

# Supporting Information

## ***N*-Tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine: A Difluoromethyl Cation Equivalent and Electrophilic Difluoromethylation of *S*-, *N*-, and *C*-Nucleophiles**

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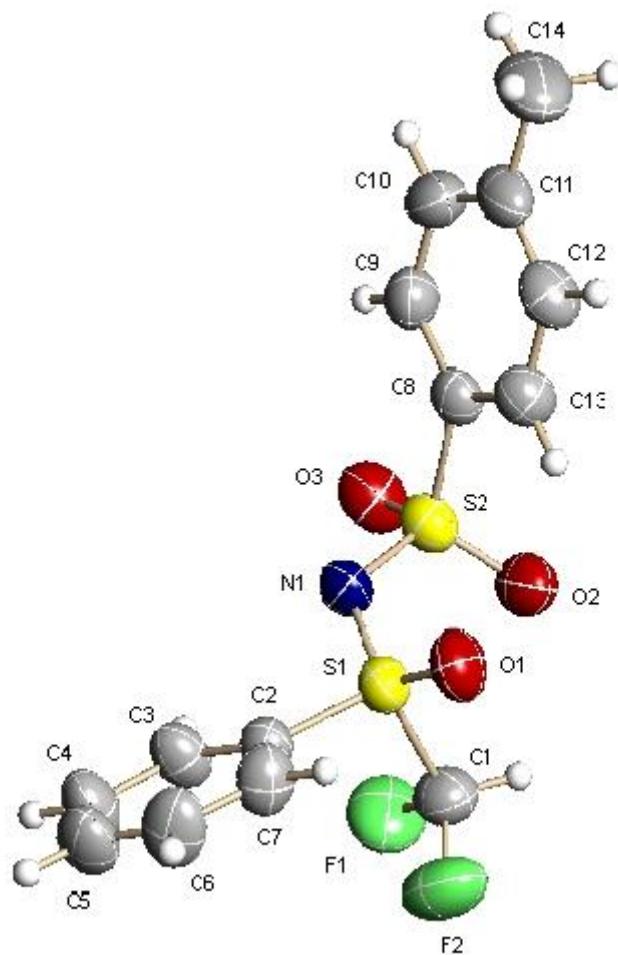
## General Methods:

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. The solvent CH<sub>3</sub>CN and DMF were distilled from CaH<sub>2</sub>, and the solvent THF was distilled from sodium. <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra were recorded on a 400 MHz or 300 MHz NMR spectrometer. <sup>1</sup>H NMR chemical shifts were determined relative to internal (CH<sub>3</sub>)<sub>4</sub>Si (TMS) at  $\delta$  0.0 or to the signal of a residual protonated solvent: CDCl<sub>3</sub>  $\delta$  7.26. <sup>13</sup>C NMR chemical shifts were determined relative to internal TMS at  $\delta$  0.0. <sup>19</sup>F NMR chemical shifts were determined relative to CFCl<sub>3</sub> at  $\delta$  0.0. Mass spectra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI, ESI or MALDI mode.

## Preparation of *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (2):

Under N<sub>2</sub> atmosphere, difluoromethyl phenyl sulfoxide (**3**) (2.0 g, 11.4 mmol, 1.0 equiv.) was added to a solution of Cu(TfO)<sub>2</sub> (0.41 g, 1.14 mmol, 10 %mol) in CH<sub>3</sub>CN (45 ml) at rt. PhI=NTs (**4**) (5.33 g, 14.3 mmol, 1.3 equiv.) was then dropped in one batch. The mixture was heated to 50 °C for 24h. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:5, v/v) as eluent to give product **2** (2.34 g, 6.78 mmol, yield: 60%). Mp. 96–98 °C. IR (film): 3037, 1600, 1450, 1325, 1241, 1155, 1054, 661, 539 cm<sup>-1</sup>. <sup>1</sup>H NMR:  $\delta$  8.03 (d,  $J$  = 8.1 Hz, 2H), 7.91 (d,  $J$  = 8.4 Hz, 2H), 7.81 (t,  $J$  = 7.5 Hz, 1H), 7.65 (t,  $J$  = 7.8 Hz, 2H), 7.30 (d,  $J$  = 8.4 Hz, 2H), 7.17 (t,  $J$  = 55.2 Hz, 1H), 2.41 (s, 3H). <sup>19</sup>F NMR:  $\delta$  -114.7 (dd,  $^2J_{F-F}$  = 247.0 Hz,  $^3J_{H-F}$  = 53.6 Hz, 1F).  $\delta$  -120.8 (dd,  $^2J_{F-F}$  = 247.9 Hz,  $^3J_{H-F}$  = 55.0 Hz, 1F). <sup>13</sup>C NMR:  $\delta$  143.8, 139.5, 136.2, 130.8, 129.8, 129.6, 128.0, 126.9, 115.5 (t,  $J$  = 289.5 Hz), 21.6. MS (ESI): *m/z* 368 (M+Na<sup>+</sup>). Anal. Calcd. for C<sub>14</sub>H<sub>13</sub>F<sub>2</sub>NO<sub>3</sub>S<sub>2</sub>: C, 48.68; H, 3.79; N, 4.06; Found: C, 48.62; H, 3.99; N, 3.90.

**ORTEP Drawing of Compound 2:**



**Typical procedure for electrophilic difluoromethylation of S-nucleophiles with reagent 2 (Table 1, entries 1-9):**

Under  $\text{N}_2$  atmosphere,  $\text{NaH}$  (60%, wt.%, 11 mg, 1.1 equiv.) was added to a solution of 4-nitrobenzenethiol (**5b**) (40 mg, 1.0 equiv.) in  $\text{DMF}$  (4 ml) at rt. After stirring for 30 min, compound **2** (107 mg, 1.2 equiv.) was added, the mixture was heated to  $60^\circ\text{C}$  for 14 h. Then, the reaction was quenched by adding excess amount of  $\text{H}_2\text{O}$ , followed by extraction with  $\text{Et}_2\text{O}$ . The organic phase was washed successively with  $\text{NaOH}$  (5%) and brine, and then dried over anhydrous  $\text{MgSO}_4$ . After the solution was filtered and

the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **6b** (40 mg, yield: 76%) as a yellow liquid. <sup>1</sup>H NMR:  $\delta$  8.24 (d,  $J$  = 8.7 Hz, 2H), 7.73 (d,  $J$  = 8.4 Hz, 2H), 6.95 (t,  $J$  = 55.8 Hz, 1H). <sup>19</sup>F NMR:  $\delta$  -91.2 (d,  $J$  = 55.3 Hz, 2F). MS (EI,  $m/z$ , %): 205 ( $M^+$ , 100.00). The characterization data was consistent with the previous report.<sup>1</sup>

### Characterization data for the isolated compounds:

*(difluoromethyl)(2,5-dimethoxyphenyl)sulfane (6c):* Pink liquid. IR (film): 2838, 1494, 1274, 1224, 1044, 797, 735  $\text{cm}^{-1}$ . <sup>1</sup>H NMR:  $\delta$  7.09 (d,  $J$  = 3.0 Hz, 1H), 6.96 (t,  $J$  = 58.2 Hz, 1H), 6.86–6.95 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H). <sup>19</sup>F NMR:  $\delta$  -92.5 (d,  $J$  = 57.2 Hz, 2F). <sup>13</sup>C NMR:  $\delta$  153.7, 129.0, 127.6, 121.4, 120.6 (t,  $J$  = 271.8 Hz), 116.6, 112.5, 56.6, 55.8. MS (EI,  $m/z$ , %): 220 ( $M^+$ , 7.50), 123 (100.00). HRMS (EI): calcd. for  $\text{C}_9\text{H}_{10}\text{F}_2\text{O}_2\text{S}$ : 220.0370; Found: 220.0367.

