Organic Letters

Supporting Information to Accompany:

**Asymmetric Syntheses of 1-Aryl-2,2,2-trifluoroethylamines via
Diastereoselective 1,2-Addition of Arylmetals to 2-Methyl-*N*-(2,2,2-
trifluoroethylidene)propane-2-sulfinamide**

Vouy Linh Truong,^{*} Madeleine S. Ménard and Isabelle Dion

*Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic
Research*

16711 Trans Canada Highway, Kirkland, Québec H9H 3L1, Canada

vouylinh_truong@merck.com

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Experimental Section

General: All anhydrous solvents were used as received from either Aldrich or Acros. Molecular sieves pellets 4 Å were purchased from Acros and used as received. (*S*)-(-)-*tert*-butylsulfinamide was purchased from Astatech, Inc. Trifluoroacetaldehyde hydrate 75% in aqueous solution was purchased from Apollo Scientific LTD. *n*-BuLi (2.5 M in hexanes) was purchased from Aldrich in Sure/SealTM bottles and used as received. All glassware was flame dried under a nitrogen atmosphere. Unless otherwise noted all reactions were run under a nitrogen atmosphere. Purification by flash chromatography used 230-400 mesh silica gel. Unless otherwise noted, ¹H NMR (400 MHz), ¹³C NMR (100 MHz) and ¹⁹F NMR spectra were recorded on Avance 400 instrument. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane. Chiral HPLC analysis was run on Chiracel OD-R (4.6 X 250 mm), Chiralpak AD (4.6 X 250 mm) or Chiralpak AS (4.6 X 250 mm) columns.

HPLC method A: 95:5 hexanes: EtOH (0.1% Et₂NH), flow rate: 1 mL/min, 35 °C, UV detection at 254 nm; 25 µL injection.

HPLC Method B: 95:5 hexanes: isopropanol (0.1% Et₂NH), flow rate: 1 mL/min, 35 °C, UV detection at 254 nm; 25 µL injection.

Preparation of 2-Methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide (3): To a solution of (*S*)-(-)-*tert*-butylsulfinamide (*S*)-**1** (200 mg, 1.65 mmol) in toluene (3.3 mL) were added trifluoroacetaldehyde hydrate **2a** (75% in aqueous solution, 200 µL, 1.82 mmol) and molecular sieves pellets 4 Å (1g). The reaction mixture was stirred at 40 °C for 6 hours under nitrogen. Directly used for next reaction. For characterization purposes, this reaction was performed in toluene-*d*₆. ¹H NMR (toluene-*d*₆) δ 7.89 (s, 1H), 0.90 (s, 9H); ¹⁹F NMR (toluene-*d*₆) δ -70.15;

^{13}C NMR (toluene- d_6) δ 152.50 (q, J = 40.25 Hz), 119.22 (q, J = 276.67 Hz), 57.80, 21.56.

General Procedure for the Synthesis of Sulfinamides (5a-f): A solution of bromide reagent (3.0 eq) in THF (3.3 mL) in a flame dried round bottom flask under nitrogen was cooled to $-78\text{ }^\circ\text{C}$, a solution of *n*-BuLi (2.5 M in hexanes, 1.65 mL, 4.13 mmol) was added dropwise. The reaction mixture was aged at $-78\text{ }^\circ\text{C}$ for 1 hour. The crude 2-Methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide **3** (1.65 mmol) in toluene (3.3 mL) was cooled to $-78\text{ }^\circ\text{C}$ and transferred dropwise via cannula to the reaction mixture. The resulting mixture was aged at $-78\text{ }^\circ\text{C}$ for five minutes and transferred to a cooled ($0\text{ }^\circ\text{C}$) saturated aqueous ammonium chloride. The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*.

(*S*)-2-Methyl-*N*-[(1*S*)-2,2,2-trifluoro-1-phenylethyl]propane-2-sulfinamide 5a:

Using the procedure described above, the reaction gave a yellow oil which was purified by silica gel column chromatography (25:75 EtOAc:Hexanes) to give 302 mg of a pale yellow oil in 66% yield. ^1H NMR (CD_3COCD_3) δ 7.63-7.58 (m, 2H), 7.47-7.42 (m, 3H), 5.40 (br d, J = 8.2 Hz, 1H), 5.12-5.03 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ 133.92, 129.04, 128.83, 128.56, 127.69 (q, J = 282.12 Hz), 61.00 (q, J = 30.44 Hz), 56.11, 21.75; HRMS (+ESI): calcd for $\text{C}_{12}\text{H}_{16}\text{F}_3\text{NOS}$ $[\text{M}+\text{H}]^+$ 280.09781; found: 280.09775.

