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Journal of Molecular Catalysis A: Chemical 243 (2006) 89–98
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Chiral 8-substituted 10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo [7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-ols as enantioselective catalysts in the addition of diethylzinc to substituted benzaldehydes

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Received 25 February 2005; received in revised form 27 July 2005; accepted 28 July 2005
Available online 21 September 2005

Abstract

Chiral 8-substituted 10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$] undeca-2(7),3,5-trien-8-ols were prepared from highly enantiopure (>97% ee) (1*R*)-(+)-α-pinene. The enantioselectivity was assessed in the addition of diethylzinc to substituted benzaldehydes to yield alcohols of the (*S*)-configuration, with an enantiomeric excess that typically ranges from 45 to 79%. Importantly, the electron-releasing substituents at the *meta*-position of the substituted benzaldehydes exhibited high enantioselectivity during alkylation using diethylzinc.

Keywords: Enantioselective catalyst; Diethylzinc; Asymmetric alkylation; Chiral ligand; Enantiomeric excess

1. Introduction

The asymmetric catalysis of organic reactions to provide enantiomerically enriched products is extremely important in modern synthetic and pharmaceutical chemistry [1–7]. The catalyzed asymmetric C–C bond-forming reaction in which diorganozinc reagents are enantioselectively added to aldehydes, represents one of the most important and fundamental asymmetric reactions [8,9]. Since the first work in this area by Oguni and Omi [10], various chiral ligands, including β-amino alcohols [11–40], BINOL [41–54], salen [55–57], TADDOL [58–67], pyridyl alcohol [68–79] and their derivatives have been employed in such reactions. Chiral ligands with diol generally need a Lewis acid, such as Ti(O–*i*–Pr)$_4$ to establish a chiral environment for the asymmetric addition of diethylzinc to aldehydes. While chiral ligands with amino alcohol or pyridyl alcohol constitute an asymmetric environment with two molecules of diethylzinc, one acts as a Lewis acid, and the other acts as a nucleophile [80–83]. The interaction between diethylzinc and an amino alcohol generates a chelated ethylzinc alkoxide (A), which is in equilibrium with a dimeric species (B) [81]. Only the monomer is catalytically active, and the adjacent Zn and O ring atoms, displaying complementary Lewis acid and Lewis base characteristics, are believed to coordinate with one molecule of aldehyde and one molecule of diethylzinc, respectively, to assemble the key species (C) where the ethyl group is transferred (Scheme 1).

The authors are interested in synthesizing and applying of chiral bipyridine derivatives as ligands for metal complexes in enantioselective catalysis [84], and are attracted by the possibility of modifying the structures of (D) and (E) by altering the position of the hydroxyl group (Fig. 1). This substitution leads to a new class of ligands **5**–**9**, **13** and **14**, substantially influencing the steric interactions between the ligand and the substrate, both of which are coordinated to the metal, so the stereoselectivity is expected to improve as the chirogenic element of the ligand gets closer to the metal center.

This study reports the synthesis of diastereomeric pure 8-substituted 10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-ols (**5**–**9**), and **13**–**14**. These ligands in the enantioselectively catalyzed addition of diethylzinc to substituted benzaldehydes were investigated.

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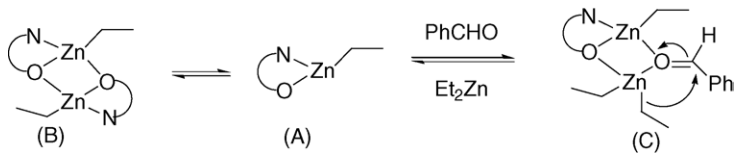
doi:10.1016/j.molcata.2005.07.047



Scheme 1.

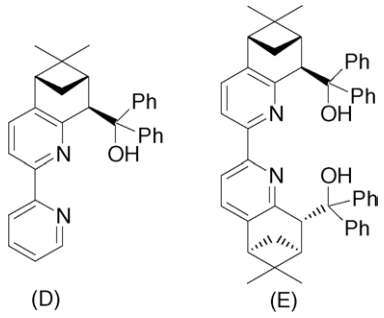
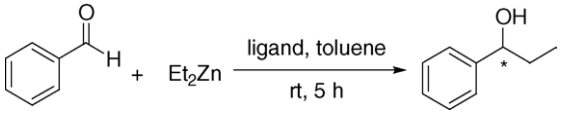


Fig. 1. The structures of chiral bipyridyl-type ligand (D) and (E).

Table 1
Asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of various chiral ligands



Entry	Ligands	Yield (%)	Ee (%)
1	**5**	86	30
2	**6**	81	70
3	**7**	76	28
4	**8**	61	30
5	**9**	62	30
6	**13**	73	70
7	**14**	<5	53

