Supporting Information For:
Modular Synthesis of Cyclic β-Difluoroamines

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1 General Experimental

1.1 Reagents and solvents

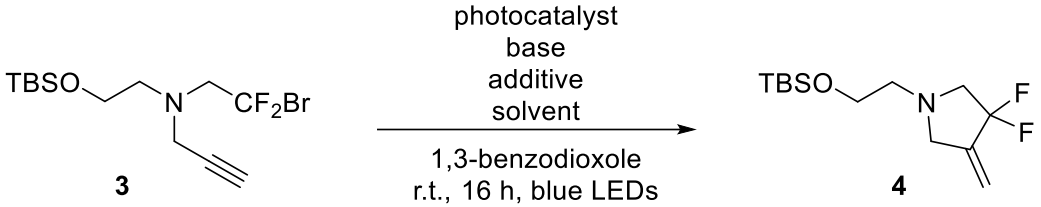
Reagents were purchased from commercial suppliers and used directly without further purification. Unless indicated, technical grade solvents were purchased from commercial suppliers and used without further purification, except THF which was pre-dried over sodium wire and obtained from a solvent tower, where degassed solvent was passed through two columns of activated alumina and 7-micron filter under a 4-bar pressure. Petrol refers to the fraction of petroleum ether boiling between 40–60 °C. All water was deionised before use and all reactions are conducted under an Ar atmosphere unless otherwise stated.

1.2 Analysis and characterisation

Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica-gel plates 60 F254 plates and visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate. Column chromatography was carried out using Fluorochem silica gel 60 Å (40-63 mesh). Melting points were calculated using a Stuart SMP3 and Fourier Transform Infrared Spectrometry (IR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of absorption (cm^{-1}). High Resolution Mass Spectrometry (HRMS) were measured on a Bruker microTOF II with Electron Spray Ionisation (ESI). ^{1}H NMR spectra were recorded on either a Bruker AV 400, AV(III) 400HD or AV(III) 500HD in $CDCl_3$, DMSO or MeOH-d_4. ^{1}H NMR chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz), with residual protic solvent as the internal reference ($CDCl_3$ δ = 7.26 ppm, DMSO δ = 2.50 ppm, MeOH-d_4 δ = 3.31 ppm). The proton spectra are reported as follows: δ (multiplicity, coupling constant J, number of protons). Abbreviations used include s – singlet, d – doublet, t – triplet, q – quartet, sept – septet, m – multiplet, br – broad, app. – apparent. ^{13}C NMR were recorded on a 400 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to the ^{13}C signals in the solvent (central peak of $CDCl_3$ δ = 77.16 ppm, DMSO δ = 39.52 ppm, MeOH-d_4 δ = 49.03 ppm) and coupling constants (*J*) are given in Hertz (Hz). All ^{13}C NMR are reported as proton decoupled spectra. ^{19}F NMR were recorded on a 376 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to $CFCl_3$ at 0.00 ppm and are reported as proton decoupled spectra. Where appropriate, COSY, HMQC and HMBC experiments were performed to aid assignment. All photoredox reactions were conducted in borosilicate glass disposable culture tubes (approximate wall thickness 0.6 mm), or in a 250 mL borosilicate glass measuring cylinder.

2 Reaction Optimisation

Supplementary Table 1. Optimisation of alkynyl amine cyclisation



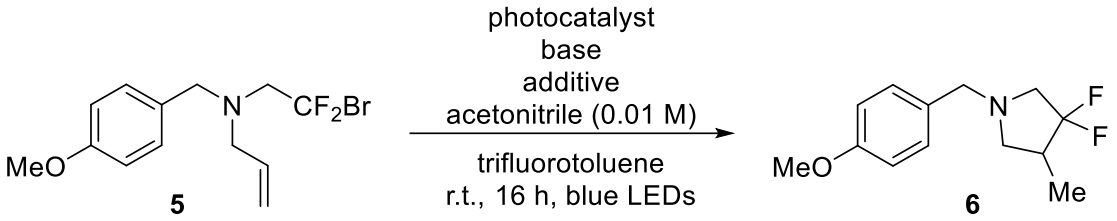
To a 10 mL culture tube was added *N*-(2-bromo-2,2-difluoroethyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **3** (0.05 mmol), photocatalyst (as table), base (as table), H-source additive (as table) and solvent (as table). The culture tube was sealed and the mixture was sparged with Ar for 15 minutes. The blue LEDs were switched on and the reaction was stirred at room temperature for 16 hours. 1,3-Benzodioxole (1 equiv.) was added, and the mixture was stirred at room temperature for 5 minutes, then analysed by NMR.

entry	catalyst (mol%)	base	base equiv.	H-source	H-source equiv.	solvent	conc/ M	product yield /%	starting material yield /%
1	$Ir(ppy)_3$ (1)	DIPEA	10	none	-	MeCN	0.01	44	0
2	$Ir(ppy)_3$ (1)	Et_3N	10	none	-	MeCN	0.01	56	0
3	$Ir(ppy)_3$ (1)	Bu_3N	10	none	-	MeCN	0.01	25	0
4	$Ir(ppy)_3$ (1)	DMAP	10	none	-	MeCN	0.01	0	100
5	$Ir(ppy)_3$ (1)	K_2CO_3	10	none	-	MeCN	0.01	0	100
6	$Ir(ppy)_3$ (1)	K_3PO_4	10	none	-	MeCN	0.01	0	100
7	$Ir(ppy)_3$ (1)	Et_3N	1.5	none	-	MeCN	0.01	0	70
8	$Ir(ppy)_3$ (1)	Et_3N	3	none	-	MeCN	0.01	0	33
9	$Ir(ppy)_3$ (1)	Et_3N	5	none	-	MeCN	0.01	34	17
10	$Ir(ppy)_3$ (1)	Et_3N	10	none	-	MeCN:MeOH 1:1	0.01	18	0
11	$Ir(ppy)_3$ (1)	Et_3N	10	none	-	toluene	0.01	8	100
12	$Ir(ppy)_3$ (1)	Et_3N	10	none	-	THF	0.01	22	-[a]
13	$Ir(ppy)_3$ (1)	Et_3N	10	Hantzsch ester	1.5	MeCN	0.01	7	0
14	$Ir(ppy)_3$ (1)	Et_3N	10	HCOOH	1.5	MeCN	0.01	71	0
15	$Ir(ppy)_3$ (1)	Et_3N	10	TTMSS	1.5	MeCN	0.01	12	0
16	$Ir(ppy)_3$ (1)	Et_3N	5	Hantzsch ester	1.5	MeCN	0.01	60	0
17	$Ir(ppy)_3$ (1)	Et_3N	5	HCOOH	1.5	MeCN	0.01	71	8
18	$Ir(ppy)_3$ (1)	Et_3N	5	TTMSS	1.5	MeCN	0.01	45	0
19	$Ir(ppy)_3$ (1)	Et_3N	10	HCOOH	3	MeCN	0.01	72	0
20	$Ir(ppy)_3$ (1)	Et_3N	10	HCOOH	5	MeCN	0.01	77	0
21	$Ir(ppy)_3$ (1)	Et_3N	10	HCOOH	10	MeCN	0.01	5	93
22	$Ir(ppy)_3$ (1)	none	-	HCOOH	1.5	MeCN	0.01	0	93
23	$Ir(ppy)_3$ (1)	Et_3N	5	HCOOH	3	MeCN	0.01	60	0
24	$Ir(ppy)_3$ (1)	Et_3N	5	HCOOH	5	MeCN	0.01	5	62

entry	catalyst (mol%)	base	base equiv.	H-source	H-source equiv.	solvent	conc/ M	product yield /%	starting material yield /%
25	$Ir(ppy)_3$ (1)	Et_3N	5	TRIP thiol	1.5	MeCN	0.01	0	56
26	$Ir(ppy)_3$ (1)	Et_3N	10	HCOOH	7	MeCN	0.01	38	0
27	$Ir(ppy)_3$ (1)	Et_3N	10	HCOOH	6	MeCN	0.01	48	0
28	$Ir(ppy)_3$ (1)	Et_3N	5	Et_3N.HI salt	5	MeCN	0.01	20	92
29	$Ir(ppy)_3$ (1)	Et_3N	10	CH_3COOH	5	MeCN	0.01	88	4
30	$Ir(ppy)_3$ (1)	Et_3N	10	C_6H_5COOH	5	MeCN	0.01	0	100
31	$Ir(ppy)_3$ (1)	Et_3N	10	NaOAc	5	MeCN	0.01	70	0
32	$Ir(ppy)_3$ (1)	Et_3N	10	CF_3COOH	5	MeCN	0.01	51	0
33	$Ir(ppy)_3$ (1)	Et_3N	15	CH_3COOH	5	MeCN	0.01	0	100
34	$Ir(ppy)_3$ (1)	Et_3N	10	CH_3COOH	4	MeCN	0.01	16	83
35	$Ir(ppy)_3$ (1)	Et_3N	10	CH_3COOH	5	MeCN	0.1	26	60
36	$Ir(ppy)_3$ (1)	Et_3N	10	CH_3COOH	5	MeCN	0.0075	26	56
37	$Ir(ppy)_3$ (1)	Et_3N	10	CH_3COOH	5	MeCN	0.005	90	0
38	$Ir(ppy)_3$ (1)	Et_3N	10	malonic acid	2.5	MeCN	0.01	22	58
39	Eosin Y (1)	Et_3N	10	CH_3COOH	5	MeCN	0.01	13	83
40	Eosin Y (5)	Et_3N	10	CH_3COOH	5	MeCN	0.01	25	58
41	4CzIPN (1)	Et_3N	10	CH_3COOH	5	MeCN	0.01	29	63
42	4CzIPN (5)	Et_3N	10	CH_3COOH	5	MeCN	0.01	75	3
43	$Ir(ppy)_3$ (0.5)	Et_3N	10	CH_3COOH	5	MeCN	0.01	69	0
44	$Ir(ppy)_3$ (3)	Et_3N	10	CH_3COOH	5	MeCN	0.01	46	0
45	$[Ir(dtbbpy)(ppy)_2]PF_6$ (1)	Et_3N	10	CH_3COOH	5	MeCN	0.01	54	0
46	9-Mesityl-10-methylacridinium tetrafluoroborate (5)	Et_3N	10	CH_3COOH	5	MeCN	0.01	5	95
47	$Cu(dap)_2$ chloride (1)	Et_3N	10	CH_3COOH	5	MeCN	0.01	0	97
48	$Ru(bpy)_3Cl_2$ (1)	Et_3N	10	CH_3COOH	5	MeCN	0.01	7	92

[a]unable to integrate product signals

Supplementary Table 2. Optimisation of alkenyl amine cyclisation



To a 10 mL culture tube was added *N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-en-1-amine **5** (0.05 mmol), photocatalyst (as table), base (as table), H-source additive (as table) and acetonitrile (100 mL/mmol). The culture tube was sealed and the mixture was sparged with Ar for 15 minutes. The blue LEDs were switched on and the reaction was stirred at room temperature for 16 hours. Trifluorotoluene (1 equiv.) was added and the mixture was stirred at room temperature for 5 minutes, then analysed by NMR.

entry	catalyst (mol%)	base	base equiv.	H-source	H-source equiv.	product yield /%	starting material yield /%
1	$Ir(ppy)_3$ (1)	DIPEA	10	none	-	44	0
2	$Ir(ppy)_3$ (1)	Et_3N	10	none	-	38	0
3	$Ir(ppy)_3$ (1)	Et_3N	10	AcOH	5	10	51
4	$Ir(ppy)_3$ (1)	DIPEA	10	HCOOH	5	49	13
5	$Ir(ppy)_3$ (1)	DIPEA	10	TTMSS	5	97	0
6	4CzIPN (5)	DIPEA	10	none	-	48	0
7	$Ir(ppy)_3$ (1)	DIPEA	5	TTMSS	5	95	0
8	$Ir(ppy)_3$ (1)	DIPEA	10	TTMSS	10	94	0
9	$Ir(ppy)_3$ (1)	DMAP	10	TTMSS	10	93	0
10	$Ir(ppy)_3$ (5)	DIPEA	10	none	-	55	0
11	$Ir(ppy)_3$ (1)	none	-	TTMSS	5	0	0
12	$Ir(ppy)_3$ (1)	DIPEA	5	TTMSS	2	85	0
13	$Ir(ppy)_3$ (1)	DIPEA	2	TTMSS	2	53	0
14	$Ir(ppy)_3$ (1)	DIPEA	10	TTMSS	2	73	0
15	$Ir(ppy)_3$ (1)	DIPEA	5	TTMSS	1	37	0
16	$Ir(ppy)_3$ (1)	DIPEA	20	TTMSS	2	93	0
17	$Ir(ppy)_3$ (1)	DIPEA	10	triethylsilane	5	21	14
18	$Ir(ppy)_3$ (1)	DIPEA	10	triethoxysilane	5	35	9
19	$Ir(ppy)_3$ (1)	DIPEA	10	triisopropylsilanethiol	5	77	0
20	4CzIPN (5)	DIPEA	10	TTMSS	5	97	0
21	4CzIPN (5)	DBU	10	TTMSS	5	86	0
22	4CzIPN (5)	DABCO	10	TTMSS	5	97	0

3 Experimental Procedures and Characterisation of Compounds

3.1 General procedures

1. Amidation reaction using ethyl bromodifluoroacetate

To ethyl bromodifluoroacetate (1.1 equiv.) at 0°C was added the appropriate amine (1 equiv.) dropwise over 10 minutes. The flask was purged with Ar and stirred at room temperature for 16 hours. To the reaction mixture was added ethyl acetate (20 mL/g), water (10 mL/g), HCl (5 mL/g of a 1 M aq. solution), $NaHCO_3$ (5 mL/g of a sat. aq. solution) and brine (5 mL/g of a sat. aq. solution) and the mixture was extracted with ethyl acetate (3 × 20 mL/g). The combined organics were dried over magnesium sulfate and concentrated to give a residue which was used in the next step without further purification.

2. Two-Component Bromodifluoroalkylation Reaction

To an oven-dried flask fitted with a water condenser under an argon atmosphere was added the appropriate secondary amine (1 equiv.), and THF (0.5 mL/mmol). $PhSiH_3$ (3 equiv.) and bromodifluoroacetic acid (2 equiv.) in THF (0.5 mL/mmol) were added at 70 °C and the reaction mixture was heated at 70 °C until TLC analysis indicated complete secondary amine consumption. The reaction mixture was cooled to room temperature and $NaHCO_3$ (10 mL/g of a sat. aq. solution) was added. The mixture was extracted with diethyl ether (3 × 10 mL/g). The combined organics were dried ($MgSO_4$) and concentrated to ~2 mL volume, then purified as specified.

3. Three-Component Bromodifluoroalkylation Reaction

To an oven-dried flask fitted with a water condenser under an argon atmosphere was added the appropriate primary amine (1 equiv.), aldehyde (1 equiv.) and THF (0.5 mL/mmol), followed by $PhSiH_3$ (0.5 equiv.). The reaction was stirred at 70 °C for 10 minutes. Further $PhSiH_3$ (3 equiv.) and bromodifluoroacetic acid (2 equiv.) in THF (0.5 mL/mmol) were added and the reaction mixture was heated at 70 °C until TLC analysis indicated complete consumption. The reaction mixture was cooled to room temperature and $NaHCO_3$ (10 mL/g of a sat. aq. solution) was added. The mixture was extracted with diethyl ether (3 × 10 mL/g). The combined organics were dried ($MgSO_4$) and concentrated to ~2 mL volume, then purified as specified.

4. Photoredox Radical Cyclisation Reaction of Alkynyl Amines

To a culture tube was added the appropriate amine (1 equiv.), $Ir(ppy)_3$ (1 mol%), Et_3N (10 equiv.), AcOH (5 equiv.) and acetonitrile (100 mL/mmol). The culture tube was sealed and the mixture was sparged with Ar for 20 minutes. The blue LEDs were switched on and the reaction was stirred at room temperature until complete amine consumption, and then concentrated. The crude material was purified as specified.

5. Photoredox Radical Cyclisation Reaction of Alkenyl Amines

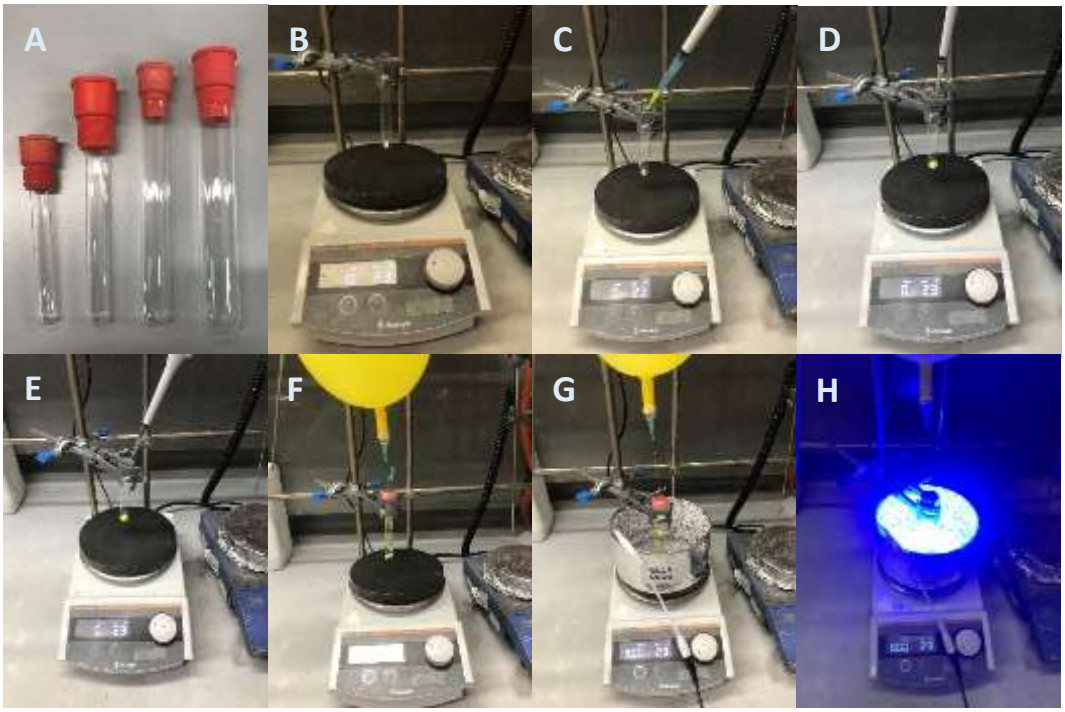
To a culture tube was added the appropriate amine (1 equiv.), $Ir(ppy)_3$ (1 mol%), DIPEA (10 equiv.), TTMSS (5 equiv.) and acetonitrile (100 mL/mmol). The culture tube was sealed and the mixture was sparged with Ar for 20 minutes. The blue LEDs were switched on and the reaction was stirred at room temperature until complete amine consumption. KF on alumina (40 wt%, 6 g/mmol) was added and the mixture was stirred at room temperature for 15 minutes, then filtered and concentrated. The crude material was purified as specified.

3.2 Graphical guide for the photoredox radical cyclisation reaction

Supplementary Figure 1. Photoredox Batch Set up

a) Component parts for the photoredox set-up. b) Reel of LEDs. c) Close-up of LED dish showing the reel of LEDs wrapped inside a crystallising dish in rows and foil on the base.

Supplementary Figure 2. Reaction Set up

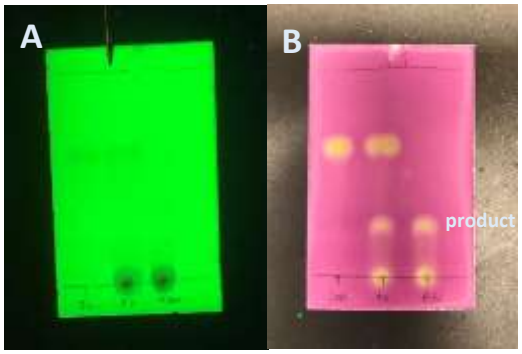


a) Choice of culture tube size depending on reaction scale. b) Culture tube with magnetic stirrer bar and amine/amide starting material. c) Addition of catalyst stock solution. d) Addition of tertiary amine base. e) Addition of hydrogen-donor (not required for cyclisation of amides). f) Addition of solvent. g) Culture tube sealed, placed inside LED dish, then sparged with Ar. h) Exit needle removed and LEDs turned on to initiate the reaction.

Supplementary Figure 3. Work-up procedure for cyclisation of alkenyl amines

a) Addition of KF on alumina (40 wt%) to reaction mixture. b) Mixture stirred vigorously for 15 minutes. c) Mixture filtered through a short pad of silica. d) KF on alumina, excess TTMSS and photocatalyst do not pass into the flask below.

Supplementary Figure 4. Reaction Analysis



a) TLC of reaction mixture (UV light, left to right – amine starting material, co-spot and reaction mixture). b) TLC of reaction mixture ($KMnO_4$, left to right – amine starting material, co-spot and reaction mixture).

3.3 Frequently asked questions

How easy is it to replicate the photoredox irradiation set-up?

Very simply. Blue LEDs can be found on many online retailers and often come with the power supply. Most labs will also have access to crystallising dishes of varying size. As can be seen in Section 0, LEDs are wrapped around the inside of a crystallising dish numerous times. The end of the LED reel is pre-attached to a female-connector (although this could also be done manually if required).

Does the reaction have to be run under strict anhydrous and inert conditions?

The reaction is not run under anhydrous conditions, but dissolved gases are removed from the reaction mixture *via* sparging and the reaction is conducted under an argon atmosphere. Control experiments (see section 0) were conducted to observe the importance of each of these factors.

Why is KF on alumina added after cyclisation of alkenyl amines?

Cyclisation of alkenyl amines required addition of TTMSS as a H-source. KF on alumina scavenges the excess silane as otherwise it causes difficulty in purification of the desired product.

Does reaction continue if the lights are turned off?

No, the reaction only proceeds when the mixture is irradiated.

Is the glassware used in the reaction important?

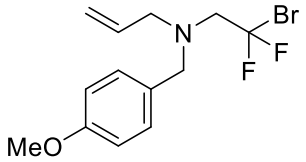
We have used borosilicate glass disposable culture tubes (approximate wall thickness 0.6 mm) or a 250 mL borosilicate glass measuring cylinder (see Section 3.2). The key is the capability for light penetration through the glass into the reaction mixture in order to excite the photocatalyst. Thin-walled glass such as that found in culture tubes is therefore ideal. The vessel chosen also needs to be placed under inert atmosphere, so this also needs to be considered.

What is the largest scale possible?

In batch, this is dependent on the largest size of culture tube available but also on the dimensions of the LED set-up. Maximising surface area of irradiation is an important factor. Our system has been scaled-up to 2 mmol using a measuring cylinder (see section 3.2), with a continuous flow of nitrogen and LEDs wrapped around the glassware itself. This system could easily be replicated for larger glassware as desired. A flow system would allow further scale-up of the reaction and full details of this will be reported in due course.

3.4 Synthesis of tertiary amine starting materials

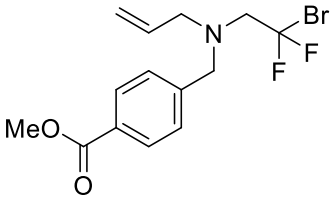
_N_-(2-Bromo-2,2-difluoroethyl)-_N_-(4-methoxybenzyl)prop-2-en-1-amine 5



Allylamine (75.0 µL, 1.00 mmol) and *p*-anisaldehyde (122 µL, 1.00 mmol) were subjected to General Procedure 3, stirring for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-5% diethyl ether in petroleum ether) to give **5** (165 mg, 517 µmol, 52% yield) as a colourless oil.

R_f (98:2 petroleum ether: ethyl acetate) = 0.26; **ν_{max}** (thin film)/cm^{-1} 3076, 3002, 2935, 2909, 2835, 1612, 1510; **δ_H** (500 MHz, $CDCl_3$) 7.28 – 7.23 (m, 2H, Ar*H*), 6.89 – 6.85 (m, 2H, Ar*H*), 5.84 (ddt, *J* = 17.7, 9.7, 6.5 Hz, 1H, *H*C=CH_2), 5.21 – 5.19 (m, 1H, HC=CH_2), 5.19 – 5.16 (m, 1H, HC=CH_2), 3.81 (s, 3H, OCH_3), 3.79 (s, 2H, NCH_2Ar), 3.32 (t, *J* = 13.4 Hz, 2H, NCH_2CF_2Br), 3.26 (d, *J* = 6.5 Hz, 2H, NCH_2CH); **δ_C** (126 MHz, $CDCl_3$) 159.0 (Ar*C*(OCH_3)), 134.9 (H*C*=CH_2), 130.5 (Ar*C*q), 130.2 (Ar*C*H), 124.2 (t, *J* = 310.3 Hz, *C*F_2Br), 118.6 (HC=*C*H_2), 113.9 (Ar*C*H), 62.0 (t, *J* = 22.0 Hz, N*C*H_2CF_2Br), 58.0 (N*C*H_2Ar), 56.7 (N*C*H_2CH), 55.4 (O*C*H_3); **δ_F** (376 MHz, $CDCl_3$) – 49.55; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{16}{}^{79}BrF_2NO$ 320.0456; found 320.0457 (+0.40 ppm).

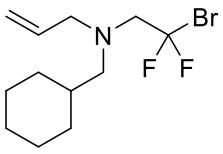
Methyl 4-((allyl(2-bromo-2,2-difluoroethyl)amino)methyl)benzoate 34



Allylamine (748.0 µL, 10.0 mmol) and methyl-4-formylbenzoate (1.64 g, 10.0 mmol) were subjected to General Procedure 3, stirring for 17 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 24:1 pentane in diethyl ether) to give **34** (1.98 g, 5.69 mmol, 57% yield) as a colourless oil.

R_f (9:1 pentane: diethyl ether) = 0.35; **ν_{max}** (thin film)/cm^{-1} 3005, 2981, 2951, 1719, 1611, 1434, 1274, 1190, 1100, 922, 756; **δ_H** (500 MHz, $CDCl_3$) 8.03 – 7.97 (m, 2H, Ar*H*), 7.45 – 7.40 (m, 2H, Ar*H*), 5.84 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H, *H*C=CH_2), 5.23 – 5.14 (m, 2H, HC=CH_2), 3.93 – 3.89 (m, 5H, OCH_3 and NCH_2Ar), 3.36 (t, *J* = 13.3 Hz, 2H, NCH_2CF_2Br), 3.26 (dt, *J* = 6.5, 1.3 Hz, 2H, NCH_2CH); **δ_C** (126 MHz, $CDCl_3$) 167.1 (Ar*C*(O)OCH_3)) , 144.1 (Ar*C*q), 134.4 (H*C*=CH_2), 129.9 (Ar*C*H), 129.4 (Ar*C*q), 128.7 (Ar*C*H), 123.8 (t, *J* = 310.0 Hz, *C*F_2Br), 119.0 (HC=*C*H_2), 62.4 (t, *J* = 22.2 Hz, N*C*H_2CF_2Br) , 58.4 (ArC(O)O*C*H_3), 57.0 (N*C*H_2Ar), 52.2 (N*C*H_2CH); **δ_F** (376 MHz, $CDCl_3$) –49.91; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{17}{}^{79}BrF_2NO_2$ 348.0405; found 348.0407 (+0.50 ppm).

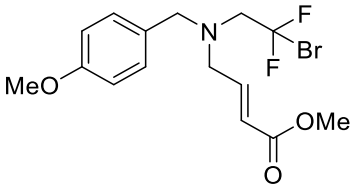
***N*-(2-Bromo-2,2-difluoroethyl)-N-(cyclohexylmethyl)prop-2-en-1-amine 35**



Allylamine (748 mg, 10.0 mmol) and bromodifluoroacetic acid (3.5 g, 20.0 mmol) were subjected to General Procedure 3, stirring for 17 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with pentane) to give **35** (1.09 g, 3.68 mmol, 37% yield) as a colourless oil.

R_f (99:1 pentane: diethyl ether) = 0.43; **ν_{max}** (thin film)/cm^{-1} 2922, 2850, 2823, 1449, 1282, 1079, 1013, 919, 775; **δ_H** (500 MHz, $CDCl_3$) 5.82 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H, *H*C=CH_2), 5.21 – 5.12 (m, 2H, HC=C*H*$_2$), 3.31 – 3.22 (m, 4H, NC*H*$_2$CH & NC*H*$_2$$CF_2Br$), 2.44 (d, *J* = 7.2 Hz, 2H, C*H*$_2$Cy), 1.83 – 1.62 (m, 5H, Cy), 1.43 (ddt, *J* = 11.1, 7.4, 3.7 Hz, 1H, Cy), 1.28 – 1.09 (m, 3H, Cy), 0.88 – 0.76 (m, 2H, Cy); **δ_C** (126 MHz, $CDCl_3$) 135.3 (H*C*=CH_2), 124.3 (t, *J* = 310.5 Hz, NCH_2CF_2Br), 117.9 (HC=*C*H_2), 64.0 (t, *J* = 21.7 Hz, NCH_2CF_2Br), 62.0 (NCH_2CH=CH_2), 58.1 (NCH_2Cy), 36.5 (*C*H_{Cy}), 31.5 (*C*H_2−Cy), 27.0 (*C*H_2−Cy), 26.2 (*C*H_2−Cy); **δ_F** (376 MHz, $CDCl_3$) –50.07; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{21}{}^{79}BrF_2N$ 296.0820; found 296.0811 (+2.90 ppm).

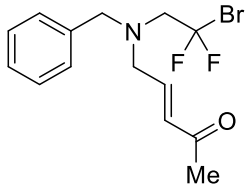
Methyl (*E*)-4-((2-bromo-2,2-difluoroethyl)(4-methoxybenzyl)amino)but-2-enoate 36



To a stirred solution of *N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-en-1-amine (265 mg, 827 µmol) and methyl acrylate (0.372 mL, 4.14 mmol) in DCM (1.6 mL) was added nitro-Grela (11.1 mg, 16.5 µmol). The mixture was stirred at room temperature for 72 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-20% diethyl ether in pentane) to give **36** (166 mg, 438 µmol, 53% yield) as a colourless oil.

R_f (80:20 petroleum ether: diethyl ether) = 0.30; **ν_{max}** (thin film)/cm^{-1} 3000, 2952, 2907, 2837, 1721; **δ_H** (400 MHz, $CDCl_3$) 7.24 (d, *J* = 8.5 Hz, 2H, ArC*H*), 6.92 (dt, *J* = 15.8, 6.2 Hz, 1H, NH_2CC(*H*)=CH), 6.87 (d, *J* = 8.5 Hz, 2H, ArC*H*), 6.00 (dt, *J* = 15.8, 1.5 Hz, 1H, H_2CC(H)=C*H*), 3.81 (br s, 5H, NCH_2Ar and ArC(OC*H*$_3$)), 3.75 (s, 2H, OC*H*$_3$, ester), 3.43 (d, *J* = 6.2 Hz, 2H, NC*H*$_2$C(H)=CH), 3.34 (t, *J* = 13.3 Hz, 2H, NC*H*$_2$$CF_2Br$); **$\delta_C$** (101 MHz, $CDCl_3$) 166.6 (*C*=O), 159.2 (Ar*C*(OCH_3)), 145.0 (NCH_2*C*(H)=CH), 130.1 (Ar*C*), 129.8 (Ar*C*q), 123.7 (t, *J* = 310.0 Hz, CF_2Br), 123.4 (HC=*C*(H)C=O), 114.0 (Ar*C*H), 62.6 (t, *J* = 22.4 Hz, NCH_2CF_2Br), 58.2 (N*C*H_2Ar), 55.4 (ArC(O*C*H_3)), 54.4 (NCH_2C(H)=CH), 51.8 (O*C*H_3, ester); **δ_F** (376 MHz, $CDCl_3$) –49.96; **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{15}H_{18}{}^{79}BrF_2NO_3$ 400.0330; found 400.0331 (+0.10 ppm).

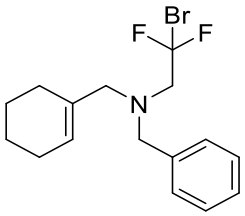
(*E*)-5-(Benzyl(2-bromo-2,2-difluoroethyl)amino)pent-3-en-2-one 37



To a stirred solution of *N*-benzyl-N-(2,2-difluoroethyl)prop-2-en-1-amine (232 mg, 800 µmol) and methyl vinyl ketone (0.330 mL, 4.00 mmol) in DCM (1.6 mL) was added nitro-Grela (10.7 mg, 16.0 µmol). The mixture was stirred at 40 °C for 23 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 10-20% diethyl ether in pentane) to give **37** (161 mg, 483 µmol, 61% yield) as a colourless oil.

R_f (90:10) petroleum ether: diethyl ether) = 0.13; **ν_{max}** (thin film)/cm^{-1} 3087, 3063, 3030, 3006, 2924, 2834, 1698, 1675, 1631; **δ_H** (400 MHz, $CDCl_3$) 7.39 – 7.31 (m, 4H, Ar*H*), 7.34 – 7.25 (m, 1H, Ar*H*), 6.71 (dt, *J* = 16.1, 6.1 Hz, 1H, *H*C=CHC(O)CH_3), 6.18 (d, *J* = 16.1 Hz, 1H, HC=C*H*C(O)CH_3), 3.90 (s, 2H, NC*H*$_2$Ar), 3.47 (d, *J* = 6.1 Hz, 1H, NC*H*$_2$C(H)=C), 3.38 (t, *J* = 13.2 Hz, 2H, NC*H*$_2$$CF_2Br$), 2.24 (s, 3H, C*H*$_3$); **$\delta_C$** (101 MHz, $CDCl_3$) 198.3 (*C*=O), 143.9 (H*C*=CHC(O)CH_3), 137.9 (Ar*C*q), 132.8 (HC=*C*HC(O)CH_3), 128.9 (Ar*C*H), 128.6 (Ar*C*H), 127.7 (Ar*C*H), 123.5 (t, *J* = 309.8 Hz, *C*F_2Br), 63.1 (t, *J* = 22.4 Hz, *C*H_2CF_2Br), 59.3 (NCH_2Ar), 55.2 (NCH_2C(H)=C), 27.1 (*C*H_3); **δ_F** (376 MHz, $CDCl_3$) –0.22; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{16}{}^{79}BrF_2NO$ 332.0456; found 332.0460 (+1.00 ppm).

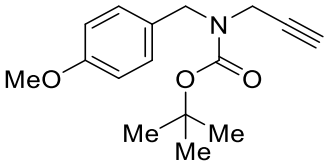
***N*-Benzyl-2-bromo-*N*-(cyclohex-1-en-1-ylmethyl)-2,2-difluoroethan-1-amine 38**



To a stirred solution of cyclohexene-1-carboxylic acid (1.00 g, 7.93 mmol) and benzylamine (577 µL, 5.28 mmol) in toluene (5.3 mL) at 110 °C was added phenylsilane (489 µL, 3.96 mmol). The reaction mixture was stirred at 110 °C for 16 hours, then $Zn(OAc)_2$ (969 µg, 528 µmol) and further phenylsilane (1.95 mL, 15.8 mmol) were added. The reaction mixture was stirred at 110 °C for 8 hours, then cooled to room temperature. Ethyl acetate (20 mL) was added and the mixture was extracted with HCl (3 × 10 mL of a 3 M aq. solution) The combined aqueous layers were basified until pH 12 with NaOH (6 M aq. solution). The mixture was extracted with dichloromethane (3 × 15 mL). The combined organics were dried over magnesium sulfate and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, eluting with 10% methanol in dichloromethane) to give a yellow oil which was dissolved in THF (0.9 mL) and heated to 70 °C. $PhSiH_3$ (655 µL, 5.31 mmol) was added, followed by bromodifluoroacetic acid (619 mg, 3.54 mmol) in THF (0.9 mL). The reaction mixture was stirred at 70 °C for 21 hours then cooled to room temperature. $NaHCO_3$ (20 mL of a sat. aq. solution) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated to ~2 mL volume. The material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in petroleum ether). The mixed fractions were repurified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in pentane) to give **38** (314 mg, 912 µmol, 12% yield) as a colourless oil.

R_f (pentane) = 0.53; **ν_{max}** (thin film)/cm^{-1} 3087, 3064, 3028, 2998, 2926, 2856, 2808, 1668, 1603; **δ_H** (400 MHz, $CDCl_3$) 7.38 – 7.26 (m, 5H, Ar*H*), 5.60 (app s, 1H, C*H*, alkene), 3.79 (s, 2H, NCH_2), 3.30 (t, *J* = 13.7 Hz, 2H, NCH_2CF_2Br), 3.09 (s, 2H, NCH_2), 2.06 – 1.93 (m, 4H, C$H_2CH_2CH_2CH_2$), 1.67 – 1.49 (m, 4H, $CH_2CH_2CH_2CH_2$); **δ_C** (101 MHz, $CDCl_3$) 138.9 (*C*, alkene), 135.4 (Ar*C*, quaternary), 129.0 (Ar*C*), 128.4 (Ar*C*), 127.4 (Ar*C*), 126.2 (*C*H, alkene), 124.3 (t, *J* = 310.8 Hz, CF_2Br), 62.3 (t, *J* = 21.7 Hz, NCH_2CF_2Br), 61.8 (NCH_2), 58.6 (t, *J* = 1.7 Hz, NCH_2Ar), 26.9 (HC=C-CH_2), 25.4 (C=CH-CH_2), 22.8 ($CH_2CH_2CH_2CH_2$), 22.6 ($CH_2CH_2CH_2CH_2$); **δ_F** (376 MHz, $CDCl_3$) –48.56; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{20}{}^{79}BrF_2N$ 344.0820; found 344.0822 (+0.70 ppm).

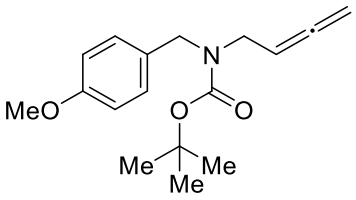
***tert*-Butyl (4-methoxybenzyl)(prop-2-yn-1-yl)carbamate 39**



To a 0 °C solution of 4-methoxybenzylamine (2.87 mL, 22.0 mmol) in dichloromethane (60 mL) was added Boc_2O (4.36 g, 20.0 mmol). The mixture was stirred at room temperature for 16 hours. Water (15 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated to give a residue which was dissolved in DMF (5 mL) and added dropwise over 20 minutes to a 0 °C suspension of NaH (960 mg, 24.0 mmol of a 60% dispersion in mineral oil) in DMF (15 mL). The mixture was stirred at 0 °C for 30 minutes. To the mixture was added propargyl bromide (2.67 mL, 24.0 mmol of 80% w/w solution in toluene) dropwise over 10 minutes. The reaction mixture was stirred at room temperature for 16 hours. To the reaction mixture was added water (100 mL) and brine (50 mL of a sat. aq. solution) and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organics were dried over magnesium sulfate and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, eluting with 5-10% diethyl ether in pentane) to give **39** (3.53 g, 12.8 mmol, 64% yield) as a yellow oil.

R_f (90:10 petroleum ether: diethyl ether) = 0.46; **ν_{max}** (thin film)/cm^{-1} 3291, 3262, 3002, 2976, 2933, 2873, 2837, 1689; **δ_H** (400 MHz, $CDCl_3$) 7.18 (d, *J* = 8.1 Hz, 2H, Ar*H*), 6.83 (d, *J* = 8.1 Hz, 2H, Ar*H*), 4.46 (s, 2H, NCH_2Ar), 4.12 – 3.82 (m, 2H, NCH_2, propargyl), 3.75 (s, 3H, OCH_3), 2.21 (t, *J* = 2.5 Hz, 1H, C*H*, alkyne), 1.47 (s, 9H, (C(CH_3)$_3$)); **δ_C** (101 MHz, $CDCl_3$) 159.0 (Ar*C*(OMe)), 154.9 (*C*=O), 129.4 (Ar*C*H), 129.1 (Ar*C*q), 113.9 (Ar*C*H), 80.4 (*C*(CH$_3$)$_3$), 79.4 (*C*q, alkyne), 71.7 (*C*H, alkyne), 55.1 (OCH_3), 48.4 (NCH_2Ar), 34.9 (NCH_2, propargyl), 28.3 (C(CH_3)$_3$); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{21}NO_3$ 276.1594; found 276.1589 (+1.90 ppm).

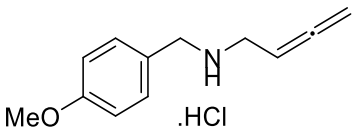
***tert*-Butyl buta-2,3-dien-1-yl(4-methoxybenzyl)carbamate 40**



tert-Butyl (4-methoxybenzyl)(prop-2-yn-1-yl)carbamate **39** (135 mg, 0.491 mmol), CuI (46.8 mg, 0.246 mmol) and $(CHO)_n$ (73.9 mg, 2.46 mmol) were dissolved in 1,4-dioxane (2.5 mL). Diisopropylamine (138 µL, 0.982 mmol) was added and the reaction mixture stirred at 110 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL) and filtered through a silica plug, washing with ethyl acetate (50 mL) and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO_2, eluting with 10% diethyl ether in pentane) to give **40** (136 mg, 0.470 mmol, 96% yield) as a pale-yellow oil.

R_f (90:10 petroleum ether: diethyl ether) = 0.18; **ν_{max}** (thin film)/cm^{-1} 3062, 3032, 2975, 2932, 2871, 2836, 1955, 1687, 1612; **δ_H** (400 MHz, $CDCl_3$) 7.17 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.08 (d, *J* = 19.2 Hz, 1H, *H*C=C=CH$_2$), 4.74 (d, *J* = 3.9 Hz, 2H, HC=C=CH_2), 4.37 (s, 2H, NCH_2Ar), 3.90 – 3.63 (m, 5H, OCH_3 and NCH_2C(H)=C), 1.48 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$) 209.1 (HC=*C*=CH$_2$), 158.9 (Ar*C*(OMe)), 155.6 (*C*=O), 130.3 (Ar*C*H), 129.4 (Ar*C*q), 113.9 (Ar*C*H), 87.0 (H*C*=C=CH$_2$), 79.8 (*C*(CH$_3$)$_3$), 76.2 (HC=C=*C*H$_2$), 55.2 (OCH$_3$), 48.9 (N*C*H$_2$Ar), 44.7 (N*C*H$_2$C(H)=C), 28.5 (C(*C*H$_3$)$_3$); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{23}NO_3$ 290.1751; found 290.1741 (+3.50 ppm).

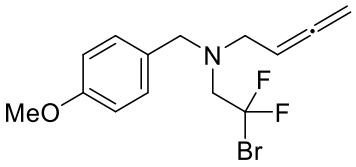
***N*-(4-Methoxybenzyl)buta-2,3-dien-1-amine hydrochloride 41**



To a 0 °C solution of *tert*-butyl buta-2,3-dien-1-yl(4-methoxybenzyl)carbamate **40** (128 mg, 0.441 mmol) in dioxane (0.62 mL) was added HCl (0.53 mL of a 4 M solution in dioxane). The mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture was filtered, washing with diethyl ether to give **41** (69.5 mg, 0.308 mmol, 70%) as a white solid.

m.p. 145–148 °C; **ν_{max}** (thin film)/cm^{-1} 3065, 2990, 2956, 2936, 2911, 2856, 2836, 2790, 2759, 2717, 2650, 2623, 2480, 1949, 1742, 1614; **δ_H** (500 MHz, MeOH-d_4) 7.50 – 7.40 (m, 2H, Ar*H*), 7.07 – 6.96 (m, 2H, Ar*H*), 5.38 (tt, *J* = 7.0, 7.0 Hz, 1H, *H*C=C=CH$_2$), 5.07 (dt, *J* = 7.0, 2.5 Hz, 2H, HC=C=CH_2), 4.18 (s, 2H, NHCH_2Ar), 3.83 (s, 3H, OCH_3), 3.65 (dt, *J* = 7.0, 2.5 Hz, 2H, NCH_2C(H)=C); **δ_C** (126 MHz, MeOH-d_4) 211.7 (HC=*C*=CH$_2$), 162.2 (Ar*C*(OMe)), 132.6 (Ar*C*H), 124.1 (Ar*C*q), 115.6 (Ar*C*H), 83.1 (H*C*=C=CH$_2$), 78.1 (HC=C=*C*H$_2$), 55.9 (O*C*H$_3$), 51.1 (NH*C*H$_2$Ar), 46.6 (NH*C*H$_2$C(H)=C); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{15}NO$ 190.1226; found 190.1223 (+1.60 ppm).

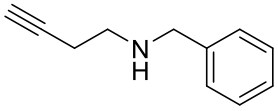
***N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)buta-2,3-dien-1-amine 42**



N-(4-Methoxybenzyl)buta-2,3-dien-1-amine hydrochloride **41** (162 mg, 0.719 mmol) and Et_3N (100 µL, 0.719 mmol) were subjected to General Procedure 2, stirring at 70 °C for 14 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in petroleum ether) to give **42** (218 mg, 0.656 mmol, 91% yield) as a colourless oil.

R_f (95:5 petroleum ether: diethyl ether) = 0.41; **ν_{max}** (thin film)/cm^{-1} 3063, 3034, 2997, 2955, 2935, 2909, 2836, 1953, 1612; **δ_H** (400 MHz, $CDCl_3$) 7.29 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.89 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.15 (tt, *J* = 6.7, 5.0 Hz, 1H, *H*C=C=CH_2), 4.77 (dt, *J* = 6.7, 2.5 Hz, 2H, HC=C=CH_2), 3.85 (s, 2H, NCH_2Ar), 3.82 (s, 3H, OCH_3), 3.39 (t, *J* = 13.3 Hz, 2H, NCH_2CF_2Br), 3.36 – 3.29 (m, 2H, NCH_2C(H)=C); **δ_C** (101 MHz, $CDCl_3$) 209.9 (HC=*C*=CH_2), 159.1 (Ar*C*(OMe)), 130.3 (Ar*C*q), 130.2 (Ar*C*H), 124.0 (t, *J* = 309.7 Hz, *C*F_2Br), 113.8 (Ar*C*H), 86.0 (H*C*=C=CH_2), 75.3 (HC=C=*C*H_2), 62.1 (t, *J* = 22.5 Hz, N*C*H_2CF_2Br), 57.7 (N*C*H_2Ar), 55.3 (O*C*H_3), 52.3 (NH*C*H_2C(H)=C); **δ_F** (376 MHz, $CDCl_3$) –9.94; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{16}{}^{79}BrF_2NO$ 332.0456; found 332.0455 (+0.40 ppm).

***N*-Benzylbut-3-yn-1-amine 43**

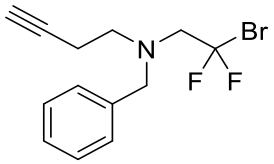


To a 0 °C suspension of 3-butyn-1-ol (1.51 mL, 20.0 mmol) and Et_3N (5.58 mL, 40.0 mmol) in dichloromethane (100 mL) was added methane sulfonylchloride (3.10 mL, 40.0 mmol) dropwise over 10 minutes. The mixture was stirred at room temperature for 4 hours, then water (20 mL) was added dropwise over 5 minutes. Dichloromethane (50 mL), water (20 mL) and $NaHCO_3$ (30 mL of a sat. aq. solution) were added and the mixture was extracted with dichloromethane (2 × 50 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was added to a stirred solution of Et_3N (5.58 mL, 40.0 mmol), benzylamine (4.37 mL, 40.0 mmol) in THF (100 mL). The mixture was stirred at 70 °C for 21 hours. The reaction mixture was cooled to room temperature and ethyl acetate (50 mL), water (30 mL) and brine (20 mL of a sat. aq. solution) were added. The mixture was extracted with ethyl acetate (2 × 50 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-80% ethyl acetate in petroleum ether, then 2-5% methanol in dichloromethane). The mixed fractions were purified again by flash column chromatography (SiO_2, eluting with 0-10% methanol in dichloromethane). The residues were combined to give **43** (1.36 g, 8.55 mmol, 43% yield) as a yellow/orange oil.

R_f (95:5 dichloromethane/methanol) = 0.42; **ν_{max}** (thin film)/cm^{-1} 3293, 3085, 6062, 3027, 2915, 2835, 2117; **δ_H** (400 MHz, $CDCl_3$) 7.39 – 7.21 (m, 5H, Ar*H*), 3.82 (s, 2H, NCH_2Ar), 2.81 (t, *J* = 6.6 Hz, 2H, NCH_2CH_2), 2.42 (td, *J* = 6.6, 2.7 Hz, 2H, NCH_2CH_2), 1.99 (t, *J* = 2.7 Hz, 1H, CH, alkyne); **δ_C** (101 MHz, $CDCl_3$) 140.1 (Ar*C*q), 128.4 (Ar*C*H), 128.1 (Ar*C*H), 127.0 (Ar*C*H), 82.5 (*C*q, alkyne), 69.6 (*C*H, alkyne), 53.3 (NCH_2), 47.3 (NCH_2), 19.5 (H_2C-C≡CH); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{13}N$ 160.1121; found 160.1123 (+1.40 ppm).

Data are consistent with the literature.[1]

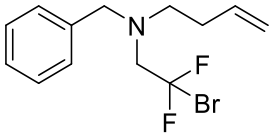
***N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-yn-1-amine 44**



N-Benzylbut-3-yn-1-amine **43** (0.203 g, 1.27 mmol) was subjected to General Procedure 2, stirring at 70 °C for 17 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in petroleum ether) to give **44** (290 mg, 961 µmol, 75% yield) as a colourless oil.

R_f (98:2 petroleum ether: diethyl ether) = 0.47; **ν_{max}** (thin film)/cm^{-1} 3305, 3087, 3065, 3030, 2919, 2834; **δ_H** (400 MHz, $CDCl_3$) 7.39 – 7.27 (m, 5H, Ar*H*), 3.93 (s, 2H, NCH_2Ar), 3.46 (t, *J* = 13.3 Hz, 2H, N*CH*$_2$CF$_2$Br), 2.94 (t, *J* = 7.3 Hz, 2H, N*CH*$_2$CH$_2$), 2.35 (td, *J* = 7.3, 2.6 Hz, 2H, NCH$_2$*CH*$_2$), 1.97 (t, *J* = 2.6 Hz, 1H, C*H*, alkyne); **δ_C** (101 MHz, $CDCl_3$) 138.4 (Ar*C*q), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 127.6 (Ar*C*H), 123.9 (t, *J* = 310.4 Hz, *C*F_2Br), 82.4 (*C*q, alkyne), 69.7 (*C*H, alkyne), 63.6 (t, *J* = 22.2 Hz, *C*H_2CF_2Br), 58.7 (NCH$_2$Ar), 52.8 (NCH$_2$CH$_2$), 17.7 (NCH$_2$*C*H$_2$); **δ_F** (376 MHz, $CDCl_3$) –50.56; **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{14}{}^{79}BrF_2N$ 324.0170; found 324.0170 (+0.10 ppm).

