Ti-Catalyzed Regio- and Enantioselective Synthesis of Unsaturated α-Amino Nitriles, Amides, and Acids. Catalyst Identification through Screening of Parallel Libraries

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Due to the significance of α-amino acids in chemistry and biology, the search for efficient methods that lead to the formation of these important compounds in the optically pure form continues.[1] Several procedures have been devised that afford α-amino acids in high selectivity, but many of these protocols rely on the use of chiral auxiliaries.[2] Other approaches depend on catalytic enantioselective reduction of dehydroamino acids, and several chiral hydrogenation catalysts have been disclosed that deliver optically pure α-amino acids in high yield and selectivity.[3,4] Recently, we reported a Ti-catalyzed process for the asymmetric cyanide addition to aryl imines, which affords the derived aryl amino nitriles efficiently and with exceptional enantiocontrol;[5,6] the identity of the optimal catalyst was determined through synthesis and screening of parallel ligand libraries.[7] Subsequent hydrolysis of the nitrile and simultaneous deprotection of the amine unit afford the desired optically pure aryl α-amino acids. These protocols thus allow access to α-amino acids that are not available by the catalytic asymmetric hydrogenation reaction.

After these studies we began to examine the catalytic asymmetric cyanide addition to α,β-unsaturated imines (Scheme 1). We reasoned that if these reactions proceed regioselectively (1,2- vs 1,4-addition) and enantioselectively, an efficient route to various unsaturated α-amino acids would be at hand and the generality of the catalytic asymmetric Strecker process would be

Scheme 1

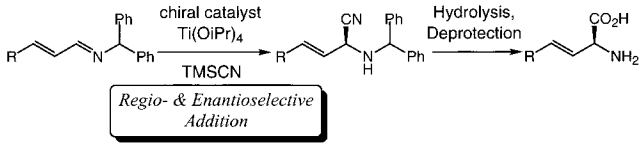
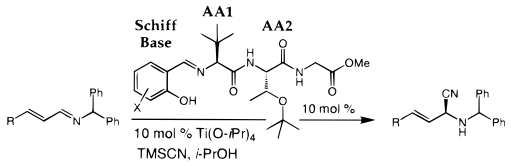
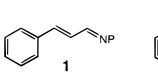
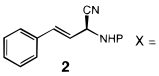
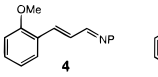
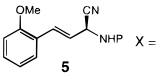
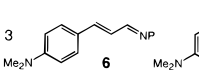
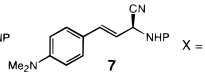
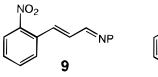
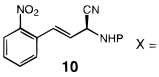


Table 1. Ti-Catalyzed Enantioselective Addition of Cyanide to α,β-Unsaturated Arylimines[a]



entry	substrate (P=CHPh$_2$)	product	Schiff base of optimum ligand	conv; ee (%)[b,c]	purified yield (%),[d] purified ee (%)
1	 **1**	 **2**	X = 1-naphthyl **3**	>98; 84	80; 97
2	 **4**	 **5**	X = 1-naphthyl **3**	94; 78	61; 97
3	 **6**	 **7**	X = 3,5-DiBr **8**	>98; 76	93; 76
4	 **9**	 **10**	X = 3,5-DiBr **8**	>98; 90	87; 97

[a] Conditions: 10 mol % Ti(*i*-OPr)$_4$, 10 mol % chiral ligand, 2 equiv TMSCN, toluene, 24 h; hexanes workup (see Supporting Information). Entries 1−2 at +4 °C, entries 3−4 at −20 °C. 1.5 equiv of *i*-PrOH added over 20 (entries 1−2) or 10 h (entries 3−4). [b] Determined by analysis of the ^{1}H NMR (400 MHz) of the upurified reaction mixture. [c] Determined by chiral HPLC analysis in comparison with authentic materials (Chiralcel OD, entries 1−3; Chiralpak AD, entry 4). [d] Purified by recrystallization.

significantly enhanced. The following considerations provided us with additional impetus: (1) β,γ-Unsaturated α-amino acids have biologically significant properties (e.g., antibiotic[8] and enzyme inhibitory[9] properties). (2) β,γ-Unsaturated amino acids are not easily accessed by catalytic hydrogenation.[10] (3) The resident alkene unit in the intermediate amino nitrile may in principle be stereoselectively functionalized en route to more complex α-amino acids.