*(difluoromethyl)(2-methoxyphenyl)sulfane (6f):* Colorless liquid. IR (film): 2943, 1587, 1481, 1277, 1250, 1077, 1025, 753  $\text{cm}^{-1}$ . <sup>1</sup>H NMR:  $\delta$  7.52 (d,  $J$  = 7.5 Hz, 1H), 7.36–7.42 (m, 1H), 6.93–6.98 (m, 2H), 6.94 (t,  $J$  = 54.4 Hz, 1H), 3.89 (s, 3H). <sup>19</sup>F NMR:  $\delta$  -92.5 (d,  $J$  = 57.8 Hz, 2F). <sup>13</sup>C NMR:  $\delta$  159.5, 136.6, 131.5, 121.3, 120.6 (t,  $J$  = 271.5 Hz), 115.0, 111.5, 56.0. MS (EI,  $m/z$ , %): 190 ( $M^+$ , 0.82), 248 (100.00). HRMS (EI): calcd. for  $\text{C}_8\text{H}_8\text{F}_2\text{OS}$ : 190.0264; Found: 190.0271.

*3-(difluoromethyl)benzo[d]thiazole-2(3H)-thione (6ha):* White solid. <sup>1</sup>H NMR:  $\delta$  8.08 (t,  $J$  = 57.6 Hz, 1H), 7.44 (d,  $J$  = 8.1 Hz, 1H), 7.18–7.39 (m, 3H). <sup>19</sup>F NMR:  $\delta$  -106.0 (d,  $J$  = 56.7 Hz, 2F). The characterization data was consistent with the previous report.<sup>2</sup>

*2-(difluoromethylthio)benzo[d]thiazole (6hb):* Yellow liquid. <sup>1</sup>H NMR:  $\delta$  7.91 (d,  $J$  = 8.1 Hz, 1H), 7.74 (d,  $J$  = 7.8 Hz, 1H), 7.56 (t,  $J$  = 55.8 Hz, 1H). 7.17–7.43 (m, 2H).

<sup>19</sup>F NMR:  $\delta$  –93.1 (d,  $J$  = 55.8 Hz, 2F). MS (EI,  $m/z$ , %): 217 ( $M^+$ , 35.77), 167 (100.00). The characterization data was consistent with the previous report.<sup>2</sup>

*5-(difluoromethylthio)-1-phenyl-1*H*-tetrazole (6i):* White solid. <sup>1</sup>H NMR:  $\delta$  7.82 (d,  $J$  = 7.8 Hz, 2H), 7.46–7.55 (m, 3H), 7.55 (d,  $J$  = 57.0 Hz, 1H). <sup>19</sup>F NMR:  $\delta$  –102.9 (d,  $J$  = 56.7 Hz, 2F). MS (EI,  $m/z$ , %): 228 ( $M^+$ , 3.64), 123 (100.00). The characterization data was consistent with the previous report.<sup>3</sup>

#### **Difluoromethylation of sodium 4, 6-dimethylpyrimidine-2-thiolate (5j) With Reagent 2 (Table 1, entry 10):**

Under N<sub>2</sub> atmosphere, compound **2** (102 mg, 1.2 equiv) was added to the solution of sodium 4, 6-dimethylpyrimidine-2-thiolate (**5j**) (40 mg, 1 equiv) in DMF (4 ml). After stirring for 14 h at 60 °C, the reaction was quenched by adding excess amount of H<sub>2</sub>O, followed by extraction with Et<sub>2</sub>O. The organic phase was washed with brine, and then dried over anhydrous MgSO<sub>4</sub>. After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel column chromatography to give product **6j** (33 mg, 71%). Colorless solid. <sup>1</sup>H NMR:  $\delta$  7.85 (d,  $J$  = 55.8 Hz, 1H), 6.81 (s, 1H), 2.43 (s, 6H). <sup>19</sup>F NMR:  $\delta$  –99.5 (d,  $J$  = 57.8 Hz, 2F). The characterization data was consistent with the previous report.<sup>4</sup>

#### **Typical procedure for electrophilic difluoromethylation of N-nucleophiles with reagent 2 (Table 2, entries 1-9).**

The *N*-difluoromethylated products were prepared by the same procedure for *S*-difluoromethylation with reagent **2** which is described above.

#### **Characterization date for the isolated compounds:**

*1-(difluoromethyl)-5,6-dimethyl-1*H*-benzo[d]imidazole (8a):* White solid. mp. 131–132 °C. IR (film): 1513, 1470, 1371, 1212, 1083, 1046, 867 cm<sup>–1</sup>. <sup>1</sup>H NMR:  $\delta$  7.99 (s, 1H), 7.59 (s, 1H), 7.38 (s, 1H), 7.26 (t,  $J$  = 60.3 Hz, 1H), 2.39 (d,  $J$  = 4.8 Hz,

2H).  $^{19}\text{F}$  NMR:  $\delta$  –93.9 (d,  $J$  = 60.1 Hz, 2F).  $^{13}\text{C}$  NMR:  $\delta$  142.5, 138.3, 134.2, 133.2, 120.8, 111.2, 109.0 (t,  $J$  = 247.5 Hz, 1H), 20.5, 20.1. MS (ESI):  $m/z$  197 (M+H $^+$ ). HRMS (M+H $^+$ ): calcd. for C<sub>10</sub>H<sub>11</sub>F<sub>2</sub>N<sub>2</sub>: 197.08848; Found: 197.0873.

*1-(difluoromethyl)-2-phenyl-1H-benzo[d]imidazole (8b)*: Colorless liquid.  $^1\text{H}$  NMR:  $\delta$  7.71–7.86 (m, 4H), 7.55–7.59 (m, 3H), 7.38–7.43 (m, 2H), 7.28 (t,  $J$  = 58.8 Hz, 1H).  $^{19}\text{F}$  NMR:  $\delta$  –94.8 (d,  $J$  = 58.1 Hz, 2F). The characterization data was consistent with the previous report.<sup>5</sup>

*1-(difluoromethyl)-6-nitro-1H-benzo[d]imidazole (8ca)* and *1-(difluoromethyl)-5-nitro-1H-benzo[d]imidazole (8cb)*: White solid. IR (film): 3115, 1622, 1521, 1346, 1305, 1051, 810 cm $^{-1}$ .  $^1\text{H}$  NMR:  $\delta$  8.76 (d,  $J$  = 2.1 Hz, 1H), 8.60 (d,  $J$  = 1.8 Hz, 1H), 8.32–8.41 (m, 4H), 7.96 (d,  $J$  = 9.3 Hz, 1H), 7.76 (d,  $J$  = 9.0 Hz, 1H), 7.49 (t,  $J$  = 59.7 Hz, 1H), 7.46 (t,  $J$  = 60.0 Hz, 1H).  $^{19}\text{F}$  NMR:  $\delta$  –94.3 (d,  $J$  = 61.5 Hz, 2F), –94.5 (d,  $J$  = 58.4 Hz, 2F).  $^{13}\text{C}$  NMR:  $\delta$  148.1, 145.1, 145.0, 143.6, 143.4, 142.2, 134.5, 129.9, 121.4, 120.4, 119.9, 117.5, 111.6, 108.8 (t,  $J$  = 251.7 Hz), 108.2. MS (EI,  $m/z$ , %): 213 (100.00). HRMS (EI): calcd. for C<sub>8</sub>H<sub>5</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub>: 213.0340; Found: 213.0355.

