Electronic Supplementary Information

Highly C-selective difluoromethylation of β-ketoesters by using TMSCF2Br/lithium hydroxide/N,N,N-trimethylhexadecan-1-ammonium bromide

Jiandong Wang,[a] Etsuko Tokunaga,[a] Norio Shibata*[a,b]

[a] Department of Nanopharmaceutical Sciences & Department of Life Science and Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan
[b] Institute of Advanced Fluorine-Containing Materials, Zhejiang Normal University, 688 Yingbin Avenue, 321004 Jinhua, China.
nozshiba@nitech.ac.jp

contents

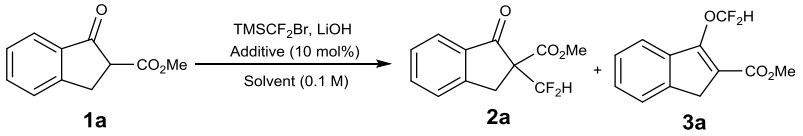
1. General information:

All reactions were performed in a flame-dried glassware (10 mL) under positive pressure of nitrogen unless mentioned otherwise. Solvents were transferred via syringe and were introduced into reaction vessels though a rubber septum. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and $KMnO_4$ in water/heat. Column chromatography was carried out on columns packed with flash silica gel (60N spherical neutral size 40-50 μm). The ^{1}H-NMR (300 MHz), ^{19}F-NMR (659 MHz or 282 MHz), ^{13}C-NMR (125 MHz or 175 MHz) spectra for solution in $CDCl_3$ were recorded on a Buruker Avance 500, a Varian Mercury 300 and Jeol 700 NMR spectrometers. Chemical shifts (δ) are expressed in ppm downfield from internal TMS (δ = 0.00) as an internal standard. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A (EI-MS) and SHIMAZU LCMS-2020 (ESI-MS). High resolution mass spectrometry (HRMS) was recorded on a Waters Synapt G2 HDMS (ESI-MS) with a TOF analyzer. Solvents were dried and distilled before use.

2. General procedure for difluoromethylation of β-keto esters 1

The solution of β-ketoesters **1** (0.1 mmol), base (0.3 mmol), ammonium salts (additive) such as hexadecyltrimethylammonium bromide (10 mol%) in 1.0 mL dry solvent, was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (0.3 mmol) was added slowly, and the reaction mixture was monitored by TLC and upon the completion of the reaction at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to crude ^{19}F-NMR to give the C/O isomer ratio (trifluoromethyl benzene 8.2 μL as internal standard). Subsequently, the desired difluoromethylated β-ketoesters **2** can be purified by chromatography on silica gel (hexane/ethyl acetate).

3. Table S-1 Optimization of Difluoromethylation of β-ketoesters **1a**



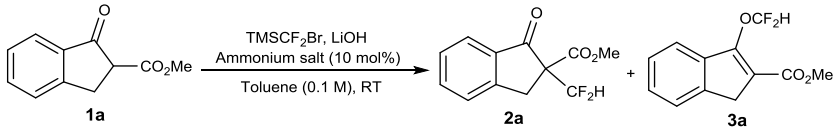
1a **2a** **3a**

Entry	$TMSCF_2Br$ (equiv)	LiOH (equiv)	Additive[a] (Ammonium salts)	*T* (ºC)	Solvent	Time (h)	Yield[b] (%)	C/O[c]
1	2.0	3.0	A-1	RT	DCM	16	45	98:2
2	2.0	3.0	A-2	RT	DCM	24	67	95:5
3	2.0	3.0	A-3	RT	DCM	24	29	92:8
4	2.0	3.0	A-4	RT	DCM	24	30	87:13
5	2.0	3.0	A-5	RT	DCM	24	33	90:10
6	2.0	3.0	A-1	RT	Toluene	16	77	96:4
7	2.0	3.0	---	RT	Toluene	26	66	92:8
8	2.0	3.0	A-1	-20	Toluene	24	64	91:9
9	2.0	3.0	A-1	50	Toluene	6	47	95:5
10	1.2	3.0	A-1	RT	Toluene	24	31	90:10
11	3.0	3.0	A-1	RT	Toluene	4	90	98:2
12	3.0	3.0	---	RT	Toluene	16	80	95:5
13	3.0	3.0	---	RT	DCM	24	80	95:5
14	4.0	3.0	A-1	RT	Toluene	3	87	97:3
15	3.0	2.0	A-1	RT	Toluene	4	87	97:3
16	2.0	1.5	A-1	RT	Toluene	24	70	88:12
17	2.0	4.0	A-1	RT	Toluene	3	46	95:5
18	3.0	3.0	A-1	RT	Toluene (0.05 M)	4	89	97:3
19	3.0	3.0	A-1	RT	Hexane	10	52	91:9
20	3.0	3.0	A-1	RT	1,4-dioxane	10	53	86:17
21	3.0	3.0	A-1	RT	Et_2O	10	57	78:22
22	3.0	3.0	A-1	RT	CH_3CN	10	10	89:11
23	3.0	3.0	A-1	RT	DMF	12	50	97:3
24	3.0	3.0	A-1	RT	DMSO	12	0	ND

[a] Additive (Ammonium salts): **A-1** = Hexadecyltrimethylammonium bromide; **A-2** = tetra-*n*-butylammonium bromide; **A-3** = didecyldimethylammonium bromide; **A-4** = Methyl tri-octylammonium chloride; **A-5** = Tetrabutylammonium iodide. [b] Yields of **2a** were determined by crude ^{19}F-NMR and trifluoromethylbenzene as internal standard. [c] The C/O ratio of difluoromethylated β-ketoesters **2a** and **3a** was confirmed by crude ^{19}F-NMR

After screening additives (ammonium salts)(entries 1-7, and entries 11-13), reaction temperature (entries 6-9), the equivalent of $TMSCF_2Br$ and activator LiOH (entries 10-17), reaction concentration (entry 18), and reaction solvents (entries 19-24), the combination of β-ketoesters **1**/ $TMSCF_2Br$ (3.0 equiv)/ LiOH (3.0 equiv)/ Additive-1 (**A-1**, hexadecyltrimethylammonium bromide, 10 mol%) in toluene (0.1 M) at room temperature for 4 hours, was selected as the optimized reaction condition. Additionally, adding ammonium bromide **A-1** as additive can shorten the reaction time effectively and have slight positive effect on yields and regionselectivity (entry 6 vs entry 7, entry 11 vs entries 12-13).

4. Table S2 The function of ammonium salt in controlling C/O selectivity[a,b]



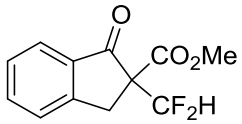
Entry	$TMSCF_2Br$ (equiv)	LiOH (equiv)	Ammonium salt (10 mol%)	Time (h)	Yield[a] (%)	C/O[b]
1	2.0	3.0	---	26	66	92:8
2	2.0	3.0	$CH_3(CH_2)_{15}(CH_3)_3NBr$	16	77	96:4
3	2.0	3.0	$(n\text{-Bu})_4NBr$	16	54	93:7
4	2.0	3.0	$(n\text{-Bu})_4NCl$	16	53	90:10
5	2.0	3.0	$(n\text{-Bu})_4NI$	16	57	88:12
6	2.0	3.0	$(n\text{-Bu})_4N(ClO_4)$	16	54	92:8
7	2.0	3.0	$(n\text{-Bu})_4N(PF_6)$	16	66	91:9
8	2.0	3.0	$(n\text{-Bu})_4N(NO_3)$	16	29	93:7
9	3.0	3.0	---	16	80	95:5
10	3.0	3.0	$CH_3(CH_2)_{15}(CH_3)_3NBr$	4	90	98:2
11	3.0	3.0	$(n\text{-Bu})_4NBr$	4	80	96:4
12	3.0	3.0	$(n\text{-Bu})_4NCl$	4	72	96:4
13	3.0	3.0	$(n\text{-Bu})_4NI$	4	87	97:3
14	3.0	3.0	$(n\text{-Bu})_4N(NO_3)$	4	46	96:4
15[c]	3.0	3.0	$CH_3(CH_2)_{15}(CH_3)_3NBr$	4	90	98:2

[a] Reaction was careered out as follows; $TMSCF_2Br$ was added after 10 min mixing of **1a** and LiOH in the presence or absence of ammonium salts in 1.0 mL toluene. Yields of **2a** were determined by crude ^{19}F-NMR and trifluoromethylbenzene as internal standard.
[b] The C/O ratio of difluoromethylated β-ketoesters **2a** and **3a** was confirmed by crude ^{19}F-NMR
[c] The simultaneous addition of $TMSCF_2Br$ and LiOH into the solution of **1a** and ammonium bromide in 1.0 mL toluene.

Evaluating the function of ammonium salt were shown on **Table S1** (entries 1-7) and **Table S2**:
(**1)**. When 2.0 equiv of $TMSCF_2Br$ was used in DCM or toluene, the ammonium salts with bromide counter ion showed higher C/O control than other anions such as Cl^-, I^-, ClO_4^-, PF_6^- and NO_3^- (**Table S1**, entries 1-7 and **Table S2**, entries 2-8); **(2)**. When 3.0 equivalent of $TMSCF_2Br$ was used in toluene, the halogen-based anions gave similar results with minor difference both in yield and selectivity (**Table S2**, entries 11-14) and tetrabutylammonium nitrate gave moderate yield (46%); **(3)**. Adding hexadecyltrimethylammonium bromide as additive can shorten the reaction time to 4 hours, but only slightly increase both in the yield and C/O selectivity can be observed (**Table S2**, entries 1-2, entries 9-10) comparing to omitting the additive. For instance, when 2.0 equiv of $TMSCF_2Br$ was used, comparing to the absence of additive (66% yield, C/O = 92:8), the desired difluoromethylated product **2a** was obtained in 77% yield with high C/O control (C/O = 96:4). Meanwhile, although high yield (90%) with better C/O control (C/O = 98:2) was observed when 3.0 equivalent of $TMSCF_2Br$ was used, good result both in yield (80%) and selectivity (C/O = 95:5) also can be found when omitting the additive. The results above indicated that the adding of ammonium salt probably prompted the generation of difluorocarbene from $TMSCF_2Br$, thereby accelerating the difluoromethylation process However, the exact role of ammonium salts and their bromide counter ion was still unclear.

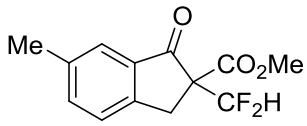
5. The preparation of difluoromethylated β-ketoesters 2a-u

Methyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2a**[1,2,3]



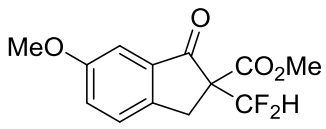
The solution of methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1a** (19.1 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2a** (18.5 mg, 77% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 6.60 (t, *J* = 55.2 Hz, 1H), 3.79 (s, 3H), 3.56 (ABq, J_{AB} = 17.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.0 (dd, *J* = 287.7, 55.1 Hz, 1F), -129.3 (dd, *J* = 287.8, 55.4 Hz, 1F).

Methyl 2-(difluoromethyl)-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2b**[1,2]



The solution of methyl 6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1b** (20.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2b** (18.5 mg, 71% yield) as white solid, Mp 65.0-66.1 °C. ^{1}H NMR (300 MHz, CDC_3) δ 7.57 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 6.58 (t, *J* = 55.2 Hz, 1H), 3.78 (s, 3H), 3.58 (ABq, J_{AB} = 17.6 Hz, 2H), 2.41 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.06 (dd, *J* = 287.6, 55.1 Hz, 1F), -129.48 (dd, *J* = 287.6, 55.4 Hz, 1F).

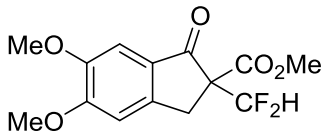
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2c**[1,2]



The solution of methyl 6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1c** (22.0 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the

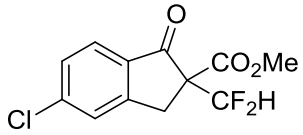
reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2c** (20.0 mg, 74% yield) as white solid, Mp 76.0-77.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 1H), 7.29–7.23 (m, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.58 (t, *J* = 55.2 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.55 (ABq, J_{AB} = 17.3 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.04 (dd, *J* = 287.6, 55.1 Hz, 1F), -129.53 (dd, *J* = 287.6, 55.4 Hz, 1F).

Methyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2d**[1,2]



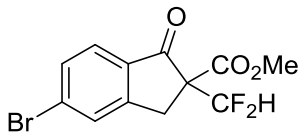
The solution of methyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1d** (25.0 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 20:1) to afford **2d** (26.0 mg, 85% yield) as white solid, Mp 101.6-103.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.97 (s, 1H), 6.58 (t, *J* = 55.3 Hz, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H), 3.53 (ABq, J_{AB} = 17.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.19 (dd, *J* = 286.8, 55.2 Hz, 1F), -129.76 (dd, *J* = 286.8, 55.5 Hz, 1F).

Methyl 5-chloro-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2e**[1,2]



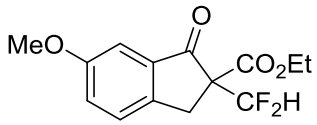
The solution of methyl 5-chloro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1e** (22.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 20:1) to afford **2e** (17.3 mg, 63% yield) as yellow solid, Mp 86.4-87.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 1H), 7.57 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 6.58 (t, *J* = 55.1 Hz, 1H), 3.80 (s, 3H), 3.62 (ABq, J_{AB} = 17.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -125.98 (dd, *J* = 288.3, 54.9 Hz, 1F), -129.17 (dd, *J* = 288.3, 55.3 Hz, 1F).

Methyl 5-bromo-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2f**[1,2]



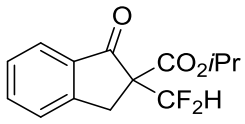
The solution of methyl 5-bromo-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1f** (26.9 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2f** (22.2 mg, 68% yield) as yellow solid, Mp 85.3-86.3 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 6.57 (t, *J* = 55.1 Hz, 1H), 3.79 (s, 3H), 3.61 (ABq, J_{AB} = 17.8, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -125.95 (dd, *J* = 288.3, 54.9 Hz, 1F), -129.15 (dd, *J* = 288.3, 55.3 Hz, 1F).

Ethyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2g**



The solution of ethyl 6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1g** (23.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2g** (23.0 mg, 81% yield) as colorless oil. MS (ESI) calcd for $C_{14}H_{14}F_2NaO_4^+$ [$(M+Na)^+$]: 307.0758 found 307.0765; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.58 (t, *J* = 55.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.54 (ABq, J_{AB} = 17.3, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.18 (dd, *J* = 287.3, 55.1 Hz, 1F), -129.46 (dd, *J* = 287.3, 55.5 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8 (d, *J* = 6.9 Hz), 166.0 (d, *J* = 12.2 Hz), 159.8, 147.1, 135.3 (d, *J* = 3.7 Hz), 127.2, 125.8, 115.5 (dd, *J* = 247.2, 241.0 Hz), 105.9, 65.4 (dd, *J* = 23.9, 21.0 Hz), 62.7, 55.7, 29.3, 13.9; IR (neat): 3012, 2944, 1745, 1710, 1594, 1455, 1371, 1259, 1025, 765 cm^{-1}.

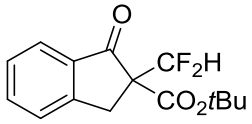
isopropyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2h**[1,2]



The solution of isopropyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1h** (21.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was diluted with ethyl acetate,

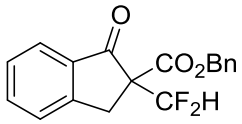
and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2h** (22.9 mg, 85% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 6.59 (t, *J* = 55.3 Hz, 1H), 5.19–4.99 (m, 1H), 3.62 (ABq, J_{AB} = 17.6, 2H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.35 (ddd, *J* = 287.2, 55.1, 7.4 Hz, 1F), -129.18 (ddd, *J* = 287.3, 55.6, 7.3 Hz, 1F).

tert-butyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2i**[1]



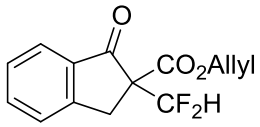
The solution of tert-butyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1i** (23.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2i** (23.9 mg, 83% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 6.53 (t, *J* = 55.4 Hz, 1H), 3.58 (ABq, J_{AB} = 17.5, 2H), 1.45 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.63 (dd, *J* = 286.8, 55.1 Hz, 1F), -128.77 (dd, *J* = 286.8, 55.8 Hz, 1F).

Benzyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2j**[1]



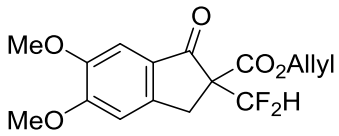
The solution of benzyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1j** (26.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford **2j** (24.1 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.38–7.26 (m, 5H), 6.62 (t, *J* = 55.2 Hz, 1H), 5.22 (d, *J* = 2.5 Hz, 2H), 3.65 (ABq, J_{AB} = 17.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -125.86 (dd, *J* = 287.8, 55.1 Hz, 1F), -129.12 (dd, *J* = 287.8, 55.4 Hz, 1F).

Allyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2k**[1]



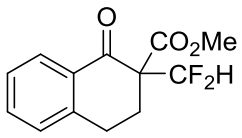
The solution of allyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1k** (21.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 100:1) to give **2k** (21.8 mg, 80% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 55.2 Hz, 1H), 5.95–5.73 (m, 1H), 5.37–5.15 (m, 2H), 4.68 (d, *J* = 5.6 Hz, 2H), 3.65 (ABq, J_{AB} = 17.6, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -125.95 (dd, *J* = 287.7, 55.1 Hz, 1F), -129.25 (dd, *J* = 287.8, 55.4 Hz, 1F).

Allyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2l**



The solution of allyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1l** (27.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2l** (28.9 mg, 88% yield) as colorless oil. MS (ESI-TOF) calcd for $C_{16}H_{16}F_2NaO_5^+$ [$(M+Na)^+$]: 349.0863 found 349.0870. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.96 (s, 1H), 6.59 (t, *J* = 55.3 Hz, 1H), 5.96–5.74 (m, 1H), 5.40–5.16 (m, 2H), 4.68 (dt, *J* = 5.5, 1.3 Hz, 2H), 4.00 (s, 3H), 3.90 (s, 3H), 3.53 (ABq, J_{AB} = 17.4, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.12 (dd, *J* = 286.8, 55.2 Hz, 1F), -129.71 (dd, *J* = 286.8, 55.5 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9 (d, *J* = 7.0 Hz), 166.0 (d, *J* = 12.3 Hz), 156.7, 150.0, 149.9, 130.9, 126.6 (d, *J* = 3.8 Hz), 118.9, 115.5 (dd, *J* = 246.9, 241.1 Hz), 107.2, 105.1, 66.7, 65.1 (dd, *J* = 24.2, 20.6 Hz), 56.5, 56.2, 29.59 (d, *J* = 2.6 Hz). IR (neat): 3012, 2944, 2844, 1745, 1710, 1594, 1445, 1371, 1259, 1232, 1120, 1085, 765 cm^{-1}.

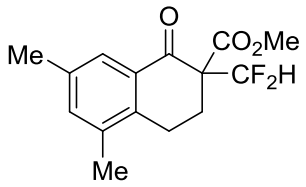
Methyl 2-(difluoromethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2m**[1]



The solution of methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **1m** (20.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl

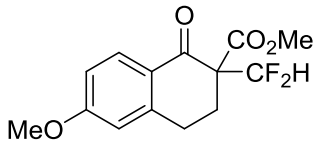
acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2m** (21.6 mg, 83% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.9 Hz, 1H), 7.53 (td, *J* = 7.5, 1.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 6.60 (t, *J* = 55.3 Hz, 1H), 3.75 (s, 3H), 3.32 (ddd, *J* = 16.7, 11.5, 5.0 Hz, 1H), 3.07-2.98 (m, 1H), 2.71-2.62 (m, 1H), 2.46 (ddd, *J* = 14.0, 11.5, 5.2 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -127.33 (dd, *J* = 283.3, 55.1 Hz, 1F), -131.80 (dd, *J* = 283.3, 55.5 Hz, 1F).

Methyl 2-(difluoromethyl)-5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2n**



The solution of methyl 5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **1n** (23.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2n** (22.9 mg, 81% yield) as white solid, 89.5-91.2 ºC. MS (ESI) calcd for $C_{15}H_{16}F_2NaO_3^+$ [(M+Na)$^+$]: 305.0960 found 305.0966. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.23 (s, 1H), 6.59 (t, *J* = 55.3 Hz, 1H), 3.72 (s, 3H), 3.14–2.87 (m, 2H), 2.74–2.62 (m, 1H), 2.47–2.34 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -127.60 (dd, *J* = 282.9, 55.1 Hz, 1F), -132.26 (dd, *J* = 282.8, 55.6 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.6 (d, *J* = 6.1 Hz), 166.6 (d, *J* = 8.4 Hz), 139.1, 137.1, 136.5, 136.1, 130.9 (d, *J* = 2.4 Hz), 126.1, 115.8 (dd, *J* = 247.7, 245.5 Hz), 60.3 (t, *J* = 21.4 Hz), 53.2, 22.4 (t, *J* = 3.7 Hz), 21.9, 20.8, 19.2; IR (neat): 2965, 2929, 1745, 1685, 1602, 1467, 1371, 1236, 1072, 738 cm^{-1}.

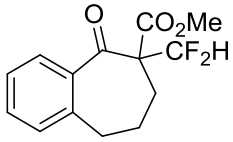
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2o**



The solution of methyl 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **1o** (23.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2o** (26.2 mg, 91% yield) as white solid, Mp 76.1-77.2 ºC. MS (ESI) calcd for $C_{14}H_{14}F_2NaO_4^+$ [(M+Na)$^+$]: 307.0758 found 307.0764. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.61 (t, *J* = 55.4 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.31 (ddd, *J* = 16.7, 11.5, 5.0 Hz, 1H), 3.05 – 2.91 (m, 1H), 2.68 – 2.56 (m, 1H), 2.44 (ddd, *J* = 13.9, 11.5, 5.1

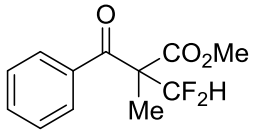
Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -127.53 (dd, *J* = 282.5, 55.2 Hz, 1F), -132.15 (dd, *J* = 282.5, 55.6 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.4 (d, *J* = 6.2 Hz), 167.0 (d, *J* = 9.3 Hz), 164.5, 146.3, 130.9, 124.6 (d, *J* = 2.5 Hz), 116.0 (t, *J* = 246.4 Hz), 113.9, 112.5, 60.54 (t, *J* = 21.6 Hz), 55.6, 53.2, 25.4, 22.99 (t, *J* = 3.8 Hz); IR (neat): 3016, 2944, 1741, 1681, 1606, 1494, 1442, 1168, 1259, 1220, 1072, 892 cm^{-1}.

Methyl 6-(difluoromethyl)-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate **2p**



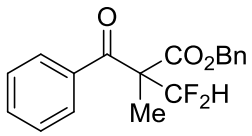
The solution of methyl 5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate **1p** (21.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2p** (21.9 mg, 82% yield) as colorless oil. MS (ESI) calcd for $C_{14}H_{14}F_2NaO_3^+$ [$(M+Na)^+$]: 291.0803 found 291.0810. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H), 7.32–7.24 (m, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.40 (t, *J* = 55.2 Hz, 1H), 3.66 (s, 3H), 3.08–2.81 (m, 2H), 2.55–2.38 (m, 1H), 2.28–2.04 (m, 2H), 2.04–1.84 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.20 (dd, *J* = 266.9, 41.1 Hz, 1F), -127.35 (dd, *J* = 267.0, 41.3 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.2 (d, *J* = 3.9 Hz), 167.3 (dd, *J* = 6.1, 2.1 Hz), 139.1, 138.5, 132.1, 129.3, 129.2, 126.7, 115.9 (t, *J* = 248.9 Hz), 65.6 (t, *J* = 20.0 Hz), 53.1, 32.7, 24.72 (t, *J* = 3.4 Hz), 23.0; IR (neat): 3008, 2952, 2877, 1749, 1625, 1598, 1442, 1243, 1149, 1120, 997 cm^{-1}.

Methyl 2-benzoyl-3,3-difluoro-2-methylpropanoate **2q**



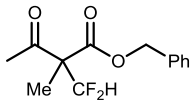
The solution of methyl 2-methyl-3-oxo-3-phenylpropanoate **1q** (19.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2q** (17.1 mg, 70% yield) as colorless oil. MS (ESI) calcd for $C_{12}H_{12}F_2NaO_3^+$ [$(M+Na)^+$]: 265.0647 found 265.0648. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91–7.75 (m, 2H), 7.64–7.53 (m, 1H), 7.50–7.40 (m, 2H), 6.52 (t, *J* = 55.1 Hz, 1H), 3.76 (s, 3H), 1.71 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.82 (dd, *J* = 282.0, 54.8 Hz, 1F), -129.81 (dd, *J* = 282.0, 55.5 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2 (d, *J* = 6.1 Hz), 168.8 (dd, *J* = 6.6, 1.4 Hz), 134.6 (d, *J* = 1.9 Hz), 133.6, 128.8, 128.6, 115.2 (dd, *J* = 250.3, 243.7 Hz), 61.7 (t, *J* = 21.1 Hz), 53.5, 13.9 (dd, *J* = 5.5, 3.3 Hz); IR (neat): 3015, 2948, 1745, 1698, 1583, 1459, 1247, 1081, 997, 694.

Benzyl 2-benzoyl-3,3-difluoro-2-methylpropanoate **2r**



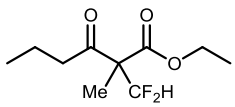
The solution of benzyl 2-methyl-3-oxo-3-phenylpropanoate **1r** (26.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2r** (23.8 mg, 75% yield) as colorless oil. MS (ESI) calcd for $C_{18}H_{16}F_2NaO_3^+$ [$(M+Na)^+$]: 341.0960 found 265.0963. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.29–7.21 (m, 3H), 7.18–7.11 (m, 2H), 6.51 (t, *J* = 55.1 Hz, 1H), 5.18 (s, 2H), 1.70 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.67 (dd, *J* = 282.0, 54.8 Hz, 1F), -129.39 (dd, *J* = 282.0, 55.4 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2 (d, *J* = 6.0 Hz), 168.1 (dd, *J* = 6.4, 1.3 Hz), 134.5 (d, *J* = 1.7 Hz), 134.2, 133.5, 128.7, 128.60, 128.57, 128.5, 128.4, 115.2 (dd, *J* = 250.4, 244.0 Hz), 68.2, 61.8 (t, *J* = 21.0 Hz), 14.1 (dd, *J* = 5.5, 3.3 Hz). IR (neat): 3035, 2944, 1749, 1685, 1587, 1494, 1452, 1388, 1251, 1085, 985, 746, 694 cm^{-1}.

Benzyl 2-(difluoromethyl)-2-methyl-3-oxobutanoate **2s**



The solution of benzyl 2-methyl-3-oxobutanoate **1s** (20.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2s** (15.5 mg, 52% yield) as colorless oil. MS (ESI) calcd for $C_{13}H_{14}F_2NaO_3^+$ [$(M+Na)^+$]: 279.0809 found 279.0815. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 6.37 (t, *J* = 55.1 Hz, 1H), 5.22 (s, 2H), 2.16 (s, 3H), 1.54 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.59 (dd, *J* = 285.7, 55.1 Hz, 1F), -129.28 (dd, *J* = 285.6, 55.0 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.1 (d, *J* = 5.4 Hz), 167.2 (dd, *J* = 7.6, 2.2 Hz), 134.5, 128.6, 128.7, 128.2, 115.0 (dd, *J* = 246.6, 245.7 Hz), 67.9, 63.8 (t, *J* = 21.4 Hz), 26.9 (t, *J* = 1.6 Hz), 12.4 (t, *J* = 4.1 Hz). IR (neat): 2992, 2954, 1735, 1448, 1355, 1263, 1189, 1120, 1064 cm^{-1}.

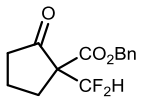
Ethyl 2-(difluoromethyl)-2-methyl-3-oxohexanoate **2t**



The solution of ethyl 2-methyl-3-oxohexanoate **1t** (17.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10

min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2t** (16.8 mg, 74% yield) as colorless oil. MS (ESI) calcd for $C_{10}H_{16}F_2NaO_3^+$ [$(M+Na)^+$]: 245.0960 found 245.0970. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (t, *J* = 55.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.60–2.31 (m, 2H), 1.66–1.55 (m, 2H), 1.52 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.86 (dd, *J* = 284.9, 55.2 Hz, 1F), -129.83 (dd, *J* = 284.8, 55.2 Hz, 1F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5 (d, *J* = 5.3 Hz), 167.5 (dd, *J* = 7.9, 1.9 Hz), 115.2 (dd, *J* = 246.3, 245.1 Hz), 63.6 (t, *J* = 21.2 Hz), 62.3, 40.8, 16.7, 13.9, 13.4, 12.1 (t, *J* = 4.1 Hz). IR (neat): 2962, 2919, 2854, 1727, 1263, 1087 cm^{-1}.

