C2-Symmetric Sc(III)-Complexes as Chiral Lewis Acids. Catalytic Enantioselective Aldol Additions of Silylketene Acetals and Enolsilanes to Glyoxylate Esters

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Supporting Information

General Information. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Dichloromethane (CH_2Cl_2) was purified by passage through a bed of activated alumina.[1] All other solvents and reagents were purified prior to use following the guidelines of Perrin and Armarego.[2] $ScCl_3$•$(thf)_3$ was prepared according to a literature procedure[3] and was stored in an inert atmosphere dry box. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D$ (c g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H NMR spectra were recorded on Inova Varian-500 (500 MHz) or Mercury Varian-400 (400 MHz) spectrometers and are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration; proton assignments). Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments. Proton-decoupled ^{13}C NMR spectra were recorded on Mercury Varian-400 (100 MHz) or Inova Varian-500 (125 MHz) spectrometers and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 77.0 ppm). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers in the Harvard University Mass Spectrometry Laboratory. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1050 Series HPLC equipped with a variable wavelength detector using either Chiralcel OD-H or Chiralcel AD columns (0.46 cm x 25 cm) from Daicel.

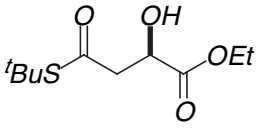
The (*S*,*S*)-bis(phenyloxazolinyl)pyridine and (*S*,*S*)-bis(*tert*-butyloxazolinyl)pyridine were prepared as previously described.[4] Ethyl glyoxylate was purchased from Fluka as a 1:1 solution in toluene and purified as detailed below. The (Z) silylketene acetals were prepared from the corresponding thioesters using standard protocols.[5]

General Procedure A: The Addition of Thiosilylketene Acetals to Ethyl Glyoxylate Catalyzed by 1a. To an oven-dried-4 mL vial containing a magnetic stirring bar was added, in an inert atmosphere box, (*S*,*S*)-bis(phenyloxazolinyl)pyridine (18.0 mg, 0.049 mmol) and $ScCl_3$•$(thf)_3$ (16.6 mg, 0.045 mmol). The vial was fitted with a serum cap, removed from the inert atmosphere box and charged with CH_2Cl_2 (2.0 mL). The resulting suspension was stirred at room tmperature for 0.5 h to give a colorless solution. The resulting solution was added to a vial of $AgSbF_6$ (15.5 mg, 0.045 mmol) and the white suspension stirred for 0.5 h at room temperature. The catalyst was cooled to −78 °C and the silylketene acetal (0.45 mmol) was added followed by distilled ethyl glyoxylate-toluene solution (see below) (100 µL, 0.68 mmol). The resulting solution was stirred at −78 °C until the thiosilylketene acetal was completely consumed (3-10 h), as determined by TLC (20% EtOAc/hexanes). The reaction mixture was then filtered through a 0.3 x 2 cm plug of silica gel with Et_2O (10 mL). Concentration of the ether solution gave the unpurified silyl ether which was dissolved in EtOAc (10 mL) and 1N HCl (0.2 mL). After stirring at room temperature for 0.5 h, this solution was poured into a separatory funnel and diluted with Et_2O (20 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide the hydroxy esters. Purification by flash chromatography provided the title compounds.

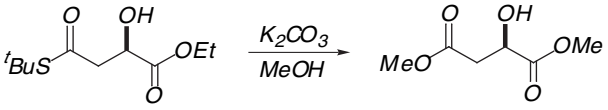
General Procedure B: The Addition of Aryl Enolsilanes to Ethyl Glyoxylate Catalyzed by 1b. To an oven-dried 4 mL vial containing a magnetic stirring bar was added, in an inert atmosphere box, (*S*,*S*)-bis(*tert*-butyloxazolinyl)pyridine (16.1 mg, 0.049 mmol) and $ScCl_3$•$(thf)_3$ (16.6 mg, 0.045 mmol). The vial was fitted with a serum cap, removed from the inert atmosphere box and charged with CH_2Cl_2 (2.0 mL). The resulting suspension was stirred at room tmperature for 1.0 h to give a colorless solution. The resulting solution was added to a vial of $AgSbF_6$ (15.5 mg, 0.045 mmol) and the white suspension stirred for 0.5 h at room temperature then cooled to −78 °C. To this cooled solution, was added the aryl enolsilane (0.45 mmol), chlorotrimethylsilane (TMSCl, 110 µl, 0.90 mmol), and the distilled ethyl glyoxylate-toluene solution (see below) (100 µL, 0.68 mmol). The resulting solution was stirred at −78 °C until the enolsilane was completely consumed (~16 h), as determined by TLC (20% EtOAc/hexanes). The reaction mixture was then filtered through a 0.3 x 2 cm plug of silica gel with Et_2O (10 mL). Concentration of the ether solution gave the crude silyl ether which was dissolved in EtOAc (10 mL) and 1*N* HCl (0.2 mL). After stirring at room temperature for 0.5 h, this solution was poured into a separatory funnel and diluted with Et_2O (20 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to

