Enantioselective Synthesis of Bridged- or Fused-Ring Bicyclic Ketones by a Catalytic Asymmetric Michael Addition Pathway

Duan Liu, Sungwoo Hong and E. J. Corey*

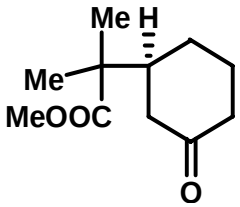
Department of Chemistry and Chemical Biology

Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

Supplementary Materials

Materials and Methods. Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of nitrogen using freshly distilled dry solvents. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Flash chromatography was performed using Baker silica gel (40 μm particle size). NMR spectra were recorded on Varian Innova-500, or Mercury-400 instruments and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on Avatar 360 FT-IR spectrometer. Low-resolution and high-resolution mass spectral analyses were performed at the Harvard University Mass Spectrometry Center. Analytical high performance liquid chromatography (HPLC) was performed on Isco 2350 Series or Waters 626 HPLC using the indicated chiral column. Gas chromatography (GC) analyses were performed on Hewlett-Packard 6850 Series GC System equipped with flame ionization detector using a J & W Scientific Cyclosil-B column (30 m x 0.25 mm). Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and MeCN were distilled from calcium hydride. Toluene, DME and THF were distilled from sodium.

Oxazaborolidinium Catalyst (*S*)-5. A 100-mL, two-necked, round-bottomed flask equipped with a stir bar, a glass stopper and a 50-mL pressure-equalizing addition funnel (containing a cotton plug and ca. 10 g of 4A molecular sieves,[1] and functioning as a Soxhlet extractor) fitted on top with a reflux condenser and a nitrogen inlet adaptor was charged with (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol (2.59 g, 10.25 mmol, from Aldrich or Lancaster), tri-*o*-tolylboroxine[2] (1.21 g, 3.42 mmol) and 40 mL of toluene. The resulting solution was heated to reflux (bath temperature ~ 145 °C). After 3 h, the reaction mixture was cooled to *ca.* 60 °C and the addition funnel and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated by distillation (air-cooling) to a volume of *ca.* 15 mL. This distillation protocol was repeated three times by re-charging with 3 x 35 mL of toluene. The solution was then allowed to cool to room temperature and the distillation head was quickly replaced with a vacuum adaptor. Concentration *in vacuo* (*ca*. 0.1 mmHg, 1 h) afforded the corresponding oxazaborolidine as clear oil. To an aliquot of the oxazaborolidine precursor (0.286 mmol, theoretical) in toluene (2.0 mL) at –25 °C was added trifluoromethanesulfonimide (0.10 M solution in toluene, freshly prepared, 2.0 mL, 0.20 mmol) dropwise. After 20 min at –20 °C, a colorless homogeneous catalyst solution of (*S*)-**5** was ready for use in the Mukaiyama Michael reactions. The catalyst solution of (*R*)-**5** was prepared from (*R*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol in a similar manner.



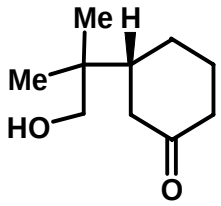
***S*-6**

[1] Molecular sieves (pellets) were dried *in vacuo* at *ca.* 200 °C with a gas burner for 10 min prior to use.
[2] Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808-3809-.

(*S*)-(–)-2-Methyl-2-(3-oxocyclohexyl)propionic Acid Methyl Ester (*S*-6). To a solution of the freshly prepared catalyst (*S*)-**5** (0.05 mmol, 20 mol%) in toluene (2 mL) were successively added a solution of triphenylphospine oxide (17.4 mg, 0.0625 mmol, 25 mol%) in toluene (0.5 mL), 2-cyclohexen-1-one (**2**) (24.2 μL, 0.25 mmol), and 1-methoxy-2-methyl-1-(trimethylsilyloxy) propene (**4**) (75.8 μL, 0.375 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 16 h and then quenched by addition of 100 μL of Et_3N. The mixture was warmed to room temperature, and then THF (5 mL) and aqueous 2 N HCl (1 mL) were carefully added. The resulting mixture was stirred at 23 °C for 10 min and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc:hexanes, 1:9) to afford (*S*)-**6** (45 mg, 91%) as a colorless oil: $[\alpha]_D^{25}$ –20.0 (*c* 1.0, $CHCl_3$, 90% ee), lit.[3] $[\alpha]_D^{25}$ –14.7 (*c* 0.8, $CHCl_3$, 82% ee); IR (film) 2950, 1713, 1434, 1260, 1194, 1136 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.37-1.96 (m, 6H), 1.77-1.70 (m, 1H), 1.59-1.50 (m, 1H), 1.38-1.30 (m, 1H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 177.3, 51.8, 45.8, 45.2, 43.2, 41.1, 26.3, 25.0, 22.0, 21.7. The IR and ^1H NMR and ^{13}C NMR spectral data of (*S*)-**6** were identical to those reported in the literature for the racemic compound.[4] Enantioselectivity was determined by HPLC analysis using a Chiralpak IA column (1% *i*-PrOH in hexanes; 1.0 mL/min; λ 290 nm); retention times: 9.8 min (minor), 11.6 min (major).

