Supporting Information for

Catalytic Enantioselective Synthesis of Sterically Demanding Alcohols Using Di(2°-alkyl)zinc Prepared by the Refined Charette's Method

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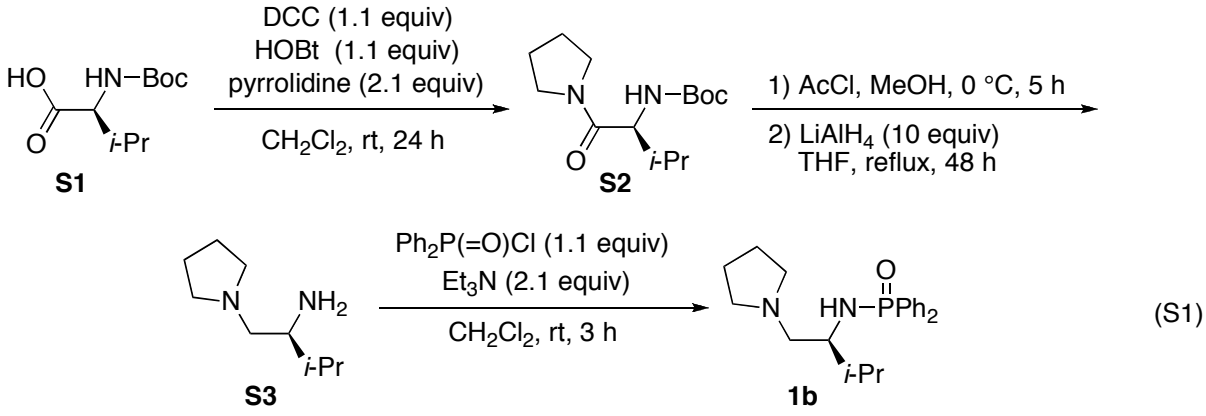
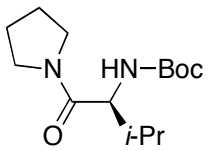
1. General methods: ^{1}H NMR spectra were measured on a JEOL ECS-400 (400 MHz) spectrometer at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on JEOL ECS-400 (100 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.10 ppm). ^{31}P NMR spectra were measured on a JEOL ECS-400 (161 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (H_3PO_4 at 0 ppm). ^{19}F NMR spectra were measured on a JEOL ECS-400 (376 MHz) spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CF_3C_6H_5$ at –63.24 ppm). High resolution mass spectral analyses (HRMS, FAB, EI, ESI) were performed at Chemical Instrument Center, Nagoya University (JEOL JMS-700, QSTAR). IR spectra were determined by a FT-IR spectrometer. High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL, CHIRALPAK; OD-H, AD-H, AS-3. GC analysis was performed with Shimadzu 17A instruments using CP-Cyclodextrin-β-2,3,6-M-19 (i.d. 0.25 mm × 25 m; CHROMPACK; GL Science Inc.) or CHIRALDEX B-DM, B-TA, G-TA (i.d. 0.25 mm × 20 m; Tokyo Kasei Kogyo Co., LTD). All experiments were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck TLC plates (silica gel 60G F_{254} 0.25 mm) were used. The products were purified by neutral column chromatography on silica gel (Kanto Chemical Co., Inc. 37560). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. All dry solvents and reagents were obtained from commercial source and were distilled before use. *i*-PrMgCl (2.0 *M* in Et_2O), *s*-BuMgCl (2.0 *M* in Et_2O), *c*-PentylMgCl (2.0 *M* in Et_2O), *c*-HexMgCl (2.0 *M* in Et_2O) were purchased from Aldrich.

2. Preparation of chiral ligand 1b.[1]



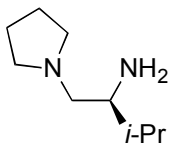
(S1)

The 1st. step of Eq. S1: To a solution of **S1** (4.35 g, 20 mmol) in dry CH_2Cl_2 (100 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (DCC) (4.54 g, 22 mmol) and 1-hydroxybenzotriazole (HOBt) (2.97g, 22 mmol) and pyrrolidine (2.99 g, 42 mmol) at 0 °C. After being stirred for 15 min at the same temperature, the reaction mixture was allowed to warm to ambient temperature and was stirred for 24 h. The reaction was quenched with 10 % citric acid (20 mL). The mixture was stirred for 10 min with a formation of white solid. The white solid was filtered and the filtrate was extracted with $CHCl_3$. The combined organics were washed with 10 % citric acid, saturated $NaHCO_3$, and brine. The organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by neutral column chromatography on silica gel using *n*-hexane–EtOAc (v/v = 3/1–1/1) as eluent to give **S2** (82% yield, 4.43 g).



(*S*)-*tert*-Butyl 3-methyl-1-oxo-1-(pyrrolidin-1-yl)butan-2-ylcarbamate (S2): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, *J* = 10.5 Hz, 3H), 0.96 (d, *J* = 10.8 Hz, 3H), 1.43 (s, 9H), 1.80-2.04 (m, 5H), 3.10-3.60 (m, 3H), 3.68 (m, 1H), 4.25 (t, *J* = 8.7 Hz, 1H), 5.27 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.5, 24.2, 26.0, 28.4, 31.5, 45.8, 46.7, 57.0, 79.3, 155.9, 170.7. IR (KBr) 3291, 2971, 2874, 1708, 1637, 1499, 1443, 1250, 1171 cm^{-1}. HRMS (FAB) calcd for $C_{14}H_{27}N_2O_3$ $[M+H]^+$ 271.2022, found 271.2024.

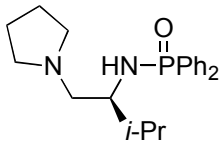
The 2nd. step Eq. S1: To a solution of **S2** (1.35 g, 5 mmol) in MeOH (50 mL) was added dropwise acetyl chloride (6.5 mL) at 0 °C. After being stirred at 0 °C for 5 h, the reaction mixture was allowed to warm to ambient temperature, and was stirred for 1 h, and then the solution was concentrated *in vacuo*. Resultant product in THF (10 mL) was added *via* cannula to the 25 mL of THF solution with lithium aluminum hydride (1.89 g, 50 mmol) at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was allowed to reflux and was stirred at that temperature for 48 h. Then, the reaction was quenched with Na_2SO_4 (2.5 g) and water (4 mL) with vigorous stirring at 0 °C for 30 min. The white–pale gray suspension was filtered and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on Cromatorex® NH-DM1020 using *n*-hexane–EtOAc (v/v = 3/1–1/1) as eluent to give the **S3** (61% yield, 0.476 g).



(*S*)-3-Methyl-1-(pyrrolidin-1-yl)butan-2-amine (S3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.30-1.70 (br, 2H), 1.56 (m, 1H), 1.70-1.80 (m, 4H), 2.23 (dd, *J* = 11.4, 3.3 Hz, 1H), 2.30-2.52 (m, 3H), 2.52-2.63 (m, 2H), 2.67 (m,

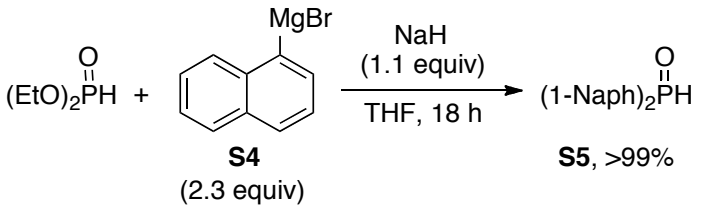
1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 19.4, 23.5, 32.2, 54.4, 55.0, 61.0. IR (neat) 3303, 2958, 2928, 2786, 1714, 1463 cm^{-1}. HRMS (FAB+) calcd for $C_9H_{21}N_2$ $[M+H]^+$ 157.1705, found 157.1706.

