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Supporting Information

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Supporting Information

Photoinduced Aryl Ketone-Catalyzed Phenylation of C(sp^3)–H Bonds Attached to the Heteroatom of Ethers and *N*-Boc-amines via Concerted Homolytic Aromatic Substitution

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Contents

Additional Experimental Data

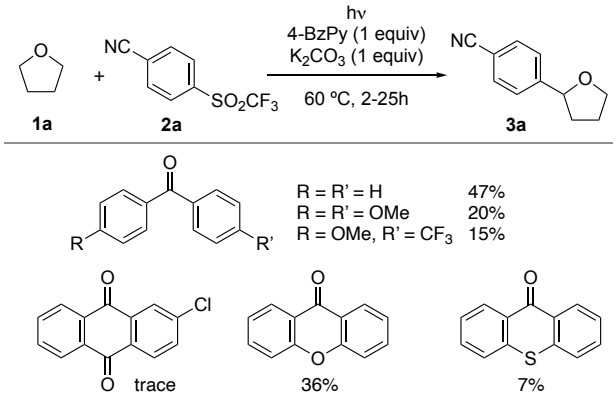


Figure S1. Screening of aryl ketones. Conditions: **2a** (0.2 mmol, 1 equiv), 4-BzPy (0.2 mmol, 1 equiv), THF (**1a**, 4 mL as solvent, 49 mmol, 247 equiv), K_2CO_3 (0.2 mmol, 1 equiv), photoirradiation using 365 nm LED light under Ar atmosphere at 60 °C. Yield was determined by ^{1}H NMR analysis of the crude mixture.

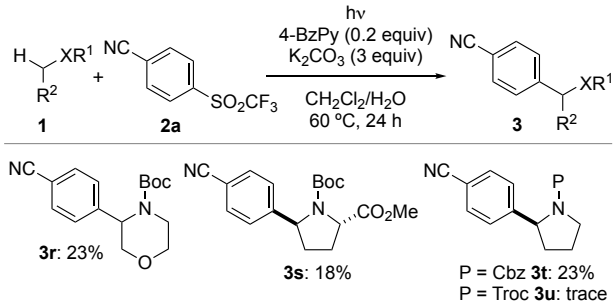
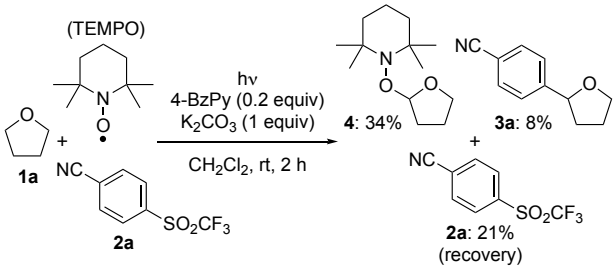


Figure S2. Substrate applicability of the C–H phenylation. Conditions: starting substance **1** (2 mmol, 10 equiv), **2a** (0.2 mmol, 1 equiv), 4-BzPy (0.04 mmol, 0.2equiv), K_2CO_3 (0.6 mmol, 3 equiv), CH_2Cl_2/H_2O = 3/1 (2 mL), photoirradiation using 365 nm LED light under Ar atmosphere at 60 °C. Isolated yields are shown.



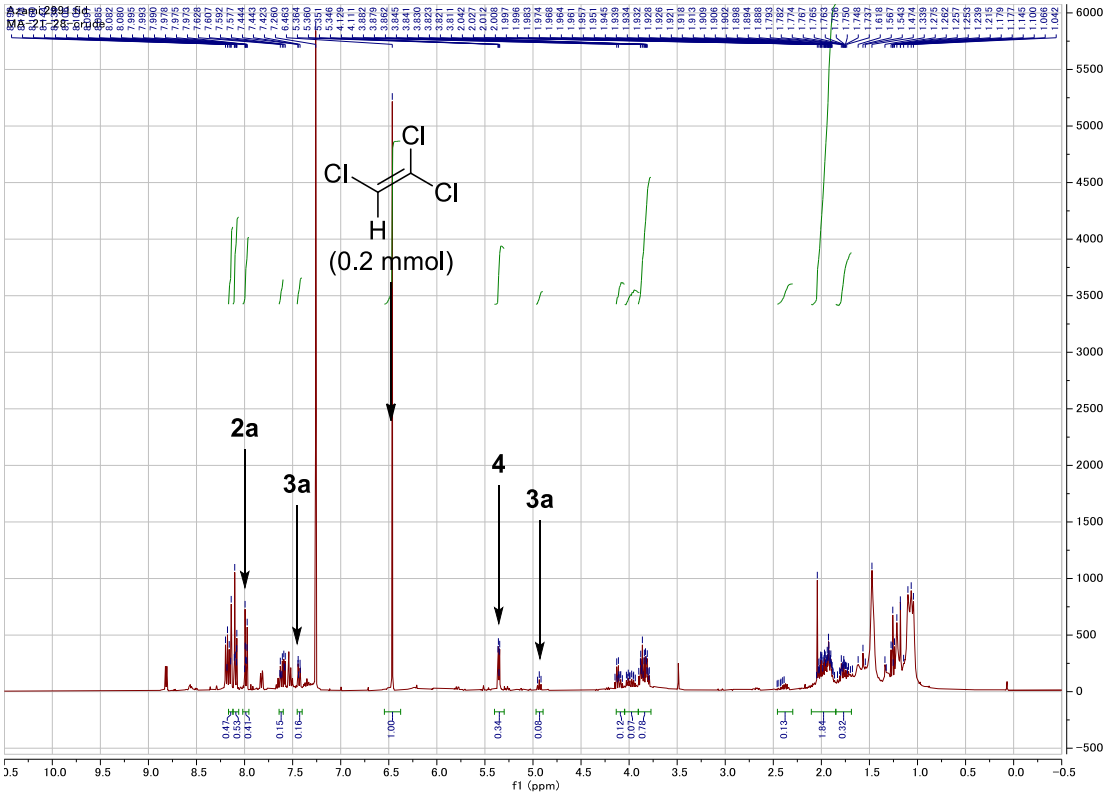


Figure S3. Radical capture experiment using TEMPO. Conditions: THF **1a** (2 mmol, 10 equiv), **2a** (0.2 mmol, 1 equiv), 4-BzPy (0.04 mmol, 0.2equiv), K_2CO_3 (0.2 mmol, 1 equiv), CH_2Cl_2/H_2O = 3/1 (2 mL), photoirradiation using 365 nm LED light under Ar atmosphere at rt.

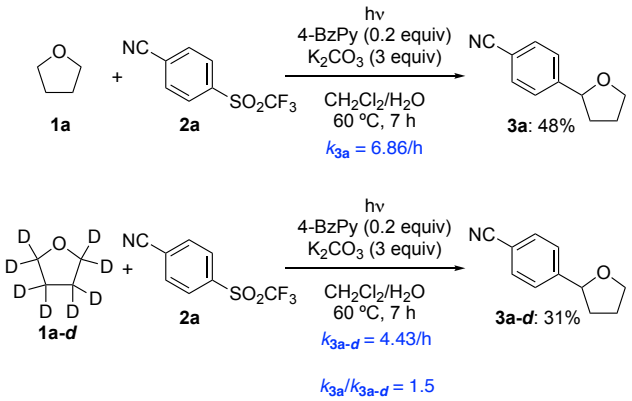


Figure S4. Measurement of the kinetic isotope effect on the phenylation of THF (**1a**). Conditions: THF **1a** or THF-d_8 **1a-*d*** (2 mmol, 10 equiv), **2a** (0.2 mmol, 1 equiv), 4-BzPy (0.04 mmol, 0.2equiv), K_2CO_3 (0.6 mmol, 3 equiv), CH_2Cl_2/H_2O = 3/1 (2 mL), photoirradiation using 365 nm LED light under Ar atmosphere at rt.

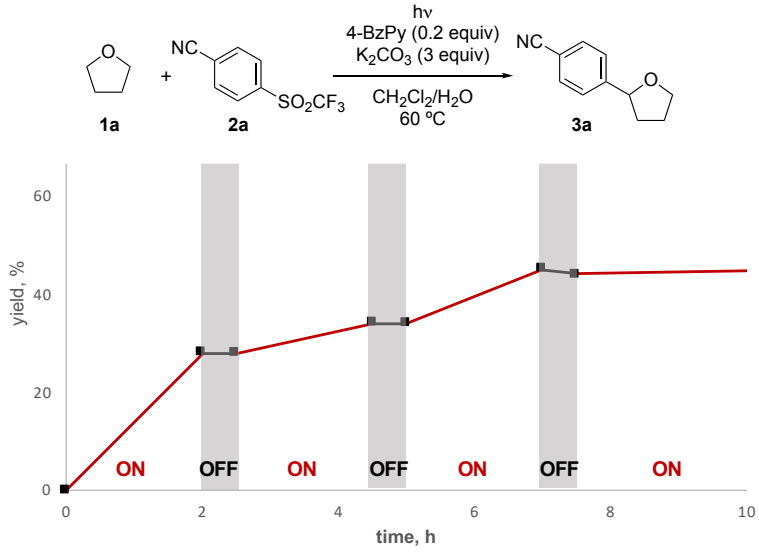
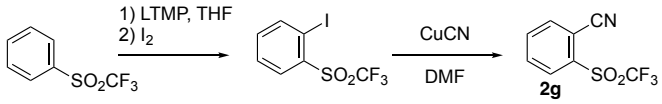


Figure S5. Time course of the phenylation of THF (**1a**) with light ON/OFF. Conditions: THF **1a** (2 mmol, 10 equiv), **2a** (0.2 mmol, 1 equiv), 4-BzPy (0.04 mmol, 0.2equiv), K_2CO_3 (0.6 mmol, 3 equiv), CH_2Cl_2/H_2O = 3/1 (2 mL), photoirradiation using 365 nm LED light under Ar atmosphere at 60 °C.

*Preparation and Analytica Data of the Phenyl Precursors **2***

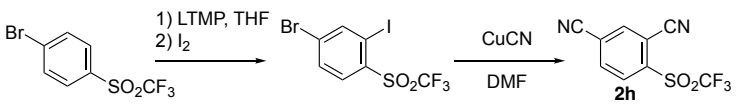
General information

All reactions sensitive to air or moisture were carried out under an argon atmosphere with anhydrous conditions unless otherwise noted. Analytical TLC was performed on E. Merck silica gel 60 F254 precoated plates. Column chromatography was performed with silica gel (Fuji Silysia) or using a Biotage Isolera system. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III-400 (400 MHz) or Bruker DRX500 (500 MHz) spectrometer. Chemical shifts are reported in δ (ppm) relative to residual solvent signals for ^{1}H NMR: $CHCl_3$ (7.26) and ^{13}C NMR: $CDCl_3$ (77.0). Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. HRMS were recorded on a Thermo Fisher Scientific Orbitrap Exploris 4800/240/120 instrument. 4-(Trifluoromethylsulfonyl)benzonitrile (**2a**, CAS Reg. No. 312-21-0) was purchased from Nacalai Tesque and used as received.



To a stirring solution of 2,2,6,6-tetramethylpiperidine (0.27 mL, 1.6 mmol) in dry THF (3.0 mL) at -78 ℃ was added *n*-BuLi (1.6 M solution in hexane, 0.94 mL, 1.5 mmol) at -78 ℃, and mixture was stirred at -78 ℃ for 1 h. The prepared LTMP was transferred to a solution of (trifluoromethylsulfonyl)benzene (210.2 mg, 1 mmol) in dry THF (2.0 mL) via a cannula and the mixture was stirred at -78 ℃ for 1 h. Then, a solution of I_2 (507.6 mg, 2 mmol) in dry THF (5 mL) was transferred to the resultant mixture via a cannula and the mixture was stirred at -78 ℃ for 1 h. After warming up to rt, aq. $Na_2S_2O_3$ was added and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography to give 1-iodo-2-(trifluoromethylsulfonyl)benzene (63% yield, 208.5 mg) as a yellow oil[1]. To a stirring solution of 1-iodo-2-(trifluoromethylsulfonyl)benzene (208.5 mg, 0.63 mmol) in dry DMF (3 mL) was added CuCN (66.3 mg, 0.74 mmol) and mixture was stirred at 150 ℃ for 3 h. The reaction mixture was diluted with Et_2O and filtered through the Celite pad. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography to give 2-(trifluoromethylsulfonyl)benzonitrile (**2g**, 63% yield, 91.4 m) as a white powder[2].

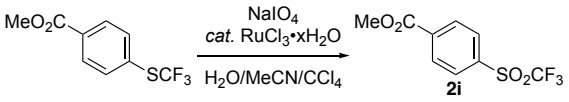
[CAS Reg. No. 2376171-41-2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-8.03 (2H, m), 8.03-8.10 (1H, m), 8.28 (1H, dd, J = 7.7, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.1, 119.6 (q, $^{1}J_{C\text{-}F}$ = 324.3 Hz); 132.9, 133.6, 133.71, 133.77, 136.60, 136.62.



To a stirring solution of 2,2,6,6-tetramethylpiperidine (0.27 mL, 1.6 mmol) in dry THF (3.0 mL) at -78 ℃ was added *n*-BuLi (1.6 M solution in hexane, 0.94 mL, 1.5 mmol) at -78 ℃, and mixture was stirred at -78 ℃ for 1 h. The prepared LTMP was transferred to a solution of 1-bromo-4-(trifluoromethrlsulfonyl)benzene (289.1 mg, 1 mmol) in dry THF (2.0 mL) via a cannula and the mixture was stirred at -78 ℃ for 1 h. Then, a solution of I_2 (507.6 mg, 2 mmol) in dry THF (5 mL) was transferred to the resultant mixture and the mixture was stirred at -78 ℃ for 1 h. After warming up to rt, aq. $Na_2S_2O_3$ was added and mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography to give 1-bromo-3-iodo-4-(trifluoromethylsulfonyl)benzene (61% yield, 253.7 mg) as a yellow oil.

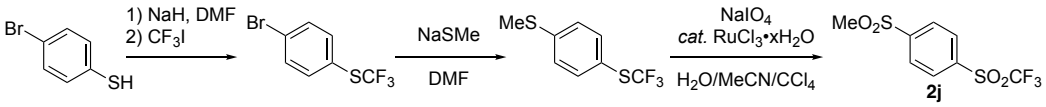
To a stirring solution of 1-bromo-3-iodo-4-(trifluoromethylsulfonyl)benzene (193.3 mg, 0.47 mmol) in dry DMF (3 mL) was added CuCN (105.7 mg, 1.2 mmol) and mixture was stirred at 150 ℃ for 3.5 h. The reaction mixture was diluted with Et_2O and filtered through the Celite pad. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography to give 1,3-dicyano-4-(trifluoromethylsulfonyl)benzonitrile (**2h**, 57% yield, 70.0 mg) as a white powder.

mp 101.5-103.1 ℃; IR (ATR) 3103, 3044, 2241, 1388, 1377, 1230, 1200, 1120, 768, 719, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (1H, dd, J = 8.3, 1.6 Hz), 8.29 (1H, d, J = 1.6 Hz), 8.42 (1H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.3, 114.5, 115.7, 119.0 (q, $^1J_{C\text{-}F}$ = 324.7 Hz), 121.0, 134.4, 136.6, 136.8, 139.0; HRMS (APCI) calcd for $C_9H_4O_2F_3S$ $[M+H]^+$ 260.9940 found 260.9948.



To a stirring solution of methyl 4-trifluoromethylthiobenzoate (168.7 mg, 0.71 mmol, 1 equiv) in H_2O-MeCN-CCl_4 (2:1:1, 4 mL) was added $RuCl_3 \cdot xH_2O$ (2.07 mg, 0.01 mmol, 1.4 mol%) at rt, and the mixture was stirred for 5 min.[1] $NaIO_4$ (303.7 mg, 1.4 mmol, 2 equiv.) was added to the mixture, and the mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with Et_2O and filtered through the Celite pad. The organic layer was separated and the aqueous layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography (silica gel, hexane/AcOEt = 20/1 to 10/1) to give methyl 4-(trifluoromethylsulfonyl)benzoate[3] (**2i** ,53% yield, 101.0 mg) as a white powder.

[CAS Reg. No. 88489-67-2]; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.00 (3H, s), 8.13 (2H, br d, J = 8.5 Hz), 8.32 (2H, br d, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.0, 119.6 (q, $^1J_{C\text{-}F}$ = 323.7 Hz), 130.80, 130.87, 135.2, 137.3, 164.0.

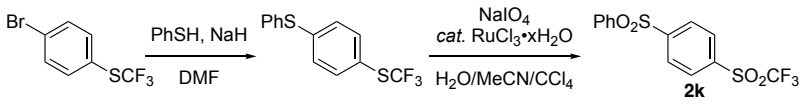


To a stirring suspension of NaH (60% w/w in oil, 0.51 g, 12.7 mg, 1.2 equiv.) in dry DMF (10 mL) was added 4-bromobenzenethiol (2.0 g, 10.6 mg, 1 mmol) at 0 ℃, and the mixture was stirred at 0 ℃ for 1 h. CF_3I (16.5 mL, 12.7 mmol, 2 equiv. 17 wt% in THF) was added to the mixture, and the mixture was stirred at rt for 4 h. Then, sat. NH_4Cl was added to the mixture and the mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (silica gel, hexane) to give 1-bromo-4-(trifluoromethylthio)benzene (100% yield) as a yellow oil.

To a stirring mixture of 1-bromo-4-(trifluoromethylthio)benzene (118.5 mg, 0.5 mmol) in dry DMF (2.5 mL) was added methyl mercaptan sodium salt (42.1 mg, 0.6 mmol) and the mixture was stirred for 17 h. The mixture was extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to give 1-(methylthio)-4-(trifluoromethylthio)benzene (48% yield, 53.9 mg) as a colorless oil[4].

To a stirring solution of 1-(methylthio)-4-(trifluoromethylthio)benzene (53.4 mg, 0.24 mmol, 1 equiv) in H_2O-MeCN-CCl_4 (2:1:1, 2 mL) was added $RuCl_3 \cdot xH_2O$ (0.5 mg, 0.002 mmol, 0.83 mol%) at rt, and the mixture was stirred for 5 min.[1] $NaIO_4$ (205.3 mg, 0.96 mmol, 4 equiv.) was added to the mixture, and the mixture was stirred at rt for 0.5 h. The reaction mixture was diluted with Et_2O and filtered through the Celite pad. The organic layer was separated and the aqueous layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography (silica gel, hexane/AcOEt = 5/1 to 2/1) to give 1-(methylsulfonyl)-4-(trifluoromethylsulfonyl)benzene[5] (**2j**, 53% yield, 36.7 mg) as a white powder.

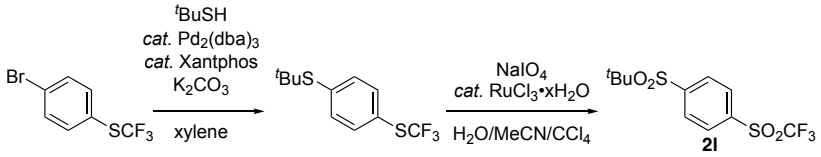
[CAS Reg. No. 2262-06-8]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.14 (3H, s), 8.27 (4H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.1, 119.6 (q, $^1J_{C\text{-}F}$ = 324.1 Hz), 128.9, 131.9, 136.5, 147.9.



To a stirring suspension of NaH (60% w/w in oil, 48.0 mg, 1.2 mmol) in dry DMF (5 mL) was added benzenethiol (0.1 mL, 1 mmol) at 0 ℃, and mixture was stirred at 0 ℃ for 1 h. 1-Bromo-4-(trifluoromethylthio)benzene (237.0 mg, 1 mmol) was added to the mixture, and the mixture was stirred at 100 ℃ for 19 h. Then, sat. NH_4Cl was added to quench the reaction and the mixture was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to give 1-(phenylthio)-4-(trifluoromethylthio)benzene (86% yield, 246.8 mg) as a colorless oil.

To a stirring solution of 1-(phenylthio)-4-(trifluoromethylthio)benzene (246.8 mg, 0.86 mmol, 1 equiv) in H_2O-MeCN-CCl_4 (2:1:1, 4 mL) was added $RuCl_3 \cdot xH_2O$ (1.9 mg, 0.009 mmol, 1 mol%) at rt, and the mixture was stirred for 5 min.[1] $NaIO_4$ (735.8 mg, 3.4 mmol, 4 equiv.) was added to the mixture, and the mixture was stirred at rt for 0.5 h. The reaction mixture was diluted with Et_2O and filtered through the Celite pad. The organic layer was separated and the aqueous layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography (silica gel, hexane/AcOEt = 10/1 to 5/1) to give 1-(methylsulfonyl)-4-(trifluoromethylsulfonyl)benzene (**2k**, 42% yield, 246.8 mg) as a white powder.

mp 158.5-159.7 °C; IR (ATR) 3096, 3069, 1370, 1325, 1209, 1156, 833, 725, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.58 (2H, m), 7.58-7.65 (1H, m), 7,76 (2H, *J* = 8.6 Hz), 7.93-8.02 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 119.6 (q, $^1J_{C\text{-}F}$ = 324.0 Hz), 128.2, 128.9, 129.8, 131.7, 134.3, 135.7, 139.5, 149.5; HRMS (APCI) calcd for $C_{13}H_{10}F_3O_4S_2$ $[M+H]^+$ 350.9967 found 350.9964.

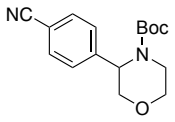


To a stirring suspension of K_2CO_3 (69.1 mg, 0.5 mmol) in dry xylene (2 mL) was added *tert*-butylmercaptan (0.11 mL, 1 mmol) at 0 °C, and mixture was stirred 0 °C for 5.5 h. A solution of 1-bromo-4-(trifluoromethylthio)benzene (205.6 mg, 0.8 mmol), $Pd_2(dba)_3$ (73.3 mg, 0.08 mmol), Xantphos (52.1 mg, 0.09 mmol) in dry xylene (10 mL) was transferred via a cannula to the prepared potassium thiolate solution. The mixture was stirred and heated at reflux for 11 h. After cooling to room temperature, the mixture was diluted with EtOAc (20 mL), washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was then purified by silica gel chromatography (hexane) to give 1-(*tert*-butylthio)-4-(trifluoromethylthio)benzene (69% yield, 146.2 mg) as a colorless oil[6].

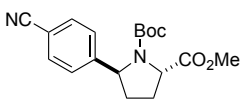
To a stirring solution of 1-(*tert*-butylthio)-4-(trifluoromethylthio)benzene (134.4 mg, 0.5 mmol, 1 equiv) in H_2O-MeCN-CCl_4 (2:1:1, 4 mL) was added $RuCl_3 \cdot xH_2O$ (0.5 mg, 0.002 mmol, 0.4 mol%) at rt, and the mixture was stirred for 5 min.[1] $NaIO_4$ (205.3 mg, 0.96 mmol, 4 equiv.) was added to the mixture, and the mixture was stirred at rt for 0.5 h. The reaction mixture was diluted with Et_2O and filtered through the Celite pad. The organic layer was separated and the aqueous layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressured. The crude mixture was purified by silica gel column chromatography (silica gel, hexane/AcOEt = 10/1 to 5/1) to give 1-(*tert*-butylsulfonyl)-4-(trifluoromethylsulfonyl)benzene (**2l**, 26% yield, 42.7 mg) as a white powder.

mp 203.1-205.4 °C; IR (ATR) 3095, 2917, 1369, 1325, 1189, 1137, 724, 705, 638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (9H, s), 8.20 (2H, br d, *J* = 8.7 Hz), 8.24 (2H, br d, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5, 60.7, 119.6 (q, $^1J_{C\text{-}F}$ = 324.2 Hz) 131.0, 131.8, 136.4, 143.7; HRMS (APCI) calcd for $C_{11}H_{14}F_3O_4S_2$ $[M+H]^+$ 331.0280 found 331.0275.

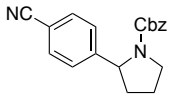
*Analytical Data of the Phenylated Products **3***



***N*-(*tert*-Butoxycarbonyl)-2-(4-cyanophenyl)morpholine (3r)**[7]; purified by flash column chromatography (silica gel, hexane/AcOEt = 10/1 to 2/1), 22% yield (12.8 mg); [CAS Reg. No. 1588517-11-6]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (9H, s), 3.06 (1H, ddd, *J* = 13.7, 12.0, 3.8 Hz), 3.60 (1H, td, *J* = 12.0, 3.1 Hz), 3.81 (1H, br d, *J* = 14.4 Hz), 3.85-3.95 (2H, m), 4.31 (1H, br d, *J* = 12.2 Hz), 5.10 (1H, br s), 7.58 (2H, br d, *J* = 8.5 Hz), 7.65 (2H, br d, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 40.0, 53.1, 66.9, 68.7, 80.8, 111.2, 118.6, 128.4, 132.2, 145.0, 154.6.

