Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Chiral *O,N,O*-tridentate Phenol Ligands Derived From Camphor

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ABSTRACT Chiral O,N,O-tridentate phenol ligands bearing a camphor backbone were found to be effective chiral catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes, resulting in high enantioselectivities (80–95% ee) at room temperature. *Chirality 28:65–71, 2016.*

KEY WORDS: tridentate chiral ligand; enantioselective addition; asymmetric catalysis

Optically pure secondary alcohols serve as important intermediates in the synthesis of pharmaceuticals. For example, PNU-142721,[1] (*S*)-duloxetine,[2] Singulair,[3] neobenodine,[4] fluoxetine,[5] and tomoxetin[6] (Fig. 1) are all physiologically active compounds based on optically pure secondary alcohols. Therefore, the development of efficient methods for the preparation of optically pure secondary alcohols has received much attention, and the asymmetric addition of diethylzinc to aldehydes is one of the most effective approaches for preparing them.[7,8]

Although many bidentate chiral ligands have been prepared and tested in the catalytic asymmetric addition of diethylzinc to aldehydes,[9–23] the development of efficient tridentate ligands have not been studied extensively. Tridentate ligands should confer more rigidity to the reactive zinc chelate catalyst structures, thereby allowing better discrimination between the two enantiotopic faces of an aldehyde in the transition state complex. Recently, some tridentate and polydentate chiral ligands have been synthesized and applied to the enantioselective addition of diethylzinc to aldehydes.[24–41] In this line, Hayashi et al. have developed O,N,O-ligands based on Schiff bases derived from *tert*-leucinol and salicylaldehyde, which were effective for the asymmetric addition of diethylzinc to aldehydes (up to 96% enantiomeric excess [*ee*] for benzaldehyde). Although most of these ligands provide good results, some of them are difficult to purify or prepare efficiently. Since camphor skeleton has proven to be highly effective as a chiral template in asymmetric synthesis,[42–48] and on the basis of the above, we became interested in developing new tridentate aminodiols ligands based on 2-aminoisoborneol and phenol, and derived from Schiff bases obtained from camphor.

Herein we report novel *O,N,O*-tridentate chiral ligands for the enantioselective addition of diethylzinc to aldehydes. These tridentate ligands **1** (Fig. 2) have the following characteristics: 1) they have two different types of oxygen atoms, binding to zinc in distinct ways, and 2) the substituents on the aromatic ring induce electronic and steric effects.

MATERIALS AND METHODS

General Methods

^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a 400 MHz spectrometer. Chloroform (δ = 7.26) or dimethyl sulfoxide (DMSO) (δ = 2.49) was used as internal standard in ^{1}H NMR spectra. The central peak of $CDCl_3$ (δ = 77.0) or DMSO-d_6 (δ = 39.5) was used as internal standard in ^{13}C NMR spectra. The *ee* value of secondary alcohols were determined by high-performance liquid chromatography (HPLC) analysis on chiral columns using isopropanol and *n*-hexane as the mobile phase.

(1*R*,4*S*)-(−)-1,7,7-Trimethyl-2,3-dione-bicyclo[2.2.1]heptane (2). To a solution of camphor (2.00 g, 13.0 mmol) in acetic anhydride (3.30 mL) was added selenium dioxide (3.31 g, 30.0 mmol) and heated to reflux for 19 h. The solution was cooled to room temperature and filtered to remove the black selenium precipitate. The residue was washed with acetic anhydride (10.0 mL). The liquid was added to cold water (50 mL) to separate camphorquinone **2** from acetic anhydride, then filtered by Buchner funnel. The filtrate was neutralized with saturated NaOH(aq) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford the crude product, which was subjected to the next reaction without any purification. The crude product was a yellow solid (2.14 g, 99%). $[\alpha]_D^{25} = -96.8°$ (c = 1.00, $CHCl_3$) [Lit.[49] $[\alpha]_D^{25} = -108.3°$ (c = 1.86, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 2.63 (d, *J* = 5.2 Hz, 1H), 2.18–2.12 (m, 1H), 1.94–1.86 (m, 1H), 1.67–1.59 (m, 2H), 1.10 (s, 3H), 1.06 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 204.8, 202.8, 58.6, 57.9, 42.5, 29.9, 22.2, 21.1, 17.4, 8.8. The data match those of the literature report.[49]

(1*R*,4*S*)-(+)-3-(Hydroxyimino)-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (3). To a solution of camphorquinone **2** (2.00 g, 12.0 mmol) in ethanol (9.00 mL) was added the solution of hydroxylamine hydrochloride (1.00 g, 14.4 mmol) and sodium acetate (1.78 g, 21.6 mmol) in water (5.00 mL) at room temperature. The resulting solution was stirred for 1 h at room temperature. Ethanol was removed by rotary evaporator, and the residual mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give oxime **3** as a yellow solid (2.15 g, 99%). The crude compound was recrystallized from ether to afford the desired product as off-white solids (1.74 g, 80%, *E*:*Z* = 2.95:1, the ratio was determined by crude NMR spectrum). $[\alpha]_D^{25} = +198.8$ (c = 1.00, $CHCl_3$) [Lit.[50] $[\alpha]_D^{25} = +199°$ (c = 1.41, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.88 (br, 1H, C=NOH), 3.25 (d, *J* = 4.4 Hz, 1H), 2.04–2.00 (m, 1H), 1.82–1.74 (m, 1H), 1.59–1.52 (m, 2H), 1.02 (s, 3H), 1.00 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 204.4, 159.8, 58.5, 46.6, 44.9, 30.6, 23.7, 20.7, 17.6, 8.9. The data match those of the literature report.[50]

