Advanced Synthesis & Catalysis

Supporting Information

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Guanidine-Thiourea Bifunctional Organocatalyst for the Asymmetric Henry (Nitroaldol) Reaction

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Supporting Information

General Remarks

Flash chromatography was performed using Silica gel 60 (spherical, particle size 0.040-0.100 mm; Kanto Co., Inc., Japan). Optical rotations were measured with a JASCO DIP polarimeter 370. IR spectra were measured with JASCO VALOR-III FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL ALPHA500 instrument. Mass spectra were recorded on JEOL JMA-HX110 spectrometer.

Spectral data for 1a-1g and 2-4

1a: $[\alpha]_D^{22}$ = -44.1° (*c* 1.50, CH_3OH). IR (KBr) 3218, 3066, 1631, 1547, 1473, 1385, 1279, 1178, 1133 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *d*?8.05 (s, 4H), 7.62 (s, 2H), 7.31-7.21 (m, 10H), 5.04 (br s, 2H), 3.64 (br s, 2H), 3.46 (br s, 2H), 3.26 (t, *J* = 7.2 Hz, 2H), 3.15 (dd, *J* = 14.5 Hz, 4.6 Hz, 2H), 2.90 (dd, *J* = 14.5 Hz, 10.0 Hz, 2H), 1.64 (m, 2H), 1.42 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) *d*?182.73, 156.39, 142.20, 138.50, 132.83 (J_{CF} = 33.1 Hz), 130.00, 129.71, 127.85, 124.57 (J_{CF} = 273.1 Hz), 124.33 (br), 118.69 (br), 55.61, 46.68, 42.98, 38.85, 31.96, 21.15, 14.03. HRMS (FAB, M-Cl) calcd for $C_{41}H_{42}F_{12}N_7S_2$ 924.2752, found 924.2773.

1b: $[\alpha]_D^{22}$ = -47.0° (*c* 1.89, CH_3OH). IR (KBr) 3212, 3054, 1620, 1553, 1471, 1377, 1280, 1179, 1133 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *d*?8.22 (s, 4H), 7.71 (s, 2H), 7.31-7.20 (m, 10H), 5.09 (br s, 2H), 3.43 (br d, *J* = 7.3 Hz, 2H), 3.19 (t, *J* = 7.5 Hz, 2H), 2.96 (m, 2H), 2.81 (m, 2H), 1.46 (m, 4H), 1.19 (m, 4H), 0.82 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (125 MHz, CD_3OD) *d*?182.40, 161.28, 142.53, 138.45, 132.82 (J_{CF} = 33.1 Hz), 130.24, 129.63, 127.83, 124.76 (br), 124.61 (J_{CF} = 273.1 Hz), 118.84 (br), 56.37, 49.87, 48.84, 39.61, 30.34, 20.87, 13.93. HRMS (FAB, M-Cl) calcd for $C_{45}H_{50}F_{12}N_7S_2$ 980.3378, found 980.3359.

1c: $[\alpha]_D^{22}$ = -107.1° (*c* 1.02, CH_3OH). IR (KBr) 3252, 3053, 1627, 1553, 1472, 1377, 1280, 1178, 1134 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *d*?8.14 (s, 4H), 7.60 (s, 2H), 7.29-7.21 (m, 10H), 5.07 (br s, 2H), 3.44 (br s, 2H), 3.36 (br s, 2H), 3.25 (br s, 2H), 2.89 (m, 4H), 2.00-1.83 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD) *d*?183.08, 157.53, 142.69, 138.59, 132.67 (J_{CF} = 33.1 Hz), 130.25, 129.68, 127.85, 124.62 (J_{CF} = 271.0 Hz), 123.80 (br), 118.21 (br), 56.14, 50.45, 48.59, 39.43, 26.26. HRMS (FAB, M-Cl) calcd for $C_{41}H_{40}F_{12}N_7S_2$ 922.2595, found 922.2616.