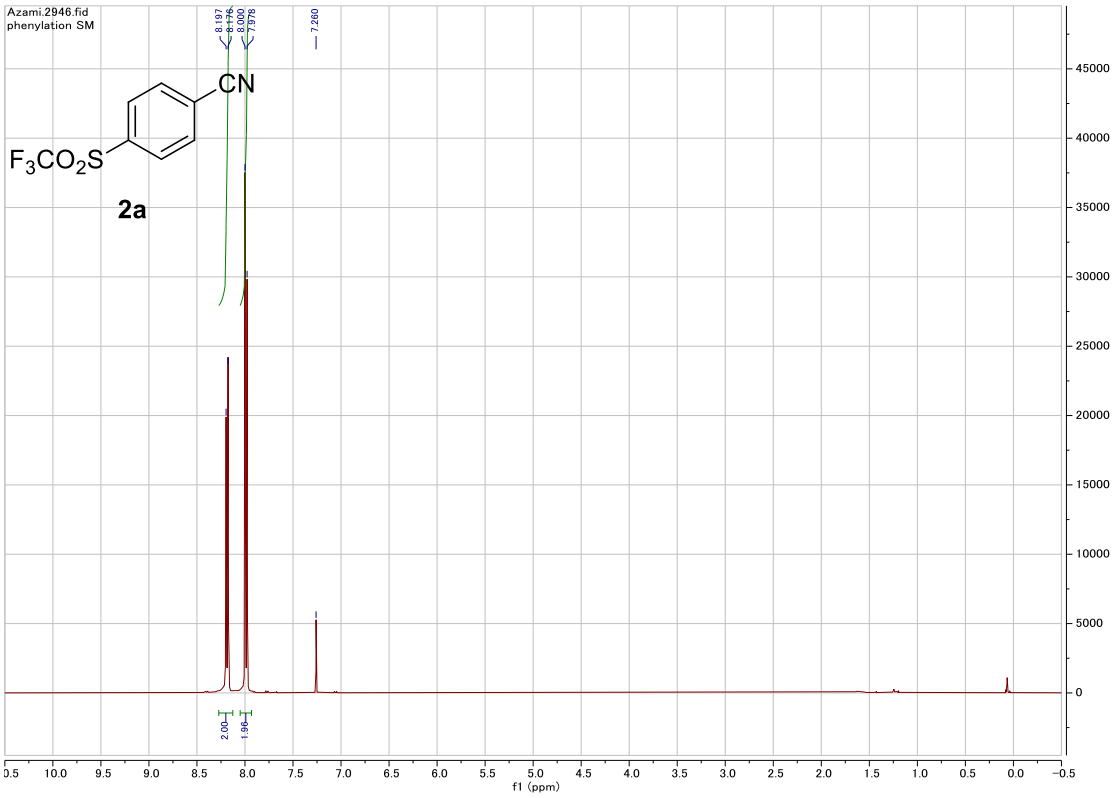


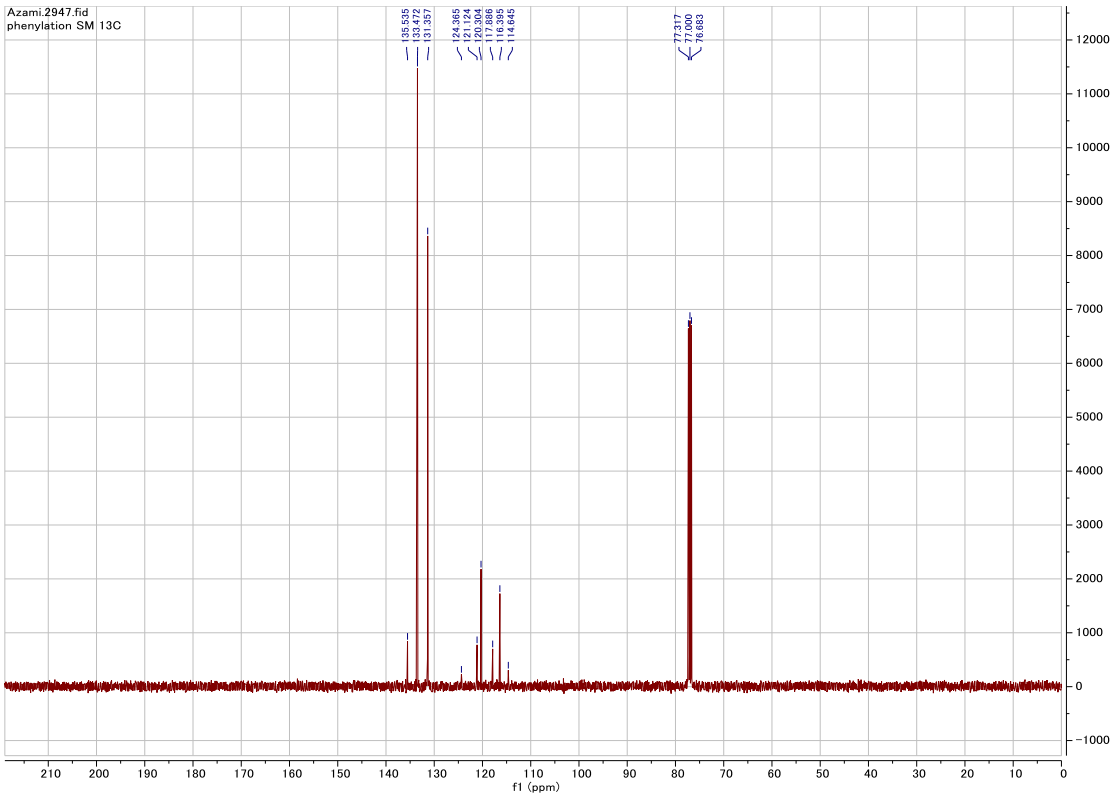
***N*-(*tert*-Butoxycarbonyl)-[*5S*-(4-cyanophenyl)]-*L*-proline methyl ester (3s)**[8]; purified by flash column chromatography (silica gel, hexane/AcOEt = 10/1 to 4/1) and obtained as an inseparable mixture of two rotamers (50 : 50), 18% yield (12.1 mg); [CAS Reg. No. 896731-61-6]; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (4.5/9H, s), 1.40 (4.5/9H, s), 1.69-1.86 (1H, m), 1.94-2.03 (1H, m), 2.15-2.31 (1H, m), 2.44-2.61 (1H, m), 3.772 (1.5/3H, s), 3.776 (1.5/3H, s), 4.53 (0.5/1H, dd, *J* = 9.9, 1.8 Hz), 4.64 (0.5/1H, dd, *J* = 9.9, 1.8 Hz), 5.05 (0.5/1H, dd, *J* = 8.8, 2.2 Hz), 5.20 (0.5/1H, dd, *J* = 8.8, 2.2 Hz), 7.28 (1/2H, br d, *J* = 6.4 Hz), 7.29 (1/2H, br d, *J* = 6.4 Hz), 7.61 (1/2H, br d, *J* = 6.4 Hz), 7.62 (1/2H, br d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 28.02, 28.09, 28.2, 32.3, 33.3, 52.1, 52.3, 59.8, 60.2, 61.0, 61.3, 80.6, 80.8, 110.7, 110.8, 118.7, 118.8, 126.1 (overlapped), 132.2, 132.4, 149.0, 150.0, 153.5, 153.9, 172.8, 173.1.

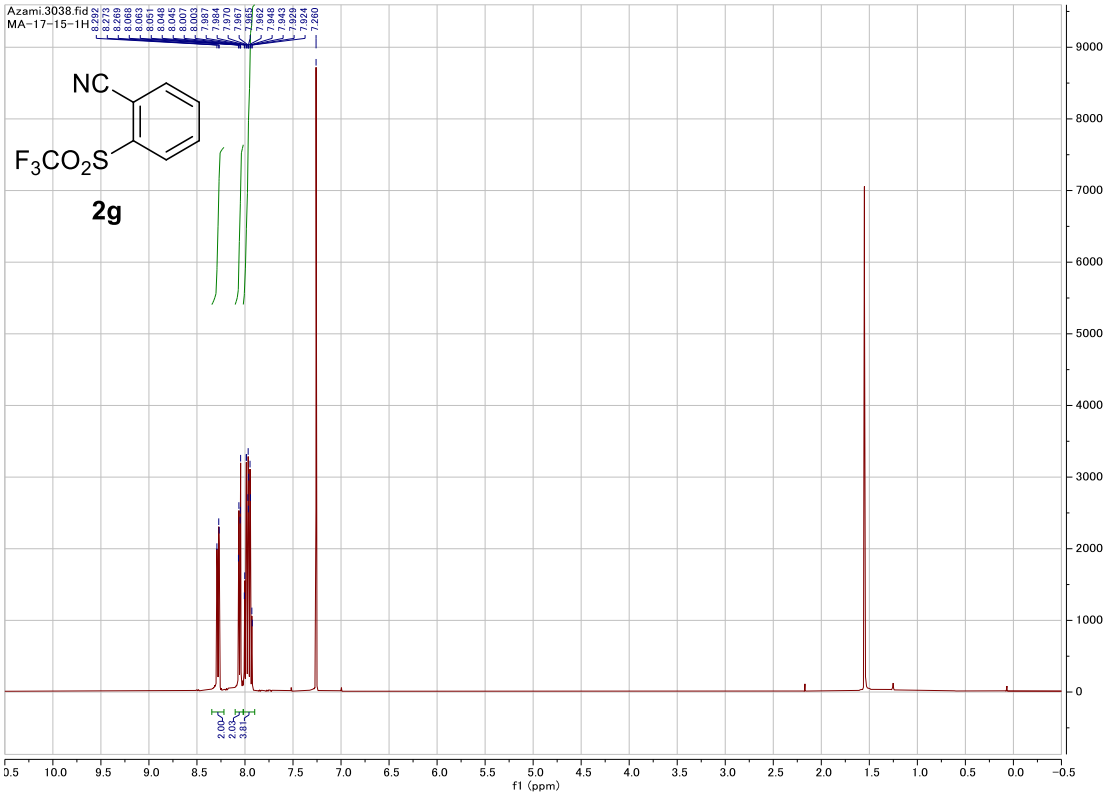


***N*-(Benzyloxycarbonyl)-2-(4-cyanophenyl)pyrrolidine (3t)**[7]; purified by flash column chromatography (silica gel, hexane/AcOEt = 10/1 to 2/1) and obtained as an inseparable mixture of two rotamers, 23% yield (14.1 mg); [CAS Reg. No. 1588517-10-5]; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77-1.98 (3H, m), 2.30-2.45 (1H, m), 3.59-3.78 (2H, m), 4.82-4.97 (1H, m), 4.97-5.22 (2H, m), 6.90 (1H, br d, *J* = 5.8 Hz), 7.13-7.47 (6H, m), 7.49-7.66 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (detectable signals) 23.0, 23.7, 34.6, 35.7, 47.2, 47.7, 60.9, 61.2, 66.8, 67.0, 110.6, 118.1, 126.2, 127.5, 127.9, 128.2, 128.41, 128.47, 132.3, 136.2, 136.6, 149.0, 149.8, 154.7, 154.9.

NMR Charts


Azami.2946.fid
phenylation SM
8.197
8.178
8.000
7.978
7.260
CN
F_3CO_2S
2a
2.00
1.96
f1 (ppm)


Azami.2947.fid
phenylation SM 13C
135.535
133.472
131.357
124.365
121.124
120.284
117.886
116.395
114.645
77.317
77.000
76.683
f1 (ppm)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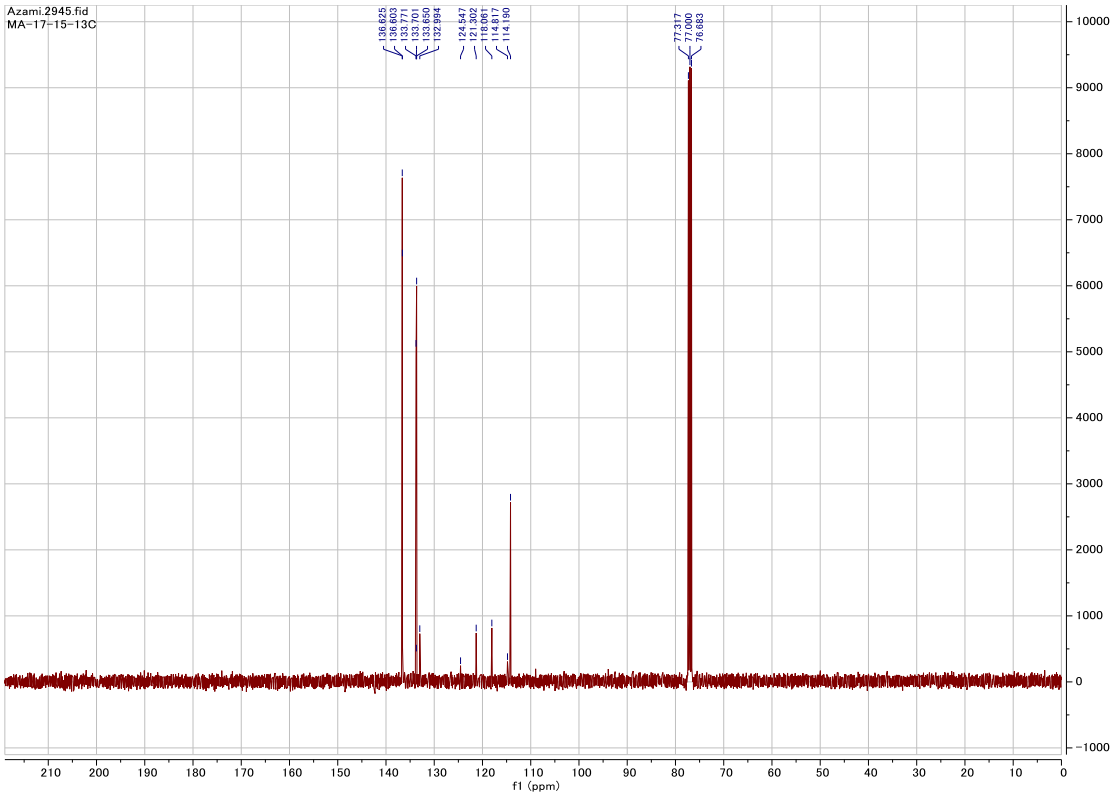
F3CO2S
2g
f1 (ppm)


Azami.2945.fid
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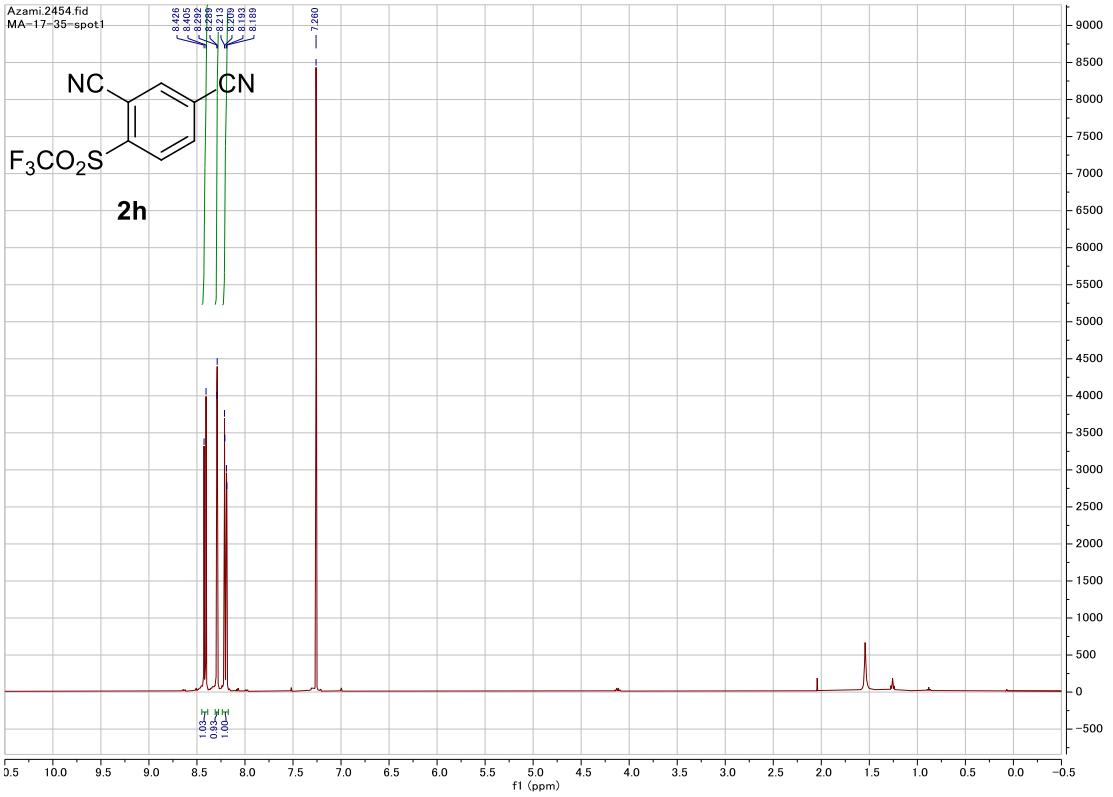
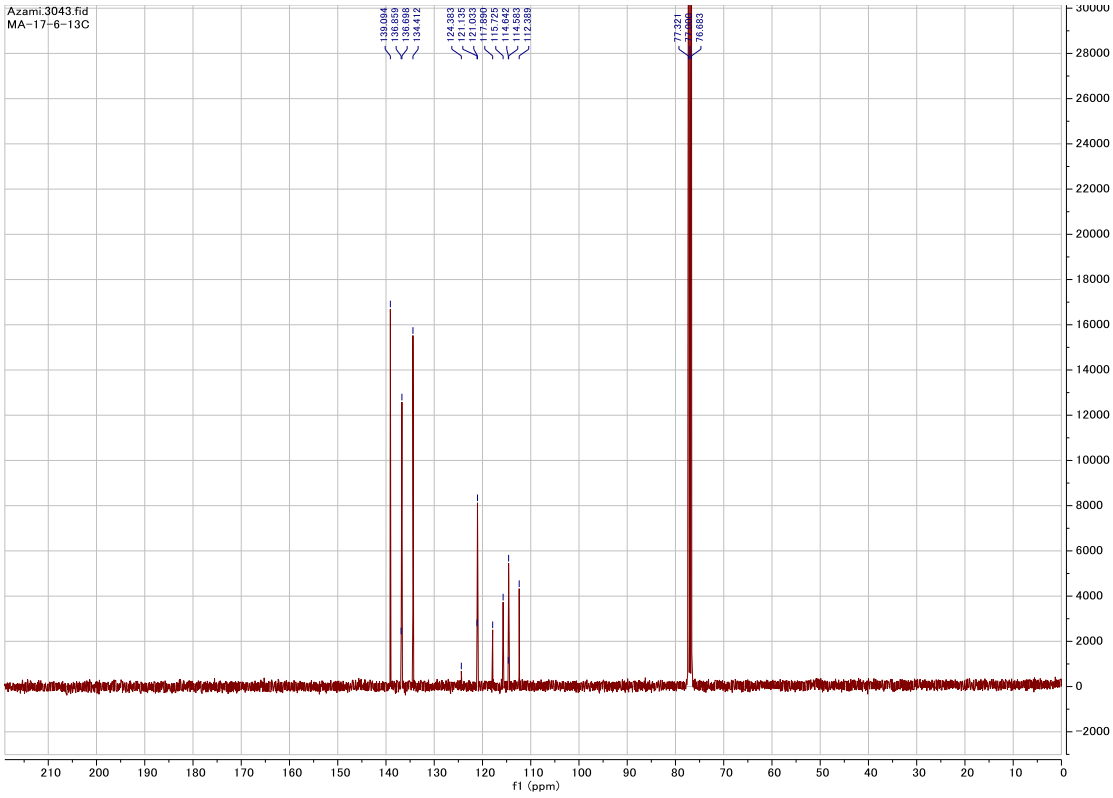
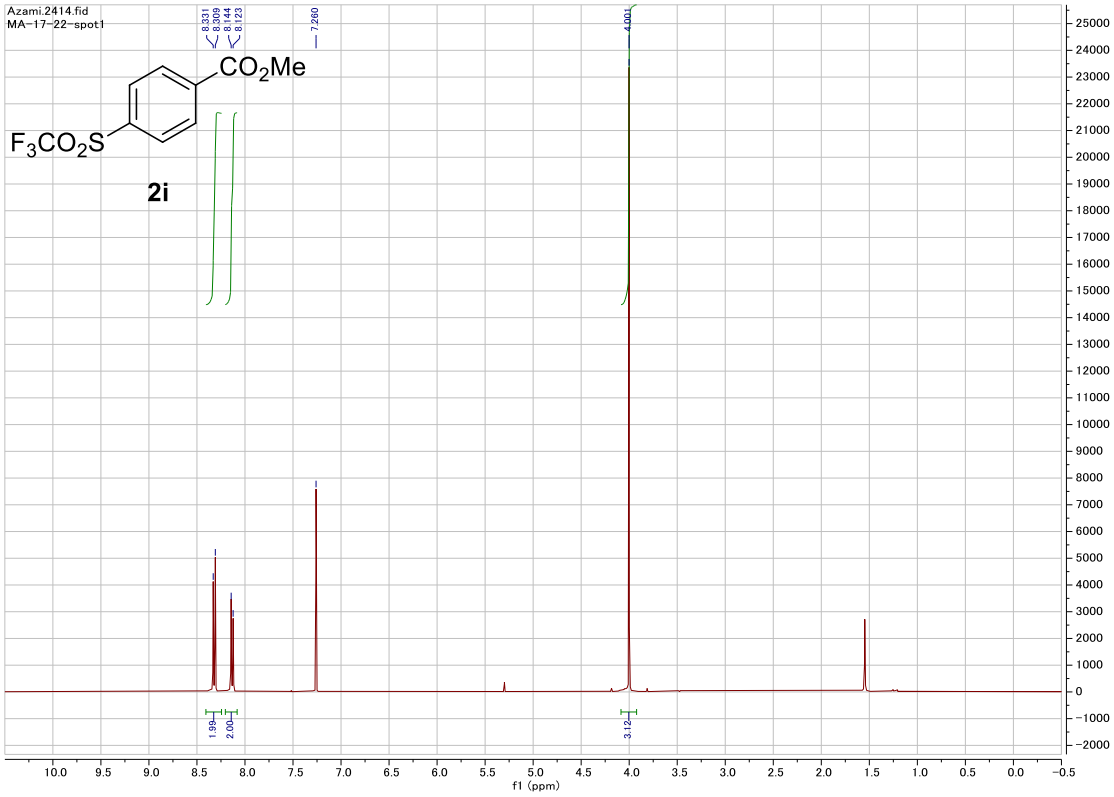
f1 (ppm)


Azami.2454.fid
MA-17-35-spot1
8.426
8.405
8.292
8.289
8.213
8.209
8.193
8.189
7.260
NC
CN
F3CO2S
2h
1.03
0.93
1.00
f1 (ppm)


Azami.3043.fid
MA-17-6-13C
139.094
136.659
136.488
134.412
124.983
121.135
121.033
117.890
115.725
114.464
114.253
114.583
112.389
77.321
77.000
76.683
f1 (ppm)


Azami.2414.fid
MA-17-22-spot1
8.331
8.309
8.144
8.123
7.280
4.001
CO_2Me
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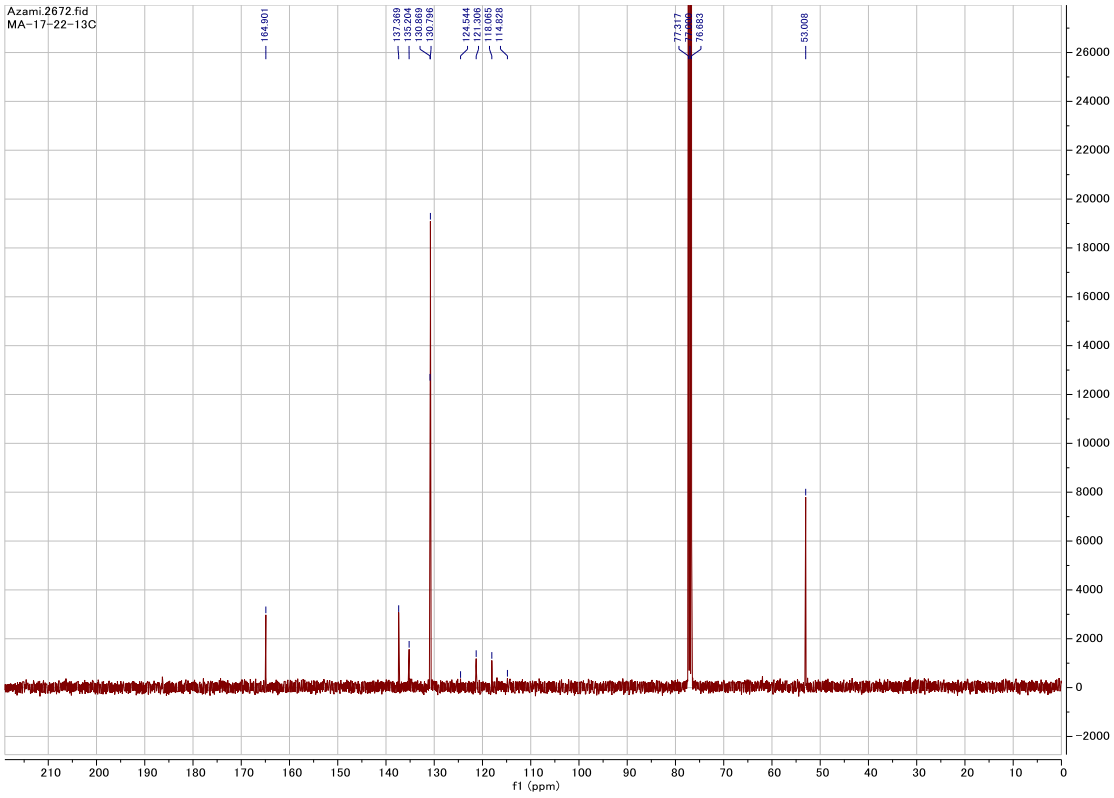
2i
1.99
2.00
3.12
f1 (ppm)


Azami.2672.fid
MA-17-22-13C
164.901
137.369
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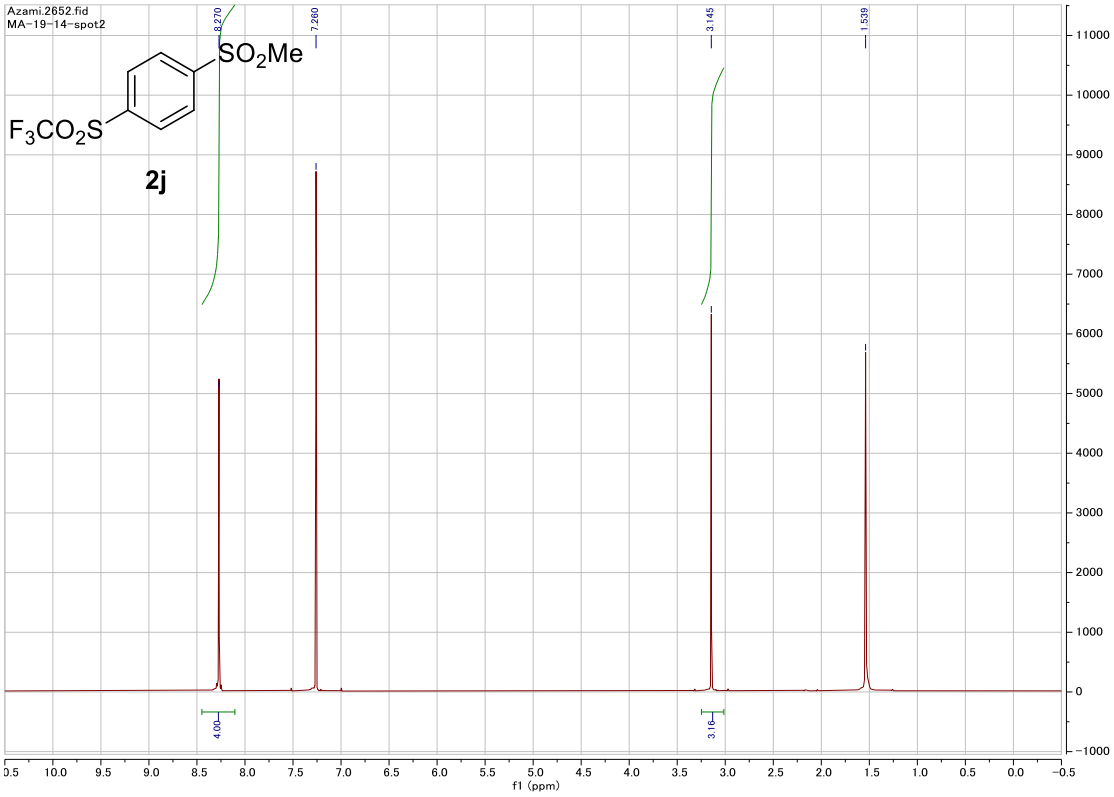
130.869
130.796
124.544
121.966
118.065
114.828
77.317
76.683
53.008
f1 (ppm)


