Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 17 (2006) 1842–1845

Tetrahedron: *Asymmetry*

Synthesis of modified H_4-BINOL ligands and their applications in the asymmetric addition of diethylzinc to aromatic aldehydes

Yong-Na Lu, Qun-Sheng Guo, Fu-Yong Jiang and Jin-Shan Li*

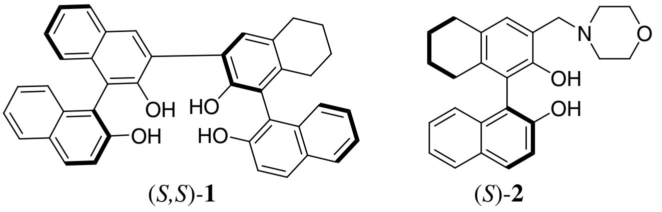
State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

Received 17 May 2006; accepted 23 June 2006
Available online 25 July 2006

Abstract—Two new ligands (*S*,*S*)-3-(1,1′-bi-2-naphthol-3-yl)-5,6,7,8-tetrahydro-1,1′-bi-2-naphthol [(*S*,*S*)-**1**] and (*S*)-3-(morpholin-4-ylmethyl)-H_4-BINOL [(*S*)-**2**] have been synthesized via Suzuki cross-coupling reaction and a Mannich-type reaction, respectively. In the presence of titanium tetraisopropoxide, 0.8 mol % of ligand (*S*,*S*)-**1** catalyzed the asymmetric addition of diethylzinc to aromatic aldehydes in good yield and with high enantioselectivity.

1. Introduction

1,1′-Bi-2-naphthol (BINOL) is one of the most effective chiral ligands in asymmetric catalysis.[1] Recent research showed that catalysts based on the partially hydrogenated BINOL ligands, 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (H_8-BINOL)[2] and 5,6,7,8-tetrahydro-1,1′-bi-2-naphthol (H_4-BINOL),[3] exhibited better efficiency and enantioselectivity for asymmetric reactions than those obtained from their BINOL ligands,[4] due to the steric and electronic modulation in the binaphthyl backbone.[5] However, very few substituted H_4-BINOL ligands have been synthesized and studied.[3,4h] Herein, we report the synthesis of two new modified H_4-BINOL ligands (*S*,*S*)-**1** and (*S*)-**2** (Fig. 1) and their catalytic activity in titanium complex catalyzed enantioselective addition of diethylzinc to aromatic aldehydes.



(*S*,*S*)-**1** (*S*)-**2**

Figure 1.

2. Results and discussion

Ligand (*S*,*S*)-**1** was synthesized by a Suzuki cross-coupling reaction (Scheme 1). The hydroxyl groups of (*S*)-BINOL were protected with methoxymethyl (MOM) groups to afford (*S*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene (*S*)-**3**.[6] The lithium salt of (*S*)-**3** reacted with $B(OMe)_3$ and the mixture was hydrolyzed with 2 M HCl to afford (*S*)-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl-3-boronic acid (*S*)-**4** in pure form in 55% yield after purification by column chromatography on silica gel.[7] The bromination of (*S*)-**5** gave 3-bromo-H_4-BINOL (*S*)-**6** in excellent yield.[4h] The hydroxyl groups of (*S*)-**6** were protected with methoxymethyl (MOM) groups to afford (*S*)-**7**. After Suzuki cross-coupling[8] of (*S*)-**7** with (*S*)-**4** in the presence of aq Na_2CO_3 and $Pd(PPh_3)_4$ in THF at reflux for 36 h and deprotection of the MOM groups compound (*S*,*S*)-**1** was obtained.