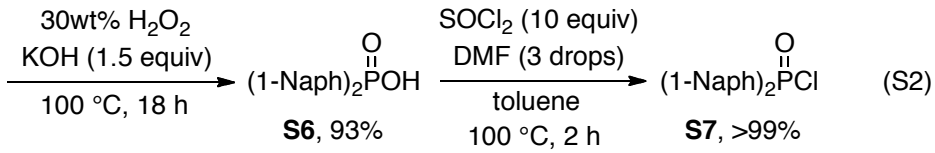
The 3rd. step Eq. S1: To a solution of **S3** (312 mg, 2 mmol) in THF (5 mL) was added Et_3N (0.59 mL, 4.2 mmol) at room temperature. Diphenylphosphinic chloride (0.42 ml, 2.2 mmol) in THF (5 mL) was added via cannula to the solution at 0 °C. After being stirred for 15 min at 0 °C, the reaction mixture was allowed to warm to ambient temperature and stirred for 3 h. The resulting mixture was cooled in ice bath, and diluted with $CHCl_3$ and water. The product was extracted with $CHCl_3$ and combined organic layer was washed with brine. The combined extracts were dried over $MgSO_4$ and filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on Cromatorex® NH-DM1020 using *n*-hexane–EtOAc as eluent (v/v = 3/1–1/1) to give the corresponding phosphoramide **1b** (72% yield, 0.513 g).



(*S*)-*N*-(3-Methyl-1-(1-pyrrolidinyl)2-butanyl) diphenylphosphinic amide (1b):[1] H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.3 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H), 1.69 (m, 4H), 1.99 (m, 1H), 2.30–2.55 (m, 5H), 2.59 (dd, J = 12.6, 7.8 Hz, 1H), 3.15 (m, 1H), 3.27 (m, 1H), 7.38–7.50 (m, 6H), 7.85–7.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 18.1, 23.6, 30.3, 54.3, 55.3, 57.9 (d, J = 5.7 Hz), 128.3 (d, J = 12.0 Hz), 131.5 (d, J = 2.8 Hz), 131.6 (d, J = 2.3 Hz), 132.1 (d, J = 9.8 Hz), 132.2 (d, J = 9.2 Hz), 133.6 (d, J = 124.3 Hz), 133.7 (d, J = 129.5 Hz). ^{31}P NMR (161 MHz, $CDCl_3$) δ 22.8. IR (KBr) 3158, 2957, 2777, 1590, 1458, 1354, 1283, 1179, 1107, 1049 cm^{-1}. $[\alpha]_D^{20}$ = –9.2 (*c* 1.00, THF). HRMS (FAB+) calcd for $C_{21}H_{30}N_2OP$ $[M+H]^+$ 357.2096, found 357.2095.

3. Preparation of chiral ligand 1a.[1]





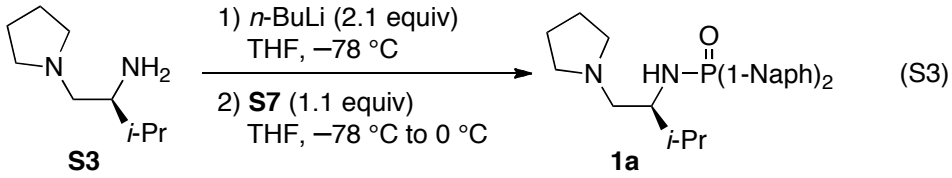
(S2)

(Preparation of compound **S4**) The mixture of magnesium turnings (1.89 g, 78 mmol) and iodine (ca. 10 mg) was stirred vigorously at room temperature for 2 h. After THF (150 mL) was added to the mixture, 1-bromonaphthalene (10.5 mL, 75 mmol) was added slowly over 10 min. After the exothermic reaction finished, a black solution of **S4** was prepared. If necessary, the solution was titrated prior to use against a solution of 1,10-phenanthoroline/*n*-BuLi/*s*-BuOH in benzene.

(Preparation of compound **S5**) To a suspension of sodium hydride (60% dispersion in mineral oil, 1.32 g, 33 mmol) in THF (15 mL) was added dropwise diethyl phosphite (3.87 mL, 30 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was cooled to –78 °C. Then, the prepared 1-bromonaphthylmagnesium bromide solution (**S4**, 75 mmol) was added to the suspension at –78 °C. The mixture was allowed to warm to room temperature, and was stirred at that temperature for 12 h. Then, the reaction was quenched at 0 °C with saturated NH_4Cl aqueous solution, where the color of the mixture changed from dark green to bright gray. The mixture was dried over $MgSO_4$ (10–20 g). The brown organic phase was filtered, and the solid residue was washed with THF (100 mL) for three times. The filtrate was concentrated *in vacuo*, and desired compound (**S5**) was obtained (9.06 g, >99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.65 (m, 6H), 7.80-8.12 (m, 4H), 8.04 (d, J = 8.4 Hz, 2H), 8.31 (d, J = 8.4 Hz, 2H), 9.72 (s, 1H). ^{31}P NMR (161 MHz, $CDCl_3$) δ 18.7.

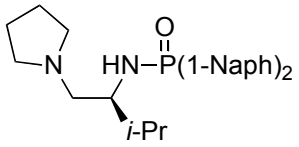
(Preparation of compound **S6**) To a mixture of compound **S5** (9.06g, 30 mmol) and 30% H_2O_2 aqueous solution (70 mL) was added dropwise carefully 1–2 mL of KOH aqueous solution (2.5 g, 45 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min, and at room temperature for 10 min. The mixture was heated carefully to 100 °C, and stirred at that temperature for 18 h. Then, the reaction was quenched at 0 °C with 1 *M* HCl aqueous solution to acidify the solution (pH = 1). A white precipitate (**S6**) was filtered, washed with *n*-hexane, and dried *in vacuo* (8.88 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (br, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.42 (t, J = 7.2 Hz, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 7.2 Hz, 1H), 8.19 (d, J = 6.9 Hz, 1H), 8.51 (d, J = 8.4 Hz, 2H). ^{31}P NMR (161 MHz, $CDCl_3$) δ 37.5.

(Preparation of compound **S7**) To a mixture of compound **S6** (8.88 g, 27.9 mmol) and *N*,*N*-dimethylformamide (3–5 drops) in toluene (30 mL) was added thionyl chloride (20.4 mL, 280 mmol) at room temperature. The mixture was heated to 100 °C, and stirred at that temperature for 2 h. Then, volatiles were removed *in vacuo* at room temperature for 12 h. Compound **S7** was obtained in >99% yield (9.40 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.63 (m, 6H), 7.91-8.00 (m, 2H), 8.04 (d, J = 7.2 Hz, 1H), 8.08-8.16 (m, 3H), 8.63-8.72 (m, 2H). ^{31}P NMR (161 MHz, $CDCl_3$) δ 47.0.



