fluoroalkyl substituents at the amide nitrogen. The resulting trapped enolates were obtained in yields as high as 94%, and enantiomeric excesses up to 92% (**eq 8**).[91] In a related study, Clayden and co-workers[92] reported a lithiation of chiral benzamides containing the α-PEA moiety, which triggered a stereospecific cyclization process (**eq 9**).

6. α-Phenylethylamine in Organocatalysts

The use of small organic molecules to accelerate chemical reactions, has been of great relevance in organic chemistry. The lack of sensitivity to moisture and oxygen, ready availability, low cost, and low toxicity confer high advantages to organocatalysts over metal catalysts in the production of drugs.[93] Several asymmetric organic reactions have made use of organocatalysts containing a chiral α-PEA fragment to induce chirality in the final products. In recent years, numerous reports have described the development of the asymmetric aldol reaction (**Figure 2**).[93–97] In an excellent example, Chimni and Mahajan[94] employed protonated chiral prolinamide derivative **46** as asymmetric organocatalyst for the enantioselective aldol reaction in water with good yields and moderate enantioselectivity. Gryko and co-workers[95] designed organocatalyst **47** by replacing the amide functionality in **46** with the thioamide group in order to increase the acidity of the N–H bond and, as a consequence, to increase yields and enantiomeric excesses (up to 99% ee). Recently, Singh and collaborators[96] utilized chiral primary and tertiary diamine **48** to catalyze the *syn*-aldol (with unprotected hydroxyacetone) and *anti*-aldol (with cyclic ketones) reactions in aqueous media with high diastereo- and enantioselectivities. Recently, our group described the synthesis of chiral urea **49**, which incorporates (*R*)- or (*S*)-α-PEA, and its application as a Lewis base in the asymmetric aldol reaction.[97]

In other relevant organocatalytic reactions, Tsogoeva and co-workers[98] have developed a group of chiral thiourea

derivatives, e.g. **50**, as bifunctional catalysts for the nitro-Michael addition (addition of acetone to nitroolefins), achieving higher enantioselectivities than with proline derivatives. Similarly, Kelleher et al.[99] synthesized spirolactam organocatalyst **51** for the asymmetric conjugate addition of aldehydes to nitroolefins in excellent yields, with good diastereoselectivity and enantioselectivity using low catalyst loadings (5 mol %). Our group demonstrated the potential of α-PEA derivatives such as **52**, in the enantioselective amination of α-substituted α-cyanoacetates with azodicarboxylates as electrophiles.[100] González-Olvera et al. described the preparation and use of chiral diazabicyclo[2.2.1]heptane **53** as organocatalyst for the enantioselective Biginelli reaction, giving rise to good yields and enantioselectivities.[101] On the other hand, Zhao, Zhou, and collaborators employed a chiral cyclic β-amino alcohol, **54**, as co-catalyst (in combination with L-proline) in the enantioselective Baylis–Hillman reaction between *o*-nitrobenzaldehyde and methyl vinyl ketone, obtaining the corresponding keto alkenyl alcohol with good selectivity.[102] In a preliminary study, Peris and Miller reported the desymmetrization of prochiral ketones through the Baeyer–Villiger oxidation by employing an α-PEA-containing peptide, **55**, to give the corresponding lactones with modest enantioselectivities.[103] Finally, Hansch et al.[104] prepared enantiomerically pure thiomorpholine **56**, which includes the α-PEA fragment, for application in sulfur ylide mediated asymmetric epoxidation of aldehydes with excellent yields, enantioselectivities, and diastereoselectivities (**Figure 3**).

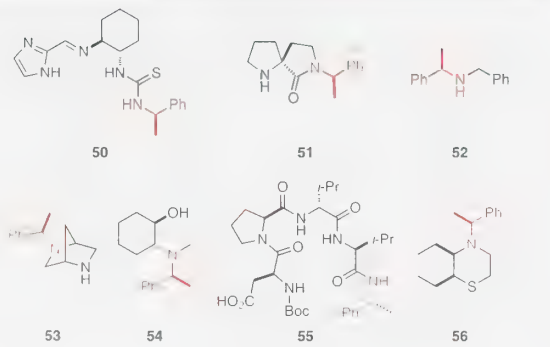


Figure 3. Remarkable, α-PEA-Containing Organocatalysts Utilized in Various Asymmetric Reactions. *(Ref. 98–104)*

7. Concluding Remarks

Because of its low price, accessibility in both enantiomeric forms, facile incorporation in starting materials, and easy removal from final products, α-phenylethylamine (α-PEA) continues to stand as an important chiral reagent in asymmetric synthesis. This is attested to by the great number of methodologies that are available for its application as chiral ligand, in the resolution of racemic mixtures, as chiral auxiliary, as chiral base, and in the development of new organocatalysts. The present review has described noteworthy recent developments in the chemistry of α-PEA, which may motivate chemists involved in enantioselective synthesis to take advantage of this versatile molecule.

8. Acknowledgements

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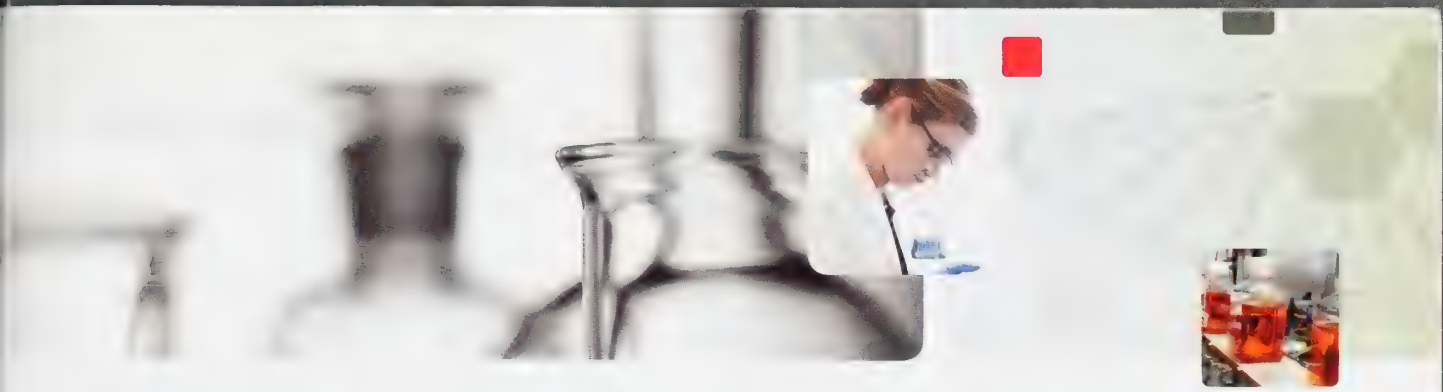

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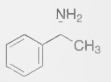

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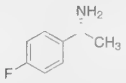

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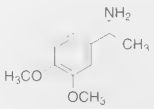

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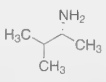

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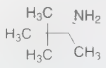

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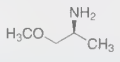

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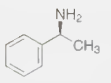

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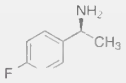

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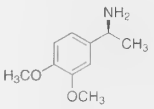

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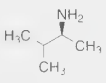

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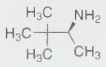

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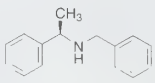

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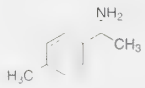

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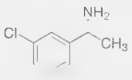

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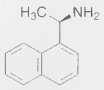

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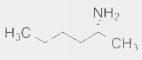

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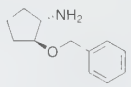

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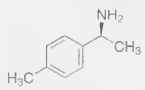

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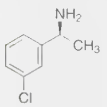

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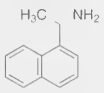

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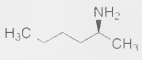

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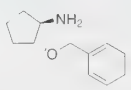

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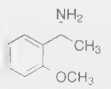

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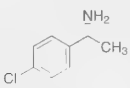

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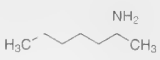

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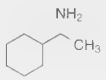

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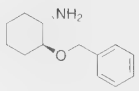

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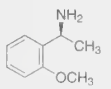

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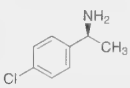

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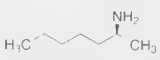

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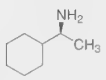

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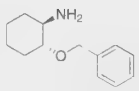

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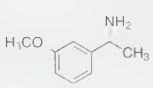

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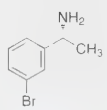

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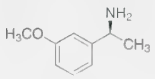
ChiPros Chiral Amines (Cont'd)



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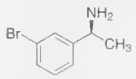

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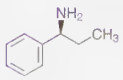

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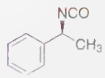

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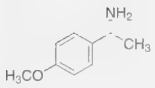

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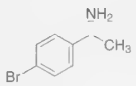

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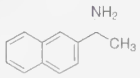

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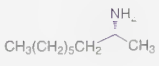

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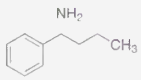

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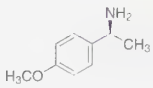

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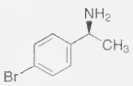

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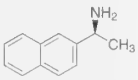

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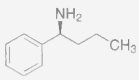

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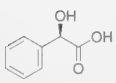
ChiPros Chiral Acids



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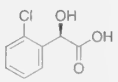

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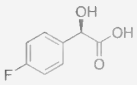

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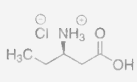

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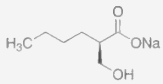

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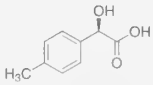

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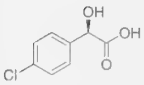

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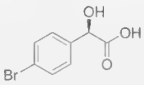

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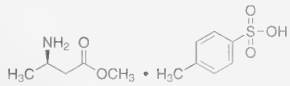

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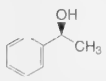

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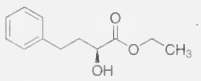

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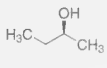

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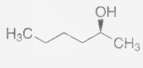

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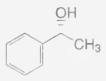

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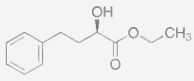

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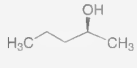

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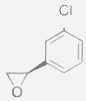

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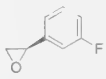

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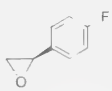

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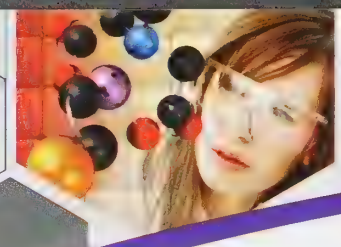

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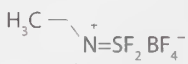
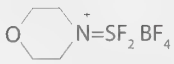


XtalFluor-E
Cat. No. 719439



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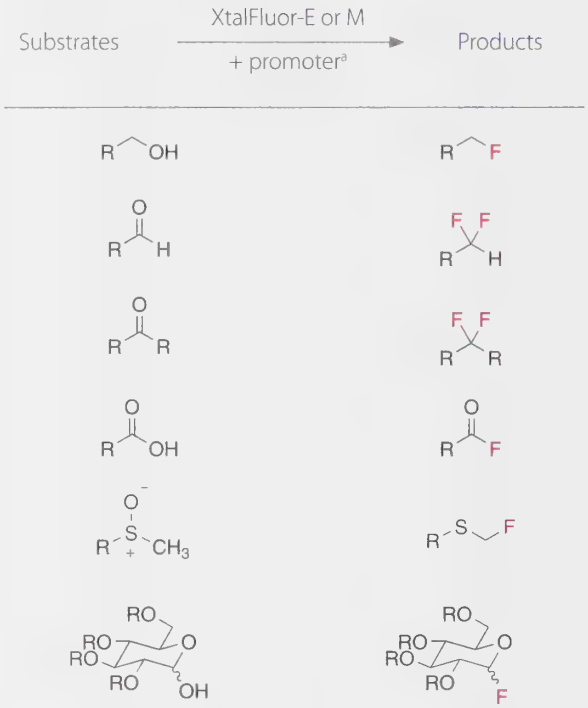
Representative Scope



[a] Promoters: DBU, $Et_3N{\cdot}3HF$, or $Et_3N{\cdot}2HF$

References: (1) Beaulieu, F. et al. *Org. Lett.* **2009**, *11*, 5050. (2) L'Heureux, A. et al. *J. Org Chem.* **2010**, *75*, 3401

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2-Iodoxybenzenesulfonic Acid (IBS) Catalyzed Oxidation of Alcohols

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Outline

1. Introduction

The oxidation of alcohols to the corresponding carbonyl compounds is one of the most important transformations in synthetic organic chemistry.[1] Over the past two decades, hypervalent iodine compounds have received a great deal of attention due to their mild and chemoselective oxidizing properties and to the fact that, unlike toxic heavy-metal-based reagents, they are environmentally benign.[2] We recently published a review on the oxidation of alcohols with stoichiometric or catalytic hypervalent iodine compounds.[3] The present review focuses on the discovery and development of 2-iodoxybenzenesulfonic acid (IBS, **1**) and related hypervalent iodine compounds. It also covers advances in hypervalent iodine catalyzed alcohol oxidations and related transformations reported between 2005 and 2010.

2. Hypervalent Iodine Catalysts for Alcohol Oxidation

To date, various hypervalent iodine (λ^3- and λ^5-iodane) reagents have been developed as oxidants for alcohols.[3] 2-Iodoxybenzoic acid (IBX, **2**) and Dess–Martin periodinane (DMP, **3**) are the best known and most commonly used hypervalent iodine reagents (**Figure 1**). Dess and Martin used **2** as a precursor for **3**.[4] In the early studies, **2** was synthesized from 2-iodobenzoic acid (**4**) and potassium bromate ($KBrO_3$) in aqueous sulfuric acid.[4a] Although **2** was later reported to be explosive,[5] Dess and Martin subsequently speculated that some bromate or other impurity may have been included in samples that were found to be explosive, but that IBX (**2**) itself should be non-explosive.[4b] The first use of **2** for alcohol oxidation in DMSO was reported in 1994 by Frigerio and Santagostino.[6] The simple, one-step preparation of **2** from **4** with Oxone®, an environmentally safe oxidant, has made **2** a popular reagent (**eq 1**).[7] To date, **2** has been employed as a powerful and selective oxidant that mediates a variety of transformations such as the oxidation of alcohols, phenols, and amines; the dehydrogenation of ketones, aldehydes, and N-heterocycles; and the oxidative cleavage of dithioacetals.[2,3] Several research groups have attempted to improve on **2** by structurally modifying it, or by developing polymer-supported analogues.[3] Additionally, Quideau's group reported a stabilized formulation of IBX, SIBX, containing benzoic acid and isophthalic acid, which offered some advantages, such as safety and ease of workup.[8]

In 2005 and 2006, Vinod[9] and Giannis[10] independently reported the oxidation of alcohols catalyzed by **2**—generated in situ from **4** or 2-iodosobenzoic acid (IBA)—in the presence of Oxone® as co-oxidant (**Scheme 1**). Vinod's group employed 20–40 mol % of **4** in a water–acetonitrile biphasic solvent system, in which primary and secondary alcohols were oxidized to carboxylic acids and ketones, respectively (**eq 2**).[9] In contrast, Giannis's group utilized a water–ethyl acetate biphasic solvent system in the presence of 10 mol % each of **4** and tetrabutylammonium hydrogen sulfate [$(n\text{-Bu})_4NHSO_4$] as a phase-transfer catalyst. Under these conditions, primary benzylic alcohols were oxidized to the corresponding aldehydes, which did not undergo further oxidation (**eq 3**).[10] These two reports stated that it was not necessary to isolate beforehand the hypervalent iodine compounds, which are potentially shock-sensitive explosive oxidants.

Page and co-workers demonstrated that several primary and secondary alcohols can be oxidized to the respective aldehydes and ketones under reflux conditions in acetonitrile or dichloroethane in the presence of tetraphenylphosphonium monoperoxysulfate (TPPP, $Ph_4P^+HSO_5^-$) and a catalytic amount of **4** (**eq 4**).[11] TPPP was derived from Oxone® by simple counterion exchange with tetraphenylphosphonium chloride. This catalytic system enables the oxidation of primary alcohols to the corresponding aldehydes without further oxidation to the carboxylic acids.

The selective oxidation of benzylic C–H bonds to the corresponding carbonyl functionalities has been achieved using a catalytic amount of **4** and Oxone® in aqueous acetonitrile (**Scheme 2**).[12] The authors hypothesized that the active

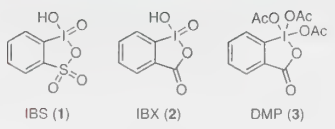
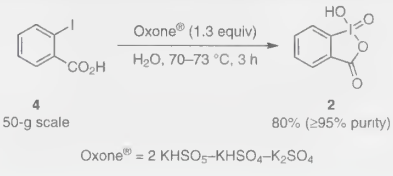
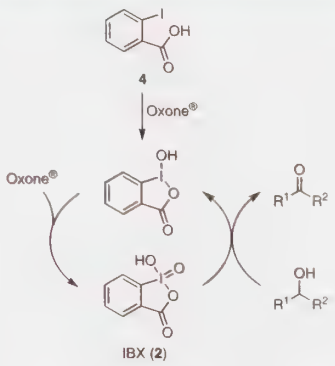


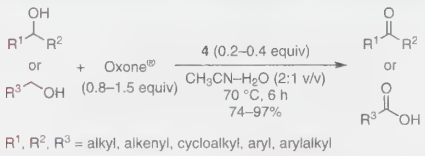
Figure 1. IBS (**1**), IBX (**2**), and DMP (**3**).



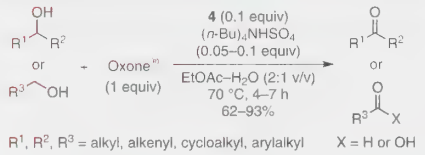
eq 1



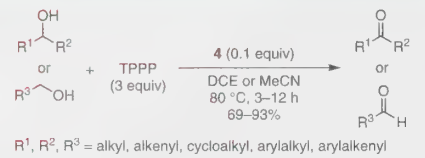
Scheme 1. The Oxidation of Alcohols Catalyzed by IBX (**2**) Generated in Situ. *(Ref. 9,10)*



eq 2 *(Ref. 9)*



eq 3 *(Ref. 10)*

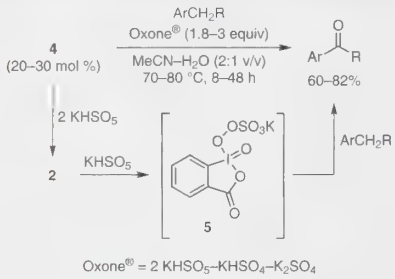


eq 4 *(Ref. 1*

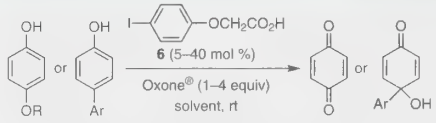
hypervalent iodine oxidant generated in situ might not be IBX (**2**), but a soluble derivative of IBX, **5**, incorporating a peroxy ligand ($KHSO_5$). This species is believed to oxidize a benzylic C–H bond via a single-electron-transfer (SET) mechanism.[12]

Yakura's group reported that *para*-alkoxyphenols and *para*-arylphenols are oxidized in excellent yields to the corresponding *para*-quinones and *para*-quinols, respectively, using catalytic amounts of 4-iodophenoxyacetic acid (**6**) with Oxone® as a co-oxidant in aqueous acetonitrile (**eq 5**).[13]

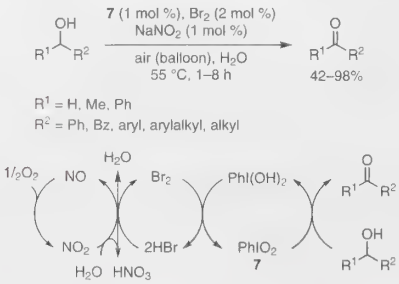
An efficient, catalytic aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones has been carried out by Liu and co-workers by using a mixture of iodoxybenzene ($PhIO_2$, **7**, 1 mol %), Br_2 (2 mol %), and $NaNO_2$ (1 mol %) in water (**Scheme 3**).[14] The proposed reaction mechanism includes three redox cycles. In the first redox cycle, **7** is the active species that oxidizes the alcohol to the corresponding carbonyl compound, and is reduced to dihydroxyiodobenzene ($PhI(OH)_2$). In the second cycle, $PhI(OH)_2$ is reoxidized to **7** with Br_2, which is reduced to HBr. In the third and final cycle, the oxidation of NO with O_2 produces NO_2, which reoxidizes HBr to Br_2. However, we were not able to effect the oxidation of alcohols under Liu's



Scheme 2. The Oxidation of Benzylic C–H Bonds with Oxone® Catalyzed by **5** Generated in Situ. *(Ref.*



eq 5 *(Ref. 13)*



Scheme 3. Liu's Aerobic Oxidation of Alcohols Catalyzed by $PhIO_2$ (**7**). *(Ref. 14)*

conditions,[15] which led us to suggest, on the basis of several control experiments, that the actual oxidant of the alcohols in this case is Br_2 rather than $PhIO_2$.[15]

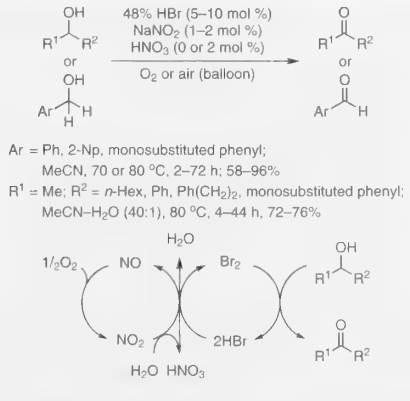
Moreover, our group disclosed that the simple and environmentally benign catalytic system consisting of HBr and $NaNO_2$ is very effective for the aerobic oxidation of alcohols (**Scheme 4**).[15] Primary benzylic alcohols are selectively oxidized to the corresponding aldehydes in acetonitrile under a balloon pressure of O_2. Secondary alcohols are oxidized to the corresponding ketones in the presence of a small amount of water. Furthermore, the aerobic oxidation of alcohols can also be achieved under a balloon pressure of air instead of pure O_2 with the HBr–$NaNO_2$–HNO_3 catalytic system.[15]

Li and co-workers developed an effective system for the oxidation of alcohols under an atmosphere of oxygen, without the need for any additional solvent or transition-metal catalyst, by using catalytic amounts of phenyliodine diacetate (PIDA (**8**))–TEMPO–KNO_2 (**Scheme 5**).[16]

In 2009, Yusubov, Zagulyaeva, and Zhdankin reported an efficient tandem catalytic system, based on a Ru(V)-catalyzed reoxidation of iodosobenzene (PhIO, **9**) to $PhIO_2$ (**7**), for the oxidation of alcohols and hydrocarbons to carbonyl compounds by employing stoichiometric amounts of Oxone® at room temperature (**Scheme 6**).[17]

Very recently, Nemykin, Zhdankin, and co-workers reported the room temperature, Fe(III)–porphyrin-catalyzed oxygenation of the anthracene ring to the anthraquinone system in the presence of a substoichiometric amount of iodobenzene and an excess of Oxone® (**Scheme 7**).[18] The proposed reaction mechanism includes two catalytic redox cycles. Accordingly, the active λ^3-iodane species, generated in solution by treatment of iodobenzene with Oxone®, is responsible for the oxidation of the Fe(III)–porphyrin to the oxo-Fe(IV)$^+$–porphyrin complex, which then acts as the actual oxygenating agent.

The same year, a catalytic, room-temperature oxidation of alcohols was effected with *meta*-chloroperbenzoic acid (*m*-CPBA) or potassium peroxodisulfate ($K_2S_2O_8$) in the presence of a catalytic amount of iodobenzene and *N*-hydroxyphthalimide (NHPI) or TEMPO in aqueous acetonitrile (**Scheme 8**).[19] In both cases, iodobenzene was oxidized by *m*-CPBA or $K_2S_2O_8$ in situ to a λ^3-iodane species, a reoxidant of NHPI or TEMPOH to phthalimide-*N*-oxyl radical (PINO) or TEMPO, which then oxidizes the alcohols.



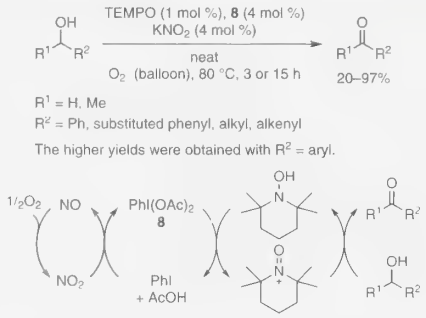
Scheme 4. Ishihara's Bromine-Catalyzed Aerobic Oxidation of Alcohols. *(Ref 15)*

3. 2-Iodoxybenzenesulfonic Acid (IBS)

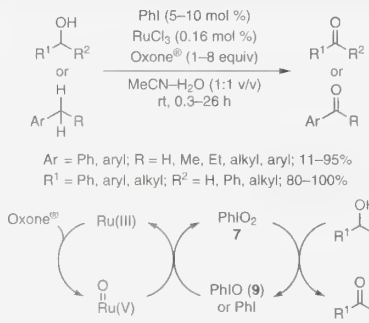
3.1. Related Hypervalent Iodine Reagents

3.1.1. HMBI and λ^3-Iodane Derivatives

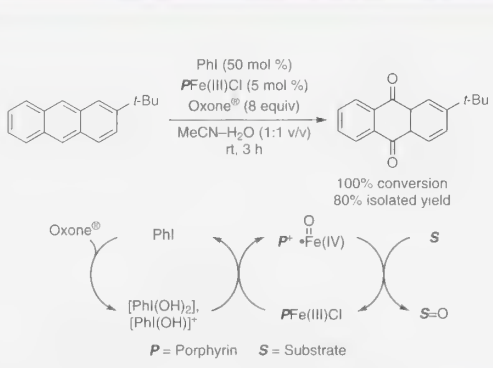
In 1993, Koser and co-workers first reported that the oxidation of 2-iodo-5-methylbenzenesulfonic acid (**10**) with peracetic acid leads to 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI, **11**) (**Scheme 9**).[20] In 2007, Justik reported that the sodium salt (**10**•Na) could be directly oxidized to **11** through in situ protonation with a small amount of concentrated sulfuric acid (see Scheme 9).[21] HMBI (**11**) was utilized to



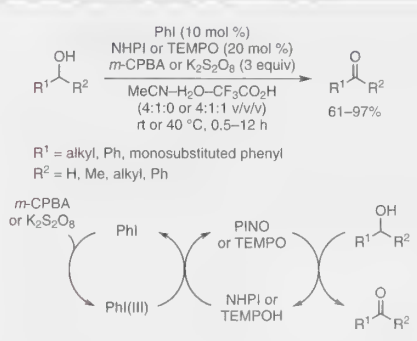
Scheme 5. TEMPO–PIDA (**8**) Co-catalyzed Aerobic Oxidation of Alcohols. *(Ref 16)*



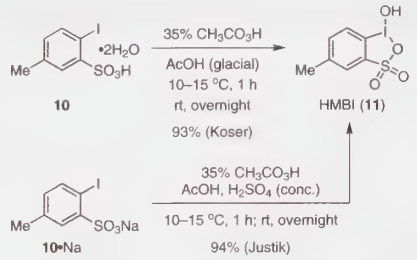
Scheme 6. Ru(III)–$PhIO_2$ (**7**) Co-catalyzed Oxidations with Oxone®.