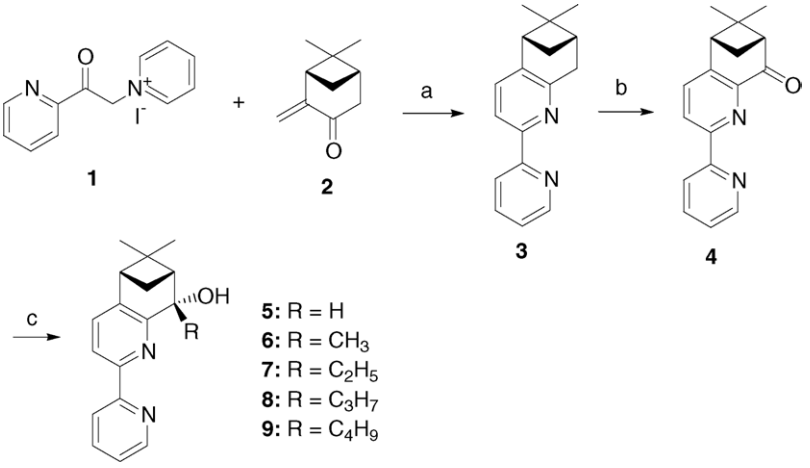
2. Results and discussion

2.1. Synthesis of the ligands 5–9 and 13–14

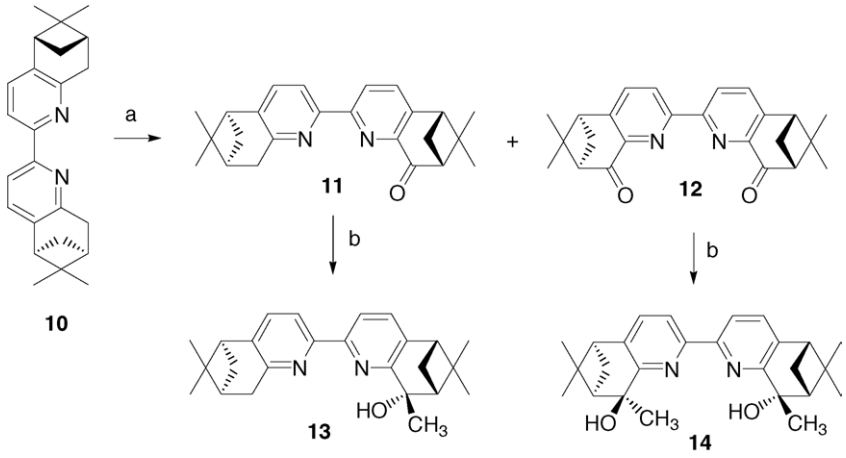
Scheme 2 outlines the synthesis of ligands **5**–**9**. (1*R*)-(+)-α-Pinene was readily photooxygenated in the presence of acetic anhydride, pyridine, DMAP and TPP to produce directly α,β-unsaturated ketone **2** [85]. Moreover, 2-acetylpyridine was heated with iodine in pyridine at 100–110 °C for 3 h and recrystallized from ethanol to yield pyridinium salt **1** [86]. Compounds **1** and **2** were heated with ammonium acetate in glacial acetic acid at 100–110 °C overnight to yield bipyridyl-type compound **3** [87–88]. Compound **3** was oxidized to ketone **4** using potassium permanganate, and then reduced using sodium borohydride, lithium aluminum hydride or diisobutylaluminum hydride to yield the corresponding alcohol **5** ($NaBH_4$, 97% de; $LiAlH_4$, 97% de; DIBAL-H, 81% de). When sodium borohydride and lithium aluminum hydride were used as reductants, more diastereoselective products were produced. Compounds **6**–**9** were prepared by reacting compound **4** with the corresponding Grignard reagents. Compound **10** [84] was treated with potassium permanganate to produce ketone **11** (24% yield) and diketone **12** (33% yield), and to recover the starting material (15%). Subsequently, compounds **11** and **12** reacted with methylmagnesium iodide to yield the corresponding alcohol **13** and diol **14** (Scheme 3).

2.2. Asymmetric addition of diethylzinc to benzaldehyde in the presence of various ligands

The asymmetric alkylation of benzaldehyde using diethylzinc in hexane at room temperature in the presence of 5 mol% of ligands yielded enantiomeric excesses of 1-phenyl-1-propanol, as shown in Table 1. The stereochemical outcome depends mainly



Scheme 2. (a) NH_4OAc, AcOH, 100–110 °C, 16 h; (b) $KMnO_4$, *t*-BuOH, 75–80 °C, 24 h; (c) (1) **5**: $NaBH_4$ or $LiAlH_4$ or DIBAL-H, THF; (2) **6**: MeMgI, Et_2O, rt, 1 h; (3) **7**: EtMgBr, Et_2O, rt, 1 h; (4) **8**: PrMgBr, Et_2O, rt, 1 h; (5) **9**: BuMgBr, Et_2O, rt, 1 h.



Scheme 3. (a) $KMnO_4$, *t*-BuOH, H_2O, 75–80 °C, 24 h; (b) MeMgI, Et_2O, rt,1 h.

on the stereogenic centers in the 8-position of the pyridyl-pinane-ring (ligand **6**). In fact, the other substituent on the 8-position of the ligands did not increase the stereoselectivity. The optimized ligands were **6** (70% ee), and **13** (70% ee). Therefore the following asymmetric reactions were performed in the presence of ligand **6**.

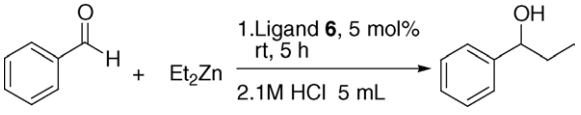
2.3. Asymmetric addition of diethylzinc to benzaldehyde using ligand *6* in various solvents

The asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of ligand **6** in various solvents at room temperature, yielded enantiomeric excesses of 1-phenyl-1-propanol, as presented in Table 2. The optimal solvent was hexane (75% ee).

2.4. Asymmetric addition of diethylzinc to benzaldehyde using ligand *6* at various temperatures

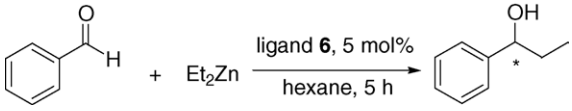
The asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of ligand **6** at various temperatures, yielded enantiomeric excesses of 1-phenyl-1-propanol, as shown in Table 3. The optimal temperature was 20 °C (75% ee).

Table 2
Asymmetric addition of diethylzinc to benzaldehyde using ligand **6** in various solvents



Entry	Solvent	Yield (%)	Ee (%)
1	Acetonitrile	30	50
2	Diethy ether	59	73
3	Dichloromethane	74	60
4	Toluene	81	70
5	Toluene/hexane	67	73
6	Hexane	83	75

Table 3
Enantiomeric excess of the alkylation of benzaldehyde in the presence of **6** at various temperatures



Entry	Temperature (°C)	Yield (%)	Ee (%)
1	40	51	62
2	20	83	75
3	0	63	69
4	−20	<5[a]	58

[a] The reaction was stirred for 72 h.

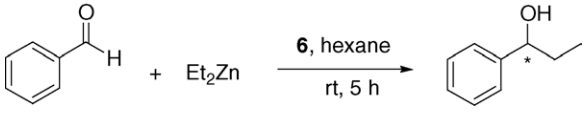
2.5. Asymmetric addition of diethylzinc to benzaldehyde using various amount of ligand *6*

The asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of various amounts of ligand **6**, yielded enantiomeric excesses of 1-phenyl-1-propanol, as indicated in Table 4. The optimal amount of catalyst was 5 mol% of ligand **6** (75% ee).

