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Tetrahedron: *Asymmetry* 15 (2004) 3561–3571

Synthesis of a C_2-symmetric chiral bipyridyldiol ligand and its application in the enantioselective addition of diethylzinc to substituted benzaldehydes

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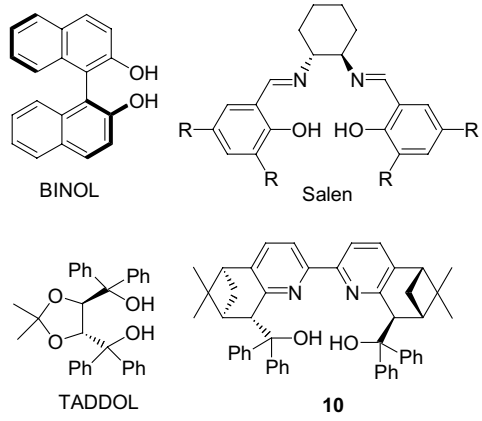
Received 13 August 2004; accepted 29 September 2004

Abstract—Herein the synthesis of a novel C_2-symmetric ligand comprising of a central bipyridine-pinene-derived core and two functionalized diphenylmethanol subunits is described. [8′-(Hydroxy-diphenyl-methyl)-10,10,10′,10′-tetramethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′(7′),3′,5′-hexaen-8-yl]-diphenyl-methanol **10** is a suitable catalyst for the enantioselective addition of dialkylzinc to various aromatic aldehydes with asymmetric inductions of up to 99% ee. Importantly, the correlation of Hammett substituent constants and enantiomeric excess, with the electron-donating group at the *para*-position and the electron-withdrawing group at the *meta*-position of substituted benzaldehydes were demonstrated to give high enantioselectivity in alkylations using diethylzinc.

1. Introduction

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is extremely important in modern synthetic and pharmaceutical chemistry.[1] In particular, enantioselective catalysis is one of the most efficient processes for environmental protection. Consequently, the development of enantioselective catalysts is one of the most important challenges in modern organic chemistry. Extremely promising candidates for such enantioselective catalysts are metal complexes that bear chiral organic ligands. Among the 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.[2] Since the first report by Oguni and Omi,[3] various chiral ligands, including α-amino alcohols,[4] BINOL,[5] salen,[6] TADDOL[7], pyridyl alcohol,[8] and their derivatives, have been used in this type of reaction. However, C_2-symmetric binaphthols (BINOLs),[9] have been relatively neglected, probably due to their lower catalytic activity and enantioselectivity for the organozinc addition reaction.[10] Recently, some modified BINOLs[11] were reported to be effective for the addition of diorganozinc reagents to aldehydes, but the parent BINOL itself is relatively inert to the reaction. The active catalytic species in the addition of diethylzinc to aldehydes can be assumed to be monomeric zinc alkoxides; the cleavage of the higher aggregates may lead to an activation of the catalyst system.[12] The addition of a chiral nitrogen activator to the BINOLs–zinc catalyst system should be one of the most efficient methods of activation, owing to its strong ability to coordinate the zinc cation, which facilitates the alkyl transfer. Consequently, a monomeric zinc complex



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doi:10.1016/j.tetasy.2004.09.031

is expected to form in a similar manner to a chiral salen–zinc complex.[5j,13]

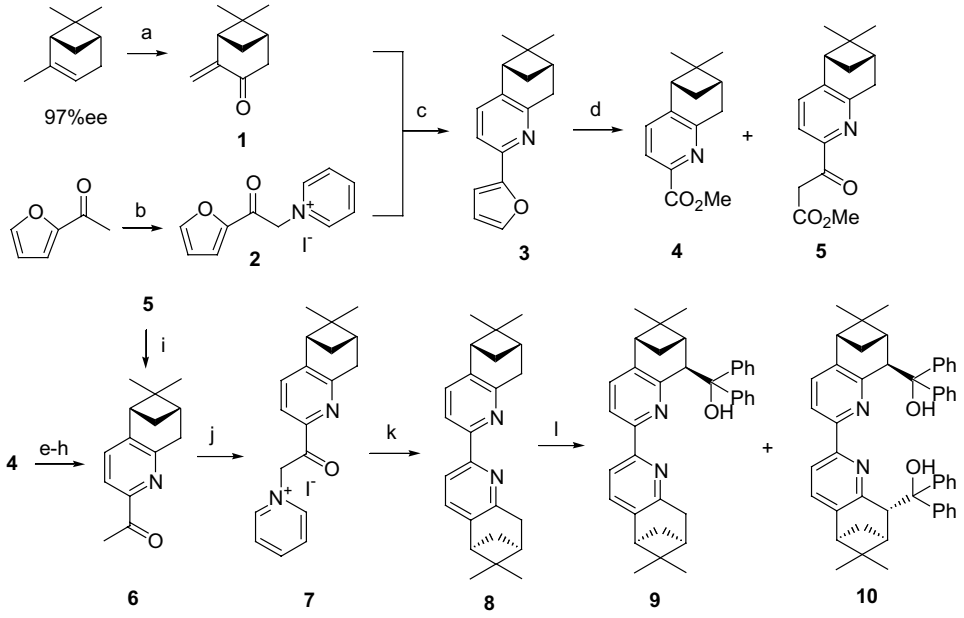
Kishi et al.,[14] von Zelewsky et al.,[15] and Malkov et al.[16] described the synthesis of ligand **8** and its derivatives. According to the above reports, compound **10** is designed to fulfill the requirements of C_2-symmetric, TADDOL-like steric hinder, salen-like, and bipyridine-type ligand for activating diethylzinc. Herein we report the synthesis of compound **10** and the addition of diethylzinc to substituted benzaldehydes with the catalysis of a chiral bipyridyldiol **10** in the presence of Ti(O-*i*-Pr)$_4$.

2. Results and discussion

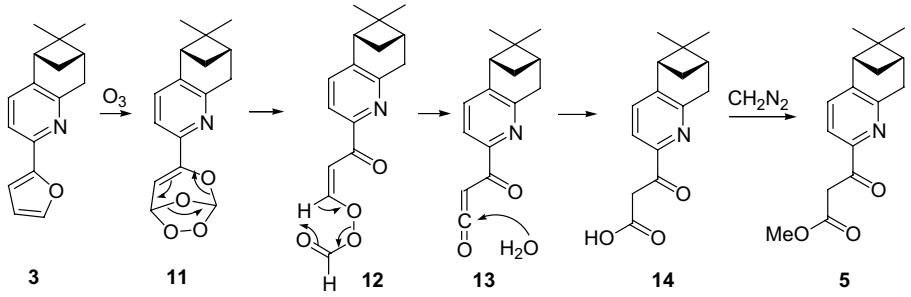
The synthesis of ligand **10** is outlined in Scheme 1. (1*R*)-(+)-α-Pinene was readily photooxygenated in the presence of acetic anhydride, pyridine, DMAP, and TPP to yield directly α,β-unsaturated ketone **1**.[17] Moreover, 2-acetylfuran was heated with iodine in pyridine at 100–110 °C for 3 h and then recrystallized from ethanol to produce pyridinium salt **2**.[18] Compounds **1** and **2** were heated with ammonium acetate in glacial acetic acid at 100–110 °C overnight to yield furyl-pyridine **3**.[14,19] Compound **3** was oxidized by ozonolysis and treated via diazomethane to afford esters **4** and **5** (ca. 2:1). Compound **4** is the common product of ozonolysis, which was reduced by $LiAlH_4$ to produce a primary alcohol. The primary alcohol was oxidized via a Swern oxidation to yield an aldehyde, which was then reacted with MeMgBr to produce a secondary alcohol. The secondary alcohol was oxidized via a Swern oxidation to produce ketone **6**. Product **5** could be decarboxylated by treatment with H_2SO_4 to give ketone **6**. Moreover, compound **6** was treated with iodine in pyridine to yield pyridinium salt **7**, which when reacted with enone **1** and ammonium acetate produced bipyridine **8**. Bipyridyldiol **10** was prepared by treatment of compound **8** with *n*-butyllithium, and in a one-pot reaction where 2 equiv of benzophenone were added in two successive steps to produce **9** and **10**. Compound **9** was converted to **10** by treatment **9** with *n*-butyllithium and benzophenone.

