Asymmetric Synthesis of a New Salen Type-titanium Complex as the Catalyst for Asymmetric Trimethylsilylcyanation of Aldehydes

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This work describes the asymmetric synthesis of a new salen-type ligand via a Diels-Alder reaction and Curtius rearrangement. The ligand with a norbornane skeleton was used in the trimethylsilylcyanation of aldehydes, but the enantioselectivity was 55%ee. The norborane skeleton was cleaved to destroy this rigidity, and the eanatioselectivity was thereby increased to 85%ee.

Keywords: Asymmetric synthesis; Diels-Alder reaction; Curtius rearrangement; Trimethylsilylcyanation.

1. INTRODUCTION

Optically active cyanohydrins are highly versatile intermediates in the organic synthesis of various classes of chiral compounds, including α-hydroxy carboxylic acids,[1] α-hydroxy aldehydes,[2] α-hydroxy ketones[3] and β-amino alcohols.[4] The catalytic enantioselective silylcyanation of carbonyl compounds is a simple and convenient means of forming such compounds using Lewis acids, such as Ti(O-*i*-Pr)$_4$,[5] $TiCl_4$,[6] $AlCl_3$,[7] R_2AlCl[8] and others,[9] in combination with chiral ligands. Tri and tetra-coordinated chiral salen-type ligands are by far the most attractive and widely used ligand system employed in these reactions because of their relatively simple synthesis and their ability to be structurally tuned at numerous points. Chiral salen-type ligands with various architectures have been found to differ at either the diamine part or the aldehyde moieties, and have been demonstrated to be excellent ligands in a variety of asymmetric transformations. Accordingly the synthesis of new chiral diamines with interesting structural features is always desirable. Two novel tetradendate Jacobsen-type chiral ligands (**8** and **13**), derived from C_1 symmetric diamines (Fig. 1), were designed and synthesized, and employed as enantioselective catalysts of the asymmetric addition of TMSCN to aldehydes to for cyanohydrins in the presence of Ti(O^iPr)$_4$.

2. RESULTS AND DISCUSSION

The synthesis of ligands depends on an asymmetric Diels-Alder reaction with high diastereoselectivity as a key step. This process avoids the need for any chiral resolving agent otherwise, as the in case of diamines **6** and **12**, the participation of various chiral diacids because of different dihedral angles involved. The synthesis of **8** proceeds by Scheme I, which involves the known Lewis acid-Et_2AlCl catalyzed Diels-Alder reaction between cyclopentadiene and (-)-menthol-derived dimenthyl fumarate (**1**) at -78 °C.[10] The cycloaddition proceeds with high diastereoselectivity, and after hydrolysis, affords the bicycle[2.2.1]hep-5-ene-2,3-dicarboxylic acid (**3**) with the (2*S*,3*S*) absolute configuration. Hydrogenation of **3** produced bicyclo[2.2.1]-heptane-2,3-dicarboxylic acid (**4**), which was converted to diamine by Curtius rearrangement.[11] Accordingly, compound **4** was treated with thionyl chloride and sodium azide and the acid azide **5** thus formed was refluxed in benzene, before being treated with 8 M hydrochloric acid to yield diamine **6**. Salen ligand **8** was prepared following the Jacobsen method[12] by condensation with hydroxyl alde-

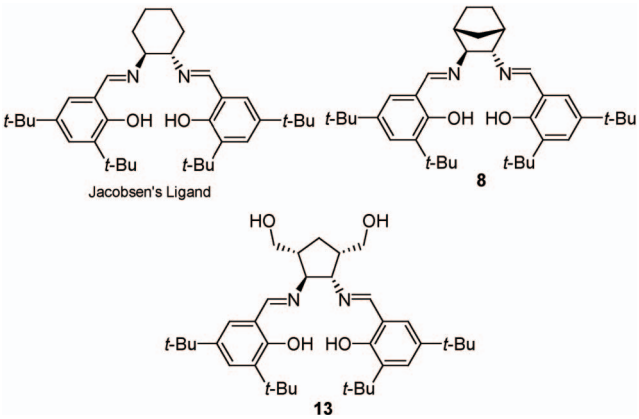
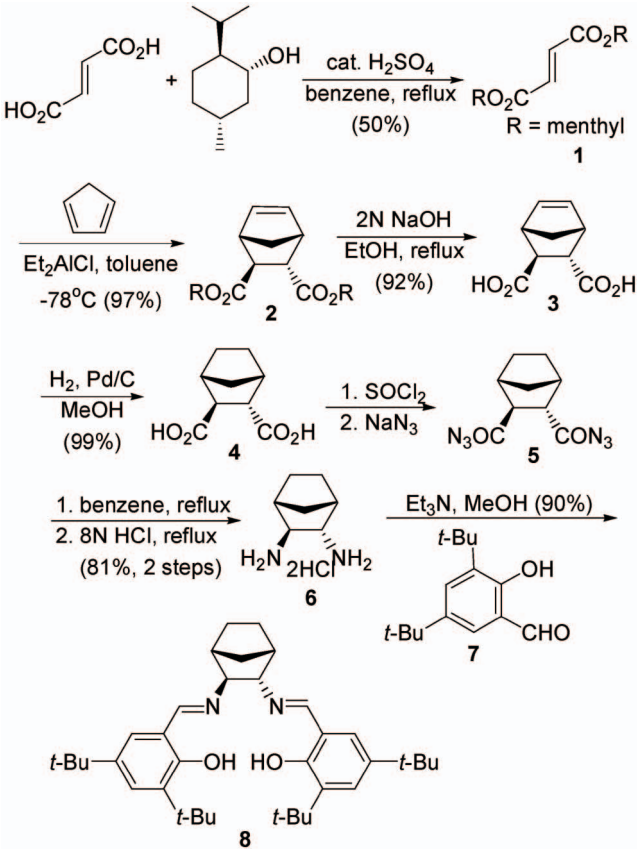


Fig. 1. Structures of Jacobsen-type c_1-symmetric chiral ligands.

Scheme I Synthetic route to ligand **8**

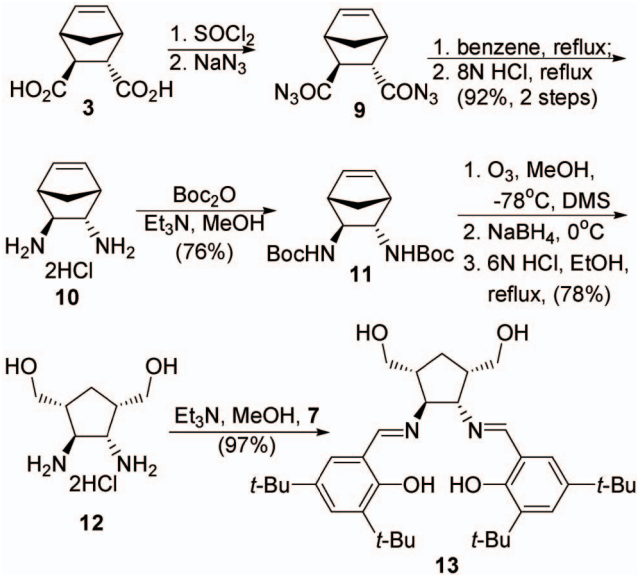


hyde **7**, in 95% yield. Chiral HPLC analysis revealed that the enantiomeric purity of the diamines exceeded 99% in both case by chiral HPLC analysis.

The efficiency of the chiral salen ligand **8** in the asymmetric trimethylsilylcyanation of benzaldehyde was investigated using trimethylsilylcyanide in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ in acetonitrile at -40 °C. The reaction afforded cyanohydrin in 43%ee in 63% isolated yield. Optimization of the ligand system using Et_2AlCl in hexane at -20 °C gave the same result (45%ee). Increasing the reaction temperature to the reflux temperature of acetonitrile slightly improved the enantioselectivity (55%ee in both cases). The lower selectivity associated with **8** was related to the larger dihedral angle of the diimine groups caused by the bicyclic ring system. Therefore, further ligand optimization was conducted by modifying the system to a monocyclic system. Hence, compound **13** was designed to reveal the necessary of monocyclic system.