Azami.2652.fid
MA-19-14-spot2
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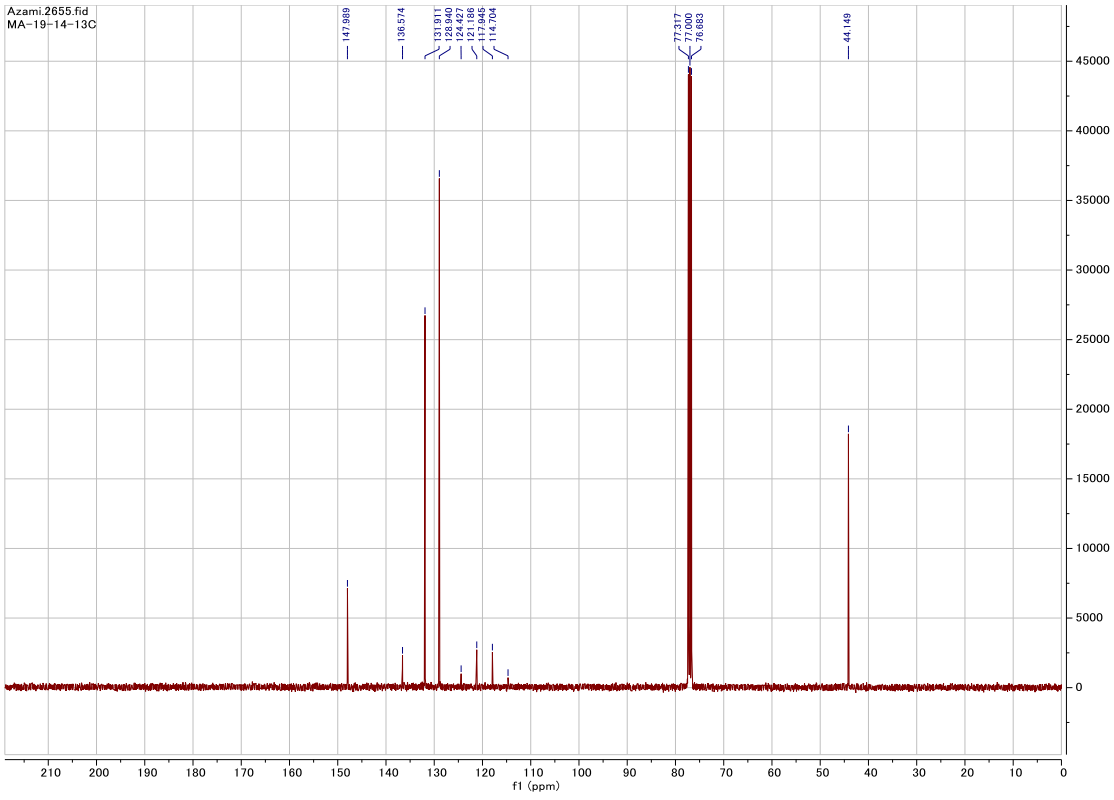
7.260
3.145
1.539
SO_2Me
F_3CO_2S
2j
4.00
3.16
f1 (ppm)


Azami.2655.fid
MA-19-14-13C
147.989
136.574
131.511
130.940
124.427
121.186
117.945
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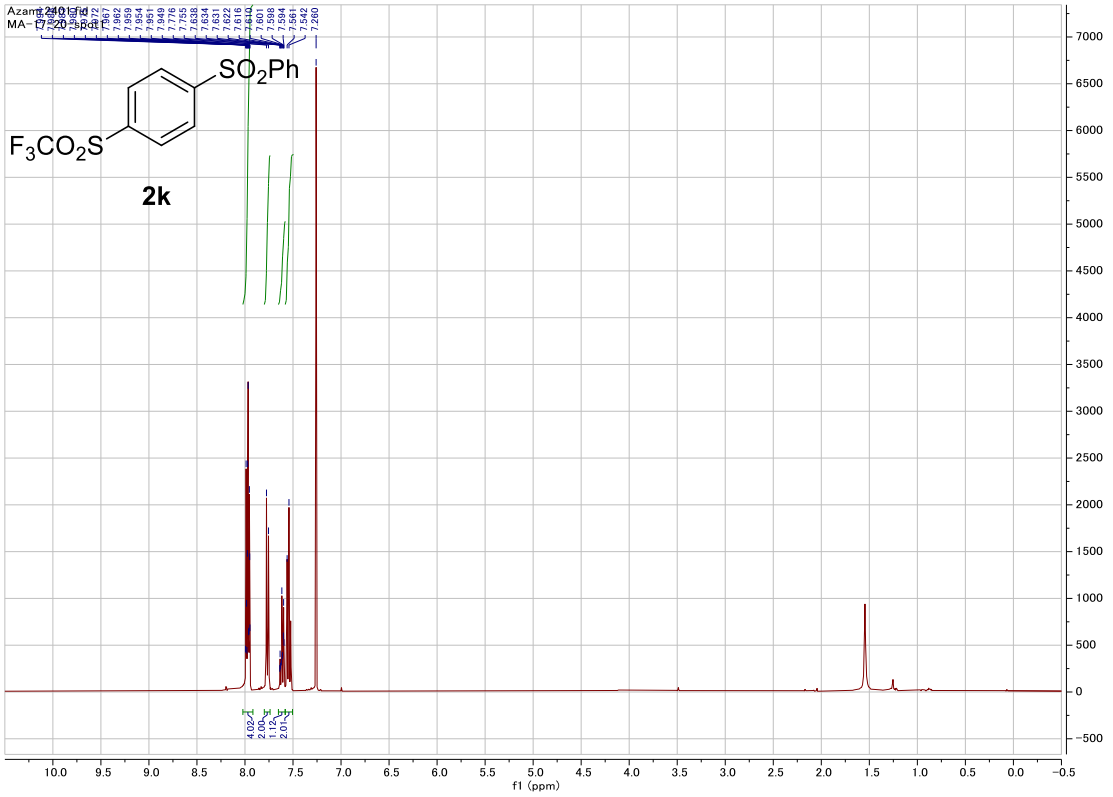
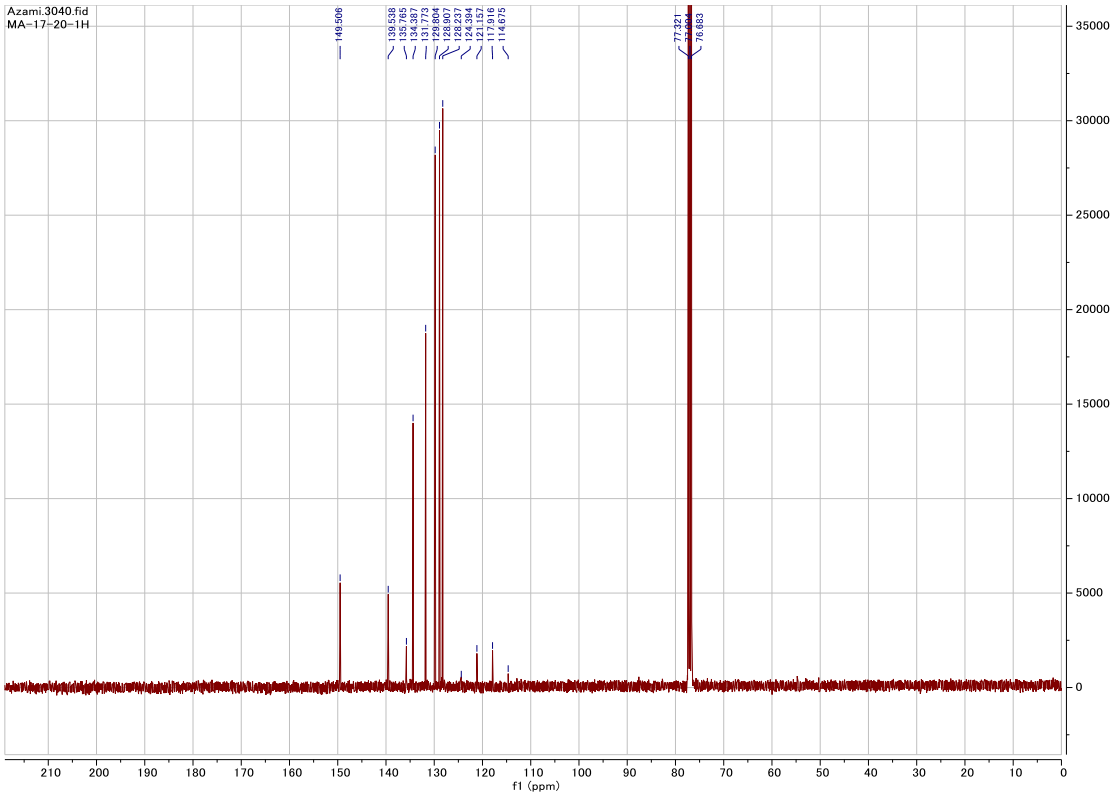
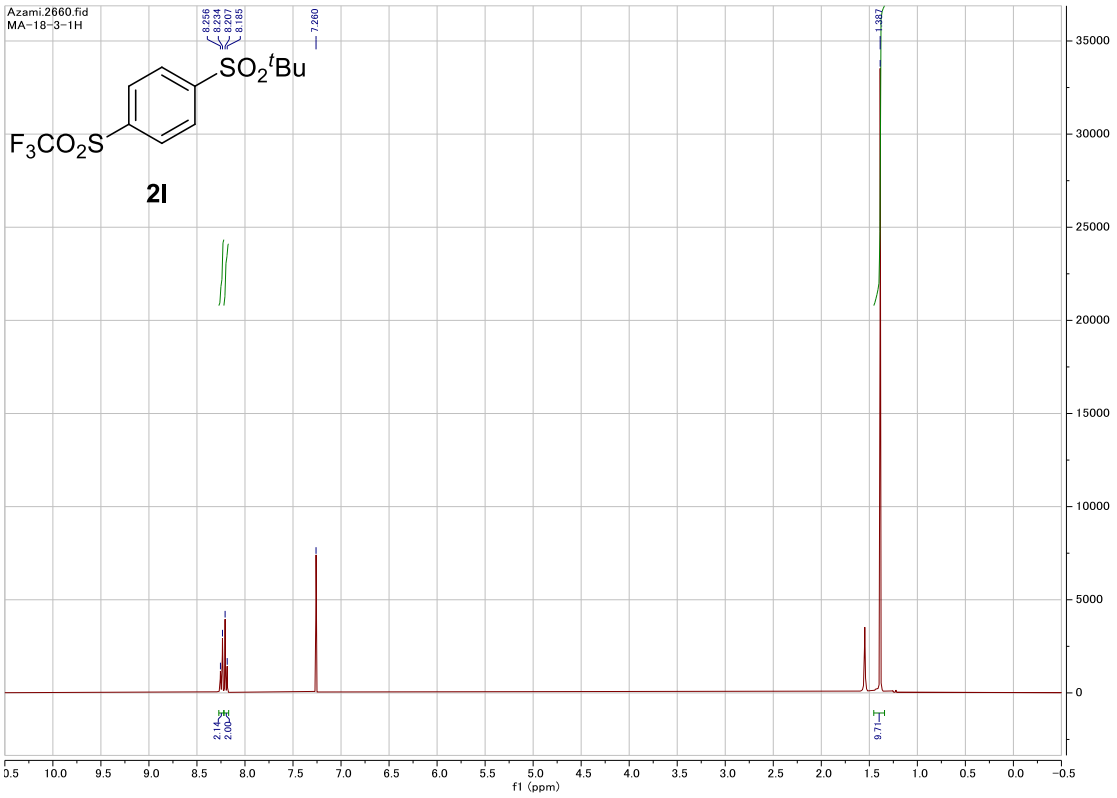
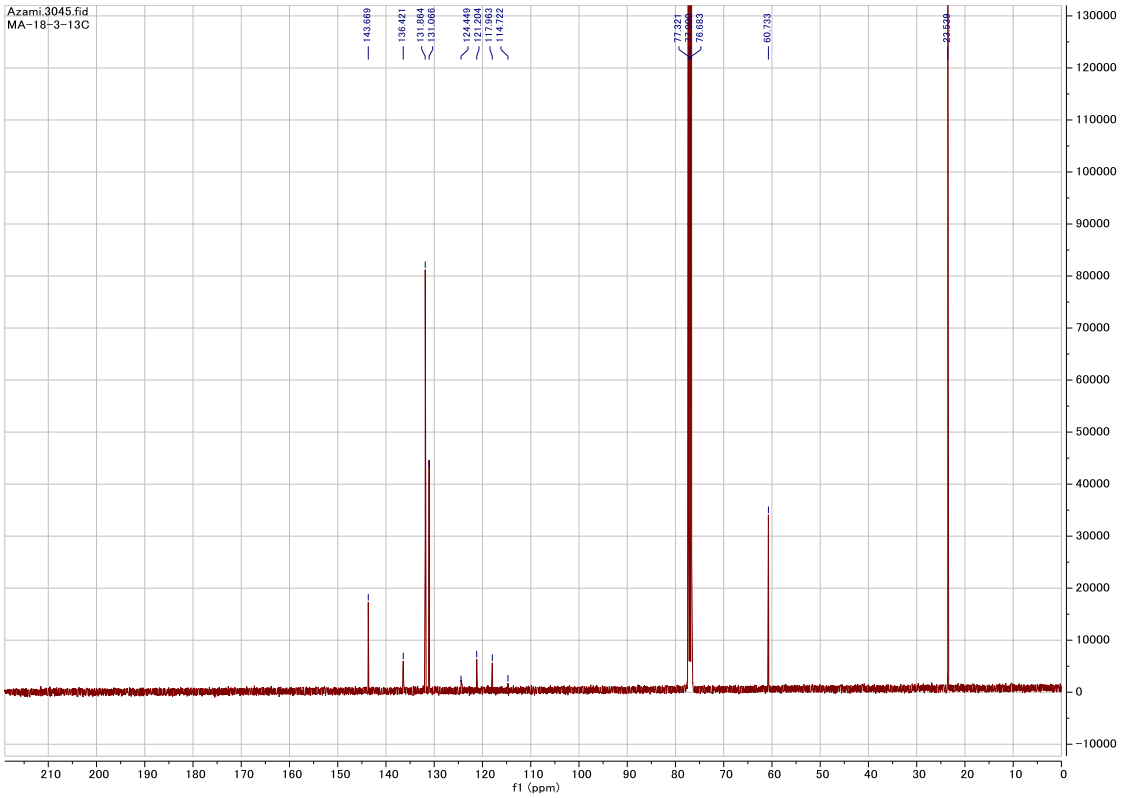
77.317
77.000
76.683
44.149
f1 (ppm)


Azami.2401.fid
MA-17-20-1H
SO2Ph
F3CO2S
2k
f1 (ppm)


Azami.3040.fid
MA-17-20-1H
149.506
139.538
135.765
134.387
131.773
129.064
128.907
128.237
124.394
121.152
117.146
114.675
77.321
77.004
76.683
f1 (ppm)


Azami.2660.fid
MA-18-3-1H
8.256
8.234
8.207
8.185
7.260
1.387
$SO_2{}^tBu$
F_3CO_2S
2l
2.14
2.00
9.71
f1 (ppm)


Azami.3045.fid
MA-18-3-13C
143.669
136.421
131.864
131.066
124.449
121.244
117.963
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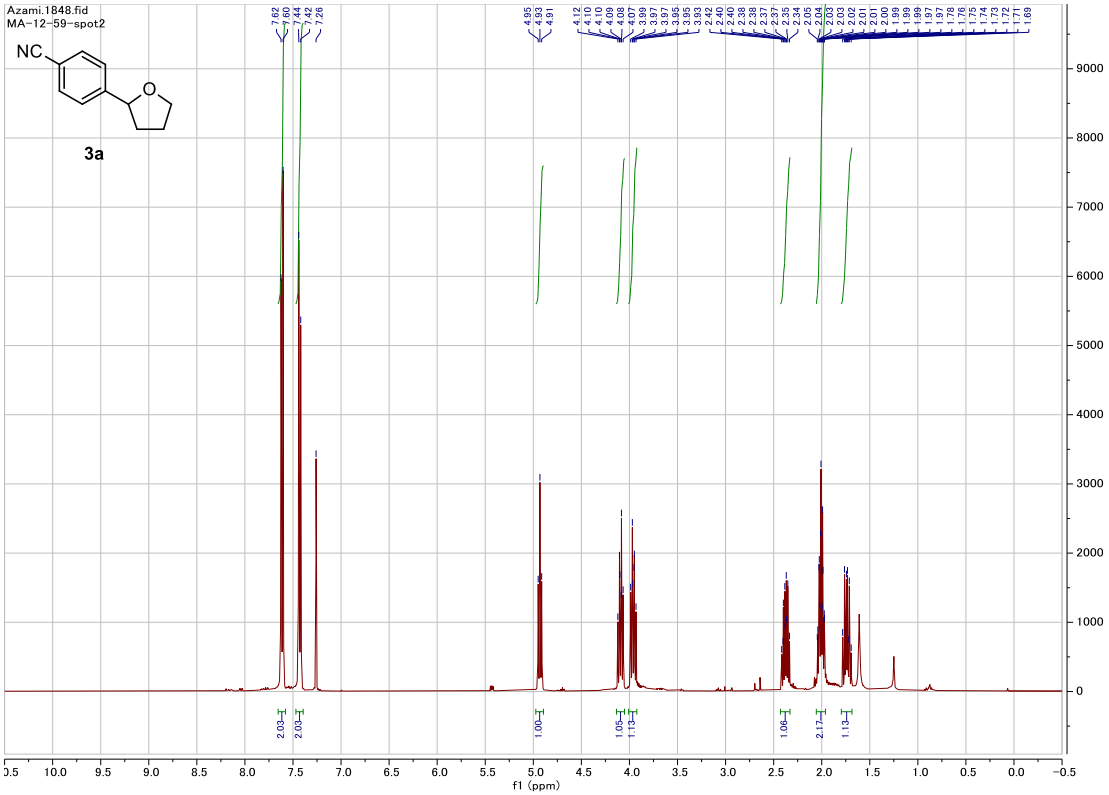
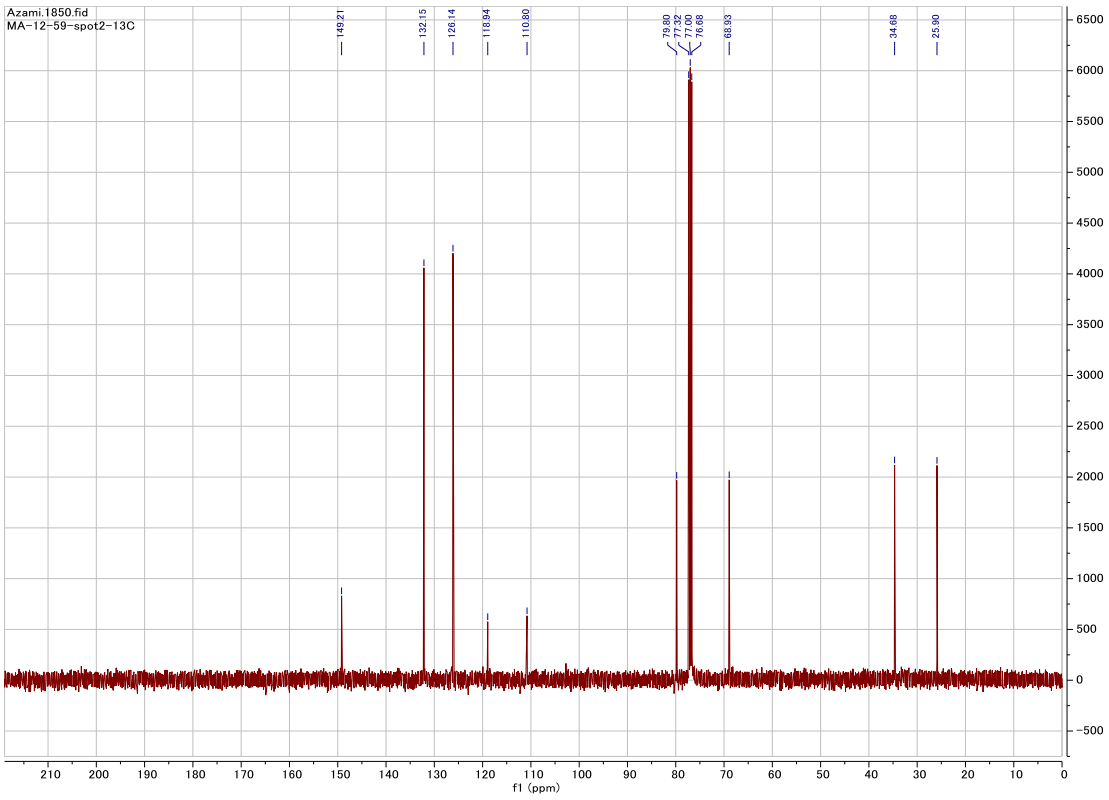
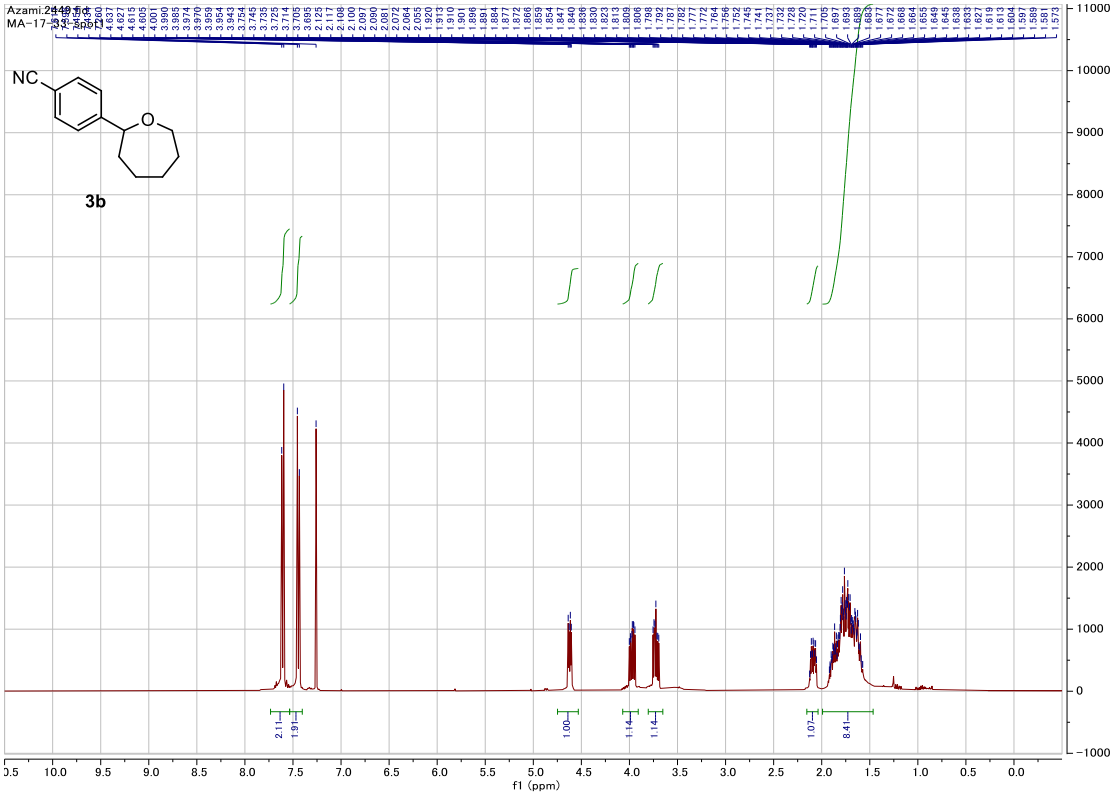
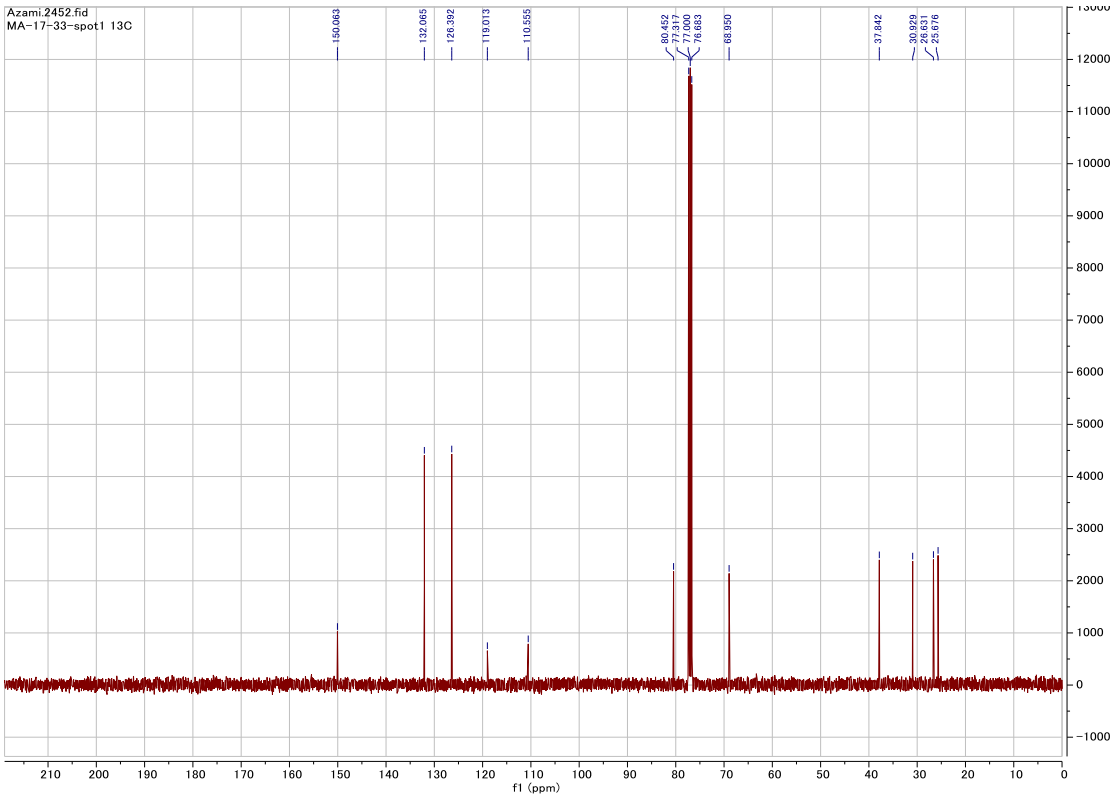
77.000
76.683
60.733
23.539
f1 (ppm)


Azami.1848.fid
MA-12-59-spot2
NC
O
3a
f1 (ppm)


Azami.1850.fid
MA-12-59-spot2-13C
149.21
132.15
126.14
118.94
110.80
79.80
77.32
77.00
76.68
68.93
34.68
25.90
f1 (ppm)


NC
O
3b
f1 (ppm)


