Supporting Information

Small Molecule Disruptors of the Glucokinase-Glucokinase Regulatory Protein Interaction: 3. Structure–Activity Relationships within the Aryl Carbinol Region of the *N*-Arylsulfonamido-*N′*-aryl-piperazine Series

Nobuko Nishimura,*,† Mark H. Norman,*,† Longbin Liu,† Kevin C. Yang,† Kate S. Ashton,† Michael D. Bartberger,€ Samer Chmait,€ Jie Chen,§ Rod Cupples,‡ Christopher Fotsch,† Joan Helmering,‡ Steven R. Jordan,€ Roxanne K. Kunz,† Lewis D. Pennington,† Steve F. Poon,† Aaron Siegmund,† Glenn Sivits,‡ David J. Lloyd,‡ Clarence Hale,‡ and David J. St. Jean, Jr.†

Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799
† Department of Therapeutic Discovery - Medicinal Chemistry
€ Department of Therapeutic - Molecular Structure and Characterization
‡ Department of Metabolic Disorders
§ Department of Pharmacokinetics & Drug Metabolism

Table of Contents

Tables with standard deviations:

Table 1.

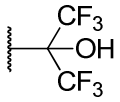
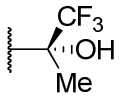
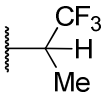
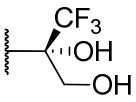
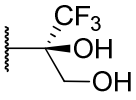
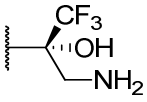
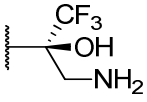
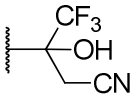
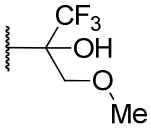
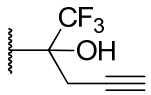
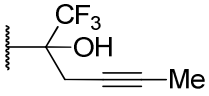
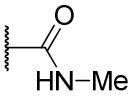
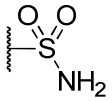
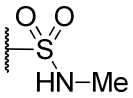
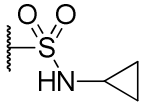
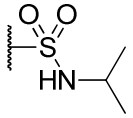
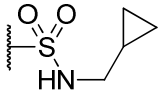
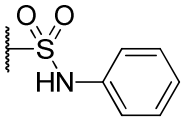
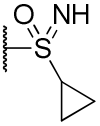
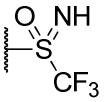
Cmpd number	R	Alpha IC_{50} (μM)[b]	Mouse Translocation EC_{50} (μM)[b]
1		0.004 ± 0.002	0.202 ± 0.112
2		0.009 ± 0.002	0.120 ± 0.068
10		25.0 ± 1.41 (n = 2)	NA
11		1.05 ± 0.184	1.56 ± 1.57
51		0.028 ± 0.002	0.098 ± 0.053
52		0.006 ± 0.004	0.089 ± 0.054
67		0.374 ± 0.364	5.67 ± 5.10
68		0.047 ± 0.019	0.537 ± 0.270
62		0.028 ± 0.003	0.219 ± 0.120
63		0.016 ± 0.005	0.202 ± 0.058
64		0.006 ± 0.003	0.130 ± 0.048
65		0.005 ± 0.001	0.137 ± 0.064

Table 2.

Cmpd number	R	Alpha IC_{50} (μM)[b]	Mouse Translocation EC_{50} (μM)[b]
12		1.09 ± 0.264	>12.5
13		3.07 ± 0.428	4.05 ± 1.63
14		3.36 ± 1.87	>12.5
20		0.401 ± 0151	0.936 ± 0.091 (n = 2)
49		0.061 ± 0.023	0.037 ± 0.011
15		0.035 ± 0.013	0.097 ± 0.014
16		0.101 ± 0.045	0.254 ± 0.214
21		0.235 ± 0.028	0.178 ± 0.024 (n = 2)
17		0.320 ± 0.167	0.271 ± 0.096
18		1.60 ± 0.662	>12.5
48		0.310 ± 0.178	0.704 ± 0.274
47		0.256 ± 0.177	0.208 ± 0.177
22		0.045 ± 0.019	0.567 ± 0.442

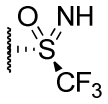
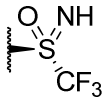
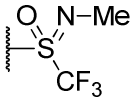
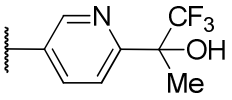
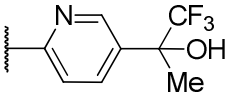
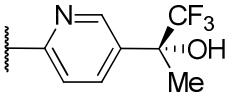
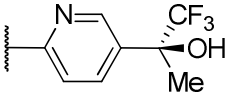
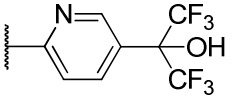
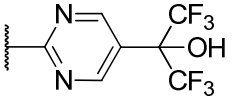
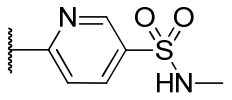
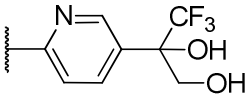
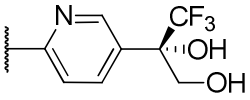
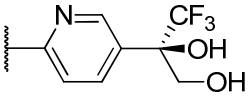
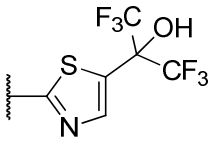
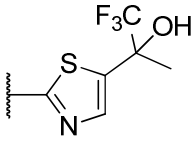
23		0.182 ± 0.013	2.22 ± 1.62
24		0.017 ± 0.006	0.388 ± 0.018
19		0.266 ± 0.090	2.06 ± 1.57

Table 3.

Cmpd number	R	Alpha IC_{50} (μM)[b]	Mouse Translocation EC_{50} (μM)[b]
25		0.069 ± 0.019	1.19 ± 0.306
28		0.018 ± 0.042	0.294 ± 0.185
29		0.013 ± 0.005	0.160 ± 0.039
30		0.013 ± 0.007	0.382 ± 0.172
26		0.010 ± 0.003	0.421 ± 0.196
88		0.010 ± 0.001	2.20 ± 2.29
27		0.068 ± 0.009	0.381 ± 0.269
53		0.024 ± 0.002	0.145 ± 0.057
54		0.013 ± 0.003	0.349 ± 0.252
55		0.070 ± 0.030	0.155 ± 0.059

74		0.081 ± 0.032	>12.5
80		0.049 ± 0.015	>12.5

Syntheses of intermediates:

Benzyl (3*S*)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (4) and benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (6).

A 2-L Erlenmeyer flask was charged with 2-piperazinone (36.5 g, 364 mmol), sodium carbonate (116 g, 1090 mmol), dioxane (600 mL), and water (150 mL). To this was slowly added benzyl chloroformate (62.1 g, 364 mmol) at room temperature over 20 min. After the addition was complete, the mixture was stirred for 2 h and then diluted with water and extracted with EtOAc (2 L). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a white solid. To this solid was added 500 mL of DCM, triethylamine (128 mL, 911 mmol), DMAP (4.45 g, 36.4 mmol), and di-*tert*-butyl dicarbonate (119 g, 546 mmol). After stirring at room temperature for 1 h, the mixture was diluted with water and the organics were separated. The organics were dried ($MgSO_4$), filtered, and concentrated to give a brown oil. To this oil was added 100 mL of DCM followed by 1 L of hexane. The resulting white solid was collected by filtration to give 4-benzyl 1-*tert*-butyl 2-oxo-1,4-piperazinedicarboxylate (101 g).

A 150-mL round-bottomed flask was charged with 4-benzyl 1-*tert*-butyl 2-oxo-1,4-piperazinedicarboxylate (1.41 g, 4.22 mmol) and THF (5 mL). 1-Propynylmagnesium bromide (0.5 M in THF, 20.0 mL, 10.0 mmol) was added at 0 °C slowly. The mixture was stirred at 0 °C for 2 h. Saturated aqueous NH_4Cl (40 mL) was added and the aqueous phase was extracted with EtOAc (200 mL, then 2 × 100 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under a vacuum. The crude product was purified by column chromatography (50 g of silica, 0 to 50% EtOAc in hexanes) to afford benzyl (2-((*tert*-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate (1.55 g) as a clear oil.

