Asymmetric Addition of Alkylzinc Reagents to Cyclic α,β -Unsaturated Ketones and a Tandem Enantioselective Addition/Diastereoselective Epoxidation with Dioxxygen

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Chart with the Structures and Compound Labels

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General Methods. All reactions using dialkylzinc and titanium(IV) isopropoxide were carried out in a Vacuum Atmospheres dry box or under nitrogen using standard Schlenk techniques. NMR spectra were obtained on a Brüker 500 MHz Fourier transform spectrometer at the University of Pennsylvania NMR facility. ^1H NMR spectra were referenced to tetramethylsilane in CDCl_3 ; $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were referenced to residual solvent. All reagents were obtained from Aldrich Chemical Company; ketone substrates were obtained from Aldrich or Acros Organics unless otherwise specified. Titanium(IV) isopropoxide and all liquid ketone substrates were distilled prior to use. 1.0 M dialkylzinc and 1.4 M titanium(IV) isopropoxide solutions were prepared and stored in a Vacuum Atmospheres dry box.

Synthesis of Substrate Ketones.

Preparation of 2-Phenylcyclohexen-1-one. 2-Phenylcyclohexen-1-one was prepared according to literature procedure.¹

Preparation of 2-Benzylidenecyclohexanone. 2-Benzylidenecyclohexanone was prepared according to literature procedure.²

Enantioselective Addition of Dialkylzinc Reagents to Cyclic Enones.

General Procedure A. The bis(sulfonamide) ligand (10 mol%) was weighed into the reaction vessel, and the dialkylzinc (1.0 M toluene solution, 3 equiv) and the titanium(IV) isopropoxide (1.4 M hexane solution, 1.2 equiv) were added at room temperature. After 5 min, the substrate ketone (1.0 equiv) was added neat. The homogeneous reaction mixture was stirred at room temperature. After completion, it was quenched with small amount of water (1-1.5 mL), dried over MgSO_4 , concentrated under reduced pressure, and purified by column chromatography on silica gel.

Preparation of 1,2,4,4-Tetramethyl-cyclohex-2-enol (S1). General procedure A was applied to 2,4,4-trimethyl-2-cyclohexen-1-one on a 77 μ L (0.5 mmol) scale, using 1.5 mL of dimethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S1** (65 mg, 84% yield, 99% ee) as an oil: $[\alpha]_D^{20} = +37.5$ (*c* 1.20, CHCl₃); ¹H NMR (C₆D₆, 500 MHz) δ 0.87 (s, 3H), 0.92 (s, 3H), 1.17 (s, 3H), 1.32 (ddd, *J* = 12.9, 8.7, 3.8 Hz, 1H), 1.44 (ddd, *J* = 12.9, 8.7, 3.8 Hz, 1H), 1.58-1.67 (m, 2H), 1.68 (s, 3H), 5.04 (s, 1H) ppm; ¹³C{¹H} NMR (C₆D₆, 125 MHz) δ 17.9, 27.1, 29.3, 29.9, 32.4, 34.7, 37.0, 69.9, 134.7, 136.7 ppm; IR (NaCl) 3363, 2958, 2859, 1717, 1454, 1360, 1067 cm⁻¹; HRMS calcd for C₁₀H₁₆ (M – H₂O)⁺: 136.1252, found 136.1258.

Preparation of 1-Ethyl-2,4,4-trimethyl-cyclohex-2-enol (S2). General procedure A was applied to 2,4,4-trimethyl-2-cyclohexen-1-one on a 77 μ L (0.5 mmol) scale, using 1.5 mL of diethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S2** (64 mg, 76% yield, 98% ee) as an oil: $[\alpha]_D^{20} = +65.5$ (*c* 1.13, CHCl₃); ¹H NMR (C₆D₆, 500 MHz) δ 0.80 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 3H), 0.93 (s, 3H), 1.27-1.32 (m, 1H), 1.42-1.60 (m, 4H), 1.65 (s, 3H), 1.75 (ddd, *J* = 14.2, 11.2, 3.1 Hz, 1H), 5.14 (s, 1H) ppm; ¹³C{¹H} NMR (C₆D₆, 125 MHz) δ 8.5, 17.9, 28.4, 30.6, 31.7, 31.9, 32.2, 33.9, 72.0, 135.9, 136.3 ppm; IR (NaCl) 3394, 2953, 1716, 1455, 1360, 1234 cm⁻¹; HRMS calcd for C₁₁H₁₈ (M – H₂O)⁺: 150.1408, found 150.1361.