(1*R*,2*S*,3*R*,4*S*)-3-Amino-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane (4). To a solution of LAH (2.00 g, 52.7 mmol) in dry THF (15.0 mL) was added the solution of camphorquinone oxime **3** (3.19 g, 17.6 mmol) in THF (15.0 mL) at 0°C over a period of 30 min. The solution was allowed to warm to ambient temperature and heated to reflux for 1 h. After cooling to room

Contract grant sponsor: National Science Council of the Republic of China
Contract grant number: 102WFA0500216
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Received for publication 16 April 2015; Accepted 22 July 2015
DOI: 10.1002/chir.22543
Published online 21 October 2015 in Wiley Online Library (wileyonlinelibrary.com).

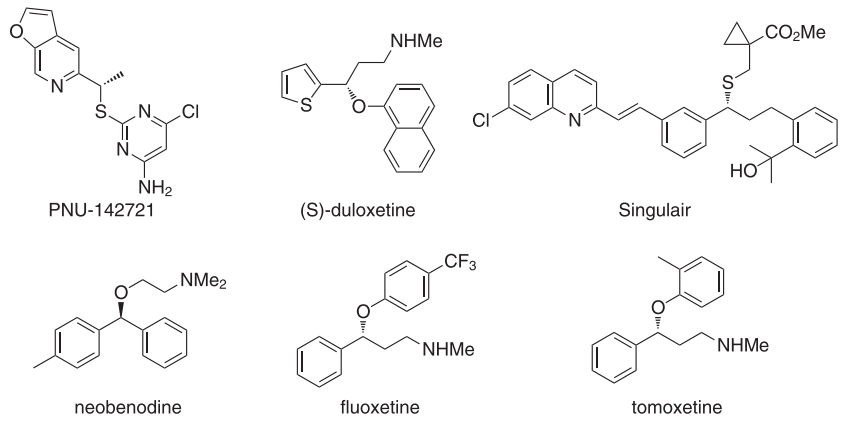


Fig. 1. Some examples of pharmaceutical products.

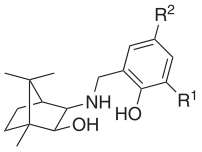


Fig. 2. The stucture of *O,N,O*-tridentate ligands 1.

temperature, the mixture was quenched by water (1 mL) and filtered by Buchner funnel. The precipitate was washed by EtOAc (20 mL × 3). The filtrate was dried over $MgSO_4$, filtered, and concentrated to afford crude product **4** as a white solid (2.86 g, 96%). $[\alpha]_D^{25} = -3.6°$ (c = 1.00, MeOH) [Lit.[50] $[\alpha]_D^{25} = -6.2$ (c = 1.08, MeOH)]; ^1H NMR ($CDCl_3$, 400 MHz, δ): 3.38 (d, *J* = 7.2 Hz, 1H), 3.06 (d, *J* = 7.2 Hz, 1H), 1.74–1.67 (m, 1H), 1.56 (d, *J* = 4.8 Hz, 1H), 1.43–1.39 (m, 1H), 1.06 (s, 3H), 1.05–0.96 (m, 1H), 0.95 (s, 3 H), 0.90–0.87 (m, 1H), 0.79 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 79.0, 57.3, 53.3, 48.7, 46.6, 33.1, 26.9, 21.9, 21.2, 11.4. The data match those of the literature report.[50]

General Procedure for Ligand 1

Aldehyde or its derivative (5.61 mmol) in MeOH (10.0 mL) was added to a solution of amino alcohol **4** (5.61 mmol) in MeOH (15.0 mL) at room temperature and the reaction was stirred for 2 h. Then $NaBH_4$ (0.420 g, 11.2 mmol) was added. After 2 h, methanol was removed and the residue was extracted with EtOAc (10 mL × 3). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated to afford the crude product, which was purified by chromatography (EtOAc/hexane = 1/20–1/5) to give ligand **1**.

(1*R*,2*S*,3*R*,4*S*)-3-(Benzylamino)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane (1a). Benzaldehyde (0.570 mL, 5.61 mmol), amino alcohol **4** (1.00 g, 5.91 mmol), MeOH (25.0 mL) and $NaBH_4$ (0.420 g, 11.2 mmol) were used to afford desired product **1a** (0.90 g, 62%) as a white solid. Mp = 82–84°C ; $[\alpha]_D^{25}$ = +26.8 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.36–7.25 (m, 5H), 3.80 (s, 2H), 3.43 (d, *J* = 7.2 Hz, 1H), 2.82 (d, *J* = 7.2 Hz, 1H), 1.74–1.64 (m, 1H), 1.59 (d, *J* = 4.4 Hz, 1H), 1.47–1.39 (m, 1H), 1.05 (s, 3H), 1.03–0.97 (m, 2H), 0.95 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 139.9, 128.5, 128.0, 127.2, 78.7, 65.6, 54.8, 51.8, 48.8, 46.6, 32.9, 27.2, 21.9, 21.3, 11.3; HRMS (EI, m/z): M^+ calcd for $C_{17}H_{25}NO$, 259.1936; found, 259.1933; Anal. Calcd. for $C_{17}H_{25}NO$: C 78.72, H 9.71, N 5.40, O 6.17; found: C 78.44, H 9.35, N 5.16, O 6.51.