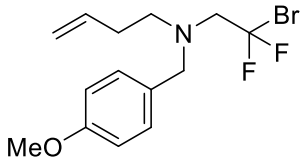
***N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-en-1-amine 45**



3-Buten-1-amine (462 µL, 5.00 mmol) and benzaldehyde (510 µL, 5.00 mmol) were subjected to General Procedure 3, stirring for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 1% diethyl ether in pentane) to give **45** (673 mg, 221 µmol, 44% yield) as a colourless oil.

R_f (99:1 pentane: diethyl ether) = 0.23; **ν_{max}** (thin film)/cm^{-1} 3065, 3029, 2977, 2926, 2831, 1494, 1205, 1079, 908, 697; **δ_H** (500 MHz, $CDCl_3$) 7.38 – 7.26 (m, 5H, Ar*H*), 5.76 (ddt, *J* = 17.0, 10.3, 6.8, Hz, 1H, *H*C=CH$_2$), 5.09 – 4.96 (m, 2H, HC=C*H*$_2$), 3.88 (s, 2H, NCH_2Ar), 3.38 (t, *J* = 13.6, 2H, NCH_2CF_2Br), 2.76 (td, *J* = 7.4, 1.5 Hz, 2H, NCH_2CH$_2$), 2.30 – 2.22 (m, 2H, NCH$_2$CH_2); **δ_C** (126 MHz, $CDCl_3$) 138.7 (Ar*C*q), 136.2 (H*C*=CH$_2$), 128.8 (Ar*C*H), 128.5 (Ar*C*H), 127.4 127.4 (Ar*C*H), 124.1 (t, *J* = 310.8 Hz, *C*F_2Br), 116.1 (HC=*C*H$_2$), 63.3 (t, *J* = 21.9 Hz, N*C*H$_2CF_2$Br), 58.9 (N*C*H$_2$Ar), 53.7 (N*C*H$_2$CH$_2$), 32.0 (NCH$_2$*C*H$_2$); **δ_F** (376 MHz, $CDCl_3$) –49.82; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{16}{}^{79}BrF_2N$ 304.0507; found 304.0502 (+1.50 ppm).

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)but-3-en-1-amine 46**

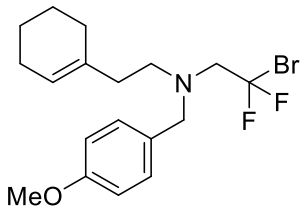


But-3-en-1-amine (0.46 mL, 5.00 mmol) and *p*-anisaldehyde (0.61 mL, 5.00 mmol) were subjected to General Procedure 3, stirring for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 1-2% diethyl ether in pentane) to give **46** (299 mg, 895 µmol, 18% yield) as a colourless oil.

R_f (19:1 pentane: diethyl ether) = 0.31; **ν_{max}** (thin film)/cm^{-1} 2936, 2835,1612, 1463, 1301, 1246, 1074; **δ_H** (500 MHz, $CDCl_3$) 7.27 – 7.21 (m, 2H, Ar*H*), 6.90 – 6.83 (m, 2H, Ar*H*), 5.75 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, *H*C=CH$_2$), 5.09 – 4.95 (m, 2H, HC=C*H*$_2$), 3.81 (s, 3H, OCH_3), 3.80 (s, 2H, NCH_2Ar), 3.34 (t, *J* = 13.6 Hz, 2H, NCH_2CF_2Br), 2.77 – 2.69 (m, 2H, NCH_2CH), 2.29 – 2.20 (m, 2H, NCH$_2$CH_2); **δ_C** (126 MHz, $CDCl_3$) 159.0 (Ar*C*(OCH$_3$)), 136.3 (H*C*=CH$_2$), 130.6 (Ar*C*q), 130.0 (Ar*C*H), 124.2 (t, *J* = 312.4 Hz, *C*F_2Br), 116.1 (HC=*C*H$_2$), 113.8

(Ar*C*H), 63.1 (t, *J* = 21.9 Hz, N*C*H$_2$CF$_2$Br), 58.2 (N*C*H$_2$Ar), 55.4 (O*C*H$_3$), 53.5 (N*C*H$_2$CH), 32.0 (NCH$_2$*C*H); **δ_F** (376 MHz, CDCl$_3$) –49.72; **HRMS** (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_{19}{}^{79}BrF_2NO$ 334.0613; found 334.0612 (+0.10 ppm).

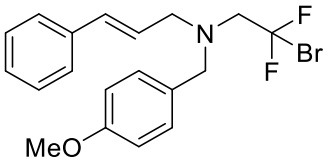
2-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2,2-difluoro-*N*-(4-methoxybenzyl)ethan-1-amine 47



2-(Cyclohex-1-en-1-yl)ethan-1-amine (0.7 mL, 5.00 mmol) and *p*-anisaldehyde (0.61 mL, 5.00 mmol) were subjected to General Procedure 3, stirring for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 2% diethyl ether in pentane) to give **47** (782 mg, 2.02 mmol, 40% yield) as a colourless oil.

R_f (49:1 pentane: diethyl ether) = 0.28; **ν_{max}** (thin film)/cm^{-1} 2996, 2926, 2935, 2854, 2834, 1611, 1510, 1244, 1070; **δ_H** (500 MHz, CDCl$_3$) 7.26 – 7.23 (m, 2H, Ar*H*), 6.88 – 6.84 (m, 2H, Ar*H*), 5.42 – 5.36 (m, 1H, C*H*, alkene), 3.81 (s, 3H, OC*H*$_3$), 3.79 (s, 2H, NC*H*$_2$Ar), 3.33 (t, *J* = 13.6 Hz, 2H, NC*H*$_2$CF$_2$Br), 2.79 – 2.69 (m, 2H, NC*H*$_2$CH$_2$), 2.17 – 2.06 (m, 2H, CH$_2$C*H*$_2$N), 1.99 – 1.91 (m, 2H, C*H*HCH$_2$CH$_2$C*H*H), 1.89 – 1.80 (m, 2H, CH*H*CH$_2$CH$_2$CH*H*), 1.62 – 1.49 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$); **δ_C** (126 MHz, CDCl$_3$) 158.9 (Ar*C*(OCH$_3$)), 135.6 (*C*, alkene, quaternary), 130.8 (Ar*C*, quaternary), 130.0 (Ar*C*), 124.4 (t, *J* = 311.5 Hz, *C*F$_2$Br), 122.6(*C*H, alkene), 113.8 (Ar*C*), 63.0 (t, *J* = 21.9 Hz, N*C*H$_2$CF$_2$Br), 58.1 (N*C*H$_2$), 55.4 (O*C*H$_3$), 52.5 (N*C*H$_2$CH$_2$), 35.7 (*C*H$_2$CH$_2$N), 28.5 (HC=C-*C*H$_2$), 25.4 (C=CH-*C*H$_2$), 23.1(CH$_2$*C*H$_2$CH$_2$CH$_2$), 22.5 (CH$_2$CH$_2$*C*H$_2$CH$_2$); **δ_F** (376 MHz, CDCl$_3$) –49.59; **HRMS** (ESI) m/z: [M+H]$^+$ calcd for $C_{18}H_{25}{}^{79}BrF_2NO$ 410.0902; found 410.0898 (+0.90 ppm).

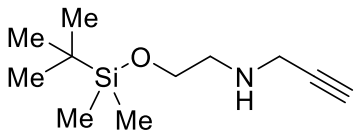
(*E*)-*N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)-3-phenylprop-2-en-1-amine 48



4-Methoxybenzylamine (261 µL, 2.00 mmol) and cinnamaldehyde (252 µL, 2.00 mmol) were subjected to General Procedure 3, stirring for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 2-5% ethyl acetate in petroleum ether) to give **48** (451 mg, 1.14 mmol, 57% yield) as a pale yellow oil.

R_f (95:5 petroleum ether: ethyl acetate) = 0.43; **ν_{max}** (thin film)/cm^{-1} 3103, 3081, 3060, 3026, 3003, 2954, 2933, 2909, 2835, 1611; **δ_H** (400 MHz, CDCl$_3$) 7.42 – 7.22 (m, 7H, Ar*H*), 6.94 – 6.84 (m, 2H, Ar*H*), 6.52 (d, *J* = 15.8 Hz, 1H, *H*C=CH(CH$_2$)), 6.31 – 6.18 (m, 1H, HC=C*H*(CH$_2$)), 3.86 (d, *J* = 2.5 Hz, 2H, NC*H*$_2$), 3.82 (app d, *J* = 1.9 Hz, 3H, OC*H*$_3$), 3.44 (d, *J* = 6.7 Hz, 2H, NC*H*$_2$), 3.38 (td, *J* = 13.4, 2.5 Hz, 2H, C*H*$_2$CF$_2$Br); **δ_C** (101 MHz, CDCl$_3$) 159.16 (Ar*C*(OCH$_3$)), 137.0 (Ar*C*q), 133.5 (H*C*=CH(CH$_2$)), 130.5 (Ar*C*q), 130.2 (Ar*C*H), 128.7 (Ar*C*H), 127.8 (Ar*C*H), 126.5 (Ar*C*H), 126.4 (HC=*C*H(CH$_2$)), 124.2 (t, *J* = 310.3 Hz, *C*F$_2$Br), 113.9 (Ar*C*H), 62.1 (t, *J* = 22.1 Hz, *C*H$_2$CF$_2$Br), 58.2 (N*C*H$_2$), 56.1 (N*C*H$_2$), 55.4 (O*C*H$_3$); **δ_F** (376 MHz, CDCl$_3$) –9.47; **HRMS** (ESI) m/z: [M+H]$^+$ calcd for $C_{19}H_{20}{}^{79}BrF_2NO$ 396.0769; found 396.0767 (+0.60 ppm).

***N*-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine 49**

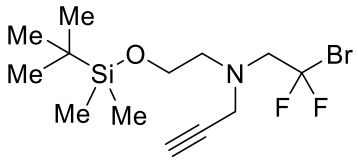


To a solution of ethanolamine (0.604 mL, 10.0 mmol) and imidazole (1.02 g, 15.0 mmol) in dichloromethane (5 mL) was added a solution of TBSCl (1.81 g, 12.0 mmol) in dichloromethane (10 mL) dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 17 hours. The reaction mixture was poured into water (20 mL). The mixture was extracted with dichloromethane (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated. To the resultant residue was added DIPEA (1.16 mL, 6.67 mmol) and dichloromethane (50 mL). Propargyl bromide (0.743 mL, 6.67 mmol of an 80% w/w solution in toluene) was added dropwise at 0 °C over 2 hours. The reaction mixture was stirred at room temperature for a further 3 hours. The reaction mixture was poured into $NaHCO_3$ (30 mL of a sat. aq. solution). The mixture was extracted with dichloromethane (3 × 30 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate in petroleum ether) to give **49** (523 mg, 2.45 mmol, 37% yield) as a yellow oil.

R_f (80:20 petroleum ether: ethyl acetate) = 0.28; **ν_{max}** (thin film)/cm^{-1} 3311, 2954, 2929, 2886, 2857, 1462; **δ_H** (400 MHz, $CDCl_3$) 3.74 (t, *J* = 5.2 Hz, 2H, OCH_2), 3.46 (d, *J* = 2.4 Hz, 2H, NCH_2C≡CH), 2.79 (t, *J* = 5.2 Hz, 2H, NC$H_2$$CH_2$), 2.21 (t, *J* = 2.4 Hz, 1H, C*H*, alkyne), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 6H, Si(CH_3)$_2$); **δ_C** (101 MHz, $CDCl_3$) 82.3 (*C*q, alkyne), 71.4 (*C*H, alkyne), 62.5 (OCH_2), 50.7 (N$CH_2$$CH_2$), 38.3 (N$CH_2$C≡CH), 26.0 (SiC(*C*$H_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), –5.2 Si(*C*$H_3$)$_2$; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{14}F_2NO_2$ 254.0987; found 254.0985 (+1.00 ppm).

Data are consistent with the literature.[2]

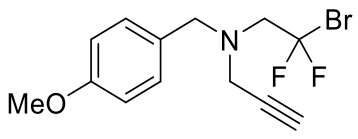
***N*-(2-Bromo-2,2-difluoroethyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine 3**



N-(2-((tert-Butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **49** (1.72 g, 8.07 mmol) was subjected to General Procedure 2, stirring at 70 °C for 15 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in petroleum ether) to give **3** (1.68 g, 4.73 mmol, 59% yield) as a colourless oil.

R_f (98:2 petroleum ether: ethyl acetate) = 0.41; **ν_{max}** (thin film)/cm^{-1} 3309, 2954, 2930, 2897, 2886, 2858, 1472; **δ_H** (400 MHz, $CDCl_3$) 3.76 (t, *J* = 5.9 Hz, 2H, OCH_2), 3.58 (d, *J* = 2.4 Hz, 2H, CH_2C≡CH), 3.45 (t, *J* = 13.0 Hz, 2H, NC$H_2$$CF_2$Br), 2.86 (t, *J* = 5.9 Hz, 2H, NC$H_2$$CH_2$), 2.23 (t, *J* = 2.4 Hz, 1H, C*H*, alkyne), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 6H, Si(CH_3)$_2$); **δ_C** (101 MHz, $CDCl_3$) 123.4 (t, *J* = 307.8 Hz, *C*F_2Br), 79.1 (*C*q, alkyne), 73.1 (*C*H, alkyne), 63.8 (t, *J* = 22.8 Hz, N$CH_2$$CF_2$Br), 62.5 (O$CH_2$), 57.2 (N$CH_2$$CH_2$), 44.8 (t, *J* = 1.6 Hz, NCH_2C≡CH), 26.0 (SiC(*C*H_3)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), –5.3 (Si(*C*H_3)$_2$); **δ_F** (376 MHz, $CDCl_3$) –51.63; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{24}{}^{79}BrF_2NOSi$ 356.0851; found 356.0847 (+1.10 ppm).

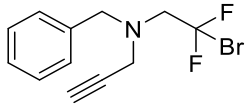
***N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine 29**



Propargylamine (0.448 mL, 7.00 mmol) and *p*-anisaldehyde (0.850 mL, 7.00 mmol) were subjected to General Procedure 3, stirring for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 2-5% ethyl acetate in petroleum ether) to give **29** (1.26 g, 3.96 mmol, 56% yield) as a colourless oil.

R_f (90:10 petroleum ether: ethyl acetate) = 0.40; **ν_{max}** (thin film)/cm^{-1} 3299, 3000, 2956, 2935, 2908, 2836; **δ_H** (500 MHz, $CDCl_3$) 7.35 – 7.31 (m, 2H, Ar*H*), 6.92 – 6.87 (m, 2H, Ar*H*), 3.83 (s, 2H, NCH_2Ar), 3.82 (s, 3H, OCH_3), 3.42 (d, *J* = 2.5 Hz, 2H, NCH_2), 3.39 (t, *J* = 12.6 Hz, 2H, CH_2CF_2Br), 2.29 (t, *J* = 2.5 Hz, 1H, C*H*, alkyne); **δ_C** (126 MHz, $CDCl_3$) 159.2 (Ar*C*(OCH_3)), 130.4 (Ar*C*H), 129.7 (Ar*C*q), 123.4 (t, *J* = 307.8 Hz, *C*F_2Br), 113.9 (Ar*C*H), 78.3 (*C*q, alkyne), 73.6 (*C*H, alkyne), 62.6 (t, *J* = 23.3 Hz, *C*H_2CF_2Br), 58.2 (N*C*H_2Ar), 55.3 (O*C*H_3), 42.3 (N*C*H_2); **δ_F** (376 MHz, $CDCl_3$) –50.69; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{14}{}^{79}BrF_2NO$ 318.0300; found 318.0295 (+1.30 ppm).

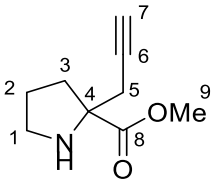
***N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)prop-2-yn-1-amine 50**



Propargylamine (320 µL, 5.00 mmol) and benzaldehyde (508 µL, 5.00 mmol) were subjected to General Procedure 3, stirring for 14 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in pentane). The mixed fractions were repurified by flash column chromatography (SiO_2, eluting with 0-0.5% diethyl ether in pentane). The residues were combined to give **50** (546 mg, 1.89 mmol, 38% yield) as a colourless oil.

R_f (98:2 petroleum ether: ethyl acetate) = 0.39; **ν_{max}** (thin film)/cm^{-1} 3303, 3088, 3065, 2932, 2897, 2843; **δ_H** (400 MHz, $CDCl_3$) 7.43 – 7.37 (m, 2H, Ar*H*), 7.37 – 7.31 (m, 2H, Ar*H*), 7.31 – 7.27 (m, 1H, Ar*H*), 3.88 (s, 2H, NCH_2Ar), 3.41 (d, *J* = 2.5 Hz, 2H, NCH_2), 3.39 (t, *J* = 12.5 Hz, 2H, CH_2CF_2Br), 2.27 (t, *J* = 2.5 Hz, 1H, C*H*, alkyne); **δ_C** (101 MHz, $CDCl_3$) 137.7 (Ar*C*q), 129.2 (Ar*C*H), 128.6 (Ar*C*H), 127.8 (Ar*C*H), 123.4 (t, *J* = 307.8 Hz, *C*F_2Br), 78.3 (*C*q, alkyne), 73.6 (*C*H, alkyne), 62.8 (t, *J* = 23.4 Hz, *C*H_2CF_2Br), 58.9 (N*C*H_2), 42.5 (t, *J* = 1.7 Hz, N*C*H_2); **δ_F** (376 MHz, $CDCl_3$) –50.77; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{12}{}^{79}BrF_2N$ 288.0194; found 288.0184 (+3.40 ppm).

Methyl 2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate hydrochloride 51



.HCl

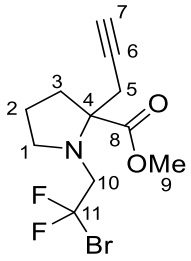
To a -78 °C solution of diisopropylamine (2.24 mL, 16.0 mmol) in THF (15 mL) was added *n*-BuLi (6.81 mL, 15.0 mmol of a 2.2M solution in hexanes) dropwise over 15 minutes. The mixture was stirred at -78 °C for 30 minutes after which time a solution of *N*-Boc proline methyl ester (2.29 g, 10.0 mmol) in THF (5 mL) was added dropwise over 10 minutes. The mixture was stirred at -78 °C for 30 minutes, then a solution of propargyl bromide (2.00 mL, 18 mmol of an 80% w/w solution in toluene) was added dropwise over 10 minutes. The mixture was stirred at -78 °C for 4 hours. Isopropanol (1.91 mL, 25.0 mmol) was added and the mixture was warmed to room temperature. NH_4Cl (20 mL of a sat. aq. solution) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 5-10% ethyl acetate in pentane) to give a residue which was dissolved in dioxane (10 mL). HCl (8.9 mL of a 4 M solution in dioxane) was added at 0 °C. The mixture was warmed to room temperature and stirred for 23 hours. The reaction mixture was filtered, then triturated with diethyl ether to give **51** (1.29 g, 6.33 mmol, 63%) as a light brown solid.

m.p. 172–174 °C (literature m.p. 180 °C); **ν_{max}** (thin film)/cm^{-1} 3171, 2999, 2945, 2917, 2877, 2848, 2779, 2742, 2676, 2649, 2594, 2528, 2471, 2413, 2393, 1757, 1561; **δ_H** (500 MHz, methanol-d_4) 3.91 (s, 3H, *H*-9), 3.48 (dd, *J* = 8.0, 5.7 Hz, 2H, *H*-1), 3.15 (dd, *J* = 17.6, 2.7 Hz, 1H, *H*-5), 2.93 (app ddd, *J* = 17.6, 2.7, 2.7 Hz, 1H,

H-5), 2.74 (dd, *J* = 2.7, 2.7 Hz, 1H, *H*-7), 2.51 – 2.41 (m, 1H, *H*-3), 2.28 – 2.09 (m, 2H, *H*-3 and *H*-2), 2.09 – 1.98 (m, 1H, *H*-2); **δ_C** (126 MHz, MeOD) 171.1 (*C*-8), 77.2 (*C*-6), 75.2 (*C*-7), 72.9 (*C*-4), 54.7 (*C*-9), 47.6 (*C*-1), 35.5 (*C*-3), 26.2 (*C*-5), 24.2 (*C*-2); **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_9H_{13}NO_2$ 190.0838; found 190.0836 (+1.10 ppm).

Data are consistent with the literature.[3]

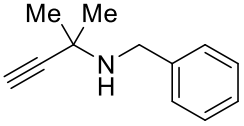
Methyl 1-(2-bromo-2,2-difluoroethyl)-2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate 52



Methyl 2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate hydrochloride **51** (407 mg, 2.00 mmol) and Et_3N (279 µL, 2.00 mmol) were subjected to General Procedure 2, stirring at 70 °C for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 2% diethyl ether in pentane) to give **52** (188 mg, 606 µmol, 30% yield) as a colourless oil.

R_f (95:5 petroleum ether: diethyl ether) = 0.26; **ν_{max}** (thin film)/cm^{-1} 3306, 2954, 2917, 2871, 2841, 1729; **δ_H** (400 MHz, $CDCl_3$) 3.78 – 3.65 (m, 4H, *H*-9 and *H*-10), 3.46 – 3.35 (m, 2H, *H*-1 and *H*-10), 2.95 (ddd, *J* = 8.5, 8.5, 6.7 Hz, 1H, *H*-1), 2.72 – 2.61 (m, 2H, *H*-5), 2.26 (ddd, *J* = 12.9, 7.9, 5.2 Hz, 1H, *H*-3), 2.09 – 1.98 (m, 2H, *H*-3 and *H*-7), 1.94 – 1.82 (m, 2H, *H*-2); **δ_C** (101 MHz, $CDCl_3$) 174.0 (*C*-8), 123.5 (t, *J* = 308.2 Hz, *C*-11), 80.4 (*C*-8), 70.9 (*C*-7), 70.7 (*C*-4), 60.7 (t, *J* = 23.7 Hz, *C*-10), 54.7 (*C*-1), 52.1 (*C*-9), 35.8 (*C*-3), 26.9 (*C*-5), 22.2 (*C*-2); **δ_F** (376 MHz, $CDCl_3$) –51.04, –51.08; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{15}{}^{79}BrF_2NO_2$ 310.0249; found 310.0250 (+0.30 ppm).

***N*-Benzyl-2-methylbut-3-yn-2-amine 53**

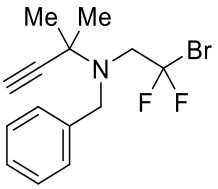


To a solution at 0 °C of 1,1-dimethyl prop-2-ynylamine (2.10 mL, 20.0 mmol) was added DIPEA (348 µL, 5.00 mmol) and dichloromethane (30 mL). was added a solution of benzyl bromide (595 µL, 5.00 mmol) in dichloromethane (5 mL) was added dropwise over 1 hour. The mixture was stirred at room temperature for 21 hours. The reaction mixture was poured into $NaHCO_3$ (20 mL of a sat. aq. solution) and extracted with dichloromethane (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 10-20% diethyl ether in pentane) to give **53** (506 mg, 2.92 mmol, 58%) as a colourless solid.

R_f (90:10 petroleum ether: diethyl ether) = 0.21; **m.p.** 42–44 °C; **ν_{max}** (thin film)/cm^{-1} 3302, 3121, 3031, 2980, 2911, 2860, 2832, 2080; **δ_H** (400 MHz, $CDCl_3$) 7.39 – 7.22 (m, 5H, Ar*H*), 3.88 (s, 2H, NCH_2), 2.36 (s, 1H, C*H*, alkyne), 1.43 (s, 6H, $C(CH_3)_2$); **δ_C** (101 MHz, $CDCl_3$) 140.7 (Ar*C*q), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 127.1 (Ar*C*H), 89.1 (*C*q, alkyne), 70.0 (*C*H, alkyne), 50.1 ($C(CH_3)_2$), 49.1 (NCH_2), 29.7 ($C(CH_3)_2$); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{15}N$ 174.1277; found 174.1266 (+6.70 ppm).

Data are consistent with the literature.[4]

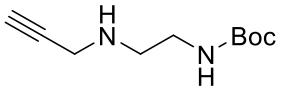
***N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-2-methylbut-3-yn-2-amine 54**



To an oven-dried flask fitted with a water condenser under an argon atmosphere was added *N*-benzyl-2-methylbut-3-yn-2-amine **53** (436 mg, 2.52 mmol) and THF (1.25 mL). Then bromodifluoroacetic acid (881 mg, 5.04 mmol) in THF (1.25 mL) and $PhSiH_3$ (933 µL, 7.56 mmol) were added at 70 °C and the reaction was heated at 70 °C for 16 hours. The reaction mixture was charged with further bromodifluoroacetic acid (881 mg, 5.04 mmol) and $PhSiH_3$ (933 µL, 7.56 mmol) and stirred at 70 °C for 86 hours. The reaction mixture was cooled to room temperature. Diethyl ether (15 mL) and $NaHCO_3$ (15 mL of a sat. aq. solution) were added. The mixture was extracted with diethyl ether (3 × 15 mL). The combined organics were dried ($MgSO_4$) and concentrated to ~2 mL volume. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in pentane) to give **54** (245 mg, 774 µmol, 31% yield) as a colourless oil.

R_f (98:2 petroleum ether: diethyl ether) = 0.70; **ν_{max}** (thin film)/cm^{-1} 3301, 3088, 3064, 3028, 2987, 2938, 2855; **δ_H** (400 MHz, $CDCl_3$) 7.42 – 7.37 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 2H, Ar*H*), 7.24 – 7.17 (m, 1H, Ar*H*), 4.06 (s, 2H, NCH_2Ar), 3.54 (t, *J* = 13.6 Hz, 2H, NCH_2CF_2Br), 2.32 (s, 1H, C*H*, alkyne), 1.36 (s, 6H, C(CH_3)$_2$); **δ_C** (101 MHz, $CDCl_3$) 141.5 (Ar*C*q), 128.3 (Ar*C*H), 127.5 (Ar*C*H), 126.7 (Ar*C*H), 123.5 (t, *J* = 309.0 Hz, *C*F_2Br), 86.7 (*C*q, alkyne), 70.6 (*C*H, alkyne), 62.9 (t, *J* = 21.7 Hz, *C*H_2CF_2Br), 57.9 (N*C*H_2Ar), 56.0 (*C*(CH$_3$)$_2$), 29.9 (C(*C*H$_3$)$_2$); **δ_F** (376 MHz, $CDCl_3$) –50.52; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{16}{}^{79}BrF_2N$ 316.0507; found 316.0504 (+0.90 ppm).

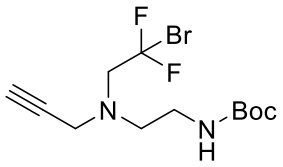
***tert*-Butyl (2-(prop-2-yn-1-ylamino)ethyl)carbamate 55**



To a 0 °C solution of ethylene diamine (6.69 mL, 10.0 mmol) in dichloromethane (12 mL) was added a solution of Boc_2O (2.18 g, 10.0 mmol) in dichloromethane (6 mL). The mixture was stirred at room temperature for 17 hours after which water (20 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated. To the residue was dissolved in dichloromethane (16 mL) and to this solution was added DIPEA (528 µL, 3.03 mmol). At 0 °C, a solution of propargyl bromide (338 µL, 3.03 mmol of an 80% w/w solution in toluene) in dichloromethane (5 mL) was added dropwise over 1.5 hours. The mixture was stirred at room temperature for 6 hours. The reaction mixture was poured into $NaHCO_3$ (20 mL of a sat. aq. solution) and extracted with dichloromethane (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 70-100% ethyl acetate in pentane) to give **55** (290 mg, 1.46 mmol, 48%) as a yellow oil.

R_f (70:30 petroleum ether: ethyl acetate) = 0.13; **ν_{max}** (thin film)/cm^{-1} 3303, 3254, 2975, 2931, 2853, 2836, 1688; **δ_H** (400 MHz, $CDCl_3$) 4.98 (s, 1H, N*H,* amine), 3.40 (d, *J* = 2.4 Hz, 2H, NHCH_2C), 3.21 (dt, *J* = 5.8, 5.8 Hz, 2H, NHCH_2CH_2NHBoc), 2.79 (t, *J* = 5.8 Hz, 2H, NHCH_2CH_2NHBoc), 2.20 (t, *J* = 2.4 Hz, 1H, C*H,* alkyne), 1.42 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$) 156.2 (*C*=O), 82.1 (*C*q, alkyne), 79.3 (*C*(CH$_3$)$_3$), 71.6 (*C*H, alkyne), 48.0 (NHCH_2*C*H_2NHBoc), 40.1 (NH*C*H_2CH_2NHBoc), 37.9 (NH*C*H_2C), 28.5 (C(*C*H$_3$)$_3$); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{18}N_2O_2$ 199.1441; found 199.1443 (+0.80 ppm).

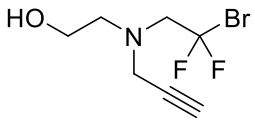
***tert*-Butyl (2-((2-bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethyl)carbamate 56**



tert-Butyl (2-(prop-2-yn-1-ylamino)ethyl)carbamate **55** (0.290 g, 1.46 mmol) was subjected to General Procedure 2, stirring at 70 °C for 16 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 5-10% diethyl ether in pentane). The material was purified again by flash column chromatography (SiO_2, eluting with 2-15% diethyl ether in pentane) to give **56** (37.7 mg, 110 µmol, 8% yield) as a colourless oil.

R_f (80:20 petroleum ether: diethyl ether) = 0.40; **ν_{max}** (thin film)/cm^{-1} 3434, 3306, 2978, 2932, 2850, 1697, 1503; **δ_H** (400 MHz, $CDCl_3$) 4.94 (br s, 1H, N*H*, carbamate), 3.52 (d, *J* = 2.4 Hz, 2H, CH_2, propargyl), 3.31 (t, *J* = 12.6 Hz, 2H, C*H*CF_2Br), 3.21 (dt, *J* = 5.8, 5.8 Hz, 2H, BocHNCH_2CH_2), 2.82 (t, *J* = 5.8 Hz, 2H, BocHNCH_2CH_2), 2.23 (t, *J* = 2.4 Hz, 1H, C*H*, alkyne), 1.43 (s, 9H, C(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$) 156.1 (*C*=O), 123.2 (t, *J* = 307.5 Hz, *C*F_2Br), 79.4 (*C*$(CH_3)_3$), 78.1 (*C*q, alkyne), 73.6 (*C*H, alkyne), 63.3 (t, *J* = 23.4 Hz, *C*H_2CF_2Br), 54.7 (BocHNCH_2*C*H_2), 43.5 (*C*H_2, propargyl), 38.3 (BocHN*C*H_2CH_2), 28.5 (C(*C*H_3)$_3$); **δ_F** (376 MHz, $CDCl_3$) –51.42; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{19}{}^{79}BrF_2N_2O_2$ 341.0671; found 341.0674 (+1.00 ppm).

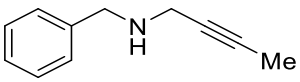
2-((2-Bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethan-1-ol 57



N-(2-Bromo-2,2-difluoroethyl)-*N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **3** was dissolved in dioxane (2.8 mL). HCl (2.4 mL of a 4 M solution in dioxane) was added at 0 °C. The mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was poured into $NaHCO_3$ (20 mL of a sat. aq. solution) and extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over sodium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 5-20% ethyl acetate in pentane) to give **57** (365 mg, 1.51 mmol, 75%) as a colourless oil.

R_f (50:50 petroleum ether: ethyl acetate) = 0.54; **ν_{max}** (thin film)/cm^{-1} 3424, 3302, 2946, 2883, 2847; **δ_H** (400 MHz, $CDCl_3$) 3.62 (t, *J* = 5.2 Hz, 2H, CH_2OH), 3.55 (d, *J* = 2.4 Hz, 2H, NCH_2, propargyl), 3.34 (t, *J* = 12.5 Hz, 2H, NCH_2CF_2Br), 2.88 (t, *J* = 5.2 Hz, 2H, CH_2CH_2OH), 2.43 (br s, 1H, O*H*), 2.25 (t, *J* = 2.4 Hz, 1H, C*H*, alkyne); **δ_C** (101 MHz, $CDCl_3$) 123.1 (t, *J* = 307.2 Hz, *C*F_2Br), 78.1 (*C*q, alkyne), 73.7 (*C*H, alkyne), 63.1 (t, *J* = 23.5 Hz, N*C*H_2CF_2Br), 59.2 (*C*H_2OH), 57.2 (*C*H_2CH_2OH), 43.8 (t, *J* = 1.4 Hz, N*C*H_2, propargyl); **δ_F** (376 MHz, $CDCl_3$) –51.29; **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_7H_{10}{}^{79}BrF_2NO$ 241.9987; found 241.9985 (+0.50 ppm).

***N*-Benzylbut-2-yn-1-amine 58**

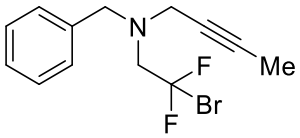


To a solution at 0 °C of benzylamine (5.46 mL, 50.0 mmol), DIPEA (1.74 mL, 10.0 mmol) and dichloromethane (40 mL) was added a solution of 1-bromo-2-butyne (1.33 g, 10.0 mmol) in dichloromethane (10 mL) dropwise over 20 minutes. The mixture was stirred at room temperature for 8 hours. The reaction mixture was poured into $NaHCO_3$ (20 mL of a sat. aq. solution) and extracted with dichloromethane (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20-50% ethyl acetate in pentane) to give **58** (1.04 g, 6.53 mmol, 65%) as a pale yellow oil.

R_f (80:20 petroleum ether: ethyl acetate) = 0.10; **ν_{max}** (thin film)/cm^{-1} 3315, 3085, 3062, 3027, 2918, 2840, 2809; **δ_H** (400 MHz, $CDCl_3$) 7.42 – 7.20 (m, 5H, Ar*H*), 3.86 (s, 2H, NHC*H*$_2$Ar), 3.38 (q, *J* = 2.4 Hz, 2H, NHC*H*$_2$), 1.85 (t, *J* = 2.4 Hz, 3H, C*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 139.8 (Ar*C*q), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 127.2 (Ar*C*H), 79.4 (*C*q, alkyne), 77.4 (*C*q, alkyne), 52.6 (NH*C*H$_2$Ar), 38.0 (NH*C*H$_2$), 3.7 (*C*H$_3$); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{13}N$ 160.1121; found 160.1116 (+3.10 ppm).

Data are consistent with the literature.[5]

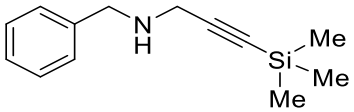
***N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-2-yn-1-amine 59**



N-Benzyl-2-methylbut-3-yn-2-amine **58** (638 mg, 4.00 mmol) was subjected to General Procedure 2, stirring at 70 °C for 20 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in pentane) to give **59** (721 mg, 2.38 mmol, 60% yield) as a yellow oil.

R_f (98:2 petroleum ether: diethyl ether) = 0.29; **ν_{max}** (thin film)/cm^{-1} 3088, 3064, 3031, 2922, 2895, 2842; **δ_H** (400 MHz, $CDCl_3$) 7.43 – 7.37 (m, 2H, Ar*H*), 7.37 – 7.30 (m, 2H, Ar*H*), 7.30 – 7.27 (m, 1H, Ar*H*), 3.85 (s, 2H, NC*H*$_2$Ar), 3.53 – 3.16 (m, 4H, NC*H*$_2$ and NC*H*$_2$), 1.88 (t, *J* = 2.3 Hz, 3H, C*H*$_3$); **δ_C** (101 MHz, $CDCl_3$) 138.1 (Ar*C*q), 129.2 (Ar*C*H), 128.5 (Ar*C*H), 127.6 (Ar*C*H), 123.6 (t, *J* = 308.0 Hz, *C*F$_2$Br), 81.3 (*C*q, alkyne), 73.5 (*C*q, alkyne), 62.9 (t, *J* = 23.1 Hz, N*C*H$_2$CF$_2$Br), 59.0 (N*C*H$_2$Ar), 43.1 (t, *J* = 1.7 Hz, N*C*H$_2$), 3.6 (*C*H$_3$); **δ_F** (376 MHz, $CDCl_3$) – 50.50; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{14}{}^{79}BrF_2N$ 302.0350; found 302.0352 (+0.40 ppm).

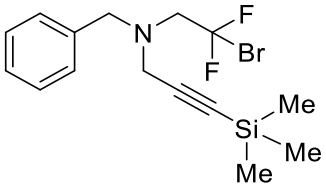
***N*-Benzyl-3-(trimethylsilyl)prop-2-yn-1-amine 60**



To a solution at 0 °C of benzylamine (5.46 mL, 50.0 mmol), DIPEA (1.74 mL, 10.0 mmol) and dichloromethane (40 mL) was added a solution of 3-bromo-1-(trimethylsilyl)-1-propyne (1.91 g, 10.0 mmol) in dichloromethane (10 mL) dropwise over 20 minutes. The mixture was stirred at room temperature for 8 hours. The reaction mixture was poured into $NaHCO_3$ (20 mL of a sat. aq. solution) and extracted with dichloromethane (3 × 20 mL). The combined organics were dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 10-20% ethyl acetate in pentane) to give **60** (1.65 g, 7.62 mmol, 76%) as a pale yellow oil.

R_f (80:20 petroleum ether: ethyl acetate) = 0.22; **ν_{max}** (thin film)/cm^{-1} 3067, 3028, 2959, 2899, 2838, 2164; **δ_H** (400 MHz, $CDCl_3$) 7.42 – 7.16 (m, 5H, Ar*H*), 3.88 (s, 2H, NHC*H*$_2$Ar), 3.44 (s, 2H, NHC*H*$_2$), 0.19 (s, 9H, Si(C*H*$_3$)$_3$); **δ_C** (101 MHz, $CDCl_3$) 139.5 (Ar*C*q), 128.6 (Ar*C*H), 128.6 (Ar*C*H), 127.3 (Ar*C*H), 104.3 (*C*q, alkyne), 88.5 (*C*q, alkyne), 52.5 (NH*C*H$_2$Ar), 38.6 (NH*C*H$_2$), 0.2 (Si(*C*H$_3$)$_3$); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}NSi$ 218.1360; found 218.1364 (+2.10 ppm).

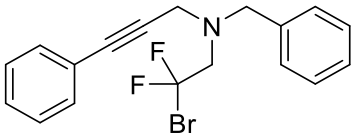
***N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-(trimethylsilyl)prop-2-yn-1-amine 61**



N-Benzyl-3-(trimethylsilyl)prop-2-yn-1-amine **60** (870 mg, 4.00 mmol) was subjected to General Procedure 2, stirring at 70 °C for 20 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in pentane) to give **61** (732 mg, 2.03 mmol, 51% yield) as a yellow oil.

R_f (98:2 petroleum ether: diethyl ether) = 0.33; **ν_{max}** (thin film)/cm^{-1} 3088, 3065, 3031, 2960, 2927, 2899, 2841; **δ_H** (400 MHz, $CDCl_3$) 7.41 – 7.37 (m, 2H, Ar*H*), 7.36 – 7.31 (m, 2H, Ar*H*), 7.31 – 7.27 (m, 1H, Ar*H*), 3.86 (s, 2H, NCH_2Ar), 3.40 (s, 2H, NCH_2C≡C), 3.37 (t, *J* = 12.4 Hz, 2H, NCH_2CF_2Br), 0.21 (s, 9H, Si(CH_3)$_3$); **δ_C** (101 MHz, $CDCl_3$) 137.8 (Ar*C*q), 129.2 (Ar*C*H), 128.6 (Ar*C*H), 127.7 (Ar*C*H), 123.5 (t, *J* = 307.9 Hz, *C*F_2Br), 100.4 (*C*q, alkyne), 90.7 (*C*q, alkyne), 62.9 (t, *J* = 23.3 Hz, N*C*H_2CF_2Br), 58.9 (N*C*H_2Ar), 43.6 (N*C*H_2C≡C), 0.2 (Si(*C*H_3)$_3$); **δ_F** (376 MHz, $CDCl_3$) –50.59; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{20}{}^{79}BrF_2NSi$ 360.0589; found 360.0577 (+3.30 ppm).

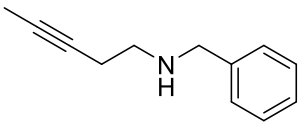
***N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-phenylprop-2-yn-1-amine 62**



To a solution of 3-phenyl-2-propyn-1-ol (902 mg, 6.82 mmol) and Et_3N (1.90 mL, 13.6 mmol) in dichloromethane (35 mL) was added MsCl (1.05 mL, 13.6 mmol). The mixture was stirred at room temperature for 16 hours. $NaHCO_3$ (15 mL of a sat. aq. solution) was added. The mixture was extracted with dichloromethane (3 × 15 mL). The combined organics were dried ($MgSO_4$) and concentrated. To the residue was added benzylamine (3.72 mL, 34.1 mmol), Et_3N (1.90 mL, 13.6 mmol) and THF (35 mL). The mixture was stirred at room temperature for 16 hours. $NaHCO_3$ (20 mL of a sat. aq. solution) was added. The mixture was extracted with diethyl ether (3 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated. The material was purified by flash column chromatography (SiO_2, eluting with 10-50% diethyl ether in pentane) to give a yellow residue (1.02 g). To a portion of the residue (448 mg) in THF (1 mL) was added bromodifluoroacetic acid (700 mg, 4.00 mmol) in THF (1 mL) and $PhSiH_3$ (740 µL, 6.00 mmol) were added at 70 °C and the reaction was heated at 70 °C for 16 hours. The reaction mixture was cooled to room temperature. $NaHCO_3$ (15 mL of a sat. aq. solution) was added. The mixture was extracted with diethyl ether (3 × 15 mL). The combined organics were dried ($MgSO_4$) and concentrated to ~2 mL volume. The crude material was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in pentane) to give **62** (363 mg, 996 µmol, 34% yield) as a colourless oil.

R_f (95:5 petroleum ether: diethyl ether) = 0.50; **ν_{max}** (thin film)/cm^{-1} 3084, 3062, 3031, 2992, 2926, 2897, 2840; **δ_H** (400 MHz, $CDCl_3$) 7.52 – 7.41 (m, 4H, Ar*H*), 7.39 – 7.27 (m, 6H, Ar*H*), 3.97 (s, 2H, NCH_2C≡C), 3.65 (s, 2H, NCH_2Ar), 3.48 (t, *J* = 12.6 Hz, 2H, NCH_2CF_2Br); **δ_C** (101 MHz, $CDCl_3$) 137.7 (Ar*C*q), 132.0 (Ar*C*H), 129.3 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 127.8 (Ar*C*H), 125.7 (Ar*C*q), 123.3 (t, *J* = 307.8 Hz, *C*F_2Br), 123.0 (Ar*C*H), 86.0 (*C*q, alkyne), 83.7 (*C*q, alkyne), 62.9 (t, *J* = 23.4 Hz, N*C*H_2CF_2Br), 59.1 (N*C*H_2C≡C), 43.5 (N*C*H_2Ar); **δ_F** (376 MHz, $CDCl_3$) –50.52; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{16}{}^{79}BrF_2N$ 364.0507; found 364.0505 (+0.50 ppm).

***N*-Benzylpent-3-yn-1-amine 63**



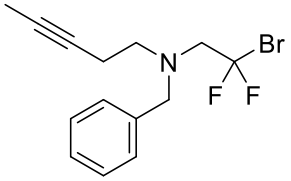
To a suspension of 3-pentyn-1-ol (0.92 mL, 10.0 mmol) and Et_3N (2.09 mL, 15.0 mmol) in dichloromethane (20 mL) was added methane sulfonylchloride (0.74 mL, 10.0 mmol) dropwise over 10 minutes at 0 °C. The mixture was stirred at room temperature for 2 hours. Then water (30 mL) was added, and it was extracted with dichloromethane (3 × 30 mL). The combined organic extractions were washed aq. 1.0 M HCl (1 × 30 mL), $NaHCO_3$ (1 × 30 mL of a sat. aq. solution) and brine solution (1 × 30 mL). The organic phase was then dried

over magnesium sulfate, filtered, and concentrated. The resultant residue was added dropwise over 10 minutes to a stirred benzylamine (6.55 mL, 60.0 mmol). The neat reaction mixture was stirred vigorously at room temperature for 18 hours. 2.0 M NaOH (30 mL) was added to the reaction and extracted with diethyl ether (3 × 40 mL). The combined organics were washed with brine (1 × 50 mL), and subsequently dried over magnesium sulfate and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 20% ethyl acetate in cyclohexane) to give **63** (1.44 g, 8.30 mmol, 83% yield) as a pale-yellow oil.

R_f (4:1 cyclohexane: diethyl ether) = 0.11; **ν_{max}** (thin film)/cm^{-1} 3062, 3026, 2917, 1494, 1453, 1175, 1118, 963, 734; **δ_H** (500 MHz, $CDCl_3$) 7.37 – 7.28 (m, 4H, Ar*H*), 7.28 – 7.23 (m, 1H, Ar*H*), 3.82 (s, 2H, NHCH_2Ar), 2.75 (t, *J* = 6.6 Hz, 2H, NHCH_2), 2.40 – 2.30 (m, 2H, CH_2CC), 1.78 (t, *J* = 2.5 Hz, 3H, CH_3), 1.70 (br s, 1H, N*H*); **δ_C** (126 MHz, $CDCl_3$) 140.4 (Ar*C*q), 128.5 (Ar*C*H), 128.2 (Ar*C*H), 127.1(Ar*C*H), 78.5 (*C*q, alkyne), 77.0 (*C*q, alkyne), 53.6 (NH*C*H_2Ar), 48.0 (NH*C*H_2), 19.9 (*C*H_2CC), 3.7 (*C*H_3); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{16}N$ 174.1277; found 174.1276 (+0.60 ppm).

Data are consistent with the literature.[6]

***N*-Benzyl-N-(2-bromo-2,2-difluoroethyl)pent-3-yn-1-amine 64**

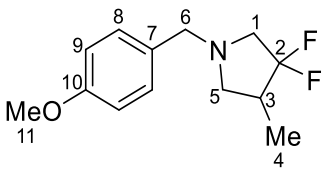


N-Benzylpent-3-yn-1-amine **63** (433 mg, 2.50 mmol) and bromodifluoroacetic acid (875 mg, 5.00 mmol) were subjected to General Procedure 2, stirring for 18 hours. The crude material was purified by flash column chromatography (SiO_2, eluting with 49:1, pentane: diethyl ether) to give **64** (676 mg, 2.14 mmol, 86% yield) as a colourless oil.

R_f (19:1 pentane: diethyl ether) = 0.31; **ν_{max}** (thin film)/cm^{-1} 2918, 2847,1494, 1453, 1371, 1081, 1012, 736, 698; **δ_H** (500 MHz, $CDCl_3$) 7.38 – 7.30 (m, 4H, Ar*H*), 7.30 – 7.23 (m, 1H, Ar*H*), 3.91 (s, 2H, NHCH_2Ar), 3.44 (t, *J* = 13.3 Hz, 2H, NHCH_2CF_2Br), 2.86 (t, *J* = 7.4 Hz, 2H, NHCH_2), 2.33 – 2.25 (m, 2H, CH_2CC), 1.76 (t, *J* = 2.5 Hz, 3H, CH_3); **δ_C** (126 MHz, $CDCl_3$) 138.6 (Ar*C*q), 128.7 (Ar*C*H) , 128.5 (Ar*C*H), 127.5 (Ar*C*H), 124.0 (t, *J* = 310.5 Hz, *C*F_2Br), 77.1 (*C*q, alkyne), 77.0 (*C*q, alkyne), 63.6 (t, *J* = 22.1 Hz), 58.7 (NH*C*H_2Ar), 53.2 (NH*C*H_2), 17.9 (*C*H_2CC), 3.6 (*C*H_3); **δ_F** (376 MHz, $CDCl_3$) –50.53; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{17}{}^{79}BrF_2N$ 316.0507; found 316.0513 (+2.10 ppm).

3.5 Cyclised alkenyl amines

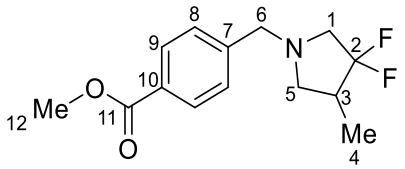
3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpyrrolidine 6



N-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-en-1-amine **5** (79.6 mg, 249 µmol) was subjected to General Procedure 5, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (Al_2O_3, eluting with 5-20% ethyl acetate in pentane) to give **6** (47.3 mg, 196 µmol, 79% yield) as a yellow oil.

R_f (80:20 petroleum ether: ethyl acetate) = 0.53; **ν_{max}** (thin film)/cm^{-1} 3073, 3034, 2971, 2936, 2887, 2835, 2804, 2754; **δ_H** (400 MHz, $CDCl_3$) 7.25 – 7.17 (m, 2H, Ar*H*), 6.91 – 6.82 (m, 2H, Ar*H*), 3.81 (s, 3H, *H*-11), 3.61 – 3.46 (m, 2H, *H*-6), 3.17 (ddd, *J* = 18.4, 13.6, 10.7 Hz, 1H, *H*-1), 3.04 (dd, *J* = 9.2, 7.3 Hz, 1H, *H*-5), 2.66 (ddd, *J* = 18.4, 13.6, 11.3 Hz, 1H, *H*-1), 2.57 – 2.37 (m, 1H, *H*-3), 2.17 (dd, *J* = 9.1, 9.1 Hz, 1H, *H*-5), 1.06 (app dd, *J* = 7.1, 2.2 Hz, 3H, *H*-4); **δ_C** (101 MHz, $CDCl_3$) 159.0 (*C*-10), 130.0 (*C*-7), 130.0 (Ar*C*H), 129.5 (dd, *J* = 250.6, 250.6 Hz, *C*-2), 113.9 (Ar*C*H), 61.7 (dd, *J* = 29.3, 29.3 Hz, *C*-1), 59.9 (dd, *J* = 6.0, 1.3 Hz, *C*-5), 59.4 (*C*-11), 55.4 (*C*-6), 40.9 (dd, *J* = 24.3, 21.7 Hz, *C*-3), 10.9 (app d, *J* = 10.3 Hz, *C*-4); **δ_F** (376 MHz, $CDCl_3$) –94.36 (d, *J* = 228.6 Hz), –106.63 (d, *J* = 228.6 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{17}F_2NO$ 242.1351; found 242.1350 (+0.30 ppm).

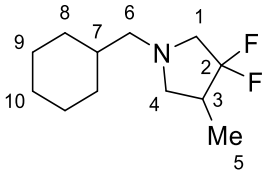
Methyl 4-((3,3-difluoro-4-methylpyrrolidin-1-yl)methyl)benzoate 7



Methyl 4-((allyl(2-bromo-2,2-difluoroethyl)amino)methyl)benzoate **34** (87.0 mg, 250 µmol) was subjected to General Procedure 5, stirring at room temperature for 18 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2 eluting with 0-10% diethyl ether in pentane) to give **7** (52.6 mg, 195 µmol, 78% yield) as a colourless oil.