A 3-L round-bottomed flask was charged with benzyl 2-((*tert*-butoxycarbonyl)amino)ethyl)(2-oxo-3-pentyn-1-yl)carbamate (82.17 g, 219 mmol) and 300 mL of DCM. After cooling to -10 °C, TFA (169 mL, 2200 mmol) was added and the resulting dark solution was stirred at room temperature for 15 min. Sodium triacetoxyborohydride (186 g, 878 mmol) was then added portion-wise over 10 min. After 2 h, the mixture was concentrated, diluted with EtOAc (1 L), and neutralized with 5 N NaOH. The layers were separated and the organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The resulting orange oil was purified via column chromatography (750 g of silica gel, 0 to 4.5 % MeOH/DCM) to give benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (**6**) (43.67 g) as a brown foam.

A 20-mL vial was charged with benzyl 3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.616 g, 2.38 mmol), di-*tert*-butyl dicarbonate (0.979 g, 4.49 mmol), DMAP (0.0287 g, 0.235 mmol), TEA (0.90 mL, 6.5 mmol) and DCM (8 mL). The mixture was stirred at room temperature for 30 min. The reaction mixture was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL). The organic phase was washed with saturated aqueous sodium chloride (40 mL), dried over sodium sulfate, filtered, and concentrated under a vacuum. The crude product was purified by column chromatography (25 g of silica, 0 to 50% EtOAc in hexanes) to afford 4-benzyl 1-*tert*-butyl 2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate (0.488 g) as a colorless oil.

The individual enantiomers of 4-benzyl 1-*tert*-butyl 2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate were isolated using chiral SFC. The method used was as follows: Chiralpak® ADH column (30 x 250 mm, 5 μm) using 12% ethanol in supercritical CO_2 (total flow was 170 mL/min). This separated the two enantiomers with enantiomeric excesses greater than 98%. The first eluting peak was subsequently identified as 4-benzyl 1-*tert*-butyl (2*S*)-2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate and used in the next step.

A 100-mL round-bottomed flask was charged with 4-benzyl 1-*tert*-butyl (2*S*)-2-(1-propyn-1-yl)-1,4-piperazinedicarboxylate (0.145 g, 0.405 mmol), TFA (1.0 mL, 13 mmol) and DCM (2 mL). The mixture was stirred at room temperature for 40 min. The mixture was concentrated and solid $NaHCO_3$ was added followed by saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with 1N NaOH (40 mL), saturated aqueous $NaHCO_3$ (40 mL), water (40 mL) and saturated aqueous sodium chloride (40 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated under a vacuum to afford benzyl (3*S*)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (0.100 g) as a pale-yellow clear oil which solidified upon standing to give a pale-yellow solid. ^{1}H NMR (400MHz, MeOD) δ ppm 7.47 - 7.13 (m, 5 H), 5.27 - 5.00 (m, 2 H), 3.88 - 3.58 (m, 3 H), 3.48 - 3.33 (m, 2 H), 3.22 - 3.02 (m, 1 H), 2.89 - 2.63 (m, 1 H), 1.80 (s, 3 H). m/z (ESI, +ve ion) 259.1 $(M+H)^+$.

(3*S*)-1-benzyl-3-(1-propyn-1-yl)piperazine (5).

A 1-L round-bottoemd flask was charged with (2*S*)-2-((*tert*-butoxycarbonyl)amino)-4-pentynoic acid (42.0 g, 197 mmol), ethyl 2-(benzylamino)acetate (40.0 g, 207 mmol), HATU (90 g, 240 mmol) and 200 mL of DMF. To this was added *N*-ethyl-*N*-isopropylpropan-2-amine (51.5 mL, 296 mmol). After 15 min of stirring at room temperature, the mixture was diluted with water (300 mL) and extracted with 20% EtOAc in diethyl ether (1 L). The layers were separated and the organic was washed with 2 M HCl, water, sat. aq. $NaHCO_3$ and brine. The extracts were dried and concentrated to give an off-white solid. To this was added 200 mL of DCM and TFA (152 mL, 1970 mmol). After stirring at room temperature for 30 min, the mixture was concentrated and then azetroped with 100 mL toluene (2 ×). To the brown oil obtained was added ammonia (2 M in MeOH, 394 mL). The mixture was stirred at room temperature for 30 min. The mixture was concentrated, dissolved in EtOAc, and washed with water. The organics were dried ($MgSO_4$), filtered, and concentrated to give a white solid that was triturated with diethyl ether to give (3*S*)-1-benzyl-3-(2-propyn-1-yl)-2,5-piperazinedione (37.3 g) as a white solid.

A 1-L round-bottomed flask was charged with (3*S*)-1-benzyl-3-(2-propyn-1-yl)-2,5-piperazinedione (37.3 g, 154 mmol) and 150 mL of THF. To this was slowly added aluminum (III) lithium hydride (1M in THF, 539 mL, 539 mmol). After the addition was complete the mixture was heated at 80 °C for 12 h. The mixture was then cooled to 0 °C and solid sodium sulfate decahydrate was added until bubbling ceased. The mixture was filtered and the filtrate was concentrated to give (3*S*)-1-benzyl-3-(2-propyn-1-yl)piperazine (18.1 g) as a yellow oil.

To a solution of (3*S*)-1-benzyl-3-(2-propyn-1-yl)piperazine (2.3 g, 11 mmol) in THF (50 mL) was added potassium *t*-butoxide (2.41 g, 21.5 mmol). The reaction mixture was stirred at room temperature for 30 min, then quenched with water (200 mL) and EtOAc (300 mL) was added. The organic phase was dried over sodium sulfate, filtered and concentrated under a vacuum to give a solid that was purified by silica gel column chromatography (0 to 10% MeOH in DCM) and then recrystallized from hexanes to afford (3*S*)-1-benzyl-3-(1-propyn-1-yl)piperazine (2.16 g) as an off-white solid. ^{1}H NMR (400MHz, CD_3OD) δ ppm 7.42 - 7.21 (m, 5 H), 3.59 - 3.49 (m, 3 H), 2.93 (td, *J* = 2.9, 12.4 Hz, 1 H), 2.86 - 2.73 (m, 2 H), 2.68 (d, *J* = 11.3 Hz, 1 H), 2.22 - 2.04 (m, 2 H), 1.80 (d, *J* = 2.3 Hz, 3 H).

***tert*-Butyl (3*S*)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (72).**

(2*R*)-1,4-bis(tert-butoxycarbonyl)-2-piperazinecarboxylic acid (25 g, 76 mmol) was mixed into 145 mL of THF. Borane tetrahydrofuran complex (1 M in THF, 144 mL, 144 mmol) was added to the mixture dropwise via addition funnel. The mixture was then heated to 50 °C and stirred for 3 h. The mixture was allowed to cool to room temperature and carefully quenched with ~30 mL of 1.0 N HCl. The mixture was then diluted with EtOAc (300 mL) and washed with 1.0 N NaOH (2 × 200 mL) and saturated aqueous NaCl (200 mL), then dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded a sticky solid which was disolved in DMF (300 mL). Sodium hydride (60% dispersion in mineral oil, 3.03 g, 76 mmol) was added to the mxiture in two portions. After 1.5 h, the bubbling subsided and the reaction was qhenched with saturated aqueous NH_4Cl (200 mL). The mixture was diluted with 200 mL of water and extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with water (2 × 200 mL) and saturated aqueous NaCl (200 mL), then dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded a whtie solid. The product was reccrystallized from EtOAc/hexanes to afford *tert*-butyl (8a*R*)-3-oxotetrahydro[1,3]oxazolo[3,4-a]pyrazine-7(1H)-carboxylate (11.1 g, 61%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.43 (t, *J* = 8.6 Hz, 1 H), 4.24 (br s, 1 H), 4.10 (br s, 1 H), 4.02 - 3.89 (m, 1 H), 3.86 - 3.66 (m, 2 H), 3.01 (dt, *J* = 3.7, 12.7 Hz, 1 H), 2.88 - 2.73 (m, 1 H), 2.73 - 2.51 (m, 1 H), 1.48 (s, 9 H).

