Electronic Supplementary Material (ESI) for Chemical Communications.

^{18}F-Fluoroform: a ^{18}F-trifluoromethylating agent for the synthesis of $SCF_2{}^{18}F$-aromatic derivatives

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Supporting information

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Section A: Non radioactive chemistry

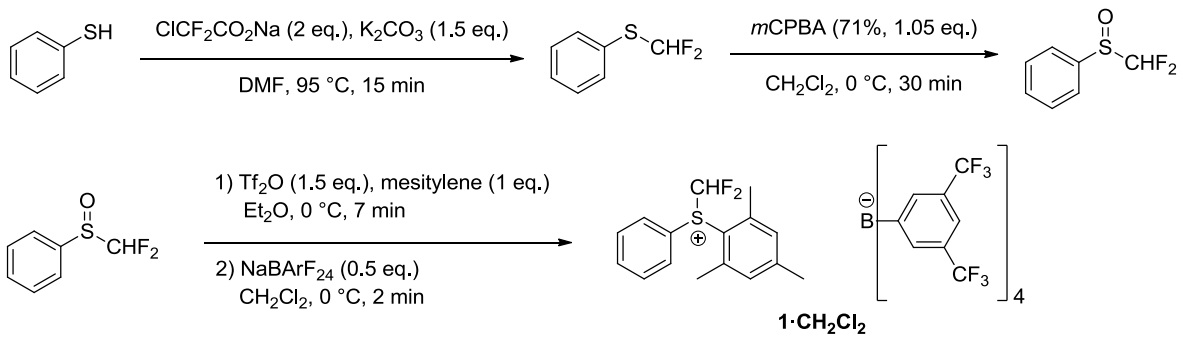
1. General information

All reactions were carried out using oven dried glassware and magnetic stirring under an atmosphere of argon unless otherwise stated. Flash chromatography was performed with silica gel (0.040-0.063 mm). Analytical thin layer chromatography was performed on silica gel aluminum plates with F-254 indicator and visualized by UV light (254 nm) and/or chemical staining with a $KMnO_4$ solution or a phosphomolybdic acid solution. ^{1}H NMR spectra were recorded on a Bruker DXP 300 at 300.1 MHz, ^{13}C NMR spectra at 75.5 MHz and ^{19}F NMR spectra at 282.4 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) relative to the residual solvent peak for $CDCl_3$ (δH = 7.26 ppm; δC = 77.0 ppm or relative to external $CFCl_3$: δ = 0 ppm), CH_3CN (δH = 1.94 ppm; δC = 118.26 ppm, 1.32 ppm or relative to external $CFCl_3$: δ = 0 ppm). The following abbreviations have been used: δ (chemical shift), *J* (coupling constant), br (broad), s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), qq (quadruplet of quadruplet). High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier. IR spectra were recorded on a PerkinElmer Spectrum 100, the wave numbers (ν) of recorded IR-signals (ATR) are quoted in cm^{-1}. Melting points were recorded on a Heizbank system Kofler WME and were uncorrected.

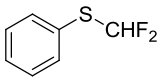
2. Materials

CH_2Cl_2 and thiophenol were distilled over CaH_2 prior to use. Mesitylene and THF were distilled over Na/benzophenone prior to use. CH_3CN, DMF and MeOH (sealed bottle over molecular sieves) and sodium chlorodifluoroacetate (96%) were purchased from Acros Organics. *m*CPBA (71%), *t*BuOK (≥ 98%) and trifluoromethanesulfonic anhydride (99%) were purchased from Aldrich. HCF_3 (98%) from Apollo Scientific. 4-Bromothiophenol**,** 4-chlorothiophenol, 4-cyanobenzenesulfonyl chloride, 4-fluorothiophenol**,** 4-mercaptobenzoic acid, 2-mercaptopyridine, 2-naphthalenethiol, 4-*tert*-butylthiophenol, thiophenol, 1,2-di(pyridin-2-yl)disulfane, 1,2-bis(4-chlorophenyl)disulfane, 1,2-bis(4-methoxyphenyl)disulfane, 1,2-diphenyldiselane, 1,2-diphenyldisulfane, *S*-phenyl benzene-sulfonothioate were purchased from Acros Organics, Aldrich, Alfa Aesar, Maybridge and TCI.

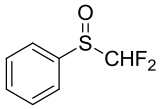
3. Synthesis of reagent 1·CH_2Cl_2



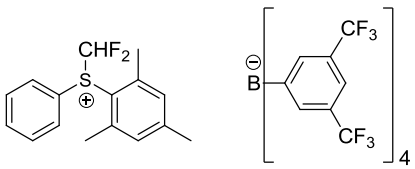
1·CH_2Cl_2



Difluoromethylphenyl sulfide. Synthesized following the slightly modified procedure reported by Akita and co-workers.[1] Sodium chlorodifluoroacetate (13.72 g, 90 mmol, 2 eq.) and K_2CO_3 (9.34 g, 67.5 mmol, 1.5 eq.) were added in a 500 mL two necked flask and dried under high vacuum for 1 h. DMF (99%, 150 mL) was added at RT, followed by the addition of the thiophenol dropwise (4.59 mL, 45 mmol, 1 eq.). The reaction mixture was stirred at 95 °C for 15 min (exothermic reaction) and then cooled to RT. Water (130 mL) and pentane (130 mL) were added. The layers were separated and the organic layer was washed with water (4 x 130 mL), dried over $MgSO_4$ and concentrated under vacuum to furnish a colorless oil (6.3 g, 88%) which was directly used without further purification. $\mathbf{R_f}$ (pentane): 0.56. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ7.52-7.44 (m, 2H), 7.36-7.24 (m, 3H), 6.72 (t, *J* = 57.0, 1H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ135.3, 129.7, 129.3, 126.1 (t, *J* = 3.0 Hz), 121.0 (t, *J* = 275.6 Hz). **^{19}F NMR** ($CDCl_3$, 282.4 MHz) δ -91.3 (d, *J* = 56.8 Hz, 2F). **IR** (cm^{-1}) ν: 3062, 2926, 1579, 1476, 1440, 1297, 1321, 1065, 1024, 797, 736, 688. **HRMS** (EI) calcd for $C_7H_6F_2S$ *m/z* 160.01583 $[M]^+$, found 160.01444 (8.69 ppm). The data were consistent with literature.[1]



Difluoromethylphenylsulfoxide. Synthesized following the slightly modified procedure reported by Olah and co-workers.[2] *m*CPBA (71%, 1.79 g, 7.36mmol, 1.05 eq.) was added at 0 °C to a stirred solution of difluoromethylphenyl sulfide (1.04 g, 7mmol, 1eq.) in CH_2Cl_2 (18mL). The resulting mixture was stirred at 0 °C for 30 minutes and then filtered. An aqueous 1 $mol.L^{-1}$ NaOH solution (5 mL) was added until a pH of 14 was reached and then CH_2Cl_2 (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude reaction mixture was purified by flash chromatography on silica gel (petroleum ether/diethyl ether = 70:30, height 15 cm, width 4 cm) to yield a colorless oil (0.88 g, 72%). $\mathbf{R_f}$ (petroleum ether/diethyl ether = 70:30): 0.30. **^{1}H NMR** ($CDCl_3$, 300.1 MHz) δ 7.75-7.69 (m, 2H), 7.65-7.55 (m, 3H), 6.04 (t, *J* = 55.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ 136.7 (t, *J* = 3.2 Hz), 133.0, 129.7, 125.6, 121.0 (t, *J*= 289.2 Hz). **^{19}F NMR** ($CDCl_3$, 282.4 MHz) δ -119.3 (dd, *J*= 283.8, 55.4 Hz, 1F), -120.3 (dd, *J* = 283.8, 55.4 Hz, 1F). **IR** (cm^{-1}): 3063, 2976, 1479, 1446, 1280, 1088, 1047, 1023, 743, 686. **HRMS** (EI) calcd for $C_7H_6F_2OS$ *m/z* 176.01074 $[M]^+$, found 176.01096 (1.25 ppm). The data were consistent with literature.[2]



$C_{16}H_{17}F_2S^+$ $C_{32}H_{12}BF_{24}^-$

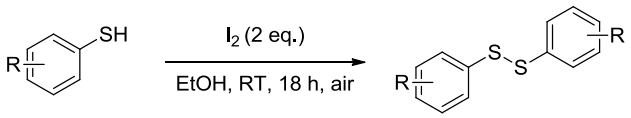
1·CH_2Cl_2

_S_-Difluoromethyl-_S_-mesityl-_S_-phenylsulfonium*tetra*(3,5di(trifluoromethyl)phenyl)borate·CH_2Cl_2 (1·CH_2Cl_2)

Synthesized following our previously described procedure.[3] Technical grade solvents were used to perform the reaction. Triflic anhydride (0.34 mL, 2.40 mmol, 1.5 eq.) was added dropwise at 0 °C to a stirred solution of difluoromethylphenylsulfoxide (0.28 g, 1.60 mmol, 1 eq.) and mesitylene (0.27 mL, 1.60 mmol, 1 eq.) in Et_2O (16 mL). After stirring for 7 min, the solvent was removed using a syringe. The residual red oil was washed with cold Et_2O (10 mL) at 0°C and the solvent was removed again. Solid $NaBArF_{24}$ (0.8 mmol, 0.71 g, 0.5 eq.) was added followed by CH_2Cl_2 (8mL). After stirring for 2 min at 0 °C, the mixture was diluted with cold toluene (20 mL) and filtered over cotton (the filtered was not washed). The filtrate was diluted with petroleum ether (400 mL) to obtain a cloudy solution. CH_2Cl_2 (50 mL) was added and the mixture was kept for 1 day at room temperature under air. The salt was filtered off to give the pure compound **1·CH_2Cl_2** as colorless crystals (0.45 g, 46%). **^{1}H NMR** (CD_3CN, 300.1MHz) δ 7.98 (t, J = 52.5 Hz,1H), 7.84-7.58 (m, 17H), 7.34 (s, 2H), 5.42 (CH_2Cl_2), 2.45 (s, 6H), 2.38 (s, 3H). **^{13}C NMR** (CD_3CN, 75.5 MHz) δ 162.8 (q, J = 49.8 Hz + septet, J = 16.6 Hz), 150.2, 146.6, 135.8, 135.3, 134.1, 132.7, 130.1 (qq, J = 31.0, 2.3 Hz), 129.5,125.6 (q, J = 271.8 Hz), 120.6 (dt, J = 298.2, 3.8 Hz), 118.3, 111.3, 22.1 (br s), 21.6 (br d, J = 3.0 Hz). **^{19}F NMR** (CD_3CN, 282.4 MHz) δ -63.2 (s, 24F), -94.2 (dd, J = 225.6, 52.5 Hz, 1F), -95.3 (dd, J = 225.6, 52.5 Hz, 1F). **HRMS** (ESI^+) calcd for $C_{16}H_{17}F_2S$ *m/z* 279.1019 [M^+], found 279.1021. **HRMS** (ESI^-) calcd for $C_{32}H_{12}F_{24}B$ *m/z* 863.0649 [M^-], found 863.0662. The data were consistent with literature.[3]

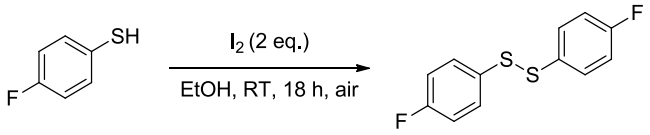
4. Procedures for the synthesis of disulfides

Procedure A for the synthesis of disulfides **2b**, **2d** and **2g**[4]



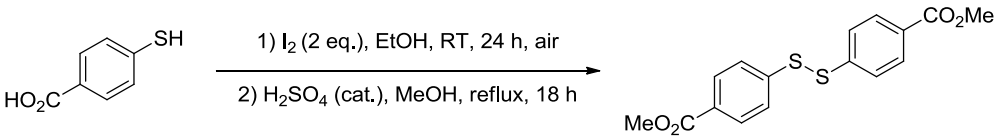
I_2 (2 eq.) was added to a stirred solution of the thiophenol derivative (1 eq.) in ethanol (C = 1 mol.L^{-1}). The reaction mixture was stirred for 18 h under an air atmosphere at RT. The product was obtained by filtration over a sintered-glass filter. If required, the product was purified by flash chromatography on silica gel.

Procedure B for the synthesis of the1,2-bis(4-fluorophenyl) disulfane **2c**[4]



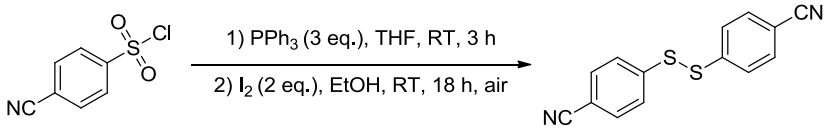
I_2 (4 g, 15.8 mmol,2 eq.) was added to a stirred solution of the 4-fluorothiophenol (0.86 mL, 7.9 mmol, 1 eq.) in ethanol (8mL). The reaction mixture was stirred for 18 h under an air atmosphere at RT. The reaction mixture was quenched by addition of water (10 mL) and by addition of solid $Na_2S_2O_3$ until complete disappearance of the brown color. Then, ethanol was removed under vacuum and EtOAc was added (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel to yield the desired product **2c**.

Procedure C for the synthesis of the dimethyl 4,4'-disulfanediyldibenzoate **2h**[4]



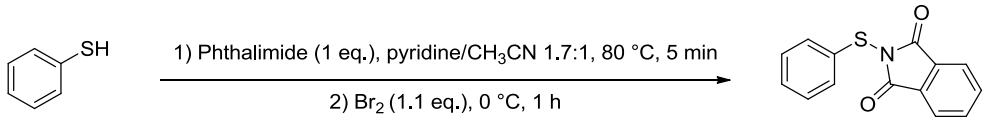
I_2 (9.9 g, 39 mmol, 2 eq.) was added to a stirred solution of the 4-mercaptobenzoic acid (3 g, 19.5 mmol, 1 eq) in ethanol (24 mL). The reaction mixture was stirred for 24 h under an air atmosphere at RT. 4,4'-disulfanediyldibenzoic acid was obtained by filtration over a sintered-glass filter and was directly engaged without further purification. Then 4,4'-disulfanediyldibenzoic acid (2.5 g, 8.16 mmol, 1 eq) was then dissolved in MeOH (30mL) and conc. H_2SO_4 (4mL) was added. The resulting mixture was refluxed (65 °C) for 18 h and filtered off over a sintered-glass filter. The crude solid was purified by flash chromatography on silica gel to yield the desired product **2h**.

Procedure D for the synthesis of the 4,4'-disulfanediyldibenzonitrile **2i** [4],[5]



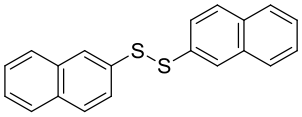
PPh_3 (9.8 g, 37.2 mmol, 3 eq.) was added to a solution of 4-cyanobenzenesulfonyl chloride (2.5 g, 12.4 mmol, 1 eq.) in THF (50 mL). The resulting mixture was stirred for 3h at RT and then concentrated under vacuum. The residue was dissolved in EtOAc (50 mL) and petroleum ether (300 mL) was slowly added. The white precipitate (Ph_3PO) was filtered off and the filtrate was concentrated under vacuum to give a mixture of the 4,4'-disulfanediyldibenzonitrile and the corresponding thiol. The reaction mixture was dissolved in ethanol (13 mL) and I_2 (6.1 g, 24 mmol, 2 eq.) was added. The reaction mixture was stirred for 18 h under an air atmosphere at RT. The desired product **2i** was obtained by filtration over a sintered-glass and used without further purification.

5. Procedure for the synthesis of 2-(phenylthio)isoindoline-1,3-dione4a[6]



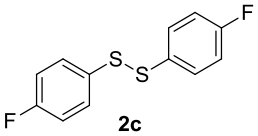
A mixture of phthalimide (0.8 g, 5.87 mmol, 1 eq.) and thiophenol (0.63 mL, 6.16 mmol, 1.05 eq.) in CH_3CN (2.6 mL) and pyridine (4.5 mL) was stirred for 5 min at 80 °C and then cooled down to 0 °C. A solution of Br_2 (0.33 mL, 6.46 mmol, 1.1 eq.) in CH_3CN (2.9 mL) was added dropwise for 10 min at 0 °C and the resulting mixture was further stirred at 0 °C for 1h. Then, water (12mL) was added dropwise at 0 °C and the resulting heterogeneous solution was filtered off. The crude product was recrystallized in MeOH (10 mL) to give the desired compound **4a**.

6. Purification and characterization of substrates



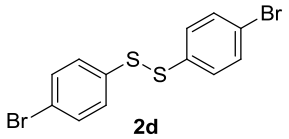
2b

1,2-Di(naphthalen-2-yl)disulfane2b. The product was synthesized according to the procedure A from 2-naphtalenethiol (0.99 g, 6.20 mmol). **2b** was obtained by filtration of the reaction mixture followed by purification by flash chromatography on silica gel (width 3 cm, height 15 cm, petroleum ether) to yield a yellow solid (0.98 g, 99%). $\mathbf{R_f}$ (petroleum ether): 0.42. **mp**: 145-146 °C. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ 8.02-7.98 (m, 2H), 7.83-7.71 (m,6H), 7.64 (dd, *J* = 8.7, 1.8 Hz, 2H), 7.51-7.42 (m, 4H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ 134.2, 133.4, 132.5, 129.0, 127.7, 127.4, 126.7, 126.5, 126.2, 125.6. **IR** (cm^{-1}) ν: 3052, 1581, 1498, 1337, 1268, 1132, 864, 813, 738, 478. **HRMS** (EI) calcd for $C_{20}H_{14}S_2$ *m/z* 318.05369 $[M]^+$, found 318.05434 (2.05 ppm).The data were consistent with literature.[7]



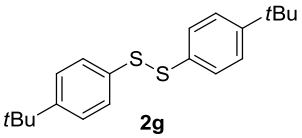
2c

1,2-Bis(4-fluorophenyl) disulfane 2c. The product was synthesized according to the procedure B from 4-fluorothiophenol (0.84 mL, 7.90mmol). **2c** was purified by flash chromatography on silica gel (width 6 cm, height 17 cm, petroleum ether) to yield a yellow oil (1 g, 99%). $\mathbf{R_f}$ (petroleum ether/diethyl ether 80:20): 0.45. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ 7.54-7.36 (m, 4H), 7.00 (dd, *J* = 8.4, 8.4 Hz, 4H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ 162.5 (d, *J* = 248.4 Hz), 132.1 (d, *J* = 3.8 Hz), 131.2 (d, *J* = 8.3 Hz), 116.2 (d, *J* = 22.7 Hz). **^{19}F NMR** ($CDCl_3$, 282.4 MHz): δ -114.0 to -113.9 (m, 2F). **IR** (cm^{-1}) ν: 3066, 1587, 1485, 1396, 1223, 1154, 1077, 1012, 820, 620, 499. **HRMS** (EI) calcd for $C_{12}H_8F_2S_2$ *m/z* 254.00355 $[M]^+$, found 254.00446 (3.58 ppm). The data were consistent with literature.[7]



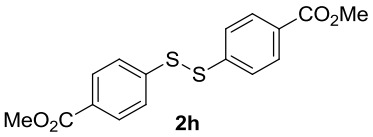
2d

1,2-Bis(4-bromophenyl)disulfane2d. The product was synthesized according to the procedure A from 4-bromothiophenol (1.32 g, 7.0 mmol). **2d** was obtained by filtration of the reaction mixture to yield a yellow solid (1.24 g, 95%). $\mathbf{R_f}$ (petroleum ether): 0.69. **mp**: 99-100 °C. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ 7.46-7.39(m, 4H), 7.37-7.30 (m, 4H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ 135.7, 132.2, 129.3, 121.5. **IR** (cm^{-1}) ν: 3069, 1466, 1383, 1079, 1066, 1005, 811, 495, 475. **HRMS** (EI) calcd for $C_{12}H_8Br_2S_2$ *m/z* 373.84342 $[M]^+$, found 373.84445 (2.76 ppm). The data were consistent with literature.[7]