2.6. Asymmetric addition of diethylzinc to substituted benzaldehydes in the presence of ligand *6*

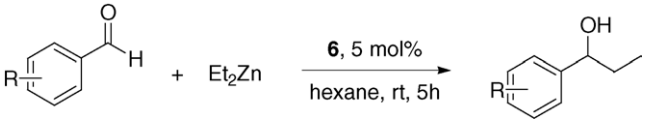
The enantioselective formation of carbon-carbon bonds via the asymmetric addition of dialkylzinc to aldehydes continues

Table 4
Enantiomeric excess of the alkylation of benzaldehyde in the presence of various amount of ligand **6**



Entry	**6** (mol%)	Yield (%)	Ee (%)
1	1	58	66
2	5	83	75
3	10	60	74
4	20	4	68

Table 5
Asymmetric alkylation of substituted benzaldehyde using diethylzinc, in the presence of ligand **6**



Entry	R	Yield (%)[b]	Ee (%)	$[\alpha]_D^{18}$ (c) CH_2Cl_2	Configuration
1	H	83	75	−31.6 (1.35)	*S*
2	*o*-OCH_3	85	56	−12.7 (1.30)	*S*
3	*m*-OCH_3	76	68	−21.2 (1.32)	N/A[a]
4	*p*-OCH_3	66	58	−22.5 (1.24)	*S*
5	*o*-Cl	41	–	−32.9 (1.31)	*S*
6	*m*-Cl	36	62	−22.3 (1.00)	*S*
7	*p*-Cl	42	63	−25.0 (1.14)	*S*
8	*o*-CH_3	37	78	−42.9 (0.97)	*S*
9	*m*-CH_3	43	45	−17.8 (1.26)	N/A[a]
10	*p*-CH_3	31	65	−27.7 (1.24)	*S*
11	*m*-$N(CH_3)_2$	8	79	−30.2 (1.36)	N/A[a]
12	*m*-CN	51	51	−18.4 (1.39)	N/A[a]
13	*p*-CN	89	46	−17.3 (1.23)	N/A[a]

[a] The configurations were not determined.
[b] The yields were obtained using 1 mmol of substituted benzaldehydes and weighted after purified by flash chromatography.

to be very important in developing the enantioselective methodology [8,9]. Numerous pyridine-alcohol derivatives have been established to be effective chiral catalysts [68–79], so following research in this area [84], the authors evaluated the potential utility of new ligands **5**–**9** and **13**–**14** in this catalytic process. Substituted benzaldehyde was asymmetrically alkylated in the presence of catalyst **6**, as described below. Diethylzinc was added to a solution of ligand **6** (5 mol%) and aldehydes in hexane at room temperature, and stirred for 5 h. The reaction was quenched by adding 1N HCl. Following purification by flash chromatography, the enantiomeric excess of the product was determined by high performance liquid chromatography (HPLC), and the yields, %ee and the specific rotation were as presented in Table 5. The absolute configurations of all products were determined by comparing the signs of the specific rotations (α_D) [88–91]. The stereochemical outcome mainly depends on the stereogenic centers at the 8-position of the pyridyl-pinane-ring (ligand **6**). In fact, the ligands with further substituents at the 8-position did not exhibit a higher stereoselectivity. The enantioselectivities obtained using the 8-methyl-substituted ligand **6** were in the range 45–79% ee. All products were in the *S*-configuration, as determined by comparing the signs of the specific rotations (α_D) in the literature. The electron-releasing substituents on the *meta*-position of the substituted benzaldehydes yielded high enantioselectivity. The electron-releasing substituents of benzaldehydes may promote the π–π interaction between the pyridine group of ligand **6** and the aromatic ring of benzaldehyde. Therefore, the aromatic ring of benzaldehydes may be fixed tightly, such that the *Si*-face of the carbonyl group is preferentially alkylated increasing the enantioselectivity.

The correlation between the Hammett substituent constants and the enantiomeric excesses in the alkylation of *meta*-substituted benzaldehydes using diethylzinc, was strong. Importantly, the stronger electron-releasing substituents at the *meta*-position increased the enantiomeric excesses (*m*-NMe_2, 79%), whereas the stronger electron-withdrawing substituents at the *meta*-position reduced enantiomeric excesses (*m*-Cl, 62%; *m*-CN, 51%) (Fig. 2). The stronger electron-withdrawing and -releasing substituents at the *para*-position reduced the enantiomeric excesses (*p*-CN, 46%; *p*-OMe, 58%), while the moderately electron-releasing and -withdrawing substituents at the *para*-position increased enantiomeric excesses (*p*-Me, 65%; *p*-Cl, 63%) (Fig. 3).

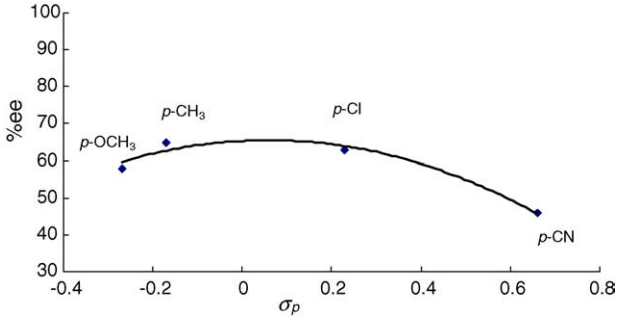


Fig. 2. The correlation of substituent constants (σ_p) and the enantiomeric excess of the alkylation of *para*-substituted benzaldehydes in the presence of **6**.

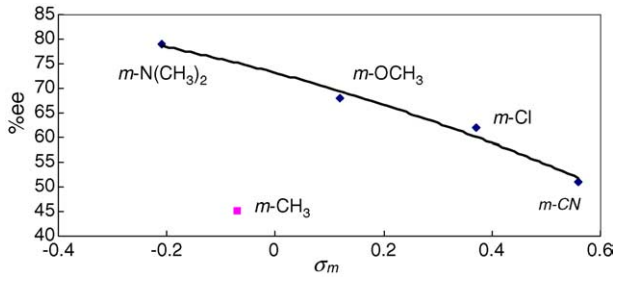


Fig. 3. The correlation of substituent constants (σ_m) and the enantiomeric excess of the alkylation of *meta*-substituted benzaldehydes in the presence of **6**.

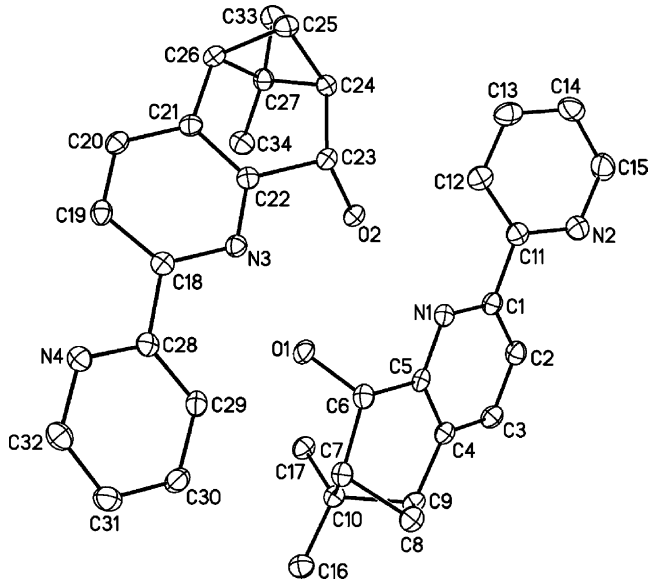


Fig. 4. Crystal structure of (1*S*,7*S*,8*R*)-(+)-10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-ol **5**.

