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Efficient asymmetric addition of diethylzinc to aldehydes using 3-hydroxyazetidine derivatives as chiral ligands

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A new series of chiral 3-hydroxyazetidines has been prepared from (*S*)-1-(4-methoxyphenyl)ethylamine. These ligands have shown excellent catalytic activities and enantiomeric selectivities in asymmetric addition of diethylzinc to aromatic aldehydes. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: azetidines; chiral ligands; asymmetric addition; diethylzinc; aldehyde

Introduction

The stereoselective addition of organometallics to one of the two heterotopic faces of a carbonyl group has been extensively studied.[1–5] The enantioselective addition of organozinc to carbonyl compounds is of particular importance in organic synthesis, because the products, chiral alcohols, are ubiquitous in the structure of natural products and drug compounds, and are also important precursors for many other functional organic molecules.[6–10] Therefore, it is not surprising that the efforts have focused on the development of chiral ligands which work for catalytic asymmetric addition of diethylzinc to aldehydes over the last two decades.[1–10] Although a variety of ligands, such as chiral amino alcohols, amino thiols, amino disulfides, amino diselenides, diamines and diols, for the asymmetric diethylzinc addition reactions have been reported,[1–10] only a small number of effective ligands are obtained by simple synthetic methods. Thus, the development of easily accessible, stable, operationally simple and effective ligands is still a desirable goal. In recent years, chiral azetidine has been extensively used as a chiral auxiliary,[11] but only a few studies have focused on the applications of its derivatives as chiral catalysts.[12–24] Chiral azetidines that can effectively catalyze the diethylzinc addition with high levels of enantioselectivity have been reported;[19–24] however, no example of chiral hydroxyazetidine (hydroxyl group seated on the azetidine ring) for enantioselective catalysis has been described. Thus, research on asymmetric addition of diethylzinc to aldehydes catalyzed by chiral hydroxyazetidines remains an interesting topic in asymmetric synthesis. Taking the advantage of the chirality of (*R*)-1-phenylethylamine or (*S*)-1-phenylethylamine, we have designed and prepared a series of chiral 3-hydroxyazetidines and 3-aminoazetidines, and they have been successfully applied to the asymmetric addition of diethylzinc to aldehydes.[25–26] In our attempt to further explore the chemistry of small-ring functionalized heterocycles, we recently have expanded our research to a new series of chiral 3-hydroxyazetidines derived from (*S*)-1-(4-methoxyphenyl)ethylamine. Herein we report the synthesis of these new chiral 3-hydroxyazetidines and their use in the asymmetric addition of diethylzinc to aldehydes.

Experimental

General methods

All chemicals were purchased from Aldrich Chemical Co. and Beijing Chemical Co. and used as received unless otherwise noted. Infrared spectra were obtained on an Avatar 360 Fourier transform spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer. All chemical shifts were reported in δ units with reference to the residual protons of the deuterated solvents for proton and carbon chemical shifts. Melting points were measured on an X-6 melting point apparatus and were uncorrected. Optical rotations were measured on a Perkin–Elmer 343 polarimeter, and mass spectra were obtained with a TRACE MS spectrometer. Elemental analyses were performed on a Vario EL elemental analyzer. Enantiomeric excesses were determined by gas chromatography with an FID detector using chiral column SGE β-CYCLODEX, 25 m × 0.25 mm i.d. on a Varian CP-3800 instrument.

General procedure for the preparation of chiral azetidines from (*S*)-1-(4-methoxyphenyl)ethylamine

The synthesis of 1-[1′-(4-methoxyphenyl)ethyl]-2-phenyl-3-hydroxylazetidine (**L1**) is representative. Anhydrous $MgSO_4$ (4.8 g, 40 mmol) was added to a CH_2Cl_2 (60 ml) solution of benzaldehyde (2.14 g, 20 mmol) and (*S*)-1-(4-methoxyphenyl)ethylamine (3.02 g, 20 mmol) at room temperature. After this solution had been stirred at room temperature for 12 h, $MgSO_4$ was filtered off. Triethylamine (4.04 g, 40 mmol) was added to the solution at −10 °C with stirring. This solution was stirred for 1 h at this temperature, then acetoxyacetyl chloride (5.46 g, 40 mmol) was added. The resulting solution was slowly warmed up to room temperature and stirred for 24 h. Triethylamine hydrochloride was filtered off, and the filtrate was washed with saturated $NaHCO_3$ (50 ml). After drying over $MgSO_4$, solvent

