A Systematic Study of Chiral Homoprolinols and Their Derivatives in the Catalysis of Enantioselective Addition of Diethylzinc to Aldehydes

CHANG-LU LIU,[1,2] CHANG-YONG WEI,[1] SHI-WEN WANG,[1] AND YUN-GUI PENG[1]*

[1]*School of Chemistry and Chemical Engineering, Southwest University, Beibei, Chongqing 400715, P. R. China*
[2]*Department of Chemistry and Chemical Engineering, Sichuan University of Arts and Science, Dazhou 635000, P. R. China*

ABSTRACT Homoprolinol analogs, a class of optically active γ-amino alcohols, were examined systematically in the enantioselective addition reactions of diethylzinc to aldehydes. By comparison of the results catalyzed by these γ-amino alcohols with those by the β-amino alcohols based on pyrrolidine architecture reported in the literature references, we have observed that the γ-amino alcohols are superior to the corresponding β-amino alcohols when the nitrogen and the oxygen are unsubstituted. Among the homoprolinols we tested, **2b** gave the best results (45–88% yields, 44–81% ee) in the addition reactions. To the best of our knowledge, **2b** has been noticed as one of the most efficient γ-amino alcohol catalysts based on pyrrolidine framework. *Chirality 23:921–928, 2011.*

KEY WORDS: γ-amino alcohol; homoprolinol; enantioselective addition; diethylzinc

INTRODUCTION

As an important approach to synthesize useful and optically active secondary alcohols, the asymmetric alkylation of carbonyl compounds with organozinc reagents has been of great interest.[1,2] Since the first report by Oguni to use (*S*)-leucinol as chiral ligand in the addition of diethylzinc to benzadehyde with moderate enantiomeric excess,[3] and Noyori's work with (-)-3-exo-(dimethylamino)isoborneol (DAIB) as chiral ligand,[4–9] tremendous efforts have been focused on exploring new amino alcohols as efficient catalysts and diverse ligand structures have been developed to date.[10–68] Among them, β-amino alcohols have been studied extensively and proven to be the best ligands.[10–23] Comparatively, γ-amino alcohols have been studied less than β-amino alcohols even though satisfactory results were achieved with the former ligands.[24–35]

Martínez et al. studied the catalytic activity of norbornane-derived β- and γ-amino alcohols **1a–1f** (Figure 1) in the addition of dialkylzincs to aldehydes and presented a qualitative empirical explanation to the observed enantioselectivity imposed by those amino alcohols.[27] Mechanistic studies have demonstrated that the enantioselectivity is determined by both the bulkiness of the substituent on nitrogen and the size of the chelated ring in the transition states (TSs). Comparison of the catalytic results of **1a** and **1d**, **1b** and **1e** led to the conclusion that both the β-amino alcohols **1a** and **1b** are superior to the corresponding γ-amino alcohol **1d** and **1e**, respectively, in enantioselectivity. It has been proposed that a more flexible six-membered alkylzinc-chelated aminoalkoxide complex was formed in the TS when γ-amino alcohols were used as catalysts while a stable five-membered TS was formed in the case of β-amino alcohol. On the contrary, β-amino alcohol **1c** is inferior to γ-amino alcohol **1f**, which maybe explained by the influence of the nitrogen substituents on catalytic behavior. Similarly, the catalytic abilities of β- and γ-amino alcohols derived from other chiral architectures apart from norbornane, such as menthane,[30] varied greatly with different substituent on the nitrogen, and no general trend could be found to determine whether β-amino alcohol backbones is better than γ-amino alcohol backbones or not.

Pyrrolidine-based chiral β-amino alcohols such as prolinol and its derivatives, prepared from (*S*)-proline, have been proven to be very efficient in the catalysis of the enantioselective addition of diethylzinc to aldehydes by Wang's group.[21] Cicchi et al. have developed several homoprolinols with *N*-methyl and 3-*tert*-butoxy group, which are homologous γ-amino alcohols, and applied them to the alkylation of benzaldehyde with diethylzinc. However, those ligands only showed moderate asymmetric induction (up to 54% ee) effect.[32] Inspired by work of Martínez group's in norbornane-derived β- and γ- amino alcohol systems,[27] in which the catalytic behavior was found to be greatly influenced by the substituent on the nitrogen, we believe that a systematic screening of the substituent in homoprolinol system may provide an opportunity to find better γ-amino alcohol catalysts based on chiral pyrrolidine framework.

With an interest in developing an efficient chiral organocatalytic system, we have previously designed and synthesized a series of novel γ-amino alcohols **2a–2g** and have demonstrated their usefulness in the direct asymmetric Michael addition of carbonyl compounds to nitroalkenes.[69] To explore the catalytic applications of the γ-amino alcohols and their derivatives further, we have performed systematic studies on other types of catalytic addition reactions. Herein, we report the catalytic results of **2a–2i** (Figure 2) in the addition reaction of diethylzinc to aldehydes.

EXPERIMENTAL GENERAL METHODS

All solvents were purified by standard procedures and distilled before use. Diethylzinc was purchased from Acros Organics. Aromatic aldehydes had been freshly distilled before use. Unless otherwise indicated,

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: Natural Science Foundation of China (NSFC); The Municipal Science Foundation of Chongqing City (CSTC); The Fundamental Research Funds for the Central Universities; Contract grant numbers: NSFC-20872120, CSTC-2009BB5110.

*Correspondence to: Yun-Gui Peng, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, P. R. China.
E-mail: pengyungui@hotmail.com or pyg@swu.edu.cn

Received for publication 3 July 2011; Accepted 22 July 2011
DOI: 10.1002/chir.21017
Published online 20 September 2011 in Wiley Online Library (wileyonlinelibrary.com).

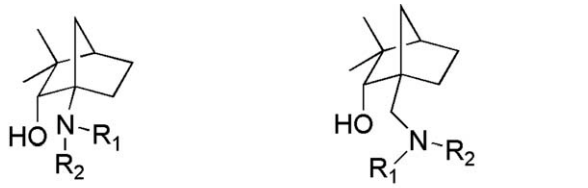


Fig. 1. Reported results of the asymmetric addition of diethylzinc to benzaldehyde catalyzed by selected norbornane-based β- and γ-amino alcohols derivatives.

the other reagents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm silica gel plates visualized with UV light and/or by staining with ethanol phosphomolybdic acid. Flash column chromatography was performed on silica gel H (10–40 μ). NMR spectra were recorded on 300 MHz instruments. Chemical shifts (*d*) are given in ppm relative to trimethyl silane (TMS), coupling constants (*J*) in Hz. IR spectra were recorded on a PerkinElmer-GX spectrometer. Melting points were determined on an X-6 digital melting-point apparatus and were uncorrected. Optical rotations were measured on a PerkinElmer 341 Polarimeter at λ = 589 nm. Analytical high-performance liquid chromatography (HPLC) was carried out on WATERS 510 instrument (2487 dual λ absorbance Detector and 515 HPLC pump) using chiral column. Time of flight high resolution mass spectrometer (TOF HRMS) was recorded on a Bruker Apex-2.

The Procedure for the Synthesis of Compound 4

Methyl homoprolinate hydrochloride **3** (3.6 g, 20 mmol) and triethyl amine (TEA) (7 ml, 50 mmol) were dissolved in dry CH_2Cl_2 (40 ml). The solution was cooled down to 0°C with ice bath. $(Boc)_2O$ (5.4 g, 24.7 mmol) was added dropwise. After the addition, the reaction mixture was warmed to r.t. slowly and stirred overnight and then diluted with CH_2Cl_2 and separated the organic phase. The aqueous solution was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were washed with saturated NH_4Cl solution, brine, and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by silica gel chromatography to give **4**[70] (4.65 g, 96%) as light yellow oil.

