

Continuous activation of phenoxide and CF₃I for multiple trifluoromethylations

*Yusei Nakashima, Shinjiro Kusano, Tsukasa Inishi, Yasuyuki Nitta, Takashi Nishikata**

*Graduate School of Science and Engineering, Yamaguchi University 2-16-1 Tokiwadai,
Ube, Yamaguchi, 755-8611, Japan*

Contents

1. General Information	S2
2. Optimization and Comparison of Reaction Conditions	S4
3. Mechanistic Studies	S6
4. General Procedure	S9
5. References	S19
6. Spectral Charts for Products	S44

1. General Information

All reactions were carried out under nitrogen (99.95%) atmosphere. For TLC analyses precoated Kieselgel 60 F254 plates (Merck, 0.25 mm thick) were used; for column chromatography Silica Flash® P60 (SiliCycle, 40–63 μm) was used. Visualization was accomplished by UV light (254 nm), ^1H , ^{13}C , and ^{19}F NMR spectra were obtained using a JEOL 500 MHz NMR spectrometer. Chemical shifts for ^1H NMR were described in parts per million (chloroform as an internal standard $\delta = 7.26$) in CDCl_3 , unless otherwise noted. Chemical shifts for ^{13}C NMR were expressed in parts per million in CDCl_3 as an internal standard ($\delta = 77.16$), unless otherwise noted. High resolution mass analyses (HRMS) were obtained using an ACQUITY UPLC/TOF-MS for ESI. Infrared spectra were recorded on Agilent Technologies Cary 630 FTIR. Anhydrous solvents were purchased from Kanto Chemical Co., Ltd. Other chemicals were purchased from TCI, Aldrich, and Wako and directly used without further purification. UV-visible absorption spectra were recorded on a JASCO V-750 spectrometer. Fluorescence spectra were recorded on a JASCO FP-8250 fluorescence spectrometer. CF_3I was obtained from Tosoh Finechem corporation.

The light source and the material of the irradiation vessel

Hepatochem EvoluChem™ PhotoRedOx Device, equipped with EvoluChem™ LED 18W light. A cardboard cover was placed over the reactor during reactions. Capable of carrying out up to 8 reactions at one time (4 mL vials).

LED light manufacture: EvoluChem™

Model: EvoluChem LED 18W, P201-18-2 450-455 nm

or EvoluChem LED 30W, HCK1012-01-008 450 nm

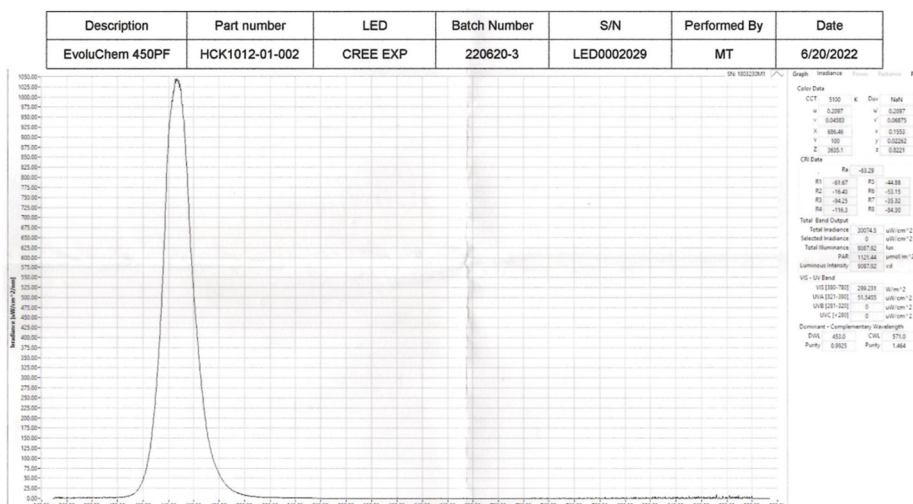


Figure S1. Spectral distribution and intensity

Material of the irradiation vessel: borosilicate reaction vial

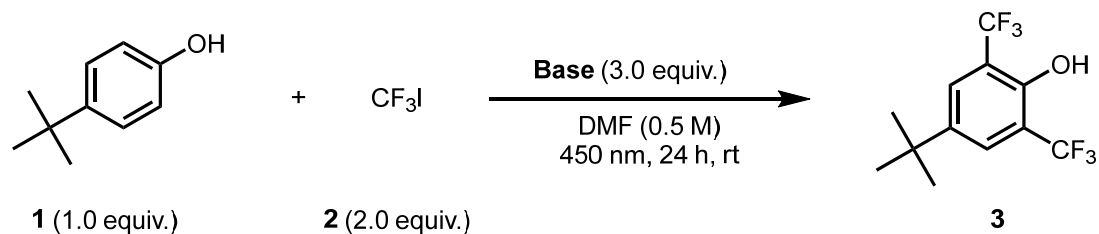
Not use any filters



Figure S2. Photoredox reaction set-up.

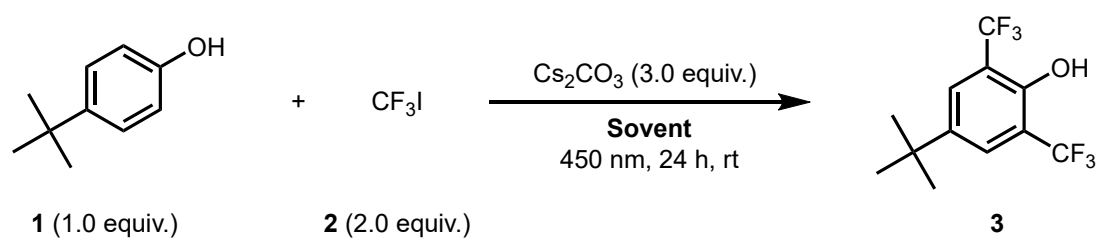
2. Optimization and Comparison of Reaction Conditions

Table S1. Optimization of solvent



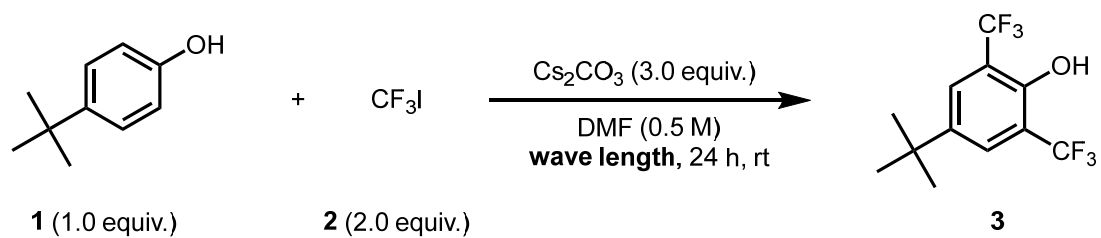
Entry	Base	NMR Yield of 3
1	none	0%
2	Cs_2CO_3	67%
3	Li_2CO_3	0%
4	Na_2CO_3	0%
5	K_2HPO_4	0%
6	<i>t</i> BuOK	27%
7	NEt_3	0%
8	<i>i</i> PrNEt	0%
9	DABCO	20%

Table S2. Optimization of base



Entry	Solvent	NMR Yield of 3
1	DMF	67%
2	DMSO	56%
3	AcOEt	39%
4	Acetone	0%
5	MeCN	34%
6	1,4-dioxane	33%
7	THF	16%

Table S3. Optimization of wave length

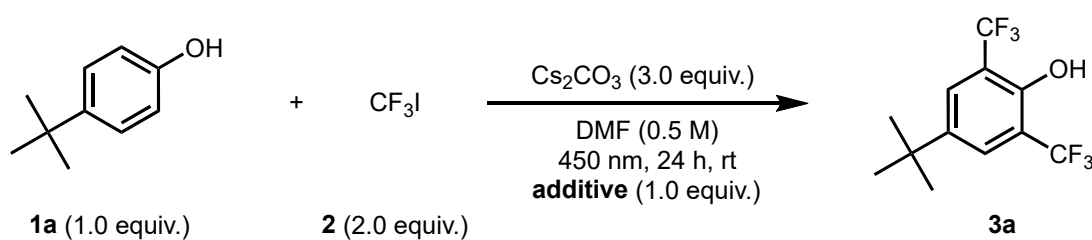


Entry	wave lenght	NMR Yield of 3
1	365 nm	33%
2	405 nm	24%
3	450 nm	67%
4	545 nm	trace
5	w/o light	0%

3. Mechanistic Studies

Radical inhibitor test

An oven-dried 5.0 mL screw-cap vial equipped with a magnetic stir bar was charged with phenol **1a** (75.1 mg, 0.5 mmol, 1.0 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and 1,4-dinitrobenzene (84.1 mg, 0.5 mmol, 1.0 equiv.) as single electron transfer inhibitor or TEMPO (78.1 mg, 0.5 mmol, 1.0 equiv.) or BHT (110.2 mg, 0.5 mmol, 1.0 equiv.) as radical inhibitor. After flashing nitrogen gas (purity 99.95%), CF₃I **2** (1.0 mmol, 2.0 equiv.) was added as DMF solution and dried DMF (1.0 mL) were added into the vial by syringe under nitrogen atmosphere. The reaction mixture was vigorously stirred under irradiation of 18W 450 nm LED at room temperature for 24 h. After this time, the reaction mixture was carefully quenched with 3M HCl aq. at 0°C and extracted with Et₂O. The combined organic layers were filtered through MgSO₄, and then concentrated by rotary evaporation. Yield was determined by ¹⁹F NMR analysis using benzotrifluoride as an internal standard.



Entry	Condition	NMR Yield of 3
1	w BHT	35%
2	w TEMPO	trace
3	w 1,4-Dinitrobenzene	0%

Figure S3. Radical inhibitor test

UV-Vis Experiments

UV-Vis spectra of the individual component were recorded, including substrate CF₃I, 4-tBuPhenol, Cs₂CO₃. All of the samples were prepared as a 10.0 μM solution in glovebox and used freshly for the measurement.

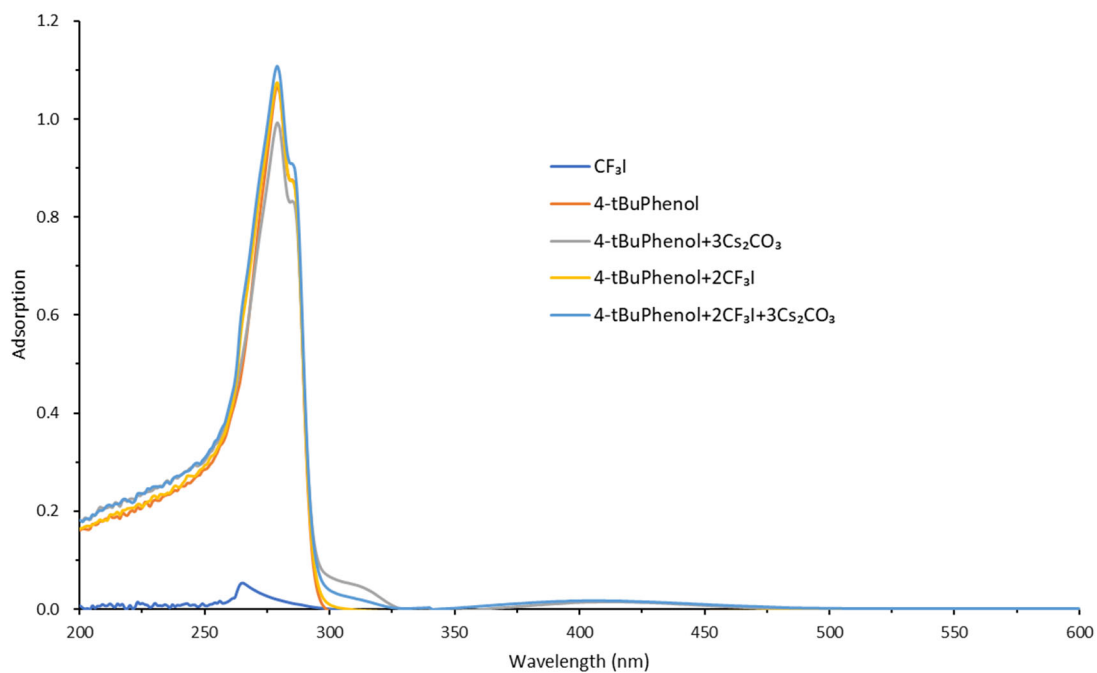


Figure S4. UV-Vis spectra of the related component recorded in DMF

Luminescence quenching experiment

All **1a** + Cs_2CO_3 solutions were excited at 410 nm and the emission intensity at 481 nm was observed. In a typical experiment, the DMF solution of **1a** + Cs_2CO_3 was added the appropriate amount of quencher, CF_3I (**2**) in a 1.0 cm quartz cuvette. After preparing the solution, the emission spectra of the samples were collected.

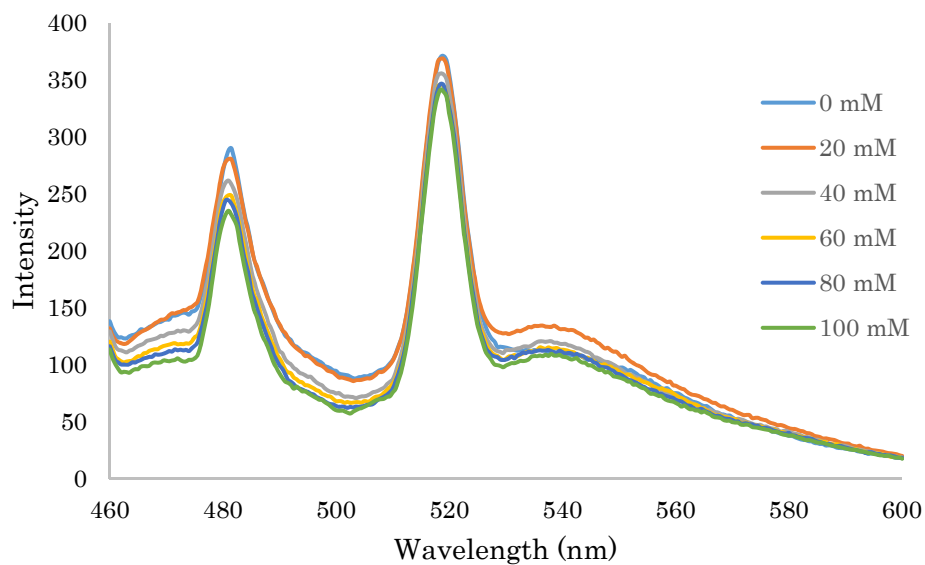


Figure S5. Luminescence spectral changes of **1a** + Cs_2CO_3 ($1.0 \times 10^{-3} \text{ M}$, $\lambda_{\text{ex}} = 410 \text{ nm}$) upon the addition of CF_3I (**2**) as quencher in degassed DMF.

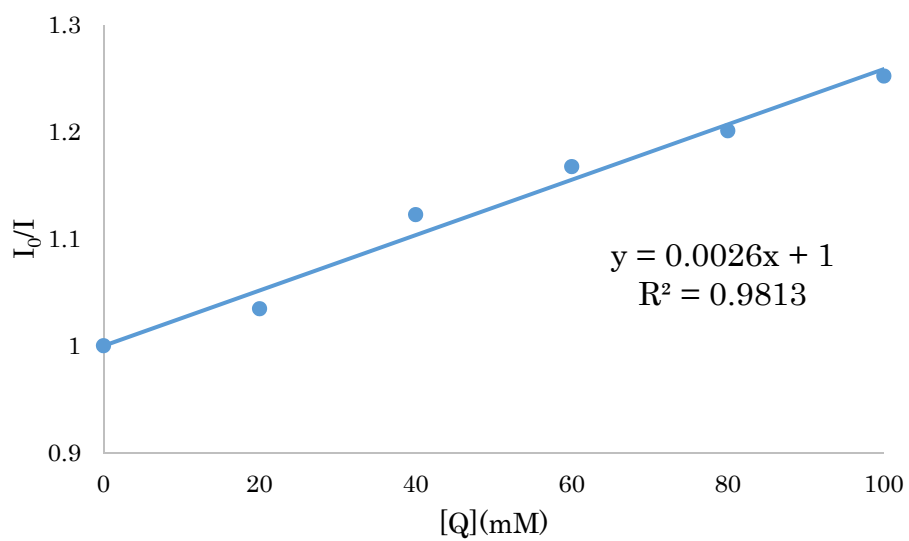


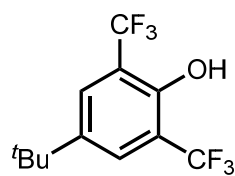
Figure S6. Stern-Volmer plot.

4. General procedure

General procedure for the synthesis of **3**

An oven-dried 5.0 mL screw-cap vial equipped with magnetic stir bar was charged with corresponding phenol **1** (0.5 mmol, 1.0 equiv.) and Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.). After flashing nitrogen gas (purity 99.95%), CF₃I **2** (1.0 mmol, 2.0 equiv.) was added as DMF solution and dried DMF (1.0 mL) were added into the vial by syringe under nitrogen atmosphere. The reaction mixture was vigorously stirred under irradiation of 18W 450 nm LED at room temperature for 24 h. After this time, the reaction mixture was carefully quenched with 3M HCl aq. at 0°C and extracted with Et₂O. The combined organic layers were filtered through MgSO₄, and then concentrated by rotary evaporation. Yield was determined by ¹⁹F NMR analysis using benzotrifluoride as an internal standard. After the mixture was concentrated by evaporation, the residue was purified by flash chromatography, eluting hexane/EtOAc to afford the product **3**.

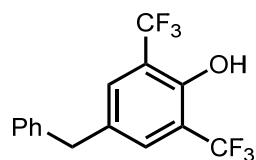
4-(tert-butyl)phenol (**3a**)¹



3a

Following the general procedure above, using phenol **1a** (75.1 mg, 0.5 mmol, 1.0 equiv.), CF₃I (1.0 mmol, 2.0 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3a** (88.7 mg, 62%); ¹H NMR (CDCl₃) δ: 1.33 (s, 9H), 5.90 (brs, 1H), 7.70 (s, 2H). ¹³C NMR (CDCl₃) δ: 31.2, 34.6, 118.3 (q, *J* = 30.3 Hz), 123.9 (q, *J* = 273.2 Hz), 127.7 (q, *J* = 4.6 Hz), 144.0, 149.6. ¹⁹F NMR (CDCl₃) δ: -60.7.

4-benzyl-2,6-bis(trifluoromethyl)phenol (**3b**)

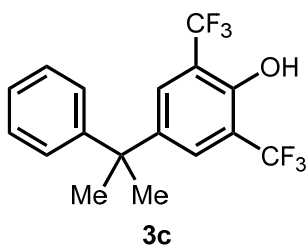


3b

Following the general procedure above, using phenol **1b** (92.1 mg, 0.5 mmol, 1.0 equiv.), CF₃I (1.0 mmol, 2.0 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3b** (67.2 mg, 42%); ¹H NMR (CDCl₃) δ: 3.98 (s, 2H), 5.92 (brs, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.24-7.27 (m, 1H), 7.33 (t, *J* = 8.0

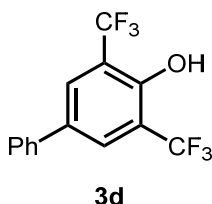
Hz, 2H), 7.53 (s, 2H). ^{13}C NMR (CDCl_3) δ : 40.8, 118.9 (q, $J = 30.7$ Hz), 123.5 (q, $J = 272.9$ Hz), 126.9, 128.8, 129.0, 131.0 (d, $J = 4.5$ Hz), 134.0, 139.5, 150.3. ^{19}F NMR (CDCl_3) δ : -60.9; HRMS (TOF-MS) calcd. for $\text{C}_{15}\text{H}_9\text{F}_6\text{O}$ (M-H^+): 319.0558; found 319.0557

4-(2-phenylpropan-2-yl)-2,6-bis(trifluoromethyl)phenol (**3c**)



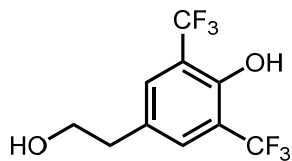
Following the general procedure above, using phenol **1c** (106.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (1.0 mmol, 2.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3c** (85.3 mg, 49%); IR (neat) ν 3618, 2973, 1613, 1490, 1363, 1271, 1111 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.69 (s, 6H), 5.92 (brs, 1H), 7.17 (d, $J = 7.5$ Hz, 2H), 7.22 (t, $J = 6.8$ Hz, 1H), 7.30 (t, $J = 7.6$ Hz, 2H), 7.55 (s, 2H). ^{13}C NMR (CDCl_3) δ : 30.8, 42.8, 118.3 (q, $J = 30.4$ Hz), 123.6 (q, $J = 273.1$ Hz), 126.5, 126.7, 128.6, 129.1 (d, $J = 4.4$ Hz), 143.7, 148.9, 149.8. ^{19}F NMR (CDCl_3) δ : -60.7; HRMS (TOF-MS) calcd. for $\text{C}_{17}\text{H}_{13}\text{F}_6\text{O}$ (M-H^+): 347.0871; found 347.0873

3,5-bis(trifluoromethyl)-[1,1'-biphenyl]-4-ol (**3d**)



Following the general procedure above, using phenol **1d** (153.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (2.0 mmol, 4.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3d** (81.1 mg, 53%); IR (neat) ν 3540, 1610, 1478, 1260, 1118 cm^{-1} ; ^1H NMR (CDCl_3) δ : 6.07 (brs, 1H), 7.41 (t, $J = 7.8$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 2H), 7.54 (d, $J = 8.0$ Hz, 2H), 7.92 (s, 2H). ^{13}C NMR (CDCl_3) δ : 119.2 (q, $J = 30.9$ Hz), 123.5 (q, $J = 272.8$ Hz), 126.9(m), 127.0, 128.4(m), 129.3(m), 134.3, 138.1, 151.0; ^{19}F NMR (CDCl_3) δ : -60.9; HRMS (TOF-MS) calcd. for $\text{C}_{14}\text{H}_7\text{F}_6\text{O}$ (M-H^+): 305.0401; found 305.0404

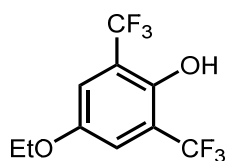
4-(2-hydroxyethyl)-2,6-bis(trifluoromethyl)phenol (**3e**)



3e

Following the general procedure above, using phenol **1e** (69.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (1.0 mmol, 2.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3e** (43.9 mg, 32%); IR (neat) ν 3454, 2960, 2904, 1606, 1492, 1280, 1113 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.41 (t, $J = 5.2$ Hz, 1H), 2.88 (t, $J = 6.3$ Hz, 2H), 3.89 (q, $J = 5.7$ Hz, 2H), 5.96 (brs, 1H), 7.60 (s, 2H). ^{13}C NMR (DMSO-d_6) δ : 37.2, 61.4, 120.2 (q, $J = 29.7$ Hz), 123.5 (q, $J = 273.7$ Hz), 131.2 (d, $J = 3.9$ Hz), 132.5, 151.1. ^{19}F NMR (CDCl_3) δ : -60.9.; HRMS (TOF-MS) calcd. for $\text{C}_{10}\text{H}_7\text{F}_6\text{O}_2$ (M-H^+): 273.0350; found 273.0353

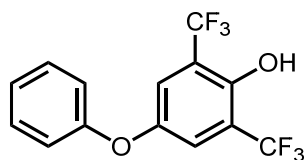
4-ethoxy-2,6-bis(trifluoromethyl)phenol (**3f**)



3f

Following the general procedure above, using phenol **1f** (69.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (1.0 mmol, 2.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3f** (46.6 mg, 34%); IR (neat) ν 3625, 2987, 1612, 1477, 1355, 1260, 1111 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.42 (t, $J = 7.0$ Hz, 3H), 4.03 (q, $J = 7.0$ Hz, 2H), 5.60 (brs, 1H), 7.23 (s, 2H). ^{13}C NMR (CDCl_3) δ : 14.7, 64.8, 116.7 (d, $J = 4.9$ Hz), 119.7 (q, $J = 31.0$ Hz), 123.2 (q, $J = 273.0$ Hz), 145.2, 152.2; ^{19}F NMR (CDCl_3) δ : -61.2.; HRMS (TOF-MS) calcd. for $\text{C}_{10}\text{H}_7\text{F}_6\text{O}_2$ (M-H^+): 273.0350; found 273.0350

4-phenoxy-2,6-bis(trifluoromethyl)phenol (**3g**)

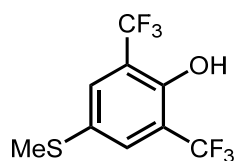


3g

Following the general procedure above, using phenol **1g** (93.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (2.0 mmol, 4.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of

18W 450 nm LED at room temperature for 24 h, yielded the product **3g** (88.6 mg, 55%); IR (neat) ν 3620, 3071, 1592, 1479, 1361, 1115 cm^{-1} ; ^1H NMR (CDCl_3) δ : 5.83 (brs, 1H), 6.98 (d, $J = 8.0$ Hz, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 7.37-7.40 (m, 4H). ^{13}C NMR (CDCl_3) δ : 118.8, 120.0 (q, $J = 31.2$ Hz), 121.1 (q, $J = 4.8$ Hz), 123.0 (q, $J = 272.2$ Hz), 124.4, 130.3, 147.3, 150.2, 156.5. ^{19}F NMR (CDCl_3) δ : -61.2.; HRMS (TOF-MS) calcd. for $\text{C}_{14}\text{H}_7\text{F}_6\text{O}_2$ (M-H^+): 321.0350; found 321.0351

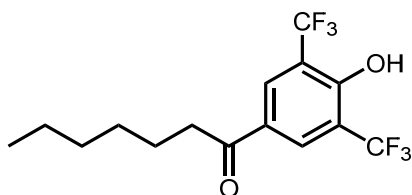
4-(methylthio)-2,6-bis(trifluoromethyl)phenol (**3h**)



3h

Following the general procedure above, using phenol **1h** (70.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (1.0 mmol, 2.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3h** (55.2 mg, 40%); IR (neat) ν 3524, 1596, 1475, 1347, 1264, 1105 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.51 (s, 3H), 5.95 (brs, 1H), 7.62 (s, 2H). ^{13}C NMR (CDCl_3) δ : 17.2, 119.6 (q, $J = 30.9$ Hz), 123.1 (q, $J = 273.1$ Hz), 129.9 (d, $J = 4.3$ Hz), 131.0, 149.7. ^{19}F NMR (CDCl_3) δ : -61.1; HRMS (TOF-MS) calcd. for $\text{C}_9\text{H}_5\text{F}_6\text{OS}$ (M-H^+): 274.9965; found 274.9967

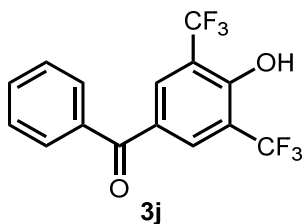
1-(4-hydroxy-3,5-bis(trifluoromethyl)phenyl)heptan-1-one (**3i**)



3i

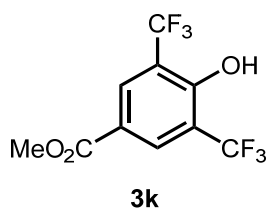
Following the general procedure above, using phenol **1i** (103.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (1.0 mmol, 2.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3i** (80.4 mg, 47%); IR (neat) ν 3242, 2932, 2963, 1682, 1594, 1493, 1238, 1109 cm^{-1} ; ^1H NMR (CDCl_3) δ : 0.90 (t, $J = 7.0$ Hz, 3H), 1.31-1.40 (m, 6H), 1.74 (quint, $J = 7.5$ Hz, 2H), 2.94 (t, $J = 7.3$ Hz, 2H), 8.34 (s, 2H). ^{13}C NMR (CDCl_3) δ : 14.1, 22.6, 24.1, 29.0, 31.7, 38.4, 119.1 (q, $J = 31.6$ Hz), 123.0 (q, $J = 273.5$ Hz), 129.7, 131.0 (d, $J = 4.9$ Hz), 155.4, 197.2. ^{19}F NMR (CDCl_3) δ : -61.1.; HRMS (TOF-MS) calcd. for $\text{C}_{15}\text{H}_{15}\text{F}_6\text{O}_2$ (M-H^+): 341.0976; found 341.0978

(4-hydroxy-3,5-bis(trifluoromethyl)phenyl)(phenyl)methanone (**3j**)



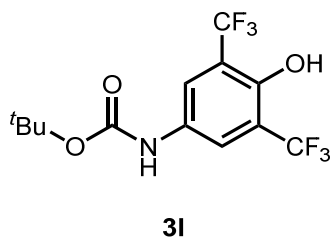
Following the general procedure above, using phenol **1j** (167.1 mg, 0.5 mmol, 1.0 equiv.), CF₃I (2.0 mmol, 4.0 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3j** (61.8 mg, 37%); IR (neat) ν 3164, 1488, 1254, 1116, 930 cm⁻¹; ¹H NMR (CDCl₃) δ : 6.74 (brs, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.66 (t, J = 7.7 Hz, 1H), 7.75 (d, J = 7.1 Hz, 2H), 8.24 (s, 2H). ¹³C NMR (CDCl₃) δ : 119.0 (q, J = 31.7 Hz), 123.0 (q, J = 273.2 Hz), 128.9, 129.9, 130.1, 133.0 (q, J = 4.8 Hz), 133.3, 136.5, 155.1, 193.3. ¹⁹F NMR (CDCl₃) δ : -61.1; HRMS (TOF-MS) calcd. for C₁₅H₇F₆O₂ (M-H⁺): 333.0350; found 333.0353

Methyl 4-hydroxy-3,5-bis(trifluoromethyl)benzoate (**3k**)



Following the general procedure above, using phenol **1k** (76.1 mg, 0.5 mmol, 1.0 equiv.), CF₃I (1.0 mmol, 2.0 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3k** (69.2 mg, 48%); IR (neat) ν 3349, 2965, 1708, 1603, 1440, 1264, 1100 cm⁻¹; ¹H NMR (CDCl₃) δ : 3.96 (s, 3H), 6.48 (brs, 1H), 8.43 (s, 2H). ¹³C NMR (CDCl₃) δ : 52.9, 119.0 (q, J = 32.0 Hz), 122.9 (d, J = 819.2 Hz), 122.9 (t, J = 137.5 Hz), 132.6, 155.5, 164.7. ¹⁹F NMR (CDCl₃) δ : -61.1; HRMS (TOF-MS) calcd. for C₁₀H₅F₆O₃ (M-H⁺): 287.0143; found 287.0143

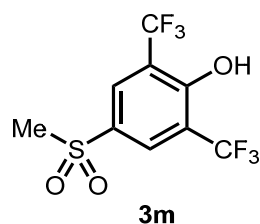
tert-butyl (4-hydroxy-3,5-bis(trifluoromethyl)phenyl)carbamate (**3l**)



