Cu-Mediated C–H $^{18}$F-Fluorination of Electron-Rich (Hetero)Arenes

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I. General Considerations, Methods, and Materials

\(^1\)H NMR spectra were obtained on a Varian MR400 (400.52 MHz for \(^1\)H; 376.87 MHz for \(^19\)F), a Varian vnmrs 500 (500.01 MHz for \(^1\)H; 470.56 MHz for \(^19\)F), a Varian vnmrs 700 (699.76 MHz for \(^1\)H; 175.95 MHz for \(^13\)C), or a Varian Inova 500 (499.90 MHz for \(^1\)H) spectrometer. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent peak (CDCl\(_3\)): \(^1\)H: \(\delta = 7.26\) ppm, \(^13\)C: \(\delta = 77.16\) ppm; DMSO-\(d_6\): \(^1\)H: \(\delta = 2.50\) ppm, \(^13\)C: \(\delta = 39.52\) ppm; CD\(_3\)OD: \(^1\)H: \(\delta = 3.30\) ppm, \(^13\)C: \(\delta = 49.00\) ppm; CD\(_2\)CN: \(^1\)H: \(\delta = 1.94\) ppm). \(^19\)F NMR spectra are referenced to standard trichlorofluoromethane (CFCl\(_3\); \(\delta = 0.00\) ppm for \(^19\)F). NMR spectra were recorded at room temperature unless otherwise noted. The abbreviations for \(^1\)H and \(^19\)F multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) heptet (hept), doublet of doublet (dd), doublet of doublet of doublet (ddd), doublet of triplet (dt), doublet of doublet of triplet (ddt), triplet of doublet (td), pentet of doublet (pd), broad singlet (bs) and multiplet (m). Coupling constants (J) are reported in hertz (Hz). Melting points were determined with a Mel-Temp 3.0 (Laboratory Devices, Inc) and are uncorrected. High-resolution mass spectra were recorded on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Infrared spectroscopy was performed on a Perkin-Elmer Spectrum BX FT-IR spectrometer, and peaks are reported in cm\(^{-1}\). Thin layer chromatography (TLC) was performed on Macherey-Nagel GmbH & Co. pre-coated TLC-plates SIL G-25 UV\(_{254}\) (0.25 mm silica gel with fluorescent indicator UV\(_{254}\)). Flash column chromatography was conducted using a Biotage Isolera One system with SNAP Ultra column cartridges.

Commercial reagents and solvents were used as received unless otherwise noted. Anhydrous acetonitrile, \(N\)-methyl aniline, cesium carbonate, potassium carbonate, anisole, 4-fluoroanisole, methyl 2-methoxybenzoate, 1,3-dimethoxybenzene, \(o\)-xylene, spray-dried potassium fluoride, and benzyl bromide were obtained from Sigma Aldrich. \(p\)-Toluenesulfonyl chloride, methyl 5-fluoro-2-hydroxybenzoate, benzyl phenyl ether, 18-crown-6, and benzyl chloroformate were obtained from Acros. Anhydrous dichloromethane was obtained from Acros and was stored over activated molecular sieves. Toluene and magnesium sulfate were obtained from Fisher Chemical. Iodine, \(p\)-toluenesulfonic acid monohydride, 4-fluoro-\(N\)-methylaniline, 1-fluoro-2,4-dimethoxybenzene, 1-phenyl-2-pyrrolidinone, 2,2,2-trifluoroethanol, dimethyl carbonate, and triethylamine were obtained from Alfa Aesar. Anhydrous \(N\),\(N\)'-dimethylformamide was obtained from Alfa Aesar and was stored over activated molecular sieves. 4-Fluorotoluene, 2-fluoroanisole, and 4-fluoro-\(o\)-xylene were obtained from Matrix Scientific. \(m\)-Chloroperoxybenzoic acid (85\%) was obtained from AK Scientific. 5-Fluoro-2,3-dihydrobenzofuran was obtained from Apollo Scientific. Anhydrous diethyl ether was obtained from EMD Millipore Corporation. 2-Bromoanisole, 2-bromo-4-fluoroanisole, 2,3-dihydrobenzofuran, 1-(4-fluorophenyl)-2-pyrrolidinone, 3-methylthiophene, 1,3-dimethyluracil, 3-chloro-6,11-dihydro-6-methyl-5,5,11-trioxodibenzo[c,f][1,2]thiazepine, fluorouracil, \(N\)-Fluoro-\(N\)'-chloromethyltriethylenediamine bis(tetrafluoroborate) (SelectFluor) and 4-benzzyloxyfluorobenzene were obtained from Oakwood Products. Nimesulide, 4-(3,5-dimethylpyrazol-1-yl)benzonitrile, and methyl 1-methylpyrrole-2-carboxylate were obtained from Combi-Blocks. 1,3,5-Trimethylbenzene was obtained from TCI America. 3-Fluoroanisole and 2,6-diisopropylphenol were obtained from Ark Pharm, Inc. DMSO-\(d_6\), CD\(_3\)OD, CDCl\(_3\) were obtained from Cambridge Isotope Laboratories. Copper(II) trifluoromethanesulfonate was obtained from Strem. Ethyl acetate (EtOAc), hexanes (Hex), methanol (MeOH) and dichloromethane (DCM) for column chromatography were obtained from VWR International.

II. Synthesis and Characterization of Starting Materials

![Diagram](https://via.placeholder.com/150)
**N,4-Dimethyl-N-phenylbenzenesulfonamide (1h).** A previously reported procedure was used for the synthesis of 1h from N-methyl aniline. Recrystallization from MeOH led to the isolation of 1h as a white solid (1.08 g, 45% yield, mp 92-93 °C). $^1$H NMR (401 MHz, CDCl$_3$) $\delta$ 7.43 (d, J = 7.9 Hz, 2H), 7.33-7.21 (multiple peaks, 5H), 7.13-7.06 (m, 2H), 3.16 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 143.6, 141.6, 133.4, 129.4, 128.8, 127.9, 127.3, 126.6, 38.1, 21.6; FT-IR 1594.9, 1491.0, 1342.2, 1170.1, 1063.0 cm$^{-1}$; HRMS m/z calculated for C$_{14}$H$_{16}$NO$_2$S [M+H]: 262.0897, found 262.0896.

**Benzyl methyl(phenyl)carbamate (1i).** To a 50 mL round bottom flask equipped with a magnetic stir bar were added N-methyl aniline (1.0 mL, 9.2 mmol, 1.0 equiv) and benzyl chloroformate (1.6 mL, 11 mmol, 1.2 equiv) in DCM (18 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C using an ice bath and triethylamine (1.9 mL, 14 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 15 h at room temperature. Upon completion, the mixture was diluted with DCM (5.0 mL) and washed with water (3 x 25 mL) and brine (25 mL). The organic phase was dried with magnesium sulfate and concentrated in vacuo. Purification by silica gel flash chromatography (25 g Biotage SNAP-Ultra silica column, gradient from 0% to 3% EtOAc:Hex) led to the isolation of 1i as a colorless oil (860 mg, 39% yield), R$_f$ = 0.16 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain), which was stored in the freezer until use. $^1$H NMR (700 MHz, DMSO-d$_6$, 90 °C) $\delta$ 7.39-7.33 (multiple peaks, 4H), 7.33-7.27 (multiple peaks, 5H), 7.22 (t, J = 7.3 Hz, 1H), 5.13 (s, 2H), 3.27 (s, 3H); $^{13}$C NMR (176 MHz, DMSO-d$_6$, 90 °C) $\delta$ 154.2, 142.8, 136.4, 128.2, 128.7, 125.3, 125.1, 66.1, 36.9; $^{1}$H NMR (401 MHz, DMSO-d$_6$, 90 °C) $\delta$ 155.5, 143.3, 136.7, 128.9, 128.5, 128.0, 127.7, 126.2, 67.3, 37.9; FT-IR 1694.2, 1595.0, 1422.9, 1298.6, 1150.8, 1002.7, 913.8 cm$^{-1}$; HRMS m/z calculated for C$_{15}$H$_{16}$NO$_2$ [M+H]: 242.1176, found 242.1176.

**2-(Benzylxylo)-1,3-diisopropylbenzene (1p).** To a 25 mL round bottom flask equipped with a magnetic stir bar was added 2,6-diisopropylphenol (1.0 mL, 5.6 mmol, 1.0 equiv) in DMF (8.0 mL) under a nitrogen atmosphere. To the mixture were added K$_2$CO$_3$ (1.6 g, 11 mmol, 2.0 equiv) and benzyl bromide (1.0 mL, 8.4 mmol, 1.5 equiv). The mixture was stirred for 4 h at room temperature before being quenched with H$_2$O (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with H$_2$O (7 x 10 mL) and brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. Purification by silica gel flash chromatography (0% to 10% Et$_3$O:Hex) led to the isolation of 1p as a colorless oil (330 mg, 22% yield), R$_f$ = 0.53 (9:1 Hex:Et$_3$O, visualized by 254 nm light and phosphomolybdic acid (PMA) stain). $^1$H NMR (401 MHz, CDCl$_3$) $\delta$ 7.54-7.47 (m, 2H), 7.43 (m, 2H), 7.39-7.33 (m, 1H), 7.17-7.11 (multiple peaks, 3H), 4.81 (s, 2H), 3.40 (hept, J = 6.9 Hz, 2H), 1.25 (d, J = 6.9 Hz, 12H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 153.3, 142.1, 137.9, 128.7, 128.0, 127.5, 124.9, 124.2, 76.5, 26.7, 24.3; FT-IR 1454.9, 1255.1, 1181.1, 1098.1, 1017.4, 759.0 cm$^{-1}$; HRMS m/z calculated for C$_{15}$H$_{25}$O [M+H]: 269.1900, found 269.1893.
N-Benzyl-N-(4-nitro-2-phenoxypyphenyl)ethanesulfonamide (1q). To a 25 mL round bottom flask equipped with a magnetic stir bar was added nimesulide (1.0 g, 3.2 mmol, 1.0 equiv) in DMF (5.0 mL) under a nitrogen atmosphere. To the mixture were added K₂CO₃ (900 mg, 6.5 mmol, 2.0 equiv) and benzyl bromide (0.58 mL, 4.9 mmol, 1.5 equiv). The mixture was stirred for 4 h at room temperature before being quenched with H₂O (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were washed with H₂O (7 x 10 mL) and brine (10 mL), then dried with magnesium sulfate and concentrated in vacuo. Recrystallization from EtOH led to the isolation of 1q as a white solid (1.13 g, 88% yield, mp 126-128 °C). ¹H NMR (401 MHz, CDCl₃) δ 7.78 (dd, J = 8.7, 2.5 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.36-7.27 (multiple peaks, 7H), 7.08 (d, J = 8.0 Hz, 2H), 4.92 (s, 2H), 3.09 (s, 3H); ¹³C NMR (176 MHz, CDCl₃) δ 155.5, 154.2, 148.0, 135.5, 134.5, 134.2, 130.9, 128.8, 128.3, 126.0, 120.0, 117.7, 112.2, 54.0, 40.5; FT-IR 1586.5, 1512.7, 1486.0, 1323.6, 1202.2, 1176.8, 1022.7, 824.8 cm⁻¹; HRMS m/z calculated for C₂₀H₁₉N₂O₅Na [M+H]⁺: 399.1009, found 399.1007.

Hydroxy(mesityl)-2-iodaneyl 4-methylbenzenesulfonate. A previously reported procedure was used for the synthesis of MesI(OH)OTs from 1,3,5-trimethylbenzene.² To a 250 mL round bottom flask equipped with a magnetic stir bar was added iodine (2.3 g, 9.0 mmol, 0.50 equiv) in DCM (60 mL). To the stirring solution were added 1,3,5-trimethylbenzene (2.5 mL, 18 mmol, 1.0 equiv), m-CPBA (80%, 5.8 g, 27 mmol, 1.5 equiv), and TsOH•H₂O (3.4 g, 18 mmol, 1.0 equiv). The solution was stirred at room temperature for 12 h, before being concentrated in vacuo. To the residue was added diethyl ether (75 mL), and the mixture was stirred at room temperature for an additional 30 min. The precipitate was collected by filtration and dried to afford MesI(OH)OTs as a white solid (6.41 g, 82% yield, mp 105-106 °C). The ¹H and ¹³C NMR spectroscopic data match those previously reported in the literature.²⁻³

Mesityl(4-methoxyphenyl)diodonium trifluoromethanesulfonate (2a). To a solution of MesI(OH)OTs (430 mg, 1.0 mmol, 1.0 equiv) in DCM (4.0 mL) in a 20 mL vial equipped with a stir bar was added arenne 1a (0.11 mL, 1.0 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.18 mL, 1.0 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et₂O was added to precipitate the diarylidonium salt. The mixture was stirred for 30 min before the diarylidonium salt was collected by filtration, washed with Et₂O, and dried under vacuum, leading to the isolation of 2a as a grey solid (314 mg, 63% yield), which was stored in the freezer until use. ¹H NMR (401 MHz, CDCl₃) δ 7.64 (d, J = 9.1 Hz, 2H), 7.09 (s, 2H), 6.93 (d, J = 9.1 Hz, 2H), 3.82 (s, 3H), 2.64 (s, 6H), 2.35 (s, 3H); ¹³C NMR (176 MHz, CDCl₃) δ 162.7, 144.5, 142.3, 135.5, 130.5, 121.2, 118.2, 100.1, 55.9, 27.2, 21.2; ¹⁹F NMR (377 MHz, CDCl₃) δ –78.8 (s, 3F); FT-IR 1572.3, 1486.1, 1239.6, 1176.8, 1022.7, 824.8 cm⁻¹; HRMS m/z calculated for C₁₆H₁₈OI [M]⁺: 353.0397, found 353.0399.

