Supplementary Materials for

Defluorinative Functionalization Approach led by Difluoromethyl Anion Chemistry

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General Information

Equipment

GC analyses were performed on a SHIMADZU GC-2014 gas chromatograph (column, Rtx-200; 0.25 mm x 30 m). GC yields were calculated by GC analyses with *n*-undecane as an internal standard using calibration lines derived from commercial compounds with internal standards. NMR spectra were recorded on JEOL JNM-ECZ400S spectrometers (400 MHz for ^{1}H, using Me_4Si as a standard (0.0 ppm); 100 MHz for ^{13}C, using $CHCl_3$ in $CDCl_3$ as a standard (77.0 ppm); 376 MHz for ^{19}F, using C_6F_6 as a standard (-162.9 ppm) in $CDCl_3$ as a standard). NMR yields were calculated by ^{19}F NMR with C_6F_6 as an internal standard. EI mass spectra were recorded on JMS-T2000GC spectrometer. ESI mass spectra were recorded on Exactive Plus HPLC: UltiMate 3000. APCI mass spectra were recorded on Exactive Plus HPLC: UltiMate 3000. Some of the mass spectra were measured by the Instrumental Analysis Service at Hokkaido University. GPC separation was performed on Japan Analytical Industry Co., Ltd LC-9201. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40-100 μm). All batch reactions were carried out in flame-dried glassware under an argon atmosphere.

Flow system

Stainless steel (SUS304) T-shaped micromixers with inner diameters of 250 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 1000 μm purchased from GL Sciences were used unless otherwise stated. The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). The flow microreactor system was immersed in a cryogenic mixture bath with dry ice and acetone to control the temperature. Solutions were continuously introduced to the flow microreactor system using syringe pumps (Harvard PHD2000), equipped with gastight syringes purchased from SGE. All reactions were carried out under an atmosphere of argon.

Materials

Dry tetrahydrofuran (THF), diethyl ether (Et_2O), 1,2-dimethoxyethane (DME), and triglyme were purchased from Kanto Chemical Co., Inc. and used without further purification. Dry diglyme and Potassium were also purchased from Sigma-Aldrich. Naphthalene (Np) was purchased from FUJIFILM Wako Pure Chemical Corporation. Substrates, electrophiles, and some other reagents were purchased from Tokyo Chemical Industry Co., Ltd., FUJIFILM Wako Pure Chemical Corporation, Kanto Chemical Co., Inc., and Sigma-Aldrich. Some compounds were synthesized by the reported procedure.

Experimental Procedures

Preparation of Metal Naphthalenide (MNp)

Naphthalene (3.7 g, 28.6 mmol, 1.3 equiv) was dissolved in anhydrous THF (100.0 ml) (0.22 M). Metal (K, Li, Na, 22.0 mmol, 1.0 equiv) was added and the mixture was stirred for 2 h at ambient temperature until the solution became dark green.

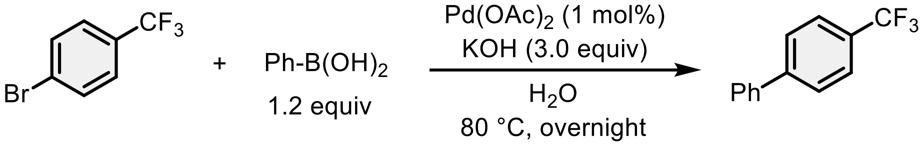
Fig. S1. Potassium Naphthalenide (KNp)

Procedure for preparation of starting materials and electrophiles

General Procedure of desalination process

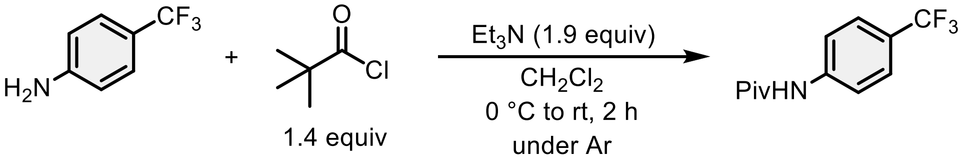
Benzotrifluoride derivatives hydrochloride was dissolved in CH_2Cl_2 (20 mL) and slowly added sat. aq. $NaHCO_3$ (20 mL), extracted. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Obtained benzotrifluoride derivatives used to react after drying.

4-phenyl-benzotrifluoride



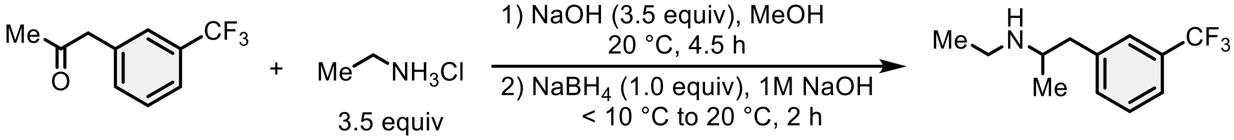
4-bromo-benzotrifluoride (5.0 g, 22 mmol), phenylboronic acid (3.2 g, 26.6 mmol, 1.2 equiv.), $Pd(OAc)_2$ (4.5 mg, 1 mol%), KOH (3.7 g, 67 mmol, 3 eq.), and H_2O (50 mL) were added to 100 mL two-necked round bottom flask and stirred overnight at 80 °C. After the reaction, the reaction mixture was extracted with EtOAc (3 x 5 mL), washed brine, and the organic layer was dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc= 10:1) to give the product. The NMR spectral data were identical to those reported in the literature (*49*).

3,3-Dimethyl-1-[4-(trifluoromethyl)phenyl]-2-butanone



To a 100 mL two-necked round bottom flask was added substrate (4.9 g, 30.4 mmol) in CH_2Cl_2 (30 mL), cooled at 0 °C, then, triethylamine (5.8 g, 57.3 mmol, 1.9 equiv) was added dropwise. Pivaloyl chloride was added dropwise for 2 hours keeping below 10 °C. The reaction mixture was washed with water (2 x 50 mL) and sat. aq. NH_4Cl (2 x 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained solid was washed with hexane and filtration. The NMR spectral data were identical to those reported in the literature (*50*).

1-(3-(Trifluoromethyl)phenyl)-*N*-ethylpropan-2-amine (*51*)



To a stirred suspension of NaOH (17.4 g, 3.5 equiv) in methanol (85 mL) was added dropwise ethylamine hydrochloride (35.3 g, 3.5 equiv) in methanol (80 mL), over 30 minutes. Following l-(3-trifluoromethyl)phenyl-propan-2-one (24.8 g, 122.7 mmol) was added to the mixture. The mixture was stirred at 20 °C for 4.5 hours, then cooled to 0 °C. Solution of sodium borohydride (4.7 g, 1.0 equiv) in 1M sodium hydroxide (10 mL) was added dropwise keeping the below 10 °C, and then was stirred at 20 °C for 2 hours. The reaction mixture was methanol (270 mL) removed then water (100 mL) was added and the mixture was extracted with hexane (100 mL). The aqueous phase was eliminated and the organic phase was washed with water (3 x 100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was distilled under reduced pressure with a distillation of the vigreux column. The distillation heads were eliminated, and the bottom residue was purified through column chromatography (hexane/EtOAc= 10:1) on silica gel to yield free base fenfluramine as a colorless oil.

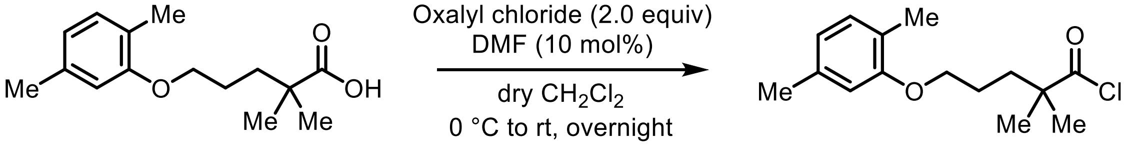
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.35 (m, 4H), 2.95-2.85 (m, 1H), 2.82 (dd, *J*=13.2, 6.4 Hz, 1H), 2.76-2.68 (m, 1H), 2.65-2.57 (m, 2H), 1.09-1.03 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.47, 132.68, 130.75, 130.43-130.28 (m), 128.69, 125.84 (t, *J*= 3.7 Hz), 122.97 (dt, *J*= 7.5, 3.7 Hz), 54.41, 43.32, 41.47, 20.11, 15.38 (d, *J*= 3.2 Hz).

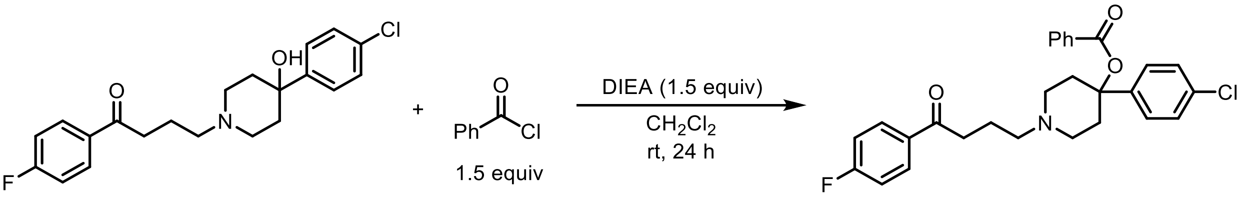
^{19}F NMR (376 MHz, $CDCl_3$) δ -63.77 (s, 3F).

Gemfibrozil chloride (*52*)



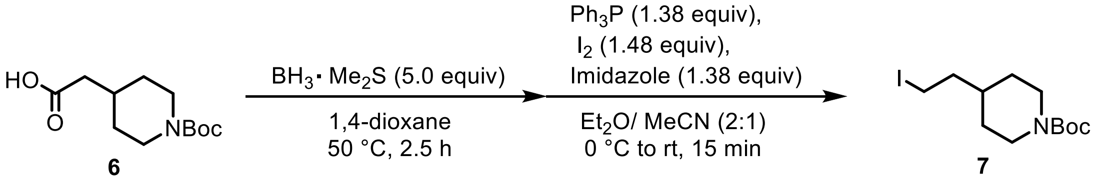
To a 100 mL two-necked round bottom flask was added Gemfibrozil (17.6 mmol), dry CH_2Cl_2 (40.0 mL), and 10 mol% of *N*, *N*-dimethyl formamide (DMF). The reaction mixture was cooled to 0 °C and stirred for 5 minutes. Then oxalyl chloride (4.3 g, 33.9 mmol, 2.0 equiv) was added dropwise to the reaction mixture and stirred at ambient temperature overnight. The resulting mixture was concentrated under reduced pressure and used directly without further purification for the reaction.

Benzonic acid haloperidol ester (*53*)



To a 50 mL two-necked round bottom flask was added Haloperidol (3.0 g, 7.8 mmol) in CH_2Cl_2 (30 mL). Ethyldiisopropylamine (DIEA) (2.0 mL, 11.7 mmol) and benzoyl chloride (1.4 mL, 11.7 mmol) were added, and then the reaction mixture was stirred at ambient temperature for 24 hours. The solution was quenched with sat. aq. $NaHCO_3$ (100 mL), was extracted into CH_2Cl_2 (4 x 100 mL), and concentrated. The residue was purified through column chromatography (MeOH/dichloromethane= 10:1) on silica gel. The NMR spectral data were identical to those reported in the literature.

2-(*N*-*tert*-Butoxycarbonyl-4-piperodonyl) ethyl iodide (*54*)



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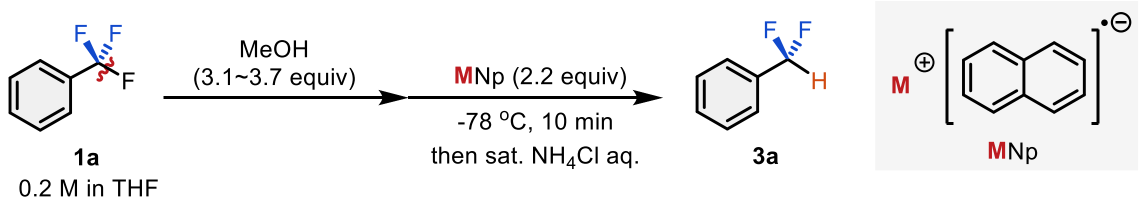
To a 200 mL two-necked round bottom flask was added *N*-tert-Butoxycarbonyl-4-piperidineacetic acid **6** (5.1 g, 21.0 mmol) in 1, 4-dioxane (100 mL) and dimethyl sulfide borane (9.8 mL, 5.0 equiv), and were stirred at 50 °C for 2.5 hours. Then the reaction mixture was concentrated under reduced pressure. The residue was quenched with water (50 mL), and extracted with Et_2O/EtOAc (200 mL, 1:1), washed with 1M aq. NaOH (50 mL) and brine (50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Following the obtained crude product (4.6 g), Imidazole (1.9 g, 1.38 equiv), and triphenylphosphine (7.2 g, 1.38 equiv) were added to 200 mL two-necked round bottom flask and cooled to 0 °C. The reaction mixture was stirred and I_2 (7.4 g, 1.48 equiv) was added dropwise. Then the reaction mixture was stirred at ambient temperature for 15 minutes and was added to Et_2O (200 mL). The solution was washed with sat. aq. Na_2SO_4 (2 x 200 mL), sat. aq. $CaSO_4$ (200 mL), and brine. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by short-column chromatography (hexane) and concentrated under reduced pressure to afford the pure product as a brown oil in 70 % overall yield (4.92 g). The NMR spectral data were identical to those reported in the literature.

General procedure for hydrodefluorination in the batch reactor.

Method A (in the presence of methanol)

To a 10 mL test tube were added benzotrifluoride (29.2 mg, 0.2 mmol), methanol (3.1–3.7 equiv), and THF (2 mL). To a stirred solution at -78 °C, and then metal naphthalenide (0.22 M in THF) was added dropwise. After stirring for 10 min, the reaction mixture was quenched with sat. aq. NH_4Cl (5 mL). The organic layer was analyzed by gas chromatography with an undecane as an internal standard.

Table S1. Hydrodefluorination using metal naphtalenides in the presence of methanol*



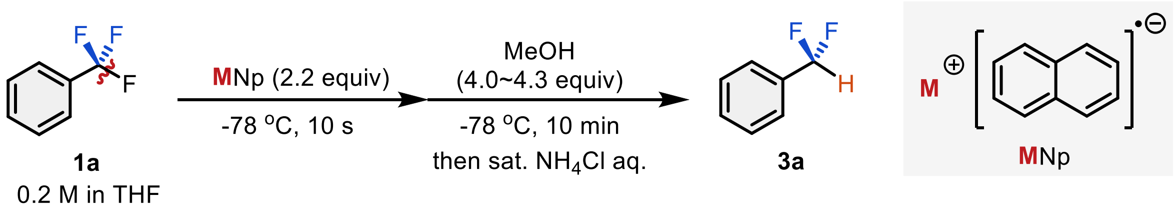
entry	metal	yield of 3**a** / %	Recovery of **1a** / %
1	Li	trace	77
2	Na	7	70
3	K	3	53

*Reaction conditions: **1a** (0.2 mmol), MeOH (3.1–3.7 equiv), MNp (2.2 equiv), -78 °C, 10 min. Yields and conversions were determined by gas chromatography with an internal standard.

Method B (in the absence of methanol)

To a 10 mL test tube were added benzotrifluoride (29.2 mg, 0.2 mmol), and THF (2 mL). To a stirred solution at -78 °C, and then metal naphthalenide (0.22 M in THF) was added dropwise. After stirring for 10 sec, and then methanol (4.0–4.3 equiv) was added. The mixture was stirred for 10 min, the reaction mixture was quenched with sat. aq. NH_4Cl (5 mL). The organic layer was analyzed by gas chromatography with an undecane as an internal standard.

Table S2. Hydrodefluorination using metal naphtalenides in the absence of methanol*

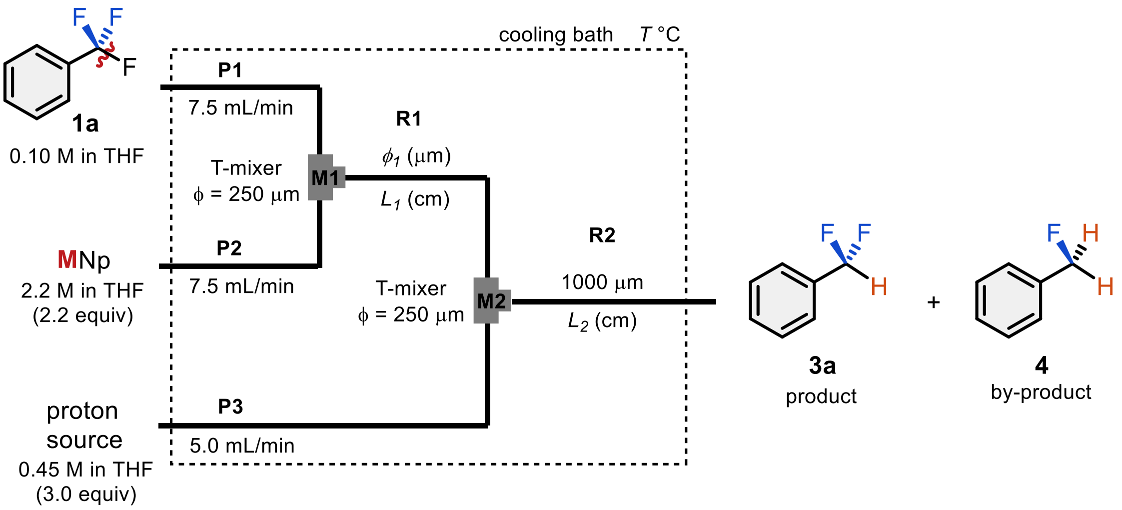


entry	metal	yield of 3**a** / %	Recovery of **1a** / %
1	Li	n.d.	55
2	Na	n.d.	54
3	K	trace	47

*Reaction conditions: **1a** (0.2 mmol), MeOH (4.0–4.3 equiv), MNp (2.2 equiv), -78 °C, 10 min. Yields and conversions were determined by gas chromatography with an internal standard.

Optimization of hydrodefluorination in the absence of methanol under the flow

Scheme S1.



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter ϕ= 250 µm)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter ϕ= 1000 µm, length L= 100 cm)) was used. The flow microreactor system was cooled by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in solvent) (flow rate: 7.5 mL/ min) and a solution of metal naphtalenide (MNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (0.45 M in solvent) (flow rate: 5.0 mL/ min) in **M2**. The resulting solution was passed through **R2** (inner diameter ϕ= 1000 µm). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl. The yields of difluoromethyl benzene (**3a**) were determined by gas chromatography with an undecane as an internal standard. The optimizations are summarized in Table S3.

Table S3.

entry	metal	proton source	**R1**		**R2**	t^{R1}	t^{R2}	solvent	T	yield of **3a**	recovery of **1a**	yield of **4q**
	/equiv	/equiv	ϕ_1 /µm	L_1 /cm	L_2 /cm	/sec	/sec	/volume ratio	/°C	/%	/%	/%
1	Li/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-60	n.d.	28	n.d.
2	Li/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF	-60	n.d.	20	n.d.
3	Li/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF	-60	n.d.	19	n.d.
4	Li/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF	-60	n.d.	19	n.d.
5	Li/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF	-60	n.d.	19	n.d.
6	Na/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-60	32	10	n.d.
7	Na/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF	-60	29	10	n.d.
8	Na/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF	-60	20	17	n.d.
9	Na/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF	-60	20	26	n.d.
10	Na/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF	-60	trace	19	n.d.

11	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-60	68	14	n.d.
12	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF	-60	70	15	n.d.
13	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF	-60	66	14	n.d.
14	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF	-60	66	14	n.d.
15	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF	-60	60	13	n.d.
16	K/ 2.1	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	60	20	3
17	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	75	9	6
18	K/ 2.5	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	72	3	10
19	K/ 3.0	MeOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	61	5	17
20	K/ 2.2	MeOH/1.5	250	3.5	200	0.0069	4.7	THF	-78	20	35	trace
21	K/ 2.2	MeOH/2.0	250	3.5	200	0.0069	4.7	THF	-78	56	22	3
22	K/ 2.2	MeOH/5.0	250	3.5	200	0.0069	4.7	THF	-78	69	13	-
23	K/ 2.2	TFE/1.5	250	3.5	200	0.0069	4.7	THF	-78	51	27	trace
24	K/ 2.2	TFE/2.0	250	3.5	200	0.0069	4.7	THF	-78	50	32	trace
25	K/ 2.2	TFE/3.0	250	3.5	200	0.0069	4.7	THF	-78	41	42	trace
26	K/ 2.2	AcOH/1.5	250	3.5	200	0.0069	4.7	THF	-78	31	42	trace
27	K/ 2.2	AcOH/2.0	250	3.5	200	0.0069	4.7	THF	-78	29	50	trace
28	K/ 2.2	AcOH/3.0	250	3.5	200	0.0069	4.7	THF	-78	19	59	trace
29	K/ 2.2	MeOH/3.0	250	3.5	50	0.0069	1.2	THF	-78	51	trace	10
30	K/ 2.2	MeOH/3.0	250	3.5	100	0.0069	2.4	THF	-78	63	10	trace
31	K/ 2.2	MeOH/3.0	250	3.5	300	0.0069	7.1	THF	-78	66	13	5
32	K/ 2.2	MeOH/3.0	250	3.5	400	0.0069	9.4	THF	-78	62	8	4
34	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-78	74	trace	9
35	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-78	73	5	trace
36	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-78	77	4	trace
37	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-78	69	3	trace
38	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-78	71	trace	trace
39	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-78	71	6	trace
40	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-78	67	3	trace
41	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-78	68	trace	trace
42	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF†	-78	64	15	trace
43	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF†	-78	62	17	trace

44	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF†	-78	60	16	trace
45	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF†	-78	58	15	trace
46	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF†	-78	57	12	trace
47	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF†	-78	55	13	trace
48	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF†	-78	54	13	trace
49	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF†	-78	48	12	trace
50	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/ diglyme /10:1	-78	50	trace	15
51	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/ diglyme /10:1	-78	67	5	10
52	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/ diglyme /10:1	-78	73	trace	trace
53	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/ diglyme /10:1	-78	75	trace	trace
54	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/ triglyme /10:1	-78	46	4	14
55	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/ triglyme /10:1	-78	60	9	12
56	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/ triglyme /10:1	-78	74	trace	4
57	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/ triglyme /10:1	-78	71	trace	4
58	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-20	30	24	trace
59	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-20	26	26	trace
60	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-20	15	30	trace
61	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-20	trace	25	trace
62	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-20	trace	22	trace

63	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-20	trace	19	trace
64	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-20	trace	31	trace
65	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-20	trace	31	trace
66	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-40	54	22	trace
67	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-40	54	22	trace
67	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-40	44	24	trace
68	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-40	45	22	trace
69	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-40	38	24	trace
70	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-40	38	22	trace
71	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-40	22	33	trace
72	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-40	20	27	trace
73	K/ 2.2	MeOH/3.0	250	3.5	200	0.0069	4.7	THF/DME /10:1	-60	71	12	trace
74	K/ 2.2	MeOH/3.0	500	3.5	200	0.027	4.7	THF/DME /10:1	-60	73	15	trace
75	K/ 2.2	MeOH/3.0	1000	3.5	200	0.11	4.7	THF/DME /10:1	-60	73	14	trace
76	K/ 2.2	MeOH/3.0	1000	12.5	200	0.39	4.7	THF/DME /10:1	-60	72	13	trace
77	K/ 2.2	MeOH/3.0	1000	25	200	0.97	4.7	THF/DME /10:1	-60	72	14	trace
78	K/ 2.2	MeOH/3.0	1000	50	200	1.6	4.7	THF/DME /10:1	-60	68	13	trace
79	K/ 2.2	MeOH/3.0	1000	100	200	3.1	4.7	THF/DME /10:1	-60	58	7	trace
80	K/ 2.2	MeOH/3.0	1000	200	200	6.3	4.7	THF/DME /10:1	-60	49	6	trace

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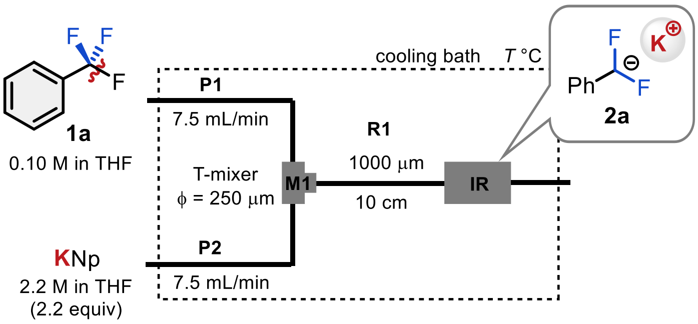
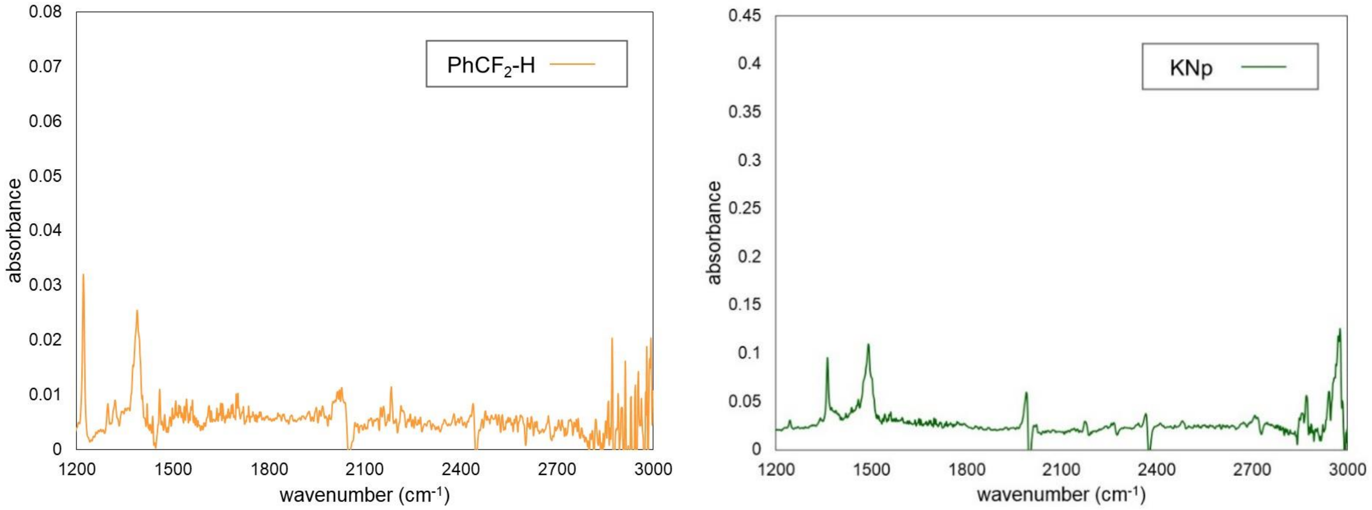
[†] 5.0 equiv of 1,2-dimethoxyethane was used for the benzotrifluoride.

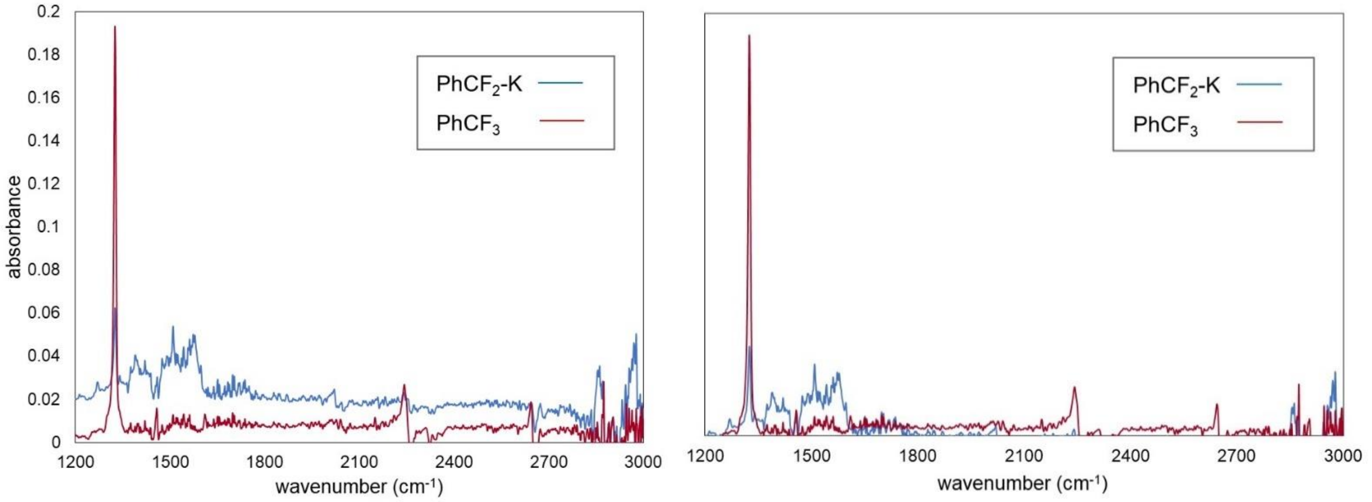
In-line IR monitoring of generation of difluoromethyl benzyl anion 2a



A flow microreactor system consisting of two T-shaped micromixers **M1** (inner diameter ϕ= 250 μm), PTFE tube **R1** (inner diameter ϕ= 1000 μm, length L= 10 cm)), two tube precooling units **P1** and **P2** (inner diameter ϕ= 1000 μm, length L= 100 cm), and **IR** unit was used. The flow microreactor system was cooled at -20 °C or -78 °C by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF) (flow rate: 7.5 mL/ min) and a solution of potassium naphtalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) were introduced to **M1** by syringe pumps. Then, a solution was passed through **R1** and **IR**. After a steady state was reached, IR measurement was started.

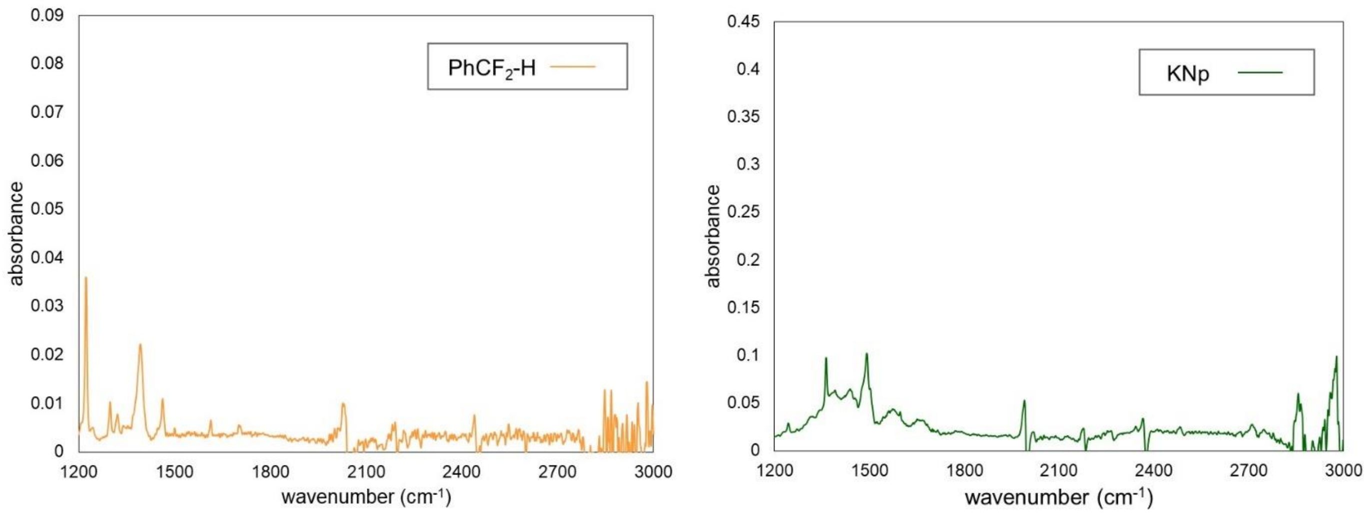

(A) $PhCF_2H$

(B) KNp

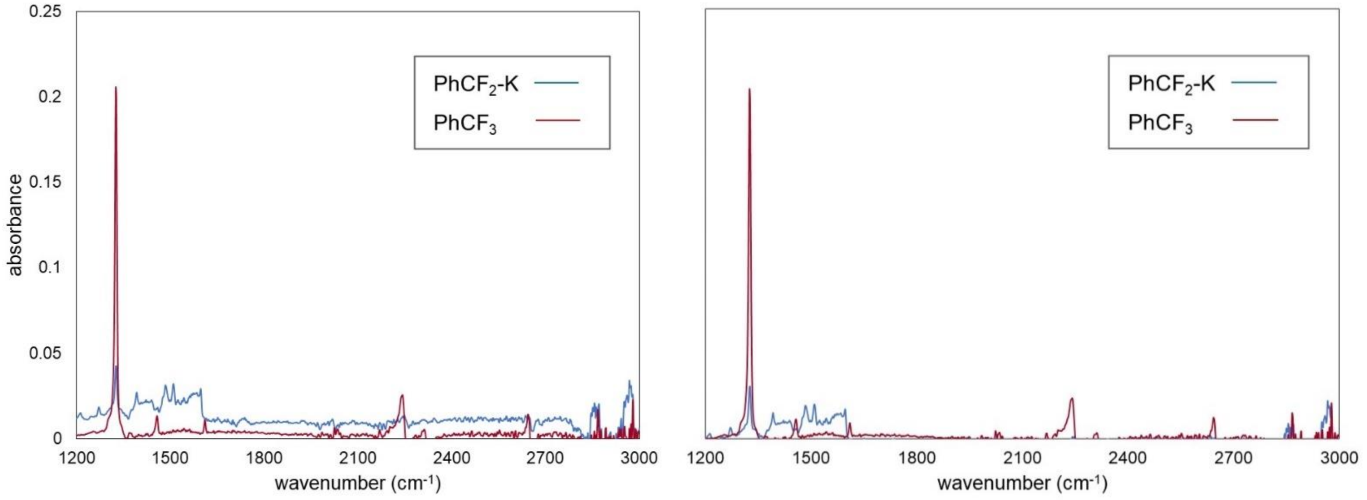

(C) $PhCF_2K + PhCF_3$

(D) $PhCF_2K + PhCF_3$ (1200 cm^{-1} corrected to zero)

Fig. S2. In-line IR of $PhCF_2H$, KNp, $PhCF_3$ and reactive intermediate at -20 °C.



(A) $PhCF_2H$ (B) KNp



(C) $PhCF_2K + PhCF_3$ (D) $PhCF_2K + PhCF_3$ (1200 cm^{-1} corrected to zero)

Fig. S3. In-line IR of $PhCF_2H$, KNp, $PhCF_3$ and reactive intermediate at -78 °C.

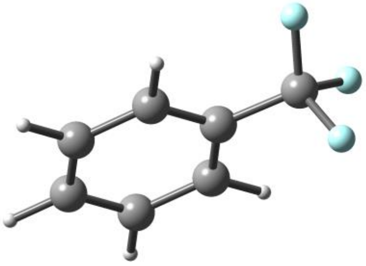
DFT calculation studies

DFT calculation studies have been performed with a Gaussian16 program package to estimate the FT-IR spectra of benzotrifluoride ($PhCF_3$), its hydrodefluorination product ($PhCF_2H$), and the reactive intermediate (*55*). We have employed B3LYP density functional and 6-31G+(d) basis set, in combination with the dispersion force correction model according to Grimme's D3 method (*56*) and the IEFPCM solvation model for THF (*57*).

Table S4. Summary of the calculated frequencies and energies for the optimized geometries of relevant species

structure	characteristic vibrational frequency (cm^{-1})	E_{zero} (hartree)	G_{298} (hartree)
$PhCF_3$	1317	-569.227756	-569.262995
$PhCF_2H$ (conformer A)	1381	-469.964233	-469.997953
$PhCF_2H$ (conformer B)	1423	-469.965395	-469.998575
$PhCF_2K$	1524, 1640	-1069.299657	-1069.337557
THF	-	-232.347890	-232.374573
$PhCF_2K(thf)_4$	1524, 1640	-1998.765184	-1998.842716
$K^+(naphthalene)^{\bullet-}$	1402, 1526	-985.696956	-985.734795
naphthalene	-	-385.773840	-385.803767
K^+	-	-599.834426	-599.849602
F^-	-	-99.978235	-99.992394

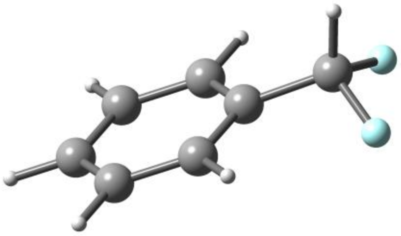
Table S5. Optimized ground-state geometry of $PhCF_3$



C	-2.14480000	1.21170000	0.00180000
C	-0.74840000	1.21670000	-0.02100000
C	-0.05500000	0.00110000	-0.03490000
C	-0.74700000	-1.21560000	-0.02110000
C	-2.14330000	-1.21240000	0.00180000
C	-2.84230000	-0.00070000	0.01350000
H	-2.68590000	2.15360000	0.00830000

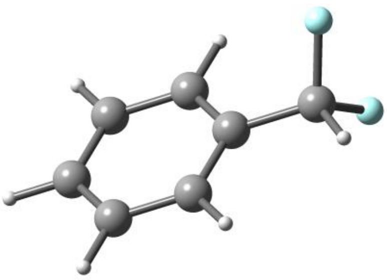
H	-0.20390000	2.15550000	-0.03310000
H	-0.20120000	-2.15370000	-0.03320000
H	-2.68320000	-2.15500000	0.00840000
H	-3.92870000	-0.00140000	0.02960000
C	1.44710000	0.00050000	-0.00520000
F	1.98210000	-1.08250000	-0.62880000
F	1.93520000	-0.01890000	1.27110000
F	1.98320000	1.10050000	-0.59670000

Table S6. Optimized Ground State Geometry of the simplified reactive intermediate (PhCF$_2$H_1)



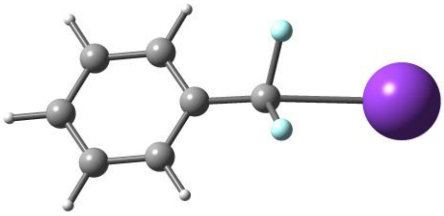
C	-1.91124252	1.21202119	-0.04456122
C	-0.52018777	1.21281324	0.08901138
C	0.17518937	-0.00114375	0.15408806
C	-0.52408950	-1.21349976	0.09819610
C	-1.91500664	-1.20953206	-0.03526381
C	-2.61049195	0.00213816	-0.10664131
H	-2.44664024	2.15577703	-0.10192190
H	0.02260564	2.15196557	0.13350668
H	0.01584590	-2.15403405	0.14964331
H	-2.45337546	-2.15201080	-0.08532136
H	-3.69218554	0.00341861	-0.21096602
C	1.66835239	-0.00447028	0.35348369
F	2.24253375	-1.10834312	-0.25323014
F	2.24529899	1.11075099	-0.22841365
H	1.98811488	-0.01674772	1.39997614

Table S7. Optimized Ground State Geometry of the simplified reactive intermediate ($PhCF_2H$_2)



C	2.08534968	-1.08350662	0.00440905
C	0.70195341	-1.29163317	0.00731613
C	-0.16816346	-0.19689611	0.00333170
C	0.34182618	1.10948659	-0.00347944
C	1.72152413	1.31422134	-0.00624293
C	2.59438385	0.21789627	-0.00233294
H	2.76011707	-1.93495870	0.00751884
H	0.30413872	-2.30362324	0.01248221
H	-0.33922503	1.95583720	-0.00641141
H	2.11807207	2.32575943	-0.01137219
H	3.66885872	0.38063028	-0.00437924
C	-1.64847267	-0.42401461	0.00522870
F	-2.24209751	0.19179092	1.09941825
F	-2.23997552	0.16136629	-1.10679828
H	-1.94371099	-1.47538209	0.01920043

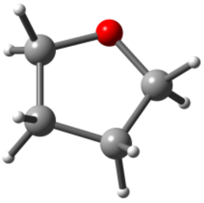
Table S8. Optimized Ground State Geometry of the simplified reactive intermediate



C	2.87982095	1.18861474	-0.20862282
C	1.49014342	1.20660646	-0.06724787
C	0.75356785	0.00612490	0.01275204
C	1.46431826	-1.21107249	-0.05244264
C	2.85355680	-1.22519253	-0.19325131
C	3.57349713	-0.02616936	-0.27585731
H	3.42506738	2.12881131	-0.26187277
H	0.96388687	2.15547983	-0.01619434
H	0.91717436	-2.14770189	0.00875138
H	3.37837870	-2.17747916	-0.23539400

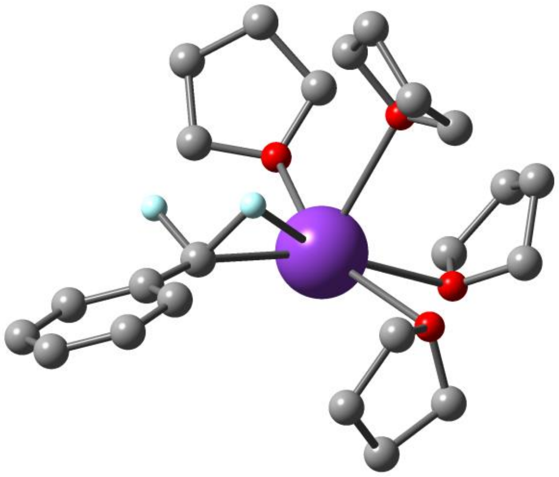
H	4.65471398	-0.03863682	-0.38868141
C	-0.72658200	0.01780255	0.02527907
F	-1.15611676	-1.07850909	0.90616479
F	-1.14139082	1.17681594	0.82289304
K	-3.49429408	-0.02871160	-0.53219917

Table S9. Optimized Ground State Geometry of the simplified reactive intermediate (THF)



C	-1.19067069	0.45967233	-0.00000010
O	0.00000036	1.26206451	-0.00000030
C	1.19067088	0.45967188	-0.00000059
C	0.77478834	-1.02733370	0.00000081
C	-0.77478868	-1.02733366	0.00000019
H	-1.78017675	0.72061133	0.88838738
H	-1.78017683	0.72061094	-0.88838764
H	1.78017604	0.72060940	-0.88838911
H	1.78017724	0.72061072	0.88838672
H	1.17004705	-1.54175609	-0.88124601
H	1.17004633	-1.54175423	0.88124904
H	-1.17004718	-1.54175467	-0.88124751
H	-1.17004787	-1.54175452	0.88124767

Table S10. Optimized Ground State Geometry of the simplified reactive intermediate

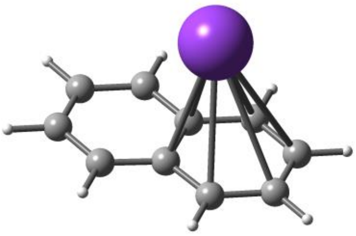


C	5.79211170	0.02663312	0.46896259

C	4.39629237	0.00549321	0.50791272
C	3.65942250	-0.88923549	-0.29876918
C	4.38112468	-1.76534288	-1.13877367
C	5.77668845	-1.74266454	-1.17283404
C	6.49572535	-0.84390820	-0.37326281
H	6.33487123	0.72383073	1.10447370
H	3.86366117	0.68438146	1.16724340
H	3.83543939	-2.46493834	-1.76605855
H	6.30792521	-2.43349476	-1.82472864
H	7.58232627	-0.82485303	-0.40387623
C	2.18664610	-0.81459978	-0.36960415
F	1.68157223	-2.17387416	-0.52595712
F	1.70906940	-0.49794117	0.98243491
K	-0.49172296	0.14155231	-0.79559406
O	-2.16481762	-2.06204454	-1.21371300
C	-3.26084242	-2.32197281	-0.30903226
C	-1.53285036	-3.31418836	-1.59214374
C	-3.01157051	-3.72579749	0.24026198
H	-3.26089181	-1.53493550	0.45034333
H	-4.20670257	-2.27837238	-0.86878692
C	-2.39066638	-4.42783533	-0.97875728
H	-1.48366759	-3.35821396	-2.68562477
H	-0.51247086	-3.31315528	-1.19080303
H	-3.92797071	-4.20576859	0.59794522
H	-2.29332431	-3.68917192	1.06754238
H	-3.17654344	-4.73957408	-1.67740917
H	-1.79768800	-5.30901578	-0.71552247
O	-1.62001646	-0.04324983	1.83109507
C	-1.25183917	-1.24815665	2.54962143
C	-1.31996438	1.10691855	2.64994504
C	-0.58343024	-0.79705626	3.86091765
H	-2.15460417	-1.84580861	2.72192316
H	-0.56603959	-1.81707845	1.91305800
C	-0.17739975	0.65501813	3.55563678
H	-1.06176916	1.93140852	1.98081746
H	-2.21094325	1.38317921	3.23528688
H	0.26681787	-1.43222334	4.12671323
H	-1.30175689	-0.82505998	4.68895812
H	0.76704707	0.67680477	3.00227027
H	-0.07856232	1.27343313	4.45367209

O	-2.78178902	1.70191328	-1.50767139
C	-3.91442020	0.92894493	-1.97237677
C	-3.24313677	2.56210867	-0.45008136
C	-4.98118052	0.98010569	-0.84997713
H	-4.28715589	1.36598578	-2.90807171
H	-3.55032533	-0.08239361	-2.17474172
C	-4.26113616	1.70973228	0.30407926
H	-2.36983517	2.85689114	0.13576115
H	-3.71014904	3.46375255	-0.87837002
H	-5.32278709	-0.01856388	-0.56233524
H	-5.85675213	1.54988711	-1.17966808
H	-3.73165878	0.99822614	0.94626508
H	-4.94100768	2.30555916	0.92182274
O	0.17880390	2.83835111	0.02649396
C	0.18035603	3.76512754	-1.07262348
C	1.50971505	2.89374132	0.57417027
C	1.54338289	3.57210110	-1.76464406
H	-0.68396416	3.53291593	-1.69987098
H	0.07277679	4.78895732	-0.68148389
C	2.44613578	2.97899350	-0.64494123
H	1.59672710	3.78419238	1.21604032
H	1.65342999	1.99603405	1.17813931
H	1.92752419	4.51718382	-2.16139834
H	1.45536589	2.87096896	-2.60098000
H	3.32152233	3.60194860	-0.43566622
H	2.79566610	1.97920309	-0.91664931

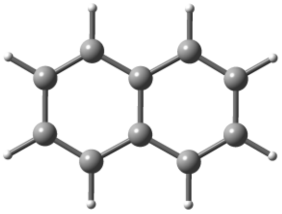
Table S11. Optimized Ground State Geometry of the simplified reactive intermediate



C	2.14944810	-1.14211421	-0.69383404
C	0.95318360	-0.88216790	-1.40527154
C	-0.27563174	-0.62198939	-0.72612517
C	-0.27509194	-0.61519950	0.73075424
C	0.95412863	-0.86947450	1.41141861

C	2.14991306	-1.13572778	0.70147860
H	-1.49792544	-0.34708007	-2.49295445
H	3.06705487	-1.34941013	-1.24156450
H	0.95364160	-0.89521894	-2.49429384
C	-1.49412975	-0.33754923	-1.40363307
C	-1.49293334	-0.32381063	1.40649537
H	0.95562749	-0.87159123	2.50051549
H	3.06794938	-1.33792558	1.25039663
C	-2.68386320	-0.05265498	0.69806599
C	-2.68444728	-0.05948962	-0.69687551
H	-1.49590648	-0.32315921	2.49586219
H	-3.60043222	0.15863841	1.24610875
H	-3.60146388	0.14650492	-1.24618734
K	0.96568410	2.16106886	-0.00803809

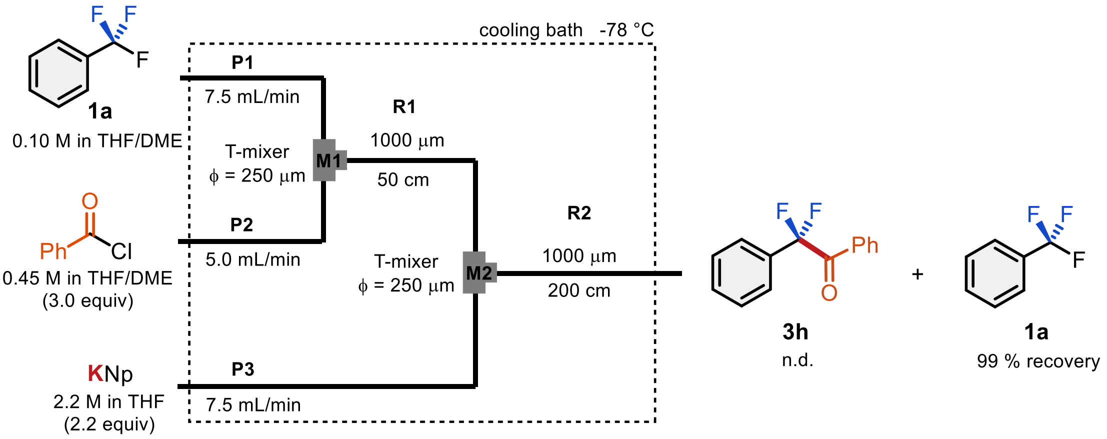
Table S12. Optimized Ground State Geometry of the simplified reactive intermediate (Naph-0)



C	-0.00000000	2.43739124	0.70981639
C	0.00000000	1.24617498	1.40549179
C	-0.00000000	0.00000000	0.71774994
C	0.00000000	-0.00000000	-0.71774994
C	0.00000000	1.24617498	-1.40549179
C	0.00000000	2.43739124	-0.70981639
H	0.00000000	-1.24433104	2.49338250
H	-0.00000000	3.38227422	1.24702970
H	0.00000000	1.24433104	2.49338250
C	-0.00000000	-1.24617498	1.40549179
C	-0.00000000	-1.24617498	-1.40549179
H	0.00000000	1.24433104	-2.49338250
H	0.00000000	3.38227422	-1.24702970
C	-0.00000000	-2.43739124	-0.70981639
C	-0.00000000	-2.43739124	0.70981639
H	0.00000000	-1.24433104	-2.49338250
H	-0.00000000	-3.38227422	-1.24702970
H	-0.00000000	-3.38227422	1.24702970

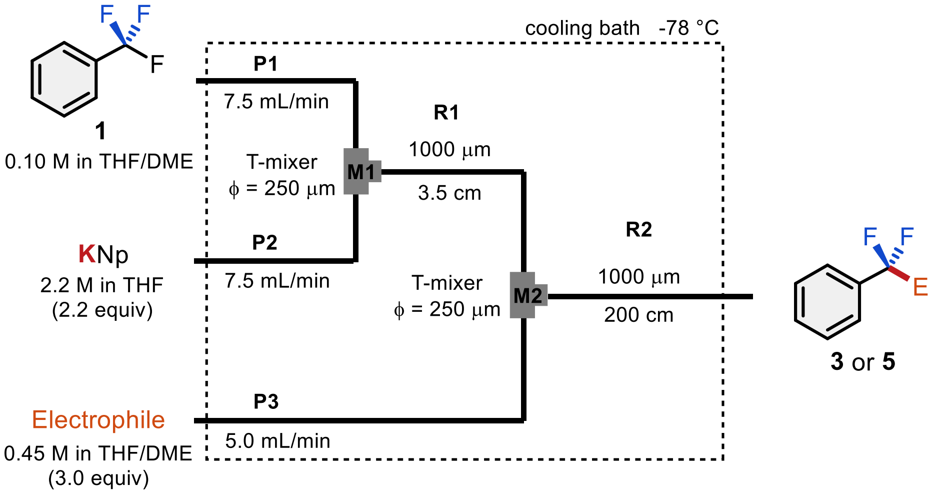
Defluorinative functionalization in the presence of the benzoyl chloride

Scheme S2.