General Procedure for the Synthesis of Ligands 2a–2e

Synthesis of (S)-1,1-bis(4-methylphenyl)-2-(pyrrolidin-2-yl)ethanol 2b. *To a solution of* ***4*** *(18.72 g, 80 mmol) in dry tetrahydrofuran (THF) (500 ml) at −78°C under a nitrogen atmosphere, RMgBr (240 ml of 1 M solution in THF) was added dropwise. The mixture was warmed to r.t. gradually and stirred overnight. The reaction was quenched by saturated aqueous NH_4Cl, and THF was removed under reduced pressure to give a milky residue. The residue was partitioned between ethyl acetate and saturated NH_4Cl solution. The organic layers were collected, washed with brine, and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified by silica gel chromatography to give pure* ***5b*** *in good yields (7.3 g, 96%).*

5b (4.9 g, 12.4 mmol) was added into the mixture of NaOH (14.87 g, 372 mmol) in 90 ml anhydrous ethanol and stirred for 2 days under refluxed at 98°C. Ethanol was removed in vacuo. Water was added to dissolve excess NaOH. The aqueous solution was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were washed with saturated NH_4Cl solution, saturated $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give **2b**[71] (3.48 g) as white solid; yield (95%). mp 88–89°C, $[\alpha]_D^{25}$ = +22.3 (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.39–1.55 (m, 2H), 1.76–1.86 (m, 2H), 1.96–2.05 (dd, *J* = 14.0 Hz, 11.9 Hz, 1H), 2.26 (s, 3H), 2.31 (s, 3H), 2.34–2.39 (dd, *J* = 14.1 Hz, 2.99 Hz, 1H), 2.81–2.93 (m, 2H), 3.22–3.29 (m, 1H), 7.05 (d, *J* = 8.01 Hz, 2H), 7.11 (d, *J* = 7.96 Hz, 2H), 7.30 (d, *J* = 8.15 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.89, 20.93, 25.9, 32.8, 43.9, 45.5, 55.8, 77.8, 125.3, 126.2, 128.62, 128.65, 135.4, 135.7, 144.8, 146.2 ppm; IR (KBr) ν 3412, 3329, 3242, 3022, 2959, 2853, 1613, 1508, 1409, 1180, 1086, 822, 806, 778, 729, 585, 566 cm^{-1}. TOF HRMS: calcd. for $C_{20}H_{26}NO$ $[M + H]^+$ 296.2014; found 296.2083.

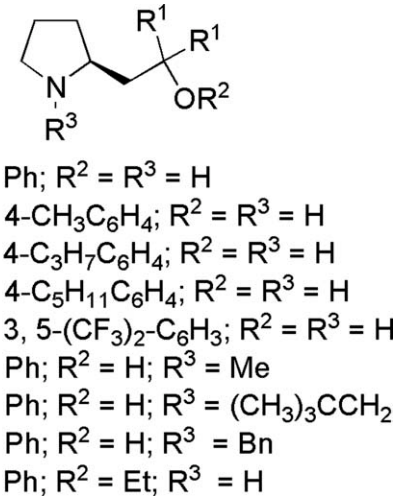


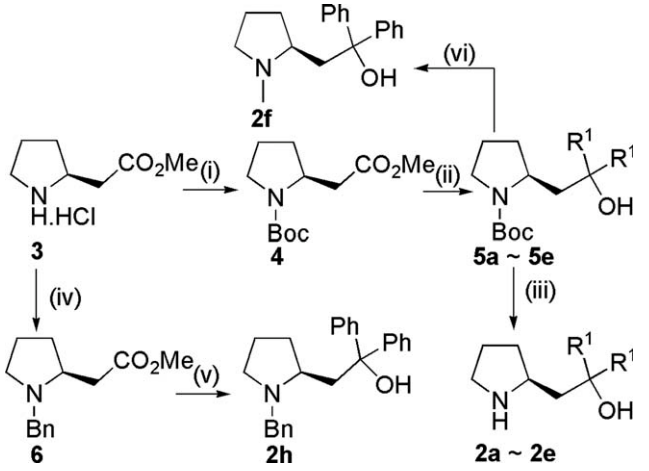
Fig. 2. Pyrrolidine-based γ-amino alcohols and derivatives.

(S)-1,1-Diphenyl-2-(pyrrolidin-2-yl)ethanol 2a. White solid; mp 136–137°C, $[\alpha]_D^{25}$= +24.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.41–1.58 (m, 2H), 1.78–1.88 (m, 2H), 1.99–2.08 (dd, *J* = 13.9 Hz, 11.9 Hz, 1H), 2.17 (s, 1H), 2.38–2.44 (dd, *J* = 14.1 Hz, 2.98 Hz, 1H), 2.80–2.96 (m, 2H), 3.23–3.30 (m, 1H), 7.13–7.34 (m, 6H), 7.42–7.45 (d, *J* = 7.63 Hz, 2H), 7.52–7.55 (d, *J* = 7.59 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 25.9, 32.8, 43.8, 45.5, 55.7, 78.0, 125.4, 126.0, 126.3, 127.9, 147.7, 148.8 ppm; IR(KBr) ν 3414, 3328, 3256, 2958, 2853, 1617, 1492, 1445, 1125, 1061, 748, 697 cm^{-1}. TOF HRMS: calcd. for $C_{18}H_{21}NO$ $[M + H]^+$ 268.1701; found 268.1703.

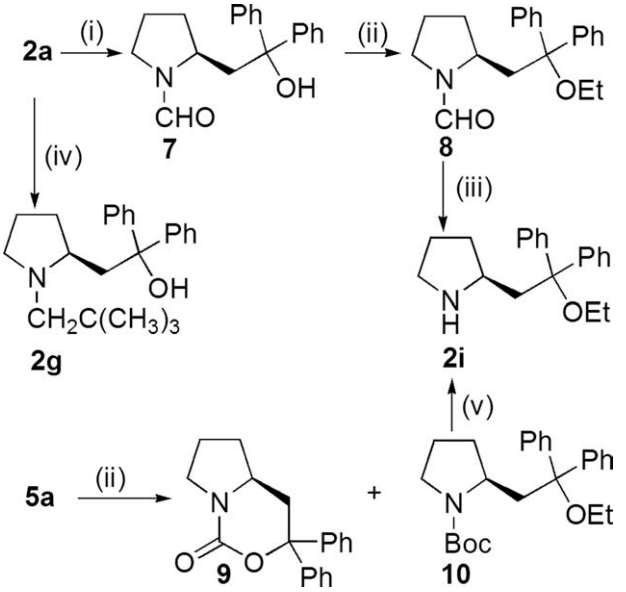
(S)-1,1-Bis(4-propylphenyl)-2-(pyrrolidin-2-yl)ethanol 2c. Colorless oil, $[\alpha]_D^{25}$ = +14.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.89–0.98 (m, 6H), 1.42–1.68 (m, 6H), 1.81–1.87 (m, 2H), 1.99–2.08 (dd, *J* = 13.7 Hz, 12.1 Hz, 1H), 2.37–2.42 (dd, *J* = 14.1 Hz, 2.78 Hz, 1H), 2.49–2.59 (m, 4H), 2.83–2.93 (m, 2H), 3.26–3.29 (m, 1H), 7.06–7.14 (m, 4H), 7.35(d, *J* = 8.07 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.8, 13.9, 24.45, 24.47, 25.9, 32.7, 37.56, 37.59, 44.0, 45.4, 55.8, 77.8, 125.2, 126.1, 127.9, 128.0, 140.1, 140.5, 144.9, 146.4 ppm; IR (neat) ν 2958, 1613, 1452, 1295, 1260, 1182, 1101, 1018, 841, 745, 602 cm^{-1}. TOF HRMS: calcd. for $C_{24}H_{34}NO$ $[M + H]^+$ 352.264; found 352.264.