tert-Butyl (8a*R*)-3-oxotetrahydro[1,3]oxazolo[3,4-a]pyrazine-7(1H)-carboxylate (11.7 g, 48.3 mmol) was dissolved into 150 mL of EtOH. The mixture was heated to 80 °C. Lithium hydroxide monohydrate (20.3 g, 483 mmol) in 110 mL of water was added to the mixture. The mixture was then heated at reflux and stirred for 1 h. The mixture was allowed to cool to room temperature and neutralized with 3.0 N HCl (~130 mL). The mixture was extracted with DCM (3 × 250 mL). The combined organic extracts were dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded (10.33 g, 99 %) as a yellow oil that gradually solidifed to a white crystaline solid

upon standing. ^{1}H NMR (400MHz, $CDCl_3$) δ 3.87 (br. s., 2 H), 3.65 (dd, *J* = 3.6, 10.7 Hz, 1 H), 3.50 (dd, *J* = 6.8, 10.6 Hz, 1 H), 2.99 (d, *J* = 11.9 Hz, 1 H), 2.91 (t, *J* = 11.3 Hz, 1 H), 2.84 - 2.62 (m, 3 H), 1.90 (br. s., 1 H), 1.67 (br. s., 1 H), 1.46 (s, 9 H).

Imidazole (30.2 g, 444 mmol) was dissolved into 240 mL of DCM and chilled to 0 °C. Thionyl chloride (9.76 mL, 134 mmol) was added slowly to the mixture. After 5 min, the mxiture was warmed to room temperature and stirred for 1 h. The mixture was then cooled to -78 °C. *tert*-Butyl (3*R*)-3-(hydroxymethyl)-1-piperazinecarboxylate (10.33 g, 47.8 mmol) in DCM (240 mL) was added dropwis via addition funnel. The mixture was then allowed to warm to room temperature and stirred for 18h. The mixture was quenched with saturated aqueous NH_4Cl (200 mL) and diluted with water (200 mL). The mixture was partitioned and the aqueous portion was extracted with DCM (200 mL). The combined organic extracts were dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded *tert*-butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3*H*)-carboxylate 1-oxide (12.2 g, 98 %) as a white solid.

tert-Butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3*H*)-carboxylate 1-oxide (12.2 g, 46.6 mmol) was mixed in MeCN (300 mL) and EtOAc (50 mL) and chilled to 0 °C. Sodium periodate (12.96 g, 60.6 mmol) in water (100 mL) was added, followed by ruthenium chloride hydrate (0.021 g, 0.093 mmol). The mixture was allowed to warm to roomtemperature and stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (200 mL) and water (200 mL) and extracted DCM (2 × 300 mL). The combined organic extracts were dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded (11.6 g, 89 % yield) as a tan solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.63 (t, *J* = 7.0 Hz, 1 H), 4.23 (t, *J* = 8.4 Hz, 2 H), 4.07 (br. s., 1 H), 3.76 - 3.59 (m, 1 H), 3.45 (d, *J* = 11.7 Hz, 1 H), 3.25 - 3.08 (m, 1 H), 2.96 (dt, *J* = 2.7, 11.1 Hz, 2 H), 1.47 (s, 9 H).

(Trimethylsilyl)acetylene (3.96 mL, 28.0 mmol) was disolved in THF (100 mL) and chilled to -78 °C. *n*-Butyllithium (2.5 M in hexanes, 10.78 mL, 26.9 mmol) was added to the mixture. After 5 min, the mixutre was warmed to 0 °C and stirred for 15 min. The mixture was cooled to -78 °C. *tert*-Butyl (3a*R*)tetrahydro[1,2,3]oxathiazolo[3,4-a]pyrazine-5(3*H*)-carboxylate 1,1-dioxide (3.0 g, 10.8 mmol) in THF (15 mL) was added dropwise to the mixture. The mixture was allowed to gradually warm to room temperature. After 3 h, the reaction was quenched with 0.5 N HCl (100 mL) and the mixture was stirred for 18 h. The mixture was basified with aqueous 10 N NaOH and the mixture was extracted with EtOAc (2 × 100mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL) and dried ($MgSO_4$). Filtration and concentration under reduced pressure, followed by silica gel column chromatography (1 to 10% MeOH in DCM) afforded *tert*-butyl (3*S*)-3-(3-(trimethylsilyl)-2-propyn-1-yl)-1-piperazinecarboxylate (2.6 g, 81 %) as an orange solid.

tert-Butyl (3*S*)-3-(3-(trimethylsilyl)-2-propyn-1-yl)-1-piperazinecarboxylate (2.6 g, 8.8 mmol) was dissolved into THF (40 mL). Potassium *tert*-butoxide (2.95 g, 26.3 mmol) was added. The mixture was stirred for 2 h. The reaction was quenched with saturated aquesou NH_4Cl (30 mL) and diluted with water (30 mL). The mixture was extracted with DCM (2 × 100 mL) and the combined organic extracts dried ($MgSO_4$). Filtration and concentration under reduced pressure, followed by silica gel column chromatography (1 to 10% MeOH in DCM) afforded *tert*-butyl (3*S*)-3-(1-propyn-1-yl)-1-piperazinecarboxylate (1.56 g, 79 %) as a tan solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 3.80

(br s, 1 H), 3.64 (td, *J* = 3.4, 13.1 Hz, 1 H), 3.48 (dd, *J* = 2.4, 5.6 Hz, 1 H), 3.19 - 2.96 (m, 3 H), 2.74 - 2.64 (m, 1 H), 1.81 (d, *J* = 2.2 Hz, 3 H), 1.79 - 1.75 (m, 1 H), 1.46 (s, 9 H).

***tert*-Butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate (9).**

A 3-L round-bottomed flask was charged with 5-nitro-2-pyridinamine (75.0 g, 539 mmol) and 500 mL of DCM. To this was added triethylamine (82 g, 810 mmol), di-*tert*-butyl dicarbonate (129 g, 593 mmol), and *N,N*-dimethylpyridin-4-amine (32.9 g, 270 mmol). After stirring at room temperature for 18 h, the mixture was diluted with water and the solid was collected by filtration. The yellow solid was washed with MeOH to give *tert*-butyl (5-nitro-2-pyridinyl)carbamate (94.6 g) as a light-yellow solid.

A 3-L round-bottomed flask was charged with *tert*-butyl (5-nitro-2-pyridinyl)carbamate (96.4 g, 403 mmol), 500 mL of MeOH, 500 mL of THF, and 100 mL of sat. aq. NH_4Cl. Zinc (105 g, 1610 mmol) was slowly added (over 10 min) to this solution. The mixture was stirred at room temperature for 12 h, then filtered. The filtrate was concentrated and then diluted with EtOAc and washed with water. The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting solid was recrystallized from MeOH to give *tert*-butyl(5-amino-2-pyridinyl)carbamate (38.6 g) as a light-yellow solid.

A 3-L round-bottomed flask was charged with sodium nitrite (15.3 g, 221 mmol), 100 mL of water and 500 mL of MeCN. After cooling to 0 °C, conc. hydrochloric acid (231 mL, 2770 mmol) was slowly added keeping the internal temperature below 10 °C. After stirring at 0 °C for 10 min, *tert*-butyl (5-amino-2-pyridinyl)carbamate (38.6 g, 184 mmol) was added as a suspension in acetonitrile (200 mL). The mixture was stirred for 30 min, then 150 mL of AcOH, copper(ii) chloride (12.4 g, 92.2 mmol), and copper(i) chloride (0.183 g, 1.85 mmol) were added. SO_2 gas was bubbled through the solution for 15 min. The mixture was stirred at 0 °C for 30 min, then about 500 mL of ice-cold water was added. The resulting precipitate was collected by filtration and dried over $MgSO_4$ to give *tert*-butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate (15.5 g) as a white solid. ^1H NMR (400MHz, $CDCl_3$) δ ppm 8.93 (br s, 1 H), 8.63 - 8.42 (m, 1 H), 8.35 - 7.94 (m, 2 H), 1.58 (s, 9 H).

