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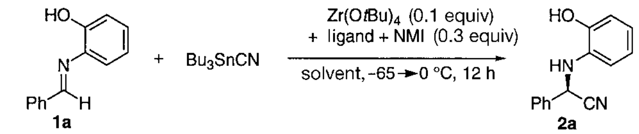
Catalytic, Enantioselective Synthesis of α-Aminonitriles with a Novel Zirconium Catalyst**

Haruro Ishitani, Susumu Komiyama, and Shū Kobayashi*

α-Aminonitriles are useful intermediates for the synthesis of amino acids[1] and nitrogen heterocycles such as thiadiazoles and imidazoles.[2] The Strecker reactions of aldimines with cyanides provide one of the most efficient methods for the preparation of α-aminonitriles,[3] and several diastereoselective approaches for the synthesis of optically active α-aminonitriles have been reported.[4] In 1996 Lipton et al. reported the first catalytic enantioselective Strecker-type reactions with use of a dipeptide ligand as catalyst.[5] Although efficient catalytic reactions provide α-aminonitriles derived from benzaldehyde derivatives in high enantioselectivities, low selectivities were observed in the reactions of aldimines derived from aliphatic and heterocyclic aldehydes.[6] Here we report chiral zirconium-catalyzed Strecker reactions of aldimines with tributyltin cyanide (Bu_3SnCN), which provide various types of α-aminonitriles in high yields and with high enantioselectivities.

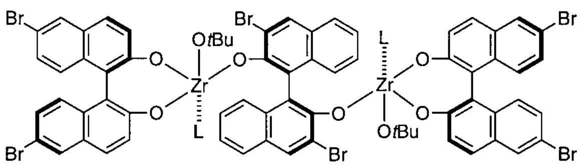
Recently, we reported the first catalytic enantioselective Mannich[7] and aza-Diels–Alder reactions[8] with a chiral zirconium catalyst. In these reactions, the zirconium catalyst effectively activates aldimines, which leads to efficient catalytic processes. We then used a zirconium catalyst in asymmetric Strecker reactions. In the presence of a zirconium catalyst (10 mol%) that was prepared from $Zr(OtBu)_4$, (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-6-Br-BINOL, 2 equiv),[9] and *N*-methylimidazole (NMI, 3 equiv), aldimine **1a** was treated with Bu_3SnCN[10] in dichloromethane at −45 °C. The reaction proceeded smoothly to afford the corresponding α-aminonitrile in 70% yield with 55% *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) with use of a chiral zirconium catalyst prepared from $Zr(OtBu)_4$ (1 equiv), (*R*)-6-Br-BINOL (1 equiv), (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3-Br-BINOL),[11] and NMI (3 equiv; Table 1). Use of other solvents resulted in a slight decrease in selectivity. The free hydroxyl group of the aldimine was important for obtaining both high yield and high selectivity.[7] When the aldimine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, the corresponding α-aminonitrile derivatives were obtained in much lower yields and with lower enantioselectivities (aniline: 29% yield, 1% *ee*; 2-methoxyaniline: 45% yield, 5% *ee*).

Table 1. Influence of ligands and solvents.



Ligand (equiv)	Solvent	Yield [%]	*ee* [%]
(*R*)-6-Br-BINOL (0.2)	CH_2Cl_2	70	55
(*R*)-6-Br-BINOL (0.2)	toluene/benzene (1/1)	72	69
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	toluene/benzene (1/1)	92	91
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	toluene	93	86
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	toluene/C_2H_5CN (1/1)	91	86
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	benzene/CH_2Cl_2 (1/1)	97	83
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	CH_2Cl_2	85	71

It was interesting 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 the zirconium binuclear complex **3** was formed under the reaction conditions (Scheme 1). Complex **3** consists of two zirconium centers, two (*R*)-6-Br-BINOL and two NMI units, and one (*R*)-3-Br-BINOL unit. The structure of this composition is very stable



Scheme 1. Structure of the chiral zirconium catalyst **3** (L = NMI).

