

SUPPLEMENTARY INFORMATION

Synthesis of Aryl α,α -Difluoroethyl Thioethers a new Structure Motif in Organic Chemistry, extending to Aryl α,α -Difluoro Oxyethers

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General Experimental Procedures

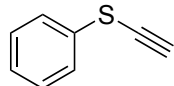
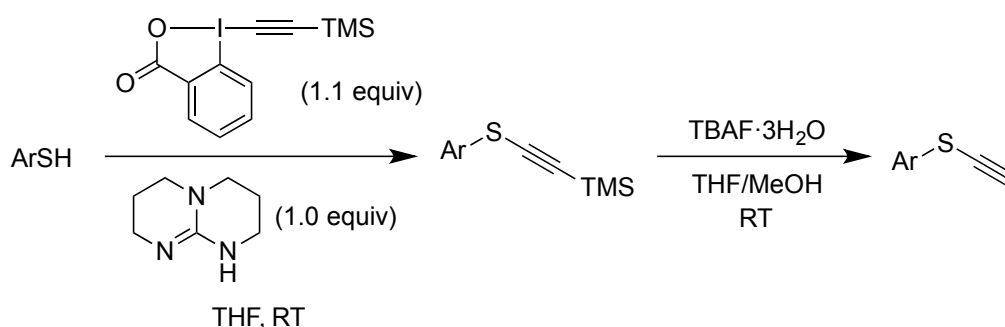
All commercially available reagents were purchased from Alfa Aesar, Fisher Scientific, Fluorochem and Sigma Aldrich, and used without further purification. 1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX) was prepared in accordance with the literature procedures.^[1] CH₂Cl₂ and toluene were obtained from the MBraun SPS-800 Solvent Purification System, by passing the solvent through two drying columns under an argon atmosphere. Reactions involving the use of HF·Py were carried out in Teflon round-bottom flasks.

Thin layer chromatography (TLC) was performed on Merck TLC silica gel 60 F₂₅₄ supported on aluminum seat. Column chromatography was performed on Merck Geduran silica gel 40-63 micron.

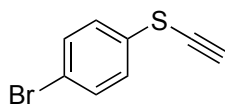
NMR spectra were acquired on Bruker Avance II 400 spectrometer (¹H at 400 MHz, ¹³C at 100 MHz, ¹⁹F at 376 MHz) or Bruker Avance 500 spectrometer (¹H at 500 MHz, ¹³C at 126 MHz, ¹⁹F at 471 MHz). Chemical shift data are reported as δ in units of parts per million relative to residual solvent.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

Preparation of ethynyl(aryl)sulfanes

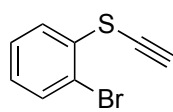


Ethynyl(phenyl)sulfane 1b: A solution of 1,3,5-Triazabicyclo[4.4.0]dec-5-ene (TBD) (0.696 g, 5.00 mmol) and benzenethiol **4b** (0.51 mL, 4.95 mmol) in THF (60 mL) was stirred at room temperature for a few minutes. TMS-EBX (1.90 g, 5.51 mmol) was added and the solution was stirred at room temperature for 5 min. Then, TBAF·3H₂O (0.317 g, 1.00 mmol) and MeOH (20 mL) were added to the reaction mixture and stirred at room temperature for 1 h. After that, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound **1b** (0.574 g, 4.28 mmol, 86% yield) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.46 (m, 2H), 7.35 (m, 2H), 7.25 (t, *J*_{H-H} = 7.2 Hz, 1H), 3.26 (s, 1H). The data were in good agreement with the literature values.^[1]



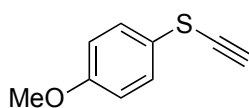
(4-Bromophenyl)(ethynyl)sulfane 1e: According to the procedure described for **1b**, TBD (2.17 g, 15.6 mmol), and 4-bromobenzethiol **4e** (2.95 g, 15.6 mmol) in THF (200 mL) were stirred at room temperature. After few minutes TMS-EBX (5.92 g, 17.2 mmol) was added. Purification using silica gel column chromatography (petroleum ether) gave a colorless solid, to which THF (24 mL), MeOH (8 mL) and TBAF·3H₂O (0.500 g, 1.58 mmol) were added. The residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound **1e** (3.12 g, 14.6 mmol, 94% yield) as a white solid; M.p. = 35–36 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.47 (d, *J*_{H-H} = 8.8 Hz, 2H), 7.31 (d, *J*_{H-H} = 8.8 Hz, 2H), 3.28 (s, 3H). ¹³C NMR

(126 MHz, CDCl₃, rt): δ 132.5, 130.9, 128.2, 120.8, 87.8, 70.4. HRMS (ESI), calculated for C₈H₅SBr [M⁺] 211.9295; found 211.9290.

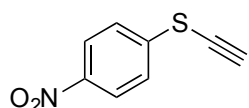


(2-Bromophenyl)ethynyl sulfane 1f: According to the procedure described for **1b**, TMS-EBX (1.89 g, 5.50 mmol) was added to a solution of TBD (0.697 g, 5.00 mmol), and 2-bromobenzenethiol (0.978 g, 5.17 mmol) THF (60 mL). Purification using silica gel column chromatography (petroleum ether) gave ((2-bromophenyl)thio)ethynyl)trimethylsilane as a colorless oil (1.46 g, 5.11 mmol, 99% yield). ¹H NMR (400 MHz, CDCl₃, rt): δ 7.68 (dd, $J_{\text{H-H}} = 8.0, 1.6$ Hz, 1H), 7.49 (dd, $J_{\text{H-H}} = 8.0, 1.2$ Hz, 1H), 7.37 (m, 1H), 7.09 (m, 1H), 0.27 (s, 9H). Analysis conform to the literature.^[3]

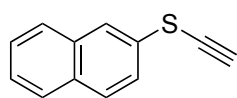
TBAF·3H₂O (0.129 g, 0.408 mmol) was added to a solution ((2-bromophenyl)thio)ethynyl)trimethylsilane (1.17 g, 4.10 mmol), THF (6 mL), MeOH (2 mL). Purification by silica gel column chromatography (petroleum ether) afforded the title compound **1f** (0.796 g, 3.74 mmol, 91% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.73 (dd, $J_{\text{H-H}} = 8.0, 1.2$ Hz, 1H), 7.51 (dd, $J_{\text{H-H}} = 8.0, 1.2$ Hz, 1H), 7.37 (ddd, $J_{\text{H-H}} = 8.0, 8.0, 1.2$ Hz, 1H), 7.11 (ddd, $J_{\text{H-H}} = 8.0, 7.6, 1.2$ Hz, 1H), 3.39 (s, 1H). ¹³C NMR (126 MHz, CDCl₃, rt): δ 133.5, 132.9, 128.4, 127.8, 127.3, 119.9, 89.0, 70.6. HRMS (ESI), calculated for C₈H₅BrS [M+H]⁺ 212.9375; found 212.9379.



Ethynyl(4-methoxyphenyl)sulfane 1g: According to the procedure described for **1b**, TMS-EBX (1.90 g, 5.51 mmol) was added to a solution of TBD (0.696 g, 5.00 mmol), and 4-methoxybenzenethiol **4g** (0.62 mL, 5.0 mmol), in THF (60 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 19/1) gave a colorless oil which was reacted with TBAF·3H₂O (0.115 g, 0.363 mmol) in THF (6 mL), MeOH (2 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 29/1 → 19/1) afforded the title compound **1g** (0.591 g, 3.60 mmol, 72% yield) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.40 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 6.90 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 3.80 (s, 3H), 3.13 (s, 1H). ¹³C NMR (101 MHz, CDCl₃, rt): δ 159.4, 129.7, 121.7, 115.2, 85.2, 72.8, 55.5. HRMS (EI), calculated for C₉H₈OS [M]⁺ 164.0296; 164.0295.

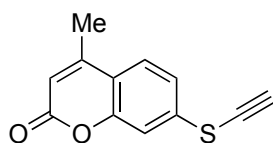


Ethynyl(4-nitrophenyl)sulfane 1j: According to the procedure described for **1b**, TMS-EBX (1.90 g, 5.51 mmol) was reacted with 4-nitrobenzenethiol **4j** (0.778 g, 5.01 mmol), TBD (0.694 g, 4.98 mmol) in THF (60 mL). Purification by silica gel column chromatography (petroleum ether/Et₂O = 19/1) gave white solid which was treated with TBAF·3H₂O (66 mg, 0.21 mmol) in THF (3 mL), MeOH (1 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 19/1) gave the title compound **1j** (0.210 g, 1.17 mmol, 23% yield) as a white solid; M.p. = 78–79 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 8.21 (d, $J_{\text{H-H}} = 7.2$ Hz, 2H), 7.58 (d, $J_{\text{H-H}} = 7.2$ Hz, 2H), 3.44 (s, 1H). ¹³C NMR (126 MHz, CDCl₃, rt): δ 146.6, 141.5, 126.1, 124.4, 90.0, 68.4. HRMS (ESI), calculated for C₈H₅NO₂S [M]⁺ 179.0039; 179.0037.

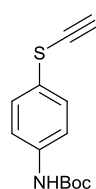


Ethynyl(naphthalen-2-yl)sulfane 1h: According to the procedure described for **1b**, TMS-EBX (1.90 g, 5.51 mmol) was added to TBD (0.694 g, 4.98 mmol), and naphthalene-2-thiol **4h** (0.802 g, 5.00 mmol) in THF (60 mL). TBAF·3H₂O (0.330 g, 1.05 mmol) and MeOH (20 mL) were added to the reaction mixture. Purification using silica gel column chromatography (petroleum ether) afforded the title compound **1h** (0.476 g, 2.58 mmol, 52% yield) as a white solid. ¹H

NMR (400 MHz, CDCl₃, rt): δ 7.92 (d, $J_{\text{H-H}} = 1.6$ Hz, 1H), 7.83–7.77 (m, 3H), 7.53–7.45 (m, 3H), 3.32 (s, 1H). The data were in good agreement with the literature values.^[4]

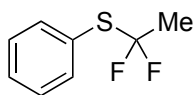
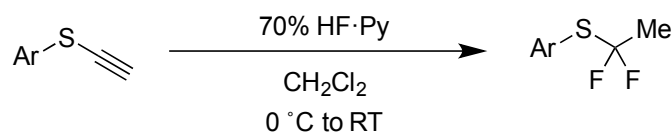


7-(Ethynylthio)-4-methyl-2H-chromen-2-one 1i: According to the procedure described for **1b**, TMS-EBX (1.89 g, 5.50 mmol) was added to a solution of TBD (0.694 g, 4.98 mmol), and 7-mercapto-4-methylcoumarin **4i** (0.961 g, 5.00 mmol) in THF (60 mL). Purification using silica gel column chromatography (petroleum ether/Et₂O = 3/1→1/1) gave white solid that was treated with TBAF·3H₂O (0.153 g, 0.486 mmol) in THF (7.5 mL), MeOH (2.5 mL). Purification using silica gel column chromatography (petroleum ether/EtOAc = 4/1→3/1) afforded the title compound **1i** (0.931 g, 4.31 mmol, 86% yield) as a white solid. M.p. = 140–141 °C (decomposition); **¹H NMR** (400 MHz, CDCl₃, rt): δ 7.55 (d, $J_{\text{H-H}} = 8.4$ Hz, 1H), 7.46 (d, $J_{\text{H-H}} = 1.6$ Hz, 1H), 7.30 (dd, $J_{\text{H-H}} = 8.4, 2.0$ Hz, 1H), 6.27 (q, $J_{\text{H-H}} = 1.2$ Hz, 1H), 3.42 (s, 1H), 2.43 (d, $J_{\text{H-H}} = 1.2$ Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃, rt): δ 160.4, 154.0, 152.0, 137.4, 125.2, 121.6, 118.6, 114.9, 114.1, 89.5, 68.9, 18.8. HRMS (ESI), calculated for C₁₂H₉O₂S [M+H]⁺ 217.0323; 217.0326.



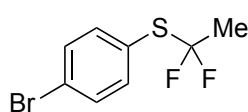
Ethynyl (4-N-tert-butoxycarbonylamino)phenyl)sulfane 1h: The title compound was prepared following the 1 Procedure described for **1b**, using 4-(N-Boc-amino)benzenethiol 4h (1.31 g, 5.83 mmol), TMS-EBX (2.2 g, 6.40 mmol) and tetramethylene guanidine (0.86 mL, 6.97 mmol) in dry THF (20 mL). The crude product was passed through pad of silica gel (petroleum ether:dichloromethane 7:3) to provide a white solid, which was dissolved in THF:MeOH (15:5 mL). A 1M TBAF solution in THF (5.81 mL, 5.83 mmol) was added and the mixture was stirred at room temperature for 30 min. The mixture was poured brine and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layer was dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether:dichloromethane 7:3) to afford the title compound **1h** (0.83 g, 95% yield) as a white solid. M.p. = 106 °C. **¹H NMR** (400 MHz, CDCl₃, rt): δ 7.37 (br s, 4H), 6.49 (br s, H), 3.18 (s, 1H), 1.51 (s, 9H). **¹³C NMR** (100 MHz, CDCl₃): δ 152.5, 137.8, 128.3, 124.5, 119.4, 85.9, 80.9, 71.9, 28.3. HRMS (ESI), calculated for C₁₃H₁₄O₂NS [M-H]⁻ 249.0828; found 248.0743.

Hydrofluorination of ethynyl(aryl)sulfanes

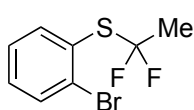


(1,1-Difluoroethyl)(phenyl)sulfane 3b: A 10 mL Teflon round-bottom flask was charged with ethynyl(phenyl)sulfane **1b** (0.136 g, 1.02 mmol) and magnetic bar. The flask was capped with a rubber septum, evacuated, and then flushed three times with argon. Dry CH₂Cl₂ (4 mL), was added and the mixture was cooled to 0 °C. Then 70% HF·Py (104 μ L, 4.0 mmol) was added and the mixture stirred at room temperature for overnight. Then, additional 70% HF·Py (104 μ L, 4.0 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred at room temperature for 16 h. The reaction was quenched by slow addition of sat. NaHCO₃, and the resulting mixture was extracted with CH₂Cl₂ (20 mL x 3). The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane) to afford the title compound **3b** (0.100 g, 0.576 mmol, 57% yield) as a colorless oil. **¹H NMR** (400 MHz, CDCl₃, rt): δ 7.63–7.60 (m, 2H), 7.45–7.36 (m,

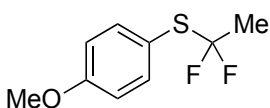
3H), 1.92 (t, $J_{\text{H-F}} = 16.8$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3 , rt): $\delta -66.55$ (q, $J_{\text{F-H}} = 16.5$ Hz, 2F). The data matched those reported in the literature.^[5]



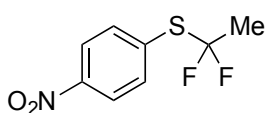
(4-Bromophenyl)(1,1-difluoroethyl)sulfane 3e: According to the procedure described for **3b**, 70% $\text{HF}\cdot\text{Py}$ (104 μL , 4.0 mmol) was reacted with (4-bromophenyl)(ethynyl)sulfane **1e** (0.212 g, 0.995 mmol) in dry CH_2Cl_2 (4 mL). Purification using silica gel column chromatography (petroleum ether) afforded the title compound **3e** (0.182 g, 0.719 mmol, 72% yield including 2% of monofluorinated product) as a colorless oil. ^1H NMR (400 MHz, CDCl_3 , rt): δ 7.52 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 7.46 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 1.93 (t, $J_{\text{H-F}} = 16.8$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3 , rt): $\delta -66.46$ (q, $J_{\text{F-H}} = 16.5$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3 , rt): δ 137.6, 132.4, 128.1 (q, $J_{\text{C-F}} = 277$ Hz), 126.5, 124.8, 26.2 (q, $J_{\text{C-F}} = 25.8$ Hz). HRMS (CI): calculated for $\text{C}_8\text{H}_7\text{BrF}_2\text{S}$ $[\text{M}]^+$ 253.9395, required 253.9399.



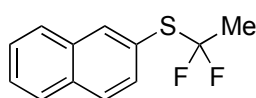
(2-Bromophenyl)(1,1-difluoroethyl)sulfane 3f: According to the procedure described for **3b**, 70% $\text{HF}\cdot\text{Py}$ (104 μL , 4.0 mmol) was reacted with (2-bromophenyl)(ethynyl)sulfane **1f** (0.216 g, 1.02 mmol) in dry CH_2Cl_2 (4 mL). Purification using silica gel column chromatography (petroleum ether) afforded the title compound **3f** (0.170 g, 0.672 mmol, 66% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3 , rt): δ 7.77 (dd, $J_{\text{H-H}} = 8.0, 1.6$ Hz, 1H), 7.69 (dd, $J_{\text{H-H}} = 8.0, 1.6$ Hz, 1H), 7.33 (ddd, $J_{\text{H-H}} = 7.6, 7.6, 1.6$ Hz, 1H), 7.25 (ddd, $J_{\text{H-H}} = 8.0, 7.6, 1.6$ Hz, 1H), 1.97 (t, $J_{\text{H-F}} = 16.8$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3 , rt): $\delta -65.96$ (q, $J_{\text{F-H}} = 16.9$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3 , rt): δ 137.8, 133.8, 131.2, 130.2, 129.4, 128.6 (q, $J_{\text{C-F}} = 278$ Hz), 128.0, 26.4 (q, $J_{\text{C-F}} = 25.8$ Hz). HRMS (ESI), calculated for $\text{C}_8\text{H}_5\text{NO}_2\text{S}$ $[\text{M}]^+$ required 253.9399; found 253.9404.



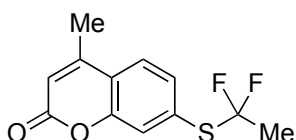
(1,1-Difluoroethyl)(4-methoxyphenyl)sulfane 3g: According to the procedure described for **3b**, 70% $\text{HF}\cdot\text{Py}$ (104 μL , 4.0 mmol) was reacted with ethynyl(4-methoxyphenyl)sulfane **1g** (0.164 g, 1.00 mmol) in dry CH_2Cl_2 (4 mL). Purification using silica gel column chromatography (petroleum ether/ $\text{Et}_2\text{O} = 100/0 \rightarrow 49/1$) afforded the title compound **3g** (0.104 g, 0.509 mmol, 51% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3 , rt): δ 7.53 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 6.90 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 3.83 (s, 3H), 1.89 (t, $J_{\text{H-F}} = 16.8$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3 , rt): $\delta -67.52$ (q, $J_{\text{F-H}} = 16.5$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3 , rt): δ 161.2, 138.2, 128.4 (t, $J_{\text{C-F}} = 275$ Hz), 118.1, 114.7, 55.5, 26.0 (t, $J_{\text{C-F}} = 26.3$ Hz). HRMS (CI): calculated for $\text{C}_9\text{H}_{11}\text{F}_2\text{OS}$ $[\text{M}+\text{H}]^+$ required 205.0499, found 205.0494.



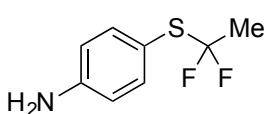
(1,1-Difluoroethyl)(4-nitrophenyl)sulfane 3j: According to the procedure described for **3b**, 70% $\text{HF}\cdot\text{Py}$ (416 μL , 16.0 mmol) was reacted with ethynyl(4-nitrophenyl)sulfane **1j** (0.179 g, 0.997 mmol) in dry CH_2Cl_2 (4 mL) in dry CH_2Cl_2 (4 mL). Purification using silica gel column chromatography (petroleum ether/ $\text{Et}_2\text{O} = 29/1$) afforded the title compound **3j** (0.185 g, 0.843 mmol, 85% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3 , rt): δ 8.22 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 7.76 (d, $J_{\text{H-H}} = 8.8$ Hz, 2H), 2.00 (t, $J_{\text{H-F}} = 16.4$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3 , rt): $\delta -65.29$ (q, $J_{\text{F-H}} = 16.5$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3 , rt): δ 148.4, 136.3, 135.3, 128.1 (t, $J_{\text{C-F}} = 278$ Hz), 124.0, 26.4 (t, $J_{\text{C-F}} = 25.5$ Hz). HRMS (EI), calculated for $\text{C}_8\text{H}_7\text{NO}_2\text{F}_2\text{S}$ $[\text{M}]^+$ 220.0246; found 220.0247.



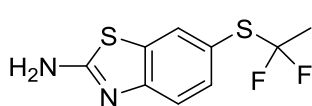
(1,1-Difluoroethyl)(naphthalen-2-yl)sulfane 3h: According to the procedure described for **3b**, 70% HF·Py (104 μ L, 4.0 mmol) was reacted with ethynyl(naphthalen-2-yl)sulfane **1h** (0.185 g, 1.00 mmol) in dry CH_2Cl_2 (4 mL). Purification using silica gel column chromatography (petroleum ether) afforded the title compound **3h** (0.109 g, 0.486 mmol, 49% yield) as a colorless oil. **$^1\text{H NMR}$** (400 MHz, CDCl_3 , rt): δ 8.14 (d, $J_{\text{H-H}} = 0.8$ Hz, 1H), 7.87–7.84 (m, 3H), 7.66 (dd, $J_{\text{H-H}} = 8.4$, 1.6 Hz, 1H), 7.57–7.51 (m, 2H), 1.96 (t, $J_{\text{H-F}} = 16.8$ Hz, 3H). **$^{19}\text{F NMR}$** (376 MHz, CDCl_3 , rt): δ –66.18 (q, $J_{\text{F-H}} = 16.9$ Hz, 2F). **$^{13}\text{C NMR}$** (126 MHz, CDCl_3 , rt): δ 136.3, 133.6, 133.5, 132.3, 128.8, 128.7 (t, $J_{\text{C-F}} = 276$ Hz), 128.2, 127.9, 127.5, 126.8, 124.9, 26.4 (t, $J_{\text{C-F}} = 26.3$ Hz). HRMS (EI), calculated for $\text{C}_{12}\text{H}_{10}\text{F}_2\text{S}$ $[\text{M}]^+$ required 224.0476; found 224.0475.



7-((1,1-Difluoroethyl)thio)-4-methyl-2H-chromen-2-one 3i: According to the procedure described for **3b**, 70% HF·Py (104 μ L, 4.0 mmol) 7-(ethynylthio)-4-methyl-2H-chromen-2-one **1i** (0.217 g, 1.00 g) in dry CH_2Cl_2 (4 mL) at 35 $^\circ\text{C}$. Purification using silica gel column chromatography (petroleum ether/EtOAc = 5/1 \rightarrow 4/1) to afford the title compound **3i** (0.218 g, 0.849 mmol, 85% yield) as a white solid; M.p. = 96–97 $^\circ\text{C}$. **$^1\text{H NMR}$** (400 MHz, CDCl_3 , rt): δ 7.60 (d, $J_{\text{H-H}} = 6.0$ Hz, 1H), 7.58 (s, 1H), 7.51 (dd, $J_{\text{H-H}} = 8.4$, 1.6 Hz, 1H), 6.34 (q, $J_{\text{H-H}} = 1.2$ Hz, 1H), 2.45 (d, $J_{\text{H-H}} = 1.2$ Hz, 3H), 1.98 (t, $J_{\text{H-F}} = 16.4$ Hz, 3H). **$^{19}\text{F NMR}$** (376 MHz, CDCl_3 , rt): δ –65.59 (q, $J_{\text{F-H}} = 16.5$ Hz, 2F). **$^{13}\text{C NMR}$** (126 MHz, CDCl_3 , rt): δ 160.2, 153.2, 151.8, 132.0, 130.7, 128.2 (t, $J_{\text{F-H}} = 278$ Hz), 125.0, 123.4, 120.8, 116.2, 26.3 (t, $J_{\text{F-H}} = 25.7$ Hz), 18.8. HRMS (EI), calculated for $\text{C}_{12}\text{H}_{10}\text{F}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ required 257.0448; found 257.0450.



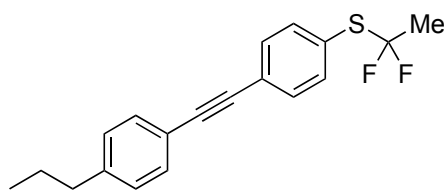
4-((1,1-Difluoroethyl)thio)aniline 3k: A mixture of (1,1-difluoroethyl)(4-nitrophenyl)sulfane **3j** (0.112 g, 0.509 mmol), EtOH (7 mL), concentrated HCl and SnCl_2 (0.756 g, 3.99 mmol) was stirred at 80 $^\circ\text{C}$ for 1 h. After cooling to room temperature, aqueous K_2CO_3 solution was added and the mixture was extracted with EtOAc (50 mL \times 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to afford the title compound **3k** (65.7 mg, 0.347 mmol, 68% yield) as brown oil. **$^1\text{H NMR}$** (500 MHz, CDCl_3 , rt): δ 7.37 (d, $J_{\text{H-H}} = 8.5$ Hz, 2H), 6.65 (d, $J_{\text{H-H}} = 8.5$ Hz, 2H), 3.86 (br s, 2H), 1.87 (t, $J_{\text{H-F}} = 16.5$ Hz, 3H). **$^{19}\text{F NMR}$** (471 MHz, CDCl_3 , rt): δ –67.92 (q, $J_{\text{F-H}} = 16.5$ Hz, 2F). **$^{13}\text{C NMR}$** (126 MHz, CDCl_3 , rt): δ 148.4, 138.1, 128.6 (t, $J_{\text{C-F}} = 275$ Hz), 115.4, 114.8, 25.9 (t, $J_{\text{C-F}} = 26.5$ Hz). HRMS (EI), calculated for $\text{C}_8\text{H}_9\text{F}_2\text{NS}$ $[\text{M}+\text{H}]^+$ required 190.0497; found 190.0496.



6-(1,1-Difluoroethoxy)-2-benzothiazolamine 16b: According to the procedure described for **3b**, 70% HF·Py (1.32 mL, 51.4 mmol) Ethynyl (4-N-tert-butoxycarbonylaminophenyl)sulfane **1k** (1.6 g, 6.42 mmol) in dry CH_2Cl_2 (10 mL) at 0 $^\circ\text{C}$ for 3 hrs. The crude product was passed through pad of silica gel ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 7:3) to give 4-[(1,1-difluoroethyl)thio]aniline **3k** (0.945 g) as a brown oil which was used for next step. 4-[(1,1-Difluoroethyl)thio]aniline **3k** (0.47 g of the crude) and potassium thiocyanate (1.23 g, 12.70 mmol) were placed in a flask and evacuated and flushed with Ar for three times. After addition of glacial acetic acid (10 mL) the mixture was stirred vigorously at room temperature for 15 minutes. Then a solution of bromine (0.109 mL, 2.05 mmol) in acetic acid (0.5 mL) was added and the mixture was stirred at 35 $^\circ\text{C}$ for 24 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL), made alkaline with 35% aqueous NH_4OH and extracted with EtOAc (100 mL \times 3). The combined organic layers were dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column

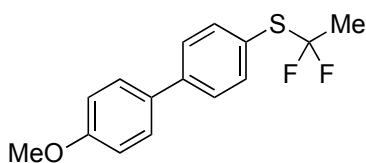
chromatography (CH₂Cl₂/EtOAc 8:2 to 7:3) to afford the title compound **16b** (0.156 g, 20% yield) as a white solid; M.p. = 152 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.83 (d, *J*_{H-H} = 1.7 Hz, 1H, H-7), 7.53 (d, *J*_{H-H} = 1.7, 8.5 Hz, 1H, H-4), 7.49 (d, *J*_{H-H} = 8.5 Hz, 1H, H-5), 5.74 (br s, 2H), 1.91 (t, *J*_{H-F} = 16.6 Hz, 3H). ¹⁹F NMR (476.5 MHz, CDCl₃): δ -67.1. ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 153.2, 134.5, 132.0, 129.0, 128.3 (t, *J*_{C-F} = 274.9 Hz), 120.0, 119.3, 26.0 (t, *J*_{C-F} = 26.1 Hz). HMRS-ESI calculated for C₉H₈N₂F₂S₂ ([M -1]⁻) required 245.0019; found 245.0016.