Benzyl 1-(difluoromethyl)-2-oxocyclopentane-1-carboxylate **2u**[1]



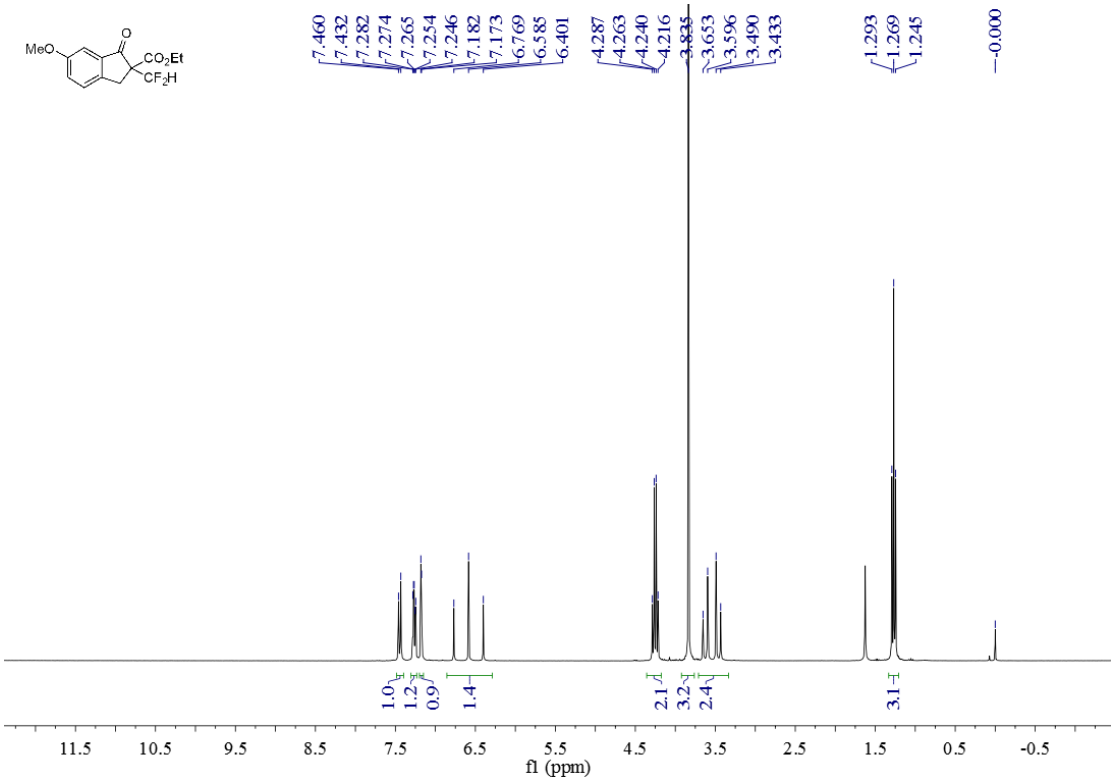
The solution of benzyl 2-oxocyclopentane-1-carboxylate **1u** (21.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), $CH_3(CH_2)_{15}(CH_3)_3NBr$ (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **2r** (7.6 mg, 28% yield) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.28 (m, 5H), 6.37 (t, *J* = 55.4 Hz, 1H), 5.20 (s, 2H), 2.70–2.27 (m, 4H), 2.20–1.83 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.55 (dd, *J* = 288.2, 55.1 Hz, 1F), -128.00 (dd, *J* = 288.3, 55.5 Hz, 1F).

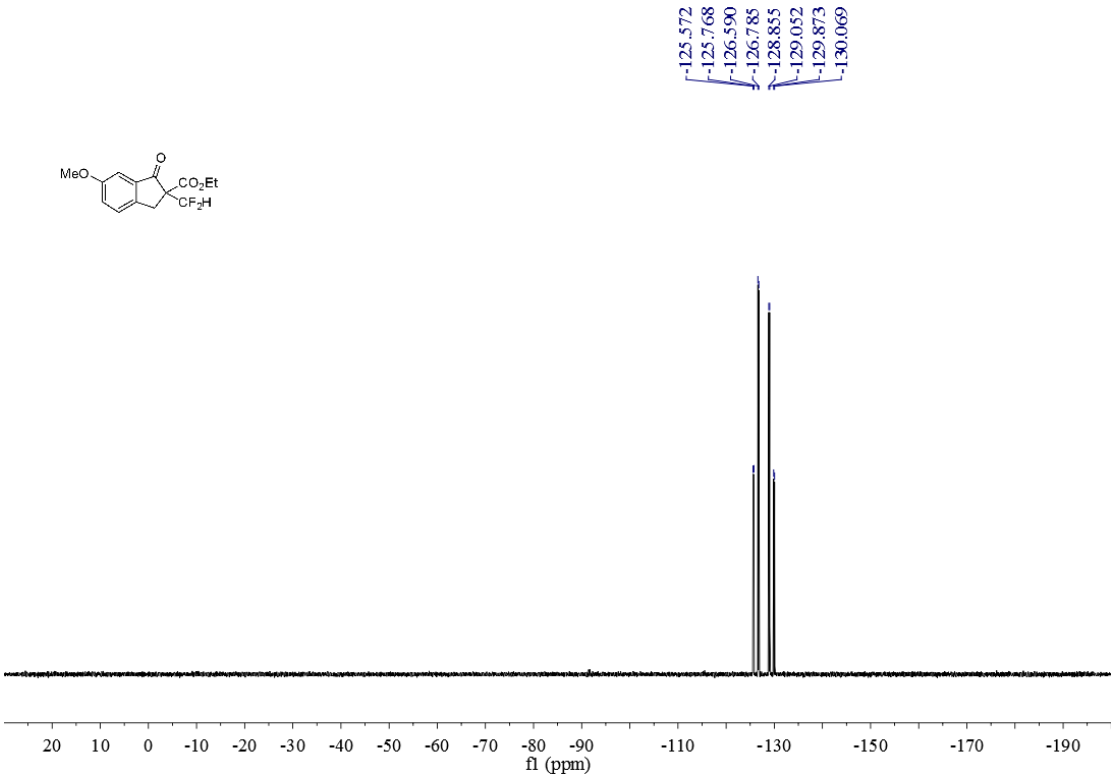
Reference:

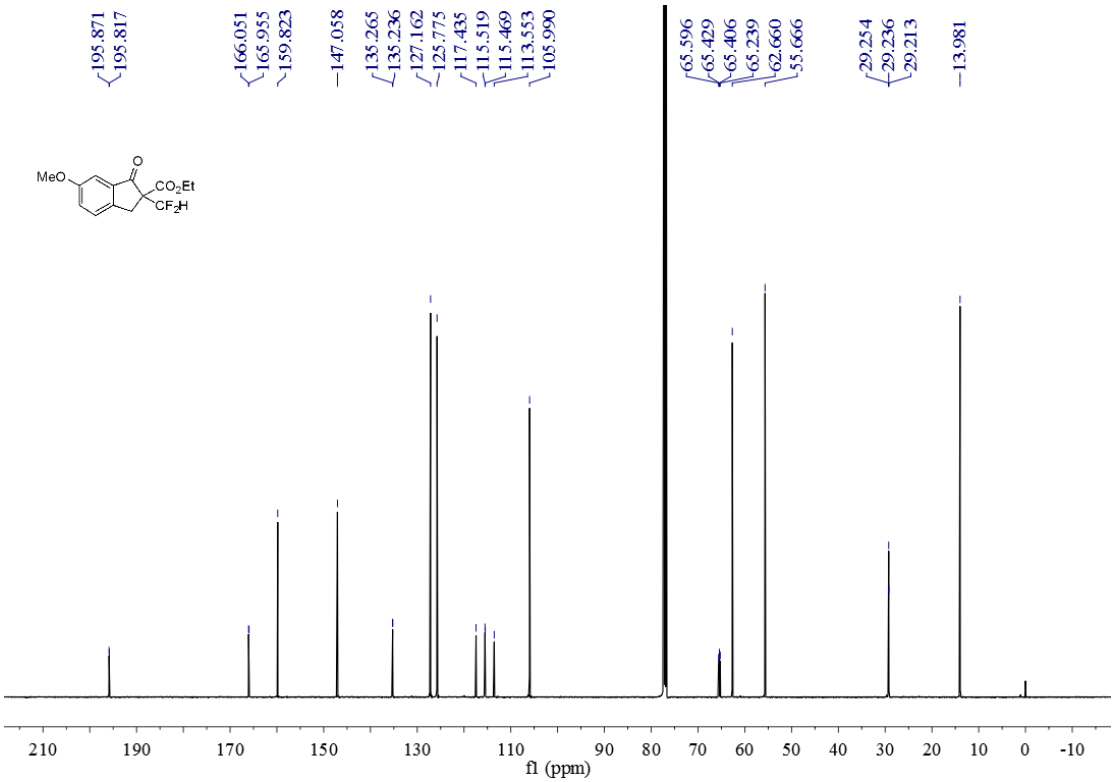
1. G. Liu, X. Wang, X. Lu, X.-H. Xu, E. Tokunaga and N. Shibata, *ChemistryOpen*, 2012, **1**, 227.
2. Y.-D. Yang, X. Lu, G. Liu, E. Tokunaga, S. Tsuzuki and N. Shibata, *ChemistryOpen*, 2012, **1**, 221.
3. Y.-D. Yang, X. Wang, S. Tsuzuki, E. Tokunaga and N. Shibata, *Bull. Korean Chem. Soc.* 2014, **35**, 1851.

6. Copies of ^{1}H, ^{19}F and ^{13}C NMR spectra of unknown compounds (2g, 2l, 2n-t)

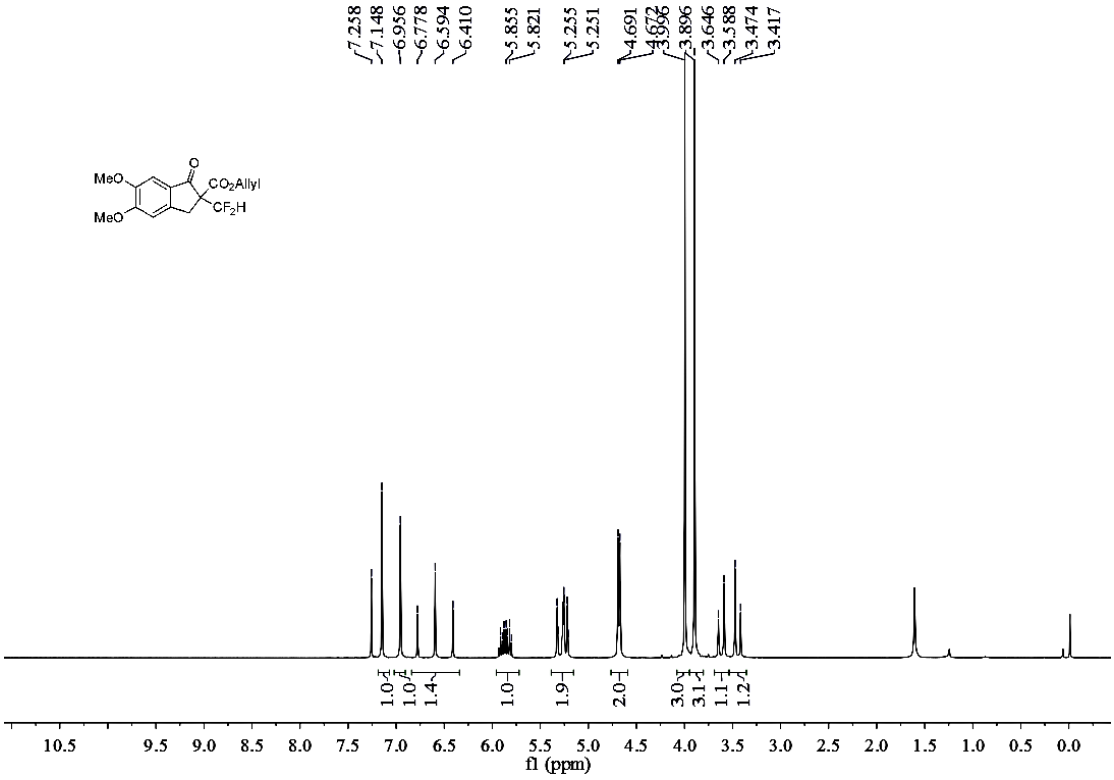
Ethyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2g**

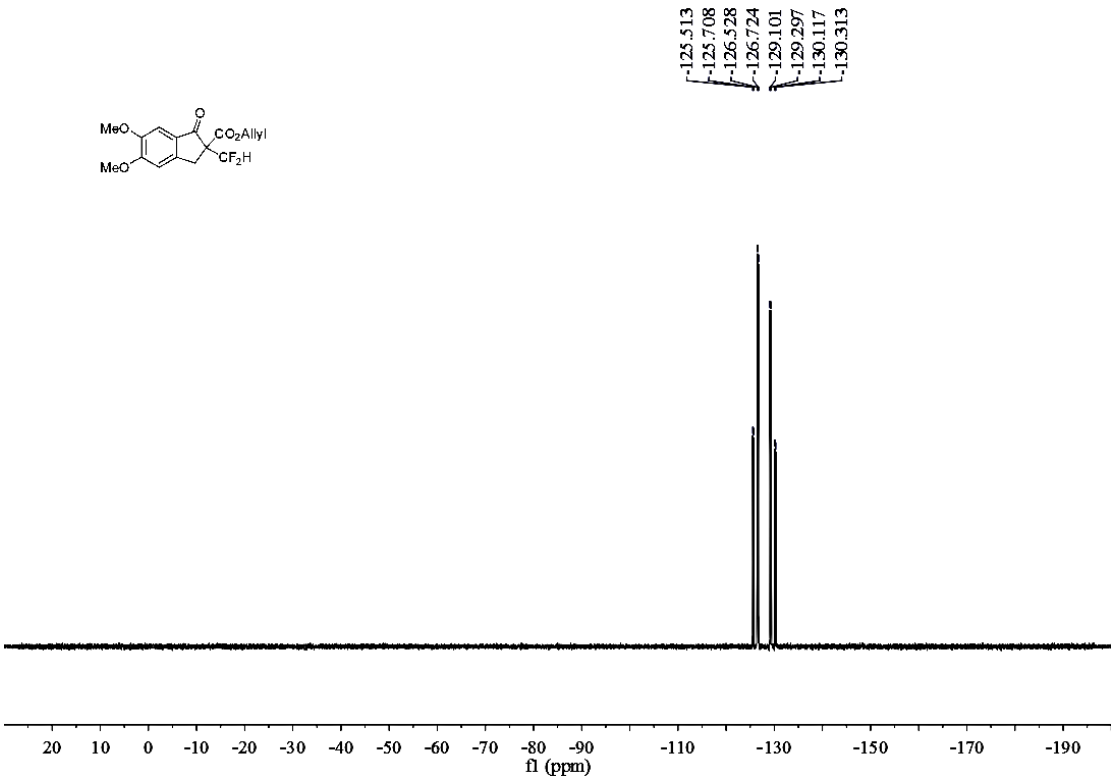


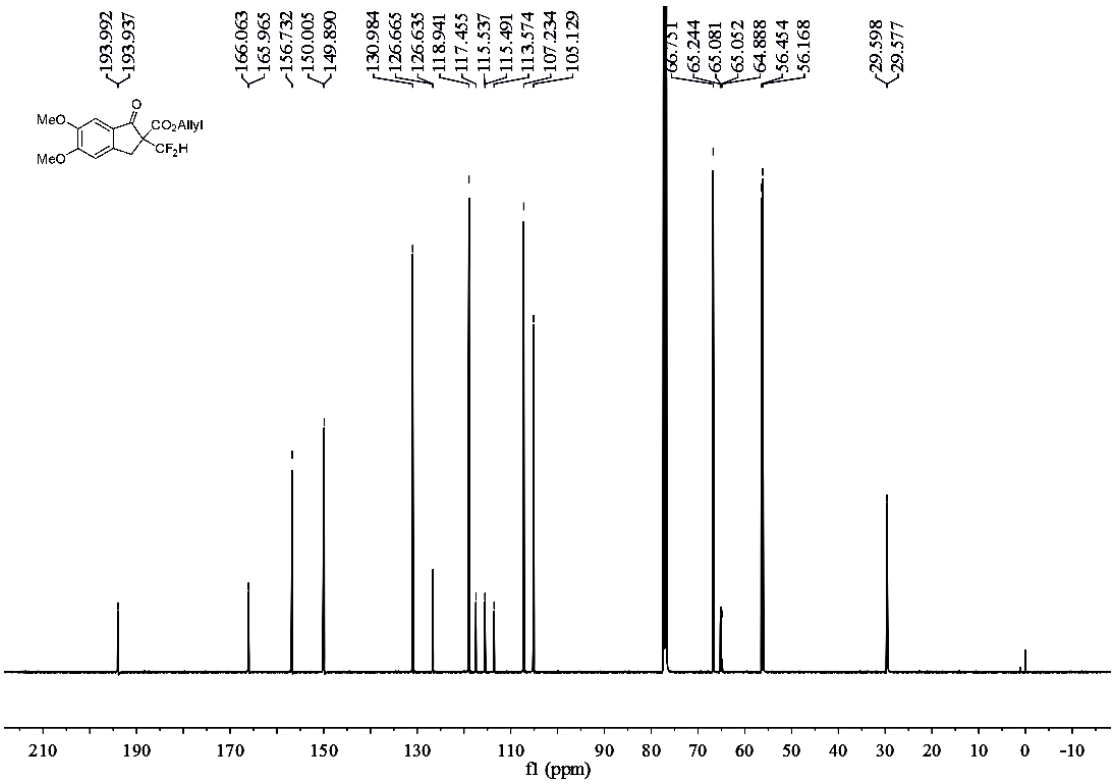




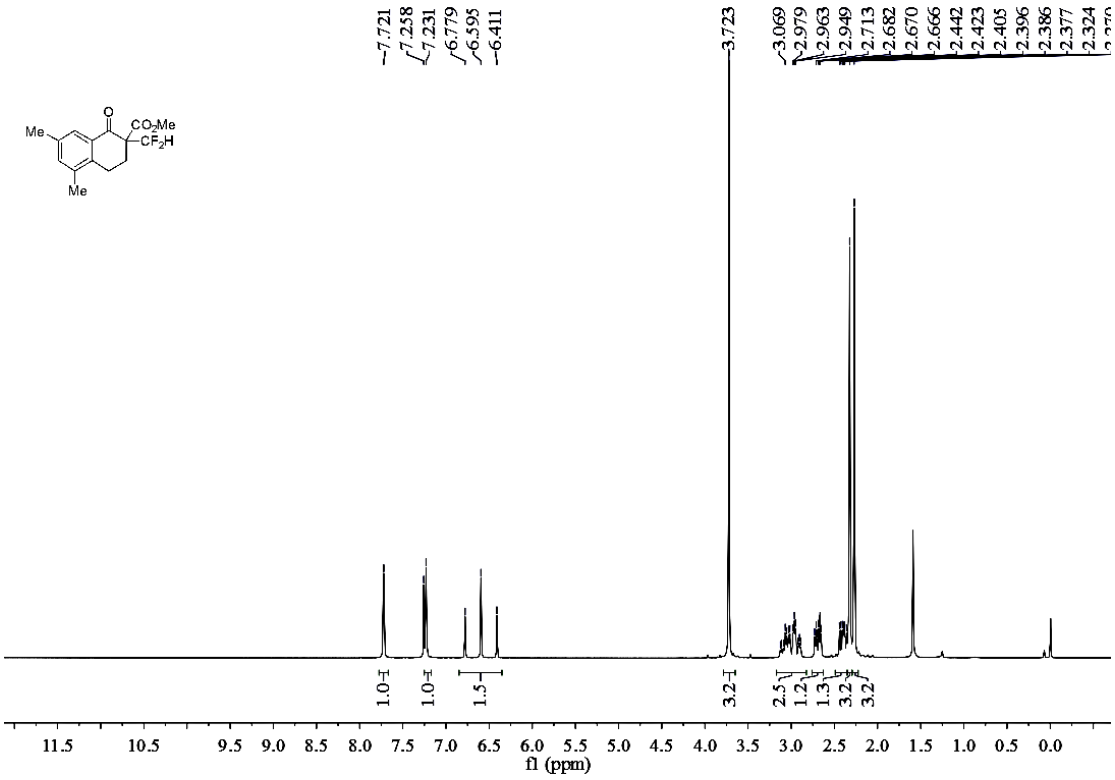
Allyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2l**

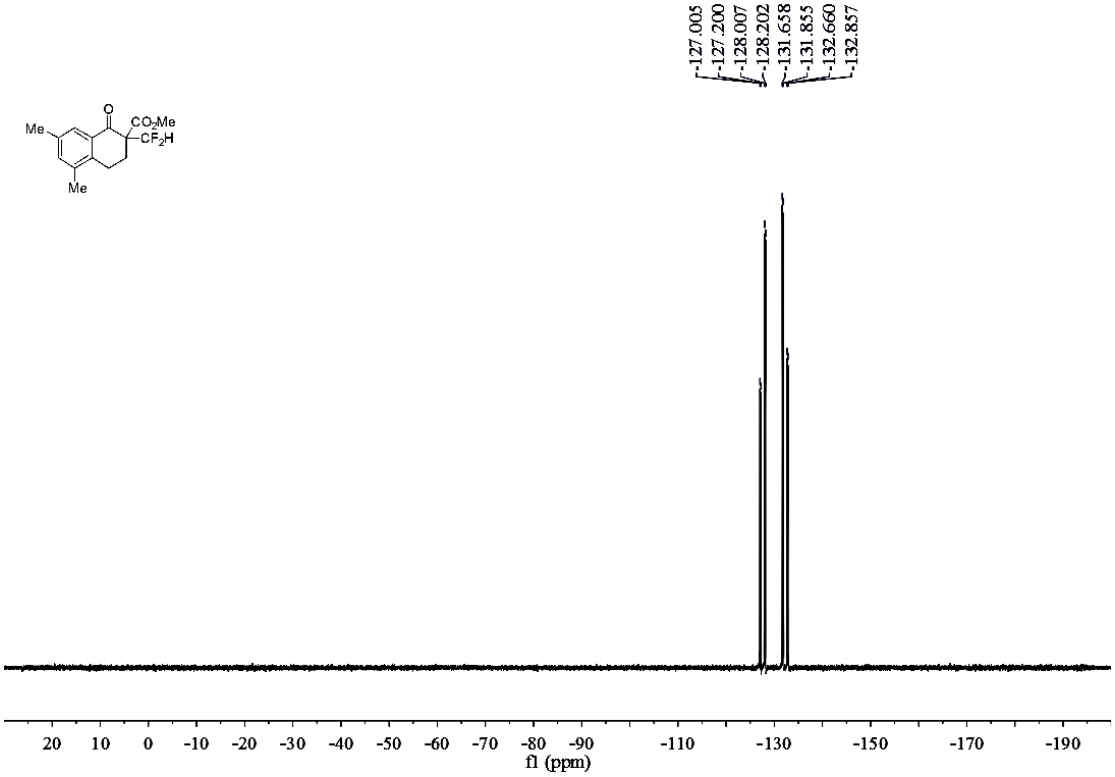


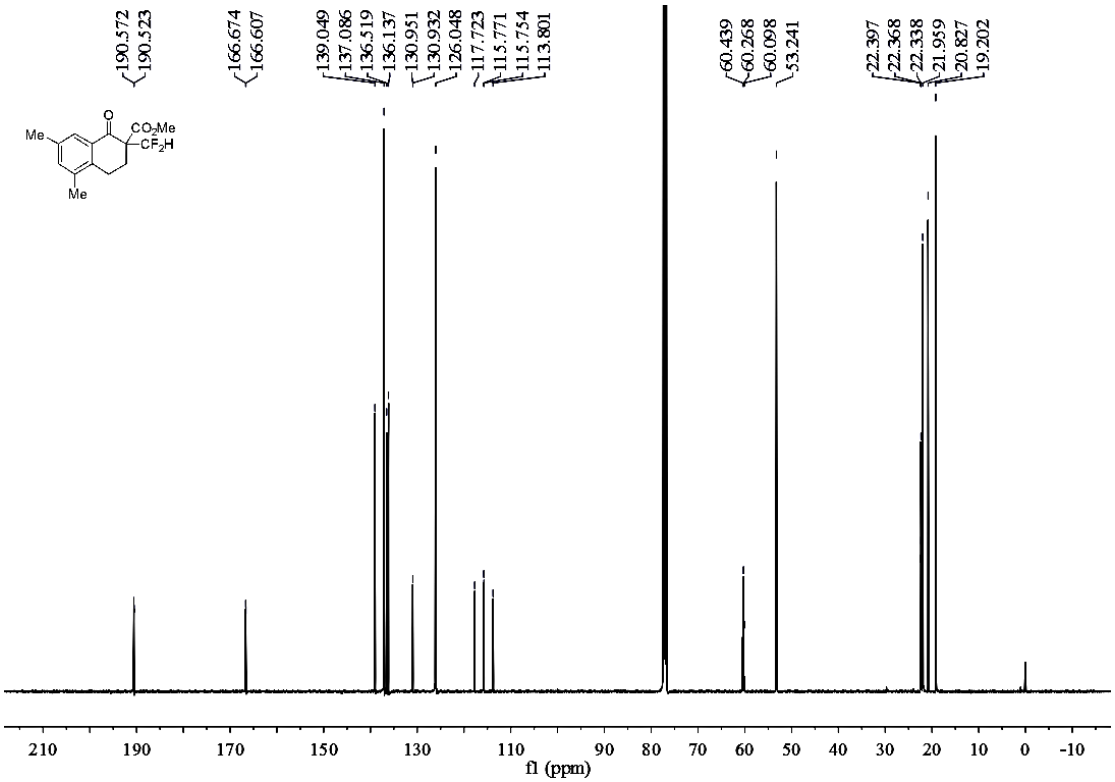

-125.513
-125.708
-126.528
-126.724
-129.101
-129.297
-130.117
-130.313
MeO
MeO
O
CO2Allyl
CF2H
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190
f1 (ppm)


193.992
193.937
166.063
165.965
156.732
150.005
149.890
130.984
126.665
126.635
118.941
117.455
115.537
115.491
113.574
107.234
105.129
65.751
65.244
65.081
65.052
64.888
56.454
56.168
29.598
29.577
MeO
MeO
O
CO2Allyl
CF2H
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

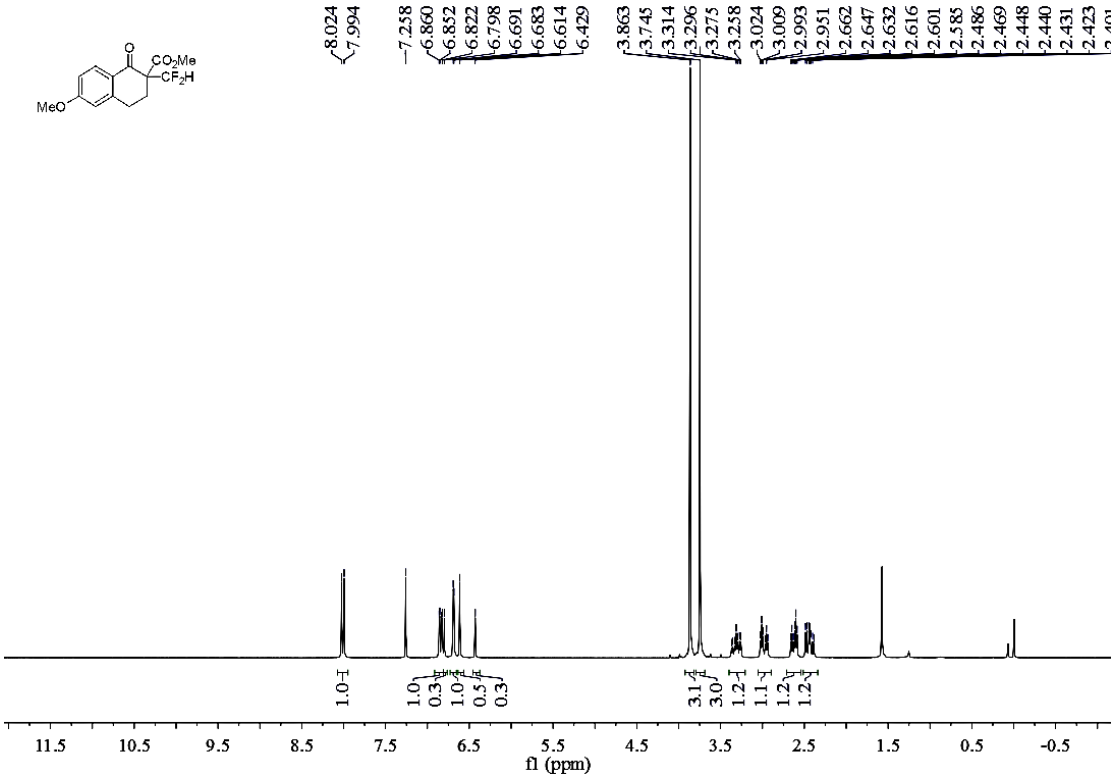
Methyl 2-(difluoromethyl)-5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2n**

