Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction

Mark S. Kerr and Tomislav Rovis*

*Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523*

Supporting Information

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, or KMnO₄ followed by heating.

KHMDS was purchased from Aldrich Chemical Co. as a 0.5 M solution in toluene and used without purification. Racemic material was prepared by the method of Ciganek.¹

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ¹H NMR and spectra were recorded on a Varian 300 or 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ , ppm) from an internal standard (tetramethylsilane [TMS] or deuterated chloroform [CDCl₃]), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), integration, and coupling constant (Hz). ¹³C NMR were recorded on a Varian 75 or 100 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from (CDCl₃) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using a Chiracel OD-H, AD, or OB-H (0.46 cm X 25 cm) chiral column. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chiraldex B-DM or Chiraldex B-PH capillary gas chromatography column. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell.

General procedure for the asymmetric intramolecular Stetter reaction of aromatic substrates: A flame-dried round bottom flask was charged with triazolium salt (0.02

¹ Ciganek, E. *Synthesis* **1995**, 1311.

mmol, 0.2 eq) and evacuated for 5 minutes, then covered with argon. Substrate (0.1 mmol, 1 eq) was added in toluene (1 mL) via syringe, followed by addition of triethylamine (0.2 mmol, 2 eq to substrate) via syringe and the solution was stirred at ambient temperature under argon for 24 hours. The reaction was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes, to afford analytically pure product.

General procedure for the asymmetric intramolecular Stetter reaction of aliphatic substrates: A flame-dried round bottom flask was charged with triazolium salt (0.02 mmol, 0.2 eq) and toluene (1 mL) under argon. To this solution was added KHMDS (0.5M in toluene) (0.02 mmol, 0.2 eq) via syringe and the solution was stirred at ambient temperature for 5 minutes. Substrate (0.01 mmol, 1 eq) was added in toluene (1 mL) via syringe and allowed to stir for 24 h at ambient temperature. The reaction was then poured onto a column of silica gel and eluted with a suitable solution of ethyl acetate in hexanes, to afford analytically pure product.

(R)-(2-Ethyl-3-oxo-2,3-dihydro-benzofuran-2-yl)-acetic acid methyl ester (6):

According to the general procedure, aldehyde **4** (24.0 mg, 0.10 mmol) in toluene (1 mL) was added to catalyst **5c** (9.0 mg, 0.02 mmol) followed by addition of triethylamine (0.029 mL, 0.20 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 23.0 mg (96%) of **6** as a clear oil: R_f (3:1 hexanes to ethyl acetate) = 0.24; $[\alpha]_D^{25} = -74^\circ$ (CH₂Cl₂); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 mL/min. Major enantiomer: 20.4 minutes, minor enantiomer: 32.6 minutes; ¹H NMR (300 MHz, CDCl₃) δ 7.69 (dd, 1H, *J* = 8.4, 1.5 Hz), 7.59 (ddd, 1H, *J* = 8.1, 7.1, 1.8 Hz), 7.05 - 7.10 (m, 2H), 3.51 (s, 3H), 3.02 (d, 1H, *J* = 16.0 Hz), 2.94 (d, 1H, *J* = 16.0 Hz), 1.89 (q, 2H, *J* = 7.3 Hz), 0.83 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 202.8, 171.8, 169.2, 137.9, 124.3, 122.0, 113.1, 89.2, 76.7, 52.1, 40.6, 30.0, 7.7; IR (NaCl, neat) 2974, 2962, 1721, 1614, 1464 cm⁻¹; HRMS (EI+) calcd for C₁₃H₁₄O₄, 234.0892. Found 234.0887.