Azami.2452.fid
MA-17-33-spot1 13C
150.063
132.065
126.392
119.013
110.555
80.452
77.317
77.000
76.683
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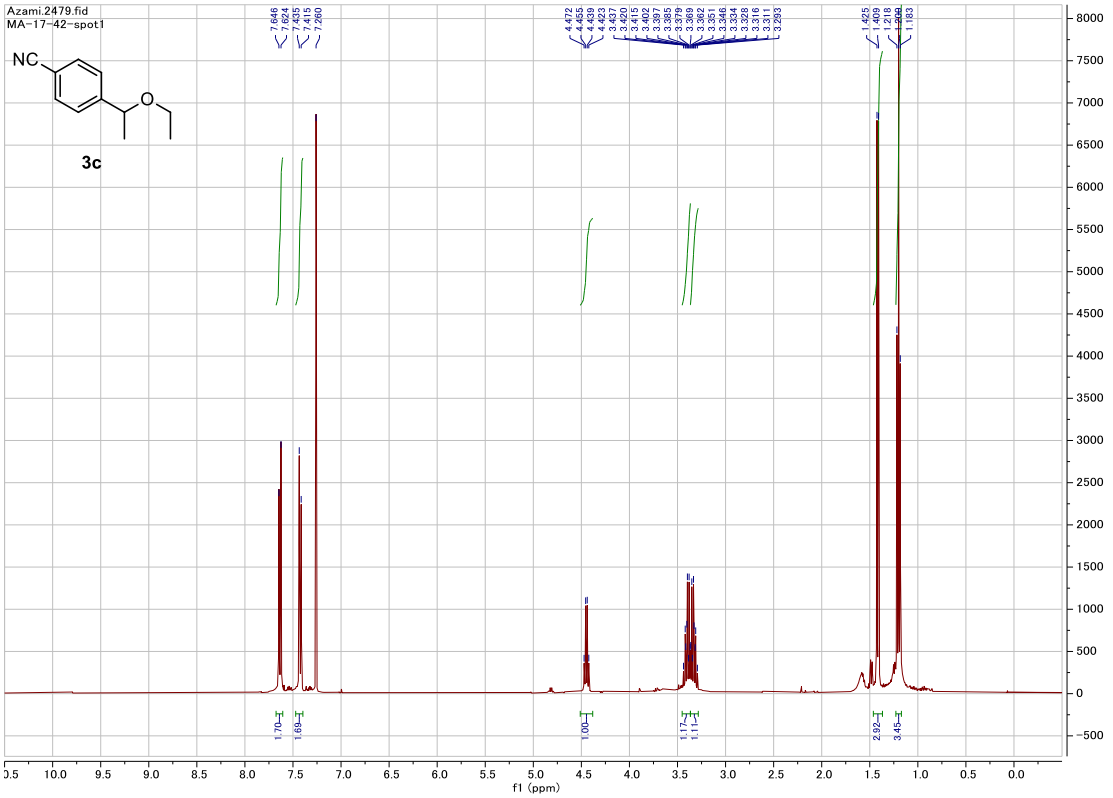
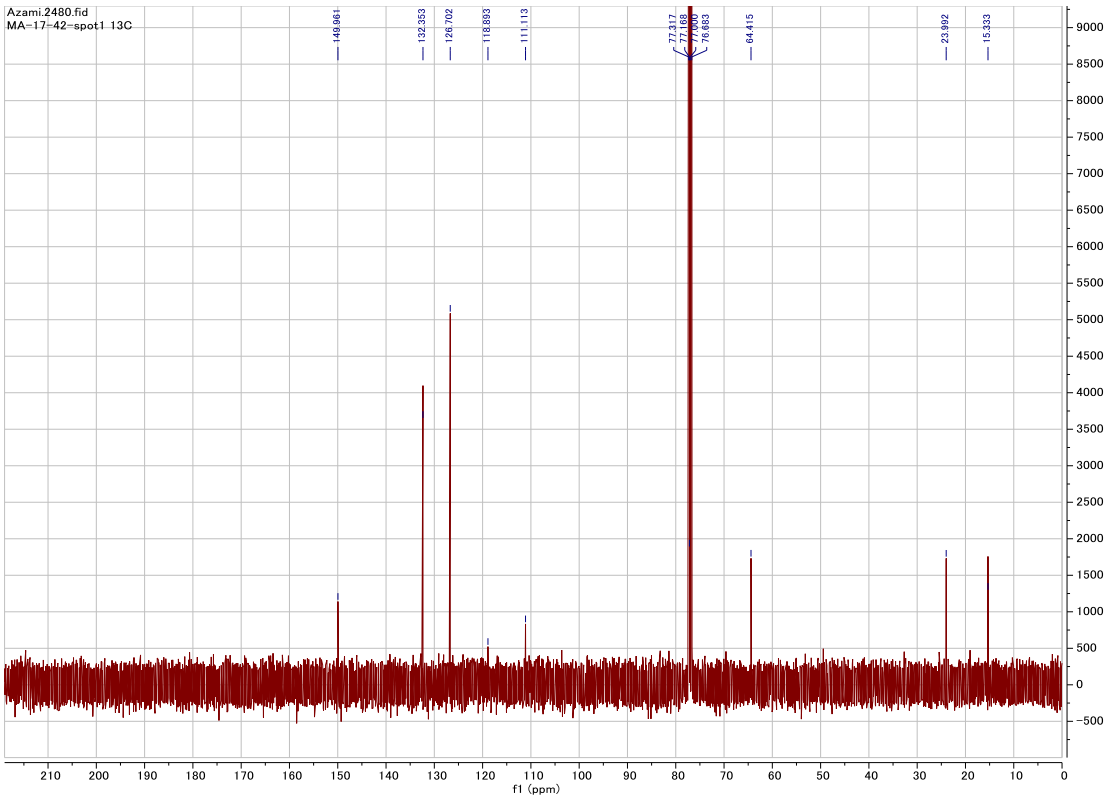
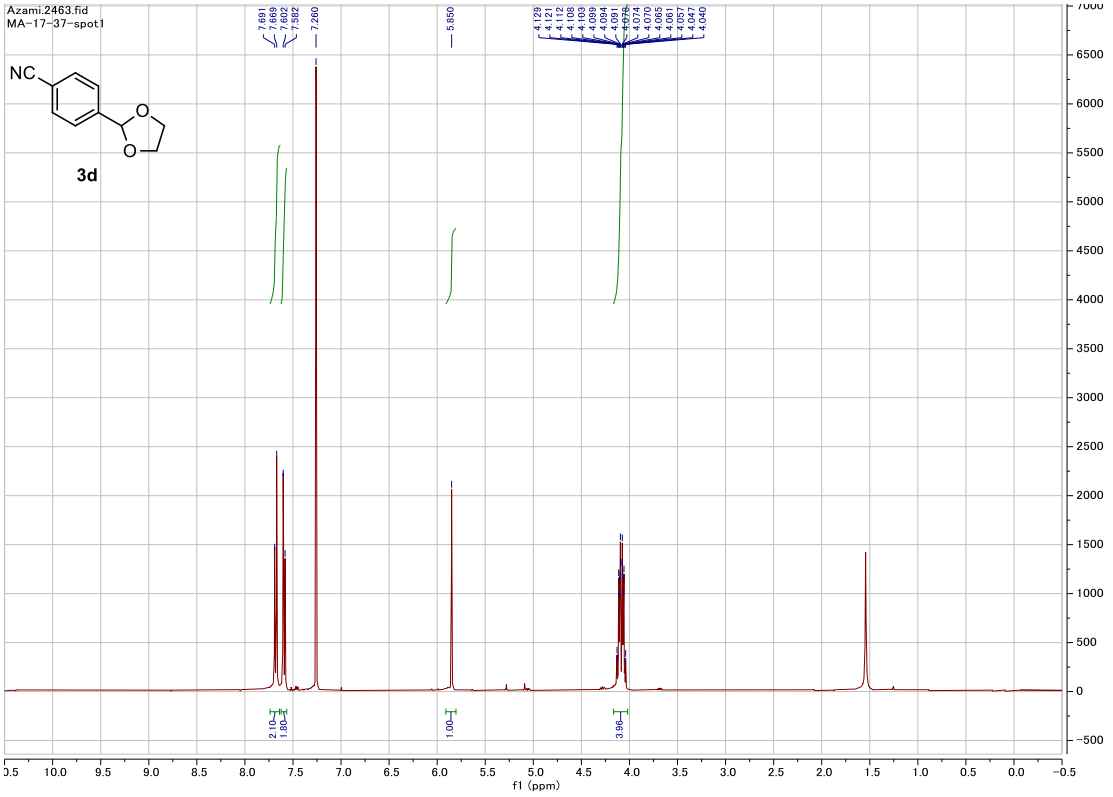
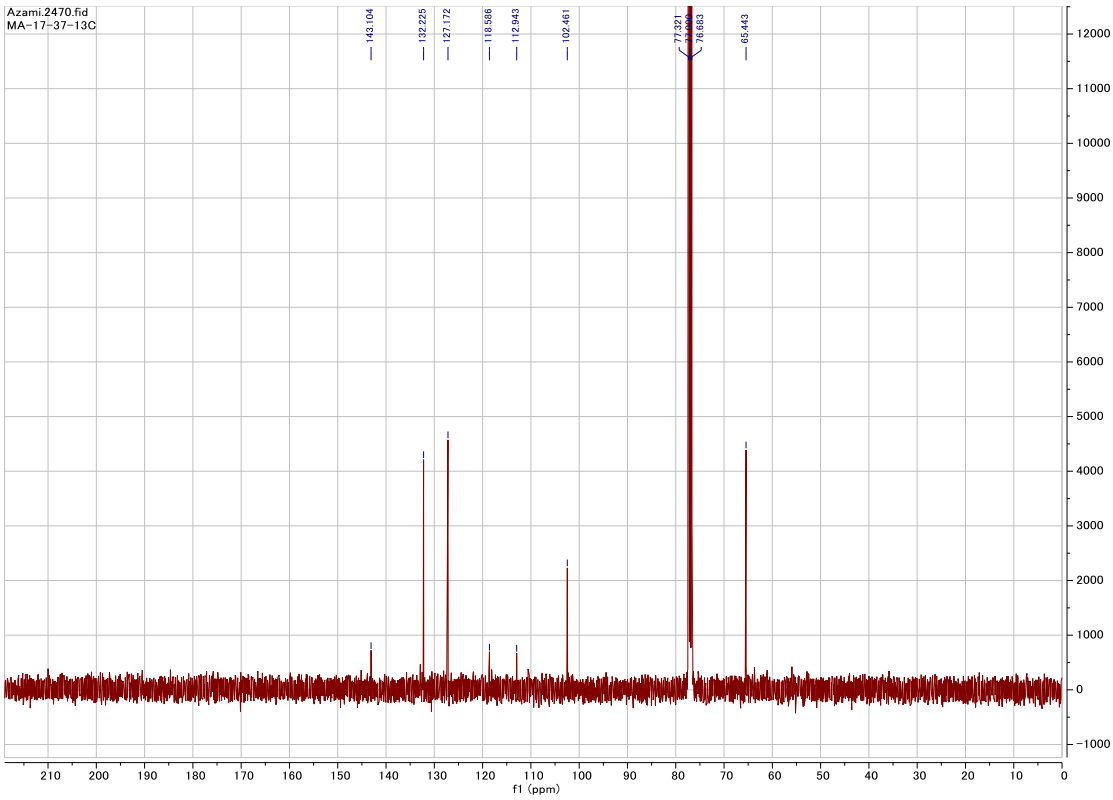
37.842
30.929
30.631
25.676
f1 (ppm)


Azami.2479.fid
MA-17-42-spot1
NC
O
3c
f1 (ppm)


Azami.2480.fid
MA-17-42-spot1 13C
f1 (ppm)


Azami.2463.fid
MA-17-37-spot1
NC
O
O
3d
7.691
7.669
7.602
7.582
7.260
5.850
4.129
4.121
4.112
4.108
4.103
4.099
4.094
4.091
4.078
4.074
4.070
4.065
4.061
4.057
4.047
4.040
2.10
1.80
1.00
3.96
f1 (ppm)


Azami.2470.fid
MA-17-37-13C
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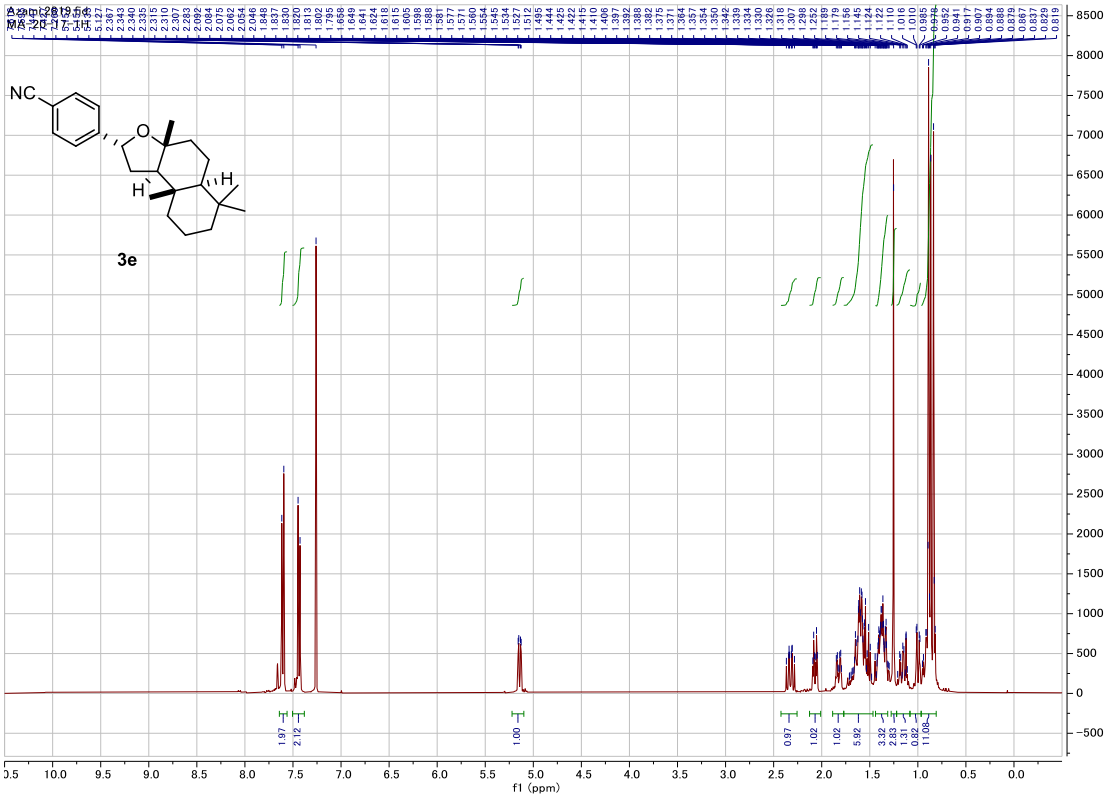
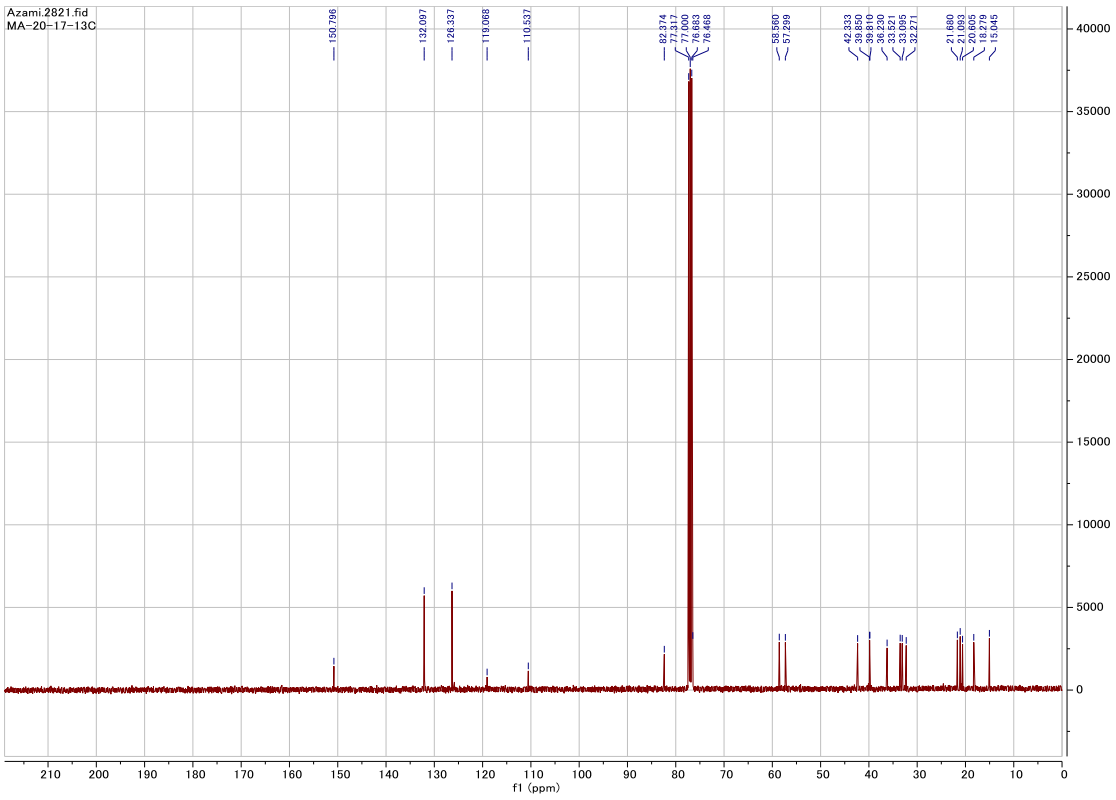
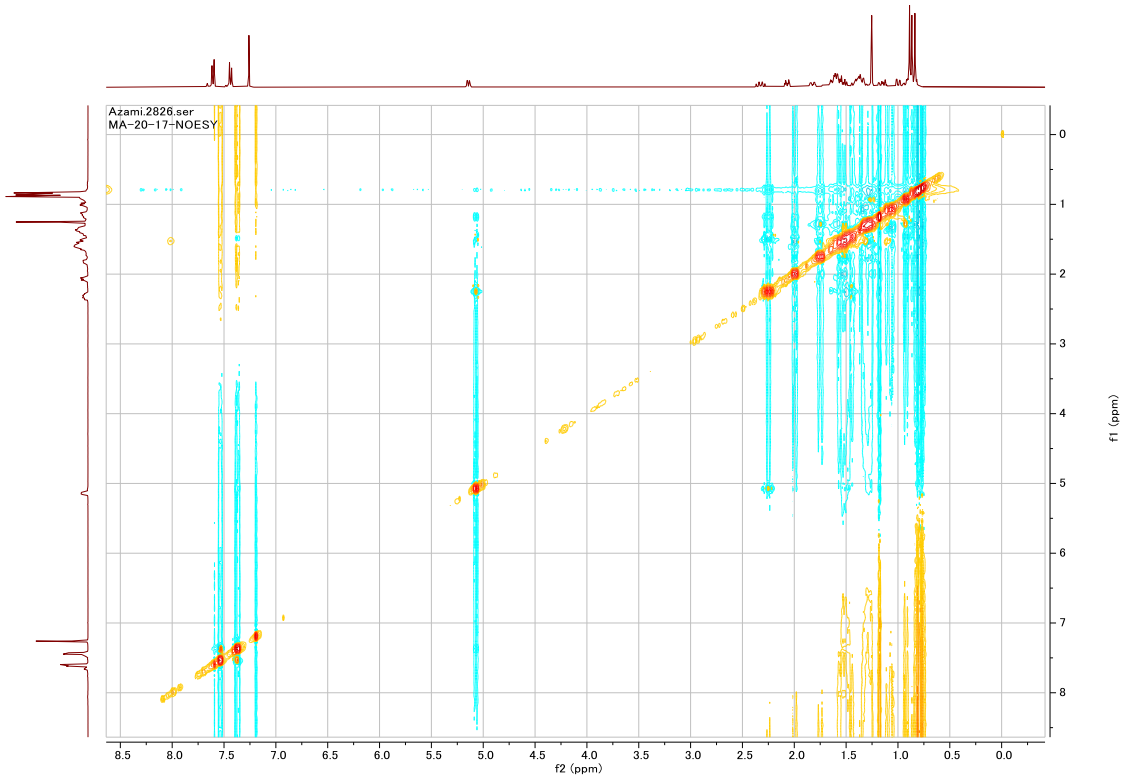
132.225
127.172
118.586
112.943
102.461
77.321
77.000
76.683
65.443
f1 (ppm)


NC
O
H
H
3e
f1 (ppm)


Azami.2821.fid
MA-20-17-13C
f1 (ppm)


Azami.2826.ser
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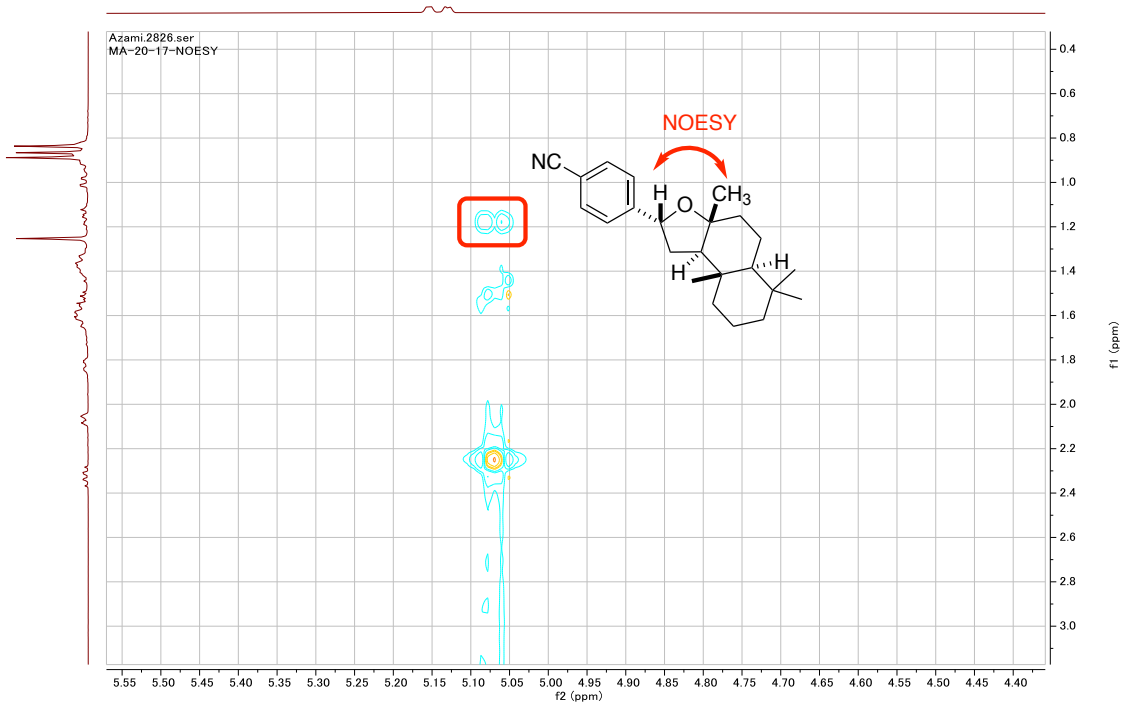
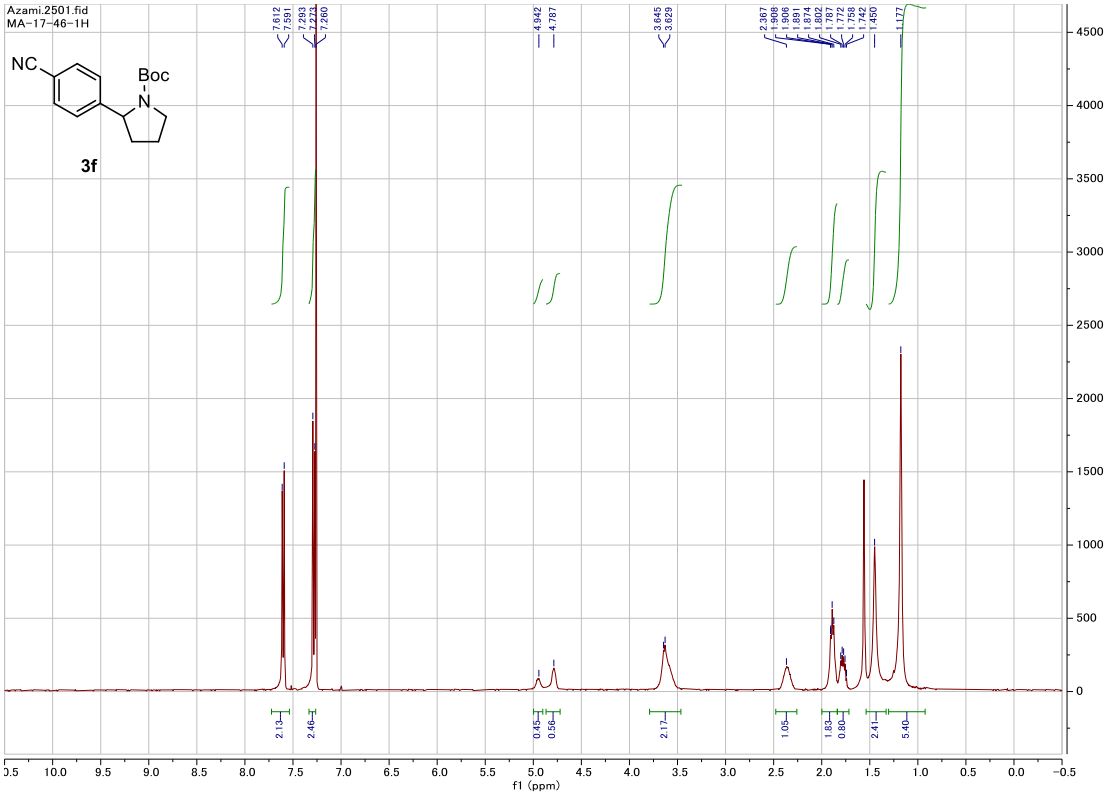
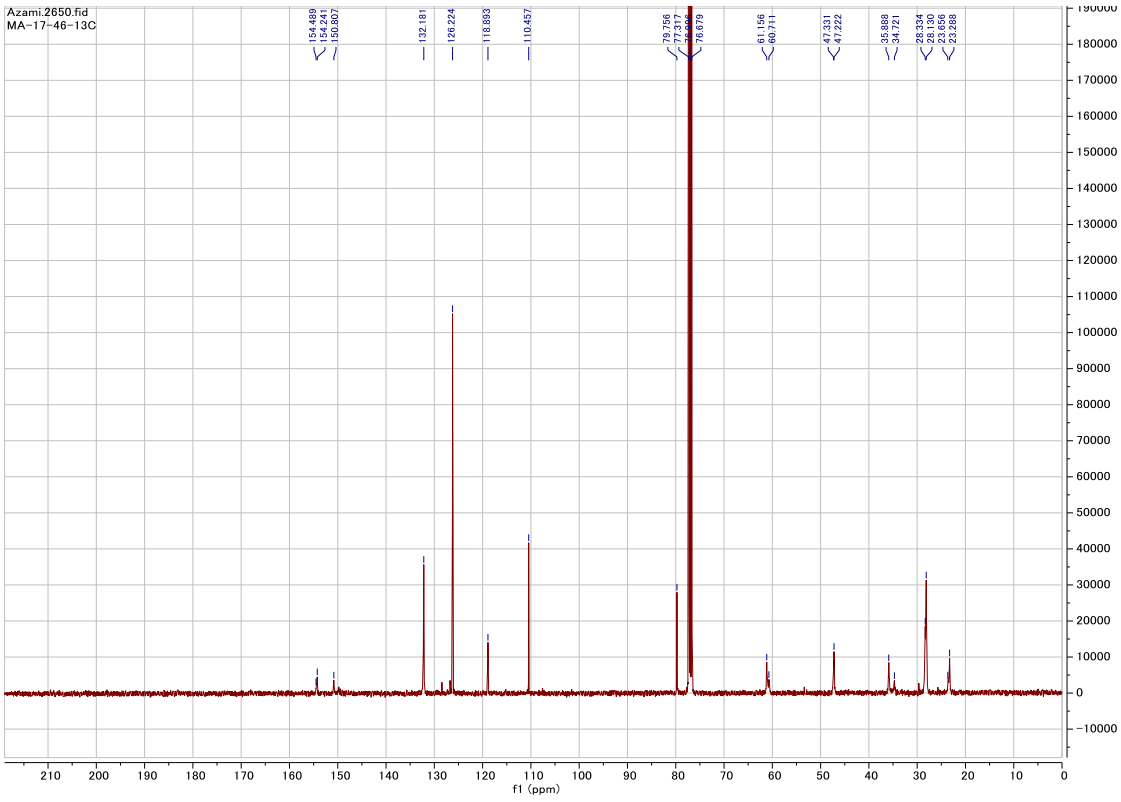
f2 (ppm)
f1 (ppm)