(S3)

(Preparation of compound **1a**) To a solution of **S3** (1.05 g, 6.7 mmol) in THF (10 mL) was added *n*-BuLi (1.6 *M* in *n*-hexane, 8.8 mL) at –78 °C. Compound **S7** (2.48 g, 7.4 mmol) in THF (10 mL) was added slowly via cannula to the solution at –78 °C. After being stirred for 30 min at –78 °C, the reaction mixture was allowed to warm to 0 °C over 3 h. The resulting mixture was cooled in ice bath, and quenched with saturated NH_4Cl aqueous solution. The product was extracted with EtOAc and combined organic layer was washed with brine. The combined extracts were dried over $MgSO_4$ and filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on Cromatorex® NH-DM1020 using *n*-hexane–EtOAc as eluent (v/v = 2/1), and recrystalized in *n*-hexane–EtOAc (v/v = 3/1) to give the corresponding phosphoramide **1a** (76% yield, 2.32 g).



(*S*)-*N*-(3-Methyl-1-(pyrrolidin-1-yl)butan-2-yl)-*P*,*P*-di(naphthalen-1-yl)phosphinic amide (1a):[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 1.63 (m, 4H), 2.20-2.65 (m, 7H), 3.40-3.60 (m, 2H), 7.36-7.56 (m, 6H), 7.80-8.02 (m, 5H), 8.21 (dd, *J* = 15.9, 7.2 Hz, 1H), 8.87 (m, 1H), 8.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 18.6, 23.6, 31.1, 54.3, 55.6, 57.1 (d, *J* = 5.7 Hz), 124.4 (d, *J* = 14.4 Hz), 124.5 (d, *J* = 14.4 Hz), 126.2 (d, *J* = 4.6 Hz), 127.0, 127.6 (d, *J* = 2.8 Hz), 128.7, 130.4 (d, *J* = 121.5 Hz), 130.6 (d, *J* = 124.3 Hz), 132.7 (d, *J* = 2.8 Hz), 132.8 (d, *J* = 2.8 Hz), 133.4 (d, *J* = 11.5 Hz), 133.5 (d, *J* = 9.8 Hz), 133.7 (d, *J* = 5.8 Hz), 133.8 (d, *J* = 5.8 Hz), 133.9 (d, *J* = 9.7 Hz), 134.0 (d, *J* = 7.5 Hz). ^{31}P NMR (161 MHz, $CDCl_3$) δ 28.7. IR (KBr) 3210, 2958, 2782, 1457, 1175, 1158 cm^{-1}. $[\alpha]_D^{20}$ = +20.8 (*c* 1.00, THF). HRMS (FAB+) calcd for $C_{29}H_{34}N_2OP$ $[M+H]^+$ 457.2409, found 457.2405.

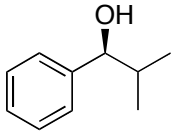
4. General procedure for the preparation of salt-free di(2°-alkyl)zinc reagents (0.44 *M* Et_2O solution).

To a test tube equipped with a magnetic stirrer charged with $ZnCl_2$ (682 mg, 5 mmol) and NaOMe (676 mg, 12.5 mmol) was added Et_2O (5 mL) at room temperature under a nitrogen atmosphere. The suspension was stirred for 20 min and cooled to 0 °C for another 10 min. RMgCl in 2.0 *M* Et_2O solution (titrated, 4 mL, 8 mmol) was added dropwise with vigorous stirring over 10 min at 0 °C, and the suspension was allowed to stir at room temperature for 2 h. The mixture was centrifuged for 10 min (4,000 rpm) and the the di(2°-alkyl)zinc reagents (0.44 *M* Et_2O solution) was gently transferred via cannula into a well-dried pyrex Schlenk tube to be stored before use.

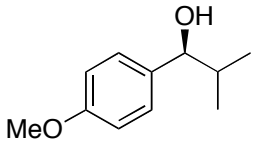
5. General procedure for the catalytic enantioselective addition of di(2°-alkyl)zinc reagents to aldehydes (Tables 1 and 2).

A well-dried pyrex Schlenk tube was charged with **1a** (22.8 mg, 0.05 mmol) and the salt-free di(2°-alkyl)zinc reagents (0.44 *M* Et_2O solution) (3.4 mL, 1.5 mmol) at room temperature under a nitrogen atmosphere. Et_2O was removed under the reduced pressure to generate the solvent-free di(2°-alkyl)zinc reagents containing **1a** in situ. (After the removal of Et_2O, toluene (0.4 mL) was added when (*c*-Hex)$_2$Zn was used.) Aldehyde (**2**) (0.5 mmol) was added to the mixture at room temperature. The resulting mixture was stirred at room temperature for 2 h. After hydrolysis with 10 mL of sat. NH_4Cl aqueous solution, the product was extracted with ether (10 mL × 3) and washed with brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the crude product was purified by neutral silica gel column chromatography (eluent: *n*-hexane/Et_2O or *n*-pentane/Et_2O), to give the desired products (**3**). The enantiomeric purity was determined by GC or HPLC on chiral column.

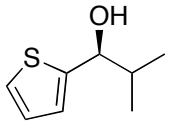
6. Products (3) from aldehydes.



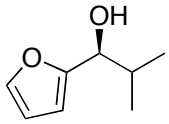
(*S*)-2-Methyl-1-phenylpropan-1-ol (3a):[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.85 (s, 1H), 1.96 (octet, *J* = 6.9 Hz, 1H), 4.36 (m, 1H), 7.20-7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 19.0, 35.3, 80.1, 126.6, 127.4, 128.2, 143.6. IR (neat) 3390, 2958, 2927, 2871, 1454, 1022 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{14}O$ $[M]^+$ 150.1045, found 150.1052. $[\alpha]_D^{20} = -46.8$ (94% ee, *c* 1.0, Et_2O) (lit.[3] $[\alpha]_D^{20} = -48.4$ (95% ee (*S*), *c* 1.34, Et_2O)). Chiral GC CP-Cyclodextrin-β-2,3,6-M-19, 110 °C, t_R = 36.5 min (minor, *R*), 38.0 min (major, *S*).



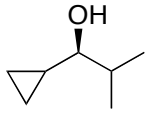
(*S*)-1-(4-Methoxyphenyl)-2-methylpropan-1-ol (3b):[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.83 (br, 1H), 1.96 (octet, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 4.36 (d, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.0, 35.3, 55.3, 79.8, 113.6, 127.7, 135.8, 158.9. IR (neat) 3446, 2957, 1612, 1509, 1246, 1173, 1034 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{16}O_2$ $[M]^+$ 180.1150, found 180.1156. $[\alpha]_D^{20} = -31.1$ (96% ee, *c* 2.0, $CHCl_3$) (lit.[5] $[\alpha]_D^{25} = +37.6$ (88% ee (*R*), *c* 1.8, CH_2Cl_2)). Chiral GC CHIRALDEX B-DM, 110 °C, t_R = 37.9 min (minor, *R*), 39.7 min (major, *S*).



(*S*)-2-Methyl-1-(thiophen-2-yl)propan-1-ol (3c):[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.96 (octet, *J* = 6.9 Hz, 1H), 1.18 (br, 1H), 4.54 (d, *J* = 6.9 Hz, 1H), 6.86-6.91 (m, 2H), 7.16 (dd, *J* = 4.6, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 19.0, 35.9, 76.0, 124.3, 124.4, 126.5, 147.6. IR (neat) 3407, 2961, 1466, 1383, 1260, 1019 cm^{-1}. LRMS (CI) 139 $[M–OH]^+$. $[\alpha]_D^{20} = -12.3$ (95% ee, *c* 0.13, $CHCl_3$) (lit.[6] +14.2 (91% ee (*R*), *c* 1.02, $CHCl_3$) Chiral GC CHIRALDEX B-DM, 80 °C, t_R = 58.1 min (minor, *R*), 59.5 min (major, *S*).