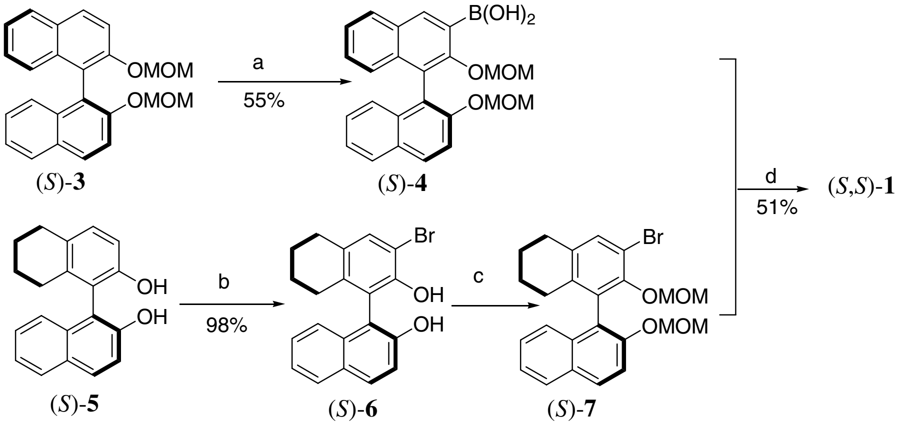
We conducted the reaction of the enantiomerically pure (*S*)-H_4-BINOL with paraformaldehyde and morpholine in dioxane at 60 °C.[9] This one-pot process led to the formation of (*S*)-3-(morpholin-4-ylmethyl)-H_4-BINOL [(*S*)-**2**] in 98% yield (Scheme 2).

The plate-like colorless single crystals of (*S*)-**2** were obtained from Et_2O–CH_2Cl_2–petroleum ether solution. The crystal structure of (*S*)-**2** was determined by X-ray diffraction as shown in Figure 2.[10] The dihedral angle between the two naphthalene systems is 108.6(3)°. The bond angle C(3)–C(21)–N(1) is 111.3(2)° and slightly larger than the

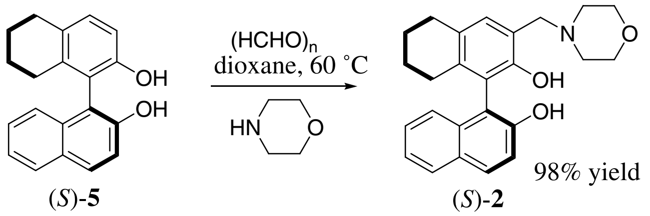
---

* Corresponding author. Tel.: +86 22 23504230; fax: +86 22 23503627; e-mail: jinshanl@nankai.edu.cn

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.06.042



Scheme 1. Reagents and conditions: (a) (i) 1.1 equiv *n*-BuLi, −78 °C, (ii) $B(OMe)_3$, −78 °C, (iii) 2 M HCl, 0 °C, 55%; (b) 1.2 equiv Br_2, 12 h, 98%; (c) K_2CO_3, $ClCH_2OCH_3$, acetone, rt; (d) (i) $Pd(PPh_3)_4$, aq Na_2CO_3, THF/reflux, 36 h; (ii) 2 M HCl, 0 °C.



Scheme 2. Synthesis of 3-morphoplinylmethyl-H_4-BINOL.

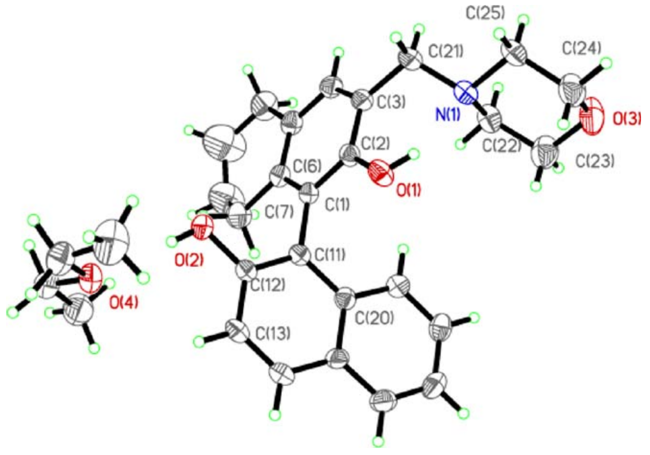
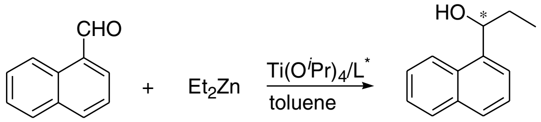


Figure 2. The molecular structure of (*S*)-**2** including one Et_2O molecule.

ideal tetrahedral value of 109.5°. The conformation of the morpholine ring is a stable chair form.