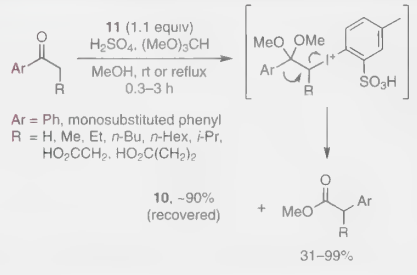
Scheme 7. Fe(III)–Porphyrin–Iodine(III) Co-catalyzed Oxidation of the Anthracene Nucleus. *(Ref 18)*



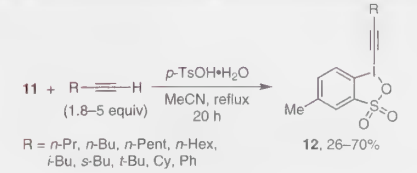
Scheme 8. Nitroxyl Radical–Iodine(III) Co-catalyzed Oxidation of Alcohols with *m*-CPBA or $K_2S_2O_8$. *(Ref. 19)*



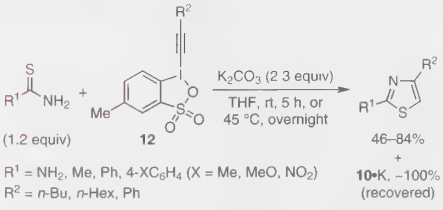
Scheme 9. Koser's and Justik's Syntheses of HMBI. *(Ref. 20,21)*



eq 6 *(Ref. 21)*



eq 7 *(Ref*



eq 8 *(Ref*

convert alkanophenones to alkyl esters of 2-arylalkanoic acids by oxidative rearrangement (**eq 6**).[21] The use of **11** offers several advantages over other similar oxidizing agents, including facile workup of the reaction mixture and recovery of the reduced iodine reagent.

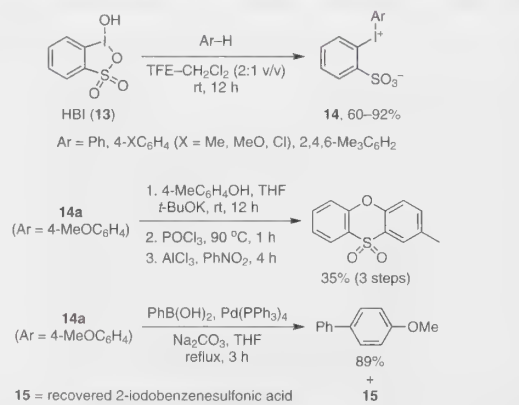
In the same 1993 report, Koser also disclosed the synthesis of 1*H*-1-(1-alkynyl)-5-methyl-1,2,3-benziodoxathiole 3,3-dioxides (AMBIs, **12**) from **11** and the corresponding terminal alkynes in low-to-good yields (**eq 7**).[20] Such AMBIs were later employed by Ishiwata and Togo to prepare thiazoles from the corresponding thioamides (**eq 8**).[22] The reduced iodo compound **10**•K was recovered quantitatively by simple filtration of the reaction mixture, and could be converted to **12** to be reused for the preparation of thiazoles.[22]

In a subsequent report, Justik's group disclosed that the reaction of 1*H*-1-hydroxy-1,2,3-benziodoxathiole 3,3-dioxide (HBI, **13**) with arenes produces 2-[(aryl)iodonio]benzenesulfonates (**14**) in moderate-to-high yields (**Scheme 10**).[23] HBI (**13**) was prepared from sodium 2-iodobenzenesulfonate (**15**•Na) similarly to the way its methyl analogue, **11**, was prepared (see Scheme 9). The zwitterionic sulfonates, **14**, were employed in the synthesis of 2-sulfonyloxyarenes and as potential recyclable aryl-transfer reagents in transition-metal-catalyzed cross-coupling reactions (see Scheme 10).[23]

3.1.2. IBS and λ^5-Iodane Derivatives

Zhdankin and co-workers first reported in 2006 the preparation and full characterization of IBS (**1**), a λ^5-iodane and a thia analogue of IBX (**2**).[24] IBS (**1**)—which is the cyclic tautomeric form of 1*H*-1-hydroxy-1,2,3-benziodoxathiole 1,3,3-trioxide—was synthesized by two different methods: (i) the direct oxidation of 2-iodobenzenesulfonic acid (**15**) with Oxone® (Method **A**) or (ii) by hydrolysis of the methyl ester of IBS, **16**, (Method **B**)[25] (**Scheme 11**). Method **A** results in a low-purity IBS, while Method **B** yields IBS of a high purity. IBS (**1**) is thermally unstable and highly reactive toward organic solvents such as acetonitrile, DMSO, and methanol.[24] Because of this instability (reductive decomposition to the corresponding λ^3-iodane) and reactivity, these researchers did not investigate its oxidative ability.[24]

The pseudocyclic λ^5-iodanes, IBS ester (**16**)[25] and amides (**17**),[26] have been prepared by oxidation of the corresponding 2-iodobenzenesulfonic ester and 2-iodobenzenesulfonamide with dimethyldioxirane (**Scheme 12**).[26] The starting material



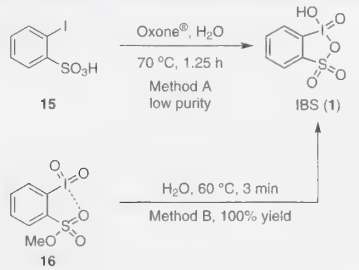
Scheme 10. Preparation and Application of 2-[(Aryl)iodonio]-benzenesulfonates (**14**). *(Ref.*

for these monovalent iodines, 2-iodobenzenesulfonyl chloride, was synthesized from **15**•Na (see Scheme 12).[25] IBS amides **17** can selectively oxidize benzyl alcohols to aldehydes.[26] While IBS esters **16** could not oxidize alcohols, they are useful for the oxidation of other organic functional groups, such as sulfides and secondary amines to the respective sulfoxides and imines (**Scheme 13**).[25]

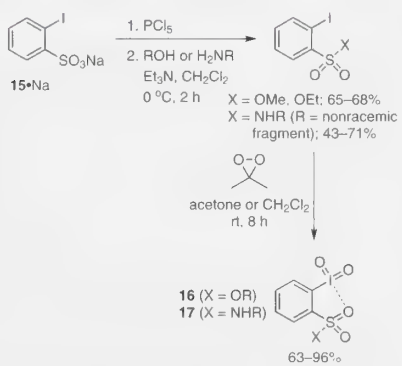
3.2. Discovery of IBS as a Catalyst for Alcohol Oxidation with Oxone®

To develop a more powerful hypervalent iodine catalyst for selective alcohol oxidation, we became interested in modifying the arene moiety of IBX (**2**) (**Figure 2**).[27] We discovered that electron-donating groups in the benzene ring, as in **18** and **19**, resulted in λ^5-iodanes that were superior to **2** as catalysts for the oxidation of alcohols with Oxone® under nonaqueous conditions, even though Oxone® was almost insoluble in most organic solvents. In contrast, electron-withdrawing groups, as in **20**, resulted in λ^5-iodanes with lower reactivity than **2**. The stability of these IBX catalysts was strongly influenced by solvents and the substituents; for instance, the 3-methyl- and 4,5-dimethoxy-substituted IBXs, **21** and **22**, decomposed under both aqueous and nonaqueous oxidation conditions.[27]

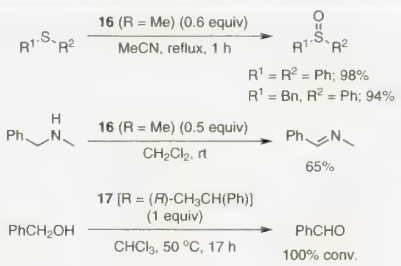
We then turned our attention to IBS (**1**) for the purpose of developing an even more powerful catalyst for alcohol oxidation. Our reasoning was that the Lewis acidity of the iodine(V) atom in **1** would be higher than that in **2** due to the strong electron-withdrawing sulfonate group in **1**.[27,28] Although **1** is not stable enough to isolate in pure form and examine in stoichiometric reactions, it can be prepared in situ in the presence of the alcohol substrate from **15**, **15**•Na, or **15**•K and Oxone®. We compared the catalytic efficiencies of in situ generated **1** and **2** in the oxidation of 5-nonanol (**Figure 3**, **1** in red and **2** in blue).[27] In nonaqueous nitromethane and acetonitrile, **1** was superior to **2** (red square and circle vs blue open-square and open circle; in nitromethane, TOF $\geq 50\ h^{-1}$ vs $16\ h^{-1}$, respectively). In sharp contrast, **2** was superior to **1** in aqueous media (red diamond vs blue open diamond).



Scheme 11. Zhdankin's First Reported Synthesis of IBS (**1**). *(Ref 24)*



Scheme 12. Synthesis of Pseudocyclic λ^5-Iodanes **16** and **17**.



Scheme 13. Facile Oxidations with IBS Ester **16** and IBS Amide **17**. *(Ref 25,26)*

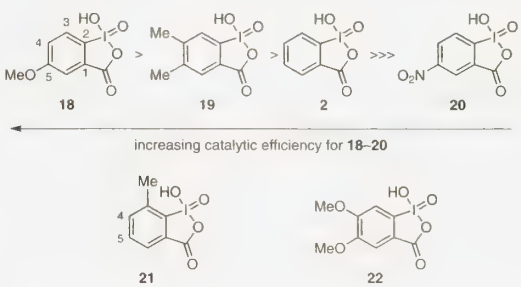


Figure 2. Catalytic Efficiencies of Arene-Substituted IBXs. *(Ref 27)*

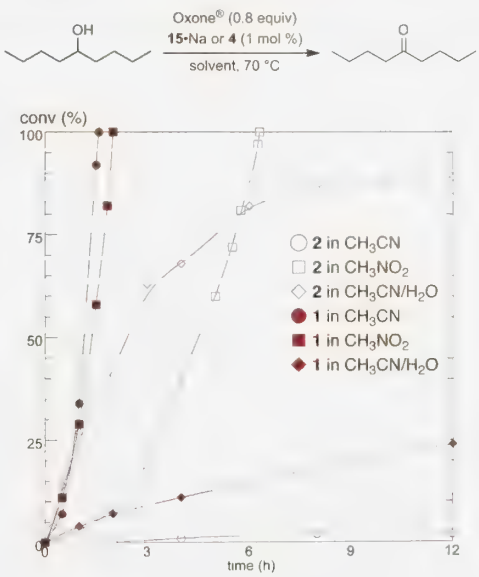


Figure 3. The Catalytic Efficiencies, in Aqueous or Nonaqueous Media, of IBS (**1**) and IBX (**2**) Generated in Situ from **15**•Na and **4**, Respectively. *(Ref 27)*

Moreover, **1** was sufficiently active in less polar, but more environmentally benign, ethyl acetate; while the **2**-catalyzed oxidation of alcohols was very slow in nonaqueous solvents such as ethyl acetate or acetonitrile. We investigated the substituent effect on the IBS-catalyzed oxidation of alcohols: IBS derivatives substituted with electron-donating groups, as in 5-Me-IBS (**23**) and 4,5-Me_2-IBS (**24**) (**Figure 4**), were superior to **1**, although the differences in the catalytic efficiencies were not large. The oxidation rates of reactions catalyzed by IBS were further accelerated by the use of powdered Oxone® due to its increased surface area. Additionally, vigorous stirring of the heterogeneous reaction mixture is essential for the efficient grinding of Oxone® and efficient alcohol oxidation. In a nonaqueous solvent system, the desired carbonyl products were obtained in nearly pure form by simple filtration of most wastes derived from Oxone® and washing with water to remove catalyst derivatives.[27]

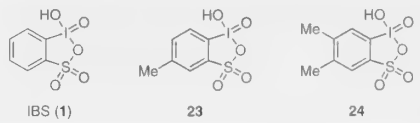
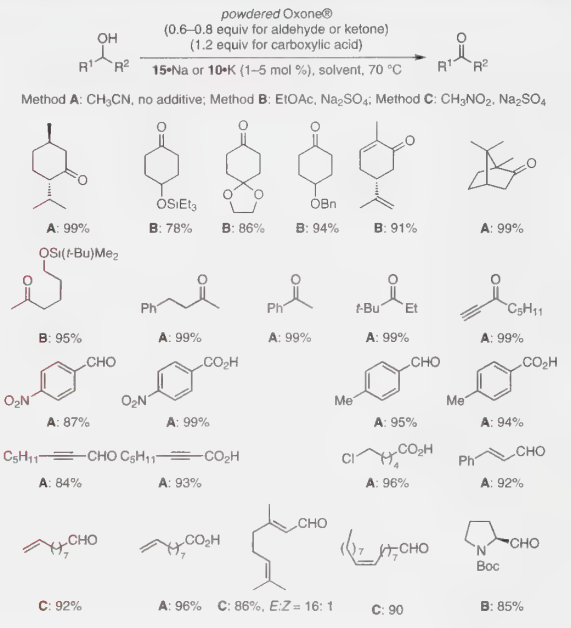
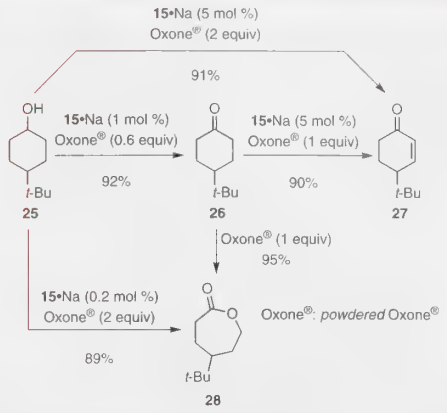


Figure 4. IBS Derivatives Substituted with Electron-Donating Groups. *(Ref*



eq 9 *(Ref. 27)*



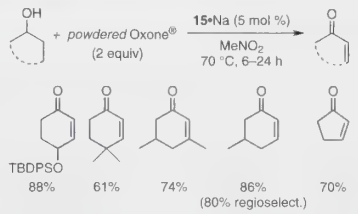
Scheme 14. The IBS-Catalyzed Selective Oxidation of **25** to **26** or **27**. *Ref. 27)*

Structurally diverse primary and secondary alcohols were oxidized with **1** or **23** under optimized conditions (**eq 9**).[27] Not only primary, α,β-unsaturated alcohols—such as allylic, propargylic, and benzylic alcohols—but also aliphatic alcohols were selectively oxidized to the corresponding aldehydes and carboxylic acids in excellent yields by controlling the amount of Oxone® added in the presence of **15**•Na or **10**•K. In particular, Methods **B** and **C** were effective for the selective oxidation of acid-sensitive alcohols and primary aliphatic alcohols to the corresponding aldehydes, respectively. This protocol was also applied to the chemoselective oxidation of alcohols bearing several functional or protective groups such as silyloxy, benzyloxy, ketal, alkenyl, alkynyl, and halo groups (see eq 9).[27]

In 2000, Nicolaou and co-workers reported the direct oxidative dehydrogenation, via a single-electron-transfer (SET) mechanism, of saturated alcohols and carbonyl compounds by using stoichiometric amounts of IBX (**2**) in DMSO.[29,30] During the course of our research on the oxidation of cycloalkanols, we found that the selective oxidation of 4-*tert*-butylcyclohexanol (**25**) to 4-*tert*-butylcyclohexanone (**26**) and the subsequent oxidation of **26** to 4-*tert*-butyl-2-cyclohexenone (**27**) and 5-*tert*-butyl-2-oxepanone (**28**) proceeded in excellent yields by controlling the amounts of **15**•Na and Oxone® (**Scheme 14**).[27] Five- and six-membered cycloalkanols were transformed into the corresponding enones in good yields (**eq 10**).[27]

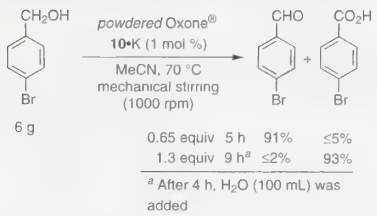
3.3. Large-Scale Oxidations

The selective oxidation of primary alcohols to the corresponding aldehydes or carboxylic acids would be a powerful tool in organic synthesis. The transition-metal- or nitroxyl-radical-catalyzed oxidation of alcohols to ketones or aldehydes has attracted a lot of attention because aqueous H_2O_2 or gaseous O_2 can be used as a stoichiometric oxidant.[1] However, it is technically difficult to control the amount of gaseous O_2 added as an oxidant. Moreover, while aqueous H_2O_2 and gaseous O_2 are often concentrated under evaporation and high pressure, respectively, to increase their reactivity, such treatments are dangerous because these materials can be explosive. Although aqueous H_2O_2 and gaseous O_2 are more atom-economical than Oxone®, the latter offers several advantages for selective large-scale oxidations such as stability, simple handling, controllable addition, and nontoxic nature.



eq 10 *(Ref. 27)*

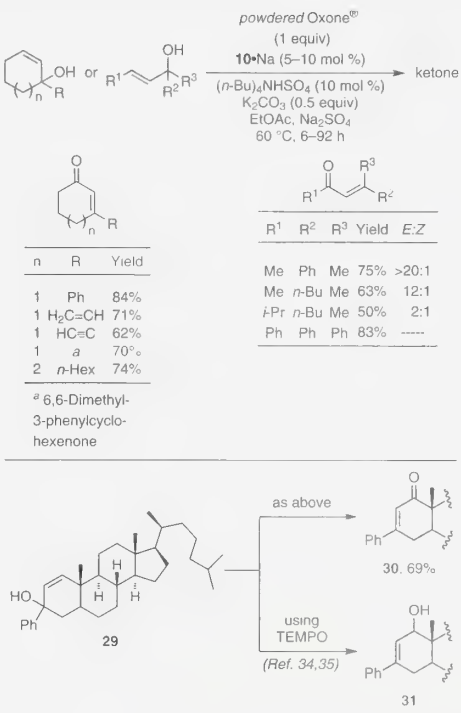
4-Bromobenzyl alcohol (6 g) was selectively oxidized to the corresponding aldehyde and carboxylic acid in excellent yield by controlling the amount of Oxone® added in the presence of **10**•K (1 mol %): 0.65 equiv was used for selective oxidation to the aldehyde, while 1.3 equiv was employed for oxidation to 4-bromobenzoic acid (**eq 11**).[31]



eq 11 *(Ref. 31)*

3.4. Application to the Oxidative Rearrangement of Tertiary Allylic Alcohols

The oxidative rearrangement of tertiary allylic alcohols to β-disubstituted α,β-unsaturated ketones or aldehydes using oxochromium(VI)-based reagents (Collins reagent, PCC, PDC) has been widely used in synthetic organic chemistry.[32] In 2004, Iwabuchi and co-workers reported that IBX (**2**) could be used instead of hazardous Cr(VI) for the oxidative rearrangement of tertiary allylic alcohols.[33] In 2008, the same research group reported that TEMPO-derived oxoammonium salts (TEMPO$^+$ BF_4^- and TEMPO$^+$ SbF_6^-) were more effective as stoichiometric reagents for this transformation of acyclic tertiary allylic alcohols in acetonitrile.[34] In that same year, Iwabuchi[35] and Vatèle[36] independently reported the first *catalytic* oxidative rearrangement of tertiary allylic alcohols. Iwabuchi's group utilized catalytic amounts of TEMPO with $NaIO_4$–SiO_2 as co-oxidant in dichloromethane to convert several cyclic and acyclic tertiary allylic alcohols into the corresponding enones in good yields.[35] In contrast, Vatèle developed a Lewis acid [$Bi(OTf)_3$ or Re_2O_7] promoted oxidative rearrangement using catalytic amounts of TEMPO with PhIO (**9**) as co-oxidant.[36] As part of our continuing interest in the use of IBS/Oxone® catalytic oxidation systems in organic synthesis, we reported the development of an oxidative rearrangement of tertiary allylic alcohols to enones with powdered Oxone® promoted by catalytic quantities of **10**•Na (**Scheme 15**).[37] 5-Me-IBS (**23**) is generated in situ and serves as the actual catalyst for the oxidation. Interestingly, **1** was less effective than **23** as catalyst in this case. The addition of inorganic bases, such as K_2CO_3, and a phase-transfer catalyst, such as tetra-*n*-butylammonium hydrogen sulfate [$(n\text{-Bu})_4NHSO_4$], extended the substrate scope for oxidative rearrangement reactions (see Scheme 15). Cyclic and acyclic substrates gave the corresponding enones in moderate to high yields. Notably, sterically demanding steroid alcohol **29** was converted into the desired enone **30** in 69% yield (see Scheme 15). In contrast, Iwabuchi's group reported that **29** was rearranged to allylic alcohol **31**, which was not oxidized to **30** under TEMPO-mediated conditions, due to considerable steric hindrance.[34,35] Our protocol should be recognized as a practical method for the oxidative rearrangement of tertiary alcohols, since it does not require any toxic, dangerous, or expensive reagents.[37]

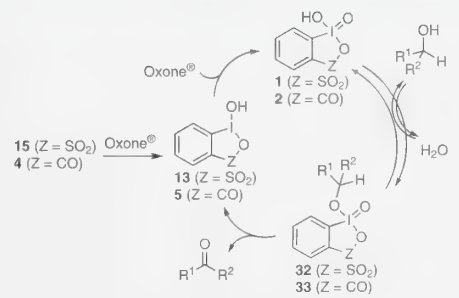


Scheme 15. IBS-Catalyzed Oxidative Rearrangement of Tertiary Allylic Alcohols. *(Ref. 37)*

3.5. Theoretical Calculations and Reaction Mechanism

The oxidation of alcohols with IBS consists of two steps, which are essentially identical to those of the IBX oxidation proposed by Santagostino:[38] a fast pre-equilibrium step and a rate-determining disproportionation step. The catalytic cycle of **1**, which is prepared in situ from **15**, can be accomplished by regenerating **1** through the oxidation of **15** with Oxone® (**Scheme 16**).

Based on the theoretical study by Su and Goddard on the oxidation of alcohols with IBX (**2**),[39] we also determined that the twisting of alkoxyperiodinanes **32-A** to the intermediates **32-B** was the rate-limiting step (**Scheme 17**).[27] Interestingly, **32** has a much lower twisting barrier than **33** (**33-A**→**33-B**: 10.3 kcal/mol vs **32-A**→**32-B**: 6.5 kcal/mol).[27] The I(V)–OCO and I(V)–OSO_2 distances in **33-A** and **32-A** are correlated with the twisting barriers: 2.252 Å for **32-A** > 2.193 Å for **33-A**. Based



Scheme 16. Proposed Catalytic Cycle for IBS- and IBX-Catalyzed Oxidations. *(Ref. 27)*

on theoretical calculations, we assumed that the relatively ionic character of the intramolecular hypervalent iodine–OSO_2 bond of IBS might lower the twisting barrier of the alkoxyperiodinane intermediate **32-A**. We are able to confirm that Goddard's *hypervalent twisting* would be the rate-determining step for the *stoichiometric oxidation* of alcohols with not only IBX (**2**) but also IBS (**1**). In contrast, it was reasonable to assume that the rate-determining step of *I(V)-catalyzed oxidations* might be the regeneration of I(V) species because: (i) the catalytic oxidation of alcohols was accelerated with powdered Oxone®, and (ii) control experiments indicated that the 5-methyl substituent of 5-Me-IBX had no influence on the oxidation of alcohols, while the 5-methyl substituent of 5-Me-IBS (**23**) accelerated the oxidation from I(III) to I(V).[27]

4. Conclusion

Over the past two decades, IBX (**2**) and other hypervalent iodine compounds have received considerable attention because of their mild and chemoselective oxidizing properties and because they are environmentally benign in contrast to the well-known but highly toxic heavy metal oxidants.[2] However, the stoichiometric use of **2** has been limited because it is potentially shock-sensitive and weakly soluble in common organic solvents.[2] Over the past five years, several research groups have reported alcohol oxidation reactions catalyzed by in situ generated IBX or related hypervalent iodines. These developments have been highlighted in this review.[9 19] Although IBS (**1**) is not stable enough to isolate in pure form and examine in stoichiometric reactions, we have reported that IBS's **1** and **23** can be prepared in situ from pre-IBS **15**•Na and **10**•K and Oxone® in the presence of an alcohol substrate. We have also disclosed that **1** and **23** show greater catalytic activity than IBX (**2**) under nonaqueous conditions.[27] Consequently, we have developed a highly efficient and chemoselective oxidation of various alcohols to carbonyl compounds with powdered Oxone® in the presence of catalytic amounts of IBS. Our findings could lead to new possibilities in hypervalent-iodine-catalyzed oxidative transformations.

5. Acknowledgement

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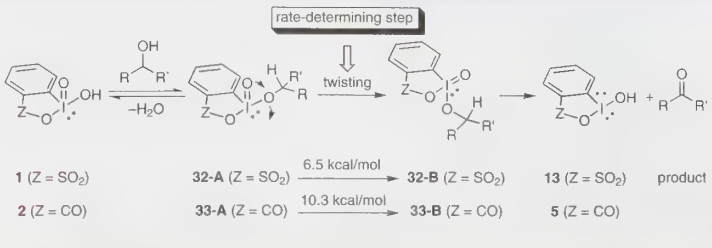

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Keywords: λ^5-Iodanes; IBS; Oxone®; alcohol oxidation; chemoselective oxidation; catalytic oxidation.

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Muhammet Uyanik was born in 1981 in Samsun, Turkey, and received his Ph.D. degree in 2007 from Nagoya University under the direction of Professor Kazuaki Ishihara. He was appointed Assistant Professor at Nagoya University in 2007. In 2009, Dr. Uyanik received the Shionogi Award in Synthetic Organic Chemistry, Japan, and, in 2010, an Incentive Award for Young Scientists from the Tokai Branch of The Society of Synthetic Organic Chemistry, Japan. His research interests include oxidation reactions and asymmetric catalysis.

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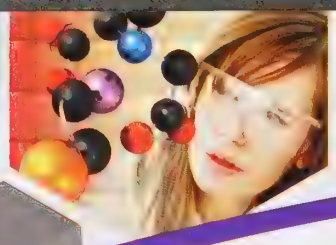


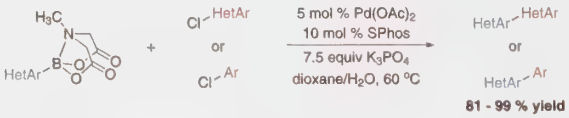
Boronic Acid Surrogates

The use boronic acids and esters for Suzuki–Miyaura cross-coupling reactions is an invaluable tool for the construction of complex molecules. However, complications associated with the purification and handling of these sensitive organometallic reagents have detracted from the use of this method. To address these issues, two new classes of stable boron anion equivalents have been developed and are now available from Aldrich: MIDA boronates and trifluoroborate salts.