1-Bromo-4-(2,2,2-trifluoro-1-methylethyl)benzene (ArBr for 11).

A 500-mL round-bottomed flask was charged with 1,4-dibromobenzene (30.3 g, 128 mmol) and diethyl ether (200 mL). After cooling to -78 °C, *n*-BuLi (2.5 M in hexanes, 59.0 mL, 148 mmol) was added. This mixture was stirred for 15 min at -78 °C, then 1,1,1-trifluoro-2-propanone (24.2 mL, 257 mmol) was added. Stirring was continued at -78 °C for 30 min and then the mixture was quenched with saturated aqueous NH_4Cl (100 mL). The mixture was extracted with EtOAc (250 mL), dried ($MgSO_4$), filtered, and concentrated to give an oil. Purification via column chromatography (0 to 30% EtOAc in hexanes) gave 2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol (21.5 g, 64%) as a colorless oil.

In a 50-mL round-bottomed flask was added 2-(4-bromophenyl)-1,1,1-trifluoro-2-propanol (2.3 g, 8.6 mmol), $SOCl_2$ (7.0 mL, 96 mmol), and pyridine (0.08 mL, 1.0 mmol). The mixture was heated to 70 °C for 70 min and then allowed to cool to room temperature. The mixture was concentrated and the residue was dissolved in EtOAc (30 mL), washed with sat. aq. $NaHCO_3$ (10 mL), dried (Na_2SO_4), filtered, and concentrated

to give a 2:1 mixture (by ^{1}H NMR) of 1-bromo-4-(1-(trifluoromethyl)ethenyl)benzene and 1-bromo-4-(1-chloro-2,2,2-trifluoro-1-methylethyl)benzene as a clear oil (2.3 g, 99% combined yield).

A mixture of 1-bromo-4-(1-(trifluoromethyl)ethenyl)benzene and 1-bromo-4-(1-chloro-2,2,2-trifluoro-1-methylethyl)benzene (2:1 ratio, 2.2 g, 4.1 mmol), triethylamine (1.0 mL, 7.2 mmol), and platinum(IV) oxide (120 mg, 0.528 mmol) in MeOH-EtOAc (1:1, 100 mL) was purged with a balloon of H_2 (4×) and stirred at room temperature. After 23 h, more platinum(IV) oxide (100 mg, 0.440 mmol) was added. After an additional 23 h, the mixture was filtered through a pad of diatomaceous earth. The filtrate was washed with water, HCl (1 N, 5 mL), and saturated NH_4Cl (10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to a clear oil (1.0 g). The oil was purified by chromatography on silica using hexanes as eluent to give 1-bromo-4-(2,2,2-trifluoro-1-methylethyl)benzene (0.55 g, 53%) as a clear oil. MS (ESI pos. ion) *m/z*: calc'd for $C_9H_8BrF_3$: 251.976; found 252 (GCMS). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.0 Hz, 2 H), 7.19 (d, *J* = 7.2 Hz, 2 H), 3.33 - 3.47 (m, 1 H), 1.49 (d, *J* = 6.1 Hz, 3 H).

4-Bromo-*N*-methylbenzamide (ArBr for 13).

In 250-mL round-bottom flask, a stirred solution of 4-bromobenzoic acid (2 g, 9.9 mmol) in DMF (20 mL) was treated sequentially with HOBt (2 g, 14.8 mmol), methyl amine hydrochlrodie (0.724 g, 10.8 mmol), EDC·HCl (2.83 g,14.8 mmol) and DIPEA (3.5 mL, 20 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere then quenched with cold water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water, brine, and dried (Na_2SO_4). The residue obtained was concentrated under reduced pressure to give 4-bromo-*N*-methylbenzamide (1.3 g, 62%) as a white solid. MS (ESI pos. ion) *m/z*: calc'd for C_8H_8BrNO: 212.979; found 214.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, *J* = 5.0 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.67 (dd, *J* = 8.6, 1.9 Hz, 2H), 2.77 (dd, *J* = 4.8, 1.6 Hz, 3H).

1-Bromo-4-(methylsulfinyl)benzene (ArBr for 14 and 48).

In 250-mL round-bottomed flask, a stirred solution of (4-bromophenyl)(methyl)sulfane (17 g, 84.1 mmol) in acetic acid (20mL) maintained at 0 ^{o}C was treated with H_2O_2 (35%, 12 mL, 125 mmol) over period of 10 min. The mixture was allowed to gradually warm to room temperature and stirred overnight. The reaction mixture was neutralized with NaOH (12 N, 35mL) solution at 0 ^{o}C and extracted with DCM (3 × 100 mL). The combined organic extracts were washed with water, brine, and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give 1-bromo-4-(methylsulfinyl)benzene (16.5 g, 90%) as a white solid. MS (ESI pos. ion) *m/z*: calc'd for C_7H_7BrOS: 217.940; found 218.9. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*= 8.7 Hz, 2 H), 7.53 (d, *J* = 8.7 Hz, 2 H), 2.73 (s, 3 H).

4-Bromo-*N*-methylbenzenesulfonamide (ArBr for 15).

To a stirring solution of 4-bromobenzenesulfonyl chloride (2.0 g, 7.8 mmol) and DIPEA (1.50 mL, 8.61 mmol) in DCM (25 mL) at 0 ºC, was added methanamine (2 M in THF, 7.83 mL, 15.7 mmol). After 10 min, the reaction mixture was treated with 1 M

KH_2PO_4 (50 mL). The solution was concentrated under reduced pressure and then purified by silica gel chromatography (0 to 4% of MeOH/CH_2Cl_2) to afford 4-bromo-*N*-methylbenzenesulfonamide (1.80 g) as a white solid. MS (ESI pos. ion) *m/z*: calc'd for $C_7H_8BrNO_2S$: 248.946; found 249.9.

4-Bromo-*N*-cyclopropylbenzenesulfonamide (ArBr for 16).

In a 50-mL round-bottomed flask, cyclopropylamine (0.22g, 3.9 mmol) was dissolved in DCM (10 mL) under nitrogen atmosphere and maintained at 0 ^oC. Et_3N (1.13 mL, 7.84 mmol) and 4-bromobenzenesulfonyl chloride (1.0 g, 3.9 mmol) were sequentially added to the above reaction mixture and the reaction mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction mixture was diluted with ice-cold water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography (elution 30% EtOAc-hexanes) to give 4-bromo-*N*-cyclopropylbenzenesulfonamide (0.80 g, 71%) as a brown solid. MS (ESI pos. ion) *m/z*: calc'd for $C_9H_{10}BrNO_2S$: 274.962; found 276.0 (M+1). ^1H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 2.7 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.73 (d, J = 8.0 Hz, 2 H), 2.11 (td, J = 6.8, 3.3 Hz, 1 H), 0.48 (dd, J = 7.2, 4.8 Hz, 2 H), 0.37 (q, J = 3.8 Hz, 2 H).

4-Bromo-*N*-(cyclopropylmethyl)benzenesulfonamide (ArBr for 17 and 49).

In a 50-mL round-bottomed flask, 1-cyclopropylmethanamine (0.28 g, 3.9 mmol) was dissolved in DCM (10 mL) under nitrogen atmosphere and maintained at 0 ^oC. Et_3N (1.13 mL, 7.84 mmol) and 4-bromobenzenesulfonyl chloride (1.0 g, 3.9 mmol) were sequentially added to the above reaction mixture and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ice-cold water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution 30% EtOAc-hexanes) to give 4-bromo-*N*-(cyclopropylmethyl)benzenesulfonamide (0.80 g, 71%) as a brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1 H), 7.83 - 7.79 (m, 2 H), 7.76 - 7.67 (m, 2 H), 2.65 (d, J = 6.7 Hz, 2 H), 0.82 - 0.72 (m, 1 H), 0.39 - 0.29 (m, 2 H), 0.11 - 0.03 (m, 2 H).