(*S*)-2-Methyl-*N*-[(1*S*)-2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl]propane-2-sulfinamide 5b: Using the procedure described above, the reaction gave a yellow oil which was purified by silica gel column chromatography (35:65

EtOAc:Hexanes) to give 283 mg of a pale yellow oil in 55% yield. ¹H NMR (CD₃COCD₃) δ 7.51 (d, *J* = 8.38 Hz, 2H), 6.99 (d, *J* = 8.38 Hz, 2H), 5.26 (br d, *J* = 7.70 Hz, 1H), 5.03-4.96 (m, 1H), 3.84 (s, 3H), 1.15 (s, 9H); ¹³C NMR (CD₃COCD₃) δ 160.33, 130.20, 125.48, 125.27 (q, *J* = 281.81 Hz), 113.91, 60.38 (q, *J* = 30.23 Hz), 56.00, 54.73, 21.81; HRMS (+ESI): calcd for C₁₃H₁₈F₃NO₂S [M+H]⁺ 310.10860; found: 310.10831.

(*S*)-2-Methyl-*N*-{(1*S*)-2,2,2-trifluoro-1-[4-(methylthio)phenyl]ethyl}propane-2-sulfinamide 5c: Using the procedure described above, the reaction gave a yellow oil which was purified by silica gel column chromatography (25:75 EtOAc:Hexanes) to give 286 mg of a pale yellow oil in 53% yield. ¹H NMR (CD₃COCD₃) δ 7.53 (d, *J* = 8.71 Hz, 2H), 7.34 (d, *J* = 8.71 Hz, 2H), 5.37 (br d, *J* = 7.98 Hz, 1H), 5.08-5.01 (m, 1H), 2.53 (s, 3H), 1.16-1.15 (m, 9H); ¹³C NMR (CD₃COCD₃) δ 140.28, 130.09, 129.40, 125.78, 125.16 (q, *J* = 281.12 Hz), 60.52 (q, *J* = 31.29 Hz), 56.16, 21.86, 14.20; HRMS (+ESI): calcd for C₁₃H₁₈F₃NOS₂ [M+H]⁺ 326.08572; found: 326.08547.

(*S*)-2-Methyl-*N*-[(1*S*)-2,2,2-trifluoro-1-(4-fluorophenyl)ethyl]propane-2-sulfinamide 5d: Using the procedure described above, the reaction gave a yellow oil which was purified by silica gel column chromatography (35:65 EtOAc:Hexanes) to give 246 mg of a colorless oil in 50% yield. ¹H NMR (CD₃COCD₃) δ 7.70-7.63 (m, 2H), 7.27-7.21 (m, 2H), 5.43 (br d, *J* = 8.10 Hz, 1H), 5.18-5.10 (m, 1H), 1.16 (s, 9H). ¹³C NMR (CD₃COCD₃) δ 163.02 (d, *J* = 246.42 Hz), 130.57 (d, *J* = 8.66 Hz), 130.15 (d, *J* = 2.00 Hz), 125.06 (q, *J* = 281.70 Hz), 115.38 (d, *J* = 21.70 Hz), 60.20 (q, *J* = 30.55 Hz), 56.12, 21.73; HRMS (+ESI): calcd for C₁₂H₁₅F₄NOS [M+H]⁺ 298.08856; found: 298.08832.