Following the general procedure above, using phenol **1l** (104.6 mg, 0.5 mmol, 1.0 equiv.), CF₃I (1.0

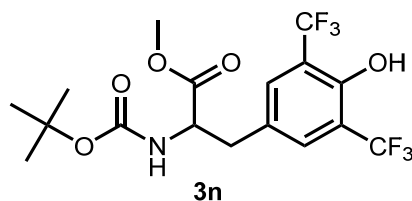
mmol, 2.0 equiv.), 4CzIPN (19.7 mg, 0.025 mmol, 0.05 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 5 h, yielded the product **3l** (69.0 mg, 40%); IR (neat) ν 3611, 3302, 3115, 2981, 1692, 1565, 1493, 1141, 1108 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.52 (s, 9H), 5.79 (brs, 1H), 6.50 (brs, 1H), 7.76 (s, 2H). ¹³C NMR (CDCl₃) δ : 28.3, 81.7, 119.4 (q, J = 31.1 Hz), 121.1, 123.2 (q, J = 272.9 Hz), 131.7, 147.1, 152.7. ¹⁹F NMR (CDCl₃) δ : -61.1.; HRMS (TOF-MS) calcd. for C₁₃H₁₂F₆NO₃ (M-H⁺): 344.0721; found 344.0724

4-(methylsulfonyl)-2,6-bis(trifluoromethyl)phenol (**3m**)



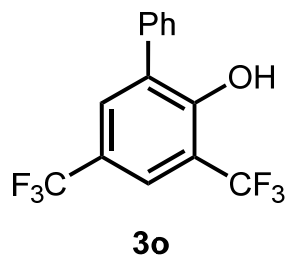
Following the general procedure above, using phenol **1m** (86.1 mg, 0.5 mmol, 1.0 equiv.), CF₃I (2.0 mmol, 4.0 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3m** (95.5 mg, 62%); IR (neat) ν 3417, 3107, 2934, 1604, 1481, 1252, 1102 cm⁻¹; ¹H NMR (CDCl₃) δ : 3.12 (s, 3H), 8.33 (s, 2H). ¹³C NMR (DMSO-d₆) δ : 43.6, 120.2 (q, J = 30.6 Hz), 122.8 (q, J = 273.1 Hz), 130.7, 130.8, 158.4; ¹⁹F NMR (CDCl₃) δ : -61.3.; HRMS (TOF-MS) calcd. for C₉H₅F₆O₃S (M-H⁺): 306.9864; found 306.9865

methyl 2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy-3,5-bis(trifluoromethyl)phenyl)propanoate (**3n**)



Following the general procedure above, using phenol **1n** (147.7 mg, 0.5 mmol, 1.0 equiv.), CF₃I (1.0 mmol, 2.0 equiv.), Cs₂CO₃ (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3n** (64.7 mg, 30%); IR (neat) ν 3350, 2982, 1686, 1491, 1252, 1114 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.41 (s, 9H), 3.03 (dd, J = 5.9 and 14.3 Hz, 1H), 3.21 (dd, J = 5.6 and 14.0 Hz, 1H), 3.74 (s, 3H), 4.57 (q, J = 6.7 Hz, 1H), 5.12 (d, J = 7.6 Hz, 1H), 6.52 (brs, 1H), 7.46 (s, 2H). ¹³C NMR (CDCl₃) δ : 28.3, 37.2, 52.6, 54.3, 80.6, 119.0 (q, J = 30.8 Hz), 123.3 (q, J = 273.3 Hz), 128.8, 131.7, 151.1, 155.1, 171.8. ¹⁹F NMR (CDCl₃) δ : -60.9.; HRMS (TOF-MS) calcd. for C₁₇H₁₈F₆NO₅ (M-H⁺): 430.1089; found 430.1091

3,5-bis(trifluoromethyl)-[1,1'-biphenyl]-2-ol (**3o**)



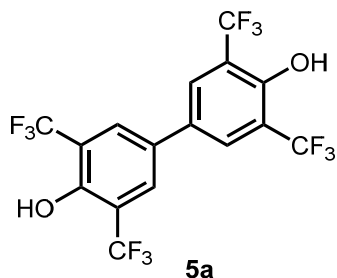
Following the general procedure above, using phenol **1o** (85 mg, 0.5 mmol, 1.0 equiv.), CF_3I (1.0 mmol, 2.0 equiv.), Cs_2CO_3 (488.7 mg, 1.5 mmol, 3.0 equiv.) and DMF (1.0 mL) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **3o** (101 mg, 66%); IR (neat) ν 3530, 1375, 1269, 1118, 1059, 905, 777, 702, 668 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.06 (s, 1H), 7.47-7.45 (m, 2H), 7.52 (t, $J = 7.39$ Hz, 1H), 7.58 (t, $J = 7.31$ Hz, 2H), 7.69 (s, 1H), 7.84 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 117.9 (q, $J = 32.1$ Hz), 123.0 (q, $J = 33.8$ Hz), 123.7 (q, $J = 271.6$ Hz), 123.2 (q, $J = 272.9$ Hz), 124.3-124.1(m), 129.2, 129.7, 130.2, 130.7, 130.9 (q, $J = 3.3$ Hz), 133.8, 153.5; ^{19}F NMR (470 MHz, CDCl_3) δ -61.7 (s), -62.5 (s); HRMS (TOF-MS) calcd. for $\text{C}_{14}\text{H}_7\text{F}_6\text{O}$ ($\text{M}-\text{H}^+$): 305.0401; found 305.0402

General procedure for the synthesis of **5**

An oven-dried 5.0 mL screw-cap vial equipped with magnetic stir bar was charged with corresponding phenol **4** (0.5 mmol, 1.0 equiv.) and Cs₂CO₃ (977.4 mg, 3.0 mmol, 6.0 equiv.). After flashing nitrogen gas (purity 99.95%), CF₃I **2** (7.0 mmol, 14.0 equiv.) was added as DMF solution and dried DMF were added into the vial by syringe under nitrogen atmosphere. The reaction mixture was vigorously stirred under irradiation of 18W 450 nm LED at room temperature for 24 h.

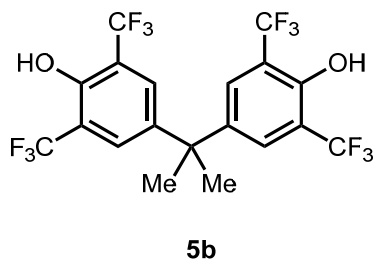
After this time, the reaction mixture was carefully quenched with 3M HCl aq. at 0°C and extracted with Et₂O. The combined organic layers were filtered through MgSO₄, and then concentrated by rotary evaporation. Yield was determined by ¹⁹F NMR analysis using benzotrifluoride as an internal standard. After the mixture was concentrated by evaporation, the residue was purified by flash chromatography, eluting hexane/EtOAc to afford the product **5**.

3,3',5,5'-tetrakis(trifluoromethyl)-[1,1'-biphenyl]-4,4'-diol (**5a**)



Following the general procedure above, using bisphenol **4a** (93.1 mg, 0.5 mmol, 1.0 equiv.), CF₃I (7.0 mmol, 14.0 equiv.), and Cs₂CO₃ (977.4 mg, 3.0 mmol, 6.0 equiv.) under irradiation of 30W 450 nm LED at room temperature for 24 h, yielded the product **5a** (68.7 mg, 30%); IR (neat) ν 3601, 3557, 1624, 1478, 1343, 1255, 1130, 1085 cm⁻¹; ¹H NMR (CDCl₃) δ : 6.20 (brs, 2H), 7.85 (s, 4H). ¹³C NMR (DMSO-d₆) δ : 120.7 (q, J = 30.0 Hz), 123.3 (q, J = 273.0 Hz), 129.6 (d, J = 14.8 Hz), 129.9, 152.8. ¹⁹F NMR (CDCl₃) δ : -61.0.; HRMS (TOF-MS) calcd. for C₁₆H₅F₁₂O₂ (M-H⁺): 457.0098; found 457.0100

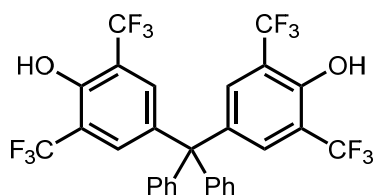
4,4'-(propane-2,2-diyl)bis(2,6-bis(trifluoromethyl)phenol) (**5b**)



Following the general procedure above, using bisphenol **4b** (114.1 mg, 0.5 mmol, 1.0 equiv.), CF₃I (7.0 mmol, 14.0 equiv.), and Cs₂CO₃ (977.4 mg, 3.0 mmol, 6.0 equiv.) under irradiation of 18W 450

nm LED at room temperature for 24 h, yielded the product **5b** (135.1 mg, 54%); IR (neat) ν 3607, 2989, 1614, 1487, 1362, 1264, 1167, 1087 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.70 (s, 6H), 6.04 (brs, 1H), 7.51 (s, 4H). ^{13}C NMR (DMSO-d_6) δ : 30.2, 42.4, 120.6 (q, $J = 29.3$ Hz), 123.7 (q, $J = 272.8$ Hz), 129.3, 141.7, 151.8; ^{19}F NMR (CDCl_3) δ : -60.8.; HRMS (TOF-MS) calcd. for $\text{C}_{19}\text{H}_{11}\text{F}_{12}\text{O}_2$ (M-H^+): 499.0567; found 499.0570

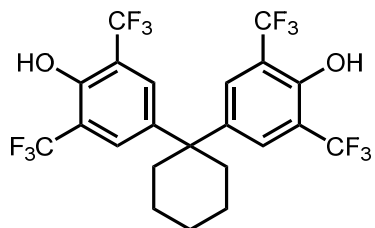
4,4'-(diphenylmethylene)bis(2,6-bis(trifluoromethyl)phenol) (**5c**)



5c

Following the general procedure above, using bisphenol **4c** (176.2 mg, 0.5 mmol, 1.0 equiv.), CF_3I (10.0 mmol, 20.0 equiv.), and Cs_2CO_3 (1466.1 mg, 4.5 mmol, 9.0 equiv.) under irradiation of 30W 450 nm LED at room temperature for 24 h, yielded the product **5c** (156.1 mg, 50%); IR (neat) ν 3609, 3561, 2362, 1616, 1488, 1263, 1104 cm^{-1} ; ^1H NMR (CDCl_3) δ : 6.11 (brs, 2H), 7.07 (d, $J = 7.9$ Hz, 4H), 7.28-7.38 (m, 6H), 7.53 (s, 4H). ^{13}C NMR (DMSO-d_6) δ : 63.0, 119.8 (q, $J = 29.7$ Hz), 123.1 (q, $J = 271.7$ Hz), 127.1, 128.6, 130.1, 132.1, 137.3, 144.5, 151.7. ^{19}F NMR (CDCl_3) δ : -60.9.; HRMS (TOF-MS) calcd. for $\text{C}_{29}\text{H}_{15}\text{F}_{12}\text{O}_2$ (M-H^+): 623.0880; found 623.0882

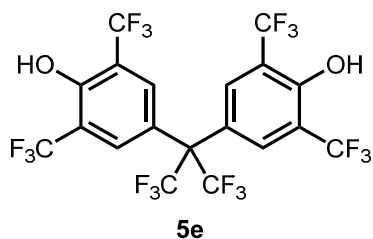
4,4'-(cyclohexane-1,1-diyl)bis(2,6-bis(trifluoromethyl)phenol) (**5d**)



5d

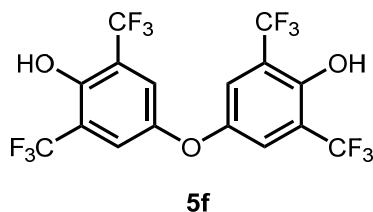
Following the general procedure above, using bisphenol **4d** (134.2 mg, 0.5 mmol, 1.0 equiv.), CF_3I (7.0 mmol, 14.0 equiv.), and Cs_2CO_3 (977.4 mg, 3.0 mmol, 6.0 equiv.) under irradiation of 30W 450 nm LED at room temperature for 24 h, yielded the product **5d** (132.4 mg, 49%); IR (neat) ν 3319, 2935, 2864, 1616, 1492, 1289, 1249, 1165, 1113 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.54 (brs, 6H), 2.25 (brs, 4H), 6.00 (brs, 1H), 7.55 (s, 4H). ^{13}C NMR (DMSO-d_6) δ : 22.2, 25.2, 35.7, 45.0, 120.4 (q, $J = 29.8$ Hz), 123.3 (q, $J = 273.4$ Hz), 129.2, 139.2, 151.2. ^{19}F NMR (CDCl_3) δ : -60.8.; HRMS (TOF-MS) calcd. for $\text{C}_{22}\text{H}_{15}\text{F}_{12}\text{O}_2$ (M-H^+): 539.0880; found 539.0883

4,4'-(perfluoropropane-2,2-diyl)bis(2,6-bis(trifluoromethyl)phenol) (**5e**)



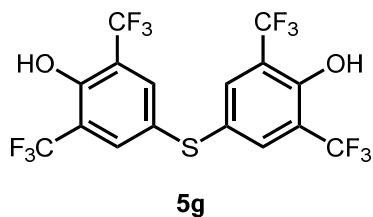
Following the general procedure above, using bisphenol **4e** (168.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (7.0 mmol, 14.0 equiv.), and Cs_2CO_3 (977.4 mg, 3.0 mmol, 6.0 equiv.) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **5e** (170.3 mg, 56%); IR (neat) ν 3620, 1497, 1278, 1259, 1100, 904 cm^{-1} ; ^1H NMR (CDCl_3) δ : 6.44 (brs, 2H), 7.69 (s, 4H). ^{13}C NMR (DMSO-d_6) δ : 62.8 (quint, $J = 26.5$ Hz), 120.6 (q, $J = 30.5$ Hz), 121.7, 122.7 (q, $J = 272.7$ Hz), 123.3 (q, $J = 287.5$ Hz), 131.7, 155.0. ^{19}F NMR (CDCl_3) δ : -61.2, -64.1.; HRMS (TOF-MS) calcd. for $\text{C}_{19}\text{H}_5\text{F}_{18}\text{O}_2$ (M-H^+): 607.0002; found 607.0003

4,4'-oxybis(2,6-bis(trifluoromethyl)phenol) (**5f**)



Following the general procedure above, using bisphenol **4f** (101.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (10.0 mmol, 20.0 equiv.), and Cs_2CO_3 (1466.1 mg, 4.5 mmol, 9.0 equiv.) under irradiation of 30W 450 nm LED at room temperature for 24 h, yielded the product **5f** (71.1 mg, 30%); IR (neat) ν 3604, 3098, 1616, 1478, 1353, 1258, 1101 cm^{-1} ; ^1H NMR (CDCl_3) δ : 5.95 (brs, 2H), 7.37 (s, 4H). ^{13}C NMR (DMSO-d_6) δ : 122.1 (q, $J = 29.7$ Hz), 122.8 (q, $J = 273.1$ Hz), 148.9, 149.4. ^{19}F NMR (CDCl_3) δ : -61.3.; HRMS (TOF-MS) calcd. for $\text{C}_{16}\text{H}_5\text{F}_{12}\text{O}_3$ (M-H^+): 473.0047; found 473.0049

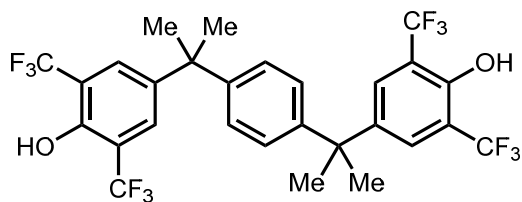
4,4'-thiobis(2,6-bis(trifluoromethyl)phenol) (**5g**)



Following the general procedure above, using bisphenol **4g** (109.1 mg, 0.5 mmol, 1.0 equiv.), CF_3I (7.0 mmol, 14.0 equiv.), and Cs_2CO_3 (977.4 mg, 3.0 mmol, 6.0 equiv.) under irradiation of 30W 450

nm LED at room temperature for 24 h, yielded the product **5g** (68.6 mg, 28%); IR (neat) ν 3552, 3098, 1605, 1474, 1344, 1294, 1253, 1094 cm^{-1} ; ^1H NMR (CDCl_3) δ : 6.18 (brs, 2H), 7.72 (s, 4H). ^{13}C NMR (DMSO-d_6) δ : 121.8 (q, $J = 30.4$ Hz), 123.2 (q, $J = 273.6$ Hz), 125.9, 134.6, 153.7; ^{19}F NMR (CDCl_3) δ : -61.2.; HRMS (TOF-MS) calcd. for $\text{C}_{16}\text{H}_5\text{F}_{12}\text{O}_2\text{S}$ (M-H^+): 488.9819; found 488.9821

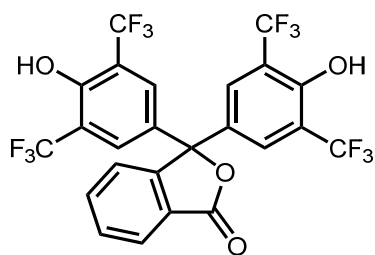
4,4'-(1,4-phenylenebis(propane-2,2-diyl))bis(2,6-bis(trifluoromethyl)phenol) (**5h**)



5h

Following the general procedure above, using bisphenol **4h** (173.2 mg, 0.5 mmol, 1.0 equiv.), CF_3I (7.0 mmol, 14.0 equiv.), and Cs_2CO_3 (977.4 mg, 3.0 mmol, 6.0 equiv.) under irradiation of 30W 450 nm LED at room temperature for 24 h, yielded the product **5h** (157.7 mg, 51%); IR (neat) ν 3625, 2974, 1710, 1615, 1490, 1364, 1260, 1098 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.68 (s, 12H), 5.92 (brs, 2H), 7.11 (s, 4H), 7.52 (s, 4H). ^{13}C NMR (DMSO-d_6) δ : 29.9, 41.8, 120.0 (q, $J = 29.4$ Hz), 123 (q, $J = 272.8$ Hz), 126.5, 128.5, 142.8, 146.6, 150.9. ^{19}F NMR (CDCl_3) δ : -61.6.; HRMS (TOF-MS) calcd. for $\text{C}_{28}\text{H}_{21}\text{F}_{12}\text{O}_2$ (M-H^+): 617.1350; found 617.1349

3,3-bis(4-hydroxy-3,5-bis(trifluoromethyl)phenyl)isobenzofuran-1(3H)-one (**5i**)



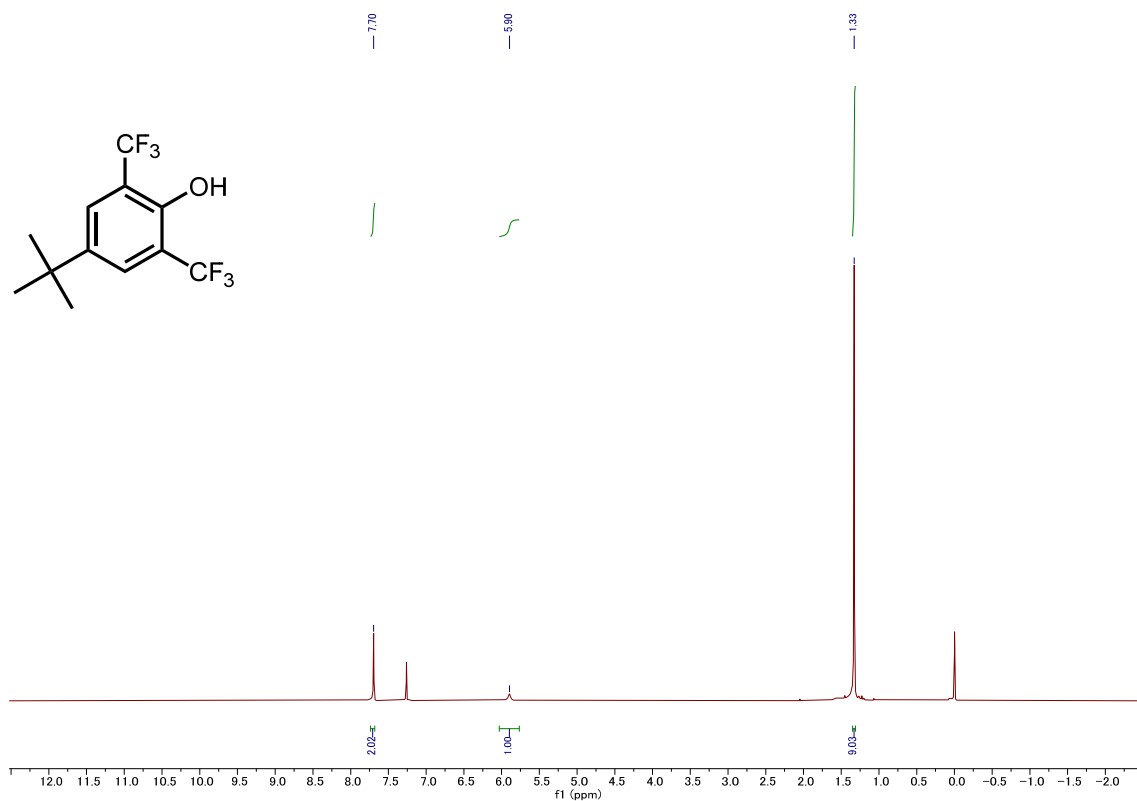
5i

Following the general procedure above, using bisphenol **4i** (159.2 mg, 0.5 mmol, 1.0 equiv.), CF_3I (7.0 mmol, 14.0 equiv.), and Cs_2CO_3 (977.4 mg, 3.0 mmol, 6.0 equiv.) under irradiation of 18W 450 nm LED at room temperature for 24 h, yielded the product **5i** (156.4 mg, 53%); IR (neat) ν 3585, 3236, 1750, 1488, 1366, 1261, 1108 cm^{-1} ; ^1H NMR (DMSO-d_6) δ : 7.69 (t, $J = 7.3$ Hz, 1H), 7.73 (s, 4H), 7.89-7.93 (m, 2H), 8.14 (d, $J = 7.9$ Hz, 1H). ^{13}C NMR (DMSO-d_6) δ : 88.8, 120.6 (q, $J = 30.4$ Hz), 123.0 (q, $J = 274.3$ Hz), 124.5, 124.6, 126.3, 129.5 (d, $J = 4.6$ Hz), 130.7, 131.5, 135.7, 149.9, 154.1, 168.1. ^{19}F NMR (CDCl_3) δ : -61.1.; HRMS (TOF-MS) calcd. for $\text{C}_{24}\text{H}_9\text{F}_{12}\text{O}_4$ (M-H^+): 589.0309; found 589.0309

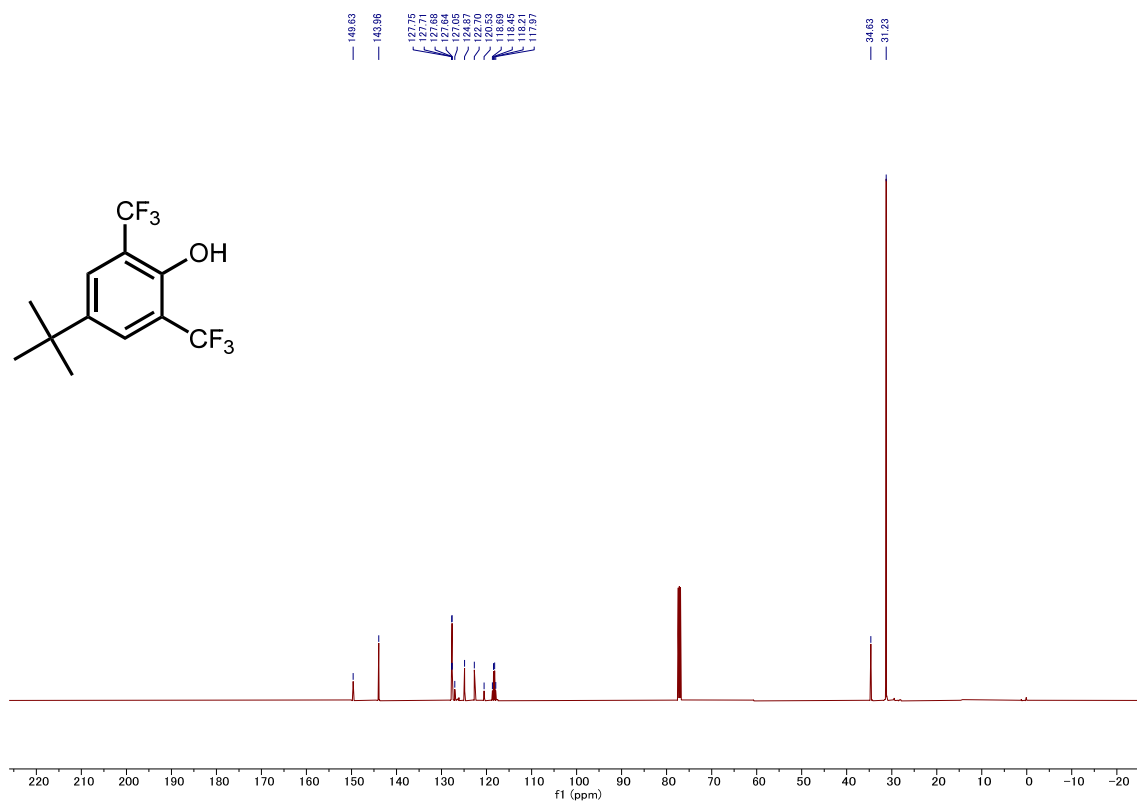
References

- (1) Umemoto, T.; Ando, A. *Bull. Chem. Soc. Jpn*, **1986**, *59*, 447–452.

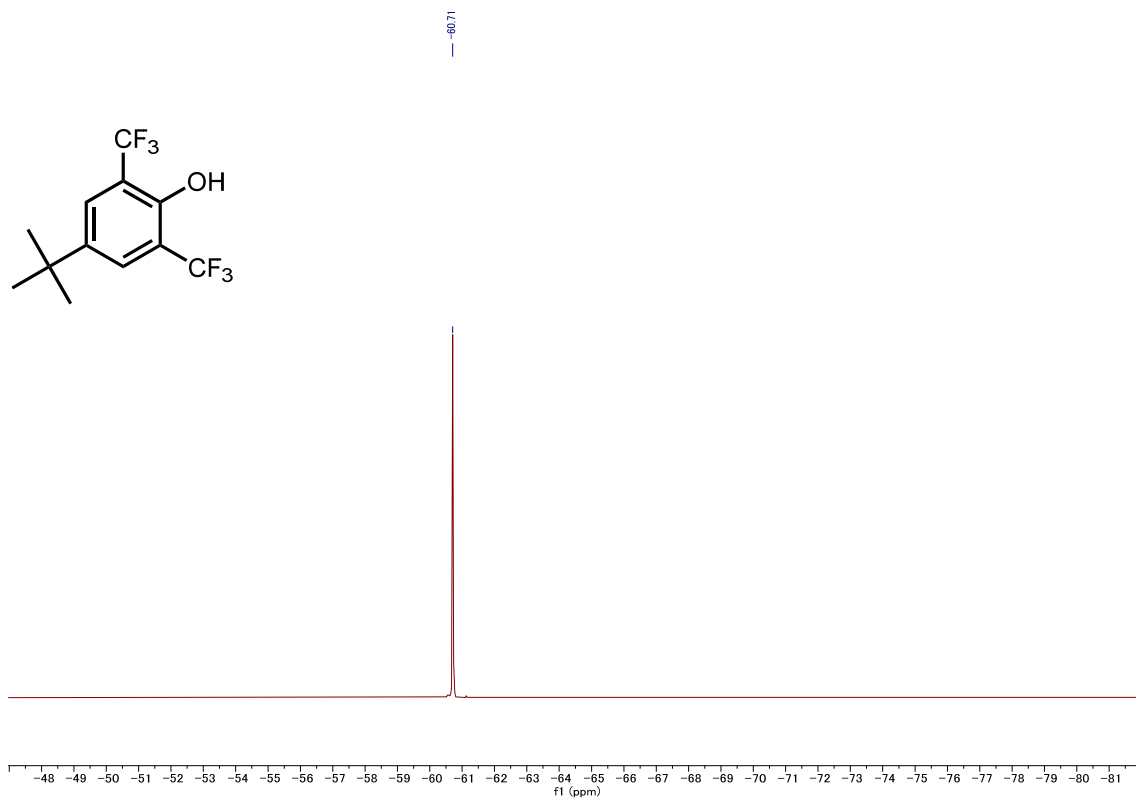
¹H NMR (500 MHz, CDCl₃)



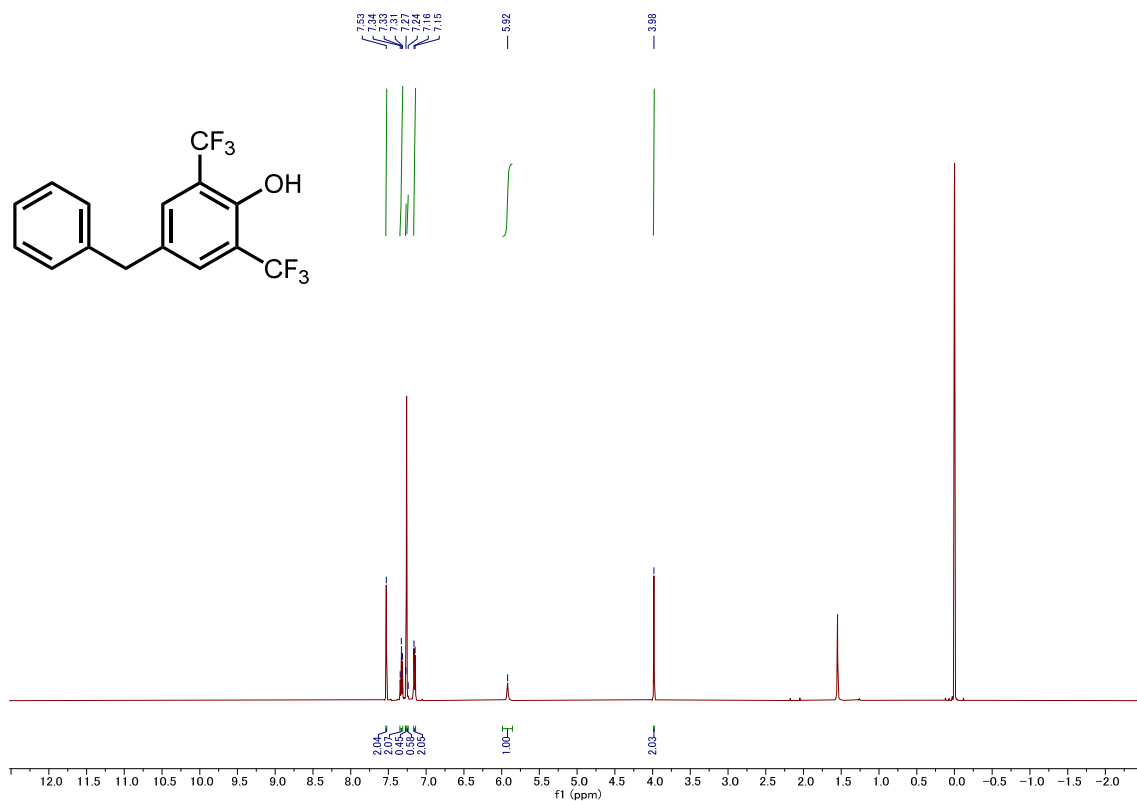
¹³C NMR (125 MHz, CDCl₃)