Scheme II represents the synthesis of **13**. Compound **3** underwent Curtius rearrangement, as described above, to yield diamine **10**. The amino groups were protected by

Scheme II Synthesis of ligand **13**

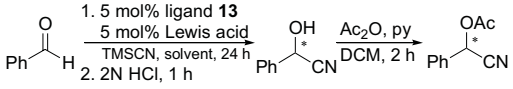


N-Boc groups and the cleavage of the double bond by ozonolysis yieled the corresponding dialdehyde, which was reduced to diol **12** by sodium borohydride. The removal of Boc groups under acidic conditions and the coupling of the resulting diamine with **7** produced salen ligand **13** in 97% yield.[19] Attempts to open the ring by the ozonolysis of other intermedites **2** or **3** were unsuccessful and formed several unidentified products.

Following the synthesis of the designed ligand **13** with such structural features as a small dihedral angle (close to Jacobsen ligand), and additional binding primary alcoholic groups, the asymmetric addition of TMSCN to aldehydes was screened. The reaction was optimized using two Lewis acids Et_2AlCl and $Ti(O\text{-}i\text{-}Pr)_4$ in various solvents and at various reaction temperatures. Table 1 presents the results. Under identical reaction conditions, Et_2AlCl gave higher yields of cyanohydrin than $Ti(O\text{-}i\text{-}Pr)_4$, although $Ti(O\text{-}i\text{-}Pr)_4$ gave higher enantioselectivities. THF as a reaction solvent afforded the most favorable enantioselectivities among the solvents screened. Similarly, reactions conducted at lower temperatures (-78 °C) afforded the best enantioselectivity (71%ee), but with low yield (8%).

Isopropyl alcohol and molecular sieves (4 Å) were used as additives (Table 2) to improve the enantiomeric excess of the trimethylsilylcyanation of benzaldehyde. Isopropyl alcohol (2 equivalents) and molecular sieves (60 mg) exhibited the best enantioselectivities (85%ee), but

Table 1. Enantiomeric excess (ee%) of the trimethylsilylcyanation of benzaldehyde in the various conditions in the presence of ligand **13**



Entry	Lewis acid	Solvent	Temp. (°C)	Yield (%)	ee (%)[a]
1	Et_2AlCl[a]	Toluene	-20	86	3
2	Et_2AlCl[a]	Hexane	-20	86	13
3	Et_2AlCl[a]	THF	-20	90	15
4	Et_2AlCl[a]	CH_3CN	-20	95	28
5	Et_2AlCl[a]	CH_2Cl_2	-20	91	29
6	Et_2AlCl[a]	CH_2Cl_2	-40	65	23
7	$Ti(O^iPr)_4$	Toluene	-40	26	21
8	$Ti(O^iPr)_4$	Hexane	-40	71	33
9	$Ti(O^iPr)_4$	CH_2Cl_2	-40	51	17
10	$Ti(O^iPr)_4$	CH_3CN	-40	8	29
11	$Ti(O^iPr)_4$	THF	-40	25	59
12	$Ti(O^iPr)_4$	THF	-78	8	71

[a] The ee% of product was determined by HPLC on chiral OD column.

Table 2. Enantiomeric excess (ee%) of the trimethylsilylcyanation of benzaldehyde in the various additives in the presence of ligand **13**

Entry	Additive	Yield (%)	ee (%)[a]
1	-	8	71
2	30 mg 4 Å MS	10	73
3	60 mg 4 Å MS	23	85
4	120 mg 4 Å MS	25	79
5	1eq. IPA	11	79
6	2eq. IPA	10	85
7	4eq. IPA	5	79
8	60 mg 4 Å MS + 2eq. IPA	25	79

[a] The ee% of product was determined by HPLC on chiral OD column.

Table 3. Enantiomeric excess (ee%) of the trimethylsilylcyanation of benzaldehyde in the various amount of catalyst

Entry	Ligand **13**/$Ti(O^iPr)_4$	Yield (%)	ee (%)
1	1 mol%	10	48
2	5 mol%	23	85
3	10 mol%	32	75
4	15 mol%	39	45
5	20 mol%	45	39

[a] The ee% of product was determined by HPLC on chiral OD column.

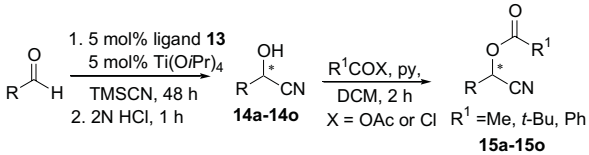
molecular sieves without added isopropyl alcohol were associated with a higher yield (23%).

Table 4. Enantiomeric excess (ee%) of the trimethylsilylcyanation of benzaldehyde in the various time in the presence of ligand **13**

Entry	Time (h)	Yield (%)	ee (%)
1	24	8	63
2	48	23	85
3	72	33	69
4	96	45	63
5	168	83	61

[a] The ee% of product was determined by HPLC on chiral OD column.

Table 5. Enantiomeric excess (ee%) of the trimethylsilylcyanation of various benzaldehydes in the presence of ligand **13**



Entry	Aldehyde	Yield (%)[a]	$[\alpha]_D$ (*c*) $CHCl_3$[b]	ee (%)[c] (config.)[e]
1	benzaldehyde	23	+20.3 (1.28)	85 (*R*)[16]
2	*o*-anisaldehyde	12	+4.2 (1.19)	23 (*R*)[17]
3	*m*-anisaldehyde	8	+12.7 (1.02)	47 (*R*)[13]
4	*p*-anisaldehyde	10	+8.0 (1.19)	27 (*R*)[13]
5	*o*-tolualdehyde	23	+18.1 (1.12)	45 (*R*)[18]
6	*m*-tolualdehyde	20	+1.4 (1.05)	5 (*R*)[19]
7	*p*-tolualdehyde	21	+13.8 (0.05)	30 (*R*)[19]
8	*o*-chlorobenzaldehyde	32	-1.09 (1.37)	25 (*S*)[14]
9	*m*-chlorobenzaldehyde	28	+13.9 (1.57)	47 (*R*)[19]
10	*p*-chlorobenzaldehyde	37	+6.4 (1.09)	21 (*R*)[19]
11	*m*-cyanobenzaldehyde	15	+2.7 (0.91)	17 (-)[d]
12	*p*-cyanobenzaldehyde	11	+2.3 (1.01)	3 (*R*)[13]
13	(*E*)-cinnamaldehyde	10	+6.25 (0.64)	65 (*R*)[15]
14	hydrocinnamaldehyde	18	-2.4 (1.55)	55 (*R*)[15]
15	isobutyraldehyde	55	+9.5 (1.37)	75 (*R*)[15]

[a] Isolated yield of **14a-14o**; [b] The specific rotation of **14a-14o**; [c] The ee% of **15a-15o** determined by HPLC on chiral OD column; [d] The configuration could not be determined; [e] The absolute configurations were assigned based on comparison with the literature data.

An optimal catalyst loading of 5 mol% of **13**:Ti(O*i*-Pr)$_4$ (1:1) gave the product with high stereoselection while higher loadings reduced the enantiomeric excess, despite the expected higher yields (Table 3). The same catalyst system with longer reaction times (48 h) gave favorable results; however, extending the reaction time reduced the enantioselectivity (Table 4).

The optimal conditions were THF solvent, -78 °C, molecular sieves as additive, 5 mol% of catalyst ($Ti(OiPr)_4$ and ligand **13**) and a reaction time of 48 h. This optimal reaction conditions were utilized for the reaction of substituted benzaldehydes and TMSCN (Table 5); the best enantioselective substrate was benzaldehyde (85%ee) with *R* configuration (exception *o*-chlorobenzaldehyde). The nonaromatic aldehydes (entry 13-15) were also used in the trimethysilylcyanation, giving good enantioselectivity (55-75%ee).

3. CONCLUSION

In summary, a new class of chiral salen-type ligands were synthesized by the simple procedures of a Lewis acid-catalyzed asymmetric Diels-Alder reaction between cyclopentadiene and (–)-menthol-derived dimenthyl fumarate and Curtius rearrangement. Preliminary results indicate that the norbornane ring may fix the diimine groups in the excessively rigid *trans* configuration, affecting enantioselectivity. Comparing ligand **8** and **13** suggests that the norbornane ring is essential to the enantioselectivity.

