C_2-Symmetric Cu(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective [2 + 2] Cycloadditions of Silyl Ketenes

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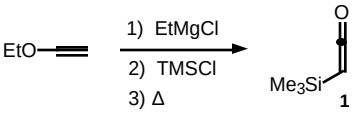
Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Solvents and reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] $CuCl_2$ and $AgSbF_6$ were purchased from the Cerac Chemical company, stored in an inert atmosphere dry box and used without further purification. 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 potassium permanganate solution followed by heating. Melting points were measured with a Büchi SMP-20 melting point apparatus equipped with an Omega Model 450 AET thermocouple and are uncorrected. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_\lambda^{T\ ^\circ C}$ (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 a Bruker AM-500 (500 MHz) or Varian Inova-500 (500 MHz) spectrometer and are reported in ppm using solvent ($CDCl_3$ at 7.26 ppm) as an internal standard. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sep = septuplet, m = multiplet; coupling constant(s) in Hz; integration; proton assignments). Ambiguous assignments were resolved on the basis of standard one dimensional proton decoupling experiments or two dimensional COSY and NOESY experiments. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AM-500 (125 MHz) or Varian Inova-500 (125 MHz) spectrometer 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. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Gas chromatography was performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split-mode capillary injection system and flame ionization detector using a DB 1701 capillary column (30 m x 0.25 mm). Gas chromatography with mass spectral detection was carried out on a Hewlett-Packard 5890 Series II Gas chromatograph equipped with a Hewlett-Packard 5971 Mass Selective Detector using a DB-1701 capillary column (30 m x 0.25 mm) employing chemical ionization with methane/helium gases. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series HPLC with a diode array detector or on a Hewlett-Packard 1050 Series HPLC equipped with a variable wavelength detector using the indicated chiral column.

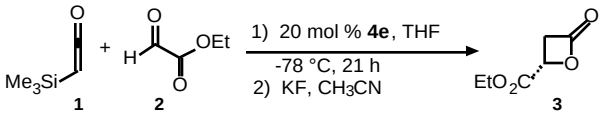


1

Preparation of (trimethylsilyl)ketene (1).[2] To a stirring solution of 25 g ethoxyacetylene[3] (50% weight solution in hexanes, 357 mmol) in THF (800 mL) at 0 °C was added 196 mL (2 M in THF, 393 mmol) of ethyl magnesium chloride. The solution was stirred for 3 h while warming to r.t. After evolution of ethane had ceased, 50 mL (393 mmol) of freshly distilled trimethylsilyl chloride was added. The reaction was stirred overnight (15 h) and then concenterated *in vacuo*. The magnesium salts were precipitated upon addition of pentanes and the resulting slurry was carefully decanted and then filtered through celite. The crude product was concentrated *in vacuo* and carefully distilled, yielding 28 g (55% yield) of clear, colorless trimethylsilylethoxyacetylene: bp 37-38 °C (8 torr); all spectral data matched literature values.[4]

Trimethylsilylethoxyacetylene was slowly distilled (120 °C bath temperature, 760 torr) to produce (trimethylsilyl)ketene (**1**). The crude product was further purified by a second distillation affording 21 g (92% yield) of pure (trimethylsilyl)ketene (**1**): bp 87-88 °C (760 torr); all spectral data matched literature values.[2]

Distillation procedure for ethyl glyoxalate (2): To an oven-dried 25 mL round bottom flask fitted with a magnetic stirring bar and a short path distillation apparatus was added 10 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 glyoxalate/toluene was collected (head temp 120–130°C). ^{1}H NMR indicates the distilled glyoxylate solution to be typically a 8:2 mixture of ethyl glyoxalate:toluene.



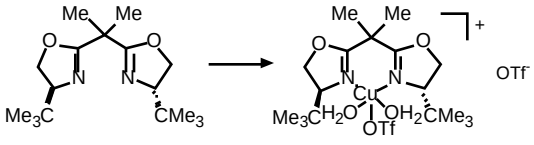
1 2 3

(2*S*)-4-Oxo-oxetane-2-carboxylic acid ethyl ester (3). A dry flask was charged with 7.4 mg (0.025 mmol) of (*S,S*)-*t*Bu-box and 7.2 mg of Cu(OTf)$_2$ (0.02 mmol) in an inert atmosphere (N_2) glove box.[5] The flask was brought out of the glove box and 2 mL of THF was added *via* syringe. The mixture was stirred for 1 h, cooled to -78 °C and treated with 12 µL (1 equiv., 0.1 mmol) of freshly distilled ethyl glyoxalate (**2**) followed by addition of 14 µL (1 equiv., 11 mg, 0.1 mmol) of (trimethylsilyl)ketene (**1**). After 21 h at -78 °C the reaction mixture was filtered through a plug of NH_4OH treated SiO_2 and concentrated *in vacuo*. ^{1}H NMR of the crude, silylated intermediate revealed a >95:5 *cis:trans* ratio (*cis* 4.95 ppm, *J* = 7.2 Hz; *trans* 4.57 ppm, *J* = 4.5 Hz).

To a rapidly stirring solution of the silylated intermediate in 1 mL of CH_3CN was added 12 mg (0.2 mmol) of KF. After 20 min at r.t., the solution was filtered through a plug of florisil and SiO_2. Concentration *in vacuo* provided 14 mg (99% yield) of pure **3** (if required, **3** may be purified by flash chromatography on silica gel eluted with 30% diethyl ether in hexanes). Analytical data for **3:** $[\alpha]_D^{25}$ = -8.3° (*c* 0.75, $CHCl_3$); IR (film) 3026, 1846, 1749, 1215, 759, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (1H, dd, *J* = 6.5, 4.5 Hz), 4.32 (1H, q, *J* = 7.1 Hz), 4.31 (1H, q, *J* = 7.1 Hz), 3.78 (1H, dd, *J* = 16.5, 6.5 Hz), 3.61 (1H, dd, *J* = 16.5, 4.5 Hz), 1.33 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 165.7, 65.3, 62.5, 43.5, 14.1; HRMS (EI): Exact mass calcd for $C_6H_8O_4$ $[M]^+$, 145.0501. Found 145.0506.

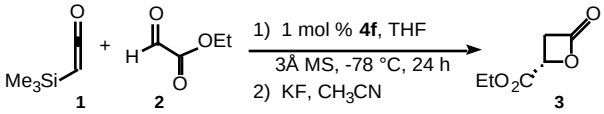
Assay of enantiomeric excess: GC (Cyclodex β, 80-95 °C, 0.5 °/min, 5 min initial, 25 psi; t_r (major) = 19.9, t_r (minor) = 20.4), 95% ee.

