Catalytic Asymmetric Strecker Synthesis. Preparation of Enantiomerically Pure α-Amino Acid Derivatives from Aldimines and Tributyltin Cyanide or Achiral Aldehydes, Amines, and Hydrogen Cyanide Using a Chiral Zirconium Catalyst

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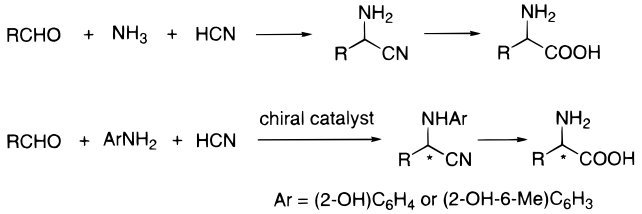
Abstract: Catalytic enantioselective Strecker-type reactions of aldimines with tributyltin cyanide (Bu_3SnCN) proceeded smoothly in the presence of a novel chiral zirconium catalyst. High levels of enantioselectivities in the synthesis of α-amino nitrile derivatives with wide substrate generality were obtained via these reactions. In addition, hydrogen cyanide (HCN) was successfully used instead of Bu_3SnCN as the cyanide source. Catalytic asymmetric Strecker amino acid synthesis starting from achiral aldehydes, amines, and HCN using a chiral zirconium catalyst has also been achieved. The three-component asymmetric process reported here significantly improves upon the original Strecker reaction, and has advantages over previous reactions using unstable imines (Schiff bases) as starting materials. Moreover, high yields and enantioselectivities have been obtained even in the reactions using aliphatic aldehydes, and both enantiomers of various types of α-amino acid derivatives can be prepared. As demonstrations to show the utility of this reaction, efficient syntheses of homophenylalanine, leucine amide, and pipecolic acid derivatives have been performed. Finally, two novel binuclear zirconium complexes (**3** and **4**) are postulated to be active chiral catalysts in the reactions of aldimines with Bu_3SnCN and the three-component reactions, respectively, and low loading levels of the chiral catalysts (1−2.5 mol %) have been accomplished in both cases.

Introduction

Unnatural α-amino acids are expected to play key roles in improving the original properties and functions of proteins,[1] and development of efficient methods for the preparation of various types of α-amino acids is desired not only in the field of organic chemistry but also in many biology-related areas. The Strecker amino acid synthesis, treatment of aldehydes with ammonia and hydrogen cyanide (or equivalents), and subsequent hydrolysis of the intermediate α-amino nitriles providing α-amino acids (Scheme 1) was first reported in 1850.[2] While it has been applied to the synthesis of racemic α-amino acids on an industrial scale, recent demands have on the preparation of chiral α-amino acids. Although several methods using chiral imines (Schiff bases) have been reported in the literature, stoichiometric amounts of chiral sources are needed according to these diastereoselective approaches.[3−7] In addition, the Schiff bases employed in these reactions are limited to those derived from aromatic aldehydes in most cases, because aliphatic Schiff bases are often unstable and lower yields and selectivities have been observed. In this paper, we report chiral zirconium-catalyzed Strecker reactions of aldimines with tributyltin cyanide (Bu_3SnCN), and also a three-component asymmetric process using achiral aldehydes, amines, and hydrogen cyanide (HCN).[8] High yields and enantioselectivities have been obtained even in the reactions

Scheme 1. Classical Strecker Reaction (above) and Asymmetric Version



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(1) Barrett. G. C., Ed. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985.

(2) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148. Cf.: Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27.

(3) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.

(4) Williams, R. M.; Hendrix, A. J. *Chem. Rev.* **1992**, *92*, 889.

(5) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(6) Recently, catalytic asymmetric cyanation reactions of Schiff bases have been reported. (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. Engl.* **1998**, *37*, 3186. (e) Krueger, C. A.; Kuntz, K. W.; Dzieba, C. D.; Wirschum, 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. In all these cases, no example of the three-component reactions that succeed to the original Strecker reaction was reported. In addition, lower selectivities were obtained using Shiff bases derived from aliphatic aldehydes, which restricts use of these reactions for α-amino acid syntheses.