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was removed to give a crude mixture (**2**). The mixture was dissolved in 40 ml of dry THF, then the solution was added to a suspension of aluminum chloride (3.10 g, 23 mmol) and lithium aluminum hydride (0.88 g, 23 mmol) in 50 ml of dry THF with stirring at reflux. After this mixture had been refluxed for 2 h, then cooled to 0 °C, 20 ml of water was carefully added. The water phase was extracted with dichloromethane and dried over $MgSO_4$. Removal of the solvent gave a crude mixture, 1-(1′-phenylethyl)-2-phenyl-3-hydroxylazetidine (**L1**), which was further purified by chromatography (hexane/ethyl acetate = 6/1) to give pure compounds (2*R*,3*R*)-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]-2-phenylazetidin-3-ol (**L1a**) and (2*S*,3*S*)-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]-2-phenylazetidin-3-ol (**L1b**).

(2*R*,3*R*)-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]-2-phenylazetidin-3-ol (**L1a**). Yield: 1.47 g, 26%. Colorless crystals, m.p.: 128–129 °C; $[\alpha]_D^{20} = -106.2$ (*c* 0.15, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.03 (d, $J = 6.0$ Hz, 3H, Me), 1.62 (br, s, 1H, O*H*), 3.02 (m, 1H, C*H*), 3.13 (m, 1H, C*H*), 3.47 (m, 1H, C*H*), 3.84 (s, 3H, OMe), 4.40 (m, 2H, C*H*), 6.91 (d, $J = 8.0$ Hz, 2H, aryl H), 7.34 (m, 3H, aryl H), 7.44 (m, 2H, aryl H), 7.61 (d, $J = 8.0$ Hz, 2H, aryl H). ^{13}C NMR ($CDCl_3$): δ 22.8 (CH_3), 55.2 (OCH_3), 58.8 (CH_2), 65.8 (CH), 67.2 (CH), 72.3 (CH), 113.7, 127.6, 127.9, 128.2, 128.4, 135.8, 138.4, 158.6 (aryl *C*). IR (KBr): ν 3217, 2923, 1517, 1458, 1292, 1251, 1161, 835, 702 cm^{-1}. MS (EI): *m/z* 283 (M^+). Anal. calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.01; H, 7.11; N, 4.80.

(2*S*,3*S*)-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]-2-phenylazetidin-3-ol (**L1b**). Yield: 3.06 g, 54%. Colorless crystals, m.p.: 121–122 °C; $[\alpha]_D^{20} = +151.3$ (*c* 0.27, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.31 (d, $J = 6.5$ Hz, 3H, Me), 1.68 (s, 1H, O*H*), 3.29 (m, 1H, C*H*), 3.47 (m, 2H, C*H*), 3.68 (s, 3H, OMe), 4.24 (m, 1H, C*H*), 4.40 (m, 1H, C*H*), 6.61 (d, $J = 8.5$ Hz, 2H, aryl H), 7.10–7.26 (m, 7H, aryl H). ^{13}C NMR ($CDCl_3$): δ 19.6 (CH_3), 55.2 (OCH_3), 58.6 (CH_2), 65.8 (CH), 65.9 (CH), 71.8 (CH), 113.1, 127.1, 127.8, 128.0, 129.0, 134.3, 137.0, 158.5 (aryl *C*). IR (KBr): ν 3219, 2950, 1516, 1453, 1246, 1162, 1020, 833, 776, 548 cm^{-1}. MS (EI): *m/z* 282 ($M^+ - 1$). Anal. calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.08; H, 7.09; N, 4.76.

(2*R*,3*R*)-2-(2-chlorophenyl)-1-[(*S*)-1-(4-methoxyphenyl)ethyl]-azetidin-3-ol (**L2a**). Yield: 1.65 g, 26%. Colorless crystals, m.p.: 139–140 °C; $[\alpha]_D^{20} = -114.5$ (*c* 0.11, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.06 (d, $J = 7.0$ Hz, 3H, Me), 1.50 (br, 1H, O*H*), 3.09 (m, 1H, C*H*), 3.14 (m, 1H, C*H*), 3.51 (m, 1H, C*H*), 3.83 (s, 3H, OMe), 4.62 (m, 1H, C*H*), 4.68 (m, 1H, C*H*), 6.89 (d, $J = 8.5$ Hz, 2H, aryl H), 7.25–7.40 (m, 5H, aryl H), 8.09 (d, $J = 7.5$ Hz, 1H, aryl H). ^{13}C NMR ($CDCl_3$): δ 22.8 (CH_3), 55.2 (OCH_3), 59.1 (CH_2), 64.9 (CH), 67.3 (CH), 69.7 (CH), 113.8, 126.6, 128.2, 128.5, 129.0, 130.7, 132.0, 135.7, 136.3, 158.7 (aryl *C*). IR (KBr): ν 3254, 2966, 1515, 1440, 1248, 1034, 837, 757, 555 cm^{-1}. MS (EI): *m/z* 317 (M^+). Anal. calcd for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 68.09; H, 6.17; N, 4.33.