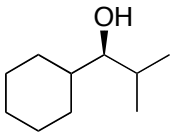


(*S*)-1-(Furan-2-yl)-2-methylpropan-1-ol (3d):[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.93 (s, 1H), 2.10 (octet, *J* = 6.9 Hz, 1H), 4.37 (m, 1H), 6.22 (d, *J* = 3.3 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 18.7, 33.4, 73.5, 106.5, 110.0, 141.7, 156.2. IR (neat) 3420, 2961, 1468, 1150, 1008 cm^{-1}. HRMS (EI) calcd for $C_8H_{12}O_2$ $[M]^+$ 140.0837, found 140.0843. $[\alpha]_D^{20} = -16.0$ (90% ee, *c* 0.15, $CHCl_3$) (lit.[7] $[\alpha]_D^{25} = +18.1$ (>95% ee (*R*), *c* 1.04, $CHCl_3$)). Chiral GC CP-Cyclodextrin-β-2,3,6-M-19, 70 °C, t_R = 59.0 min (minor, *R*), 62.5 min (major, *S*).

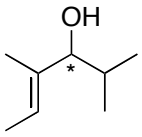


(*S*)-1-Cyclopropyl-2-methylpropan-1-ol (3e):[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20-0.31 (m, 2H), 0.42-0.62 (m, 2H), 0.91 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.69 (br, 1H), 1.81 (m, 1H), 2.58 (dd, *J* = 8.7, 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.9, 3.7, 15.6, 18.2, 18.7, 34.4, 81.9. IR (neat) 3443, 2959, 2874, 1685, 1626, 1382, 1022 cm^{-1}. LRMS (CI) 97 $[M–OH]^+$. The absolute configuration of **3e** was determined by esterification with *N*-(*t*-butoxycarbonyl)-(*R*)-alanine; $[\alpha]_D^{20} = +5.0$ (96% ee, *c* 1.2, $CHCl_3$) (lit.[9] $[\alpha]_D^{22} = -4.96$ (94%

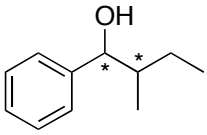
ee (*R*), *c* 2.40, $CHCl_3$)). Chiral GC CHIRALDEX B-TA, 45 °C, t_R = 11.3 min (major, *S*), 14.2 min (minor, *R*).



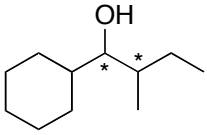
(*S*)-1-Cyclohexyl-2-methylpropan-1-ol (3f):[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.95-1.92 (m, 13H), 3.03 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 19.9, 26.2, 26.4, 26.5, 27.7, 29.7, 29.9, 40.6, 81.1. IR (neat) 3388, 2926, 2852, 1448, 1078 cm^{-1}. LRMS (CI) 139 $[M–OH]^+$. $[\alpha]_D^{20}$ = +13.6 (>99% ee, *c* 1.0, $CHCl_3$) (lit.[11] $[\alpha]_D^{18}$ = +0.25 (4% ee (*S*), neat)). Chiral GC CHIRALDEX B-DM, 80 °C, t_R = 28.7 min (major, *S*), 29.8 min (minor, *R*).



2,4-Dimethylhex-4-en-3-ol (3g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.55 (br, 1H), 1.58 (s, 3H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.76 (octet, *J* = 6.6 Hz, 1H), 3.56 (d, *J* = 6.9 Hz, 1H), 5.43 (q, *J* = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 13.0, 18.7, 19.4, 31.1, 84.3, 121.8, 137.3. IR (neat) 3391, 2956, 2922, 2869, 1457, 1379, 1010 cm^{-1}. HRMS (FAB+) calcd for $C_8H_{16}O$ $[M]^+$ 128.1201, found 128.1199. $[\alpha]_D^{20}$ = +10.0 (97% ee, *c* 0.8, $CHCl_3$). Chiral GC CHIRALDEX G-TA, 40 °C, t_R = 21.3 min (minor), 25.6 min (major).

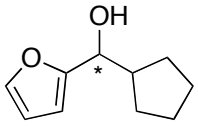


2-Methyl-1-phenylbutan-1-ol (3h):[12] ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers, *anti*/*syn* =55/45) δ 0.74 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.95-1.90 (m, 8H), 4.44 (d, *J* = 7.2 Hz, 1H), 4.53 (d, *J* = 6.0 Hz, 1H), 7.23-7.37 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereomers, *anti*/*syn* =55/45) *anti*-**3h**: δ 11.3, 15.1, 24.9, 41.7, 78.9, 126.7, 127.5, 128.6 143.6; *syn*-**3h**: δ 11.7, 14.0, 25.9, 42.0, 78.1, 126.4, 127.3, 128.6, 143.9. IR (neat) 3389, 2962, 2930, 2875, 1454, 1037, 1006 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{16}O$ $[M]^+$ 164.1201, found 164.1206. Chiral HPLC analysis of the corresponding derivative 3,5-dinitrobenzoate; AD-H × 3, *n*-hexane/*i*-PrOH = 19/1, 0.3 mL/min, *anti*-**3h**: t_R = 67.7 min (minor), 85.7 min (major); *syn*-**3h**: t_R = 69.1 min (minor), 90.3 min (major).

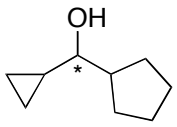


1-Cyclohexyl-2-methylbutan-1-ol (3i):[13] ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereomers, *anti*/*syn* =59/41) δ 0.84 (d, *J* = 6.9 Hz, 3H), 0.86-0.93 (m, 9H),

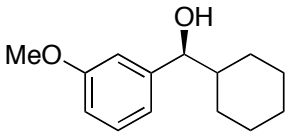
0.93-2.00 (m, 30H), 3.09 (m, 1H), 3.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereomers, *anti*/*syn* =59/41) δ 11.5, 11.8, 12.5, 15.9, 23.5, 26.1, 26.2, 26.3, 26.5 (2C), 26.6, 26.8, 27.1, 29.0, 29.4, 30.2, 36.1, 26.7, 40.3, 70.7, 78.8, 80.5. IR (neat) 3388, 2925, 2852, 1449, 1378, 1120, 1082 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{22}O$ $[M]^+$ 170.1671, found 170.1670. Chiral HPLC analysis of the corresponding derivative 3,5-dinitrobenzoate; OD-H × 3, *n*-hexane/*i*-PrOH = 40/1, 0.35 mL/min, *anti*-**3i**: t_R = 87.8 min (minor), 89.2 min (major), *syn*-**3i**: t_R = 83.1 min (minor), 85.5 min (major).



Cyclopentyl(furan-2-yl)methanol (3j): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (m, 1H), 1.40-1.73 (m, 5H), 1.87 (m, 1H), 2.02 (s, 1H), 2.38 (m, 1H), 4.42 (d, J = 8.7 Hz, 1H), 6.21 (d, J = 2.7 Hz, 1H), 6.31 (dd, J = 2.7, 0.9 Hz, 1H), 7.35 (d, J = 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.7, 29.1, 29.3, 44.7, 71.9, 106.2, 110.0, 141.8, 156.7. IR (neat) 3388, 2953, 2867, 1504, 1452, 1151, 1009 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{14}O_2$ $[M]^+$ 166.0994, found 166.0992. $[\alpha]_D^{20}$ = –6.4 (96% ee, *c* 1.0, $CHCl_3$). Chiral GC analysis of the corresponding derivative acetate which was transformed from **3j** by using Ac_2O/Et_3N/DMAP in CH_2Cl_2; CHIRALDEX G-TA, 90 °C, t_R = 22.6 min (minor), 25.9 min (major).