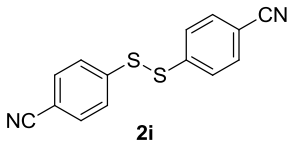
2g

1,2-Bis(4-(tert-butyl)phenyl)disulfane 2g. The product was synthesized according to the procedure A from 4-*tert*-butylthiophenol (2.07 mL, 12mmol, 1 eq.). **2g** was obtained by filtration of the reaction mixture to yield a yellow solid (1.20 g, 61%). $\mathbf{R_f}$ (petroleum ether): 0.61. **mp**: 95-96 °C. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ 7.52-7.44 (m, 4H), 7.40-7.33 (m, 4H), 1.33 (s, 18H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ 150.4, 134.0, 127.7, 126.1, 34.5, 31.2. **IR** (cm^{-1}) ν: 2956, 2927, 2861, 1484, 1395, 1361, 1265, 1113, 1009, 822, 547. **HRMS** (EI) calcd for $C_{20}H_{26}S_2$ *m/z* 330.14759 $[M]^+$, found 330.14679 (-2.42 ppm). The data were consistent with literature.[7]



2h

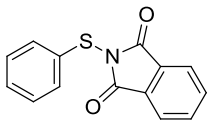
Dimethyl 4,4'-disulfanediyldibenzoate 2h. The product was obtained according to the procedure C from 4-mercaptobenzoic acid (3 g, 19.5 mmol, 1 eq). **2h** was isolated by purification by flash chromatography (width 4 cm, height 14 cm, petroleum ether/diethyl ether 60:40) as a white solid (1.3 g, 40%). $\mathbf{R_f}$ (petroleum ether/diethyl ether 60:40): 0.53. **mp**: 130-131 °C. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ 7.96 (d, *J* = 8.7 Hz, 4H), 7.52 (d, *J* = 8.7, 4H), 3.89 (s, 6H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ 166.3, 142.1, 130.2, 128.8, 125.9, 52.2. **IR** (cm^{-1}) ν: 2949, 1713, 1589, 1434, 1274, 1108, 752, 686. **HRMS** (ESI) calcd for $C_{16}H_{18}NO_4S_2$ *m/z* 352.0677 $[M+NH_4]^+$, found 352.0678 (0.3 ppm). The data were consistent with literature.[7]



2i

4,4'-Disulfanediyldibenzonitrile 2i. The product was obtained according to the procedure D from 4-cyanobenzenesulfonyl chloride (2.50 g, 12.4 mmol). **2i** was obtained by filtration of the reaction mixture to yield a white solid (1.06 g, 64%). $\mathbf{R_f}$ (petroleum ether/diethyl ether = 80:20): 0.20. **mp**:

188-189 °C. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ 7.64-7.51 (m, 8H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ142.0, 132.7, 126.4, 118.1, 110.8. **IR** (cm^{-1}) ν: 2924, 2224, 1588, 1483, 1398, 1179, 1071, 1015, 817, 539. **HRMS** (EI) calcd for $C_{14}H_8N_2S_2$ *m/z* 268.01289 $[M]^+$, found 268.01412 (4.59 ppm). The data were consistent with literature.[7]



4a

2-(Phenylthio)isoindoline-1,3-dione 4a. The product was synthesized according to the procedure for the synthesis of 2-(phenylthio)isoindoline-1,3-dione from phthalimide (0.80 g, 5.87mmol, 1.05 eq.). **4a** was obtained by filtration as a white solid (0.60 g, 42%). **R_f** (petroleum ether/diethyl ether 80:20): 0.24. **mp**: 162-163 °C. **^{1}H NMR** ($CDCl_3$, 300.1 MHz): δ 7.97-7.89 (m, 2H), 7.82-7.73 (m, 2H), 7.64-7.57 (m, 2H), 7.38-7.28 (m, 3H). **^{13}C NMR** ($CDCl_3$, 75.5 MHz): δ 167.7, 135.0, 134.7, 131.9, 130.9, 129.3, 124.0. **IR** (cm^{-1}) ν: 3052, 1714, 1471, 1374, 1216, 1083, 886, 765, 715. **HRMS** (ESI) calcd for $C_{14}H_{13}N_2O_2S$ *m/z* 273.0698 $[M+NH_4]^+$, found 273.0704 (2.2 ppm). The data were consistent with literature.[8]

7. References

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[4] R. S. Sengar, V. N. Nemykin, P. Basu, *New J. Chem.* **2003**, *27*, 1115-1123.

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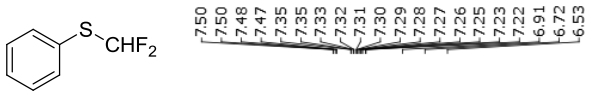
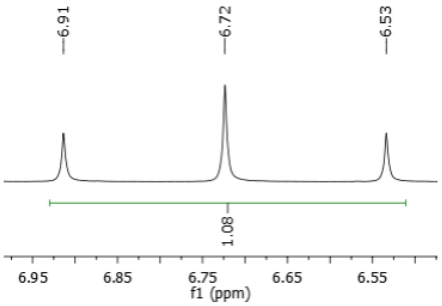
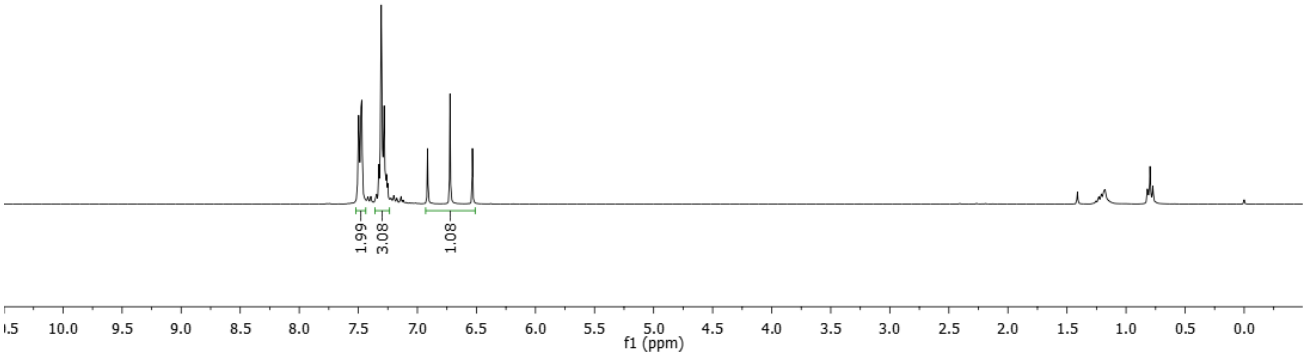
[7]Y. Zheng, F.-L. Qing, Y. Huang, X.-H. Xu, *Adv. Synth. Catal.* **2016,** *358*, 3477-3481.

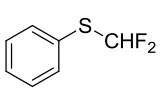
[8] Z. Song, Y. Wu, T. Xin, C. Jin, X. Wen, H. Sun, Q.-L. Xu, *Chem. Commun.* **2016**, *52*, 6079-6082.

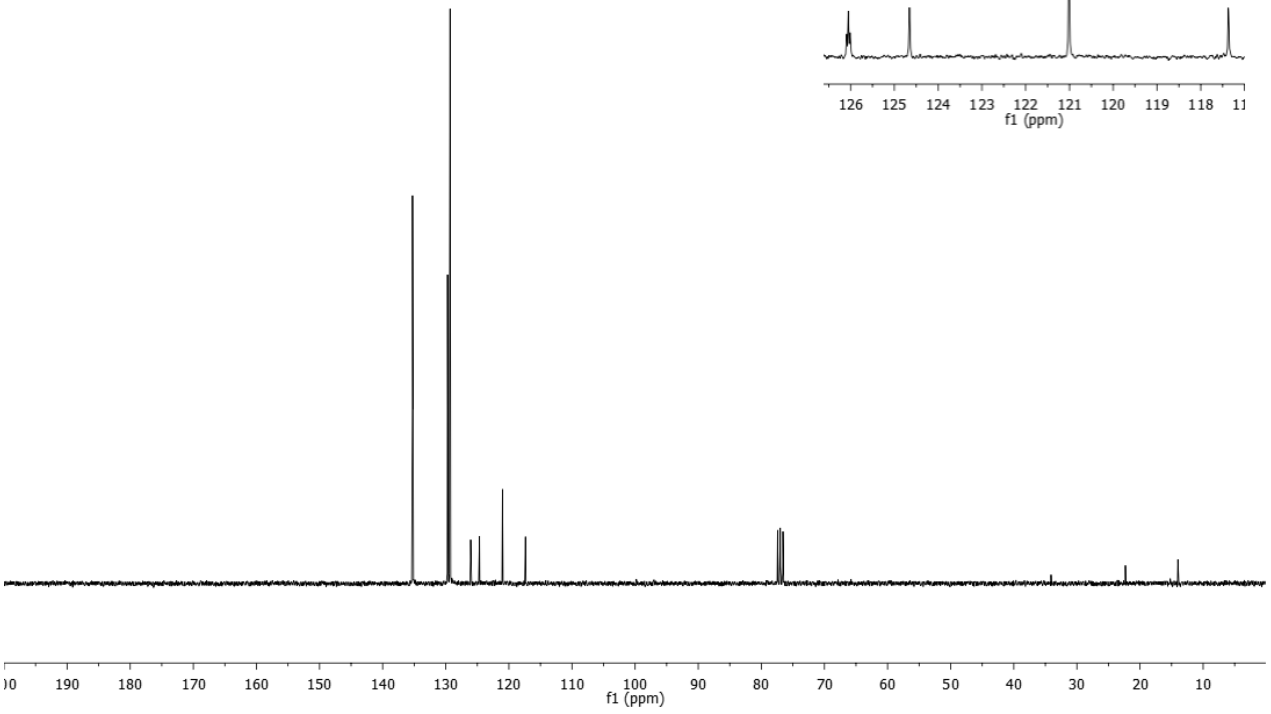
8. Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra

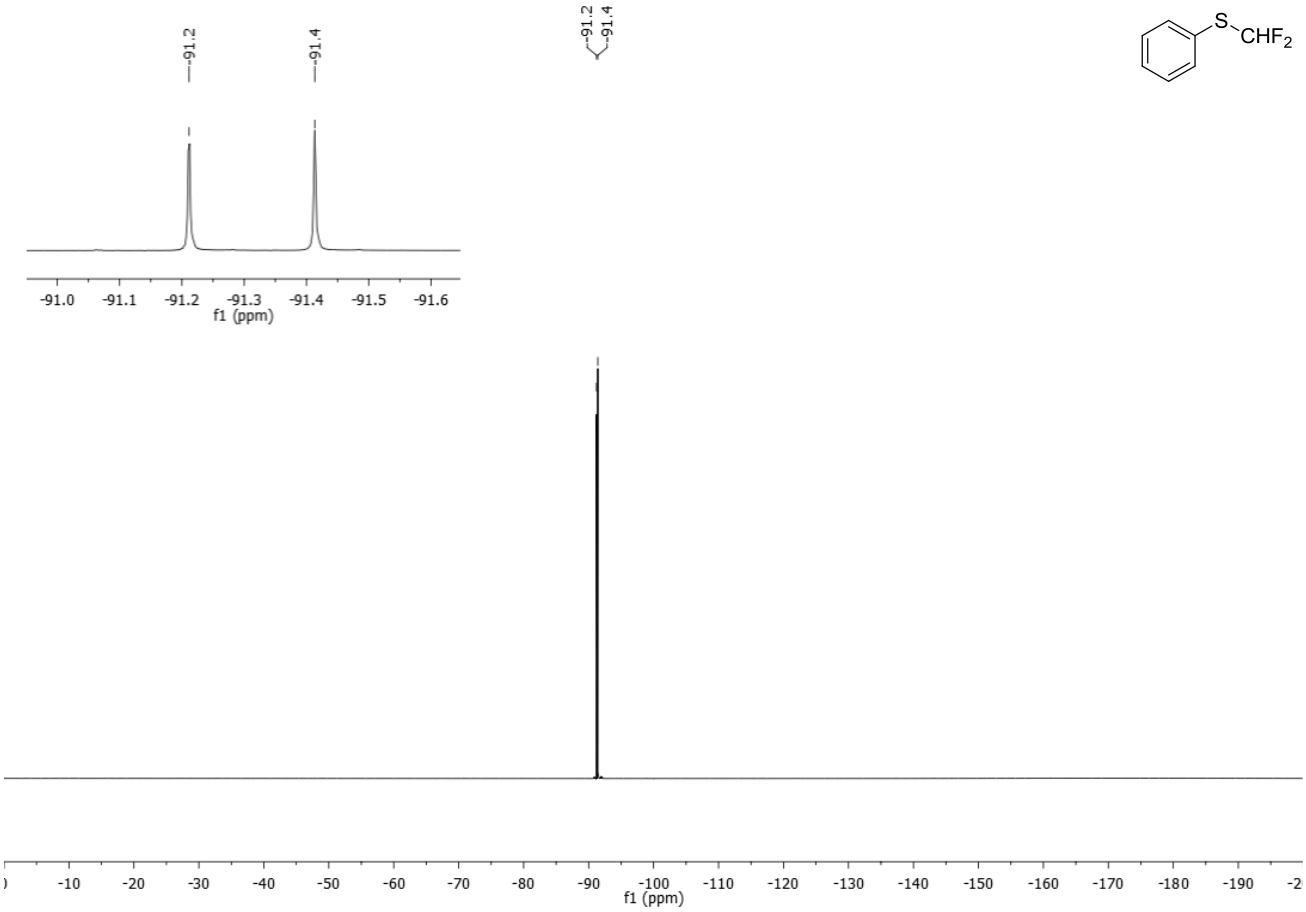


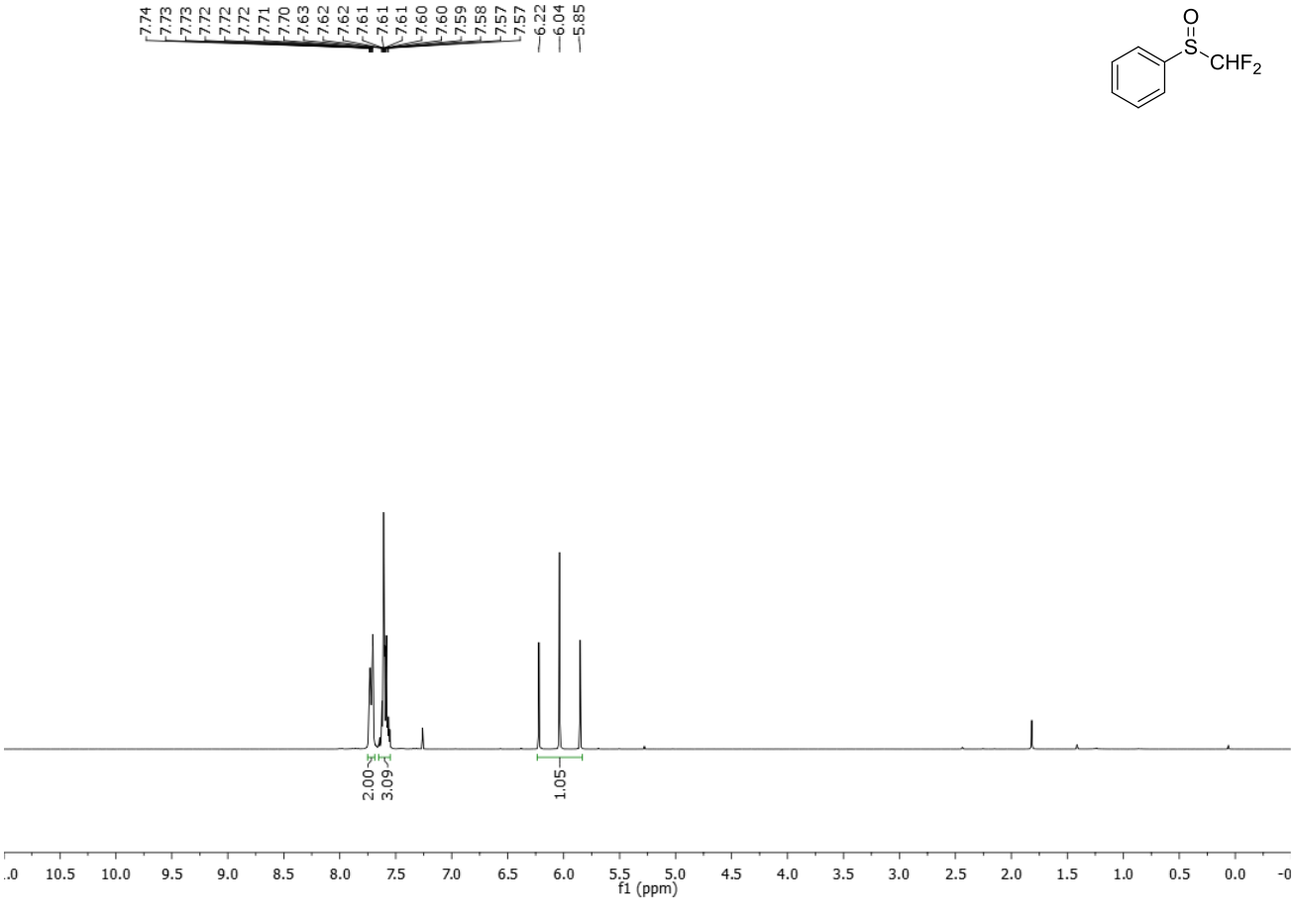


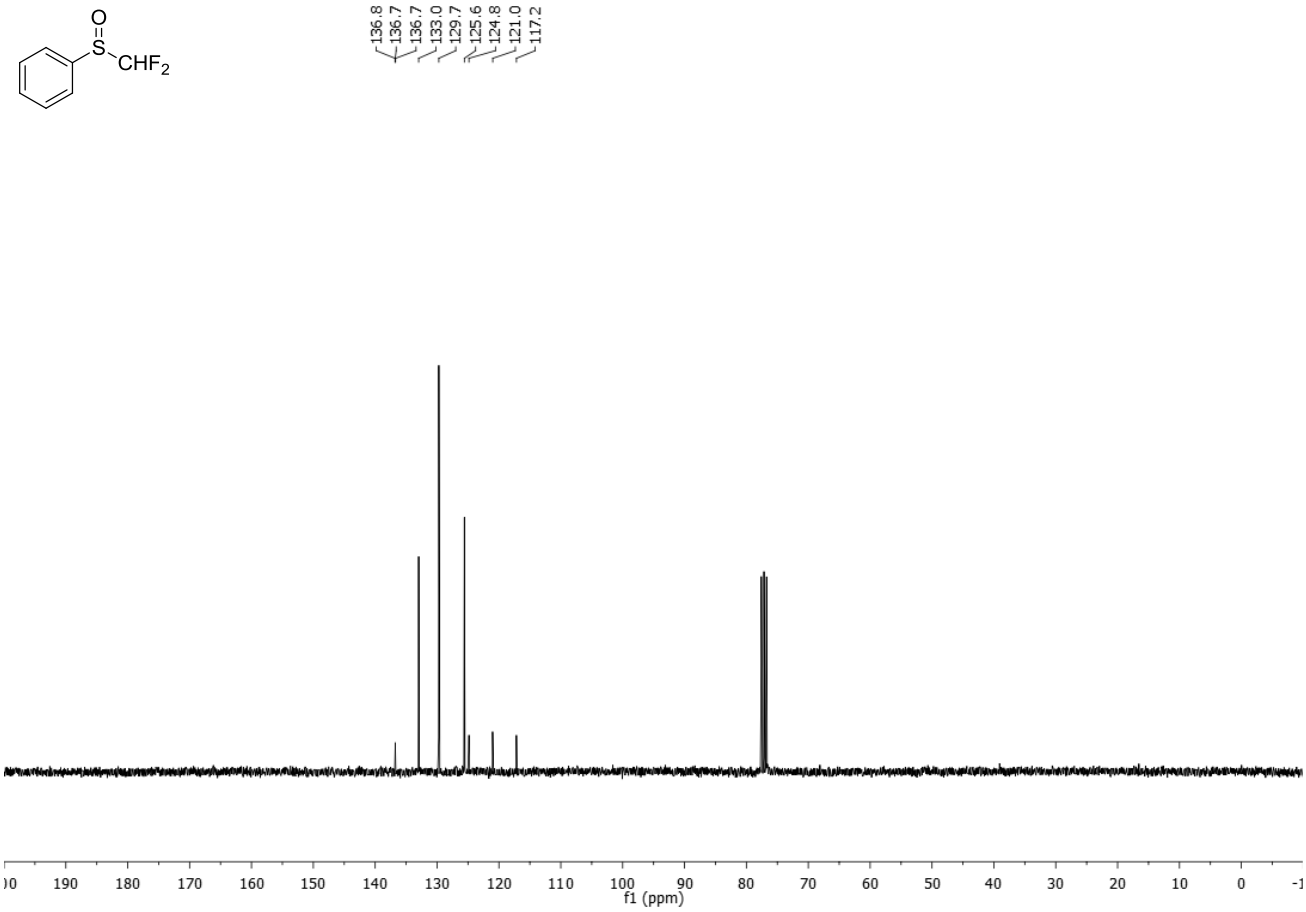


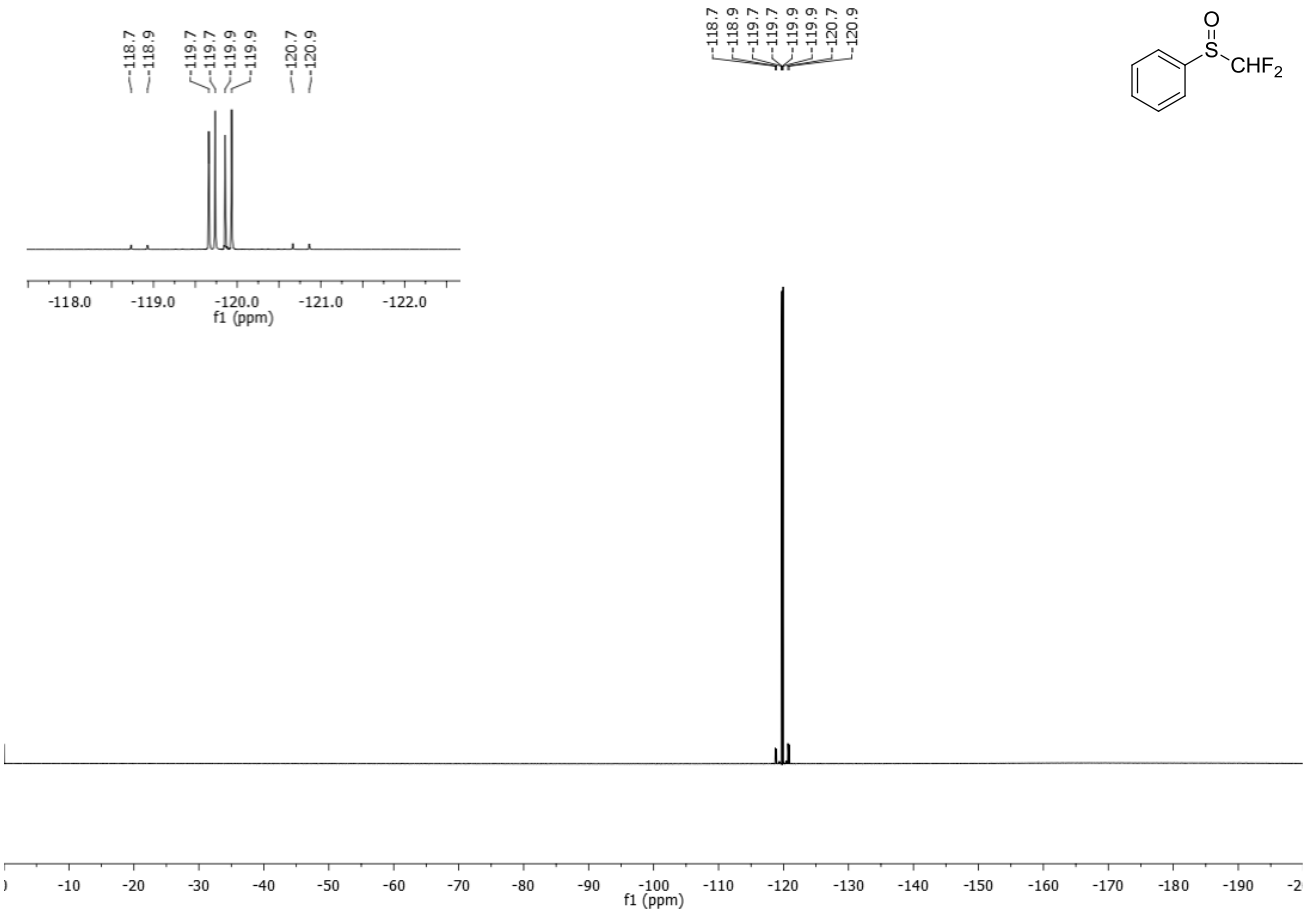





-91.2
-91.4
-91.2
-91.4
S
CHF2
-91.0 -91.1 -91.2 -91.3 -91.4 -91.5 -91.6
f1 (ppm)
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


7.74 7.73 7.73 7.72 7.72 7.72 7.71 7.70 7.63 7.62 7.62 7.61 7.61 7.61 7.60 7.60 7.59 7.58 7.57 7.57
6.22
6.04
5.85
O
S
CHF2
2.00
3.09
1.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O
S
CHF2
136.8
136.7
136.7
133.0
129.7
125.6
124.8
121.0
117.2
f1 (ppm)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118.9
119.7
119.7
119.9
119.9
120.7
120.9
-118.0
-119.0
-120.0
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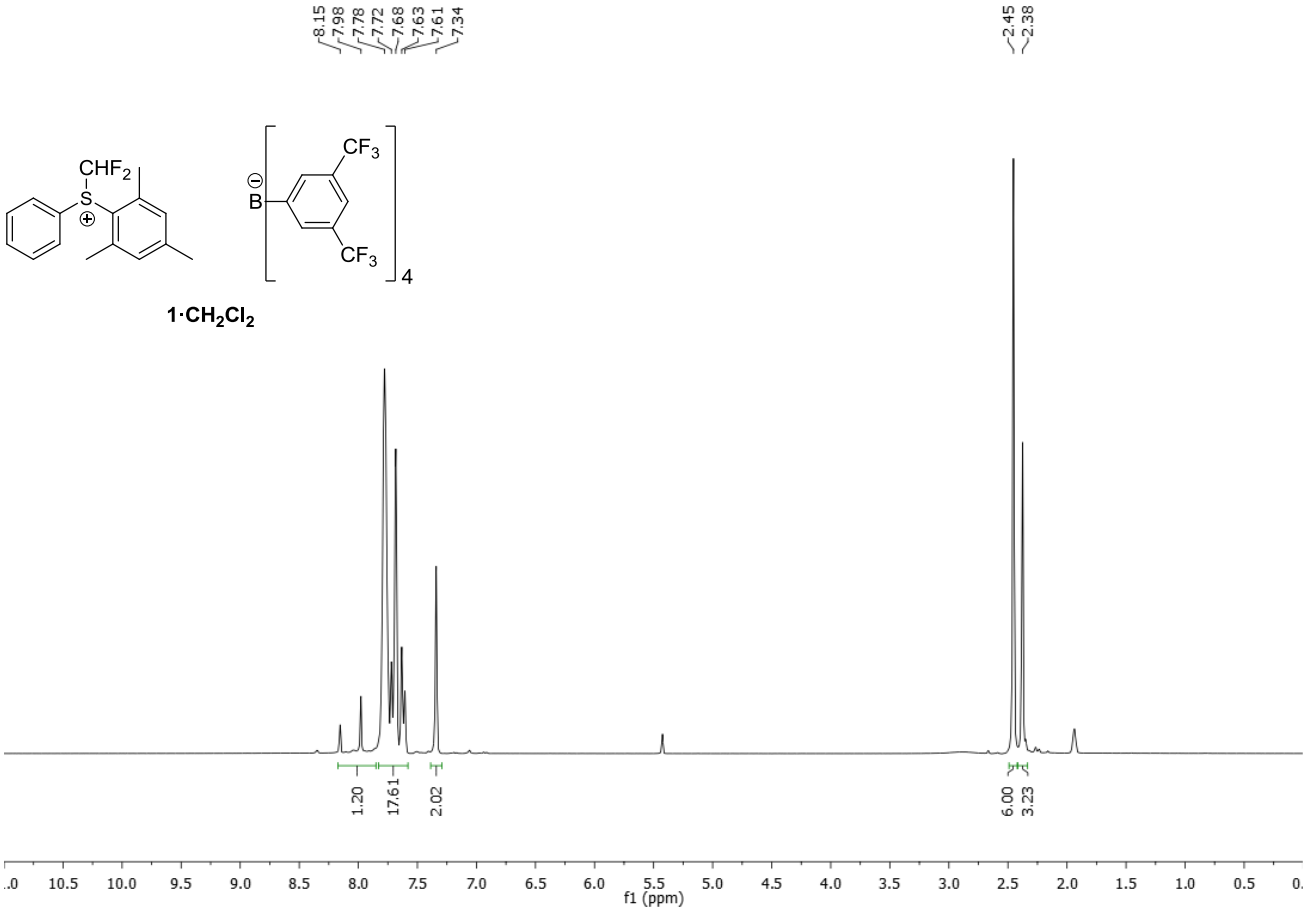
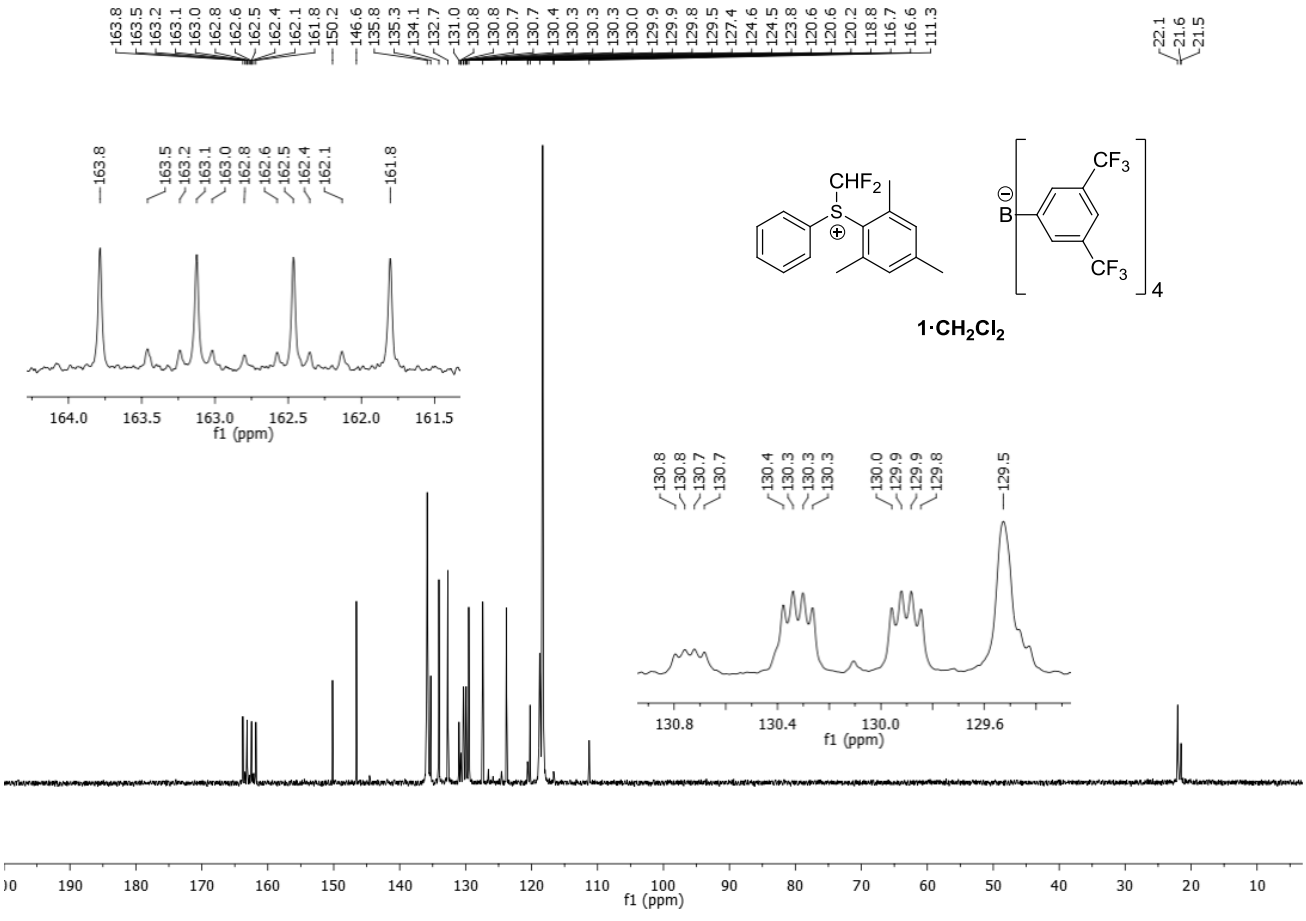
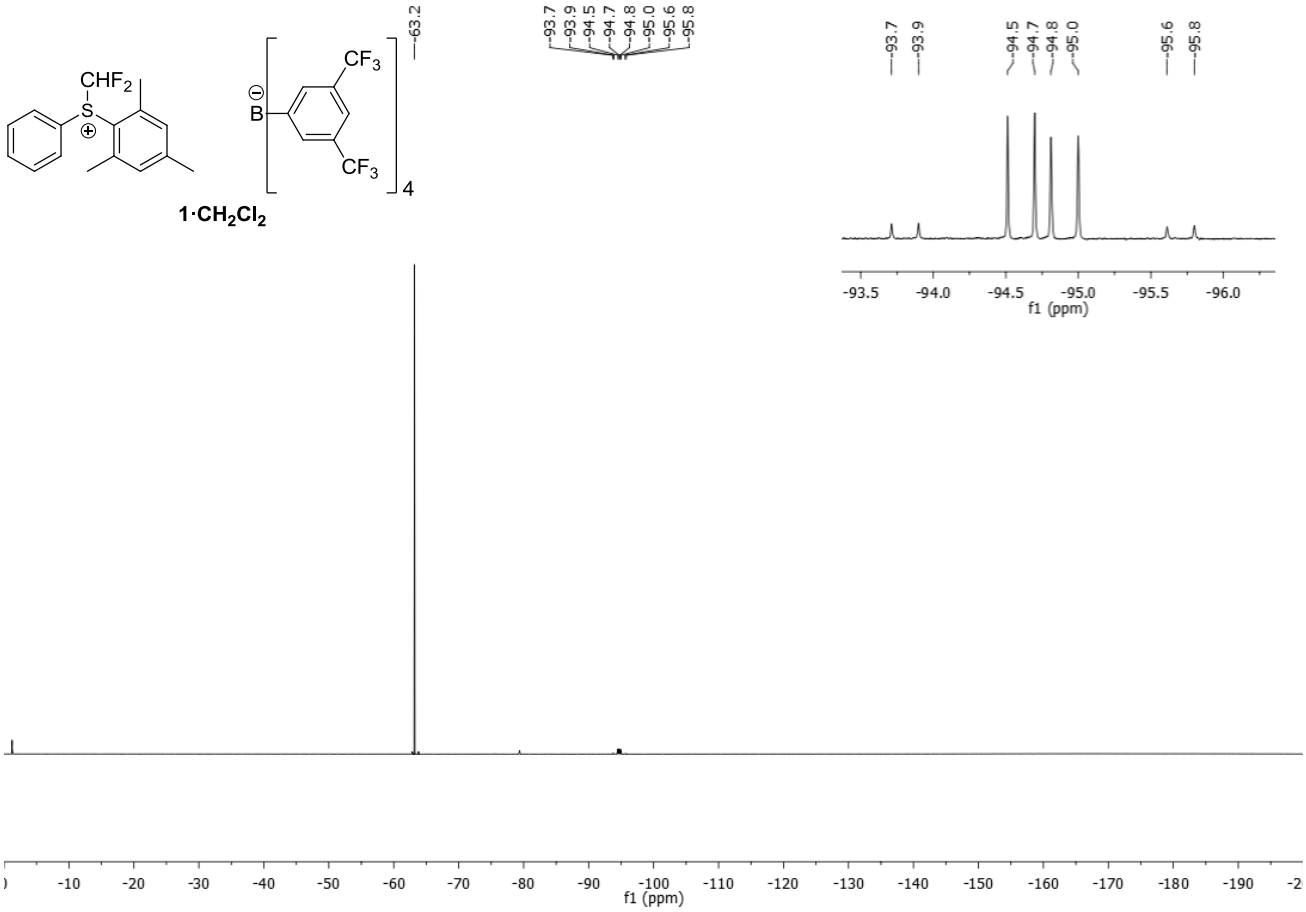
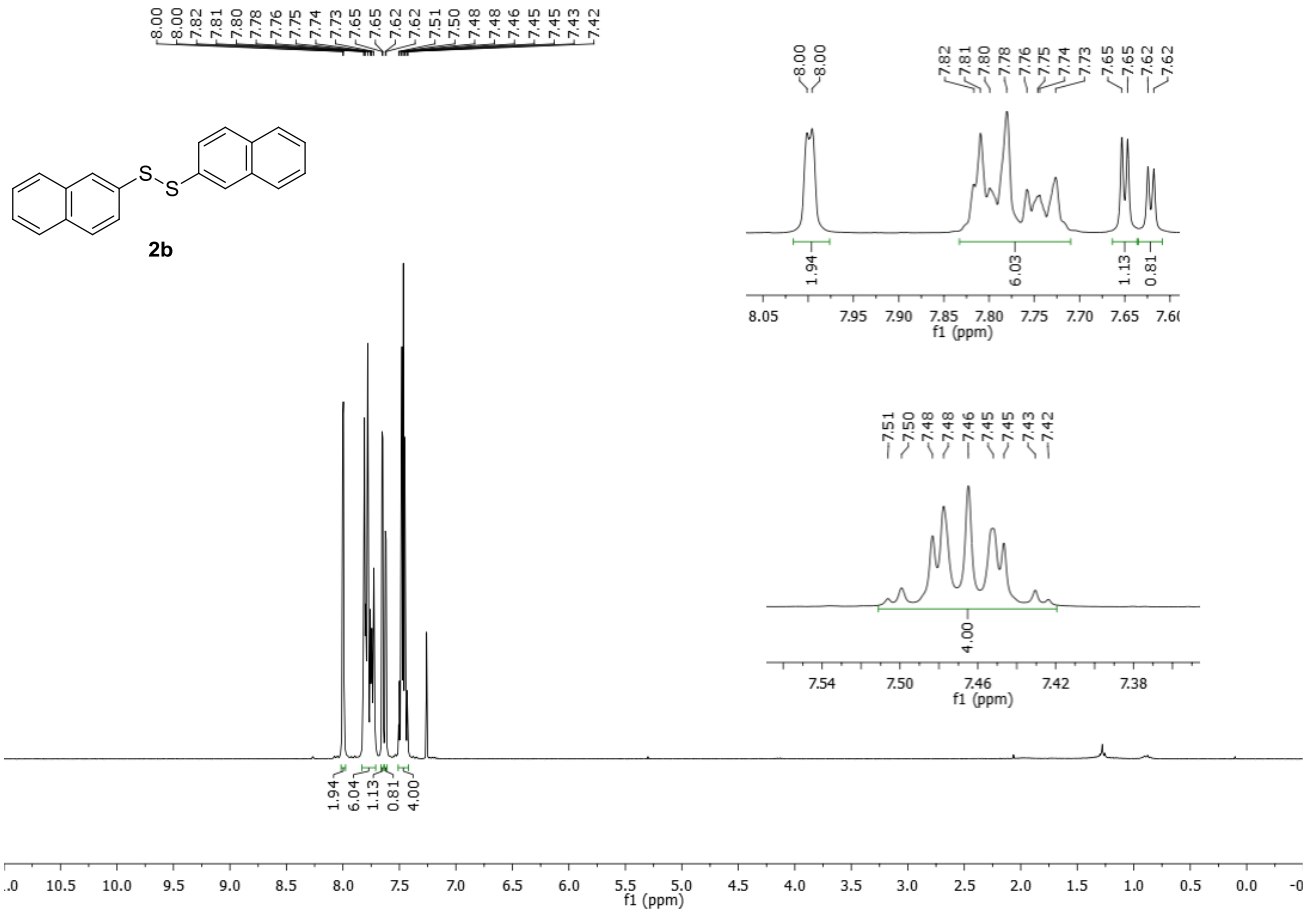
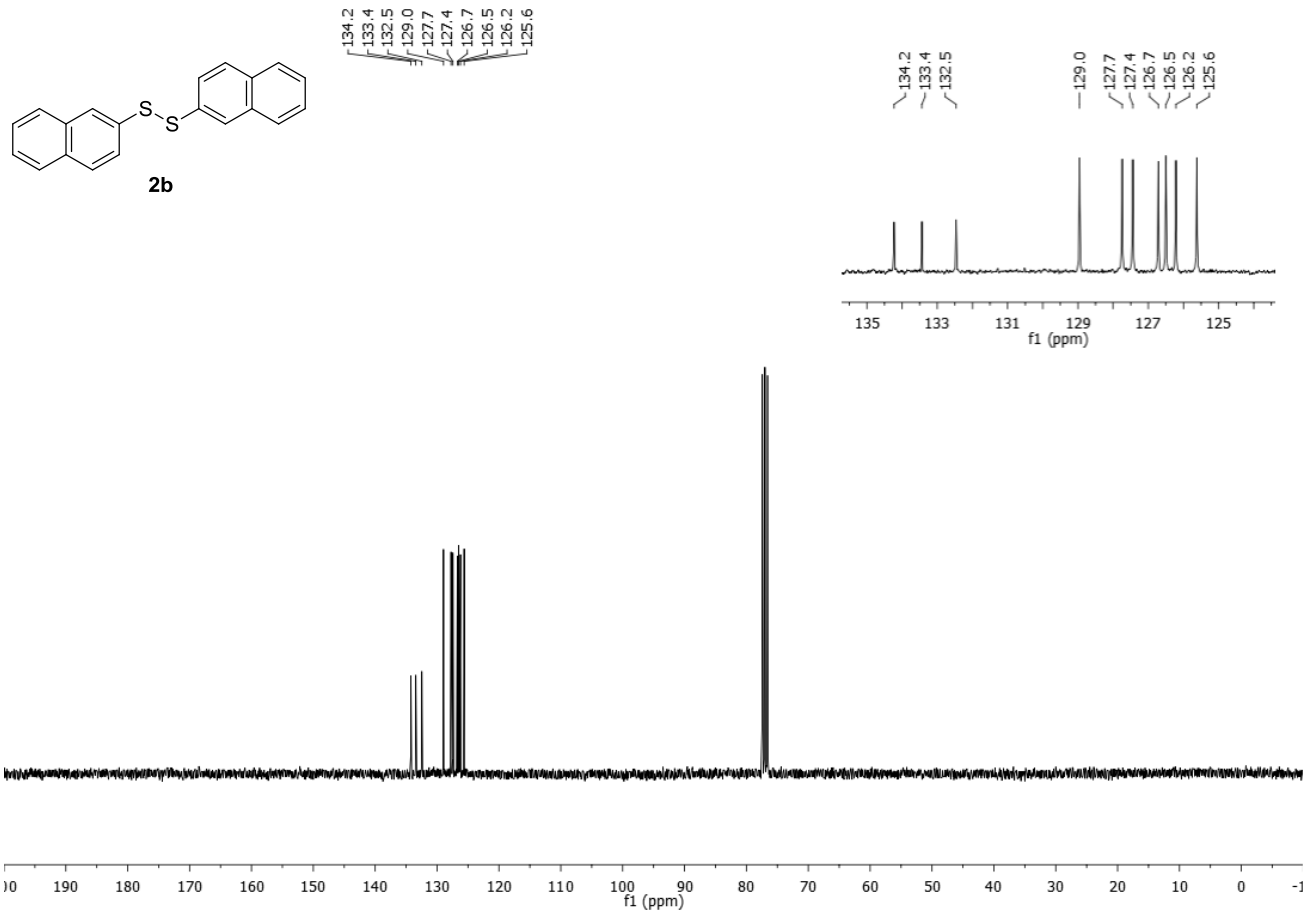
-122.0
f1 (ppm)
O
S
CHF2
f1 (ppm)


