Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Direct Arylation of Fluorinated Aromatics with Aryl sulfonates

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Supporting Information

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Synthesis and Characterization of Aryl Sulfonates

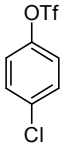
All aryl trifluorosulfonates were synthesized according to the procedure below except phenyl trifluoromethanesulfonate, 4-methoxyphenyl trifluoromethanesulfonate, 4-nitrophenyl trifluoromethanesulfonate, 4-acetylphenyl trifluoromethanesulfonate, 1-naphthyl trifluoromethanesulfonate and 3,5-dimethoxyphenyl trifluoromethanesulfonate and which were commercially available.

General Procedure for the Synthesis of Aryl Trifluoromethanesulfonates:[1] To a solution of phenol (5 mmol) and pyridine (7.5 mmol) in CH_2Cl_2 (25 mL) was added triflic anhydride (6 mmol) dropwise at 0 °C. The reaction was then left to stir at room temperature to completion as monitored by thin layer chromatography. The reaction mixture was quenched with 2M aq. HCl solution and washed successively with saturated $NaHCO_3$ and brine. After drying with Na_2SO_4, the organic solvent was removed under reduced pressure. The crude product was purified *via* flash column chromatography.

General Procedure for the Synthesis of Aryl Methanesulfonates:[2] To a solution of phenol (5 mmol) and pyridine (7.5 mmol) in CH_2Cl_2 (25 mL) was added methanesulfonyl chloride (6 mmol) dropwise at 0 °C. The reaction was then left to stir at room temperature to completion as monitored by thin layer chromatography. The reaction mixture was quenched with 2M aq. HCl solution and washed successively with saturated $NaHCO_3$ and brine. After drying with Na_2SO_4, the organic solvent was removed under reduced pressure. The crude product was purified *via* flash column chromatography.

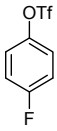
Characterization of aryl sulfonates

4-Chlorophenyl trifluoromethanesulfonate (1c)[3]



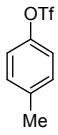
Prepared according to general procedure using 4-chlorophenol. Colorless oil; Yield: 69%; ^{1}H NMR δ 7.42 (d, J = 9.1 Hz, 2H), 7.23 (dt, J = 9.0, 2.8 Hz, 2H); ^{13}C NMR δ 147.9, 134.3, 130.3, 122.7, 118.8 (q, J = 320.7 Hz); EI-MS [M^+] *m/z* 260.

4-Fluorophenyl trifluoromethanesulfonate (1d)[4]



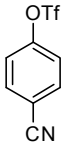
Prepared according to general procedure using 4-fluorophenol. Colorless oil; Yield: 77%; ^{1}H NMR δ 7.19 – 7.16 (m, 2H), 7.07 – 7.02 (m, 2H); ^{13}C NMR δ 162.9, 160.4, 145.3, 120.1 (dd, J = 605.2, 16.5 Hz), 118.7 (q, J = 320.8 Hz); EI-MS [M^{+}] *m/z* 244.

4-Methylphenyl trifluoromethanesulfonate (1f)[3]



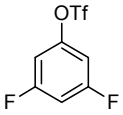
Prepared according to general procedure using *p*-cresol. Colorless oil; Yield: 95%; ^{1}H NMR δ 7.09 (dt, J = 9.4, 1.3 Hz, 2H), 7.02 (dt, J = 8.8, 2.4 Hz, 2H), 2.23 (s, 3H): ^{13}C NMR δ 147.6, 138.6, 130.7, 121.0, 118.8 (q, J = 320.6 Hz), 20.7. EI-MS [M^{+}] *m/z* 240.

4-Cyanophenyl trifluoromethanesulfonate (1h)[1]



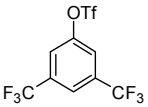
Prepared according to general procedure using 4-cyanophenol. Colorless oil; Yield: 65%; ^{1}H NMR δ 7.79 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 152.0, 134.5, 122.6, 118.7 (q, J = 323.3 Hz), 113.0; EI-MS [M^{+}] *m/z* 251.

