Article

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Synthesis of Chiral Pyridylphenols for the Enantioselective Addition of Diethylzinc to Aldehydes

Pei-Shan Wu and Chinpiao Chen*

Department of Chemistry, National Dong Hwa University, Shoufeng, Hualien 974, Taiwan, Republic of China

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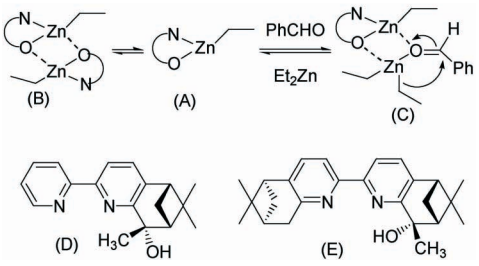
Chiral 8-substituted 2-(8,10,10-trimethyl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-trien-5-yl)-phenols were prepared from a high enantiopurity (>97% ee) of (1*R*)-(+)-α-pinene, and assessed in the enantioselective addition of diethylzinc to substituted benzaldehydes, giving the (*S*)-alcohols with enantiomeric excess ranging from 33% to 89%. Interestingly, in all cases, except for those of *ortho*-chlorobenzaldehyde, *ortho*- and *para*-methoxybenzaldehydes, the ee was >71%. The plot of the Hammett substitution constants vs. enantiomeric excess of the diethylzinc addition to either the *ortho*- or *para*-substituted benzaldehydes shows a linear correlation.

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

INTRODUCTION

Asymmetric catalysis provides enantiomerically-enriched products in organic reactions, which is very important in modern synthetic and pharmaceutical chemistry.[1] Notably, enantioselective catalysis is one of the most efficient environmentally benign processes. Therefore, the development of enantioselective catalysts is the greatest challenges in modern organic chemistry. The most promising candidates for such enantioselective catalysts are metal complexes that bear chiral organic ligands. The enantioselective addition of diorganozinc reagents to aldehydes is one of the most important and fundamental asymmetric reactions[2] among the asymmetric catalysis of C-C bond-forming reactions. Since the initial report by Oguni,[3] various chiral ligands including α-amino alcohols,[4] BINOL,[5] diamine,[6] diol,[7] pyridyl alcohol,[8] salen,[9] TADDOL,[10] and others[11] have been used in this type of reaction. 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 chiral ligands with amino alcohol or pyridyl alcohol form an asymmetric environment with two molecules of diethylzinc, one performs as a Lewis acid, and another performs as a nucleophile.[12] The interaction between diethylzinc and an amino alcohol produces a chelated ethylzinc alkoxide (A) which is in equilibrium with a dimeric species (B).[12d] 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 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). Recently, we demonstrated that bipyridyl alcohols (D) and (E) act as interesting chiral catalysts in the enantioselective addition of diethylzinc to various substituted benzaldehydes, provided that the alcohols of the (*S*)-configuration and enantiomeric excess generally range from 45% to 79%.[13] The moderate degree of asymmetric induction encouraged us to modify the 5-pyridyl ring of the ligand (D) for various aldehydes.

Scheme I



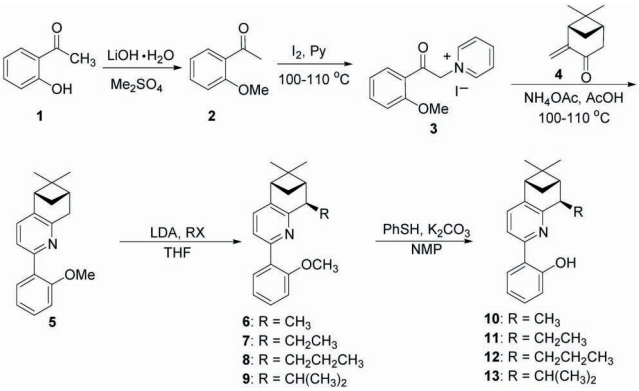
RESULTS AND DISCUSSION

Synthesis of ligands 10-13

The synthesis of ligands **10**–**13** is outlined in Scheme II. 1-(2-Hydroxy-phenyl)-ethanone (**1**) readily converts to methyl ether in the presence of LiOH and dimethylsulfate to yield **2**. Moreover, 2-methoxyacetophenone was heated with iodine in pyridine at 100–110 ºC for 3 hr and recrystallized from ethanol to produce pyridinium salt **3**. Com-

* Corresponding author. Tel: +886-3-8633597; Fax: +886-3-8630475; E-mail: chinpiao@mail.ndhu.edu.tw

Scheme II

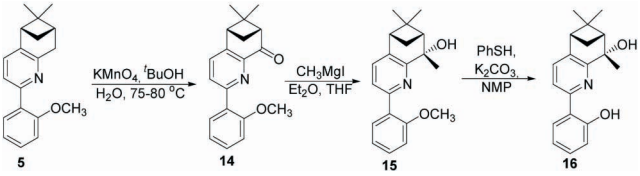


pounds **3** and **4** were heated with ammonium acetate in glacial acetic acid at 100–110 ºC overnight to yield 2-anisolylpyridine **5**. Compounds **6**–**9** were prepared by treating compound **5** with LDA and alkyl halides. The methyl ether of compounds **6**–**9** were cleaved by treating them with phenyl thiol and K_2CO_3 in NMP solution to produce compounds **10**–**13**.[14]

Synthesis of ligand 16

The synthesis of ligand **16** is outlined in Scheme III. Compound **5** was oxidized using potassium permanganate to form ketone **14**. Compound **15** was prepared by reacting compound **14** with the Grignard reagent (MeMgI). An efficient protocol reported in the literature for the demethylation of **15** to **16** in good purity using KOPh[14] was therefore attempted.

Scheme III



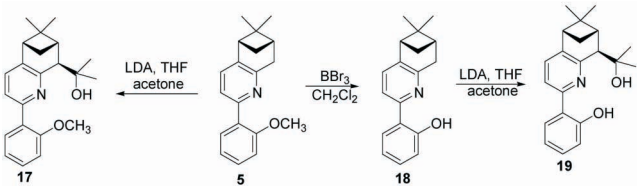
Synthesis of ligands 17 and 19

The synthesis of ligands **17** and **19** is outlined in Scheme IV. Compound **17** was prepared by treating compound **5** with LDA and acetone. The methyl ether of compound **5** was cleaved by treating it with BBr_3 to produce compound **18**. Compound **19** was obtained by treating compound **18** with LDA and acetone.

Application in asymmetric catalytic reaction

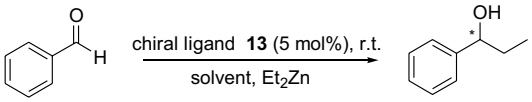
The enantiomeric excesses of 1-phenyl-1-propanol were acquired through the asymmetric addition of benzaldehyde using diethylzinc in the presence of chiral ligand **13**

Scheme IV



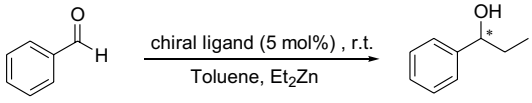
at room temperature with various solvents (Table 1): toluene (57%), dichloromethane (56%), hexane (53%), acetonitrile (43%) and tetrahydrofuran (33%). Toluene was therefore selected as the reaction solvent in the following reactions. The asymmetric addition of benzaldehyde using diethylzinc in toluene at room temperature in the presence of 5% of ligands yielded enantiomeric excesses of 1-phenyl-1-propanol, as shown in Table 2. The stereochemical outcome depends mainly on the stereogenic centres in the 8-position of the pyridyl-pinane-ring (ligand **10**). In fact, the other substituent on the 8-position of the ligands did not

Table 1. Asymmetric addition of diethylzinc to benzaldehyde using ligand **13** in various solvents



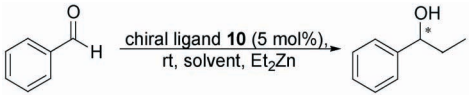
Entry	Slovent	Ee (%)	Yield (%)
1	Hexane	53	85
2	Toluene	57	90
3	CH_2Cl_2	56	75
4	CH_3CN	43	76
5	THF	33	62

Table 2. Asymmetric addition of benzaldehyde using diethylzinc, in the presence of various chiral ligands



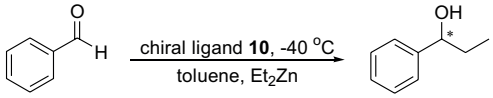
Entry	Chiral ligand	Ee (%)	Yield (%)
1	**10**	64	63
2	**11**	57	66
3	**12**	55	90
4	**13**	57	90
5	**16**	9	41
6	**16**/Ti(O^iPr)$_4$	0	53
7	**17**	40	75
8	**19**	2	40
9	**19**/Ti(O^iPr)$_4$	35	84

Table 3. Enantiomeric excess of the addition of benzaldehyde in the presence of **10** at various temperatures



Entry	Temp (ºC)	Ee (%)	Yield (%)
1	40	72	93
2	rt	64	63
3	4	67	72
4	- 20	73	81
5	- 40	79	42
6	- 78	78	46

Table 4. Enantiomeric excess of the addition of benzaldehyde in the presence of various amount of ligand **10**



Entry	Ligand mol %	Ee (%)	Yield (%)
1	1	79	37
2	5	79	42
3	10	79	85
4	15	78	80
5	20	78	86

increase the stereoselectivity. The optimized ligands were **10** (64% ee). Therefore, the following asymmetric reactions were performed in the presence of ligand **10**. The same reactions were conducted in toluene at various temperatures (Table 3), and the enantimeric excesses of 1-phenyl-1-propanol were acquired at –78 ºC (78%), –40 ºC (79%), –20 ºC (73%), 4 ºC (67%), rt (64%), and 40 ºC (72%). Therefore the following asymmetric reactions were performed in toluene at –40 ºC. The asymmetric addition of benzaldehyde, using diethylzinc in the presence of various amounts of ligand **10**, yielded enantiomeric excesses of 1-phenyl-1-propanol, as shown in Table 4. The optimal amount catalyst was 10 mol% of ligand **10** (79% ee).