(1*R*,2*S*,3*R*,4*S*)-3-[(2-Hydrooxybenzyl)-amino)]-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane (1b). 2-Hydroxybenzaldehyde (0.600 mL, 5.61 mmol), amino alcohol **4** (1.00 g, 5.91 mmol), MeOH (25.0 mL) and $NaBH_4$ (0.420 g, 11.2 mmol) were used to afford desired product **1b** (1.11 g, 72%) as a white solid. Mp = 91–94°C ; $[\alpha]_D^{25}$ = +28.1 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.16 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.94 (d, *J* = 13.4 Hz, 1H), 3.77 (d, *J* = 7.6 Hz, 1H), 2.79 (d, *J* = 7.6 Hz, 1H), 1.78 (d, *J* = 4.4 Hz, 1H), 1.72–1.65 (m, 1H), 1.51–1.45 (m, 1H), 1.72–1.65 (m, 1H), 1.14 (s, 3H), 1.03–0.95 (m, 2H), 0.93 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 158.0, 128.7, 128.3, 123.3, 118.9, 116.3, 80.0, 66.1, 53.0, 50.1, 49.1, 46.7, 33.1, 26.7, 21.7, 21.0, 11.3; HRMS (EI, m/z): M^+ calcd for $C_{17}H_{25}NO_2$, 275.1885; found, 275.1877; Anal. Calcd. for $C_{17}H_{25}NO_2$: C 74.14, H 9.15, N 5.09, O 11.62; found: C 73.59, H 9.35, N 4.86, O 11.50.

(1*R*,2*S*,3*R*,4*S*)-3-[(2-Methoxybenzyl)-amino] -2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (1c). 2-Methoxybenzaldehyde (0.57 mL, 5.61 mmol), amino alcohol **4** (1.00 g, 5.91 mmol), MeOH (25.0 mL), and $NaBH_4$ (0.420 g, 11.2 mmol) were used to afford desired product **1c** (0.75 g, 46%) as a yellow solid. Mp = 81–82°C ; $[\alpha]_D^{25}$ = 21.9 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, δ): 7.26 (td, *J* = 15.6, 1.6 Hz, 1H), 7.21 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.93–6.87 (m, 2H), 3.86 (s, 3H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.45 (d, *J* = 7.6 Hz, 1H), 2.78 (d, *J* = 7.6 Hz, 1H), 1.67–1.60 (m, 1H), 1.46 (d, *J* = 4.4 Hz, 1H), 1.42–1.35 (m, 1H), 1.03 (s, 3H), 1.00–0.96 (m, 2H), 0.94 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 157.7, 129.8, 128.5, 128.1, 120.4, 110.2, 78.7, 65.4, 55.2, 51.9, 50.6, 48.7, 46.5, 32.9, 27.1, 21.9, 21.3, 11.4; HRMS (EI, m/z): M^+ calcd for $C_{18}H_{27}NO_2$, 289.2042; found, 289.2038; Anal. Calcd. for $C_{18}H_{27}NO_2$: C 74.70, H 9.40, N 4.84, O 11.06; found: C 74.09, H 8.90, N 4.90, O 10.90.

(1*R*,2*S*,3*R*,4*S*)-3-[(2-Hydroxy-5-methylbenzyl)-amino]-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (1d). 2-Hydroxy-5-methylbenzaldehyde (0.760 g, 5.61 mmol), amino alcohol **4** (1.00 g, 5.91 mmol), MeOH (25.0 mL), and $NaBH_4$ (0.420 g, 11.2 mmol) were used to afford desired product **1d** (1.44 g, 89%) as a white solid. Mp = 132–134°C ; $[\alpha]_D^{25}$ = 25.3 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, δ): 6.96 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 3.96 (d, *J* = 13.6 Hz, 1H), 3.90 (d, *J* = 13.6 Hz, 1H), 3.75 (d, *J* = 7.6 Hz, 1H), 2.87 (d, *J* = 7.6 Hz, 1H), 2.24 (s, 3H), 1.76 (d, *J* = 4.4 Hz, 1H), 1.71–1.64 (m, 1H), 1.51–1.43 (m, 1H), 1.14 (s, 3H), 1.03–0.96 (m, 2H), 0.93 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 155.7, 129.0, 128.9, 127.9, 123.0, 116.0, 80.0, 66.1, 53.0, 50.0, 49.0, 46.7, 33.1, 26.7, 21.7, 21.0, 20.4, 11.3; HRMS (EI, m/z): M^+ calcd for $C_{18}H_{27}NO_2$, 289.2042; found, 289.2039; Anal. Calcd. for $C_{18}H_{27}NO_2$: C 74.70, H 9.40, N 4.84, O 11.06; found: C 74.29, H 9.20, N 4.74, O 11.37.