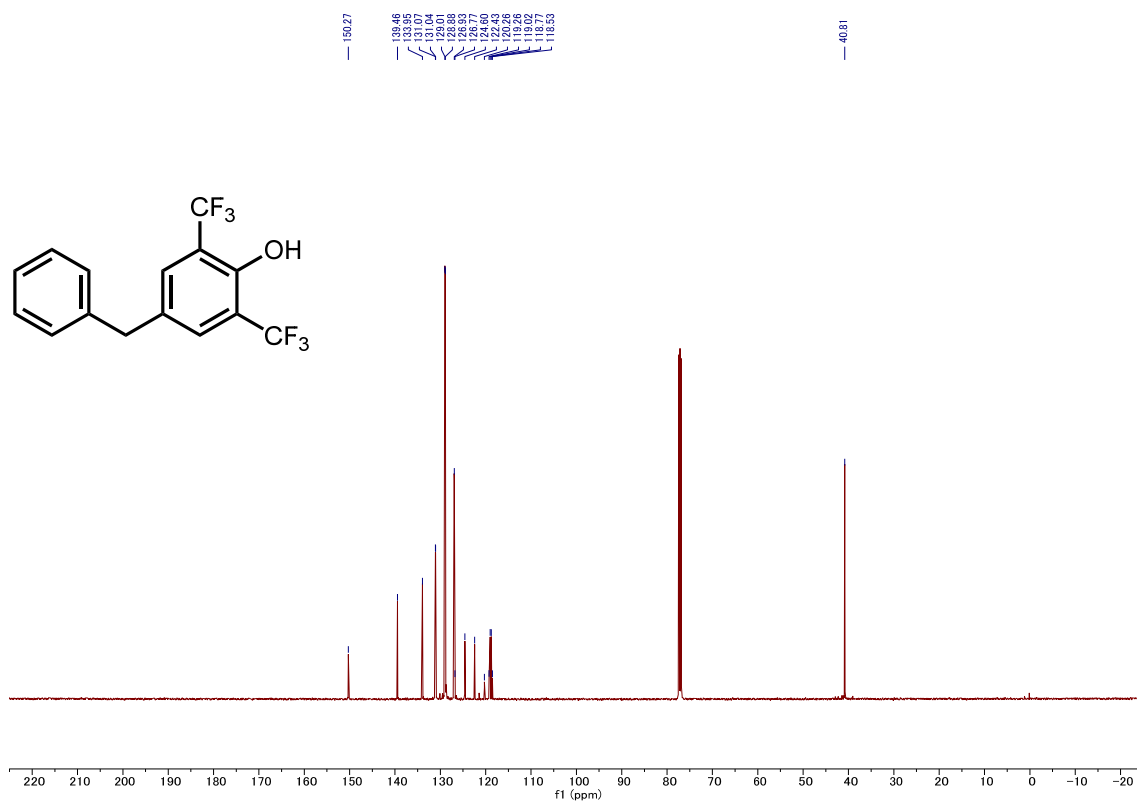
^{19}F NMR (471 MHz, CDCl_3)



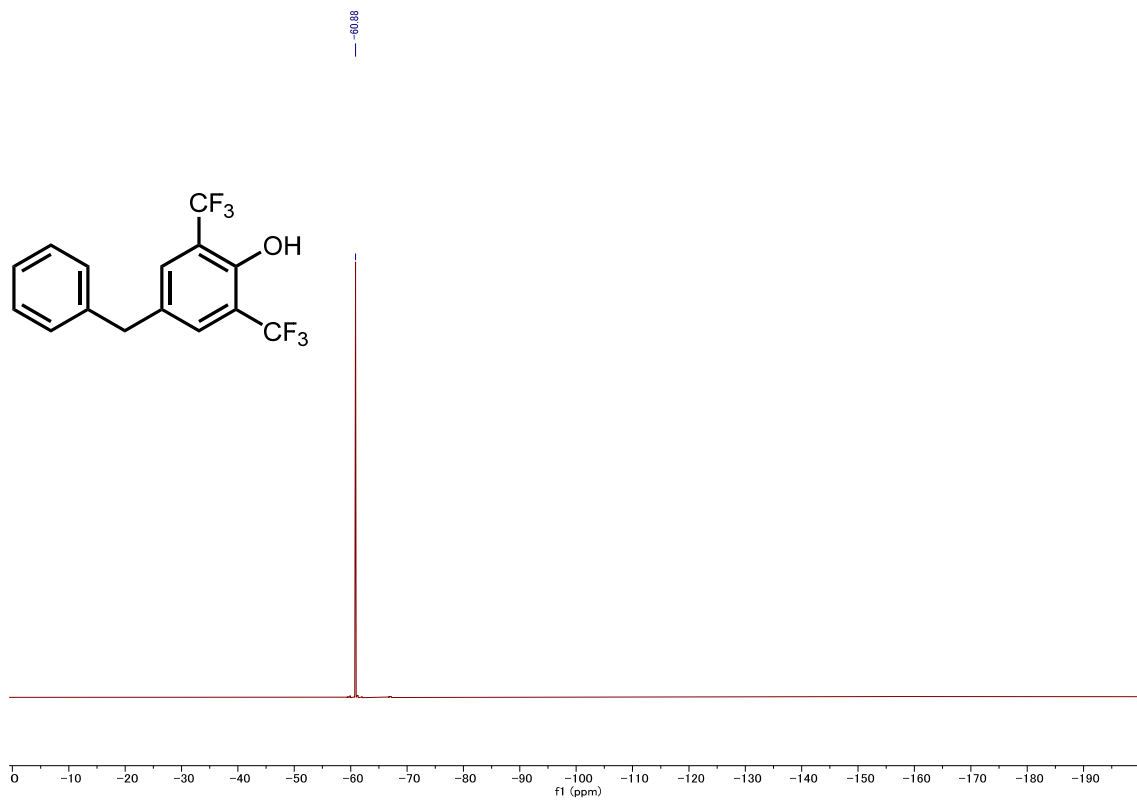
¹H NMR (500 MHz, CDCl₃)



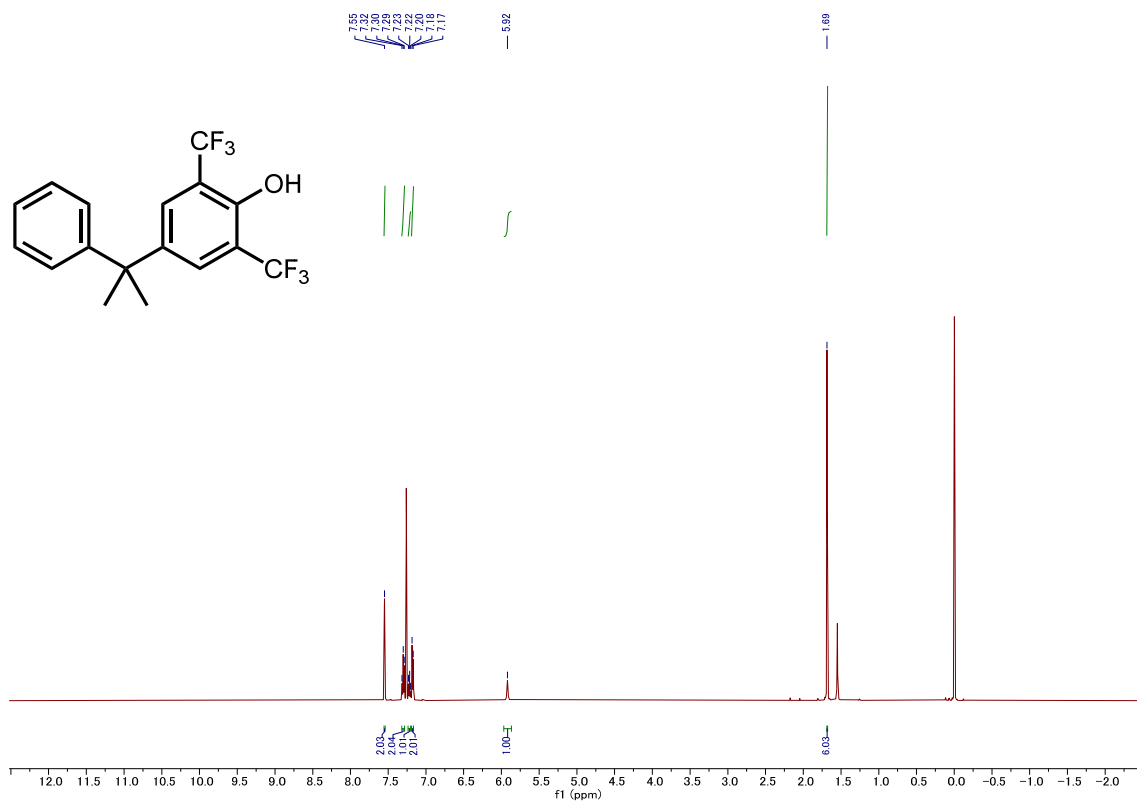
¹³C NMR (125 MHz, CDCl₃)



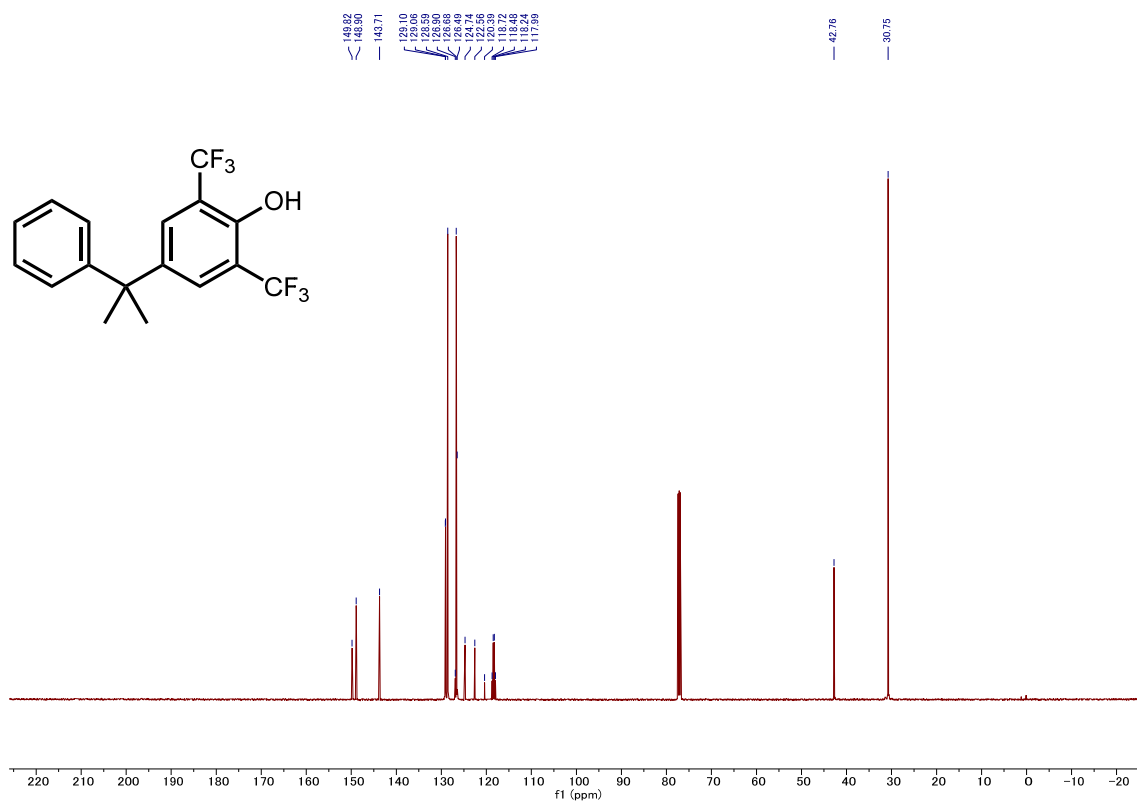
^{19}F NMR (471 MHz, CDCl_3)



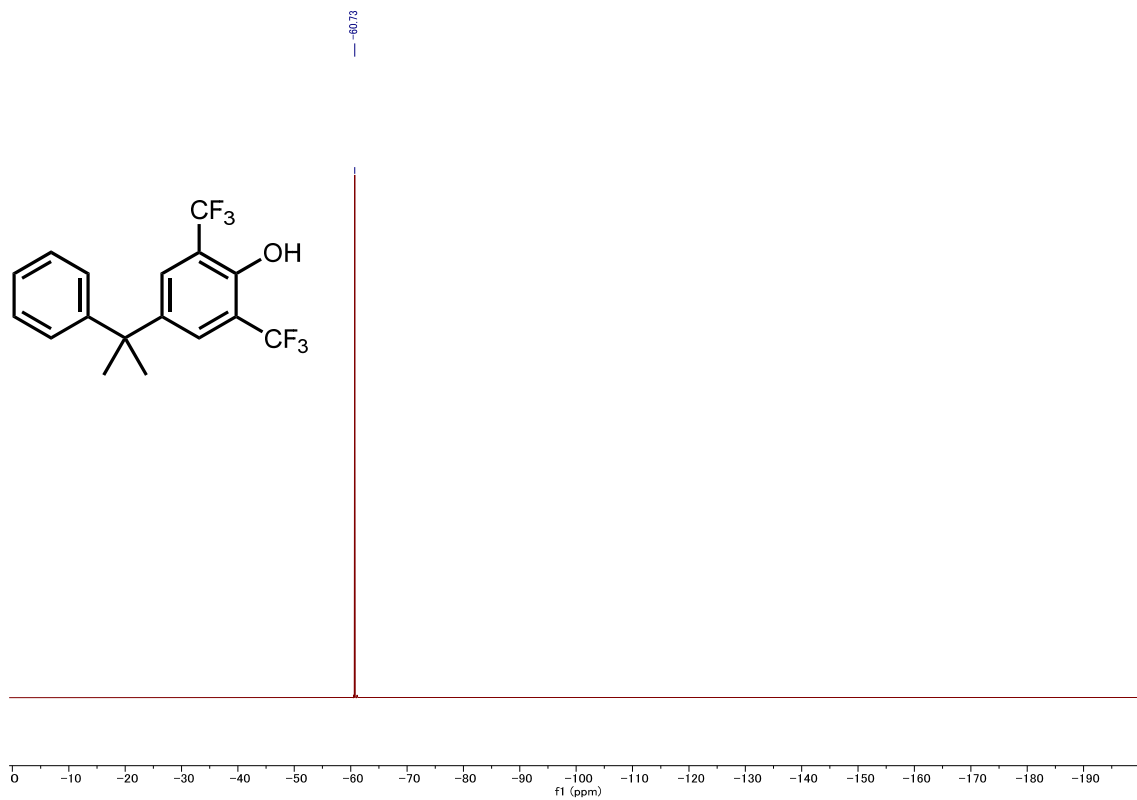
^1H NMR (500 MHz, CDCl_3)



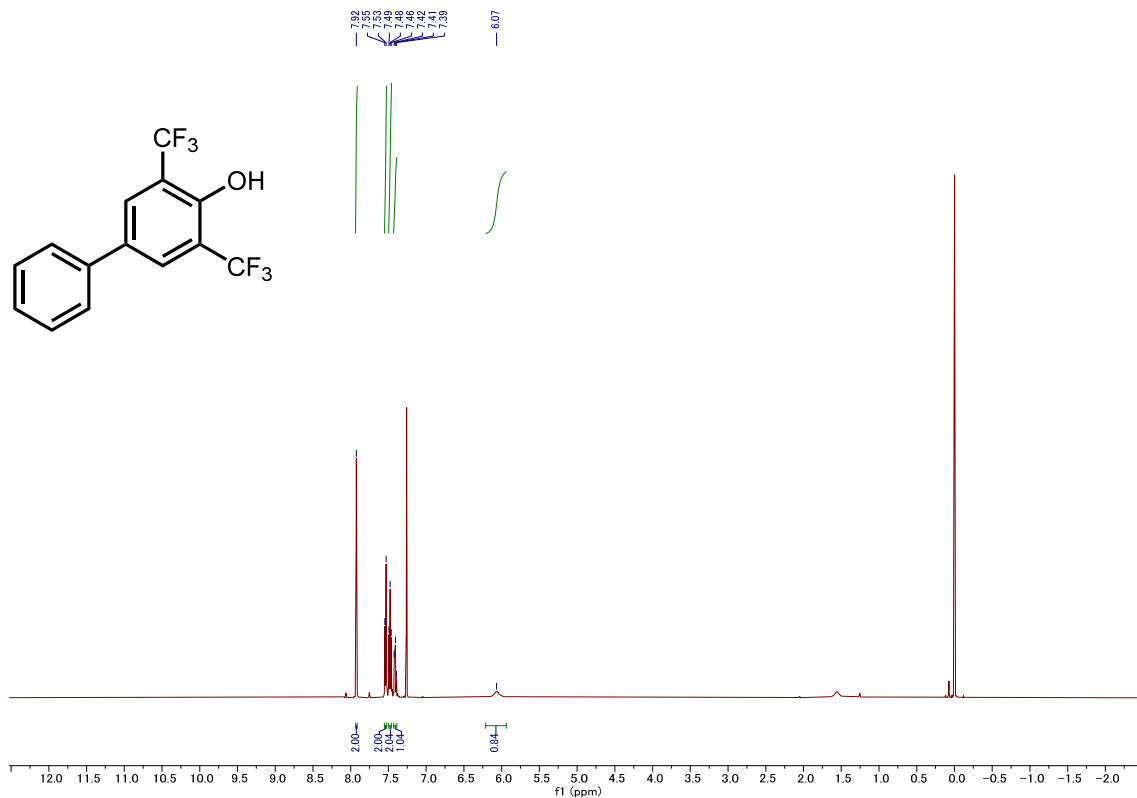
^{13}C NMR (125 MHz, CDCl_3)



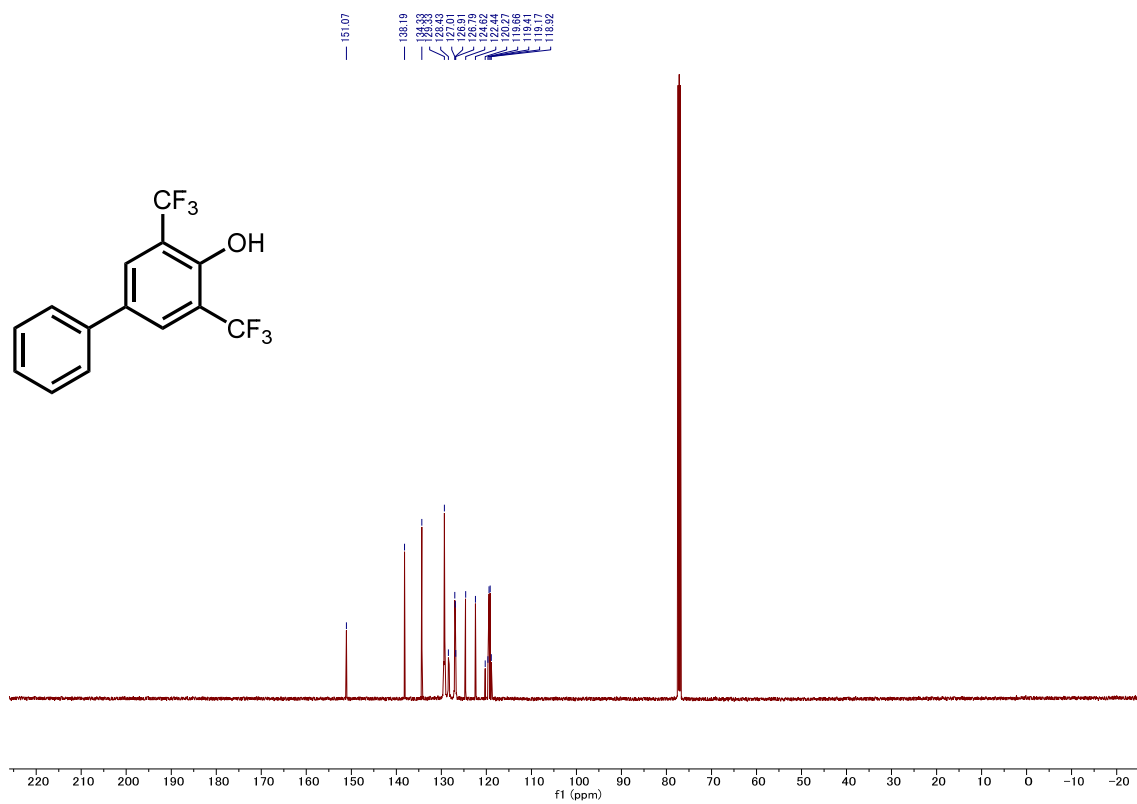
^{19}F NMR (471 MHz, CDCl_3)



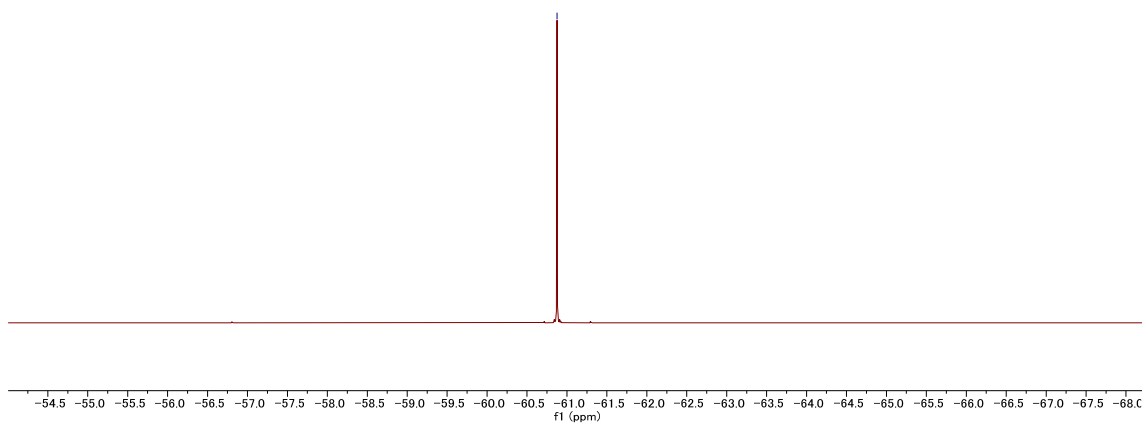
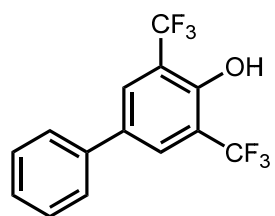
¹H NMR (500 MHz, CDCl₃)



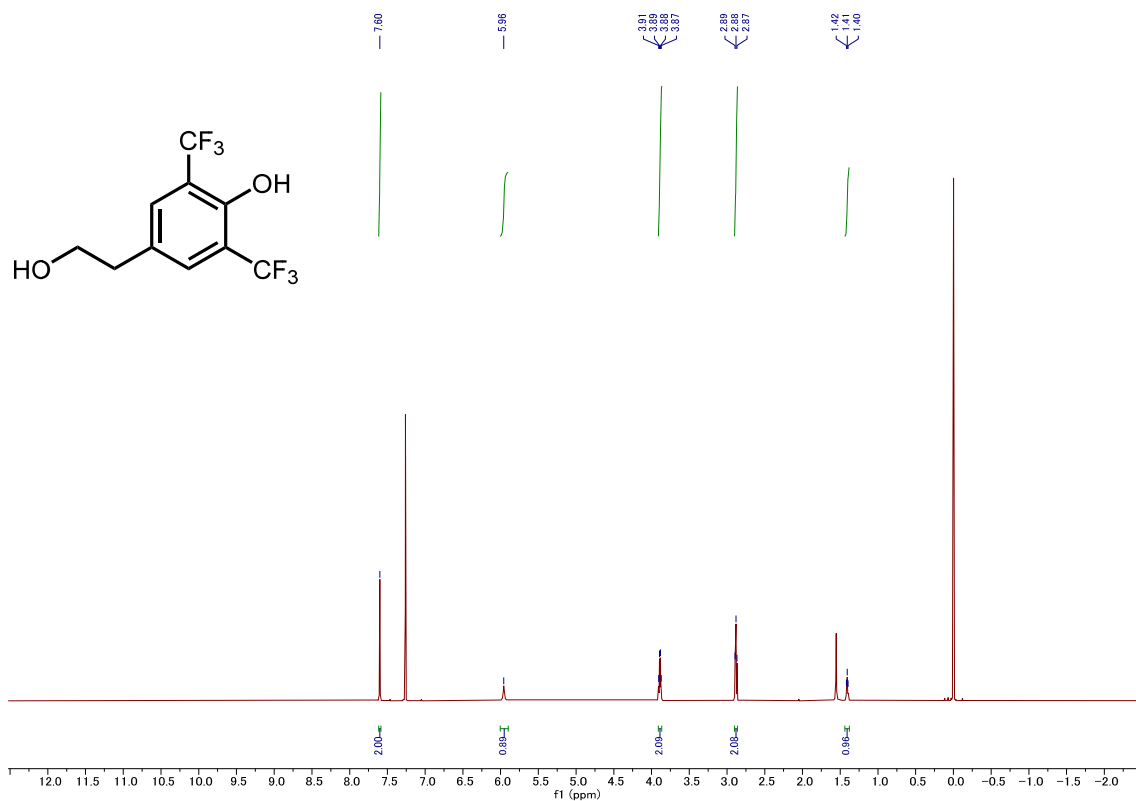
¹³C NMR (125 MHz, CDCl₃)



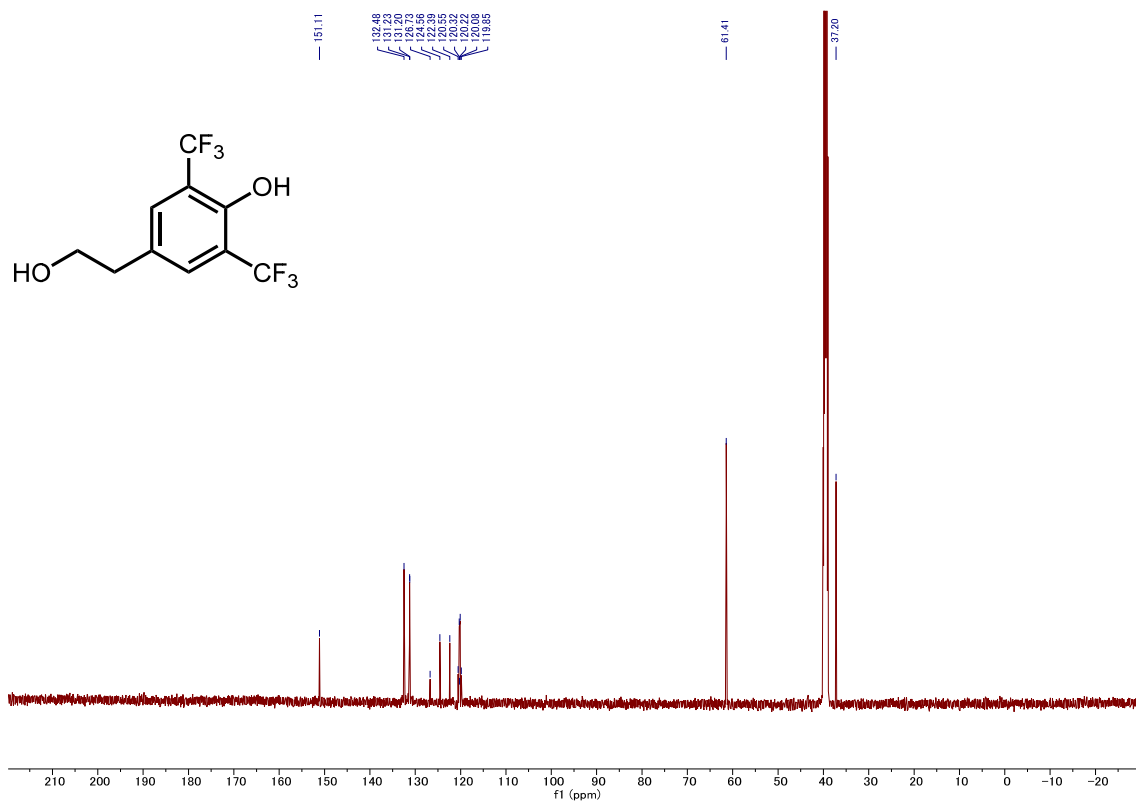
^{19}F NMR (471 MHz, CDCl_3)



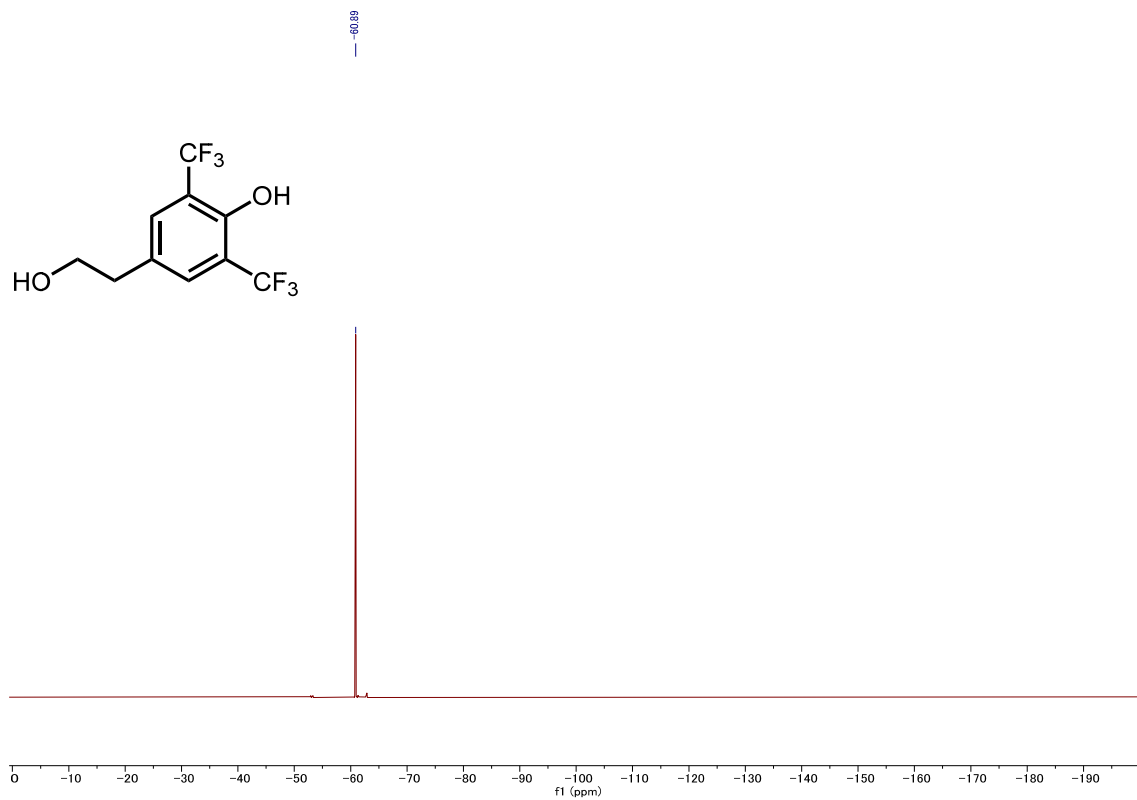
^1H NMR (500 MHz, CDCl_3)