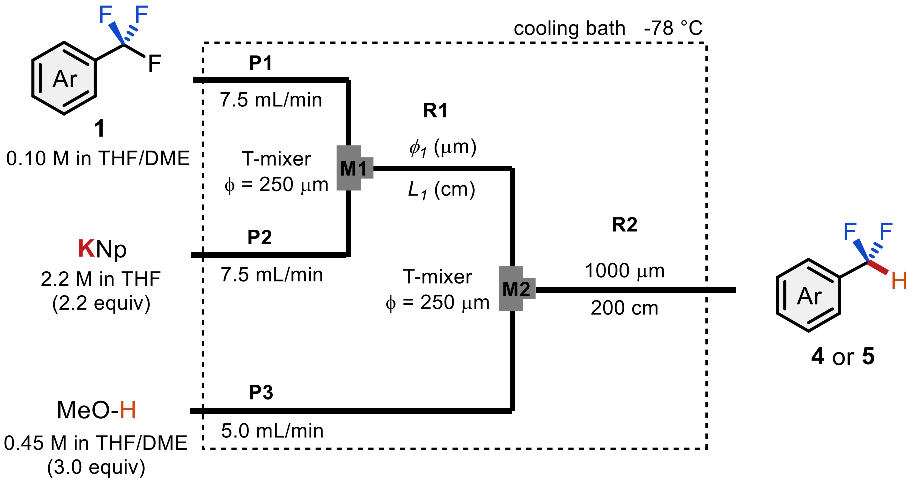
A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter ϕ= 250 μm)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter ϕ= 1000 μm, length L= 100 cm)) was used. The flow microreactor system was cooled at -78 °C by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/ min) and a solution of benzoyl chloride (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/ min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (inner diameter ϕ= 1000 μm, length L= 50 cm) and was mixed with a solution of potassium naphtalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) in **M2**. The resulting solution was passed through **R2** (inner diameter ϕ= 1000 μm, length L= 200 cm). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl. The yield of **3h** and recovery of **1a** were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). However, this system did not give a corresponding compound **3h,** and substrate **1a** was quantitatively recovered.

General procedure of defluorinative functionalization of benzotrifluoride under flow microreactor system

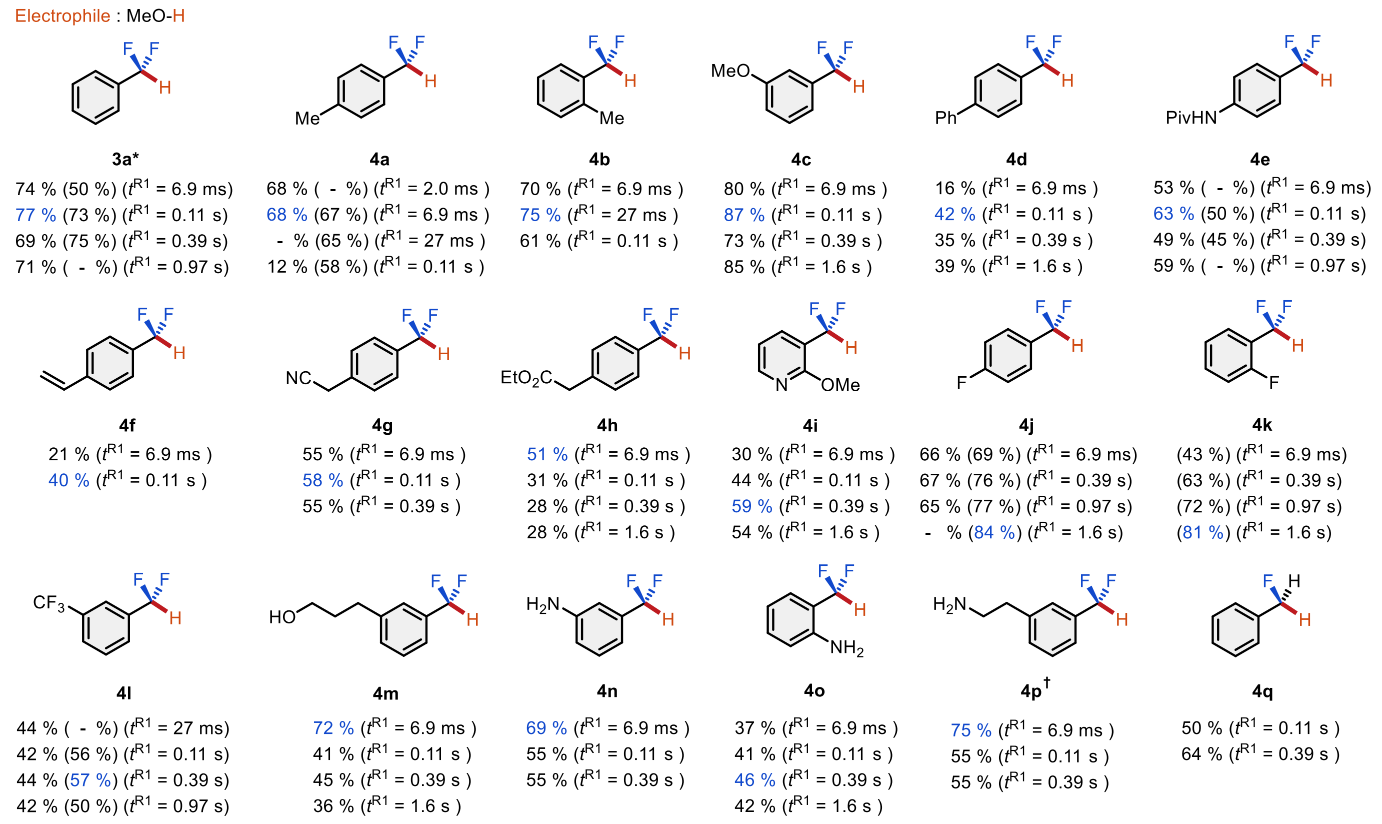


A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter ϕ= 250 μm)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter ϕ= 1000 μm, length L= 100 cm)) was used. The flow microreactor system was cooled at -78 °C by a cooling bath. A solution of benzotrifluoride (**1a**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/ min) and a solution of potassium naphtalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** (inner diameter ϕ= 1000 μm, length L= 3.5 cm) and was mixed with a solution of electrophile (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/ min) in **M2**. The resulting solution was passed through **R2** (inner diameter ϕ= 1000 μm, length L= 200 cm). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl. The yields of corresponding difluoromethyl arenes (**4**) were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was extracted with EtOAc (3 x 5 mL), and was washed with brine. The combined organic layers were dried over Na_2SO_4, and filtered, concentrated under vacuum. Then, the crude product was purified by flash column chromatography on silica gel to give a product.

General procedure of hydrodefluorination of aryl bearing fluorine atoms under flow microreactor system



A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2** (inner diameter ϕ= 250 μm)), two microtube reactors (**R1** and **R2**), and three tube precooling units (**P1**, **P2**, and **P3** (inner diameter ϕ = 1000 μm, length L= 100 cm)) was used. The flow microreactor system was cooled at -78 °C by a cooling bath. A solution of benzotrifluoride derivatives (**1**) (0.10 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 7.5 mL/ min) and a solution of potassium naphtalenide (KNp) (0.22 M in THF) (flow rate: 7.5 mL/ min) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of methanol (0.45 M in THF/1,2-dimethoxyethane (DME)= 10/1) (flow rate: 5.0 mL/ min) in **M2**. The resulting solution was passed through **R2** (inner diameter ϕ= 1000 μm, length L= 200 cm). After a steady state was reached, the outcoming solution was collected for 20 seconds in a vessel containing 4 mL of sat. aq. NH_4Cl. The yields of corresponding difluoromethyl arenes (**4**) were determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was extracted with EtOAc (3 x 5 mL), and was washed with brine. The combined organic layers were dried over Na_2SO_4, and filtered, concentrated under vacuum. Then, the crude product was purified by flash column chromatography on silica gel to give a product. The optimizations are summarized in Fig. S4.



3a*
74 % (50 %) (t^{R1} = 6.9 ms)
77 % (73 %) (t^{R1} = 0.11 s)
69 % (75 %) (t^{R1} = 0.39 s)
71 % (- %) (t^{R1} = 0.97 s)

4a
68 % (- %) (t^{R1} = 2.0 ms)
68 % (67 %) (t^{R1} = 6.9 ms)
- % (65 %) (t^{R1} = 27 ms)
12 % (58 %) (t^{R1} = 0.11 s)

4b
70 % (t^{R1} = 6.9 ms)
75 % (t^{R1} = 27 ms)
61 % (t^{R1} = 0.11 s)

4c
80 % (t^{R1} = 6.9 ms)
87 % (t^{R1} = 0.11 s)
73 % (t^{R1} = 0.39 s)
85 % (t^{R1} = 1.6 s)

4d
16 % (t^{R1} = 6.9 ms)
42 % (t^{R1} = 0.11 s)
35 % (t^{R1} = 0.39 s)
39 % (t^{R1} = 1.6 s)

4e
53 % (- %) (t^{R1} = 6.9 ms)
63 % (50 %) (t^{R1} = 0.11 s)
49 % (45 %) (t^{R1} = 0.39 s)
59 % (- %) (t^{R1} = 0.97 s)

4f
21 % (t^{R1} = 6.9 ms)
40 % (t^{R1} = 0.11 s)

4g
55 % (t^{R1} = 6.9 ms)
58 % (t^{R1} = 0.11 s)
55 % (t^{R1} = 0.39 s)

4h
51 % (t^{R1} = 6.9 ms)
31 % (t^{R1} = 0.11 s)
28 % (t^{R1} = 0.39 s)
28 % (t^{R1} = 1.6 s)

4i
30 % (t^{R1} = 6.9 ms)
44 % (t^{R1} = 0.11 s)
59 % (t^{R1} = 0.39 s)
54 % (t^{R1} = 1.6 s)

4j
66 % (69 %) (t^{R1} = 6.9 ms)
67 % (76 %) (t^{R1} = 0.39 s)
65 % (77 %) (t^{R1} = 0.97 s)
- % (84 %) (t^{R1} = 1.6 s)

4k
(43 %) (t^{R1} = 6.9 ms)
(63 %) (t^{R1} = 0.39 s)
(72 %) (t^{R1} = 0.97 s)
(81 %) (t^{R1} = 1.6 s)

4l
44 % (- %) (t^{R1} = 27 ms)
42 % (56 %) (t^{R1} = 0.11 s)
44 % (57 %) (t^{R1} = 0.39 s)
42 % (50 %) (t^{R1} = 0.97 s)

4m
72 % (t^{R1} = 6.9 ms)
41 % (t^{R1} = 0.11 s)
45 % (t^{R1} = 0.39 s)
36 % (t^{R1} = 1.6 s)

4n
69 % (t^{R1} = 6.9 ms)
55 % (t^{R1} = 0.11 s)
55 % (t^{R1} = 0.39 s)

4o
37 % (t^{R1} = 6.9 ms)
41 % (t^{R1} = 0.11 s)
46 % (t^{R1} = 0.39 s)
42 % (t^{R1} = 1.6 s)

4p†
75 % (t^{R1} = 6.9 ms)
55 % (t^{R1} = 0.11 s)
55 % (t^{R1} = 0.39 s)

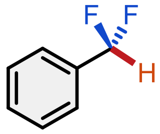
4q
50 % (t^{R1} = 0.11 s)
64 % (t^{R1} = 0.39 s)

Fig. S4. Scope of substrates of hydrodefluorination.

Using THF/diglyme (10:1) instead of THF/DME in parentheses. *The yield of **3a** was determined by gas chromatography with an undecane as an internal standard. †Quench was carried out by methanol instead of sat. aq. NH_4Cl.

Defluorinative functionalization products characterizations

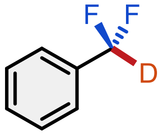
Difluoromethyl benzene (3a)



3a

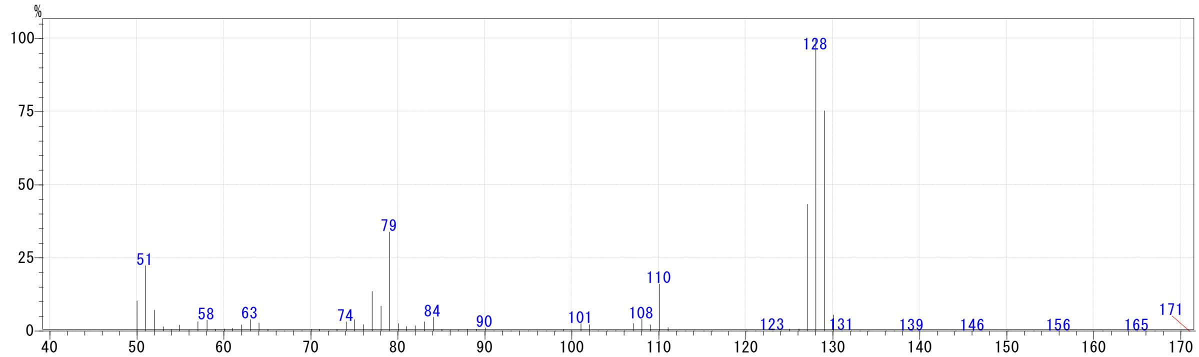
Obtained in 77 % yield (Maximum yield). Yields were determined by GC analysis (^{t}R 6.0 min) (initial oven temperature, 50 °C (5 min); temperature increase rate, 10 °C/min (25 min); final temperature, 300 °C) using an internal standard (undecane). The NMR spectral data were identical to those reported in the literature (*30*).

Deuterated difluoromethyl benzene (3b)

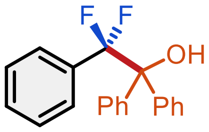


3b

Obtained in 74 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl$_3$) δ -112.40 (s, 2F). ^{19}F NMR data matches previously reported data (*58*). The identity of the product was further confirmed by GCMS analysis.



2,2-Difluoro-1,1,2-triphenylethanol (3c)



3c

Obtained in 66 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.4) to afford the pure product as a white solid.

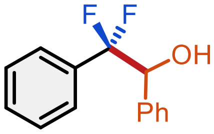
NMR Spectroscopy:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47-7.44 (m, 4H), 7.32 (t, *J*= 7.3 Hz, 1H), 7.28-7.25 (m, 4H), 7.20 (t, *J*= 7.7 Hz, 2H), 7.07 (d, *J*= 7.6 Hz, 2H), 2.78 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 141.50, 134.22 (t, *J*= 26.2 Hz), 129.51, 127.99 (d, *J*= 4.7 Hz), 127.76, 127.71, 127.38 (t, *J*= 6.4 Hz), 127.00, 123.20 (t, *J*= 255.8 Hz), 80.85 (t, *J*= 28.9 Hz).

^{19}F NMR (376 MHz, CDCl$_3$) δ -102.57 (s, 2F).

1,2-Diphenyl-2,2-difluoroethanol (3d)



3d

Obtained in 71 % yield. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, Rf= 0.2) to afford the pure product as a white solid (126.7 mg).

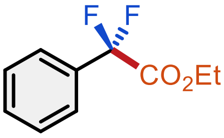
NMR Spectroscopy:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40-7.17 (m, 10H), 5.04 (t, *J*= 10.1 Hz, 1H), 2.63 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 135.70, 133.65 (t, *J*= 25.9 Hz), 129.96, 128.61, 127.83 (t, *J*= 9.2 Hz), 126.23 (t, *J*= 6.3 Hz), 123.55, 121.0, 118.61, 76.85 (t, *J*= 30.7 Hz).

^{19}F NMR (376 MHz, CDCl$_3$) δ -108.09 (d, *J*= 9.1 Hz, 2F).

2,2-Difluoro-2-phenylacetic acid ethyl ester (3e)



3e

Obtained in 55 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.5) to afford the pure product as a colorless oil.

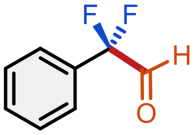
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.60 (m, 2H), 7.52-7.43 (m, 3H), 4.30 (q, *J*= 7.1 Hz, 2H), 1.30 (t, *J*= 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.21 (t, *J*= 35.4 Hz), 132.77 (t, *J*= 25.5 Hz), 130.95 (d, *J*= 2.2 Hz), 128.61, 125.40 (t, *J*= 6.3 Hz), 113.35 (t, *J*= 251.9 Hz), 63.11, 13.84.

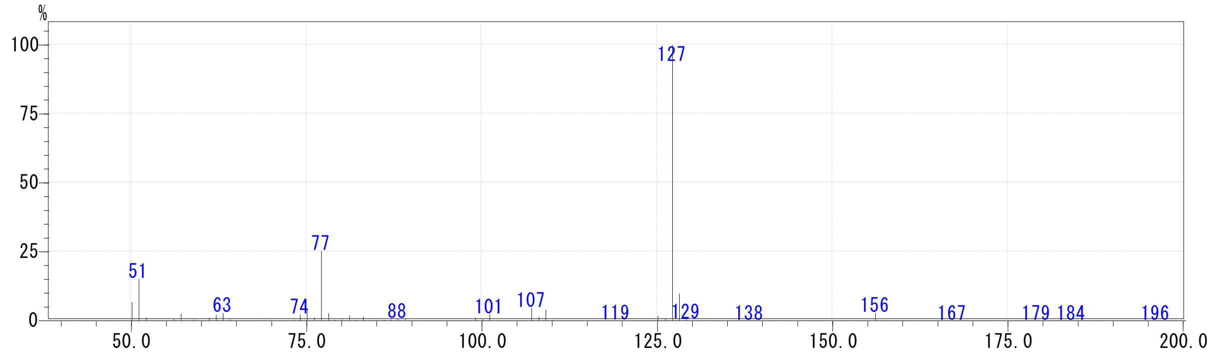
^{19}F NMR (376 MHz, $CDCl_3$) δ -105.07 (s, 2F).

2,2-Difluoro- 2-(phenyl)acetaldehyde (3f)

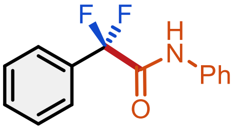


3f

Obtained in 48 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.66 (s, 2F). ^{19}F NMR data matches previously reported data (*59*). The identity of the product was further confirmed by GCMS analysis.



N-Phenyl-2-phenyl-2,2-difluoroacetamide (3g)



3g

Obtained in 83 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, Rf= 0.3) to afford the pure product as a white solid.

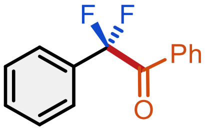
NMR Spectroscopy:

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 (s, 1H), 7.69-7.67 (m, 2H), 7.59-7.56 (m, 2H), 7.53-7.45 (m, 3H), 7.36 (t, *J*= 8.0 Hz, 2H), 7.19 (t, *J*= 7.5 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 161.80 (t, *J*= 30.8 Hz), 136.00, 132.55 (t, *J*= 25.4 Hz), 131.08 (t, *J*= 1.9 Hz), 129.20, 128.68, 125.63, 125.56 (t, *J*= 5.3 Hz), 120.11, 114.76 (t, *J*= 254.3 Hz).

^{19}F NMR (376 MHz, CDCl$_3$) δ -103.58 (s, 2F).

2,2-Difluoro-1,2-diphenylethane-1-one (3h)



3h

Obtained in 55 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.5) to afford the pure product as a yellow oil in 66 % isolated yield (115.2 mg).

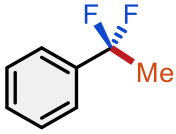
NMR Spectroscopy:

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04-8.02 (m, 2H), 7.63-7.57 (m, 3H), 7.50-7.43 (m, 5H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 188.89 (t, *J*= 30.8 Hz), 134.19, 133.03 (t, *J*= 25.0 Hz), 132.02, 130.88 (d, *J*= 1.7 Hz), 130.22 (t, *J*= 2.9 Hz), 128.79, 128.60, 125.54 (t, *J*= 5.8 Hz), 116.86 (t, *J*= 253.2 Hz).

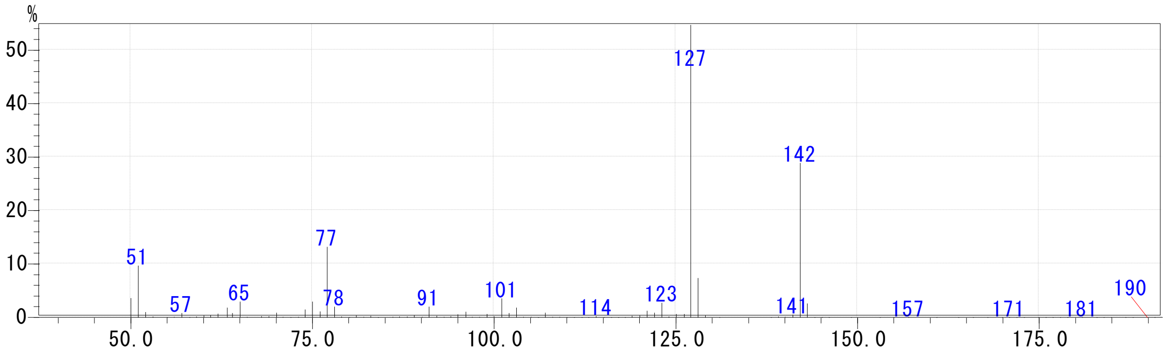
^{19}F NMR (376 MHz, CDCl$_3$) δ -98.76 (s, 2F).

(1,1-Difluoroethyl)benzene (3i)

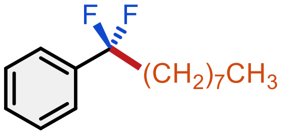


3i

Obtained in 76 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl$_3$) δ -88.62 (q, *J*= 17.5 Hz, 2F). ^{19}F NMR data matches previously reported data (*60*). The identity of the product was further confirmed by GCMS analysis.

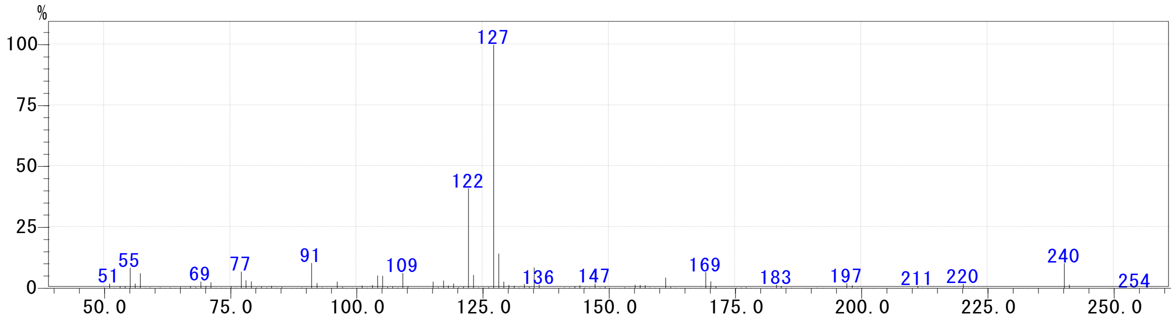


(1,1-Difluorononyl)benzene (3j)

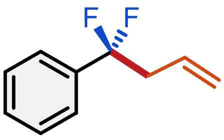


3j

Obtained in 71 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl$_3$) δ -96.27 (t, *J*= 16.1 Hz, 2F). ^{19}F NMR data matches previously reported data (*61*). The identity of the product was further confirmed by GCMS analysis.

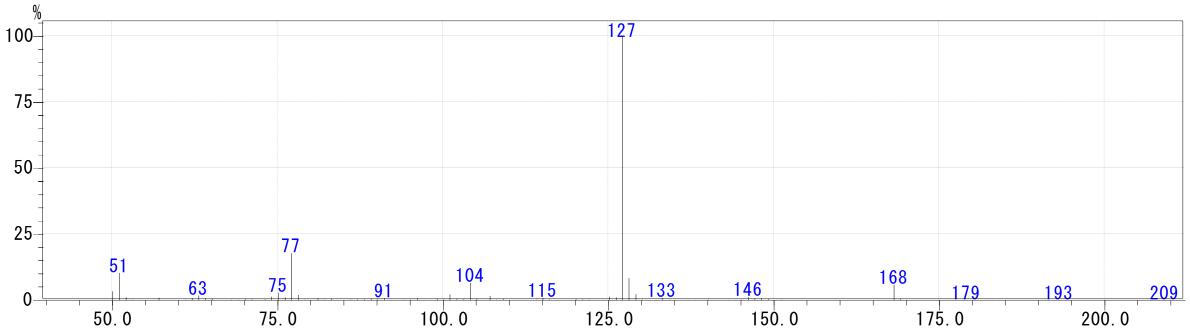


1,1-Difluoro-1-phenyl-3-butene (3k)

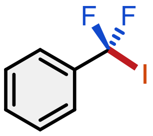


3k

Obtained in 41 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl$_3$) δ -96.20 (t, *J*= 16.4 Hz, 2F). ^{19}F NMR data matches previously reported data (*62*). The identity of the product was further confirmed by GCMS analysis.

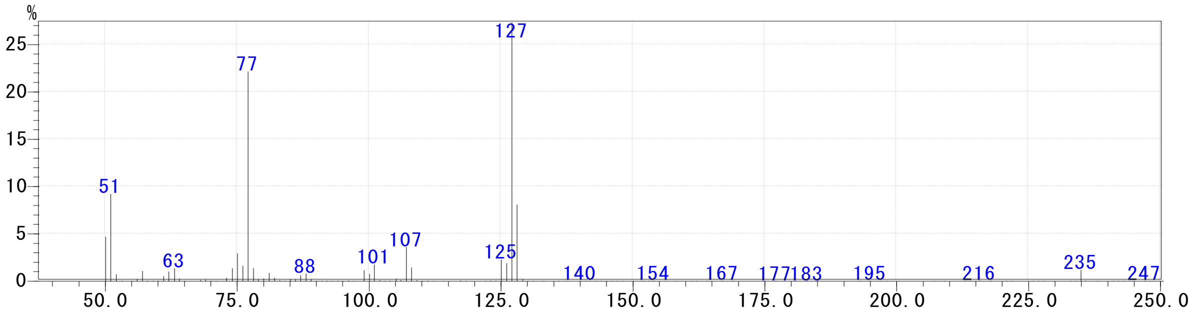


(Difluoroiodomethyl)benzene (3l)

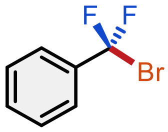


3l

Obtained in 65 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl$_3$) δ -38.06 (s, 2F). ^{19}F NMR data matches previously reported data (*63*). The identity of the product was further confirmed by GCMS analysis.

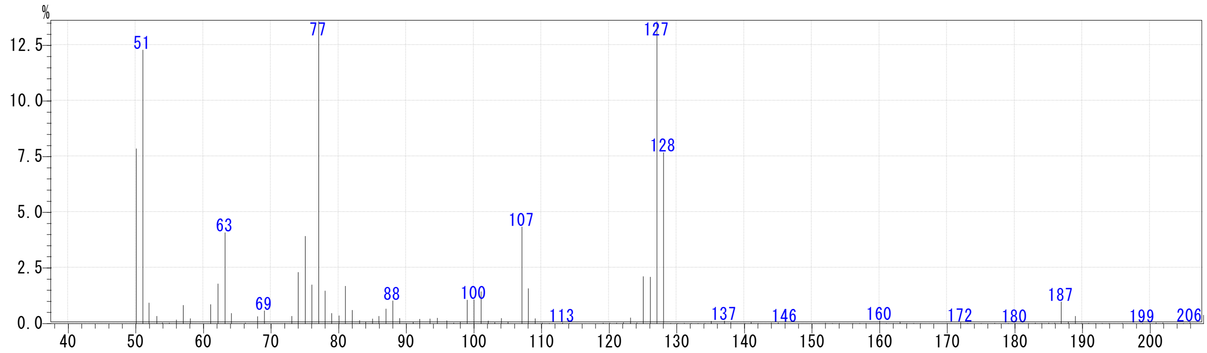


(Bromodifluoromethyl)benzene (3m)

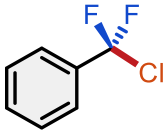


3m

Obtained in 56 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -44.74 (s, 2F). ^{19}F NMR data matches previously reported data (*64*). The identity of the product was further confirmed by GCMS analysis.

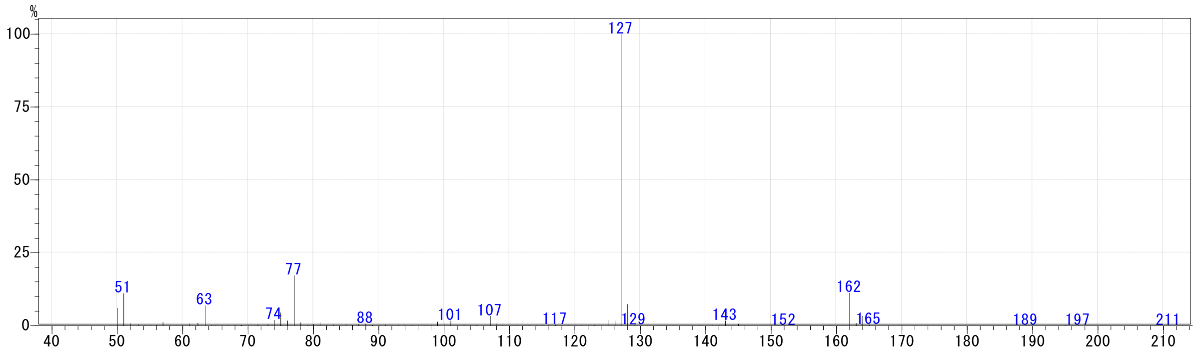


(Chlorodifluoromethyl)benzene (3n)

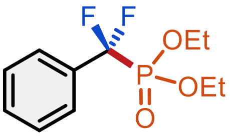


3n

Obtained in 80 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -49.78 (s, 2F). ^{19}F NMR data matches previously reported data (*65*). The identity of the product was further confirmed by GCMS analysis.



Diethyl difluoro(phenyl)methylphosphonate (3o)



3o

Obtained in 48 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product (0.25 mmol scale) was purified by GPC to afford the pure product as yellow oil in 55 % isolated yield (36.8 mg).

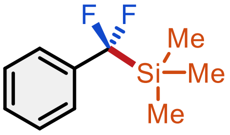
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J*= 8.0, 0.9 Hz, 2H), 7.49-7.44 (m, 3H), 4.26-4.09 (m, 2H), 1.31 (t, *J*= 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 132.78-132.21 (m), 130.75 (t, *J*= 1.9 Hz), 128.39, 126.24-126.09 (m), 121.71-114.30 (m), 64.74 (d, *J*= 6.7 Hz), 16.28 (d, *J*= 5.6 Hz).

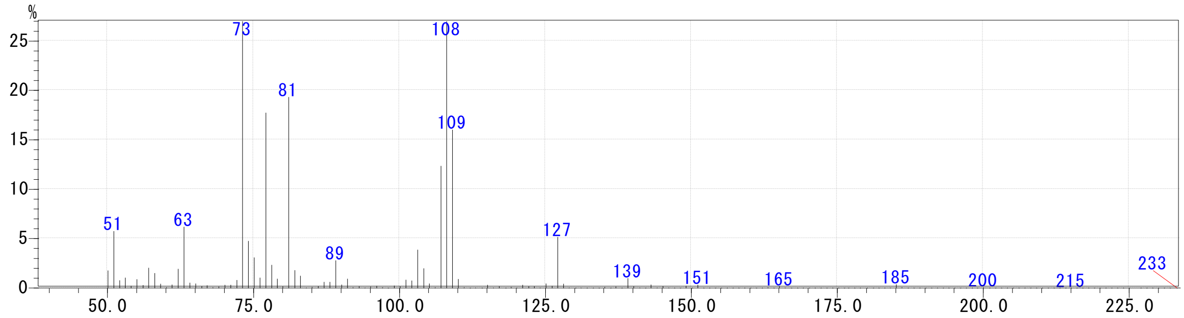
^{19}F NMR (376 MHz, $CDCl_3$) δ -109.72 (d, *J*= 120.6 Hz, 2F).

(Difluoro(trimethylsilyl)methyl)benzene (3p)

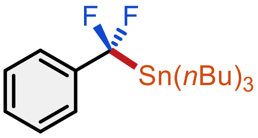


3p

Obtained in 85 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.44 (s, 2F). ^{19}F NMR data matches previously reported data (*66*). The identity of the product was further confirmed by GCMS analysis.



Tributhyl(difluoro(phenyl)methyl)stannane (3q)



3q

Obtained in 63 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC to afford the pure product as yellow oil. HRMS (ESI) *m/z* Calcd for $C_{19}H_{32}F_2SnNa[M+Na]^+$ 441.1395; Found: 441.1385.

NMR Spectroscopy:

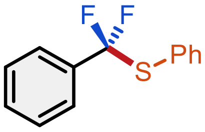
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.33-7.28 (m, 3H), 1.54-1.22 (m, 13H), 1.01-0.97 (m, 5H), 0.86 (d, *J*= 14.6 Hz, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.69 (t, *J*= 16.8 Hz), 136.04 (d, *J*= 293.8 Hz), 128.41, 128.16 (t, *J*= 2.7 Hz), 123.23 (t, *J*= 8.3 Hz), 28.53 (d, *J*= 1.5 Hz), 27.22 (d, *J*= 1.8 Hz), 13.59 (d, *J*= 1.6 Hz), 9.94 (d, *J*= 3.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -97.53--98.29 (m, 2F).

Note: The title compound was unstable and decomposed after several days of storage at ambient temperature.

((Difluorophenylmethyl)thio)benzene (3r)



3r

Obtained in 80 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane only, Rf= 0.5) to afford the pure product as a white solid.

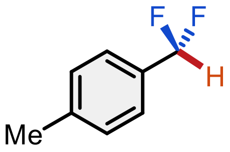
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.57 (dd, *J*= 7.7, 1.3 Hz, 2H), 7.45-7.35 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.36, 135.89 (t, *J*= 25.0 Hz), 130.56, 129.87, 128.97, 128.32, 127.58, 127.45, 125.37 (t, *J*= 4.8 Hz).

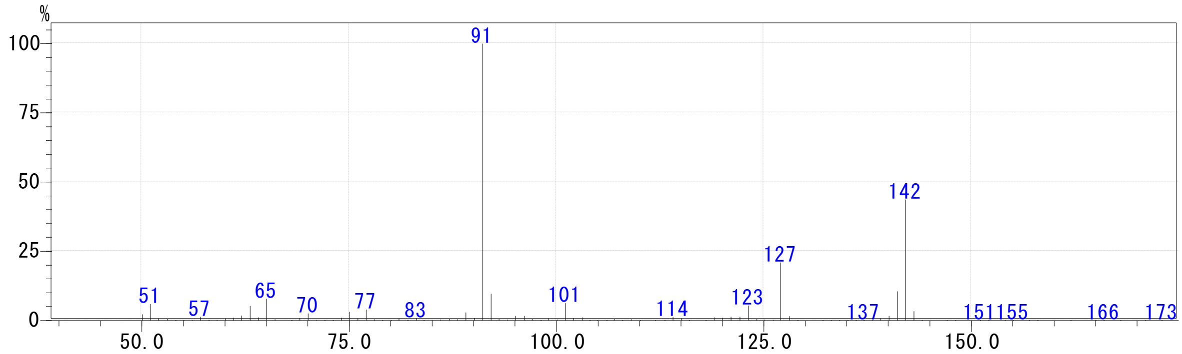
^{19}F NMR (376 MHz, $CDCl_3$) δ -72.99 (s, 2F).

1-(Difluoromethyl)-4-methylbenzene (4a)

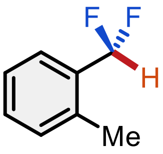


4a

Obtained in 84 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.80 (d, *J*= 57.4 Hz, 2F). ^{19}F NMR data matches previously reported data (*67*). The identity of the product was further confirmed by GCMS analysis.

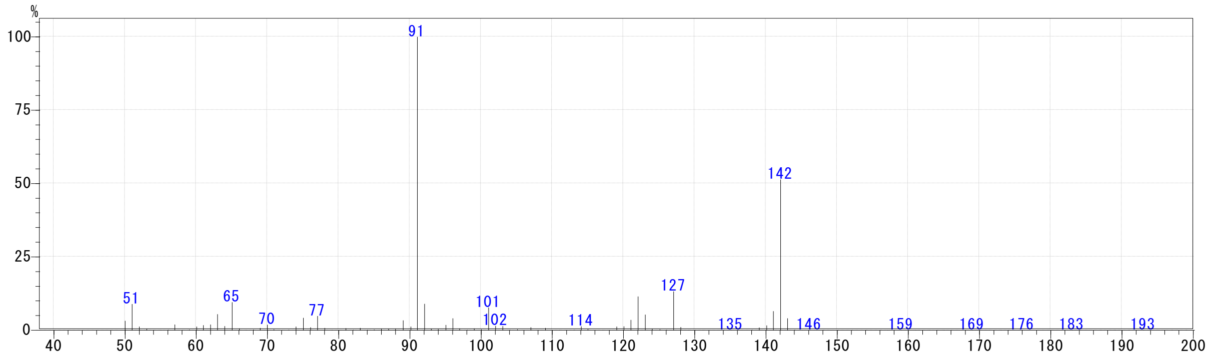


1-(Difluoromethyl)-2-methylbenzene (4b)

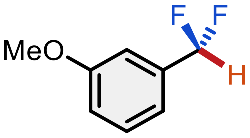


4b

Obtained in 75 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.21 (d, *J*= 54.1 Hz, 2F). ^{19}F NMR data matches previously reported data (*67*). The identity of the product was further confirmed by GCMS analysis.

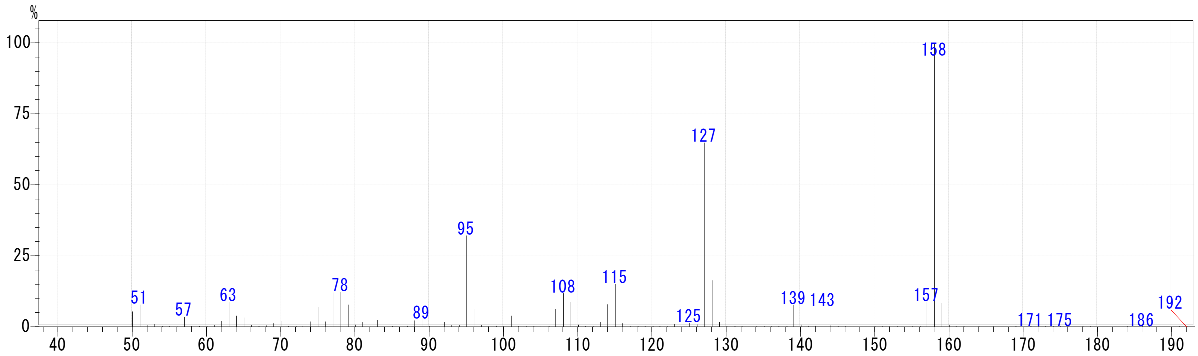


1-(Difluoromethyl)-3-methoxybenzene (4c)

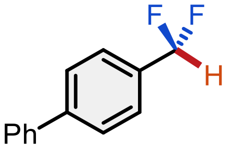


4c

Obtained in 87 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.74 (d, *J*= 53.8 Hz, 2F). ^{19}F NMR data matches previously reported data (*30*). The identity of the product was further confirmed by GCMS analysis.



4-(Difluoromethyl)-1,1’-biphenyl (4d)



4d

Obtained in 42 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.4) to afford the pure product as a white solid.

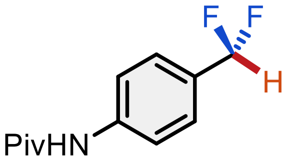
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*= 8.1 Hz, 2H), 7.61-7.57 (m, 4H), 7.48-7.45 (m, 2H), 7.41-7.37 (m, 1H), 6.70 (t, *J*= 56.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.66 (d, *J*= 1.9 Hz), 140.15, 133.16 (t, *J*= 22.1 Hz), 128.90, 127.89, 127.42, 127.23, 126.01 (t, *J*= 5.8 Hz), 114.72 (t, *J*= 238.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.56 (d, *J*= 57.2 Hz, 2F).

N-(4-(difluoromethyl)phenyl)pivalamide (4e)



4e

Obtained in 63 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.2) to afford the pure product as a white solid.

HRMS (ESI) *m/z* Calcd for $C_{12}H_{15}F_2NONa[M+Na]^+$ 250.1014; Found: 250.1010.

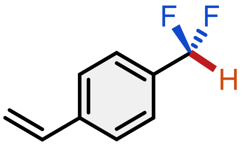
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J*= 8.6 Hz, 2H), 7.47 (d, *J*= 8.6 Hz, 2H), 6.61 (t, *J*= 56.6 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.81, 140.15, 129.86 (t, *J*= 22.7 Hz), 126.37 (t, *J*= 6.0 Hz), 119.72, 114.51 (t, *J*= 238.0 Hz), 39.69, 27.51.

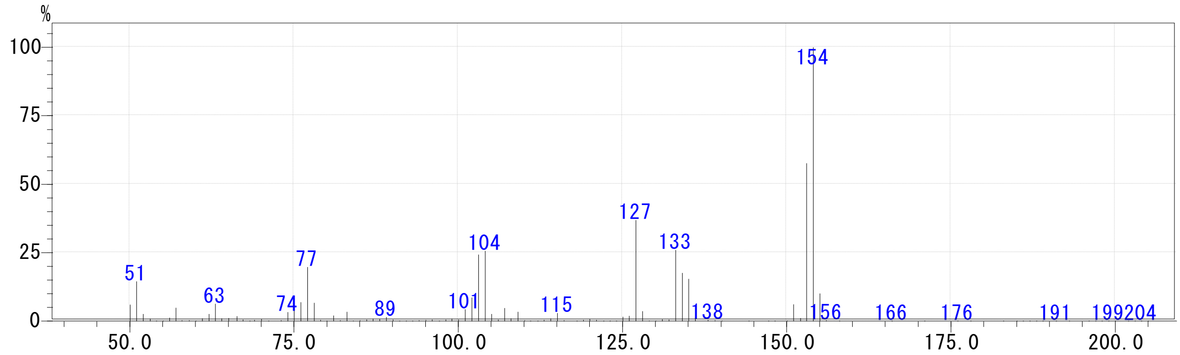
^{19}F NMR (376 MHz, $CDCl_3$) δ -110.82 (d, *J*= 56.7 Hz, 2F).

1-(Difluoromethyl)-4-vinylbenzene (4f)

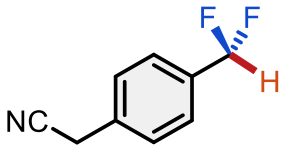


4f

Obtained in 40 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.54 (d, *J*= 57.1 Hz, 2F). ^{19}F NMR data matches previously reported data (*68*). The identity of the product was further confirmed by GCMS analysis.

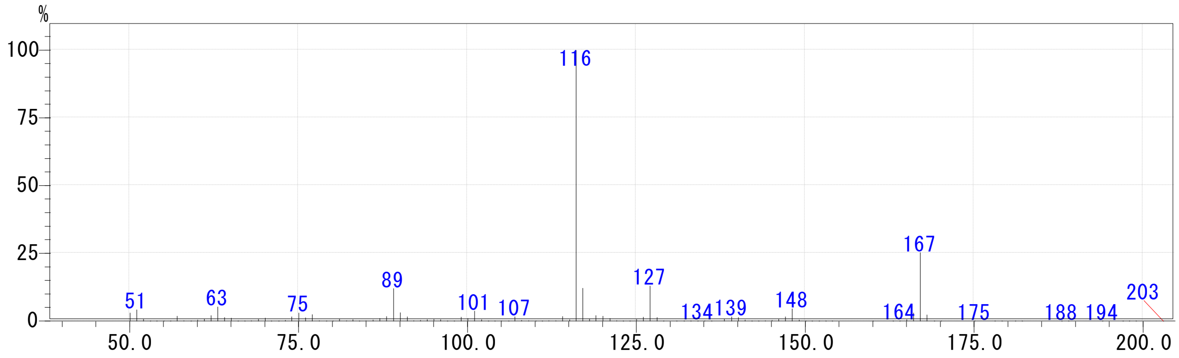


4-(Difluoromethyl)benzeneacetonitrile (4g)

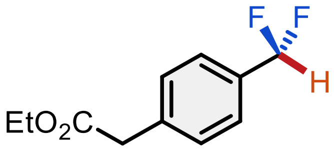


4g

Obtained in 58 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl$_3$) δ -112.19 (d, *J*= 53.7 Hz, 2F). ^{19}F NMR data matches previously reported data (*69*). The identity of the product was further confirmed by GCMS analysis.

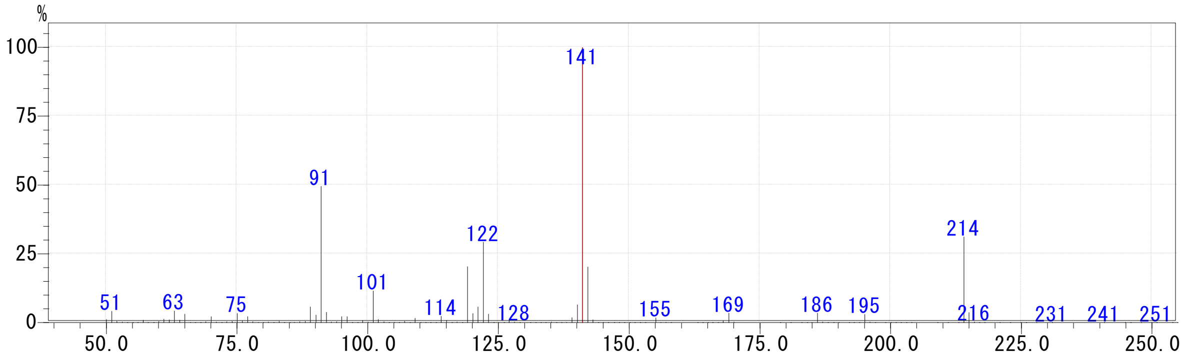


Ethyl 4-(difluoromethyl)benzene acetate (4h)

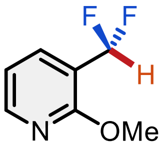


4h

Obtained in 51 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, CDCl$_3$) δ -111.56 (d, *J*= 55.6 Hz, 2F). ^{19}F NMR data matches previously reported data (*70*). The identity of the product was further confirmed by GCMS analysis.