1d: $[\alpha]_D^{23}$ = -29.0° (*c* 1.34, CH_3OH). IR (neat) 3262, 3063, 1668, 1628, 1547, 1472, 1384, 1278, 1178, 1136 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *d*?8.00 (s, 4H), 7.62 (s, 2H), 7.29-7.21 (m, 10H), 5.02 (br s, 2H), 3.64 (br s, 2H), 3.43 (br s, 2H), 3.19 (t, *J* = 6.9 Hz, 2H), 3.12 (dd, *J* = 14.7 Hz, 4.3 Hz, 2H), 2.86 (dd, *J* = 14.7 Hz, 8.9 Hz, 2H), 1.61 (m, 2H), 1.37-1.23 (m, 10H), 0.84 (t, *J* = 6.9 Hz, 3H). [13]C NMR (125 MHz, CD_3OD) *d*?182.34, 156.28, 142.02, 138.41, 132.50 (J_{CF} = 33.1 Hz), 130.07, 129.66, 127.83, 124.52 (J_{CF} = 271.0 Hz), 124.50 (br), 118.84 (br), 55.78, 46.55, 38.87, 32.93, 30.31 (br), 28.00, 23.63. HRMS (FAB, M-Cl) calcd for $C_{45}H_{50}F_{12}N_7S_2$ 980.3378, found 980.3373.

1e: $[\alpha]_D^{22}$ = -40.3° (*c* 1.08, CH_3OH). IR (KBr) 3269, 2926, 1631, 1546, 1473, 1385, 1278, 1179, 1136 cm^{-1}. [1]H NMR (500 MHz, CD_3OD) *d*?8.03 (s, 4H), 7.59 (s, 2H), 7.28-7.20 (m, 10H), 5.00 (br s, 2H), 3.62 (br s, 2H), 3.42 (br s, 2H), 3.23 (t, *J* = 7.3 Hz, 2H), 3.13 (dd, *J* = 14.6 Hz, 3.4 Hz, 2H), 2.86 (dd, *J* = 14.6 Hz, 9.8 Hz, 2H), 1.63 (m, 2H), 1.38-1.22 (m, 30H), 0.88 (t, *J* = 7.0 Hz, 3H). [13]C NMR (125 MHz, CD_3OD) *d*?183.09, 156.38, 142.46, 138.53, 132.72 (J_{CF} = 33.1 Hz), 129.96, 129.69, 127.82, 123.95 (br), 122.44 (J_{CF} = 271.0 Hz), 118.36 (br), 55.33, 46.71, 43.13, 38.83, 33.06, 30.74 (br), 30.69, 30.62, 30.44, 30.38, 29.90, 28.04, 23.71, 14.42. HRMS (FAB, M-Cl) calcd for $C_{55}H_{70}F_{12}N_7S_2$ 1120.4943, found 1120.4949.

1f: $[\alpha]_D^{24}$ = -51.7° (*c* 1.27, CH_3OH). IR (KBr) 3195, 3064, 1645, 1604, 1548, 1473, 1382, 1279, 1179, 1133 cm^{-1}. [1]H NMR (500 MHz, CD_3OD) *d*?8.10 (s, 4H), 7.96 (s, 2H), 7.86 (s, 1H), 7.58 (s, 2H), 7.29-7.19 (m, 10H), 5.10 (br s, 2H), 3.65 (m, 4H), 3.03 (br d, *J* = 10.4 Hz, 2H), 2.88 (br, 2H) [13]C NMR (125 MHz, CD_3OD) *d*?183.13, 156.62, 142.46, 139.15, 138.33, 134.28 (J_{CF} = 33.1 Hz), 132.64 (J_{CF} = 33.1 Hz), 130.06, 129.64, 127.83, 126.50 (br), 124.59 (J_{CF} = 273.1 Hz), 124.26 (J_{CF} = 271.0 Hz), 123.79 (br), 121.34 (br), 118.26 (br), 55.45, 47.55, 38.93. HRMS (FAB, M-Cl) calcd for $C_{45}H_{36}F_{18}N_7S_2$ 1080.2186, found 1080.2190.

1g: $[\alpha]_D^{24}$ = -80.5° (*c* 1.11, CH_3OH). IR (KBr) 3276, 3062, 1630, 1591, 1545, 1473, 1385, 1279, 1178, 1134 cm^{-1}. [1]H NMR (500 MHz, CD_3OD) *d*?8.10 (s, 4H), 7.59 (s, 2H), 7.29-7.19 (m, 10H), 6.51 (d, *J* = 2.1 Hz, 2H), 6.42 (t, *J* = 2.1 Hz, 1H), 5.10 (br, 2H), 3.71 (s, 6H), 3.63 (m, 4H), 3.05 (br d, *J* = 10.7 Hz, 2H), 2.85 (br s, 2H). [13]C NMR (125 MHz,

CD_3OD) δ 183.16, 163.30, 156.49, 142.51, 138.43, 137.67, 132.67 (J_{CF} = 33.1 Hz), 130.06, 129.68, 127.83, 124.62 (J_{CF} = 273.1 Hz), 123.79 (br), 123.95 (br), 118.31 (br), 105.08, 100.39, 56.00, 55.42, 47.21, 38.95. HRMS (FAB, M-Cl) calcd for $C_{45}H_{42}F_{12}N_7O_2S_2$ 1004.2650, found 1004.2639.