Palladium-catalyzed cross-coupling reactions of (4-Bromophenyl)(1,1-difluoroethyl)sulfane

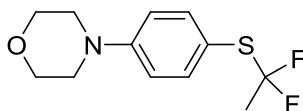


(1,1-Difluoroethyl)(4-((4-propylphenyl)ethynyl)phenyl)sulfane 9: A 25 mL round-bottom flask was charged with CuI (9.7 mg, 51 μmol), PdCl₂(PPh₃)₂ (35.1 mg, 50 μmol), NEt₃ (2 mL) and DMF (2 mL). The flask was degassed under reduced pressure and flushed with Ar for three times. (4-

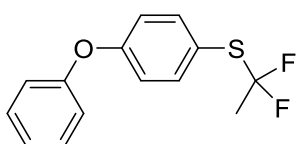
Bromophenyl)(1,1-difluoroethyl)sulfane **3e** (0.254 g, 1.01 mmol) and 1-ethynyl-4-propylbenzene (0.176 g, 1.22 mmol) were added and the mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with Et₂O and washed with sat. NH₄Cl (20 mL x 3). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound **9** (0.206 g, 0.650 mmol, 65% yield) as a colorless solid; M.p. 69–70 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.57 (d, *J*_{H-H} = 8.4 Hz, 2H), 7.51 (d, *J*_{H-H} = 8.4 Hz, 2H), 7.45 (d, *J*_{H-H} = 8.4 Hz, 2H), 7.17 (d, *J*_{H-H} = 8.4 Hz, 2H), 2.60 (t, *J*_{H-H} = 7.6 Hz, 2H), 1.93 (t, *J*_{H-F} = 16.6 Hz, 3H), 1.65 (m, 2H), 0.94 (t, *J*_{H-H} = 7.4 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃, rt): δ -66.24 (q, *J*_{F-H} = 16.5 Hz, 2F). ¹³C NMR (126 MHz, CDCl₃, rt): δ 143.7, 135.9, 132.1, 131.7, 128.7, 128.4 (q, *J*_{C-F} = 276 Hz), 127.4, 125.3, 120.1, 91.8, 88.0, 38.1, 26.3 (q, *J*_{C-F} = 26.0 Hz), 24.5, 13.9. HRMS (EI), calculated for C₁₅H₁₄F₂OS [M]⁺ required 280.0733; found 280.0735.



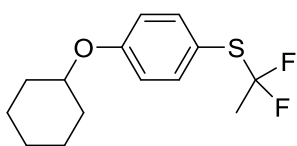
(1,1-Difluoroethyl)(4'-methoxy-[1,1'-biphenyl]-4-yl)sulfane 10: A 50 mL round-bottom flask was degassed under reduced pressure and refilled with Ar. The flask was charged with H₂O (degassed by Ar bubbling, 1 mL), K₂CO₃ (0.416 g, 3.01 mmol), (4-methoxyphenyl)boronic acid (0.183 g, 1.20 mmol), toluene (purified, 4 mL), (4-bromophenyl)(1,1-difluoroethyl)sulfane **3e** (0.255 g, 1.01 mmol) and Pd(PPh₃)₄ (58.7 mg, 51 μmol). The mixture was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted with Et₂O and washed with brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/Et₂O = 49/1) to afford the title compound **10** (0.258 g, 0.919 mmol, 91% yield) as a white solid. M.p. 99–100 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.64 (d, *J*_{H-H} = 8.4 Hz, 2H), 7.57–7.53 (m, 4H), 6.99 (d, *J*_{H-H} = 8.8 Hz, 2H), 3.86 (s, 3H), 1.95 (t, *J*_{H-F} = 16.8 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃, rt): δ -66.56 (q, *J*_{F-H} = 16.5 Hz, 2F). ¹³C NMR (126 MHz, CDCl₃, rt): δ 159.7, 142.4, 136.6, 132.6, 128.5 (t, *J*_{C-F} = 276 Hz), 128.4, 127.4, 125.5, 114.3, 55.5, 26.3 (t, *J*_{C-F} = 26.5 Hz). HRMS (EI), calculated for C₁₉H₁₈F₂S [M]⁺ required 316.1097; found 316.1097.



4-(1,1-Difluoroethylthio)phenylmorpholine 8: An oven-dried flask equipped with a magnetic stirring bar was charged with Pd(dba)₃ (5 mol%, 0.0363 g, 0.0397 mmol), BINAP (0.075 g, 0.119 mmol), 18-crown-6 (0.315 g, 1.19 mmol) and NaOBu-*t* (1.5 eq., 0.115 g, 1.20 mmol). The flask was capped with a rubber septum, evacuated, and then flushed three times with argon. 1-bromo-4-(1,1-difluoroethylthio)benzene **3e** (0.200 g, 0.794 mmol), morpholine (0.104 mL, 1.20 mmol), and degassed toluene (10 mL) were then successively added by syringe. The reaction mixture was then heated at 35 °C until the starting material had been completely consumed as judged by TLC (18 h). The mixture was cooled to room temperature, adsorbed onto silica gel, and then purified by column chromatography (pentane/dichloromethane 9:1 to 8:2) to afford the title compound **8** (0.15 g, 73%) as a pale yellow solid; M.p. = 98 °C. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.48 (d, *J*_{H-H} = 9.0 Hz, 2H, H-3,5), 6.87 (d, *J*_{H-H} = 9.0 Hz, 2H, H-2,6), 3.86 (t, *J*_{H-H} = 4.9 Hz, 2H), 3.21 (t, *J*_{H-H} = 4.9 Hz, 2H), 1.88 (t, *J*_{H-F} = 16.6 Hz, 3H). ¹⁹F NMR (476.5 MHz, CDCl₃): δ -67.6. ¹³C NMR (100 MHz, CDCl₃): δ 152.3, 137.7, 128.4 (t, *J*_{C-F} = 275.0 Hz), 116.1, 115.2, 66.7, 48.3, 25.9 (t, *J*_{C-F} = 26.3 Hz). HMRS-ESI (C₉H₉ON₂F₂S) ([M + 1]⁺) required 231.0398; found: 231.0398.



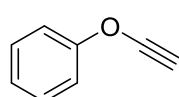
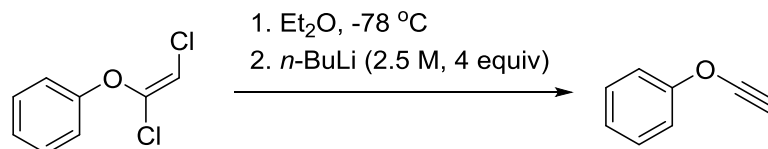
4-Phenoxy-4-[(1,1-difluoroethyl)thio]benzene 7: An oven-dried flask equipped with a magnetic stirring bar was charged with CuI (0.0064 g, 0.0034 mmol), K₃PO₄ (0.289 g, 1.36 mmol), picolinic acid (0.009 g, 0.068 mmol) and phenol (0.095, 1.02 mmol). The flask was capped with a rubber septum, evacuated, and then flushed three times with argon. 1-bromo-4-(1,1-difluoroethylthio)benzene **3e** (0.170 g, 0.672 mmol) and degassed DMSO (5 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (24 h). The mixture was cooled to room temperature, poured into water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic phase was dried with MgSO₄, filtered and solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane/dichloromethane 8:2) to afford the title compound **7** (0.077 g, 43%) as colourless oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.48 (d, *J*_{H-H} = 9.0 Hz, 2H, H-3,5), 6.87 (d, *J*_{H-H} = 9.0 Hz, 2H, H-2,6), 3.86 (t, *J*_{H-H} = 4.9 Hz, 2H), 3.21 (t, *J*_{H-H} = 4.9 Hz, 2H), 1.88 (t, *J*_{H-F} = 16.6 Hz, 3H). ¹⁹F NMR (476.5 MHz, CDCl₃): δ -67.6. ¹³C NMR (100 MHz, CDCl₃): δ 152.3, 137.7, 128.4 (t, *J*_{C-F} = 275 Hz), 116.1, 115.2, 166.7, 48.3, 119.3, 25.9 (t, *J*_{C-F} = 26.3 Hz). HMRS-ESI (C₁₄H₁₂F₂OS) ([M]⁺) 266.0577; found: 266.0577.



Cyclohexoyl-4-[(1,1-difluoroethyl)thio]benzene ether 6: An oven-dried flask equipped with a magnetic stirring bar was charged with CuI (0.0064 g, 0.0034 mmol), K₃PO₄ (0.289 g, 1.36 mmol), picolinic acid (0.009 g, 0.068 mmol) and phenol (0.095, 1.02 mmol). The flask was capped with a rubber septum, evacuated, and then flushed three times with argon. 1-bromo-4-(1,1-difluoroethylthio)benzene **3e** (0.170 g, 0.67 mmol) and degassed DMSO (5 mL) were then successively added by syringe. The reaction mixture was then heated at 100 °C until the starting material had been completely consumed as judged by TLC (24 h). The mixture was cooled to room temperature, poured into water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic phase was dried with MgSO₄, filtered and solvent was removed under reduced pressure. The product was purified by column chromatography (pentane/dichloromethane 8:2) to afford the title compound **6** (0.089 g, 49%) as colourless oil. ¹H NMR (400 MHz, CDCl₃, rt): δ 7.49 (d, *J*_{H-H} = 8.8 Hz, 2H, H-3,5), 6.88 (d, *J*_{H-H} = 8.8 Hz, 2H, H-2,6), 4.26 (m, 1H), 1.95-2.02 (m, 2H), 1.88 (t, *J*_{H-F} = 16.7 Hz, 3H), 1.76-1.61 (m, 2H), 1.26-1.43 (m, 2H). ¹⁹F NMR (476.5 MHz, CDCl₃):

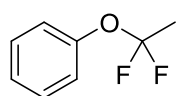
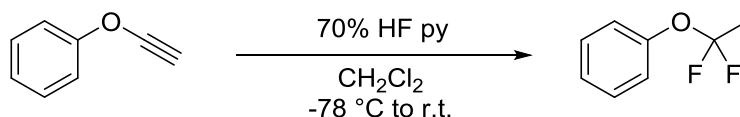
δ -67.6. ^{13}C NMR (100 MHz, CDCl_3): δ 159.5, 138.0, 128.3 (t, $J_{\text{C-F}} = 275.2$ Hz), 128.3 (t, $J_{\text{C-F}} = 275.2$ Hz), 116.3, 75.5, 166.7, 31.7, 25.9 (t, $J_{\text{C-F}} = 26.4$ Hz), 25.6. HMRS-ESI ($\text{C}_{14}\text{H}_{12}\text{F}_2\text{OS}$) ($[\text{M}]^+$)

Preparation of ethynyl(oxy)benzene **11b**⁷

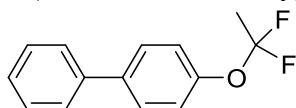


A solution of (*E*)-1-(1,2-dichlorovinyl)oxybenzene⁷ (2.17 g, 11.5 mmol) in Et_2O (120 mL) was cooled to -78 °C and stirred for 30 min. *n*BuLi (18 mL, 46.00 mmol, 2.5 M) was added dropwise and stirred at -78 °C for 1 h. The mixture is left to reach -40 °C over the course of 1 h, and stirred at -40 °C for 2 h. The reaction mixture was quenched by addition of water (100 mL) at cold temperature. The organic phase was separated, and the aqueous phase extracted thrice with Et_2O (3 x 100 mL). The combined organic phases were washed successively with a saturated solution of ammonium chloride and brine, dried over MgSO_4 and evaporated under reduced pressure. No further purification was required. Ethynyl(oxy)benzene **11b** was obtained as a brown oil (1.17 g, 9.90 mmol, 86 % yield). ^1H NMR (500 MHz, CDCl_3 , rt): δ 7.42 – 7.34 (m, 2H), 7.30 (dt, $J = 7.9, 1.1$ Hz, 2H), 7.22 – 7.12 (m, 1H), 2.09 (s, 1H). The data were in good agreement with the literature values.⁷

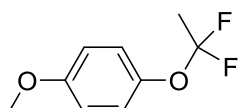
Hydrofluorination of ethynyl(oxy)benzene **12b**



Ethynyl(oxy)benzene (1 g, 8.47 mmol) was added into a 50 mL Teflon round-bottom flask and dissolved into CH_2Cl_2 (5 mL). The solution was cooled to -78 °C and stirred for 15 min. $\text{HF}\cdot\text{py}$ (6 mL, 67.8 mmol) was added to the flask and the reaction mixture was stirred for 18 h and left to reach room temperature. The reaction was quenched by slow addition of the solution into a saturated solution of NaHCO_3 (150 mL). The resulting mixture was extracted thrice with CH_2Cl_2 (3 x 200 mL). The combined organic layers were washed with brine, dried over MgSO_4 and evaporated under reduced pressure. The residue was further purified by washing with CuSO_4 (7%, 25 mL) and extracting with Et_2O (3 x 25 mL), which afforded the product **12b** as a colourless oil. (75% yield). ^1H NMR (500 MHz, CDCl_3 , rt): δ 7.36 – 7.30 (m, 2H), 7.22 – 7.15 (m, 3H), 1.92 (t, $J = 13.3$ Hz, 3H) ^{19}F NMR (471 MHz, CDCl_3 , rt): δ -64.4 (q, $J_{\text{F-H}} = 13.2$ Hz, 2F) ^{13}C NMR (126 MHz, CDCl_3 , rt): δ 129.3, 125.4, 124.0 (t, $J = 261.5$ Hz), 121.8, 22.8 (t, $J = 32$ Hz).

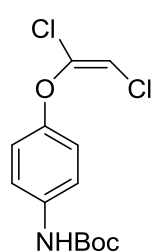
4-(1,1-Difluoroethoxy)biphenyl 12c

4-(Ethynyloxy)-1,1'-biphenyl (1.5 g, 7.73 mmol) was placed in a 25 mL Teflon round-bottom flask which was evacuated and flushed with argon three times. Then dry CH_2Cl_2 (10 mL) was added and the mixture was cooled to 0 °C. 70% HF·Py (0.6 mL, 24 mmol) was added to the solution and stirred at rt for overnight. The mixture was poured into ice-cold sat. NaHCO_3 , and the resulting mixture was extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether) to afford the title compound as a white solid (1.53 g, 85% yield). M.p. = 59 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3 , rt): δ 7.55-7.58 (m, 2H), 7.56 (d, $J_{\text{H-H}} = 8.7$ Hz, 2H), 7.44 (tt, $J_{\text{H-H}} = 7.4, 1.4$ Hz, 1H), 7.35 (d, $J_{\text{H-H}} = 7.4, 1.4$ Hz, 2H), 7.25 (d, $J_{\text{H-H}} = 8.7$ Hz, 2H), 1.97 (t, $J_{\text{H-F}} = 13.3$ Hz, 3H). $^{19}\text{F NMR}$ (376 MHz, CDCl_3 , rt): δ -64.4 (q, $J_{\text{F-H}} = 13.3$ Hz, 2F). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 150.2, 140.4, 138.5, 128.8, 128.0, 127.0, 127.1, 124.4 (t, $J_{\text{C-F}} = 263.3$ Hz), 22.9 (t, $J_{\text{C-F}} = 32.6$ Hz). HRMS (ESI), calculated for $\text{C}_{14}\text{H}_{12}\text{OF}_2$ $[\text{M}]^+$ 234.0856; found 134.0853.

1-Methoxy-4-(1,1-trifluoroethoxy)benzene 12d

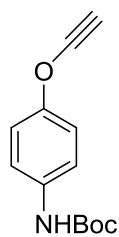
70% HF·Py (3.9 mL, 15.4 mmol) was added to solution of 1-(ethynyloxy)-4-methoxybenzene (4.0 g, 3.0 mmol) in DCM (10 mL) in a Teflon flask at 0 °C and the reaction stirred for 16 hrs. The mixture was poured into ice-cold sat. NaHCO_3 , and the resulting mixture was extracted with CH_2Cl_2 . The organic layer was washed with brine, dried over MgSO_4 , and concentrated under reduced pressure.

Purification silica gel column chromatography (petroleum ether: CH_2Cl_2 10:0 to 8:2) to provide the title compound **12d** (3.21 mg, 76% yield) as a pale yellow oil. $^1\text{H NMR}$ (400 MHz, CDCl_3 , rt): δ 7.11 (d, $J_{\text{H-H}} = 9.0$ Hz, 2H), 6.86 (d, $J_{\text{H-H}} = 9.0$ Hz, 2H), 3.79 (s, 3H), 1.92 (t, $J_{\text{H-F}} = 13.3$ Hz, 3H). $^{19}\text{F NMR}$ (376 MHz, CDCl_3 , rt): δ -64.6 (q, $J_{\text{F-H}} = 13.3$ Hz, 2F). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 157.2, 143.9, 124.2 (t, $J_{\text{C-F}} = 263.1$ Hz), 123.1, 114.3, 55.6, 22.7 (t, $J_{\text{C-F}} = 32.3$ Hz). HRMS (ESI), calculated for $\text{C}_9\text{H}_{10}\text{O}_2\text{F}_2$ $[\text{M}]^+$ 188.0649; found 188.0652.

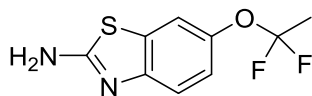


E-1-(1,2-Dichloronyl)oxy-N-tert-butoxycarbonylaniline. A solution of 4-*N*-tert-butoxycarbonylaminophenol (4 g, 19.13 mmol) in dry DMF (5 mL) was added to a suspension of NaH (0.81 g, 20.25 mmol) in dry DMF (20 mL) under Ar and the resulting mixture was stirred at room temperature for 1 h. Afterwards 1,1,2-trichloroethylene (1.73 mL, 19.13 mmol) was slowly added and the resulting mixture was stirred 50 °C for 16h. After completion the mixture was poured into water and the organics were extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL x 4), dried over MgSO_4 and concentrated under reduced pressure. The crude product was subjected to flash column chromatography (petroleum ether: CH_2Cl_2 8:2) to give E-1-(1,2-dichloronyl)oxy-N-tert-butoxycarbonylaniline (4.3 g, 74%) as a white solid. M.p. = $^1\text{H NMR}$ (400 MHz, CDCl_3 , rt): δ 7.35 (d, $J_{\text{H-H}} = 9.0$ Hz, 2H), 7.00 (d, $J_{\text{H-H}} = 9.0$ Hz, 2H), 6.45 (bs, 1H), 5.90 (s, 1H), 1.51 (s, 9H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 152.8, 149.4, 135.4, 121.7, 120.0, 103.1, 28.3. HRMS

(ESI), calculated for $C_9H_{10}O_2F_2$ $[M]^+$ 188.0649; found 188.0652.



tert-Butyl N-(4-ethynoxyphenyl)carbamate: 1.6 M n-Butyllithium (16 mL, 25.5 mmol) was added dropwise to a solution of compound **18** (2.0 g, 6.6 mmol) in anhydrous diethyl ether (30 mL) at -78°C . The reaction mixture was then maintained at -78°C and -40°C for 1 h and 2 h respectively, ethanol (10 mL) was added dropwise. After 10 min, the reaction mixture was then diluted with ether (100 mL) and then washed with saturated solution of ammonium chloride (50 mL). The organic phase was later washed twice with water (100 mL) and then finally with brine (50 mL), dried over MgSO_4 , filtered and concentrated to give brown solid. The solid was purified by column chromatography (petroleum ether: DCM 8:2) to give the title compound **19** (1.38 g, 90%) as a white solid. M.p. = 107°C . $^1\text{H NMR}$ (400 MHz, CDCl_3 , rt): δ 7.35 (d, $J_{\text{H-H}} = 9.0$ Hz, 2H), 7.21 (d, $J_{\text{H-H}} = 9.0$ Hz, 2H), 6.46 (bs, 1H), 2.06 (s, 1H), 1.52 (s, 9H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 152.8, 151.1, 135.4, 119.9, 115.4, 84.8, 33.0, 28.3. HRMS (ESI), calculated for $C_9H_{10}O_2F_2$ $[M]^+$ 188.0649; found 188.0652.



6-(1,1-Difluoroethoxy)-2-benzothiazolamine 16a: According to the procedure described for **16b**, 70% $\text{HF}\cdot\text{Py}$ (1.4 mL, 49 mmol) Ethynyl tert-Butyl N-(4-ethynoxyphenyl)carbamate (2.45 g, 10.5 mmol) in dry CH_2Cl_2 (10 mL) at 0°C for 8 hrs. The crude product was passed through pad of silica gel ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 7:3) to give 4-(1,1-difluoroethoxy)aniline (0.945 g) as a brown oil.

4-(1,1-Difluoroethoxy)aniline (0.22 g, 1.27 mmol) and potassium thiocyanate (0.49 g, 5.08 mmol) were placed in a flask and evacuated and flushed with Ar for three times. After addition of glacial acetic acid (5 mL) the mixture was stirred vigorously at room temperature for 15 minutes. Then a solution of bromine (0.065 mL, 1.27 mmol) in acetic acid (0.5 mL) was added and the mixture was stirred at 35°C for 24 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL), made alkaline with 35% aqueous NH_4OH and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 8:2 to 7:3) to afford the title compound **16a** (0.215 g, 38% yield over 2 steps) as a white solid; M.p. = 149°C . $^1\text{H NMR}$ (400 MHz, CDCl_3 , rt): δ 7.47 (d, $J_{\text{H-H}} = 8.7$ Hz, 1H, H-5), 7.43 (d, $J_{\text{H-H}} = 2.4$ Hz, 1H, H-5), 7.12 (d, $J_{\text{H-H}} = 8.7$ Hz, 1H, H-5), 5.44 (br s, 2H), 1.91 (t, $J_{\text{H-F}} = 13.3$ Hz, 3H). $^{19}\text{F NMR}$ (476.5 MHz, CDCl_3): δ -64.5. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 165.9, 149.8, 145.5, 132.0, 124.4 (t, $J_{\text{C-F}} = 262.1$ Hz), 120.7, 119.3, 114.7, 22.7 (t, $J_{\text{C-F}} = 32.1$ Hz). HMRS-ESI ($C_9H_9ON_2F_2S$) ($[M + 1]^+$) 231.0398; found: 231.0398.

Measurement of lipophilicities (LogP) by reverse-phase HPLC

The evaluation of lipophilicity values was conducted using a Phenomenex Luna C₁₈ 100A (250 mm × 4.60 mm) 5μ column in a Shimadzu Prominence HPLC. A series of reference compounds were injected (5–10 μL of 0.5 mg/mL in AcCN) and their retention times (R_t) plotted against their known LogP values to obtain a reference graph. The retention times of all compounds were measured using 60 : 40 AcCN : water as eluent, with a flow rate of 1 mL/min.

The references compounds have been well-studied and consensus Log P values have been described.

The values used are those recommended by Hansch and Leo (1987, 1995) or Sangster (1989).^{8,9,10}

The characteristic retention times (R_t) of each of the reference molecules was used to calculate their capacity factor (k), using the following equation:

$$\text{Capacity factor (k)} = \frac{\text{Retention Time} - \text{Dead Time of the column}}{\text{Dead Time of the column}}$$

Where the dead time of the column is the time that takes for an unretained molecule (such as the solvent) to pass through the column; in this study that time was 1.965 min.

Table S1

Reference	LogP	Rt 1	Rt 2	Rt 3	Average Rt	Capacity factor (k)	Logk
Phenol	1.50	4.300	4.300	4.295	4.298	1.187	0.075
2-Fluorophenol	1.71	4.201	4.208	4.495	4.301	1.189	0.075
Benzofuran	2.67	8.375	8.375	8.383	8.378	3.263	0.514
Toluene	2.73	10.256	10.274	10.253	10.261	4.222	0.626
o-Xylene	3.12	13.252	13.276	13.579	13.369	5.804	0.764
Naphthalene	3.35	12.733	12.734	12.758	12.742	5.484	0.739
Cumene	3.66	17.059	17.066	17.167	17.097	7.701	0.887
t-butylbenzene	4.11	23.445	23.413	23.259	23.372	10.894	1.037
Butylbenzene	4.26	29.961	30.434	30.449	30.281	14.410	1.159
Anthracene	4.45	24.455	24.461	24.508	24.475	11.455	1.194
Pyrene	4.88	32.699	32.620	32.802	32.707	15.645	1.353

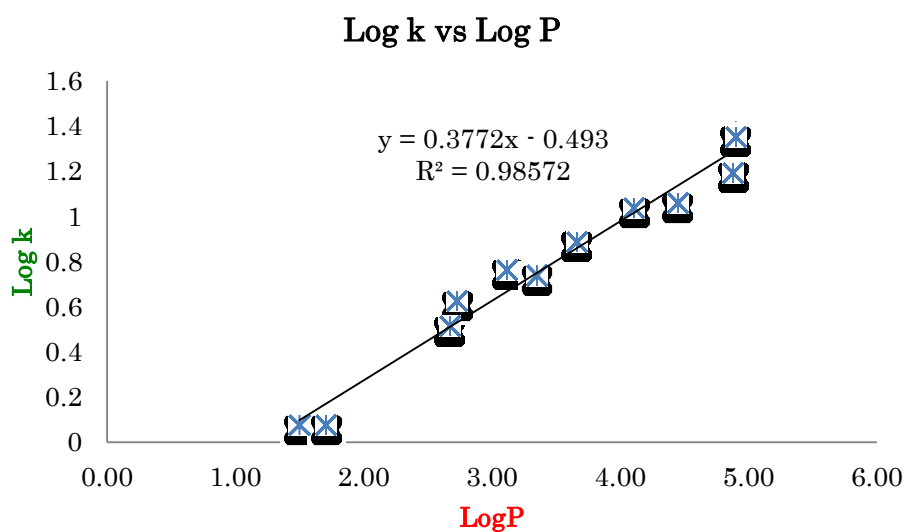
Table S1, collates Log P values of the reference compounds⁸⁻¹⁰

(in red), along with the experimental retention times observed for each molecule, which were measured in triplicates to avoid and detect possible measuring errors. An average retention time was calculated using each of the three values obtained, and this average value was used to calculate the capacity factor for each reference (using the equation described above). Finally, the logarithm of k was calculated (displayed in green).

The logarithm of the capacity factor (Y axis) was represented against the Log P of the reference compounds (X axis), to obtain a regression line and its corresponding equation.

Using this equation, and by measuring the retention time of the studied compounds, the LogP values can be approximated.

The calculated log k (Y-axis) values were plotted against their reported LogP values (X-axis) to obtain a linear regression equation, as represented in **Plot S1**.

**Plot S1**. Regression line obtained for the reference compounds

The equation obtained in **Plot S1** was afterwards used to calculate the LogP values from a series of compounds by substitution of the logarithm of their capacity factor values in the equation above. All the retention times obtained experimentally, the calculated capacity factors and their logarithms are shown in **Table S2**, along with the LogP values (blue), estimated by substitution of the log k values in the regression line equation in **Plot S1**.

Table S2. Estimation of LogP (blue) by using the logarithm of the measured capacity factors (green)

Compound	LogP	Rt 1	Rt 2	Rt 3	Average Rt	Capacity factor (k)	Logk
PhSCF3	3.70	17.672	17.675	17.680	17.676	7.995	0.903
PhSCH2CH3	3.42	14.317	14.284	14.334	14.312	6.283	0.798
PhSCF2CH3	3.38	13.892	13.879	13.876	13.882	6.065	0.783
PhSCH2CF3	3.30	13.050	13.051	13.032	13.044	5.638	0.751
PhSCH3	2.87	9.612	9.609	9.618	9.613	3.892	0.590
PhOCF3	3.35	13.493	13.508	13.491	13.497	5.869	0.769
PhOCH2CH3	2.96	10.421	10.088	10.120	10.210	4.196	0.623
PhOCF2CH3	2.87	9.561	9.568	9.583	9.571	3.871	0.588
PhOCH2CF3	2.83	9.283	9.279	9.479	9.347	3.757	0.575
PhOCH3	2.51	7.552	7.602	7.566	7.573	2.854	0.455

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Computational Details

Full geometry optimisations were performed in the gas phase in the given symmetry at the B3LYP^{1,2}/6-31+G(d,p) level, followed by computation of the harmonic vibrational frequencies at the same level (which were also used to evaluate corrections to free energies at standard temperature and pressure) and single-point energy calculations at the B3LYP-D3³/6-311+G(2d,p) level.

