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April 12, 2000

Dear Isabel and Alfred Bader,

As you know, I have started my Ph.D. program here at Harvard in summer 1998. Since then I have been working on discovery, development and application of a general catalyst for asymmetric Strecker reaction. Our work on the catalyst optimization and aldimine substrate scope (see: M. S. Sigman, P. Vachal, E. N. Jacobsen *Angew. Chem. Int. Ed.* **2000**, *39*, 1279.) as well as the first catalytic highly enantioselective Strecker reaction on ketoimines (see: P. Vachal, E. N. Jacobsen *Org. Lett.* **2000**, *2*, 867.) were recently published. I am attaching a copy of both papers since I want to keep you informed about the progress of my work that would never be possible without your generosity.

Thank you very much for your support again.

Petr Vachal

Enantioselective Catalytic Addition of HCN to Ketoimines. Catalytic Synthesis of Quaternary Amino Acids

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Enantioselective Catalytic Addition of HCN to Ketoimines. Catalytic Synthesis of Quaternary Amino Acids

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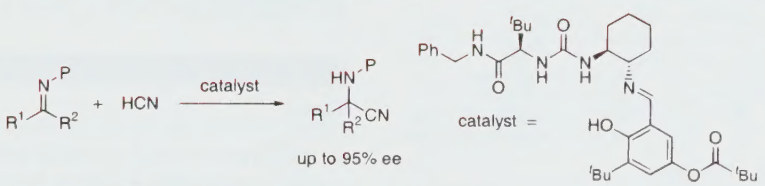
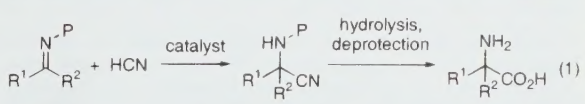
ABSTRACT



Highly enantioselective addition of HCN to ketoimines has been achieved for the first time using readily accessible and recyclable Schiff base catalysts. Essentially quantitative isolated yield and enantioselectivity of up to 95% ee was obtained. Furthermore, some of the Strecker adducts could be recrystallized in high recovery, yielding optically pure materials. Conversion of the α-aminonitrile adducts to the corresponding α-quaternary α-amino acids was effected in high yield by a formylation/hydrolysis sequence.

Compounds bearing α-quaternary α-amino acid units as structural components display a wide assortment of interesting biological properties.[1] For example, derivatives of α-methyl phenylglycine and its analogues have shown promising inhibitory activity toward metabotropic glutamate receptors,[2] platelet aggregation,[3] and proteases including trypsin and matrix metalloproteinases.[4] Interest in quaternary amino acids is fueled further by the fact that derivatives of these compounds exhibit unusual conformational constraints.[5] As a result, significant effort has been directed toward uncovering general and practical protocols for the preparation of optically pure quaternary amino acids. Most of the methods identified thus far rely on optically active starting materials or the use of stoichiometric chiral auxiliaries,[6] although successful catalytic approaches have been reported very recently.[7] In principle, a most attractive and versatile solution would be provided through a catalytic enantioselective addition of HCN across the C=N bond of ketoimines (eq 1). While considerable progress has been made



(1)

recently in the development of effective catalysts for the asymmetric hydrocyanation of aldimines,[8] there are no

(1) Enzyme–inhibitors, see, for example: (a) Saari, W. S.; Halczenko, W.; Cochran, D. W.; Dobrinska, M. R.; Vincek, W. C.; Titus, D. C.; Gaul, S. L.; Sweet, C. S. *J. Med. Chem.* **1984**, *27*, 713. (b) Fenteany, G.; Standeart, R. F.; Lane W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726. Antibiotic structures, see, for example: (c) Hanessian S.; Haskell T. H. *Tetrahedron Lett.* **1964**, 2451. Peptidomimetics, see, for example: (d) Jung, G.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367. (e) Veber, D. F.; Freidinger R. M. *Trends Neurosci.* **1995**, *8*, 392.

(2) (a) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120. (b) Sekiyama, N.; Hayashi, Y. Nakanishi, S.; Jane, D. E.; Tse, H.-W.; Birse, E. F.; Watkins, J. C. *Br. J. Pharmacol.* **1996**, *117*, 1493. (c) Ma, D.; Tian, H. *Tetrahedron: Asymmetry* **1996**, *6*, 1567.