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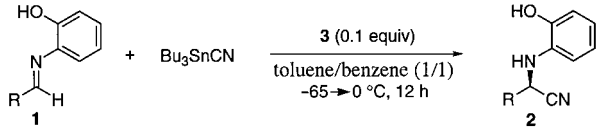
and is formed even with different molar ratios of $Zr(OtBu)_4$, (*R*)-6-Br-BINOL, (*R*)-3-Br-BINOL, and NMI; formation of **3** upon combination of 1 equiv of $Zr(OtBu)_4$, 1 equiv of (*R*)-6-Br-BINOL, 0.5–1 equiv of (*R*)-3-Br-BINOL, and 2–3 equiv of NMI was confirmed by ^1H and ^{13}C NMR spectroscopy.[12]

We then examined several different Strecker reactions (Table 2). Aldimines derived from aromatic aldehydes as well as aliphatic and heterocyclic aldehydes reacted with Bu_3SnCN smoothly to afford the corresponding α-aminonitrile derivatives in high yields and with high enantiomeric excesses. Since both enantiomers of the chiral ligands 6-Br-BINOL and 3-Br-BINOL are readily available, both enatiomers of α-aminonitrile 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. It is stable in water and does not react to produce HCN. This is in contrast to trimethylsilyl cyanide (TMSCN), which is easily hydrolyzed to form HCN even in the presence of a small amount of water.[13] After the reaction was completed, all tin sources were quantitatively recovered as bis(tributyltin) oxide, which can be converted into tributyltin chloride[14] and then into Bu_3SnCN.[9, 15]

Table 2. Catalytic, asymmetric Strecker reactions.

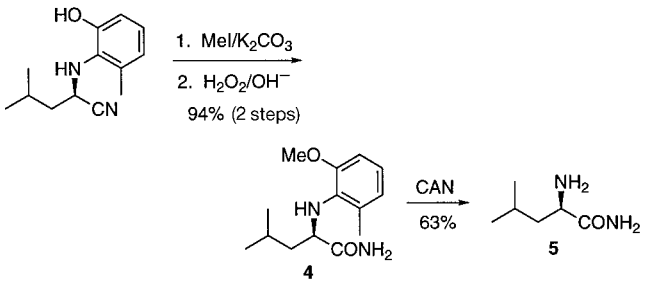


Entry	R	Yield [%]	ee [%]
1	1-Naphthyl	98	91
2	Ph	92	91
3	*p*-ClC_6H_4	90	88
4	*p*-$MeOC_6H_4$	97	76
5	*o*-MeC_6H_4	96	89[a]
6	*o*-MeC_6H_4	93	89 (*S*)[b]
7		85	87
8		89	80
9		89	92
10	$Ph(CH_2)_2$	55	83[c]
11	*i*Bu	79	83[c]
12	C_8H_{17}	72	74[c]

[a] When 0.05 equiv of **3** were used, a yield of 94% and 87% ee were obtained. [b] 0.1 equiv of *ent*-**3** were used. [c] The imine was prepared in situ from the corresponding aldehyde and 2-amino-3-methylphenol in the presence of 4-Å molecular sieves.

α-Aminonitrile **2b** was easily converted into leucinamide according to Scheme 2. Thus, after methylation of the phenolic OH group of **2b** with methyl iodide and potassium bicarbonate, the nitrile group was converted into an amide moiety.[16] Treatment of **4** with cerium ammonium nitrate (CAN)[17] gave leucinamide (**5**). The absolute configuration (*R*) was assigned by comparison of the configuration of the hydrochloride with that of an authentic sample.[18]

Catalytic enantioselective Strecker reactions of aldimines with Bu_3SnCN have been developed with use of a novel chiral zirconium binuclear catalyst. High enantioselectivities in the synthesis of α-aminonitrile derivatives with a wide range of substrates have been achieved.



Scheme 2. Synthesis of leucinamide (**5**).

Experimental Section

3: To a solution of $Zr(OtBu)_4$ (0.04 mmol) in toluene (0.25 mL) was added (*R*)-6-Br-BINOL (0.04 mmol) and (*R*)-3-Br-BINOL (0.04 mmol) in toluene (0.5 mL) and NMI (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 the residue was dried for 3 h at 50 °C in vacuo. ^1H NMR (CD_2Cl_2): $\delta = 1.22$ (s, *t*BuO), 2.60 (s, 3H, NMe), 5.59 (s, 1H, H4 or H5 of NMI), 5.65 (s, 1H, H4 or H5 of NMI), 6.02 (s, 1H, H_2 of NMI), 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 (dd, 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, 1H, $J = 8.9$ Hz); ^{13}C NMR (CD_2Cl_2): $\delta = 30.6$ (*t*BuO), 34.0 (NMe), 114.2, 114.4, 117.6, 117.7, 118.7, 118.8, 119.1 (C4 and C5 of NMI), 122.0, 124.6, 124.7, 125.7, 126.1, 126.5, 126.6, 126.7, 126.8, 126.9, 127.0, 127.1, 127.2, 127.6, 128.86, 128.90, 128.93, 129.0, 130.5, 132.0, 132.9 (C2 of NMI), 155.5, 159.3, 159.9; other signals were assigned to free (*R*)-3-Br-BINOL.