Absolute configuration: To a vigorously stirred solution of (2*S*)-4-oxetanone-2-carboxylic acid ethyl ester (**3**) (25 mg, 0.17 mmol) in MeOH (3 mL) was added K_2CO_3 (47 mg). After 10 min the resulting suspension was passed through a cotton plug with Et_2O (10 mL) and then washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL). The resulting ether layer was dried over anhydrous Na_2SO_4, filtered and concentrated to provide dimethyl malate as a colorless oil in 18% yield (5 mg, 0.14 mmol) after flash chromatography with 40% EtOAc in hexanes. This material exhibited spectral data and an optical rotation that was identical in all respects to (*S*)-Dimethyl Malate.[6]



4f

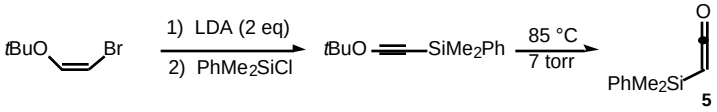
[Cu{(*S,S*)-*t*Bu-box}(H_2O)$_2$(OTf)][OTf] (4f). To an oven-dried round-bottom flask containing a magnetic stir bar was added, in an inert atmosphere glove box, 2,2-bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane ((*S,S*)-*t*Bu-box)[5] (162.8 mg, 0.554 mmol) and copper(II) trifluoromethanesulfonate (200.0 mg, 0.554 mg). The flask was fitted with a serum cap, removed from the glove box and charged with 20 mL of THF. The reaction was stirred under argon for 1h, affording a clear green solution to which was added distilled water (19.9 mg, 1.108 mmol). The resulting blue solution was concentrated *in vacuo* to afford a blue solid. Hexane (5 mL) was added and the solvent was removed *in vacuo* to afford the product as a light blue powder (372 mg, 0.538 mmol, 97% yield). Anal. Calcd for $C_{19}H_{34}CuF_6N_2O_{10}S_2$: C, 32.97; H, 4.95; N, 4.05. Found: C, 33.22; H, 5.03; N, 3.95.



(2*S*)-4-Oxo-oxetane-2-carboxylic acid ethyl ester (3). A dry flask was charged with 6.7 mg (0.01 mmol) of [Cu{(*S,S*)-*t*Bu-box}(H_2O)$_2$(OTf)][OTf] (**4f**) and 8 mg of powdered 3 Å molecular sieves (dried at 300 °C for 24 h). The flask was fitted with a septum and 10 mL of THF was added *via* syringe. The mixture was stirred for 30 min, cooled to -78 °C and treated with 128 µL (1 equiv., 1.0 mmol) of freshly distilled ethyl glyoxalate (**2**) followed by addition of 155 µL (1.1 equiv., 126 mg, 1.10 mmol) of (trimethylsilyl)ketene (**1**). After 48 h at -78 °C the reaction mixture was filtered through a plug of SiO_2 and concentrated *in vacuo*. To the silylated intermediate in 1 mL of CH_3CN was added 120 mg (1.0 equiv., 2.0 mmol) of KF. After 20 min at r.t., the solution was filtered through a plug of florisil and SiO_2. Concentration *in vacuo* provided 111 mg (77% yield) of pure **3** (if required, **3** may be purified by flash chromatography on silica gel eluted with 30% diethyl ether in hexanes). Analytical data for **3:** see above.

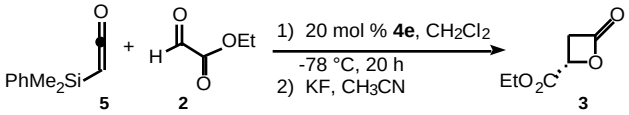
Assay of enantiomeric excess: GC (Cyclodex β, 80-95 °C, 0.5 °/min, 5 min initial, 25 psi; t_r (major) = 19.9, t_r (minor) = 20.4), 93% ee.

Absolute configuration: see above



(Dimethylphenylsilyl)ketene (5).[7] To a flame dried flask containing a magnetic stir bar and 100 mL of THF was added 17.4 mL (124 mmol) of diisopropylamine followed by dropwise addition of 49.5 mL of *n*BuLi (2.22 M, 110 mmol). The resulting lithium diisopropylamide solution was then cooled to -60 °C and 8.95 g (50 mmol) of (Z)-1-bromo-2-*tert*-butoxyethene[8] in 20 mL of THF was slowly added *via* cannula. The reaction was allowed to warm to r.t. over 2 h, after which it was cooled to -20 °C and 10.1 mL (60 mmol) of chlorodimethylphenyl silane was added. The reaction was stirred overnight (21 h) at r.t. and then poured into 100 mL of sat. $NaHCO_3$. The organic layer was seperated and the aqueous layer was washed with 50 mL of pet. ether. The combined organic extracts were washed with 0.5 N HCl (2 x 100 mL), water (150 mL), and sat. NaCl (150 mL). The organic layer was then dried with Na_2SO_4 and concentrated *in vacuo* . The crude product was filtered through a short plug of SiO_2 with pet. ether and concentrated *in vacuo* to give 7.34 g (63%) of the crude acetylene.

The crude product (7.34 g) was heated to 85 °C at 7 torr and (dimethylphenylsilyl)ketene (**5**) slowly distilled over. The crude ketene **5** was further purified by a second distillation affording 1.55 g (28% yield) of pure (dimethylphenylsilyl)ketene (**5**): bp 53-56 °C (2 torr); all spectral data matched literature values.[9]

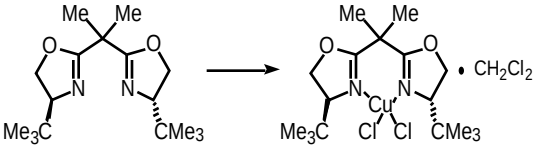


(2*S*)-4-Oxo-oxetane-2-carboxylic acid ethyl ester (3). A dry flask was charged with 7.4 mg (0.025 mmol) of (*S,S*)-*t*Bu-box and 7.2 mg of Cu(OTf)$_2$ (0.02 mmol) in an inert atmosphere (N_2) glove box. The flask was brought out of the glove box and 2 mL of THF was added *via* syringe. The mixture was stirred for 1 h, cooled to -78 °C and treated with 12 µL (0.1 mmol) of freshly distilled ethyl glyoxalate (**2**) followed by addition of 18 µL (18 mg, 0.1 mmol) of (dimethylphenylsilyl)ketene (**5**). After 20 h at -78 °C the reaction mixture was filtered through a plug of NH_4OH treated SiO_2 and concentrated *in vacuo*. ^{1}H NMR of the crude, silylated intermediate (**6**) revealed a >95:5 *cis:trans* ratio (*cis* 4.91 ppm, *J* = 7.2 Hz; *trans* 4.55 ppm, *J* = 4.5 Hz).