(7) For achiral Strecker reactions, see: (a) Ojima, I.; Inaba, S.; Nakatsugawa, K. *Chem. Lett.* **1975**, 331. (b) Mai, K.; Patil, G. *Tetrahedron Lett.* **1984**, *25*, 4583. (c) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115.

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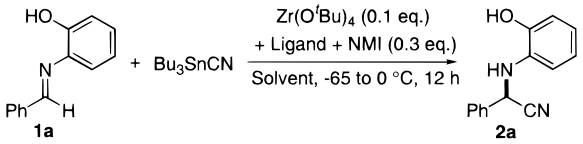
Table 1. Effect of Ligands and Solvents



ligand (equiv)	solvent	yield (%)	ee (%)
(*R*)-6-Br-BINOL (0.2)	CH_2Cl_2	70	55
	toluene−benzene (1:1)	72	69
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	toluene−benzene (1:1)	92	91
	toluene	93	86
	toluene−C_2H_5CN (1:1)	91	86
	benzene−CH_2Cl_2 (1:1)	97	83
	CH_2Cl_2	85	71

using aliphatic aldehydes, and both enantiomers of various types of α-amino acid derivatives can be prepared based on these reactions.

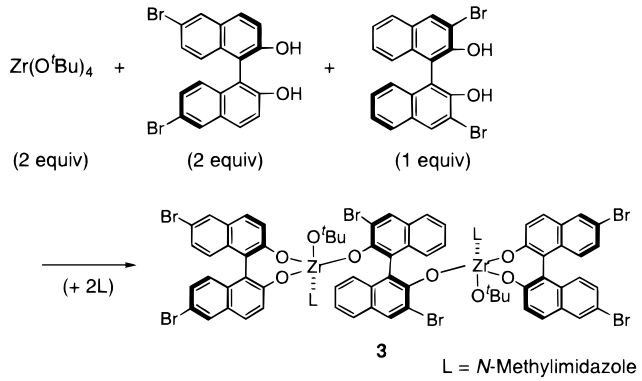
Results and Discussion

Recently, we have reported the first catalytic enantioselective Mannich-type reactions[9] and aza Diels−Alder reactions[10] using a chiral zirconium catalyst. In these reactions, the zirconium catalyst effectively activates aldimines and efficient catalytic processes have been accomplished. We then intended to use a zirconium catalyst in asymmetric Strecker-type reactions. As a cyanide source, we first chose Bu_3SnCN[11] because Bu_3SnCN is easy to handle in laboratories. Bu_3SnCN is stable in water and produces no HCN. This is in contrast to trimethylsilyl cyanide (TMSCN) which easily hydrolyzes to form HCN even in the presence of a small amount of water. In the presence of 10 mol % of a zirconium catalyst, which was prepared from $Zr(O^tBu)_4$, 2 equiv of (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-6-Br-BINOL),[12] and 3 equiv of 1-methylimidazole (NMI), aldimine **1a** was treated with Bu_3SnCN in dichloromethane at −65 °C. The reaction proceeded smoothly to afford the corresponding α-amino nitrile in 70% yield with 55% enantiomeric excess (ee). After several reaction conditions were examined, the best results (92% yield, 91% ee) were obtained when the reaction was carried out in benzene−toluene (1:1) using a chiral zirconium catalyst prepared from 1 equiv of $Zr(O^tBu)_4$, 1 equiv each of (*R*)-6-Br-BINOL and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3-Br-BINOL),[13] and 3 equiv of *N*-methylimidazole (NMI) (Table 1). Use of other solvents slightly decreased the selectivity. The free hydroxyl group of the aldimine was important in obtaining both high yield and high selectivity. When the aldimine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, the corresponding α-amino nitrile derivatives were obtained in much lower yields and lower ee's (aniline, 29% yield, 1% ee; 2-methoxyaniline, 45% yield, 5% ee).