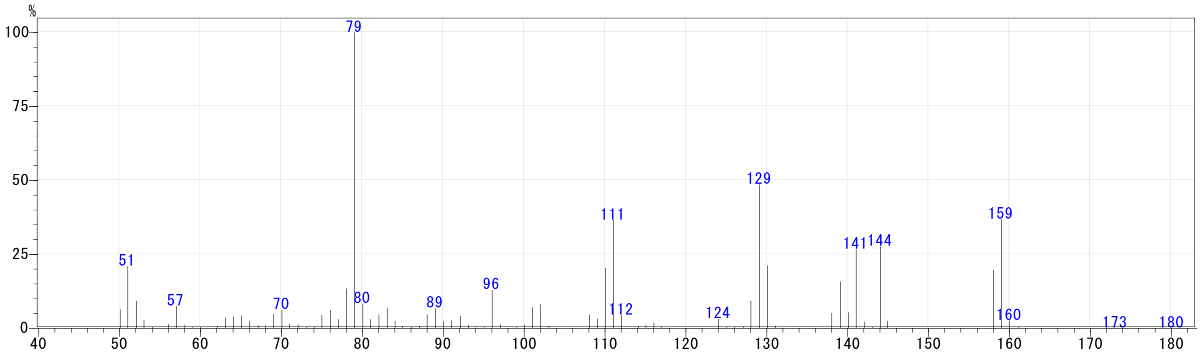


3-(Difluoromethyl)-2-methoxypyridine (4i)



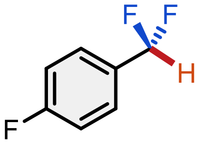
4i

Obtained in 59 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.74 (d, *J*= 57.1 Hz, 2F). The identity of the product was further confirmed by GCMS analysis.
HRMS (APCI) *m/z* Calcd for for $C_7H_8F_2NO[M+H]^+$ 160.0569; Found: 160.0568.



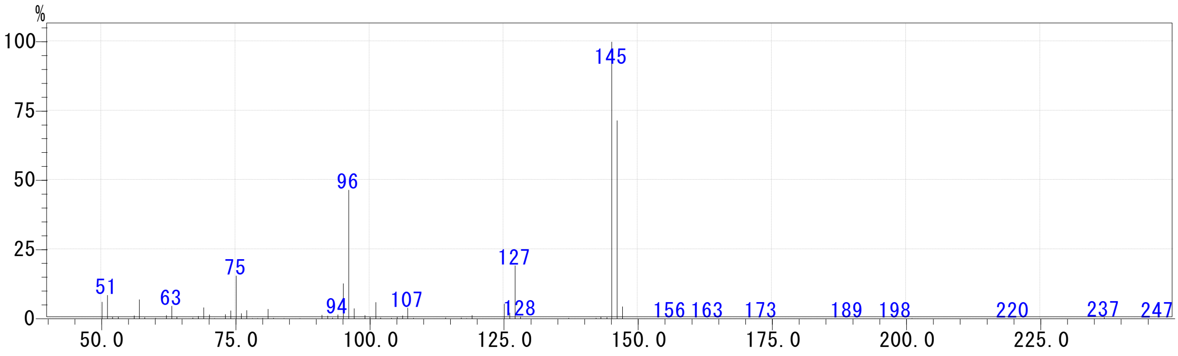
Note: The title compound could not be isolated due to highly volatile.

1-(Difluoromethyl)-4-fluorobenzene (4j)

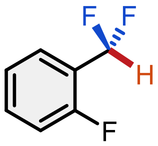


4j

Obtained in 84 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.65 (d, *J*= 55.8 Hz, 2F), -110.6 (s, 1F). ^{19}F NMR data matches previously reported data (*30*). The identity of the product was further confirmed by GCMS analysis.

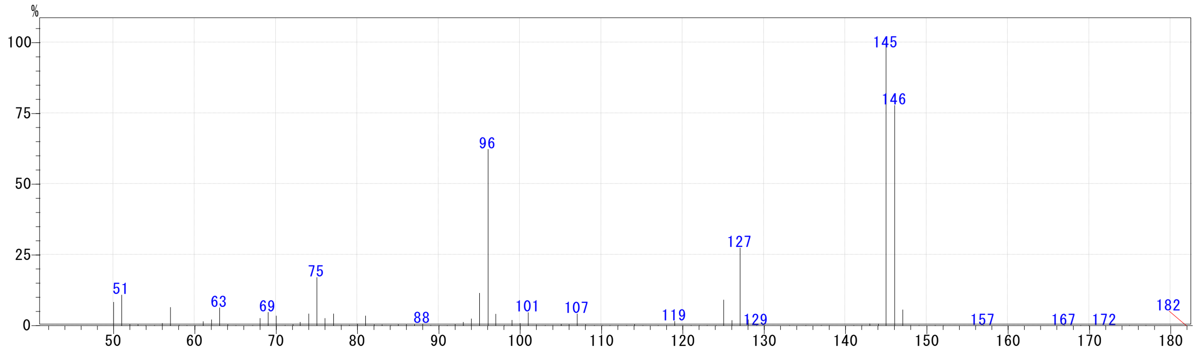


1-(Difluoromethyl)-2-fluorobenzene (4k)

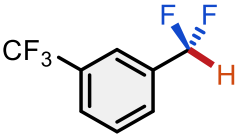


4k

Obtained in 81 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.19 (d, *J*= 55.9 Hz, 2F), -120.96 (s, 1F). ^{19}F NMR data matches previously reported data (*71*). The identity of the product was further confirmed by GCMS analysis.

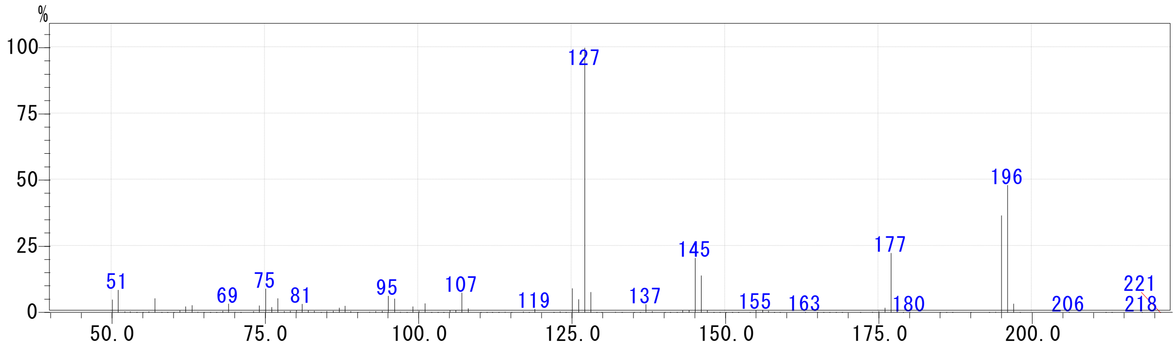


1-(Difluoromethyl)-3-(trifluoromethyl)benzene (4l)

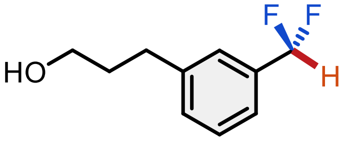


4l

Obtained in 57 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.98 (s, 3F), -112.89 (d, *J*= 55.9 Hz, 2F). ^{19}F NMR data matches previously reported data (*72*). The identity of the product was further confirmed by GCMS analysis.



3-(3-(difluoromethyl)phenyl)propan-1-ol (4m)



4m

Obtained in 72 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOA = 3:1, Rf= 0.1) to afford the pure product as a colorless oil.

HRMS (EI) *m/z* Calcd for $C_{10}H_{12}F_2O[M]^+$ 186.0851; Found: 186.0852.

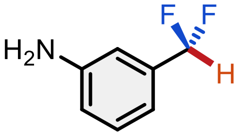
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dq, *J*= 13.2, 6.9 Hz, 4H), 6.63 (t, *J*= 56.5 Hz, 1H), 3.69 (t, *J*= 6.1 Hz, 2H), 2.77 (t, *J*= 7.8 Hz, 2H), 1.95-1.88 (m, 2H), 1.30 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.53, 134.45 (t, *J*= 22.1 Hz), 130.85, 128.75, 125.45 (t, *J*= 6.2 Hz), 123.14 (t, *J*= 5.9 Hz), 114.83 (t, *J*= 238.9 Hz), 62.02, 32.91 (d, *J*= 214.8 Hz), -0.02.

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.59 (d, *J*= 52.3 Hz, 2F).

3-(Difluoromethyl)aniline (4n)



4n

Obtained in 69 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (hexane/EtOAc= 10:1, Rf= 0.1) to afford the pure product as a yellow oil.

HRMS (ESI) *m/z* Calcd for for $C_7H_8F_2N[M+H]^+$ 144.0619; Found: 144.0618.

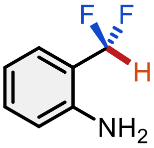
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J*= 7.7 Hz, 1H), 6.88-6.75 (m, 3H), 6.55 (td, *J*= 56.6, 1.3 Hz, 1H), 3.79 (s, 1H), 1.57 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ129.67, 117.13 (t, *J*= 1.8 Hz), 115.57 (t, *J*= 6.4 Hz), 114.77, 112.39, 111.56 (t, *J*= 6.2 Hz), 77.20.

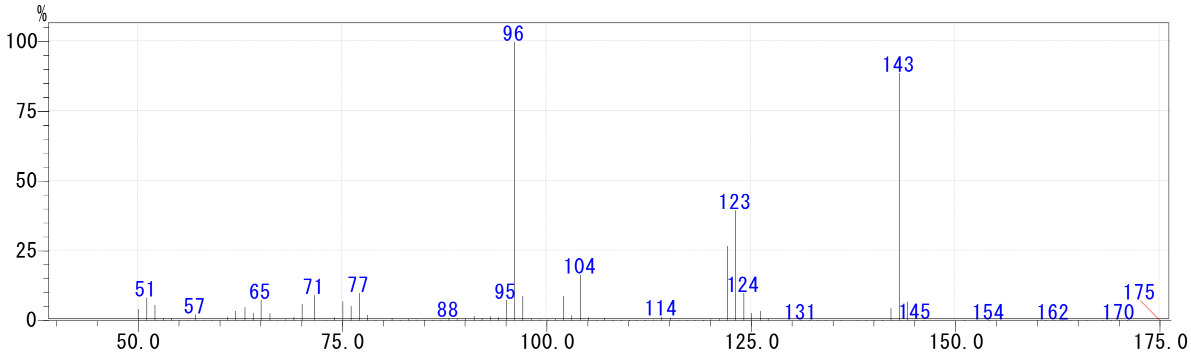
^{19}F NMR (376 MHz, $CDCl_3$) δ -111.86 (d, *J*= 57.1 Hz, 2F).

2-(Difluoromethyl)aniline (4o)

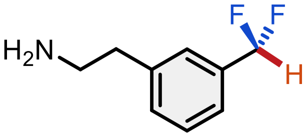


4o

Obtained in 46 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.56 (d, *J*= 55.5 Hz, 2F). ^{19}F NMR data matches previously reported data (*73*). The identity of the product was further confirmed by GCMS analysis.



2-(3-(difluoromethyl)phenyl)ethan-1-amine (4p)



4p

Obtained in 75 % yield (Maximum yield). The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The reaction mixture was purified by flash column chromatography (methanol only, Rf= 0.1) to afford the pure product as a white solid.

HRMS (ESI) *m/z* Calcd for $C_9H_{12}F_2N[M+H]^+$ 172.0932; Found: 172.0931.

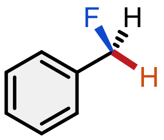
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 4H), 6.63 (t, *J*= 56.5 Hz, 1H), 2.99 (t, *J*= 6.9 Hz, 2H), 2.80 (t, *J*= 6.9 Hz, 2H), 1.26 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.58, 134.50 (t, *J*= 22.1 Hz), 131.20 (d, *J*= 1.9 Hz), 128.80, 125.81 (t, *J*= 5.8 Hz), 123.42 (t, *J*= 6.2 Hz), 114.76 (t, *J*= 238.8 Hz), 43.35, 39.88.

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.61 (d, *J*= 58.0 Hz, 2F).

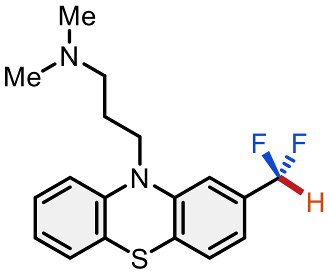
(Fluoromethyl)benzene (4q)



4q

Obtained in 64 % yield (Maximum yield). Yields were determined by GC analysis (^{t}R 6.7 min) (initial oven temperature, 50 °C (5 min); temperature increase rate, 10 °C/min (25 min); final temperature, 300 °C) using an internal standard (undecane). The NMR spectral data were identical to those reported in the literature (*30*).

3-(2-(Difluoromethyl)-10H-phenothiazin-10-yl)-*N*, *N*-dimethylpropan-1-amine (5a)



5a

Obtained in 80 % yield. The crude product was purified by flash column chromatography on silica gel (hexane/Acetone/Et_3N= 91:6:3, Rf= 0.1) to afford the pure product as a yellow oil (70.2 mg).

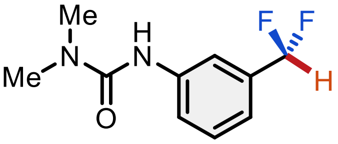
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.12 (m, 3H), 7.02 (d, *J*= 9.1 Hz, 2H), 6.96-6.90 (m, 2H), 6.58 (t, *J*= 56.5 Hz, 1H), 3.94 (t, *J*= 7.0 Hz, 2H), 2.40 (t, *J*= 7.0 Hz, 2H), 2.21 (s, 6H), 1.94 (t, *J*= 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.67, 144.59, 133.43 (t, *J*= 22.2 Hz), 128.43, 128.41, 127.45, 127.42, 124.28, 122.80, 119.56 (t, *J*= 6.6 Hz), 116.94, 115.72, 114.57, 112.12 (t, *J*= 5.9 Hz), 57.02, 45.50 (d, *J*= 17.2 Hz), 25.04.

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.49 (d, *J*= 57.4 Hz, 2F).

3-(3-(Difluoromethyl)phenyl)-1,1-dimethylurea (5b)



5b

Obtained in 54 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, Rf= 0.2) to afford the pure product as a white solid in 53 % isolated yield (28.2 mg).
HRMS (ESI) *m/z* Calcd for $C_{10}H_{12}F_2N_2ONa[M+Na]^+$ 237.0810; Found: 237.0806.

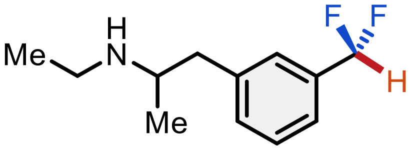
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.49 (dd, *J*= 8.1, 1.0 Hz, 1H), 7.36 (t, *J*= 7.9 Hz, 1H), 7.17 (d, *J*= 7.5 Hz, 1H), 6.60 (t, *J*= 56.5 Hz, 1H), 6.43 (s, 1H), 3.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.43, 139.37 (d, *J*= 99.2 Hz), 134.94 (t, *J*= 22.1 Hz), 129.05 (d, *J*= 60.6 Hz), 123.75-120.57 (m), 119.73 (t, *J*= 6.2 Hz), 116.82 (q, *J*= 8.2 Hz), 113.62 (d, *J*= 239.0 Hz), 36.39.

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.93 (d, *J*= 53.3 Hz, 2F).

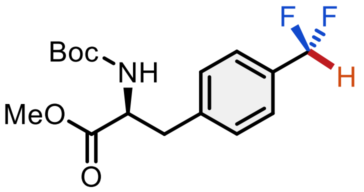
1-(3-(difluoromethyl)phenyl)-*N*-ethylpropan-2-amine (5c)



5c

Obtained in 72 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.63 (d, *J*= 52.0 Hz, 2F). Determination of the yield and the compound characterization were performed using a purified mixture of the target product and its monofluoromethyl and trifluoromethyl analogs.
HRMS (ESI) *m/z* Calcd for $C_{12}H_{18}F_2N[M+H]^+$ 214.1402; Found: 214.1402.

Methyl-(R)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoate (5d)



5d

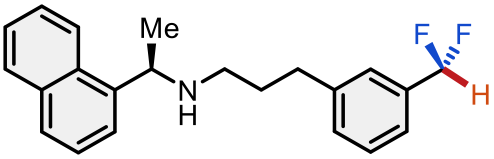
Obtained in 46 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.68 (d, *J*= 54.1 Hz, 2F). ^{19}F NMR data matches previously reported data (*30*). Determination of the yield and the compound characterization were performed using a purified mixture of the target product and its monofluoromethyl and trifluoromethyl analogs.

NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J*= 7.7 Hz, 2H), 7.22 (d, *J*= 7.8 Hz, 2H), 6.62 (t, *J*= 56.5 Hz, 1H), 4.99 (d, *J*= 7.7 Hz, 1H), 4.61 (q, *J*= 6.9 Hz, 1H), 3.72 (s, 3H), 3.21-3.05 (m, 2H), 1.41 (s, 9H).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.68 (d, *J*= 54.1 Hz, 2F).

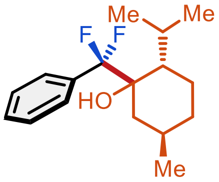
(S)-3-(3-(Difluoromethyl)phenyl)-*N*-(1-(naphthalen-1-yl)ethyl)propan-1-amine (5e)



5e

Obtained in 69 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.56 (d, *J*= 53.4 Hz, 2F). ^{19}F NMR data matches previously reported data (*30*). Determination of the yield and the compound characterization were performed using a purified mixture of the target product and its monofluoromethyl and trifluoromethyl analogs.

(2S,5R)-1-(Difluoro(phenyl)methyl)-2-isopropyl-5-methylcyclohexan-1-ol (5f)



5f

Obtained in 69 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC and flash column chromatography on silica gel (hexane/EtOAc= 10:0.5, Rf= 0.4) to afford the pure product as a colorless oil in 32 % isolated yield (23.2 mg).

HRMS (ESI) *m/z* Calcd for $C_{17}H_{24}F_2ONa[M+Na]^+$ 305.1687; Found: 305.1686.

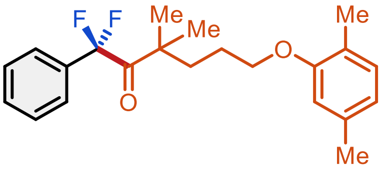
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J*= 7.4, 2.1 Hz, 2H), 7.42 (q, *J*= 3.4 Hz, 3H), 2.64 (7, *J*= 6.9 Hz, 1H), 1.95 (s, 1H), 1.72-1.64 (m, 2H), 1.59-1.45 (m, 3H), 1.26 (dt, *J*= 13.3, 2.9 Hz, 1H), 1.00 (d, *J*= 6.8 Hz, 3H), 0.94 (t, *J*= 7.3 Hz, 4H), 0.77 (d, *J*= 6.4 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.26 (t, *J*= 27.0 Hz), 129.59, 127.89, 126.55 (t, *J*= 6.7 Hz), 126.78-121.75 (m), 78.76 (dd, *J*= 27.0, 24.1 Hz), 45.47, 43.26 (d, *J*= 4.3 Hz), 34.63, 31.09, 27.44, 26.75 (t, *J*= 4.2 Hz), 23.24, 22.14, 20.21, 17.89.

^{19}F NMR (376 MHz, $CDCl_3$) δ -101.25 (d, *J*= 246.7 Hz, 1F), -103.29 (d, *J*= 248.5 Hz, 1F), -107.23(d, *J*= 248.5 Hz, 1F), -110.30 (d, *J*= 248.3 Hz, 1F).

6-(2,5-Dimethylphenoxy)-1,1-difluoro-3,3-dimethyl-1-phenylhexan-2-one (5g)



5g

Obtained in 56 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC to afford the pure product as a colorless oil in 41 % isolated yield (37.2 mg).

HRMS (ESI) *m/z* Calcd for $C_{22}H_{26}F_2O_2Na[M+Na]^+$ 383.1793; Found: 383.1789.

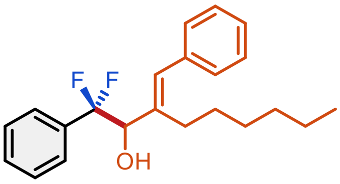
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.47-7.41 (m, 3H), 7.01 (d, *J*= 7.5 Hz, 1H), 6.66 (d, *J*= 7.4 Hz, 1H), 6.59 (s, 1H), 3.88 (t, *J*= 6.2 Hz, 2H), 2.31 (s, 3H), 2.17 (s, 3H), 1.90-1.86 (m, 2H), 1.66-1.58 (m, 2H), 1.26 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.12 (t, *J*= 29.4 Hz), 156.85, 136.45, 133.03 (d, *J*= 25.0 Hz), 130.63, 130.28, 128.51, 125.72 (t, *J*= 6.2 Hz), 123.55, 120.69, 119.79-114.68 (m), 111.83, 67.63, 47.32 (d, *J*= 1.8 Hz), 36.18 (d, *J*= 2.5 Hz), 24.85, 24.33 (t, *J*= 1.9 Hz), 21.39, 15.75.

^{19}F NMR (376 MHz, $CDCl_3$) δ -100.18 (s, 2F).

(E)-3-Benzylidene-1,1-difluoro-1-phenylnonan-2-ol (5h)



5h

Obtained in 71 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by GPC and flash column chromatography on silica gel (hexane/EtOAc= 10:1, Rf= 0.2) to afford the pure product as a colorless oil in 34 % isolated yield (30.0 mg).

HRMS (ESI) *m/z* Calcd for $C_{22}H_{26}F_2ONa[M+Na]^+$ 367.1844; Found: 367.1841.

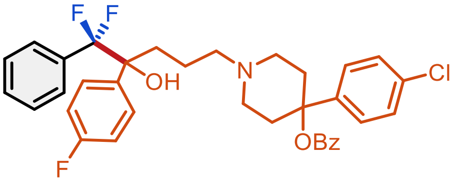
NMR Spectroscopy:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50-7.40 (m, 5H), 7.30 (t, *J*= 7.5 Hz, 2H), 7.23-7.19 (m, 1H), 7.09 (d, *J*= 7.2 Hz, 2H), 6.36 (s, 1H), 4.65 (td, *J*= 9.7, 4.0 Hz, 1H), 2.35-2.29 (m, 1H), 2.26 (d, *J*= 4.1 Hz, 1H), 1.89 (ddd, *J*= 14.2, 10.1, 4.7 Hz, 1H), 1.55 (s, 3H), 1.49-1.37 (m, 2H), 1.29-1.20 (m, 7H), 0.85 (t, *J*= 6.9 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 138.15, 136.94, 133.98 (t, *J*= 25.8 Hz), 130.13, 130.01 (t, *J*= 1.7 Hz), 128.44, 128.15, 127.95, 126.75, 126.33 (t, *J*= 6.4 Hz), 121.69 (t, *J*= 249.4 Hz), 76.84 (t, *J*= 29.4 Hz), 31.42 , 29.64, 29.38, 28.70, 22.52, 14.03.

^{19}F NMR (376 MHz, CDCl$_3$) δ -105.75--107.38 (m, 2F).

4-(4-Chlorophenyl)-1-(5,5-difluoro-4-(4-fluorophenyl)-4-hydroxy-5-phenylpentyl)piperidin-4-yl benzoate (5i)



5i

Obtained in 30 % yield. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 3:2, Rf= 0.4) to afford the pure product as a yellow viscous oil (46.5 mg).

HRMS (ESI) *m/z* Calcd for $C_{35}H_{34}ClF_3NO_3[M+H]^+$ 608.2174; Found:608.2167.

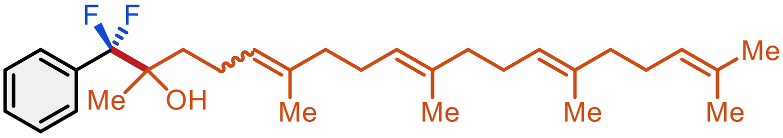
NMR Spectroscopy:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97-7.95 (m, 2H), 7.56 (tt, *J*= 7.4, 1.4 Hz, 1H), 7.42 (t, *J*= 7.7 Hz, 2H), 7.37-7.29 (m, 7H), 7.22 (t, *J*= 7.6 Hz, 2H), 7.17-7.14 (m, 2H), 6.93 (t, *J*= 8.7 Hz, 2H), 2.85-2.67 (m, 3H), 2.55-1.97 (m, 9H), 1.64 (dddd, *J*= 10.4, 7.7, 5.0, 2.5 Hz, 1H), 1.49-1.39 (m, 1H), 1.31-1.26 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 164.52, 163.35, 160.90, 142.05, 136.83 (t, *J*= 2.5 Hz), 134.70 (t, *J*= 26.5 Hz), 133.50, 133.11, 130.59, 129.67 (d, *J*= 7.7 Hz), 129.45, 129.14, 128.71, 128.46, 127.33 (t, *J*= 6.5 Hz), 126.96, 126.18, 114.26 (d, *J*= 21.1 Hz), 79.76, 77.59 (dd, *J*= 53.5, 25.7 Hz), 58.52, 50.21, 47.45, 34.60 (t, *J*= 51.0 Hz), 20.68.

^{19}F NMR (376 MHz, CDCl$_3$) δ -105.81 (d, *J*= 242.3 Hz, 1F), -109.38 (d, *J*= 241.0 Hz, 1F), -116.86 (d, *J*= 12.4 Hz, 1F).

(9E,13E)-1,1-Difluoro-2,6,10,14,18-pentamethyl-1-phenylnonadeca-5,9,13,17-tetraen-2-ol (5j)



5j

Obtained in 72 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, Rf= 0.3) to afford the pure product as a colorless oil in 57 % isolated yield (44.9 mg). HRMS (ESI) *m/z* Calcd for $C_{30}H_{44}F_2ONa[M+Na]^+$ 481.3252; Found: 481.3245.

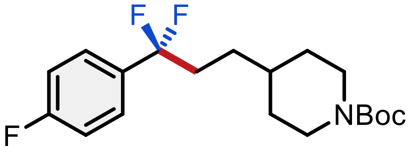
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J*= 5.7, 1.9 Hz, 2H), 7.43 (t, *J*= 6.3 Hz, 3H), 5.11-5.07 (m, 4H), 2.15-1.95 (m, 14H), 1.68-1.56 (m, 18H), 1.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) 135.93 (d, *J*= 18.4 Hz), 135.30-134.89 (m), 134.20 (t, *J*= 27.0 Hz), 131.26, 129.73, 127.84, 126.86 (t, *J*= 6.7 Hz), 125.43-120.44 (m), 75.68 (t, *J*= 27.9 Hz), 39.70-39.65 (m), 35.39 (dt, *J*= 32.7, 1.7 Hz), 31.89, 26.73-21.42 (m), 20.35 (t, *J*= 2.9 Hz), 17.66, 15.97 (t, *J*= 2.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.17 (d, *J*= 18.3 Hz, 2F).

tert-Butyl 4-(3,3-difluoro-3-(4-fluorophenyl)propyl)piperidine-1-carboxylate (8)



8

Obtained in 61 % yield. The yield was determined by ^{19}F NMR integration relative to the internal standard (hexafluorobenzene). The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc= 10:1, Rf= 0.2) to afford the pure product as a yellow oil in 52 % isolated yield (47.0 mg). HRMS (ESI) *m/z* Calcd for $C_{19}H_{26}F_3NO_2Na[M+Na]^+$ 380.1808; Found: 380.1805.

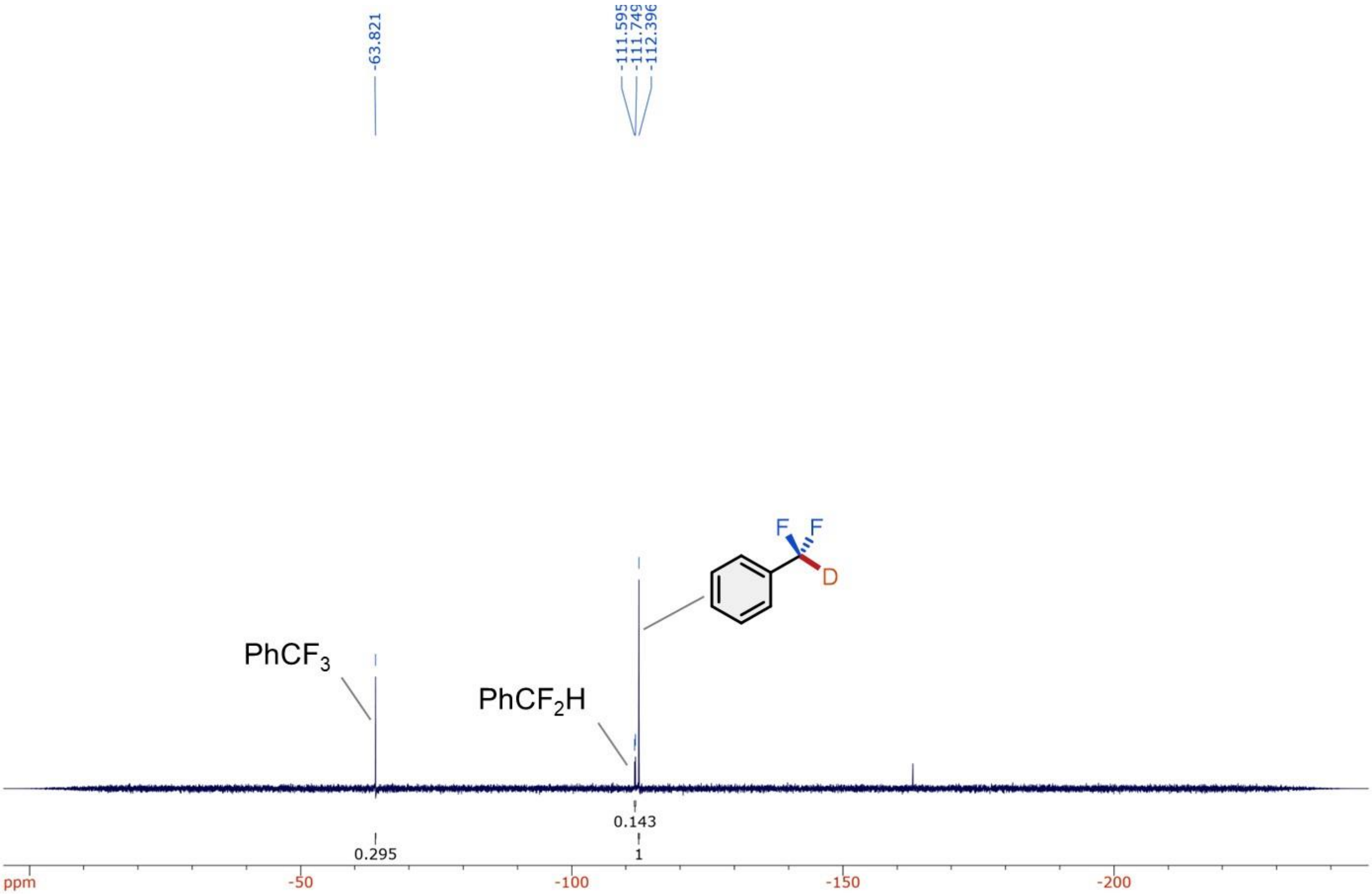
NMR Spectroscopy:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J*= 8.7, 5.3 Hz, 2H), 7.10 (t, *J*= 8.6 Hz, 2H), 4.07 (s, 2H), 2.65 (t, *J*= 10.9 Hz, 2H), 2.18-2.06 (m, 2H), 1.62 (d, *J*= 13.5 Hz, 2H), 1.44 (s, 9H), 1.38-1.33 (m, 3H), 1.11-1.01 (m, 2H).

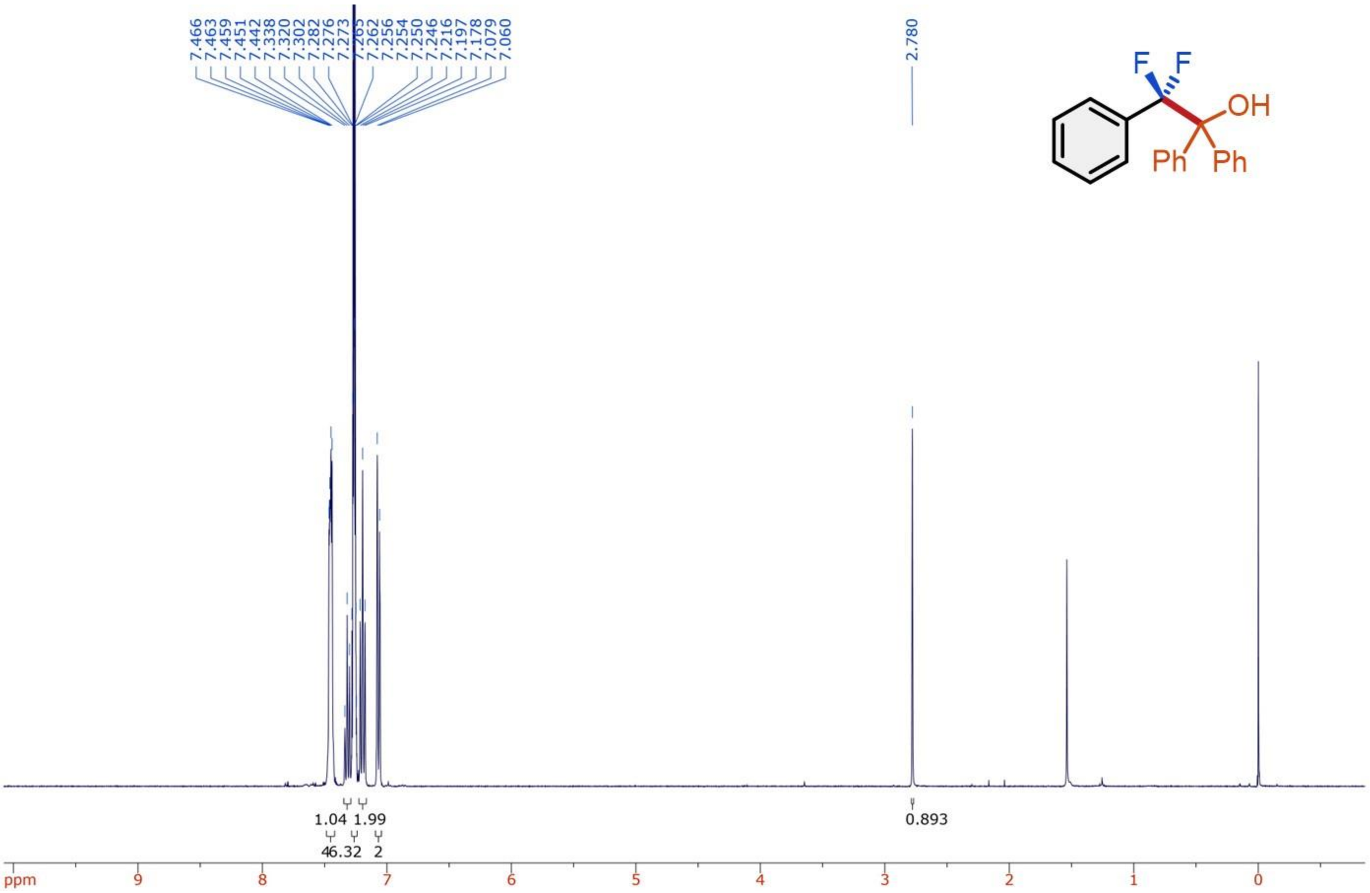
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.57, 162.10, 154.78, 133.56 (d, *J*= 3.5 Hz), 133.28 (d, *J*= 3.0 Hz), 127.09-126.88 (m), 122.74 (t, *J*= 242.4 Hz), 115.54, 115.32, 79.27, 36.34 (t, *J*= 27.6 Hz), 35.56, 31.85 (t, *J*= 2.1 Hz), 28.94 (t, *J*= 3.7 Hz), 28.41.

^{19}F NMR (376 MHz, $CDCl_3$) δ -95.96 (q, *J*= 15.1 Hz, 2F), -112.70 (s, 1F).