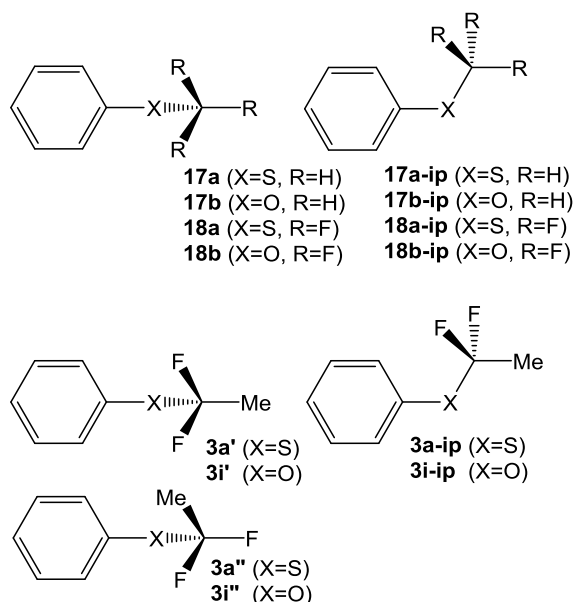


Chart S1

Compounds and rotamers studied computationally are sketched in Chart S1. For validation purposes, phenyl ethers **17** and **18** were included, because for the oxo-species it is known that methyl ethers prefer an in-plane conformation (**17b-ip**), whereas trifluoromethyl ethers are perpendicular (**18b**). This preference is nicely reproduced at the chosen level (e.g. **17b-ip** is more stable than **17b**, and **18b** is more stable than **18b-ip**, Table S1). Similar preferences are obtained for the analogous thio ethers **17a** and **18a**.

Table S1: Relative energies ΔE (in kcal/mol, B3LYP-D3/6-311+G(2d,p) level) and free energies ΔG^a of conformers of compounds **17** and **18** (Chart S1, all in C_s symmetry).^b

Compd	NImag ^c	ΔE	ΔG	Compd	NImag ^c	ΔE	ΔG
17a	(1)	1.0	1.6	17a-ip	(0)	0.0	0.0
18a	(0)	0.0	0.0	18a-ip	(1)	2.6	4.2
17b	(1)	2.9	2.8	17b-ip	(0)	0.0	0.0
18b	(0)	0.0	0.0	18b-ip	(0)	0.6	1.3

^aAt 298K; thermodynamic corrections at B3LYP/6-31+G(d,p) level. ^bRelative to the most stable conformer in each row. ^cIn parentheses: number of imaginary frequencies (0 and 1 denoting minimum and transition state, respectively).

For the target compound **3a** and its oxygen analog **3i** conformational analyses were performed in order to identify the most stable rotamers about the C-O and C-S single bonds. When one F atom in the trifluoromethyl ethers is replaced with a methyl group, the preference for a perpendicular orientation of the resulting difluoroethyl group decreases slightly, but is still very pronounced (compare, e.g. the relative energies of **3a-ip** in Table S2 and **18a-ip** in Table S1). In-plane conformations can only be obtained when the C-Me group is anti to the aryl-X bond (**3a-ip** and **3i-ip**). The corresponding gauche rotamers (which cannot be fixed by imposing symmetry) optimise directly to the corresponding perpendicular gauche forms **3a''** and **3i''**. The perpendicular forms with anti orientation of the C-Me group (**3a'** and **3i'**) are the most stable conformations, but the gauche rotamers are only around a kcal/mol or less higher, so that both variants should exist in an equilibrium. For instance for the thioether **3a**, the computed difference in ΔG , 0.8 kcal/mol, translates into an equilibrium composition of **3a':3a''** of ca. 64:36 at room temperature (from a Boltzmann distribution, taking the double degeneracy of chiral **3a''** into account).

Table S2: Relative energies ΔE (in kcal/mol, B3LYP-D3/6-311+G(2d,p) level) and free energies ΔG^a of conformers of compounds **3a** and **3i** (Chart S1).^b

Compd	Symm ^c	ΔE	ΔG	Compd	Symm ^c	ΔE	ΔG
3a'	C_s (0)	0.0	0.0	3i'	C_s (0)	0.0	0.0
3a''	C_1 (0)	0.1	0.8	3i''	C_1 (0)	1.3	1.0
3a-ip	C_s (1)	2.1	3.9	3i-ip	C_s (0)	0.4	0.8

^aAt 298K; thermodynamic corrections at B3LYP/6-31+G(d,p) level. ^bRelative to the most stable conformer in each column. ^cPoint group (in parentheses: number of imaginary frequencies, 0 and 1 denoting minimum and transition state, respectively).

Plots of the electrostatic potential of the lowest difluoroethylether minima, **3a'** and **3i'**, are shown in Figure S1, which show the expected negative potential at the fluorine sites. The predicted dipole moments for **3a'** and **3i'** are 0.53 D and 1.03 D, respectively at the B3LYP/6-311+G(2d,p) level (3.48 D and 3.27 D for the gauche minima **3a''** and **3i''**, which might therefore become more favourable in a polar solvent).

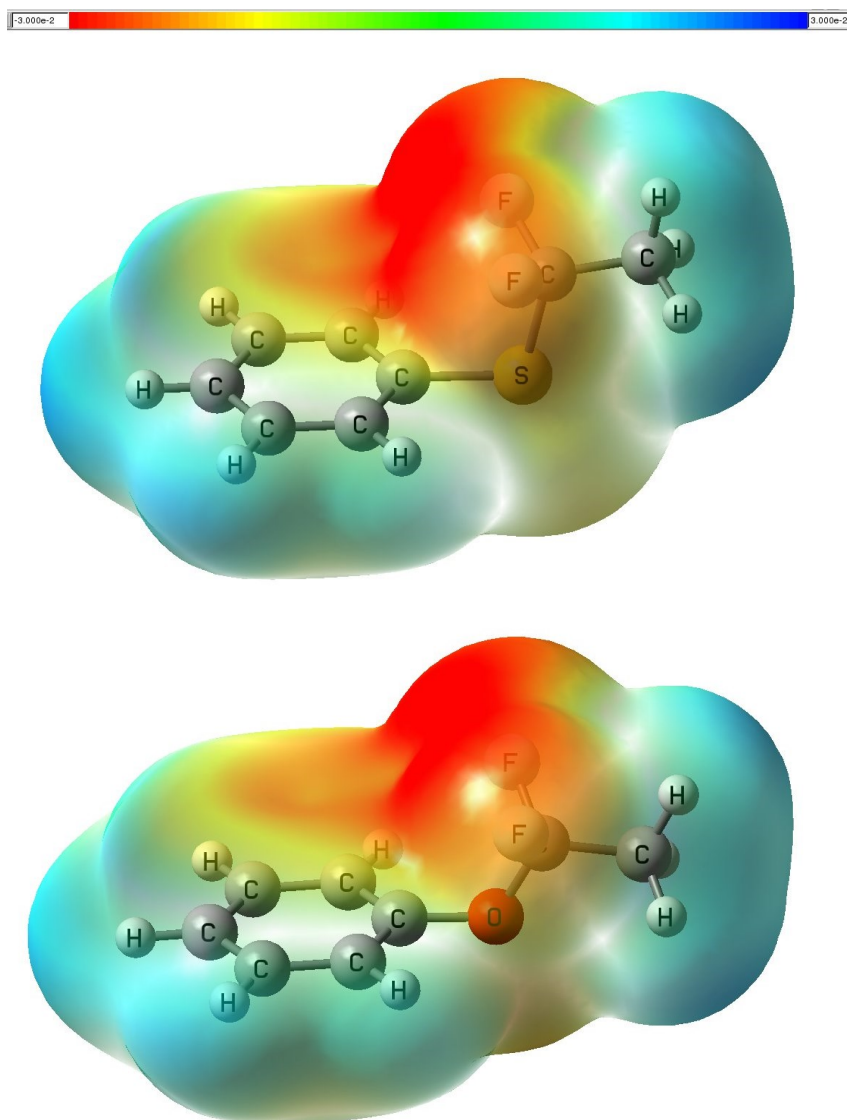
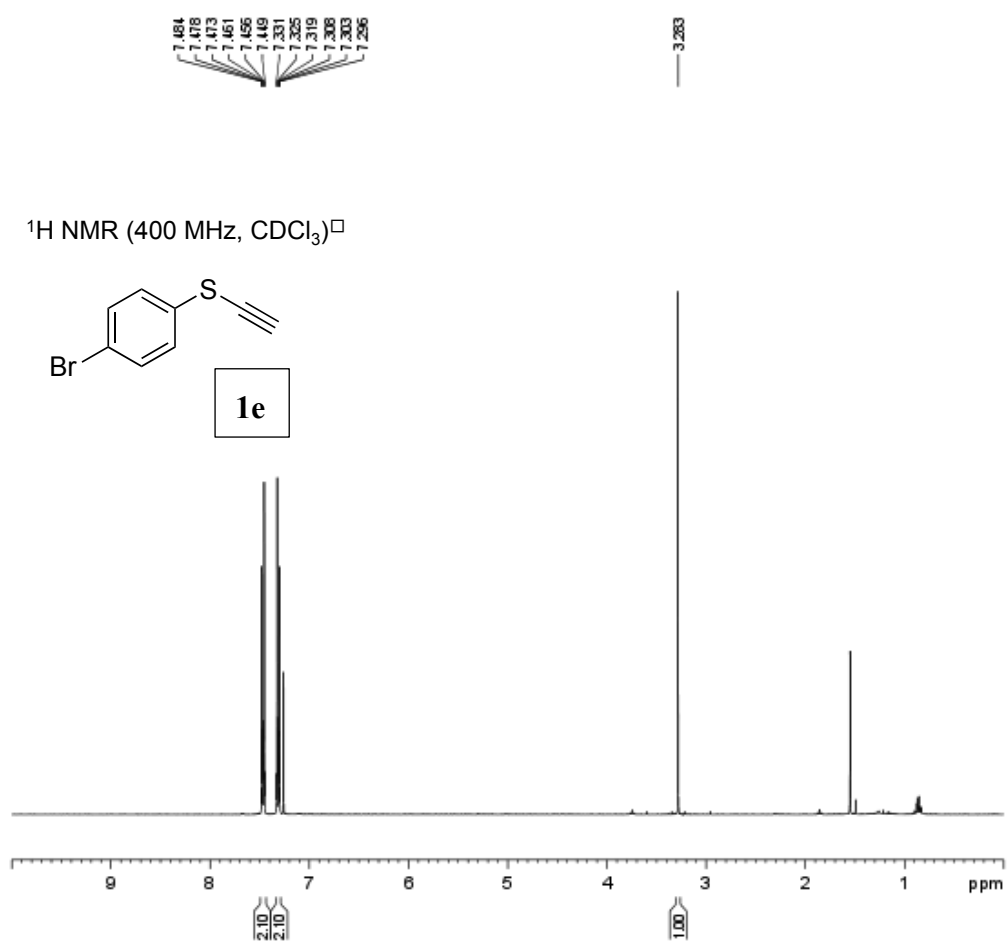


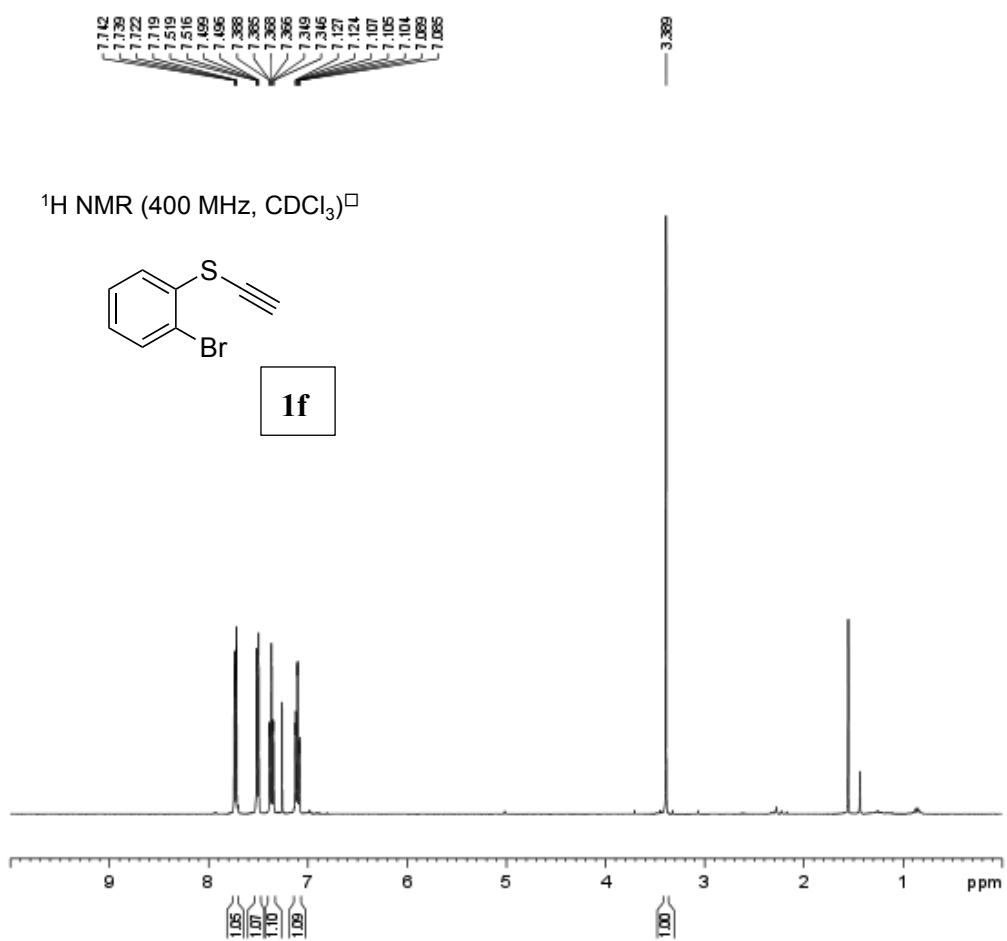
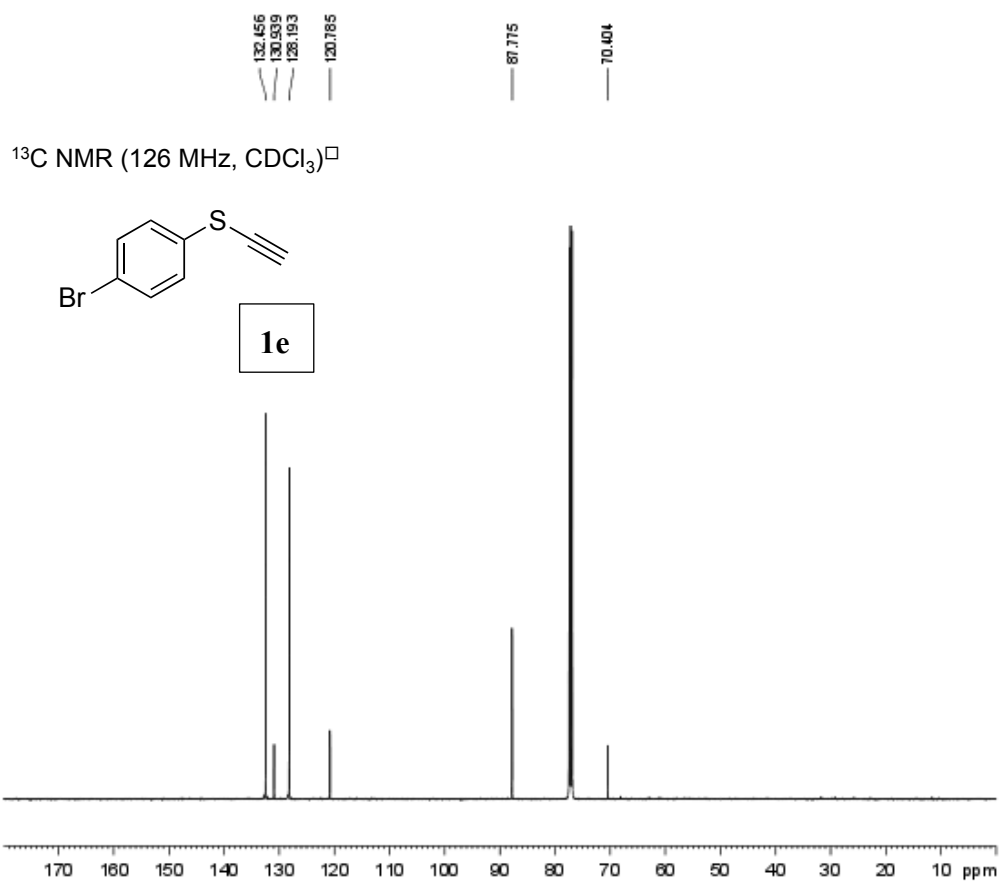
Figure S1: Electrostatic potentials for **3a'** (top) and **3i'** (bottom) at the B3LYP/6-311+G(2d,p) level, plotted on a colour scale from -0.003 a.u. (red) to +0.003 a.u. (blue) and mapped onto an isodensity surface ($\rho = 4 \cdot 10^{-4}$ a.u.).

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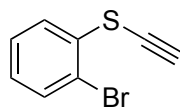
NMR Spectra of synthesised compounds



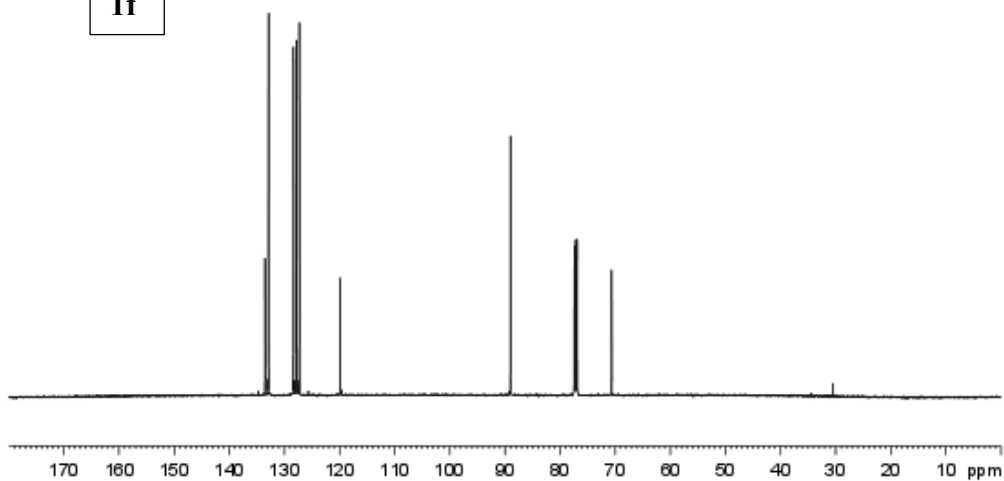




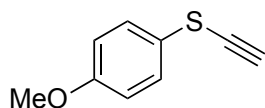
^{13}C NMR (126 MHz, CDCl_3) \square



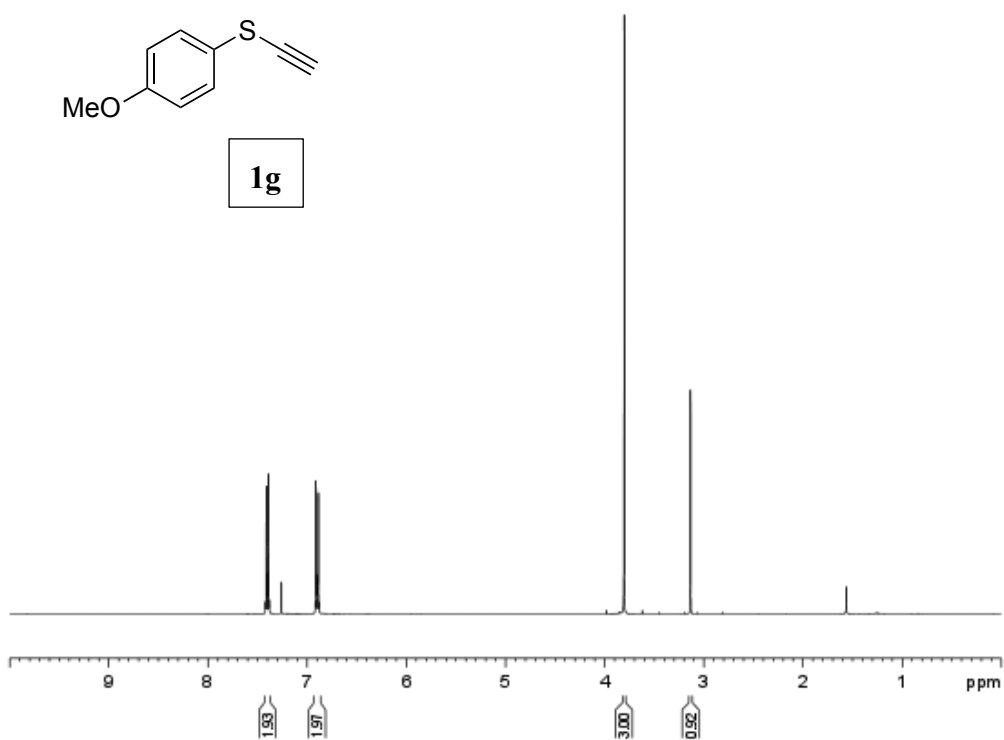
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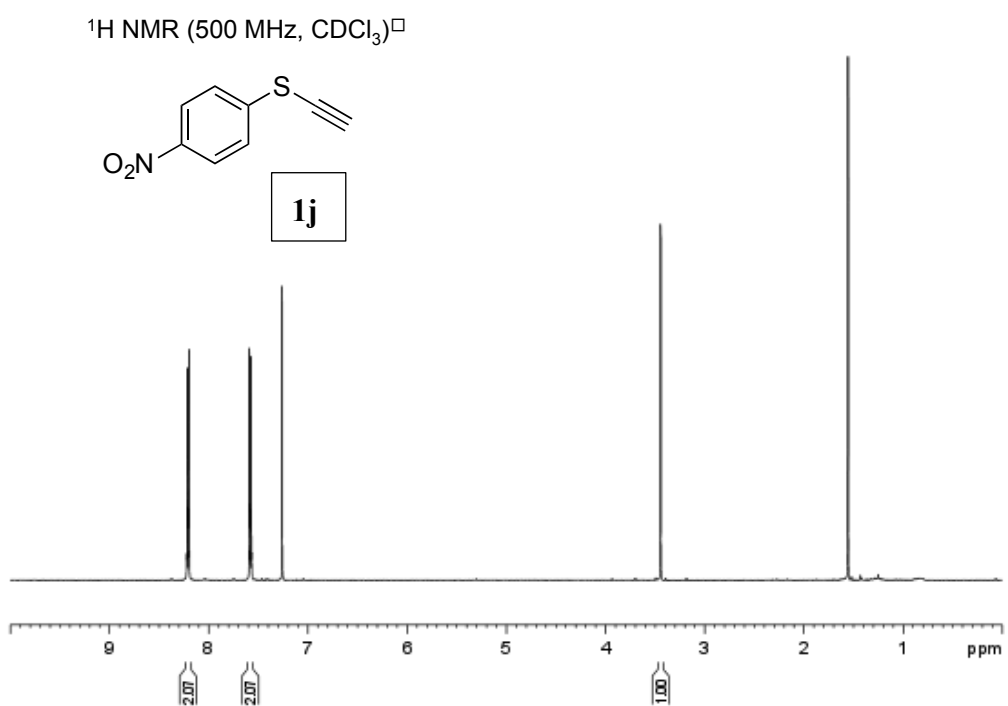
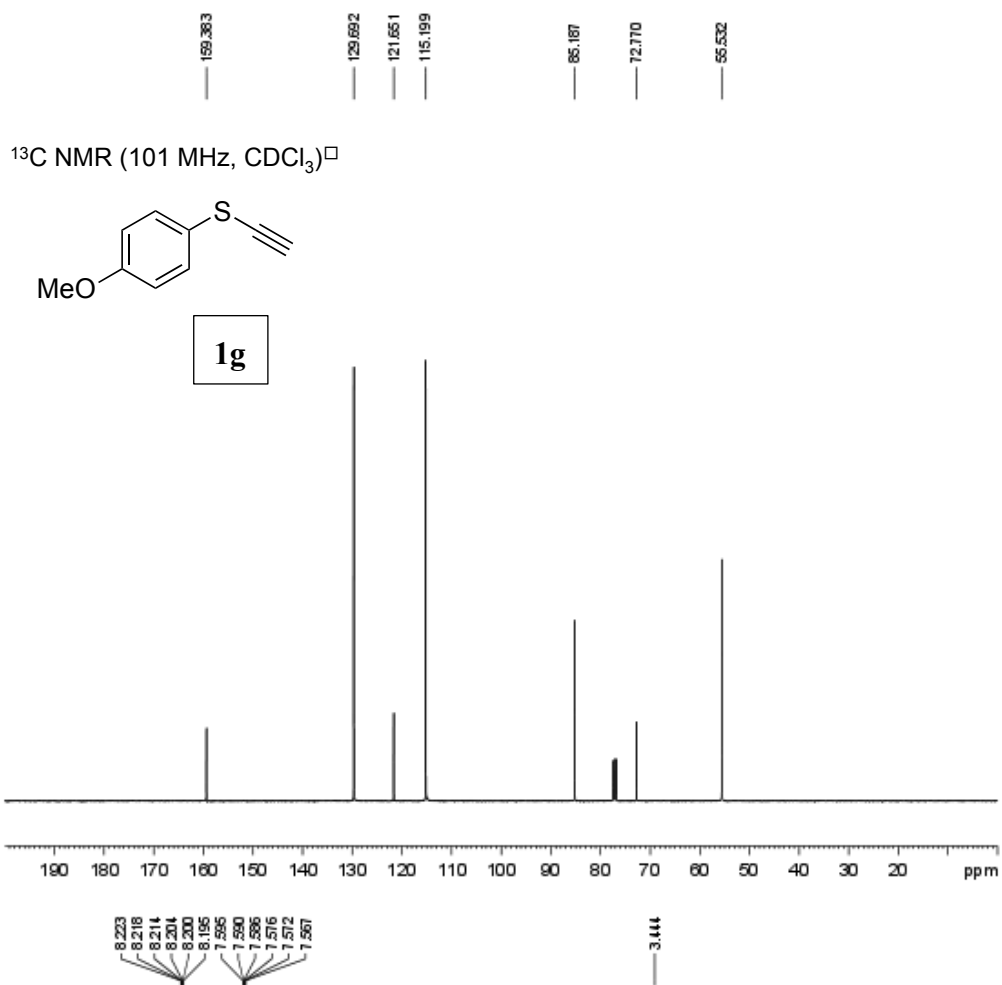