The Michael adduct (*R*)-**6** was obtained with the catalyst (*R*)-**5** in a similar manner. $[\alpha]_D^{25}$ +21.8 (*c* 1.3, $CHCl_3$, 90% ee)

[3] Chordia, M. D.; Harman, W. D. *J. Am. Chem. Soc.* **2000**, *122*, 2725-2736.
[4] Loh, T.; Wei, L. *Tetrahedron* **1998**, *54*, 7615-7624.

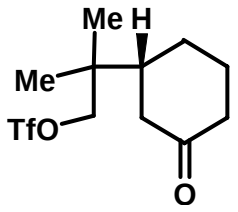


***R*-7**

(*R*)-(+)-3-(2-Hydroxy-1,1-dimethylethyl)cyclohexanone (*R*-7). To a solution of (*R*)-**6** (1.56 g, 7.87 mmol) in MeOH (25 mL) was added trimethyl orthoformate (1.72 mL, 15.7 mmol), followed by *p*-TSA (74.8 mg, 0.39 mmol). The resulting solution was stirred at 23 °C for 2 h, and then saturated aqueous $NaHCO_3$ (10 mL) was carefully added. The methanol was removed *in vacuo,* the resulting residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to produce the crude dimethyl ketal (1.69 g) suitable for use in the next step without further purification.

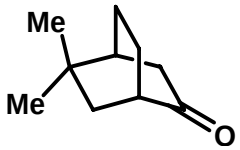
To a suspension of lithium aluminum hydride (0.39 g, 10.2 mmol) in THF (25 mL) was added dropwise a solution of the above dimethyl ketal (1.69 g, 7.87 mmol) in THF (15 mL) at 0 ^{o}C. The reaction mixture was stirred for 2 h at 0 °C. After stirring for additional 1 h at 23 °C, H_2O (0.4 mL), aqueous 30% KOH (0.4 mL), and H_2O (1.2 mL) were consecutively added. The resulting mixture was vigorously stirred for 12 h and was filtered through a short plug of Celite eluting with THF. The filtrate was concentrated *in vacuo*, and the residue was dissolved in a mixture of acetone (20 mL) and aqueous 2N HCl (2 mL). The resulting mixture was stirred at 23 °C for 2 h, and the solvent was removed *in vacuo*. The residue was diluted with brine (10 mL) and extracted with CH_2Cl_2 (3 ×10 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc:hexanes, 3:7) to afford (*R*)-**7** (1.22 g, 91%) as a colorless oil: $[\alpha]_D^{25}$ +16.1 (*c* 1.0,

$CHCl_3$); IR (film) 3425, 2962, 2875, 1700, 1216, 1048, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.28 (d, *J* = 1 Hz, 2H), 2.89 (s, 1H), 2.32-2.24 (m, 2H), 2.19-2.12 (m, 1H), 2.06-1.99 (m, 2H), 1.83 (d, *J* = 13 Hz, 1H), 1.74-1.68 (m, 1H), 1.54-1.44 (m, 1H), 1.34-1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 69.6, 43.9, 42.9, 41.1, 37.1, 25.5, 25.4, 21.5, 21.2; LRMS (ES+) calcd for $C_{10}H_{18}O_2$ (MH^+) 171.1, found 171.2.