Due to the results of our studies regarding the addition of cyanide to aryl- and alkylimines,[5] we selected Ti(O*i*-Pr)$_4$ as the metal salt of choice and diphenylmethylene as the amine protecting group. Tripeptide ligand libraries were then prepared and the reaction of unsaturated imine **1** with TMSCN was screened in the presence of Ti(O*i*-Pr)$_4$ (10 mol % ligand and metal complex). Screening of a total of approximately 60 peptidic ligands[11] indicates that the most selective ligand (**3**) is the one

(1) (a) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon: Oxford, 1989. (b) O'Donnell, M. J., Ed. *Tetrahedron Symposia in Print*; Tetrahedron: Oxford, 1988; Vol. 44, 5253−5614. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650.

(2) For representative recent examples, see: (a) Davis, F. A.; Portonovo, P. S.; Ready, R. E.; Chiu, Y. *J. Org. Chem.* **1996**, *61*, 440−441. (b) Zhu, J.; Deur, C.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 7704−7710. (c) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656−673.

(3) Burk, M. J.; Kalberg, C. S.; Pizzano, S. *J. Am. Chem. Soc.* **1998**, *120*, 4345−4353 and references therein.

(4) For representative recent non-hydrogenation catalytic asymmetric methods to α-amino acids, see: (a) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Scwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778. (b) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548−4549. (c) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347−5350. (d) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671−8674. (e) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazel, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844−4849.

(5) 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*, 4284−4285.

(6) For related studies on catalytic asymmetric CN addition to imines, see: (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910−4911. (b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902. (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315−5316. (d) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3186−3188. (e) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160.

(7) 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.

(8) For example, see: Huroda, Y.; Okuhara, M.; Goto, T.; Kohaska, M.; Aoki, H.; Imanaka, H. *J. Antibiotics* **1980**, *33*, 132−136.

(9) For example, see: Girodeau, J. M.; Agouridas, C.; Masson, M.; Pineau, R.; Le Goffic, F. *J. Med. Chem.* **1986**, *29*, 1023−1030.

(10) For Rh-catalyzed hydrogenation of α,β,γ,δ-unsaturated acetamide esters to obtain allylglycines, see: Burk, M. J.; Bedingfield, K. M.; Kiesman, W. F.; Allen, J. G. *Tetrahedron Lett.* **1999**, *40*, 3093−3096 and references therein. Presumably, the site-selective hydrogenation is due to the coordination between the Rh-based catalyst and the acetamide directing group.

(11) See the Supporting Information for details on the identity of the ligands screened. Since the screening for entries 1 of Tables 1 and 2, in addition to those reported in ref 5, indicated that *t*-Leu and Thr(*t*-Bu) are optimal AA1 and AA2 units, respectively, only the Schiff base libraries were screened for the remaining substrates.

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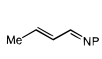
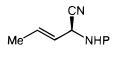
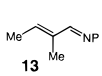
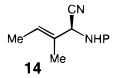
Table 2. Ti-Catalyzed Enantioselective Addition of Cyanide to α,β-Unsaturated Alkenylimines[a]

entry	substrate (P=CHPh$_2$)	product	Schiff base of optimum ligand		conv (%)[b]	ee (%)	[c]purified yield (%),[d] purified ee (%)
1	 **11**	 **12**	X = 3,5-diBr	**8**	>98	85	84; 85
2	 **13**	 **14**	X = 3,5-diCl	**15**	>98	94	86; 94
3	 **16**	 **17**	X = 1-naphthyl	**3**	>98	95	80; 95

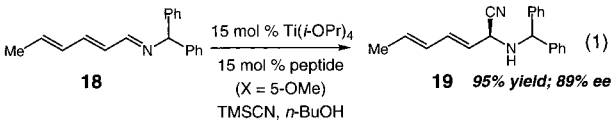
[a] Conditions: 15 mol % Ti(*i*-OPr)$_4$, 15 mol % chiral ligand, 2 equiv TMSCN, toluene, −20 °C. 1.5 equiv of *n*-BuOH added over 10 h. [b] Determined by analysis of the ^{1}H NMR (400 MHz) of the unpurified reaction mixture. [c] Determined by chiral HPLC analysis in comparison with authentic materials (Chiralcel OD, entries 1 and 3; Chiralcel OJ, entry 2). [d] Yield after silica gel chromatography.

with 2-hydroxy-1-naphthaldehyde Schiff base and *t*-Leu at the AA1 and Thr(*t*-Bu) at the AA2 position (84% ee).[12] As depicted in entry 1 of Table 1, when the reaction is repeated with the optimal ligand (+4 °C) on larger scale with the addition of *i*-PrOH (to improve efficiency),[5] the unpurified aminonitrile **2** can be obtained in 84% ee (>98% conversion). *Recrystallization of the resulting white solid affords **2** in 80% purified yield and 97% ee*. Careful analysis of the reaction mixture indicated <2% of the 1,4-addition product. It is important to note that the corresponding saturated imine (derived from 3-phenylpropanal) undergoes catalytic cyanide addition under identical conditions with notably lower levels of enantiocontrol (15−25% yield, 24% ee).