(S)-1,1-Bis(4-pentylphenyl)-2-(pyrrolidin-2-yl)ethanol 2d. White solid; mp 76–77°C, $[\alpha]_D^{25}$ = +22.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.83–0.90 (q, *J* = 14.3 Hz, 6H), 1.27–1.45 (m, 9H), 1.47–1.61 (m, 5H), 1.78–1.82 (m, 2H), 1.94–2.03 (dd, *J* = 13.7 Hz, 12.1 Hz, 1H), 2.33–2.39 (dd, *J* = 14.0 Hz, 2.7 Hz, 1H), 2.49–2.58 (m, 4H), 2.81–2.90 (m, 2H), 3.26 (m, 1H), 7.06 (d, *J* = 8.1 Hz, 2H,), 7.11 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.9, 14.0, 22.50, 22.52, 26.0, 31.0, 31.1, 31.4, 31.6, 32.8, 35.40, 35.47, 44.0, 45.4, 55.7, 77.8, 125.2, 126.1, 127.8, 127.9, 140.4, 140.7, 145.0, 146.4 ppm; IR (KBr) ν 3329, 3271, 3026, 2998, 2926, 2854, 1615, 1573, 1508, 1461, 1412, 1377, 1290, 1128, 1105, 904, 826, 728 cm^{-1}. TOF HRMS: calcd. for $C_{28}H_{42}NO$ $[M + H]^+$ 408.3266; found 408.3232.

(S)-1,1-Bis(3,5-bis(trifluoromethyl)phenyl)-2-(pyrrolidin-2-yl)ethanol 2e. White solid; mp 125–126°C, $[\alpha]_D^{25}$ = –4.8 (*c* = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.50–1.64 (m, 2H), 1.85–1.96 (m, 2H), 1.98–2.07 (dd, *J* = 14.1 Hz, 12.2 Hz, 1H), 2.45–2.50 (dd, *J* = 14.3 Hz, 2.97 Hz, 1H), 2.81–2.90 (m, 1H), 2.98–3.05 (m, 1H), 3.24–3.32 (m, 1H), 7.73 (s, 1H), 7.78 (s, 1H), 7.90 (s, 2H), 8.03 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5



Scheme 1. Reagents and conditions: (i) $(Boc)_2O/Et_3N$, CH_2Cl_2, 96%; (ii) R^1MgBr, THF, 96%; (iii) NaOH(S), C_2H_5OH, 95%; (iv) BnCl, DIPEA, toluene, 0–110°C, reflux 6 h; (v) PhMgBr, THF, 0°–r.t., 24 h, 94% (two steps); (vi) **5a**, $LiAlH_4$, THF, 79%.



Scheme 2. Reagents and conditions: (i) HCO_2Et, 55°C, 2 days, 95%, (ii) EtI, NaH, THF,)°C–r.t., overnight, 99%; (iii) NaOH, Dioxane, 120°C, 3 days, 87%; (iv) 1) $(CH_3)_3CCOCl$, quant. 2) $LiAlH_4$/THF, 49%; (v) NaOH(S), C_2H_5OH, 95%.

MHz): δ = 25.9, 32.7, 43.1, 45.4, 55.5, 77.4, 117.8, 121.1 (q), 121.5, 125.1, 125.4, 125.5, 126.3, 128.7, 131.4 (q), 132.2, 132.4, 132.3 (q), 149.3, 150.0 ppm; IR (KBr) ν 3339, 3087, 2968, 1622, 1462, 1374, 1278, 1122, 1027, 982, 890, 842, 710, 681 cm^{-1}. TOF HRMS: calcd. for $C_{22}H_{18}F_{12}NO$ $[M + H]^+$ 540.1197; found 540.1223.

The Procedure for the Synthesis of Ligand 2f

$LiAlH_4$ (76 mg, 2 mmol) was carefully added in batches into the solution of **5a** (0.367 g, 1 mmol) in THF (5 ml) with ice bath cooling, and stirred until no gas bubble existed. The mixture was refluxed for 2–3 h further and then cooled to 0°C. Water was added dropwise to quench the reaction and the solid was removed by filtration. The THF was removed in vacuo, and the residue solution was extracted with ethyl acetate (3 × 30 ml). The combined organic layers were washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give **2f**[72] (0.221 g) as white solid; Yield (79%). mp 78–79°C, $[\alpha]_D^{25}$ = −25.2 (c = 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.31–1.40 (m, 1H), 1.71–1.82 (m, 2H), 1.86–1.96 (m, 1H), 2.10 (s, 3H), 2.16 (s, 1H), 2.33–2.39 (m, 1H), 2.42–2.50 (m, 1H), 2.80–2.87 (m, 1H), 3.06–3.15 (m, 1H), 7.12–7.34 (m, 5H), 7.45–7.47 (d , J = 7.57 Hz, 2H), 7.55–7.57 (d, J = 7.54 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 22.6, 29.2, 42.8, 42.9, 53.4, 63.7, 124.8, 125.4, 125.5, 125.7 127.4, 148.0 ppm.

The Procedure for the Synthesis of Ligand 2g

The solution of pivaloyl chloride (0.195 ml, 1.5 mmol) in dried ethyl ether was added dropwise into the mixture of **2a** (0.268 g, 1 mmol) and triethylamine (0.56 ml, 4 mmol) in dried ethyl ether (5 ml) with ice bath. The mixture was slowly warmed to rt and stirred further for 3 h. Then diluted with ethyl ethanoate and washed with saturated NH_4Cl solution, saturated $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give white solid (0.35 g, 100% yield). With the same procedure for the synthesis of ligand **2f**, use the obtained white solid as start material to give **2g**[72,73] (0.163 g) as white solid; Yield (49%). mp 74–76°C, $[\alpha]_D^{25}$ = –34.90 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.85 (s, 9H), 1.37–1.40 (m, 1H), 1.70–1.84 (m, 3H), 1.88–1.92 (d, J = 13.1 Hz, 1H), 2.03–2.08 (m, 1H), 2.11–2.15 (d, J = 12.86 Hz, 1H), 2.25–2.30 (m, 1H), 2.65–2.72 (m, 1H), 3.07–3.16 (m, 2H), 7.11–7.33 (m, 6H), 7.42–7.45 (d, J = 7.54 Hz, 2H), 7.57–7.60 (d, J = 7.52 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 22.0, 28.6, 29.2, 32.5, 42.8, 52.9, 67.4, 70.3, 78.2, 125.2, 126.1, 126.2, 126.6, 127.8 127.9, 128.0, 147.5, 149.3 ppm.

The Procedure for the Synthesis of Ligand 2h

Benzyl chloride (1.27 ml, 11 mmol) was added to the solution of **3** (1.795 g, 10 mmol) and diisopropylethylamine (DIPEA) (3.85 ml, 22 mmol) in toluene at 0°C. The mixture was heated to 110°C and refluxed for 6 h, then cooled to r.t. Water was added and the solution was extracted with EtOAc twice. The combined organic layers were washed with saturated brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was dissolved in dried THF (20 ml). Phenyl magnesium bromide (30 mmol) was added dropwise to the upper solution within 10 min at 0°C. The mixture was stirred at r.t. for 24 h and quenched with saturated NH_4Cl solution. After work up, gave **2h**[74] (3.55 g) as white solid; Yield (94%). mp 134–136°C, $[\alpha]_D^{25}$ = +22.3 (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.39–1.47 (m, 1H), 1.70–1.81 (m, 2H), 1.92–2.01 (m, 1H), 2.15–2.23 (m, 1H), 2.36–2.42 (m, 1H), 2.48–2.56 (m, 1H), 2.80–2.89 (m, 1H), 3.10–3.22 (m, 2H), 3.43–3.47 (m, 1H), 7.12–7.32 (m, 13H), 7.46–7.48 (d, J = 7.42 Hz, 2H), 7.58–7.61 (d, J = 7.34 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 22.6, 30.0, 43.7, 49.7, 59.8, 63.4, 78.2, 125.4, 126.0, 126.1, 126.3, 127.1, 127.9, 128.0, 128.4, 128.8, 138.3, 147.7, 148.7 ppm.