The ozonolysis of the furan group of compound **3** produced a carboxylic acid. Following esterification by diazomethane, we obtained compound **4** along with unexpected compound **5**. To rationalize the formation of compound **5**, the reaction mechanisms shown in Scheme 2 are proposed. A 1,3-dipolar addition of ozone to the double bond of the furanyl group of compound **3** yields the initial ozonide. However, initial ozonide is extremely unstable and cleaves to an aldehyde and a zwitterion intermediate. Recombination of aldehyde and zwitterion yields ozonide **11**. Ozonide **11** then cleaves through the intermediate **12** to yield ketene **13**, which reacts with the contaminated moisture to produce **14**, and then treats with diazomethane to produce methyl ester **5**.

The asymmetric alkylation of benzaldehyde using diethylzinc, in the presence of chiral ligand **10** and Ti(O-*i*-Pr)$_4$ in various solvents (Table 1) at room temperature gave the following enantiomeric excesses of 1-phenyl-1-propanol: in toluene (91%), in tetrahydrofuran (91%), in acetonitrile (89%), and in hexane (14%). Therefore toluene was selected as the reaction solvent in the following

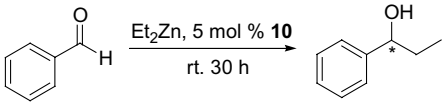


Scheme 1. Reagents and conditions: (a) O_2, TPP, DMAP, Ac_2O, pyridine, CH_2Cl_2, Na-lamp (400 W), 50%; (b) I_2, pyridine, 100-110 °C, 56%; (c) NH_4OAc, AcOH, 100–110 °C, 84%; (d) O_3, CH_2Cl_2–CH_3OH (2:1), −78 °C; CH_2N_2, Et_2O, 0 °C, **4** (42%), **5** (21%); (e) $LiAlH_4$, THF, rt, 72%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 91%; (g) CH_3MgI, Et_2O, rt, 77%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 100%; (i) H_2SO_4, AcOH, H_2O, reflux, 88%; (j) I_2, pyridine, 100–110 °C; (k) **1**, NH_4OAc, AcOH, 100–110 °C, 39%; (l) *n*-BuLi, Et_2O, 0 °C to rt, benzophenone, Et_2O, −78 °C, **9** (82%), **10** (8%).



Scheme 2. The proposed mechanisms for producing product **5**.

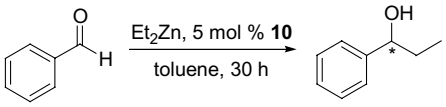
Table 1. Enantiomeric excess (ee%) of the alkylation of benzaldehyde in the presence of Ti(IV)–**10** complex in various solvents



Entry	Solvents	Ee (%)
1	Toluene	91
2	THF	91
3	CH_3CN	89
4	Hexane	14

reactions. The same reactions were conducted in toluene at various temperatures (Table 2), enantiomeric excesses of 1-phenyl-1-propanol: 0 °C (91%), 20 °C (91%), 40 °C (59%), 60 °C (33%), and 80 °C (6%). Therefore the following asymmetric reactions were performed in toluene at room temperature. The asymmetric alkylation of benzaldehyde using diethylzinc in toluene was performed in the absence of Ti(O-*i*-Pr)$_4$, and the reaction remained incomplete even under stirring at room temperature for three days. This phenomenon showed the binaphthols (BINOLs)[5] with low catalytic activity for the organozinc addition reaction, although the reactivity could be improved by the addition of a nitrogen activator to the BINOLs–zinc catalyst system.[5j] Chiral ligand **10** integrated the diol and bipyridyl moieties, with the former performed as a BINOL-like system while the bipyridyl group performed as a nitrogen activator.

Table 2. Enantiomeric excess (ee%) of the alkylation of benzaldehyde in the presence of Ti(IV)–**10** complex at various temperatures



Entry	Temp (°C)	Ee (%)
1	0	91
2	20	91
3	40	59
4	60	33
5	80	6

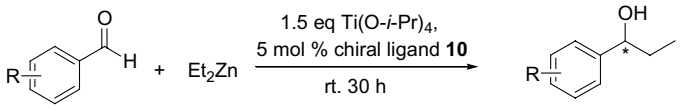
The asymmetric alkylation of substituted benzaldehyde using diethylzinc was performed in the presence of catalyst Ti(IV)–**10** complex as described below. A solution of ligand **10** and Ti(O-*i*-Pr)$_4$ in toluene was stirred at room temperature for 10 min after which a solution of Et_2Zn (1 M in hexane) was added and stirred for 10 min. Lastly the aldehydes were added and stirred at room temperature for 30 h. The reaction was quenched by adding 1 M HCl. After purification by flash chromatography, the enantiomeric excess of the product was determined by HPLC, with the yields, % ee and specific rotation were shown in Table 3. The absolute configurations of all products were determined by comparing the sign of the specific rotations.[22]

The electronic effects in asymmetric hydroborations[20] and epoxidations[21] have been reported. However, there appears to have been no systematic study of how purely electronic effects influence the degree of asymmetric induction. The correlation of Hammett substituent constants and enantiomeric excesses of the alkylation of *meta*-substituted benzaldehydes using diethylzinc, was very high correlation. Importantly the stronger electron-withdrawing substituents on the *meta*-position exhibited higher enantiomeric excesses (*m*-NO_2, >99%; *m*-CN, >99%; *m*-Cl, 98%), while the stronger electron-releasing substituents on the *meta*-position showed lower enantiomeric excesses (*m*-NMe_2, 7%; *m*-Me, 44%; *m*-OMe, 83%) (Fig. 1). On the other hand, the stronger electron-releasing substituents on the *para*-position exhibited higher enantiomeric excesses (*p*-NMe_2, 94%; *p*-OMe, 91%; *p*-Me, 65%), while the stronger electron-withdrawing substituents on the *para*-position displayed lower enantiomeric excesses (*p*-Cl, 7%; *p*-CN, 11%; *p*-NO_2, 47%) (Fig. 2). Moreover, the stronger electron-withdrawing and electron-releasing substituents on the *ortho*-position displayed lower enantiomeric excesses (*o*-NO_2, 3%; *o*-OMe, 6%), while the weaker electron-withdrawing and electron-releasing substituents on the *ortho*-position showed higher enantiomeric excesses (*o*-Cl, 92%; *o*-Me, >99%) (Fig. 3).

