Synthesis and Application of 3-Substituted (*S*)-BINOL as Chiral Ligands for the Asymmetric Ethylation of Aldehydes

ZHI-GUANG ZHANG,[1] ZHI-BING DONG,[1,2] AND JIN-SHAN LI[1]*

[1]*State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China*
[2]*School of Chemistry and Chemical Engineering, Jiangsu University, Zhenjiang 212013, People's Republic of China*

ABSTRACT A series of (*S*)-BINOL ligands substituted at the 3 position with some five-membered nitrogen-containing aromatic heterocycles were effectively prepared and their catalytic abilities were evaluated in the asymmetric addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide. Under the optimized reaction conditions, titanium complex of (*S*)-3-(1*H*-benzimidazol-1-yl)-1,1′-bi-2-naphthol was found to be the most efficient catalyst for asymmetric ethylation of various aldehydes to generate the corresponding secondary alcohols in up to 99% yield and 91% ee. *Chirality 22:820–826, 2010.*

KEY WORDS: BINOL; titanium; nitrogen-containing aromatic heterocycle; asymmetric addition

INTRODUCTION

Enantioselective construction of carbon–carbon bonds is one of the most important and vigorously pursued areas in organic chemistry.[1–7] Since the pioneering work of Oguni et al. in 1984,[8,9] asymmetric ethylation of carbonyl compounds in the presence of catalytic amounts of chiral ligands has attracted great attention in recent years,[10–19] not only because it is an effective and excellent method to form chiral carbon–carbon bonds but also because the products, optically active alcohols, are valuable building blocks for many naturally occurring compounds, pharmacologically and biologically interesting molecules.[20–23] Therefore, numerous kinds of chiral ligands, such as amino alcohols (*N*,*O*-ligands), diamines (*N*,*N*-ligands), and diols (*O*,*O*-ligands) have been designed and evaluated in the catalytic asymmetric addition of diethylzinc to aldehydes.[24–31] As an important *O*,*O*-ligand, BINOL and its derivatives have been widely studied and earned a prominent status because of their outstanding performance in a good number of asymmetric reactions.[32–39]

In connection with our interest in the design and preparation of a set of novel chiral ligands, for example, the BINOL ligands bearing sulfur or nitrogen-containing heterocycles at 3 or 3,3′ positions, and their applications in the asymmetric ethylation of several kinds of aldehydes and α,β-unsaturated ketones,[40–46] herein, we report the synthesis of 3-substituted BINOL bearing imidazole and triazole groups and their utilization in the asymmetric addition of diethylzinc to various aldehydes in the presence of titanium tetraisopropoxide. Although the (*R*) configuration of Ligand-**1**, Ligand-**3**, and Ligand-**6** have been prepared and used as chiral ligands in the enantioselective cyanation of aldehydes,[47] their applications in the asymmetric ethylation of aldehydes have not been reported so far. What is more, benzimidazole, benzotriazole, and 5-chlorobenzotriazole were also conveniently introduced at the 3 position of (*S*)-BINOL and tested in the reaction of diethylzinc with benzaldehyde.

EXPERIMENTAL

General Methods

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-400 instrument in $CDCl_3$ or d_6-DMSO solution with TMS as internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were obtained on a Varian QFT-ESI mass spectrometer. Melting points were determined with XRC-1 and are uncorrected. All experiments which are sensitive to moisture or air were carried out under an argon atmosphere using standard Schlenk techniques. Diethylzinc (1.5 M in toluene) was purchased from Acors. All anhydrous solvents were purified and dried by standard techniques just before use.

The preparation of 3-substituted (*S*)-BINOL ligands and their intermediates (*S*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (*S*)-1. This known compound was prepared according to the literature method[48] in 98% yield as colorless crystals. M.p. 92–93°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.14 (s, 6H), 4.97 (d, J = 6.6 Hz, 2H), 5.08 (d, J = 6.6 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.20–7.24 (m, 2H), 7.32–7.36 (m, 2H), 7.57 (d, J = 9.2 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), and 7.95 (d, J = 9.2 Hz, 2H).

*Correspondence to: J.-S. Li, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China. E-mail: jinshanl@nankai.edu.cn
Received for publication 27 August 2009; Accepted 1 December 2009
DOI: 10.1002/chir.20842
Published online 21 April 2010 in Wiley Online Library (wileyonlinelibrary.com).

(*S*)-3-dihydroxyborane-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (*S*)-2.[49] To a solution of **(*S*)-1** (3.74 g, 10 mmol) in anhydrous THF (40 ml) was added *n*-BuLi (4.2 ml, 11 mmol, 2.61 M in hexane) at 0°C under Ar and the reaction mixture was stirred for 5 h. $B(OCH_3)_3$ (3.4 ml, 30 mmol) was added slowly at −78°C. The solution was allowed to warm to r.t. and left stirring overnight. The reaction mixture was cooled to 0°C, and 30 ml saturated NH_4Cl aqueous solution was added, and the reaction mixture was stirred for 2 h. Et_2O (40 ml) was added and stirred for 30 min. The phases were separated and the aqueous phase was extracted with Et_2O (20 ml × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (5:1) to give **(*S*)-2** (3.722 g, 89%) as a white solid. M.p. 204–205°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.09 (s, 3H), 3.17 (s, 3H), 4.47 (d, *J* = 4.8 Hz, 1H), 4.63 (d, *J* = 4.8 Hz, 1H), 5.06 (d, *J* = 6.8 Hz, 1H), 5.12 (d, *J* = 6.8 Hz, 1H), 6.04 (s, 2H), 7.17 (t, *J* = 8.0 Hz, 2H), 7.28–7.34 (m, 3H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.97 (t, *J* = 8.8 Hz, 2H), and 8.55 (s, 1H).