(R)-(5-Bromo-2-ethyl-3-oxo-2,3-dihydro-benzofuran-2-yl)-acetic acid methyl ester (8):

According to the general procedure, aldehyde **7** (37.0 mg, 0.123 mmol) in toluene (1 mL) was added to catalyst **5c** (12.0 mg, 0.025 mmol) followed by addition of triethylamine 0.036 mL (0.25 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 34.0 mg (92%) of **8** as a clear oil: R_f (4:1 hexanes to ethyl acetate) = 0.38; $[\alpha]_D^{25} = -44^\circ$ (CH₂Cl₂); HPLC analysis - Chiracel OD-H column, 90:10 hexanes to isopropanol 1.0 mL/min. Major enantiomer: 9.0 minutes, minor enantiomer: 27.6 minutes; ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, 1H, *J* = 2.1 Hz), 7.63 (dd, 1H, *J* = 8.7, 2.1 Hz), 6.97 (d, 1H, *J* = 8.7 Hz), 3.50 (s, 3H), 3.01 (d, 1H, *J* = 16.6 Hz), 2.94 (d, 1H, *J* = 16.6 Hz), 1.83 (q, 2H, *J* = 7.5 Hz), 0.80 (t, 3H, *J* = 7.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 201.6, 170.5, 169.2, 140.4, 126.9, 123.9, 114.9, 114.5, 90.1, 52.1, 40.5, 30.0, 7.5; IR (NaCl, neat) 2973, 1726, 1608, 1464, 1272, 1171 cm⁻¹.

(R)-(2-Ethyl-3-oxo-2,3-dihydro-benzo[*b*]thiophen-2-yl)-acetic acid methyl ester (9):

According to the general procedure, aldehyde **9** (20.0 mg, 0.080 mmol) in toluene (1 mL) was added to catalyst **5c** (7.5 mg, 0.016 mmol) followed by addition of triethylamine (0.023 mL, 0.16 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 19.0 mg (95%) of **10** as a white crystalline solid: R_f (3:1 hexanes to ethyl acetate) = 0.26; $[\alpha]_D^{25} = +10^\circ$ (CHCl₃); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 0.5 ml/ min. Minor enantiomer: 19.1 minutes, major enantiomer: 33.7 minutes; ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, 1H, *J* = 7.7 Hz), 7.53 (dd, 1H, *J* = 7.3, 0 Hz), 7.38 (d, 1H, *J* = 7.7 Hz), 7.2 (dd, 1H, *J* = 7.3, 0 Hz), 3.57 (s, 3H), 3.07 (d, 1H, *J* = 16.9 Hz), 2.97 (d, 1H, *J* = 16.5 Hz), 1.94 (q, 2H, *J* = 7.3 Hz), 0.88 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 203.9, 170.5, 152.2, 135.8, 131.5, 126.8, 124.9, 124.2, 63.4, 52.0, 42.6, 34.3, 9.0; IR (NaCl, neat) 2964, 1730, 1701, 1594, 1429 cm⁻¹; HRMS (EI+) calcd for C₁₃H₁₄O₃S, 250.0664. Found 250.0653.

(R)-(2-Methyl-1-oxo-indan-2-yl)-acetic acid ethyl ester (12):

According to the general procedure, aldehyde **11** (20.0 mg, 0.085 mmol) in toluene (1 mL) was added to catalyst **5c** (8.0 mg, 0.017 mmol) followed by addition of triethylamine (0.025 mL, 0.17 mmol) and allowed to stir at ambient temperature for 24 hours. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 19.0 mg (95%) of **12** as a clear oil: $[\alpha]_D^{25} = +22^\circ$ (EtOH); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 7.2 minutes, Major enantiomer: 11.1 minutes. Spectral data matched literature description.²

(R)-3-(2-Oxo-propyl)-3-phenyl-chroman-4-one (14)