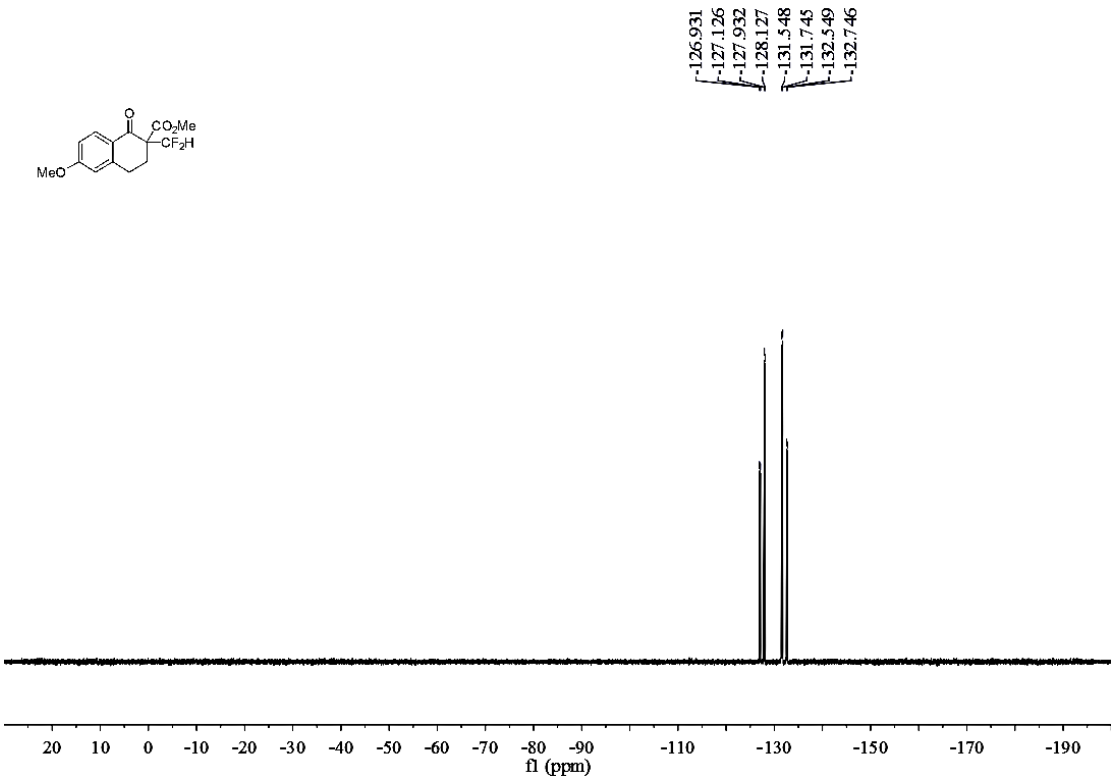


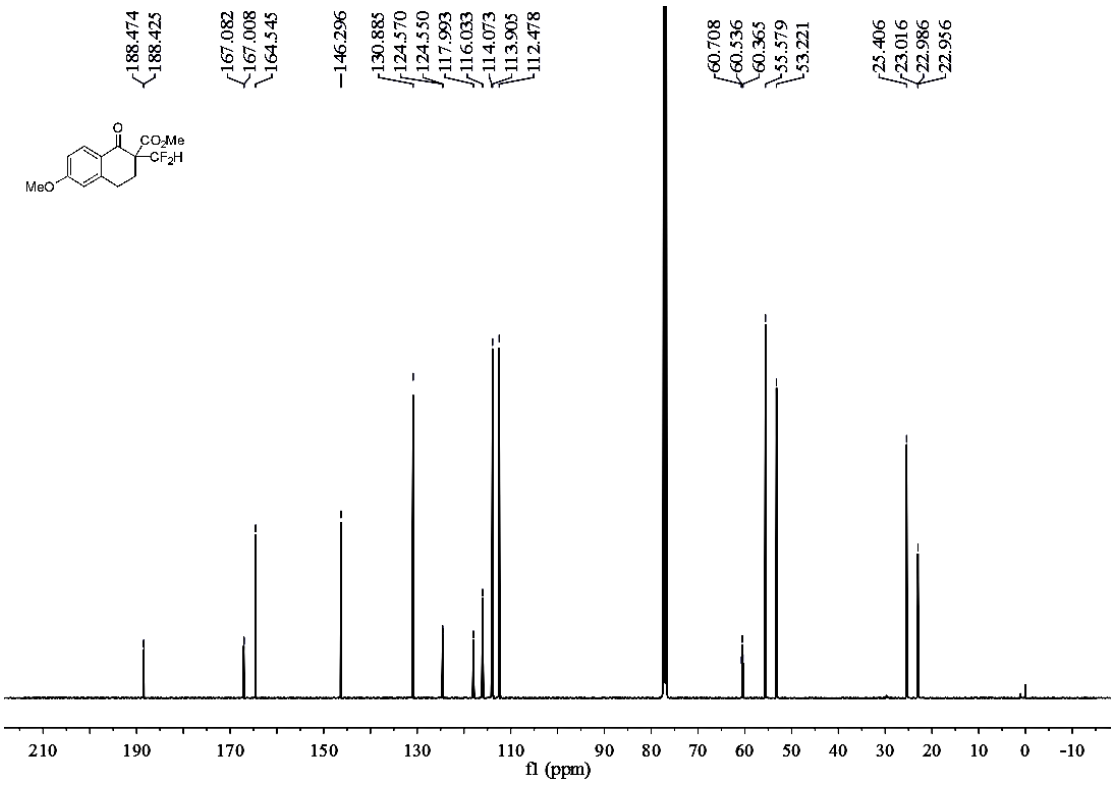




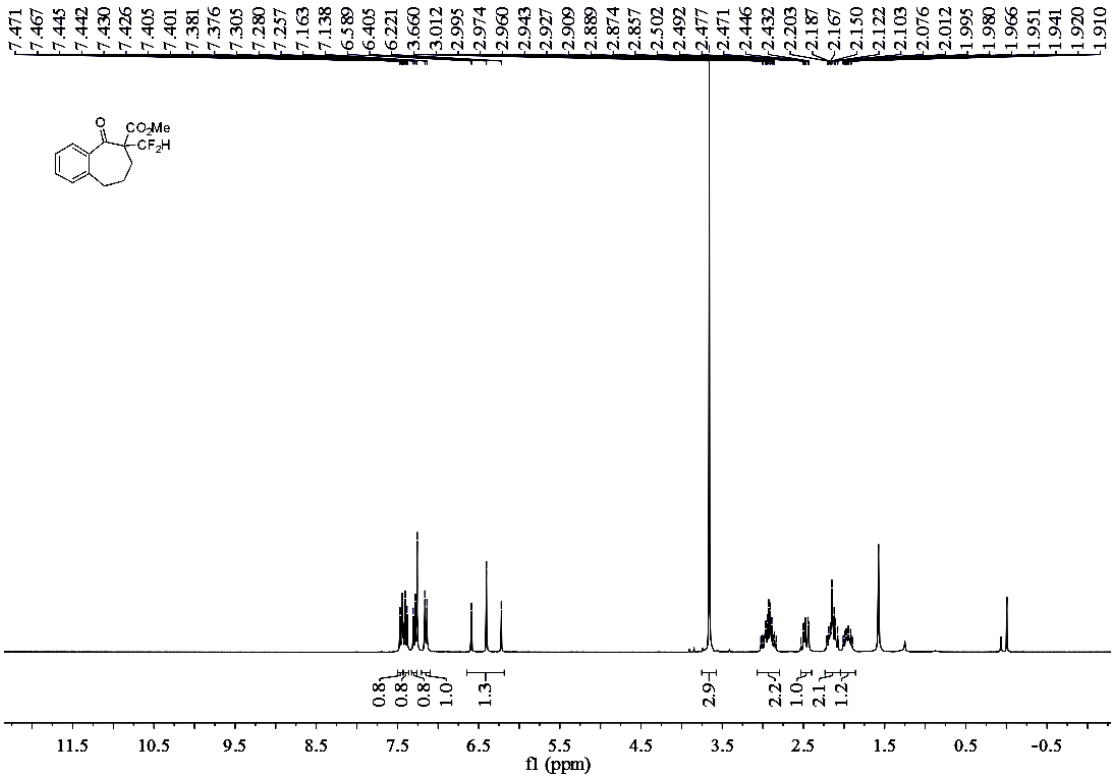
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2o**

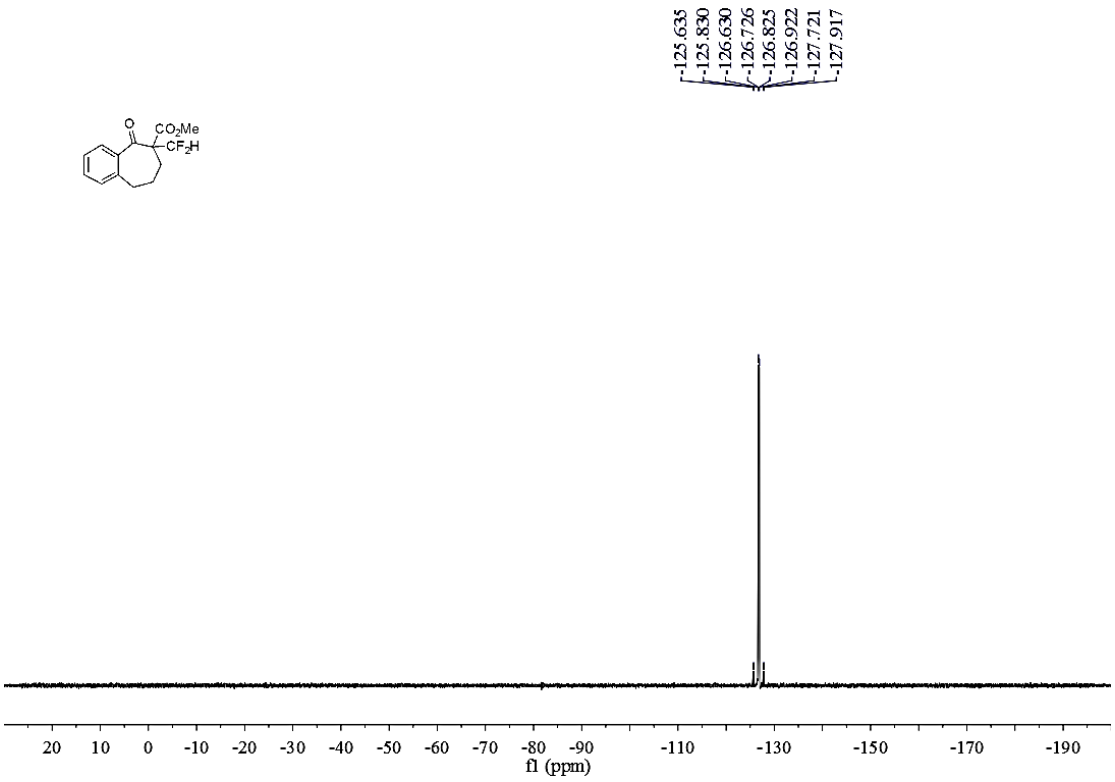


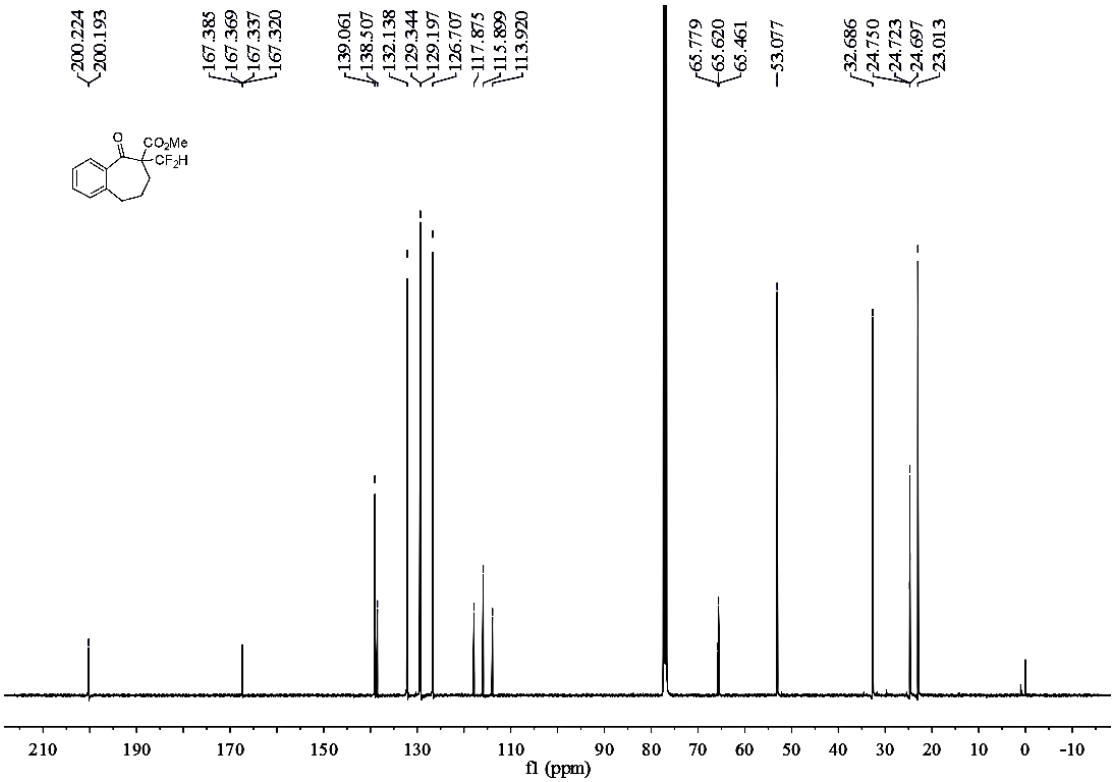

-126.931
-127.126
-127.932
-128.127
-131.548
-131.745
-132.549
-132.746
CO2Me
CF2H
MeO
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190
f1 (ppm)


188.474
188.425
167.082
167.008
164.545
146.296
130.885
124.570
124.550
117.993
116.033
114.073
113.905
112.478
60.708
60.536
60.365
55.579
53.221
25.406
23.016
22.986
22.956
CO2Me
CF2H
MeO
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

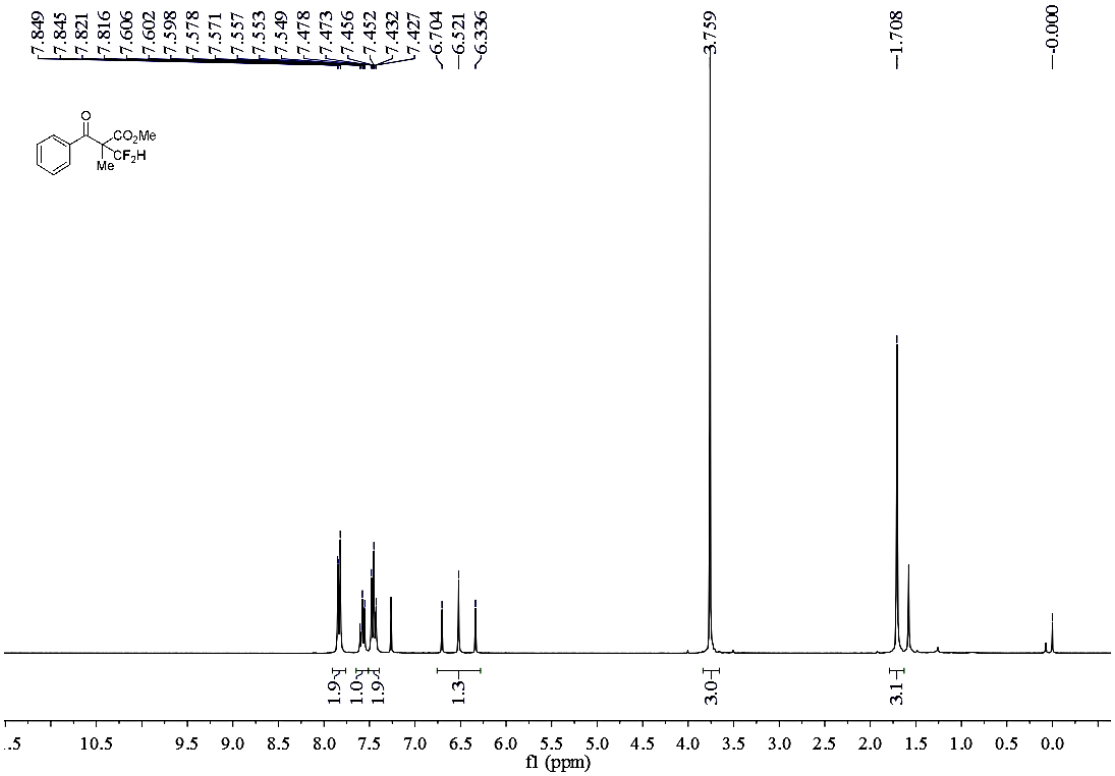
Methyl 6-(difluoromethyl)-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate **2p**

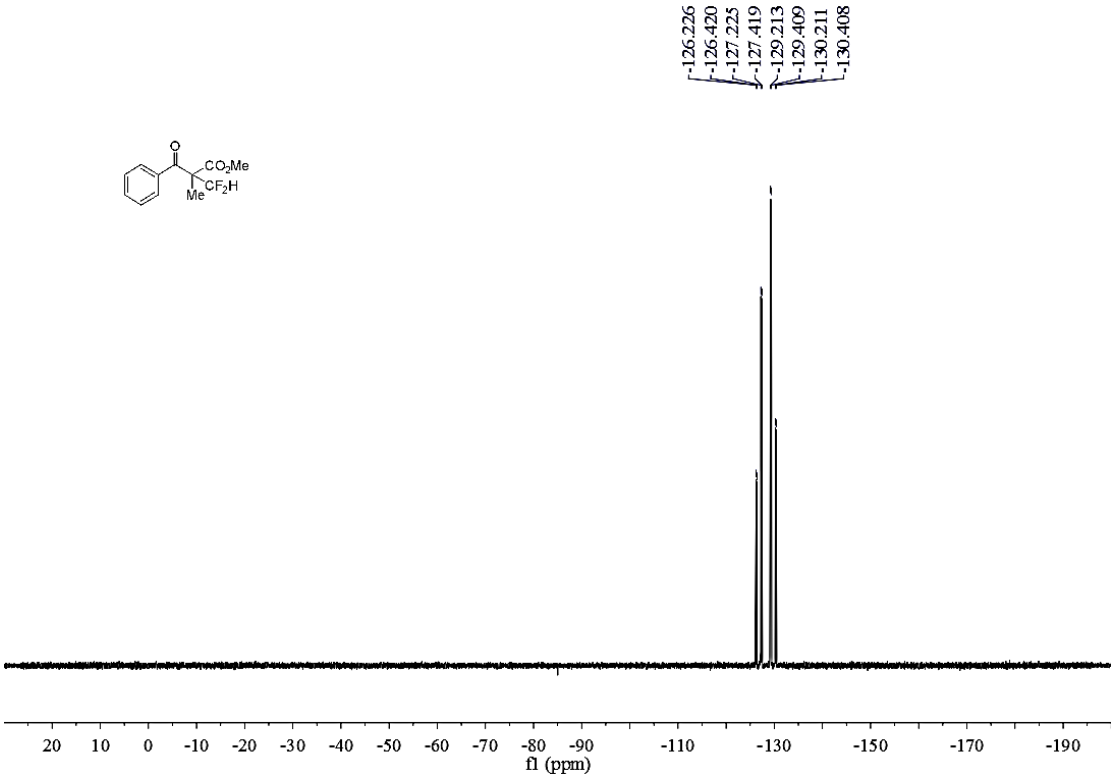


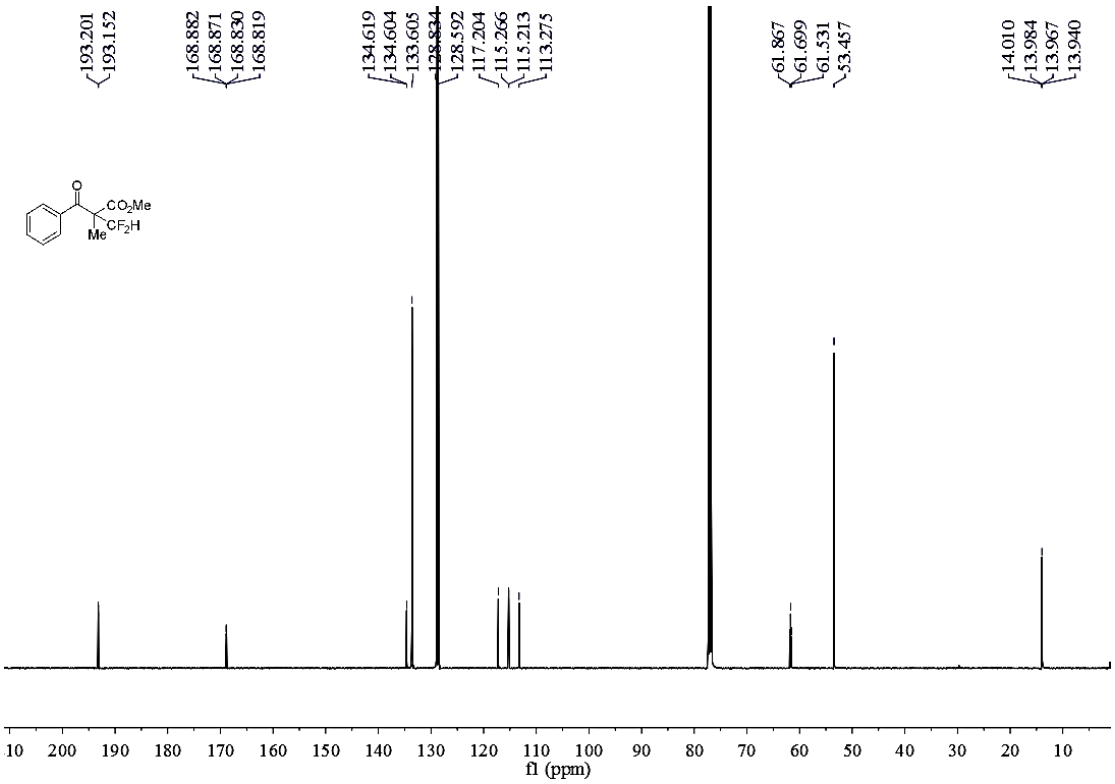




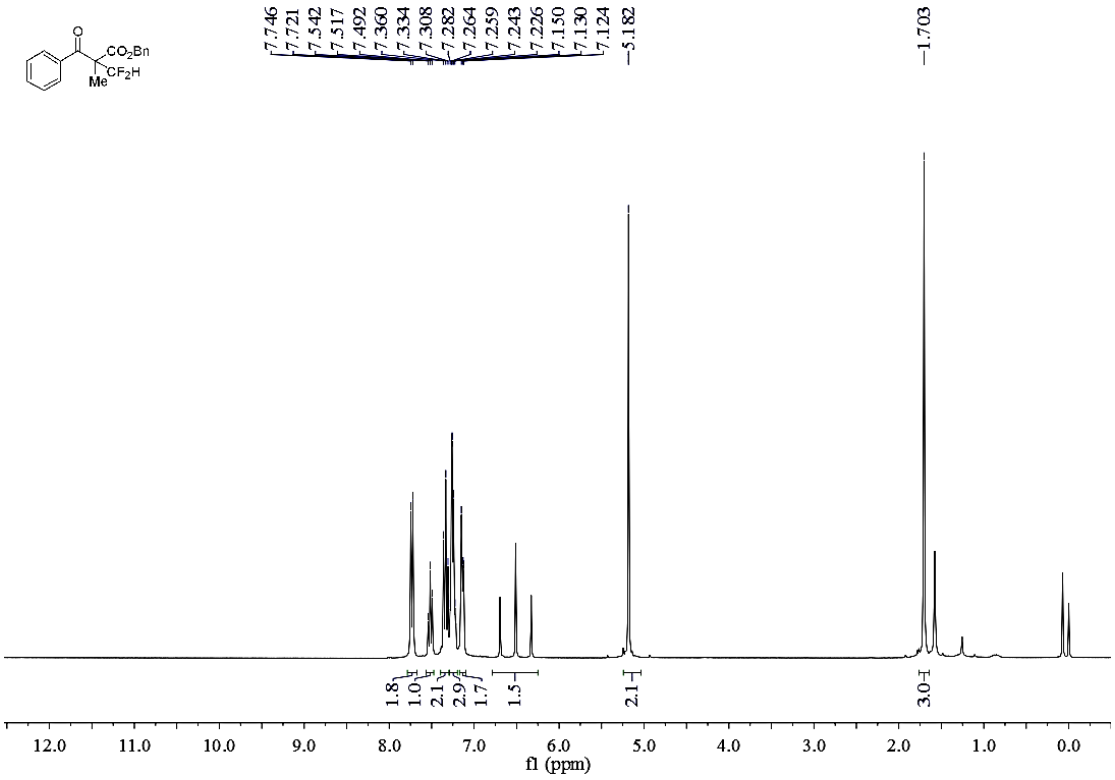
Methyl 2-benzoyl-3,3-difluoro-2-methylpropanoate **2q**

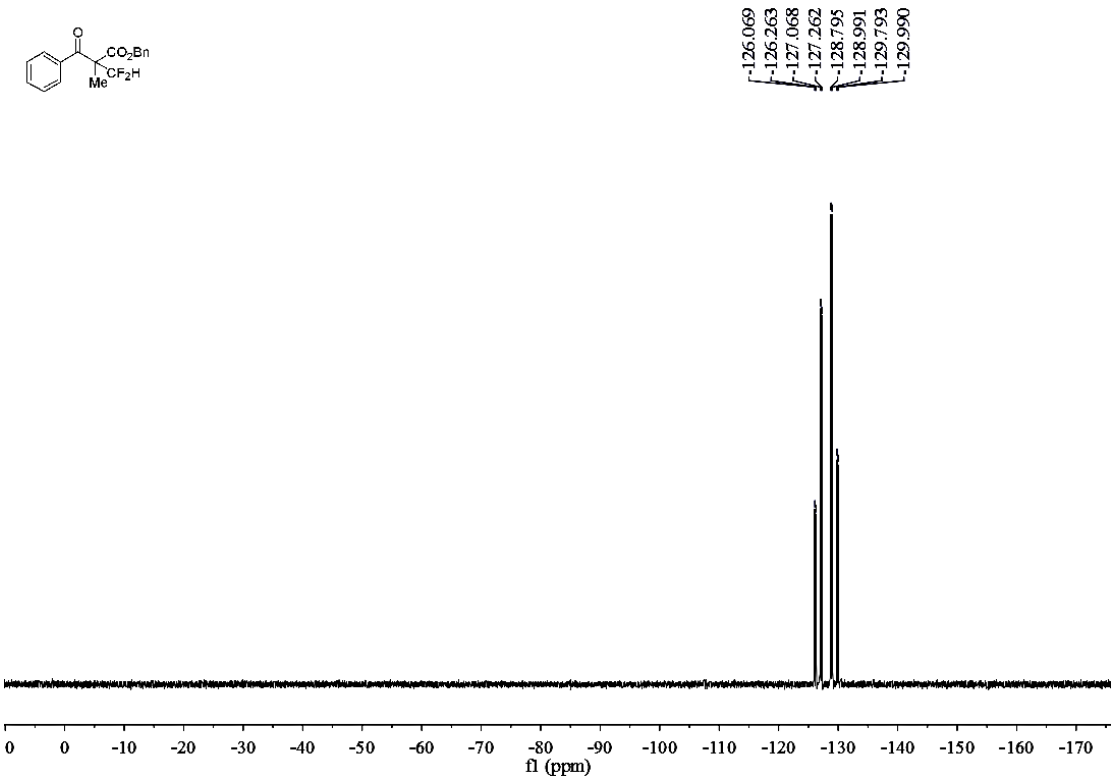


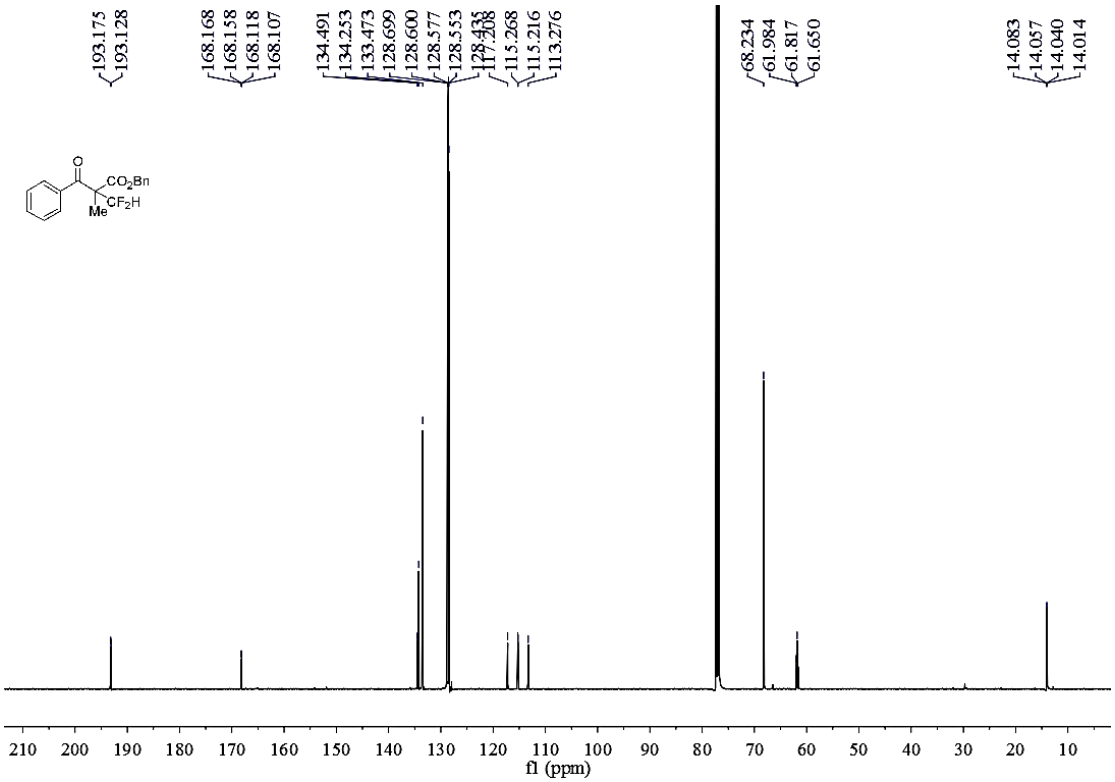

-126.226
-126.420
-127.225
-127.419
-129.213
-129.409
-130.211
-130.408
CO2Me
Me
CF2H
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190
f1 (ppm)


193.201
193.152
168.882
168.871
168.830
168.819
134.619
134.604
133.605
128.834
128.592
117.204
115.266
115.213
113.275
61.867
61.699
61.531
53.457
14.010
13.984
13.967
13.940
CO2Me
Me
CF2H
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