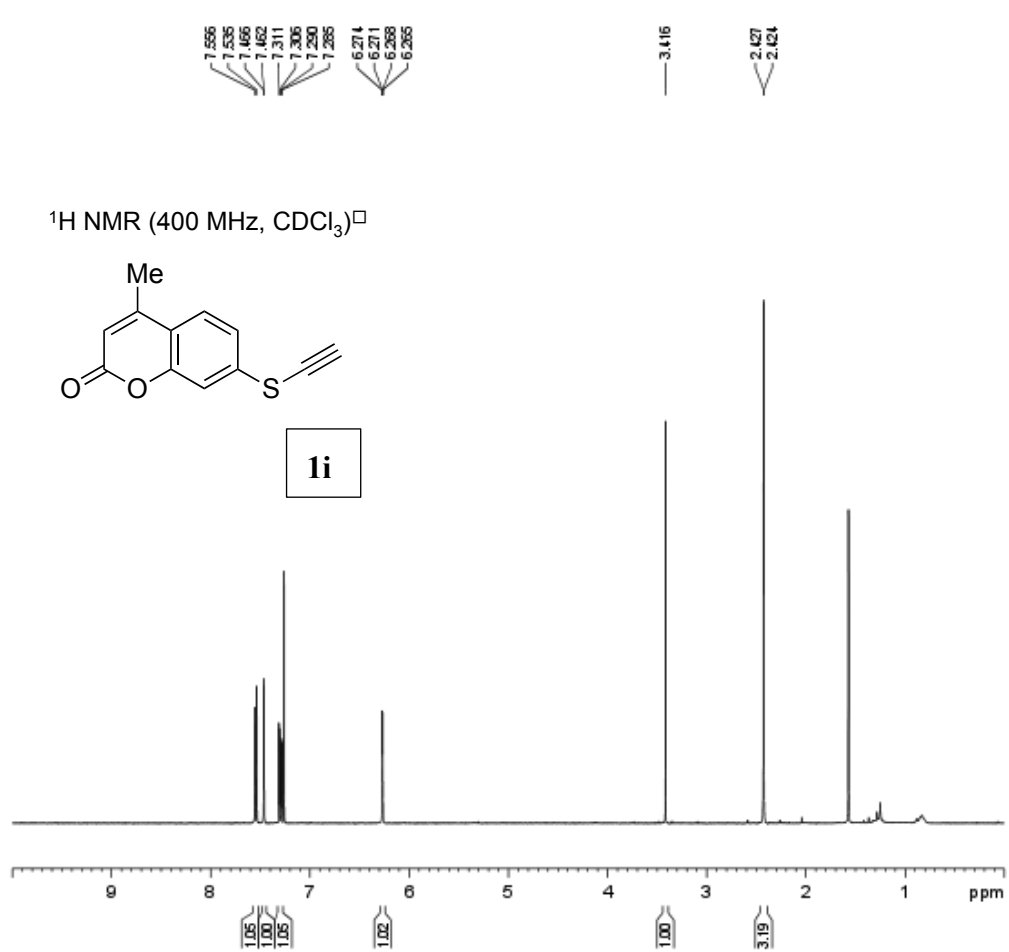
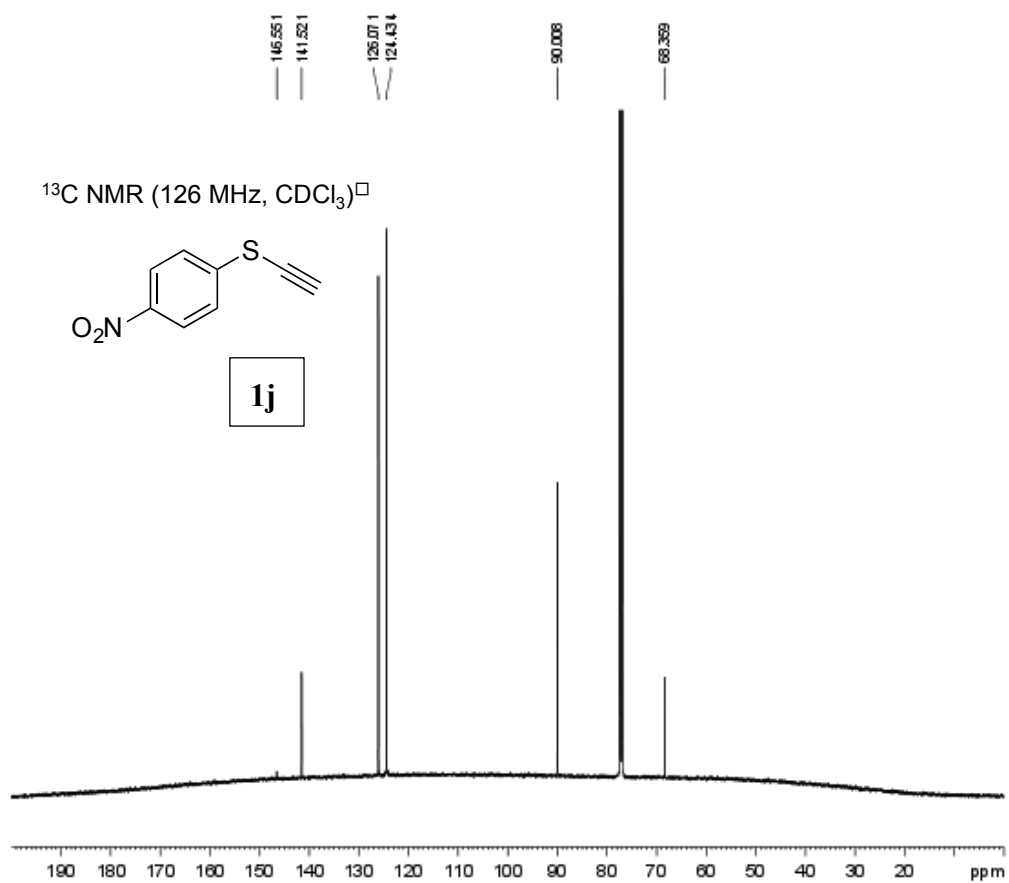
^1H NMR (400 MHz, CDCl_3) \square

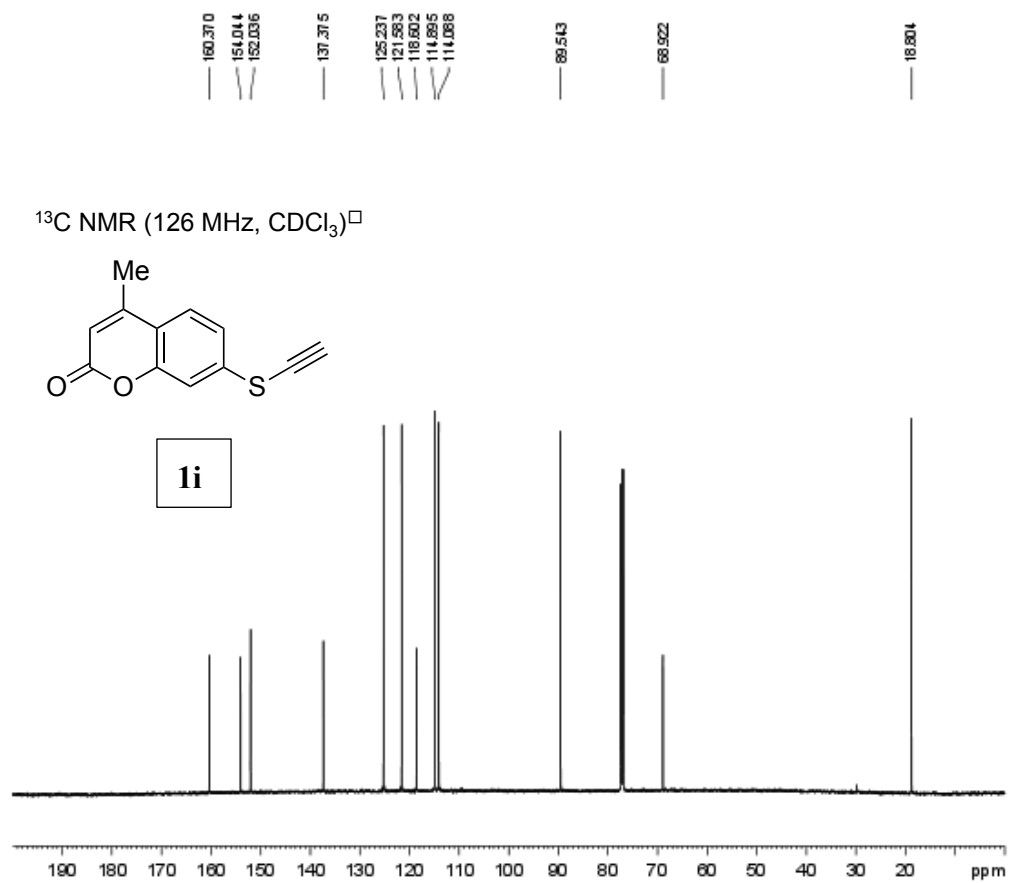


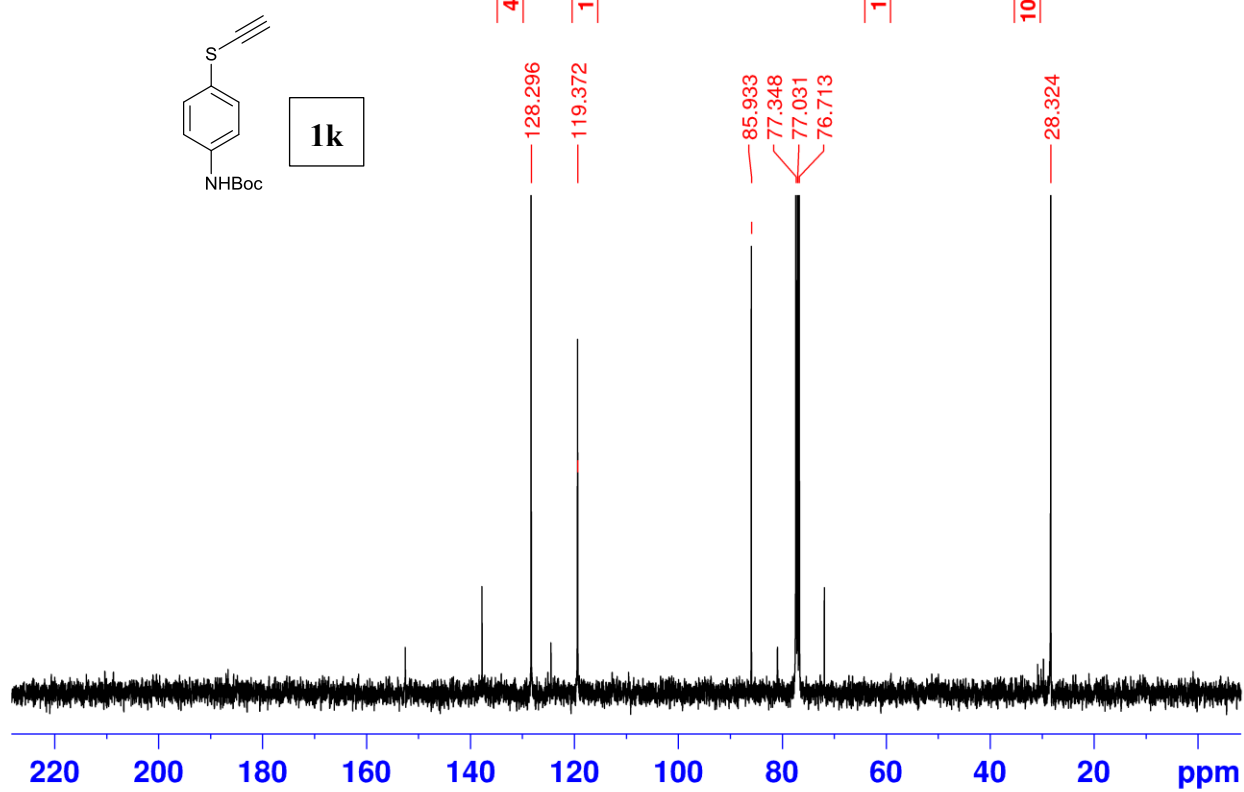
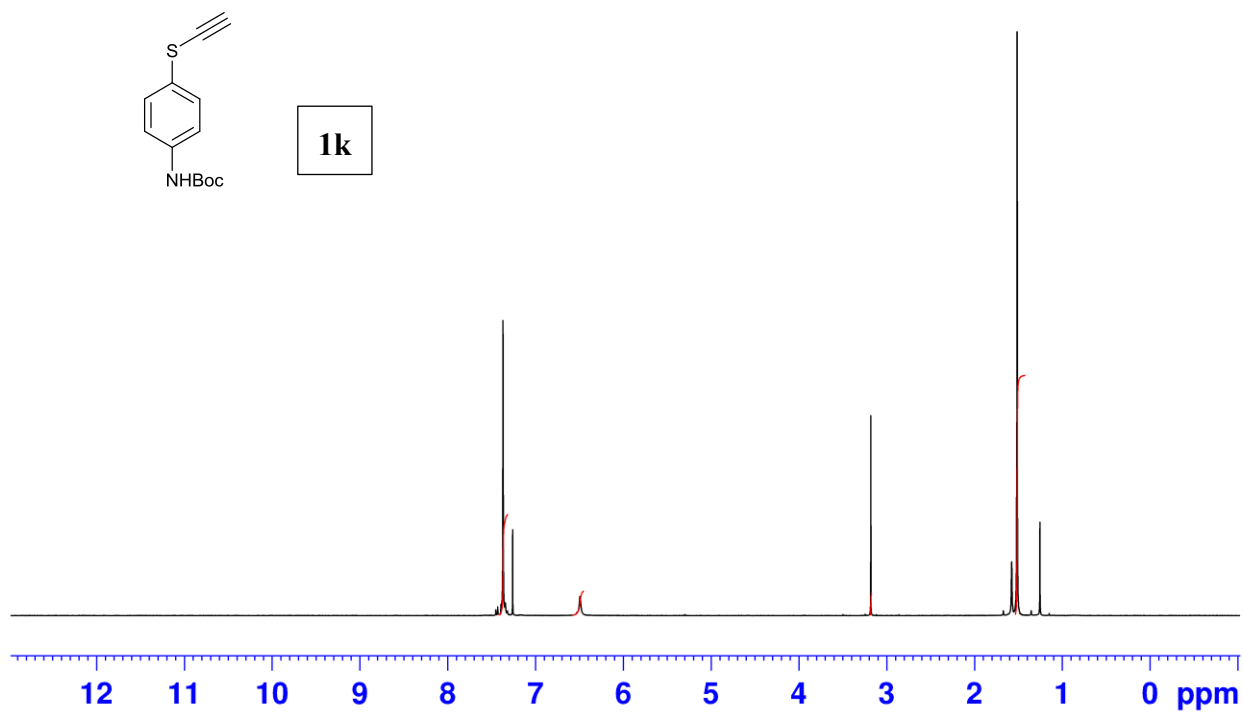
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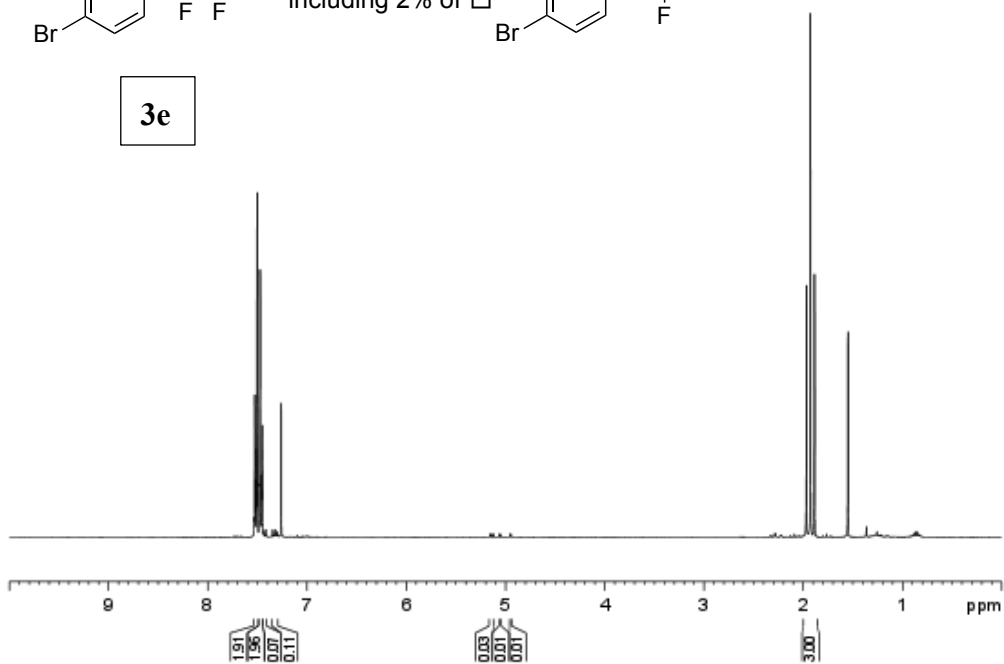
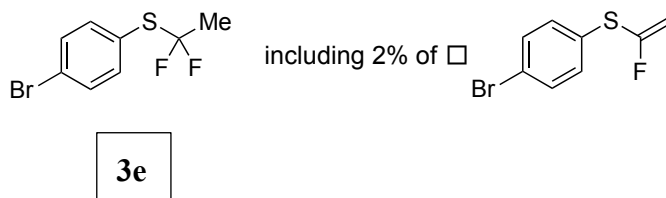


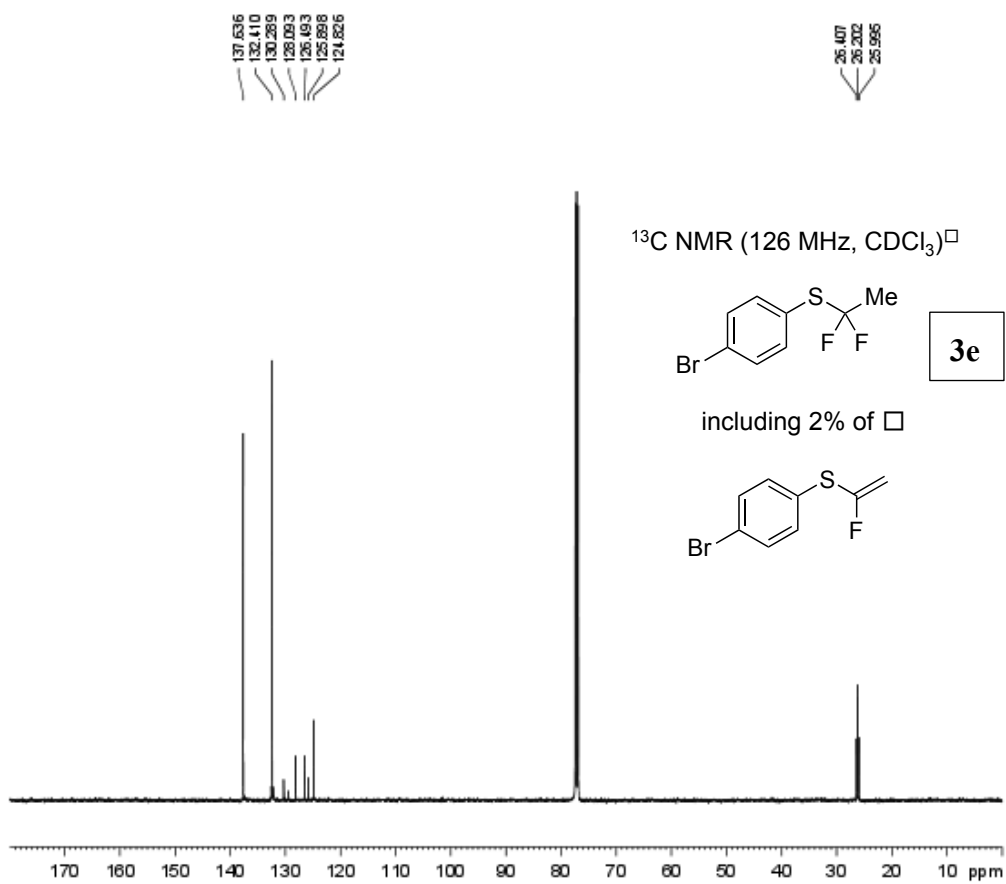
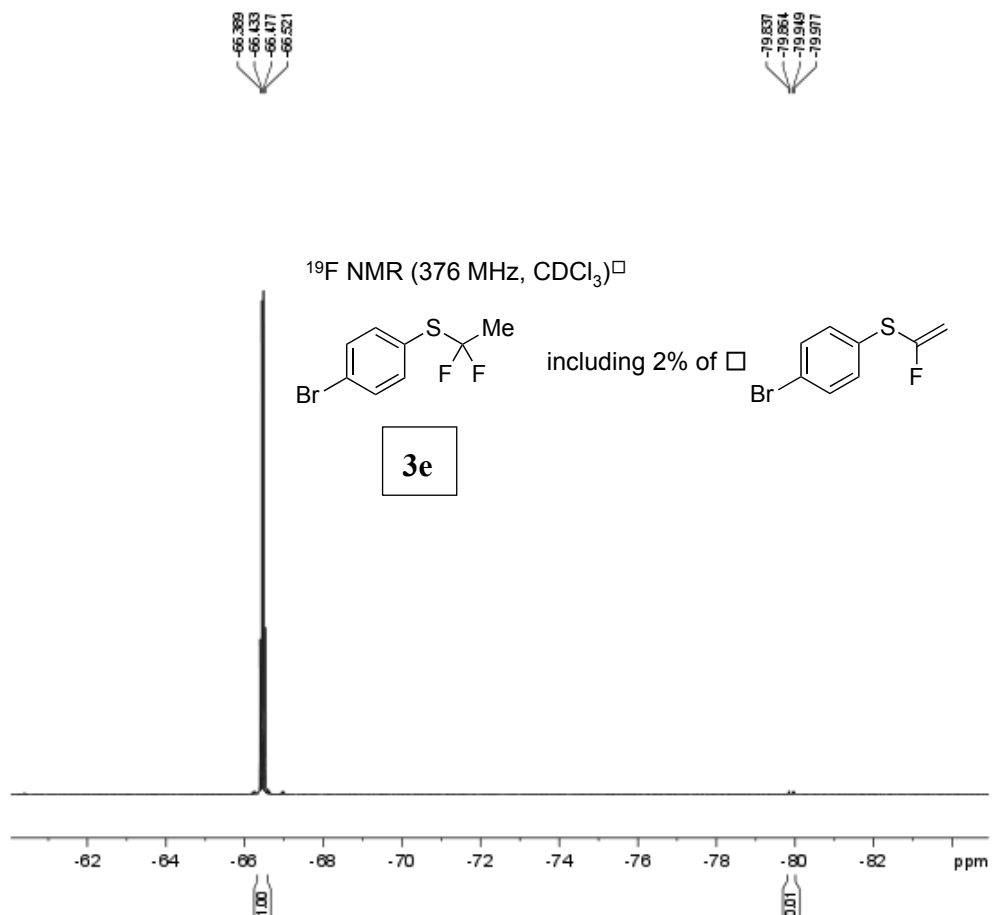


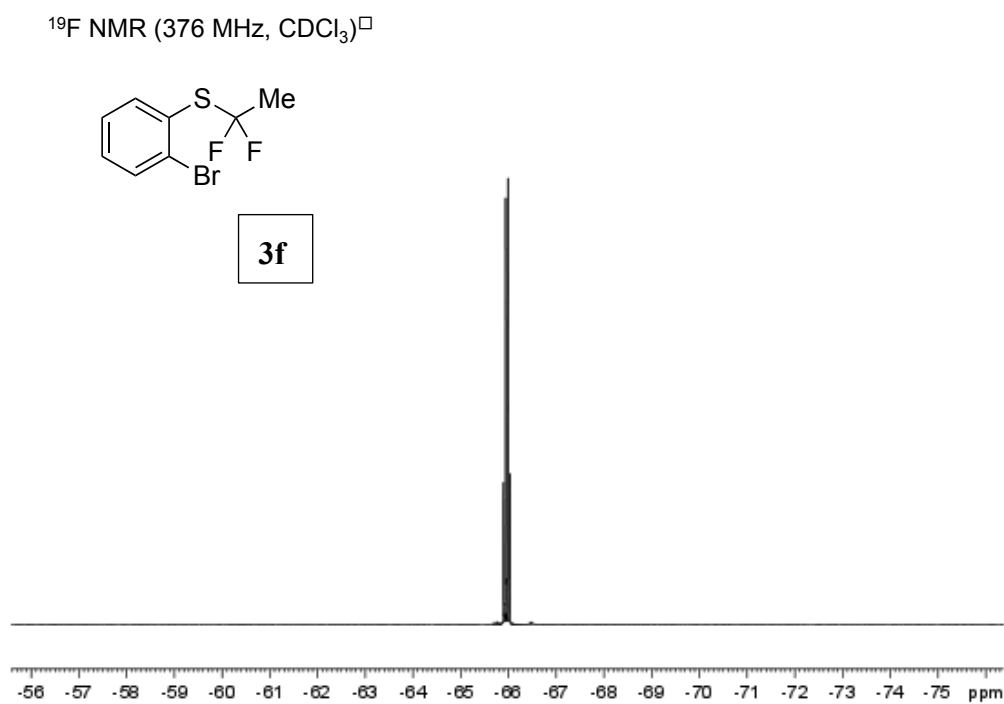
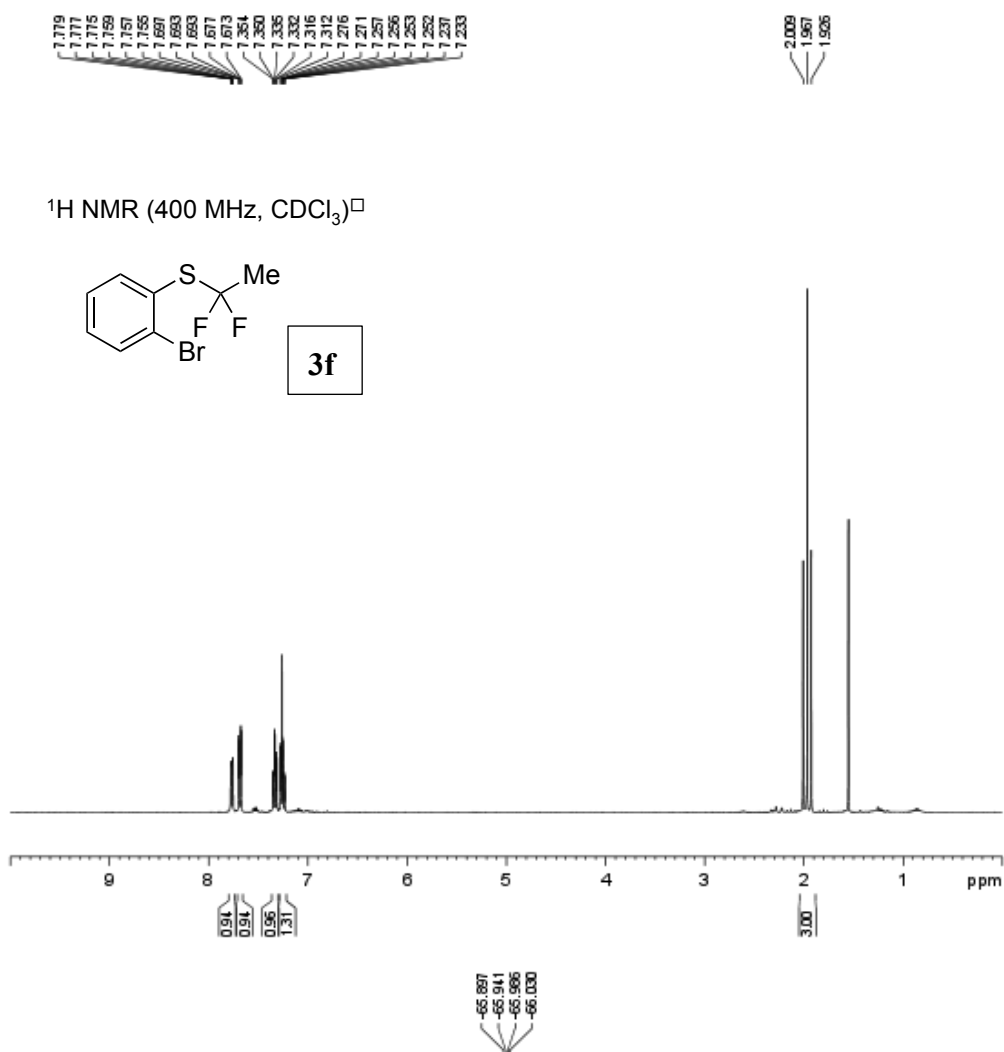