To a rapidly stirring solution of the silylated intermediate in 1 mL of CH_3CN was added 12 mg (0.2 mmol) of KF. After 20 min at r.t., the solution was filtered through a plug of florisil and SiO_2. Concentration *in vacuo* provided 14 mg (>99% yield) of pure **3** (if required, **3** may be purified by flash chromatography on silica gel eluted with 30% diethyl ether in hexanes). Analytical data for **3:** see above.

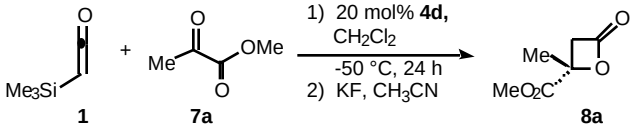
Assay of enantiomeric excess: GC (Cyclodex β, 80-95 °C, 0.5 °/min, 5 min initial, 25 psi; t_r (major) = 19.9, t_r (minor) = 20.4), 92% ee.

Absolute configuration: see above.



[Cu{(*S,S*)-*t*Bu-box}]Cl_2•CH_2Cl_2.[5,10] A round-bottom flask with a magnetic stirrer was charged with 2,2-bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane ((*S,S*)-*t*Bu-box), 1.472 g, 5.0 mmol, 1.0 equiv) and $CuCl_2$ (0.672 g, 5.0 mmol, 1.0 equiv). Methylene chloride (20 mL) was added *via* syringe and the reaction stirred 20 h, until the insoluble $CuCl_2$ had solubilized. The green solution was transfered *via* cannula under nitrogen to a syringe fitted with a 0.45 μ filter, and into a Schlenk flask. The solvent was removed *in vacuo* to deliver 2.52 g (99%) of a light green powder: mp >180 °C; $[\alpha]_D^{25}$ = -251° (*c* 1.06, CH_2Cl_2); IR (CH_2Cl_2) 2968, 1655, 1484, 1371, 1239, 1135, 947 cm^{-1}. Anal. Calcd for $C_{18}H_{32}Cl_4CuN_2O_2$: C, 42.08; H, 6.28; N, 5.45. Found: C, 42.21; H, 6.24; N, 5.51.

General Procedure (A) for the catalyzed reaction of (trimethylsilyl)ketene and α-keto esters (7a-f) and diones (9, 11) with complex 4d. A dry flask was charged with [Cu{(*S,S*)-*t*Bu-box}]Cl_2•CH_2Cl_2 complex (0.2 equiv.) and $AgSbF_6$ (0.44 equiv.) in an inert atmosphere (N_2) glove box. The flask was brought out of the glove box, wrapped in foil and CH_2Cl_2 was added *via* syringe to form a 0.02 M solution. After stirring for 1 h at r.t., the resulting green suspension was transfered to a syringe. The needle of the syringe was replaced with a 0.45 μ syringe filter and disposable needle. The suspension was then filtered into a dry flask with a stir bar and enough CH_2Cl_2 to form a 0.01 M solution of catalyst **4d**. The resulting pale green solution was cooled to the indicated temperature and 1.0 equiv. of chelating substrate was added followed by 1.2 equiv. of (trimethylsilyl)ketene. After the indicated time, the reaction mixture was filtered through a plug of SiO_2 with diethyl ether and concentrated *in vacuo*. The residue was then dissolved in 1 mL of CH_3CN and 2 eq of KF was added. After strring 20 min at r.t., the solution was filtered through a plug of florisil and SiO_2. Concentration *in vacuo* provided substituted β-lactones **8a-f, 10, and 12** (if required, **8a-f, 10, and 12** may be purified by flash chromatography on silica gel eluted with 30% diethyl ether in hexanes).

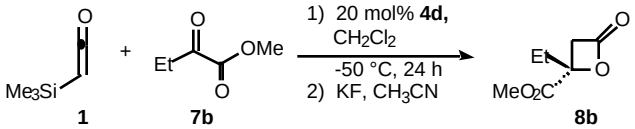


1 **7a** **8a**

(2*S*)-2-Methyl-4-oxo-oxetane-2-carboxylic acid methyl ester (8a). According to general procedure A, 2 mL of a 0.01 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 9 μL (10 mg, 0.10 mmol) of methyl pyruvate (**7a**) and 14 μL (11 mg, 0.10 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A to afford 14 mg (0.1 mmol, >99%) of the title compound as a clear, colorless oil. Analytical data for **8a**: $[\alpha]_D^{25}$ = -11.7° (*c* 1.1, $CHCl_3$); IR (film) 3026, 1841, 1744, 1210, 1041, 754, 662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84 (3H, s), 3.74 (1H, d, *J* = 16.3 Hz), 3.36 (1H, d, *J* = 16.3 Hz), 1.82 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 165.7, 73.9, 53.3, 48.3, 22.0; HRMS (CI, NH_3): Exact mass calcd for $C_6H_8O_4$ $[M + NH_4]^+$, 162.0766. Found 162.0763.

Assay of enantiomeric excess: GC (Cyclodex β, 70-95 °C, 0.5 °/min, 5 min initial, 20 psi; t_r (major) = 21.8, t_r (minor) = 22.5), 95% ee.

Absolute configuration: The absolute configuration of **8a** was assigned by analogy to **3**.



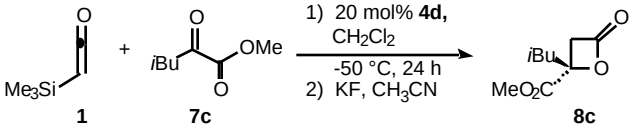
1 **7b** **8b**

(2*S*)-2-Ethyl-4-oxo-oxetane-2-carboxylic acid methyl ester (8b). According to general procedure A, 3 mL of a 0.013 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 22 μL (23 mg, 0.20 mmol) of α-keto ester **7b** and 35 μL (29 mg, 0.25 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A and purified by flash chromatography on silica gel eluted with 30% diethyl ether in hexanes to afford 29 mg (0.18 mmol, 92%) of the title compound as a clear, colorless oil. Analytical data for **8b**: $[\alpha]_D^{25}$ = -10.3° (*c* 1.1, $CHCl_3$); IR (film) 2960, 1838, 1747, 1440, 1256, 1171, 1137, 899, 811, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.84 (3H, s), 3.65 (1H, d, *J* = 16.6 Hz), 2.18 (1H, dq, *J* =

14.6, 7.3 Hz), 2.07 (1H, dq, *J* = 14.6, 7.3 Hz), 1.02 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 166.0, 77.1, 53.1, 46.1, 28.7, 7.8; HRMS (CI, NH_3): Exact mass calcd for $C_7H_{10}O_4$ $[M + NH_4]^+$, 176.0923. Found 176.0928.