New MIDA Boronates from Aldrich

Benefits of MIDA Boronates

- Bench-top and chromatographically stable
- Good solubility properties and monomeric in nature
- Controlled release for in situ cross-couplings



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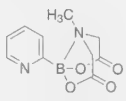
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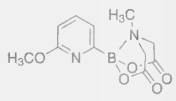
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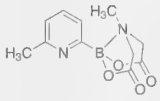
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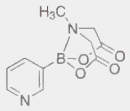
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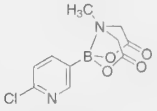
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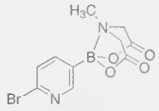
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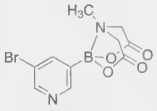
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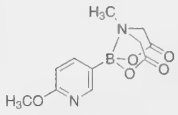
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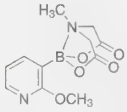
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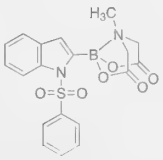
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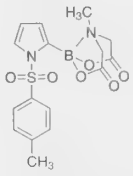
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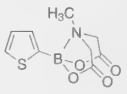
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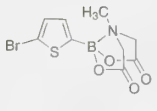
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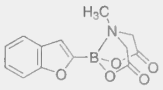
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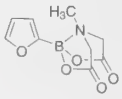
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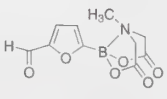
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New Trifluoroborate Salts from Aldrich

Benefits of Trifluoroborate Salts

- Air- and moisture-stable
- Tetracoordinated monomeric species
- Less prone to protodeborylation

X = Cl, Br, I, OTf | 684961 | 75 - 99 % yield

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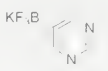

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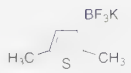

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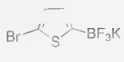

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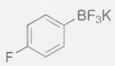

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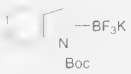

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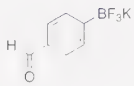

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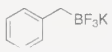

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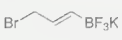

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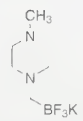

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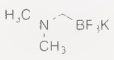

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ALDRICH Chemistry

Remembering Dr. Jai P. Nagarkatti (1947–2010)

Recent Advances in the Application of α-Phenylethylamine (α-PEA) in the Preparation of Enantiopure Compounds

2-Iodoxybenzenesulfonic Acid (IBS) Catalyzed Oxidation of Alcohols

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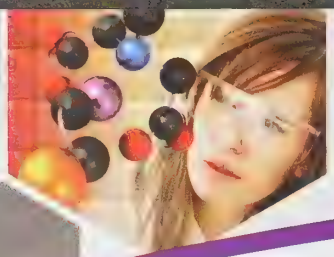

ALDRICH Chemistry

Aldrich Congratulates the 2010 Winners of the Nobel Prize in Chemistry

Professors **Ei-ichi Negishi**, **Akira Suzuki**, and **Richard F. Heck** have been awarded the 2010 Nobel Prize in Chemistry by The Royal Swedish Academy of Sciences for their trailblazing contributions to the area of "palladium-catalyzed cross couplings in organic synthesis".

Photo courtesy of Purdue U./ Andrew Hancock

Distinguished Professor
Ei-ichi Negishi
Purdue University, U.S.A.

Photo courtesy of Hokkaido U.

Distinguished Professor Emeritus
Akira Suzuki
Hokkaido University, Japan

Photo courtesy of U. of Delaware

Professor Emeritus
Richard F. Heck
University of Delaware, U.S.A.

Aldrich congratulates these distinguished chemistry pioneers on this achievement and thanks them for their lasting contributions to organic synthesis. Our company is proud to have had close collaborations with Professors Negishi and Suzuki, two former associates of another Nobel laureate and longtime Aldrich collaborator and member of the Board of Directors, the late Professor H. C. Brown.

The *Aldrichimica Acta* has had the distinct privilege of publishing high-impact review articles by a number of chemistry Nobel laureates, such as Professors Derek H. R. Barton, Herbert C. Brown, Elias James Corey, Ei-ichi Negishi, George A. Olah, Charles J. Pedersen, Vladimir Prelog, and K. Barry Sharpless.

The tradition of supporting future scientific leaders is strong at Sigma-Aldrich. Throughout our history, we have acknowledged scientific excellence through sponsorship of awards, symposia, and graduate-level research in the fields of chemistry, life science, and materials science. A number of previous winners of Sigma-Aldrich sponsored American Chemical Society awards (e.g., Professors George A. Olah, K. Barry Sharpless, and Ei-ichi Negishi) have gone on to receive the ultimate recognition, the Nobel Prize in Chemistry.

To access highly informative *Aldrichimica Acta* reviews written by Nobel laureates and other chemistry luminaries, visit *aldrich.com/acta*

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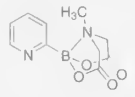
(1) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961



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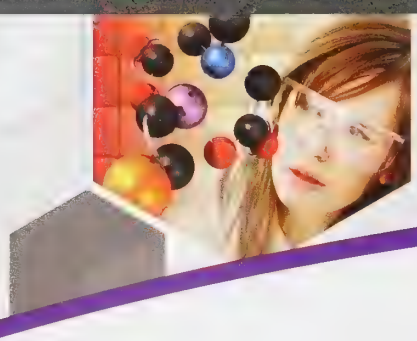
Photograph © Rosie Sandifer

Taos Pueblo Snow (oil on canvas, 40.6 × 70.0 cm) was painted in 2009 by the American painter and sculptor Rosie Sandifer (b. 1946) following a visit to the Pueblo. It depicts the centuries-old, Native American village with the same name. Taos Pueblo is located about two miles north of the town of Taos, New Mexico, and is one of the longest continually inhabited places in the U.S.A. It has been designated a World Heritage Site by UNESCO and a National Historic Landmark by the U.S. Government.

Equally gifted at painting and sculpting, Sandifer paints her impressions of what she observes in nature by simplifying to the essentials the effects of fleeting light on the subject, as evidenced by the white, brown, and turquoise that dominate in this painting. While her subject matter has included landscapes, figures, and animals, she has tended to focus on Western landscapes. She has participated in numerous solo, group, and juried exhibitions, and her paintings and sculptures are on display in a number of museums and public places in the U.S. Currently a resident of Santa Fe, NM, Sandifer received her extensive art education and training most notably at the Froman Painting School in Cloudcroft, NM, and the Art Students League in Stowe, VT, where she was influenced by Frank Mason, a classical realist painter and one of the most acclaimed modern American painters and teachers.

This painting is provided courtesy of the artist and is in her private collection.



ALDRICH Chemistry

New Oxetane Building Blocks

Oxetanes have historically been of modest interest to synthetic and medicinal chemists, perhaps with the natural product paclitaxel or TAXOL® being the best known example of an oxetane-containing substance. Presently, oxetanes are receiving greater attention as attractive modules for drug discovery, largely due to a series of reports from Rogers-Evans, Carreira, and coworkers. These reports have demonstrated the improved physico- and biochemical properties of a molecular scaffold when an oxetane unit replaces a *gem*-dimethyl unit[1] and the ability for an oxetane ring to function as a surrogate for a carbonyl group.[2,1b] Another recent report has disclosed the use of 1,6-substituted azaspiro[3.3]heptanes containing an oxetane ring as alternatives to unstable 1,3-heteroatom-substituted cyclohexanes.[3] In most cases, 3-oxetanone, **731536**, was the principal building block employed by the authors to install the oxetane unit (**Scheme 1**).

References: (1) (a) Wuitschik, G. et al. *Angew. Chem., Int Ed.* **2006**, *45*, 7736. (b) Wuitschik, G. et al. *J. Med. Chem* **2010**, *53*, 3227. (2) Wuitschik, G. et al. *Angew. Chem., Int Ed.* **2008**, *47*, 4512. (3) Burkhard, J. A. et al. *Org. Lett* **2010**, *12*, 1944

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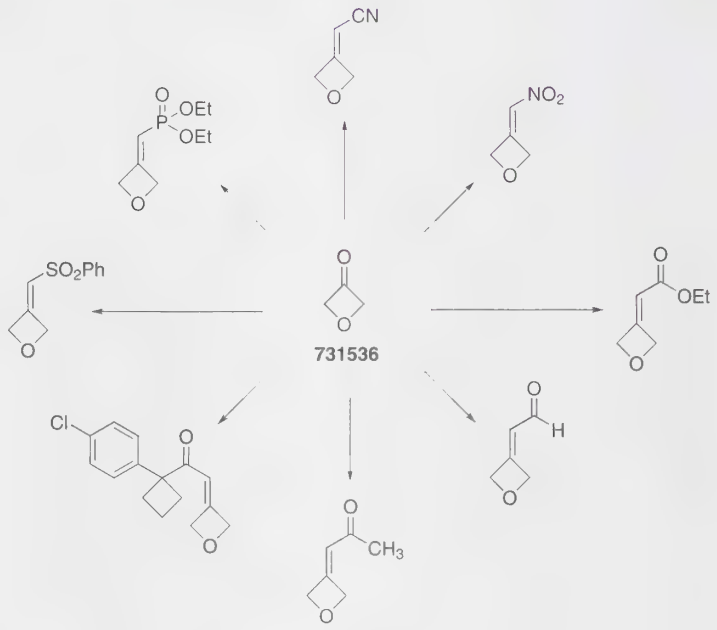


Scheme 1. Oxetane Derivatives Synthesized from 3-Oxetanone

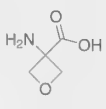
We are pleased to offer a wide selection of new oxetane building blocks for a variety of applications in synthetic and medicinal chemistry.


731536


733296


731560


731579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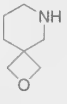
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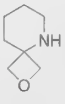
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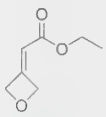
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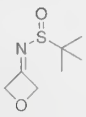
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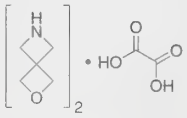
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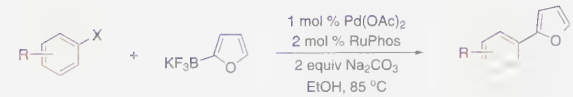
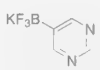


X = Cl, Br, I, OTf 684961 75 - 99 % yield

Reference: (1) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem* **2009**, *74*, 973. (2) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49



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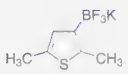

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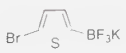

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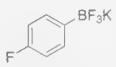

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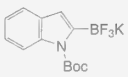

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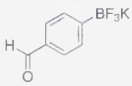

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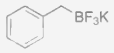

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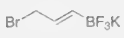

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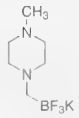

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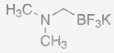

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THE GROWING ROLE OF ORGANOCATALYSIS IN ASYMMETRIC SYNTHESIS

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Asymmetric N-Heterocyclic Carbene (NHC) Catalyzed Acyl Anion Reactions

Recent Advances in the Asymmetric Catalytic Mannich Reaction

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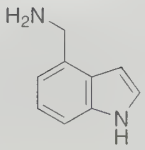
References: (1) Horton, D. A. et al. *Chem. Rev.* **2003**, *103*, 893 and references therein. (2) (a) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 1031. (b) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 8689. (c) Song, J. J. et al. *Chem. Soc. Rev.* **2007**, *36*, 1120. (d) Huang, W.-S. et al. *J. Med. Chem.* **2010**, *53*, 4701. (e) Buckley, G. M. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3656. (f) Buckley, G. M. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3291.



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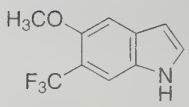

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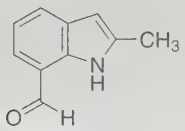

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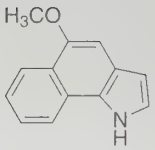

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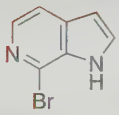

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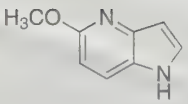

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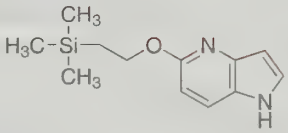

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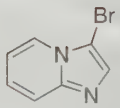

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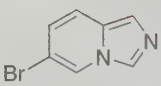

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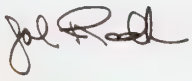
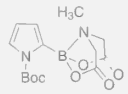


John Radke
Director of Marketing, Chemistry

Professor Alison Thompson of the Department of Chemistry at Dalhousie University recently suggested that we introduce *N*-Boc-pyrrole-2-boronic acid MIDA ester. This air- and moisture-stable reagent serves as a 2-heterocyclic boronic acid surrogate that is useful in Suzuki–Miyaura cross-coupling reactions.

Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.



733539

733539 ***N*-Boc-pyrrole-2-boronic acid MIDA ester, 95%** 250 mg, 1 g

Naturally, we made this useful heterocyclic reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

TABLE OF CONTENTS

ABOUT OUR COVER

River Landscape with a Resting Traveller (oil on panel, 46×66.5 cm) was painted most likely in the mid-1650s by Jan Lievens (1607–1674), who was one of the most prominent painters of the Dutch Golden Age. He is usually mentioned in the same breath as Rembrandt, because the two artists shared much during their early years. Because of Rembrandt's greater achievement, Lievens was long assumed to have been his follower, but recently it has become clear that he was initially the leader. Although younger, he was a celebrated child prodigy who established himself years before his colleague.

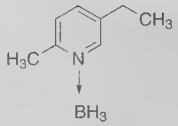
Detail from ***River Landscape with a Resting Traveller***

Lievens's later success lay in following and interpreting the grand figurative style of Flemish masters such as Peter Paul Rubens and Anthony van Dyck, much favored among the elite. He could study such works while in Antwerp, where he also saw the contemplative landscapes by Rubens and other artists. These reflected the Flemish tradition of rich, lively, and decorative fantasy landscapes, in contrast to the more sober realism exercised by Dutch landscapists. In his own landscapes, Lievens tried a more fluid brush handling and rolling forms. In this late scene, he places a weary traveler reclining against a tree in a lush forest. He also betrays his penchant for arranging a screen of trees against a light background that pierces between the trunks to generate drama and rhythm. The result is slightly otherworldly, an invitation to escape from the urban confines and daily pressures, that would have appealed to many collectors in both Flanders and Holland.

This painting is part of the Bader Collection of Dutch and Flemish Paintings, whose future home will be the Agnes Etherington Art Centre of Queen's University, Kingston, ON, Canada.

ALDRICH Chemistry

When you need a stable liquid Reductive Amination Reagent



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PEMB is a liquid Pyridine Borane Complex useful for reductive amination chemistry

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- Mild reducing agent for imines and oximes
- Reaction with protic solvents is very slow
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- Can be used solvent-free for reductive aminations
- Chemically efficient: two of three hydrides are utilized

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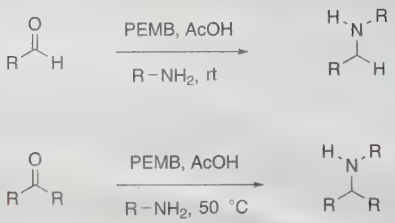
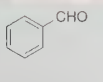
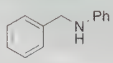
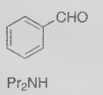
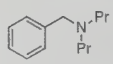
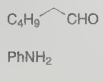
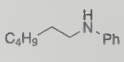
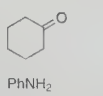
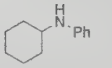
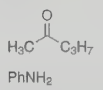
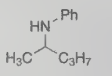


Examples

Aldehyde and Amine	Conditions	Product	% Yield in MeOH (% Yield Neat)
	PEMB, AcOH, MeOH, 25 °C		72 (80)
	PEMB, AcOH, MeOH, 25 °C		0 (96)
	PEMB, MeOH, 25 °C		92 (94)
	PEMB, AcOH, MeOH, 25 °C		92 (93)
	PEMB, AcOH, MeOH, 50 °C		74 (94)

For more examples and experimental details, please see: Burkhardt, E. R.; Coleridge, B. M. *Tetrahedron Lett.* **2008**, *49*, 5152.

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Distillation Adapter for On-The-Fly Sampling

SIGMA-ALDRICH
Labware

Distillation is the most widely used bulk separation method in the laboratory as well as in industry. Beyond purification, it is widely utilized to characterize complex fluids (such as fuels) through measurement of the distillation curve, a plot of the boiling temperature against volume distilled. A common theme in both of these applications is the desire to understand the composition. In purification, the goal is to monitor the distillation progress; and in fluid characterization, one seeks to relate the composition to the temperature data.

Features and Benefits

A distillate sampling adapter (**Figure 1**), installed after a condenser or distillation column, can provide this important capability without the need for cumbersome, expensive, and often unreliable fraction collectors.[1-3] The flow of the distillate is focused to drop into a 0.05 mL "hammock" that is positioned directly below the flow path The sampling port, equipped with a vacuum-tight valve, allows access to the hammock with a standard chromatographic syringe through a septum. To sample the distillate, one simply positions the chromatographic syringe, preferably equipped with a blunt-tipped needle, in the well of the hammock. It is a simple matter to withdraw samples as the distillation progresses. The sample can then be directly injected into the gas chromatograph or spectrometer, or injected into an autosampler vial for analysis later. Indeed, any analytical technique that is applicable for liquid samples ranging in volume from 1 to 50 microliters can be used to characterize the distillate

The distillate sampling adapter is offered with several joint options , and is designed to work with existing modular distillation glassware. It is simply a matter of replacing the existing vacuum adapter with a distillate sampling adapter. No further modification to the setup is required.

For more information, visit **Aldrich.com/labware**

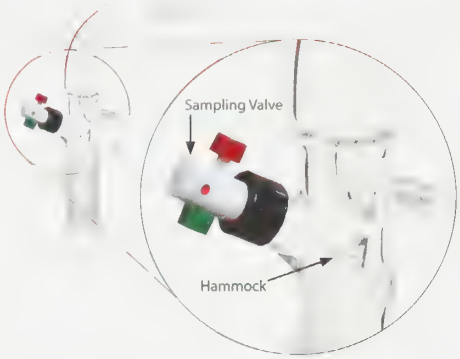

Figure 1. Distillate sampling adapter

Aldrich® Distillate Sampling Adapter, with Vacuum Connection and PTFE Valve

Joint Size	Cat. No.
14/20	Z569895
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29/32	Z569917
Replacement valve septa	33310-U
Septum inserter for valve	33311
Hamilton 701SNR syringe, 10 µL, 22s gauge blunt tip needle	58380-U

References:

(1) Bruno, T. J.; Ott, L. S.; Smith, B. L.; Lovestead, T. M. Complex fluid analysis with the advanced distillation curve approach. *Anal. Chem.* **2010**, *82*, 777

(2) Bruno, T. J.; Ott, L. S.; Lovestead, T. M.; Huber, M. L. The composition-explicit distillation curve technique: relating chemical analysis and physical properties of complex fluids. *J. Chromatogr., A* **2010**, *1217*, 2703

(3) Bruno, T. J.; Ott, L. S.; Lovestead, T. M.; Huber, M. L. Relating complex fluid composition and thermophysical properties with the advanced distillation curve approach. *Chem. Eng. Tech.* **2010**, *33*, 363

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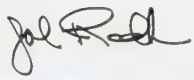
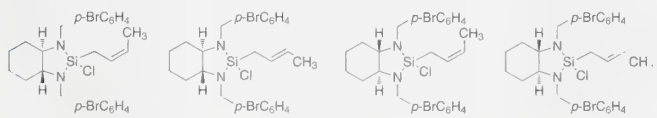


John Radke
Director of Marketing, Chemistry

Professor Jeffrey Bode at the University of Wisconsin-Madison recently suggested that we introduce Leighton's chiral crotylsilane reagents. These air-stable, crystalline solids may be stored at room temperature and are useful for the enantioselective crotylation of aldehydes and other carbonyl compounds

(a) Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517. (b) Leighton, J. L. *Aldrichimica Acta* **2010**, *43*, 3



733199 733180 733075 733083

733199	**(*R*,*R*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(2*Z*)-crotyl-*1H*-1,3,2-benzodiazasilole, 97%**	1 g
733180	**(*R*,*R*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(2*E*)-crotyl-*1H*-1,3,2-benzodiazasilole**	250 mg 1 g
733075	**(*S*,*S*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(2*Z*)-crotyl-*1H*-1,3,2-benzodiazasilole, 97%**	1 g 5 g
733083	**(*S*,*S*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(2*E*)-crotyl-*1H*-1,3,2-benzodiazasilole**	250 mg 1 g

Naturally, we made these useful crotylation reagents available. It was no bother at all, just a pleasure to be able to help

Do you have a compound that you would like to see listed in our catalog? Would it help you in your research by saving you time and money? If so, please send us your suggestion: we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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Detail from *The Maas at Dordrecht*. Photograph

Aelbert Jacobsz Cuyp (1620–1691) of the Golden Age of Dutch Art painted *The Maas at Dordrecht* (oil on canvas, 114.9 × 170.2 cm) around 1650. It is possible that Cuyp was commissioned to commemorate an event that may have occurred during the summer of 1646. At that time, an enormous fleet of ships carrying around thirty thousand soldiers was anchored at Dordrecht presumably for symbolic purposes rather than for specific military ones as peace was finally at hand. The Peace of Münster, which ended the Eighty Years' War with Spain, was signed only two years later, in 1648.

One of Cuyp's finest paintings, this work depicts a flurry of maritime activity, while the intricately painted pleyt (riverboat) and adjacent rowboat in the right foreground are clearly the painting's focal point. Not only are the boats authentically depicted, but they also contain numerous figures that have personality and purpose. Most of the ships on the river have their sails raised and flags flying as though they are about to embark. The early morning light floods the scene and creates striking patterns on the clouds, sails, and water, adding a dramatic character to the setting. The weight and massiveness of Cuyp's forms give this work a tangibility that few other marine painters could achieve.

This painting is part of the Andrew W. Mellon Collection at the National Gallery of Art, Washington, DC.

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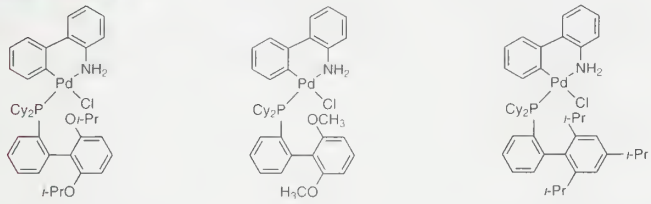
Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073.



753246 **753009** **741825**

753246	Chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)-[2-(2′-amino-1,1′-biphenyl)]palladium(II)	250 mg 1 g 5 g
753009	Chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)-[2-(2′-amino-1,1′-biphenyl)]palladium(II)	250 mg 1 g 5 g
741825	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-[2-(2′-amino-1,1′-biphenyl)]palladium(II)	250 mg 1 g 5 g

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John Radke
Director of Marketing, Chemistry

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Seashore with Fishermen (oil on canvas, 101.9 × 127.6 cm) was painted around 1781/1782 by the British portrait and landscape painter, Thomas Gainsborough (1727–1788). While better-known as a portraitist for the more lucrative portraits of royalty and nobility that he painted most of his life to support his family, he never lost his fondness for landscape painting.

Gainsborough painted this landscape in his later years, when he reportedly declared that he was tired of painting portraits. Depicting fishermen struggling against strong winds and waves to launch their boat into the water, he imparts a measure of spontaneity and sensibility to the scene. His personal style is reflected in the way he merges the figures with the scene behind them, and in his handling of paint for which he was much admired.

This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

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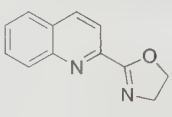

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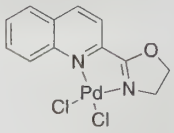

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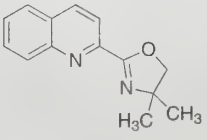

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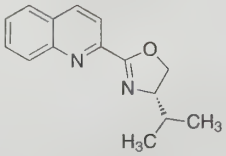

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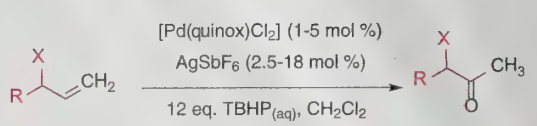

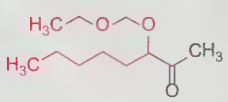

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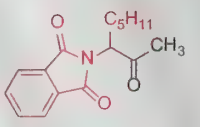
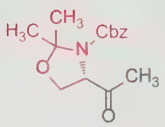
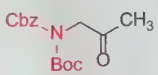


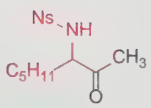
82%, 20 min



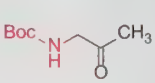
69%, 16 h



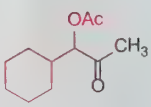
95%, 2.5 h



88%, 4 h



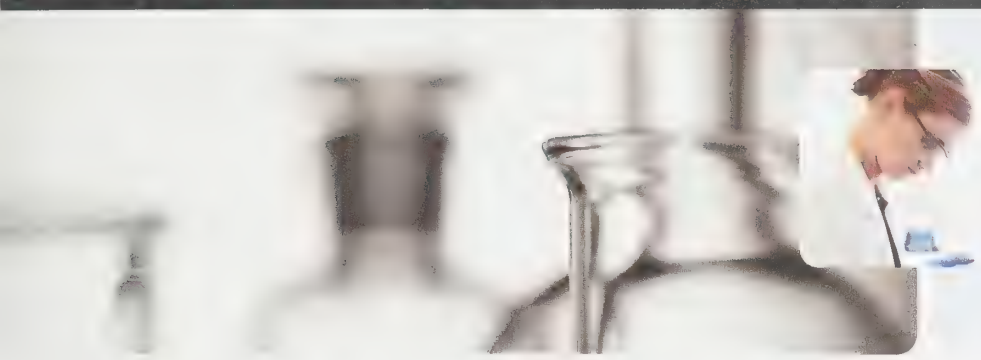
74%, 2.5 h



89%, 17 h

Scheme 1: Pd-quinox catalyzed Wacker oxidation of allylic functionalized terminal alkenes.

References: (1) Michel, B. W.; Camelio, A. M.; Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 6076. (2) Michel, B. W.; McCombs, J. R.; Winkler, A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 7312. (3) Michel, B. W.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 8317.



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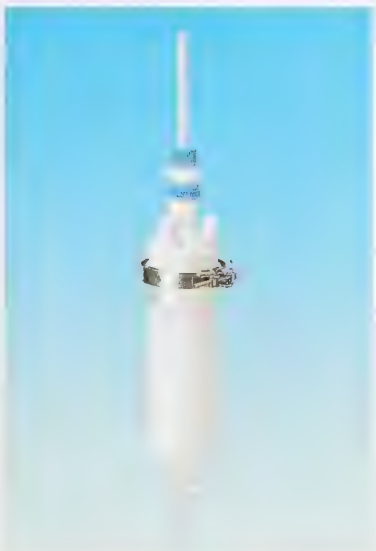

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Other components same as above	
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About Prof. Paul Knochel

Currently at the Department of Chemistry of Ludwig Maximilian University in Munich, Germany, Professor Paul Knochel's research interests include the development of novel organometallic reagents and methods for use in organic synthesis, asymmetric catalysis, and natural product synthesis.

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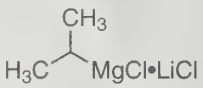

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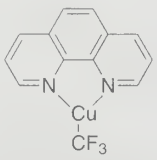

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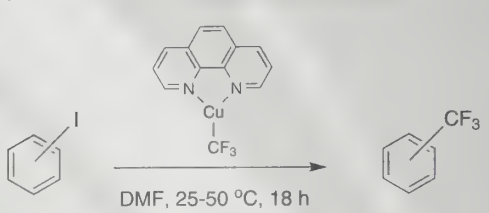
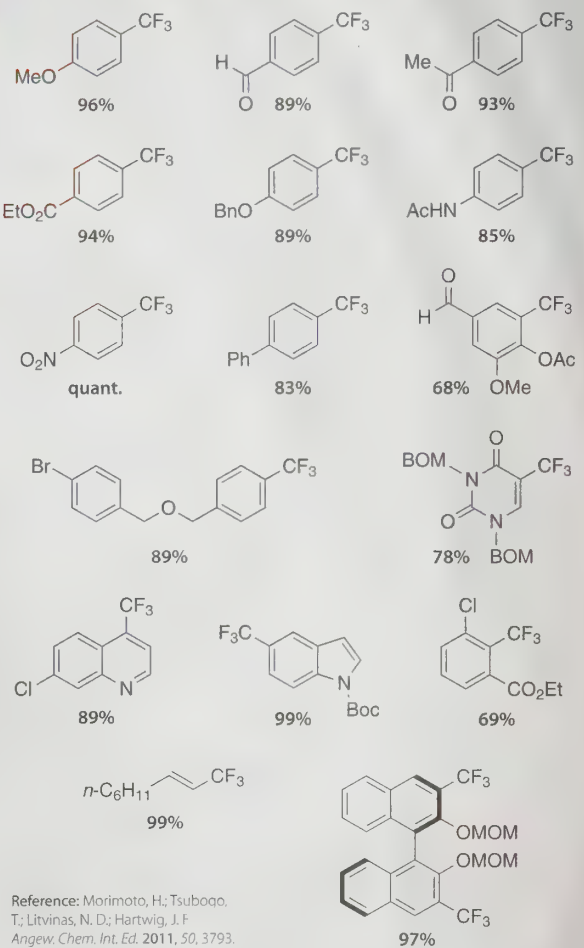


Representative Reaction Scope



Reference: Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

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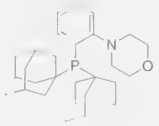
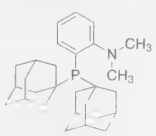
(a) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071
(b) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8686



751618



751413

751618	Di(1-adamantyl)-2-morpholinophenylphosphine (Mor-DalPhos)	250 mg 1 g
751413	Di(1-adamantyl)-2-dimethylaminophenylphosphine (Me-Dalphos)	250 mg 1 g

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Venice: The Dogana and San Giorgio Maggiore (oil on canvas, 91.5 × 122.0 cm) was completed in 1834 by Joseph Mallord William Turner (London, 1775–1851). A prolific British artist and an influential member of the Romantic Movement of the late eighteenth and first half of the nineteenth century, he elevated landscape painting to a level not achieved before and introduced several innovations to the genre. His talent manifested itself very early in life, and he was much admired as an artist in life and death, with institutions, works, and artistic prizes dedicated to preserving his legacy.