(*S*)-3-(1H-imidazol-1-yl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (*S*)-3. **(*S*)-2** (8.36 g, 20 mmol) was added in one portion to a vigorously stirred mixture of imidazole (2.72 g, 40 mmol) and a catalytic amount of CuCl (198.0 mg, 2 mmol) in absolute methanol (100 ml). The mixture was then refluxed for 3 h under dry Oxygen. The reaction was filtered and the filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel eluting with Petroleum Ether/Acetone (2:1) to give **(*S*)-3** (8.193 g, 95%) as a white powder. $[\alpha]_D^{25} = -92$ (*c* 0.45, CH_2Cl_2); M.p. 117–118°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.51 (s, 3H), 3.24 (s, 3H), 4.31 (d, *J* = 6.0 Hz, 1H), 4.37 (d, *J* = 6.0 Hz, 1H), 5.10 (d, *J* = 6.8 Hz, 1H), 5.16 (d, *J* = 6.8 Hz, 1H), 7.19–7.40 (m, 5H), 7.43–7.52 (m, 3H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.90 (t, *J* = 8.4 Hz, 3H), 7.98 (s, 1H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 56.02, 56.31, 94.81, 98.99, 116.24, 119.34, 120.84, 124.29, 124.56, 125.23, 126.06, 126.16, 126.94, 127.06, 127.89, 128.04, 129.49, 129.63, 130.34, 130.53, 130.88, 133.12, 133.72, 138.00, 147.25, 152.86; HR-MS (ESI) calcd for $C_{27}H_{25}N_2O_4$ $[M^+ + H]$: 441.1814, found: 441.1809.

(*S*)-3-(1H-benzimidazol-1-yl)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl (*S*)-4. This compound was prepared by the same method as **(*S*)-3**. Colorless crystals, Yield 95%; $[\alpha]_D^{25} = -110.5$ (*c* 2.0, CH_2Cl_2); M.p. 132–134°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.25 (s, 3H), 3.27 (s, 3H), 4.21 (d, *J* = 8.0 Hz, 1H), 4.29 (d, *J* = 2.4 Hz, 1H), 5.15 (d, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 2.4 Hz, 1H), 7.28–7.42 (m, 7H), 7.49–7.55 (m, 2H), 7.63 (d, *J* = 9.2 Hz, 1H), 7.69–7.96 (m, 3H), 8.00 (d, *J* = 8.8 Hz, 1H), 8.07 (s, 1H), 8.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 56.05, 94.83, 99.13, 111.14, 116.23, 119.22, 120.31, 122.61, 123.60, 124.28, 125.18, 126.17, 126.22, 126.98, 127.25, 127.99, 128.09, 128.30, 129.36, 129.63, 130.36, 130.65, 133.53, 133.71, 134.76, 143.38, 143.72, 148.66, 152.84; HR-MS (ESI) calcd for $C_{31}H_{27}N_2O_4$ $[M^+ + H]$: 491.1971, found: 491.1965.

(S)-3-(1H-imidazol-1-yl)-1,1′-bi-2-naphthol, Ligand-1.[47] **(*S*)-3** (8.19 g, 18.6 mmol) was dissolved in the mixed solvent of CH_3OH/CH_2Cl_2 (30 ml/30 ml). Five milliliters of HCl (12 M) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 3 h, neutralized with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (30 ml × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/CH_3OH (40:1) to give Ligand-**1** (6.226 g, 95%) as a pale-yellow solid. $[\alpha]_D^{25} = -66.2$ (*c* 2.0, CH_3OH); M.p. 205–206°C; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 6.80 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 7.11 (s, 1H), 7.20–7.29 (m, 3H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.61 (s, 1H), 7.88–7.94 (m, 3H), and 8.07 (s, 2H).

(S)-3-(1H-benzimidazol-1-yl)-1,1′-bi-2-naphthol, Ligand-2. Ligand-**2** was prepared from **(*S*)-4** by the same method as Ligand-**1**. Colorless crystals, Yield 95%; $[\alpha]_D^{25} = -85$ (*c* 2.0, CH_2Cl_2); M.p. 203–205°C; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 6.96 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.27–7.30 (m, 5H), 7.37 (t, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 4.4 Hz, 1H), 7.78 (t, *J* = 4.8 Hz, 1H), 7.89–7.95 (m, 2H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H), 8.50 (s, 1H), 8.84 (s, 1H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 111.47, 113.23, 118.41, 118.77, 119.53, 121.93, 122.46, 122.88, 123.67, 123.94, 124.50, 125.61, 126.09, 126.31, 126.80, 127.84, 128.07, 128.13, 128.27, 129.66, 133.45, 134.13, 134.66, 143.16, 144.39, 147.99, 153.83; HR-MS (ESI) calcd for $C_{27}H_{19}N_2O_2$ $[M^+ + H]$: 403.1447, found: 403.1441.

(*S*)-3-Iodo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl, (*S*)-5. To a solution of **(*S*)-1** (3.74 g, 10 mmol) in anhydrous THF (40 ml) was added *n*-BuLi (4.2 ml, 11 mmol, 2.61 M in hexane) at 0°C under Ar and the reaction mixture was stirred for 5 h. A solution of I_2 (0.508 g, 20 mmol) in 20 ml THF was added slowly at −78°C. The solution was allowed to warm to r.t. and left stirring overnight. The reaction mixture was cooled to 0°C, and 30 ml saturated $Na_2S_2O_3$ aqueous solution was added, and the reaction mixture was stirred for 2 h. Et_2O (40 ml) was added and stirred for 30 min. The phases were separated and the aqueous phase was extracted with Et_2O (20 ml × 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (10:1) to give **(*S*)-5** (4.5 g, 90%). Yellow powder; M.p. 124–125°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.72 (s, 3H), 3.21 (s, 3H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 7.2 Hz, 1H), 5.06 (d, *J* = 9.2 Hz, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 7.15–7.44 (m, 6H), 7.60 (d, *J* = 12 Hz, 1H), 7.80 (d, *J* = 10.8 Hz, 1H), 7.87 (d, *J* = 10.8 Hz, 1H), and 7.98 (d, *J* = 12 Hz, 1H).

