

Electronic Supplementary Information

No-carrier-added [^{18}F]fluoroarenes from the radiofluorination of diaryl sulfoxides

Joong-Hyun Chun,^a Cheryl L. Morse,^a Frederick T. Chin^{a,b} and Victor W. Pike*^a

^a*Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Building 10, Room B3 C346A, 10 Center Drive, Bethesda, MD 20892-1003, USA*

^b*Present address: Molecular Imaging Program at Stanford (MIPS), Department of Radiology, Stanford University School of Medicine, Stanford, CA 94305 USA*

Experimental Section.....	S-2
Appendix 1. ^1H - and ^{13}C - NMR spectra of diaryl sulfoxides prepared for this study.	S-15
Appendix 2. Examples of radio-HPLC chromatograms from the analyses of the quenched reaction mixtures from the radiofluorinations of diaryl sulfoxides.....	S-34

Experimental Section

General

^1H - (400 MHz), ^{13}C - (100 MHz) and ^{19}F - (376 MHz) NMR spectra were recorded at room temperature in CDCl_3 on an Avance-400 spectrometer (Bruker; Billerica, MA, USA). ^1H and ^{13}C chemical shifts are reported in δ units (ppm) downfield from that of tetramethylsilane (δ 0 ppm) and ^{19}F chemical shifts are reported in δ (ppm) relative to the chemical shift for CFCl_3 (δ 0 ppm). Abbreviations br, s, d, dd, dt, t, m and q denote broad, singlet, doublet, double doublet, double triplet, triplet, multiplet and quartet, respectively. High resolution mass spectra (HRMS) were acquired from the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign (Urbana, IL, USA) under electron ionization conditions using a double-focusing high-resolution mass spectrometer (Autospec; Micromass Inc., USA). Melting points were determined with a Mel-Temp apparatus (Electrothermal; Fisher Scientific).

Materials

Dichloromethane and *N,N*-dimethylformamide (DMF) were purchased in Sure/SealTM bottles (Sigma-Aldrich; Milwaukee, WI) and used without further treatment. Diphenyl sulfoxide (**10**), bis(4-methylphenyl) sulfoxide (**11**) and *m*-CPBA (77% max. content) were also purchased from Sigma-Aldrich and used as received. Reference fluoroarenes were purchased from either Sigma-Aldrich or Alfa Aesar (Ward Hill, MA) and used without purification. Bis(4-pyridinyl) sulfide was obtained from TCI (Tokyo, Japan). Bis(3-nitrobenzene) disulfide was obtained from TCI America (Portland, OR). Acetonitrile (high purity, Burdick & Jackson; Morristown, NJ) for HPLC mobile phase was also used without further treatment. NCA [^{18}F]fluoride ion was obtained through the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction by irradiating [^{18}O]water (95 atom %) for 90–120 min with a proton beam (16.5 MeV; 20 μA) produced by a PETrace cyclotron (GE Medical Systems; Milwaukee, MI). QMA (quaternary methylammonium) anionic resin cartridges were supplied by ORTG (Oakdale, TN).

Synthesis of diaryl sulfoxides

Bis(4-nitrophenyl) sulfoxide (1). Bis(4-nitrophenyl) sulfide (1.38 g, 5 mmol) was dissolved in CH₂Cl₂ (25 mL) at 0 °C. A solution of *m*-CPBA (0.867 g, 5.01 mmol) in CH₂Cl₂ (20 mL) was added dropwise over 30 min to the cooled solution. The mixture was stirred for 6 h at 0 °C and then extracted sequentially with 10% NaOH (20 mL x 2), 5% HCl (20 mL), and 10% NaHCO₃ (20 mL). The organic layer was dried over MgSO₄, and filtered. Solvent was removed under reduced pressure to give **1** as a pale yellow solid (1.44 g, 83%); mp = 182–184 °C (lit.¹ 178.5–179.5 °C); ¹H-NMR δ 8.36 (d, *J* = 8.8 Hz, 4H), 7.90 (d, *J* = 8.8 Hz, 4H); ¹³C-NMR δ 151.5, 149.8, 125.4, 124.9; HRMS, Calc'd. for C₁₂H₈O₅N₂: 292.0154, Found: 292.0156.

The following diaryl sulfoxides (**2** and **3**) were prepared likewise from the appropriate diaryl sulfides.

Bis(4-cyanophenyl) sulfoxide (2). White solid (0.44 g, 70%); mp = 183–185 °C (lit.² 171–174 °C); ¹H-NMR δ 7.80 (s, br, 8H); ¹³C-NMR (CDCl₃) δ 149.9, 133.3, 125.0, 117.3, 115.5; HRMS, Calc'd. for C₁₄H₈OSN₂: 252.0357, Found: 252.0359.

Bis(4-trifluoromethylphenyl) sulfoxide (3). White solid (0.36 g, 67%); mp = 99–100 °C; ¹H-NMR δ 7.78 (dd, *J* = 8.4, 24.8 Hz, 8H); ¹³C-NMR δ 149.3, 133.5 (q, *J*_{C-F} = 33 Hz), 126.7 (q, *J*_{C-F} = 4 Hz), 125.0, 122.0; ¹⁹F-NMR δ –62.99; HRMS, Calc'd. for C₁₄H₈OSF₆: 338.0200, Found: 338.0206.

Bis(4-fluorophenyl) sulfoxide (4). Aluminum chloride (0.54 g, 4 mmol) and fluorobenzene (0.38 mL, 4 mmol) were mixed with silica gel (0.2 g). Thionyl chloride (0.24 g, 2 mmol) was added dropwise and stirred for 5 min. The dark yellow mixture was carefully quenched with 10% HCl (30 mL) and extracted with CH₂Cl₂ (15 mL x 2). The combined organic layers were dried over MgSO₄ and concentrated. Column chromatography of the crude product on silica gel (10% MeOH/ CH₂Cl₂, R_f = 0.7) gave **4** as a white solid (0.29 g, 61%); mp = 46–48 °C (lit.³ 48 °C; lit.⁴ oil); ¹H-NMR δ 7.65–7.61 (m, 4H), 7.20–7.14 (m, 4H); ¹³C-NMR δ 164.3 (d, *J*_{C-F} = 250 Hz), 141.0 (d, *J*_{C-F} = 4 Hz), 127.0 (d, *J*_{C-F} = 9 Hz), 116.7 (d, *J*_{C-F} = 22 Hz); ¹⁹F-NMR δ –107.9; HRMS, Calc'd. for C₁₂H₈OSF₂: 238.0264, Found: 238.0261.

Bis(4-bromophenyl) sulfoxide (5). Aluminum chloride (0.54 g, 4 mmol) and bromobenzene (0.42 mL, 4 mmol) were mixed with silica gel (0.2 g). Thionyl chloride

(0.24 g, 2 mmol) was added dropwise and stirred for 4 min. The pink mixture was carefully quenched with 10% HCl (30 mL) and the precipitate and silica were collected by vacuum filtration. The solids were reconstituted in CH₂Cl₂ and filtered through Celite. The filtrate was concentrated and this crude product was recrystallized from ethanol to give **5** as a white solid (0.33 g, 46%); mp = 158–160 °C (lit.⁵ 154–155 °C); ¹H-NMR δ 7.62–7.60 (m, 4H), 7.51–7.49 (m, 4H); ¹³C-NMR δ 144.4, 132.7, 126.2, 126.0; HRMS, Calc'd. for C₁₂H₈OSBr₂: 357.8663, Found: 357.8670.

The following diaryl sulfoxides (**6–9**) were prepared from the appropriate diaryl sulfides as described for **1**.

Bis(3-nitrophenyl) sulfoxide (6). White solid (0.28 g, 72%); mp = 166–167 °C; ¹H-NMR δ 8.56 (t, *J* = 1.6 Hz, 2H), 8.25 (dq, *J* = 0.8, 2, 5.2 Hz, 2H), 8.25 (dt, *J* = 1.2, 5.2 Hz, 2H), 7.76 (t, *J* = 8 Hz, 2H); ¹³C-NMR δ 148.8, 147.4, 131.1, 129.9, 126.4, 119.6; HRMS, Calc'd. for C₁₂H₈O₅SN₂: 292.0154, Found: 292.0144.

Bis(4-pyridinyl) sulfoxide (7). White solid (0.12 g, 20%); mp = 129–131 °C; ¹H-NMR δ 8.77 (d, *J* = 5.2 Hz, 4H), 7.60 (dd, *J* = 1.6, 4.4 Hz, 4H); ¹³C-NMR δ 154.3, 150.9, 118.1; HRMS, Calc'd. for C₁₀H₈OSN₂: 204.0357, Found: 204.0366.

Bis(3-pyridinyl) sulfoxide (8).⁶ White solid (99 mg, 29%); mp = 134–136 °C; ¹H-NMR δ 8.85 (d, *J* = 2 Hz, 2H), 8.74 (dd, *J* = 1.6, 4.8 Hz, 2H), 8.03 (dt, *J* = 1.6, 4.4 Hz, 2H), 7.49–7.45 (m, 2H); ¹³C-NMR δ 152.6, 146.3, 141.5, 132.4, 124.5; HRMS, Calc'd. for C₁₀H₈OSN₂: 204.0357, Found: 204.0361.

Bis(2-pyridinyl) sulfoxide (9).⁷ White solid (0.44 g, 52%); mp = 100–101 °C; ¹H-NMR δ 8.64–8.63 (m, 2H), 8.05–8.02 (m, 2H), 7.88 (dt, *J* = 2, 8 Hz, 2H), 7.36–7.33 (m, 2H); ¹³C-NMR δ 164.0, 150.0, 138.0, 125.0, 120.0; HRMS, Calc'd. for C₁₀H₈OSN₂: 204.0357, Found: 204.0355.

Bis(4-methoxyphenyl) sulfoxide (12).⁸ Thionyl chloride (1.19 g, 10 mmol) was added carefully to cooled (0 °C) anisole (24 mL, 184 mmol). Triflic acid (6.45 g, 43 mmol) was added slowly to the resulting pale yellow solution, while keeping the temperature low. The reaction mixture was stirred for 1 h at 0 °C, gradually warmed to rt and then stirred an extra hour. The resulting purple solution was poured onto ice, neutralized with 30% NaHCO₃ (30 mL) and extracted with CH₂Cl₂ (30 mL x 2). The combined organic layers were dried over MgSO₄ and concentrated. After column chromatography of the

crude product on silica gel (50% EtOAc/hexane, $R_f = 0.25$), **12** was obtained as a white solid (1.44 g, 55%); mp = 94–95 °C; $^1\text{H-NMR}$ δ 7.53 (dd, $J = 5.2, 9.6$ Hz, 4H), 6.95 (d, $J = 4.8$ Hz, 4H), 3.83 (s, 6H); $^{13}\text{C-NMR}$ δ 161.7, 137.0, 126.8, 114.6, 55.4.

The following diaryl sulfoxides (**13–20**) were prepared from the appropriate diaryl sulfides, as described for **1**.

4-Nitrophenyl(phenyl) sulfoxide (13).⁹ Pale yellow solid (1.30 g, 61%); mp = 112–115 °C; $^1\text{H-NMR}$ δ 8.32 (dd, $J = 1.6, 6.8$ Hz, 2H), 7.33 (dd, $J = 1.6, 6.8$ Hz, 2H), 7.70–7.66 (m, 2H), 7.51–7.50 (m, 3H); $^{13}\text{C-NMR}$ δ 153.0, 149.3, 144.4, 132.1, 129.8, 125.3, 124.9, 124.5; HRMS, Calc'd. for $\text{C}_{12}\text{H}_9\text{O}_3\text{SN}$: 247.0303, Found: 247.0300.

4-Cyanophenyl(4'-nitrophenyl) sulfoxide (14). White solid (0.20 g, 73%); mp = 192–193 °C; $^1\text{H-NMR}$ δ 8.25 (dt, $J = 2.4, 4.4$ Hz, 2H), 7.89–7.86 (m, 2H), 7.84–7.78 (m, 4H); $^{13}\text{C-NMR}$ δ 151.6, 149.9, 149.8, 133.4, 125.3, 125.0, 124.8, 117.3, 115.7; HRMS, Calc'd. for $\text{C}_{13}\text{H}_8\text{O}_3\text{SN}_2$: 272.0256, Found: 272.0250.

4-Fluorophenyl(4'-nitrophenyl) sulfoxide (15). Pale yellow solid (0.95 g, 18%); mp = 125–128 °C; $^1\text{H-NMR}$ (δ 8.33 (d, $J = 8.8$ Hz, 2H), 7.82 (d, $J = 8.8$ Hz, 2H), 7.71–7.67 (m, 2H), 7.20 (t, $J = 8.4$ Hz, 2H); $^{13}\text{C-NMR}$ δ 166.0, 163.5, 152.7, 149.3, 140.0 (d, $J_{\text{C-F}} = 3$ Hz), 127.5 (d, $J_{\text{C-F}} = 10$ Hz), 124.9 (d, $J_{\text{C-F}} = 60$ Hz), 117.3 (d, $J_{\text{C-F}} = 30$ Hz); $^{19}\text{F-NMR}$ δ –106.1; HRMS, Calc'd. for $\text{C}_{12}\text{H}_8\text{O}_3\text{SNF}$: 265.0209, Found: 265.0205.

2-Methyl-4-nitrophenyl(phenyl) sulfoxide (16). Pale yellow solid (0.45 g, 69%); mp = 110–111 °C; $^1\text{H-NMR}$ δ 8.26 (d, $J = 8.8$ Hz, 2H), 8.03 (s, 1H), 7.63 (d, $J = 6.8$ Hz, 2H), 7.49 (d, $J = 5.6$ Hz, 3H), 2.41 (s, 3H); $^{13}\text{C-NMR}$ δ 150.4, 149.2, 143.1, 136.9, 132.1, 129.7, 126.3, 125.6, 125.4, 122.0, 18.7; HRMS, Calc'd. for $\text{C}_{13}\text{H}_{11}\text{O}_3\text{SN}$: 261.0460, Found: 261.0465.

2-Methyl-4-nitrophenyl(4'-nitrophenyl) sulfoxide (17). White solid (0.38 g, 78%); mp = 175–176 °C; $^1\text{H-NMR}$ δ 8.34 (d, $J = 12.8$ Hz, 2H), 8.27 (dd, $J = 2, 8.4$ Hz, 1H), 8.15 (d, $J = 8.8$ Hz, 1H), 8.09 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H), 2.57 (s, 3H); $^{13}\text{C-NMR}$ δ 150.5, 149.7, 149.4, 137.4, 126.4, 126.1, 126.0, 125.4, 124.8, 122.5, 19.0; HRMS, Calc'd. for $\text{C}_{13}\text{H}_{10}\text{O}_5\text{SN}_2$: 306.0310, Found: 306.0318.