Preparation of 1,2-Dimethyl-cyclopent-2-enol (S3).³ General procedure A was applied to 2-methyl-2-cyclopenten-1-one on a 150 μ L (1.5 mmol) scale, using 4.5 mL of dimethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 93 / 7) to give **S3** (92.5 mg, 55% yield, 98% ee) as an oil: $[\alpha]_D^{20} = +9.08$ (*c* 1.30, CHCl₃). Spectral data for this compound is consistent with the previous characterization.³

Preparation of 1-Ethyl-2-methyl-cyclopent-2-enol (S4). General procedure A was applied to 2-methyl-2-cyclopenten-1-one on a 100 μ L (1.0 mmol) scale, using 3 mL of diethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 93 / 7) to give **S4** (82 mg, 65% yield, 96% ee) as an oil: $[\alpha]_D^{20} = +15.7$ (*c* 1.0, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.81 (t, $J = 7.5$ Hz, 3H), 1.39-1.46 (m, 1H), 1.58 (s, 3H), 1.58-1.71 (m, 2H), 1.92-1.99 (m, 2H), 2.10-2.16 (m, 1H), 5.29 (s, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 8.7, 11.6, 29.1, 31.3, 37.4, 86.2, 126.9, 144.0 ppm; IR (NaCl) 3371, 3036, 2963, 2927, 2854, 1699, 1461, 1377 cm^{-1} ; HRMS calcd for C_8H_{13} ($\text{M} - \text{OH}$) $^+$: 109.1017, found 109.1022.

Preparation of 1-Methyl-2-pentyl-cyclopent-2-enol (S5).⁴ General procedure A was applied to 2-pentyl-2-cyclopenten-1-one on a 83 μ L (0.50 mmol) scale, using 1.5 mL of dimethylzinc solution. Chromatography on silica gel (hexanes / EtOAc : 93 / 7) to give **S5** (52.2 mg, 62% yield, 99% ee) as an oil: $[\alpha]_D^{20} = +7.57$ (*c* 0.77, CHCl_3). Spectral data for this compound is consistent with the previous characterization.⁴

Preparation of 1-Ethyl-2-pentyl-cyclopent-2-enol (S6). General procedure A was applied to 2-pentyl-2-cyclopenten-1-one on a 83 μ L (0.50 mmol) scale, using 1.5 mL of diethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 93 / 7) to give **S6** (45.6 mg, 50% yield, 99.0% ee) as an oil: $[\alpha]_D^{20} = +10.8$ (*c* 0.67, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.84 (t, $J = 7.5$ Hz, 3H), 0.91 (t, $J = 6.9$ Hz, 3H), 1.27-1.33 (m, 4H), 1.44-1.54 (m, 3H), 1.63-1.73 (m, 2H), 1.85-2.08 (m, 4H), 2.13-2.22 (m, 1H), 5.35 (m, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 8.7, 14.3, 23.0, 26.1, 28.2, 29.2, 31.5, 32.4, 37.7, 86.6, 125.2, 148.6 ppm; IR (NaCl) 3370, 3059, 2925, 2856, 1699, 1461, 1073, 1033 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{20}$ ($\text{M} - \text{H}_2\text{O}$) $^+$: 164.1565, found 164.1557.

Preparation of 1-Methyl-2-phenyl-cyclohex-2-enol (S7). General procedure A was applied to 2-phenylcyclohexen-1-one¹ on a 86.2 mg (0.5 mmol) scale, using 1.5 mL of

dimethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S7** (51 mg, 54% yield, 95% ee) as an oil: $[\alpha]_D^{20} = -1.92$ (*c* 0.55, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 1.23 (s, 3H), 1.70-1.85 (m, 3H), 1.86-1.92 (m, 1H), 2.07-2.16 (m, 1H), 2.20-2.27 (m, 1H), 5.75 (dd, $J = 4.6, 3.2$ Hz, 1H), 7.21-7.45 (m, 5H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 19.5, 26.5, 28.8, 39.9, 70.4, 127.0, 128.2, 129.1, 129.4, 141.8, 144.3 ppm; IR (NaCl) 3409, 3053, 3019, 2931, 2864, 1682, 1595, 1490, 1369, 1179, 1025 cm^{-1} ; HRMS calcd for $\text{C}_{13}\text{H}_{14}$ ($\text{M} - \text{H}_2\text{O}$) $^+$: 170.1096, found 170.1092.