3. Conclusion

In conclusion we have developed a novel chiral bipyridinyldiol **10**. This compound was prepared from highly enantiopure (>97% ee) (1*R*)-(+)-α-pinene. Bipyridinyldiol **10** can act as an interesting chiral catalyst in the enantioselective addition of diethylzinc to various substituted benzaldehydes, providing alcohols of (*S*)-configuration with enantiomeric excesses generally ranging

Table 3. The Hammett substituent constants (σ_o, σ_m, and σ_p) and enantiomeric excess (ee%) of the alkylation of substituted benzaldehydes with Ti(IV)–**10** complex



Entry	R	Yield[b] (%)	Ee (%)	Substituent constants[22a]	$[\alpha]_D^{18}$ (c, $CHCl_3$)	Configuration
1	*o*-OMe	79	6	σ_o, +0.12	−1.0 (2.12)	*S*[22d]
2	*m*-OMe	75	83	σ_m, +0.12	−19.5 (1.10)	N/A[a]
3	*p*-OMe	70	91	σ_p, −0.27	−31.5 (2.10)	*S*[22b]
4	*o*-Me	72	>99	σ_o, +0.29	−62.4 (1.41)	*S*[22c]
5	*m*-Me	78	44	σ_m, −0.07	−12.1 (2.43)	N/A[a]
6	*p*-Me	82	65	σ_p, −0.17	−27.3 (1.41)	*S*[22c]
7	*o*-Cl	85	92	σ_o, +1.28	−50.2 (2.10)	*S*[22c]
8	*m*-Cl	96	98	σ_m, +0.37	−28.4 (3.74)	*S*[22c]
9	*p*-Cl	54	7	σ_p, +0.23	−2.7 (1.19)	*S*[22b]
10	*o*-NO_2	13	3	σ_o, +1.99	−5.45 (0.65)	N/A[a]
11	*m*-NO_2	21	>99	σ_m, +0.71	−28.3 (1.35)	N/A[a]
12	*p*-NO_2	24	47	σ_p, +0.78	−15.2 (1.52)	N/A[a]
13	*m*-NMe_2	32	7	σ_m, −0.21	−5.6 (2.31)	N/A[a]
14	*p*-NMe_2	28	94	σ_p, −0.83	−24.6 (3.37)	N/A[a]
15	*m*-CN	41	>99	σ_m, +0.56	−41.7 (4.13)	N/A[a]
16	*p*-CN	94	11	σ_p, +0.66	−6.2 (1.15)	N/A[a]
17	H	67	91	σ, 0		N/A[a]

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

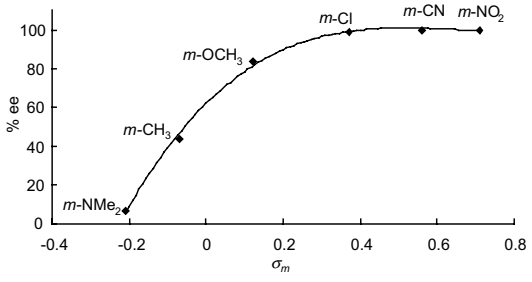


Figure 1. The correlation of substituent constants (σ_m) and the enantiomeric excesses of the alkylation of *meta*-substituted benzaldehydes in the presence of Ti(IV)–**10** complex.

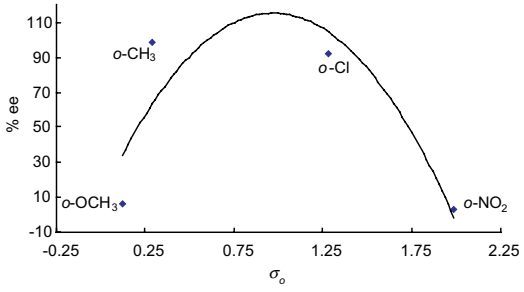


Figure 3. The correlation of substituent constants (σ_o) and the enantiomeric excesses of the alkylation of *ortho*-substituted benzaldehydes in the presence of Ti(IV)–**10** complex.

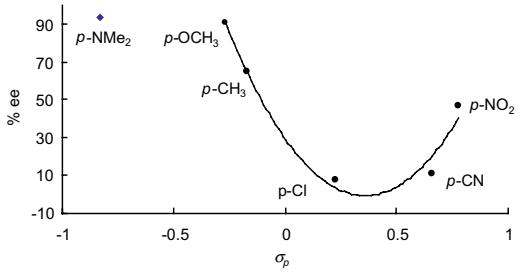


Figure 2. The correlation of substituent constants (σ_p) and the enantiomeric excesses of the alkylation of *para*-substituted benzaldehydes in the presence of Ti(IV)–**10** complex.

from 3–99%. Importantly, the electron-releasing substituents at the *para*-position of the substituted benzaldehydes gave high enantioselectivity during alkylation using diethylzinc. Additionally, electron-withdrawing substituents at the *meta*-position of substituted benzaldehydes gave high enantioselectivity. Moreover, the weaker electron-withdrawing and electron-releasing at the *ortho*-position of substituted benzaldehydes showed higher enantioselectivity. An investigation is currently underway exploring other asymmetric reactions to rationalize this correlation.

4. Experimental

4.1. General

All reactions were carried out in anhydrous solvents. THF and diethyl ether were distilled from sodium–benzophenone under argon. Toluene, CH_3CN, CH_2Cl_2, and hexane were distilled from CaH_2. ^1H NMR spectra were acquired at 300 or 500 MHz (indicated in each case), and ^{13}C NMR were acquired at 75.5 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were determined on a Micromass Platform II

mass spectrometer at a 70 eV. High resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on an ATI Mattson spectrometer. All asymmetric reactions were carried out in dry glassware under nitrogen using a standard glovebox. Enantiomeric excesses were determined on a Lab Alliance Series III high performance liquid chromatography (HPLC) with 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. Et_2Zn (1 M) solution in hexane was purchased from Sigma–Aldrich Co.