(1*R*,2*S*,3*R*,4*S*)-3-[(2-Hydroxy-5-methoxybenzyl)-amino]-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (1e). 2-Hydroxy-5-methoxybenzaldehyde (0.700 mL, 5.61 mmol), amino alcohol **4** (1.00 g, 5.91 mmol), MeOH (25.0 mL), and $NaBH_4$ (0.420 g, 11.2 mmol) were used to afford desired product **1e** (1.39 g, 81%) as a yellow solid. Mp = 138–139°C ; $[\alpha]_D^{25}$ = 23.9° (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, δ): 6.76 (d, *J* = 8.8 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 3.97

(d, J = 13.6 Hz, 1H), 3.89 (d, J = 13.6 Hz, 1H), 3.75 (d, J = 7.6 Hz, 1H), 3.74 (s, 3H), 2.77 (d, J = 7.6 Hz, 1H), 1.75 (d, J = 4.8 Hz, 1H), 1.71–1.64 (m, 1H), 1.50–1.44 (m, 1H), 1.13 (s, 3H), 1.02–0.94 (m, 2H), 0.92 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 152.4, 151.9, 124.0, 116.5, 114.4, 113.4 , 80.0, 66.1, 55.8, 53.1, 50.1, 49.1, 46.7, 33.1, 26.7, 21.7, 21.0, 11.3; HRMS (EI, m/z): M^+ calcd for $C_{18}H_{27}NO_3$, 305.1991; found, 305.1984; Anal. Calcd. for $C_{18}H_{27}NO_3$: C 70.79, H 8.91, N 4.59, O 15.72; found: C 70.69, H 9.13, N 4.31, O 15.40.

(1*R*,2*S*,3*R*,4*S*)-3-[(2-Hydroxy-5-nitrobenzyl)-amino] -2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (1f). 2-Hydroxy-5-nitrobenzaldehyde (0.490 g, .2.95 mmol), amino alcohol **4** (0.500 g, 2.95 mmol), 2,2,2-trifluoroethanol (20.0 mL), and $NaBH_4$ (0.21 g, 5.90 mmol) were used to afford desired product **1f** (0.43g, 45 %) as a yellow solid. Mp = 216–218°C ; $[\alpha]_D^{25}$ = 28.6 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.94 (d, J = 3.2 Hz, 1H), 7.89 (dd, J = 9.2, 3.2 Hz, 1H), 6.36 (d, J = 9.2 Hz, 1H), 4.04 (d, J = 13.6 Hz, 1H), 3.91 (d, J = 13.6 Hz, 1H), 3.64 (d, J = 7.6 Hz, 1H), 2.89 (d, J = 7.6 Hz, 1H), 1.84 (d, J = 4.0 Hz, 1H), 1.62–1.59 (m, 1H), 1.40–1.35 (m, 1H), 1.05 (s, 3H), 1.00–0.89 (m, 2H), 0.83 (s, 3H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 174.0, 132.6, 126.3, 126.1, 121.4, 117.6, 77.1, 64.3, 50.9, 48.7, 48.1, 46.3, 32.1, 26.2, 21.4, 20.8, 11.4; HRMS (EI, m/z): M^+ calcd for $C_{17}H_{24}N_2O_4$, 320.1736; found, 320.1728.

(1*R*,2*S*,3*R*,4*S*)-3-[(3-*tert*-Butyl-2-hydroxybenzyl)-amino] -2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (1g). 3-*tert*-Butyl-2-hydroxybenzaldehyde (2.45 mL, 13.6 mmol), amino alcohol **4** (3.00 g, 17.7 mmol), MeOH (30.0 mL), and $NaBH_4$ (1.03 g, 27.3 mmol) were used to afford desired product **1g** (3.84 g, 85%) as a white solid. Mp = 118–119°C ; $[\alpha]_D^{25}$ = 28.5 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.19 (dd, J = 7.6, 1.2 Hz, 1H), 6.88 (d, J = 6.4 Hz, 1H), 6.71 (t, J = 8.0, 7.6 Hz, 1H), 4.04 (d, J = 13.6 Hz, 1H), 3.90 (d, J = 13.6 Hz, 1H), 3.76 (d, J = 7.6 Hz, 1H), 2.77 (d, J = 7.6 Hz, 1H), 1.75 (d, J = 4.4 Hz, 1H), 1.69–1.61 (m, 1H), 1.50–1.44 (m, 1H), 1.42 (s, 9H), 1.15 (s, 3H), 1.02–0.96 (m, 2H), 0.93 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 157.2, 136.7, 126.4, 125.8, 123.6, 118.1, 80.2, 66.2, 53.6, 49.9, 49.0, 46.7, 34.6, 33.2, 29.5, 26.6, 21.7, 21.0, 11.3; HRMS (EI, m/z): M^+ calcd for $C_{21}H_{33}NO_2$, 331.2511; found, 331.2504; Anal. Calcd. for $C_{21}H_{33}NO_2$: C 76.09, H 10.03, N 4.23, O 9.65; Found: C 76.10, H 9.83, N 4.03, O 9.75.