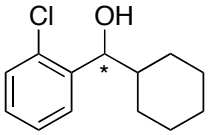


Cyclopentyl(cyclopropyl)methanol (3k): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (m, 2H), 0.47 (m, 1H), 0.55 (m, 1H), 0.91 (m, 1H), 1.30-1.70 (m, 7H), 1.80 (m, 2H), 2.04 (sextet, J = 8.1 Hz, 1H), 2.69 (t, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.9, 3.6, 17.3, 25.3, 25.6, 28.9, 29.1, 47.0, 80.6. IR (neat) 3392, 2952, 2868, 1455, 1024 cm^{-1}. LRMS (CI) 123 $[M–OH]^+$. $[\alpha]_D^{20}$ = –5.0 (99% ee, *c* 0.4, $CHCl_3$). Chiral HPLC analysis of the corresponding derivative 3,5-dinitrobenzoate which was transformed from **3k** by using Ac_2O/Et_3N/DMAP in CH_2Cl_2; OD-H × 2, *n*-hexane/*i*-PrOH = 40/1, 0.5 mL/min, t_R = 60.4 min (minor), 64.6 min (major).

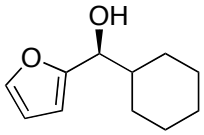


(*S*)-Cyclohexyl(3-methoxyphenyl)methanol (3l):[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-2.05 (m, 12H), 3.80 (s, 3H), 4.33 (d, J = 7.2 Hz, 1H), 6.80 (d, J = 7.2 Hz, 1H), 6.86 (s, 1H), 6.87 (d, J = 7.2 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.1, 26.4, 28.8, 29.4, 44.9, 55.2, 79.3, 112.1, 112.8, 119.1, 129.2, 145.4, 159.6. IR (neat) 3419, 2924, 2851, 1600, 1486, 1451, 1259, 1045 cm^{-1}. HRMS (EI) calcd for $C_{14}H_{20}O_2$ $[M]^+$ 220.1463, found 220.1470. $[\alpha]_D^{20}$ = –21.0 (97% ee, *c* 1.5, THF) (lit.[14] $[\alpha]_D^{25}$ = +18.5 (>99% ee (*R*), *c* 0.60, $CHCl_3$)). Chiral HPLC analysis; OD-H, *n*-hexane/*i*-PrOH = 19/1, 0.5 mL/min, t_R = 12.1 min

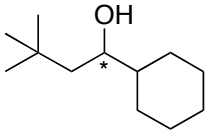
(major, *S*), 19.7 min (minor, *R*).



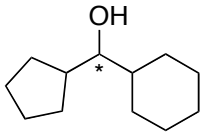
(2-Chlorophenyl)(cyclohexyl)methanol (3m):[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05-2.10 (m, 12H), 4.90 (d, J = 6.4 Hz, 1H), 7.18 (td, J = 7.2, 1.2 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.48 (dd, J =7.5 Hz, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.3, 26.4, 27.8, 29.4, 44.0, 74.9, 126.8, 128.2, 128.3, 129.3, 132.5, 141.1. IR (neat) 3374, 2927, 2852, 1448, 1035, 1016. cm^{-1}. HRMS (EI) calcd for $C_{13}H_{17}ClO$ $[M]^+$ 224.0968, found 224.0972. $[\alpha]_D^{20}$ = –52.4 (90% ee, *c* 1.8, $CHCl_3$). Chiral GC CP-Cyclodextrin-β-2,3,6-M-19, 160 °C, t_R = 31.1 min (major), 32.1 min (minor).



(*S*)-Cyclohexyl(furan-2-yl)methanol (3n):[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-2.05 (m, 12H), 4.38 (d, J = 7.5 Hz, 1H), 6.22 (d, J = 3.3 Hz, 1H), 6.33 (dd, J = 3.3, 1.8 Hz, 1H), 7.37 (d, J = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.0, 26.4, 28.8, 29.1, 42.9, 72.8, 106.6, 110.0, 141.8, 156.0. IR (neat) 3420, 2926, 2853, 1669, 1450, 1149, 1008 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{16}O_2$ $[M]^+$ 180.1150, found 180.1156. $[\alpha]_D^{20}$ = –16.4 (84% ee, *c* 1.1, $CHCl_3$) (lit.[16] $[\alpha]_D^{25}$ = +20.0 (>98% ee (*R*), *c* 1.19, $CHCl_3$)). Chiral GC analysis of the corresponding derivative acetate which was transformed from **3n** by using Ac_2O/Et_3N/DMAP in CH_2Cl_2; CHIRALDEX B-DM, 100 °C, t_R = 21.2 min (minor, *R*), 23.1 min (major, *S*).

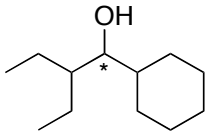


1-Cyclohexyl-3,3-dimethylbutan-1-ol (3o): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 0.96-1.32 (m, 8H), 1.41 (dd, J = 14.4, 1.2 Hz, 1H), 1.60-1.82 (m, 5H), 3.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.4, 26.6, 27.5, 29.0, 30.1 (3C), 30.2, 45.4, 48.3, 73.5. IR (KBr) 3423, 2924, 2852, 1473, 1447, 1364, 1062 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{22}$ $[M–H_2O]^+$ 166.1722, found 166.1720. $[\alpha]_D^{20}$ = +8.0 (82% ee, *c* 0.4, $CHCl_3$) Chiral GC analysis; CHIRALDEX B-DM, 100 °C, t_R = 23.1 min (minor), 28.8 min (major).

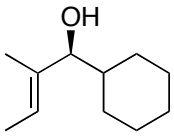


Cyclohexyl(cyclopentyl)methanol (3p):[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75-1.43 (m, 9H), 1.46-1.70 (m, 7H), 1.70-1.85 (m, 4H), 2.01 (sextet, J = 7.2 Hz, 1H), 3.19 (dd, J = 7.2, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 25.6, 26.3, 26.5, 26.6, 26.7, 28.6, 29.2, 30.4, 41.9, 43.0, 80.2. IR (neat) 3375, 2925, 2852, 1449, 1108, 1069 cm^{-1}. HRMS (EI) calcd for

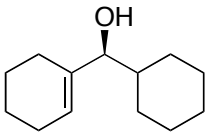
$C_{12}H_{21}$ $[M–OH]^+$ 165.1643, found 165.1650. $[\alpha]_D^{20}$ = +5.0 (>99% ee, *c* 0.3, $CHCl_3$). Chiral HPLC analysis of the corresponding derivative 3,5-dinitrobenzoate which was transformed from **3p** by using 3,5-dinitrobenzoyl chloride/Et_3N/DMAP in CH_2Cl_2; OD-H × 2, *n*-hexane/*i*-PrOH = 19/1, 0.5 mL/min, t_R = 34.9 min (major), 36.4 min (minor).