Detail from *Venice: The Dogana and San Giorgio Maggiore*
Photograph © Board of Trustees, National Gallery of Art, Washington

This painting depicts a bustling maritime scene in the Grand Canal of Venice, which Turner had visited several times. (Another Venetian cityscape, painted seven years earlier by another British Romantic Movement artist, R. P. Bonington, has graced the cover of *Aldrichimica Acta*, Vol. 43, No. 1.) Turner intended this work as a celebration of commerce, as symbolized by the statue of Fortune atop the Dogana (Customs building) in the foreground. While Turner was not concerned with a faithful depiction of the scene, as evidenced by the apparent widening of the canal and placement of San Giorgio's church, his skill as a draftsman and his mastery of perspective drawing are evident in his precise, linear rendering of the buildings and sharp angles. His color combinations, freely handled layers of paint, and the sparkling water and light sky exemplify his lifelong preoccupation with the effects and significance of light in an awe-inspiring natural world.

This painting is part of the Widener Collection at the National Gallery of Art, Washington, DC.

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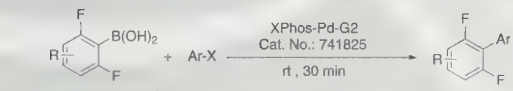

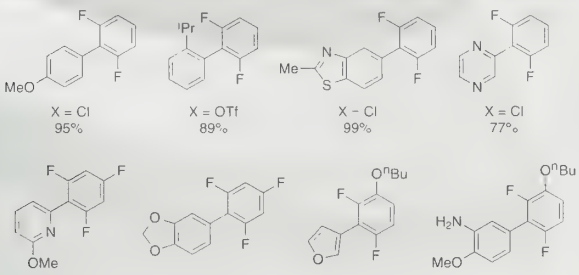

References:
(1) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (2) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (3) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (4) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073.

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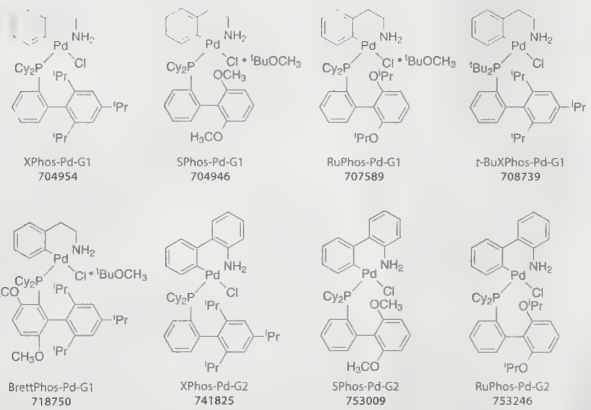

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Professor Bruce H. Lipshutz

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About Prof. Bruce Lipshutz

Bruce Lipshutz has been on the faculty at UC Santa Barbara for the past 33 years. From his early contributions in the form of reagents such as SEM-Cl and higher order cyanocuprates to heterogeneous catalysts in the form of nickel- and copper-in-charcoal, his research focus has been on providing technologies that are broadly applicable to synthetic problems. More recently, he has turned his attention to "green" chemistry, with the goal of developing micellar catalysis as an environmentally benign way of carrying out transition-metal-catalyzed cross-coupling reactions in water at room temperature.

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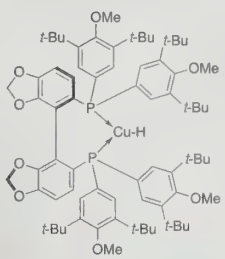

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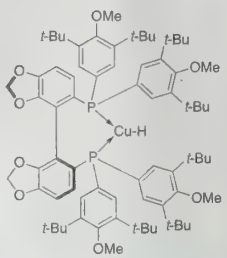

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(a) Emmett, E. J.; Richards-Taylor, C. S.; Nguyen, B.; Garcia-Rubia, A.; Hayterb, B. R.; Willis, M. C. *Org. Biomol. Chem.* **2012**, *10*, 4007. (b) Ye, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 7753. (c) Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. *Org. Lett.* **2011**, *13*, 4876. (d) Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372

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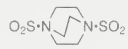

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Detail from ***Forest of Fontainebleau*** Photograph © Board of Trustees, National Gallery of Art, Washington

Forest of Fontainebleau (oil on canvas, 175.6 × 242.6 cm) was painted in 1834 by the French artist Jean-Baptiste-Camille Corot (1796–1875). Corot was a prolific painter with a talent that ranged widely from mainly landscapes to portraits, nudes, etchings, and other forms. He even dabbled in photography later on in his life. Unlike a number of his famous contemporaries, his rise to prominence in the artistic world was slow: He did not take up painting until his mid-twenties, and it wasn't until his mid-forties that he began to get the recognition he deserved, first from fellow artists, and then from art critics, official France, collectors, and the public. His artistic training consisted mainly of apprenticeships with Neoclassicist painters Achille-Etna Michallon and Jean-Victor Bertin and three trips a few years apart to Italy where he honed his landscape painting skills. Corot lived his life as a simple and humble man who was a mentor and a philanthropist to many young and struggling artists, and his work is thought to foreshadow the impressionist movement

Forest of Fontainebleau is a good example of the genre of painting known as "historical" landscape, which Corot excelled at, and in which a historical or biblical theme is incorporated into the painting in order to "elevate" it in the eyes of art critics and gain public attention. In this case, the biblical connection is inferred from several clues* Corot inserted in the painting. Corot's strong naturalist strain, controlled paint strokes, and tendency to favor brown and black colors are reflected in this unpretentious and simply rendered composition depicting a rough forest that stands in sharp contrast to the serene young woman

This painting is part of the Chester Dale Collection at the National Gallery of Art, Washington, DC.

** Can you find the clues in the painting? What do the clues reveal about the young woman reading? To find out visit* ***Aldrich.com/acta/aoc453***

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- Mild conditions

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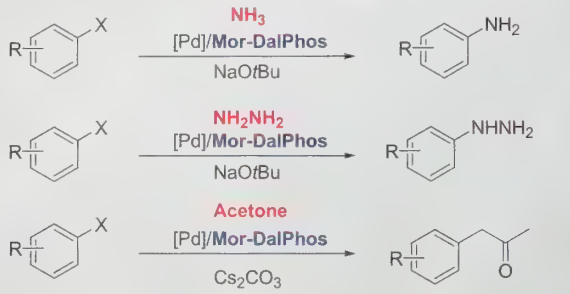

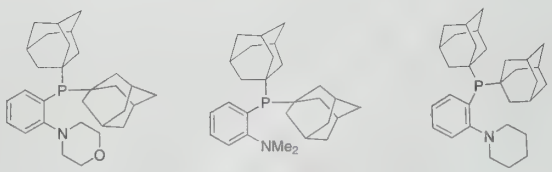

751618
Mor-DalPhos

751413
Me-DalPhos

759198
New

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(1) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4071. (2) Lundgren, R. J.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8686. (3) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (4) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem.—Eur. J.* **2010**, *16*, 1983. (5) Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, *132*, 18026.

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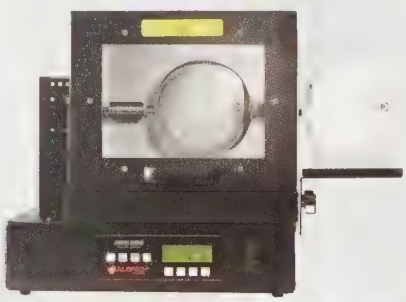

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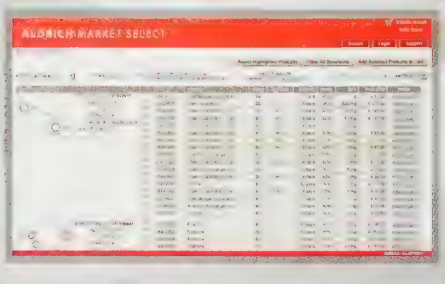

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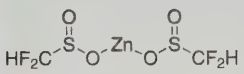

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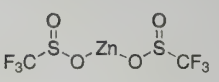

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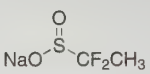

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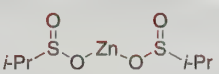

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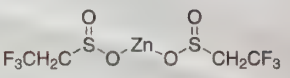

TFES
L511234

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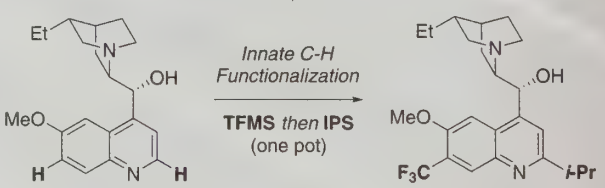

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Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.

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Scott Batcheller
R&D and Marketing Manager
Chemical Synthesis

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ABOUT OUR COVER

Farmhouse in Provence
National Gallery of Art, Washington

As a young man, van Gogh worked in various jobs in Holland, England, France, and Belgium. Only at age 27, in 1880, did he start his formal art training in Brussels, and continued his training in Holland, where he discovered the work of Rubens, before moving permanently to France in 1886. In Paris, van Gogh studied with Cormon; became acquainted with Pissarro, Monet, and Bernard; and befriended Gauguin. Between 1880 and 1890, van Gogh created close to 900 paintings, before his career was cut short by his suicide at the age of 37. He lived a difficult life: unhappy romances, lack of commercial success, relying on family for financial support, and severe mental illness most of his adult life. It is ironic that an individual who would influence the art world so greatly after his death thought of his life as a terrible waste and of himself as an utter failure.

Van Gogh's early "Dutch period" painting style, with somber tones and dark colors dominating, reflected the artistic influences he came under while in Holland and his strong interest in drawing and painting figures. However, he quickly abandoned the dark colors in favor of brighter, more vibrant colors and bold brushstrokes after moving to Paris and getting introduced to the impressionist and post-impressionist styles. ***Farmhouse in Provence*** (oil on canvas, 46.1 × 60.9 cm), which was completed in June 1888 after van Gogh relocated to the South of France, is a good example of this later style and of his belief that color ought to be the primary medium of expression in a painting. His love of the various shades of yellow* and his strive for realism are evident in the rich golden tones that dominate this painting. Also evident are his quick and thick brushstrokes and the swirling cloud lines that foreshadow the more dramatic swirling-cloud pattern in his masterpiece of about a year later, *The Starry Night*. His use of juxtaposed complementary colors mirrors the technique used by impressionists to enhance the vividness of their works.

This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

What could be behind van Gogh's affinity for the color yellow? To find out, visit **Aldrich.com/acta461**

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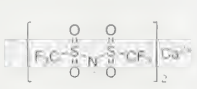
(1) Begouin, J.-M.; Capitta, F.; Wu, X.; Niggemann, M. *Org. Lett.* **2013**, *15*, 1370. (2) Niggemann, M.; Meel, M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3684. (3) Niggemann, M.; Bisek, N. *Chem.—Eur. J.* **2010**, *16*, 11246 (4) Haven, T.; Kubik, G.; Haubenreisser, S.; Niggemann, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 401.



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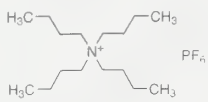

Bu_4NPF_6
281026

753122	Calcium(II) bis(trifluoromethanesulfonimide), 95%	1 g
281026	Tetrabutylammonium hexafluorophosphate, 98%	5 g 25 g 100 g

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Josef Zihlmann
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Detail from ***Breezing Up (A Fair Wind)***
National Gallery of Art, Washington

Winslow Homer completed ***Breezing Up (A Fair Wind)*** (oil on canvas, 61.5 x 97 cm) in 1876, the U.S. centennial year. One of the most celebrated American artists of the nineteenth and early part of the twentieth centuries, Homer had little formal training as a painter, and seems to have developed his plein-air [illegible] who excelled in several media and travelled widely, depicting a variety of themes, from battlegrounds of the Civil [illegible] le scenes of recreation.

An iconic American painting and one of Homer's most celebrated works, ***A Fair Wind*** received wide acclaim when it was first exhibited in 1876, and was chosen by the U.S. Postal Service in 1962 for a commemorative postage stamp honoring the artist. This [illegible]ape touches upon a favorite theme of his, the struggles of man against powerful natural forces. Here the light sail boat is returning home with the day's catch and [illegible] seemingly relaxed crew, unbothered or perhaps accustomed to the choppy waters. Unlike [illegible]ome of his later seascapes, this has a warm feel and more optimistic message,* perhaps meant to make a statement about the future of the young country following the uncertain and dangerous years of the Civil War.

This painting is a gift of the W. L. and May T. Mellon Foundation to the National Gallery of Art, Washington, DC.

* *Homer included a traditional symbol of hope in this painting. Can you guess what it is? To find out, visit Aldrich.com/acta462*

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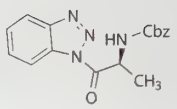

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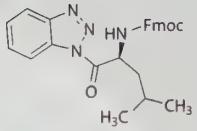

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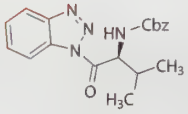

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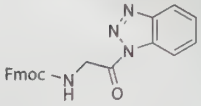

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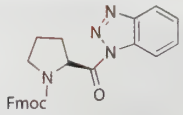

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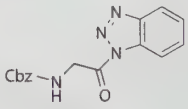

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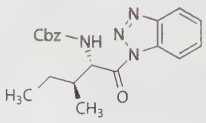

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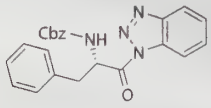

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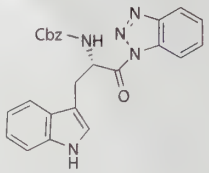

737704
Z-Trp-Bt

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King Abdulaziz University
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Keywords. benzotriazole; peptide synthesis; peptidomimetics; conjugates; methodology; coupling reagent.

Abstract. *N*-(Protected α-aminoacyl)benzotriazoles are efficient acylating reagents that offer many advantages in the preparation of peptides and their mimetics and conjugates. Advances in methodology, made possible by these novel reagents, have given rise to solution- and solid-phase preparative techniques for generating complex peptides and peptide conjugates, which are useful in the construction of diverse libraries of building blocks for medicinal chemistry.

Outline

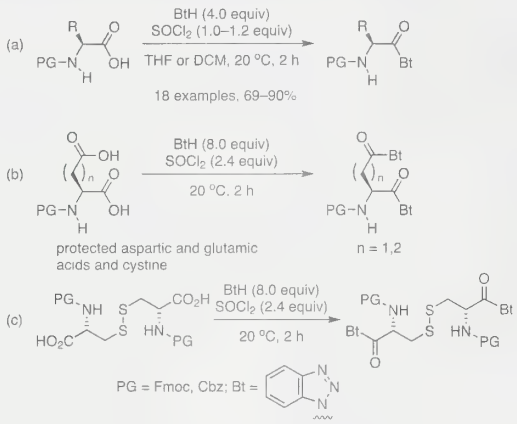
1. Introduction

Azolides are compounds in which an azole residue is attached to an acyl group. It has long been known that the azole nucleus in azolides can behave as a leaving group, and this property was explored widely by Staab as early as 1960.[1,2] Katritzky and co-workers have reported that, of the azoles, benzotriazole is a particularly versatile synthetic auxiliary with attractive properties, easily inserted into or removed from molecules and endowing them with a range of useful reactivities.[3] Much of this work has been summarized[4] and, from 1985 to 2012,

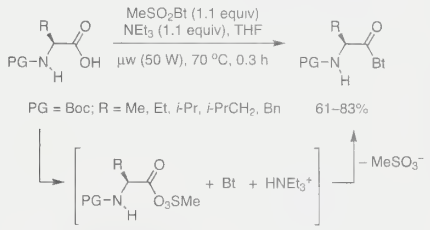
some 1,000 publications have appeared dealing with benzotriazole. We have since found that benzotriazolides (*N*-acylbenzotriazoles) have many advantageous properties relative to acid chlorides. More recently, the utility of benzotriazolides in peptide chemistry has achieved prominence, and reports of numerous applications have appeared as highlighted in this review.

2. Synthesis of Aminoacylbenzotriazoles

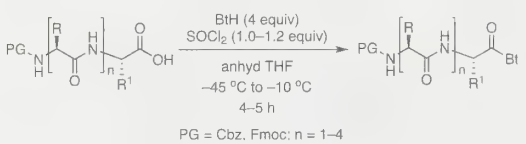
Acylbenzotriazoles are versatile reagents in which the benzotriazol-1-yl (Bt) group serves as a surrogate for halogen and is easily displaced by nitrogen, sulfur, oxygen, or carbon nucleophiles.[4] Acylbenzotriazoles, however, offer numerous advantages over their halogen analogues since they are isolated in high yields, in crystalline form, are usually stable in air (and even to water for short periods at 20 °C), and are more reactive than the corresponding *N*-acylimidazoles. Thus, they can effect peptide coupling in H_2O–THF or H_2O–MeCN by using unprotected amino acids with the distinct advantage that, if the temperature is controlled, chirality within the component amino acids is preserved. Although synthesis of aminoacylbenzotriazoles requires protection of the α-amino function with either Boc, Fmoc, or Cbz (or by protonation); other common functional groups, especially OH but also SH, $CONH_2$, and CO_2H can be left unprotected.



Scheme 1. Preparation of Fmoc- or Cbz-Protected α-Aminoacylbenzotriazoles. *(Ref. 5,9)*



Scheme 2. Preparation of Boc-Protected α-Aminoacylbenzotriazoles from Acid-Sensitive or Boc-Protected Amino Acids. *(Ref. 6,7)*



eq 1 *(Ref. 11)*

2.1. From Fmoc- or Cbz-Protected Amino Groups

The first general method for the preparation of aminoacylbenzotriazoles involves the condensation of a protected amino acid with benzotriazole and thionyl chloride (1.0–1.2 equiv) in THF or DCM (**Scheme 1**, Part (a)).[5–9] Excess benzotriazole is required to neutralize the two equivalents of HCl formed, and the method is not applicable to benzotriazolides containing the acid-sensitive Boc group. A wide range of amino acids may be used affording high yields. In addition, di-Bt derivatives are generated when aspartic acid, glutamic acid, or the S–S dimer of cysteine comprise the starting amino acids (Scheme 1, Parts (b) and (c)). The method is extremely versatile, and excess benzotriazole is easily removed by washing with either acid or base. Most significantly, chirality within the starting amino acids is retained in the majority of cases and the protected aminoacylbenzotriazoles may be stored at room temperature for many weeks.

2.2. From Boc-Protected Amino Groups

In cases where the amino acid is Boc-protected or sensitive to thionyl chloride, the sodium or trialkylammonium salt of the amino acid may be converted into the benzotriazolide by treatment with 1-(methanesulfonyl)benzotriazole (BtO_2SMe or BtMs) (**Scheme 2**).[6,7] This clean, preparative method is enhanced in some cases by crystallization of the triazolide from water with concurrent removal of the water-soluble methanesulfonate byproduct.

The thionyl chloride method can often be employed to prepare N-protected α-aminoacylbenzotriazoles (61–99%) without protection of potentially reactive side chains such as aliphatic OH (Ser, Thr), aromatic OH (Tyr), thiol SH (Cys), indole NH (Trp), and amide NH (Asn or Gln).[7–9] There are, however, amino acids (e.g., His, Glu, Lys, and Asp) with side chains that do require protection (e.g., with Ts, Bn, or Cbz groups) in order to generate good yields of the benzotriazolides by reaction with either BtH–$SOCl_2$ or BtMs.[10]

3. Synthesis of Oligopeptidoyl Benzotriazolides

All of the methods employed to prepare Fmoc-, Cbz-, and Boc-protected aminoacylbenzotriazoles may also be used to prepare N-protected benzotriazolides of dipeptides. Likewise, N-protected tri- through hexapeptides may be converted into the corresponding benzotriazolides (**eq 1**).[11] Each benzotriazolide may then couple with amino acids or peptides to form N-protected tetra- through heptapeptides (vide infra).

4. Application to the Synthesis of Peptides

4.1. Natural Peptides and Isopeptides

A wide range of amino acids including many of those with additional, unprotected functional groups (Ser, Tyr, Cys, Trp, Pro, Asp, Glu, Lys, and Arg) couple with N-protected aminoacylbenzotriazoles in aqueous acetonitrile (MeCN–H_2O, 7:3) at 20 °C to produce dipeptides in 47–98% yields (**eq 2**).[9,12–17] Enantiopure dipeptides (LL and LD)

are obtained in high purity (>99% in most cases) without the use of chromatography, thus highlighting the significant utility of the method. However, protection of a carboxylic acid function as its benzyl ester is advantageous in some instances.

The synthesis of tripeptides is achieved by either a fragment-coupling procedure[9,12,16] or by stepwise coupling.[12,15] In the former, N-protected dipeptides are converted into their benzotriazole derivatives at –10 °C (in order to avoid racemization), which are then coupled with amino acids to form tripeptides (**Scheme 3**).[15,18,19] Tri- and tetrapeptides are similarly prepared in good yields (74–94%) by a stepwise procedure, but usually at a lower temperature (–10 °C) again to prevent racemization.[9]

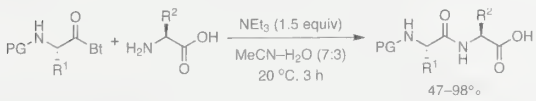
The first examples of penta-, hexa-, and heptapeptides prepared by the Bt technology were generated using microwave-assisted, solid-phase peptide synthesis (SPPS). In this technique, *N*-Fmoc-α-aminoacyl benzotriazolides were employed to attach Fmoc-protected α-aminoacyl groups to a Rink resin, which was then utilized for the synthesis of di- to heptapeptides in 20–68% yields.[18,20,21] In contrast, and although useful, SPPS and enzymatic techniques often afford low yields,[22,23] and are unsuitable for larger-scale preparations.

Recently, N-protected α-tri-, tetra-, and pentapeptidoylbenzotriazoles were coupled with free amino acids, dipeptides, and tripeptides in aqueous acetonitrile at 0 °C to afford N-terminal-protected polypeptides in isolated yields of 61–92%.[11] This reaction has been applied to amino acids (or small peptides) containing free OH, SH, or indole NH groups, and proceeds with no detectable racemization (**eq 3**);[11] it applies equally well to the synthesis of isopeptides.[24]

4.2. Difficult to Prepare Peptide Sequences

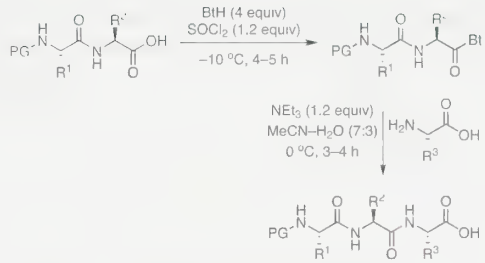
Peptaibols, a group of antibiotics isolated from soil fungi, contain hindered amino acids such as 2-methylalanine (Aib), 2-ethylalanine, and 2,2-diethylglycine and, hence, α-substituted and α,α-disubstituted amino acids are important in peptide and medicinal chemistry.[25] Likewise, N-substituted peptides are important since they are constituents of cyclosporins[26] and exhibit antibiotic,[27] anticancer,[28] and antiviral[29] activities. Benzotriazole technology has proved valuable in the synthesis of hindered dipeptides from either N-protected Aib benzotriazolides and amino acids (**Scheme 4**, Part (a)) or C-terminus Aib dipeptides from N-protected aminoacylbenzotriazoles (Scheme 4, Part (b)) in isolated yields of 67–92%.[17]

It is well known that certain peptide sequences, particularly those containing valine (e.g., H-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-NH_2), are difficult to prepare, and the classical approaches are often characterized by low yields, aggregation, and β-sheet formation leading to racemization. The stepwise SPPS synthesis of difficult peptides utilizing N-protected aminoacylbenzotriazoles and microwave acceleration has been shown to facilitate amide-bond formation (22–37% yields, 89 to >99% purities) and to reduce aggregation.[21]



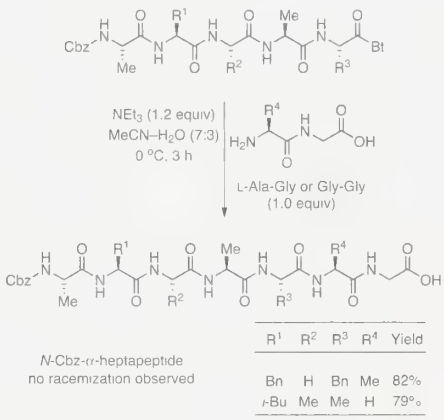
PG = Boc, Cbz, Fmoc
R^1 = Me, *i*-Pr, Bn, $MeS(CH_2)_2$, $H_2N(O)C(CH_2)_2$, (indol-3-yl)CH_2
R^2 = Me, *i*-Pr, Bn, $HOCH_2$, $HSCH_2$, $MeS(CH_2)_2$, $H_2N(O)C(CH_2)_2$, (indol-3-yl)CH_2

eq 2 *(Ref. 9,12)*



PG = Cbz, Fmoc; R^1 = Me, Bn, $MeS(CH_2)_2$, (indol-3-yl)CH_2
R^2 = Me, Bn, $MeS(CH_2)_2$, $H_2N(O)C(CH_2)_2$, (indol-3-yl)CH_2
R^3 = Me, *s*-Bu, Bn, $HOCH_2$, $HSCH_2$, $MeS(CH_2)_2$, (indol-3-yl)CH_2

Scheme 3. Preparation of Tripeptides by Fragment Coupling. *(Ref. 15,18,19)*

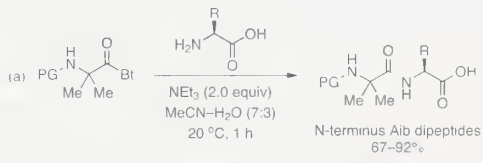


N-Cbz-α-heptapeptide
no racemization observed

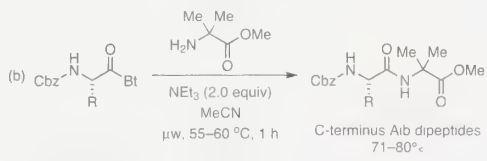
R^1	R^2	R^3	R^4	Yield
Bn	H	Bn	Me	82%
i-Bu	Me	Me	H	79%