4. EXPERIMENTAL

4.1. General Chemical Procedures

All reactions were carried out in anhydrous solvents. Tetrhydrofuran and diethyl ether were distilled from sodium-benzophenone under argon. Toluene, acetonitrile, dichloromethane, and hexane were distilled from calcium hydride. ^{1}H NMR spectra were acquired at 400 (indicated in each case), and ^{13}C NMR were acquired at 100.6 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were determined on a Micromass Platform II mass spectrometer at a 70 eV. High resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on a JASCO FT/IR 410 spectrometer. All asymmetric reactions were carried out in dry glassware under nitrogen using a standard glovebox. Enantiomeric excesses were determined on a Lab Alliance Series III high performance liquid 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.

4.2. Preparation of ligand 8

Synthesis of bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl) fumarate 1

A solution of fumaric acid (4.89 g, 42.18 mmol), (–)-menthol (37.52 g, 240.52 mmol) and concentrated sulfuric acid (2 mL) in benzene (50 mL) was refluxed for 15 h. The reaction was traced by TLC until the fumaric acid was completely consumed. The reaction solution was cooled to room temperature and washed with water (twice), saturated sodium bicarbonate solution (twice), and brine (once). The organic phase then was dried over anhydrous magnesium sulfate, and after filtration and concentration the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:99, 1:9) as the mobile phase. After concentration, compound **1** (16.53 g, 42.16 mmol) yield 99% was produced, and (–)-menthol (18.77 g, 120.32 mmol) recycled yield 50% was obtained. $[\alpha]_D^{26.9}$ = -93.6° (*c* 1.70, $CHCl_3$). IR (KBr): 2955, 2869, 1719, 1455, 1294, 1257, 1148, 990 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.82 (s, 2H), 4.82-4.75 (dt, J_1 = 10.8 Hz, J_2 = 4.3 Hz, 2H), 2.04-2.00 (m, 2H), 1.90-1.82 (m, 2H), 1.70-1.67 (m, 4H), 1.55-1.39 (m, 4H), 1.12-0.97 (m, 4H), 0.93-0.87 (m, 14H), 0.76-0.74 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 164.5, 133.8, 75.2, 47.0, 40.7, 34.1, 31.3, 26.1, 23.3, 22.0, 20.7, 16.2. MS *m/z*: 393 (M^++1, 11), 255 (29), 154 (36), 139 (97), 95 (49), 83 (100), 55 (71). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{24}H_{41}O_4$, 393.3005; found, 393.3013.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate 2

To a solution of **1** (16.53 g, 42.16 mmol) in anhydrous toluene (100 mL) was added Et_2AlCl (46 mL, 1M in hexanes) dropwisely at -78 °C under argon and stirred for 20 min. Cyclopentadiene (4.9 mL, 59.02 mmol) was then added slowly and stirred for 4 h. The reaction solution was cooled in ice-bath, and was added water (10 mL) to quench the reaction and stirred for 1 h. The organic phase was washed with 1M HCl (twice), saturated sodium bicarbonate solution (twice) and brine (once). The organic phase then was dried over anhydrous magnesium sulfate, and after filtration and concentration the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:49) as the mobile phase. After concentration, compound **2** (18.77 g, 40.98

mmol) yield 97% was produced. mp: 80-82 °C. $[\alpha]_D^{27.8}$ = -0.51° (*c* 5.20, $CHCl_3$). IR (KBr): 2951, 2866, 1724, 1455, 1265, 1174, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 6.30-6.28 (dd, J_1 = 5.6 Hz, J_2 = 3.1 Hz, 1H), 6.03-6.01 (dd, J_1 = 5.6 Hz, J_2 = 2.7 Hz, 1H), 4.72-4.65 (dt, J_1 = 21.7 Hz, J_2 = 4.3 Hz, 1H), 4.60-4.54 (dt, J_1 = 21.7 Hz, J_2 = 4.3 Hz, 1H), 3.36-3.34 (t, *J* = 4.2 Hz, 1H), 3.26 (s, 1H), 3.10 (s, 1H), 2.67-2.66 (dd, J_1 = 4.5 Hz, J_2 = 1.4 Hz, 1H), 2.00-1.87 (m, 4H), 1.69-1.65 (m, 4H), 1.62-1.59 (d, *J* = 8.6 Hz, 1H), 1.50-1.35 (m, 5H), 1.09-0.93 (m, 4H), 0.91-0.88 (m, 14H), 0.76-0.73 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 174.0, 172.8, 137.6, 134.8, 74.5, 74.4, 48.0, 47.7, 47.3, 47.2, 46.9, 46.9, 45.8, 40.8, 40.8, 34.2, 31.3, 31.3, 26.2, 26.0, 23.2, 23.1, 22.0, 20.8, 16.0. MS *m/z*: 458 (M^+, 0.4), 320 (4), 182 (43), 138 (100), 94 (4), 83 (75), 66 (33), 55 (27). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{29}H_{46}O_4$, 458.3396; found, 458.3392.

Synthesis of (1*S*,2*S*,3*S*,4*R*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid 3

A suspenion of **2** (18.77 g, 40.98 mmol) and 2 M NaOH (195 mL) in ethanol (390 mL) was refluxed at 120 °C for 24 h. The reaction was traced by TLC until the compound **2** was completely consumed. The reaction solution was cooled to room temperature and concentrated until one third of the solution remained. The remained solution was extracted with hexane (twice), and the organic solution was washed with brine. The organic phase then was dried over anhydrous magnesium sulfate, and after filtration and concentration gave (–)-menthol (11.50 g, 73.71 mmol) recycled yield 90%. The aqueous phase was cooled in ice-bath and acidified by adding concentrated hydrochloric acid to pH 2 and some solid precipitated. The aqueous solution was extracted with ethyl acetate (twice), and the extracts were washed with brine. The organic phase then was dried over anhydrous magnesium sulfate and after filtration and concentration gave **3** (6.90 g, 37.91 mmol) yield 92%. mp: 170-173 °C. $[\alpha]_D^{20.1}$ = +127.4° (*c* 1.29, MeOH). IR (KBr): 3420, 2983, 2923, 1700, 1422, 1279, 948 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ): 6.28-6.25 (dd, J_1 = 5.6 Hz, J_2 = 3.1 Hz, 1H), 6.04-6.02 (dd, J_1 = 5.6 Hz, J_2 = 2.3 Hz, 1H), 3.16-3.13 (m, 2H), 3.01 (s, 1H), 2.40-2.39 (m, 1H), 1.48-1.46 (d, *J* = 8.4 Hz, 1H), 1.33-1.30 (dd, J_1 = 8.4 Hz, J_2 = 1.3 Hz, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ): 175.8, 174.6, 137.9, 135.4, 47.9, 47.5, 47.3, 47.2, 45.3. MS *m/z*: 182 (M^+, 0.1), 137 (4), 120 (1), 91 (16), 66 (100). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_9H_{10}O_4$, 182.0579; found, 182.0588.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid 4

A solution of **3** (5.79 g, 31.81 mmol) in methanol (50 mL) was added 10% Pd/C (0.58 g), and under hydrogen atmosphere (1 atm) stirred for 1 h. The reaction was traced by TLC until 3 was completely consumed. The reaction mixture was filtered through a cake of celite, and the filtrate was concentrated to produce **4** (5.82 g, 31.63 mmol) in 99% yield. mp: 162-165 °C. $[\alpha]_D^{20.1}$ = +25.7° (*c* 1.35, MeOH). IR (KBr): 3225, 2977, 2958, 1682, 1389 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, δ): 3.14-3.12 (m, 1H), 2.71-2.69 (d, *J* = 4.9 Hz, 1H), 2.60 (s, 1H), 2.55-2.54 (d, *J* = 3.9 Hz, 1H), 1.67-1.58 (m, 1H), 1.54-1.52 (m, 1H), 1.50-1.41 (m, 1H), 1.37-1.28 (m, 3H). ^{13}C NMR (100.6 MHz, CD_3OD, δ): 176.7, 175.5, 49.4, 48.6, 41.7, 40.0, 37.6, 28.4, 23.7. MS *m/z*: 185 (M^++1, 22), 167 (39), 154 (100), 136 (92), 120 (18), 107 (41), 89 (44), 77 (52), 67 (33). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_9H_{13}O_4$, 185.0814; found, 185.0825.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]heptane-2,3-dicarbonyl diazide 5