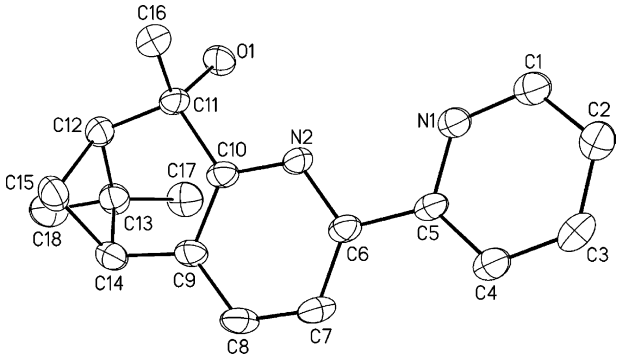


Fig. 5. Crystal structure of (1*S*,8*S*,9*R*)-(+)-8,10,10-trimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-ol **6**.

2.7. X-Ray crystallography

A sample of (1*S*,7*S*,8*R*)-(+)-10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-ol **5** was prepared from **4**. An analysis of the X-ray crystal structure (Fig. 4) verified that the hydrogenation of carbonyl group on the less hindered side produced highly diastereoselective product **5**. Crystal data: single crystals (crystal size: 0.30 mm × 0.20 mm × 0.10 mm) of **5** are monoclinic at 100(2) K, space group, *P*2(1)2(1)2(1) with $a = 10.3946(6)$ Å, $\alpha = 90^\circ$, $b = 11.0188(7)$ Å, $\beta = 90^\circ$, $c = 23.7162(14)$ Å, $\gamma = 90^\circ$ and $Z = 8$ ($D_{calcd} = 1.312$ Mg/m^3; absorption coefficient = 0.086 mm^{-1}). A total 6746 [R(int) = 0.0379] independent data were collected (θ range for collection: 1.72–28.31°; completeness to $2\theta = 28.31^\circ$: 99.8%; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2: 0.966; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0420$, $wR_2 = 0.0945$; R indices (all data): $R_1 = 0.0507$, $wR_2 = 0.0975$; largest difference peak and hole: 0.282 and −0.271 e Å^{-3}).

A sample of (1*S*,8*S*,9*R*)-(+)-8,10,10-trimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$] undeca-2(7),3,5-trien-8-ol **6** was prepared from **4**. An X-ray crystal structure (Fig. 5) verified that methylation of the carbonyl group using methylmagnesium bromide from the less hindered side to produced highly diastereoselective product **6**. Crystal data: single crystals (crystal size: 0.20 mm × 0.10 mm × 0.10 mm) of **6** are monoclinic at 295 K, space group, *P*2(1) with $a = 7.4035(3)$ Å, $\alpha = 90^\circ$, $b = 8.0574(3)$ Å, $\beta = 90.675(2)^\circ$, $c = 28.5185(10)$ Å, $\gamma = 90^\circ$ and $Z = 4$ ($D_{calcd} = 1.303$ Mg/m^3; absorption coefficient = 0.236 mm^{-1}). A total 7652 independent data were collected (θ range for collection: 0.71 to 28.27°; completeness to $2\theta = 28.27^\circ$: 99.9%; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2: 0.821; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0396$, $wR_2 = 0.0940$; R indices (all data): $R_1 = 0.0721$, $wR_2 = 0.1077$; Largest difference peak and hole: 0.0274 and −0.267 e Å^{-3}).

3. Conclusions

In summary, a new class of chelating ligands of type **6** was prepared. Their activity in catalyzing the asymmetric addition of diethylzinc to substituted benzaldehydes was demonstrated. These ligands were prepared from highly enantiopure (1*R*)-(+)-α-pinene (>97% ee). Bipyridyl alcohol **6** acts as an interesting chiral catalyst of the enantioselective addition of diethylzinc to various substituted benzaldehydes, providing alcohols of the (*S*)-configuration and enantiomeric excess, generally ranged from 45 to 79%. Importantly, the electron-releasing substituents at the *meta*-position of the substituted benzaldehydes exhibited high enantioselectivity during alkylation using diethylzinc. Other asymmetric reactions are currently being examined to rationalize this correlation.

4. Experimental

4.1. General methods

All reactions were carried out in anhydrous solvents. THF and diethyl ether were distilled from sodium-benzophenone under argon. Toluene, CH_3CN, CH_2Cl_2, and hexane were distilled from CaH_2. ^{1}H NMR spectra were acquired at 300 or 500 MHz (indicated in each case), and ^{13}C NMR were acquired at 125.7 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were determined on a Micromass Platform II mass spectrometer at a 70 eV. High resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on an ATI Mattson spectrometer. All asymmetric reactions were carried out in dry glassware under nitrogen using a standard glovebox. Enantiomeric excesses were determined on a Lab Alliance Series III high performance liquid chromatography with Chiralcel OD-H chiral column (Daicel Chemical Industries Ltd.). Optical rotations were measured on a JASCO P-1010 polarimeter at the indicated temperature with a sodium lamp (D line,

589 nm). Flash column chromatography was performed using MN silica gel 60 (70–230 mesh) purchased from Macherey-Nagel. Et_2Zn (1 M) solution in hexane was purchased from Sigma–Aldrich Co.