Assay of enantiomeric excess: GC (Cyclodex β, 70-95 °C, 0.5 °/min, 5 min initial, 20 psi; t_r (major) = 33.0, t_r (minor) = 33.7), >99% ee.

Absolute configuration: The absolute configuration of **8b** was assigned by analogy to **3**.

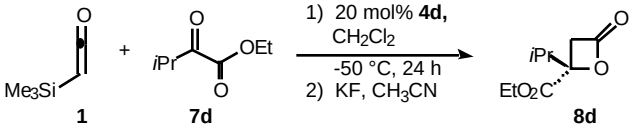


1 **7c** **8c**

(2*S*)-2-Isobutyl-4-oxo-oxetane-2-carboxylic acid methyl ester (8c). According to general procedure A, 4 mL of a 0.015 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 43 μL (43 mg, 0.30 mmol) of α-keto ester **7c** and 49 μL (40 mg, 0.35 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A to afford 49 mg (0.26 mmol, 87%) of the title compound as a clear, colorless oil. Analytical data for **8c**: $[\alpha]_D^{25}$ = -13.9° (*c* 1.8, $CHCl_3$); IR (film) 2961, 1844, 1747, 1240, 1217, 1173, 1109, 823, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (3H, s), 3.71 (1H, d, *J* = 16.6 Hz), 3.37 (1H, d, *J* = 16.1 Hz), 2.08 (1H, dd, *J* = 14.4, 7.1 Hz), 1.98 (1H, dd, *J* = 14.2, 6.8 Hz), 1.77 (1H, ddq, *J* = 6.8, 6.8, 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 166.1, 76.8, 53.2, 48.0, 44.3, 25.2, 23.0, 22.9; HRMS (CI, NH_3): Exact mass calcd for $C_9H_{14}O_4$ $[M + NH_4]^+$, 204.1236. Found 204.1228.

Assay of enantiomeric excess: HPLC analysis (Chiracel OD-H, 10% *i*PrOH/hexanes, 0.7 mL/min, 215 nm; t_r (minor) = 8.7, t_r (major) = 12.5), 83% ee.

Absolute configuration: The absolute configuration of **8c** was assigned by analogy to **3**.

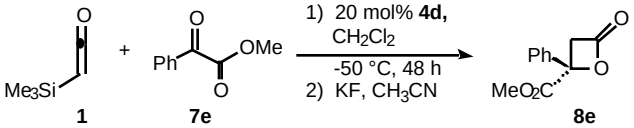


1 **7d** **8d**

(2*S*)-2-Isopropyl-4-oxo-oxetane-2-carboxylic acid ethyl ester (8d). According to general procedure A, 5 mL of a 0.016 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 58 μL (58 mg, 0.40 mmol) of α-keto ester **7d** and 63 μL (51 mg, 0.45 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A to afford 64 mg (0.34 mmol, 86%) of the title compound as a clear, colorless oil. Analytical data for **8d**: $[\alpha]_D^{25}$ = +2.8° (*c* 1.5, $CHCl_3$); IR (film) 2976, 1843, 1739, 1282, 1217, 1182, 1140, 954, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24-4.35 (2H, m), 3.59 (1H, d, *J* = 16.6 Hz), 3.40 (1H, d, *J* = 16.6 Hz), 2.40 (1H, heptet, *J* = 6.8 Hz), 1.32 (3H, t, *J* = 6.8 Hz), 1.06 (3H, d, *J* = 6.8 Hz), 1.04 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 166.4, 79.6, 62.3, 43.7, 32.7, 16.4, 16.1, 14.1.

Assay of enantiomeric excess: GC (Cyclodex β, 90-140 °C, 0.5 °/min, 5 min initial, 20 psi; t_r (major) = 24.4, t_r (minor) = 25.1), 85% ee.

Absolute configuration: The absolute configuration of **8d** was assigned by analogy to **3**.

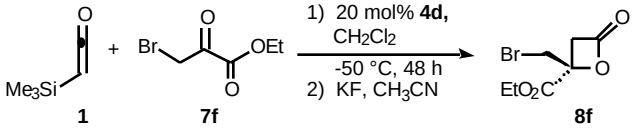


1 **7e** **8e**

(2*S*)-2-Phenyl-4-oxo-oxetane-2-carboxylic acid methyl ester (8e). According to general procedure A, 4 mL of a 0.015 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 49 μL (49 mg, 0.30 mmol) of α-keto ester **7e** and 49 μL (40 mg, 0.35 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A to afford 49 mg (0.24 mmol, 79%) of the title compound as a clear, colorless oil. Analytical data for **8e**: $[\alpha]_D^{25}$ = +59.5° (*c* 0.8, $CHCl_3$); IR (film) 3029, 2958, 1846, 1746, 1280, 1166, 1128, 750, 735, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.49 (5H, m), 4.19 (1H, d, *J* = 16.6 Hz), 3.82 (3H, s), 3.71 (1H, d, *J* = 16.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 165.4, 135.5, 129.3, 128.8, 125.5, 76.5, 53.6, 49.4; HRMS (EI): Exact mass calcd for $C_{11}H_{10}O_4$ $[M]^+$, 206.0579. Found 206.0580.

Assay of enantiomeric excess: HPLC analysis (Chiracel OD-H, 10% *i*PrOH/hexanes, 0.7 mL/min, 215 nm; t_r (minor) = 11.6, t_r (major) = 17.1), 87% ee.

Absolute configuration: The absolute configuration of **8e** was assigned by analogy to **3**.