*1-(difluoromethyl)-2-phenyl-1H-imidazole (8d)*: White solid.  $^1\text{H}$  NMR:  $\delta$  7.60–7.63 (m, 2H), 7.52–7.55 (m, 3H), 7.42 (s, 1H), 7.25 (s, 1H), 7.08 (d,  $J$  = 59.4 Hz, 1H).  $^{19}\text{F}$  NMR:  $\delta$  –90.9 (d,  $J$  = 59.8 Hz, 2F). The characterization data was consistent with the previous report.<sup>6</sup>

*2-(difluoromethyl)-5-phenyl-2H-tetrazole (8ea)*: Colorless liquid.  $^1\text{H}$  NMR:  $\delta$  8.21–8.24 (m, 2H), 7.68 (d,  $J$  = 57.3 Hz, 1H), 7.49–7.56 (m, 3H).  $^{19}\text{F}$  NMR:  $\delta$  –97.8 (d,  $J$  = 56.1 Hz, 2F). The characterization data was consistent with the previous report.<sup>6</sup>

*I-(difluoromethyl)-5-phenyl-1H-tetrazole (8eb):* Colorless liquid.  $^1\text{H}$  NMR:  $\delta$  7.86 (d,  $J$  = 8.1 Hz, 2H), 7.67 (d,  $J$  = 57.6 Hz, 1H), 7.57–7.66 (m, 3H).  $^{19}\text{F}$  NMR:  $\delta$  –94.8 (d,  $J$  = 57.2 Hz, 2F). The characterization data was consistent with the previous report.<sup>6</sup>

*I-(difluoromethyl)-1H-benzo[d]imidazole (8f):* White solid.  $^1\text{H}$  NMR:  $\delta$  8.13 (s, 1H), 7.85–7.88 (m, 1H), 7.61–7.64 (m, 1H), 7.37–7.44 (m, 2H), 7.34 (d,  $J$  = 60.3 Hz, 1H).  $^{19}\text{F}$  NMR:  $\delta$  –94.1 (d,  $J$  = 60.9 Hz, 2F). The characterization data was consistent with the previous report.<sup>5</sup>

*I-(difluoromethyl)-1H-benzo[d][1,2,3]triazole (8g):* White solid.  $^1\text{H}$  NMR:  $\delta$  8.15 (d,  $J$  = 8.4 Hz, 1H), 7.86 (d,  $J$  = 3.6 Hz, 1H), 7.83 (t,  $J$  = 62.1 Hz, 1H), 7.66 (d,  $J$  = 7.2 Hz, 1H), 7.50 (t,  $J$  = 8.1 Hz, 1H).  $^{19}\text{F}$  NMR:  $\delta$  –97.5 (d,  $J$  = 53.3 Hz, 2F). The characterization data was consistent with the previous report.<sup>5</sup>

*2-(difluoromethyl)-1-phenylpyrazolidin-3-one (8h):* Colorless liquid.  $^1\text{H}$  NMR:  $\delta$  7.26 (t,  $J$  = 7.8 Hz, 2H), 7.11 (d,  $J$  = 72.0 Hz, 1H), 6.95 (d,  $J$  = 7.5 Hz, 2H), 6.86 (t,  $J$  = 7.5 Hz, 1H), 3.83 (t,  $J$  = 9.6 Hz, 2H), 3.02 (t,  $J$  = 9.6 Hz, 2H).  $^{19}\text{F}$  NMR:  $\delta$  –97.5 (d,  $J$  = 53.3 Hz, 2F). The characterization data was consistent with the previous report.<sup>7</sup>

### Typical procedure for electrophilic difluoromethylation of C-nucleophiles with reagent 2 (Table 3, entries 1–5):

Under  $\text{N}_2$  atmosphere, butyllithium (1.6 M, 0.29ml, 1.0 equiv) was added to a solution of phenylacetylene (**9a**) (48 mg, 1.0 equiv) in THF (3 ml) at 0°C. After stirring for 0.5 h, reagent **2** (81 mg, 0.5 equiv) was added at –78°C, then the mixture was gradually warmed to room in 6h. The reaction was quenched by adding excess amount of  $\text{H}_2\text{O}$ , followed by extraction with  $\text{Et}_2\text{O}$ . The yield which was determined by  $^{19}\text{F}$  NMR spectroscopy using  $\text{PhCF}_3$  as internal standard is 87%. The organic phase was washed with brine, and then dried over anhydrous  $\text{MgSO}_4$ . After the solution was filtered and the solvent was evaporated under vacuum, the residue was subjected to silica gel

column chromatography to give product **10a** (11 mg, 30%). The isolated yield is low due to the high volatility of the products **10a**). Colorless liquid.  $^1\text{H}$  NMR:  $\delta$  7.53–7.51 (m, 2H), 7.39–7.36 (m, 3H), 6.52 (t,  $J$  = 54.9 Hz, 1H).  $^{19}\text{F}$  NMR:  $\delta$  –105.6 (d,  $J$  = 54.9 Hz, 2F). The characterization data was consistent with the previous report.<sup>8</sup>

*1-(3,3-difluoroprop-1-ynyl)-4-methoxybenzene (**10b**):*  $^{19}\text{F}$  NMR:  $\delta$  –104.5 (d,  $J$  = 56.4 Hz, 2F).

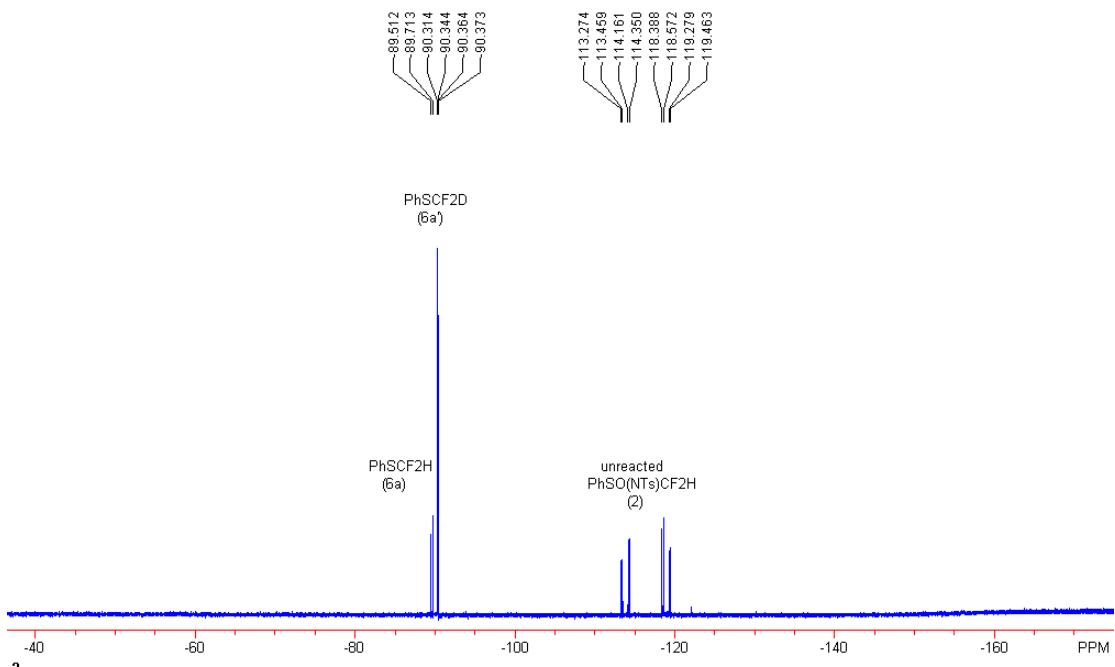
*1-(3,3-difluoroprop-1-ynyl)-4-methylbenzene (**10c**):*  $^{19}\text{F}$  NMR:  $\delta$  –107.2 (d,  $J$  = 54.4 Hz, 2F).