8.15
7.98
7.78
7.72
7.68
7.63
7.61
7.34
2.45
2.38
CHF2
S
B
CF3
CF3
4
1·CH2Cl2
1.20
17.61
2.02
6.00
3.23
f1 (ppm)

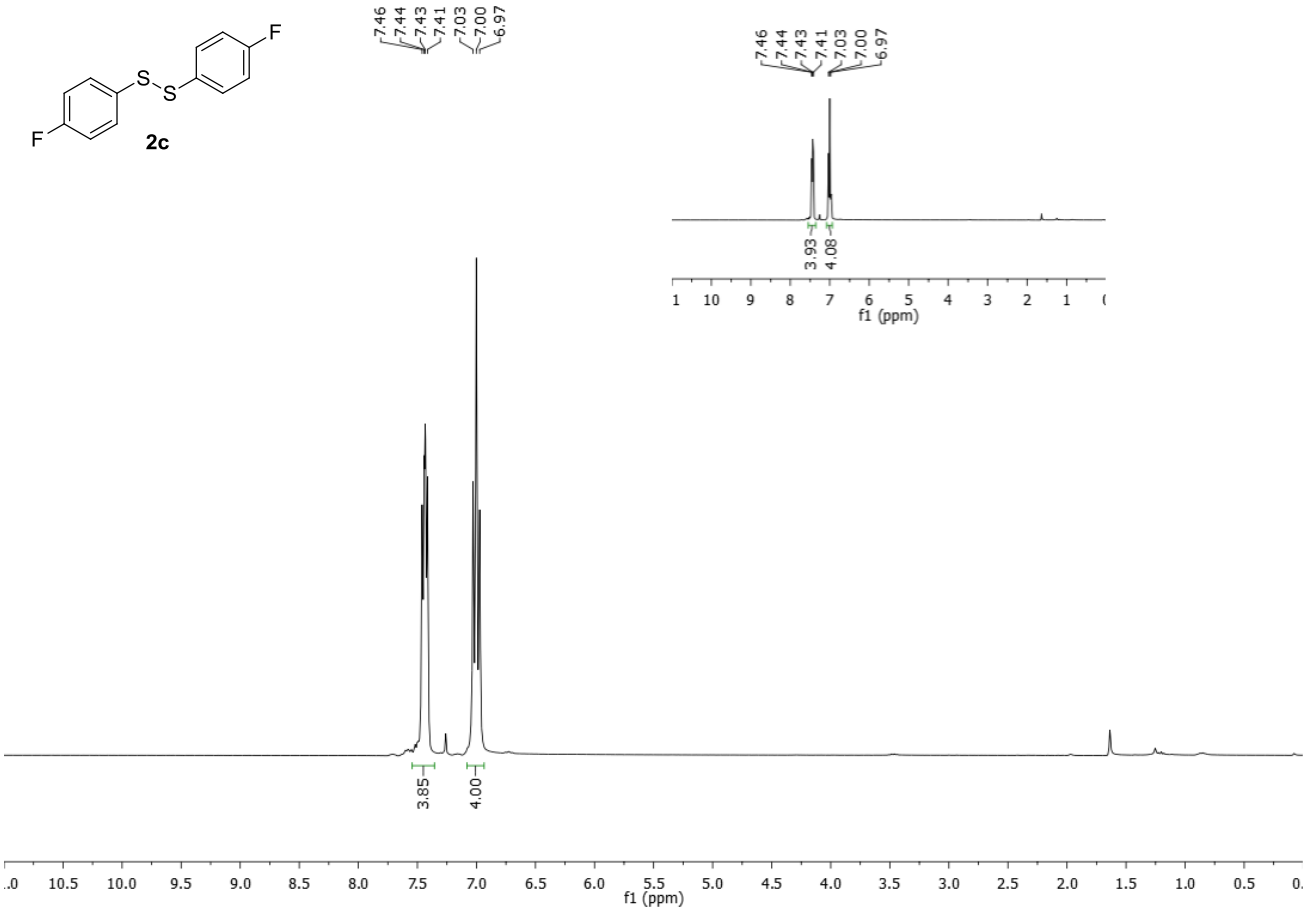

163.8
163.5
163.2
163.1
163.0
162.8
162.6
162.5
162.4
162.1
161.8
150.2
146.6
135.8
135.3
134.1
132.7
131.0
130.8
130.8
130.7
130.7
130.4
130.3
130.3
130.3
130.0
129.9
129.9
129.8
129.5
127.4
124.6
124.5
123.8
120.6
120.6
120.2
118.8
116.7
116.6
111.3
22.1
21.6
21.5
CHF2
S
B
CF3
CF3
4
1·CH2Cl2
f1 (ppm)


CHF2
S
B
CF3
CF3
4
1·CH2Cl2
-63.2
-93.7
-93.9
-94.5
-94.7
-94.8
-95.0
-95.6
-95.8
f1 (ppm)

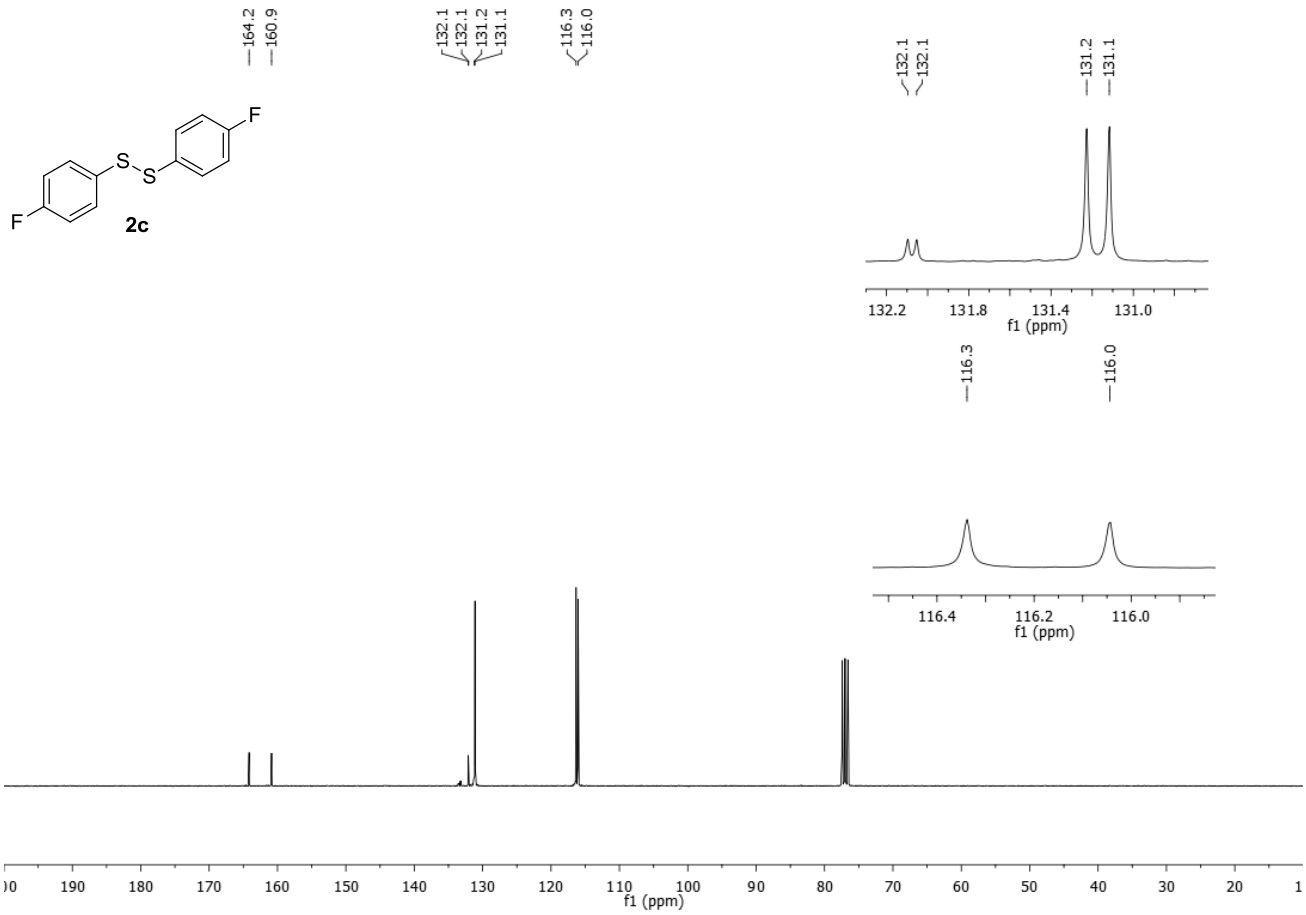

S
S
2b
8.00
7.82
7.81
7.80
7.78
7.76
7.75
7.74
7.73
7.65
7.62
7.51
7.50
7.48
7.46
7.45
7.43
7.42
1.94
6.04
1.13
0.81
4.00
f1 (ppm)

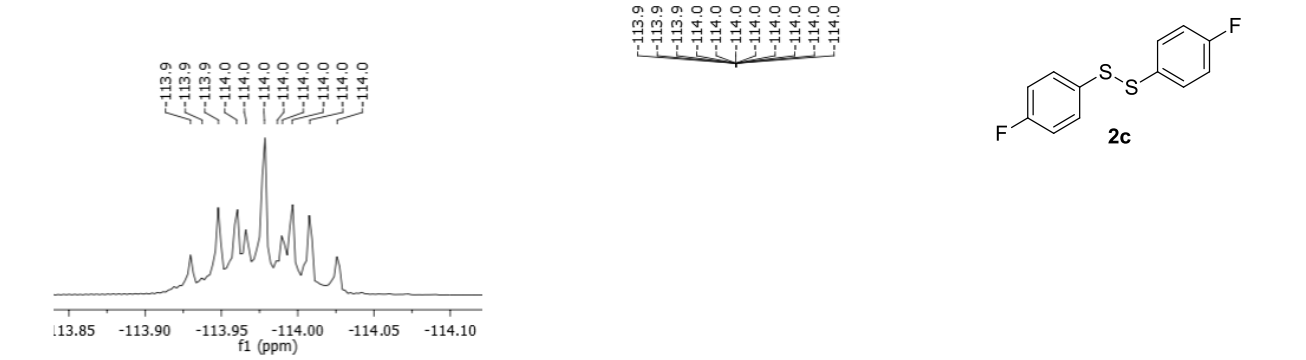

134.2
133.4
132.5
129.0
127.7
127.4
126.7
126.5
126.2
125.6
f1 (ppm)

2b


7.46
7.44
7.43
7.41
7.03
7.00
6.97
3.93
4.08
3.85
4.00
f1 (ppm)

2c


164.2
160.9
132.1
132.1
131.2
131.1
116.3
116.0
F
S
S
F
2c
132.1
132.1
131.2
131.1
132.2
131.8
131.4
131.0
f1 (ppm)
116.3
116.0
116.4
116.2
116.0
f1 (ppm)
f1 (ppm)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-113.9
-113.9
-114.0
-114.0
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-114.0
-114.0
-114.0
-114.0
-114.0
-113.85
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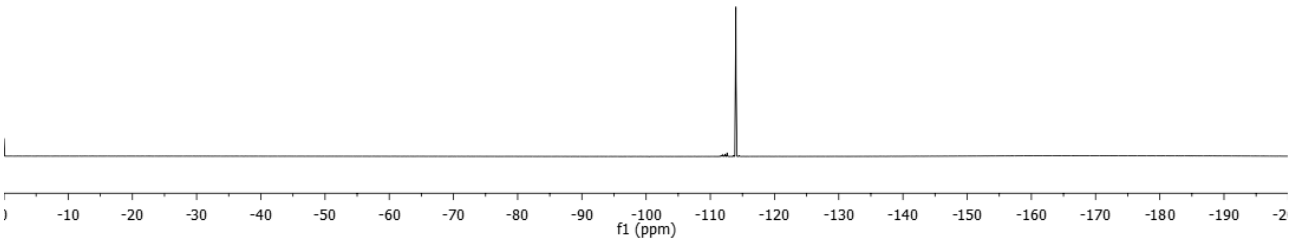
-113.95
-114.00
-114.05
-114.10
f1 (ppm)
F
S
S
F
2c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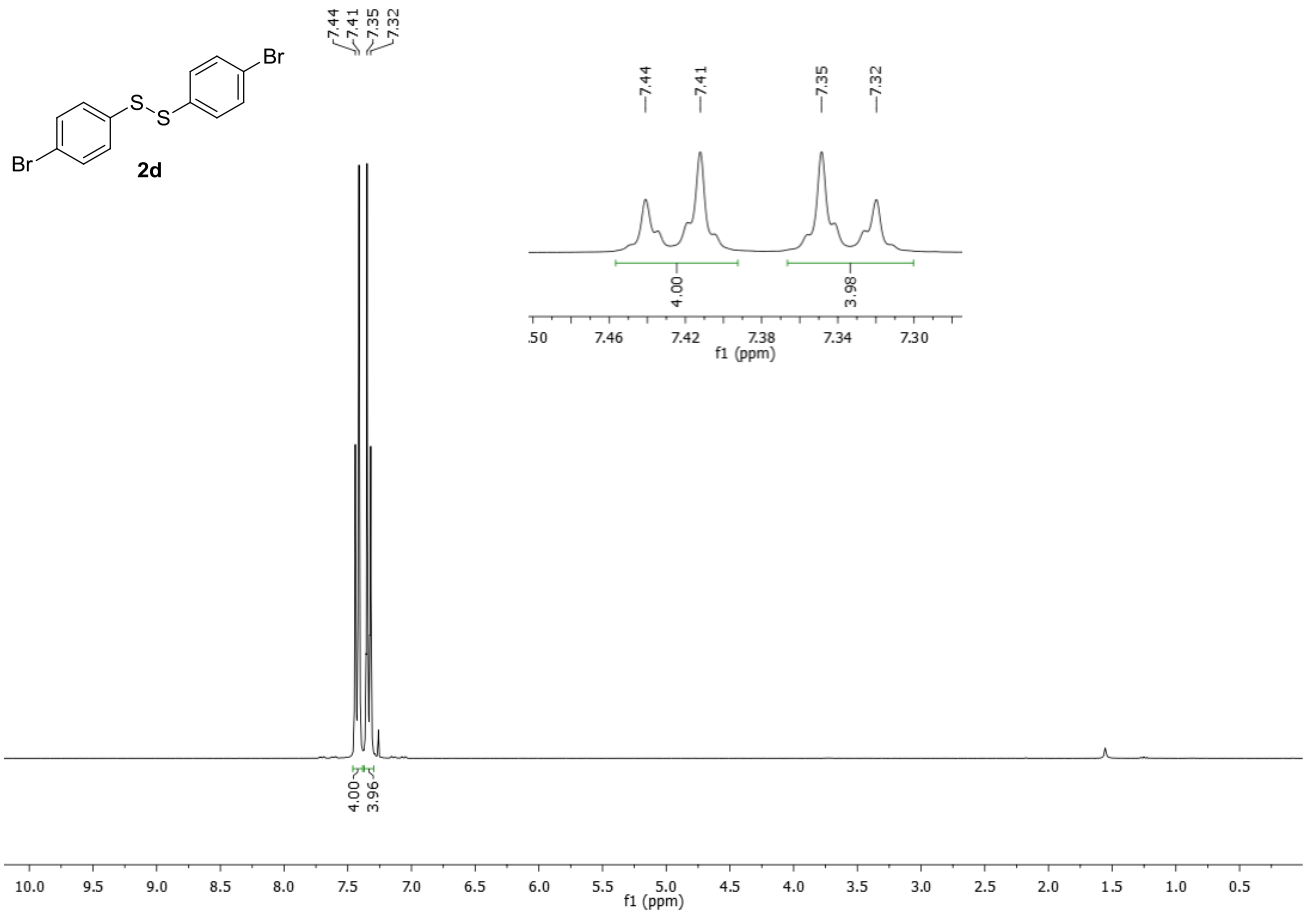
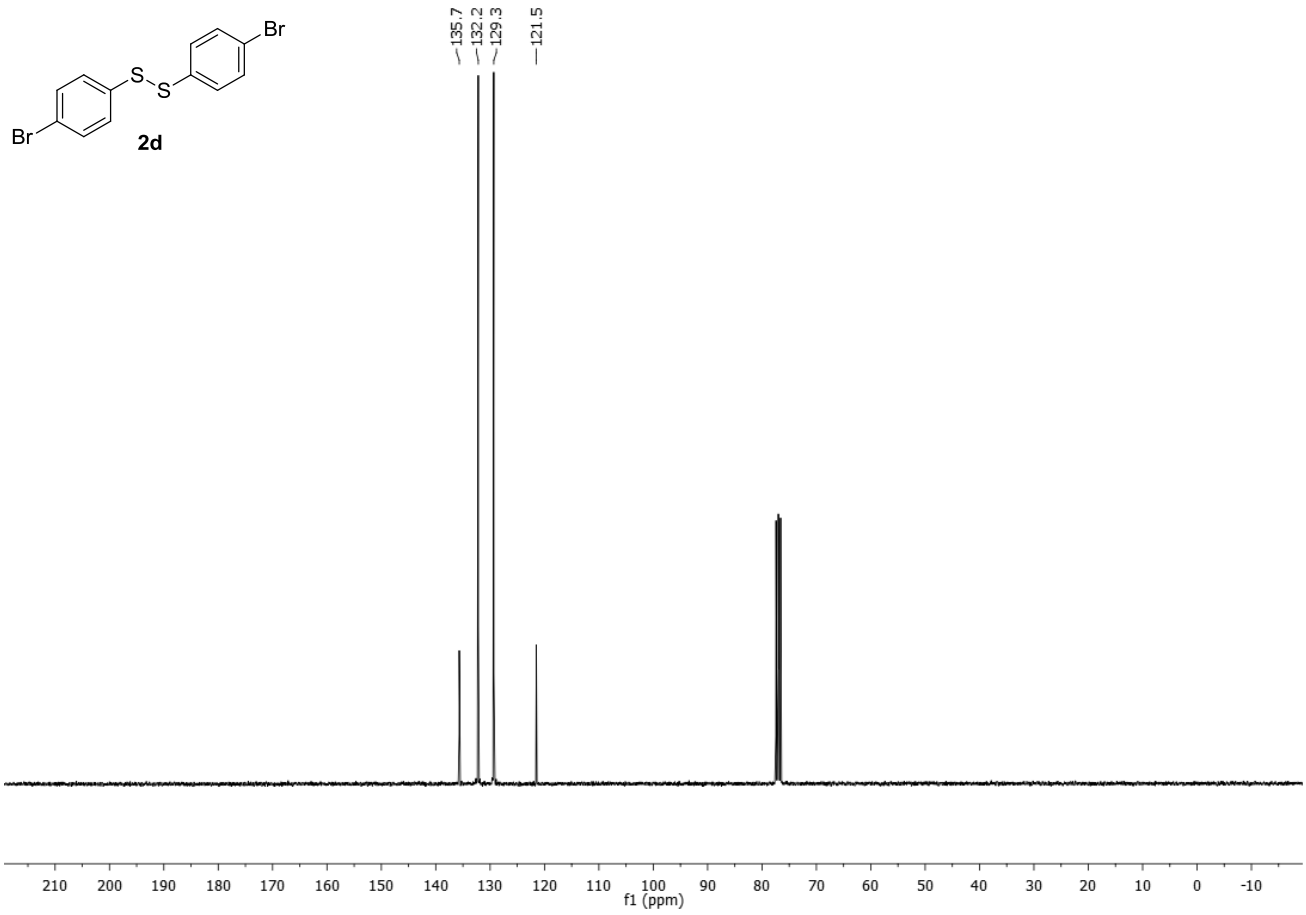