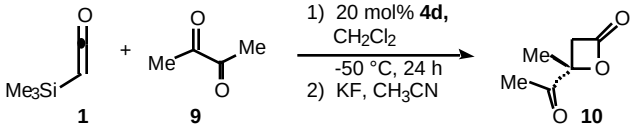


1 **7f** **8f**

(2*S*)-2-Bromomethyl-4-oxo-oxetane-2-carboxylic acid ethyl ester (8f). According to general procedure A, 4 mL of a 0.015 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 58 µL (58 mg, 0.30 mmol) of α-keto ester **7f** and 49 µL (40 mg, 0.35 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A to afford 71 mg (0.30 mmol, >99%) of the title compound as a clear, colorless oil. Analytical data for **8f**: $[\alpha]_D^{25}$ = +19.7° (*c* 1.7, $CHCl_3$); IR (film) 3027, 2985, 1847, 1745, 1319, 1228, 1201, 1133, 1054, 964, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.34 (2H, q, *J* = 7.3 Hz), 3.94 (1H, d, *J* = 11.2 Hz), 3.85 (1H, d, *J* = 16.6 Hz), 3.84 (1H, d, *J* = 11.2 Hz), 3.62 (1H, d, *J* = 16.6 Hz), 1.35 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 164.4, 74.0, 63.3, 46.5, 31.8, 14.0; HRMS (CI, NH_3): Exact mass calcd for $C_7H_9BrO_4$ $[M + NH_4]^+$, 254.0028. Found 254.0019.

Assay of enantiomeric excess: HPLC analysis (Chiracel OD-H, 10% *i*PrOH/hexanes, 0.7 mL/min, 215 nm; t_r (minor) = 13.4, t_r (major) = 15.8), 91% ee.

Absolute configuration: The absolute configuration of **8f** was assigned by analogy to **3**.

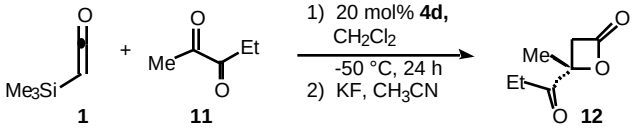


1 **9** **10**

(4*S*)-4-Acetal-4-methyl-oxetan-2-one(10). According to general procedure A, 4 mL of a 0.01 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 18 µL (17 mg, 0.20 mmol) of 2,3-butanedione **9** and 35 µL (29 mg, 0.25 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A to afford 24 mg (0.19 mmol, 95%) of the title compound as a clear, colorless oil. Analytical data for **10**: $[\alpha]_D^{25}$ = -42.9° (*c* 1.4, $CHCl_3$); IR (film) 3025, 1836, 1724, 1217, 1160, 1045, 838, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.59 (1H, d, *J* = 16.6 Hz), 3.30 (1H, d, *J* = 17.1 Hz), 2.34 (3H, s), 1.72 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 166.1, 79.1, 46.8, 24.8, 21.4; HRMS (CI, NH_3): Exact mass calcd for $C_6H_8O_3$ $[M + NH_4]^+$, 146.0817. Found 146.0811.

Assay of enantiomeric excess: GC (Cyclodex β, 60-95 °C, 0.3 °/min, 5 min initial, 20 psi; t_r (major) = 17.8, t_r (minor) = 18.5), >99% ee.

Absolute configuration: The absolute configuration of **10** was assigned by analogy to **3**.



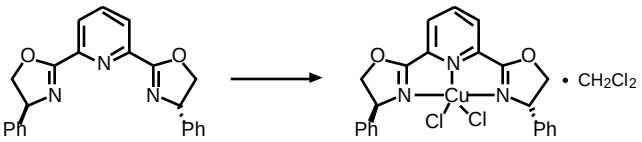
1 **11** **12**

(4*S*)-4-Methyl-4-propionyl-oxetan-2-one(12). According to general procedure A, 5 mL of a 0.016 M solution of catalyst **4d** (20 mol%) was treated at -50 °C with 42 µL (40 mg, 0.40 mmol) of 2,3-pentanedione **11** and 63 µL (51 mg, 0.45 mmol) of (trimethylsilyl)ketene (**1**). After 24 h, the reaction was worked up according to general procedure A to afford 54 mg (0.38 mmol, 95%) of the title compound as a clear, colorless oil. Analytical data for **12**: $[\alpha]_D^{25}$ = -55.4° (*c* 1.2, $CHCl_3$); IR (film) 2984, 1837, 1723, 1216, 1033, 850, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.56 (1H, d, *J* = 17.1 Hz), 3.31 (1H, d, *J* = 16.6 Hz), 2.65-2.79 (2H, m), 1.71 (3H, s), 1.10 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 166.2, 79.2, 47.2, 30.4, 21.9, 7.1; HRMS (CI, NH_3): Exact mass calcd for $C_7H_{10}O_3$ $[M + NH_4]^+$, 160.0974. Found 160.0967.

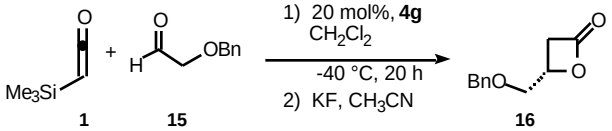
Assay of regioselectivity: ^1H NMR (500 MHz, methyl ketone **17** (major)**:** 1.71 ppm (3H, s); ethyl ketone (minor): 2.34 ppm (3H, s)), 95:5.

Assay of enantiomeric excess: HPLC analysis (Chiracel OD-H, 5% *i*PrOH/hexanes, 0.7 mL/min, 215 nm; t_r (major) = 15.4, t_r (minor) = 18.2), 85% ee.

Absolute configuration: The absolute configuration of **12** was assigned by analogy to **3**.

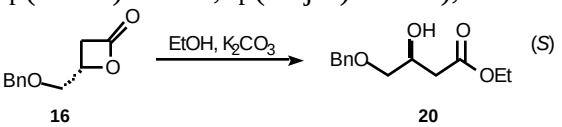


[Cu{(*S,S*)-Ph-pybox}]Cl_2•CH_2Cl_2.[11] Prepared in an analogous manner as [Cu{(*S,S*)-*t*Bu-box}]Cl_2•CH_2Cl_2.