2: $[\alpha]_D^{24}$ = -45.0° (*c* 1.04, CH_3OH). IR (KBr) 3269, 2927, 1631, 1546, 1473, 1385, 1278, 1182, 1137 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 8.14 (s, 4H), 7.61 (s, 2H), 4.62 (br s, 2H), 3.57 (br s, 2H), 3.31 (br s, 2H), 3.24 (t, *J* = 7.2 Hz, 2H), 1.63 (m, 2H), 1.32 (d, *J* = 6.7 Hz, 6H), 1.29-1.19 (m, 32H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 182.90, 156.41, 142.79, 132.70 (J_{CF} = 33.1 Hz), 124.67 (J_{CF} = 273.1 Hz), 124.00 (br), 118.23 (br), 43.13, 33.08, 30.76 (br), 30.59, 30.56, 30.46, 30.30, 29.88, 27.94, 23.73, 17.81, 14.44. HRMS (FAB, M-Cl) calcd for $C_{43}H_{62}F_{12}N_7S_2$ 968.4317, found 968.4341.

3: $[\alpha]_D^{24}$ = -71.0° (*c* 0.98, CH_3OH). IR (KBr) 3274, 2929, 1631, 1545, 1474, 1385, 1278, 1181, 1136 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 8.29 (s, 4H), 7.59 (s, 2H), 4.67 (br, 2H), 3.42 (br, 4H), 3.22 (m, 2H), 1.99 (m, 2H), 1.60 (m, 2H), 1.29-1.16 (m, 30H), 1.04 (d, *J* = 3.4 Hz, 6H), 1.02 (d, *J* = 3.7 Hz, 6H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 183.82, 156.51, 142.90, 132.64 (J_{CF} = 33.1 Hz), 126.82 (J_{CF} = 273.1 Hz), 123.44 (br), 118.01 (br), 58.82, 45.58, 43.12, 33.06, 31.05, 30.72 (br), 30.66, 30.53, 30.30, 30.20, 30.02, 27.91, 23.71, 20.18, 17.58, 14.42. HRMS (FAB, M-Cl) calcd for $C_{47}H_{70}F_{12}N_7S_2$ 1024.4943, found 1024.4929.

4: $[\alpha]_D^{24}$ = -124.8° (*c* 1.38, CH_3OH). IR (KBr) 3274, 2928, 1630, 1535, 1472, 1385, 1277, 1184, 1138 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ 8.30 (s, 4H), 7.61 (s, 2H), 3.64 (br d, *J* = 12.5 Hz, 2H), 3.17 (m, 2H), 1.54 (m, 2H), 1.27-1.16 (m, 30H), 1.02 (br s, 18H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD) δ 184.00, 156.44, 143.04, 132.64 (J_{CF} = 33.1 Hz), 124.70 (J_{CF} = 271.0 Hz), 123.15 (br), 117.91 (br), 61.82, 43.23, 35.23, 33.08, 30.74 (br), 30.67, 30.58, 30.46, 30.30, 30.18, 27.84, 27.05, 23.73, 14.44. HRMS (FAB, M-Cl) calcd for $C_{49}H_{74}F_{12}N_7S_2$ 1052.5256, found 1052.5242.

Typical procedure for asymmetric Henry reaction

To a mixture of **1e** (12.9 mg, 0.0112 mmol), KI (9.3 mg, 0.0558 mmol) and nitromethane (65.2 µL, 1.12 mmol) in toluene (1.12 mL)/5 mM KOHaq (1.12 mL) was added cyclohexanecarboxaldehyde (**10a**) at 0°C. The resulting mixture was stirred vigorously at 0°C for 24 h. Then saturated NH_4Claq was added, and the organic layer was extracted with ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 20/1 → 5/1 → chloroform/methanol = 9/1) to give **11a** (17.4 mg, 91%) and **1e** (12.8 mg, 99% recovery). The enantiomeric excess of **11a** (92% ee) was determined by means of chiral HPLC analysis. (Chiralcel OD-H, 0.46 cm (*f*) × 25 cm (L), *n*-hexane/2-propanol = 97/3, 1.0 mL/min, (*R*) major; 19.3 min, (*S*) minor; 21.2 min). The absolute stereochemistry of **11a** was determined based on the retention time reported by Trost et al and Evans et al, respectively.[1] [2]