It was quite interesting to find that use of a mixture of (*R*)-6-Br-BINOL and (*R*)-3-Br-BINOL gave the best results. We then carefully examined the structure of the zirconium catalyst, and it was indicated from NMR studies that a zirconium binuclear complex (**3**) was formed under the conditions used (Scheme 2). The binuclear complex consists of 2 equiv of zirconium, (*R*)-6-Br-BINOL, and NMI and 1 equiv of (*R*)-3-Br-BINOL. The structure appears to be very stable as the same complex was formed even when different molar ratios of $Zr(O^tBu)_4$, (*R*)-6-Br-BINOL, (*R*)-3-Br-BINOL, and NMI were combined. Formation of **3** was confirmed by ^1H and ^{13}C NMR spectra when 1 equiv of $Zr(O^tBu)_4$ and (*R*)-6-Br-BINOL, 0.5−1 equiv of (*R*)-3-Br-BINOL, and 2−3 equiv of NMI were combined (Figure 1).[14]

We then examined several examples of the Strecker-type reactions, and the results are summarized in Table 2. Aldimines

Scheme 2. Preparation of Chiral Zirconium Catalyst **3**



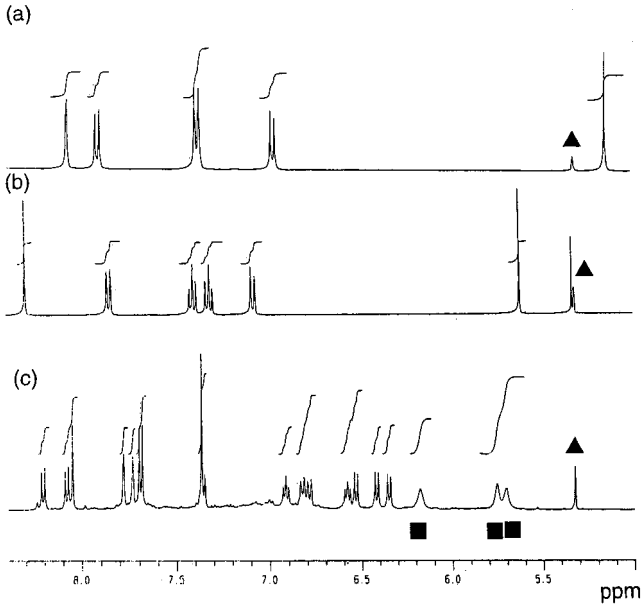


Figure 1. (a) ^1H NMR spectra of 6-Br-BINOL, (b) ^1H NMR spectra of 3-Br-BINOL, and (c) ^1H NMR spectra of chiral zirconium catalyst **3**: (■) *N*-methylimidazole and (▲) CD_2Cl_2 (internal standard).

(8) For a preliminary communication using Bu_3SnCN as a cyanation source, see 6d.

(9) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 6984. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.

(10) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 979.

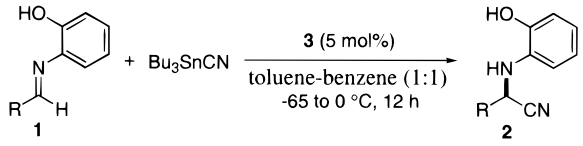
(11) Commercially available (Aldrich, etc.). (a) Luijten, J. G. A.; van der Kerk, G. J. M. *Investigations in the Field of Organotin Chemistry*; Tin Research Institute: Greenford, 1995; p 106. (b) Tanaka, M. *Tetrahedron Lett.* **1980**, *21*, 2959. (c) Harusawa, S.; Yoneda, R.; Omori, Y.; Kurihara, T. *Tetrahedron Lett.* **1987**, *28*, 4189.

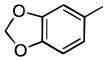
(12) For the use of 6,6′-dibromo-1,1′-bi-2-naphthol, see: (a) Terada, M.; Motoyama, Y.; Mikami, K. *Tetrahedron Lett.* **1994**, *35*, 6693. (b) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.

(13) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253.

(14) This could be partially due to the lower reactivity of (*R*)-3-Br-BINOL compared to (*R*)-6-Br-BINOL and equilibrium of the coordination of NMI to the zirconium center. After careful examination, the best results and reproducibility were obtained when the catalyst was prepared by combining 1 equiv of $Zr(O^tBu)_4$, 1 equiv of (*R*)-6-Br-BINOL and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3-Br-BINOL), and 3 equiv of NMI.