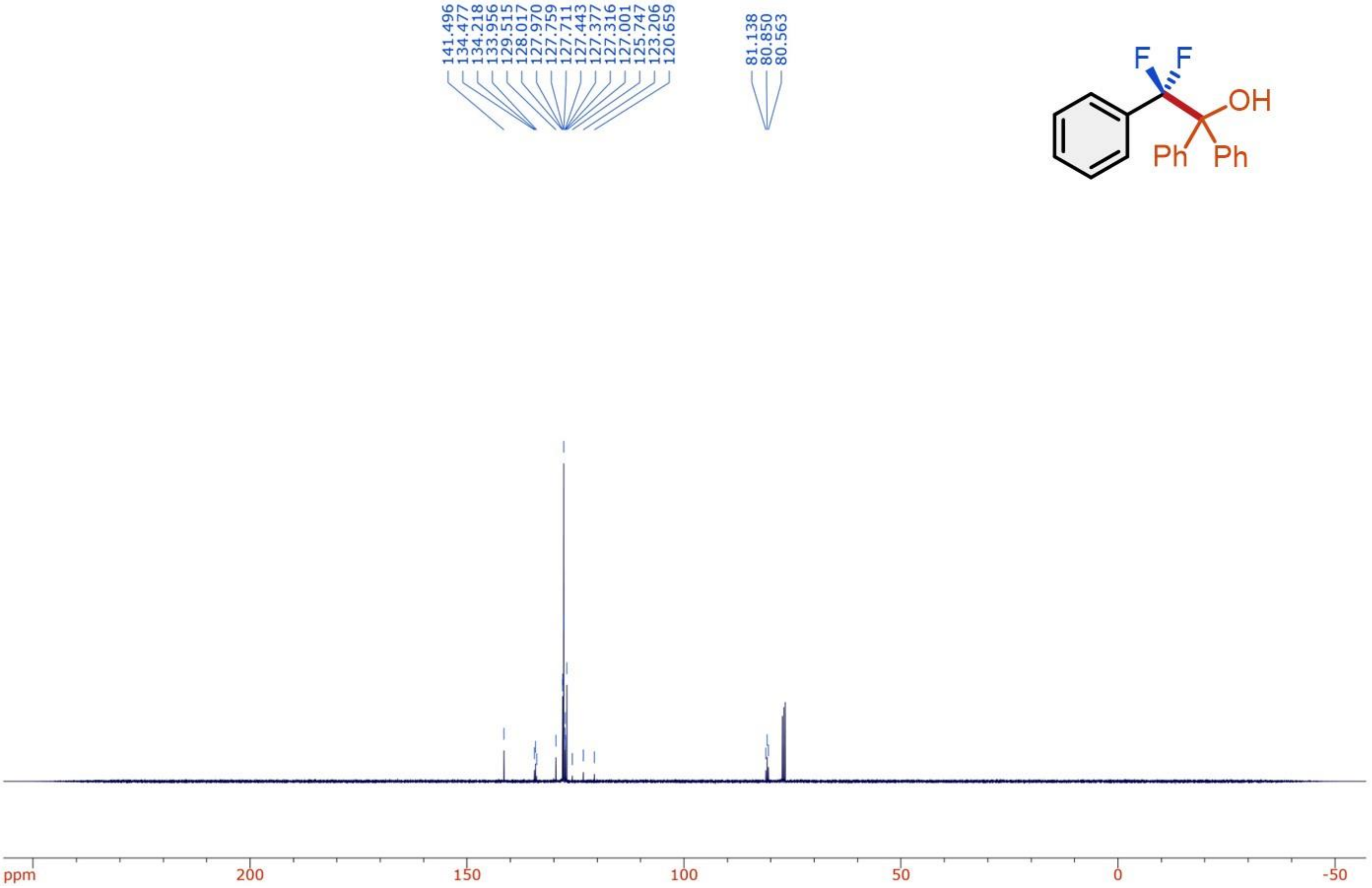
^{19}F NMR spectrum of crude of 3b



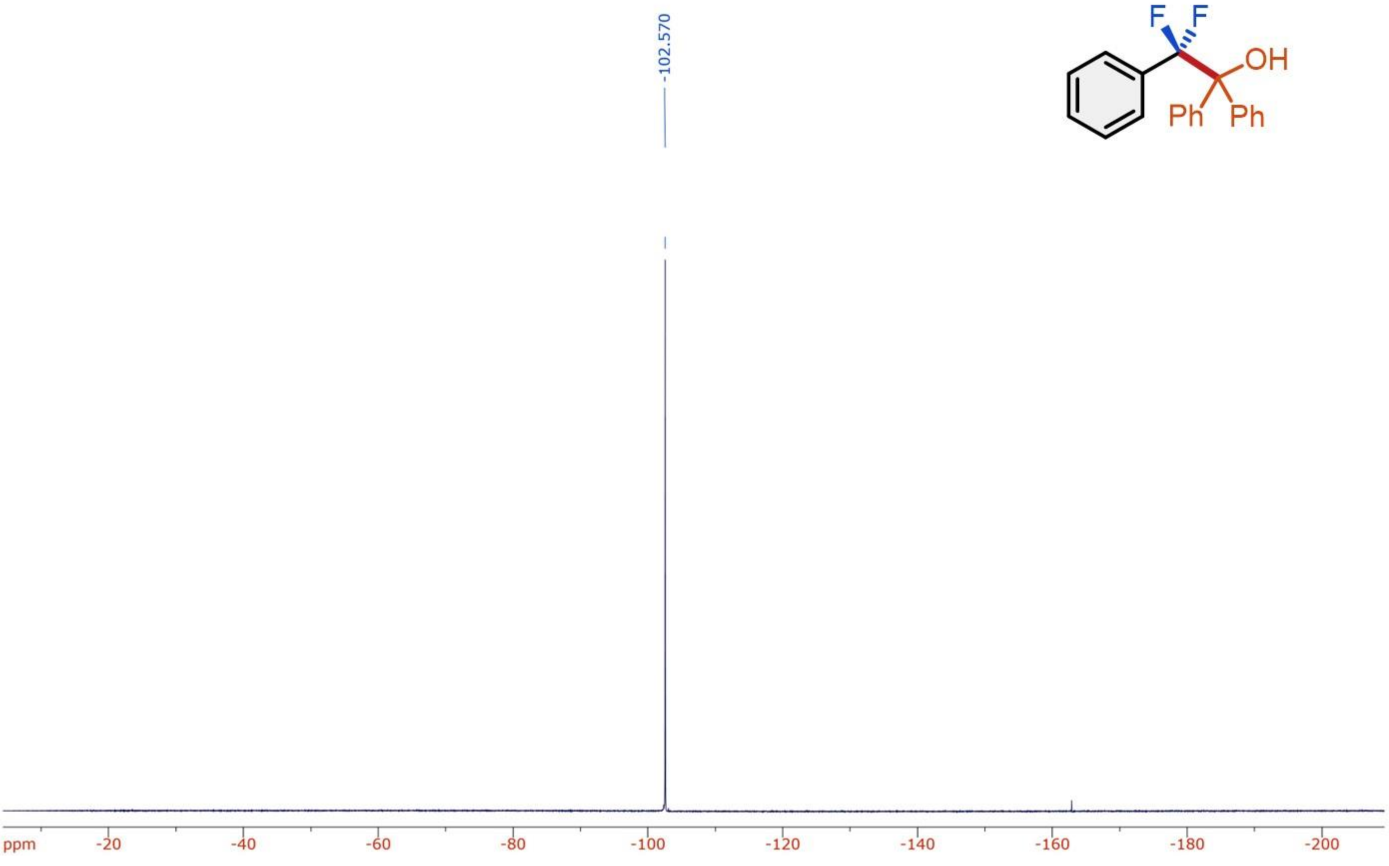
^{1}H NMR spectrum of 3c



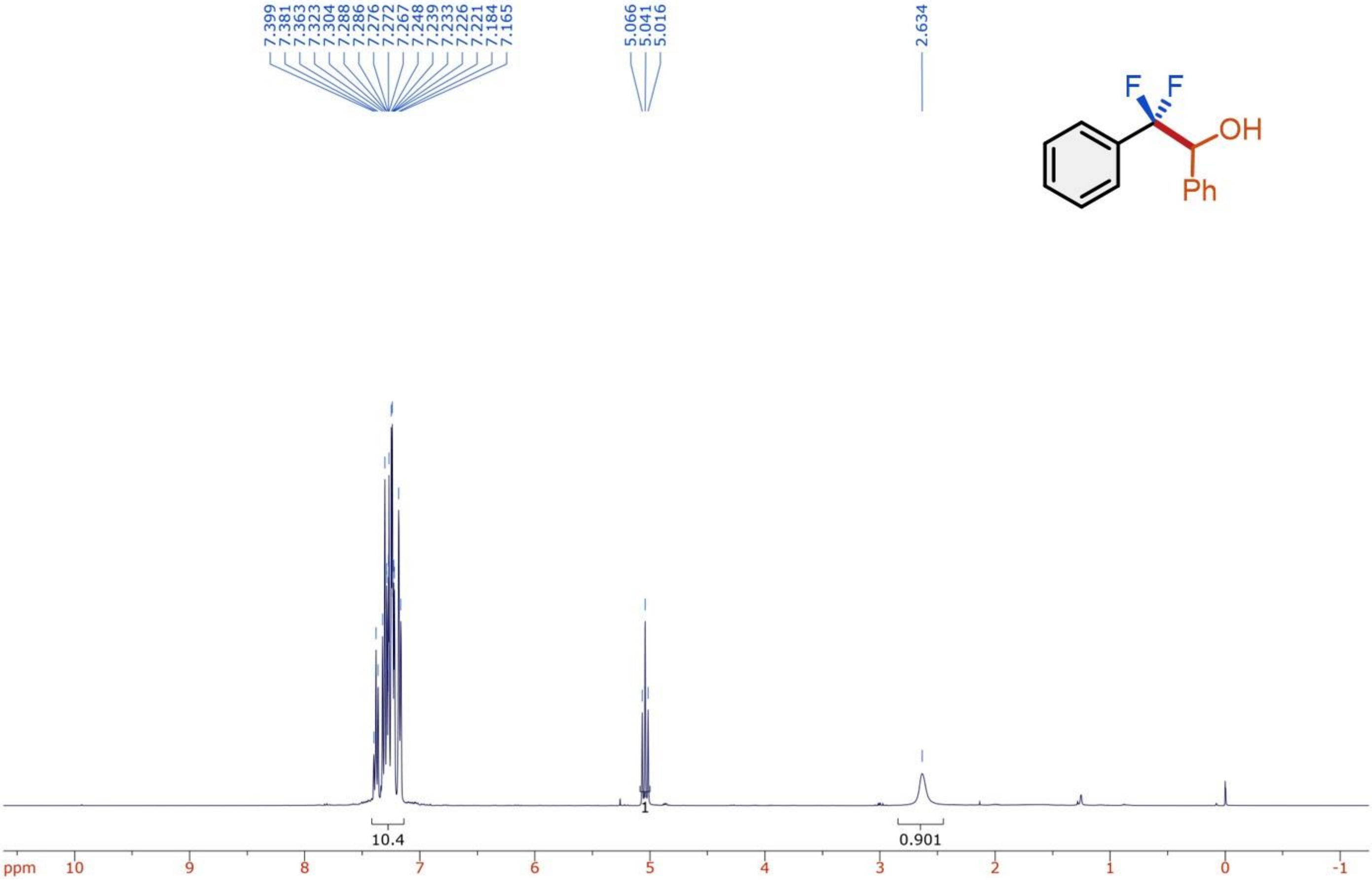
^{13}C NMR spectrum of 3c



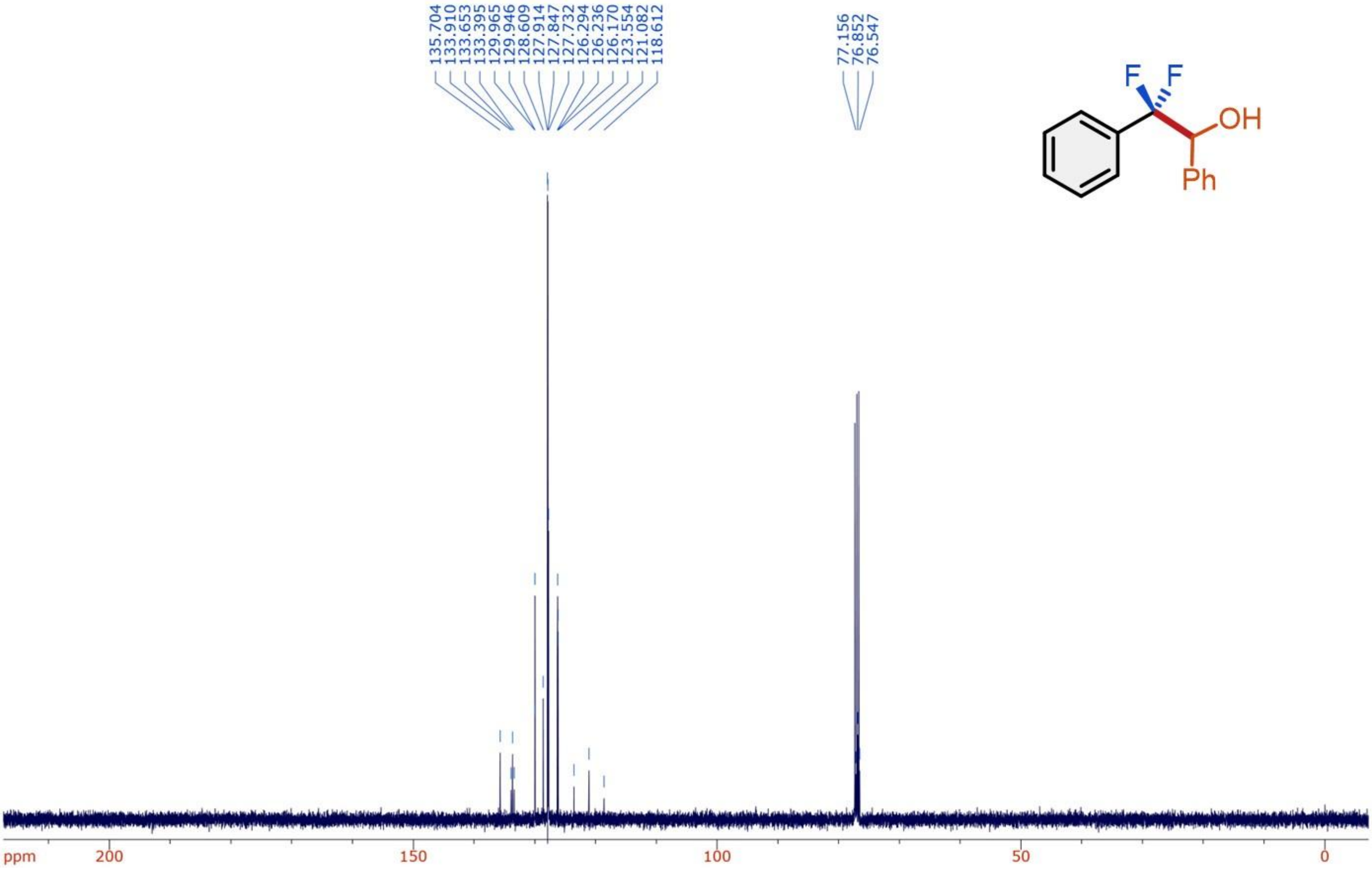
^{19}F NMR spectrum of 3c



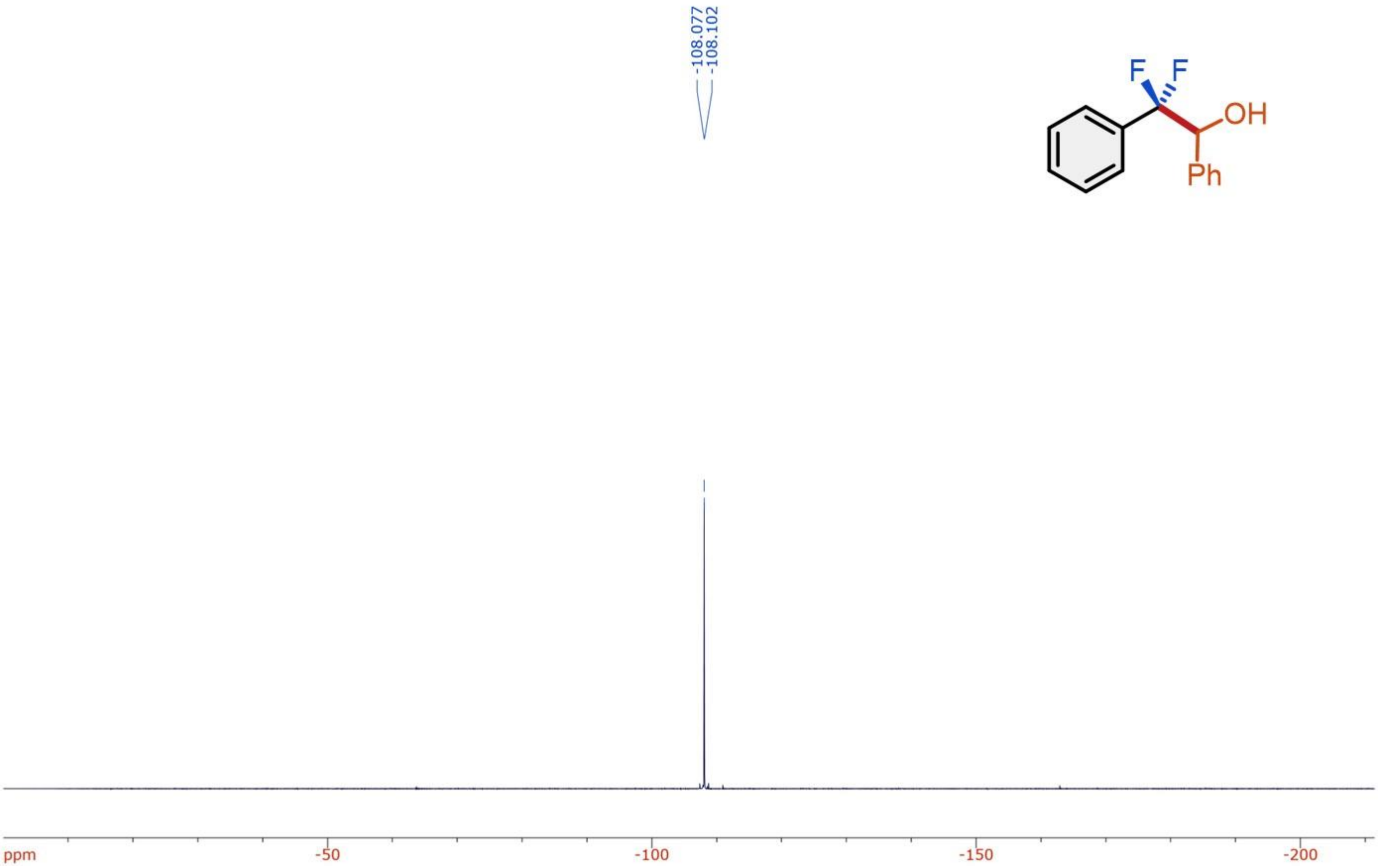
^{1}H NMR spectrum of 3d



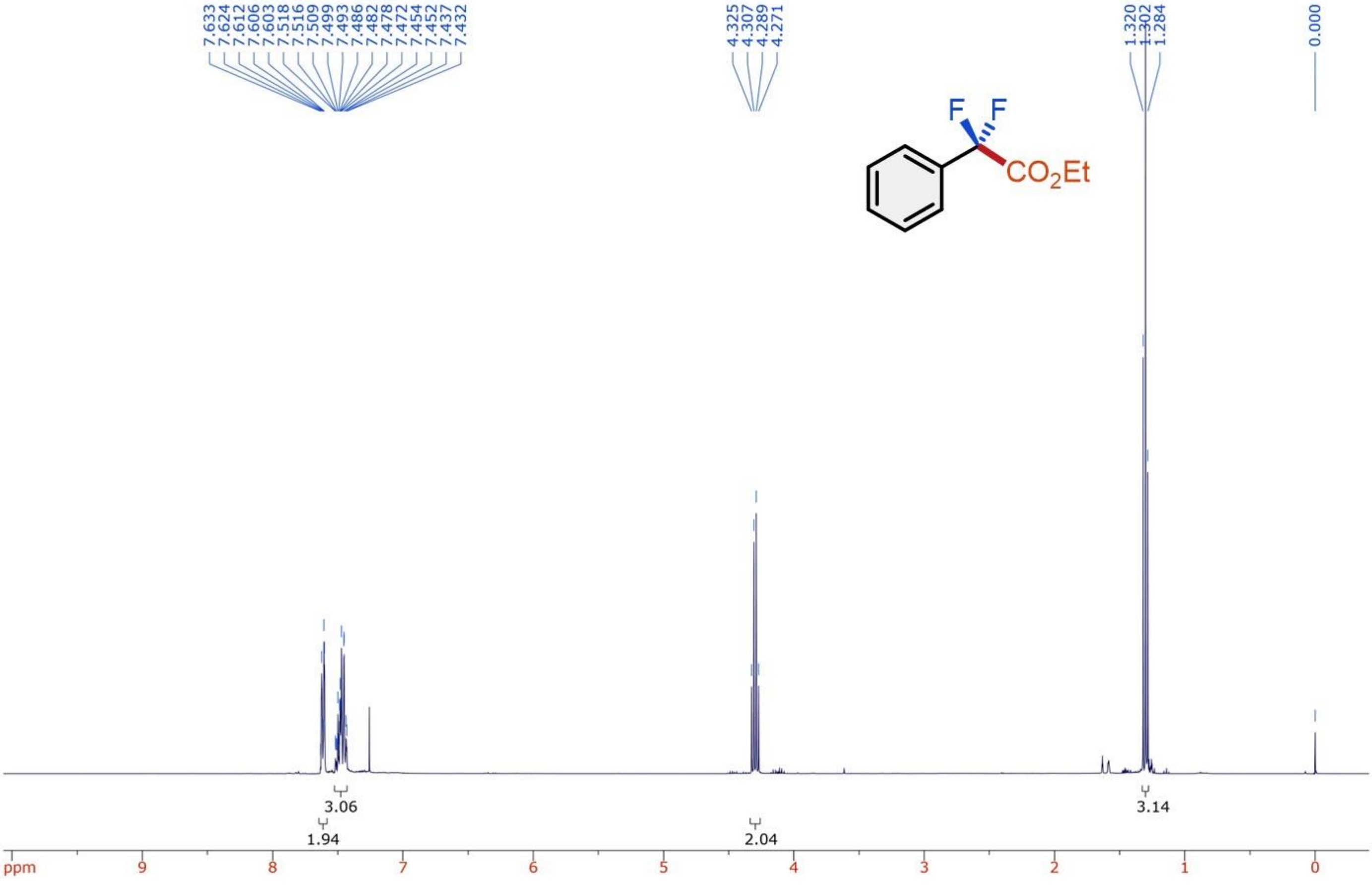
^{13}C NMR spectrum of 3d



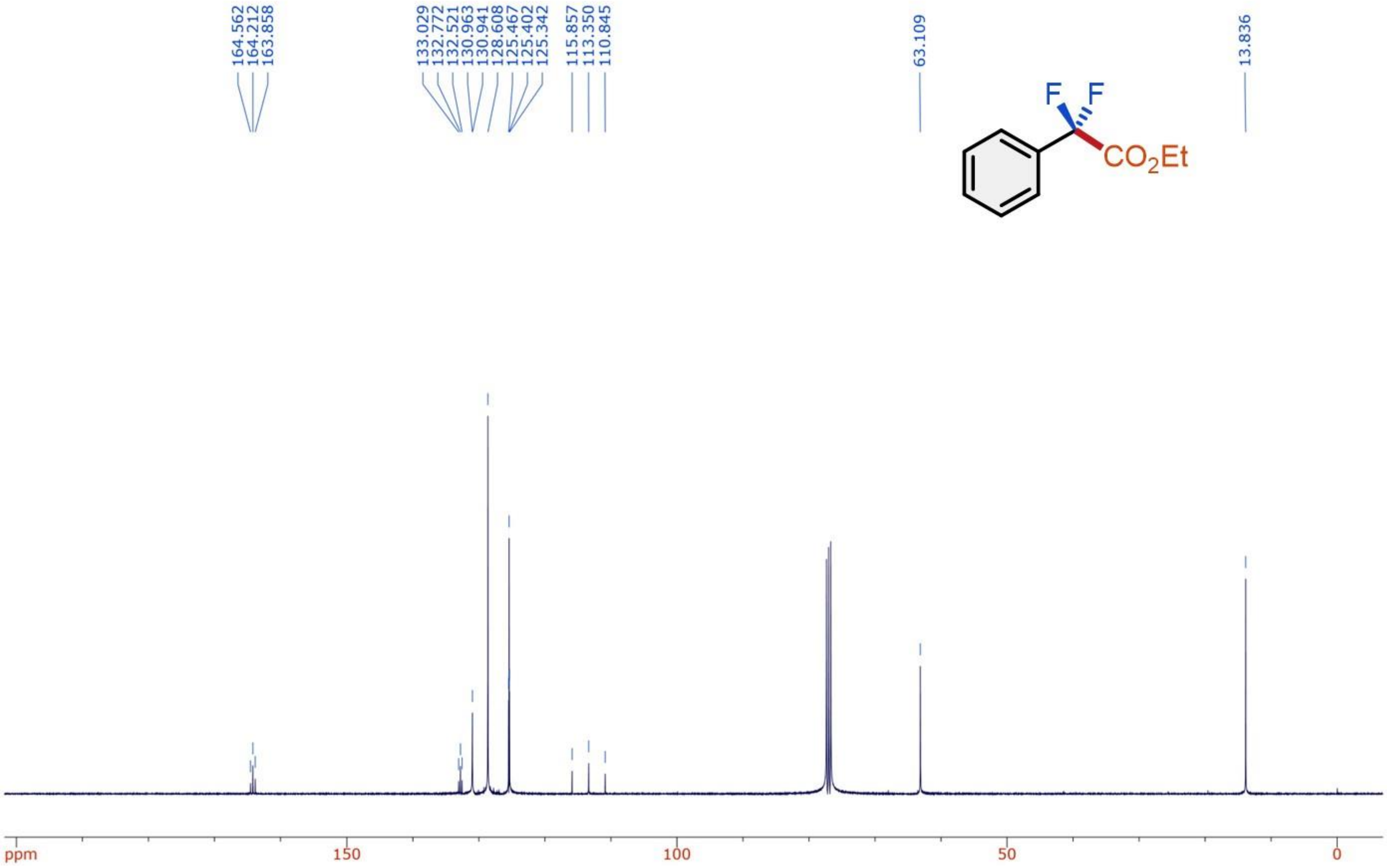
^{19}F NMR spectrum of 3d



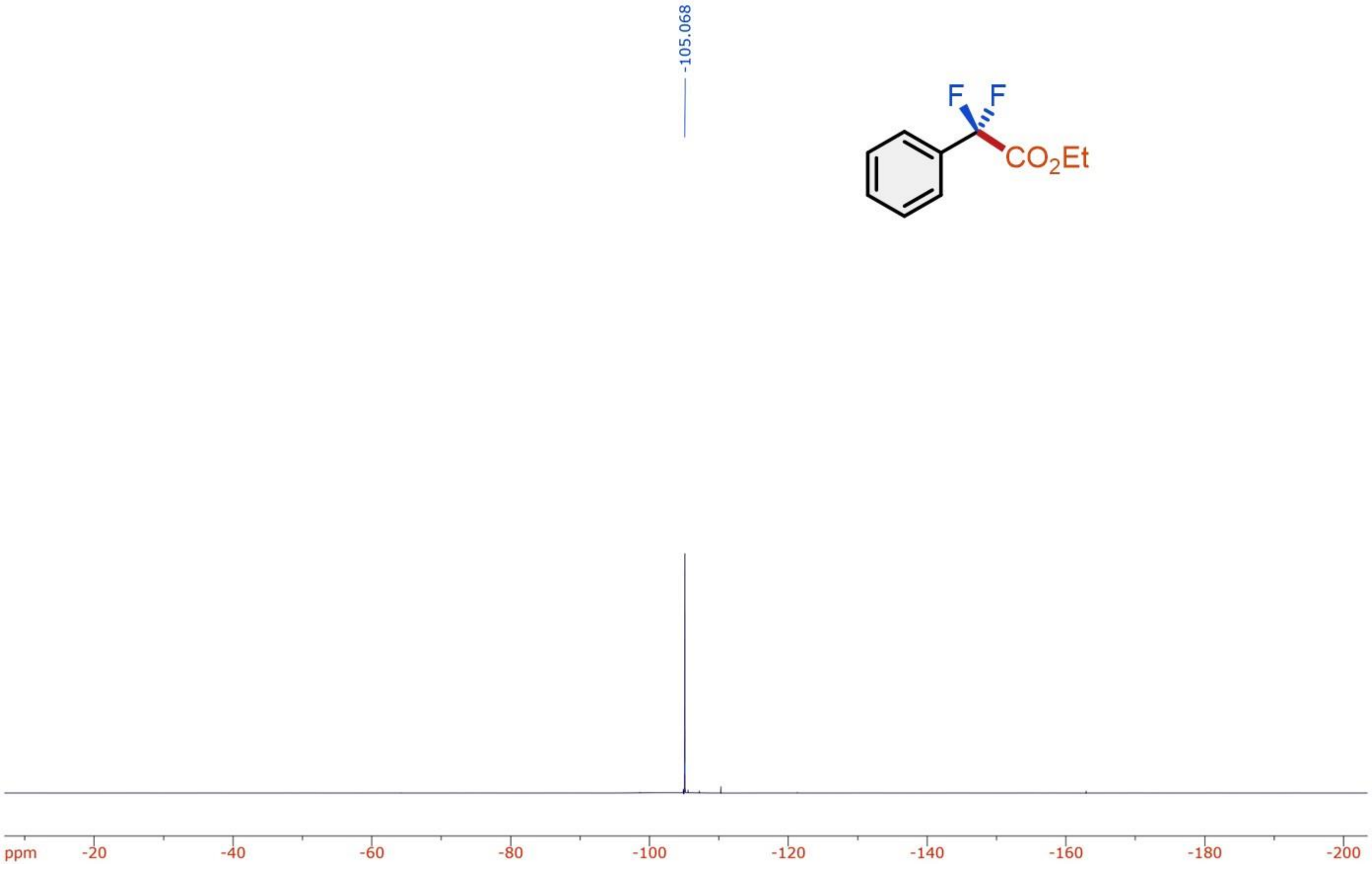
^{1}H NMR spectrum of 3e



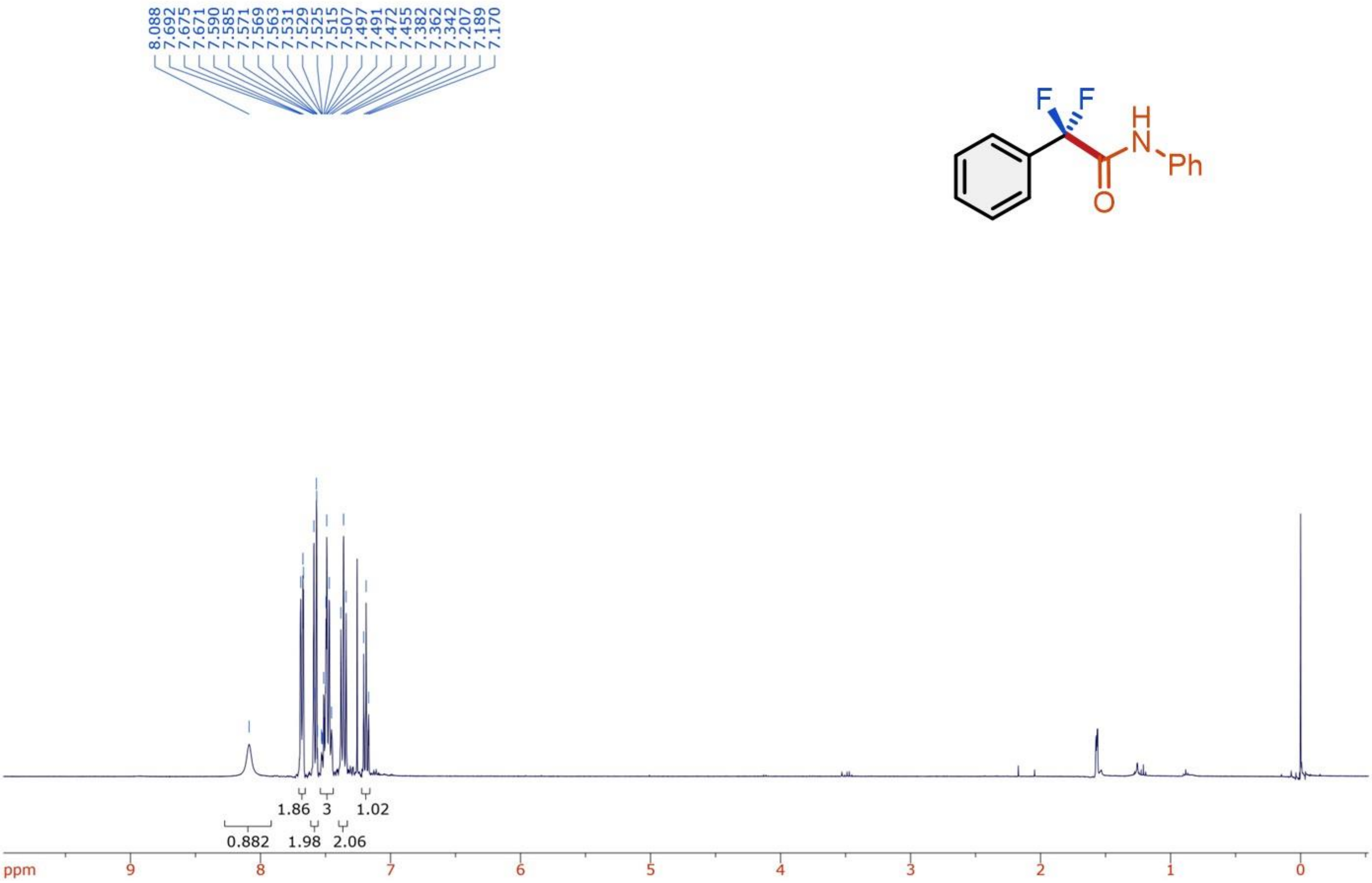
^{13}C NMR spectrum of 3e



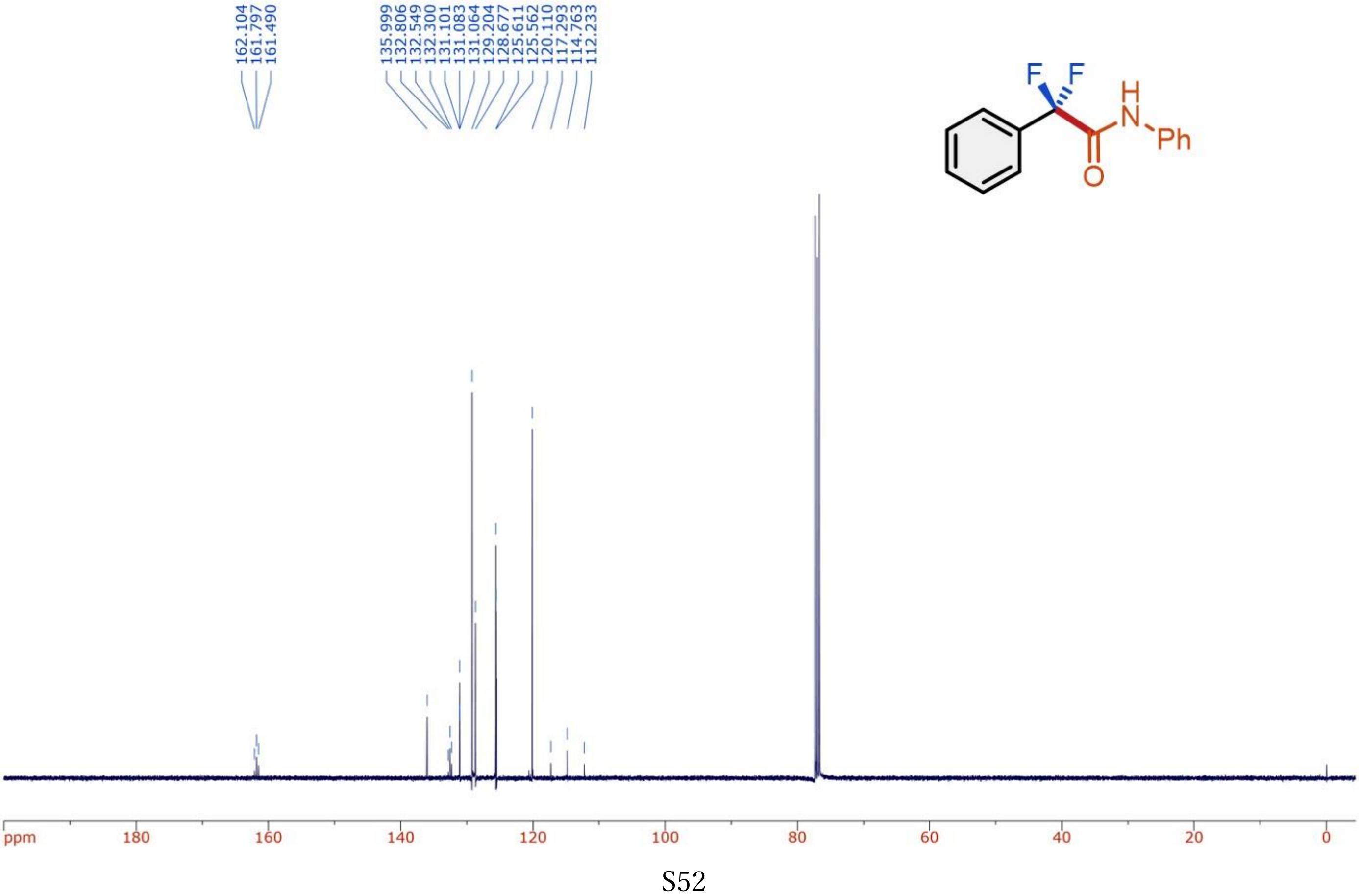
^{19}F NMR spectrum of 3e



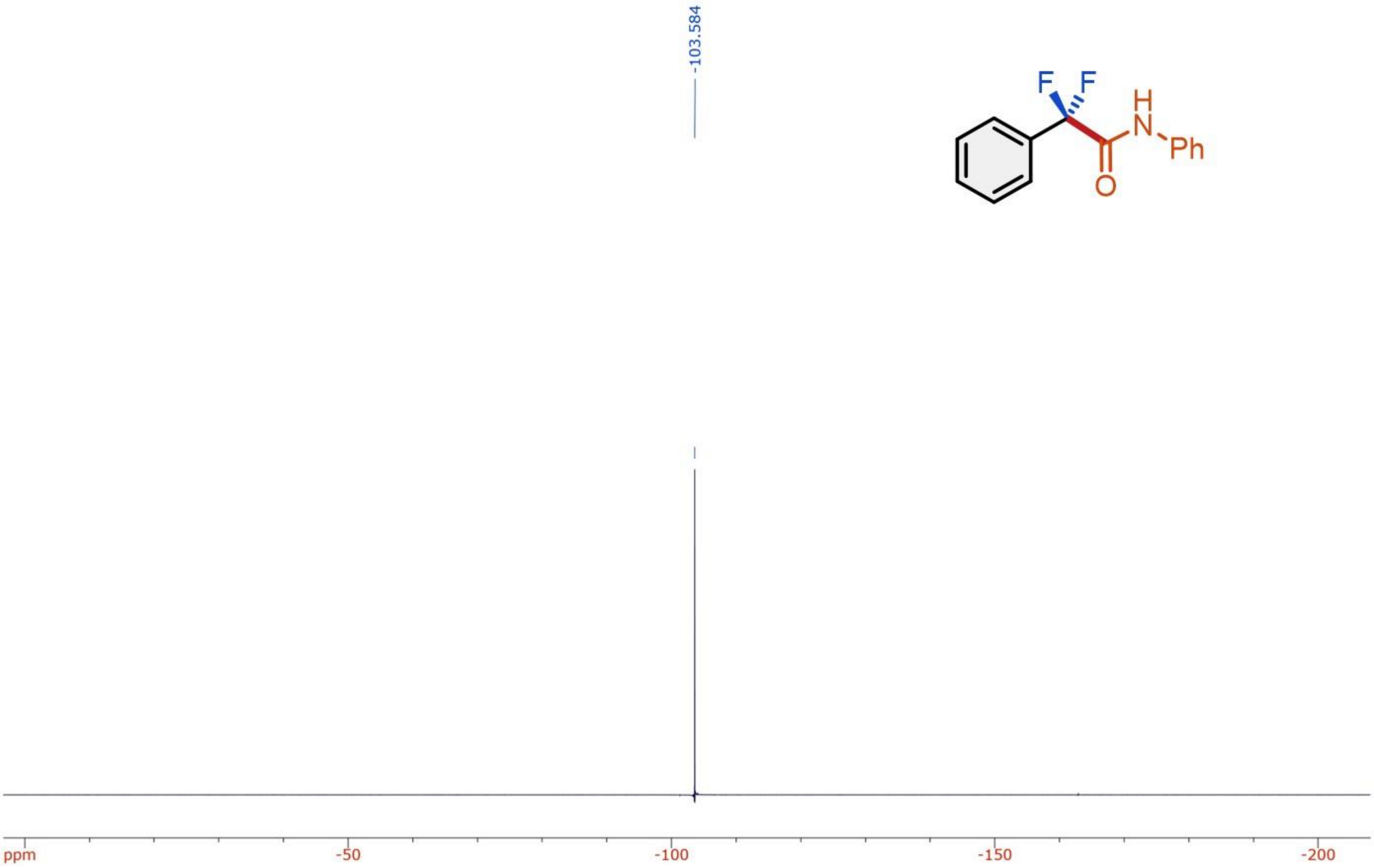
^{1}H NMR spectrum of 3g



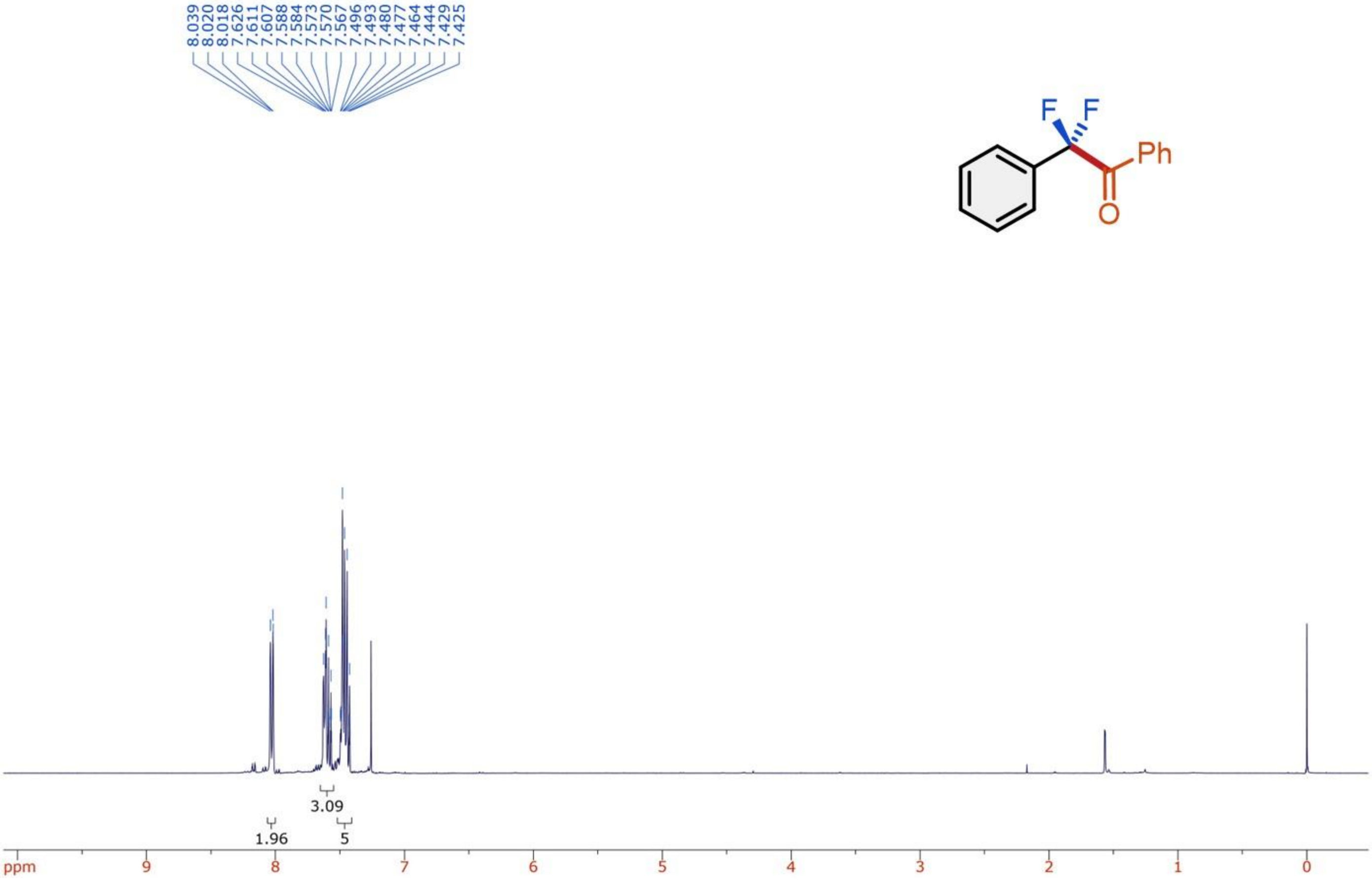
^{13}C NMR spectrum of 3g



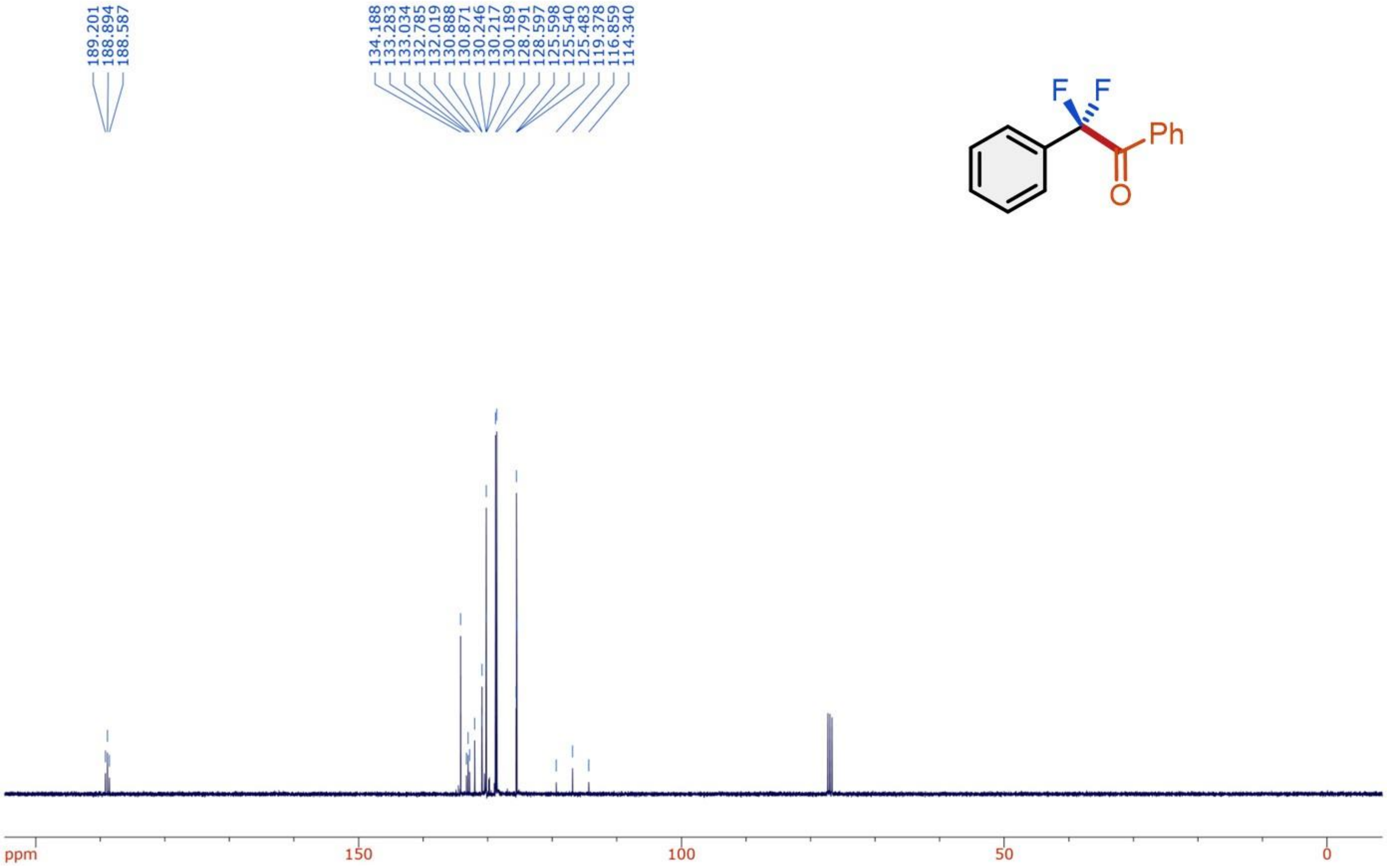
^{19}F NMR spectrum of 3g



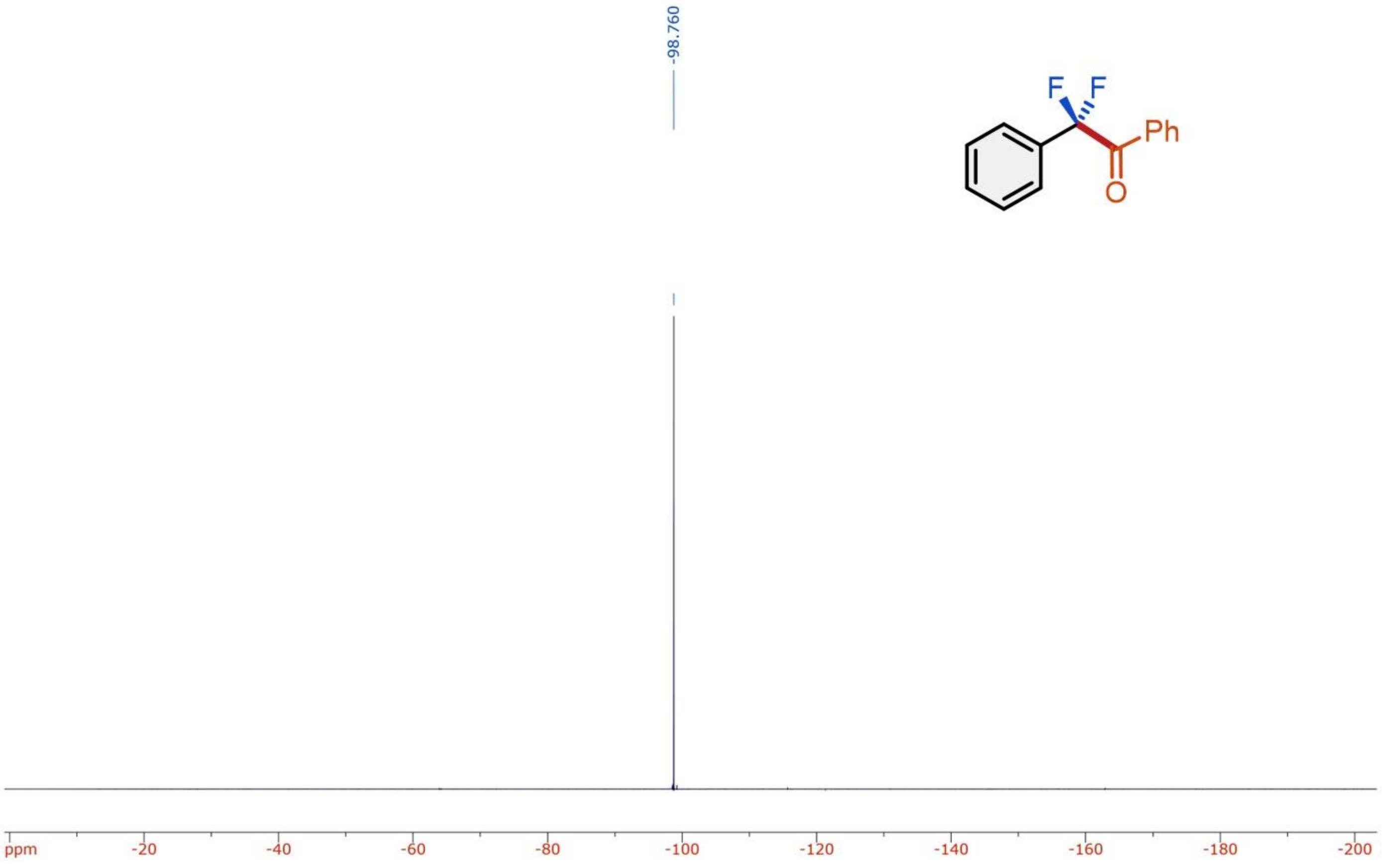