4-Bromo-*N*-phenylbenzenesulfonamide (ArBr for 18).

In a 50-mL round-bottomed flask, aniline (0.36 g, 3.92 mmol) was dissolved in pyridine (10 mL) at room temperature under nitrogen atmosphere and maintained at 0 ^oC. 4-Bromobenzenesulfonyl chloride (1.0 g, 3.92 mmol) was added to the above solution under a nitrogen atmosphere. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 1 h. The reaction mixture was diluted with ice-cold water (10 mL) and EtOAc (20 mL). The organic layer was separated, washed with water, brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give 4-bromo-*N*-phenylbenzenesulfonamide (0.42 g, 35%) as a brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1 H), 7.67 (d, J = 8.8 Hz, 2 H), 7.65 (d, J = 8.8 Hz, 2 H), 7.26-7.22 (m, 2 H), 7.12 – 7.00 (m, 3 H).

1-Bromo-4-(*N*-methyl-*S*-(trifluoromethyl)sulfonimidoyl)benzene (ArBr for 19).

In a 20-mL re-sealable reaction tube, a solution of 1-bromo-4-(*S*-(trifluoromethyl) sulfonimidoyl)benzene (0.5 g, 1.7 mmol, see ArBr for **22**) in THF (10 mL) was treated with potassium carbonate (1.2 g, 8.7 mmol) at room temperature under a nitrogen atmosphere and stirred for 10 min. Methyl iodide (0.55 mL, 8.7 mmol) was added to the above solution. The reaction tube was sealed and reaction mixture was heated at 80 ^{o}C for 12 h. The reaction mixture was allowed to cool to room temperature and diluted with water and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give of 1-bromo-4-(*N*-methyl-*S*-(trifluoromethyl)sulfonimidoyl)benzene (350 mg, 66%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J*= 8.4 Hz, 2 H), 3.08 (s, 3 H).

4-Bromo-*N*-(1-methylethyl)benzenesulfonamide (for 21).

In a 100-mL round-bottomed flask, 4-bromobenzene-1-sulfonyl chloride (0.5 g, 2.0 mmol) was dissolved in DCM (5 mL) at room temperature under nitrogen atmosphere. Pyridine (2.5 mL) and isopropyl amine (140 mg, 2.35 mmol) were added sequentially to the above solution. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 2 h. The reaction mixture was diluted with ice-cold water (10 mL) and DCM (20 mL). The organic layer was separated, washed with water, brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure to give 4-bromo-*N*-(1-methylethyl)benzenesulfonamide (0.54 g, 99%) as a white solid. MS (ESI pos. ion) *m/z*: calc'd for $C_9H_{12}BrNO_2$: 276.977; found 278.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 - 7.78 (m, 2 H), 7.77 - 7.69 (m, 3 H), 3.31 - 3.18 (m, 1 H), 0.95 (d, *J* = 6.4, 6 H).

1-Bromo-4-(*S*-(trifluoromethyl)sulfonimidoyl)benzene (ArBr for 22).

A 250-mL, 3-necked, round-bottomed flask equipped with thermometer was charged with 1-bromo-4-((trifluoromethyl)sulfanyl)benzene (5.00 g, 19.5 mmol) and toluene (50 mL). The solution was cooled to 1 to 2 ºC in ice-water bath. 3-Chlorobenzoperoxoic acid (4.81 g, 21.5 mmol) was added portion-wise over a 15 min period, using total of 10 mL of toluene for rinsing. The internal temperature stayed under 3 ºC during the addition. The resulting white cloudy mixture was stirred at about 1 ºC for 6 h. The reaction mixture was allowed to warm up to room temperature slowly and stirred for overnight at room temperature. 2 M K_3PO_4 (50 mL) was added slowly to the reaction mixture. The mixture was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with water (60 mL) and saturated aqueous sodium chloride (60 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under a vacuum. The crude product was purified by column chromatography (150 g of silica, 0 to 10% EtOAc in hexanes) to afford 1-bromo-4-((trifluoromethyl)sulfinyl)benzene (4.29 g, 81%) as glassy white solid.

A 20-mL vial was charged with 1-bromo-4-((trifluoromethyl)sulfinyl)benzene (2.03 g, 7.42 mmol) and acetonitrile (0.600 mL, 11.5 mmol). The mixture was cooled to -15 ºC and trifluoromethanesulfonic anhydride (1.90 mL, 11.3 mmol) was added dropwise. The mixture was stirred at -15 ºC for overnight. Water (7.4 mL) was added to the mixture followed by sodium hydroxide (0.594 g, 14.8 mmol) and potassium

permanganate (1.17 g, 7.38 mmol). The vial was capped and the dark mixture was stirred at 110 ºC under N_2 for 2 h. The mixture was cooled to room temperature and extracted with DCM (3 × 30 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under a vacuum. The crude product was purified by column chromatography (0 to 10% EtOAc in hexanes) to afford 1-bromo-4-(*S*-(trifluoromethyl)sulfonimidoyl)benzene (1.04 g, 49%) as a white solid. MS (ESI pos. ion) *m/z*: calc'd for $C_7H_5BrF_3NOS$: 286.923; found 287.9. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2 H), 7.84 - 7.74 (m, 2 H), 3.64 (br. s., 1 H).

2-(5-Bromo-2-pyridinyl)-1,1,1-trifluoro-2-propanol (for 25).

To a 100-mL round-bottomed flask, 1-(5-bromopyridin-2-yl)ethanone (0.257 g, 1.29 mmol) and (trifluoromethyl)trimethylsilane (0.230 mL, 1.56 mmol) were dissolved into DME (5 mL). The mixture was cooled to 0 °C and cesium fluoride (0.012 g, 0.080 mmol) was added. The mixture was stirred at 0 °C for 2.5 h. TBAF (1.5 mL, 1.5 mmol) was added and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were washed with saturated aqueous NaCl (40 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc in hexanes 0 - 25%) to afford 2-(5-bromo-2-pyridinyl)-1,1,1-trifluoro-2-propanol (0.312 g, 90%) as a clear oil. MS (ESI pos. ion) *m/z*: calc'd for $C_8H_7BrF_3NO$: 268.966; found 269.9. ^{1}H NMR (300MHz ,$CDCl_3$) δ 8.68 (d, *J* = 0.6 Hz, 1 H), 7.95 (dd, *J* = 2.2, 8.5 Hz, 1 H), 7.44 (d, *J* = 8.5 Hz, 1 H), 5.84 (s, 1 H), 1.73 (d, *J* = 0.6 Hz, 3 H).

2-(6-Bromo-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 2-(6-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (ArX for 26).

To a stirred mixture of 6-chloronicotinyl chloride (0.603 g, 3.43 mmol) and tetramethylammonium fluoride (0.978 g, 10.5 mmol) in DME (10 mL) in 100-mL round-bottomed flask, trimethyl(trifluoromethyl)silane (1.6 mL, 10.8 mmol) was added at once at -78 °C. The mixture allowed to warm up to room temperature slowly. The stirring at room temperature was continued for 20 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (30 mL). The aqueous phase was extracted with EtOAc (40 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (EtOAc in hexanes 0 - 40%) to afford 2-(6-chloropyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (0.556 g, 58%) as a flaky glassy solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.2 Hz, 1 H), 8.02 (dd, *J* = 2.2, 8.4 Hz, 1 H), 7.47 (d, *J* = 8.6 Hz, 1 H), 4.25 (s, 1 H).

To a stirred solution of 2-(6-chloropyridin-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (0.162 g, 0.580 mmol) in DCM (2 mL) in 20 mL scintillation vial, hydrobromic acid in acetic acid (0.50 mL, 3.04 mmol) was added dropwise at room temperature. The light-orange mixture was stirred at room temperature for 5 h, then the mixture was warmed up to 50 °C to remove DCM. HBr (1 mL) was added and the mixture was stirred at 50 °C for 10 h. Solid $NaHCO_3$ was added followed by saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo to afford mixture of 2-(6-bromo-3-

pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol and 2-(6-chloro-3-pyridinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (0.170 g, 50%) as a tan solid. LCMS indicated the ratio was ~1:1.