3,5-Difluorophenyl trifluoromethanesulfonate (1j)



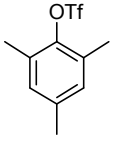
Prepared according to general procedure using 3,5-difluorophenol. Colorless oil; Yield: 69%; ^{1}H NMR δ 6.93 – 6.86 (m, 3H); ^{13}C NMR δ 163.0 (dd, J = 252.7, 14.2 Hz), 149.8 (t, J = 13.9 Hz), 118.6 (q, J = 320.7 Hz), 106.0 (dd, J = 30.2, 11.8 Hz), 104.4 (t, J = 25.2 Hz); ^{19}F NMR δ -72.9 (s, 3F), -105.6 (s, 2F); EI-MS [M^{+}] *m/z* 262; HRMS (EI) *m/z* for $C_7H_3F_5O_3S$ calcd 261.9723, found 261.9734.

3,5-Bis(trifluoromethyl)phenyl trifluoromethanesulfonate (1l)



Prepared according to general procedure using 3,5-bis(trifluoromethyl)phenol. Colorless oil; Yield: 94%; ^{1}H NMR δ 7.97 (s, 1H), 7.79 (s, 2H); ^{13}C NMR δ 149.5, 134.2 (q, J = 34.9 Hz), 122.3 (dt, J = 7.7, 3.8 Hz), 122.1 (q, J = 272.8 Hz), 118.7 (q, J = 320.0 Hz); ^{19}F NMR δ -64.7 (s, 6F), -74.1 (s, 3F) EI-MS [M^{+}] *m/z* 362; HRMS (EI) *m/z* for $C_9H_3F_9O_3S$ calcd 361.9659, found 361.9666.

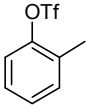
2,4,6-Trimethylphenyl trifluoromethanesulfonate (1v)[5]



Prepared according to general procedure using 2,4,6-trimethylphenol. Colorless oil;

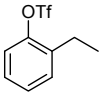
Yield : 90%; ^{1}H NMR δ 6.91 (s, 1H), 2.34 (s, 3H), 2.28 (s, 1H); ^{13}C NMR δ 144.9, 137.8, 131.0, 130.4, 118.6 (q, J = 319.8 Hz), 20.6, 17.0; EI-MS [M^{+}] *m/z* 268.

2-Methylphenyl trifluoromethanesulfonate (1x)[1]



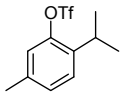
Prepared according to general procedure using *o*-cresol. Colourless oil; Yield: 84%; ^{1}H NMR δ 7.29 (dd, J = 7.2, 2.1 Hz, 1H), 7.28 – 7.22 (m, 3H), 2.38 (s, 3H); ^{13}C NMR δ 148.6, 132.2, 130.9, 128.3, 127.6, 121.2, 118.7 (q, J = 319.9 Hz), 16.2; EI-MS [M^{+}] *m/z* 240.

2-Ethylphenyl trifluoromethanesulfonate (1y)



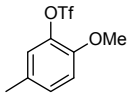
Prepared according to general procedure using 2-ethylphenol. Colorless oil; Yield: 90%; ^{1}H NMR δ 7.38 – 7.22 (m, 5H), 2.76 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H); ^{13}C NMR δ 148.0, 136.6, 130.5, 128.4, 127.6, 121.2, 118.6 (q, J = 320.0 Hz), 23.0, 14.0; ^{19}F NMR δ -74.1 (s, 3H); EI-MS [M^{+}] *m/z* 254 HRMS (EI) *m/z* for $C_9H_9F_3O_3S$ calcd 254.0224 found 254.0227.

