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Highly Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Novel Chiral *tert*-Amino Alcohols

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A series of novel chiral *tert*-amino alcohols **4a-h** derived from enantiomerically pure phenylalanine were synthesized efficiently and used as chiral ligands in the catalytic enantioselective ethylation of aldehydes with diethylzinc (diethylzinc-to-aldehyde addition). The use of 10 mol % of the amino alcohols led to the corresponding *sec*-alcohols with excellent enantioselectivities (up to 100% ee) and high yields.

Key Words: Amino alcohol, Asymmetric addition, Aldehydes, Alkylation

Introduction

The alkylation of aldehydes by dialkylzinc to form a C-C bond represents an important synthetic strategy in the preparation of secondary alcohols.[1] The asymmetric strategy of this reaction was first reported by Oguni and Omi in 1984[2] and further developed in the past few years.[3] Under the catalytic condition of chiral amino alcohols, the ethylation of aldehydes with diethylzinc (diethylzinc-to-aldehyde addition) proceeded enantioselectively,[4] affording the corresponding chiral secondary alcohols.[5] The search for versatile and efficient catalysts that can accommodate a wide range of the alkylation reagents and aldehyde substrates has since evolved into one of the most active research fields in catalytic asymmetric synthesis today.[6] In relation to this, we focused our interest on developing efficient chiral catalysts derived from cheap and readily available starting materials and from easy and straightforward synthetic routes. Herein, we report the easy synthesis of chiral *tert*-amino alcohols derived from phenylalanine and their efficient application in the asymmetric diethylzinc-to-aldehyde addition.

Experimental

General. All reagents were commercially available and used without further purification. Unless otherwise stated, all reactions were performed in oven dry apparatus and stirred magnetically. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker DRX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with tetramethylsilane (TMS) as internal standard. The infared (IR) spectra were recorded from samples in KBr pellets. High resolution-mass spectrometry (HR-MS) spectra were obtained on an Agilent LC/Msd TOF electrospray instrument. Optical rotations were measured on a HORIBA SEPA-300 polarimeter. Enantiomeric excesses (ee) were determined on a Waters-1525 instrument (Chiralcel OD-H column). All anhydrous solvents were distilled under N_2 atmosphere from the following drying agents immediately before use: THF was distilled from Na/benzophenone ketyl and hexane was dried and distilled from Na. Column chromatography was conducted using 200 - 300 mesh silica gel.

Synthesis of products 2-4.

Methyl-2-(benzylamino)-3-phenylpropanoate (2): A dry round-bottom flask was charged with **1** (17.92 g, 0.1 mol) and MeOH (150 mL). Benzaldehyde (10.80 g, 0.1 mol) was slowly added to this mixture. The resulting mixture was stirred vigorously at room temperature for 30 min. After confirmation of reaction completion by TLC, $NaBH_4$ (2.28 g, 0.06 mol) was added slowly at 0 °C. The mixture was stirred at room temperature for 12 h and then refluxed for 1 h. After removal of the solvent, H_2O was added to dissolve inorganic salt, and the mixture was extracted with AcOEt (4 × 100 mL). The organic layers were combined, washed with brine, and dried by anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (petroleum ether/AcOEt = 5:1, v/v) to afford the colorless oil **2**. Yield: 25.81 g, 96%; $[\alpha]_D^{20}$ = −7.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (s, 1H), 2.97 (q, *J* =2.1, 2H), 3.55 (t, *J* = 7.0, 1H), 3.64 (m, 4H), 3.82 (d, *J* = 13.2, 1H), 7.15-7.27 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.2, 52.1, 52.4, 62.5, 127.1, 127.4, 128.6, 128.8, 129.6, 137.7, 140.0, 175.5; IR 699, 741, 1201, 1400, 1735, 3128 cm^{-1}; HR-MS *m*/*z* 270.1149 ($C_{17}H_{19}NO_2^+$, $[M+H]^+$, calc. 270.1149).