2,6-Dimethyl-4-nitrophenyl(phenyl) sulfoxide (18). White solid (0.60 g, 54%), mp = 123–124 °C; $^1\text{H-NMR}$ δ 7.92 (s, 2H), 7.50–7.43 (m, 5H), 2.61 (s, 6H); $^{13}\text{C-NMR}$ δ 148.9,

146.4, 142.4, 141.9, 130.3, 129.2, 124.4, 19.7; HRMS, Calc'd. for C₁₄H₁₃O₃SN: 275.0616, Found: 275.0606.

2,6-Dimethyl-4-nitrophenyl(4'-nitrophenyl) sulfoxide (19). Beige solid (0.69 g, 68%); mp = 191–192 °C; ¹H-NMR δ 8.34 (dd, *J* = 2, 6.8 Hz, 2H), 7.96 (s, 2H), 7.65 (dd, *J* = 2, 6.8 Hz, 2H), 2.62 (s, 6H); ¹³C-NMR δ 150.2, 149.3, 149.0, 145.3, 142.0, 125.6, 124.7, 124.3, 19.8; HRMS, Calc'd. for C₁₄H₁₂O₅SN₂: 320.0467, Found: 320.0474.

2-Methylphenyl(phenyl) sulfoxide (20).¹⁰ White solid (0.62 g, 62%); mp = 54–55 °C; ¹H-NMR δ 7.95 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.61–7.59 (m, 2H), 7.45–7.34 (m, 5H), 7.17 (d, *J* = 7.2 Hz, 1H), 2.36 (s, 3H); ¹³C-NMR δ 144.6, 142.9, 135.7, 131.0, 130.9, 129.3, 127.1, 125.8, 124.7, 18.5.

Synthesis of diaryl sulfides for making diaryl sulfoxides

Bis(4-nitrophenyl) sulfide (A). Nitrobenzene (15.8 g, 125 mmol) was mixed with DMF (50 mL) and the resultant white slurry was heated to 50 °C for 30 min under nitrogen. Sodium sulfide (12.0 g, 50 mmol) was slowly added to the stirred mixture which became dark red. This mixture was stirred overnight at 50 °C under nitrogen and then poured onto ice (~ 300 mL). The yellow precipitate was collected by vacuum filtration and recrystallized from ethanol to give **A** as a yellow solid (8.4 g, 48%); mp = 161–164 °C (lit.¹ 159.5–160.5 °C); ¹H-NMR δ 8.22 (dt, *J* = 2.4, 8.8 Hz, 4H), 7.50 (dt, *J* = 2.4, 8.8 Hz, 4H); ¹³C-NMR δ 147.1, 142.7, 131.1, 124.6.

Likewise were prepared diaryl sulfides **B** and **C**, as follows.

Bis(4-cyanophenyl) sulfide (B).¹¹ From 4-chlorobenzonitrile as a white solid (1.07 g, 82%); mp = 134–135 °C; ¹H-NMR δ 7.62 (dd, *J* = 1.6, 6.8 Hz, 4H), 7.62 (d, *J* = 8.4 Hz, 4H); ¹³C-NMR δ 140.6, 133.0, 131.2, 118.1, 111.4.

Bis(4-trifluoromethylphenyl) sulfide (C).¹² From 4-chlorobenzotrifluoride as a colorless solid (0.61 g, 34%); mp = 34–35 °C; ¹H-NMR δ 7.56 (d, *J* = 8 Hz, 4H), 7.43 (d, *J* = 8 Hz, 4H); ¹³C-NMR δ 139.6, 131.0, 129.8 (q, *J*_{C-F} = 30 Hz), 126.3 (q, *J*_{C-F} = 3 Hz), 123.9 (q, *J*_{C-F} = 270 Hz); ¹⁹F-NMR δ –62.8.

Bis(3-nitrophenyl) sulfide (D).¹³ 3-Nitrobenzenethiol (1.55 g, 10 mmol) was mixed with 3-chloronitrobenzene (1.57 g, 10 mmol) and K₂CO₃ (4.84 g, 35 mmol) in DMF (30 mL). The resultant purple mixture was stirred overnight at 100 °C and then poured onto

ice-water (100 mL), which was then extracted with CH₂Cl₂ (30 mL x 2). The combined organic layers were dried over MgSO₄ and concentrated. Column chromatography of the oily crude product on silica gel (10% EtOAc/hexane, R_f = 0.4) gave **D** as an off-white solid (0.55 g, 20%); mp = 54–56 °C; ¹H-NMR δ 8.21–8.16 (m, 4H), 7.69–7.67 (m, 2H), 7.56 (t, *J* = 8 Hz, 2H); ¹³C-NMR δ 148.9, 136.8, 136.7, 130.4, 125.8, 122.9.

Bis(3-pyridinyl) sulfide (E).¹⁴ Anhydrous sodium sulfide (2.81 g, 36 mmol) was added to a stirred solution of trimethylsilyl chloride (1.30 g, 12 mmol) in DMF (6 mL), while the reaction vessel was kept below 16 °C. 3-Bromopyridine (1.26 g, 8 mmol) was added and the mixture refluxed overnight. Water (20 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (30 mL x 2). The combined organic layers were dried over MgSO₄. Column chromatography of the crude product on silica gel (EtOAc, R_f = 0.25, streak) gave **E** as a pale yellow oil (0.45 g, 57%); ¹H-NMR δ 8.61 (d, *J* = 4 Hz, 2H), 8.52 (dd, *J* = 1.6, 6.4 Hz, 2H), 7.67–7.64 (m, 2H), 7.28–7.25 (m, 2H); ¹³C-NMR δ 151.7, 148.7, 138.7, 131.9, 124.1.

The procedure for **D** was also used to prepare compounds **F–N**, as follows:

Bis(2-pyridinyl) sulfide (F).⁷ From 2-iodopyridine and 2-thiopyridine as a pale yellow oil (0.80 g, 71%); ¹H-NMR δ 8.55 (dd, *J* = 1.2, 6 Hz, 2H), 7.62 (dt, *J* = 2, 7.6 Hz, 2H), 7.45 (d, *J* = 8 Hz, 2H), 7.18–7.15 (m, 2H); ¹³C-NMR δ 156.7, 150.2, 137.0, 125.8, 121.7.

4-Nitrophenyl(phenyl) sulfide (G). From 4-chloronitrobenzene and benzenethiol as a pale yellow solid (8.06 g, 92%); mp = 52–55 °C (lit.¹⁵ 54–55 °C); ¹H-NMR δ 8.07 (dt, *J* = 2.8, 4.8 Hz, 2H), 7.56–7.54 (m, 2H), 7.48–7.45 (m, 2H), 7.18 (dt, *J* = 2.4, 4.4 Hz, 2H); ¹³C-NMR δ 148.5, 145.3, 134.8, 130.4, 130.0, 129.7, 126.6, 124.0.

4-Cyanophenyl(4'-nitrophenyl) sulfide (H). From 4-chlorobenzonitrile and 4-nitrobenzenethiol as a yellow solid (0.21 g, 81%); mp = 154–156 °C (lit.¹⁶ 153–154 °C); ¹H-NMR δ 8.19 (dt, *J* = 2.8, 4.8 Hz, 2H), 7.65 (dd, *J* = 2, 6.8 Hz, 2H), 7.48 (dt, *J* = 1.6, 6.4 Hz, 2H), 7.43 (dd, *J* = 2, 6.8 Hz, 2H); ¹³C-NMR δ 146.9, 143.4, 139.9, 133.1, 131.8, 130.5, 124.5, 118.0, 111.9.

4-Fluorophenyl(4'-nitrophenyl) sulfide (I). From 4-chloronitrobenzene and 4-fluorobenzenethiol as a pale yellow solid (1.55 g, 98%); mp = 95–98 °C (lit.¹⁷ 97–99.5 °C); ¹H-NMR δ 8.09–8.06 (m, 2H), 7.58–7.54 (m, 2H), 7.26–7.12 (m, 4H); ¹³C-

NMR δ 164.9, 162.4, 148.5 (d, J_{C-F} = 1 Hz), 145.3, 137.3 (d, J_{C-F} = 1 Hz), 126.2, 124.1, 117.4 (d, J_{C-F} = 20 Hz); ^{19}F -NMR δ -110.0.

2-Methyl-4-nitrophenyl(phenyl) sulfide (J). From 2-bromo-5-nitrotoluene and thiophenol as a yellow solid (needles, 0.93 g, 54%); mp = 71–72 °C; ^1H -NMR δ 8.01 (d, J = 2 Hz, 1H), 7.83 (dd, J = 2, 8.8 Hz, 1H), 7.51–7.44 (m, 5H), 6.84 (d, J = 8.8 Hz, 1H), 2.46 (s, 3H); ^{13}C -NMR δ 147.4, 145.1, 136.1, 134.7, 130.4, 130.0, 129.4, 124.5, 121.4, 20.1; HRMS, Calc'd. for $\text{C}_{13}\text{H}_{11}\text{O}_2\text{SN}$: 245.0511, Found: 245.0509.

2-Methyl-4-nitrophenyl(4'-nitrophenyl) sulfide (K). From 2-bromo-5-nitrotoluene and 4-nitrobenzenethiol as an off-white solid (1.56 g, 53%); mp = 130–131 °C; ^1H -NMR δ 8.18 (d, J = 8.8 Hz, 3H), 8.03 (dd, J = 2.4, 8.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H); ^{13}C -NMR δ 146.1, 145.3, 141.9, 139.9, 139.1, 131.5, 128.4, 124.0, 123.2, 120.5, 19.3; HRMS, Calc'd. for $\text{C}_{14}\text{H}_{12}\text{O}_4\text{SN}_2$: 304.0518, Found: 304.0517.

2,6-Dimethyl-4-nitrophenyl(phenyl) sulfide (L).¹⁸ From 2-bromo-1,3-dimethyl-5-nitrobenzene and benzenethiol as a yellow solid (1.21 g, 93%); mp = 47–48 °C (lit.¹⁷ 53.5–55 °C); ^1H -NMR δ 8.00 (s, 2H), 7.23–7.20 (m, 2H), 7.14 (d, J = 7.2 Hz, 1H), 6.95 (d, J = 7.6 Hz, 2H), 2.49 (s, 6H); ^{13}C -NMR δ 147.5, 145.1, 139.6, 135.9, 129.2, 126.7, 125.8, 122.3.

2,6-Dimethyl-4-nitrophenyl(4'-nitrophenyl) sulfide (M). From 2-bromo-1,3-dimethyl-5-nitrobenzene and 4-nitrobenzenethiol as a pale yellow solid (1.02 g, 67%); mp = 137–138 °C; ^1H -NMR δ 8.08 (dd, J = 2.4, 8.8 Hz, 4H), 7.01 (dd, J = 2.4, 9.2 Hz, 2H), 2.54 (s, 6H); ^{13}C -NMR δ 148.4, 145.8, 145.6, 145.5, 136.5, 125.6, 124.5, 123.1, 22.2; HRMS, Calc'd. for $\text{C}_{14}\text{H}_{12}\text{O}_4\text{SN}_2$: 304.0518, Found: 304.0525.

2-Methylphenyl(phenyl) sulfide (N).¹⁹ From 2-iodotoluene and benzenethiol as a white solid (0.93 g, 66%); mp = 59–60 °C; ^1H -NMR δ 7.30–7.11 (m, 9H), 2.37 (s, 3H); ^{13}C -NMR δ 140.0, 136.2, 133.8, 133.1, 130.6, 129.7, 129.2, 128.0, 126.8, 126.4.

Prepared starting materials

3-Nitrobenzenethiol (O).²⁰ Sodium borohydride (0.83 g, 22 mmol) was added portionwise to a yellow solution of bis(3-nitrobenzene) disulfide (1.71 g, 5.5 mmol) in anhydrous THF (20 mL) at rt under argon atmosphere. The resultant purple mixture was stirred for 2 h at rt. The reaction mixture was then acidified by dropwise addition of 1M

HCl, (monitored with litmus paper). The product was extracted with CH₂Cl₂ (20 mL x 2). The combined organic layers were dried over MgSO₄, and concentrated *in vacuo* to give **O** as a pale yellow oil (1.58 g, 91%); ¹H-NMR δ 8.09 (t, *J* = 2 Hz, 1H), 7.83 (dq, *J* = 1.2, 5.2 Hz, 1H), 7.57–7.55 (m, 1H), 7.41 (t, *J* = 8 Hz, 1H), 3.79 (s, 1H); ¹³C-NMR δ 148.2, 134.5, 133.9, 129.6, 123.2, 120.2.

2,6-Dimethyl-4-nitrophenyl trifluorosulfonate (P).²¹ Pyridine (4.0 mL) was added to 2,6-dimethyl-4-nitrophenol (3.3 g, 20 mmol) in CH₂Cl₂ (50 mL) and the mixture was cooled to 0 °C. Triflic anhydride (3.6 mL, 21 mmol) was added dropwise over 20 min. The reaction mixture was stirred for 3 h at 0 °C and then water (30 mL) was added. The organic layer was washed successively with 1M HCl (30 mL x 2), water (30 mL x 2), and 1M NaOH (30 mL), dried over MgSO₄ and finally concentrated under reduced pressure to give **P** as a light brown solid (1.98 g, 22%); mp = 62–63 °C; ¹H-NMR δ 8.03 (s, 2H), 2.50 (s, 6H); ¹³C-NMR δ 150.3, 146.4, 133.8, 124.8, 118.5 (d, *J*_{C-F} = 317 Hz), 17.5; ¹⁹F-NMR δ –73.0 HRMS, Calc'd. for C₉H₈O₅SNF₃: 299.0075, Found: 299.0077.

2-Bromo-1,3-dimethyl-5-nitrobenzene (Q).²¹ Compound **P** (4.8 g, 16 mmol) was mixed with LiBr (4.7g, 54 mmol) in DMF (50 mL) and refluxed for about 20 h to give a dark mixture. Water (50 mL) was added and the resultant mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with water (150 mL x 2), dried over MgSO₄ and concentrated *in vacuo*. Column chromatography of the crude product on silica gel (20% EtOAc/hexane, *R_f* = 0.7) gave **Q** as a brown solid (1.98 g, 48%); mp = 97–98 °C; ¹H-NMR δ 7.94 (s, 2H), 2.52 (s, 6H); ¹³C-NMR δ 146.3, 140.1, 134.9, 122.5, 24.1; HRMS, Calc'd. for C₈H₈O₂NBr: 228.9738, Found: 228.9748.

2-Fluoro-1,3-dimethyl-5-nitrobenzene (R). CsF (76 mg, 0.5 mmol) was added to a solution of **P** (0.11 g, 0.35 mmol) in DMF (5 mL) and refluxed for 16 h. Water (30 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (30 mL x 2). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Preparative TLC (20% EtOAc/hexane, *R_f* = 0.2) of the crude product gave **R** as a yellow solid (9.6 mg, 16%); mp = 172–173 °C; ¹H-NMR δ 7.93 (s, 2H), 2.32 (s, 6H); ¹³C-NMR δ 157.8, 140.8, 124.5, 123.7, 15.9; ¹⁹F-NMR δ –73.5.