(2*S*,3*S*)-2-(2-chlorophenyl)-1-[(*S*)-1-(4-methoxyphenyl)ethyl]-azetidin-3-ol (**L2b**). Yield: 3.30 g, 52%. Colorless crystals, m.p.: 104–105 °C; $[\alpha]_D^{20} = +96.3$ (*c* 0.16, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.35 (d, $J = 6.0$ Hz, 3H, Me), 1.52 (br, 1H, O*H*), 3.36 (m, 1H, C*H*), 3.45 (m, 2H, C*H*), 3.68 (s, 3H, OMe), 4.59 (m, 1H, C*H*), 4.64 (m, 1H, C*H*), 6.64 (d, $J = 8.5$ Hz, 2H, aryl H), 7.02–7.17 (m, 5H, aryl H), 7.47 (m, 1H, aryl H). ^{13}C NMR ($CDCl_3$): δ 18.7 (CH_3), 55.2 (OCH_3), 58.6 (CH_2), 65.2 (CH), 65.7 (CH), 69.1 (CH), 113.3, 125.9, 127.9, 128.4, 129.0, 130.7, 131.7, 134.2, 134.6, 158.7 (aryl *C*). IR (KBr): ν 3244, 2966, 1515, 1440, 1248, 1034, 837, 756, 557 cm^{-1}. MS (EI): *m/z* 317 (M^+). Anal. calcd for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.96; H, 6.02; N, 4.34.

(2*R*,3*R*)-2-(3-chlorophenyl)-1-[(*S*)-1-(4-methoxyphenyl)ethyl]-azetidin-3-ol (**L3a**). Yield: 1.52 g, 24%. Colorless crystals, m.p.: 143–144 °C, $[\alpha]_D^{20} = -76.1$ (*c* 0.16, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.03 (d, $J = 6.5$ Hz, 3H, Me), 1.60 (br, 1H, O*H*), 3.04 (m, 1H, C*H*), 3.11 (m, 1H, C*H*), 3.45 (m, 1H, C*H*), 3.82 (s, 3H, OMe), 4.33 (m, 1H, C*H*), 4.42 (m, 1H, C*H*), 6.89 (d, $J = 8.5$ Hz, 2H, aryl H), 7.31–7.49 (m, 5H, aryl H), 7.63 (s, 1H, aryl H). ^{13}C NMR ($CDCl_3$): δ 22.7 (CH_3), 55.2 (OCH_3), 58.7 (CH_2), 65.9(CH), 67.0 (CH), 71.7 (CH), 113.7, 126.0, 127.7, 128.0, 128.2, 129.6, 134.4, 135.4, 140.8, 158.7 (aryl *C*). IR (KBr): ν 3205, 2969, 1515, 1248, 1034, 836, 788, 558 cm^{-1}. MS (EI): *m/z* 317 (M^+). Anal. Calcd for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.95; H, 6.00; N, 4.09.