6-Chloro-*N*-methyl-3-pyridinesulfonamide (ArCl for 27).

A 100-mL round-bottomed flask was charged with 6-chloro-3-pyridinesulfonyl chloride (0.526 g, 2.48 mmol)[i], Et_3N (1.04 mL, 7.45 mmol), and DCM (10 mL). Methylamine (2.0 M solution in THF, 1.30 mL, 2.60 mmol) was added dropwise at room temperature. The mixture was stirred at room temperature for 15 min and partitioned between water (30 mL) and DCM (30 mL). The aqueous phase was extracted with DCM (30 mL). The combined organic phases were washed with saturated aqueous NaCl (50 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica gel column chromatography (0 to 60% EtOAc in hexanes) to afford 6-chloro-*N*-methyl-3-pyridinesulfonamide (0.429 g) as a white solid. MS (ESI pos. ion) *m/z*: calc'd for $C_6H_7ClN_2O_2S$: 205.992 found 207.0 (M+1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.5 Hz, 1 H), 8.08 (dd, *J* = 2.6, 8.4 Hz, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 4.57 (d, *J* = 4.2 Hz, 1 H), 2.73 (d, *J* = 5.3 Hz, 3 H).

2-(6-Bromopyridin-3-yl)-1,1,1-trifluoropropan-2-ol (ArBr for 28).

To a stirred mixture of 5-acetyl-2-bromopyridine (9.67 g, 48.3 mmol) in DME (100 mL) in 500-mL round-bottomed flask, (trifluoromethyl)trimethylsilane (8.60 mL, 58.2 mmol) was added followed by cesium fluoride (0.388 g, 2.55 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min. 5 N hydrochloric acid (20 mL, 100 mmol) was added and the cold bath was removed. The mixture was stirred at room temperature for overnight. Saturated aqueous $NaHCO_3$ (150 mL) was added slowly while stirring. EtOAc (50 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (100 mL). The combined organic phases were washed with water (200 mL) and saturated aqueous NaCl (200 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford 2-(6-bromopyridin-3-yl)-1,1,1-trifluoropropan-2-ol (12.79 g, 98%) as a light-brown oil which solidified upon standing. This material was used without further purification. MS (ESI pos. ion) *m/z*: calc'd for $C_8H_7BrF_3NO$: 268.966; found 270.0.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1 H), 7.78 (d, *J* = 8.4 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 2.73 (s, 1 H), 1.82 (s, 3 H).

1-Bromo-4-(cyclopropylsulfanyl)benzene (ArBr for 47).

In a 20-mL re-sealable reaction tube, a mixture of 4-bromobenzenethiol (0.5 g, 2.6 mmol) and potassium *tert*-butoxide (0.6 g, 5.3 mmol) in DMSO (5 mL) were stirred at room temperature for 10 minutes. Bromocyclopropane (0.35 g, 2.9 mmol) was added to the above mixture at room temperature under nitrogen atmosphere. The reaction tube was sealed under an argon atmosphere and the reaction mixture was heated at 100 ^{o}C for 12 h. The reaction mixture was allowed to cool to room temperature and filtered through a diatomaceous earth pad. The filtrate was diluted with cold water (30 mL) and ethyl acetate (30 mL). The organic layer was separated, washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the residue obtained was purified by silica gel column chromatography (1% EtOAc-hexanes) to give of 1-bromo-4-(cyclopropylsulfanyl)benzene (300 mg, 50%) as a

white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6.8 Hz, 2 H), 7.22 (d, *J* = 6.8 Hz, 2 H), 2.19 - 2.14 (m, 1 H), 1.12 – 1.04 (m, 2 H), 0.71 - 0.67 (m, 2 H).

4-(4-Bromophenyl)-2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolane (ArBr for 51 and 52).

To a 50-mL round-bottomed flask was added potassium *t*-butoxide (0.450 g, 4.01 mmol), DMSO (5.0 mL) and trimethylsulfoxonium iodide (1.00 g, 4.54 mmol). The resulting mixture was stirred at room temperature for 40 min. To this reaction mixture was added 1-(4-bromophenyl)-2,2,2-trifluoroethanone (1.0 g, 4.0 mmol) in DMSO (5.0 mL) dropwise via an addition funnel. The reaction mixture was stirred at room temperature for 30 min then quenched with water (1 mL). The mixture was partitioned between EtOAc (70 mL) and water (30 mL). The organic layer was washed with water (4 × 30 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel column chromatography (10 to 20% acetone in hexanes) to afford 2-(4-bromophenyl)-2-(trifluoromethyl)oxirane (0.610 g, 58%) as a pale-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 - 7.50 (m, 2 H), 7.41 (d, *J* = 8.3 Hz, 2 H), 3.42 (d, *J* = 5.3 Hz, 1 H), 2.97 - 2.78 (m, 1 H).

To a 20-mL vial was added 2-(4-bromophenyl)-2-(trifluoromethyl)oxirane (0.200 g, 0.750 mmol), dioxane (2.0 mL), and water (3.0 mL). The resulting mixture was heated at 85 °C for 48 h. The reaction mixture was allowed to cool to room temperature and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel column chromatography (10 to 30% acetone in hexanes) to afford 2-(4-Bromophenyl)-3,3,3-trifluoro-1,2-propanediol (0.20 g, 94%) as a white solid. MS (ESI pos. ion) *m/z*: calc'd for $C9_8H_8BrF_3O$: 283.966; found 284.8 (M+1). ^{1}H NMR (300MHz, $CDCl_3$) δ 7.60 - 7.52 (m, 2 H), 7.49 - 7.41 (m, 2 H), 4.32 (dd, *J* = 4.7, 11.8 Hz, 1 H), 3.85 (dd, *J* = 5.5, 11.8 Hz, 1 H), 3.74 (s, 1 H), 1.88 (t, *J* = 6.3 Hz, 1 H).

To a solution of 2-(4-bromophenyl)-3,3,3-trifluoro-1,2-propanediol (14.5 g, 51.0 mmol) in acetone (200 mL) was added 2,2-dimethoxypropane (19.0 mL, 153 mmol) and *p*-toluenesulfonic acid (0.485 g, 2.54 mmol). The resulting mixture was stirred at room temperature for 20 h. Additional 2,2-dimethoxypropane (19.0 mL, 153 mmol) and *p*-toluenesulfonic acid (0.485 g, 2.54 mmol) were added and the reaction was stirred at room temperature for another 20 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was concentrated and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (60 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel column chromatography (0 to 8% EtOAc in hexanes) to afford 4-(4-bromophenyl)-2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolane (15.7 g, 95%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 - 7.47 (m, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.71 (d, *J* = 9.4 Hz, 1 H), 4.20 (dd, *J* = 1.4, 9.4 Hz, 1 H), 1.61 (s, 3 H), 1.33 (s, 3 H).

2-Bromo-5-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)pyridine (ArBr for 53).

To a solution of 2-bromo-5-formylpyridine (4.0 g, 22 mmol) in DME (60 mL) was added trifluoromethyltrimethylsilane (4.77 mL, 32.3 mmol) and cesium fluoride

(0.653 g, 4.30 mmol). The reaction mixture was stirred at room temperature under N_2 for 14 h. The reaction was quenched with 1N HCl and stirred for 20 min and the reaction mixture was concentrated. The residue was partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (2 × 75 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel column chromatography (10 to 30% acetone in hexanes) to afford 1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethanol (4.4 g, 80%) as a colorless liquid. MS (ESI pos. ion) *m/z*: calc'd for $C_7H_5BrF_3NO$: 254.951; found 255.9 (M+1). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.46 (d, *J* = 2.3 Hz, 1 H), 7.73 (dd, *J* = 2.4, 8.3 Hz, 1 H), 7.57 (d, *J* = 8.2 Hz, 1 H), 5.17 - 5.01 (m, 1 H), 2.87 (d, *J* = 4.5 Hz, 1 H).