4.2. General procedure for the synthesis of 8-alkyl-10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-ol

*4.2.1. (1S,9S)-5-Furan-2-yl-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (**3**)*

A mixture of compound **1** (2.67 g, 8.2 mmol), compound **2** (3.21 g, 9.8 mmol), and ammonium acetate (5.05 g, 65.6 mmol) in glacial acetic acid (20.0 mL) under argon atmosphere was heated at 100–110 °C for 3 h. After cooling to room temperature, the reaction mixture was filtrated through celite to remove the precipitate, and the filtrate was basified by aqueous solution of sodium hydroxide until the aqueous solution become basic. The aqueous solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel (The silica gel was deactivated by ammonia gas.) as the stationary phase and using ethyl acetate–hexane (1:19, 1:9) as the mobile phase producing compound **3** (1.52 g, 6.1 mmol). Yield: 74%. $[\alpha]_D^{24}$ + 100° (c 1.07, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.67–8.64 (m, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.80–7.75 (m, 1H), 7.34–7.31 (d, J = 6.9 Hz, 1H), 7.27–7.24 (m, 1H), 3.18 (d, J = 8.0 Hz, 2H), 2.82–2.79 (m, 1H), 2.74–2.67 (m, 1H), 2.42–2.40 (m, 1H), 1.42 (s, 3H), 1.31 (d, J = 9.5 Hz, 1H), 0.68 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 156.4, 156.0, 152.8, 148.8, 142.7, 137.2, 134.1, 123.2, 121.2, 118.3, 46.4, 40.1, 39.5, 36.5, 31.8, 26.0, 21.3. IR (KBr): 2983, 2917, 1577, 1556, 1432, 796, 754 cm^{-1}. MS m/z: 251 (M^+ + H, 100), 239 (6), 235 (4). HRMS-FAB (m/z): [M^+] calcd for $C_{17}H_{18}N_2$, 250.1470; found 250.1463.

*4.2.2. 10,10-Dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-one (**4**)*

A solution of compound **3** (2.08 g, 8.3 mmol), *tert*-butyl alcohol (100.0 mL) and water (20.0 mL) was heated at 75–80 °C, and added potassium permanganate (7.03 g, 44.4 mmol). After stirred for 12 h, another portion of potassium permanganate (7.03 g, 44.4 mmol) was added, and stirred for 12 h. The hot reaction mixture was filtrated through celite to remove the manganese dioxide, and washed with 20% *tert*-butyl alcohol in water (40 mL). The filtrate was added 20% aqueous solution of sodium bisulfite (10.0 mL) to reduce the remained potassium permanganate, and then the *tert*-butyl alcohol was removed by rotary evaporator. The remained aqueous solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19, 1:4, 3:7) as the mobile phase producing compound **4** (1.70 g, 6.4 mmol). Yield: 77%. mp 187–188 °C. $[\alpha]_D^{22}$ + 184° (c 1.15, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.65–8.67 (m, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.83–7.82 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.34–7.31 (m, 1H), 3.16–3.10 (m, 3H), 2.23–2.17 (m, 2H), 1.63 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 199.7, 154.7, 154.4, 148.1, 147.6, 146.8, 137.8, 135.3, 124.3, 124.1, 122.1, 58.2, 52.6, 47.3, 39.2, 26.6, 22.6. IR (KBr): 2969, 1708, 1587, 1434, 1187, 792 cm^{-1}. MS m/z: 265 (M^+ + H, 100), 239 (32). HRMS-FAB (m/z): [M^+] calcd for $C_{17}H_{16}N_2O$, 264.1263; found 264.1261.

*4.2.3. (1S,7S,8R)-(+)-10,10-Dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-ol (**5**)*

A mixture of lithium aluminum hydride (15.2 mg, 0.4 mmol) in tetrahydrofuran (10.0 mL) was added a solution of compound **4** (106.0 mg, 0.4 mmol) in tetrahydrofuran (5.0 mL) by canula at room temperature. The reaction was traced by TLC until compound **4** was completely consumed. The reaction was quenched by adding two drops of water, and dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19, 1:5, 3:7) as the mobile phase producing compound **5** (90.0 mg, 0.3 mmol). Yield: 87%. $[\alpha]_D^{17}$ + 125° (c 1.01, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.69–8.67 (m, 1H), 8.4 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 7.9 Hz, 1H), 7.82–7.81 (m, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.32–7.30 (m, 1H), 5.04 (d, J = 3.1 Hz, 1H), 3.26 (s, 1H), 2.84–2.76 (m, 2H), 2.67–2.62 (m, 1H), 1.48 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 157.9, 153.6, 151.4, 148.4, 142.7, 138.3, 135.1, 124.1, 121.4, 120.2, 73.4, 47.1, 46.2, 40.5, 34.0, 26.6, 23.0. IR (KBr): 3401, 3243, 2911, 1433, 1060, 782 cm^{-1}. MS m/z: 267 (M^+ + H, 100), 239 (26). HRMS-FAB (m/z): [M^+] calcd for $C_{17}H_{18}N_2O$, 266.1419; found 266.1413.

*4.2.4. (1S,8S,9R)-(+)-8,10,10-Trimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^{2,7}] undeca-2(7),3,5-trien-8-ol (**6**)*

To a mixture of magnesium (100.0 mg, 4.1 mmol) in diethyl ether (40.0 mL) in a two-neck round-bottom flask equipped with a reflux condenser was added iodomethane (0.63 mL, 4.1 mmol) in a dropwise, manner under argon atmosphere. After 1 h, all magnesium was consumed. A solution of compound **4** (264 mg, 1.0 mmol) in tetrahydrofuran (30.0 mL) was added to the fresh prepared MeMgI in a dropwise manner at 0 °C, and then stirred at room temperature for 1 h. The reaction was quenched by water, and the aqueous solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (3:7) as the mobile phase producing compound **6** (174.0 mg, 0.6 mmol). Yield: 62%. $[\alpha]_D^{19}$ + 73° (c 1.02, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.67–8.65 (m, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.2 (d, J = 7.8 Hz, 1H), 7.81–7.78 (m, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.30–7.26 (m, 1H), 2.86–2.76 (m, 3H), 2.42–2.38 (m, 1H), 1.65 (s, 3H), 1.56 (d, J = 9.1 Hz, 1H), 1.49 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 160.0, 155.9, 153.2, 148.7, 140.8, 137.0, 133.8, 123.3, 120.8, 119.3,

76.0, 51.7, 47.1, 43.1, 34.5, 28.9, 26.9, 23.9. IR (KBr): 3419, 2923, 1432, 1099, 781 cm^{-1}. MS *m/z*: 281 (M^+ + H, 100), 263 (17). HRMS-FAB (*m/z*): [M^+] calcd for $C_{18}H_{20}N_2O$, 280.1576; found 280.1575.