The enantioselective formation of carbon-carbon bonds via the asymmetric addition of dialkylzinc to aldehydes continues to be very important in the development of the enantioselective method. Numerous pyridine-alcohol derivatives have been established to be effective chiral catalysts so, following research in this area, the authors have evaluated the potential utility of new ligands **10**–**13** in this catalytic process. Substituted benzaldehyde was asymmetrically alkylated in the presence of catalyst **10** as described below. Diethylzinc was added to a solution of ligand **10** (10 mol%) in toluene at –40 ºC and stirred for 30 h. The reaction was quenched by adding 1N 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 shown in Table 5. The absolute configurations of all products were determined by comparing the signs of specific rotations (α_D).[15] The stereochemical outcome mainly depends on the stereogenic centers in the 8-position of the pyridyl-pinane-ring (ligand **10**). In fact, the ligands with further substituents at the 8-position did not exhibit higher stereoselectivity. The enantioselectivities obtained using the 8-methyl-substituted ligand **10** were in the range of 33–89% ee. All products were *S*-configuration determined by comparing the signs of specific rotations (α_D) in the literature. Notably, similarly high levels of reactivity and enantioselectivity were observed for aliphatic aldehydes under identical reaction conditions (Table 5, entries 14 and 15).

The plot of Hammett substituent constants vs. enantiomeric excess of the addition of *para*-substituted benzaldehydes using diethylzinc shows a linear correlation. Importantly the moderate electron-releasing substituents on the *para*-position exhibited higher enantiomeric excesses (*p*-CH_3, 89%), while the stronger electron-withdrawing substituents on the *para*-position showed lower enantiomeric excesses (*p*-Cl, 75%; *p*-CN, 71%) (Fig. 1). On the other hand, the substituents on the *meta*-position did not exhibit high correlation of Hammett substituent constants and enantiomeric excesses of the alkylation of substituted benzaldehydes using diethylzinc (enantiomeric ex-

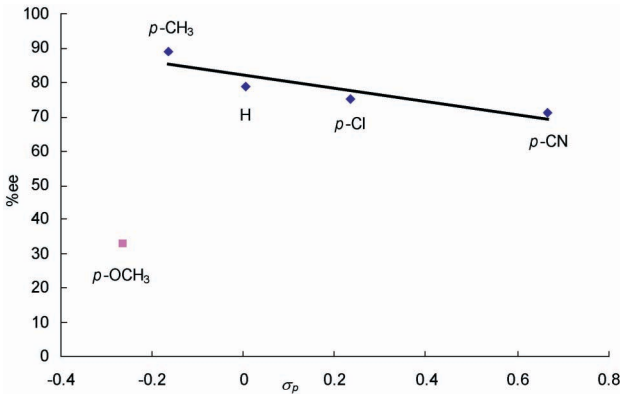
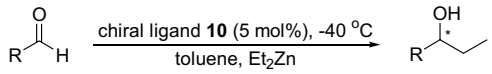


Fig. 1. The correlation of substituent constants (σ_p) and the enantiomeric excess of the alkylation of *para*-substituted benzaldehydes in the presence of **10**.

Table 5. Asymmetric addition of substituted benzaldehyde using diethylzinc, in the presence of ligand **10**



Entry	R	Yield (%)	ee (%)[d]	$[\alpha]_D$ (c) CH_2Cl_3	Cofiguration
1	C_6H_5 (**20**)	85	79	-44.8 (1.25)	*S*
2	2-Me-C_6H_4 (**21**)	70	75 [a]	-44.8 (1.25)	*S*
3	3-Me-C_6H_4 (**22**)	64	77	-31.9 (1.20)	*S*
4	4-Me-C_6H_4 (**23**)	52	89	-37.6 (1.00)	*S*
5	2-MeO-C_6H_4 (**24**)	51	41	-9.8 (1.00)	*S*
6	3-MeO-C_6H_4 (**25**)	86	75 [a]	-29.5 (1.20)	*S*
7	4-MeO-C_6H_4 (**26**)	40	33	-15.1 (1.10)	*S*
8	2-Cl-C_6H_4 (**27**)	72	39 [b]	-23.4 (1.05)	*S*
9	3-Cl-C_6H_4 (**28**)	91	83	-29.8 (0.95)	*S*
10	4-Cl-C_6H_4 (**29**)	93	75	-31.4 (1.00)	*S*
11	3-CN-C_6H_4 (**30**)	94	79 [a]	-18.4 (1.05)	NA
12	4-CN-C_6H_4 (**31**)	91	71 [b]	-26.0 (1.00)	NA
13	3-$(Me)_2N$-C_6H_4 (**32**)	87	77	-25.7 (1.15)	NA
14	*c*-C_6H_{11} (**33**)	77	81 [c]	-5.3 (1.00)	*S*
15	*n*-C_6H_{13} (**34**)	56	65 [c]	+4.3 (1.00)	*S*
16	(*E*)-cinnamyl (**35**)	66	39	-3.6 (1.25)	*S*

[a] The ee% was determined by converting the alcohols to acetates.
[b] The ee% was determined by converting the alcohols to benzoyates.
[c] The ee% was determined by converting the alcohols to Mosher's ester and determined by ^{19}F NMR.
[d] The ee% was determined by Chiracel OD-H HPLC column and the absolute configuration was assigned based on comparison with the literature data.

cesses ranged from 75% to 83%) (Fig. 2). The stronger electron-releasing substituents on the *para*- and *ortho*-position displayed lower enantiomeric excesses (*p*-OCH_3, 33%; *o*-OCH_3, 41%) (Fig. 1 and 3). Moreover, the stronger electron-withdrawing substituents on the *ortho*-position displayed lower enantiomeric excesses (*o*-Cl, 39%), while the weaker electron-releasing substituents on the *ortho*-position showed higher enantiomeric excesses (*o*-Me, 75%) (Fig. 3).

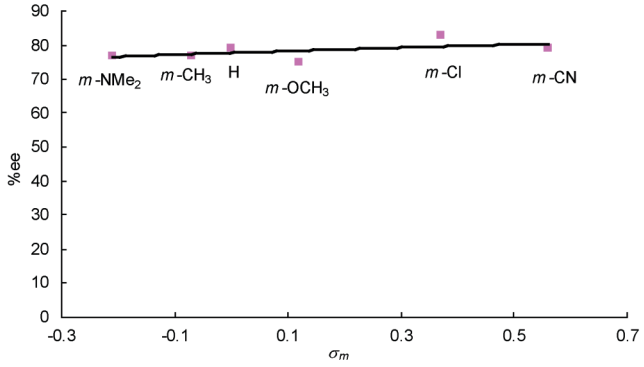


Fig. 2. The correlation of substituent constants (σ_m) and the enantiomeric excess of the alkylation of *meta*-substituted benzaldehydes in the presence of **10**.

CONCLUSIONS

In summary, a new class of chelating ligands of type **10** was prepared. Their catalytic activity in the asymmetric addition of diethylzinc to substituted benzaldehydes was demonstrated. These ligands were prepared from highly

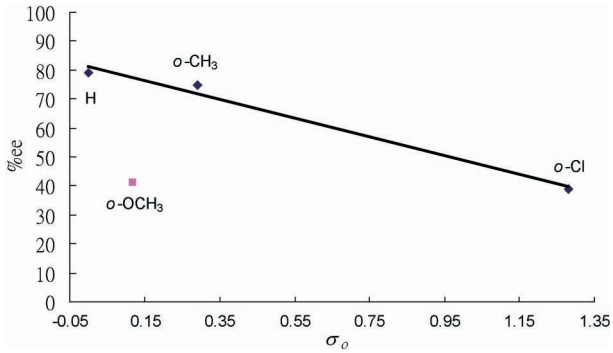


Fig. 3. The correlation of substituent constants (σ_o) and the enantiomeric excess of the alkylation of *ortho*-substituted benzaldehydes in the presence of **10**.

enantiopure (1*R*)-(+)-α-pinene (>97% ee). Pridylphenol **10** acts as an interesting chiral catalyst in the enantioselective addition of diethylzinc to various substituted benzaldehydes, affording the (*S*)-alcohols with ee ranging from 33% to 89%.