(3) Stilz, H. U.; Jablonka, B.; Just, M.; Knolle, J.; Paulus, E. F.; Zoller, G. *J. Med. Chem.* **1996**, *39*, 2118.

(4) Hirayama, R.; Yamamoto, M.; Tsukida, T.; Matsuo, K.; Obata, Y.; Sakamoto, F.; Ikeda, S. *Bioorg. Med. Chem.* **1997**, *5*, 765.

(5) Miyashita, K.; Miyabe, H.; Tai, K.; Kurozumi, C.; Iwaki, H.; Imanishi, T. *Tetrahedron* **1999**, *55*, 12109 and references therein.

(6) (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (c) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, 1337. (d) Moody, C. J.; Gallagher, P. T.; Lightfoot, A. P.; Slawin, A. M. Z. *J. Org. Chem.* **1999**, *64*, 4419.

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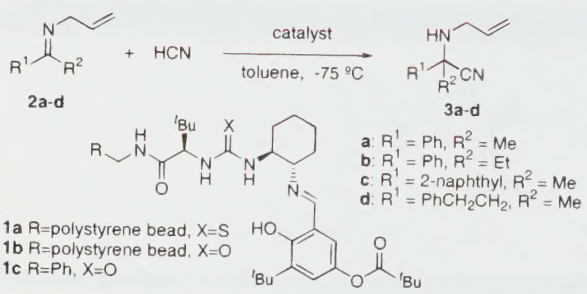
reported examples of enantioselective catalytic Strecker reactions involving ketoimines. We report here the first success in this area, and outline a new and practical method for the preparation of α-substituted amino acids and their derivatives. The approach is illustrated in the gram-scale synthesis of optically pure (>99.9% ee) α-methyl phenylglycine.

Resin-bound catalyst **1a** was discovered and optimized for the Strecker reaction of aldimines using a combinatorial parallel library approach.[8b,g] This catalyst displays remarkable substrate scope in the asymmetric hydrocyanation of aldimines,[8g] and we used it as a starting point for the evaluation of ketoimines using acetophenone-derived **2a**[9] as a model substrate. With 4 mol % of **1a** and 1.25 equiv of HCN[10] at −75 °C, complete conversion of imine **2a** occurred within 180 h and the Strecker adduct **3a** was obtained in high yield and 85% ee (Table 1, entry 1). The reactivity of

Table 1



entry	product	catalyst	t (h)	yield[a] (%)	ee[b] (%)
1	**3a**	**1a** (4 mol %)	180	98	85
2	**3a**	**1b** (4 mol %)	80	99	82
3	**3a**	**1c** (2 mol %)	30	97	85
4	**3b**	**1c** (2 mol %)	17	96	69
5	**3c**	**1c** (2 mol %)	65	97	89
6	**3d**	**1c** (2 mol %)	17	98	41

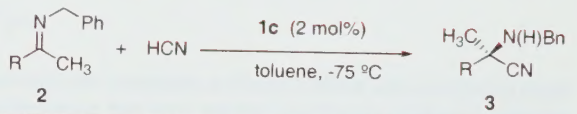
[a] Isolated yield of product determined to be >99% pure by HPLC analysis. [b] All ee's were determined by GC or HPLC chromatography using commercial chiral columns. See Supporting Information.

the catalyst was improved measurably by replacing the thiourea with a urea linkage. Under the same conditions as used with catalyst **1a**, urea **1b** catalyzed the formation of Strecker adduct **3a** within less than half the time yet with similar enantioselectivity (entry 2). The soluble analogue **1c** displayed higher reactivity yet, allowing complete reaction within 30 h using only 2 mol % catalyst (entry 3).

A series of ketoimines were evaluated using catalyst **1c**, and moderate-to-high enantioselectivity was obtained in the formation of the corresponding Strecker adducts (Table 1, entries 3−6). The products (**3a−d**) were found to be stable under neutral conditions, but they underwent rapid decomposition under either acidic or basic conditions via a retro-Strecker reaction. Attempts to protect the amino group to prevent the decomposition pathway were only partially successful. Even highly reactive electrophiles such as trifluoroacetic anhydride provided only moderate yields (40−50%) of the corresponding amide.

