Supplementary Information

Enantioselective Syntheses of *trans*-3,4-Difluoropyrrolidines and Investigation of their Applications in Catalytic Asymmetric Synthesis

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General. Analytical thin-layer chromatography (TLC) was performed on 0.25 mm thick pre-coated, aluminum-backed silica gel plates, visualized by UV illumination or iodine vapor, or developed by charring with either (a) 5% anisaldehyde in ethanol-acetic acid-sulfuric acid (95:5:1 by volume), (b) 2% vanillin in ethanol-sulfuric acid (98:2), (c) 1% potassium permanganate in 0.5 M potassium carbonate solution, or (d) 2.0 M sulfuric acid saturated with cerium(IV) sulfate. Flash column chromatography was performed on alumina (63 to 200 μm) or silica (40 to 63 μm , 230 to 400 mesh). Melting points were determined on a hot stage apparatus and are uncorrected. Optical rotations were recorded on a digital polarimeter using the sodium-D line. ^1H NMR spectra were recorded at 250 MHz in CDCl_3 and ^{13}C NMR spectra were recorded at 62 MHz in CDCl_3 unless otherwise stated, and using tetramethylsilane as the internal standard. ^{19}F NMR spectra were observed on ^1H channel de-tune (heteronuclear probe) and were recorded at 565 MHz, or were assigned as ^1H coupled or ^1H decoupled at 376 MHz. ^{19}F chemical shift values are expressed in ppm relative to internal trichlorofluoromethane. Infra red spectra were recorded as KBr plates, chloroform solution, or neat as liquid films. Mass spectra were obtained either as electron impact (HRMS_{EI}) or fast atom bombardment (HRMS_{FAB}) in a *m*-nitrobenzoic acid (+Na) matrix. High pressure liquid chromatographic analyses (HPLC) were performed using a Daicel chiralcel OD chiral phase column (250 x 4.6 mm) with isocratic elution at 20 $^\circ\text{C}$, flow rate 0.5 to 1.0 mL per minute, with UV absorption being detected between 205-254 nm.

All reactions were performed under an atmosphere of dry nitrogen except for those reactions conducted in aqueous media. Solvents were rigorously dried and purified prior to use. Solvent was transferred *via* cannulation (stainless steel double-tipped needle) under balloon pressure. Evaporation of the solvent refers to removal under reduced pressure.

(3*R*,4*R*)-1-Cyclohexyl-3,4-diacetoxypyrrolidine-2,5-dione (2b). Prepared according to the General Procedure A, using (3*R*,4*R*)-3,4-diacetoxypyrrolidine-2,5-dione (**1**), (20.0 g, 92.6 mmol) and cyclohexylamine (9.17 g, 92.6 mmol) with purification by chromatography over silica gel (3:17 ethyl acetate: 40-60 °C petroleum ether). The appropriate fractions were combined, filtered through a glass wool plug and the eluent was evaporated under reduced pressure to give **2b** (19.5 g, 71%) as a clear gum; $[\alpha]_D^{34} +65.7$ (c 5.0, chloroform); IR $\nu_{\max}$ (film) 2940, 2810, 1750, 1720 cm^{-1} ; ^1H NMR δ 5.36 (2H, s), 3.89 (1H, tt, $J = 10.5, 3.5$ Hz), 2.07 (6H, s), 1.98 (4H, m), 1.73 (2H, m), 1.54 (2H, m) and 1.18 (2H, m); ^{13}C NMR δ 169.8, 169.3, 72.5, 52.5, 28.8, 28.4, 25.6, 24.9, 20.3; LRMS_{FAB} m/e (rel. intensity %; +ve *m*-NO₂C₆H₅-CO₂H MATRIX) 298 ($[\text{M}+\text{H}]^+$, 89), 256 (100), 238 (39), 214 (35), 174 (22), 156 (15), 137 (18), 114 (13). HRMS_{FAB} Calcd for C₁₄H₂₀NO₆: $[\text{M}+\text{H}]^+$ 298.1291. Found: 298.1278.