General Procedures for the Asymmetric Addition of Diethylzinc to Aldehydes

To a 10-mL round-bottomed flask containing ligand (57.0 mg, 20 mol%) in toluene (1.80 mL) was added diethylzinc solution (2.50 mmol, 1.5 M in toluene) at ambient temperature. After stirring for 1 h at room temperature, to the mixture was added aldehyde (1.00 mmol) at room temperature. After stirring for 2.5 h, the reaction was quenched with 1.0 M HCl(aq) (2.50 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by flash chromatography (Hexane:EtOAc = 20:1). The *ee* value was determined by HPLC on a chiral stationary phase.

1-Phenylpropan-1-ol (7a) (example from Table 2, entry 1). The use of benzaldehyde **6a** (1.00 mmol) gave chiral adduct **7a** (0.124 g) in 91% yield. HPLC (Chiralcel OD, 2% IPA/*n*-hexane, 1.5 mL/min, 254 nm): $t_{r(major)}$: 10.95 min, $t_{r(minor)}$: 8.63 min, 90% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.36–7.26 (m, 5H), 4.59 (t, J = 6.4 Hz, 1H), 1.90–1.72 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H).

1-(4-Methylphenyl)propan-1-ol (7b) (example from Table 2, entry 2). The use of 4-tolualdehyde **6b** (1.00 mmol) gave chiral adduct **7b** (0.143 g) in 95% yield. HPLC (Chiralcel OB, 2% IPA/*n*-hexane, 0.5 mL/min, 254 nm): $t_{r(major)}$: 20.10 min, $t_{r(minor)}$: 23.49 min, 91% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.26–7.15 (m, 4H), 4.56 (t, J = 6.4 Hz, 1H), 2.35 (s, 3H), 1.86–1.68 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H).

1-(3-Methylphenyl)propan-1-ol (7c) (example from Table 2, entry 3). The use of 3-tolualdehyde **6c** (1.00 mmol) gave chiral adduct **7c** (0.132 g) in 88% yield. HPLC (Chiralcel OD, 2% IPA/*n*-hexane, 0.5 mL/min, 254 nm): $t_{r(major)}$: 31.83 min, $t_{r(minor)}$: 22.34 min, 88% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.26–7.08 (m, 4H), 4.56 (t, J = 6.4 Hz, 1H), 2.36 (s, 3H), 1.86–1.71 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H).

1-(2-Methylphenyl)propan-1-ol (7d) (example from Table 2, entry 4). The use of 2-tolualdehyde **6d** (1.00 mmol) gave chiral adduct **7d** (0.126 g) in 84% yield. HPLC (Chiralcel OB, 10% IPA/*n*-hexane, 0.5 mL/min, 254 nm): $t_{r(major)}$: 8.42 min, $t_{r(minor)}$: 10.46 min, 92% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.47–7.12 (m, 4H), 4.85 (t, J = 6.4 Hz, 1H), 2.34 (s, 3H), 1.80–1.73 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H).

1-(4-Methoxyphenyl)propan-1-ol (7e) (example from Table 2, entry 5). The use of 4-anisaldehyde **6e** (1.00 mmol) gave chiral adduct **7e** (0.160 g) in 96% yield. HPLC (Chiralcel OD, 2% IPA/*n*-hexane, 1.0 mL/min, 254 nm): $t_{r(major)}$: 23.96 min, $t_{r(minor)}$: 21.77 min, 91% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.28–6.87 (m, 4H), 4.54 (t, J = 6.8 Hz, 1H), 3.80 (s, 3H), 1.86–1.65 (m, 2 H), 0.90 (t, J = 7.6 Hz, 3H).

1-(3-Methoxyphenyl)propan-1-ol (7f) (example from Table 2, entry 6). The use of 3-anisaldehyde **6f** (1.00 mmol) gave chiral adduct **7f** (0.153 g) in 92% yield. HPLC (Chiralcel OB, 2% IPA/*n*-hexane, 1.0 mL/min, 254 nm): $t_{r(major)}$: 16.15 min, $t_{r(minor)}$: 19.45 min, 88% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.28–6.80 (m, 4H), 4.57 (t, J = 6.4 Hz, 1H), 3.81 (s, 3H), 1.87–1.71 (m, 2H), 0.92 (t, J = 7.6 Hz, 3H).

1-(2-Methoxyphenyl)propan-1-ol (7g) (example from Table 2, entry 7). The use of 2-anisaldehyde **6g** (1.00 mmol) gave chiral adduct **7g** (0.150 g) in 90% yield. HPLC (Chiralcel OB, 2% IPA/*n*-hexane, 1.0 mL/min, 254 nm): $t_{r(major)}$: 9.77 min, $t_{r(minor)}$: 14.52 min, 83% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.30–6.87 (m, 4 H), 4.76 (t, J = 6.4 Hz, 1H), 3.85 (s, 3H), 1.84–1.78 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).

1-(4-Chlorophenyl)propan-1-ol (7h) (example from Table 2, entry 8). The use of 4-chlorobenzaldehyde **6h** (1.00 mmol) gave chiral adduct **7h** (0.154 g) in 90% yield. HPLC (Chiralcel OD, 2.5% IPA/*n*-hexane, 1.0 mL/min, 254 nm): $t_{r(major)}$: 11.53 min, $t_{r(minor)}$: 12.74 min, 88% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.32–7.25 (m, 4H), 4.57 (t, J = 6.4 Hz, 1H), 1.82–1.67 (m, 2H), 0.89 (t, J = 7.6 Hz, 3H).