A solution of **4** (6.22 g, 33.82 mmol) in thionyl chloride (15 mL, 207.2 mmol) was refluxed at 100 °C for 1.5 h. The refluxing condenser was changed to distillation condenser to remove the excess of thionyl chloride. The remained residue was dried under vacuum for 2 h to give a brown liquid. To the brown liquid was added acetone (10 mL) and a solution of NaN_3 (6.59 g, 101.46 mmol) in water (10 mL), and stirred for 1 h. The reaction was quenched by adding a little water, and extracted with chloroform (twice). The organic phase was washed with saturated sodium bicarbonate solution (once) and brine (once). The organic phase then was dried over anhydrous magnesium sulfate, and after filtration and concentration (do not heat) under vacuum gave crude product without further purification for the next step reaction. IR (KBr): 2969, 2881, 2140, 1635, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 3.23-3.20 (m, 1H), 2.82-2.80 (dd, J_1 = 5.3 Hz, J_2 = 1.0 Hz, 1H), 2.66-2.64 (m, 1H), 2.61-2.60 (d, *J* = 3.9 Hz, 1H), 1.66-1.60 (m, 1H), 1.55-1.44 (m, 2H), 1.39-1.25 (m, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 181.0, 180.0, 51.4, 50.4, 42.0, 40.6, 38.0, 28.7, 23.9.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]heptane-2,3-diamine; hydrochloride 6

The crude product **5** solution in benzene (48 mL) was refluxed for 2 h, and then cooled to room temperature. To this cooling solution was added 8 M HCl (90 mL) and refluxed for 4 h. The reaction solution was cooled to room

temperature and extracted with diethyl ether. The aqueous phase was concentrated to give a white solid, which was washed with anhydrous tetrahydrofuran. The solid was dried under vacuum to produce **6** (5.46 g, 27.57 mmol) in 81% yield. mp: 270 °C (decomposed). $[\alpha]_D^{23}$ = +17.7° (*c* 1.23, H_2O). IR (KBr): 3432, 2985, 2884, 1558, 1488, 1056 cm^{-1}. ^1H NMR (400 MHz, D_2O, δ): 3.45-3.43 (m, 1H), 3.04-3.03 (m, 1H), 2.52-2.50 (m, 1H), 2.33-2.32 (m, 1H), 1.69-1.61 (m, 2H), 1.54-1.41 (m, 2H), 1.35-1.28 (m, 1H), 1.25-1.18 (m, 1H). ^{13}C NMR (100.6 MHz, D_2O, δ): 57.2, 57.2, 40.9, 39.7, 34.4, 25.9, 19.3. MS *m/z*: 126 (M^+, 23), 108 (14), 97 (16), 92 (12), 85 (23), 70 (51), 56 (100). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_9H_{14}N_2$, 126.1157; found, 126.1149.

Synthesis of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde 7

A solution of 2,4-di-*tert*-butylphenol (12.82 g, 62.23 mmol) and HMTA (17.42 g, 124.46 mmol) in glacial acetic acid (30 mL) was refluxed for 2 h. The cooled reaction solution was added 33% sulfuric acid (30 mL) and refluxed for 1 h. When the reaction solution was cooled to 80 °C, the solution was transferred to a separatory funnel. The organic phase was concentrated, and the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (5:95) as the mobile phase to give a yellow powder **7** (6.55 g, 27.99 mmol) in 45% yield. mp: 53-55 °C. ^1H NMR (400 MHz, $CDCl_3$, δ): 11.64 (s, 1H), 9.87 (s, 1H), 7.59-7.58 (d, *J* = 2.4 Hz, 1H), 7.35-7.34 (d, *J* = 2.4 Hz, 1H), 1.43 (s, 1H), 1.33 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 197.3, 159.1, 141.6, 137.5, 131.9, 127.8, 120.0, 35.0, 34.2, 31.3, 29.3. IR (KBr): 2959, 2871, 1648, 1439, 1248 cm^{-1}.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-*N*,*N*′-Bis-(3,5-di-*tert*-butyl-2-hydroxy-benzylidene)-bicyclo[2.2.1]heptane-2,3-diamine 8

To a solution of **6** (0.72 g, 3.65 mmol) and **7** (1.71 g, 7.30 mmol) in methanol (30 mL) was added Et_3N (3.05 mL, 21.90 mmol), and stirred at room temperature for 16 h. The reaction was monitored by TLC until the starting materials were consumed completely. The reaction solution was concentrated to give a yellow solid, which was dissolved in dichloromethane and washed with water (once) and brine (once). The organic phase was dried over anhydrous magnesium sulfate. After filtration and concentration the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:49) as the mobile phase to produce a yellow powder **8** (1.84 g, 3.29 mmol) in 90% yield. mp: 202-204 °C. $[\alpha]_D^{27.8}$ = +364.7° (*c* 1.26, $CHCl_3$). IR (KBr): 2957, 2869, 1624, 1593, 1440, 1249, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 13.68 (s,1H), 13.63 (s, 1H), 8.34 (s, 1H), 8.26 (s, 1H), 7.38 (d, *J* = 1.5 Hz, 1H), 7.06-7.04 (t, *J* = 2.4 Hz, 1H), 3.58-3.56 (m, 1H), 3.18-3.16 (m, 1H), 2.45-2.43 (m, 1H), 2.33-2.32 (d, *J* = 4.5 Hz, 1H), 2.15-2.13 (d, *J* = 10.1 Hz, 1H), 2.04-1.98 (m,1H), 1.73-1.80 (m, 1H), 1.57-1.51 (m, 3H), 1.47 (s, 9H), 1.46 (s, 9H), 1.28 (s, 18H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 166.1, 164.2, 158.0, 157.9, 140.2, 136.6, 127.0, 126.9, 126.2, 118.0, 117.8, 80.5, 79.9, 45.3, 43.4, 36.4, 35.1, 34.2, 31.7, 31.6, 29.8, 29.7, 29.5, 27.3, 22.1. MS *m/z*: 558 (M^+, 40), 325 (100), 296 (13), 264 (7), 244 (11), 219 (5). HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{37}H_{54}N_2O_2$, 558.4185; found, 558.4177.

4.3. Preparation of ligand 13

Synthesis of (1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl diazide 9

A solution of **3** (0.82 g, 4.5 mmol) in thionyl chloride (2 mL, 27.6 mmol) was refluxed at 100 °C for 1.5 h. The refluxing condenser was changed to distillation condenser to remove the excess of thionyl chloride. The remained residue was dried under vacuum for 2 h to give a brown liquid. To the brown liquid was added acetone (2 mL) and a solution of NaN_3 (0.88 g, 13.5 mmol) in water (2 mL), and stirred for 1 h. The reaction was quenched by adding a little water, and extracted with chloroform (twice). The organic phase was washed with saturated sodium bicarbonate solution (once) and brine (once). The organic phase then was dried over anhydrous magnesium sulfate, and after filtration and concentration (do not heat) under vacuum gave crude product **9** without further purification for the next step reaction. IR (KBr): 2975, 2877, 2140, 1702, 1641, 1170, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 6.22-6.19 (dd, J_1 = 5.5 Hz, J_2 = 3.2 Hz, 1H), 6.05-6.03 (dd, J_1 = 5.6 Hz, J_2 = 2.8 Hz, 1H), 3.34-3.32 (m, 1H), 3.20-3.18 (m, 1H), 3.09-3.07 (m, 1H), 2.61-2.60 (dd, J_1 = 4.4 Hz, J_2 = 1.4 Hz, 1H), 1.51-1.49 (m, 1H), 1.41-1.38 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 180.6, 179.4, 137.5, 135.0, 50.2, 49.4, 48.0, 47.0, 46.0.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-bicyclo[2.2.1]hept-5-ene-2,3-diamine; hydrochloride 10

The crude product **9** solution in benzene (10 mL) was refluxed for 2 h, and then cooled to room temperature. To this cooling solution was added 8 M HCl (15 mL) and refluxed for 4 h. The reaction solution was cooled to room temperature and extracted with diethyl ether (twice). The aqueous phase was concentrated to give a white solid,

which was washed with anhydrous tetrahydrofuran. The solid was dried under vacuum to produce a purple powder **10** (0.81 g, 4.15 mmol) in 92% yield. mp: 250 °C (decomposed). $[\alpha]_D^{24}$ = +51.2° (*c* 1.12, H_2O). IR (KBr): 3444, 3073, 2989, 2923, 1562, 1488, 1052 cm^{-1}. ^1H NMR (400 MHz, D_2O, δ): 6.36-6.34 (dd, J_1 = 5.6 Hz, J_2 = 3.5 Hz, 1H), 6.17-6.15 (dd, J_1 = 5.8 Hz, J_2 = 2.7 Hz, 1H), 3.71-3.69 (m, 1H), 3.12-3.10 (m, 1H), 3.03-3.02 (m, 1H), 2.99-2.97 (m, 1H), 1.76-1.68 (m, 2H). ^{13}C NMR (100.6 MHz, D_2O, δ): 138.4, 133.9, 55.8, 55.5, 46.5, 44.9, 44.8. MS *m/z*: 125 (M^++1, 19), 107 (21), 89 (13), 77 (18), 63 (9). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_7H_{13}N_2$, 125.1079; found, 125.1076.