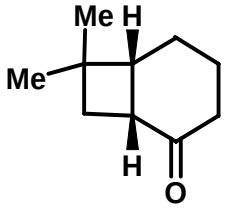
***R*-8**

(*R*)-(+)-Trifluoromethanesulfonic Acid 2-Methyl-2-(3-oxocyclohexyl)propyl Ester (*R*)-8. To a mixture of (*R*)-**7** (325 mg, 1.91 mmol) and 2,6-lutidine (0.233 mL, 2.00 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added Tf_2O (0.336 mL, 2.00 mmol) dropwise. The reaction mixture was stirred for 1 h at 0 °C and then saturated aqueous NH_4Cl (5 mL) was carefully added. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:5) to afford (*R*)-**8** (420 mg, 73%) as a pale pink oil: $[\alpha]_D^{25}$ +11.2 (*c* 1.0, $CHCl_3$); IR (film) 2970, 2875, 1713, 1410, 1246, 1202, 1144, 930, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.28 (dd, *J* = 9.5, 29.0 Hz, 2H), 2.42-2.38 (m, 2H), 2.28-2.21 (m, 1H), 2.17-2.07 (m, 2H), 1.92-1.88 (m, 1H), 1.81-1.74 (m, 1H), 1.64-1.54 (m, 1H), 1.44-1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.6, 118.6 (q, *J* = 318 Hz), 82.8, 43.8, 42.6, 41.0, 37.0, 25.6, 25.0, 21.5, 20.8; LRMS (ES+) calcd for $C_{11}H_{19}F_3O_5S$ ($M+H_2O^+$) 302.1, found 302.1.



***R*-9**

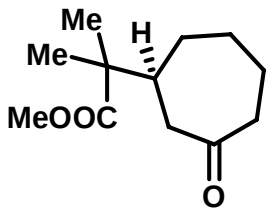
(*R*)-(–)-5,5-Dimethylbicyclo[2.2.2]octan-2-one (*R*-9). To a solution of (*R*)-**8** (121 mg, 0.4 mmol) in THF (4.0 mL) at -78 °C was added dropwise a solution of KHMDS (0.5 M in toluene, 0.8 mL). The reaction mixture was stirred at -78 °C for 30 min and then quenched by addition of saturated aqueous NH_4Cl (0.1 mL). After warmed to room temperature, the THF was removed in *vacuo*. The residue was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ether:pentane, 1:5) to afford (*R*)-**9** (49 mg, 80%) as a colorless oil: $[\alpha]_D^{25}$ –37.4 (*c* 1.0, $CHCl_3$); IR (film) 2950, 2869, 1727, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.57-2.52 (m, 1H), 2.24-2.22 (m, 1H), 2.10-2.00 (m, 2H), 1.77-1.69 (m, 3H), 1.60-1.46 (m, 3H), 1.12 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.9, 44.2, 42.1, 39.9, 39.0, 30.6, 30.2, 29.9, 21.9, 21.8; LRMS (ES+) calcd for $C_{10}H_{17}O$ (MH^+) 153.1, found 153.1.



***R*-3**

(*R*)-(+)-7,7-Dimethylbicyclo[4.2.0]octan-2-one (*R*-3). To a solution of (*R*)-**8** (151 mg, 0.5 mmol) in isopropanol (1.0 mL) at -50 °C was added TMSCl (64 μL, 0.5 mmol), followed by

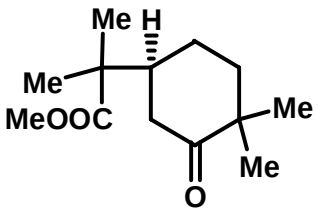
pyrrolidine (125 μL, 1.5 mmol). The resulting homogeneous mixture was kept at -50 °C for 48 h and then quenched by addition of saturated aqueous NH_4Cl (0.1 mL) at the same temperature. After warmed to room temperature, the reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (ether:pentane, 1:5) to afford (*R*)-**3** (55 mg, 72%) as a colorless oil: $[\alpha]_D^{25}$ –105.2 (*c* 0.8, $CHCl_3$); IR (film) 2939, 2865, 1702, 1457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.96 (q, *J* = 8.8 Hz, 1H), 2.43 (dq, *J* = 1, 8.8 Hz, 1H), 2.36-2.33 (m, 2H), 2.03-1.96 (m, 3H), 1.79-1.71 (m, 2H), 1.65-1.58 (m, 1H), 1.16 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 45.0, 39.47, 39.46, 37.3, 36.1, 29.8, 23.8, 22.9, 22.6; LRMS (ES+) calcd for $C_{10}H_{17}O$ (MH^+) 153.1, found 153.1. Selectivity (*R*-**3**/*R*-**9**, 10:1) was determined by ^1H NMR (500 MHz, $CDCl_3$) analysis of the crude mixture: δ 1.16 (s, *R*-**3**), δ 1.13 (s, *R*-**9**).



