Chiral Aryl Pyridyl Alcohols as Enantioselective Catalysts in the Addition of Diethylzinc to Substituted Benzaldehydes

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Chiral (5-aryl-10,10-dimethyl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-yl)-diphenyl-methanols were prepared from highly enantiopure (1*R*)-(+)-α-pinene (> 97% ee), and applied in the enantioselective addition of diethylzinc to substituted benzaldehydes, to yield alcohols with the (*S*)-configuration with an enantiomeric excess that typically ranges from 19 to 86%. Importantly, the electron-withdrawing substituents at the *meta*-position of the substituted benzaldehydes exhibited high enantioselectivity during alkylation using diethylzinc.

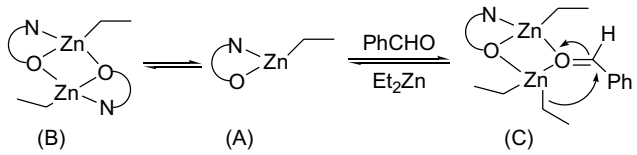
Keywords: Enantioselective catalysts; Diethylzinc; Benzaldehyde; Hammett substituent constants.

INTRODUCTION

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is extremely important in modern synthetic and pharmaceutical chemistry.[1-4] Among asymmetric catalysis of C-C bond-forming reactions, the enantioselective addition of diorganozinc reagents to aldehydes represents one of the most important and fundamental asymmetric reactions.[5,6] Since the first report by Oguni,[7] various chiral ligands, including α-amino alcohols,[8-21] BINOL,[22-26] salen,[27,28] TADDOL,[29] pyridyl alcohol,[30-37] and their derivatives have been used in this type of reaction. The chiral ligands with diol generally need a Lewis acid such as Ti(O-*i*-Pr)$_4$ to form a chiral environment to induce an asymmetric addition of diethylzinc to aldehydes. While the chiral ligands with amino alcohol or pyridyl alcohol form an asymmetric environment with two molecules of diethylzinc, one performs as Lewis acid, and another plays as a nucleophile.[38-41] The interaction between diethylzinc and an amino alcohol produces a chelated ethylzinc alkoxide (A), which is in equilibrium with a dimeric species (B).[39] Only the monomer is catalytically active, and the adjacent Zn and O ring atoms, displaying complementary Lewis acid and Lewis base characters, are believed to respectively coordinate one molecule of aldehyde and one molecule of diethylzinc to assemble the key species (C) where the ethyl group transfer occurs (Scheme I).

Given the authors' interest in the synthesis and application of chiral bipyridine derivatives as ligands in metal complexes in enantioselective catalysis,[42-44] the possibility of modifying the structure of **7** by changing the pyridyl group is of interest (Fig. 1). This substitution yields ligands **6-10**.[45,46] This characteristic affects the steric interactions between the ligand and the substrate, both coordinated to the metal, and, therefore, the stereoselectivity.

Scheme I



RESULTS AND DISCUSSION

Scheme II outlines the synthesis of compounds **6-10**. (1*R*)-(+)-α-Pinene was readily photooxygenated in the

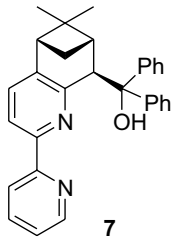


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Fig. 1.

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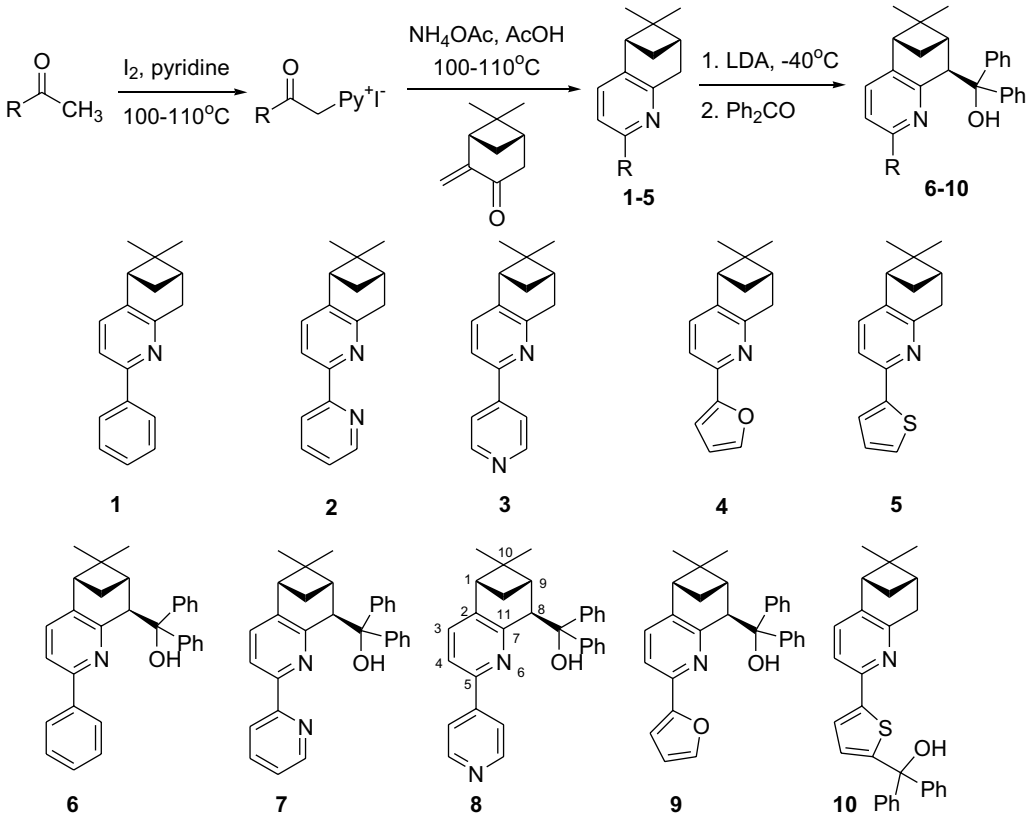
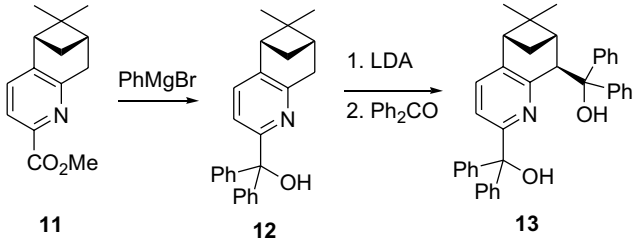
Scheme II