Radiochemistry

Microfluidic reactions. Cyclotron-produced no-carrier-added [^{18}F]fluoride ion (3.7–7.4 GBq) in [^{18}O]water (250–400 μL ; 95 atom %) was first adsorbed onto a QMA anionic resin cartridge within the CE module of a NanoTek apparatus (Advion; Louisville, TN), and then released with a solution of K_2CO_3 (0.8 mg; 5.8 μmol) and K 2.2.2 (4.5 mg; 11.9 μmol) in MeCN- H_2O (9: 1 v/v; 450 μL) into a 2-mL V-vial. The solution was dried by two cycles of azeotropic evaporation with acetonitrile (0.6 mL) under nitrogen flow at 95 $^\circ\text{C}$. The dry $^{18}\text{F}^-$ -K 2.2.2- K^+ complex (3.7–5.6 GBq) was dissolved in DMF (260 μL). A solution of diaryl sulfoxide precursor (10 mM) was prepared in DMF. Each of the two solutions (260 μL) was loaded into a separate storage loop of the microfluidic apparatus. The detailed configuration of this commercial microfluidic system was described in our earlier publication.²² For radiofluorination reactions, each solution (10–20 μL) was infused simultaneously into the micro-reactor (4-m coiled glass silica tube; internal diameter, 100 μm ; internal volume, 31.4 μL) of the apparatus at a set flow rate in the range 4–10 $\mu\text{L}/\text{min}$ and at a pre-set temperature. The micro-reactor effluent was immediately quenched with MeCN- H_2O (1: 1 v/v; 3 mL) and analyzed by radio-HPLC as described below. Precursor amount, temperature and flow rate were varied to search for high radiochemical yields (RCYs). Results are presented in the main text (Tables 1 and 2).

Batch reactions. Cyclotron-produced no-carrier-added [^{18}F]fluoride ion (9.25–10.0 GBq) in [^{18}O]water (400–500 μL ; 95 atom %) was delivered into a glass vial containing K 2.2.2 (4.5 mg, 11.9 μmol) and K_2CO_3 (0.8 mg, 5.8 μmol) in MeCN- H_2O (0.1 mL, 9:1 v/v). The solution was transferred to a TRACERlab $\text{FX}_{\text{F-N}}$ module (GE Healthcare) and diluted with MeCN (1 mL). The mixture was evaporated to dryness at 90 $^\circ\text{C}$ under reduced pressure with a nitrogen flow. MeCN (2 mL) was added again and then evaporated to dryness. DMF (1.5 mL) or DMSO (1.5–1.7 mL) was added to the dry [^{18}F]fluoride ion-K 2.2.2- K^+ complex and the reconstituted solution rinsed into a septum-sealed glass V-vial (3 mL). Recovery of [^{18}F]fluoride from the drying vessel was approximately 75%. For radiofluorination reactions, the [^{18}F]fluoride ion solution (0.1 mL) was added to diaryl sulfoxide precursor (5 mg) dissolved in either DMF or DMSO (0.2 mL) corresponding to the solvent of the [^{18}F]fluoride ion solution. The reaction

mixture was heated to 120 °C for 15 min or 200 °C for 15 or 30 min. Then an aliquot (about 50 μ L) was removed, quenched with MeCN-H₂O (1 mL, 1:1 v:v) and analyzed by radio-HPLC, as described below. Results are presented in Table S1.

Radio-HPLC Analysis. The RCYs of [¹⁸F]fluoroarenes were measured by reverse phase radio-HPLC on a Luna C18 column (250 \times 4.6 mm i.d., 10 μ m; Phenomenex; Torrance, CA), upon their identification by comparison of their retention times with those of reference fluoroarenes detected by their UV absorbances. Four different chromatographic methods were applied to analyze the radioactive products, as follows.

Method A: For analysis of compounds **7–9**. Elution at 1.00 mL/min, initially with MeCN-H₂O (50: 50, v/v) with MeCN increased linearly from 50 to 60% over 7 min.

Method B: For analysis of compounds **2, 10–15** and **18–20**. Elution at 1.25 mL/min, initially with MeCN-H₂O (60: 40, v/v) with MeCN increased linearly from 60 to 90% over 7 min.

Method C: For analysis of compounds **1, 4, 6** and **17**. Elution at 1.50 mL/min, initially with MeCN-H₂O (60: 40, v/v) with MeCN increased linearly from 60 to 70% over 7 min.

Method D: For analysis of compounds **3, 5** and **16**. Elution at 1.75 mL/min, initially with MeCN-H₂O (60: 40, v/v) with MeCN increased linearly from 60 to 90% over 7 min.

Table S1. RCYs of NCA [¹⁸F]fluoroarenes from the radiofluorination of diaryl sulfoxides in 15-min batch reactions compared with those from microfluidic reactions.

Substrate	[Product] Radiochemical yields (%) ^a			
	Microreactor ^b	DMF 180°C	DMSO 120°	DMSO 200°
1	[1a] 91	[1a] 92	n.d.	[1a] 90
2	[2a] 82	[2a] 77	n.d.	[2a] 85
3	[3a] 66	[3a] 15	n.d.	[3a] 48
4	[4a] 21	n.d.	[1a] 0	n.d.
5	[5a] 7	n.d.	[5a] 0	n.d.
6	[6a] 2	n.d.	n.d.	[6a] 1
7	[7a] 94	[7a] 28	[7a] 6	[7a] 25
8	[8a] 4	n.d.	n.d.	[8a] 3
9	[9a] 68	[9a] 2	n.d.	[9a] 53
12	[12a] 0	n.d.	n.d.	[12a] 0
14	[1a] 93; [2a] <1	n.d.	[1a] 62; [2a] <1	n.d.
16	[16a] 73; [10a] 0	n.d.	n.d.	[16a] 72; [10a] 0
17	[17a] 46; [1a] 43	n.d.	[17a] 53; [1a] 42	n.d.
18	[18a] 61; [10a] 0	n.d.	n.d.	[18a] 58; [10a] 0

^aFrom HPLC analysis. ^bData from Tables 1 and 2 in main text. n.d. = not determined.

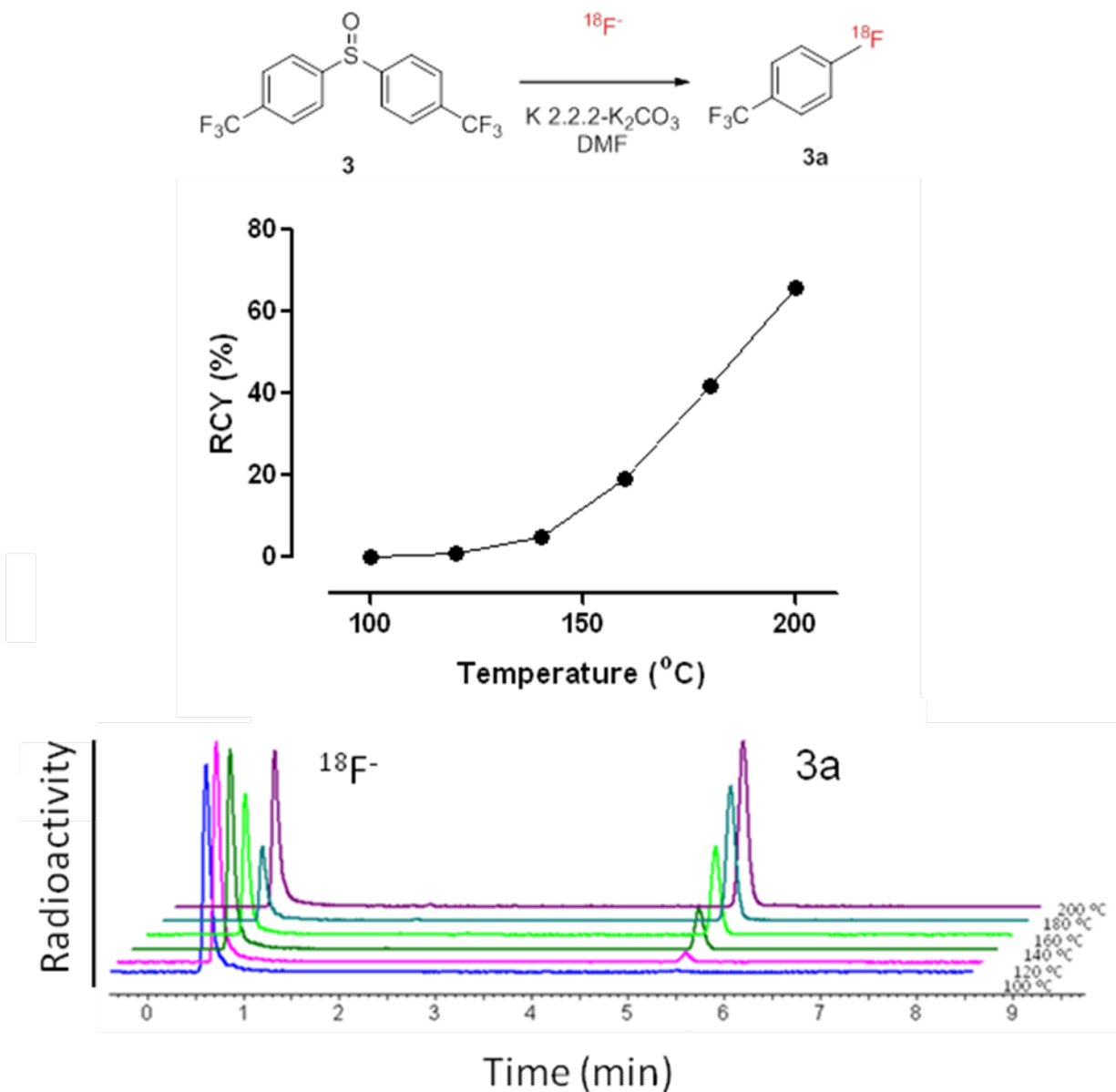


Figure S1. Radiochromatograms from the HPLC analyses of quenched reaction effluents from the radiofluorination of **3** in DMF. The results are from reactions at progressively increasing temperatures with a fixed reaction (residence) time of 251 s. The RCYs in the plot are not corrected for radioactivity adsorption in the apparatus, nor for the low amount of radioactive decay to time of sample injection on HPLC.

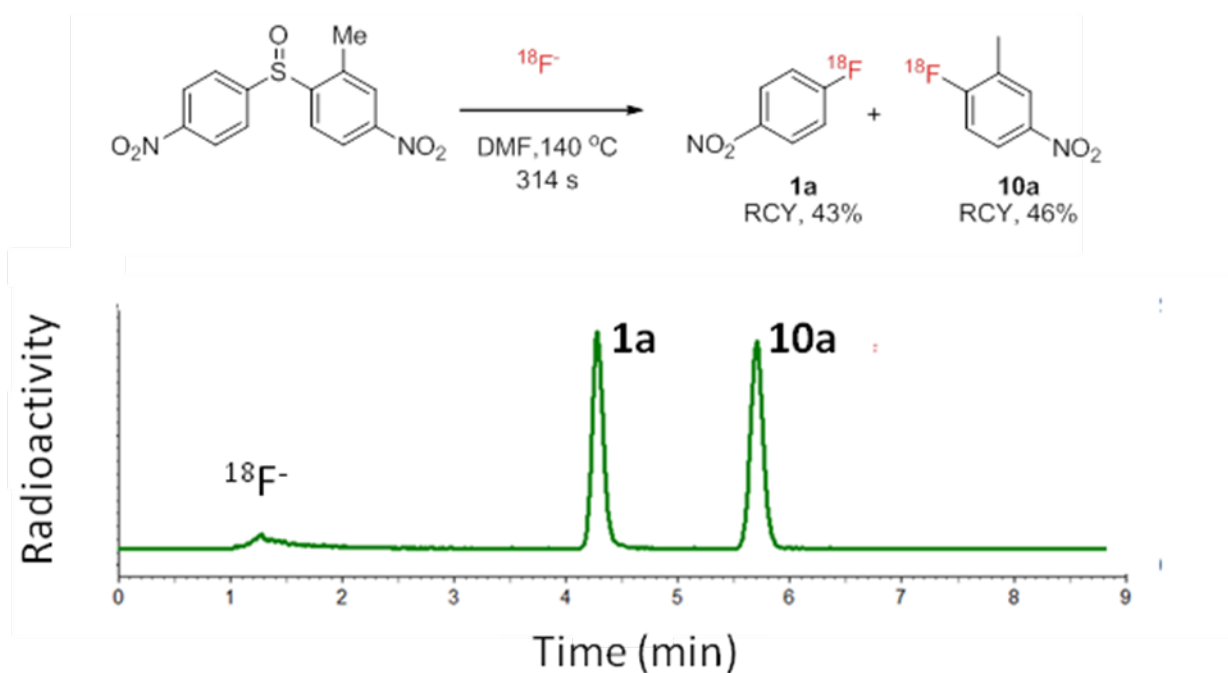


Figure S2. Radiochromatogram from the HPLC analysis of reaction product from the radiofluorination of **17** showing high fluorine-18 incorporation into **1a** and **10a**.