Ligand-**3**–Ligand-**6** and their precursors were synthesized according to the similar procedure described by Gau and co-workers.[47]

(*S*)-3-(1H-1,2,4-triazol-1-yl)-2′-methoxymethoxy-1,1′-binaphthyl-2-ol, (*S*)-6. White solid, Yield 60%; M.p. 194–195°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.19 (s, 3H), 5.08 (d, J = 6.8 Hz, 1H), 5.13 (d, J = 6.8 Hz, 1H), 7.16 (q, J = 8.4 and 8.8 Hz, 2H), 7.28–7.31 (m, 4H), 7.40 (t, J = 6.8 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.05 (t, J = 7.2 and 9.2 Hz, 2H), 8.20 (s, 1H), and 8.26 (s, 1H).

(*S*)-3-(1H-benzotriazol-1-yl)-2′-methoxymethoxy-1,1′-binaphthyl-2-ol, (*S*)-7. White powder, Yield 70%; $[\alpha]_D^{25}$ = −80 (*c* 2.0, CH_2Cl_2); M.p. 159–160°C; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 3.14(s, 3H), 5.17 (d, J = 6.8 Hz, 1H), 5.21 (d, J = 6.8 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.38–7.32 (m, 2H), 7.43–7.39 (m, 2H), 7.51–7.46 (m, 1H), 7.63–7.56 (m, 2H), 7.67 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 9.12 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 55.85, 94.58, 111.94, 117.33, 118.55, 119.00, 119.83, 124.41, 124.51, 124.65, 124.85, 124.96, 126.26, 127.23, 127.61, 128.01, 128.45, 128.61, 129.03, 129.95, 130.46, 134.04, 134.461, 145.62, 147.76, 153.56; HR-MS (ESI) calcd for $C_{28}H_{22}N_3O_3$ [M^++H]: 448.1661, found: 448.1656.

(*S*)-3-(5-chloro-1H-benzotriazol-1-yl)-2′-methoxymethoxy-1,1′-binaphthyl-2-ol, (*S*)-8. Colorless crystals, Yield 76%; $[\alpha]_D^{25}$ = −90 (*c* 2.0, CH_2Cl_2); M.p. 120–122°C; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 3.15 (d, J = 8.4 Hz, 3H), 5.15–5.23 (m, 2H), 6.96 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 6.8 and 8.0 Hz, 2H), 7.39–7.44 (m, 2H), 7.53 (m, 1H), 7.59 (m, 1H), 7.66 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H), 8.06 (m, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.36 (t, J = 8.4 and 9.6 Hz, 1H), 9.20 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 55.88, 94.51, 111.81, 112.87, 115.46, 117.22, 117.31, 118.38, 119.18, 120.20, 121.53, 124.43, 124.60, 124.88, 124.96, 125.04, 125.47, 127.61, 128.03, 128.14, 128.60, 129.03, 129.08, 129.11, 129.23, 129.93, 130.49, 134.02, 134.05, 134.56; HR-MS (ESI) calcd for $C_{28}H_{20}ClN_3NaO_3$ [M^++Na]: 504.1091, found: 504.1085.

(*S*)-3-(1H-pyrazol-1-yl)-2′-methoxymethoxy-1,1′-binaphthyl-2-ol, (*S*)-9. White solid, Yield 58%; M.p. 188–189°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.20 (s, 3H), 5.03 (d, J = 7.6 Hz, 1H), 5.16 (d, J = 7.6 Hz, 1H), 6.60 (t, J = 2.0Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.21–7.25 (m, 2H), 7.32–7.38 (m, 3H), 7.61 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.85–7.91 (m, 2H), 7.98 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 2.8 Hz, 1H), 11.34 (s, 1H).

(S)-3-(1H-1,2,4-triazol-1-yl)-1,1′-bi-2-naphthol, Ligand-3. White crystals, Yield 98%; $[\alpha]_D^{25}$ = −99.9 (*c* 2.0, THF); M.p. > 224°C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.91 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 7.20–7.29 (m, 3H), 7.37 (t, J = 8.8 Hz, 2H), 7.89 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.31 (s, 1H), 8.33 (s, 1H), 9.10 (s, 1H), 9.24 (s, 1H), 9.51 (s, 1H).

(S)-3-(1H-benzotriazol-1-yl)-1,1′-bi-2-naphthol, Ligand-4. White powder, Yield 94%; $[\alpha]_D^{25}$ = −82 (*c* 2.0, CH_2Cl_2); M.p. 216–218°C; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 7.24 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.33–7.47 (m, 5H), 7.48–7.52 (m, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 111.67, 111.94, 116.82, 118.49, 119.72, 123.75, 124.20, 124.68, 124.96, 125.03, 125.22, 126.85, 127.32, 128.29, 128.33, 128.61, 129.04, 131.04, 133.87, 133.92, 134.13, 145.44, 146.97, 153.21; HR-MS (ESI) calcd for $C_{26}H_{18}N_3O_2$ [M^++H]: 404.1399, found: 404.1394.