Preparation of 1-Ethyl-2-phenyl-cyclohex-2-enol (S8). General procedure A was applied to 2-phenylcyclohexen-1-one¹ on a 86.2 mg (0.5 mmol) scale, using 1.5 mL of diethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S8** (40.5 mg, 40% yield, 95% ee) as an oil: $[\alpha]_D^{20} = -9.67$ (*c* 0.60, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 0.65 (t, $J = 7.5$ Hz, 3H), 1.40-1.47 (m, 1H), 1.50-1.56 (m, 1H), 1.67-1.75 (m, 5H), 2.0-2.07 (m, 1H), 2.14-2.20 (m, 1H), 5.78 (dd, $J = 5.2, 2.5$ Hz, 1H), 7.16-7.23 (m, 3H), 7.35-7.38 (m, 2H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz) δ 8.4, 18.8, 26.4, 32.8, 35.3, 72.8, 126.8, 128.0, 128.9, 131.1, 141.9, 143.5 ppm; IR (NaCl) 3459, 3054, 3019, 2936, 2866, 1710, 1599, 1490, 1439, 1172 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{16}$ ($\text{M} - \text{H}_2\text{O}$) $^+$: 184.1252, found 184.1254.

Preparation of 2-Benzylidene-1-methyl-cyclohexanol (S9).⁵ General procedure A was applied to 2-benzylidenecyclohexanone² on a 93.2 mg (0.5 mmol) scale, using 1.5 mL of dimethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S9** (20 mg, 20% yield, 99% ee) as an oil: $[\alpha]_D^{20} = +0.86$ (*c* 0.81, CH_2Cl_2). Spectral data for this compound is consistent with the previous characterization.⁵

Preparation of 2-Benzylidene-1-ethyl-cyclohexanol (S10). General procedure A was applied to 2-benzylidenecyclohexanone² on a 93.2 mg (0.5 mmol) scale, using 1.5 mL

of diethylzinc solution. The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S10** (34.6 mg, 32% yield, 99% ee) as an oil: $[\alpha]_D^{20} = +21.4$ (*c* 1.40, CH₂Cl₂); ¹H NMR (C₆D₆, 500 MHz) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.10-1.19 (m, 1H), 1.22-1.35 (m, 2H), 1.40-1.50 (m, 3H), 1.62-1.74 (m, 3H), 2.81-2.85 (m, 1H), 6.78 (s, 1H), 7.06-7.25 (m, 5H) ppm; ¹³C{¹H} NMR (C₆D₆, 125 MHz) δ 7.6, 23.9, 27.2, 27.8, 30.6, 41.8, 75.1, 121.9, 126.4, 128.5, 129.5, 139.1, 146.4 ppm; IR (NaCl) 3430, 3078, 3035, 3021, 2928, 2855, 1651, 1598, 1493, 1445, 1261, 1163, 1126 cm⁻¹; HRMS calcd for C₁₅H₁₈ (M – H₂O)⁺: 198.1409, found 198.1409.

Preparation of 1-Ethyl-cyclohex-2-enol (S11).⁶ General procedure A was applied to 2-cyclohex-1-one on a 97 μ L (1.0 mmol) scale, using 3 mL of diethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 93 / 7) to give **S11** (95 mg, 75% yield, 52% ee) as an oil: $[\alpha]_D^{20} = +48.7$ (*c* 1.55, CHCl₃). Spectral data for this compound is consistent with the previous characterization.⁶

Preparation of 1-Ethyl-3,5,5-trimethyl-cyclohex-2-enol (S12). General procedure A was applied to 3,5,5-Trimethyl-2-cyclohexen-1-one on a 150 μ L (1.0 mmol) scale, using 3 mL of diethylzinc solution. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S12** (84 mg, 50% yield, 61% ee) as an oil: $[\alpha]_D^{20} = +21.9$ (*c* 1.23, CH₃OH); ¹H NMR (C₆D₆, 500 MHz) δ 0.88 (s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H), 1.05 (s, 3H), 1.32 (d, *J* = 14.0 Hz, 1H), 1.39-1.50 (m, 4H), 1.55 (s, 3H), 1.59 (bs, 1H), 5.27 (s, 1H) ppm; ¹³C{¹H} NMR (C₆D₆, 125 MHz) δ 8.1, 24.1, 27.5, 30.1, 32.0, 37.3, 44.8, 47.4, 71.2, 126.9, 134.8 ppm; IR (NaCl) 3389, 2949, 2824, 1673, 1453, 1376, 1364, 1177 cm⁻¹; HRMS calcd for C₁₁H₁₈ (M – H₂O)⁺: 150.1408, found 150.1362.