Synthesis of (1*R*,2S,3*S*,4*S*)-(3-*tert*-butoxycarbonyl-aminobicyclo[2.2.1]hept-5-en-2-yl)-carbamic acid *tert*-butyl ester 11

To a solution of **10** (0.78 g, 4 mmol) in methanol (10 mL) was added Et_3N (1.7 mL, 12.2 mmol) and Boc_2O (2 mL, 8.8 mmol) subsequently, and stirred at room temperature for 12 h. The reaction was monitored by TLC until the starting materials were consumed completely. The solvent was removed to give a white crude product, which was dissolved in ethyl acetate and washed with water (once) and brine (once). The organic phase then was dried over anhydrous magnesium sulfate, and after filtration and concentration the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (3:7) as the mobile phase to give a white powder compound **11** (0.99 g, 3.05 mmol) in 76% yield. mp: 200-202 °C. $[\alpha]_D^{28}$ = +51.9° (*c* 1.13, $CHCl_3$). IR (KBr): 3336, 3313, 2977, 2931, 1677, 1535, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 6.33-6.31 (dd, J_1 = 4.8 Hz, J_2 = 2.8 Hz, 1H), 6.16-6.14 (dd, J_1 = 5.6 Hz, J_2 = 2.6 Hz, 1H), 4.89 (br, 1H), 4.40 (br, 1H), 3.71 (s, 1H), 3.05 (s, 1H), 2.92 (s, 1H), 2.83 (s, 1H), 1.67-1.64 (m, 1H), 1.60-1.57 (m, 1H), 1.44 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 155.5, 155.4, 138.1, 134.2, 79.3, 60.0, 58.8, 48.7, 45.4, 45.3, 28.4. MS *m/z*: 325 (M^++1, 61), 269 (45), 258 (34), 213 (61), 202 (19), 169 (37), 152 (8), 57 (100). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{17}H_{29}N_2O_4$, 325.2127; found, 325.2139.

Synthesis of (1*R*,2*S*,3*S*,5*S*)-(2-*tert*-butoxycarbonyl-amino-3,5-bis-hydroxymethyl-cyclopentyl)-carbamic acid tert-butyl ester

To a solution of **11** (0.94 g, 2.9 mmol) in methanol (20 mL) at -78 °C was passed an ozone through the reaction solution for 5 min. The reaction was monitored by TLC until the starting material was consumed completely. An argon gas was bubbled through the reaction solution for 10 min, and DMS (1.5 mL) was added. The reaction solution was kept stirring, and the temperature was raised from -78 °C to 0 °C in 4 h. Subsequently $NaBH_4$ (0.22 g, 5.8 mmol) was added, and stirred at 0 °C for 1 h. The reaction was quenched by adding a small amount of water, and the solvent was removed to give a white solid product. The crude product was dissolved in chloroform, and washed with water (once) and brine (once). The organic phase was dried over anhydrous magnesium sulfate, after filtration and concentration and recrystallized from chloroform to produce a white powder **A** (0.82 g, 2.3 mmol) in 79% yield. mp: 178-180 °C. $[\alpha]_D^{24.4}$ = -12.8° (*c* 1.10, MeOH). IR (KBr): 3359, 2981, 2935, 1677, 1527, 1176 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, δ): 3.72-3.67 (t, *J* = 8.6 Hz, 1H), 3.51-3.47 (m, 1H), 3.43-3.32 (m, 4H), 2.18-2.13 (m, 1H), 1.91-1.84 (m, 1H), 1.79-1.70 (m, 1H), 1.37-1.34 (m, 1H), 1.32 (s, 1H). ^{13}C NMR (100.6 MHz, CD_3OD, δ): 157.3, 157.1, 78.8, 78.7, 62.8, 61.8, 57.9, 57.6, 44.5, 39.6, 28.1, 27.3. MS *m/z*: 361 ($[M+1]^+$, 84), 305 (25), 289 (14), 249 (52), 231 (37), 205 (100), 187 (41), 161 (49), 144 (29), 126 (25). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{17}H_{33}N_2O_6$, 361.2339; found, 361.2346.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-(2,3-diamino-4-hydroxy-methyl-cyclopentyl)-methanol; hydrochloride 12

To a solution of **A** (0.30 g, 0.84 mmol) in EtOH (10 mL) was added 6 M HCl (1 mL), and refluxed for 3 h. The reaction was monitored by TLC until the starting material was consumed completely. The reaction solution was cooled to room temperature, and the solvent was removed. The residue was dissolved in water, and the aqueous phase was extracted with diethyl ether (twice). The aqueous phase was concentrated and dried under vacuum to give a yellow solid **12** (0.19 g, 0.84 mmol) in 99% yield. $[\alpha]_D^{23.7}$ = -13.6° (*c* 1.36, MeOH). IR (KBr): 3421, 3390, 1592, 1488, 1060, 1014 cm^{-1}. ^1H NMR (400 MHz, D_2O, δ): 3.84-3.80 (dd, J_1 = 8.0 Hz, J_2 = 5.3 Hz, 1H), 3.68-3.59 (m, 2H), 3.56-3.48 (m, 3H), 2.58-2.48 (m, 1H), 2.27-2.17 (m, 1H), 1.97-1.90 (m, 1H), 1.42-1.33 (m, 1H). ^{13}C NMR (100.6 MHz, D_2O, δ): 61.6, 59.4, 57.9, 56.2, 43.8, 40.1, 27.5.

Synthesis of (1*R*,2*S*,3*S*,4*S*)-(–)-{2,3-bis-[(3,5-di-*tert*-butyl-2-hydroxy-benzylidene)-amino]-4-hydroxymethyl-cyclopentyl}-methanol 13

To a solution of **7** (0.39 g, 1.68 mmol) and **12** (0.19 g, 0.84 mmol) in methanol (10 mL) was added Et_3N (0.35 mL, 2.52 mmol), and stirred at room temperature for 16 h. The reaction was monitored by TLC until the starting materials

were consumed completely. The reaction solution was concentrated to give a yellow solid, which was dissolved in dichloromethane and washed with water (once) and brine (once). The organic phase was dried over anhydrous magnesium sulfate. After filtration and concentration the residue was purified by flash column chromatography using silica gel as a stationary phase and using ethyl acetate-hexane (1:19, 1:2) as the mobile phase to produce a yellow powder **13** (0.48 g, 0.81 mmol) in 97% yield. mp: 98-100 °C. $[\alpha]_D^{26.9}$ = +260.0° (*c* 1.15, $CHCl_3$). IR (KBr): 3363, 2981, 2931, 2854, 1681, 1523, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 13.49 (br, 1H), 13.35 (br, 1H), 8.33 (s, 1H), 8.30 (s, 1H), 7.37-7.35 (dd, J_1 = 4.6 Hz, J_2 = 2.4 Hz, 2H), 7.04-7.01 (dd, J_1 = 7.0 Hz, J_2 = 5.3 Hz, 2H), 3.99-3.95 (m,1H), 3.85-3.74 (m, 4H), 3.72-3.68 (m, 1H), 2.71-2.62 (m, 1H), 2.49-2.40 (m, 1H), 2.28-2.22 (m, 1H), 1.82-1.75 (m, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.26 (s, 9H), 1.25 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 167.2, 167.0, 158.2, 158.0, 140.2, 140.1, 136.7, 136.5, 127.4, 127.1, 126.4, 126.3, 117.7, 117.7, 77.7, 76.5, 63.4, 63.0, 46.7, 43.8, 35.0, 34.1, 34.1, 31.4. 29.5, 29.0. MS *m/z*: 593 ($[M+1]^+$, 91), 537 (10), 360 (15), 328 (43), 272 (9), 234 (59), 218 (60), 202 (22), 147 (12), 73 (25), 57 (100). HRMS-FAB (*m/z*): $[M+1]^+$ calcd for $C_{37}H_{57}N_2O_4$, 593.4318; found, 593.4329.