*4.2.5. (1S,8S,9R)-(+)-8-Ethyl-10,10-dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^{2,7}] undeca-2(7),3,5-trien-8-ol (**7**)*

Compound **7** was prepared using the same method as 4.2.4, and ethylmagnesium bromide was prepared from bromoethane (0.32 mL, 4.3 mmol). The crude product was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:9) as the mobile phase producing compound **7** (25.0 mg, 0.1 mmol). Yield: 9%. $[\alpha]_D^{17}$ + 65° (c 0.93, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.66–8.64 (m, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 782–7.76 (m, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.29–7.25 (m, 1H), 2.79–2.76 (m, 2H), 2.55–2.53 (m, 1H), 2.20–2.18 (m, 1H), 1.84–1.79 (m, 1H), 1.57 (d, *J* = 9.6 Hz, 1H), 1.56 (s, 3H), 1.08 (m, 3H), 0.75 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 161.2, 155.1, 151.8, 148.0, 141.2, 138.1, 133.9, 123.6, 121.0, 119.4, 77.5, 47.5, 47.0, 42.8, 33.1, 29.7, 27.1, 23.8, 14.1. IR (KBr): 3568, 3419, 2933, 2359, 1432 cm^{-1}. MS *m/z*: 295 (M^+ + H, 100), 277 (19). HRMS-FAB (*m/z*): [M^+] calcd for $C_{19}H_{22}N_2O$, 294.1732; found 294.1718.

*4.2.6. (1S,8S,9R)-(+)-10,10-Dimethyl-8-propyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.0^{2,7}] undeca-2(7),3,5-trien-8-ol (**8**)*

Compound **8** was prepared using the same method as 4.2.4, and propylmagnesium bromide was prepared from bromopropane (0.32 mL, 4.3 mmol). The crude product was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19) as the mobile phase producing compound **8** (62.0 mg, 0.2 mmol). Yield: 20%. $[\alpha]_D^{23}$ + 33° (c 1.14, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.67–8.65 (m, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.8 (m, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.30–7.26 (m, 1H), 2.79–2.76 (m, 2H), 2.55–2.51 (m, 2H), 2.10–2.08 (m, 1H), 1.78–1.75 (m, 2H), 1.62–1.59 (d, *J* = 9.7 Hz, 1H), 1.49 (s, 3H), 0.99–0.92 (m, 3H), 0.74 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 161.4, 154.8, 151.3, 147.7, 141.4, 138.6, 134.0, 123.7, 121.2, 119.5, 77.5, 48.1, 47.0, 43.0, 42.8, 33.1, 27.0, 23.8, 15.8, 14.7. IR (KBr): 3426, 2956, 2869, 2360, 1432, 779 cm^{-1}. MS *m/z*: 309 (M^+ + H, 100), 291 (39), 283 (21), 275 (10). HRMS-FAB (*m/z*): [M^+] calcd for $C_{20}H_{24}N_2O$, 308.1889; found 308.1888.

*4.2.7. (1S,8S,9R)-(+)-10,10-Dimethyl-8-butyl-5-pyridin-2-4yl-6-aza-tricyclo[7.1.1.0^{2,7}] undeca-2(7),3,5-trien-8-ol (**9**)*

A mixture of magnesium (73.0 mg, 3.0 mmol) in diethyl ether (20.0 mL) in a two-neck round-bottom flask equipped with a reflux condenser and under argon atmosphere, was added bromobutane (0.33 mL, 3.0 mmol) drop wisely, and after 1 h, all magnesium was consumed. A solution of compound **4** (264.0 mg, 1.0 mmol) in tetrahydrofuran (30.0 mL) was added to the fresh prepared BuMgBr drop wisely at 0 °C the solution became purple color, and stirred at room temperature for 1 h. The reaction was quenched by water, and the aqueous solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19) as the mobile phase producing compound **9** (57.0 mg, 0.18 mmol). Yield: 18%. $[\alpha]_D^{23}$ + 29° (c 1.16, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.66–8.64 (m, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.80 (m, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.29–7.27 (m, 1H), 2.79–2.73 (m, 2H), 2.54–2.50 (m, 1H), 2.15–2.05 (m, 1H), 1.85–1.65 (m, 2H), 1.60 (d, *J* = 9.5 Hz, 1H), 1.49 (s, 3H), 1.39–1.34 (m, 2H), 1.25 (s, 1H), 0.94 (m, 3H), 0.74 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 161.3, 155.0, 151.6, 147.9, 141.3, 138.3, 134.0, 123.6, 121.1, 119.4, 77.5, 48.1, 47.0, 42.7, 40.4, 33.1, 27.1, 24.8, 23.8, 23.3, 14.2. IR (KBr): 3419, 2931, 2867, 1432, 781 cm^{-1}. MS *m/z*: 323 (M^+ + H, 100), 305 (27), 279 (7). HRMS-FAB (*m/z*): [M^+] calcd for $C_{21}H_{26}N_2O$, 322.2045; found 322.2043.

*4.3. General procedure for the synthesis of (1S,1′S,8S,8′S,9R,9′R)-(+)-8,10,10,8′,10′,10′-hexamethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′,4′,6′-hexaene-8,8′-diol (**14**)*

*4.3.1. (1S,1′S,9R,9′S)-(+)-10,10,10′,10′-Tetramethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}] undecyl]-2(7),3,5,2′,4′,6′-hexaen-8-one (**11**) and (1S,1′S,9R,9′R)-(+)-10,10,10′,10′-tetramethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′,4′,6′-hexaene-8,8′-dione(**12**)*

A solution of compound **10** (172.0 mg, 0.5 mmol), *tert*-butyl alcohol (100.0 mL) and water (20.0 mL) was heated at 75–80 °C, and added potassium permanganate (791.0 mg, 5.0 mmol). After stirred for 12 h, another portion of potassium permanganate (791.0 mg, 5.0 mmol was added, and stirred for 12 h. The hot reaction mixture was filtrated through celite to remove the manganese dioxide, and washed with 20% *tert*-butyl alcohol in water (40.0 mL). The filtrate was added 20% aqueous solution of sodium bisulfite (10.0 mL) to reduce the remained potassium permanganate, and then the *tert*-butyl alcohol was removed by rotary evaporator. The remained aqueous solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19, 1:4, 1:1, 3:1) as the mobile phase producing compound **11** (42 mg, 0.12 mmol), yield 24%; compound **12** (61.0 mg, 0.16 mmol), yield 33%; recovered starting material **10** (25.0 mg, 0.07 mmol), 15%.