One-Pot Synthesis of Epoxy Alcohols.

General Procedure B (Addition of ZnMe₂). After carrying out the asymmetric dimethylzinc addition reaction, diethylzinc solution (1.0 M toluene solution, 1.5-2 equiv)

was added to the reaction mixture at 0 °C. O₂ pressure was then applied from a balloon filled with O₂. After stirring for 10 min the reaction mixture was warmed up to room temperature. When the epoxidation was complete, it was quenched with small amount of water (~2 mL), dried over MgSO₄, concentrated under reduced pressure, and purified by column chromatography on silica gel.

General Procedure C (Addition of ZnEt₂). Right after the asymmetric diethylzinc addition reaction was complete (tlc), O₂ pressure was applied from a balloon at 0 °C and then the same procedure was followed as in general procedure B.

Preparation of 1,2,5,5-Tetramethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (S13). General procedure B was applied to 2,4,4-trimethyl-2-cyclohexen-1-one on a 77 μL (0.5 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 85 / 15) to give **S13** (70 mg, 82% yield, 99% ee) as an oil: $[\alpha]_D^{20} = -3.07$ (*c* 1.40, CHCl₃); ¹H NMR (C₆D₆, 500 MHz) δ 0.73 (s, 3H), 0.86-0.92 (m, 1H), 0.99 (s, 3H), 1.14-1.19 (m, 2H), 1.16 (s, 3H), 1.23 (s, 3H), 1.51-1.56 (m, 1H), 1.99 (bs, 1H), 2.47 (s, 1H) ppm; ¹³C{¹H} NMR (C₆D₆, 125 MHz) δ 18.3, 24.9, 26.3, 26.9, 29.8, 33.0, 34.9, 64.2, 70.4, 71.5 ppm; IR (NaCl) 3461, 2950, 2866, 1453, 1365, 1243, 1120, 1088 cm⁻¹; HRMS calcd for C₁₀H₁₇O (M – OH)⁺: 153.1279, found 153.1281.

Preparation of 2-Ethyl-1,5,5-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (S14). General procedure C was applied to 2,4,4-trimethyl-2-cyclohexen-1-one on a 77 μL (0.5 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 90 / 10) to give **S14** (73 mg, 80% yield, 99% ee) as an oil: $[\alpha]_D^{20} = -5.27$ (*c* 1.48, CHCl₃); ¹H NMR (C₆D₆, 500 MHz) δ 0.74 (s, 3H), 0.86 (ddd, *J* = 13.5, 9.9, 3.4 Hz, 1H), 0.92 (t, *J* = 7.4 Hz, 3H), 1.01 (s, 3H), 1.17 (ddd, *J* = 13.5, 9.9, 3.4 Hz, 1H), 1.23 (s, 3H), 1.25-1.33 (m, 2H), 1.43 (ddd, *J* = 13.5, 9.9, 3.4 Hz, 1H), 1.64-1.72 (m, 1H), 2.02 (bs, 1H), 2.47 (s, 1H) ppm; ¹³C{¹H} NMR (C₆D₆, 125 MHz) δ 7.9, 18.2, 26.6, 26.7,

29.3, 29.5, 29.7, 32.5, 64.6, 71.5, 72.4 ppm; IR (NaCl) 3464, 2968, 2871, 1469, 1443, 1377, 1119, 1064 cm^{-1} ; HRMS calcd for $\text{C}_{11}\text{H}_{21}\text{O}_2$ (MH)⁺: 185.1542, found 185.1537.

Preparation of 1,2-Dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S15). General procedure B was applied to 2-methyl-2-cyclopenten-1-one on a 150 μL (1.5 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 80 / 20) to give **S15** (96 mg, 50% yield, 98% ee) as an oil: $[\alpha]_{\text{D}}^{20} = -22.6$ (*c* 1.64, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.99 (s, 3H), 1.03-1.11 (m, 1H), 1.23 (s, 3H), 1.29 (dd, $J = 12.6, 8.3$ Hz, 1H), 1.42-1.47 (m, 1H), 1.55-1.68 (bs, 1H), 1.64 (dd, $J = 12.6, 8.3$ Hz, 1H), 2.85 (s, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 11.8, 23.4, 25.3, 36.2, 62.2, 66.8, 78.2 ppm; IR (NaCl) 3456, 2972, 1443, 1372, 1261, 1193, 1133 cm^{-1} ; HRMS calcd for $\text{C}_7\text{H}_{11}\text{O}$ ($\text{M} - \text{OH}$)⁺: 111.0809, found 111.0807.