*1-(3,3-difluoroprop-1-ynyl)-4-methoxy-2-methylbenzene (**10d**):*  $^{19}\text{F}$  NMR:  $\delta$  –105.5 (d,  $J$  = 55.0 Hz, 2F).

*2-(3,3-difluoroprop-1-ynyl)-6-methoxynaphthalene (**10e**):*  $^{19}\text{F}$  NMR:  $\delta$  –106.1 (d,  $J$  = 55.6 Hz, 2F).

### **Difluoromethylation of Sodium Thiophenolate With Reagent **2** By Added **10** Equivalents of $\text{D}_2\text{O}$ (Scheme 3, Eq 1):**

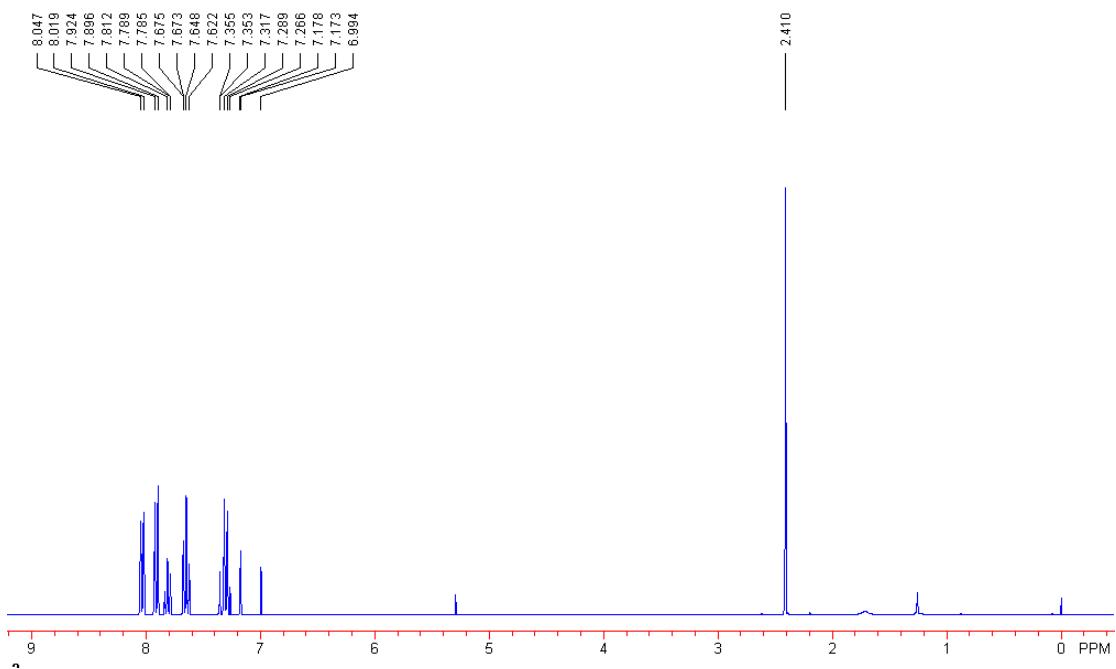
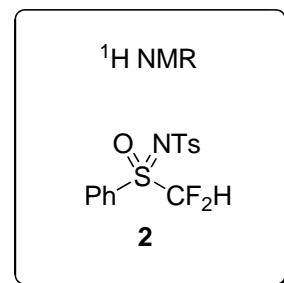
Under  $\text{N}_2$  atmosphere, compound **2** (73 mg, 1.3 equiv), and  $\text{D}_2\text{O}$  (33  $\mu\text{l}$ , 10.0 equiv) was added to the sodium thiophenolate (**5a'**) (90% purity, 24 mg, 1.0 equiv) in DMF (4 ml). After stirring for 14 h at 60°C, the reaction mixture was detected by  $^{19}\text{F}$  NMR:  $\text{PhSCF}_2\text{H}$  (**6a**): –89.6 (d,  $J$  = 56.1 Hz),  $\text{PhSCF}_2\text{D}$  (**6a'**): –90.3 (t,  $J$  = 7.6 Hz). The overall yield of **6a** and **6a'** is 80%, and the ratio of **6a** : **6a'** is 1:6.