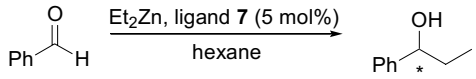
presence of acetic anhydride, pyridine, DMAP and TPP to yield directly α,β-unsaturated ketone.[47] Additionally, 2-acetyl-aromatic compounds were heated with iodine in pyridine at 100-110 °C for 3 h and recrystallized from ethanol to produce pyridinium salts.[48,49] Pyridinium salts and α,β-unsaturated ketone were then heated with ammonium acetate in glacial acetic acid at 100-110 °C overnight to yield the corresponding pyridines **1**-**5**.[49] Next, compounds **1**-**4** were treated with LDA at -40 °C, and a solution of benzophenone in THF was added to generate the corresponding alcohols **6**-**9**. Additionally, compound **5** treated under the same conditions did not yield the expected product, but gave compound **10**. Meanwhile, compound **13** was prepared from compound **11** by treating it with phenylmagnesium bromide to generate compound **12**, and then **12** was treated with LDA and benzophenone (Scheme III).

Scheme III



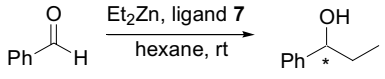
The asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of ligand **7** in hexane at various temperatures yielded the enantiomeric excesses of 1-phenyl-1-propanol, as presented in Table 1. The temperature does not significantly influence the enantiomeric excesses of 1-phenyl-1-propanol. The same reaction in the presence of various amounts of ligand **7** yielded enantiomeric excesses of 1-phenyl-1-propanol, as presented in Table 2. The optimal catalytic amount was 5 mol% of ligand **7** (65% ee). The asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of ligand **7** (5 mol%) in various solvents at room temperature yielded the enantiomeric excesses of 1-phenyl-1-propanol, as presented in Table 3. The optimized solvent was toluene (57% ee). Benzaldehyde was asymmetrically alkylated using diethylzinc in toluene at room temperature and in the presence of 5 mol% of ligand. Table 4 summarizes the enantiomeric excesses of 1-phenyl-1-propanol. The optimized ligand was **8** (67%

Table 1. Enantiomeric excesses of the alkylation of benzaldehyde in the presence of **7** at various temperatures



Entry	Temp. (ºC)	Yield (%)	Ee (%)
1	25	68	65
2	0	74	66
3	-20	70	67

Table 2. Enantiomeric excesses of the alkylation of benzaldehyde in the presence of various amounts of **7**

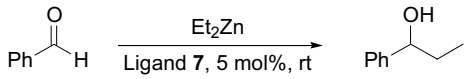


Entry	**8** (mol%)	Time (h)	Yield (%)	Ee (%)
1	5.0	8	68	65
2	1.0	8	53	62
3	0.5	8	63	62

ee).

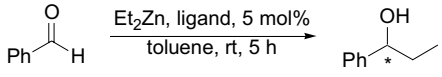
The enantioselective formation of carbon-carbon bonds by the asymmetric addition of dialkylzinc to aldehydes continues to be very important in the development of the enantioselective approach methodology.[5,6] Numerous pyridine-alcohol derivatives have been demonstrated to be effective chiral catalysts.[30-37] Therefore, following research in this field,[39] the authors evaluated the potential utility of ligands **6-10** and **13** in this catalytic process. Substituted benzaldehydes were asymmetrically alkylated in the presence of catalyst **8** as described below. Diethylzinc was added to a solution of ligand **8** (5 mol%) and aldehyde in toluene at room temperature and stirred for 5 h. The reaction was then quenched by adding 1M HCl. Following purification by flash chromatography, the enantiomeric excess of the product was determined by HPLC, and the yields, % ee and the specific rotation were as presented in Table 5. Next, the absolute configurations of all products were determined by comparing the signs of the specific rotations (α_D).[50-53] The stereochemical outcome depends mainly on the stereogenic centers in the 8-position of the pyridyl-pinane-ring (ligand **8**).[45] In fact, the benzaldehyde asymmetrically alkylated using diethylzinc was affected by the aromatic groups at the 5-position of ligands (Scheme II, Table 4). The enantioselectivities obtained using the 5-(pyridin-4-yl)-substituted ligand **8** were in the range 19-

Table 3. Asymmetric addition of diethylzinc to benzaldehyde using ligand **7** in various solvents



Entry	Solvent	Yield (%)	Ee (%)
1	Acetonitrile	60	40
2	Diethy ether	88	55
3	Dichloromethane	88	45
4	Toluene	88	57
5	Toluene/hexane	90	52
6	Hexane	85	55