(S)-3-(5-chloro-1H-benzotriazol-1-yl)-1,1′-bi-2-naphthol, Ligand-5. White powder, Yield 94%; $[\alpha]_D^{25}$ = −110.3 (*c* 2.0, CH_3OH); M.p. 163–164°C; ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm) 6.99–7.07 (m, 2H), 7.27–7.41 (m, 5H), 7.64 (s, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.91–7.95 (m, 2H), 8.03–8.06 (m, 1H), 8.32 (t, J = 6.0 Hz, 2H), 9.05–9.07 (m, 1H), 9.52 (t, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ (ppm) 111.57, 112.97, 113.36, 118.62, 118.77, 120.97, 122.54, 123.99, 124.59, 124.94, 125.45, 126.42, 127.06, 127.51, 127.66, 128.09, 128.29, 128.45, 128.57, 129.79, 132.92, 134.08, 134.24, 134.63, 143.87, 145.78, 147.34, 153.83; HR-MS (ESI) calcd for $C_{26}H_{16}ClN_3NaO_2$ [M^++Na]: 460.0829, found: 460.0823.

(S)-3-(1H-pyrazol-1-yl)-1,1′-bi-2-naphthol, Ligand-6. White solid. Yield 92%; $[\alpha]_D^{25}$ = −71.9 (*c* 2.0, CH_2Cl_2); M.p. 185–187°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.63 (s, 1H), 7.17 (q, J = 4.4 and 8.4 Hz, 2H), 7.32 (t, J = 6.8 Hz, 2H), 7.41 (t, J = 6.8 and 8.8 Hz, 3H), 7.80 (s, 1H), 7.91 (m, 4H), 8.06 (s, 1H), 8.30 (d, J = 2 Hz, 1H), 11.76 (s, 1H).

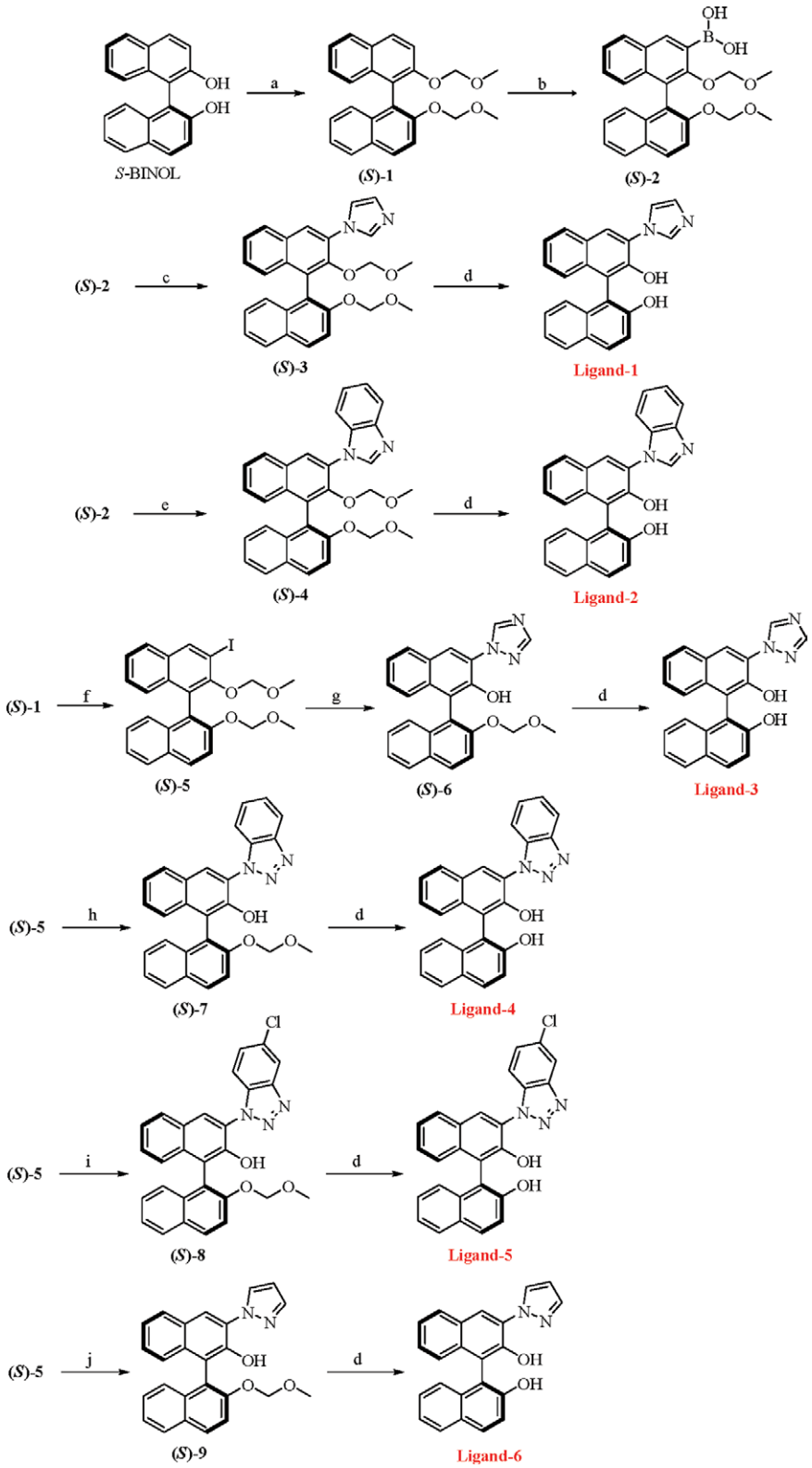
General Procedure for Enantioselective Addition of Diethylzinc to Aldehydes