provide the α-hydroxy-γ-ketoesters. Purification by flash chromatography provided the title compounds.

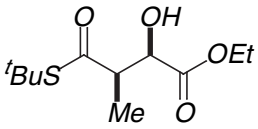
Distillation procedure for ethyl glyoxylate: To an oven-dried 25 mL round bottom flask fitted with a magnetic stirring bar and a short path distillation apparatus was added 5 mL of ethyl glyoxylate/toluene solution. The distillation pot was warmed to 140–150 °C to remove most of the toluene (head temp 110-118 °C). The distillation pot was warmed to 160–170 °C and the remaining ethyl glyoxylate/toluene was collected (head temp 120–130 °C). ^{1}H NMR indicates the distilled glyoxylate solution to be typically a 4:1 mixture of ethyl glyoxylate:toluene.



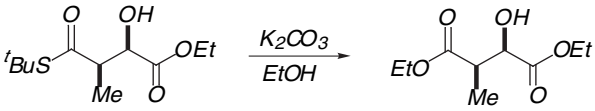
Preparation of (3*R*)–*tert*-Butyl 3-Hydroxy-3-carboethoxy-propanethioate (3a, Table 1, entry 1). The indicated compound was prepared according to General Procedure A employing the silylketene acetal derived from *tert*-butyl thioacetate (103 μL, 0.45 mmol) to provide the pure product as a colorless oil in 92% yield (97 mg, 0.41 mmol) after flash chromatography with 20% EtOAc/hexanes; $[\alpha]_D^{rt}$ -28.2° (*c* = 1.0, $CHCl_3$); IR (neat) 3480, 2982, 1730, 1704, 1260, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (m, 1H, C*H*OH), 4.28-4.25 (m, 2H, CH_3CH_2O), 3.13 (d, *J* = 5.5 Hz, 1H, O*H*), 2.94 (ABq, J_{AB} = 6.5 Hz, 2H, ^{t}BuS(CO)CH_2), 1.46 (s, 9H, $(CH_3)_3$), 1.30 (t, *J* = 7.0 Hz, 3H, CH_3CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 173.5, 67.4, 62.1, 47.7, 46.9, 29.7, 29.6, 14.1; HRMS (CI/NH_3) exact mass calcd for $(C_{10}H_{18}O_4S+H)^+$ requires *m/z* 235.1004 found *m/z* 235.1002. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexanes:isopropanol), 0.7 mL/min; major enantiomer t_r = 11.5 min, minor enantiomer t_r = 12.9 min; 90% ee.



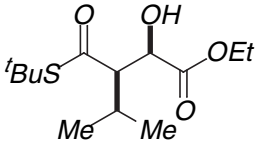
Determination of the Absolute Configuration of (3*R*)-*tert*-Butyl-3-Carboethoxy-3-hydroxypropanethioate by Correlation with (*R*)-Dimethyl Malate. To a vigorously stirred solution of **3a** (70 mg, 0.27 mmol) in MeOH (6 mL) was added K_2CO_3 (70 mg). After 10 min, the resulting suspension was passed through a cotton plug with Et_2O (15 mL) and then washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide dimethyl malate as a colorless oil in 51% yield (32 mg, 0.14 mmol) after flash chromatography with 40% EtOAc/hexanes. This material exhibited spectral data and an optical rotation that was identical in all respects to (*R*)-dimethyl malate.[6]; $[\alpha]_D^{rt}$ +6.2° (*c* = 0.50, Et_2O); $[\alpha]_D^{rt}$ (lit[6]) +6.6° (*c* = 1.0, Et_2O).