(S)-2-Methyl-N-[(1S)-2,2,2-trifluoro-1-(3,5-difluorophenyl)ethyl]propane-2-sulfonamide 5e: Using the procedure described above, the reaction gave a yellow oil which was purified by silica gel column chromatography (0 to 35% of EtOAc in Hexanes) to give 185 mg of a pale yellow oil in 36% yield. Major isomer: ^1H NMR (CD_3COCD_3) δ 7.64-7.56 (m, 1H), 7.20-7.16 (m, 2 H), 5.52-5.36 (m, 2H), 1.17 (m, 9H). Minor isomer: ^1H NMR (CD_3COCD_3) δ 7.64-7.56 (m, 1H), 7.20-7.16 (m, 2 H), 5.52-5.36 (m, 1H), 5.22 (d, $J = 10.12$ Hz, 1H), 1.20 (m, 9H). Major isomer: ^{13}C NMR (CD_3COCD_3) δ 1602.25-159.70 (m), 132.43-132.17 (m), 124.60 (q, $J = 282.84$ Hz), 112.33-112.07 (m), 110.56-110.17 (m), 56.47, 52.59 (q, $J = 34.22$ Hz), 21.50. Minor isomer: δ 162.25-159.70 (m), 132.43-132.17 (m), 124.47 (q, $J = 282.84$ Hz), 112.33-112.07 (m), 110.56-110.17 (m), 56.55, 51.49 (q, $J = 34.22$ Hz), 21.50; HRMS (+ESI): calcd for $\text{C}_{12}\text{H}_{14}\text{F}_5\text{NOS}$ $[\text{M}+\text{H}]^+$ 316.07912; found: 316.07890.

(S)-2-Methyl-N-[(1S)-2,2,2-trifluoro-1-(2-methylphenyl)ethyl]propane-2-sulfonamide 5f: Using the procedure described above, the reaction gave a yellow oil which was purified by silica gel column chromatography (25:75 EtOAc:Hexanes) to give 193 mg of a pale yellow oil in 40% yield. ^1H NMR (CD_3COCD_3) δ 7.63 (d, $J = 6.69$ Hz, 1H), 7.33-7.27 (m, 3H), 5.39 (br d, $J = 7.93$ Hz, 1H), 5.28-5.22 (m, 1H), 2.47 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ 137.12, 132.20, 130.60, 128.93, 128.12, 126.28, 125.54 (q, $J = 283.85$ Hz), 56.06, 56.03 (q, $J = 30.20$ Hz), 21.68, 18.87; HRMS (+ESI): calcd for $\text{C}_{13}\text{H}_{18}\text{F}_3\text{NOS}$ $[\text{M}+\text{H}]^+$ 294.11364; found: 294.11340.

(S)-2-Methyl-N-[(1S)-2,2,2-trifluoro-1-pyridin-2-ylethyl]propane-2-sulfonamide 5g: A solution of the 2-bromopyridine (175 μL , 1.82 mmol) in Et_2O (3.3 mL) in a flame dried round bottom flask under nitrogen was cooled to -78°C ,

a solution of *n*-BuLi (2.5 M in hexanes, 730 μ L, 1.82 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 15 minutes. The crude *N*-*tert*-butanesulfinyl imine **3** (1.65 mol) in toluene (3.3 mL) was cooled to -78 °C and transferred via cannula to the reaction mixture. The resulting mixture was aged at -78 °C for five minutes and transferred to a cooled (0 °C) saturated aqueous ammonium chloride. The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give a yellow oil which was purified by silica gel column chromatography (15:85 Et₂O: dichloromethane) to give a yellow solid. This solid was then recrystallized overnight in a mixture of *tert*-butyl methyl ether in hexanes that afforded 69 mg of a white solid in 15 % yield. ¹H NMR (CD₃COCD₃) δ 8.67 (d, *J* = 4.86 Hz, 1H), 7.94-7.89 (m, 1H), 7.65 (d, *J* = 7.88 Hz, 1H), 7.49-7.45 (m, 1H), 5.79 (br d, *J* = 9.21 Hz, 1H), 5.28-5.20 (m, 1H), 1.15 (s, 9H); ¹³C NMR (CD₃COCD₃) δ 152.47 (d, *J* = 1.35 Hz), 149.26, 137.14, 124.95 (q, *J* = 282.12 Hz), 124.18, 123.95, 59.18 (q, *J* = 30.09 Hz), 56.42, 21.42; HRMS (+ESI): calcd for C₁₁H₁₅F₃N₂OS [M+H]⁺ 281.09312; found: 281.09299.

General Procedure for the Cleavage of Sulfinamides (5a-g) to Give the Chiral Amine Hydrochlorides (6a-g): To a solution of sulfinamides **5a-g** (1.0 eq) in methanol (0.5M) was added 2.0 equivalents of HCl (4.0 M) in 1,4-dioxane. The reaction mixture was stirred at room temperature for 1 hour. The solvent was evaporated *in vacuo* and the residue was suspended in ether. The suspension was then filtered and washed with ether.