EXPERIMENTAL

General Chemical Procedures

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, xylene and hexane were distilled from CaH_2. ^1H NMR spectra were obtained at 300 or 400 MHz (as indicated), and ^{13}C NMR spectra were obtained at 75.5 or 100.6 MHz using a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) and high resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded using a JASCO FT/IR 410 spectrometer. All asymmetric reactions were conducted in dry glassware under nitrogen using a standard glovebox. Enantiomeric excesses were determined using Lab Alliance Series III high performance liquid chromatography (HPLC) with a Chiracel OD-H chiral column (Daicel Chemical Industries, LTD). Optical rotations were measured using a JASCO P-1010 polarimeter at the indicated temperature using a sodium lamp (D line, 589 nm). Flash column chromatography was performed using MN silica gel 60 (70–230 mesh) purchased from Macherey-Nagel.

Synthesis of ligands 10–13

2-Methoxyphenyl methyl ketone 2

A solution of 1-(2-hydroxy-phenyl)-ethanone (**1**) (35.2 mL, 300 mmol) and $LiOH·H_2O$ (24.8 g, 590 mmol) in THF (400 mL) was stirred at room temperature for 1 h, and then dimethyl sulfate (42 mL, 293 mmol) was added. After completion of the reaction (TLC, 60 h), the solvent was removed under reduced pressure. The residue was dissolved in 2 M NaOH, and the resulted solution was extracted with diethyl ether (3 ×). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford compound **2** (38.5 g, 256.0 mmol, 86%). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.71-7.69 (dd, J = 7.7, 1.8 Hz, 1H), 7.44-7.40 (m, 1H), 6.97-6.92 (m, 2H), 3.86 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 199.8, 158.9, 133.7, 130.3, 128.2, 120.5, 111.6, 55.5, 31.8. IR (KBr): 3074, 3003, 2944, 2840, 1674, 1598, 1578, 1486, 1437, 1358, 1292, 1247, 1163, 1126, 1023, 967, 805, 758, 595, 534 cm^{-1}.

1-[2-(2-Methoxyphenyl)-2-oxoethyl]pyridinium iodide 3

To a solution of 2-methoxyphenyl methyl ketone **2** (45.0 mL, 300.0 mmol) in pyridine (328 mL) was added a solution of iodine (83.0 g, 327 mmol) in pyridine (75.0 mL), and the resulting solution was heated at 100–110 ºC for 3 h. The reaction solution was stood for 10 h, filtered, washed with ethanol, and then recrystallized twice in ethanol. The crystal was dried under vacuum yielding compound **3** (43.8 g, 123.0 mmol). Yield: 41%.

(5*S*,7*S*)-(+)-5,6,7,8-Tetrahydro-6,6-dimethyl-2-(2-methoxyphenyl)-5,7-methanoquinoline 5

A mixture of compound **4** (1.2 g, 8.0 mmol), compound **3** (4.72 g, 13.0 mmol), and ammonium acetate (4.14 g, 53.0 mmol) in glacial acetic acid (8.8 mL) under argon atmosphere was heated at 100–110 ºC for 20 h. After cooling to room temperature, the reaction mixture was transferred to a 1-L Erlenmeyer flask, ethyl acetate (200 mL) and water (200 mL) were added, and the mixture was basified by 6 M 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 as the stationary phase and using ethyl acetate-hexane (1:19) as the mobile phase producing compound **5** (0.74 g, 2.6 mmol). Yield: 33%. mp: 110-111 ºC. $[\alpha]^{23.4}_D$ +71.0º (*c* 1.03, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.80-7.78 (dd, J_1 = 7.5, 1.3 Hz, 1H), 7.51-7.49 (d, J = 7.8 Hz, 1H), 7.34-7.30 (t, J = 7.8 Hz, 1H), 7.22-7.20 (d, J = 7.8 Hz, 1H), 7.08-7.04 (t, J = 7.4 Hz, 1H), 6.98-6.96 (d, J = 8.2 Hz, 1H), 3.83 (s, 3H), 3.19-3.18 (d, J = 2.0 Hz, 2H), 2.79-2.76 (t, J = 5.6 Hz, 1H), 2.71-2.66 (m, 1H), 2.40-2.38 (m, 1H), 1.42 (s, 3H), 1.34-1.32 (d, J = 9.5 Hz, 1H), 0.70 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 156.8, 156.3, 152.9, 139.7, 132.6, 131.1, 129.6, 121.5, 121.0, 111.3, 55.6, 46.3, 40.3, 39.5, 36.7, 32.0, 26.15, 21.4. IR (KBr): 3045, 2931, 2832, 1600, 1583, 1492, 1444, 1423, 1263, 1240, 1120, 1068, 1025, 944, 821, 752 cm^{-1}. MS *m/z*: 279 (M^+, 100), 279 (100), 264 (68), 250 (28), 236 (45), 221 (23), 126 (28), 77 (7). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{19}H_{21}NO$, 279.1623; found, 279.1614.

(1*S*,8*R*,9*S*)-8-Isopropyl-5-(2-methoxy-phenyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene 9

To a solution of diisopropylamine (121 μL, 1.2 mmol) in THF (5 mL) at 0 ºC was added *n*-BuLi (0.76 mL, 1.2

mmol, 1.6 M in hexane) and stirred for 30 min. The prepared LDA solution was cooled to -78 ºC, and a solution of **5** (0.28 g, 1.0 mmol) in THF (6 mL) was transfered to LDA solution by cannula. The solution became a blue color and was stirred at -78 ºC for 2 h. A solution of 2-bromopropane (113 μL, 3.0 mmol) in THF (10 mL) was added and stirred overnight at room temperature. The solution became orange color and quenched by adding water. The resulting solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous $MgSO_4$. 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 **9** (0.18 g, 0.6 mmol, 56%). $[\alpha]^{16.8}_D$ +17.2º (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.94-7.91 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.62-7.60 (d, *J* = 7.8 Hz, 1H), 7.35-7.31 (m, 1H), 7.22-7.20 (d, *J* = 7.8 Hz, 1H), 7.10-7.07 (t, *J* = 7.4 Hz, 1H), 7.01-6.99 (d, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.00 (s, 1H), 2.96-2.92 (m, 1H), 2.76-2.73 (t, *J* = 5.6 Hz, 1H), 2.62-2.57 (m, 1H), 2.40-2.37 (m, 1H), 1.44 (s, 3H), 1.41-1.42 (d, *J* = 5.7 Hz, 2H), 1.22-1.20 (d, *J* = 6.9 Hz, 3H), 0.89-0.87 (t, *J* = 6.9 Hz, 3H), 0.68 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 158.7, 157.1, 152.3, 140.2, 132.4, 131.2, 129.7, 129.2, 121.5, 121.1, 111.6, 55.6, 49.1, 46.6, 42.0, 41.3, 30.3, 29.6, 26.5, 22.3, 21.2, 20.0. IR (KBr): 2953, 2923, 2868, 1599, 1582, 1492, 1463, 1434, 1385, 1294, 1259, 1239, 1121, 1067, 1026, 853, 828, 751 cm^{-1}. MS *m/z*: 321 (M^+, 9), 306 (20), 278 (100), 264 (21), 250 (18), 236 (68), 221 (16). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{22}H_{27}NO$, 321.2093; found, 321.2096.

(1*S*,8*R*,9*S*)-8-Isopropyl-10,10-dimethyl-6-aza-tricyclo-[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-phenol 13

To a solution of **9** (0.09 g, 0.3 mmol) in anhydrous NMP (0.53 mL) was added PhSH (28 μL, 0.6 mmol) and K_2CO_3 (2.0 mg, 0.03 mmol), and heated to 250 ºC for refluxing 30 min (TLC). The reaction mixture was cooled to room temoerature and a 5% NaOH (25 mL) was added, then the aqueous solution was neutralized by adding 1 M HCl to pH = 8. The aqueous phase was extracted with diethyl ether three times, and the combined extracts were dried over anhydrous $MgSO_4$. 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 **13** (0.08 g, 0.25 mmol, 86%). $[\alpha]^{20.7}_D$ -17.5º (*c* 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.78-7.76 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.63-7.61 (d, *J* = 8.1 Hz, 1H), 7.37-7.35 (d, *J* = 8.1 Hz, 1H), 7.28-7.23 (m, 1H), 7.01-6.98 (dd, *J* = 9.3, 0.8 Hz, 1H), 6.90-6.86 (m, 1H), 2.99-2.98 (m, 1H), 2.82-2.78 (m, 1H), 2.76-2.74 (t, *J* = 5.8 Hz, 1H), 2.63-2.58 (m, 1H), 2.40-2.36 (m, 1H), 1.57-1.39 (d, *J* = 7.0 Hz, 1H), 1.43 (s, 3H), 1.15-1.13 (d, *J* = 7.0 Hz, 3H), 0.83-0.81 (d, *J* = 7.1 Hz, 3H), 0.63 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.6, 156.0, 154.7, 141.0, 134.8, 130.7, 125.8, 119.5, 118.7, 118.3, 115.9, 48.6, 46.6, 42.2, 40.7, 30.3, 29.7, 26.3, 22.0, 21.0, 19.7. IR (KBr): 2956, 2931, 2862, 1584, 1503, 1470, 1411, 1292, 1255, 1117, 853, 760, 747, 608 cm^{-1}. MS *m/z*: 307 (M^+, 35), 292 (11), 264 (100), 236 (20), 222 (76), 128 (8). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{21}H_{25}NO$, 307.1936; found, 307.1947.