1-(3-Chlorophenyl)propan-1-ol (7i) (example from Table 2, entry 9). The use of 3-chlorobenzaldehyde **6i** (1.00 mmol) gave chiral adduct **7i** (0.154 g) in 90% yield. HPLC (Chiralcel OB, 2% IPA/*n*-hexane, 1.0 mL/min, 254 nm): $t_{r(major)}$: 8.47 min, $t_{r(minor)}$: 10.23 min, 84% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.34–7.18 (m, 4H), 4.56 (t, J = 6.4 Hz, 1H), 1.82–1.70 (m, 2H), 0.91 (t, J = 7.6 Hz, 3H).

1-(2-Chlorophenyl)propan-1-ol (7j) (example from Table 2, entry 10). The use of 2-chlorobenzaldehyde **6j** (1.00 mmol) gave chiral adduct **7j** (0.145 g) in 85% yield. HPLC (Chiralcel OB, 5% IPA/*n*-hexane, 0.5 mL/min, 254 nm): $t_{r(major)}$: 9.11 min, $t_{r(minor)}$: 11.22 min, 80% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.56–7.17 (m, 4H), 5.07 (t, J = 3.6 Hz, 1H), 1.85–1.70 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H).

1-(4-Bromophenyl)propan-1-ol (7k) (example from Table 2, entry 11). The use of 4-bromobenzaldehyde **6k** (1.00 mmol) gave chiral adduct **7k** (0.191 g) in 89% yield. HPLC (Chiralcel OB, 5% IPA/*n*-hexane, 0.5 mL/min, 254 nm): $t_{r(major)}$: 13.10 min, $t_{r(minor)}$: 14.29 min, 90% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.48–7.20 (m, 4H), 4.57 (t, J = 6.8 Hz, 1H), 1.82–1.66 (m, 2H), 0.90 (t, J = 7.6 Hz, 3H).

1-(2-Fluorophenyl)propan-1-ol (7l) (example from Table 2, entry 12). The use of 2-fluorobenzaldehyde **6l** (1.00 mmol) gave chiral adduct **7l** (0.136 g) in 88% yield. HPLC (Chiralcel OD, 2% IPA/*n*-hexane, 0.5 mL/min, 254 nm): $t_{r(major)}$: 14.02 min, $t_{r(minor)}$: 19.51 min, 85% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.47–6.99 (m, 4H), 4.94 (dd, J = 10.8, 6.4 Hz, 1H), 1.82–1.67 (m, 2H), 0.89 (t, J = 7.6 Hz, 3H).

1-(Naphthalen-1-yl)propan-1-ol (7m) (example from Table 2, entry 13). The use of 1-naphthaldehyde **6m** (1.00 mmol) gave chiral adduct **7m** (0.168 g) in 90% yield. HPLC (Chiralcel OD, 2% IPA/*n*-hexane, 1.0 mL/min, 254 nm): $t_{r(major)}$: 26.10 min, $t_{r(minor)}$: 51.55 min, 95% *ee*; ^{1}H

NMR ($CDCl_3$, 400 MHz, δ): 8.14–7.47 (m, 7H), 5.4 (t, J = 7.6 Hz, 1H), 2.05–1.90 (m, 2H), 1.04 (t, J = 7.6 Hz, 3H).

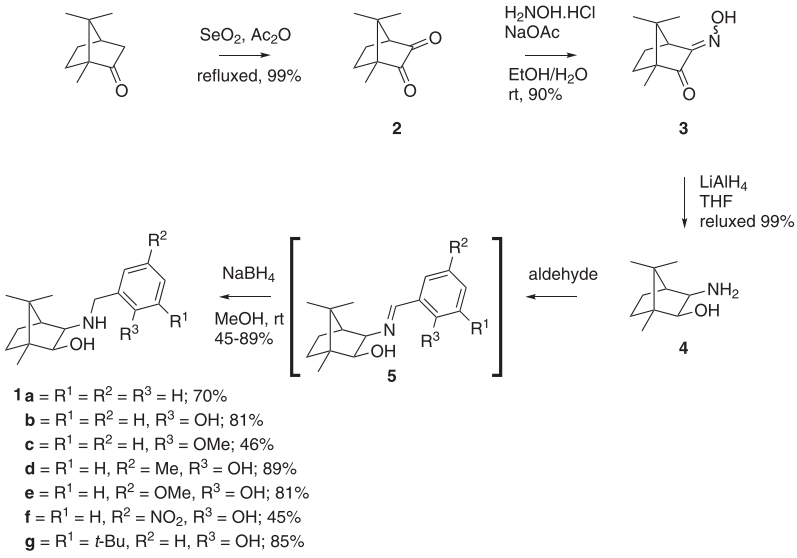
1-(Naphthalen-2-yl)propan-1-ol (7n) (example from Table 2, entry 14). The use of 2-naphthaldehyde **6n** (1.00 mmol) gave chiral adduct **7n** (0.169 g) in 91% yield. HPLC (Chiralcel OD, 2% IPA/*n*-hexane, 1.0 mL/min, 254 nm): $t_{r(major)}$: 31.93 min, $t_{r(minor)}$: 38.11 min, 88% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.85–7.47 (m, 7H), 4.77 (t, J = 6.8 Hz, 1H), 1.95–1.84 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H).