Br
S
S
Br
2d
7.44
7.41
7.35
7.32
4.00
3.98
f1 (ppm)
4.00
3.96
f1 (ppm)


Br
S
S
Br
2d
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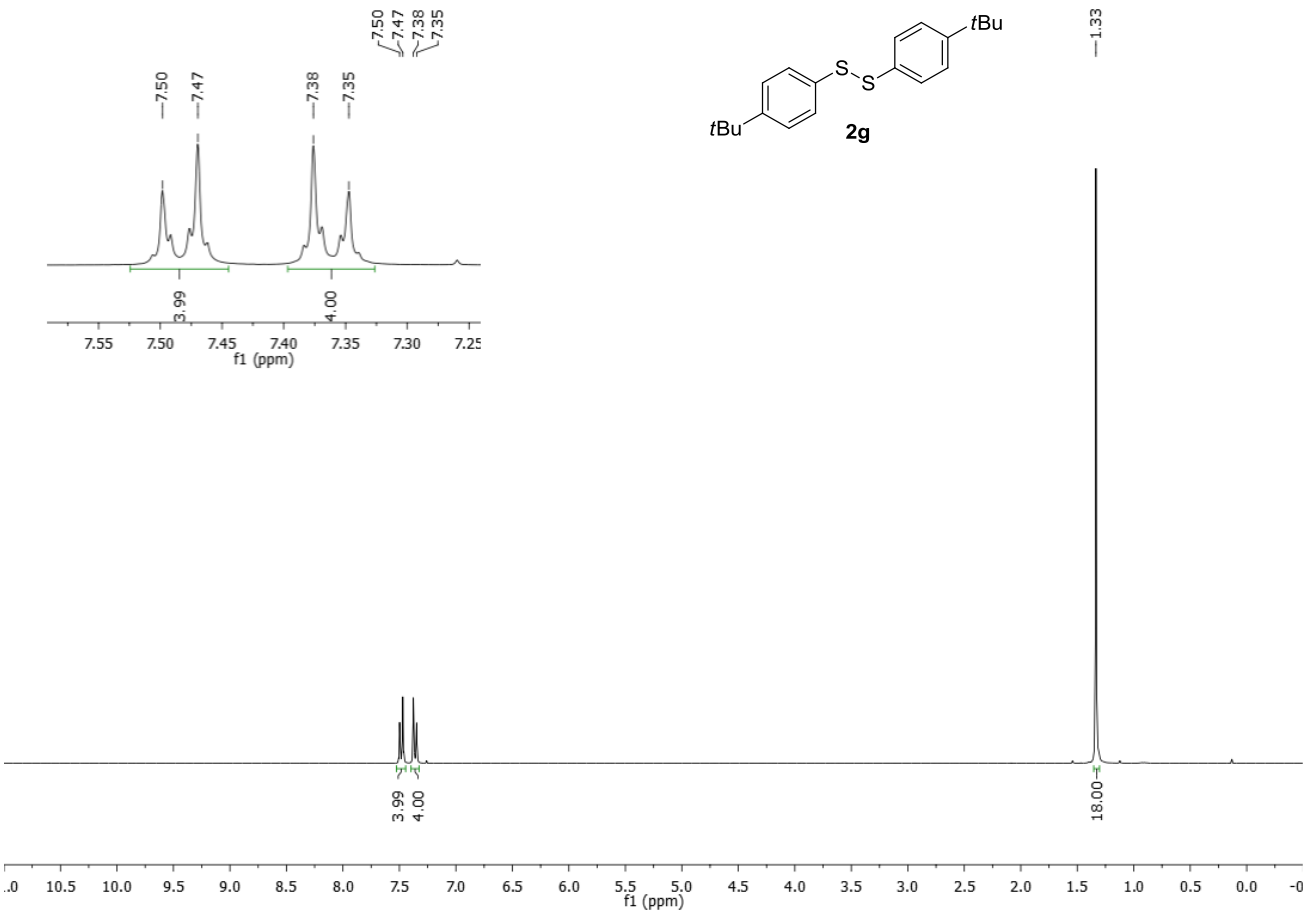
132.2
129.3
121.5
f1 (ppm)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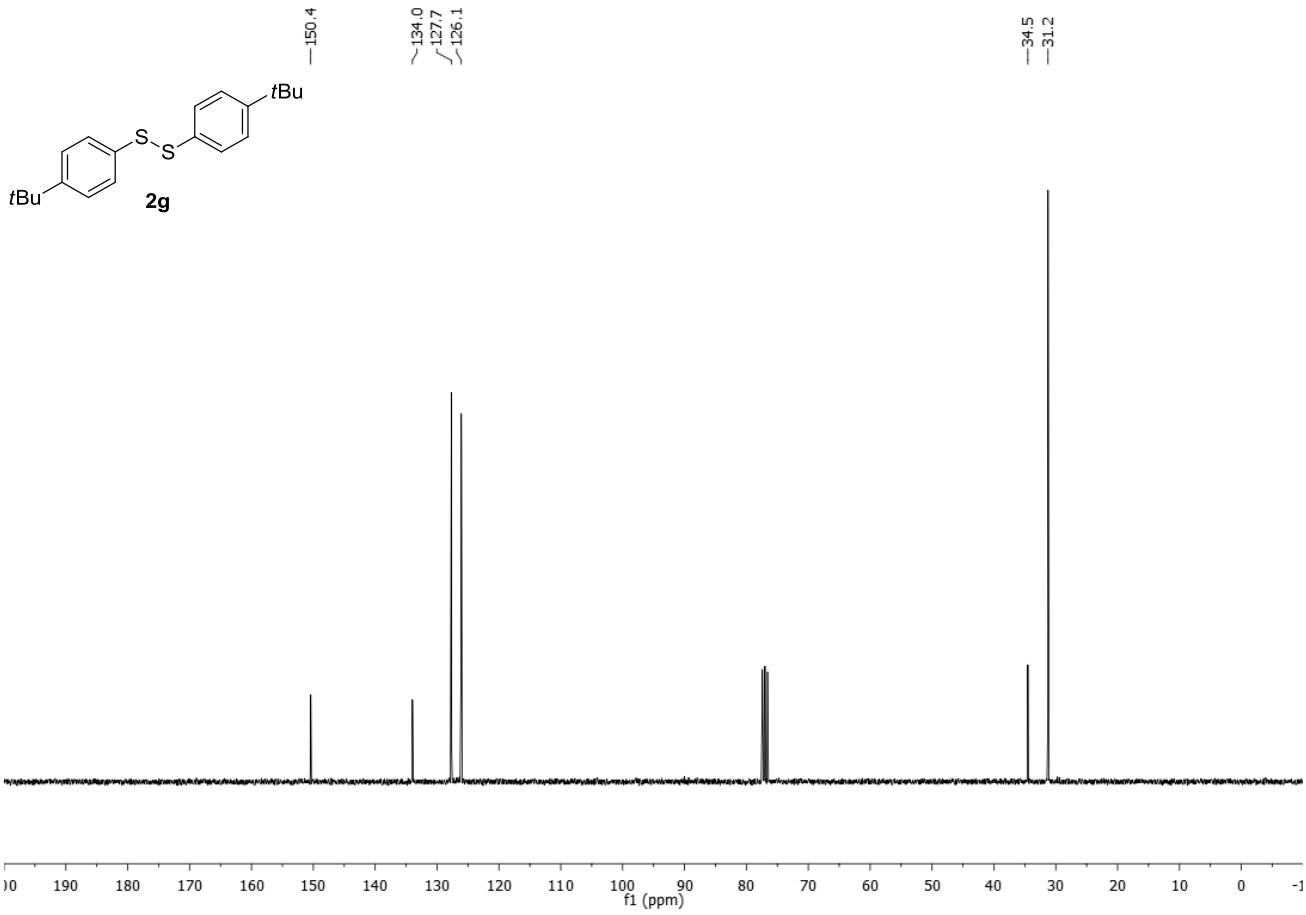
7.38
7.35
3.99
4.00
7.55 7.50 7.45 7.40 7.35 7.30 7.25
f1 (ppm)
tBu
S
S
tBu
2g
1.33
3.99
4.00
18.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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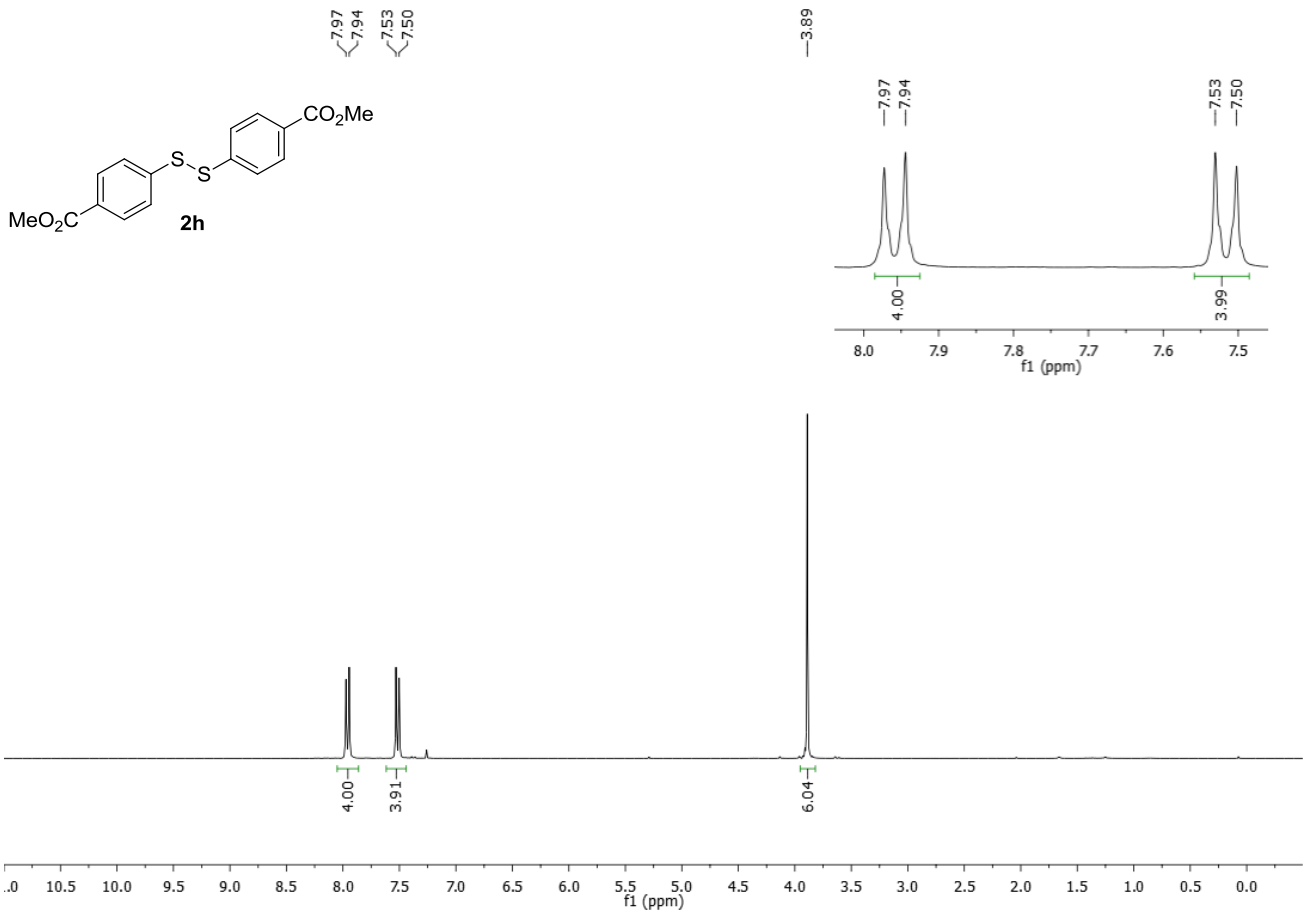
134.0
127.7
126.1
34.5
31.2
tBu
S
S
tBu
2g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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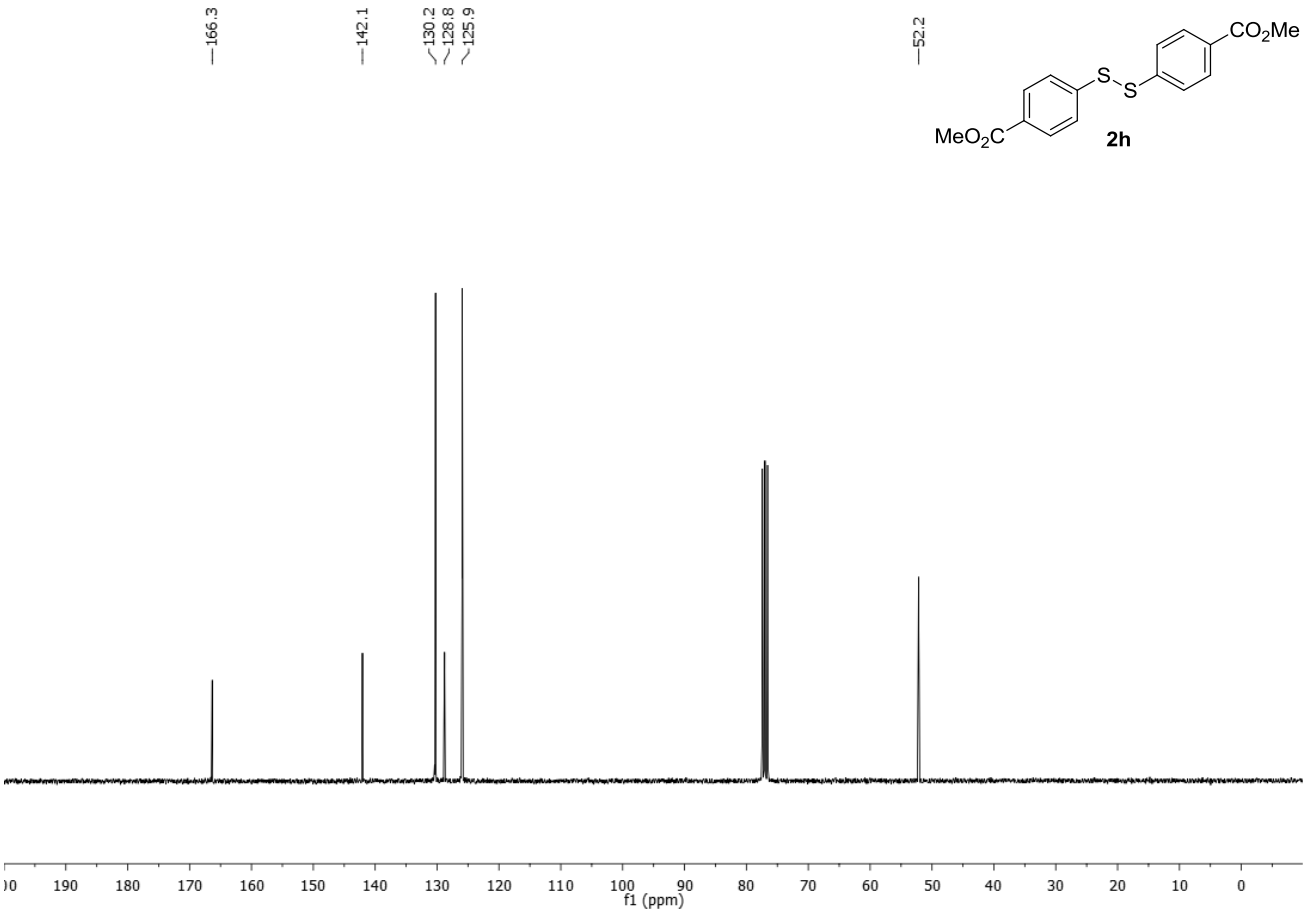
7.94
7.53
7.50
3.89
CO2Me
S
S
MeO2C
2h
4.00
3.99
8.0
7.9
7.8
7.7
7.6
7.5
f1 (ppm)
4.00
3.91
6.04
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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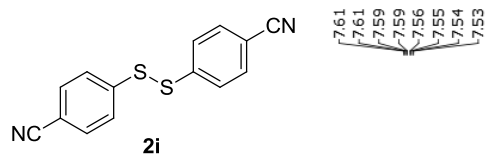
142.1
130.2
128.8
125.9
52.2
CO2Me
S
S
MeO2C
2h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CN
S
S
NC