2-Isopropyl-5-methylphenyl trifluoromethanesulfonate (1z)



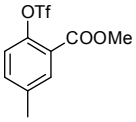
Prepared according to general procedure using thymol. Colorless oil; Yield: 93%; ^{1}H NMR δ 7.27 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 3.24 (ht, J = 8.8 Hz, 1H), 2.35 (s, 1H), 1.24 (d, J = 6.9 Hz, 1H); ^{13}C NMR δ 146.9, 138.0, 137.7, 129.4, 127.4, 121.5, 118.6 (q, J = 319.9 Hz), 26.8, 23.2, 20.8; ^{19}F NMR δ -74.2 (s, 3H); EI-MS [M^{+}] *m/z* 282; HRMS (EI) *m/z* for $C_{11}H_{13}F_3O_3S$ calcd 282.0537 found 282.0541.

2-Methoxy-5-methylphenyl trifluoromethanesulfonate (1a1)



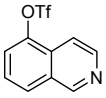
Prepared according to general procedure using 2-methoxy-5-methylphenol. Colorless oil; Yield: 87%; ^{1}H NMR δ 7.11 (ddd, J = 8.4, 2.0, 0.7 Hz, 1H), 7.02 (d, J = 1.7 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 2.31 (s, 3H); ^{13}C NMR δ 149.1, 138.4, 130.9, 129.5, 122.8, 118.8 (q, J = 320.3 Hz), 113.0, 56.2, 20.3; ^{19}F NMR δ -74.2 (s, 3F); EI-MS [M^{+}] *m/z* 270; HRMS (EI) *m/z* for $C_9H_9F_3O_4S$ calcd 270.0174 found 270.0162.

Methyl 5-methyl-2-(((trifluoromethyl)sulfonyl)oxy)benzoate (1b1)



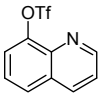
Prepared according to general procedure using methyl 5-methylsalicylate. Colorless oil; Yield: 87%; ^{1}H NMR δ 7.88 (d, J = 1.9 Hz, 1H), 7.40 (ddd, J = 8.4, 2.3, 0.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 2.42 (s, 3H); ^{13}C NMR δ 164.4, 146.2, 138.8, 134.7, 133.1, 124.0, 122.5, 118.7 (q, J = 320.7 Hz), 52.6, 20.8; ^{19}F NMR δ 73.7 (s, 3F); EI-MS [M^{+}] *m/z* 298; HRMS (ESI) *m/z* for $C_{10}H_9F_3O_5SNa$ [M+Na]$^{+}$ calcd 321.0020 found 321.0013.

Isoquinolin-5-yl trifluoromethanesulfonate (1c1)[6]



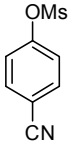
Prepared according to general procedure using 5-hydroxyisoquinoline. Off-white solid; Yield: 67%; ^{1}H NMR δ 9.38 (s, 1H), 8.71 (d, J = 6.0 Hz, 2H), 8.05 (s, 1H), 7.89 (d, J = 5.9 Hz, 1H), 7.70 (dt, J = 15.7, 7.3 Hz, 2H); ^{13}C NMR δ 151.7, 144.4, 143.6, 129.6, 129.4, 128.4, 127.4, 122.9, 118.7 (q, J = 320.6 Hz), 114.1; EI-MS [M^{+}] *m/z* 272.

Quinolin-8-yl trifluoromethanesulfonate (1d1)[3]



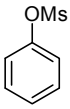
Prepared according to general procedure using 8-hydroxyquinoline. White solid; Yield: 74%; ^{1}H NMR δ 9.07 (dd, J = 4.2, 1.6 Hz, 1H), 8.24 (dd, J = 8.4, 1.6 Hz, 1H), 7.87 (dd, J = 8.1, 1.4 Hz, 1H), 7.66 – 7.51 (m, 3H); ^{13}C NMR δ 151.7, 146.1, 141.0, 135.8, 129.8, 128.2, 126.0, 122.7, 121.1, 118.9 (q, J = 320.5 Hz); EI-MS [M^{+}] *m/z* 272.