(3*S*,4*S*)-1-Cyclohexylpyrrolidine-3,4-diol (3b). Prepared according to the General Procedure B, using (3*R*,4*R*)-1-cyclohexyl-3,4-diacetoxypyrrolidine-2,5-dione (**2b**), (15.0 g, 50.3 mmol). The residue was adsorbed onto neutral alumina and the impregnated dispersion was applied to the top of a pre-packed flash column of silica gel and eluted with 1:4 methanol:chloroform. The appropriate fractions were combined, filtered through a glass wool plug and the eluent was evaporated to give **3b** (2.79 g, 34%) as a white solid, mp 127-130 °C. An analytical sample was obtained by recrystallization from acetone as prisms, mp 129-130 °C; $[\alpha]_D^{32} +29.7$ (c 1.43, methanol); IR $\nu_{\max}$ (KBr) 3345, 2915, 2850, 1445 cm^{-1} ; ^1H NMR (DMSO-*d*₆) δ 4.73 (2H, d, $J = 4.9$ Hz), 3.79 (2H, d, $J = 5.0$ Hz), 2.78 (2H, dd, $J = 8.5, 5.2$ Hz), 2.31 (2H, dd, $J = 10.5, 4.9$ Hz), 1.95 (1H, m), 1.68 (4H, m), 1.13 (6H, m); ^{13}C NMR (DMSO-*d*₆) δ_C 77.3, 62.6, 58.3, 31.1, 26.1, 24.6, 24.5; LRMS_{FAB} m/e (rel. intensity %; +ve *m*-NO₂C₆H₅CO₂H MATRIX) 186 ($[\text{M}+\text{H}]^+$, 100), 184 (35), 198 (3), 169 (5) and 142 (13). HRMS_{FAB} Calcd for C₁₀H₂₀NO₂: $[\text{M}+\text{H}]^+$ 186.1494. Found: 186.1480. Anal. Calcd for C₁₀H₁₉NO₂: C, 64.83; H, 10.43; N, 7.56. Found: C, 64.67; H, 10.60; N, 7.51.

(3*S*,4*S*)-1-Phenyl-3,4-bis(trifluoromethanesulfonyloxy)pyrrolidine (4c). Prepared according to the General Procedure C, using (3*S*,4*S*)-1-phenylpyrrolidine-3,4-diol (**3c**) (1.0 g, 5.6 mmol), pyridine (0.93 g, 11.8 mmol) as the base, and trifluoromethanesulfonic anhydride (3.16 g, 11.2 mmol). Work-up was as described above, with purification by flash column chromatography over silica gel eluting with 1:49 ethyl acetate:40-60 °C petroleum ether pre-cooled to 5 °C. The appropriate fractions were combined, filtered through a glass wool plug and evaporated to give **4c** (1.0 g, 41%) as a pink solid, mp 125-126 °C. An analytical sample was obtained by preparative thin-layer chromatography on silica (General Procedure C) followed by recrystallization from ethyl acetate by the slow diffusion of *n*-hexane vapor at 5 °C to give **4c** as clear needles, mp 126.5-127 °C; $[\alpha]_D^{34} +46.2$ (c 0.99, chloroform); IR $\nu_{\max}$ (KBr), 2990, 1600, 1510, 1410, 1370, 1200 cm^{-1} ; ^1H NMR δ 7.30 (2H, m), 6.88 (1H, t, $J = 9.0$ Hz), 6.60 (2H, d, $J = 9.0$ Hz), 5.52 (2H, t, $J = 2.5$ Hz) 3.95 (2H, dd, $J = 11.0, 5.0$ Hz), 3.65 (2H, dd, $J = 11.0, 3.0$); ^{13}C NMR δ 145.5, 129.7, 118.9, 118.5 (q, $J_{\text{CF}} = 314.4$ Hz), 112.6, 85.4, 51.3; ^{19}F NMR δ -74.9 (s); LRMS_{FAB} m/e (rel. intensity %; +ve *m*-NO₂C₆H₅CO₂H MATRIX) 442 (M^+ , 100), 310 (13) and 144 (70). HRMS_{FAB} Calcd for C₁₂H₁₁F₆NO₆S₂: (M^+) 442.9932. Found: 442.9921. Anal. Calcd for C₁₂H₁₁F₆NO₆S₂: C, 32.51; H, 2.50; N, 3.16. Found: C, 32.61; H, 2.14; N, 3.03.