Replacement of the *N*-allyl protective group with an *N*-benzyl group in the imine substrates led to more stable Strecker adducts and slightly increased enantioselectivity as well. Under identical reaction conditions to those described above (2 mol % **1c**, 1.25 equiv of HCN, −75 °C) good reactivity and 90% ee was achieved with acetophenone-derived imine **2e** (Table 2, entry 1). Since our goal was a practical protocol for preparation of α-alkyl amino acids, it was critical to demonstrate that the *N*-benzyl group could be removed while still preserving the quaternary center, which is also a benzylic amine. Indeed, selective debenzy-

Table 2



entry	product	R	t (h)	yield[a] (%)	ee[c] (%)
1	**3e**	C_6H_5	24	97	90
2	**3f**	p-$CH_3C_6H_4$	80	98[b]	91
3	**3g**	p-BrC_6H_4	80	quant	93
				(76)	(>99.9)
4	**3h**	p-$NO_2C_6H_4$	80	quant	93
				(79)	(>99.9)
5	**3i**	p-$CH_3OC_6H_4$	60	98	88
6	**3j**	p-$CF_3C_6H_4$	65	quant	95
				(75)	(>99.9)
7	**3k**	m-BrC_6H_4	60	97[b]	91
8	**3l**	o-BrC_6H_4	90	45	42
9	**3m**	$(CH_3)_3C$	15	98	70

[a] Isolated yield, >99% pure by HPLC analysis unless noted otherwise; yields in parentheses were obtained after recrystallization from hexanes. [b] >97% pure by HPLC analysis. [c] All ee's were determined by GC or HPLC chromatography using commercial chiral columns (see Supporting Information); ee's in parentheses were obtained after recrystallization from hexanes.

(7) (a) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (b) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532. (c) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Vyskocil, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1723. (d) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236.

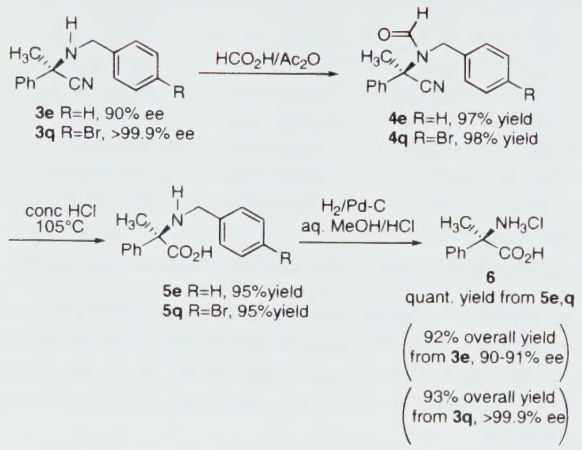
(8) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Sigman, M. S.: Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (d) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew Chem. Int. Ed. Eng.* **1998**, *37*, 3186. (e) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (f) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (g) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.*, in press. (h) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. Submitted for publication.

(9) All ketoimines were prepared by reaction of the appropriate ketone and amine in dichloromethane in the presence of 3 Å sieves. Full experimental details are provided as Supporting Information.

(10) Solutions of hydrogen cyanide were generated prior to the Strecker reaction by combination of equimolar amounts of TMSCN and methanol in toluene at 5 °C for 2 h.

lation[11] of *N*-benzyl α-methyl phenylglycine (**5e**) could be effected under mild conditions (10% Pd−C and 1 atm H_2, 1.7 N HCl in MeOH/H_2O) to yield α-methyl phenylglycine (**6**) in quantitative yield as its hydrochloride salt (Scheme 1).