Methyl-2-[benzyl(methyl)amino]-3-phenylpropanoate (3a): To a mixture of **2** (13.43 g, 0.05 mol) and K_2CO_3 (20.70 g, 0.15 mol) in dry DMF (100 mL), iodomethane (7.81 g, 0.055 mol) was added dropwise. The mixture was stirred at room temperature for 8 h. After confirmation of reaction completion by TLC, H_2O was added to dissolve the inorganic salts. The mixture was extracted with AcOEt (3 × 100 mL). The organic layers were combined, washed with brine and H_2O, and dried by anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (petrol/AcOEt = 25 : 1, v/v) to afford the colorless oil **3a**. Yield: 12.11 g, 85%; $[\alpha]_D^{20}$ = −81.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.99 (q, *J* = 7.3, 1H), 3.13 (q, *J* = 8.0, 1H), 3.62 (m, 2H), 3.67 (s, 3H), 3.81 (d, *J* = 13.6, 1H), 7.16-7.27 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3, 38.4, 51.5, 59.3, 67.8, 126.8, 127.4, 128.6, 128.7, 129.1, 129.7, 138.9, 139.7, 172.8; IR 698, 739, 1162, 1400, 1447, 1731, 3009, 3129 cm^{-1}; HR-MS *m*/*z* 284.1605 ($C_{18}H_{21}NO_2^+$, $[M+H]^+$, calc. 284.1606).

Methyl-2-(benzyl(ethyl)amino)-3-phenylpropanoate (3b): To a mixture of **2** (13.43 g, 0.05 mol) in anhydrous THF (50 mL), NaH (1.44 g, 0.06 mol) was added slowly. The mixture was stirred at room temperature for 0.5 h under N_2 atmosphere. Bromoethane (6.0 g, 0.055 mol) was added dropwise at 0 °C and stirred at room temperature for 2 h. After TLC indicated complete consumption of material **2**, saturated NH_4Cl solution was added slowly at 0 °C. The aqueous layer was extracted with AcOEt (3 × 100 mL). The organic layers were combined, washed with brine and H_2O, and dried by anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (petrol/AcOEt = 50 : 1, v/v) to afford the colorless oil **3b**. Yield: 14.46 g, 97%; $[\alpha]_D^{20} = -106.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.0, 3H), 2.54 (q, *J* = 6.6, 1H), 2.77 (q, *J* = 7.2, 1H), 2.94 (q, *J* = 7.6, 1H), 3.11 (q, *J* = 7.7, 1H), 3.57 (d, *J* = 14.4, 1H), 3.66 (m, 4H), 3.97 (d, *J* = 14.4, 1H), 7.11-7.25 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 36.6, 45.1, 51.5, 55.1, 64.3, 126.6, 127.1, 128.5, 128.6, 128.9, 129.8, 139.0, 140.5, 173.5; IR 693, 738, 1164, 1399, 1732, 3190 cm^{-1}; HR-MS *m/z* 298.1758 ($C_{19}H_{23}NO_2^+$, $[M+H]^+$, calc. 298.1762).

General procedure for the preparation of amino alcohols (4a-h). Compound **3** (5 mmol) diluted to 10 mL with anhydrous THF was added to a solution of the corresponding alkylmagnesium iodide/bromide, which was prepared immediately before use in a 0 °C bath. The reaction was then allowed to proceed at room temperature for 36 h. After confirmation of reaction completion by TLC, the solution was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with AcOEt (3 × 50 mL). The organic layers were combined, washed with brine, and dried by anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography to afford pure amino alcohols **4a-h** (Yield: 68 - 90%).

3-(Benzyl(ethyl)amino)-2-methyl-4-phenylbutan-2-ol (4a/4b): Slight yellow and ropy oil; Yield: 0.96 g, 68%; $[\alpha]_D^{20} = +53.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.26 (s, 3H), 2.24 (s, 3H), 2.85 (q, *J* = 4.1, 1H), 3.01 (q, *J* = 9.7, 1H), 3.07 (q, *J* = 4.0, 1H), 3.49 (d, *J* = 13.2, 1H), 3.58 (d, *J* = 13.0, 1H), 3.66 (s, 1H), 7.16-7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 29.8, 32.8, 39.7, 61.8, 71.8, 74.6, 126.7, 127.4, 127.6, 128.6, 128.8, 128.9, 129.0, 129.7, 139.8, 141.1; IR 701, 736, 1029, 1167, 1399, 2968, 3181 cm^{-1}; HR-MS *m/z* 284.1970 ($C_{19}H_{25}NO^+$, $[M+H]^+$; calc. 284.1970).