The effectiveness of the two ligands in the titanium complex catalyzed enantioselective addition of diethylzinc to 1-naphthaldehyde was tested.[11] The active catalyst was formed in situ by mixing the ligand with titanium tetraisopropoxide in toluene.[12] The amount of ligand (*S*,*S*)-**1** varied from 10 to 0.1 mol %. It was found that the enantioselectivity was still high (84.7% ee) when using 0.8 mol % of (*S*,*S*)-**1**. (Table 1, entries 1–12). Decreasing the amount of (*S*)-**2** from 20 to 5 mol % led to a large decrease in the enantioselectivity (Table 1, entries 13–15).

Table 1. Catalytic asymmetric addition of diethylzinc (1.0 M in toluene) to 1-naphthaldehyde



Entry	Ligand[a] (mol %)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	(*S*,*S*)-**1** (10)	95	88.3	*S*
2	(*S*,*S*)-**1** (5)	92	88.2	*S*
3	(*S*,*S*)-**1** (4)	96	88.0	*S*
4	(*S*,*S*)-**1** (3)	92	87.8	*S*
5	(*S*,*S*)-**1** (2)	95	87.5	*S*
6	(*S*,*S*)-**1** (1)	92	82.7	*S*
7	(*S*,*S*)-**1** (0.8)	96	84.7	*S*
8	(*S*,*S*)-**1** (0.6)	91	82.8	*S*
9	(*S*,*S*)-**1** (0.5)	92	77.7	*S*
10	(*S*,*S*)-**1** (0.4)	91	77.8	*S*
11	(*S*,*S*)-**1** (0.2)	85	74.6	*S*
12	(*S*,*S*)-**1** (0.1)	92	57.1	*S*
13	(*S*)-**2** (20)	96	79.3	*S*
14	(*S*)-**2** (10)	89	78.8	*S*
15	(*S*)-**2** (5)	80	68.6	*S*

[a] $Ti(O^iPr)_4/Et_2Zn/$1-naphthaldehyde = 1.2:3:1; reaction temperature: 0 °C; reaction time: 5 h.

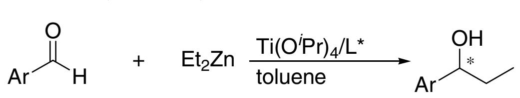
[b] Isolated yield.

[c] Data were determined by GC analysis: initial 100 °C, 1 °C/min to 200 °C on a Chiral beta-DEX 120 capillary column.

[d] The absolute configuration of the product was determined by comparing the specific rotation with the literature data.[13]

With conditions optimized for 1-naphthaldehyde, the use of ligands (*S*,*S*)-**1** and (*S*)-**2** was extended to the asymmetric addition of diethylzinc to other aromatic aldehydes. The molar ratio of (*S*,*S*)-**1**/$Ti(O^iPr)_4/Et_2Zn$/aldehyde was set up to be 0.008:1.2:3:1 and that of (*S*)-**2**/$Ti(O^iPr)_4/Et_2Zn$/aldehyde was set up to be 0.1:1.2:3:1. The results are summarized in Table 2. (*S*,*S*)-**1** showed high enantioselectivity in this reaction while (*S*)-**2** only showed moderate enantioselectivity. For (*S*,*S*)-**1**, introducing 1,1′-binaphthol-3-yl group at the 3 position of 5,6,7,8-tetrahydro-1,1′-binaphthol possibly tended to create a larger dihedral angle[4f] and thus led to high enantioselectivity.

Table 2. Enantioselective addition of diethylzinc (1.0 M in toluene) to aldehydes with (*S*,*S*)-**1** and (*S*)-**2**