As illustrated in entries 2−3 of Table 1, the more electron rich unsaturated imines **4** and **6** undergo Ti-catalyzed addition, albeit with lower enantioselectivity (78% and 76% ee, respectively). Whereas catalyst screening indicates that **3** is also the ligand of choice for **4**, tripeptide Schiff base **8** proves to be the more effective ligand for the asymmetric synthesis of **7**. In contrast to amino nitrile **7**, recrystallization of **5** leads to improvement of its enantiopurity (61% yield, 97% ee). It merits mention that reaction of **6** at 4 °C leads to only 51% ee; accordingly, the asymmetric cyanide addition shown in entry 3 was performed at −20 °C to improve stereochemical control. As shown in entry 4 of Table 1, the electron-deficient unsaturated imine undergoes cyanide addition to afford aminonitrile **10** with the highest selectivity (90% ee); recrystallization of **10** delivers the amino nitrile in 87% yield and 97% ee (see the Supporting Information for details).

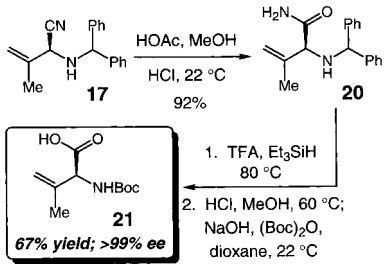
As the data in Table 2 indicate, the Ti-catalyzed cyanide addition may also be performed with aliphatic unsaturated imines; in these cases product recrystallization does not lead to the improvement of product ee. Several additional points regarding these asymmetric reactions are the following: (1) Comparison of the data in entries 1−3 indicates that the presence of a substituent α to the C=N leads to higher levels of enantioselectivity (compare entry 1 to entries 2−3). (2) Higher catalyst loadings are required in comparison to the aromatic substrates in Table 1, otherwise the more effective uncatalyzed background reaction leads to diminution of stereoselectivity. (3) As before, in the absence of the unsaturation, significantly lower levels of asymmetric induction are attained: Ti-catalyzed cyanide addition to the imine derived from isobutyraldehyde proceeds in 94% yield and 57% ee (vs 95% ee in entry 3, Table 2).

Ti-catalyzed asymmetric additions to doubly unsaturated imines proceed with appreciable levels of enantioselectivity as well. The example depicted in eq 1 is illustrative (**18** → **19**). Similar to the trend observed for substrates in Table 2, the ee is <90% in the absence of the α-alkyl substituent.



Treatment of optically enriched aminonitriles to acidic conditions leads to the formation of the derived primary amides. The example shown in Scheme 2 is illustrative (**17** (94% ee) → **20** (94% ee)). Several conditions were examined for the conversion of the amide to the derived unsaturated α-amino acid. After extensive experimentation, we established that sequential exposure of the amide to TFA and Et$_3$SiH (amine deprotection) and methanolic acid (amide hydrolysis) leads to the formation of the optically pure amino acid (>99% ee);[13] subsequent catalytic hydrogenation of **21** (H$_2$, 10% Pd(C)) affords (*S*)-valine in 94% isolated yield and >99% ee. Several issues regarding the hydrolysis/deprotection of optically enriched amino nitriles deserve comment: (1) Hydrolysis of conjugated aminonitriles is significantly more difficult than those of the saturated aryl or alkyl derivatives. Accordingly, the conditions presented here for cyanide hydrolysis are less severe than those reported previously.[5] A change of conditions is required, since the originally reported protocols result in substantial loss of HCN and reformation of the imine (aldehyde) substrate. (2) In the case of Boc-protected amino acid **21** (Scheme 2), no detectable loss of enantiopurity is observed. However, it is possible that under these conditions some loss of enantiopurity occurs; for example, the amide formed from amino nitrile **2** (97% ee) is obtained in 84% ee (77% yield).

Scheme 2



In summary, we disclose Ti-catalyzed regio- and enantioselective addition of cyanide to unsaturated imines. Both aromatic and aliphatic substrates may be used to obtain unsaturated amino nitriles in good yield and enantiomeric excesses. Cyanide hydrolysis and amine deprotection can be carried out to afford optically enriched α-amino amides and acids; in certain cases, these conversions lead to slight lowering of enantiopurity. Research toward establishing more general conditions for the conversion of nitriles to acids is in progress. Future studies also include stereoselective functionalization of the unsaturated amino nitriles and the development of additional asymmetric C−C bond forming processes through screening of parallel catalyst libraries.

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

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(12) The corresponding *n*-Bu amide may be used equally effectively instead of the Gly derivative within the chiral ligand.

(13) Loss of the minor enantiomer (~3%) is presumably achieved in the crystallization of the amino acid.