2-(Benzyl(ethyl)amino)-3-ethyl-1-phenylpentan-3-ol (4c): Slight yellow oil. Yield: 1.32 g, 85%. $[\alpha]_D^{20} = +12.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.4, 3H), 0.96 (t, *J* = 7.4, 3H), 1.34 (m, 1H), 1.51 (m, 1H), 1.68 (m, 1H), 1.80 (m, 1H), 2.31 (s, 3H), 2.83 (q, *J* = 3.7, 1H), 3.01 (q, *J* = 10.4, 1H), 3.25 (q, *J* = 3.8, 1H), 3.44 (d, *J* = 13.3, 1H), 3.53 (d, 1H), 7.14-7.33 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.0, 8.3, 14.6, 28.3, 29.7, 32.4, 40.1, 62.3, 69.3, 75.2, 126.6, 127.5, 128.7, 128.9, 129.1, 129.7, 139.9, 141.5; IR 699, 734, 1121, 1400, 1641, 3017, 3130 cm^{-1}. HR-MS *m/z* 312.2280 ($C_{21}H_{29}NO^+$, $[M+H]^+$; calc. 312.2283).

4-(1-(Benzyl(ethyl)amino)-2-phenylethyl)heptan-4-ol (4d): Slight yellow oil. Yield: 1.36 g, 80%. $[\alpha]_D^{20} = +13.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82-0.92 (m, 6H), 1.21-1.55 (m, 11H), 1.68 (m, 1H), 2.31 (d, *J* = 3.9, 3H), 2.97 (q, *J* = 3.7, 1H), 3.08 (m, 1H), 3.24 (d, *J* = 10.0, 1H), 3.44 (d, *J* = 13.2, 1H), 3.67 (m, 1H), 3.81 (s, 1H), 7.15-7.35 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 15.5, 17.0, 17.2, 32.5, 36.2, 38.0, 39.4, 40.2, 59.3, 67.7, 70.2, 75.4, 126.6, 127.3, 127.5, 128.7, 128.9, 129.2, 129.7, 140.0, 141.4; IR 697, 737, 1018, 1127, 1399, 3136 cm^{-1}. HR-MS *m/z* 340.2593 ($C_{23}H_{33}NO^+$, $[M+H]^+$; calc. 340.2596).

2-(Benzyl(ethyl)amino)-1,1,3-triphenylpropan-1-ol (4e): Slight yellow and ropy oil. Yield: 1.83 g, 90%. $[\alpha]_D^{20} = -37.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.94 (s, 3H), 3.00 (m, 1H), 3.15 (m, *J* = 14.3, 1H), 3.23 (d, *J* = 13.2, 1H), 3.44 (d, *J* = 13.2, 1H), 4.15 (d, *J* = 11.3, 1H), 5.64 (s, 1H), 6.99-7.61 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.3, 39.2, 62.1, 74.0, 79.6, 126.8, 127.3, 127.4, 127.6, 127.8, 128.1, 128.2, 128.6, 128.7, 128.9, 129.0, 129.6, 139.7, 141.0, 144.9, 146.4; IR 697, 741, 1062, 1161, 1397, 1439, 1593, 3013, 3108, 3196, 3590 cm^{-1}. HR-MS *m/z* 408.2280 ($C_{29}H_{29}NO^+$, $[M+H]^+$; calc. 408.2283).