Table 2. Catalytic Asymmetric Strecker-Type Reactions Using Bu_3SnCN



entry	R	yield/%	ee/%
1	Ph	92	91
2	1-Nap	98	91
3	*p*-ClPh	90	88
4	*p*-MeOPh	97	76
5	*o*-MePh	96	89[a]
6	*o*-MePh	93	89 (*S*)[b]
7		85	87
8		89	80
9		89	92
10	$Ph(CH_2)_2$	55	83[c]
11	^{i}Bu	79	83[c]
12	C_8H_{17}	72	74[c]

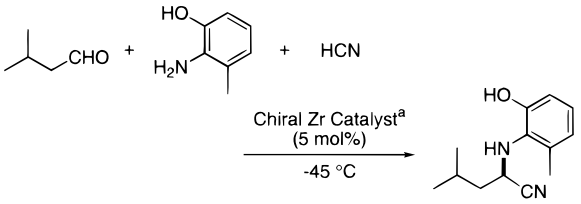
[a] When 2.5 mol % of **3** was used, 94% yield and 87% ee were obtained. [b] *ent-**3*** (5 mol %) was used. [c] The imine was prepared from the corresponding aldehyde and 2-amino-3-methylphenol in situ in the presence of MS 4A.

derived from various aromatic aldehydes as well as aliphatic and heterocyclic aldehydes reacted with Bu_3SnCN smoothly to afford the corresponding α-amino nitrile derivatives in high yields with high enantiomeric excesses. Since both enantiomers of the chiral sources (6-Br-BINOL and 3-Br-BINOL) are readily available, both enatiomers of α-amino nitrile derivatives can be easily prepared according to this protocol. In addition, it is noteworthy that Bu_3SnCN has been successfully used as a safe cyanide source,[15] and that, after the reaction was completed, all tin sources were quantitatively recovered as bis(tributyltin) oxide, which has been converted to tributyltin chloride[16] and then to Bu_3SnCN.[11,17]

We then decided to develop a catalytic asymmetric version of the Strecker synthesis (three-component reactions)[18] and to use HCN instead of Bu_3SnCN. Although HCN is very toxic, it is cheap and suitable for industrial use. To a chiral zirconium catalyst prepared from 2 equiv of $Zr(O^tBu)_4$, 2 equiv of (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-6-Br-BINOL), 1 equiv of (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3-Br-BINOL), and 3 equiv of *N*-methylimidazole (NMI) in toluene (5 mol %, 0.04 M) were added isobutylaldehyde, 2-amino-3-methylphenol, and HCN at −45 °C in the presence of molecular sieves (4A), and the mixture was stirred for 12 h. After a typical workup, the desired α-amino nitrile was obtained in 63% yield with 65% ee. To improve the yield and selectivity, several reaction conditions were examined (Table 3). It was found that the selectivity was improved when HCN was added to the catalyst first and this solution was then added to the mixture of the aldehyde and the amine. The best results (99% yield, 94% ee) were obtained when the catalyst was prepared at lower concentration (0.01 M) in dichloromethane and the reaction was performed in the same solvent without molecular sieves. The same levels of yield and selectivity were achieved when 2.5 mol % of the Zr catalyst was used, and it was noted that an excellent yield and enantiomeric excess were obtained in the Strecker reaction using an aliphatic aldehyde.

Several examples of the zirconium-catalyzed asymmetric Strecker reaction are summarized in Table 4. The following characteristics of these reactions are noted. (1) Catalytic asymmetric three-component reactions, which succeed the original Strecker reaction, have been accomplished. (2) In all cases, chiral α-amino nitriles were obtained from both achiral aldehydes and amines using a small amount of a chiral source.

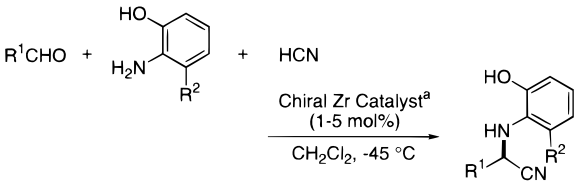
Table 3. Effect of Solvents and Concentration



entry	solvent	additive	concn (M)	yield (%)	ee (%)
1[b]	toluene	MS 4A	0.04	63	65
2[c]	toluene	MS 4A	0.04	49	79
3[c]	CH_2Cl_2	MS 4A	0.04	63	85
4[c]	CH_2Cl_2	none	0.01	99	94

[a] See text. [b] Aldehyde, amine, and HCN were added to catalyst **3**. [c] HCN was added to catalyst **3** first and this catalyst solution was added to the mixture of aldehyde and amine.