According to the general procedure, aldehyde **13** (20.0 mg, 0.071 mmol) in toluene (1 mL) was added to catalyst **5c** (3.5 mg, 0.007 mmol) followed by addition of triethylamine (0.010 mL, 0.070 mmol) and allowed to stir at ambient temperature for 12 hours. At this time, another aliquot of catalyst (3.5 mg, 0.007 mmol) was added with another 2 eq triethylamine (0.010 mL, 0.070 mmol) and allowed to stir for another 12 hours at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 11.0 mg (55%) of **14** as a colorless oil: R_f (2:1 hexanes to ethyl acetate) = 0.34; $[\alpha]_D^{25} = -88^\circ$ (CH₂Cl₂); HPLC analysis - Chiracel OD-H column, 95:5 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 14.3 minutes, major enantiomer: 19.5 minutes; ¹H NMR (300 MHz, CDCl₃) δ 7.90 (dd, 1H, *J* = 7.7, 1.3 Hz), 7.41 (d, 2H, *J* = 7.9 Hz), 7.36 (ddd, 1H, *J* = 8.7, 1.5, 0 Hz), 7.29 (dd, 2H, *J* = 7.3, 0 Hz), 7.21 (dd, 1H, *J* = 7.2, 0 Hz), 6.94 (dd, 1H, *J* = 7.2, 0 Hz), 6.83 (d, 1H, *J* = 8.3 Hz), 5.10 (d, 1H, *J* = 12.1 Hz), 4.99 (d, 1H, *J* = 12.0 Hz), 3.18 (d, 1H, *J* = 17.5 Hz), 2.99 (d, 1H, *J* = 17.5 Hz), 2.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 206.1, 193.2, 161.1, 136.7, 136.1, 129.1, 128.1, 128.0, 126.9, 121.5, 120.3, 117.8, 71.5, 51.7, 49.1, 31.3; IR (NaCl, neat) 2923, 1717, 1684, 1606, 1408, 1458 cm⁻¹; HRMS (FAB+) calcd for M+H, 281.1178. Found 281.1175.

² Iwaya, K.; Tamura, T.; Nakamura, M.; Hasegawa, E. *Tetrahedron Lett.* **2003**, *44*, 9317.

(S)-2-Methyl-2-(2-oxo-2-phenyl-ethyl)-cyclopentanone (16): According to the general procedure, catalyst **5c** (5.5 mg, 0.012 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.024 mL, 0.012 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **E-15** (13.0 mg, 0.060 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 11.0 mg (85%) of **16** as a white solid: Rf (3:1 hexanes to ethyl acetate) = 0.35; $[\alpha]_D^{25} = -4^\circ$ (CH₂Cl₂); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 9.8 minutes, Major enantiomer: 11.2 minutes; ¹H NMR (300 MHz, CDCl₃) δ 7.92 (d, 2H, *J* = 7.3 Hz), 7.55 (dd, 1H, *J* = 6.2, 0 Hz), 7.44 (dd, 2H, *J* = 7.7, 0 Hz), 3.36 (d, 1H, *J* = 20.0 Hz), 3.29 (d, 1H, *J* = 20.0 Hz), 2.68 (ddd, 1H, *J* = 18.7, 9.2, 1.5 Hz), 2.39 (dddd, 1H, *J* = 18.7, 6.6, 2.2, 2.2 Hz), 1.77 – 2.22 (m, 4H), 1.11 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 223.2, 198.0, 136.9, 133.4, 128.8, 128.1, 46.7, 46.1, 37.4, 35.1, 23.4, 19.2; IR (NaCl, neat) 2955, 1727, 1679, 1398, 1356 cm⁻¹; HRMS (EI+) calcd for C₁₄H₁₆O₂, 216.1150. Found 216.1147.