Preparation of 2-Ethyl-1-methyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S16). General procedure C was applied to 2-methyl-2-cyclopenten-1-one on a 100 μL (1.0 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 85 / 15) to give **S16** (85 mg, 60% yield, 97% ee) as an oil: $[\alpha]_{\text{D}}^{20} = -8.19$ (*c* 1.16, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.80 (t, $J = 7.5$ Hz, 3H), 1.10 (dddd, $J = 13.9, 10.0, 8.7, 1.2$ Hz, 1H), 1.13-1.22 (m, 1H), 1.23 (s, 3H), 1.26-1.33 (m, 1H), 1.50-1.58 (m, 2H), 1.65-1.73 (m, 2H), 2.90 (s, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 7.9, 12.1, 25.9, 28.9, 32.4, 62.8, 67.1, 80.7 ppm; IR (NaCl) 3457, 2967, 2936, 1440, 1375, 1182, 1123 cm^{-1} ; HRMS calcd for $\text{C}_8\text{H}_{13}\text{O}$ ($\text{M} - \text{OH}$)⁺: 125.0966, found 125.0965.

Preparation of 2-Methyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S17). General procedure B was applied to 2-pentyl-2-cyclopenten-1-one on a 165 μL (1.0 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 85 / 15) to give **S17** (123 mg, 67% yield, 99% ee) as an oil: $[\alpha]_{\text{D}}^{20} = -12.9$ (*c* 1.05, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.89 (t, $J = 7.0$ Hz, 3H), 1.07 (s, 3H), 1.08-1.13 (m, 1H), 1.18-1.30 (m, 5H), 1.34 (dd, $J = 12.6, 8.3$ Hz, 1H), 1.46-1.58 (m, 3H), 1.65-1.71 (m,

2H), 1.92-2.0 (m, 1H), 2.96 (s, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 14.3, 23.0, 23.4, 24.5, 25.3, 25.7, 32.7, 36.9, 60.6, 69.3, 78.8 ppm; IR (NaCl) 3456, 2934, 2861, 1462, 1362, 1183, 1132 cm^{-1} ; HRMS calcd for $\text{C}_{11}\text{H}_{20}\text{O}_2$ (M) $^{+}$: 184.1463, found 184.1464.

Preparation of 2-Ethyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S18). General procedure C was applied to 2-pentyl-2-cyclopenten-1-one on a 83 μL (0.5 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 90 / 10) to give **S18** (60 mg, 60% yield, 99% ee) as an oil: $[\alpha]_{\text{D}}^{20} = -5.18$ (c 0.83, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.82 (t, $J = 7.8$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H), 1.07-1.12 (m, 1H), 1.18-1.35 (m, 7H), 1.46-1.73 (m, 6H), 1.97 (ddd, $J = 14.3, 10.5, 4.2$ Hz, 1H), 2.99 (s, 1H), ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 8.0, 14.3, 23.0, 24.4, 25.86, 25.90, 28.7, 32.7, 33.0, 61.2, 69.4, 81.3 ppm; IR (NaCl) 3480, 3016, 2956, 2859, 1709, 1463, 1378, 1176, 1120 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2$ (M) $^{+}$: 198.1620, found 198.1625.

Preparation of 4-Ethyl-2-phenyl-1-oxa-spiro[2.5]octan-4-ol (S19). General procedure C was applied to 2-benzylidenecyclohexanone² on a 93.2 mg (0.5 mmol) scale. The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S19** (40 mg, 34% yield, 97% ee) as an oil: $[\alpha]_{\text{D}}^{20} = +12.2$ (c 1.35, CH_2Cl_2); ^1H NMR (C_6D_6 , 500 MHz) δ 1.01 (t, $J = 7.4$ Hz, 3H), 1.04-1.11 (m, 2H), 1.22-1.24 (m, 1H), 1.24-1.32 (m, 1H), 1.36-1.47 (m, 3H), 1.48-1.54 (m, 1H), 1.55-1.64 (m, 1H), 1.75-1.78 (m, 1H), 1.99 (bs, 1H), 4.42 (s, 1H), 7.01-7.05 (m, 1H), 7.08-7.14 (m, 2H), 7.24-7.27 (m, 2H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 7.7, 23.5, 23.7, 25.6, 27.9, 38.5, 60.1, 68.7, 71.4, 126.6, 127.5, 128.3, 136.7 ppm; IR (NaCl) 3489, 3087, 3061, 2932, 2961, 1644, 1604, 1498, 1450, 1377, 1172, 1151 cm^{-1} ; HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$ (M) $^{+}$: 232.1463, found 232.1461.