(1*S*,8*R*,9*S*)-5-(2-Methoxy-phenyl)-8,10,10-trimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene 6

Compound **6** was prepared following the same procedure as in the preparation of **9** using CH_3I (187 μL, 3.0 mmol) to produce **6** (0.22 g, 0.7 mmol, 75%). mp: 68-70 ºC. $[\alpha]^{17.5}_D$ +47.6º (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.89-7.87 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.56-7.54 (dd, *J* = 7.8, 0.5 Hz, 1H), 7.35-7.30 (m, 1H), 7.20-7.18 (d, *J* = 7.8 Hz, 1H), 7.09-7.05 (m, 1H), 7.00-6.98 (dd, *J* = 6.2, 0.6 Hz, 1H), 3.86 (s, 3H), 3.29-3.23 (m, 1H), 2.78-2.76 (t, *J* = 5.6 Hz, 1H), 2.59-2.53 (m, 1H), 2.18-2.15 (m, 1H), 1.46-1.44 (d, *J* = 7.1 Hz, 3H), 1.43 (s, 3H), 1.37-1.34 (d, *J* = 9.8 Hz, 1H), 0.69 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 160.2, 157.0, 152.6, 139.6, 132.3, 131.2, 129.6, 129.2, 121.6, 121.1, 111.5, 55.6, 47.0, 46.9, 41.4, 39.0, 28.7, 26.4, 21.0, 18.4. IR (KBr): 2955, 2927, 2869, 1600, 1583, 1492, 1434, 1300, 1240, 1179, 1123, 1026, 857, 831, 753 cm^{-1}. MS *m/z*: 293 (M^+, 24), 278 (100), 250 (41), 234 (20), 115 (7). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{20}H_{23}NO$, 293.1780; found, 293.1776.

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

Compound **10** was prepared following the same procedure as in the preparation of **13** to produce **10** (0.17 g, 0.6 mmol, 61%). $[\alpha]^{20.1}_D$ +31.3º (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.78-7.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62-7.60 (d, *J* = 8.1 Hz, 1H), 7.37-7.34 (d, *J* = 8.1 Hz, 1H), 7.29-7.25 (m, 1H), 7.03-7.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.91-6.89 (m, 1H), 6.89-6.87 (t, *J* = 7.0 Hz, 1H), 3.25-3.23 (m, 1H), 2.82-2.78 (dd, *J* = 10.2, 5.6 Hz, 1H), 2.61-2.58 (m, 1H), 2.17-2.15 (m, 1H), 1.43 (s, 3H), 1.34-1.31 (d, *J* = 9.9 Hz, 1H), 0.67 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.7, 157.4, 154.9, 140.2, 134.7, 130.7, 125.7, 119.4,

118.7, 118.4, 115.8, 46.9, 46.7, 41.5, 38.2, 28.8, 26.3, 20.9, 18.0. IR (KBr): 3675, 3329, 2967, 2928, 2868, 1585, 1500, 1467, 1458, 1411, 1289, 1254, 1215, 852, 749, 611 cm^{-1}. MS *m/z*: 279 (M^+, 56), 264 (96), 250 (13), 236 (100), 222 (21), 210 (14), 115 (11), 77 (8). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{19}H_{21}NO$, 279.1623; found, 279.1632.

(1*S*,8*R*,9*S*)-8-Ethyl-5-(2-methoxy-phenyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene 7

Compound **7** was prepared following the same procedure as in the preparation of **9** using 1-bromoethane (224 μL, 3.0 mmol) to produce **7** (0.11 g, 0.4 mmol, 36%). mp 87-89 ºC. $[\alpha]^{18.0}_D$ +31.3º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.90-7.88 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.57-7.55 (d, *J* = 7.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.20-7.18 (d, *J* = 7.8 Hz, 1H), 7.10-7.06 (t, *J* = 7.5 Hz, 1H), 6.99-6.97 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 2.99-2.96 (m, 1H), 2.78-2.75 (t, *J* = 5.6 Hz, 1H), 2.57-2.53 (m, 1H), 2.51-2.44 (m, 1H), 2.39-2.36 (m, 1H), 1.57-1.47 (m, 1H), 1.45 (s, 3H), 1.35-1.33 (d, *J* = 9.7 Hz, 1H), 1.09-1.06 (t, *J* = 7.4 Hz, 3H), 0.68 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.7, 157.0, 152.5, 139.6, 132.3, 131.2, 129.6, 129.2, 121.5, 121.1, 111.5, 55.6, 46.8, 46.1, 42.8, 41.1, 28.6, 26.5, 25.3, 21.1, 12.5. IR (KBr): 2956, 2928, 2869, 1600, 1583, 1492, 1463, 1436, 1398, 1302, 1261, 1240, 1180, 1123, 1068, 1027, 942, 831, 752, 605 cm^{-1}. MS *m/z*: 307 (M^+, 10), 292 (18), 278 (100), 264 (35), 250 (16), 236 (22). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{21}H_{25}NO$, 307.1936; found, 307.1932.

(1*S*,8*R*,9*S*)-2-(8-Ethyl-10,10-dimethyl-6-aza-tricyclo-[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-phenol 11

Compound **11** was prepared following the same procedure as in the preparation of **13** to produce **11** (0.17 g, 0.6 mmol, 60%). $[\alpha]^{20.6}_D$ +9.5º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.78-7.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62-7.60 (d, *J* = 8.1 Hz, 1H), 7.36-7.34 (d, *J* = 8.1 Hz, 1H), 7.29-7.25 (m, 1H), 7.02-7.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.91-6.87 (m, 1H), 2.98-2.94 (m, 1H), 2.81-2.78 (t, *J* = 5.6 Hz, 1H), 2.60-2.55 (m, 1H), 2.39-2.31 (m, 1H), 2.30-2.25 (m, 2H), 1.58-1.52 (m, 1H), 1.45 (s, 3H), 1.42-1.40 (d, *J* = 6.8 Hz, 1H), 1.33-1.31 (d, *J* = 9.9 Hz, 3H), 1.09-1.05 (t, *J* = 7.4 Hz, 3H), 0.69 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.6, 156.0, 154.8, 140.2, 134.6, 125.7, 119.4, 118.7, 118.3, 115.8, 46.8, 45.3, 42.6, 41.2, 28.6, 26.4, 25.1, 20.9, 12.3. IR (KBr): 2961, 2931, 2873, 1585, 1503, 1471, 1411, 1377, 1292, 1256, 1218, 1149, 1094, 1019, 851, 823, 801, 749, 606 cm^{-1}. MS *m/z*: 293 (M^+, 58), 278 (25), 264 (100), 250 (58), 236 (22), 222 (37), 128 (8), 77 (5). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{20}H_{23}NO$, 293.1780; found, 293.1770.

(1*S*,8*R*,9*S*)-5-(2-Methoxy-phenyl)-10,10-dimethyl-8-propyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene 8

Compound **8** was prepared following the same procedure as in the preparation of **9** using 1-bromopropane (273 μL, 3.0 mmol) to produce **8** (0.11 g, 0.4 mmol, 34%). mp: 107-109 ºC. $[\alpha]^{17.1}_D$ +21.8º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.91-7.89 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.56-7.54 (d, *J* = 7.8 Hz, 1H), 7.33-7.31 (m, 1H), 7.19-7.18 (d, *J* = 7.8 Hz, 1H), 7.10-7.06 (m, 1H), 6.99-6.97 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 3.08-3.06 (dd, *J* = 6.5, 2.9 Hz, 1H), 2.77-2.75 (t, *J* = 5.7 Hz, 1H), 2.62-2.52 (m, 1H), 2.35-2.32 (m, 2H), 1.52-1.48 (m, 3H), 1.43 (s, 3H), 1.36-1.34 (d, *J* = 9.7 Hz, 1H), 1.02-0.98 (t, *J* = 6.9 Hz, 3H), 0.67 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.8, 157.1, 152.5, 139.6, 132.3, 131.3, 129.6, 129.2, 121.4, 121.1, 111.5, 55.6, 46.8, 44.2, 43.4, 41.0, 34.7, 28.5, 26.5, 21.1, 20.9, 14.4. IR (KBr): 2950, 2928, 2868, 1599, 1582, 1492, 1462, 1436, 1396, 1300, 1259, 1239, 1174, 1123, 1026, 828, 751 cm^{-1}. MS *m/z*: 321 (M^+, 10), 279 (51), 278 (100), 264 (18), 250 (14), 236 (36), 221 (12). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{22}H_{27}NO$, 321.2093; found, 321.2085.