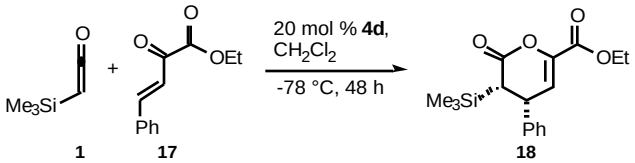


(4*S*)-4-Benzyloxymethyl-oxetan-2-one (16). A dry flask was charged with 20 mg (0.2 equiv., 0.04 mmol) of [Cu{(*S,S*)-Ph-pybox}]Cl_2•CH_2Cl_2 complex and 30 mg of $AgSbF_6$ (0.44 equiv., 0.088 mmol) in an inert atmosphere (N_2) glove box. The flask was brought out of the glove box, wrapped in foil and 2 mL of CH_2Cl_2 was added *via* syringe to form a 0.02 M solution. After stirring for 1 h at r.t., the resulting green suspension was transfered to a syringe. The needle of the syringe was replaced with a 0.45 µ syringe filter and disposable needle. The suspension was then filtered into a dry flask with a stir bar and 2 mL of CH_2Cl_2 to form a 0.01 M solution of catalyst **4d**. The resulting pale green solution was cooled to -40 °C and 28 µL (1.0 equiv., 30 mg, 0.2 mmol) of (benzyloxy)acetaldehyde (**15**) was added followed by 35 µL (1.2 equiv., 22 mg, 0.25 mmol) of (trimethylsilyl)ketene (**1**). After 20 h at -40 °C, the reaction mixture was filtered through a plug of SiO_2 and concentrated *in vacuo*. The residue was then dissolved in 1 mL of CH_3CN and 2 eq (~12 mg) of KF was added. After stirring 20 min at r.t., the solution was filtered through a plug of florisil and SiO_2. Concentration *in vacuo* affords 35 mg (0.18 mmol, 92%) of the title compound as a clear, colorless oil. Analytical data for **16**: $[\alpha]_D^{25}$ = +15.4° (*c* 1.2, $CHCl_3$); IR (film) 3015, 1831, 1215, 1113, 759, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.29 (5H, m), 4.67 (1H, m), 4.64 (1H, d, *J* = 12.0 Hz), 4.60 (1H, d, *J* = 12.0 Hz), 3.82 (1H, dd, *J* = 11.7, 3.1 Hz), 3.72 (1H, dd, *J* = 11.7, 4.4 Hz), 3.46 (1H, dd, *J* = 16.2, 5.9 Hz), 3.41 (1H, dd, *J* = 16.2, 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 137.4, 128.6, 128.0, 127.8, 73.7, 69.4, 69.3, 39.8; HRMS (EI): Exact mass calcd for $C_{11}H_{12}O_3$ $[M]^+$, 210.1130. Found 210.1136.

Assay of enantiomeric excess: HPLC analysis (Chiracel OD-H, 20% *i*PrOH/hexanes, 1 mL/min, 210 nm; t_r (minor) = 10.1, t_r (major) = 15.4), 87% ee.



Absolute configuration: To 30 mg (0.16 mmol) of **16** in 1 mL of dry EtOH was added ~10 mg of K_2CO_3 . The solution was stirred for 2 h at r.t. and then filtered through a cotton plug. The solution was then washed with 5 mL of sat. NH_4Cl (aq.) followed by 5 mL of sat. NaCl. The solution was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on SiO_2 eluted with 30% EtOAc in hexanes giving 8 mg (22%) of the known ethyl ester. Analytical data: all spectral data matched literature values.[11] $[\alpha]_D^{25}$ = -7.8° (*c* 0.4, CH_2Cl_2); $[\alpha]_D^{25}$ = -8.8° (*c* 2.1, CH_2Cl_2) lit.[11]value for (*S*) ethyl ester.

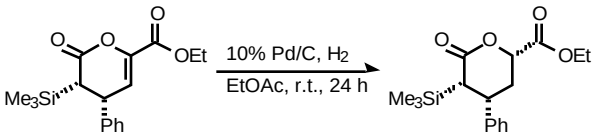


(4*R*, 5*S*)-6-Oxo-4-phenyl-5-(trimethyl-silanyl)-5,6-dihydro-4H-pyran-2-carboxylic acid ethyl ester (18). A dry flask was charged with 8.6 mg (0.2 equiv., 0.02 mmol) of [Cu{(*S,S*)-*t*Bu-box}]Cl_2•CH_2Cl_2 complex and 14 mg of $AgSbF_6$ (0.42 equiv., 0.042 mmol) in an inert atmosphere (N_2) glove box. The flask was brought out of the glove box, wrapped in foil and 1 mL of CH_2Cl_2 was added *via* syringe to form a 0.02 M solution. After stirring for 1 h at r.t., the resulting green suspension was transfered to a syringe. The needle of the syringe was replaced with a 0.45 µ syringe filter and disposable needle. The suspension was then filtered into a dry flask with a stir bar and 2 mL of CH_2Cl_2 to form a 0.007 M solution of catalyst **4d**. The resulting pale green solution was cooled to -78 °C and 20 µL (1.0 equiv., 20 mg, 0.1 mmol) of **17** was added followed by 21 µL (1.5 equiv., 17 mg, 0.15 mmol) of (trimethylsilyl)ketene (**1**). After 48 h at -78 °C, the reaction mixture

was filtered through a plug of NH_4OH treated SiO_2. Concentration *in vacuo* affords 30 mg (0.096 mmol, 96%) of the title compound as an amorphous yellow solid. Analytical data for **18**: $[\alpha]_D^{25}$ = +134.8° (*c* 0.4, $CHCl_3$); IR (film) 3026, 2964, 1733, 1656, 1313, 1251, 1215, 1097, 846, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18-7.36 (5H, m), 6.81 (1H, d, *J* = 5.4 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 4.05 (1H, dd, *J* = 7.3, 5.4 Hz), 2.52 (1H, d, *J* = 6.8 Hz), 1.35 (3H, t, *J* = 7.3 Hz), -0.15 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 142.8, 138.9, 129.2, 128.1, 127.9, 118.6, 74.3, 61.9, 39.4, 36.7, 14.2, -1.4; HRMS (EI): Exact mass calcd for $C_{17}H_{22}O_4Si$ $[M]^+$, 318.1288. Found 318.9792.

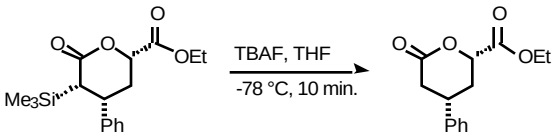
Assay of diastereoselectivity: ^1H NMR (500 MHz); no minor diastereomer detected.

Assay of enantiomeric excess: HPLC analysis (Chiracel OD-H, 7% *i*PrOH/hexanes, 0.7 mL/min, 210 nm; t_r (minor) = 13.1, t_r (major) = 18.4), 97% ee.