Spectral data for **11a**: [1] [2] ^{1}H NMR (400 MHz, $CDCl_3$) *d* 4.48 (dd, J = 13.1 Hz, 2.7 Hz, 1H), 4.42 (dd, J = 13.1 Hz, 8.9 Hz, 1H), 4.10 (m, 1H), 2.42 (br s, 1H), 1.82 (m, 2H), 1.68 (m, 2H), 1.47 (m, 1H), 1.30-1.06 (m, 6H). The enantiomeric excess of **11a** was determined by the use of chiral HPLC analysis. (Chiralcel OD-H, 0.46 cm (*f*) × 25 cm (L), *n*-hexane/2-propanol = 97/3, 1.0 mL/min, (*R*) major; 19.3 min, (*S*) minor; 21.2 min).

Spectral data for **11b**: [1]H NMR (400 MHz, $CDCl_3$) *d* 4.48 (dd, *J* = 13.2 Hz, 2.7 Hz, 1H), 4.39 (dd, *J* = 13.2 Hz, 9.0 Hz, 1H), 4.14 (m, 1H), 2.56 (br s, 1H), 1.93 (m, 1H), 1.84 (m, 1H), 1.76-1.57 (m, 5H), 1.47 (m, 1H), 1.28 (m, 1H). The enantiomeric excess of **11b** was determined by the use of chiral HPLC analysis. (Chiralcel OD-H, 0.46 cm (*f*) × 25 cm (L), *n*-hexane/2-propanol = 98/2, 1.0 mL/min, (*R*) major; 22.5 min, (*S*) minor; 25.0 min).

Spectral data for **11c**:[1] [2] [1]H NMR (400 MHz, $CDCl_3$) *d* 4.53 (dd, *J* = 12.9 Hz, 2.0 Hz, 1H), 4.37 (dd, *J* = 12.9 Hz, 10.1 Hz, 1H), 4.04 (dd, *J* = 10.1 Hz, 2.0 Hz, 1H), 2.42 (br s, 1H), 0.99 (s, 9H). The enantiomeric excess of **11c** was determined by the use of chiral HPLC analysis. (Chiralcel OD-H, 0.46 cm (*f*) × 25 cm (L), *n*-hexane/2-propanol = 97/3, 1.0 mL/min, (*R*) major; 15.1 min, (*S*) minor; 18.8 min).

Spectral data for **11d**:[1] [2] [1]H NMR (400 MHz, $CDCl_3$) *d* 4.48 (dd, *J* = 13.2 Hz, 3.2 Hz, 1H), *d* 4.40 (dd, *J* = 13.2 Hz, 8.5 Hz, 1H), 4.11 (m, 1H), 1.81 (m, 1H), 1.01 (d, *J* = 4.1 Hz, 3H), 0.97 (d, *J* = 4.4 Hz, 3 H). The enantiomeric excess of **11d** was determined by the use of chiral HPLC analysis. (Chiralcel OD-H, 0.46 cm (*f*) × 25 cm (L), *n*-hexane/2-propanol = 97/3, 1.0 mL/min, (*R*) major; 18.3 min, (*S*) minor; 21.7 min).

Spectral data for **11e**:[1] [1]H NMR (400 MHz, $CDCl_3$) *d* 4.46 (d, *J* = 2.2 Hz, 1H), 4.43 (s, 1H), 4.42-4.31 (m, 1H), 2.38 (d, *J* = 4.6 Hz, 1H), 1.56-1.21 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 6 H). The enantiomeric excess of **11e** was determined by the use of chiral HPLC analysis. (Chiralcel OD-H, 0.46 cm (*f*) × 25 cm (L), *n*-hexane/2-propanol = 98/2, 1.0 mL/min, (*R*) major; 21.0 min, (*S*) minor; 25.2 min).

Spectral data for **11f**:[1][2] ^{1}H NMR (400 MHz, $CDCl_3$) *d*?7.38-7.18 (m, 5H), 4.41 (s, 1H), 4.39 (d, *J* = 2.0 Hz, 1H), 4.35-4.26 (m, 1H), 2.92-2.20 (m, 2H), 2.64 (br s, 1H), 1.94-1.72 (m, 2H). The enantiomeric excess of **10f** was determined by the use of chiral HPLC analysis. (Chiralcel AD-H, 0.46 cm (*f*) × 25 cm (L), *n*-hexane/2-propanol = 95/5, 1.0 mL/min, (*R*) major; 23.2 min, (*S*) minor; 29.5 min).

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