Scheme 1

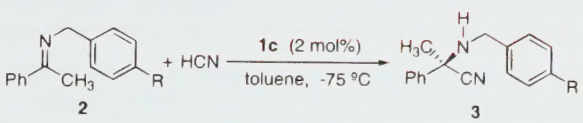


Catalyst **1c** proved effective for the asymmetric hydrocyanation of a variety of *N*-benzyl ketoimines (Table 2). Strecker adducts **3e**−**k** were isolated in essentially quantitative yield by filtration of the crude product mixtures through a short silica gel column. High enantioselectivity was obtained with imines bearing both electron-withdrawing (e.g., **2h** and **2j**) and electron-donating aromatic substituents (e.g., **2f** and **2i**). While the *m*-bromo-subustituted derivative **2k** underwent hydrocyanation in excellent yield and 91% ee, the *ortho*-substituted analogue **2l** proved to be a problematic substrate. The Strecker adduct **3l** was found to undergo complete decomposition within several hours at room temperature and could only be isolated in marginal yield and enantioselectivity (entry 8). In contrast, the aliphatic ketoimine substrate **2m** (R = *t*Bu) underwent clean reaction, and adduct **3m** was isolated in 70% ee. Some of the Strecker adducts (**3g**, **3h**, and **3j**) were isolated as crystalline compounds, and recrystallization from hexanes afforded optically pure (>99.9% ee) materials in high recovery (75−79% overall isolated yield). Furthermore, since catalyst **1c** is soluble in hexanes, no chromatographic purification was necessary as the catalyst remained dissolved in the mother liquors.

Even though *N*-benzyl-protected Strecker adducts **3e**−**m** are more stable than their *N*-allyl analogues, efforts to effect the direct hydrolysis of the nitrile functionality under acidic or basic conditions were still unsuccessful as a result of a competing retro-Strecker pathway. It was, however, possible to protect **3e** as its formamide derivative **4e** using in situ generated acetic formic anhydride under solvent free conditions (Scheme 1).[12] The quaternary center in **4e** was stable toward strongly acidic conditions, and sequential hydrolysis of the nitrile and formamide groups could be effected using concentrated hydrochloric acid to yield amino acid **5e** in nearly quantitative yield. Debenzylation of **5e** was achieved as described above to afford α-methyl phenylglycine (**6**) in 90−91% ee. Unfortunately, it was not possible to enhance the optical purity of **6** nor of any of its precursors by recrystallization.

Examination of a series of benzyl derivatives as *N*-protective groups for the Strecker reaction revealed generally little influence of substituents on enantioselectivity (Table 3), and in the case of *p*-bromobenzyl derivative **3q**, the adduct was isolable as a crystalline compound. Recrystallization of the crude product from hexanes yielded optically pure (>99.9% ee) material in 75% overall recovery. Optically pure **3q** was converted to α-methyl phenylglycine (**6**) in 93% overall yield and >99.9% ee (70% overall yield from imine **2q**) following the protocol in Scheme 1.[13]

Table 3



2 **3**

entry	product	R	*t* (h)	yield[a] (%)	ee[c] (%)
1	**3n**	OCH_3	36	97	93
2	**3o**	CF_3	50	95	92
3	**3p**	$(CH_3)_3C$	30	95	89
4	**3q**	Br	40	95 (75)	92 (>99.9)

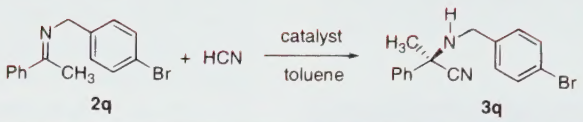
The asymmetric hydrocyanation of **2q** can be carried out successfully under a variety of experimental conditions. For example, elevation of the temperature from −75 °C to +5 °C led to a decrease in the requisite reaction time from 40 h to 8 min, and the adduct **3q** was still obtained in essentially quantitative yield and in 87% ee (Table 4, entries 1 and 2). This material could be recrystallized to optical purity in 72% overall yield. Furthermore, catalyst **1c** was easily recovered by chromatography in 97% yield, and reused in the Strecker reaction with results identical to those obtained with freshly prepared catalyst (entry 3). As noted above, the resin-bound catalyst (**1b**) is substantially less reactive but it offers distinctive operational advantages because it is more easily separated and recycled. With 10 mol % **1b** at −40 °C, the hydrocyanation of **2q** required 6 h to reach completion, and the Strecker adduct was isolated in quantitative yield and 90% ee simply by catalyst removal by filtration followed

(11) Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, *22*, 3748.

(12) Edwards, R. *J. Am. Chem. Soc.* **1942**, *64*, 1583.

(13) The absolute stereochemistry of **6** was assigned by comparison of its optical rotation with literature values: (a) Terashima, S.; Yamada, S. I. *Chem. Pharm. Bull.* **1968**, *15*, 1953. (b) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schoenholzer, P.; Spiegler, C.; Mueller, K. *Helv. Chim. Acta* **1995**, *78*, 563.