Entry	Ligand[a] (%)	Ar	Yield[b] (%)	ee[c] (%)	Config.[e]
1	(*S*,*S*)-**1**	Ph	80	82.5[d]	*S*[14]
2	(*S*,*S*)-**1**	*p*-ClC_6H_4	70	81.1	*S*[15]
3	(*S*,*S*)-**1**	*p*-BrC_6H_4	89	82.4	*S*[16]
4	(*S*,*S*)-**1**	*p*-$MeOC_6H_4$	71	81.3[d]	*S*[17]
5	(*S*,*S*)-**1**	*o*-$MeOC_6H_4$	91	83.4	*S*[18]
6	(*S*,*S*)-**1**	1-Naphthyl	96	84.7	*S*
7	(*S*)-**2**	Ph	94	77.8	*S*
8	(*S*)-**2**	*p*-ClC_6H_4	75	64.8	*S*
9	(*S*)-**2**	*p*-BrC_6H_4	96	70.0	*S*
10	(*S*)-**2**	*o*-$MeOC_6H_4$	98	63.8	*S*
11	(*S*)-**2**	1-Naphthyl	89	78.8	*S*

[a] (*S*,*S*)-**1**/$Ti(O^iPr)_4/Et_2Zn$/aldehyde = 0.008:1.2:3:1; (*S*)-**2**/$Ti(O^iPr)_4/Et_2Zn$/aldehyde = 0.1:1.2:3:1; solvent: toluene; reaction temperature: 0 °C; reaction time: 5 h.

[b] Isolated yield.

[c] Data were determined by GC analysis using a chiral column (Chiral beta-DEX 120 capillary column).

[d] Data were determined by HPLC analysis using a chiral OD column.

[e] The absolute configuration of the product was determined by comparing the specific rotation with the literature data.

3. Conclusion

We have synthesized two new modified H_4-BINOL ligands (*S*,*S*)-**1** and (*S*)-**2**, respectively, via a Suzuki cross-coupling reaction and Mannich-type reaction. The titanium complex of (*S*,*S*)-**1** was found to be a very effective catalyst in the asymmetric addition of diethylzinc to a variety of aromatic aldehydes.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument in $CDCl_3$ solution with TMS as internal standard. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. IR spectra were recorded as KBr plates on a Bruker Equinox 55 spectrometer. Elemental analysis was performed with a Yanaco CHN Corder MT-3 elemental analyzer. The high-resolution mass spectra (EI-HRMS) were measured on an Autospec-AltimaETOF (UK, Micromass) spectrometer. All experiments which are sensitive to moisture or air were carried out under an argon atmosphere using standard Schlenk techniques. Diethylzinc (1.0 M solution in toluene) was prepared according to literature method.[19] $Pd(PPh_3)_4$ was purchased from Aldrich. All anhydrous solvents were purified and dried by standard techniques just before use.

4.2. Synthesis of (*S*,*S*)-3-(1,1′-bi-2-naphthol-3-yl)-5,6,7,8-tetrahydro-1,1′-bi-2-naphthol (*S*,*S*)-1

Under argon, (*S*)-**4** (3.25 g, 7.8 mmol) was combined with (*S*)-**7** (2.87 g, 7.8 mmol), $Pd(PPh_3)_4$ (0.46 g, 0.4 mmol), THF (40 mL), H_2O (20 mL), and Na_2CO_3 (3.3 g, 31.2 mmol). The resulting mixture was heated at reflux for 36 h. The organic layer was separated and the aqueous layer extracted with AcOEt. The combined organic phases were dried over $MgSO_4$. After removal of the solvent, the residue was resolved in CH_2Cl_2 (35 mL) and MeOH (35 mL). To this solution was added 15 mL HCl (12 M) at 0 °C. The mixture was stirred at room temperature for 12 h and poured into water (80 mL), extracted with CH_2Cl_2, washed with water, and then saturated $NaHCO_3$, and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was submitted to column chromatography on silica gel with petroleum ether/ethyl acetate (3:1) as eluent to give a khaki oil. After recrystallization in Et_2O and petroleum ether, compound (*S*,*S*)-**1** was obtained as a khaki powder (2.3 g, 51.3% yield). Mp 210–212 °C; $[\alpha]_D^{25} = -19.51$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.51–1.65 (m, 2H), 1.66–1.74 (m, 2H), 2.09–2.30 (m, 2H), 2.80 (t, $J = 6.6$ Hz, 2H), 4.98 (s, 1H), 5.15 (s, 1H), 5.17 (s, 1H), 5.34 (s, 1H), 7.15–7.43 (m, 11H), 7.75 (d, $J = 10.5$ Hz, 1H) 7.89–8.01 (m, 4H), 8.10 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.75, 22.75, 25.98, 29.16, 107.56, 111.53, 112.04, 112.54, 113.77, 117.84, 118.02, 119.55, 123.82, 124.09, 124.30, 124.40, 124.45, 127.46, 127.46, 128.45, 128.49, 129.04, 129.12, 129.34, 129.52, 129.58, 130.52, 130.98, 131.90, 132.03, 133.00, 133.00, 133.50, 133.73, 133.73, 138.70, 149.00, 150.50, 151.44, 152.7; IR (KBr): 3514, 3222, 3056, 2927, 2847, 1620, 1509, 1456, 1189, 866, 812 cm^{-1}; HRMS (EI) calcd for $C_{40}H_{30}O_4$: 574.2144; found: 574.2136.