4-Cyanophenyl methanesulfonate[7] (4a)



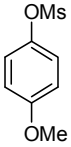
Prepared according to general procedure using 4-cyanophenol. White solid; Yield: 98%; ^{1}H NMR δ 7.72 (d, J = 8.9 Hz, 2H), 7.40 (d, J = 8.9 Hz, 2H), 3.2 (s, 3H); ^{13}C NMR δ 151.8, 134.1, 122.9, 117.6, 111.3, 38.1; EI-MS [M^{+}] *m/z* 197.

Phenyl methanesulfonate[2] (4b)



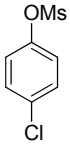
Prepared according to general procedure using phenol. White solid; Yield: 70%; ^{1}H NMR δ 7.50 – 7.31 (m, 2H), 7.30 – 7.09 (m, 3H), 3.06 (s, 3H); ^{13}C NMR δ 149.3, 130.0, 127.4, 122.0, 37.3. ; EI-MS [M+] m/z 172.

4-Methoxyphenyl methanesulfonate[2] (4c)



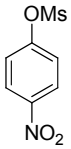
Prepared according to general procedure using 4-methoxyphenol. White solid; Yield: 95%; ^{1}H NMR δ 7.20 (d, J = 9.2 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 3.8 (s, 3H), 3.1 (s, 3H); ^{13}C NMR δ 158.5, 142.6, 123.0, 114.9, 55.6, 36.9; EI-MS [M^{+}] m/z 202.

4-Cyanophenyl methanesulfonate[8]



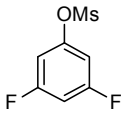
Prepared according to general procedure using 4-chlorophenol. White solid; Yield: 98%; ^{1}H NMR δ 7.38 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 3.14 (s, 3H); ^{13}C NMR δ 147.5, 133.1, 130.1, 123.4, 37.5; EI-MS [M^{+}] m/z 206.

4-Nitrophenyl methanesulfonate[9]



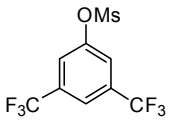
Prepared according to general procedure using phenol. White solid; Yield: 88%; ^{1}H NMR δ 8.32 (d, J = 9.1 Hz, 2H), 7.47 (d, J = 9.2 Hz, 2H), 3.25 (s, 3H); ^{13}C NMR δ 153.2, 146.3, 125.7, 122.8, 38.3; EI-MS [M+] m/z 217.

3.5-Difluoromethylphenyl methanesulfonate



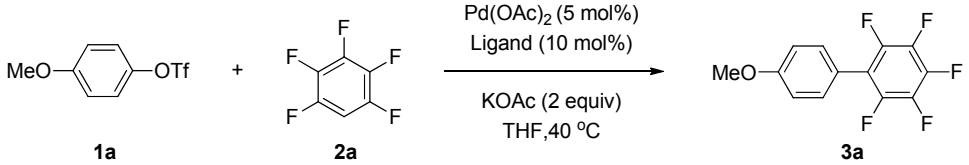
Prepared according to general procedure using 3,5-difluorophenol. Colorless oil; Yield: 81%; ^{1}H NMR δ 6.93-6.85 (m, 2H), 6.82 (tt, J = 8.7, 2.3 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR δ 164.3 (d, J = 14.5 Hz), 161.8 (d, J = 14.5 Hz), 149.9, 106.8 – 105.9 (m), 103.3 (t, J = 25.3 Hz), 37.9; ^{19}F NMR δ 106.7 (s, 2F); EI-MS [M^{+}] m/z 208.

3.5-Bis(trifluoromethyl)phenyl methanesulfonate [10]



Prepared according to general procedure using 3,5-bis(trifluoromethyl)phenol. Colorless oil; Yield: 81%; ^{1}H NMR δ 7.86 (s, 1H), 7.76 (s, 2H), 3.28 (s, 3H); ^{13}C NMR δ 149.1, 133.7 (q, J = 34.5 Hz), 123.8, 122.9 (d, J = 3.0 Hz), 121.2 (dd, J = 11.9, 8.2 Hz), 38.4; EI-MS [M^{+}] m/z 308.