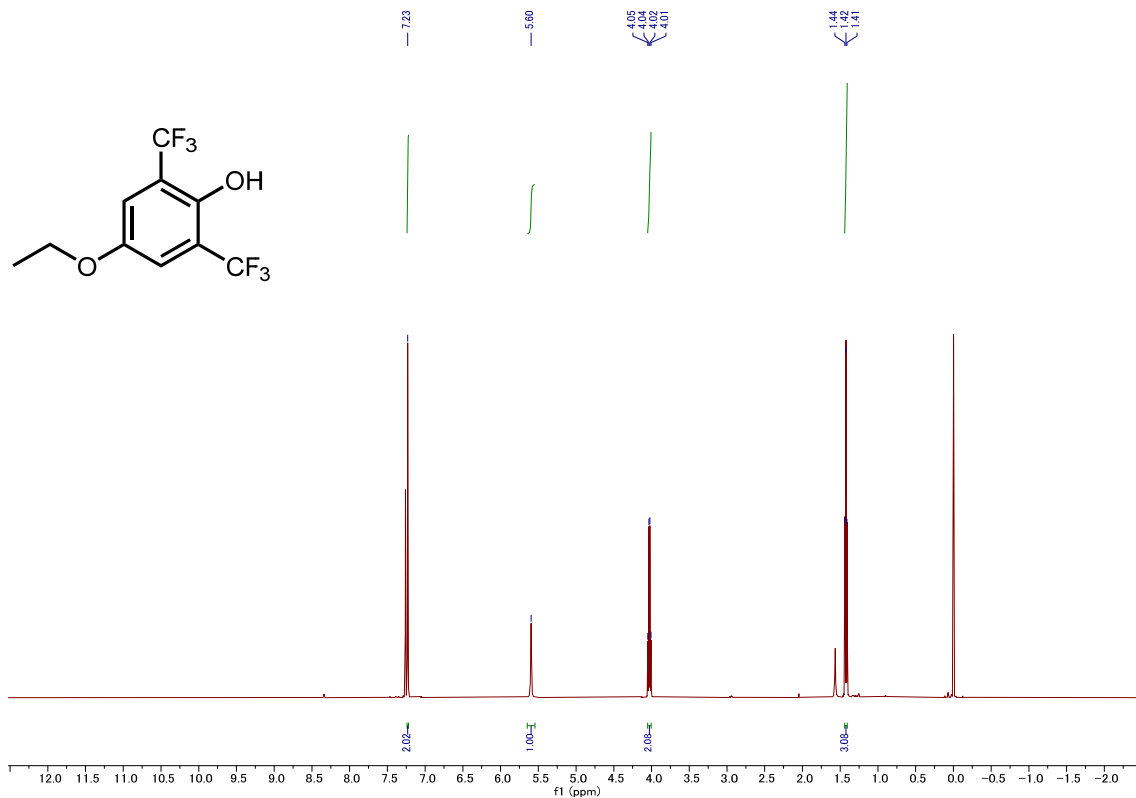
^{13}C NMR (125 MHz, CDCl_3)



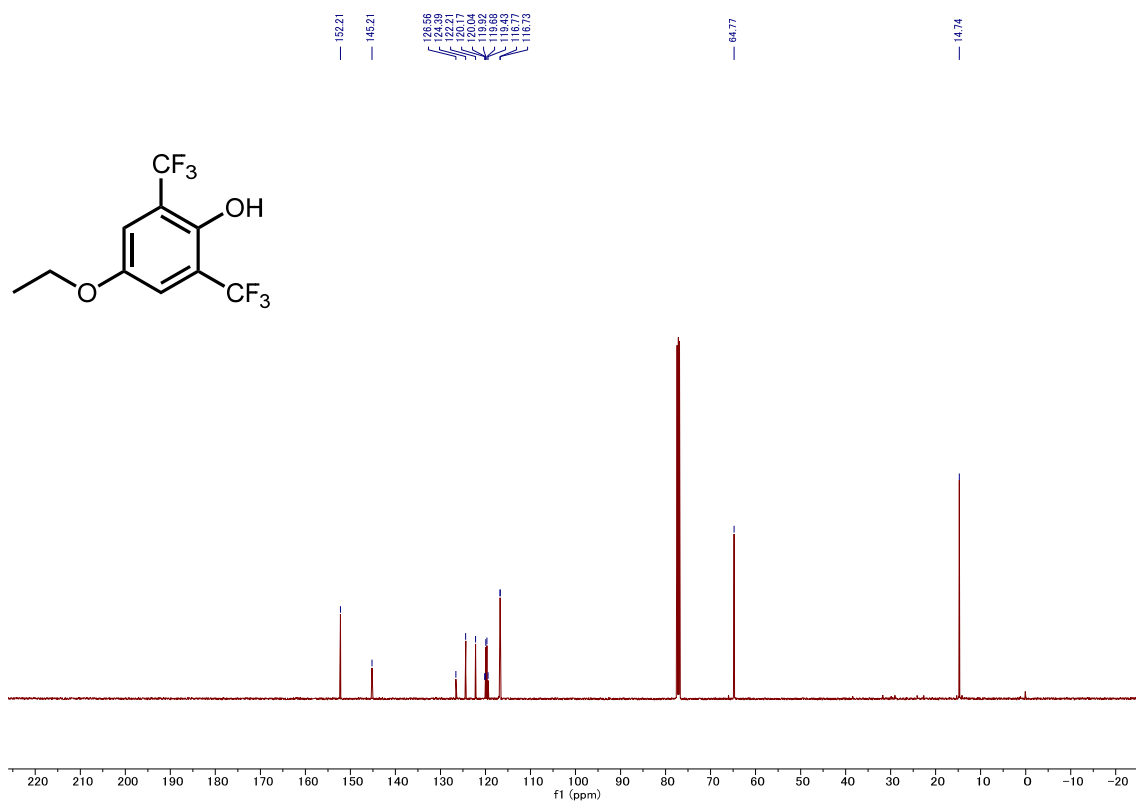
^{19}F NMR (471 MHz, d-DMSO)



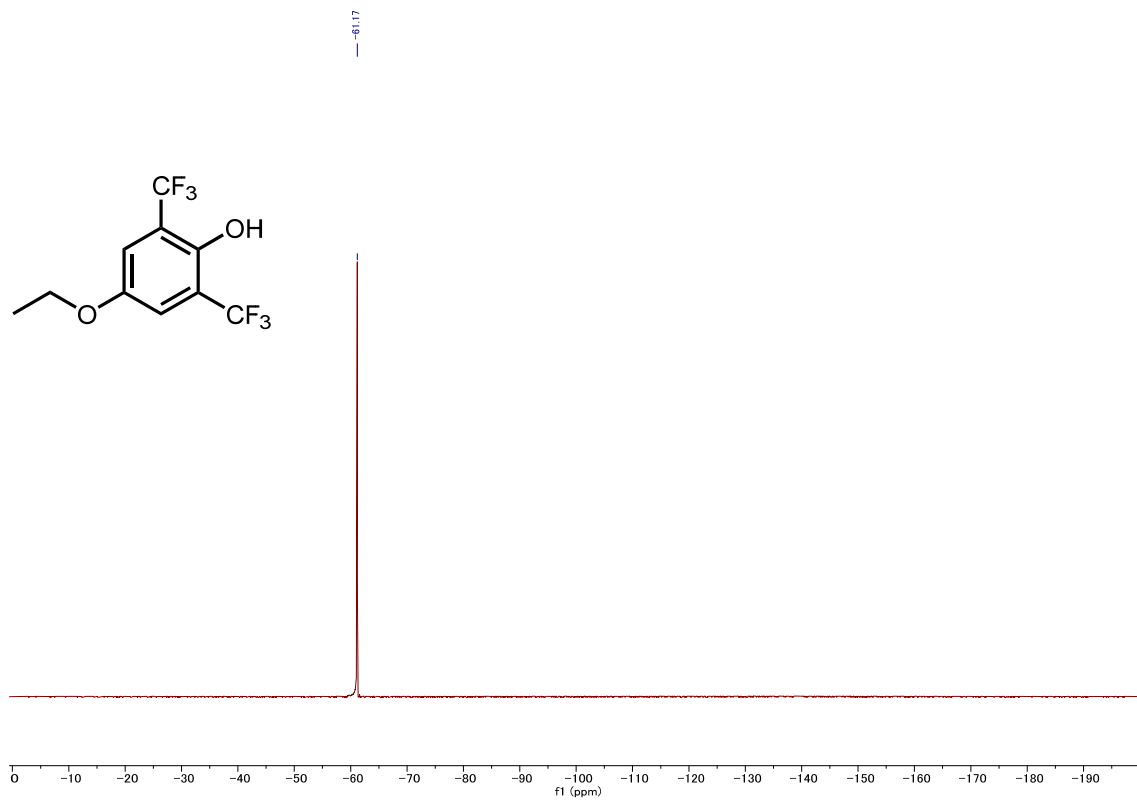
^1H NMR (500 MHz, CDCl_3)



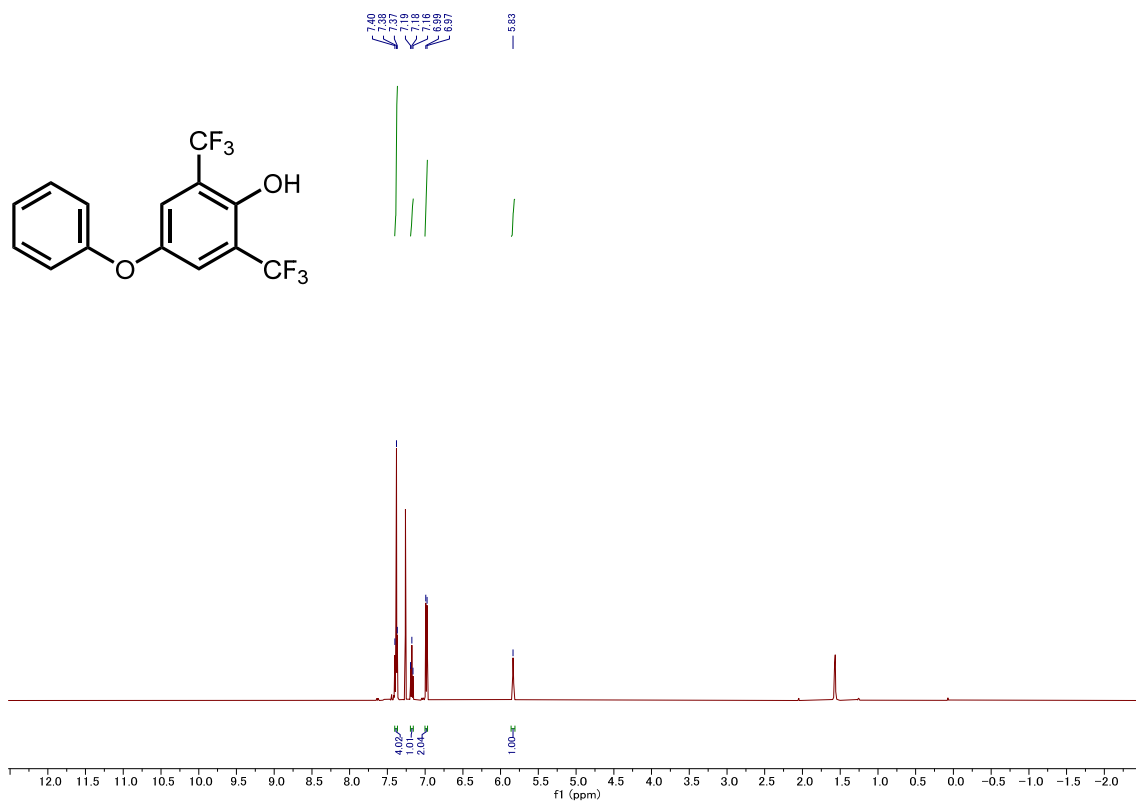
^{13}C NMR (125 MHz, CDCl_3)



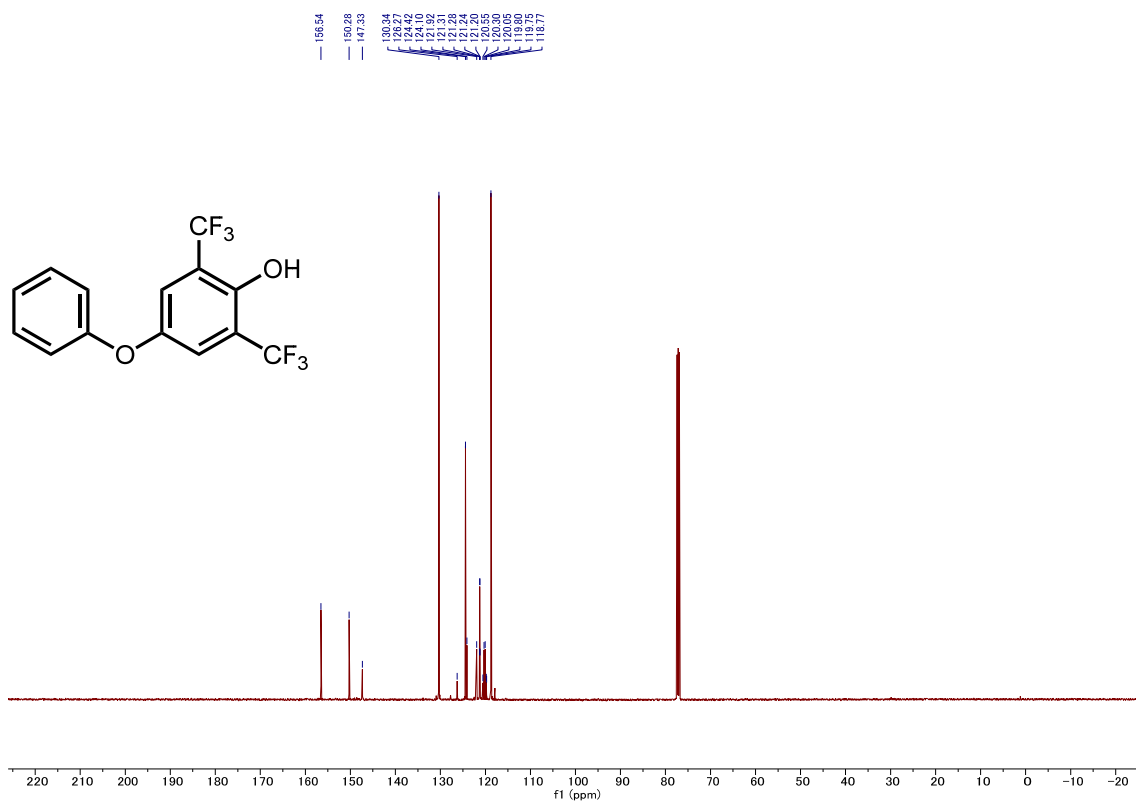
^{19}F NMR (471 MHz, CDCl_3)



^1H NMR (500 MHz, CDCl_3)

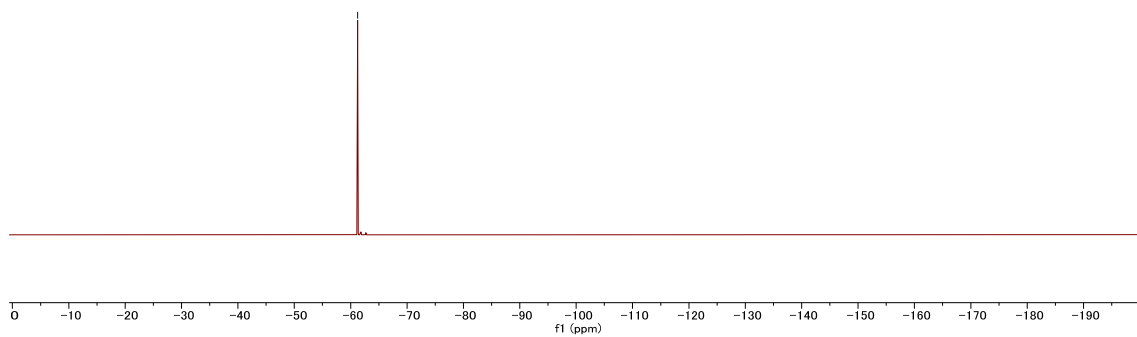
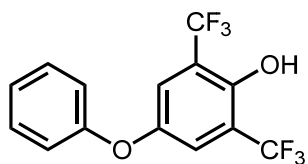


^{13}C NMR (125 MHz, CDCl_3)

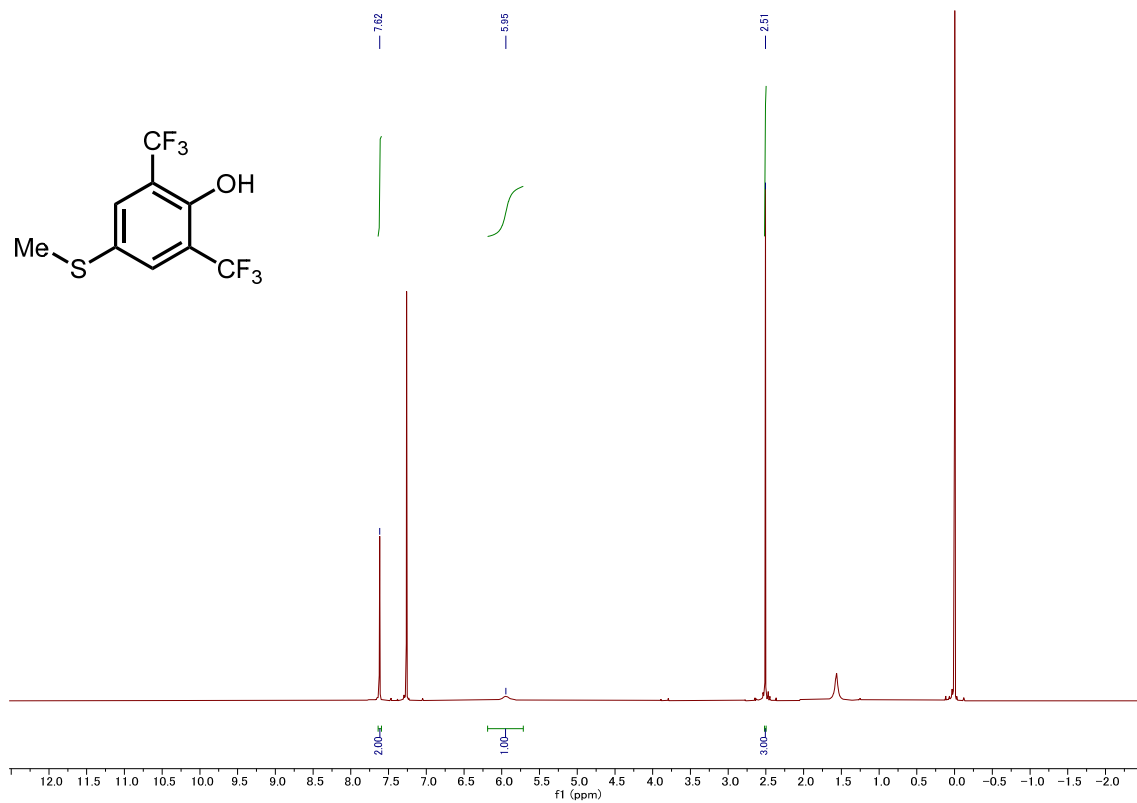


^{19}F NMR (471 MHz, CDCl_3)

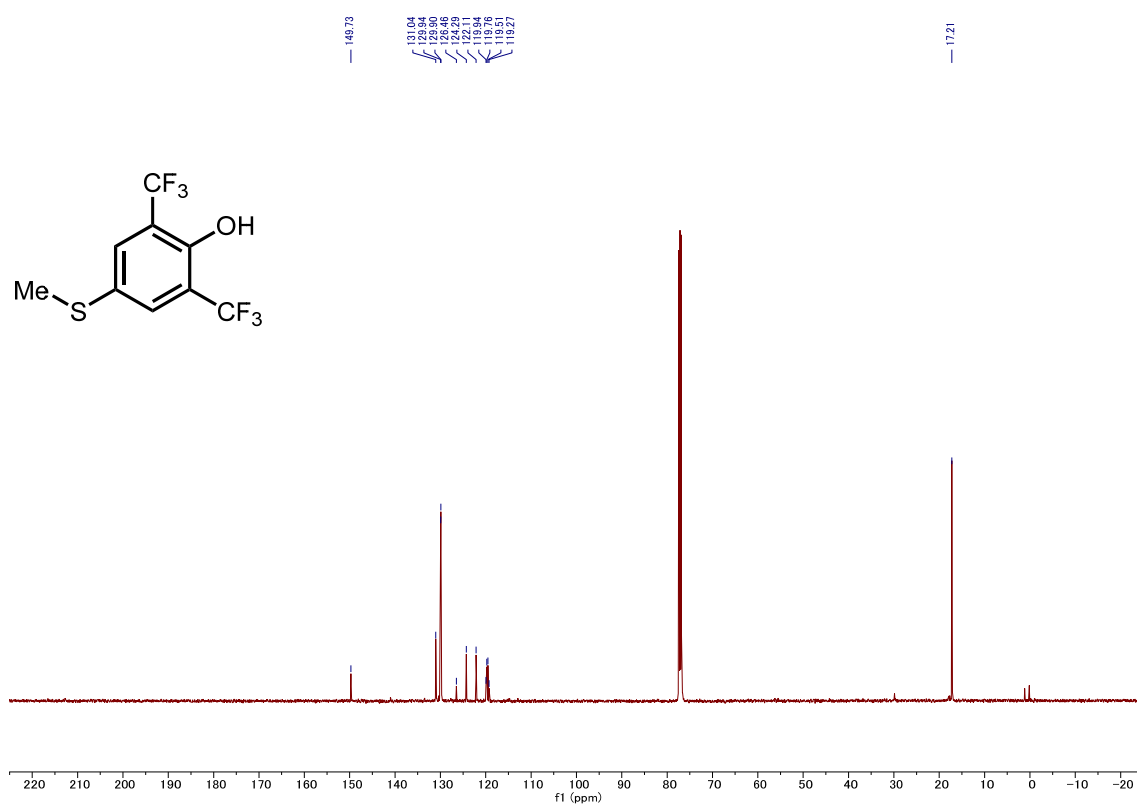
-61.24



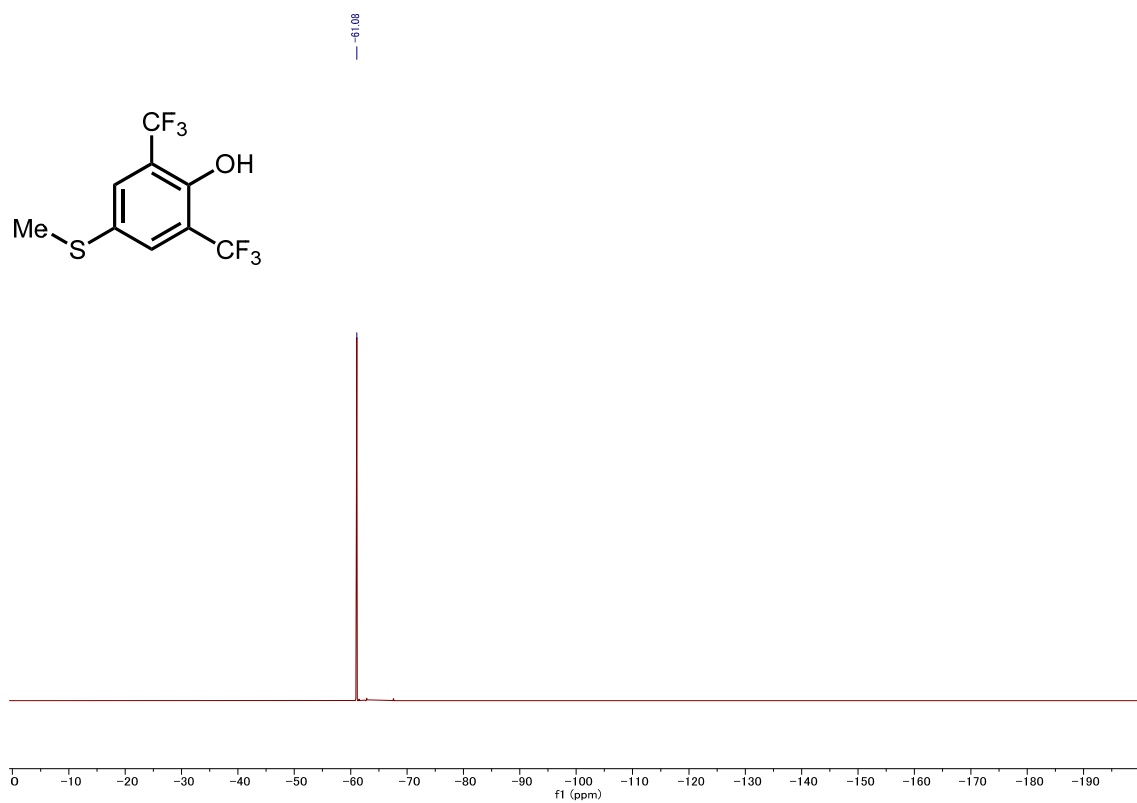
^1H NMR (500 MHz, CDCl_3)



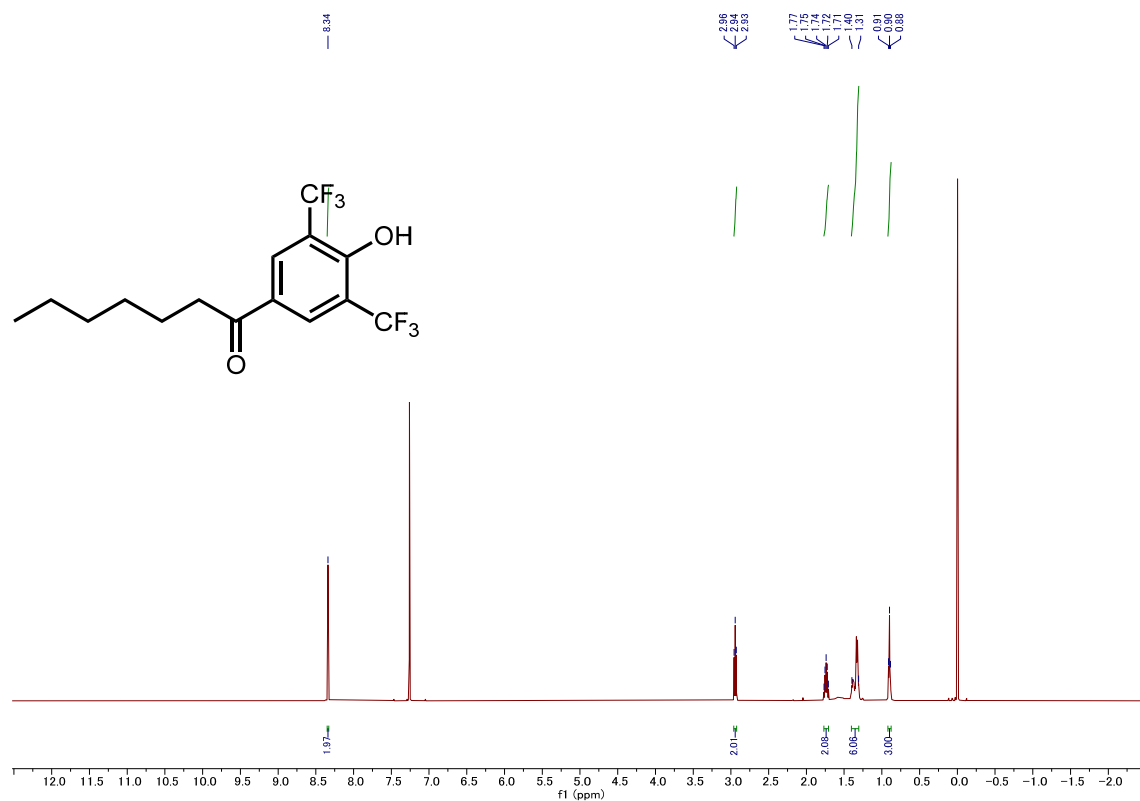
^{13}C NMR (125 MHz, CDCl_3)



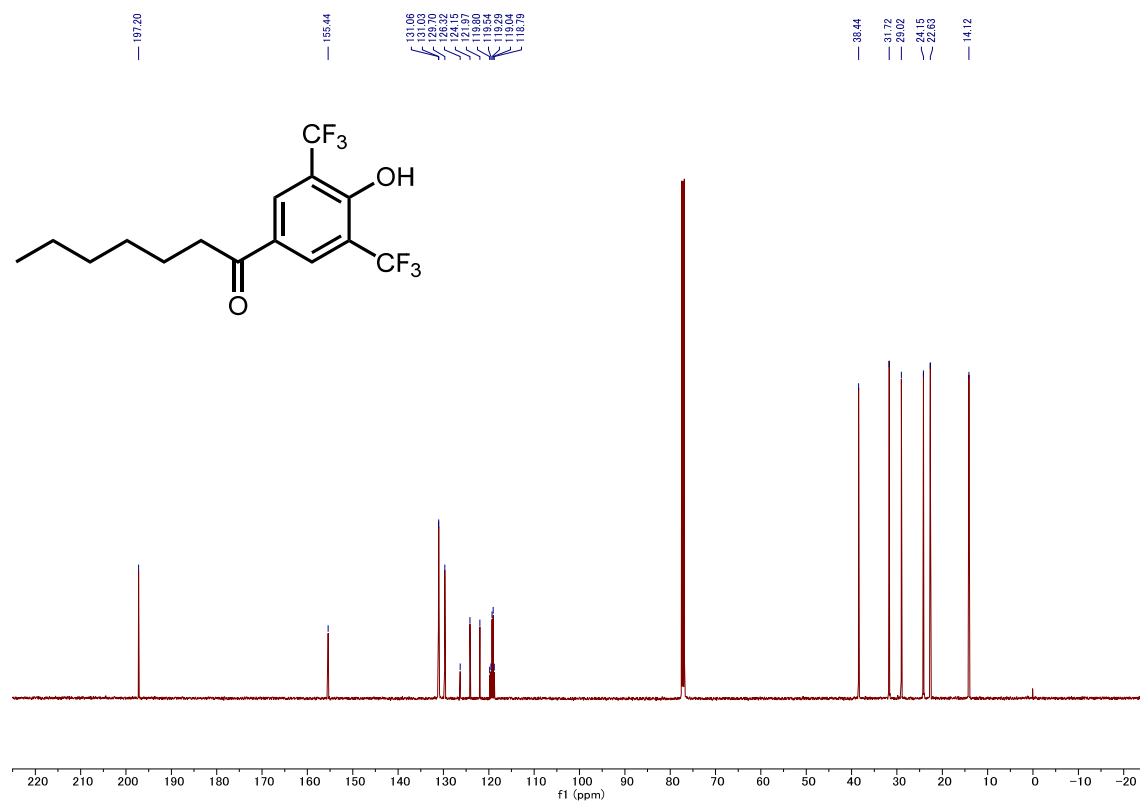
^{19}F NMR (471 MHz, CDCl_3)