The Procedure for the Synthesis of Ligand 2i

2a (2.67 g, 10 mmol) was dissolved in ethyl formate (80 ml) and stirred at 55°C for 48 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give **7** (95% yield). NaH (0.36 g, 15 mmol) was added to the solution of **7** and ethyl iodide (1 ml, 12.3 mmol) in THF at 0°C. After the addition, removed the ice bath, warmed to r.t. and continued to stir for 12 h, then cooled to 0°C, cold saturated NH_4Cl solution was added to quench the reaction, the THF was removed in vacuo and the residue solution was extracted with EtOAc twice. The combined organic layers were washed with saturated salt solution, and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography to obtain **8** (99% yield). The solution of KOH (15%, 50 ml) was added to the solution of **8** (3.2 g, 9.9 mmol) in 1, 4-dioxane (5mL) and refluxed for 72 h. After cooling to room temperature, water was added, and the mixture was extracted three times with ether. The combined organic layers were washed with saturated brine, and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give **2i**[71,75,76] (2.54 g) as colorless oil; Yield (87%). $[\alpha]_D^{25}$ = +92.2 (c = 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.10–1.24 (m, 4H), 1.48–1.71 (m, 3H), 2.47–2.53 (q, J = 4.8, 1H), 2.61–2.67 (m, 3H), 2.81–2.86 (m, 1H), 2.88–2.92 (m, 1H), 3.10–3.15 (m, 1H), 3.22–3.27 (m, 1H), 7.10–7.38 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 75.5

TABLE 1. Enantioselective addition of diethylzinc to benzaldehyde in the presence of γ-amino alcohols 2a–2i[a]

Entries	Cat. (%)	Solvent (v/v)	T (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)	Config.[d]
1	**2a** (10)	Hex/Tol (1:1)	−10	86	65	70	*S*
2	**2b** (10)	Hex/Tol (1:1)	−10	90	86	81	*S*
3	**2c** (10)	Hex/Tol (1:1)	−10	64	59	72	*S*
4	**2d** (10)	Hex/Tol (1:1)	−10	64	54	73	*S*
5	**2e** (10)	Hex/Tol (1:1)	−10	117	35	62	*S*
6	**2f** (10)	Hex/Tol (1:1)	−10	96	62	41	*S*
7	**2g** (10)	Hex/Tol (1:1)	−10	141	45	37	*S*
8	**2h** (10)	Hex/Tol (1:1)	−10	96	72	27	*S*
9	**2i** (10)	Hex/Tol (1:1)	−10	96	57	6	*S*
10	**2b** (10)	Hex	−10	90	44	70	*S*
11	**2b** (10)	Tol	−10	90	48	56	*S*
12	**2b** (10)	Hex/DCM (1:1)	−10	96	54	65	*S*
13	**2b** (10)	Hex/THF (1:1)	−10	96	40	68	*S*
14	**2b** (10)	Hex/Et_2O 1:1	−10	96	42	67	*S*
15	**2b** (10)	Hex/Tol (2:1)	−10	113	81	70	*S*
16	**2b** (10)	Hex/Tol (1:2)	−10	96	79	74	*S*
17	**2b** (10)	Hex/Tol (1:1)	−20	110	54	68	*S*
18	**2b** (10)	Hex/Tol (1:1)	0	90	75	69	*S*
19	**2b** (10)	Hex/Tol (1:1)	10	65	66	67	*S*
20[e]	**2b** (10)	Hex/Tol (1:1)	−10	90	88	78	*S*
21[f]	**2b** (10)	Hex/Tol (1:1)	−10	90	79	82	*S*
22	**2b** (5)	Hex/Tol (1:1)	−10	96	22	67	*S*
23	**2b** (20)	Hex/Tol (1:1)	−10	96	87	75	*S*

[a]Unless specified, reactions performed with 3 equiv. diethylzinc in the presence of **2b** in the solution of total volume of 6 ml (0.083 M).
[b]Isolated yield.
[c]Determined by chiral HPLC with a ChiralPak AS-H column.
[d]Determined by comparison of the optical rotation value with the literature.
[e]The total volume of solution was 3 ml (0.167 M).
[f]The total volume of solution was 12 ml (0.042 M).

MHz): δ = 15.3, 23.7, 31.9, 41.2, 45.5, 54.6, 57.6, 81.6, 126.4, 126.6, 126.8, 127.7, 127.8, 145.7, 145.9 ppm.

General Procedure for the Enantioselective Addition of Diethylzinc to Aldehydes

2b (14.5 mg, 0.05 mmol) was dissolved in the mixture solvent of anhydrous toluene (3 ml) and *n*-hexane (1.5 ml) under an argon atmosphere, and cooled to 0°C. Et_2Zn (1 M, 1.5 mmo1) was added to the solution and stirred at 0°C for 1 h, then cooled to −10°C and freshly distilled benzaldehyde (0.051 ml, 0.5 mmo1) was added. The reaction mixture was stirred for the appropriate time to complete the reaction (TLC monitoring). Hydrochloric acid (1 M, 3 ml) was added to quench the reaction at 0°C, and the solution was extracted with EtOAc (4 × 10 ml), the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give the product 1-phenyl-1-propanol (58 mg, 86% yield) as colorless liquid with 81% ee.

RESULTS AND DISCUSSION

The synthetic routes to **2a–2f** and **2h** were summarized in Scheme 1. Starting from methyl homoprolinate hydrochloride **3**, Boc protection followed by Grignard addition gave **5a–5e**, which were treated with NaOH to afford the γ-amino alcohols **2a–2e**. Direct reduction of **5a** with $LiAlH_4$ gave **2f**. Alternatively, protection of **3** with Bn group followed by the treatment of phenyl magnesium bromide, afforded **2h**.

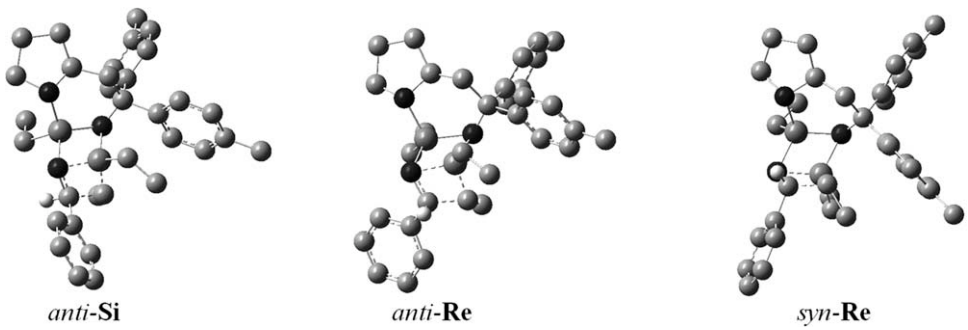
2g and **2i** were prepared starting from **2a** (Scheme 2). Acylation of **2a** with pivaloyl chloride followed by reduction with $LiAlH_4$ gave **2g**. The attempts to synthesize **2i** from **5a** gave very low yield of **10**. This maybe ascribed to the formation of the unexpected oxazinone byproduct **9**. We postulated that the hydroxyl group deprotonated by NaH favorably attacked the carbonyl of Boc. In order to avoid this side reaction, we chose **2a** as the starting material, in which the nitrogen was protected by formyl (CHO). Thus, acylation of **2a** with ethyl formate gave **7**, which was etherified with ethyl iodide to afford **8**. Removal of the formyl group of **8** with NaOH afforded **2i**.