Preparation of (2*R*,3*R*)-*tert*-butyl-3-carboethoxy-3-hydroxy-2-methylpropanethioate (3b, Table 1, entry 2). The indicated compound was prepared according to General Procedure A employing the silylketene acetal derived from *tert*-butyl thiopropionate as a 95:5 mixture of *Z:E* isomers (112 μL, 0.45 mmol) to provide the pure product as a colorless oil in 93% yield (104 mg, 0.42 mmol) after flash chromatography with 20% EtOAc/hexanes; 92 : 8 *syn:anti,* 93% *syn* ee. *Syn* isomer: $[\alpha]_D^{rt}$ +21.0° (*c* = 0.5, $CHCl_3$); IR (neat) 3450, 2981, 1732, 1703, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.53 (dd, *J* = 4.0, 4.0 Hz, 1H, C*H*OH), 4.27 (q, *J* = 7.0 Hz, 2H CH_3CH_2O), 3.03 (d, *J* = 5.0 Hz, 1H, O*H*), 2.99-2.96 (m, 1H, C*H*CH_3), 1.47 (s, 9H, $(CH_3)_3$), 1.31 (t, *J* = 3.5 Hz, 3H, CH_3CH_2O), 1.19 (d, *J* = 7.5 Hz, 3H, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 173.1, 71.5, 62.1, 51.6, 29.8, 29.7, 14.2, 11.6; HRMS (CI/NH_3) exact mass calcd for $(C_{11}H_{20}O_4S+H)^+$ requires *m/z* 249.1161 found *m/z* 249.1158. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (97.5 : 2.5 hexanes:isopropanol), 0.7 mL/min; major enantiomer t_r = 9.35 min, minor enantiomer t_r = 8.25 min; 95% ee.

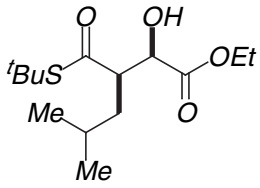


Determination of the Relative and Absolute Configuration of (2*R*,3*R*)-*tert*-butyl-3-Carboethoxy-3-hydroxy-2-methylpropanethioate by Correlation with (2*R*,3*R*)-Diethyl-3-Methylmalate. To a vigorously stirred solution of **3b** (24 mg, 0.09 mmol) in EtOH (2 mL) was added K_2CO_3 (24 mg). After 15 min, the resulting suspension was passed through a cotton plug with Et_2O (15 mL) and then washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide diethyl 3-methylmalate as a colorless oil in 78% yield (15 mg, 0.07 mmol) after flash chromatography with 40% EtOAc/hexanes. This material exhibited spectral data and an optical rotation that was identical in all respects to (2*R*,3*R*)-diethyl-3-methylmalate.[7]; $[\alpha]_D^{rt}$ +2.8° (*c* = 0.33, Et_2O); $[\alpha]_D^{rt}$ (lit[7]) +2.8° (*c* = 1.47, Et_2O).

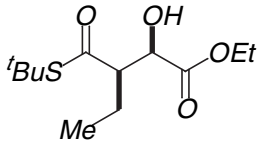


Preparation of (2*R*,3*R*)-*tert*-butyl 3-Carboethoxy-3-hydroxy-2-isopropylpropanethioate (3c, Table 1, entry 3). The indicated compound was prepared according to the General Procedure A employing the silylketene acetal derived from *tert*-butyl thioisovalerate as a 95:5 mixture of *Z:E* isomers (110 μL, 0.45 mmol) to provide the pure product as a colorless oil in 90% yield (112 mg, 0.40 mmol) after flash chromatography with 10% EtOAc/hexanes; 95 : 5 syn:anti, 99% syn ee. Syn isomer: $[\alpha]_D^{rt}$ +25.1° (*c* = 0.75, $CHCl_3$); IR (neat) 3530, 2963, 2872, 1733, 1699, 1478, 1141 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.34 (dd, *J* = 3.5, 3.5 Hz, 1H, C*H*OH), 4.28-4.20 (m, 2H, CH_3CH_2O), 3.29 (d, *J* = 11.0 Hz, 1H, O*H*), 2.51 (dd, *J* = 3.0, 3.5 Hz, 1H, C*H*$CH(CH_3)_2$), 2.30-2.26 (m, 1H,