Table 4. The asymmetric alkylation of benzaldehyde using diethylzinc in the presence of various chiral ligands

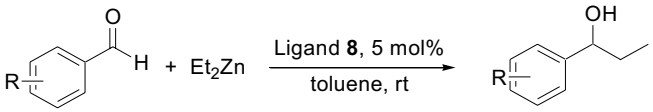


Entry	Ligands	Yield (%)	Ee (%)
1	**6**	70	60
2	**7**	88	57
3	**8**	80	67
4	**9**	75	55
5	**10**	63	9
6	**13**	-	8

86% ee. Some products were in the (*S*)-configuration, as determined by comparing the signs of the specific rotations (α_D) in the literature.[14] The electron-releasing substituents at the *meta*-position of the substituted benzaldehydes reduced enantioselectivity. The electron-withdrawing substituents of benzaldehydes may enhance π-π interaction between the pyridine group of ligand **8** 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 favors alkylation and increases enantioselectivity.

The correlation of Hammett substituent constants with enantiomeric excesses in the alkylation of *meta*-substituted benzaldehydes using diethylzinc was strong. Importantly, the stronger electron-releasing substituents at the *meta*-position corresponded to the lower enantiomeric excesses (*m*-OMe, *m*-Me, 66%), whereas the stronger electron-withdrawing substituents at the *meta*-position resulted in greater enantiomeric excesses (*m*-Cl, 86%; *m*-CN, 73%) (Fig. 4). Electron-releasing substituents at the *ortho*-position increased enantiomeric excesses (*o*-OMe, 54%; *o*-Me,

Table 5. The asymmetric alkylation of benzaldehyde using diethylzinc in the presence of ligand **8**



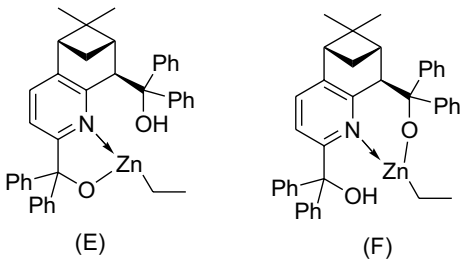
Entry	R	Yield (%)	Ee (%)	$[\alpha]^{T}_{D}$ (c), CH_2Cl_2 [α]/T °C/c (g/mL)	Configuration
1	H	80	67	-18.2/24.1/1.02	*S*
2	*o*-OCH_3	88	54	-14.4/25.0/1.02	*S*
3	*m*-OCH_3	90	66	-17.7/23.5/1.10	*N/A*[c]
4	*p*-OCH_3	90	60	-22.3/25.5/1.07[a]	*S*
5	*o*-Cl	77	19	+20.9/23.5/1.05[b]	*N/A*[c]
6	*m*-Cl	81	86	-16.9/25.5/1.13	*S*
7	*p*-Cl	93	70	-19.0/24.3/1.03	*S*
8	*o*-CH_3	44	67	+52.8/23.7/0.88[b]	*N/A*[c]
9	*m*-CH_3	70	66	-8.6/24.1/1.02	*N/A*[c]
10	*p*-CH_3	80	69	+15.3/23.5/1.01[b]	*N/A*[c]
11	*m*-CN	79	73	-0.18/24.0/0.30	*N/A*[c]
12	*p*-CN	80	67	+49.8/25.5/0.65[b]	*N/A*[c]

[a] The ee% and [α] were determined by the pivolate.
[b] The ee% and [α] were determined by the benzoates.
[c] The configurations were not determined.

67%), while electron-withdrawing substituents at that position reduced enantiomeric excesses (*m*-Cl, 19%) (Fig. 5). Fig. 3 is the Hammett plot of the substituents on the *para*-position.

The unexpected ligand **10** was synthesized and applied in the asymmetric addition of dialkylzinc to benzaldehyde. The enantiomeric excess of the resulting 1-phenyl-1-propanol was very low (9%). The stereochemical outcome depends mainly on the stereogenic centers in the 8-position of the pyridyl-pinane-ring. In ligand **10**, the reaction center may shift toward the thioenyl group that is far away from the stereogenic centers and can not cause high enantioselectivity. Meanwhile, ligand **13** was used in the asymmetric addition of dialkylzinc to benzaldehyde, and the enantiomeric excess of 1-phenyl-1-propanol was very low (8%). The steric energy was calculated using the MM2 program (CS Chem3D Pro). Calculation results indicate that intermediate (E) has a lower steric energy (49.322 kcal/mol) than intermediate (F) (54.283 kcal/mol). Intermediate (E) is more stable than intermediate (F), and the reaction center might shift far away from the stereogenic centers and can not induce high enantioselectivity. This result may similarly prove that ligand **10** is responsible for an extremely low enantioselectivity (Fig. 2).

In summary, a class of chelating ligands **7**-**10** and **13**



MM2 steric energy: 49.322 kcal/mol

MM2 steric energy: 54.283 kcal/mol

Fig. 2.

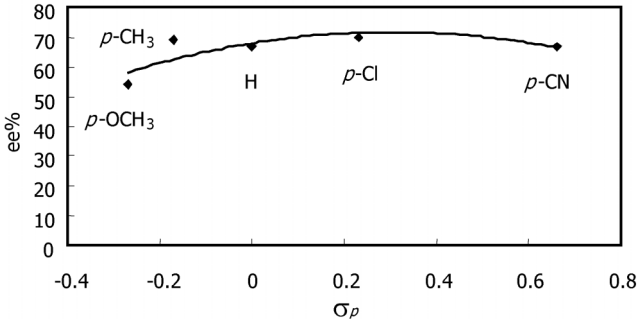


Fig. 3. The correlation of substituent constants (σ_p) and the enantiomeric excesses of the alkylation of *para*-substituted benzaldehydes in the presence of ligand **8**.