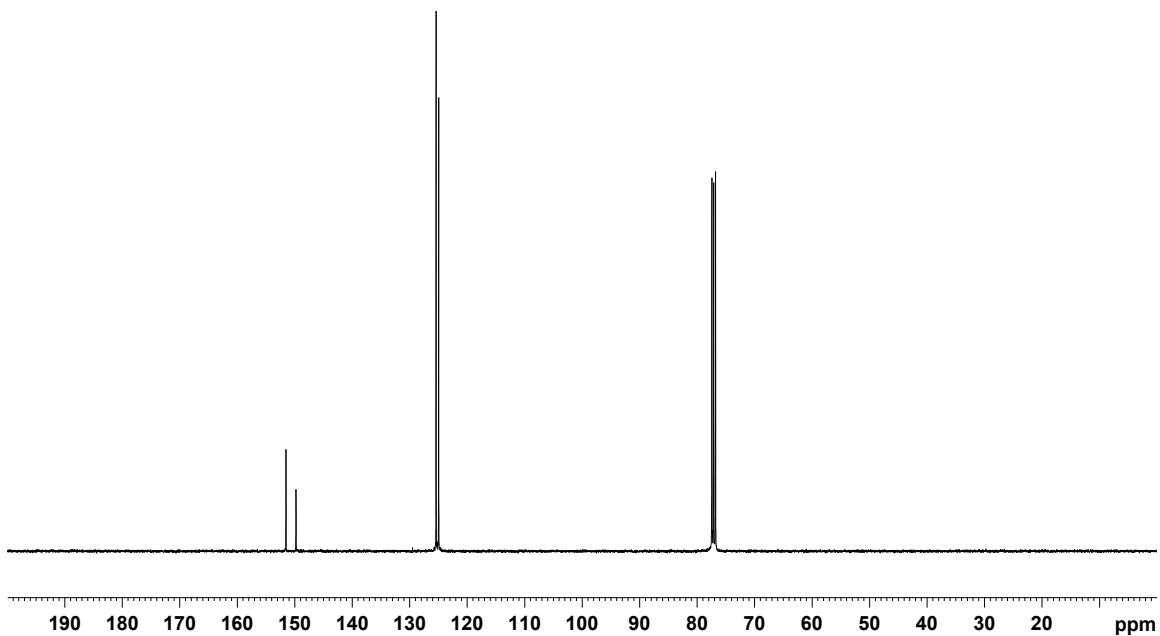
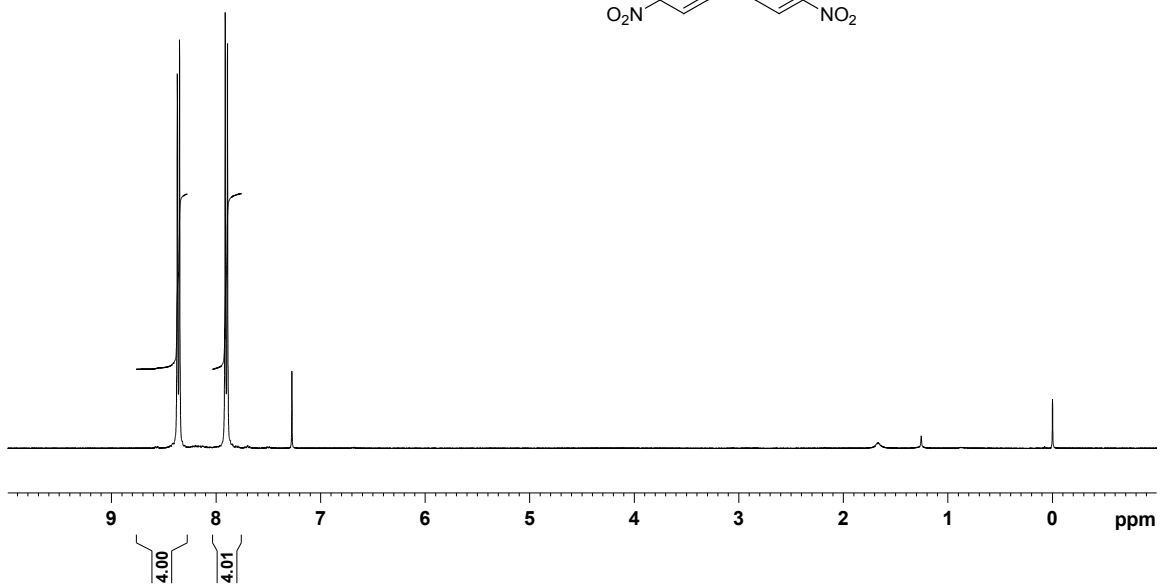
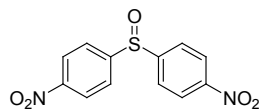
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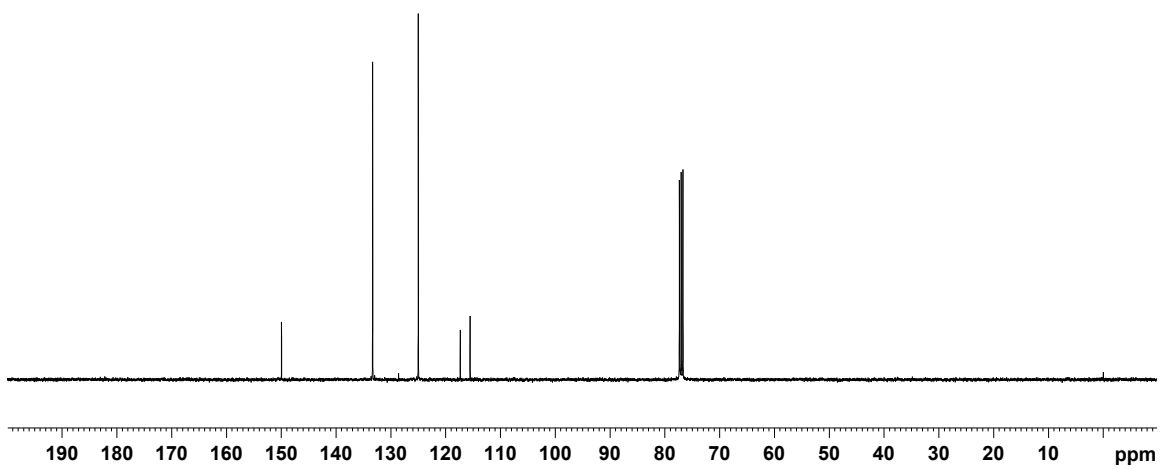
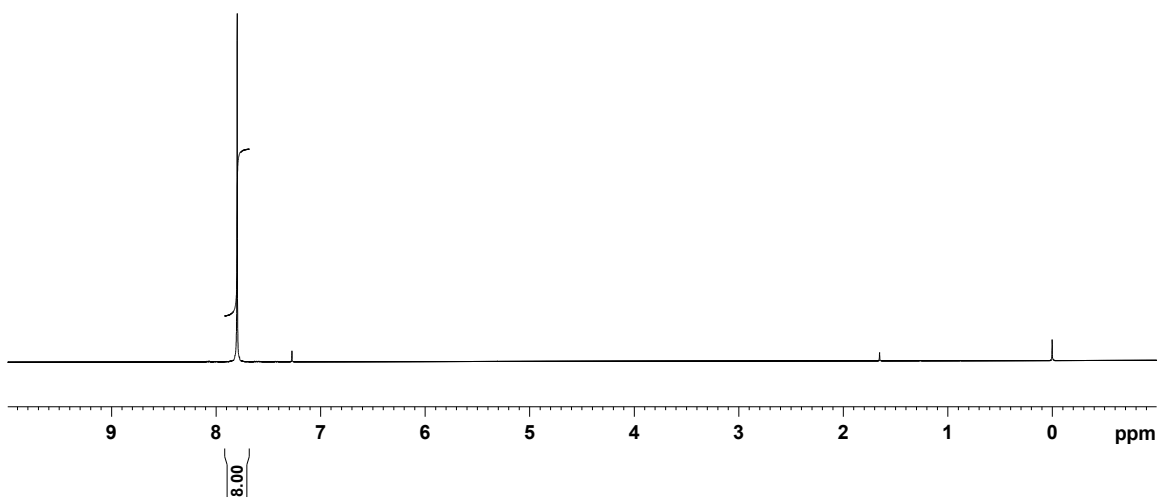
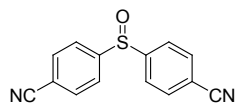
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Appendix 1. ^1H - and ^{13}C - NMR spectra of diaryl sulfoxides prepared for this study.