(1S)-2,2,2-Trifluoro-1-phenylethanamine hydrochloride 6a: Using the procedure described above, 132 g of **5a** gave 86 mg of a white solid in 86% yield.

^1H NMR (CD_3OD) δ 7.58 (s, 5H), 5.38 (q, J = 7.49 Hz, 1H); ^{19}F NMR (CD_3OD) δ -74.90; ^{13}C NMR (CD_3OD) δ 130.64, 129.19, 128.37, 128.15, 123.44 (q, J = 280.41 Hz), 55.32 (q, J = 32.57 Hz); HRMS (+ESI): calcd for $\text{C}_8\text{H}_8\text{F}_3\text{N}$ $[\text{M}+\text{H}]^+$ 176.06815; found: 176.06816; HPLC (Method A, Chiralcel OD-R column): t_{Rmajor} = 8.48 min; t_{Rminor} = 9.23 min. $[\alpha]_{\text{D}}^{23}$ = + 17.0 (c = 1.0, MeOH), lit. (ref 3) $[\alpha]_{\text{D}}^{25}$ = + 28.6 (c = 0.65, MeOH)

(1S)-2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanamine hydrochloride 6b: Using the procedure described above, 118 mg of **5b** gave 79 mg of a white solid in 86% yield. ^1H NMR(CD_3OD) δ 7.50 (d, J = 8.55 Hz, 2H), 7.09 (d, J = 8.55 Hz, 2H), 5.29 (q, J = 7.54 Hz, 1H), 3.86 (s, 3H); ^{19}F NMR (CD_3OD) δ -75.13; ^{13}C NMR (CD_3OD) δ 159.72, 128.01, 121.65 (q, J = 280.34 Hz), 117.90, 112.58, 53.07 (q, J = 32.75 Hz), 52.77; HRMS (+ESI): calcd for $\text{C}_9\text{H}_{10}\text{F}_3\text{NO}$ $[\text{M}+\text{H}]^+$ 206.07889; found: 206.07872; HPLC (Method A, Chiralpak AD column): t_{Rmajor} = 8.90 min; t_{Rminor} = 8.38 min. $[\alpha]_{\text{D}}^{23}$ = + 19.4 (c = 1.0, MeOH).

(1S)-2,2,2-Trifluoro-1-[4-(methylthio)phenyl]ethanamine hydrochloride 6c: Using the procedure described above, 131 mg of **5c** gave 88 mg of a white solid in 85% yield. ^1H NMR (CD_3OD) δ 7.48 (d, J = 8.32 Hz, 2H), 7.42 (d, J = 8.32 Hz, 2H), 5.32 (q, J = 7.45 Hz, 1H), 2.54 (s, 3H); ^{19}F NMR (CD_3OD) δ -75.05; ^{13}C NMR (CD_3OD) δ 143.29, 128.50, 126.01, 124.03, 123.45 (q, J = 279.60 Hz), 54.98 (q, J = 32.67 Hz), 13.46; HRMS (+ESI): calcd for $\text{C}_9\text{H}_{10}\text{F}_3\text{NS}$ $[\text{M}+\text{H}]^+$ 222.05609; found: 222.05588; HPLC (Method A, Chiralcel OD-R column): t_{Rmajor} = 11.49 min; t_{Rminor} = 13.35 min; $[\alpha]_{\text{D}}^{23}$ = + 21.1 (c = 1.0, MeOH).

(1S)-2,2,2-Trifluoro-1-(4-fluorophenyl)ethanamine hydrochloride 6d: Using the procedure described above, 75 mg of **5d** gave 49 mg of a white solid in 84% yield. ^1H NMR (CD_3OD) δ 7.66-7.62 (m, 2H), 7.35-7.31 (m, 2H), 5.43 (q, $J = 7.46$ Hz, 1H); ^{19}F NMR (CD_3OD) δ -75.01, -111.33; ^{13}C NMR (CD_3OD) δ 164.12 (d, $J = 249.80$ Hz), 130.89 (d, $J = 8.86$ Hz), 124.31 (d, $J = 1.59$ Hz), 123.35 (q, $J = 280.29$ Hz), 116.17 (d, $J = 22.30$ Hz), 54.63 (q, $J = 32.86$ Hz); HRMS (+ESI): calcd for $\text{C}_8\text{H}_7\text{F}_4\text{N}$ $[\text{M}+\text{H}]^+$ 194.05872; found: 194.05874; HPLC (Method A, Chiralpak AD column): $t_{\text{Rmajor}} = 9.29$ min; $t_{\text{Rminor}} = 8.01$ min. $[\alpha]_{\text{D}}^{23} = +17.9$ ($c = 1.0$, MeOH).