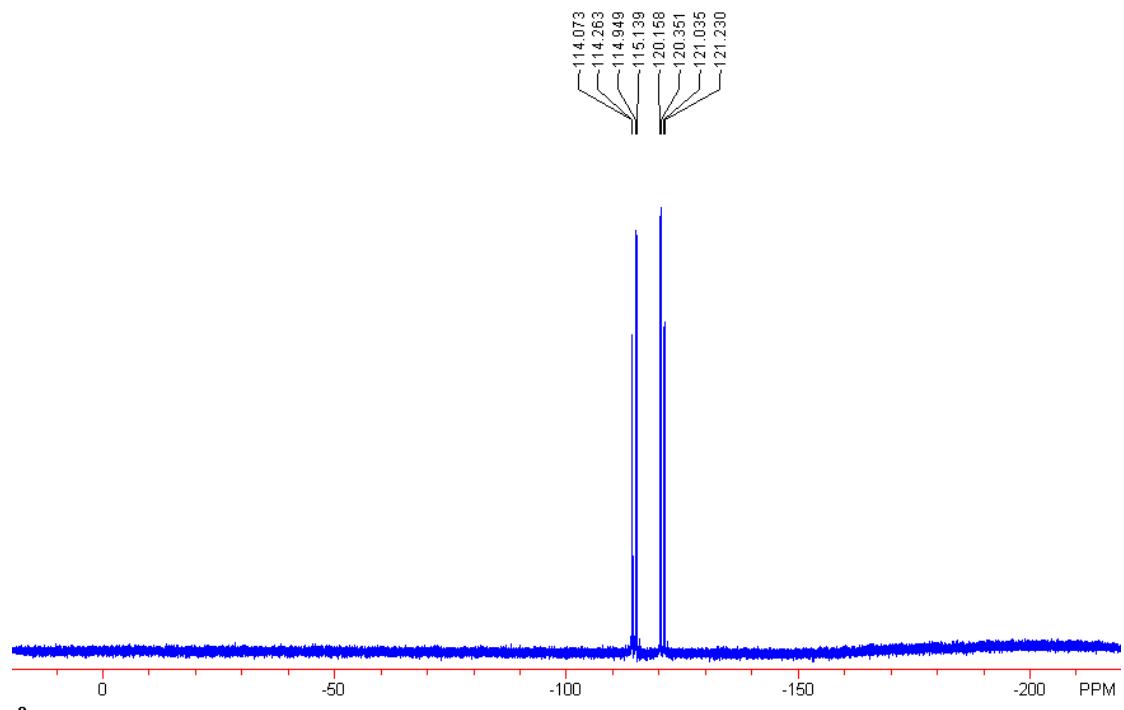
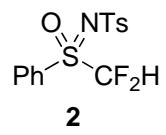
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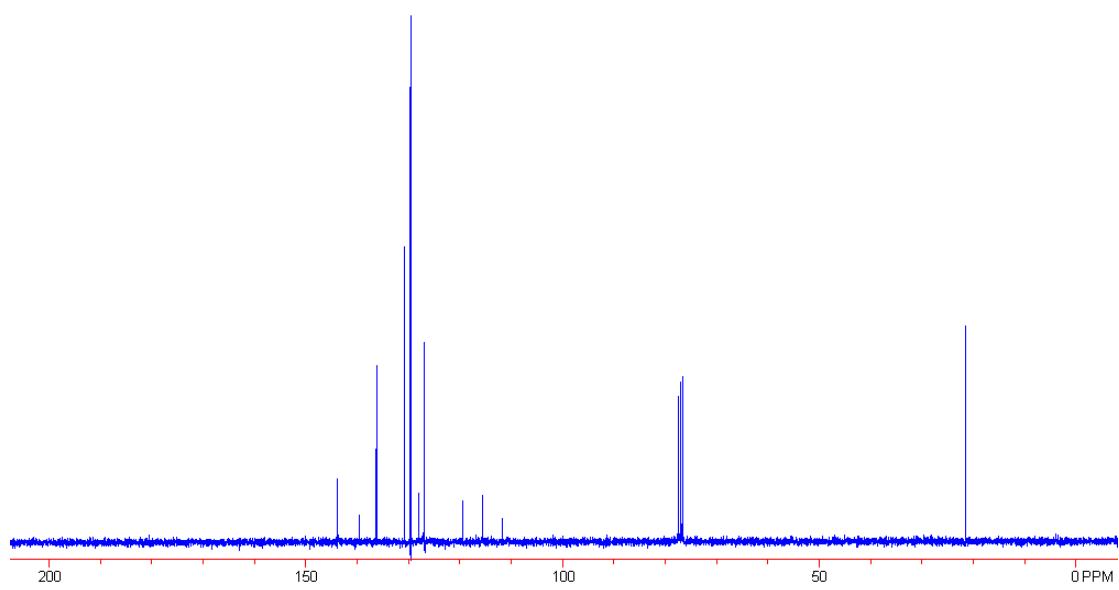
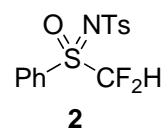
**$^1\text{H}$ ,  $^{19}\text{F}$ , and  $^{13}\text{C}$  NMR spectra of all new products:**



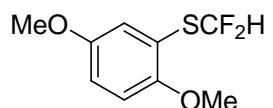
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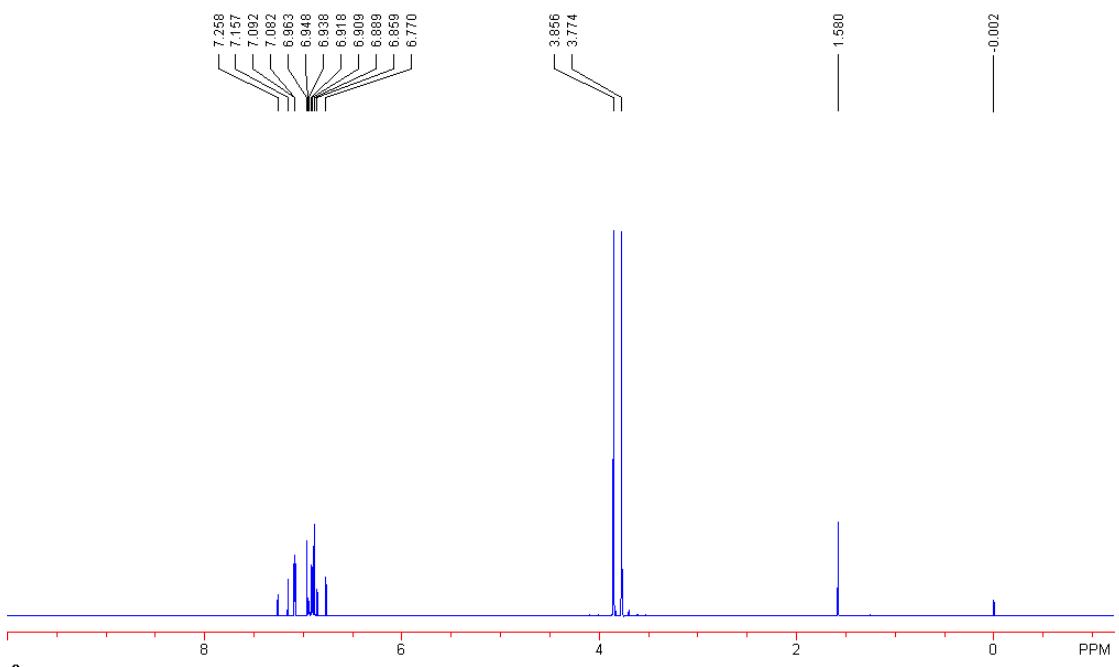
<sup>13</sup>C NMR



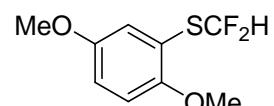
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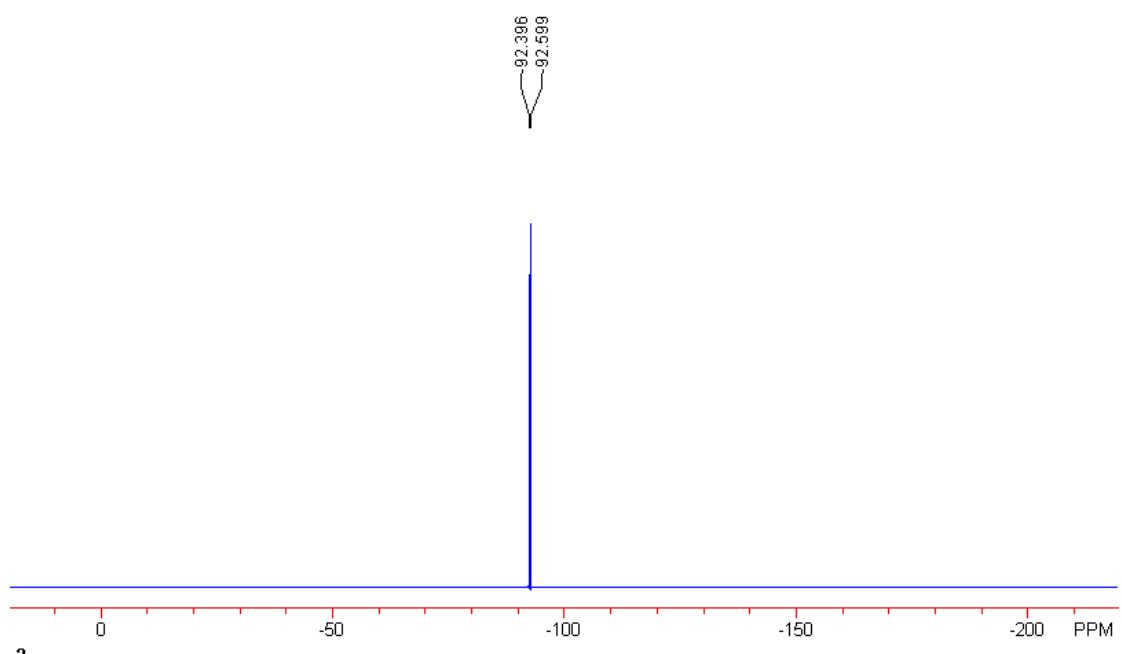
**6c**