^{1}H NMR spectrum of 3h



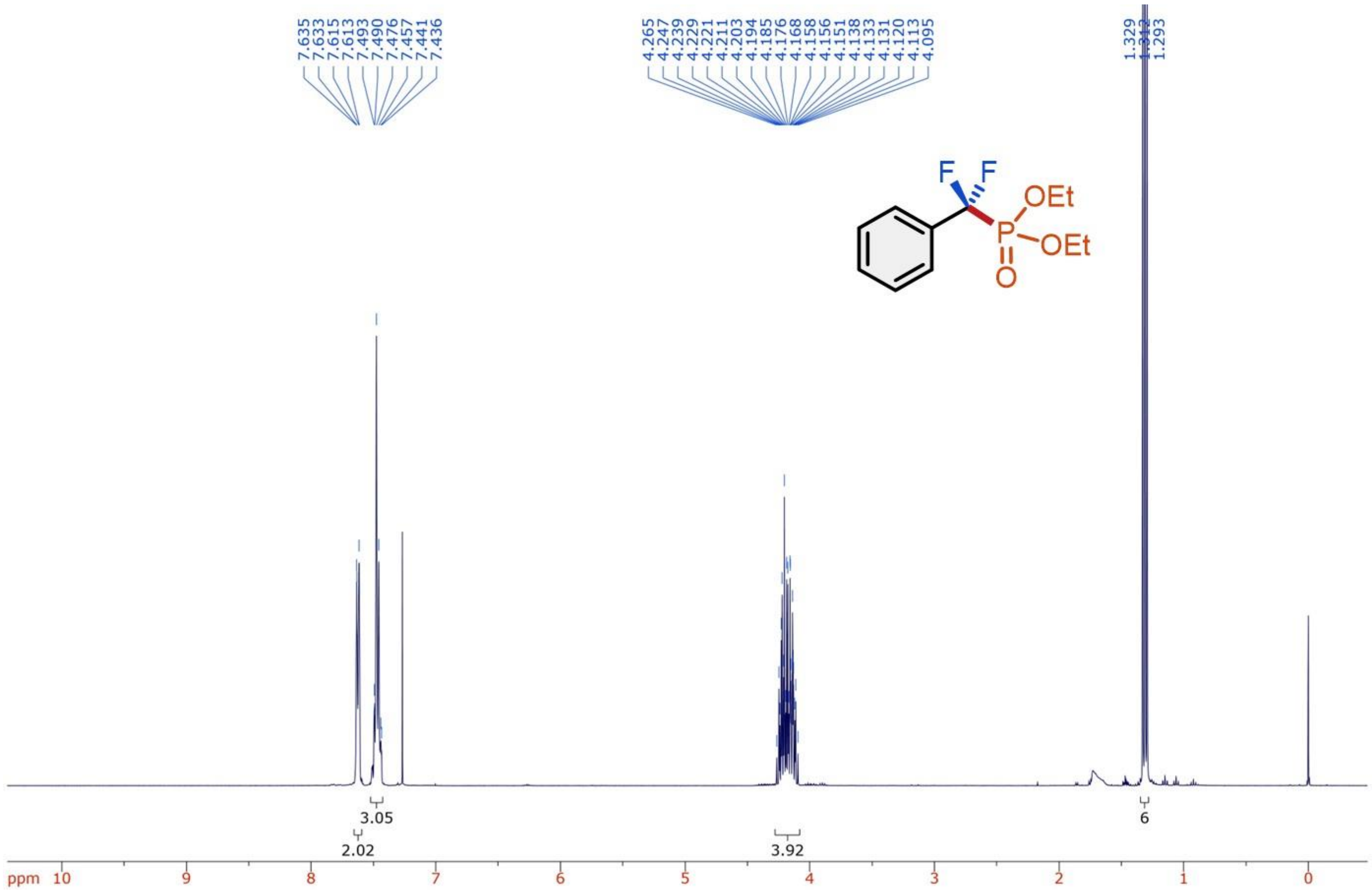
^{13}C NMR spectrum of 3h



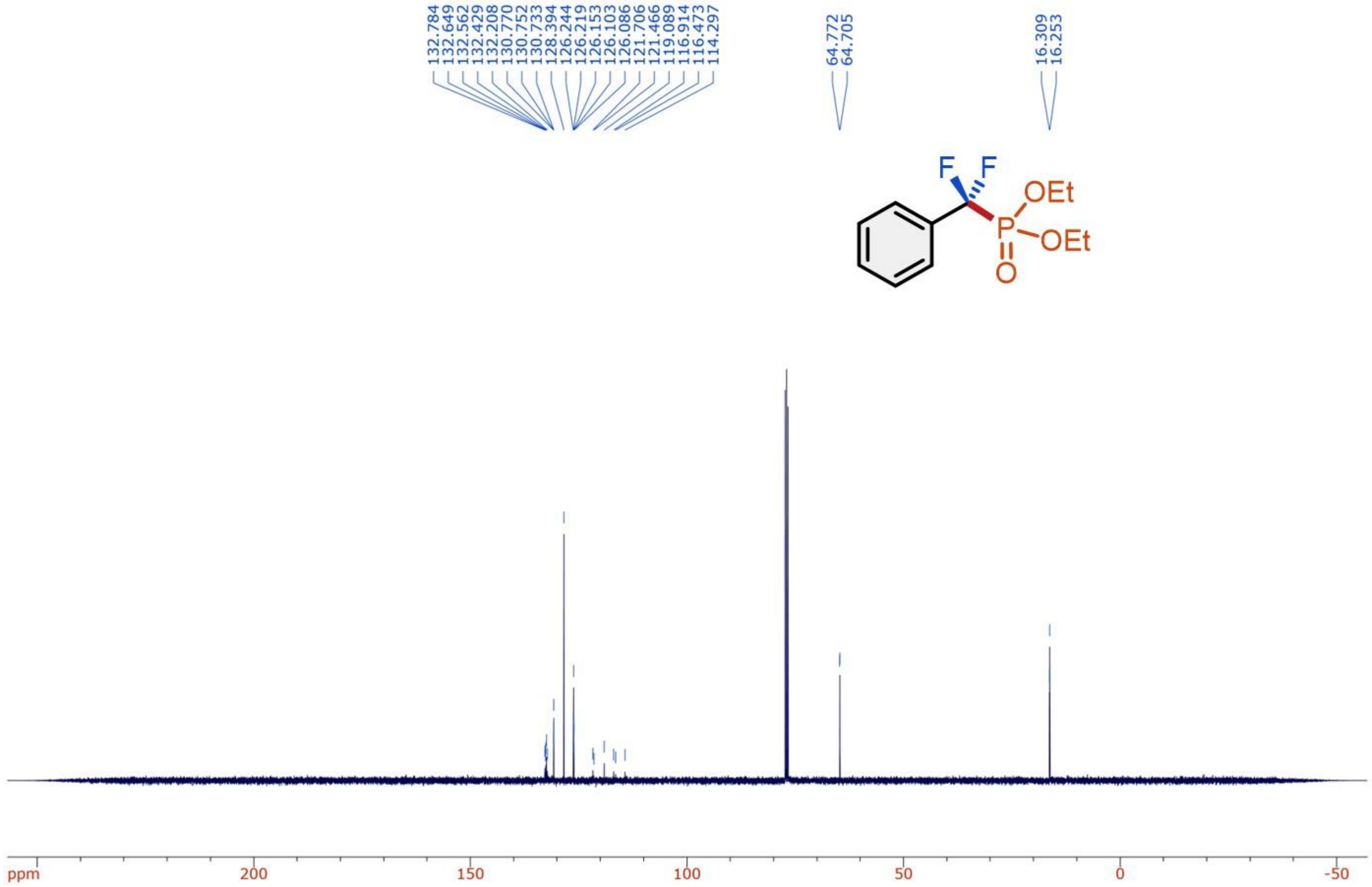
^{19}F NMR spectrum of 3h



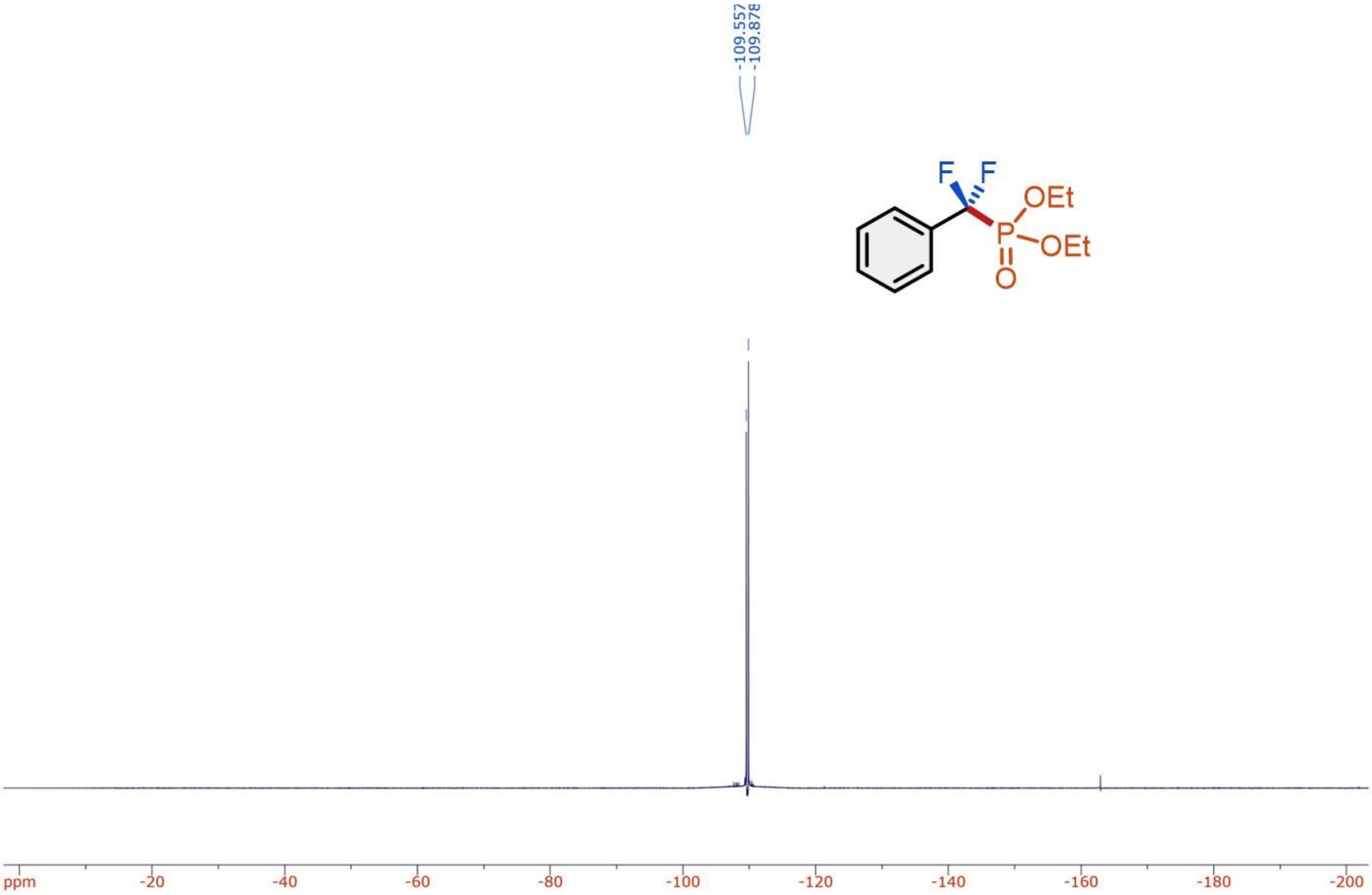
^{1}H NMR spectrum of 3o



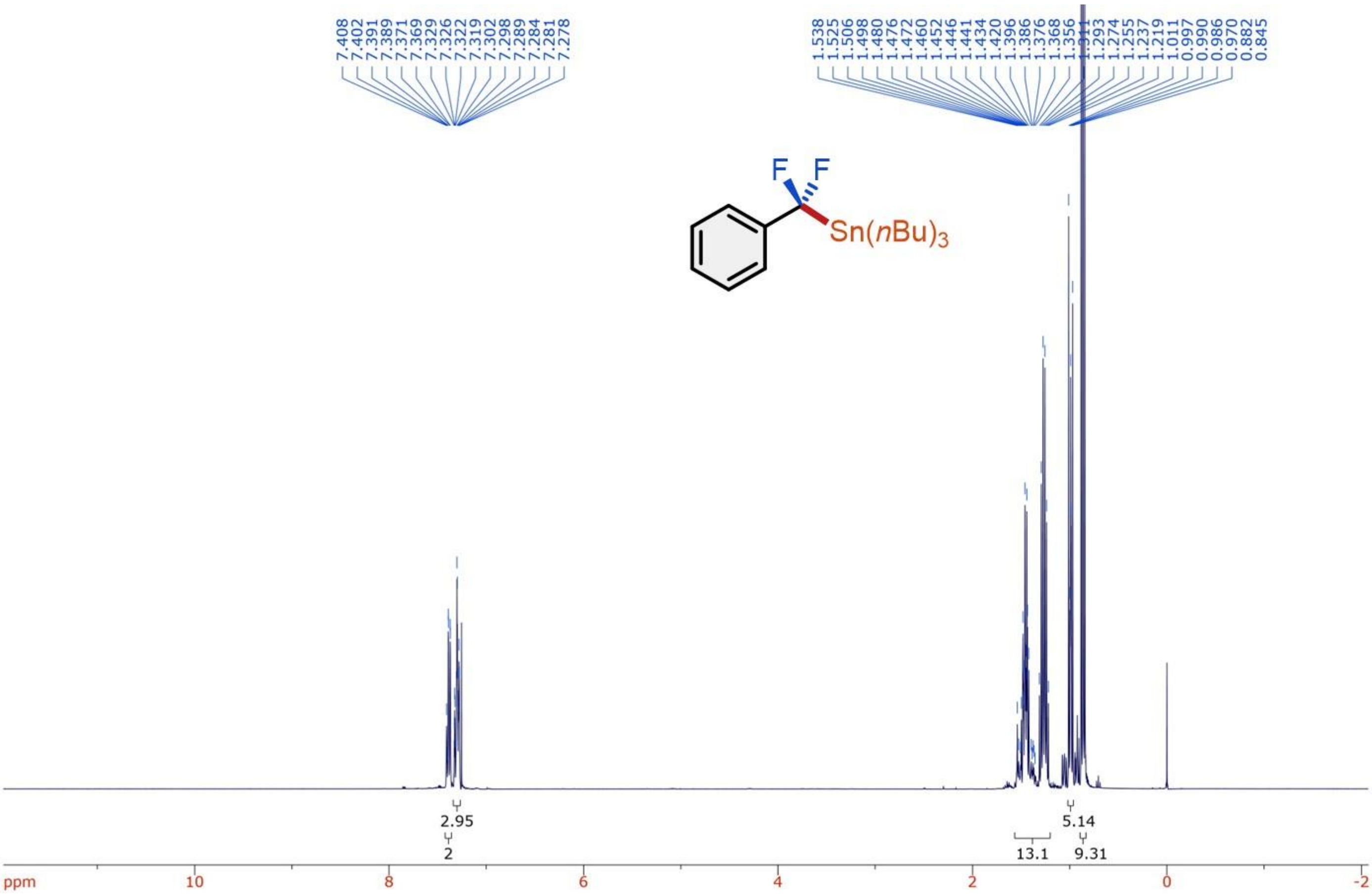
^{13}C NMR spectrum of 3o



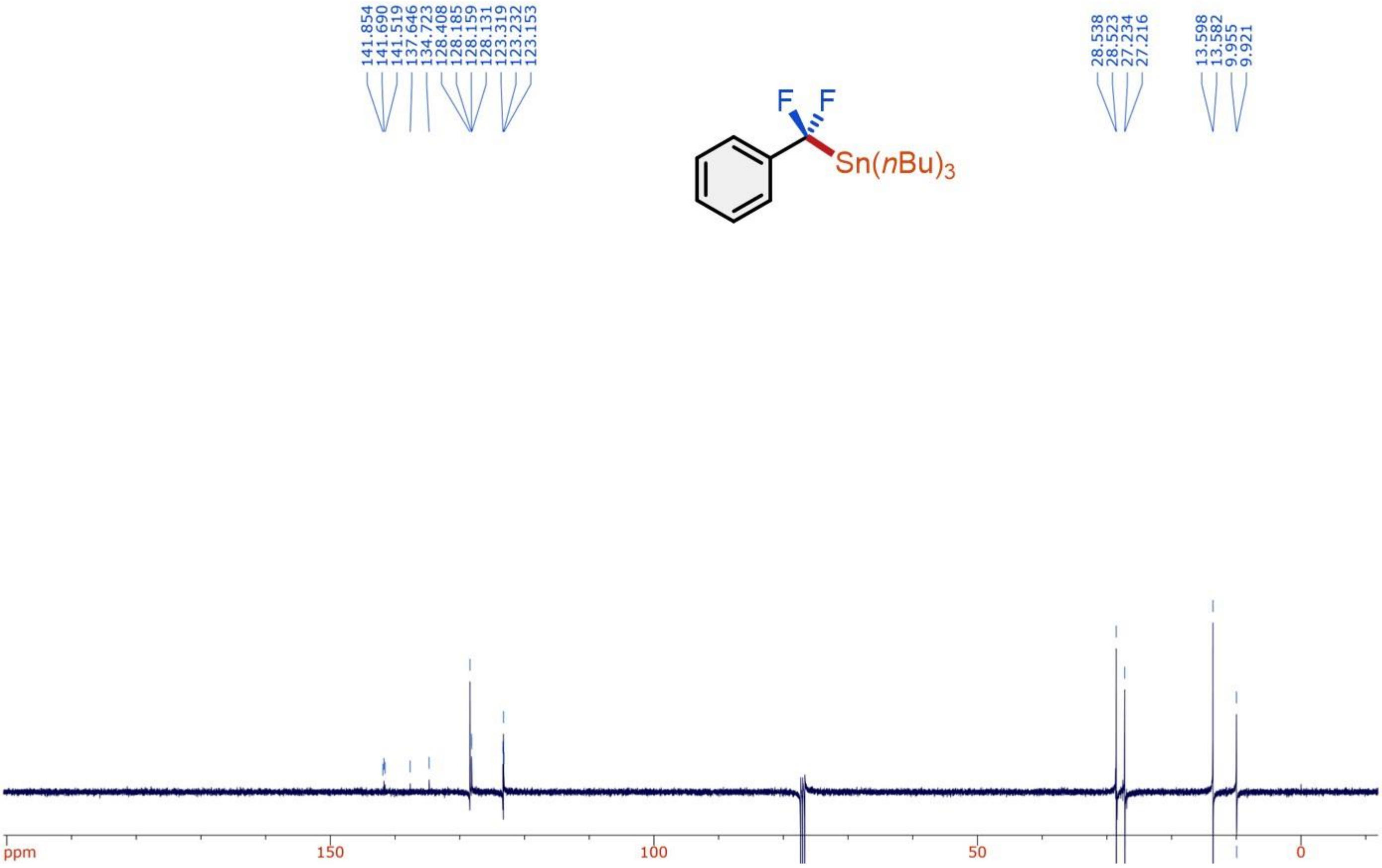
^{19}F NMR spectrum of 3o



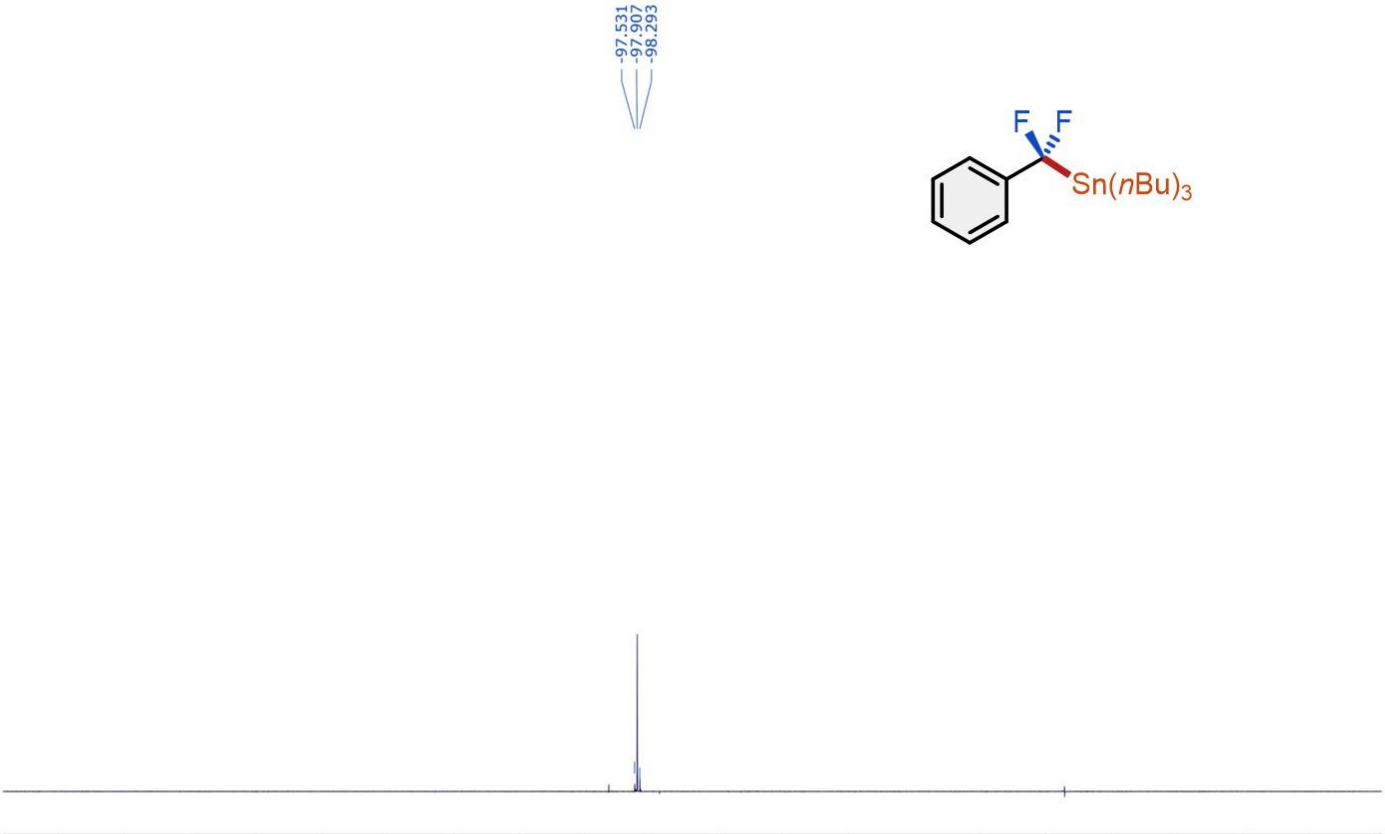
^{1}H NMR spectrum of 3q



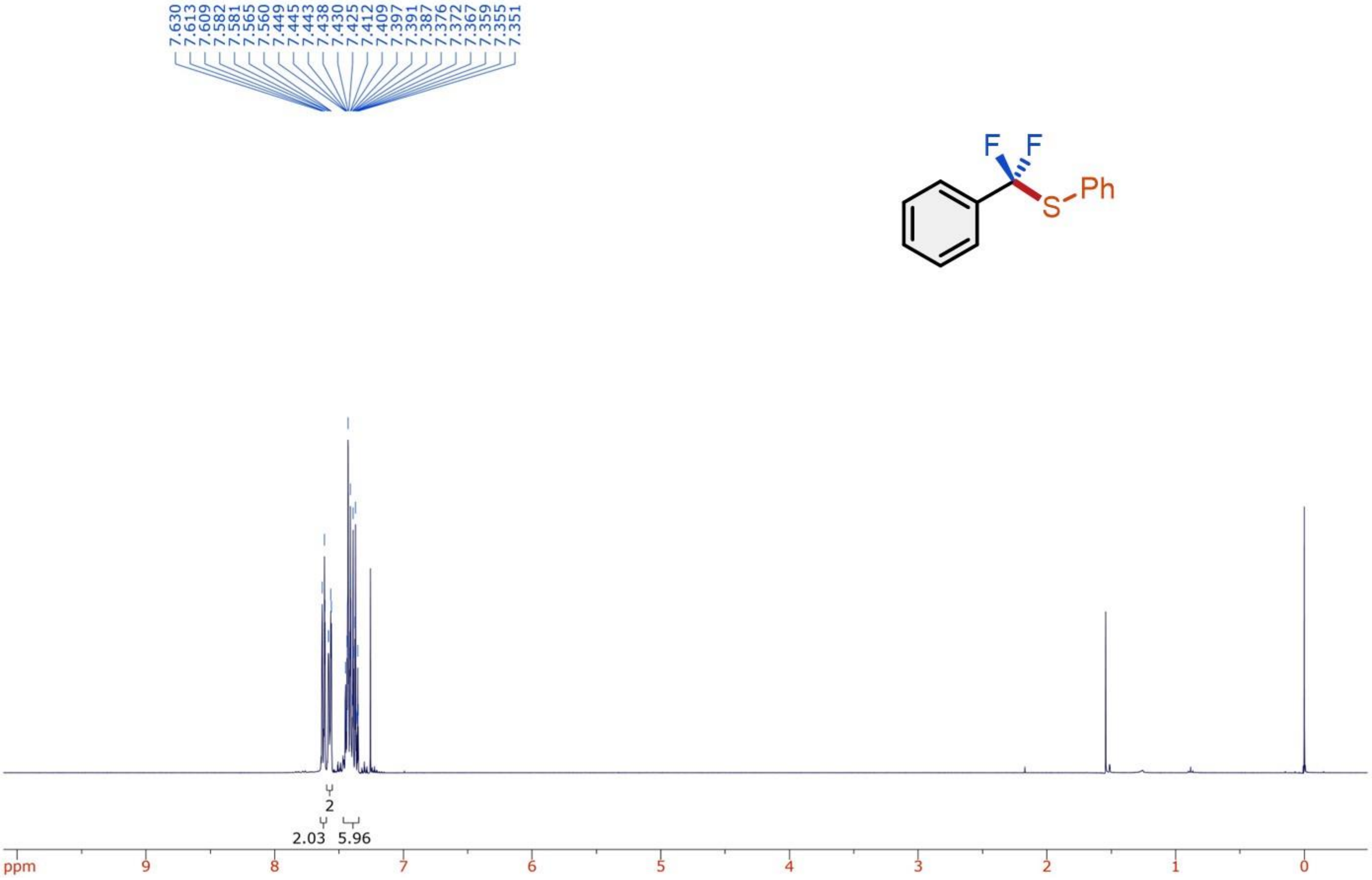
^{13}C NMR spectrum of 3q



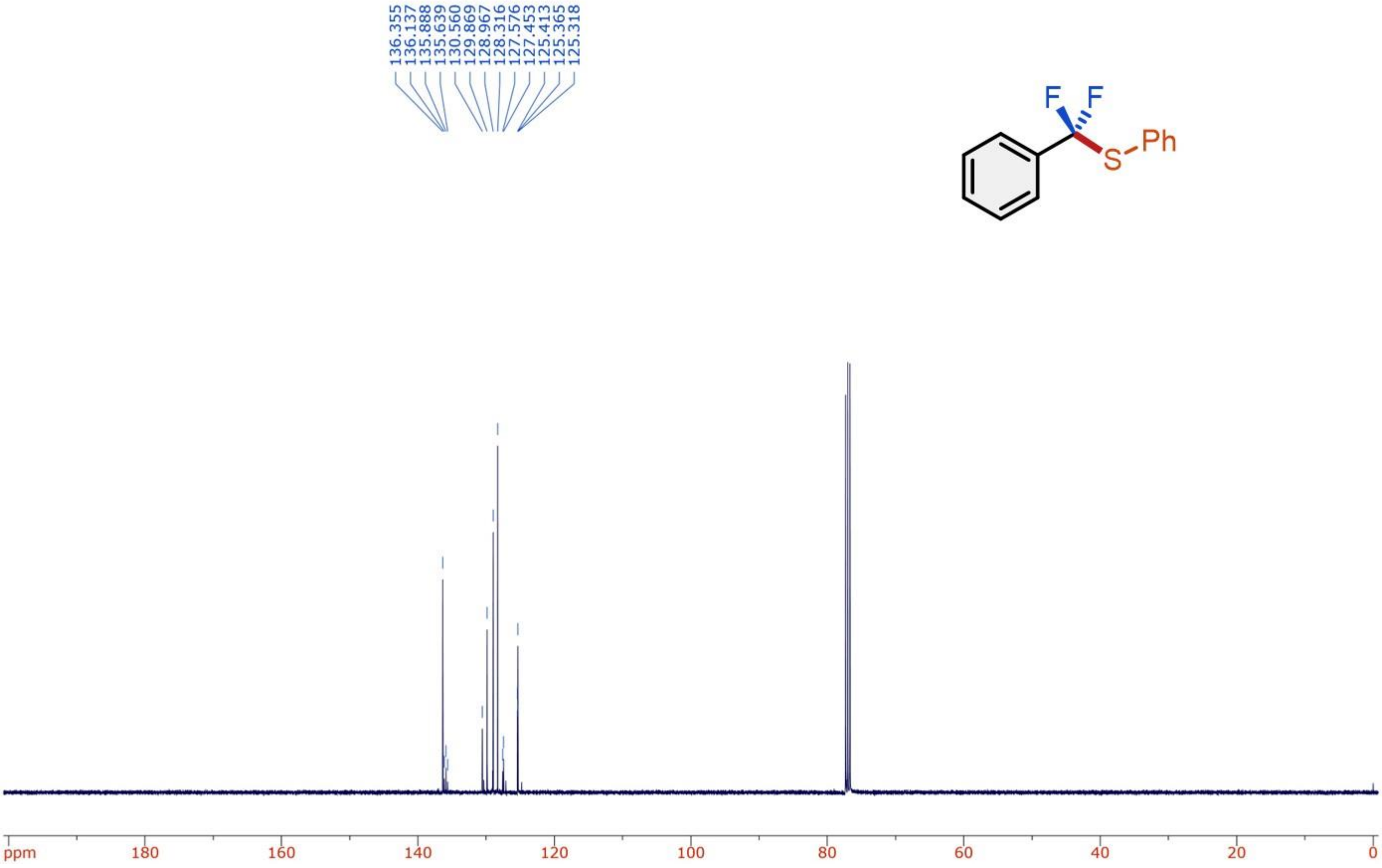
^{19}F NMR spectrum of 3q



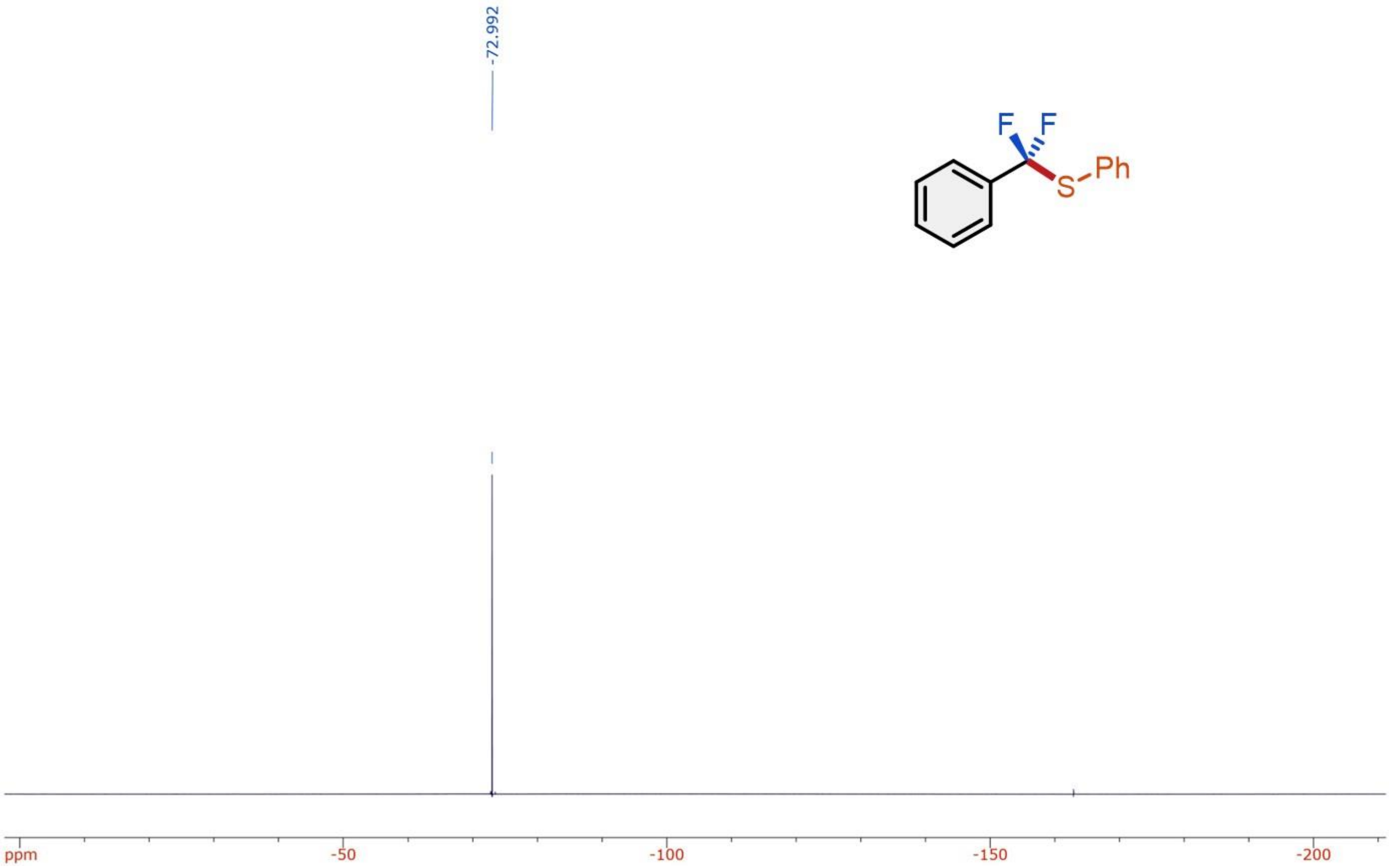
^{1}H NMR spectrum of 3r



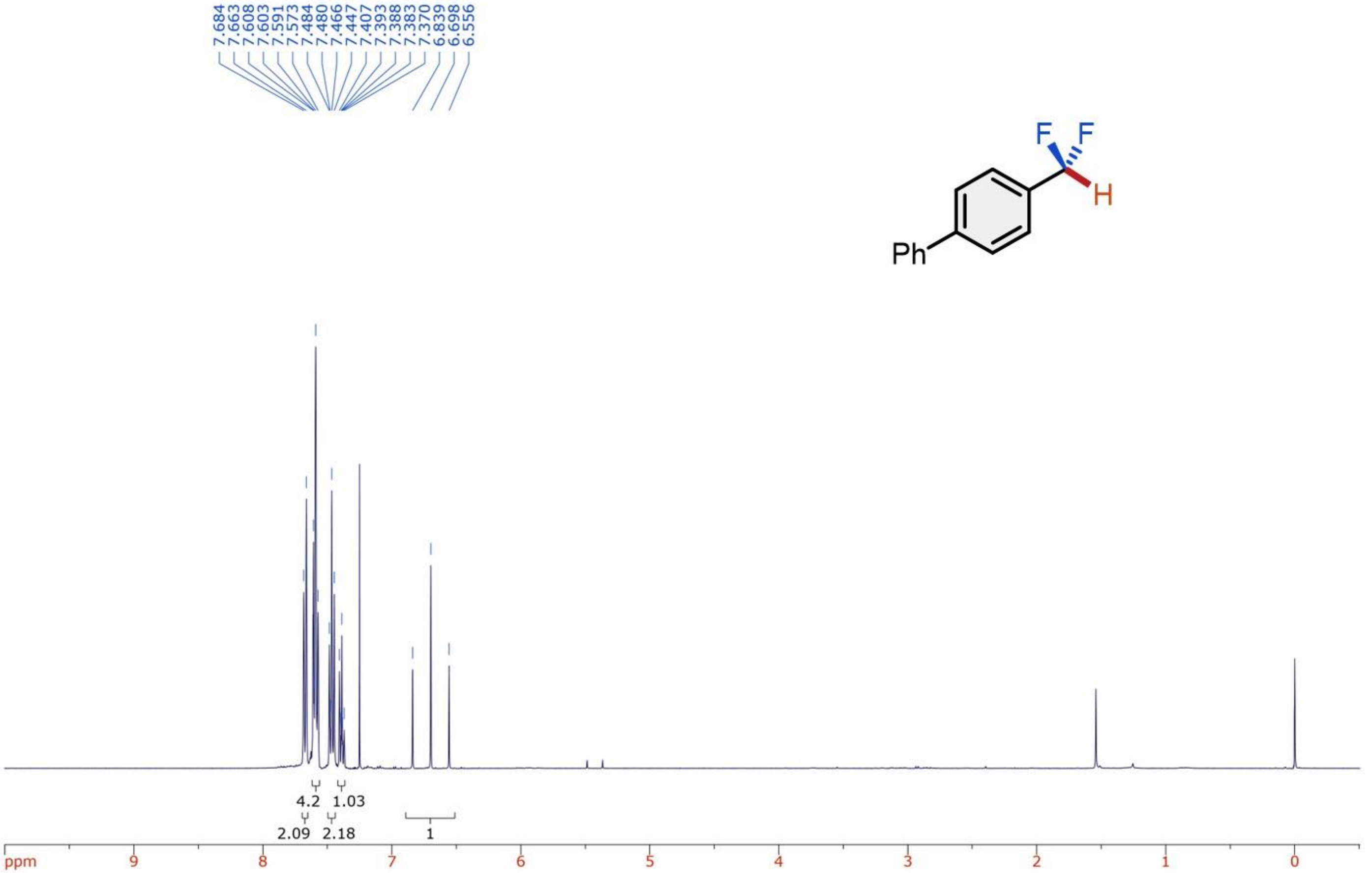
^{13}C NMR spectrum of 3r



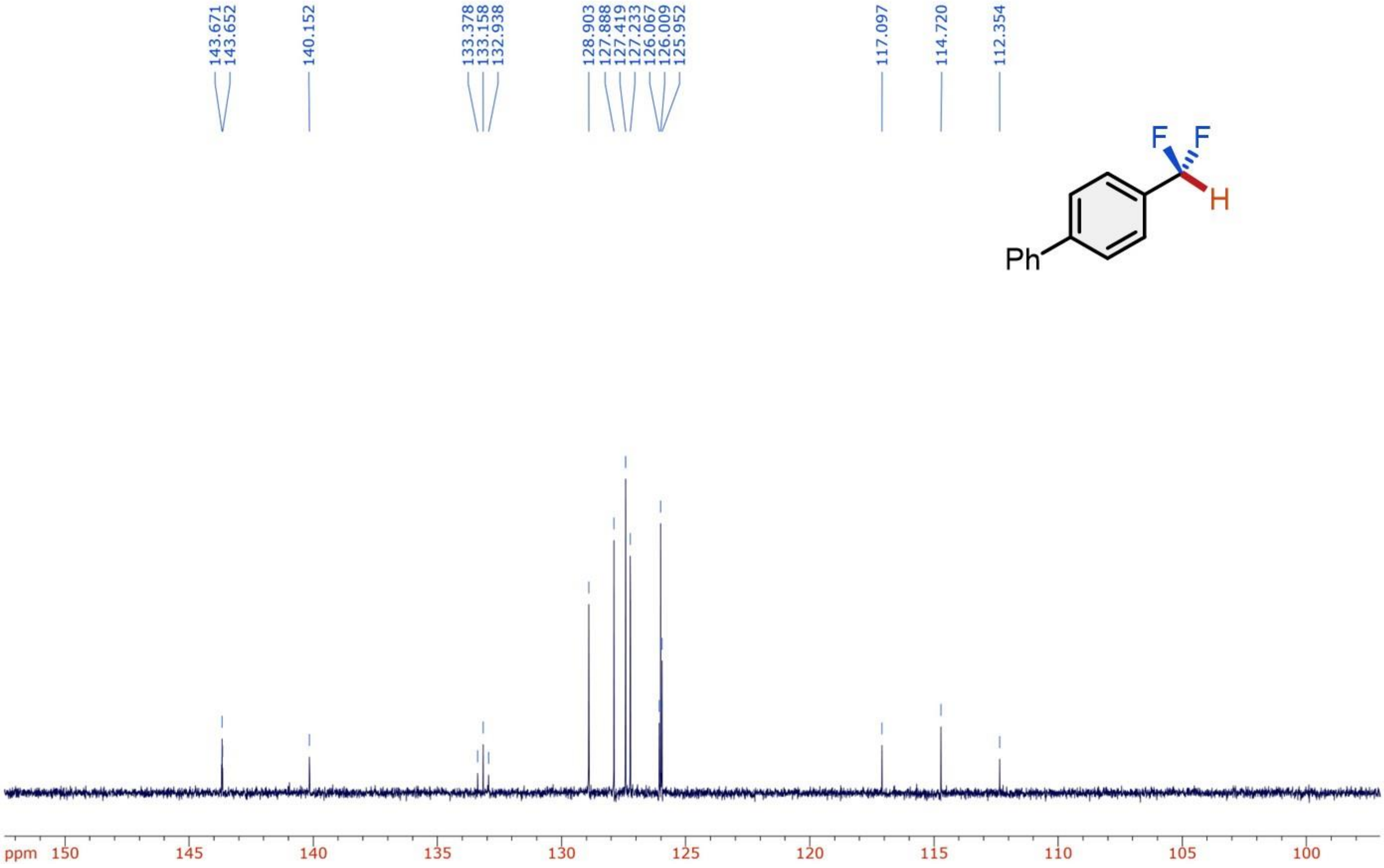
^{19}F NMR spectrum of 3r



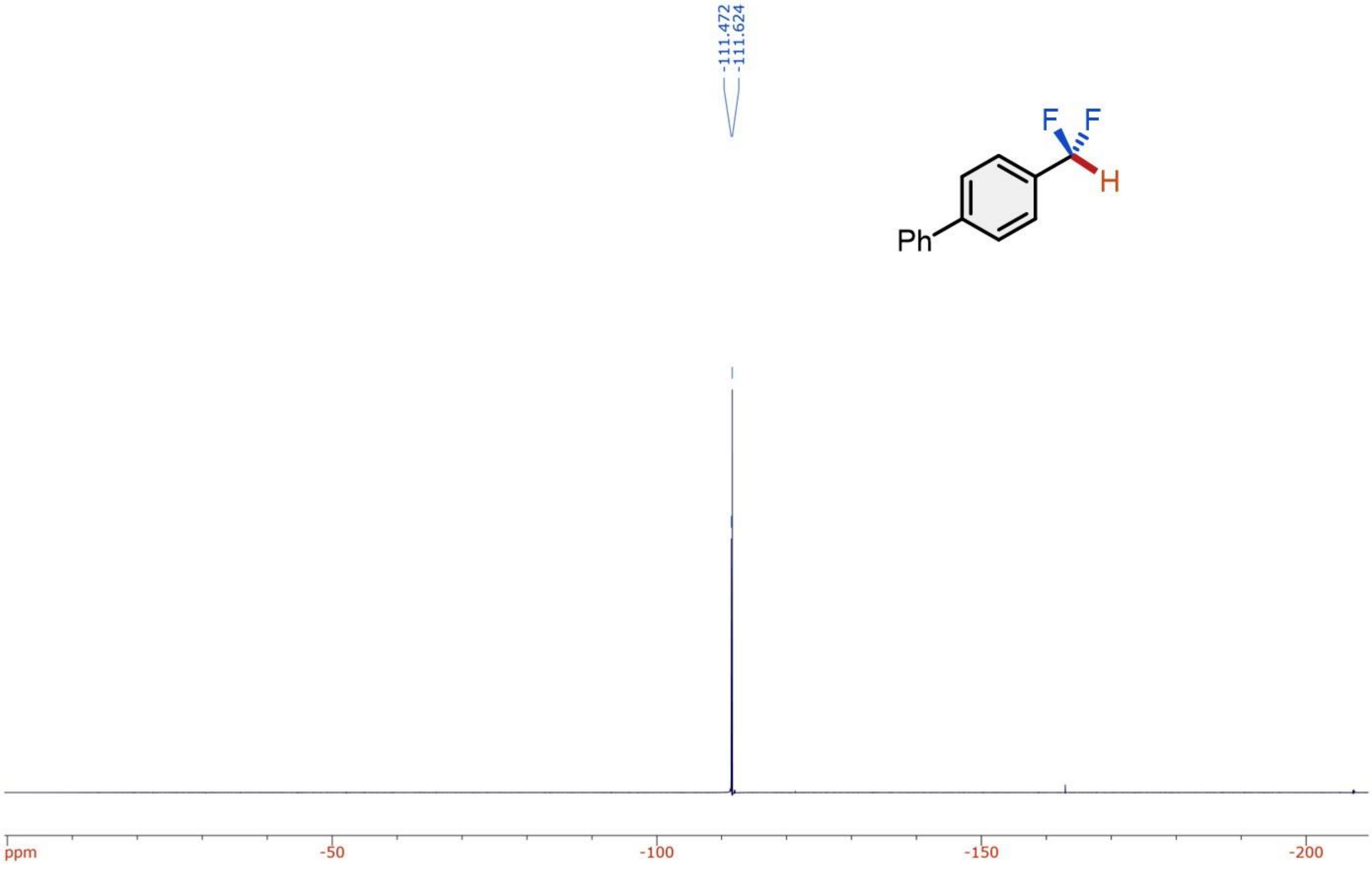
^{1}H NMR spectrum of 4d



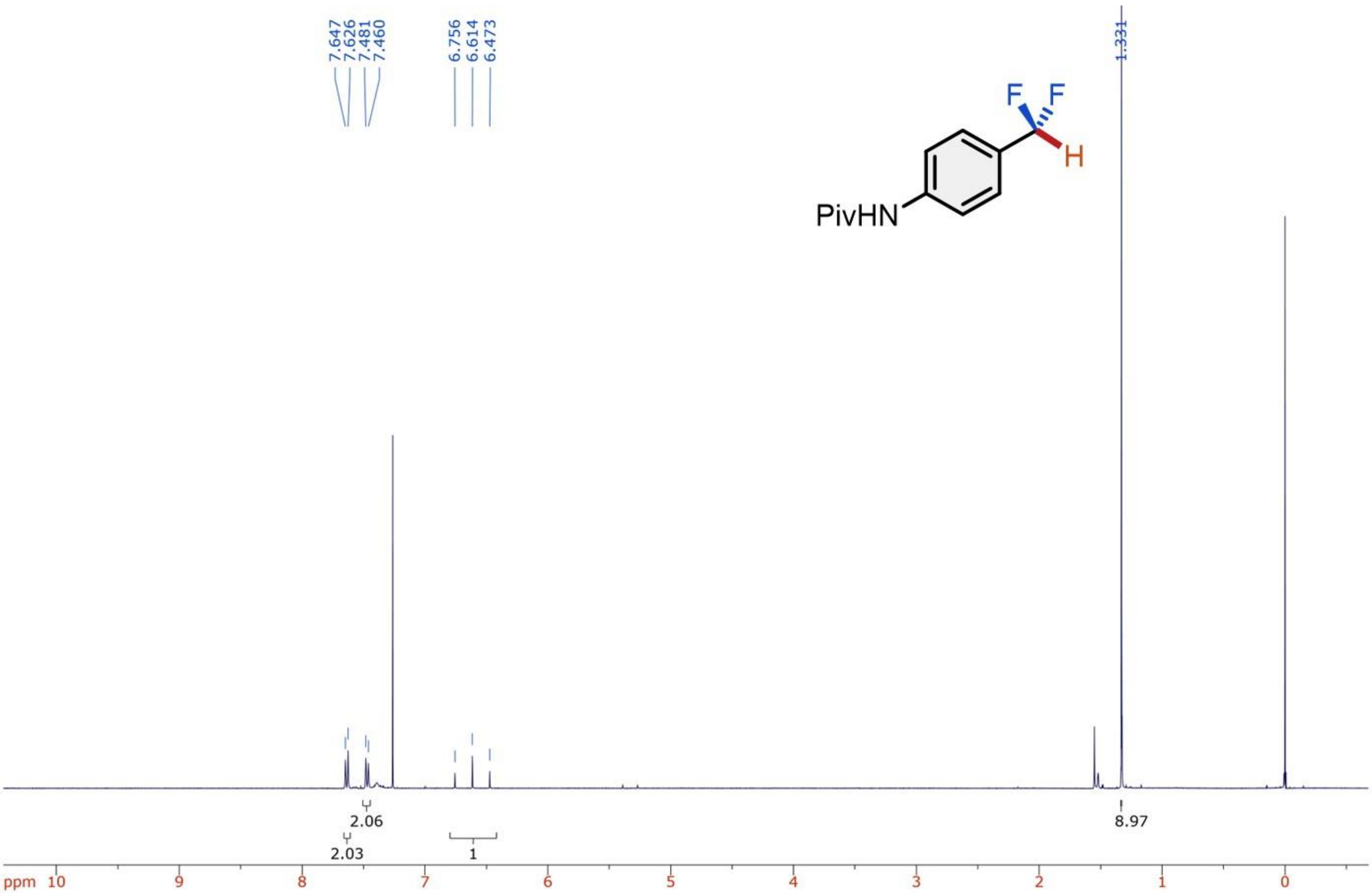
^{13}C NMR spectrum of 4d