4.4. Typical procedure for the enantioselective addition of TMSCN to aldehydes catalyzed by the complex of Ti-ligand

To a solution of ligand (2.5 μmol) and 4 Å MS in THF (1.5 mL) was added $Ti(O\text{-}i\text{-}Pr)_4$ (2.5 μmol) and the mixture was stirred at room temperature for 1 h. Subsequently aldehyde (0.5 mmol) was added, and stirred at room temperature for 30 min. The reaction mixture was cooled to -78 °C, and trimethylsilylcyanide (1 mmol) was added. Following stirring for 48 h at this temperature, 2 M HCl (3 mL) was added to the reaction solution. After further stirring for 1 h at room temperature; filtrating through celite; extracting with ethyl acetate (twice); drying with anhydrous magnesium sulfate and concentrating the reaction mixture followed by column chromatography (eluent: hexane/acetone 9:1) to yield the expected cyanohydrin.

Determination the enantiomeric excess (ee%) of cyanohydrin

Method A: The pure cyanohydrin was directly converted into the corresponding acetates by reaction with acetic anhydride and pyridine in CH_2Cl_2 at room temperature for 2 h. After concentration, the residue was purified by column chromatography (eluent: hexane/acetone 19:1) to yield the acetylated cyanohydrin, which was used for further analysis. Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralcel OD-H column, *n*-hexane/2-propanol = 90:10 or *n*-hexane/2-propanol/acetonitrile = 80:1:1, flow rate 0.25 mL/min or 1.0 mL/min).

Method B: The pure cyanohydrin was directly converted into the corresponding pivalates by reaction with pivaloyl chloride and pyridine in CH_2Cl_2 at room temperature for 2 h. After concentration, the residue was purified by column chromatography (eluent: hexane/acetone 19:1) to yield the acetylated cyanohydrin, which was used for further analysis. Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralcel OD-H column, *n*-hexane/2-propanol = 90:10, flow rate 0.25 mL/min).

Method C: The pure cyanohydrin was directly converted into the corresponding benzoates by reaction with benzoyl chloride and pyridine in CH_2Cl_2 at room temperature for 12 h. After concentration, the residue was purified by column chromatography (eluent: hexane/acetone 19:1) to yield the acetylated cyanohydrin, which was used for further analysis. Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralcel OD-J column, *n*-hexane/2-propanol = 90:10, flow rate 0.5 mL/min).

2-Hydroxy-2-phenylacetonitrile 14a. Yield: 23%. $[\alpha]_D^{26.1}$ = +20.3° (*c* 1.28, $CHCl_3$). IR (KBr): 3405 (br), 2958, 2927, 1454, 1253, 1191, 1083, 1041, 844, 759, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.50-7.46 (m, 2H), 7.44-7.40 (m, 3H), 5.48 (s, 1H), 4.03 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 135.3, 129.7, 129.1, 126.9, 119.1, 63.3. GC-MS *m/z*: 133, 115, 105, 77, 51.

2-Acetoxy-2-phenylacetonitrile 15a. Yield: 95%. $[\alpha]_D^{25.8}$ = +4.1° (*c* 1.16, $CHCl_3$). IR (KBr): 2954, 2919, 2850, 1457, 1373, 1211, 1022, 755, 694, 601, 570 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.53-7.51 (m, 2H), 7.46-7.45 (m, 3H), 6.41 (s, 1H), 3.09 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.9, 131.7, 130.4, 129.2, 127.9, 116.1, 62.8, 20.5. GC-MS *m/z*: 175, 133, 115, 105, 89, 77, 63, 43, 28, 18. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate 0.25 mL/min), t_R of *R* isomer 28.02 min, t_R of *S* isomer 30.27 min, *R*:*S* = 92.4:7.6, ee%: 85%.

2-Hydroxy-2-(2-methoxyphenyl)acetonitrile 14b. Yield: 12%. $[\alpha]_D^{26.3}$ = +4.2° (*c* 1.19, $CHCl_3$). IR (KBr): 3413 (br), 2927, 2842, 1600, 1492, 1465, 1253, 1025, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.43-7.38 (m, 2H), 7.03-

6.97 (m, 2H) 5.56-5.54 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H), 3.50-3.48 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 156.7, 131.2, 128.0, 123.6, 121.1, 118.9, 111.2, 60.2, 55.7. GC-MS *m/z*: 163, 146, 136, 118, 105, 92, 77, 65, 51.

2-Acetoxy-2-(2-methoxyphenyl)acetonitrile 15b. Yield: 95%. $[\alpha]_D^{23.9}$ = +2.18° (*c* 1.17, $CHCl_3$). IR (KBr): 2942, 2842, 1754, 1496, 1257, 1214, 1022, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.57-7.55 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.45-7.40 (m, 1H), 7.06-7.02 (m, 1H), 6.95-6.93 (d, J = 8.3 Hz, 1H), 6.70 (s, 1H), 3.88 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.9, 156.7, 131.8, 128.7, 120.9, 119.9, 116.3, 111.1, 58.1, 55.7, 20.4. GC-MS *m/z*: 205, 163, 144, 135, 116, 103. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol/acetonitrile = 80:1:1, flow rate 0.25 mL/min), t_R of *R* isomer 41.21 min, t_R of *S* isomer 43.92 min, *R*:*S* = 38.1:61.9, ee%: 23%.

2-Hydroxy-2-(3-methoxyphenyl)acetonitrile 14c. Yield: 8%. $[\alpha]_D^{26.3}$ = +12.7° (*c* 1.02, $CHCl_3$). IR (KBr): 3421 (br), 2927, 2842, 1604, 1492, 1262, 1041, 852 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.37-7.33 (t, J = 7.9 Hz, 1H), 7.11-7.09 (d, J = 7.7 Hz, 1H), 7.06-7.05 (m, 1H), 6.97-6.94 (dd, J_1 = 8.3 Hz, J_2 = 2.2 Hz, 1H), 5.51 (s, 1H), 3.83 (s, 3H), 3.02 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 160.1, 136.7, 130.3, 118.7, 118.6, 115.6, 112.0, 63.6, 55.4. GC-MS *m/z*: 163, 146, 136, 107, 92, 77, 65, 51.

2-Acetoxy-2-(3-methoxyphenyl)acetonitrile 15c. Yield: 98%: $[\alpha]_D^{25.9}$ = +1.7° (*c* 0.94, $CHCl_3$). IR (KBr): 2927, 2842, 1754, 1604, 1492, 1211, 1025, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.38-7.34 (t, J = 7.9 Hz, 1H), 7.10-7.08 (d, J = 7.6 Hz, 1H), 7.03-6.97 (m, 2H), 6.37 (s, 1H), 3.83 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.9, 160.1, 133.0, 130.3, 120.0, 116.1, 116.0, 113.2, 62.7, 55.4, 20.5. GC-MS *m/z*: 205, 163, 146, 135, 116, 108. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 30.60 min, t_R of *S* isomer 35.21 min, *R*:*S* = 73.3:26.7, ee%: 47%.

2-Hydroxy-2-(4-methoxyphenyl)acetonitrile 14d. Yield: 10%. $[\alpha]_D^{26.4}$ = +8.0° (*c* 1.19, $CHCl_3$). IR (KBr): 3424 (br), 2938, 2838, 1612, 1511, 1253, 1176, 1029, 833 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.46-7.44 (d, J = 8.8 Hz, 2H), 6. 96-6.94 (d, J = 8.8 Hz, 2H), 5.48-5.47 (d, J = 4.3 Hz, 1H), 3.83 (s, 3H), 2.66 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 160.5, 128.3, 127.5, 119.1, 114.5, 63.0, 55.4. GC-MS *m/z*: 163, 145, 135, 107, 92, 77, 63, 51.

2-Acetoxy-2-(3-methoxyphenyl)acetonitrile 15d. Yield: 95%. $[\alpha]_D^{24.1}$ = -4.7° (*c* 1.14, $CHCl_3$). IR (KBr): 2938, 2842, 1754, 1515, 1253, 1214, 1176, 1025, 829 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.46-7.44 (d, J = 8.8 Hz, 2H), 6.96-6.94 (d, J = 8.8 Hz, 2H), 6.35 (s, 1H), 3.83 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 169.0, 161.1, 129.6, 123.8, 116.4, 114.5, 62.6, 55.4, 20.5. GC-MS *m/z*: 205, 163, 146, 135, 116, 103. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 32.90 min, t_R of *S* isomer 36.15 min, *R*:*S* = 63.8:36.2, ee%: 27%.