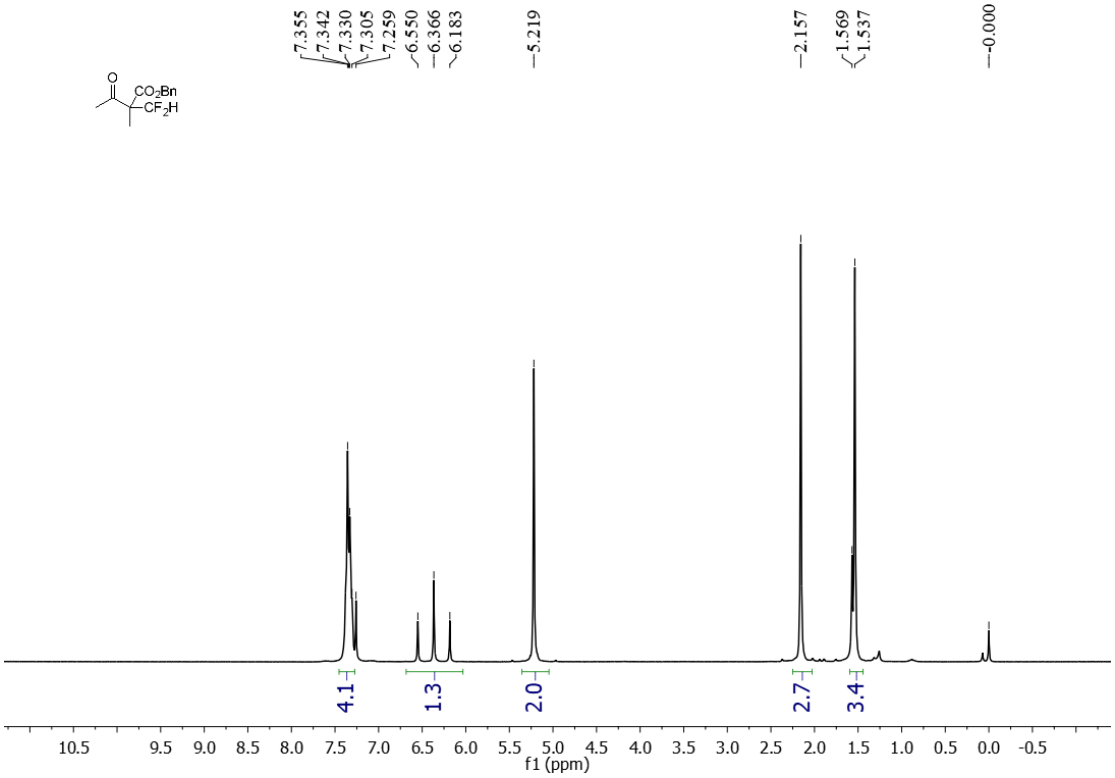
Benzyl 2-benzoyl-3,3-difluoro-2-methylpropanoate **2r**

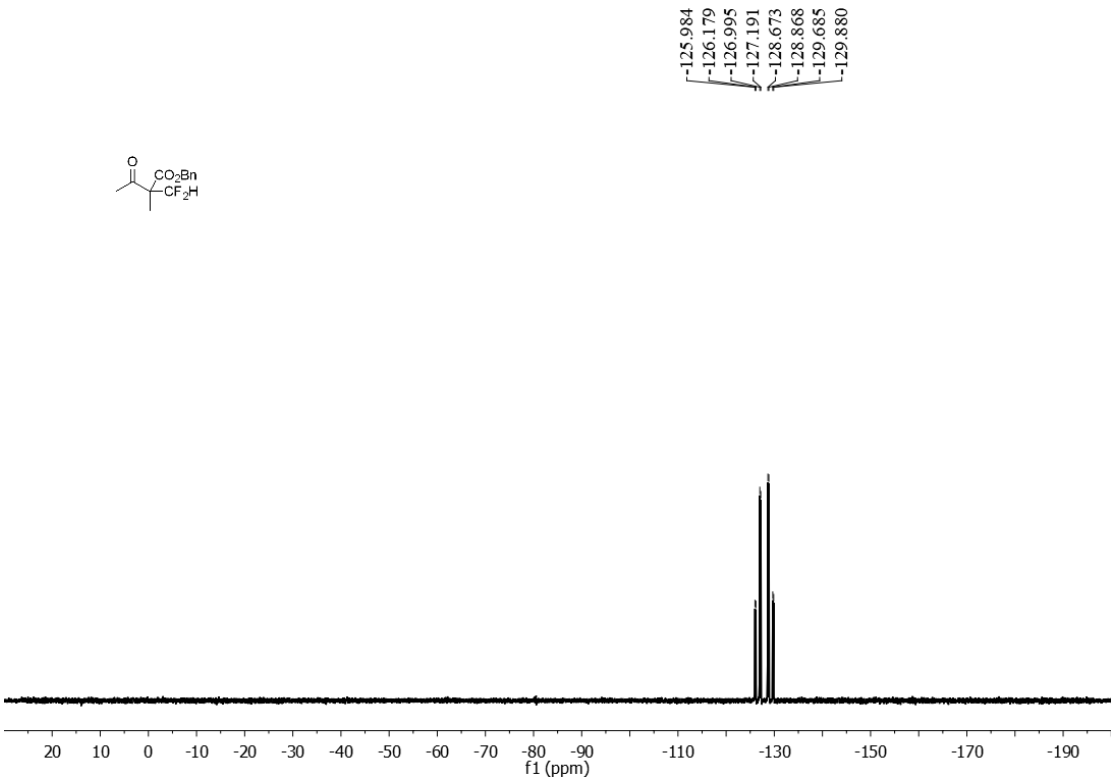


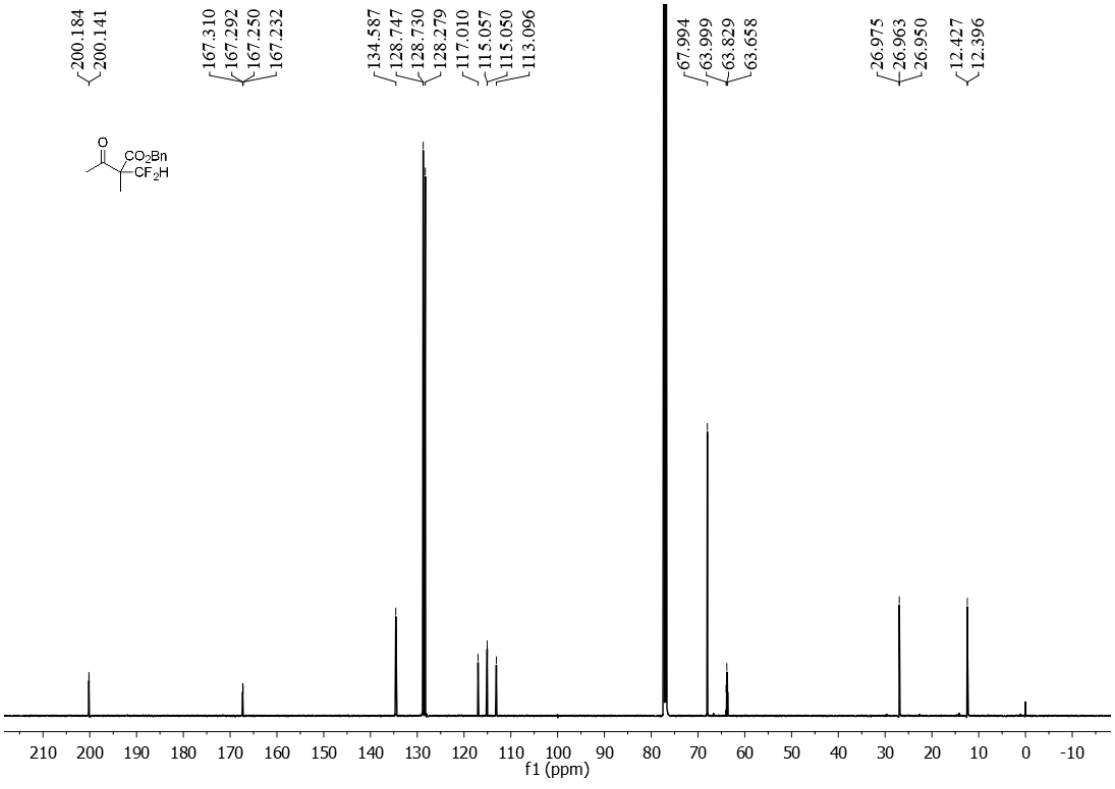




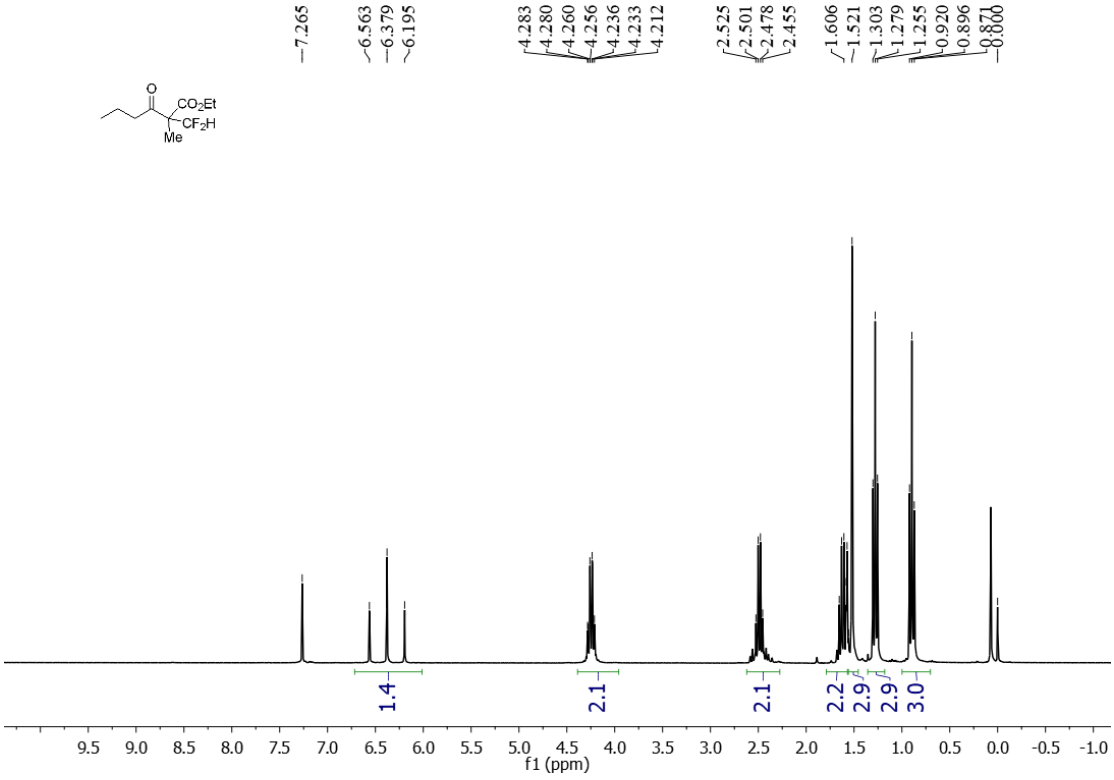
Benzyl 2-(difluoromethyl)-2-methyl-3-oxobutanoate **2s**

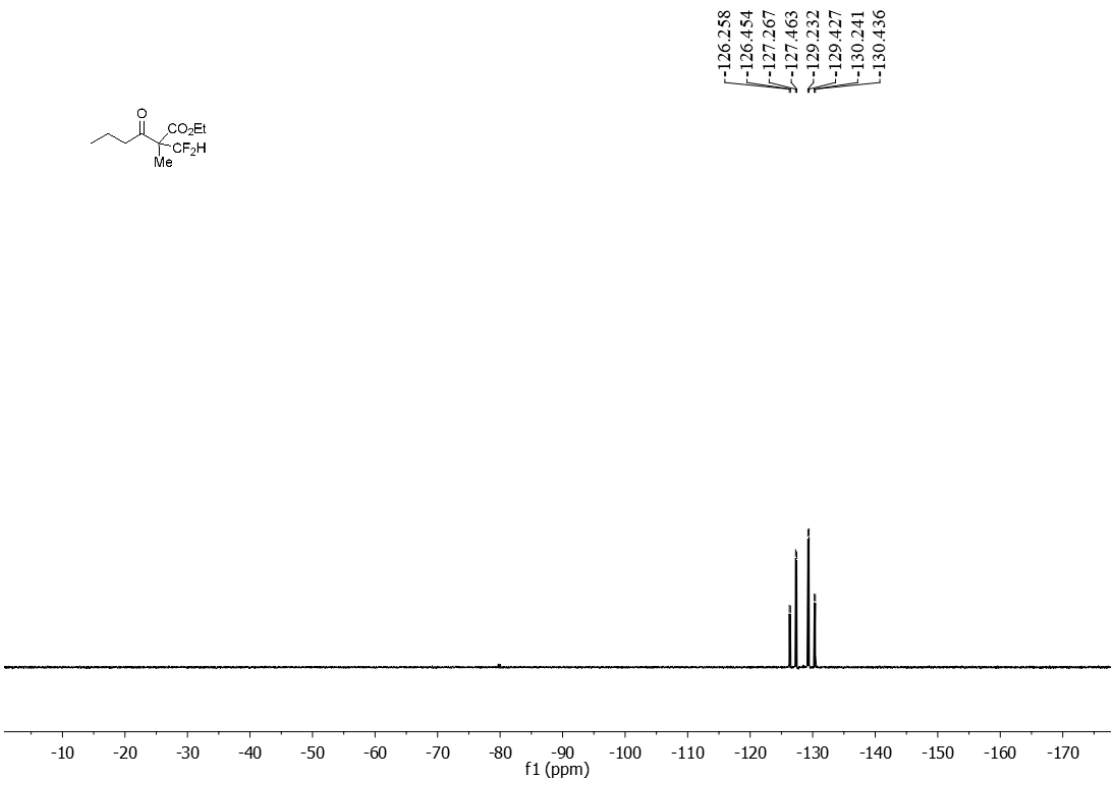


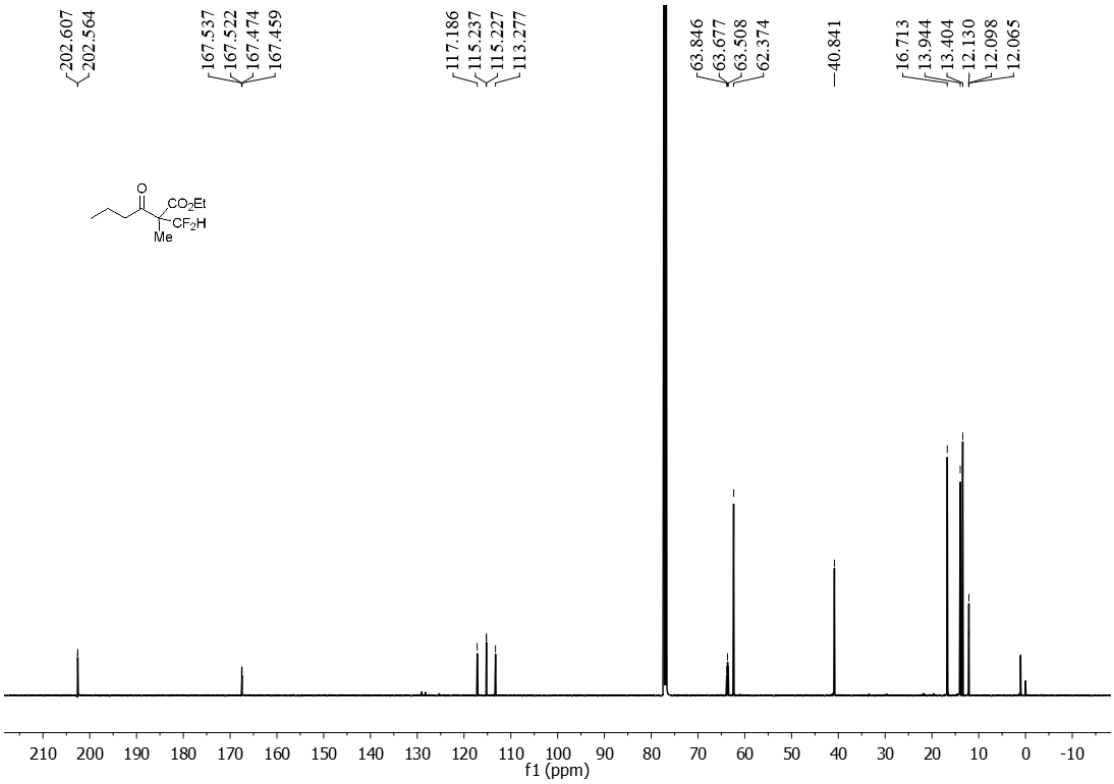

-125.984
-126.179
-126.995
-127.191
-128.673
-128.868
-129.685
-129.880
O
CO2Bn
CF2H
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -110 -130 -150 -170 -190
f1 (ppm)


200.184
200.141
167.310
167.292
167.250
167.232
134.587
128.747
128.730
128.279
117.010
115.057
115.050
113.096
67.994
63.999
63.829
63.658
26.975
26.963
26.950
12.427
12.396
O
CO2Bn
CF2H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Ethyl 2-(difluoromethyl)-2-methyl-3-oxohexanoate **2t**

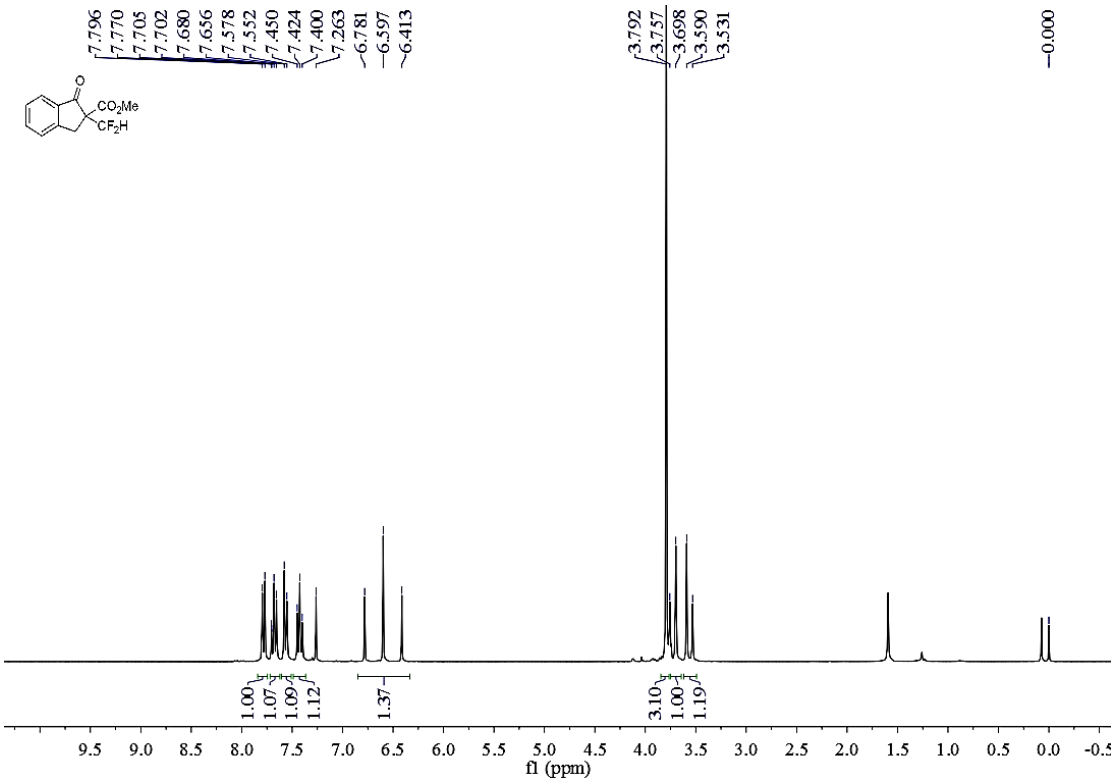


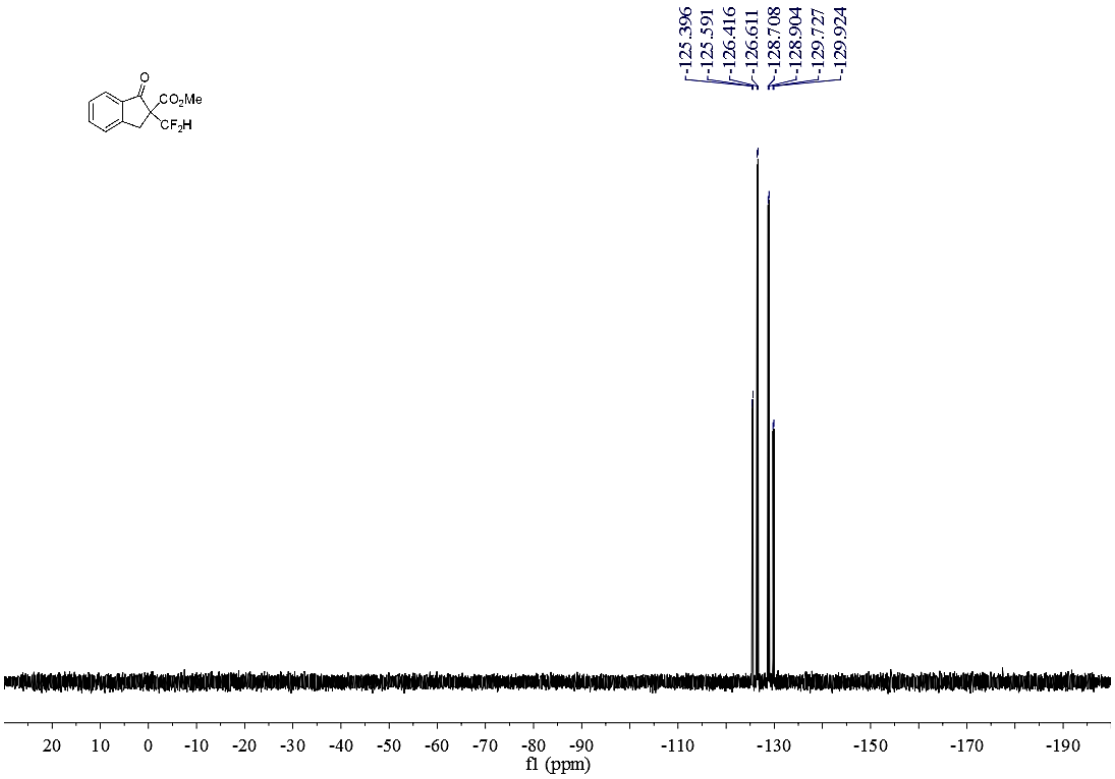



202.607
202.564
167.537
167.522
167.474
167.459
117.186
115.237
115.227
113.277
63.846
63.677
63.508
62.374
40.841
16.713
13.944
13.404
12.130
12.098
12.065
O
CO2Et
CF2H
Me
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

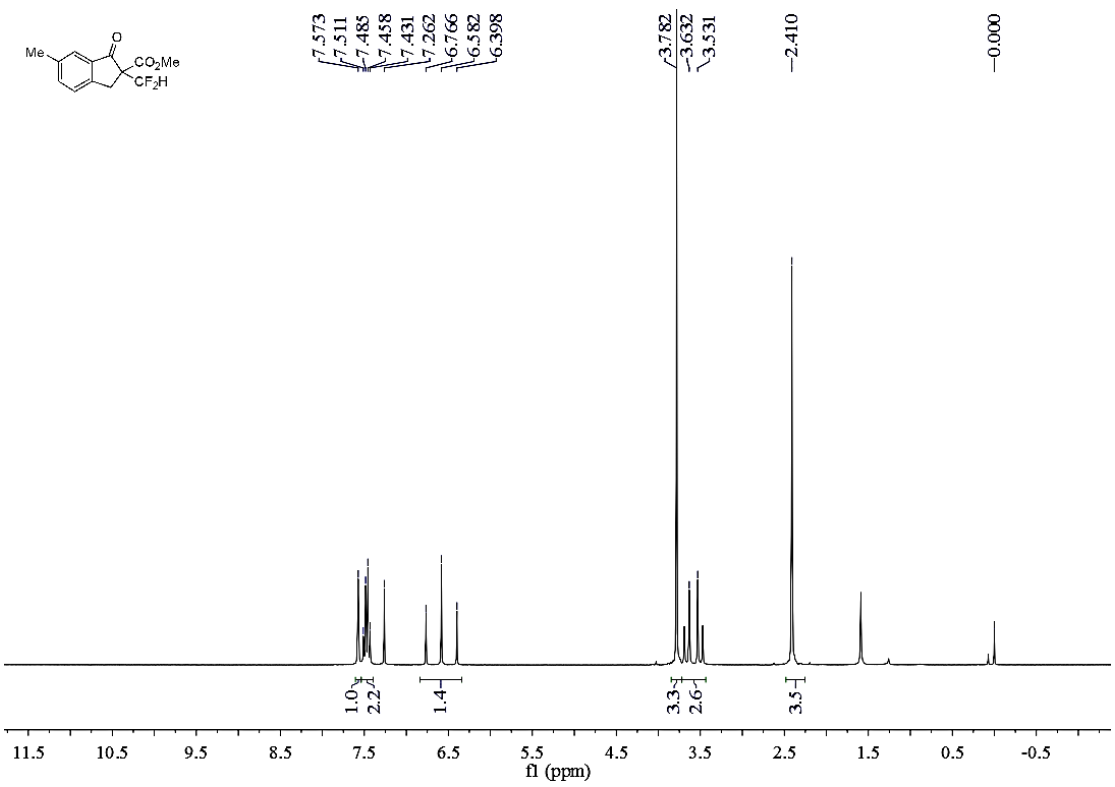
7. Copies of ^{1}H ^{19}F NMR spectra of known compounds (2a-f, 2h-k, 2m, 2u)

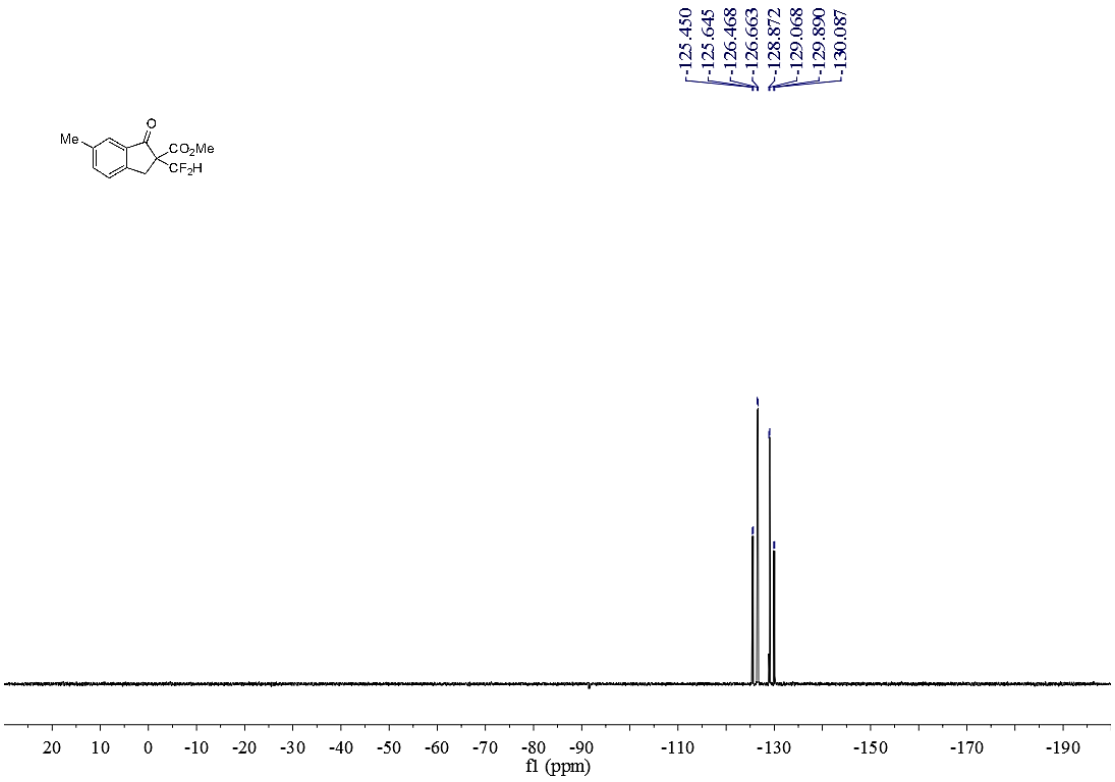
Methyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2a**