Example of the synthesis of N-terminal-protected polypeptides

eq 3 *(Ref. 11)*



PG = Cbz, Fmoc; AA = L-Phe-OH, L-Trp-OH, L-Met-OH

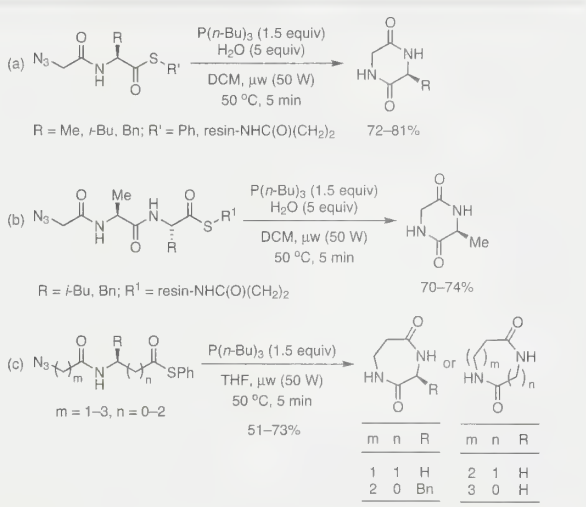


L-Phe-Bt, L-Trp-Bt, L-Met-Bt, Gly-Bt

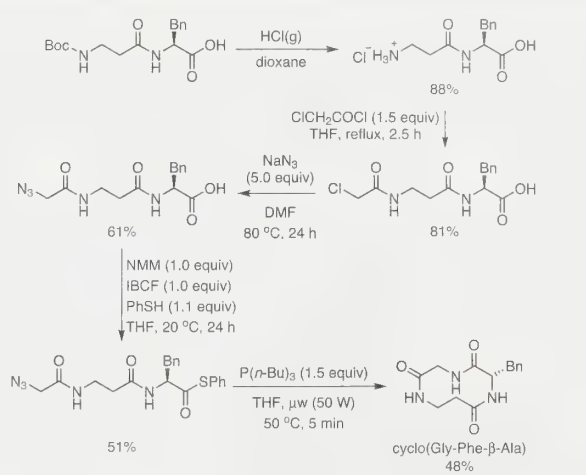
Scheme 4. Peptide Sequences with Sterically Hindered Amino Acid Residues from *N*-(Cbz-α-aminoacyl)benzotriazoles

4.3. Cyclic Dipeptides (2,5-Diketopiperazines) and Tripeptides

Solution- and solid-phase (**Scheme 5**, Part (a)) Staudinger-type cyclizations afford efficient routes to hetero-2,5-diketopiperazines from protected azido dipeptide thioesters under microwave irradiation.[30] However, attempts to synthesize cyclic *tripeptides* by this method resulted in the unprecedented cleavage of an amide group rather than a thioester to form 2,5-diketopiperazines again (Scheme 5, Part (b)),[30] an observation that highlights the stability of a six-membered ring over its nine-membered analogue. Seven- and eight-membered-ring cyclic dipeptides can, however, be prepared in moderate-to-good yields by a Staudinger-type ring closure of a series of azido dipeptide thioesters (Scheme 5, Part (c)).[31] The work was extended to the solution-phase synthesis of a ten-membered-ring cyclic tripeptide in 48% yield (**Scheme 6**).[31]



Scheme 5. Attempted Syntheses of Cyclic Tripeptides, Leading Instead to Cyclic Dipeptides (2,5-Diketopiperazines). *(Ref. 30,31)*



Scheme 6. Solution-Phase Synthesis of a Ten-Membered-Ring Cyclic Tripeptide. *(Ref. 31)*

5. Synthesis of Peptidomimetics

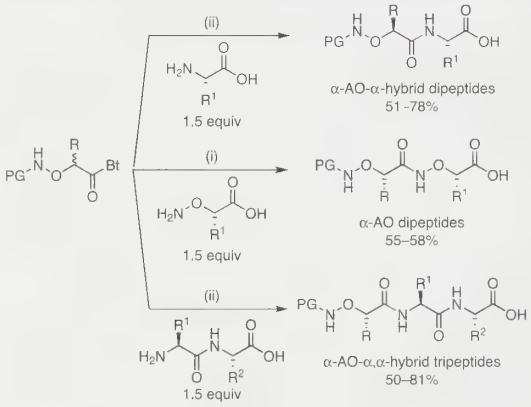
Peptidomimetics are small, protein-like molecules designed to mimic natural peptides by replacement of an amide bond or other element of the natural peptide. Clinical applications of bioactive natural peptides, for instance as hormones or enzyme inhibitors, have been limited by their susceptibility to rapid hydrolysis by peptidases. The corresponding peptidomimetics are not subject to this limitation, and, consequently, have been designed to exhibit high affinity for specific receptors, good metabolic stability toward endogenous proteases, greater oral bioavailability, and longer duration of action. To meet the need for good synthetic approaches to these peptidomimetics, flexible, high-yield, enantiospecific benzotriazole-mediated synthetic routes to six different structural types of peptidomimetics have been developed. These syntheses employ microwave-assisted benzotriazole acylation as the key step.[32–34]

5.1. Aminoxypeptides

α-Aminoxy acids [$RCH(ONH_2)CO_2H$] are peptidomimetics that resist enzymatic degradation. Peptidomimetics as a class are of interest as bioisosteric α-amino acids and as analogues of β-amino acids.[35–38] They have been used to prepare aminoxypeptides, α-aminoxy-α-hybrid dipeptides, and α-aminoxy-α,α-hybrid tripeptides from unprotected amino acids. This methodology has been extended to other aminoxy-hybrid dipeptides and tripeptides starting from protected aminoxyacyl benzotriazolides (**Scheme 7**).[38]

5.2. Depsipeptides

Depsipeptides contain both amino acid and hydroxy acid units with amide and/or ester bonds. Natural depsipeptides exhibit antifungal, antimicrobial, and anti-inflammatory activities, and certain depsipeptides have been used in cancer treatment.[39] A comparative study of standard coupling agents used to produce depsipeptides revealed variable yields and often long coupling times.[40] *N*-Cbz(depsidipeptidoyl)benzotriazoles were found to be useful for coupling with amino acids (N-acylation)



Scheme 7. Preparation of Aminoxy and Other Peptides from α-Aminoxy Benzotriazolides. *(Ref. 38)*

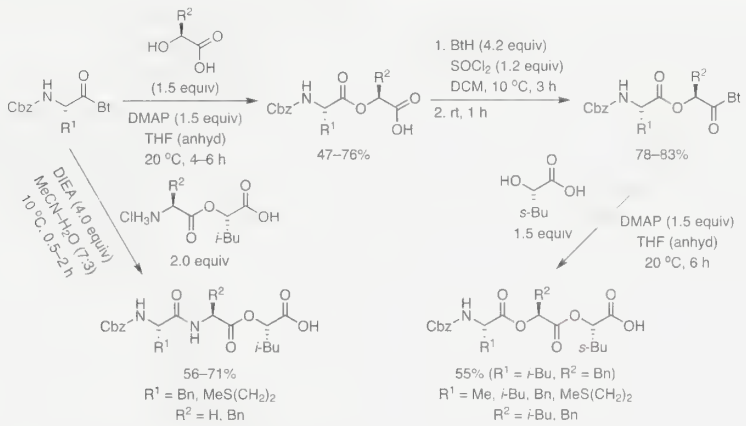
and α-hydroxy acids (O-acylation) to give depsidi- and depsitripeptides in good yields under mild conditions (**Scheme 8**).[41] This approach was applied to the preparation of unprotected depsidipeptides, which were converted into unprotected depsitripeptides.

5.3. Azapeptides

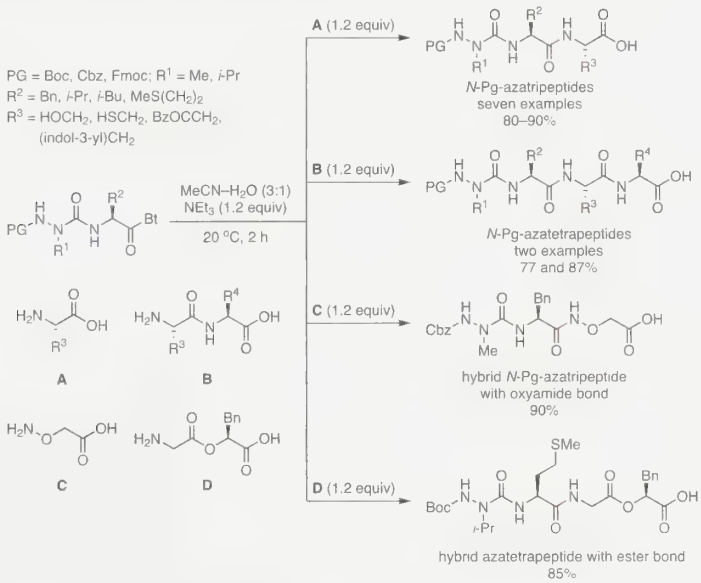
Azapeptides are peptidomimetics in which the α-CH group of one or more amino acid residues is replaced by a nitrogen atom. They are of interest for the generation of receptor ligands, enzyme inhibitors, and clinically approved drugs,[42] and those with electrophilic moieties act as inhibitors of cysteine proteases.[43,44] *N*-(*N*-Pg-α-Azadipeptidoyl)-benzotriazoles have been prepared from amino acid esters in four steps and 48–77% overall yields and utilized for the synthesis of *N*-Pg-azatripeptides, *N*-Pg-azatetrapeptides, and hybrid azapeptides (**Scheme 9**).[45] This methodology proved valuable for the insertion of an aza-amino acid unit into an azatripeptide chain for the synthesis of the previously unknown aza-analogues of the endogenous opioid peptide neurotransmitter Leu-enkephalin, found in animals and humans.[45]

5.4. Hydrazinopeptides

The replacement of an α-amino acid unit by a β-amino acid unit is a well-known strategy in the search for pharmacologically active peptides,[46]



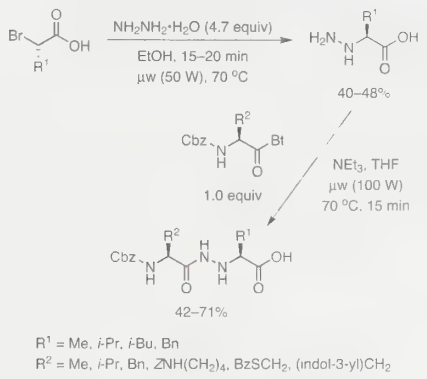
Scheme 8. Depsitripeptides from Cbz(depsidipeptidoyl)benzotriazoles. *(Ref. 41)*



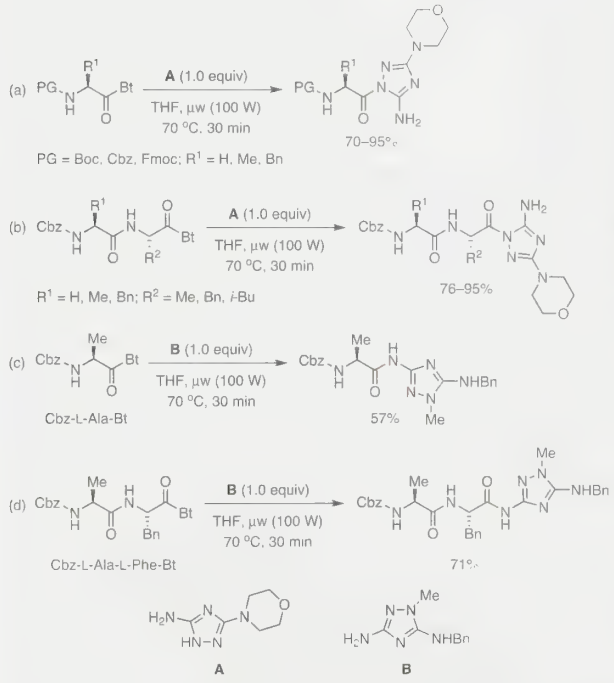
Scheme 9. Preparation of Azapeptides from *N*-(*N*-Pg-α-Azadipeptidoyl)benzotriazoles. *(Ref. 45)*

and replacement of the C^{α} and/or the C^{β} atom in such β-amino acid building blocks by a hetero atom offers an attractive extension of the β-peptide concept.[47]

An alternate pathway to chirally pure α-hydrazino acids[48] is based on microwave irradiation during the conversion of α-bromo acids into α-hydrazino acids by hydrazine hydrate. The corresponding benzotriazolides afford hydrazine hybrid peptides (**Scheme 10**).[49]



Scheme 10. Preparation of Hydrazinodipeptides. *(Ref. 49)*



Scheme 11. Microwave-Assisted Acylation of (a) 3,5-Diamino-1,2,4-triazole and (b) the Exocyclic Amino Group of 3,5-Diamino-1,2,4-triazole. *(Ref. 52)*

5.5. Heterocyclic Peptidomimetics

1,2,4-Triazoles have been employed for the bioisosteric replacement of the amide bond,[50] since 1,2,4-triazoles exhibit a wide range of antifungal and antibacterial activities.[51] 3,5-Diamino-1,2,4-triazole has been coupled to di- and tripeptides at either ring or exocyclic nitrogens, using the benzotriazole methodology, to give potential building blocks for the preparation of peptidomimetics (**Scheme 11**).[52]

5.6. Cyclic Peptidomimetics

In 2009, the benzotriazole methodology was extended to achieve cysteine S-acylation under mild conditions.[53] This has now been employed to couple an *N*-acylbis(benzotriazole) with cysteine to give a bis(*S*-acylcysteine), which, upon treatment with another equivalent of *N*-acylbis(benzotriazole), affords cyclic peptide mimetics in 64–72% yields (**Scheme 12**).[54]

6. Synthesis of Tagged Peptides and Peptidomimetics

6.1. Fluorescent Labels

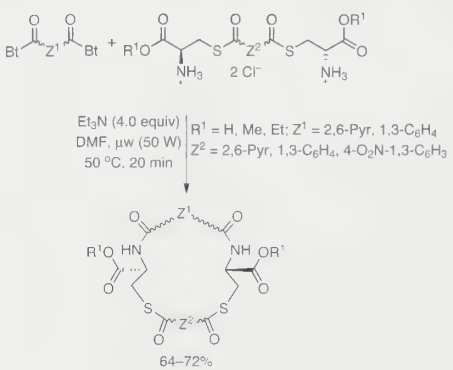
Fluorescent labeling of biological systems is of great importance. There is also increasing interest in establishing methods for the incorporation of non-natural amino acids into proteins without suppression of binding ability.[55]

6.1.1. Coumarin-Labeled Peptides and Peptidomimetics

Coumarins are constituents of many commercially important fluorescent dyes since they offer high-emission quantum yields, photostability, and good solubility in most solvents. Synthetic methods for the incorporation of coumarin into amino acids and peptides are now available. (Coumarin-3-ylcarbonyl)benzotriazoles react readily with a variety of aminoxy acids in aqueous acetonitrile at room temperature to form coumarin-labeled aminoxy acids.[56] Coumarin-labeled amino acids have been prepared in a similar way[57] and coumarin-labeled aminoxy hybrid peptides have been obtained in two steps from the respective benzotriazoles (**Scheme 13**).[56] The 7-methoxycoumarin derivatives have quantum yields of 0.35–0.71 and may therefore be useful in peptide assays.

6.1.2. 6-Chloro-2,3-naphthalimides and Water-Soluble Fluorescent Tags

Organic fluorophores that contain a naphthalene nucleus are of interest since, on binding with a substrate, they often exhibit significant changes



Scheme 12. Preparation of Cyclic Peptidomimetics. *(Ref. 54b)*

in their fluorescence spectra, quantum yields, and lifetimes in different solvents. The benzotriazole methodology offers access to new 6-chloro-2,3-naphthalimide derivatives (**Scheme 14**).[58]

6.2. Azo-Dye-Labeled Peptides

Azo-arene carboxylic acids are widely used as molecular switches in life sciences.[59–61] The coupling of an azo-dye carboxylic acid to a biological moiety has, in many cases, required harsh conditions and given poor yields.[62,63] In contrast, *N*-(4-arylazobenzoyl)benzotriazole and glycine in DMF–water at 20 °C give the coupled product in 99% yield. Similarly, other amino acids undergo this facile coupling (**Scheme 15**).[64]

7. Peptide Conjugates

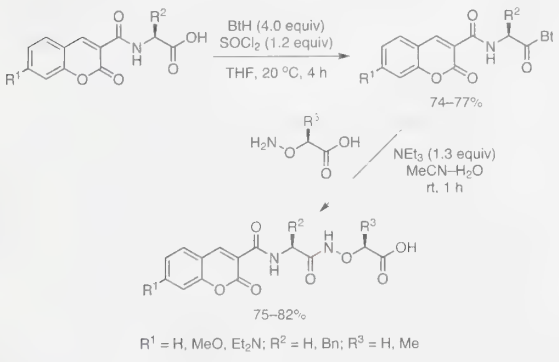
Conjugates comprise peptides attached to another molecular skeleton, usually through either the carboxyl group (C-terminus) or the amino group (N-terminus) of an amino acid.

7.1. Conjugates of Sugars

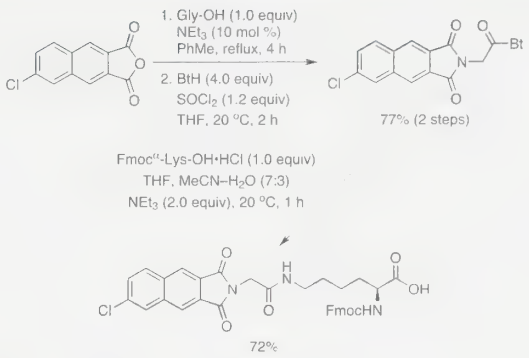
Numerous naturally occurring carbohydrate conjugates link a sugar glycosidically to an α-amino acid unit of a peptide or protein. Considerable effort has been devoted to the synthesis of N- and O-linked glycopeptide conjugates utilizing both solution- and solid-phase methodologies.[65–69] The benzotriazole methodology is advantageous for the solution-phase synthesis of chirally pure *O*-(α-aminoacyl)-[70] and *N*-(α-aminoacyl)sugar conjugates.[71] A typical procedure utilizes DMAP catalysis and microwave irradiation to give 82–92% yields of O- or N-coupled products (**Scheme 16**, Part (a)).[71] The same benzotriazole-based method also provides a convenient and efficient route to Cbz-protected tri- and tetrapeptide conjugates with sugars (Scheme 16, Part (b)).[72]

7.2. Conjugates of Heterocycles

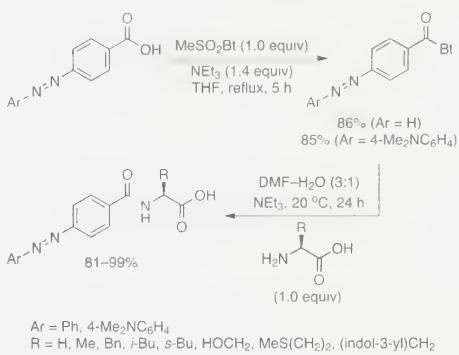
(α-Aminoacyl)amino-substituted heterocycles are of considerable importance as synthetic intermediates (e.g., for endomorphin-2 (EM-2) analogues),[73] and because of their diverse biological activity (e.g., as inhibitors of bacterial RND efflux pump[74–76] and of tumor necrosis factor-α converting enzyme (TACE) GW 3333[77]). Until recently, only a few reports had described the preparation of α-aminoacyl conjugates



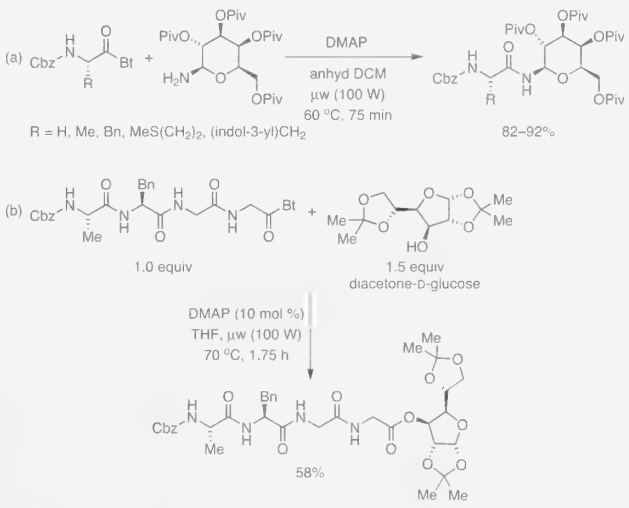
Scheme 13. Preparation of Coumarin-Labeled Aminoxy Hybrid Peptides *(Ref. 56)*



Scheme 14. Preparation of 6-Chloro-2,3-naphthalimide and Water-Soluble Fluorescent Tags. *(Ref. 58)*



Scheme 15. Preparation of Azo-Dye-Labeled Amino Acids. *(Ref. 64)*



Scheme 16. Examples of (a) (α-Aminoacyl)sugar Conjugate and (b) Tetrapeptide Sugar Conjugate Synthesis. *(Ref. 71–73)*

of heterocycles by C- or N-acylation of heterocycles with amino acids. Kraus and co-workers[78] reported that "N-acylation of weakly nucleophilic heterocyclic amines by protected amino acid is not a straightforward reaction which could be achieved under any standard coupling conditions".

N-Aminoacyl benzotriazolides now enable the synthesis of chirally pure α-aminoacyl conjugates of heterocycles even from weakly nucleophilic heterocyclic amines by N-acylation in DMF under microwave irradiation.[79] The analogous C-acylation of lithiated methylpyridine or methylquinolone in THF at –20 °C for 1–3 h with *N*-aminoacyl benzotriazolides gave the corresponding α-aminoacyl C-linked conjugates (**Scheme 17**).[80] The convenient and efficient formation of Cbz-protected tri- (e.g., Z-L-Val-L-Phe-Gly-NH-(2-Pyr)) and tetrapeptide (e.g., Z-L-Phe-Gly-L-Leu-Gly-NH-(*N*-methylpiperazine)) conjugates with heterocyclic nuclei of biological importance succeeds under a variety of reaction conditions.[72,80]

7.3. Conjugates of Vitamins

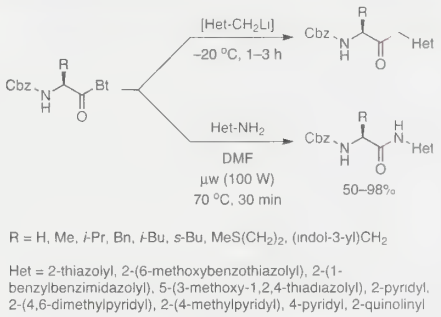
Recent approaches to enhance vitamin uptake include covalently bonding the vitamins to peptides. Water-soluble vitamins are usually transported into cells by potocytosis.[81] Zhang and McCormick[82] have proposed the delivery of vitamin B6 by receptor-mediated transport in eukaryotic cells with the amine of a peptide–vitamin conjugate, which facilitates the cell uptake of peptide and transport into the cytosol.[82,83] The benzotriazole methodology enables the efficient coupling of amino acids and peptides to vitamins, again utilizing microwave irradiation to shorten reaction times and minimize epimerization.[84]

Niacin and biotin benzotriazolides couple with free amino acids, dipeptides, and tripeptides (NEt_3, $MeCN–H_2O$, μw, 70 °C) to give the corresponding bioconjugates **1** and **2** in yields of 43–81% and 35–82%, respectively (**Figure 1**).[84] Amino acid and peptide conjugates of vitamin D3 (Figure 1, **3**) are obtained by O-acylation of cholecalciferol with Cbz-protected acylbenzotriazoles in the presence of DMAP in THF and under microwave irradiation (50 W, 70 °C) for 1–2 h.[84] Amino acid and peptide conjugates of α-tocopherol (Figure 1, **4**) are formed by O-acylation of α-tocopherol with Cbz-protected acylbenzotriazoles under microwave irradiation (20 W, 50 °C, 0.3 h) in anhydrous DMF in the presence of potassium carbonate.[84]

7.4. Conjugates of Pharmaceuticals

Improving the efficacy of therapeutics, particularly through enhanced local delivery to a diseased cell, is an important topic in pharmaceutical R&D. These techniques are helping to solve traditional drug delivery challenges, such as poor cellular uptake and/or non-specific toxicity.

The utilization of prodrugs that temporarily mask the acidic groups of NSAIDs may increase uptake and reduce irritation caused by direct contact.[85,86] Indomethacin, diclofenac,[87] ibuprofen, and naproxen,[87–91] are among well-known NSAIDs that have been modified by linking to natural amino acids, as reported by numerous investigators. We have recently shown that ibuprofen and naproxen bioconjugates are readily



Scheme 17. α-Aminoacyl Conjugates of Amino-Substituted Heterocycles *(Ref. 79,80)*

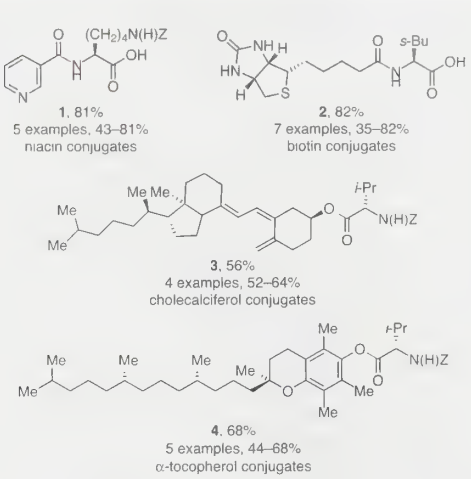
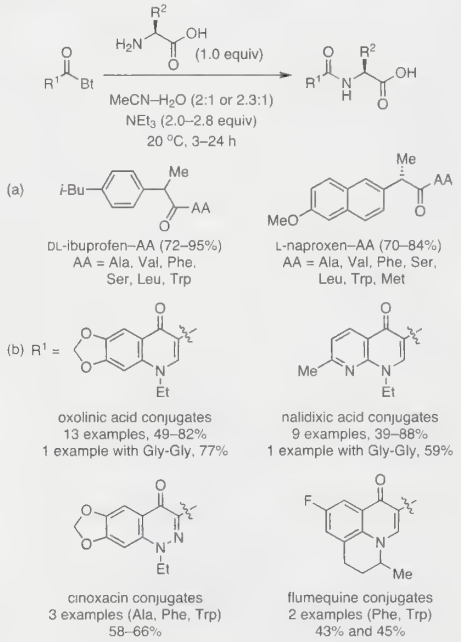


Figure 1. Peptide Conjugates of Vitamins Prepared by the Benzotriazole Methodology. *(Ref. 84)*



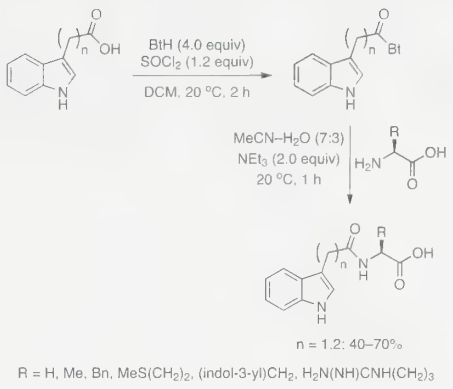
Scheme 18. Preparation of Peptide Conjugates of Pharmaceuticals. *(Ref. 92,100)*

prepared by reacting NSAID benzotriazolides with amino acids and dipeptides in aqueous acetonitrile–triethylamine at 20 °C (**Scheme 18**, Part (a)).[92]

Prodrugs formed by linking quinolone acids with amino acid esters are more lipophilic than the parent drugs,[93,94] and show enhanced in vivo antibacterial properties[95,96] with pronounced therapeutic effects against *Pseudomonas aeruginosa*,[97] *Escherichia coli*,[98] *Staphylococcus aureus*,[98] and *Salmonella typhi*.[96] Additional wide-ranging biological activities include anti-allergic,[99] antihypertensive,[99] bronchodilation,[99] and binding to bovine serum albumin.[92] Amino acid conjugates of quinolone antibiotics were prepared in 39–88% yields by coupling free amino acids with benzotriazole-activated oxolinic acid, nalidixic acid, cinoxacin, or flumequine (Scheme 18, Part (b)).[100,101]

7.5. Conjugates of Plant Hormones

Indole-3-acetic acid (IAA), an indispensable plant hormone (auxin), also occurs naturally as "conjugates" linked to amino acids.[102] Gene expression and cell division, elongation, and differentiation in plant tissue are all regulated by these indole-3-acetic acid auxins. Another endogenous plant hormone, indole-3-propionic acid (IPA), and its amino acid conjugates interact with serum albumin.[103] Plant hormone benzotriazolides—prepared in 86–90% yields by standard treatment of indole-3-acetic acid and indole-3-propionic acid—coupled with diverse amino acids to give conjugates in 40–70% yields (**Scheme 19**).[104]



Scheme 19. Preparation of Conjugates of Plant Hormones. *(Ref. 104)*

7.6. Aminoxy Acid Conjugates of Peptidomimetics and Hydrazino Acid Conjugates

The benzotriazole methodology enables convenient and efficient synthesis of novel aminoxy acid containing conjugates even at hindered nucleophilic centers in steroids, terpenes, sugars, and nucleosides.[105] The benzotriazolides of α-hydrazino acids were used to generate hydrazine acid conjugates through N-, O-, S-, and C-acylations in good yields (49–88%).[49]

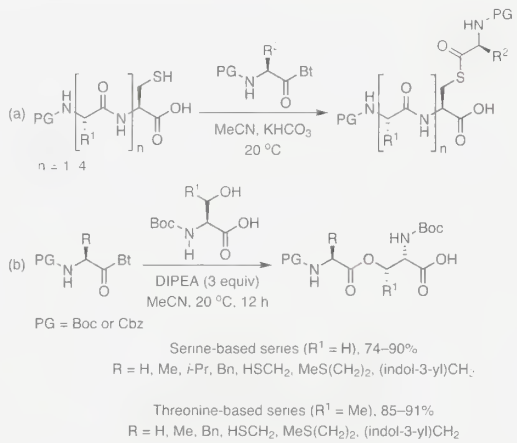
8. Differential N-, O-, and S-Acylations

Isopeptides are used for the detection and capture of ubiquitinating and de-ubiquitinating enzymes using activity-based protein profiling (ABPP).[106] The presence of an additional amino group in *N*-, *O*-, or *S*-acyl isopeptides generally increases their hydrophilicity, which is advantageous in effecting their purification by HPLC. The native peptides can then be generated from the corresponding *N*-, *O*-, or *S*-acyl isopeptides via an N to N,[107] O to N,[108] or S to N[6,109,110] intramolecular acyl migration reaction. These findings have led to the synthesis of peptides containing difficult sequences.[111]

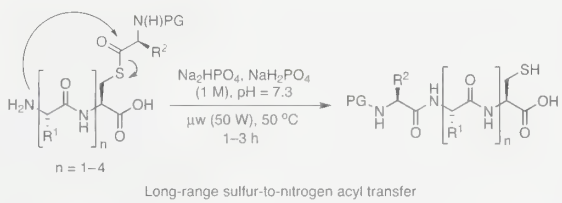
8.1. S- and O-Acyl Isopeptides

S-Acyl isopeptides are usually less likely to aggregate in solution and therefore are easier to synthesize and purify relative to the corresponding native peptides. S-Acylation of protected cysteine-containing peptides was carried out in the presence of $KHCO_3$ at 20 °C in acetonitrile (**Schemes 20**, Part (a)).[6,109,110] Selective S-acylation of cysteine was also carried out in acetonitrile–water mixture in the absence of base.