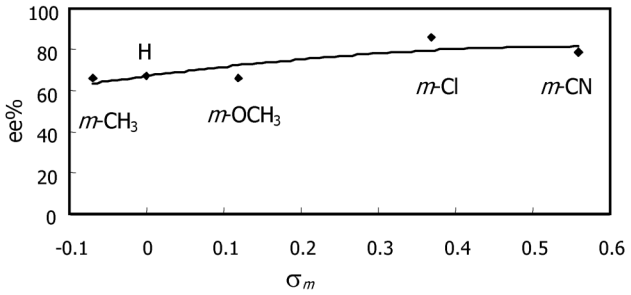


Fig. 4. The correlation of substituent constants (σ_m) and the enantiomeric excesses of the alkylation of *meta*-substituted benzaldehydes in the presence of ligand **8**.

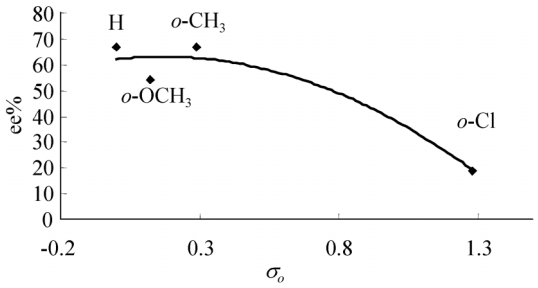


Fig. 5. The correlation of substituent constants (σ_o) and the enantiomeric excesses of the alkylation of *ortho*-substituted benzaldehydes in the presence of ligand **8**.

was prepared. Their catalytic activity in 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 **8** acts as an interesting chiral catalyst in the enantioselective addition of diethylzinc to various substituted benzaldehydes, yielding alcohols with the (*S*)-configuration and an enantiomeric excess that ranged generally from 19 to 86%. Importantly, the electron-withdrawing 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.

EXPERIMENTAL SECTION

General Chemical Procedures

All reactions were carried out in anhydrous solvents. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone under argon. Toluene, acetonitrile, dichloromethane, and hexane were distilled from calcium hydride. ^{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 a JASCO FT/IR 410 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 chromatograph (HPLC) with a Chiracel 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. Diethylzinc (1 M) solution in hexane was purchased from Sigma-Aldrich Co.

General procedure for the preparation of 10,10-dimethyl-5-aryl-6-azatricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (1-5)

The general procedure is demonstrated by the preparation of compound **4**. A mixture of pyridinium salt (1.26 g, 4.0 mmol), pinenone (0.66 g, 4.0 mmol), and ammonium acetate (2.46 g, 32.0 mmol) in glacial acetic acid (5.5 mL) under argon atmosphere was heated at 100-110 °C for 10 h. After cooling to room temperature, the reaction mixture was diluted with water, and the aqueous solution was basified by sodium carbonate until the aqueous solution become basic. The aqueous phase 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) as the mobile phase producing compound **4**.

10,10-Dimethyl-5-phenyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (1)

Yield: 56%. $[\alpha]_D^{22.4}$ +100.0° (c 1.06, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.98 (dd, J = 7.1, 1.5 Hz, 2H), 7.48-7.28 (m, 5H), 3.21 (d, J = 2.8 Hz, 2H), 2.81 (t, J = 5.6 Hz, 1H), 2.72-2.69 (m, 1H), 2.41-2.40 (m, 1H), 1.43 (s, 3H), 1.33 (d, J = 9.5 Hz, 1H), 0.70 (s, 3H). IR (KBr, thin film): 3057, 2981, 1567, 1439, 1234, 1024, 834, 779, 740, 695

cm^{-1}. MS-FAB *m/z*: 250 (M^++1, 100), 234 (12), 220 (13), 206 (23), 194 (15), 133 (34).

10,10-Dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]-undeca-2(7),3,5-triene (2)

Yield: 84%. $[\alpha]_D^{20}$ +102.8° (c 2.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.67 (m, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.81 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.28-7.26 (m, 1H), 3.20 (d, *J* = 2.8 Hz, 2H), 2.83 (t, *J* = 5.6 Hz, 1H), 2.74-2.67 (m, 1H), 2.42-2.38 (m, 1H), 1.42 (s, 3H), 1.33 (d, *J* = 9.5 Hz, 1H), 0.68 (s, 3H). IR (KBr, thin film): 3057, 2985, 2918, 1557, 1432, 1108, 944, 861, 796, 754, 609 cm^{-1}. MS-FAB *m/z*: 251 (M^++1, 100), 235 (10), 221 (12), 207 (20), 195 (20), 133 (79).

10,10-Dimethyl-5-pyridin-4-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]-undeca-2(7),3,5-triene (3)

Yield: 60%. mp: 69-70 °C. $[\alpha]_D^{18.9}$ +104.5° (c 1.01, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.69 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.88 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 3.19 (d, *J* = 2.8 Hz, 2H), 2.84-2.69 (m, 2H), 2.43-2.39 (m, 1H), 1.43 (s, 3H), 1.32 (d, *J* = 9.6 Hz, 1H), 0.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 157.3, 151.3, 150.1, 164.6, 142.3, 133.5, 120.5, 120.3, 117.7, 117.4, 46.1, 40.0, 39.3, 36.5, 31.7, 25.8, 21.1. IR (KBr, thin film): 3068, 2932, 1597, 1441, 1236, 1065, 1022, 814, 598 cm^{-1}. MS-FAB *m/z*: 251 (M^++1, 100), 235 (13), 221 (17), 207 (23), 195 (17), 133 (42), 77 (7). HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{19}N_2$, 251.1548; found, 251.1548.