4.2. Synthesis of bipyridyldiol 10

4.2.1. (2*S*,5*S*)-6,6-Dimethyl-2-methylene-bicyclo[3.1.1]-heptan-3-one 1. To a solution of (2*R*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene (31.0 mL, 183 mmol), acetic anhydride (17.9 mL, 190 mmol), pyridine (7.4 mL, 92 mmol), DMAP (457 mg, 3.7 mmol), and TPP (13 mg, 21 μmol) in dichloromethane (169 mL) was passed through oxygen gas and irradiated with a sodium lamp (400 W) under a −78 °C dry ice condenser. The reaction was traced by TLC until the (2*R*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-2-ene was completely consumed. The reaction solution was washed with saturated sodium bicarbonate solution, 1 M hydrochloric acid, aqueous solution of copper sulfate, and brine. The organic phase then was dried over anhydrous magnesium sulfate, and after filtration and concentration the resulting brown solution was distilled at 75–78 °C (3 mmHg) to produce compound **1** (13.7 g, 92 mmol). Yield: 50%. $[\alpha]_D^{16} = -69.9$ (*c* 1.11, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.97 (d, $J = 1.6$ Hz, 1H), 5.0 (d, $J = 1.6$ Hz, 1H), 2.78–2.55 (m, 4H), 2.21–2.19 (m, 1H), 1.36 (s, 3H), 1.31–1.28 (d, $J = 10.2$ Hz, 1H), 0.81 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 149.1, 117.4, 48.2, 42.5, 40.8, 38.5, 32.4, 30.9, 26.0, 21.5. IR (dry film): 2929, 1706, 1625 cm^{-1}. MS *m*/*z* (% relative intensity): 151 (M+1, 89), 150 (M^+, 49), 135 (57), 107 (100). HRMS-EI *m*/*z*: $[M]^+$ calcd for $C_{10}H_{14}O$, 150.1044; found, 150.1051.

4.2.2. 1-(2-Furan-2-yl-2-oxo-ethyl)-pyridinium; iodide 2. To a solution of 2-acetylfuran (10.0 mL, 100 mmol) in pyridine (25.0 mL) was added a solution of iodine (25.4 g, 100 mmol) in pyridine (75.0 mL), and the resulting solution heated at 100–110 °C for 3 h. The reaction solution was left to stand overnight, filtered, washed with ethanol, and then recrystallized twice in ethanol. The crystal was dried under vacuum to yield compound **2** (17.7 g, 56.3 mmol). Yield: 56%.

4.2.3. (1*S*,9*S*)-5-Furan-2-yl-10,10-dimethyl-6-aza-tricyclo[7.1.1.0$_{2,7}$]undeca-2(7),3,5-triene 3. A mixture of compound **1** (6.5 g, 43.3 mmol), compound **2** (17.7 g, 56.3 mmol), and ammonium acetate (26.7 g, 346 mmol) in glacial acetic acid (60.0 mL) under an argon atmosphere was heated at 100–110 °C for 10 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 basified by sodium carbonate until the aqueous solution became basic. The aqueous solution was extracted with ethyl acetate five times, and the combined extracts 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 to produce compound **3** (8.7 g, 36.2 mmol). Yield: 84%. $[\alpha]_D^{16} = +88.6$ (*c* 1.43, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.50 (d, $J = 1.7$ Hz, 1H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.20 (d, $J = 7.7$ Hz, 1H), 6.90 (d, $J = 3.3$ Hz, 1H), 6.50 (d, $J = 3.3$ Hz, 1H), 3.15 (d, $J = 2.8$ Hz, 2H), 2.70 (m, 2H), 2.30 (m, 1H), 1.40 (s, 3H), 1.29 (d, $J = 9.4$ Hz, 1H), 0.67 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 156.9, 154.0, 146.8, 142.7, 140.5, 134.7, 115.5, 111.7, 107.2, 46.4, 40.2, 39.5, 36.7, 31.9, 26.0, 21.3. IR (neat): 3116, 2918, 1606, 1587, 1493, 737, 596 cm^{-1}. MS *m*/*z* (% relative intensity): 239 (M^+, 75), 224 (53), 196 (100), 167 (30). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{17}NO$, 239.1310; found, 239.1304.

4.2.4. (1*S*,9*S*)-10,10-Dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]-undeca-2(7),3,5-triene-5-carboxylic acid methyl ester 4. A solution of compound **3** (8.4 g, 35.2 mmol) in methanol–dichloromethane (120:240 mL) was passed through the ozone at −78 °C, and the reaction traced by TLC until compound **3** disappeared. Argon was passed through the reaction solution another 2 min. The solvent was removed using a rotary evaporator to give a brown residue, at which point the minimum amount of methanol was used to dissolve the residue. Sufficient diazomethane in ether was added to the resulting brown solution until nitrogen bubbling stopped. After concentration to produce a brown residue, the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate–hexane (1:9, 1:5, 1:1) as the mobile phase. After concentration, compound **4** (3.4 g, 14.7 mmol) yield 42%, and compound **5** (2.0 g, 7.4 mmol) yield 21% were produced. Compound **4**: $[\alpha]_D^{16} = +71.0$ (*c* 1.39, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.88 (d, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 3.99 (s, 3H), 3.22 (d, $J = 2.8$ Hz, 2H), 2.86 (m, 2H), 2.40 (m, 1H), 1.41 (s, 3H), 1.28 (d, $J = 9.7$ Hz, 1H), 0.63 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 165.7, 157.2, 146.1, 144.7, 133.2, 122.3, 52.4, 46.3, 39.6, 39.0, 36.3, 31.1, 25.5, 20.9. IR (neat): 3613, 3461, 3421, 2925, 1737, 1720, 1575, 1427 cm^{-1}. MS *m*/*z* (% relative intensity): 231 (M^+, 38), 188 (63), 156 (74), 128 (100). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{17}NO_2$, 231.1259; found, 231.1252.

4.2.5. 3-((1*S*,9*S*)-10,10-Dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]-undeca-2(7),3,5-trien-5-yl)-3-oxo-propionic acid methyl ester 5. $[\alpha]_D^{16} = +77.1$ (*c* 1.48, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.81 (d, $J = 7.7$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 4.21 (d, $J = 3.8$ Hz, 2H), 3.74 (s, 3H),

3.11 (d, $J = 2.8$ Hz, 2H), 2.85 (m, 2H), 2.40 (m, 1H), 1.42 (s, 3H), 1.28 (d, $J = 9.7$ Hz, 1H), 0.67 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 194.4, 169.0, 156.5, 149.8, 147.1, 133.5, 119.5, 52.1, 46.7, 44.6, 39.8, 39.4, 36.3, 31.4, 25.8, 21.2. IR (neat): 3376, 2971, 2937, 2873, 2103, 1749, 1698, 1569 cm^{-1}. MS *m/z* (% relative intensity): 273 (M^+, 90), 242 (40), 198 (74), 128 (100). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{16}H_{19}NO_3$, 273.1364; found, 273.1356.