Azami.2826.ser
MA-20-17-NOESY
NOESY
NC
H
O
CH3
H
H
f2 (ppm)
f1 (ppm)


Azami.2501.fid
MA-17-46-1H
NC
Boc
N
3f
7.612
7.591
7.293
7.272
7.260
4.942
4.787
3.645
3.629
2.367
1.908
1.896
1.891
1.874
1.802
1.787
1.772
1.758
1.742
1.450
1.177
2.13
2.46
0.45
0.56
2.17
1.05
1.83
0.80
2.41
5.40
f1 (ppm)


Azami.2650.fid
MA-17-46-13C
154.489
154.041
150.807
132.181
126.224
118.893
110.457
79.756
77.317
77.000
76.679
61.156
60.711
47.331
47.222
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34.721
28.334
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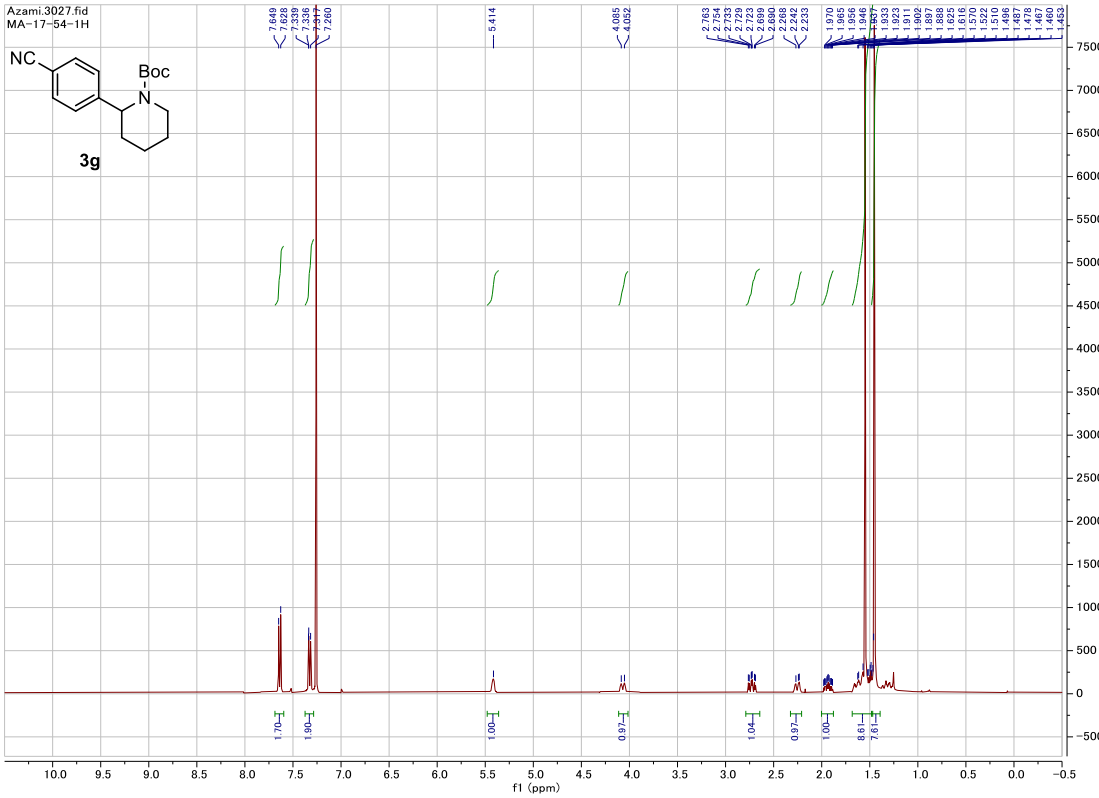
23.856
23.268
f1 (ppm)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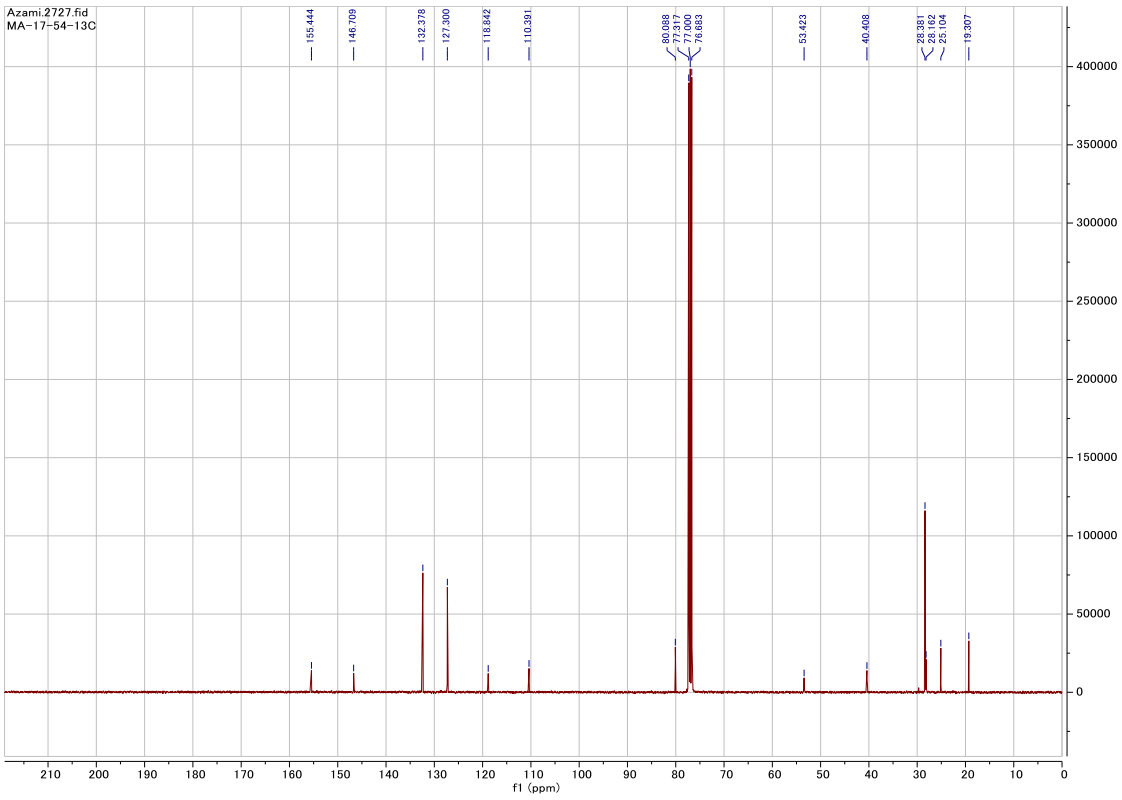
MA-17-54-1H
NC
Boc
N
3g
f1 (ppm)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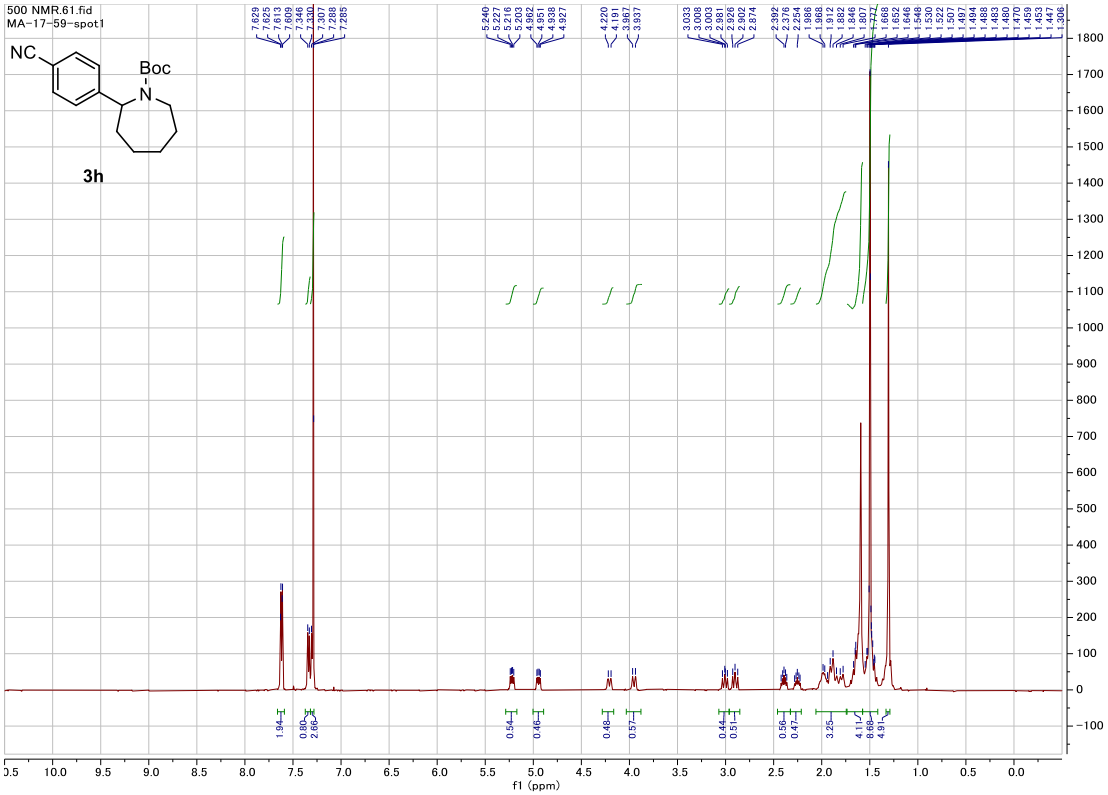
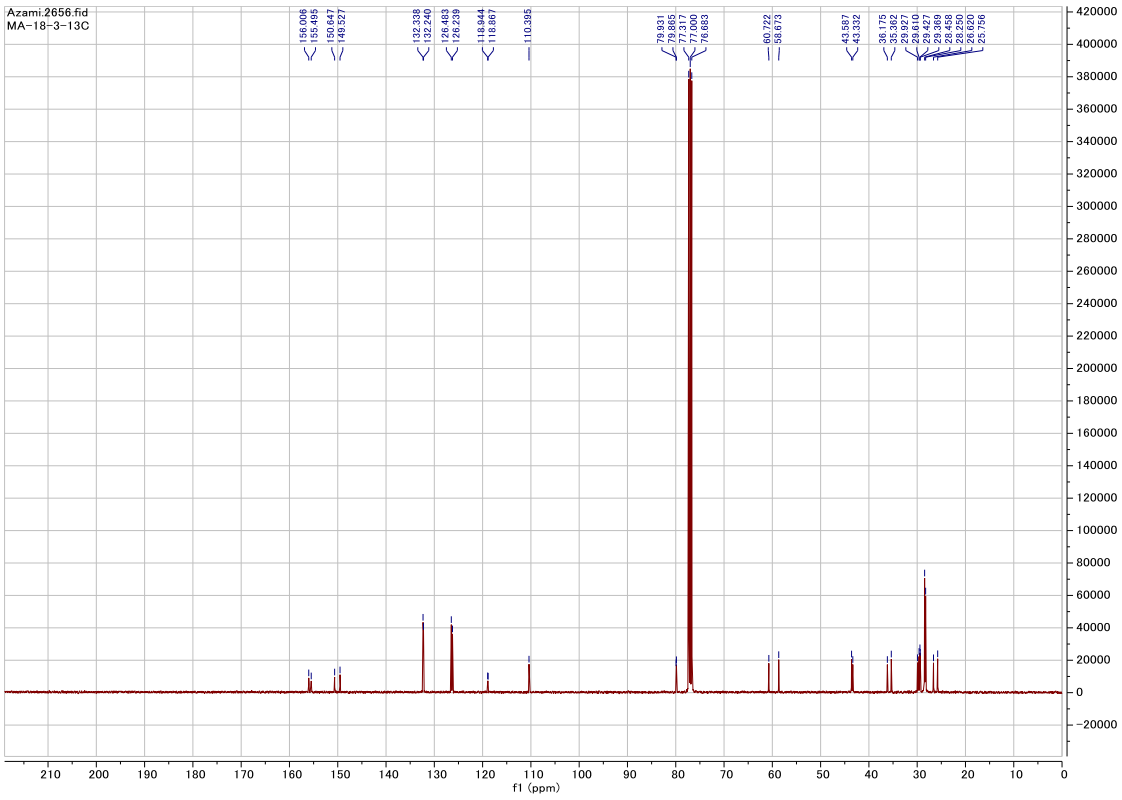
f1 (ppm)


500 NMR.61.fid
MA-17-59-spot1
NC
Boc
N
3h
f1 (ppm)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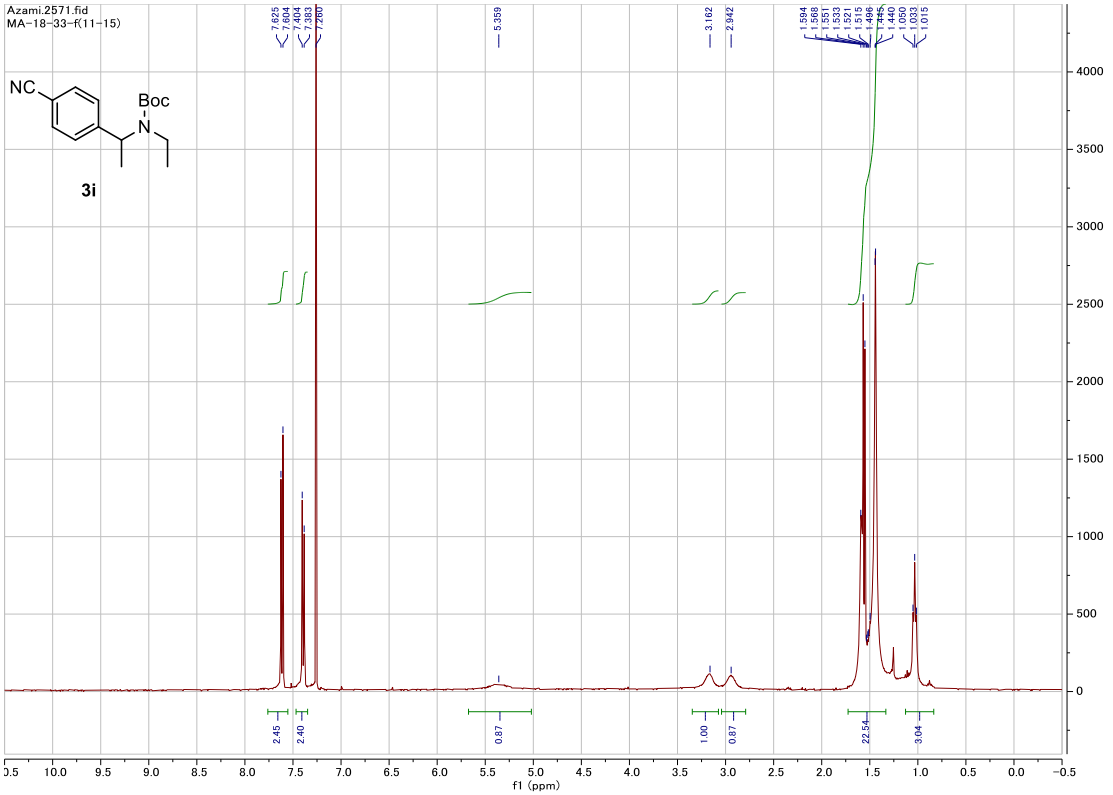
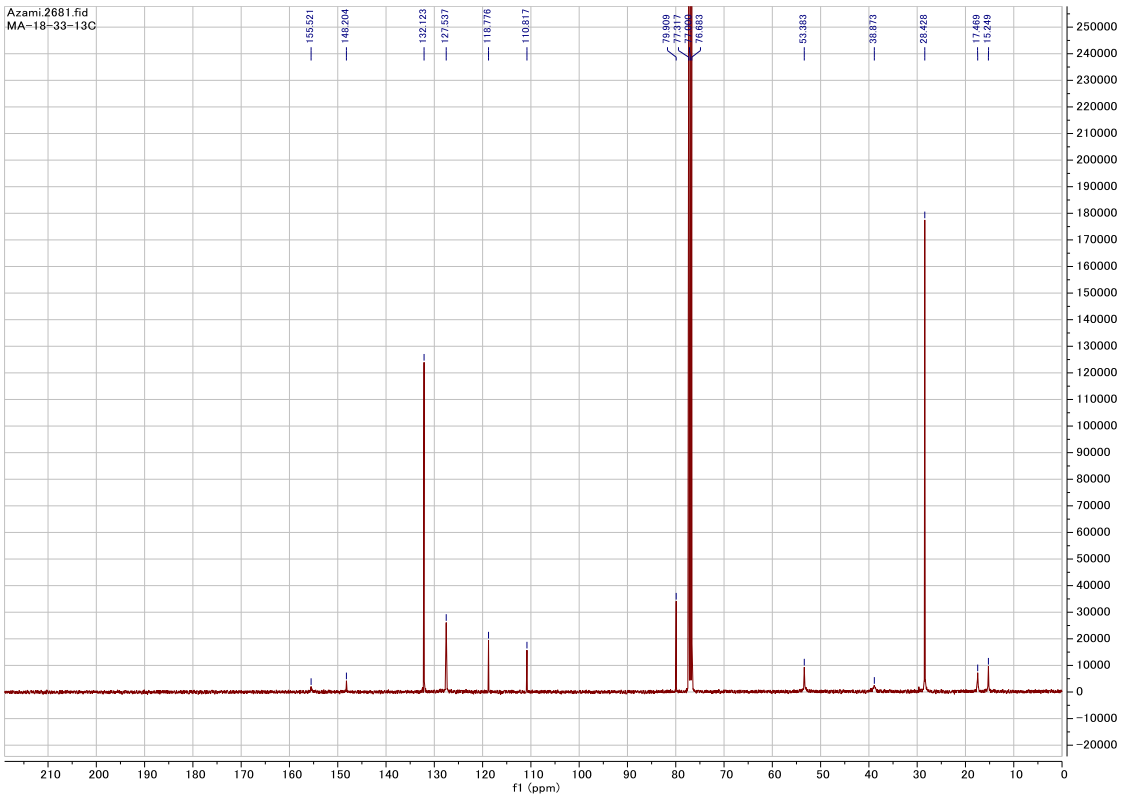
f1 (ppm)


Azami.2571.fid
MA-18-33-f(11-15)
NC
Boc
N
3i
7.625
7.604
7.484
7.463
7.260
5.359
3.162
2.942
1.594
1.568
1.551
1.533
1.521
1.515
1.486
1.445
1.440
1.050
1.033
1.015
2.45
2.40
0.87
1.00
0.87
22.54
3.04
f1 (ppm)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155.521
148.204
132.123
127.537
118.776
110.817
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77.317
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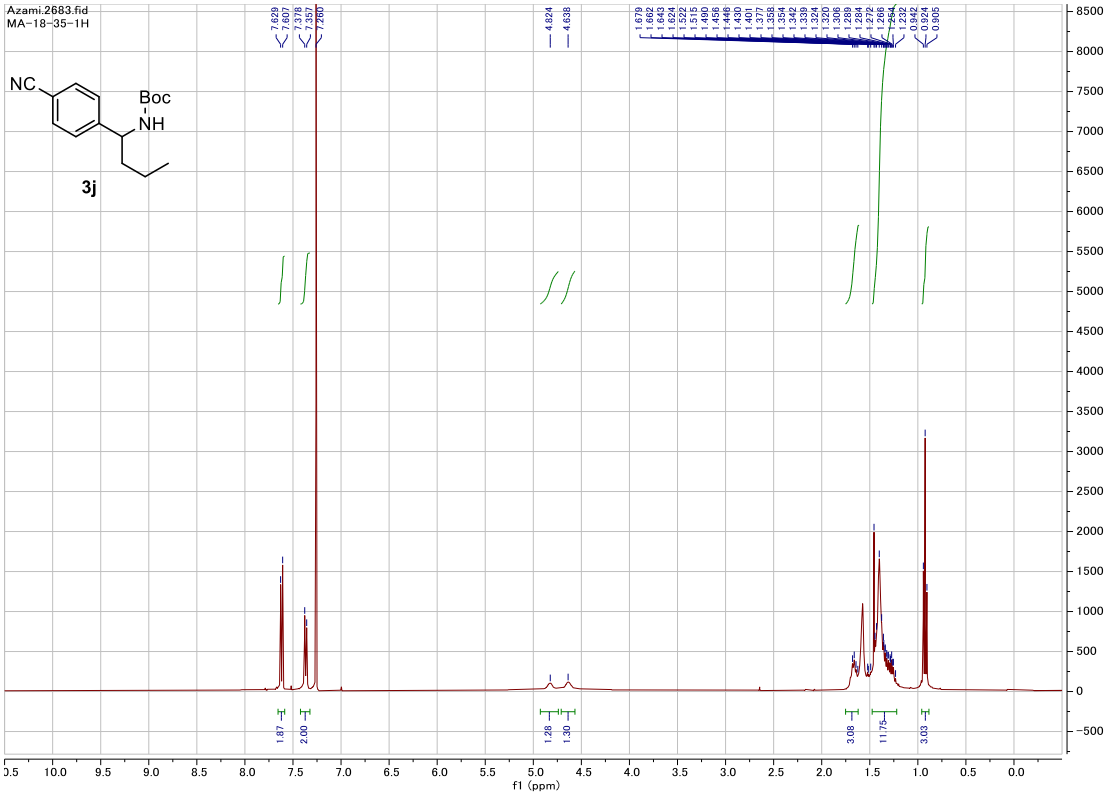
38.873
28.428
17.469
15.249
f1 (ppm)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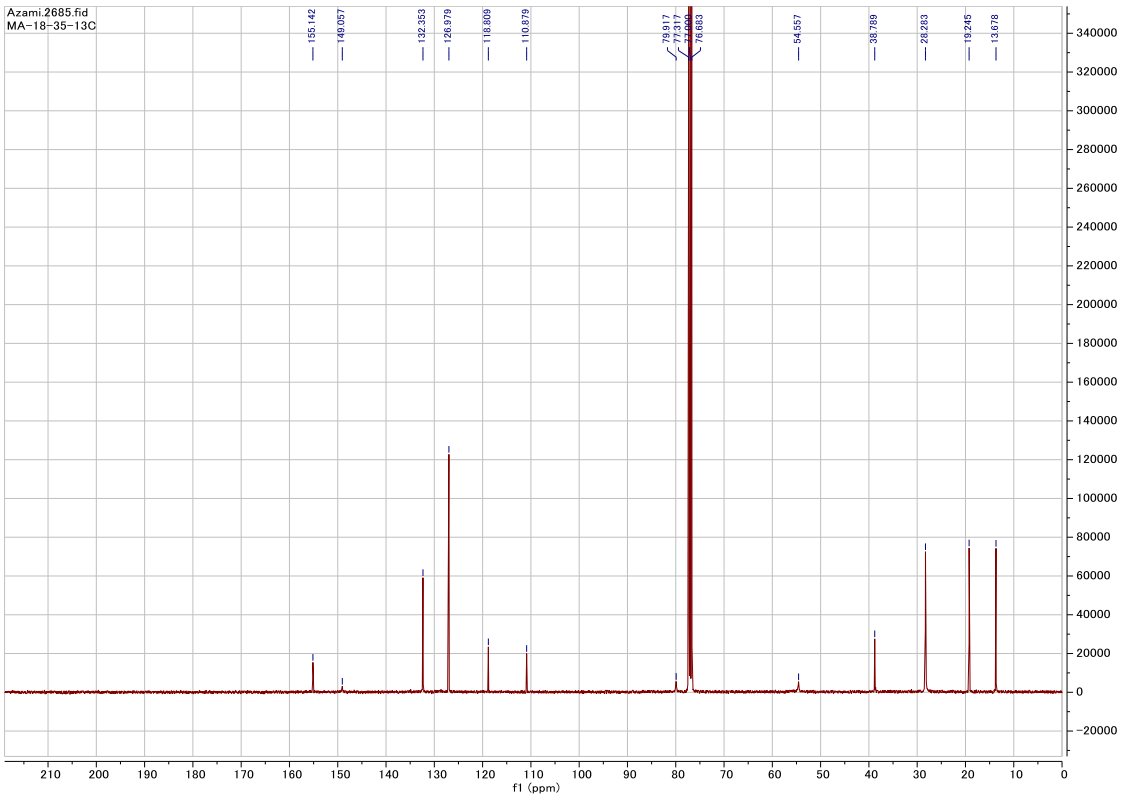
MA-18-35-1H
NC
Boc
NH
3j
f1 (ppm)


Azami.2685.fid
MA-18-35-13C
f1 (ppm)