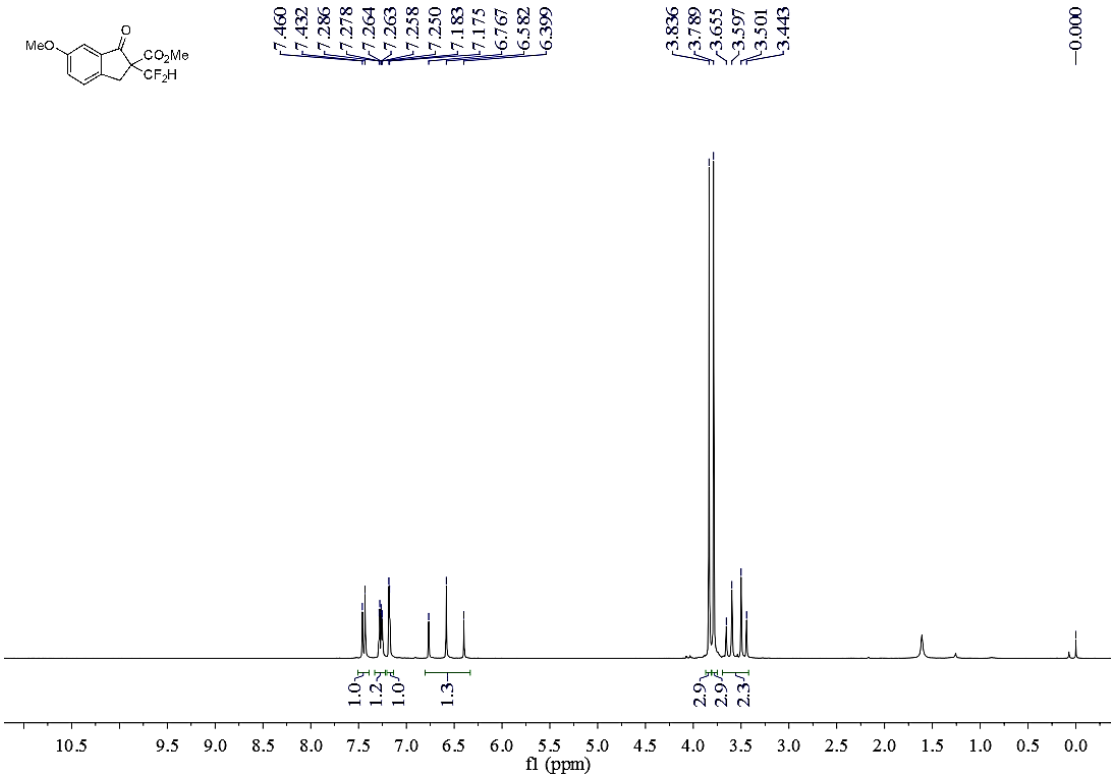


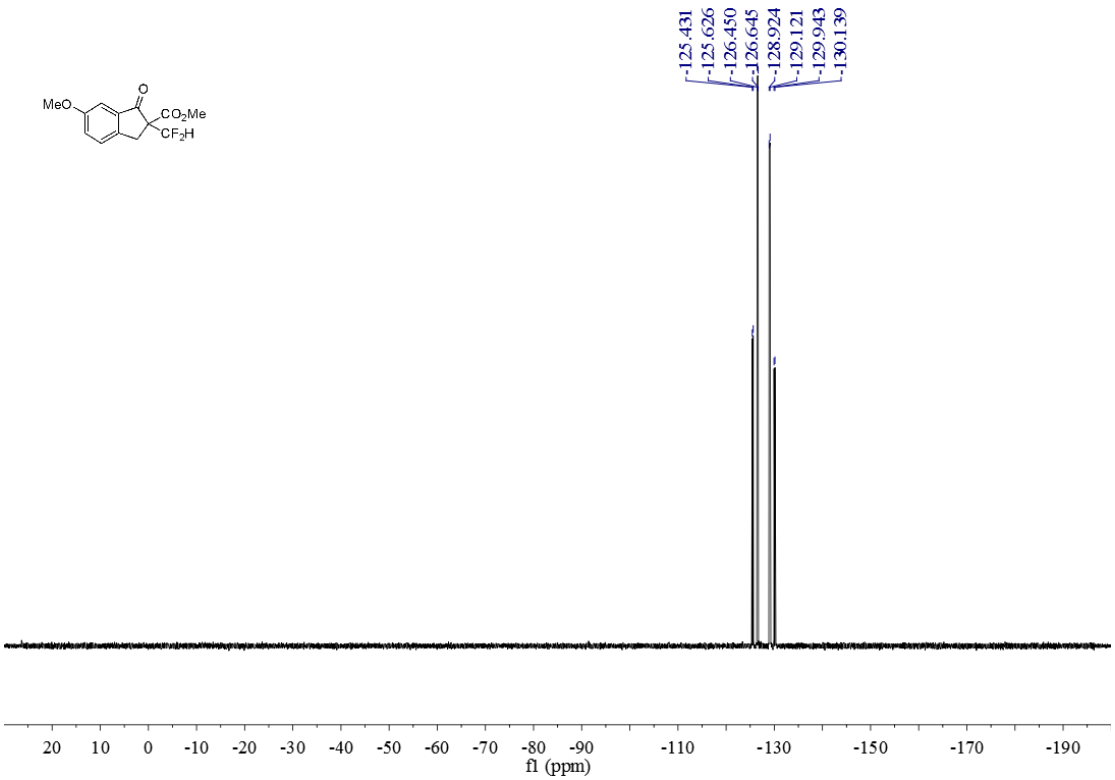
Methyl 2-(difluoromethyl)-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2b**



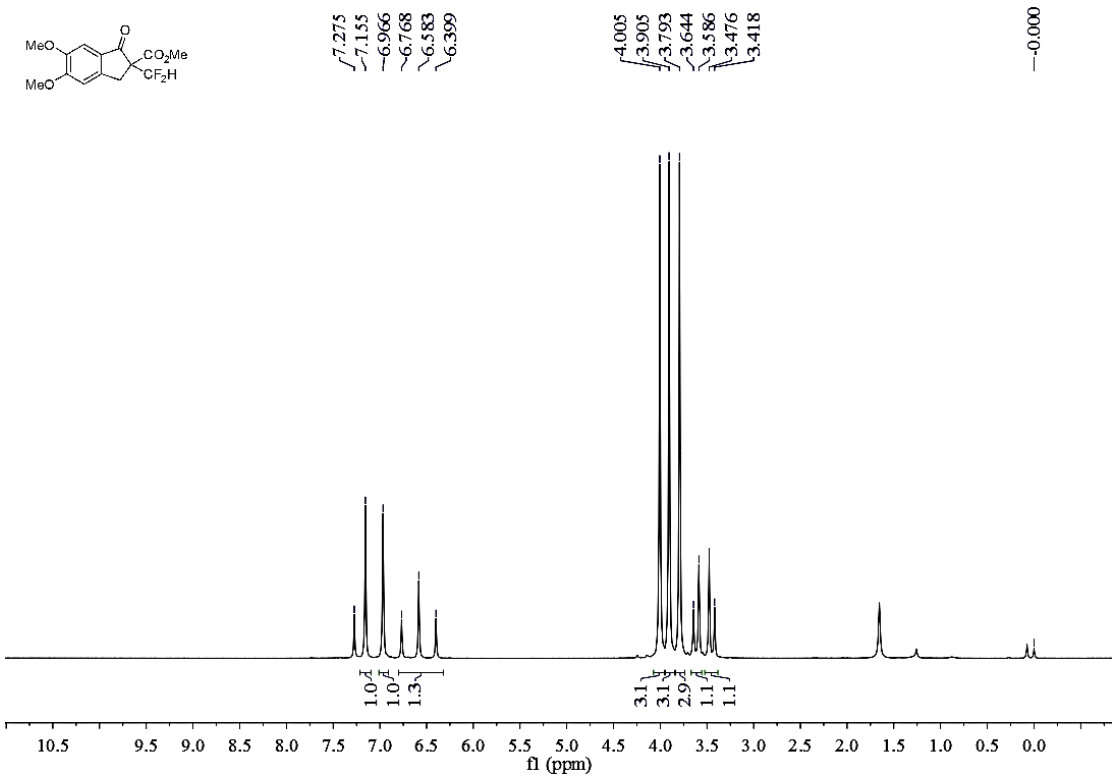


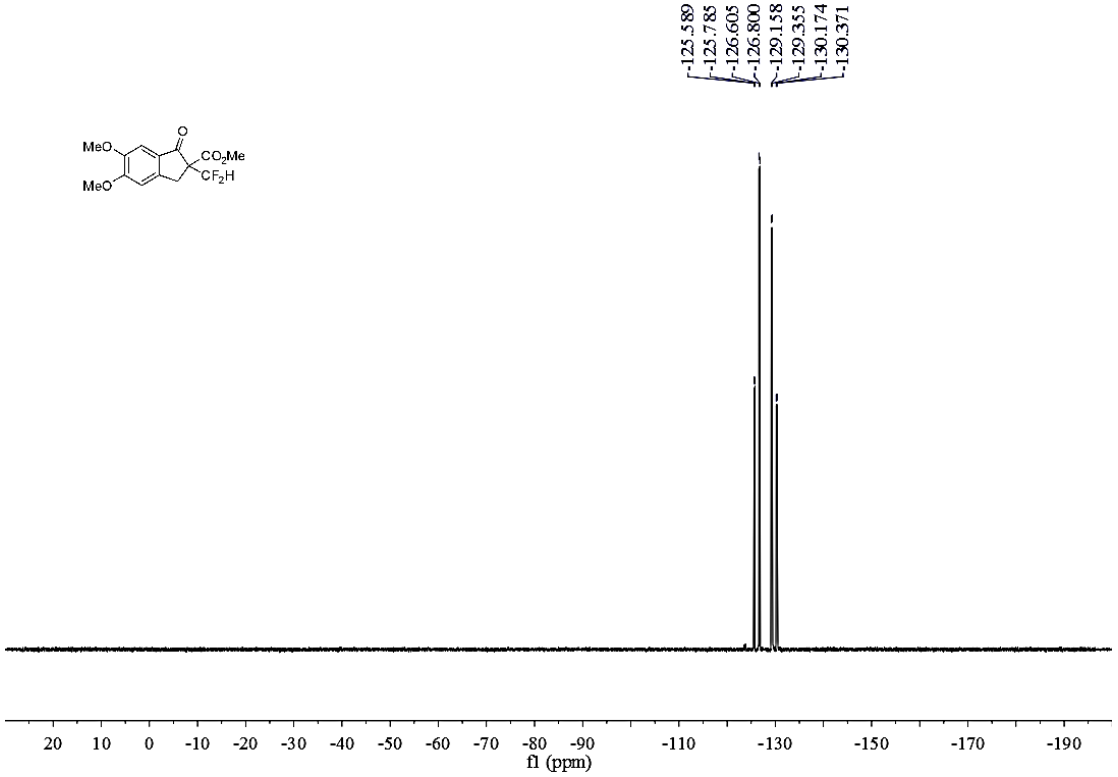
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2c**



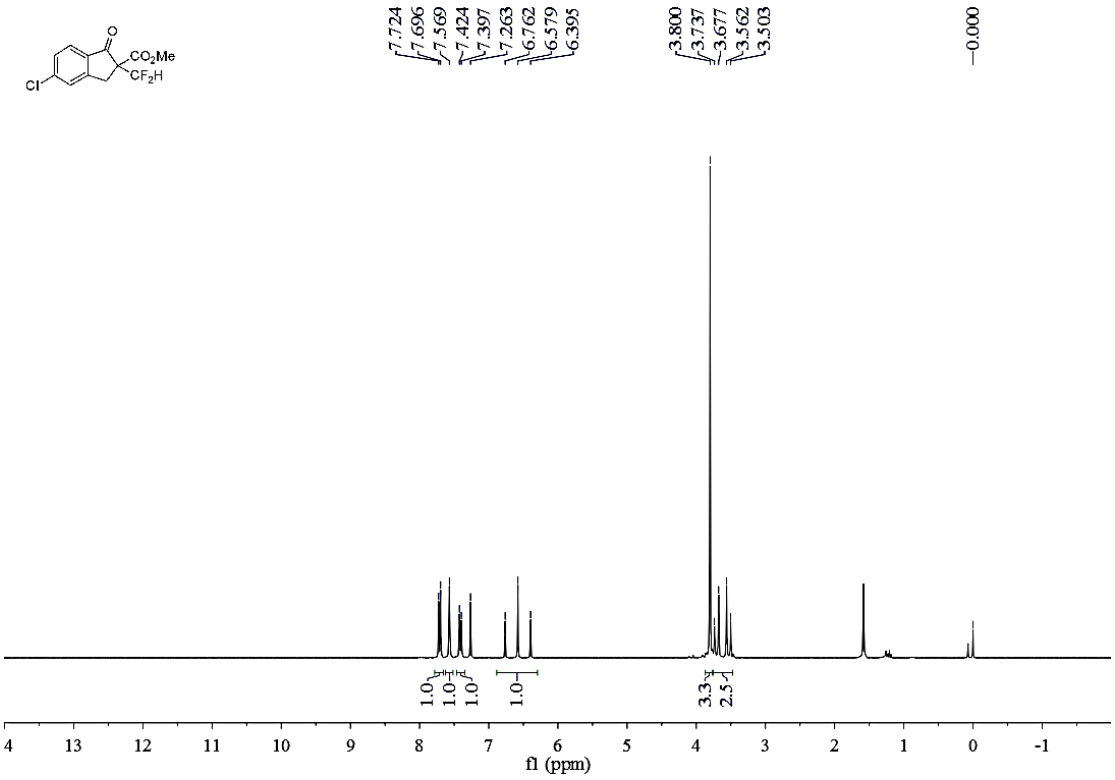


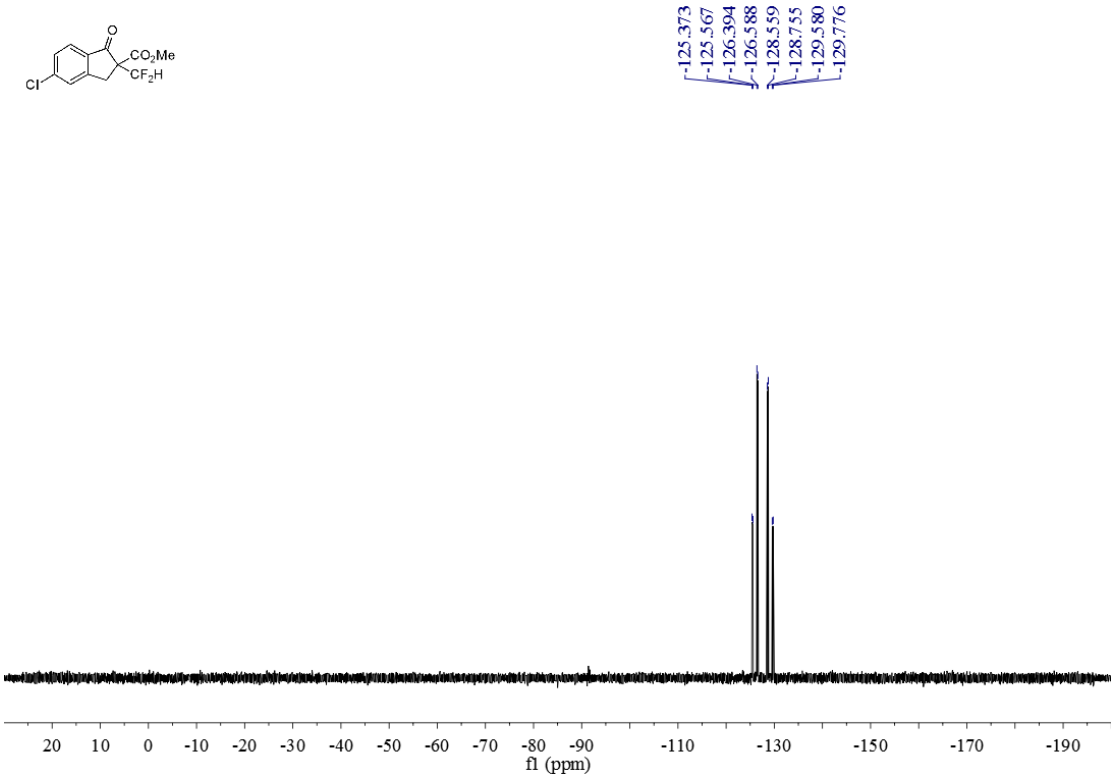
Methyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2d**



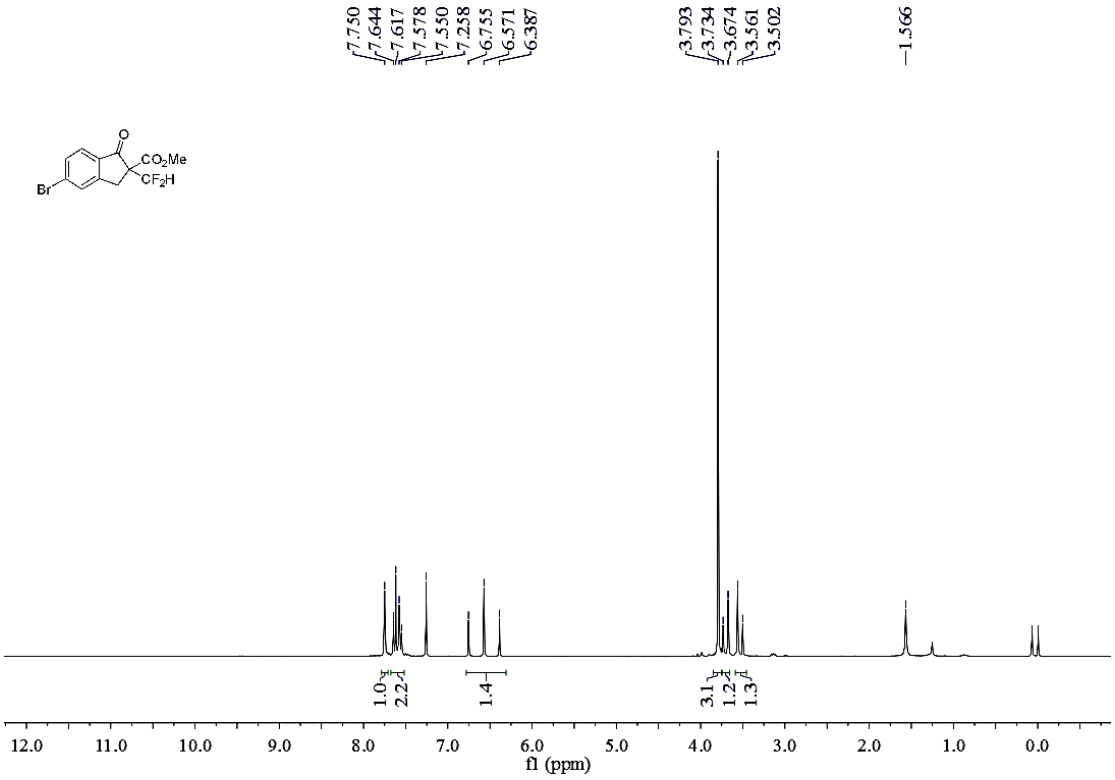


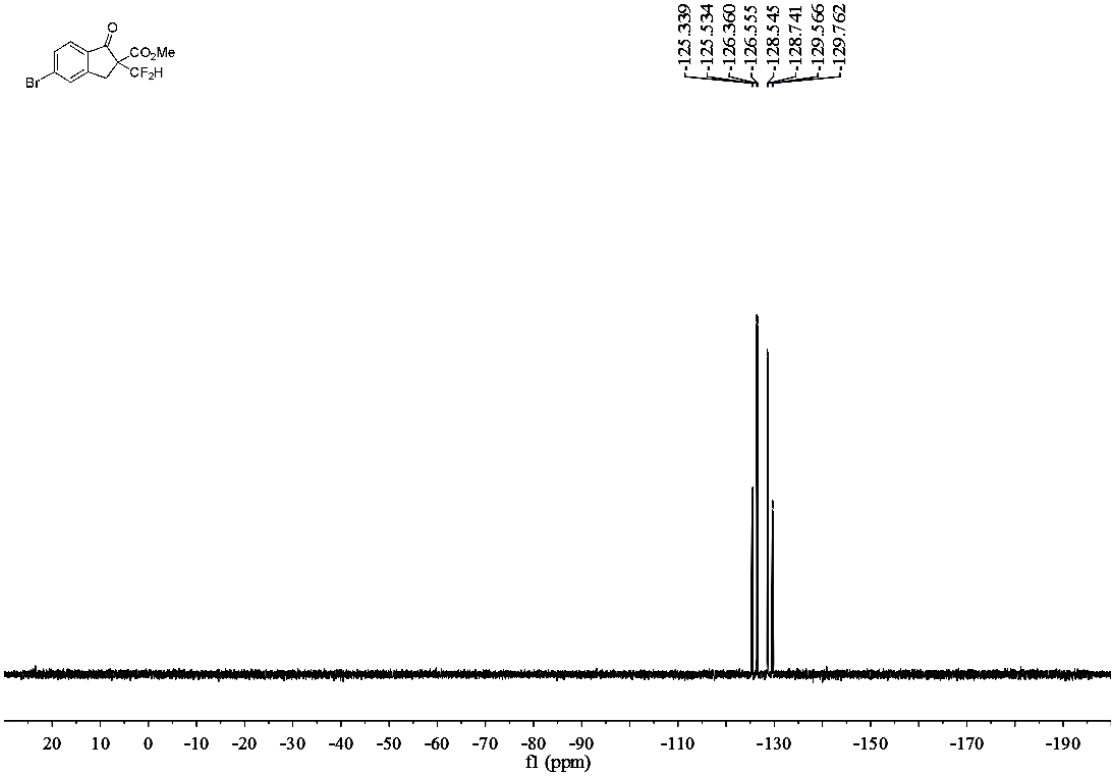
Methyl 5-chloro-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2e**



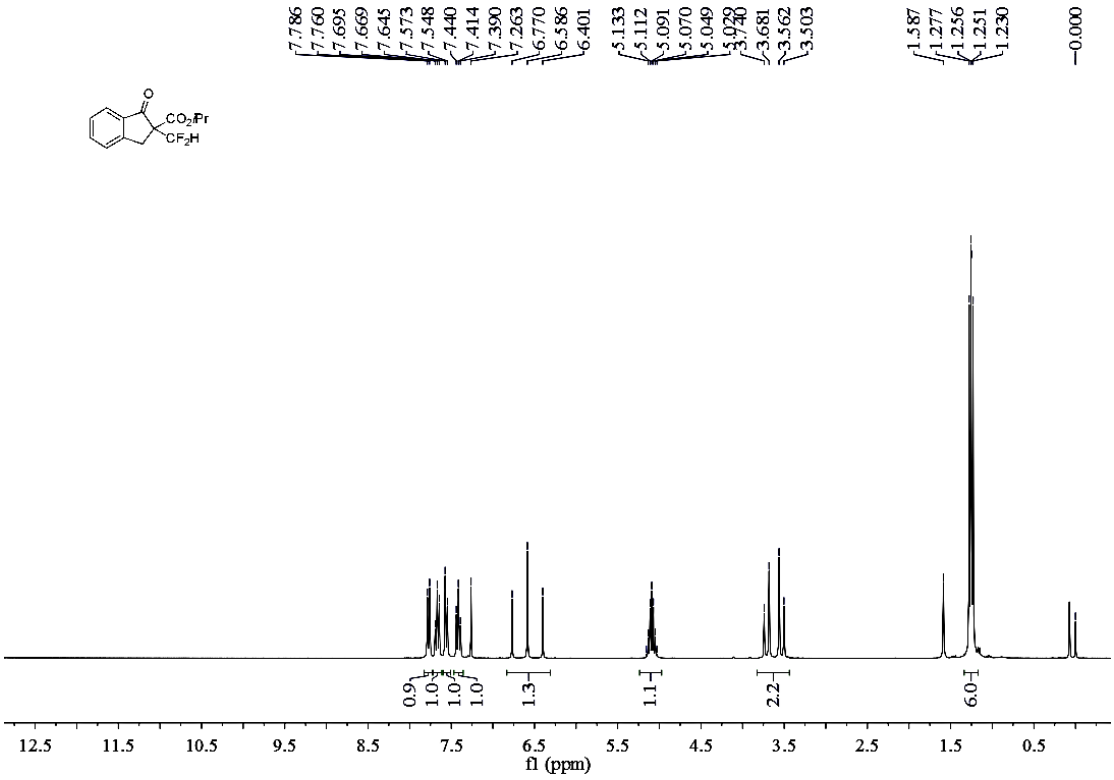


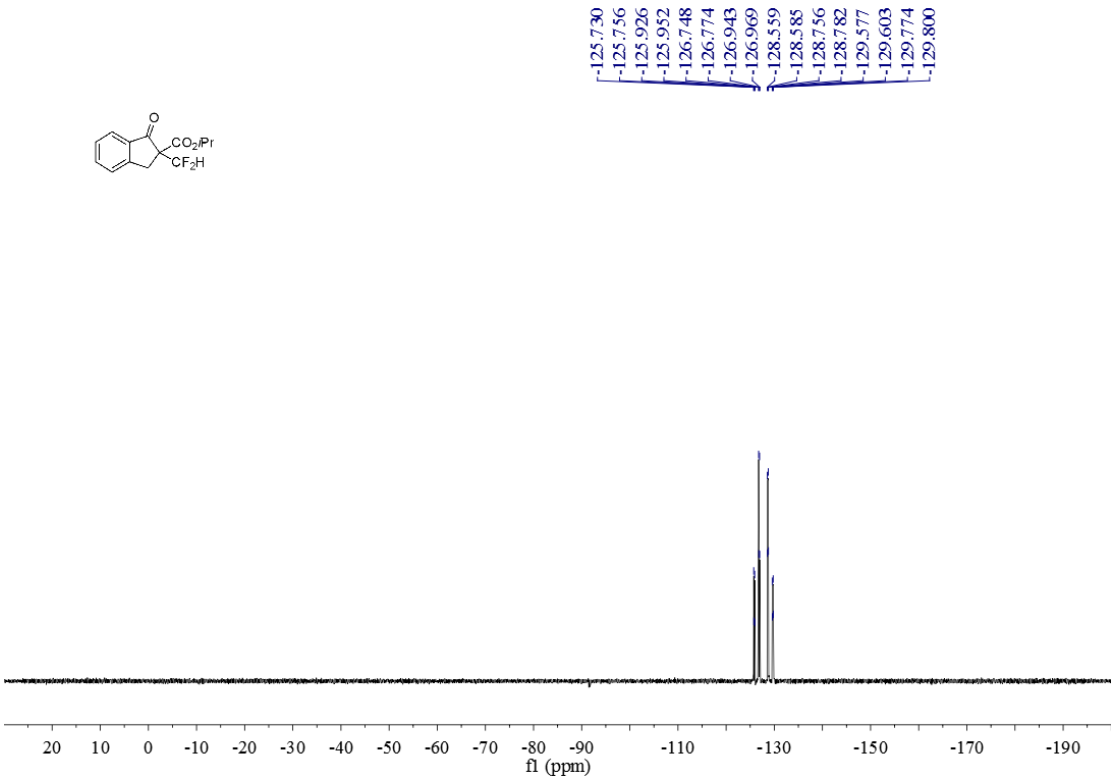
Methyl 5-bromo-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2f**



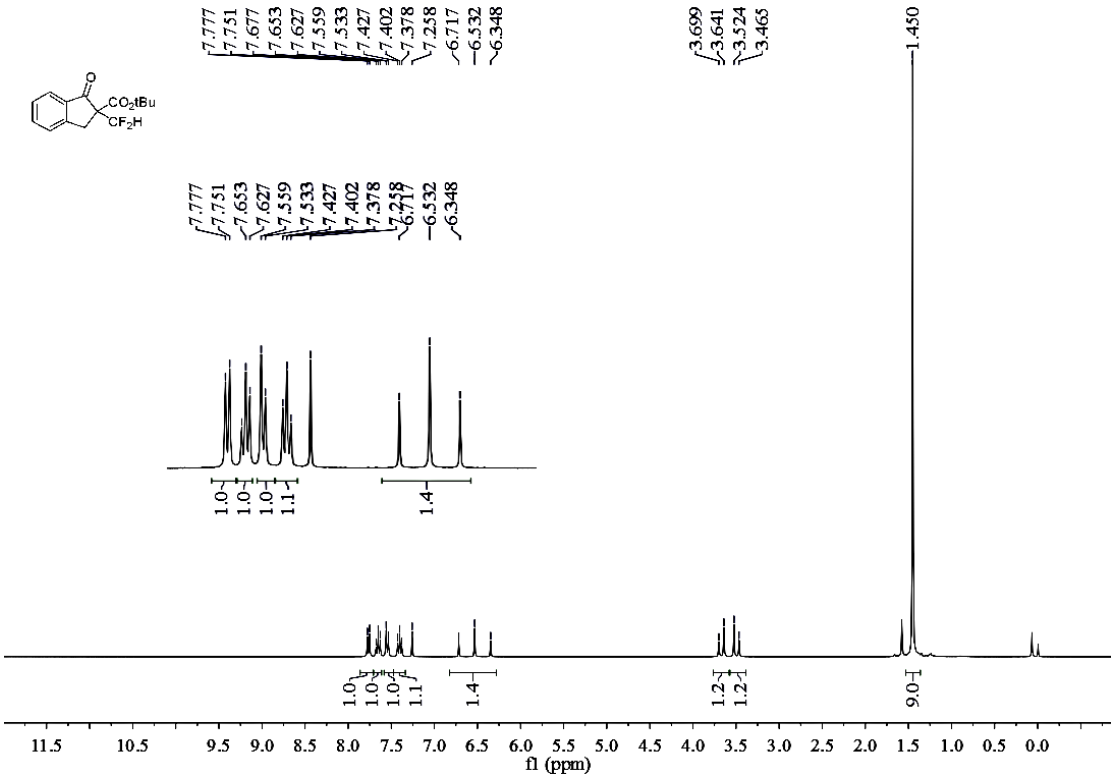


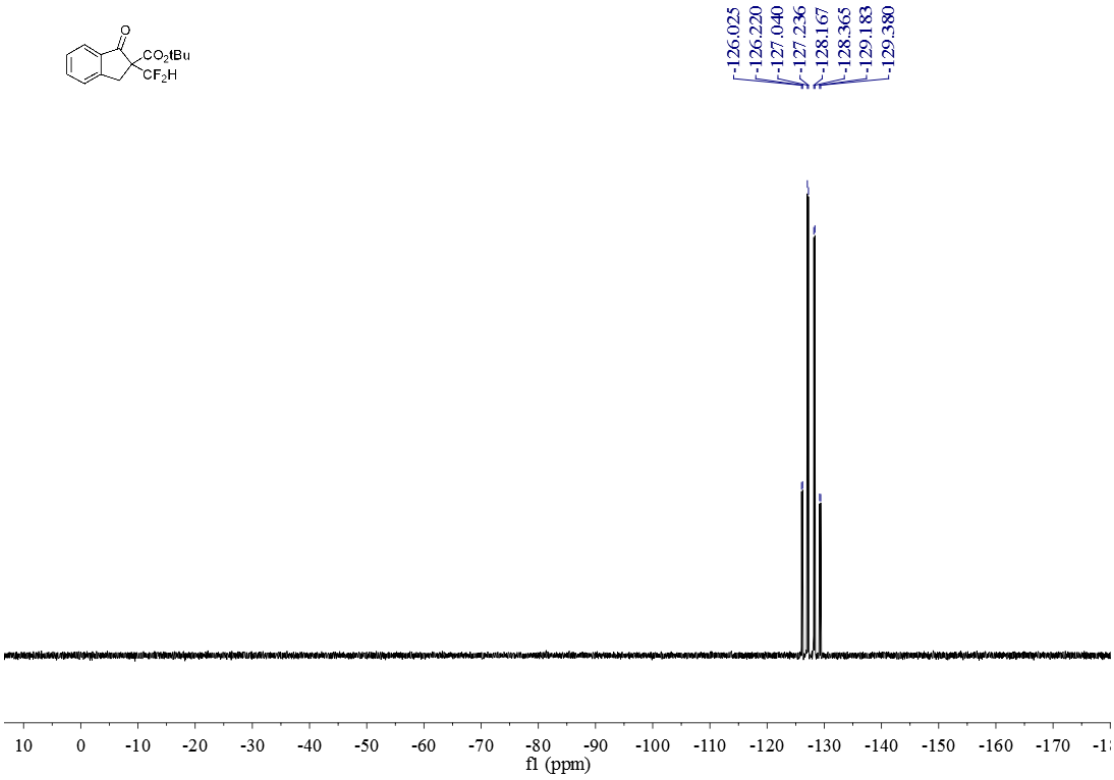
isopropyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2h**