4.2.6. 1-((1*S*,9*S*)-10,10-Dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]-undeca-2(7),3,5-trien-5-yl)-ethanone 6. A solution of compound **4** (3.2 g, 13.7 mmol) in THF (25 mL) was added to a mixture of lithium aluminum hydride (623 mg, 16.4 mmol) in tetrahydrofuran (30 mL) at room temperature under an argon atmosphere. After stirring at room temperature for 30 min, the reaction was quenched by adding water. The reaction mixture was filtered through Celite and washed with tetrahydrofuran, and the combined organic solution 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 the use of ethyl acetate–hexane (1:10, 2:5) as the mobile phase produced a primary alcohol (1*S*,9*S*)-(10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-methanol (2.0 g, 9.9 mmol). Yield: 72%. $[\alpha]_D^{16} = +65.3$ (*c* 0.95, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.20 (d, $J = 7.5$ Hz, 1H), 7.93 (d, $J = 7.5$ Hz, 1H), 4.70 (s, 2H), 3.64 (s, 1H), 3.09 (d, $J = 2.8$ Hz, 2H), 2.77 (m, 2H), 2.39 (m, 1H), 1.40 (s, 3H), 1.27 (d, $J = 9.4$ Hz, 1H), 0.63 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 155.3, 155.2, 141.3, 134.9, 118.0, 63.5, 46.0, 39.8, 39.4, 35.4, 31.8, 25.8, 21.1. IR (neat): 3224, 2927, 2832, 1585, 1467, 1423, 1076, 1074 cm^{-1}. MS *m/z* (% relative intensity): 203 (M^+, 80), 160 (100), 142 (99), 130 (76). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{13}H_{17}NO$, 203.1310; found, 203.1305. DMSO (1.4 mL, 19.7 mmol) was added dropwise to a solution of oxalyl chloride (988 μL, 11.8 mmol) in dichloromethane (50 mL) at −78 °C under an argon atmosphere. After stirring for 20 min, a solution of (1*S*,9*S*)-(10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-methanol (2.0 g, 9.9 mmol) in dichloromethane (20 mL) added. The reaction solution was then stirred for 40 min, and triethylamine (6.75 mL, 48.4 mmol) was added. Subsequently, the reaction solution was warmed to room temperature, stirred at room temperature for 30 min, and then water added. The resulting solution was extracted three times with dichloromethane, and the combined extracts 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 using ethyl acetate–hexane (1:9) as the mobile phase to produce an aldehyde, (1*S*,9*S*)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-5-carbaldehyde (1.8 g, 9 mmol). Yield: 91%. $[\alpha]_D^{16} = +73.0$ (*c* 1.4, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.0 (s, 1H), 7.77 (d, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 7.6$ Hz, 1H), 3.21 (d, $J = 2.8$ Hz, 2H), 2.89 (t, $J = 5.6$ Hz, 1H), 2.75 (m, 1H), 2.44 (m, 1H), 1.43 (s, 3H), 1.31 (d, $J = 9.7$ Hz, 1H), 0.65 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 192.9, 157.7, 150.4, 147.6, 133.5, 119.6, 46.7, 39.7, 39.3, 36.1, 31.3, 25.7, 21.1. IR (thin film): 2967, 2932, 2807, 2682, 1708, 1574 cm^{-1}. MS *m/z* (% relative intensity): 201 (M^+, 24), 200 (27), 158 (100), 130 (26). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{13}H_{15}NO$, 201.1153; found, 201.1145. The iodomethane (2.0 mL, 21.7 mmol) was added to a suspension of magnesium (473 mg, 19.7 mmol) in sodium dried diethyl ether (50 mL), and refluxed for 5 h. Freshly prepared methylmagnesium iodide was added to a solution of (1*S*,9*S*)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene-5-carbaldehyde (1.8 g, 9.0 mmol) in diethyl ether (50 mL), and stirred at room temperature under an argon atmosphere for 1.5 h. A saturated aqueous solution of ammonium chloride then was added to the reaction solution, and the organic phase separated. The aqueous solution was extracted three times using diethyl ether, and the combined organic phase 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 using ethyl acetate–hexane (1:9, 1:5) as the mobile phase, thus producing a diastereoisomers mixture of secondary alcohol 1-((1*S*,9*S*)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-ethanol (1.5 g, 7 mmol). Yield: 77%. $[\alpha]_D^{16} = +63.7$ (*c* 0.9, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.20 (d, $J = 7.6$ Hz, 1H), 7.94 (m, 1H), 4.84 (m, 1H), 4.43 (m, 1H), 3.08 (d, $J = 2.7$ Hz, 2H), 2.75 (m, 2H), 2.36 (m, 1H), 1.50 (m, 3H), 1.40 (s, 3H), 1.29 (m, 1H), 0.63 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 159.3, 154.8, 140.9, 134.7, 116.6, 68.2, 46.0, 39.9, 39.4, 35.6, 31.8, 25.9, 23.9, 21.2. IR (neat): 3257, 2971, 2919, 2719, 1926, 1589, 1463, 1419, 1105 cm^{-1}. MS *m/z* (% relative intensity): 217 (M^+, 100), 202 (66), 174 (75), 156 (95). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{14}H_{19}NO$, 217.1466; found, 217.1458. DMSO (1.0 mL, 14.1 mmol) was added dropwise to a solution of oxalyl chloride (705 L, 8.4 mmol) in dichloromethane (35 mL) at −78 °C under an argon atmosphere. After stirring for 20 min, a solution of 1-((1*S*,9*S*)-10,10-dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-trien-5-yl)-ethanol (1.5 g, 7 mmol) in dichloromethane (20 mL) was added. The reaction was then stirred for 40 min, and triethylamine (4.8 mL, 34.4 mmol) added. The reaction solution was warmed to room temperature, and stirred for 30 min before adding water. The resulting solution was extracted with dichloromethane thrice, and the combined extracts 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 (1:9) as the mobile phase to produce compound **6** (1.5 g, 7 mmol). Yield: 100%. $[\alpha]_D^{16} = +73.0$ (*c* 1.4, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.77 (d, $J = 7.6$ Hz, 1H), 7.32 (d, $J = 7.7$ Hz, 1H), 3.15 (d, $J = 2.8$ Hz, 2H), 2.85 (m, 5H), 2.40 (m, 1H), 1.42 (s, 3H), 1.29 (d, $J = 9.6$ Hz, 1H), 0.64 (s, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 199.7, 156.3, 150.9, 146.4, 133.5, 119.1, 46.6, 39.8, 39.3, 36.3, 31.4, 25.9, 25.8, 21.1. IR (neat): 3367, 2927, 1695, 1571 cm^{-1}. MS *m/z* (% relative intensity): 215 (M^+, 46), 200 (43), 172 (100), 130 (23). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{14}H_{17}NO$, 215.1310; found, 215.1312.

4.2.7. 1-((1*S*,9*S*)-10,10-Dimethyl-6-aza-tricyclo[7.1.1.0^{2,7}]-undeca-2(7),3,5-trien-5-yl)-ethanone 6. A solution of compound **5** (1.9 g, 6.8 mmol) in concd sulfuric acid (1 mL), glacial acetic acid (10 mL), and water (3 mL) was refluxed for 13 h. The reaction solution was cooled in an ice bath and basified by adding 2 M sodium hydroxide aqueous solution until the solution became basic. The resultant solution was extracted three times with diethyl ether, and the combined extracts 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 to produce compound **6** (1.3 g, 6.0 mmol). Yield: 88%.