Typical experimental procedure for the catalytic enantioselective Strecker reactions: To $Zr(OtBu)_4$ (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 solution of **1** (0.4 mmol) and Bu_3SnCN (0.44 mmol) in benzene (1.0 mL) was added. The mixture was stirred and warmed from −65 to 0 °C over 12 h, and a saturated aqueous solution of $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with dichloromethane. After a usual work up, the crude product was subjected to chromatography on silica gel to give the desired adduct. The optical purity was determined by HPLC analysis with a chiral column (see below). Since most of the adducts were unstable, they were characterized after methylation of the phenolic OH group as follows: The adduct was treated with a 20% MeI/acetone solution (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 subjected to chromatography on silica gel to afford the corresponding methylated product quantitatively.

2-(2-Hydroxyphenyl)amino-2-phenylacetonitrile: HPLC (Daicel Chiralcel OD, hexane/*i*PrOH 9/1, flow rate 1.0 mL min^{-1}): $t_R = 40.0$ min (major product), 49.7 min (minor product).

2-(2-Methoxyphenyl)amino-2-phenylacetonitrile: ^1H NMR ($CDCl_3$): $\delta =$ 3.81 (s, 3H), 4.67 (d, 1H, $J = 8.3$ Hz), 5.43 (d, 1H, $J = 8.3$ Hz), 6.90–6.95 (m, 4H), 7.42–7.47 (m, 3H), 7.59–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta =$ 49.8, 55.4, 110.0, 111.6, 118.2, 119.6, 121.2, 127.2, 129.2, 129.4, 134.1, 134.5, 147.4; HR-MS calcd for $C_{15}H_{14}N_2O$ [M^+]: 238.1106, found: 238.1093.

4: The aminoamide **4** was synthesized according to the literature precedure.[16] The methylated adduct was prepared as described above, and the crude product (0.4 mmol) was dissolved in dichloromethane (1.0 mL). After the solution was cooled to 0 °C, a catalytic amount of Bu_4NHSO_4 (0.08 mmol), an excess amount of 30% aqueous hydrogen

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peroxide, and 20% aqueous NaOH were added successively. The mixture was stirred for 1 h at the same temperature, and then warmed to room temperature. The reaction was monitored by thin-layer chromatography (TLC), and when there was no more starting material (ca. 2 h), ether was added, and the aqueous layer was extracted with dichloromethane. The pure N-protected leucinamide **4** was obtained in 94% yield from the cyanation product (two steps) after isolation by column chromatography on silica gel ($CHCl_3$/MeOH 19/1). ^{1}H NMR ($CDCl_3$): $\delta = 0.85$ (d, 3H, $J =$ 6.4 Hz), 0.95 (d, 3H, $J = 6.4$ Hz), 1.58–1.63 (m, 1H), 1.78–1.87 (m, 2H), 2.77 (s, 3H), 3.82 (s, 3H), 3.82 (br s, 1H), 6.71–6.82 (m, 3H), 6.88 (br s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 18.6$, 21.7, 23.35, 23.38, 24.9, 55.6, 60.0, 108.9, 120.8, 124.0, 127.3, 135.6, 149.8, 178.6.

5: The N-protected aminoamide **4** (0.38 mmol) was dissolved in 80% wet MeOH (5.0 mL). CAN (2.0 mmol) was added at 0 °C, and the mixture was stirred for 6 h at the same temperature. Water was added, and the acidic solution was washed with dichloromethane. The aqueous solution was made alkaline by adding 1N NaOH, and was then extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed, and the pure D-leucinamide **5** was obtained without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 0.93$ (d, 3H, $J = 6.4$ Hz), 0.97 (d, 3H, $J = 6.4$ Hz), 1.39 (ddd, 1H, $J = 4.9$, 9.8, 13.8 Hz), 1.65 (ddd, 1H, $J = 4.3$, 4.9, 13.8 Hz), 1.55–1.80 (m, 3H), 3.76 (dd, 1H, $J =$ 4.3, 9.8 Hz), 6.37 (br s, 1H), 7.22 (br s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 21.0$, 23.1, 24.4, 43.7, 53.1, 178.8; HR-MS calcd for $C_6H_{14}N_2O$ [M^+]: 130.1107, found: 130.1091; (*R*)-leucinamide hydrochloride: $[\alpha]_D^{25} = -8.2$ ($c = 0.22$ in H_2O).[18]

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[13] 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 led to the corresponding α-aminonitrile in 33% yield and with 63% *ee*; with triethylsilyl cyanide this product was obtained in 65% yield and with 63% *ee* (not optimized).

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