(1*S*,8*R*,9*S*)-2-(10,10-Dimethyl-8-propyl-6-aza-tricyclo-[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-phenol 12

Compound **12** was prepared following the same procedure as in the preparation of **13** to produce **12** (0.22 g, 0.7 mmol, 72%). $[\alpha]^{20.7}_D$ -11.8º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.78-7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 1H), 7.35-7.34 (d, *J* = 3.2 Hz, 1H), 7.29-7.25 (m, 1H), 7.05-7.02 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.91-6.87 (m, 1H), 3.08-3.04 (m, 1H), 2.80-2.77 (t, *J* = 5.6 Hz, 1H), 2.60-2.54 (m, 1H), 2.36-2.32 (m, 1H), 2.19-2.11 (m, 1H), 1.60-1.52 (m, 2H), 1.44 (s, 3H), 1.34-1.31 (d, *J* = 9.9 Hz, 1H), 1.04-1.00 (t, *J* = 7.2 Hz, 3H), 0.69 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.6, 157.2, 154.8, 140.2, 134.6, 130.6, 125.8, 119.5, 118.7, 118.3, 115.8, 46.7, 43.3, 43.2, 41.1, 34.5, 28.6, 26.4, 20.9, 20.8, 14.2. IR (KBr): 2950, 2931, 2862, 1585, 1503, 1471, 1411, 1380, 1292, 1256, 1218, 1149, 1124, 1015, 852, 823, 749, 606 cm^{-1}. MS *m/z*: 307 (M^+, 37), 292 (10), 278 (17), 264 (100), 236 (24), 222 (64), 128 (11). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{21}H_{25}NO$, 307.1936; found, 307.1929.

(1*S*,9*R*)-5-(2-Methoxy-phenyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-one 14

A solution of compound **5** (4.00 g, 14.0 mmol), *tert*-butyl alcohol (143 mL) and water (28.6 mL) was heated at

80 ºC, and added potassium permanganate (12.3 g, 77.7 mmol). After stirred for 12 hr, the hot reaction mixture was filtrated through celite to remove the manganese dioxide, and washed with 20% *tert*-butyl alcohol in water (20 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 **14** (3.00 g, 10.2 mmol). Yield: 72%. mp 187–188 ºC. $[\alpha]^{23.5}_D$ +152.6º (*c* 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.92-7.89 (d, *J* = 10.6 Hz, 1H), 7.89-7.87 (d, *J* = 8.3 Hz, 1H), 7.59-7.57 (d, *J* = 8.0 Hz, 1H), 7.35-7.32 (t, *J* = 7.6 Hz, 1H), 7.20-7.18 (d, *J* = 8.2 Hz, 1H), 7.15-7.11 (t, *J* = 7.5 Hz, 1H), 5.19 (s, 2H), 3.43 (s, 3H), 3.12-3.10 (d, *J* = 9.1 Hz, 3H), 2.21-2.19 (t, *J* = 4.6 Hz, 1H), 1.61 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 200.0, 156.9, 155.1, 147.7, 144.4, 133.7, 131.7, 130.1, 128.3, 128.0, 121.2, 111.2, 58.2, 55.6, 52.8, 47.1, 39.5, 26.7, 22.7. IR (KBr): 2954, 2836, 1708, 1585, 1492, 1442, 1303, 1257, 1189, 1066, 1022, 860, 754, 725, 582 cm^{-1}. MS *m/z*: 293 (M^+, 33), 278 (26), 264 (100), 250 (78), 236 (28), 77 (9). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{19}H_{19}NO_2$, 293.1416; found, 293.1414.

(1*S*,8*S*,9*R*)-5-(2-Methoxy-phenyl)-8,10,10-trimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-ol 15

A mixture of magnesium (72.0 mg, 3.0 mmol) in diethyl ether (30.0 mL) equipped with a reflux condenser and under argon atmosphere, was added iodomethane (0.46 mL, 3.0 mmol) drop wisely, and after 1 hr, all magnesium was consumed. A solution of compound **14** (0.3 g, 1.0 mmol) in tetrahydrofuran (30.0 mL) was added to the fresh prepared MeMgI drop wisely at 0 ºC, and then stirred at room temperature. After completion of the reaction (TLC, 1 h), the reaction was quenched by ammonium chloride solution, and the aqueous solution was extracted with diethyl ether 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 **15** (0.22 g, 0.7 mmol). Yield: 88%. $[\alpha]^{21.3}_D$ +107.0º (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.94-7.92 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.69-7.67 (d, *J* = 7.8 Hz, 1H), 7.38-7.34 (m, 1H), 7.29-7.26 (d, *J* = 7.8 Hz, 1H), 7.11-7.07 (m, 1H), 7.02-6.99 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 2.92 (br, 1H), 2.83-2.74 (m, 2H), 2.41-2.38 (t, *J* = 6.2 Hz, 1H), 1.65 (s, 3H), 1.58-1.55 (d, *J* = 9.9 Hz, 1H), 1.49 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 160.0, 157.0, 153.2, 138.2, 132.7, 131.2, 129.6, 129.1, 123.2, 121.0, 111.5, 76.1, 55.6, 51.9, 47.1, 43.2, 34.7, 29.0, 27.1, 24.1. IR (KBr): 3564, 3445, 2926, 2868, 1600, 1583, 1569, 1493, 1463, 1437, 1367, 1302, 1244, 1098, 1025, 923, 751 cm^{-1}. MS *m/z*: 309 (M^+, 16), 307 (10), 294 (100), 276 (67), 266 (48), 252 (36), 236 (39), 128 (4), 77 (5). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{20}H_{23}NO_2$, 309.1729; found, 309.1721.

(1*S*,8*S*,9*R*)-5-(2-Hydroxy-phenyl)-8,10,10-trimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-ol 16

To a solution of **15** (0.18 g, 0.5 mmol) in anhydrous NMP (1.10 mL) was added PhSH (58 μL, 0.5 mmol) and K_2CO_3 (4.0 mg, 0.03 mmol), and heated to 250 ºC for refluxing 30 min (TLC). The reaction mixture was cooled to room temperature and a 5% NaOH (25 mL) was added, then the aqueous solution was neutralized by adding 1 M HCl to pH = 8. The aqueous phase was extracted with diethyl ether three times, and the combined extracts were dried over anhydrous $MgSO_4$. 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 **16** (0.22 g, 0.7 mmol). Yield: 84%. $[\alpha]^{20.7}_D$ +103.0º (*c* 1.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.78-7.75 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.70-7.68 (d, *J* = 8.2 Hz, 1H), 7.46-7.43 (d, *J* = 8.2 Hz, 1H), 7.30-7.26 (m, 1H), 7.03-7.01 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.93-6.89 (m, 1H), 2.85-2.77 (m, 2H), 2.44 (br, 1H), 2.40-2.37 (t, *J* = 6.2 Hz, 1H), 1.65 (s, 3H), 1.54-1.51 (d, *J* = 9.8 Hz, 1H), 1.49 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.4, 157.0, 155.7, 138.9, 135.1, 130.9, 125.9, 119.4, 118.9, 118.4, 117.7, 75.9, 52.6, 47.1, 43.1, 35.0, 28.5, 27.0, 24.0. IR (KBr): 3468, 2927, 1586, 1471, 1411, 1368, 1290, 1251, 1221, 1151, 1102, 1059, 845, 752, 620 cm^{-1}. MS *m/z*: 295 (M^+, 22), 266 (39), 250 (80), 240 (100), 235 (12). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{19}H_{21}NO_2$, 295.1572; found, 295.1570.