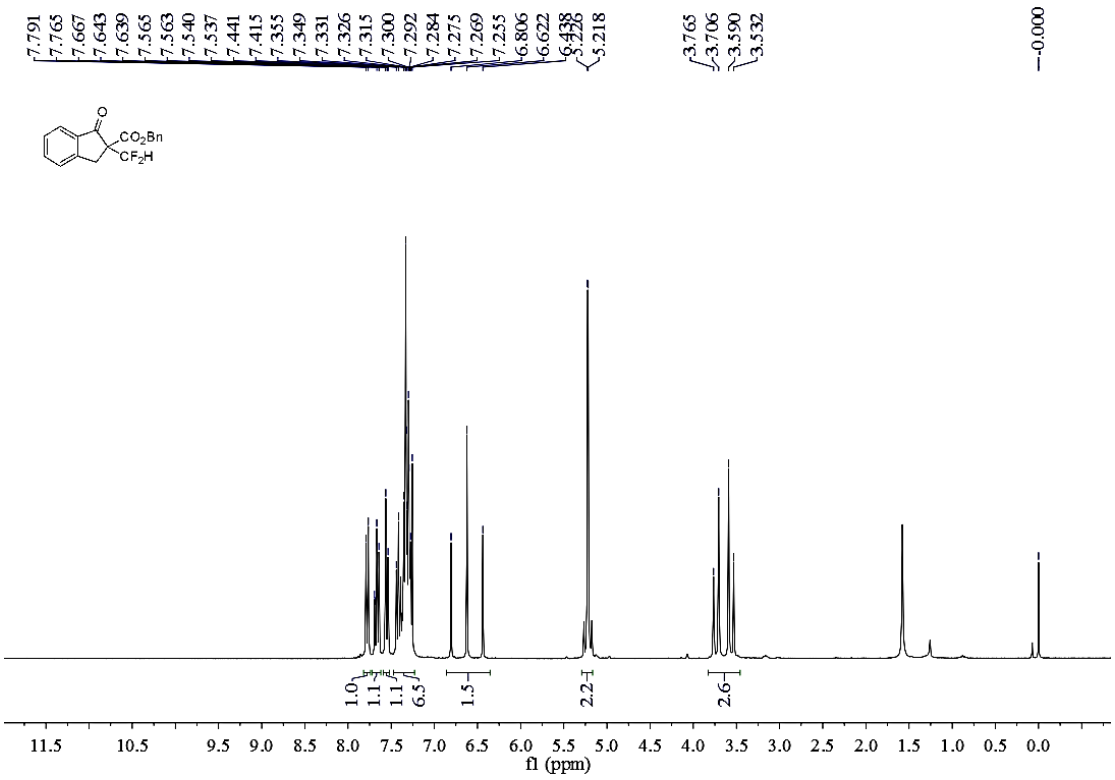


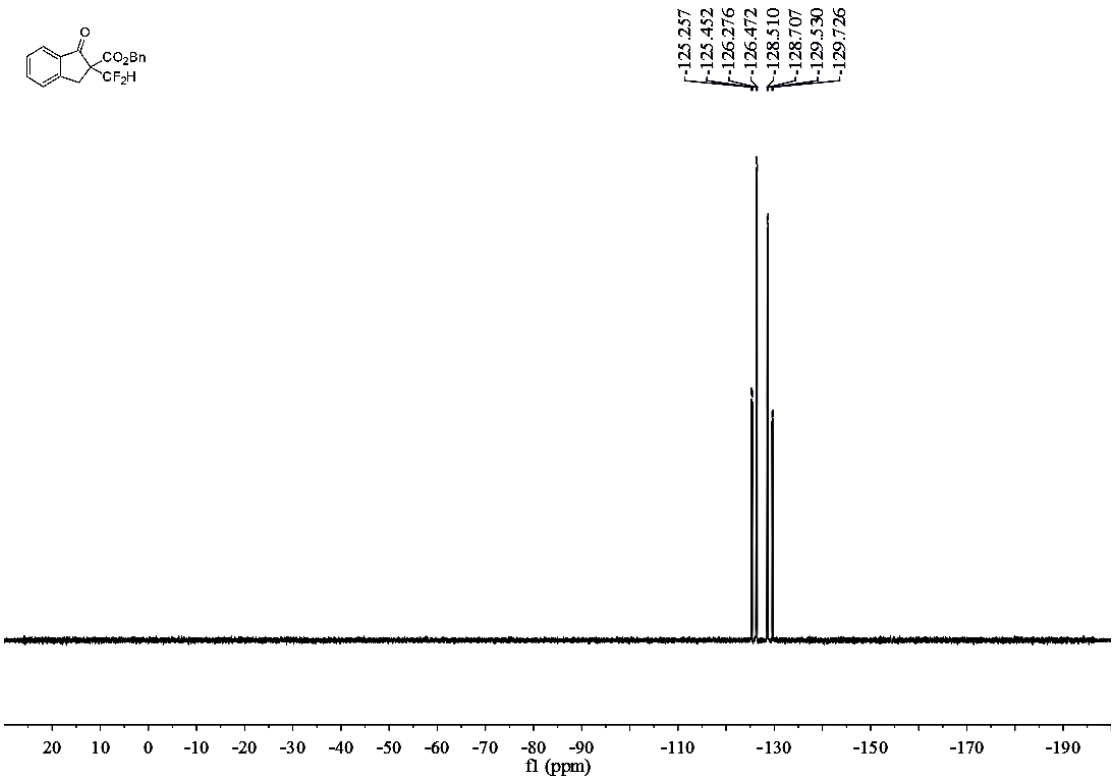
tert-butyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2i**



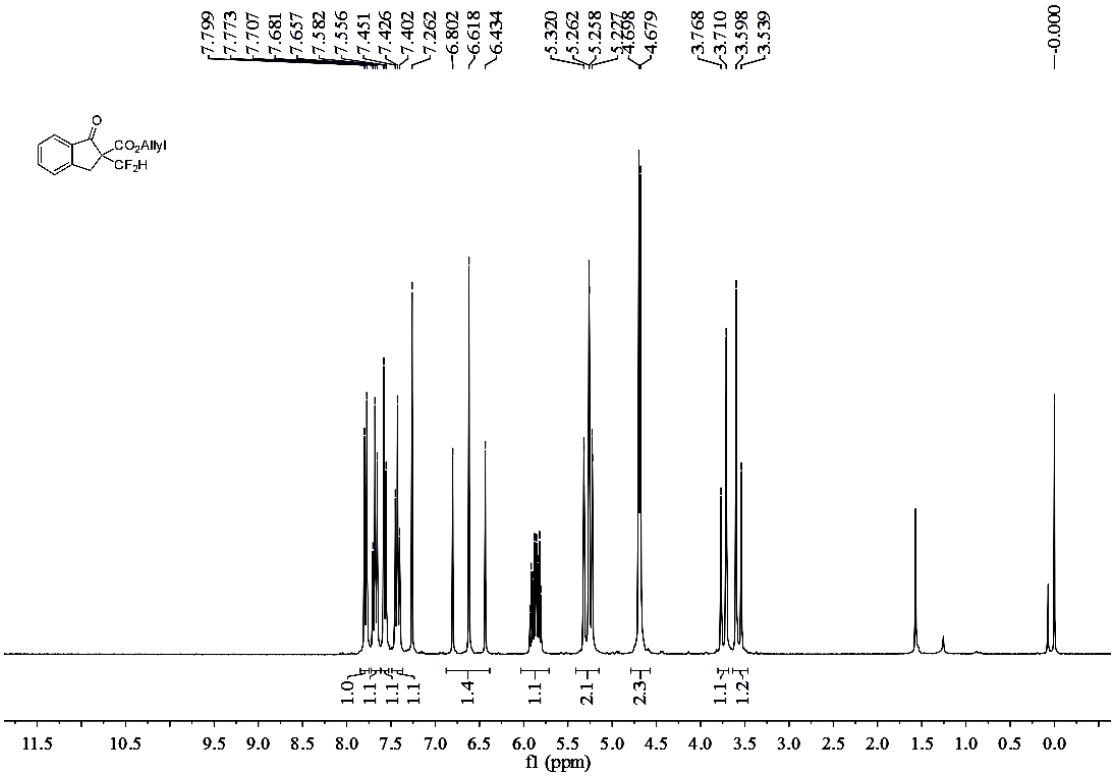


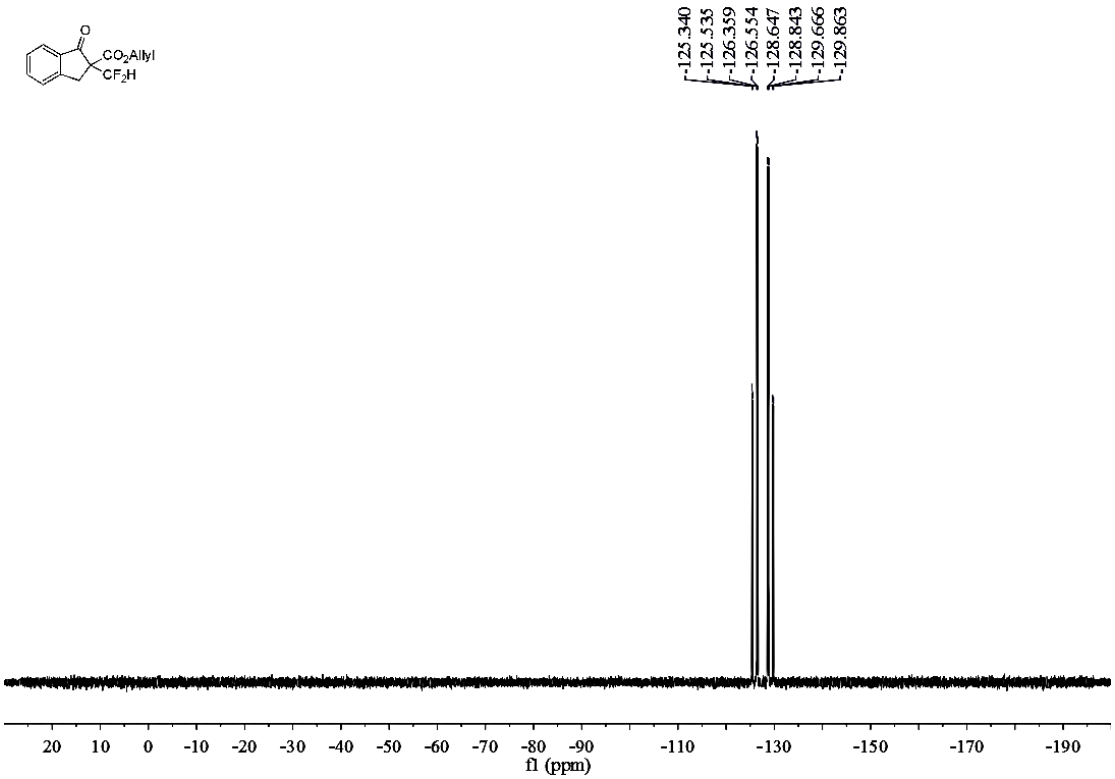
Benzyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2j**



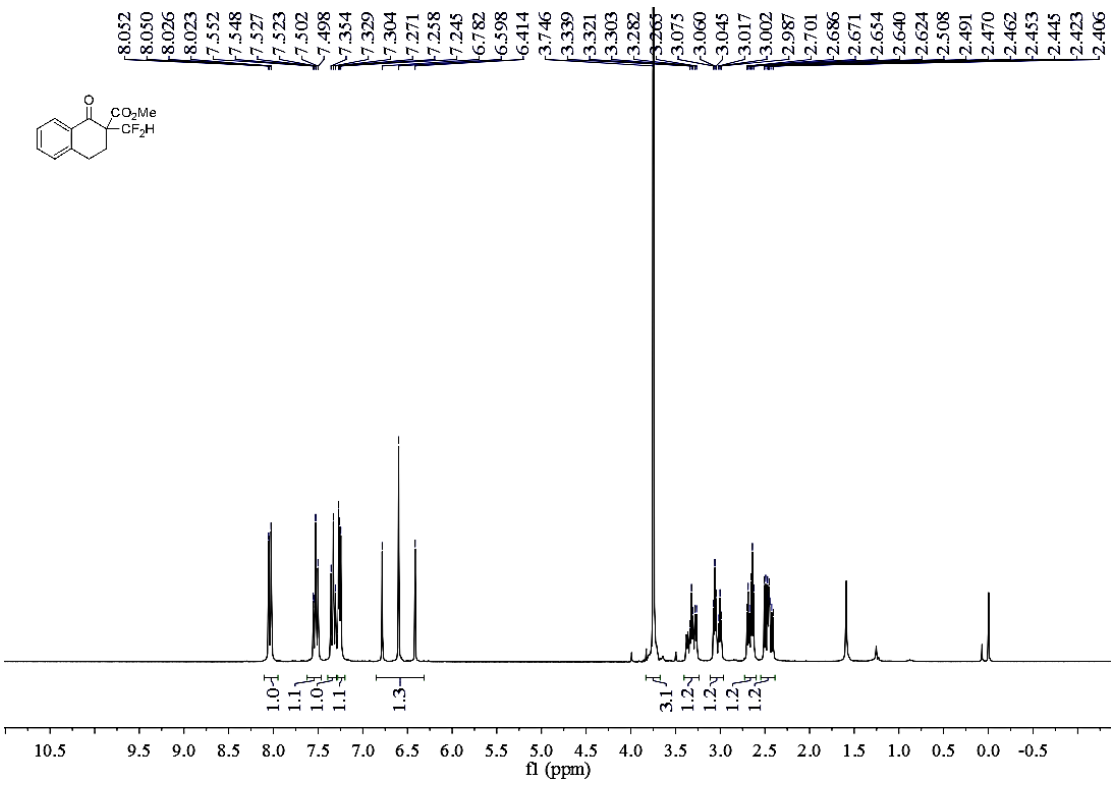


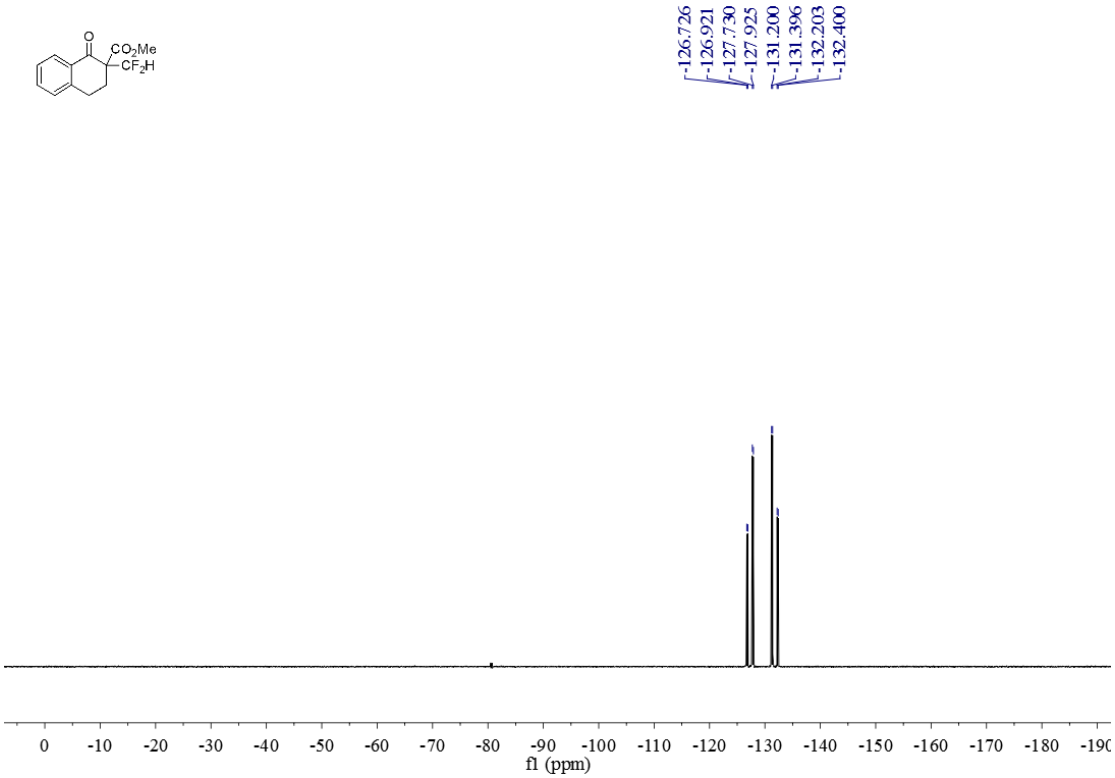
Allyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2k**



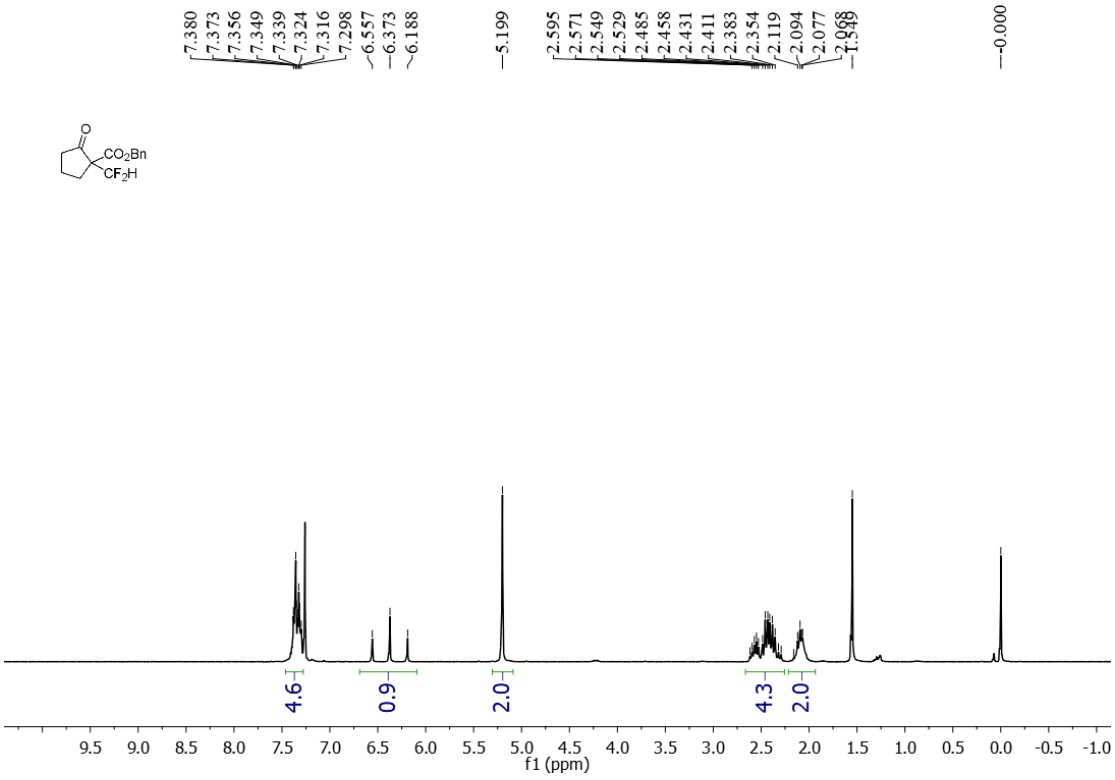


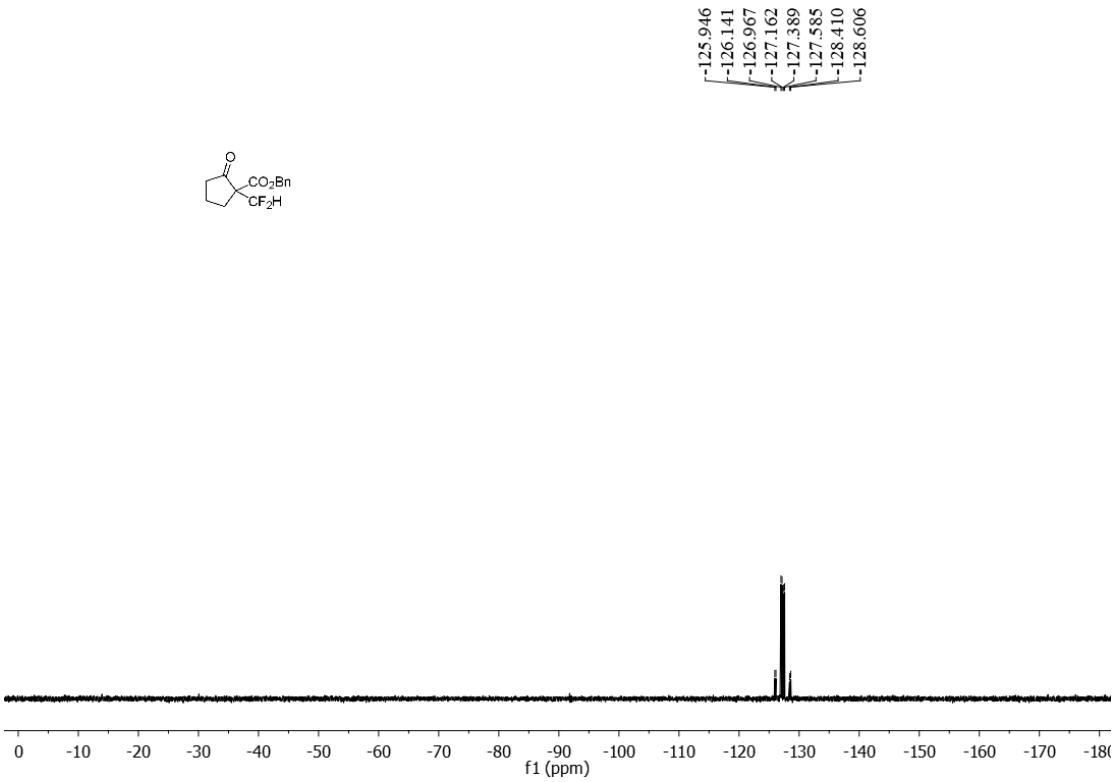
Methyl 2-(difluoromethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2m**





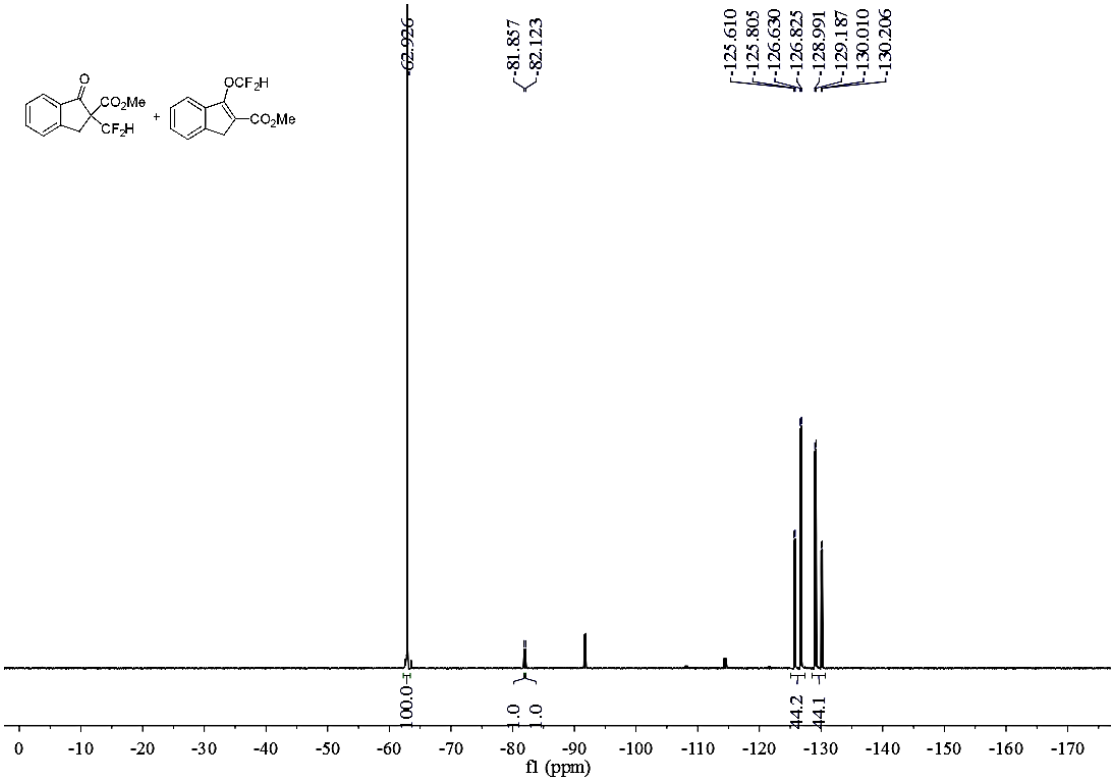
Benzyl 1-(difluoromethyl)-2-oxocyclopentane-1-carboxylate **2u**



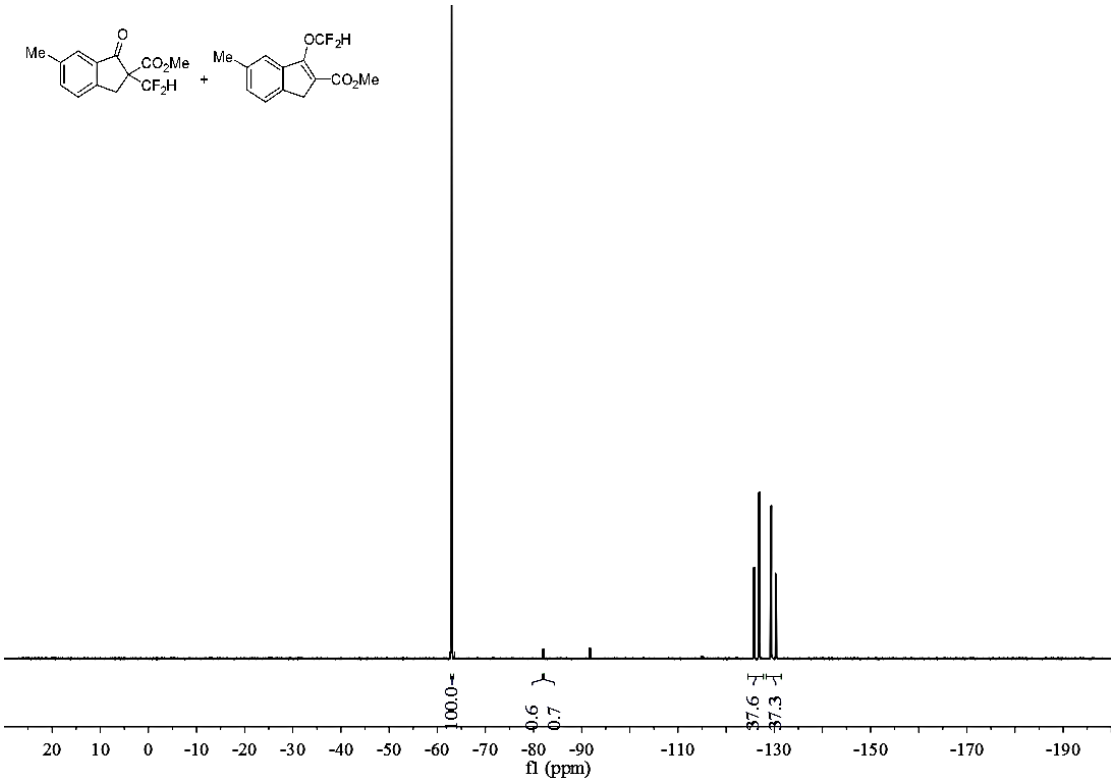


8. Copies of ^{19}F NMR spectra of crude mixtures for determining the C/O ratios

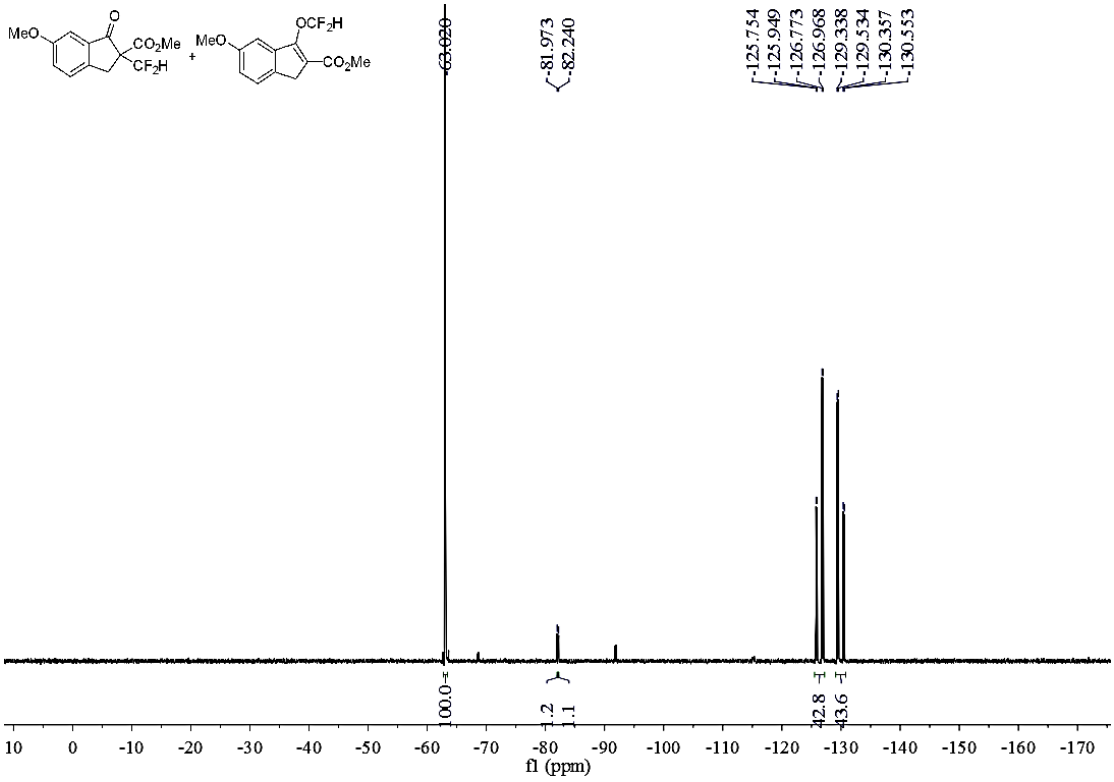
Methyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2a**