(3*S*,4*S*)-1-(4-Iodophenyl)-3,4-bis(trifluoromethanesulfonyloxy)pyrrolidine (4d). Prepared according to the General Procedure C, using (3*S*,4*S*)-1-(4-iodophenyl)pyrrolidine-3,4-diol (**3d**), (0.575 g, 1.90 mmol), triethylamine (0.40 g, 4.0 mmol) and trifluoromethanesulfonic anhydride (0.56 g, 2.0 mmol). Work-up was as described in the General Procedure C, with purification by flash column chromatography over silica gel eluting with 1:32 ethyl acetate:40-60 °C petroleum ether pre-cooled to 5 °C. The appropriate fractions were combined, filtered through a glass wool plug and evaporated to give **4d** (0.40 g, 37%) as a yellow solid, mp 92-94 °C. An analytical sample was obtained by preparative thin-layer chromatography on silica (General Procedure C, three plate elutions with *n*-hexane) followed by recrystallization from chloroform by the slow diffusion of *n*-hexane vapor at 5 °C to give **4d** as colorless needles, mp 96-97 °C; $[\alpha]_D^{34} +23.3$ (c 1.51, chloroform); IR $\nu_{\max}$ (KBr), 2820, 1590, 1580, 1490, 1420, 1370, 1135 cm^{-1} ; ^1H NMR δ 7.56 (2H, d, $J = 9.0$ Hz), 6.39 (2H, d, $J = 9.0$ Hz), 5.53 (2H, dd, $J = 3.5, 1.0$ Hz), 3.95 (2H, dd, $J = 12.0, 4.6$ Hz), 3.68 (2H, dd, $J = 12.0, 2.0$ Hz); ^{13}C NMR δ 145.0, 138.3, 118.1 (q, $J_{\text{CF}} = 317.3$ Hz), 114.7, 85.0, 80.4, 51.2; ^{19}F NMR δ_F -74.9 (s); LRMS_{FAB} m/e (rel. intensity %; +ve *m*-NO₂C₆H₅-CO₂H MATRIX) 568 (M^+ , 100),

270 (27), 154 (30) and 136 (37). HRMS_{FAB} Calcd for C₁₂H₁₀F₆INO₆S₂: (M⁺) 568.8898. Found: 568.8910

(3*S*,4*S*)-1-(2-Benzoyloxyethyl)-3,4-bistrifluoromethanesulfonyloxypyrrolidine (4f). To a stirred suspension of (3*S*,4*S*)-1-(2-benzoyloxyethyl)pyrrolidine-3,4-diol (**3f**) (2.42 g, 10.2 mmol) and triethylamine (2.17 g, 21.4 mmol) in 60 mL of anhydrous, degassed dichloromethane at –85 °C under an atmosphere of dry nitrogen was added dropwise a solution of trifluoromethanesulfonic anhydride (6.05 g, 21.4 mmol) in dry dichloromethane (45 mL) by means of a stainless steel, double-tipped needle. The mixture was allowed to warm slowly to 20 °C and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 16 h. Quenching with water (40 mL) was followed by work-up as described in General Procedure C (K₂CO₃ as the drying agent), with column chromatography using 1:9 ethyl acetate:40–60 °C petroleum ether (pre-cooled to 5 °C), giving **4f** (2.15 g, 42%) as a dark liquid. An analytical sample was obtained by preparative silica plate thin-layer chromatography as described in General Procedure C, giving **4f** as a clear liquid; [α]_D³⁰ +12.0 (c 0.9, chloroform); IR ν_{max} (film) 2870, 2830, 1495, 1420, 1360, 1141 cm^{–1}; ¹H NMR δ_H 7.32 (5H, m), 5.38 (2H, t, *J* = 4.8 Hz), 4.54 (2H, s), 3.61 (2H, t, *J* = 5.5 Hz), 3.42 (2H, dd, *J* = 13.0, 7.5 Hz), 3.10 (2H, dd, *J* = 13.0, 4.0 Hz), 2.88 (2H, m); ¹³C NMR δ 137.7, 128.6, 128.0, 127.9, 118.5 (q, ¹*J*_{HH} 320.6 Hz), 87.2, 73.4, 67.7, 57.9, 54.5; ¹⁹F NMR δ –78.3 (s); LRMS_{FAB} *m/e* (rel. intensity %; +ve *m*-NO₂C₆H₅CO₂H MATRIX) 502 ([M+H]⁺, 100), 419 (13), 394 (20), 380 (11), 352 (6), 220 (38), 202 (27) and 112 (17). HRMS_{FAB} Calcd for C₁₅H₁₈F₆NO₇S₂: [M+H]⁺ 502.0433. Found: 502.0429.