The γ-amino alcohols **2a–2i** were then tested in the enantioselective addition of diethylzinc to benzaldehyde and the results were summarized in Table 1. Good results could be obtained when the reaction proceeded in the mixed solvent of hexane and toluene (1:1) at −10°C. Under such conditions, **2a–2i** were further examined (entries 1–9). Significant differences in both catalytic and enantioselective activities of **2a–2i** were observed. When the reaction was catalyzed by **2a**, 65% yield and 70% ee were obtained. The enantionselectivity was better than that of the reaction catalyzed by the corresponding β-amino alcohol (70.3% yield and 55.2% ee).[21] The catalytic activities were significantly influenced by R^1. When R^1 was changed from phenyl (**2a)** to *para*-methylphenyl (**2b**), the yield and enantioselectivity of the products were increased from 65 to 86% and 70–81% ee, respectively. An increase in the size of *para*-substituent on the phenyl ring led to a decrease in catalytic reactivity, that is, 59% yield for **2c** and 54% yield for **2d**, as well as a decrease in enantioselectivity, 72% ee for **2c** and 73% ee for **2d**. Introduction of two electron-withdrawing groups (—CF_3) on the phenyl ring (**2e**) led to a sharp decrease in reactivity giving only 35% yield with moderate enantioselectivity (62% ee). The substituents R^2 and R^3 also affected the reactivity and enantioselectivity greatly. When the substituent R^3 was changed from hydrogen (**2a**) to methyl (**2f**), the reactivity remained the same; however, the enantioselectivity decreased from 70 to 41% ee. An increase in the size of the substituent by

TABLE 2. Asymmetric addition reaction of diethylzinc and other aldehydes using 2b as the catalyst[a]

Entries	Aldehydes	Time (h)	Yield[b] (%)	E.e.[c] (%)	Config.[d]
1	Benzaldehyde	90	86	81	*S*
2	2-Fluorobenzaldehyde	88	71	68	*S*
3	4-Fluorobenzaldehyde	88	74	80	*S*
4	4-Chlorobenzaldehyde	84	83	75	*S*
5	4-Bromobenzaldehyde	84	88	74	*S*
6	3-Methylbenzaldehyde	92	72	75	*S*
7	4-Methylbenzaldehyde	92	63	66	*S*
8	4-(Methylthio)benzaldehyde	144	78	78	*S*
9	2-Methoxybenzaldehyde	89	82	80	*S*
10	3-Methoxybenzaldehyde	89	45	77	*S*
11	4-Methoxybenzaldehyde	92	67	78	*S*
12	1-Naphthaldehyde	90	71	63	*S*
13	2,3-Dimethoxybenzaldehyde	90	88	68	*S*
14	3,4-Dimethoxybenzaldehyde	92	75	71	*S*
15	2,4-Dichlorobenzaldehyde	92	82	64	*S*
16	Cinnamaldehyde	92	73	47	*S*
17	Cyclohexanecarboxaldehyde	48	52	72	*S*
18	Hexanal	50	45	44	*S*

[a]All reactions performed with 3 equiv diethylzinc in the presence of 10 mol % **2b** in 6 ml Hex/Tol (1:1) at −10°C.
[b]Isolated yield.
[c]Determined by chiral HPLC with a ChiralPak AS-H column.
[d]Determined by comparison of the optical rotation value with the literature.



Scheme 3. Enantioselectivity controlling transition states.

neopentyl group (**2g**) and benzyl group (**2h**), led to further decrease in enantioselectivity (37 and 27% ee, respectively). It is interesting to note that the yield increased slightly (72%) in the case of **2h**. Similar effect of *N*-substituent-induced difference in enantioselectivity of other γ-amino alcohol catalysts derived from α-pinene has already been observed by Fülöp group.[28] We also tested **2i** in the reaction, the enantioselectivity decreased sharply giving the product with only 6% ee. Therefore, among the examined γ-amino alcohols **2a–2i**, the most promising catalyst was **2b**.

In order to achieve high reactivity and enantioselectivity, various reaction conditions were investigated. A series of solvent systems, including hexane, toluene, the mixture of hexane and toluene, dichloromethane (DCM), Et_2O, and THF, were screened using **2b** as the catalyst (Table 1, entries 2, 10–16). The best result was still achieved in the mixed solvent of hexane/toluene (1:1). We also optimized the reaction temperature and found that the highest yield and the best enantioselectivity were achieved at −10°C (Table 1, entries 2, 17–19). When the reaction proceeded at −20°C, both the yield and the enantioselectivity were decreased from 86% yield and 81% ee to 54% yield and 68% ee even with elongation of reaction time (Table 1, entries 2, 17) . When the reaction proceeded at 0 and 10°C, the similar enantioselectivities were observed ranging from 67% to 69% ee (Table 1, entries 17–19). In terms of the effect of concentration on the reaction, we found that concentration has only slight influence on yield and enantioselectivity (Table 1, entries 2, 20, and 21). The influence of catalyst loading on the reaction was examined as well. When the catalyst load was reduced to 5 mol % from 10 mol %, the catalytic performance of **2b** decreased dramatically. When the catalyst load increased to 20 mol %, the yield of the product remained almost the same as that catalyzed by 10 mol %; however, the enantioselectivity decreased slightly from 81 to 75% ee (Table 1, entries 2, 22, and 23).

With the optimal conditions in hand, the scope of the reaction was examined (Table 2). The results showed that the reaction has broad applicability. In general, aldehydes possessing either electron-withdrawing or electron-donating groups on their aromatic ring reacted smoothly to afford the corresponding alcohols with moderate to good yields (45–88%) and enantioselectivities (63–81% ee) (Table 2, entries 1–15). The electronic property of the substituents on aro-

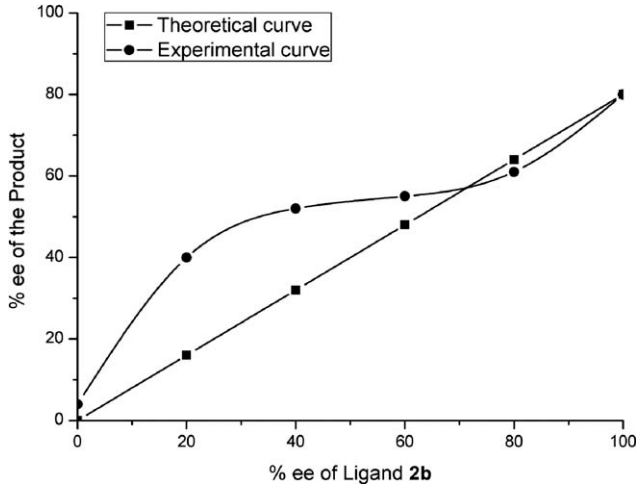


Fig. 3. Nonlinear effect study of γ-amino alcohol **2b**.

matic ring had influences on reactivity. The presence of an electron-donating substituent at the para position of substrates caused the reactivity to decrease (Table 2, entries 1, 7, and 11). In the aspect of stereoselectivity, similar results were achieved to those reported by Walsh.[77] Influences of electronic property of the substituents on the enantioselectivity which exist in the catalytic system of β-amino alcohols, described by Noyori,[78] have not yet been observed in this catalytic system. This may be attributed to the increase of conformational flexibility in the TS of γ-amino alcohols (Scheme 3). The substitution patterns of substrates also had some influences on reactivity and enantioselectivity. For example, when the substitution of methoxy group was changed from 2- to 3-position, the yield decreased from 82 to 45%, and enantioselectivity decreased slightly from 80 to 77% ee (Table 2, entries 9 and 10). Cinnamaldehyde also gave the corresponding alcohol in 73% yield and remarkably lower enantioselectivity (47% ee) (Table 2, entry 16). Cyclohexanecarboxaldehyde and hexanal had been applied in the catalytic system but only moderate yields and enantioselectivities were obtained (Table 2, entries 17, 18). Under the reaction conditions, and with aliphatic aldehyde substrates, the aldol reaction took place as the side reaction, resulting in the low yields. In addition, when compared with aromatic aldehydes, aliphatic aldehyde substrates with lower steric hindrance substituents were reacted to give products with lower enantioselectivity due to lower energy difference between the two competitive *anti*-types TSs (*anti*-Si and *anti*-Re). Therefore, hexanal gave the corresponding product with only 44% ee in comparison with 72% ee in the case of cyclohexanecarboxaldehyde.