1-Cyclohexyl-2-ethylbutan-1-ol (3q): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-1.82 (m, 16H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 1.91 (m, 1H), 3.27 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 11.8, 20.3, 22.2, 26.1, 26.4, 26.6, 28.4, 29.9, 40.4, 42.5, 77.2. IR (neat) 3397, 2926, 2852, 1449, 1378, 1261, 1010 cm^{-1}. LRMS (CI) 167 $[M–OH]^+$. $[\alpha]_D^{20}$ = +6.0 (99% ee, *c* 0.8, $CHCl_3$). Chiral GC CP-Cyclodextrin-β-2,3,6-M-19, 100 °C, t_R = 54.3 min (minor), 56.5 min (major).



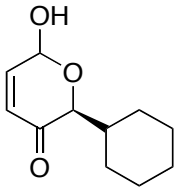
(*S*)-1-Cyclohexyl-2-methylbut-2-en-1-ol (3r): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75-1.00 (m, 2H), 1.05-1.30 (m, 4H), 1.35-1.50 (m, 3H), 1.58 (s, 3H), 1.60 (d, *J* = 6.2 Hz, 3H), 1.62-1.80 (m, 2H), 1.99 (m, 1H), 3.61 (d, *J* = 8.6 Hz, 1H), 5.40 (d, *J* = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9, 13.0, 26.0, 26.2, 26.5, 29.3, 29.6, 40.6, 83.3, 122.1, 137.0. IR (neat) 3374, 2924, 2851, 1448, 1379, 1005 cm^{-1}. HRMS (EI) calcd for $C_{11}H_{20}O$ $[M]^+$ 168.1514, found 168.1520. $[\alpha]_D^{20}$ = –10.0 (99% ee, *c* 1.0, $CHCl_3$). Chiral GC CP-Cyclodextrin-β-2,3,6-M-19, 100 °C, t_R = 40.6 min (major, *S*), 43.7 min (minor, *R*). The absolute stereochemistry of **3r** was determined by the ^{1}H NMR analysis of MTPA-esters (Mosher's method).



(*S*)-Cyclohexenyl(cyclohexyl)methanol (3s):[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-2.15 (m, 20H), 3.59 (d, *J* = 8.1 Hz, 1H), 5.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7 (2C), 23.3, 25.1, 26.0, 26.2, 26.5, 29.2, 29.6, 40.5, 82.0, 124.5, 138.9. IR (neat) 3374, 2924, 2851, 1448, 1006 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{22}O$ $[M]^+$ 194.1671, found 194.1677. $[\alpha]_D^{20}$ = +2.8 (98% ee, *c* 1.0, $CHCl_3$). Chiral GC CHIRALDEX B-DM, 120 °C, t_R = 34.6 min (major, *S*), 41.1 min (minor, *R*). The absolute stereochemistry of **3s** was determined by the ^{1}H NMR analysis of MTPA-esters (Mosher's method).

7. Synthesis of a γ-hydroxy-β-pyrone (Eq. 1, left).

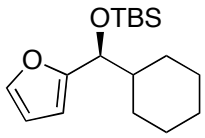
To a solution of **3n** (54.0 mg, 0.3 mmol) in THF (0.6 mL) and H_2O (0.15 mL) was added *N*-bromosuccinimide (NBS) (58.7 mg, 0.33 mmol) at room temperature. The mixture was stirred at that temperature for 4 h. The mixture was purified by neutral column chromatography on silica gel using *n*-hexane–EtOAc (v/v = 8/1–2/1) as eluent to give **4** as a mixture of two diastereomers (dr = 73/27) (94% yield, 55.3 mg).



(2*S*)-2-Cyclohexyl-6-hydroxy-2*H*-pyran-3(6*H*)-one (4) (ca. 7/3 diastereomer mixture):[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ (major) 1.05-2.20 (m, 11H), 3.42 (br, 1H), 4.38 (d, *J* = 2.7 Hz, 1H), 5.65 (bs, 1H), 6.10 (d, *J* = 10.2 Hz, 1H), 6.89 (dd, *J* = 10.2, 3.3 Hz, 1H); (minor) 1.05-2.20 (m, 11H), 3.73 (br, 1H), 3.89 (d, *J* = 2.7 Hz, 1H), 5.62 (bs, 1H), 6.10 (dd, *J* = 10.2, 1.8 Hz, 1H), 6.93 (d, *J* = 10.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (major) 26.2, 26.5, 26.6, 29.3, 38.4, 78.4, 87.6, 128.1, 144.4, 196.8; (minor) 26.1, 26.4, 26.7, 29.4, 38.6, 83.0, 91.2, 129.5, 148.1, 196.3. IR (neat) 3402, 2927, 2854, 1685, 1450, 1033 cm^{-1}. HRMS (FAB+) calcd for $C_{11}H_{16}NaO_3$ $[M+Na]^+$ 219.0997, found 219.1000. HPLC analysis; Daicel Chiralpack AD-3, *n*-hexane/*i*-PrOH = 49/1, 0.5 mL/min, major isomer: t_R = 88.6 min (minor), 94.1 min (major); minor isomer: t_R = 76.9 min (major), 79.3 min (minor).

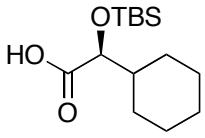
8. Synthesis of an α-alkoxy carboxylic acid (Eq. 1, right).

To a solution of **3n** (54.0 mg, 0.3 mmol) in acetonitrile (7.5 mL) were added imidazole (41 mg, 0.6 mmol) and TBSCl (49.7 mg, 0.33 mmol) at 0 ºC. The mixture was warmed to room temperature, and stirred for 4 h. The mixture was purified by neutral column chromatography on silica gel using *n*-hexane–EtOAc (v/v = 20/1) as eluent to give **S8** (>99% yield, 88.3 mg).



(*S*)-*tert*-Butyl(cyclohexyl(furan-2-yl)methoxy)dimethylsilane (S8): ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.15 (s, 3H), –0.01 (s, 3H), 0.85 (s, 9H), 0.86-1.03 (m, 2H), 1.05-1.29 (m, 3H), 1.35 (m, 1H), 1.58-1.79 (m, 4H), 1.93 (m, 1H), 4.31 (d, *J* = 7.2 Hz, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 6.28 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.32 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, –4.9, 18.3, 25.8, 26.1, 26.2, 26.6, 29.0, 29.2, 43.9, 73.5, 106.5, 109.8, 141.0, 156.8. IR (neat) 2928, 2855, 1471, 1253, 1151, 1101, 1063, 1006 cm^{-1}. HRMS (FAB+) calcd for $C_{17}H_{30}NaO_2Si$ $[M+Na]^+$ 317.1913, found 317.1923.

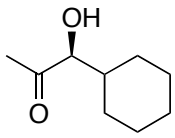
Compound **S8** (88.3 mg, 0.3 mmol) was dissolved in MeOH (5 mL), and the solution was cooled to –78 ºC. Ozone was bubbled through the cooled solution until a blue color was obtained (ca. for 1 h). Nitrogen was then bubbled through for 10 min. The mixture was allowed to warm to room temperature and stirred for 12 h. Removal of solvent followed by neutral column chromatography on silica gel using *n*-hexane–EtOAc (v/v = 1/1–1/2) as eluent to give **5** as (96% yield, 78.8 mg).



(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-cyclohexylacetic acid (5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.14 (s, 3H), 0.95 (s, 9H), 1.05-1.82 (m, 11H), 4.07 (d, J = 3.6 Hz, 1H), 8.99 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, –4.8, 18.2, 25.7, 26.0, 26.1, 26.2, 27.0, 29.2, 42.5, 74.8, 175.0. IR (neat) 3100, 2929, 2856, 1719, 1254, 1141 cm^{-1}. HRMS (FAB+) calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$ 273.1886, found 273.1888. $[\alpha]_D^{20}$ = –12.8 (84% ee, *c* 1.0, $CHCl_3$).