5-Furan-2-yl-10,10-dimethyl-6-aza-tricyclo[7.1.1.$0^{2,7}$]-undeca-2(7),3,5-triene (4)

Yield: 76%. $[\alpha]_D^{20}$ +97.0° (c 0.95, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.50 (d, *J* = 1.1 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 3.3 Hz, 1H), 6.50 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.17 (d, *J* = 2.8 Hz, 2H), 2.78-2.65 (m, 2H), 2.40-2.36 (m, 1H), 1.40 (s, 3H), 1.30 (d, *J* = 9.5 Hz, 1H), 0.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 157.0, 154.1, 146.8, 142.7, 140.6, 133.5, 115.5, 111.8, 107.3, 46.5, 40.2, 39.6, 36.7, 32.0, 26.1, 21.3. IR (KBr, thin film): 3043, 2922, 1589, 1447, 1243, 1085, 1005, 811, 734, 595 cm^{-1}. MS-FAB *m/z*: 240 (M^++1, 100), 218 (16), 133 (46), 75 (23). HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{18}NO$, 240.1388; found, 240.1389.

10,10-Dimethyl-5-thiophen-2-yl-6-aza-tricyclo-[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene (5)

Yield: 54%. mp: 80-81 °C. $[\alpha]_D^{23}$ +104.0° (c 1.03, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.53 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.36-7.31 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 3.15 (d, *J* = 2.8 Hz, 2H), 2.77-2.64 (m, 2H), 2.40-2.36 (m, 1H), 1.40 (s, 3H), 1.30 (d, *J* = 9.4 Hz, 1H), 0.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 156.8, 150.0, 145.6, 140.4, 133.6, 128.0, 126.4, 123.6, 115.6, 46.3, 40.2, 39.5, 36.6, 32.1, 26.1, 21.4. IR (KBr, thin film): 3046, 2925, 1571, 1421, 1222, 1111, 943, 817, 707 cm^{-1}. MS-FAB *m/z*: 256 (M^++1, 64), 241 (18), 133 (30), 75 (100), 57 (63). HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{18}NS$, 256.1160; found, 256.1155.

General procedure for the preparation of (10,10-dimethyl-5-aryl-6-azatricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-yl)-diphenyl-methanol (6-10)

The general procedure is demonstrated by the preparation of compound **9**. *n*-Butyllithium (0.60 mL, 1.0 mmol, 1.6 M in hexane) was added to a solution of diisopropylamine (0.13 mL, 1.0 mmol) in tetrahydrofuran (0.6 mL) at 0 °C and stirred for 15 min to give a LDA solution. The LDA solution was cooled to -40 °C, and then was added to a solution of compound **4** (204.0 mg, 0.9 mmol) in tetrahydrofuran (4.3 mL) by canula, and stirred at -40 °C for 2 h. Then the reaction temperature was decreased to -78 °C, and a solution of benzophenone (155 mg, 0.9 mmol) in tetrahydrofuran (4.0 mL) was added. The reaction temperature was increased to room temperature and stirred overnight. The reaction was quenched by adding water, and the reaction mixture was extracted with ethyl acetate. 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 (1:49) as the mobile phase, thus producing compound **9** (65.0 mg, 0.15 mmol).

(10,10-Dimethyl-5-phenyl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-8-yl)-diphenyl-methanol (6)

Yield: 40%. mp: 148-149 °C. $[\alpha]_D^{23.5}$ -446.4° (c 1.09, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.15 (br, 1H), 8.04 (d, *J* = 1.5 Hz, 1H), 8.01 (d, *J* = 1.2 Hz, 1H), 7.55 (m, 10H), 7.10 (s, 5H), 4.47 (s, 1H), 2.66 (t, *J* = 6.0 Hz, 1H), 2.57 (t, *J* = 5.3 Hz, 1H), 1.40 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 1H), 0.90 (s, 3H). IR (KBr, thin film): 3118, 3060, 2956, 1585, 1475, 1027, 767, 719, 698 cm^{-1}. MS-FAB *m/z*: 432 (M^++1, 8), 414 (5), 372 (4), 354 (4), 248 (23), 234 (29), 220 (17), 206 (39), 167 (100), 105 (67), 77 (63).

(10,10-Dimethyl-5-pyridin-2-yl-6-aza-tricyclo[7.1.1.$0^{2,7}$]-undeca-2(7),3,5-trien-8-yl)-diphenyl-methanol (7)

Yield: 69%. mp: 99-100 °C. $[\alpha]_D^{25.5}$ -403.0° (c 1.05,

CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 9.90 (br, 1H), 8.70 (d, 1H), 8.28 (dd, *J* = 13.5, 8.0 Hz, 2H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.47-7.30 (m, 7H), 7.10 (s, 5H), 4.48 (s, 1H), 2.64-2.57 (m, 2H), 2.11-2.04 (m, 1H), 1.40 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 1H), 0.9 (s, 3H). IR (KBr, thin film): 3150, 3058, 2925, 1578, 1431, 1025, 788, 700 cm^{-1}. MS-FAB *m/z*: 433 (M^++1, 8), 415 (6), 249 (32), 235 (41), 221 (26), 207 (52), 167 (100), 105 (82), 77 (70).