Azami.2690.fid
MA-18-26-1H
NC
Boc
N
Ph
3k
7.610
7.589
7.367
7.345
7.310
7.292
7.272
7.260
7.202
7.199
7.196
7.185
7.180
7.176
7.165
7.162
7.159
7.077
7.077
7.108
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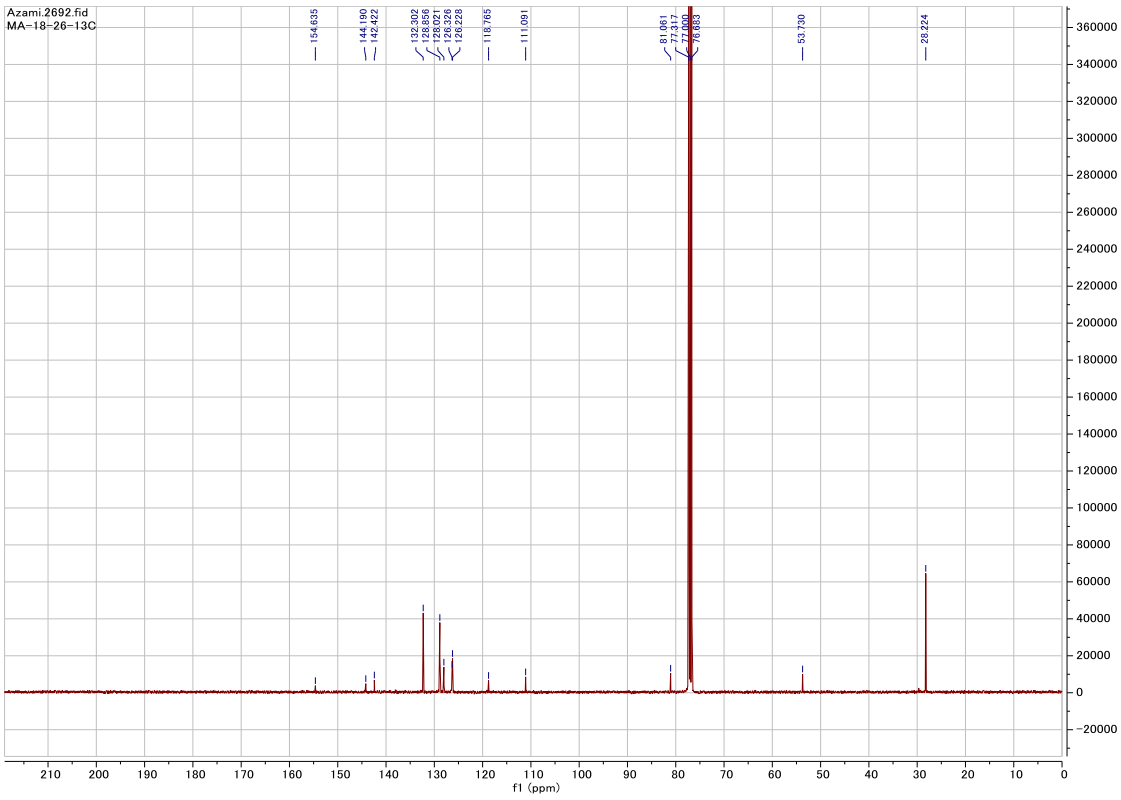
1.496
1.93
2.15
2.36
2.76
1.63
2.00
8.66
f1 (ppm)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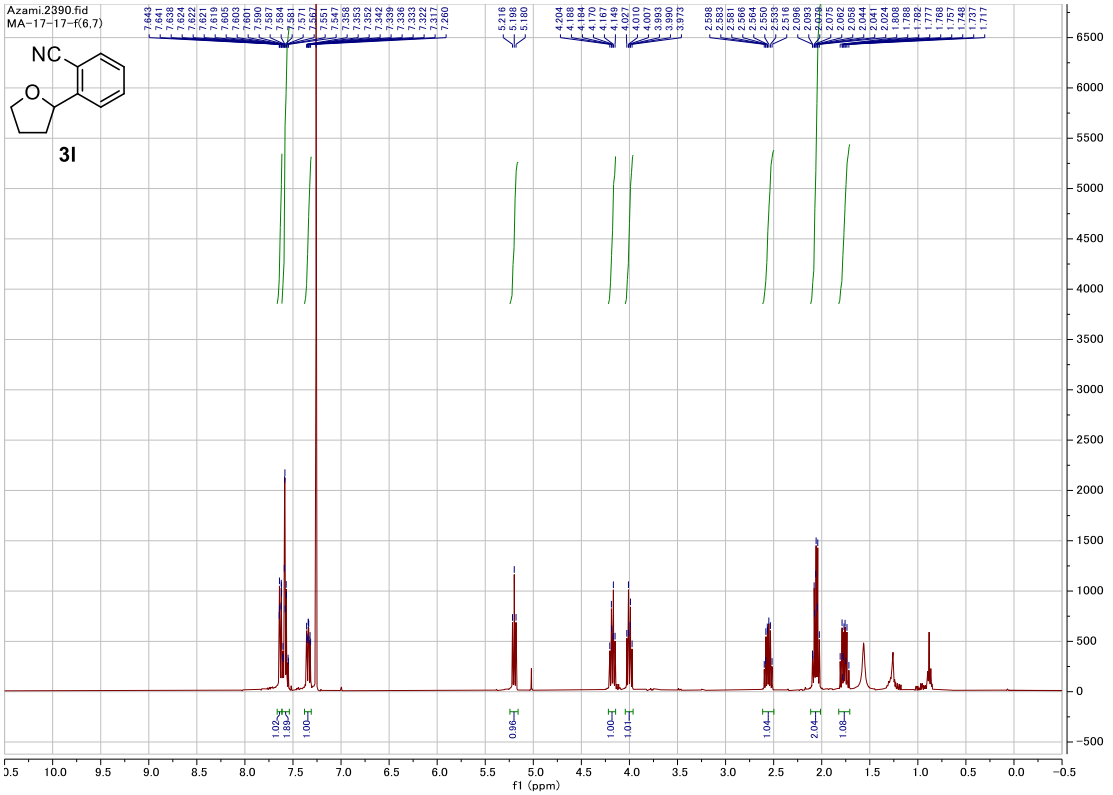
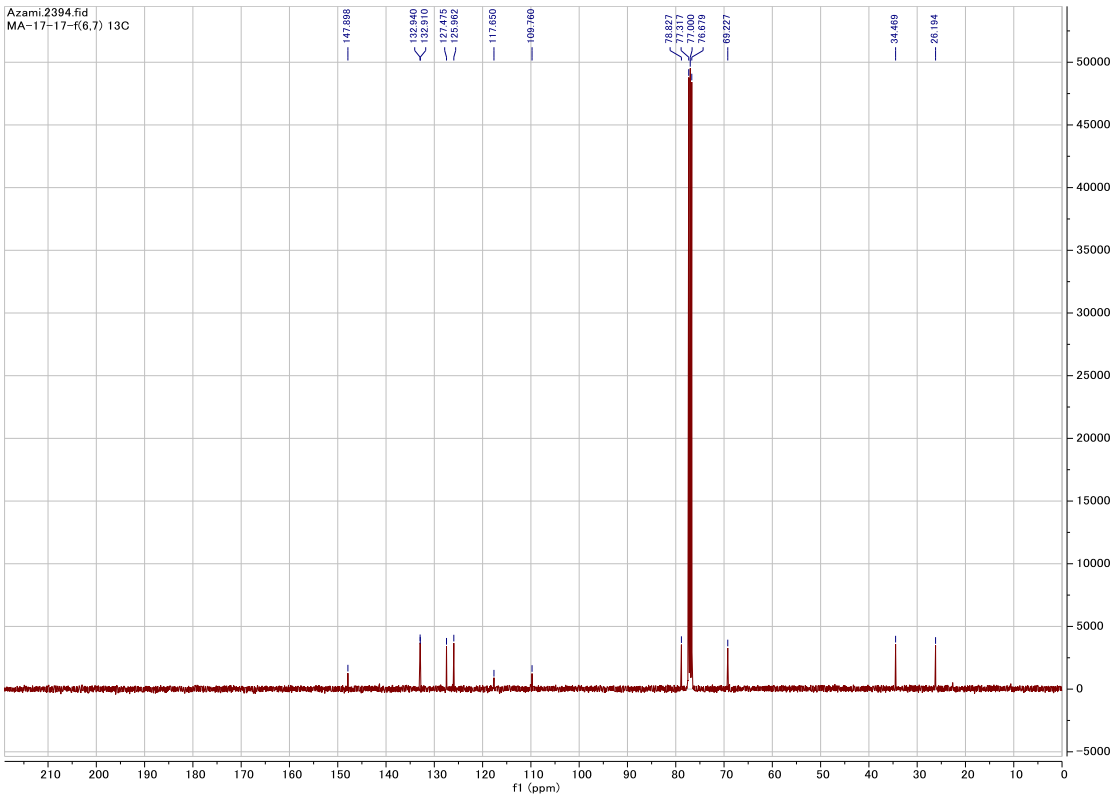
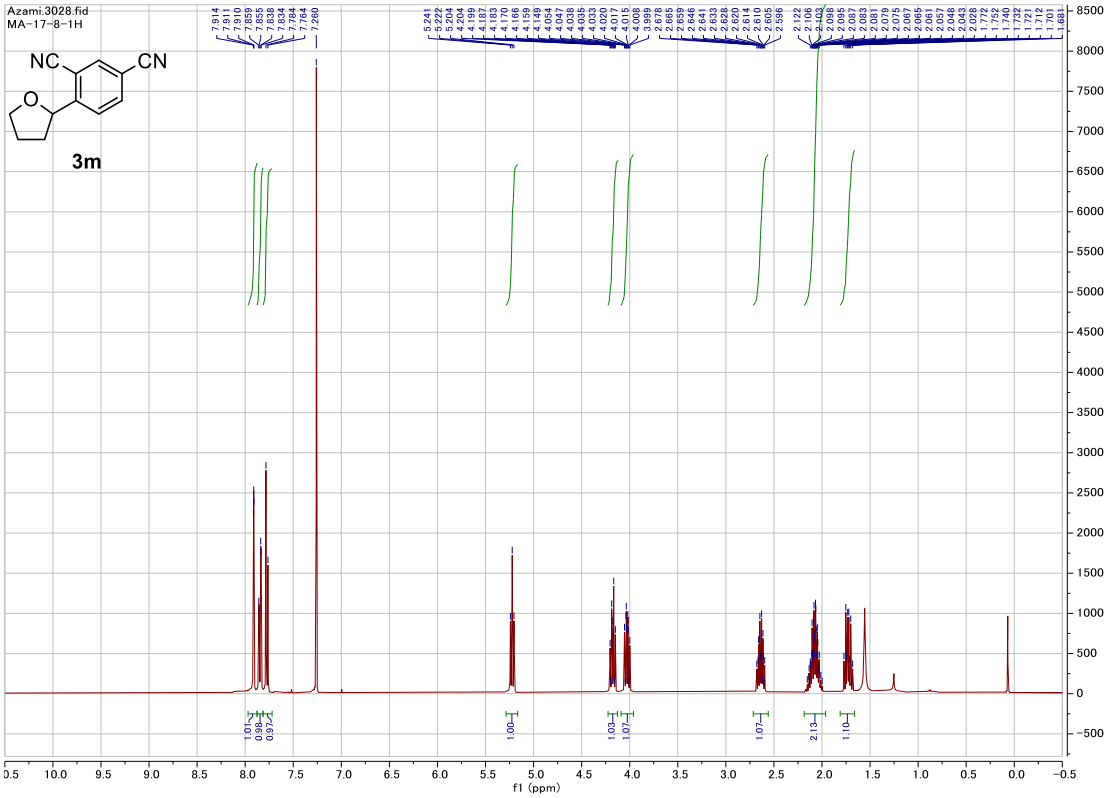
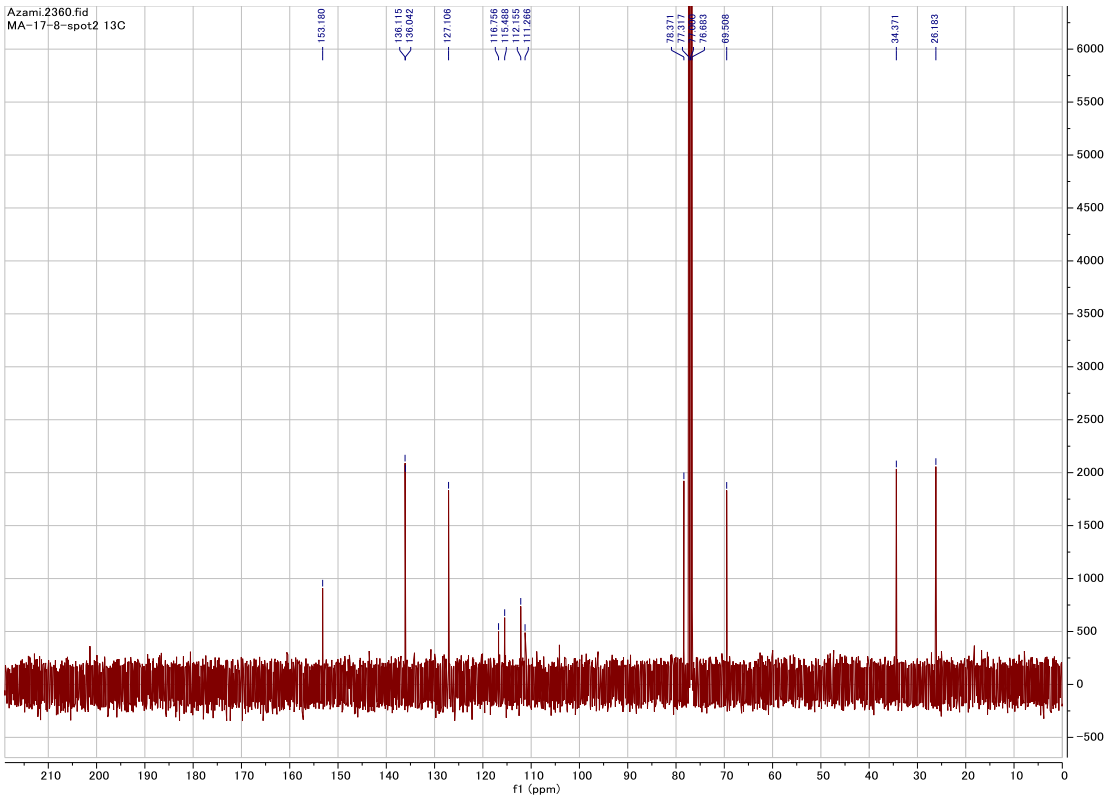
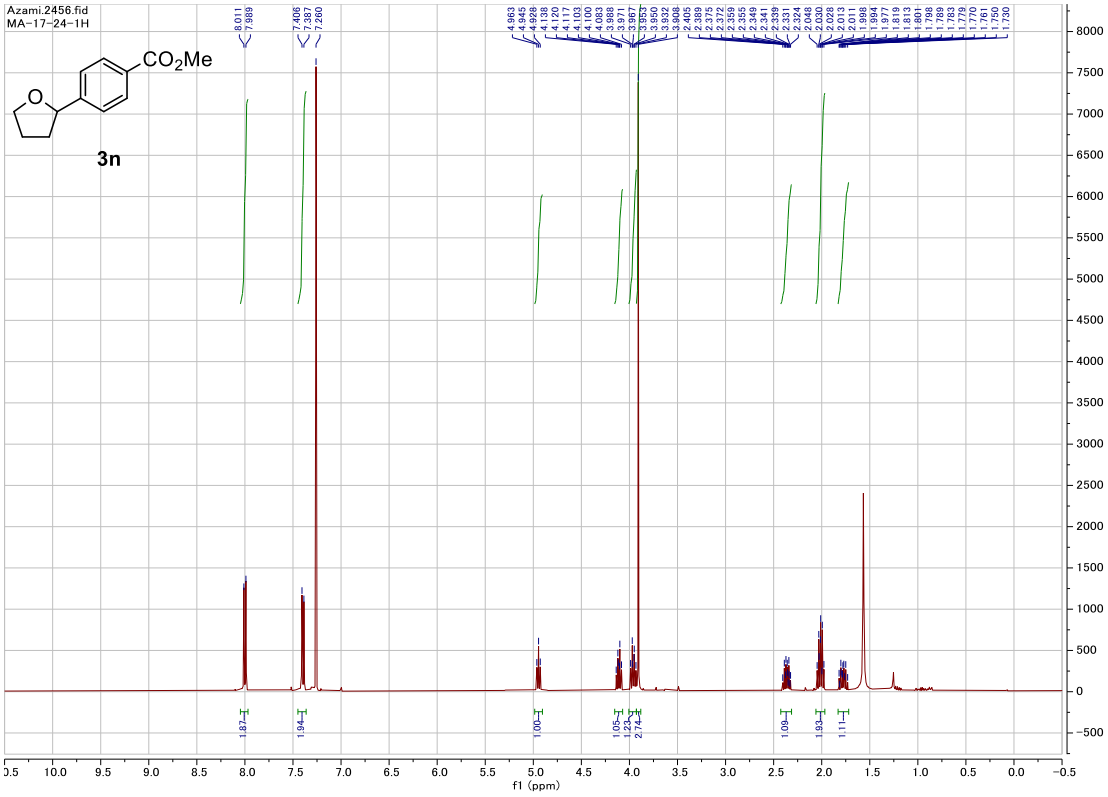
MA-18-26-13C
154.635
144.190
142.422
132.302
128.856
128.027
126.326
126.228
118.765
111.091
81.061
77.317
77.000
76.683
53.730
28.224
f1 (ppm)

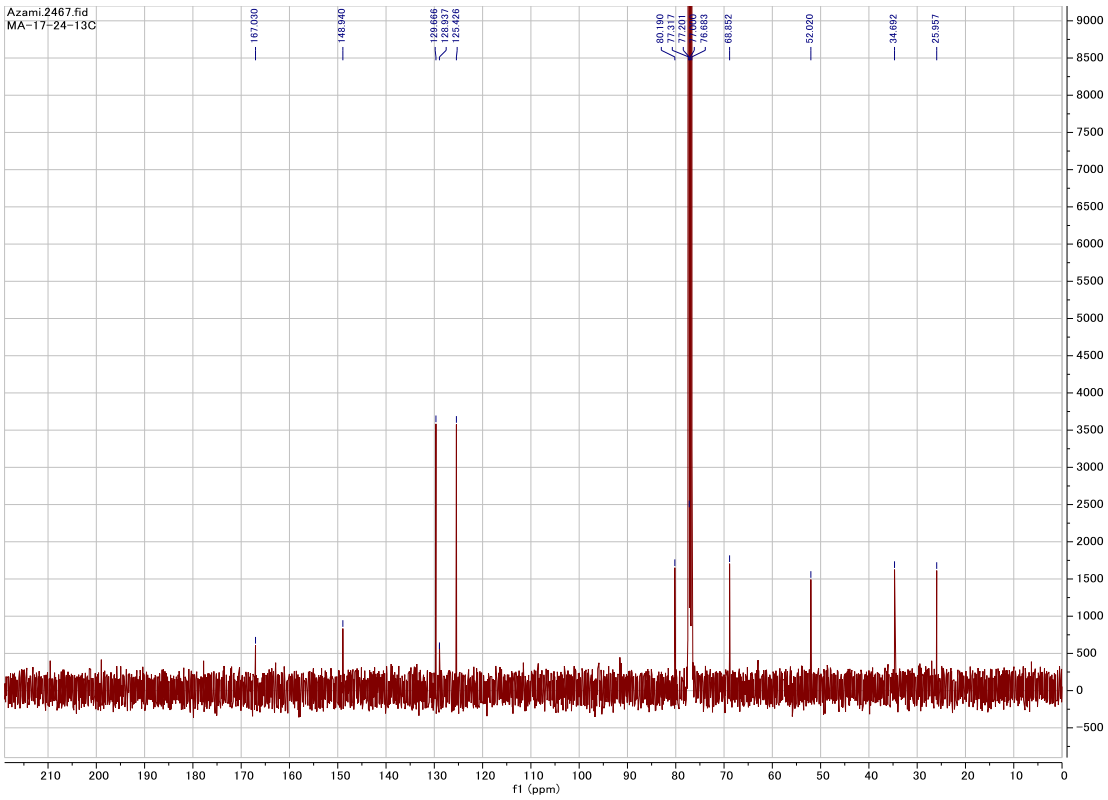

Azami.2390.fid
MA-17-17-f(6,7)
NC
O
3l
f1 (ppm)

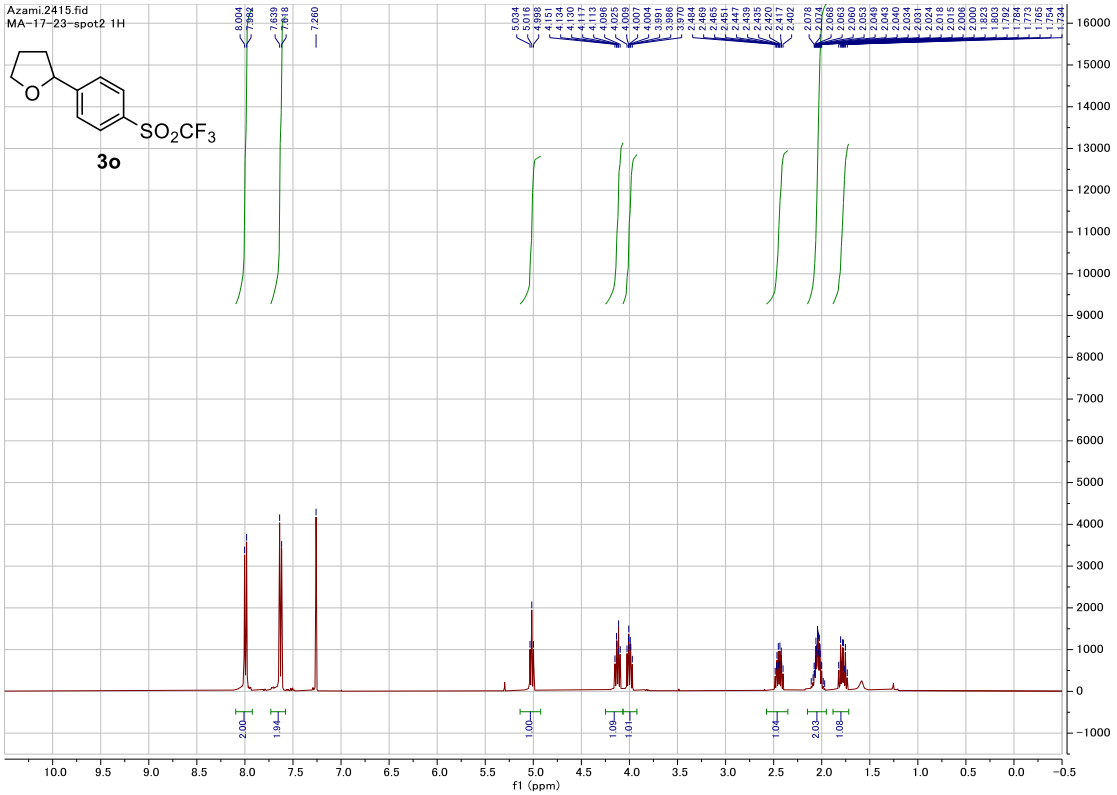

Azami.2394.fid
MA-17-17-f(6,7) 13C
147.898
132.940
132.910
127.475
125.962
117.650
109.760
78.827
77.317
77.000
76.679
69.227
34.469
26.194
f1 (ppm)

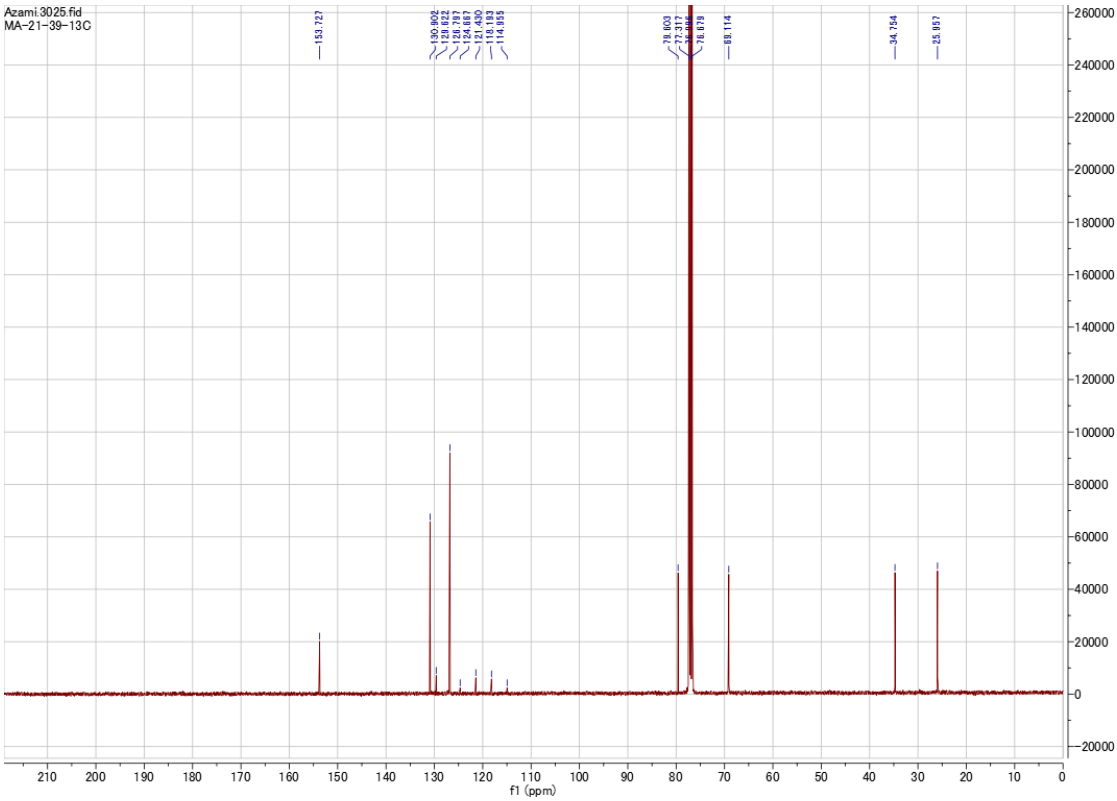

Azami.3028.fid
MA-17-8-1H
NC
CN
O
3m
f1 (ppm)