Table 4. Catalytic Asymmetric Strecker Reactions Using HCN



R^1	R^2	catalyst (mol %)	yield (%)	ee (%)
Ph	H	5	80	86
α-Nap	H	5	83	85
$Ph(CH_2)_2$	CH_3	2.5	85	94
$Ph(CH_2)_2$	CH_3	2.5	76	93 (*S*)[b]
C_8H_{17}	CH_3	2.5	83	90
C_8H_{17}	CH_3	1	86	84
C_8H_{17}	CH_3	2.5	93	91[c]
^{i}Bu	CH_3	5	99	94
^{i}Bu	CH_3	2.5	94	91
c-C_6H_{11}	CH_3	5	95	94
^{t}Bu	CH_3	5	quant	86
^{t}Bu	CH_3	2.5	quant	88[c]

[a] See text. [b] (*S*)-3-Br-BINOL and (*S*)-6-Br-BINOL were used. [c] $Zr(O^n Pr)_4$ was used instead of $Zr(O^tBu)_4$.

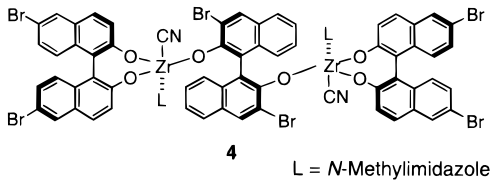
(15) When TMSCN was used in this system, moderate yields and moderate enantiomeric excesses were observed. The reaction of the aldimine prepared from 1-naphthaldehyde and 2-aminophenol with TMSCN, 33% yield, 63% ee; with triethylsilyl cyanide, 65% yield, 63% ee (not optimized).

(16) (a) Brown, J. M.; Chapman, A. C.; Harper, R.; Mowthorpe, D. J.; Davies, A. G.; Smith, P. J. *J. Chem. Soc., Dalton* **1972**, 338. (b) Davies, A. G.; Kleinschmidt, D. C.; Palan, P. R.; Vasishtha, *S. C. J. Chem. Soc. C* **1971**, 3972.

(17) Quite recently, we have developed scandium triflate-catalyzed Strecker-type reactions of aldehydes, amines, and Bu_3SnCN (achiral reactions). In these reactions, complete recovery of tin compounds toward environmentally friendly chemical processes has been achieved. Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 981.

(18) For utility and advantages of three-component reactions, see: (a) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 981.

Scheme 3. A Key Catalyst in the Three-Component Reactions

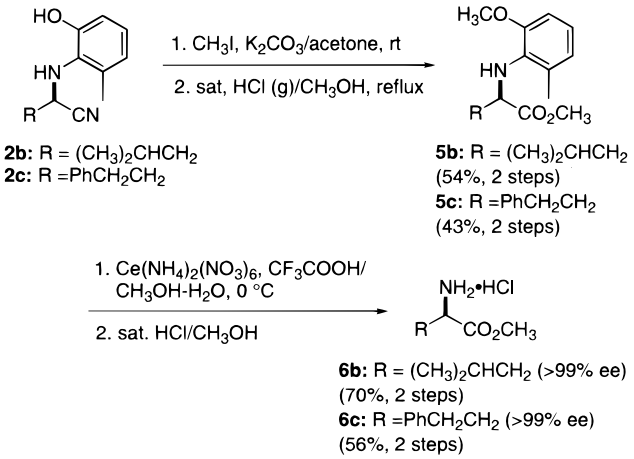


High yields and selectivities were obtained even when 1 mol % of the catalyst was employed. (3) Aromatic aldehydes as well as aliphatic aldehydes including primary, secondary, and tertiary aldehydes worked well to afford the corresponding α-amino nitriles in excellent enantiomeric excesses. (4) Not only microscale experiments but also larger scale syntheses (>10 mmol) were successfully performed. (5) Both enantiomers of α-amino nitriles could be readily prepared by using the enantiomeric zirconium catalyst. (6) Less expensive $Zr(O^nPr)_4$ could be used instead of $Zr(O^tBu)_4$.