(1S)-2,2,2-Trifluoro-1-(3,5-difluorophenyl)ethanamine hydrochloride 6e: Using the procedure described above, 123 mg of **5e** gave 54 mg of a white solid in 56% yield. ^1H NMR (CD_3OD) δ 7.75-7.65 (m, 1H), 7.28-7.23 (m, 2H), 5.74-5.65 (m, 1H); ^{19}F NMR (CD_3OD) δ -75.08, -113.47; ^{13}C NMR (CD_3OD) δ 162.36-159.80 (m), 134.26-135.04 (m), 122.93 (q, $J = 280.83$ Hz), 112.48-112.23 (m), 104.45-104.12 (m), 46.67; HRMS (+ESI): calcd for $\text{C}_8\text{H}_6\text{F}_5\text{N}$ $[\text{M}+\text{H}]^+$ 212.04921; found: 212.04932; HPLC (Method A, Chiralpak AD column): $t_{\text{Rmajor}} = 6.14$ min; $t_{\text{Rminor}} = 5.84$ min. $[\alpha]_{\text{D}} = +4.0$ ($c = 1.0$, MeOH).

(1S)-2,2,2-Trifluoro-1-(2-methylphenyl)ethanamine hydrochloride 6f: Using the procedure described above, 118 mg of **5f** gave 47 mg of a white solid in 52% yield. ^1H NMR (CD_3OD) δ 7.56 (d, $J = 7.71$ Hz, 1H), 7.47-7.38 (m, 3H), 5.55 (q, $J = 7.27$ Hz, 1H), 2.49 (s, 3H); ^{19}F NMR (CD_3OD) δ -74.70; ^{13}C NMR (CD_3OD) δ 138.09, 131.27, 130.48, 126.81, 126.63, 126.61, 123.71 (q, $J = 280.64$ Hz), 51.41 (q, $J = 32.63$ Hz), 18.24; HRMS (+ESI): calcd for $\text{C}_9\text{H}_{10}\text{F}_3\text{N}$ $[\text{M}+\text{H}]^+$ 190.08383;

found: 190.08381; HPLC (Method A, Chiralcel OD-R column): $t_{\text{Rmajor}} = 11.02$ min; $t_{\text{Rminor}} = 9.74$ min; $[\alpha]_{\text{D}}^{23} = + 5.4$ (c = 1.0, MeOH).

(1S)-2,2,2-Trifluoro-1-pyridin-2-ylethanamine hydrochloride 6g: Using the procedure described above, 7.6 mg of **5g** gave 5.3 mg of a white solid in 69% yield. ^1H NMR (CD_3OD) δ 8.76-8.69 (m, 1H), 7.98-7.94 (m, 1H), 7.63 (d, $J = 7.02$ Hz, 1H), 7.57-7.53 (m, 1H), 5.59-5.51 (m, 1H); ^{19}F NMR (CD_3OD) δ -74.33. ^{13}C NMR (CD_3OD) δ 149.70, 146.85, 137.70, 125.35, 124.28, 123.03 (q $J = 281.44$ Hz), 55.04 (q, $J = 29.63$ Hz); HRMS (+ESI): calcd for $\text{C}_7\text{H}_7\text{F}_3\text{N}_2$ $[\text{M}+\text{H}]^+$ 177.06345; found: 177.06341; HPLC (Method B, Chiralpak AS column): $t_{\text{Rmajor}} = 8.96$ min; $t_{\text{Rminor}} = 7.44$ min; $[\alpha]_{\text{D}}^{23} = + 5.0$ (c = 0.36, MeOH).

NMR solvent: CD₃COCD₃

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NMR solvent: CD₃OD

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