Table 4



2q 3q

entry	catalyst	$[\mathbf{2q}]_{initial}$ (M)	T (°C)	t	yield[a] (%)	ee[b] (%)
1	**1c** (2 mol %)	0.1	−75	40 h	97 (75)	92 (>99.9)
2	**1c** (2 mol %)	0.5	+5	8 min	95 (72)	87 (>99.9)
3	**1c** (recycled, 2 mol %)	0.5	+5	8 min	96 (73)	88 (>99.9)
4	**1c** (0.1 mol %)	0.5	+5	2.5 h	96 (70, 53[c])	69 (91, >99.9[c])
5	**1b** (6 mol %)	0.1	−70	120 h	quant. (76)	91 (>99.9)
6	**1b** (10 mol %)	0.3	−40	6 h	quant. (77)	90 (>99.9)
7	**1b** (1st recyle, 10 mol %)	0.3	−40	6 h	quant. (76)	90 (>99.9)
8	**1b** (2nd recyle, 10 mol %)	0.3	−40	6 h	quant. (77)	91 (>99.9)

[a,b] See Table 3. [c] Overall yield and ee obtained after second recrystallization from hexanes.

by solvent evaporation. Recrystallization from hexanes provided **3q** in 77% overall yield and >99.9% ee (entry 6). Recycling of **1b** had no deleterious effect on reactivity or enantioselectivity (entries 7 and 8).

Given that Schiff bases **1a**−**c** were selected from parallel libraries for the enantioselective Strecker reaction of one specific imine substrate (*N*-benzylpivalaldimine),[8g] it is striking that these catalysts in fact promote the hydrocyanation of an extraordinary range of imines with high enantioselectivity. Despite their relatively small size (FW of **1c** = 621) and the broad substrate scope they display, these Strecker catalysts have interesting features reminiscent of enzymes. For instance, they operate in the absence of a metal; they appear to "fold" into well-defined, rigid structures; and their reactions obey clean Michaelis−Menten kinetics.[14] The addition of ketoimines to the list of useful substrates is significant, as it allows a practical approach to a variety of useful α-quaternary amine derivatives in enantiopure form. We hope that this finding may enable even broader application of quaternary amino acids and related building blocks in both drug discovery and fundamental research.

(14) Zondlo, N. J.; Sigman, M. S.; Jacobsen, E. N. Manuscript in preparation.

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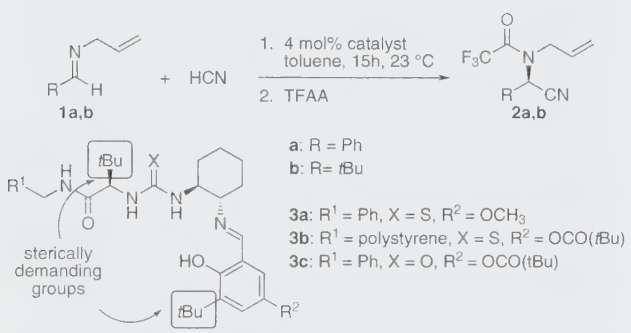
Supporting Information Available: Complete experimental procedures, analytical data, and chiral chromatographic analyses of hydrocyanation products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005636+

A General Catalyst for the Asymmetric Strecker Reaction**

Matthew S. Sigman, Petr Vachal, and Eric N. Jacobsen*

α-Amino acid derivatives are broadly useful chiral building blocks, with especially important applications in complex natural product and combinatorial syntheses. Substantial progress has been made toward the development of efficient methods for the preparation of these compounds, with a growing emphasis on the identification of enantioselective catalytic approaches with practical potential.[1, 2] One of the most attractive strategies amenable to asymmetric catalysis is the addition of hydrogen cyanide to imines (the Strecker reaction, Scheme 1),[3] and promising enantioselective variants of this reaction have been uncovered very recently.[4] Here we report new catalysts for the Strecker reaction that display high enantioselectivity and broad substrate scope for both aromatic and aliphatic imines. These catalysts can be used either in solution or covalently linked to polystyrene resin, with the latter retaining full reactivity and enantioselectivity after repeated recycling.



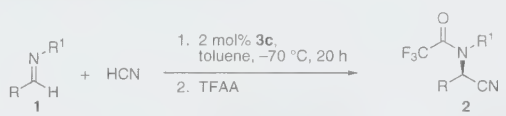
Scheme 1. Asymmetric Strecker reaction with catalysts **3**.