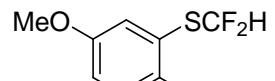
<sup>19</sup>F NMR



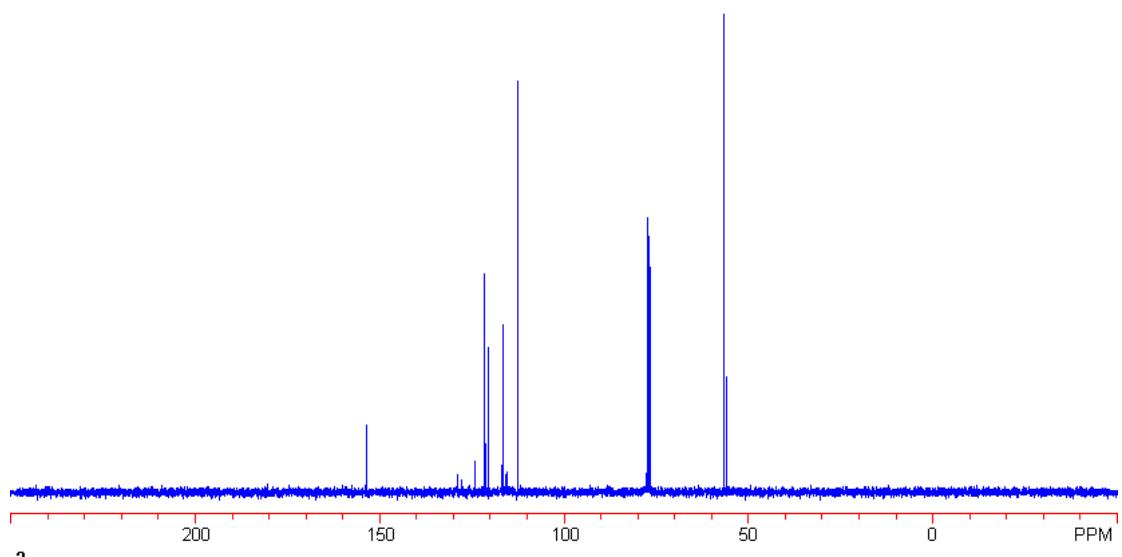
6c

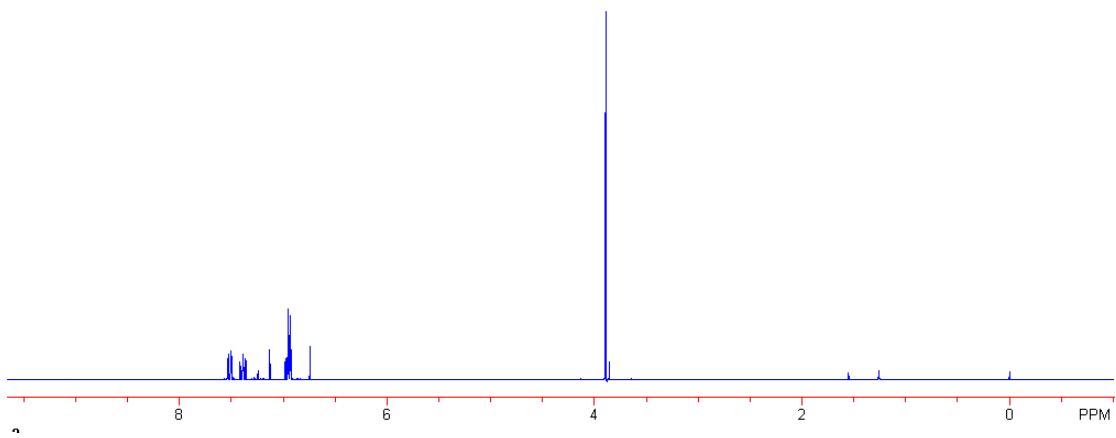
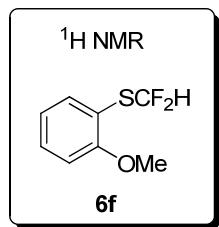


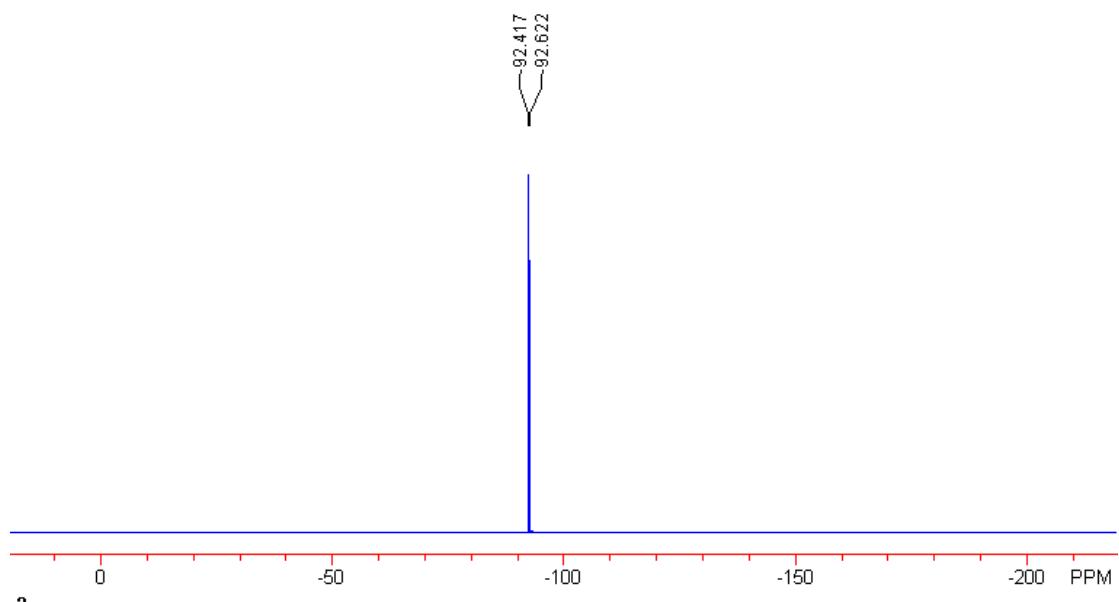
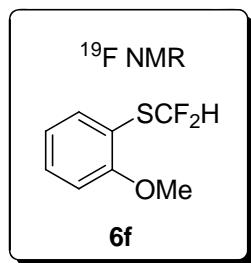
<sup>13</sup>C NMR