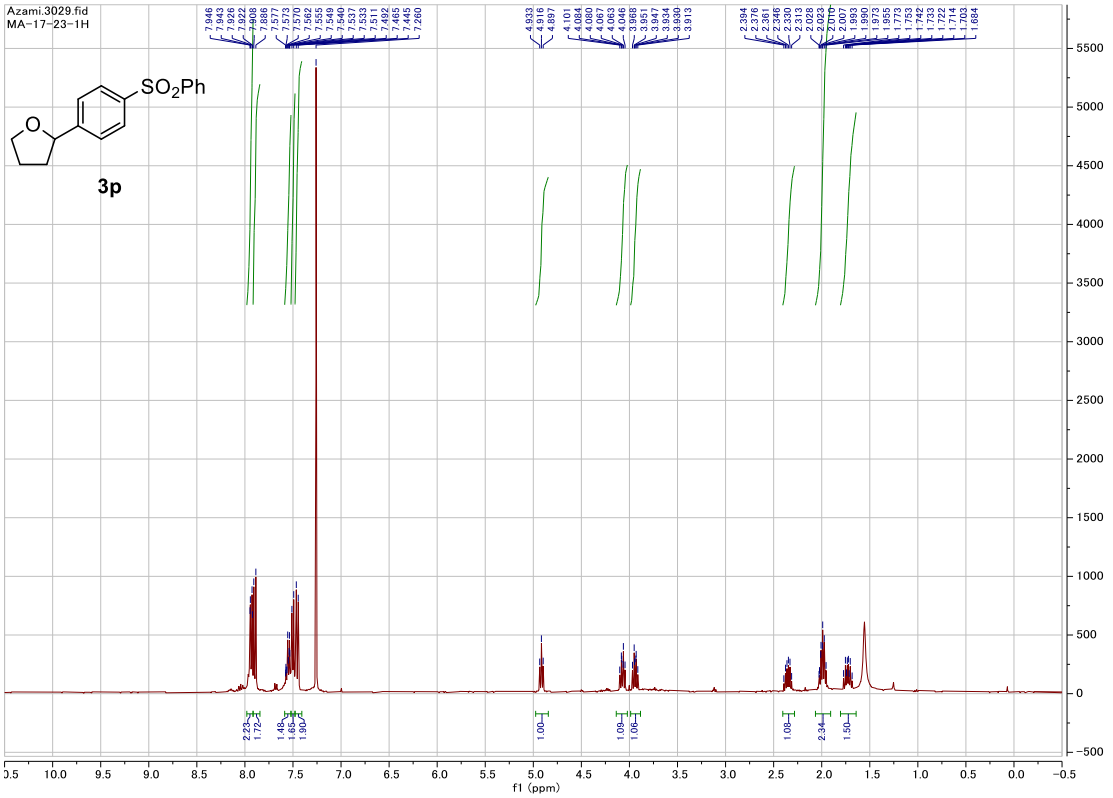

Azami.2360.fid
MA-17-8-spot2 13C
153.180
136.115
136.042
127.106
116.756
115.668
112.155
111.266
78.371
77.317
76.683
69.508
34.371
26.183
f1 (ppm)

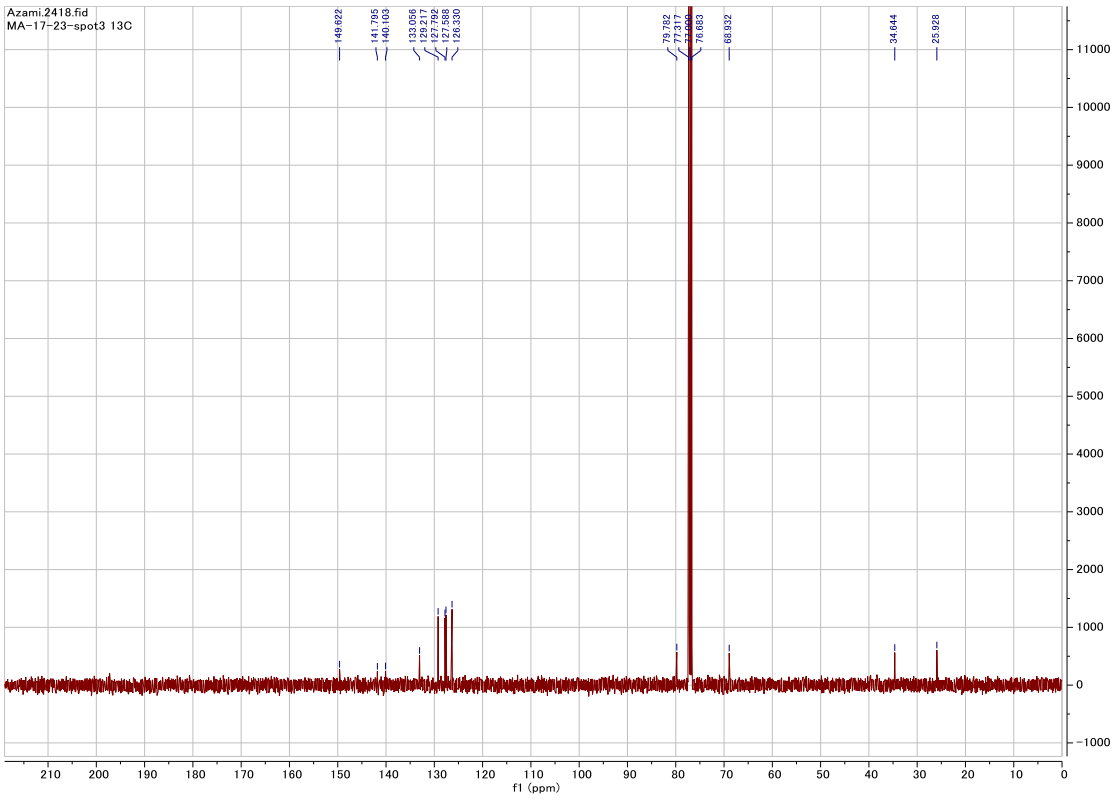

Azami.2456.fid
MA-17-24-1H
CO2Me
O
3n
f1 (ppm)

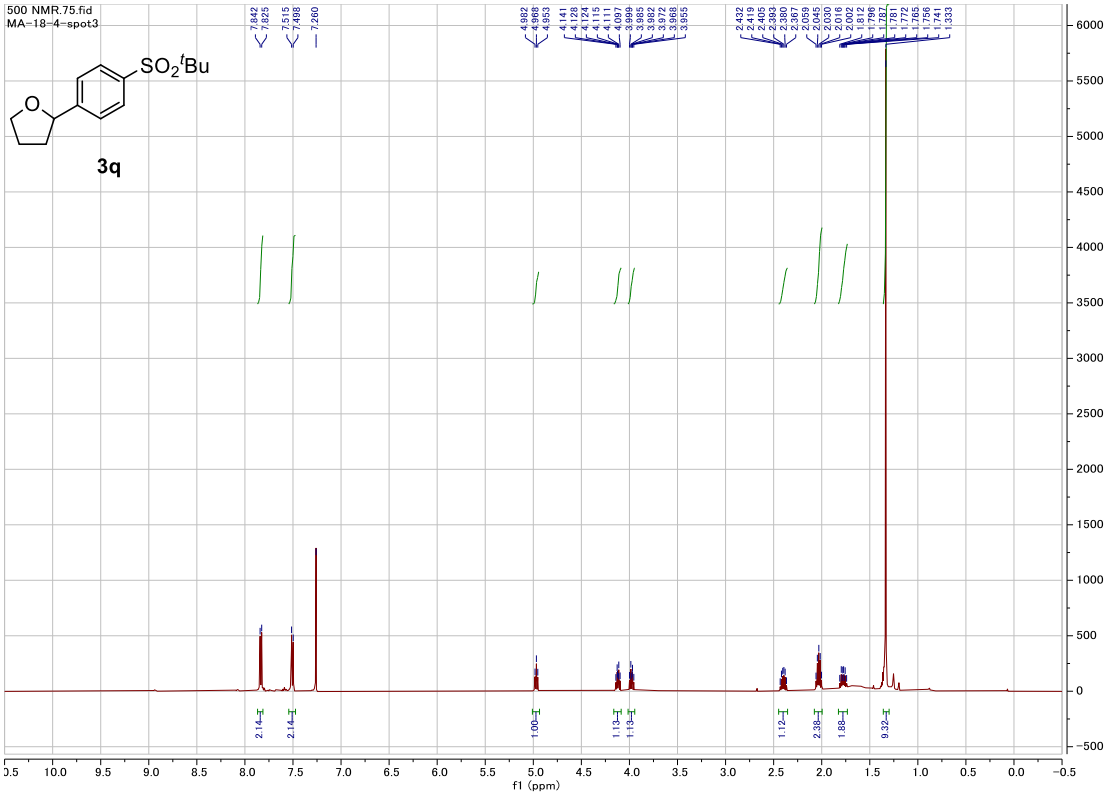

Azami.2467.fid
MA-17-24-13C
167.030
148.940
129.666
128.937
125.426
80.190
77.317
77.201
77.000
76.683
68.852
52.020
34.682
25.957
f1 (ppm)

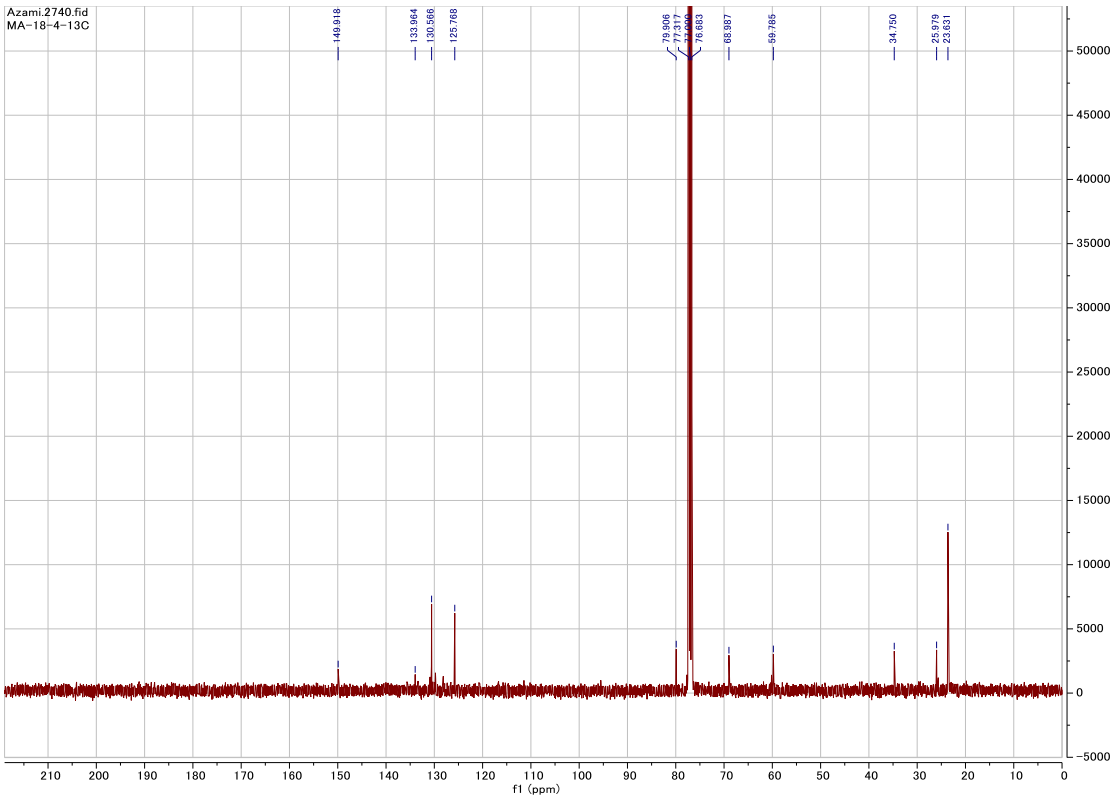

Azami.2415.fid
MA-17-23-spot2 1H
3o
f1 (ppm)

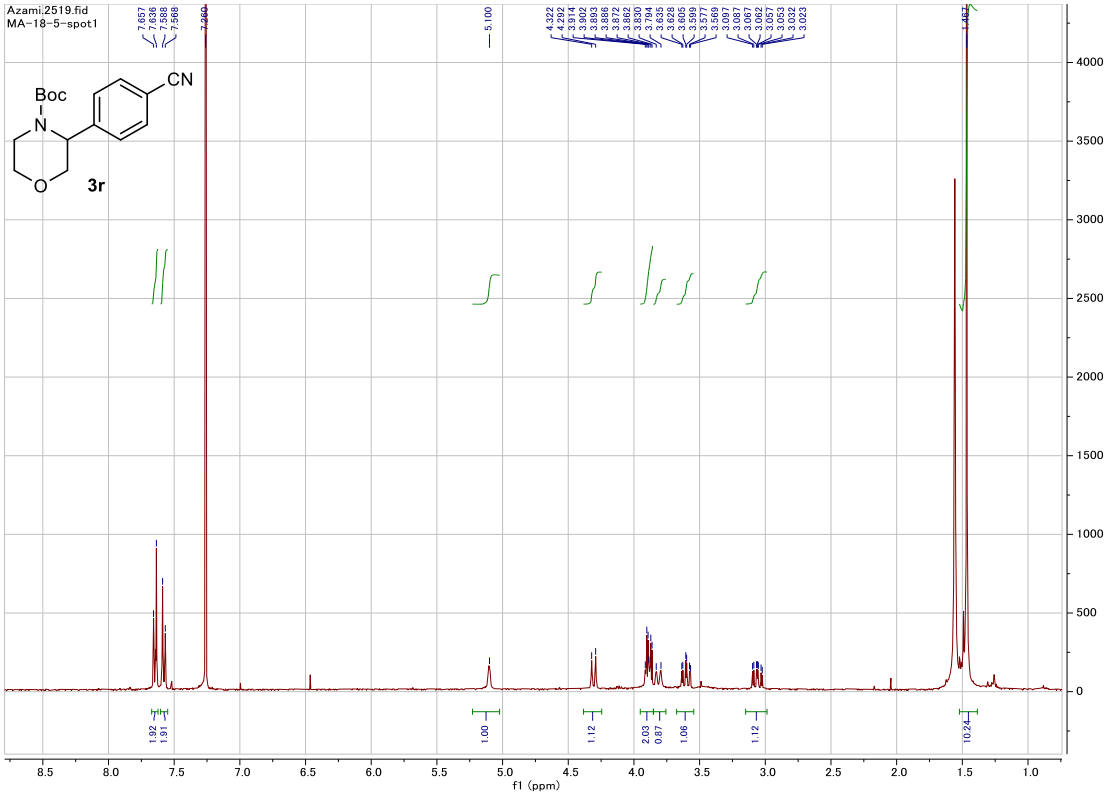

Azami.3025.fid
MA-21-39-13C
f1 (ppm)

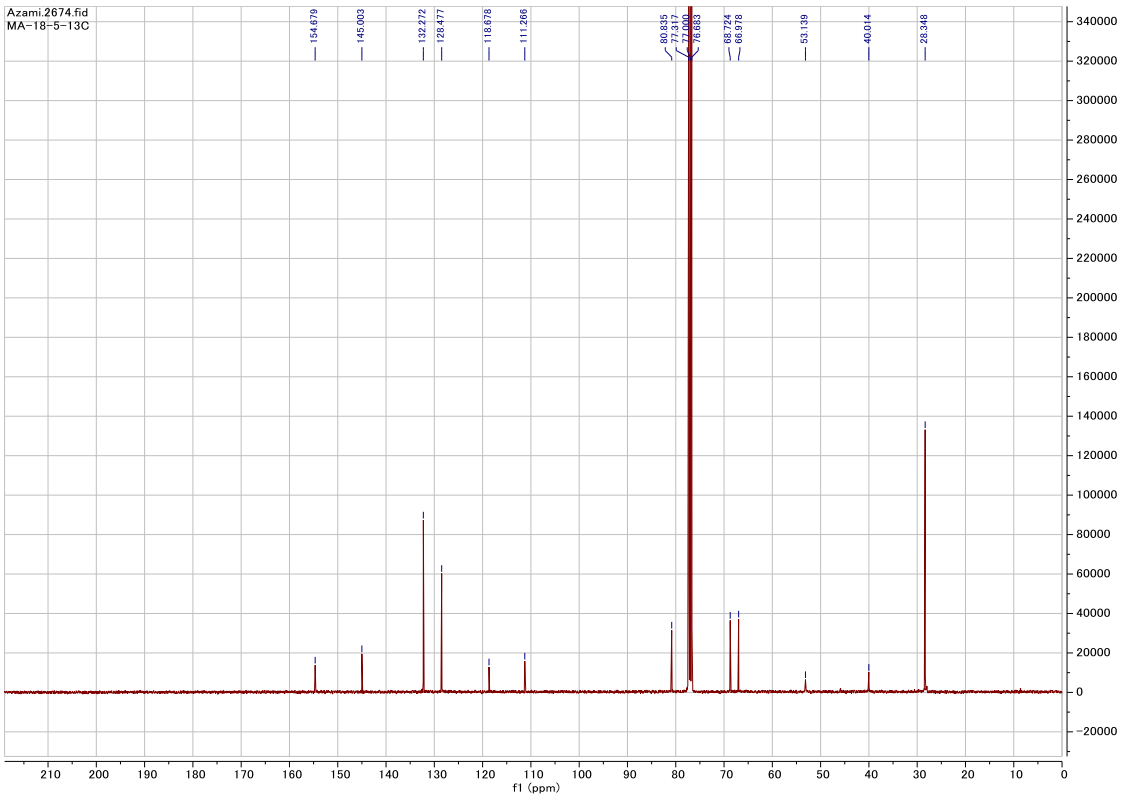

Azami.3029.fid
MA-17-23-1H
SO2Ph
O
3p
f1 (ppm)

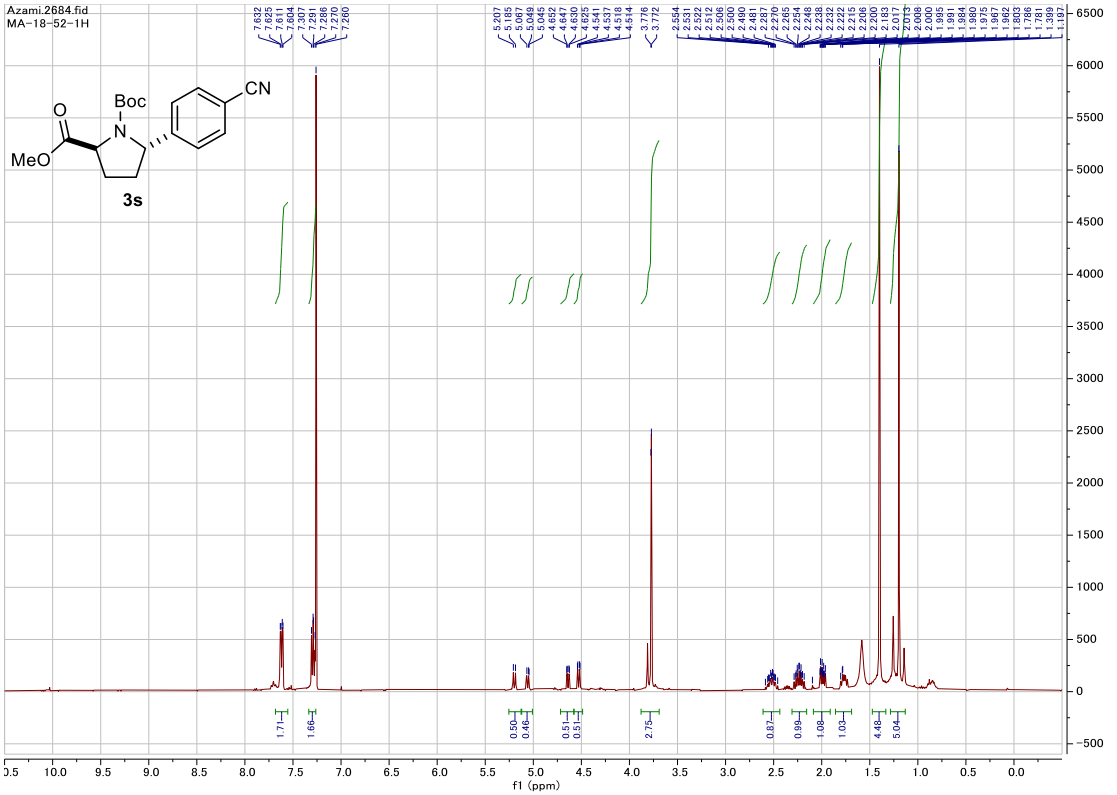

Azami.2418.fid
MA-17-23-spot3 13C
149.622
141.795
140.103
133.056
129.217
127.980
127.588
126.330
79.782
77.317
76.683
68.932
34.644
25.928
f1 (ppm)

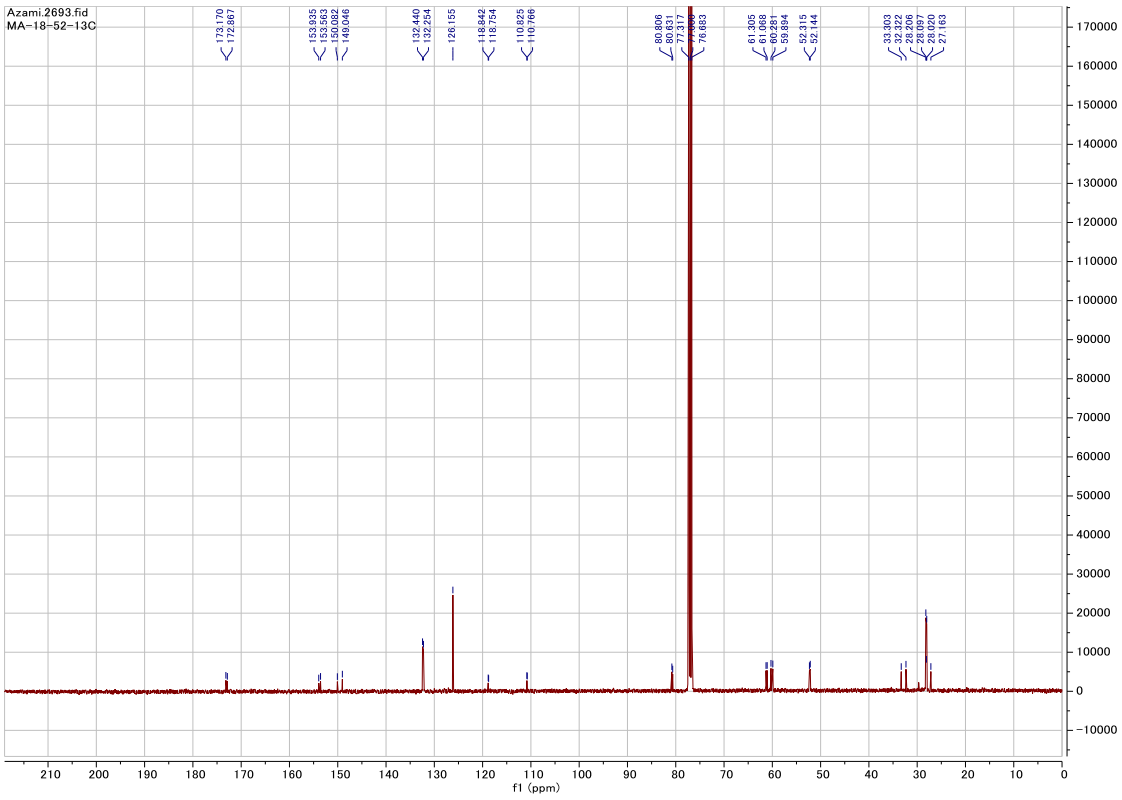

500 NMR.75.fid
MA-18-4-spot3
SO2tBu
O
3q
f1 (ppm)

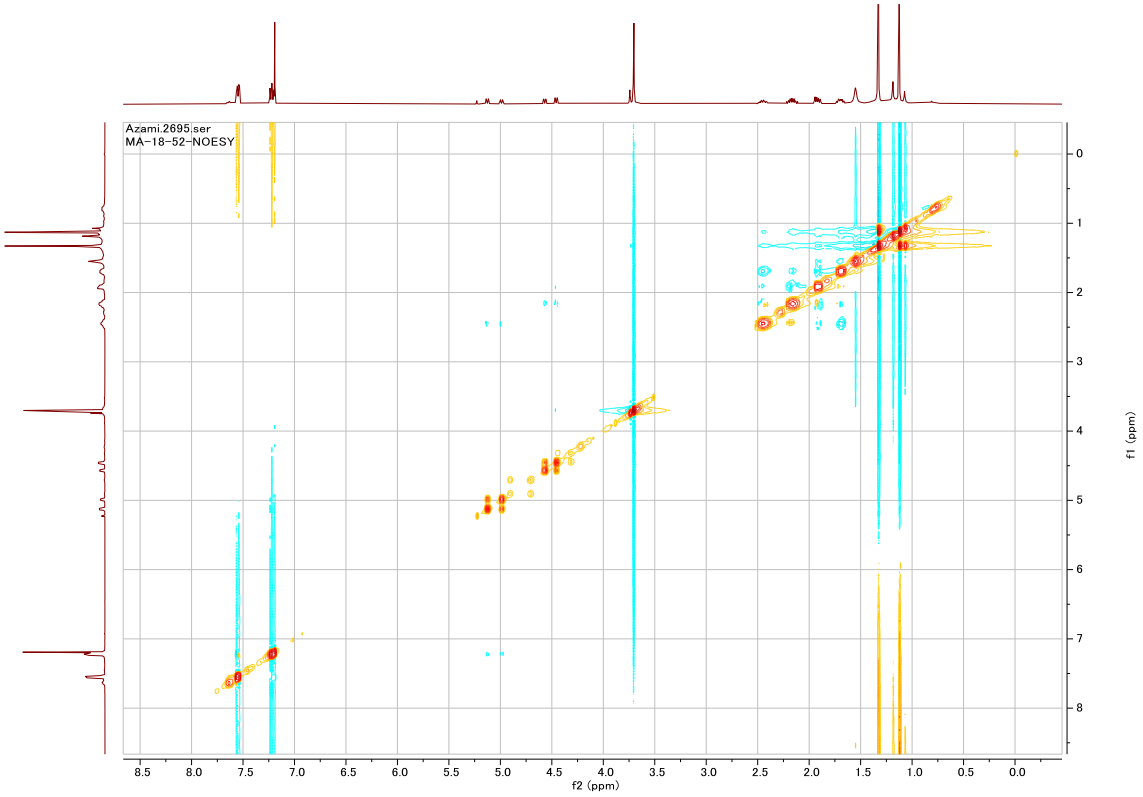

Azami.2740.fid
MA-18-4-13C
f1 (ppm)