CHC*H*$(CH_3)_2$), 1.43 (s, 9H, (C*H*$_3)_3$), 1.32 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$O), 1.05 (d, *J* = 6.5 Hz, 3H, (C*H*$_3)_2$CH), 1.01 (d, *J* = 6.5 Hz, 3H, (C*H*$_3)_2$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 173.1, 70.4, 61.6, 48.9, 29.7, 29.5, 27.8, 21.0, 20.1, 14.2; HRMS (CI/NH_3) exact mass calcd for $(C_{13}H_{24}O_4S+H)^+$ requires *m/z* 277.1474 found *m/z* 277.1470. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98.5 : 1.5 hexanes:isopropanol), 0.7 mL/min; major enantiomer t_r = 20.0 min, minor enantiomer t_r = 19.2 min; 99% ee.

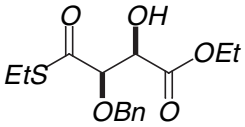


Preparation of (2*R*,3*R*)-*tert*-butyl 3-Carboethoxy-3-hydroxy-2-isobutylpropanethioate (3d, Table 1, entry 4). The indicated compound was prepared according to the General Procedure A employing the silylketene acetal derived from *tert*-butyl thio-4-methylpentanoate as a 95:5 mixture of *Z:E* isomers (117 μL, 0.45 mmol) to provide the pure product as a colorless oil in 94% yield (123 mg, 0.42 mmol) after flash chromatography with 10% EtOAc/hexanes; 93 : 7 syn:anti, 93% syn ee. Syn isomer: $[\alpha]_D^{rt}$ -10.2° (*c* = 0.20, $CHCl_3$); IR (neat) 3502, 2960, 1740, 1700, 1218 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (dd, *J* = 2.5, 4.0 Hz, 1H, C*H*OH), 4.27 (q, *J* = 7.0 Hz, 2H, CH$_3$C*H*$_2$O), 3.03 (d, *J* = 5.5 Hz, 1H, O*H*), 2.98-2.95 (m, 1H, C*H*CH$_2$CH(CH$_3)_2$), 1.85 (ddd, *J* = 5.0, 9.5, 8.5 Hz, 2H, C*H*$_2$CH(CH$_3)_2$), 1.47 (s, 9H, (C*H*$_3)_3$), 1.32 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$O), 1.25-1.19 (m, 1H, CH$_2$C*H*(CH$_3)_2$), 0.90 (apparent t, *J* = 7.5 Hz, 6H, CH$_2$CH(C*H*$_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 173.0, 71.8, 62.1, 55.6, 48.6, 36.2, 29.7, 25.8, 23.2, 21.8, 14.2; HRMS (CI/NH_3) exact mass calcd for $(C_{14}H_{26}O_4S+NH_4)^+$ requires *m/z* 308.1896 found *m/z* 308.1884. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98.5 : 1.5 hexanes:isopropanol), 0.7 mL/min; major enantiomer t_r = 9.15 min, minor enantiomer t_r = 7.94 min; 93% ee.