O-Acylation of protected serine and protected threonine with various *N*-Pg-(α-aminoacyl)benzotriazoles in the presence of diisopropylethylamine in acetonitrile at 20 °C for 12 h gave *O*-acylisoserine and *O*-acylisothreonine dipeptides without racemization (Scheme 20, Part (b)). *O*-Acylisotyrosine tripeptides were also prepared in yields of 74–91% by reacting tyrosine-containing protected dipeptides with *N*-Pg-(α-aminoacyl)benzotriazole in the presence of DBU in acetonitrile at 20 °C for 12 h.[24]



Scheme 20. Synthesis of *S*- and *O*-acyl Isopeptides. *(Ref. 6,9,24,110)*



eq 4 *(Ref. 6,109,110)*

8.2. Ligation at a Distance

8.2.1. S to N Acyl Migration

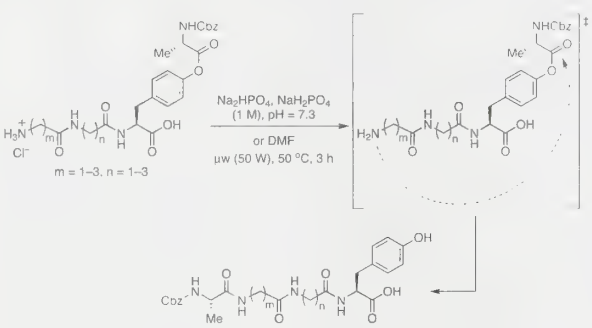
The S to N acyl migration through various cyclic transition states was investigated by carrying out the ligation experiment on mono-isopeptides under microwave irradiation (50 W) at 50 °C for 1–3 h using 1 M NaH_2PO_4–Na_2HPO_4 phosphate buffer to maintain pH 7.3 (**eq 4**). The rates and yields of long-range S to N acyl transfers were found to depend significantly on the size of the macrocyclic transition state (TS), with the rates qualitatively following the TS ring-size trend 5 > 10 ~ 11 > 14, 16, 17 > 12 > 13, 15, 19 > 18 >>> 9 > 8.[6,109,110]

8.2.2. O to N Acyl Migration

The chemical ligation of serine isopeptide through O to N acyl transfer via 8- and 11-membered-ring transition states occurs without the use of an auxiliary group (**eq 5**).[108] In contrast, threonine isopeptide failed to undergo acyl migration even under more basic conditions and longer reaction times.[112] Chemical ligation studies of tyrosine isopeptides (μw, 50 W, 50 °C, 3 h, using 1 M phosphate buffer and DMF -piperidine) via 12- to 19-membered-ring cyclic transition states showed that intramolecular O to N acyl transfer occurs with 12- to 14-membered-ring TS's under basic conditions and with 15- to 19-membered-ring TS's in aqueous media.[108]

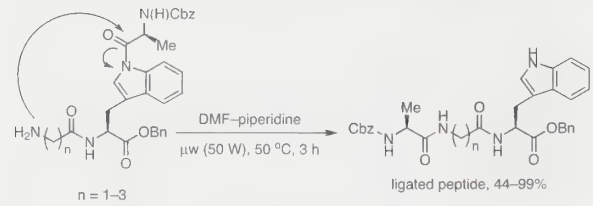
8.2.3. N to N Acyl Migration

Tryptophan isopeptides with α-, β-, or γ-amino acid units were synthesized, and the acyl migration from the indole nitrogen to the terminal NH_2 was studied under microwave irradiation. Intramolecular acyl transfer through 10-, 11-, and 12-membered-ring transition states was favored over that through a 7-membered-ring TS, and acyl migration occurred more readily in basic, nonaqueous media relative to aqueous buffered conditions (**eq 6**).[107]



Traceless chemical ligation through long-range oxygen-to-nitrogen acyl transfer

eq 5 *(Ref. 108)*



Ligation via long-range nitrogen-to-nitrogen acyl transfer

eq 6 *(Ref. 107)*

9. Conclusions and Comparison with Alternative Methodologies

9.1. Carboxyl Group Activation by Isolation of an Intermediate

The most obvious method for activating the carboxyl group of an amino acid for peptide bond formation at room temperature or below is by forming the corresponding acid chloride.[113] This type of activation has been carried out with chlorinating reagents such as pivaloyl chloride,[114] phthaloyl dichloride,[115] thionyl chloride,[116] and oxalyl chloride.[117] However, an amino acid chloride bearing an acid labile protecting group can easily racemize through the oxazolone, which limits the application of acid chlorides despite their high reactivity and low cost. Amino acid fluorides are less moisture-sensitive than acyl chlorides, but the fluorinating reagents are expensive and hazardous, and the peptide-forming reactions require purification by chromatography.[118]

The acyl azide method of peptide coupling was developed about 100 years ago. It is not attractive for routine use because it involves four distinct steps, including two stable intermediates that require purification.[119] An additional side reaction that occurs at higher temperature is rearrangement of the acyl azide into the alkyl isocyanate, which can react with nucleophiles to yield a peptide urea that is difficult to remove from the product.[120] Recently, El-Faham and Albericio published a review on the use of different peptide coupling reagents including benzotriazoles.[121]

9.2. Carboxyl Group Activation without Isolation of an Intermediate

Besides acyl halides and acyl azides, other methods for peptide coupling include the use of various reagents, where the intermediates are not isolated. A traditional approach to form peptide bonds is the carbodiimide method, using dicyclohexylcarbodiimide (DCC). However, despite being compatible with solid-phase synthesis (SPS) that uses *tert*-butoxycarbonyl (Boc) chemistry, DCC is not compatible with the fluorenylmethoxycarbonyl (Fmoc) group. When DCC is utilized in solution, traces of the byproduct, DCU, are difficult to remove, even after passage through a chromatography column. Thus, DCC has been replaced by reagents such as diisopropylcarbodiimide (DIC), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide (EDC), and *N*-cyclohexyl-*N'*-isopropylcarbodiimide (CIC), all of which are relatively soluble in DCM and therefore more suitable for Fmoc-SPS. Additives such as 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *N*-hydroxysuccinimide (HOSu), and others increase the efficiency of carbodiimide-mediated reactions and decrease the degree of racemization.[122]

Phosphonium reagents were developed to avoid racemization and side reactions that can occur with carbodiimide reagents. Coste et al. introduced chloro- and bromotris(dimethylamino)phosphonium hexafluorophosphate (CloP and BroP) as peptide-coupling reagents with noticeable racemization in the Young test.[123] HOBt may be used in combination with (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) to suppress racemization. However, the intermediates formed in the coupling reaction are highly unstable and BOP is reported to be highly carcinogenic.[124]

The search for better coupling reagents based on DCC led to carbonyl diimidazole (CDI).[125] Rapoport introduced the imidazolium

reagent 1,1'-carbonylbis(3-methylimidazolium) triflate (CBMIT) by bis-methylating CDI with methyl triflate.[126] This reagent showed no sign of racemizing the amino acid residues in the presence of $CuCl_2$ or $Cu(OTf)_2$. However, CBMIT is moisture-sensitive and, due to its polarity, the method is restricted to polar solvents such as nitromethane.[127] The reactivity of these reagents also increases in the presence of additives like HOAt, HOBt, or DMAP.

Aminium or uronium reagents such as *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HBTU) and *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU) all react directly with the amine moiety of the amino acid residue to give a guanidine side product, which terminates the peptide chain.[128]

Benzotriazole offers an extremely useful alternative to all the above methods by affording a versatile range of coupling procedures under the mild conditions required to avoid racemization.

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Siva S. Panda was born in Orissa, India, and received his bachelor's degree (B.Pharm.) in 2002 from the Roland Institute of Pharmaceutical Sciences, Berhampur, India, and his master's degree (M.Pharm.) in 2005 from Manipal College of Pharmaceutical Sciences, Manipal, India. He then joined the Dabur Research Foundation, Sahibabad, India, as a research scientist for a period of one year and worked on the synthesis of Mitoxantrone, an anticancer drug. Siva obtained his Ph.D. degree in synthetic organic chemistry in 2010 under the supervision of Prof. Subhash C. Jain at the University of Delhi, Delhi, India. He is currently working as a postdoctoral associate with Prof. Alan R. Katritzky at the Center for Heterocyclic Compounds, University of Florida, Gainesville, FL, where his research involves the synthesis of novel peptides, peptide bioconjugates, peptidomimetics in solution, and ligation studies of various cyclic transition states in S to N, N to N, and O to N acyl migrations.

C. Dennis Hall retired from his academic position at King's College, London, in 1999, and joined Prof. Katritzky's research group at the University of Florida, where he serves as a group leader, administrator for the online journal *ARKIVOC*, and co-organizer of the Florida Heterocyclic and Synthetic Conferences (Flohet). Since joining Katritzky's group, he has co-authored some 40 papers in the fields of heterocyclic chemistry, QSAR, insect control, and synthetic ion channels.

Eric Scriven is a native of Wales, U.K. After working at BISRA and Esso Ltd, he attended the University of Salford and graduated in 1965 with a degree in chemistry. He obtained his M.Sc. Degree from the University of Guelph, and his Ph.D. degree in 1969 from the University of East Anglia (with Prof. Katritzky). After postdoctoral years at the University of Alabama and University College, London, he was appointed Lecturer in Organic Chemistry at the University of Salford. There, his research interests centered on the reactivity of azides and nitrenes. He joined Reilly Industries in 1979, where he served as Director of R&D from 1991 to 2003. He is currently at the University of Florida. He has edited two books: *Azides and Nitrenes: Reactivity and Utility* (1984) and *Pyridines: from Lab to Production* (2013). He and Professor H. Suschitzky were founding editors of *Progress in Heterocyclic Chemistry* that has been published annually since 1989. He collaborated with Professors Katritzky and Rees as Editors-in-Chief of *Comprehensive Heterocyclic Chemistry II* (1996), and with Professors Katritzky, Ramsden, and Taylor on the third edition of the work. Currently, he is Publishing Editor of *ARKIVOC*, an online journal of organic chemistry free to readers and authors.

Alan R. Katritzky was educated at Oxford and Cambridge (Lecturer and Founder Fellow of Churchill College). Founder Dean of the School of Chemical Sciences at East Anglia from 1962, he transferred in 1980 as inaugural Kenan Professor to the University of Florida. His research in heterocyclic chemistry has covered inter alia *N*-oxides, benzotriazole methodology, electrophilic and nucleophilic substitutions, computational QSPR relationships, and peptide chemistry. He holds 14 honorary doctorates from 10 Eurasian countries and associate or foreign memberships of five national academies. He is Cavalieri Ufficiale (Italy) and Honorary Fellow of St. Catherine's College, Oxford, and of the Polish and Italian Chemical Societies. Over 1,000 graduate students and postdocs have trained in his group. He created the not-for-profit Arkat USA, Inc., which organizes the Flohet Conferences and publishes the open-access journal *ARKIVOC*. Contributions to the secondary literature include editing *Comprehensive Heterocyclic Chemistry* (40 volumes in 3 editions), *Advances in Heterocyclic Chemistry* (106 volumes), *Handbook of Heterocyclic Chemistry* (3rd edition, 2010), and *Heterocycles in Life and Society* (2nd edition, 2011).

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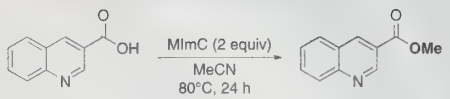
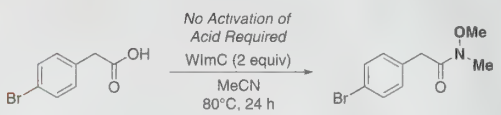
Esterification

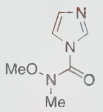


91% yield

Weinreb Amide Synthesis



92% yield



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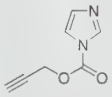
748730
MImC



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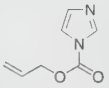

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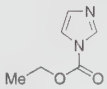

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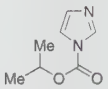

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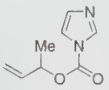

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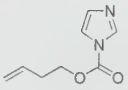

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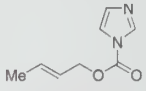

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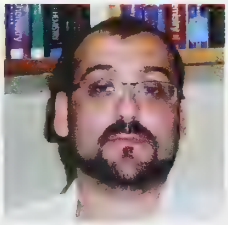
Recent Advances in the Prins Cyclization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Keywords. Prins reaction; tetrahydropyrans; dihydropyrans; tetrahydrofurans; dioxanes; piperidines; azepines; lactones; spiro compounds; macrocycles; natural products.

Abstract. The Prins reaction is often a key step in the synthesis of various heterocyclic rings that are important structural components of many classes of biologically active compounds and natural products. This review presents and discusses recent significant applications of this important reaction, and offers insight into its mechanism and regio- and stereochemical outcomes.

Outline

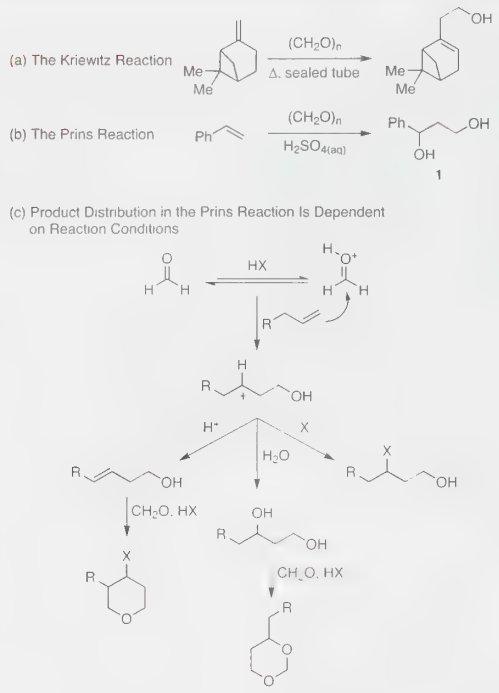
1. Introduction

The Prins reaction is often related to the Kriewitz reaction, an example of which is the reaction of β-pinene with paraformaldehyde to produce an unsaturated alcohol through a thermal ene rearrangement (**Scheme 1**, Part (a)).[1–3] When the reaction between an alkene and formaldehyde is conducted in the presence of an acid catalyst—such as the reaction of styrene with paraformaldehyde in the presence of aqueous sulfuric acid to give diol **1** (Scheme 1, Part (b))—it is called the Prins reaction. Numerous protic and Lewis acids are known to catalyze the reaction, and excellent reviews have been published on the early work.[1–3] The products generally obtained in this condensation are formed as complex mixtures of 1,3-dioxanes, 1,3-glycols, tetrahydropyrans, and allylic and homoallylic alcohols, with the composition of the mixture being dependent on the specific experimental conditions employed (Scheme 1, Part (c)). In the presence of water, the intermediate carbocation leads to the formation of 1,3-glycols and 1,3-dioxanes, while 3-alkyl-4-halotetrahydropyrans are obtained through the intermediacy of the homoallylic alcohols.

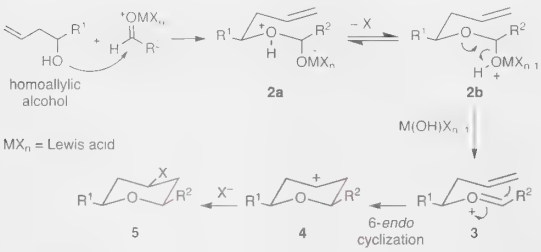
The Prins reaction plays a key role in the synthesis of such important product classes as dihydrofurans, dihydropyrans, piperidines, and oxabicyclo and spiro compounds. This review presents a survey and a discussion of pertinent and interesting recent developments relating to the stereochemical course and mechanism of the Prins reaction and to its advantageous application in organic synthesis.

2. Mechanistic Considerations

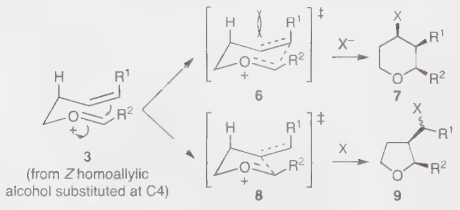
The Prins cyclization involves a homoallylic alcohol, an aldehyde, and a Lewis acid. The latter acts as catalyst and, depending on experimental conditions, it can also serve as a source of a nucleophilic anion. In the presently accepted mechanism, the reaction is initiated by complexation of the Lewis acid with the aldehyde, which activates the carbonyl carbon toward attack by the hydroxyl group of the alcohol, generating the hemiacetal intermediate **2**. Loss of the Lewis acid fragment from



Scheme 1. Condensation Reactions of Olefins with Paraformaldehyde and the Dependence of Product Distribution on the Reaction Conditions. *(Ref. 1–3)*



Scheme 2. General Mechanism of the Prins Cyclization. *(Ref. 2)*



Scheme 3. Regioselectivity in the Prins Cyclization. *(Ref. 4)*

the hemiacetal forms the key oxonium ion intermediate, **3**, which assumes the more stable chair conformation in which the substituents are pseudoequatorial. Subsequent 6-*endo* cyclization of **3** selectively leads to secondary tetrahydropyranyl carbocation **4**, which captures the halide to give rise to the 2,4,6-trisubstituted tetrahydropyran product (**Scheme 2**).[2]

2.1. Regioselectivity for 5- vs 6-Membered Rings

When the double bond geometry in the homoallylic alcohol is switched from *E* to *Z*, tetrahydrofurans can be formed in competition with tetrahydropyrans. This regioselectivity can be studied by examining the stereochemistry of intermediates present in the accepted mechanism of this reaction. Under the Prins cyclization conditions, the *Z* homoallylic alcohol reacts with the activated aldehyde to give rise to oxonium ion **3**. Two competing transition states can then be formed from **3**: six-membered-ring transition state **6** has a 1,3-diaxial interaction between H and the substituent R^1, while five-membered-ring transition state **8** has greater torsional and angular strains. When the R^1 substituent is sufficiently large, an increase in the activation barrier of the process results, which slows the formation of tetrahydropyran product **7** in favor of tetrahydrofuran product **9** (**Scheme 3**).[4]

2.2. Stereoselectivity of Nucleophile Capture at C4 of the Tetrahydropyran Ring

2.2.1. Alder's Model: Equatorial Selectivity

On the basis of theoretical calculations employing Density Functional Theory (DFT), Alder and co-workers concluded that the all-cis 2,4,6-trisubstituted product of the Prins cyclization is favored by stabilization of the cationic intermediate **10** through hyperconjugation. When the hydrogen attached to the carbocation center is pseudoaxial, the empty p orbital of the positively charged carbon overlaps more efficiently with the coplanar σ_{C-C} and σ^*_{C-C} orbitals and with the orbital of the nonbonding electrons of oxygen. Nucleophilic attack thus occurs from the exo face (convex), leading to the 2,4,6-trisubstituted tetrahydropyran product with all three substituents in equatorial positions (**eq 1**).[5]

2.2.2. Rychnovsky's Model: Axial Selectivity

Rychnovsky investigated the capture of bromide and iodide at C4 of **10** by reacting α-acetoxy ester **11** with TMSBr, AcBr, HBr, or TMSI and lutidine in dichloromethane. High axial stereoselectivity at C4 was observed for the resulting Prins cyclization product **16** (**Scheme 4**).[6] In contrast, when $SnBr_4$ was employed, the major product was the equatorial epimer **19**. In the proposed mechanism, some Lewis acids; such as TMSBr, AcBr, and HBr; act as donors of bromide by forming the intimately associated ion pairs **14** and **15**. The slightest movement (least motion pathway) in **15**, results in Br^- attacking C4 in the axial position (endo attack) to form **16**. When $SnBr_4$ is employed as the Lewis acid, the in situ formed $[SnBr_5]^-$ in ion pair **17** is less nucleophilic than bromide, allowing separation of the ion pair by the solvent. In the resulting intermediate, **18**, exo (convex) attack leads to the formation of product **19** with an equatorial bromine at C4.

2.3. Diastereoselectivity of the Prins Cyclization

Substituents at C2 and C6 of tetrahydropyrans formed by the Prins cyclization are preferentially cis.[7a] Methodologies for forming the C2/C6 anti isomers are not well established. These isomers are present in some structures of natural products, such as the psymberins[7b] and the apicularens.[7c] Panek's group has succeeded in synthesizing enantiomerically pure *anti*-2,6-dihydropyrans by the Prins cyclization with the aid of TMSOTf.[7c–e]

Loh and co-workers investigated steric and electronic effects in the Prins cyclization of homoallylic *anti*-α-hydroxy esters, leading to 4-chloro-2,6-disubstituted THPs. This study demonstrated that groups with high electron density in the pseudoaxial position stabilize the oxonium ion by inductive electronic effects, and favor a transition state that forms the anti isomer, **20a**; while steric effects favor the transition state leading to the syn isomer, **20b**. In both cases, equatorial attack of the nucleophile is preferred (**Scheme 5**).[8]

3. Recent Synthetic Applications

Saturated six-membered-ring oxygen and sulfur heterocycles are features found in the structures of a variety of biologically important natural products such as polyether antibiotics, marine toxins, pheromones, and pharmaceutical agents. Tetrahydropyran is also the structural core of most carbohydrates, oligomers, and polymers, which play crucial roles in living organisms. It is therefore not surprising that considerable efforts have been expended toward developing facile and viable syntheses of tetrahydropyran-containing compounds.

3.1. Substituted 1,3-Dioxanes

When olefins are condensed with aldehydes in aqueous solutions of mineral acid catalysts, alkyldioxanes (cyclic formals or acetals of 1,3-butanediols) and 1,3-butanediols are formed. The distribution of these two products varies with the concentration of the solution of the acid catalyst and the reaction temperature. Amrute et al. studied the catalytic activity of MoO_3/SiO_2 (7 wt %) in the Prins cyclization of a series of olefins with paraformaldehyde (2 equiv) in 1,2-dichloroethane at 80 °C.[9] 72–90% conversions and 96–100% selectivities were observed for the corresponding 4-alkyl- and 4-phenyl-substituted 1,3-dioxane products. Du and Tian synthesized 1,3-dioxanes in moderate-to-high yields from formalin (aqueous formaldehyde), styrene derivatives, and trifluoromethanesulfonic acid (TfOH).[10] The use of organic acid as catalyst for the Prins reaction was unprecedented. It is worth noting that this approach avoids the use of organic solvents by conducting the reaction in water, which makes it a more environmentally friendly process.

Yang and co-workers explored the use of water-stable and recyclable Brønsted acidic ionic liquids as environmentally benign catalysts for the Prins cyclization. The effectiveness of these ionic liquids was compared in the model reaction of styrene with formaldehyde at 94–96 °C, whereby [BMIM][HSO_4] was found to be the most effective catalyst (**eq 2**).[11] The 1,3-dioxane products were obtained in good yields, and the catalysts, after vacuum distillation at 80 °C, were recovered and reused in subsequent runs, thus reducing the risks to the environment by avoiding the use of organic solvents and enabling large-scale applications of the Prins cyclization.