R_f (9:1 pentane: diethyl ether) = 0.19; **ν_{max}** (thin film)/cm^{-1} 2976, 2953, 2809, 2757, 1719, 1612, 1435, 1274, 1178, 1107, 758; **δ_H** (400 MHz, $CDCl_3$) 8.03 – 7.96 (m, 2H, Ar*H*), 7.42 – 7.35 (m, 2H, Ar*H*), 3.91 (s, 3H, *H*-12), 3.71 – 3.59 (m, 2H, *H*-6), 3.17 (dt, *J* = 13.6, 10.7 Hz, 1H, *H*-1), 3.08 – 3.00 (m, 1H, *H*-5), 2.77 – 2.62 (m, 1H, *H*-1), 2.58 – 2.38 (m, 1H, *H*-3), 2.21 (t, *J* = 9.0 Hz, 1H, *H*-5), 1.06 (dd, *J* = 7.1, 2.2 Hz, 3H, *H*-4); **δ_C** (101 MHz, $CDCl_3$) 167.1 (*C*-11), 143.4 (*C*-10), 131.8 (*C*-7), 129.9 (Ar*C*H), 129.4 (dd, *J* = 250.7, 250.0 Hz, *C*-2), 128.6 (Ar*C*H), 61.8 (app t, *J* = 29.6 Hz, *C*-1), 60.0 (d, *J* = 6.3 Hz, *C*-5) 59.7 (*C*-12), 52.2 (*C*-6), 40.9 (dd, *J* = 26.1, 21.7 Hz, *C*-3) , 10.9 (app d, *J* = 10.1 Hz, *C*-4); **δ_F** (376 MHz, $CDCl_3$) –94.64 (d, *J* = 229.0 Hz), –106.78 (d, *J* = 229.0 Hz).; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{17}F_2NNaO_2$ 292.1120; found 292.1120 (+0.30 ppm).

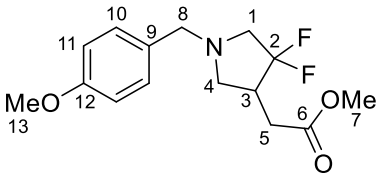
1-(Cyclohexylmethyl)-3,3-difluoro-4-methylpyrrolidine 8



N-(2-Bromo-2,2-difluoroethyl)-*N*-(cyclohexylmethyl)prop-2-en-1-amine **35** (74.1 mg, 250 µmol) was subjected to General Procedure 5, stirring at room temperature for 17 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 2% diethyl ether in cyclohexane) to give **8** (41.3 mg, 190 µmol, 76% yield) as a colourless oil.

R_f (49:1 cyclohexane: diethyl ether) = 0.42; **ν_{max}** (thin film)/cm^{-1} 2973, 2921, 2850, 2796, 1449, 1326, 1221, 1185, 1112, 917, 876 **δ_H** (500 MHz, $CDCl_3$) 3.17 (dt, *J* = 13.9, 10.7 Hz, 1H, *H*-1), 3.02 (dd, *J* = 9.0, 7.2 Hz, 1H, *H*-4), 2.65 – 2.53 (m, 1H, *H*-1), 2.53 – 2.36 (m, 1H, *H*-3), 2.28 – 2.14 (m, 2H, *H*-6), 2.10 (t, *J* = 9.0 Hz, 1H, *H*-4), 1.83 – 1.62 (m, 5H, *H*-9 & *H*-8), 1.45 – 1.31 (m, 1H, *H*-7), 1.28 – 1.09 (m, 3H, *H*-9 & *H*-8), 1.05 (dd, *J* = 7.1, 2.2 Hz, 3H, *H*-5), 0.93 – 0.80 (m, 2H, *H*-10); **δ_C** (101 MHz, $CDCl_3$) 129.6 (app t, *J* = 250.4 Hz, *C*-2), 63.3 (*C*-6), 62.4 (t, *J* = 29.0 Hz, *C*-1), 60.7 (app d, *J* = 6.4 Hz, *C*-4), 40.8 (dd, *J* = 24.3, 21.6 Hz, *C*-3), 36.6 (*C*-7), 31.9 (*C*-9), 31.8 (*C*-8), 26.9 (*C*-10), 26.2 (*C*-9),10.9 (app d, *J* = 10.3 Hz, *C*-5); **δ_F** (376 MHz, $CDCl_3$) -94.61 (d, *J* = 228.2 Hz), -106.81 (d, *J* = 228.2 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{22}F_2N$ 218.1715; found 218.1716 (+0.60 ppm).

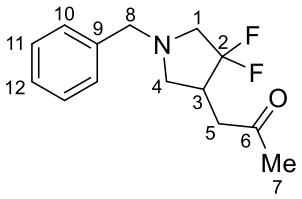
Methyl 2-(4,4-difluoro-1-(4-methoxybenzyl)pyrrolidin-3-yl)acetate 9



Methyl (*E*)-4-((2-bromo-2,2-difluoroethyl)(4-methoxybenzyl)amino)but-2-enoate **36** (94.5 mg, 250 µmol) was subjected to General Procedure 5, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 10-20% diethyl ether in pentane) to give **9** (62.7 mg, 209 µmol, 84% yield) as a yellow oil.

R_f (80:20 petroleum ether: diethyl ether) = 0.29; **ν_{max}** (thin film)/cm^{-1} 3067, 3033, 2998, 2955, 2913, 2836, 2807, 1737, 1613; **δ_H** (400 MHz, $CDCl_3$) 7.20 (d, *J* = 8.5 Hz, 2H, *H*-11), 6.85 (d, *J* = 8.5 Hz, 2H, *H*-10), 3.80 (s, 3H, *H*-13), 3.68 (s, 3H, *H*-7), 3.61 – 3.48 (m, 2H, *H*-8), 3.16 – 3.02 (m, 2H, *H*-1 and *H*-4), 2.97 – 2.78 (m, 1H, *H*-3), 2.79 – 2.61 (m, 2H, *H*-1 and *H*-5), 2.39 (dddd, *J* = 16.8, 9.5, 1.4, 1.4 Hz, 1H, *H*-5), 2.30 (app t, *J* = 8.7 Hz, 1H, *H*-4); **δ_C** (101 MHz, $CDCl_3$) 172.2 (dd, *J* = 1.4, 1.4 Hz, *C*-6), 159.0 (*C*-12), 129.9 (*C*-11), 129.7 (*C*-9), 128.8 (dd, *J* = 252.3, 252.3 Hz, *C*-2), 113.9 (*C*-10), 61.5 (dd, *J* = 28.9, 28.9 Hz, *C*-1), 59.1 (*C*-8), 58.0 (app d, *J* = 5.5 Hz, *C*-4), 55.4 (*C*-13), 52.0 (*C*-7), 42.5 (dd, *J* = 25.3, 19.9 Hz, *C*-3), 31.8 (app d, *J* = 9.9 Hz, *C*-5); **δ_F** (376 MHz, $CDCl_3$) –93.53 (d, *J* = 230.9 Hz), –104.76 (d, *J* = 230.9 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{19}F_2NO_3$ 300.1406; found 300.1407 (+0.50 ppm).

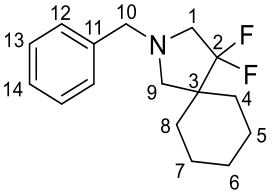
1-(1-Benzyl-4,4-difluoropyrrolidin-3-yl)propan-2-one 10



(*E*)-5-(Benzyl(2-bromo-2,2-difluoroethyl)amino)pent-3-en-2-one **37** (83.0 mg, 250 µmol) was subjected to General Procedure 5, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 20% diethyl ether in pentane) to give **10** (54.9 mg, 217 µmol, 86% yield) as a yellow oil.

R_f (80:20 petroleum ether: diethyl ether) = 0.13; **ν_{max}** (thin film)/cm^{-1} 3088, 3064, 3029, 3006, 2964, 2914, 2804, 1718; **δ_H** (400 MHz, $CDCl_3$) 7.36 – 7.23 (m, 5H, Ar*H*), 3.67 – 3.52 (m, 2H, *H*-8), 3.20 – 3.01 (m, 2H, *H*-4 and *H*-1), 2.99 – 2.81 (m, 2H, *H*-3 and *H*-5), 2.74 (ddd, *J* = 17.6, 11.6, 11.6 Hz, 1H, *H*-1), 2.50 (dddd, *J* = 18.2, 9.4, 2.4, 2.4 Hz, 1H, *H*-5), 2.24 (dd, *J* = 8.4, 8.4 Hz, 1H, *H*-4), 2.17 (s, 3H, *H*-7); **δ_C** (101 MHz, $CDCl_3$) 206.2 (*C*-6), 137.7 (*C*-9), 129.3 (dd, *J* = 252.0, 252.0 Hz, *C*-4), 128.8 (Ar*C*H), 128.5 (Ar*C*H), 127.5 (*C*-12), 61.5 (dd, *J* = 29.1, 29.1 Hz, *C*-1), 59.8 (*C*-8), 58.3 (dd, *J* = 5.5, 1.5 Hz, *C*-4), 41.5 (dd, *J* = 24.9, 20.0 Hz, *C*-3), 41.1 (dd, *J* = 7.7 Hz, *C*-5), 30.2 (*C*-7); **δ_F** (376 MHz, $CDCl_3$) –93.72 (d, *J* = 230.3 Hz), –103.90 (d, *J* = 230.3 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{17}F_2NO$ 254.1351; found 254.1353 (+0.60 ppm).

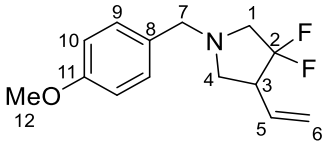
2-Benzyl-4,4-difluoro-2-azaspiro[4.5]decane 11



N-Benzyl-2-bromo-*N*-(cyclohex-1-en-1-ylmethyl)-2,2-difluoroethan-1-amine **38** (86.6 mg, 252 µmol) was subjected to General Procedure 5, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 0-1% diethyl ether in pentane) to give **11** (46.7 mg, 176 µmol, 70% yield) as a pale yellow oil.

R_f (95:5 petroleum ether: diethyl ether) = 0.33; **ν_{max}** (thin film)/cm^{-1} 3087, 3064, 3029, 2933, 2859, 2798, 2753; **δ_H** (400 MHz, $CDCl_3$) 7.42 – 7.16 (m, 5H, Ar*H*), 3.63 (s, 2H, *H*-10), 2.96 (dd, *J* = 14.2, 14.2 Hz, 2H, *H*-1), 2.66 (s, 2H, *H*-9), 1.84 – 1.52 (m, 7H, CH_2, cyclohexane), 1.39 – 1.09 (m, 3H, CH_2, cyclohexane); **δ_C** (101 MHz, $CDCl_3$) 138.4 (*C*-11), 129.7 (t, *J* = 254.4 Hz, *C*-2), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 127.3 (Ar*C*H), 62.5 (*C*-9), 61.1 (t, *J* = 29.5 Hz, *C*-1), 60.1 (*C*-10), 47.0 (t, *J* = 19.6 Hz, *C*-3), 30.0 (t, *J* = 5.7 Hz, *H*-4 and *H*-8), 25.9 (*H*-6), 23.1 (t, *J* = 1.6 Hz, *H*-5 and *H*-7); **δ_F** (376 MHz, $CDCl_3$) –107.39; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{21}F_2N$ 266.1715; found 266.1723 (+3.00 ppm).

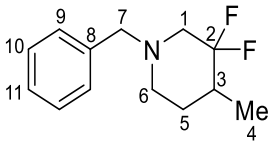
3,3-Difluoro-1-(4-methoxybenzyl)-4-vinylpyrrolidine 12



To a 50 mL culture tube was added *N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)buta-2,3-dien-1-amine **42** (82.5 mg, 248 mmol), Ir(ppy)$_3$ (1.64 mg, 2.50 µmol), DIPEA (0.871 mL, 5.00 mmol), TTMSS (154 µL, 500 µmol) and acetonitrile (25 mL). The culture tube was sealed and the mixture was sparged with Ar for 20 minutes. The blue LEDs were switched on and the reaction was stirred at room temperature for 4.5 hours. KF on alumina (40 wt%, 1.5 g) was added and the mixture was stirred for 20 minutes, then filtered and concentrated. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 5-10% diethyl ether in pentane) to give **12** (528 mg, 209 µmol, 84% yield) as a yellow oil.

R_f (90:10 petroleum ether: diethyl ether) = 0.17; **ν_{max}** (thin film)/cm^{-1} 3082, 3034, 2997, 2957, 2937, 2912, 2835, 2810, 2751; **δ_H** (400 MHz, $CDCl_3$) 7.23 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2H, Ar*H*), 5.89 – 5.71 (m, 1H, *H*-5), 5.25 – 5.13 (m, 2H, *H*-6), 3.81 (s, 3H, *H*-12), 3.66 – 3.50 (m, 2H, *H*-7), 3.20 (ddd, *J* = 13.5, 11.2, 11.0 Hz, 1H, *H*-1), 3.14 – 2.95 (m, 2H, *H*-3 and *H*-4), 2.72 (ddd, *J* = 19.1, 12.9, 11.2 Hz, 1H, *H*-1), 2.51 – 2.37 (m, 1H, *H*-4); **δ_C** (101 MHz, $CDCl_3$) 159.1 (*C*-11), 131.4 (app d, *J* = 8.6 Hz, *C*-5), 130.0 (Ar*C*H), 129.9 (Ar*C*q), 128.6 (dd, *J* = 253.4, 250.3 Hz, *C*-2), 119.1 (*C*-6), 113.9 (Ar*C*H), 61.7 (dd, *J* = 29.0, 29.0 Hz, *C*-1), 59.3 (*C*-7), 57.6 (app d, *J* = 5.9 Hz, *C*-4), 55.4 (*C*-12), 50.8 (dd, *J* = 24.7, 20.7 Hz, *C*-3); **δ_F** (376 MHz, $CDCl_3$) –93.68 (d, *J* = 230.7 Hz), –102.27 (d, *J* = 230.7 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{17}F_2NO$ 254.1351; found 254.1351 (+0.20 ppm).

1-Benzyl-3,3-difluoro-4-methylpiperidine 13

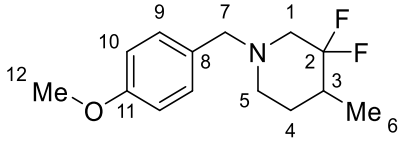


N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-en-1-amine **45** (76.2 mg, 251 µmol) was subjected to General Procedure 5, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 0-4% diethyl ether in pentane) to give **13** (37.8 mg, 168 µmol, 67% yield) as a colourless oil.

R_f (90:10 petroleum ether: diethyl ether) = 0.32; **ν_{max}** (thin film)/cm^{-1} 3087, 3064, 3029, 2975, 2943, 2926, 2885, 2858, 2813, 2772, 2937, 2682; **δ_H** (400 MHz, $CDCl_3$) 7.52 – 7.10 (m, 5H, Ar*H*), 3.69 – 3.50 (m, 2H, *H*-7), 3.06 (dddd, *J* = 11.7, 9.8, 5.8, 1.6 Hz, 1H, *H*-1), 2.86 (ddd, *J* = 11.5, 3.1, 2.6 Hz, 1H, *H*-6), 2.21 (ddd, *J* = 27.6,

11.8, 2.4 Hz, 1H, *H*-1), 2.11 (ddd, *J* = 11.6, 2.9, 1.7 Hz, 1H, *H*-6), 1.90 – 1.73 (m, 1H, *H*-3), 1.73 – 1.51 (m, 2H, *H*-5), 1.07 (d, *J* = 6.7 Hz, 3H, *H*-4); **δ_C** (101 MHz, $CDCl_3$) 137.5 (*C*-8), 129.1 (Ar*C*H), 128.5 (Ar*C*H), 127.4 (Ar*C*H), 121.3 (dd, *J* = 247.7, 240.4 Hz, *C*-2), 62.2 (*C*-7), 58.3 (dd, *J* = 31.1, 25.0 Hz, *C*-1), 52.2 (*C*-6), 37.1 (dd, *J* = 23.2, 21.1 Hz, *C*-3), 30.5 (app d, *J* = 8.4 Hz, *C*-5), 12.2 (dd, *J* = 4.9, 2.4 Hz, *C*-4); **δ_F** (376 MHz, $CDCl_3$) –105.13 (d, *J* = 239.2 Hz), –117.38 (d, *J* = 241.9 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{17}F_2N$ 226.1402; found 226.1407 (+2.20 ppm).

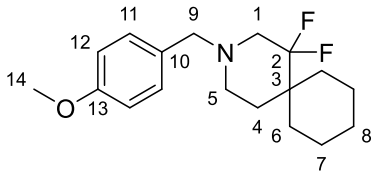
3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpiperidine 14



N-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)but-3-en-1-amine **46** (84 mg, 250 µmol) was subjected to General Procedure 5, stirring at room temperature for 17 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 5% diethyl ether in cyclohexane) to give **14** (52.3 mg, 210 µmol, 82% yield) as a colourless oil.

R_f (9:1 cyclohexane: diethyl ether) = 0.17; **ν_{max}** (thin film)/cm^{-1} 2943, 2834, 2811, 1712, 1512, 1464, 1372, 1285, 913; **δ_H** (400 MHz, $CDCl_3$) 7.25 – 7.18 (m, 2H, Ar*H*), 6.90 – 6.82 (m, 2H, Ar*H*), 3.80 (s, 3H, OCH_3), 3.57 (d, *J* = 13.1 Hz, 1H, *H*-7), 3.49 (d, *J* = 13.1 Hz, 1H. *H*-7), 3.09 – 2.97 (m, 1H, *H*-1), 2.89 – 2.78 (m, 1H, *H*-1), 2.23 – 2.02 (m, 2H, *H*-5), 1.86 – 1.70 (m, 1H, *H*-3), 1.70 – 1.49 (m, 2H, *H*-4), 1.05 (d, *J* = 6.7 Hz, 3H, CH_3); **δ_C** (101 MHz, $CDCl_3$) 159.0 (*C*-11), 130.3 (Ar*C*H), 129.4 (*C*-8), 121.3 (dd, *J* = 247.6, 240.3 Hz, *C*-2),113.8 (Ar*C*H), 61.6 (*C*-7), 58.1(dd, *J* = 31.1, 24.9 Hz, *C*-1), 55.4 (*C*-12), 52.1 (*C*-5), 37.1 (dd, *J* = 23.2, 21.2 Hz, *C*-3), 30.5 (app d, *J* = 8.4 Hz, *C*-4), 12.2, (dd, *J* = 5.0, 2.4 Hz, *C*-6); **δ_F** (376 MHz, $CDCl_3$) –105.11 (d, *J* = 239.0 Hz), –117.35 (d, *J* = 239.1 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{20}F_2NO$ 256.1507; found 256.1507 (+0.20 ppm).

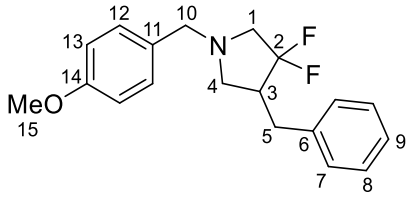
1,1-Difluoro-3-(4-methoxybenzyl)-3-azaspiro[5.5]undecane 15



2-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2,2-difluoro-*N*-(4-methoxybenzyl)ethan-1-amine **47** (97.1 mg, 250 µmol) was subjected to General Procedure 5, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 5% diethyl ether in cyclohexane) to give **15** (40.4 mg, 130 µmol, 52% yield) as a colourless oil.

R_f (9:1 cyclohexane: diethyl ether) = 0.20; **ν_{max}** (thin film)/cm^{-1} 2937, 2863, 2833, 1611, 1511, 1455, 1302, 1240, 1035; **δ_H** (500 MHz, $CDCl_3$) 7.25 – 7.18 (m, 2H, Ar*H*), 6.89 – 6.82 (m, 2H, Ar*H*), 3.80 (s, 3H, OCH_3), 3.53 (s, 2H, *H*-9), 2.61 (t, *J* = 12.0 Hz, 2H, *H*-1), 2.47 (t, *J* = 5.6 Hz, 2H, *H*-5), 1.75 (t, *J* = 5.8 Hz, 2H, *H*-4), 1.64 – 1.49 (m, 7H, cyclohexane), 1.40 – 1.29 (m, 2H, cyclohexane), 1.23 – 1.12 (m, 1H, cyclohexane); **δ_C** (126 MHz, $CDCl_3$) 159.0 (*C*-13), 130.4 (Ar*C*H), 129.4 (*C*-10), 123.3 (t, *J* = 247.2 Hz, *C*-2), 113.8 (Ar*C*H), 61.6 (*C*-9), 55.4 (*C*-14), 53.9 (t, *J* = 28.8 Hz, *C*-1), 47.7 (*C*-5), 39.1 (t, *J* = 19.6 Hz, *C*-3), 29.2 (t, *J* = 2.7 Hz, *C*-4), 28.1 (d, *J* = 4.1 Hz, *C*-6), 26.0 (C-*7*), 20.9 (*C*-8); **δ_F** (376 MHz, $CDCl_3$) – 112.99; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{26}F_2NO$ 310.1977; found 310.1977 (+0.10 ppm).

4-Benzyl-3,3-difluoro-1-(4-methoxybenzyl)pyrrolidine 16

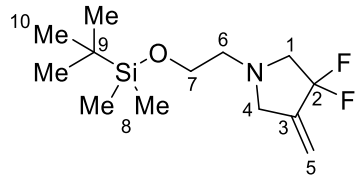


(*E*)-*N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)-3-phenylprop-2-en-1-amine **48** (99.4 mg, 251 µmol) was subjected to General Procedure 5, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 5-7% diethyl ether in pentane) to give **16** (30.0 mg, 94.4 µmol, 38% yield) as a pale yellow oil.

R_f (90:10 petroleum ether: diethyl ether) = 0.26; **ν_{max}** (thin film)/cm^{-1} 3087, 3063, 3029, 3002, 2955, 2935, 2913, 2863, 2834, 2807, 2798, 1612, 1511; **δ_H** (400 MHz, $CDCl_3$) 7.42 – 7.09 (m, 7H, Ar*H*), 6.84 (d, *J* = 8.3 Hz, 2H, Ar*H*), 3.80 (s, 3H, *H*-15), 3.63 – 3.43 (m, 2H, *H*-10), 3.18 (ddd, *J* = 13.8, 10.7, 10.7 Hz, 1H, *H*-1), 3.04 (dd, *J* = 13.7, 5.0 Hz, 1H, *H*-5), 2.89 (dd, *J* = 9.3, 7.0 Hz, 1H, *H*-4), 2.80 – 2.65 (m, 2H, *H*-1 and *H*-3), 2.60 (dd, *J* = 13.8, 10.2 Hz, 1H, *H*-5), 2.30 (dd, *J* = 9.0, 9.0 Hz, 1H, *H*-4); **δ_C** (101 MHz, $CDCl_3$) 159.0 (*C*-14), 139.5 (*C*-6), 129.9 (Ar*C*H), 129.1 (dd, *J* = 250.3, 250.3 Hz, *C*-2), 128.8 (Ar*C*H), 128.7 (Ar*C*H), 128.1 (Ar*C*q), 126.43 (Ar*C*H), 113.9 (Ar*C*H), 62.0 (dd, *J* = 29.1, 29.1 Hz, *C*-1), 59.4 (*C*-10), 58.1 (app d, *J* = 5.9, *C*-4), 55.4 (*C*-15), 47.8 (dd, *J* = 23.7, 20.4 Hz, *C*-3), 32.7 (app d, *J* = 9.5 Hz, *C*-5); **δ_F** (376 MHz, $CDCl_3$) –93.12 (d, *J* = 230.0 Hz), –104.96 (d, *J* = 230.0 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}F_2NO$ 318.1664; found 318.1663 (+0.40 ppm).

3.6 Cyclised alkynyl amines

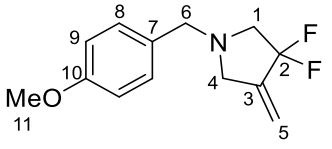
1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3,3-difluoro-4-methylenepyrrolidine 4



N-(2-Bromo-2,2-difluoroethyl)-*N*-(2-((tert-butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **3** (89.8 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 16 hours. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-5% diethyl ether in pentane) to give **4** (39.4 mg, 142 µmol, 56% yield) as a colourless oil.

R_f (90:10 petroleum ether: ethyl acetate) = 0.43; **ν_{max}** (thin film)/cm^{-1} 2955, 2929, 2907, 2887, 2857, 2812, 2777, 2714; **δ_H** (400 MHz, $CDCl_3$) 5.58 (dt, *J* = 5.5, 2.8 Hz, 1H, *H*-5), 5.30 (dt, *J* = 5.5, 2.8 Hz, 1H, *H*-5), 3.76 (t, *J* = 5.9 Hz, 2H, *H*-7), 3.44 (m, 2H, *H*-4), 3.08 (t, *J* = 11.4 Hz, 2H, *H*-1), 2.65 (t, *J* = 5.9 Hz, 2H, *H*-6), 0.89 (s, 9H, *H*-10), 0.06 (s, 6H, *H*-8); **δ_C** (101 MHz, $CDCl_3$) 142.9 (t, *J* = 20.9 Hz, *C*-3), 122.8 (t, *J* = 246.0 Hz, *C*-2), 112.0 (t, *J* = 2.1 Hz, *C*-5), 62.2 (*C*-7), 62.1 (t, *J* = 27.0 Hz, *C*-1), 57.9 (*C*-6), 57.8 (t, *J* = 3.1 Hz, *C*-4), 26.0 (*C*-10), 18.4 (*C*-9), –5.3 (*C*-8); **δ_F** (376 MHz, $CDCl_3$) –98.23; **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{13}H_{25}F_2NOSi$ 300.1566; found 300.1564 (+0.40 ppm).

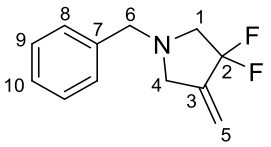
3,3-Difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine 17



N-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine **29** (80.2 mg, 252 µmol) was subjected to General Procedure 4, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 80:20 pentane/diethyl ether) to give **17** (35.4 mg, 148 µmol, 59% yield) as a colourless oil.

R_f (80:20 petroleum ether:ethyl acetate) = 0.49; **ν_{max}** (thin film)/cm^{-1} 2924, 2837, 2808, 1512; **δ_H** (400 MHz, $CDCl_3$) 7.35 – 7.18 (m, 2H, Ar*H*), 6.94 – 6.81 (m, 2H, Ar*H*), 5.59 (m, 1H, *H*-5), 5.29 (m, 1H, *H*-5), 3.82 (s, 3H, *H*-11), 3.62 (s, 2H, *H*-6), 3.34 (t, *J* = 2.2 Hz, 2H, *H*-4), 2.99 (t, *J* = 12.0 Hz, 2H, *H*-1); **δ_C** (101 MHz, $CDCl_3$) 159.1 (*C*-10), 143.1 (t, *J* = 20.9 Hz, *C*-3), 130.1 (Ar*C*H), 129.5 (*C*-5), 122.8 (t, *J* = 246.5 Hz, *C*-2), 113.9 (Ar*C*H), 112.1 (t, *J* = 2.4 Hz, *C*-5), 61.0 (t, *J* = 27.0 Hz, *C*-1), 59.4 (*C*-6), 56.60 (t, *J* = 3.1 Hz, *C*-4), 55.4 (*C*-11); **δ_F**(376 MHz, $CDCl_3$) –97.63; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{15}F_2NO$ 240.1194; found 2440.1192 (+1.10 ppm).

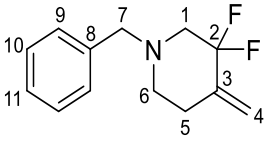
1-Benzyl-3,3-difluoro-4-methylenepyrrolidine 18



N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)prop-2-yn-1-amine **50** (72.0 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 24 hours. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-5% diethyl ether in pentane) to give **18** (35.4 mg, 169 µmol, 67% yield) as a colourless oil.

R_f (95:5 petroleum ether: diethyl ether) = 0.48; **ν_{max}** (thin film)/cm^{-1} 3107, 3064, 2957, 2923, 2805; **δ_H** (400 MHz, $CDCl_3$) 7.37 – 7.26 (m, 5H, Ar*H*), 5.59 (m, 1H, *H*-5), 5.29 (m, 1H, *H*-5), 3.67 (s, 2H, *H*-6), 3.36 (t, *J* = 2.0 Hz, 2H, *H*-4), 3.01 (t, *J* = 11.3 Hz, 2H, *H*-1); **δ_C** (101 MHz, $CDCl_3$) 143.1 (t, *J* = 21.0 Hz, *C*-3), 137.4 (Ar*C*H), 128.9 (Ar*C*H), 128.6 (Ar*C*H), 127.6 (Ar*C*q), 122.8 (t, *J* = 246.5 Hz, *C*-2), 112.1 (t, *J* = 2.5 Hz, *C*-5), 61.1 (t, *J* = 27.1 Hz, *C*-1), 60.0 (*C*-6), 56.7 (t, *J* = 3.1 Hz, *C*-4); **δ_F** (376 MHz, $CDCl_3$) –97.69; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{13}F_2N$ 210.1089; found 210.1087 (+0.70 ppm).

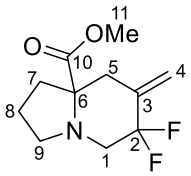
1-Benzyl-3,3-difluoro-4-methylenepiperidine 19



N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-yn-1-amine **44** (75.6 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 17.5 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 0-5% diethyl ether in pentane) to give **19** (28.3 mg, 0.127 µmol, 51% yield) as a colourless oil.

R_f (95:5 petroleum ether: diethyl ether) = 0.43; **ν_{max}** (thin film)/cm^{-1} 3088, 3064, 3029, 3004, 2951, 2917, 2879, 2813, 2773, 2743; **δ_H** (400 MHz, $CDCl_3$) 7.40 – 7.33 (m, 4H, Ar*H*), 7.31 (t, *J* = 4.3 Hz, 1H, Ar*H*), 5.40 (d, *J* = 1.0 Hz, 1H, *H*-4), 5.09 (d, *J* = 1.0 Hz, 1H, *H*-4), 3.66 (s, 2H, *H*-7), 2.77 (t, *J* = 11.1 Hz, 2H, *H*-1), 2.58 (t, *J* = 5.7 Hz, 2H, *H*-6), 2.50 (t, *J* = 5.7 Hz, 2H, *H*-5); **δ_C** (101 MHz, $CDCl_3$) 140.2 (t, *J* = 20.7 Hz, *C*-3), 137.3 (Ar*C*q), 129.0 (Ar*C*H), 128.4 (Ar*C*H), 127.4 (Ar*C*H), 117.2 (t, *J* = 242.6 Hz, *C*-2), 111.5 (t, *J* = 7.4 Hz, *C*-4), 61.6 (*C*-7), 59.5 (t, *J* = 28.7 Hz, *C*-1), 53.3 (*C*-6), 31.9 (t, *J* = 2.2 Hz, *C*-5); **δ_F** (376 MHz, $CDCl_3$) –105.54; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{15}F_2N$ 224.1245; found 224.1245 (+0.10 ppm).

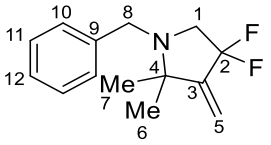
Methyl 6,6-difluoro-7-methylenehexahydroindolizine-8a(1*H*)-carboxylate 20



Methyl 1-(2-bromo-2,2-difluoroethyl)-2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **52** (78.7 mg, 254 µmol) was subjected to General Procedure 4, stirring at room temperature for 17 hours. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 5-10% diethyl ether in pentane) to give **20** (43.1 mg, 186 µmol, 73% yield) as a colourless oil.

R_f (90:10 petroleum ether: diethyl ether) = 0.20; **ν_{max}** (thin film)/cm^{-1} 2953, 2916, 2884, 2854, 1730; **δ_H** (400 MHz, $CDCl_3$) 5.40 – 5.36 (m, 1H, *H*-4), 5.11 – 5.07 (m, 1H, *H*-4), 3.68 (s, 3H, *H*-11), 3.32 – 3.22 (m, 2H, *H*-1), 3.21 – 3.09 (m, 2H, *H*-9), 2.93 (dd, *J* = 13.3, 3.8 Hz, 1H, *H*-5), 2.46 (ddddd, *J* = 13.3, 1.9, 1.9, 1.9, 1.9 Hz, 1H, *H*-5), 2.18 – 2.07 (m, 1H, *H*-7), 2.00 – 1.91 (m, 1H, *H*-8), 1.91 – 1.77 (m, 2H, *H*-7 and *H*-8); **δ_C** (101 MHz, $CDCl_3$) 174.1 (*C*-10), 138.3 (dd, *J* = 23.1, 19.8 Hz, *C*-3), 117.8 (dd, *J* = 249.8, 241.7 Hz, *C*-2), 113.8 (dd, *J* = 9.2, 6.0 Hz, *C*-4), 69.0 (*C*-6), 53.1 (dd, *J* = 31.9, 25.6 Hz, *C*-1), 51.9 (*C*-11), 50.4 (*C*-9), 39.2 (d, *J* = 4.1 Hz, *C*-5), 36.4 (d, *J* = 1.3 Hz, *C*-7), 21.9 (*C*-8); **δ_F** (376 MHz, $CDCl_3$) –95.30 (d, *J* = 240.4 Hz), –115.57 (d, *J* = 240.4 Hz); **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_{11}H_{15}F_2NO_2$ 254.0963; found 254.0962 (+0.30 ppm).

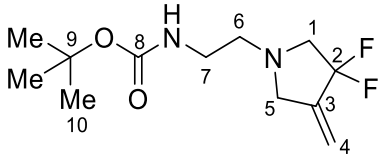
1-Benzyl-4,4-difluoro-2,2-dimethyl-3-methylenepyrrolidine 21



N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-2-methylbut-3-yn-2-amine **54** (79.0 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 24 hours. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 0-2% diethyl ether in pentane) to give **21** (37.3 mg, 157 µmol, 63% yield) as a colourless solid.

R_f (95:5 petroleum ether: ethyl acetate) = 0.56; **m.p.** 55–57 °C; **ν_{max}** (thin film)/cm^{-1} 3088, 3067, 3033, 2989, 2971, 2928, 2901, 2870, 2847, 2814, 2712; **δ_H** (400 MHz, $CDCl_3$) 7.46 – 7.17 (m, 5H, Ar*H*), 5.63 – 5.57 (m, 1H, *H*-5), 5.33 – 5.22 (m, 1H, *H*-5), 3.64 (s, 2H, *H*-8), 2.99 (tt, *J* = 11.9, 1.7 Hz, 2H, *H*-1), 1.30 (s, 3H, *H*-6), 1.29 (s, 3H, *H*-7); **δ_C** (101 MHz, $CDCl_3$) 153.6 (t, *J* = 19.6 Hz, *C*-3), 139.0 (*C*-9), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 127.2 (*C*-12), 122.6 (t, *J* = 245.0 Hz, *C*-2), 110.8 (t, *J* = 2.7 Hz, *C*-5), 62.8 (t, *J* = 2.9 Hz, *C*-4), 56.8 (t, *J* = 27.5 Hz, *C*-1), 51.6 (*C*-8), 23.6 (*C*-6 and *C*-7); **δ_F** (376 MHz, $CDCl_3$) –96.22; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{17}F_2N$ 238.1402; found 238.1404 (+1.00 ppm).

***tert*-Butyl (2-(3,3-difluoro-4-methylenepyrrolidin-1-yl)ethyl)carbamate 22**

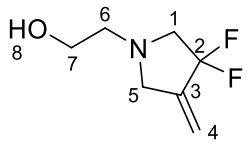


tert-Butyl (2-((2-bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethyl)carbamate **56** (30.0 mg, 87.9 µmol) was subjected to General Procedure 4, stirring at room temperature for 17 hours. The resultant residue after

concentration was purified by flash column chromatography (SiO_2, eluting with 20-50% diethyl ether in pentane) to give **22** (11.2 mg, 42.7 µmol, 48% yield) as a yellow oil.

R_f (50:50 petroleum ether: diethyl ether) = 0.31; **ν_{max}** (thin film)/cm^{-1} 3434, 3350, 2976, 2932, 2814, 1698, 1503; **δ_H** (400 MHz, $CDCl_3$) 5.73 – 5.58 (m, 1H, *H*-4), 5.43 – 5.27 (m, 1H, *H*-4), 3.42 (t, *J* = 2.1 Hz, 2H, *H*-5), 3.27 (dt, *J* = 5.9, 5.1 Hz, 2H, *H*-7), 3.05 (t, *J* = 11.3 Hz, 2H, *H*-1), 2.65 (t, *J* = 5.9 Hz, 2H, *H*-6), 1.47 (s, 9H, *H*-10); **δ_C** (101 MHz, $CDCl_3$) 156.0 (*C*-8), 142.3 (t, *J* = 21.0 Hz, *C*-3), 122.4 (t, *J* = 246.4 Hz, *C*-2), 112.3 (t, *J* = 2.3 Hz, *C*-4), 79.4, 61.0 (t, *J* = 27.3 Hz, *C*-9), 56.5 (t, *J* = 3.1 Hz, *C*-5), 54.9 (*C*-6), 38.1 (*C*-7), 28.4 (*C*-10); **δ_F** (376 MHz, $CDCl_3$) –97.89; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{12}H_{20}F_2N_2O_2$ 263.1566; found 263.1569 (+1.20 ppm).

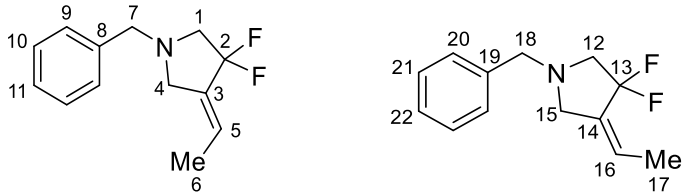
2-(3,3-Difluoro-4-methylenepyrrolidin-1-yl)ethan-1-ol 23



2-((2-Bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethan-1-ol **57** (60.6 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 16 hours. The resultant residue was purified by flash column chromatography (SiO_2, eluting with 10-20% acetone in pentane) to give **23** (30.2 mg, 185 µmol, 74% yield) as a yellow oil.

R_f (80:20 petroleum ether: acetone) = 0.15; **ν_{max}** (thin film)/cm^{-1} 3362, 2930, 2883, 2810; **δ_H** (400 MHz, $CDCl_3$) 5.72 – 5.51 (m, 1H, *H*-4), 5.39 – 5.14 (m, 1H, *H*-4), 3.65 (t, *J* = 5.3 Hz, 2H, *H*-7), 3.44 (s, 2H, *H*-5), 3.27 (br s, 1H, *H*-8), 3.07 (t, *J* = 11.3 Hz, 2H, *H*-1), 2.69 (t, *J* = 5.3 Hz, 2H, *H*-6); **δ_C** (101 MHz, $CDCl_3$) 142.4 (t, *J* = 21.0 Hz, *C*-3), 122.5 (t, *J* = 246.5 Hz, *C*-2), 112.5 (t, *J* = 2.5 Hz, *C*-4), 61.2 (t, *J* = 27.3 Hz, *C*-1), 59.4 (*C*-7), 57.4 (*C*-6), 56.8 (t, *J* = 3.1 Hz, *C*-5); **δ_F** (376 MHz, $CDCl_3$) –97.97; **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_7H_{11}F_2NO$ 164.0881; found 164.0878 (+1.90 ppm).

1-Benzyl-4-ethylidene-3,3-difluoropyrrolidine 24

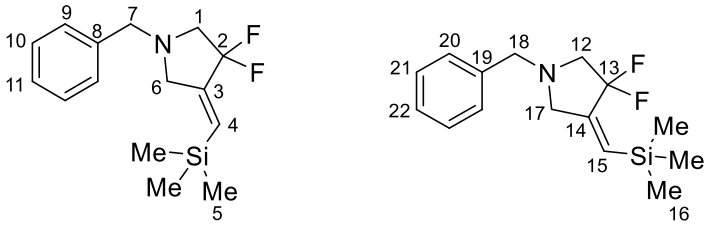


N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-2-yn-1-amine **59** (75.5 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 2-5% diethyl ether in pentane) to give **24** (421 µg, 189 µmol, 75% yield, 53:47 *E:Z*) as a colourless oil. The following data is for the 53:47 mixture of *E* and *Z* products. The stereochemistry of each component was determined by NOE interactions.

R_f (90:10 petroleum ether: diethyl ether) = 0.31; **ν_{max}** (thin film)/cm^{-1} 3087, 3064, 3030, 2921, 2804, 2765; **δ_H** (400 MHz, $CDCl_3$) 7.39 – 7.25 (m, 10H, Ar*H*), 6.11 – 5.99 (m, 1H, *H*-5), 5.80 – 5.69 (m, 1H, *H*-16), 3.70 (s, 2H, *H*-7), 3.63 (s, 2H, *H*-18), 3.41 – 3.31 (m, 2H, *H*-4), 3.31 – 3.17 (m, 2H, *H*-15), 3.00 (app t, *J* = 11.2 Hz, 4H, *H*-1 and *H*-12), 1.92 – 1.84 (m, 3H, *H*-17), 1.72 – 1.63 (m, 3H, *H*-6); **δ_C** (101 MHz, $CDCl_3$) 137.6 (Ar*C*q), 137.5 (Ar*C*q), 135.2 (t, *J* = 20.5 Hz, *C*-3), 133.6 (t, *J* = 19.2 Hz, *C*-14), 128.9 (Ar*C*H), 128.9 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 127.5 (Ar*C*H), 127.5 (Ar*C*H), 126.3 (*C*-16), 124.6 (t, *J* = 246.0 Hz, *C*-13), 123.8 (t, *J* = 2.5 Hz, *C*-5), 123.2 (t, *J* = 244.9 Hz, *C*-2), 62.7 (t, *J* = 27.7 Hz, *C*-12), 61.3 (t, *J* = 27.3 Hz, *C*-1), 60.2 (*C*-7), 60.0 (*C*-18), 57.9 (t, *J* = 3.8 Hz, *C*-

15), 54.3 (t, *J* = 3.2 Hz, *C*-4), 14.7 (t, *J* = 2.1 Hz, *C*-6), 13.9 (*C*-17); δ_F (376 MHz, $CDCl_3$) –96.12, –96.58; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{15}F_2N$ 224.1245; found 224.1243 (+1.20 ppm).

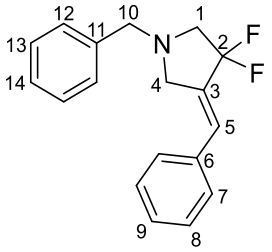
1-Benzyl-3,3-difluoro-4-((trimethylsilyl)methylene)pyrrolidine 25



N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-(trimethylsilyl)prop-2-yn-1-amine **61** (90.1 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 88 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 2-5% diethyl ether in pentane) to give **25** (450 µg, 160 µmol, 64% yield, 55:45 *E:Z*) as a pale yellow oil. The following data is for the 55:45 mixture of *E* and *Z* products. The stereochemistry of each component was determined by NOE interactions.

$\mathbf{R_f}$ (95:5 petroleum ether: diethyl ether) = 0.35; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3088, 3065, 3030, 2956, 2922, 2900, 2802, 2760, 2701; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.27 (m, 10H, Ar*H*), 6.16 (tt, *J* = 2.7, 2.7 Hz, 1H, *H*-4), 5.86 (tt, *J* = 2.7, 2.4 Hz, 1H, *H*-15), 3.70 (s, 2H, *H*-7), 3.64 (s, 2H, *H*-18), 3.41 (d, *J* = 2.7 Hz, 2H, *H*-6), 3.35 (d, *J* = 2.7 Hz, 2H, *H*-17), 3.01 (t, *J* = 11.5 Hz, 2H, *H*-12), 2.94 (t, *J* = 11.1 Hz, 2H, *H*-1), 0.17 (s, 9H, *H*-16), 0.13 (s, 9H, *H*-5); δ_C (101 MHz, $CDCl_3$) 149.4 (t, *J* = 21.1 Hz, *C*-3), 148.6 (t, *J* = 21.1 Hz, *C*-14), 137.4 (*C*-19), 137.4 (*C*-8), 130.5 (*C*-15), 129.0 (Ar*C*H), 128.9 (Ar*C*H), 128.6 (Ar*C*H), 128.6 (Ar*C*H), 127.6 (*C*-11), 127.6 (*C*-22), 126.9 (t, *J* = 2.0 Hz, *C*-4), 123.1 (t, *J* = 247.5 Hz, *C*-13), 122.1 (t, *J* = 246.6 Hz, *C*-2), 62.1 (t, *J* = 27.8 Hz, *C*-12), 60.4 (t, *J* = 3.9 Hz, *C*-17), 60.1 (*C*-7), 60.1 (*C*-18), 60.0 (t, *J* = 27.2 Hz, *C*-1), 56.7 (t, *J* = 2.9 Hz, *C*-6), -0.2 (t, *J* = 2.4 Hz, *C*-16), -0.90 (*C*-5); δ_F (376 MHz, $CDCl_3$) –94.50, –97.55; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{21}F_2NSi$ 282.1484; found 282.1487 (+0.90 ppm).

(*E*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine 26

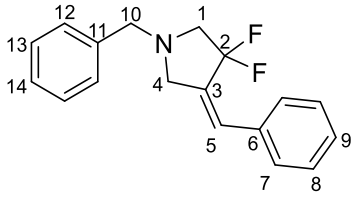


N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-phenylprop-2-yn-1-amine **62** (91.5 mg, 251 µmol) was subjected to General Procedure 4, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 1-3% diethyl ether in pentane) to give **26** (24.4 mg, 85.5 µmol, 34% yield) as a colourless oil. The *E* stereochemistry was assigned on the basis of a NOE interaction between *H*-7 and *H*-4.

$\mathbf{R_f}$ (90:10 petroleum ether: diethyl ether) = 0.16; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3129, 3106, 3087, 3061, 3029, 2958, 2923, 2884, 2804; δ_H (400 MHz, $CDCl_3$) 7.46 – 7.22 (m, 10H, Ar*H*), 6.92 (t, *J* = 2.8 Hz, 1H, *H*-5), 3.78 (s, 2H, *H*-10), 3.75 – 3.70 (m, 2H, *H*-4), 3.08 (t, *J* = 10.8 Hz, 2H, *H*-1); δ_C (101 MHz, $CDCl_3$) 137.4 (*C*-11), 135.5 (t, *J* = 2.4 Hz, (*C*-6), 134.4 (t, *J* = 20.0 Hz, *C*-3), 129.0 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.7 (Ar*C*H), 128.5 (Ar*C*H), 127.6 (Ar*C*H), 127.4 (t, *J* = 2.9 Hz, *C*-5), 124.4 (t, *J* = 246.2 Hz, *C*-2), 60.3 (d, *J* = 27.1 Hz, *C*-1), 60.0 (*C*-10), 56.1

(t, *J* = 2.9 Hz, *C*-4); δ_F (376 MHz, $CDCl_3$) –95.66; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}F_2N$ 286.1402; found 286.1399 (+1.10 ppm).

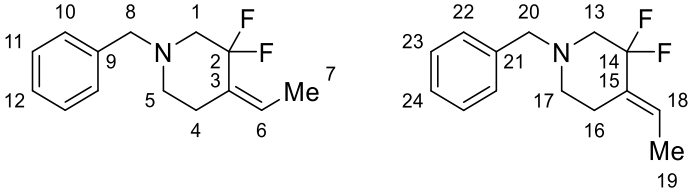
(*Z*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine 27



N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-phenylprop-2-yn-1-amine **62** (91.5 mg, 251 µmol) was subjected to General Procedure 4, stirring at room temperature for 16 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 1-3% diethyl ether in pentane) to give **27** (8.47 mg, 29.7 µmol, 12% yield) as a colourless oil. The *Z* stereochemistry was assigned on the basis of a NOE interaction between *H*-5 and *H*-4.

$\mathbf{R_f}$ (90:10 petroleum ether: diethyl ether) = 0.10; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3090, 3063, 3032, 2962, 2936, 2922, 2884, 2854, 2828, 1795; δ_H (400 MHz, $CDCl_3$) 7.54 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.42 – 7.26 (m, 8H, Ar*H*), 6.60 (t, *J* = 2.6 Hz, 1H, *H*-5), 3.70 (s, 2H, *H*-10), 3.51 (s, 2H, *H*-4), 3.11 (t, *J* = 11.7 Hz, 2H, *H*-1); δ_C (126 MHz, $CDCl_3$) 137.2 (*C*-6), 134.3 (*C*-11), 130.1 (*C*-5), 129.4 (t, *J* = 4.1 Hz, *C*-3), 129.1 (Ar*C*H), 128.7 (Ar*C*H), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 127.7 (Ar*C*H), 125.7 (Ar*C*H), 123.6 (t, *J* = 247.1 Hz, *C*-2), 62.9 (t, *J* = 28.4 Hz, *C*-1), 60.0 (*C*-10), 59.6 (t, *J* = 4.2 Hz, *C*-4); δ_F (376 MHz, $CDCl_3$) –95.35; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}F_2N$ 286.1402; found 286.1403 (+0.50 ppm).

1-Benzyl-4-ethylidene-3,3-difluoropiperidine 28

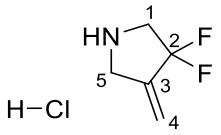


N-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)pent-3-yn-1-amine **64** (79.1 mg, 250 µmol) was subjected to General Procedure 4, stirring at room temperature for 17 hours. The resultant residue after concentration was purified by flash column chromatography (SiO_2, eluting with 4% diethyl ether in cyclohexane) to give **28** (452 µg, 190 µmol, 76% yield, 50:42 *E:Z*) as a colourless oil. The following data is for the 50:42 mixture of *E* and *Z* products. The stereochemistry of each component was determined by NOE interactions.

$\mathbf{R_f}$ (90:10 cyclohexane: diethyl ether) = 0.28; $\mathbf{\nu_{max}}$ (thin film)/cm^{-1} 3063, 3028, 2947, 2918, 2810, 1495, 1453, 1434, 1320, 1177, 1149, 1088, 1046, 915; δ_H (400 MHz, $CDCl_3$) 7.36 – 7.26 (m, 9H, Ar*H*), 6.02 – 5.93 (m, 1H, *H*-18), 5.58 – 5.48 (m, 1H, *H*-6), 3.63 (s, 2H, *H*-20), 3.62 (s, 2H, *H*-1), 2.72 (td, *J* = 11.4, 7.4 Hz, 4H, *H*-1 and *H*-13), 2.51 (q, *J* = 6.6 Hz, 4H, *H*-5 and *H*-17), 2.47 – 2.41 (m, 2H, *H*-4 and *H*-16), 2.37 (ddt, *J* = 5.3, 4.0, 1.5 Hz, 2H, *H*-4 and *H*-16), 1.91 – 1.77 (m, 3H, *H*-7), 1.67 (dt, *J* = 6.9, 2.9 Hz, 3H, *H*-19); δ_C (101 MHz, $CDCl_3$) 137.5 (*C*-9), 137.4 (*C*-21), 131.4 (t, *J* = 19.3 Hz, *C*-15), 130.4 (t, *J* = 19.6 Hz, *C*-3), 129.1 (Ar*C*H), 128.5 (Ar*C*H), 127.4 (Ar*C*H), 125.6 (t, *J* = 2.9 Hz, *C*-6), 121.0 (t, *J* = 8.4 Hz, *C*-18), 120.0 (t, *J* = 245.0 Hz, *C*F_2-2), 117.7 (t, *J* = 241.3 Hz, *C*F_2-14) , 61.9 (*C*-8), 61.8 (*C*-20), 60.0 (m, *C*-1 and *C*-13), 53.5 (*C*-5) , 52.9 (*C*-17), 33.9 (t, *J* = 3.6 Hz, *C*-4), 25.4 (t, *J* = 2.1 Hz, *C*-16),13.8 (t, *J* = 4.3 Hz, *C*-7), 12.5 (*C*-19); δ_F (376 MHz, $CDCl_3$) –96.96, –103.61; **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{18}F_2N$ 238.1402; found 238.1402 (+0.20 ppm).