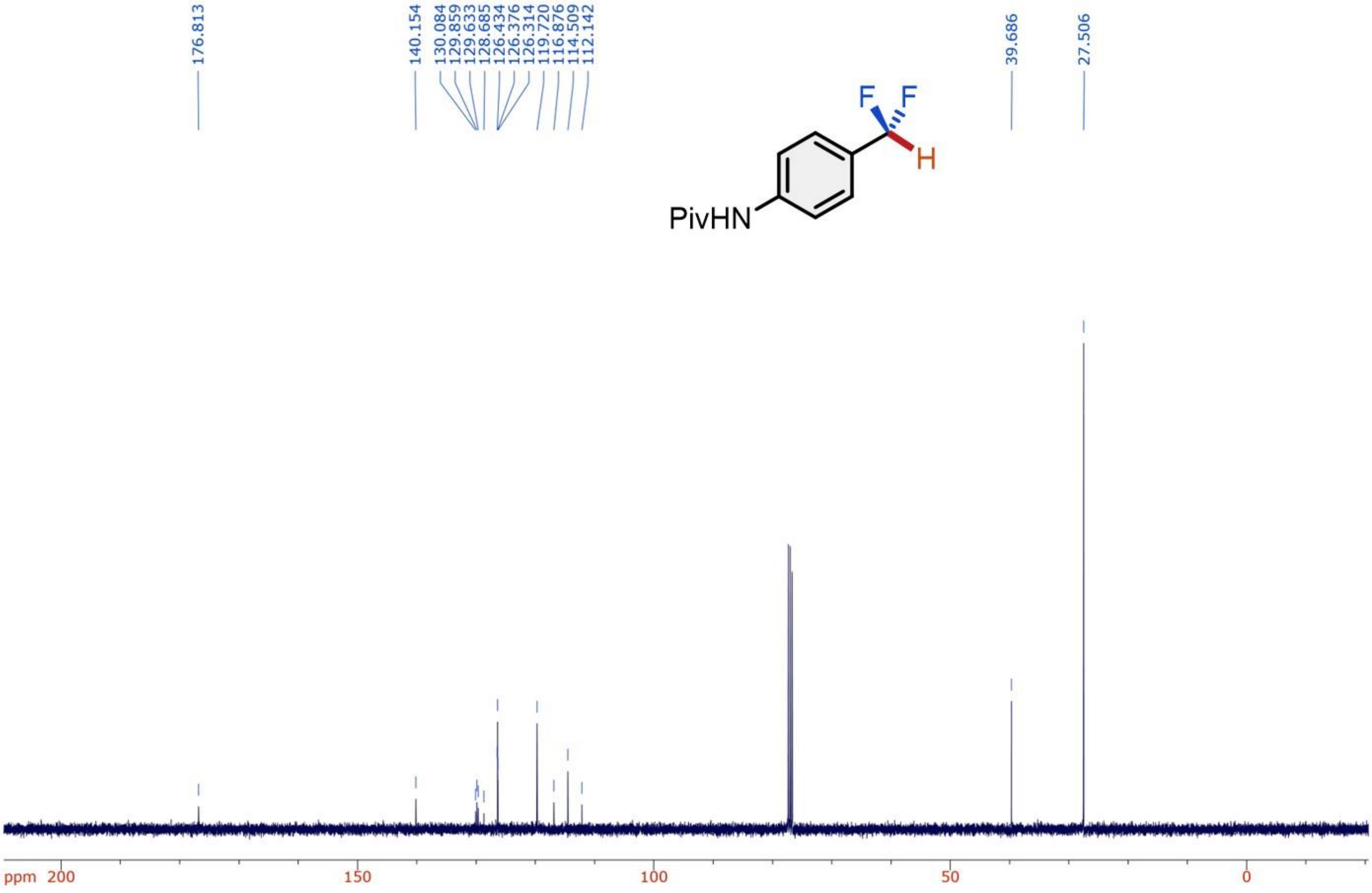
^{19}F NMR spectrum of 4d



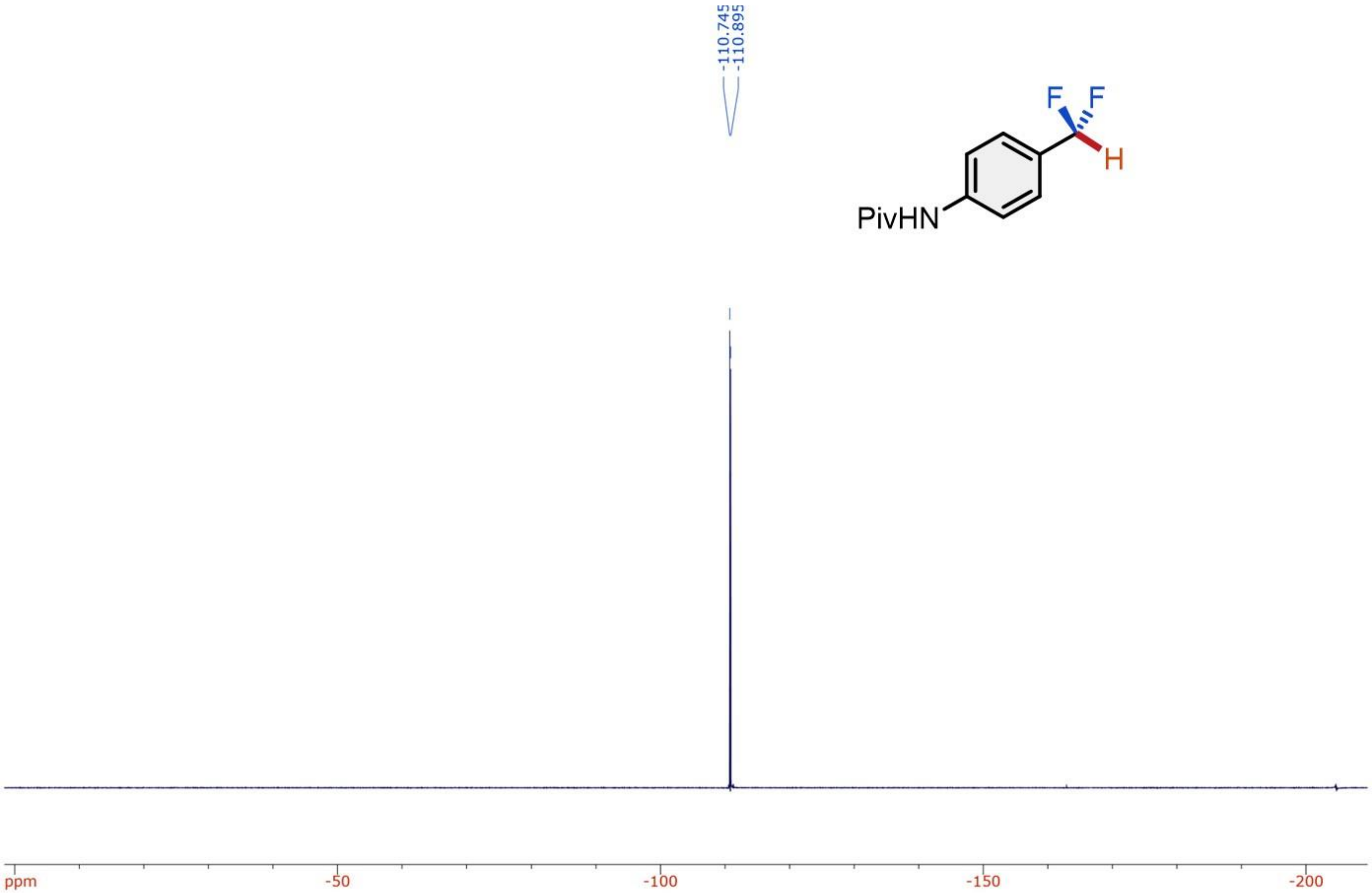
^{1}H NMR spectrum of 4e



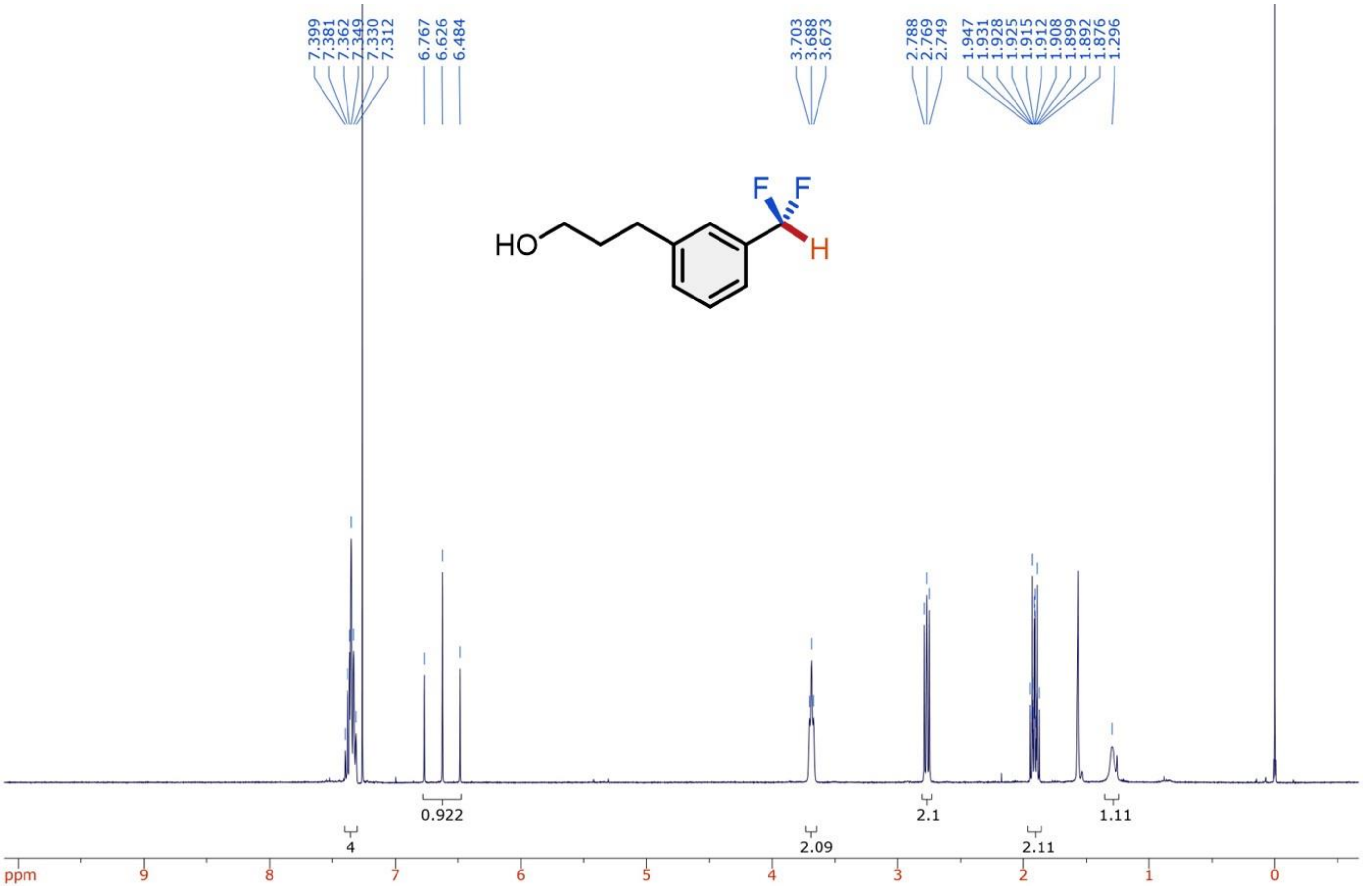
^{13}C NMR spectrum of 4e



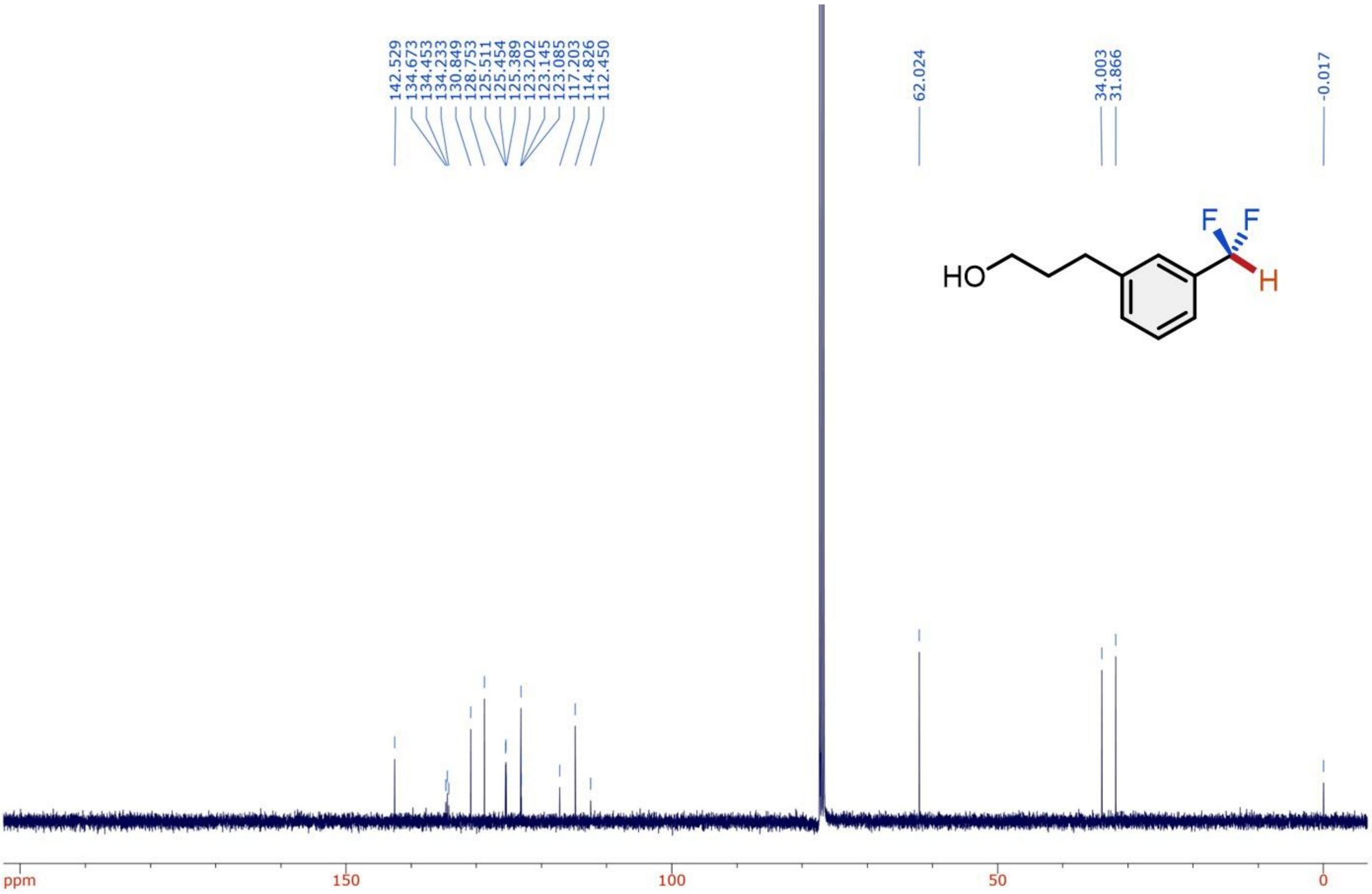
^{19}F NMR spectrum of 4e



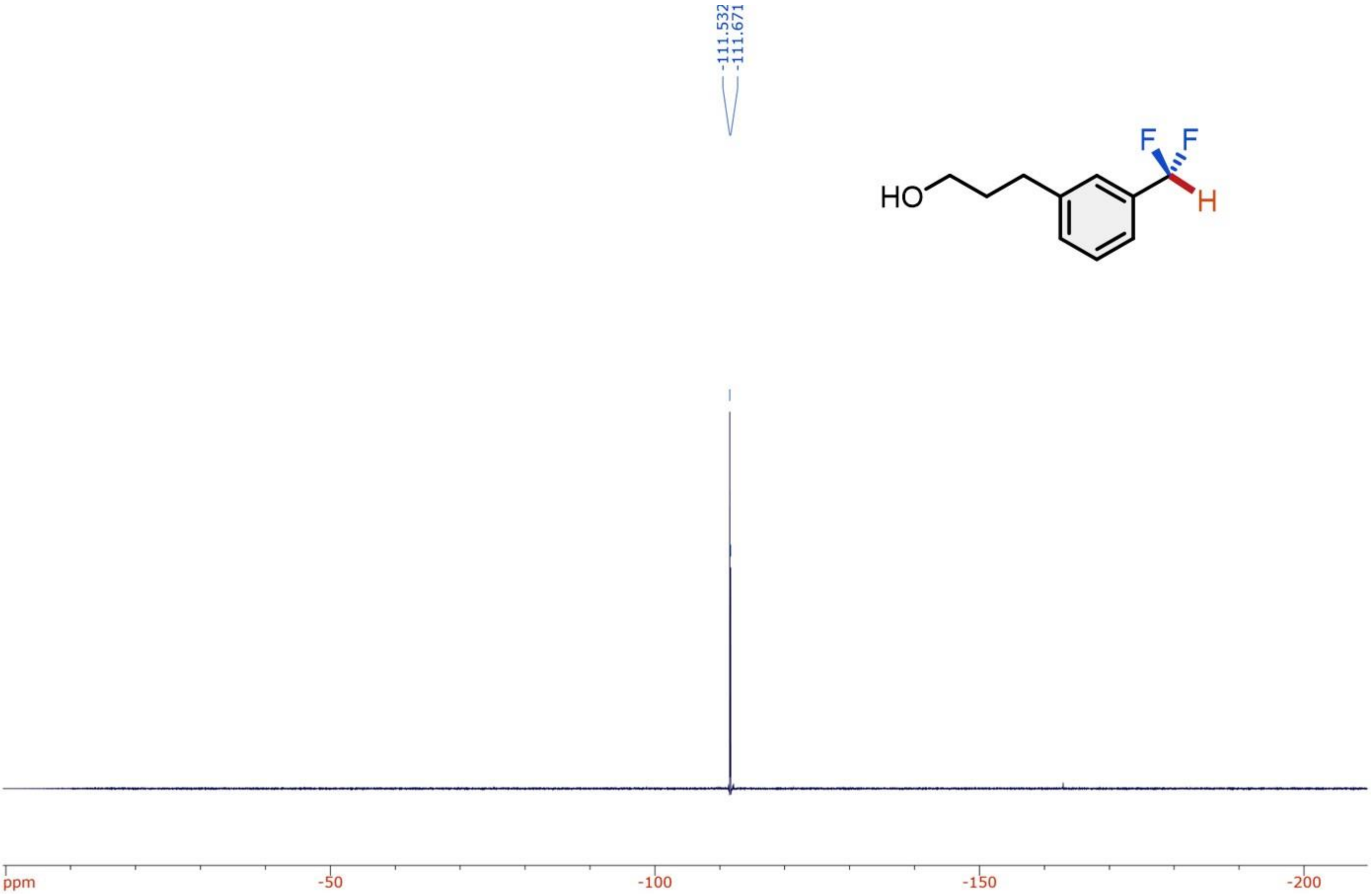
^{1}H NMR spectrum of 4m



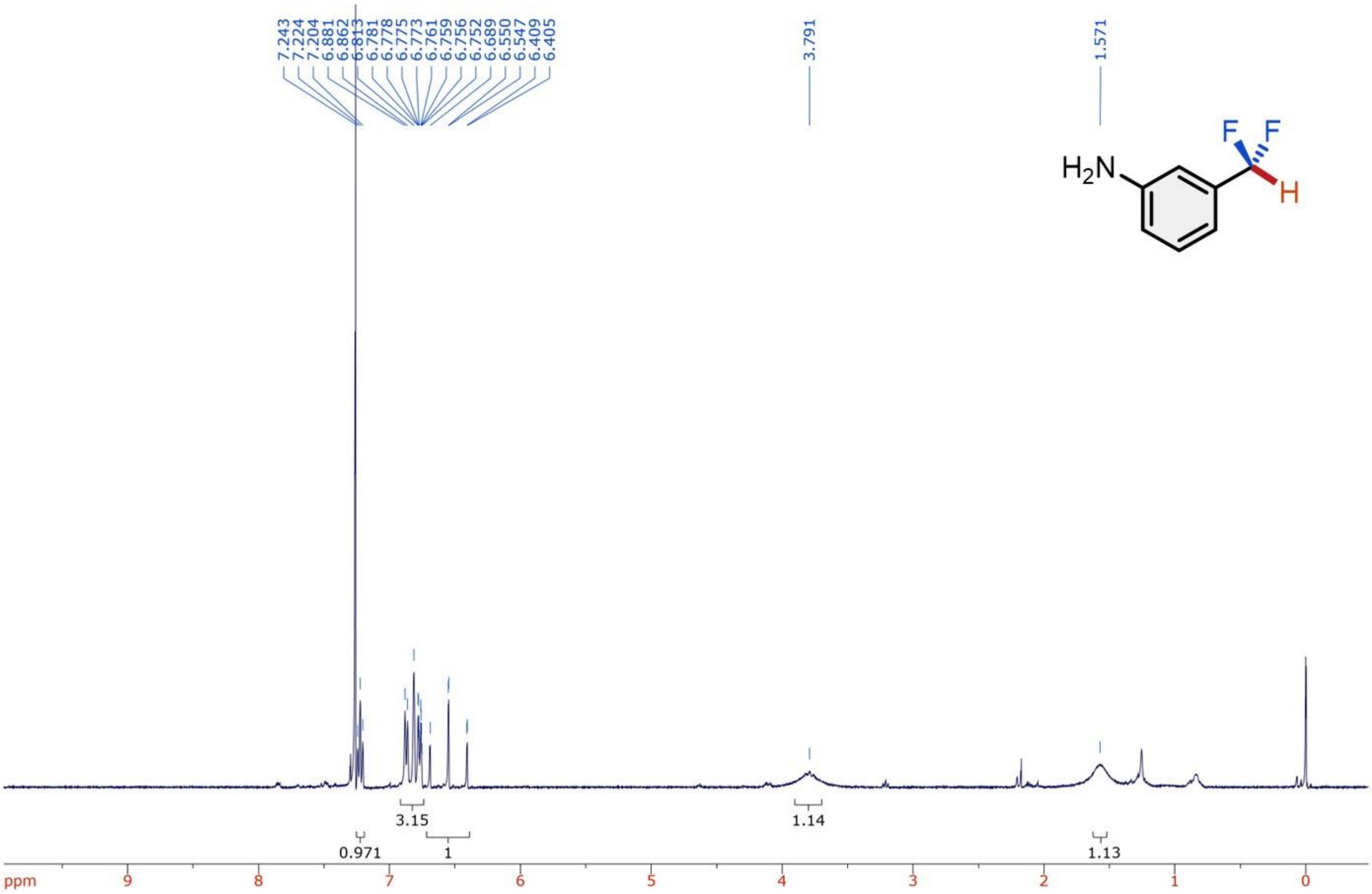
^{13}C NMR spectrum of 4m



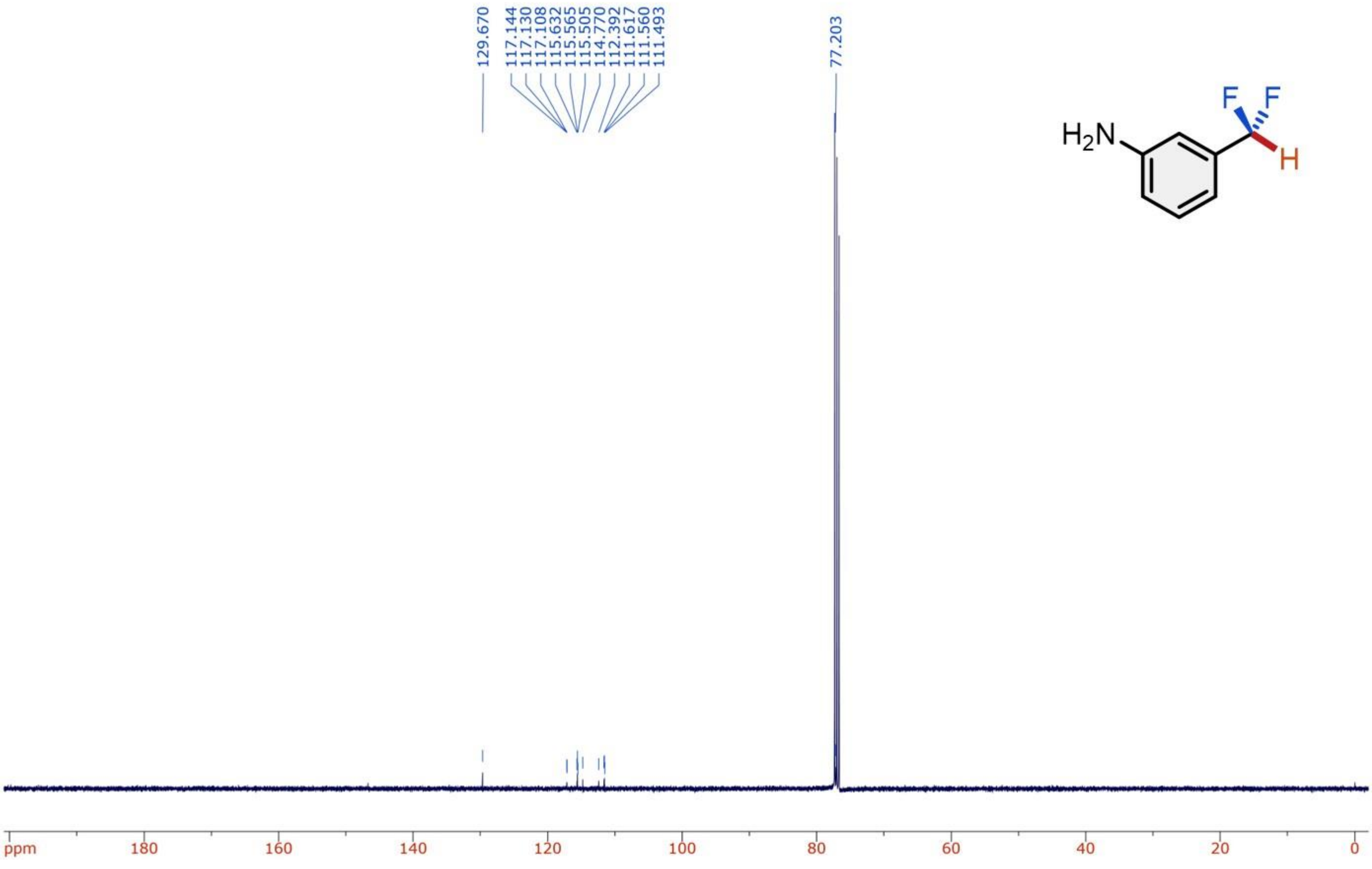
^{19}F NMR spectrum of 4m



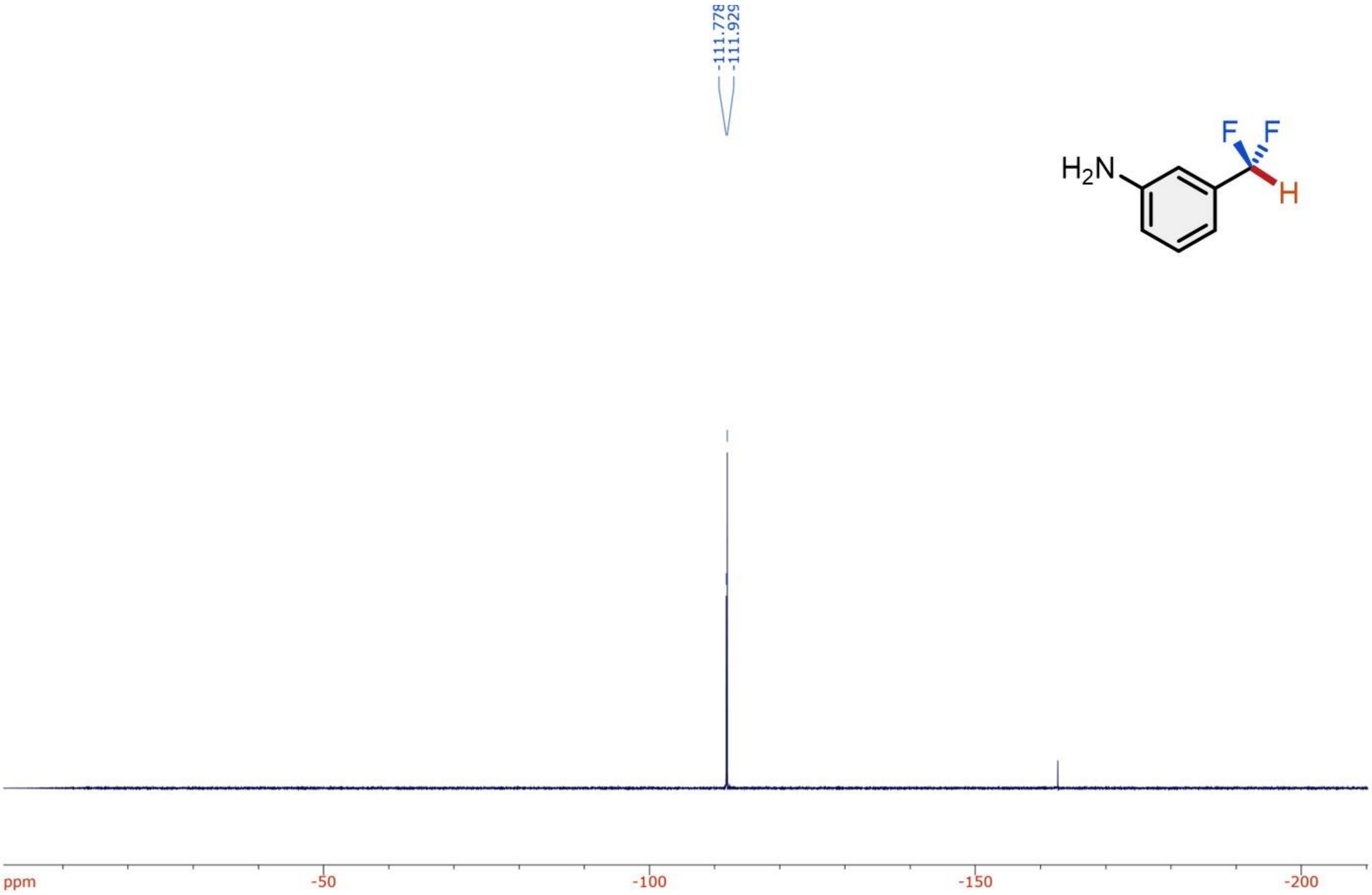
^{1}H NMR spectrum of 4n



^{13}C NMR spectrum of 4n



^{19}F NMR spectrum of 4n



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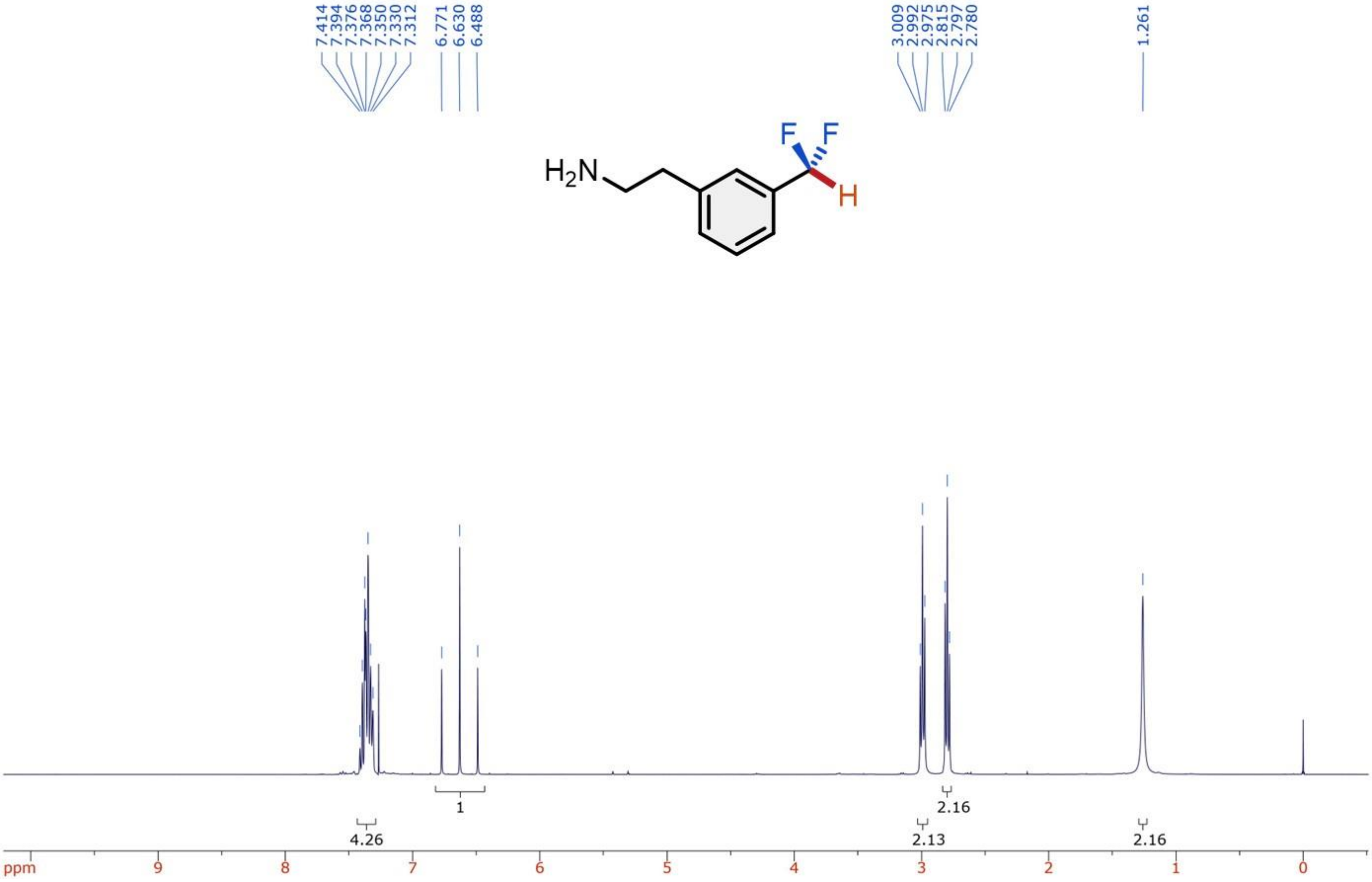
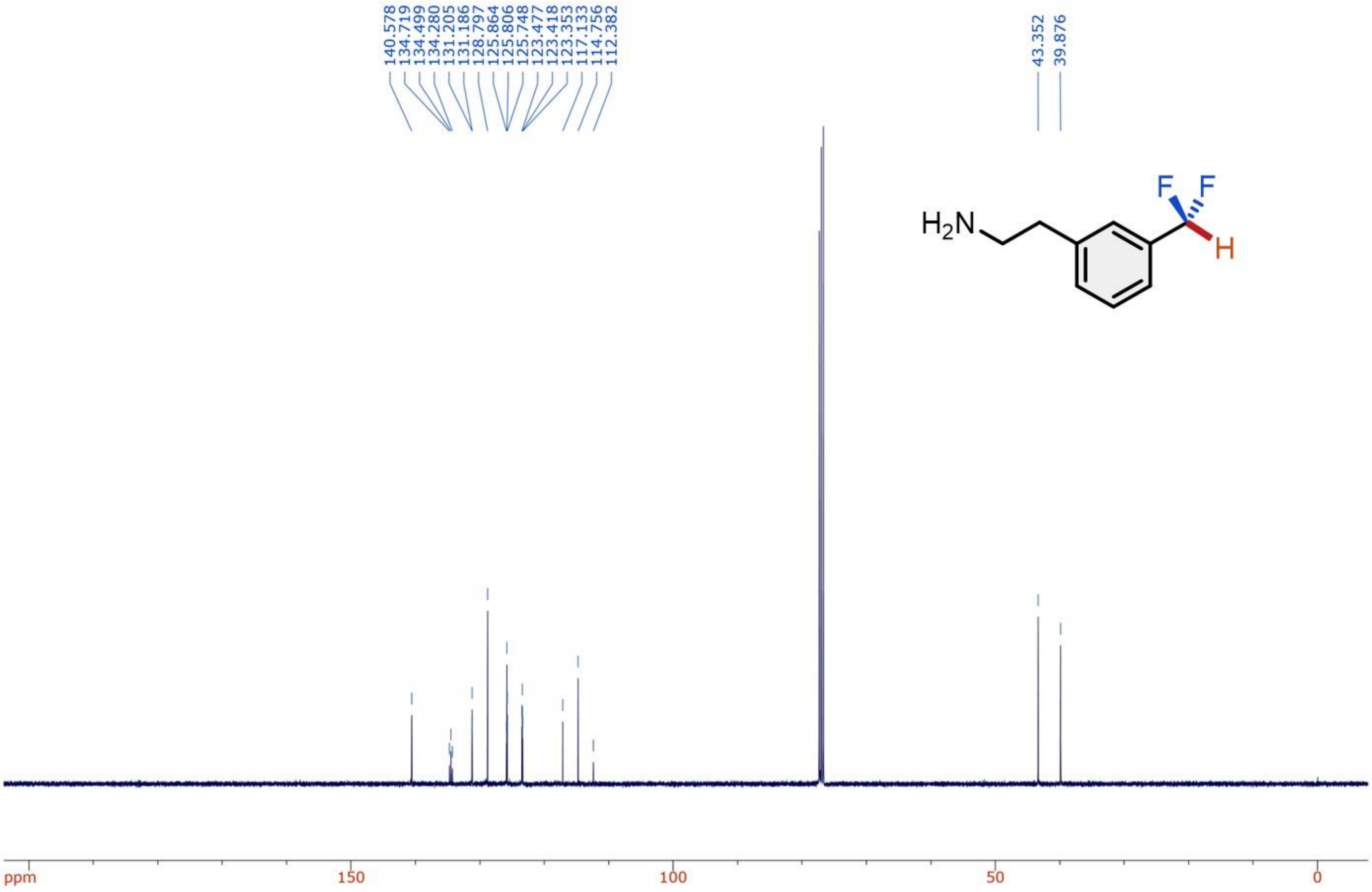


^{13}C NMR spectrum of 4p



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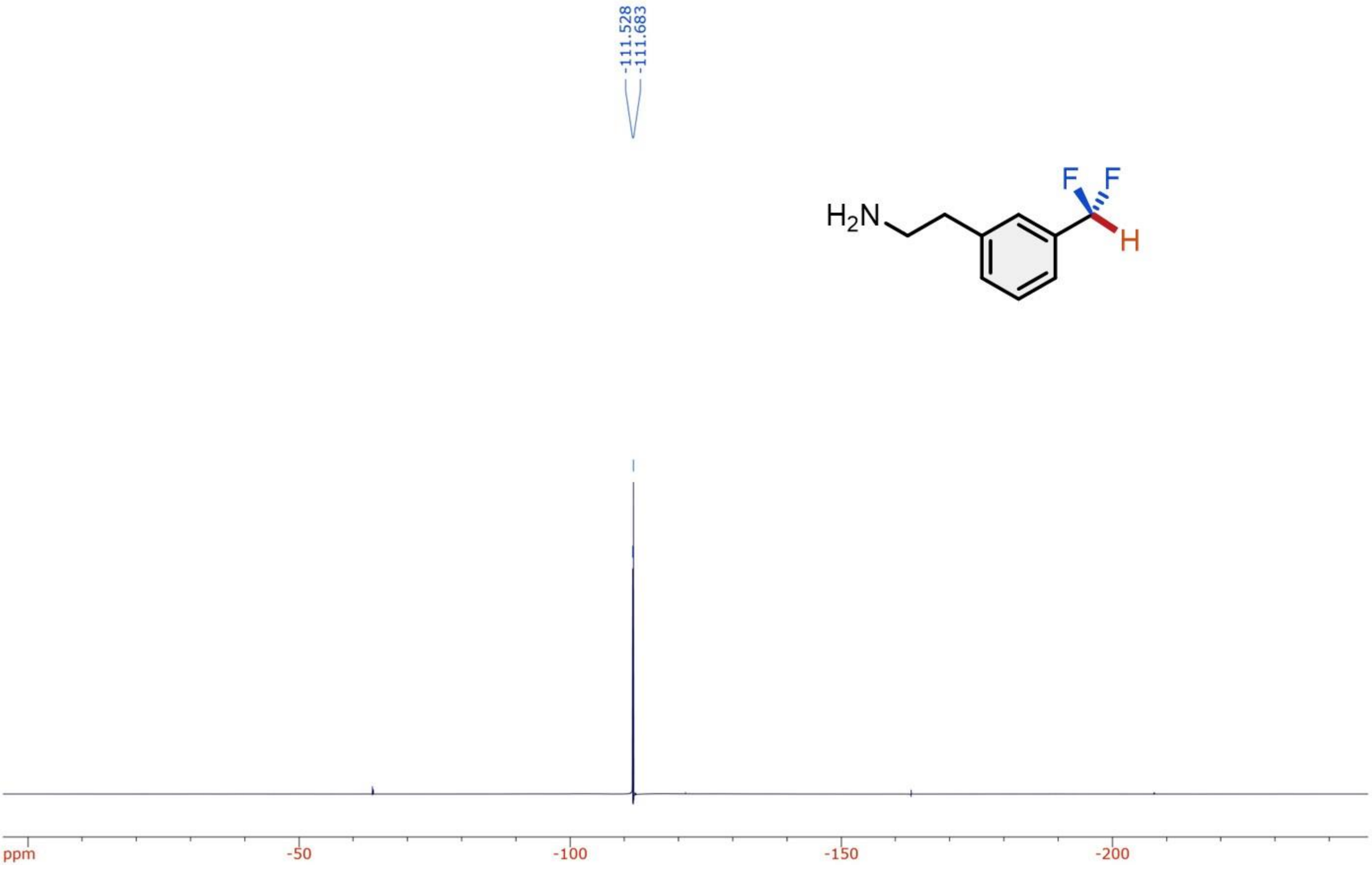
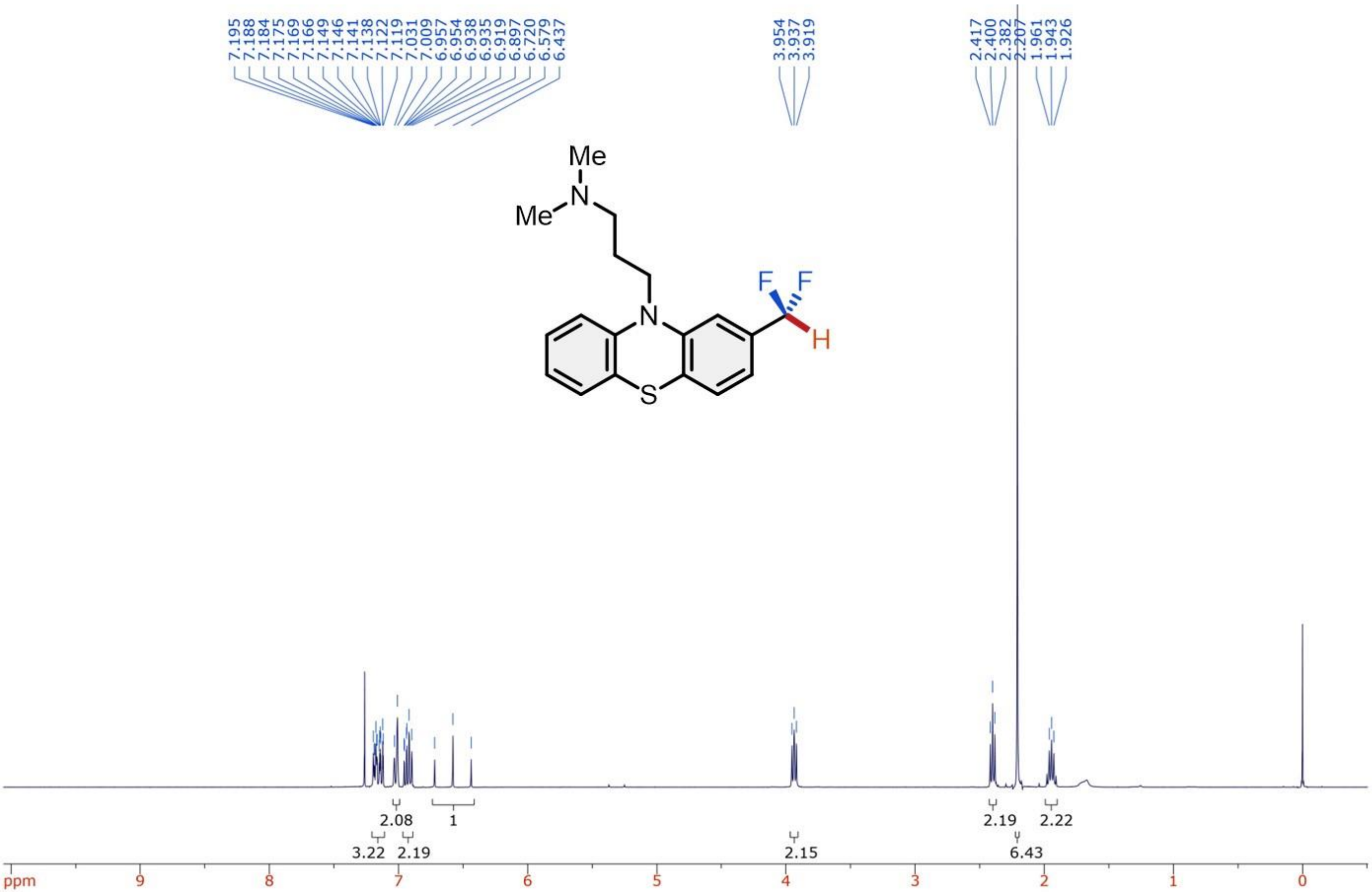
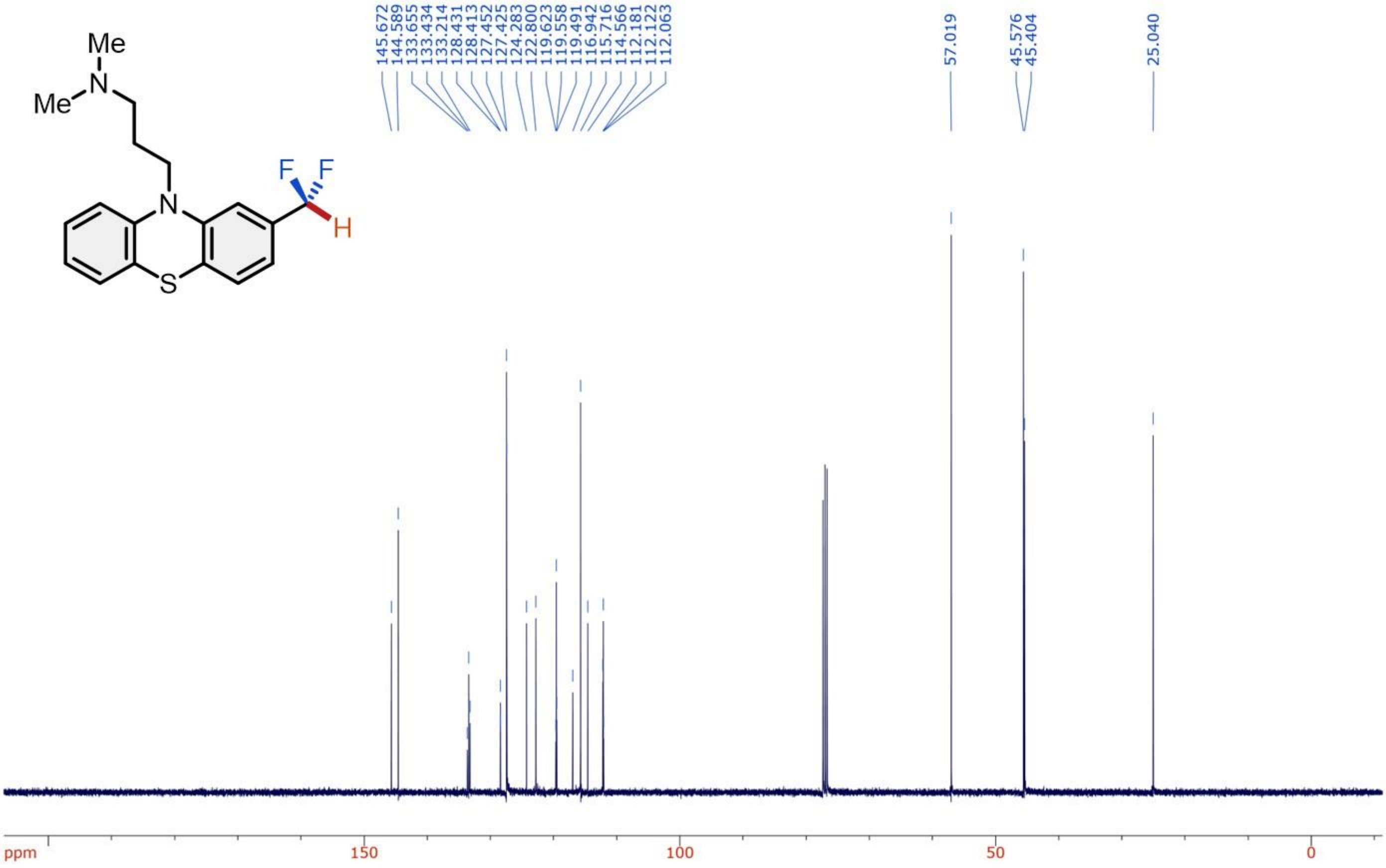