(1*S*,8*R*,9*S*)-2-[5-(2-Methoxy-phenyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-8-yl]-propan-2-ol 17

To a solution of diisopropylamine (121 μL, 1.2

mmol) in THF (5 mL) at 0 ºC was added *n*-BuLi (0.90 mL, 1.2 mmol, 1.33 M in hexane) and stirred for 30 min. The prepared LDA solution was cooled to -78 ºC, and a solution of **5** (0.28 g, 1.0 mmol) in THF (6 mL) was transfered to LDA solution by cannula. The solution became a blue color and was stirred at -78 ºC for 2 h. A solution of acetone (128 μL, 1.75 mmol) in THF (10 mL) was added and stirred overnight at room temperature. The solution became orange color and quenched by adding water. The resulting solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous $MgSO_4$. 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 **17** (0.22 g, 0.7 mmol). Yield: 61%. $[\alpha]^{20.8}_D$ -0.9º (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.05 (br, 1H), 7.74-7.72 (d, *J* = 7.4 Hz, 1H), 7.61-7.59 (d, *J* = 7.8 Hz, 1H), 7.35-7.28 (m, 1H), 7.06-7.02 (t, *J* = 7.5 Hz, 1H), 6.99-6.97 (d, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.26 (s, 1H), 2.79-2.77 (t, *J* = 5.4 Hz, 1H), 2.63-2.58 (m, 1H), 2.37-2.35 (t, *J* = 5.4 Hz, 1H), 1.44 (s, 3H), 1.43-1.38 (d, *J* = 9.3 Hz, 1H), 1.33 (s, 3H), 1.14 (s, 3H), 0.73 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 157.9, 157.0, 151.5, 140.9, 133.3, 130.8, 129.7, 128.4, 122.0, 121.1, 111.4, 74.2, 55.5, 52.9, 46.4, 42.7, 42.2, 29.5, 29.2, 27.5, 26.4, 21.2. IR (KBr): 3306, 2974, 2939, 2867, 1703, 1584, 1464, 1417, 1241, 1163, 1122, 1024, 860, 752, 646 cm^{-1}.

(5*S*,7*S*)-(+)-5,6,7,8-Tetrahydro-6,6-dimethyl-2-(2-hydroxyphenyl)-5,7-methanoquinoline 18

To a solution of **5** (1.2 g, 4.3 mmol) in dichloromethane (40 mL) was added BBr_3 (8.1 mL, 32.0 mmol, 1 M in dichloromethane) slowly under argon and the mixture was stirred at room temperature for 60 h (TLC). A 2 M NaOH solution was added, and neutralized by acetic acid to pH = 8. The resulting solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous $MgSO_4$. 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 **18** (1.02 g, 3.8 mmol). Yield: 90%. mp: 130-131 ºC. $[\alpha]^{22.0}_D$ +114.0º (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.78-7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62-7.60 (d, *J* = 8.1 Hz, 1H), 7.37-7.35 (d, *J* = 8.1 Hz, 1H), 7.28-7.24 (m, 1H), 7.02-7.00 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.90-6.86 (m, 1H), 3.14-3.13 (d, *J* = 2.8 Hz, 2H), 2.81-2.78 (t, *J* = 5.6 Hz, 1H), 2.75-2.70 (m, 1H), 2.41-2.38 (m, 1H), 1.43 (s, 3H), 1.31-1.29 (d, *J* = 9.6 Hz, 1H), 0.67 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.5, 154.8, 153.4, 140.2, 134.7, 130.6, 125.7, 119.3, 118.6, 118.4, 115.6, 46.2, 40.0, 39.7, 35.8, 32.1, 26.0, 21.2. IR (KBr): 2938, 1586, 1497, 1469, 1425, 1382, 1294, 1254, 1154, 946, 850, 768, 751, 625 cm^{-1}. MS *m/z*: 265 (M^+, 100), 250 (66), 236 (24), 222 (75), 210 (13), 128 (9), 91 (3), 77 (6). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{18}H_{19}ON$, 265.1647; found, 265.1458.

(1*S*,8*R*,9*S*)-2-[8-(1-Hydroxy-1-methyl-ethyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl]-phenol 19

To a solution of diisopropylamine (253 μL, 1.2 mmol) in THF (6 mL) at 0 ºC was added *n*-BuLi (1.5 mL, 2.4 mmol, 1.6 M in hexane) and stirred for 30 min. The prepared LDA solution was cooled to -78 ºC, and a solution of **18** (0.26 g, 1.0 mmol) in THF (6 mL) was transfered to LDA solution by cannula. The solution became a blue color and was stirred at -78 ºC for 2 h. A solution of acetone (108 μL, 1.5 mmol) in THF (20 mL) was added and stirred over night at room temperature. The reaction was quenched by adding water. The resulting solution was extracted with ethyl acetate three times, and the combined extracts were dried over anhydrous $MgSO_4$. 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 **19** (0.22 g, 0.7 mmol). Yield: 68%. $[\alpha]^{20.4}_D$ -43.3º (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.71-7.68 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.60-7.58 (d, *J* = 8.1 Hz, 1H), 7.40-7.38 (d, *J* = 8.0 Hz, 1H), 7.28-7.24 (m, 1H), 7.02-6.99 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.92-6.88 (m, 1H), 3.25-3.22 (m, 1H), 2.78-2.75 (t, *J* = 5.6 Hz, 1H), 2.61-2.56 (m, 1H), 2.45-2.41 (m, 1H), 1.57-1.55 (d, *J* = 9.8 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.21 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 158.1, 155.5, 154.4, 141.3, 135.2, 130.6, 126.5, 120.7, 119.0, 118.2, 117.4, 74.3, 53.3, 46.5, 43.2, 42.5, 30.8, 28.3, 26.2, 20.9. IR (KBr): 3393, 2953, 2869, 1583, 1471, 1384, 1293, 1253, 1122, 898, 852, 761, 749, 608 cm^{-1}. MS *m/z*: 323 (M^+, 71), 290 (23), 264 (84), 250 (87), 236 (46), 222 (100), 210 (14), 128 (10), 59 (23). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{21}H_{25}NO_2$, 323.1885; found, 323.1876.

Typical procedure for the enantioselective addition of diethylzinc to aldehydes catalyzed by the ligand 10

Aldehyde (0.5 mmol) was added to a solution of ligand **10** (14.0 mg, 2.5 μmol) in toluene (1.0 mL) at room

temperature, and then a solution of diethylzinc (1.0 mL, 1 M in hexane) was added and stirred for 30 h. The reaction was quenched by adding 1 M HCl (0.5 mL), and the reaction mixture was extracted three times 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 products. The enantiomeric excess of products was determined by HPLC (Chiralcel OD-H column, flow rate 0.25 mL/min, 10% 2-propanol in hexane, 254 nm UV detector).

The enantiomeric excesses of products were determined by the following methods.

Method A: To a solution of product (0.05 mmol) in dichloromethane (2 mL) was added acetic anhydride (0.07 mL) and pyridine (0.03 mL), and stirred for 3 h. After 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 the product. The enantiomeric excess of products were determined by HPLC (Chiralcel OD-H column, flow rate 0.25 mL/min, 10% 2-propanol in hexane, 254 nm UV detector, and EZChrom^{TM} Chromatography Data System.)

Method B: To a solution of product (0.05 mmol) in dichloromethane (2 mL) was added benzoyl chloride (0.07 mL) and pyridine (0.03 mL), and stirred for 12 h. After 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 the product. The enantiomeric excess of products were determined by HPLC (Chiralcel OD-H or OJ-H column, flow rate 0.25 or 0.5 mL/min, 10% 2-propanol in hexane, 254 nm UV detector, and EZChrom^{TM} Chromatography Data System.)

Method C: To a solution of product (0.05 mmol) in dichloromethane (2 mL) was added (+)-MTPA (21.1 mg, 0.09 mmol), DMAP (cat.) and DCC (41.3 mg, 0.2 mmol), and stirred for 12 h. After filtration 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 the product. The enantiomeric excesses of products were determined by ^{19}F NMR spectrum.

(*S*)-1-Phenyl-propan-1-ol 20

Yield: 86%. $[\alpha]^{20.6}_D$ -44.9º (*c* 1.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.38-7.32 (m, 4H), 7.31-7.25 (m, 1H), 4.59-4.56 (t, *J* = 6.5 Hz, 1H), 2.16 (br, 1H), 1.86-1.71 (m, 2H), 0.94-0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 144.6, 128.4, 127.5, 126.0, 76.0, 31.9, 10.2. IR (KBr): 3374, 2982, 2964, 2876, 1492, 1453, 1330, 1200, 1095, 1012, 973, 761, 699, 544 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 23.20 min, t_R of *S* isomer 24.76 min, *R* : *S* = 10.49 : 89.50, ee%: 79%.

(*S*)-1-*o*-Tolyl-propan-1-ol 21

Yield: 70%. $[\alpha]^{20.5}_D$ -44.8º (*c* 1.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.47-7.45 (d, *J* = 7.4 Hz, 1H), 7.26-7.13 (m, 3H), 4.87-4.84 (t, *J* = 6.4 Hz, 1H), 2.35 (s, 3H), 1.99 (br, 1H), 1.80-1.73 (m, 2H), 1.01-0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 142.8, 134.6, 130.3, 127.1, 126.2, 125.3, 72.0, 30.9, 19.1, 10.4. IR (KBr): 3368, 3065, 3024, 2964, 2876, 1487, 1461, 1379, 1091, 1052, 973, 750, 726 cm^{-1}.