Ligand-**2** (20 mg, 0.05 mmol) and Ti(O-*i*Pr)$_4$ (341 mg, 1.2 mmol) were dissolved in CH_2Cl_2 (5 ml) or other solvents under argon. The resulting mixture was stirred for 30 min at room temperature (25°C). Diethylzinc solution (1 ml, 1.5 M in toluene) was added to the above flask and the color of the solution became orange–green. After 30 min, 1 mmol of the corresponding aldehyde was added at 0°C. The mixture was stirred at 0°C for 5 h and the reaction was quenched with saturated NH_4Cl aqueous solution. The resulting mixture was filtered, extracted with ethyl acetate (10 ml × 3) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography column to afford the expected *sec*-alcohol. The enantiomeric excess was determined by chiral GC.

RESULTS AND DISCUSSION

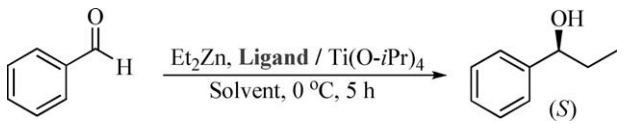
The synthetic routes for ligands Ligand-**1**–Ligand-**6** are depicted in Scheme 1.

Protection of two hydroxyl groups of (*S*)-BINOL with methoxymethyl (MOM) group using chloromethyl methyl ether gave (*S*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl



Scheme 1. Reagents and conditions: (a) THF, MOMCl, 0°C; (b) (i) THF, 1.1 equiv *n*-BuLi, 0°C, (ii) $B(OMe)_3$, −78°C, (iii) NH_4Cl; (c) CH_3OH, CuCl, imidazole, Reflux; (d) CH_2Cl_2, CH_3OH, 12 M HCl, rt; (e) CH_3OH, CuCl, benzimidazole, Reflux; (f) THF, 1.1 equiv *n*-BuLi, 0°C, (ii) I_2, −78°C, (iii) $Na_2S_2O_3$; (g) CuI, K_2CO_3, DMSO, *N*,*N*-dimethylglycine, 1,2,4-triazole; (h) CuI, K_2CO_3, DMSO, *N*,*N*-dimethylglycine, benzotriazole; (i) CuI, K_2CO_3, DMSO, *N*,*N*-dimethylglycine, 5-chlorobenzotriazole; (j) CuI, K_2CO_3, DMSO, *N*,*N*-dimethylglycine, pyrazole.

TABLE 1. Screening of reaction conditions for the asymmetric ethylation of benzaldehyde catalyzed by ligand in the presence of Ti(O-*i*Pr)$_4$[a]



Entry	Ligand (mol %)	Solvent	Yield (%)[b]	e.e. (%) [c]
1	Ligand-**1** (10)	CH_2Cl_2	>99	77
2	Ligand-**2** (10)	CH_2Cl_2	>99	81
3	Ligand-**3** (10)	CH_2Cl_2	90	74
4	Ligand-**4** (10)	CH_2Cl_2	91	79
5	Ligand-**5** (10)	CH_2Cl_2	90	75
6	Ligand-**6** (10)	CH_2Cl_2	90	41
7	Ligand-**2** (10)	Hexane	92	79
8	Ligand-**2** (10)	Toluene	85	81
9	Ligand-**2** (15)	CH_2Cl_2	>99	81
10	Ligand-**2** (5)	CH_2Cl_2	>99	83
11	Ligand-**2**(2)	CH_2Cl_2	>99	72

[a]Ti(O-*i*Pr)$_4$/Et$_2$Zn/benzaldehyde = 1.2:1.5:1.
[b]Isolated yield.
[c]Data were determined by GC analysis using a chiral column (Chiral beta-DEX 120 capillary column).

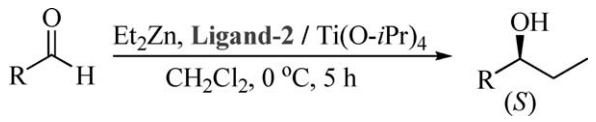
(*S*)-1 in 98% yield. Lithiation of **(*S*)-1** with 1.1 equiv. of *n*-BuLi at 0°C for 4 h, followed by the addition of $B(OCH_3)_3$ at −78°C, and subsequently quenching with saturated NH_4Cl aqueous solution generated (*S*)-3-dihydroxyborane-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl **(*S*)-2** in 89% yield, and the unreacted **(*S*)-1** could be recovered and reused. According to the procedure reported by Gau and co-workers,[47] N-arylation reaction of **(*S*)-2** with imidazole and benzimidazole successfully produced the cross-coupling products **(*S*)-3** and **(*S*)-4** nearly quantitatively. After deprotection, ligands Ligand-**1** and Ligand-**2** were obtained in 80% and 82% overall yields, respectively, starting from (*S*)-BINOL.

Iodination of **(*S*)-1** also proceeded smoothly to give **(*S*)-5** in 90% yield. CuI catalyzed cross-coupling reactions of **(*S*)-5** with 1,2,4-triazole, benzotriazole, 5-chlorobenzotriazole, or pyrazole efficiently delivered the corresponding products with good yields, and deprotection of the MOM group subsequently afforded the desired ligands Ligand-**3**, Ligand-**4**, Ligand-**5**, and Ligand-**6**.

With this sterically and electronically varied set of 3-substituted (*S*)-BINOL derivatives, first we chose the asymmetric addition of Et_2Zn to benzaldehyde as a model reaction to examine their efficiencies as chiral ligands. The active catalyst was formed in situ by mixing the ligand with 1.2 equiv. Ti(O-*i*Pr)$_4$ in CH_2Cl_2. The results are summarized in Table 1.