(S)-2-Methyl-2-(2-oxo-2-pyridin-4-yl-ethyl)-cyclopentanone (18): According to the general procedure, catalyst **5c** (8.5 mg, 0.018 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.036 mL, 0.018 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **17** (20.0 mg, 0.092 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (1:1 hexanes to ethyl acetate) provided 17.0 mg (85%) of **18** as a colorless oil: Rf (ethyl acetate) = 0.28; $[\alpha]_D^{25} = -0.8^\circ$ (CH₂Cl₂); HPLC analysis - Chiracel OB-H column, 90:10 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 25.0 minutes, major enantiomer: 28.1 minutes; ¹H NMR (300 MHz, CDCl₃) δ 8.80 (bs, 2H), 7.69 (bs, 2H), 3.32 (d, 1H, *J* = 18.7 Hz), 3.27 (d, 1H, *J* = 19.0 Hz), 2.54 – 2.68 (m, 1H), 2.40 (dddd, 1H, *J* = 18.3, 7.7, 0.0, 0.0 Hz), 1.77 – 2.20 (m, 4H), 1.11 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 222.6, 197.5, 151.1, 142.7, 121.1, 46.7, 46.1, 37.3, 34.9, 23.2, 19.1; IR (NaCl, neat) 2964, 1736, 1697, 1408, 1356, 1222 cm⁻¹; HRMS (Fab+) calcd for M+H, 218.1181. Found 218.1172.

(S)-2-Methyl-2[2-(4-nitro-phenyl)-2-oxo-ethyl]-cyclopentanone (20): According to the general procedure, catalyst **5c** (7.0 mg, 0.015 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.030 mL, 0.015 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **19** (20.0 mg, 0.077 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (4:1 hexanes to ethyl acetate) provided 18.0 mg (90%) of **20** as a yellow solid: Rf (2:1 hexanes to ethyl acetate) = 0.40; $[\alpha]_D^{25} = -17^\circ$ (CHCl₃); HPLC analysis - Chiracel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/ min. Minor enantiomer: 36.3 minutes, major enantiomer: 44.8 minutes; ¹H NMR (300 MHz, CDCl₃) δ 8.27 (d, 2H, *J* = 9.0 Hz), 8.05 (d, 2H, *J* = 8.4 Hz), 3.36 (d, 1H, *J* = 18.3 Hz), 3.30 (d, 1H, *J* = 18.3 Hz), 2.61 (ddd, 1H, *J* = 19.0, 10.9, 1.5 Hz), 2.40 (dddd *J* = 18.8, 8.3, 0, 0 Hz), 2.02 – 2.19 (m, 2H), 1.85 – 1.98 (m, 1H), 1.77 – 1.84 (m, 1H), 1.11 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 222.6,

196.1, 150.6, 141.3, 129.2, 124.1, 47.0, 46.2, 37.3, 34.9, 23.3, 19.1; IR (NaCl, neat) 3107, 2963, 1736, 1690, 1524, 1345 cm^{-1} ; HRMS (Fab+) calcd for $\text{M}+\text{H}$, 262.1079. Found 262.1068.

(S)-2-Methyl-2-(2-oxo-propyl)-cyclopentanone (22): According to the general procedure, catalyst **5c** (9.5 mg, 0.020 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.040 mL, 0.020 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **21** (16.0 mg, 0.10 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 13.0 mg (82%) of **22** as a colorless oil: $[\alpha]_{\text{D}}^{25} = +11^\circ$ (EtOH); Gas chromatography analysis-ChiralDEX B-DM column, gas flow 3ml/min with constant 110 °C oven temperature. Minor enantiomer: 12.9 min, major enantiomer: 14.5 minutes. Spectral data matched literature description.³

(S)-2-Methyl-2-(2-oxo-4-phenyl-butyl)-cyclopentanone (24): According to the general procedure, catalyst **5c** (6.0 mg, 0.013 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.026 mL, 0.013 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **23** (16.0 mg, 0.066 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (4:1 hexanes to ethyl acetate) provided 10.0 mg (63%) of the **24** as a colorless oil: R_f (3:1 hexanes to ethyl acetate) = 0.38; $[\alpha]_{\text{D}}^{25} = +22^\circ$ (CH_2Cl_2); HPLC analysis - ChiralDEX B-DM capillary gas chromatography column, 150 °C constant oven temperature, constant gas flow 3.0 ml/min. Minor enantiomer 119 minutes: major enantiomer: 125 minutes; ^1H NMR (300 MHz, CDCl_3) δ 7.27 (dd, 2H, $J = 6.6, 0$ Hz), 7.19 (d, 1H, $J = 7.4$ Hz), 7.19 (d, 2H, $J = 6.8$ Hz), 2.76 – 2.80 (m, 3H), 2.58 – 2.69 (m, 3H), 2.51 (ddd, 1H, $J = 18.3, 9.5, 1.8$ Hz), 2.33 (dddd, 1H, $J = 18.7, 7.3, 2.2, 2.2$ Hz), 1.65 – 2.10 (m, 4H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 223.0, 208.0, 141.0, 128.7, 128.5, 126.3, 50.7, 46.0, 44.6, 37.4, 35.0, 29.8, 23.1, 19.1; IR (NaCl, neat) 2961, 1736, 1713, 1454, 1072 cm^{-1} ; HRMS (EI+) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_2$, 244.1463. Found 244.1474.