11

(*S*)-(–)-2-Methyl-2-(3-oxocycloheptyl)propionic Acid Methyl Ester (11). To a solution of the freshly prepared catalyst (*S*)-**5** (0.05 mmol, 20 mol%) in toluene (2 mL) were successively added a solution of triphenylphospine oxide (17.4 mg, 0.0625 mmol, 25 mol%) in toluene (0.5 mL), 2,6-diisopropylphenol (46.3 μL, 0.25 mmol), 2-cyclohepten-1-one (**10**) (34.8 μL, 0.25 mmol), and 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (**4**) (152 μL, 0.75 mmol) at -20 °C. The reaction mixture was stirred at the same temperature for 6 h and then quenched by addition of

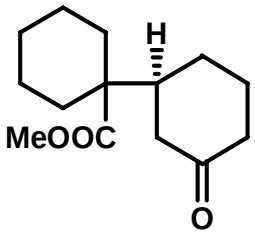
100 μL of Et_3N. The mixture was warmed to room temperature, and then THF (5 mL) and aqueous 2 N HCl (1 mL) were carefully added. The resulting mixture was stirred at 23 °C for 10 min and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc:hexanes, 1:9) to afford the desired ester **11** (53 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ –68.7 (*c* 1.0, $CHCl_3$, 99% ee); IR (film) 2933, 1729, 1702, 1447, 1246, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.58-2.32 (m, 4H), 2.10-1.85 (m, 3H), 1.76-1.70 (m, 1H), 1.60-1.49 (m, 1H), 1.42-1.32 (m, 1H), 1.23-1.13 (m, 1H), 1.12 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 177.9, 51.9, 46.5, 45.6, 43.4, 42.7, 32,2, 29.3, 24.8, 22.4, 21.1; HRMS (ES+) calcd for $C_{12}H_{21}O_3$ (MH^+) 213.1490, found 213.1485. Enantioselectivity was determined by HPLC analysis using a Chiralcel OD-H column (1% *i*-PrOH in hexanes; 1.0 mL/min; λ 290 nm); retention times: 7.1 min (minor), 8.5 min (major).



12

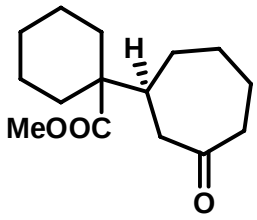
(*S*)-(–)-2-(4,4-Dimethyl-3-oxocyclohexyl)-2-methylpropionic Acid Methyl Ester (12). This compound was obtained from 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (**4**) and 6,6-dimethyl 2-cyclohexen-1-one in a similar manner to **11** as a colorless oil (80% yield): $[\alpha]_D^{25}$ –91.9 (*c* 1.0, $CHCl_3$, 92% ee); IR (film) 2973, 2950, 1729, 1708, 1463, 1266, 1191, 1146, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.38 (t, J = 13.6 Hz, 1H), 2.19-2.14 (m, 1H), 2.03-1.95 (m, 1H), 1.78-1.73 (m, 1H), 1.65-1.47 (m, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H),

1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 177.6, 52.1, 46.7, 45.5, 44.7, 39.8, 39.7, 25.21, 25.20, 22.9, 22.5, 22.1; HRMS (ES+) calcd for $C_{13}H_{23}O_3$ (MH^+) 227.1647, found 227.1637. Enantioselectivity was determined by HPLC analysis using a Chiralpak IA column (0.5% *i*-PrOH in hexanes; 1.0 mL/min; λ 290 nm); retention times: 6.3 min (minor), 6.9 min (major).