Mesityl(3-methylthiophen-2-yl)diodonium 4-methylbenzenesulfonate (s1). A previously reported procedure was used for the synthesis of s1 from 3-methylthiophene.⁴ To a solution of MesI(OH)OTs (700
mg, 1.6 mmol, 1.0 equiv) in 2,2,2-trifluoroethanol (TFE) (8.0 mL) in a 20 mL vial equipped with a stir bar was added of arene 11 (0.16 mL, 1.0 mmol, 1.0 equiv). The solution was stirred for 3 h at room temperature. To the solution was added MeOH (5 mL) before the reaction mixture was concentrated in vacuo. To the residue was added diethyl ether (10 mL), and the mixture stirred at room temperature for 30 min. The precipitate was collected by filtration and dried to afford s1 as a grey solid (619 mg, 75% yield), which was stored in the freezer until use. 1H NMR (401 MHz, CDCl₃) δ 7.60-7.51 (multiple peaks, 3H), 7.05 (d, J = 8.0 Hz, 2H), 7.01 (s, 2H), 6.93 (d, J = 5.4 Hz, 1H), 2.71 (s, 6H), 2.51 (s, 3H), 2.34-2.29 (multiple peaks, 6H); ¹³C NMR (176 MHz, CDCl₃) δ 147.5, 143.8, 142.5, 141.4, 139.5, 135.0, 130.2, 130.1, 128.6, 126.9, 126.0, 96.3, 27.4, 21.5, 17.9. FT-IR 1456.1, 1374.6, 1229.0, 1153.2, 1007.7, 819.8 cm⁻¹; HRMS m/z calculated for C₁₄H₁₀SI [M⁺]: 343.0012, found 343.0015.

III. Synthesis and Characterization of Authetic Samples of Fluorinated Arenes

A. General Procedure for the Synthesis of Fluorinated Arenes

![Diagram](https://example.com/diagram.png)

To a solution of MesI(OH)OTs (240 mg, 0.56 mmol, 1.0 equiv) in DCM (2.2 mL) in a 20 mL vial equipped with a stir bar was added 1p (150 mg, 0.56 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.10 mL, 0.56 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et₂O was added to precipitate the diaryliodonium salt. The mixture was stirred for 30 min before the diaryliodonium salt was collected by filtration, washed with Et₂O, dried under vacuum, and stored for use in subsequent fluorination reactions without any further purification.

In a glovebox, to a 20 mL vial equipped with a stir bar were added diaryliodonium salt 2p (660 mg, 1.0 mmol, 1.0 equiv), Cu(OTf)₂ (72 mg, 0.20 mmol, 20 mol %), KF (64 mg, 1.1 mmol, 1.1 equiv), and anhydrous DMF (10 mL). The reaction vial was sealed with a Teflon-lined cap, and the reaction was heated in an aluminum block at 65 °C for 16 h. After completion, the reaction was cooled to room temperature, quenched with saturated NaHCO₃, and extracted with pentane (3 x 15 mL). The combined organics were washed with H₂O (7 x 20 mL), dried with magnesium sulfate, concentrated in vacuo, and purified by silica gel flash chromatography.

B. Synthesis and Characterization of 3d, 3h-3i, 3m-3q

![Diagram](https://example.com/diagram.png)

**Methyl 5-fluoro-2-methoxybenzoate (3d).** To a 25 mL round bottom flask equipped with a magnetic stir bar was added methyl 5-fluoro-2-hydroxybenzoate (500 mg, 2.9 mmol, 1.0 equiv) in DMF (5.3 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C using an ice bath, and potassium carbonate (610 mg, 4.4 mmol, 1.5 equiv) was added followed by the dropwise addition of iodomethane (0.22 mL, 3.5 mmol, 1.2 equiv). The mixture was stirred for 5 h at room temperature. Upon completion the mixture was quenched with water (10 mL) and extracted with Et₂O (3 x 10 mL). The combined organics were washed with water (3 x 10 mL) and brine (10 mL) before being dried with magnesium sulfate, and concentrated in vacuo. Purification by silica gel flash chromatography (10 g Biotage SNAP-
Ultra silica column, 5% EtOAc:pentane led to the isolation of 3d as a colorless oil (401 mg, 74% yield), Rf = 0.12 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain). 1H NMR (401 MHz, CDCl3) δ 7.51 (dd, J = 8.7, 3.2 Hz, 1H), 7.17 (ddd, J = 9.1, 7.5, 3.2 Hz, 1H), 6.92 (dd, J = 9.1, 4.2 Hz, 1H), 3.92-3.86 (multiple peaks, 6H); 13C NMR (176 MHz, CDCl3) δ 165.6 (d, J = 2.4 Hz), 156.2 (d, J = 240.0 Hz), 155.6 (d, J = 2.1 Hz), 120.9 (d, J = 7.0 Hz), 120.0 (d, J = 22.9 Hz), 118.2 (d, J = 24.7 Hz), 113.5 (d, J = 7.7 Hz), 56.7, 52.3; 19F NMR (377 MHz, CDCl3) δ –124.3 (m, 1F). FT-IR 1731.4, 1495.8, 1435.8, 1305.9, 1242.7, 1177.6, 1071.7 cm⁻¹; HRMS m/z calculated for C9H10FO3 [M+H]+: 280.0802, found 280.0799.

N-(4-Fluorophenyl)-N,4-dimethylbenzenesulfonamide (3h). The general procedure was followed using diaryliodonium salt 2h (270 mg, 0.41 mmol, 1.0 equiv), Cu(OTf)2 (30 mg, 0.08 mmol, 20 mol%), and KF (26 mg, 0.45 mmol, 1.1 equiv) in anhydrous DMF (4.1 mL). Purification by silica gel flash chromatography (50 g Biotage SNAP-Ultra silica column, step gradient from 0% to 5% to 10% to 20% EtOAc:Hex) led to the isolation of 3h as a white solid (24 mg, 21% yield, mp 85-86 °C), Rf = 0.26 (4:1 Hex:EtOAc, visualized by 254 nm light and PMA stain). 1H NMR (700 MHz, CDCl3) δ 7.43 (d, J = 7.8 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 7.05 (dd, J = 8.7, 4.9 Hz, 2H), 6.98 (app. t, J = 8.7 Hz, 2H), 3.14 (s, 3H), 2.43 (s, 3H); 13C NMR (176 MHz, CDCl3) δ 161.7 (d, J = 247.4 Hz), 143.9, 137.7 (d, J = 3.1 Hz), 133.4, 129.6, 128.6 (d, J = 8.6 Hz), 128.1, 115.8 (d, J = 22.7 Hz), 38.4, 21.7; 19F NMR (376 MHz, CDCl3) δ –114.7 (m, 1F); FT-IR 1598.9, 1497.4, 1344.3, 1189.9, 1063.5, 873.8 cm⁻¹; HRMS m/z calculated for C14H15NSO2F [M+H]+: 280.0802, found 280.0799.

Benzyl (4-fluorophenyl)(methyl)carbamate (3i). To a 25 mL round bottom flask equipped with a magnetic stir bar were added 4-fluoro-N-methylaniline (0.50 mL, 4.2 mmol, 1.0 equiv) and benzyl chloroformate (0.71 mL, 5.0 mmol, 1.2 equiv) in DCM (8.4 mL) under a nitrogen atmosphere. The mixture was cooled to 0 °C using an ice bath and triethylamine (0.87 mL, 6.3 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 15 h at room temperature. Upon completion, the mixture was diluted with DCM (2 mL) and washed with water (3 x 15 mL) and brine (15 mL). The organic phase was dried with magnesium sulfate and concentrated in vacuo. Purification by silica gel flash chromatography (25 g Biotage SNAP-Ultra silica column, 3% EtOAc:Hex) led to the isolation of 3i as a colorless oil (394 mg, 36% yield), Rf = 0.12 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain). 1H NMR (400 MHz, DMSO-d6, 90 °C) δ 7.39-7.26 (multiple peaks, 7H), 7.16 (t, J = 8.8 Hz, 2H), 5.11 (s, 2H), 3.04 (s, 3H); 13C NMR (176 MHz, DMSO-d6, 90 °C) δ 159.6 (d, J = 243.1 Hz), 154.3, 139.1, 136.3, 127.8, 127.2, 126.9, 114.9 (d, J = 22.5 Hz), 66.2, 37.1; 19F NMR (376 MHz, DMSO-d6, 90 °C) δ –116.6 (m, 1F); FT-IR 1699.5, 1508.7, 1345.9, 1218.4, 1146.9, 1011.5 cm⁻¹; HRMS m/z calculated for C15H15NO2F [M+H]+: 260.1081, found 260.1081.
Methyl 4-fluoro-1-methyl-1H-pyrrole-2-carboxylate (3m). The general procedure was followed using diarylidonium salt 2m (490 mg, 0.92 mmol, 1.0 equiv), Cu(OTf)$_2$ (65 mg, 0.18 mmol, 20 mol %), and KF (59 mg, 1.01 mmol, 1.1 equiv) in anhydrous DMF (9.2 mL). The desired product was purified by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, 3% EtOAc:Hex) affording 3m as a colorless oil (12 mg, 8% yield), $R_f = 0.35$ (4:1 Hex:EtOAc, visualized by 254 nm light and PMA stain). $^1$H NMR (401 MHz, CDCl$_3$) $\delta$ 6.59 ($d$, $J$ = 2.2 Hz, 1H), 6.57 ($dd$, $J$ = 3.5, 2.2 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 161.5 (d, $J$ = 3.1 Hz), 150.0 (d, $J$ = 240.1 Hz), 118.6, 114.1 (d, $J$ = 27.6 Hz), 103.8 (d, $J$ = 14.9 Hz), 51.4, 37.0; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –165.7 (d, $J$ = 3.4 Hz, 1F); FT-IR 1679.7, 1435.6, 1322.1, 1244.0, 1107.7, 1054.9 cm$^{-1}$; HRMS $m/z$ calculated for C$_8$H$_8$NO$_2$F [M$^+$]: 157.0539, found 157.0534. Of note, the $^1$H, $^{13}$C and $^{19}$F NMR spectroscopic data did not match those previously reported in the literature for methyl 5-fluoro-1-methyl-1H-pyrrole-2-carboxylate.$^5$

5-Fluoro-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (3n). A previously reported procedure was used for the synthesis of 3n from fluorouracil.$^6$ To a 100 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser were added powdered K$_2$CO$_3$ (3.2 g, 23 mmol, 3.0 equiv), 18-crown-6 (410 mg, 1.5 mmol, 20 mol %), and dimethyl carbonate (7.8 mL, 92 mmol, 12 equiv) in DMF (30 mL). To the mixture was added fluorouracil (1.0 g, 7.7 mmol, 1.0 equiv) in one portion. The mixture was stirred for 15 h at 90°C. After completion, the reaction was cooled to room temperature and quenched with H$_2$O (50 mL). The solution was extracted with DCM (3 x 50 mL). The combined organics were washed with H$_2$O (7 x 50 mL), brine (50 mL), then dried with magnesium sulfate and concentrated in vacuo. Purification by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, gradient from 0% to 100% EtOAc:Hex) led to the isolation of 3n as a white solid (250 mg, 21% yield, mp 128-129°C), $R_f = 0.06$ (50% EtOAc:Hex, visualized by 254 nm light and PMA stain). $^1$H NMR (401 MHz, CDCl$_3$) $\delta$ 7.23 (d, $J$ = 5.0 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 157.5 (d, $J$ = 25.0 Hz), 150.3, 139.9 (d, $J$ = 233.8 Hz), 127.5 (d, $J$ = 32.5 Hz), 37.1, 28.4 (d, $J$ = 1.4 Hz); $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ –167.3 (m, 1F); FT-IR 1703.4, 1651.9, 1428.5, 1326.7, 1275.3, 1083.2, 1057.8 cm$^{-1}$; HRMS $m/z$ calculated for C$_8$H$_8$N$_2$O$_2$F [M+H]$^+$: 159.0564, found 159.0562.