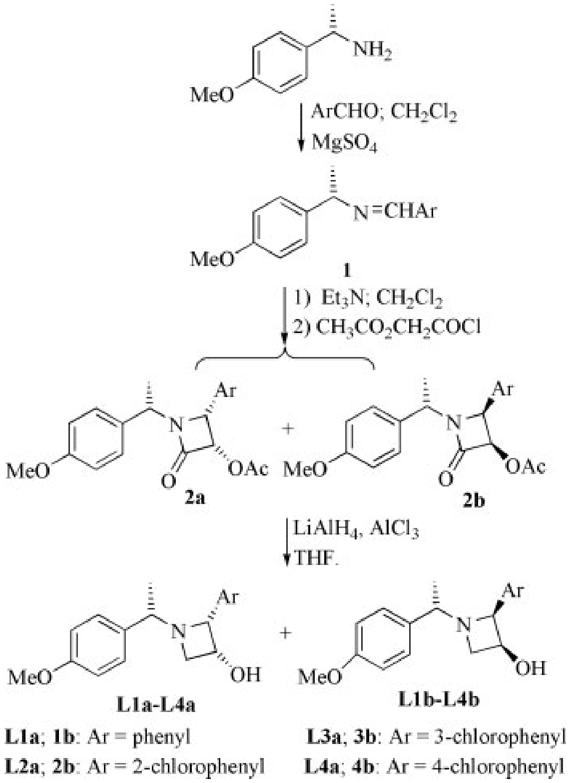
(2*S*,3*S*)-2-(3-chlorophenyl)-1-[(*S*)-1-(4-methoxyphenyl)ethyl]-azetidin-3-ol (**L3b**). Yield: 3.30 g, 52%. Colorless crystals, m.p.: 129–130 °C, $[\alpha]_D^{20} = +160.5$ (*c* 0.21, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.31 (d, $J = 5.0$ Hz, 3H, Me), 1.59 (br, 1H, O*H*), 3.28 (m, 1H, C*H*), 3.39 (m, 1H, C*H*), 3.47 (m, 1H, C*H*), 3.68 (s, 3H, OMe), 4.15 (m, 1H, C*H*), 4.41 (m. 1H, C*H*), 6.61 (d, $J = 8.5$ Hz, 2H, aryl H), 7.02–7.09 (m, 5H, aryl H), 7.16 (s, 1H, aryl H). ^{13}C NMR ($CDCl_3$): δ 19.5 (CH_3), 55.2 (OCH_3), 58.8 (CH_2), 66.0 (CH), 66.3 (CH), 71.6 (CH), 113.2, 126.0, 127.1, 128.3, 128.9, 129.0, 133.6, 134.0, 139.3, 158.7 (aryl *C*). IR (KBr): ν 3201, 1516, 1292, 1250, 1019, 836, 684, 546 cm^{-1}. MS (EI): *m/z* 316 ($M^+ - 1$). Anal. calcd for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.92; H, 6.39; N, 4.15.

(2*R*,3*R*)-2-(4-chlorophenyl)-1-[(*S*)-1-(4-methoxyphenyl)ethyl]-azetidin-3-ol (**L4a**). Yield: 1.78 g, 28%. Colorless crystals, m.p.: 133–134 °C, $[\alpha]_D^{20} = -76.4$ (*c* 0.14, CH_3OH). ^1H NMR ($CDCl_3$): δ 0.98 (d, $J = 4.0$ Hz, 3H, Me), 1.57 (br, 1H, O*H*), 3.00 (m, 1H, C*H*), 3.08 (m, 1H, C*H*), 3.43 (m, 1H, C*H*), 3.81 (s, 3H, OMe), 4.31 (m, 1H, C*H*), 4.39 (m, 1H, C*H*), 6.87 (d, $J = 7.0$ Hz, 2H, aryl H), 7.29 (d, $J = 7.9$ Hz, 2H, aryl H), 7.39 (d, $J = 7.9$ Hz, 2H, aryl H), 7.53 (d, $J = 7.0$ Hz, 2H, aryl H). ^{13}C NMR ($CDCl_3$): δ 22.7 (CH_3), 55.2 (OCH_3), 58.7 (CH_2), 65.8 (CH), 67.1 (CH), 71.7 (CH), 113.7, 128.2, 128.5, 129.3, 133.3, 135.5, 137.1, 158.7 (aryl *C*). IR (KBr): ν 3237, 2969, 1516, 1250, 1036, 831, 799 cm^{-1}. MS (EI): *m/z* 317 (M^+). Anal. calcd for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.93; H, 6.22; N, 4.22.

(2*S*,3*S*)-2-(4-chlorophenyl)-1-[(*S*)-1-(4-methoxyphenyl)ethyl]-azetidin-3-ol (**L4b**). Yield: 3.17 g, 50%. Colorless crystals, m.p.: 119–120 °C, $[\alpha]_D^{20} = +181.3$ (*c* 0.16, CH_3OH). ^1H NMR ($CDCl_3$): δ 1.28 (d, $J = 5.5$ Hz, 3H, Me), 1.55 (br, 1H, O*H*), 3.26 (m, 1H, C*H*), 3.42 (m, 1H, C*H*), 3.45 (m, 1H, C*H*), 3.67 (s, 3H, OMe), 4.15 (m, 1H, C*H*), 4.39 (m, 1H, C*H*), 6.58 (d, $J = 8.0$ Hz, 2H, aryl H), 7.04 (d, $J = 8.0$ Hz, 2H, aryl H), 7.11 (m, 4H, aryl H). ^{13}C NMR ($CDCl_3$): δ 19.7 (CH_3), 55.2 (OCH_3), 58.8 (CH_2), 65.9 (CH), 66.3 (CH), 71.4 (CH), 113.2, 127.7, 129.0, 129.5, 132.6, 134.2, 135.8, 158.7 (aryl *C*). IR (KBr): ν 3287, 2966, 1515, 1248, 1161, 1091, 843, 800, 549 cm^{-1}. MS (EI): *m/z* 317 (M^+). Anal. calcd for $C_{18}H_{20}NClO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.92; H, 5.97; N, 4.23.