The discovery and optimization of catalysts for the asymmetric Strecker reaction was approached by screening parallel synthetic libraries of resin-bound catalyst candidates and validating the most enantioselective library members by the preparation of soluble analogues.[5] In previous work,[4c] simple Schiff base libraries with the general structure shown in Scheme 1 were identified as effective catalysts for the asymmetric hydrocyanation of aromatic imine **1a**. The key elements responsible for high enantioselectivity were the presence of bulky substituents at both the amino acid position and at the 3-position of the salicylimine moiety, with **3a** emerging from the preliminary screens as an enantioselective catalyst with promising generality (Scheme 1). On the basis of these encouraging results, we have constructed a new optimization library of 70 compounds incorporating seven amino acids with large α-substituents and ten new salicylaldehyde derivatives. Each library member was evaluated for enantioselectivity in the Strecker reaction of aliphatic imine **1b** at 23 °C, and the 5-pivaloyl-substituted Schiff base **3b** proved to be the superior catalyst.[6, 7]

A soluble analogue of **3b** was prepared (**3c**) and evaluated.[8] At −78 °C, 2 mol% of **3c** catalyzed the formation of the Strecker adduct **2b** in 75% yield (isolated product) and 95% *ee*. This constitutes a substantial improvement over results obtained with catalyst **3a** (85% *ee*).[4c] Benzaldimine **1a** also underwent hydrocyanation with improved enantioselectivity (95% *ee* with catalyst **3c** vs. 91% *ee* with **3a**).

The scope of the asymmetric Strecker reaction catalyzed by **3c** proved to be remarkably broad (Table 1). Aryl imines

Table 1. Asymmetric catalytic Strecker reactions with catalyst **3c**



Entry		Imine **1** R	R'	Yield [%]	*ee* [%][b]
1	**a**	C_6H_5	allyl	74	95
2	**b**	*tert*-butyl	allyl	75	95 (91)
3	**c**	*p*-$OCH_3C_6H_4$	allyl	98	95
4	**d**	*m*-$OCH_3C_6H_4$	allyl	99	93
5	**e**	*o*-$OCH_3C_6H_4$	allyl	93	77
6	**f**	*p*-$CH_3C_6H_4$	allyl	99	95
7	**g**	*m*-$CH_3C_6H_4$	allyl	97	96
8	**h**	*o*-$CH_3C_6H_4$	allyl	96	95
9	**i**	*p*-BrC_6H_4	allyl	89	89
10	**j**	*m*-BrC_6H_4	allyl	87	90
11	**k**	*o*-BrC_6H_4	allyl	88[b]	95
12	**l**	*p*-$(CH_3)_3CC_6H_4$	allyl	89	97
13	**m**	*tert*-butyl	benzyl	88	96 (93)
14	**n**	cyclohexyl	benzyl	85	87
15	**o**	cyclohexyl	allyl	88	86
16	**p**	1-cyclohexenyl	benzyl	90	91 (87)
17	**q**	$(CH_3)_3CCH_2$	benzyl	85	90 (87)
18	**r**	$CH_3(CH_2)_4$	benzyl	69	78
19	**s**	$(CH_3)_2CH$	benzyl	74	79
20	**t**	cyclopropyl	benzyl	89	91
21	**u**	cyclooctyl	allyl	65	90

[a] Values of *ee* in parentheses were obtained with resin-bound catalyst **3b**
[b] Reaction time was 36 h.

(entries 1, 3–12) are excellent substrates, undergoing hydrocyanation in generally high enantioselectivities and yields. The bromo-substituted products **2i–k** are particularly versatile intermediates, as these can be elaborated further by using cross-coupling or Heck reactions, thereby providing access to a wide variety of arylglycine derivatives. While all of the aryl imine substrates **1a**, **c–l** exist predominantly or exclusively as the *E* isomers, this does not appear to be a requirement for high enantioselectivity. The cyclic *Z*-imine 3,4-dihydroisoquinoline (**1v**) underwent hydrocyanation with **3c** in 91% *ee*,

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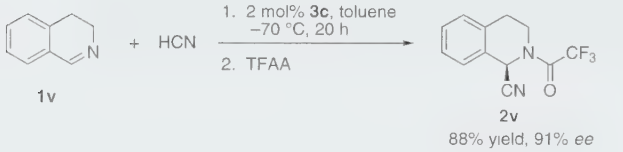
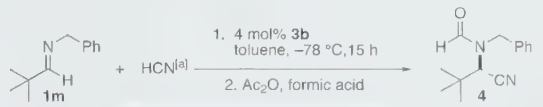
with the same sense of stereoinduction with respect to the benzylic center as the acyclic *E*-imines [Eq. (1)].[9]