3.7 Derivatisations

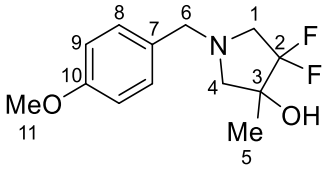
3,3-Difluoro-4-methylenepyrrolidine hydrochloride 30



To a 0 °C solution of 3,3-difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine **17** (121 mg, 500 µmol) in 1,2-DCE (1.25 mL) was added 1-chloroethyl chloroformate (59.3 µL, 550 µmol) in 1,2-DCE (0.5 mL) dropwise over 5 minutes. The mixture was stirred at 0 °C for 15 minutes, then warmed to room temperature and stirred for 30 minutes, then heated to 85 °C and stirred for 1 hour. The reaction was cooled to room temperature and concentrated. The residue was dissolved in MeOH (1 mL) and stirred at 75 °C for 1 hour. The reaction was cooled to room temperature and concentrated. The solid residue was filtered and washed with Et_2O (10 mL) to give **30** (54.7 mg, 0.352 mmol, 69%) as a colourless solid.

m.p. 152–155 °C; ν_{max} (thin film)/cm^{-1} 2971, 2885, 2802, 2730, 2673, 2600, 2541, 2466, 2327; δ_H (400 MHz, Methanol-d_4) 5.97 – 5.87 (m, 1H, *H*-4), 5.84 – 5.74 (m, 1H, *H*-4), 4.27 (t, *J* = 2.5 Hz, 2H, *H*-5), 3.89 (t, *J* = 10.9 Hz, 2H, *H*-1); δ_C (101 MHz, Methanol-d_4) 137.5 (t, *J* = 21.9 Hz, *C*-3), 122.1 (t, *J* = 246.0 Hz, *C*-2), 117.4 (t, *J* = 2.9 Hz, *C*-4), 52.0 (t, *J* = 33.6 Hz, *C*-1), 48.4 (t, *J* = 2.7 Hz, *C*-5); δ_F (376 MHz, Methanol-d_4) –100.68; **HRMS** (ESI) m/z: $[M+Na]^+$ calcd for $C_5H_7F_2N$ 142.0439; found 142.0435 (+2.50 ppm).

4,4-Difluoro-1-(4-methoxybenzyl)-3-methylpyrrolidin-3-ol 31

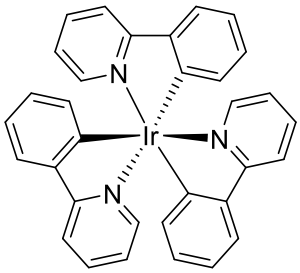


To a solution of 3,3-difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine **17** (23.9 mg, 100 µmol) and $Mn(dpm)_3$ (3.02 mg, 5.00 µmol) in isopropanol (0.5 mL) under O_2 was added $PhSiH_3$ (24.7 µL, 200 µmol). The reaction mixture was stirred at room temperature for 24 hours, then concentrated. The residue was purified by flash column chromatography (SiO_2, eluting with 10-20% ethyl acetate in pentane) to give **31** (17.3 mg, 67.0 µmol, 67% yield) as a pale yellow oil.

R_f (80:20 petroleum ether: ethyl acetate) = 0.19; ν_{max} (thin film)/cm^{-1} 3431, 2993, 2957, 2936, 2917, 2836, 2815, 1612, 1513; δ_H (400 MHz, $CDCl_3$) 7.23 – 7.16 (m, 2H, Ar*H*), 6.92 – 6.78 (m, 2H, Ar*H*), 3.80 (s, 3H, *H*-11), 3.60 (s, 2H, *H*-6), 3.18 (ddd, *J* = 15.3, 13.6, 11.5 Hz, 1H, *H*-1), 2.89 – 2.72 (m, 2H, *H*-1 and *H*-4), 2.63 – 2.53 (m, 1H, *H*-4), 1.33 (d, *J* = 3.1 Hz, 3H, *H*-5); δ_C (101 MHz, $CDCl_3$) 159.1 (*C*-10), 130.0 (Ar*C*H), 129.5 (*C*-7), 126.4 (dd, *J* = 258.8, 255.5 Hz, *C*-2), 114.0 (Ar*C*H), 77.0 (dd, *J* = 47.9, 27.8 Hz, *C*-3), 64.3 (dd, *J* = 1.5, 1.5 Hz, *C*-4), 59.7 (dd, *J* = 28.5, 28.5 Hz, *C*-1), 59.1 (*C*-6), 55.4 (*C*-11), 18.1 (app d, *J* = 5.9 Hz, *C*-5); δ_F (376 MHz, $CDCl_3$) –105.33 (d, *J* = 231.2 Hz), –117.28 (d, *J* = 231.2 Hz); **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{17}F_2NO_2$ 258.1300; found 258.1297 (+1.10 ppm).

3.8 Synthesis of photocatalysts

***fac*-Ir(ppy)$_3$ 65**

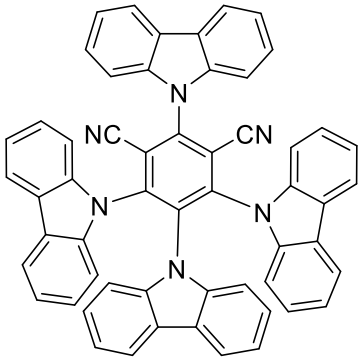


$IrCl_3.3H_2O$ (210 mg, 597 µmol) and 2-phenylpyridine (256 µL, 1.79 mmol) were suspended in 2-ethoxyethanol (12 mL) and water (4.2 mL). The mixture was heated at 150 °C for 7 hours. The precipitate was filtered and washed with ethanol (15 mL) and acetone (15 mL). The solid residue was dissolved in dichloromethane (30 mL), filtered and concentrated to give $[\mu$-Cl Ir$(ppy)_2]_2$ as a yellow solid. To this solid was added potassium carbonate (309 mg, 2.34 mmol), 2-phenylpyridine (107 µL, 746 µmol) and glycerol (7.5 mL). The mixture was heated at 220 °C under Ar for 18 hours. The reaction was cooled to room temperature. Water (15 mL) was added and the precipitate was filtered and washed with methanol (15 mL), diethyl ether (15 mL) and hexane (15 mL). The solid residue was dissolved in dichloromethane (40 mL), filtered and concentrated to give a residue which was purified by flash column chromatography (SiO_2, eluting with dichloromethane) to give **65** (266 mg, 406 µmol, 68% yield) as a yellow solid.

ν_{max} (thin film)/cm^{-1} 3037, 2991, 2981, 2925, 2847, 1697, 1600, 1580, 1561; δ_H (400 MHz, DMSO-d_6) 8.13 (d, *J* = 8.2 Hz, 3H), 7.79 (t, *J* = 7.7 Hz, 3H), 7.75 (d, *J* = 7.7 Hz, 3H), 7.48 (d, *J* = 5.3 Hz, 3H), 7.13 (t, *J* = 6.4 Hz, 3H), 6.83 – 6.76 (m, 3H), 6.83 - 6.76 (m, 6H); δ_C (101 MHz, DMSO-d_6) 165.6, 160.8, 146.8, 143.8, 136.9, 136.3, 129.1, 124.2, 122.8, 119.6, 119.1.

Data are consistent with the literature.[7]

4CzIPN 66



NaH (600 mg, 15.0 mmol of a 60% dispersion in mineral oil) was added portionwise to a stirred solution of carbazole (1.67 g, 10.0 mmol) in THF (40 mL) over 15 minutes under Ar. The mixture was stirred at room temperature for 30 minutes after which tetrafluoroisophthalonitrile (0.403 g, 2.00 mmol) was added and the mixture was stirred at room temperature for 20 hours. Water (2 mL) was added to the reaction mixture which was then concentrated under reduced pressure. The solid was filtered, washing with water (15 mL) and ethanol (15 mL). The resulting residue was purified by flash column chromatography (SiO_2, eluting with dichloromethane: petroleum ether 50:50). The resultant solid was triturated with ethanol to give **64** (1.25 g, 1.59 mmol, 79% yield) as a yellow solid.

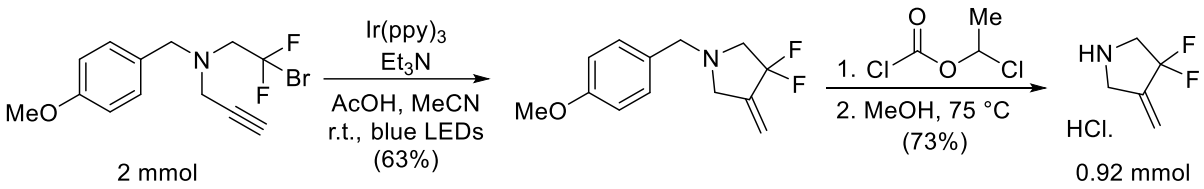
R_f (50:50 DCM: petroleum ether) = 0.37; **ν_{max}** (thin film)/cm^{-1} 3081, 3050, 3028, 2972, 2924; **δ_H** (500 MHz, $CDCl_3$) 8.22 (dt, *J* = 7.7, 1.2 Hz, 2H), 7.76 – 7.65 (m, 8H), 7.49 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 2H), 7.33 (dt, *J* = 7.7, 1.2 Hz, 2H), 7.24 – 7.19 (m, 4H), 7.13 – 7.03 (m, 8H), 6.87 – 6.78 (m, 4H), 6.63 (ddd, *J* = 8.2, 7.5, 1.2 Hz, 2H); **δ_H** (400 MHz, DMSO) 8.37 (d, *J* = 7.7 Hz, 2H), 8.20 (d, *J* = 8.2 Hz, 2H), 7.87 (dd, *J* = 7.3, 1.5 Hz, 4H), 7.80 – 7.70 (m, 6H), 7.61 – 7.43 (m, 6H), 7.20 – 7.06 (m, 8H), 6.82 (t, *J* = 7.5 Hz, 2H), 6.71 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 2H); **δ_C**

(126 MHz, $CDCl_3$) 145.4, 144.8, 140.1, 138.3, 137.1, 134.9, 127.1, 125.9, 125.1, 124.9, 124.7, 124.0, 122.5, 122.1, 121.5, 121.1, 120.6, 119.8, 116.5, 111.8, 110.1, 109.6, 109.6.

Data are consistent with the literature.[8,9]

3.9 Multi-mmol batch synthesis and PMB group deprotection

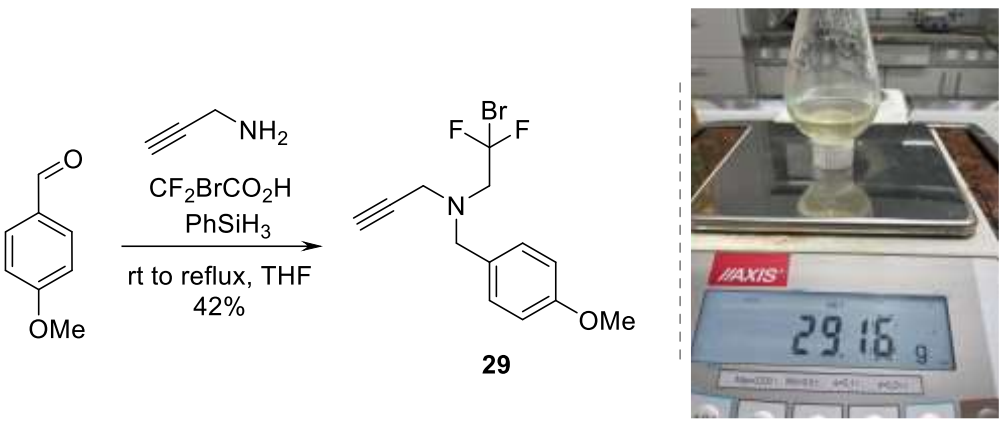
Supplementary Figure 5. 2 mmol reaction scale followed by PMB deprotection



Supplementary Figure 6. Photoredox Set-up for 2 mmol reaction

A 250 mL borosilicate glass measuring cylinder was wrapped in blue LEDs and foil, then sealed. The reactions using this set-up were conducted under a continuous flow of nitrogen.

Supplementary Figure 7. Photoredox Set-up for flow chemistry



***N*-(2-Bromo-2,2-difluoroethyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine 29**

To a 1 L conical flask equipped with a magnetic stir bar, Claisen adapter, additional funnel and air-condenser were added dry THF (250 mL), 4-methoxybenzaldehyde (30.00 g, 0.22 mol, 1.00 equiv) and propargylamine (12.14 g, 0.22 mol, 1.00 equiv) under argon at room temperature. The mixture was stirred for 10 min, and $PhSiH_3$ (12.00 g, 0.11 mol, 0.50 equiv) was added dropwise (ca. 10 min). The mixture was stirred for 10 min at room temperature, and then heated under reflux for 30 min. The heating was turned off, and a second portion of $PhSiH_3$ (71.00 g, 0.657 mol, 3.00 equiv) was added in one portion. Then and 2-bromo-2,2-difluoroacetic acid (77.09 g, 0.44 mol, 2.00 equiv) in THF (250 mL) was slowly added dropwise (vigorous gas

evolution!) to control gas evolution and exotherm (addition time: minimum 30 min or more). The resulting solution was heated under reflux overnight, cooled to a room temperature and concentrated under a reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc/hexane, 1:10, R_f = 0.4). Yield: 29.16 g, 0.0917 mol, 42%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): **δ** 7.32 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 2H), 3.42 (s, 2H), 3.37 (t, *J* = 12.6 Hz, 2H), 2.29 – 2.26 (m, 1H) ppm. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 159.3, 130.4, 129.8, 123.4 (t, *J* = 307.8 Hz), 114.0, 78.4, 73.5, 62.6 (t, *J* = 23.4 Hz), 58.3, 55.4, 42.4 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): **δ** -51.2 (s) ppm. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{15}BrF_2NO$, 318.0305; found 318.0291.

The compound slowly decomposes at room temperature under storage (ca. 10% impurity after 3 days) and must be used directly in the next step.

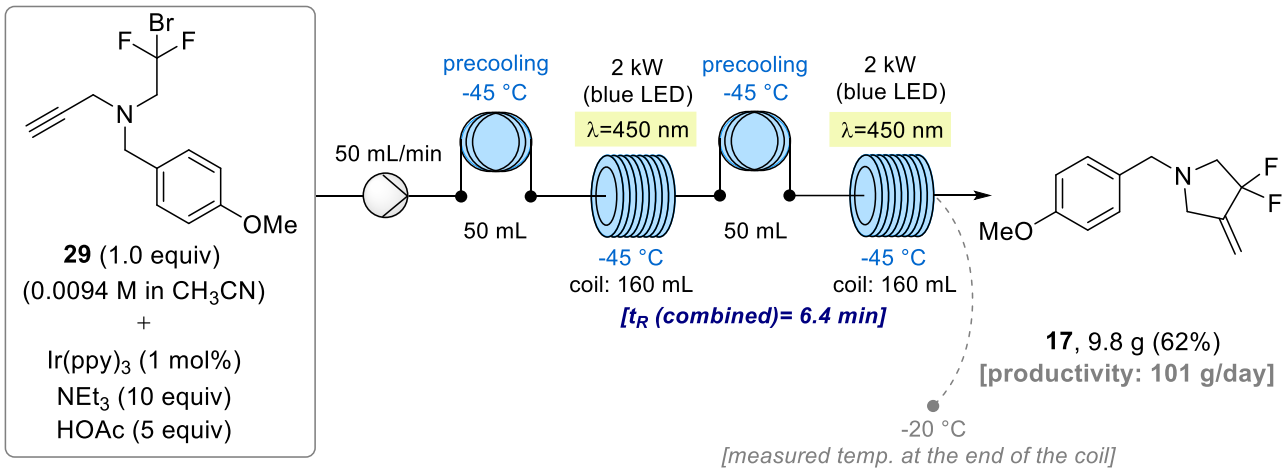


Photo of the set-up (photochemistry in flow).

Irradiated coil.

3,3-Difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine 17

A solution of compound **29** (21.00 g, 0.066 mol, 1.00 equiv), tris(2-phenylpyridine) iridium (0.434 g, 0.00066 mol, 0.01 equiv), Et_3N (66.79 g, 0.66 mol, 10.00 equiv), CH_3CO_2H (19.82 g, 0.33 mol, 5.00 equiv) in acetonitrile (7 L) was pumped (flow rate: 50 mL/min) through a coil (50 mL) that was cooled to -45 ˚C using a Huber "Unistat 510" chiller. The cooled solution was passed through a cooled coil (160 mL; -45 ˚C with Huber "Unistat 510" chiller) that was irradiated with 450 nm using blue LEDs (2kW).

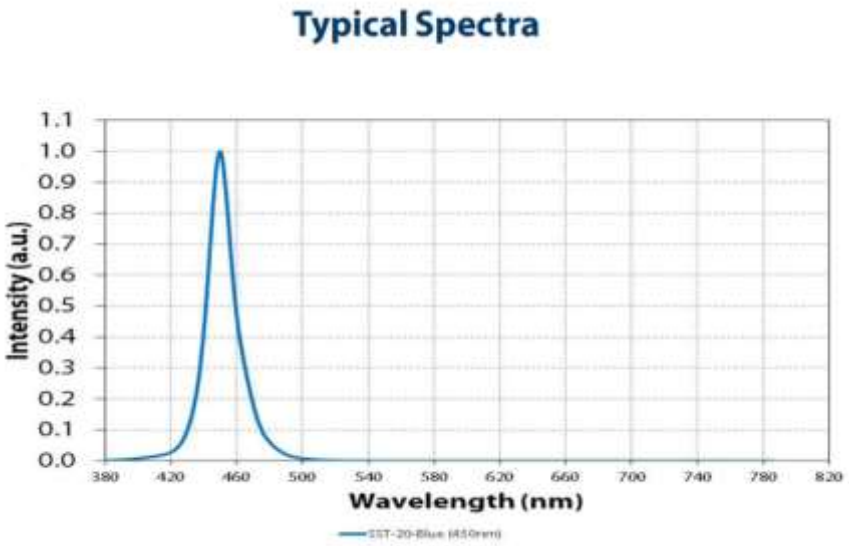
That solution was passed through another coil (50 mL) that was cooled to -45 ºC using a Huber "Unistat 510" chiller. The cooled solution was passed through a second cooled coil (160 mL; -45 ˚C with Huber "Unistat 510" chiller) that was irradiated again with 450 nm using blue LEDs (2kW). At the end of the second coil the measured temperature was ca. -20 ˚C. The solution was combined in two 5 L cans (10 L total volume) and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (300 mL), washed with a sat.

solution of Na_2CO_3 (1 × 100 mL) and passed through plug of SiO_2 (100 g). The silica gel was additionally washed with 300 mL of EtOAc/hexane (1:3). The combined solution was concentrated under reduced pressure. Yield: 9.80 g, 0.041 mol, 62%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.58 (s, 1H), 5.28 (s, 1H), 3.81 (s, 3H), 3.61 (s, 2H), 3.33 (s, 2H), 2.98 (t, *J* = 11.3 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.2, 143.1 (t, *J* = 20.9 Hz), 130.1, 129.5, 122.8 (t, *J* = 246.4 Hz), 114.0, 112.1, 61.0 (t, *J* = 27.1 Hz), 59.4, 56.6 (t, *J* = 2.9 Hz), 55.4 ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ -98.2 (s) ppm. LCMS $(M+H)^+$: 240. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{16}F_2NO$, 240.1200; found 240.1185.

For irradiation with blue LED light, we used commercially available diodes SST-20-B-B120-S450 (Luminus Devices Inc.)

https://www.digikey.com/en/products/detail/luminus-devices-inc/SST-20-B-B120-S450/15903652

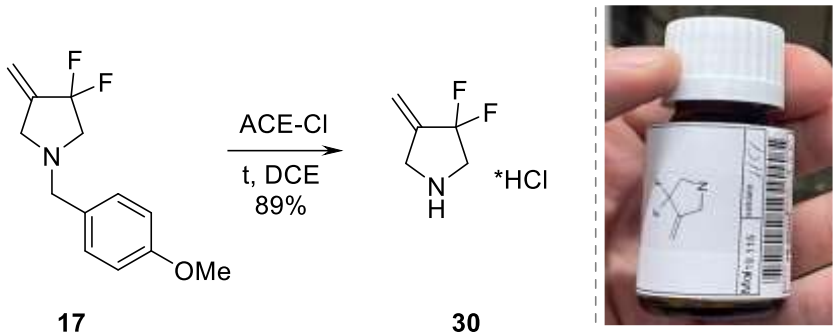
https://download.luminus.com/datasheets/Luminus_SST-20-B_Datasheet.pdf



For the coil, we used commercially available tubes 200-0375-062-OC

https://www.altaflo.com/products/fep-altafluor-200/

https://www.altaflo.com/wp-content/uploads/2017/03/altaflo-orderinginfo-v1.pdf



17 **30**

EN300-39913178

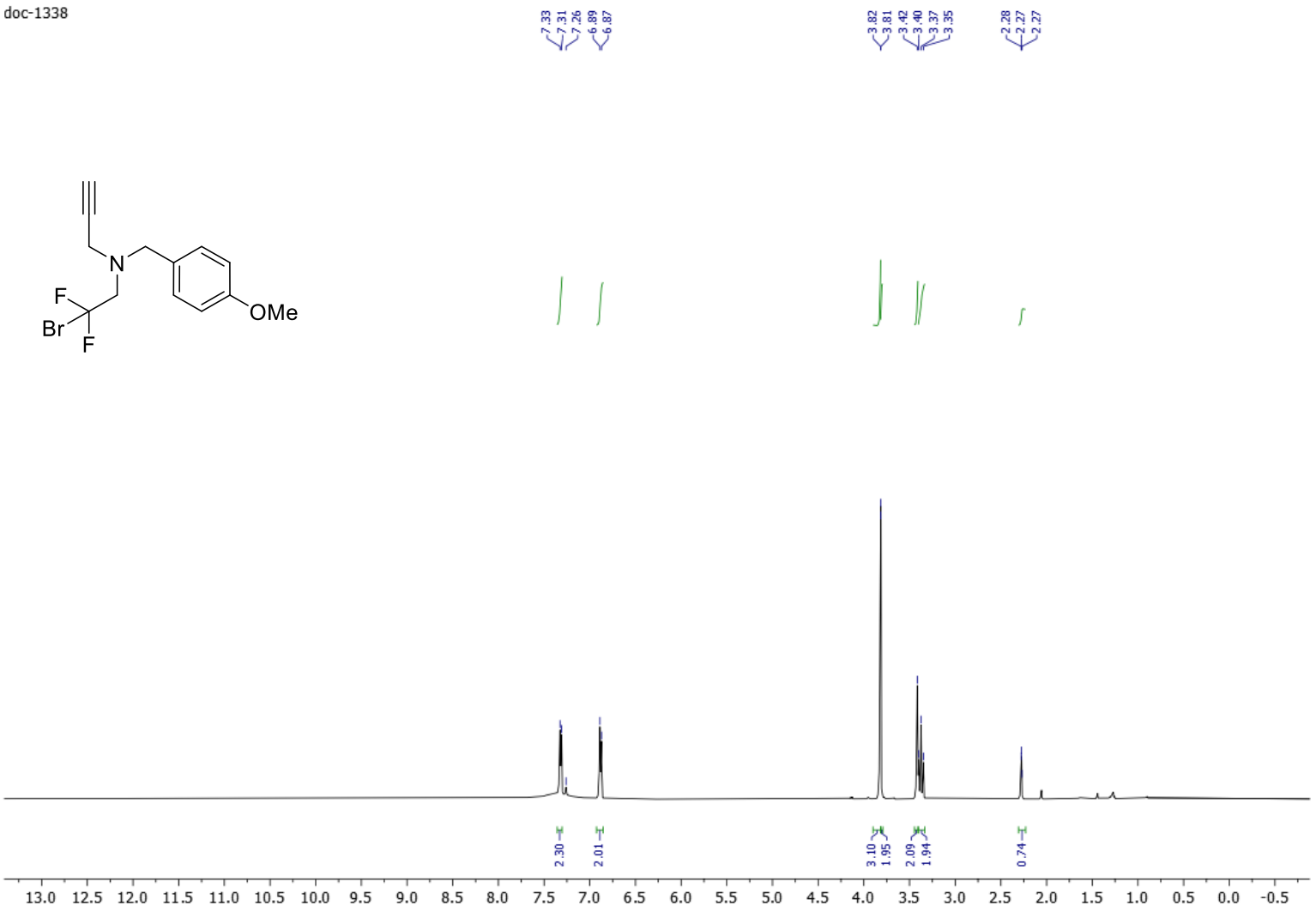
3,3-Difluoro-4-methylenepyrrolidine hydrochloride 30

To a solution of **17** (6.00 g, 0.0251 mol, 1.00 equiv) in DCE (50 mL) was added a solution of 1-chloroethyl chloroformate (3.94 g, 0.0276 mol, 1.10 equiv) in 50 mL of DCE dropwise at 0 °C (ca. 15 min). The resulting mixture was stirred for 10 min and heated under reflux for 1 h. The solution was cooled to a room temperature and concentrated under a reduced pressure. The residue was dissolved in MeOH (150 mL), heated under reflux for 1 h and then concentrated under a reduced pressure. The residue was mashed in dry Et_2O (50 mL), the formed solid was filtered off, washed with dry Et_2O (50 mL) and dried under air to give the desired product. Yield: 3.48 g, 0.0223 mol, 89%, beige solid, mp = 159-160 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.48 (s, 2H), 5.76 (dd, *J* = 30.5, 2.2 Hz, 2H), 4.09 (d, *J* = 2.0 Hz, 2H), 3.79 (t, *J* = 11.7 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 136.8 (t, *J* = 21.6 Hz), 121.6 (t, *J* = 245.7 Hz), 116.1, 49.8 (t, *J* = 32.6 Hz), 46.3 ppm. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ -97.7 (s) ppm. LCMS $(M+H)^+$: 120. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_5H_8F_2N$, 120.0625; found 120.0617.

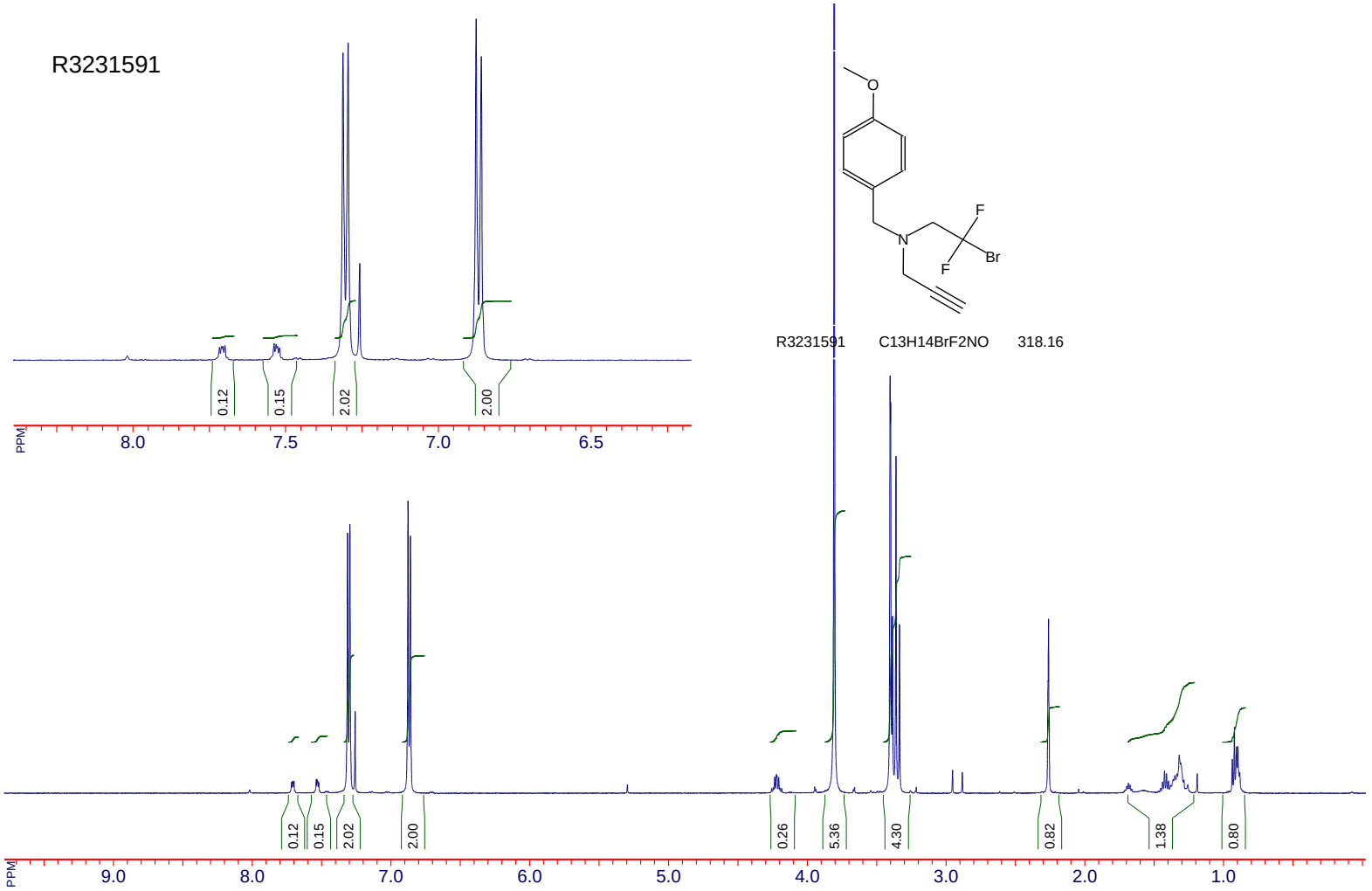
The compound (EN300-39913178) is commercially available at Enamine from stock:
https://enaminestore.com/catalog/EN300-39913178

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine 29**

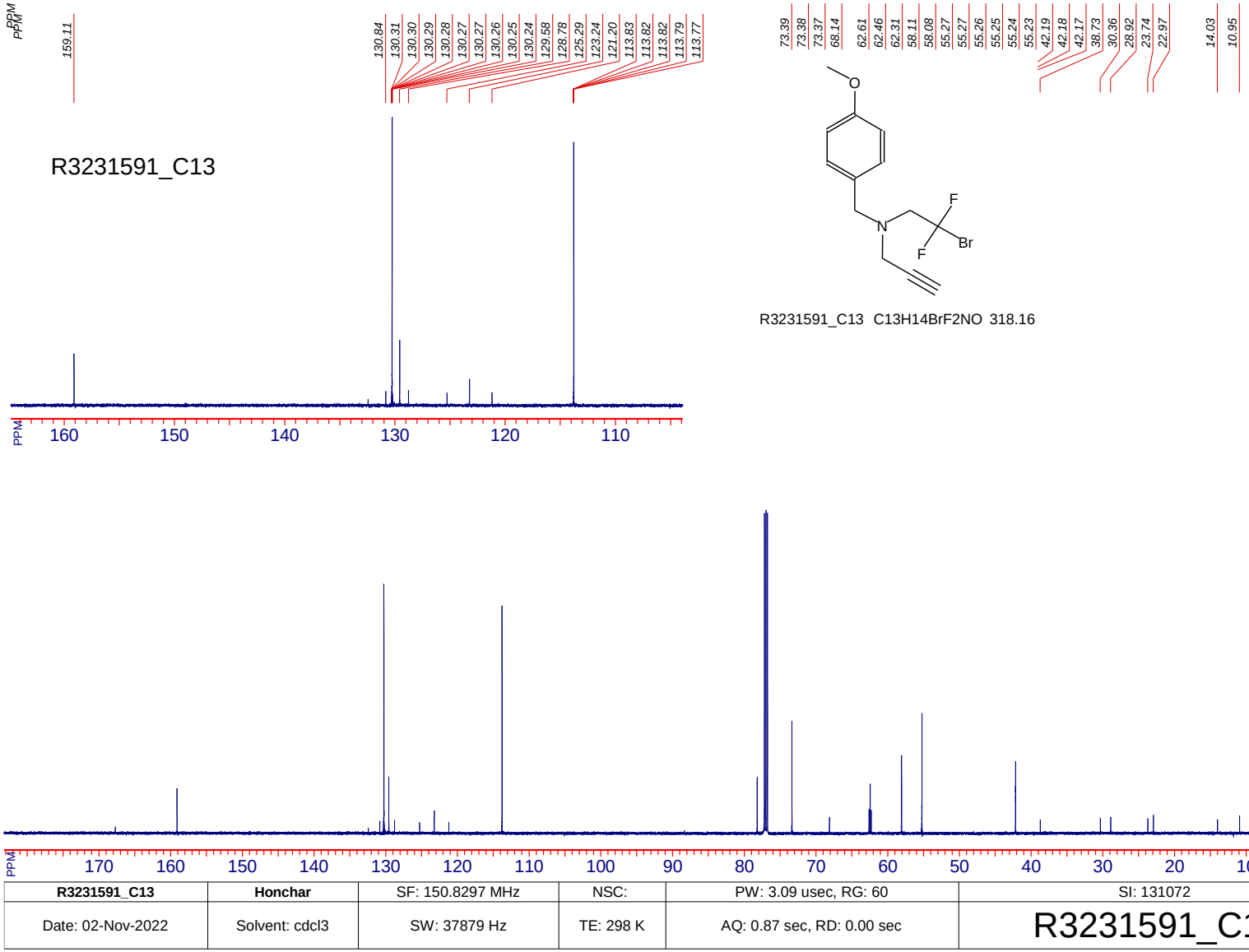
^{1}H NMR (500 MHz, $CDCl_3$)



***N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine (29)** after 3 days at a room temperature.



File name: R3231591	Operator: Victorova	SF: 499.8180 MHz	NSC: 0	PW: 13.60 usec, RG: 18	SI: 65536
Date: 02-Nov-2022	Solvent: cdcl3	SW: 9328 Hz	TE: 298 K	AQ: 1.72 sec, RD: 0.00 sec	

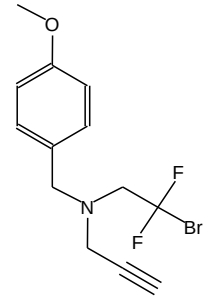


R3231591_C13	Honchar	SF: 150.8297 MHz	NSC:	PW: 3.09 usec, RG: 60	SI: 131072
Date: 02-Nov-2022	Solvent: cdcl3	SW: 37879 Hz	TE: 298 K	AQ: 0.87 sec, RD: 0.00 sec	R3231591_C13

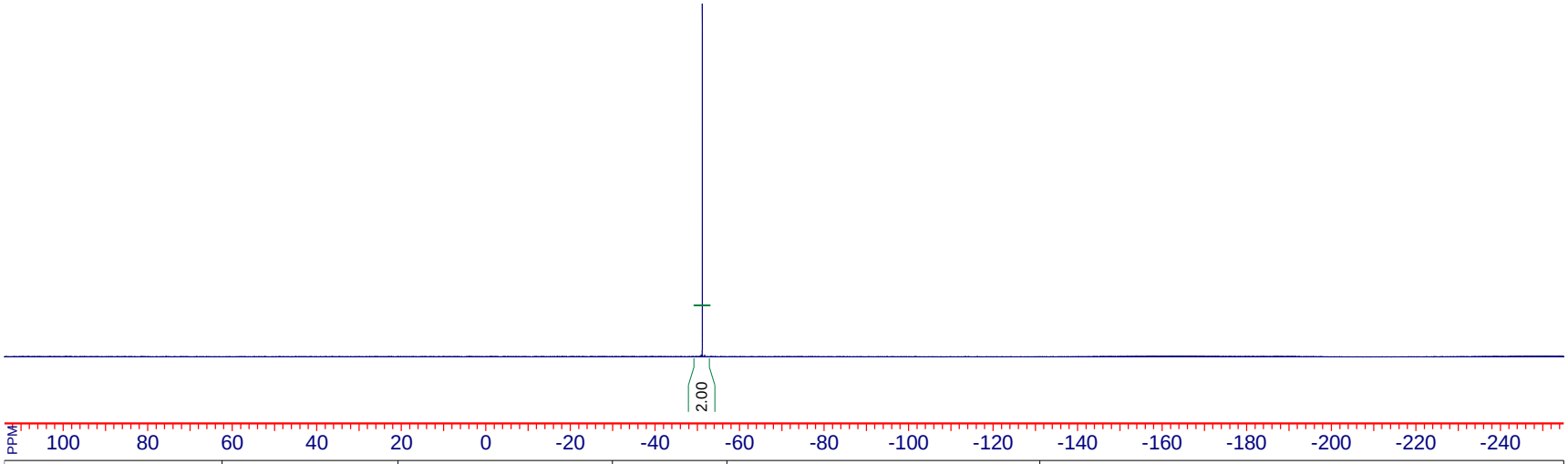
PPM

-51.20

R3231591_F19{H}



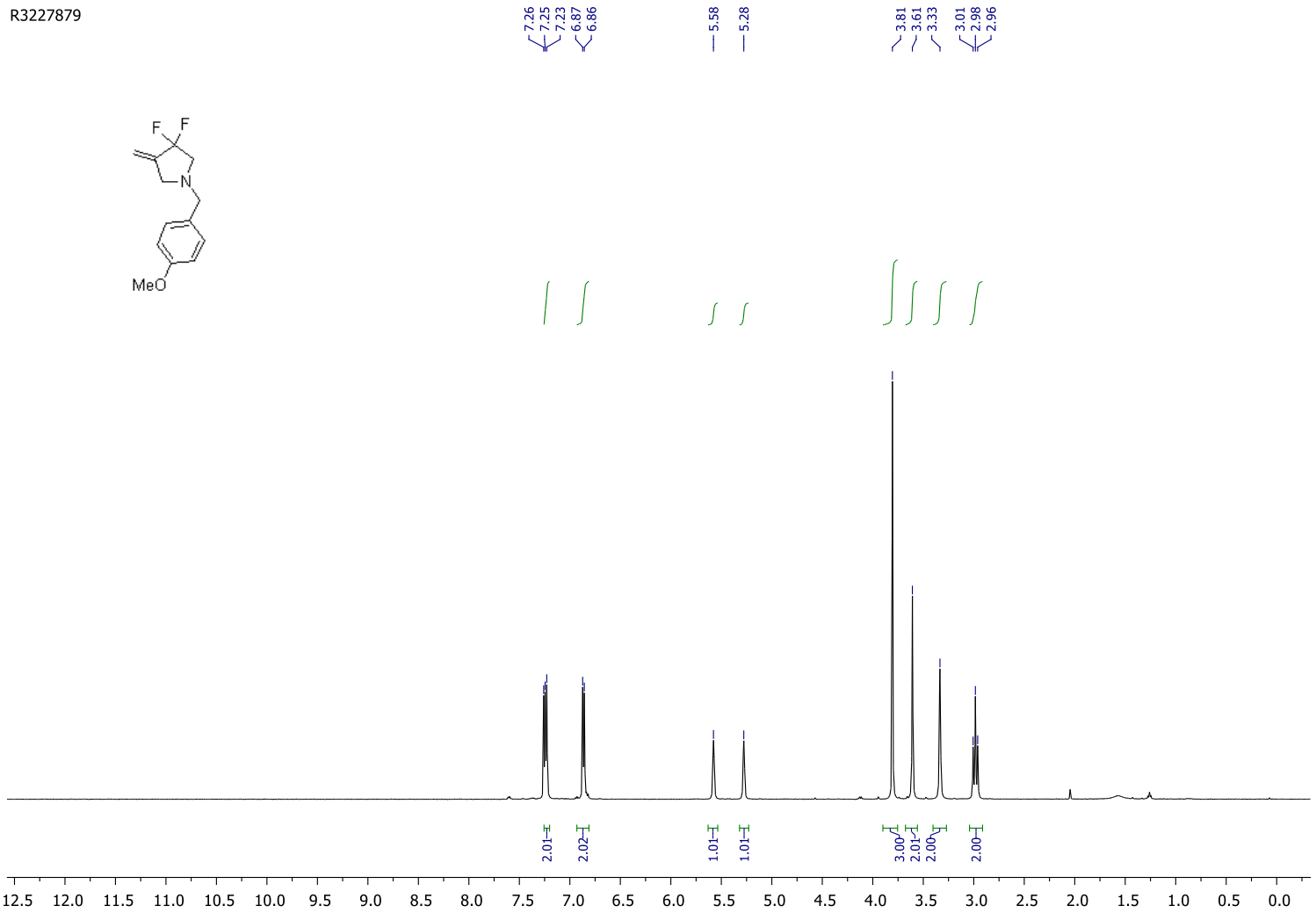
R3231591_F19{H}C13H14BrF2NO318.16



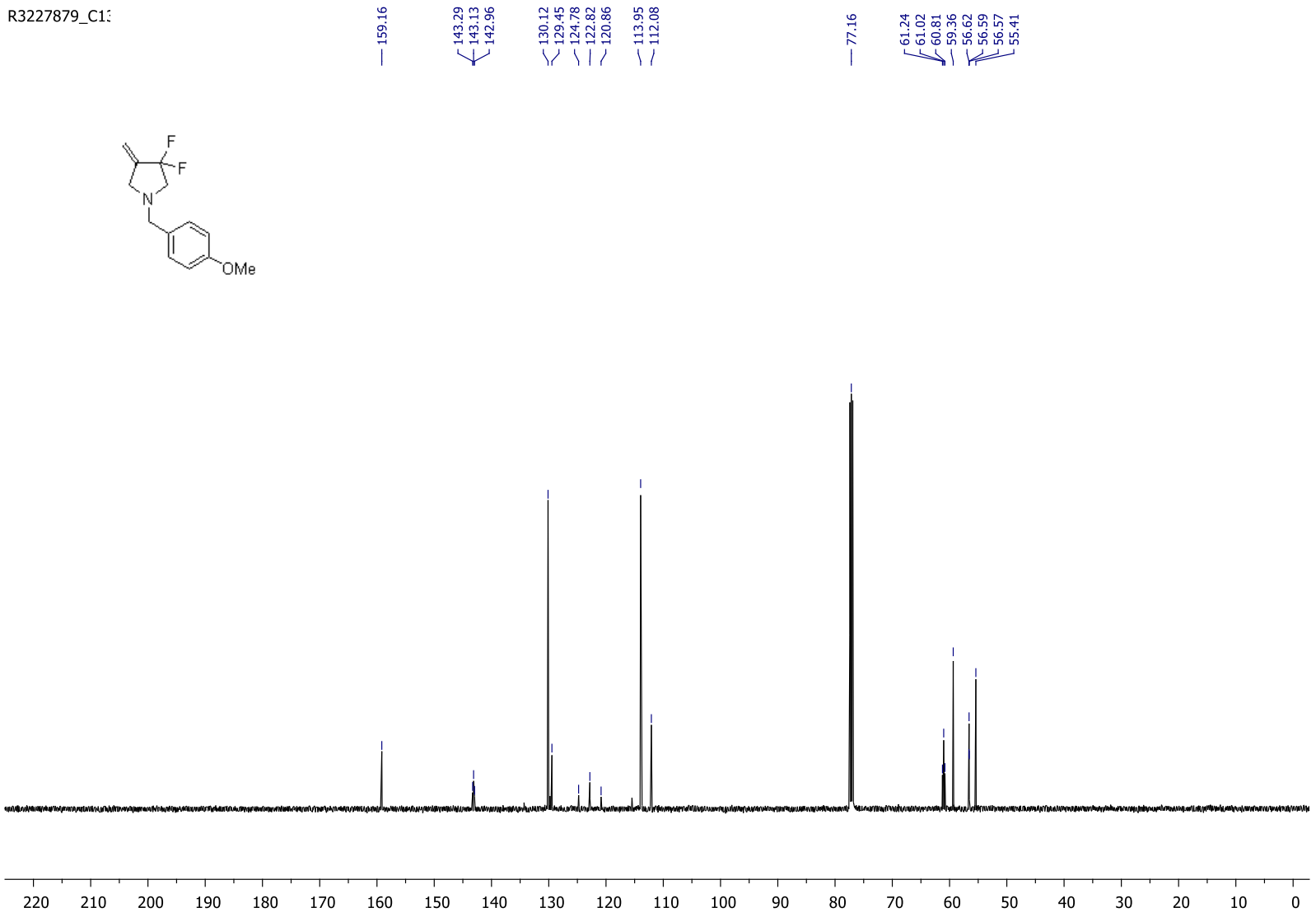
R3231591_F19{H}	Honchar	SF: 376.4986 MHz	NSC:	PW: 0.00 usec, RG: 912	SI: 262144
Date: 02-Nov-2022	Solvent: CDCl3	SW: 138889 Hz	TE: 300 K	AQ: 0.94 sec, RD: 0.00 sec	R3231591_F19{H}

3,3-Difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine (17)

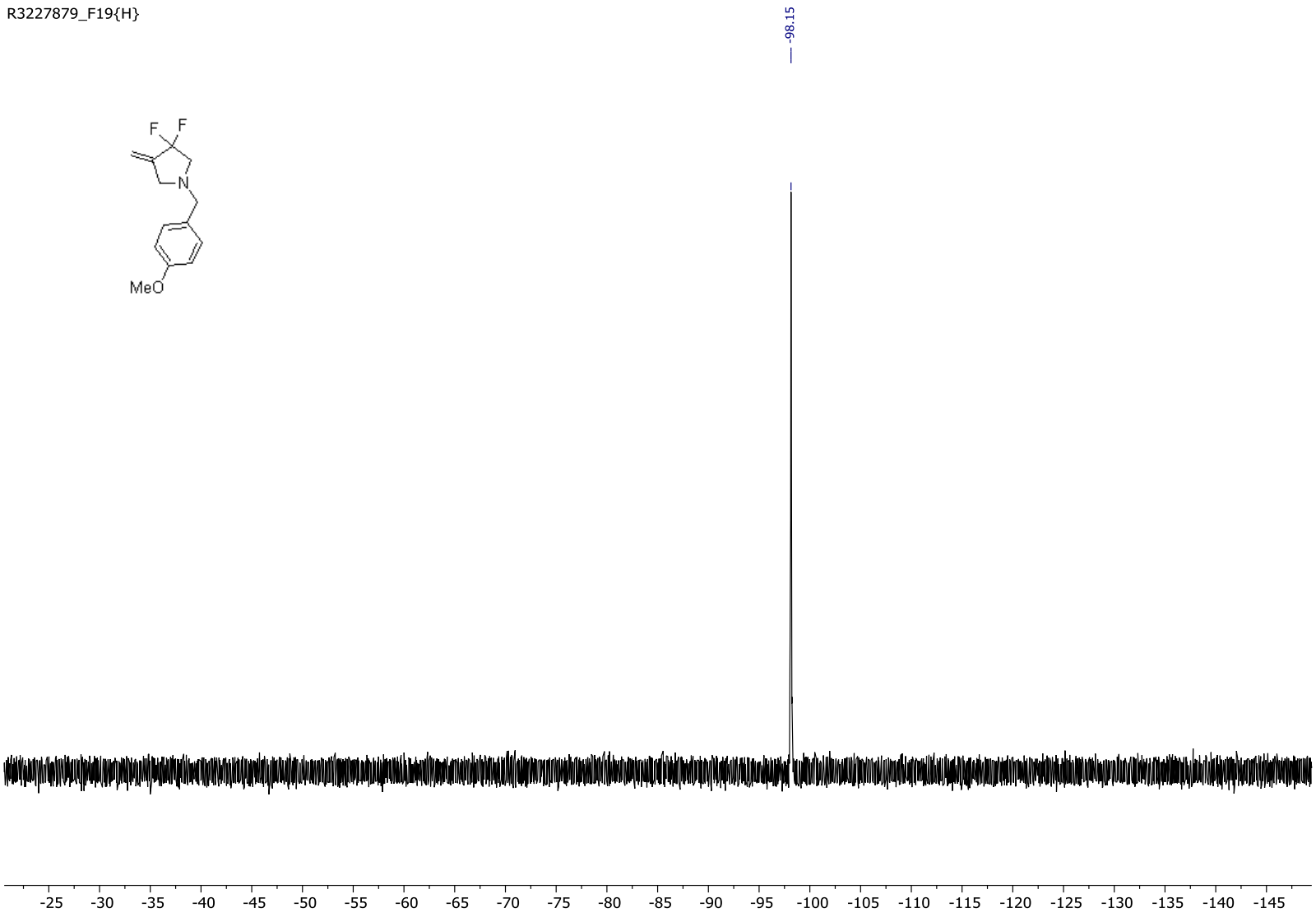
^{1}H NMR (500 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$)