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

Yield: 63%. mp: 196-197 °C. $[\alpha]_D^{25.5}$ -409.0° (c 1.02, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 9.37 (br, 1H), 8.70 (d, *J* = 6.0 Hz, 2H), 7.83 (dd, *J* = 4.6, 1.4 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.46-7.31 (m, 6H), 7.11 (s, 5H), 4.48 (s, 1H), 2.62 (d, *J* = 5.6 Hz, 2H), 2.15-2.08 (m, 1H), 1.40 (s, 3H), 1.26 (s, 1H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 158.1, 150.6, 149.6, 146.8, 145.7, 145.3, 144.7, 134.9, 128.3, 128.1, 127.8, 127.2, 127.1, 126.6, 120.5, 118.4, 81.9, 48.2, 45.8, 42.9, 41.6, 28.8, 26.3, 21.3. IR (KBr, thin film): 3219, 3059, 2925, 1600, 1548, 1444, 1031, 819, 700 cm^{-1}. MS-FAB *m/z*: 433 (M^++1, 15), 415 (6), 251 (40), 235 (38), 221 (21), 207 (44), 167 (89), 133 (42), 105 (100), 77 (79). HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{30}H_{29}N_2O$, 433.2280; found, 433.2280.

(5-Furan-2-yl-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]-undeca-2(7),3,5-trien-8-yl)-diphenyl-methanol (9)

Yield: 18%. mp: 123-124 °C. $[\alpha]_D^{25.5}$ -151.1° (c 1.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 10.07 (br, 1H), 7.53-7.31 (m, 7H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.11 (s, 5H), 7.06 (d, *J* = 3.0 Hz, 1H), 6.55 (dd, *J* = 3.3, 1.7 Hz, 1H), 4.42 (s, 1H), 2.64 (t, *J* = 5.8 Hz, 1H), 2.54 (t, *J* = 5.5 Hz, 1H), 2.10 (m, 1H), 1.39 (s, 3H), 1.26 (s, 1H), 0.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 157.3, 153.1, 146.7, 145.8, 144.5, 143.1, 142.2, 134.5, 128.4, 128.2, 128.0, 127.1, 127.0, 126.4, 115.8, 112.2, 108.1, 81.9, 47.9, 45.8, 42.9, 41.5, 29.0, 26.4, 21.3. IR (KBr, thin film): 3428, 3150, 3059, 2923, 1590, 1493, 1445, 1249, 1014, 767, 700, 634 cm^{-1}. MS-FAB *m/z*: 422 (M^++1, 7), 404 (2), 238 (5), 224 (6), 167 (46), 75 (100). HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{29}H_{28}NO_2$, 422.2120; found, 422.2120.

(10,10-Dimethyl-5-thiophen-2-yl-6-aza-tricyclo-[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-yl)-diphenylmethanol (10)

Yield: 86%. mp: 70-71 °C. $[\alpha]_D^{23.5}$ +70.9° (c 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.45-7.29 (m, 13H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 3.8 Hz, 1H), 3.10 (d, *J* = 2.8 Hz, 2H), 3.00 (s, 3H), 2.76-2.65 (m, 2H), 2.37-2.34 (m, 1H), 1.40 (s, 3H), 1.28 (d, *J* = 3.8 Hz, 1H), 0.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 156.9, 153.2, 149.9, 146.6, 145.3, 140.6, 133.6, 128.1, 127.8, 127.7, 127.5, 127.1, 123.1, 115.6, 80.2, 46.4, 40.3, 39.6, 36.6, 32.1, 26.2, 21.5. IR (KBr, thin film): 3447, 2923, 1573, 1444, 1012, 808, 758, 700, 646 cm^{-1}. MS-FAB *m/z*: 439 (M^++1, 100), 420 (43), 241 (22), 207 (31), 167 (33), 149 (42), 133 (45), 115 (61). HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{29}H_{28}NOS$, 438.1892; found, 438.1891.

General procedure for the preparation of [8-(hydroxy-diphenyl-methyl)-10,10-dimethyl-6-aza-tricyclo-[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl]-diphenyl-methanol (12-13)

(10,10-Dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-diphenyl-methanol (12)

To a suspension mixture of magnesium (534 mg, 22.0 mmol) in tetrahydrofuran (40 mL) was slowly added bromobenzene (2.32 mL, 22.0 mmol), and stirred at room temperature for 1 h to produce a phenylmagnesium bromide solution. This freshly prepared Grignard reagent was added to a solution of **11** (2.31 g, 10.0 mmol) in tetrahydrofuran (15 mL) by syringe and stirred at room temperature. The reaction was monitored by TLC. When the starting material **11** was entirely consumed, water was added to quench the reaction, and the reaction mixture was extracted with ethyl acetate. 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 (1:19) as the mobile phase, thus producing compound **12** (2.78 g, 7.8 mmol). Yield: 78%. mp: 135-136 °C. $[\alpha]_D^{25.5}$ +37.2° (c 1.55, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.35-7.24 (m, 10H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 3.12 (d, *J* = 2.8 Hz, 2H), 2.79 (t, *J* = 5.6 Hz, 1H), 2.72 (m, 1H), 2.39 (m, 1H), 1.41 (s, 3H), 1.30 (d, *J* = 9.5 Hz, 1H), 0.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.4, 154.6, 146.4, 146.3, 140.3, 133.1, 127.8, 127.4, 126.7, 119.3, 80.1, 45.6, 39.7, 39.1, 35.7, 31.5, 25.7, 21.0. IR (KBr, thin film): 3424, 3083, 3059, 3021, 2922, 1580, 1444, 1366, 1167, 1039, 842, 759, 698 cm^{-1}. MS-FAB *m/s*: 356 (M^++1, 7), 338 (63), 322 (9), 294 (26), 241 (23), 149 (21), 132 (25), 105 (16), 75 (100).