General procedure for diethylzinc addition to aldehydes

In a nitrogen-filled dry-box, the chiral ligand (0.1 mmol) was dissolved in toluene (3 ml) at room temperature, and diethylzinc (2.0 ml of 1.5 M of toluene solution, 3.0 mmol) was injected. After the mixture was stirred for 20 min, benzaldehyde (0.1 g, 1 mmol) was added dropwise via a syringe, and the mixture stirred for the corresponding reaction time under N_2. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 ml). The mixture was then extracted with Et_2O (15 ml × 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude products were purified by flash column chromatography (hexane–EtOAc). The ee values



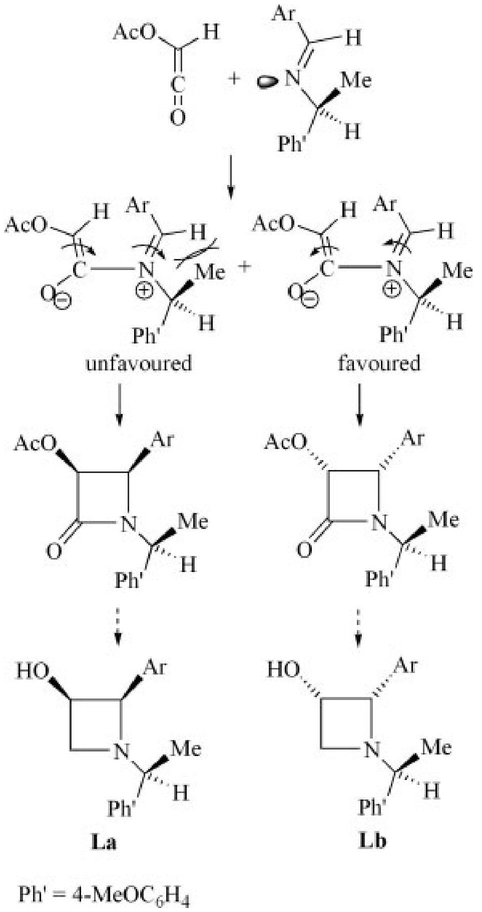
Scheme 1. Synthesis of the chiral 3-hydroxyazetidines.

of the alcohol products were determined by GC analysis using chiral column β-CYCLODEX, 25 m × 0.25 mm i.d. Conditions of GC analyses: N_2 as carrier gas (1.5 ml/min). For 1-phenylpropanol: det. = 280 °C, inj. = 240 °C, oven = 120 °C, t_R = 20.0 min for (*R*) and t_R = 20.3 min for (*S*). For 1-(2-chlorophenyl)propanol: det. = 300 °C, inj. = 300 °C, oven = 150 °C, t_R = 16.0 min for (*R*) and t_R = 16.2 min for (*S*). For 1-(3-chlorophenyl)propanol: det. = 280 °C, inj. = 280 °C, oven = 130 °C, t_R = 48.0 min for (*R*) and t_R = 48.6 min for (*S*). For 1-(4-chlorophenyl)propanol: det. = 300 °C, inj. = 300 °C, oven = 150 °C, t_R = 19.8 min for (*R*) and t_R = 20.2 min for (*S*). For 1-(2-methoxyphenyl)propanol: det. = 300 °C, inj. = 300 °C, oven = 150 °C, t_R = 17.8 min for (*R*) and t_R = 17.2 min for (*S*). For 1-(3-methoxyphenyl)propanol: det. = 280 °C, inj. = 280 °C, oven = 120 °C, t_R = 88.5 min for (*R*) and t_R = 89.2 min for (*S*). For 1-(4-methoxyphenyl)propanol: det. = 280 °C, inj. = 280 °C, oven = 130 °C, t_R = 56.3 min for (*R*) and t_R = 57.2 min for (*S*). The absolute configuration of the major enantiomer was assigned by the comparison of the optical rotation with literature data.[25]