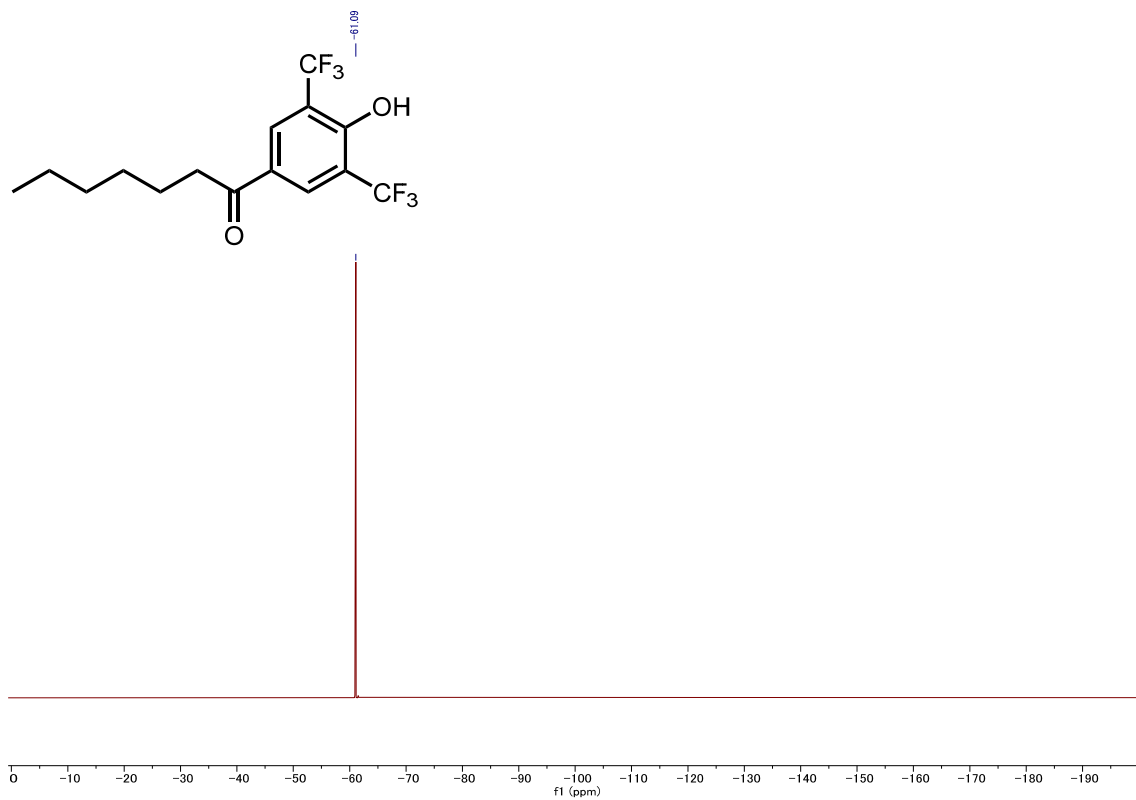
^1H NMR (500 MHz, CDCl_3)



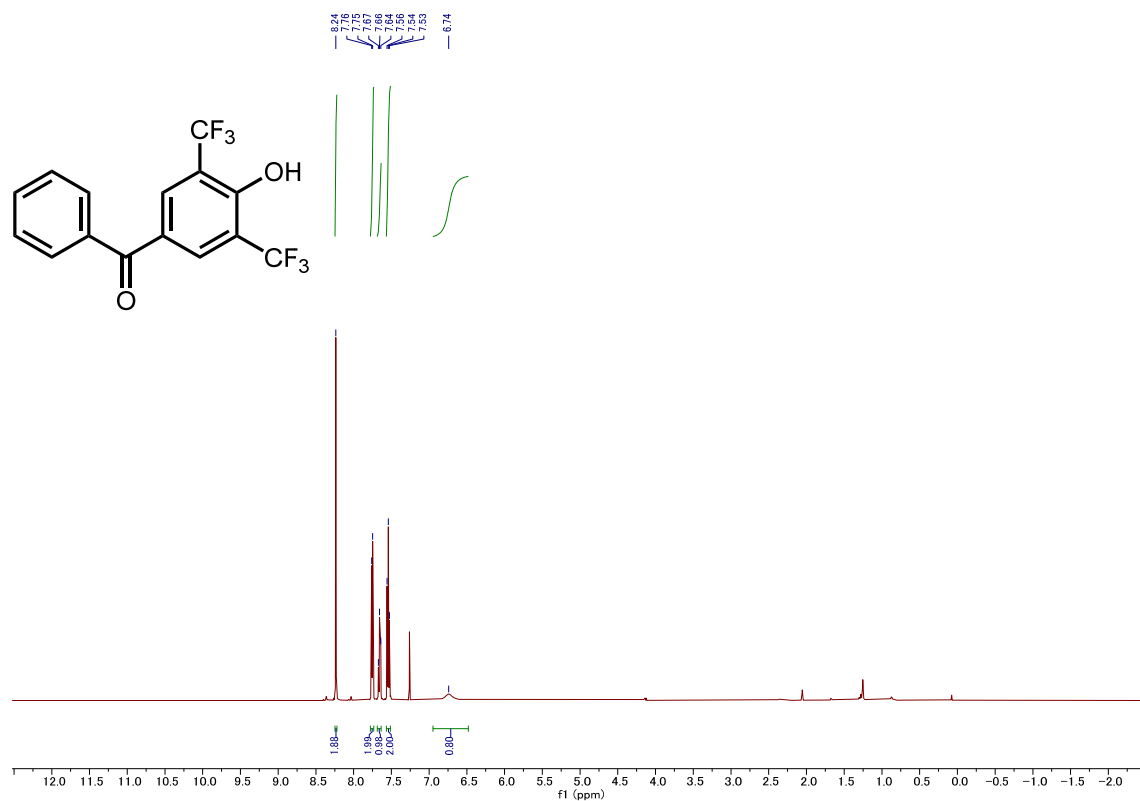
^{13}C NMR (125 MHz, CDCl_3)



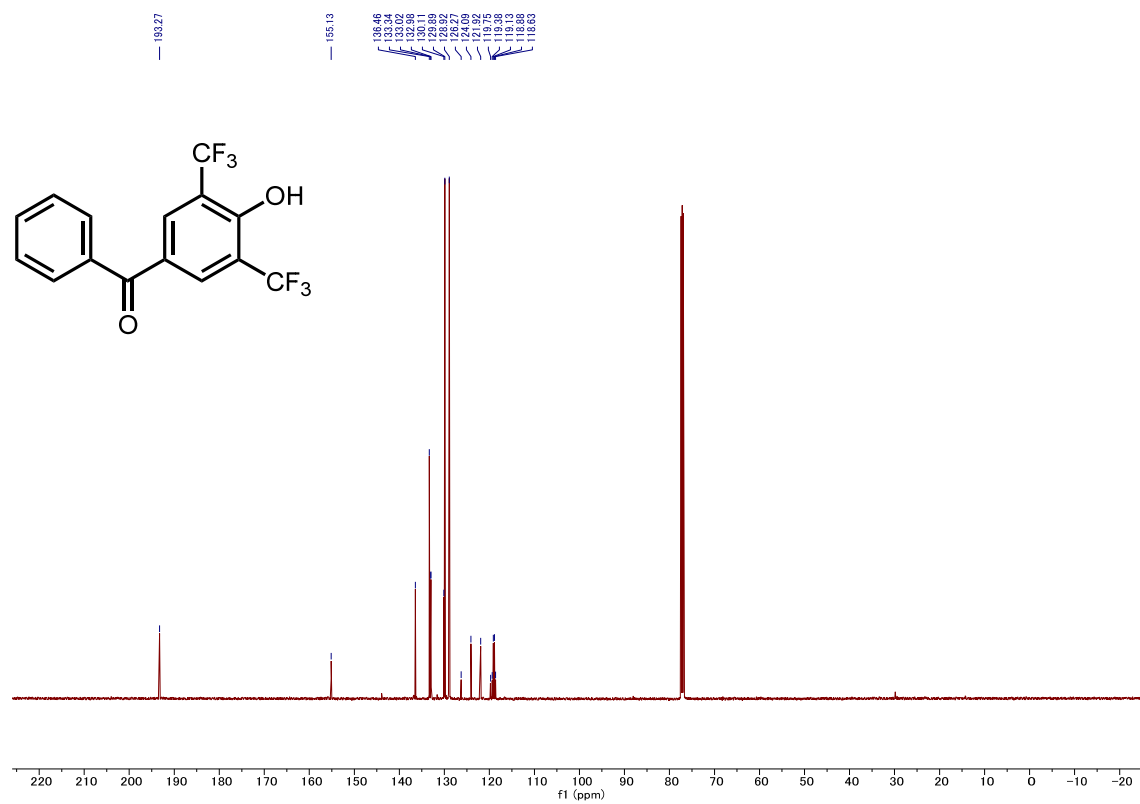
^{19}F NMR (471 MHz, CDCl_3)



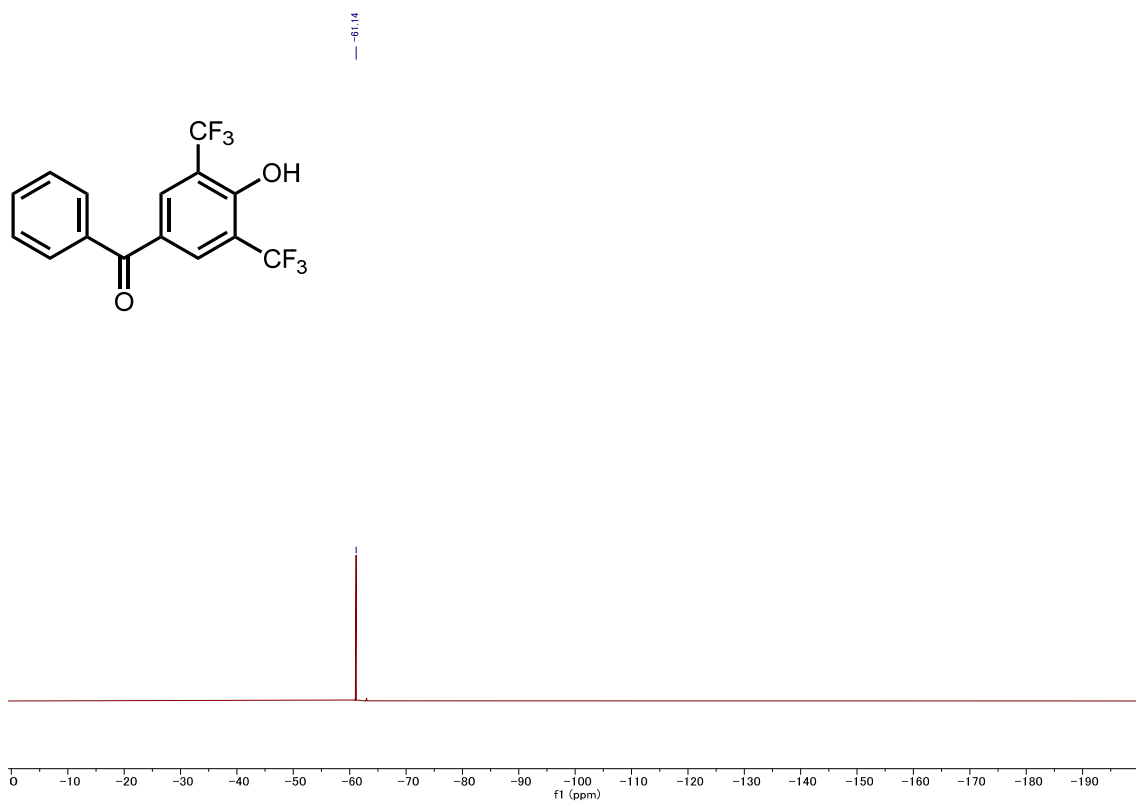
^1H NMR (500 MHz, CDCl_3)



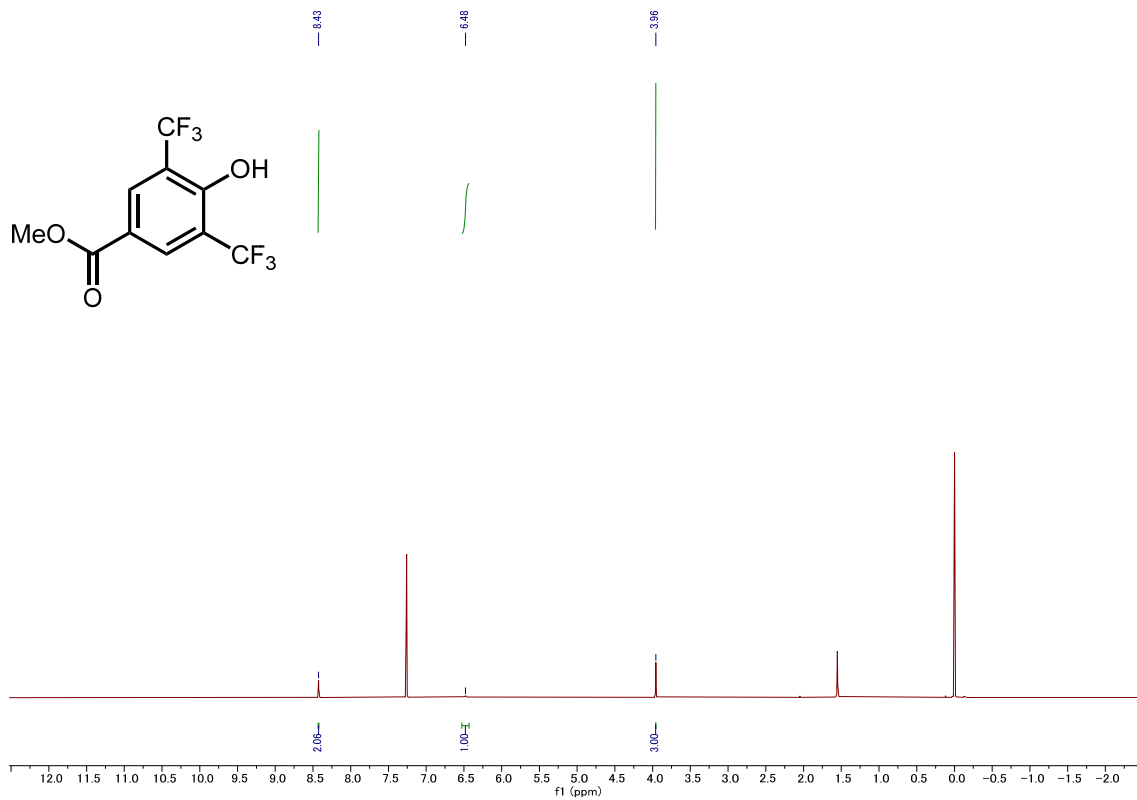
^{13}C NMR (125 MHz, CDCl_3)



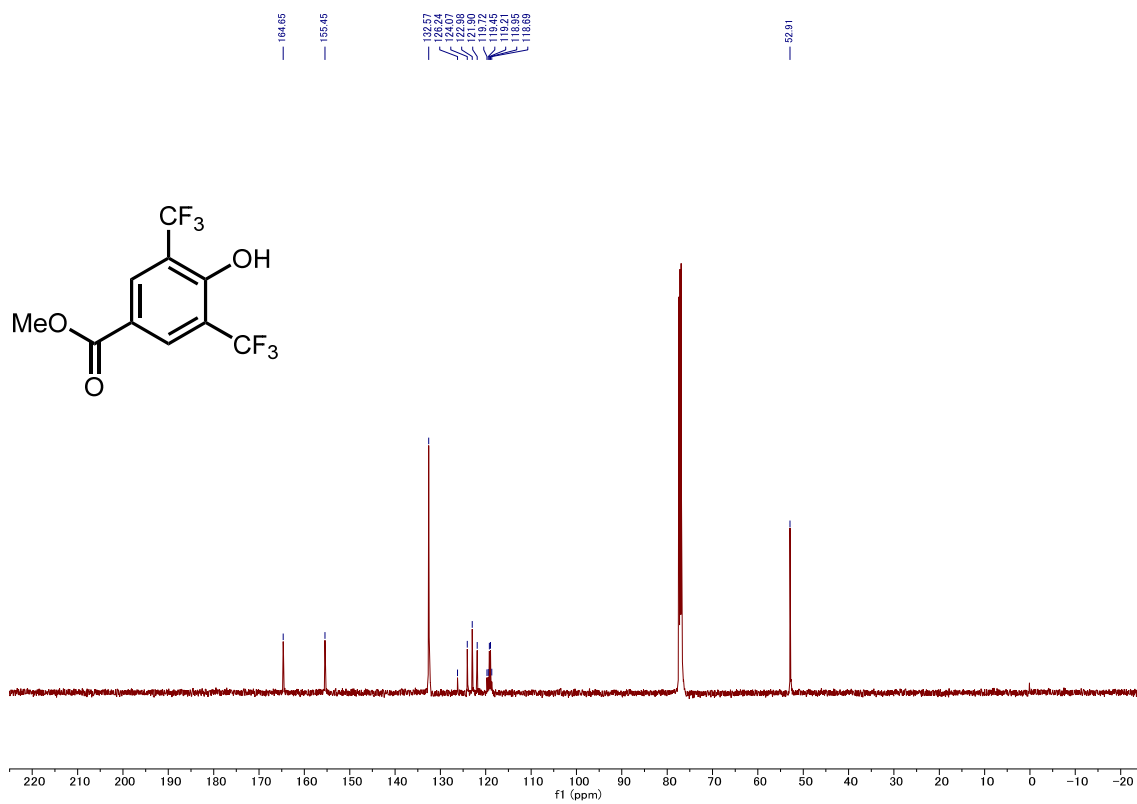
^{19}F NMR (471 MHz, CDCl_3)



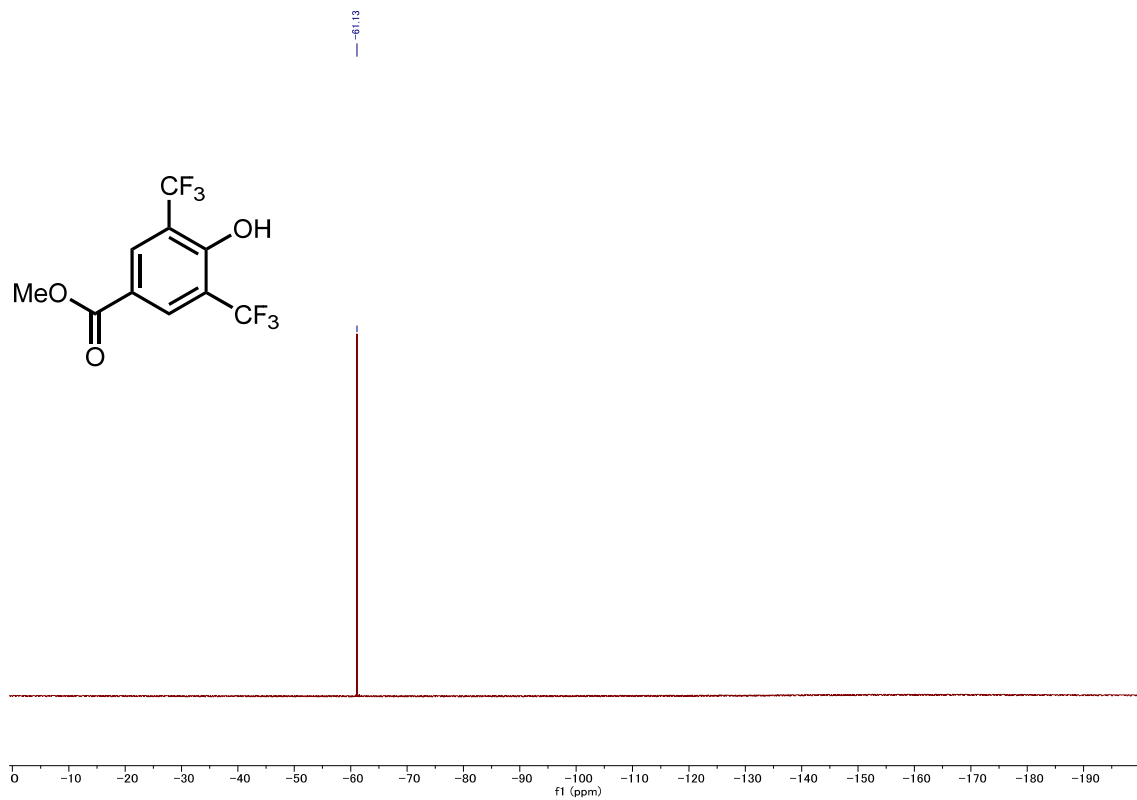
^1H NMR (500 MHz, CDCl_3)



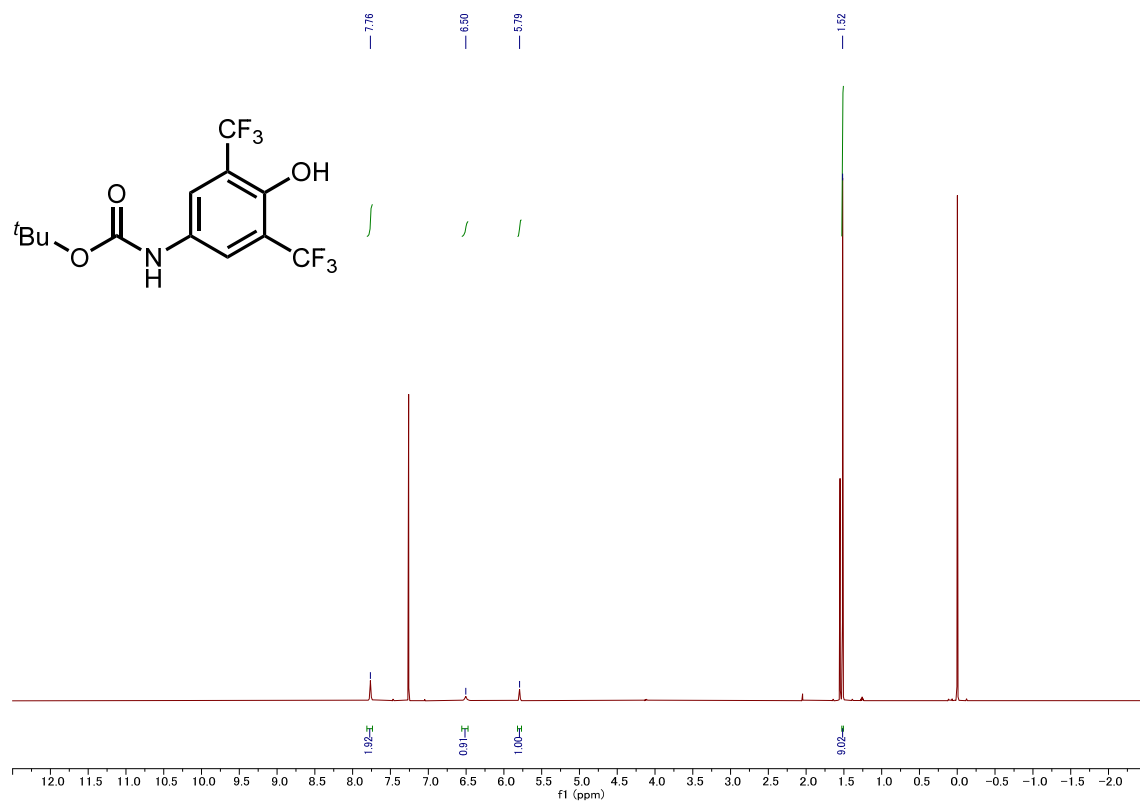
^{13}C NMR (125 MHz, CDCl_3)



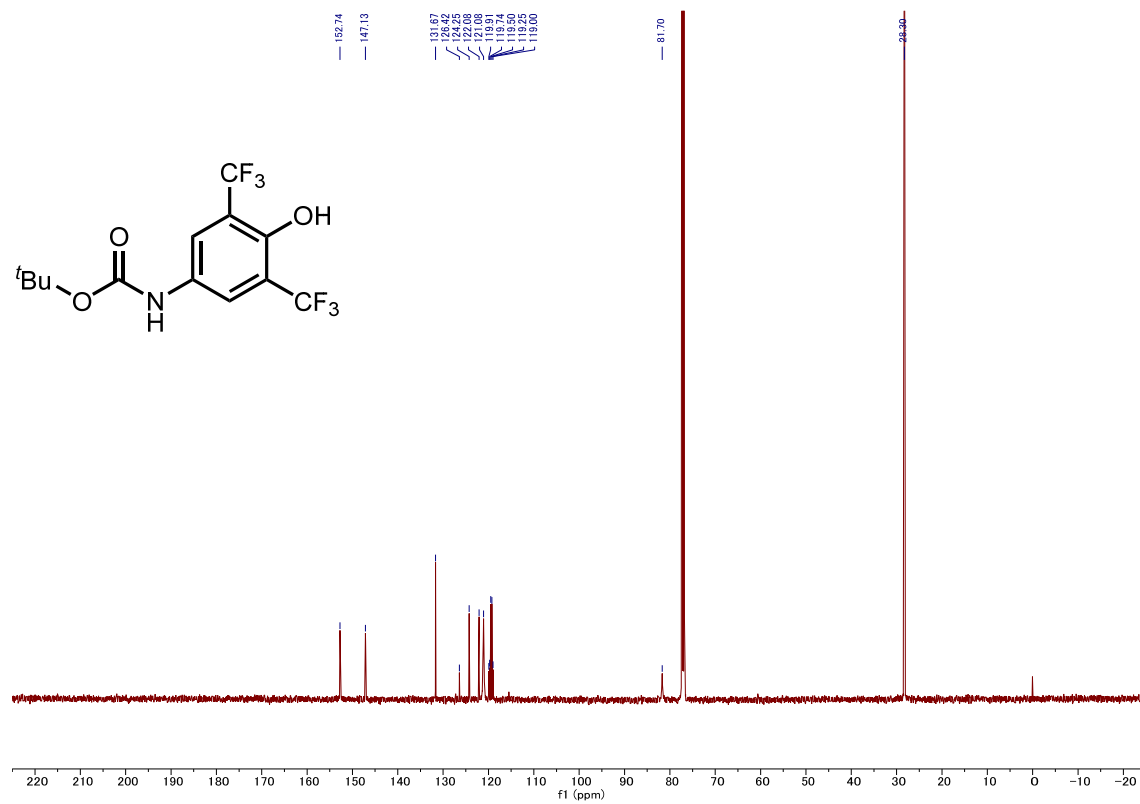
^{19}F NMR (471 MHz, CDCl_3)



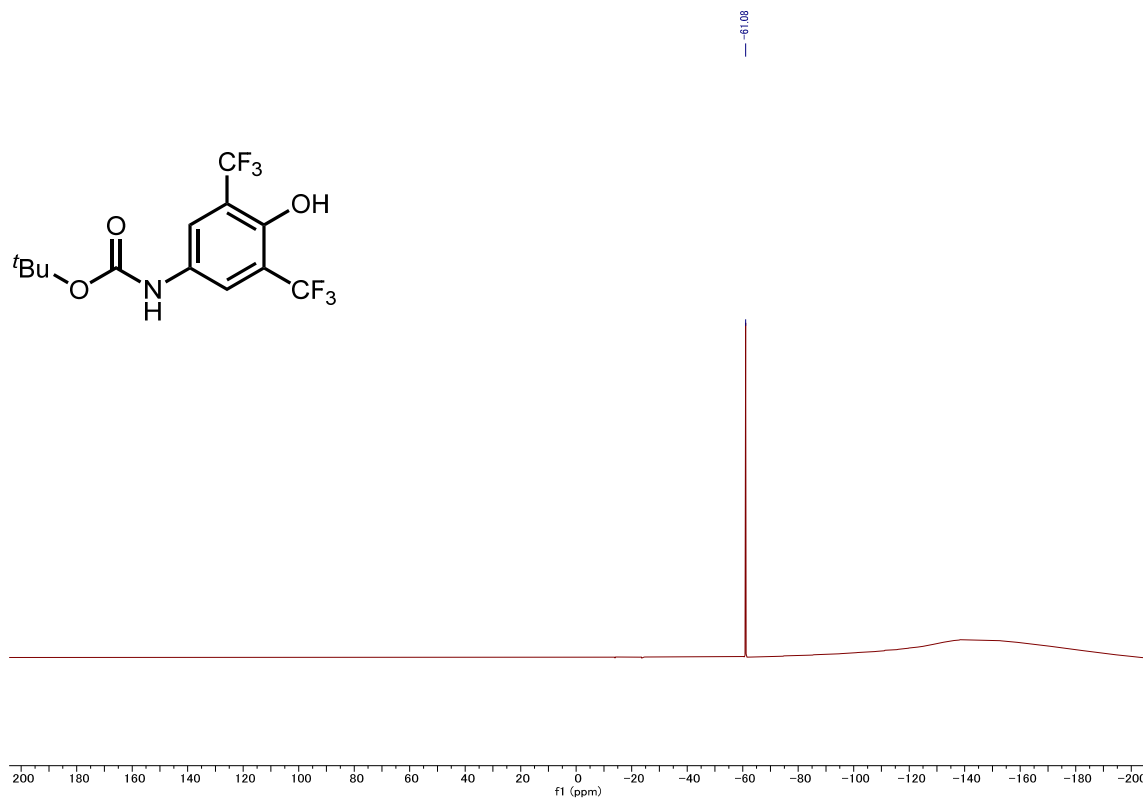
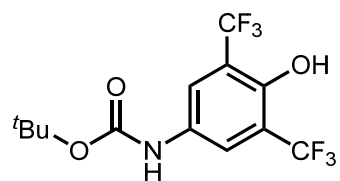
^1H NMR (500 MHz, CDCl_3)