4.2.8. (1*S*,9*S*,1′*S*,9′*S*)-10,10,10′,10′-Tetramethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′,4′,6′-hexane 8. A solution of iodine (4.95 g, 19.5 mmol) in pyridine (15 mL) was added to a solution of compound **6** (2.75 g, 12.8 mmol) in pyridine (4.0 mL), and the resulting solution heated at 100–110 °C for 16 h, after which iodine (1.00 g, 3.95 mmol) was added and the solution stirred for 3 h. The reaction solution was stored at −20 °C for 4 h, after which the solvent was removed, and the remaining solid dried under vacuum to produce compound **7**, which was not further purified before the next reaction. A mixture of compound **1** (2.82 g, 18.8 mmol), compound **7** (11.69 g, 27.8 mmol), and ammonium acetate (11.59 g, 150.4 mmol) in glacial acetic acid (25 mL) under an argon atmosphere was heated at 100–110 °C for 15 h. After cooling to room temperature, the reaction mixture was transferred to a 500-mL Erlenmeyer flask, at which point water (100 mL) was added, and the mixture basified by sodium carbonate until it became basic. The aqueous solution was extracted three times with ethyl acetate and the combined extracts 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 ethyl acetate–hexane (1:19, 1:9) as the mobile phase to produce compound **8** (1.94 g, 5.7 mmol). Yield: 39%. $[\alpha]_D^{16} = +123.7$ (*c* 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.00 (d, $J = 7.7$ Hz, 2H), 7.30 (d, $J = 7.7$ Hz, 2H), 3.18 (d, $J = 2.6$ Hz, 4H), 2.81 (m, 4H), 2.40 (m, 2H), 1.41 (s, 6H), 1.31 (m, 2H), 0.67 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ): 156.2, 152.6, 142.3, 143.4, 118.5, 46.3, 40.0, 39.4, 36.3, 31.8, 25.9, 21.2. IR (neat): 2918, 2357, 2331, 1557, 1432, 1419 cm^{-1}. MS *m*/*z* (% relative intensity): 344 (M^+, 100), 329 (27), 301 (24), 257 (15). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{24}H_{28}N_2$, 344.2252; found, 344.2250.

4.2.9. (1*S*,8*R*,9*S*,1′*S*,8′*R*,9′*S*)-[8′-(Hydroxy-diphenyl-methyl)-10,10,10′,10′-tetramethyl-[5,5′]bi[6-aza-tricyclo-[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′,4′,6′-hexaen-8-yl]-diphenyl-methanol 10. *n*-Butyllithium (1.67 mL, 2.7 mmol, 1.6 M in hexane) was added to a solution of compound **8** (920 mg, 2.7 mmol) in diethyl ether (15 mL), and stirred at 0 °C for 30 min to give a solution, which turned a darkish blue. After further stirring at room temperature for 1 h, a solution of benzophenone (486 mg, 2.7 mmol) in diethyl ether (10 mL) was added at −78 °C, after which the reaction temperature was raised to room temperature, and the solution stirred for 30 min. The solution then turned a yellowish green color. *n*-Butyllithium (1.67 mL, 2.7 mmol, 1.6 M in hexane) was then added to this solution and stirred at room temperature for 30 min until it turned a darkish blue. A solution of benzophenone (486 mg, 2.7 mmol) in diethyl ether (10 mL) was added at −78 °C, and the reaction temperature was raised to room temperature, and stirred for 3 h until the solution turned orange. The reaction was quenched by adding water. The reaction mixture was then extracted three times with diethyl ether. 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, 1:19) as the mobile phase, thus producing compound **9** (1.15 g, 2.2 mmol) yield 82%, and compound **10** (153 mg, 216 μmol) yield 8%. Compound **10**: $[\alpha]_D^{16} = -427.5$ (*c* 0.32, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 9.65 (s, 1H), 7.99 (d, $J = 7.8$ Hz, 2H), 7.37–7.1 (m, 22H), 4.47 (s, 2H), 2.61 (d, $J = 5.4$ Hz, 4H), 2.13 (m, 2H), 1.41 (s, 6H), 1.28 (d, $J = 8.9$ Hz, 2H), 0.88 (s, 6H). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ): 156.9, 150.6, 147.0, 145.8, 144.2, 135.1, 128.2, 128.1, 127.8, 127.2, 118.3, 81.9, 60.4, 48.0, 45.8, 42.9, 41.5, 29.7, 28.8, 26.3, 21.2, 21.1, 14.2. IR (KBr): 3451, 2954, 2927, 2864, 1943, 1446, 1423, 699 cm^{-1}. MS *m*/*z* (% relative intensity): 708 (M^+, 0.04), 526 (4), 344 (51), 329 (16), 301 (15). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{50}H_{48}N_2O_2$, 708.3715; found, 708.3730. Anal. Calcd for $C_{50}H_{48}N_2O_2$: C, 84.71; H, 6.82; N, 3.95. Found: C, 83.71; H, 6.62; N, 3.79.

4.2.10. (1*S*,8*R*,9*S*,1′*S*,9′*S*)-Diphenyl-(10,10,10′,10′-tetramethyl-[5,5′]bi[6-aza-tricyclo[7.1.1.0^{2,7}]undecyl]-2(7),3,5,2′,4′,6′-hexaen-8-yl)-methanol 9. $[\alpha]_D^{16} = -235.3$ (*c* 0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 10.23 (d, $J = 12.0$ Hz, 1H), 8.19 (d, $J = 7.5$ Hz, 1H), 8.00 (d, $J = 7.8$ Hz, 1H), 7.4–6.0 (m, 12H), 4.44 (s, 1H), 3.19 (d, $J = 2.4$ Hz, 2H), 2.82–2.35 (m, 4H), 2.61 (m, 1H), 2.04 (m, 1H), 1.44 (s, 3H), 1.39 (s, 3H), 1.32 (m, 2H), 0.87 (s, 1H), 0.73 (s, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 156.6, 156.3, 151.8, 146.9, 145.9, 145.8, 143.8, 142.6, 134.8, 129.0, 128.1, 127.8, 127.0, 126.4, 125.2, 118.6, 117.8, 47.7, 46.3, 45.7, 42.9, 41.4, 40.0, 39.5, 36.4, 31.8, 30.9, 29.6, 28.6, 26.3, 25.9, 21.4, 21.2, 21.1. IR (KBr): 3205, 2976, 2944, 1732, 1463, 1446, 1419, 772, 701 cm^{-1}. MS *m*/*z* (% relative intensity): 526 (M^+, 15), 508 (44), 344 (100), 329 (41), 301 (27). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{37}H_{38}N_2O$, 526.2984; found, 526.2992.

4.3. Typical procedure for the enantioselective addition of diethylzinc to aldehydes catalyzed by the complex of Ti–ligand 10

Ti(O-*i*-Pr)$_4$ (22 μL, 75 μmol) was added to a solution of ligand **10** (1.8 mg, 2.5 μmol) in toluene (1 mL) and stirred at room temperature for 10 min; then a solution of Et_2Zn (75 μL, 1 M in hexane) was added and stirred for 10 min, after which aldehydes (0.05 mmol) were added and stirred at room temperature for 30 h. The

reaction was quenched by adding 1 M HCl (0.5 mL), and the reaction mixture extracted three times with diethyl ether. The combined extracts were then 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 the 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). The data are shown in Table 3. The yields were obtained using 1 mmol of substituted benzaldehydes and weighted after being purified by flash chromatography.