(S)-2-Butyl-2-(2-oxo-2-phenyl-ethyl)-cyclopentanone (26): According to the general procedure, catalyst **5c** (5.0 mg, 0.011 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.022 mL, 0.011 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **25** (14.0 mg, 0.055 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 24 h at 25 °C. Flash column chromatography (6:1 hexanes to ethyl acetate) provided 10.0 mg (71%) of **26** as a colorless oil: R_f (4:1 hexanes to ethyl acetate) = 0.28; $[\alpha]_{\text{D}}^{25} = -30^\circ$ (CH_3CN); HPLC analysis - Chiralcel OD-H column, 97:3 hexanes to isopropanol 1.0 ml/min. Major enantiomer: 7.4 minutes, minor enantiomer: 9.2 minutes; ^1H NMR (300 MHz, CDCl_3) δ 7.92 (d, 2H, $J = 7.3$ Hz), 7.55 dd, (1H, $J = 7.3, 0$ Hz), 7.44

³ Thominiaux, C.; Roussé, S.; Desmaële, D.; d'Angelo, J.; Riche, C. *Tetrahedron: Asymmetry*. **1999**, *10*, 2015.

(dd, 2H, $J = 7.7, 0$ Hz), 3.37 (d, 1H, $J = 18.3$ Hz), 3.30 (d, 1H, $J = 18.0$ Hz), 2.70 (ddd, 1H, $J = 19.0, 9.5, 1.5$ Hz), 2.35 (dddd, 1H, $J = 18.7, 7.3, 2.2, 2.2$ Hz), 1.99 – 2.14 (m, 2H), 1.79 – 1.98 (m, 2H), 1.14 – 1.54 (m, 6H) 0.92 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 223.4, 198.2, 137.0, 133.4, 128.7, 128.2, 49.4, 45.3, 37.8, 36.4, 33.7, 26.7, 23.5, 19.1, 14.2; IR (NaCl, neat) 2957, 2929, 2858, 1734, 1685, 1158 cm^{-1} ; HRMS (EI+) calcd for $\text{C}_{17}\text{H}_{22}\text{O}_2$, 258.1620, Found 258.1611.

(S)-1-Methoxycarbonylmethyl-2-oxo-cyclopentanecarboxylic acid methyl ester (30):

According to the general procedure, catalyst **5c** (4.0 mg, 0.013 mmol) in toluene (1 mL) was treated with KHMDS (0.5M in toluene) (0.026 mL, 0.013 mmol) and allowed to stir at ambient temperature for 5 minutes. Aldehyde **29** (14.0 mg, 0.065 mmol) in toluene (1 mL) was added via syringe and the reaction was stirred for 12 h at 25°C. Flash column chromatography (4:1 hexanes to ethyl acetate) provided 12.0 mg (86%) of **30** as a colorless oil: $[\alpha]_{\text{D}}^{25} = -20^\circ$ (EtOH); Gas chromatography analysis – Chiraldex B-PH column with constant 110 °C oven temperature and constant flow of 1 ml/min. Major enantiomer: 169.3 minutes, minor enantiomer: 170.6 min. Spectral data matched literature description.⁴

⁴ Matsui, J.; Bando, M.; Kido, M.; Takeuchi, Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2183.