It could be concluded that all ligands provided excellent to almost quantitative yield, along with the significant changes in the enantioselectivity. Compared with Ligand-**1**, a sharp decrease in enantioselectivity was observed when Ligand-**6** was used as ligand (entries 1 and 6), suggesting that the position of sp^2-hybridized nitrogen atom in heterocycles plays a crucial role in the catalytic process.

TABLE 2. Asymmetric addition of diethylzinc to various aldehydes catalyzed by Ligand-2[a]



Entry	R	Yield (%) [b]	e.e. (%) [c]
1	4-fluorophenyl	>99	82
2	4-chlorophenyl	93	82
3	4-bromophenyl	98	84
4	4-methoxylphenyl	97	80
5	4-methylphenyl	92	83
6	4-trifluoromethylphenyl	78	85
7	4-dimethylaminophenyl	90	82
8	4-diethoxymethylphenyl	98	84
9	3-methoxylphenyl	93	88
10	3-methylphenyl	83	78
11	2-methoxylphenyl	>99	76
12	2-chlorophenyl	93	70
13	2,4-dichlorophenyl	>99	74
14	2,4-dimethoxyphenyl	94	64
15	3,4-dichlorophenyl	86	76
16	1-naphthyl	>99	91
17	*trans*-PhCH=CH	>99	80
18	2-Furyl	98	48 [d]
19	5-piperonyl	>99	82

[a]Ligand-**2**/Ti(O-*i*Pr)$_4$/Et$_2$Zn/aldehyde = 0.05:1.2:1.5:1.
[b]Isolated yield.
[c]Data were determined by GC analysis using a chiral column (Chiral beta-DEX 120 capillary column).
[d]Datum was determined by HPLC analysis using a chiral OD-H column.

Increasing steric hindrance of the substituents improved the enantioselectivity slightly (entries 1 and 2, 3, and 4). Reducing the electronic nature of Ligand-**4** by introducing a chlorine atom at the 5 position of benzotriazole had a weak effect on the result, which implied that the electronic property of ligand could be neglected (entries 4 and 5). As a result, Ligand-**2** was the choice of ligand in terms of yield and enantiomeric excess (entry 2). Further screening of solvents revealed that inferior results were achieved when reactions were conducted in hexane and toluene (entries 7 and 8). An increase of the ligand loading from 10 to 15 mol % did not lead to a positive result (entry 9). Much to our delight, the best enantioselectivity was realized when 5 mol % of Ligand-**2** was employed (entry 10). However, a further decrease to 2 mol % deteriorated the asymmetric induction remarkably (entry 11). Consequently, 5 mol % was regarded as the optimal amount. Based on the above observations, the condition used in entry 10 was selected in the following reactions.

Encouraged by the excellent performance of Ligand-**2** in the enantioselective ethylation of benzaldehyde, we next examined the generality of this procedure using a broad spectrum of aromatic, α,β-unsaturated, and heteroaromatic aldehydes with diverse electronic and steric properties under the optimized reaction conditions, and the results are depicted in Table 2.

As can be seen from Table 2, both the position and electronic nature of substituents on the phenyl ring could affect enantioselectivities dramatically. To our surprise, very good yields were gained in all cases. Various benzaldehyde derivatives, bearing no matter electron-withdrawing or electron-donating groups substituted at the para position, were smoothly converted to the corresponding alcohols with the similar ee value to benzaldehyde (entries 1–8). Optically active hydroxyaldehyde could be obtained when 4-(diethoxymethyl) benzaldehyde was used as substrate (entry 8), since the corresponding intermediate was not stable during the acid hydrolysis.[50] Replacing the methoxyl group with a methyl, one caused an apparent decline in enantiomeric excess, indicating that the electronic character of the substituent at meta-position of benzaldehyde plays an important role (entries 9 and 10). The presence of ortho-substituents, regardless of electronic-rich or electronic-poor groups, diminished enantioselectivities obviously (entries 11–14), although in good yields, probably because the substituents could weaken the coordination of the aldehyde to the chiral catalyst and thus reduce the effect of the chiral environment of the catalyst.[51,30] For instance, 2-methoxybenzaldehyde provided a lower ee compared with 4-methoxybenzaldehyde, and the similar phenomenon was observed in entries 2 and 12. Gratifyingly, 1-naphthaldehyde was ethylated successfully with the highest ee (entry 16). The reaction with *trans*-cinnamaldehyde gave exclusively the 1,2-addition product in good yield and 80% ee value (entry 17). To our disappointment, only an acceptable enantiomeric excess was gained in the case of 2-furaldehyde (entry 18). Asymmetric ethylation of piperonal proceeded effectively to generate (*S*)-1-(benzodioxol-5-yl)-1-propanol with 82% ee (entry 19), which is ubiquitous in the fragments of many bioactive molecules and fine chemicals.[52,53]

In summary, five-membered nitrogen-containing aromatic heterocycles were successfully introduced to the 3 position of (*S*)-BINOL to give a series of chiral ligands. Among them surveyed, Ligand-**2**, easily obtained in 82% overall yield starting from the commercially available (*S*)-BINOL through a six-step sequence, exhibited the best catalytic activity in the enantioselective addition of diethylzinc to a wide range of aromatic aldehydes and *trans*-cinnamaldehyde. Further studies will be focused on the detailed mechanism and application of this ligand to other asymmetric transformations, such as allylation, methylation, and phenylation of carbonyl compounds are currently underway in our laboratory and the results will be reported in due course.