Semipinacol Rearrangement Reaction of Epoxy Alcohols with $\text{BF}_3 \cdot \text{OEt}_2$.

General Procedure D. To a solution of epoxy alcohol (~0.5 mmol) in dry CH_2Cl_2 (~3 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (2 equiv) under nitrogen at $-50\text{ }^\circ\text{C}$. The mixture was warmed up to $0\text{ }^\circ\text{C}$ for 2 h. The reaction mixture was quenched with aqueous NH_4Cl solution (~1 mL), extracted with CH_2Cl_2 , the organic phase dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the β -hydroxy ketone.

Preparation of 3-Hydroxy-2-methyl-2-pentyl-cyclopentanone (S20). General procedure D was applied to 2-methyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (**S17**) on a 86 mg (0.47 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 80 / 20) to give **S20** (60 mg, 70% yield, 99% ee) as an oil: $[\alpha]_{\text{D}}^{20} = +66.15$ (*c* 0.78, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.77 (s, 3H), 0.87 (t, $J = 7.1$ Hz, 3H), 1.15-1.34 (m, 6H), 1.39 (ddd, $J = 18.9, 9.3, 4.8$ Hz, 1H), 1.49-1.63 (m, 3H), 1.88 (ddd, $J = 18.9, 9.3, 4.8$ Hz, 1H), 2.17 (ddd, $J = 17.6, 9.7, 7.8$ Hz, 1H), 3.52 (s, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 14.3, 19.4, 22.9, 23.9, 28.1, 30.5, 32.9, 33.9, 52.8, 77.5, 218.5 ppm; IR (NaCl) 3456, 2956, 2871, 1731, 1462, 1405, 1375 cm^{-1} ; HRMS calcd for $\text{C}_{11}\text{H}_{21}\text{O}_2$ (MH) $^+$: 185.1542, found 185.1543.

Preparation of 2-Ethyl-3-hydroxy-2-pentyl-cyclopentanone (S21). General procedure D was applied to 2-ethyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (**S18**) on a 80 mg (0.40 mmol) scale. The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 85 / 15) to give **S21** (70 mg, 89% yield, 99% ee) as an oil: $[\alpha]_{\text{D}}^{20} = -3.54$ (*c* 0.79, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.78 (t, $J = 7.5$ Hz, 3H), 0.87 (t, $J = 7.1$ Hz, 3H), 1.17-1.36 (m, 9H), 1.42-1.50 (m, 1H), 1.52-1.61 (m, 2H), 1.65-1.73 (m, 1H), 1.83 (ddd, $J = 18.8, 9.6, 6.8$ Hz, 1H), 2.16 (ddd, $J = 18.8, 9.6, 6.8$ Hz, 1H), 3.72 (t, $J = 5.1$ Hz, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 8.3, 14.3, 23.0, 23.7, 25.0, 27.4, 28.4, 33.1,

34.7, 56.3, 76.1, 218.3 ppm; IR (NaCl) 3446, 2956, 2871, 1725, 1459, 1406, 1380, 1111 cm^{-1} ; HRMS calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2 + \text{Na}$ ($\text{M} + \text{Na}$) $^{+}$: 221.1517, found 221.1507.

Preparation of 3-Hydroxy-2,2-dimethyl-cyclopentanone (S22).⁷ General procedure D was applied to 1,2-dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (**S15**) on a 80 mg (0.62 mmol) scale. The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 75 / 25) to give **S22** (60 mg, 75% yield, 98% ee) as an oil: $[\alpha]_{\text{D}}^{20} = +7.47$ (c 0.75, CHCl_3). Spectral data for this compound is consistent with the previous characterization.⁷