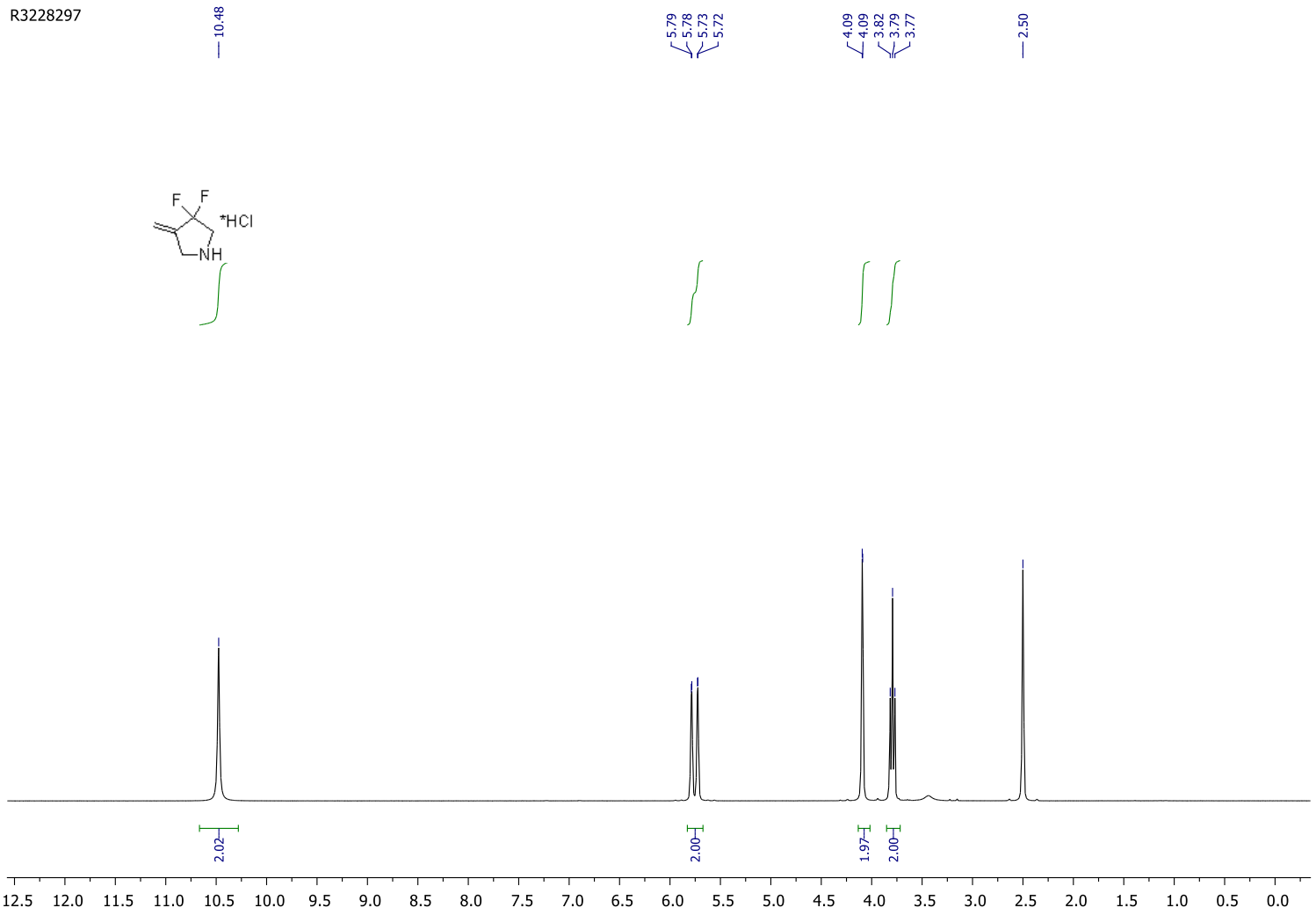


$^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$)

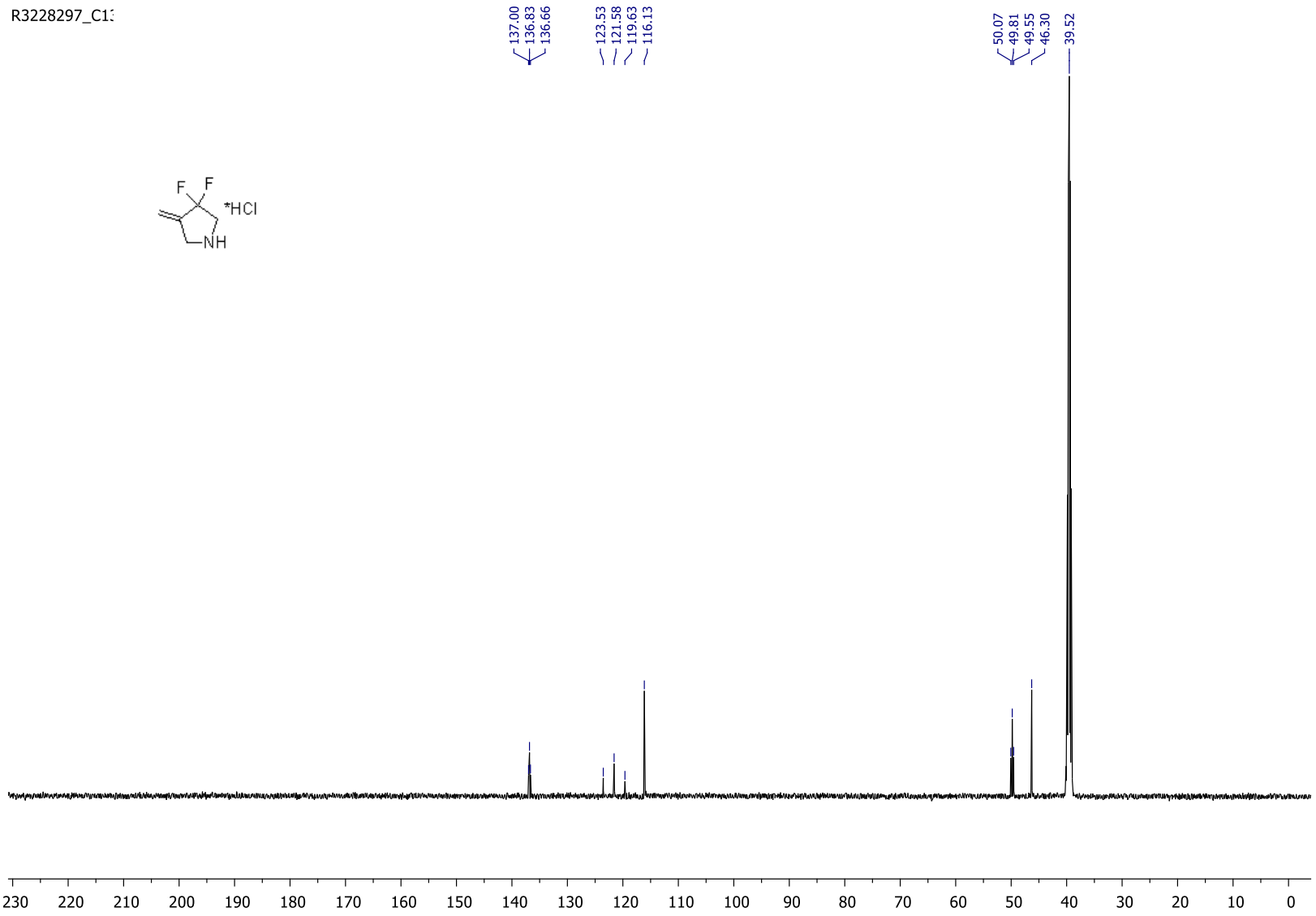


3,3-Difluoro-4-methylenepyrrolidine hydrochloride (30)

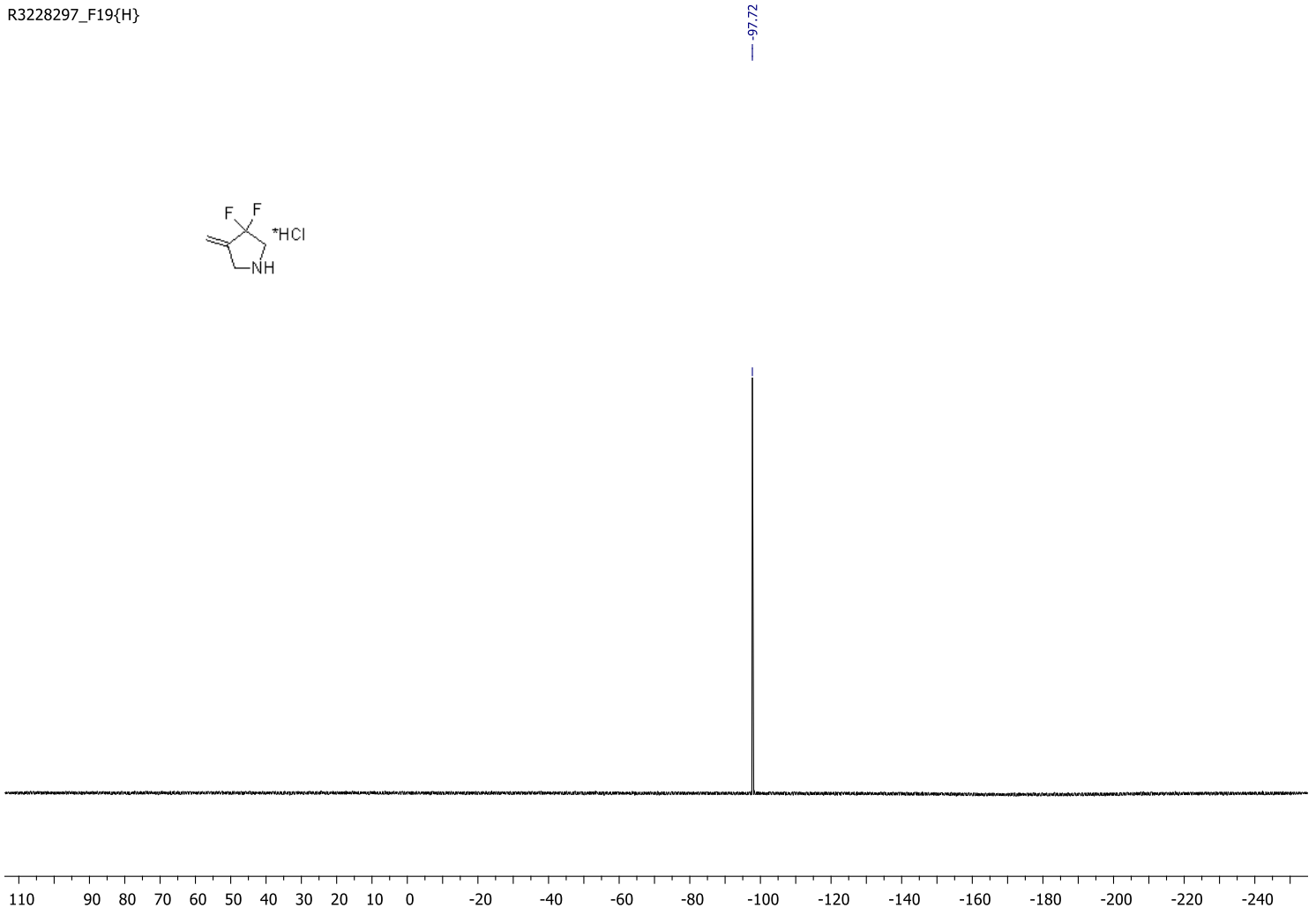
^{1}H NMR (500 MHz, DMSO-d_6)



$^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6)

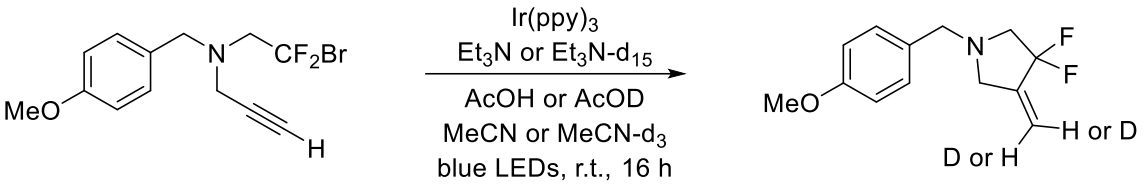


$^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6)



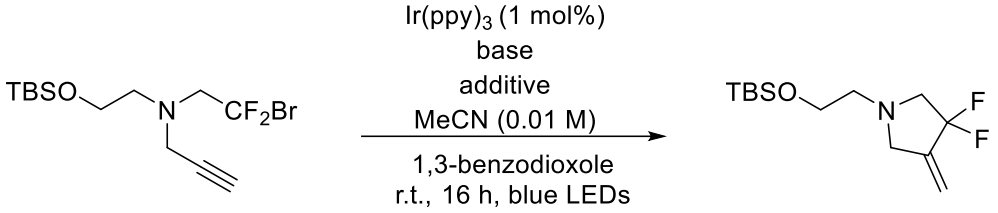
4 Mechanistic studies

Supplementary Table 4. Deuterium-labelling studies



entry	source of deuterium	*Z* signal integration	*E* signal integration	total alkene integration	^{2}H NMR signal	^{2}H incorporation
1	none	0.998	0.999	1.997	no	0%
2	AcOH-d_1	0.743	0.809	1.552	yes	45%
3	AcOH-d_4	0.765	0.786	1.551	yes	45%
4	Et_3N-d_{15}	0.868	0.776	1.644	yes	36%
5	MeCN-d_3	0.924	0.902	1.826	yes	17%
6	AcOH-d_1 and MeCN-d_3	0.884	0.865	1.749	yes	25%
7	Et_3N-d_{15} and AcOH-d^1	0.731	0.674	1.405	yes	59%
8	Et_3N-d_{15} and MeCN-d_3	0.757	0.513	1.270	yes	73%
9	Et_3N-d_{15}, AcOH-d_1 and MeCN-d_3	0.683	0.459	1.142	yes	86%
10	Et_3N-d_{15}, AcOH-d_4 and MeCN-d_3	0.668	0.481	1.149	yes	85%

Supplementary Table 5. Control experiments 1

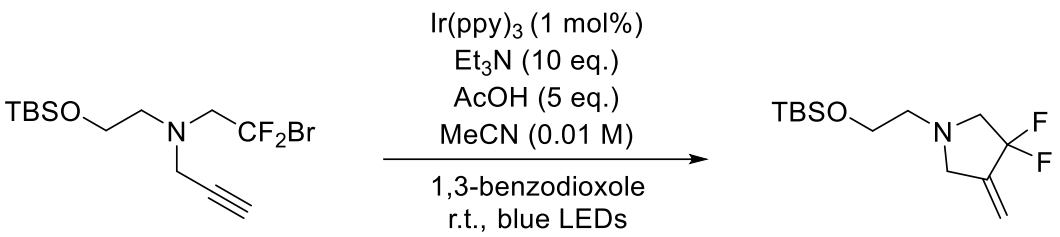


entry	base	base equiv.	H-source	H-source equiv.	product yield /%	starting material yield /%
1[a]	Et_3N	10	AcOH	5	88	4
2	Et_3N	10	none	-	56	0
3	none	-	AcOH	5	0	100
4[b]	Et_3N	10	AcOH	5	0	100
5[c]	Et_3N	10	AcOH	5	46	0
6[d]	Et_3N	10	AcOH	5	51	0
7[e]	Et_3N	10	AcOH	5	62	0
8[f]	Et_3N	10	AcOH	5	0	100
9[g]	Et_3N	10	AcOH	5	73	0

[a]optimised conditions (non-dry glassware, solvents degassed via sparging, under Ar); [b]no blue light irradiation; [c]dry glassware, solvents degassed via freeze-pump-thaw, under Ar; [d]dry glassware, solvents degassed via sparging, under Ar; [e]non-dry glassware, solvents not

degassed, under Ar; [f]non-dry glassware, solvents not degassed, open to air; [g]non-dry glassware, solvents degassed via freeze-pump-thaw, under Ar.

Supplementary Table 6. Control experiments 2

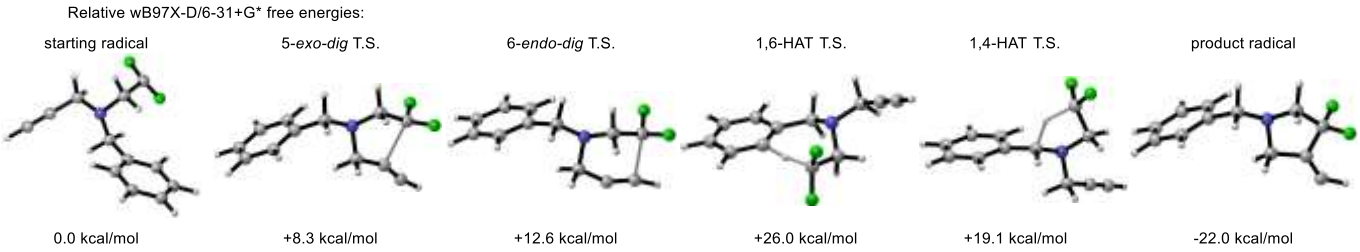


entry	blue LEDs	duration /h	product yield /%
1	on	1	27
2	off	1	25
3	on	1	54
4	off	60	53

5 Computational Investigations

Quantum chemical calculations were carried out using the Macintosh version of Spartan 2018.[10] Equilibrium geometries and transition structures were confirmed by either the absence or presence of an imaginary frequency respectively. Starting points for equilibrium geometry calculations were obtained by performing a molecular mechanics equilibrium conformer search also implemented in Spartan 2018. The theoretical model chosen was wB97X-D/6-31G* and Figure 7 summarises the relative free energies obtained with this method at 298K *in vacuo*. Other theoretical models were explored for comparison and the M06-2X/6-31+G* model gave a barrier of 8.2 kcal/mol for the 5-exo-dig cyclisation – essentially the same as the less expensive wB97X-D/6-31G* method.

Figure 7. Relative free energies.



Coordinates and energies:

Starting radical

H	0.808258	1.548149	-0.690576
C	-0.131277	1.935568	-0.287811
H	0.095883	2.849535	0.269772
C	-1.003091	2.319344	-1.456404
F	-1.228777	1.359460	-2.364093
F	-2.165742	2.910198	-1.142285
N	-0.669767	0.949657	0.640804
C	-1.841000	1.407612	1.382663
H	-1.688010	2.460556	1.644322
H	-2.767073	1.368493	0.784267
C	-0.838775	-0.393756	0.088747
H	-1.585547	-0.421849	-0.721296
H	-1.227582	-1.016342	0.902178
C	0.472357	-0.966829	-0.393234
C	2.918007	-2.024771	-1.248087

C	0.652699	-1.346084	-1.721939
C	1.533253	-1.112592	0.504750
C	2.748078	-1.638183	0.081097
C	1.868797	-1.877481	-2.148605
H	-0.161463	-1.216693	-2.429749
H	1.395486	-0.800032	1.536377
H	3.564941	-1.749923	0.788327
H	1.995438	-2.169847	-3.186870
H	3.867074	-2.436118	-1.578976
C	-2.036407	0.634863	2.614383
H	-2.363184	-0.566517	4.513832
C	-2.212575	-0.006418	3.618405

No imaginary frequencies

Label	Energy (kcal/mol)	ZPE (kJ/mol)	Gº (au)
M0001	-450903.78	533.74	-718.402764

5-*exo-dig* T.S.

H	-2.316406	0.844171	1.895091
C	-2.189675	1.121287	0.831751
H	-3.049337	0.732869	0.268911
C	-2.131179	2.615618	0.753680
F	-2.733208	3.264721	1.754295
F	-2.502092	3.150408	-0.410147
N	-0.964209	0.589813	0.256439
C	0.196407	1.204959	0.894710
H	0.298598	0.876210	1.948753
H	1.097296	0.881960	0.364073
C	-0.924845	-0.862592	0.352571
H	-1.857434	-1.242310	-0.084553
H	-0.912866	-1.195682	1.409835
C	0.253399	-1.465897	-0.377197
C	2.409248	-2.608180	-1.748991

C	0.503523	-1.126964	-1.709791
C	1.097930	-2.373018	0.260195
C	2.169417	-2.946237	-0.421408
C	1.574486	-1.694143	-2.390725
H	-0.142001	-0.403231	-2.199704
H	0.917955	-2.633458	1.300689
H	2.819156	-3.651514	0.088565
H	1.759942	-1.423297	-3.426082
H	3.245170	-3.051083	-2.282287
C	0.125289	2.683003	0.868665
H	0.699895	4.884593	0.910711
C	0.555542	3.827995	0.891951

One imaginary frequency i373

Label	Energy (kcal/mol)	ZPE (kJ/mol)	Gº (au)
M0001	-450895.15	528.07	-718.389598

6-*endo-dig* T.S.

H	-1.258961	-2.593385	-1.210984
C	-1.701935	-1.619255	-0.939145
H	-2.020830	-1.135392	-1.873034
C	-2.945295	-1.893752	-0.126725
F	-3.711512	-2.846207	-0.685587
F	-3.691966	-0.811161	0.110998
N	-0.767315	-0.732494	-0.263715
C	-0.007138	-1.403619	0.800891
H	0.738856	-2.108256	0.382931
H	0.550328	-0.641906	1.355442
C	0.138008	-0.082775	-1.206908
H	-0.477554	0.357653	-2.000708
H	0.814624	-0.811444	-1.694795
C	0.959517	1.008852	-0.558574
C	2.457698	3.059881	0.615627

C	0.329891	1.999895	0.199459
C	2.343468	1.052698	-0.715197
C	3.091256	2.075071	-0.134489
C	1.074060	3.018040	0.783610
H	-0.746497	1.950455	0.339103
H	2.842978	0.279216	-1.294060
H	4.169419	2.096421	-0.264293
H	0.574794	3.782436	1.371898
H	3.038505	3.855566	1.072702
C	-0.918719	-2.135686	1.682983
H	-2.846542	-3.109330	2.364717
C	-2.029139	-2.611524	1.887852

One imaginary frequency i407

Label	Energy (kcal/mol)	ZPE (kJ/mol)	Gº (au)
M0001	-450891.36	529.66	-718.382627

1,6-HAT T.S.

H	2.124030	0.043696	-0.649844
C	1.590876	0.914269	-0.236920
N	0.234245	1.031429	-0.756384
C	0.104350	2.043767	-1.802775
H	0.684285	1.787797	-2.710165
H	-0.948386	2.081738	-2.103889
C	-0.730271	-1.203472	-0.083406
C	-1.495059	-3.071742	1.883694
C	-1.592955	-2.263933	-0.391765
C	-0.277549	-1.126131	1.223406
C	-0.632888	-2.026899	2.211369
C	-1.970330	-3.186036	0.578153
H	-1.977761	-2.362657	-1.405293
H	-0.246391	-1.923222	3.221480
H	-2.643326	-3.996580	0.314807

H	-1.793822	-3.791603	2.640132
C	0.504748	3.377998	-1.349859
H	1.143605	5.446531	-0.665504
C	0.850567	4.474766	-0.994188
H	2.169229	1.811836	-0.478647
F	1.186193	1.911737	1.881414
F	2.742269	0.374435	1.764691
C	-0.339893	-0.237157	-1.189001
H	0.338157	-0.759474	-1.893394
H	-1.249006	-0.009571	-1.756198
H	0.675173	-0.114316	1.480097
C	1.549911	0.772795	1.267988

One imaginary frequency i1498

Label	Energy (kcal/mol)	ZPE (kJ/mol)	Gº (au)
M0001	-450875.12	517.98	-718.361302

1,4-HAT T.S.

H	1.178404	1.815277	-2.372743
C	1.411513	1.656442	-1.304511
N	0.309855	1.057873	-0.561116
C	-0.949478	1.780065	-0.640225
H	-1.320128	1.841923	-1.681645
H	-1.694492	1.214927	-0.068862
C	0.212425	-0.337613	-0.915497
H	-0.189446	-0.538459	-1.923581
C	-0.290748	-1.247610	0.125086
C	-1.182445	-3.022070	2.102936
C	-0.946087	-2.436401	-0.224318
C	-0.087218	-0.961303	1.483116
C	-0.533013	-1.841412	2.460852
C	-1.385905	-3.317110	0.756106
H	-1.113521	-2.665502	-1.274412

H	0.423657	-0.040738	1.748680
H	-0.369632	-1.608138	3.509121
H	-1.894673	-4.233295	0.470405
H	-1.528910	-3.708782	2.869690
C	-0.844879	3.135666	-0.090981
H	-0.690391	5.244280	0.738265
C	-0.761327	4.255907	0.342712
H	1.708043	2.610280	-0.858860
H	1.527780	-0.437564	-1.116162
C	2.487291	0.598225	-1.215464
F	3.211875	0.643927	-0.088159
F	3.311451	0.541205	-2.270432

One imaginary frequency i1830

Label	Energy (kcal/mol)	ZPE (kJ/mol)	Gº (au)
M0001	-450881.73	518.21	-718.372298

Product radical

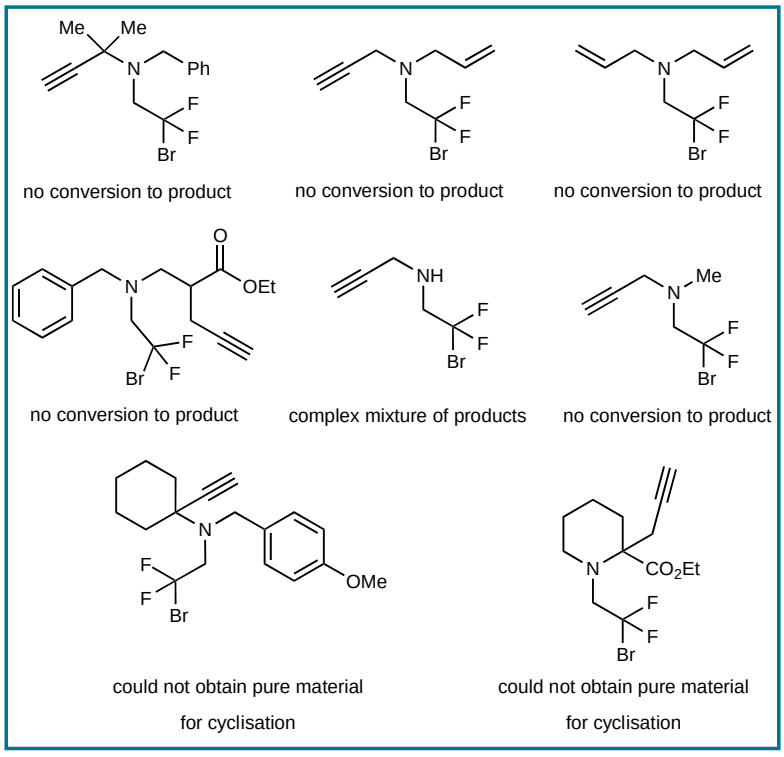
H	-2.327397	0.869511	1.865451
C	-2.170171	1.135554	0.803110
H	-3.066324	0.876257	0.232976
C	-1.862053	2.625761	0.728285
F	-2.514122	3.330440	1.689577
F	-2.254448	3.150065	-0.464350
N	-0.977844	0.532661	0.236081
C	0.158159	1.258508	0.803637
H	0.407803	0.896987	1.821015
H	1.047138	1.145176	0.178540
C	-0.907675	-0.905321	0.399682
H	-1.844865	-1.326085	0.012431
H	-0.849876	-1.188765	1.469777
C	0.262676	-1.505655	-0.347146
C	2.400786	-2.636777	-1.756700

C	0.503789	-1.145940	-1.675955
C	1.107551	-2.428033	0.267608
C	2.169627	-2.996087	-0.433062
C	1.565797	-1.706887	-2.375555
H	-0.142594	-0.410164	-2.146953
H	0.935762	-2.704765	1.305378
H	2.819772	-3.713953	0.059372
H	1.744050	-1.418229	-3.407522
H	3.230112	-3.074903	-2.304155
C	-0.339851	2.687782	0.875536
H	0.124415	4.846993	1.123429
C	0.341425	3.790114	1.038770

No imaginary frequencies

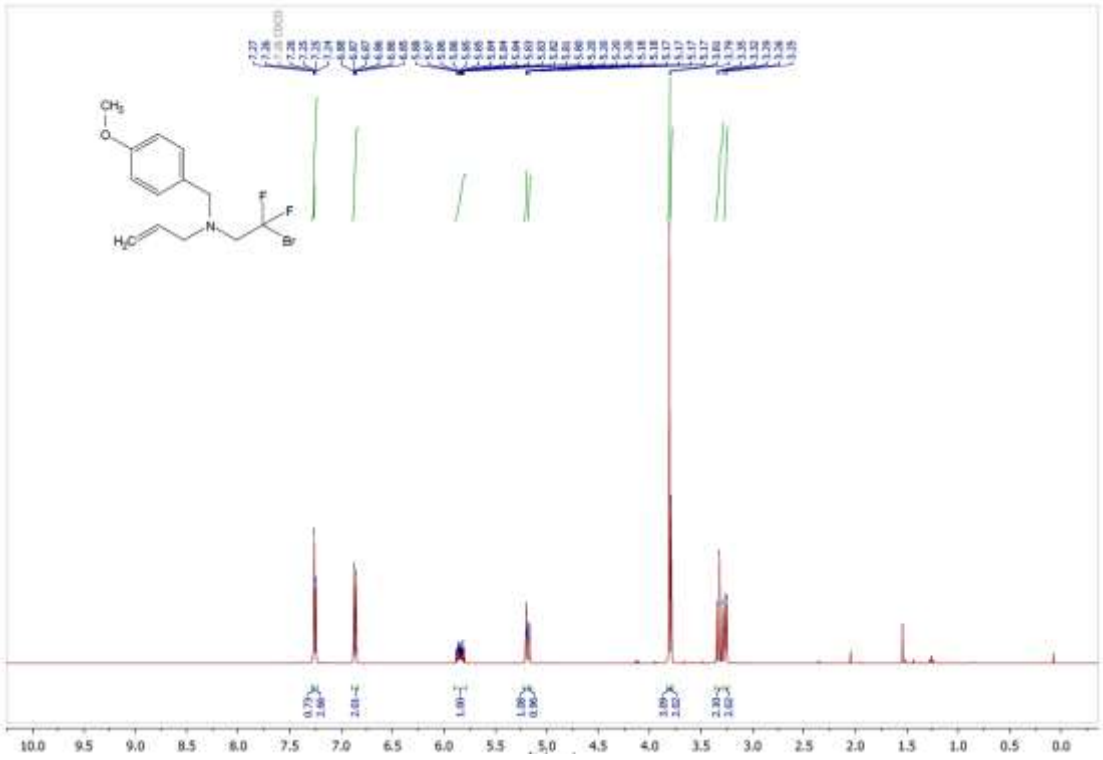
Label	Energy (kcal/mol)	ZPE (kJ/mol)	Gº (au)
M0001	-450927.72	535.96	-718.437879

6 Unsuccessful Examples

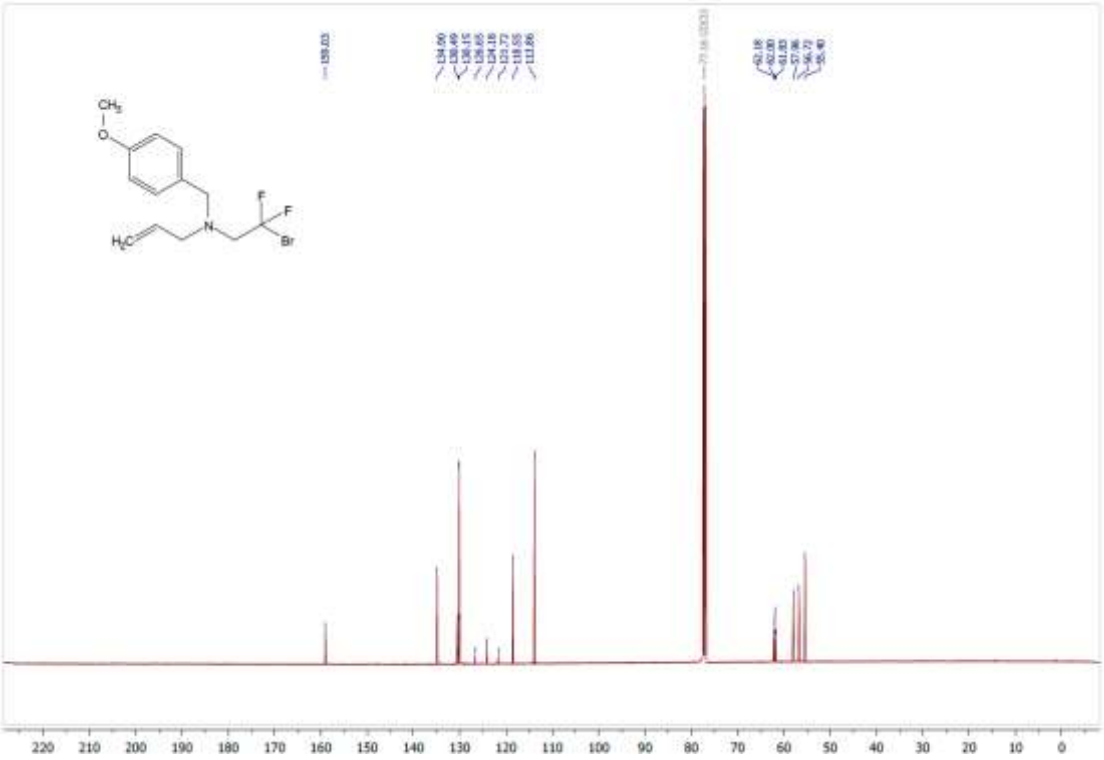


7 NMR spectra

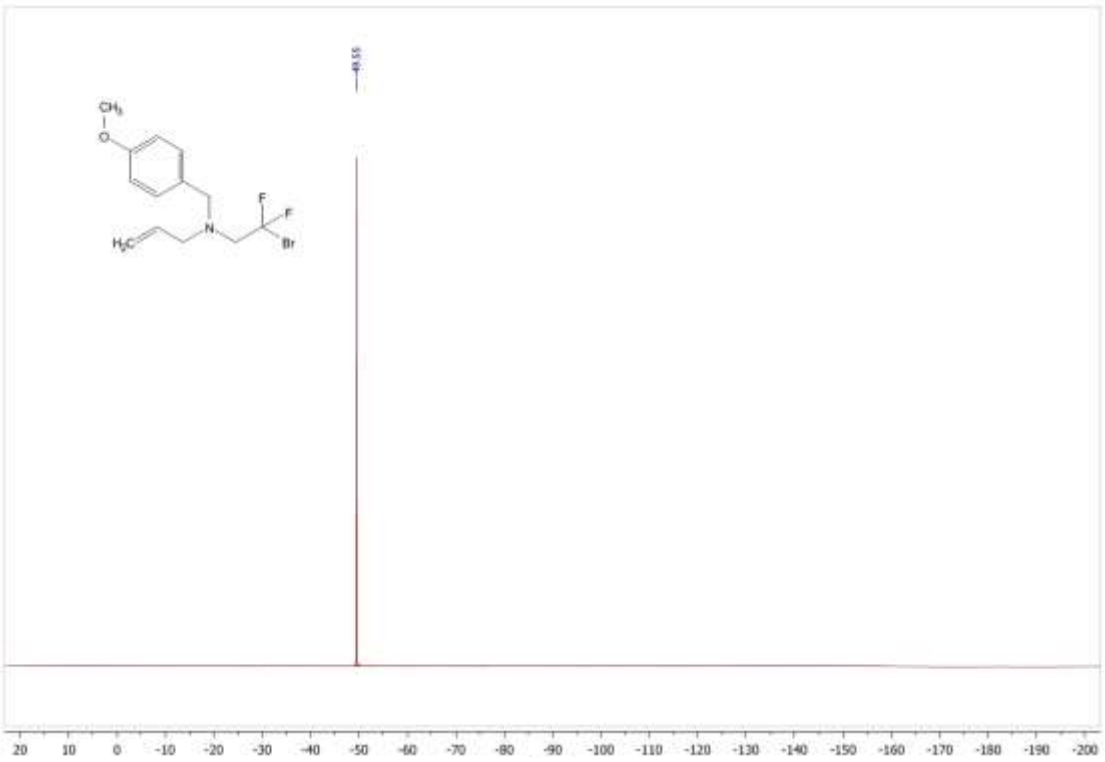
Supplementary Figure 8. ^{1}H NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-en-1-amine **5**



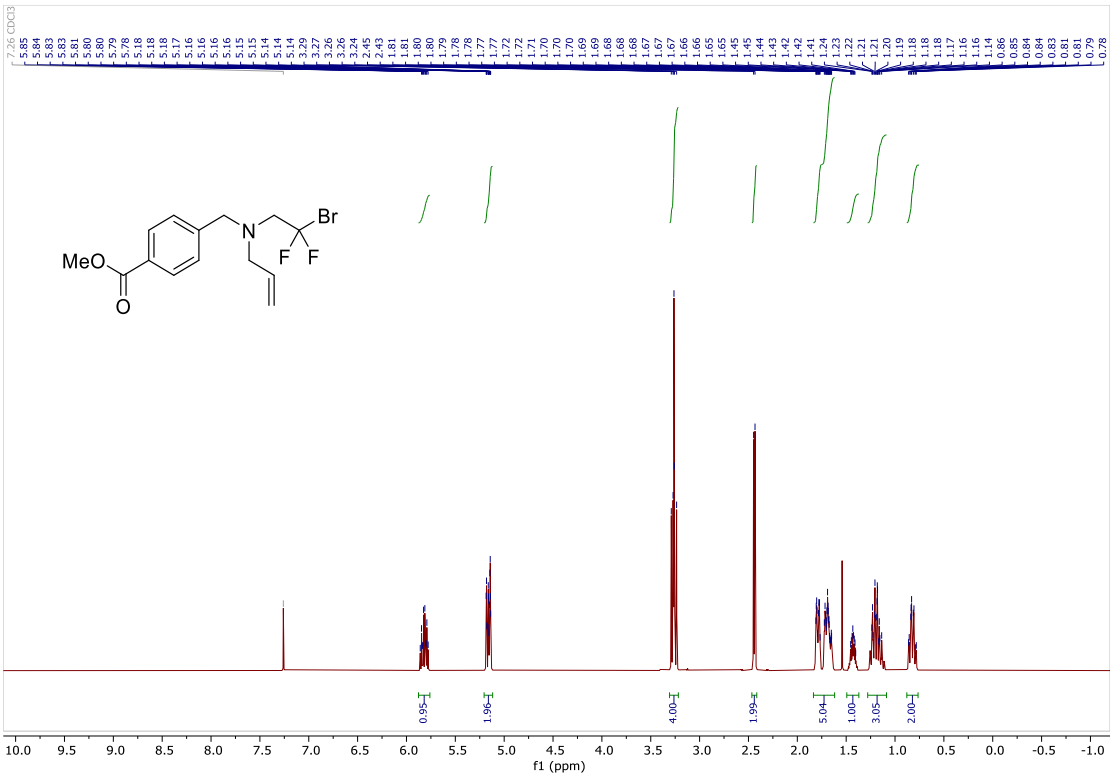
Supplementary Figure 9. ^{13}C NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-en-1-amine **5**



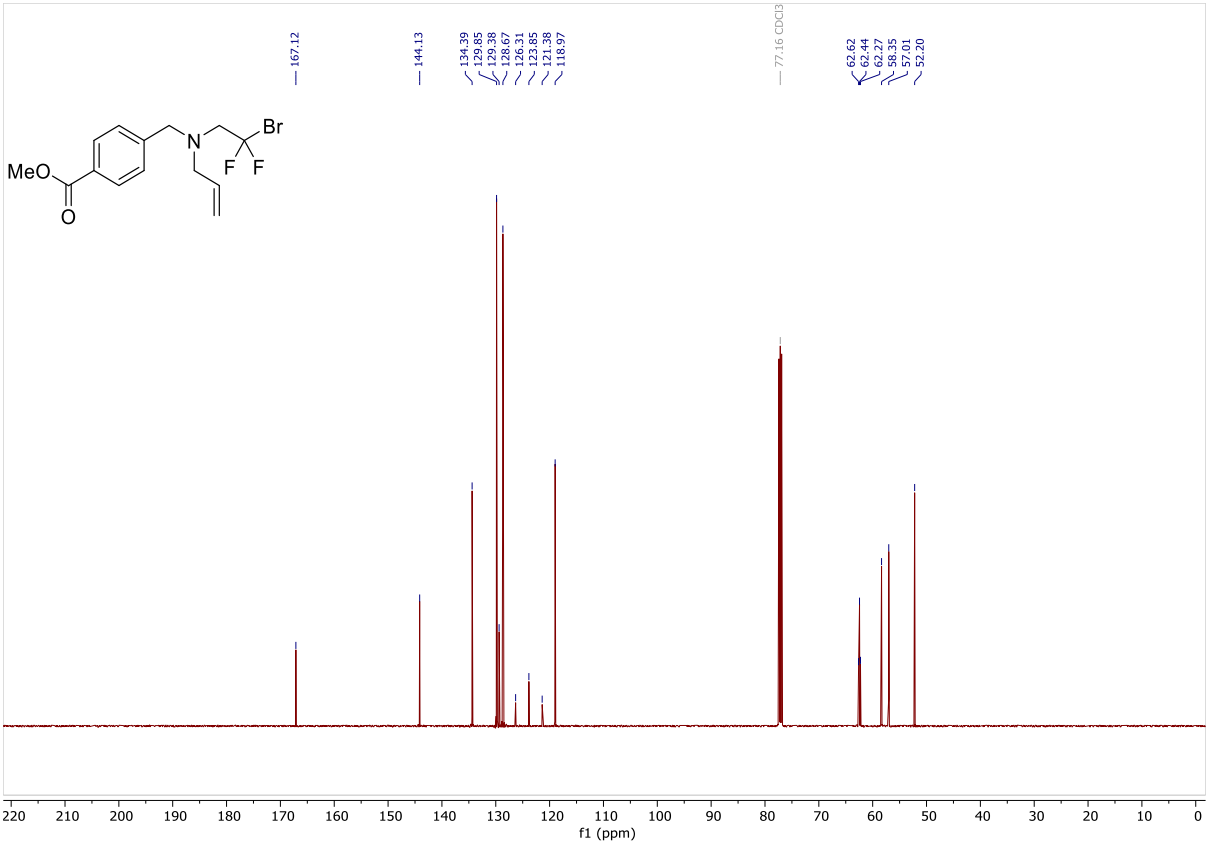
Supplementary Figure 10. ^{19}F NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-en-1-amine **5**



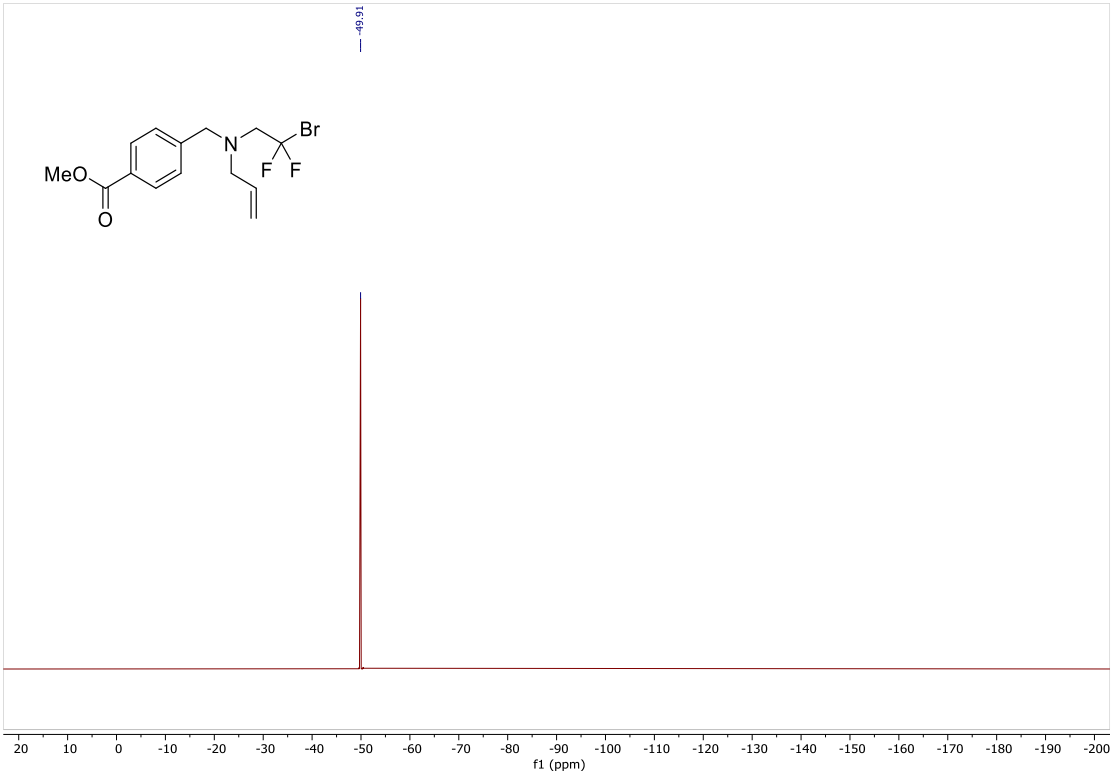
Supplementary Figure 11. ^{1}H Methyl 4-((allyl(2-bromo-2,2-difluoroethyl)amino)methyl)benzoate **34**



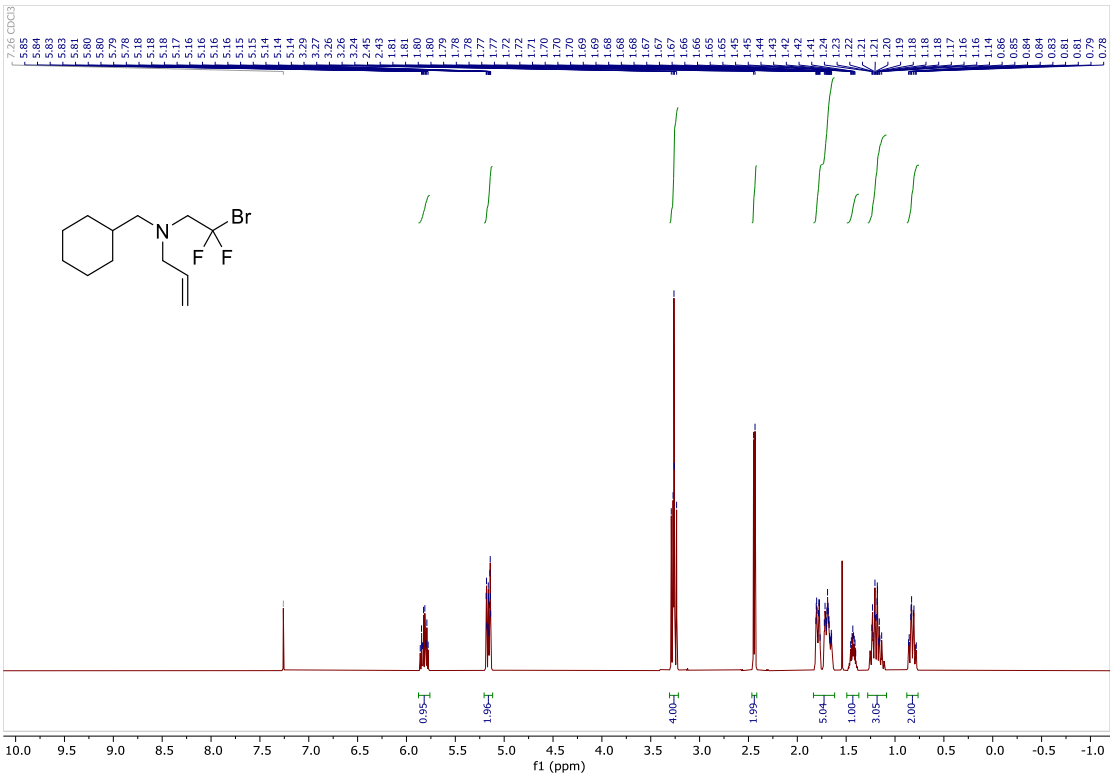
Supplementary Figure 12. ^{13}C NMR Methyl 4-((allyl(2-bromo-2,2-difluoroethyl)amino)methyl) benzoate **34**



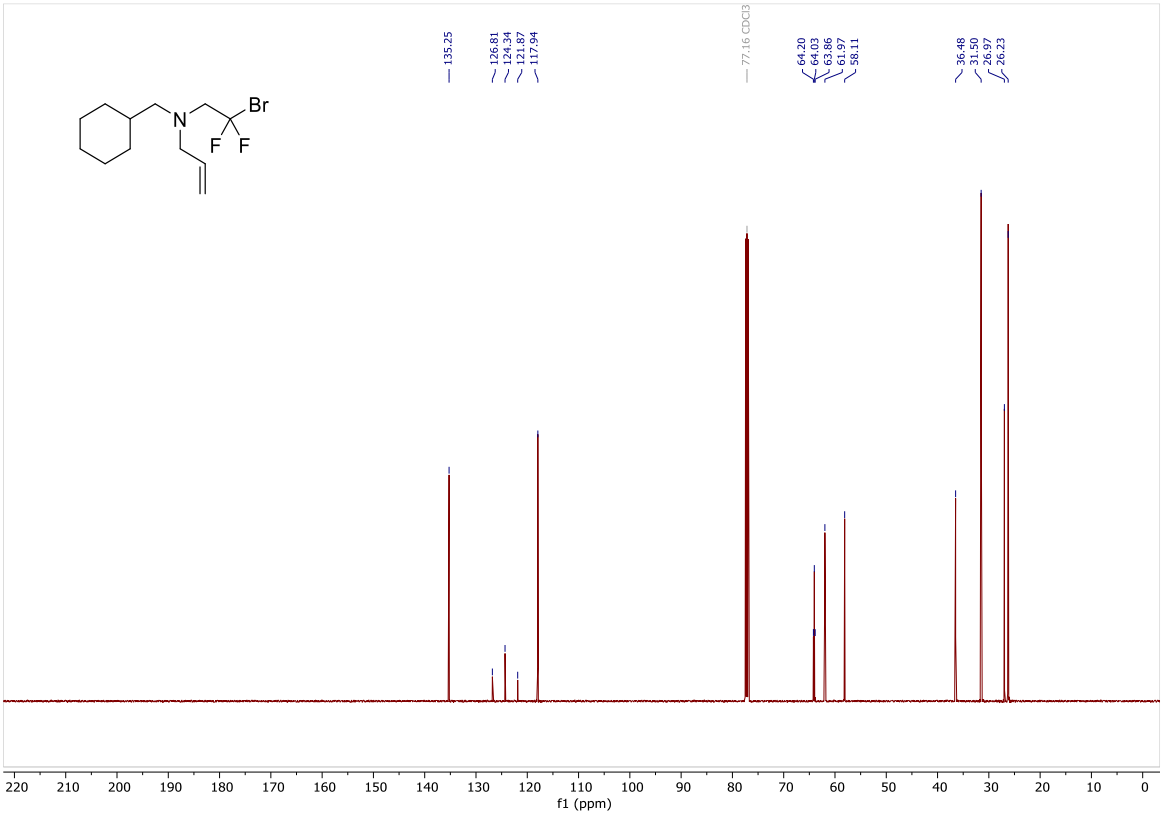
Supplementary Figure 13. ^{19}F Methyl 4-((allyl(2-bromo-2,2-difluoroethyl)amino)methyl) benzoate **34**