Catalyst **3c** also proved very effective for the hydrocyanation of a variety of aliphatic substrates (Table 1, entries 2, 13–20). Either *N*-benzyl or allyl imines could be used with no significant differences in the results obtained (entries 2 and 13, and 14 and 15). The size of the aliphatic group appears to dictate the level of enantioselectivity with these substrates, with the largest groups affording the highest *ee* values (e.g., entry 12). Given the results described above for 3,4-dihydroisoquinoline (**1v**), it appears unlikely that the lower *ee* values obtained with unhindered imines are due to the increased amount of *Z* isomer present in these substrates.



(1)

Table 2. Preparative Strecker reactions with resin-bound catalyst **3b**.[a]

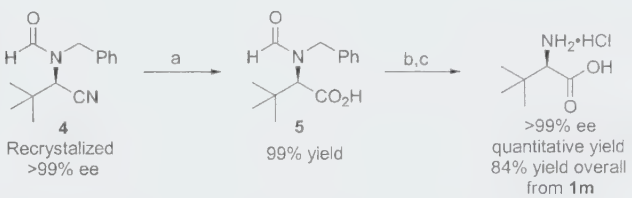


Cycle[b]	Yield [%][c]	*ee* [%]
1	97	92
2	98	93
3	98	93
4	97	93
5	97	92
6	96	93
7	98	93
8	97	93
9	98	93
10	98	93

[a] Either HCN or equimolar quantities of TMSCN (TMS = trimethylsilyl) and MeOH were employed with identical results (1.3 equiv). The scale of the reaction was 1.07 g (6.1 mmol) in all cases. [b] Catalyst was removed by filtration from the previous reaction mixture and rinsed with toluene prior to reuse. [c] Yield of isolated **2** bearing no detectable impurities as determined by ^{1}H NMR spectroscopy

In general, the soluble catalyst **3c** effected hydrocyanation of imines with 2–4% higher *ee* values than the resin-bound analogue **3b** (Table 1, entries 2 and 13, 16 and 17). On the other hand, while all of the reactions summarized in Table 1 led to quantitative product formation with no detectable byproducts, some losses were incurred upon product isolation as a result of the need to separate the catalyst chromatographically. In that respect, the polymer supported catalyst **3b**—which is easily removed from the reaction mixtures by simple filtration—holds practical advantages compared to the solution-phase analogue, despite the slightly lower enantioselectivity it displays. To assess the practical potential of the resin-bound catalyst, the Strecker reaction of pivalaldimine **1m** was examined under preparative conditions. Clean hydrocyanation of **1m** was observed with only a slight reduction in enantioselectivity (96% to 93% *ee*) by using **3b** (Table 1, entry 13). The product was isolated in nearly quantitative yield after catalyst removal by filtration, and no loss of catalyst reactivity or product enantioselectivity was observed after ten catalyst recycles (Table 2).

As noted above, one of the most important applications of the asymmetric Strecker reaction is toward the synthesis of enantiomerically enriched amino acids. We selected D-*tert*-leucine as a target because of its considerable utility as a chiral building block and its high current commercial cost (>$100 g^{-1}). Attempts to hydrolyze the amino nitrile product of the Strecker reaction of **1m** required fairly harsh conditions (concentrated acid, >90 C) and resulted in considerable decomposition. This problem was circumvented by first protecting the amino nitrile as the formamide **4**, and this allowed facile recrystallization to give enantiomerically pure material in 85% overall yield. Complete and clean hydrolysis of **4** and deformylation was accomplished in one pot (Scheme 2) by using concentrated HCl at 70 °C, although some racemization was observed (99% *ee* to 93% *ee*). In contrast, selective hydrolysis of the nitrile to the acid **5** with concentrated sulfuric acid at 45 °C for 20 h occurs with no



Scheme 2. Hydrolysis and deformylation of **4**. a) 65% (w/v) H_2SO_4, 45 C, 20 h; b) HCl (conc.), 70 C, 12 h; c) H_2, Pd/C, MeOH

racemization. Deformylation was then effected in quantitative yield by using concentrated HCl to yield the benzyl-protected amino acid; removal of the benzyl group with Pd/C under 1 atm of H_2 gas afforded *tert*-leucine in >99% *ee* and 84% overall yield from imine **1m**.