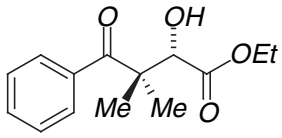


Preparation of (2*R*,3*R*)-*tert*-butyl-3-Carboethoxy-3-hydroxy-2-ethylpropanethioate (3e, Table 1, entry 5). The indicated compound was prepared according to the General Procedure A employing the silylketene acetal derived from *tert*-butyl thiobutanoate as a 95:5 mixture of *Z:E* isomers (105 μL, 0.45 mmol) to provide the pure product as a colorless oil in 90% yield (106 mg, 0.40 mmol) after flash chromatography with 15% EtOAc/hexanes; 92 : 8 syn:anti, 95% syn ee. Syn isomer: $[\alpha]_D^{rt}$ -22.1° (*c* = 0.30, $CHCl_3$); IR (neat) 3505, 2970, 1735, 1700, 1442, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (apparent t, *J* = 5.5 Hz, 1H, C*H*OH), 4.29 (q, *J* = 5.0 Hz, 2H, CH$_3$C*H*$_2$O), 3.05 (d, *J* = 5.0 Hz, 1H, O*H*), 2.83-2.79 (m, 1H, C*H*CH$_2$CH$_3$), 1.92-1.86 (m, 2H, CHC*H*$_2$CH$_3$), 1.63-1.60 (m, 1H, CHC*H*$_2$CH$_3$), 1.49 (s, 9H, (C*H*$_3)_3$), 1.34 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$O), 0.99 (t, *J* = 7.0 Hz, 3H, CHCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 173.2, 71.2, 62.1, 59.3, 48.6, 29.7, 21.1, 14.2, 11.9; HRMS (CI/NH_3) exact mass calcd for $(C_{16}H_{22}O_4S+H)^+$ requires *m/z* 263.1317

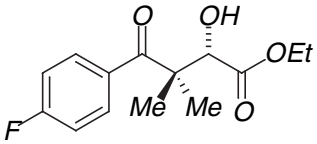
found *m/z* 263.1315. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98 : 2 hexanes:isopropanol), 0.7 mL/min; major enantiomer t_r = 8.64 min, minor enantiomer t_r = 7.61 min; 95% ee.



Preparation of (2*R*,3*R*)–ethyl-3-Carboethoxy-3-hydroxy-2-benzyloxypropanethioate (3f, Table 1, entry 6). The indicated compound was prepared according to the General Procedure A employing the silylketene acetal derived from ethylthio-2-benzyloxypropanoate as a 95:5 mixture of *Z:E* isomers (130 μL, 0.45 mmol) to provide the pure product as a colorless oil in 92% yield (130 mg, 0.41 mmol) after flash chromatography with 20→30% EtOAc/hexanes; 93:7 syn:anti, 95% syn ee. Syn isomer: $[\alpha]_D^{rt}$ +13.1° (*c* = 0.50, $CHCl_3$); IR (neat) 3527, 2962, 2926, 1734, 1670, 1457, 1364, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.32 (m, 5H, Ph*H*), 4.80 (ABq, J_{AB} = 11.5 Hz, 2H, PhCH_2O), 4.59 (dd, *J* = 2.5, 2.0 Hz, 1H, C*H*OH), 4.43 (d, *J* = 11.5 Hz, 1H, C*H*OCH$_2$Ph), 4.31 (q, *J* = 4.0 Hz, 2H, CH_3CH_2O), 3.08 (d, *J* = 6.0 Hz, 1H, O*H*), 2.96 (q, *J* = 6.5 Hz, 2H, CH_3CH_2S), 1.27 (t, *J* = 7.5 Hz, 3H, CH_3CH_2O), 1.16 (t, *J* = 7.5 Hz, 3H, CH_3CH_2S); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 174.8, 151.0, 128.6, 128.5, 128.4, 128.3, 85.2, 83.8, 74.9, 71.9, 22.9, 14.3; HRMS (CI/NH_3) exact mass calcd for $(C_{15}H_{20}O_5S+H)^+$ requires *m/z* 313.1110 found *m/z* 313.1109. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (92 : 8 hexanes:isopropanol), 0.7 mL/min; major enantiomer t_r = 12.0 min, minor enantiomer t_r = 11.2 min; 95% ee.