4.3.1. 1-Phenyl-propan-1-ol. Yield: 67%. $[\alpha]_D^{16} = -40.7$ (c 1.95, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.38–7.34 (m, 4H), 4.63–4.57 (m, 1H), 1.83–1.73 (m, 3H), 0.92 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 144.5, 128.2, 127.3, 125.9, 75.8, 31.7, 10.0. IR (KBr): 3354, 3083, 3061, 3029, 2927, 2874, 1490, 1450, 760, 742, 698 cm^{-1}. MS m/z: 134 (M^+, 9), 107 (100), 79 (51), 69 (12). HRMS-EI (m/z): $[M]^+$ calcd for $C_9H_{12}O$, 136.0888; found, 136.0884.

4.3.2. 1-(2-Methoxy-phenyl)-propan-1-ol. Yield: 79%. $[\alpha]_D^{16} = -1.0$ (c 2.12, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.31–7.21 (m, 2H), 6.98–6.87 (m, 2H), 4.81–4.75 (m, 1H), 3.85 (s, 3H), 2.53 (d, $J = 6.3$ Hz, 1H), 1.87–1.77 (m, 2H), 0.95 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 156.4, 132.2, 128.0, 126.9, 120.5, 110.3, 72.1, 55.1, 30.0, 10.3. IR (KBr): 3389, 2963, 2931, 1598, 1580, 1490, 1458, 1238, 1091, 754 cm^{-1}. MS m/z: 166 (M^+, 4), 137 (100), 121 (9), 107 (35), 77 (10). HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_{14}O_2$, 166.0993; found, 166.0991.

4.3.3. 1-(3-Methoxy-phenyl)-propan-1-ol. Yield: 75%. $[\alpha]_D^{16} = -19.5$ (c 1.10, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.34–7.24 (m, 1H), 1.98 (m, 2H), 6.83–6.80 (d, $J = 8.0$ Hz, 1H), 4.61–4.55 (m, 1H), 3.82 (s, 3H), 1.87–1.70 (m, 3H), 0.95–0.90 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 159.6, 146.3, 129.3, 118.2, 112.8, 111.3, 75.8, 55.1, 31.7, 10.0. IR (KBr): 3390, 2963, 2932, 2874, 2838, 1606, 1463, 1321, 1259, 1160, 782, 698 cm^{-1}. MS m/z: 166 (M^+, 33), 137 (95), 109 (100), 94 (32), 77 (33). HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_{14}O_2$, 166.0993; found, 166.0998.

4.3.4. 1-(4-Methoxy-phenyl)-propan-1-ol. Yield: 70%. $[\alpha]_D^{16} = -31.5$ (c 2.10, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.29–7.25 (d, $J = 8.5$ Hz, 2H), 6.90–6.87 (d, $J = 8.7$ Hz, 2H), 4.56–4.53 (m, 1H), 3.81 (s, 3H), 1.85–1.69 (m, 3H), 0.92–0.87 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 158.8, 136.7, 127.1, 113.4, 75.4, 55.1, 31.1, 10.1. IR (KBr): 3389, 2963, 2931, 1612, 1512, 1247, 1032, 831 cm^{-1}. MS m/z: 166 (M^+, 8), 137 (100), 109 (18), 94 (13), 77 (15). HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_{14}O_2$, 166.0993; found, 166.0995.

4.3.5. 1-*o*-Tolyl-propan-1-ol. Yield: 72%. $[\alpha]_D^{16} = -62.4$ (c 1.41, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.47–7.45 (d, $J = 7.2$ Hz, 1H), 7.23–7.14 (m, 3H), 4.89–4.85 (m, 1H), 2.34 (s, 3H), 1.81–1.72 (m, 3H), 1.01–0.96 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 142.6, 134.5, 130.2, 127.0, 126.1, 125.1, 71.9, 30.8, 19.0, 10.2. IR (KBr): 3367, 2963, 2931, 2873, 1458, 970, 750, 727 cm^{-1}. MS m/z: 150 (M^+, 7), 121 (100), 93 (45), 77 (24). HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_{14}O$, 150.1044; found, 150.1051.

4.3.6. 1-*m*-Tolyl-propan-1-ol. Yield: 78%. $[\alpha]_D^{16} = -12.1$ (c 2.43, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.24–7.08 (m, 4H), 4.59–4.54 (m, 1H), 2.36 (s, 3H), 2.04–1.72 (m, 3H), 0.94–0.90 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 144.5, 138.0, 128.2, 126.6, 123.0, 76.0, 31.7, 21.4, 10.1. IR (KBr): 3358, 2963, 2929, 2873, 1612, 1455, 785, 702 cm^{-1}. MS m/z: 150 (M^+, 10), 121 (100), 93 (62), 77 (61). HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_{14}O$, 150.1044; found, 150.1042.

4.3.7. 1-*p*-Tolyl-propan-1-ol. Yield: 82%. $[\alpha]_D^{16} = -27.3$ (c 1.41, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.25–7.22 (d, $J = 8.1$ Hz, 2H), 7.17–7.14 (d, $J = 7.9$ Hz, 2H), 4.59–4.54 (m, 1H), 2.55 (s, 3H), 1.87–1.71 (m, 3H), 0.93–0.88 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 141.5, 137.1, 129.0, 125.9, 75.8, 31.7, 21.0, 10.1. IR (KBr): 3362, 2963, 2927, 2873, 1509, 1455, 815, 539 cm^{-1}. MS m/z: 150 (M^+, 9), 121 (100), 93 (35), 77 (23). HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_{14}O$, 150.1044; found, 150.1039.

4.3.8. 1-(2-Chloro-phenyl)-propan-1-ol. Yield: 85%. $[\alpha]_D^{16} = -50.2$ (c 2.10, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.56–7.53 (d, $J = 7.6$ Hz, 1H), 7.34–7.19 (m, 3H), 5.10–5.04 (m, 1H), 1.92–1.90 (d, $J = 3.8$ Hz, 1H), 1.84–1.74 (m, 2H), 1.02–0.97 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 141.9, 131.8, 129.2, 128.2, 127.0, 126.9, 71.7, 30.3, 9.9. IR (KBr): 3353, 3066, 2963, 2927, 1463, 1095, 754 cm^{-1}. MS m/z: 170 (M^+, 5), 141 (100), 113 (10), 105 (12), 77 (60). HRMS-EI (m/z): $[M]^+$ calcd for $C_9H_{11}ClO$, 170.0498; found, 170.0500.

4.3.9. 1-(3-Chloro-phenyl)-propan-1-ol. Yield: 96%. $[\alpha]_D^{16} = -28.4$ (c 3.74, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.35 (s, 1H), 7.30–7.19 (m, 3H), 4.62–4.56 (m, 1H), 1.85 (d, $J = 3.5$ Hz, 1H), 1.83–1.71 (m, 2H), 0.94–0.89 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 146.6, 134.2, 129.6, 127.5, 126.1, 124.0, 75.2, 31.8, 9.9. IR (KBr): 3348, 2967, 2931, 2873, 1575, 1431, 786, 696 cm^{-1}. MS m/z: 170 (M^+, 12), 143 (29), 141 (100), 113 (18), 77 (36). HRMS-EI (m/z): $[M]^+$ calcd for $C_9H_{11}ClO$, 170.0498; found, 170.0498.