To a solution of 1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethanol (2.2 g, 8.6 mmol) in DCM (50 mL) was added manganese dioxide (4.48 g, 51.6 mmol). The reaction mixture was stirred at room temperature 72 h . The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was redissolved in THF (70 mL) and fresh manganese dioxide (7.5 g, 86 mmol) was added. The resulting mixture was stirred at room temperature for 20 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude product was purified by column chromatography (80 g of silica, 10 to 30% acetone in hexanes) to obtain 1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethanone (1.0 g, 46%) as a light-yellow liquid. ^{1}H NMR indicated this material was a mixture of ketone and its hydrate (4:1). MS (ESI pos. ion) *m/z*: calc'd for $C_7H_3BrF_3NO$: 252.935; found 272.0 ($M+H_2O+1$).

To a solution of potassium *t*-butoxide (0.177 g, 1.58 mmol) in DMSO (5 mL) at room temperature was added trimethylsulfoxonium iodide (0.381 g, 1.73 mmol). The resulting mixture was stirred at room temperature under N_2 for 30 min. A solution of 1-(6-bromopyridin-3-yl)-2,2,2-trifluoroethanone (0.400 g, 1.58 mmol) in DMSO (5 mL) was added to the mixture. The resulting mixture was stirred at room temperature for 3.5 h. The reaction mixture was partitioned between EtOAc (80 mL) and water (50 mL). The organic layer was washed with water (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (10 to 20% acetone in hexanes) to obtain 2-bromo-5-(2-(trifluoromethyl)oxiran-2-yl)pyridine (0.230 g, 55%) as a pale-yellow liquid. MS (ESI pos. ion) *m/z*: calc'd for $C_8H_5BrF_3NO$: 266.951; found 268.0 (M+1). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.3 Hz, 1 H), 7.72 (dd, *J* = 2.4, 8.3 Hz, 1 H), 7.57 (dd, *J* = 0.5, 8.3 Hz, 1 H), 3.48 (d, *J* = 5.1 Hz, 1 H), 2.96 (qd, *J* = 1.6, 5.0 Hz, 1 H).

To a solution of 2-bromo-5-(2-(trifluoromethyl)oxiran-2-yl)pyridine (0.210 g, 0.783 mmol) in 1,4-dioxane (1 mL) was added water (2.0 mL). The resulting mixture was heated at 60 °C for 3 h, then at 65 °C for 5 h (6:20 pm) before lowered the temperature to 60 °C and the reaction mixture was stirred at that temperature for overnight. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (40 g of silica, 10 to 30% acetone in hexanes) to obtain 2-(6-bromopyridin-3-yl)-3,3,3-trifluoropropane-1,2-diol (0.185 g, 83%). MS (ESI pos. ion) *m/z*: calc'd for $C_8H_7BrF_3NO_2$: 284.961; found 286.0 (M+1). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.5 Hz, 1 H), 7.79 (dd, *J* = 2.5, 8.5 Hz, 1 H), 7.55 (d, *J* = 8.3 Hz, 1 H), 4.37 (dd, *J* = 5.4, 11.8 Hz, 1 H), 3.95 - 3.79 (m, 2 H), 2.09 (dd, *J* = 5.5, 7.4 Hz, 1 H).

To a solution of 2-(6-bromopyridin-3-yl)-3,3,3-trifluoropropane-1,2-diol (0.310 g, 1.08 mmol) in acetone (5 mL) was added acetone, dimethyl acetal (0.398 mL, 3.25 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.054 mmol). The resulting mixture was stirred at room temperature under N_2 for 4 h. At that time, aditional 2,2-dimethoxypropane (0.40 mL, 3.3 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.054 mmol) were added and the reaction mixture was stirred for 40 h. The reaction was quenched by adding $NaHCO_3$ (2 mL). The mixture was concentrated and the residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (60 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel column chromatography (5 to 30% acetone in hexanes) to afford 2-bromo-5-(2,2-dimethyl-4-(trifluoromethyl)-1,3-dioxolan-4-yl)pyridine (0.290 g, 82%) as a yellow oil. MS (ESI pos. ion) *m/z*: calc'd for $C_{11}H_{11}BrF_3NO_2$: 324.993; found 326.0 (M+1). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.5 Hz, 1 H), 7.70 - 7.62 (m, 1 H), 7.59 - 7.48 (m, 1 H), 4.74 (d, *J* = 9.5 Hz, 1 H), 4.21 (dd, *J* = 1.3, 9.4 Hz, 1 H), 1.61 (s, 3 H), 1.35 (s, 3 H).

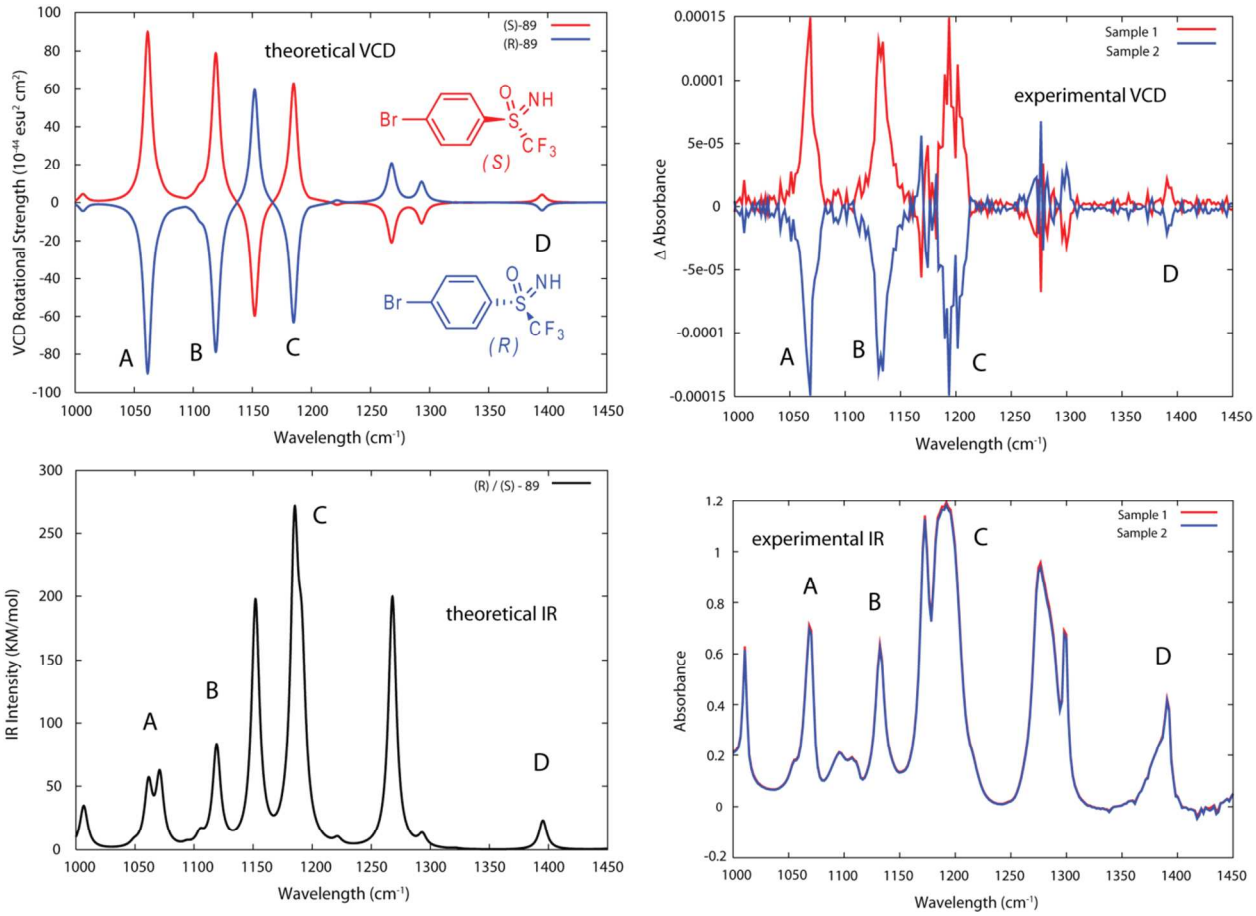
(2-Chloro-5-pyrimidinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (72).