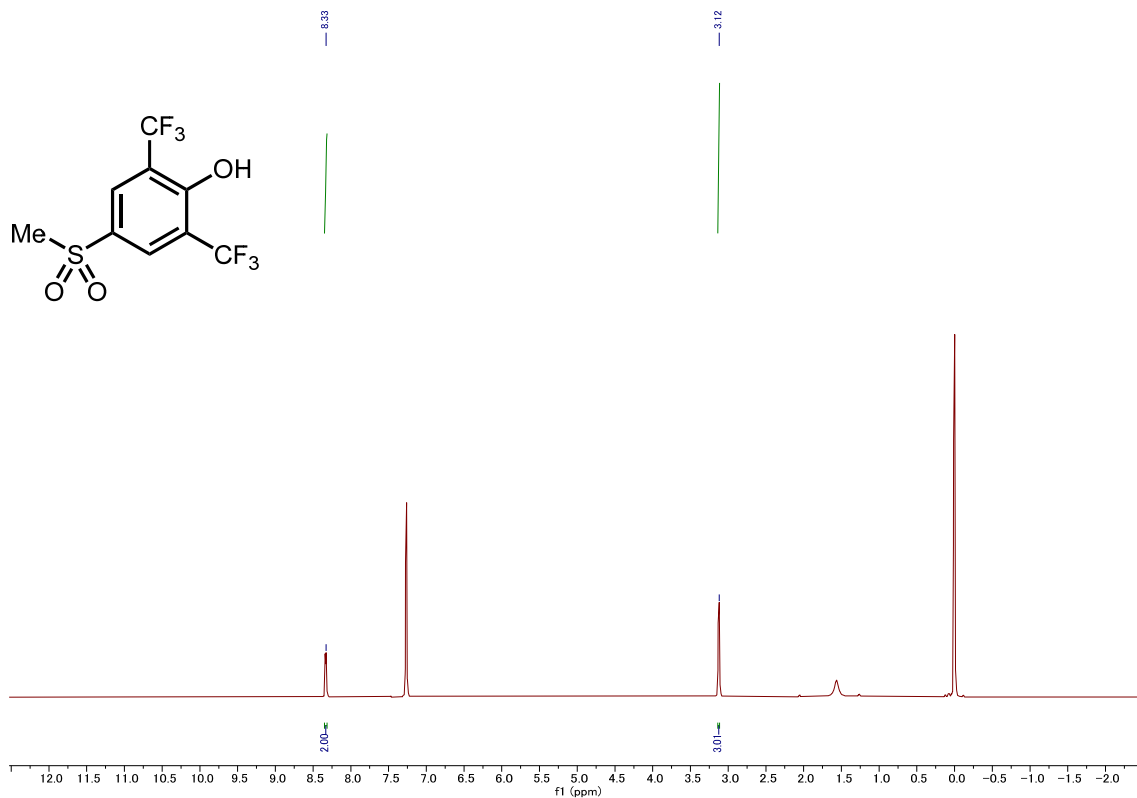
^{13}C NMR (125 MHz, CDCl_3)



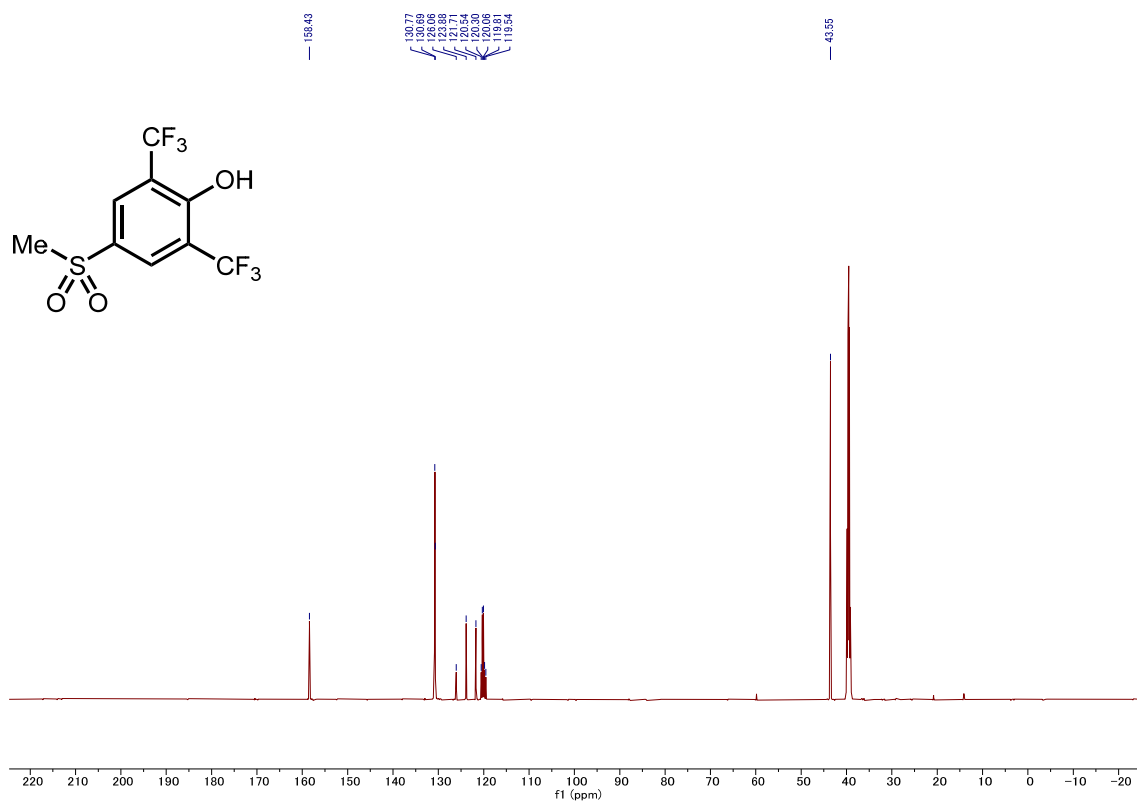
^{19}F NMR (471 MHz, CDCl_3)



^1H NMR (500 MHz, CDCl_3)



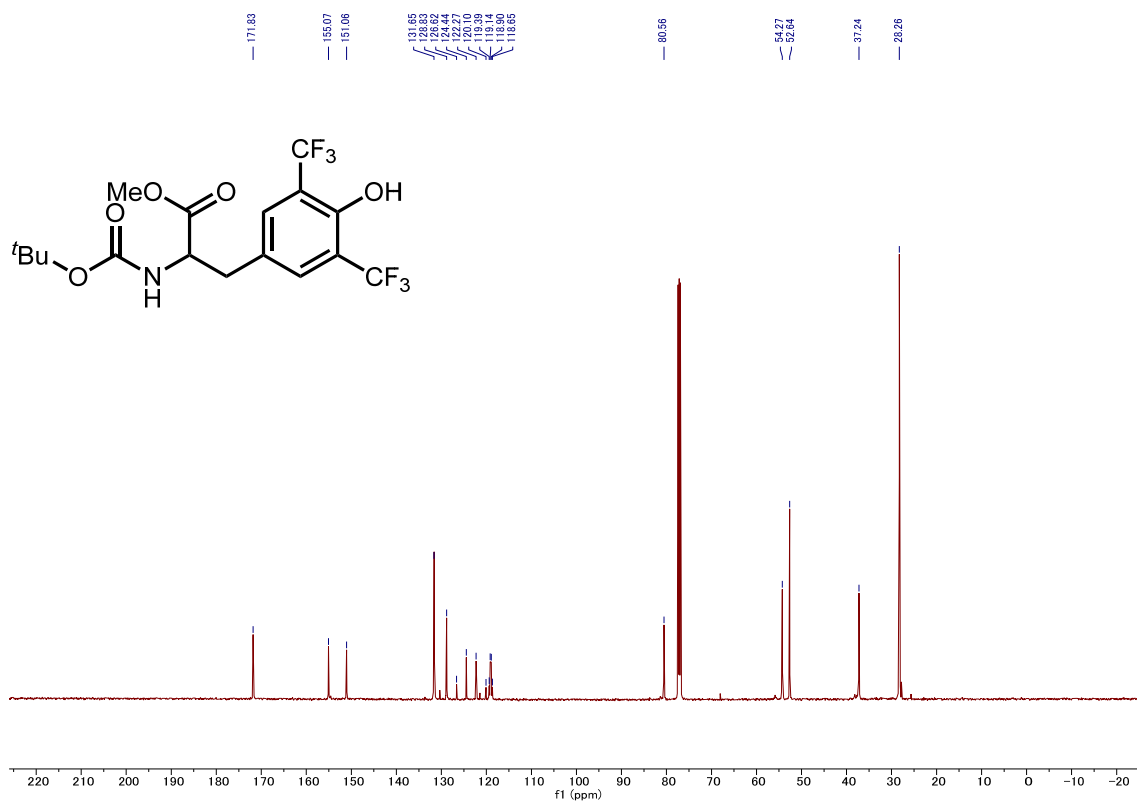
^{13}C NMR (125 MHz, $d\text{-DMSO}$)



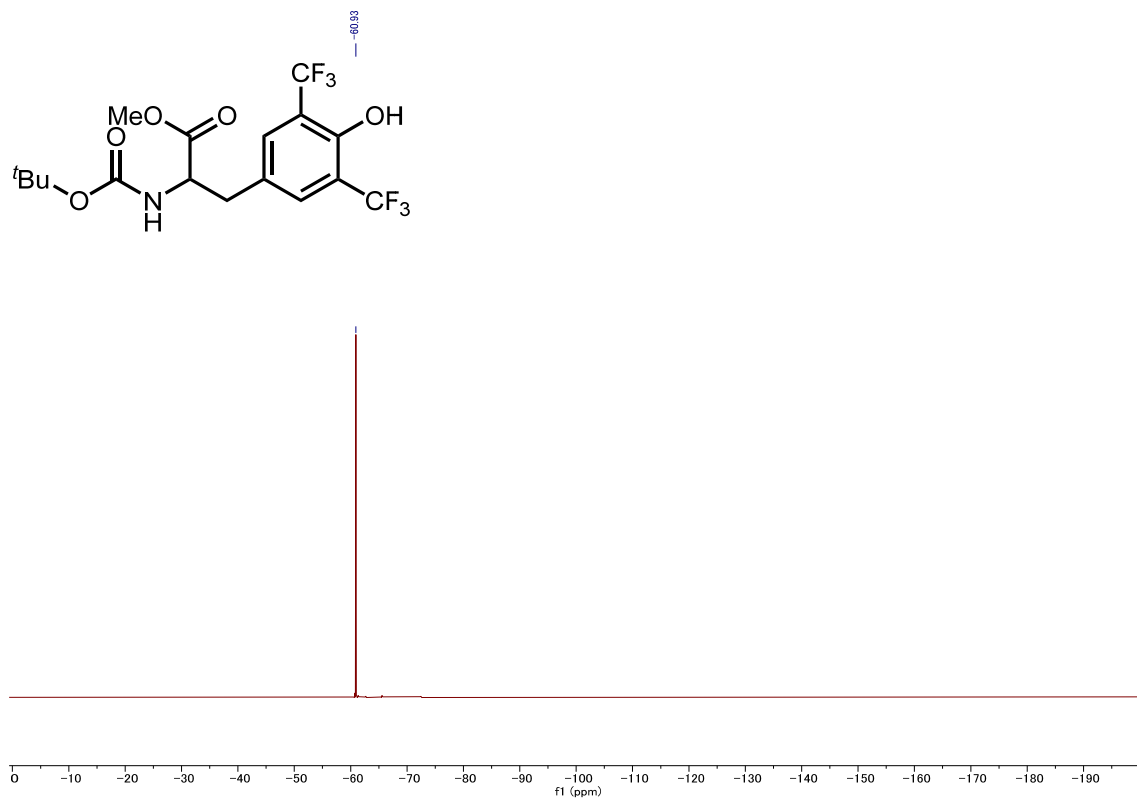
^1H NMR (500 MHz, CDCl_3)



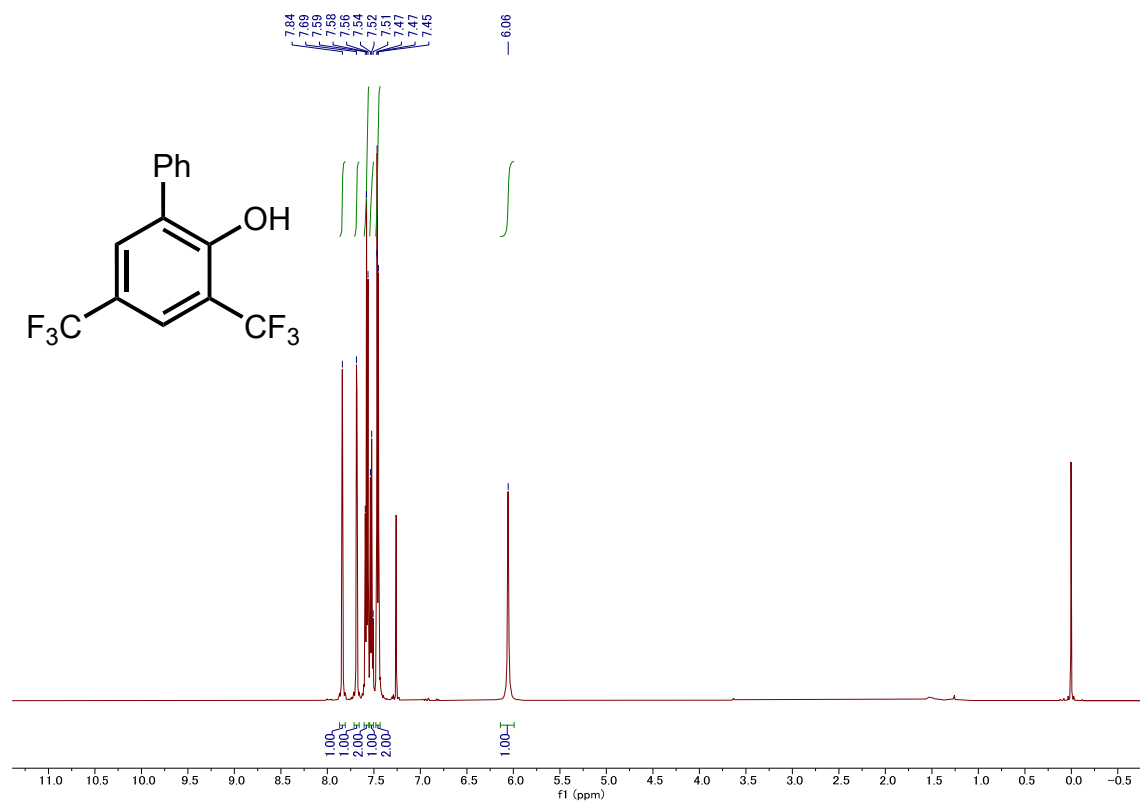
^{13}C NMR (125 MHz, CDCl_3)



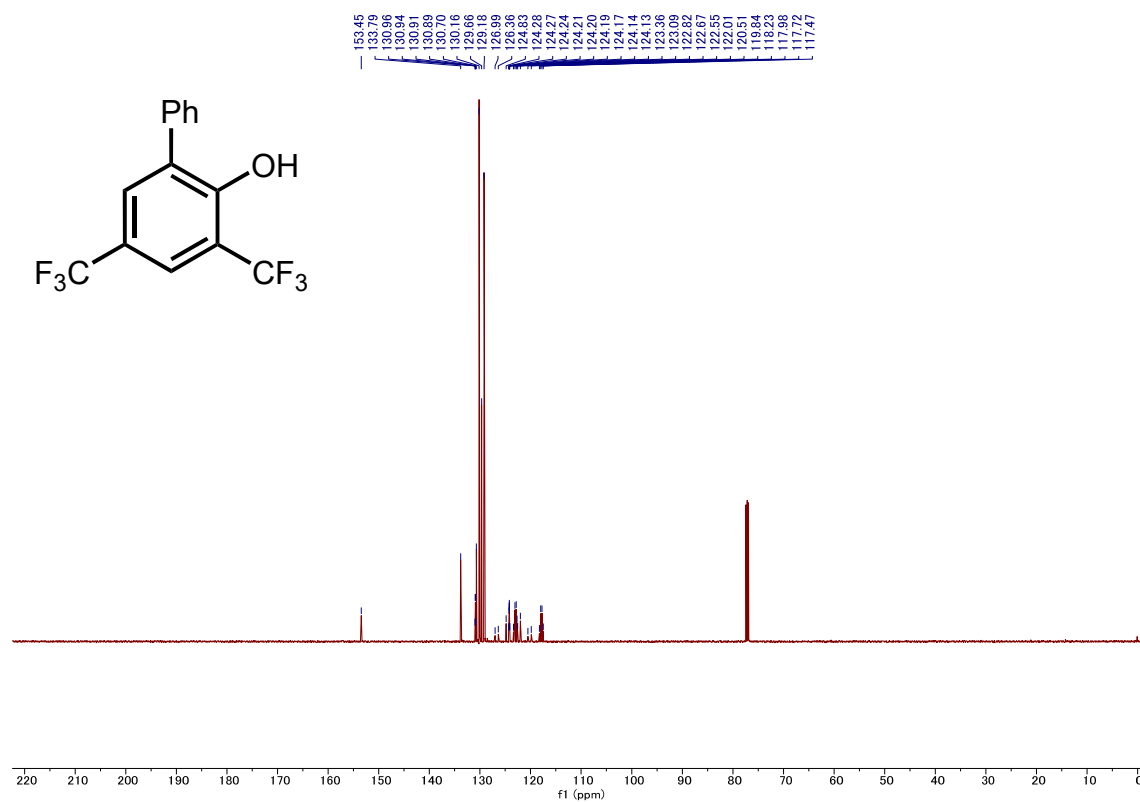
^{19}F NMR (471 MHz, CDCl_3)



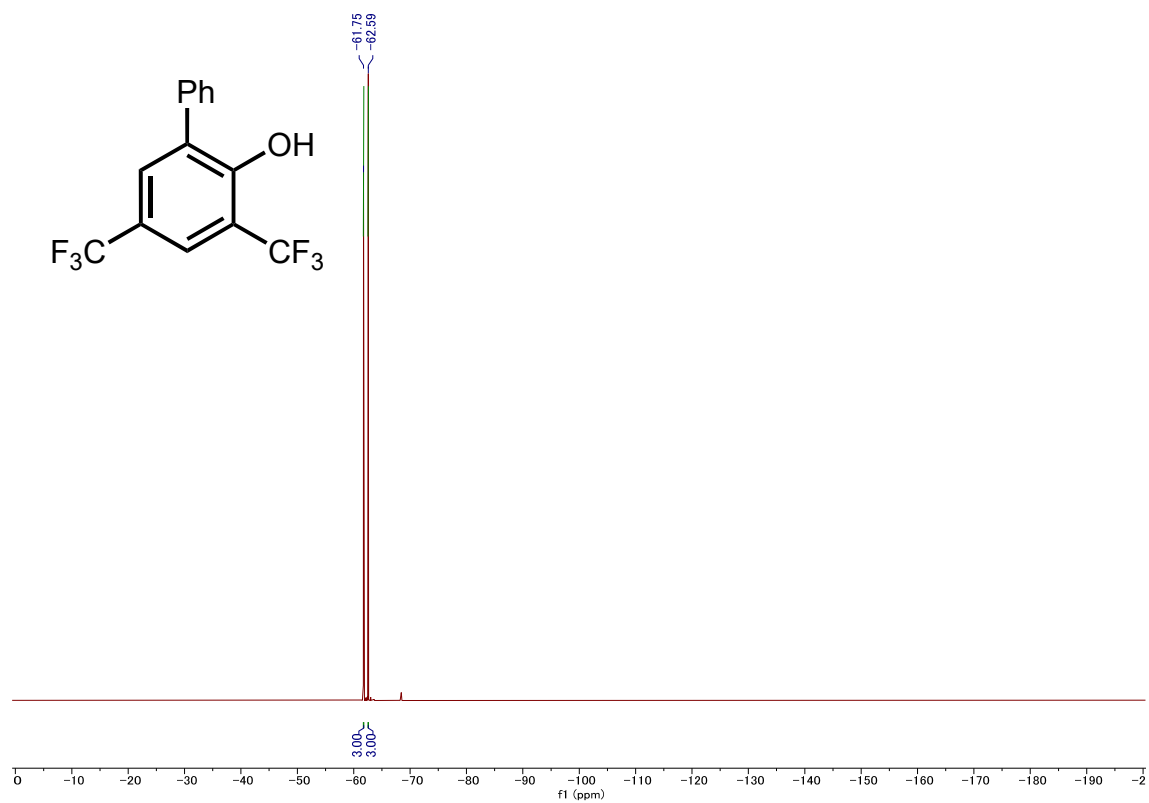
^1H NMR (500 MHz, CDCl_3)



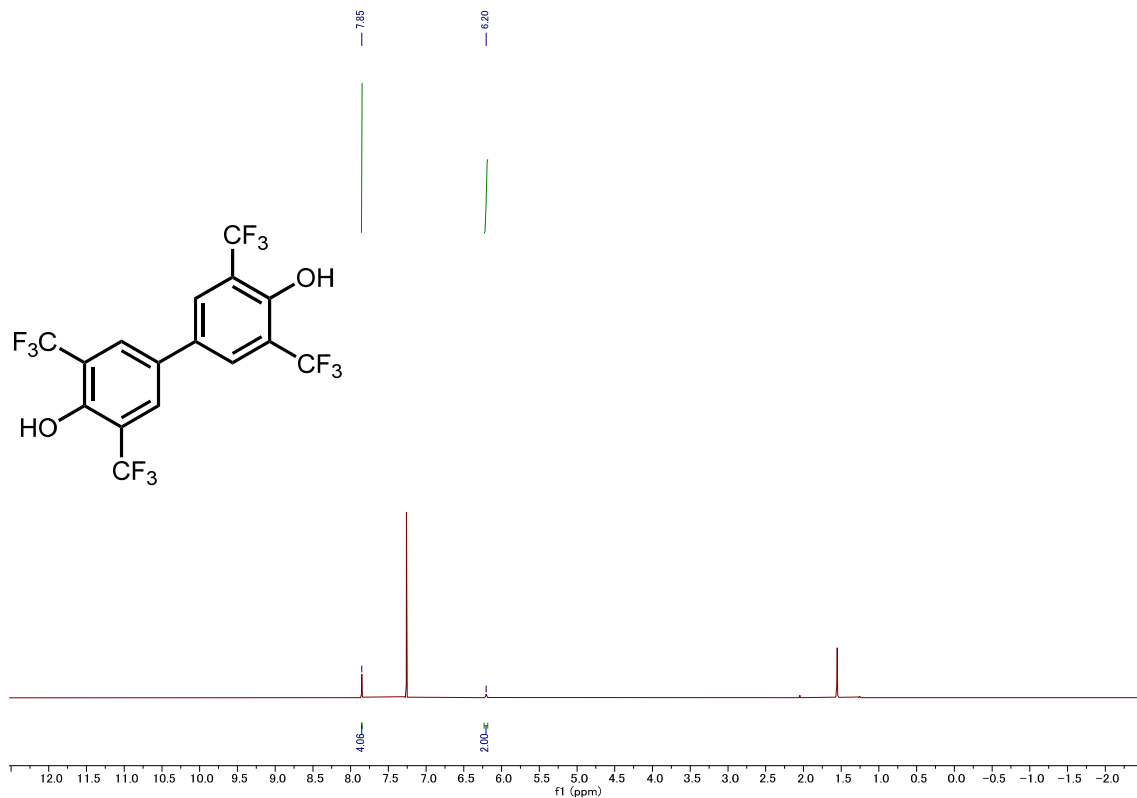
^{13}C NMR (125 MHz, CDCl_3)



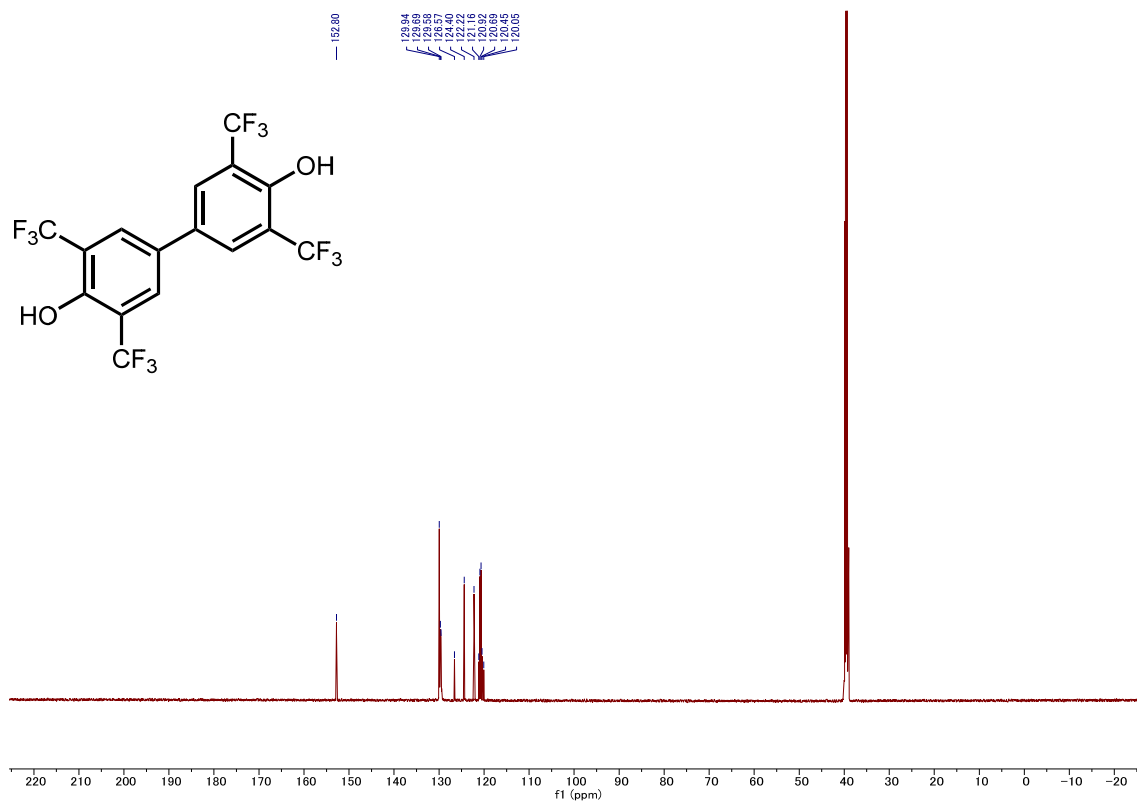
^{19}F NMR (471 MHz, CDCl_3)



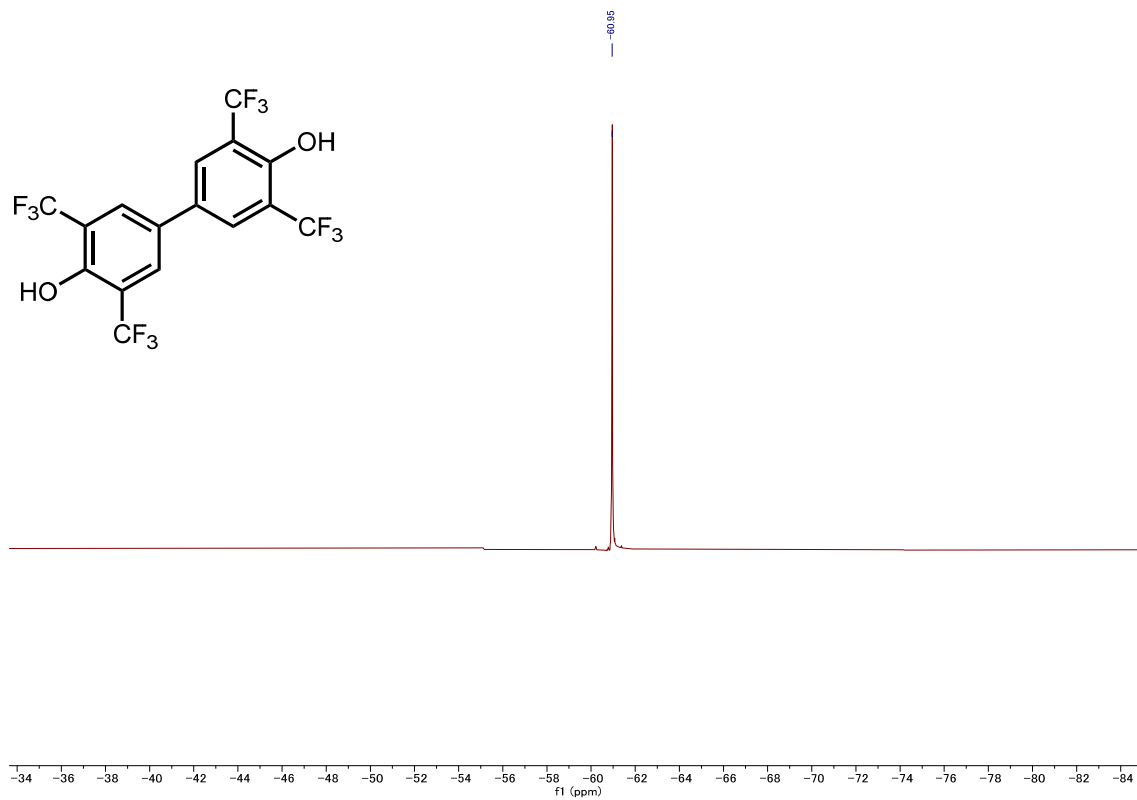
^1H NMR (500 MHz, CDCl_3)