4.3. Synthesis of (*S*)-3-(morpholin-4-ylmethyl)-5,6,7,8-tetrahydro-1,1′-bi-2-naphthol (*S*)-2

Paraformaldehyde (9.0 g, 300 mmol) was placed in a round bottom flask. Morpholine (26.1 g, 300 mmol) was added dropwise over 1 h with vigorous stirring. Since this was a strongly exothermic reaction, the addition rate was adjusted in order to keep the oil bath temperature at 60–70 °C. Then the reaction mixture was heated at 60 °C for about 12 h until it became a clear yellow solution. H_4-BINOL (2.9 g, 10 mmol) and dioxane (10 mL) were added and the solution was stirred at 60 °C for an additional 12 h. The residue was dissolved in CH_2Cl_2, washed with 1 M HCl (3 × 10 mL) and water (3 × 10 mL), and dried over Na_2SO_4. After removal of solvent, the residue was submitted to column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluent to give (*S*)-**2** (3.8 g, 98% yield) as a colorless oil. The colorless crystals of (*S*)-**2** were obtained from Et_2O–CH_2Cl_2–petroleum ether. Mp 103–105 °C; $[\alpha]_D^{25} = -30.8$ (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.54–1.62 (m, 2H), 1.68–1.76 (m, 2H), 2.07–2.31 (m, 2H), 2.59 (br s, 4H), 2.75 (t, $J = 6.15$ Hz, 2H), 3.67 (br s, 4H), 3.76 (s, 2H), 6.90 (s, 1H), 7.21–7.33 (m, 4H), 7.80–7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.49, 23.05, 25.91, 29.29, 52.99, 52.99, 61.84, 66.60, 66.59, 116.49, 117.31, 118.75, 119.12, 123.15, 124.15, 125.41, 128.32, 128.79, 129.24, 129.39, 130.31, 133.04, 138.48, 150.38, 153.98; IR (KBr): 3514, 3222, 3056, 2927, 2847, 1620, 1509, 1456, 1189, 866, 812 cm^{-1}; Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.02; H, 6.51; N, 3.80.

4.4. A typical procedure for the asymmetric addition of diethylzinc to benzaldehyde

Titanium tetraisopropoxide (0.34 g, 1.2 mmol) was added to a solution of ligand (*S*,*S*)-**1** (0.0046 g, 0.008 mmol) in 5 mL of toluene at room temperature and the reaction mixture was stirred for 15 min followed by the addition of diethylzinc (3.0 mL, 1.0 M solution in toluene) with continued stirring for 15 min. The solution was cooled to 0 °C and benzaldehyde (0.10 mL, 1.0 mmol) was introduced with a syringe. The reaction mixture was stirred at 0 °C for 5 h. The reaction was quenched with 20 mL of saturated NH_4Cl solution. The mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to solvent free. The residue was purified by column chromatography on silica gel affording 1-phenyl-1-propanol (0.11 g, 80% yield) as a colorless liquid. The optical rotation was measured. The enantiomeric excess of product was determined by HPLC on a Chiralcel OD column.

Acknowledgment

This work was supported by The National Natural Science Foundation of China (Grant No. 20372037).