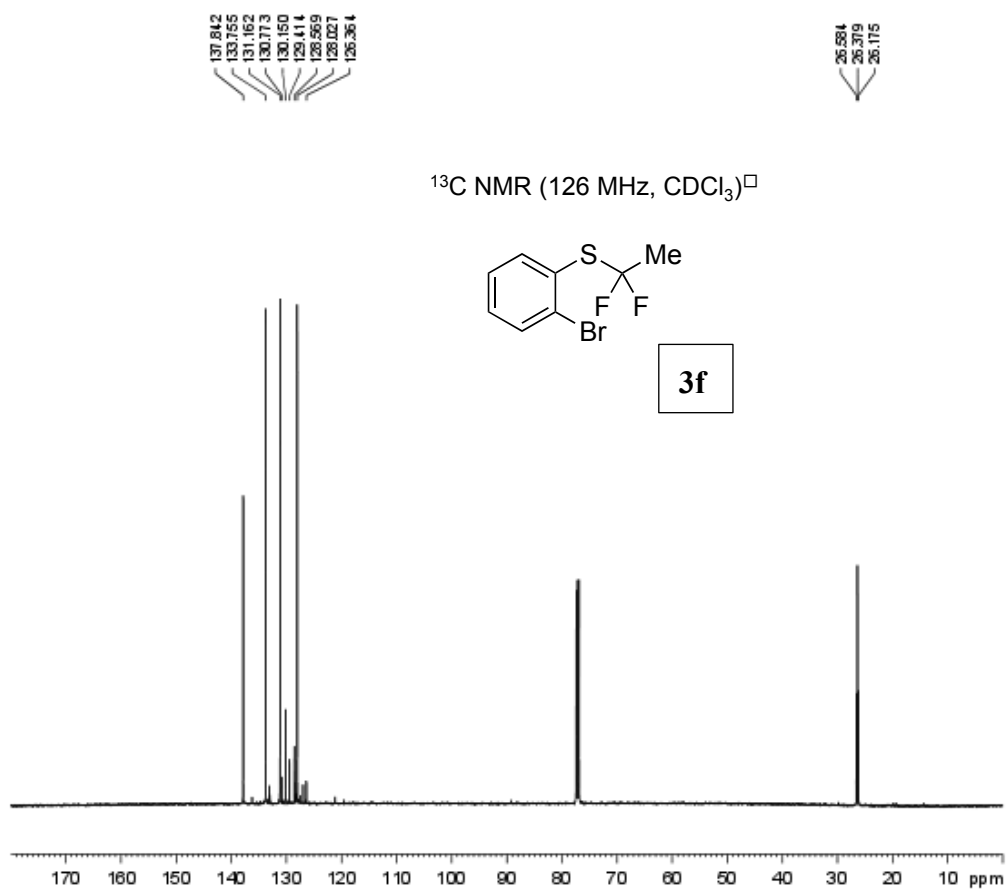


¹H NMR (400 MHz, CDCl₃) □

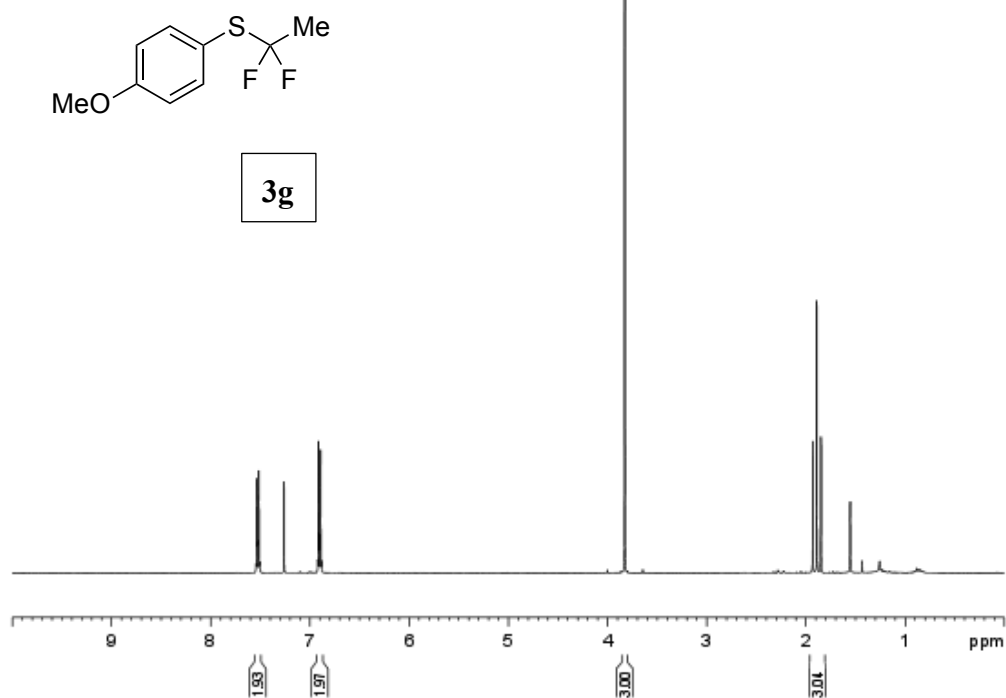


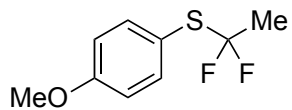
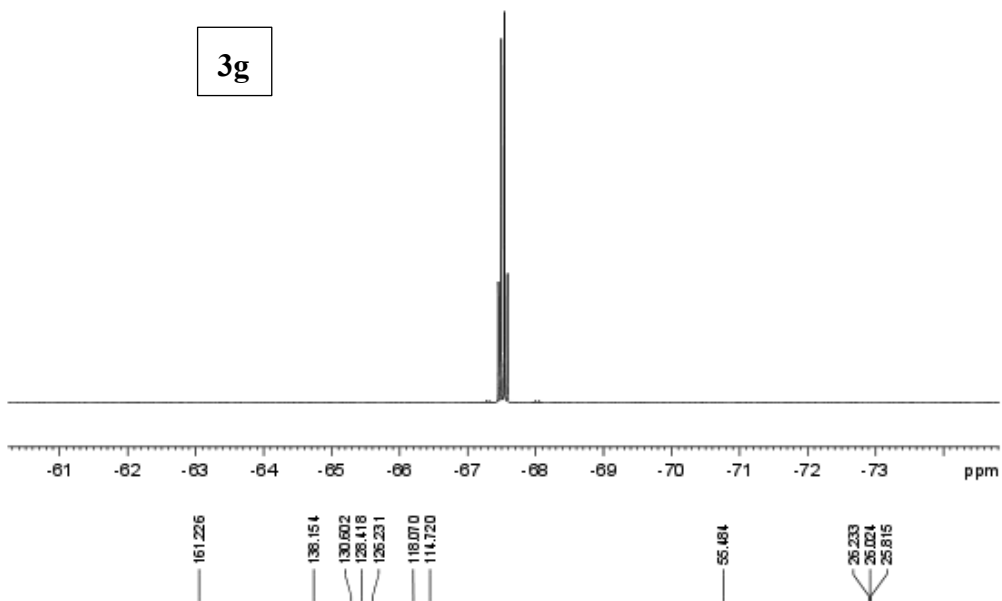
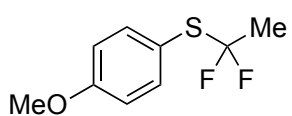
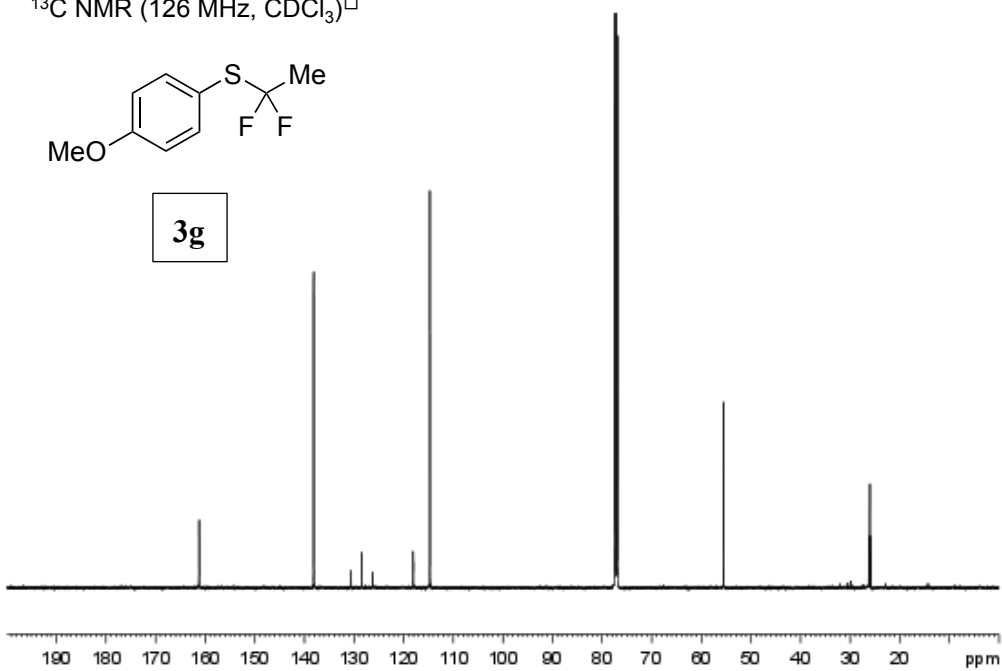






¹H NMR (400 MHz, CDCl₃)[□]

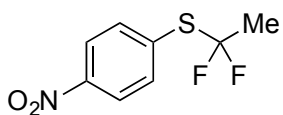


67.452
67.496
67.540
67.585 ^{19}F NMR (376 MHz, CDCl_3) \square **3g** ^{13}C NMR (126 MHz, CDCl_3) \square **3g**

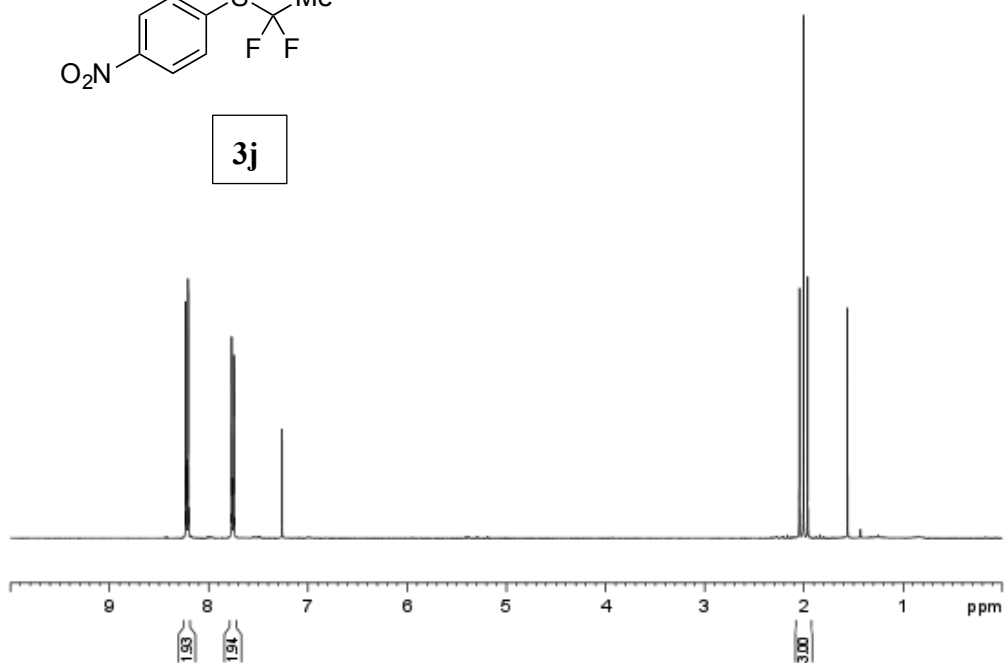
8.226
8.220
8.225
8.213
8.208
8.201
7.775
7.769
7.764
7.752
7.747
7.740

2.045
2.004
1.982

^1H NMR (400 MHz, CDCl_3) \square

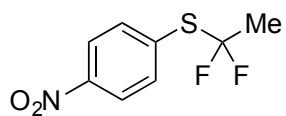


3j

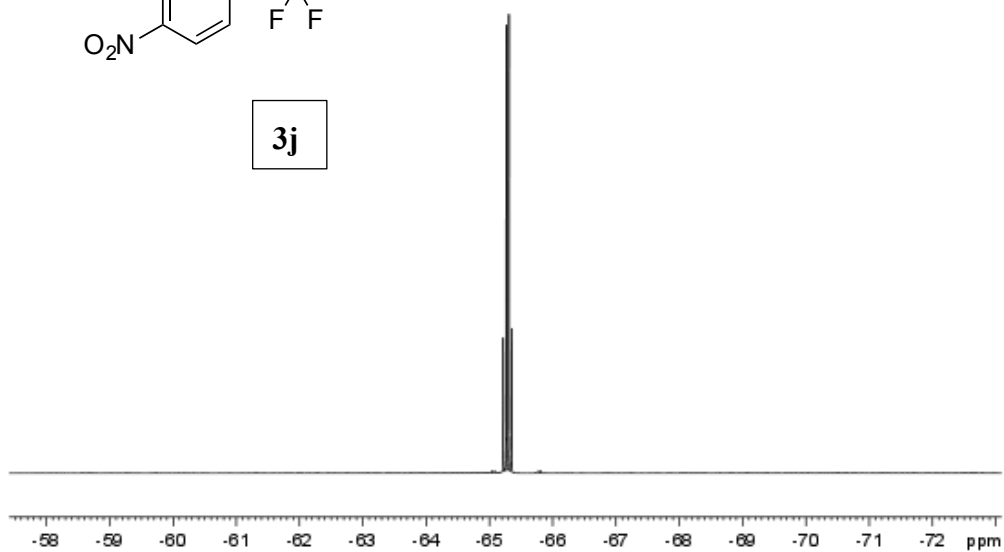


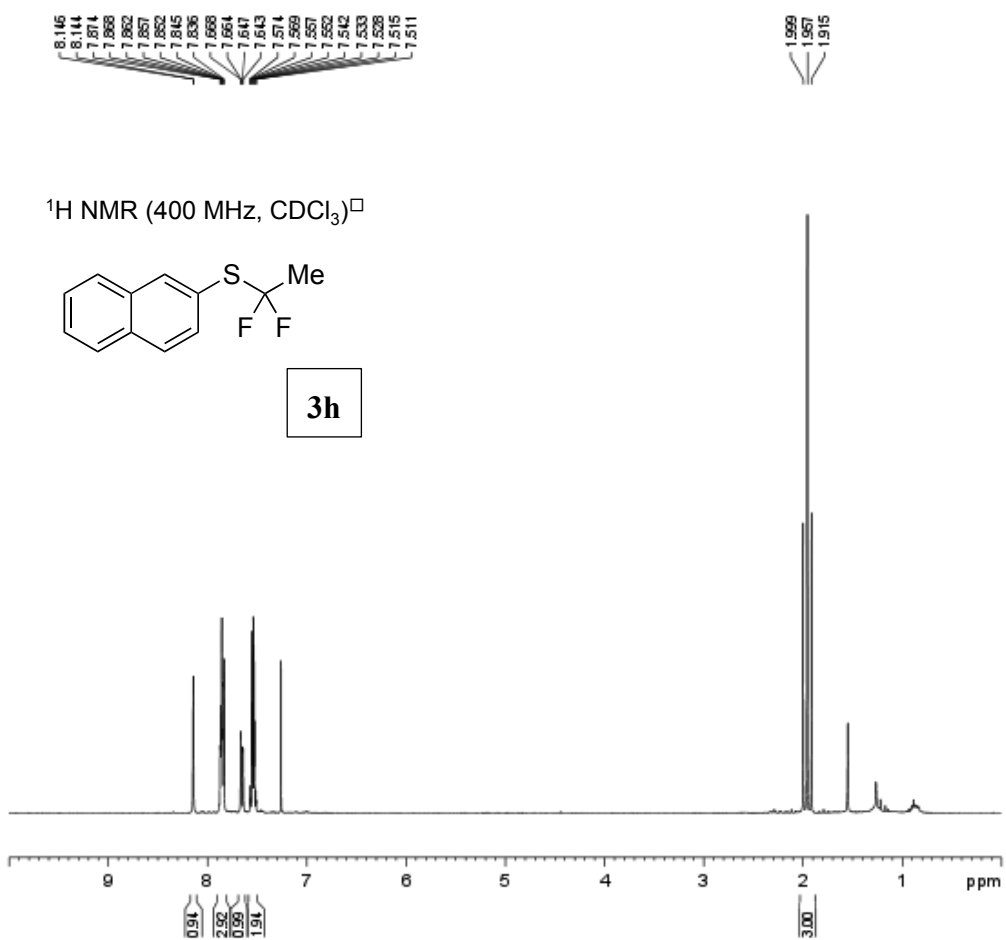
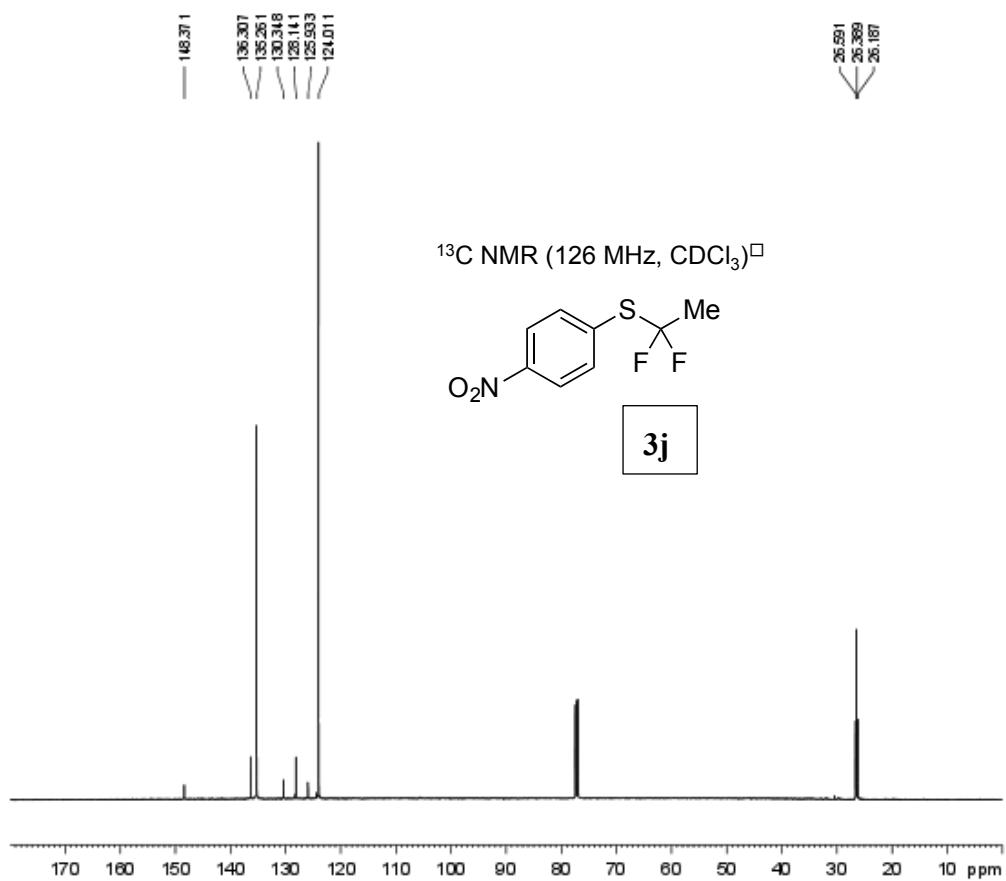
-65.218
-65.263
-65.307
-65.352

^{19}F NMR (376 MHz, CDCl_3) \square



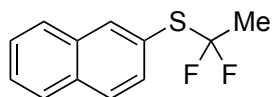
3j



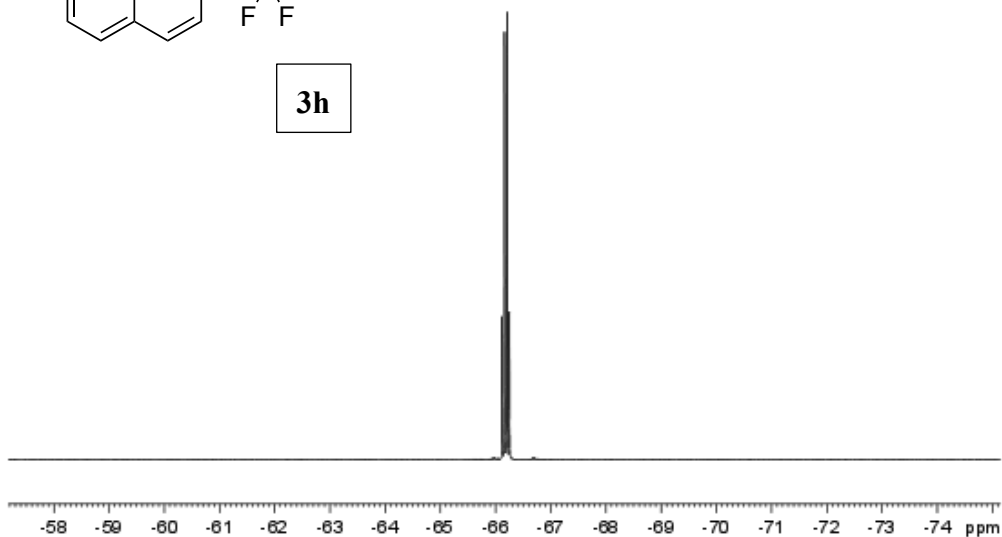


-66.118
-66.162
-66.207
-66.251

^{19}F NMR (376 MHz, CDCl_3) \square



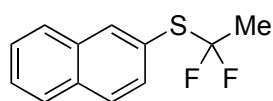
3h



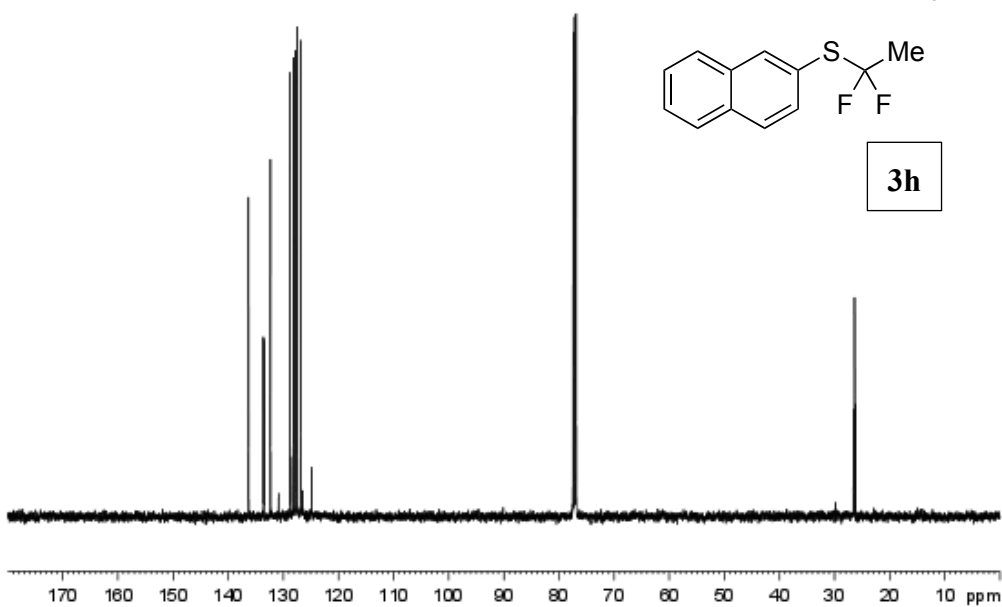
136.315
133.615
133.628
132.323
130.660
128.785
128.668
128.200
127.862
127.457
126.816
124.860

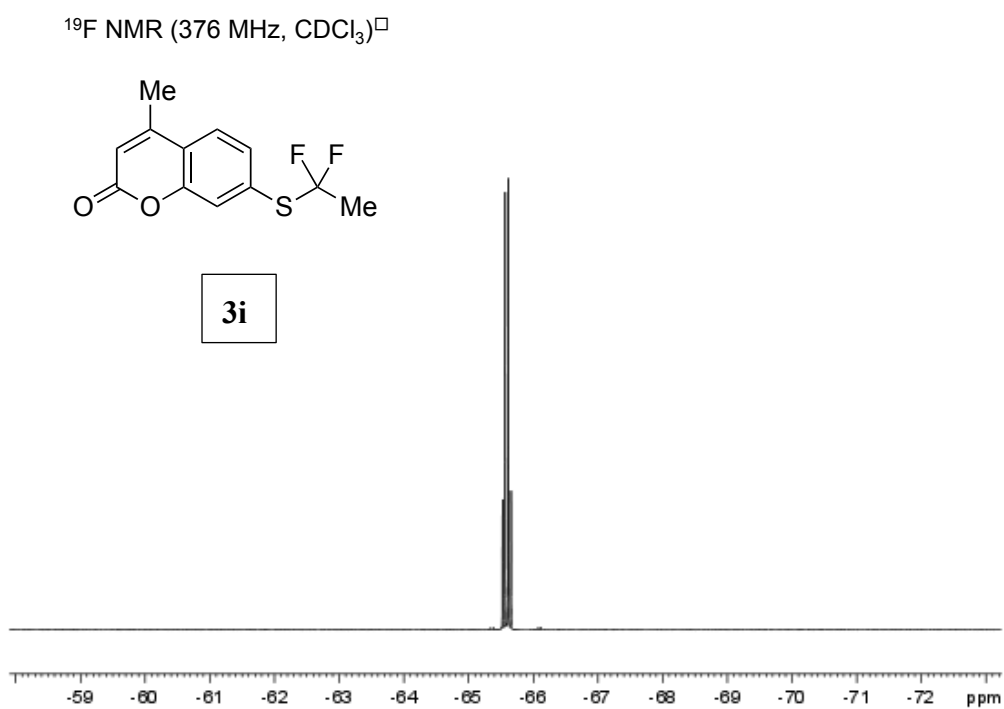
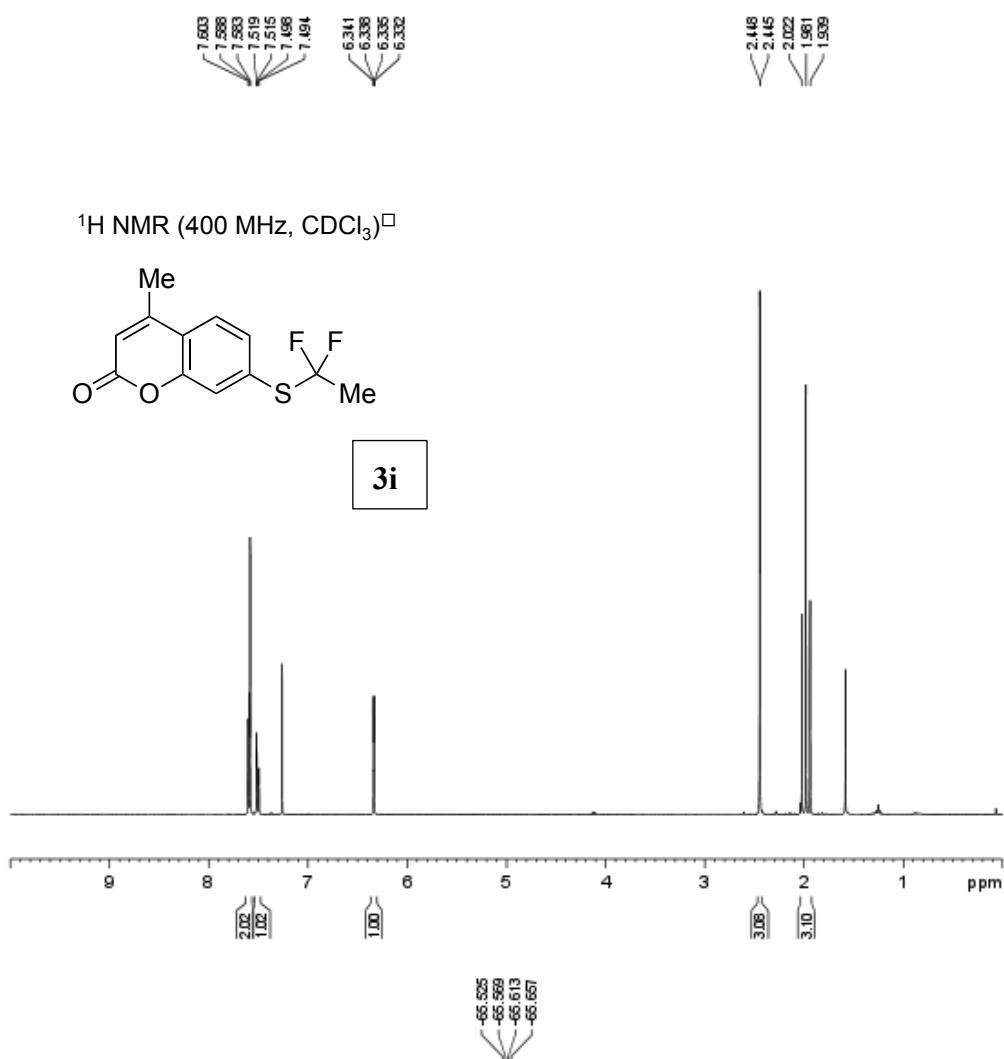
26.581
26.372
26.165