Preparation of 2-Ethyl-3-hydroxy-2-methyl-cyclopentanone (S23). General procedure D was applied to 2-Ethyl-1-methyl-6-oxa-bicyclo[3.1.0]hexan-2-ol on a 57 mg (0.4 mmol) scale. The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 80 / 20) to give **S23** (41 mg, 73% yield, 97% ee) as an oil: $[\alpha]_{\text{D}}^{20} = -48.0$ (c 0.81, CHCl_3); ^1H NMR (C_6D_6 , 500 MHz) δ 0.73 (t, $J = 7.5$ Hz, 3H), 0.92 (s, 3H), 1.18-1.29 (m, 3H), 1.34-1.44 (m, 1H), 1.62-1.68 (m, 1H), 1.75 (ddd, $J = 18.7, 9.3, 7.0$ Hz, 1H), 2.14 (ddd, $J = 18.5, 9.5, 5.4$ Hz, 1H), 3.64 (t, $J = 5.6$ Hz, 1H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 125 MHz) δ 8.5, 14.6, 28.0, 28.1, 34.7, 53.3, 75.3, 218.8 ppm; IR (NaCl) 3436, 2969, 2936, 1734, 1458, 1406 cm^{-1} ; HRMS calcd for $\text{C}_8\text{H}_{15}\text{O}_2$ (MH) $^{+}$: 143.1072, found 143.1079.

Conditions for the Determination of Enantiomeric Excesses.

The racemic alcohols were prepared by addition of Grignard reagents to the corresponding ketones. The racemic epoxy alcohols were prepared by *m*CPBA epoxidation method using the racemic alcohols. Due to the sensitivity of tertiary alcohols **S3-S6**, these product were converted to the β -hydroxy ketones which were transformed into the trifluoroacetate before ee determination by chiral capillary GC. The tertiary alcohols **S1**, **S2**, **S11**, **S12** and the epoxy alcohols **S13**, **S14** were analyzed directly by chiral capillary GC. The epoxy alcohols **S15-S18** were treated with $\text{BF}_3 \cdot \text{OEt}_2$ to the β -hydroxy ketones and

analyzed by chiral capillary GC, therefore, the ee of β -hydroxy ketones **S20-S23** must be the same as that of the corresponding epoxy alcohols **S15-S18**. The specifications for the GC analyses were as follows: Fused silica chiral capillary column (Supelco β -Dex 120): 30 m x 0.25 mm (id) x 0.25 μ m film thickness. Carrier gas: nitrogen. Inlet temperature: 250 $^{\circ}$ C. Detector: FID, 270 $^{\circ}$ C. The conditions for the resolution of the racemates by GC are given below.

1,2,4,4-Tetramethyl-cyclohex-2-enol (S1). $t_1 = 15.5$ min, $t_2 = 16.7$ min (110 $^{\circ}$ C, 1.6mL/min).

1-Ethyl-2,4,4-trimethyl-cyclohex-2-enol (S2). $t_1 = 10.5$ min, $t_2 = 11.2$ min (110 $^{\circ}$ C, 1.6mL/min).

1,2-Dimethyl-cyclopent-2-enol (S3) {after epoxidation, rearrangement, and derivatization}. $t_1 = 29.8$ min, $t_2 = 32.4$ min (70 $^{\circ}$ C, 1.5mL/min).

1-Ethyl-2-methyl-cyclopent-2-enol (S4) {after epoxidation, rearrangement, and derivatization}. $t_1 = 51.2$ min, $t_2 = 52.7$ min (70 $^{\circ}$ C, 1.5mL/min).

1-Methyl-2-pentyl-cyclopent-2-enol (S5) {after epoxidation, rearrangement, and derivatization}. $t_1 = 24.6$ min, $t_2 = 27.0$ min (110 $^{\circ}$ C, 1.6mL/min).

1-Ethyl-2-pentyl-cyclopent-2-enol (S6) {after epoxidation, rearrangement, and derivatization}. $t_1 = 32.5$ min, $t_2 = 34.4$ min (110 $^{\circ}$ C, 1.6mL/min).

1-Ethyl-cyclohex-2-enol (S11). $t_1 = 144.7$ min, $t_2 = 152.5$ min (60 $^{\circ}$ C, 1.5mL/min).

1-Ethyl-3,5,5-trimethyl-cyclohex-2-enol (S12). $t_1 = 63.8$ min, $t_2 = 67.4$ min (80 $^{\circ}$ C, 1.7mL/min).

1,2,5,5-Tetramethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (S13). $t_1 = 10.5$ min, $t_2 = 11.2$ min (110 $^{\circ}$ C, 1.6mL/min).

2-Ethyl-1,5,5-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol (S14). $t_1 = 27.2$ min, $t_2 = 30.5$ min (110 $^{\circ}$ C, 1.6mL/min).

1,2-Dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S15) {after rearrangement and derivatization}. $t_1 = 29.8$ min, $t_2 = 32.4$ min (70 $^{\circ}$ C, 1.5mL/min).