The catalytic system was then examined to determine if a nonlinear effect was present.[6,79–82] The reactions were proceeded in 6 ml toluene/hexane (1:1) with 0.25 M $(C_2H_5)_2Zn$, 0.083 M C_6H_5CHO and 8.3 mM **2b** at $-10^{\circ}C$ for 90 h (Figure 3). The results demonstrated that a positive nonlinearity occurred when the enantiomeric excess of ligand **2b** is lower to 70% ee, and that a slightly negative deviation from linearity occurred when the ee of **2b** was higher than 70%. The latter may be due to the experimental error.

The achievement of stereocontrol may be explained by the mechanism proposed by Noyori:[7–9] The γ-amino alcohol gave a tricyclic 6/4/4 TS, in which the Zn-atom is part of a flexible six-membered ring in the catalytic chelate (Scheme 3). The stable TS is the *anti*-Si and the *Si*-face of the benzaldehyde is attacked to give the observed (*S*)-alcohol. There may also exist two other higher-energy TSs, namely *anti*-Re and *syn*-Re, which lead to the (*R*)-alcohol. If the ethyl group transfers via the *anti*-Re TS, the repulsion interaction between the Zn-Et and the phenyl results higher activation energy. Via *syn*-Re, the electrostatic and nonbonded repulsion arise from the unreactive two *syn*-oriented Zn-Et spectators also lead to higher TS energy. As demonstrated by Martínez[27] and Goldfuss[83] groups, the more flexible the ligands are, the less the energy difference between *anti*-type and *syn*-type TSs. Therefore, with the increase of flexibility of ligands, stereoselectivity of the alcohols may decrease due to the competitive participation of less energetically differentiated *syn*- and *anti*-TSs. By such mechanism, the 6/4/4 TS derived from the pyrrolidine-based γ-amino alcohols is flexible and the energy difference among the *anti*-Si, *anti*-Re, and *syn*-Re is decreased. Thus, the proportion via the competitive reaction pathways *anti*-Re and *syn*-Re are increased, resulting low enantioselectivity (81% ee) of the product when γ-amino alcohol **2b** was used as chiral ligand. By such hypothesis, the origin of the nonlinear effect (NLE) can be ascribed to the reservoir effect. However, the practical situation may be more complicated. Both the ML_2 model and reservoir effect may coexist in the catalytic system as demonstrated by Kagan[79] and Blackmond.[81]

CONCLUSIONS

γ-Amino alcohols and their derivatives based on pyrrolidine were evaluated systematically in the enantioselective addition reactions of diethylzinc to aldehydes. Among the homoprolinols tested, the best results (45–88% yields, 44–81% ee) in the addition reactions were from **2b**. To the best of our knowledge, **2b** has been found to be the most efficient γ-amino alcohol catalyst based on pyrrolidine framework.

LITERATURE CITED

1. Soai K, Niwa S. Enantioselective addition of organozinc reagents to aldehydes. Chem Rev 1992;92:833–856.
2. Pu L, Yu HB. Catalytic asymmetric organozinc additions to carbonyl compounds. Chem Rev 2001;101:757–824.
3. 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.
4. Kitamura M, Suga S, Kawai K, Noyori R. Catalytic asymmetric induction. Highly enantioselective addition of dialkylzincs to aldehydes. J Am Chem Soc 1986;108:6071–6072.
5. Noyori R, Suga S, Kawai K, Okada S, Kitamura M. Enantioselective alkylation of carbonyl compounds. From stoichiometric to catalytic asymmetric induction. Pure App Chem 1988;60:1597–1606.
6. Kitamura M, Okada S, Suga S, Noyori R. Enantioselective addition of dialkylzincs to aldehydes promoted by chiral amino alcohols. Mechanism and nonlinear effect. J Am Chem Soc 1989;111:4028–4036.
7. Kitamura M, Suga S, Niwa M, Noyori R. Self and nonself recognition of asymmetric catalysts. Nonlinear effects in the amino alcohol-promoted enantioselective addition of dialkylzincs to aldehydes. J Am Chem Soc 1995;117:4832–4842.
8. Yamakawa M, Noyori R. An Ab initio molecular orbital study on the amino alcohol-promoted reaction of dialkylzincs and aldehydes. J Am Chem Soc 1995;117:6327–6335.
9. Yamakawa M, Noyori R. Asymmetric addition of dimethylzinc to benzaldehyde catalyzed by (2*S*)-3-exo-(dimethylamino)isobornenol. A theoretical study on the origin of enantioselection. Organometallics 1999;18:128–133.