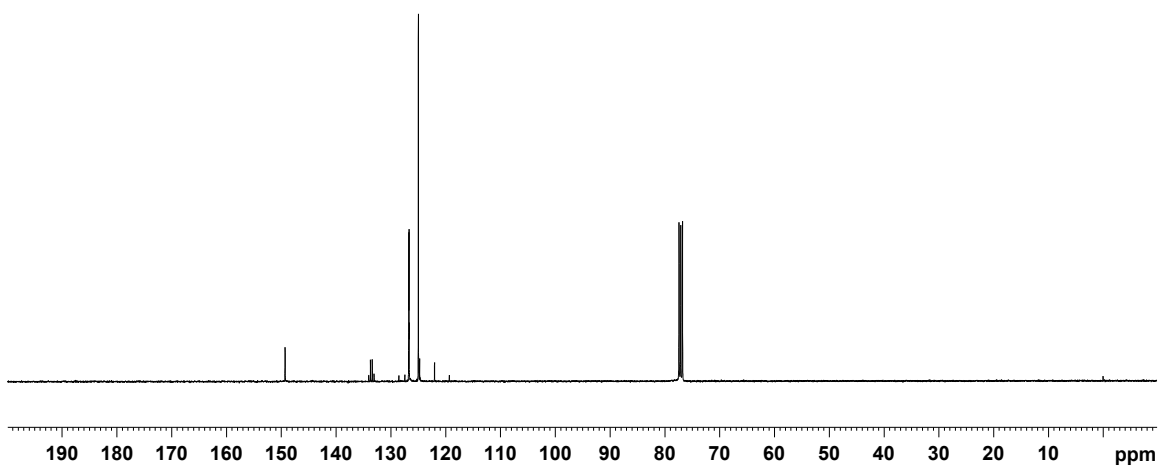
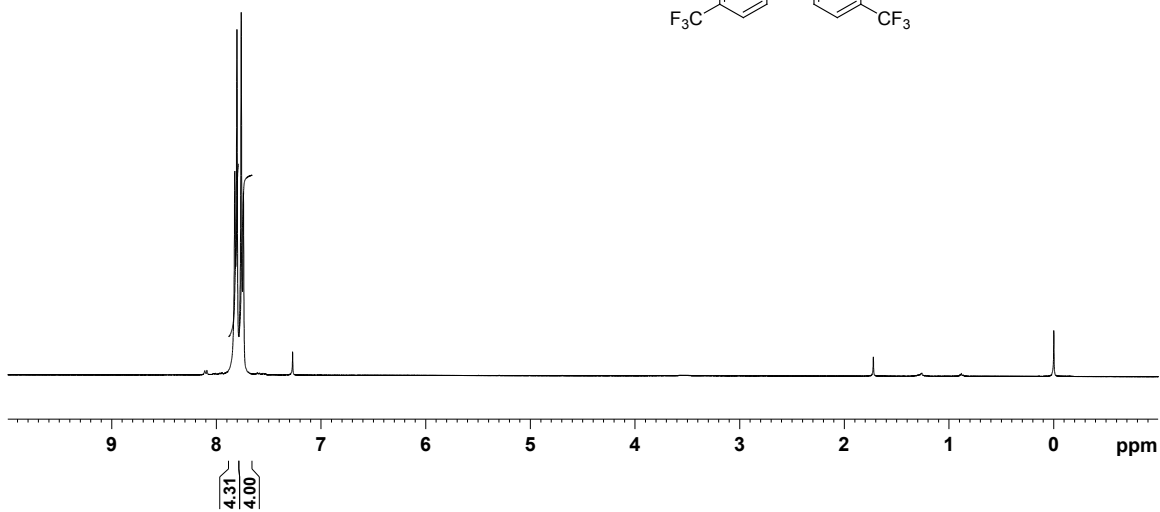
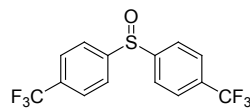
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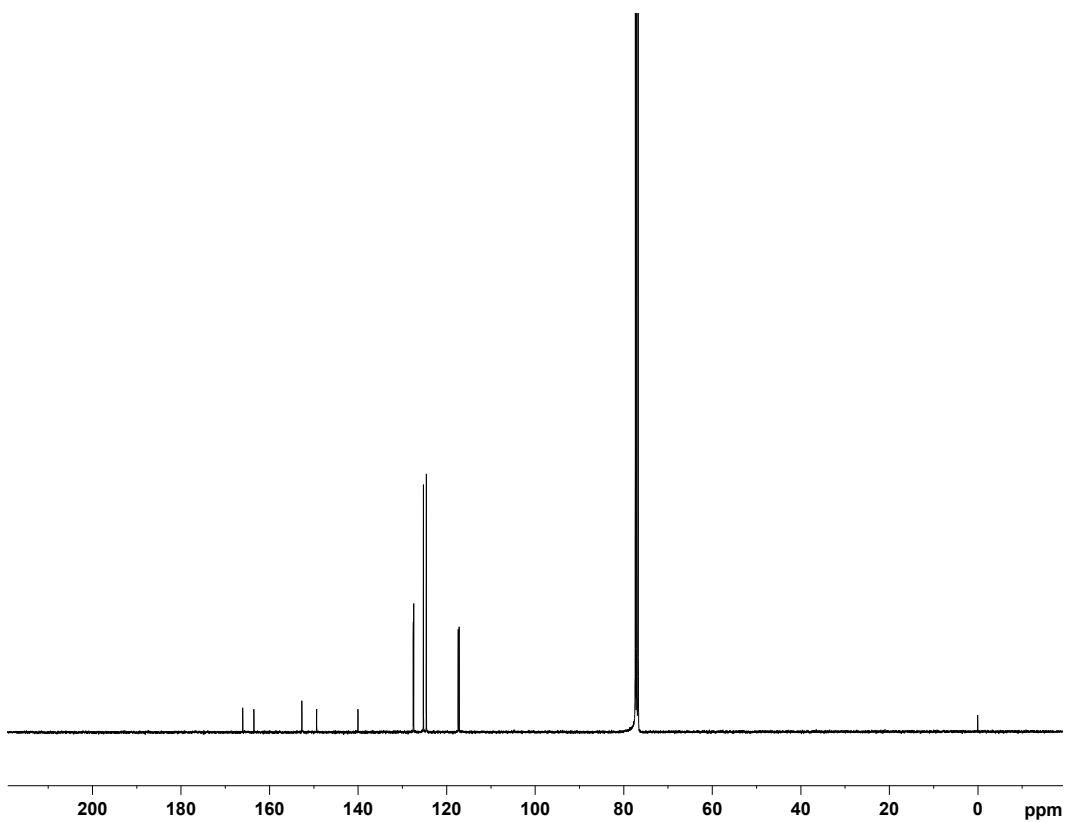
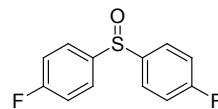
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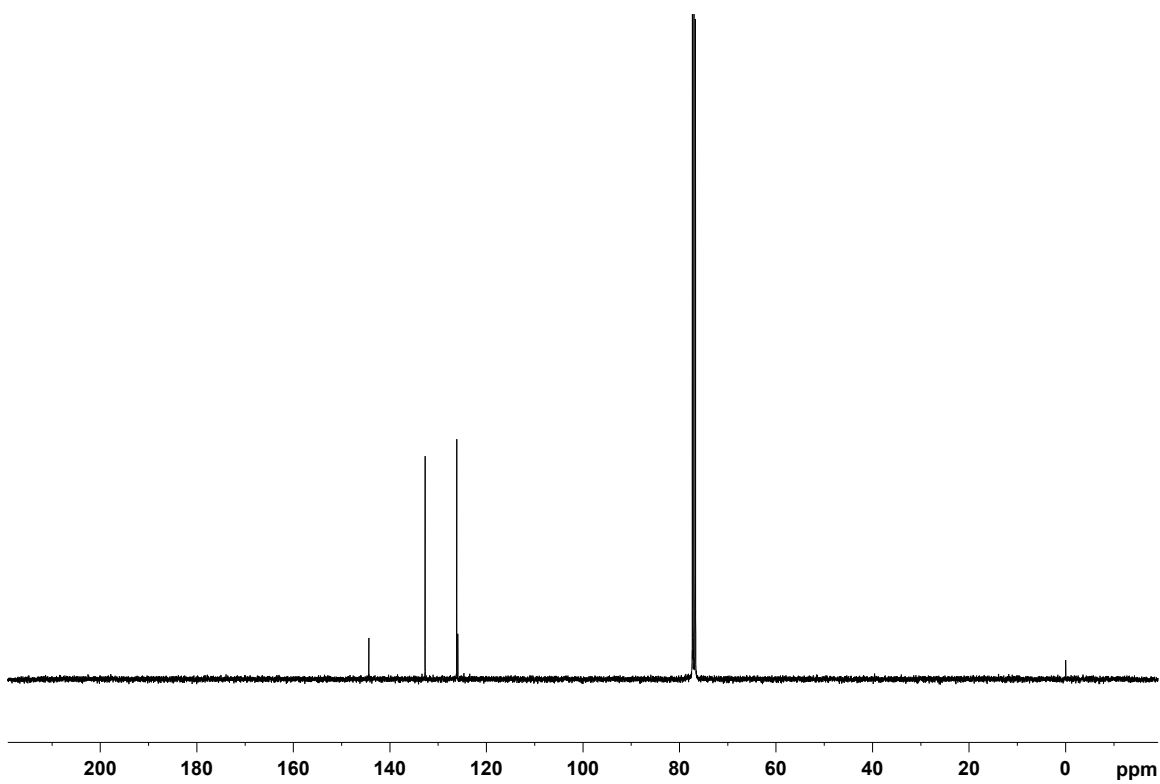
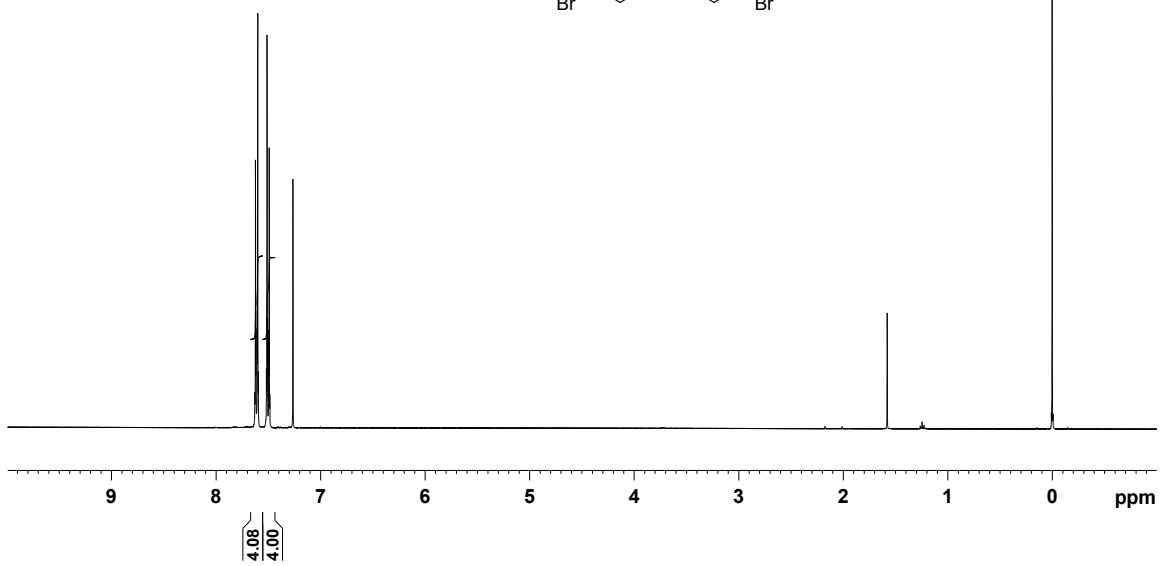
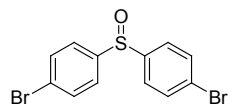
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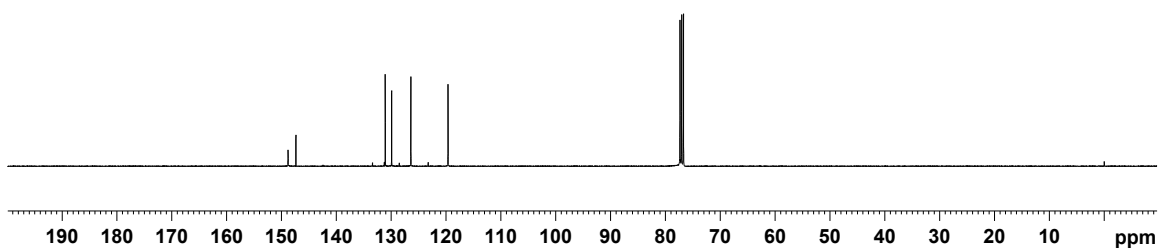
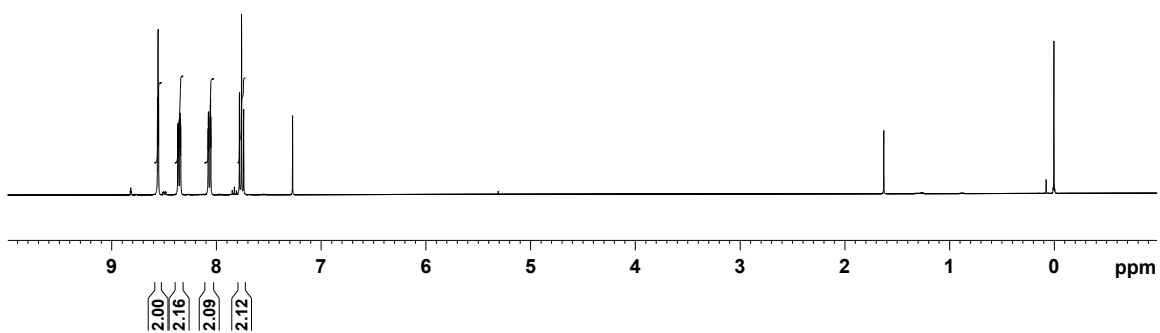
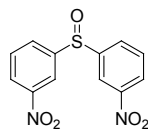
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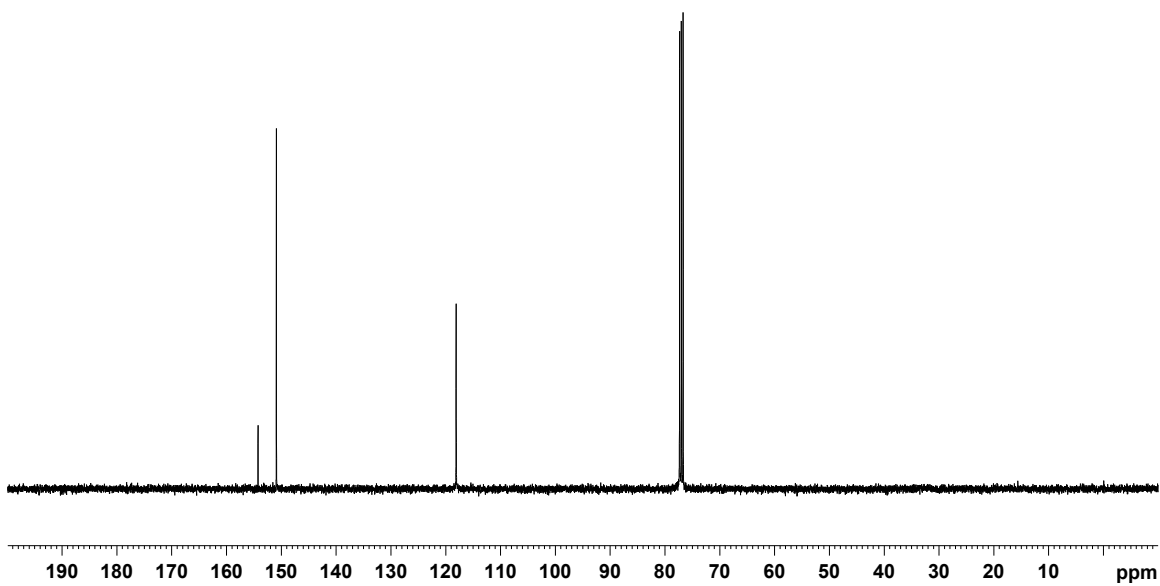
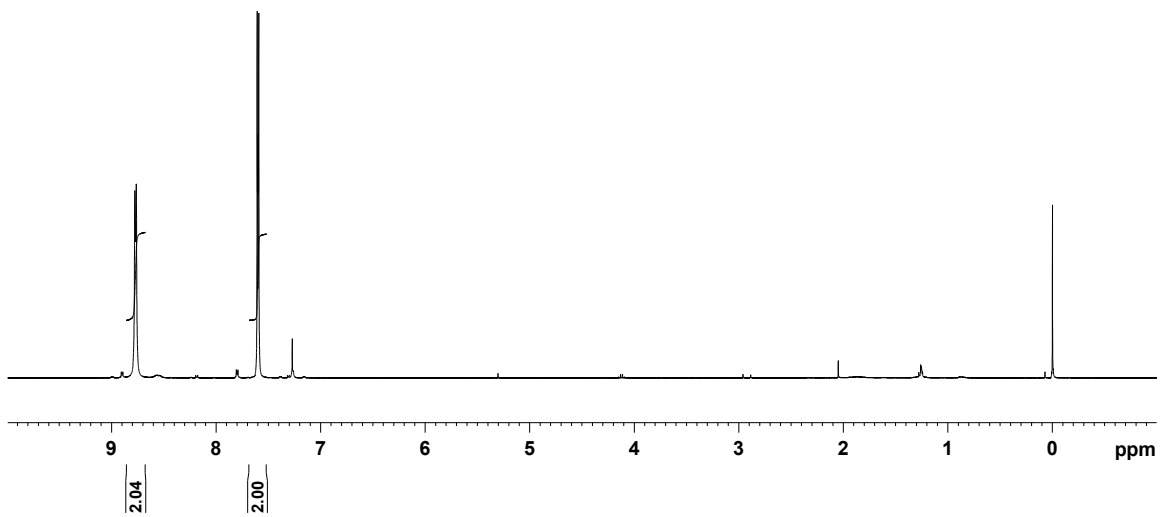
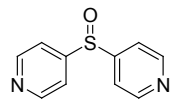
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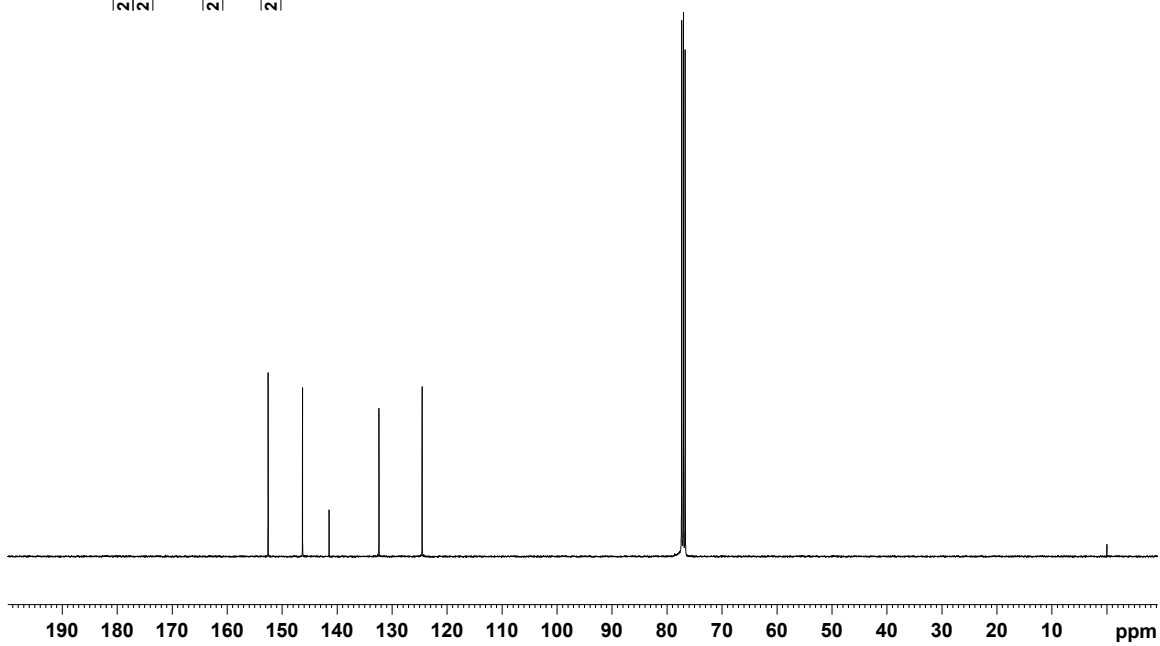
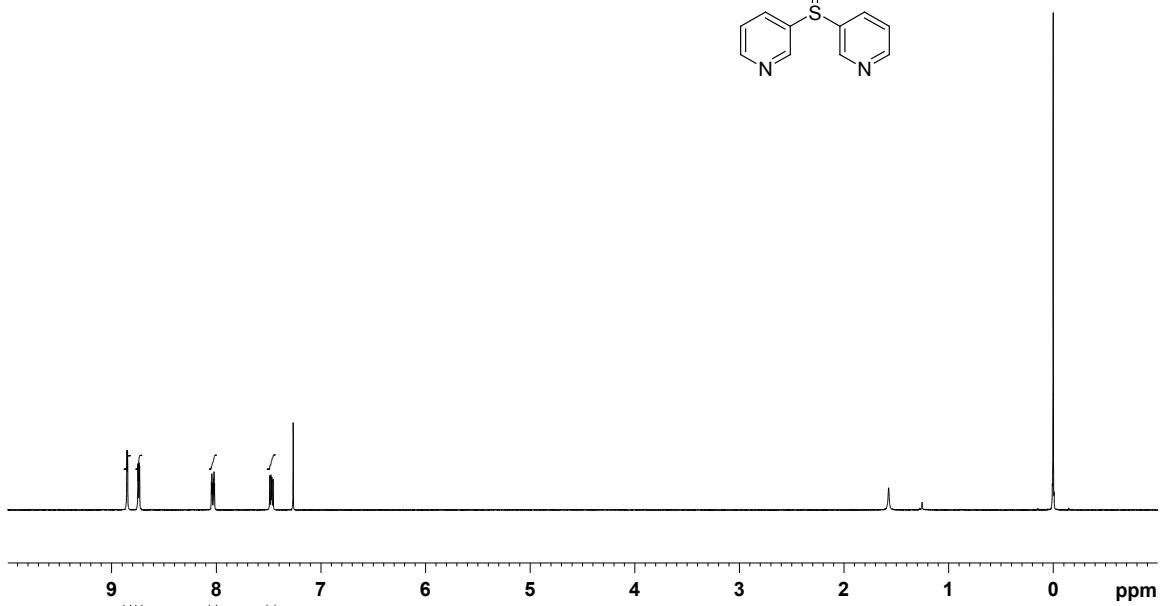
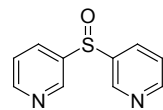
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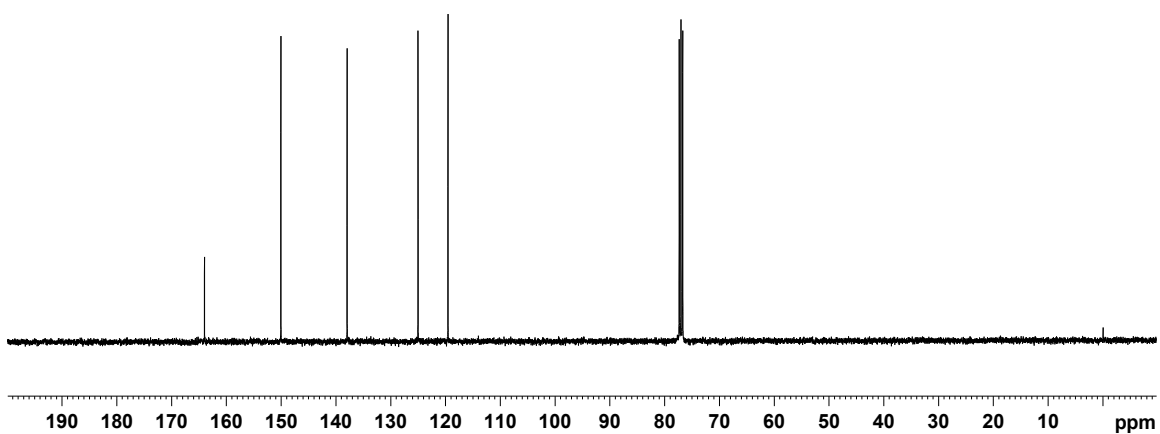
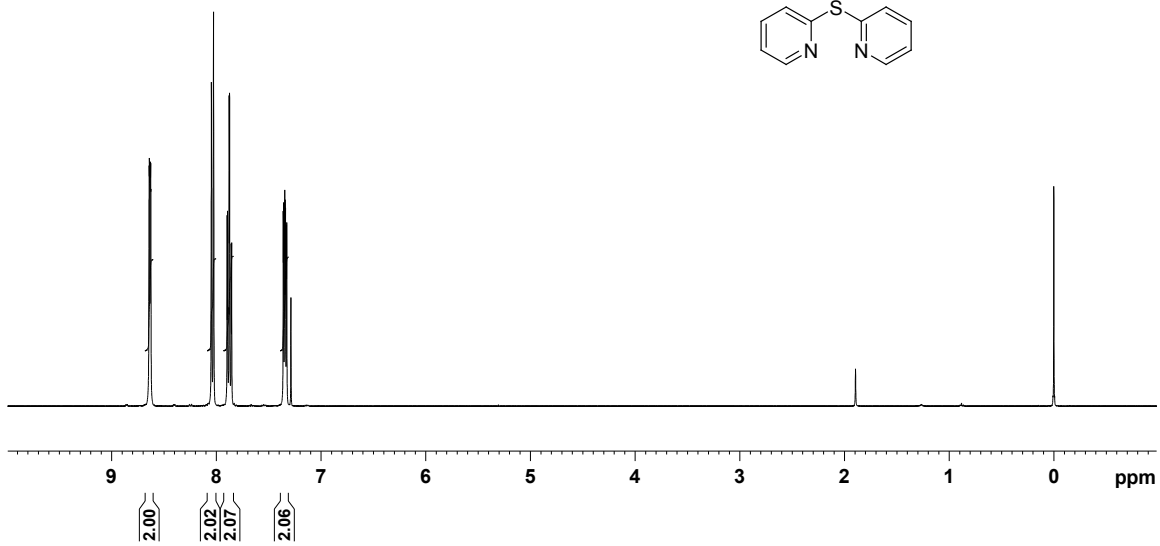
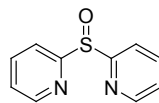
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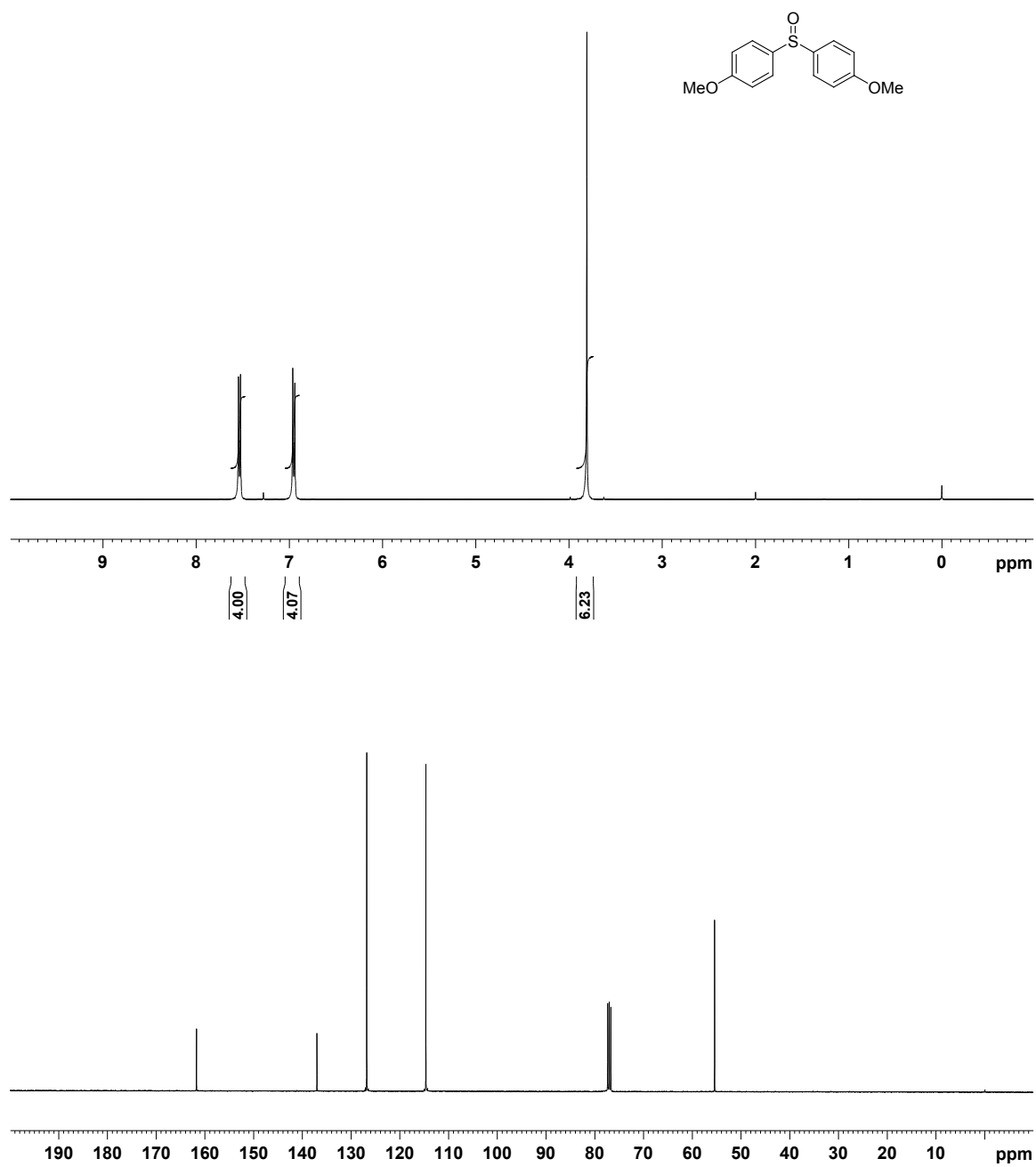
