Ti-Catalyzed Enantioselective Addition of Cyanide to Imines. A Practical Synthesis of Optically Pure α-Amino Acids

Clinton A. Krueger, Kevin W. Kuntz, Carolyn D. Dzierba, Wolfgang G. Wirschun, John D. Gleason, Marc L. Snapper,* and Amir H. Hoveyda*
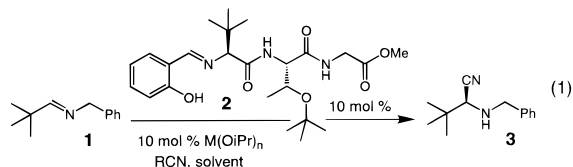
Department of Chemistry, Merkert Chemistry Center
Boston College, Chestnut Hill, Massachusetts 02467

The development of asymmetric methods for the synthesis of nonproteinogenic α-amino acids has been the subject of extensive research.[1] Nonetheless, there is a scarcity of processes that are catalytic, highly enantioselective, practical and cost-effective, and deliver α-amino acids not accessible by asymmetric hydrogenation.[2] Various recent disclosures indicate that the addition of HCN to protected imines can be promoted by peptide-derived catalysts. In a study reported by Lipton,[3] selectivities range from <10% ee (→Val) to >99% ee (→PhGly) (71−97% yield); CN hydrolysis and amine deprotection were carried out simultaneously by exposure of CN addition products to HCl. A procedure by Jacobsen[4] provides selectivities from 70% ee (→4-MeOPhGly) to 91% ee (→PhGly) (65−92% yield), but requires the removal of the *N*-allyl protecting group with a Pd catalyst in addition to a CN hydrolysis step. The latter study utilizes the high-throughput screening of parallel libraries of Schiff base-peptides to identify an optimum catalyst.[5] A (salen)Mn-catalyzed process has also been reported (*N*-allyl imines as substrates) that afford CN addition products (69−99% yield) in 37% ee (→*t*-Leu) to 95% ee (→PhGly).[6]

Herein, we report that CN addition to a variety of imines is catalyzed by Ti-tripeptide Schiff base complexes. The reaction is efficient (≥93% conversion) and proceeds with excellent enantioselectivity (85−97% ee). In most cases, optically pure (>99% ee) products can be isolated in >80% yields. Moreover, conversion to the derived α-amino acids proceeds efficiently, with inexpensive hydrolytic reagents, and without loss of enantiopurity.

Imine **1** was used as the substrate and the modular tripeptide-Schiff base **2** as the chiral ligand prototype (eq 1) in brief surveys

to establish the most appropriate metal center. Ten metal

isopropoxides were found to promote cyanide addition (TMSCN, 20 mol % ligand and metal salt, toluene, 4 °C): Ti(OiPr)$_4$ (28% ee), Zr(OiPr)$_4$ (0% ee), Al(OiPr)$_3$ (−4% ee), Sm(OiPr)$_3$ (0% ee), Hf(OiPr)$_4$ (3% ee), Ba(OiPr)$_2$ (−6% ee), Y$_5$(OiPr)$_{13}$O (−6% ee), Sr(OiPr)$_2$ (−7% ee), Yb(OiPr)$_3$ (−5% ee), Nd(OiPr)$_3$ (9% ee).[7] With Ti(OiPr)$_4$ as the metal salt of choice, a range of solvents were examined. Both trichloroethane and toluene emerged as superior media (better enantioselection); we opted for toluene due to environmental concerns and the convenience of using a less volatile solvent in library screening. Similar trends were observed for *N*-diphenyl methyl imines (cf. Table 1). We selected the latter class of substrates because, as mentioned above, CN hydrolysis and amine deprotection may be performed in a single operation. A survey of potential cyanide donors was carried out. From among seven candidates,[8] TMSCN delivered the most selective, efficient, and reproducible results.

Next, we utilized our ligand optimization protocol[5] to determine the most selective peptide-Schiff base ligand (cf. **2** in eq 1). Thus, according to the procedure reported previously, for the Ti-catalyzed addition of TMSCN to meso epoxides, the three structural modules of the chiral peptide ligand were modified systematically. In all the cases examined, the most effective ligands bear a *t*-Leu in the AA1 site (adjacent to the Schiff base) and Thr(*t*-Bu) in the AA2 position (cf. Table 1). However, depending on the imine substrate, the optimum Schiff base moiety within the ligand varies.