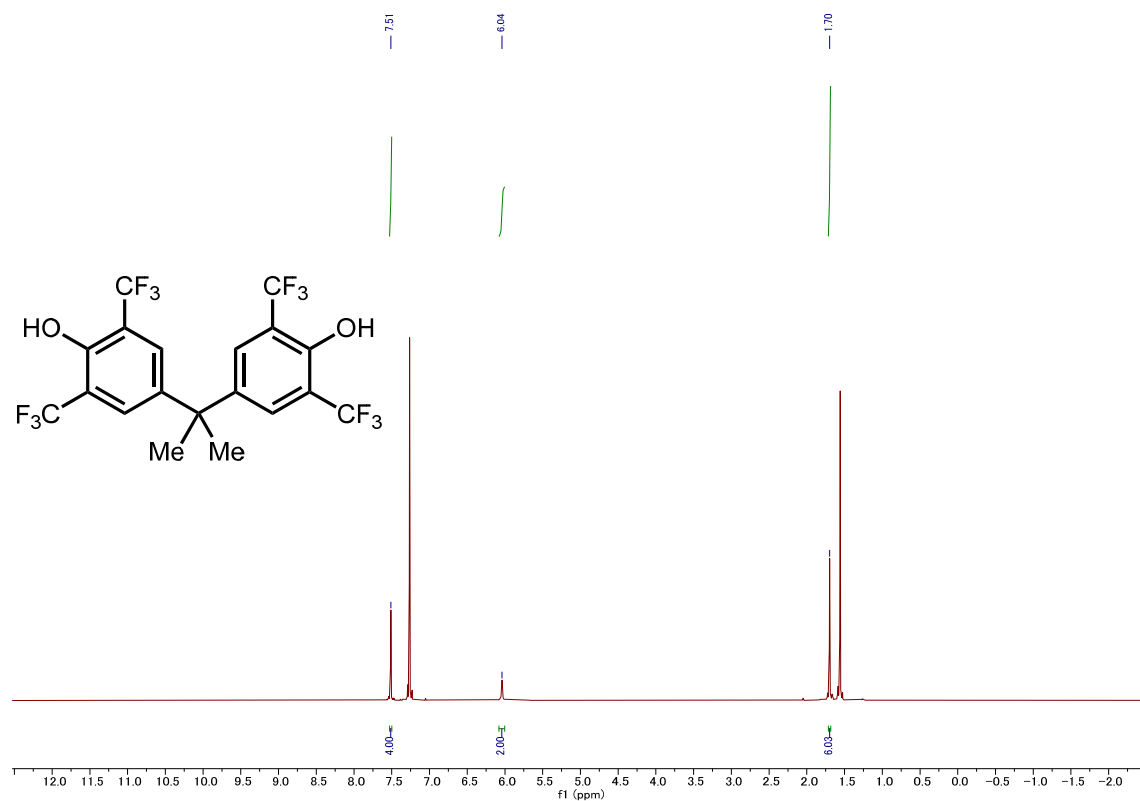
^{13}C NMR (125 MHz, d -DMSO)



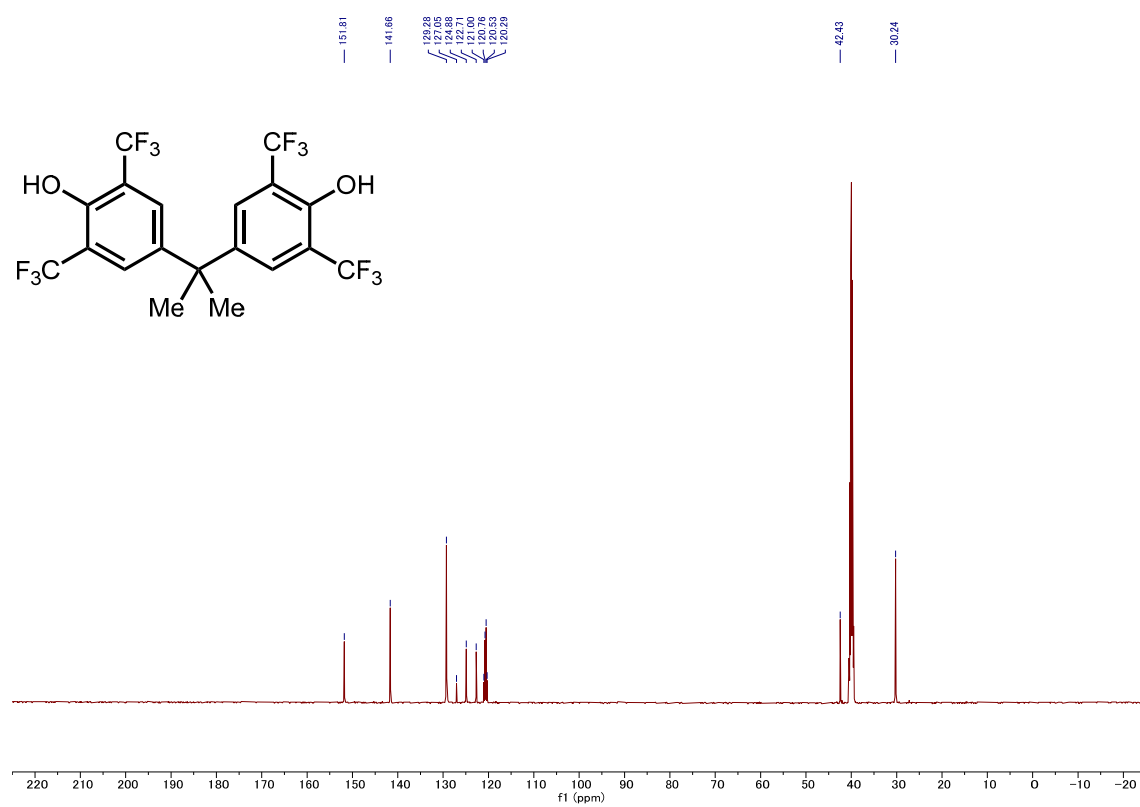
^{19}F NMR (471 MHz, CDCl_3)



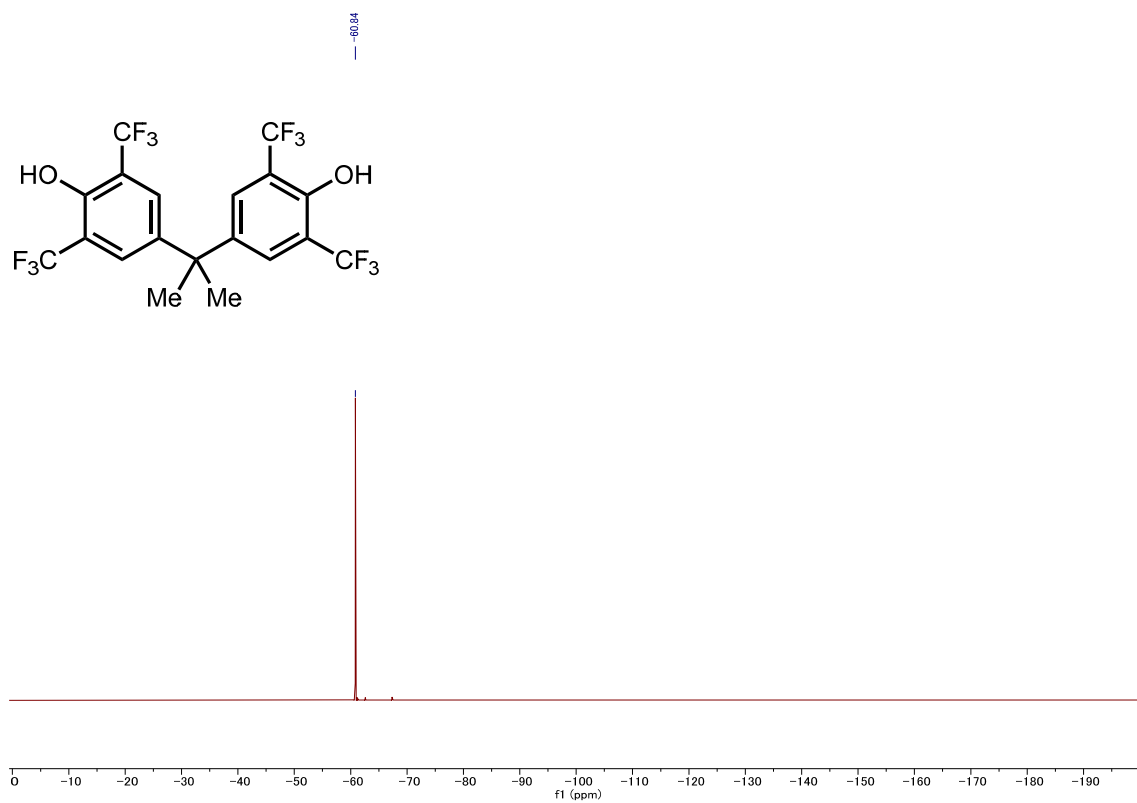
^1H NMR (500 MHz, CDCl_3)



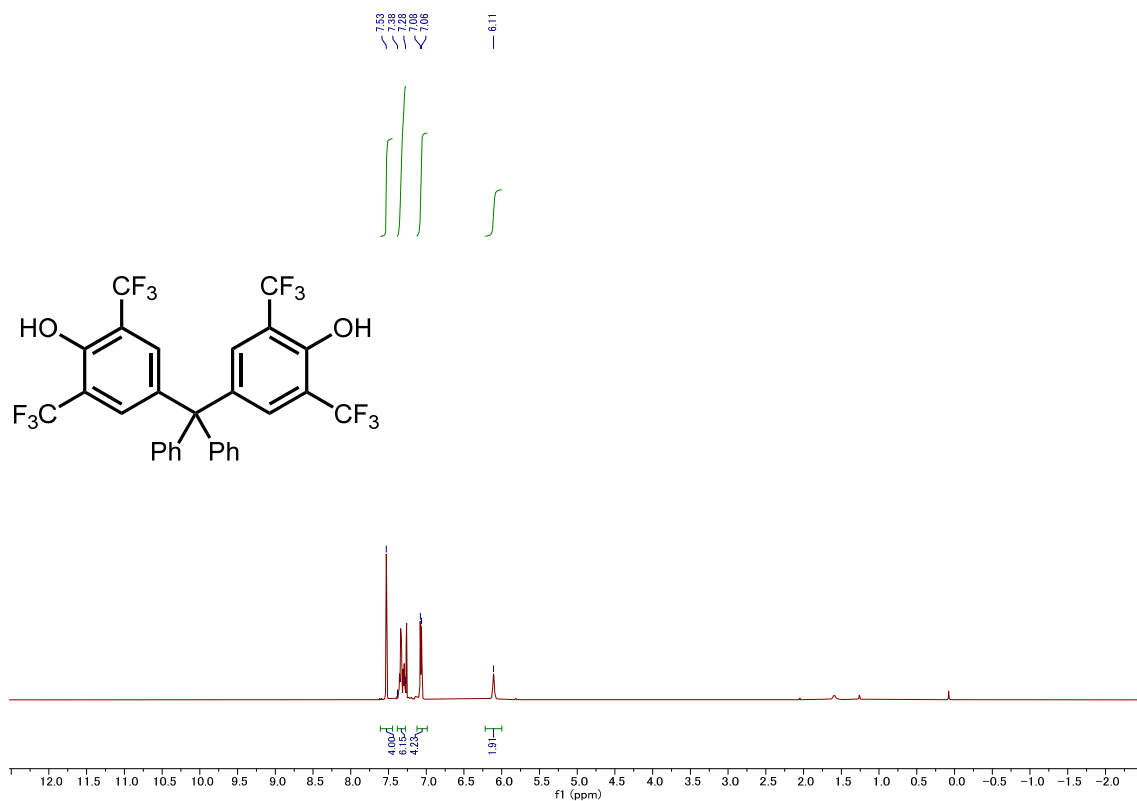
^{13}C NMR (125 MHz, $d\text{-DMSO}$)



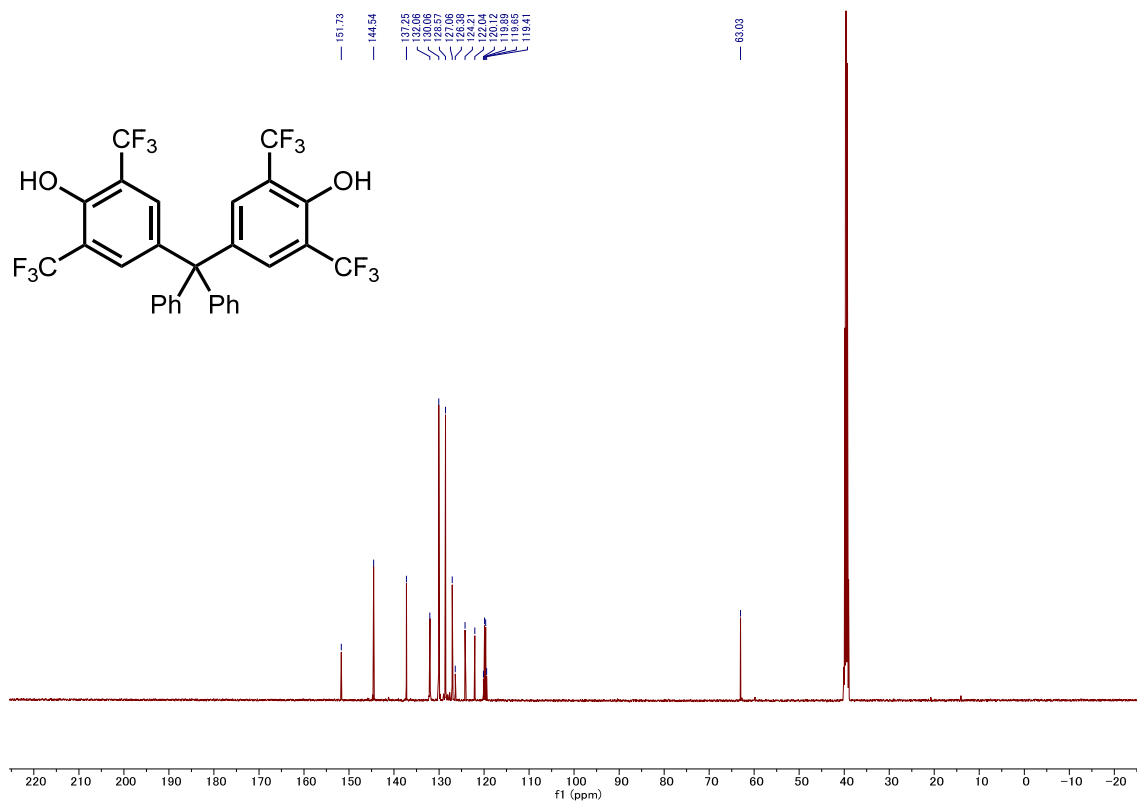
^{19}F NMR (471 MHz, CDCl_3)



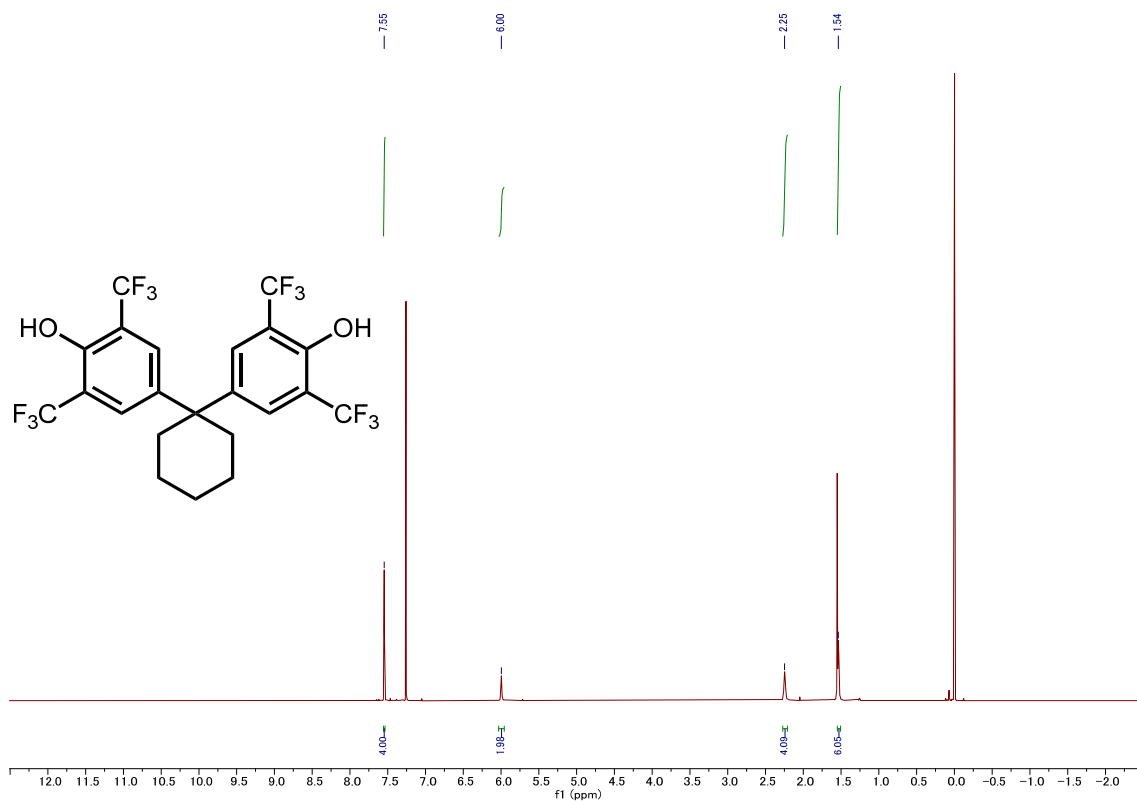
^1H NMR (500 MHz, CDCl_3)



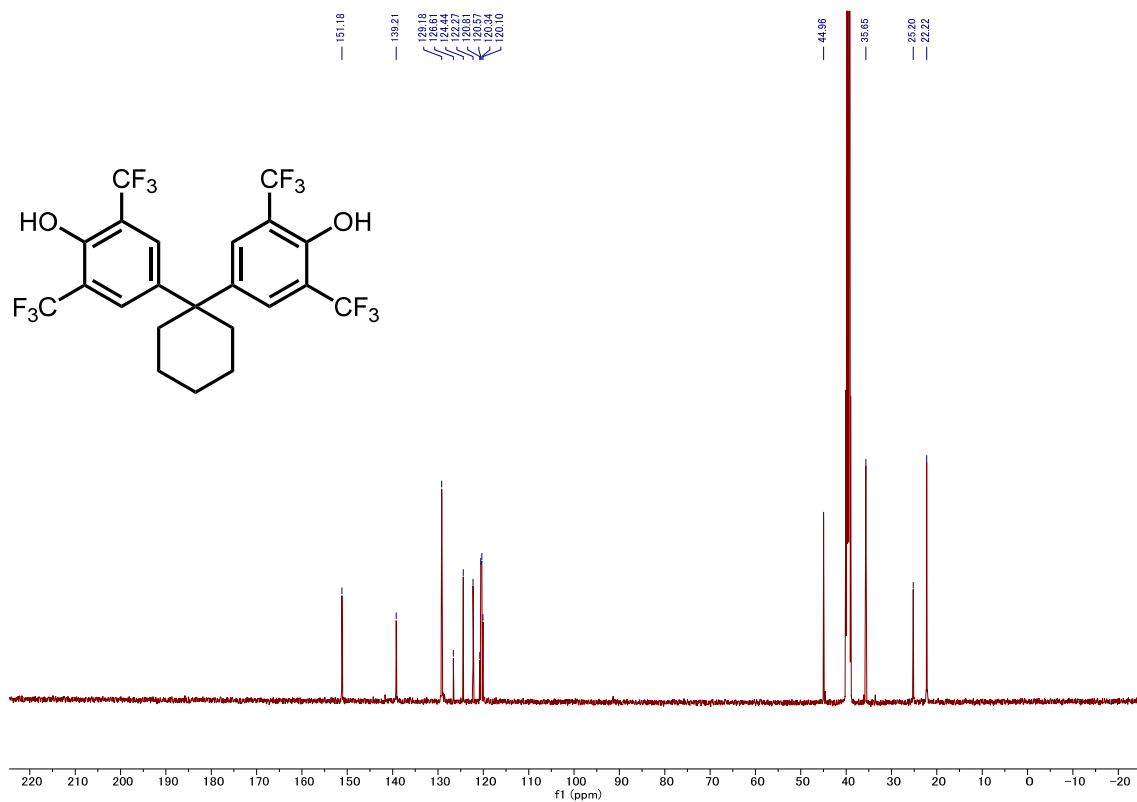
^{13}C NMR (125 MHz, $d\text{-DMSO}$)



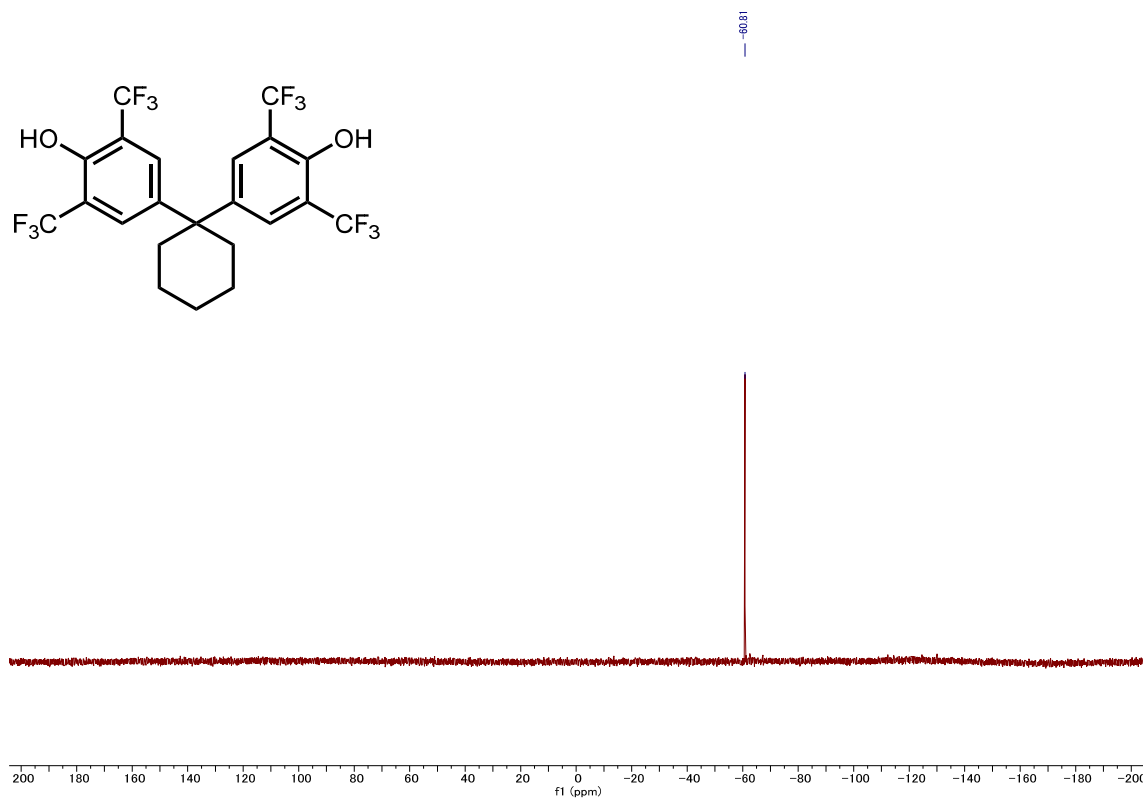
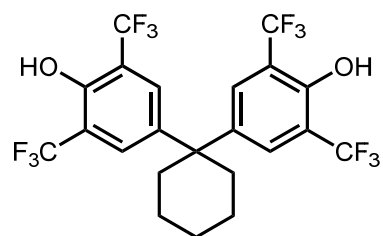
^1H NMR (500 MHz, CDCl_3)



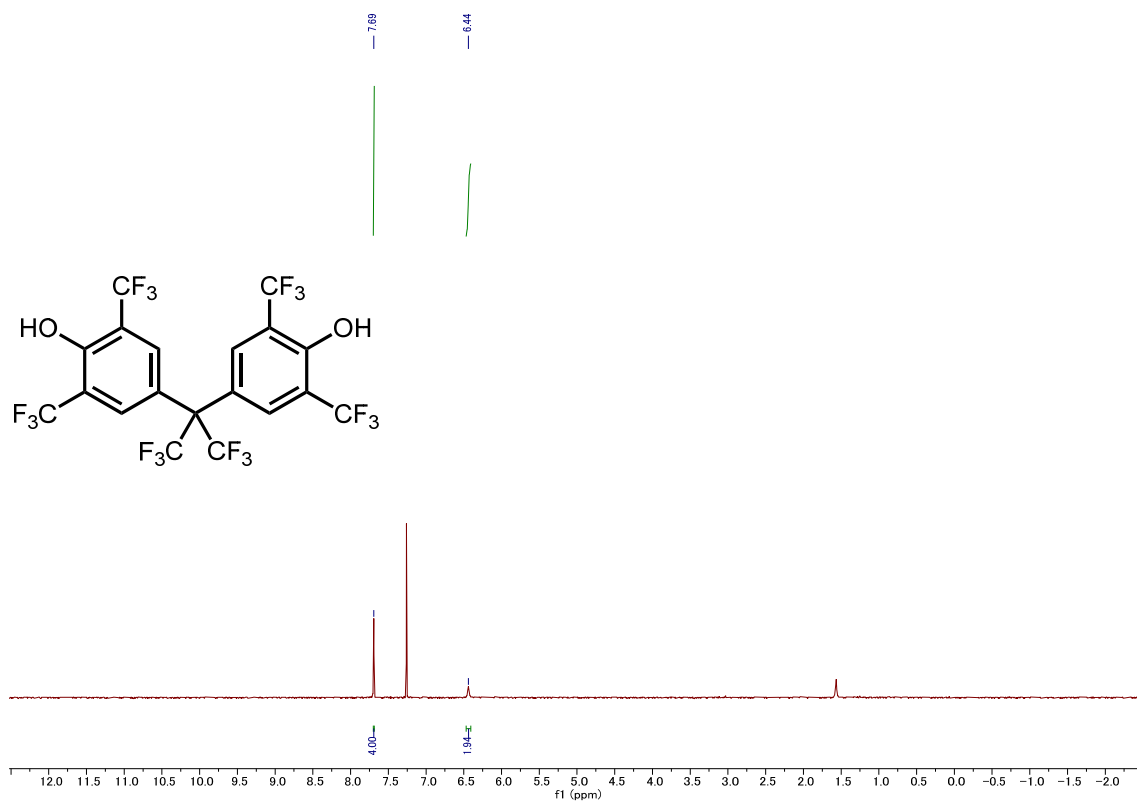
^{13}C NMR (125 MHz, $d\text{-DMSO}$)



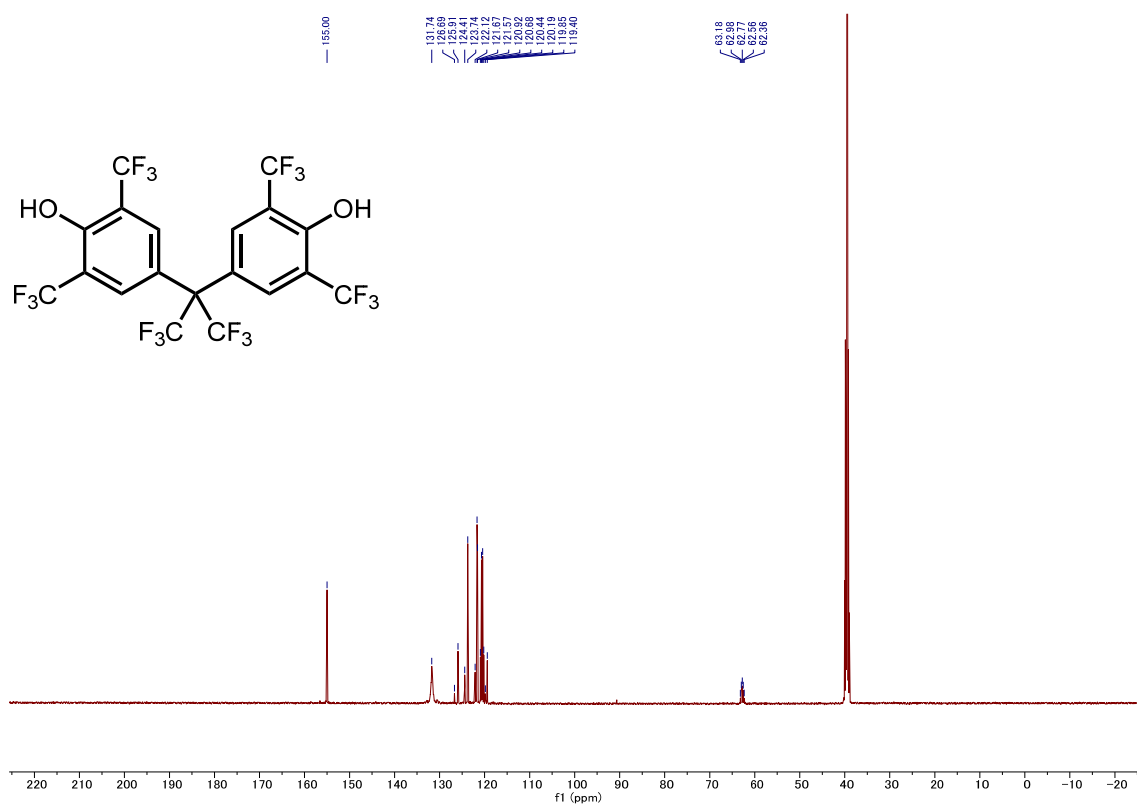
^{19}F NMR (471 MHz, CDCl_3)



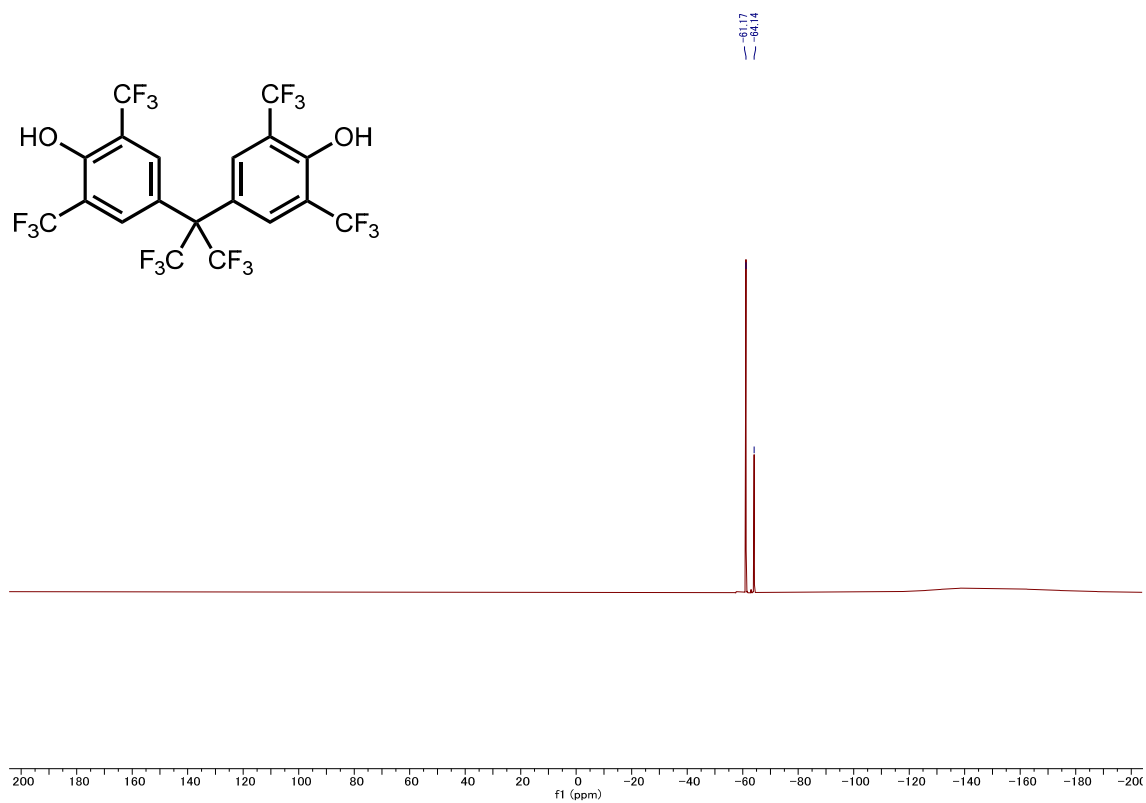
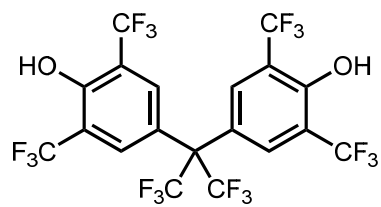
^1H NMR (500 MHz, CDCl_3)