3-Chloro-9-fluoro-6-methyl dibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide (3o). The general procedure was followed using diarylidonium salt 2o (200 mg, 0.28 mmol, 1.0 equiv), Cu(OTf)$_2$ (21 mg, 0.06 mmol, 20 mol %), and KF (18 mg, 0.31 mmol, 1.1 equiv) in anhydrous DMF (2.8 mL). Purification by silica gel flash chromatography (50 g Biotage SNAP-Ultra silica column, step gradient from 0% to 5% to 10% to 20% EtOAc:Hex) led to the isolation of 3o as a white solid (52 mg, 57% yield, mp 185-186°C), $R_f = 0.24$ (4:1 Hex:EtOAc, visualized by 254 nm light). $^1$H NMR (400 MHz, CD$_2$CN) $\delta$ 7.94 (d, $J$ = 2.1 Hz, 1H), 7.92 (app. $dd$, $J$ = 9.9, 2.8, 0.5 Hz, 1H), 7.90 (app. $d$, $J$ = 8.3 Hz, 1H), 7.81 (dd, $J$ = 8.3, 2.1 Hz, 1H), 7.53 (app. $dd$, $J$ = 9.0, 5.0, 0.5 Hz, 1H), 7.49 (app. $dd$, $J$ = 9.0, 7.0, 2.8 Hz, 1H), 3.28 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 188.0 (d, $J$ = 1.6 Hz), 160.6 (d, $J$ = 248.3 Hz), 139.4, 138.6, 137.5 (d, $J$ = 3.0 Hz), 133.8, 133.5, 133.1 (d, $J$ = 6.6 Hz), 132.3, 127.4 (d, $J$ = 8.0 Hz), 126.0, 122.4 (d, $J$ = 23.4 Hz), 118.3 (d, $J$ = 24.9 Hz), 39.5; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –115.4 (m, 1F); FT-IR 1642.1,
2-(Benzyloxy)-5-fluoro-1,3-diisopropylbenzene (3p). The general procedure was followed using diaryliodonium salt 2p (660 mg, 1.0 mmol, 1.0 equiv), Cu(OTf)₂ (72 mg, 0.20 mmol, 20 mol %), and KF (64 mg, 1.1 mmol, 1.1 equiv) in anhydrous DMF (10 mL). Purification by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, gradient from 0% to 10% EtOAc:Hex) led to the isolation of 3p as a colorless oil (139 mg, 49% yield), Rₚ = 0.62 (10% EtOAc:Hex, visualized by 254 nm light and PMA stain). \(^1\)H NMR (401 MHz, CDCl₃) δ 7.48 (d, J = 7.1 Hz, 2H), 7.42 (t, J = 7.1 Hz, 2H), 7.36 (t, J = 7.1 Hz, 1H), 6.79 (d, J = 9.5 Hz, 2H), 4.77 (s, 2H), 3.37 (pd, J = 6.8, 1.1 Hz, 2H), 1.22 (d, J = 6.8 Hz, 12H); \(^1\)³C NMR (176 MHz, CDCl₃) δ 160.1 (d, J = 240.9 Hz), 149.1 (d, J = 2.6 Hz), 144.1 (d, J = 7.1 Hz), 137.6, 128.7, 128.2, 127.5, 110.7 (d, J = 22.7 Hz), 76.7, 27.1, 24.1; \(^1\)⁹F NMR (377 MHz, CDCl₃) δ –118.2 (m, 1F); FT-IR 1596.3, 1442.1, 1331.5, 1181.6, 964.1 cm⁻¹; HRMS m/z calculated for C₁₀H₂₃OF [M⁺]: 286.1733, found 286.1740.

N-Benzyl-N-(2-(4-fluorophenoxy)-4-nitrophenyl)methanesulfonamide (3q). The general procedure was followed using diaryliodonium salt 2q (840 mg, 1.1 mmol, 1.0 equiv), Cu(OTf)₂ (76 mg, 0.21 mmol, 20 mol %), and KF (67 mg, 1.2 mmol, 1.1 equiv) in anhydrous DMF (11 mL). Purification by silica gel flash chromatography (10 g Biotage SNAP-Ultra silica column, gradient from 0% to 50% EtOAc:Hex) led to the isolation of a nearly inseparable 0.67:1.0 mixture of N-Benzyl-N-(4-nitro-2-phenoxyphenyl)methanesulfonamide (1q) and 3q (171 mg, 39% yield of 3q). The desired product could be separated by repeated column chromatography (10 g Biotage SNAP-Ultra silica column, 10% EtOAc:Hex) affording 3q as a white solid, mp 128-129 °C, Rₚ = 0.36 (1:1 Hex:EtOAc, visualized by 254 nm light and PMA stain). \(^1\)H NMR (401 MHz, CDCl₃) δ 7.80 (dd, J = 8.7, 2.5 Hz, 1H), 7.51 (d, J = 2.5 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.31-7.27 (multiple peaks, 5H), 7.22-7.13 (m, 2H), 7.04 (dd, J = 9.1, 4.3 Hz, 2H), 4.91 (s, 2H), 3.10 (s, 3H); \(^1\)³C NMR (176 MHz, CDCl₃) δ 160.4 (d, J = 245.8 Hz), 155.9, 150.1 (d, J = 2.8 Hz), 148.1, 135.4, 134.2, 128.9 (three overlapping carbons), 128.5, 121.9 (d, J = 8.5 Hz), 117.9, 117.7 (d, J = 23.6 Hz), 111.8, 54.2, 40.7; \(^1\)⁹F NMR (377 MHz, CDCl₃) δ –116.9 (m, 1F); FT-IR 1739.7, 1525.5, 1522.2, 1344.9, 1208.6, 1153.9 cm⁻¹; HRMS m/z calculated for C₁₀H₁₇N₂SO₃FNa [M+Na]⁺: 439.0734, found 439.0727.

IV. Regioisomer Assignment of mesityl(aryl)iodonium salts

A. General Procedures for the Synthesis of mesityl(aryl)iodonium salts
General Procedure A: To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added arene 1a (11 µL, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 µL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et₂O was added to precipitate the diaryliodonium salt. The mixture was stirred for 30 min before the diaryliodonium salt was collected by filtration, washed with Et₂O, dried under vacuum, and analyzed by ¹H NMR for regioisomer identification.

General Procedure B: To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added arene 1b (11 µL, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C, and trifluoroacetic anhydride (TFAA) (14 µL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h. The solution was concentrated under a stream of nitrogen, and Et₂O was added to precipitate the diaryliodonium salt. The mixture was stirred for 30 min before the diaryliodonium salt was collected by filtration, washed with Et₂O, dried under vacuum, and analyzed by ¹H NMR for regioisomer identification.
B. Regioisomer Assignment of 2a-2q

Mesityl(4-methoxyphenyl)iodonium trifluoromethanesulfonate (2a). General procedure A was followed. $^1$H NMR (401 MHz, CDCl$_3$) δ 7.64 (d, $J = 9.1$ Hz, 2H), 7.09 (s, 2H), 6.93 (d, $J = 9.1$ Hz, 2H), 3.82 (s, 3H), 2.64 (s, 6H), 2.35 (s, 3H).
(4-(Benzyloxy)phenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2b). General procedure B was followed. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66-7.59 (multiple peaks, 4H), 7.42-7.32 (multiple peaks, 5H), 7.08 (d, $J = 7.9$ Hz, 2H), 7.03 (s, 2H), 6.94 (d, $J = 9.0$ Hz, 2H), 5.04 (s, 2H), 2.61 (s, 6H), 2.35-2.30 (multiple peaks, 6H).
(3-Bromo-4-methoxyphenyl)(mesityl)iodonium trifluoromethanesulfonate (2c). General procedure A was followed. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.28 (dd, $J = 2.3$, 1.1 Hz, 1H), 7.92 (ddd, $J = 8.9$, 2.3, 1.1 Hz, 1H), 7.24-7.15 (multiple peaks, 3H), 3.88 (s, 3H), 2.60 (s, 6H), 2.30 (s, 3H).
(4-Methoxy-3-(methoxycarbonyl)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2d). General procedure A was followed. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.05 (d, $J = 2.3$ Hz, 1H), 7.93 (dd, $J = 9.3$, 2.3 Hz, 1H), 7.08 (s, 2H), 7.02 (d, $J = 9.3$ Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 2.65 (s, 6H), 2.35 (s, 3H).
(2,4-Dimethoxyphenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2e). General procedure B was followed. $^1$H NMR (401 MHz, CD$_3$OD) $\delta$ 7.90 (d, $J = 8.9$ Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 7.17 (s, 2H), 6.76 (d, $J = 2.6$ Hz, 1H), 6.67 (dd, $J = 8.9, 2.6$ Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 2.66 (s, 6H), 2.37 (s, 3H), 2.33 (s, 3H).
(2,3-Dihydrobenzofuran-5-yl)(mesityl)iodonium trifluoromethanesulfonate (2f). General procedure A was followed. $^1$H NMR (401 MHz, DMSO-$d_6$) δ 7.89 (d, $J = 1.7$ Hz, 1H), 7.77 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.19 (s, 2H), 6.88 (d, $J = 8.4$ Hz, 1H), 4.59 (t, $J = 8.8$ Hz, 2H), 3.21 (t, $J = 8.8$ Hz, 2H), 2.61 (s, 6H), 2.29 (s, 3H).
(4-(2-Oxopyrrolidin-1-yl)phenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2g). General procedure B was followed. $^1$H NMR (401 MHz, CD$_3$OD) δ 7.91 (d, $J = 9.1$ Hz, 2H), 7.82 (d, $J = 9.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.25-7.21 (multiple peaks, 4H), 3.90 (t, $J = 7.1$ Hz, 2H), 2.67 (s, 6H), 2.61 (t, $J = 8.1$ Hz, 2H), 2.39-2.33 (multiple peaks, 6H), 2.17 (p, $J = 7.6$ Hz, 2H).
(4-((N,4-Dimethylphenyl)sulphonamido)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2h). General procedure A was followed. $^1$H NMR (401 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J = 8.9$ Hz, 2H), 7.37 (d, $J = 8.2$ Hz, 2H), 7.30-7.26 (m, 2H), 7.21 (d, $J = 8.9$ Hz, 2H), 7.16 (s, 2H), 3.13 (s, 3H), 2.62 (s, 6H), 2.43 (s, 3H), 2.40 (s, 3H).
(p-Tolyl)(mesityl)iodonium trifluoromethanesulfonate (2i). General procedure A was followed. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.96 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 8.7$ Hz, 2H), 7.36-7.28 (multiple peaks, 5H), 7.21 (s, 2H), 5.11 (s, 2H), 3.26 (s, 3H), 2.60 (s, 6H), 2.29 (s, 3H).
(4-(((Benzyl)oxy)carbonyl(methyl)amino)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2j). General procedure A was followed. $^1$H NMR (401 MHz, CDCl$_3$) δ 7.56 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.12 (s, 2H), 2.63 (s, 6H), 2.42-2.34 (multiple peaks, 6H).
(4-((N,4-Dimethylphenyl)sulfonamido)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2k). General procedure A was followed. $^1$H NMR (401 MHz, DMSO-$d_6$) $\delta$ 7.76 (d, $J = 2.0$ Hz, 1H), 7.67 (dd, $J = 8.2$, 2.0 Hz, 1H), 7.21 (d, $J = 8.2$ Hz, 1H), 7.16 (s, 2H), 2.56 (s, 6H), 2.25 (s, 4H), 2.22-2.17 (multiple peaks, 6H).
(3-Methylthiophen-2-yl)(mesityl)iodonium trifluoromethanesulfonate (2l). General procedure A was followed. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J = 5.4$ Hz, 1H), 7.07 (s, 2H), 6.96 (d, $J = 5.4$ Hz, 1H), 2.73 (s, 6H), 2.53 (s, 3H), 2.33 (s, 3H).
(4-(Methoxycarbonyl)-1-methyl-1H-pyrrol-2-yl)(mesityl)iodonium trifluoromethanesulfonate (2m). General procedure A was followed. $^1$H NMR (401 MHz, DMSO-$d_6$) $\delta$ 7.93 (d, $J = 1.9$ Hz, 1H), 7.37 (d, $J = 1.9$ Hz, 1H), 7.17 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 2.63 (s, 6H), 2.27 (s, 3H).
(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(mesityl)iodonium trifluoromethanesulfonate (2n). General procedure A was followed. $^1$H NMR (401 MHz, CDCl$_3$) δ 8.83 (s, 1H), 7.05 (s, 2H), 3.53 (s, 3H), 3.33 (s, 3H), 2.76 (s, 6H), 2.33 (s, 3H).
(3-Chloro-6-methyl-5,5-dioxido-11-oxo-6,11-dihydrodibenzo[cf][1,2]thiazepin-9-yl)(mesityl)iodonium trifluoromethanesulfonate (2o). General procedure A was followed. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.51 (d, $J = 2.1$ Hz, 1H), 8.17 (dd, $J = 8.9$, 2.1 Hz, 1H), 7.91 (s, 1H), 7.83 (d, $J = 8.3$ Hz, 1H), 7.71 (d, $J = 8.3$ Hz, 1H), 7.36 (d, $J = 8.9$ Hz, 1H), 7.15 (s, 2H), 3.43 (s, 3H), 2.70 (s, 6H), 2.38 (s, 3H).
(4-(Benzyloxy)-3,5-diisopropylphenyl)(mesityl)iodonium 4-methylbenzenesulfonate (2p). General procedure A was followed. $^1$H NMR (401 MHz, CDCl$_3$) δ 7.67 (d, $J = 8.0$ Hz, 2H), 7.43-7.38 (multiple peaks, 5H), 7.37 (s, 2H), 7.13-7.05 (multiple peaks, 4H), 4.77 (s, 2H), 3.28 (p, $J = 6.9$ Hz, 2H), 2.64 (s, 6H), 2.35 (s, 3H), 2.33 (s, 3H), 1.11 (d, $J = 6.9$ Hz, 12H).
(4-(2-(N-Benzylmethylsulfonamido)-5-nitrophenoxy)phenyl)(mesityl)iodonium trifluoromethanesulfonate (2q). General procedure A was followed. $^1$H NMR (401 MHz, DMSO-$d_6$) $\delta$ 8.04 (d, $J = 8.9$ Hz, 2H), 7.98 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.57 (d, $J = 2.6$ Hz, 1H), 7.26-7.11 (multiple peaks, 9H), 4.84 (s, 2H), 3.19 (s, 3H), 2.63 (s, 6H), 2.31 (s, 3H).
V. Radiochemistry