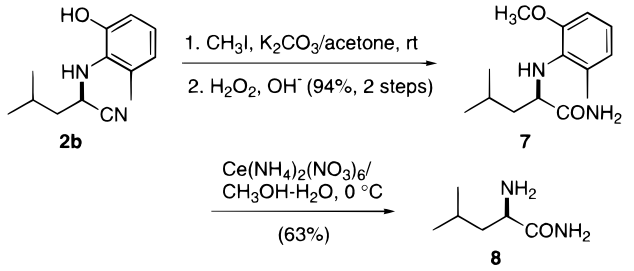
In general, it has been regarded that the Strecker three-component reactions proceed via two possible pathways: cyanation of aldimines and cyanohydrine pathways.[19] The former pathway was suggested in the present enantioselective Strecker reactions, because no cyanohydrine formation was observed during the reaction courses. As for the chiral catalyst, formation of zirconium cyanide **4** is assumed. After combining $Zr(O^tBu)_4$, (*R*)-6-Br-BINOL, (*R*)-3-Br-BINOL, NMI, and HCN, all solvents were removed under reduced pressure and the catalyst was dried (12 h/0.1 mmHg). ^{1}H NMR experiments revealed that the ^{t}BuO groups were removed from the catalyst. On the other hand, no significant change of NMR spectra was observed when the similar procedure was performed using Bu_3-SnCN instead of HCN.[20] Control experiments also revealed that the cyano groups attached to the zirconium center did not work as cyanide nucleophiles in this Strecker reaction. Formation of **4** would be fast because similar high selectivities were obtained when HCN was added after an aldehyde and an amine were injected to the catalyst (78% yield, 90% ee; cf. Table 3, entry 4).

α-Amino nitriles thus prepared were successfully converted to α-amino acid derivatives. Methylation of the phenolic hydroxyl group followed by acidic methanolysis provided the corresponding methyl esters (**5**). Oxidative cleavages were performed using cerium ammonium nitrate (CAN)[21] to give α-amino acid methyl esters (**6**). Their hydrochloric acid salts were recrystallized to afford the enantiomerically pure α-amino acid esters (Scheme 4). Homophenylalanine (2-amino-4-phenylbutanoic acid) derivatives thus prepared may serve as potential constituents of many medicinally important compounds.[23−25] Similarly, D-leucine amide (**8**) was prepared (Scheme 5). Thus,

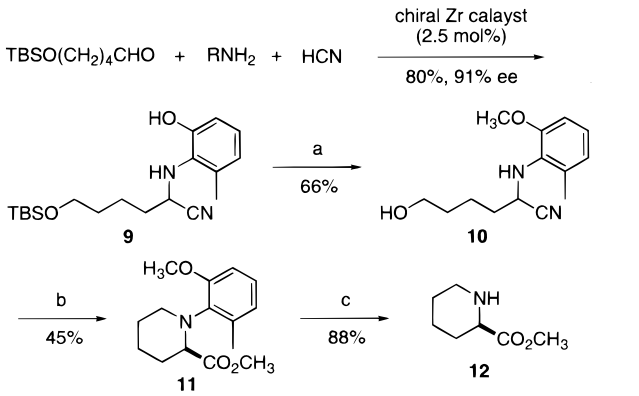
Scheme 4. Conversion of Enantiomerically Pure α-Amino Acid Esters