2-Hydroxy-2-*o*-tolylacetonitrile 14e. Yield: 23%. $[\alpha]_D^{25.8}$ = +18.1° (*c* 1.12, $CHCl_3$). IR (KBr): 3397 (br), 2923, 1492, 1461, 1292, 1245, 1241, 1180, 1037, 937, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.62-7.60 (m, 1H), 7.36-7.29 (m, 2H), 7.27-7.24 (m, 1H), 5.67 (s, 1H), 2.56 (br, 1H), 2.45 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 136.2, 133.0, 131.2, 129.9, 127.0, 126.7, 118.9, 61.4, 18.7. GC-MS *m/z*: 147, 129, 120, 91, 65, 51.

2-Acetoxy-2-*o*-tolylacetonitrile 15e. Yield: 96%. $[\alpha]_D^{24.1}$ = +9.2° (*c* 1.31, $CHCl_3$). IR (KBr): 2935, 1754, 1373, 1211, 1022, 960, 755, 570 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.57-7.55 (d, J = 7.6 Hz, 1H), 7.38-7.34 (m, 1H), 7.31-7.27 (m, 1H), 7.26-7.24 (m, 1H), 6.51 (s, 1H), 2.43, (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.9, 136.6, 131.3, 130.5, 129.8, 128.5, 126.8, 116.0, 61.0, 20.3, 18.9. GC-MS *m/z*: 189, 147, 129, 119, 103, 91, 77, 65, 51. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol/acetonitrile = 80:1:1, flow rate 0.25 mL/min), t_R of *R* isomer 34.21 min, t_R of *S* isomer 35.30 min, *R*:*S* = 27.4:72.6, ee%: 45%.

2-Hydroxy-2-*m*-tolylacetonitrile 14f. Yield: 20%. $[\alpha]_D^{26.2}$ = +1.4° (*c* 1.05, $CHCl_3$). IR (KBr): 3409 (br), 2923, 2865, 1608, 1488, 1249, 1157, 1037, 790, 748, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.35-7.32 (m, 3H), 7.25-7.24 (m, 1H), 5.50 (s, 1H), 2.67 (br, 1H), 2.40 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 139.1, 135.1, 130.5, 129.0, 127.3, 123.7, 119.1, 63.4, 21.3. GC-MS *m/z*: 147, 132, 119, 91, 65, 51.

2-Acetoxy-2-*m*-tolylacetonitrile 15f. Yield: 91%. $[\alpha]_D^{23.2}$ = +1.0° (*c* 1.23, $CHCl_3$). IR (KBr): 2935, 1754, 1373, 1214, 1022, 971, 898, 790, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.34-7.29 (m, 3H), 7.27-7.26 (m, 1H), 6.37 (s, 1H), 2.40 (s, 3H), 2.17 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.9, 139.2, 131.6, 131.1, 129.1, 128.5, 124.9, 116.2, 62.9, 21.3, 20.5. GC-MS *m/z*: 189, 147, 129, 119, 103, 91, 77, 65, 51. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 24.32 min, t_R of *S* isomer 26.84 min, *R*:*S* = 52.6:

47.4, ee%: 5%.

2-Hydroxy-2-*p*-tolylacetonitrile 14g. Yield: 21%. $[\alpha]_D^{26.3}$ = +13.8° (*c* 1.05, $CHCl_3$). IR (KBr): 3444 (br), 3031, 2927, 1511, 1415, 1184, 1037, 925, 813, 763, 528 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.43-7.41 (d, *J* = 8.0 Hz, 2H), 7.26-7.24 (d, *J* = 8.0 Hz, 2H), 5.50 (s, 1H), 2.59 (br, 1H), 2.38 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 139.8, 132.3, 129.8, 126.7, 119.1, 63.2, 21.2. GC-MS *m/z*: 147, 131, 119, 105, 91, 77, 65, 51.

2-Acetoxy-2-*p*-tolylacetonitrile 15g. Yield: 96%. $[\alpha]_D^{23.8}$ = -2.5° (*c* 1.27, $CHCl_3$). IR (KBr): 2931, 1754, 1373, 1214, 1018, 960, 813, 566 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.41-7.39 (d, *J* = 8.0 Hz, 2H), 7.26-7.24 (d, *J* = 8.0 Hz, 2H), 6.37 (s, 1H), 2.39 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 169.0, 140.7, 129.9, 128.8, 127.9, 116.3, 62.7, 21.3, 20.5. GC-MS *m/z*: 189, 147, 129, 119, 103, 91, 77, 65, 51. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 25.02 min, t_R of *S* isomer 30.23 min, *R*:*S* = 65.0: 35.0, ee%: 30%.

2-(2-Chlorophenyl)-2-hydroxyacetonitrile 14h. Yield: 32%. $[\alpha]_D^{26.8}$ = -1.09° (*c* 1.37, $CHCl_3$). IR (KBr): 3424 (br), 2931, 2865, 1473, 1442, 1191, 1072, 1033, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.72-7.68 (m, 1H), 7.43-7.40 (m, 1H), 7.38-7.34 (m, 2H), 5.84 (s, 1H), 3.93 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 132.7, 132.6, 131.0, 130.0, 128.3, 127.7, 118.0, 60.7. GC-MS *m/z*: 167, 150, 139, 132, 111, 105, 75, 61, 51.

2-(2-Chlorophenyl)-2-acetoxyacetonitrile 15h. Yield: 95%. $[\alpha]_D^{24.8}$ = +10.4° (*c* 1.67, $CHCl_3$). IR (KBr): 3073, 2923, 2850, 1758, 1373, 1207, 1056, 1025, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.73-7.71 (m, 1H), 7.47-7.44 (m, 1H), 7.42-7.37 (m, 2H), 6.70 (s, 1H), 2.19 (3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.6, 133.4, 131.7, 130.2, 129.5, 129.4, 127.6, 115.3, 60.2, 20.2. GC-MS *m/z*: 209, 167, 150, 139, 132, 123, 114, 105. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 24.33 min, t_R of *S* isomer 26.44 min, *R*:*S* = 37.5:62.5, ee%: 25%.

2-(3-Chlorophenyl)-2-hydroxyacetonitrile 14i. Yield: 28%. $[\alpha]_D^{26.7}$ = +13.9° (*c* 1.57, $CHCl_3$). IR (KBr): 3440 (br), 2927, 2854, 1477, 1430, 1191, 1099, 1041, 786, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.50 (s, 1H), 7.39-7.36 (m, 3H), 5.50 (s, 1H), 3.61 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 136.9, 135.1, 130.4, 129.9, 126.7, 124.6, 118. 5, 62.7. GC-MS *m/z*: 167, 139, 132, 111, 105, 75, 50.

2-(3-Chlorophenyl)-2-acetoxyacetonitrile 15i. Yield: 95%. $[\alpha]_D^{25.2}$ = +2.3° (*c* 1.41, $CHCl_3$). IR (KBr): 2923, 2854, 1758, 1430, 1369, 1207, 1022, 875, 786, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.51 (s, 1H), 7.45-7.37 (m, 3H), 6.37 (s, 1H), 2.18 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.7, 135.2, 133.5, 130.6, 130.5, 127.9, 125.9, 115.6, 62.0, 20.4. GC-MS *m/z*: 209, 167, 150, 139, 132, 123, 114. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 29.31 min, t_R of *S* isomer 31.49 min, *R*:*S* = 73.3:26.7, ee%: 47%.

2-(4-Chlorophenyl)-2-hydroxyacetonitrile 14j. Yield: 37%. $[\alpha]_D^{26.6}$ = +6.4° (*c* 1.09, $CHCl_3$). IR (KBr): 3432 (br), 2931, 2857, 1492, 1407, 1091, 1045, 1014, 836, 790 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.46-7.39 (m, 4H), 5.51 (s, 1H), 3.67 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 135.8, 133.7, 129.3, 128.0, 118.5, 62.8. GC-MS *m/z*: 167, 139, 132, 111, 75, 51.