Results and Discussion

Synthesis of chiral 3-hydroxyazetidines

Chiral 3-hydroxyazetidines **L1a**–**L4b** are easily prepared by a three-step procedure in moderate to good overall yields (Scheme 1). Condensation of (*S*)-1-(4-methoxyphenyl)ethylamine with the appropriate aldehyde in dichloromethane in the presence of $MgSO_4$ as drying agent affords the corresponding aldimines **1**. Subsequently, these imines, **1**, are used in the cycloaddition reaction with acetoxyketene, derived from acetoxyacetyl chloride and Et_3N.[27] Imines **1** and Et_3N are dissolved in CH_2Cl_2 at −10 °C, and acetoxyacetyl chloride is added dropwise, performing the [2 + 2] cycloaddition reaction *in situ*, giving a crude mixture of *cis*-β-lactams **2a** and **2b**, which are reduced by AlH_2Cl, prepared from $LiAlH_4$ and $AlCl_3$ in ratio of 1 : 1 in dry THF,[28] to give the 3-hydroxyazetidines **L1a–4a** and **L1b–4b** in good yields after purification by flash chromatography. The ratio of the isolated yields of **La** and **Lb** is about 1 : 2. Although the structures of 3-hydroxyazetidines **La** and **Lb** failed in X-ray diffaraction analyses, their relative configurations could be unambiguously assigned as *cis* according to the crystal structures of their analogs (2*R*,3*R*)-2-(3-methoxyphenyl)-1-[(*R*)-1-phenylethyl]azetidin-3-ol and (2*S*,3*S*)-2-(4-methoxyphenyl)-1-[(*R*)-1-phenylethyl]azetidin-3-ol derived from (*R*)-1-phenylethylamine, in which the hydroxyl group and electron lone pair on N atom are situated on the same side of the azetidine backbone, indicating that a metal ion can easily chelate to both of them.[25]



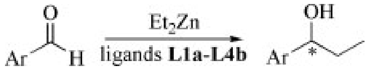
Scheme 2. Proposed mechanism.

The stereochemical outcome is in agreement with the mechanism for the cycloaddition reaction of (*E*)-aldimines to ketenes proposed by Hegedus *et al.*,[29–32] which may well explain our experimental observations that the origin of chirality has considerable influence on the yield and the configuration of the resulting products (Scheme 2).

Asymmetric addition of diethylzinc to aldehydes

Our initial experiments in the asymmetric addition of diethylzinc to benzaldehyde involve the use of 10% mol of ligands **L1a**–**L4b**

Table 1. Asymmetric addition of diethylzinc to aldehydes[a]



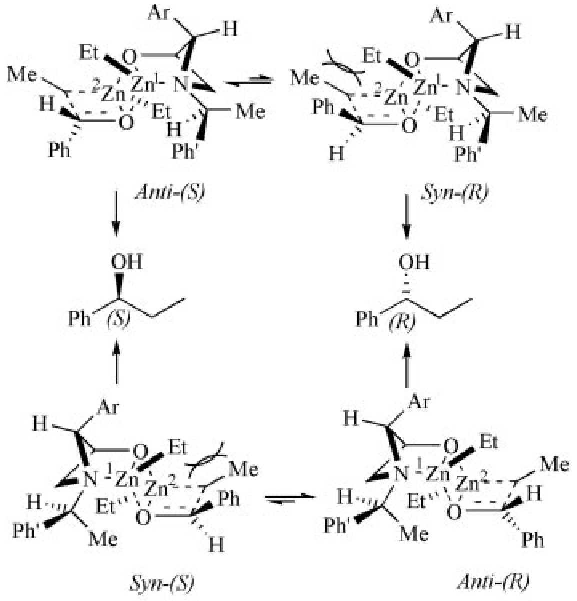
Entry	Solvent	Ar	Ligand	Yield[b] (%)	Ee[c] (%) (configuration)
1	Toluene	Ph	L1a	98	94 (*S*)
2	Toluene	Ph	**L2a**	98	97 (*S*)
3	Toluene	Ph	**L3a**	97	96 (*S*)
4	Toluene	Ph	**L4a**	87	89 (*S*)
5	Toluene	Ph	**L1b**	93	97 (*R*)
6	Toluene	Ph	**L2b**	93	89 (*R*)
7	Toluene	Ph	**L3b**	91	88 (*R*)
8	Toluene	Ph	**L4b**	87	85 (*R*)
9	Hexane	Ph	**L1a**	95	94 (*S*)
10	Hexane–toluene (1 : 1)	Ph	**L1a**	98	93 (*S*)
11	Toluene	2-$MeOC_6H_4$	**L1a**	92	96 (*S*)
12	Toluene	3-$MeOC_6H_4$	**L1a**	95	94 (*S*)
13	Toluene	4-$MeOC_6H_4$	**L1a**	98	95 (*S*)
14	Toluene	2-ClC_6H_4	**L1a**	94	97 (*S*)
15	Toluene	3-ClC_6H_4	**L1a**	96	95 (*S*)
16	Toluene	4-ClC_6H_4	**L1a**	97	96 (*S*)