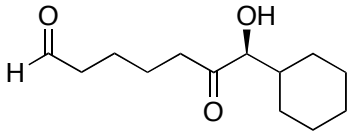
9. Synthesis of α-hydroxy ketones (Eq. 2 and Eq. 3, right).

Compound **3r** (50.4 mg, 0.3 mmol) was dissolved in MeOH (5 mL), and the solution was cooled to –78 ºC. Ozone was bubbled through the cooled solution until a blue color was obtained (ca. for 1 h). Nitrogen was then bubbled through for 10 min, and then methyl sulfide (0.22 mL, 3 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 12 h. Removal of solvent followed by neutral column chromatography on silica gel using *n*-hexane–EtOAc (v/v = 15/1–8/1) as eluent to give **6** (98% yield, 46.0 mg).



(*S*)-1-cyclohexyl-1-hydroxypropan-2-one (6):[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75-1.90 (m, 11H), 2.20 (s, 3H), 3.39 (br, 1H), 4.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.6, 25.9, 26.0, 26.6, 30.1, 41.2, 81.2, 210.0. IR (neat) 3477, 2929, 2855, 1707, 1451, 1358, 1248, 1111 cm^{-1}. HRMS (ESI+) calcd for $C_9H_{16}NaO_2$ $[M+Na]^+$ 179.1047, found 179.1043. $[\alpha]_D^{20}$ = +54.9 (84% ee, *c* 1.0, $CHCl_3$). Enantioselectivity was confirmed to be 99% ee by ^{1}H NMR analysis of the (*R*)-MTPA ester of **6** obtained.

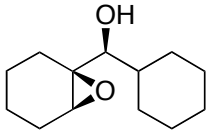
7-Cyclohexyl-7-hydroxy-6-oxoheptanal (**7**) was prepared from compound **3s** by the similar ozonolysis procedure as above.



(*S*)-7-Cyclohexyl-7-hydroxy-6-oxoheptanal (7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65-2.15 (m, 15H), 2.49 (m, 4H), 3.37 (br, 1H), 4.04 (bs, 1H), 9.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.0, 25.2, 25.8, 26.0, 26.5, 30.1, 37.9, 41.4, 43.6, 80.8, 202.0, 211.7. IR (neat) 3475, 2925, 2853, 1708, 1451, 1126 cm^{-1}. HRMS (FAB+) calcd for $C_{11}H_{16}NaO_2$ $[M+Na]^+$ 249.1467, found 249.1455. $[\alpha]_D^{20}$ = +36.8 (98% ee, *c* 0.5, $CHCl_3$). Enantioselectivity was confirmed to be 99% ee by ^{1}H NMR analysis of the (*R*)-MTPA ester of **7** obtained.

10. Synthesis of a 2,3-epoxyalcohol (Eq. 3, left).

Compound **3s** (58.2 mg, 0.3 mmol) was dissolved in THF (2 mL), and the solution was cooled to 0 ºC. To the solution, *m*-CPBA (77% purity, 121 mg, 0.54 mmol) and $NaHCO_3$ (68 mg, 0.81 mmol) were added, and the mixture was stirred at 0 ºC for 2 h. Then, the reaction was quenched with saturated Na_2SO_4 aqueous solution (20 mL), and the organic layer was extracted with Et_2O (15 mL × 3). The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ether = 12/1–8/1), to give the desired *syn*-product **8** as colorless oil (63.1 mg, >99% yield (*syn*/*anti* = 76/24), 97% ee (*syn*)).



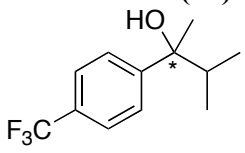
(*S*)-((1*S*,6*S*)-7-oxabicyclo[4.1.0]heptan-1-yl)(cyclohexyl)methanol (8): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-2.25 (m, 20H), 2.89 (d, *J* = 8.1 Hz, 1H), 3.04 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 19.9, 22.4, 24.4, 25.8, 26.1, 26.4, 29.1, 29.3, 40.4, 58.2, 62.0, 81.4. IR (neat) 3452, 2927, 2852, 1448, 1087, 1026 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{22}NaO_2$ $[M+Na]^+$ 233.1517, found 233.1521. $[\alpha]_D^{20}$ = –11.0 (97% ee, *c* 0.4, $CHCl_3$). Chiral GC CHIRALDEX B-DM, 150 °C, t_R = 11.7 min (major, *S,S,S*), 13.2 min (minor, *R,R,R*).

11. Representative procedure for the catalytic enantioselective addition of di(2°-alkyl)zinc reagents to ketones (Table 3).

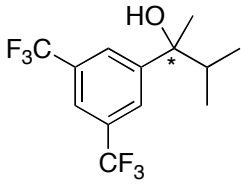
A well-dried pyrex Schlenk tube was charged with **1a** (22.8 mg, 0.05 mmol) and the salt-free *c*-Hex_2Zn (0.44 *M* Et_2O solution) (3.4 mL, 1.5 mmol) at room temperature under a nitrogen atmosphere. Et_2O was removed under the reduced pressure to generate the solvent-free *c*-Hex_2Zn containing **1a** in situ. After the removal of Et_2O, toluene (0.4 mL) was added, and the solution was cooled to 0 °C. 3',5'-Bis(trifluoromethyl)acetophenone (**9c**) (90.1 μL, 0.5 mmol) was added to the mixture dropwise at 0 °C over 12 h. The resulting mixture was stirred at 0 °C for another

12 h. After hydrolysis with 10 mL of sat. NH_4Cl aqueous solution, the product was extracted with ether (10 mL × 3) and washed with brine (10 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the crude product was purified by neutral silica gel column chromatography (eluent: *n*-hexane/Et_2O = 20/1–8/1), to give the desired product (**10f**) (95.3 mg, 56% yield). To determine the enantioselectivity, compound **10f** was transformed to the corresponding derivative acetate by using Ac_2O/Et_3N/DMAP in CH_2Cl_2.

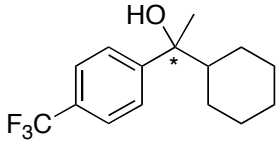
12. Products (10) from ketones.



3-Methyl-2-(4-(trifluoromethyl)phenyl)butan-2-ol (10c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 1.54 (s, 3H), 1.64 (br, 1H), 2.02 (septet, *J* = 6.9 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 17.3, 27.2, 38.5, 77.3, 121.6 (q, *J* = 271.0 Hz), 124.8, 125.7, 128.5 (q, *J* = 32.4 Hz), 151.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.84. IR (neat) 3465, 2973, 1618, 1409, 1328, 1165, 1125, 1071, 1016 cm^{-1}. HRMS (FAB+) calcd for $C_{12}H_{14}F_3$ $[M–OH]^+$ 215.1048, found 215.1053. $[\alpha]_D^{20}$ = –5.3 (>99% ee, *c* 0.30, $CHCl_3$). Chiral GC analysis of the corresponding derivative acetate; Chiral GC CP-Cyclodextrin-β-2,3,6-M-19, 120 °C, t_R = 19.3 min (minor), 20.6 min (major).