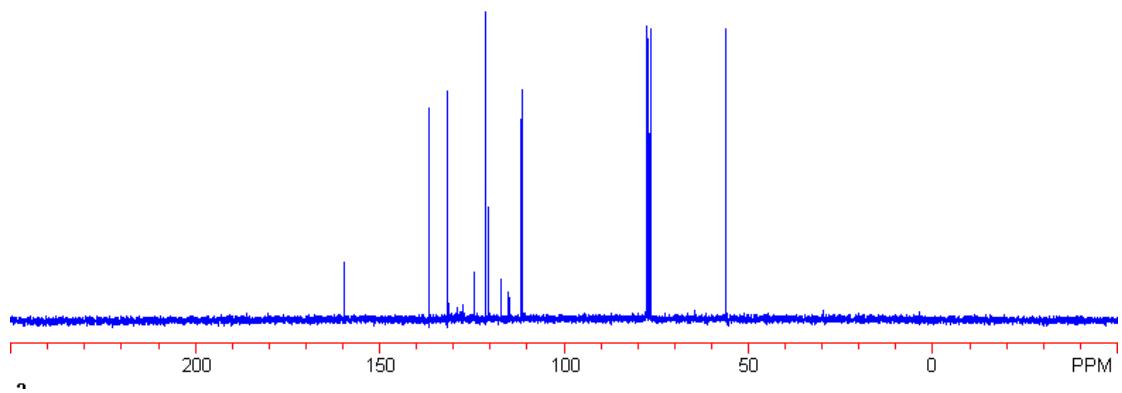
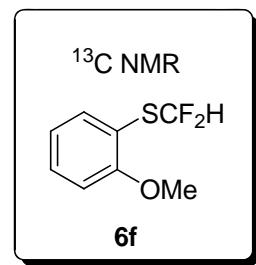


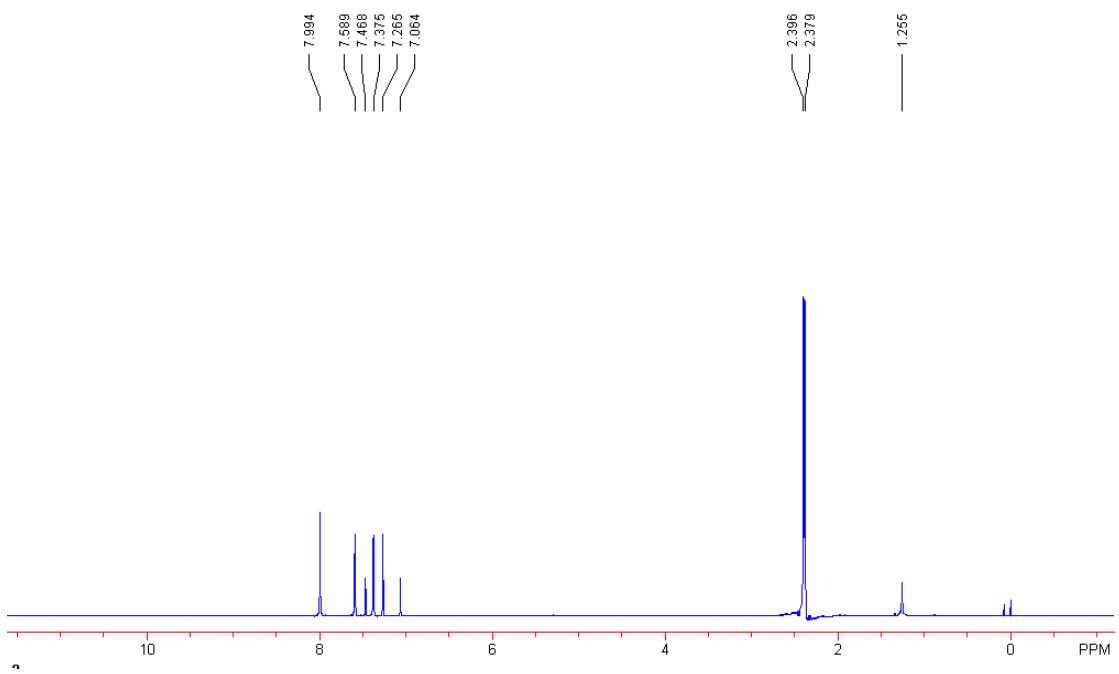
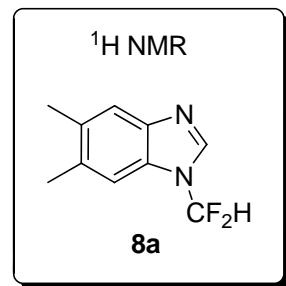
**6c**

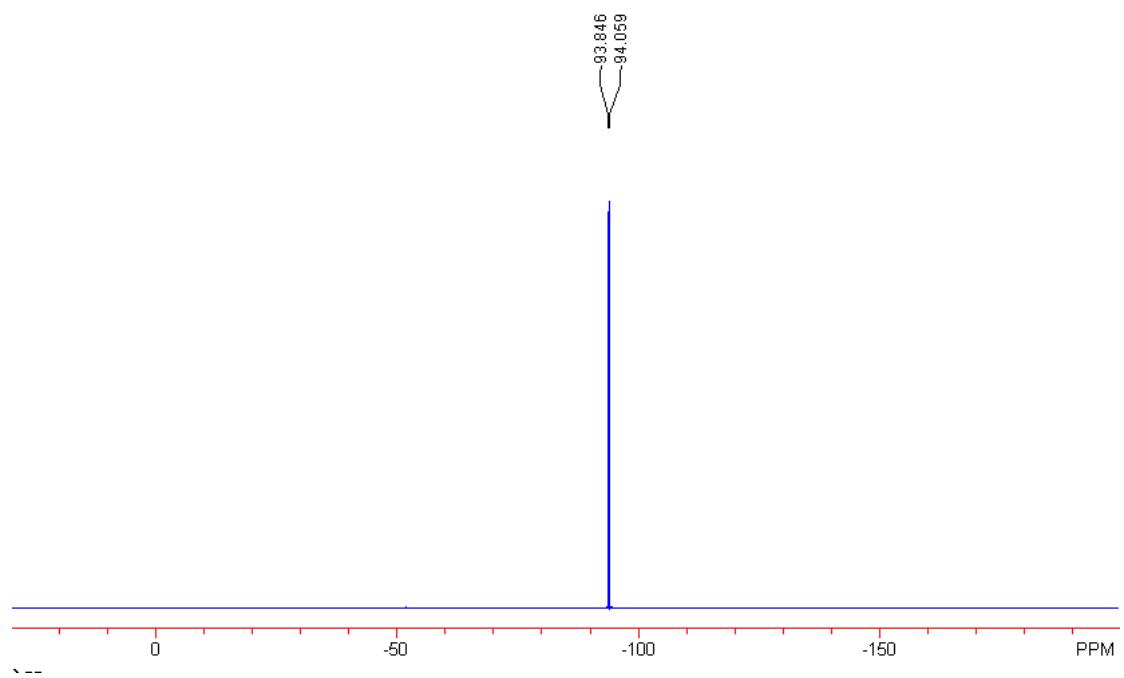
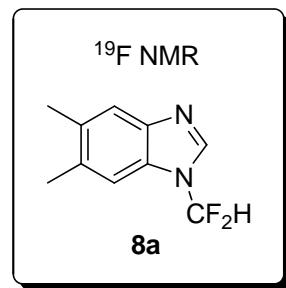