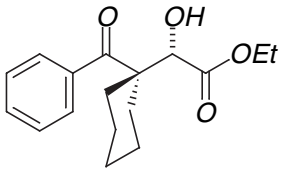


Preparation of 2(*S*)-Hydroxy-3,3-dimethyl-4-oxo-4-phenyl-butyric acid ethyl ester (6a, Table 2, entry 1). The indicated compound was preparedaccording to General Procedure B and isolated by flash chromatography (5-10 % EtOAc/hexanes) as a colorless oil (85 % yield): $[\alpha]_D$ +15.7 ˚ (*c* = 1.56, $CHCl_3$); IR (film) 3499, 3060, 2982, 2918, 1964, 1894, 1735, 1686, 1598, 1469, 1445, 1391, 1368 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.66-7.65 (m, 2H), 7.48-7.45 (m, 1H), 7.42-7.39 (m, 2H), 4.64 (s, 1H), 4.29-4.17 (m, 2H), 3.27 (br s, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 1.25 (t, 3H, *J*=7.3 Hz); ^{13}C NMR (125 MHz, $CHCl_3$) δ 173.4, 139.1, 131.1, 128.4, 127.8, 75.6, 62.3, 52.1, 22.7, 22.0, 14.3; HRMS (ES): Exact mass calcd for $C_{14}H_{18}O_4$ $[M+H]^+$, requires *m/z*: 251.1283, found *m/z*: 251.1284. Enantiomeric excess determined by HPLC with Chiracel AD column, 10% *i*PrOH/hexanes, 0.7 mL/min, 254 nm; t_r (major)=13.9, t_r (minor)=16.0), 95 % ee.

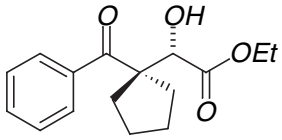


Preparation of 2(*S*)-Hydroxy-3,3-dimethyl-4-oxo-4-(4-fluorophenyl)-butyric acid ethyl ester (6b, Table 2, entry 2). The indicated compound was prepared according to General Procedure B

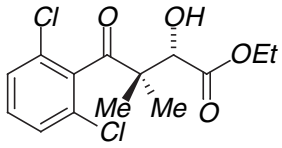
and isolated by flash chromatography (5-10 % EtOAc/hexanes) as a colorless oil (85 % yield): $[\alpha]_D$ +14.7 ˚ (*c* = 1.99, $CHCl_3$); IR (film) 3500, 3075, 2983, 2920, 1735, 1676, 1600, 1505, 1458 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.76-7.74 (m, 2H), 7.28-7.09 (m, 2H), 4.62 (d, 1H, *J*=5.9 Hz), 4.30-4.18 (m, 2H), 3.30 (d, H, *J*=5.9 Hz), 1.42 (s, 3H), 1.35 (s, 3H), 1.26 (t, 3H, *J*=7.3 Hz); ^{13}C NMR (125 MHz, $CHCl_3$) d 173.4, 164.5 (d, *J*=252.4 Hz), 135.0, 130.6 (d, *J*=8.4 Hz), 115.5 (d, *J*=21.4 Hz), 75.7, 62.4, 52.1, 22.8, 22.1, 14.3; HRMS (ES): Exact mass calcd for $C_{14}H_{17}O_4F$ $[M+H]^+$, requires *m/z*: 269.1189, found *m/z*: 269.1181. Enantiomeric excess determined by HPLC with a Chiracel AD column, 5 % *i*PrOH/hexanes, 0.7 mL/min, 254 nm; t_r (major)=22.9 min, t_r (minor)=27.3 min, 95 % ee.



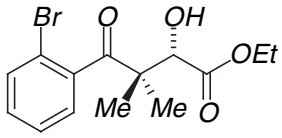
Preparation of (1-Benzoyl-cyclohexyl)-(2*S*)-hydroxy-acetic acid ethyl ester (6c, Table 2, entry 3). The indicated compound was prepared according to General Procedure B and isolated by flash chromatography (5-10 % EtOAc/hexanes) as a colorless oil (80 % yield): $[\alpha]_D$ +9.5 ˚ (*c* = 2.39, $CHCl_3$); IR (film) 3486, 3059, 2936, 2858, 2342, 1731, 1676, 1454, 1261, 1222, 1095 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.66-7.64 (m, 2H), 7.46-7.40 (m, 1H), 7.39-7.26 (m, 2H), 4.51 (d, 1H, *J*=6.8 Hz), 4.30-4.19 (m, 2H), 3.33 (d, 1H, *J*=6.4 Hz), 2.30-2.26 (m, 1H), 2.11-2.09 (m, 1H), 1.75-1.68 (m, 3H), 1.67-1.51 (m, 4H), 1.35-1.28 (m, 1H), 1.26 (t, 3H, *J*=7.3 Hz); ^{13}C NMR (125 MHz, $CHCl_3$) δ 173.5, 140.4, 130.8, 128.3, 127.5, 75.0, 62.3, 57.1, 31.1, 30.3, 25.8, 22.8, 14.3; HRMS (ES): Exact mass calcd for $C_{17}H_{22}O_4$ $[M+H]^+$, requires *m/z*: 291.1596, found *m/z*: 291.1594. Enantiomeric excess determined by HPLC with a Chiracel AD column, 3 % *i*PrOH/hexanes, 0.7 mL/min, 254 nm; t_r (major)=27.8, t_r (minor)=31.8), 97 % ee.