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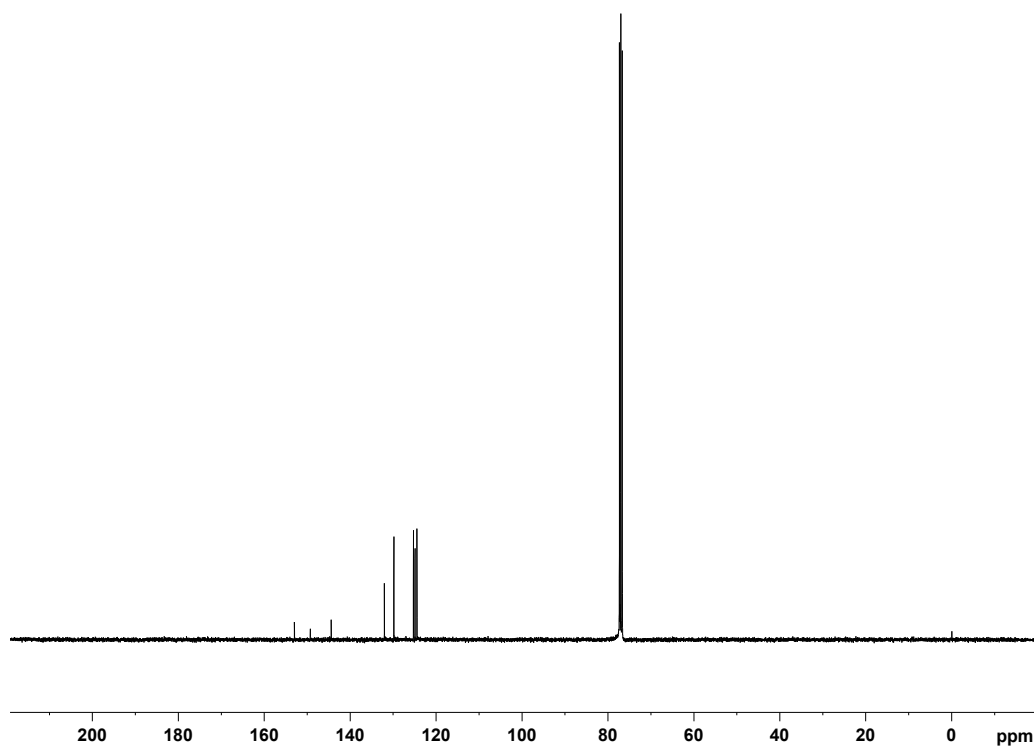
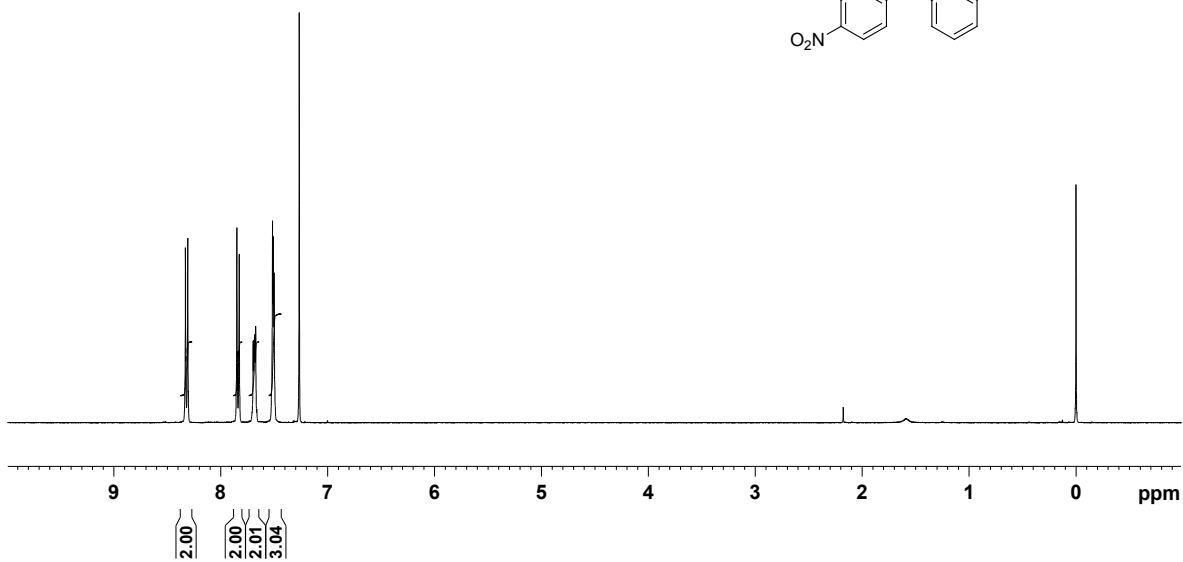
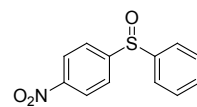
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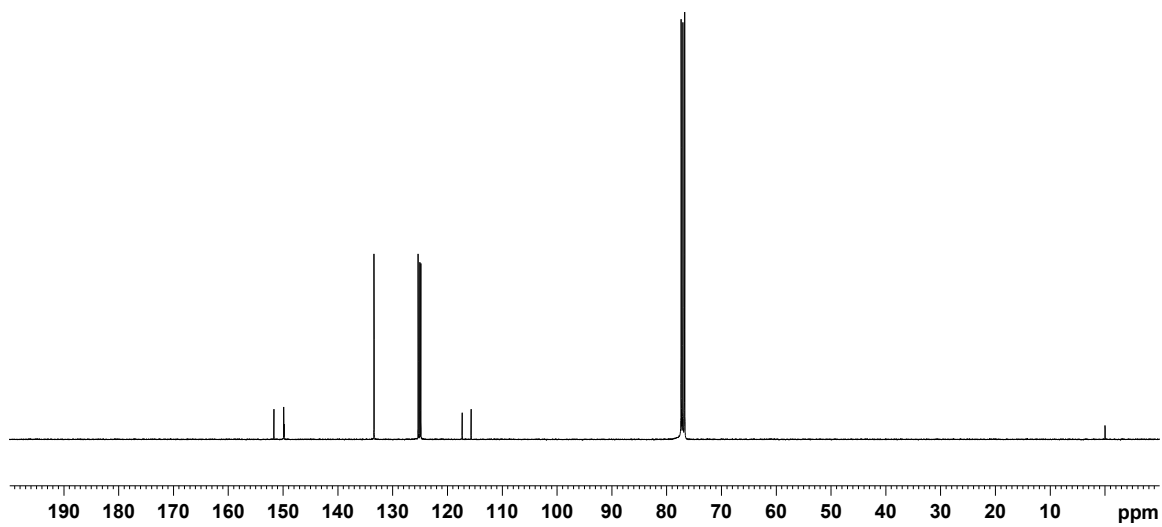
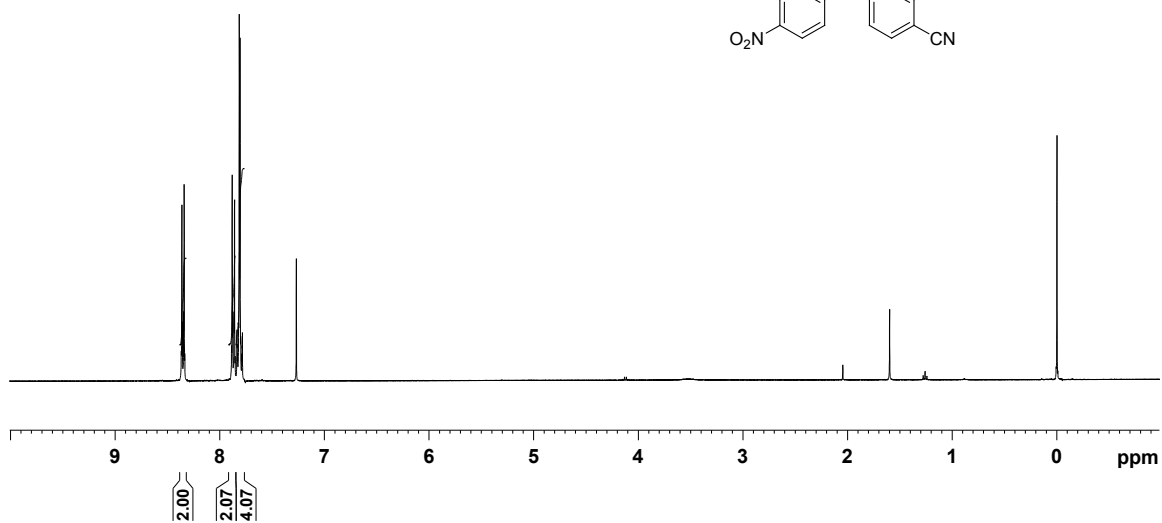
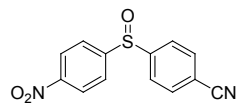
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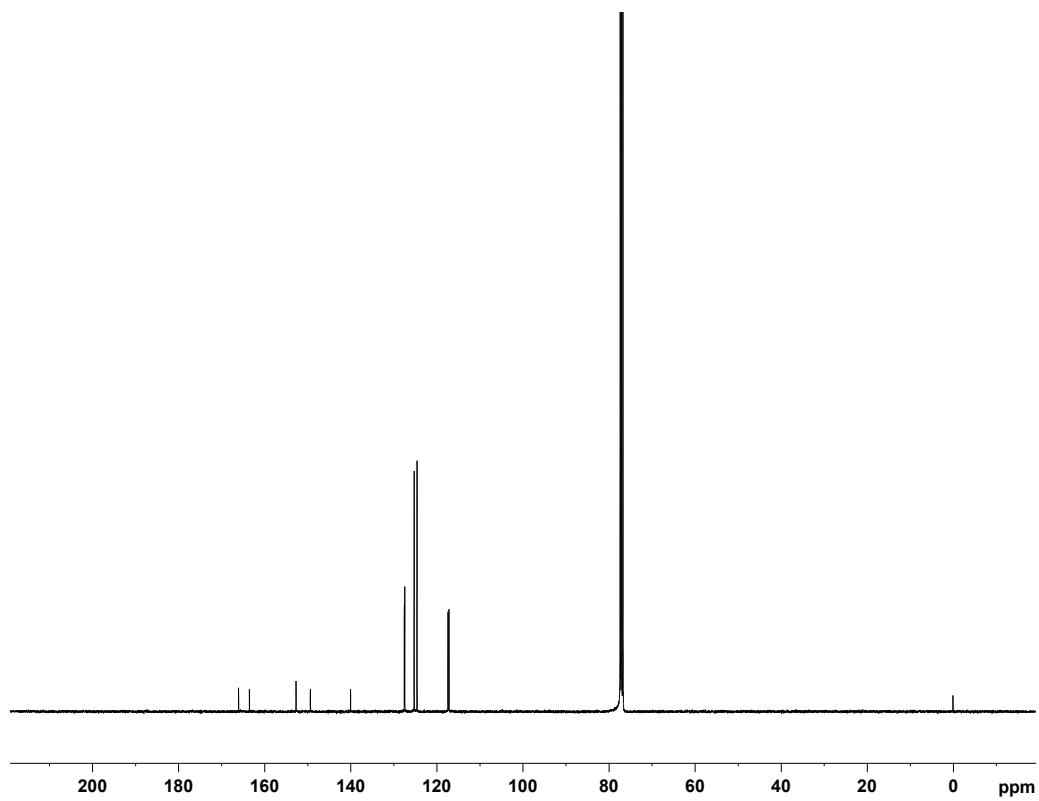
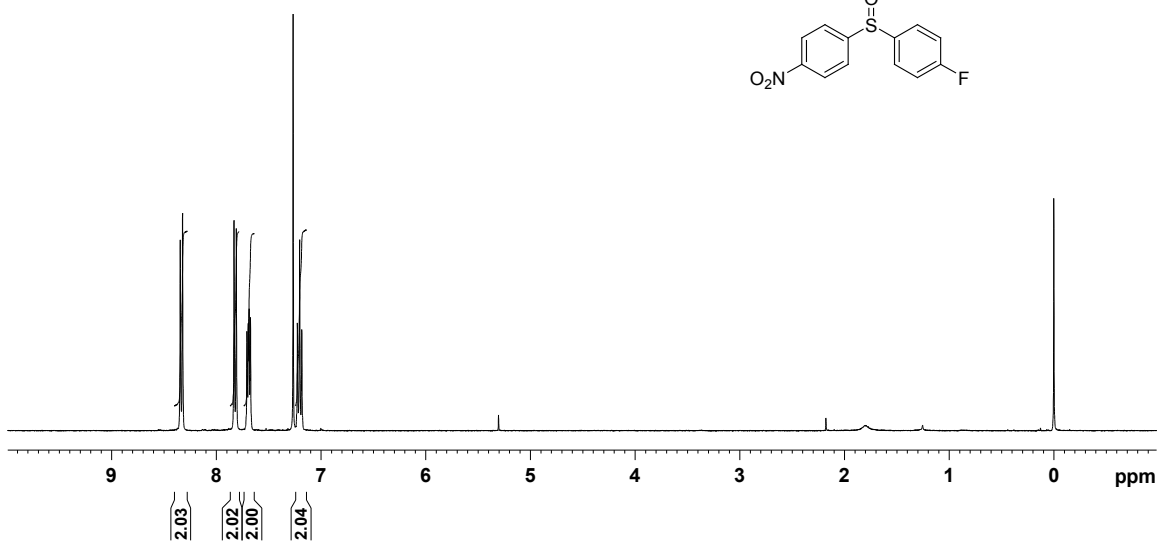
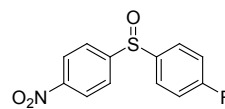
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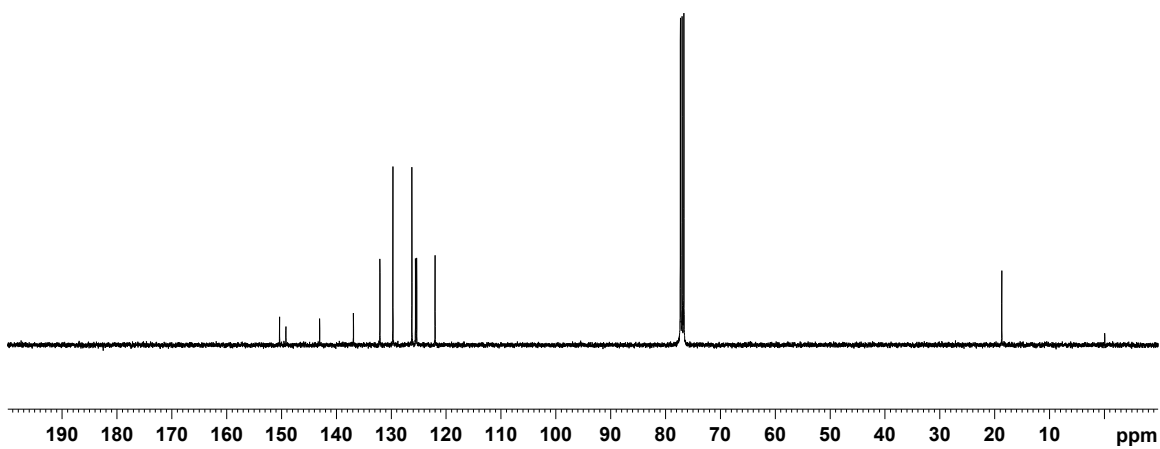
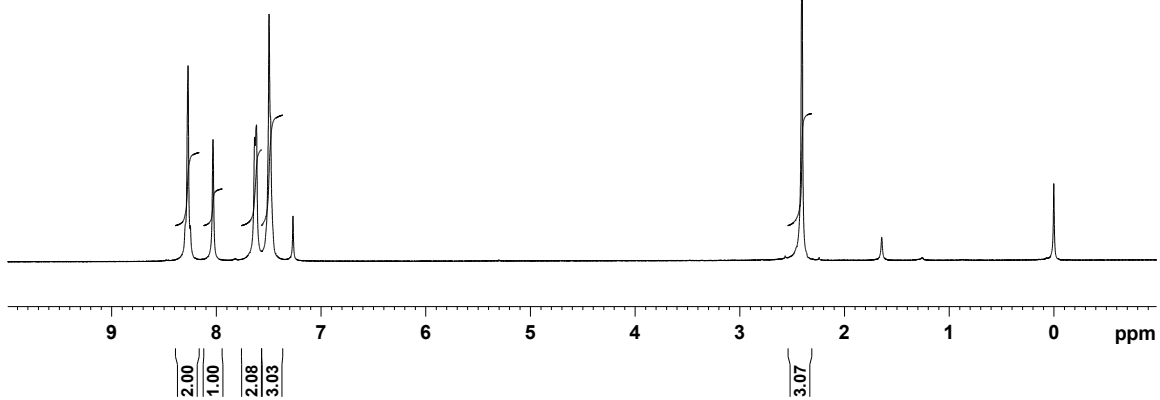
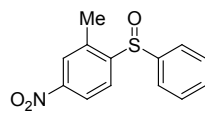
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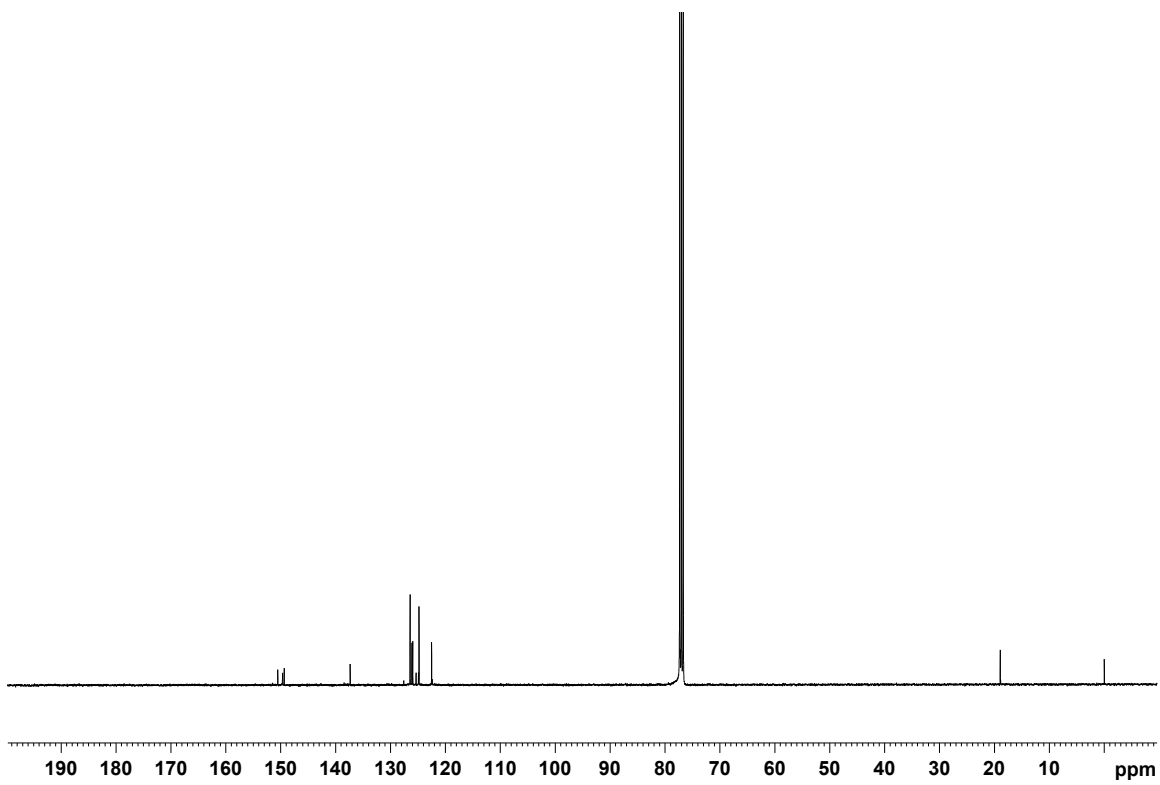
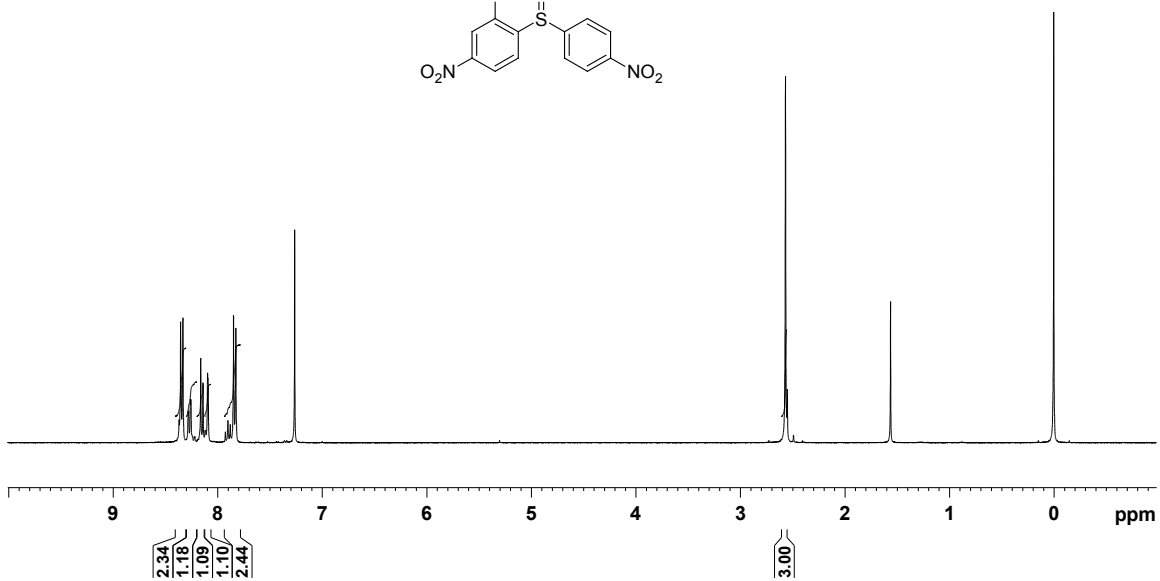
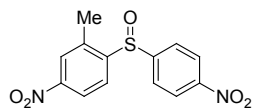
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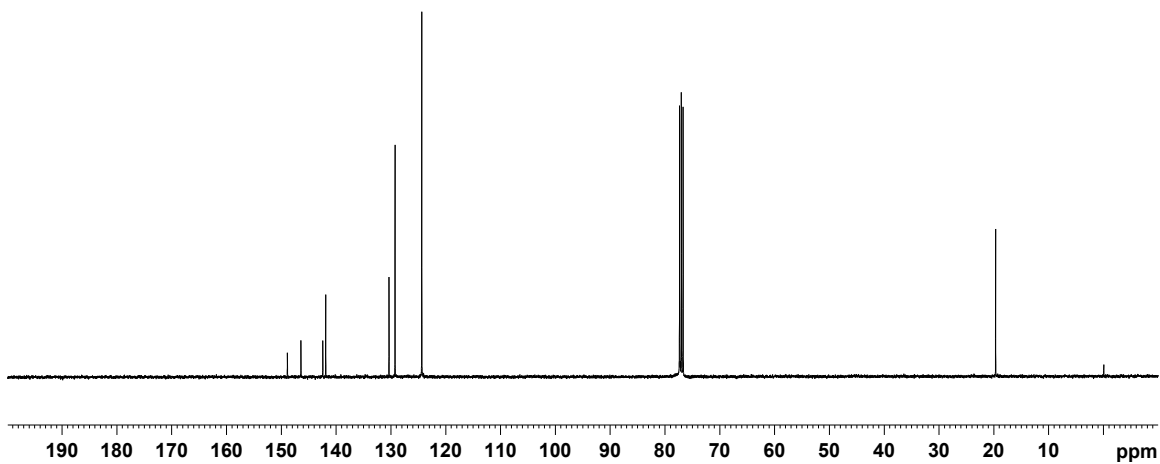
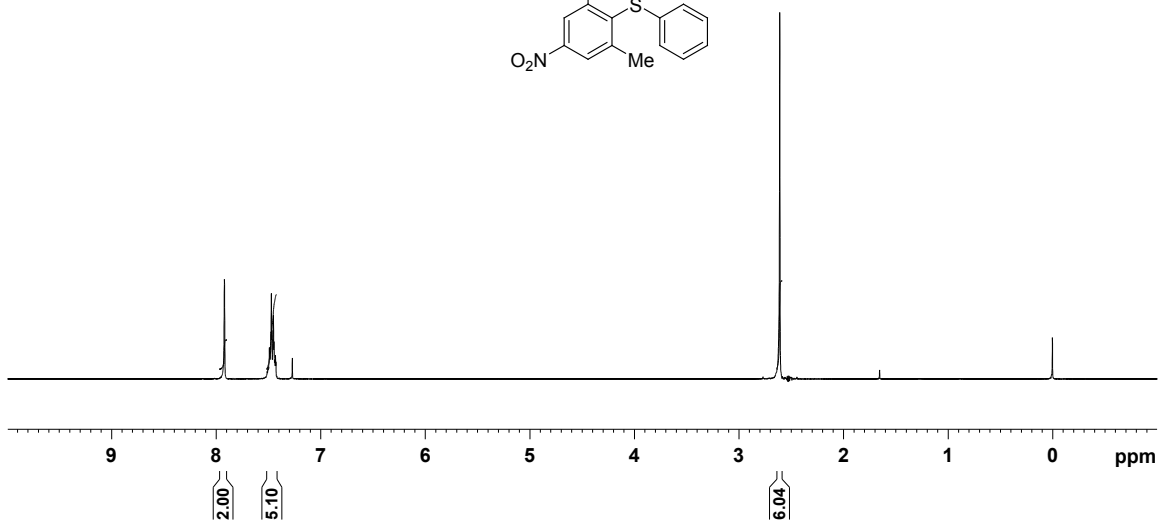
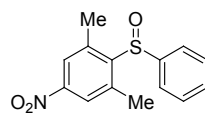
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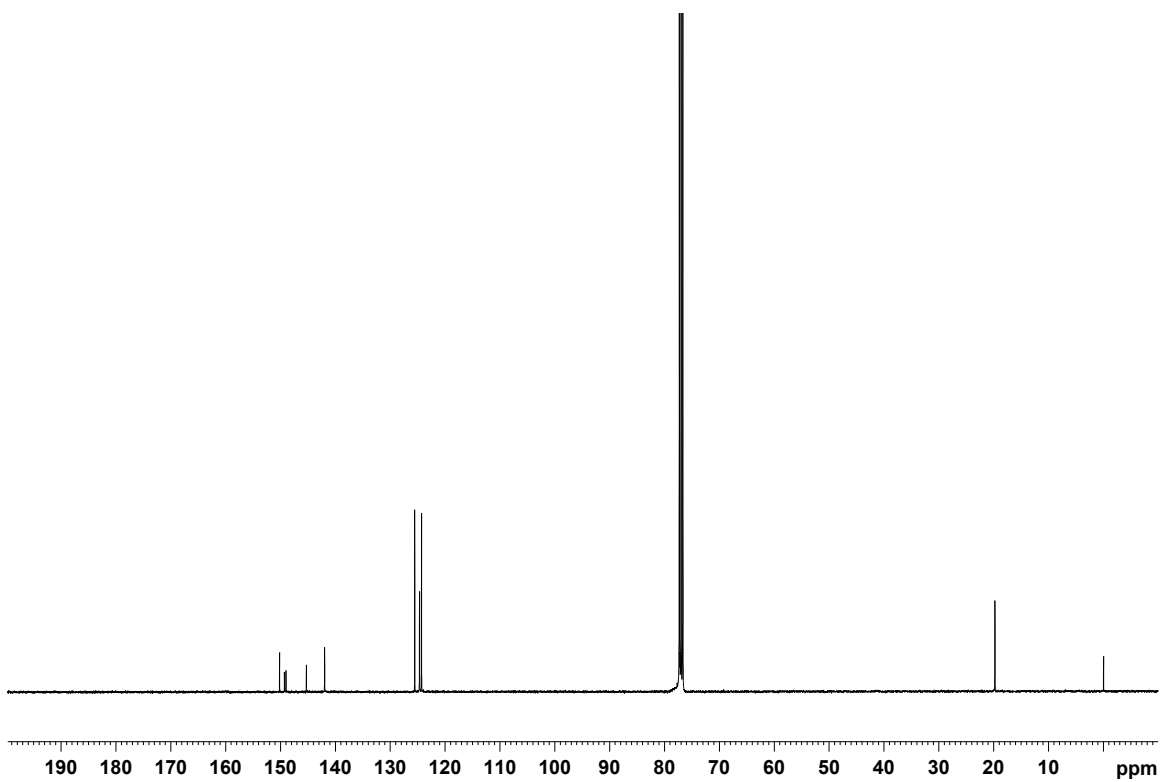
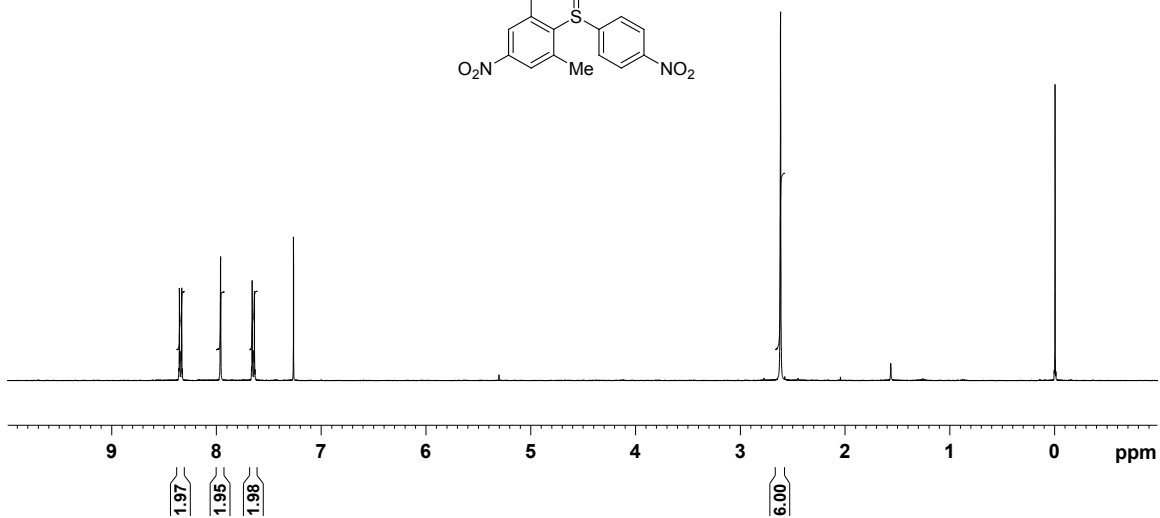
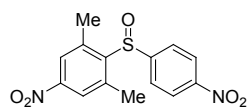
Compound 17