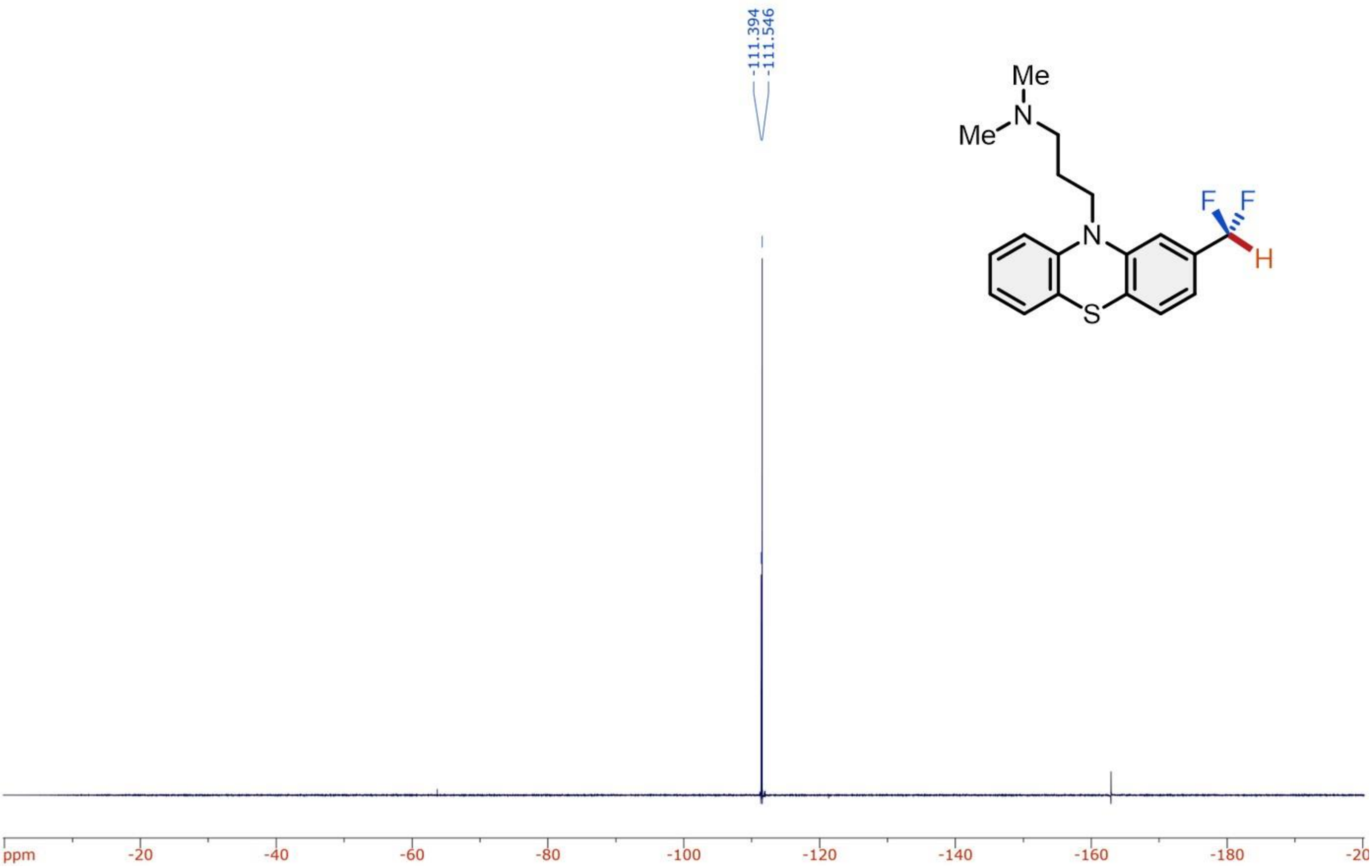
^{1}H NMR spectrum of 5a



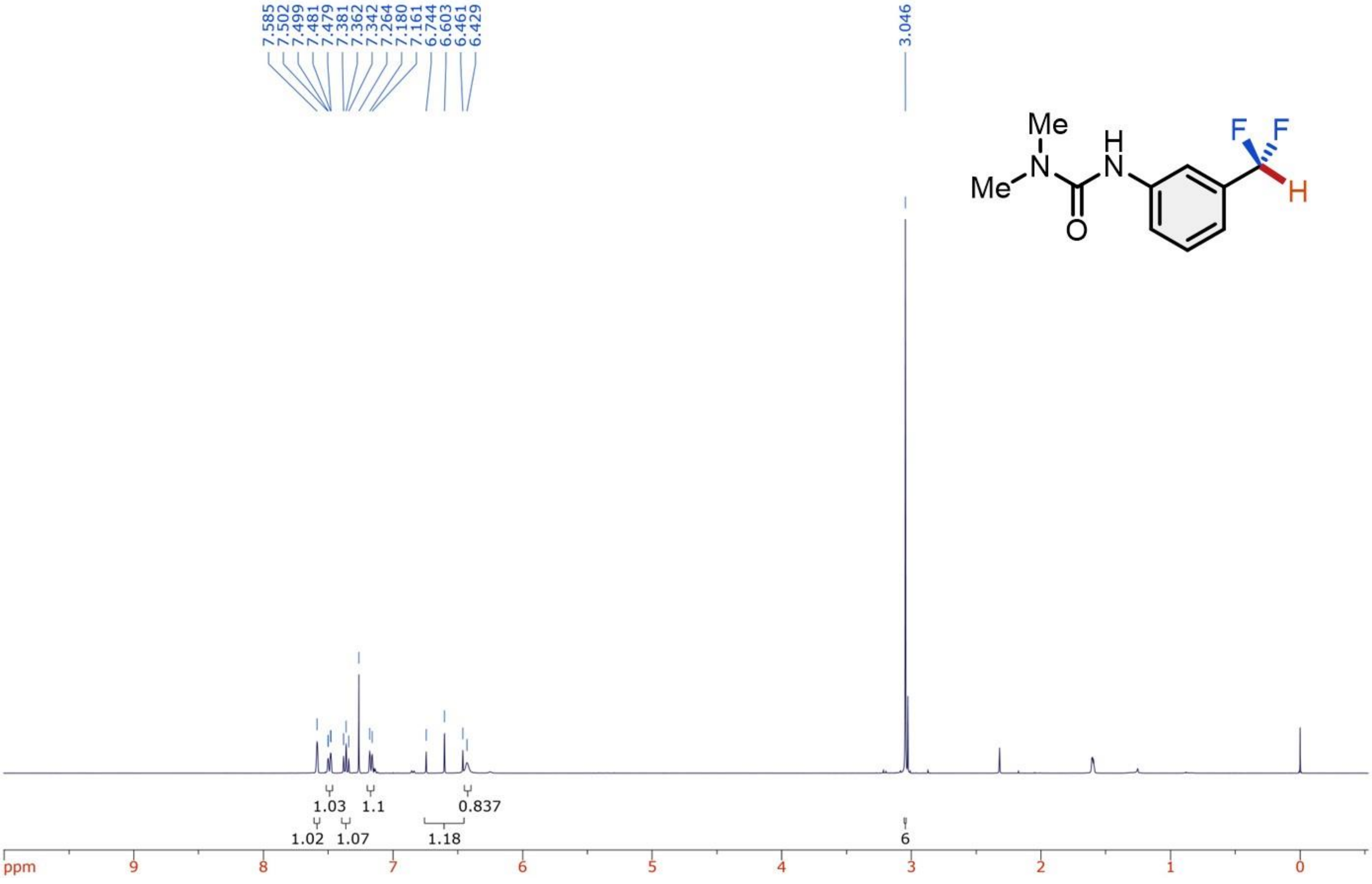
^{13}C NMR spectrum of 5a



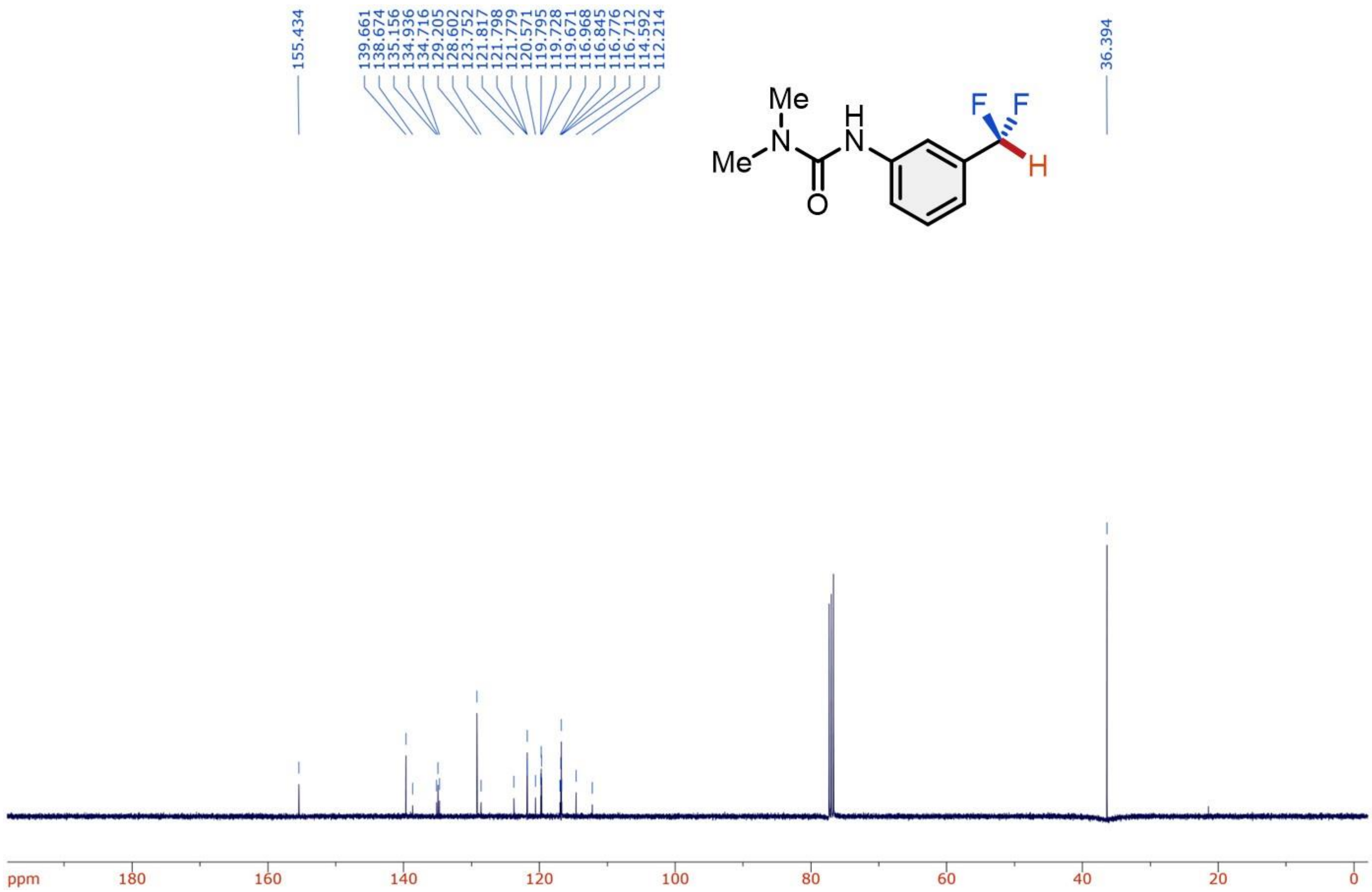
^{19}F NMR spectrum of 5a



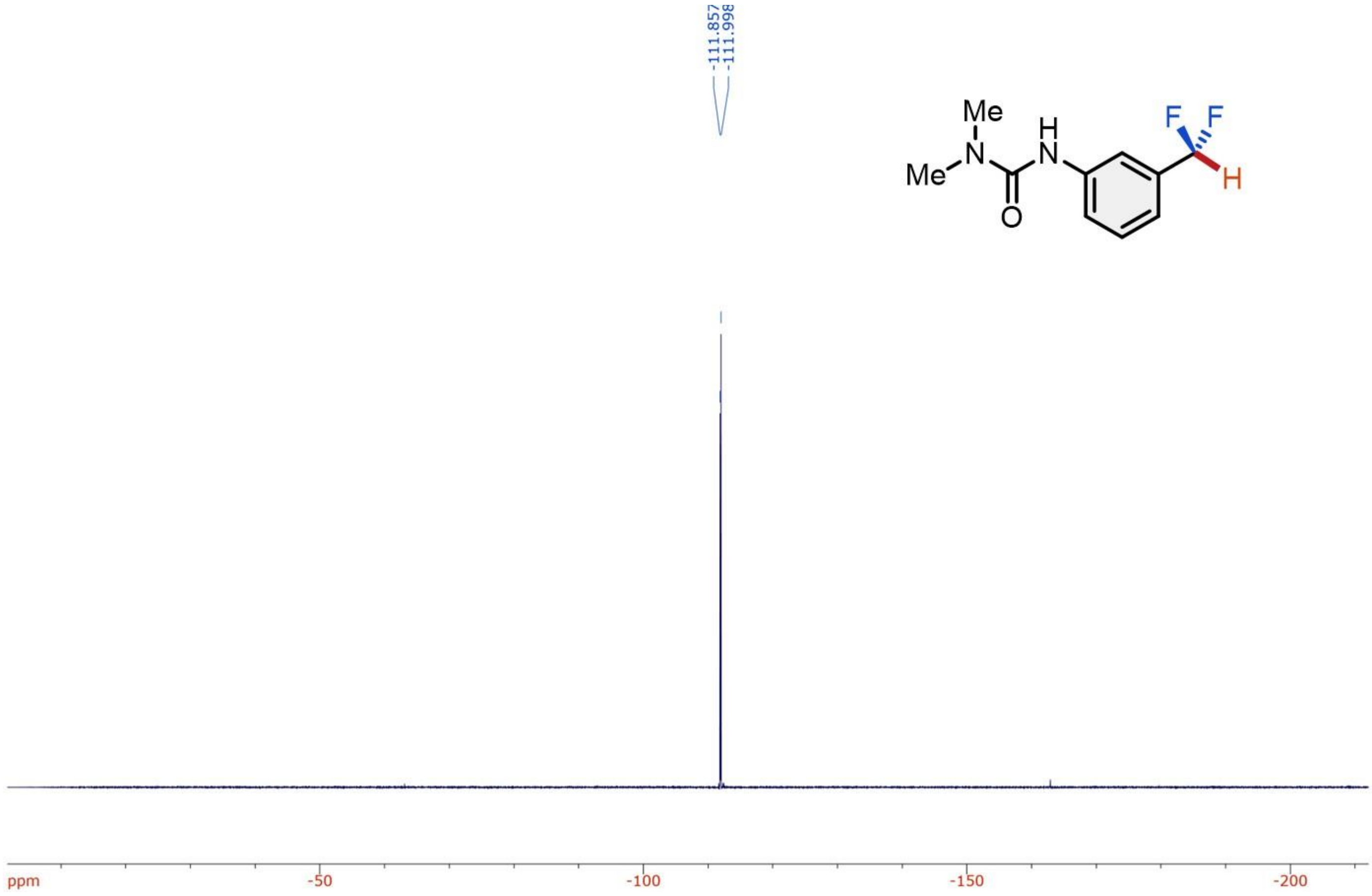
^{1}H NMR spectrum of 5b



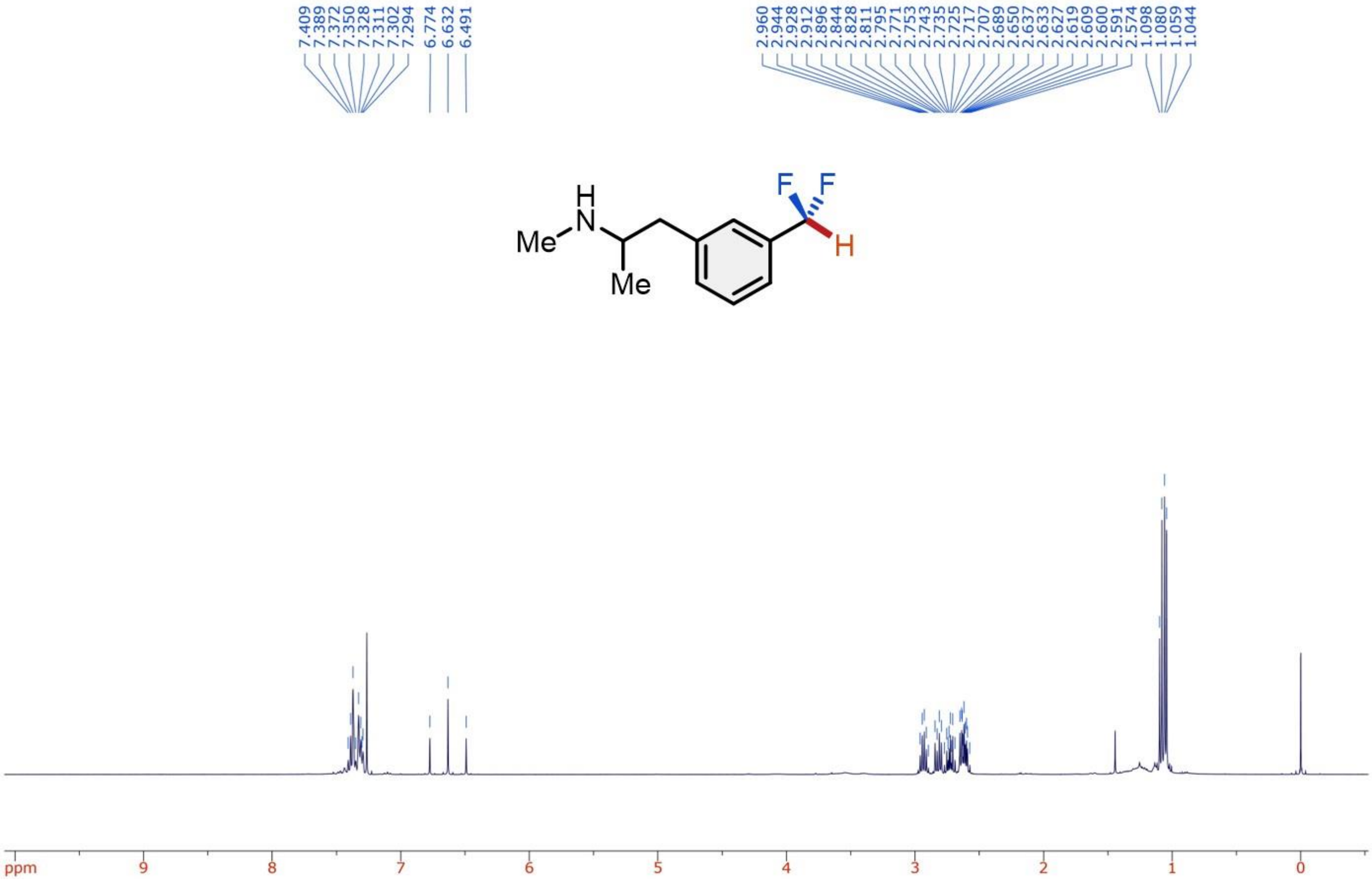
^{13}C NMR spectrum of 5b



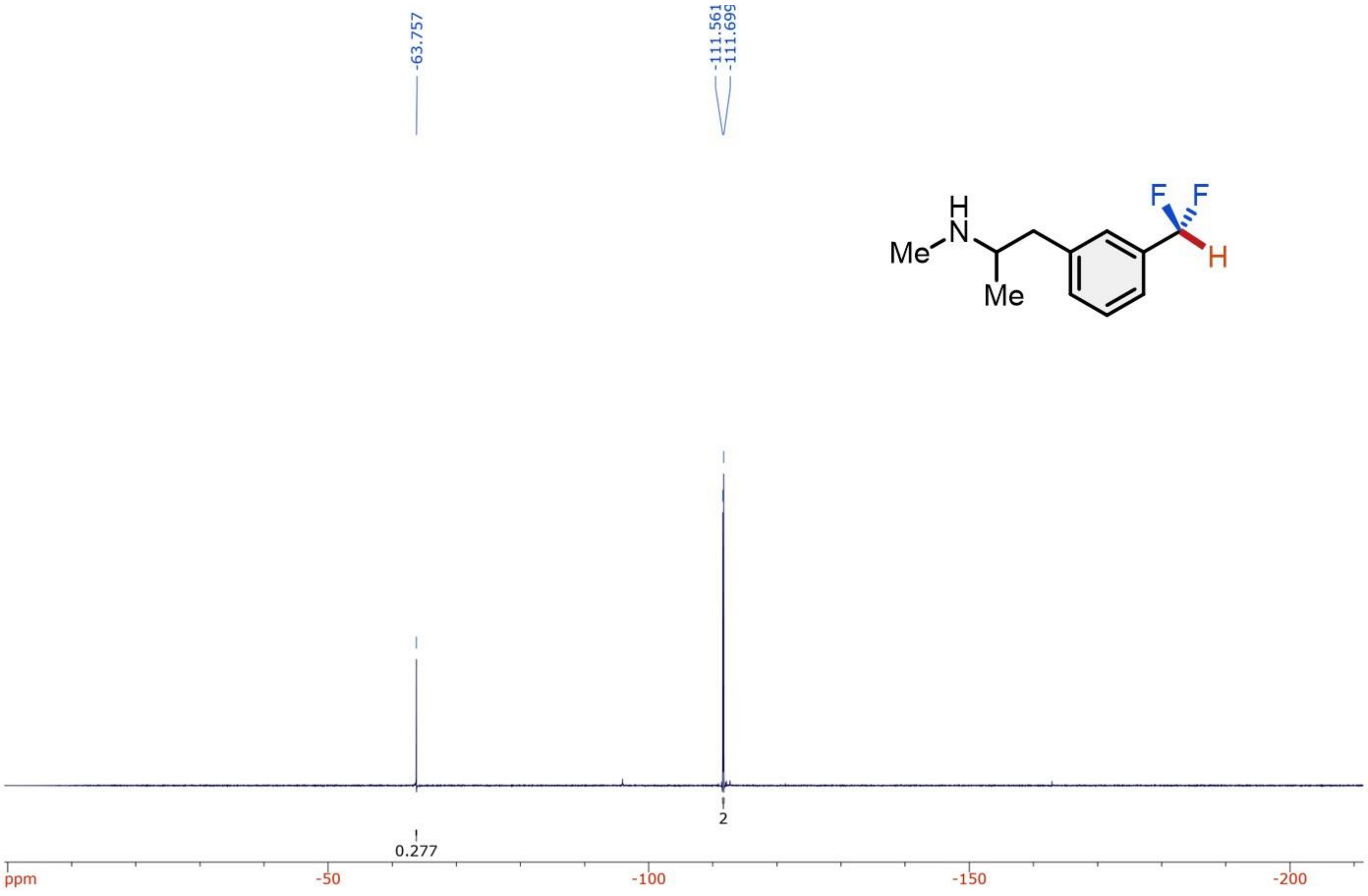
^{19}F NMR spectrum of 5b



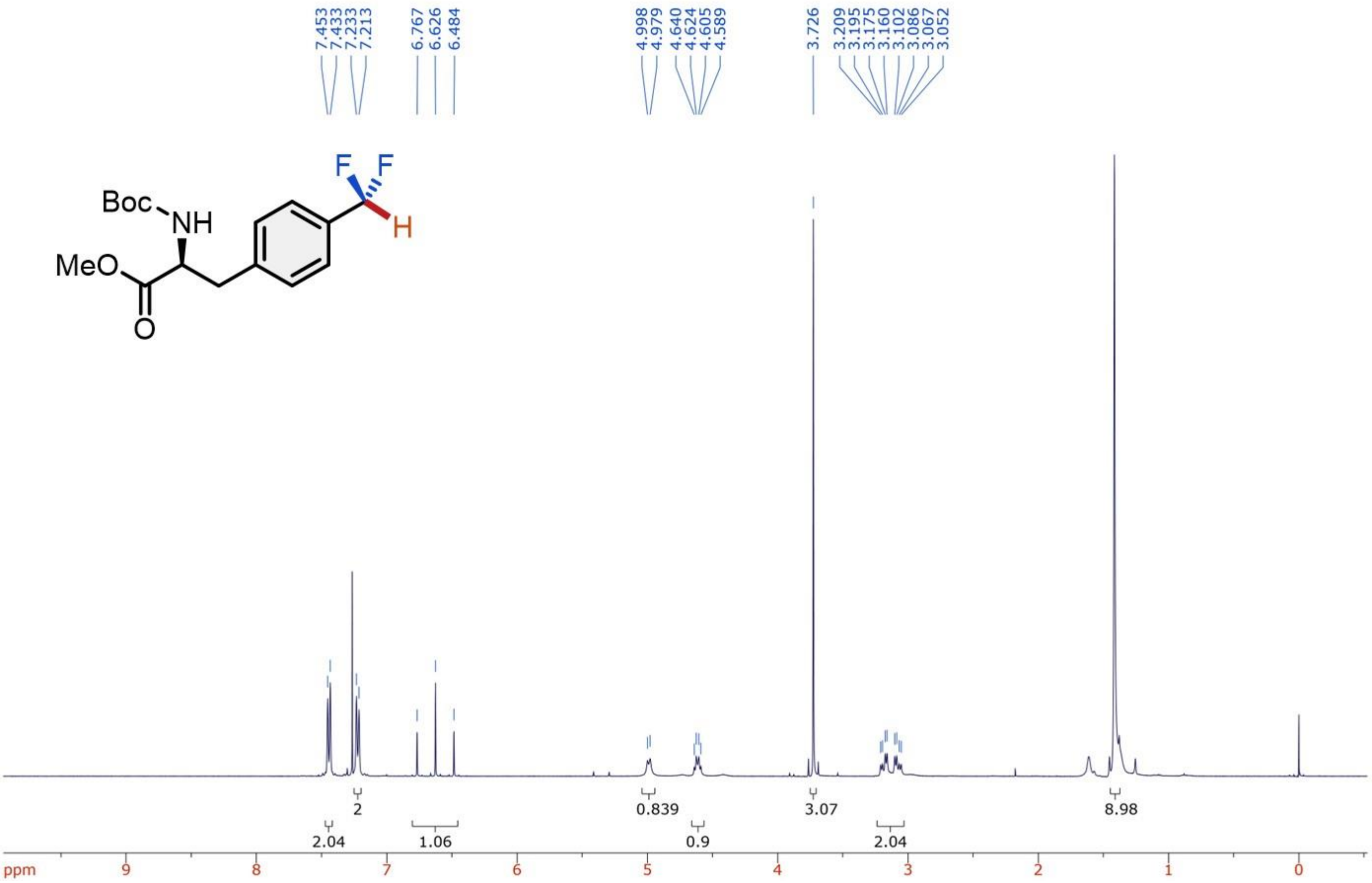
^{1}H NMR spectrum of 5c (mixture with substrate)



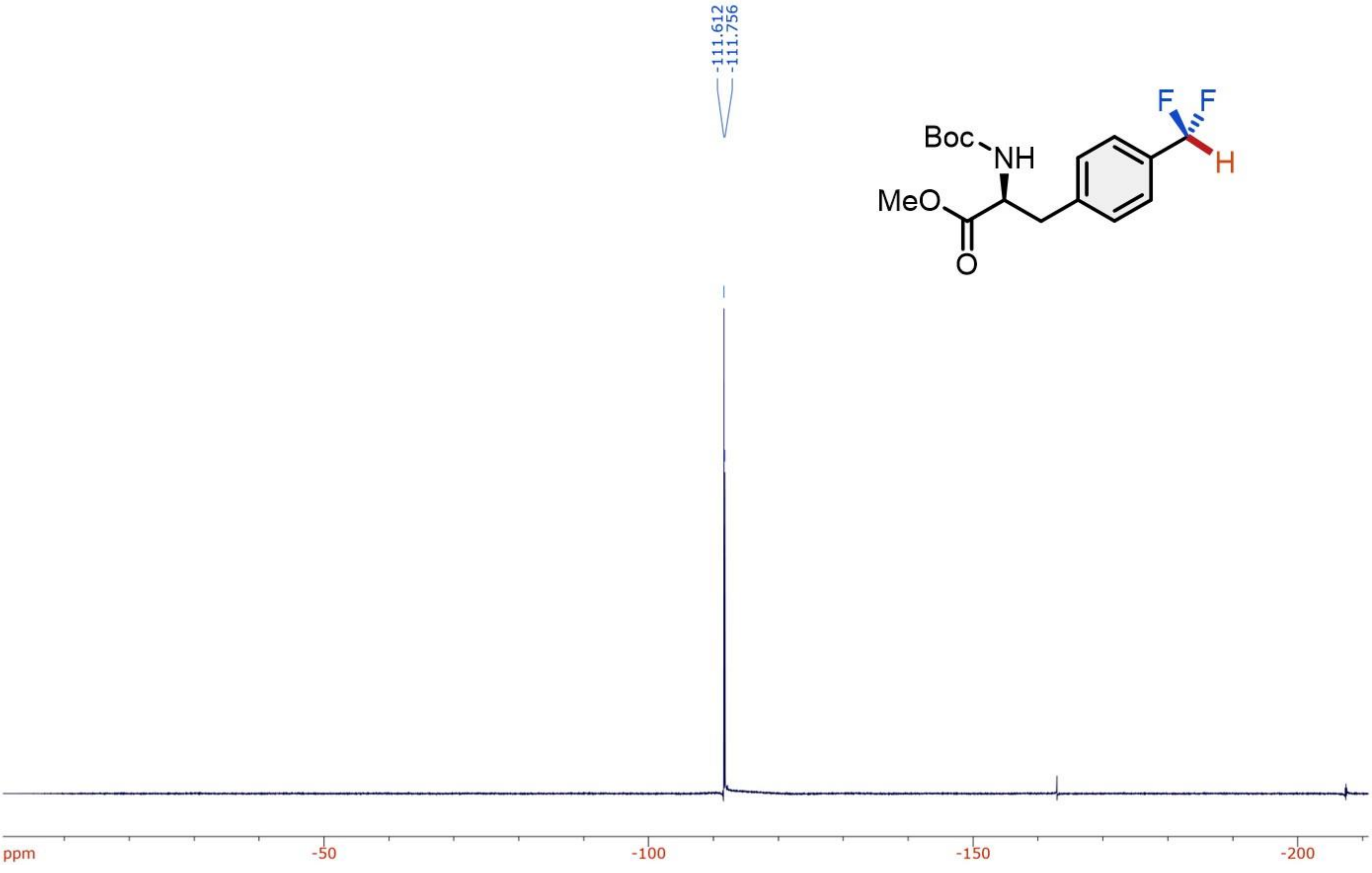
^{19}F NMR spectrum of 5c (mixture with substrate)



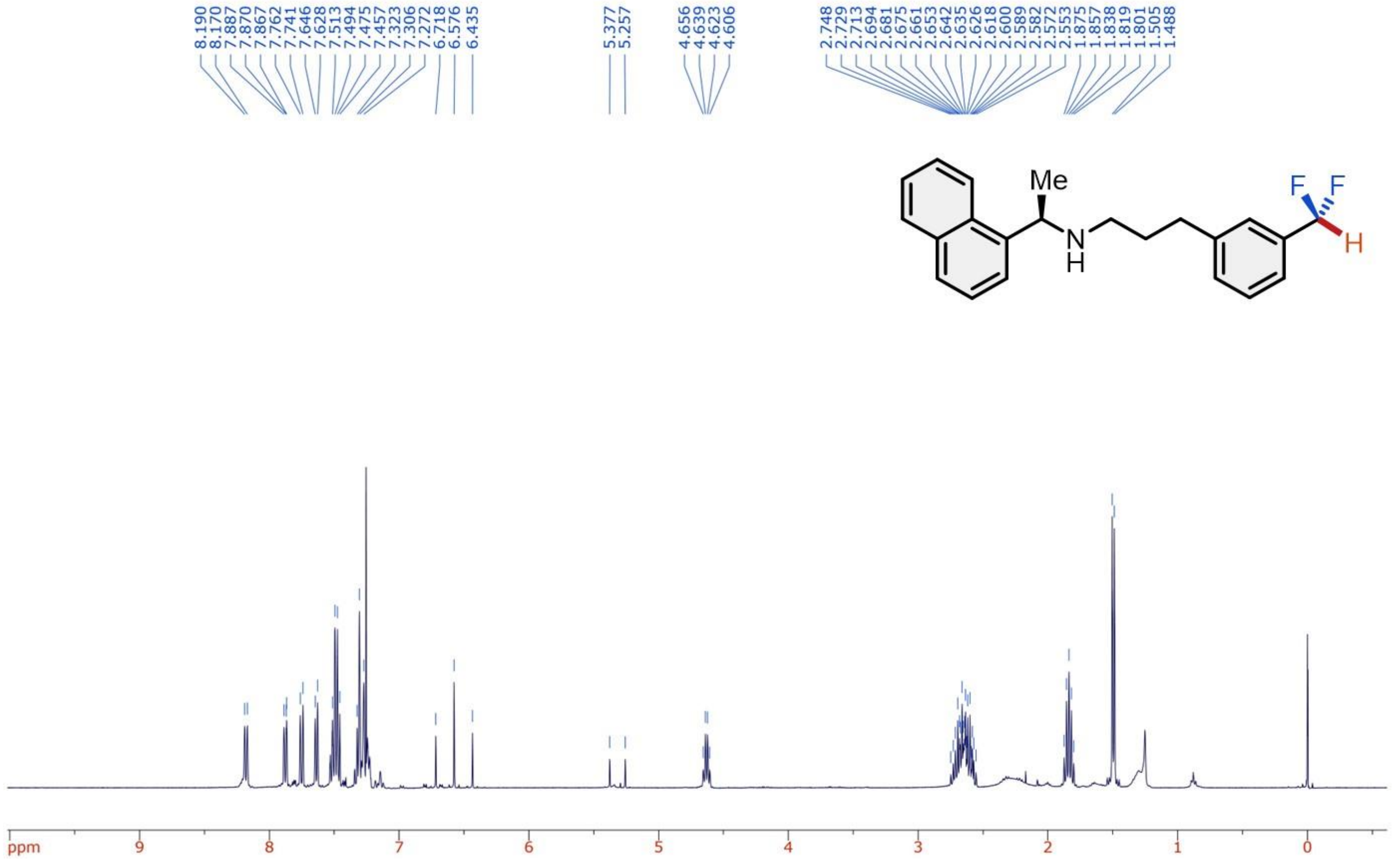
^{1}H NMR spectrum of 5d (mixture with byproduct)



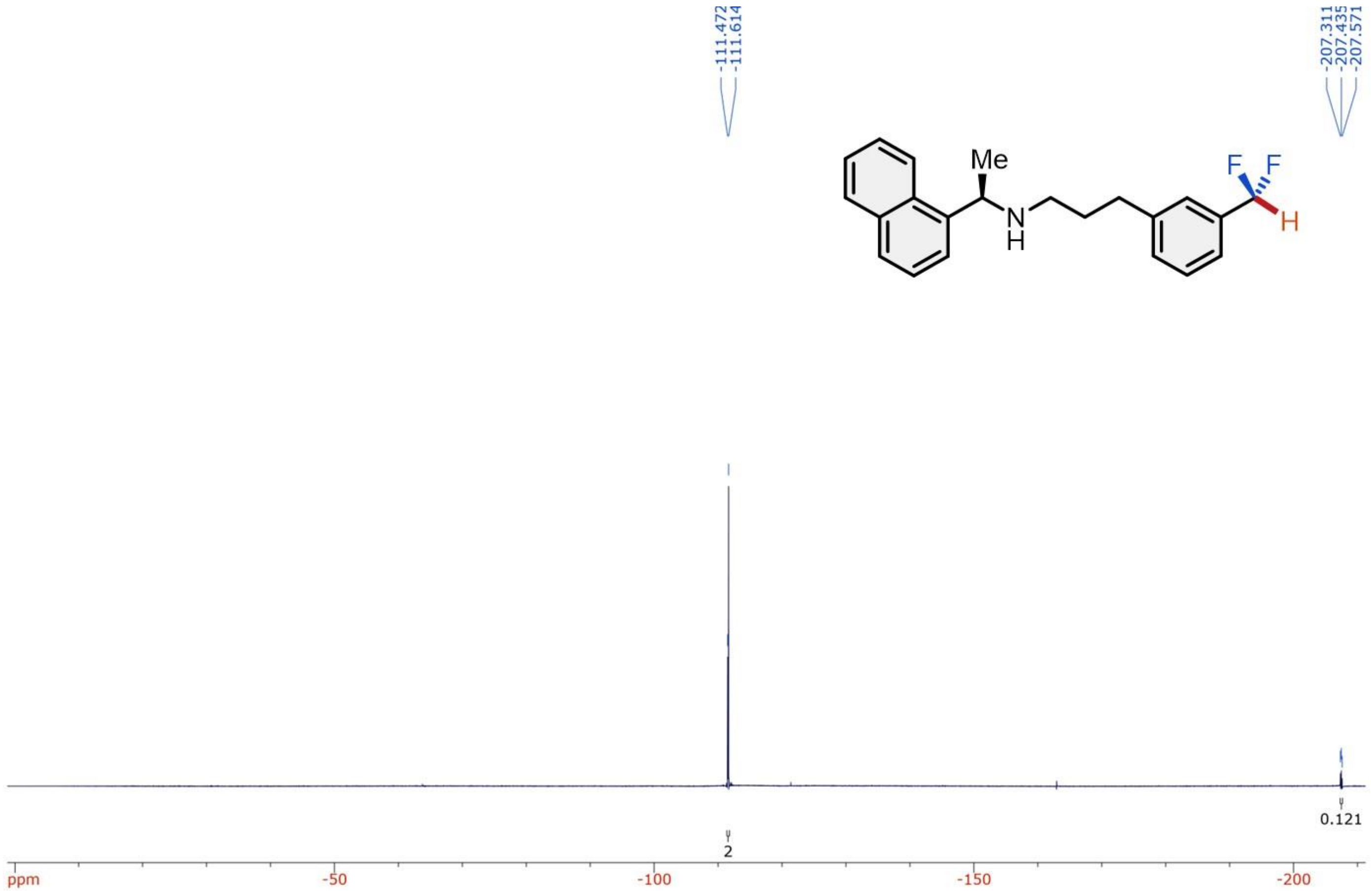
^{19}F NMR spectrum of 5d (mixture with byproduct)



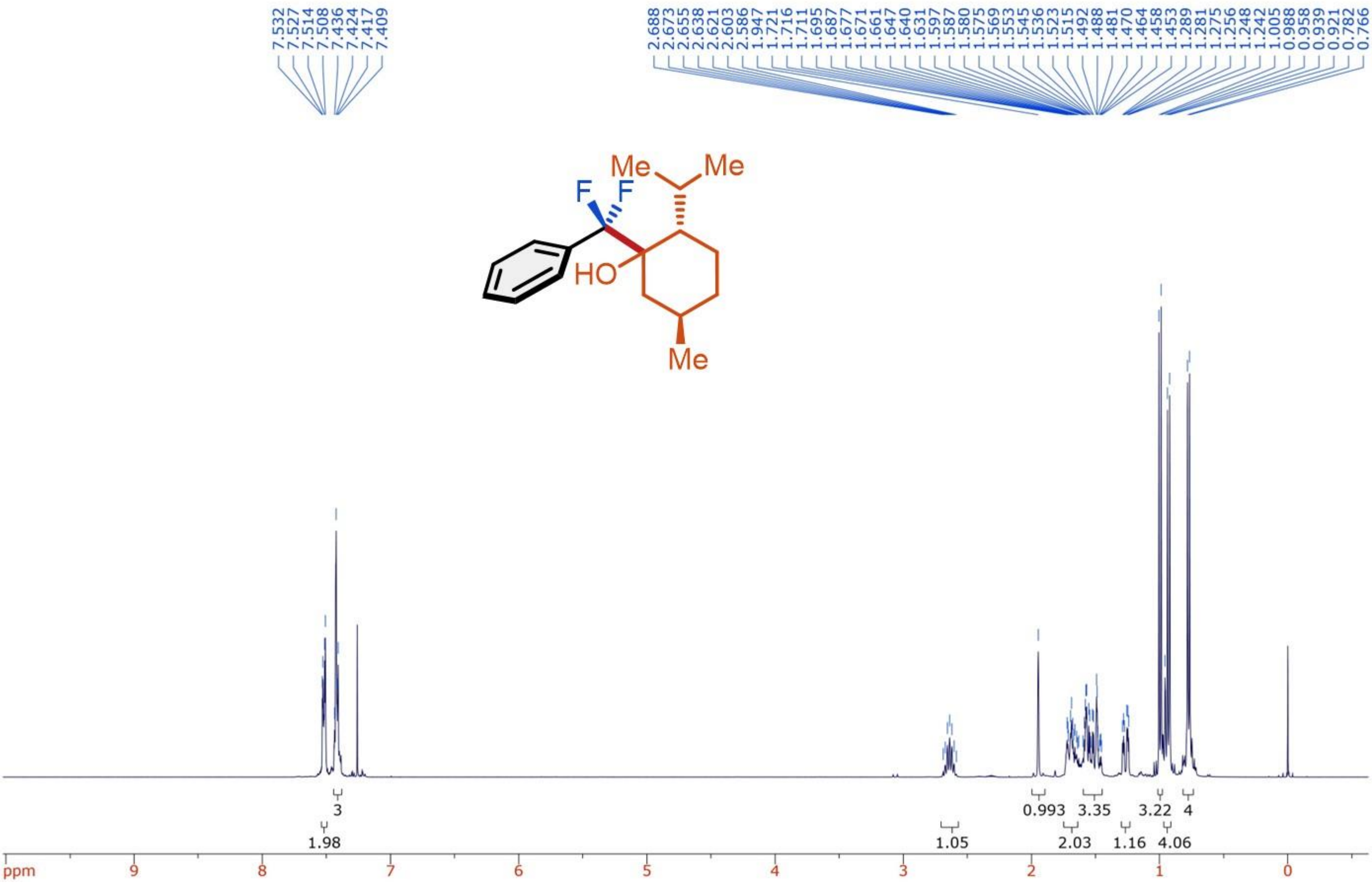
^{1}H NMR spectrum of 5e (mixture with byproduct)



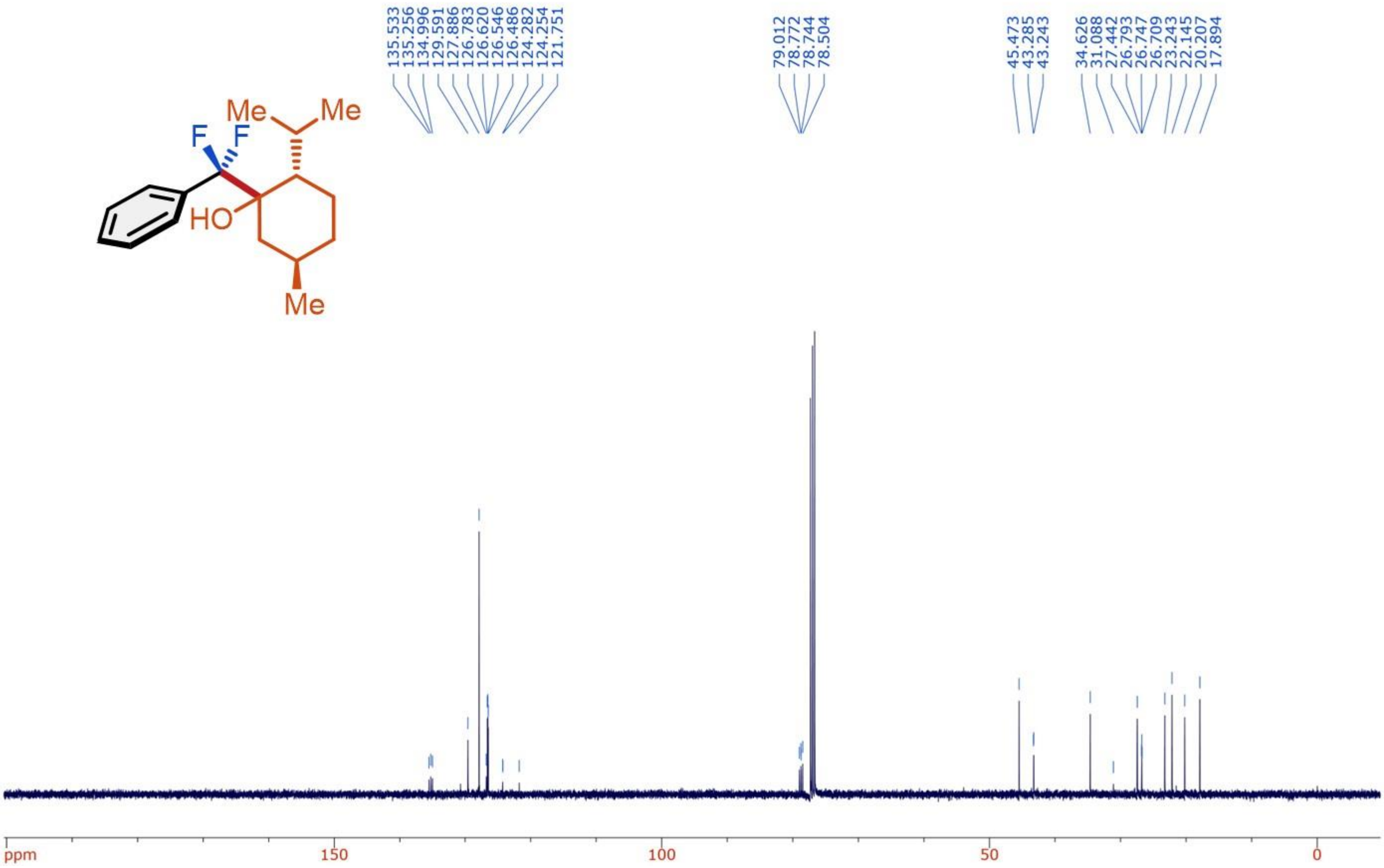
^{19}F NMR spectrum of 5e (mixture with byproduct)