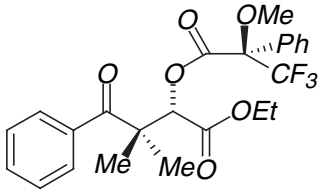
Preparation of (1-Benzoyl-cyclopentyl)-(2*S*)-hydroxy-acetic acid ethyl ester (6d, Table 2, entry 4). The indicated compound was prepared according to General Procedure B and isolated by flash chromatography (5-10 % EtOAc/hexanes) as a colorless oil (81 % yield): $[\alpha]_D$ -15.8 ˚ (*c* = 0.97, $CHCl_3$); IR (film) 3494, 2953, 1738, 1679, 1597, 1446, 1230, 1102 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.85-7.83 (m, 2H), 7.51-7.47 (m, 1H), 7.44-7.41 (m, 2H), 4.81 (d, 1H, *J*=5.9 Hz), 4.22 (m, 1H), 4.10-4.04 (m, 1H), 3.18 (d, 1H, *J*=5.9 Hz), 2.39-2.29 (m, 2H), 2.20-2.14 (m, 1H), 1.80-1.55 (m, 5H), 1.19 (t, 3H, *J*=7.3 Hz); ^{13}C NMR (125 MHz, $CHCl_3$) δ 202.8, 173.7, 137.0, 131.9, 129.0, 128.5, 74.1, 66.5, 62.6, 62.4, 34.4, 30.8, 27.6, 26.7, 14.1; HRMS (ES): Exact mass calcd for $C_{16}H_{20}O_4$ $[M+H]^+$, requires *m/z*: 277.1440, found *m/z*: 277.1432. Enantiomeric excess determined by HPLC with a Chiracel OD-H column, 1 % *i*PrOH/hexanes, 0.7 mL/min, 254 nm; t_r (major)=21.3, t_r (minor)=23.8), 98 % ee.



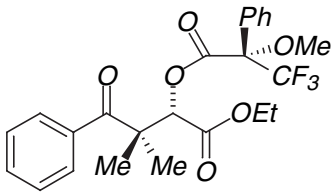
Preparation of 4-(2,6-Dichloro-phenyl)-2(*S*)-hydroxy-4-oxo-butyric acid ethyl ester (6e, Table 2, entry 5). The indicated compound was prepared according to General Procedure B and isolated by flash chromatography (5-10 % EtOAc/hexanes) as an amorphous solid (96 % yield). X-ray quality crystals were obtained by re-crystallization from EtOAc/Hexanes: $[\alpha]_D$ +13.5 ° (*c* = 3.89, $CHCl_3$); IR (film) 3437, 3082, 2981, 2913, 2360, 1741, 1725, 1580, 1560, 1429 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 7.34-7.28 (m, 3H), 4.65-4.62 (m, 1H), 4.34-4.27 (m, 2H), 3.43 (dd, 1H, *J*=3.4, 18.6 Hz), 3.36 (dd, 1H, *J*=5.9, 18.6 Hz), 3.31 (d, 1H, 5.4 Hz), 1.32 (t, 3H, *J*=6.8 Hz); ^{13}C NMR (125 MHz, $CHCl_3$) δ 173.6, 138.7, 131.2, 130.8, 128.5, 66.6, 62.3, 47.5, 14.4; HRMS (ES): Exact mass calcd for $C_{12}H_{12}O_4Cl_2$ $[M+H]^+$, requires *m/z*: 291.0191, found *m/z*: 291.0185. Enantiomeric excess determined by HPLC with a Chiracel OD-H column, 5 % *i*PrOH/hexanes, 0.7 mL/min, 225 nm; t_r (major)=22.0, t_r (minor)=25.2), 96 % ee.