References

1. (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494; (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211; (c) Kočovskú, P.; Vyskočil, S.; Smrčina, M. *Chem. Rev.* **2003**, *103*, 3213–3245; (d) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897.
2. Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930–1946.
3. Shen, X. Q.; Guo, H.; Ding, K.-L. *Tetrahedron: Asymmetry* **2000**, *11*, 4321–4327.
4. (a) Zhang, F. Y.; Yip, C. W.; Cao, Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589; (b) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651–3655; (c) Reetz, M. T.; Merk, C.; Naberfeld, G.; Rudolph, J. N. G.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273–5276; (d) Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. *J. Am. Chem. Soc.* **1997**, *119*, 4080–4081; (e) Waltz, K. M.; Carroll, P. J.; Walsh, P. J. *Organometallics* **2004**, *23*, 127–134; A review: (f) Au-Yeung, T. L.-L.; Chan, S. S.; Chan, A. S. *Adv. Synth. Catal.* **2003**, *345*, 537–555; (g) Schrock, R. R.; Jamieson, J. Y.; Dolman, S. J.; Miller, S. A.; Bonitatebus, P. J.; Hoveyda, A. H. *Organometallics* **2002**, *21*, 409–417; (h) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10–11.
5. For recent examples, see (a) Zhang, F. Y.; Pai, C. C.; Chan, A. S. C. *J. Am. Chem. Soc.* **1998**, *120*, 5808–5809; (b) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510–5516.
6. Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, 1113–1114.
7. Bai, X. L.; Liu, X. D.; Wang, M.; Kang, C. Q.; Gao, L. X. *Synthesis* **2005**, 458–464.
8. (a) Hu, Q. S.; Zheng, X. F.; Pu, L. *J. Org. Chem.* **1996**, *61*, 5200–5201; (b) Simonson, D. L.; Kinsbury, K.; Xu, M. H.; Hu, Q. S.; Sabat, M.; Pu, L. *Tetrahedron* **2002**, *58*, 8189–8193; (c) Ma, L.; White, P. S.; Lin, W. B. *J. Org. Chem.* **2002**, *67*, 7577–7586; (d) Bai, X. L.; Liu, X. D.; Wang, M.; Kang, C. Q.; Gao, L. X. *Synthesis* **2005**, *3*, 0458–0464.
9. (a) Fabris, F.; Lucchi, O. D.; Lucchini, V. *J. Org. Chem.* **1997**, *62*, 7156–7164; (b) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427–7430.
10. Crystal data for (*S*)-**2**: $C_{29}H_{37}NO_4$, $M = 463.60$, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 10.553(2)$ Å, $b = 11.512(3)$ Å, $c = 21.591(5)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2623.0(11)$ Å^3, $Z = 4$, $D = 1.174\ \mathrm{g\,cm^{-3}}$, MoK$\alpha$ ($\lambda = 0.71073$ Å), $T = 293(2)$ K, $\mu = 0.077\ \mathrm{mm^{-1}}$, crystal size (mm) $0.24 \times 0.22 \times 0.19$. Area detector data collected on a Bruker Smart 1000 diffractometer. A total of 14,387 reflections were collected ($1.89 < \theta < 25.01$). Structure solution by direct method (SHELXS-97), refinement by full-matrix least-squares using all reflections, $R_1 = 0.0472$, $wR_2 = 0.1125$, GOF = 1.032. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 607833. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
11. (a) Chen, Y.; Yekta, S.; Martyn, L. J. P.; Zheng, J.; Yudin, A. K. *Org. Lett.* **2000**, *2*, 3433–3436; (b) Guo, Q. S.; Liu, B.; Lu, Y. N.; Jiang, F. Y.; Song, H. B.; Li, J. S. *Tetrahedron: Asymmetry* **2005**, *16*, 3667–3671; (c) Guo, Q. S.; Lu, Y. N.; Liu, B.; Xiao, J.; Li, J. S. *J. Organomet. Chem.* **2006**, *691*, 1282–1287.
12. Mori, M.; Nankai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.
13. Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523–524.
14. Soai, K.; Watanabe, M. *Tetrahedron: Asymmetry* **1991**, *2*, 97–100.
15. Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218–2224.
16. Chaloner, P. A.; Perena, S. A. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2731–2735.
17. Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411–424.
18. Smaardijk, A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135–137.
19. Noller, C. R. In *Organic Syntheses*; Wiley: New York, 1943; Coll. Vol. II, p 184.