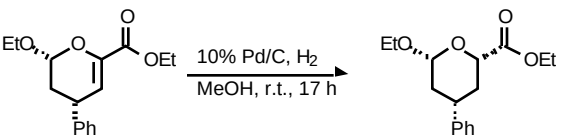
18

(2*S*, 4*S*, 5*S*)-6-Oxo-4-phenyl-5-(trimethyl-silanyl)-tetrahydro-pyran-2-carboxylic acid ethyl ester. A stirred mixture of 291 mg (0.91 mmol) of **18**, 97 mg of 10% Pd/C, and 10 mL of EtOAc was pressurized to 700 psi of H_2 in a Paar bomb. After 24 h, the bomb was slowly vented and the mixture filtered through a plug of SiO_2 and rinsed with copious amounts of EtOAc. The filtrate was concentrated *in vacuo* to give 280 mg (96%) of the title compound as a clear oil. ^1H NMR analysis revealed a single diastereomer with only trace impurities. 2D ^1H NMR analysis (NOESY and COSY) and observed NOE's confirmed the relative stereochemistry of the hydrogenated cycloadduct. If needed, the title compound may be purified by flash chromatography on silica gel eluted with 50% diethyl ether in hexanes. Analytical data: $[\alpha]_D^{25}$ = -21.7° (*c* 0.4, $CHCl_3$); IR (film) 3056, 2960, 1734, 1266, 1193, 1113, 847, 739, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (5H, m), 4.92 (1H, dd, *J* = 11.7, 4.4 Hz), 4.33-4.24 (2H, m), 3.68 (1H, ddd, *J* = 10.9, 5.1, 5.1 Hz), 2.68 (1H, dd, *J* = 5.9, 1.5 Hz), 2.60 (1H, dddd, *J* = 13.5, 4.4, 4.4, 1.5 Hz), 2.29 (1H, ddd, *J* = 13.5, 11.7, 11.7 Hz), 1.33 (3H, t, *J* = 7.3 Hz), -0.16 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 169.2, 141.4, 128.9, 127.3, 127.1, 76.6, 61.9, 39.9, 38.1, 29.9, 14.2, -0.6; HRMS (CI, NH_3): Exact mass calcd for $C_{17}H_{24}O_4Si$ $[M + NH_4]^+$, 338.1788 Found 338.1781.



(2*S*, 4*S*)-6-Oxo-4-phenyl-tetrahydro-pyran-2-carboxylic acid ethyl ester. To a solution of the hydrogenated cycloadduct (182 mg, 0.57 mmol) at -78 °C in 10 mL of THF was added a 1M solution of tetrabutyl ammonium fluoride (TBAF) in THF (620 µL, 0.62 mmol). After 10 min. at -78 °C, the reaction was diluted with 10 mL of diethyl ether and washed with sat. aq. $NaHCO_3$ (2 x 10 mL). The organic layer was separated and the aqueous extracts was extracted with diethyl ether (10 mL). The combined organics were washed with sat. aq. NaCl (20 mL), dried with Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel eluted with 40% EtOAc in hexanes affords 76 mg (54%) of the title compound. Analytical data: This material exhibited spectral data and an optical rotation that was identical in all respects to the lactone prepared from the known (4*R*, 6*R*)-6-Ethoxy-4-phenyl-5,6-dihydro-4H-pyran-2-carboxylic acid ethyl ester (see below).

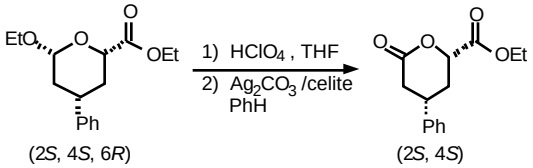
Absolute configuration:



(4*R*, 6*R*) (2*S*, 4*S*, 6*R*)

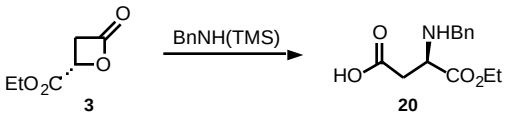
(4*R*, 6*R*)-6-Ethoxy-4-phenyl-tetrahydro-pyran-2-carboxylic acid ethyl ester. A stirred mixture of 829 mg (3.0 mmol) of the known hetero Diels-Alder cycloadduct,[12] 320 mg of 10% Pd/C, and 12 mL of MeOH was stirred for 17 h at r.t. under a balloon of H_2. The mixture was filtered through a plug of SiO_2 and rinsed with

copious amounts of EtOAc. The filtrate was concentrated *in vacuo* to give 835 mg (>99%) of the title compound as a clear oil. ^{1}H NMR (500 MHz) analysis revealed a >95:5 diastereomic ratio (minor: 4.88 ppm; major: 4.61 ppm) with only trace impurities. If needed, the title compound may be purified by flash chromatography on silica gel eluted with 15% diethyl ether in hexanes. Analytical data: $[\alpha]_D^{25}$ = -37.2° (*c* 1.2, $CHCl_3$); IR (film) 2981, 2929, 1750, 1380, 1266, 1155, 1112, 1068, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.20 (5H, m), 4.61 (1H, dd, *J* = 9.3, 2.0 Hz), 4.23 (2H, q, *J* = 6.8 Hz), 4.19 (1H, dd, *J* = 11.7, 2.4 Hz), 4.06 (1H, dq, *J* = 9.3, 6.8 Hz), 3.59 (1H, dq, *J* = 9.3, 6.8 Hz), 2.91 (1H, dddd, *J* = 12.7, 12.7, 3.9, 3.9 Hz), 2.13 (1H, dddd, *J* = 13.2, 3.9, 3.9, 2.0 Hz), 2.04 (1H, ddd, *J* = 12.7, 2.0, 2.0 Hz), 1.75 (1H, ddd, *J* = 12.7, 12.7, 9.3 Hz), 1.70 (1H, ddd, *J* = 12.7, 12.7, 12.7 Hz), 1.28 (3H, t, *J* = 6.8 Hz), 1.26 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 143.7, 128.7, 126.8, 101.9, 74.4, 74.2, 64.5, 61.1, 40.3, 37.7, 35.9, 15.1, 14.1; HRMS (CI, NH_3): Exact mass calcd for $C_{16}H_{22}O_4$ $[M + NH_4]^+$, 296.1862. Found 296.1852.



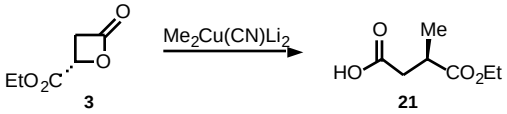
(2*S*, 4*S*, 6*R*) (2*S*, 4*S*)