[8-(Hydroxy-diphenyl-methyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl]-diphenyl-methanol (13)

n-Butyllithium (5.1 mL, 10.3 mmol, 2.0 M in hexane) was added to a solution of diisopropylamine (1.45 mL, 10.3

mmol) in tetrahydrofuran (5.6 mL) at 0 °C and stirred for 15 min to give a LDA solution. The LDA solution was cooled to -40 °C, and then was added to a solution of compound **12** (1.66 g, 4.7 mmol) in tetrahydrofuran (20 mL) by canula, and stirred at -40 °C for 2 h. Then the reaction temperature was decreased to -78 °C, and a solution of benzophenone (852 mg, 4.7 mmol) in tetrahydrofuran (16.0 mL) was added. The reaction temperature was increased to room temperature and stirred overnight. The reaction was quenched by adding water, and the reaction mixture was extracted with ethyl acetate. 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 (1:24, 1:49) as the mobile phase, thus producing compound **13** (300.0 mg, 0.56 mmol). Yield: 18%. mp: 80 °C. $[\alpha]_D^{19}$ -186.4° (c 0.55, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.37-7.09 (m, 22H), 4.40 (s, 1H), 2.61 (t, *J* = 5.6 Hz, 1H), 2.35 (m, 1H), 2.18-2.14 (m, 1H), 1.35 (s, 3H), 1.28 (d, *J* = 9.5 Hz, 1H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 160.3, 160.6, 147.1, 145.8, 145.5, 145.0, 142.4, 133.9, 128.4, 128.0, 127.9, 127.8, 127.4, 127.2, 127.1, 126.7, 126.5, 126.2, 119.4, 81.3, 81.2, 48.9, 45.7, 42.7, 41.8, 28.6, 26.2, 21.2. IR (KBr, thin film): 3433, 3087, 3056, 3028, 2930, 1735, 1574, 1445, 1242, 1041, 851, 763, 699 cm^{-1}. MS-FAB *m/s*: 538 (M^++1, 15), 520 (5), 502 (12), 460 (7), 235 (85), 167 (100). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{38}H_{35}NO_2$, 537.2668; found, 537.2667.

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

Aldehyde (0.5 mmol) was added to a solution of ligands (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).

1-*m*-Tolyl-propan-1-ol

Yield: 70%. $[\alpha]_D^{24.1}$ -8.6° (c 1.02, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.48 (t, *J* = 6.7 Hz, 1H), 3.74 (s, 3H), 2.03 (br, 1H), 1.85-1.63 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 144.6, 138.1, 128.3, 128.2, 126.7, 123.1, 76.1, 31.9, 21.5, 10.2. IR (KBr, thin film): 3365, 3026, 2927, 2873, 2964, 1608, 1459, 1159, 1043, 784, 703 cm^{-1}. MS-FAB *m/z*: 166 (M^+, 8), 149 (77), 137 (34), 121 (13), 43 (100).

1-(3-Chloro-phenyl)-propan-1-ol

Yield: 81%. $[\alpha]_D^{25.5}$ -16.9° (c 1.13, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.75-7.20 (m, 4H), 4.61 (t, *J* = 6.4 Hz, 1H), 1.98 (br, 1H), 1.83-1.71 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 146.7, 134.3, 129.7, 127.6, 126.2, 124.2, 75.3, 31.9, 10.0. IR (KBr, thin film): 3357, 3064, 2965, 1575, 1432, 1199, 1085, 782, 698 cm^{-1}. MS-FAB *m/s*: 153 (M^+-17, 42), 149 (52), 133 (82), 57 (100), 43 (70).

1-(4-Chloro-phenyl)-propan-1-ol

Yield: 93%. $[\alpha]_D^{24.3}$ -19.0° (c 1.03, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.33-7.26 (m, 4H), 4,61 (t, *J* = 6.5 Hz, 1H), 1.85-1.72 (m, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 143.0, 133.1, 128.5, 127.4, 75.3, 32.0, 10.0. IR (KBr, thin film): 3357, 3047, 3026, 2931, 2877, 2965, 1490, 1091, 1012, 825, 526 cm^{-1}. MS-FAB *m/s*: 153 (M^+-17, 13), 149 (43), 133 (93), 69 (100), 57 (84), 43 (82).

1-(2-Methoxy-phenyl)-propan-1-ol

Yield: 88%. $[\alpha]_D^{25}$ -14.4° (c 1.02, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.31-7.21 (m, 2H), 6.98-6.87 (m, 2H), 4.81 (t, *J* = 6.7 Hz, 1H), 3.87 (s, 3H), 2.54 (br, 1H), 1.89-1.70 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 156.6, 132.4, 128.2, 127.1, 120.7, 110.5, 72.3, 55.3, 30.2, 10.5. IR (KBr, thin film): 3419, 3050, 2964, 1600, 1490, 1238, 1089, 1045, 754 cm^{-1}. MS-FAB *m/s*: 167 (M^++1, 5), 149 (100), 137 (39), 121 (32), 43 (27).