2-(Benzyl(ethyl)amino)-3-ethyl-1-phenylpentan-3-ol (4f): Slight yellow oil. Yield: 1.35 g, 83%. $[\alpha]_D^{20} = +29.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69-1.00 (m, 9H), 1.21 (m, 1H), 1.47-1.72 (m, 3H), 2.41 (s, 1H), 2.80 (q, *J* = 13.9, 1H), 3.00 (q, *J* = 10.3, 1H), 3.27 (m, 2H), 3.90 (m, 1H), 4.18 (s, 1H), 7.19-7.33 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.7, 8.3, 14.9, 28.0, 29.9, 32.9, 47.0, 57.5, 65.1, 74.2, 126.7, 127.5, 128.8, 128.9, 129.3, 129.8, 140.3,141.6; IR 709, 733, 958, 1072, 1121, 1400, 2968, 3147 cm^{-1}. HR-MS *m/z* 326.2440 ($C_{22}H_{31}NO^+$, $[M+H]^+$; calc. 326.2439).

5-(1-(Benzyl(ethyl)amino)-2-phenylethyl)nonan-5-ol (4g): Slight yellow oil. Yield: 1.45 g, 77%. $[\alpha]_D^{20} = +20.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82-1.58 (m, 21H), 2.41 (s, 1H), 2.83 (m, 1H), 3.01 (m, 1H), 3.23 (s, 2H), 3.65 (s, 1H), 3.94 (s, 1H), 4.22 (s, 1H), 7.19-7.33 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.6, 14.9, 23.9, 24.2, 25.7, 26.2, 33.0, 36.6, 37.6, 47.2, 57.5, 66.1, 74.4, 126.7, 127.1, 127.5, 128.5, 128.8, 128.9, 129.3, 129.8, 140.4, 141.6; IR 701, 734, 1124, 1399, 2952, 3131 cm^{-1}. HR-MS *m/z* 382.3069 ($C_{26}H_{39}NO^+$, $[M+H]^+$; calc. 382.3065).

2-(Benzyl(ethyl)amino)-1,1,3-triphenylpropan-1-ol (4h): Slight yellow oil. Yield: 1.86 g, 88%. $[\alpha]_D^{20} = +20.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.9, 3H), 2.23 (m, 2H), 3.01 (m, 2H), 3.15 (t, *J* = 13.6, 2H), 3.47 (s, *J* = 13.5, 1H), 4.07 (d, *J* = 9.9, 1H), 5.67 (s, 1H), 7.06-7.65 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 34.6, 46.5, 56.6, 70.4, 78.4, 126.8, 127.4, 127.5, 127.6, 127.9, 128.0, 128.5, 128.8, 129.0, 129.2, 129.7, 140.0, 141.2, 144.4, 146.2; IR 698, 738, 1031, 1170, 1399, 1594, 3138 cm^{-1}. HR-MS *m/z* 422.2435 ($C_{30}H_{31}NO^+$, $[M+H]^+$; calc. 422.2439).

General procedure for asymmetric ethylation. To a solution of *tert*-amino alcohols **4** (0.3 mmol) in dry hexane (5 mL), diethylzinc (6.0 mmol, 10% in hexane) was slowly added and the solution was stirred at 0 °C for 0.5 h under N_2 atmosphere. A solution of benzaldehyde (318 mg, 3.0 mmol) in dry hexane (5 mL) was added, and the resulting reaction mixture was stirred at 0 °C for 2 h. The reaction temperature was then slowly raised to room temperature, and the reaction was further stirred for another 2 h. The disappearance of aldehyde substrate was confirmed by TLC (hexane/AcOEt = 10 : 1, v/v). The reaction was quenched with dilute aqueous NH_4Cl, and the aqueous layer was ex-

tracted with AcOEt (3 × 10 mL). The organic layers were combined, washed with brine, and dried by anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified through column chromatography (petrol/AcOEt = 15 : 1, v/v), affording pure alcohol products and recovered amino alcohols **4**. The pure alcohols were used for further chiral HPLC analysis.

1-Phenyl-1-propanol (Table 1, entry 3): Colorless oil. Yield: 392 mg, 96%. $[\alpha]_D^{20}$ = +46.8 (*c* 1.0, $CHCl_3$), 98% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.4, 3H), 1.82-1.69 (m, 2H), 2.20 (s, 1H), 4.55 (t, *J* = 6.5, 1H), 7.34-7.24 (m, 5H). Chiral HPLC (Chiralcel OD-H column): t_R = 9.12 (major), t_R = 10.67 (minor) min.