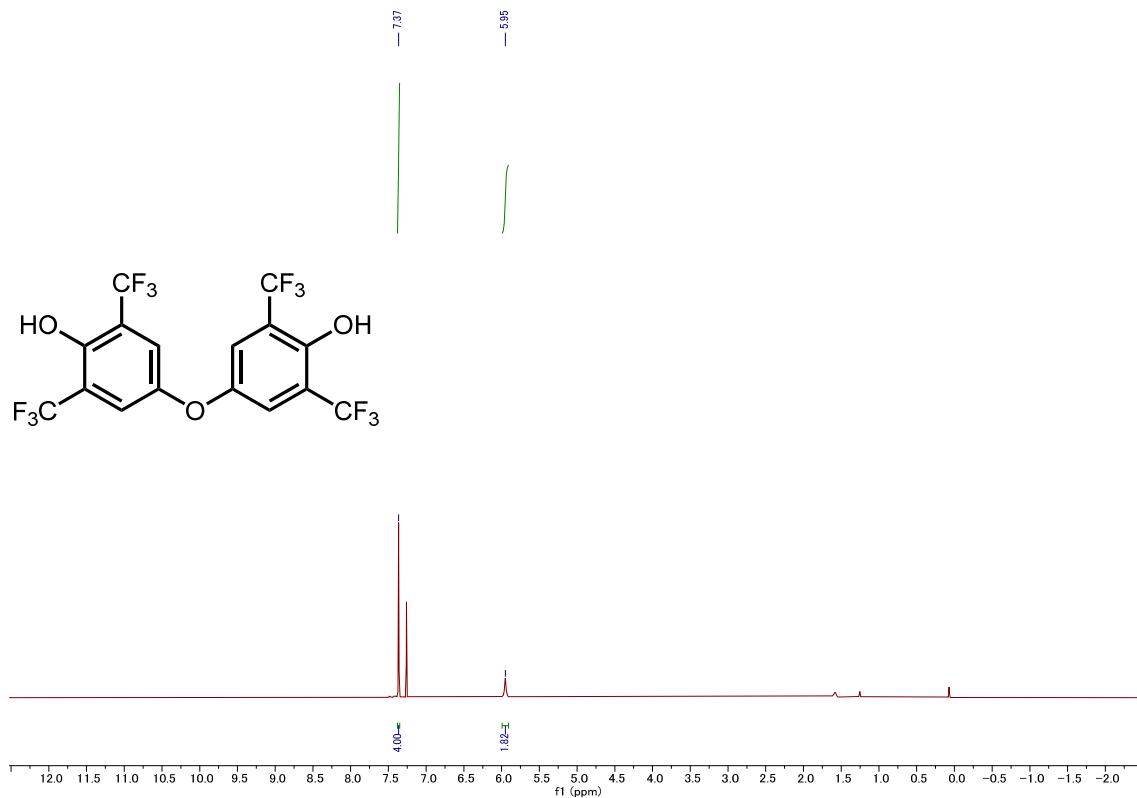
^{13}C NMR (125 MHz, $d\text{-DMSO}$)



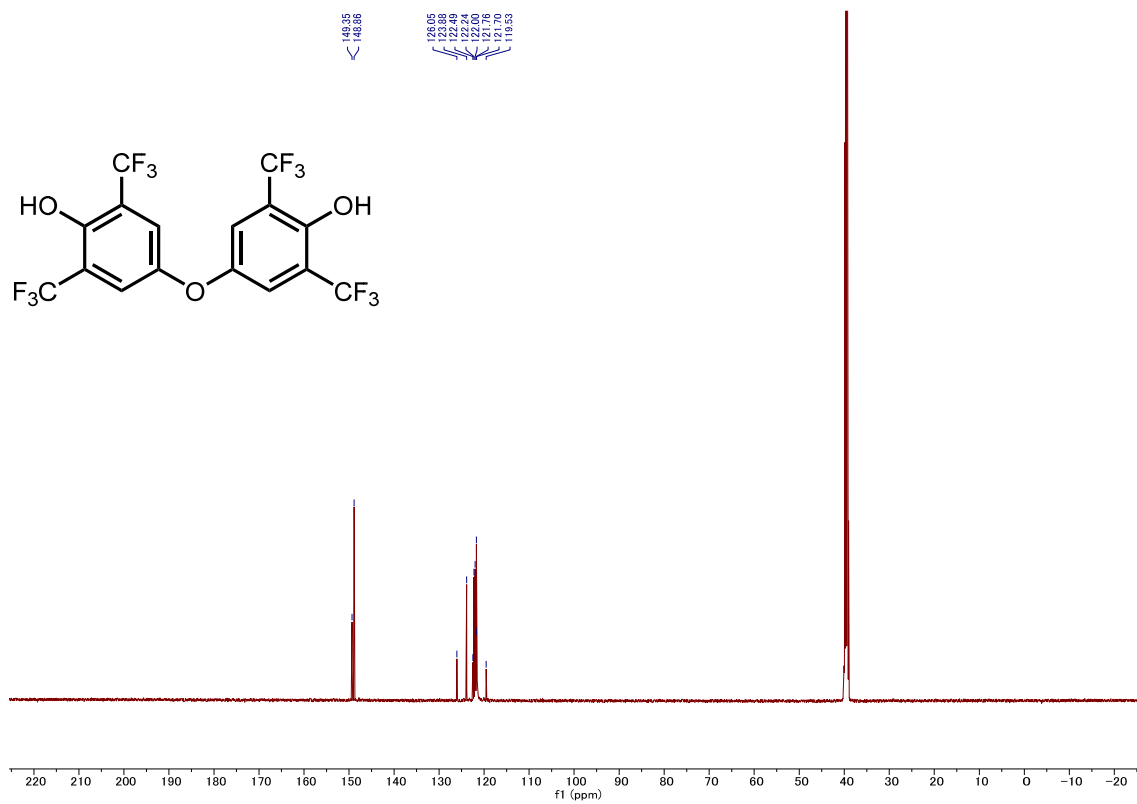
^{19}F NMR (471 MHz, CDCl_3)



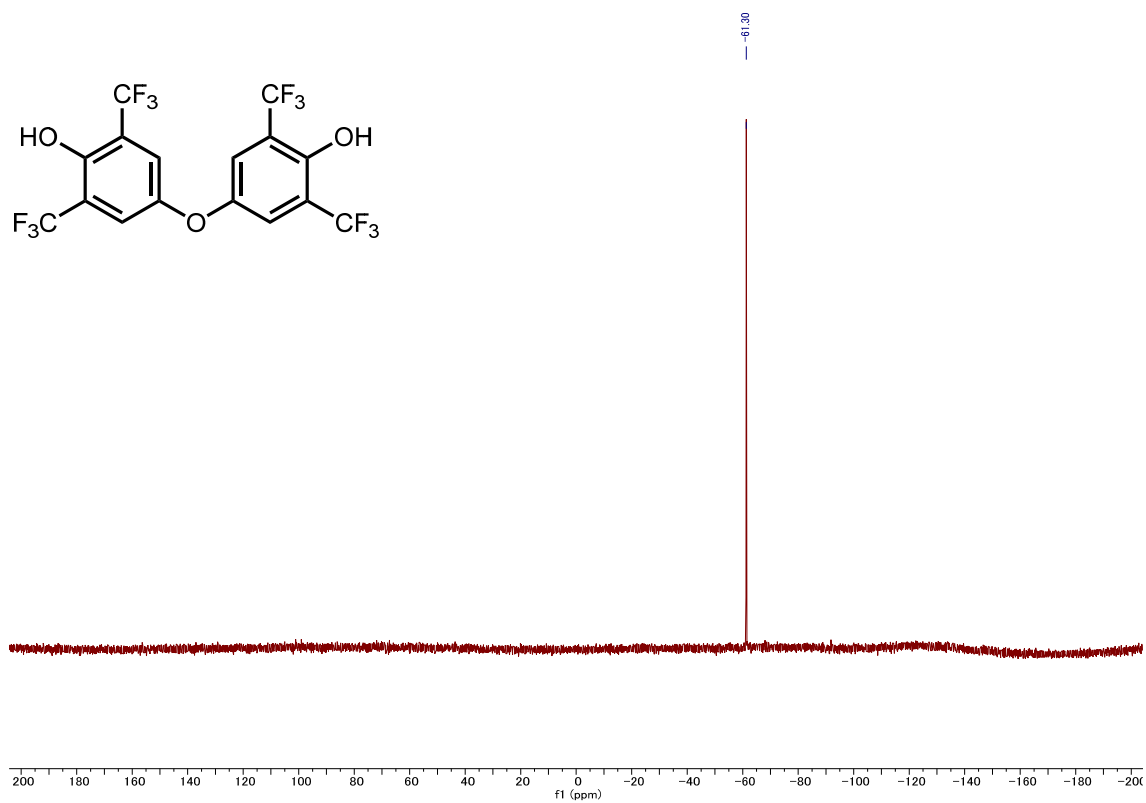
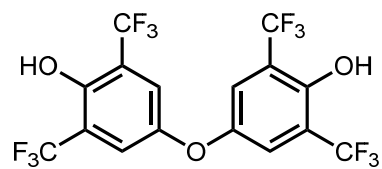
^1H NMR (500 MHz, CDCl_3)



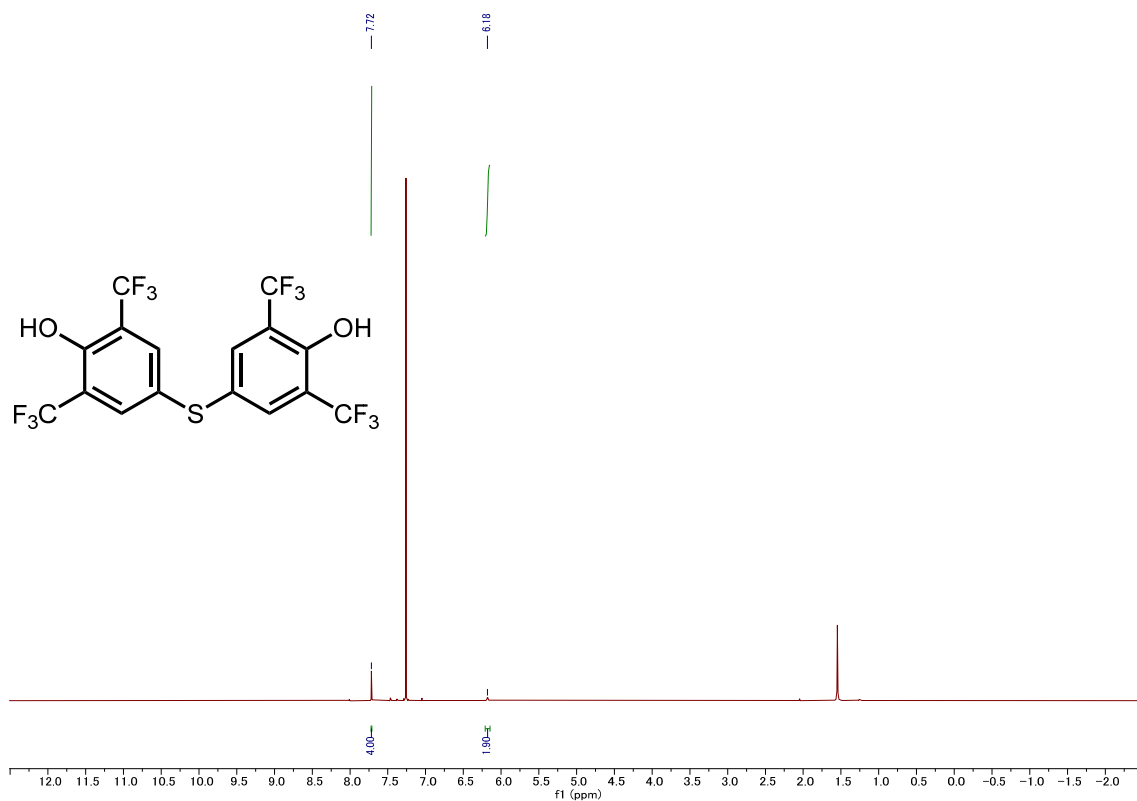
^{13}C NMR (125 MHz, $d\text{-DMSO}$)



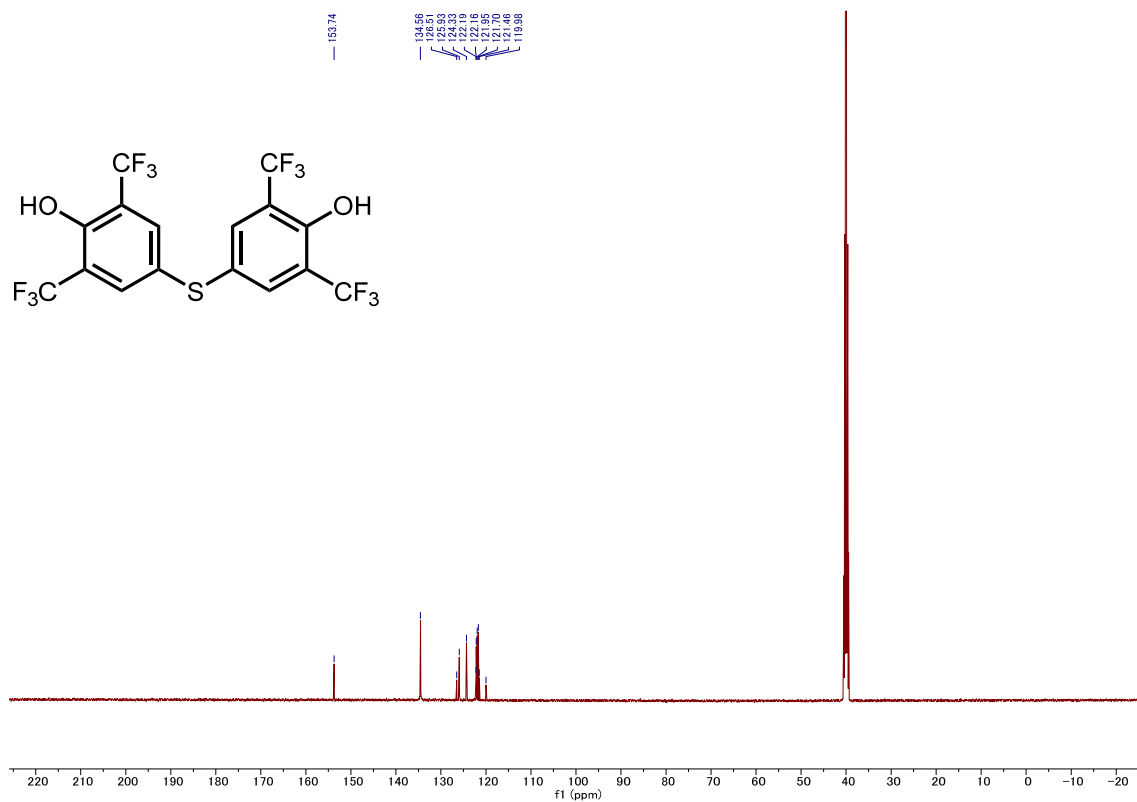
^{19}F NMR (471 MHz, CDCl_3)



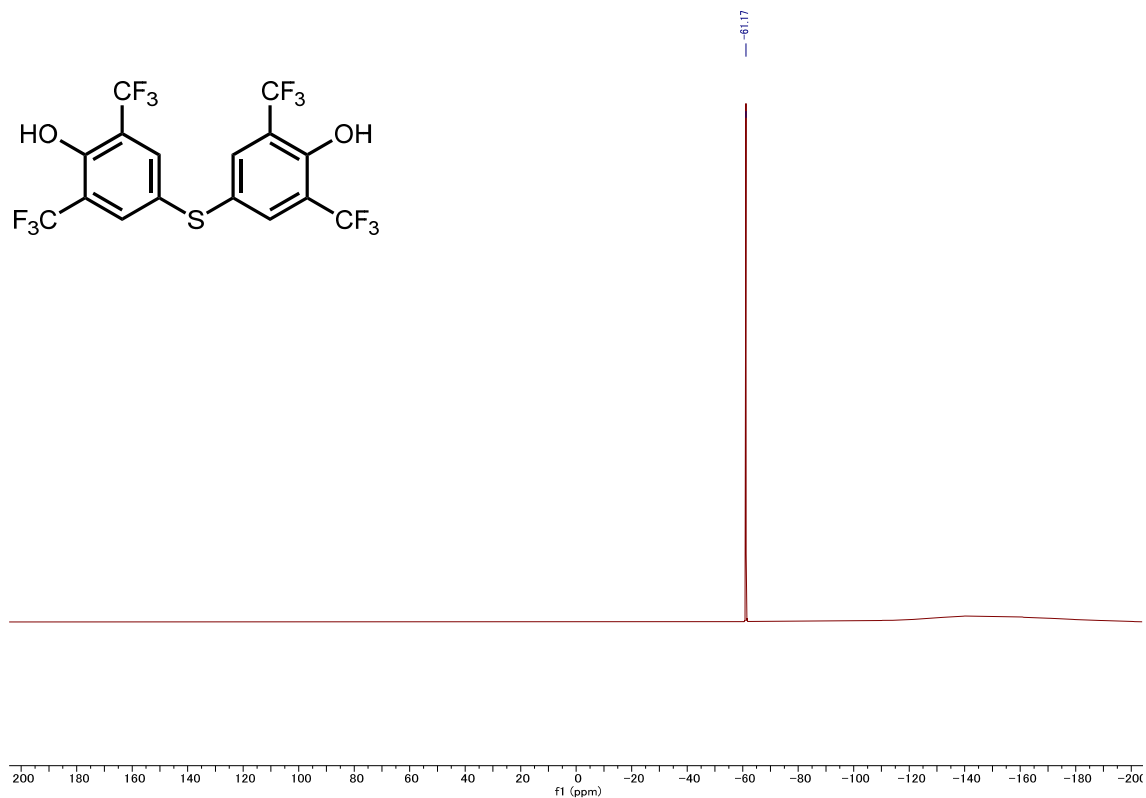
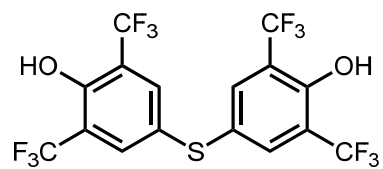
^1H NMR (500 MHz, CDCl_3)



^{13}C NMR (125 MHz, $d\text{-DMSO}$)



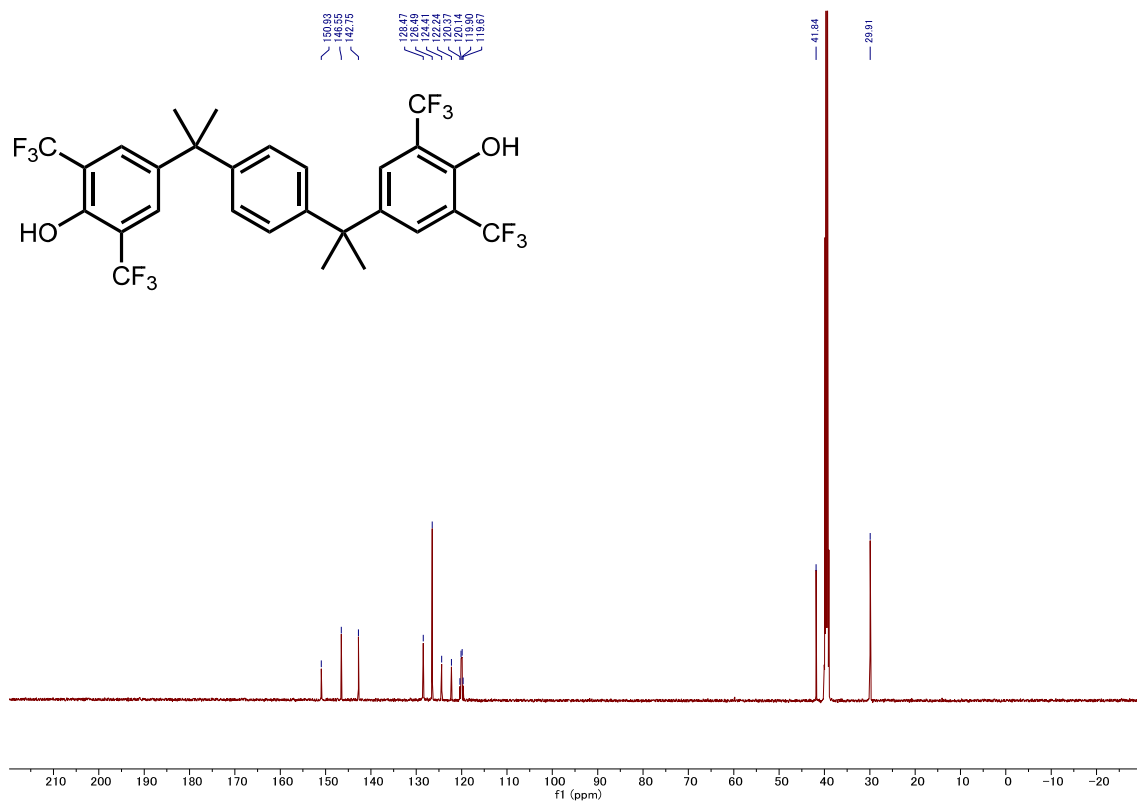
^{19}F NMR (471 MHz, CDCl_3)



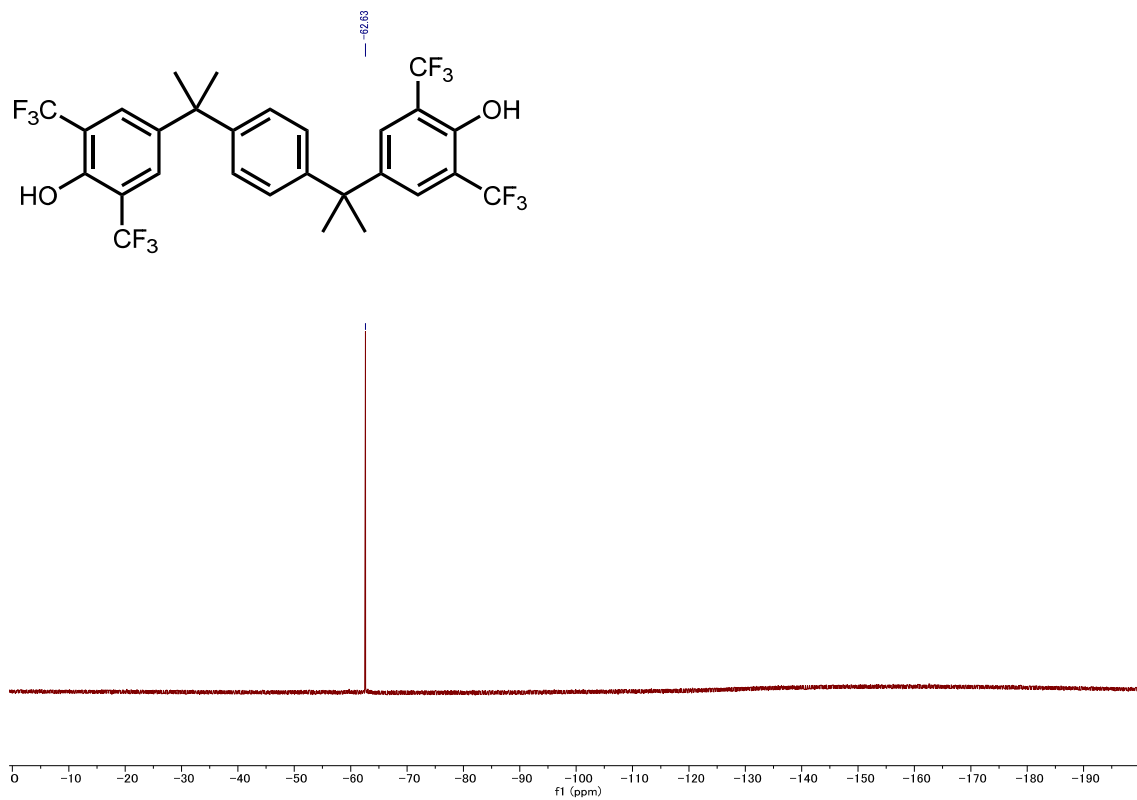
^1H NMR (500 MHz, CDCl_3)



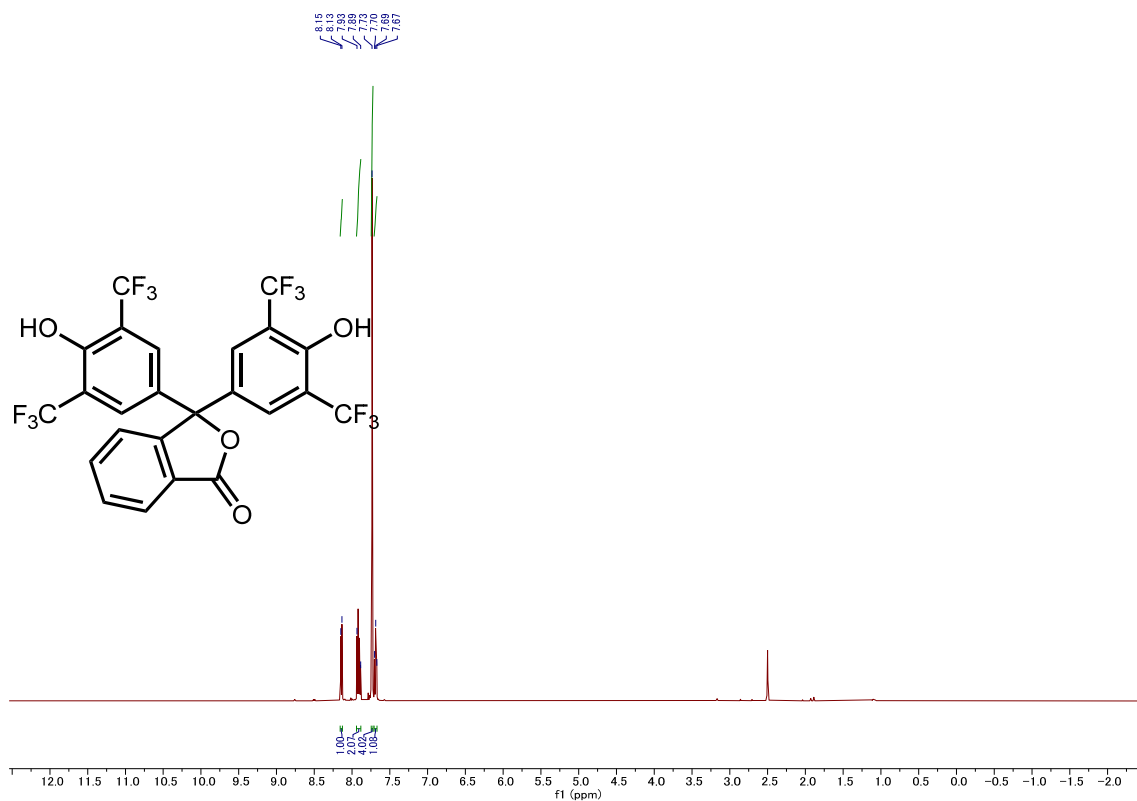
^{13}C NMR (125 MHz, $d\text{-DMSO}$)



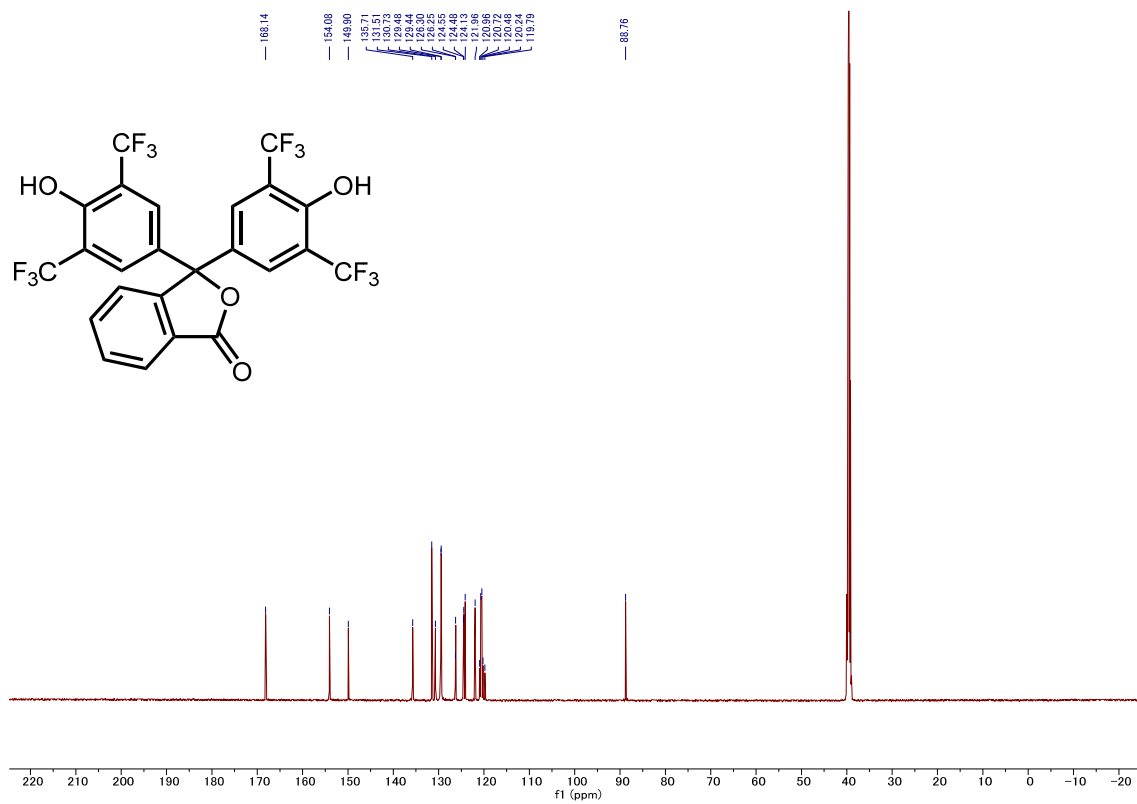
^{19}F NMR (471 MHz, CDCl_3)



¹H NMR (500 MHz, d-DMSO)



¹³C NMR (125 MHz, d-DMSO)



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