(3*R*,4*R*)-1-Cyclohexyl-3,4-difluoropyrrolidine (5b). (3*R*, 4*R*) -1-Cyclohexyl-3,4-bis(trifluoromethanesulfonyloxy)pyrrolidine (**4b**) was prepared *in situ* from (3*S*,4*S*)-1-cyclohexylpyrrolidine-3,4-diol (**3b**) according to General Procedure C and was reacted directly tetra-*n*-butylammonium fluoride (20 mL, 20 mmol; 1 M) in dry THF (75 mL) without further purification, and the crude product purified according to General Procedure D to give **5b** (0.53 g, 42%, based on recovered **4b**) as a pale brown oil. An analytical sample of **5b** (see General Procedure D) was obtained as a clear oil; [α]_D³⁰ –21.1 (c 3.51, chloroform); IR ν_{max} (KBr), 2930, 2860, 1450 cm^{–1}; ¹H δ 5.09 (2H, ddm, ²*J*_{HF} = 52.7 Hz, ³*J*_{HF} = 19.0 Hz), 3.10 (2H, ddd, ³*J*_{HF cis} = 26.5 Hz, ²*J*_{HH} = 11.0 Hz, ³*J*_{HH} = 5.3 Hz), 2.82 (2H, ddd, ³*J*_{HF-trans} = 24.8 Hz, ²*J*_{HH} = 11.0 Hz, ³*J*_{HH} = 3.0 Hz), 2.17 (1H, m), 1.90–1.55 (4H, m), 1.25 (6H, m); ¹³C NMR δ 90.3 (dd, ¹*J*_{CF} 180.7 Hz, ²*J*_{CF} 30.1), 57.5, 50.3 (d, ²*J*_{CF} 25.8 Hz), 26.1, 26.0, 21.0, 19.9; ¹⁹F NMR (376 MHz) δ –185.9 (m); LRMS_{FAB} *m/e* (rel. intensity %; +ve *m*-

NO₂C₆H₅CO₂H MATRIX) 190 ([M+H]⁺, 49), 149 (100), 136 (33) and 107 (43). HRMS_{FAB} Calcd for C₁₀H₁₈F₂N [M+H]⁺ 190.1407. Found: 190.1420.

(3*R*,4*R*)-3,4-Difluoro-1-phenylpyrrolidine (5c). (3*S*,4*S*)-1-Phenyl-3,4-bis(trifluoromethanesulfonyloxy)pyrrolidine (**4d**), (0.94 g, 2.12 mmol) was reacted directly tetra-*n*-butylammonium fluoride (6.4 mL, 6.4 mmol; 1 M) in dry THF (25 mL), and the product purified by column chromatography (1:32 ethyl acetate:40-60 °C petroleum ether), according to the General Procedure D, to give **5c** (0.295 g, 76%) as a pale green amorphous solid, mp 87-89 °C. An analytical sample was obtained by preparative thin-layer chromatography (see General Procedure D) followed by recrystallization at refrigerator temperature of 5 °C in the dark from dichloromethane by the slow diffusion of *n*-hexane vapor to give **5c** as large transparent needles, mp 89.5 °C; [α]_D³⁰ -40.6 (c 3.52, chloroform); IR ν_{max} (KBr), 2920, 2850, 1600, 1510, 1460 cm⁻¹; ¹H NMR δ 7.30 (2H, m), 6.76 (1H, t, *J* = 7.0 Hz), 6.60 (2H, d, *J* = 7.0 Hz), 5.30 (2H, ddm, ²*J*_{HF} = 49.3 Hz, ³*J*_{HF} 12.6), 3.70 (4H, m); ¹³C NMR (151 MHz) δ 146.6, 129.4, 117.1, 112.0, 92.8 (dd, ¹*J*_{CF} 180.0 Hz, ²*J*_{CF} 33.0 Hz), 51.6 (m); ¹⁹F NMR (564 MHz) δ -190.3 (m); LRMS_{FAB} *m/e* (rel. intensity %; +ve *m*-NO₂C₆H₅CO₂H MATRIX) 183 (M⁺, 26), 154 (100), 137 (84), 136 (100), 107 (78) and 105 (52). Anal. Calcd for C₁₀H₁₁F₂N: C, 65.56; H, 6.05; N, 7.65. Found: C, 65.23; H, 5.81; N, 7.44.