2-(4-Chlorophenyl)-2-acetoxyacetonitrile 15j. Yield: 75%. $[\alpha]_D^{25.2}$ = -2.5° (*c* 1.11, $CHCl_3$). IR (KBr): 3073, 2927, 2854, 1754, 1492, 1373, 1211, 1091, 1014, 960, 817, 566 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.47-7.41 (m, 4H), 6.37 (s, 1H), 2.16 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.8, 136.6, 130.2, 129.5, 129.3, 115.7, 62.1, 20.4. GC-MS *m/z*: 209, 167, 149, 139, 132, 123, 114. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 31.02 min, t_R of *S* isomer 34.80 min, *R*:*S* = 60.3:39.7, ee%: 21%.

3-(Cyano(hydroxy)methyl)benzonitrile 14k. Yield: 15%. $[\alpha]_D^{26.3}$ = +2.7° (*c* 0.91, $CHCl_3$). IR (KBr): 3482 (br), 2919, 2850, 2237, 1434, 1149, 1045, 802, 740, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.84 (s, 1H), 7.80-7.78 (d, *J* = 7.8 Hz, 1H), 7.73-7.71 (d, *J* = 7.7 Hz, 1H), 7.61-7.57 (t, *J* = 7.8 Hz, 1H), 5.62 (s, 1H), 3.89 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 136.8, 133.2, 131.0, 130.2, 130.1, 118.1, 118.0, 113.1, 62.3. GC-MS *m/z*: 130, 102, 76, 51.

Cyano(3-cyanophenyl)methyl pivalate 15k. Yield: 92%. $[\alpha]_D^{25}$ = +2.3° (*c* 0.45, $CHCl_3$). IR (KBr): 3070, 2977, 2938, 2877, 2233, 1747, 1481, 1268, 1122, 802, 690 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.79-7.74 (m, 3H), 7.62-7.58 (t, *J* = 7.8 Hz, 1H), 6.41 (s, 1H), 1.24 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 176.1, 133.8, 133.6, 131.7, 130.9, 130.3, 117.6, 115.4, 113.7, 61.7, 38.9, 26.8. GC-MS *m/z*: 242, 158, 141, 114, 102. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 36.60 min, t_R of *S* isomer 41.50 min, *R*:*S* = 41.5: 58.5, ee%: 17%.

4-(Cyano(hydroxy)methyl)benzonitrile 14l. Yield: 11%. $[\alpha]_D^{26.4}$ = +2.3° (*c* 1.01, $CHCl_3$). IR (KBr): 3382 (br), 2919, 2854, 2233, 1407, 1064, 1049, 848, 420 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.75-7.73 (d, *J* = 8.4 Hz, 2H), 7.68-7.66 (d, *J* = 8.2 Hz, 2H), 5.63 (s, 1H), 3.87 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 140.1, 132.9, 127.2, 118.0, 113.4, 62.5. GC-MS *m/z*: 130, 102, 76, 50.

Cyano(4-cyanophenyl)methyl pivalate 15l. Yield: 93%. $[\alpha]_D^{24.5}$ = -2.0° (*c* 0.35, $CHCl_3$). IR (KBr): 2977, 2919, 2850, 2233, 1747, 1477, 1265, 1118, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.77-7.75 (d, *J* = 5.5 Hz, 2H), 7.64-7.62 (d, *J* = 8.2 Hz, 2H), 6.44 (s, 1H), 1.25 (s, 9H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 176.1, 136.7, 133.0, 128.1, 117.7, 115.3, 114.3, 61.9, 38.9, 26.8. GC-MS *m/z*: 242, 158, 141, 131, 114, 102. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.25 mL/min), t_R of *R* isomer 40.55 min, t_R of *S* isomer 44.69 min, *R*:*S* = 51.5:48.5, ee%: 3%.

(*E*)-2-Hydroxy-4-phenylbut-3-enenitrile 14m. Yield: 10%. $[\alpha]_D^{24.6}$ = +6.25° (*c* 0.64, $CHCl_3$). IR (KBr): 3421 (br), 2923, 1662, 1029, 968, 748, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.40-7.33 (m, 5H), 6.90-6.86 (d, *J* = 15.8 Hz, 1H), 6.27-6.21 (dd, J_1 = 15.8 Hz, J_2 = 5.8 Hz, 1H), 5.16-5.15 (d, *J* = 5.8 Hz, 1H), 4.20 (br, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 135.0, 134.8, 129.0, 128.8, 127.1, 122.4, 118.6, 61.7.

(*E*)-1-Cyano-3-phenylallyl acetate 15m. Yield: 97%. $[\alpha]_D^{26.2}$ = -23.7° (*c* 0.51, $CHCl_3$). IR (KBr): 2935, 1751, 1373, 1214, 1022, 968, 748, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.43-7.42 (m, 2H), 7.38-7.32 (m, 3H), 6.99-6.95 (d, *J* = 15.8 Hz, 1H), 6.22-6.17 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H), 6.03-6.01 (d, *J* = 6.7 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 168.9, 137.8, 134.4, 129.4, 128.8, 127.2, 118.3, 115.5, 61.5, 20.4. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol/acetonitrile = 80:1:1, flow rate 1.00 mL/min), t_R of *R* isomer 19.68 min, t_R of *S* isomer 25.22 min, *R*:*S* = 17.8:82.2, ee%: 65%.

2-Hydroxy-4-phenylbutanenitrile 14n. Yield: 18%. $[\alpha]_D^{24.8}$ = -2.4° (*c* 1.55, $CHCl_3$) IR (KBr): 3440 (br), 2931, 2861, 1454, 1072, 748, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.35-7.31 (m, 2H), 7.26-7.21 (m, 3H), 4.43-4.40 (t, *J* = 6.8 Hz, 1H), 3.51 (br, 1H), 2.88-2.83 (m, 2H), 2.22-2.11 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 139.6, 128.7, 128.5, 126.5, 120.0, 60.3, 36.5, 30.6.

1-Cyano-3-phenylpropyl acetate 15n. Yield: 98%. $[\alpha]_D^{26.2}$ = +10.6° (*c* 1.00, $CHCl_3$). IR (KBr): 2935, 1754, 1373, 1218, 1041, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 7.34-7.30 (m, 2H), 7.26-7.24 (m, 1H), 7.22-7.18 (m, 2H), 5.28-5.25 (t, *J* = 6.8 Hz, 1H), 2.85-2.81 (m, 2H), 2.27-2.21 (m, 2H), 2.12 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 169.1, 139.0, 128.8, 128.3, 126.7, 116.7, 60.5, 33.7, 30.7, 20.3. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol/acetonitrile = 80:1:1, flow rate 1.00 mL/min), t_R of *R* isomer 22.55 min, t_R of *S* isomer 28.18 min, *R*:*S* = 22.6:77.4, ee%: 55%.

2-Hydroxy-3-methylbutanenitrile 14o. Yield: 55%. $[\alpha]_D^{27.8}$ = +9.5° (*c* 1.37, $CHCl_3$). IR (KBr): 3417 (br), 2969, 2923, 1739, 1465, 1373, 1214, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 4.25-4.24 (d, *J* = 5.8 Hz, 1H), 3.65 (br, 1H), 2.06-1.98 (m, 1H), 1.07-1.06 (d, *J* = 6.7 Hz, 3H), 1.04-1.03 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 119.3, 66.9, 33.0, 17.6, 17.2.

1-Cyano-2-methylpropyl benzoate 15o. Yield: 93%. $[\alpha]_D^{26.3}$ = +28.5° (*c* 0.88, $CHCl_3$). IR (KBr): 2973, 2935, 1735, 1253, 1095, 709 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ): 8.06-8.04 (m, 2H), 7.64-7.60 (m, 1H), 7.49-7.46 (m, 2H), 5.44-5.43 (d, *J* = 5.7 Hz, 1H), 2.35-2.27 (m, 1H), 1.21-1.20 (d, *J* = 6.7 Hz, 3H), 1.18-1.16 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ): 164.7, 133.9, 129.9, 128.6, 128.3, 116.0, 66.7, 31.3, 17.8, 17.5. HPLC (Daicel Chiralcel OD-H, *n*-hexane/2-propanol = 9:1, flow rate 0.50 mL/min), t_R of *R* isomer 12.01 min, t_R of *S* isomer 13.73 min, *R*:*S* = 87.6:12.4, ee%: 75%.

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