As illustrated in the left-hand column of Table 1, the aforementioned search allows the identification of ligands that afford the derived amino nitriles in 84−97% ee. However, these transformations proved inefficient and sluggish: conversions of 15−39% were typically obtained after 48 h (Table 1).

To address the efficiency problem, based on various experimental observations and mechanistic hypotheses, we examined the influence of several protic additives on the rate of CN addition. On a number of occasions, when transformations were carried out on larger scale, there was a notable reduction in reaction efficiency. We argued that adventitious moisture may facilitate processes performed in smaller quantities, where exclusion of undesired components is usually more difficult. Furthermore, we conjectured that, as illustrated in Scheme 1, cleavage of the Ti−N bond and removal of the Me$_3$Si unit within the purported Ti complex **III** (R = TMS) might lead to the more facile regeneration of the active catalyst **I** (enhanced turnover rate). As illustrated in Table 1 (right column), in the presence of 1.5 equiv of *i*-PrOH,[9] notable enhancements in reactivity are indeed observed.[10] *Catalyst turnover is facilitated significantly in the presence of i-PrOH*; in several instances enantioselectivities are improved as well (entries 3−5).[11]

The exact reason for the influence of *i*-PrOH on CN addition reactivity and selectivity requires additional investigation. It nonetheless merits mention that slow addition of a solution of HCN (in toluene) to a mixture of **13**, chiral ligand **9** (10 mol %),

(1) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.
(2) Burk, M. J.; Allen, G. J.; Kiesman, W. F. *J. Am. Chem. Soc.* **1998,** *120,* 657−663 and references therein.
(3) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996,** *118,* 4910−4911.
(4) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998,** *120,* 4901−4902.
(5) For initial reports on screening of parallel peptide-based libraries, see: (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996,** *35,* 1668−1671. (b) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 1704−1707. (c) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998,** *4,* 1885−1889. (d) Hoveyda, A. H. *Chem. Biol.* **1998,** *5,* R187−R191.
(6) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998,** *120,* 5315−5316. While this paper was under review, a Zr-catalyzed addition of Bu$_3$SnCN to imines was reported (highest ee = 92%): Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **1998,** *37,* 3186−3188.

(7) In the absence of a metal salt, <5% product is observed.
(8) Other cyanating agents examined were as follows: TBSCN, Bu$_4$NCN, Et$_2$AlCN, acetone cyanohydrin, *tert*-butyl isocyanide, and HCN.
(9) Other alcohols also provided enhanced catalytst turnover; as an example, with **15** as the substrate, catalytic addition proceeds to 98% conversion in the presence of 1 equiv of *p*-MeO-phenol. See entry 7 of Table 1.
(10) Initial studies indicate that the C=N bond of the chiral ligand remains largely unreacted. As an example, 85% of **9** is recovered from the reaction with **7**; the identity of the products arising from the remainder of **9** and whether they are involved in any catalytic CN addition remains to be determined.
(11) *i*-PrOH must be added over 20 h to achieve high selectivity and efficiency. As an example, initial treatment of **10** with 1 equiv of *i*-PrOH affords the desired adduct in 70% conversion after 20 h but only in 20% ee (vs 93% ee with slow addition). It is likely that rapid addition leads to (i) formation of large amounts of HCN which at 4 °C add to imines in the absence of a catalyst and (ii) displacement of the chiral ligand from the transition metal center.

Communications to the Editor

J. Am. Chem. Soc., Vol. 121, No. 17, 1999 4285

Table 1. Ti-Catalyzed Enantioselective Cyanide Addition to Imines[a]

| entry	substrate (P=CHPh$_2$)	product	Shiff base of optimum ligand	without added i-PrOH conv (%), ee (%)[b]	with added i-PrOH conv (%), ee (%)[b]	with added i-PrOH yield (%), ee (%)[b]
1	4	5	X=5-OMe 6	30, 97	99, 97	82, >99[c]
2	7	8	X=3,5-DiCl 9	22, 92	96, 93	85, >99[c]
3	10	11	X=3,5-DiCl 9	15, 88	99, 94	93, >99[c]
4	13	14	X=3,5-DiCl 9	15, 84	100, 94	99, 94[d]
5	15	16	X=5-OMe 6	20, 90	100, 93	80, >99[c]
6	17	18	X=5-OMe 6	25, 91	93, 90	87, >99[c]
7	19	20	X=3,5-DiBr 21	39, 88	100, 85[e]	97, 85[d]

[a] Conditions: 10 mol % Ti(OiPr)$_4$, 10 mol % chiral ligand, 2 equiv of TMSCN, 1.5 equiv of i-PrOH added over 20 h, toluene, 4 °C. [b] Enantioselectivities determined by HPLC in comparison with authentic racemic materials. [c] Purified by recrystallization. [d] Purified by silica gel chromatography. [e] Reaction performed in 1,1,1-trichloroethane with n-BuOH as the additive.