A. General Considerations, Methods, and Materials

Anhydrous potassium carbonate, 18-crown-6, tetrakis(acetonitrile) copper(I) triflate, trimethylsilyl triflate, and trifluoroacetic acid were obtained from Sigma Aldrich. Anhydrous acetonitrile, anhydrous DCM, and anhydrous N,N-dimethylformamide were obtained from Acros Organics. HPLC grade acetonitrile, ammonium acetate and anisole were obtained from Fisher Chemical. Ethanol was purchased from American Reagent. Potassium triflate was obtained from Oakwood Chemical. N,N-Diisopropylethylamine was obtained from Sigma Aldrich and was distilled from potassium hydroxide before use and stored under argon. Sterile 0.9% saline and sterile water for injection were purchased from Hospira. Ultrapure water was obtained from a Millipore MilliQ Gradient A10 system. Sterile vials were purchased from Hollister-Stier.

QMA-light Sep-Paks were purchased from Waters Corporation, and were flushed with 10 ml ethanol, followed by 10 mL of water, followed by 10 mL of 0.5 M aqueous sodium bicarbonate solution or 0.5 M aqueous potassium triflate solution as specified below, followed by 10 mL of water before use. Sep-Pak C18 1cc Vac cartridges were purchased from Waters Corporation, and were flushed with 10 ml ethanol, followed by 10 mL of water before use.

Glass backed thin layer chromatography (TLC) plates coated with silica gel 60F_{254} were used for radio-TLC analysis and were purchased from EMD-Millipore. Radio-TLC analysis was performed using a Bioscan AR 2000 Radio-TLC scanner (Ekert and Ziegler).

Activity in vials was counted using a CRC-15 (Capintec) detector, calibrated for fluorine-18.

High performance liquid chromatography (HPLC) was performed using a Shimadzu LC-2010A HT system, or a Shimadzu LC system (SCL-10Avp controller, SIL-10AF injector, SPD-10Avp UV detector, LC-DADvp FCV-10ALvp pump system, DGU-14A degasser and CTO-10AVP column oven) equipped with a Bioscan B-FC-1000 radiation detector in series. A 0.2 min offset was applied to all traces below to account for the detectors being in series. The following set of HPLC conditions were used, as specified below:

| HPLC Condition A: | Column: Phenomenex Luna 5 μm C18(2) 100 Å 150 mm x 4.6 mm |
| Flow Rate: 2 mL.min⁻¹ |
| Solvent A: H₂O+0.1% trifluoroacetic acid |
| Solvent B: MeCN |
| Grad/isocrat: 0-3 min, 5% B; 3-20 min, linear gradient, 5-95%B; 20-30 min, 5% B |

| HPLC Condition B: | Column: Phenomenex Luna 5 μm C18(2) 100 Å 150 mm x 4.6 mm |
| Flow Rate: 2 mL.min⁻¹ |
| Solvent A: H₂O+0.1% trifluoroacetic acid |
| Solvent B: MeCN |
| Grad/isocrat: 0-5 min, linear gradient, 5-60%B; 5-20 min, linear gradient, 60-95%B; 20-25 min, 95%B; 25-35 min, 5% B |

| HPLC Condition C: | Column: Phenomenex Synergi 4 μm Hydro-RP 80 Å 150 mm x 4.6 mm |
| Flow Rate: 2 mL.min⁻¹ |
| Solvent A: 20 mM NH₄OAc in H₂O, pH 7.4 |
| Solvent B: MeCN |
B. Radiosynthesis of $^{18}$F-labeled Arenes

i. Potassium $^{18}$F[fluoride for manual reactions

Potassium $^{18}$F[fluoride preparation was conducted on a TRACERlab FX$_{FN}$ or TRACERlab FX$_{NP}$ (General Electric, GE) automated radiochemistry synthesis module. Before $^{18}$F[fluoride delivery, ports in the module were charged under ambient atmosphere as follows:

- Port 1: K$_2$CO$_3$ (3.5 mg) in H$_2$O (0.5 mL)
- Port 2: $^{18}$F-crown-6 (15 mg) in MeCN (1 mL)
- Port 5: DMF (7.5 mL)

$^{[18}F]F$Fluoride was produced via the $^{18}$O(p,n)$^{18}$F reaction by proton irradiation (40 µA, 2-5 min) of an $^{18}$O[H$_2$O containing target in a GE PETTrace cyclotron. The $^{[18}F]F$fluoride (ca. 120-300 mCi) was swept to the synthesis module in a bolus of $^{18}$O[H$_2$O by stream of argon. The aqueous solution of $^{[18}F]F$fluoride was passed through a QMA-light Sep-Pak cartridge (NaHCO$_3$ preconditioning) to trap $^{[18}F]F$fluoride before elution into the reactor vessel with a solution of K$_2$CO$_3$ in H$_2$O (contents of Port 1). To this, a solution of 18-crown-6 in MeCN (contents of Port 2) was added, and the mixture azeotropically dried by heating the reaction vessel to 100 °C and drawing vacuum (ca. 1 kPa) for 5 min, followed by simultaneous vacuum draw and argon stream for a further 6 minutes. The dried $^{[18}F]KF\cdot18$-crown-6•K$_2$CO$_3$ complex was cooled to 50 °C before addition of DMF (contents of Port 5). The mixture was stirred for 5 min before being transferred out of the reactor under Ar pressure into a sterile vial to yield a solution of $^{[18}F]KF\cdot18$-crown-6•K$_2$CO$_3$ (30-100 mCi) in DMF. 100 µL aliquots of this solution were then used for manual methodology experiments.

ii. Optimized General Procedure for the Synthesis of $^{[18}F]Fluoroarenes

To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in anhydrous DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added arene (0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C, and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 µL (0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h before being used as a stock solution (0.25 M) of diaryliodonium in subsequent radiofluorination reactions.
To a 4 mL vial were added anhydrous dimethylformamide (DMF) (800 µL), diaryliodonium stock solution (40 µL, 10 µmol), and \(N,N\)-diisopropylethylamine (iPr\(_2\)NEt) (3.5 µL, 20 µmol). The solution was agitated with a vortex mixer and aged for 10 min at room temperature. Under an ambient atmosphere, tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate ((MeCN)\(_4\)CuOTf) (100 µL of a 100 mM solution, 10 µmol) and quinaldic acid (10 µmol) in DMF were added to the diaryliodonium/iPr\(_2\)NEt solution. The reaction vial was sealed with a PTFE/Silicone septum cap and a 100 µL aliquot of \([^{18}\text{F}]\text{KF} \cdot 18\text{-crown-6} \cdot \text{K}_2\text{CO}_3\) complex in DMF (typically 60-800 µCi, prepared as described above) was added to the reaction vial via syringe. The reaction was heated in an aluminum block at 85 °C for 20 min. After 20 min, the reaction was removed from the heat and allowed to cool to room temperature. Radiochemical conversions (RCCs) were obtained by radio-TLC analysis (2-5 µL aliquots) using a 50:50 hexanes-ethyl acetate eluent, and are not reported to reflect losses during \([^{18}\text{F}]\text{KF} \cdot 18\text{-crown-6} \cdot \text{K}_2\text{CO}_3\) preparation.

Radiochemical conversions (RCCs) were determined by dividing the integrated area under the fluoroarene peak on radio-TLC by the total integrated area of all peaks on the radio-TLC trace. The identity of the \([^{18}\text{F}]\)fluoroarene was verified using radio-HPLC (10-50 µL aliquots) and comparing samples to those that were spiked with a sample the authentic \([^{19}\text{F}]\)fluoroarene product. The ratio of \([^{18}\text{F}]\)fluoroarene to \([^{18}\text{F}]\)fluoromesitylene and other byproducts was obtained by dividing the integrated area under the \([^{18}\text{F}]\)fluoroarene or \([^{18}\text{F}]\)fluoromesitylene peak on HPLC by the total integrated area of all peaks, excluding the peak observed from \([^{18}\text{F}]\)fluoride.

### iii. Summary of Reaction Optimization Studies

#### a. Evaluation of additives for the radiofluorination of isolated 4-MeOC\(_6\)H\(_4\)-I-MesOTf (2a)

| entry | additive | RCC (%) |
|-------|----------|---------|
| 1     | none     | 46 ± 9  (n = 4) |
| 2     | AcOH     | 13 ± 4  (n = 4) |
| 3     | TFA      | 8 ± 4   (n = 4) |
| 4     | H\(_2\)O | 45 ± 7  (n = 4) |
| 5     | quinaldic acid, iPr\(_2\)NEt (10 µmol) | 62 ± 5  (n = 3) |
| 6     | quinaldic acid, iPr\(_2\)NEt (10 µmol) | 85 ± 2  (n = 3) |

Manual synthesis conditions: 4-MeOC\(_6\)H\(_4\)-I-MesOTf (2a) (10 µmol), (MeCN)\(_4\)CuOTf (10 µmol), \([^{18}\text{F}]\text{KF} \cdot 18\text{-crown-6} \cdot \text{K}_2\text{CO}_3\) complex in DMF (100 µL, 80-1200 µCi), additive (10 µmol), total volume 1.0 mL. Acetic acid (AcoH), trifluoroacetic acid (TFA).

1 Typically, 4-12 reactions were set up in parallel. As a consequence, the exact times that the mixtures remain at room temperature prior to the addition of \([^{18}\text{F}]\)fluoride varies between runs, and between days. The RCCs however appear insensitive to this variation as reflected in the small standard deviations observed.

2 Radio-TLCs for volatile products (eg. 4-fluoroanisole and 2-fluoro-4-methylthiophene) were counted immediately after developing, before the plate had dried completely.