2i

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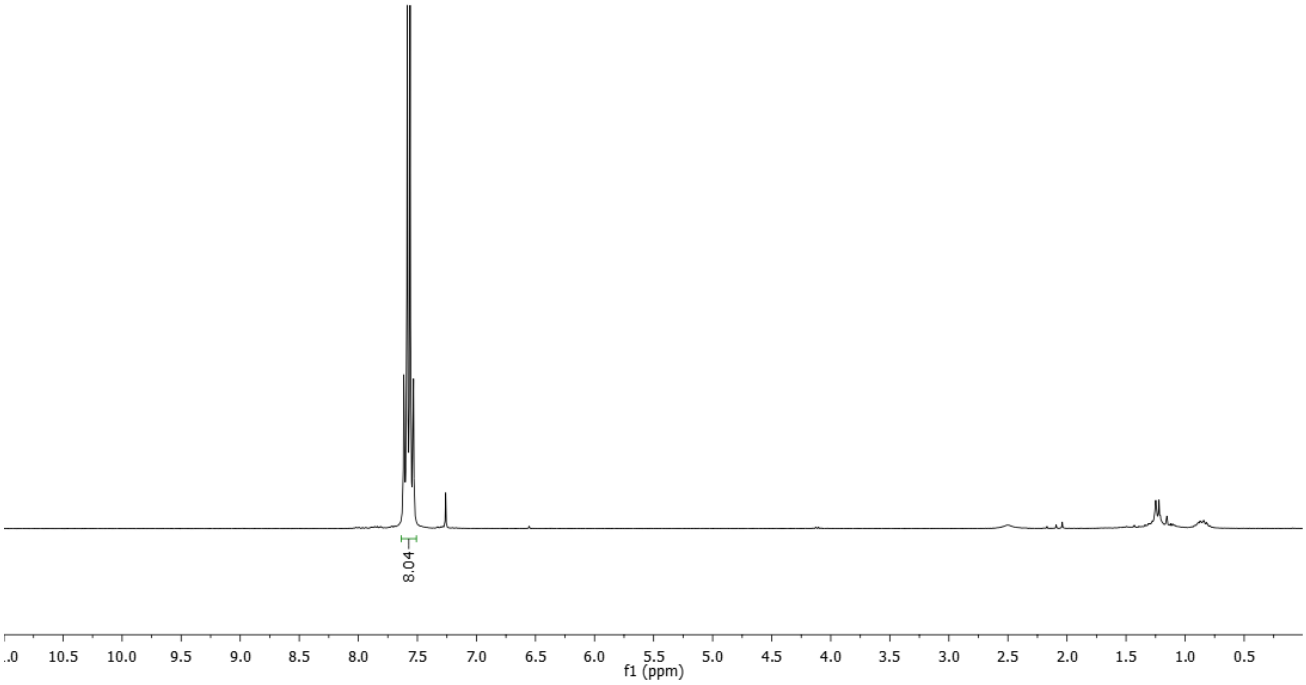
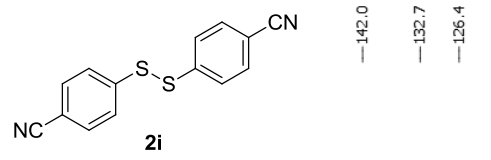
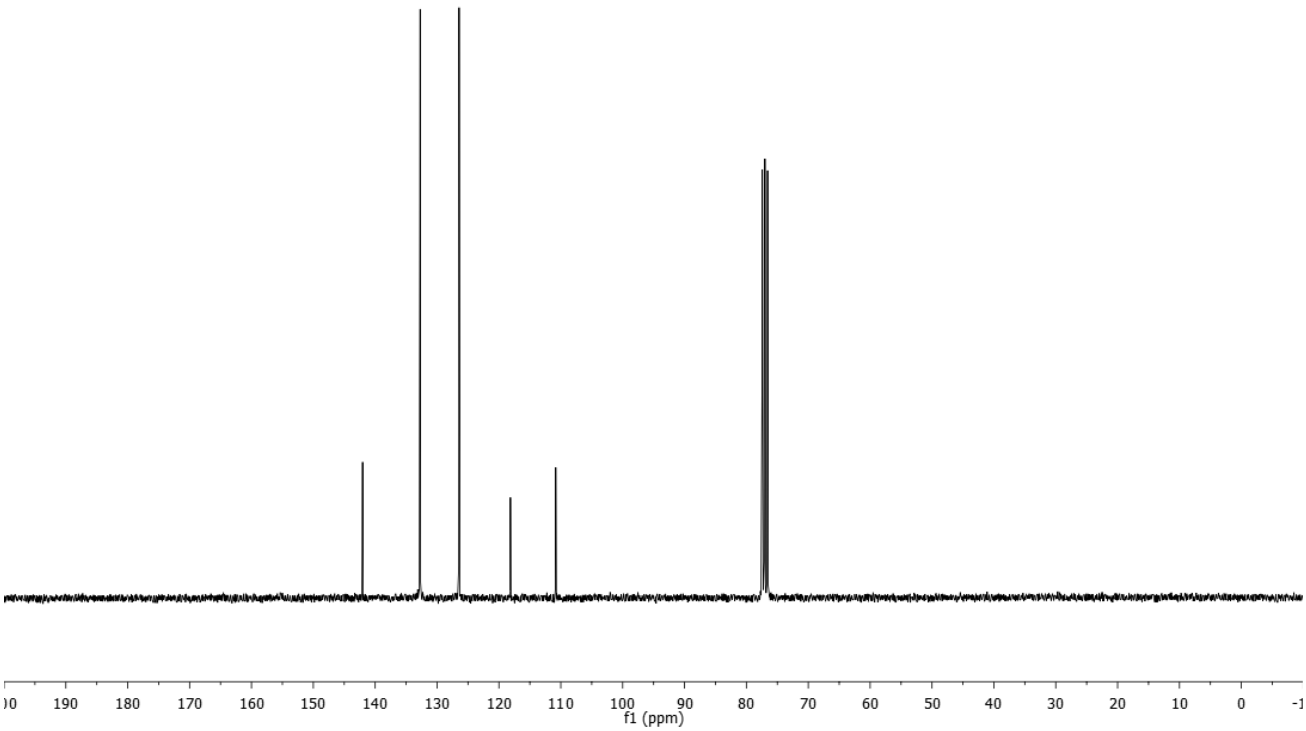
7.61
7.59
7.59
7.56
7.55
7.54
7.53


8.04
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CN
S
S
NC

2i

142.0
132.7
126.4
118.1
110.8


190
180
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110
100
90
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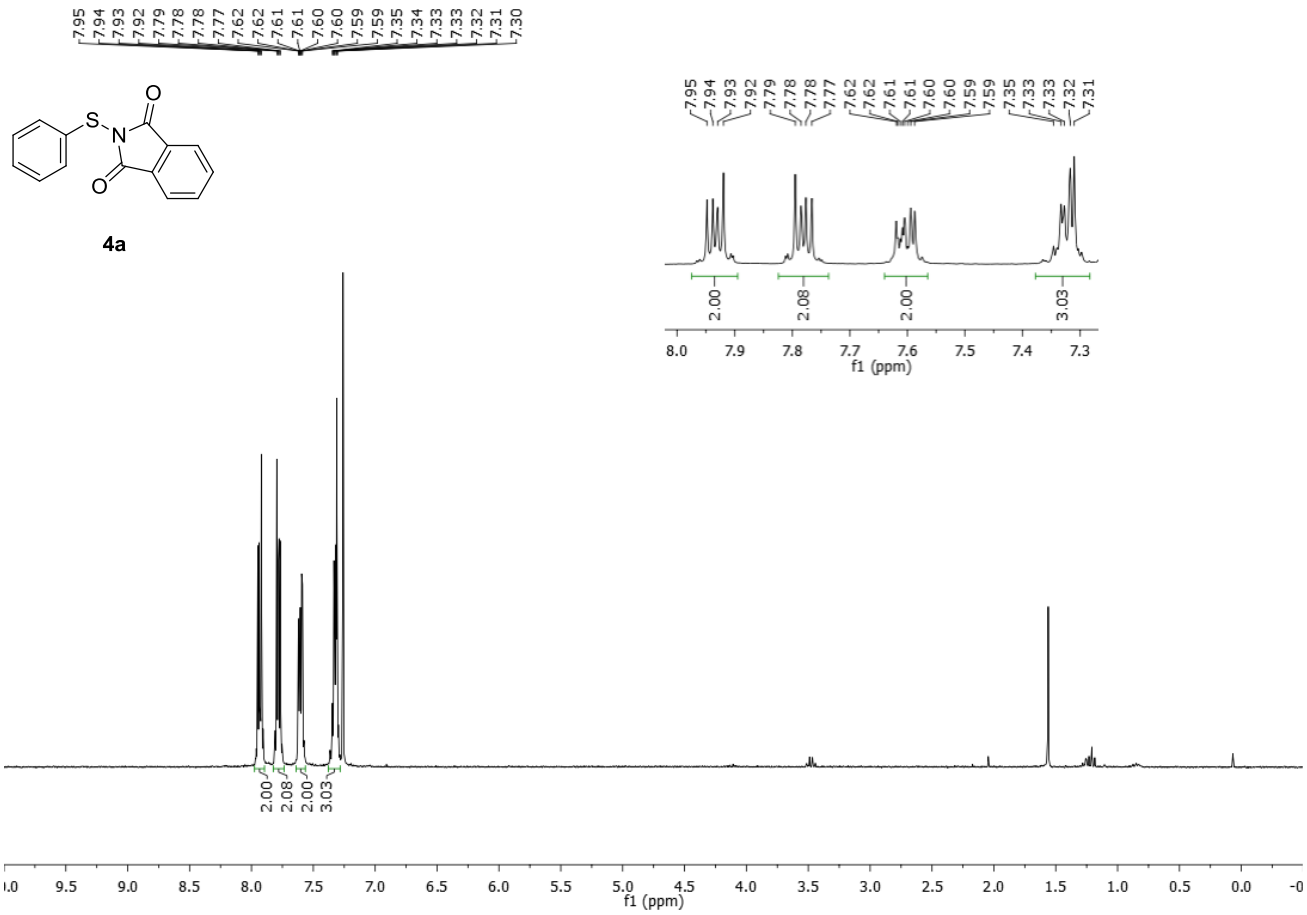
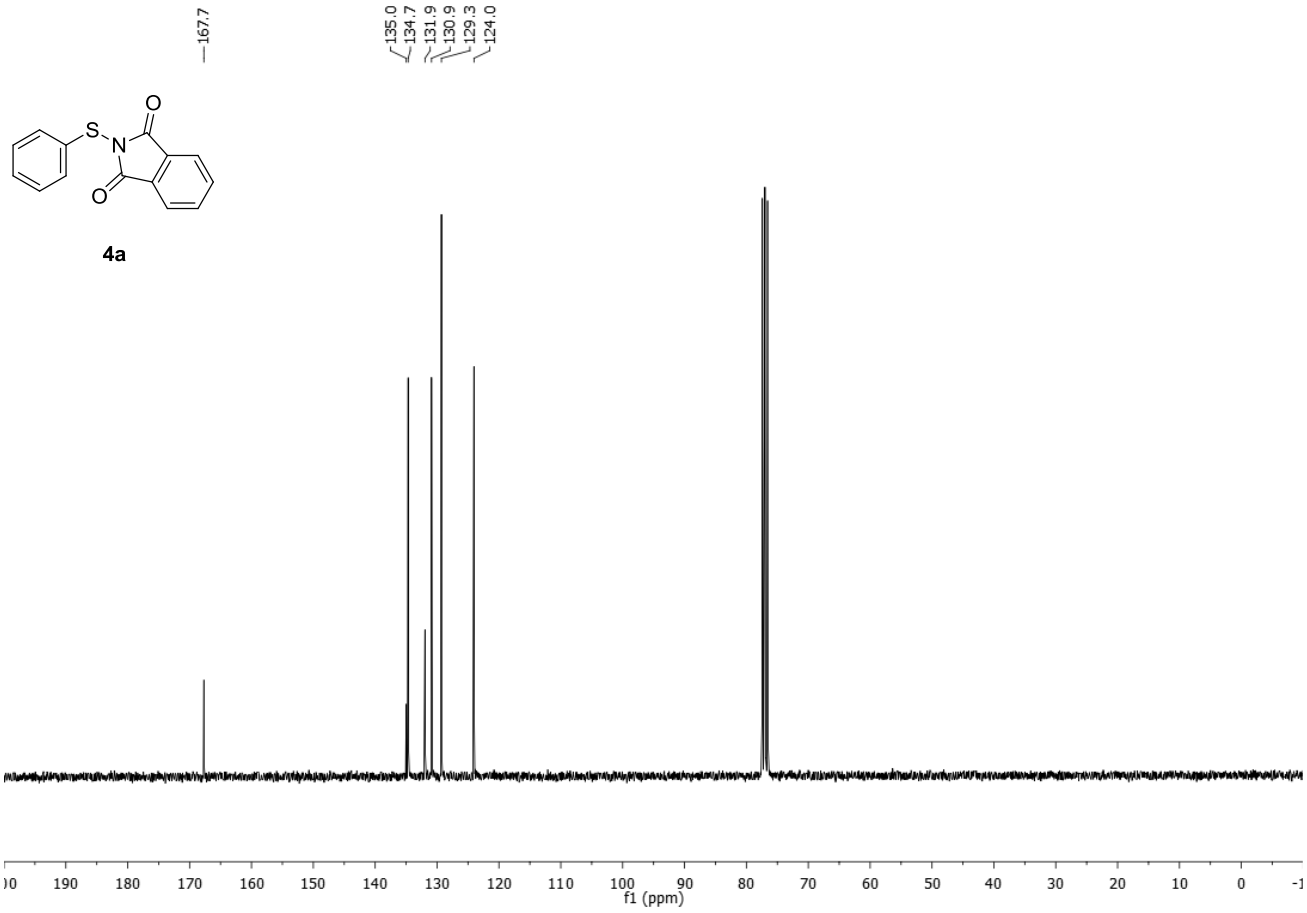
70
60
50
40
30
20
10
0
f1 (ppm)


7.95
7.94
7.93
7.92
7.79
7.78
7.78
7.77
7.62
7.62
7.61
7.61
7.60
7.60
7.59
7.59
7.35
7.34
7.33
7.33
7.32
7.31
7.30
O
S
N
O
4a
2.00
2.08
2.00
3.03
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
f1 (ppm)
2.00
2.08
2.00
3.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


167.7
135.0
134.7
131.9
130.9
129.3
124.0
O
S
N
O
4a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Section B: Radioactive chemistry

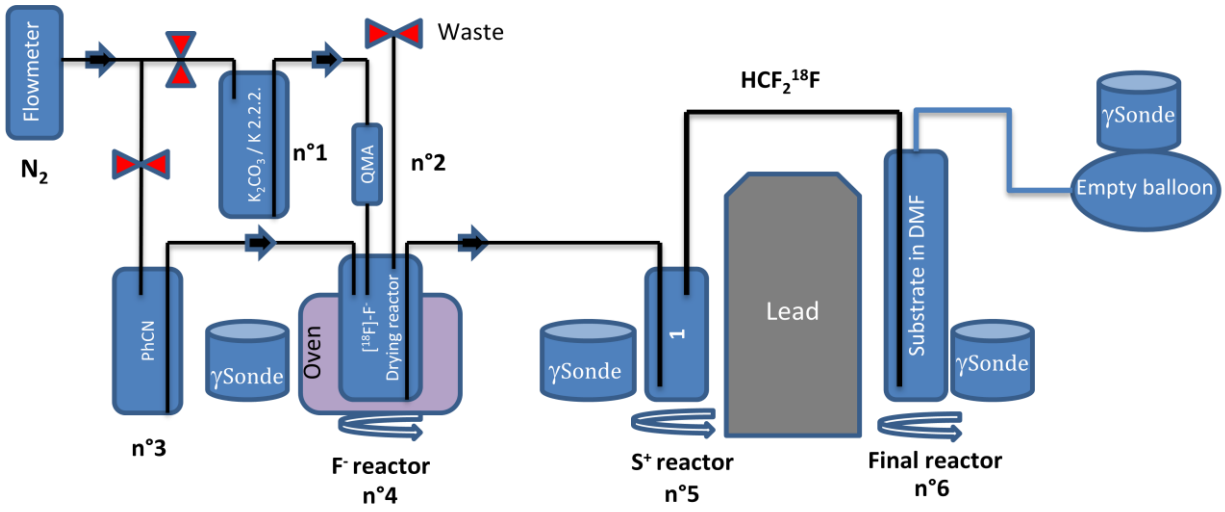
1. General information

[^{18}F]Fluoride preparation was performed on a home-made remote controlled module dedicated to the nucleophilic fluorination and piloted by the software Labview (National Instruments) (scheme 1). The different solutions were transferred from vials to vials under nitrogen pressure through 2-way or 3-way valves. Radioactivity was measured by a CAPINTEC Radioisotope Calibrator CRC-120R. HPLC analysis were performed on Gilson equipment (302 and 305 pumps) equipped with UV/VIS-151 and γ-ray 1x1" NaI detectors connected in series and monitored by a GABI Star interface module (Raytest). HPLC analysis were performed using an Interchim YP5C18-15QS Ypersphere C18 (150 x 4.6 mm) column, with a flowrate of 1.0 mL/min or 0.7 mL/min. A solution of **1·CH_2Cl_2** (0.09 g, 0.07mmol, 1eq.) in 300 µL of $CHCl_3$ was evaporated under vacuum (5 mBar) at room temperature for at least 30 minutes prior to use in order to obtain **1** free of CH_2Cl_2.

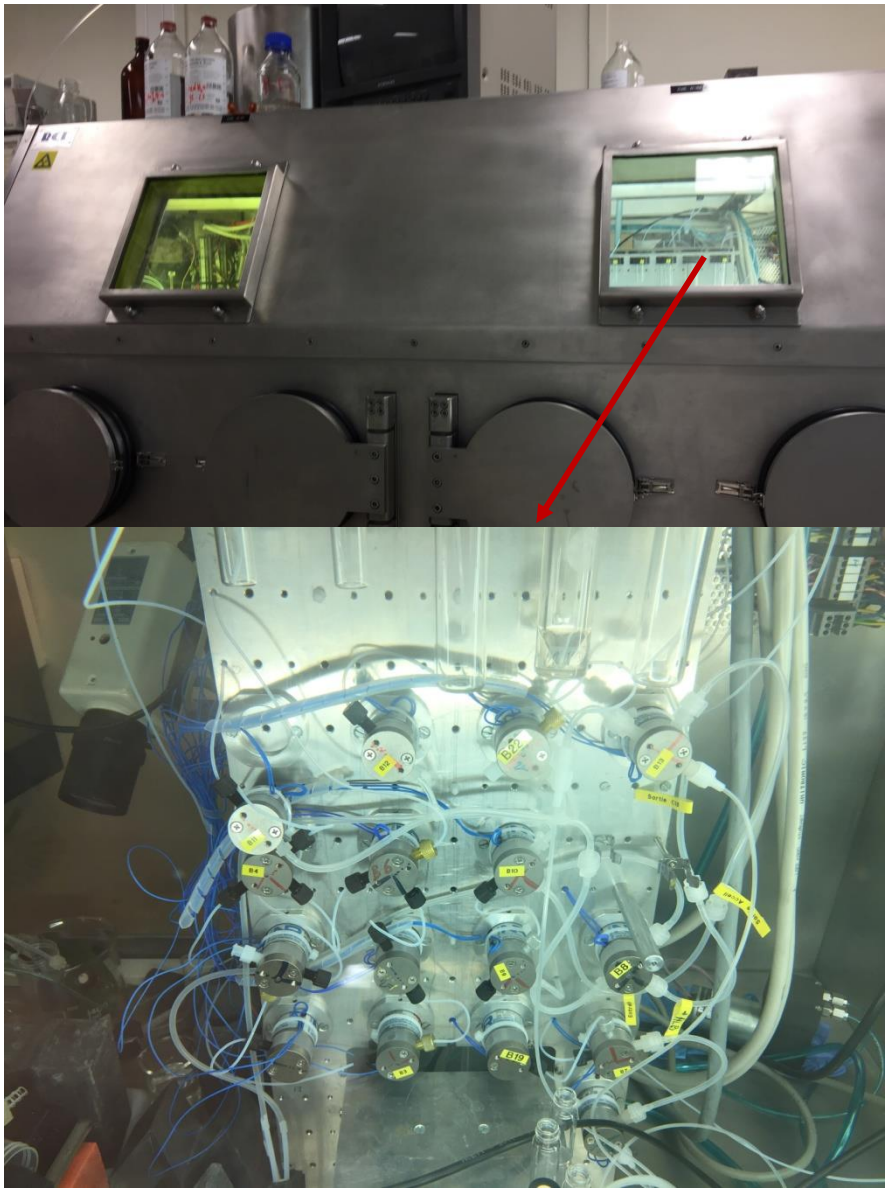
2. Material

The no-carrier-added [^{18}F]fluoride ($t_{1/2}$ = 110 min) was obtained from [^{18}O]enriched water via proton bombardment on an 18/9 IBA cyclotron, trapped on a QMA (Quaternary Methyl Ammonium) carbonate exchange cartridge (Sep-Pak light Waters 46 mg) and released from the QMA thanks to a basic solution (1 mL of an CH_3CN/H_2O (9:1) solution containing 3.5 mg of K_2CO_3 and 15 mg of K_{222}). PhCN was dried over $MgSO_4$ and distilled under reduced pressure prior to use. N_2 (Praxair 99.996 %), anhydrous CH_3CN (Aldrich, 99.8%, sealed bottle), CH_3CN for HPLC (VWR, HPLC quality), $CHCl_3$ (Fluka, 99.8 %), DMF (Acros, 99.8% extra-dry, sealed bottle over molecular sieves), Kryptofix 222 (K_{222}) (Merck), K_2CO_3 (Aldrich), *t*BuOK (Aldrich, ≥ 98%) were used as received.