1-(3-Methoxy-phenyl)-propan-1-ol

Yield: 90%. $[\alpha]_D^{23.5}$ -17.7° (c 1.10, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.29 (t, *J* = 8.1 Hz, 1H), 6.93-6.91 (m, 2H), 6.83 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.60 (t, *J* = 6.5 Hz, 1H), 3.82 (s, 3H), 1.87 (m, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.8, 146.4, 129.4, 118.3, 113.0, 111.5, 76.0, 55.2, 31.9, 11.2. IR (KBr, thin film): 3376, 3055, 2964, 1602, 1455, 1261, 1157, 1043, 858, 782,

700 cm^{-1}. MS-FAB *m/s*: 166 (M^+, 18), 149 (100), 137 (23), 121 (17), 109 (9).

1-(4-Methoxy-phenyl)-propan-1-ol

Yield: 90%. $[\alpha]_D^{25.5}$ -22.3° (c 1.07, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.29 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.57 (t, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 1.87-1.67 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 159.0, 136.8, 127.2, 113.8, 75.7, 55.3, 31.8, 10.2. IR (KBr, thin film): 3394, 3064, 2962, 1612, 1511, 1247, 1037, 829 cm^{-1}. MS-FAB *m/s*: 166 (M^+, 41), 149 (100), 132 (50), 121 (50), 109 (38).

2,2-Dimethyl-propionic acid 1-(3-cyano-phenyl)-propyl ester

Yield: 73%. $[\alpha]_D^{24}$ -0.18° (c 0.3, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.59-7.44 (m, 4H), 5.64 (dd, *J* = 5.9, 7.5 Hz, 1H), 1.95-1.78 (m, 2H), 1.22 (s, 9H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 177.6, 142.7, 131.4, 130.7, 129.8, 129.3, 118.7, 112.7, 75.8, 38.9, 29.5, 27.1, 9.7. IR (KBr, thin film): 3068, 2971, 2937, 2873, 1729, 1481, 1396, 1280, 1151, 894, 802, 694, 491 cm^{-1}. MS-FAB *m/z*: 244 (M^+ + 1, 12), 144 (26), 85 (100), 57 (36).

Benzoic acid 1-(4-cyano-phenyl)-propyl ester

Yield: 52%. $[\alpha]_D^{25.5}$ +49.8° (c 0.65, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.10 (m, 2H), 7.66-7.44 (m, 7H), 5.94 (t, *J* = 6.3 Hz, 1H), 2.06-1.95 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 165.8, 146.1, 133.7, 133.3, 132.4, 130.2, 129.9, 129.7, 128.5, 127.1, 118.7, 111.7, 29.7, 29.5, 9.8. IR (KBr): 3064, 2971, 1722, 1452, 1270, 1110, 842, 711, 561 cm^{-1}. MS-FAB *m/z*: 264 (M^+ + 1, 12), 144 (26), 132 (39), 116 (34), 105 (100), 77 (36).

Benzoic acid 1-*o*-tolyl-propyl ester

Yield: 67%. $[\alpha]_D^{23.7}$ +52.8° (c 0.88, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.12-8.09 (m, 2H), 7.56-7.54 (m, 1H), 7.48-7.43 (m, 3H), 7.20-7.17 (m, 3H), 6.17 (dd, *J* = 7.7, 5.8 Hz, 1H), 2.49 (s, 3H), 2.09-1.95 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 166.0, 139.2, 135.1, 132.9, 130.6, 130.4, 129.6, 128.4, 127.6, 126.2, 125.8, 74.8, 43.7, 29.1, 19.3, 10.2. IR (KBr, thin film): 3064, 3030, 2969, 1718, 1452, 1270, 1110, 1025, 937, 757, 709 cm^{-1}. MS-FAB *m/z*: 254 (M^+, 2), 225 (4), 132 (67), 105 (100), 77 (13).

Benzoic acid 1-*p*-tolyl-propyl ester

Yield: 89%. $[\alpha]_D^{23.5}$ +15.3° (c 1.01, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.10-8.07 (m, 2H), 7.58-7.41 (m, 3H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 5.91 (t, *J* = 6.8 Hz, 1H), 2.34 (s, 3H), 2.10-1.91 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 166.0, 137.7, 137.6, 132.8, 130.7, 129.6, 129.1, 128.3, 126.5, 77.9, 43.7, 29.5, 21.1, 10.0. IR (KBr): 3060, 3030, 2969, 1718, 1450, 1270, 1176, 1110, 1025, 813, 709 cm^{-1}. MS-FAB *m/z*: 254 (M^+, 2), 225 (4), 132 (67), 105 (100), 77 (13).

Benzoic acid 1-(2-chloro-phenyl)-propyl ester

Yield: 50%. $[\alpha]_D^{23.5}$ +20.9° (c 1.05, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.13-8.10 (m, 2H), 7.58-7.56 (m, 1H), 7.49-7.46 (m, 3H), 7.37-7.36 (m, 1H), 7.25-7.23 (m, 2H), 6.35 (t, *J* = 6.4 Hz, 1H), 2.08-1.98 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 165.7, 138.7, 133.1, 132.3, 130.3, 129.7, 128.7, 128.5, 127.1, 127.0, 74.5, 43.7, 28.6, 9.9. IR (KBr): 3064, 3032, 2971, 1722, 1600, 1452, 1268, 1108, 944, 754, 711 cm^{-1}. MS-FAB *m/z*: 275 (M^+ + 1, 4), 239 (12), 153 (49), 125 (72), 105 (100), 77 (55).

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