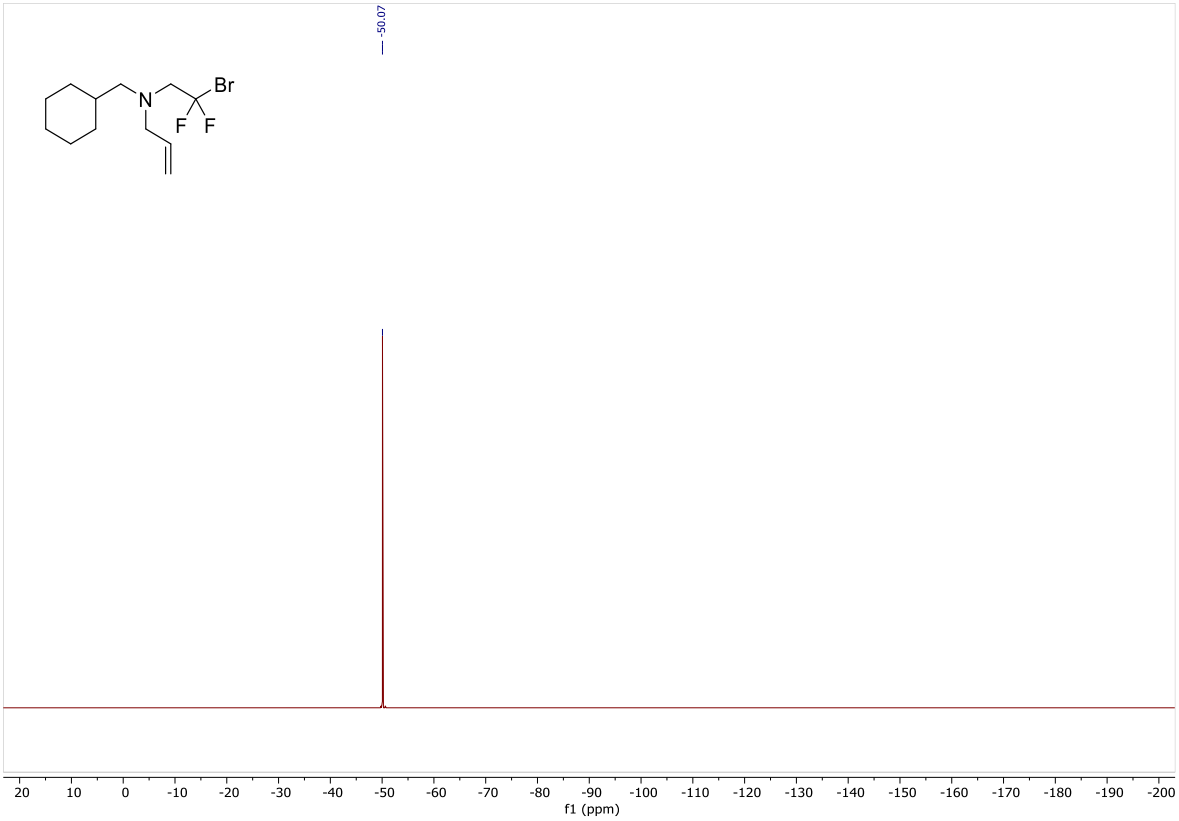
Supplementary Figure 14. ^{1}H NMR *N*-(2-Bromo-2,2-difluoroethyl)-N-(cyclohexylmethyl)prop-2-en-1-amine **35**



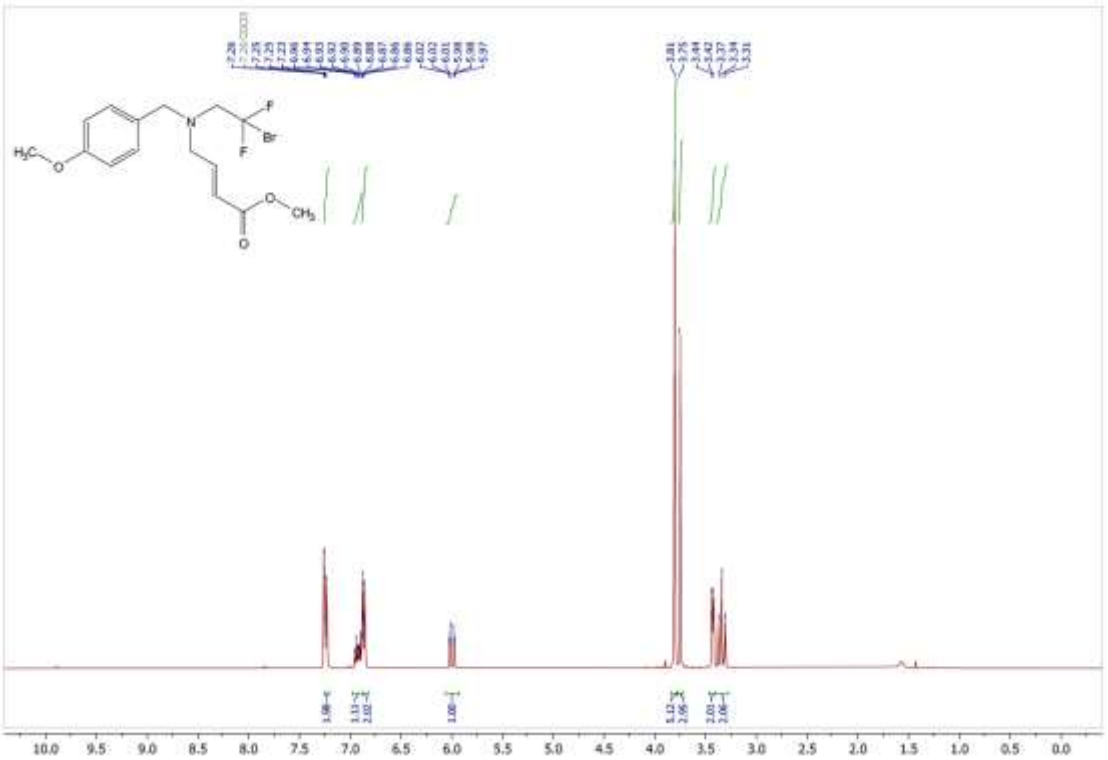
Supplementary Figure 15. ^{13}C NMR *N*-(2-Bromo-2,2-difluoroethyl)-N-(cyclohexylmethyl)prop-2-en-1-amine **35**



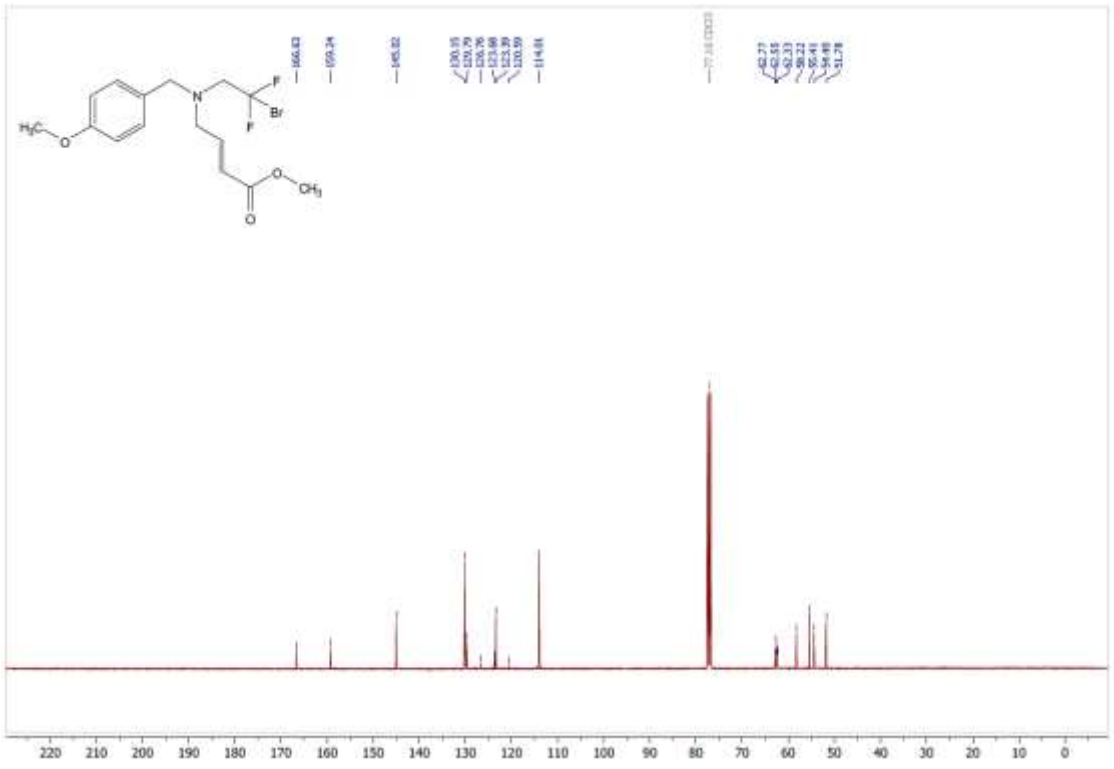
Supplementary Figure 16. ^{19}F NMR *N*-(2-Bromo-2,2-difluoroethyl)-N-(cyclohexylmethyl)prop-2-en-1-amine **35**



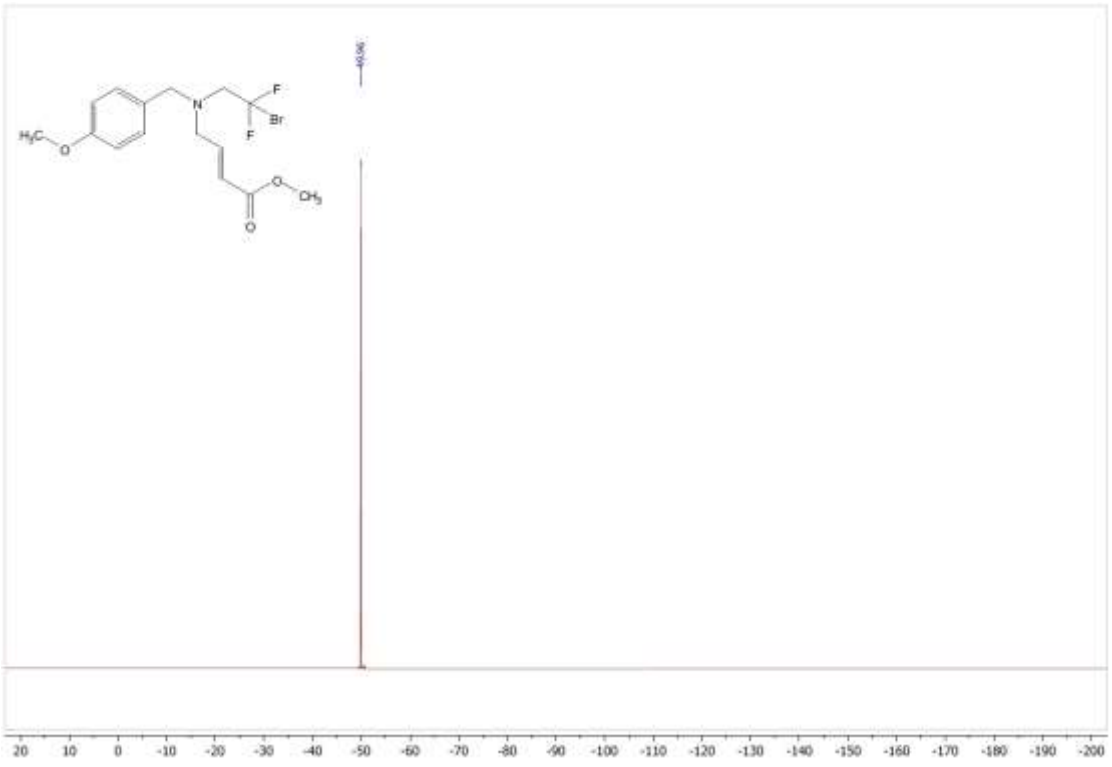
Supplementary Figure 17. ^{1}H NMR Methyl (*E*)-4-((2-bromo-2,2-difluoroethyl)(4-methoxybenzyl)amino)but-2-enoate **36**



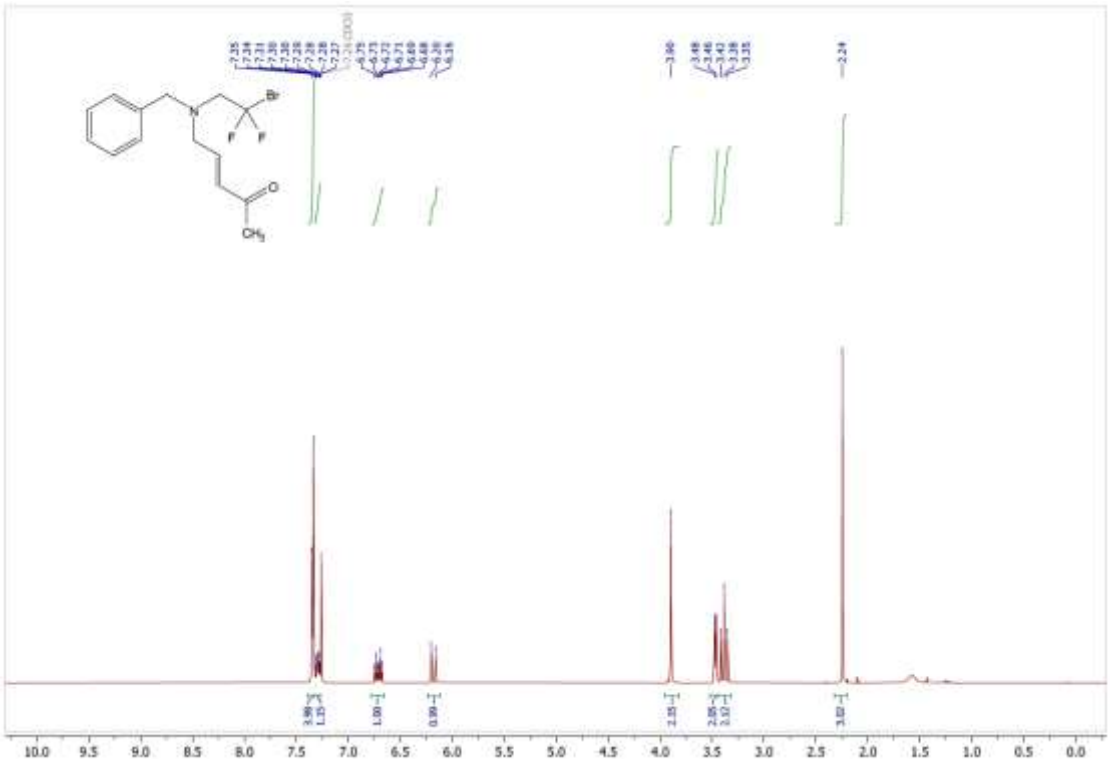
Supplementary Figure 18. ^{13}C NMR Methyl (*E*)-4-((2-bromo-2,2-difluoroethyl)(4-methoxybenzyl)amino)but-2-enoate **36**



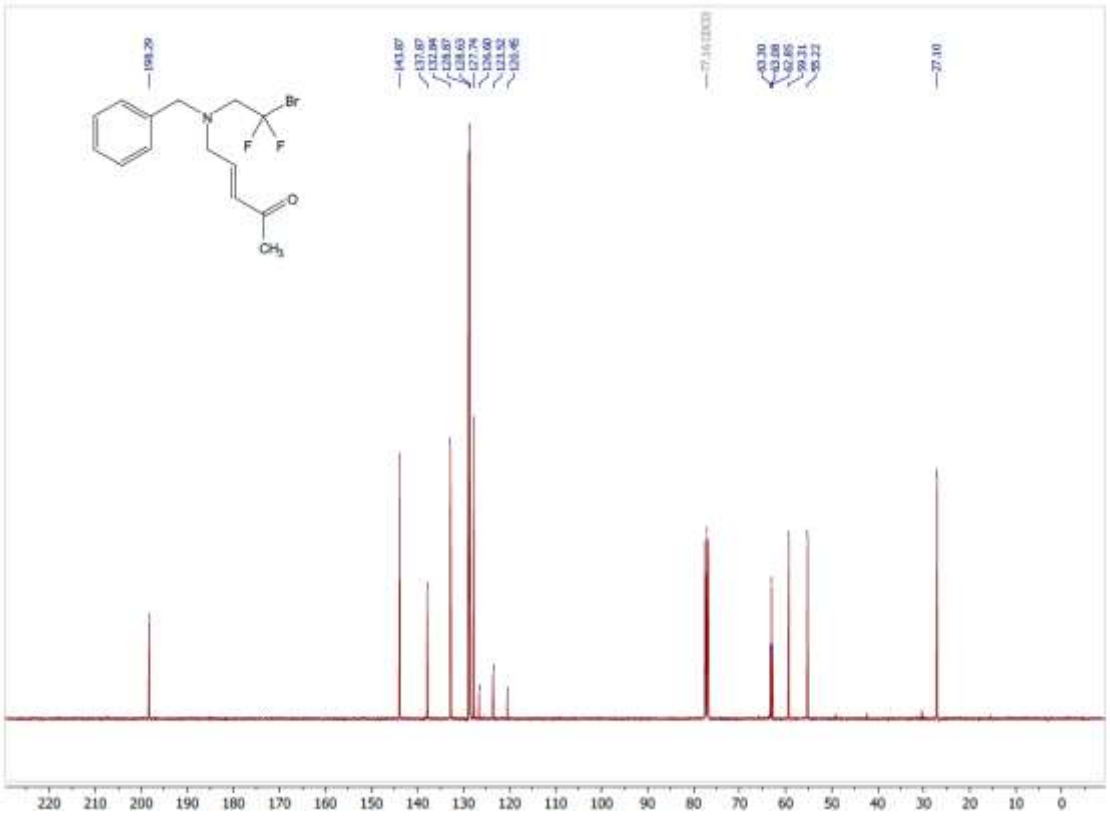
Supplementary Figure 19. ^{19}F NMR Methyl (*E*)-4-((2-bromo-2,2-difluoroethyl)(4-methoxybenzyl)amino)but-2-enoate **36**



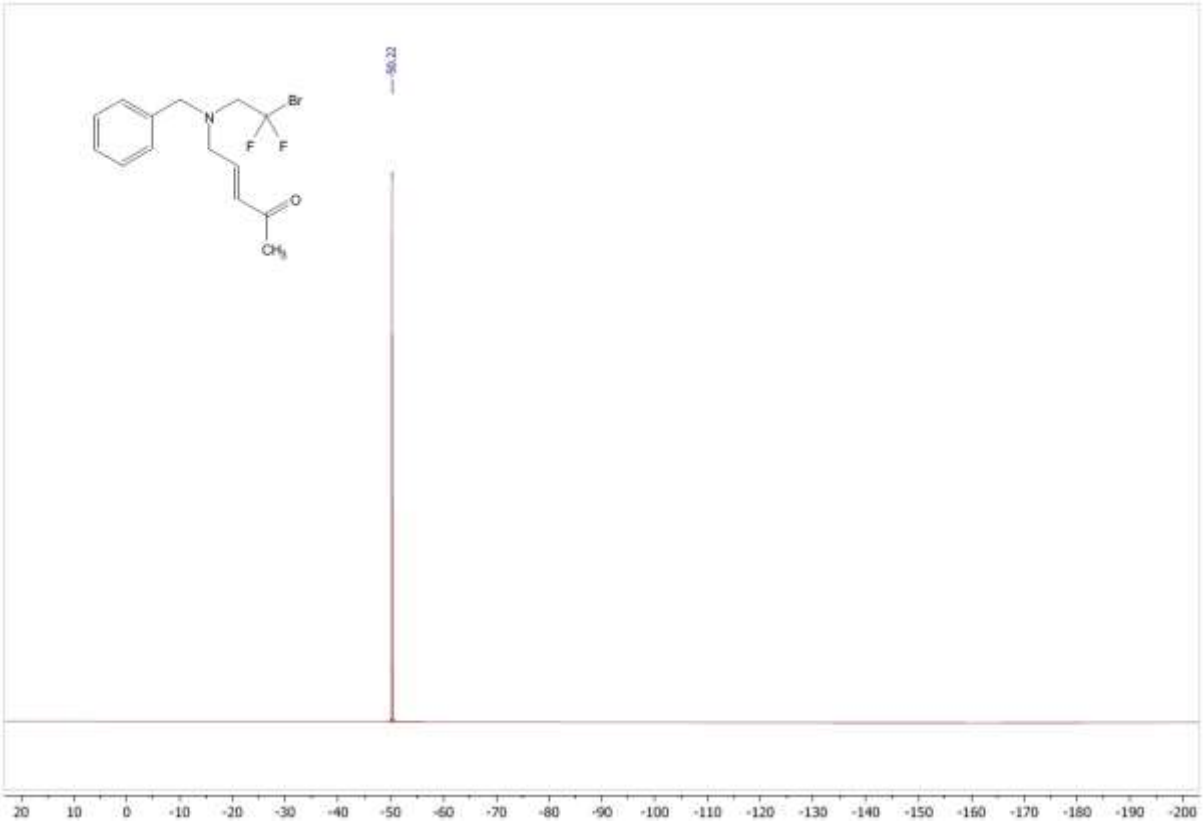
Supplementary Figure 20. ^{1}H NMR (*E*)-5-(Benzyl(2-bromo-2,2-difluoroethyl)amino)pent-3-en-2-one **37**



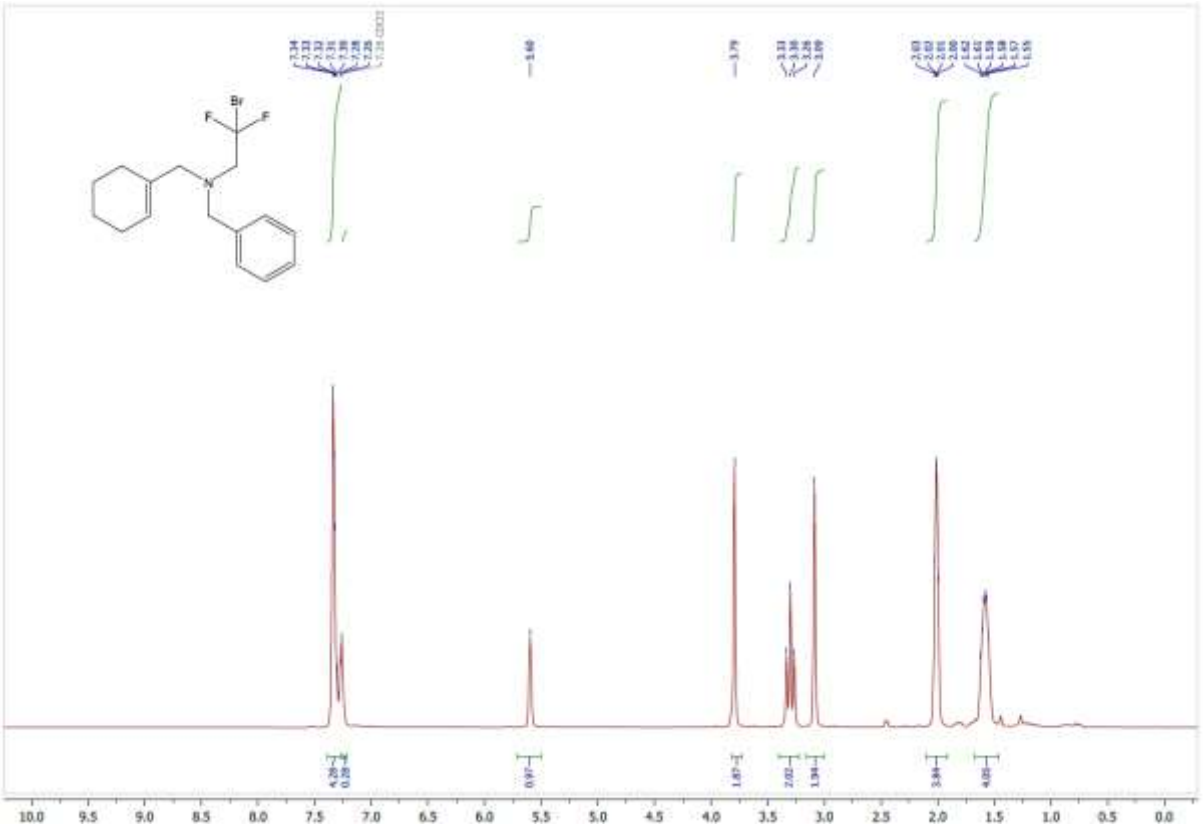
Supplementary Figure 21. ^{13}C NMR (*E*)-5-(Benzyl(2-bromo-2,2-difluoroethyl)amino)pent-3-en-2-one **37**



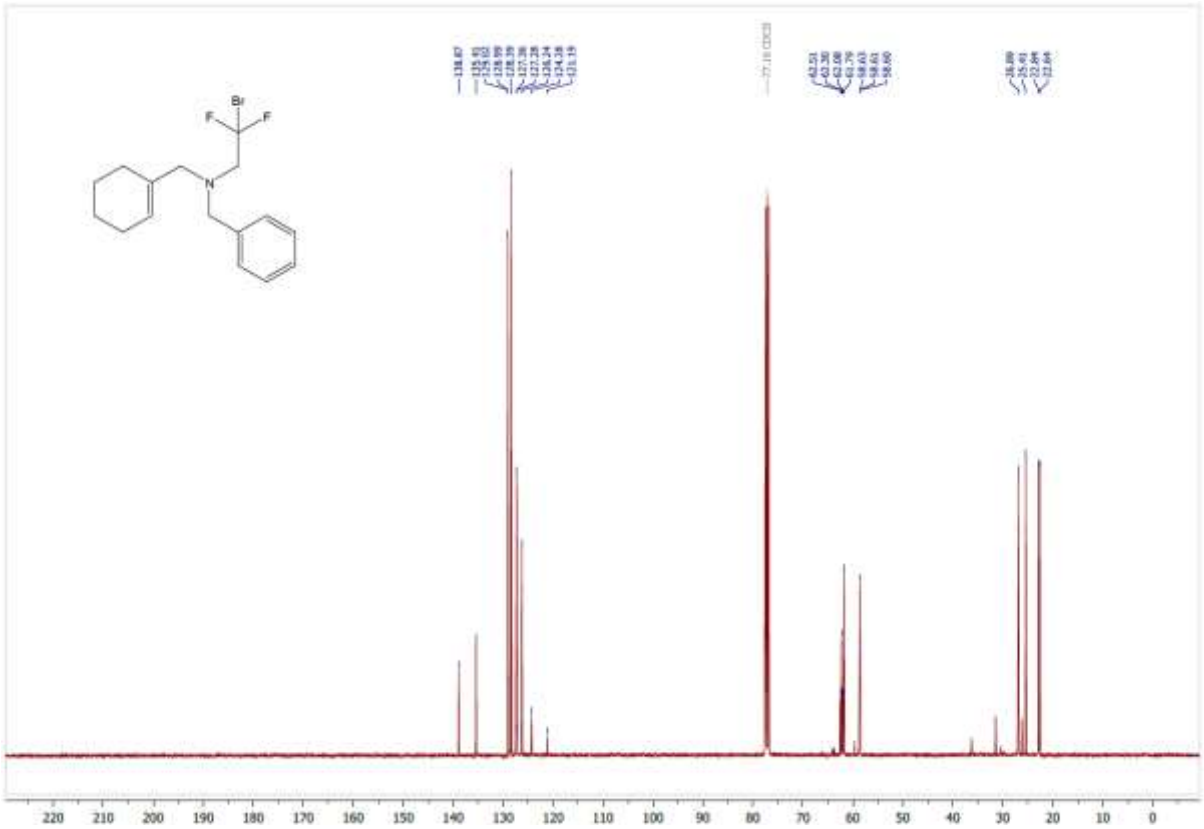
Supplementary Figure 22. ^{19}F NMR (*E*)-5-(Benzyl(2-bromo-2,2-difluoroethyl)amino)pent-3-en-2-one



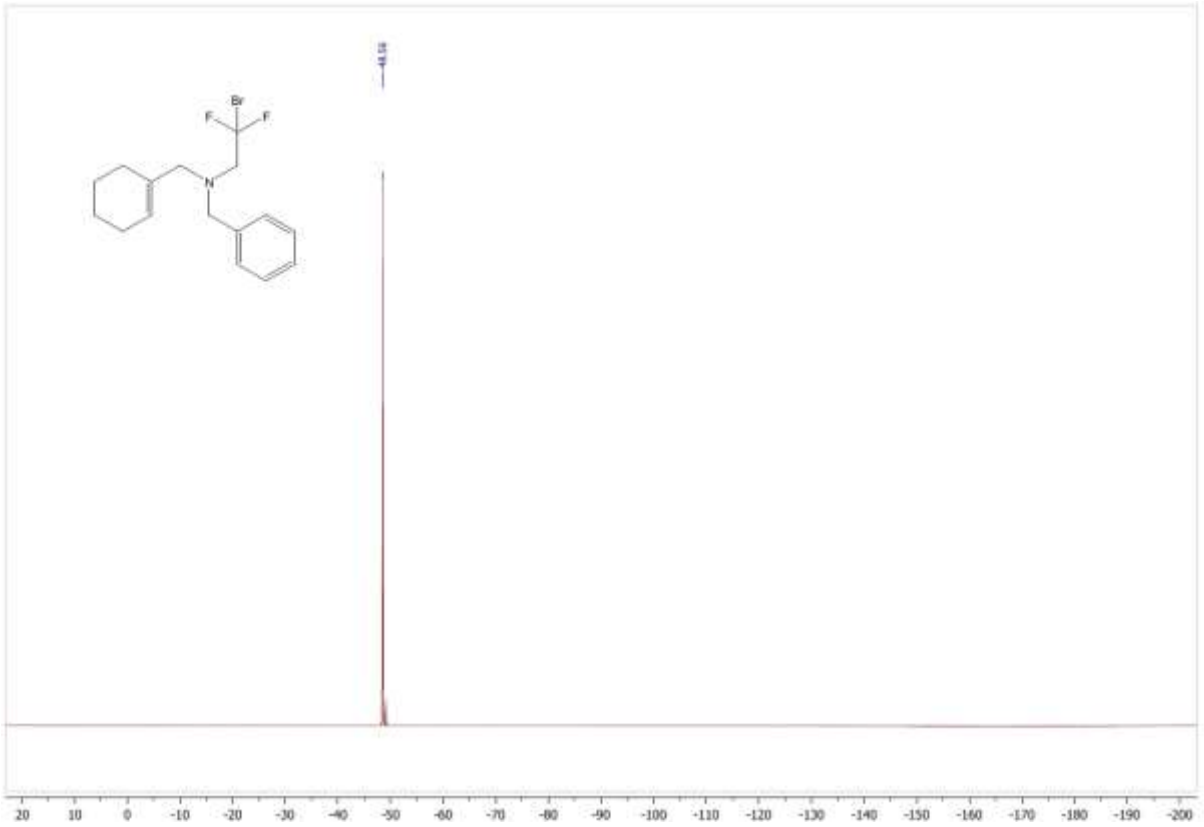
Supplementary Figure 23. ^{1}H NMR *N*-Benzyl-2-bromo-*N*-(cyclohex-1-en-1-ylmethyl)-2,2-difluoroethan-1-amine **38**



Supplementary Figure 24. ^{13}C NMR *N*-Benzyl-2-bromo-*N*-(cyclohex-1-en-1-ylmethyl)-2,2-difluoroethan-1-amine **38**

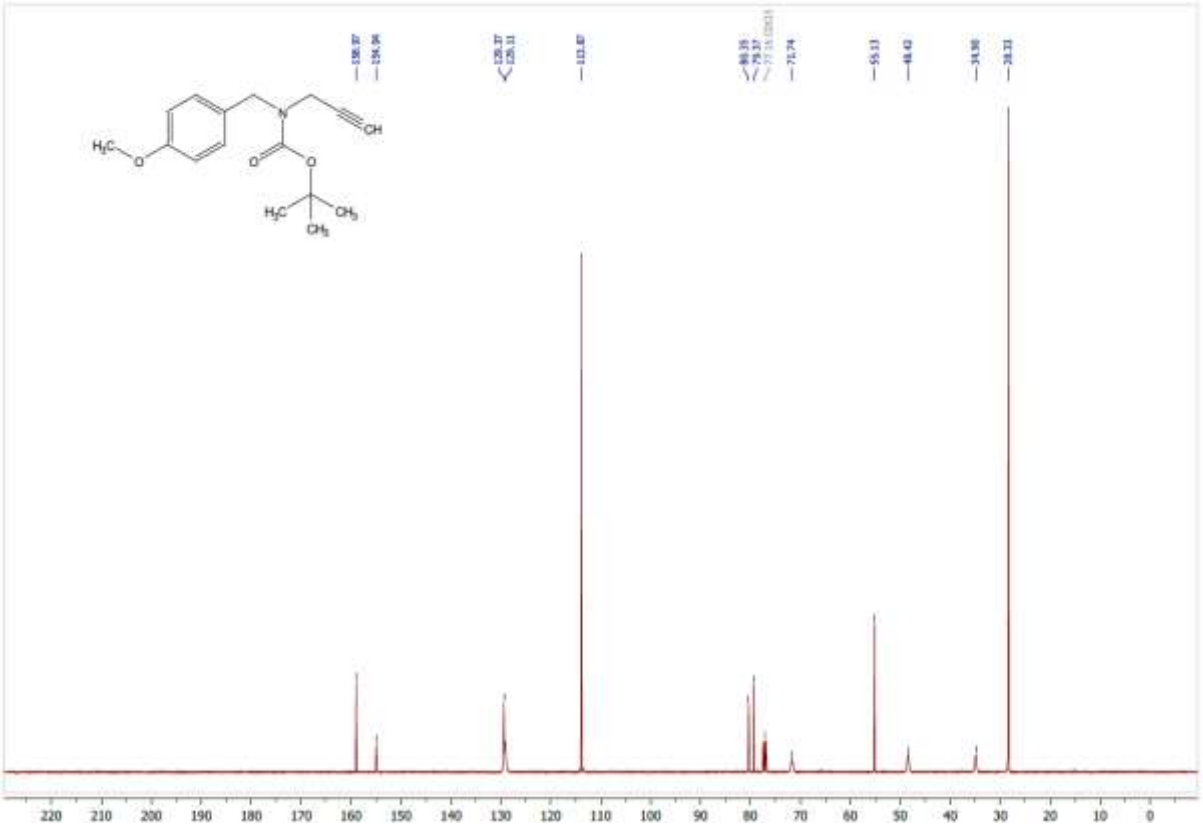


Supplementary Figure 25. ^{19}F NMR *N*-Benzyl-2-bromo-*N*-(cyclohex-1-en-1-ylmethyl)-2,2-difluoroethan-1-amine **38**

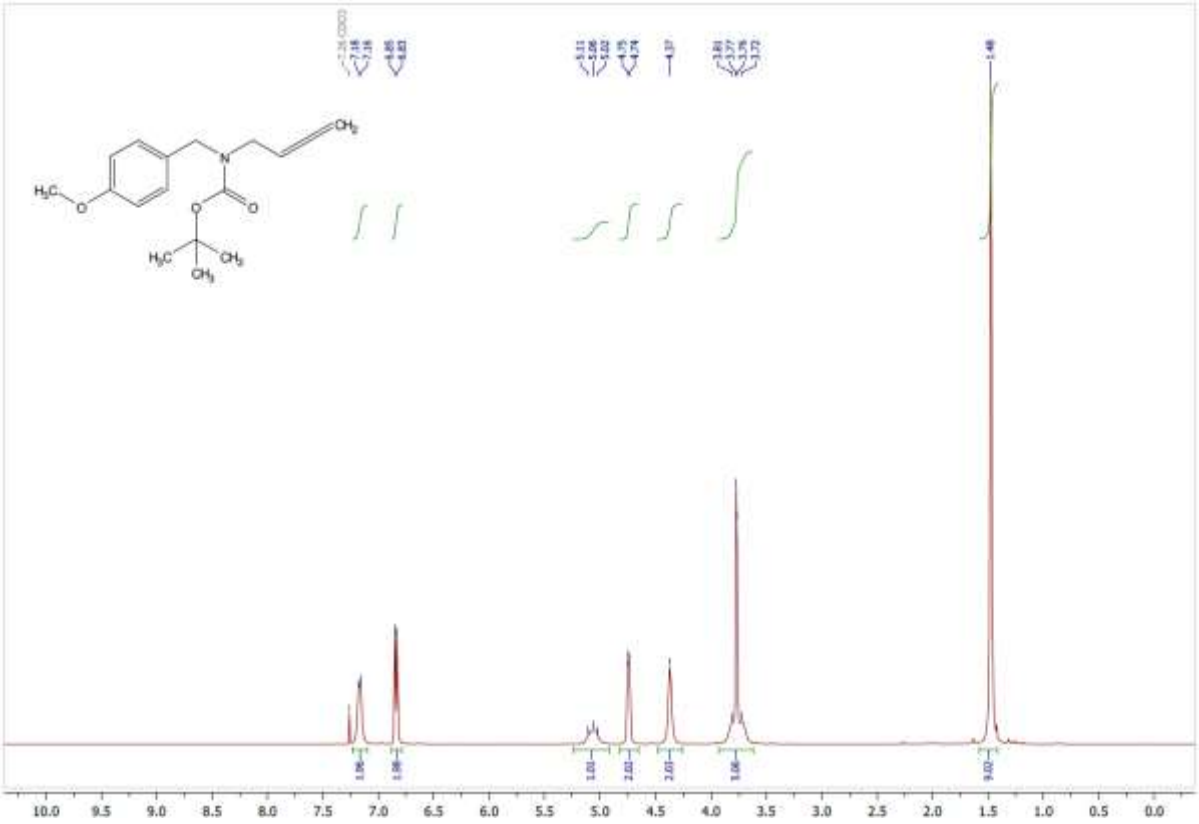


Supplementary Figure 26. ^{1}H NMR *tert*-Butyl (4-methoxybenzyl)(prop-2-yn-1-yl)carbamate **39**

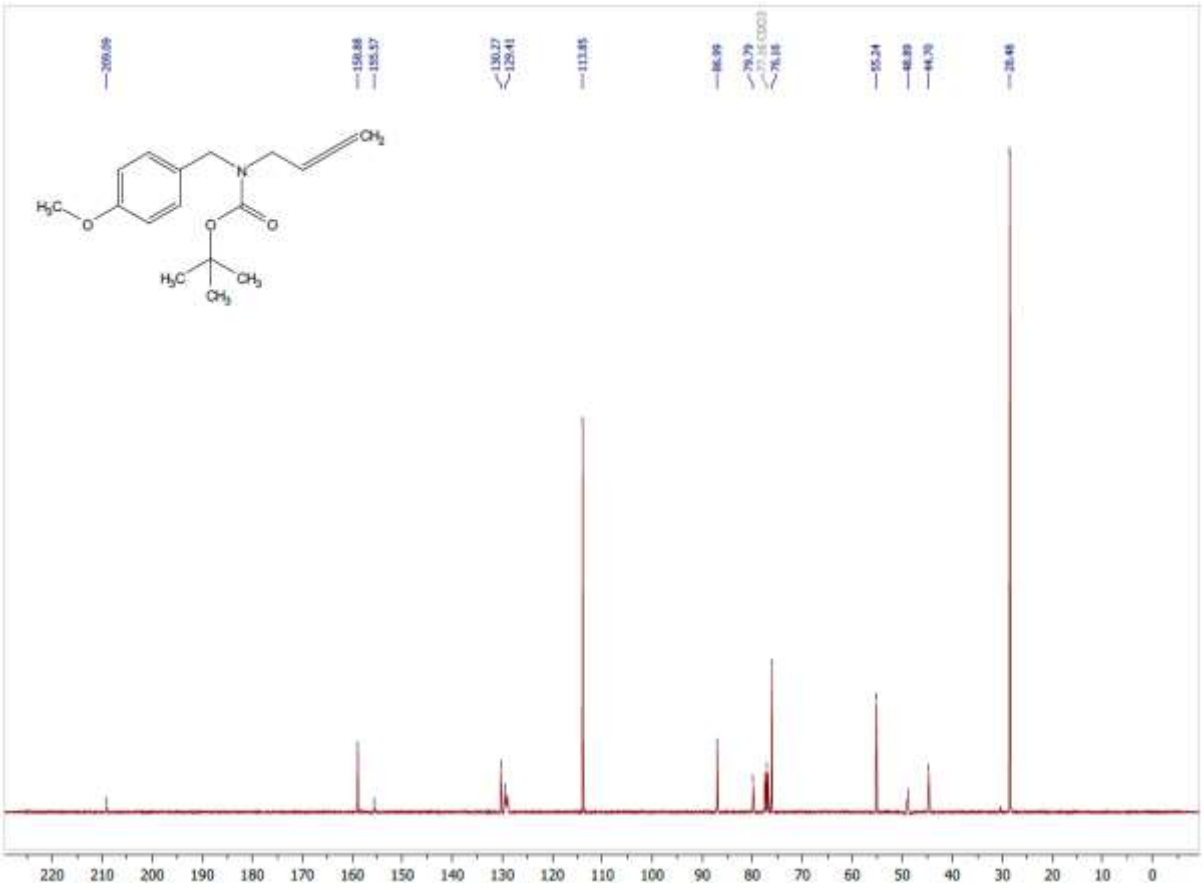
Supplementary Figure 27. ^{13}C NMR *tert*-Butyl (4-methoxybenzyl)(prop-2-yn-1-yl)carbamate **39**



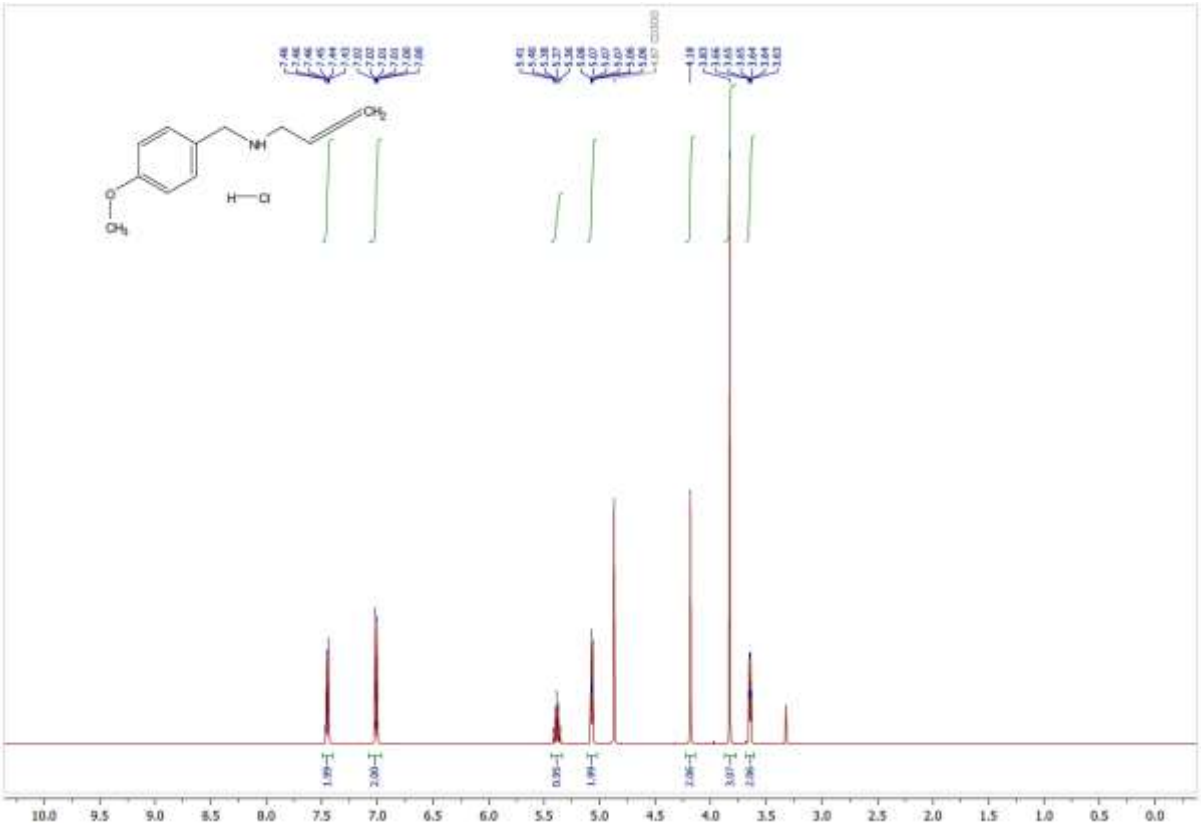
Supplementary Figure 28. ^{1}H NMR *tert*-Butyl buta-2,3-dien-1-yl(4-methoxybenzyl)carbamate **40**



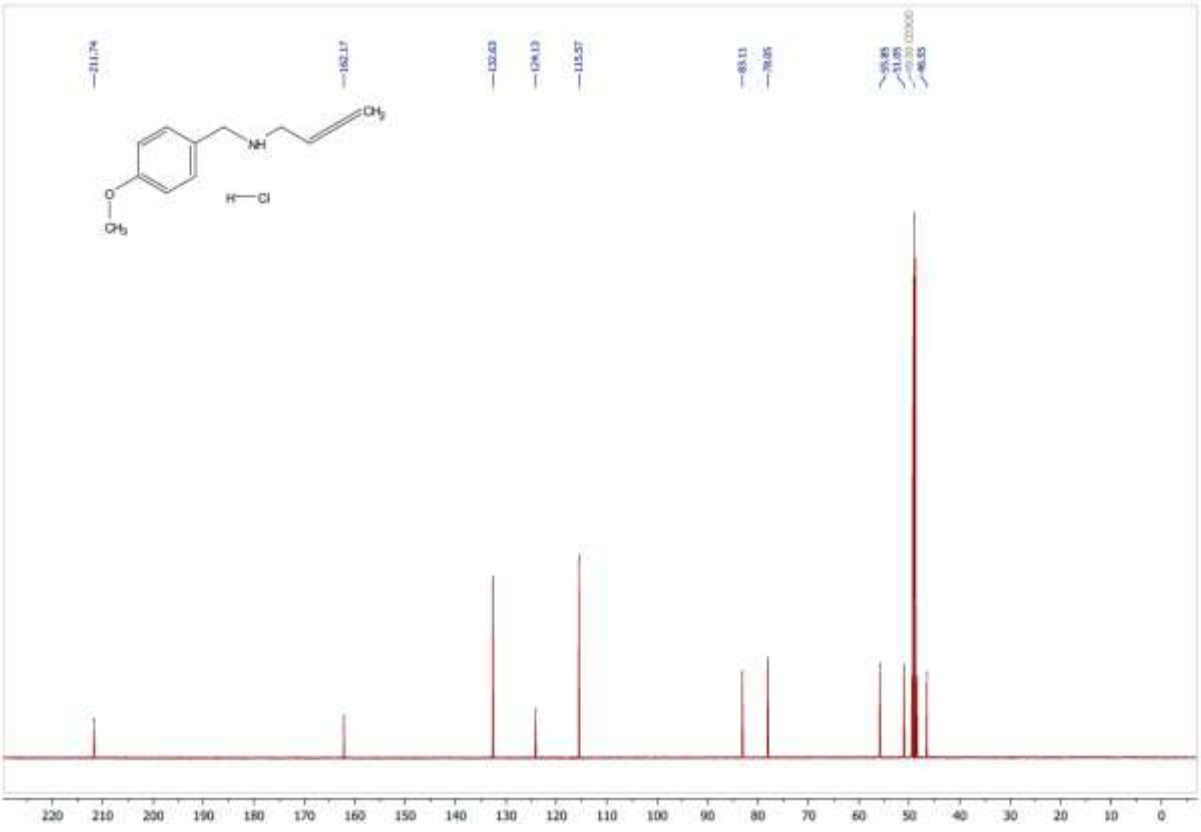
Supplementary Figure 29. ^{13}C NMR *tert*-Butyl buta-2,3-dien-1-yl(4-methoxybenzyl)carbamate **40**



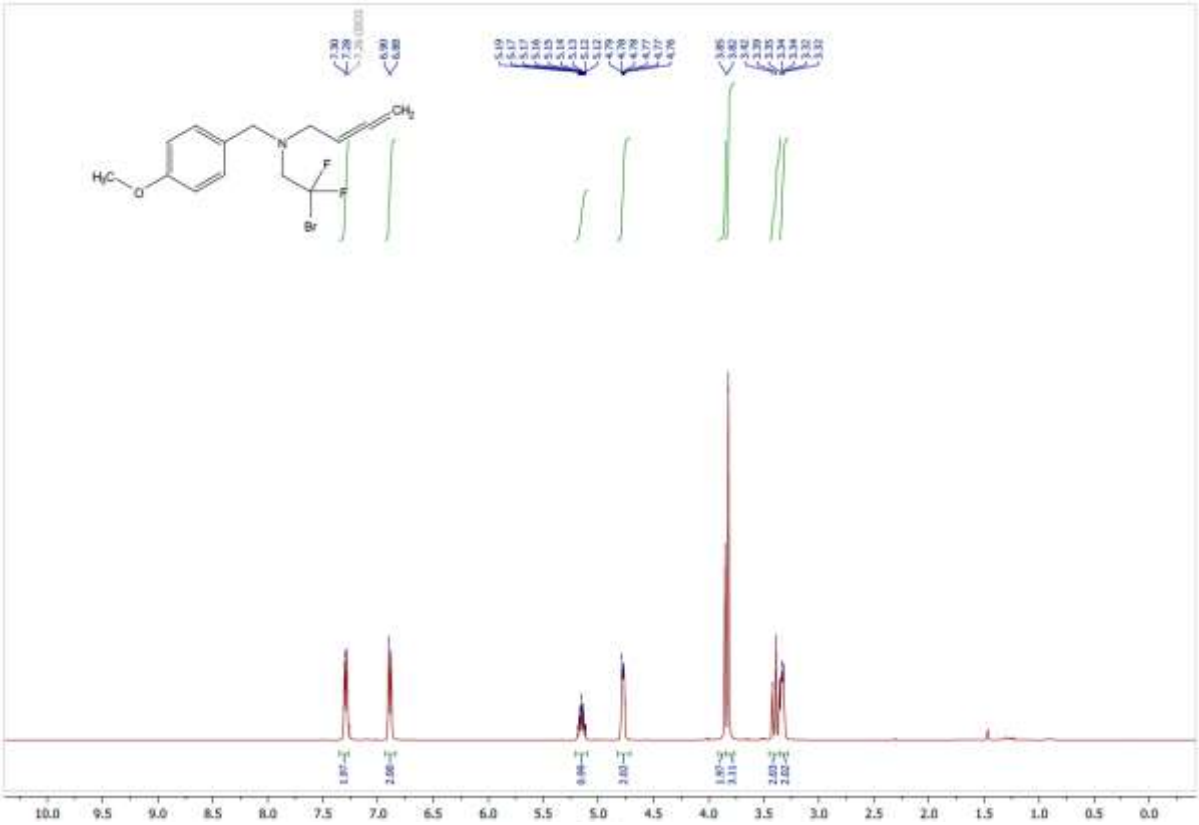
Supplementary Figure 30. ^{1}H NMR *N*-(4-Methoxybenzyl)buta-2,3-dien-1-amine hydrochloride **41**