(*S*)-1-*o*-Tolylpropyl acetate 21-1

Yield: 75.4%. $[\alpha]^{20.1}_D$ -67.5º (*c* 0.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.35-7.33 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.22-7.17 (m, 2H), 7.16-7.13 (m, 1H), 5.92-5.88 (m, 1H), 2.41 (s, 3H), 2.08 (s, 3H), 1.95-1.75 (m, 2H), 0.94-0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 170.5, 155.9, 139.2, 135.2, 130.3, 127.5, 126.1, 125.8, 108.9, 78.0, 74.0, 65.2, 30.6, 29.7, 28.9, 21.3, 19.3, 10.1. IR (KBr): 2923, 2851, 1736, 1459, 1371, 1237, 1078, 1017, 801, 757, 721 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 15.80 min, t_R of *S* isomer 16.92 min, *R* : *S* = 12.07 : 87.92, ee%: 75%.

(*S*)-1-*m*-Tolylpropan-1-ol 22

Yield: 65%. $[\alpha]^{20.7}_D$ -31.9º (*c* 1.20, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.26-7.23 (t, *J* = 7.2 Hz, 1H), 7.17-7.09 (m, 3H), 4.56-4.53 (t, *J* = 6.5 Hz, 1H), 2.37 (s, 3H), 2.09 (br, 1H), 1.86-1.71 (m, 2H), 0.94-0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 144.6, 138.0, 128.3, 128.2, 126.7, 123.1, 76.1, 31.9, 21.5, 10.2. IR (KBr): 3370, 3026, 2963, 2931, 2875, 1608, 1488, 1456, 1378, 1322, 1158, 1085, 1044, 1015, 975, 784, 703 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 20.87 min, t_R of *S* isomer 22.84 min, *R* : *S* =11.16: 88.83, ee%: 77%.

(*S*)-1-*p*-Tolylpropan-1-ol 23

Yield: 52%. $[\alpha]^{21.1}_D$ -37.6º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.24-7.22 (d, *J* = 8.1 Hz, 2H), 7.18-7.16 (d, *J* = 8.0 Hz, 2H), 4.56-4.53 (t, *J* = 6.6 Hz, 1H), 2.36 (s, 3H), 2.09 (br, 1H), 1.87-1.68 (m, 2H), 0.93-0.90 (t, *J* =

7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 141.7, 137.1, 129.1, 126.0, 75.9, 31.8, 21.1, 10.2. IR (KBr): 3378, 2963, 2875, 1903, 1614, 1514, 1455, 1378, 1098, 1403, 1012, 973, 902, 816, 538 cm^{-1}. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 32.70 min, t_R of *S* isomer 30.74 min, *R* : *S* = 5.31 : 94.67, ee%: 89%.

(*S*)-1-(2-Methoxyphenyl)propan-1-ol 24

Yield: 52%. $[\alpha]^{20.8}_D$ -9.8º (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.32-7.30 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.27-7.22 (m, 1H), 6.98-6.94 (t, *J* = 7.5 Hz, 1H), 6.79-6.77 (d, *J* = 8.2 Hz, 1H), 4.82-4.79 (t, *J* = 6.6 Hz, 3H), 3.83 (s, 3H), 2.79 (br, 1H), 1.85-1.78 (m, 2H), 0.98-0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 156.6, 132.5, 128.2, 127.1, 120.7, 110.5, 72.2, 55.3, 30.2, 10.5. IR (KBr): 3406, 2963, 2876, 2030, 1601, 1491, 1464, 1438, 1287, 1237, 1089, 1046, 1028, 974, 901, 754 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/i-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 26.82 min, t_R of *S* isomer 25.33 min, *R* : *S* = 29.71: 70.29, ee%: 41%.

(*S*)-1-(3-Methoxyphenyl)propan-1-ol 25

Yield: 87%. $\alpha]^{20.6}_D$ -29.5º (*c* 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.27-7.23 (m, 1H), 6.92-6.90 (m, 2H), 6.82-6.79 (m, 1H), 4.57-4.53 (t, *J* = 6.6 Hz, 3H), 3.80 (s, 3H), 2.10 (br, 1H), 1.86-1.68 (m, 2H), 0.93-0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 159.7, 146.4, 129.4, 118.3, 112.9, 111.5, 75.9, 55.2, 31.8, 10.2. IR (KBr): 3408, 2963, 2876, 1929, 1602, 1487, 1485, 1318, 1261, 1156, 1084, 1043, 978, 858, 782, 699, 563, 468 cm^{-1}.

(*S*)-1-(3-Methoxyphenyl)propyl acetate 25-1

Yield: 91%. $[\alpha]^{19.9}_D$ -65.2º (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.28-7.24 (d, *J* = 7.9 Hz, 1H), 6.92-6.90 (d, *J* = 7.8 Hz, 1H), 6.88-6.87 (t, *J* = 2.3 Hz, 1H), 6.84-6.81 (m, 1H), 5.66-5.62 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 2.10 (s, 3H), 1.94-1.74 (m, 2H), 0.90-0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 170.4, 159.6, 142.2, 129.4, 118.9, 113.0, 112.3, 76.8, 55.2, 29.3, 21.3, 9.9. IR (KBr): 2968, 2938, 2878, 1735, 1603, 1587, 1491, 1456, 1436, 1371, 1238, 1160, 1083, 1042, 1020, 967, 876, 783, 699 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 19.31 min, t_R of *S* isomer 20.91 min, *R* : *S* = 12.43 : 87.57, ee%: 75%.

(*S*)-1-(4-Methoxyphenyl)propan-1-ol 26

Yield: 40%. $[\alpha]^{21.0}_D$ -15.1º (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.25-7.21 (m, 2H), 6.88-6.85 (m, 2H), 4.51-4.47 (t, *J* = 6.7 Hz, 1H), 3.78 (s, 3H), 2.28 (br, 1H), 1.84-1.64 (m, 2H), 0.89-0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 158.9, 136.9, 127.2, 113.7, 75.6, 55.2, 31.8, 10.2. IR (KBr): 3400, 2962, 2934, 2875, 2054, 1888, 1612, 1585, 1513, 1463, 1301, 1097, 1037, 974, 830, 548 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 28.56 min, t_R of *S* isomer 30.61 min, *R* : *S* = 33.95 : 66.05, ee%: 33%.

(*S*)-1-(2-Chlorophenyl)propan-1-ol 27

Yield: 72%. $[\alpha]^{20.8}_D$ -23.4º (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.53-7.51 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.33-7.30 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.29-7.25 (m, 1H), 7.20-7.16 (m, 1H), 5.06-5.03 (m, 1H), 2.37 (br, 1H), 1.85-1.68 (m, 2H), 0.99-0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 142.0, 132.0, 129.3, 128.3, 127.2, 127.0, 71.9, 30.5, 10.1. IR (KBr): 3367, 3067, 2967, 2877, 1573, 1590, 1466, 1437, 1102, 1048, 1032, 976, 752, 702, 460 cm^{-1}.

(*S*)-1-(2-Chlorophenyl)propyl benzoate 27-1

Yield: 81%. $[\alpha]^{20.8}_D$ +51.7º (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.13-8.11 (dd, *J* = 5.0, 1.3 Hz, 2H), 7.60-7.56 (m, 1H), 7.49-7.45 (m, 3H), 7.39-7.37 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.27-7.19 (m, 2H), 6.35-6.32 (t, *J* = 6.4 Hz, 3H), 2.07-1.99 (m, 2H), 1.06-1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 165.7, 138.7, 133.1, 132.3, 130.3, 129.7, 129.7, 128.7, 128.5, 128.3, 127.0, 127.0, 74.5, 28.6, 9.9. IR (KBr): 3065, 2971, 2936, 1720, 1601, 1451, 1314, 1268, 1177, 1109, 1069, 1026, 944, 754, 712, 463 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 16.56 min, t_R of *S* isomer 18.61 min, *R* : *S* = 30.31 : 69.69, ee%: 39%.

(*S*)-1-(3-Chlorophenyl)propan-1-ol 28

Yield: 91%. $[\alpha]^{21.0}_D$ -29.8º (*c* 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.33-7.32 (m, 1H), 7.28-7.24 (t, *J* = 7.9 Hz, 1H), 7.24-7.21 (m, 1H), 7.20-7.18 (m, 1H), 4.56-4.53 (t, *J* = 6.5 Hz, 3H), 2.22 (br, 1H), 1.81-1.66 (m, 2H), 0.92-0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 146.7, 134.3, 129.7, 127.6, 126.2, 124.2, 75.3, 31.9, 10.0. IR (KBr): 3366, 3065, 2966, 2877, 1942, 1869, 1598, 1575, 1477, 1462, 1432, 1261, 1198, 1084, 1044, 1015, 977, 881, 785, 698, 508 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 22.84 min, t_R of *S* isomer 21.81 min, *R* : *S* = 8.17 : 91.82, ee%: 83%.