1-(4-Flurophenyl)-1-propanol (Table 2, entry 1): Colorless oil. Yield: 453 mg, 98%. $[\alpha]_D^{20}$ = +38.5 (*c* 1.0, $CHCl_3$), 100% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.4, 3H), 1.81-1.67 (m, 2H), 2.13 (s, 1H), 4.57 (t, *J* = 6.5, 1H), 7. 03 (t, *J* = 8.7, 2H), 7.30 (t, *J* = 7.6, 2H). Chiral HPLC (Chiralcel OD-H column): t_R = 29.08 (major) min.

1-(4-Chlorophenyl)-1-propanol (Table 2, entry 2): Colorless oil. Yield: 496 mg, 97%. $[\alpha]_D^{20}$ = +26.8 (*c* 1.0, benzene), 97% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.4, 3H), 1.77-1.64 (m, 2H), 2.44 (s, 1H), 4.52 (t, *J* = 6.5, 1H), 7.29-7.21 (m, 4H). Chiral HPLC (Chiralcel OD-H column): t_R = 17.45 (major), t_R = 16.78 (minor) min.

1-(4-Bromophenyl)-1-propanol (Table 2, entry 3): Colorless oil. Yield: 612 mg, 95%. $[\alpha]_D^{20}$ = +8.5 (*c* 1.0, CH_2Cl_2), 97% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.4, 3H), 1.78-1.64 (m, 2H), 2.32 (s, 1H), 4.52 (t, *J* = 6.5, 1H), 7.18 (d, *J* = 8.4, 2H), 7.45 (d, *J* = 8.3, 2H). Chiral HPLC (Chiralcel OD-H column): t_R = 37.18 (major), t_R = 36.12 (minor) min.

1-(4-Methoxyphenyl)-1-propanol (Table 2, entry 4): Colorless oil. Yield: 439 mg, 88%. $[\alpha]_D^{20}$ = +24.6 (*c* 1.0, benzene), 76% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.4, 3H), 1.82-1.66 (m, 2H), 2.28 (s, 1H), 3.78 (s, 3H), 4.50 (t, *J* = 6.6, 1H), 6.87 (d, *J* = 8.4, 2H), 7.26 (d, *J* = 8.5, 2H). Chiral HPLC (Chiralcel OD-H column): t_R = 23.94 (major), t_R = 27.03 (minor) min.

l-(2-Furyl)-propanol (Table 2, entry 5): Colorless oil. Yield: 227 mg, 60%. $[\alpha]_D^{20}$ = +10.1 ($CHCl_3$), 74% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 7.4, 3H), 1.81 (m, 2H), 2.41 (s, 1H), 4.52 (t, *J* = 6.8, 1H), 6.16 (m, 1H), 6.27 (m, 1H), 7.22-7.31 (m, 1H). Chiral HPLC (Chiralcel OD-H column): t_R = 3.390 (major), t_R = 4.665 (minor) min.

l-(2-Thienyl)-propanol (Table 2, entry 6): Colorless oil. Yield: 222 mg, 52%. $[\alpha]_D^{20}$ = +10.5 ($CHCl_3$), 95% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.4, 3H), 1.83 (m, 2H), 2.65 (s, 1H), 4.77 (t, *J* = 6.6, 1H), 6.93-6.94 (m, 2H), 7.20-7.24 (m, 1H). Chiral HPLC (Chiralcel OD-H column): t_R = 7.620 (major), t_R = 6.629 (minor) min.

1-Phenyl-3-pentanol (Table 2, entry 7): Colorless oil. Yield: 477 mg, 97%. $[\alpha]_D^{20}$ = −22.5 (*c* 1.0, EtOH), 77% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5, 3H), 1.57 (m, 3H), 1.83 (m, 2H), 2.69 (m, 1H), 2.82 (m, 1H), 3.55 (s, 1H), 7.29-7.17 (m, 5H). Chiral HPLC (Chiralcel OD-H column): t_R = 15.99 (major), t_R = 24.72 (minor) min.