(*E*)-1-Phenylpent-1-en-3-ol (7o) (example from Table 2, entry 15). The use of (*E*)-cinnamaldehyde **6o** (1.00 mmol) gave chiral adduct **7o** (0.141 g) in 87% yield. HPLC (Chiralcel OD, 10% IPA/*n*-hexane, 0.5 mL/min, 254 nm): $t_{r(major)}$: 24.44 min, $t_{r(minor)}$: 16.21 min, 60% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.40–7.22 (m, 5H), 6.56 (d, J = 15.2 Hz, 1H), 6.19 (dd, J = 16.0, 6.8 Hz, 1H), 4.24–4.19 (m, 1H), 1.72–1.62 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H).

RESULTS AND DISCUSSION

A series of *O*,*N*,*O*-tridentate ligands **1** was readily synthesized starting from camphor (Scheme 1). (1*S*,2*S*,4*S*)-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**4**) was obtained in three steps from camphor in 60% overall yield. The condensation of various aromatic aldehydes with **4** produced imines, which were subsequently reduced with sodium borohydride to afford chiral *O*,*N*,*O*-tridentate ligands **1** in good yields (45–89%).

With *O*,*N*,*O*-tridentate ligands **1** in hand, a model reaction (the addition of diethylzinc to benzaldehyde (**6a**)) was first tested to study the catalytic activity of the ligands. The reaction was carried out in the presence of 20 mol% of ligands **1** to afford the corresponding secondary alcohol **7a**; the results are listed in Table 1. To reveal the functionality of tridentate ligands for this enantioselective organozinc addition, we prepared analogous bidentate ligands **1a** and **1c**. Our results demonstrate that tridentate chiral ligand **1b** (entry 2, 87% yield, 60% *ee*) is superior to bidentate chiral ligand **1a** (entry 1, 72% yield, 34% *ee*) for the asymmetric addition. The substitution of the hydroxyl group for a methyoxy group (**1c**)



Scheme 1. The synthesis of new *O*,*N*,*O*-tridentate ligands 1a-g.

TABLE 1. Asymmetric addition of $ZnEt_2$ to benzaldehyde using chiral ligands 1

Entry	Ligand **1**	Et_2Zn (eq)	Solvent	Temp.(°C)	Time (h)	Yield **7** (%)[a]	*ee* **7** (%)[b]
1	**1a**	2.5	C_6H_{14}/C_7H_8	25	2.5	72	34 (*S*)
2	**1b**	2.5	C_6H_{14}/C_7H_8	25	2.5	87	60 (*S*)
3	**1b**	2.0	C_6H_{14}/C_7H_8	25	2.5	85	58 (*S*)
4	**1b**	1.2	C_6H_{14}/C_7H_8	25	2.5	60	57 (*S*)
5	**1b**	2.5	THF/C_6H_{14}	25	2.5	60	50 (*S*)
6	**1b**	2.5	C_6H_{14}	25	2.5	90	55 (*S*)
7	**1b**	2.5	C_7H_8	25	2.5	83	64 (*S*)
8	**1c**	2.5	C_7H_8	25	2.5	48	16 (*R*)
9	**1d**	2.5	C_7H_8	25	2.5	89	75 (*S*)
10	**1e**	2.5	C_7H_8	25	2.5	81	63 (*S*)
11	**1f**	2.5	C_7H_8	25	2.5	46	4 (*S*)
12	**1g**	2.5	C_7H_8	25	2.5	91	90 (*S*)
13	**1g**	2.5	C_7H_8	0	6.0	90	82 (*S*)
14	**1g**	2.5	C_7H_8	−20	24	93	80 (*S*)

[a]All yields were obtained by isolating of the products after purification.
[b]The *ee* value was analyzed by HPLC with a Chiralcel OD column.

resulted in a dramatic decrease of the *ee* (entry 8, 48% yield, 16% *ee*). These results suggest the structural importance of the presence of the aromatic hydroxyl group in the ligand, which allows for the O,N,O-tridentate coordination to the Zn metal center. A decrease in the amount of diethylzinc results in a lower rate of reaction (entries 2–4), and entry 7 shows that toluene is the best solvent for this reaction. Ligand screening (entries 7–12) revealed that ligand **1g** provides the best enantioselectivity at room temperature. With regard to the effect of substituents on the aromatic ring, we found that the introduction of electron-donating groups in the 4-position of the aromatic ring leads to dramatic increases in both the yield and the enantioselectivity (entries 9–11). For example, the use of ligand **1f**, bearing a nitro group in 4-position, results in poor catalytic activity (entry 11). On the other hand, ligand **1d**, bearing a methyl group in the 4-position, effects the formation of **7a** in 89% yield, with 75% *ee* (entry 9). In addition, we found that the steric effect of substituents on the aromatic rings of ligands is more important than the electronic effect (entries 9 vs. 12). The *ee* decreases slightly upon a decrease in the temperature of the reaction (entries 12–14).