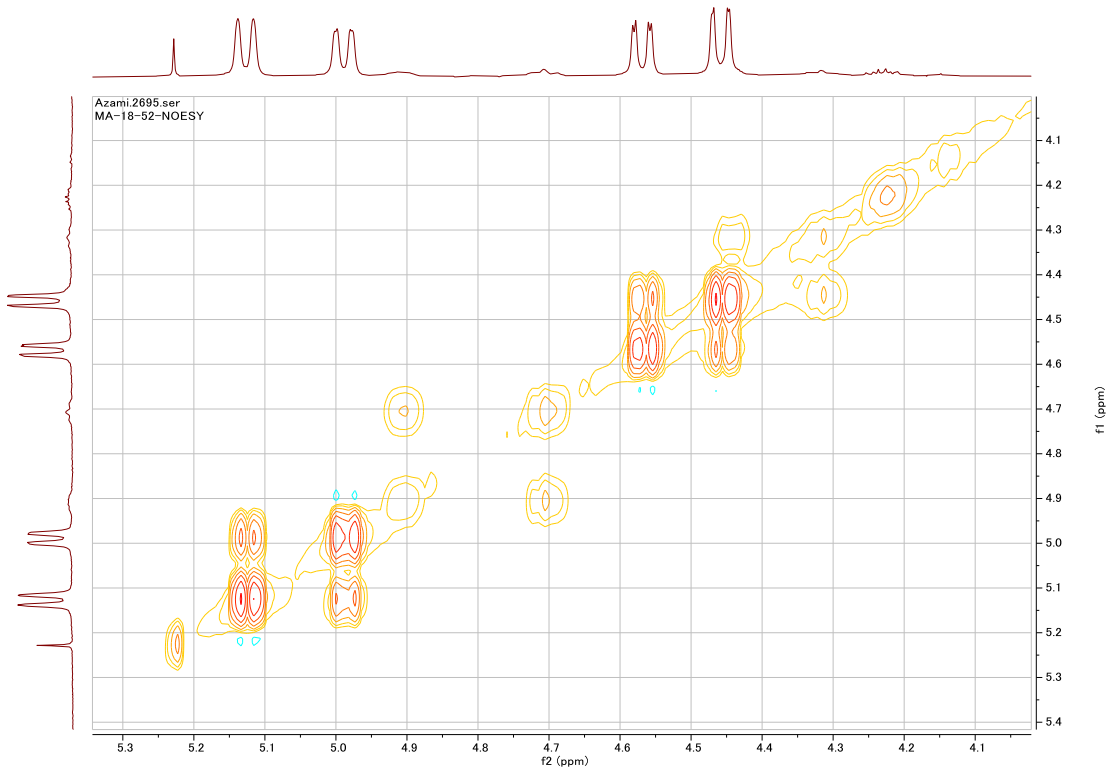

Azami.2519.fid
MA-18-5-spot1
Boc
N
O
CN
3r
f1 (ppm)

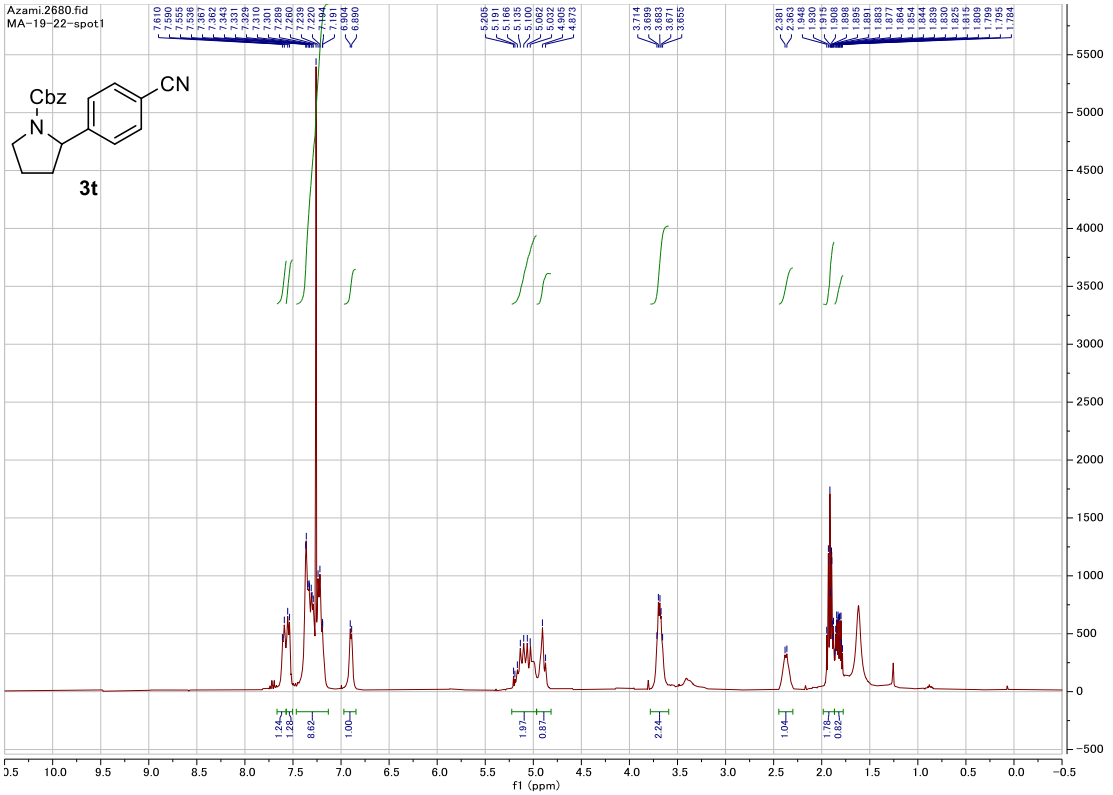

Azami.2674.fid
MA-18-5-13C
f1 (ppm)

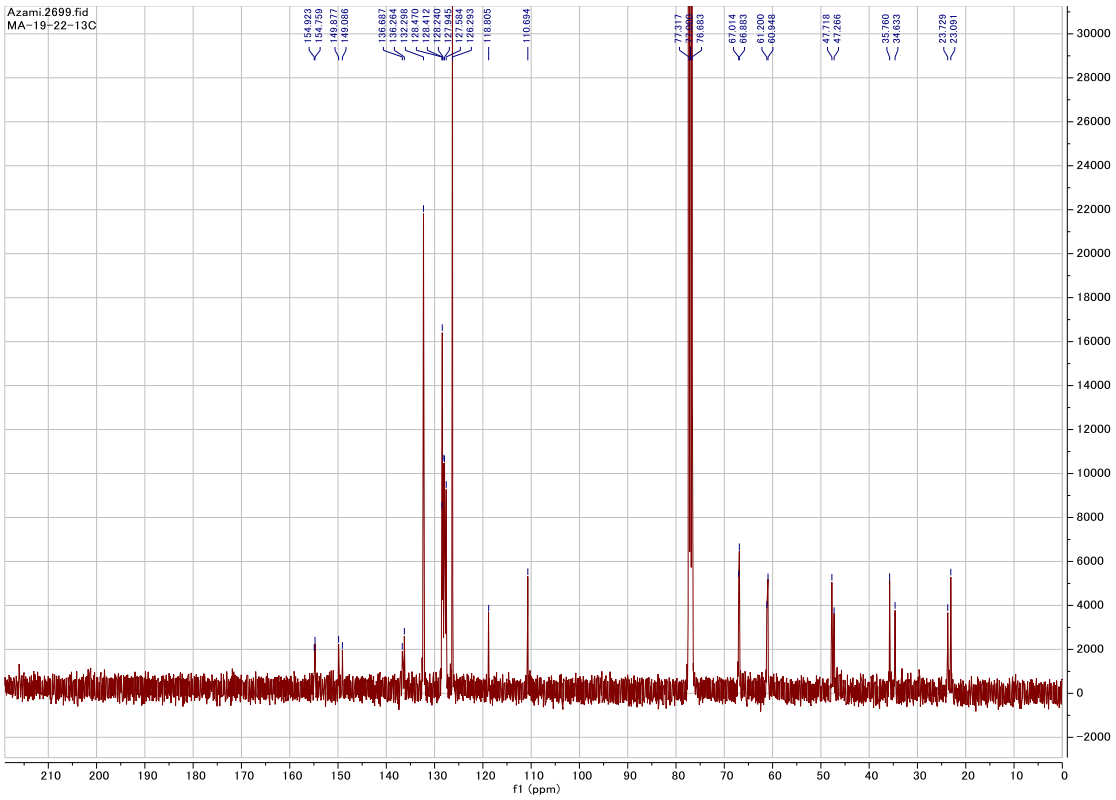

Azami.2684.fid
MA-18-52-1H
Boc
N
O
MeO
CN
3s
f1 (ppm)


Azami.2693.fid
MA-18-52-13C
f1 (ppm)


Azami.2695.ser
MA-18-52-NOESY
f2 (ppm)
f1 (ppm)


Azami.2695.ser
MA-18-52-NOESY
f2 (ppm)
f1 (ppm)


Azami.2680.fid
MA-19-22-spot1
Cbz
N
CN
3t
f1 (ppm)


Azami.2699.fid
MA-19-22-13C
f1 (ppm)

Computational Studies

Density Functional Theory (DFT) calculations were performed using the Gaussian 16 program package.[9] Geometry optimizations were performed at the B3LYP-D3 level of theory[10] with the 6-311G+(d) basis sets for C, N, O, S, and F atoms, and the 6-31G(d,p) basis sets for H atom. We ascertained that each equilibrium structure exhibited no imaginary frequencies and each TS had only one imaginary frequency. Intrinsic Reaction Coordinate (IRC) calculations followed by geometry optimizations were used to confirm the minima linked between each transition state. Solvent effects were modeled using the conductor-like polarizable continuum model (SMD)[11] for CH_2Cl_2. The energies reported are referring to free energies (298.15 K, 1 atm).

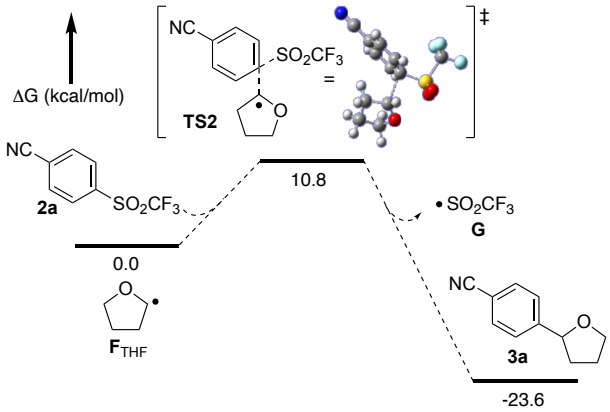


Figure S6. The homolytic aromatic substitution step using the phenyl precursor **2a**. The 0.0 point is based on the ground state of THF radical ($\mathbf{F}_{THF}$).

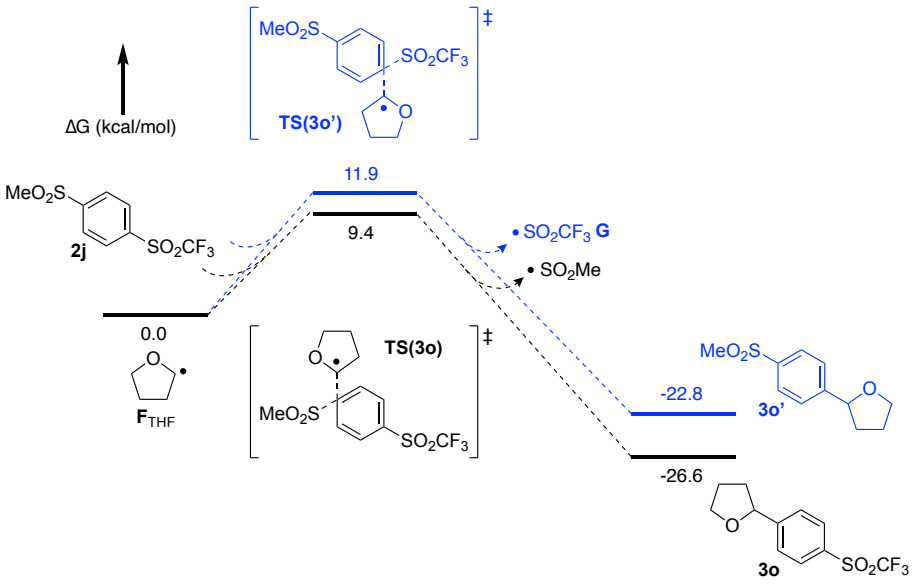
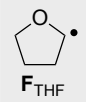


Figure S7. The homolytic aromatic substitution step using the phenyl precursor **2j**. The 0.0 point is based on the ground state of THF radical ($\mathbf{F}_{THF}$).

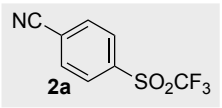
Cartesian Coordinates and Absolute Energies

The Cartesian coordinates (in Å) and Gibbs free energies (in Hartree) for all the optimized geometries were calculated at the B3LYP-D3 level of theory with the 6-311G+(d) basis sets for C, N, O, S, and F atoms, and the 6-31G(d,p) basis sets for H atom.



Energy (FREE) = -231.791657 a.u.

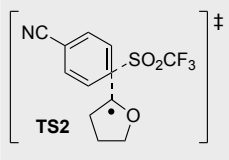
Atom	X	Y	Z
C	-0.33993413	-0.68667462	-0.95727574
C	0.17079753	-1.23128972	0.39023540
C	0.00000000	-0.00000000	1.30474136
C	-0.17079753	1.23128972	0.39023540
C	0.33993413	0.68667462	-0.95727574
H	-0.08206563	-1.31115383	-1.78699229
H	-1.40312633	-0.56629679	-0.95166127
H	1.21053015	-1.47225388	0.31412795
H	-0.35259463	-2.10236810	0.72517287
H	0.00000000	-0.00000000	2.37474136
H	-1.21053015	1.47225388	0.31412795
H	0.35259463	2.10236810	0.72517287
H	0.08206563	1.31115383	-1.78699229
H	1.40312633	0.56629679	-0.95166127



Energy (FREE) = -1210.285681 a.u.

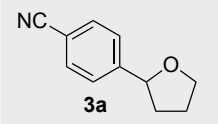
Atom	X	Y	Z
C	0.94847200	0.38109300	-1.22155200
C	2.30768800	0.09546200	-1.21938300
C	2.98626200	-0.04975600	-0.00001300
C	2.30769600	0.09631100	1.21927900
C	0.94848600	0.38190600	1.22127000
C	0.29138500	0.51595000	-0.00019200
H	0.40611500	0.51016600	-2.14871200
H	2.84572700	-0.01154000	-2.15179700
H	2.84575800	-0.01005000	2.15175300
H	0.40611900	0.51157000	2.14834100
C	4.38750700	-0.34468600	0.00010400
N	5.51721700	-0.58353000	0.00022700
S	-1.46957800	0.86895400	-0.00025500

C	-2.20211300	-0.89146900	0.00028000
O	-1.84034100	1.45378400	-1.28277200
O	-1.84023400	1.45453800	1.28195100
F	-1.79338600	-1.55116600	-1.08727600
F	-1.79251200	-1.55093300	1.08765600
F	-3.52729100	-0.80836100	0.00081100



Energy (FREE) = -1442.060158 a.u.

Atom	X	Y	Z
C	-0.62540100	0.77763300	1.32086900
C	-1.82129100	1.43975000	1.21149800
C	-2.53356800	1.45370900	-0.01528500
C	-1.97270600	0.81216300	-1.14694000
C	-0.77850200	0.14078800	-1.05323800
H	-0.06990700	0.78904900	2.24973200
H	-2.22109700	1.97730100	2.06189700
H	-2.48346600	0.87649600	-2.09943200
H	-0.32652700	-0.30894500	-1.92706800
C	-3.77567700	2.13210400	-0.11702100
N	-4.79496700	2.67691900	-0.19833400
C	-0.12708100	-0.00355500	0.21914800
O	1.99580300	-0.99951100	-1.05347100
O	2.18007300	-0.53442200	1.46334400
S	1.66384100	-0.21715900	0.13504800
C	2.30101000	1.54737800	-0.24116400
F	3.62244400	1.50235100	-0.39390800
F	1.99897500	2.37266500	0.76502000
F	1.74041900	2.00721300	-1.36378400
C	-1.87916600	-2.30487600	0.57561000
O	0.36437100	-2.93085900	0.47186300
C	-1.68257500	-3.03434200	-0.77246300
H	-2.49443000	-1.40915000	0.50174100
H	-2.33708000	-2.96264800	1.32386100
C	-0.22924400	-3.54436200	-0.70913900
H	-1.81102600	-2.33725500	-1.59941000
H	-2.39323500	-3.84971500	-0.90457200
H	0.37969900	-3.24475400	-1.56246900
H	-0.14913700	-4.62205100	-0.56404800
C	-0.46539000	-2.02469100	0.99806900
H	-0.19146400	-1.74413500	2.00782800



3a

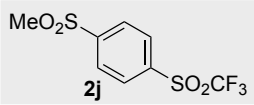
Energy (FREE) = -555.756764 a.u.

Atom	X	Y	Z
C	2.49408600	0.09194600	1.36451400
C	3.60234400	-0.73743100	1.21412300
C	4.06724800	-1.05315500	-0.07411900
C	3.40651900	-0.53128200	-1.20009200
C	2.30311300	0.30169300	-1.03485800
H	2.12923000	0.31817900	2.36294500
H	4.10405800	-1.14943600	2.08332000
H	3.76005500	-0.78432400	-2.19421400
H	1.78271000	0.69122400	-1.90314800
C	5.20597600	-1.91048900	-0.23943600
N	6.13132800	-2.60382400	-0.37399500
C	1.83921600	0.62880800	0.24692800
C	1.06969700	3.07037900	0.52313000
O	-0.24738200	1.49258200	-0.65641200
C	-0.21649200	3.76232900	0.05172500
H	1.89840900	3.27553000	-0.16424300
H	1.38244400	3.35976200	1.52994200
C	-0.70209500	2.81269400	-1.04607300
H	-0.04873700	4.77736500	-0.31924600
H	-0.94703900	3.81290300	0.86645100
H	-0.25554900	3.05159800	-2.02010100
H	-1.78964800	2.77624800	-1.15393700
C	0.68071900	1.57968800	0.44816300
H	0.14307600	1.29336500	1.36330800

• SO_2CF_3 **G**

Energy (FREE) = -886.359606 a.u.

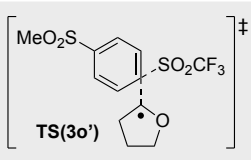
Atom	X	Y	Z
O	-1.51151400	-1.29268800	0.20275700
O	-1.51148700	1.29269600	0.20278600
S	-1.04393500	0.00003000	-0.33181900
C	0.89797400	0.00000700	0.00770800
F	1.11549000	-0.00063600	1.31396100
F	1.41439800	1.08831400	-0.54432100
F	1.41446000	-1.08774300	-0.54535900



2j

Energy (FREE) = -1705.962153 a.u.

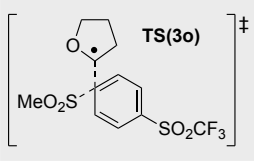
Atom	X	Y	Z
C	-0.02788400	0.40078900	-1.22355800
C	1.33667900	0.12725500	-1.22062700
C	1.99601000	0.00323200	-0.00001200
C	1.33674200	0.12900900	1.22045900
C	-0.02782000	0.40255500	1.22308100
C	-0.68202700	0.53541200	-0.00031700
H	-0.57539900	0.51381300	-2.14983900
H	1.88133100	-0.00653800	-2.14630700
H	1.88144800	-0.00345200	2.14629900
H	-0.57527700	0.51692700	2.14923000
S	-2.44587500	0.87825300	-0.00054000
C	-3.16998700	-0.88540600	0.00054500
O	-2.82028900	1.46172300	-1.28281600
O	-2.82031500	1.46330200	1.28100900
F	-2.75837900	-1.54314800	-1.08646500
F	-2.75849800	-1.54172500	1.08845600
F	-4.49578700	-0.80695200	0.00042000
C	4.50116200	1.33204000	-0.00080300
H	4.18223400	1.85217400	-0.90289400
H	4.18208900	1.85331300	0.90058000
H	5.58179400	1.18645100	-0.00062400
S	3.78020500	-0.32798900	0.00019200
O	4.10962200	-0.95921900	1.28079900
O	4.10963500	-0.96078200	-1.27964000



Energy (FREE) = -1937.742328 a.u.

Atom	X	Y	Z
C	-1.01672900	-0.43656900	1.21296300
C	0.33924900	-0.65173300	1.30378400
C	1.05772200	-1.02692800	0.15440900
C	0.41110800	-1.25150500	-1.07769400
C	-0.94168500	-1.04234100	-1.17526900
H	-1.59627100	-0.17776300	2.08937800
H	0.85541800	-0.56083900	2.25101400
H	0.98336700	-1.60239500	-1.92648900
H	-1.46138700	-1.20911100	-2.11039300
C	-1.66763700	-0.49518600	-0.06459900
O	-3.99047900	-0.62509200	-1.36792000
O	-4.03182500	-0.21777900	1.14863200

S	-3.44741700	-0.88115600	-0.02590400
C	-3.49917200	-2.66723400	0.26594100
C	-2.46630000	2.41004300	0.38179900
O	-0.61199000	1.91648800	-0.98862700
C	-1.36483100	3.47120400	0.61214800
H	-2.66452800	1.82492600	1.27999300
H	-3.42258100	2.83430300	0.07213700
C	-0.11376500	2.77354700	0.08020600
H	-1.26533100	3.75334300	1.66062600
H	-1.57024200	4.37183900	0.02982000
H	0.36916200	2.14341600	0.82845500
H	0.62694500	3.43213400	-0.36963200
C	-1.87998400	1.55395500	-0.72066300
H	-2.44718400	1.27841400	-1.60217100
S	2.81070100	-1.20394300	0.25735100
C	3.40952800	0.54554300	-0.20666300
O	3.29265100	-2.06507400	-0.81831100
O	3.21133300	-1.37914900	1.65087500
H	-3.01249000	-2.87361400	1.21801700
H	-2.99549200	-3.16854900	-0.55886500
H	-4.55530100	-2.93503700	0.30108400
F	3.01581600	0.85659100	-1.44566800
F	2.88946000	1.44695200	0.64337200
F	4.73703900	0.59852400	-0.13786800



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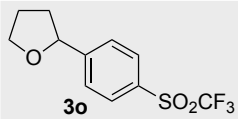
Atom	X	Y	Z
C	-0.07414200	-0.44656500	-1.32943000
C	-1.42454600	-0.68233600	-1.22530200
C	-2.08684900	-0.43888300	-0.00763100
C	-1.37830800	-0.01743700	1.13024100
C	-0.02580300	0.22436800	1.04407300
H	0.45671700	-0.65693500	-2.24885200
H	-1.97963300	-1.09277400	-2.05948000
H	-1.89683800	0.06919300	2.07692600
H	0.54708400	0.49792500	1.91982700
C	0.64175600	0.14177100	-0.22631900
O	2.96826300	0.35461000	1.07689300
O	3.01488200	-0.11221600	-1.44508300
S	2.40685100	-0.25635300	-0.12541000
C	2.40783700	-2.13764900	0.22692900

F	3.66582100	-2.53490800	0.40488100
F	1.87452700	-2.80219800	-0.80109700
F	1.69985000	-2.39721200	1.32913000
C	-0.28307200	2.85608100	-0.64188100
O	2.03447400	2.74189300	-0.41091500
C	0.05990700	3.50138400	0.72082200
H	-1.15040100	2.19800800	-0.60694600
H	-0.47086600	3.61689600	-1.40832200
C	1.60236200	3.48413500	0.76407400
H	-0.35475000	2.90903300	1.53546500
H	-0.33478000	4.51381000	0.80354900
H	2.00883600	2.96880100	1.63522200
H	2.05496400	4.47247900	0.68320600
C	0.99042400	2.13673800	-0.99248100
H	1.21532300	1.79462600	-1.99573800
S	-3.85250500	-0.70693000	0.10357700
C	-4.56037800	0.89558200	-0.36475500
H	-4.24882100	1.13147200	-1.38150700
H	-5.64285300	0.77507700	-0.31222700
H	-4.22248000	1.64825200	0.34650800
O	-4.18843700	-0.93244300	1.51457900
O	-4.23267500	-1.66779400	-0.93854700

• SO_2Me

Energy (FREE) = -588.535252 a.u.

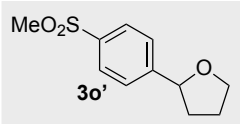
Atom	X	Y	Z
O	0.74222200	1.29514600	0.21386100
O	0.74133100	-1.29558600	0.21382300
S	0.21375700	-0.00004700	-0.28275600
C	-1.59482600	0.00043200	0.09706400
H	-1.67590900	0.00006400	1.18444500
H	-2.02126600	0.90464000	-0.33190700
H	-2.02241100	-0.90302400	-0.33229900



Energy (FREE) = -1349.795320 a.u.

Atom	X	Y	Z
C	1.33030200	-0.73624100	0.58008800
C	-0.01480700	-0.61057100	0.90975000
C	-0.76442500	0.39280100	0.29793800
C	-0.20601200	1.26607500	-0.63542700
C	1.13872500	1.12425500	-0.95242900

H	1.93470400	-1.51358900	1.02710100
H	-0.47815800	-1.26896000	1.63281500
H	-0.81390400	2.03745800	-1.08933200
H	1.58829600	1.79243500	-1.67848600
C	1.91707700	0.13180300	-0.34473800
C	4.24027000	1.08174100	0.11259800
O	3.92905700	-1.22778500	-0.31314100
C	5.60495200	0.38582600	0.16171800
H	3.83429800	1.20818800	1.12042500
H	4.25555200	2.05633300	-0.37677100
C	5.19522500	-1.07698600	0.35606300
H	6.24697200	0.75222300	0.96433600
H	6.13300000	0.51293500	-0.78753500
H	5.06584500	-1.31493200	1.41907800
H	5.89990700	-1.78909700	-0.07830800
C	3.39202100	0.05162500	-0.66215400
H	3.52769100	0.20486800	-1.74224800
S	-2.49569200	0.54807900	0.69886500
C	-3.29737900	-0.62990800	-0.56601400
O	-2.96481800	1.88202300	0.33757000
O	-2.75448500	-0.05342900	2.00288800
F	-3.00972400	-0.23295200	-1.81024700
F	-2.83528100	-1.87220800	-0.39102300
F	-4.61686900	-0.62107500	-0.39381900



Energy (FREE) = -1051.431573 a.u.

Atom	X	Y	Z
C	0.50380500	1.50639000	-0.38404600
C	-0.87117600	1.35984300	-0.24551100
C	-1.41045600	0.07430700	-0.22262300
C	-0.60466500	-1.05253900	-0.35236100
C	0.77239700	-0.88888100	-0.48937000
H	0.93233600	2.50252500	-0.41600300
H	-1.52547700	2.22005600	-0.18303600
H	-1.05453500	-2.03721100	-0.37324300
H	1.41592900	-1.74836000	-0.61900600
C	1.33805400	0.38706000	-0.49638500
C	3.48907700	1.07414800	0.69390300
O	3.50592000	-0.63463500	-0.95021700
C	3.88386900	-0.25186000	1.35668400
H	2.81332300	1.68132800	1.29636500
H	4.38030500	1.66636100	0.46882200
C	4.33083700	-1.07097500	0.14550200

H	3.01324400	-0.71339000	1.83055100
H	4.66916200	-0.14245300	2.10610700
H	4.19301700	-2.14768100	0.26908500
H	5.38280000	-0.87796200	-0.09867800
C	2.84009100	0.58967800	-0.62336800
H	3.02555000	1.29905600	-1.43688000
S	-3.18746900	-0.12997200	-0.01664300
C	-3.38876800	-0.26212200	1.77946700
H	-3.02825100	0.65665300	2.23984100
H	-4.45743500	-0.38931300	1.95387200
H	-2.83361800	-1.13134500	2.12917700
O	-3.56860900	-1.42418900	-0.59457200
O	-3.84046600	1.11519600	-0.43921400

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