3-Octanol (Table 2, entry 8): Colorless oil. Yield: 382 mg, 98%. $[\alpha]_D^{20}$ = −7.1 (*c* 1.0, $CHCl_3$), 79% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (m, 6H), 1.53-1.29 (m, 10H), 1.88 (s, 1H), 3.52 (m, 1H).

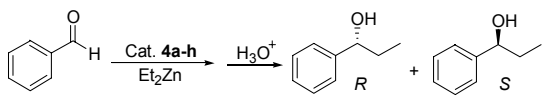
Results and Discussion

The synthesis of *tert*-amino alcohols, as illustrated in Scheme 1, was done with inexpensive and commercially available enantiomerically pure (L or D) phenylalanine methyl ester **1**. The Schiff's base, obtained in a one-pot reaction and reduced with $NaBH_4$ without further purification, gave benzyl amine **2** in excellent yield.[7] Compound **2** was then efficiently alkylated in the presence of the corresponding alkyl halides and a base, such as K_2CO_3 (NaH was used in case of less reactive RX[8]), to give tertiary amines **3**. The treatment of **3** with excess corresponding alkylmagnesium bromide completed the synthesis of *tert*-amino alcohols **4a-h**.[9] Unless otherwise indicated, all products of each step were purified by flash column chromatography on silica gel and obtained in high yield. All compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy, and HR-MS.

The catalytic reaction protocol was simple. With the desired *tert*-amino alcohols **4a-h** in hand, studies towards the evaluation of the catalysts in the diethylzinc-to-aldehyde addition system were undertaken. The reaction was first performed with benzaldehyde as the substrate in the presence of 0.1 meq of catalysts (relative to aldehyde) in hexane. In each case, the chiral ligands were easily recovered from the reaction mixture.[10] The catalytic results are summarized in Table 1.

Good to excellent enantioselectivity and high chemical conversion were observed in the diethylzinc-to-benzaldehyde addition catalyzed by *tert*-amino alcohol ligands **4a-h**. The ligand **4c** {(2*S*)-2-[benzyl(ethyl)amino]-3-ethyl-1-phenylpentan-3-ol} was the most selective ligand (98% ee, Table 1, entry 3). The enantioselectivity was apparently affected by the size of the C-alkyl group (R_2) of the ligand. Increasing the bulkiness of R_2 with methyl (**4a**), ethyl (**4c**), and propyl (**4d**) to phenyl (**4e**), with R_1 remaining as methyl in each case, led to only marginal effects on the enantioselectivity (Table 1, entries1, 3, 4 and 5). However, moderate to drastic changes in enantioselectivity (Table 1, entries 6, 7 and 8) were observed, when the sizes of R_2

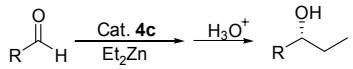
Table 1. Enantioselective diethylzinc-to-benzaldehyde addition in the presence of chiral ligands **4a-h**

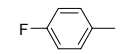
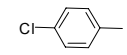
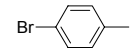
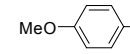
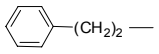


Entry[a]	Cat.	Yield (%)[b]	$[\alpha]_D^{20}$ [c]	ee%[d]	Config.[e]
1	**4a**	95	+45.4	95	R
2	**4b**	97	−42.6	90	S
3	**4c**	96	+46.8	98	R
4	**4d**	92	+45.5	95	R
5	**4e**	93	+44.1	94	R
6	**4f**	96	+41.9	89	*R*
7	**4g**	95	+43.2	91	*R*
8	**4h**	96	−15.4	33	*S*

[a]Yield was based on isolated products after flash column chromatography. [b]Optical rotation was measured in $CHCl_3$ as solvent. [c]Determined by HPLC using a Chiral OD-H column. [d]Absolute configuration was determined as *R* or *S* by comparison of the optical rotation values with those in the literature.[11]

Table 2. Enantioselective diethylzinc-to-aldehyde addition in the presence of chiral ligand **4c**