10. 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.
11. Wang MC, Zhang QJ, Li GW, Liu ZK. Highly enantioselective addition of dimethylzinc to arylaldehydes catalyzed by (2*S*)-1-ferrocenyl-methylaziridin-2-yl(diphenyl)methanol. Tetrahedron: Asymmetry 2009;20:288–292.
12. Pisani L, Superchi S. 1, 1'-Binaphthylazepine-based ligands for the enantioselective dialkylzinc addition to aromatic aldehydes. Tetrahedron: Asymmetry 2008;19:1784–1789.
13. Harada A, Fujiwara Y, Katagiri T. Improvement of the asymmetry-inducing ability of a trifluoromethylated amino alcohol by electron donation to a CF_3 group. Tetrahedron: Asymmetry 2008;19:1210–1214.
14. Parrott IIRW, Hitchcock SR. β-Amino alcohols derived from (1*R*, 2*S*)-norephedrine and (1*S*, 2*S*)-pseudonorephedrine as catalysts in the asymmetric addition of diethylzinc to aldehydes. Tetrahedron: Asymmetry 2008;19:19–26.
15. Wang MC, Hou XH, Chi CX, Tang MS. The effect of direct steric interaction between substrate substituents and ligand substituents on enantioselectivities in asymmetric addition of diethylzinc to aldehydes catalyzed by sterically congested ferrocenyl aziridino alcohols. Tetrahedron: Asymmetry 2006;17:2126–2132.
16. Dave R, Sasaki NA. Synthesis of chiral C/N-functionalized morpholine alcohols: study of their catalytic ability as ligand in asymmetric diethylzinc addition to aldehyde. Tetrahedron: Asymmetry 2006;17: 388–401.
17. Wang MC, Liu LT, Zhang JS, Shi YY, Wang DK. Synthesis of chiral ferrocenyl aziridino alcohols and use in the catalytic asymmetric addition of diethylzinc to aldehydes. Tetrahedron: Asymmetry 2004;15:3853–3859.
18. Sibi MP, Stanley LM. Enantioselective diethylzinc additions to aldehydes catalyzed by chiral relay ligands. Tetrahedron: Asymmetry 2004;15:3353–3356.
19. Boyle GA, Govender T, Kruger HG, Maguire GEM. Synthesis of chiral pentacyclo-undecane ligands and their use in the enantioselective alkylation of benzaldehyde with diethylzinc. Tetrahedron: Asymmetry 2004;15:2661–2666.
20. You JS, Shao MY, Gau HM. Enantioselective addition of diethylzinc to aldehydes catalyzed by titanium (IV) complexes of N-sulfonylated amino alcohols with two stereogenic centers. Tetrahedron: Asymmetry 2001;12:2971–2975.
21. Yang X, Shen J, Da C, Wang R, Choi MCK, Yang L, Wong K. Chiral pyrrolidine derivatives as catalysts in the enantioselective addition of diethylzinc to aldehydes. Tetrahedron: Asymmetry 1999;10:133–138.
22. Wang SX, Chen FE. Novel polymer-supported chiral catalysts for the asymmetric addition of diethylzinc to aldehydes. Chem Pharm Bull 2007;55:1011–1013.
23. Lombardo M, Chiarucci M, Trombini C. The first enantioselective addition of diethylzinc to aldehydes in ionic liquids catalysed by a recyclable ion-tagged diphenylprolinol. Chem Eur J 2008;14:11288–11291.
24. Sánchez-Carnerero EM, de las C. Engel T, Maroto BL, de la M. Cerero S. Polyoxygenated ketopinic-acid-derived γ-amino alcohols in the enantioselective diethylzinc addition to benzaldehyde. Tetrahedron: Asymmetry 2009;20:2655–2657.
25. Olsson C, Helgesson S, Frejd T. New bicyclic γ- and δ-aminoalcohols as catalysts for the asymmetric diethylzinc addition to benzaldehyde. Tetrahedron: Asymmetry 2008;19:1484–1493.
26. de las C. Engel T, Maroto BL, Martínez AG, de la M. Cerero S. N/N/O versus N/O/O and N/O amino isoborneols in the enantioselective ethylation of benzaldehyde. Tetrahedron: Asymmetry 2008;19:269–272.
27. Martínez AG, Vilar ET, Fraile AG, de la M. Cerero S, Ruiz PM, Morillo CD. The role of conformational flexibility on the catalytic activity of norbornane-derived β-, γ- and δ-amino alcohols. Tetrahedron: Asymmetry 2007;18:742–749.
28. Szakonyi Z, Balázs A, Martinek TA, Fülöp F. Enantioselective addition of diethylzinc to aldehydes catalyzed by γ-amino alcohols derived from (+)- and (-)-α-pinene. Tetrahedron: Asymmetry 2006;17:199–204.
29. Dimitrov V, Dobrikov G, Genov M. Chiral β- and γ-aminoalcohols derived from (+)-camphor and (-)-fenchone as catalysts for the enantioselective addition of diethylzinc to benzaldehyde. Tetrahedron: Asymmetry 2001;12:1323–1329.
30. Panev S, Linden A, Dimitrov V. Chiral aminoalcohols with a menthane skeleton as catalysts for the enantioselective addition of diethylzinc to benzaldehyde. Tetrahedron: Asymmetry 2001;12:1313–1321.
31. Hari Y, Aoyama T. Enantioselective addition of diethylzinc to aldehydes catalyzed by (1*R*, 2*R*)-10-(dialkylamino)isoborneols. Synthesis 2005:583-587.
32. Cicchi S, Crea S, Goti A, Brandi A. Synthesis of new enantiopoure γ-aminoalcohols: their ues as catalysts in the alkylation of benzaldehyde by diethyizinc. Tetrahedron: Asymmetry 1997;8:293–301.
33. Panda M, Phuan PW, Kozlowski MC. Theoretical and experimental studies of asymmetric organozinc additions to benzaldehyde catalyzed by flexible and constrained γ-amino alcohols. J Org Chem 2003;68:564–571.
34. Oliveira LF, Costa VEU. An efficient synthesis of enantiopure (+)- and (-)-*syn*-1, 3-aminoalcohols with a norbornane framework and their application in the asymmetric addition of $ZnEt_2$ to benzaldehyde. Tetrahedron: Asymmetry 2004;15:2583–2590.
35. Martins JED, Mehlecke CM, Gamba M, Costa VEU. Synthesis of chiral norbornane derivatives as γ-aminoalcohol catalysts: the effect of the functional group positions on the chirality transfer. Tetrahedron: Asymmetry 2006;17:1817–1823.
36. Gou S, Judeh ZMN. Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by Ti (IV) complexes of C_2-symmetrical chiral BINOL derivatives. Tetrahedron Lett 2009;50:281–283.
37. Gadenne B, Hesemann P, Moreau ,JJE. Ionic liquids incorporating camphorsulfonamide units for the Ti-promoted asymmetric diethylzinc addition to benzaldehyde. Tetrahedron Lett 2004;45:8157–8160.
38. Braga AL, Vargas F, Silveira CC, Andrade LH. Synthesis of new chiral imidazolidine disulfides derived from L-cystine and their application in the enantioselective addition of diethylzinc to aldehydes. Tetrahedron Lett 2002;43:2335–2337.
39. Pastor IM, Adolfsson H. Novel highly modular C_2-symmetric oxazoline ligands—application in titanium-catalyzed diethylzinc additions to aldehydes. Tetrahedron Lett 2002;43:1743–1746.
40. Bauer T, Tarasiuk J. α-Hydroxy carboxylic acids: new ligands for diethylzinc additions to aldehydes. Tetrahedron Lett 2002;43:687–689.
41. Pu L. Asymmetric alkynylzinc additions to aldehydes and ketones. Tetrahedron 2003;59:9873–9886.
42. Salehi P, Dabiri M, Kozehgary G, Baghbanzadeh M. An efficient method for catalytic enantioselective addition of diethylzinc to aryl aldehydes by a C_2-symmetric chiral imino alcohol. Tetrahedron: Asymmetry 2009;20:2609–2611.
43. Lesniak S, Rachwalski M, Sznajder E, Kielbasinski P. New highly efficient aziridine-functionalized tridentate sulfinyl catalysts for enantioselective diethylzinc addition to carbonyl compounds. Tetrahedron: Asymmetry 2009;20:2311–2314.
44. Ananthi N, Balakrishnan U, Vinu A, Ariga K, Velmathi S. Chiral amide from (1*S*, 2*R*)-(+)-norephedrine alkaloid in the enantioselective addition of diethylzinc to aryl and heteroaryl aldehydes. Tetrahedron: Asymmetry 2009;20:1731–1735.
45. Martínez R, Zoli L, Cozzi PG, Ramón DJ, Yus M. Synthesis of camphorsulfonamide-based quinoline ligands and their N-oxides: first use in the enantioselective addition of organozinc reagents to aldehydes. Tetrahedron: Asymmetry 2008;19:2600–2607.
46. Dean MA, Hitchcock SR. Divergent enantioselective pathways in the catalytic asymmetric addition of diethylzinc to aldehydes in the presence and absence of titanium tetraisopropoxide. Tetrahedron: Asymmetry 2008;19:2563–2567.
47. Sun J, Pan X, Dai Z, Zhu C. Synthesis of new Schiff base-camphorsulfonyl amide ligands and in situ screening in the asymmetric additions of organozinc reagents to aldehydes. Tetrahedron: Asymmetry 2008;19: 2451–2457.
48. Gilani M, Wilhelm R. New enantiopure imidazolinium carbene ligands incorporating two hydroxy groups for Lewis acid-catalyzed diethylzinc addition to aldehydes. Tetrahedron: Asymmetry 2008;19:2346–2352.
49. de las C. Engel T, Maroto BL, Martínez AG, de la M. Cerero S. Hydroxyamides versus amino alcohols in the enantioselective addition of diethylzinc to benzaldehyde. Tetrahedron: Asymmetry 2008;19:2003–2006.
50. Dabiri M, Salehi P, Kozehgary G., Heydari S, Heydari A, Esfandyari M. Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by 14-hydroxylsubstituted morphinans. Tetrahedron: Asymmetry 2008;19:1970–1972.
51. Cheng YQ, Bian Z, Kang CQ, Guo HQ, Gao LX. Chiral ligand 2-(2'-piperidinyl) pyridine: synthesis, resolution and application in asymmetric diethylzinc addition to aldehydes. Tetrahedron: Asymmetry 2008;19:1572–1575.