Table S-1: Ligand Screening[a]



Entry	Ligand	Yield (%)[b]
1	DavePhos	12
2	CyJohnphos	14
3	PhDavephos	ND
4	^{t}BuXPhos	ND
5	^{t}BuDavePhos	ND
6	JohnPhos	ND
7	$Me_4{}^{t}$BuXPhos	ND
8	PPh_3	Trace
9	PCy_3	Trace
10	PCy_3HBF_4	Trace
11	$P(C_6F_5)_3$	ND
12	dppp	ND
13	dppb	ND
14	dppf	Trace
15	XantPhos	ND
16	1,10-phenanthroline	ND
17	4,4'-dimethyl 2,2'-bipyridine	ND
18	Lutidine	ND
19	2,6-bis((R)-4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine	ND

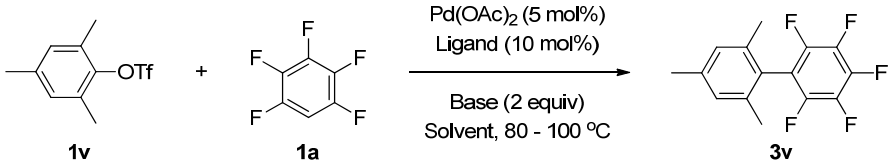
[a] The reaction was conducted at 40 °C in 1.5 mL THF as solvent for 17 h with $Pd(OAc)_2$:ligand: **1a**:**2a**:KOAc molar ratio = 1:2:20:60:40. [b] ^{1}H NMR yield using CH_2Br_2 as the internal standard, ND: not detected.

Optimization of Pd-catalyzed direct arylation of mesityl trifluoromethanesulfonate with pentafluorobenzene (Table S-2)

To a microwave reaction tube in the glove box was charged $Pd(OAc)_2$ catalyst (5.6 mg, 0.025 mmol, 5 mol%), ligand (0.05 mmol, 10 mol%)), base (1 mmol, 2 equiv), solvent (1.5 mL), mesityl trifluoromethanesulfonate (0.5 mmol, 1 equiv), and pentafluorobenzene (1.5 mmol, 3

equiv). The tube was then sealed and left to stir at the given temperature for 18 h, after which the reaction was cooled to room temperature. The reaction mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed under vacuum and the reaction yield was determined by ^1H NMR spectroscopy by the addition of dibromomethane (35 μL, 0.5 mmol) as the internal standard.

Table S-2. $Pd(OAc)_2$-catalyzed arylation of trimethylphenyl triflate with pentafluorobenzene[a]



1v 1a 3v

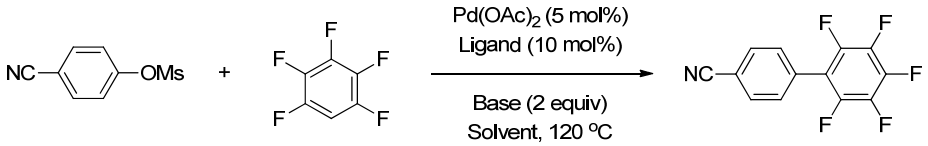
Entry	Ligand	Base	Solvent	Temperature	Yield (%)[b]
1[c]	XPhos	KOAc	DMF	100	ND[d]
2[c]	tBuXPhos	KOAc	DMF	100	ND[d]
3[c]	MePhos	KOAc	DMF	100	ND[d]
4[c]	MePhos	K_2CO_3	DMF	100	trace
5[c]	tBuMePhos	K_2CO_3	DMF	100	ND
6[c]	tBuDavePhos	K_2CO_3	DMF	100	ND
1[c]	PEt_3	K_2CO_3	DMF	100	ND
3[c]	SPhos	K_2CO_3	DMF	100	8
4[c]	SPhos	K_2CO_3	1,4-dioxane	100	30
5[e]	SPhos	K_2CO_3	1,4-dioxane	100	90
6[e]	**RuPhos**	**K_2CO_3**	**1,4-dioxane**	**100**	**99 (92)**
7[e]	RuPhos	K_2CO_3	1,4-dioxane	80	62
8[e]	RuPhos	KOAc	1,4-dioxane	80	11
9[e]	MePhos	K_2CO_3	1,4-dioxane	80	5
10[e]	MePhos	KOAc	1,4-dioxane	80	3
11[e]	RuPhos	K_2CO_3	THF	80	62
12[e]	RuPhos	K_2CO_3	MeCN	80	ND
13[e]	RuPhos	K_2CO_3	DCE	80	29