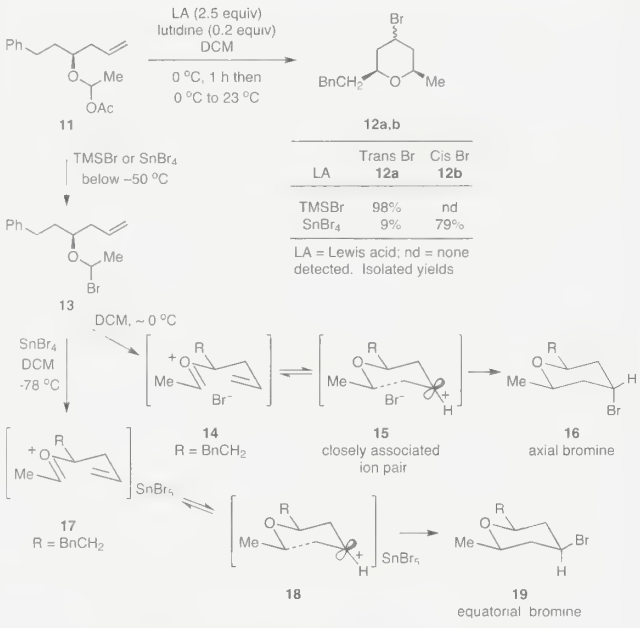
3.2. Spiro and Bicyclic Tetrahydropyrans (THPs)

Gais and co-workers have reported a modular asymmetric approach to spiroketals, spiroethers, and oxabicycles that employs a spiro- or bicycloannulation of α-hydroxydihydropyrans. The synthesis included a stereoselective Ferrier-type O- and C-glycosidation, ring-closing metathesis, and stereoselective Prins cyclization as key steps. When α-hydroxydihydropyran **21** was treated with $TiCl_4$ in dichloromethane at –78 °C, the regioisomeric spiro ethers **22** and **23** resulted from a Prins cyclization (**eq 3**).[12]

Nakamura and co-workers have described a versatile method for the synthesis of 4-substituted 6-methyl-3-oxabicyclo[3.3.1]non-6-ene-1-methanol derivatives using a Prins-type cyclization reaction between aldehydes and O-protected or unprotected 4-methylcyclohex-

Alder's model for nucleophile capture at C4 in the Prins cyclization

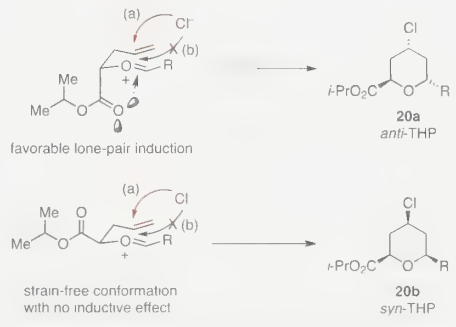
eq 1 *(Ref. 5)*



LA	Trans Br **12a**	Cis Br **12b**
TMSBr	98%	nd
$SnBr_4$	9%	79%

LA = Lewis acid; nd = none detected. Isolated yields

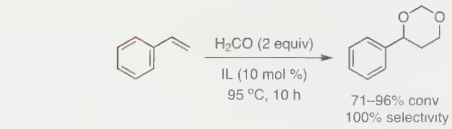
Scheme 4. [illegible]



(a) equatorial approach (favored); (b) axial approach (unfavorable)

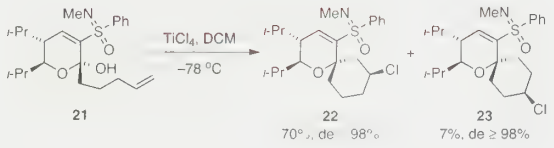
R = Cy, Et, Et_2CH, $BnCH_2$, $MeCH{=}CH_2$
Reaction conditions: $In(OTf)_3$ (20 mol %), TMSCl, DCM, 0 °C
56–62% yields; **20b:20a** = 44:56 to 51:49

Scheme 5. Diastereoselectivity of the Prins Cyclization. *(Ref. [illegible])*

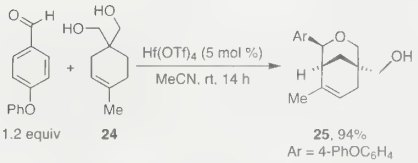


IL = $[HMIM]BF_4$, $[(CH_2)_4SO_3HMIM][HSO_4]$, $[(Ac)_2BIM]Br$, $[NMP][HSO_4]$, $[BMIM][HSO_4]$, $[BMIM][H_2PO_4]$

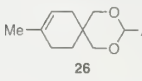
eq 2 *(Ref. 11)*



eq 3 *(Ref. 12)*

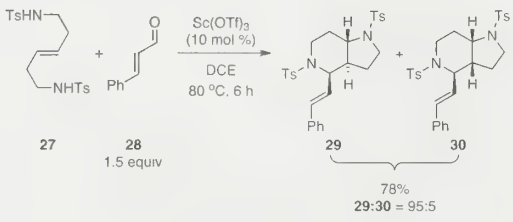


Six additional examples of aromatic aldehydes, 72–96%



26 was the major product when $Zn(OTf)_2$, $Yb(OTf)_3$, and $La(OTf)_3$ were used: 75%, 66%, and 68% yield, respectively

eq 4 *(Ref. 13)*



eq 5 *(Ref. 17)*

3-ene-1,1-dimethanol (**24**). Under the optimized reaction conditions employing hafnium triflate, various aldehydes, including functionalized benzaldehydes and heteroaromatic aldehydes, afforded the cyclization products in high yields (**eq 4**).[13] The zinc and lanthanum triflates form preferably spirodioxane **26.**

3.3. Nitrogen Heterocycles via the Aza-Prins Cyclization

The Prins cyclization of homoallylic amines (the aza-Prins cyclization) takes place in a fashion similar to that of homoallylic alcohols, whereby the nonbonding electrons on the nitrogen initiate the sequence of reaction steps by attacking the electrophilic site of the aldehyde activated by an acid catalyst. The key intermediate of the aza-Prins cyclization is an iminium ion, in analogy to the oxonium ion. Piperidines are commonly found subunits in many biologically relevant molecules including alkaloids, and are attractive structural scaffolds for drug discovery.[14] Subba Reddy showed that the BF_3•OEt_2 catalyzed aza-Prins reaction of benzaldehyde and *N*-tosyl-3-butenamine (a homoallylic amine), in the presence of anisole as solvent and nucleophile, produces the *trans*-2,4-diarylpiperidine in 83% yield.[15,16] This is the first report of the preparation of 4-arylpiperidines via an aza-Prins–Friedel–Crafts reaction sequence.

The coupling of *E*- (**27**) and *Z*-3-hexene-1,6-ditosylamides with various aldehydes, including cinnamaldehyde (**28**) in the presence of 10 mol % $Sc(OTf)_3$ in 1,2-dichloroethane gave the corresponding trans- and cis-fused saturated pyrrolopyridines **29** and **30**, respectively, in good yields by an intramolecular aza-Prins cyclization (**eq 5**).[17] Other aromatic aldehydes such as benzaldehyde, *para*-anisaldehyde, and thiophene-2-carboxaldehyde were not effective substrates in the reaction. Ketones, such as cyclohexanone, failed to give the spirodiaza bicyclic product. In contrast, aliphatic aldehydes; such as isovaleraldehyde (70%, trans:cis = 95:5), cyclohexanecarboxaldehyde (73%, trans:cis = 95:5), and propionaldehyde (66%); participated well in this reaction.

Camara et al. synthesized azepines fused to a naphthoquinone moiety by an intramolecular aza-Prins cyclization starting with an amino derivative, **31**, of lapachol (**Scheme 6**).[18] Products **32a** and **32b** were formed in 42% yield as a diastereomeric mixture, with a trans:cis ratio of about 7:3. The mechanism of C–C bond formation leading to **32a** and **32b** appears to resemble that of the intramolecular ene reaction between a carbonyl group and an alkene.[19] The authors proposed that the formation of intermediates occurs through a Prins reaction, via nucleophilic attack of H_2O or MeOH at the isoprenyl double bond, possibly followed by a concerted attack onto the protonated carbonyl. The observed diastereoselectivity is possibly induced by steric hindrance of the 4-isopropyl and 3-hydroxyl groups, despite the fact that the resulting seven-membered ring is conformationally less restricted than the corresponding six-membered ring. This synthetic method is important, since there are very few publications on the synthesis of such heterocyclic systems, which are of great interest in the scientific community because of their pharmacological applications.[20,21]

3-Azabicyclo[3.3.1]non-6-enes are structural motifs in many natural products and, with the proper choice of substituents, can serve as templates for complexity-generating transformations. Krasavin and co-workers have reported a facile synthesis of this ring system in a diastereomerically pure form by an aza-Prins cyclization involving a δ,ε-unsaturated imine and an equivalent of BF_3•OEt_2 under microwave irradiation at 180 °C for 1 h (**Scheme 7**).[22] As in the mechanism proposed earlier by Overman for the aza-Prins cyclization employed in the total synthesis of (+)-nankakurines A and B,[23] it is believed that the pair of nonbonding electrons on nitrogen participate in a regiospecific

intramolecular deprotonation of the hydrogen vicinal to the initially formed carbocation in intermediate **A**.

Subba Reddy and co-workers[24] have reported the synthesis of 2-aryl- and 2-alkyl-4-amidopiperidines in good yields and high selectivities by an aza-Prins–Ritter tandem reaction employing a slight excess of triflic acid in MeCN at 0 °C. It was observed that in the absence of triflic acid, no aza-Prins cyclization occurred even in refluxing acetonitrile. Other Brönsted acids—such as acetic acid, formic acid, and trifluoroacetic acid—were tested and, in all cases, the reaction proceeded rapidly at 0 °C; however, triflic acid provided the best conversion.

3.4. Synthesis of Furan Derivatives

Substituted dihydrofuranones (γ-butyrolactones or GBLs) are important intermediates in synthetic organic chemistry, and are commonly found as structural fragments in natural products, receptor ligands, and drug molecules.[25] Compounds containing a GBL moiety exhibit pharmacological effects some of which are muscarinic (pilocarpine) and antimuscarinic (Kaiser lactones) activities, convulsant (picrotoxin, β-substituted GBL) and anticonvulsant (α-alkyl-substituted GBLs) activities, and the ability to modulate quorum sensing.[26]

Gao and Canney reported a novel and concise approach for the synthesis of structurally diverse, substituted 5-(2-hydroxyethyl)-3,3-dihydrofuran-2(3*H*)-ones. This method relies on a modified Prins reaction that employs a catalytic amount of H_2SO_4 in glacial HOAc. In the proposed mechanism, acetic acid captures the initially formed carbocation to provide a protected hydroxyl group. The remaining aliphatic alcohol is also protected by an intramolecular esterification, leading to a caprolactone intermediate. Sequential treatment of the resulting seven-membered-ring lactone with aqueous base and then acid affords the desired hydroxyethyl lactones in moderate-to-good yields (**Scheme 8**).[26]

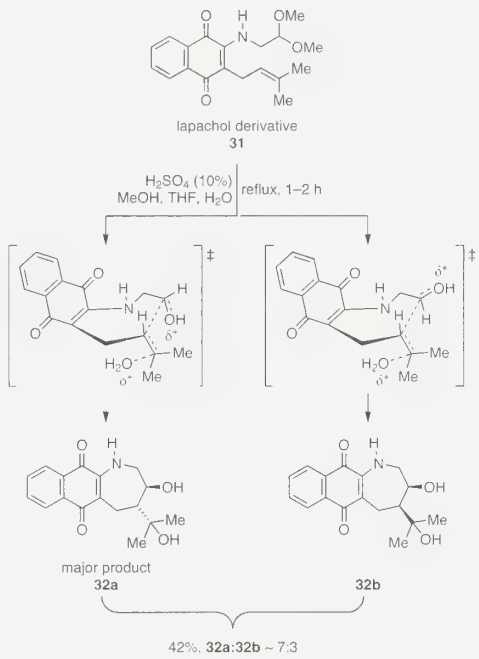
Two examples of the use of the Prins cyclization in the synthesis of furan structures fused with pyran rings (furopyrans) have recently been reported.[27,28] This ring system is commonly found in natural products such as flavonoids, pterocarpans, and catechins.[29] In the first example, 3-hexene-1,6-diol (**36**) was reacted with 4-bromobenzaldehyde in an intramolecular Prins cyclization in the presence of 10% TsOH in 1,2-dichloroethane to give the cis-fused bicyclic product **37** in 72% yield (**Scheme 9**, Part (a)).[27] In the second example, a substituted 2,6-dioxabicyclo[3.2.1]octane was similarly prepared by a tandem acetalization–intramolecular Prins cyclization starting with 4-pentene-1,2-diol (Scheme 9, Part (b)).[28] The overall process is catalyzed by a combination of $Sc(OTf)_3$ and TsOH and leads to good yields, high selectivities, and faster reaction times.

3.5. Synthesis of Halogenated Tetrahydropyrans: Halo-Prins Cyclization

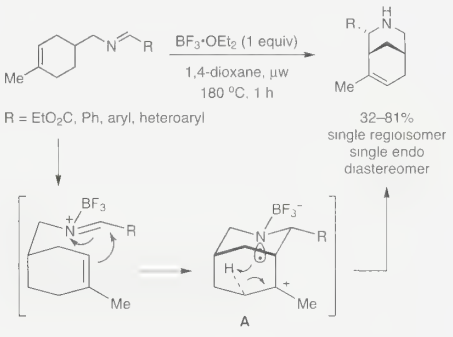
In analogy to the oxygen and nitrogen variants, the halo-Prins cyclization involves nucleophilic attack by halogen present in the reaction medium on the carbocation intermediate that arises from the oxonium ion formed after cyclization.

3.5.1. Fluorinated THPs

The introduction of fluorine atoms into organic molecules alters in important ways their biological activity, solubility, hydrophobicity, metabolism, and bulk properties.[30–32] However, few methods for the synthesis of fluorinated pyranyl motifs are known and, of these, the ones that employ BF_3•Et_2O and Et_4NF•5HF as both Lewis acids and fluorine sources successfully achieve the Prins cyclization of homoallylic alcohols into fluorinated pyranyl motifs.[33a–c] When BF_3•Et_2O is utilized in stoichiometric quantities, it contributes fluoride ion to quench the intermediate carbocation, giving rise to the fluorinated products. As an example of this approach, O'Hagan and co-workers investigated the oxa- and aza-Prins reactions for the synthesis of 4-fluoropyrans and 4-fluoropiperidines starting from homoallylic alcohols and various aldehydes. The fluorinated THP products were obtained in good yields, but with only moderate diastereoselectivity.[34] This method was extended to the aza-Prins reaction that utilizes *N*-tosylhomoallylamines to generate the corresponding 4-fluoropyrrolidines.



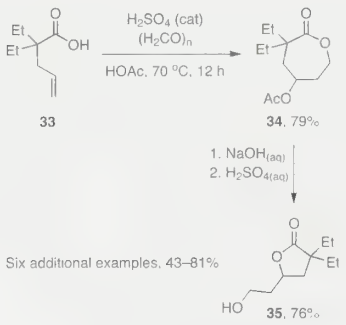
Scheme 6. Intramolecular Aza-Prins Cyclization of a Derivative of Lapachol (Ref. 18)



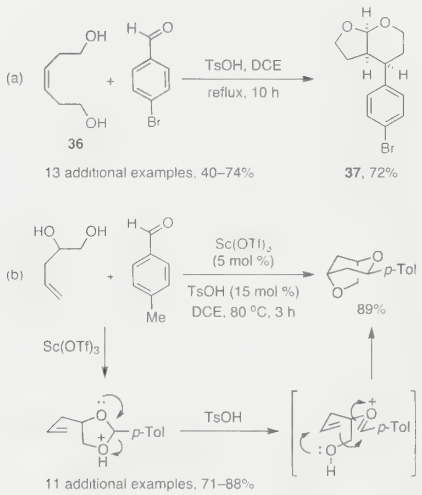
Scheme 7. Synthesis of Azabicyclo Compounds through an Aza-Prins Cyclization. (Ref.)

O'Hagan's group then investigated the Prins fluorination reactions under microwave conditions, and observed significantly reduced reaction times and higher conversions. However, there was a slight decrease in the diastereoselectivity of the reaction and, in some cases, an inversion of the diastereoselectivity. When a series of low-temperature (–20 °C) experiments were carried out in an attempt to improve the diastereoselectivity, dr increased from ~2:1 to 10:1 and yields remained good, but, not surprisingly, a significant increase in the reaction time was observed.

Prior to Loh and co-workers' recent disclosure,[35] all studies of the Prins fluorination reaction reported the almost exclusive formation of *cis*-2,6-disubstituted fluorinated di- or tetrahydropyrans. An efficient, highly diastereoselective synthesis of the *trans*-2,6-disubstituted



Scheme 8. Synthesis of Dihydrofuranones [illegible]



Scheme 9. Use of Unsaturated 1,6-Diol **36** for the Preparation of Furopyrans *(Ref. 27,28)*

counterparts—useful in the development of new pharmaceuticals—would be highly desirable. Loh's group explored the Prins reaction of various allenic alcohols, e.g. **38**, with a variety of aldehydes using different Lewis acids (LAs) and fluorine sources.[35] Their research demonstrated that BF_3•Et_2O, acting both as an efficient Lewis acid and as a source of fluoride, gives the best results. The authors proposed a mechanism in which the Prins cyclization of the allenic alcohol takes place through a distorted chair transition state, in which a lone electron pair on the carbonyl oxygen of the ester group stabilizes the partial positive charge on the oxocarbonium carbon. This forces the carbonyl group to adopt an axial orientation, leading to the desired intermediate **40** and suppressing the generation of the undesirable intermediate **41**. In turn, intermediate **40** gives rise to the desired *trans*-2,6-disubstituted fluorinated dihydropyran **39**, selectively (**Scheme 10**).[35]

Saikia and co-workers have reported that TiF_4 can efficiently be employed for the strereoselective synthesis of substituted all-cis 4-fluorotetrahydropyrans via the halo-Prins cyclization.[36] A variety of aliphatic and aromatic aldehydes were reacted with a number of homoallylic alcohols to give good yields and high diastereoselectivities of the corresponding THPs. Moreover, acyclic and cyclic ketones were subjected to the reaction and found to be less reactive (5–6 h vs 2.5–4 h for the aldehydes), giving only moderate yields (50–70% vs 80–92% for the aldehydes). Cyclic ketones afford spiro compounds, as illustrated by the reaction of cyclohexanone, which leads to spirocyclic compound **42** in 70% yield (**eq 6**).[36]

3.5.2. Chlorinated and Brominated THPs

$InCl_3$ has been demonstrated to be an excellent Lewis acid for the insertion of a chlorine atom at the 4 position of THPs by the Prins cyclization. For example, the $InCl_3$-promoted diastereoselective Prins reaction of **43** with benzaldehyde led to the pentasubstituted tetrahydropyran derivative **44** (essentially as a single product) in which five stereogenic centers (up-down-up-down-up) were controlled (**Scheme 11**, Part (a)).[4,37,38] Subba Reddy and co-workers[39] reported another example of the effectiveness of $InCl_3$, whereby the synthesis of cis-fused hexahydro-1*H*-furo[3,4-*c*]pyran scaffolds containing chlorine proceeded smoothly under mild conditions (**Scheme 11**, Part (b)).[39]

$FeCl_3$ has been employed as an inexpensive, environmentally friendly, and stable Lewis acid to promote the halo-Prins cyclization of 3-buten-1-ol with several aldehydes.[40] The cyclization affords the corresponding *cis*-4-halo-2-alkyltetrahydropyrans in generally excellent yields.[40] The reaction works quite well with both aliphatic and aromatic aldehydes and, when $FeBr_3$ is employed, the 4-bromo-substituted analogue is formed. Liu and Loh have disclosed an efficient and highly stereoselective Prins cyclization leading to *cis*-2,6-dialkyl-3,4-dibromotetrahydropyrans from terminal vinyl bromides. This method employs $InBr_3$ as the Lewis acid and TMSBr as the source of bromide ion.[41]

Cascade reactions can be very powerful transformations in organic synthesis.[42] The first examples of a Mukaiyama aldol–Prins (MAP) cascade cyclization reaction were reported by Rychnovsky's group, whereby a very reactive allylsilane served as the internal nucleophile in a rapid and clean Prins cyclization.[43] Rychnovsky and co-workers also described the use of simple alkene substrates in MAP cyclizations and the importance of selecting the appropriate Lewis acid to promote the reaction. The attraction of such a sequence is that it forms two new C–C bonds, a ring, and three new stereogenic centers. Initially, the Mukaiyama aldol addition and Prins cyclization with the simple alkene **45** was evaluated using previously optimized conditions.[43] The reaction of **45** with 2.5 equiv of dihydrocinnamaldehyde in the presence

of BF_3•OEt_2 and 2,6-di-*tert*-butylpyridine (2,6-DTBP) at –78 °C led to the unexpected product **46** in 82% yield. The more powerful Lewis acids, $TiCl_4$ and $TiBr_4$, did not produce 1,3-dioxane **46** and gave the best yields of **47**. $TiBr_4$ was particularly effective and gave adduct **47** in 72% yield (**eq 7**).[44]

3.5.3. Iodinated THPs

The mild Lewis acidic nature of molecular iodine[45] has been exploited by Yadav and co-workers in the first direct and metal-catalyst-free Prins cyclization of homoallylic alcohols with aldehydes for the rapid synthesis of highly substituted iododihydro- and iodotetrahydropyrans in good yields and selectivities under neutral conditions.[46,47] Other reagents such as LiI, KI, and NaI failed to produce the desired product. Aliphatic, simple aromatic, and moderately activated aldehydes gave higher yields of products than strongly activated or deactivated aldehydes. This same research group reported a simple and metal-catalyst-free Prins cyclization for the synthesis of highly substituted tetrahydropyrans from sugar-based homoallylic alcohols and aldehydes using molecular iodine under neutral conditions.[46]

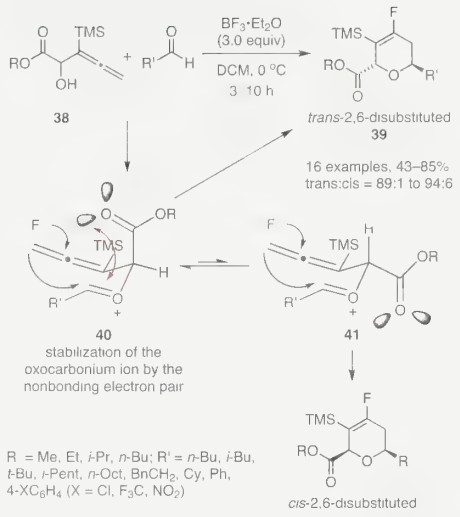
When silylated secondary homopropargylic alcohols were subjected to the same experimental protocol with aldehydes, highly substituted dihydropyrans were rapidly formed by a Prins cyclization (**Scheme 12**).[47] The reactions were completed in 3 hours or less, and the all-cis products were obtained in 72–90% yields. The cis selectivity presumably arises from an *E* oxocarbenium ion formed via a chair-like transition state. The optimal geometry of this oxocarbenium ion places the hydrogen atom at C4 in a pseudoaxial position, which favors equatorial attack of the nucleophile.

TMSI, generated in situ from TMSCl and NaI, has been employed as an iodide source in the Prins cyclization of homoallylic and homopropargylic alcohols with various ketones leading to 2,2-disubstituted 4-iodotetrahydropyrans, spirocyclic 4-iodotetrahydropyrans, and spirocyclic 4-iodo-5,6-dihydro-2*H*-pyrans.[48] In the presence of iodide, no trapping of the intermediate 4-tetrahydropyranyl carbocation by acetonitrile was detected.

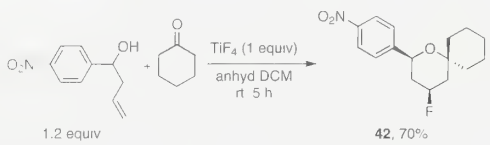
The synthesis of 4-iodotetrahydropyrans by the Prins cyclization can also be performed in the presence of a combination of $CeCl_3$•$7H_2O$ and LiI.[49] This approach can be applied to both aldehydes and ketones, but requires a higher temperature (reflux in dichloroethane), with the best results achieved with 1 equiv of $CeCl_3$. In contrast, CAN and $Ce(OTf)_3$ were not effective and led to hydroxylated side products. Gallium triiodide (35 mol %) has also been employed for the synthesis of 4-iodotetrahydropyrans at room temperature in 10–25 min and in 82–89% yields.[50]

3.6. Macrocyclization Involving the Prins Reaction

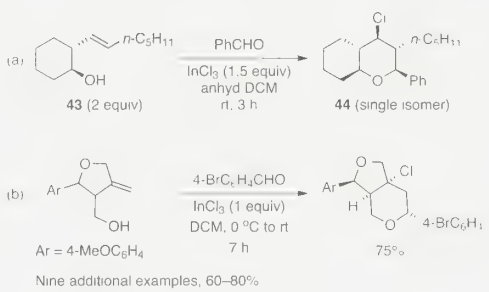
Oxacyclic macrodimers constitute an important class of natural products that possess a wide range of structural complexity and bioactivity,[51] and are popular targets for synthetic chemists.[52] Rychnovsky and co-workers introduced a new sequential dimerization–macrocyclization based on the Prins cyclization for forming symmetrical macrocycles.[53] This approach is illustrated by the optimized conditions in the example in **equation 8**. A variety of Lewis acids, including other Re and non-Re ones, were investigated and found to be inferior to $O_3ReOSiPh_3$. Other reaction parameters; such as temperature, concentration, and substrate scope; were also examined: Both acetals and aldehydes were found to be viable substrates, whereas increasing the reaction temperature to 40 °C did shorten the reaction times but did not improve the yields. The usefulness of this strategy was demonstrated in a successful synthesis of a model for clavosolide A, a marine sponge metabolite.



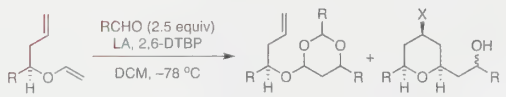
Scheme 10. Fluorinated Dihydropyrans by the Prins Cyclization of Allenic Alcohols. *(Ref. 35)*



eq 6 *(Ref. 36)*



Scheme 11. Chlorinated THPs by the Prins Cyclization of Homoallylic Alcohols. *(Ref. 4,39)*

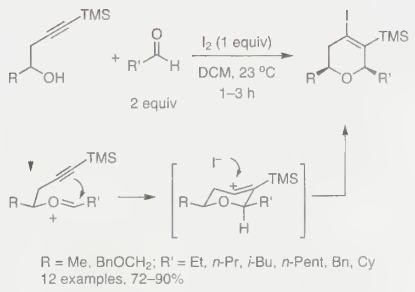


Six additional examples using $TiBr_4$: 53–82% of **47**, dr = 1:1 to 1.3:1

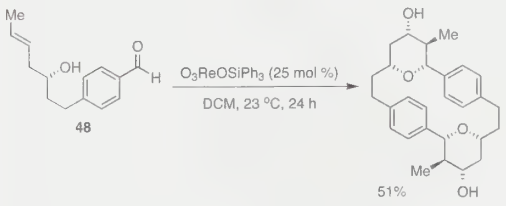
LA	X	46	47
$BF_3{\cdot}OEt_2$	---	82%	nd
$TiCl_4$	Cl	nd	62%
$TiBr_4$	Br	nd	72%

nd = not detected.

eq 7 *(Ref. 44)*



Scheme 12. Prins Cyclization of Silylated Secondary Homopropargylic Alcohols with Aldehydes under Mild, Metal-Catalyst-Free Conditions. *(Ref. 47)*



eq 8 *(Ref. 53)*

4. Conclusion

The Prins cyclization is an efficient reaction for the stereoselective synthesis of substituted tetrahydropyran rings, and has significantly advanced in the past few years, as demonstrated by the number of applications described in the literature. This reaction is, in some cases, the method of choice for the preparation of natural products and biologically active compounds that feature the tetrahydropyran moiety in their structures.

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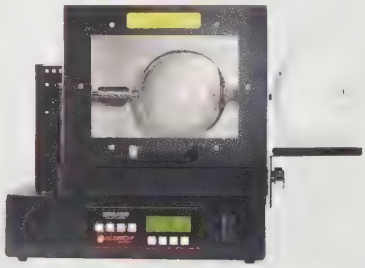

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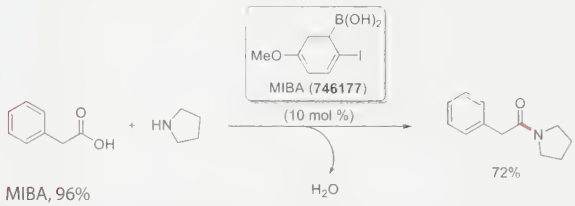

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Detail from ***A View of the Mountain Pass Called the Notch of the White Mountains (Crawford Notch).*** Courtesy National Gallery of Art, Washington, DC

Born and raised in England, Thomas Cole (1801–1848) immigrated with his family to the USA in 1818. Following a series of unremarkable jobs as engraver (England and Philadelphia) and itinerant portrait painter (Ohio), he moved, at 22, to Philadelphia to study at the Pennsylvania Academy of the Fine Arts. While he was largely self-taught, he benefitted from two trips to Western Europe, where he traveled extensively, met prominent artists such as Turner and Constable, and studied the Old Masters, such as Raphael. A founder of the Hudson River school of painting, he was a big influence on American landscape painters of the mid-19th century among whom is his pupil, Frederic Edwin Church. The subjects for many of his canvases were his beloved Hudson River valley, Catskill Mountains (New York), and White Mountains of New Hampshire.