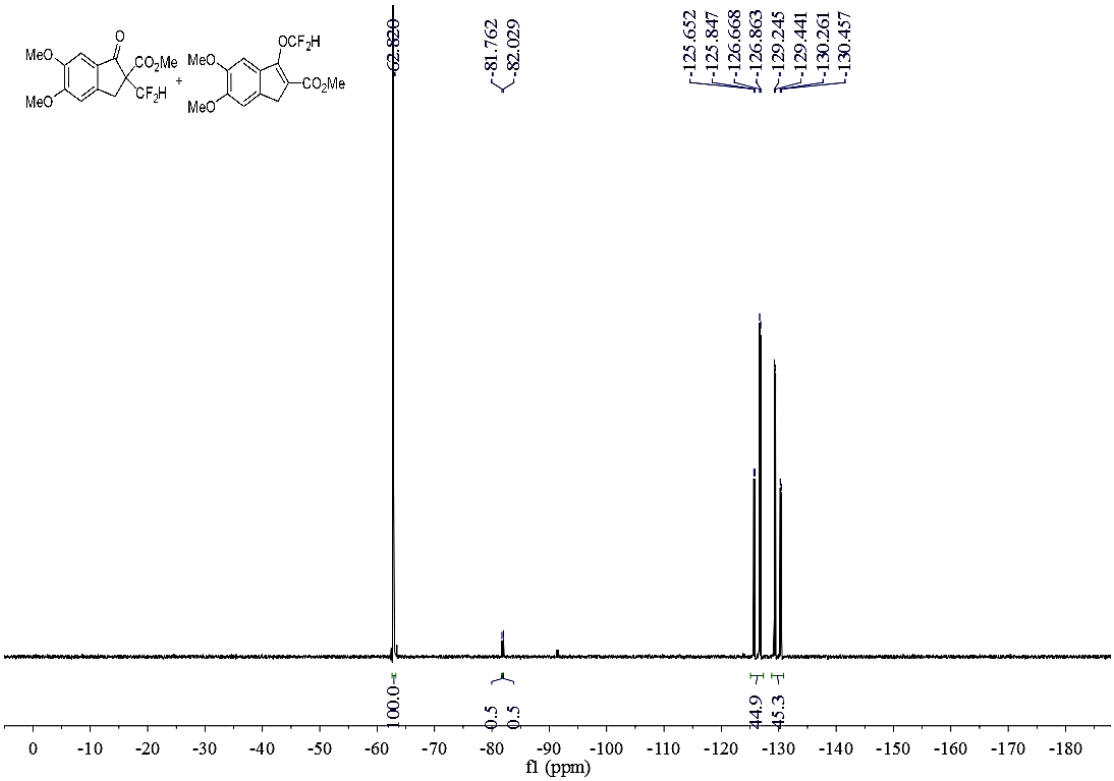
Methyl 2-(difluoromethyl)-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2b**



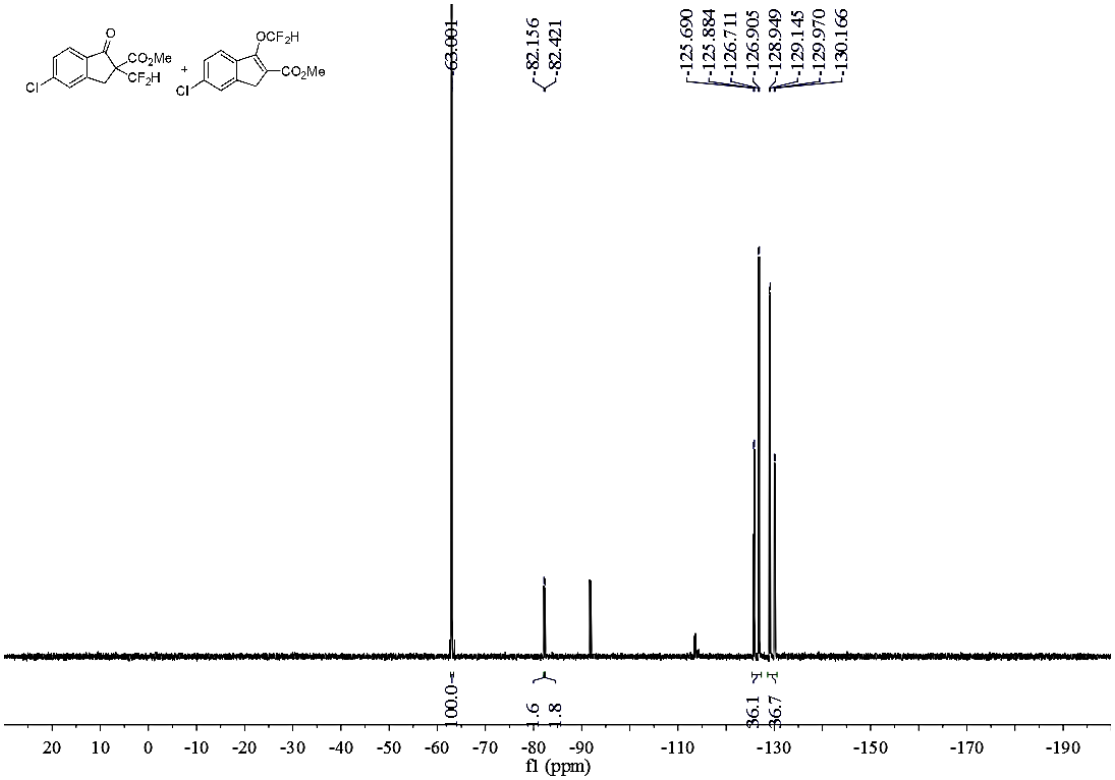
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2c**



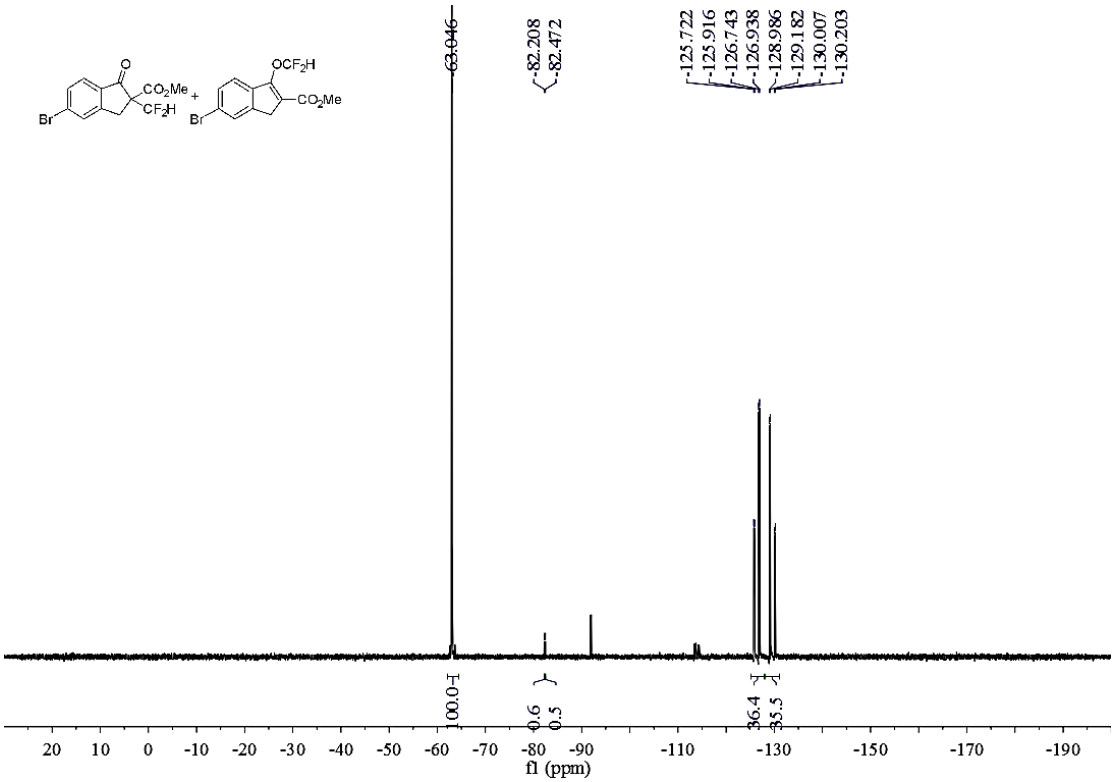
Methyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2d**



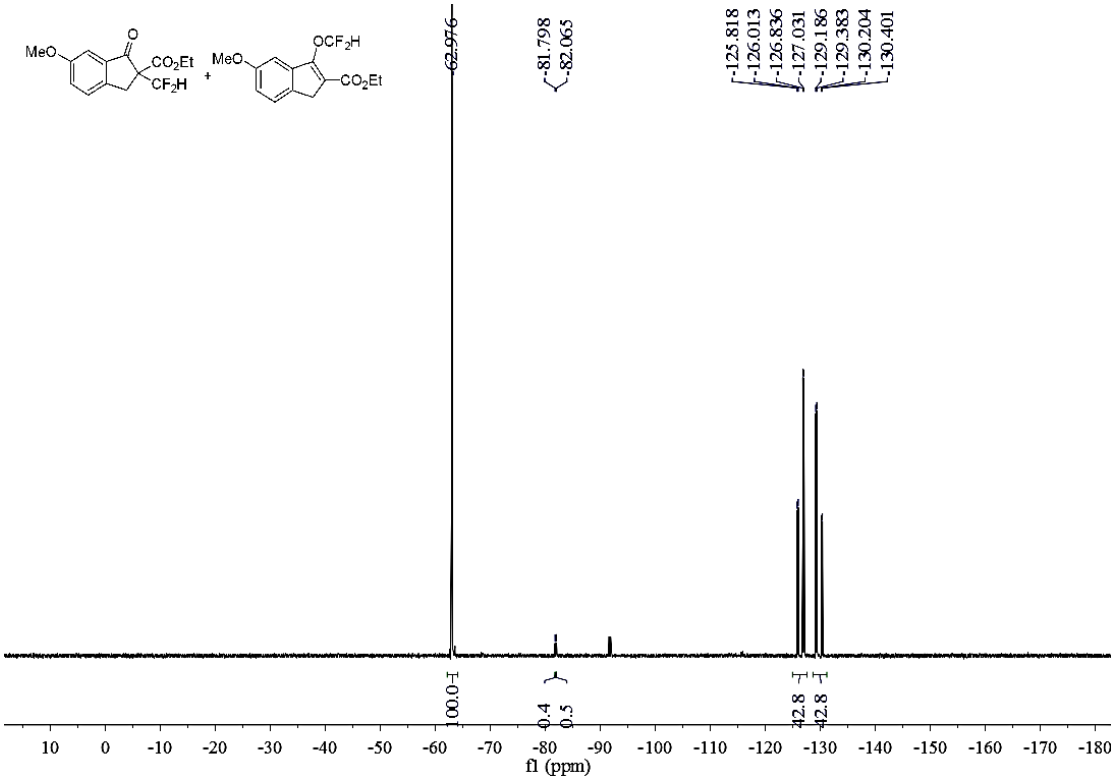
Methyl 5-chloro-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2e**



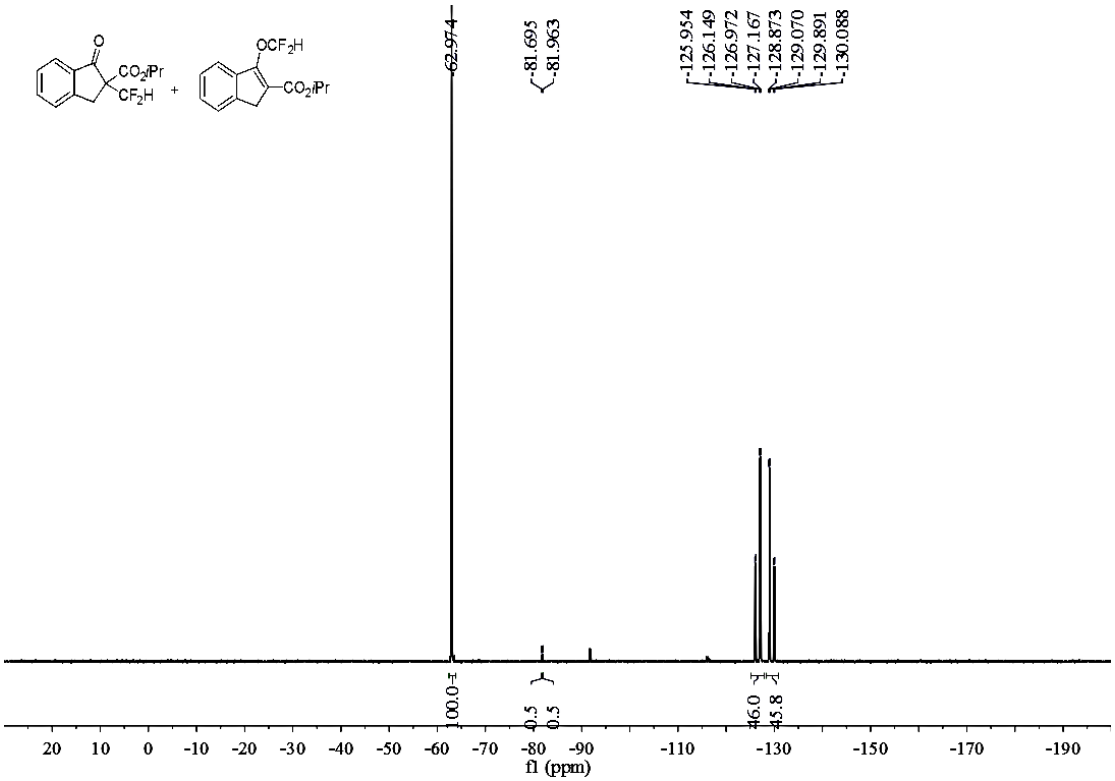
Methyl 5-bromo-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2f**



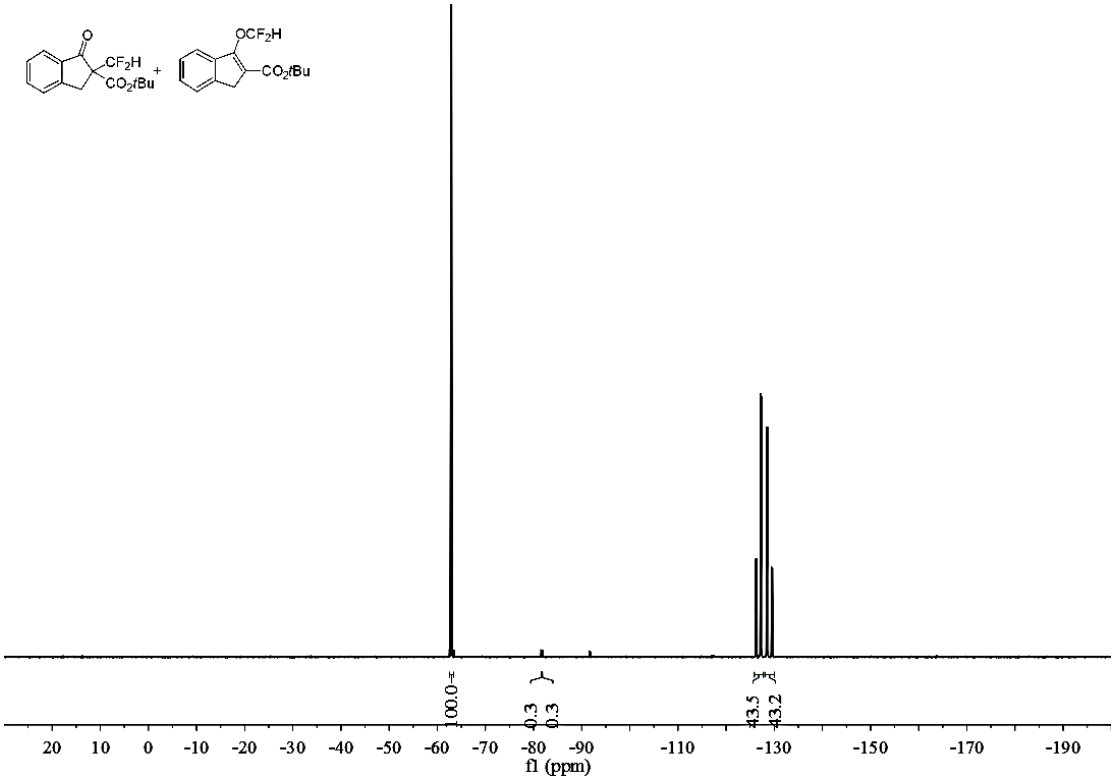
Ethyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2g**



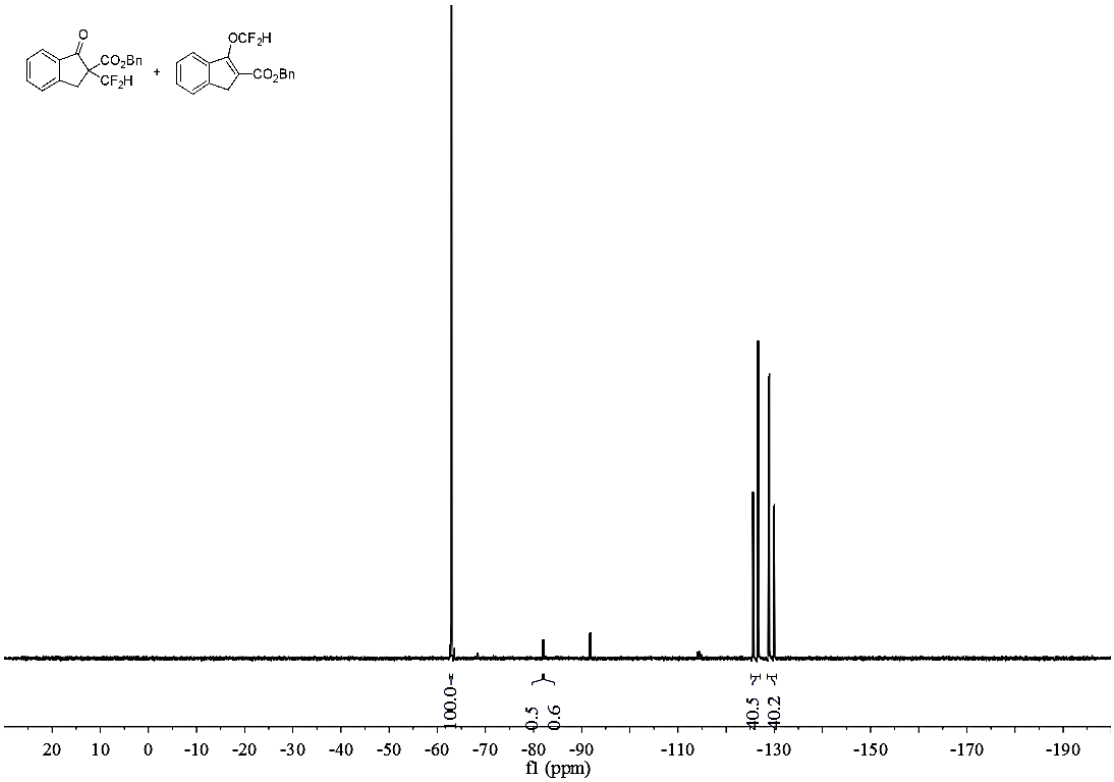
isopropyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2h**



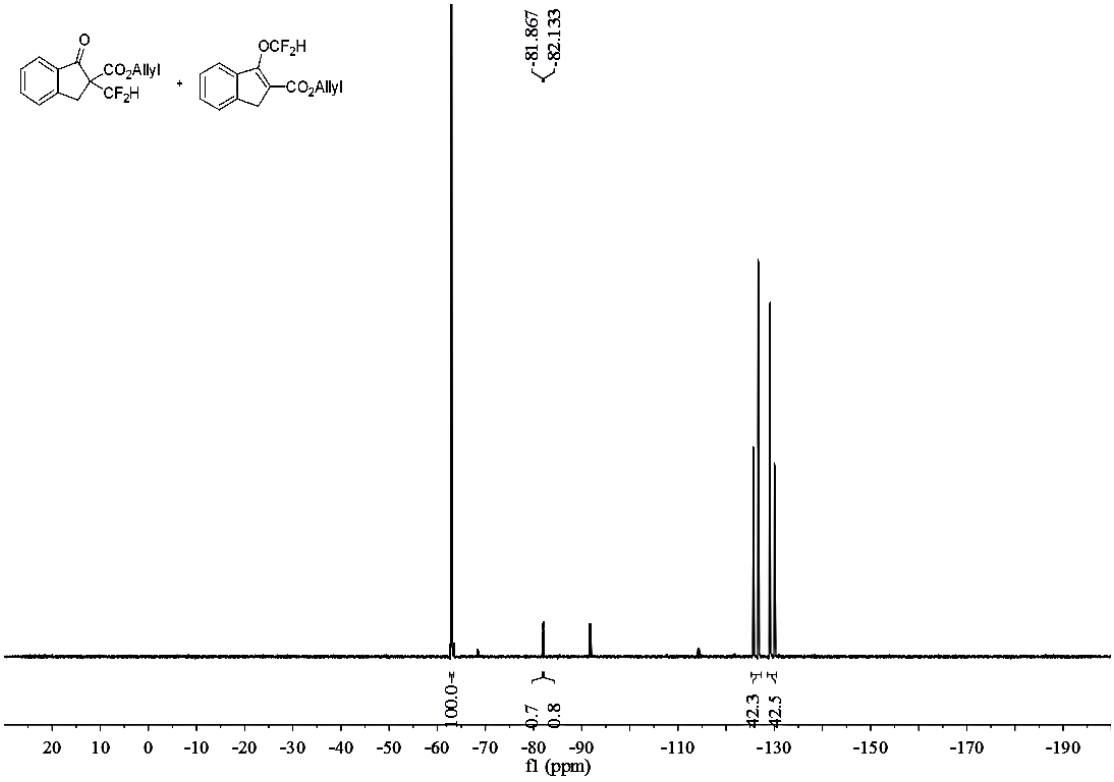
tert-butyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2i**



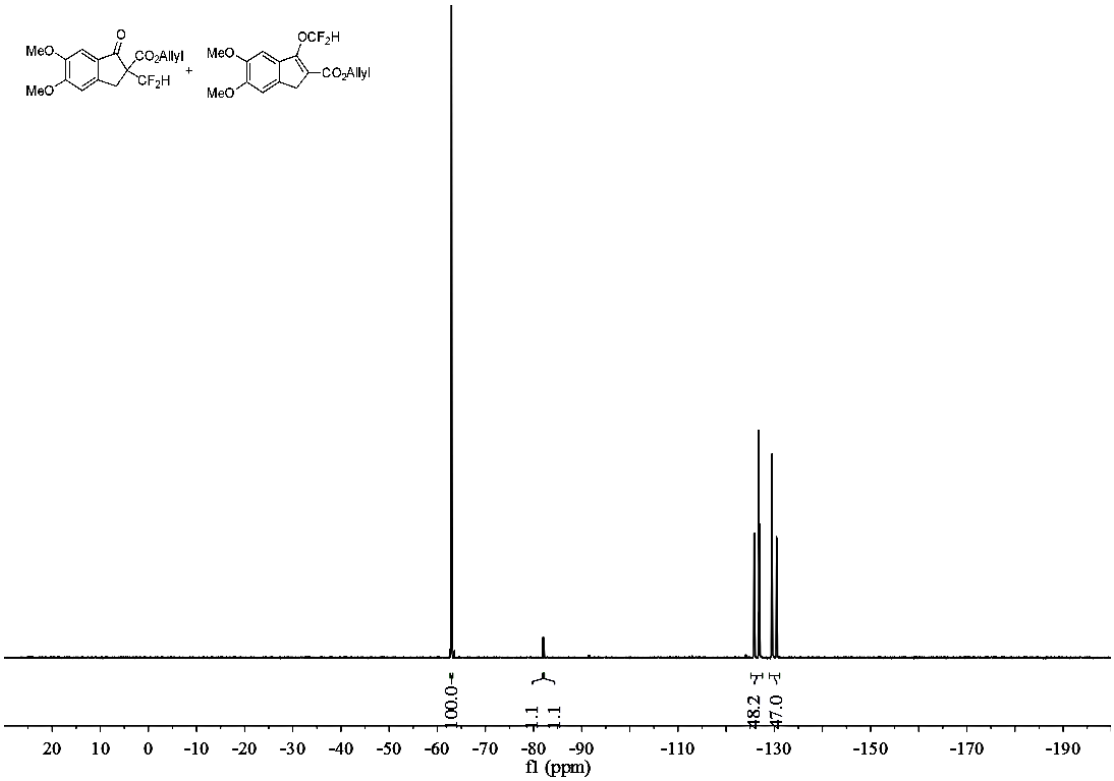
Benzyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2j**



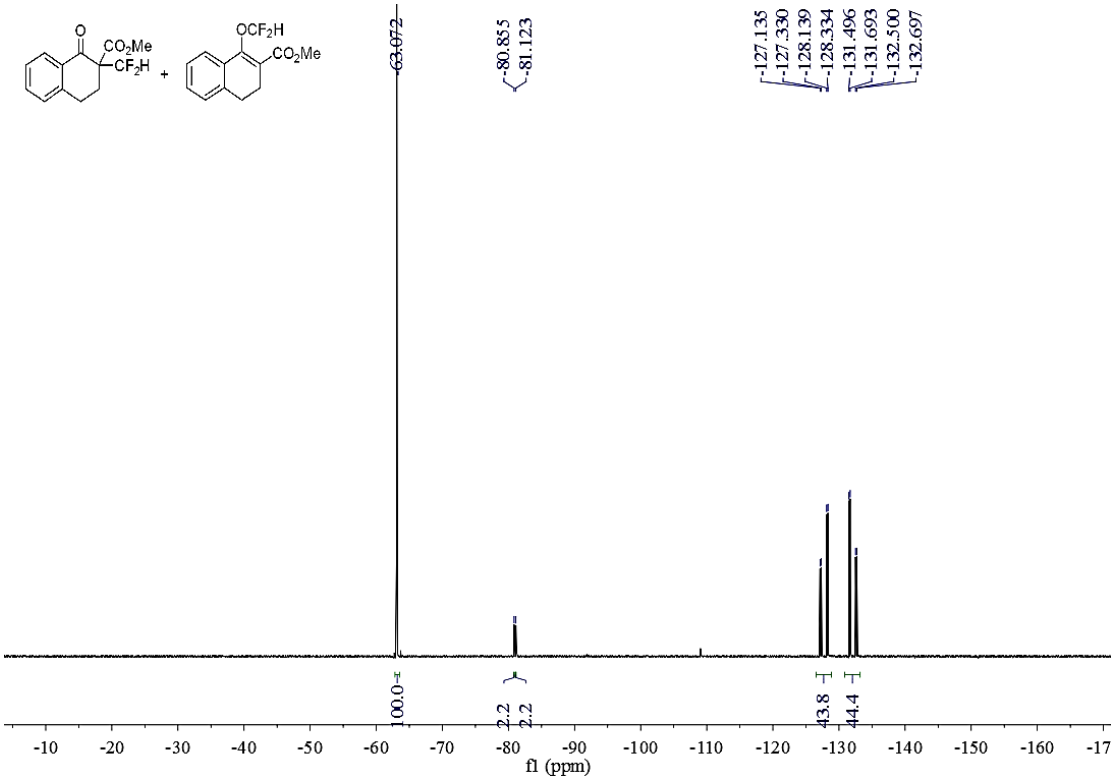
Allyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2k**