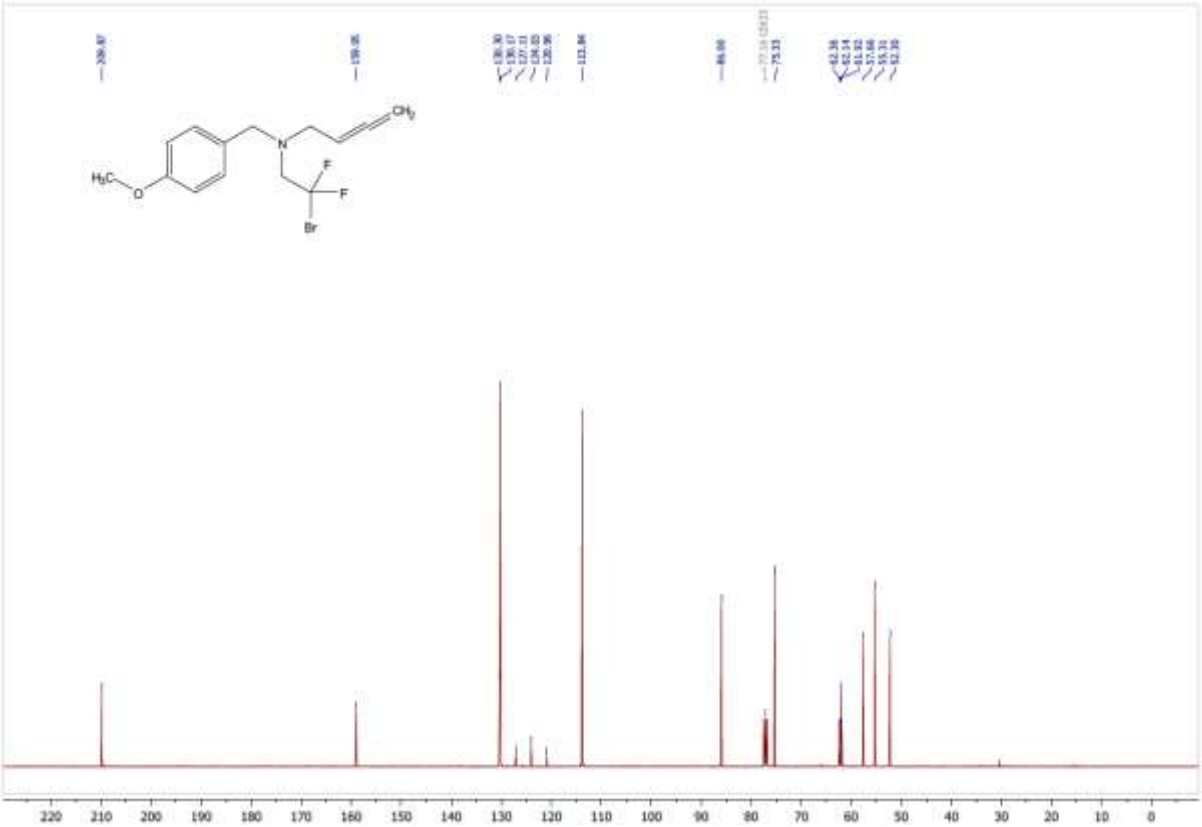
Supplementary Figure 31. ^{13}C NMR *N*-(4-Methoxybenzyl)buta-2,3-dien-1-amine hydrochloride **41**



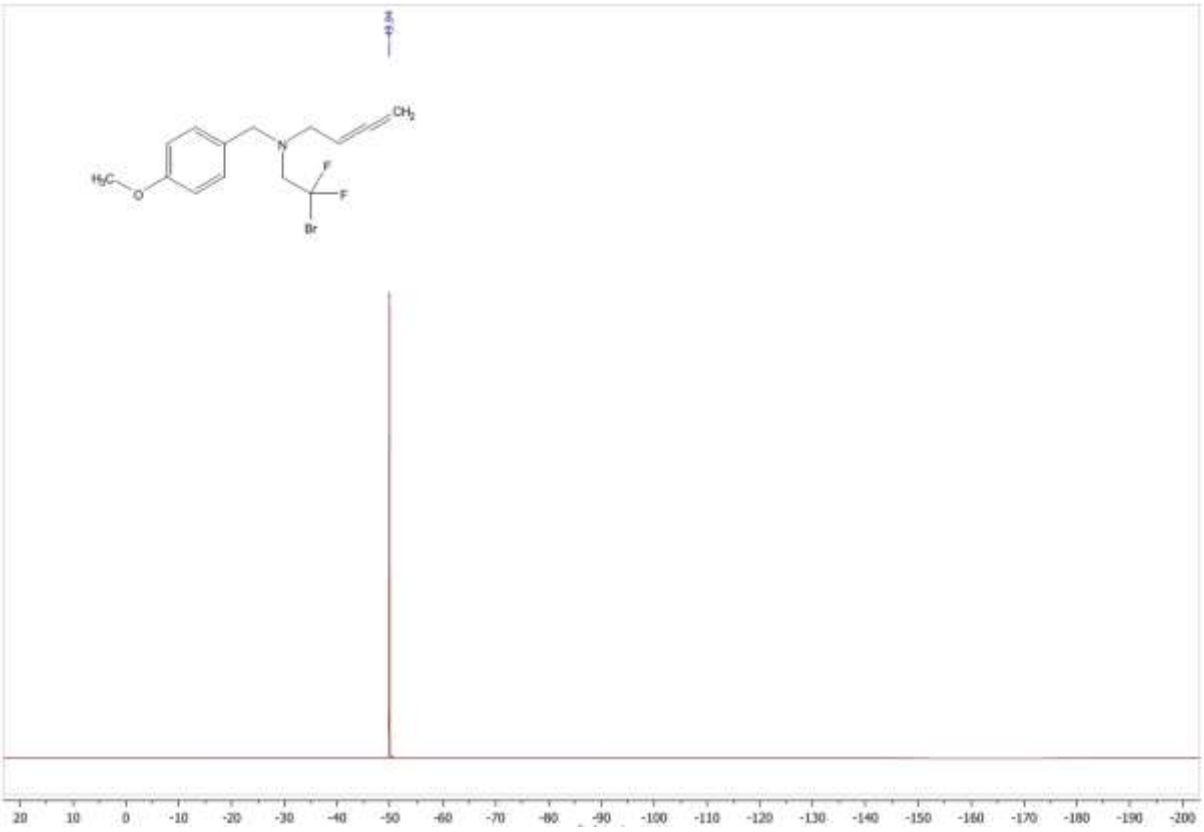
Supplementary Figure 32. ^{1}H NMR *N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)buta-2,3-dien-1-amine **42**



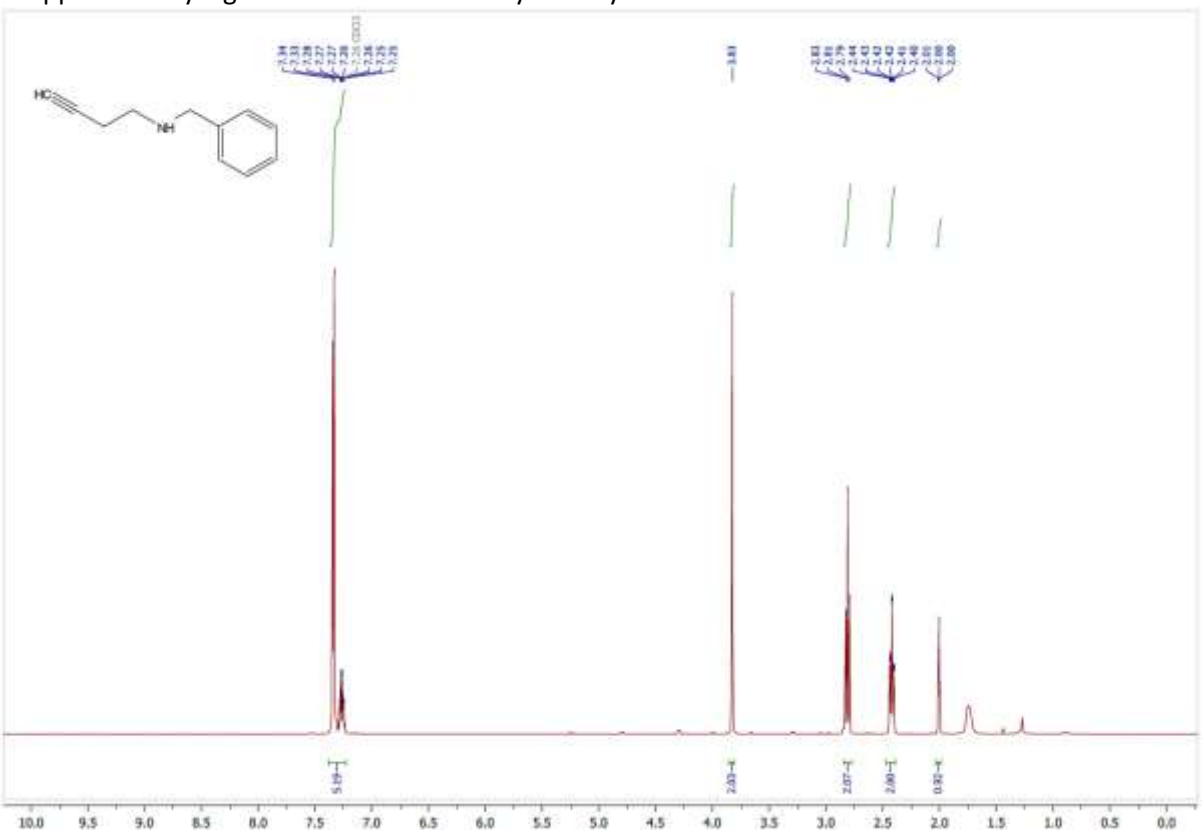
Supplementary Figure 33. ^{13}C NMR *N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)buta-2,3-dien-1-amine **42**



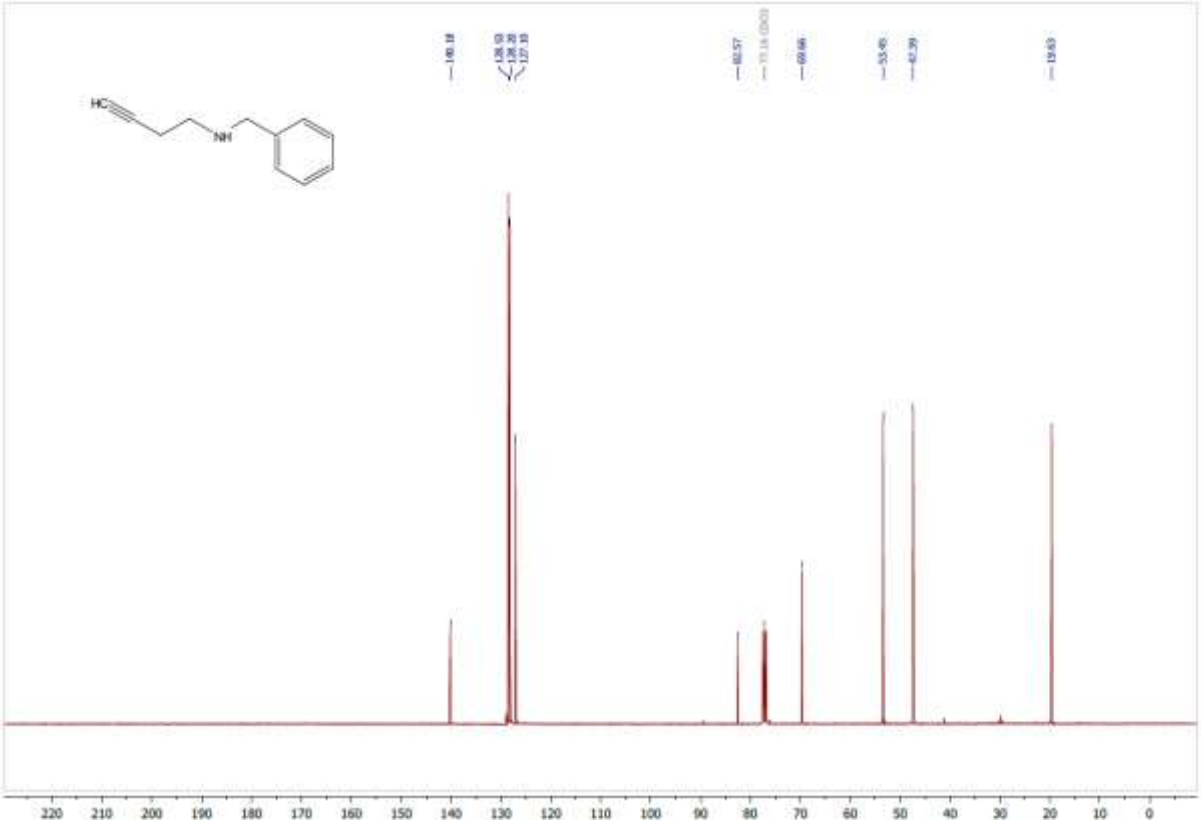
Supplementary Figure 34. ^{19}F NMR *N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)buta-2,3-dien-1-amine **42**



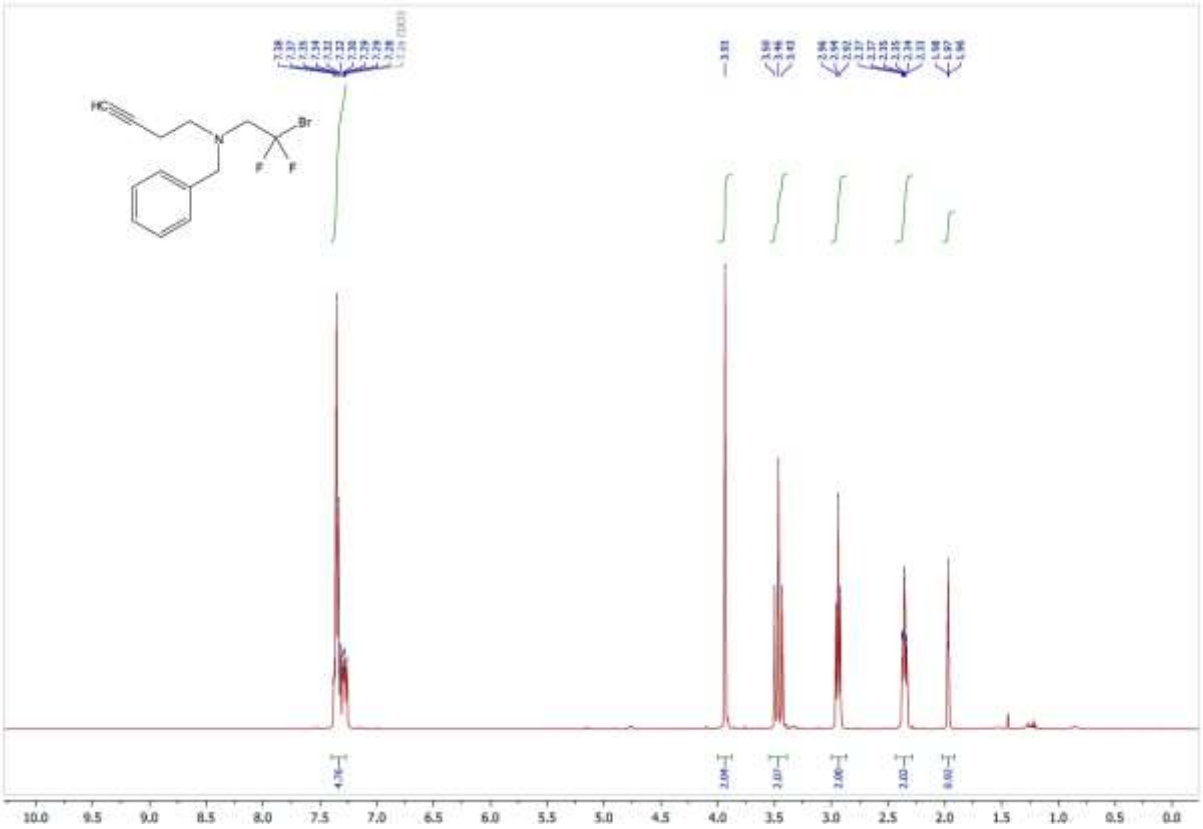
Supplementary Figure 35. ^{1}H NMR *N*-Benzylbut-3-yn-1-amine **43**



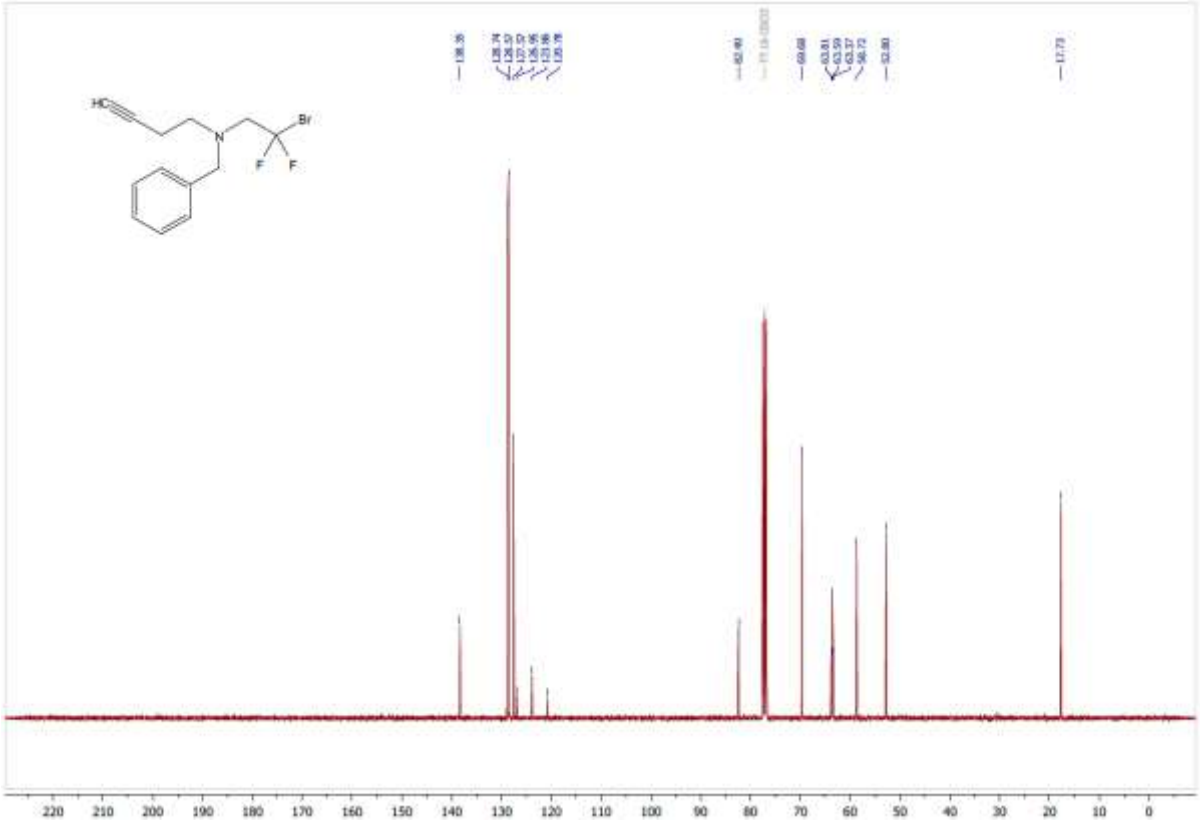
Supplementary Figure 36. ^{13}C NMR *N*-Benzylbut-3-yn-1-amine **43**



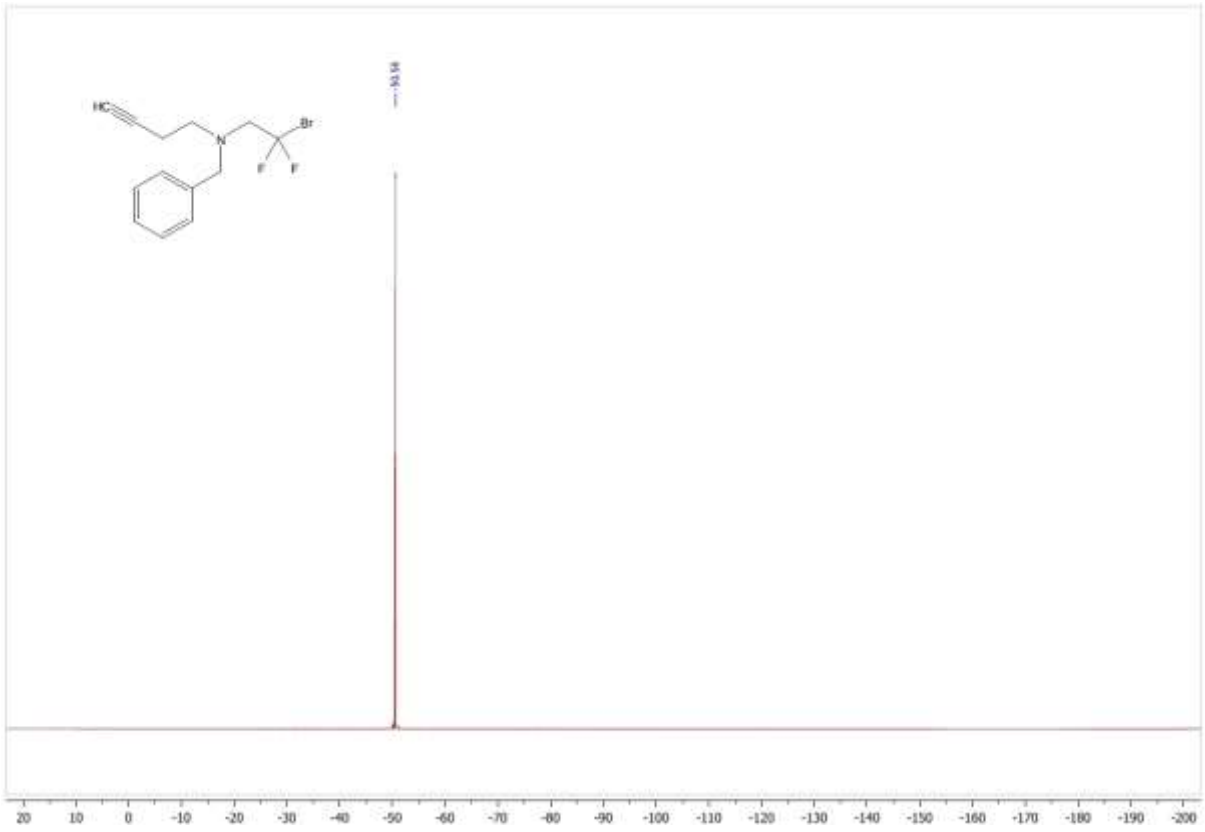
Supplementary Figure 37. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-yn-1-amine **44**



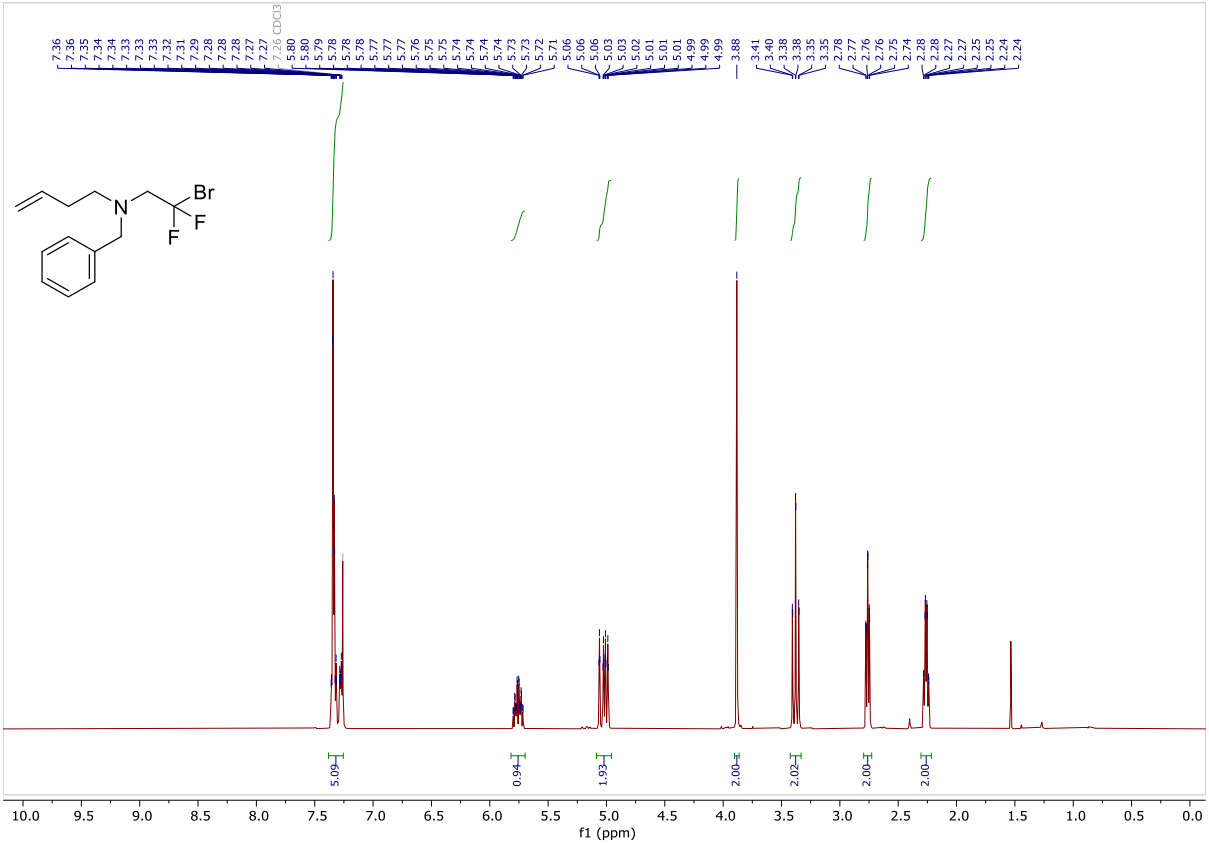
Supplementary Figure 38. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-yn-1-amine **44**



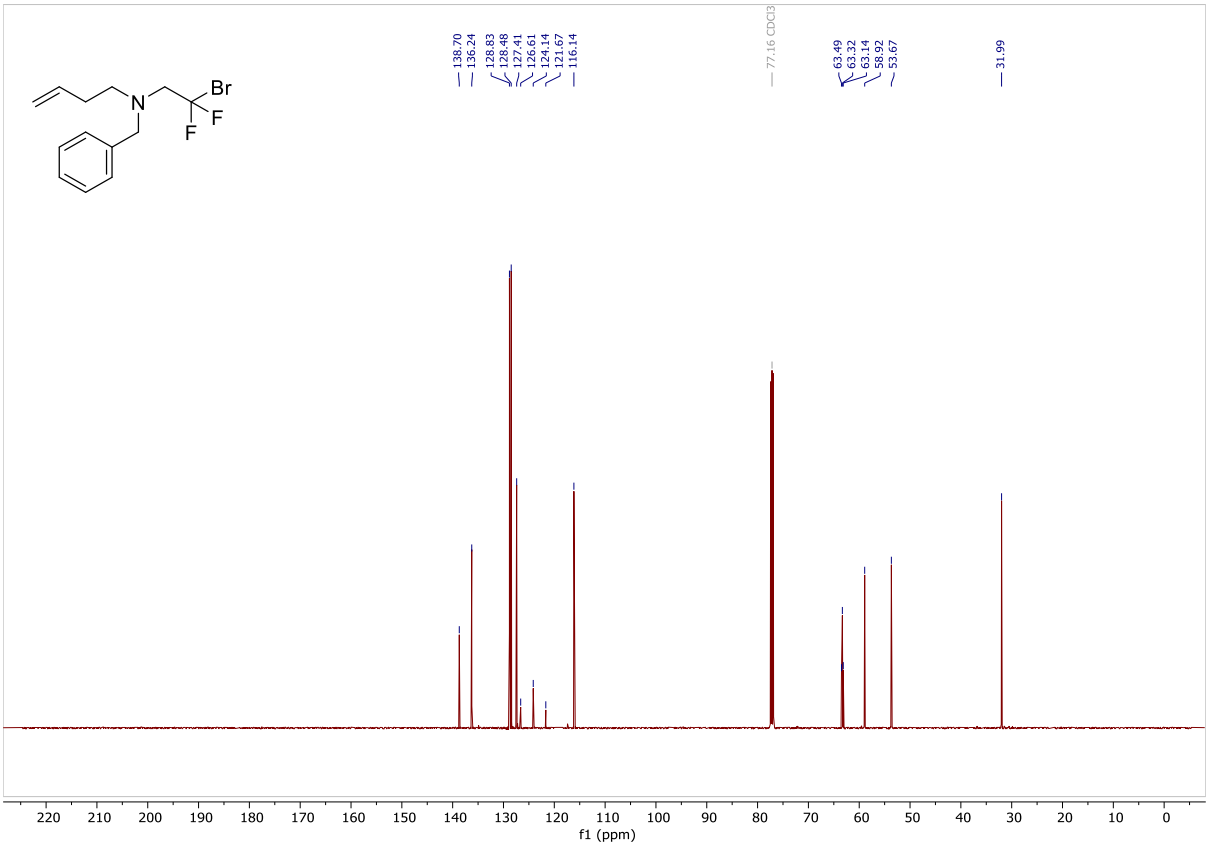
Supplementary Figure 39. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-yn-1-amine **44**



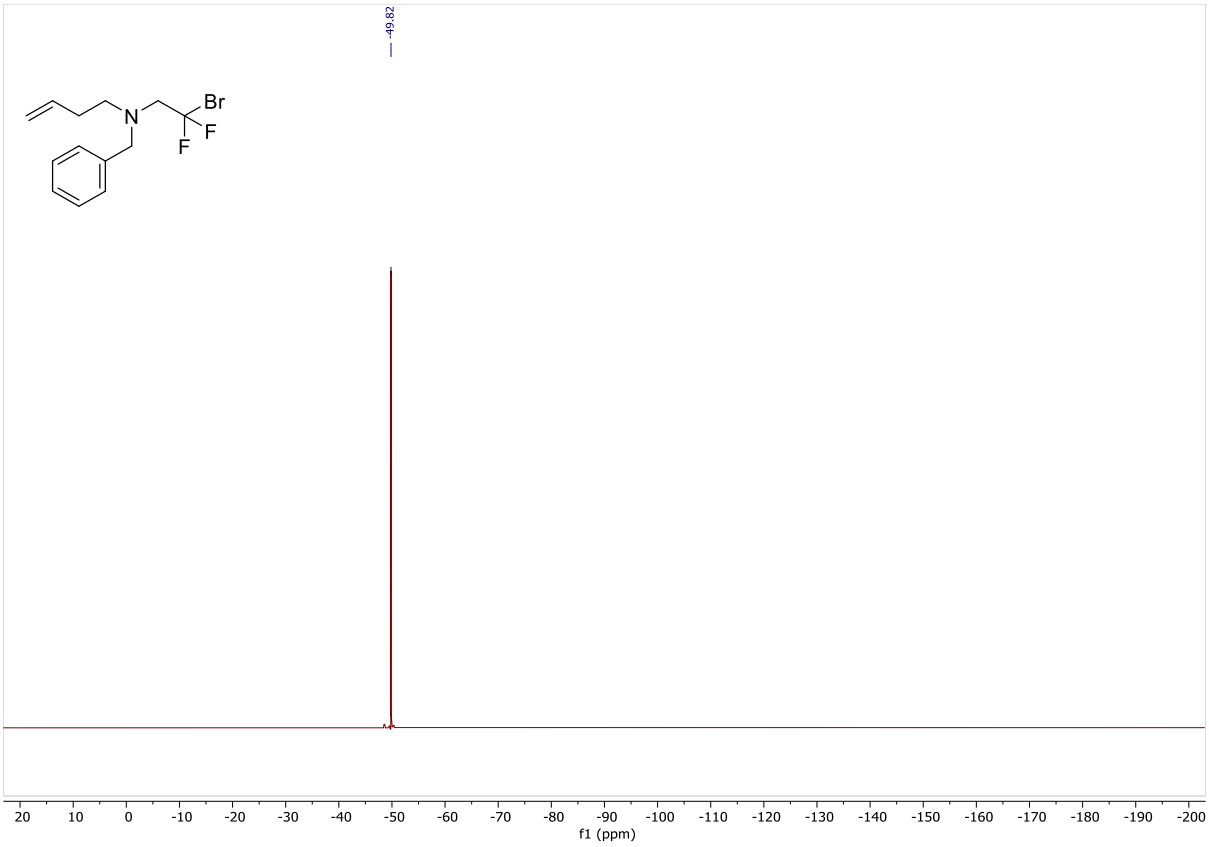
Supplementary Figure 40. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-en-1-amine **45**



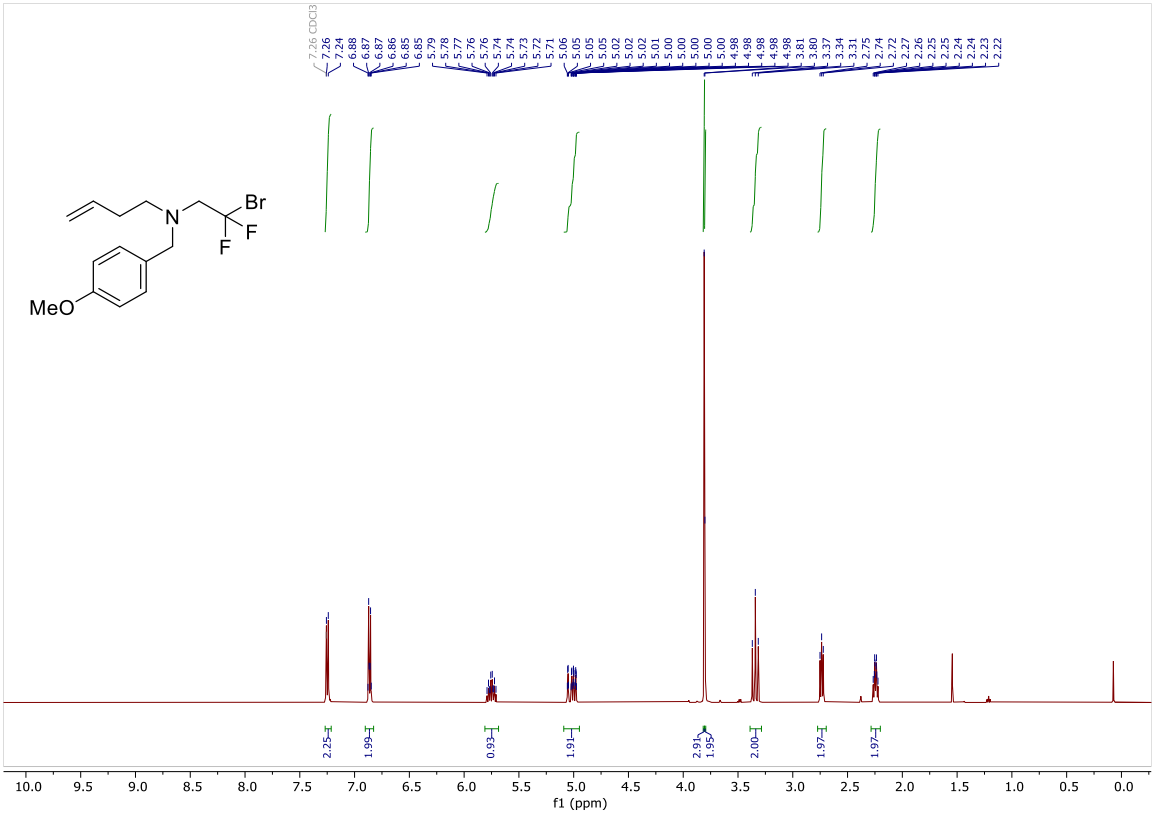
Supplementary Figure 41. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-en-1-amine **45**



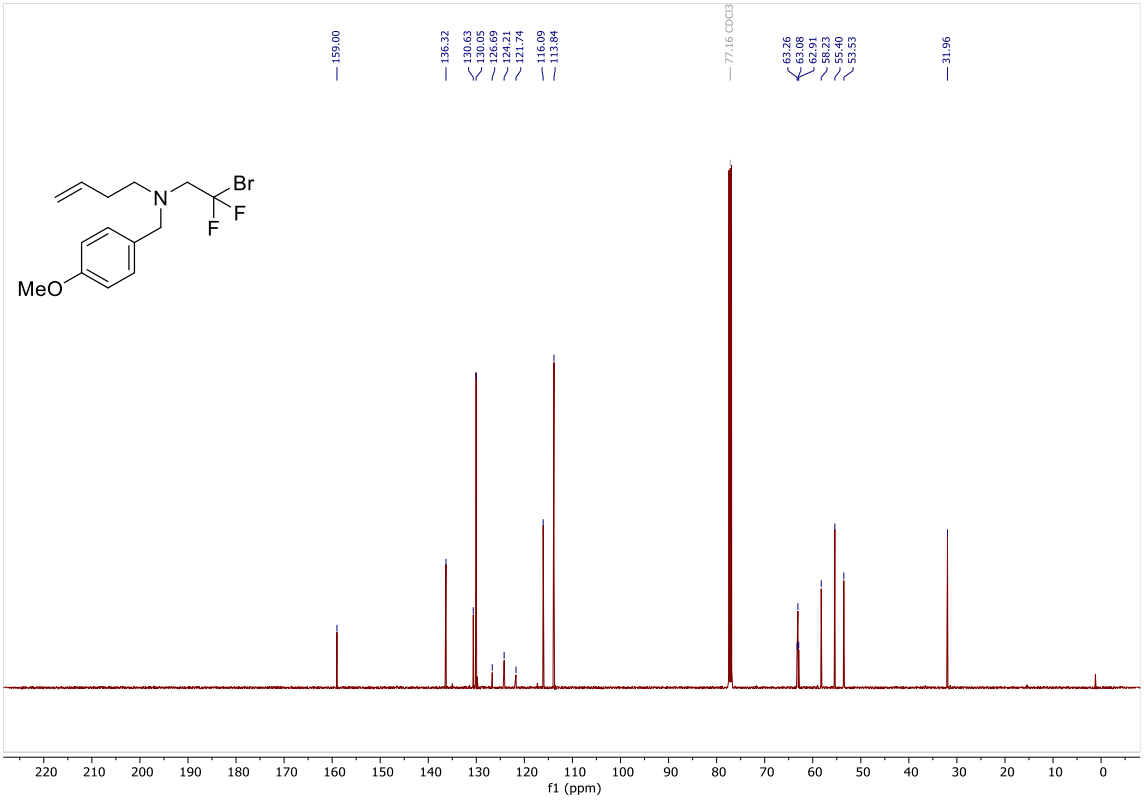
Supplementary Figure 42. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-3-en-1-amine **45**



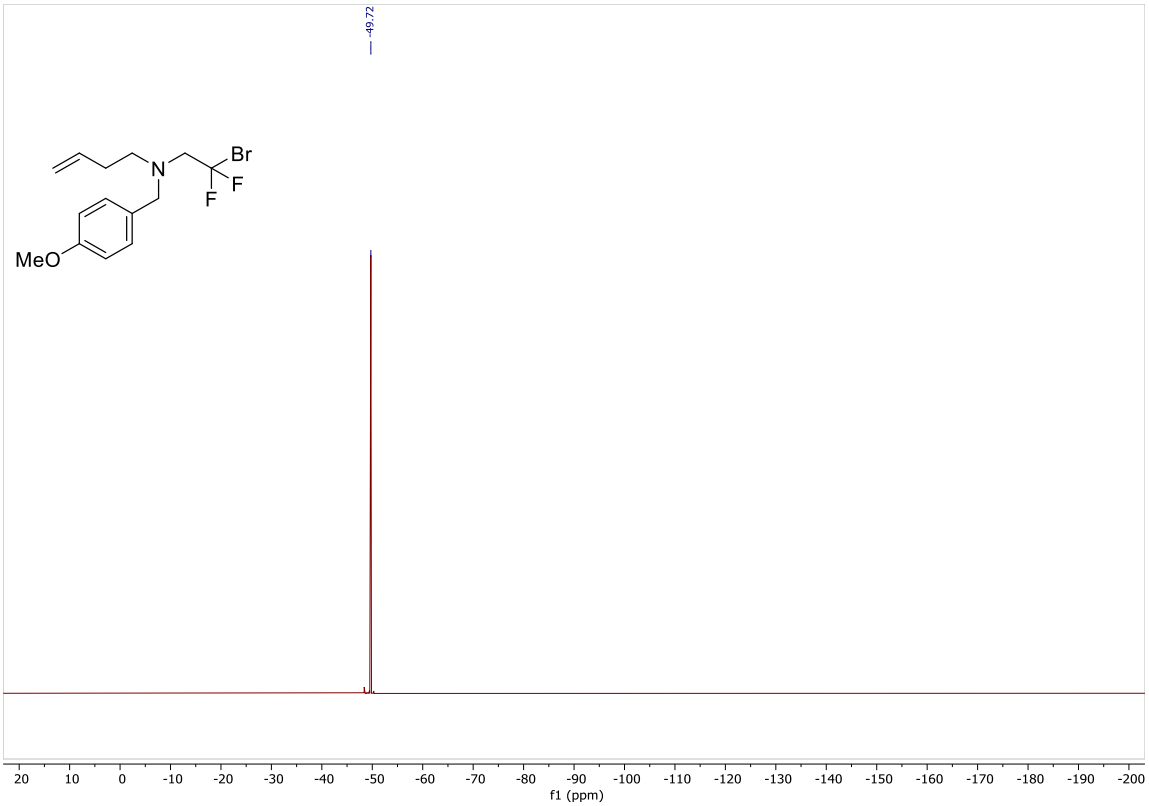
Supplementary Figure 43. ^{1}H NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)but-3-en-1-amine **46**



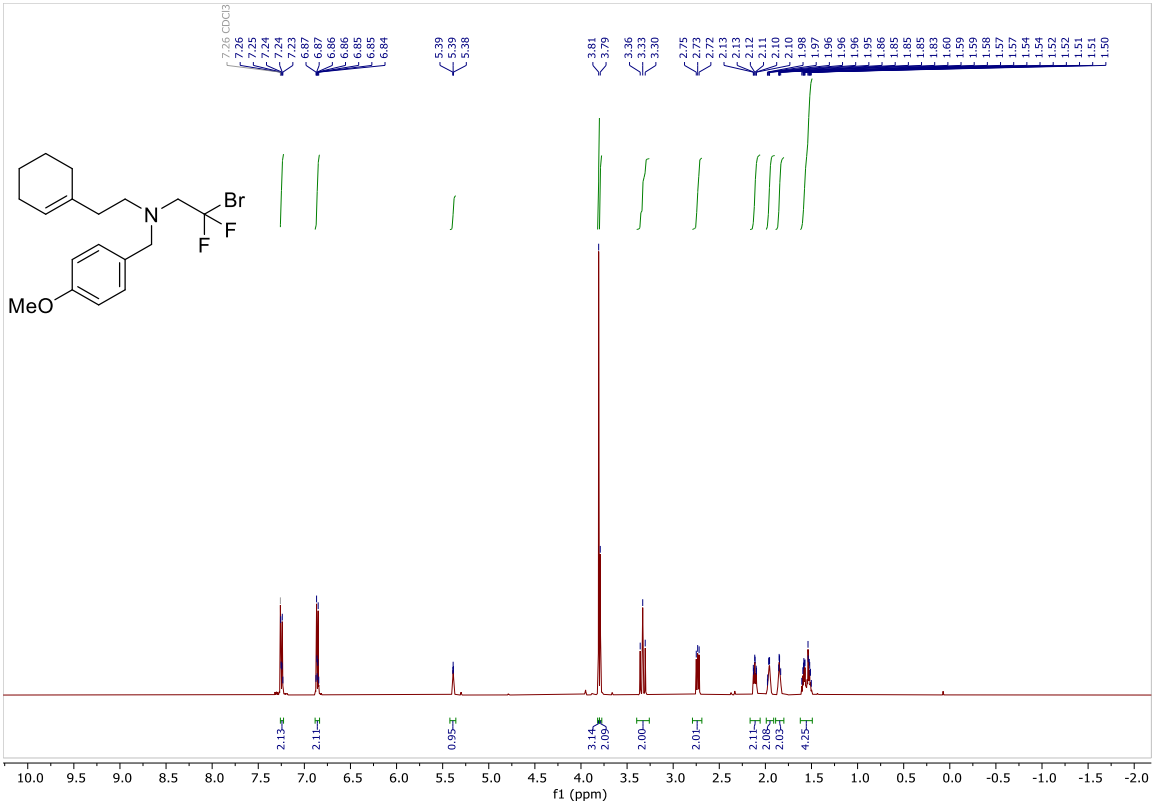
Supplementary Figure 44. ^{13}C NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)but-3-en-1-amine **46**



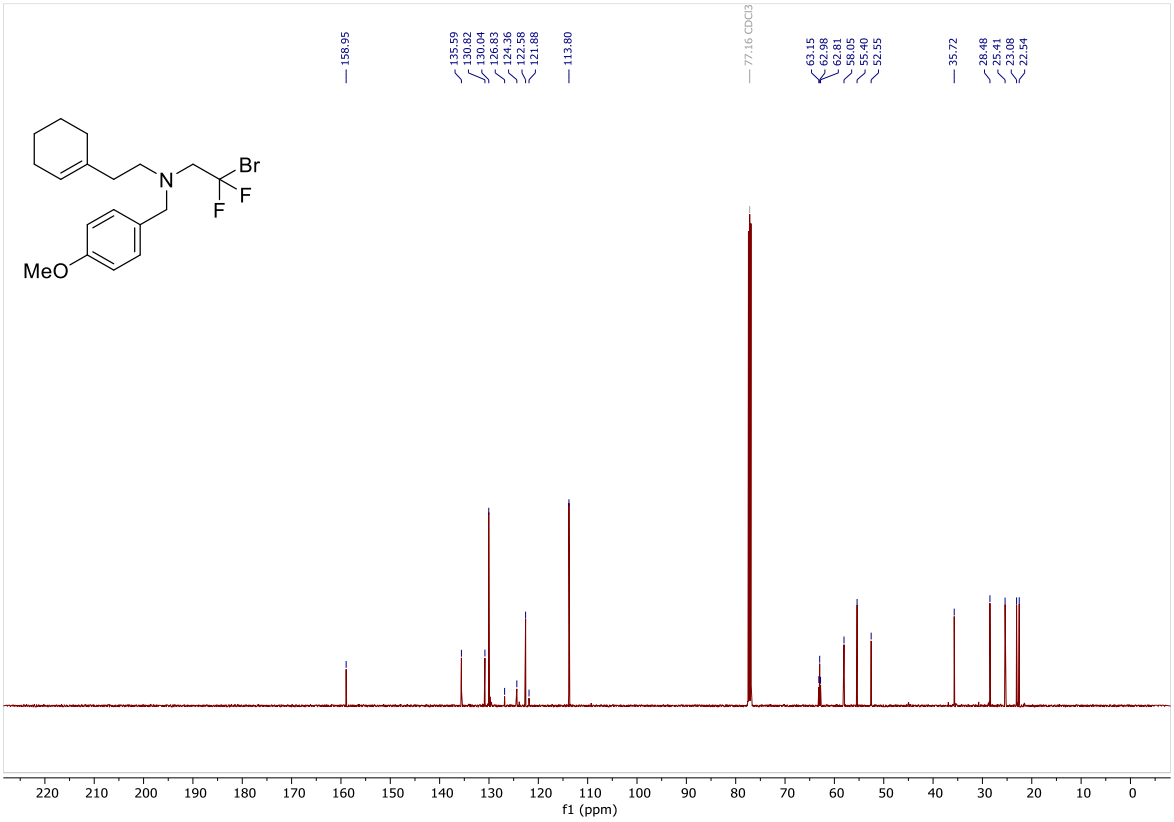
Supplementary Figure 45. ^{19}F NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)but-3-en-1-amine **46**



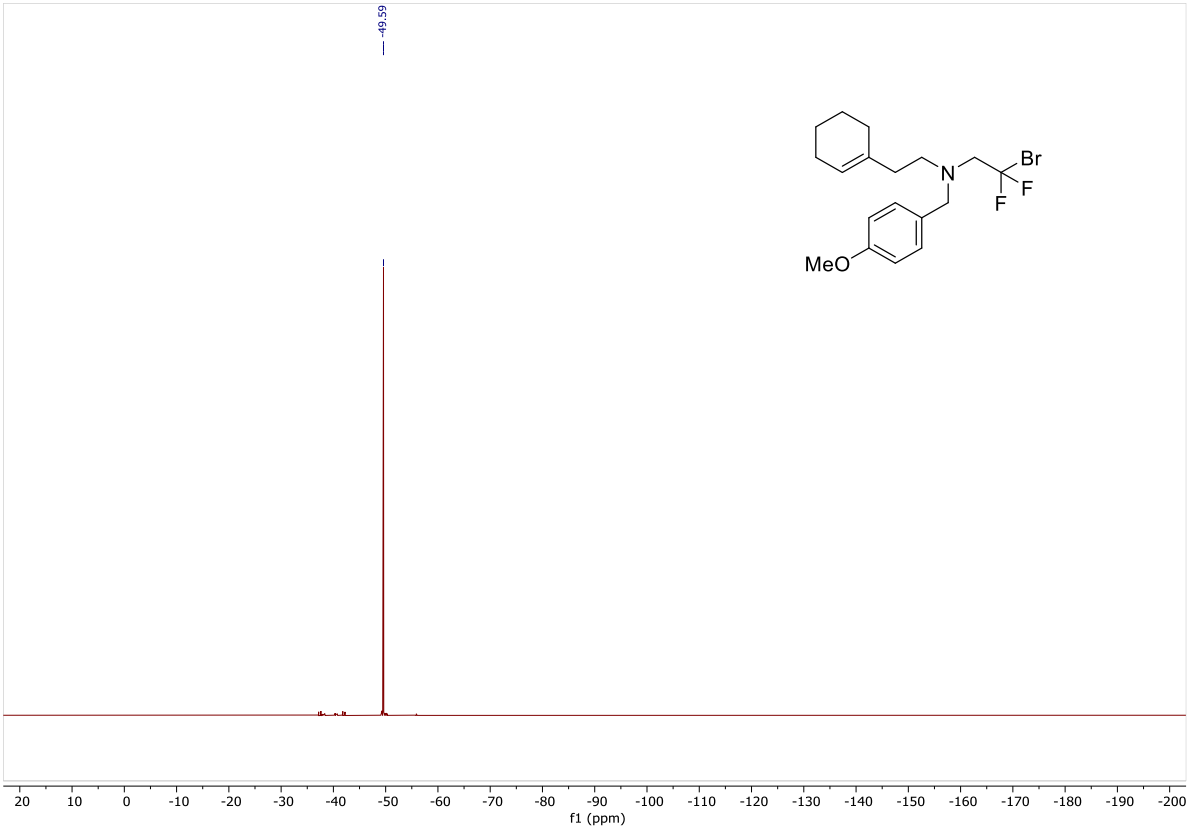
Supplementary Figure 46. ^{1}H NMR 2-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2,2-difluoro-*N*-(4-methoxybenzyl)ethan-1-amine **47**