3. Home-made remote controlled module

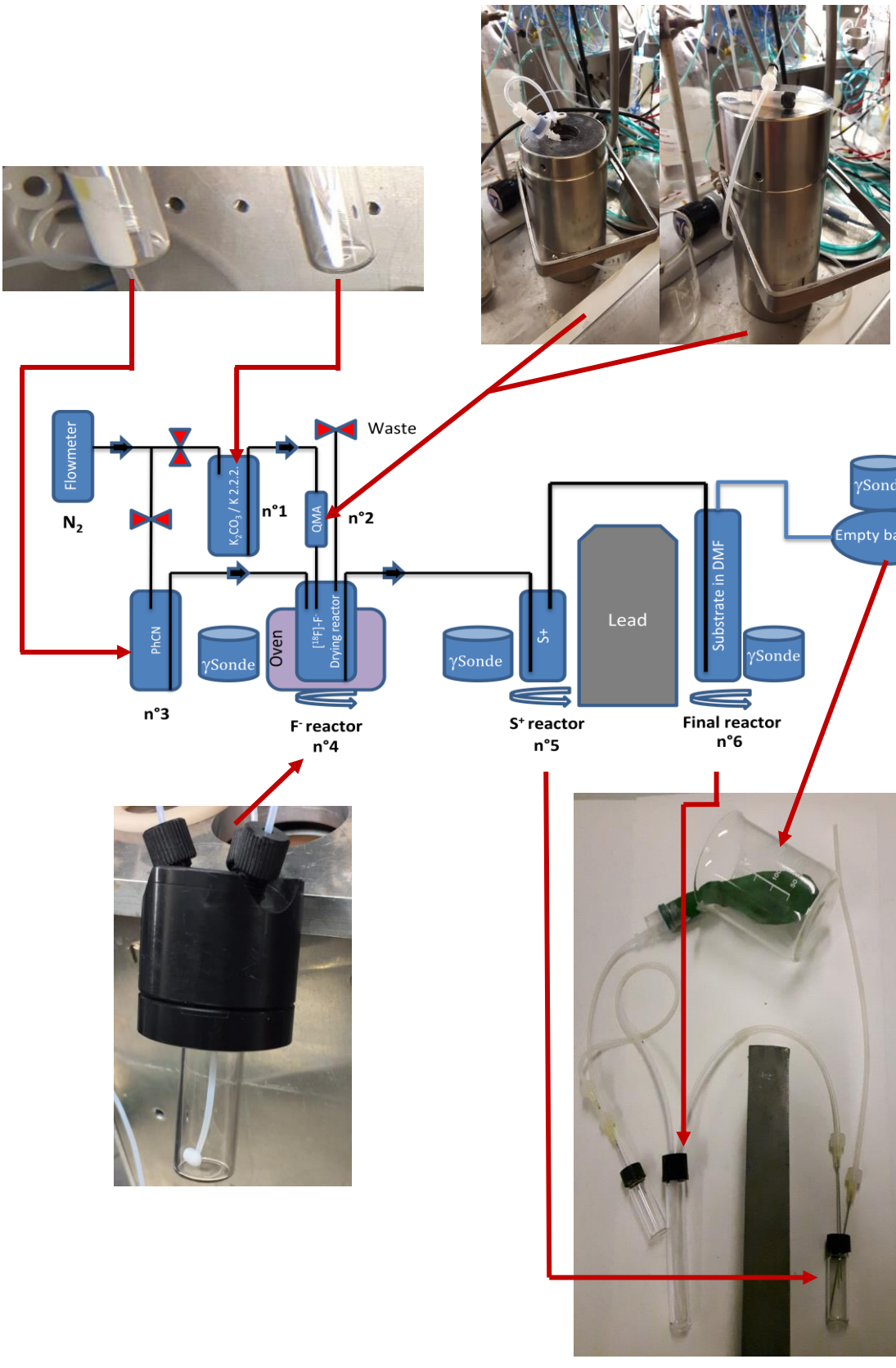


Scheme 1: home-made remote controlled module



Scheme 2: pictures of the home-made remote controlled module

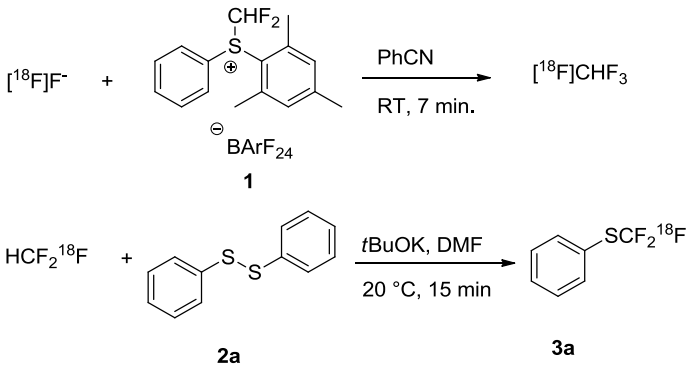
A 5 mL vial was used for the basic solution (n°1), a 5 mL vial was used for PhCN (n°3), a 5 mL tube equipped with a septum and a stirring bar was used as the F^- reactor (n°4) and a 5-mL tube equipped with a septum and a stirring bar was used as the S^+ reactor (n°5). A 8 mL tube equipped with a septum and a stirring bar was used as the final reactor n°6. The whole apparatus was washed (first with water then acetone) and dried under nitrogen. The S^+ reactor and the F^- one were dried in an oven at 130 °C for 30 minutes and cooled down to RT under a nitrogen atmosphere. Note: for compound **2b**, a 20-mL tube was used as the final reactor n°6.


Flowmeter
N2
K2CO3 / K 2.2.2.
n°1
QMA
n°2
Waste
PhCN
n°3
γSonde
Oven
[18F]-F-
Drying reactor
F- reactor
n°4
γSonde
S+
Lead
S+ reactor
n°5
Substrate in DMF
γSonde
Final reactor
n°6
γSonde
Empty balloon

4. Typical procedure for the [^{18}F]-trifluoromethylation reaction.

The typical procedure was depicted for **2a** and the similar procedure was used for all other substrates.

Note: for compound **2b**, the quantities of DMF, Et_2O and water were increased by two.



The S^+ reactor n°5 charged with **1** and the final reactor n°6 charged under air with *t*BuOK (0.12 g, 1.04mmol, 13.2 eq.) and **2a** (0.23 g, 1.04mmol, 13.2 eq.) were quickly connected to the remote controlled module and isolated from the F^- reactor n°4 thanks to a 2-way valve. Nitrogen was passed through for 5 min. The flask n°3 containing PhCN (1 mL), the one containing the basic mixture for the elution of the cartridge n°1 and the [^{18}F]fluoride cartridge n°2 were connected to the remote controlled module.

[^{18}F]Fluoride was released from QMA to the F^- reactor n°4 using the basic solution from the flask n°1. The activity was measured (reactor n°4). [^{18}F]Fluoride was then dried at 95 °C under a stream of nitrogen and magnetic stirring. After 7 minutes, 0.5 mL of CH_3CN was added at 95°C and the [^{18}F]fluoride was dried at 95°C. The same operation was repeated twice with two additional portions of CH_3CN (0.5 mL each) in the interval of 3 min. [^{18}F]Fluoride was diluted with 1 mL of PhCN at 95 °C and then cooled down to 20 °C. DMF (2 mL) was added in the final reactor n°6 under stirring at 20 °C and an empty balloon was connected to the final reactor n°6.The solution of [^{18}F]fluoride in PhCN of the F^- reactor n°4 was then transferred to the S^+ reactor n°5 at 20 °C onto neat **1** (formation and distillation of the $HCF_2{}^{18}F$).

When the activity distillation was stopping (when the signal of transferred radioactivity showed the beginning of a plateau, after about 5 minutes), the submerged tube from the S^+ reactor n°5 in the final reactor n°6 was lifted. The flow of nitrogen was stopped, the final reactor n°6 was isolated and the reaction mixture was stirred at 20 °C for 15 min. Et_2O (2 mL) and water (1 mL) were then added. The final reactor n°6 was reconnected to the radiochemical apparatus and the residual $HCF_2{}^{18}F$ was eliminated by a nitrogen flow. Activities in the different reactors (reactor n°4, 5 and 6) were measured. Then, 5 µL of the aqueous layer and 5µL of the organic layer were separately analyzed by HPLC. The HPLC analysis (70:30 CH_3CN/water) of the organic and aqueous layers showed the product of [^{18}F]trifluoromethylthiolation **3a** and its radiochemical purity (retention time ca. 4.83 min,

>99% purity). The product **3a** was obtained in 73 % radiochemical yield (*n* = 3).

Determination of the radiochemical yield (RCY) for **3a**

	F^- t_0 reactor n°4	F^- t_1 reactor n°4	S^+ reactor n°5	S^+t_1 reactor n°5	Final reactor reactor n°6	Final reactor t_1 reactor n°6
$\Delta t = t\text{-}t_0$ (min)	0	57[a]	/	54[a]	/	58[a]
A_{t1} (mCi)	/	21.4	/	28.2	/	37.2
A_0(mCi)	134.0	30.7	103.3	39.6	63.7	53.6
RCY (%)					53.6/63.7 = 84	

t_0 : correspond to the time when the procedure was started.

t_1 : correspond to the time when the reaction was quenched in the final reactor n°6and when the different activities were measured.

$A_0(F^- t_0)$, $A_{t1}(F^- t_1)$, $A_{t1}(S^+ t_1)$, A_{t1}(Final reactor t_1) were measured.

A_0 activities were obtained by calculation according to the decay-corrected activities ($A_0 = A_t$ / exp (- 0.693 x ($\Delta t/t_{1/2}$)).

a : For practical reasons, the three activities were not measured simultaneously.

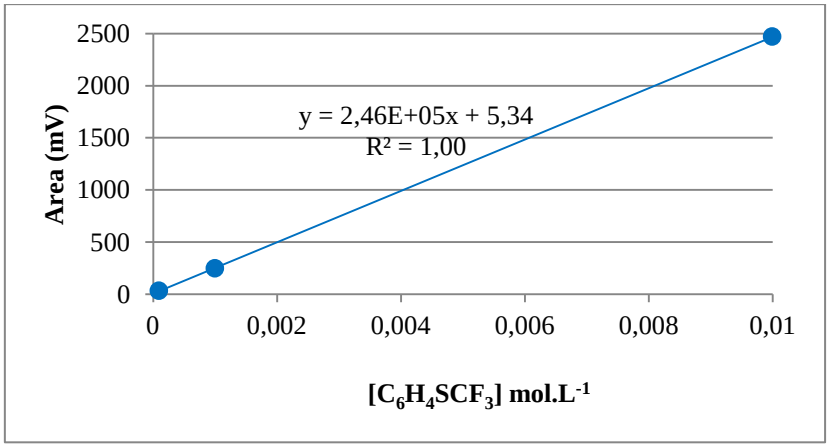
5. Determination of the specific activity

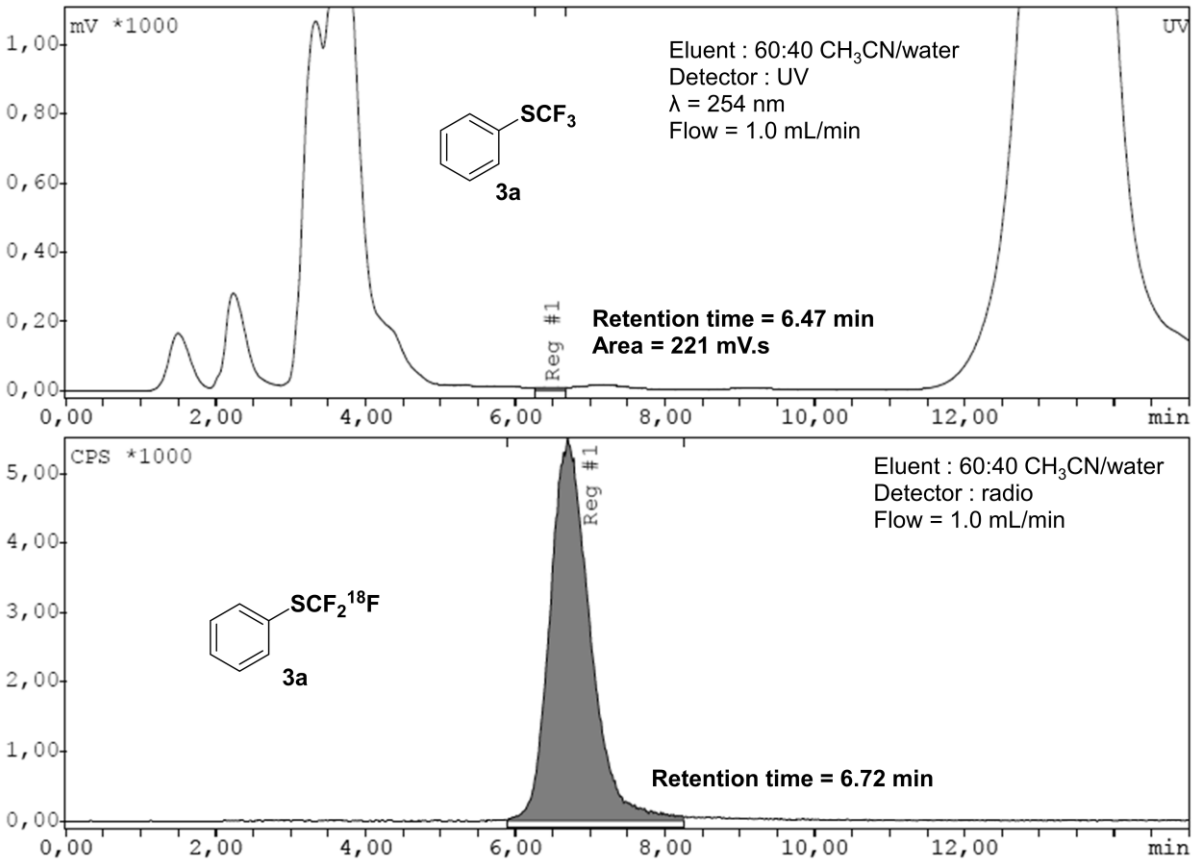
The specific activity was determined starting from 130 mCi of [^{18}F]fluoride.

Calibration curve and calculation for [^{18}F]phenyl(trifluoromethyl)sulfane 3a

The analysis were performed according to the following conditions: eluent: 60:40 CH_3CN/H_2O, flow = 1.0mL/min, λ = 254 nm.

$[C_6H_4SCF_3]$ (mol.L^{-1})	Area (mV)
0.01	2470
0.001	247
0.0001	34.1





A sample of 1.1 mL of organic layer was used to determine the specific activity. The activity of this sample was measured at t and the decay-corrected activity A_0 was calculated ($A_0 = A_t$ / exp (- 0.693 x ($\Delta t/t_{1/2}$)).

t_0 (min)	596
t (min)	646
$\Delta t = t\text{-}t_0$ (min)	50
A(t) (mCi)	4,05
A(0) (mCi)	5,55

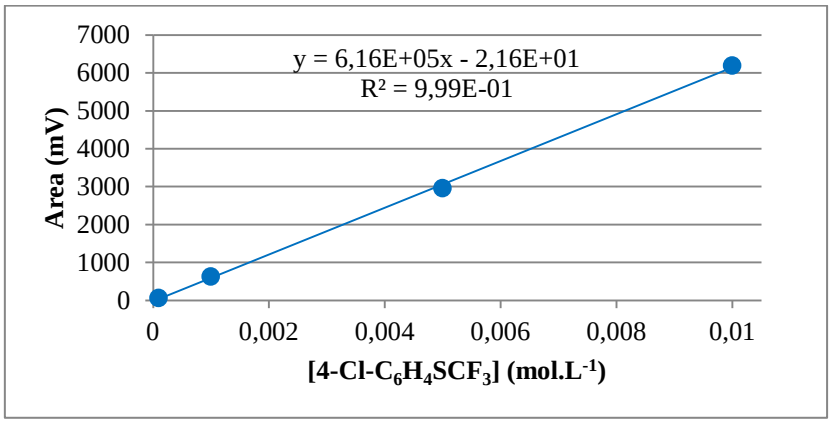
The sample was then analyzed by HPLC (5 µL) in order to determine the concentration of the sample.

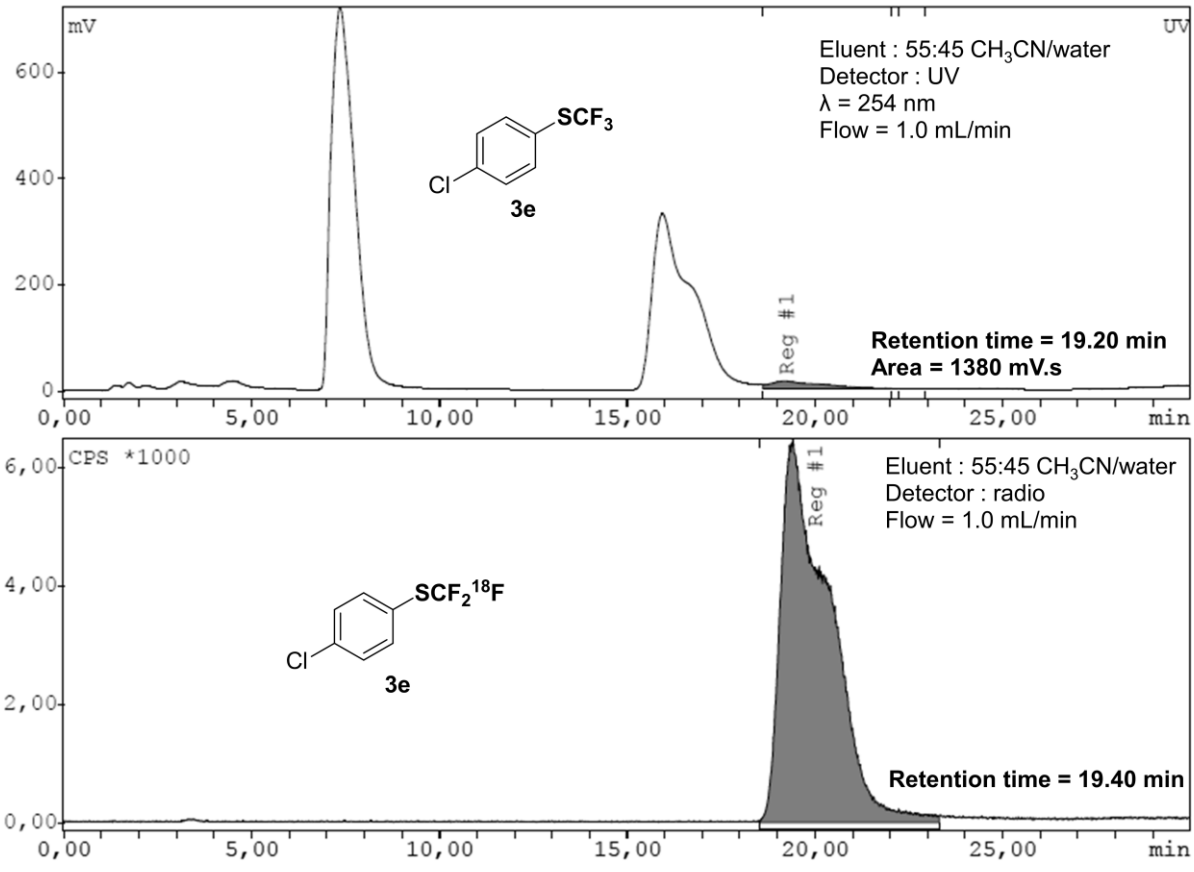
Volume of the total sample (mL)	1,1
Area($C_6H_4SCF_3$) (mV.s)	221
[$C_6H_4SCF_3$] (mol.L^{-1})	8.77E-04
n($C_6H_4SCF_3$)(mol)	9.65E-07
Specific activity (GBq.µmol^{-1})	**0.21**

Calibration curve and calculation for [^{18}F](4-chlorophenyl)(trifluoromethyl)sulfane 3e

The analyses were performed according to the following conditions: eluent 60:40 CH_3CN/water, flow = 1.0mL/min, λ = 254 nm.