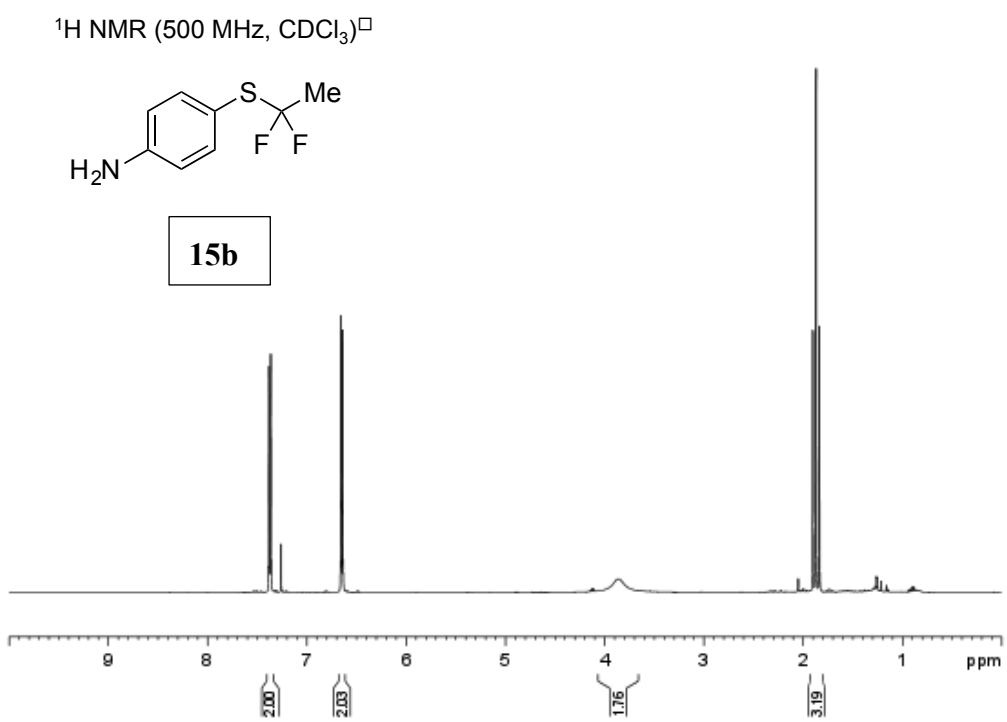
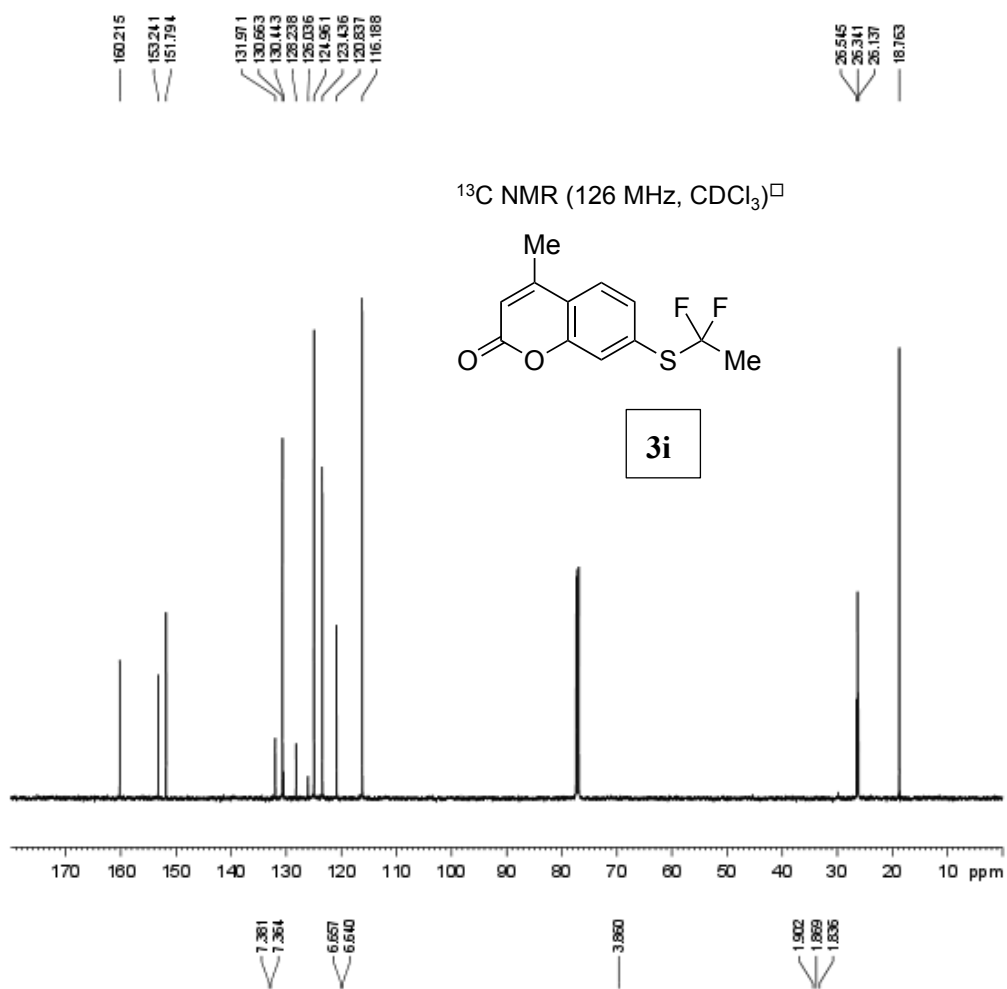
^{13}C NMR (126 MHz, CDCl_3) \square



3h

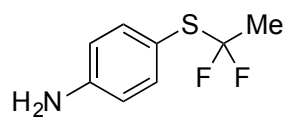




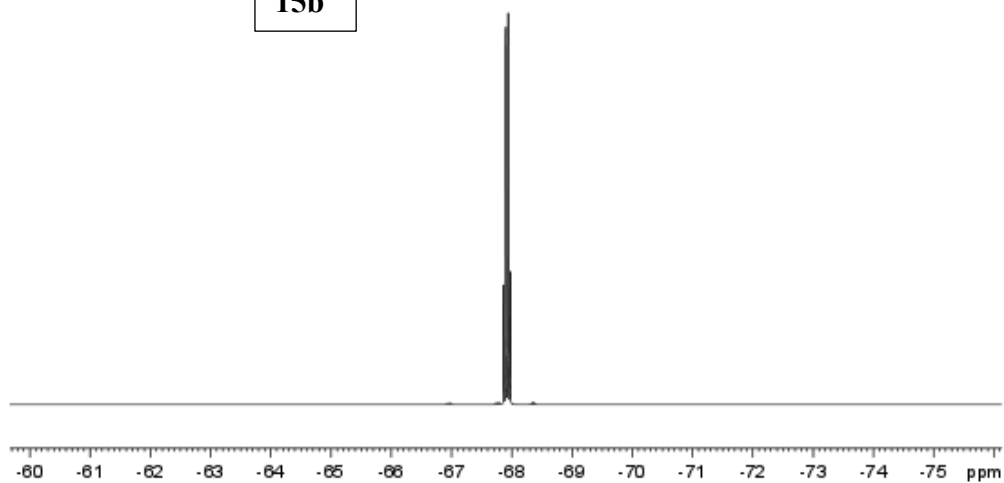


67.866
67.901
67.936
67.972

^{19}F NMR (471 MHz, CDCl_3) \square

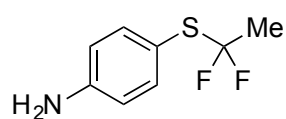


15b

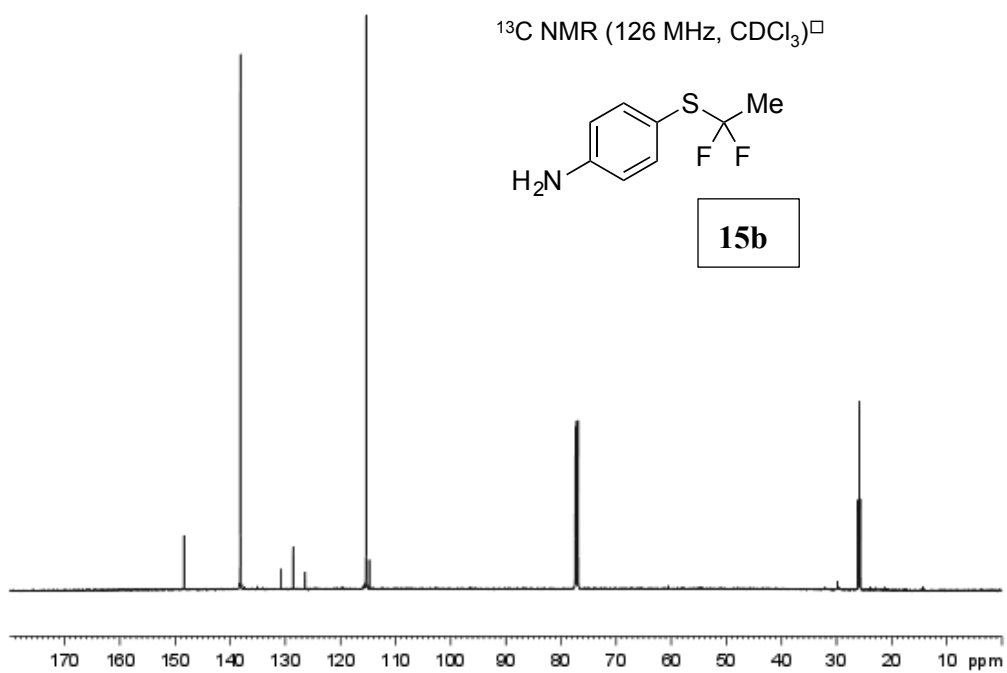


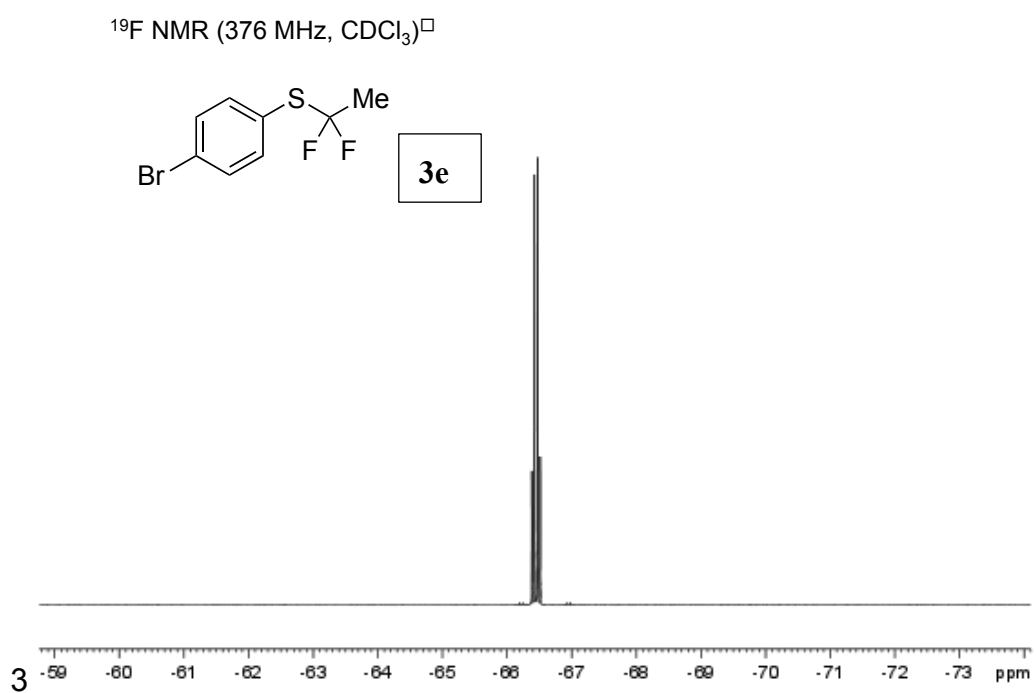
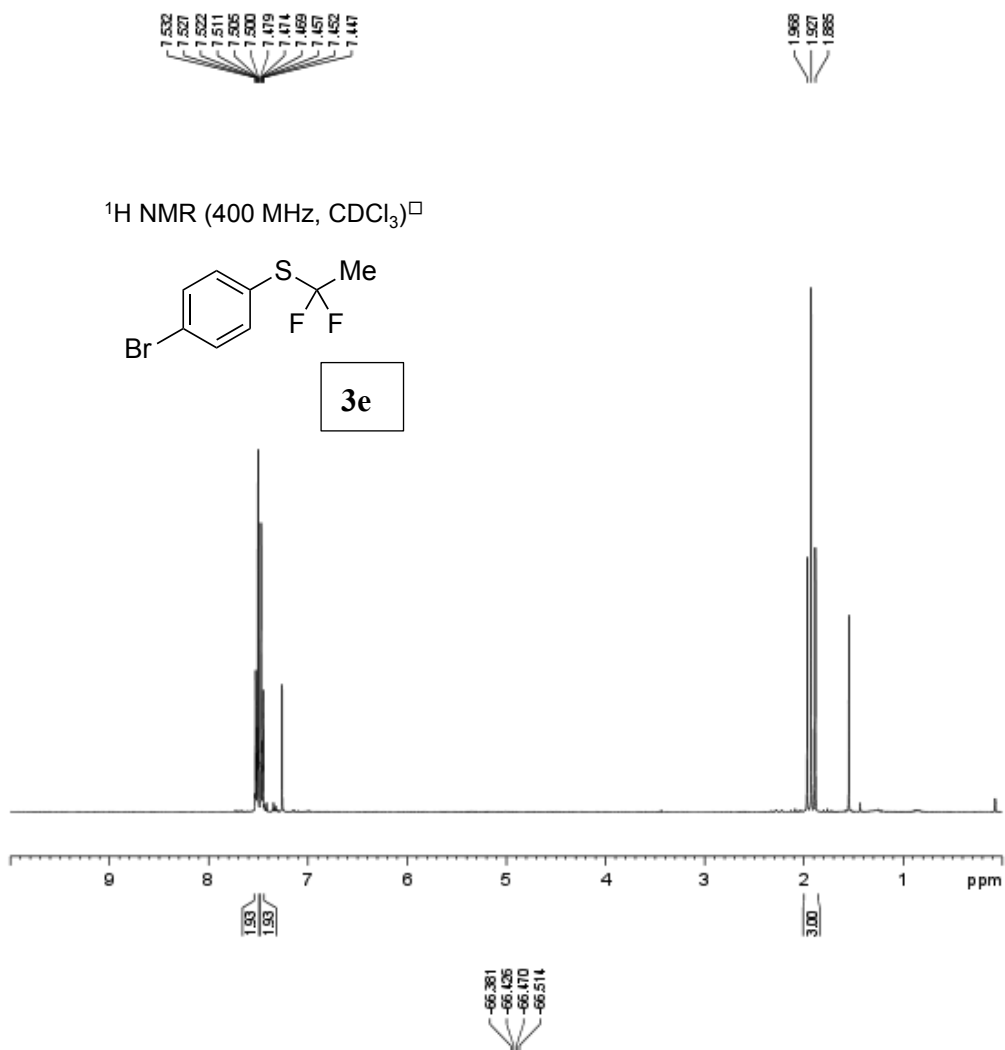
148.369
138.148
130.754
128.573
126.391
115.355
114.760
26.137
26.927
26.717

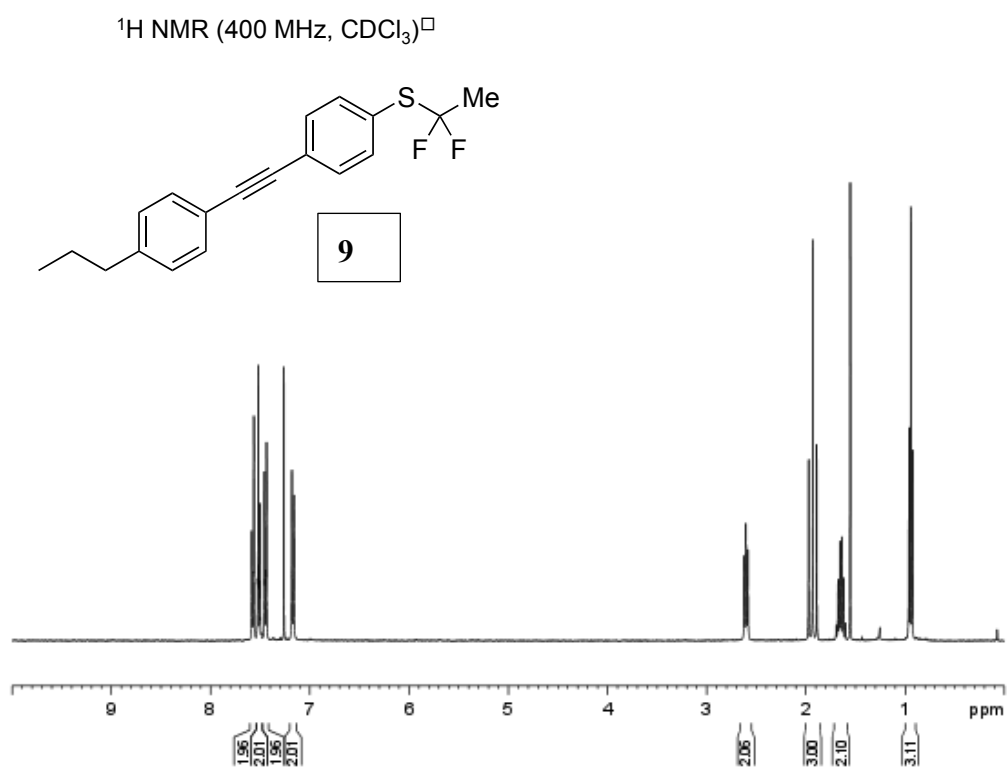
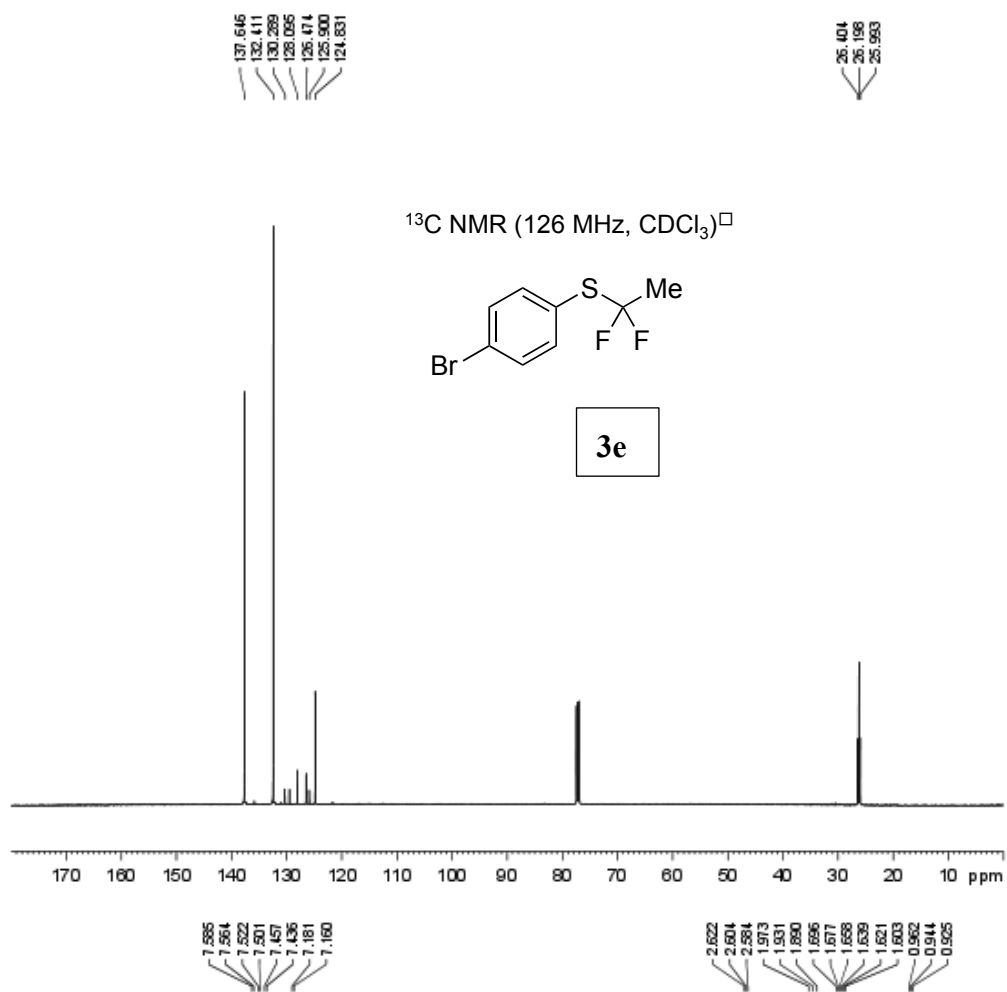
^{13}C NMR (126 MHz, CDCl_3) \square



15b

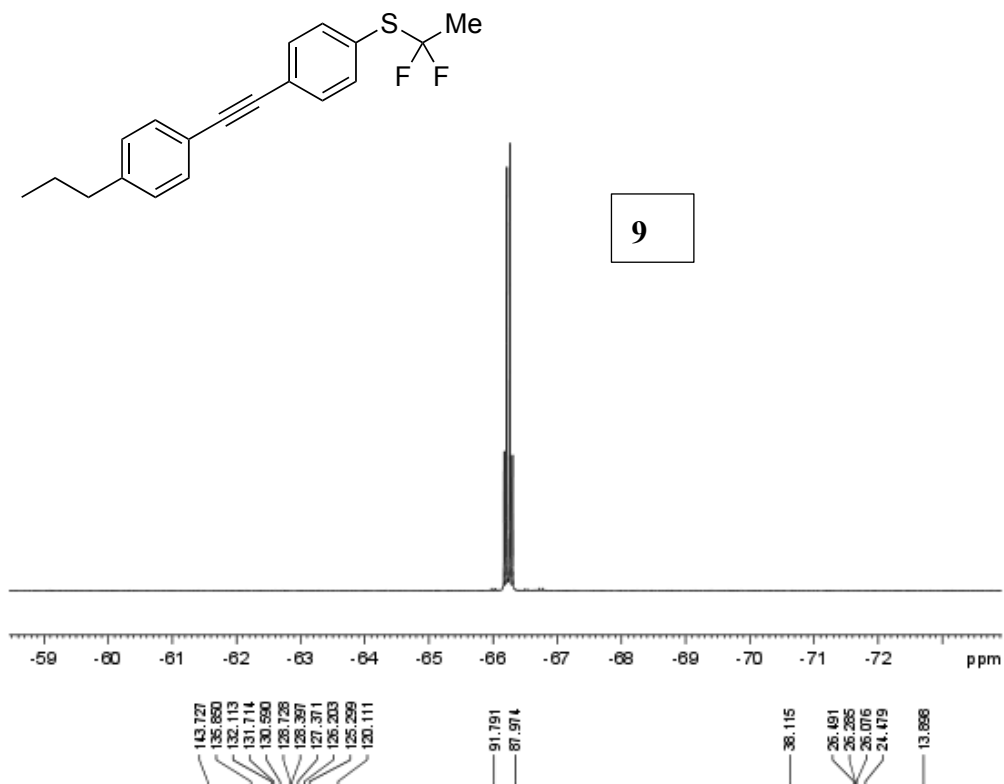




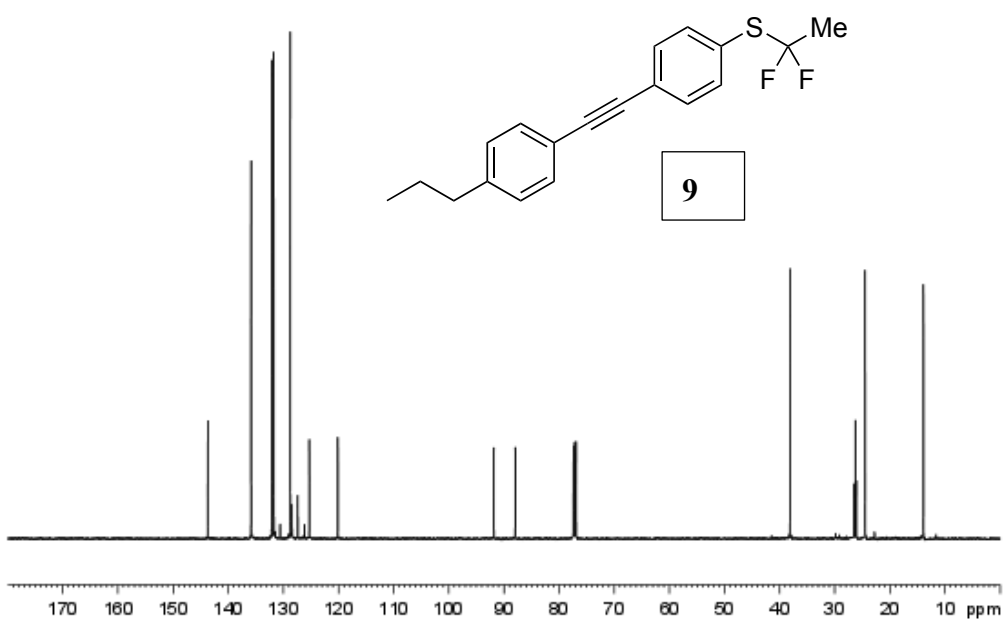


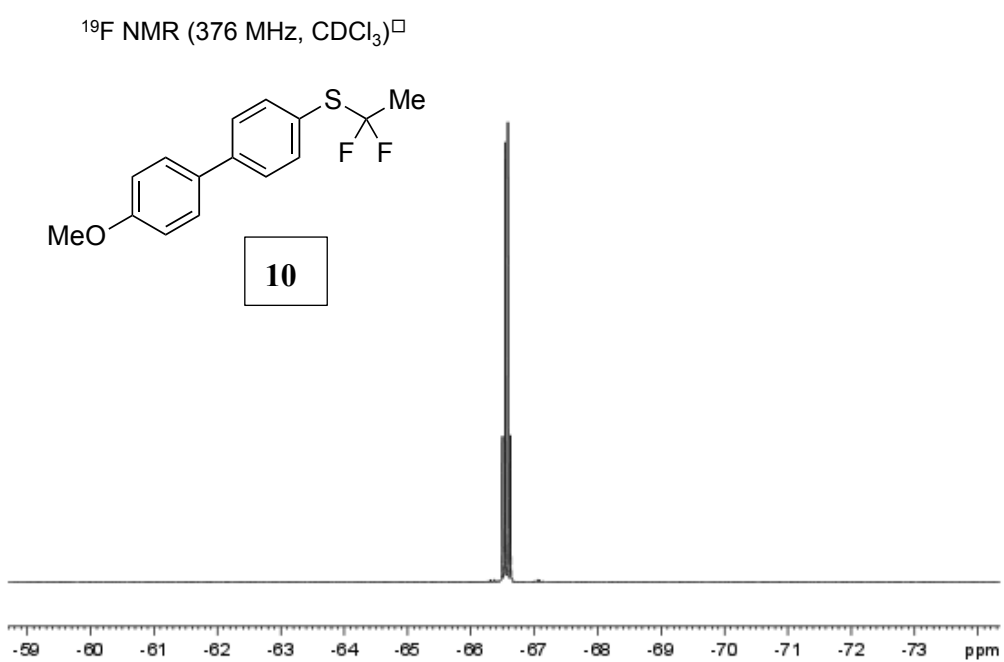
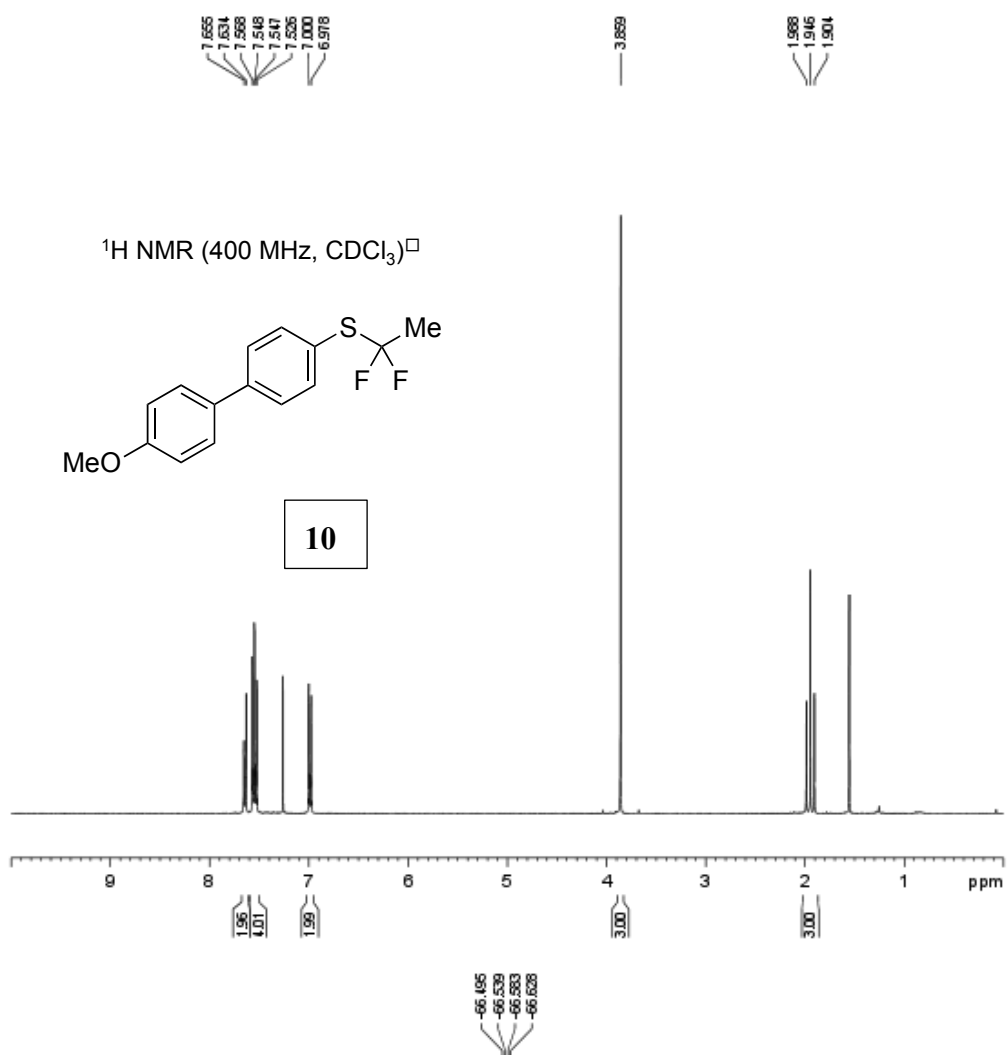
-66.169
-66.214
-66.288
-66.302