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b. Optimization of the C(sp\textsuperscript{3})–H radiofluorination of anisole (1a)\textsuperscript{a}

\[
\begin{align*}
1a & \quad + \quad \text{MeO} \quad + \quad \text{Mes} \quad + \quad \text{OTs} \\
\text{MeO} & \quad | \quad \text{OH} & \quad | \quad \text{Mes} & \quad | \quad \text{OTs} \\
\end{align*}
\]

1. \textbf{activator}, DCM, rt
2. (MeCN)\textsubscript{2}CuOTf

\[
\begin{align*}
{^{18}\text{F}}\text{KF•18-crown-6, base} \\
\text{DMF, 85 °C, 20 min}
\end{align*}
\]

| entry | activator | base | RCC 3a\textsuperscript{b} (%) |
|-------|-----------|------|-----------------------------|
| 1     | TsOH+H\textsubscript{2}O | –    | 27 ± 4 (n = 4)               |
| 2     | TsOH+H\textsubscript{2}O | \textit{iPr\textsubscript{2}}NEt (20 µmol) | 61 ± 8 (n = 9)               |
| 3     | TFIAA    | –    | 1 ± 1 (n = 3)                |
| 4     | TFIAA    | \textit{iPr\textsubscript{2}}NEt (4.0 equiv) | 13 ± 2 (n = 3)               |
| 5     | TMSOTf   | –    | 5 ± 2 (n = 5)                |
| 6     | TMSOTf   | \textit{iPr\textsubscript{2}}NEt (10 µmol) | 58 ± 0.4 (n = 3)             |
| 7     | TMSOTf   | \textit{iPr\textsubscript{2}}NEt (20 µmol) | 78 ± 4 (n = 3)               |
| 8\textsuperscript{c,d} | TMSOTf   | \textit{iPr\textsubscript{2}}NEt (20 µmol) | 87 ± 4 (n = 13)              |
| 9\textsuperscript{e} | TMSOTf   | \textit{iPr\textsubscript{2}}NEt (20 µmol) | 00 ± 0 (n = 3)               |

\textsuperscript{a} Manual synthesis conditions: 1. Anisole (1a) (10 µmol), MesI(OH)OTs (10 µmol), \textbf{activator} (10 µmol), DCM (40 µL); 2. (MeCN)\textsubscript{2}CuOTf (10 µmol), \[^{18}\text{F}]\text{KF•18-crown-6•K}_2\text{CO}_3 complex in DMF (100 µL, 80-1200 µCi), total volume 1.0 mL. \textsuperscript{b} Radiochemical conversion was determined by radio-TLC (average of n runs). The identity of 4-[^{18}\text{F}]fluoroanisole (3a) was confirmed by HPLC. \textsuperscript{c} Quinaldic acid (10 µmol) was included in step 2. \textsuperscript{d} 98:2 selectivity (3a:[^{18}\text{F}]fluoromesitylene) detected by radio-HPLC. \textsuperscript{e} (MeCN)\textsubscript{2}CuOTf was omitted. Tosylic acid (TsOH), trifluoroacetic anhydride (TFAA), trimethylsilyl trifluoromethanesulfonate (TMSOTf).

c. Base evaluation studies\textsuperscript{a}

\[
\begin{align*}
1a & \quad + \quad \text{MeO} \quad + \quad \text{Mes} \quad + \quad \text{OTs} \\
\text{MeO} & \quad | \quad \text{OH} & \quad | \quad \text{Mes} & \quad | \quad \text{OTs} \\
\end{align*}
\]

1. TMSOTf, DCM, rt
2. (MeCN)\textsubscript{2}CuOTf

\[
\begin{align*}
{^{18}\text{F}}\text{KF•18-crown-6, base} \\
\text{DMF, 85 °C, 20 min}
\end{align*}
\]

| entry | base | µmol | RCC (%) |
|-------|------|------|---------|
| 1     | \textit{iPr\textsubscript{2}}NEt | 10   | 58 ± 0.4 (n = 3) |
| 2     | \textit{iPr\textsubscript{2}}NEt | 20   | 78 ± 4 (n = 3) |
| 3     | Et\textsubscript{3}N | 10   | 44 ± 11 (n = 5) |
| 4     | Et\textsubscript{3}N | 20   | 78 ± 7 (n = 4) |
| 5     | pyridine | 10   | 6 ± 2 (n = 3) |
| 6     | pyridine | 20   | 5 ± 1 (n = 3) |
| 7     | K\textsubscript{2}CO\textsubscript{3} | 10   | 43 ± 8 (n = 3) |
| 8     | K\textsubscript{2}CO\textsubscript{3} | 20   | 31 ± 7 (n = 3) |

\textsuperscript{a} Manual synthesis conditions: 1. Anisole (1a) (10 µmol), MesI(OH)OTs (10 µmol), TMSOTf (10 µmol), DCM (40 µL); 2. (MeCN)\textsubscript{2}CuOTf (10 µmol), \[^{18}\text{F}]\text{KF•18-crown-6•K}_2\text{CO}_3 complex in DMF (100 µL, 80-1200 µCi), base (x µmol), total volume 1.0 mL.

d. Additive evaluation studies\textsuperscript{a}

\[
\begin{align*}
1a & \quad + \quad \text{MeO} \quad + \quad \text{Mes} \quad + \quad \text{OTs} \\
\text{MeO} & \quad | \quad \text{OH} & \quad | \quad \text{Mes} & \quad | \quad \text{OTs} \\
\end{align*}
\]

1. TMSOTf, DCM, rt
2. (MeCN)\textsubscript{2}CuOTf, additive (10 µmol)

\[
\begin{align*}
{^{18}\text{F}}\text{KF•18-crown-6, \textit{iPr\textsubscript{2}}NEt} \\
\text{DMF, 85 °C, 20 min}
\end{align*}
\]
| entry | additive            | RCC (%)   |
|-------|---------------------|-----------|
| 1     | TMEDA               | 85 ± 5 (n = 3) |
| 2     | Quinox              | 48 ± 7 (n = 3) |
| 3     | bpy                 | 88 ± 9 (n = 7) |
| 4     | picolinic acid      | 87 ± 4 (n = 4) |
| 5     | quinaldic acid      | 87 ± 4 (n = 13) |
| 6b    | quinaldic acid      | 87 ± 2 (n = 3) |

Manual synthesis conditions: 1. Anisole (1a) (10 µmol), MesI(OH)OTs (10 µmol), TMSOTf (10 µmol), DCM (40 µL); 2. (MeCN)$_2$CuOTf (10 µmol), iPr$_2$NEt (20 µmol), $[^{18}$F$]$KF•18-crown-6•K$_2$CO$_3$ complex in DMF (100 µL, 80-1200 µCi), additive (10 µmol), total volume 1.0 mL. $^b$ iPr$_2$NEt (25 µmol).

**e. Temperature evaluation studies**

![Reaction scheme](attachment:reaction_scheme.png)

| entry | Temperature (°C) | RCC (%)   |
|-------|------------------|-----------|
| 1     | 65               | 81 ± 14 (n = 6) |
| 2$^b$ | 85               | 87 ± 4 (n = 13) |
| 3$^c$ | 105              | 90 ± 6 (n = 5) |

Manual synthesis conditions: 1. Anisole (1a) (10 µmol), MesI(OH)OTs (10 µmol), TMSOTf (10 µmol), DCM (40 µL); 2. (MeCN)$_2$CuOTf (10 µmol), iPr$_2$NEt (20 µmol), $[^{18}$F$]$KF•18-crown-6•K$_2$CO$_3$ complex in DMF (100 µL, 80-1200 µCi), quinaldic acid (10 µmol), total volume 1.0 mL. $^b$ 98:2 selectivity (3a:$[^{18}$F$]$fluoromesitylene) detected by radio-HPLC. $^c$ 98:2 selectivity (3a:$[^{18}$F$]$fluoromesitylene) detected by radio-HPLC.

**f. Reaction time point evaluation**

![Reaction scheme](attachment:reaction_scheme.png)

| entry | Time (min) | RCC (%)   |
|-------|------------|-----------|
| 1     | 5          | 86 ± 1 (n = 3) |
| 2     | 10         | 86 ± 1 (n = 3) |
| 3     | 15         | 89 ± 1 (n = 3) |
| 4     | 20         | 87 ± 4 (n = 13) |
| 5     | 30         | 89 ± 1 (n = 3) |

Manual synthesis conditions: 1. Anisole (1a) (10 µmol), MesI(OH)OTs (10 µmol), TMSOTf (10 µmol), DCM (40 µL); 2. (MeCN)$_2$CuOTf (10 µmol), iPr$_2$NEt (20 µmol), $[^{18}$F$]$KF•18-crown-6•K$_2$CO$_3$ complex in DMF (100 µL, 80-1200 µCi), quinaldic acid (10 µmol), total volume 1.0 mL.
iv. **Radio-HPLC/Radio-TLC Analysis for $^{18}$F-labeled Arenes**

a. **$^{4}$-$^{18}$FFluoroanisole (3a)**

![Structure of $^{18}$FFluoroanisole (3a)](image)

**Radio-TLC eluent**: 50% EtOAc in hexanes

**Raw RCCs (%)**: 89, 94, 93, 90, 88, 81, 80, 85, 93, 85, 87, 87, 85. Average: 87 ± 4%. Selectivity: 98:2 (3a:4). RCC corrected for presence of 4: 85 ± 4% ($n = 13$).

In the absence of quinaldic acid - **Raw RCCs (%)**: 82, 77, 74. Average: 78 ± 4%. Selectivity: 98:2 (3a:4). RCC corrected for presence of 4: 76 ± 4% ($n = 13$).
**HPLC conditions:** Condition A
A: 4-[^{18}F]Fluoroanisole 3a reaction gamma trace overlaid with UV trace at 280 nm
B: 4-[^{18}F]Fluoroanisole 3a reaction gamma trace overlaid with UV trace at 280 nm spiked with 4-fluoroanisole
The site-selectivity of the reaction of anisole was determined by radio-HPLC analysis via comparison to authentic standards of the three possible isomers.

**HPLC conditions:** Condition E
Overlaid HPLC chromatograms for the one-pot radiofluorination of 1a.
A: UV-HPLC chromatogram of the crude reaction mixture spiked with 4-fluoroanisole 3a at 280 nm.
B: Radio-HPLC chromatogram of the crude reaction mixture.
C: UV-HPLC chromatograms of authentic samples of possible fluoroanisole isomers at 280 nm
b. Benzyl 4-[^18F]fluorophenyl ether (3b)³

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 87, 92, 93, 91. Average: 90 ± 3%. Selectivity: 98:2 (3b:4). RCC corrected for presence of 4: 88 ± 3% (n = 4).

³ The general procedure was followed using 9.0 µL (0.10 mmol, 1.0 equiv) TMSOTf.
**HPLC conditions:** Condition A  
**A:** Benzyl 4-[\(^{18}\text{F}\)]fluorophenyl ether 3b reaction gamma trace overlaid with UV trace at 280 nm  
**B:** Benzyl 4-[\(^{18}\text{F}\)]fluorophenyl ether 3b reaction gamma trace overlaid with UV trace at 280 nm spiked with benzyl 4-fluorophenyl ether 3b
c. 2-Bromo-4-[\textsuperscript{18}F]fluoroanisole (3c)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 87, 83, 87, 78. Average: 84 \pm 4\%. Selectivity: 97:3 (3c:4). RCC corrected for presence of 4: 81 \pm 4\% (n = 4).
**HPLC conditions:** Condition A
A: 2-Bromo-4-[[^18]F]fluoroanisole 3c reaction gamma trace overlaid with UV trace at 280 nm
B: 2-Bromo-4-[[^18]F]fluoroanisole 3c reaction gamma trace overlaid with UV trace at 280 nm spiked with 2-bromo-4-fluoroanisole 3c
d. Methyl 5-[^18F]fluoro-2-methoxybenzoate (3d)\(^4\)

\[
\text{MeO}_2\text{C}_\text{\[18F\]}\text{MeO}^-
\]

**Radio-TLC eluent:** 50% EtOAc in hexanes

Raw RCCs (%): 84, 88, 86, 90. Average: 87 ± 3%. Selectivity: 95:5 (3d:4). RCC corrected for presence of 4: 83 ± 3% (n = 4).

\(^4\) The general procedure was followed using 9.0 µL (0.10 mmol, 1.0 equiv) TMSOTf.
HPLC conditions: Condition A
A: Methyl 5-[18F]fluoro-2-methoxybenzoate 3d reaction gamma trace overlaid with UV trace at 280 nm
B: Methyl 5-[18F]fluoro-2-methoxybenzoate 3d reaction gamma trace overlaid with UV trace at 280 nm spiked with methyl 5-fluoro-2-methoxybenzoate 3d
e. 1-[\textsuperscript{18}F]Fluoro-2,4-dimethoxybenzene (3e)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 62, 62, 70, 70, 72, 64, 57, 64. Average: 65 ± 5%. Selectivity: 88:12 (3e:4). RCC corrected for presence of 4: 57 ± 4% ($n = 8$).
**HPLC conditions:** Condition A

**A:** $1-[^{18}\text{F}]$Fluoro-2,4-dimethoxybenzene 3e reaction gamma trace overlaid with UV trace at 280 nm

**B:** $1-[^{18}\text{F}]$Fluoro-2,4-dimethoxybenzene 3e reaction gamma trace overlaid with UV trace at 280 nm spiked with $1-[^{18}\text{F}]$Fluoro-2,4-dimethoxybenzene 3e
f. 5-[^18F]Fluoro-2,3-dihydrobenzofuran (3f)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 82, 82, 74, 85, 80. Average: 81 ± 4%. Selectivity: 98:2 (3f:4). RCC corrected for presence of 4: 79 ± 4% (n = 5).
**HPLC conditions:** Gradient Condition A

A: $5\cdot[^{18}F]\text{Fluoro-2,3-dihydrobenzofuran 3f}$ reaction gamma trace overlaid with UV trace at 280 nm

B: $5\cdot[^{18}F]\text{Fluoro-2,3-dihydrobenzofuran 3f}$ reaction gamma trace overlaid with UV trace at 280 nm spiked with 5-fluoro-2,3-dihydrobenzofuran 3f
g. \( N-(4-[^{18}F]\text{fluorphenyl})\text{pyrroldidine-2-one (3g)} \)

![Chemical Structure]

**Radio-TLC eluent:** 50% EtOAc in hexanes

![Radio-TLC chromatogram]

Raw RCCs (%): 92, 87, 75, 80, 82, 87. Average: 84 ± 6%. Selectivity: 97:3 (3g:4). RCC corrected for presence of 4: 81 ± 6% \((n = 6)\).
**HPLC conditions**: Gradient Condition A

**A**: \(N\-(4-[^{18}\text{F}]\text{fluorphenyl})\text{pyrrolidine-2-one}\) \(3g\) reaction gamma trace overlaid with UV trace at 254 nm

**B**: \(N\-(4-[^{18}\text{F}]\text{fluorphenyl})\text{pyrrolidine-2-one}\) \(3g\) reaction gamma trace overlaid with UV trace at 254 nm spiked with \(N\-(4\text{-fluorphenyl})\text{pyrrolidine-2-one}\) \(3g\)
h. $4-\textsuperscript{[18]F}\text{Fluoro-}N\text{-methyl-}N\text{-tosylaniline (3h)}^5$

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 86, 83, 84, 85, 86. Average: 85 ± 2%. Selectivity: 98:2 (3h:4). RCC corrected for presence of 4: 83 ± 1% ($n = 5$).