A 500-mL round-bottomed flask was charged with 5-bromo-2-chloropyrimidine (10.0 g, 52 mmol) and 100 mL of ether. After cooling to -78 °C, n-BuLi (2.5 M in hexanes, 22.8 mL, 57 mmol) was added. This mixture was stirred at -78 °C for 10 min, then 1,1,1,3,3,3-hexafluoro-2-propanone was bubbled through the solution for 5 min. After stirring for an additional 10 min, the reaction was quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated. Purification via column chromatography on silica gel (twice, 0 to 50% EtOAc in hexanes then 0 to 4% MeOH in CH_2Cl_2) gave (2-chloro-5-pyrimidinyl)-1,1,1,3,3,3-hexafluoro-2-propanol (3.25 g, 22%) as a yellow solid. ^{1}H NMR (400MHz, MeOH) δ = 9.01 (s, 2 H).

VCD-based assignment of (*R*)- and (*S*)-89.

Conformational ensembles of the *(S)* enantiomer of **89** were initially determined via stochastic search using the MMFF94 force field as implemented in the Molecular Operating Environment *(MOE)* suite.[ii] Structurally unique conformers were then optimized using density functional theory (B3PW91/cc-PVTZ) followed by harmonic frequency and VCD rotational strength determination as implemented in the *Gaussian 09* program system.[iii] The resultant harmonic frequency, IR intensity, and VCD rotational strengths of the resultant unique conformers were convolved using a Lorentzian function (γ = 4.0 cm^{-1}), Boltzmann-weighted based on their predicted free energies at 298.15 K, and summed to produce the final theoretical IR and VCD plots shown.

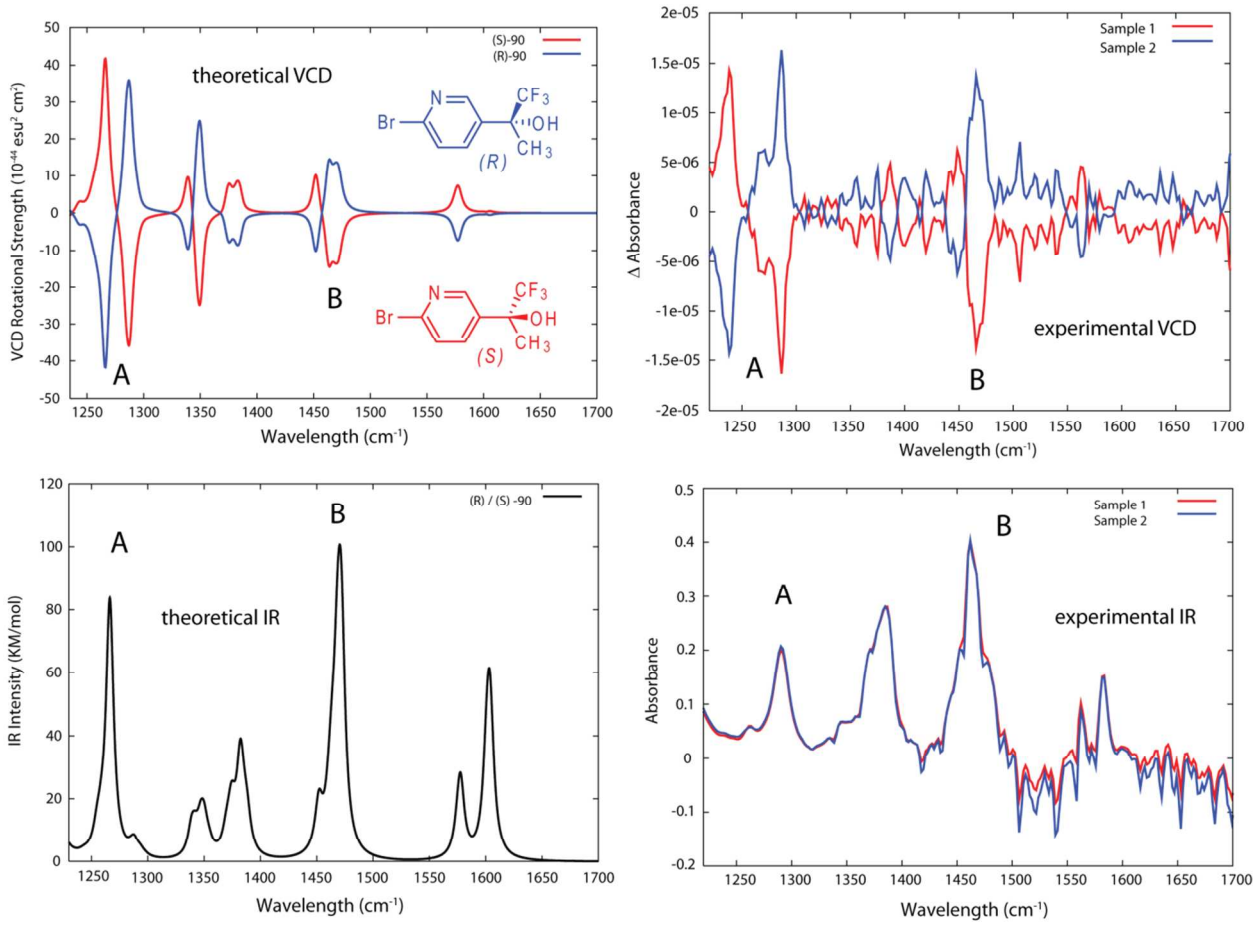
Experimental IR and VCD spectra for the isolated enantiomers of **89** (Samples 1 and 2) were acquired in $CDCL_3$ solution on a BioTools dual PEM *ChiralIR* spectrometer at a concentration of 65 mg/mL, at a resolution of 4.0 cm^{-1} and an acquisition time of 4 hours. The experimental VCD plot represents the half-difference of each acquired spectrum. Comparison of the most unambiguous signals in the theoretical and experimental achiral IR spectra (**A-D**) followed by correlation of the IR signals to their VCD counterparts afforded assignment of the individually resolved enantiomers of **89**.



Assignment: Sample 1 is *(S)*-**89**
Sample 2 is *(R)*-**89**

VCD-based assignment of (*R*)- and (*S*)-90.

Theoretical IR and VCD spectra were determined in a manner identical to that for *(R)*- and *(S)*-**89**. Experimental IR and VCD spectra for the isolated enantiomers of **90** (Samples 1 and 2) were also acquired in a similar manner (50 mg/mL in $CDCl_3$, 4.0 cm^{-1} resolution, 4 hour acquisition time.) Comparison of the most prominent, unambiguous signals in the theoretical and experimental achiral IR spectra (**A** and **B**) followed by correlation of the IR signals to their VCD counterparts afforded assignment of the individually resolved enantiomers of **90**.



Assignment: Sample 1 is *(S)*-**90**
Sample 2 is *(R)*-**90**

[i] Hogan, P. J.; Cox, B. G. Aqueous Process Chemistry: The Preparation of Aryl Sulfonyl Chlorides. *Org. Process Res. Dev*. **2009**, *13*, 875-879.

[ii] Molecular Operating Environment (MOE) 2012.10; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2012.

[iii] *Gaussian 09*, Revision D.01, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H.P.; Izmaylov, A.F.; Bloino, J.;

Zheng, G.; Sonnenberg, J.L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr., Peralta, J.E.; Ogliaro, F.; Bearpark, M.; Heyd, J.J.; Brothers, E.; Kudin, K.N.; Staroverov, V.N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J.C.; Iyengar, S.S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J.M.; Klene, M.; Knox, J.E.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Martin, R.L.; Morokuma, K.; Zakrzewski, V.G.; Voth, G.A.; P. Salvador, P.; Dannenberg, J.J.; Dapprich, S.; Daniels, A.D.; Farkas, O.; Foresman, J.B.; Ortiz, J.V.; J. Cioslowski, J.; Fox, D.J. Gaussian, Inc., Wallingford CT, 2013.