[a] Reaction conditions: Et_2Zn (300 mol %), ligand (10 mol %), at room temperature, 24 h.
[b] Isolated yield after flash chromatography.
[c] Determined by GC analysis on a chiral cyclodextrin capillary column. Absolute configuration was determined by the comparison of specific rotation with literature data.[25]

in toluene (Table 1). The initial experiments provide encouraging results since the addition reactions carried out with all azetidine ligands proceed smoothly to give the desired secondary alcohol, in high yields and excellent enantioselectivities (Table 1, entries 1–8). All the (2*R*,3*R*)-azetidine ligands (**La**) induce enantiomeric excess in (*S*)-configured alcohol, (*S*)-1-phenyl-1-propanol (Table 1, entries 1–4), while the (2*S*,3*S*)-azetidine ligands (**Lb**) induce the enantiomeric excess in (*R*)-configured alcohol in good yields and enantioselectivities (Table 1, entries 5–8). These results demonstrate the noticeable steric and electronic effects of a variety of comparable substituents at the *ortho, meta* and *para* positions of the phenyl group. For example, changing the aryl group from 4-chlorophenyl (**L4a**) to 3-chlorophenyl (**L3a**) to 2-chlorophenyl (**L2a**) results in increased yield and enantiomeric excess (Table 1, entries 2–4), and the best enantioselectivity (97% ee) is obtained using **L2a** as catalyst (Table 1, entry 2). The reaction solvents do not significantly alter or improve the enantioselectivity (Table 1, entries 9 and 10), while replacement of the hydrogen (**L1**) with an electron-withdrawing group (chloro, **L4**) at the *para* position of phenyl group results in decreased enantioselectivity (Table 1, entries 1, 4, 5 and 8).

Under similar reaction conditions, various aromatic aldehydes have been studied for the ethylation using diethylzinc as reagent catalyzed by 10% mol of **L1a** in toluene. Similar to the result for benzaldehyde, all the additions to aromatic aldehydes provide the corresponding *S*-configuration alcohols as the major isomer with excellent enantioselectivities and in high yields (Table 1, entries 11–16). Electron-deficient and electron-rich aromatic aldehydes demonstrate similar enantioselectivity in this process. These results have also shown that the 3-hydroxyazetidines derived from (*S*)-1-(4-methoxyphenyl)ethylamine are more effective chiral ligands for the asymmetric diethylzinc addition to aldehydes than those derived from (*R*)-1-phenylethylamine,[25] presumably due to the electron-rich 4-methoxyphenyl group.

The stereochemical outcome of these diethylzinc additions to aldehydes is in agreement with the *anti*-transition state structures proposed by Noyori *et al.*,[33–39] which may well explain our experimental observations that the substituted aryl groups on the azetidine backbone have considerable influence on the



Ph' = 4-$MeOC_6H_4$
Ph = C_6H_5

Scheme 3. Proposed transition states.

enantioselectivity of the ligands **L1a–4b** and the configuration of the resulting adducts (Scheme 3).

Conclusions

In summary, a new series of chiral 3-hydroxyazetidines has been synthesized from commercially available (*S*)-1-(4-methoxyphenyl)ethylamine. These ligands promote the addition of diethylzinc reagent to aldehydes under mild conditions to afford the corresponding secondary alcohols in high yield with excellent enantioselectivity. These results have shown that the chiral azetidine-based ligand is promising in asymmetric catalysis and deserves more attention. Further efforts will be focused on the applications of these ligands toward other types of asymmetric reactions, including nonlinear effects studies, and the exploration of new chiral azetidine ligands.