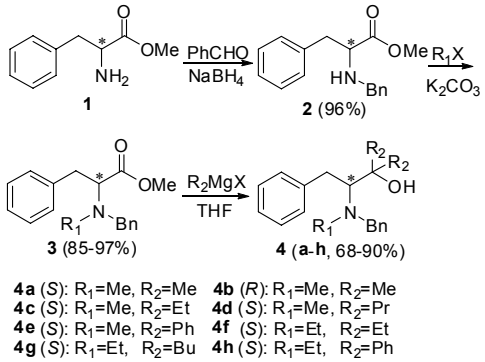
Entry	R	Yield (%)	$[\alpha]_D^{20}$	ee(%)[a]	Config.[d]
1		98	+38.5($CHCl_3$)	100[b]	R
2		97	+26.8(Benzene)	97	R
3		95	+8.5(CH_2Cl_2)	97	R
4		88	+24.6(Benzene)	76	R
5		60	+10.1($CHCl_3$)	74	R
6		52	+10.5($CHCl_3$)	95	R
7		97	−22.5(EtOH)	77	R
8		98	−7.1($CHCl_3$)	79[c]	*R*

[a]Determined by HPLC using a Chiral OD-H column. [b]Only one enantiomer was detected. [c]Reported specific rotation $[\alpha]_D^{20} = -8.9$ (*c* 1.00, $CHCl_3$) for *R* enantiomer were used for the calculation of the ee %.[11] [d]Absolute configuration was determined by comparison of the optical rotation values with those in the literature.[11,12]

were increased from ethyl (**4f**) and butyl (**4g**) to phenyl (**4h**), while R_1 remained as ethyl in each occasion. With **4h** as a ligand, the configuration of the major product was reversed (Table 1, entry 8), and there was low enantioselectivity (33% ee). It is noteworthy that a product with an opposite optical rotation was obtained after reversing the configuration of the catalyst (**4f**) (Table 1, entries 1 and 2). This is a unique feature seen in chiral ligand-catalyzed reactions.

To evaluate the generality of the results so far, we extended the utility of **4c** to other aldehydes in the diethylzinc-to-aldehyde addition system. Thus, four 4-substituted arylaldehydes (Table 2, entries 1-4), two heterocyclic aldehydes (furaldehyde (Table 2, entry 5), thiophenecarboxaldehyde (Table 2, entry 6), and two aliphatic aldehydes (Table 2, entries 7 and 8) were tested in the reaction with the catalyst **4c**. The catalytic results are summarized in Table 2.

In the reaction with the 4-substituted arylaldehydes (Table 2, entries 1-4), nearly quantitative chemical conversions (95 - 98%) were achieved, with the exception of 4-methoxybenzaldehyde (88%). High enantioselectivity (97 - 100% ee, Table 2, entries 1-3) was observed for the benzaldehydes with electron-withdrawing groups. However, a diminishing enantioselectivity was seen for the reaction using a substrate with an electron-donating substituent (76% ee, Table 2, entry 4). Lower chemical conversions were observed with furaldehyde and thiophenecarboxaldehyde as substrates (60%, 52%. Table 2, entries 5 and 6), but the enantioselectivity of thiophenecarboxaldehyde



Scheme 1. Preparation of amino alcohols **4(a-h)**.

was higher than that of furaldehyde (95% ee, 74% ee). Similarly, moderate optical yields were afforded for two aliphatic aldehydes (Table 2, entries 7 and 8).

Conclusion

In conclusion, a new series of efficient *tert*-amino alcohol ligands derived from easily accessible enantiomerically pure phenylalanine have been prepared and examined as chiral catalysts for the asymmetric ethylation of aldehyde with diethylzinc. Good to excellent enantioselectivities (up to 100%) were obtained with aryl- and 4-substituted aryl-aldehydes as substrates in the presence of the best ligand **4c** ((2*S*)-2-[benzyl(ethyl)amino]-3-ethyl-1-phenylpentan-3-ol). The reusability and catalytic activity of the amino alcohols were studied, and no significant changes were observed. Further research on the screening of other amino alcohol ligands, as well as the extension of the application to other alkylation agents and aldehyde substrates, are underway, and the results will be reported in due course.

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