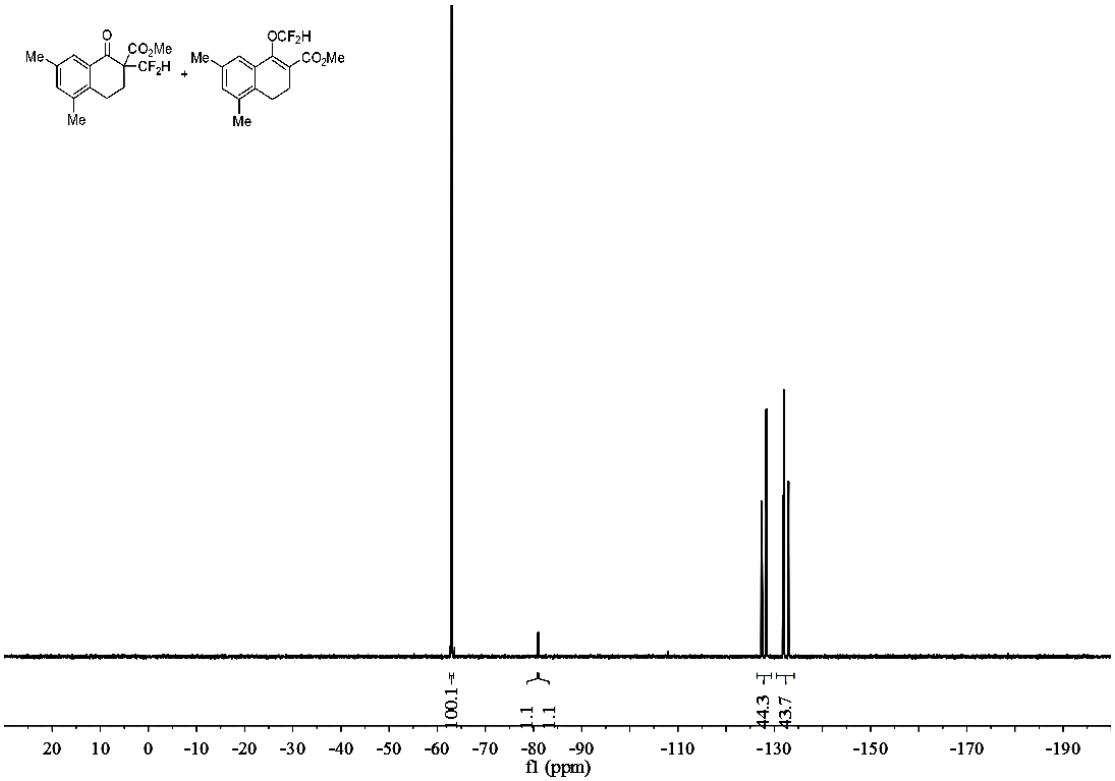
Alyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **2l**



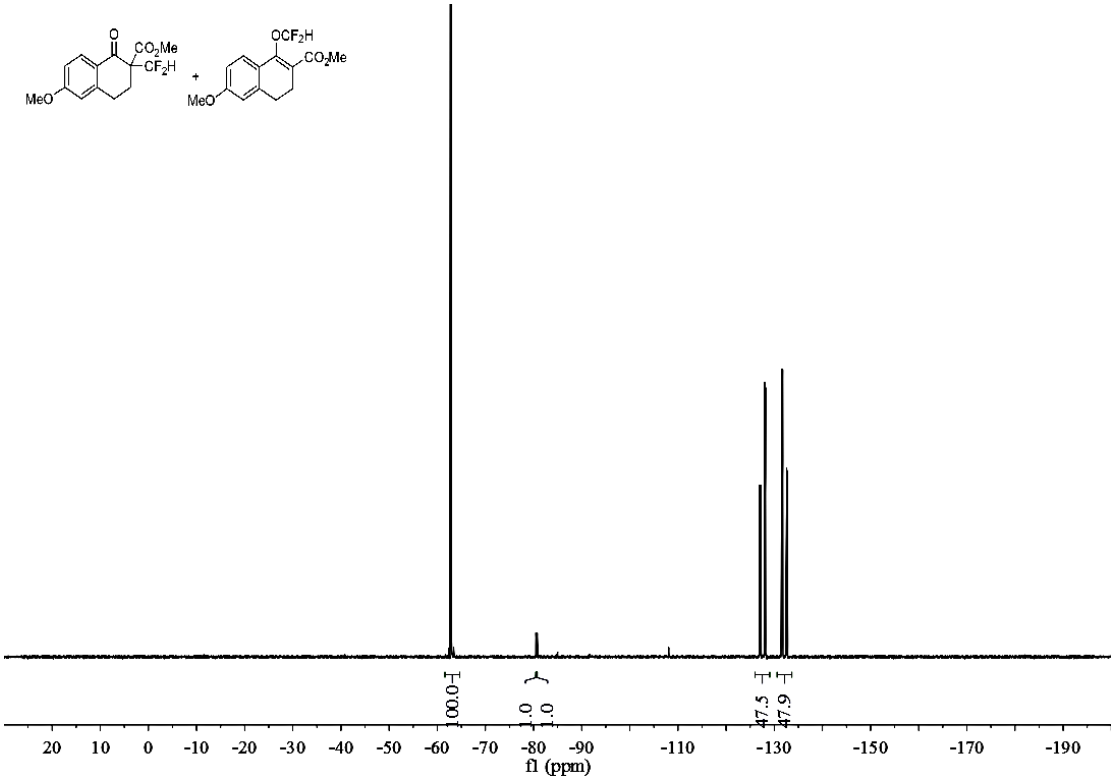
Methyl 2-(difluoromethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2m**



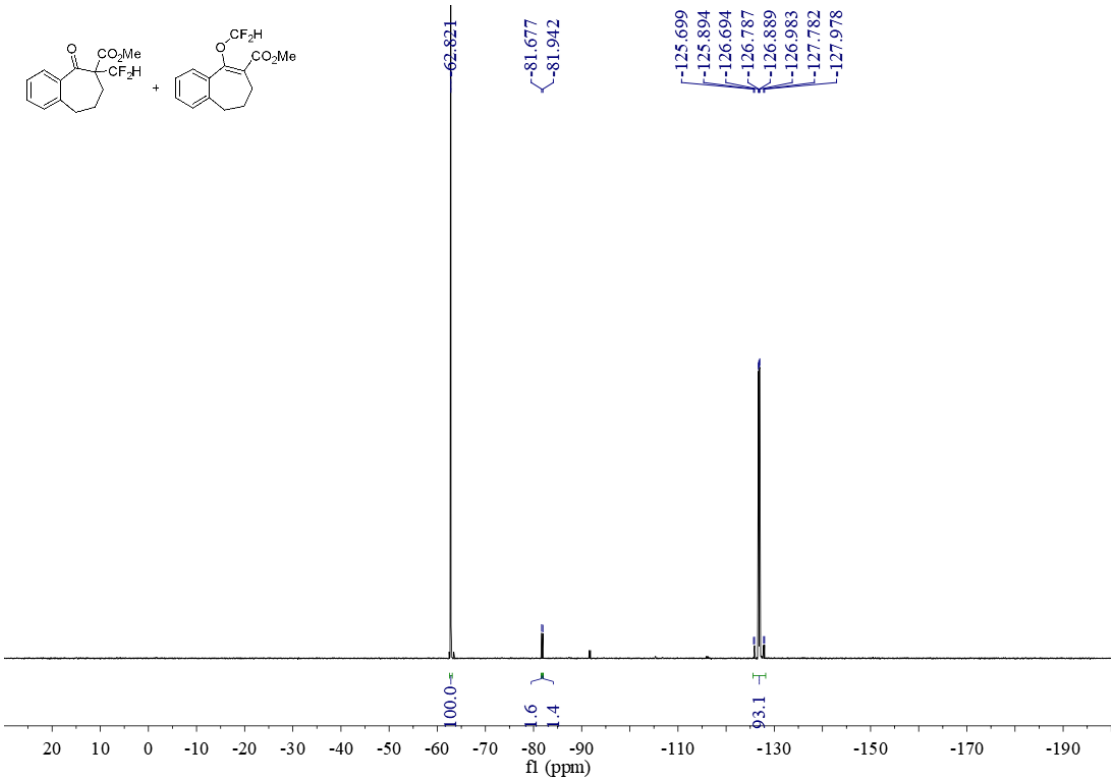
Methyl 2-(difluoromethyl)-5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate **2n**



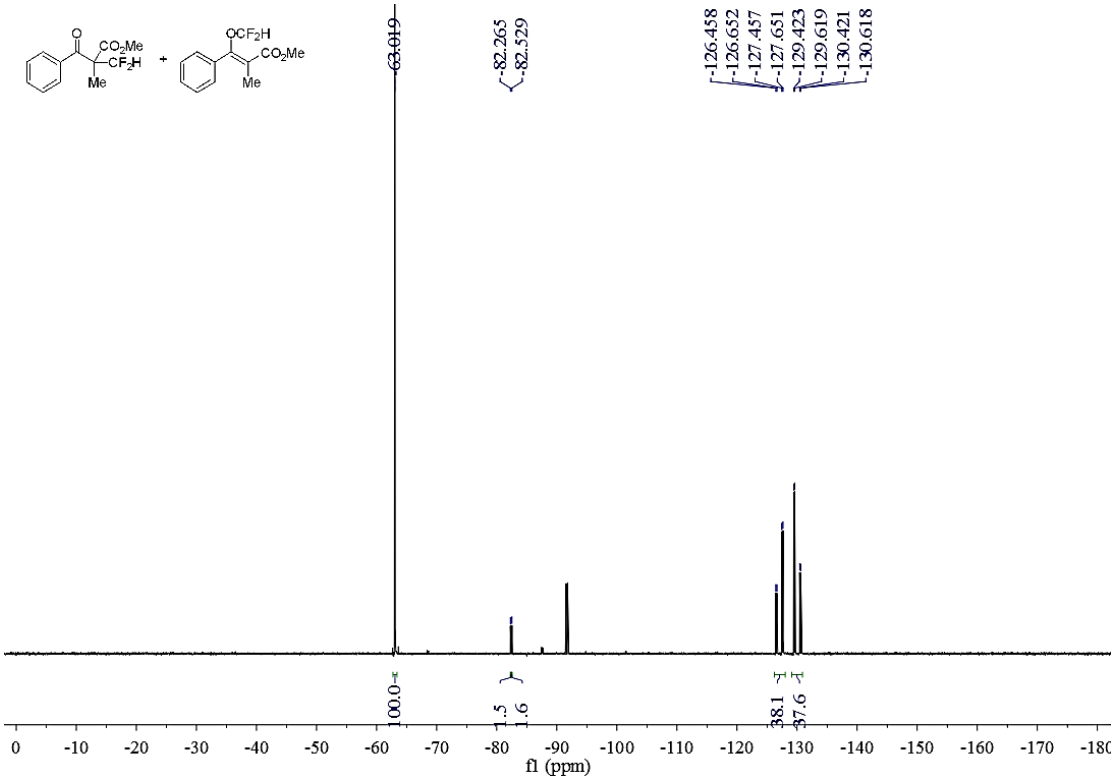
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate**2o**



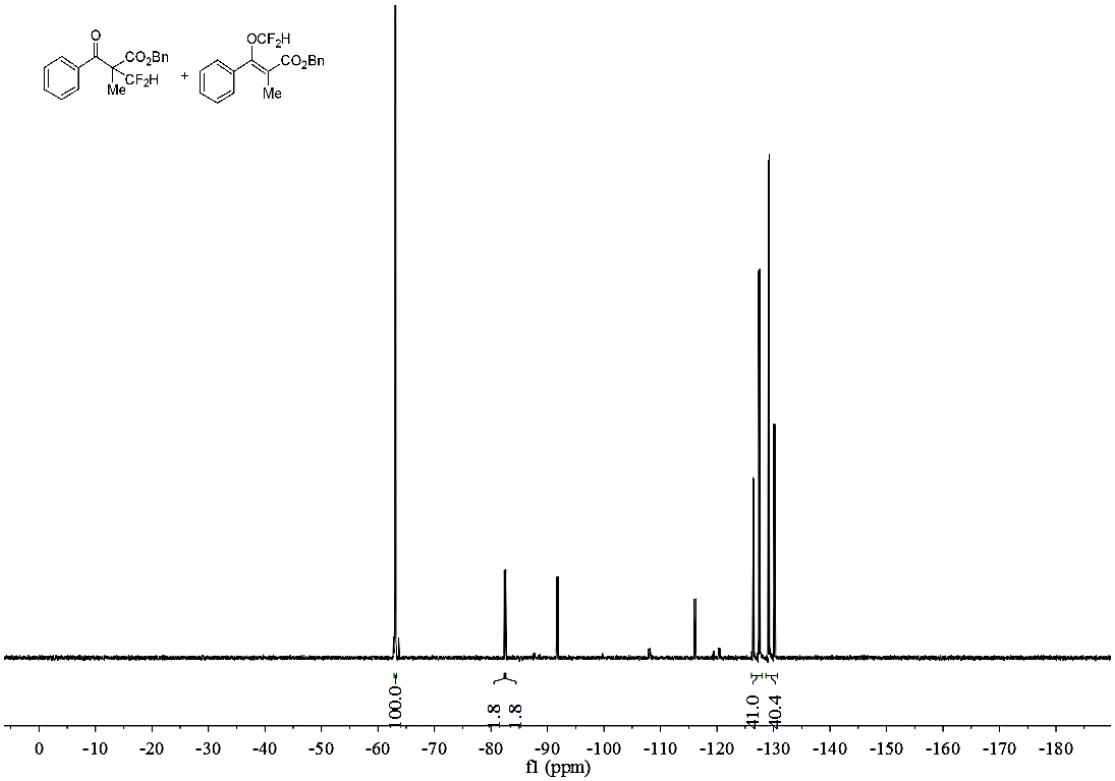
Methyl 6-(difluoromethyl)-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate **2p**



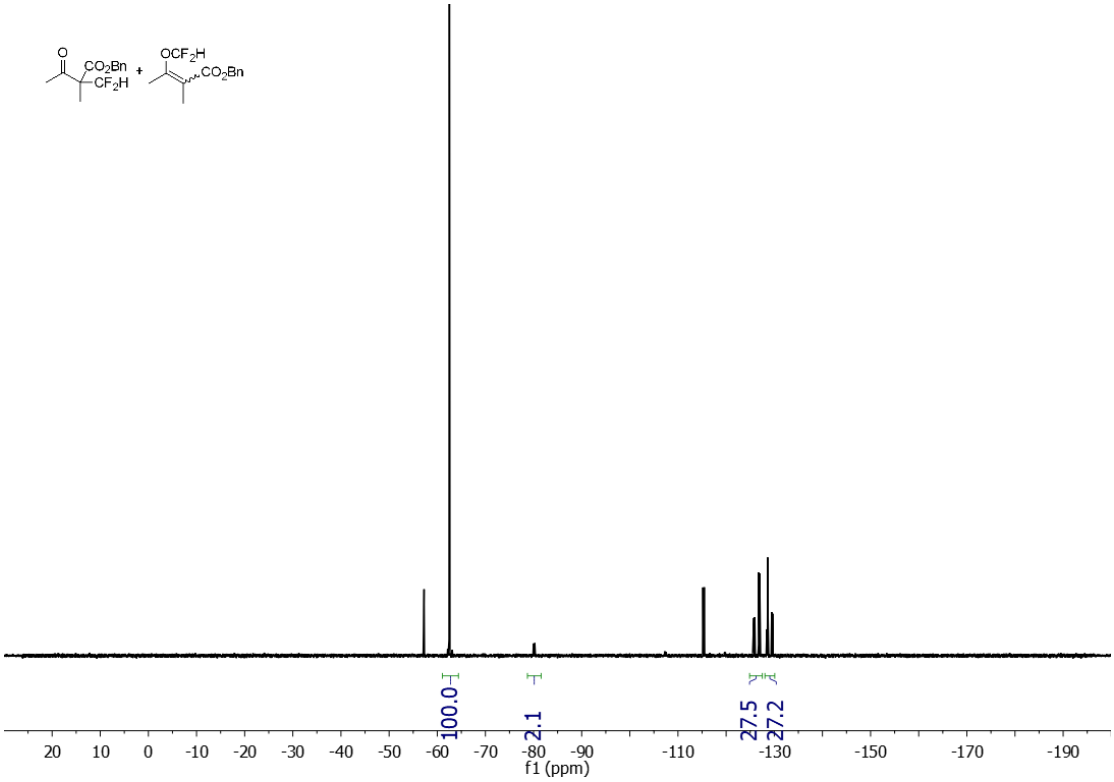
Methyl 2-benzoyl-3,3-difluoro-2-methylpropanoate **2q**



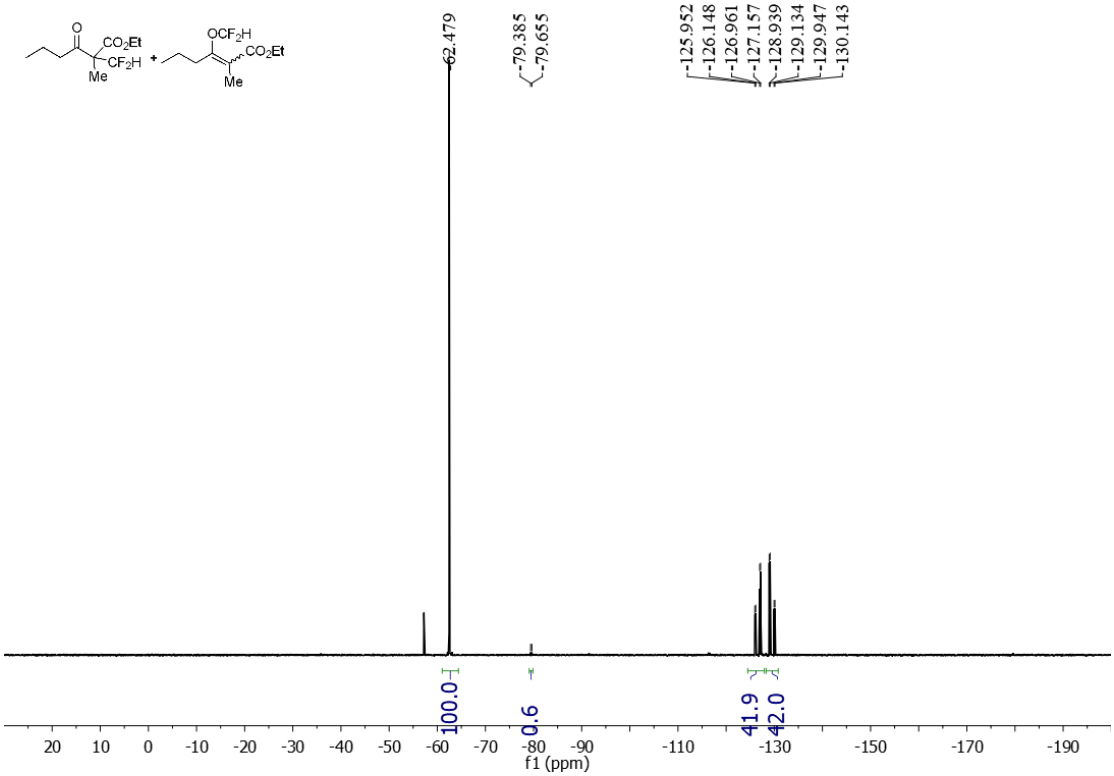
Benzyl 2-benzoyl-3,3-difluoro-2-methylpropanoate **2r**



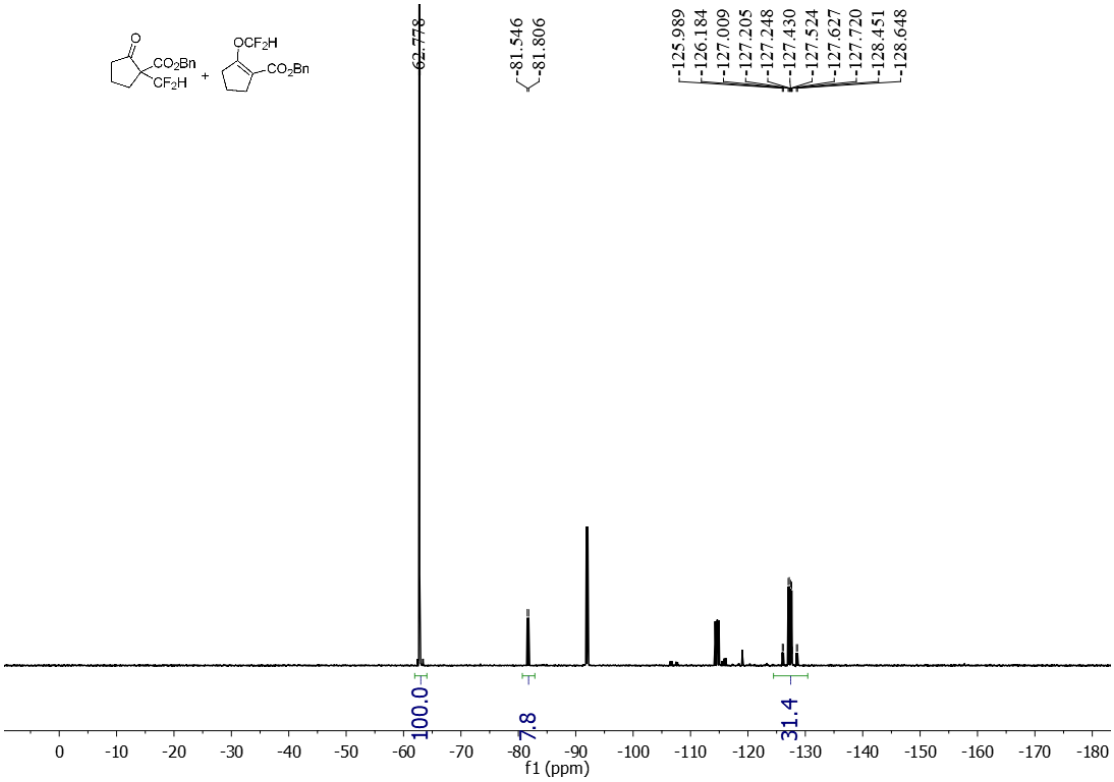
Benzyl 2-(difluoromethyl)-2-methyl-3-oxobutanoate **2s**



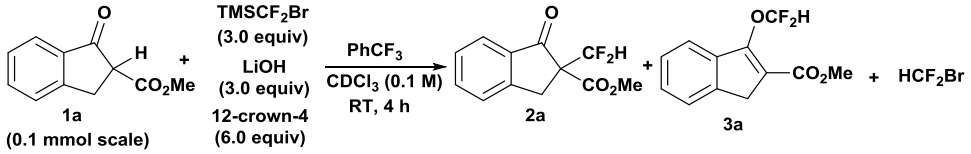
Ethyl 2-(difluoromethyl)-2-methyl-3-oxohexanoate **2t**



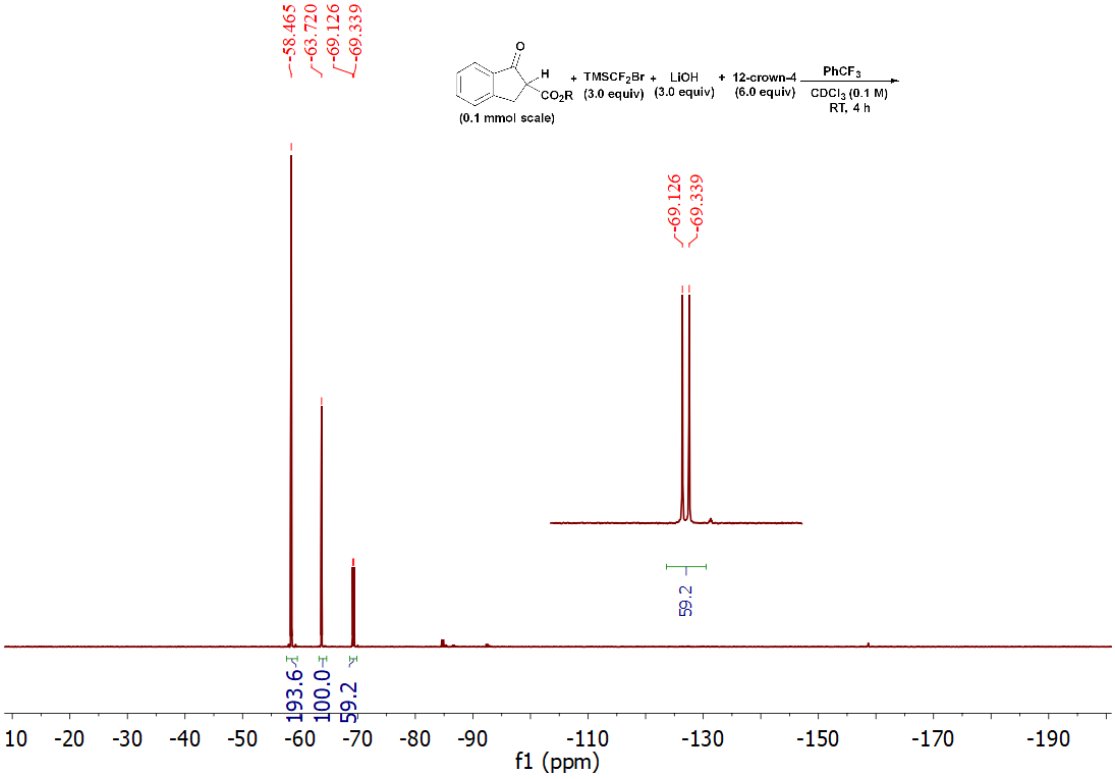
Benzyl 1-(difluoromethyl)-2-oxocyclopentane-1-carboxylate **2u**

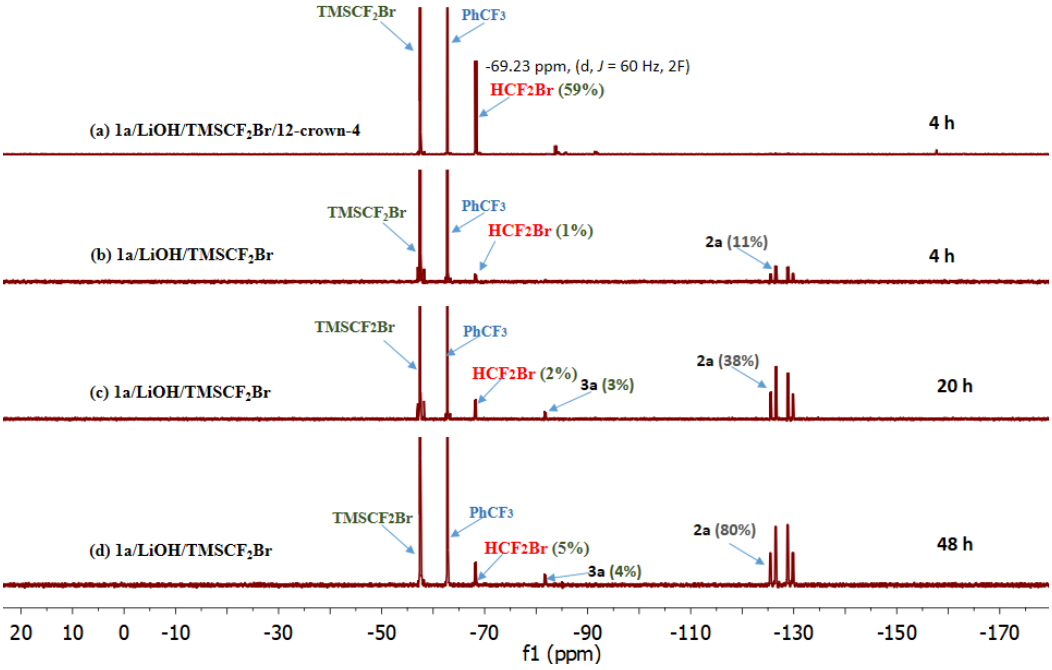


9. ^{19}F-NMR study for encapsulation of free Lithium.



Methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **1a** (19.1 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol) was added to one over-dried NMR tube sealed by a rubber septum with a N_2 balloon. After 1.0 mL $CDCl_3$ and 8.2 μL $PhCF_3$ (calculated 0.1 mmol for CF_2H group) and liquid 12-crown-4 (95μL, 0.6 mmol) were added sequentially, the solution was strongly shaked for several minutes. Subsequently, $TMSCF_2Br$ (60.9 mg, 0.3 mmol) was added dropwise accompanying with strongly shaking the NMR tube. Finally, rubber septum was removed very quickly under N_2 atmosphere and the tube was soon sealed by plastic cap. Then the cap was protected and wrapped by parafilm M. After strongly shaking for 4 hours, the HCF_2Br was detected in 59% yield and neither **2a** nor **3a** can be observed. Meanwhile, followed by the similar procedure without the addition of 12-crown-4 ether, ^{19}F-NMR study of difluoromethylation of **1a** was also investigated. After 48 hours shaking at room temperature, the unexpected protonated HCF_2Br wasobtained in 5% yield and the desired carbon-difluoromethylaed product **2a** was obtained in 80% yields with the C/O isomer ratio was determined as 95:5.




TMSCF2Br
PhCF3
-69.23 ppm, (d, J = 60 Hz, 2F)
HCF2Br (59%)
(a) 1a/LiOH/TMSCF2Br/12-crown-4
4 h
TMSCF2Br
PhCF3
HCF2Br (1%)
2a (11%)
(b) 1a/LiOH/TMSCF2Br
4 h
TMSCF2Br
PhCF3
HCF2Br (2%)
3a (3%)
2a (38%)
(c) 1a/LiOH/TMSCF2Br
20 h
TMSCF2Br
PhCF3
HCF2Br (5%)
3a (4%)
2a (80%)
(d) 1a/LiOH/TMSCF2Br
48 h
20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170
f1 (ppm)