2-Ethyl-1-methyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S16) {after rearrangement and derivatization}. $t_1 = 51.2$ min, $t_2 = 52.7$ min (70 $^{\circ}$ C, 1.5mL/min).

2-Methyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S17) {after rearrangement and derivatization}. $t_1 = 24.6$ min, $t_2 = 27.0$ min (110 °C, 1.6mL/min).

2-Ethyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (S18) {after rearrangement and derivatization}. $t_1 = 32.5$ min, $t_2 = 34.4$ min (110 °C, 1.6mL/min).

3-Hydroxy-2-methyl-2-pentyl-cyclopentanone (S20) {after rearrangement and derivatization}. The same as S17.

2-Ethyl-3-hydroxy-2-pentyl-cyclopentanone (S21) {after rearrangement and derivatization}. The same as S18.

3-Hydroxy-2,2-dimethyl-cyclopentanone (S22) {after rearrangement and derivatization}. The same as S15.

2-Ethyl-3-hydroxy-2-methyl-cyclopentanone (S23) {after rearrangement and derivatization}. The same as S16.

Chiral HPLC analyses of **S7-S10** were performed using a Chiralcel OD-H column. The analysis of **S19** was performed using a Chiralpak AS column.

1-Methyl-2-phenyl-cyclohex-2-enol (S7). $t_1 = 7.7$ min, $t_2 = 10.2$ min (hexane / 2-propanol : 95 / 5, 0.7 mL/min).

1-Ethyl-2-phenyl-cyclohex-2-enol (S8). $t_1 = 7.9$ min, $t_2 = 10.6$ min (hexane / 2-propanol : 95 / 5, 0.7 mL/min).

2-Benzylidene-1-methyl-cyclohexanol (S9). $t_1 = 12.9$ min, $t_2 = 15.1$ min (hexane / 2-propanol : 95 / 5, 0.7 mL/min).

2-Benzylidene-1-ethyl-cyclohexanol (S10). $t_1 = 10.4$ min, $t_2 = 12.3$ min (hexane / 2-propanol : 95 / 5, 0.7 mL/min).

4-Ethyl-2-phenyl-1-oxa-spiro[2.5]octan-4-ol (S19). $t_1 = 12.6$ min, $t_2 = 16.5$ min (hexane / 2-propanol : 97 / 3, 0.4 mL/min).

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1,2,4,4-Tetramethyl-cyclohex-2-enol

1,2,4,4-Tetramethyl-cyclohex-2-enol

1-Ethyl-2,4,4-trimethyl-cyclohex-2-enol

1-Ethyl-2,4,4-trimethyl-cyclohex-2-enol

1-Ethyl-2-methyl-cyclopent-2-enol

1-Ethyl-2-methyl-cyclopent-2-en-1-ol

1-Ethyl-2-pentyl-cyclopent-2-enol

1-Methyl-2-phenyl-cyclohex-2-enol

1-Methyl-2-phenyl-cyclohex-2-enol

(S7)

1-Ethyl-2-phenyl-cyclohex-2-enol

(S8)

1-Ethyl-2-phenyl-cyclohex-2-enol

2-Benzylidene-1-ethyl-cyclohexanol

2-Benzylidene-1-ethyl-cyclohexanol

(S10)

1-Ethyl-3,5,5-trimethyl-cyclohex-2-enol

1-Ethyl-3,5,5-trimethyl-cyclohex-2-enol

1,2,5,5-Tetramethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol

1,2,5,5-Tetramethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol

2-Ethyl-1,5,5-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol

2-Ethyl-1,5,5-trimethyl-7-oxa-bicyclo[4.1.0]heptan-2-ol

1,2-Dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

1,2-Dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

2-Ethyl-1-methyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

2-Ethyl-1-methyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

2-Methyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

2-Methyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

2-Ethyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

2-Ethyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol

4-Ethyl-2-phenyl-1-oxa-spiro[2.5]octan-4-ol

4-Ethyl-2-phenyl-1-oxa-spiro[2.5]octan-4-ol

3-Hydroxy-2-methyl-2-pentyl-cyclopentanone

3-Hydroxy-2-methyl-2-pentyl-cyclopentanone

2-Ethyl-3-hydroxy-2-pentyl-cyclopentanone

2-Ethyl-3-hydroxy-2-pentyl-cyclopentanone

2-Ethyl-3-hydroxy-2-methyl-cyclopentanone

2-Ethyl-3-hydroxy-2-methyl-cyclopentanone