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

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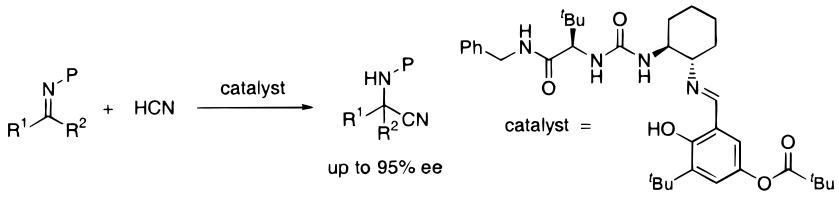
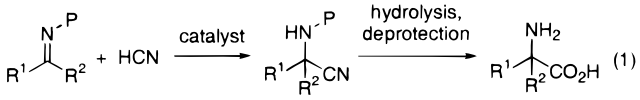
ABSTRACT



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.

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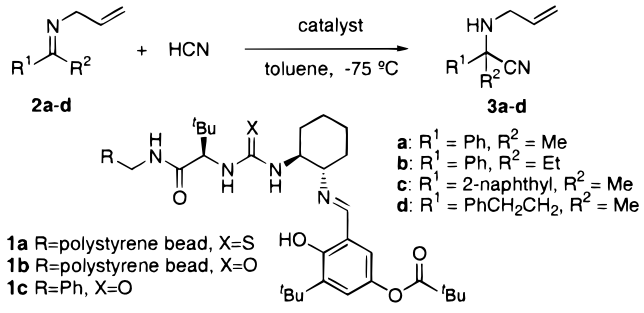
reported examples of enantioselective catalytic Strecker reactions involving ketoimines. We report here the first success in this area, and outline a new and practical method for the preparation of α-substituted amino acids and their derivatives. The approach is illustrated in the gram-scale synthesis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

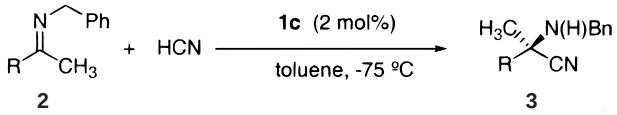
Table 1



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.

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.

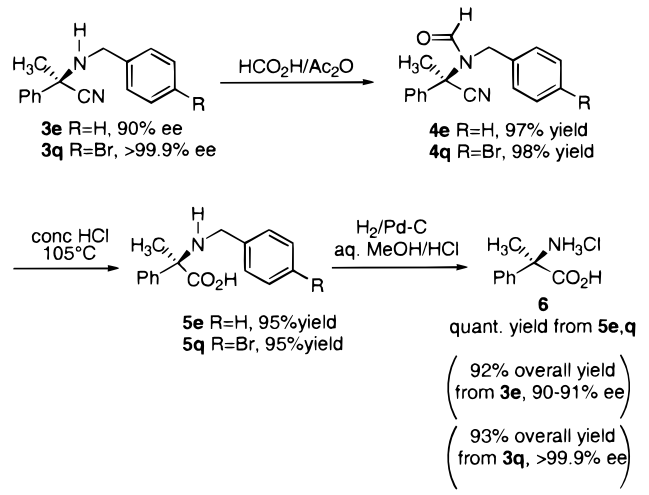
(8) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Sigman, M. S.: Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. (d) Ishitani, H.; Komiyama, S.; Kobayashi, 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

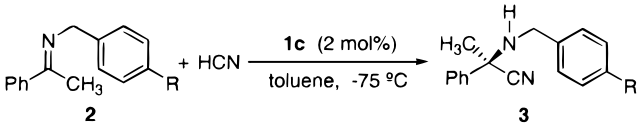


Catalyst **1c** proved effective for the asymmetric hydrocyanation of a variety of *N*-benzyl ketoimines (Table 2). Strecker adducts **3e**−**k** were isolated in essentially quantitative yield by filtration of the crude product mixtures through a short silica gel column. High enantioselectivity was 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

Table 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)

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]

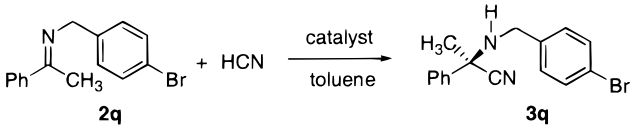
The asymmetric hydrocyanation of **2q** can be carried out successfully under a variety of experimental conditions. For example, elevation of the temperature from −75 °C to +5 °C led to a decrease in the requisite reaction time from 40 h to 8 min, and the adduct **3q** was still obtained in essentially 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.

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