TABLE 2. Asymmetric addition of $ZnEt_2$ to various aromatic aldehydes using chiral ligand 1g[a]

Entry	Aldehyde		Yield **7** (%)[b]	**7** (*ee* %)[c]
1	Benzaldehyde	**6a**	91	90 (*S*)
2	4-Tolualdehyde	**6b**	95	91[d] (*S*)
3	3-Tolualdehyde	**6c**	88	88 (*S*)
4	2-Tolualdehyde	**6d**	84	92[d] (*S*)
5	4-Anisaldehyde	**6e**	96	91 (*S*)
6	3-Anisaldehyde	**6f**	92	88[d] (*S*)
7	2-Anisaldehyde	**6g**	90	83[d] (*S*)
8	4-Chlorobenzaldehyde	**6h**	90	88 (*S*)
9	3-Chlorobenzaldehyde	**6i**	90	84[d] (*S*)
10	2-Chlorobenzaldehyde	**6j**	85	80[d] (*S*)
11	4-Bromobenzaldehyde	**6k**	89	90[d] (*S*)
12	2-Fluorobenzaldehyde	**6l**	88	85 (*S*)
13	1-Naphthaldehyde	**6m**	90	95 (*S*)
14	2-Naphthaldehyde	**6n**	91	88 (*S*)
15	(*E*)-Cinnamaldehyde	**6o**	87	60 (*S*)

[a]Reaction was completed 2.5 h at room temperature.
[b]Isolated yield was reported.
[c]The *ee* value was analyzed by HPLC with a Chiralcel OD column.
[d]The *ee* value was analyzed by HPLC with a Chiralcel OB column.

Next, the scope of aromatic aldehydes **6** that can be used for the asymmetric addition at room temperature was examined, using **1g** as a catalyst. The experimental results are summarized in Table 2. The reaction of aldehydes bearing electron-donating groups (**6b–6g**) afforded the corresponding chiral secondary alcohols **7b–7g** with high enantioselectivities (83–92% *ee*, entries 2–7), regardless of the position of the substituent. On the other hand, in the reactions using *o*-, *m*-, and *p*-chlorobenzaldehyde (**6h–6j**), the enantioselectivity depends on the position of the substituent (entries 8–10). Concerning the electronic effect of the substrate, the reaction of *p*-substituted aldehydes **6b**, **6e**, **6h**, and **6k** uniformly furnished the corresponding chiral secondary alcohols **7** with high enantioselectivities, regardless of the property of the substituent on the aromatic ring (entries 2, 5, 8, and 11). Both 1- and 2-naphthaldehyde (**6m** and **6n**; entries 13 and 14) can be applied; the best *ee* was obtained in the reaction of 1-naphthaldehyde with diethylzinc (entry 13). The reaction of the α,β-unsaturated carbonyl compound cinnamaldehyde (**6o**) affords 1,2-adduct **7o** without any 1,4-addition product, albeit with lower enantioselectivity (entry 15).

With these observations in mind, the speculation on the possible transition state of the alkyl transfer step is illustrated in Figure 3.26 The proposed complex **8** was formed in situ when diethylzinc reacted with ligand **1g** because of the greater basicity of alkoxide than that of phenoxide. After coordination to aldehyde, two possible transition states, **9** and **10**, might be formed. We assumed that the more favored transition states should be **10** because of the steric repulsion between the bulky *tert*-butyl group and the aldehyde in **9**. The predominant formation of the *S* enantiomer in the addition should involve ethyl transfer from the reagent to *si* face of the aldehyde.

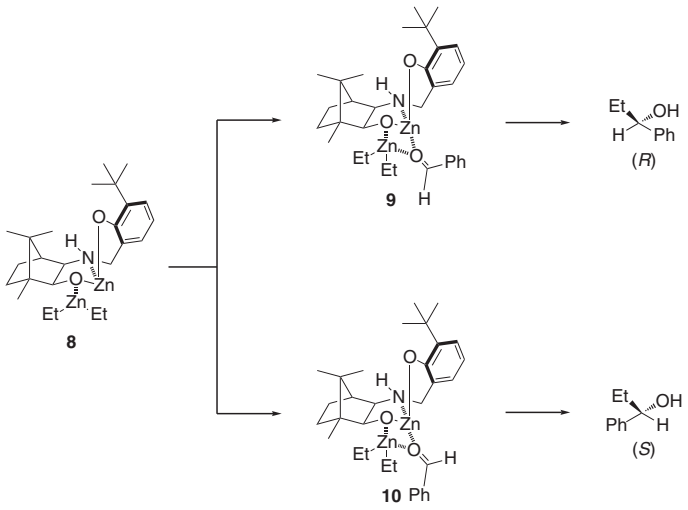


Fig. 3. Proposed two transition states and their corresponding products.

CONCLUSION

In conclusion, chiral *O*,*N*,*O*-tridentate ligands **1** derived from (+)-camphor were prepared in five steps in good overall yield, and they are highly air-stable. These ligands have two different types of oxygen atom and bind to zinc in distinct ways. Good yields and enantioselectivities were obtained in the addition reaction of Et_2Zn to aromatic aldehydes using tridentate ligand **1g**. The reactions reached completion within 2.5 h at ambient temperature. Therefore, the present method is practical and economical.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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