Scheme 1
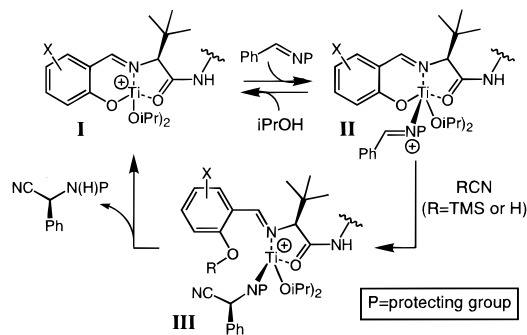
and Ti(OiPr)$_4$ (10 mol %) results in the formation of the desired addition product in 85% ee (100% conversion). This observation, and the fact that alcohols react with TMSCN to afford HCN,[12] suggests that reaction of HCN with the imine substrate *catalyzed*

(12) Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545−3548.

by Ti-peptide ligands may be facile and enantioselective. However, only at low HCN concentration does the reaction proceed predominantly through the catalyzed pathway (vs background). It is likely that slow addition of i-PrOH is required to avoid rapid HCN generation, an event that would effect nonselective and uncatalyzed transformations. It is also plausible that, with HCN, regeneration of **I** (Scheme 1) occurs more readily: the intermediate Ti−N bond (cf. **III**, R = H) should readily release the desired addition product and **I**.

Other noteworthy attributes of the addition process are as follows: (1) Products are stable and directly purified by chromatography (acylation not needed). Since all reactions proceed with high conversion and enantiocontrol, the yield of pure nonracemic adducts is high (last column, Table 1). In most instances, simple recrystallization affords analytically pure products in >80% yield and >99% ee (Table 1). (2) The positive influence of additional i-PrOH allows the reduction of catalyst loading. For example, reaction of imine **13** (entry 4) may be carried out with 5 mol % **9** and Ti(OiPr)$_4$ to afford the corresponding addition product in 98% conversion and 94% ee (22 h). With 2.5 mol % catalyst, 99% conversion is obtained in 42 h, albeit in 84% ee. (3) Conversion of amino nitriles to amino acids can be carried out in a cost-effective manner, efficiently and without loss of enantioselectivity. The example shown in Scheme 2 is representative (73% overall yield from aldehyde precursor to imine substrate). A similar procedure affords optically pure Boc-t-Leu in 40% overall yield from the corresponding aldehyde precursor.[13]

Scheme 2
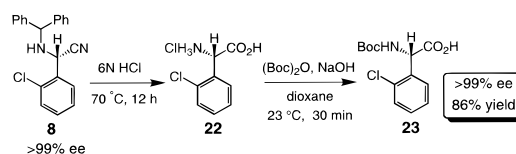
In brief, we disclose an efficient asymmetric Ti-catalyzed CN addition to imines; the catalytic asymmetric process was uncovered by high-throughput catalyst screening and mechanism-based reaction optimization. Addition products are purified to afford materials in >99% ee and >80% yield; the resulting amino nitriles are readily converted to the corresponding amino acids. It is worth noting that processes shown in entries 2−3 (Table 1) have not been reported previously, and those depicted in entries 4−6 represent the most efficient syntheses of the derived nitriles and the corresponding amino acids.[14] Additional studies on metal-catalyzed enantioselective synthesis of amino acids and their application to complex molecule synthesis are in progress and will be the subject of future reports.

Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Boc-t-Leu is obtained in 85% ee and 85% yield from the derived amino nitrile; single recrystallization affords the optically pure α-amino acid.
(14) This research was supported by the NIH (GM-57212 to A.H.H. and M.L.S.), ArQule, ArQule Catalytics and the NSF (CHE-9632278 to A.H.H.). Additional funds were provided by Albemarle and DuPont (to A.H.H.). K.W.K. is a Department of Education GAANN Fellow. W.G.W. is a Deutsche Forschungsgemeinschaft postdoctoral fellow. J.D.G. is supported by fellowships from Pfizer and the Dreyfus Foundation. M.L.S. is a Sloan Research Fellow, a DuPont Young Investigator, an Eli Lilly Grantee, and a Glaxo-Wellcome Young Investigator. A.H.H. and M.L.S. are Camille Dreyfus Teacher−Scholars.