A View of the Mountain Pass Called the Notch of the White Mountains (Crawford Notch) (oil on canvas, 102 x 155.8 cm) is a wonderful example of Cole's desire to create a more sophisticated form of landscape painting that expresses a higher meaning.* This realistic and exquisitely detailed landscape, with its warm autumnal yellow and red colors and contrasting brightly lit and dark areas, embodies Cole's romance with America's unspoiled and beautiful wilderness and his dismay at its fast disappearance as a result of encroaching human activity (represented in the foreground by the cut trees, road, structures, and farming). By rendering the human figures small and on the move and the landscape majestic, he is reflecting on man's insignificance and fleeting existence vis-à-vis nature's timeless beauty and power.

This painting was acquired by the National Gallery of Art, Washington, DC, through the Andrew W. Mellon Fund.

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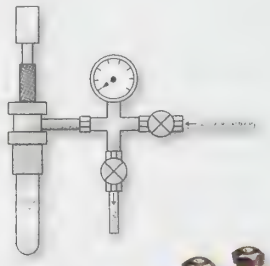

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About the Authors

Roger Sheldon is a recognized authority on Green Chemistry and Catalysis and Professor Emeritus of Biocatalysis and Organic Chemistry at Delft University of Technology. He is widely known for developing the concept of E factors for assessing the environmental footprint of chemical processes. He has a Ph.D. in organic chemistry from the University of Leicester (U.K.). Prior to joining Delft University in 1991, he was Vice President for Research and Development at DSM/Andeno from 1980 to 1990 and with Shell Research Amsterdam from 1969 to 1980. He is currently CEO of CLEA Technologies B.V., a biotech company.

Sander van Pelt studied Chemical Technology and Bioprocess Technology at Delft University of Technology. After obtaining a master's degree in 2005, during which he was an intern at Evonik and Codexis, he joined Prof. Sheldon's research group as a Ph.D. candidate. This research culminated in 2010 in a thesis entitled *The Application of Nitrile Hydratases in Organic Synthesis*. In 2010, he joined CLEA Technologies B.V., where he is currently the Chief Technical Officer.

Seda Kanbak-Aksu studied pharmacy at Hacettepe University, Ankara, Turkey. After her graduation with a B.S. degree as pharmacist, she continued her education in the Pharmaceutical Chemistry group of the same university where she obtained her M.Sc. degree. In 2004, Seda moved to the Netherlands, and, in 2005, she joined the Biocatalysis and Organic Chemistry group at Delft University of Technology, where she completed her Ph.D. studies. In 2009, she joined CLEA Technologies and is currently a Product Manager.

Jo-Anne Rasmussen obtained her Ph.D. degree at the Australian National University in Canberra, Australia, and then took a position at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Melbourne, Australia. In 2006, she started working as a scientific researcher at the Technical University of Graz, Austria, and, in 2010, moved to CLEA Technologies in Delft, where she is currently a Senior Scientist.

Michiel Janssen received a master's degree in bioprocess engineering from the then Wageningen Agricultural University (now Wageningen University) and a Ph.D. degree in applied biocatalysis from Delft University of Technology. Before joining CLEA Technologies in 2006, he spent another two years as a postdoctoral researcher at the latter university and a half year at DSM Research (Geleen, The Netherlands). His fields of interest include biocatalytic process development, enzyme immobilization, and nitroxyl radical catalytic oxidations.

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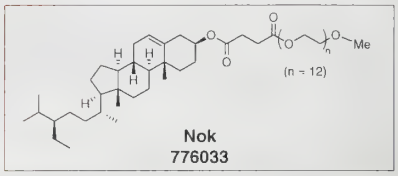

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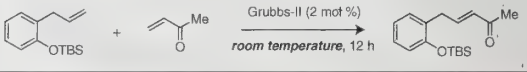
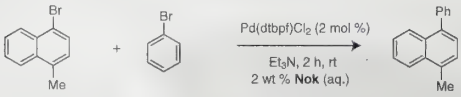
Comparable Reactivity



surfactant (2 wt % aq.)	conversion (determined by ^{1}H NMR)
PTS (**698717**)	71%
TPGS-750-M (**733857**)	77%
Nok (**776033**)	76%

Sustainable Solvent



cycle	conversion (determined by ^{1}H NMR)
1	>99%
2	>99%
3	>99%
4	>99%
5	>99%
6	>99%

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774766	Lithium diisopropylamide solution, 1.0 M in THF-hexanes	100 mL 4x25 mL
361798	Lithium diisopropylamide solution, 2.0 M in THF-heptane-ethylbenzene	100 mL 4x25 mL 4x100 mL

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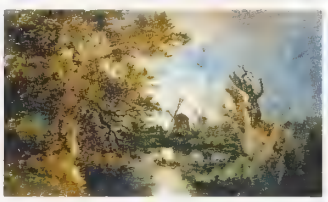

Detail from ***Moonlight on the Yare.*** Photo courtesy National Gallery of Art, Washington

Moonlight on the Yare (oil on canvas, 98.4 x 125.7 cm) was painted ca. 1816/1817 by John Crome (1768–1821), and is considered one of his most important works. Crome had a limited formal education, and his artistic training consisted of a seven-year apprenticeship with a house and sign painter and a few lessons in London with Sir William Beechey. Save for a few short visits to London and his friendship with Robert Ladbrooke and John Opie, he had little or no contact with the great artists of his time. Crome supplemented his painting and sketching career by lifelong work teaching drawing in schools and to children of the wealthy.

Crome was a founding member and later president of the Norwich School of Painters. While he did not enjoy great or wide fame during his life, his works became much more appreciated after his death, and have earned him a spot among England's prominent landscape painters. As with most of his landscapes, which are noted for their exquisite and realistic rendering of trees and their fidelity to nature, this painting is a romantic depiction of a rustic and tranquil nocturnal scene with a full moon rising into the cloudy sky over the River Yare in the Norwich area where Crome spent all his life. It is reminiscent of landscapes by seventeenth- and eighteenth-century Dutch and English masters,* which Crome greatly admired and copied early in his life as a way to hone his painting skills.

This painting is part of the Paul Mellon Collection at the National Gallery of Art, Washington, DC.

* *Which landscapes by seventeenth- and eighteenth-century Dutch and English masters does this painting remind you of? To find out, visit* ***Aldrich.com/acta471***

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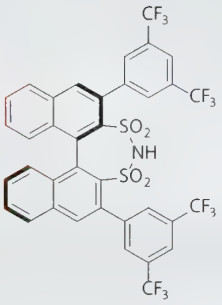

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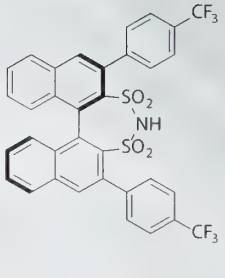

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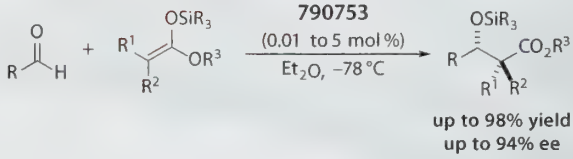

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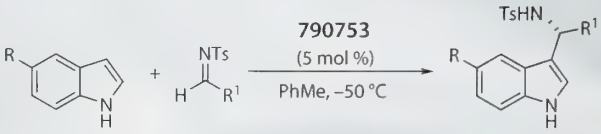
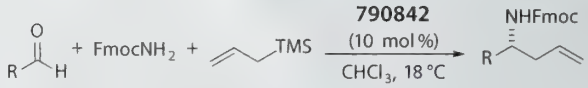


up to 95% yield
up to 95% ee



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Twin Cities campus, and worked in the laboratory of Prof. Richard Hsung. In 2007, he completed postdoctoral studies in the laboratory of Prof. K. C. Nicolaou at The Scripps Research Institute in San Diego, CA. In the same year, Kevin joined Eli Lilly and Company in Indianapolis, IN, and was promoted to Sr. Research Scientist in 2010. He is currently working as a process chemist in Lilly's continuous processing group.

Corey R. J. Stephenson received an Honours B.Sc. degree in 1998 from the University of Waterloo and a Ph.D. degree in 2005 from the University of Pittsburgh, where he worked under the direction of Prof. Peter Wipf. After carrying out postdoctoral research in the laboratory of Prof. Erick M. Carreira at ETH Zürich, Switzerland, he joined the Department of Chemistry at Boston University in 2007 as Assistant Professor and co-Principal Investigator in the Center for Chemical Methodology and Library Development (CMLD-BU). He was granted tenure and promoted to Associate Professor in February 2013. As of July 2013, he has been Associate Professor at the University of Michigan, Ann Arbor, where his research group focuses on catalysis, natural product synthesis, and continuous flow chemistry.

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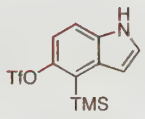

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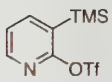

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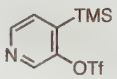

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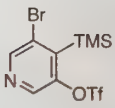

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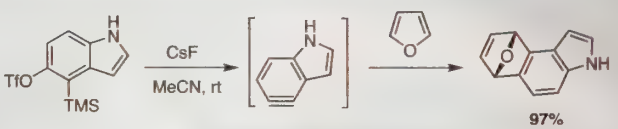

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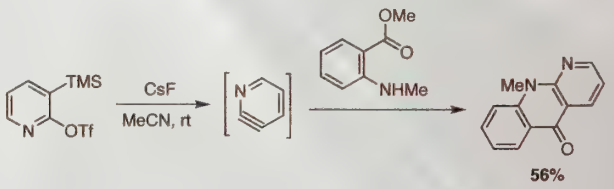

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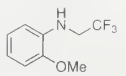

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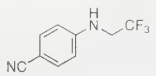

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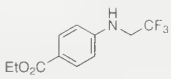

L512710

L512699	2-Methoxy-*N*-(2,2,2-trifluoroethyl)aniline	1 g
L512702	4-[*N*-(2,2,2-Trifluoroethyl)amino]benzonitrile	250 mg
L512710	4-Ethoxycarbonyl-*N*-(2,2,2-trifluoroethyl)aniline	1 g

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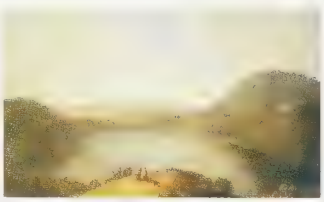

Detail from ***Lake Albano*** Photo courtesy National Gallery of Art, Washington DC

Lake Albano (oil on canvas, 121.9 x 170.4 cm) was completed in 1762 by Richard Wilson (1712/1714–1782). Born and raised in Wales, Wilson left for London at about age 15 to study portraiture under Thomas Wright. After about six years of training, he struck out on his own as a portraitist for almost two decades, but without attaining the recognition and financial success he had hoped for. In 1752, he made a trip to Italy that proved to be a turning point in his career as an artist. In Rome, he came to admire and was heavily influenced by the works of celebrated landscape painters, such as Claude Lorrain and Gaspard Dughet, who had lived and worked in the city a century earlier. In 1757 or 1758, he returned to Britain, where he devoted himself to painting primarily Welsh and Italian (often idealized) sceneries and to training a new generation of artists. The fame and success that eluded him as a portrait artist he attained as a landscape painter. Considered by many to be a pioneer of British landscape painting, Wilson has been an acknowledged strong influence on later British landscapists, in particular John Constable and Joseph Turner.

Lake Albano* embodies many of the elements that characterize Wilson's landscapes: small human figures; a body of water; a building or two, often in the middle ground of the painting; bright and generally clear skies; and delicate trees and foliage, often more prominent in the foreground. His landscapes, whether actual or idealized, depict charming and serene scenes, with human and animal figures inserted to give depth and scale but not distract from the beauty or majesty of the surroundings. While his landscapes tend to capture the general appearances of nature, his rendering of light and distance validate his keen and delicate observations of the natural world.

This painting is part of the Paul Mellon Collection at the National Gallery of Art, Washington, DC.

** Actual Lake Albano was a favorite setting for a number of landscape artists of the 18th and 19th centuries. To find out who else has painted it, visit* ***Aldrich.com/acta472***

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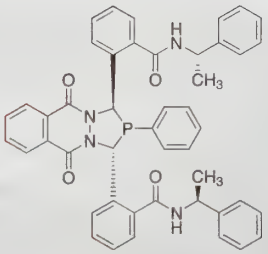
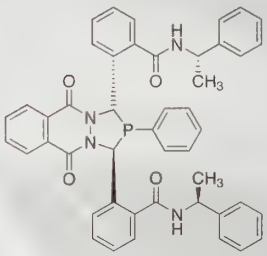


685859
(R,R,S)-DiazaPhos-PPE



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Hongchao Zheng was born in Heilongjiang, People's Republic of China. He received his B.S. degree in chemistry in 2001 and his M.Sc. degree in 2005 from Tsinghua University. After immigrating to Canada, Zheng earned a second M.Sc. degree in 2007 from McMaster University (Canada), where he worked under the guidance of Prof. Graham A. McGibbon. In the same year, he joined Professor Dennis Hall's group at the University of Alberta (Canada) to pursue his Ph.D. research in the field of boronic acid catalysis. He obtained his Ph.D. degree in 2012, and is currently conducting research in the field of gold catalysis as a postdoctoral associate in the laboratory of Professor Michel R. Gagné at the University of North Carolina at Chapel Hill (USA).

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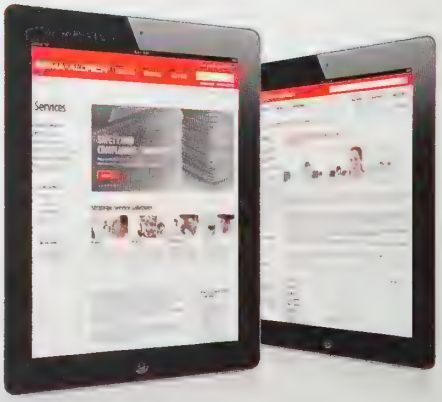

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ABOUT OUR COVER

Detail from ***Wivenhoe Park, Essex*** Photo courtesy National Gallery of Art, Washington, DC

A self-sustaining country estate*—what a fitting subject for the cover of our *Acta* issue that is dedicated to the topic of Green Chemistry and sustainability in chemical synthesis! ***Wivenhoe Park, Essex*** (oil on canvas, 56.1 × 101.2 cm) was painted in 1816 by John Constable (1776–1837), one of the great British landscapists of the 19th century, who is credited with elevating the status of this genre. Constable's interest in painting started early, but faced initial disapproval from his family; nevertheless, he was able to eventually enroll at London's Royal Academy of Art, where he received his formal training. While he never traveled abroad, he had the opportunity to study the works of earlier Dutch and French landscapists. He struggled in his early years to get recognition from the British art establishment, which he did not receive until he was into his forties. His artistic influence was greatest after his death and outside of England, particularly in France.

Constable's delight in, and profound connection to, nature is obvious in his many paintings of the countryside of his native Suffolk and other counties in southeast and southwest England. Nowhere is this more apparent than in this painting with its almost photographic quality. Here, Constable aims to capture on canvas a fleeting moment in the life of this idyllic setting and to convey to the viewer the same sensation of balance and harmony between man and nature that it evoked in him. The precise and crisp brushwork, attention to detail, and the use of billowing, brightly lit clouds to communicate movement, are characteristic of Constable's style.

This painting is part of the Widener Collection at the National Gallery of Art, Washington, DC.

** Wivenhoe Park was a working, self-sustaining country estate when Constable painted it. Can you identify some of the elements in the painting that indicate this sustainability? To find out, visit* ***Aldrich.com/acta481***

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Where We Should Focus Green Chemistry Efforts

Insight from the Co-Author of the 12 Principles of Green Chemistry

John C. Warner
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I am often asked to identify what I feel are the most important technologies that need to be improved from a Green Chemistry perspective. I am sure that I am not alone in receiving this type of question. One can understand why this question is so prevalent. It is certainly no secret that today's funding resources for scientific research are scarce. It makes sense to want to make progress in a fewer number of focused areas, rather than be spread too thin making imperceptible headway across too many pathways. It is logical to want to identify the technologies that have the most negative impact on human health and the environment, and cross-reference them with the most promising early-stage ideas. In so doing, the assumption follows that these early successes will provide confidence and momentum to expand and take on more difficult challenges.

My reaction to this question is to become quite uncomfortable: who am I to be so presumptuous as to pick what is most important? In choosing the focus areas, should we identify classes of materials: phthalates, brominated flame retardants, parabens, or plastics? Perhaps we should identify negative impacts: endocrine disruption, global climate change, carcinogenesis, or fossil fuel consumption? Maybe we should focus on areas of research: catalysis, solvents, nanotechnology, or feedstock? It seems like we need help in every area. But there isn't really any "one size fits all" winner. I would imagine different industry sectors have different top priority needs. What the petroleum industry needs is probably different from what the pharmaceutical industry needs; and people working on the front lines of patient care at a cancer hospital will likely see different needs than farmers working in the fields of a vegetable farm.

And then there is the question of how innovation should be "caused to happen" in any given area once it is selected. I often say that Green Chemistry has three long-term requirements: (i) It must have less impact on human health and the environment than some incumbent technology. But this is not enough. (ii) It also must perform better than the incumbent technology in order to be successful in replacing it. No one is going to use a cleaner that doesn't clean, just because it is greener. (iii) It also must have appropriate costs. Society has not demonstrated an overwhelming willingness to pay too much of a premium for a green technology. Reflecting upon this, Green Chemistry really provides a "holy grail" of sorts: better performance, better cost, and "Oh, by the way… it is better for human health and the environment." Given these criteria, what market barrier exists for adopting a greener product save its invention in the first place?

So the question then becomes, how does identifying a focus area that "needs improvement" catalyze innovation? How do scientists learn how to "make better products"? The United States Environmental Protection Agency has given out 5 Presidential Green Chemistry Challenge awards every year since 1996. Other international organizations have various award programs as well. Exemplifying and disseminating case studies of successful discoveries and implementations of Green Chemistry is critical. But is it enough? Does listening to a symphony teach someone to play a musical instrument? Does watching the Boston Marathon train someone how to run 26.2 miles? While illustrative examples are important, something deeper is necessary.

We really need to get at the roots of how we train chemists in the first place. We need to reflect upon the words and semantics we use in our scientific "disciplines". We have a body of knowledge called "organic chemistry". We have another body of knowledge called "physical chemistry". There is "analytical chemistry", "inorganic chemistry", and several other subdisciplines. But, it is important to realize that these subdisciplines are merely intellectual constructs. They allow us to apply the reductionist approach while learning and growing the body of knowledge. We place boundaries on a given subdiscipline for bureaucratic reasons: in order to define the scope of a journal, the syllabus of a class, or the table of contents of a textbook. But, at the end of the day, there really is no such thing as an "organic chemist". One cannot possibly function in the world of chemistry doing "only" organic chemistry. Organic chemists function simultaneously as analytical, physical, theoretical, and other types of chemist. They choose to identify organic chemistry as their "specialty"; but, in no way could they restrict themselves to doing "only" organic chemistry. All of the other subdisciplines work in the same way. It is an illusion to believe that any of these subdisciplines have any independent reality of their own. In my opinion, Green Chemistry should work the same way; and the field is growing as such. There now are many journals, classes, and textbooks in Green Chemistry. The only problem is that Green Chemistry is still seen as something of an "elective" in chemistry. Can you imagine having a student graduate with a degree in chemistry after only being shown "illustrative examples" of physical chemistry? It is inconceivable that a chemistry degree program at a university suggest that, instead of having several semester-long classes in organic chemistry, the initiated should look at examples of papers in the *Journal of Organic Chemistry*. While these hypothetical examples are laughable, we are still at a point in our evolution where Green Chemistry is treated as such. This must change.

Of course, there are moral and ethical issues surrounding this. It is an inescapable truth that the field of chemistry has a certain obligation to society to make sure that future practitioners learn some fundamental principles regarding the making of materials and products that have reduced impact on human health and the environment. But, this is also about innovation and economic competitiveness. Chemists need to treat Green Chemistry as simply a part of the fundamentals of chemistry—nothing more, and nothing less.

This is where the Green Chemistry Commitment program of the nonprofit organization Beyond Benign (www.beyondbenign.org) comes into play. Obviously, it is difficult to introduce Green Chemistry into the basic chemistry curriculum. If no one has had these classes before, who is going to teach them? Beyond Benign seeks to create a community of chemistry departments to share best practices for what uniquely works for them. If a chemistry department wants to develop a standalone class in Green Chemistry, it should do so. If a department wants to integrate it across various existing classes, it should do so. If a department wants to address Green Chemistry in the labs, it should do so. By sharing best practices, the community can grow and move from illustrative examples to basic pedagogy.

So when I am asked to identify what I feel are the most important technologies that need to be improved from a Green Chemistry perspective, my answer is instantaneous: ***education***. Imagine a world where all chemists had fundamental training in how to design technologies that had reduced impact in human health and the environment. Instead of merely picking the technologies, materials, and endpoints that we need to improve upon, let's focus on how we train the scientists in the first place; and we can consequently improve ***all***.

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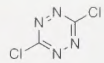

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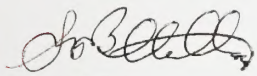

Scott Batcheller
Manager
Chemistry R&D and Product Management

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ABOUT OUR COVER

Detail from ***A Royal Party Admiring the Sunset atop the Hesselberg Mountain***. Photo courtesy National Gallery of Art, Washington, DC.

Johann Georg von Dillis (1759–1841), a German master painter of the late 18th and early 19th centuries, painted and signed ***A Royal Party Admiring the Sunset atop the Hesselberg Mountain*** in 1801. He received his first drawing lessons while attending the Gymnasium in Munich. He then studied art at the Munich Zeichnungsakademie under the guidance of F. I. Oefele and J. J. Dorner the Elder. His art career began ca. 1786 and, until his retirement in the late 1830s, consisted of official appointments by the courts of Maximilian I and Ludwig I, commissioned sketches and drawings, and a professorship of landscape painting at the Munich Royal Academy of Fine Arts. He travelled frequently and widely throughout Europe on Bavarian State business, and it was during these travels that he became acquainted with, and influenced by, the work of P.-H. de Valenciennes, S. Denis, J.-J.-X. Bidauld, W. Allston, and, especially, J. M. W. Turner. His artwork influenced such artists as C. E. F. Blechen, and his gallery work had a profound influence on the world of art in Germany, especially in Bavaria.

Von Dillis excelled at landscapes, and was instrumental in moving the genre from the classical tradition of idealized pastorals to a new, realistic form, whereby the artist draws from life, not only what he perceives with his eyes upon close examination of nature, but also what he feels within himself. This romantic approach to landscape painting values emotions, which are aroused nowhere better than in the countryside with its powerful pull on the artist, as this work demonstrates. Not only is the average person drawn to nature, but even sophisticated, urban dwellers such as this elegantly attired group of royals* and their aides can appreciate the wonders of nature. This composition (watercolor, gouache, and pen and gray ink over graphite on laid paper) measures 37 x 42.7 cm and is von Dillis's best-known work. With its crisp colors, decidedly finished look, and the artist's meticulous attention to detail, it clearly highlights von Dillis's complete immersion in the work.

This painting is part of the Wolfgang Ratjen Collection at the National Gallery of Art, Washington, DC.

** Who could the "royals" depicted in this painting be? To help solve the mystery, visit* ***Aldrich.com/acta482***

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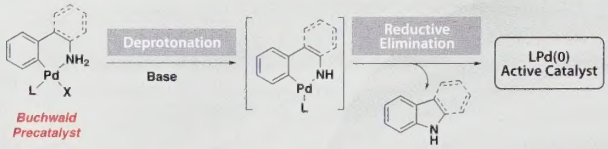

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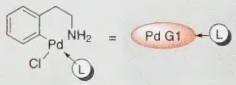

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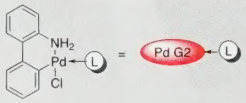

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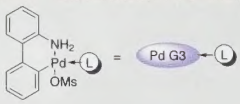

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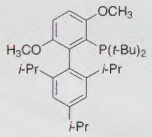

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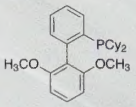

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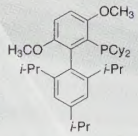

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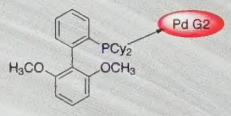

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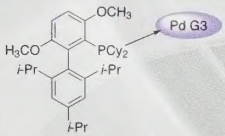

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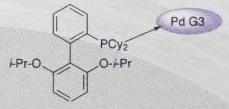

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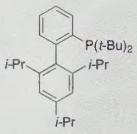

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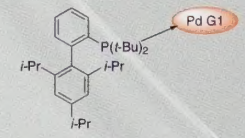

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Harry Eastman was born in 1992 in Portsmouth, England, U.K. He studied chemistry at the University of Surrey, working for a year with Professor A. M. P. Koskinen at Aalto University, and completed an M.Sci. degree in Chemistry program in 2014. He began his Ph.D. studies with Dr. Allan Watson in 2014, and is currently focused on the development of new methods for organic synthesis.

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Allan J. B. Watson obtained his M.Sci. degree in 2004 from the University of Strathclyde and his Ph.D. degree (with Professor W. J. Kerr) in 2008. This was followed by postdoctoral work with Professor D. W. C. MacMillan at Princeton University, and an industrial postdoctoral research position at GlaxoSmithKline. He returned to a lecturer position at the University of Strathclyde in 2011. His research interests are synthetic methodology, boron chemistry, medicinal chemistry, and sustainable synthesis.

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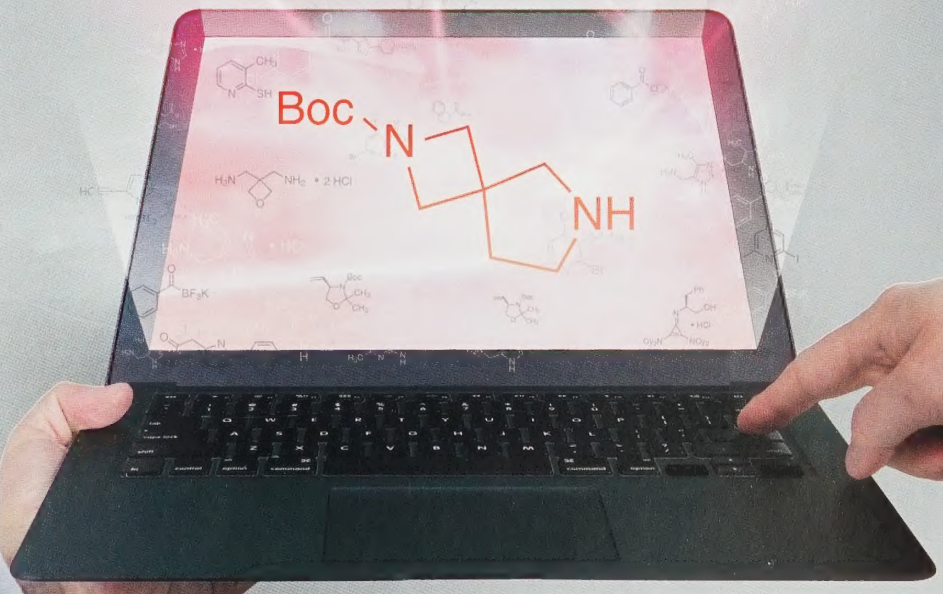

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