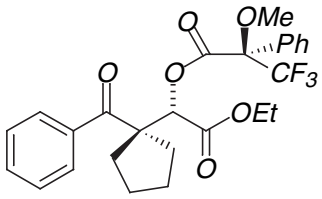
Preparation of 4-(2-Bromo-phenyl)-2(*S*)-hydroxy-4-oxo-butyric acid ethyl ester (6f, Table 2, entry 6). The indicated compound was prepared according to General Procedure B and isolated by flash chromatography (5-10 % EtOAc/hexanes) as an colorless oil (91 % yield). $[\alpha]_D$ -7.2 ° (*c* = 3.85, $CHCl_3$); IR (film) 3480, 2982, 2921, 2360, 1732, 1698, 1587, 1564, 1468, 1429 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.59 (dd, 1H, *J*=1.1, 7.7 Hz), 7.45 (dd, 1H, *J*=1.8, 7.7 Hz), 7.35 (dt, 1.1, 7.7 Hz), 7.31-7.27 (m, 1H), 4.63-4.23 (m, 1H), 4.28-4.23 (m, 2H), 3.48 (dd, 1H, *J*=4.4, 17.6 Hz), 3.41 (dd, 1H, *J*=5.9, 17.6 Hz), 3.33 (d, 1H, 5.5 Hz), 1.28 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 201.1, 173.9, 140.8, 134.1, 132.3, 129.3, 127.8, 119.1, 67.4, 62.3, 46.4, 14.4; HRMS (ES): Exact mass calcd for $C_{12}H_{13}O_4Br$ $[M+H]^+$, requires m/z: 301.0075, found m/z: 301.0074. Enantiomeric excess determined by HPLC with a Chiracel OD-H column, 5 % *i*PrOH/hexanes, 0.7 mL/min, 254 nm; t_r (major)=29.8, t_r (minor)=32.2), 91 % ee.



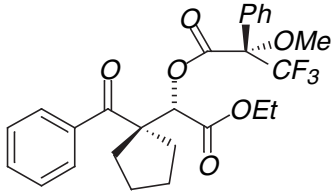
Mosher Ester Analysis for 6a: ^1H NMR (500 MHz, $CHCl_3$) δ 7.550-7.460 (m, 5H), 7.407-7.374 (m, 5H), 5.812 (s, 1H), 4.244 (q, 2H, *J*=6.84 Hz), 3.483 (d, 3H, *J*=1.0 Hz), 1.430 (s, 3H), 1.362 (s, 3H), 1.264 (t, 3H, *J*=6.8 Hz).



Mosher Ester Analysis for 6a: ^1H NMR (500 MHz, $CHCl_3$) δ (m, 2H), 7.461-7.436 (m, 3H), 7.406-7.331 (m, 5H), 5.823 (s, 1H), 4.304-4.202 (m, 2H), 3.628 (s, 3H, *J*=1.0 Hz), 1.381 (s, 3H), 1.330 (s, 3H), 1.267 (t, 3H, *J*=7.3).



Mosher Ester Analysis for 6d: ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.795-7.778 (m, 2H), 7.538-7.500 (m, 3H), 7.457-7.376 (m, 5H), 5.928 (s, 1H), 4.201-4.099 (m, 2H), 3.459 (s, 3H), 2.396-2.348 (m, 1H), 2.307-2.250 (m, 1H), 2.100-2.003 (m, 3H), 1.676-1.554 (m, 5H), 1.203 (t, 3H, *J*=7.3 Hz).



Mosher Ester Analysis for 6d: ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.715-7.699 (m, 2H), 7.627-7.611 (m, 2H), 7.517-7.488 (m, 1H), 7.435-7.378 (m, 5H), 5.869 (s, 1H), 4.222-4.158 (m, 1H), 4.148-4.083 (m, 1H), 3.628 (d, 3H, *J*=1.0 Hz), 2.338-2.286 (m, 1H), 2.184-2.126 (m, 1H), 1.956-1.863 (m, 2H), 1.604-1.475 (m, 3H), 1.388-1.313 (m, 1H), 1.203 (t, 3H, *J*=6.8 Hz).

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