Compound **11**: mp 209–210 °C. $[\alpha]_D^{24}$ + 173° (c 1.04, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.48 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 3.18–3.17 (m, 2H), 3.13–3.09 (m, 2H), 2.84–2.80 (m, 1H), 2.73–2.70 (m, 1H), 2.41–2.40 (m, 1H), 2.21–2.19 (m, 1H), 2.17 (s, 3H), 1.62 (s, 3H), 1.32 (d, *J* = 9.6 Hz, 1H), 0.81 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$,

δ): 199.8, 155.8, 153.9, 151.6, 147.6, 146.5, 143.5, 135.5, 135.2, 124.6, 119.7, 58.2, 52.7, 47.3, 46.4, 39.9, 39.5, 39.2, 35.9, 31.7, 29.6, 26.7, 25.9, 22.6, 21.2. IR (KBr): 2919, 1708, 1434 cm^{-1}. MS *m/z*: 359 (M^+ + H, 100), 327 (40). HRMS-FAB (*m/z*): [M^+] calcd for $C_{24}H_{26}N_2O$, 358.2045; found 358.2045.

Compound **12**: mp 271–272 °C. $[\alpha]_D^{24}$ + 231° (c 1.04, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.68 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 2H), 3.15–3.10 (m, 6H), 2.26–2.20 (m, 2H), 1.63 (s, 6H), 0.82 (s, 6H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 200.0, 154.7, 147.4, 146.8, 135.2, 124.7, 58.2, 52.8, 47.3, 39.3, 26.7, 22.6. IR (KBr): 3403, 2952, 2356, 2329, 1710 cm^{-1}. MS *m/z*: 373 (M^+ + H, 50), 371 (100). HRMS-FAB (*m/z*): [M^+] calcd for $C_{24}H_{24}N_2O_2$, 372.1838; found 372.1833.

*4.3.2. (1S,1′S,8S,8′S,9R)-(+)-8,10,10,10′,10′-Pentamethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′,4′,6′-hexaen-8-ol (**13**)*

To a mixture of magnesium (18.0 mg, 0.75 mmol) in diethyl ether (10.0 mL) in a two-neck round-bottom flask equipped with a reflux condenser and under argon atmosphere, was added iodomethane (0.16 mL, 1.0 mmol) drop wisely, and after 1 h, all magnesium was consumed. A solution of compound **11** (90.0 mg, 0.25 mmol) in tetrahydrofuran (30.0 mL) was added to the fresh prepared MeMgI drop wisely at 0 °C, and stirred at room temperature for 1 h. The reaction was quenched by water, and the aqueous solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:9) as the mobile phase producing compound **13** (42 mg, 0.11 mmol), yield 45%, and recovered starting material (25.0 mg, 0.07 mmol) 28%. mp 72–74 °C. $[\alpha]_D^{17}$ + 75° (c 1.68, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.15–8.04 (m, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 3.18–3.17 (m, 2H), 2.80–2.75 (m, 5H), 2.40–2.38 (m, 2H), 1.64 (s, 3H), 1.54 (d, *J* = 9.5 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 0.75 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 160.2, 156.1, 153.0, 152.9, 142.3, 140.3, 134.4, 133.8, 119.1, 117.8, 76.0, 51.8, 47.2, 46.4, 43.2, 40.1, 39.5, 36.3, 34.5, 31.9, 28.9, 27.0, 26.0, 23.9, 21.3. IR (KBr): 3418, 2971, 2922, 1434 cm^{-1}. MS *m/z*: 375 (M^+ + H, 100). HRMS-FAB (*m/z*): [M^+] calcd for $C_{25}H_{30}N_2O$, 374.2358; found 374.2352.

*4.3.3. (1S,1′S,8S,8′S9R,9′R)-(+)-8,10,10,8′,10′,10′-Hexamethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′,4′,6′-hexaene-8,8′-diol (**14**)*

To a mixture of magnesium (31.0 mg, 0.25 mmol) in diethyl ether (10.0 mL) equipped with a reflux condenser and under argon atmosphere, was added iodomethane (0.2 mL, 1.30 mmol) drop wisely, and after 1 h, all magnesium was consumed. A solution of compound **12** (93.0 mg, 0.25 mmol) in tetrahydrofuran (30.0 mL) was added to the fresh prepared MeMgI drop wisely at 0 °C, and stirred at room temperature for 1 h. The reaction was quenched by water, and the aqueous solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous magnesium sulfate. After filtering and concentration, the resulting residue was purified by flash column chromatography using silica gel as the stationary phase and using ethyl acetate–hexane (1:19, 1:9) as the mobile phase producing compound **14** (30.0 mg, 0.07 mmol), yield 29%. mp 89–90 °C. $[\alpha]_D^{19}$ + 71° (c 1.49, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.22 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 2.85–2.77 (m, 6H), 2.42–2.38 (m, 2H), 1.65 (s, 6H), 1.54 (d, *J* = 9.2 Hz, 2H), 1.48 (s, 6H), 0.79 (s, 6H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 159.9, 153.7, 140.4, 134.0, 119.2, 76.0, 51.9, 47.2, 43.2, 34.5, 29.0, 27.0, 24.1. IR (KBr): 3458, 2924, 1559, 1430, 1101 cm^{-1}. MS *m/z*: 405 (M^+ + H, 100), 387 (8), 371 (6). HRMS-FAB (*m/z*) [M^+] calcd for $C_{26}H_{32}N_2O_2$, 404.2464; found 404.2468.

4.4. Asymmetric addition of diethylzinc to aldehydes

4.4.1. General procedure for the enantioselective addition of diethylzinc to aldehydes catalyzed by chiral ligands

Aldehyde (0.5 mmol) was added to a solution of ligand (5.0 mol%) in solvent (1.0 mL) at room temperature, and then a solution of diethylzinc (1.0 mL, 1 M in hexane) was added and stirred for 5 h. The reaction was quenched by adding 1N HCl (5.0 mL), and the reaction mixture was extracted three times with dichloromethane. The combined extracts then were dried over anhydrous magnesium sulfate. After filtering and concentration, the residue was purified by flash column chromatography using silica gel as the stationary phase and ethyl acetate–hexane as the mobile phase, thus producing products. The enantiomeric excess of products were determined by HPLC (Chiralcel OD-H column, flow rate 0.25 mL/min, and KR100-5CHI-DMB column, flow rate 0.5 mL/min, 10% 2-propanol in hexane, 254 nm UV detector).

4.4.2. Asymmetric addition of diethylzinc to substituted benzaldehydes

4.4.2.1. 1-Phenyl-propan-1-ol. The enantioselectivity was determined by chiral HPLC [Chiralcel OD-H column, 10% 2-propanol/hexane, 0.25 mL/min, λ = 254 nm, retention times: *R* (minor) 22.7 min, *S* (major) 24.4 min]. $[\alpha]_D^{17}$-32° (c 1.35, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.38–7.34 (m, 4H), 4.63–4.57 (m, 1H), 1.83–1.73 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H).