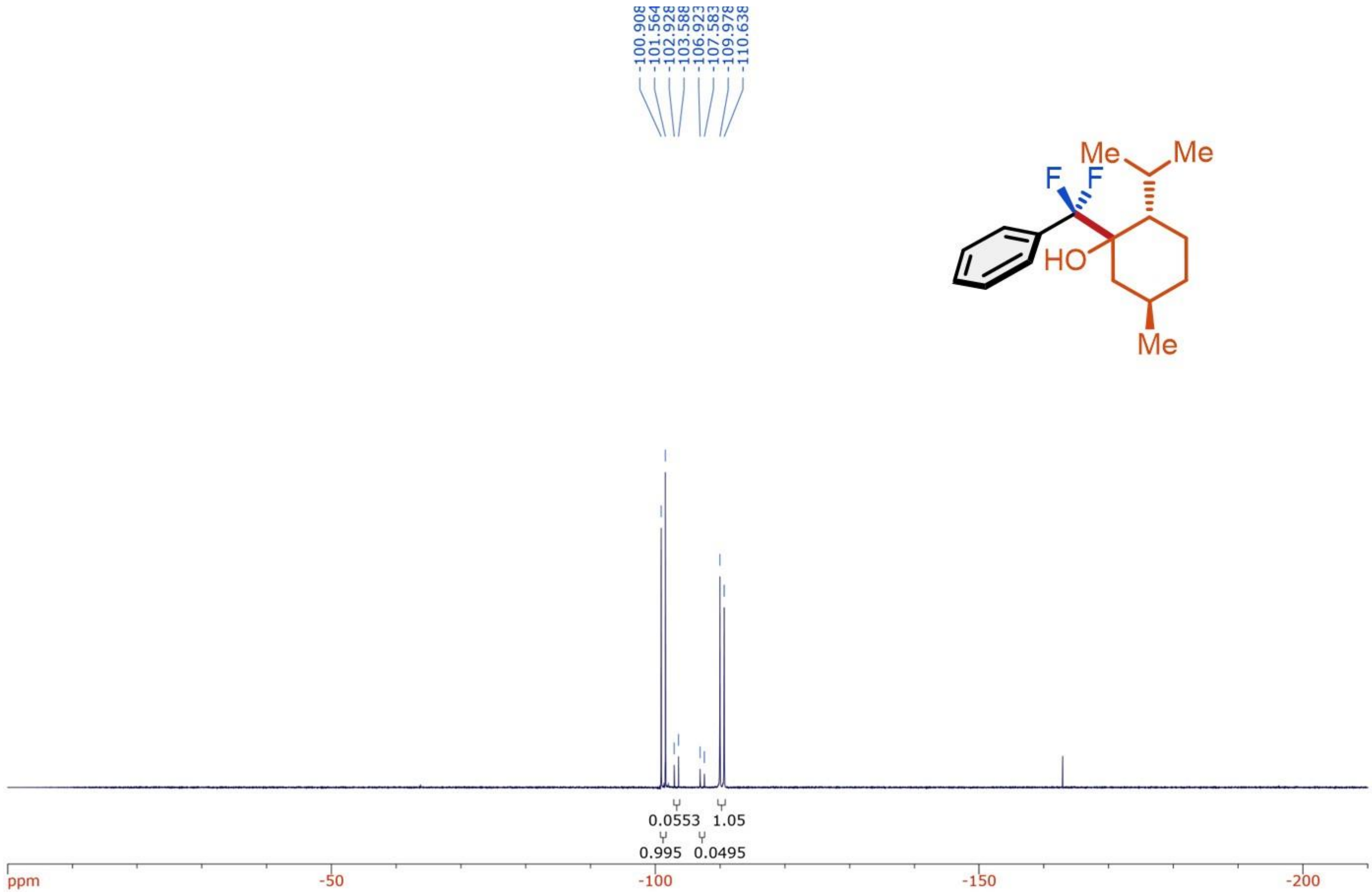
^{1}H NMR spectrum of 5f



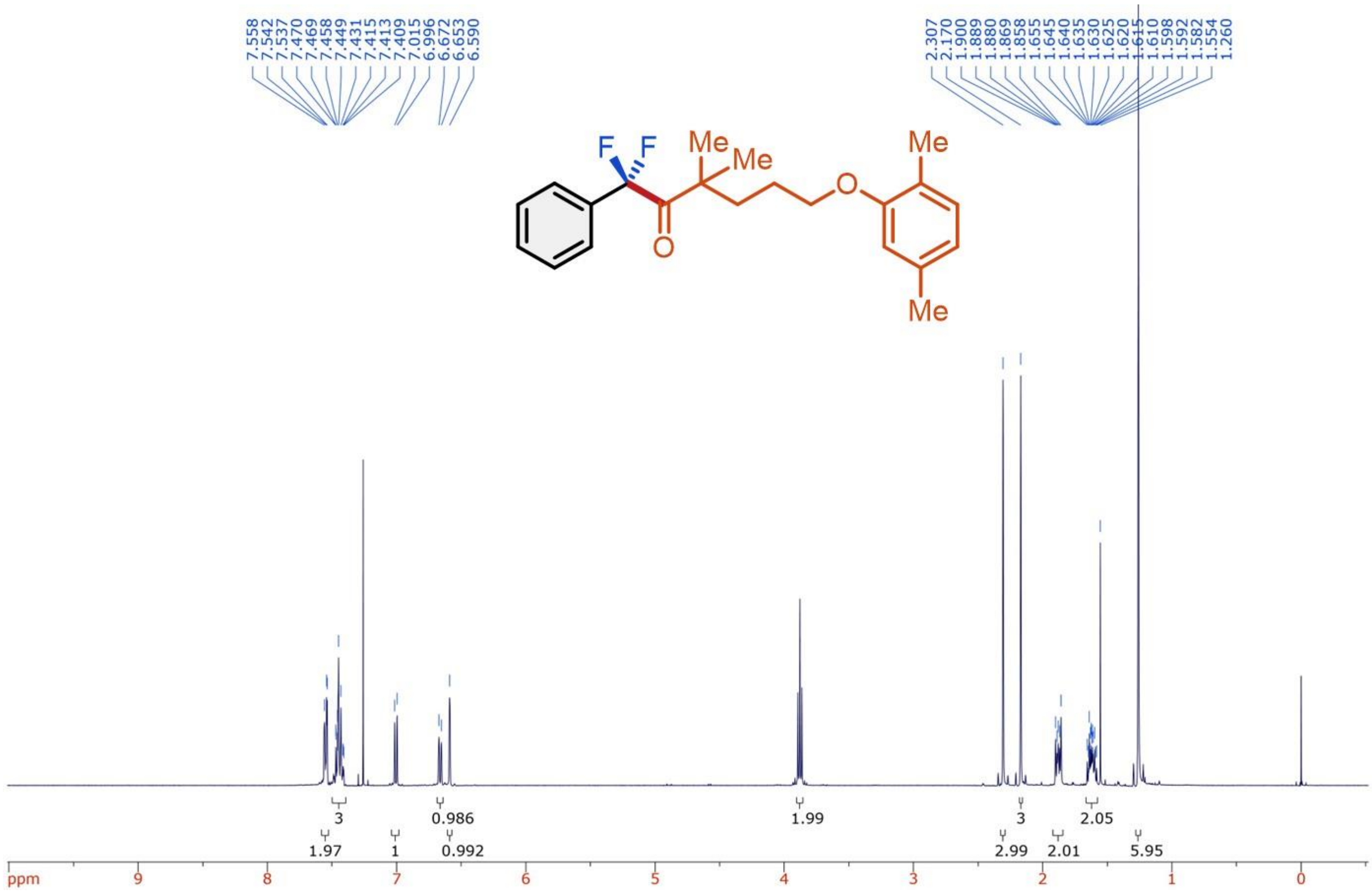
^{13}C NMR spectrum of 5f



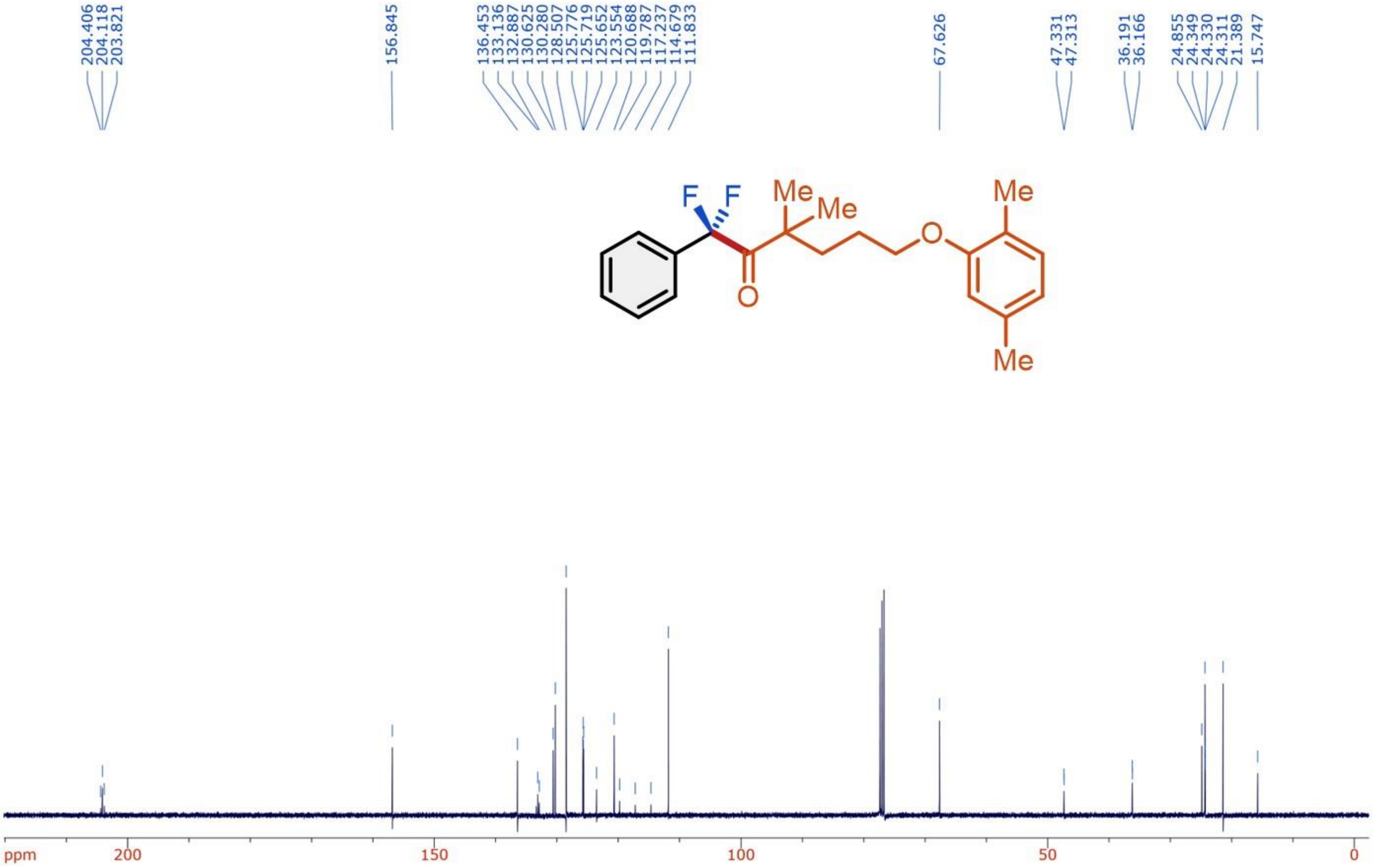
^{19}F NMR spectrum of 5f



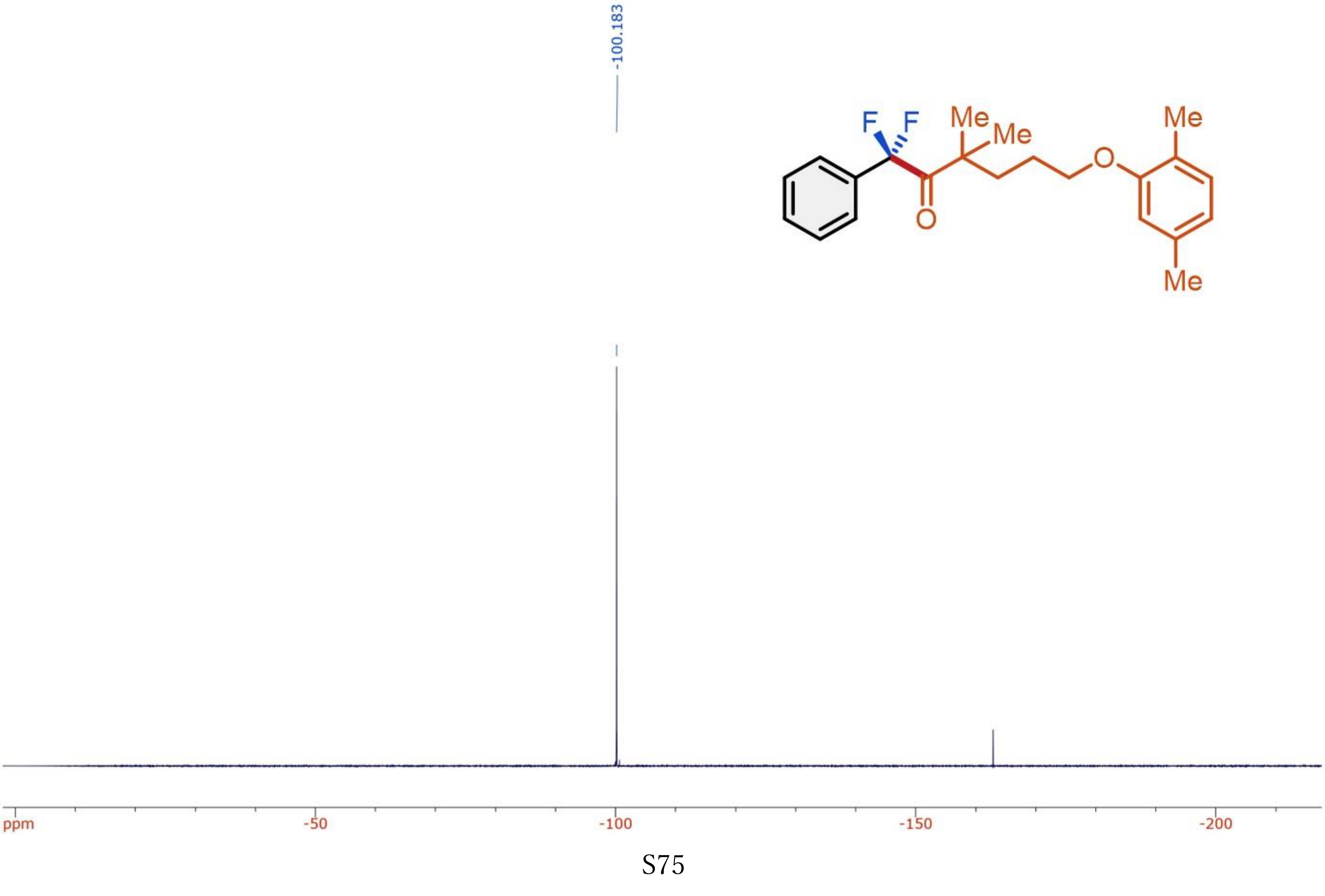
^{1}H NMR spectrum of 5g



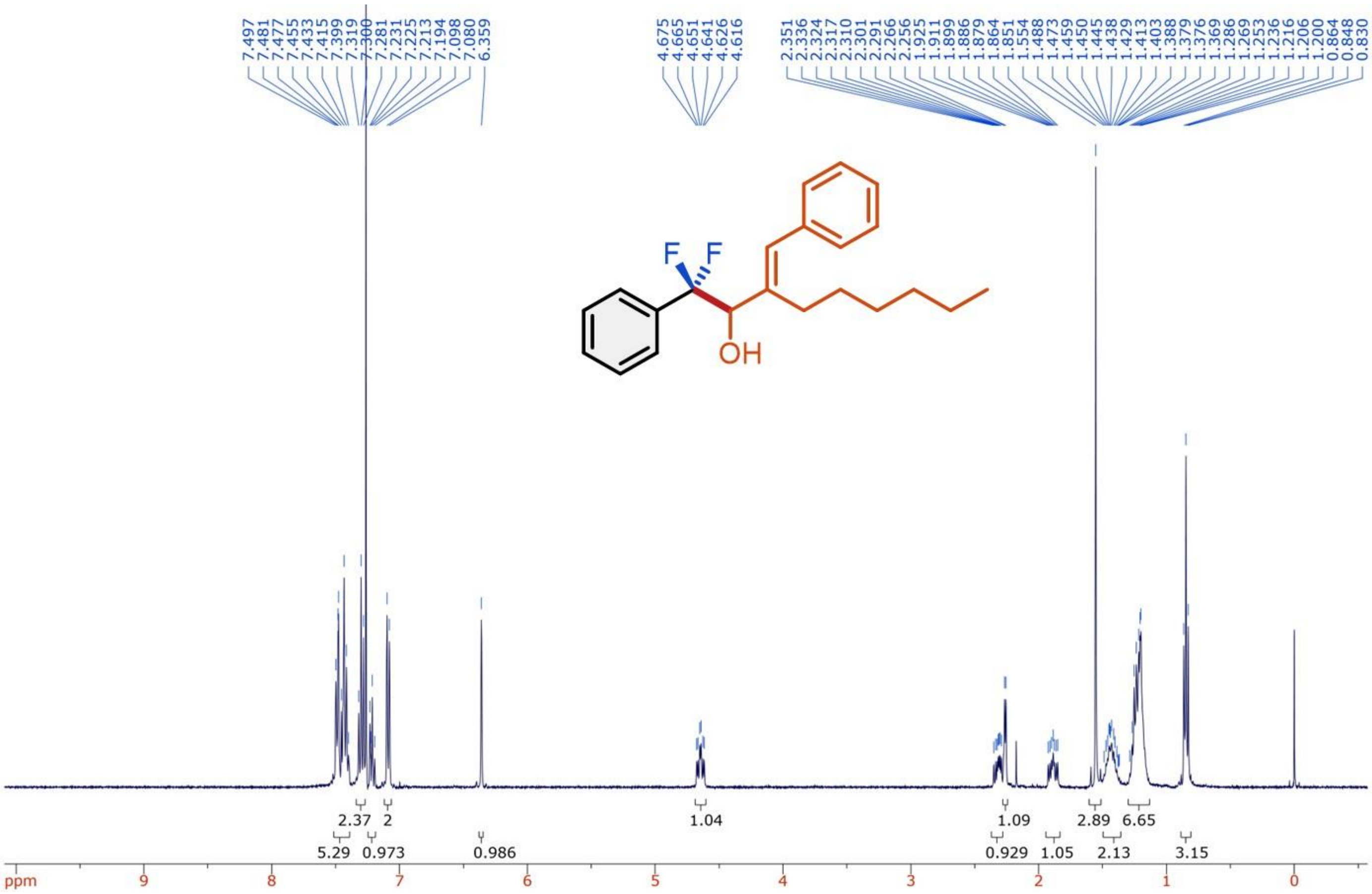
^{13}C NMR spectrum of 5g



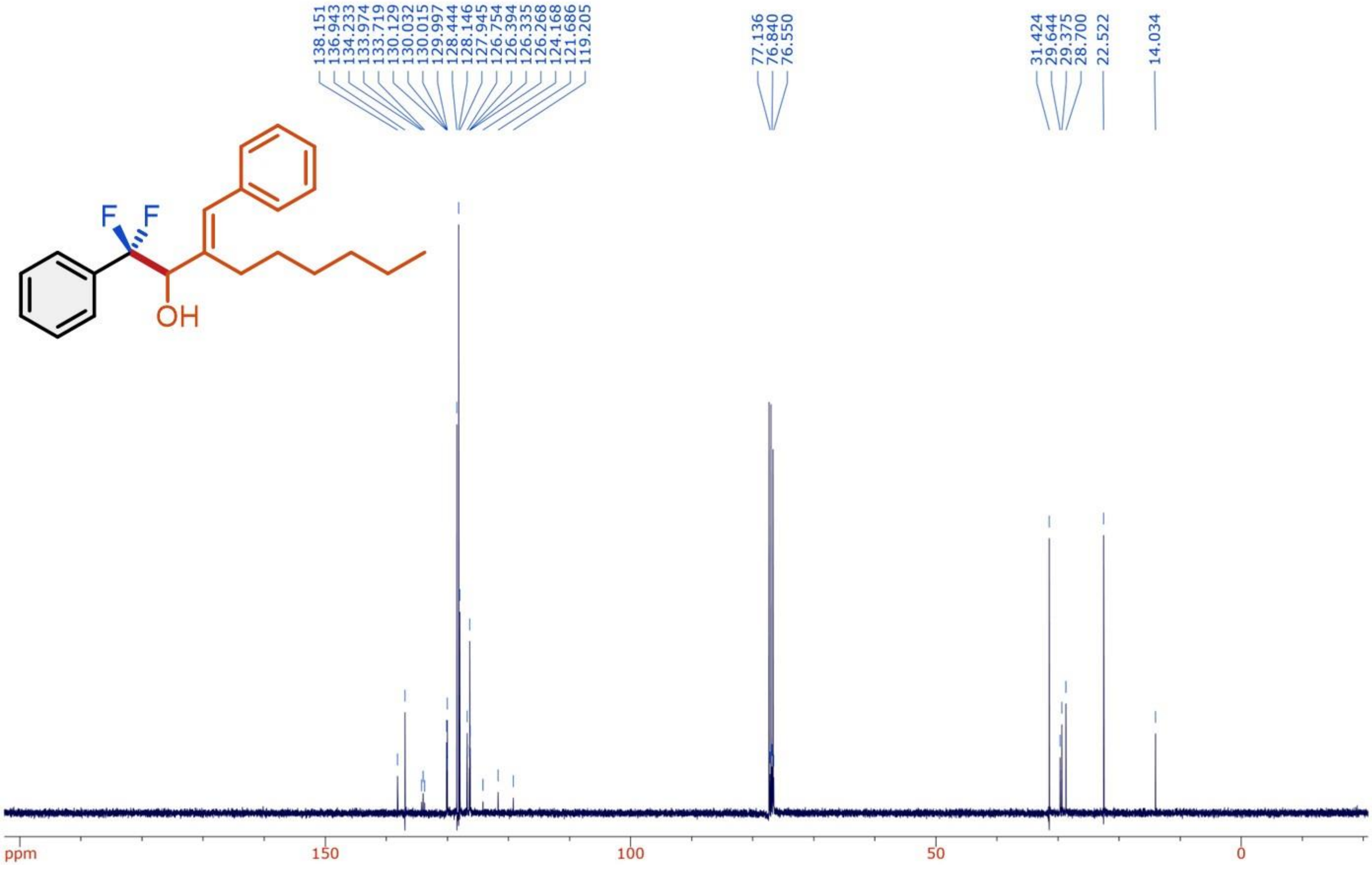
^{19}F NMR spectrum of 5g



^{1}H NMR spectrum of 5h



^{13}C NMR spectrum of 5h



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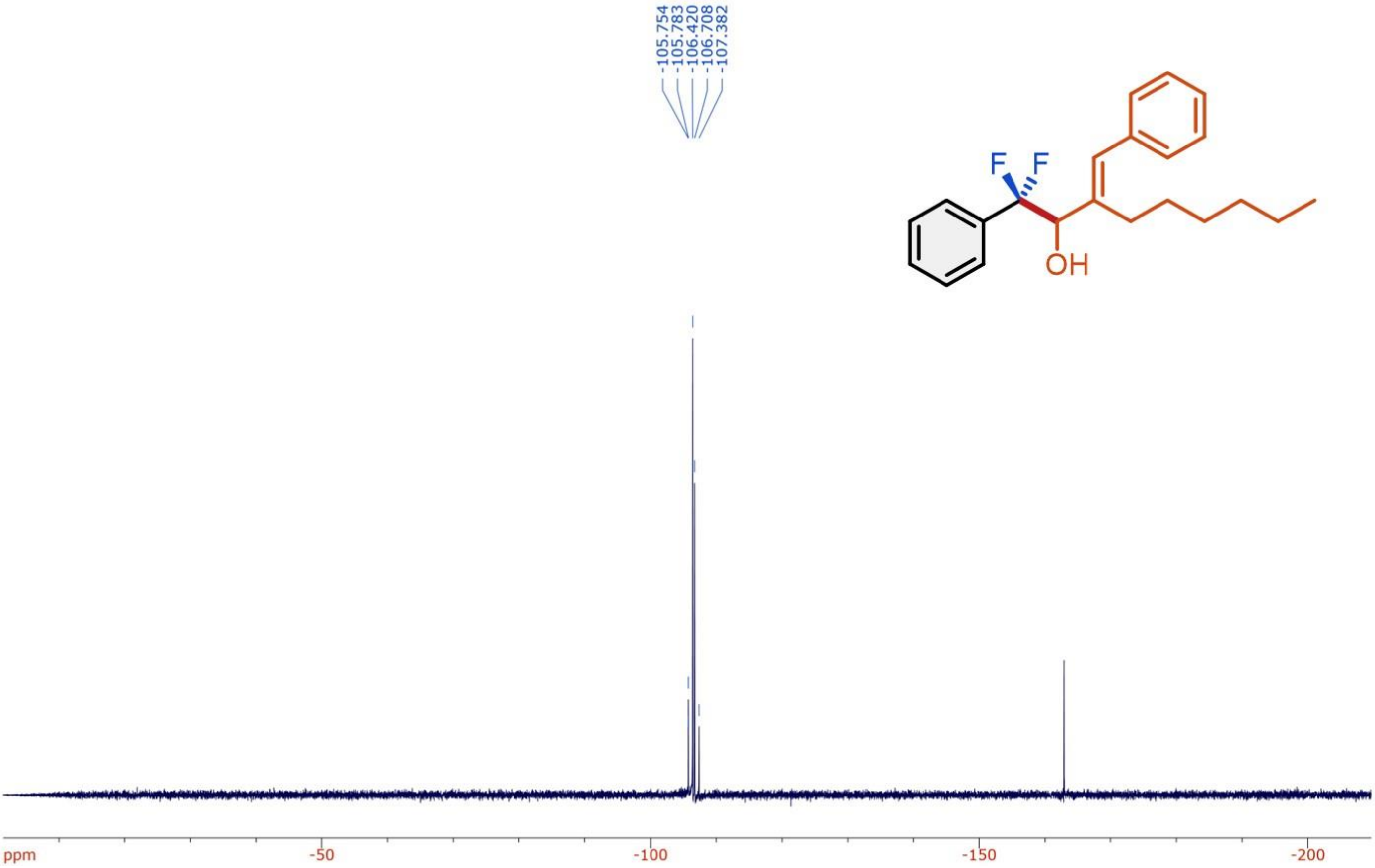
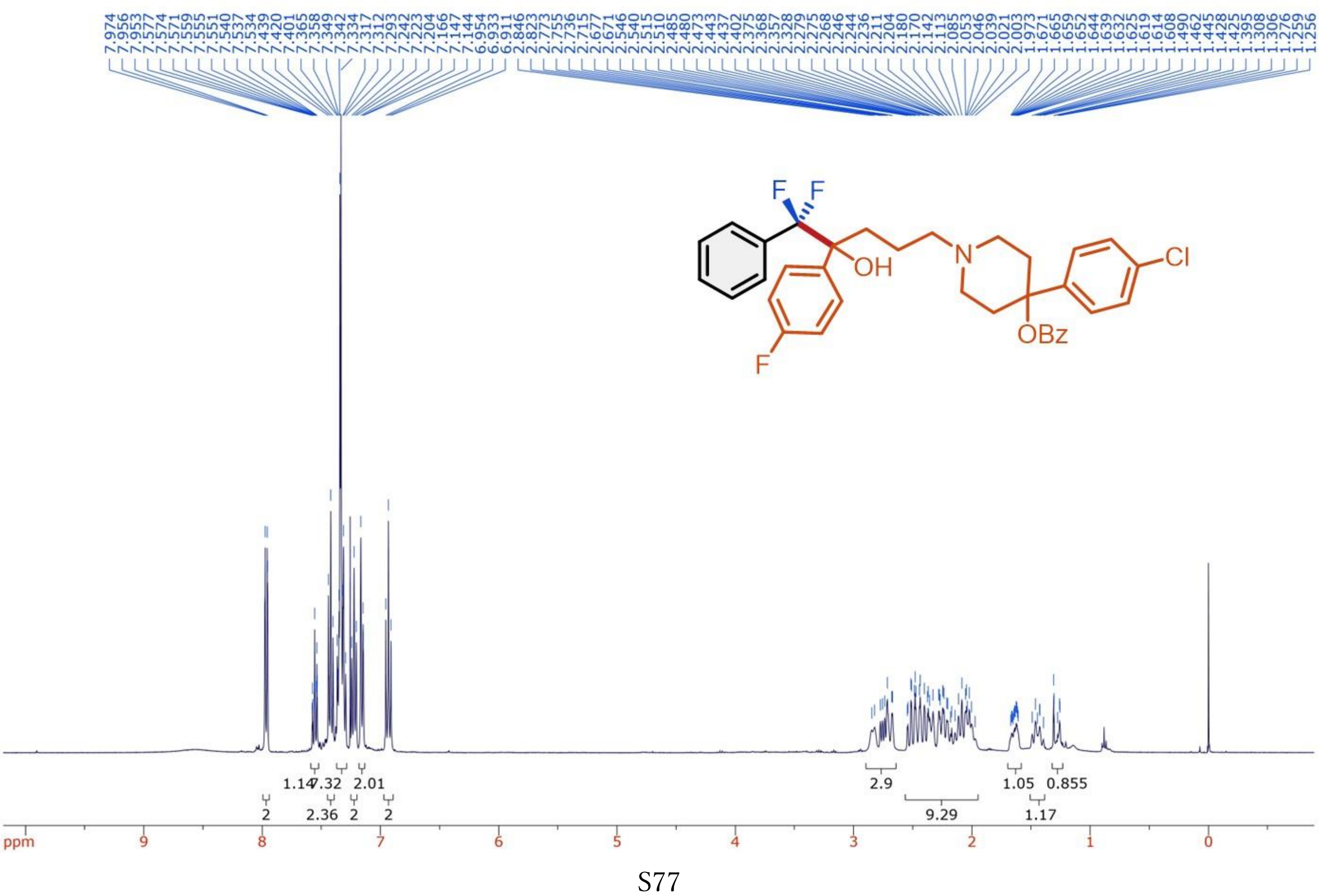
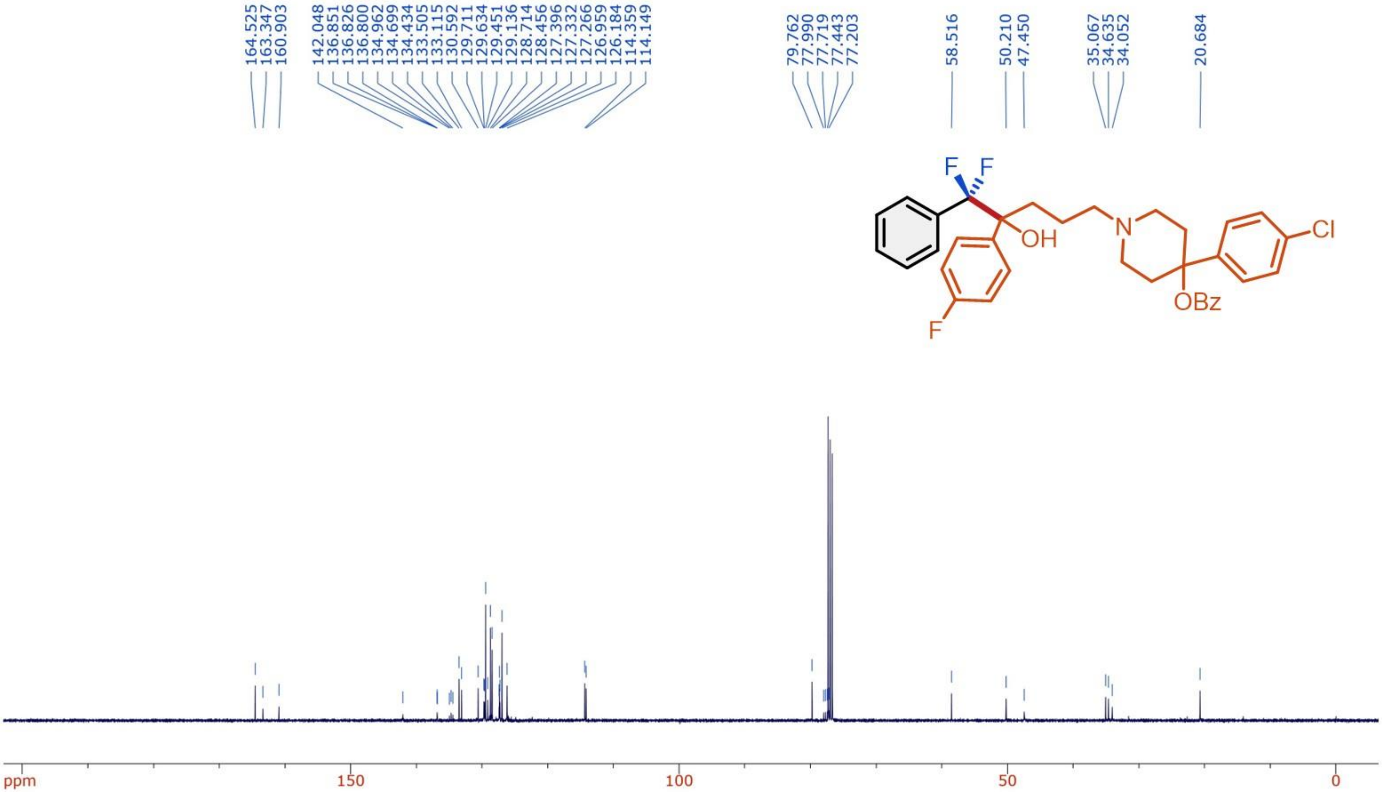


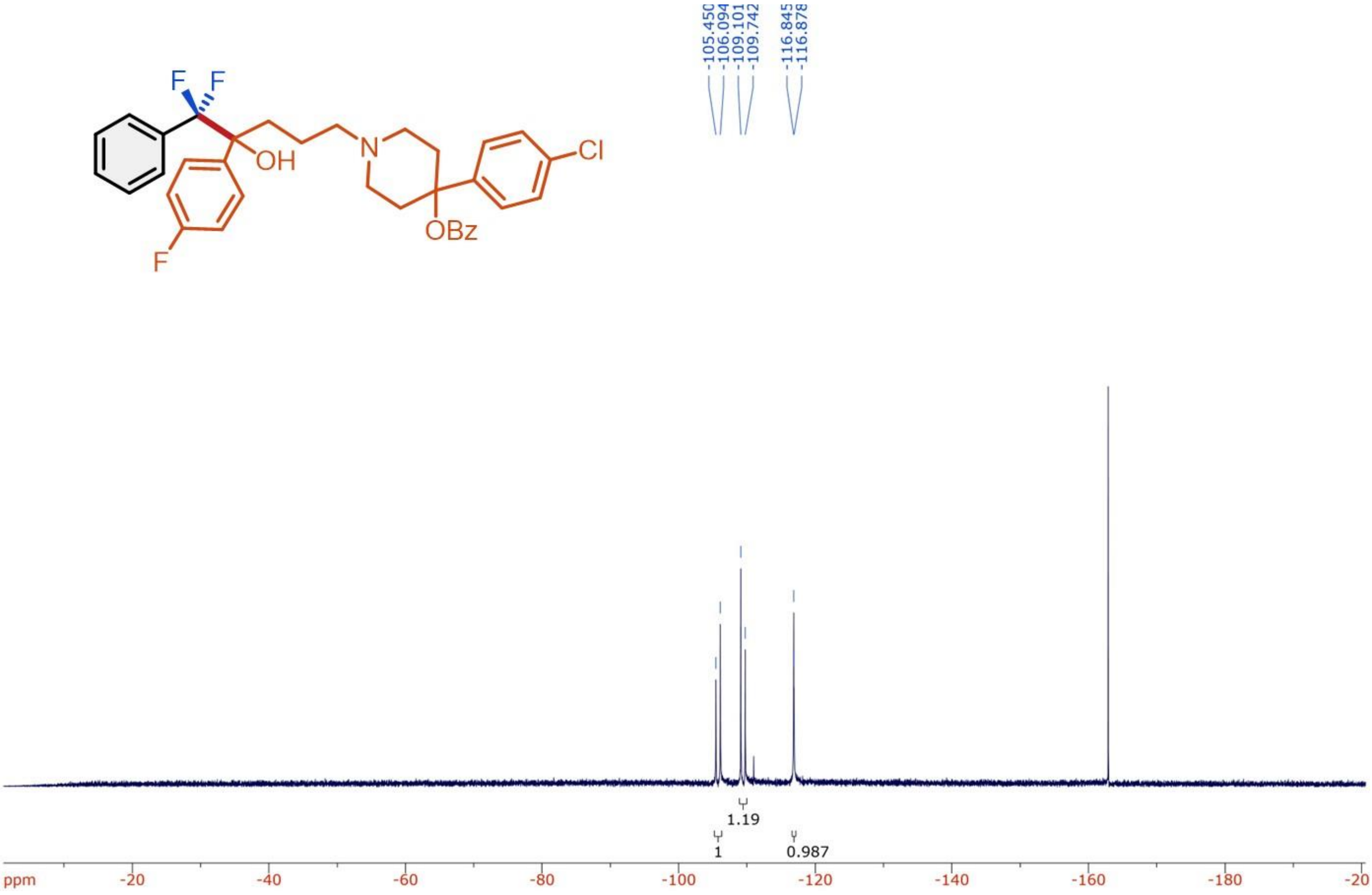
^{1}H NMR spectrum of 5i



^{13}C NMR spectrum of 5i



^{19}F NMR spectrum of 5i



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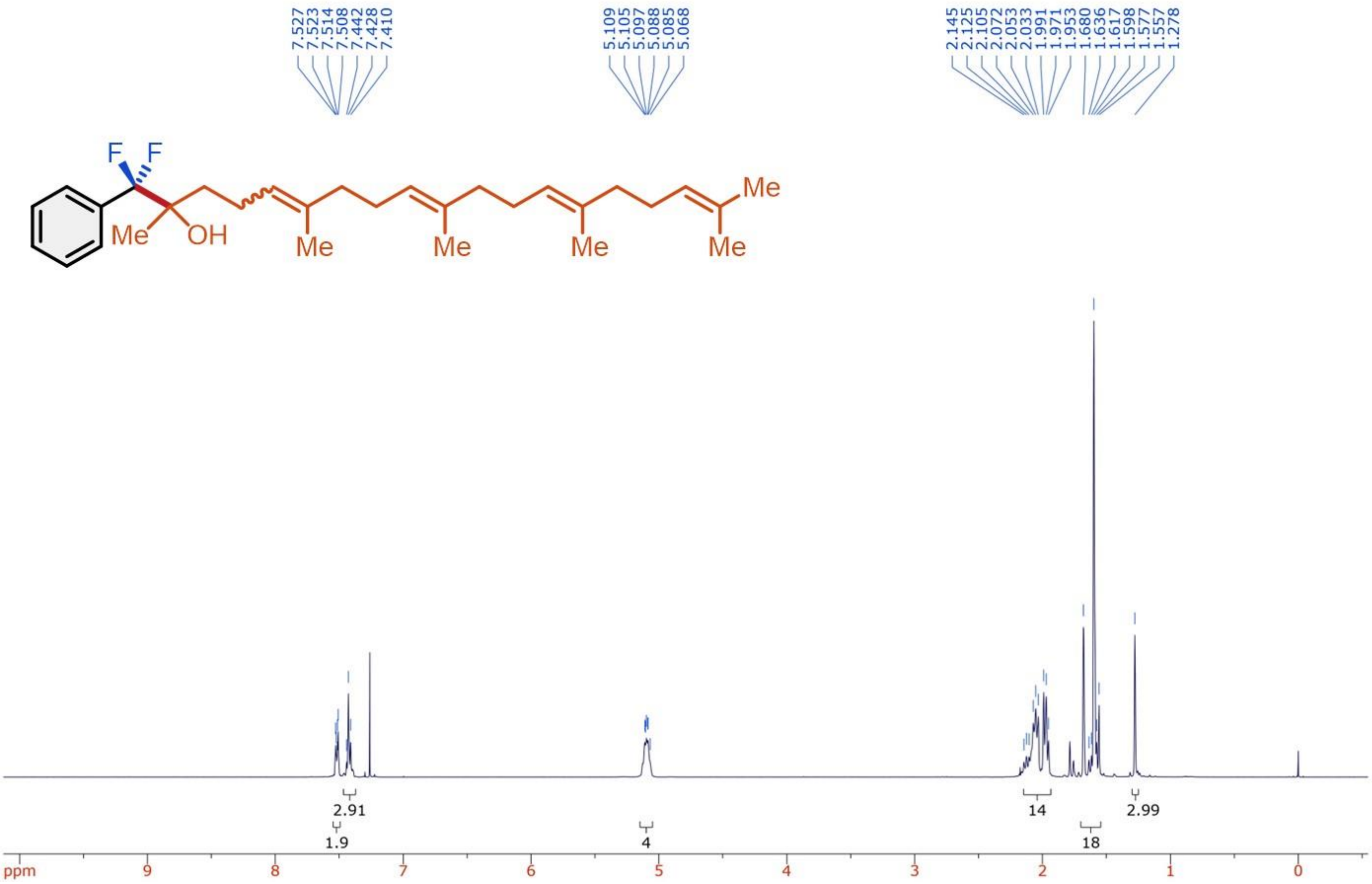

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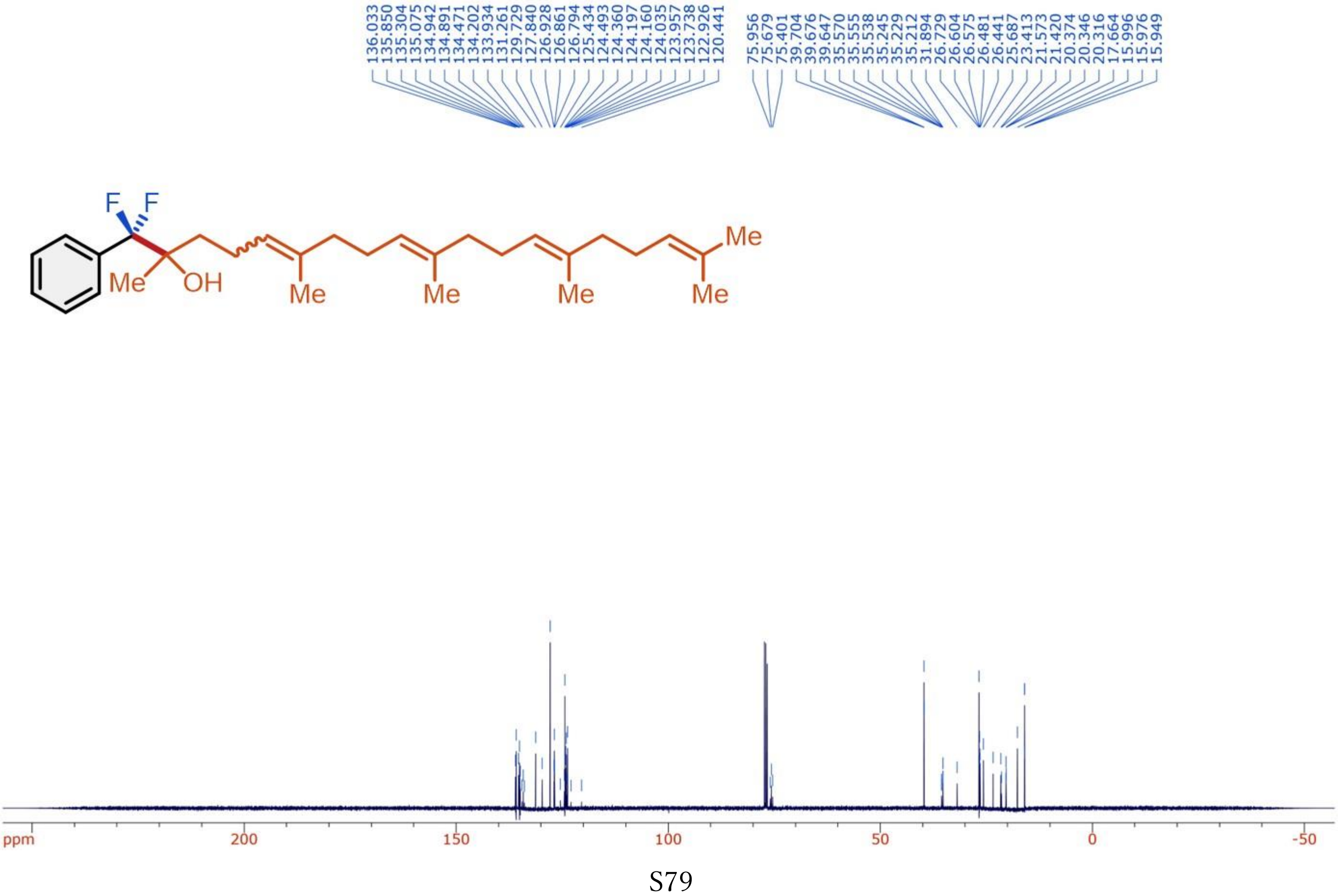

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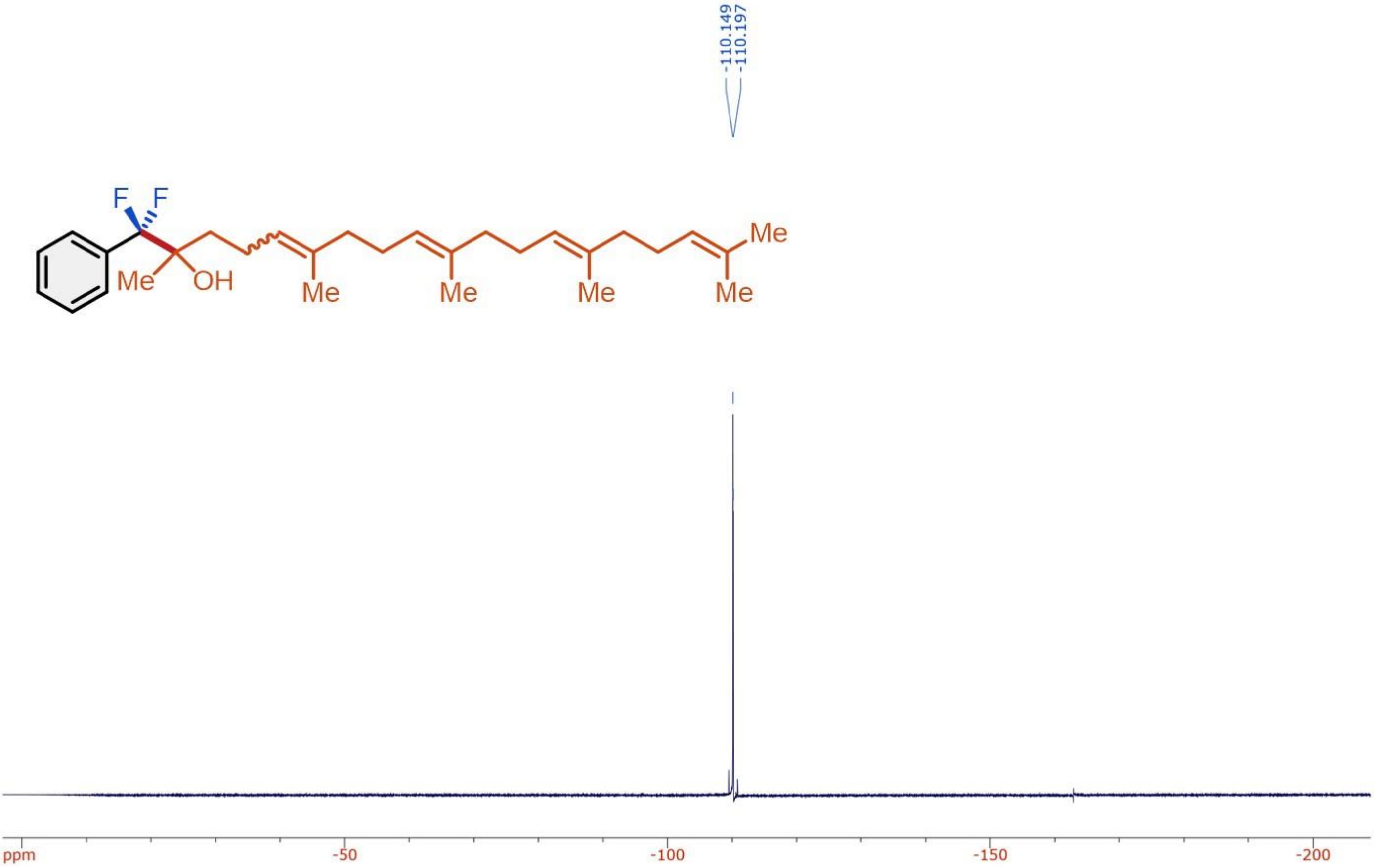
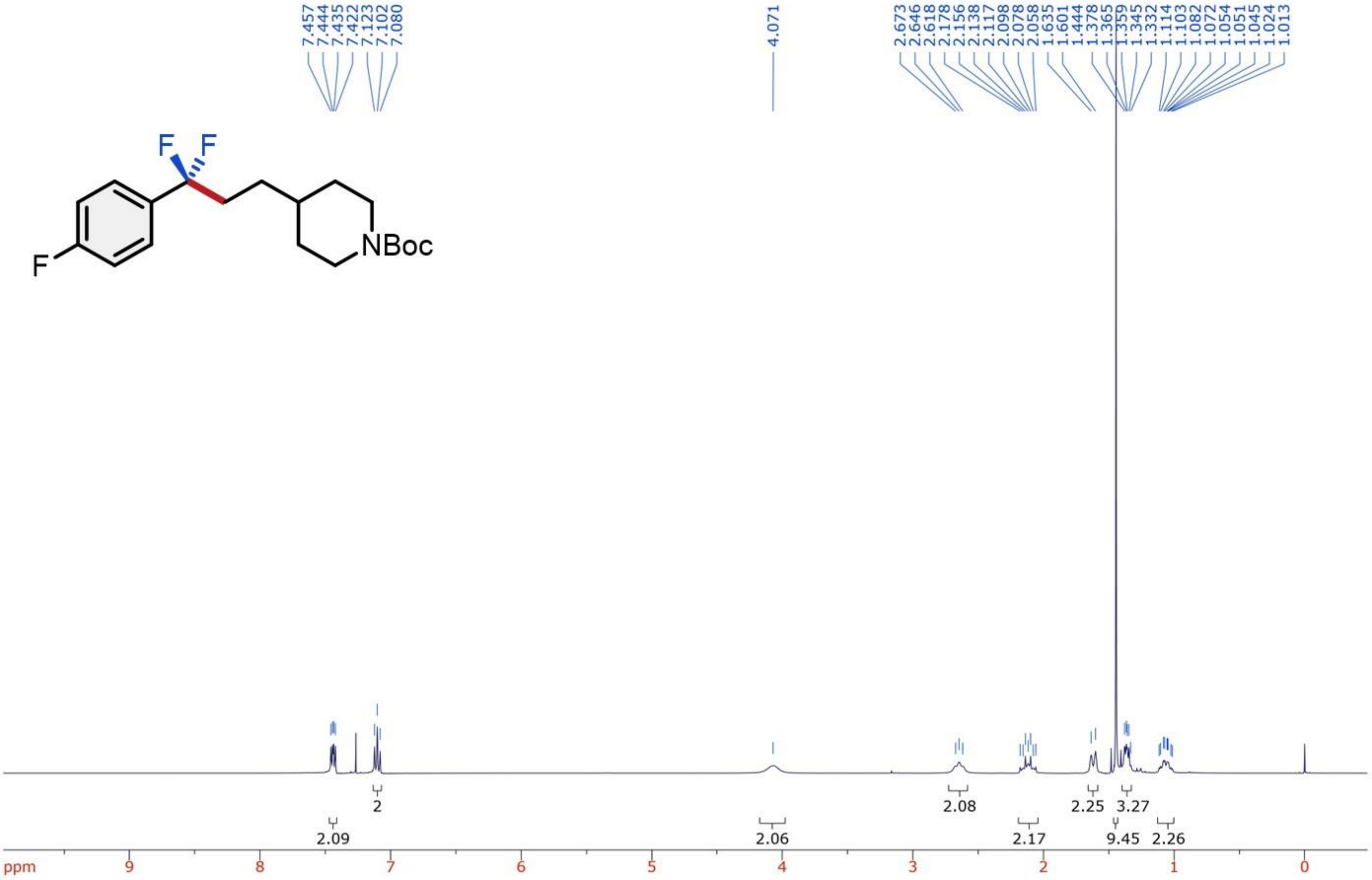


^{1}H NMR spectrum of 8



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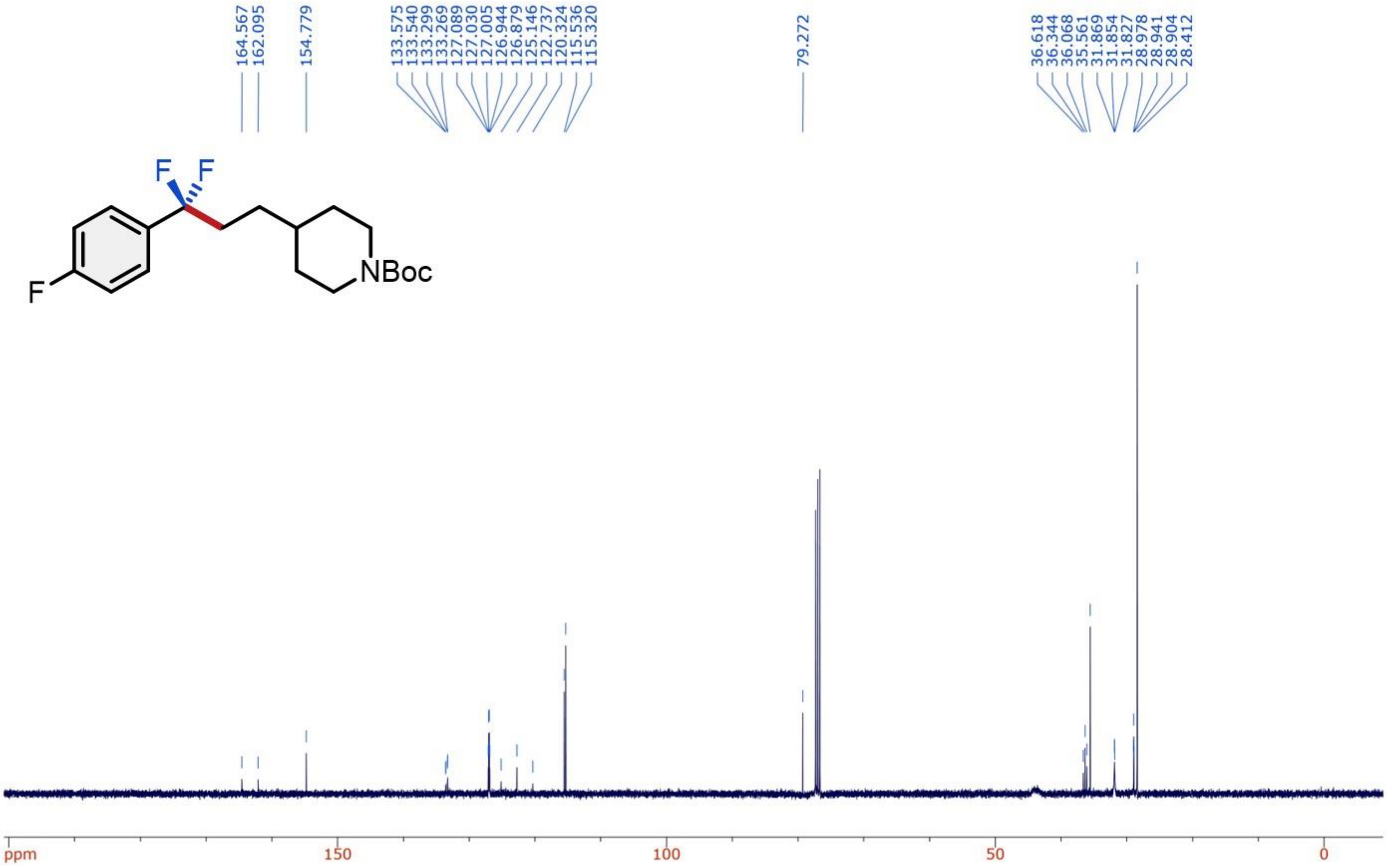

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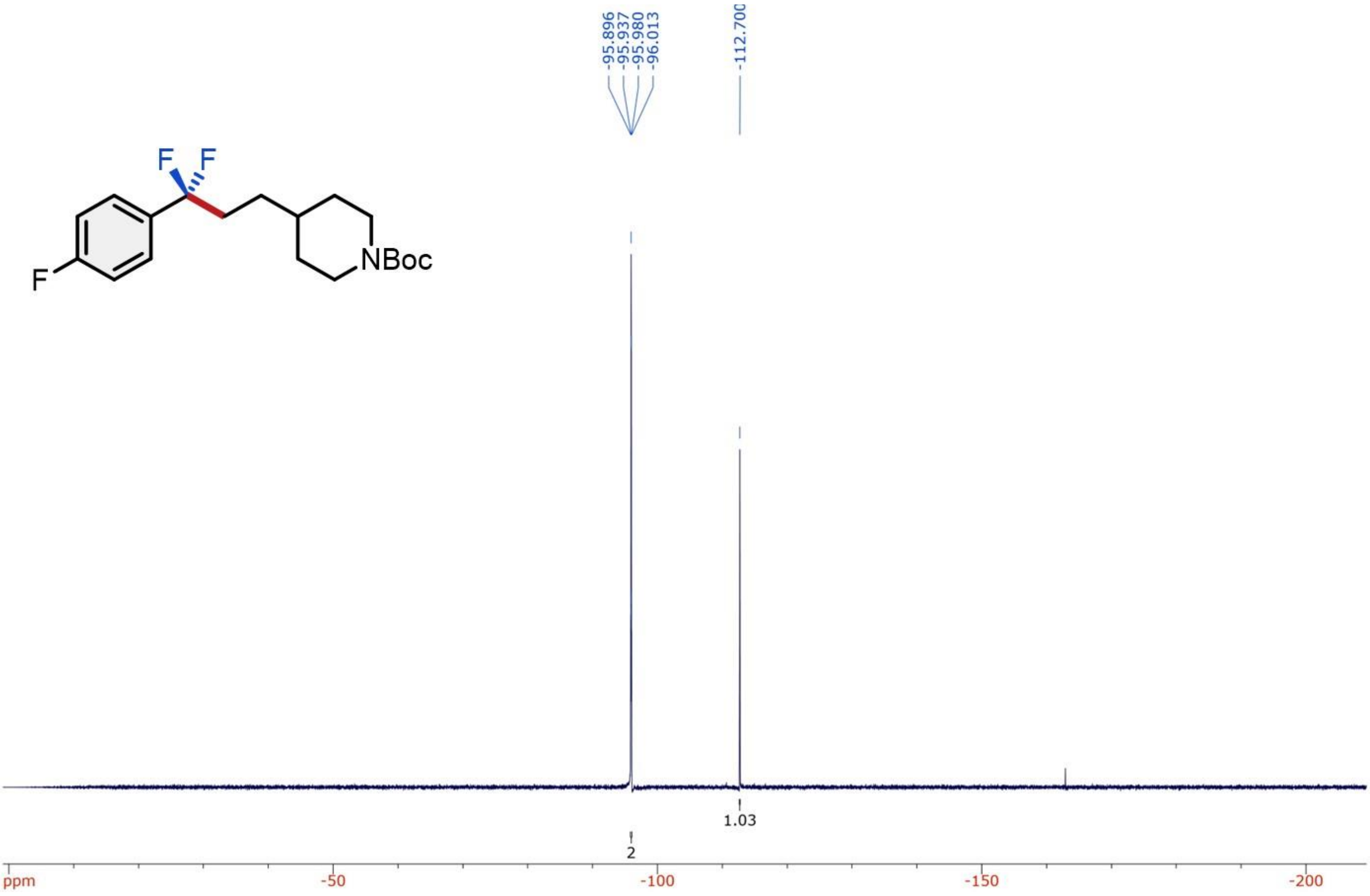

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