In summary, the asymmetric Strecker reaction catalyzed by nonmetal catalysts **3b** and **3c** provides direct access to a diverse range of unnatural aliphatic and aromatic substituted amino acid precursors in high enantiomeric excess. The catalysts are easy to prepare in solution or on solid phase. The use of the resin-bound catalyst **3b** allows Strecker product purification by simple filtration and solvent removal, and the catalyst can be reused indefinitely without loss of either activity or enantioselectivity. Preliminary kinetic experiments indicate that the reaction follows Michaelis–Menten kinetics consistent with reversible binding of imine followed by rate-limiting addition of HCN. Consistent with the notion that these catalysts are enzyme-like, all structural components of **3c** have been shown to be vital for both reactivity and enantioselectivity and thus appear to function cooperatively. Experiments to ascertain the precise mechanism of catalysis and the application of this catalyst class to other types of enantioselective reactions of imines and related electrophiles are currently under investigation.

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  0570-0833/00/3907-1280 $ 17.50+.50/0

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[6] Full details of the parallel library synthesis and evaluation are provided as Supporting Information.

[7] HCN was generated by the method of Ziegler. Alternatively, generation of HCN in situ by reaction of TMSCN and MeOH afforded identical results. K. Ziegler in *Organic Synth. Coll. Vol. 1* (Eds.: H. Gilman, A. H. Blatt), Wiley, New York, **1932**, p. 314. **Caution**: Hydrogen cyanide is a highly toxic and volatile compound that should be handled with extreme care to avoid inhalation.

[8] Whereas the thiourea derivatives proved slightly more enantioselective than the urea derivatives in the resin-bound catalysts, there was no significant difference between them in the solution analogues. On the other hand, the urea-containing catalyst **3c** proved easier to synthesize in solution than the thiourea analogue (see Supporting Information).

[9] The stereochemical assignment is based on comparison of CD spectra of **2v** with those of compounds **2f**, **g**, **i**, and **p** (see Supporting Information).

  0570-0833/00/3907-1281 $ 17.50+.50/0

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30. Juni 1994
Rec'd 8/29!

Lieber Alfred,

habe vielen Dank für Deine Briefe vom 25.07. und 12.08.1994.

Zunächst möchte ich Dir noch nachträglich herzlich zu Deinem 70. Geburtstag gratulieren und Dir weiterhin viel von Deiner bewundernswürdigen Energie und Spannkraft wünschen!

Nun zu Herrn Schiemenz. Ich kenne ihn aus meiner Zeit in Göttingen (1949 - 1957) und habe ihn später nur ein- oder höchstens zweimal kurz auf einer Tagung wiedergesehen. Obwohl wir nie näheren oder persönlichen Kontakt hatten, halte ich Herrn Schiemenz für jemanden, der nur sehr schwer von einer einmal gefaßten Meinung ablassen wird. D. h., Du kannst ihm den Brief von Herrn Dr. Rosner zuschicken - und Herr Schiemenz wird Dir sicher auch höflich antworten - aber er wird seinen Standpunkt **nicht** ändern. Deshalb nehme ich an, daß es auf der Loschmidt-Tagung im Juni 1995 zu einer lebhaften Kontroverse zwischen Dir und Herrn Schiemenz kommen wird.

Ich war Ende Juni kurz auf der Gordon Conference on Stereochemistry in Newport, R. I., und hatte dort lebhafte Diskussionen über R. B. W. mit E. Eliel und J. Whitesell, der wie ich einige Jahre im Woodward Institute in Basel gearbeitet hat. J. Whitesell wird möglicherweise meine Anregung aufnehmen, alle die "Erinnerungen" ehemaliger Mitarbeiter und Kollegen an R. B. W. in einem Buch zusammenzufassen und hat eine Kopie seines Briefes an mich an Crystal Woodward geschickt. (Deine persönlichen Erinnerungen an R. B. W. wären sicher auch sehr interessant!)

Da meine Zeit hier bei Schering Ende Juni 1995 ausläuft, arbeite ich fleißig, um noch einige Projekte abzuschließen und zu publizieren.

Mit freundlichen Grüßen
auch an Deine Gattin

Herzlich