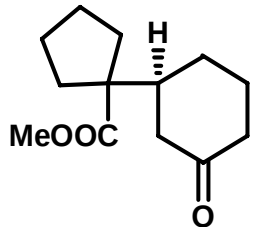
13

(*S*)-(–)-3'-Oxobicyclohexyl-1-carboxylic Acid Methyl Ester (13). This compound was obtained from [cyclohexylidene(methoxy)methoxy]trimethylsilane and 2-cyclohexen-1-one (**2**) in a similar manner to **11** as a colorless oil (86% yield): $[\alpha]_D^{25}$ –7.0 (*c* 1.7, $CHCl_3$, 90% ee); IR (film) 2958, 2925, 2860, 1721, 1455, 1200, 1133 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.43-2.31 (m, 2H), 2.23-2.03 (m, 5H), 1.93-1.88 (m, 1H), 1.81-1.73 (m, 1H), 1.65-1.45 (m, 4H), 1.34-1.07 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 175.5, 51.4, 50.4, 47.1, 43.4, 41.3, 31.8, 31.5, 26.3, 25.7, 25.2, 23.54, 23.52; HRMS (ES+) calcd for $C_{14}H_{23}O_3$ (MH^+) 239.1647 found 239.1641. Enantioselectivity was determined by HPLC analysis using a Chiralcel OD-H column (1% *i*-PrOH in hexanes; 1.0 mL/min; λ 290 nm); retention times: 9.8 min (major), 12.1 min (minor).



14

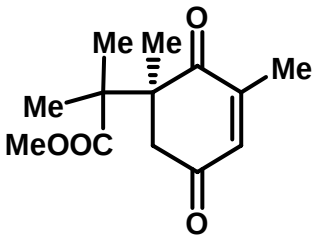
***S*)-(–)-1-(3-Oxocycloheptyl)cyclohexanecarboxylic Acid Methyl Ester (14).** This compound was obtained from [cyclohexylidene(methoxy)methoxy]trimethylsilane and 2-cyclohepten-1-one (**10**) in a similar manner as a colorless oil (89% yield): $[\alpha]_D^{25}$ –43.0 (*c* 1.0, $CHCl_3$, 88% ee); IR (film) 2929, 2858, 1725, 1702, 1451, 1200, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.53-2.35 (m, 4H), 2.08-1.86 (m, 5H), 1.78-1.71 (m, 1H), 1.64-1.49 (m, 4H), 1.34-1.06 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.1, 175.9, 51.4, 51.0, 45.2, 44.2, 43.2, 31.5, 31.3, 30.9, 29.1, 25.7, 24.7, 23.44, 23.40; HRMS (ES+) calcd for $C_{15}H_{25}O_3$ (MH^+) 253.1803 found 253.1807. Enantioselectivity was determined by HPLC analysis using a Chiralcel OJ column (1% *i*-PrOH in hexanes; 1.0 mL/min; λ 290 nm); retention times: 9.0 min (major), 11.2 min (minor).



15

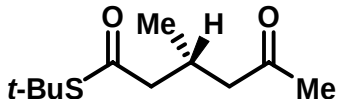
(*S*)-(–)-1-(3-Oxocyclohexyl)cyclopentanecarboxylic Acid Methyl Ester (15). To a solution of the freshly prepared catalyst (*S*)-**5** (0.05 mmol, 20 mol%) in toluene (1 mL) was added a solution of triphenylphospine oxide (17.4 mg, 0.0625 mmol, 25 mol%) in toluene (0.5 mL), followed by

[cyclopentylidene(methoxy)methoxy]trimethylsilane (134 μL, 0.625 mmol) at -20 °C. A solution in toluene (1 mL) of 2-cyclohexen-1-one (**2**) (24.2 μL, 0.25 mmol) and 2,6-diisopropylphenol (46.3 μL, 0.25 mmol) was then slowly added via a syringe drive over 4 h at -20 °C. After addition, the reaction mixture was stirred at the same temperature for 12 h and then quenched by addition of 100 μL of Et_3N. The mixture was warmed to room temperature, and then THF (5 mL) and aqueous 2 N HCl (1 mL) were carefully added. The resulting mixture was stirred at 23 °C for 10 min and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes, 1:9) to afford **15** as a colorless oil (44 mg, 79%): $[\alpha]_D^{25}$ –2.8 (*c* 1.0, $CHCl_3$, 82% ee); IR (film) 2952, 2871, 1713, 1451, 1233, 1194, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.42-2.32 (m, 2H), 2.26-1.94 (m, 6H), 1.90-1.83 (m, 1H), 1.63-1.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 176.8, 58.1, 51.8, 46.3, 44.7, 41.2, 33.9, 33.7, 27.8, 25.2, 24.83, 24.76; HRMS (ES+) calcd for $C_{13}H_{21}O_3$ (MH^+) 225.1490 found 225.1492. Enantioselectivity was determined by HPLC analysis using a Chiralcel OD-H column (0.5% *i*-PrOH in hexanes; 1.0 mL/min; λ 290 nm); retention times: 13.3 min (major), 15.3 min (minor).