In the absence of quinaldic acid - Raw RCCs (%): 53, 63, 59, 41. Average: 59 ± 10%. Selectivity: 95:5 (3h:4). RCC corrected for presence of 4: 56 ± 10% ($n = 4$).

---

$^5$ The general procedure was followed using 9.0 µL (0.10 mmol, 1.0 equiv) TMSOTf.
**HPLC conditions:** Condition A

**A:** $4\cdot^{[18}F\cdot]fluoro-N\cdot methyl\cdot N\cdot tosylaniline$ 3h reaction gamma trace overlaid with UV trace at 254 nm

**B:** $4\cdot^{[18}F\cdot]fluoro-N\cdot methyl\cdot N\cdot tosylaniline$ 3h reaction gamma trace overlaid with UV trace at 254 nm spiked with 4-fluoro-N-methyl-N-tosylaniline 3h
Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 81, 77, 77, 77. Average: 78 ± 2%. Selectivity: >99:1 (3i:4). RCC corrected for presence of 4: 78 ± 2% (n = 4).
**HPLC conditions:** Condition B  
**A:** N-Carboxybenzyl-4-[¹⁸F]fluoro-N-methylaniline 3i reaction gamma trace overlaid with UV trace at 254 nm  
**B:** N-Carboxybenzyl-4-[¹⁸F]fluoro-N-methylaniline 3i reaction gamma trace overlaid with UV trace at 254 nm spiked with N-Carboxybenzyl-4-fluoro-N-methylaniline 3i⁷

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⁷ The Rad peak at ca. 8.5 min corresponds to an unknown byproduct believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below.
j. 4-[\(^{18}\text{F}\)]Fluorotoluene (3j)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 84, 92, 82, 81. Average: 85 ± 5%. Selectivity: 98:2 (3j:4). RCC corrected for presence of 4: 83 ± 5% (n = 4).
**HPLC conditions:** Gradient Condition A

**A:** 4-[^18F]Fluorotoluene 3j reaction gamma trace overlaid with UV trace at 254 nm

**B:** 4-[^18F]Fluorotoluene 3j reaction gamma trace overlaid with UV trace at 254 nm spiked with 4-fluorotoluene 3j
k. 4-[^18F]Fluoro-o-xylene (3k)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 87, 91, 90, 94. Average: 90 ± 3%. Selectivity: 98:2 (3k:4). RCC corrected for presence of 4: 88 ± 3% (n = 4).
HPLC conditions: Condition A
A: 4-[^18]F Fluoro-o-xylene 3k reaction gamma trace overlaid with UV trace at 254 nm
B: 4-[^18]F Fluoro-o-xylene 3k reaction gamma trace overlaid with UV trace at 254 nm spiked with 4-fluoro-o-xylene 3k
l. 2-[^18F]Fluoro-3-methylthiophene (3l)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 26, 45, 27, 28, 36, 36, 43, 58, 53, 36. Average: 40 ± 11%. Selectivity: 62:38 (3l:byproducts). RCC corrected for presence of 4 and unknown byproduct (see below, ca. 21 min HPLC gamma trace): 25 ± 7% (n = 11).

In the absence of quinaldic acid - Raw RCCs (%): 30, 26, 28. Average: 28 ± 2%. Selectivity: 68:32 (3l:4). RCC corrected for presence of 4: 19 ± 1% (n = 3).

---

8 The general procedure was followed with 105 °C heating of the radiofluorination.
HPLC conditions: Gradient Condition A
A: 2-[18F]Fluoro-4-methylthiophene 3I reaction gamma trace overlaid with UV trace at 254 nm prepared from the isolated diaryliodonium salt s1. 2-[18F]Fluoro-4-methylthiophene 3I is observed with a retention time of 16.3 min, while the peak at 18.9 min corresponds to [18F]fluoromesitylene.
B: 2-[18F]Fluoro-4-methylthiophene 3I reaction gamma trace overlaid with UV trace at 254 nm prepared using the in situ approach from the C-H precursor. 2-[18F]Fluoro-4-methylthiophene 3I is observed with a retention time of 16.3 min, while the peak at 18.9 min corresponds to [18F]fluoromesitylene. The peak at retention time 15.3 min is an unknown by-product.10
C: 2-[18F]Fluoro-4-methylthiophene 3I reaction gamma trace overlaid with UV trace at 254 nm spiked with 2-[18F]Fluoro-4-methylthiophene 3I produced from isolated diaryliodonium salt 3I. Overlap of the two peaks at 16.3 min is observed.

9 The radiofluorination of s1 was carried out in accordance with a previously reported method.7 To a 4 mL vial were added 2.6 mg s1 (6.0 µmol), 2.3 mg tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate ((MeCN)4CuOTf) (6 µmol), and 500 µL anhydrous dimethylformamide (DMF). The reaction vial was sealed with a PTFE/Silicone septum cap and a 250 µL aliquot of [18F]KF·18-crown-6·K2CO3 complex in DMF (typically 60-800 µCi, prepared as described above) was added to the reaction vial via syringe. The reaction was heated in an aluminum block at 85 °C for 20 min. After 20 min, the reaction was removed from heat and allowed to cool to room temperature. Radiochemical conversions (RCCs) were obtained by radio-TLC analysis (2-5 µL aliquots) using a 50:50 hexanes-ethyl acetate eluent, and are not reported to reflect losses during [18F]KF·18-crown-6·K2CO3 preparation. Raw RCCs (%): 11, 11. Average: 11% (n = 2). Selectivity: 75:25 (3I:4). A sample of the product mixture was analyzed using radio-HPLC (10-50 µL aliquots). The sample was used as a spike to verify the identity of 3I in the C–H radiofluorination.

10 The Rad peak at ca. 15.3 min corresponds to an unknown byproduct believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below. The Rad peak at ca. 21 min corresponds to an extremely non-polar unknown byproduct also observed for 3m and 3o.
m. Methyl 5-[¹⁸F]fluoro-N-methylpyrrole-2-carboxylate (3m)¹¹

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 34, 36, 34. Average: 35 ± 1%. Selectivity: 73:27 (3m:4). RCC corrected for presence of 4: 25 ± 1% (n = 3).

In the absence of quinaldic acid - Raw RCCs (%): 12, 13, 13, 10. Average: 12 ± 1%. Selectivity: 69:31 (3m:4). RCC corrected for presence of 4: 8 ± 1% (n = 4).

¹¹ The general procedure was followed using 9.0 µL (0.10 mmol, 1.0 equiv) TMSOTf and with 105 °C heating of the radiofluorination.
HPLC conditions: Condition A
A: Methyl 5-[^18]F]fluoro-N-methylpyrrole-2-carboxylate 3m reaction gamma trace overlaid with UV trace at 254 nm

B: Methyl 5-[^18]F]fluoro-N-methylpyrrole-2-carboxylate 3m reaction gamma trace overlaid with UV trace at 254 nm spiked with methyl 5-fluoro-N-methylpyrrole-2-carboxylate 3m ($t_R$ 14.3 min). The peak with $t_R$ 18.8 min in the gamma trace is $[^18]$F]fluoromesitylene.

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12 The Rad peak at ca. 15.3 min corresponds to an unknown byproduct believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below.
n. \(N,N\)-Dimethyl-5-[\(^{18}\text{F}\)]fluorouracil (3n)

\[
\text{Radio-TLC eluent: 50\% EtOAc in hexanes}
\]

Raw RCCs (%): 37, 39, 38, 40. Average: 38 ± 1\%. Selectivity: 25:75 (3n:4). RCC corrected for presence of 4: 10 ± 1\% \((n = 4)\).

In the absence of quinaldic acid - Raw RCCs (%): 22, 23, 22, 11. Average: 20 ± 6\%. Selectivity: 24:76 (3n:4). RCC corrected for presence of 4: 5 ± 1\% \((n = 4)\).

\text{13 The general procedure was followed using 9.0 \(\mu\)L (0.10 mmol, 1.0 equiv) TMSOTf and with 105 °C heating of the radiofluorination.}
**HPLC conditions:** Condition C

**A:** N,N'-Dimethyl-5-[\textsuperscript{18}F]fluorouracil 3n reaction gamma trace overlaid with UV trace at 280 nm.

**B:** N,N'-Dimethyl-5-[\textsuperscript{18}F]fluorouracil 3n reaction gamma trace overlaid with UV trace at 280 nm spiked with N,N'-dimethyl-5-fluorouracil 3n (\(t_R\) 11.7 min). The peak with \(t_R\) 28.0 min in the gamma trace is [\textsuperscript{18}F]fluoromesitylene.
Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 32, 46, 43, 27, 19. Average: 33 ± 11%. Selectivity: 53:47 (3o:byproducts). RCC corrected for presence of 4 and unknown byproduct (see below, ca. 21 min HPLC gamma trace): 18 ± 6% (n = 5).

In the absence of quinaldic acid - Raw RCCs (%): 25, 28, 25, 20. Average: 25 ± 3%. Selectivity: 66:33 (3o:byproducts). RCC corrected for presence of 4 and unknown byproduct (see below, ~21 min HPLC gamma trace): 17 ± 2% (n = 4).
HPLC conditions: Gradient Condition A
A: 3-Chloro-9-[^18]Ffluoro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide 3o reaction gamma trace overlaid with UV trace at 254 nm\(^4\)
B: 3-Chloro-9-[^18]Ffluoro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide 3o reaction gamma trace overlaid with UV trace at 254 nm spiked with 3-Chloro-9-fluoro-6-methyldibenzo[c,f][1,2]thiazepin-11(6H)-one 5,5-dioxide 3o

\(^14\) The Rad peaks at ca. 15.3 and 19.5 min corresponds to unknown byproducts believed to originate from unreacted TMSOTf and/or TMSOTs, see control studies below. The Rad peak at ca. 21 min corresponds to an extremely non-polar unknown byproduct also observed for 3l.
p. *O-Benzyl-4-*[^18]Ffluoroprofol (3p)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 85, 85, 90, 85, 87. Average: 87 ± 2%. Selectivity: >99:1 (3p:4). RCC corrected for presence of 4: 87 ± 2% (n = 5).
HPLC conditions: Condition B
A: O-Benzyl-4-[^18F]fluoropropofol 3p reaction gamma trace overlaid with UV trace at 280 nm
B: O-Benzyl-4-[^18F]fluoropropofol 3p reaction gamma trace overlaid with UV trace at 280 nm spiked with O-benzyl-4-fluoropropofol 3p
q. *N*-Benzyl-4-[^18]F]fluoronimesulide (3q)

Radio-TLC eluent: 50% EtOAc in hexanes

Raw RCCs (%): 79, 81, 89, 90, 87, 85, 79. Average: 84 ± 5%. Selectivity: 96:4 (3q:4). RCC corrected for presence of 4: 81 ± 5% (n = 7).

In the absence of quinaldic acid - Raw RCCs (%): 54, 56, 58, 57. Average: 56 ± 2%. Selectivity: 97:3 (3q:4). RCC corrected for presence of 4: 54 ± 2% (n = 4).
HPLC conditions: Condition B  
A: \( N\)-Benzyl-4-[\(^{18}\text{F}\)fluoronimesulide 3q reaction gamma trace overlaid with UV trace at 280 nm  
B: \( N\)-Benzyl-4-[\(^{18}\text{F}\)fluoronimesulide 3q reaction gamma trace overlaid with UV trace at 280 nm, after spiking with \( N\)-benzyl-4-fluoronimesulide 3q
HPLC conditions: Condition D
A: $N$-Benzyl-4-$[^{18}\text{F}]$fluoronimesulide 3q reaction gamma trace overlaid with UV trace at 254 nm
B: $N$-Benzyl-4-$[^{18}\text{F}]$fluoronimesulide 3q reaction gamma trace overlaid with UV trace at 254 nm, after spiking with $N$-benzyl-4-fluoronimesulide 3q
C. Automated Radiosynthesis of $^{18}$F-labeled Arenes

i. Automated Synthesis of 4-$^{18}$F Fluoroanisole (3a)

To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) anhydrous DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added anisole (11 µL, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 µL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h before being used as a stock solution (0.25 M) of diaryl iodonium in the subsequent radiofluorination reaction.