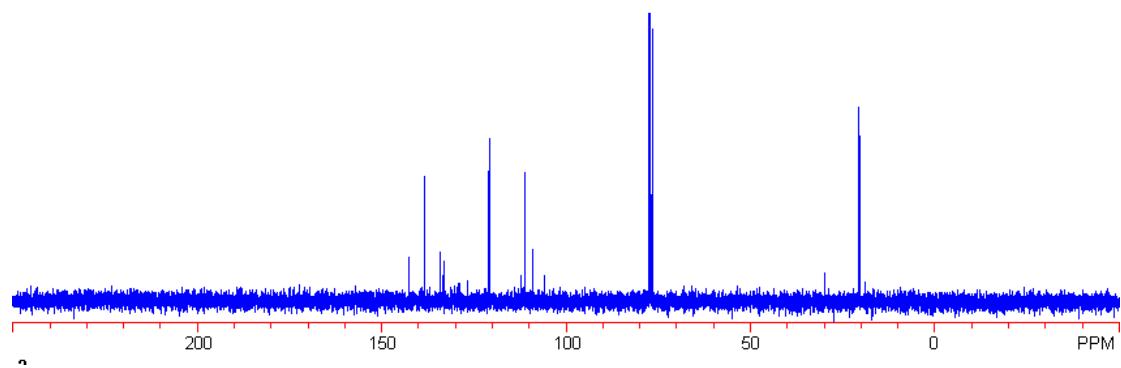
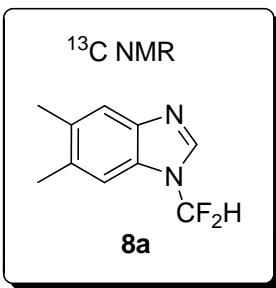




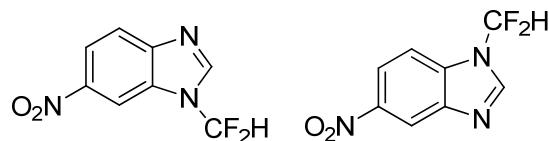






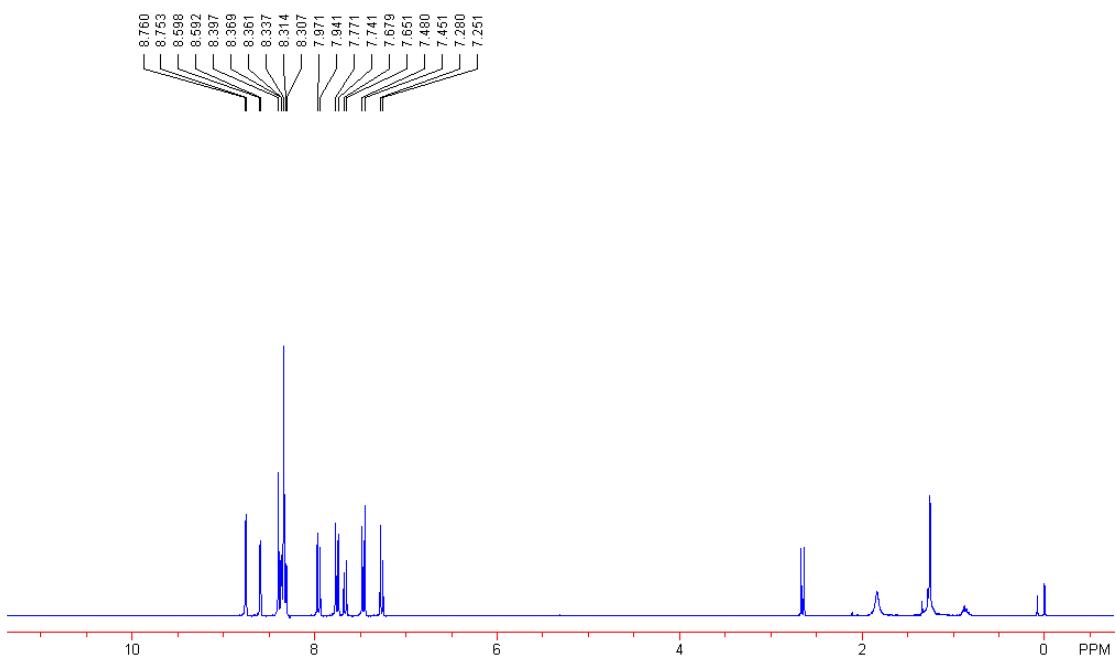


<sup>1</sup>H NMR

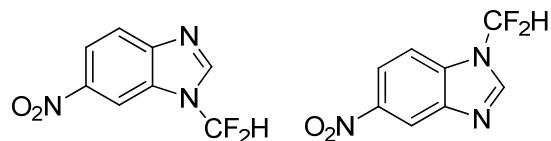


**8ca**

**8cb**



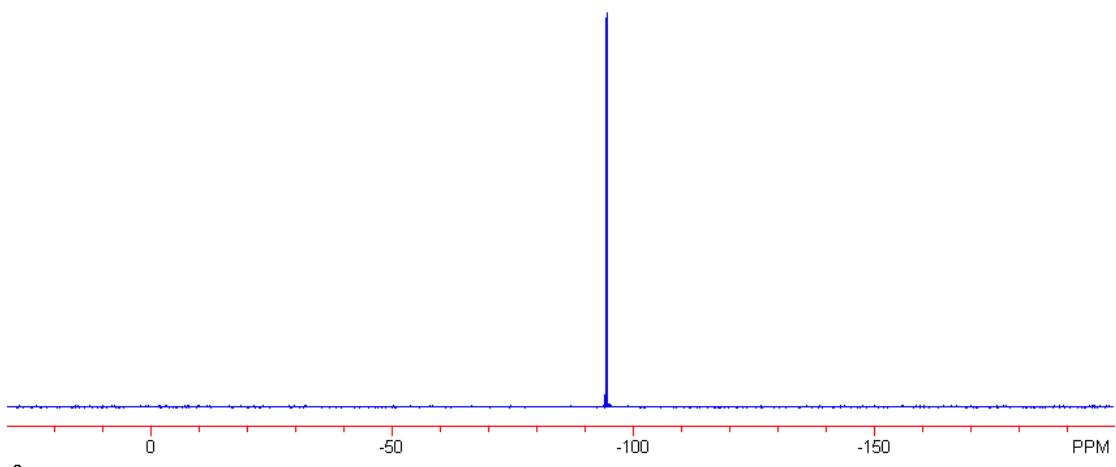
<sup>19</sup>F NMR



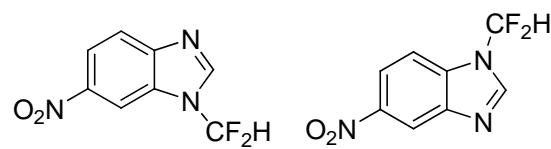
**8ca**

**8cb**

94.246  
94.392  
94.464  
94.599



<sup>13</sup>C NMR



**8ca**

**8cb**