Scheme 5. Conversion to Leucinamide



Scheme 6. Synthesis of Pipecolic Acid



[a] 1. CH_3I, K_2CO_3/acetone, rt; 2. Bu_4NF/THF. [b] 1. CBr_4, PPh_3/CH_2Cl_2; 2. sat, HCl (g)/CH_3OH, reflux. [c] $Ce(NH_4)_2(NO_3)_6$, CF_3COOH/CH_3OH-H_2O, 0 °C

after methylation of the phenolic OH of **2b** using methyl iodide and potassium bicarbonate, the nitrile group was converted to an amide moiety.[22] Treatment of **7** with cerium ammonium nitrate (CAN)[21] gave leucinamide **8**. The absolute configuration assignment (*R*) was made by comparison of its hydrochloride with the authentic sample. The present catalytic asymmetric Strecker reaction could be also used for the synthesis of other biologically important amino acid derivatives. For example, the synthesis of D-pipecolic acid methyl ester (**12**) is shown in Scheme 6. Pipecolic acid is an interesting member of the class of lysine-related compounds. The key Strecker reaction using 5-*tert*-butyldimethylsiloxypentanal was successfully carried out in the presence of **4** (2.5 mol %) to afford α-amino nitrile **9**. The following standard transformations gave **10** in a good yield. Bromination of the hydroxyl group induced spontaneous cy-

(19) (a) Leblanc, J.-P.; Gibson, H. W. *Tetrahedron Lett.* **1992**, *33*, 6295. (b) Walia, J. S.; Bannor, S. N.; Walia, A. S.; Guillot, L. *Chem. Lett.* **1974**, 1005. (c) Jacobsen, R. A. *J. Am. Chem. Soc.* **1946**, *68*, 2628. (d) Jacobsen, R. A. *J. Am. Chem. Soc.* **1945**, *67*, 1996. See also ref 7b.

(20) This indicates formation of different catalysts in the catalytic Strecker reactions using Bu_3SnCN and HCN. For catalysts **3** and **4**, **4** is more active than **3**, presumably because of the two cyano groups.

(21) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(22) McGrath, M. E.; Klaus, J. L.; Barnes, M. G.; Brömme, D. *Nature Struct. Biol.* **1997**, *4*, 105.

(23) Sahoo, S. P.; Caldwell, C. G.; Chapman, K. T.; Durette, P. L.; Esser, C. L.; Kopka, I. E.; Polo, S. A.; Sperow, K. M.; Nisdzwiechki, L. M.; Izquierdo-Martin, M.; Chang, B. C.; Harrison, R. K.; Stein, R. L.; MacCoss, M.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2441.

(24) Yamada M.; Nagashima N.; Hasegawa, J.; Takahashi S. *Tetrahedron Lett.* **1998**, *39*, 9019.

(25) Cacchi, S.; Misiti, D.; Torre, F. L. *Synthesis* **1980**, 243.

clization, and acid treatment afforded *N*-protected D-pipecolic acid methyl ester (**11**). Deprotection under standard conditions gave **12** in a good yield.

Conclusion

Catalytic enantioselective Strecker-type reactions of aldimines with Bu_3SnCN have been developed using a novel chiral zirconium binuclear catalyst. High levels of enantioselectivities in the synthesis of α-amino nitrile derivatives with wide substrate generality were obtained according to these reactions. Moreover, we have demonstrated the catalytic asymmetric Strecker amino acid synthesis, which can be achieved starting from achiral aldehydes, amines, and HCN using a chiral zirconium catalyst. It is noted that 150 years after the first discovery of the Strecker reaction, a truly efficient three-component asymmetric version has been accomplished. While the former reactions using Bu_3SnCN are suitable for laboratory-scale experiments, industrial applications are expected in the three-component catalytic asymmetric Strecker process.

Experimental Section

A Typical Experimental Procedure for the Catalytic Enantioselective Strecker-Type Reactions of Aldimines with Bu_3SnCN. To $Zr(O^tBu)_4$ (0.04 mmol) in toluene (0.25 mL) was added (*R*)-6-Br-BINOL (0.04 mmol), (*R*)-3-Br-BINOL (0.04 mmol), and NMI (0.12 mmol) in toluene (0.75 mL) at room temperature. The mixture was stirred for 1 h at the same temperature, and then cooled to −65 °C. A benzene solution (1.0 mL) of **1** (0.4 mmol) and Bu_3SnCN (0.44 mmol) was added. The mixture was stirred and warmed from −65 to 0 °C over 12 h, and saturated aqueous $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with dichloromethane. After a usual workup, the crude product was chromatographed on silica gel to give the desired adduct. The optical purity was determined by HPLC analysis using a chiral column (see the Supporting Information).