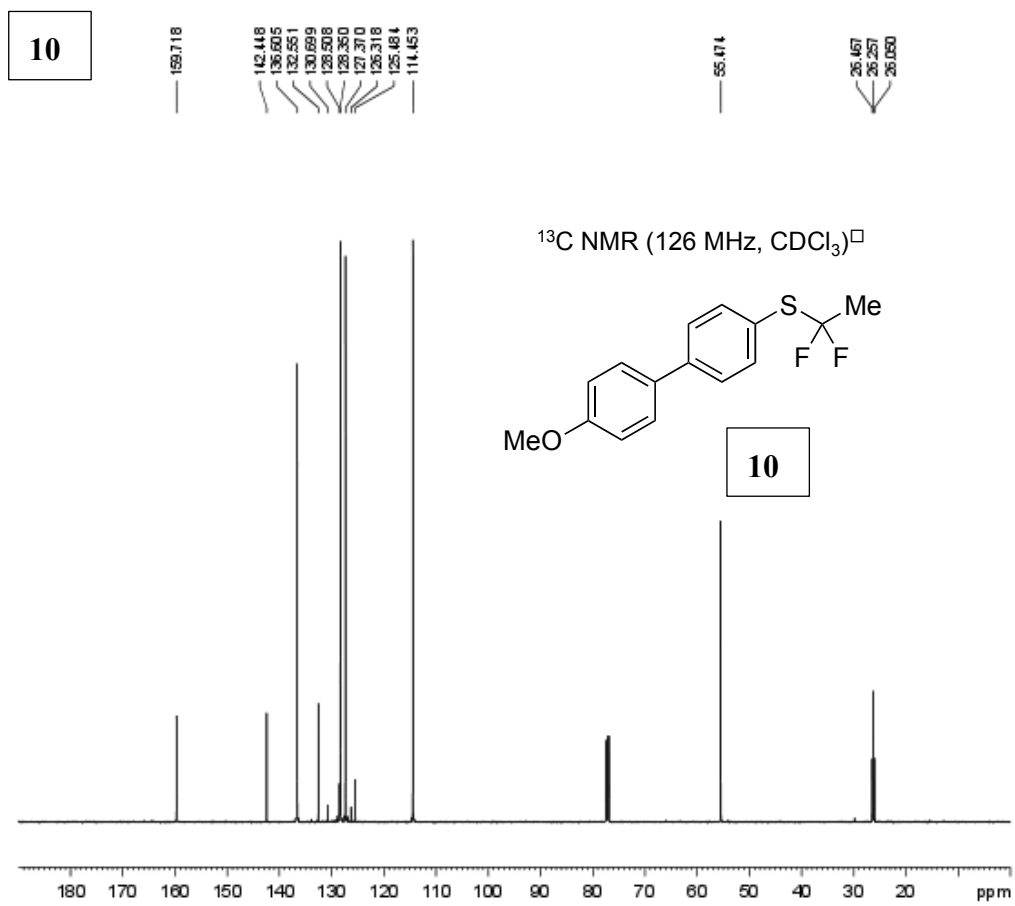
^{19}F NMR (376 MHz, CDCl_3) $^{\square}$



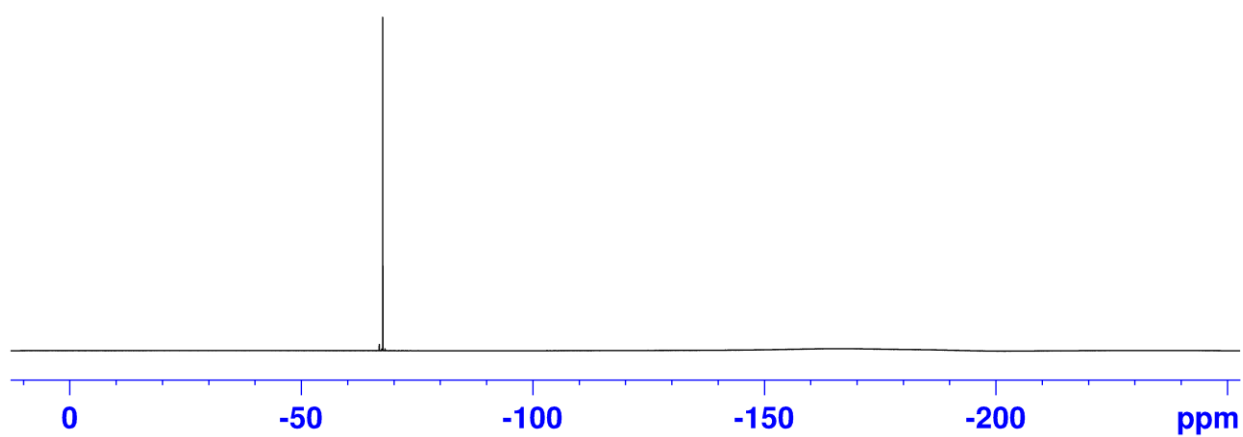
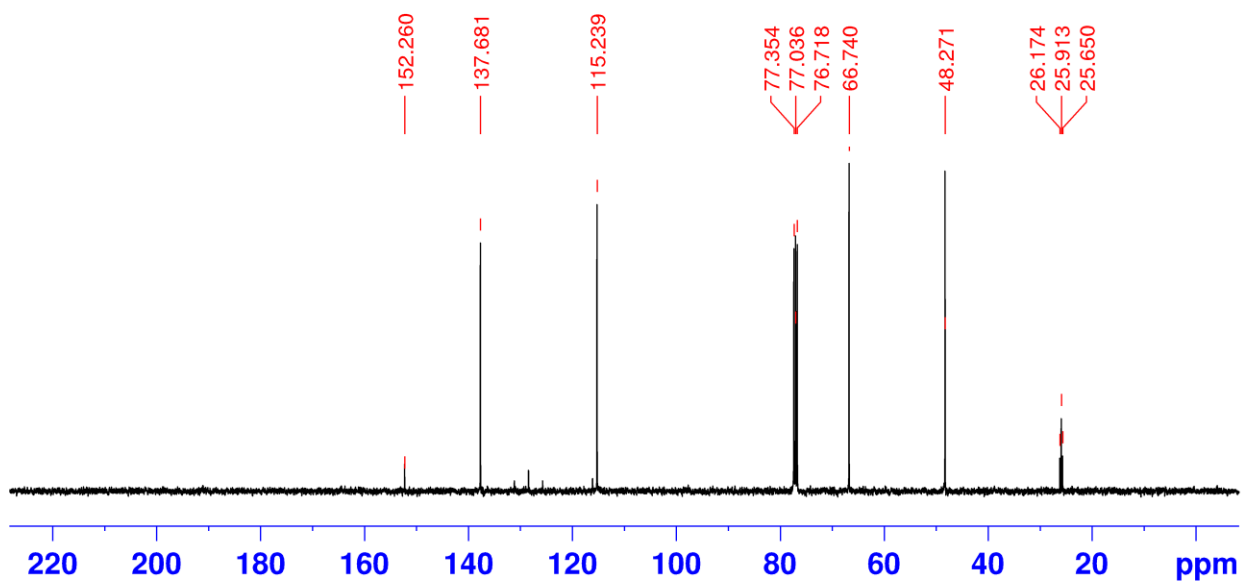
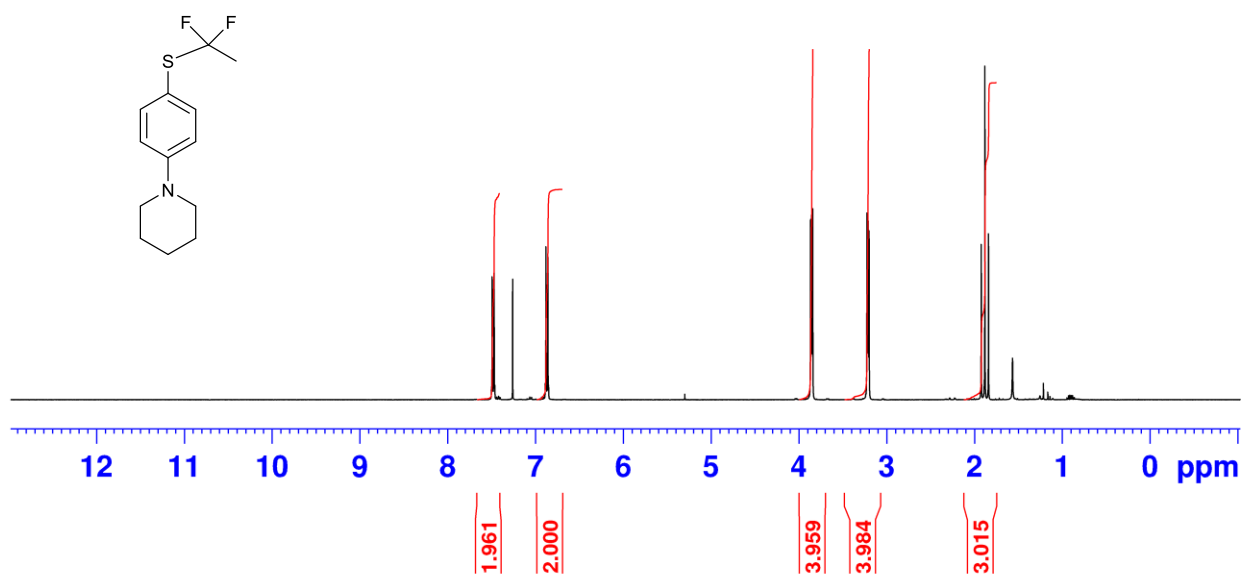
^{13}C NMR (126 MHz, CDCl_3) $^{\square}$





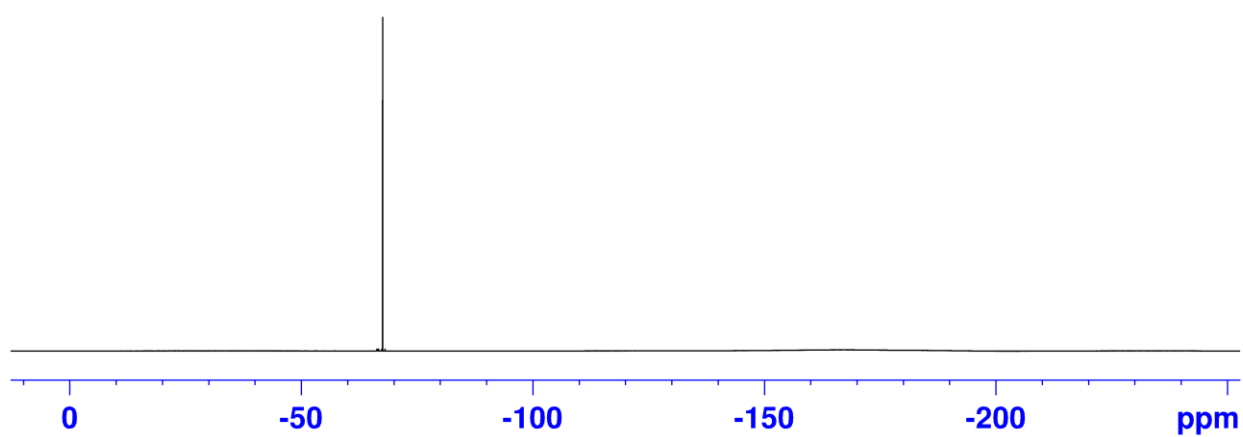
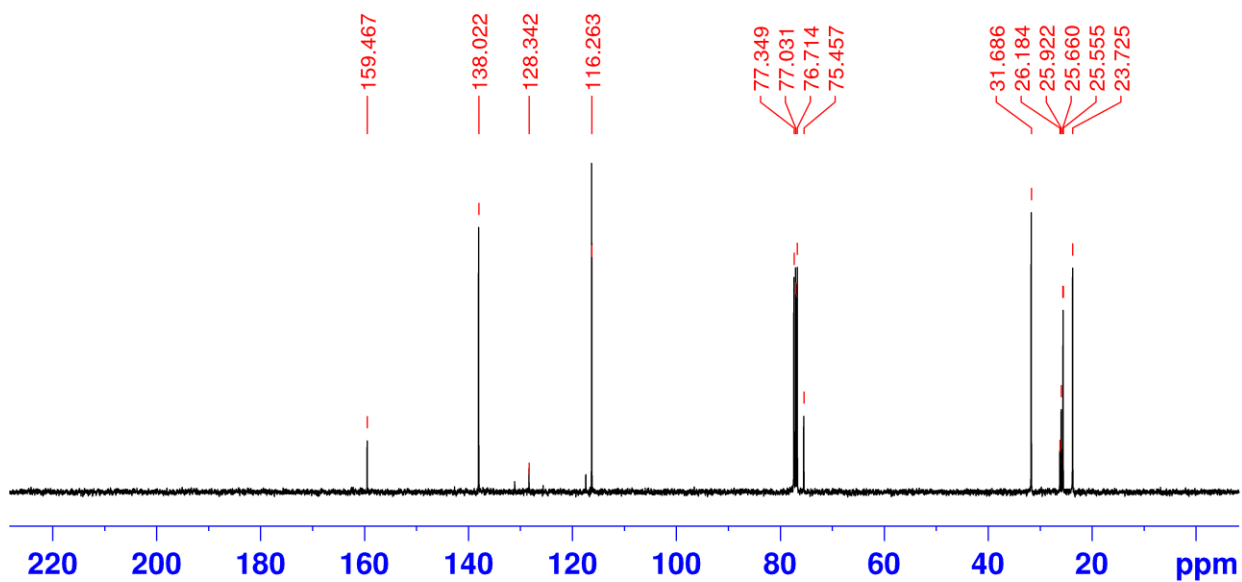
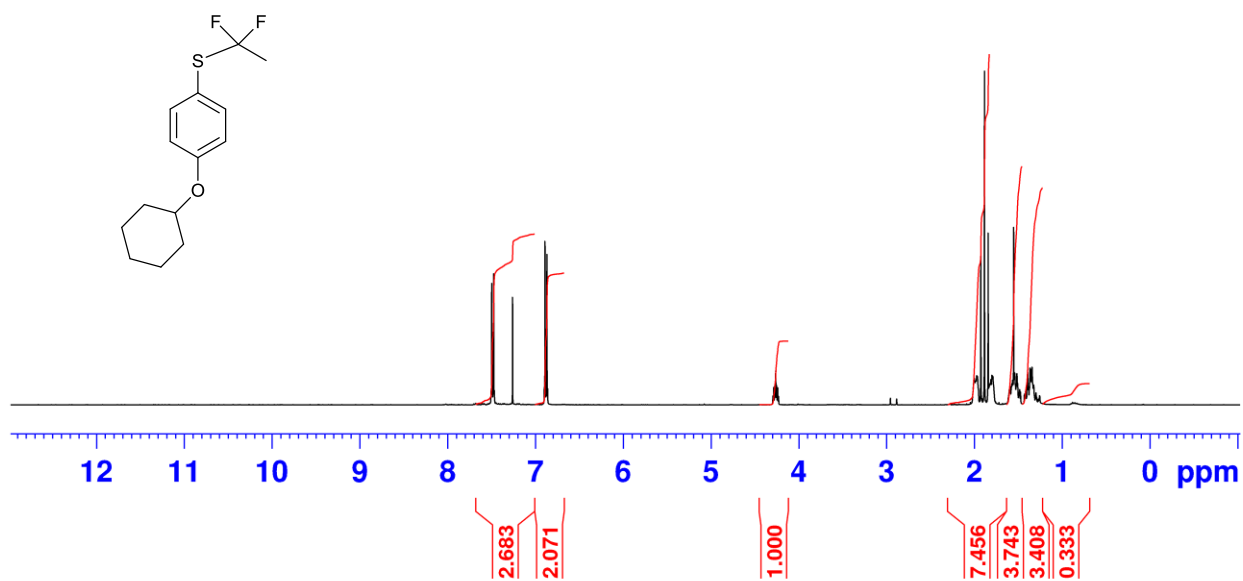


S41



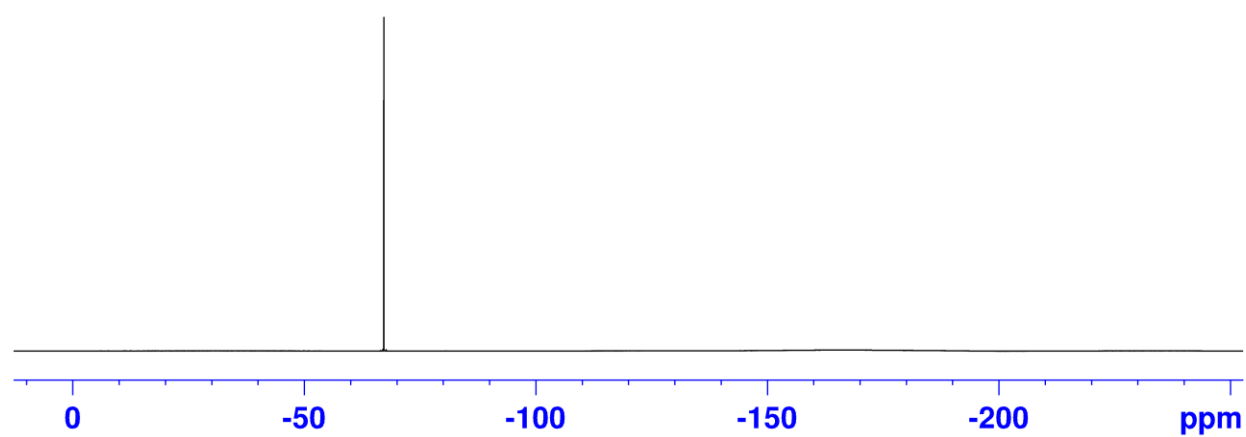
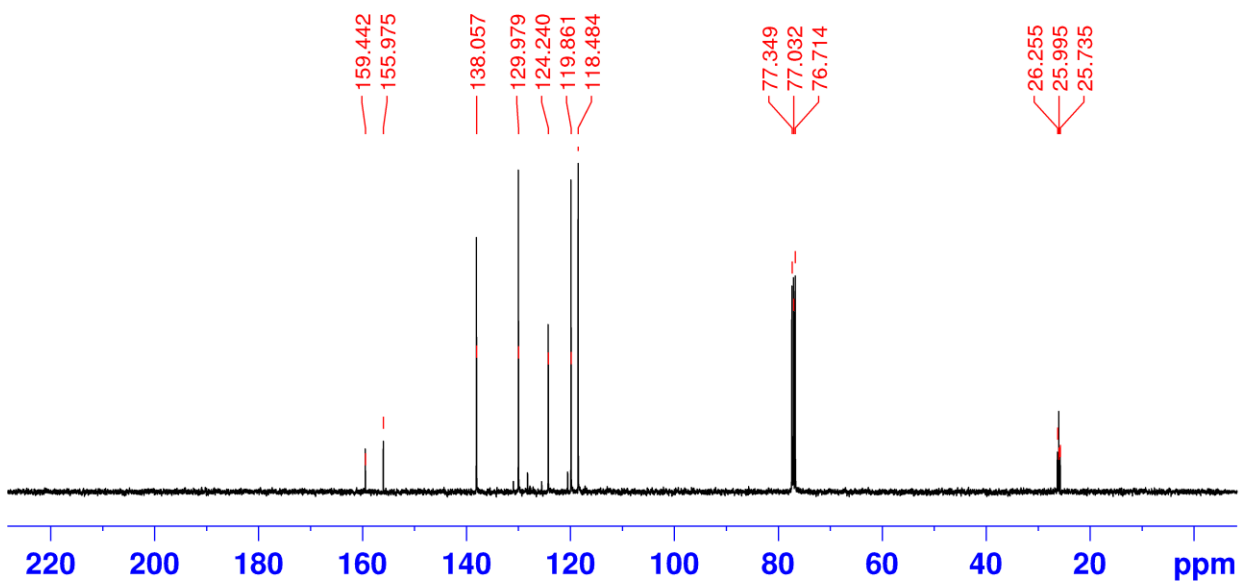
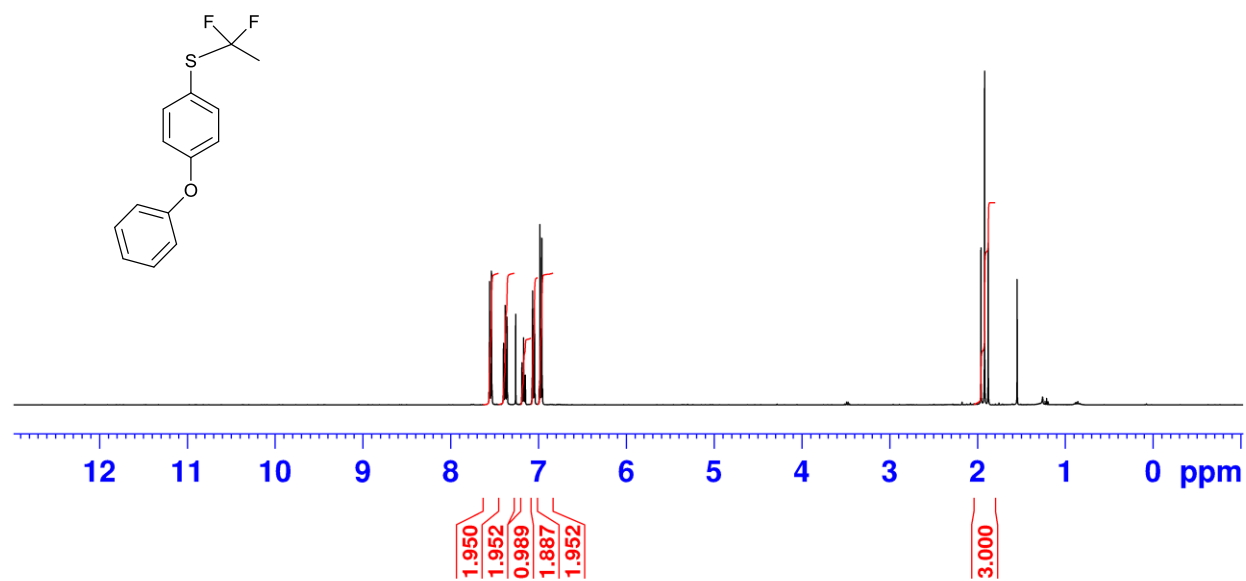
S41

S43



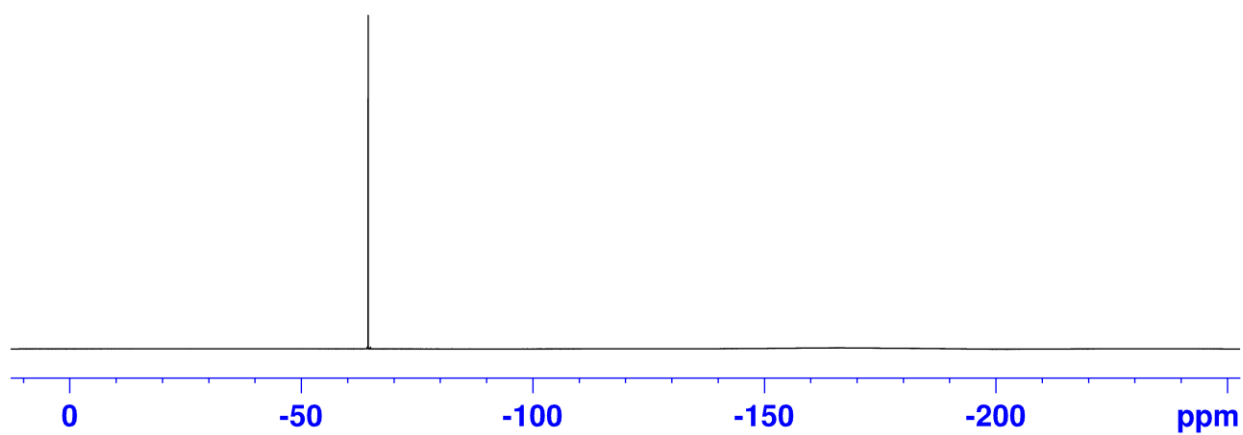
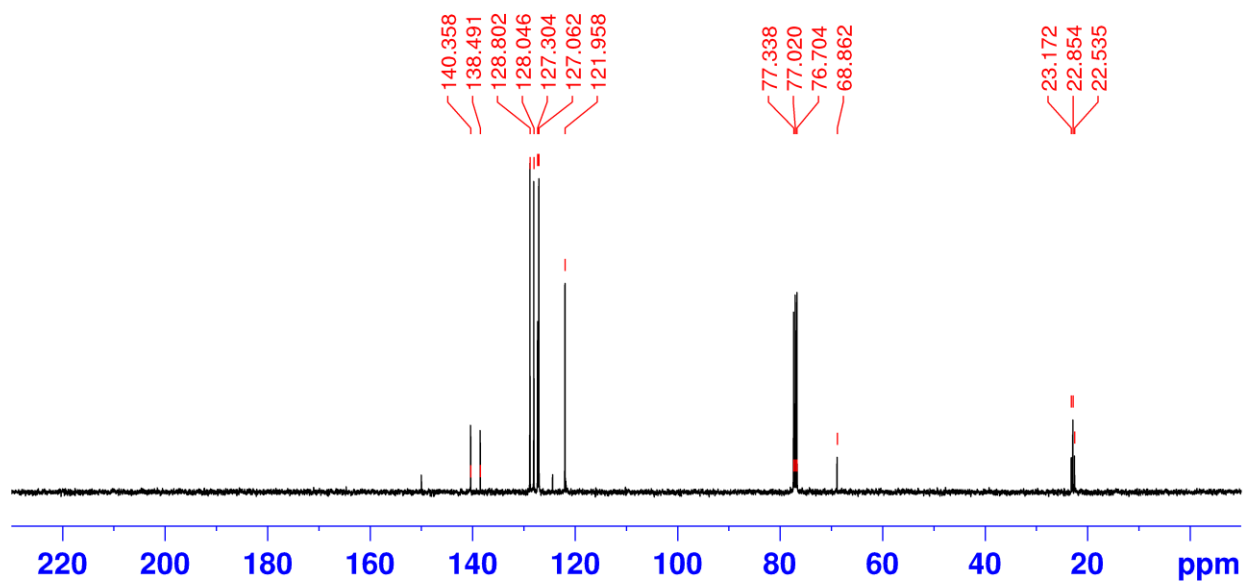
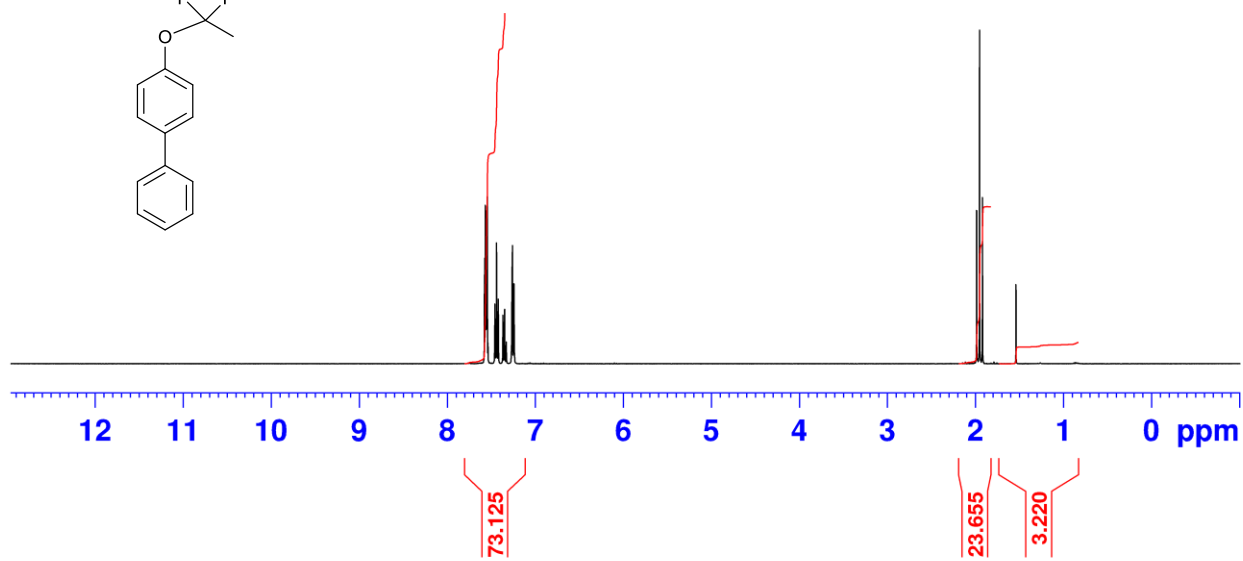
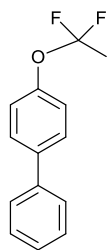
S43