(3*R*,4*R*)-1-(4-Iodophenyl)-3,4-difluoropyrrolidine (5d). (3*S*,4*S*)-1-(4-Iodophenyl)-3,4-bis(trifluoromethanesulfonyloxy)pyrrolidine (**4d**), (0.315 g, 0.55 mmol) was reacted with tetra-*n*-butylammonium fluoride (1.65 mL, 1.65 mmol; 1 M) in dry THF (5 mL), and the product purified by column chromatography (1:33 ethyl acetate:40-60 °C petroleum ether), according to the General Procedure D, to give **5d** (0.154 g, 90%) as a yellow powder, mp 134-137 °C. An analytical sample was obtained by preparative thin-layer chromatography (see General Procedure D) followed by recrystallization at refrigerator temperature of 5 °C in the dark from acetone by the slow diffusion of *n*-hexane vapor to give **5d** as clear prisms, mp 140-141 °C; [α]_D³⁰ -25.0 (c 1.02, chloroform); IR ν_{max} (KBr), 2980, 2850, 1580, 1490, 1460 cm⁻¹; ¹H NMR δ 7.49 (2H, d, *J* = 9.0 Hz), 6.35 (2H, d, *J* = 9.0 Hz), 5.27 (2H, dm, ²*J*_{HF} = 58.0 Hz, ³*J*_{HF} = 10.0 Hz), 3.70 (2H, m), 3.56 (2H, m); ¹³C NMR δ 146.6, 137.9, 114.2, 92.5 (dd, ¹*J*_{CF} = 180.6 Hz, ²*J*_{CF} = 33.1 Hz), 78.0, 51.6 (dt, ²*J*_{CF} = 22.0 Hz, ³*J*_{CF} = 6.2 Hz); ¹⁹F NMR (376 MHz, CFCl₃ internal standard) δ -188.5 (m); LRMS_{FAB} *m/e* (rel. intensity %; +ve *m*-NO₂C₆H₅CO₂H MATRIX) 309 ([M+H]⁺, 63), 308 (M⁺, 17), 154 (67), 136 (66), 115 (39); HRMS_{FAB} Calcd for C₁₀H₁₀F₂IN (M⁺) 308.9826. Found: 308.9840. Anal. Calcd for C₁₀H₁₀F₂IN: C, 38.86; H, 3.26; N, 4.53. Found: C, 38.87; H, 3.05; N, 4.32.

(3*R*,4*R*)-1-(2-Benzoyloxyethyl)-3,4-difluoropyrrolidine (5f). (3*S*,4*S*)-1-(2-Benzoyloxyethyl)-3,4-bis(trifluoromethanesulfonyloxy)pyrrolidine (**4f**) (2.12 g, 4.23 mmol) in dry THF (65 mL) was reacted with tetra-*n*-butylammonium fluoride (12.7 mL, 12.7 mmol; 1 M) in dry THF (5 mL), the product quenched with saturated aqueous ammonium chloride (5 mL), and then purified by column chromatography (1:9 ethyl acetate:40-60 °C petroleum ether) according to the General Procedure D, giving **5f** (0.53 g, 52%) as a pale brown liquid. An analytical sample was obtained by preparative thin-layer chromatography (three plate elutions with 1:19 diethyl ether:40-60 °C petroleum ether; see General Procedure D) giving **5f** as a colorless oil; $[\alpha]_D^{30}$ -20.5 (c 0.16, chloroform); IR $\nu_{\max}$ (film) 2925, 2860, 2800, 1560, 1495 cm^{-1} ; ^1H NMR (600 MHz) δ 7.40-7.25 (5H, m), 5.12 (2H, dddd, $^2J_{\text{HF}} = 56.0$ Hz, $^3J_{\text{HF}} = 19.0$ Hz, $^3J_{\text{HH}} = 5.5$ Hz, $^3J_{\text{HH}} = 4.0$ Hz), 4.54 (2H, s), 3.61 (2H, t, $^3J_{\text{HH}} = 5.5$ Hz), 3.11 (2H, ddd $^3J_{\text{HF}} = 26.0$ Hz, $^2J_{\text{HH}} = 11.0$ Hz, $^3J_{\text{HH}} = 5.5$ Hz), 2.86 (2H, m), 2.80 (2H, m); ^{13}C NMR (150 MHz) δ 138.1 (*ipso*-phenyl), 128.4 (*o*-, *m*- and *p*-phenyl), 95.5 (dd, $^1J_{\text{CF}} = 180.8$ Hz, $^2J_{\text{CF}} = 30.0$), 73.1, 68.7, 58.5 (d, $^2J_{\text{CF}} = 27.2$ Hz), 55.0; ^{19}F NMR (565 MHz) δ -185.4 (m); LRMS_{EI} *m/e* (rel. intensity %) 241 (M^+ , 10), 201 (50), 135 (17), 120 (100) and 91 (15). HRMS_{EI} Calcd for $\text{C}_{13}\text{H}_{17}\text{F}_2\text{NO}$: (M^+) 241.1278. Found: 241.1278.

F1: RESULTING RH-VI SE

77.2409

42.5458

58.2469

51.1145

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157.118
148.714
148.714

84.938
88.458
87.583

201 X 425

100 X 700