Since some of the adducts were unstable, they were characterized after methylation of phenolic OH group as follows: The adduct was treated with 20% MeI-acetone (5 mL) and K_2CO_3 (200 mg). After the mixture was stirred at room temperature for 6 h, saturated aqueous NH_4Cl was added to quench the reaction. After extraction of the aqueous layer with dichloromethane, the crude product was chromatographed on silica gel to afford the corresponding methylated product (quant).

A Typical Experimental Procedure for the Catalytic Enantioselective Three-Component Strecker Reactions. A typical experimental procedure of the Strecker reactions follows: To a dichloromethane solution (3.0 mL) of 6-Br-BINOL (0.04 mmol), 3-Br-BINOL (0.04 mmol), and NMI (0.12 mmol) was added a dichloromethane solution (1.0 mL) of $Zr(O^tBu)_4$ (0.04 mmol) at room temperature. After the mixture was stirred for 1 h, a dichloromethane solution (0.2 mL) of HCN (0.8 mmol) was added at 0 °C and the mixture was further stirred for 3 h at the same temperature. The resulting solution was then added to a mixture of an aldehyde (0.4 mmol) and an amine (0.4 mmol) in dichloromethane (1 mL) at −45 °C. After the mixture was stirred for 12 h, HCN was added if the reaction was not completed. Saturated aqueous $NaHCO_3$ was then added to quench the reaction, and after a usual workup, the crude product was chromatographed on silica gel to give the desired adduct. The optical purity was determined by HPLC analysis using a chiral column (see the Supporting Information).

Since some of the adducts were unstable, they were characterized after methylation of the phenolic OH group as shown above.

Chiral Zirconium Catalyst 3. To the solution of $Zr(O^tBu)_4$ (0.04 mmol) in toluene (0.25 mL) was added (*R*)-6,6′-dibromo-BINOL (0.04 mmol) and (*R*)-3,3′-dibromo-BINOL (0.04 mmol) in toluene (0.5 mL) and 1-methylimidazole (0.12 mmol) in toluene (0.25 mL) at room temperature. After the mixture was stirred for 1 h at the same temperature, solvent was removed and then dried for 3 h at 50 °C in vacuo.

^1H NMR (CD_2Cl_2) δ 1.22 (s, ^{t}BuO), 2.60 (s, 3H, N*Me*), 5.63 (d, 2H, $J = 29.9$ Hz, H_4 and H_5 of 1-methylimidazole), 6.02 (s, 1H, H_2 of 1-methylimidazole), 6.33 (d, 1H, $J = 8.5$ Hz), 6.41 (d, 1H, $J = 9.1$ Hz), 6.52 (d, 1H, $J = 9.1$ Hz), 6.55 (dd, 1H, $J = 7.0$, 8.5 Hz), 6.78 (d, 1H, $J = 9.1$ Hz), 6.82 (d, 1H, $J = 9.1$ Hz), 6.90 (t, 1H, $J = 7.0$, 8.0 Hz), 7.33 (d, 1H, $J = 8.0$ Hz), 7.67 (d, 1H, $J = 8.9$ Hz), 7.69 (d, 1H, $J = 8.9$ Hz), 7.72 (s, 1H), 7.78 (s, 1H), 8.03 (s, 1H), 8.08 (d, 1H, $J = 8.9$ Hz), 8.20 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR (CD_2Cl_2) δ 30.6 (^{t}BuO), 34.0 (N*Me*), 114.2, 114.4, 117.6, 117.7, 118.7, 118.8, 119.1 (C_4 and C_5 of 1-methylimidazole), 122.0, 124.6, 124.7, 125.7, 126.1, 126.5, 126.6, 126.7, 126.8, 126.9, 127.0, 1217.1, 127.2, 127.6, 128.86, 128.90, 128,93, 129.0, 139.5, 132.0, 132.9 (C_2 of 1-methylimidazole), 155.5, 159.3, 159.9.

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Supporting Information Available: Experimental Section and ^1H and ^{13}C NMR data of products (PDF). This material is available free of charge via the Internet at hppt://pubs.acs.org.

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