LITERATURE CITED

1. Noyori R. Asymmetric catalysis in organic synthesis. New York: Wiley; 1994.
2. Regan AC. Asymmetric processes. J Chem Soc Perkin Trans 1 1998;1151–1166.
3. Coldham I. Main group organometallics in synthesis. J Chem Soc Perkin Trans 1 1998;1343–1364.
4. Soai K, Niwa S. Enantioselective addition of organozinc reagents to aldehydes. Chem Rev 1992;92:833–856.
5. Noyori R, Kitamura M. Enantioselective addition of organometallic reagents to carbonyl compounds: chirality transfer, multiplication and amplification. Angew Chem Int Ed 1991;30:49–69.
6. Corey EJ, Guzman-Perez A. The catalytic enantioselective construction of molecules with quaternary carbon stereocenters. Angew Chem Int Ed 1998;37:388–401.
7. Ren T. Peripheral covalent modification of inorganic and organometallic compounds through C-C bond formation reactions. Chem Rev 2008;108:4185–4207.
8. Oguni N, Omi T, Yamamoto Y, Nakamura A. Enantioselective addition of diethylzinc to arylaldehydes catalyzed by chiral cobalt(II) and palladium(II) complexes. Chem Lett 1983;841–842.
9. Oguni N, Omi T. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by a small amount of chiral 2-amino-1-alcohols. Tetrahedron Lett 1984;25:2823–2824.
10. Evans DA, Black WC. Total synthesis of (+)-A83543A [(+)-lepicidin A]. J Am Chem Soc 1993;115:4497–4513.
11. Oppolzer W, Radinov RN. Synthesis of (R)-(-)-muscone by an asymmetrically catalyzed macrocyclization of an ω-alkynal. J Am Chem Soc 1993;115:1593–1594.
12. Viso A, De La Pradilla RF, Urena M. Synthesis of chiral sulfinamidosulfonamides and their evaluation as ligands for the enantioselective ethylation of aldehydes. Tetrahedron 2009;65:3757–3766.
13. Hui XP, Chen CA, Wu KH, Gau HM. Polystyrene-supported N-sulfonylated amino alcohols and their applications to titanium(IV) complexes catalyzed enantioselective diethylzinc additions to aldehydes. Chirality 2007;19:10–15.
14. Wu ZL, Wu HL, Wu PY, Uang BJ. Asymmetric addition of diethylzinc to aldehydes catalyzed by a camphor-derived β-amino alcohol. Tetrahedron: Asymmetry 2009;20:1556–1560.
15. Yang XF, Hirose T, Zhang GY. Catalytic enantioselective arylation of aryl aldehydes by chiral aminophenol ligands. Tetrahedron: Asymmetry 2009;20:415–419.
16. Forrat VJ, Ramón DJ, Yus M. Enantioselective addition of organozinc reagents to ketones catalyzed by grafted isoborneolsulfonamide polymers and titanium isopropoxide. Tetrahedron: Asymmetry 2009;20: 65–67.
17. Wang MC, Zhang QJ, Li GW, Liu ZK. Highly enantioselective addition of dimethylzinc to arylaldehydes catalyzed by (2S)-1-ferrocenyl-methylaziridin -2-yl(diphenyl)methanol. Tetrahedron: Asymmetry 2009;20: 288–292.
18. Kang SW, Ko DH, Kim KH, Ha DC. Highly enantioselective additions of diethylzinc to aldehydes using 2-triflamido-methyl-2′-hydroxy-1,1′-binaphthyl. Org Lett 2003;5:4517–4519.
19. Walsh PJ. Titanium-catalyzed enantioselective additions of alkyl groups to aldehydes: mechanistic studies and new concepts in asymmetric catalysis. Acc Chem Res 2003;36:739–749.
20. Soai K, Shibata T. Alkylation of carbonyl groups. In: Jacobsen EN, Pfaltz A, Yamamoto H, editors. Comprehensive asymmetric catalysis. Berlin: Springer-Verlag; 1999. p 911–922.
21. Pu L, Yu HB. Catalytic asymmetric organozinc additions to carbonyl compounds. Chem Rev 2001;101:757–854.
22. Knochel P, Singer RD. Preparation and reactions of polyfunctional organozinc reagents in organic synthesis. Chem Rev 1993;93:2117–2188.
23. Knochel P. Handbook of functionalized organometallics. Weinheim, Germany: Wiley-VCH; 2005.
24. Zhang FY, Yip CW, Cao R, Chan ASC. Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by Ti(BINOL) complex. Tetrahedron: Asymmetry 1997;8:585–589.
25. Heckel A, Seebach D. Immobilization of TADDOL with a high degree of loading on porous silica gel and first applications in enantioselective catalysis. Angew Chem Int Ed 2000;39:163–165.
26. Huang J, Clanni J, Antoline JE, Hsung RP, Kozlowskl MC. De novo chiral amino alcohols in catalyzing asymmetric additions to aryl aldehydes. Org Lett 2006;8:1565–1568.
27. Tanaka T, Yasuda Y, Hayashi M. New chiral schiff base as a tridentate ligand for catalytic enantioselective addition of diethylzinc to aldehydes. J Org Chem 2006;71:7091–7093.
28. Coeffard V, Müller-Bunz H, Guiry PJ. The synthesis of new oxazoline-containing bifunctional catalysts and their application in the addition of diethylzinc to aldehydes. Org Biomol Chem 2009;7:1723–1734.