[4-Cl-$C_6H_4SCF_3$] (mol.L^{-1})	Area (mV)
0.01	6190
0.005	2960
0.001	629
0.0001	60.6





A sample of 1.0 mL of organic layer was used to determine the specific activity. The activity of this sample was measured at t and the decay-corrected activity A_0 was calculated ($A_0 = A_t$ / exp (- 0.693 x ($\Delta t/t_{1/2}$)).

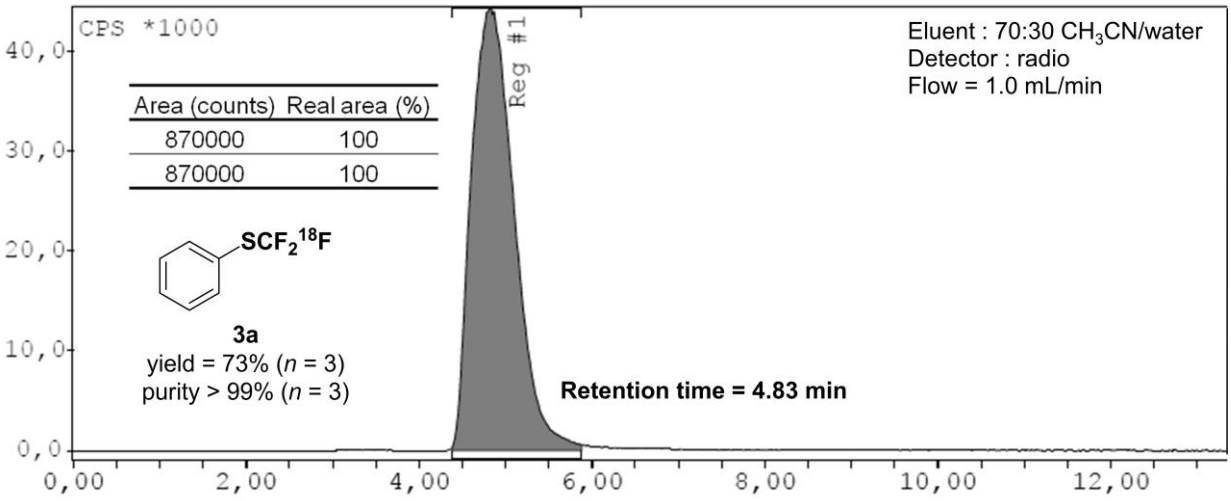
t_0 (min)	874
t (min)	940
$\Delta t = t\text{-}t_0$ (min)	66
A(t) (mCi)	15.4
A(0) (mCi)	23.34

The sample was then analyzed by HPLC (5 µL) in order to determine the concentration of the sample.

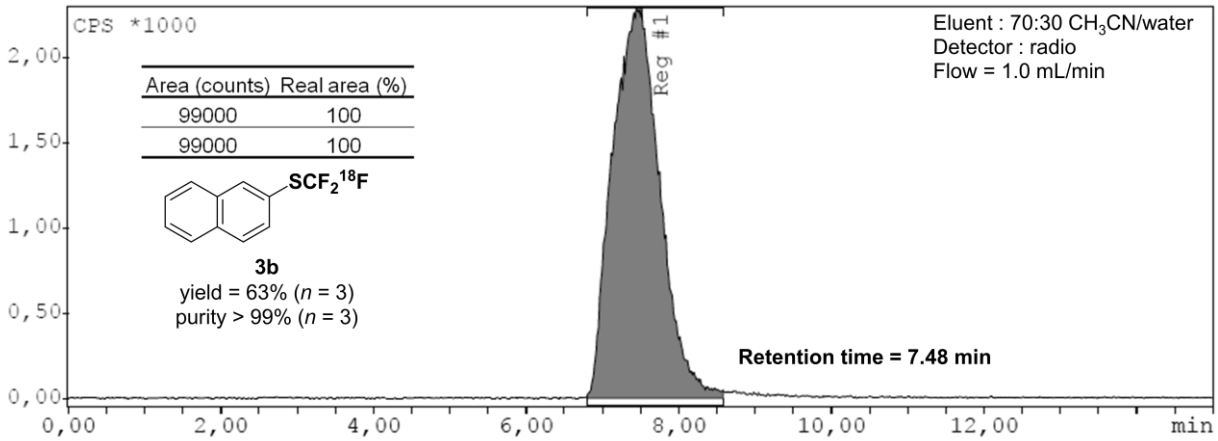
Volume of the total sample (mL)	1,0
Area(4-Cl-$C_6H_4SCF_3$) (mV.s)	1380
[4-Cl-$C_6H_4SCF_3$] (mol.L^{-1})	2.28E-03
n(4-Cl-$C_6H_4SCF_3$)(mol)	2.28E-06
Specific activity (GBq.µmol^{-1})	**0.38**

6. HPLC chromatograms of $SCF_2{}^{18}F$-containing products

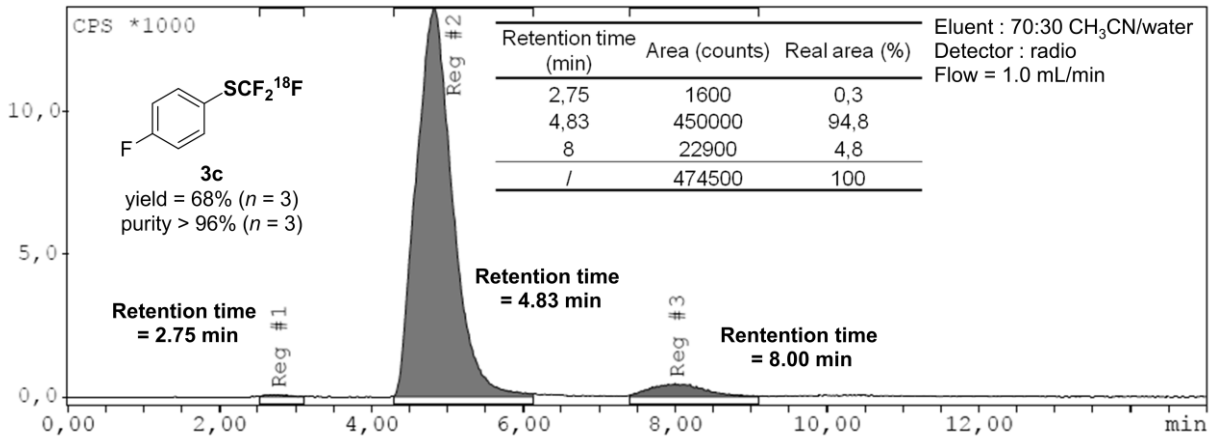
[^{18}F]Phenyl(trifluoromethyl)sulfane 3a



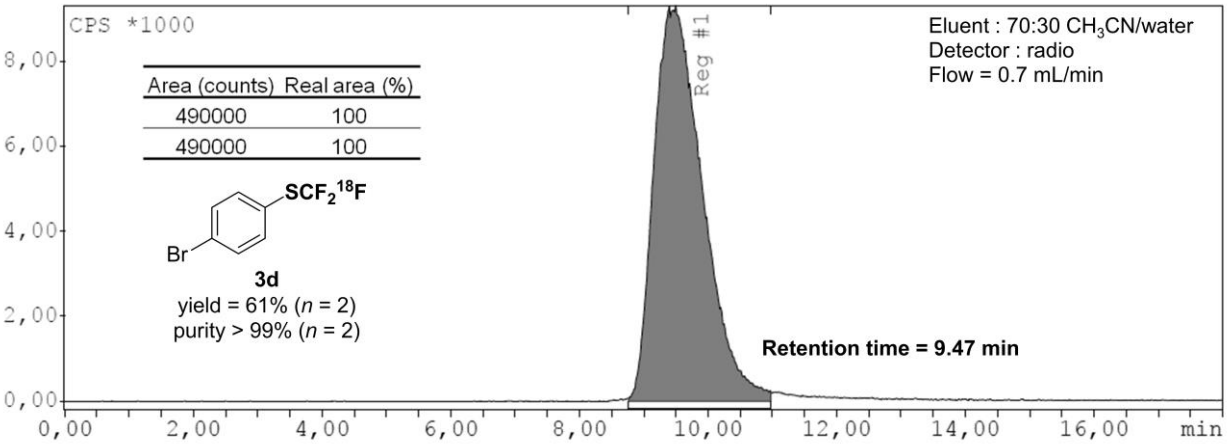
[^{18}F]Naphthalen-2-yl(trifluoromethyl)sulfane 3b



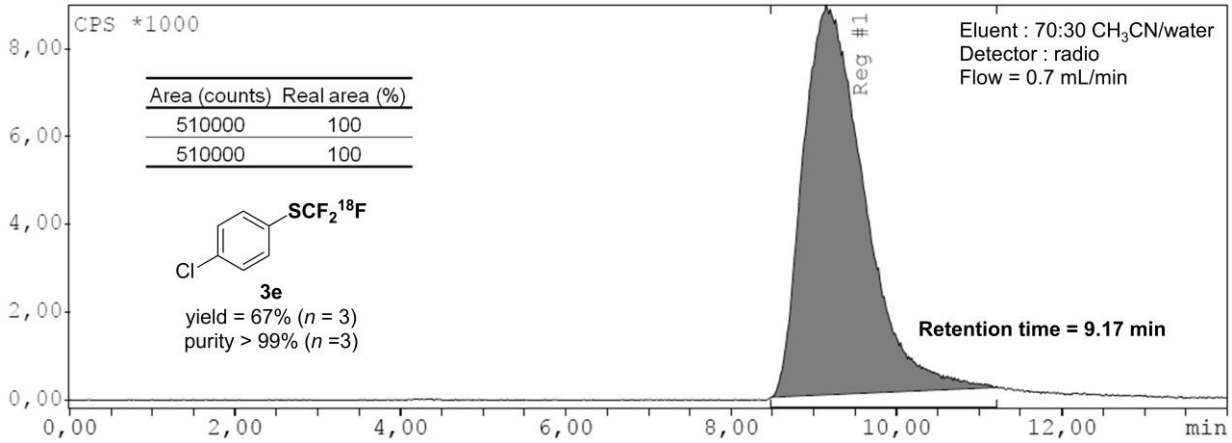
[^{18}F](4-Fluorophenyl)(trifluoromethyl)sulfane 3c



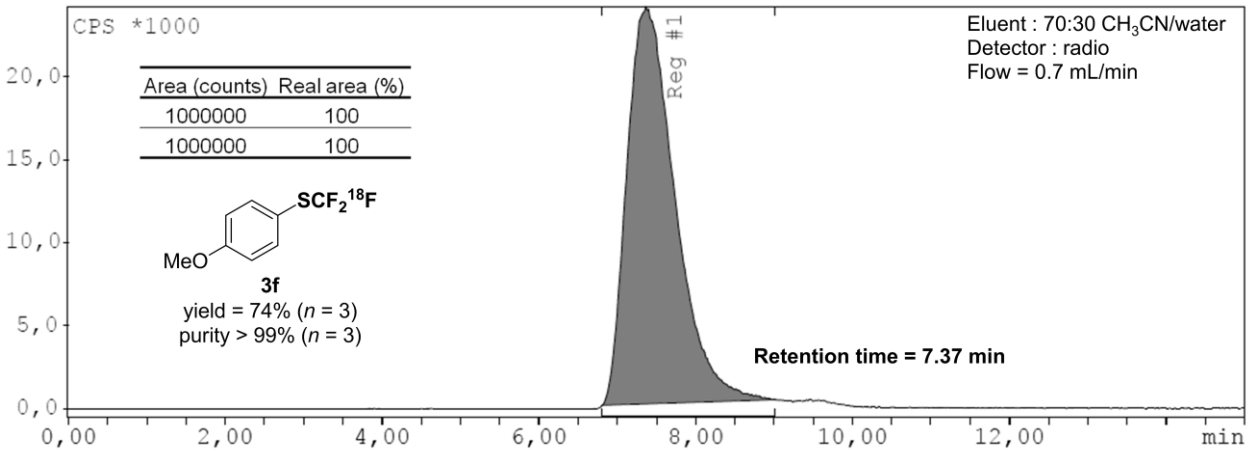
[^{18}F](4-Bromophenyl)(trifluoromethyl)sulfane 3d



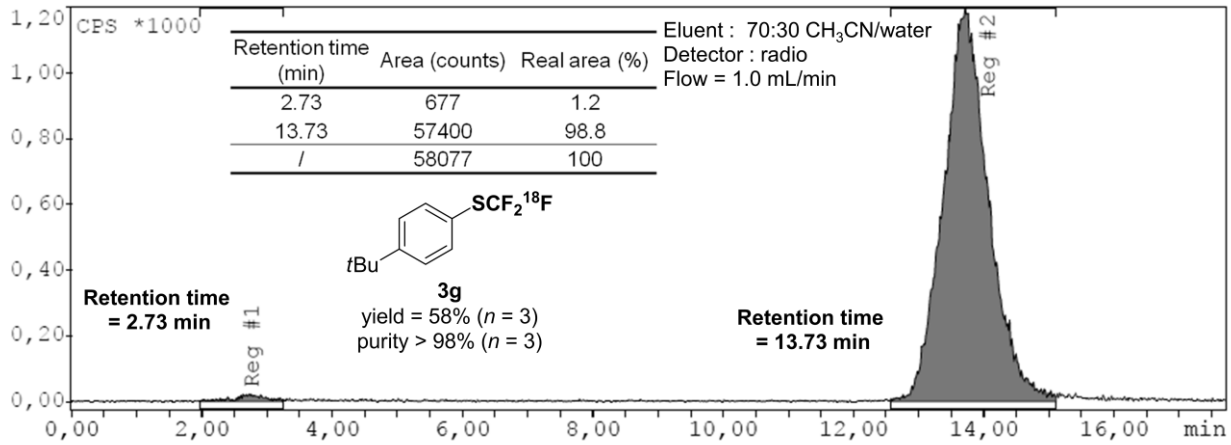
[^{18}F](4-chlorophenyl)(trifluoromethyl)sulfane 3e



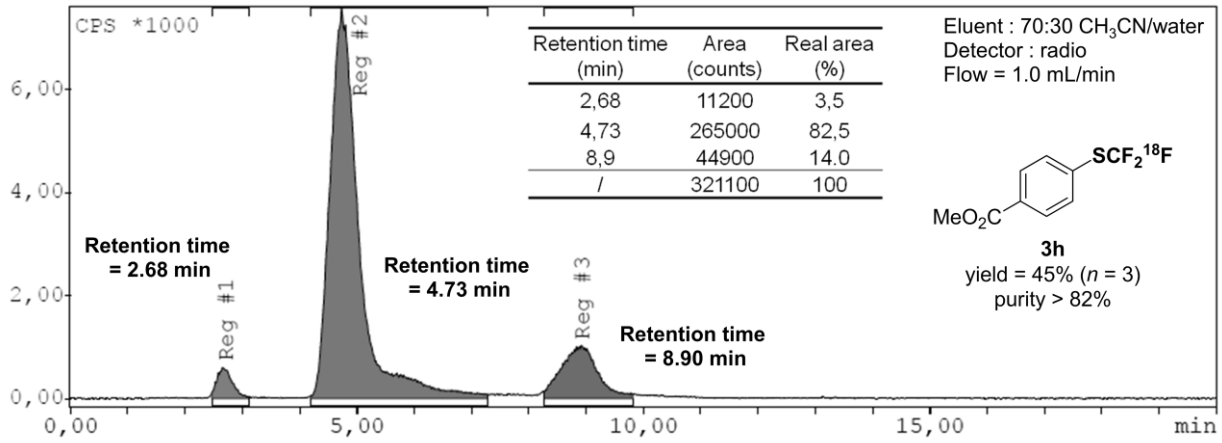
[^{18}F](4-Methoxyphenyl)(trifluoromethyl)sulfane 3f



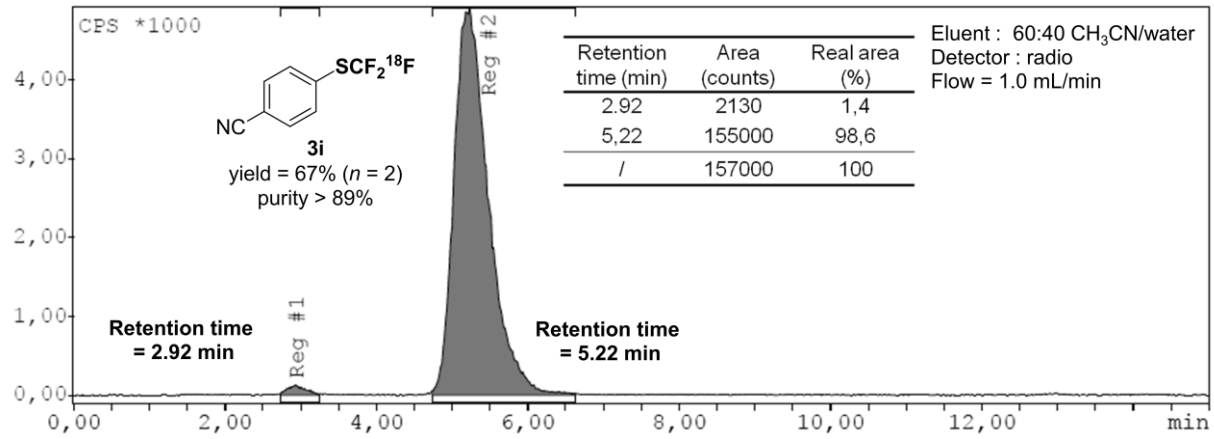
[^{18}F](4-(*Tert*-butyl)phenyl)(trifluoromethyl)sulfane 3g



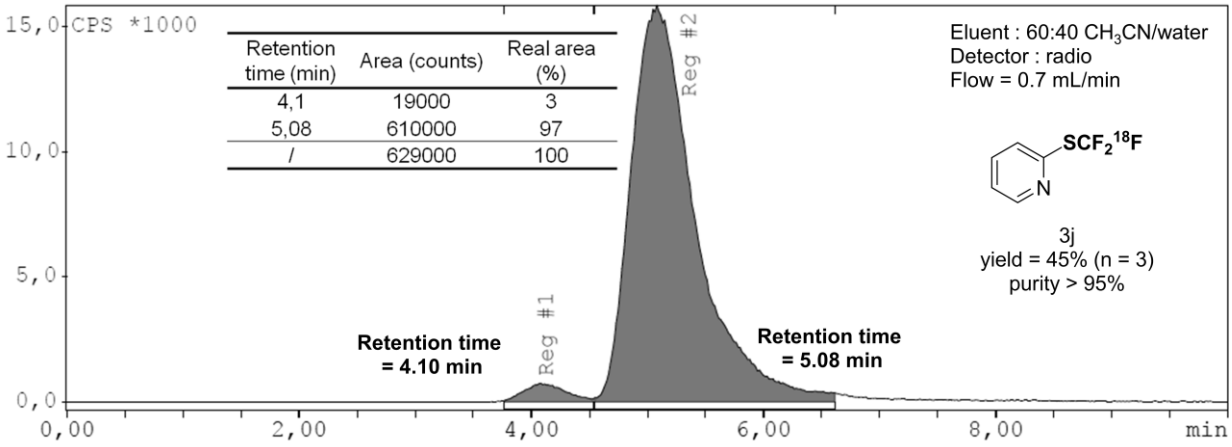
[^{18}F]Methyl 4-((trifluoromethyl)thio)benzoate 3h



[^{18}F]4-((Trifluoromethyl)thio)benzonitrile 3i



[^{18}F]2-((Trifluoromethyl)thio)pyridine 3j



[^{18}F]Phenyl(trifluoromethyl)selane 3k