(2*S*, 4*S*)-6-Oxo-4-phenyl-tetrahydro-pyran-2-carboxylic acid ethyl ester.[13] A dry flask fitted with a reflux condenser was charged with 88 mg (0.32 mmol) of the hydrogenated acetal in 5 mL of THF followed by addition of a 10% aqueous solution of $HClO_4$ (1.3 mL). The reaction was heated to reflux for 1.5 h, cooled, and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (10 mL), sat. aq. NaCl (10 mL), and dried with Na_2SO_4. Concentration *in vacuo* afforded the crude product as a clear oil. A dry flask fitted with a reflux condenser was charged with 2 g of Ag_2CO_3 on celite followed by the crude product dissolved in 20 mL of benzene. The mixture was heated to reflux for 1 h, cooled, and filtered through a pad of celite with copious amounts of CH_2Cl_2, and concentrated *in vacuo* to afford 10.3 mg (13%) of the desired lactone product. Analytical data: $[\alpha]_D^{25}$ = +7.0° (*c* 0.4, $CHCl_3$); IR (in $CHCl_3$) 3026, 2929, 1740 (br.), 1375, 1227, 1195, 1095, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.18 (5H, m), 4.96 (1H, dd, *J* = 11.2, 3.9 Hz), 4.26 (2H, q, *J* = 6.8 Hz), 3.25 (1H, dddd, *J* = 12.2, 12.2, 4.4, 4.4 Hz), 2.94 (1H, ddd, *J* = 17.6, 5.4, 2.0 Hz), 2.63 (1H, dd, *J* = 17.6, 12.2 Hz), 2.50 (1H, dddd, *J* = 13.7, 3.9, 3.9, 2.0 Hz), 2.07 (1H, ddd, *J* = 13.7, 12.2, 12.2 Hz), 1.31 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 141.7, 129.1, 127.6, 126.4, 76.9, 62.1, 37.4, 37.2, 33.1, 14.2; HRMS (CI, NH_3): Exact mass calcd for $C_{14}H_{16}O_4$ $[M + NH_4]^+$, 266.1393. Found 266.1398.



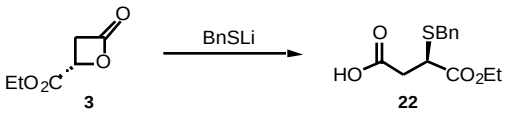
3 **20**

(2*R*)-2-Benzylamino-succinic acid 1-ethyl ester (20). To a solution of 194 mg (1.08 mmol) of *N*-benzyl-*N*-(trimethylsilyl)amine[14] in CH_3CN (4 mL) at 0 °C was added 133 mg (0.92 mmol) of **3** in 3 mL of CH_3CN. The reaction was stirred at room temperature for 24 h, cooled to 0 °C, and 20 mL of 0.1 M HCL was added. The mixture was then stirred at room temperature for 30 min. and then extracted. The aqueous phase was washed with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were concentrated *in vacuo* to afford 225 mg (97%) of **20**. If needed, the title compound may be purified by flash chromatography on silica gel eluted with 20% MeOH in CH_2Cl_2. Analytical data: $[\alpha]_D^{25}$ = +35.6° (*c* 1.04, $CHCl_3$); IR (in CH_2Cl_2) 3054, 2985, 2636, 1750, 1582, 1417, 1272, 1096, 1054, 1016, 706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (1H, br, s), 7.52 (2H, d, *J* = 5.9 Hz), 7.41-7.35 (3H, m), 4.33 (2H, br, m), 4.22 (2H, q, *J* = 6.8 Hz), 3.76 (1H, br, s), 3.13 (1H, br, d, *J* = 16.6 Hz), 2.96 (1H, br, d, *J* = 17.0 Hz), 1.27 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 168.4, 131.0, 130.5, 129.4, 129.2, 62.7, 54.6, 50.5, 35.4, 14.0; HRMS (CI, H^+): Exact mass calcd for $C_{13}H_{17}NO_4$ $[M + H]^+$, 252.1236. Found 252.1228.



3 **21**

(2*R*)-2-Methyl-succinic acid 1-ethyl ester (21). To a dry flask with a magnetic stir bar was added 112 mg CuCN (1.25 mmol). The flask was evacuated and flushed with nitrogen three times. Dry THF (6 mL) was then added and the mixture was cooled to -78 °C followed by addition of 1.3 mL of MeLi (1.6 M in diethyl ether, 2.05 mmol). The reaction was warmed until a homogeneous solution formed (-20 °C). The solution was then cooled to -78 °C and 100 mg (0.694 mmol) of **3** dissolved in 4 mL of THF was added over 5 min. After stirring at -78 °C for 1 h and at -45 °C for 30 min., 21 mL (15 eq) of degassed 0.5 M HCl was added at 0 °C, followed by 8 mL of MeOH. The mixture was stirred at 0 °C for 20 min. and then the salts were filtered and washed with 30 mL of diethyl ether. The organic phase was separated and the aqueous phase was washed with diethyl ether (3 x 30 mL). The combined organic layers were then washed with sat. NaCl (aq., 50 mL), sat. EDTA (pH = 3, 50 mL), and sat. NaCl (aq., 50 mL). The solution was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The title compound was then purified by flash chromatography on silica gel eluted with 50% EtOAc in hexanes to afford 92 mg (83%) of **21**. Analytical data: all spectral data matched literature values.[15] $[\alpha]_D^{25}$ = +5.7° (*c* 1.1, $CHCl_3$); $[\alpha]_D^{25}$ = -5.1° (*c* 1.1, $CHCl_3$) lit.[15a] value for (*S*) **21**.



3 **22**

(2*R*)-2-Benzylsulfide-succinic acid 1-ethyl ester (22). In a dry flask with a magnetic stir bar and 620 µL of THF at 0 °C was added 317 µL (2.41 M in hexanes, 0.763 mmol) of *n*-BuLi, followed by 90 µL (0.763 mmol). To this solution was then added 100 mg (0.694 mmol) of **3** dissolved in 620 µL of CH_3CN. The reaction was stirred at 0 °C for 1 h, followed by addition of 1 M HCl (2 mL). The organic phase was separated and the aqueous washed with CH_2Cl_2 (3 x 2 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The title compound was then purified by flash chromatography on silica gel eluted with 40% EtOAc in hexanes to afford 158 mg (85%) of **22**. Analytical data: $[\alpha]_D^{25}$ = +8.3° (*c* 1.39, $CHCl_3$); IR (film) 3054, 2984, 2933, 1731, 1714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.26 (1H, br, s), 7.37-7.29 (4H, m), 7.29-7.23 (1H, m), 4.20 (2H, dq, *J* = 6.8, 2.9 Hz), 3.91 (1H, d, *J* = 13.7 Hz), 3.84 (1H, d, *J* = 13.2 Hz), 3.53 (1H, dd, *J* = 10.3, 5.4 Hz), 2.99 (1H, dd, *J* = 17.6, 10.3 Hz), 2.62 (1H, dd, *J* = 17.6, 5.4 Hz), 1.29 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 171.5, 137.0, 129.1, 128.6, 127.5, 61.6, 40.5, 36.1, 36.0, 14.1; HRMS (EI): Exact mass calcd for $C_{13}H_{16}O_4S$ $[M]^+$, 268.0769. Found 268.0766.

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