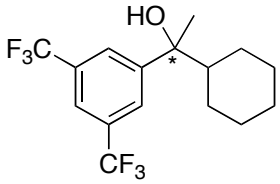


2-(3,5-Bis(trifluoromethyl)phenyl)-3-methylbutan-2-ol (10d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.58 (s, 3H), 2.00 (br, 1H), 2.02 (septet, *J* = 6.9 Hz, 1H), 7.76 (s, 1H), 7.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 17.2, 27.3, 38.6, 76.6, 120.5, 123.5 (q, *J* = 270.8 Hz), 125.7, 131.2 (q, *J* = 32.4 Hz), 150.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.24. IR (neat) 3449, 2972, 1375, 1279, 1175, 1134 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{12}F_6$ $[M–H_2O]^+$ 282.0843, found 282.0845. $[\alpha]_D^{20}$ = –7.0 (>99% ee, *c* 2.0, $CHCl_3$). Chiral GC analysis of the corresponding derivative acetate; Chiral GC CP-Cyclodextrin-β-2,3,6-M-19, 90 °C, t_R = 44.1 min (minor), 45.7 min (major).



1-Cyclohexyl-1-(4-(trifluoromethyl)phenyl)ethanol (10e): ^{1}H NMR (400

MHz, $CDCl_3$) δ 0.90-1.83 (m, 12H), 1.53 (s, 3H), 7.51 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.5, 26.6, 27.0, 27.1, 27.3, 48.9, 76.6, 124.2 (q, J = 269.8 Hz), 124.8, 125.8, 128.7 (q, J = 32.4 Hz), 151.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.81. IR (neat) 3447, 2933, 2855, 1327, 1164, 1125, 1072 cm^{-1}. HRMS (FAB+) calcd for $C_{15}H_{18}F_3$ $[M–OH]^+$ 255.1361, found 255.1355. $[\alpha]_D^{20}$ = –7.2 (>99% ee, *c* 1.0, $CHCl_3$). Chiral GC analysis of the corresponding derivative acetate; CHIRALDEX B-DM, 120 °C, t_R = 43.4 min (minor), 44.6 min (major).



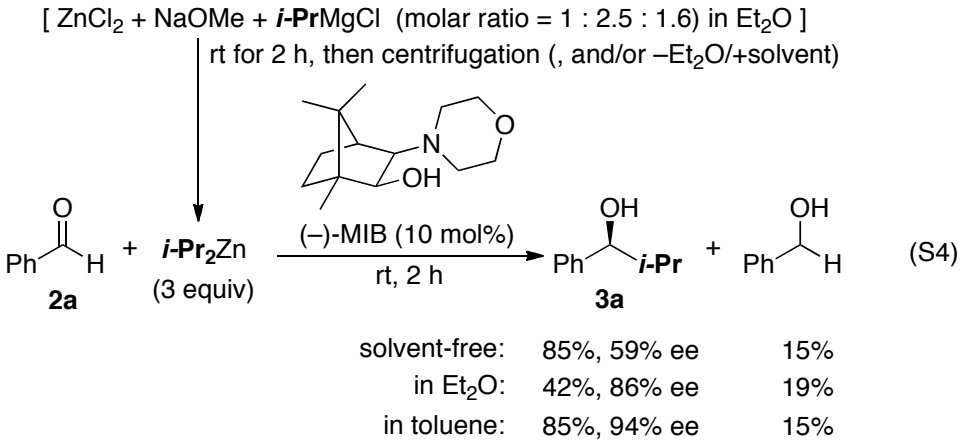
1-(3,5-Bis(trifluoromethyl)phenyl)-1-cyclohexylethanol (10f): ^1H NMR (400 MHz, $CDCl_3$) δ 0.90-1.84 (m, 12H), 1.57 (s, 3H), 7.75 (s, 1H), 7.86 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.4, 26.9, 27.2, 48.9, 76.5, 120.5, 123.6 (q, J = 270.8 Hz), 125.8, 131.1 (q, J = 32.4 Hz), 150.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.17. IR (neat) 3466, 2934, 2857, 1452, 1375, 1276, 1134 cm^{-1}. HRMS (FAB+) calcd for $C_{16}H_{17}F_6$ $[M–OH]^+$ 323.1234, found 323.1236. $[\alpha]_D^{20}$ = –7.6 (>99% ee, *c* 1.0, $CHCl_3$). Chiral GC analysis of the corresponding derivative acetate; CHIRALDEX B-DM, 105 °C, t_R = 26.1 min (minor), 27.7 min (major).

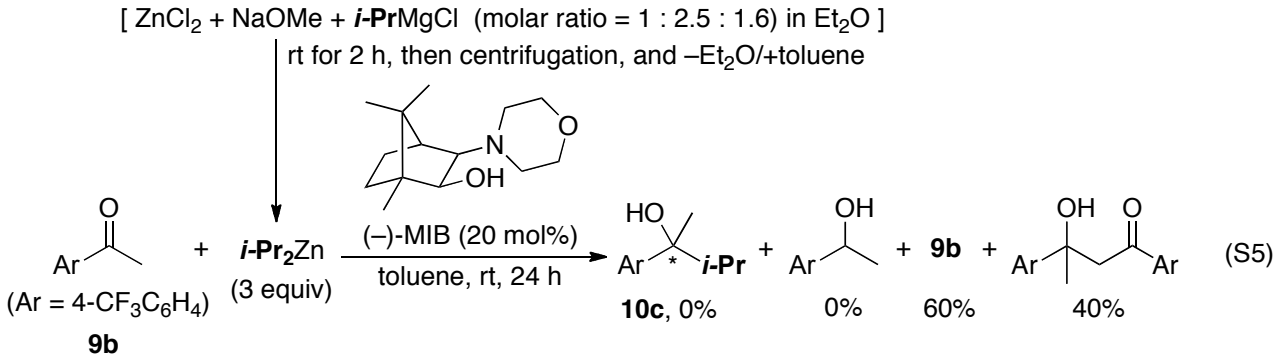
13. (–)-MIB-catalyzed enantioselective isopropylation of aldehyde and ketone.

It was noted that (–)-MIB [(2*S*)-(–)-3-*exo*-(*N*-morpholino)isoborneol], which has been known as a representative chiral ligand for di(1°-alkyl)zinc addition to aldehydes, was less effective than chiral ligand **1** for the isopropylation of **2a** (Eq. S4). Even under the optimized solvent-free reaction conditions, reduction byproduct (BnOH) was obtained in significant yield (15%), and desired **3a** was provided in 85% yield with 59% ee. In Et_2O or toluene, the enantioselectivity of **3a** was greatly improved (86% ee or 94% ee, respectively) due to the positive solvent effect for (–)-MIB, although undesired BnOH was still generated in the respective yield of 19% or 15%. In general for many catalysts, the solvent-free conditions can promote the conversion of the reactions, while solvent conditions sometimes can improve the enantioselectivity since solvents would dissociate oligomeric catalysts to more desired monomeric or dimeric ones. Our chiral phosphoramide ligands (**1a** and **1b**) are sterically so demanding enough to prevent the oligomerization of the catalysts without regard to solvent or solvent-free conditions. Therefore, our chiral ligands, which are unlike other chiral ligands, were effective to establish both high reactivity and high enantioselectivity particularly under the solvent-free conditions.

Moreover, (–)-MIB (20 mol%) did not promote the isopropylation of 4'-(trifluoromethyl)acetophenone (**9b**) under the optimized toluene-solution conditions (Eq. S5). In this reaction, instead of the desired product (**10c**), a mixture of **9b** and the aldol product was

provided. Therefore, chiral ligand **1a** was essential to establish the enantioselective 2°-alkyl addition to ketones.





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