(*S*)-1-(4-Chlorophenyl)propan-1-ol 29

Yield: 93%. $[\alpha]^{21.3}_D$ -31.4º (*c* 1.00, $CHCl_3$). ^{1}H NMR

(400 MHz, $CDCl_3$, δ): 7.30-7.28 (dd, *J* = 6.5, 1.8 Hz, 2H), 7.24-7.22 (dd, *J* = 2.8, 1.8 Hz, 2H), 4.55-4.51 (t, *J* = 6.6 Hz, 1H), 2.31 (br, 1H), 1.81-1.63 (m, 2H), 0.90-0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 143.0, 133.0, 128.5, 127.4, 75.2, 31.9, 10.0. IR (KBr): 3366, 2966, 2933, 2877, 1902, 1597, 1492, 1463, 1409, 1090, 1013, 975, 902, 824, 548, 527, 461 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 22.60 min, t_R of *S* isomer 21.49 min, *R* : *S* = 12.48 : 87.51, ee%: 75%.

3-(1-Hydroxypropyl)benzonitrile 30

Yield: 94%. $[\alpha]^{20.4}_D$ -27.4º (*c* 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.61-7.60 (s, 1H), 7.56-7.54 (m, 1H), 7.53-7.50 (m, 1H), 7.44-7.40 (t, *J* = 7.6 Hz, 1H), 4.63-4.60 (t, *J* = 6.4 Hz, 1H), 2.61 (br, 1H), 1.79-1.67 (m, 2H), 0.91-0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 146.2, 131.0, 130.5, 120.6, 129.1, 118.9, 112.2, 74.7, 32.0, 9.8. IR (KBr): 3437, 3068, 2967, 2934, 2877, 2231, 1965, 1903, 1583, 1434, 1320, 1229, 1149, 1089, 1047, 981, 901, 801, 693, 490 cm^{-1}.

1-(3-Cyanophenyl)propyl acetate 30-1

Yield: 89%. $[\alpha]^{21.5}_D$ -57.5º (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.61-7.53 (m, 3H), 7.46-7.43 (t, *J* = 8.0 Hz, 1H), 5.66-5.63 (t, *J* = 6.2 Hz, 1H), 2.10 (s, 3H), 1.96-1.75 (m, 2H), 0.90-0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 170.1, 142.3, 131.4, 130.9, 130.0, 129.2, 118.6, 112.7, 76.1, 29.2, 21.0, 9.6. IR (KBr): 2971, 2930, 2230, 1737, 1372, 1235, 1085, 1043, 1021, 903, 800, 694, 517, 488 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R 23.55 and 24.81 min. ee%: 79%.

4-(1-Hydroxypropyl)benzonitrile 31

Yield: 91%. $[\alpha]^{19.7}_D$ -26.0º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.57-7.55 (d, *J* = 7.8 Hz, 2H), 7.42-7.40 (d, *J* = 8.3 Hz, 2H), 4.64-4.61 (t, *J* = 6.4 Hz, 1H), 2.74 (br, 1H), 1.73-1.67 (m, 2H), 0.89-0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 150.2, 132.2, 126.7, 119.0, 110.8, 74.9, 32.0, 9.8. IR (KBr): 3435, 2967, 2934, 2877, 2229, 1608, 1503, 1460, 1408, 1202, 1097, 1046, 1016, 980, 965, 847, 564 cm^{-1}.

1-(4-Cyanophenyl)propyl benzoate 31-1

Yield: 90%. $[\alpha]^{20.6}_D$ +35.4º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.09-8.07 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.66-7.64 (d, *J* = 8.4 Hz, 2H), 7.61-7.57 (t, *J* = 7.5 Hz, 1H), 7.52-7.45 (m, 4H), 5.93-5.90 (t, *J* = 7.0 Hz, 1H), 2.10-1.92 (m, 2H), 1.00-0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 165.7, 146.1, 133.3, 132.4, 129.9, 129.7, 128.5, 128.3, 127.0, 118.7, 111.7, 29.5, 9.8. IR (KBr): 3063, 2972, 2936, 2229, 1720, 1610, 1451, 1314, 1270, 1176, 1110, 1069, 1025, 842, 711, 561 cm^{-1}. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R 33.15 and 38.18 min. ee%: 71%.

1-(3-(Dimethylamino)phenyl)propan-1-ol 32

Yield: 87%. $[\alpha]^{21.9}_D$ -25.7º (*c* 1.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.24-7.20 (t, *J* = 7.8 Hz, 2H), 6.74-6.64 (m, 3H), 4.56-4.53 (t, *J* = 6.6 Hz, 1H), 2.96 (s, 6H), 1.87-1.74 (m, 3H), 0.96-0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 150.8, 145.7, 129.1, 114.3, 111.8, 110.1, 76.6, 40.7, 31.8, 10.4. IR (KBr): 3390, 2961, 2874, 1604, 1581, 1498, 1438, 1350, 1228, 1138, 1046, 997, 965, 909, 853, 776, 698, 467 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.50 mL/min), t_R 19.83 and 28.23 min ee%: 77%.

(*S*)-1-Cyclohexylpropan-1-ol 33

Yield: 77%. $[\alpha]^{19.9}_D$ -5.3º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 3.30-3.25 (m, 1H), 1.80-1.65 (m, 5H), 1.55-0.98 (m, 9H), 0.97-0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 77.5, 43.2, 29.3, 27.8, 26.8, 26.6, 26.4, 26.2, 10.2. IR (KBr): 3371, 2926, 2852, 1449, 1123, 971, 892 cm^{-1}.

(*S,2R*)-1-Cyclohexylpropyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 33-1

Yield: 57%. $[\alpha]^{21.7}_D$ +15.9º (*c* 1.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.58-7.57 (m, 2H), 7.41-7.38 (m, 4H), 4.91-4.89 (m, 1H), 3.58-3.56 (m, 3H), 1.76-1.58 (m, 8H), 1.23-1.00 (m, 7H), 0.93-0.89 (t, *J* = 7.4 Hz, 2H), 0.81-0.78 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 129.4, 128.2, 127.4, 82.6, 55.7, 55.4, 40.2, 34.9, 28.6, 27.5, 26.3, 26.1, 26.0, 25.5, 24.7, 23.5, 9.8. IR (KBr): 3031, 2932, 2855, 1743, 1496, 1451, 1256, 1183, 1121, 1081, 1055, 1018, 994, 898, 765, 716, 645 cm^{-1}. ^{19}F NMR (376 MHz, $CDCl_3$, δ): -71.19 (*R*) and -71.23 (*S*); *R* : *S* = 1.00 : 9.63, ee%: 81%.

(*S*)-Nonan-3-ol 34

Yield: 57%. $[\alpha]^{22.0}_D$ +4.3º (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 3.52-3.47 (m, 1H), 1.51-1.27 (m, 13H), 0.93-0.89 (t, *J* = 7.4 Hz, 3H), 0.87-0.84 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 73.3, 36.9, 31.8, 30.1, 29.4, 25.6, 22.6, 14.0, 9.8. IR (KBr): 3348, 2950, 2858, 1464, 1378, 1337, 1123, 1057, 966, 724, 599 cm^{-1}.

((*S,2R*)-)-Nonan-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 34-1

Yield: 38%. $[\alpha]^{22.1}_D$ +3.6º (*c* 1.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.57-7.55 (m, 2H), 7.41-7.39 (m,

4H), 5.06-5.03 (m, 1H), 3.58-3.56 (m, 3H), 1.70-1.56 (m, 4H), 1.28-1.20 (m, 8H), 0.95-0.82 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 166.4, 132.6, 129.5, 128.3, 127.4, 78.8, 55.4, 33.0, 31.6, 29.0, 26.7, 24.8, 22.5, 14.0, 9.6. IR (KBr): 3307, 3065, 2932, 2857, 2119, 1961, 1744, 1496, 1452, 1256, 1168, 1122, 994, 765, 716, 644, 508 cm^{-1}. ^{19}F NMR (376 MHz, $CDCl_3$, δ): -71.29 (*R*) and -71.37 (*S*); *R* : *S* = 1.00 : 4.86, ee%: 65%.

(*E,S*)-1-Phenylpent-1-en-3-ol 35

Yield: 67%. $[\alpha]^{21.6}_D$ -3.6º (*c* 1.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40-7.39 (d, *J* = 7.4 Hz, 2H), 7.35-7.31 (t, *J* = 7.2 Hz, 2H), 7.27-7.24 (t, *J* = 7.2 Hz, 1H), 6.60-6.56 (d, *J* = 6.8 Hz, 1H), 6.26-6.20 (dd, *J* = 15.9, 6.8 Hz, 1H), 4.23-4.18 (m, 1H), 2.50 (br, 1H), 1.73-1.63 (m, 2H), 1.01-0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 136.9, 132.5, 130.3, 128.6, 127.6, 126.5, 74.3, 30.3, 9.8. IR (KBr): 3655, 3026, 2964, 2875, 1946, 1876, 1803, 1599, 1493, 1450, 1331, 1130, 1058, 1006, 965, 896, 747, 693, 551 cm^{-1}. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90 : 10, flow rate 0.25 mL/min), t_R of *R* isomer 7.71 min, t_R of *S* isomer 11.03 min, *R* : *S* = 30.69 : 69.31, ee%: 39%.

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