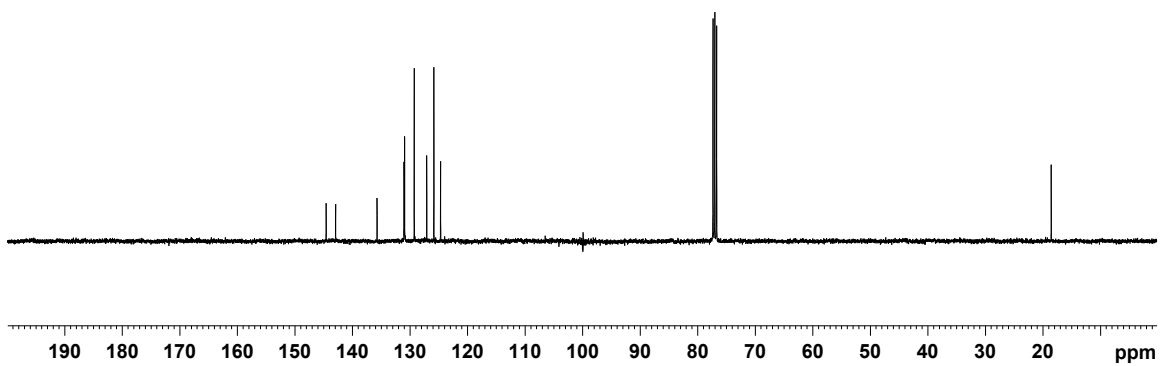
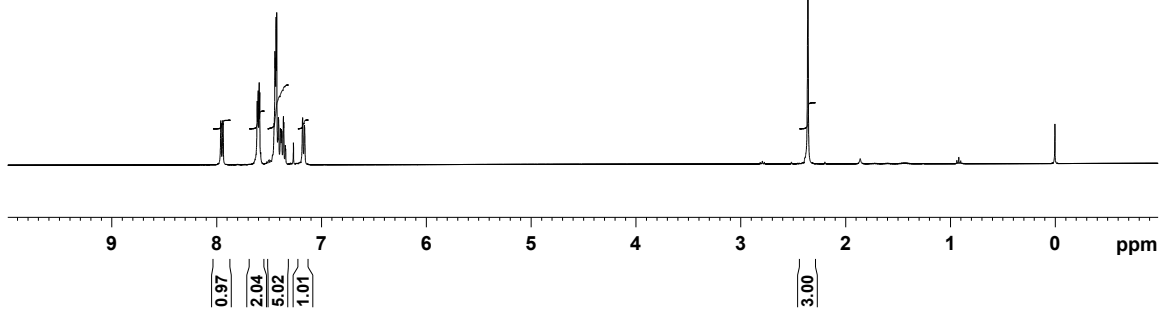
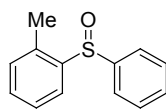
Compound 18