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References

[1] I. Ojima, *Catalytic Asymmetric Synthesis*. VCH: Cambridge, **1993**.
[2] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*. Wiley: New York, **1994**.
[3] R. E. Gawley, J. Aube, *Principles of Asymmetric Synthesis* (Eds.: J. E. Baldwin, P. D. Magnus). Pergamon: Oxford, **1996**.
[4] N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*. Springer: Berlin, **1999**.
[5] M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*. Wiley-VCH: Weinheim, **1998**.
[6] L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757.
[7] L. Pu, *Tetrahedron* **2003**, *59*, 9873.
[8] K. Soai, S. Nlwa, *Chem. Rev.* **1992**, *92*, 833.
[9] R. Noyori, M. Kitamura, *Angew. Chem., Int. Edn Engl.* **1991**, *30*, 49.
[10] M. Yus, D. J. Ramon, *Pure Appl. Chem.* **2005**, *77*, 2111.
[11] F. Couty, G. Evano, D. Prim, *Mini-Rev. Org. Chem.* **2004**, *1*, 133.
[12] A. V. Rama Rao, M. K. Gurjar, V. Kaiwar, *Tetrahedron: Asymmetry* **1992**, *3*, 859.
[13] W. Behnen, C. Dauelsberg, S. Wallbaum, J. Martens, *Synth. Commun.* **1992**, *22*, 2143.
[14] W. Behnen, T. Mehler, J. Martens, *Tetrahedron: Asymmetry* **1993**, *4*, 1413.
[15] W. A. J. Starmans, L. Thijs, B. Zwanenburg, *Tetrahedron* **1998**, *54*, 629.
[16] W. A. J. Starmans, R. W. A. Walgers, L. Thijs, R. de Gelder, J. M. M. Smits, B. Zwanenburg, *Tetrahedron* **1998**, *54*, 4991.
[17] M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520.
[18] A. G. M. Barrett, P. D. Dozzo, A. J. P. White, D. J. Williams, *Tetrahedron* **2002**, *58*, 7303.
[19] M. Shi, J. K. Jiang, *Tetrahedron: Asymmetry* **1999**, *10*, 1673.
[20] J. Wilken, S. Erny, S. Wassmann, J. Martens, *Tetrahedron: Asymmetry* **2000**, *11*, 2143.
[21] P. J. Hermsen, J. G. O. Cremers, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.* **2001**, *42*, 4243.
[22] F. Couty, D. Prim, *Tetrahedron: Asymmetry* **2002**, *13*, 2619.
[23] M. C. Wang, W. X. Zhao, X. D. Wang, M. P. Song, *Synlett* **2006**, 3443.
[24] M. C. Wang, Q. J. Zhang, W. X. Zhao, X. D. Wang, X. Ding, T. T. Jing, M. P. Song, *J. Org. Chem.* **2008**, *73*, 168.
[25] Z. Zhang, M. Li, G. Zi, *Chirality* **2007**, *19*, 802.
[26] Z. Zhang, X. Bai, R. Liu, G. Zi, *Inorg. Chim. Acta* **2008**, DOI: 10.1016/j.ica.2008.07.019.
[27] F. Duran, L. Ghosez, *Tetrahedron Lett.* **1970**, *11*, 245.
[28] Y. Dejaegher, S. Mangelinckx, N. D. Kimpe, *J. Org. Chem.* **2002**, *67*, 2075.
[29] L. Bianchi, C. Dell'Erba, M. Maccagno, A. Mugnoli, M. Novi, G. Petrillo, F. Sancassan, C. Tavani, *Tetrahedron* **2003**, *59*, 10195.
[30] G. I. Georg, P. He, J. Kant, Z.-J. Wu, *J. Org. Chem.* **1993**, *58*, 5771.
[31] L. S. Hegedus, J. Montgomery, Y. Narukawa, D. C. Snustad, *J. Am. Chem. Soc.* **1991**, *113*, 5784.
[32] S. Dumas, L. S. Hegedus, *J. Org. Chem.* **1994**, *59*, 4967.
[33] C. Wolf, C. J. Francis, P. A. Hawes, M. Shah, *Tetrahedron: Asymmetry* **2002**, *13*, 1733.
[34] J. Huang, J. C. Lanni, J. E. Antoline, R. P. Hsung, M. C. Kozlowski, *Org. Lett.* **2006**, *8*, 1565.
[35] T. Rasmussen, P.-O. Norrby, *J. Am. Chem. Soc.* **2003**, *125*, 5130.
[36] J. Vazquez, M. A. Pericas, F. Maseras, A. Lledos, *J. Org. Chem.* **2000**, *65*, 7303.
[37] M. Yamakawa, R. Noyori, *Organometallics* **1999**, *18*, 128.
[38] B. Goldfuss, K. N. Houk, *J. Org. Chem.* **1998**, *63*, 8998.
[39] M. Yamakawa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 6327.