[a] Reactions were conducted in 1.5 mL solvent at the stated temperature for 18 h with **1v**:**3a**:$Pd(OAc)_2$:ligand:base molar ratio = 20:60:1:2:40. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture with CH_2Br_2 as internal standard, ND = not detected. [c] Reactions were carried out under reflux under Ar atmosphere.[d] Formation of side products eg mesitylene and mesitylphenol observed based on GCMS analysis of crude reaction mixture, not observed when K_2CO_3 was used as base. [e] Reactions were carried out under sealed tube conditions.

Optimization of Pd-catalyzed direct arylation of *p*-cyanophenyl methanesulfonate with pentafluorobenzene (Table S-3)

To a microwave reaction tube in the glove box was charged $Pd(OAc)_2$ catalyst (0.025 mmol, 5 mol%), ligand (0.05 mmol, 10 mol%), base (1 mmol, 2 equiv), solvent (1.5 mL), *p*-cyanophenyl methanesulfonate (0.5 mmol, 1 equiv), and pentafluorobenzene (1.5 mmol, 3 equiv). The tube was then sealed and left to stir at the given temperature for 18 h, after which the reaction was cooled to room temperature. The reaction mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed under vacuum and the reaction yield was determined by ^1H NMR spectroscopy by the addition of dibromomethane (35 μL, 0.5 mmol) as the internal standard.

Table S-3. $Pd(OAc)_2$-catalyzed arylation of *p*-cyanophenyl methanesulfonate with pentafluorobenzene[a]



Entry	Ligand	Base	Solvent	Yield (%)[b]
1	XPhos	K_2CO_3	DMF/^{t}BuOH	ND[d]
2	XPhos	K_2CO_3	PhMe/^{t}BuOH	14
3	**SPhos**	**K_2CO_3**	**PhMe/^{t}BuOH**	**70**
4	RuPhos	K_2CO_3	PhMe/^{t}BuOH	12
5	SPhos	K_2CO_3	PhMe	37
6	SPhos	K_2CO_3	^{t}BuOH	16

7	SPhos	K_2CO_3	dioxane	ND
8	CyJohnPhos	K_2CO_3	DMF	ND
9	MePhos	K_2CO_3	PhMe/^{t}BuOH	ND
10	DavePhos	K_2CO_3	PhMe/^{t}BuOH	ND
11	CataCXium PInCy	K_2CO_3	PhMe/^{t}BuOH	ND
12	CataCXium PCy	K_2CO_3	PhMe/^{t}BuOH	ND
13	BrettPhos	K_2CO_3	PhMe/^{t}BuOH	20
14	CMPhos	K_2CO_3	PhMe/^{t}BuOH	17
15	XantPhos	K_2CO_3	PhMe/^{t}BuOH	ND
16	SPhos	KOAc	PhMe/^{t}BuOH	45
17	SPhos	K_3PO_4	PhMe/^{t}BuOH	18
18	SPhos	Cs_2CO_3	PhMe/^{t}BuOH	25
19	SPhos	CsOAc	PhMe/^{t}BuOH	37
20	SPhos	CsOPiv	PhMe/^{t}BuOH	25
21	SPhos	CsF	PhMe/^{t}BuOH	12

[a] Reactions were conducted under sealed tube conditions in 1.5 mL solvent at 120 °C for 18 h with p-cyanophenyl mesylate:pentafluorobenzene:$Pd(OAc)_2$:ligand:base molar ratio = 20:60:1:2:40. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture with CH_2Br_2 as internal standard, ND = not detected.

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