Automated syntheses were conducted on a GE TRACERLab FXFN automated radiochemistry synthesis module. Before $^{18}$F fluoride delivery, ports in the module were charged under ambient atmosphere as follows:

- Port 1: KOTf (5 mg) and K$_2$CO$_3$ (50 µg) in H$_2$O (0.5 mL)
- Port 2: 18-crown-6 (15 mg) in MeCN (1.0 mL)
- Port 3: (MeCN)$_4$CuOTf (3.7 mg, 10 µmol, 1.0 equiv) and quinaldic acid (1.7 mg, 10 µmol, 1.0 equiv) in DMF (0.5 mL)
- Port 4: diaryl iodonium stock solution (see above) in DCM (40 µL, 10 µmol, 1.0 equiv) and diisopropylethylamine (3.5 µL, 20 µmol, 2.0 equiv) in DMF (0.5 mL)
- Port 5: DMF (3.0 mL)
- Port 6: DMF (3.0 mL).

$^{18}$F Fluoride (ca. 1500 mCi) was produced in a GE PETTrace cyclotron as described above for the manual reactions and swept to the synthesis module in a bolus of $[^{18}$O]$\mathrm{H}_2\mathrm{O}$ by stream of argon. The aqueous solution of $[^{18}$F]fluoride was passed through a pre-conditioned QMA-light cartridge (Sep-Pak, potassium triflate preconditioning) to trap $[^{18}$F]fluoride, before the $[^{18}$F]fluoride was eluted into the reactor vessel with a solution of KOTf in H$_2$O (contents of Port 1). To this, a solution of 18-crown-6 in MeCN (contents of Port 2) was added, and the mixture azeotropically dried by heating the reaction vessel to 100 °C and drawing vacuum (ca. 1 kPa) for 5 minutes, followed by simultaneous vacuum draw and argon stream for an additional 6 minutes. The dried $[^{18}$F]KF•18-crown-6•K$_2$CO$_3$ complex (ca. 750 mCi) was cooled to 50 °C before addition of (MeCN)$_4$CuOTf and quinaldic acid in DMF (contents of Port 3). The mixture was stirred for 3 min before addition of diaryl iodonium stock solution and diisopropylethylamine in DMF (contents of Port 4). The reaction vessel was sealed and heated to 85 °C, and held at this temperature for 30 min before being cooled to 50 °C, diluted with DMF (contents of Port 5) and transferred out of the reactor under argon pressure into a vented sterile vial. The reactor was then rinsed with a further measure of DMF (contents of Port 6), and this too transferred to the sterile vial to yield a mixture of 4-$^{18}$F fluoroanisole (3a) and unreacted $[^{18}$F]KF (total 300-400 mCi) in 7 mL of DMF.

Radiochemical conversions (RCCs) were obtained by radio-TLC analysis (2-5 µL aliquots) using a 50:50 hexanes-ethyl acetate eluent, and are not reported to reflect losses of radioactivity during $[^{18}$F]KF•18-crown-6•K$_2$CO$_3$ preparation or radioactivity remaining in the reactor after transfers (c.a 250 mCi). Radiochemical conversions (RCCs) were determined by dividing the integrated area under the fluoroarene peak on radio-TLC by the total integrated area of all peaks on the radio-TLC trace. RCC was found to be 56 ± 4% (n=4).
**Radio-TLC eluent:** 50% EtOAc in hexanes
An aliquot (200 µmol) removed for HPLC analysis using HPLC Condition E., which confirmed the product’s identity as 4-[¹⁸F]fluoroanisole (3a).

**HPLC conditions:** Condition E  
A: 4-[¹⁸F]fluoroanisole 3a reaction gamma trace overlaid with UV trace at 280nm  
B: 4-[¹⁸F]fluoroanisole 3a reaction gamma trace overlaid with UV trace at 280nm spiked with 4-fluoroanisole
The specific activity of the $^{18}$F-fluoroanisole ($3a$) was determined as follows. After the diluted reaction mixture was transferred from the hot-cell to a vial, the total activity in the vial ($[^{18}\text{F}]\text{fluoride}+4-[^{18}\text{F}]\text{fluoroanisole}$) was counted using a CAPINTEC (CRC-15R) well counter, and the RCC of the reaction (ratio of ($[^{18}\text{F}]\text{fluoride}$ to $4[^{18}\text{F}]\text{fluoroanisole}$) was determined by analysis of a small aliquot (2-5 µL) of the mixture by the radio-TLC method described above. The activity of the product ($4[^{18}\text{F}]\text{fluoroanisole}$ only) in the vial was determined by multiplication of the total activity in the product vial by the RCC, which, after division by the total volume of the solution, yields a concentration of activity (Ci•mL$^{-1}$).

An aliquot of known volume of this sample was then analyzed by HPLC using HPLC Condition E, and the area of the UV peak corresponding to the $4[^{18}\text{F}]\text{fluoroanisole}$ was determined. The molar concentration (mol•L$^{-1}$) of the product in the sample was then determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of the 4-fluoroanisole. Division of the concentration of activity for the $4[^{18}\text{F}]\text{fluoroanisole}$ (Ci•mL$^{-1}$) by the molar concentration of the product (mol•L$^{-1}$) gives the end of synthesis (EOS) specific activity (Ci•mmol$^{-1}$). EOS specific activity was found to be $2700 \pm 1900$ Ci•mmol$^{-1}$ (n = 4).

ii. Automated Synthesis of $N$-Benzyl-4-$[^{18}\text{F}]$fluoronimesulide ($3q$)

To a solution of MesI(OH)OTs (43 mg, 0.10 mmol, 1.0 equiv) in anhydrous DCM (0.40 mL) in a 4 mL vial equipped with a stir bar was added $N$-benzylmimesulide (40 mg, 0.10 mmol, 1.0 equiv). The stirring solution was cooled to 0 °C and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (18 µL, 0.10 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 18 h before being used as a stock solution (0.25 M) of diaryliodonium in the subsequent radiofluorination reaction.

Automated syntheses were conducted on a GE TRACERLab FX$^{FN}$ automated radiochemistry synthesis module. Before $[^{18}\text{F}]\text{fluoride}$ delivery, ports in the module were charged under ambient atmosphere as follows:

- Port 1: KOTf (5 mg) and K$_2$CO$_3$ (50 µg) in H$_2$O (0.5 mL)
- Port 2: 18-crown-6 (15 mg) in MeCN (1.0 mL)
- Port 3: (MeCN)$_3$CuOTf (3.7 mg, 10 µmol, 1.0 equiv) and quinaldic acid (1.7 mg, 10 µmol, 1.0 equiv) in DMF (0.5 mL)
- Port 4: diaryliodonium stock solution (see above) in DCM (40 µL, 10 µmol, 1.0 equiv) and disopropylethylamine (3.5 µL, 20 µmol, 2.0 equiv) in DMF (0.5 mL)
- Port 6: 50% MeCN in H$_2$O, 20 mM NH$_4$OAc, pH 4.5 (2 mL)
- Port 7: 0.9% isotonic sterile saline solution (9.5 mL)
- Port 8: EtOH (0.5 mL)
- Port 9: sterile water (10 mL)
- Dilution flask: MilliQ water (50 mL).

$[^{18}\text{F}]\text{Fluoride}$ (ca. 1500 mCi) was produced in a GE PETTrace cyclotron as described above for the manual reactions and swept to the synthesis module in a bolus of $[^{18}\text{O}]\text{H}_2\text{O}$ by stream of argon. The aqueous solution of $[^{18}\text{F}]\text{fluoride}$ was passed through a pre-conditioned QMA-light cartridge (Sep-Pak, potassium triflate preconditioning) to trap $[^{18}\text{F}]\text{fluoride}$, before the $[^{18}\text{F}]\text{fluoride}$ was eluted into the reactor vessel with a solution of KOTf in H$_2$O (contents of Port 1). To this, a solution of 18-crown-6 in MeCN (contents of Port 2) was added, and the mixture azeotropically dried by heating the reaction vessel to 100 °C and drawing vacuum (ca. 1 kPa) for 5 minutes, followed by simultaneous vacuum draw and argon stream for an additional 6 minutes. The dried $[^{18}\text{F}]\text{KF}•18$-crown-6•KOTf complex (ca. 900 mCi) was cooled to 50 °C before addition of (MeCN)$_3$CuOTf and quinaldic acid in DMF (contents of
Port 3). The mixture was stirred for 3 min before addition of diaryliodonium stock solution and diiso-
propylethylamine in DMF (contents of Port 4). The reaction vessel was sealed and heated to 85 °C, and
held at this temperature for 30 min before being cooled to 50 °C, diluted with HPLC buffer (contents of
Port 6) and transferred out of the reactor under argon pressure into an intermediate vial (ca. 180 mCi
remains in the reactor), before being loaded onto the HPLC sample loop.

Purification was performed using semi-preparative HPLC using a Phenomenex Luna 5 µm PFP (2)100
Å 250 mm x 10 mm column, at 4 mL.min$^{-1}$ with 50% MeCN in H$_2$O, 20 mM NH$_4$OAc, pH 4.5 as mo-
bile phase and the gamma peak eluting at 28.5-30.5 min was collected and diluted into 50 mL of water
(contents of the dilution flask). The solution was then passed through a Sep-Pak C18 1cc Vac, the car-
tridge washed with sterile water (contents of Port 9), before the product was eluted into a collection vial
with ethanol (contents of Port 8). The Sep-Pak C18 1cc Vac was then flushed with isotonic saline (con-
tents of Port 7), and this too transferred to the collection vial. The resultant product solution was then
transferred to a sterile vial for analysis. Total synthesis time was c.a 109 min. Activity in the product
vial was counted (41 ± 31 mCi, n = 3), representing 2.8 ± 1.9% non-decay corrected radiochemical yield
(RCY) of the final product.

An aliquot (200 µmol) removed for HPLC analysis using HPLC Condition D., which confirmed the
product’s identity as N-benzyl-4-[^18F]fluoronimesulide (3q).
HPLC conditions: Condition D

A: N-Benzyl-4-[18F]fluoronimesulide 3q reaction gamma trace overlaid with UV trace at 280 nm

B: N-Benzyl-4-[18F]fluoronimesulide 3q reaction gamma trace overlaid with UV trace at 280 nm, after spiking with N-benzyl-4-fluoronimesulide 3q

The specific activity of the N-benzyl-4-[18F]fluoronimesulide (3q) was determined as follows. A 20 µL aliquot was analyzed by HPLC using HPLC Condition D, and the area of the UV peak (280 nm) corresponding to the N-benzyl-4-fluoronimesulide (t_R = 9.2 min) was determined. The molar concentration (mol•L^-1) of N-benzyl-4-fluoronimesulide in the sample was then determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of N-benzyl-4-fluoronimesulide. The concentration of activity was determined by dividing the total activity by the volume of the solution (10 mL), and division of the concentration of activity for the N-benzyl-4-[18F]fluoronimesulide (3q) (Ci•mL^-1) by the molar concentration of the product (mol•L^-1) gives the end of synthesis (EOS) specific activity (Ci•mmol^-1). EOS specific activity was found to be 2840 ± 690 Ci•mmol^-1 (n = 3).

In the UV chromatogram of the isolated product, the presence of N-benzynimesulide (1q) (CH-precursor for the fluorination) was also observed (t_R = 8.2 min). The molar quantity of N-benzynimesulide (1q) was determined by linear regression analysis against a standard curve generated from injection of identical volumes of solutions of known concentration of N-benzynimesulide. The effective specific activity of the product was then determined using the sum of the molar concentration
of the C–H entity and the C–F entity. EOS effective specific activity was found to be 1500 ± 820 Ci•mmol⁻¹ (n = 3).