4.4.2.2. 1-(2-Methoxy-phenyl)-propan-1-ol. Retention times: *S* (major) 24.5 min, *R* (minor) 25.7 min]. $[\alpha]_D^{18}$-13° (c 1.30, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.31–7.21 (m, 2H), 6.98–6.87 (m, 2H), 4.81–4.75 (m, 1H), 3.85 (s, 3H), 2.53 (d, *J* = 6.3 Hz, 1H), 1.87–1.77 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

4.4.2.3. 1-(3-Methoxy-phenyl)-propan-1-ol. Retention times: minor 32.5 min, major 34.1 min]. $[\alpha]_D^{17}$-22° (c 1.32, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.34–7.24 (m, 1H), 6.98 (m, 2H), 6.83–6.80 (d, *J* = 8.0 Hz, 1H), 4.61–4.55 (m, 1H), 3.82 (s, 3H), 1.87–1.70 (m, 3H), 0.95–0.90 (t, *J* = 7.4 Hz, 3H).

4.4.2.4. 1-(4-Methoxy-phenyl)-propan-1-ol. Retention times: *R* (minor) 28.2 min, *S* (major) 29.8 min]. $[\alpha]_D^{17}$-23° (c 1.24, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.29–7.25 (d, *J* = 8.5 Hz, 2H), 6.90–6.87 (d, *J* = 8.7 Hz, 2H), 4.56–4.53 (m,

1H), 3.81 (s, 3H), 1.85–1.69 (m, 3H), 0.92–0.87 (t, J = 7.4 Hz, 3H).

4.4.2.5. 1-o-Tolyl-propan-1-ol. Retention times: *S* (major) 22.1 min, *R* (minor) 22.5 min]. $[\alpha]_D^{18}$-43° (c 0.97, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.47–7.45 (d, J = 7.2 Hz, 1H), 7.23–7.14 (m, 3H), 4.89–4.85 (m, 1H), 2.4 (s, 3H), 1.81–1.72 (m, 3H), 1.01–0.96 (t, J = 7.4 Hz, 3H).

4.4.2.6. 1-m-Tolyl-propan-1-ol. Retention times: minor 20.8 min, major 22.9 min]. $[\alpha]_D^{18}$-18° (c 1.26, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.24–7.08 (m, 4H), 4.59–4.54 (m, 1H), 2.36 (s, 3H), 2.04–1.72 (m, 3H), 0.94–0.90 (t, J = 7.4 Hz, 3H).

4.4.2.7. 1-p-Tolyl-propan-1-ol. Retention times: *S* (major) 22.0 min, *R* (minor) 22.7 min]. $[\alpha]_D^{18}$-28° (c 1.24, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.25–7.22 (d, J = 8.1 Hz, 2H), 7.17–7.14 (d, J = 7.9 Hz, 2H), 4.59–4.54 (m, 1H), 2.55 (s, 3H), 1.87–1.71 (m, 3H), 0.93–0.88 (t, J = 7.4 Hz, 3H).

4.4.2.8. 1-(2-Choloro-phenyl)-propan-1-ol. $[\alpha]_D^{18}$-33° (c 1.31, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.56–7.53 (d, J = 7.6 Hz, 1H), 7.34–7.19 (m, 3H), 5.10–5.04 (m, 1H), 1.92–1.90 (d, J = 3.8 Hz, 1H), 1.84–1.74 (m, 2H), 1.02–0.97 (t, J = 7.4 Hz, 3H).

4.4.2.9. 1-(3-Choloro-phenyl)-propan-1-ol. Retention times: *S* (major) 21.8 min, *R* (minor) 22.7 min]. $[\alpha]_D^{18}$-22.3° (c 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.35 (s, 1H), 7.30–7.19 (m, 3H), 4.62–4.56 (m, 1H), 1.85 (d, J = 3.5 Hz, 1H), 1.83–1.71 (m, 2H), 0.94–0.89 (t, J = 7.4 Hz, 3H).

4.4.2.10. 1-(4-Choloro-phenyl)-propan-1-ol. Retention times: *S* (major) 21.5 min, *R* (minor) 22.4 min]. $[\alpha]_D^{18}$-25° (c 1.14, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ):7.33–7.28 (m, 4H), 4.62–4.57 (m, 1H), 1.82–1.71 (m, 2H), 0.93–0.90 (t, J = 7.4 Hz, 3H).

4.4.2.11. 1-(3-Dimethylamino-phenyl)-propan-1-ol. Retention times: minor 24.7 min, major 27.2 min]. $[\alpha]_D^{17}$-30° (c 1.30, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.16–7.13 (m, 1H), 6.73–6.64 (m, 3H), 4.57–4.52 (t, J = 6.5 Hz, 1H), 2.96 (s, 6H), 1.83–1.77 (m, 3H), 0.96–0.91 (t, J = 7.4 Hz, 3H).

4.4.2.12. 3-(1-Hydroxy-propyl)-benzonitrile. Retention times: minor 31.5 min, major 32.5 min]. $[\alpha]_D^{17}$-18° (c 1.39, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.66 (s, 1H), 7.06–7.55 (m, 3H), 4.15–4.08 (m, 1H), 1.96–1.95 (d, J = 3.4 Hz, 1H), 1.80–1.74 (m, 2H), 0.95–0.90 (t, J = 7.3 Hz, 3H).

4.4.2.13. 4-(1-Hydroxy-propyl)-benzonitrile. Retention times: major 18.6 min, minor 19.0 min. The enantiomeric excess was determined by converting the product to its pivaloate. $[\alpha]_D^{17}$-17° (c 1.12, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.65–7.46 (d, J = 7.2 Hz, 2H), 7.44–7.41 (d, J = 6.8 Hz, 2H), 4.69 (s, 1H), 2.00 (s, 1H), 1.81–1.71 (m, 2H), 0.95–0.90 (t, J = 7.4 Hz, 3H).

Acknowledgements

The authors thank Ms. Hsu, L.M. at Instruments Center, National Chung Hsing University, and Ms. Lin, S.C., Ms. Tan, H.C., and Ms. Liao, F.L. at Instrument Center, National Tsing Hwa University for their help in obtaining HRMS, ^{13}C NMR spectra, and X-ray crystallography, and the National Science Council the Republic of China for financially supporting this research under contract NSC 92-2113-M-259-006.

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