17

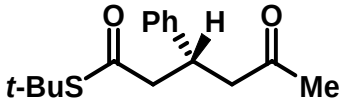
(*S*)-(–)-2-(1,3-Dimethyl-2,5-dioxocyclohex-3-enyl)-2-methyl-propionic Acid Methyl Ester (17). This compound was obtained from 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (**4**) and 2,6-dimethylbenzoquinone (**16**) in a similar manner as a colorless oil (87% yield): $[\alpha]_D^{25}$ –15.2 (*c* 1.0, $CHCl_3$, 90% ee); IR (film) 2985, 2954, 1723, 1675, 1434, 1272, 1191, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, *J* = 0.9, 1.2 Hz, 1H), 3.63 (s, 3H), 3.35 (d, *J* = 16.2 Hz, 1H), 2.59 (dd, *J* = 0.9, 16.2 Hz, 1H), 1.99 (d, *J* = 1.2 Hz, 3H), 1.40 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 197.5, 177.2, 150.2, 136.3, 51.9, 51.3, 48.3, 48.1, 22.5, 22.1, 21.9, 16.9; LRMS (ES+) calcd for $C_{13}H_{19}O_4$ (MH^+) 239.1 found 239.1. Enantioselectivity was determined by HPLC analysis using a Chiralcel OJ column (1% *i*-PrOH in hexanes; 1.0 mL/min; λ 254 nm); retention times: 20.7 min (major), 25.2 min (minor).



21

(*S*)-(–)-*tert*-Butyl (*R*)-3-Methyl-5-oxohexanethioate (21). To a solution of the freshly prepared catalyst (*S*)-**5** (0.05 mmol, 20 mol%) of toluene (2 mL) were successively added a solution of triphenylphospine oxide (17.4 mg, 0.0625 mmol, 25 mol%) in toluene (0.5 mL), 2,6-diisopropylphenol (139 μL, 0.75 mmol), pent-3-en-2-one (**19**) (27.0 μL, 0.25 mmol), and (1-*tert*-butylsulfanylvinyloxy)trimethylsilane (**18**) (173 μL, 0.75 mmol) at -78 ^oC. The reaction mixture was stirred at -78 °C for 24 h and then quenched by addition of 100 μL of Et_3N. The mixture was warmed to room temperature, and then THF (5 mL) and aqueous 6 N HCl (1 mL) were carefully added. The resulting mixture was stirred at 23 °C for 10 min and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4)

and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc:hexanes, 1:9) to afford the desired ester **21** (53 mg, 99%) as a colorless oil: $[\alpha]_D^{25}$ –5.7 (*c* 1.0, $CHCl_3$, 90% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54-2.41 (m, 3H), 2.36-2.24 (m, 2H), 2.12 (s, 3H), 1.44 (s, 9H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 199.4, 50.6, 49.7, 48.0, 30.3, 29.7, 27.1, 19.7 (The ^{1}H NMR and ^{13}C NMR spectral data were identical to those reported in the literature).[5] Enantioselectivity was determined by HPLC analysis using a Chiralcel AD column (0.5% *i*-PrOH in hexanes; 0.5 mL/min; λ 254 nm); retention times: 9.8 min (major), 10.6 min (minor).



22

(*S*)-(–)-*tert*-Butyl (*R*)-3-Phenyl-5-oxohexanethioate (22). This compound was obtained from 4-phenyl-3-buten-2-one (**20**) (36.5 mg, 0.25 mmol) and (1-*tert*-butylsulfanylvinyloxy) trimethylsilane (**18**) (173 μL, 0.75 mmol) in a manner similar to **21** as a white solid (99% yield): $[\alpha]_D^{25}$ –29.4 (*c* 1.0, $CHCl_3$, 84% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 3.70 (quintet, *J* = 7.2 Hz, 1H), 2.87-2.68 (m, 4H), 2.04 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 198.5, 142.6, 128.5, 127.4, 126.8, 50.4, 49.0, 48.1, 38.0, 30.3, 29.6 (The ^{1}H NMR and ^{13}C NMR spectral data were identical to those reported in the literature).[5] Enantioselectivity was determined by HPLC analysis using a Chiralcel AD column (0.5% *i*-PrOH in hexanes; 0.5 mL/min; λ 254 nm); retention times: 20.6 min (major), 24.0 min (minor).

[5] Wang, X.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T. *J. Org. Chem.* **2003**, *68*, 10046-10057.