4.3.10. 1-(4-Chloro-phenyl)-propan-1-ol. Yield: 54%. $[\alpha]_D^{16} = -2.7$ (c 1.19, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.33–7.28 (m, 4H), 4.62–4.57 (m, 1H), 1.82–1.71 (m, 2H), 0.93–0.90 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 142.9, 133.0, 128.4, 127.3, 75.2, 31.9, 9.9. IR (KBr): 3348, 2963, 2927, 2873, 1593, 1490, 1090, 1010, 821 cm^{-1}. MS m/z: 170 (M^+, 7), 141 (100), 113 (12), 77 (60). HRMS-EI (m/z): $[M]^+$ calcd for $C_9H_{11}ClO$, 170.0498; found, 170.0494.

4.3.11. 1-(2-Nitro-phenyl)-propan-1-ol. Yield: 12%. $[\alpha]_D^{16} = -5.5$ (*c* 0.65, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.91–7.88 (d, $J = 8.1$ Hz, 1H), 7.81–7.78 (d, $J = 7.8$ Hz, 1H), 7.66–7.39 (m, 2H), 5.18–5.16 (m, 1H), 2.26 (d, $J = 3.8$ Hz, 1H), 1.82–1.80 (m, 2H), 1.07–1.02 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 148.0, 139.8, 133.3, 128.0, 124.3, 70.6, 31.0, 10.4. IR (KBr): 3390, 2967, 2923, 1952, 1730, 1525, 1348, 973, 742 cm^{-1}. MS *m/z*: 152 (100), 136 (6), 107 (21), 77 (35). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_9H_{11}NO_3$, 181.0738; found, 181.0735.

4.3.12. 1-(3-Nitro-phenyl)-propan-1-ol. Yield: 21%. $[\alpha]_D^{16} = -28.3$ (*c* 1.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.23 (s, 1H), 8.15–8.11 (d, $J = 8.1$ Hz, 1H), 7.70–7.68 (d, $J = 7.6$ Hz, 1H), 7.55–7.49 (m, 1H), 4.77–4.73 (m, 1H), 2.04 (s, 1H), 1.84–1.79 (m, 2H), 0.97–0.93 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 148.3, 146.6, 132.0, 129.2, 122.3, 120.9, 74.7, 32.1, 29.6, 9.7. IR (KBr): 3394, 2967, 2927, 2873, 1529, 1351, 1095, 736, 691 cm^{-1}. MS *m/z*: 181 (M^+, 1), 152 (100), 105 (7), 77 (5). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_9H_{11}NO_3$, 181.0738; found, 181.0742.

4.3.13. 1-(4-Nitro-phenyl)-propan-1-ol. Yield: 24%. $[\alpha]_D^{16} = -15.2$ (*c* 1.52, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 8.22–8.19 (d, $J = 8.7$ Hz, 2H), 7.53–7.50 (d, $J = 8.7$ Hz, 2H), 4.78–4.73 (m, 1H), 1.97 (s, 1H), 1.84–1.74 (m, 2H), 0.97–0.92 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 151.9, 147.1, 126.6, 123.6, 74.8, 32.1, 29.6, 9.7. IR (KBr): 3385, 2966, 2931, 2455, 1921, 1679, 1517, 1344, 853, 754 cm^{-1}. MS *m/z*: 181 (M^+, 0.1), 176 (4), 166 (22), 141 (100), 123 (33), 113 (33), 112 (83), 85 (79), 77 (6). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_9H_{11}NO_3$, 181.0738; found, 181.0743.

4.3.14. 1-(3-Dimethylamino-phenyl)-propan-1-ol. Yield: 32%. $[\alpha]_D^{16} = -5.6$ (*c* 2.31, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.16–7.13 (m, 1H), 6.73–6.64 (m, 3H), 4.57–4.52 (t, $J = 6.5$ Hz, 1H), 2.96 (s, 6H), 1.83–1.77 (m, 3H), 0.96–0.91 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 146.3, 129.6, 129.4, 114.0, 113.0, 112.2, 75.5, 42.3, 31.8, 10.2. IR (KBr): 3376, 2958, 2923, 1601, 1494, 1348, 773, 698 cm^{-1}. MS *m/z*: 179 (M^+, 79), 151 (10), 148 (18), 122 (100), 107 (24), 77 (24). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{11}H_{17}NO$, 179.1310; found, 179.1311.

4.3.15. 1-(4-Dimethylamino-phenyl)-propan-1-ol. Yield: 28%. $[\alpha]_D^{16} = -24.6$ (*c* 1.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.23–7.19 (d, $J = 8.8$ Hz, 2H), 6.74–6.71 (d, $J = 8.6$ Hz, 2H), 4.52–4.47 (t, $J = 6.7$ Hz, 1H), 2.88 (s, 6H), 1.84–1.68 (m, 3H), 0.92–0.87 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 129.8, 127.0, 125.1, 116.6, 75.0, 43.8, 29.6, 18.4, 10.0. IR (KBr): 3371, 2958, 2922, 2873, 1612, 1522, 1342, 812 cm^{-1}. MS *m/z*: 179 (M^+, 15), 161 (17), 150 (100), 120 (10), 77 (10). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{11}H_{17}NO$, 179.1310; found, 179.1315.

4.3.16. 3-(1-Hydroxy-propyl)-benzonitrile. Yield: 41%. $[\alpha]_D^{16} = -41.7$ (*c* 4.13, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.66 (s, 1H), 7.60–7.55 (m, 3H), 4.15–4.08 (m, 1H), 1.96–1.95 (d, $J = 3.4$ Hz, 1H), 1.80–1.74 (m, 2H), 0.95–0.90 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 146.0, 145.0, 130.3, 129.6, 127.1, 125.4, 118.8, 112.3, 74.7, 32.0, 9.7. IR (KBr): 3425, 2967, 2927, 2362, 2229, 1676, 773, 689 cm^{-1}. MS *m/z*: 161 (M^+, 4), 132 (100), 104 (37), 77 (23).

4.3.17. 4-(1-Hydroxy-propyl)-benzonitrile. Yield: 94%. $[\alpha]_D^{16} = -6.2$ (*c* 1.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.65–7.46 (d, $J = 7.2$ Hz, 2H), 7.44–7.41 (d, $J = 6.8$ Hz, 2H), 4.69 (s, 1H), 2.00 (s, 1H), 1.81–1.71 (m, 2H), 0.95–0.90 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (125.7 MHz, $CDCl_3$, δ): 150.0, 132.0, 126.5, 118.8, 110.7, 74.8, 31.9, 9.7. IR (KBr): 3433, 2969, 2933, 2229, 1930, 1610, 1412, 1097, 980, 845 cm^{-1}. MS *m/z*: 161 (M^+, 4), 132 (100), 104 (36), 77 (17).

Acknowledgements

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

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