29. Binder CM, Bautista A, Zaidlewicz M, Krzemńiski MP, Oliver A, Singaram B. Dual stereoselectivity in the dialkylzinc reaction using (-)-β-pinene derived amino alcohol chiral auxiliaries. J Org Chem 2009;74:2337–2343.
30. Hsieh SH, Gau HM. Enantioselective addition of diethylzinc to aldehydes catalyzed by titanium(IV) complexes of *n*-sulfonylated -amino alcohols with four stereogenic centers. Chirality 2006;18:569–574.
31. Hui XP, Chen CA, Gau HM. Synthesis of new *N*-sulfonylated amino alcohols and application to the enantioselective addition of diethylzinc to aldehydes. Chirality 2005;17:51–56.
32. Brunel JM. BINOL: a versatile chiral reagent. Chem Rev 2005;105: 857–898.
33. Harada T, Kanda K. Enantioselective alkylation of aldehydes catalyzed by a highly active titanium complex of 3-substituted unsymmetric BINOL. Org Lett 2006;8:3817–3819.
34. Kocovsky P, Vyskocil S, Smrcina M. Non-symmetrically substituted 1,1′-binaphthyls in enantioselective catalysis. Chem Rev 2003;103: 3213–3246.
35. Pu L. 1,1′-Binaphthyl dimers, oligomers, and polymers: molecular recognition, asymmetric catalysis, and new materials. Chem Rev 1998;98:2405–2494.
36. Shen X, Guo H, Ding KL. The synthesis of a novel non-C2 symmetric H4-BINOL ligand and its application to titanium-catalyzed enantioselective addition of diethylzinc to aldehydes. Tetrahedron: Asymmetry 2000;11:4321–4327.
37. Harada S, Kumagai N, Kinoshita T, Matsunaga S, Shibasaki M. Direct catalytic asymmetric michael reaction of hydroxyketones: asymmetric Zn catalysis with a Et2Zn/linked-BINOL complex. J Am Chem Soc 2003;125:2582–2590.
38. Mikami K, Terada M, Nakai T. Catalytic asymmetric glyoxylate-ene reaction: a practical access to α-hydroxy esters in high enantiomeric purities. J Am Chem Soc 1990;112:3949–3954.
39. Denmark SE, Fu J. Catalytic enantioselective addition of allylic organometallic reagents to aldehydes and ketones. Chem Rev 2003;103: 2763–2794.
40. Guo QS, Liu B, Lu YN, Jiang FY, Song HB, Li JS. Synthesis of 3 or 3, 3′-substituted BINOL ligands and their application in the asymmetric addition of diethylzinc to aromatic aldehydes. Tetrahedron: Asymmetry 2005;16:3667–3671.
41. Guo QS, Lu YN, Liu B, Xiao J, Li JS. A facile synthesis of 3 or 3, 3′-substituted binaphthols and their applications in the asymmetric addition of diethylzinc to aldehydes. J Organomet Chem 2006;691: 1282–1287.
42. Liu B, Jiang FY, Song HB, Li JS. A novel trinuclear titanium(IV) complex with a C3 axis along Ti1–Ti2–Ti3 containing 3-[(1H-1,2, 4-triazol-1-yl)methyl]-BINOLate ligands: synthesis, structure, and reactivity. Tetrahedron: Asymmetry 2006;17:2149–2153.
43. Liu B, Dong ZB, Fang C, Song HB, Li JS. 3-Substituted BINOL Schiff bases and their reductive products for catalytic asymmetric addition of diethylzinc to aldehydes. Chirality 2008;20:828–832.
44. Dong ZB, Liu B, Fang C, Li JS. A facile synthesis and the asymmetric catalytic activity of BINOL-based thiazole (thiadiazole) thioether ligands. J Organomet Chem 2008;693:17–22.
45. Lu YN, Guo QS, Jiang FY, Li JS. Synthesis of modified H4-BINOL ligands and their applications in the asymmetric addition of diethylzinc to aromatic aldehydes. Tetrahedron: Asymmetry 2006;17:1842–1845.
46. Jiang FY, Liu B, Dong ZB, Li JS. Titanium(IV) as an essential promoter in the asymmetric addition of diethylzinc to aldehydes catalyzed by aminonaphthol and imme ligands based on 3-substituted binaphthol. J Organomet Chem 2007;692:4377–4380.
47. Yang F, Wei SP, Cheng CA, Xi PH, Yang L, Lan JB, Gau HM, You JS. A new strategy for designing non-C-2-symmetric monometallic bifunctional catalysts and their application in enantioselective cyanation of aldehydes. Chem Eur J 2008;14:2223–2231.
48. Shi M, Wang CJ. Axially dissymmetric binaphthyldiimine chiral Salen-type ligands for catalytic asymmetric addition of diethylzinc to aldehyde. Tetrahedron: Asymmetry 2002;13:2161–2166.
49. Bai XL, Liu XD, Wang M, Kang CQ, Gao LX. Synthesis of new bisbinols linked by a 2, 2′-bipyridine bridge. Synthesis 2005;458–464.
50. Soai K, Hori H, Kawahara M. Highly enantioselective synthesis of optically active hydroxyaldehydes using a chiral catalyst. Tetrahedron: Asymmetry 1990;1:769–770.
51. Chan ASC, Zhang FY, Yip CW. Novel asymmetric alkylation of aromatic aldehydes with triethylaluminum catalyzed by titanium (1,1′-bi-2-naphthol) and titanium (5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) complexes. J Am Chem Soc 1997;119:4080–4081.
52. John R. Amaryllidaceae, sceletium, imidazole, oxazole, thiazole, peptide and miscellaneous alkaloids. Nat Prod Rep 2002;19:223–258.
53. Joncour A, Décor A, Liu JM, Dau Meth O. Asymmetric synthesis of antimicrotubule biaryl hybrids of allocolchicine and steganacin. Chem Eur J 2007;13:5450–5464.