S44



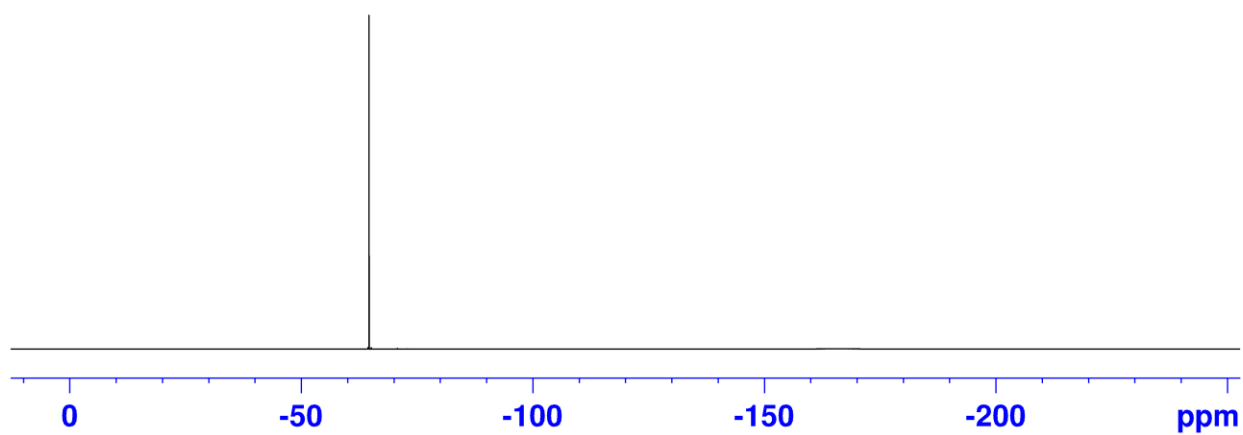
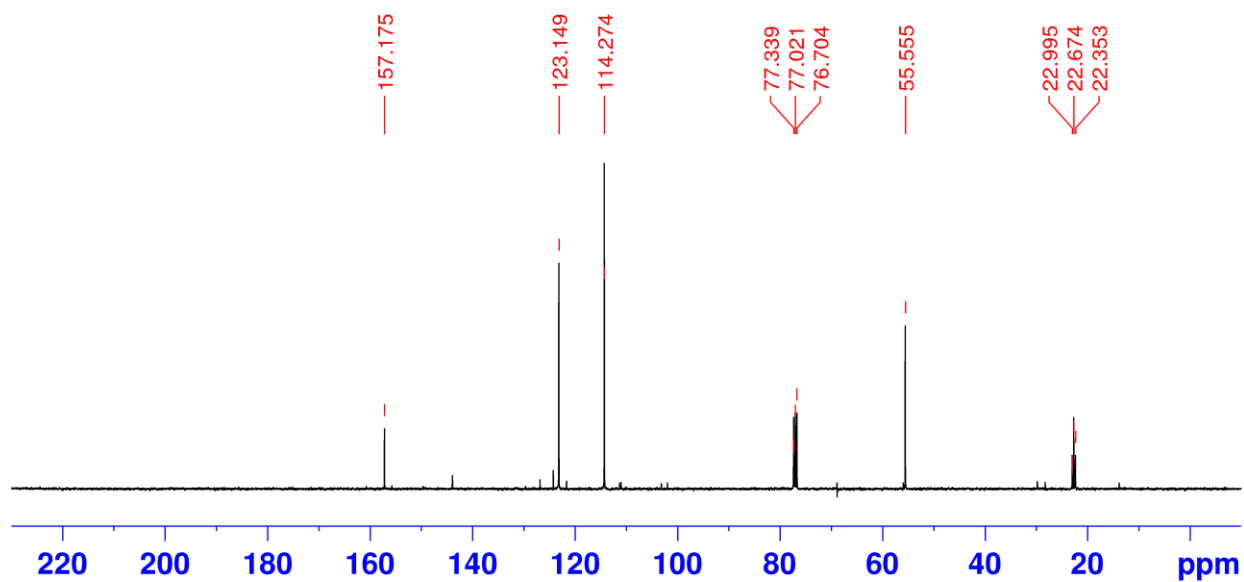
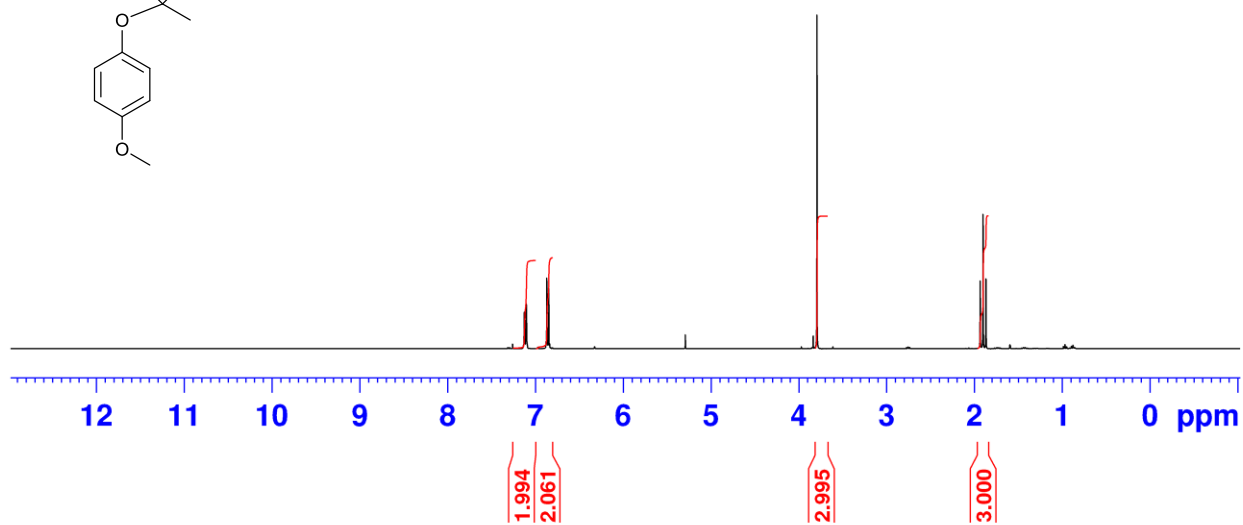
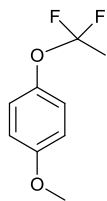
S44

S46



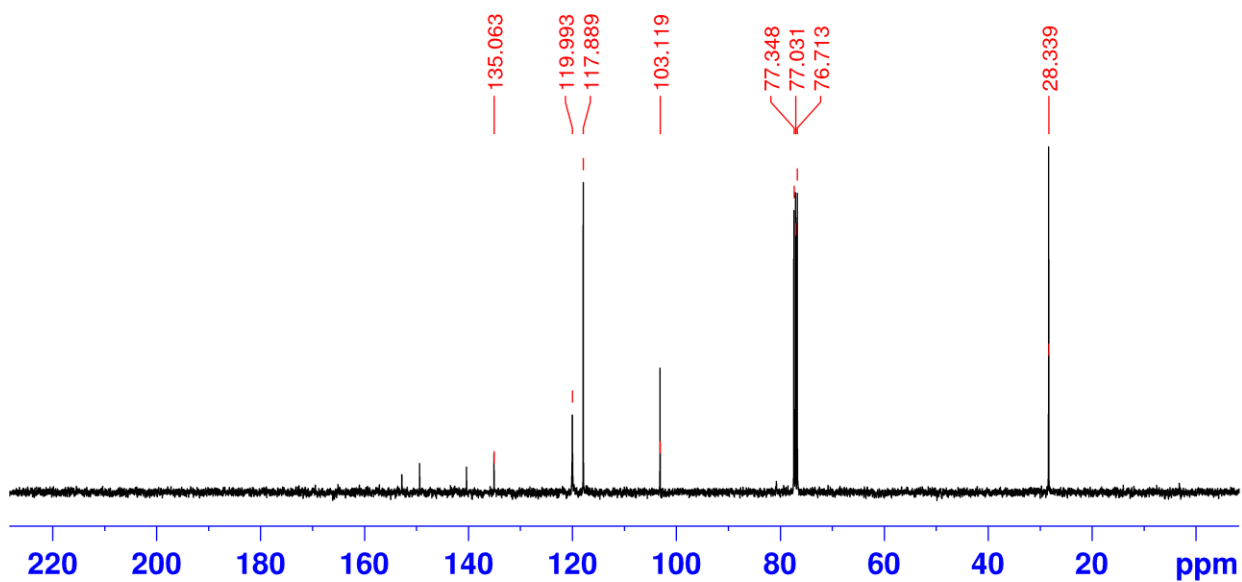
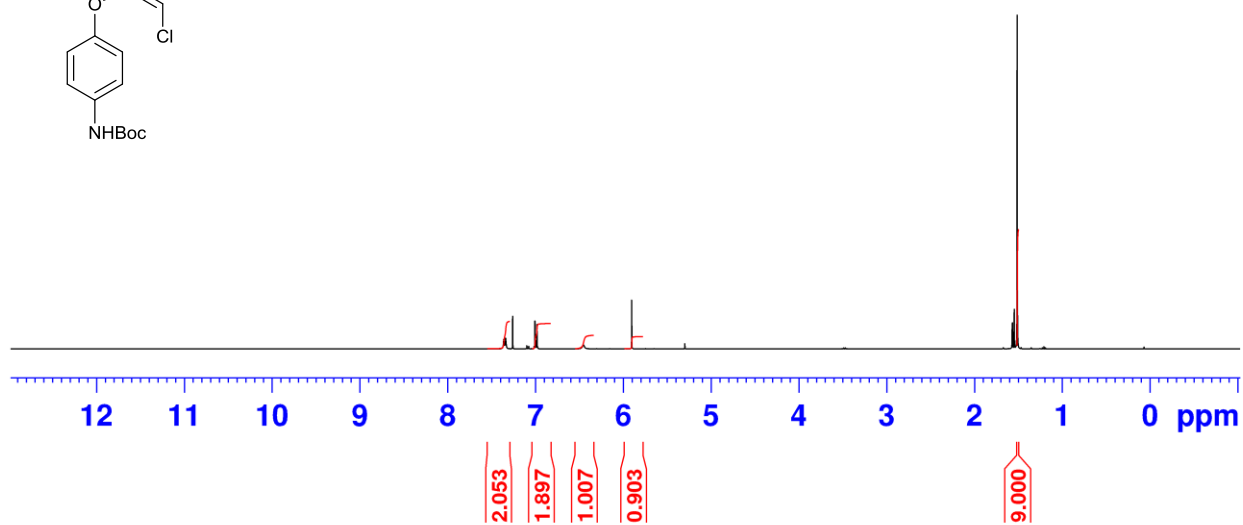
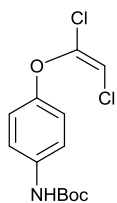
S46

S47

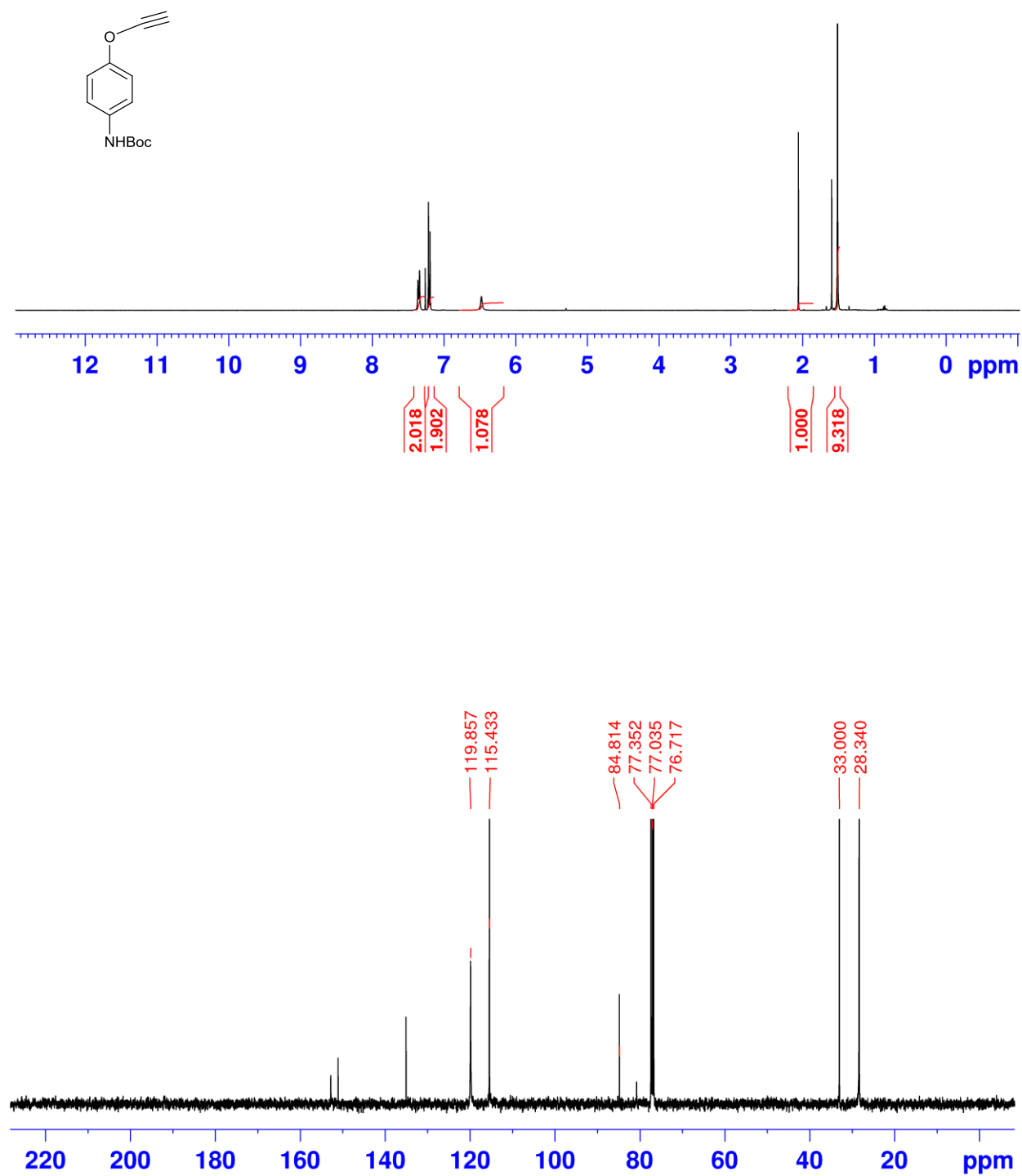


S47

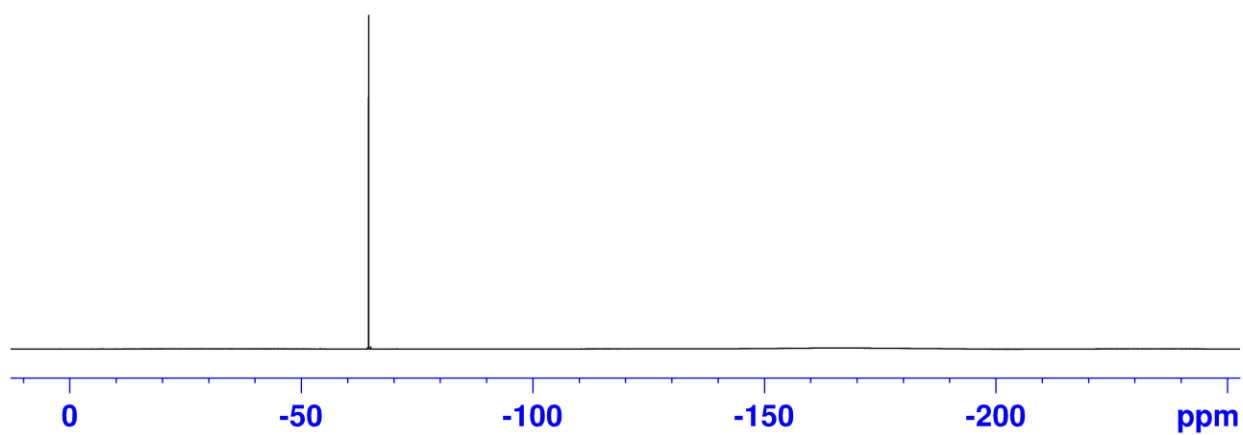
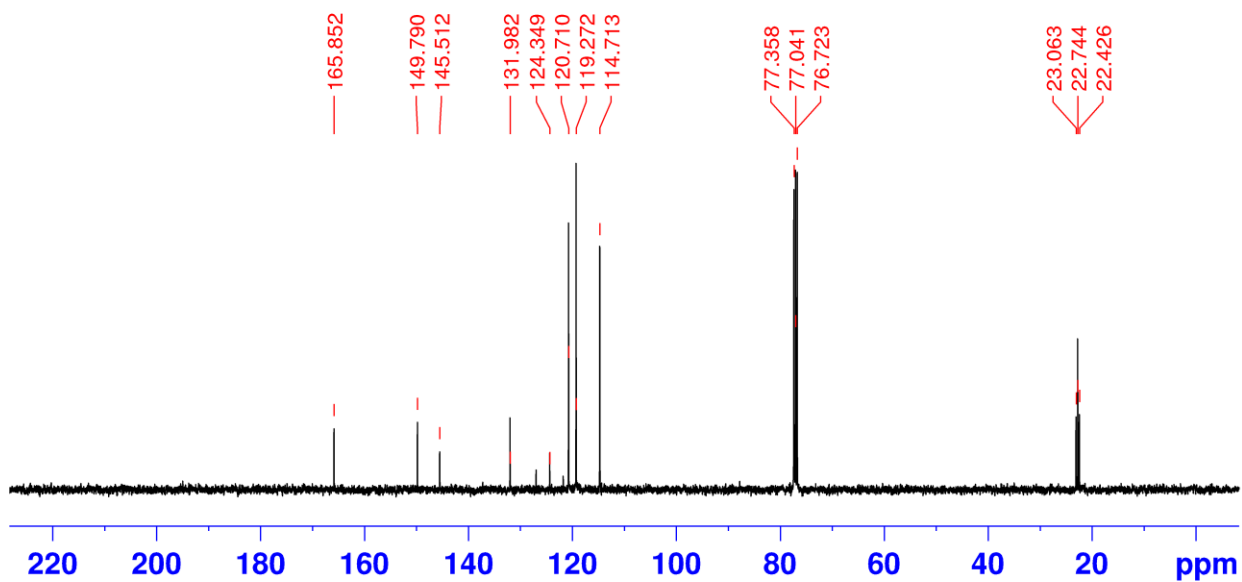
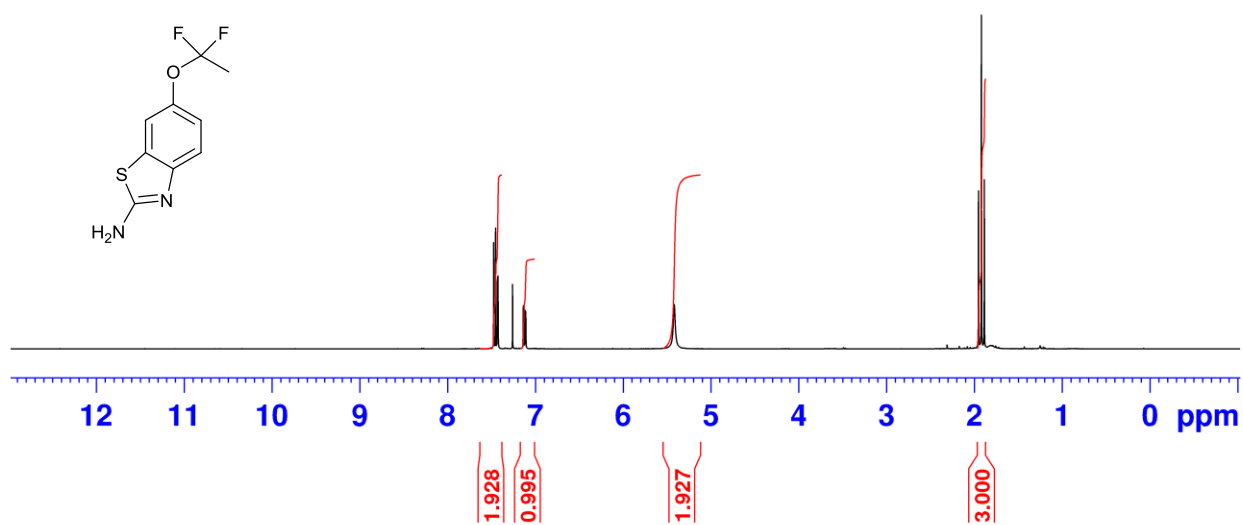
S48



S48

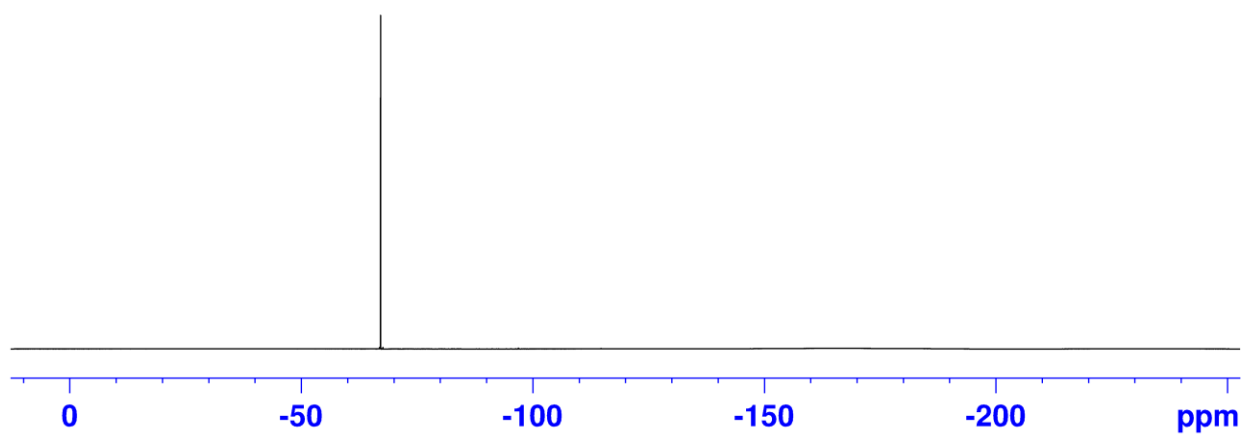
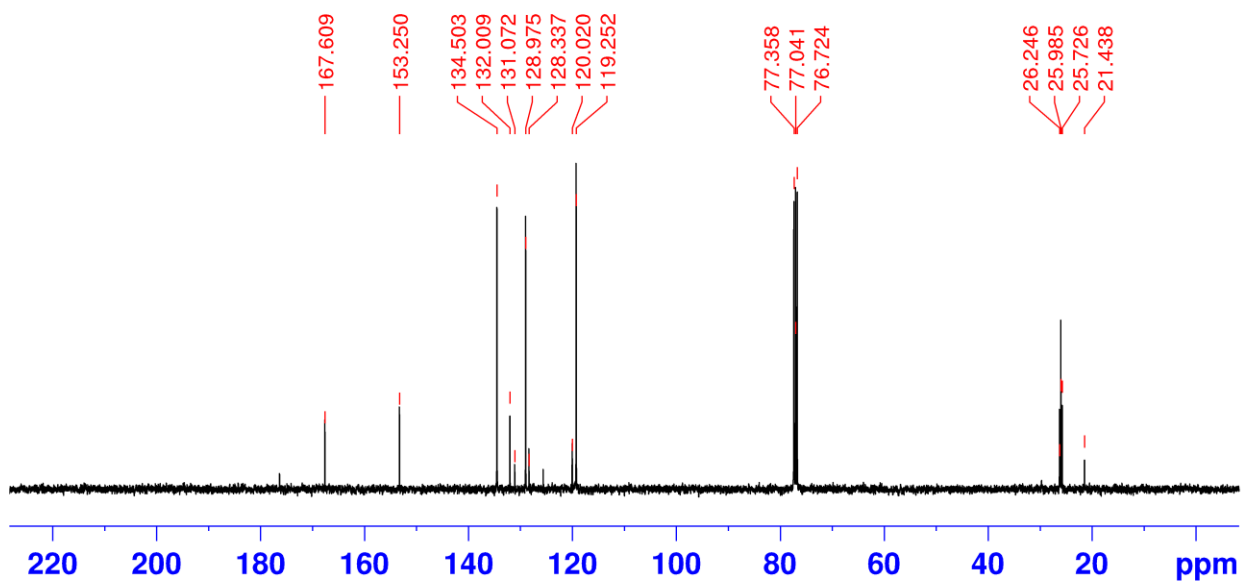
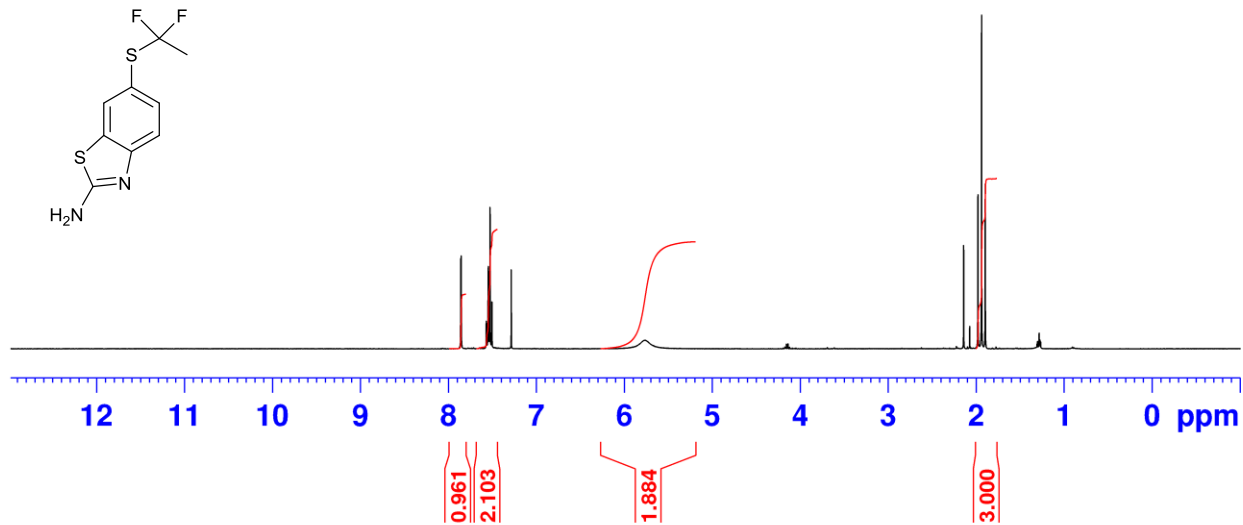
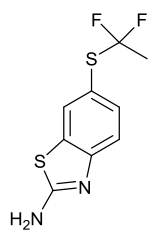


S51



S51

S52



S52