Compound 19

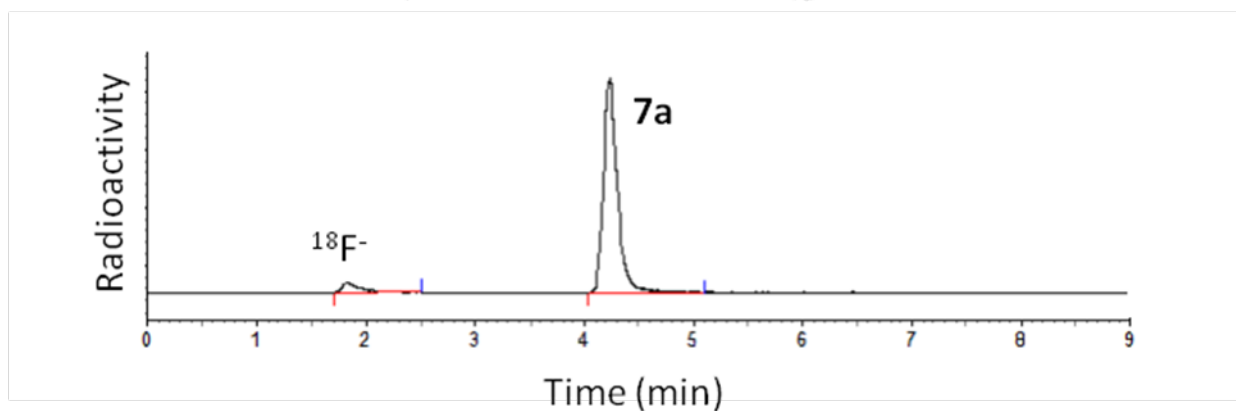
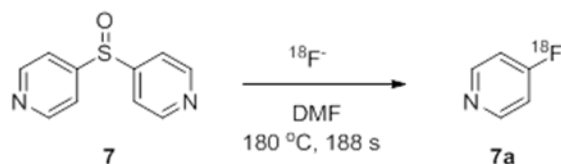


Compound 20

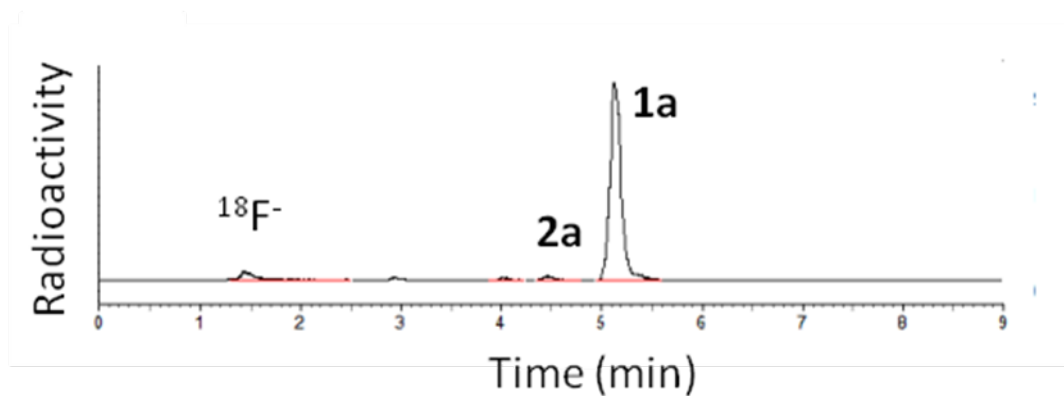
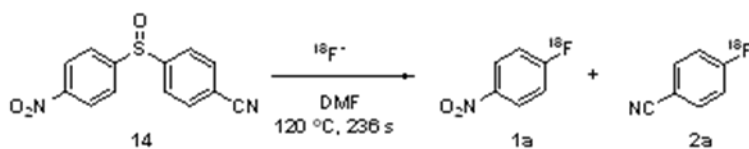


Appendix 2. Examples of radio-HPLC chromatograms from the analyses of quenched reaction mixtures from the radiofluorinations of diaryl sulfoxides.

Radiofluorination of **7**



Radiofluorination of **14**



Radiofluorination of **15**