52. Martins JED, Wills M. Synthesis of a series of novel N, N-dialkyl-TsDPEN ligands and their application to enantioselective addition of dialkylzinc to benzaldehyde. Tetrahedron: Asymmetry 2008;19:1250–1255.
53. Parrott IIRW, Dore DD, Chandrashekar SP, Bentley JT, Morgan BS, Hitchcock SR. Enantioselective diethylzinc addition to aldehydes via chiral, non-racemic β-hydroxysalicylhydrazone catalysts. Tetrahedron: Asymmetry 2008;19:607–611.
54. Burguete MI, Collado M, Escorihuela J, Luis SV. Efficient chirality switching in the addition of diethylzinc to aldehydes in the presence of simple chiral α-amino amides. Angew Chem Int Ed 2007;46:9002–9005.
55. Parrott IIRW, Hitchcock SR. Intramolecular chiral relay at stereogenic nitrogen: oxazolidine catalysts derived from *Ephedra* alkaloids. Tetrahedron: Asymmetry 2007;18:377–382.
56. Mastranzo VM, Santacruz E, Huelgas G, Paz E, Sosa-Rivadeneyra MV, Bernès S, Juaristi E, Quintero L, Parrodi CA. Synthesis of chiral ligands containing the *N*-(*S*)-α-phenylethyl group and their evaluation as activators in the enantioselective addition of Et_2Zn to benzaldehyde. Tetrahedron: Asymmetry 2006;17:1663–1670.
57. Pathak K, Bhatt AP, Abdi SHR, Kureshy RI, Khan NH, Ahmad I, Jasra RV. Enantioselective addition of diethylzinc to aldehydes using immobilized chiral BINOL-Ti complex on ordered mesoporous silicas. Tetrahedron: Asymmetry 2006;17:1506–1513.
58. Unaleroglu C, Aydina AE, Demir A S. Synthesis of novel norephedrine-based chiral ligands with multiple stereogenic centers and their application in enantioselective addition of diethylzinc to aldehyde and chalcone. Tetrahedron: Asymmetry 2006;17:742–749.
59. Ricci G, Ruzziconi R. ([2]Paracyclo[2](5, 8)quinolinophan-2-yl)carbinols as catalysts for diethylzinc addition to aldehydes: cooperative effects of planar and central chirality on the asymmetric induction. Tetrahedron: Asymmetry 2005;16:1817–1827.
60. Bisai A, Singh PK, Singh VK. Enantioselective diethylzinc addition to aldehydes catalyzed by Ti (IV) complex of unsymmetrical chiral bis(sulfonamide) ligands of trans-cyclohexane 1, 2-diamine. Tetrahedron 2007;63:598–601.
61. Arnott G, Hunter R. Enantioselective addition of diethylzinc to benzaldehyde catalysed by chiral, bridged resorcinarenes: a stereoselectivity model based on chirality transfer. Tetrahedron 2006;62:992–1000.
62. Scarpi D, Occhiato EG., Guarna A. N-Substituent effects on the diethylzinc addition to benzaldehyde catalysed by bicyclic 1, 4-aminoalcohols. Tetrahedron: Asymmetry 2009;20:340–350.
63. Yang X F, Hirose T, Zhang GY. Synthesis of novel chiral tridentate aminophenol ligands for enantioselective addition of diethylzinc to aldehydes. Tetrahedron: Asymmetry 2008;19:1670–1675.
64. Tanyeli C, Sünbül M. Asymmetric synthesis of 1, 4-amino alcohol ligands with a norbornene backbone for use in the asymmetric diethylzinc addition to benzaldehyde. Tetrahedron: Asymmetry 2005;16:2039–2043.
65. Faux N, Razafimahefa D, Picart-Goetgheluck S, Brocard J. Preparation of enantiopure 1, 4-amino alcohols derived from [3]ferrocenophanes: use in the asymmetric addition of diethylzinc to benzaldehyde. Tetrahedron: Asymmetry 2005;16:1189–1197.
66. Martínez AG, Vilar ET, Fraile AG, de la M. Cerero S, Maroto BL. 2-*exo*-versus 2-*endo*-hydroxyl in δ-amino norbornan-2-ol-based catalysts: investigating the role of the C (2) configuration in the asymmetric induction. Tetrahedron: Asymmetry 2004;15:753–756.
67. Roudeau R, Pardo DG, Cossy J. Enantioselective diethylzinc addition to aromatic and aliphatic aldehydes using (3*R*, 5*R*)-dihydroxypiperidine derivatives catalyst. Tetrahedron 2006;62:2388–2394.
68. Martínez AG, Vilar ET, Fraile AG, de la M. Cerero S, Maroto BL. Understanding the catalytic role of flexible chiral δ-aminoalcohols: the 1-(2-aminoethyl)norbornan-2-ol model. Tetrahedron 2005;61:3055–3064.
69. Wang SW, Chen J, Chen GH, Peng YG. Homodiphenylprolinol methyl ester as a highly efficient catalyst for asymmeric michael addition of ketones to nitroalkenens. Synlett 2009;9:1457–1462.
70. Ponnusamy E, Fotadar U, Spisni A, Fiat D. A novel method for the rapid, non-aqueous *t*-butoxycarbonylation of some ^{17}O-labeled amino acids and ^{17}O-N.M.R. parameters of the products. Synthesis 1986:48-49.
71. Chi Y, Gellman SH. Diphenylprolinol methyl ether: a highly enantioselective catalyst for michael addition of aldehydes to simple enones. Org Lett 2005;7:4253–4256.
72. Hayashi Y, Tamura T, Shoji M. The chiral diamine mediated asymmetric Baylis-Hillman reaction. Adv Synth Catal 2004;346:1106–1110.
73. Sibi MP, Manyem S. Lanthanide Lewis acid-mediated enantioselective conjugate radical additions. Org Lett 2002;4:2929–2932.
74. Palomo C, Landa A, Mielgo A, Oiarbide M, Puente Á, Vera S. Water-compatible iminium activation: organocatalytic michael reactions of carbon-centered nucleophiles with enals. Angew Chem Int Ed 2007;46:8431–8435.
75. Zeng QH, Hu XP, Liang XM, Zheng Z. Synthesis of novel monophosphoramidite ligands derived from L-proline for Rh-catalyzed asymmetric hydrogenation of alpha-dehydroamino acid esters. Chin Chem Lett 2005;16:1321–1323.
76. Hengartner U, Batcho AD, Blount JF, Leimgruber W, Larscheid ME, Scott JW. New syntheses of racemic tryptophans. J Org Chem 1979;44:3748–3752.
77. Chen YK, Costa AM, Walsh PJ. Substrate dependence of nonlinear effects: mechanistic probe and practical applications. J Am Chem Soc 2001;123:5378–5379.
78. Kitamura M, Oka H, Noyori R. Asymmetric addition of dialkylzincs to benzaldehyde derivatives catalyzed by chiral β-amino alcohols. Evidence for the monomeric alkylzinc aminoalkoxide as catalyst. Tetrahedron 1999;55:3605–3614.
79. Guillaneux D, Zhao SH, Samuel O, Rainford D, Kagan HB. Nonlinear effects in asymmetric catalysis. J Am Chem Soc 1994;116:9430–9439.
80. Girard C, Kagan HB. Nonlinear effects in asymmetric synthesis and stereoselective reactions: ten years of investigation. Angew Chem Int Ed 1998;37:2922–2959.
81. Blackmond DG. Kinetic aspects of nonlinear effects in asymmetric catalysis. Acc Chem Res 2000;33:402–411.
82. Satyanarayana T. Abraham S. Kagan HB. Nonlinear effects in asymmetric catalysis. Angew Chem Int Ed 2009;48:456–494.
83. Goldfuss ,B, Steigelmann ,M, Khan ,SI, Houk ,KN. Rationalization of enantioselectivities in dialkylzinc additions to benzaldehyde catalyzed by fenchone derivatives. J Org Chem 2000;65:77–82.