D. Control Experiments

\[
\text{TMSOTf} \quad \frac{(\text{MeCN})_4\text{CuOTf}}{\text{quinaldic acid, } iPr_2\text{NEt}} \quad \frac{[^{18}\text{F}]\text{KF} \cdot 18\text{-crown-6}}{\text{DMF}, 85 ^\circ \text{C}, 20 \text{ min}} \quad \text{unknown}^{18}\text{F} + \text{unknown}^{18}\text{F}
\]

To a 4 mL vial were added anhydrous dimethylformamide (DMF) (800 µL), TMSOTf (1.8 µL, 10 µmol), and \( N,N \)-diisopropylethylamine (\( iPr_2\text{NEt} \)) (3.5 µL, 20 µmol). The solution was agitated with a vortex mixer and aged for 10 min at room temperature. Under an ambient atmosphere, tetrakis(acetonitrile)copper(I) trifluoromethanesulfonate ((MeCN)_4CuOTf) (100 µL of a 100 mM solution, 10 µmol) and quinaldic acid (10 µmol) in DMF was added to the diaryliodonium/\( iPr_2\text{NEt} \) solution. The reaction vial was sealed with a PTFE/Silicone septum cap and a 100 µL aliquot of \([^{18}\text{F}]\text{KF} \cdot 18\text{-crown-6} \cdot K_2\text{CO}_3 \) complex in DMF (typically 60-800 µCi, prepared as described above) was added to the reaction vial via syringe. The reaction was heated in an aluminum block at 85 °C for 20 min. After 20 min, the reaction was removed from heat and allowed to cool to room temperature. Radiochemical conversion (RCC) was obtained by radio-TLC analysis (2–5 µL aliquots) using a 50:50 hexanes-ethyl acetate eluent, and are not reported to reflect losses during \([^{18}\text{F}]\text{KF} \cdot 18\text{-crown-6} \cdot K_2\text{CO}_3 \) preparation. The samples were further analyzed using radio-HPLC (10-50 µL aliquots). While a 0% RCC was observed by radio-TLC, unknown byproducts were observed in the gamma trace of radio-HPLC at ca. 15.3 and 19.5 min.
**Radio-TLC eluent:** 50% EtOAc in hexanes
**HPLC conditions:** Condition A

**A:** UV trace at 280 nm of a control reaction between TMSOTf and $[^{18}\text{F}]\text{KF} \cdot 18$-crown-$6 \cdot \text{K}_2\text{CO}_3$

**B:** Gamma trace of a control reaction between TMSOTf and $[^{18}\text{F}]\text{KF} \cdot 18$-crown-$6 \cdot \text{K}_2\text{CO}_3$
E. Unreactive or Non-Compatible Substrates

VI. References

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VII. NMR Spectra
$^1\text{H NMR (401 MHz, CDCl}_3\text{)}$

![Proton Spectrum](image)
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_v128_13C_CDCl3
Carbon-13

$^N$Ts

1h

143.80  77.24 (dd)  7.716 (dd)
141.62  77.24 (dd)  7.716 (dd)
133.44  132.88 (dd)  7.277 (dd)  126.60
138.37  128.84 (dd)  7.277 (dd)  127.77
128.84 (dd)  7.277 (dd)  128.84 (dd)  126.60
122.88 (dd)  7.277 (dd)  122.88 (dd)  122.88 (dd)
**1H NMR (700 MHz, d6-DMSO)**

MSM_v131_1H_90deg_d6DMSO
Proton Spectrum

![NMR Spectrogram](image-url)

**NMR Peaks:**
- 7.38 ppm: H NMR (700 MHz, d6-DMSO)
- 7.72 ppm: H NMR (700 MHz, d6-DMSO)
- 3.27 ppm: H NMR (700 MHz, d6-DMSO)
- 2.97 ppm: H NMR (700 MHz, d6-DMSO)
- 2.50 ppm: H NMR (700 MHz, d6-DMSO)

**Chemical Structures:**
- Cbz

**Additional Information:**
- Cbz is a protecting group commonly used in organic synthesis.
- The spectrum shows typical aromatic and aliphatic proton signals.

**Legend:**
- **H NMR:** Proton nuclear magnetic resonance
- **d6-DMSO:** Deuterated dimethyl sulfoxide solvent.

**Notes:**
- The spectrum was recorded at 700 MHz, indicating high-resolution NMR conditions.
- The multiplicity of peaks suggests the presence of different types of protons.

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**S81**
^{13}\text{C} \text{ NMR (176 MHz, } d_6\text{-DMSO)}

MSM_v131_13C_90deg_d6DMSO
Carbon-13

\[
\begin{array}{l}
\text{N} \\
\text{Cbz} \\
\text{1i}
\end{array}
\]

\begin{align*}
15.4 & \, 23 \\
14.2 & \, 83 \\
128.2 & \, 20 \\
127.2 & \, 22 \\
126.8 & \, 16 \\
125.3 & \, 10 \\
\text{C} \end{align*}

\begin{align*}
\text{f1 (ppm)} & \, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 0, -1
\end{align*}

S82
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_v131_13C_CDC13
Carbon-13

1i

N-Cbz
$^{1}H$ NMR (401 MHz, CDCl$_3$)

MSM_v162_1H_CDCl3
Proton Spectrum
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_v162_13C_CDCl3
Carbon-13

1p

[Diagram of chemical structure]

- 153.26
- 142.06
- 137.89
- 128.69
- 128.04
- 127.51
- 124.88
- 124.21
- 77.34 (CDC13)
- 77.16 (CDC13)
- 76.98 (CDC13)
- 76.52
- 26.73
- 24.78

S85
**$^1$H NMR (401 MHz, CDCl$_3$)**

**Proton Spectrum**

1. PhO
2. Ms
3. N
4. Bn
5. 1q

- **Chemical Shifts:**
  - 7.79, 7.77, 7.58, 7.54, 7.49, 7.34, 7.32, 7.31, 7.29, 7.09
  - 4.92
  - 3.09

- **Remarks:**
  - S86
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_v166_13C_CDC13

Carbon-13
$^1$H NMR (401 MHz, CDCl$_3$)

MSM_vii088_1H_CDCl3
Proton Spectrum

![NMR spectrum](image)
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_vii088_13C_CDCl3
Carbon-13

2a

MeO

MeO

Mes

OTf
**19F NMR (377 MHz, CDCl₃)**

STANDARD FLUORINE PARAMETERS

![Graph of 19F NMR spectrum showing a peak at -78.80 ppm with a chemical structure labeled 2a.](image-url)
\[ ^1H \text{ NMR (401 MHz, CDCl}_3 \text{)} \]

MSM_vii078_1H_CDCI3
Proton Spectrum

\[ \text{S1} \]

\[ \text{OTs} \]

f1 (ppm)

.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0

S91
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_vii078_13C_CDCl3

Carbon-13

![Chemical Structure](image)
$^1$H NMR (401 MHz, CDCl$_3$)

Proton Spectrum

MSM_vii074_1H_CDCli3

3d

MeO$_2$C-F

MeO

S93
$^{13}$C NMR (176 MHz, CDCl$_3$)

Carbon-13

MeO$_2$C

MeO

3d

MeO$_2$C

MeO

3d

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)
$^{19}$F NMR (377 MHz, CDCl$_3$)

STANDARD FLUORINE PARAMETERS

MeO$_2$C-\(\cdot\)F

MeO

3d
$^1$H NMR (700 MHz, CDCl$_3$)

Proton Spectrum

MSM_vii022_1H_CDCl3

$^1$H NMR (700 MHz, CDCl$_3$)

S96
\[ ^{13}C \text{ NMR (176 MHz, CDCl}_3 \text{)} \]

MSM_vii022_13C_CDCl3
Carbon-13

\[
\text{Me} \quad \text{F} \\
\text{N} \quad \text{Ts} \\
3h
\]

\[
\begin{align*}
162.35 & & 180.94 \\
143.86 & & 137.69 \\
137.86 & & 133.38 \\
129.65 & & 129.66 \\
128.62 & & 128.06 \\
115.90 & & 115.77 \\
77.34 & & 76.55 \\
76.90 & & 76.56 \\
38.43 & & 21.70 \\
\end{align*}
\]
**19F NMR (376 MHz, CDCl₃)**

MSM_vii022_19F_CDCl3
Fluorine-19

![NMR Spectrum]

-114.70 ppm

f1 (ppm)

S98
$^1$H NMR (400 MHz, $d_6$-DMSO)

Proton Spectrum

- 3.24 ppm (HDO)
- 3.04 ppm
- 2.51 ppm (dms)
- 2.50 ppm (dms)
- 2.49 ppm (dms)

$\text{N}_3\text{i}$Me$^\text{Cbz}$

F

3i
$^{13}$C NMR (176 MHz, $d_6$-DMSO)

MSM_vii036c_13C_90deg_d6DMSO
Carbon-13

3i

$\text{Cbz}_N^{\text{Me}}\text{F}$
$^{13}$C NMR (176 MHz, CDCl$_3$)

Carbon-13

Me

F

Cbz

3i

161.35
159.95
139.22
138.53
128.44
128.96
127.70
115.70
115.57
77.34 (dd)
77.38 (dd)
76.98 (dd)
67.33
37.90
$^{19}$F NMR (376 MHz, $d_6$-DMSO)

Fluorine-19
\textbf{\textsuperscript{1}H NMR (401 MHz, CDCl\textsubscript{3})}

MSM\_vii020\_1H\_CDCl3
Proton Spectrum

![NMR Spectrum]

-7.26 ddd, 3H
2.00 d, 3H
3.08 s, 3H
3.22 s, 3H
3.80 m, 2H
3.87 m, 2H
6.56 m, 2H
6.57 m, 2H
6.58 m, 2H
6.59 m, 2H
7.20 s, 1H
1.55 HDO
1.92 t, 2H
2.05 t, 2H
2.07 t, 2H
2.09 t, 2H
2.11 t, 2H
3.22 t, 2H
3.24 t, 2H
3.26 t, 2H
4.04 t, 2H
4.06 t, 2H
4.08 t, 2H
4.10 t, 2H
4.12 t, 2H
5.20 t, 2H
5.22 t, 2H
5.24 t, 2H
5.26 t, 2H
5.28 t, 2H
6.20 t, 2H
6.22 t, 2H
6.24 t, 2H
6.26 t, 2H
6.28 t, 2H
7.20 t, 2H
7.22 t, 2H
7.24 t, 2H
7.26 t, 2H
7.28 t, 2H
8.00 t, 2H
8.02 t, 2H
8.04 t, 2H
8.06 t, 2H
8.08 t, 2H
9.00 t, 2H
9.02 t, 2H
9.04 t, 2H
9.06 t, 2H
9.08 t, 2H

S10\textsuperscript{e}
$^{13}$C NMR (176 MHz, CDCl$_3$)

Carbon-13

$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_vii020_13C_CDCl3
$^{19}\text{F NMR (376 MHz, CDCl}_3\text{)}$

MSM_vii020_19F_CDCl3

Fluorine-19

\[
\begin{array}{c}
\text{F} \\
\text{Me} \\
\text{O} \\
\text{Me} \\
3m
\end{array}
\]
**1H NMR (401 MHz, CDCl₃)**

MSM_vii070_1H_CDCI3
Proton Spectrum

![NMR Spectrum](image_url)

- **Chemical Shifts (ppm):**
  - 3.40, 3.39
  - 3.02, 3.97
  - 2.97, 3.3
  - 7.26, 7.24, 7.23

**Resonances:**
- 1H Combine
- 156 H2O
**13C NMR (176 MHz, CDCl₃)**

MSM_vii070_13C_CDCl3

**Carbon-13**

![NMR Spectrogram](image)
$^{19}\text{F NMR}$ (377 MHz, CDCl$_3$)

MSM_vii070_19F_CDCl3

STANDARD FLUORINE PARAMETERS

$\begin{array}{c}
\text{Me} - \text{N} - \text{O} - \text{F} \\
\text{O} - \text{N} - \text{Me} \\
\text{Me}
\end{array}$

$3n$
^1H NMR (400 MHz, CD$_3$CN)
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_vii018_f1_13C

Carbon-13

[Spectrogram Image]

187.96
161.28
159.86
139.39
138.53
137.51
133.82
133.71
132.42
127.37
126.01
122.29
118.37
77.34 (dd, 3)
76.98 (dd, 3)
59.49
**19F NMR (376 MHz, CDCl₃)**

Fluorine-19

![Chemical Structure](image)

- δ = -15.44 ppm
$\textbf{1H NMR (401 MHz, CDCl}_3\text{)}$

MSM_vii036A_1H_CDC13

Proton Spectrum

\[
\begin{array}{cccc}
7.49 & 7.38 & 7.34 & 6.81 \\
7.44 & 7.40 & 7.36 & 6.82 \\
7.42 & 7.40 & 7.38 & 6.83 \\
7.40 & 7.38 & 7.37 & 6.83 \\
\end{array}
\]

BnO

3p
$^{13}$C NMR (176 MHz, CDCl$_3$)

MSM_vii036A_13C_CDCl3

Carbon-13

BnO

3p

160.79 159.42
149.02 148.56
144.12 137.64
128.73 128.16
127.52 110.73
110.80

-27.05 -24.07

S113
\textbf{\textsuperscript{19}F NMR (377 MHz, CDCl\textsubscript{3})}

\textit{MSM_vii036A_19F_CDCl3}

STANDARD FLUORINE PARAMETERS

\[ \text{SF} \text{ NMR (377 MHz, CDCl}_3) \]
\textbf{\textsuperscript{1}H NMR (401 MHz, CDCl\textsubscript{3})}

Proton Spectrum

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{nmr_spectrum.png}
\end{figure}
**13C NMR (176 MHz, CDCl₃)**

**MSM_vii036B_13C_CDCl3**

Carbon-13

![13C NMR spectrum with peak assignments]
\textbf{\(^{19}\text{F NMR (377 MHz, CDCl}_3\))}

MSM_vii036B_19F_CDC13
STANDARD FLUORINE PARAMETERS

\begin{align*}
\text{F} & & \text{NO}_2 \\
\text{O} & & \\
\text{Ms} & & \text{Bn} \\
3q & & \\
\end{align*}