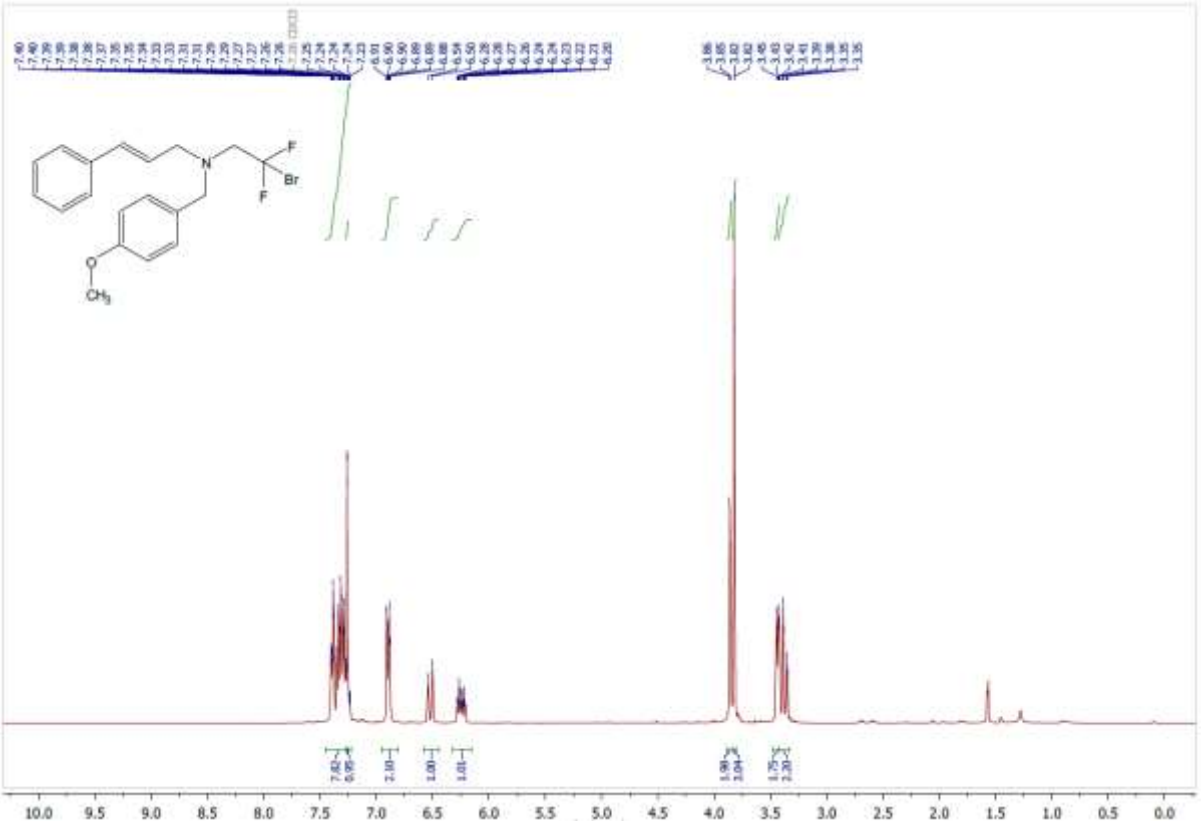
Supplementary Figure 47. ^{13}C NMR 2-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2,2-difluoro-*N*-(4-methoxybenzyl)ethan-1-amine **47**



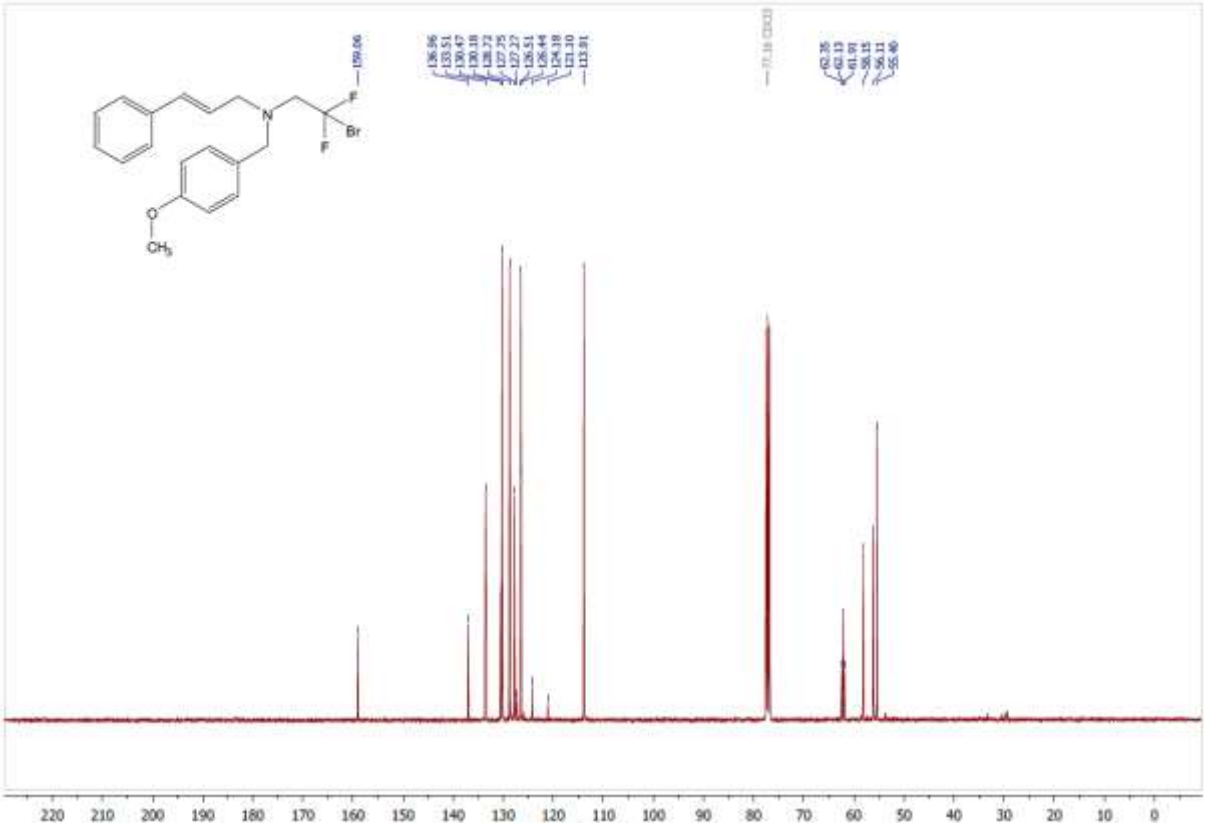
Supplementary Figure 48. ^{19}F NMR 2-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2,2-difluoro-*N*-(4-methoxybenzyl)ethan-1-amine **47**



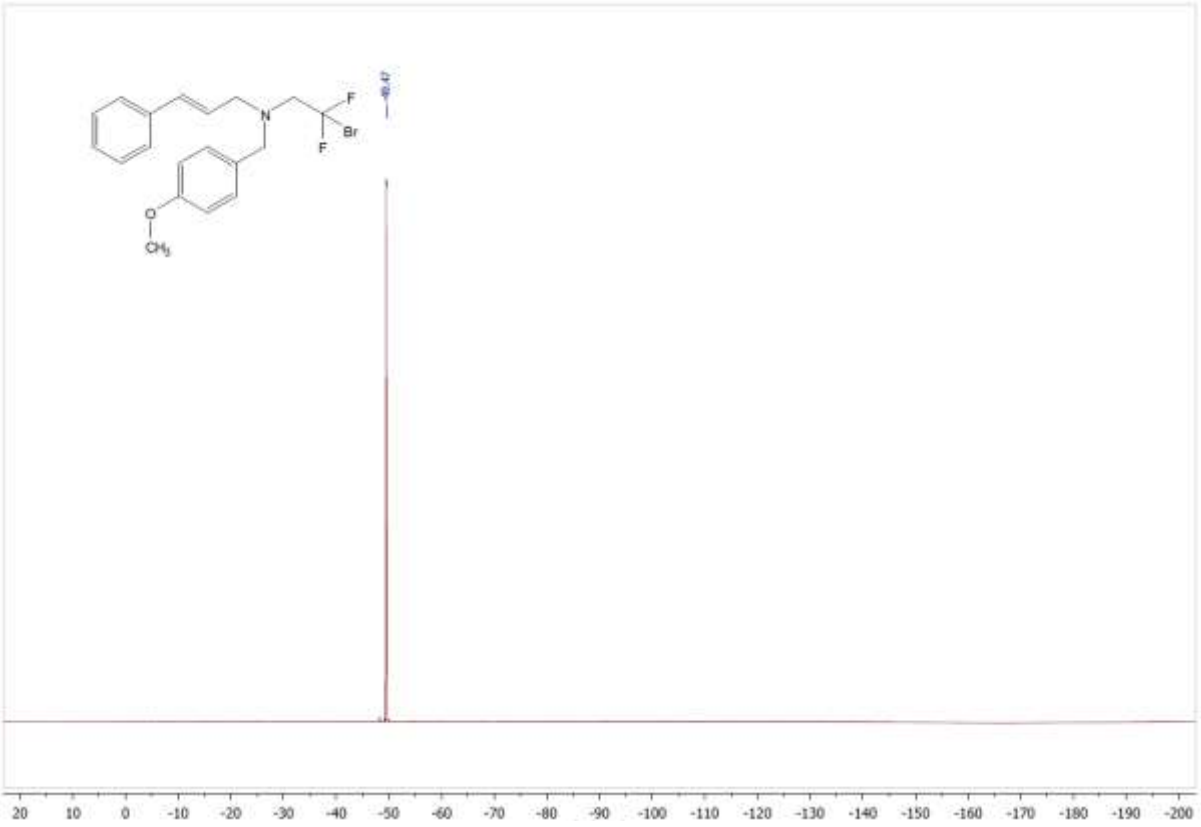
Supplementary Figure 49. ^{1}H NMR (*E*)-*N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)-3-phenylprop-2-en-1-amine **48**



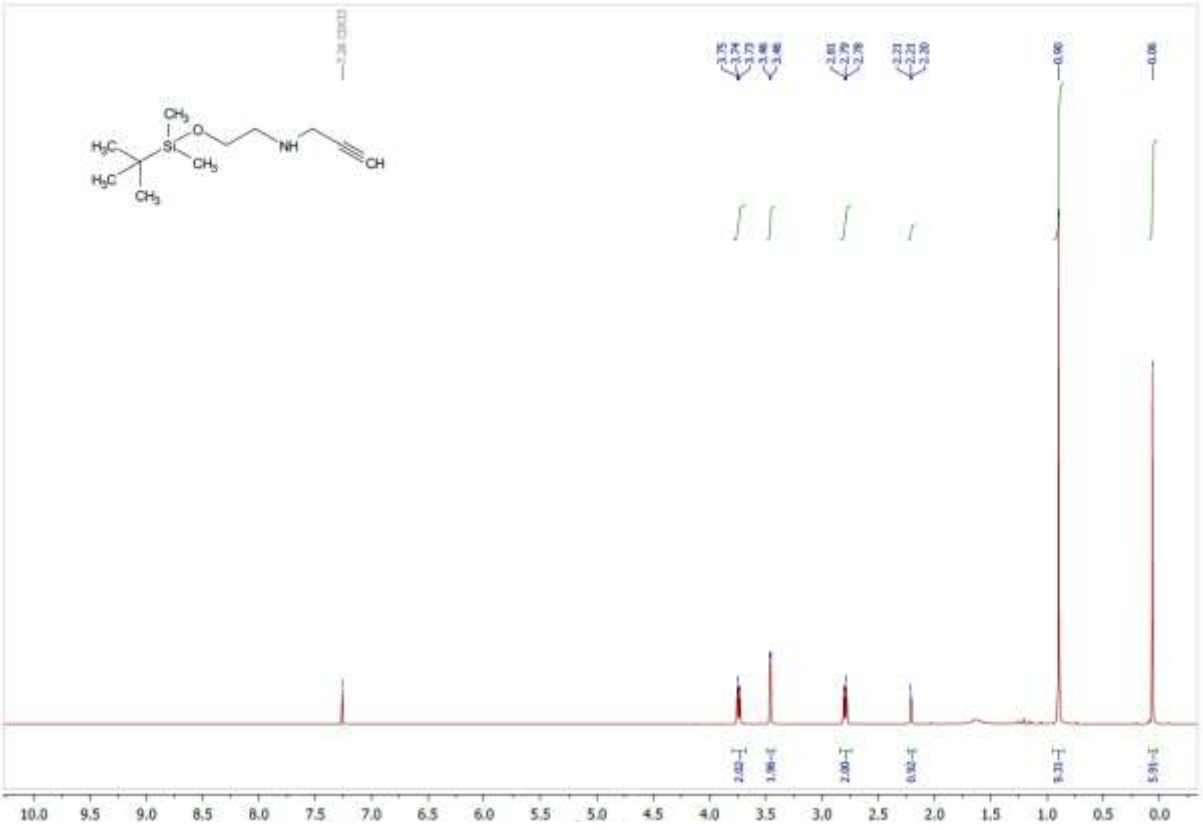
Supplementary Figure 50. ^{13}C NMR *(E)*-*N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)-3-phenylprop-2-en-1-amine **48**



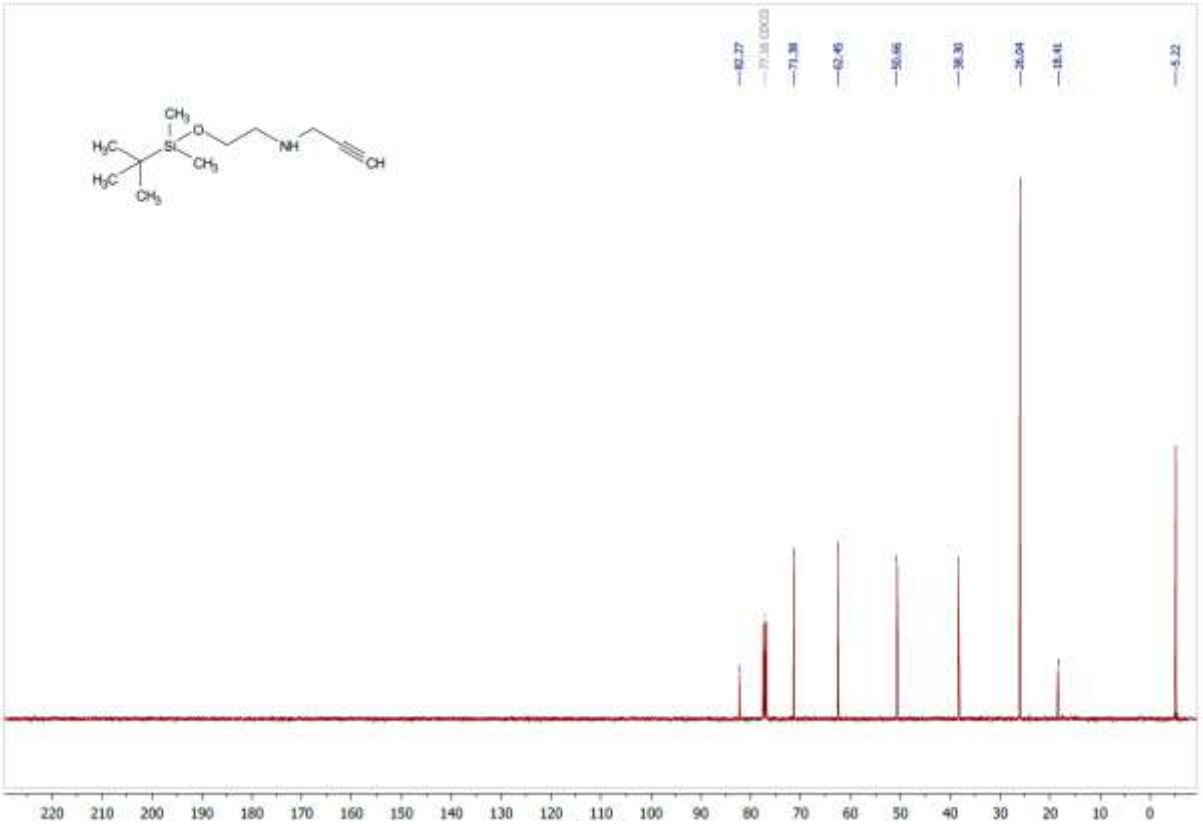
Supplementary Figure 51. ^{19}F NMR *(E)*-*N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)-3-phenylprop-2-en-1-amine **48**



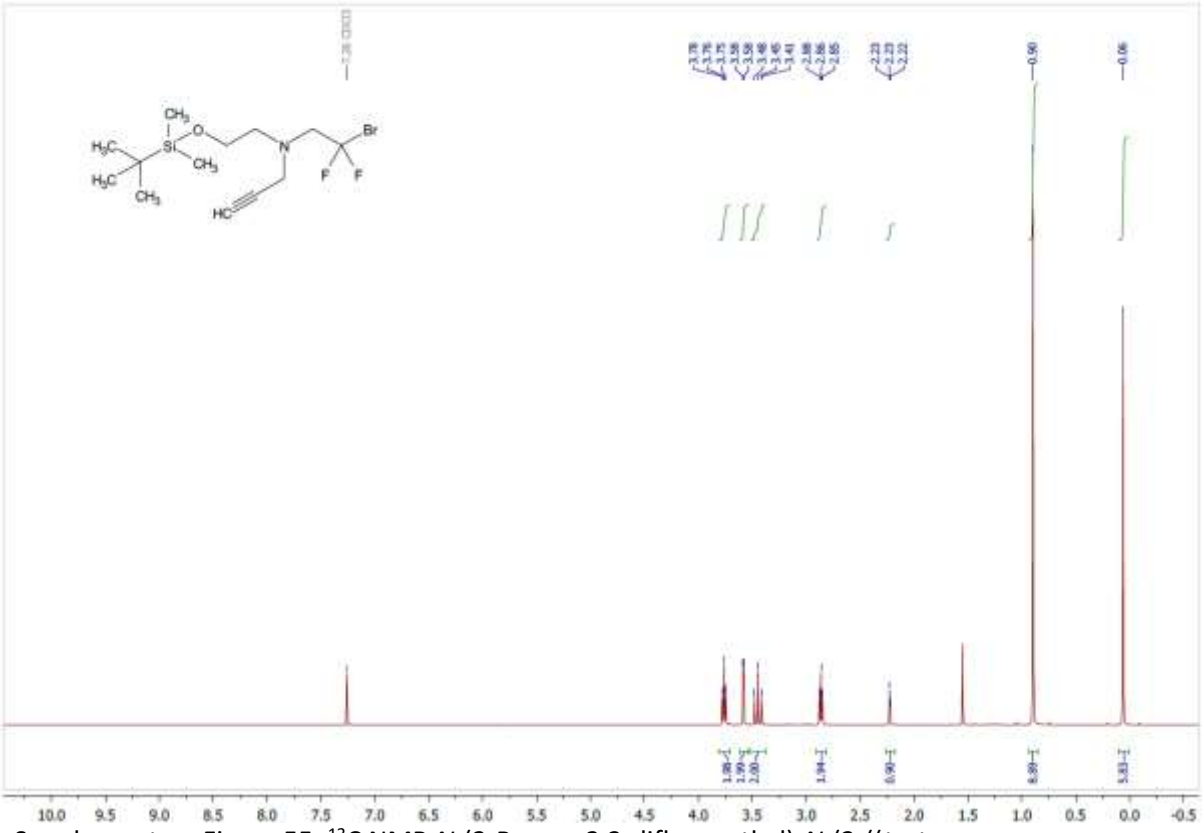
Supplementary Figure 52. ^{1}H NMR *N*-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **49**



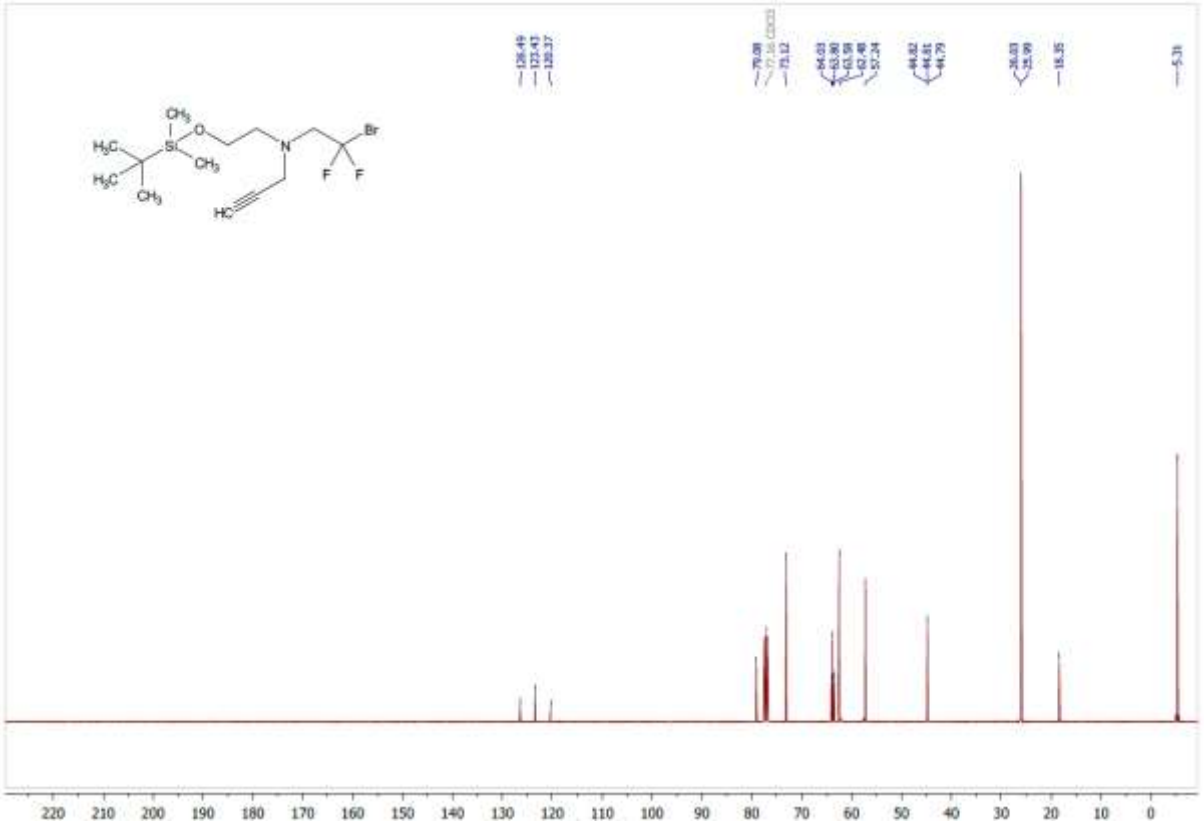
Supplementary Figure 53. ^{13}C NMR *N*-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **49**



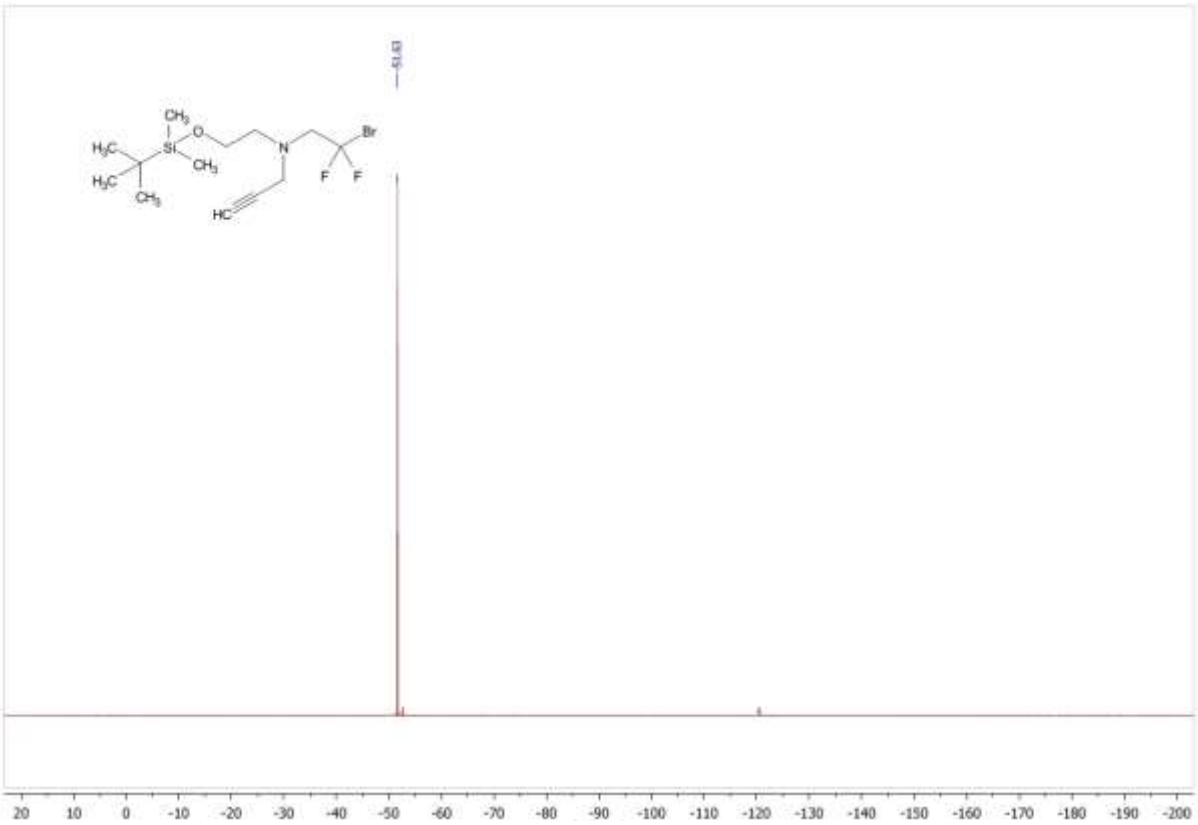
Supplementary Figure 54. ^{1}H NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **3**



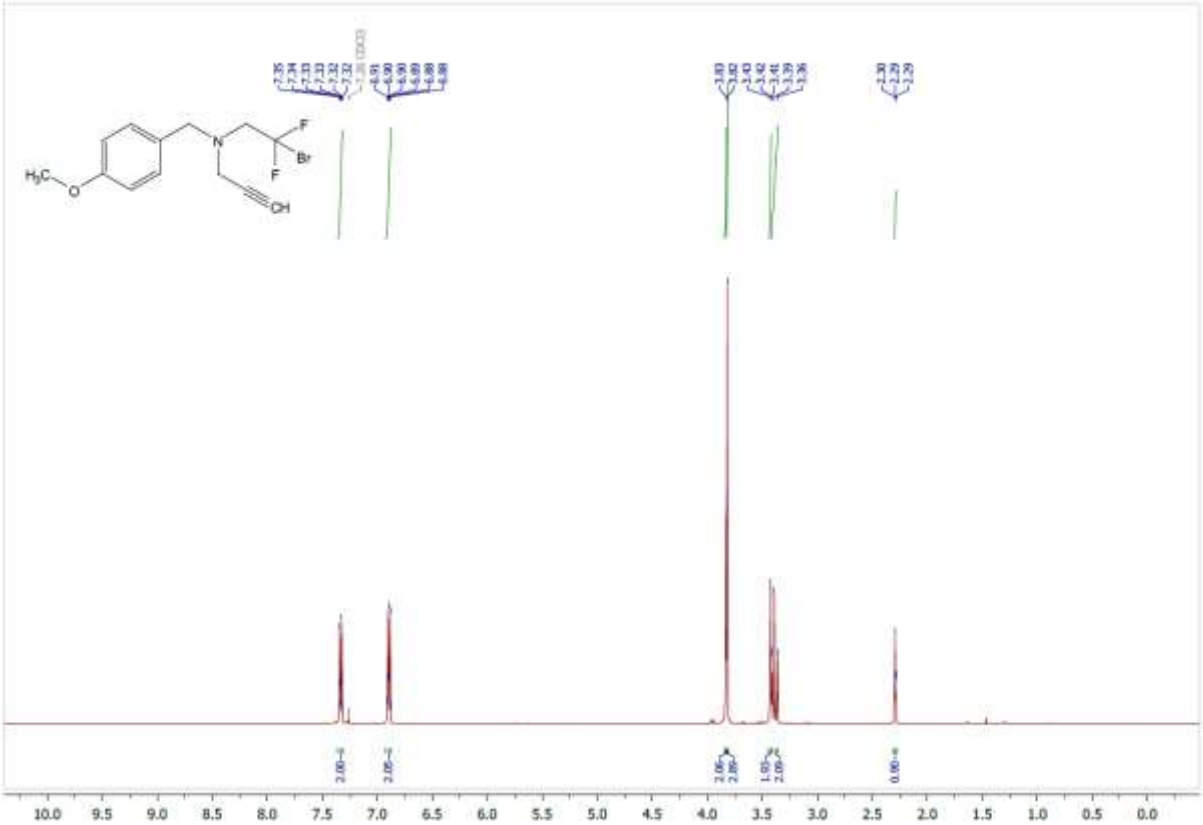
Supplementary Figure 55. ^{13}C NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **3**



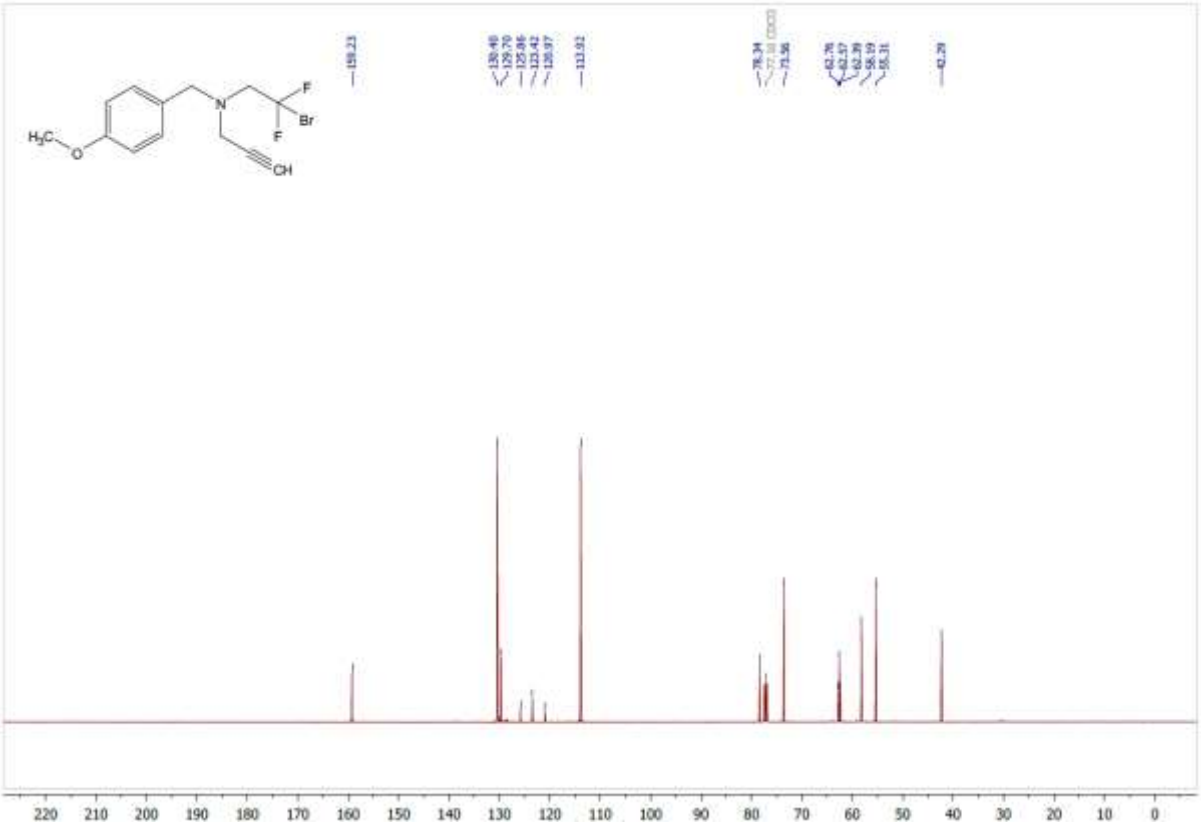
Supplementary Figure 56. ^{19}F NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)prop-2-yn-1-amine **3**



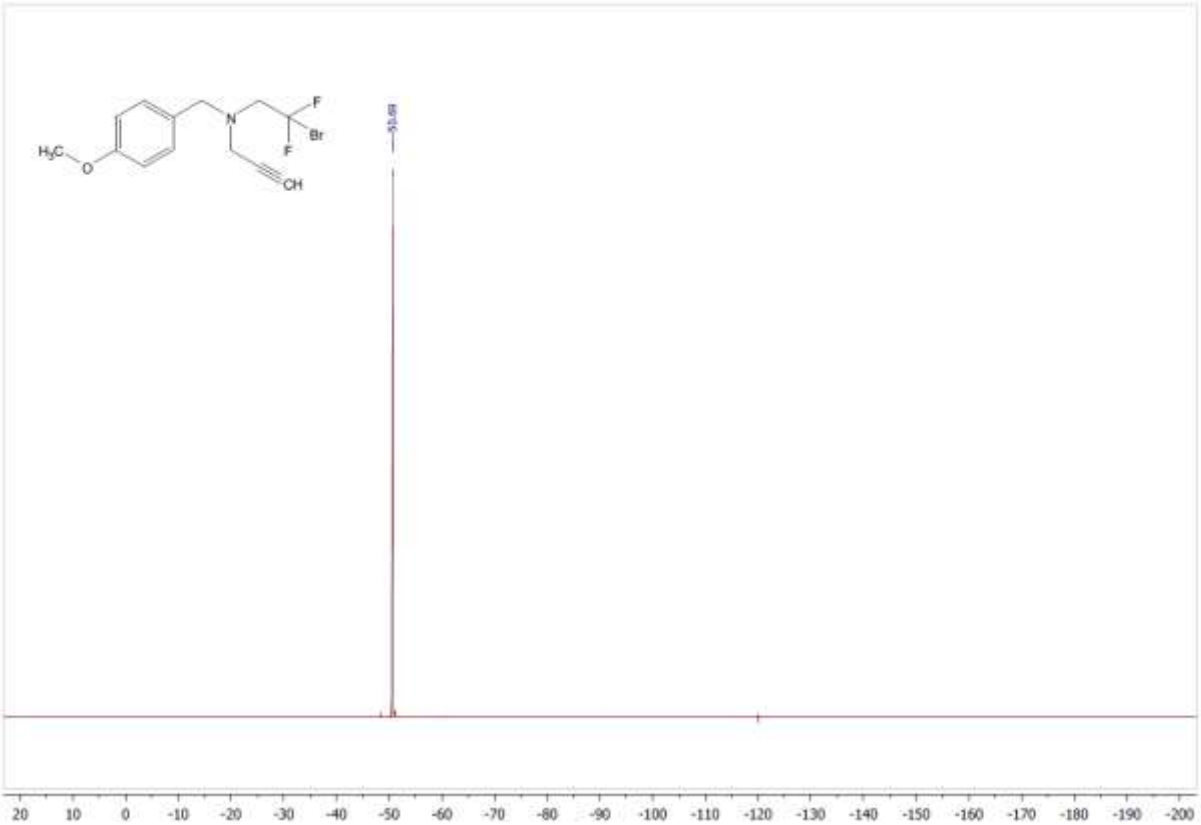
Supplementary Figure 57. ^{1}H NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine **29**



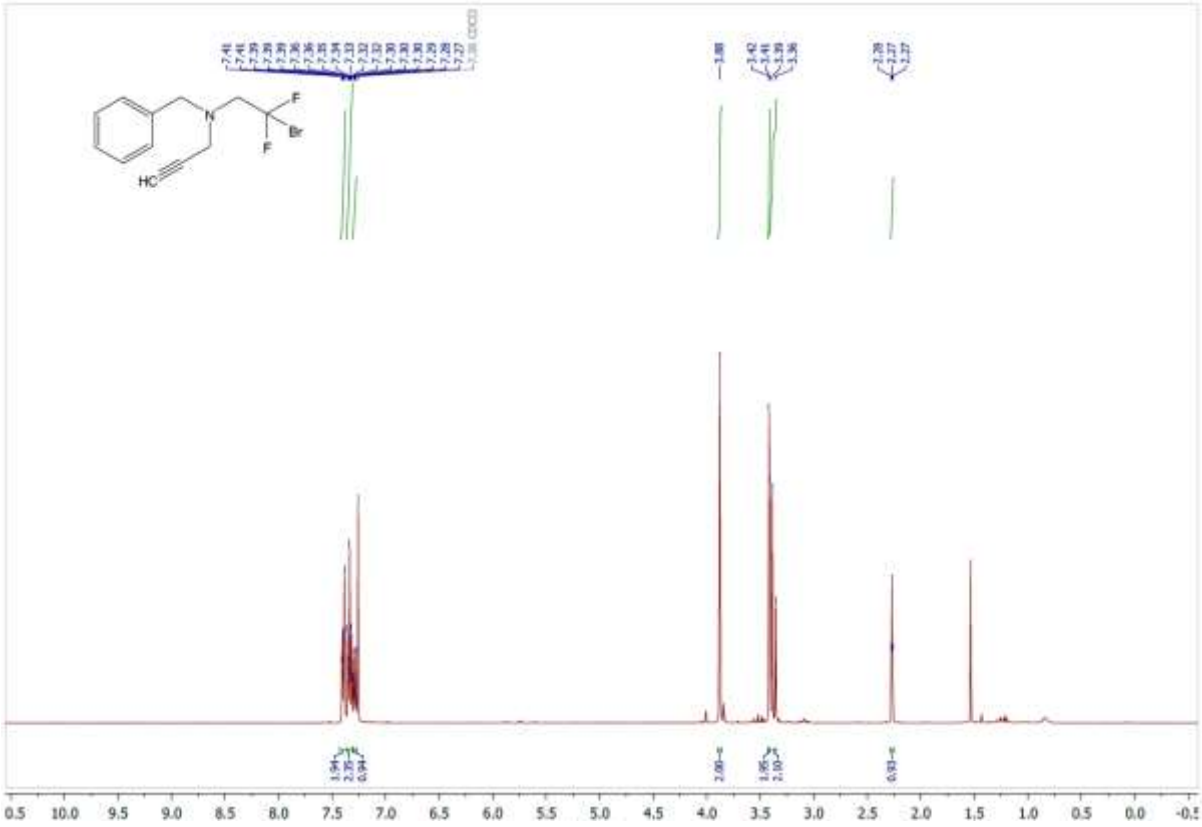
Supplementary Figure 58. ^{13}C NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine **29**



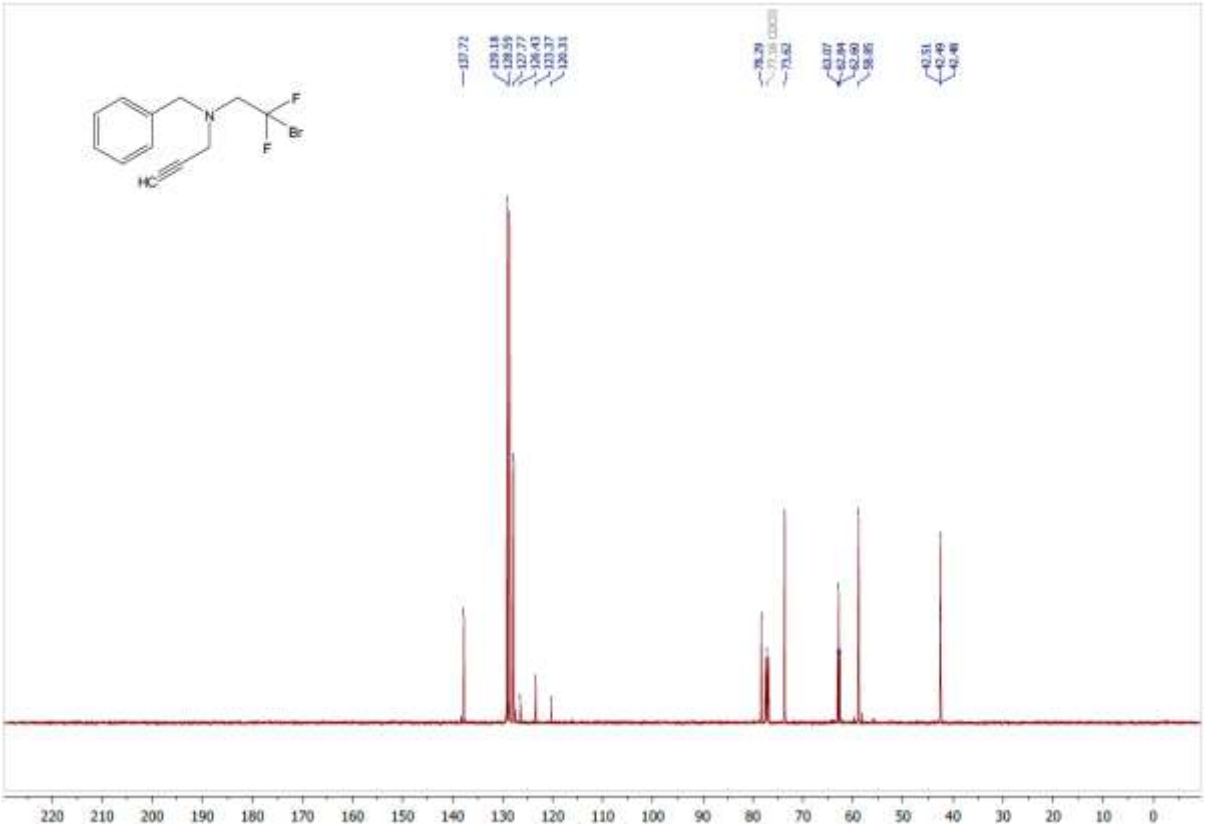
Supplementary Figure 59. ^{19}F NMR *N*-(2-Bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)prop-2-yn-1-amine **29**



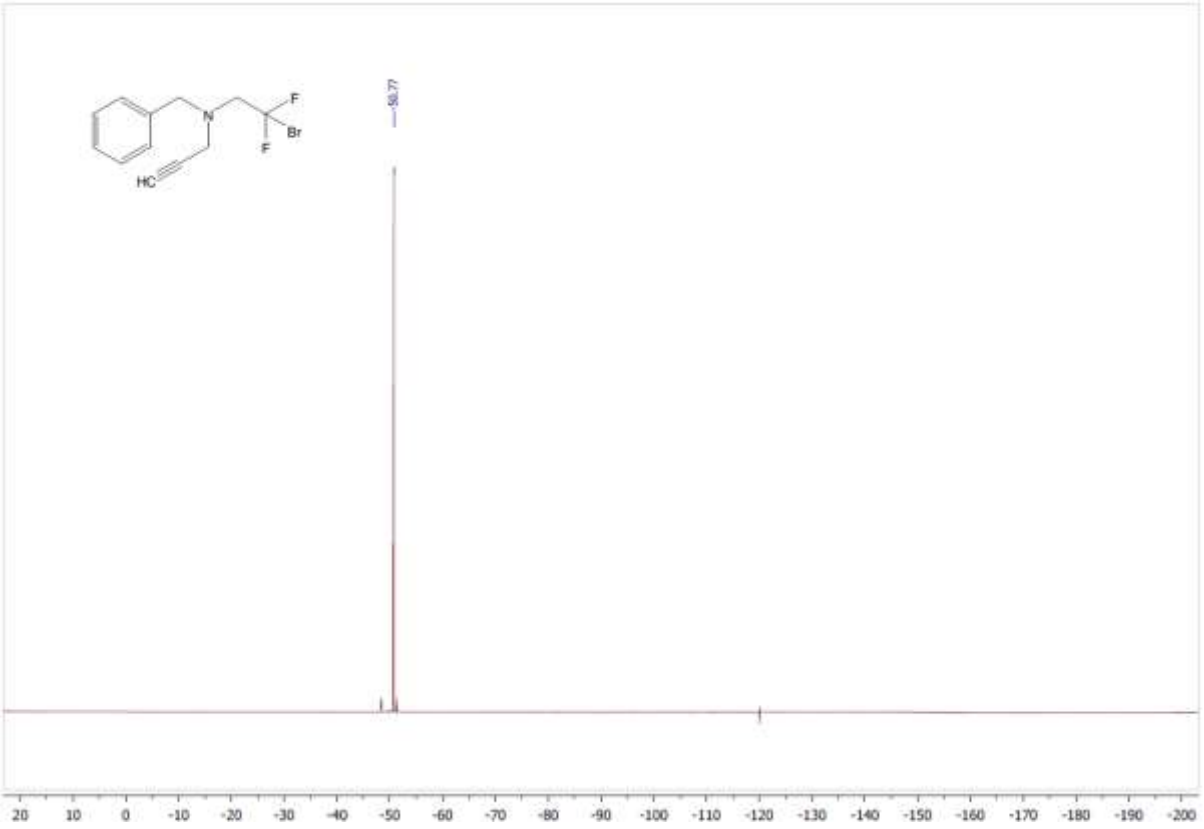
Supplementary Figure 60. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)prop-2-yn-1-amine **50**



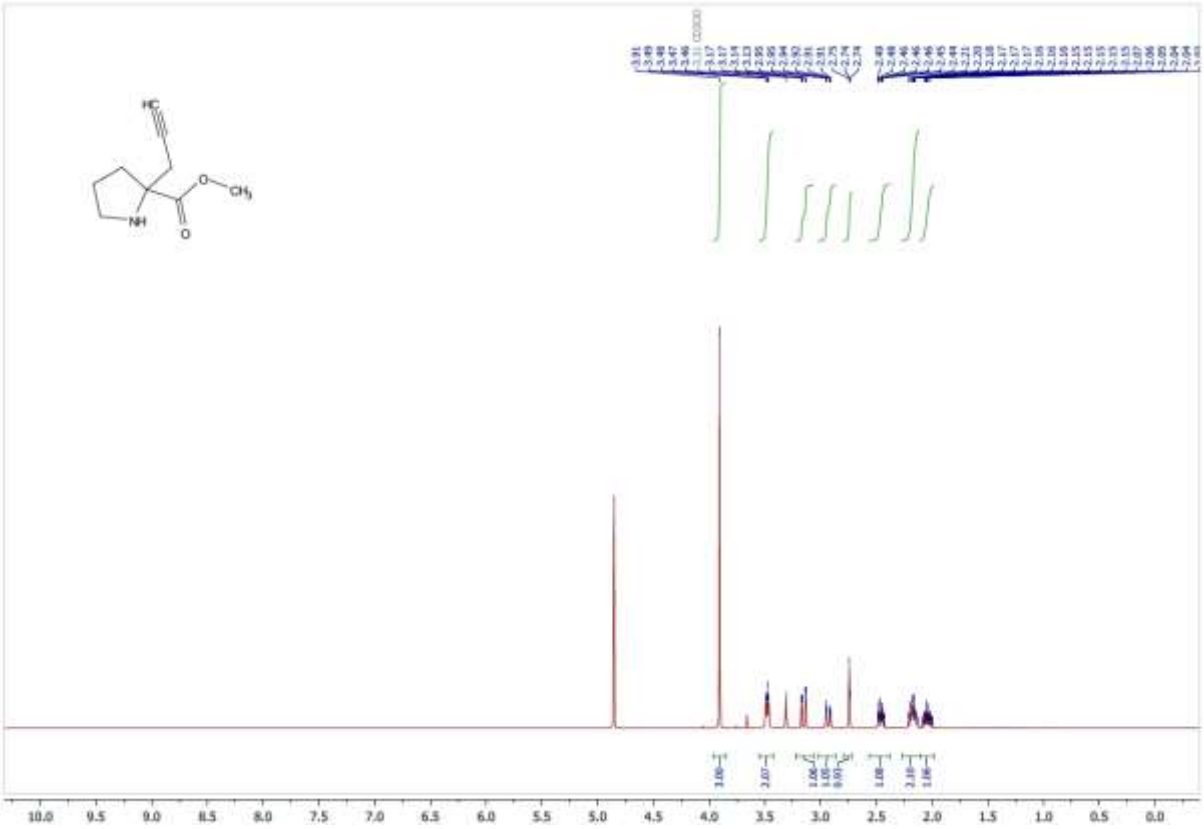
Supplementary Figure 61. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)prop-2-yn-1-amine **50**



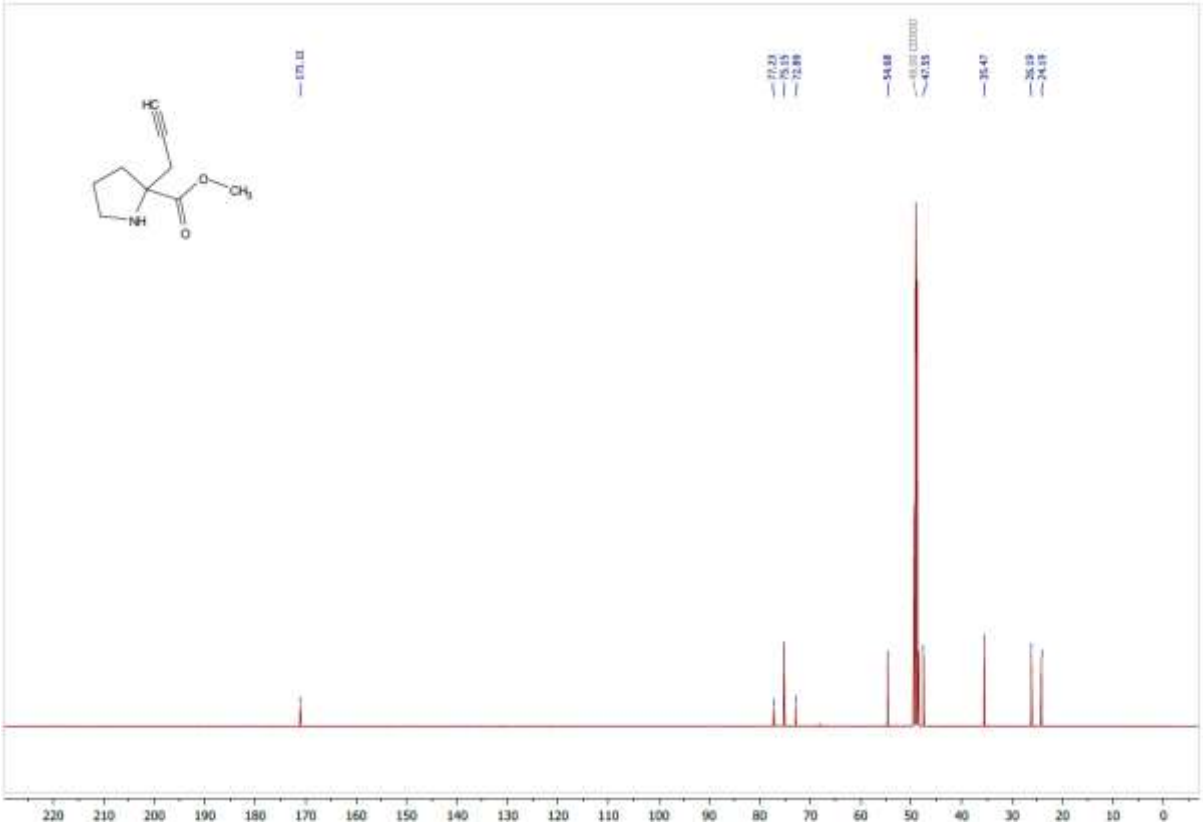
Supplementary Figure 62. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)prop-2-yn-1-amine **50**



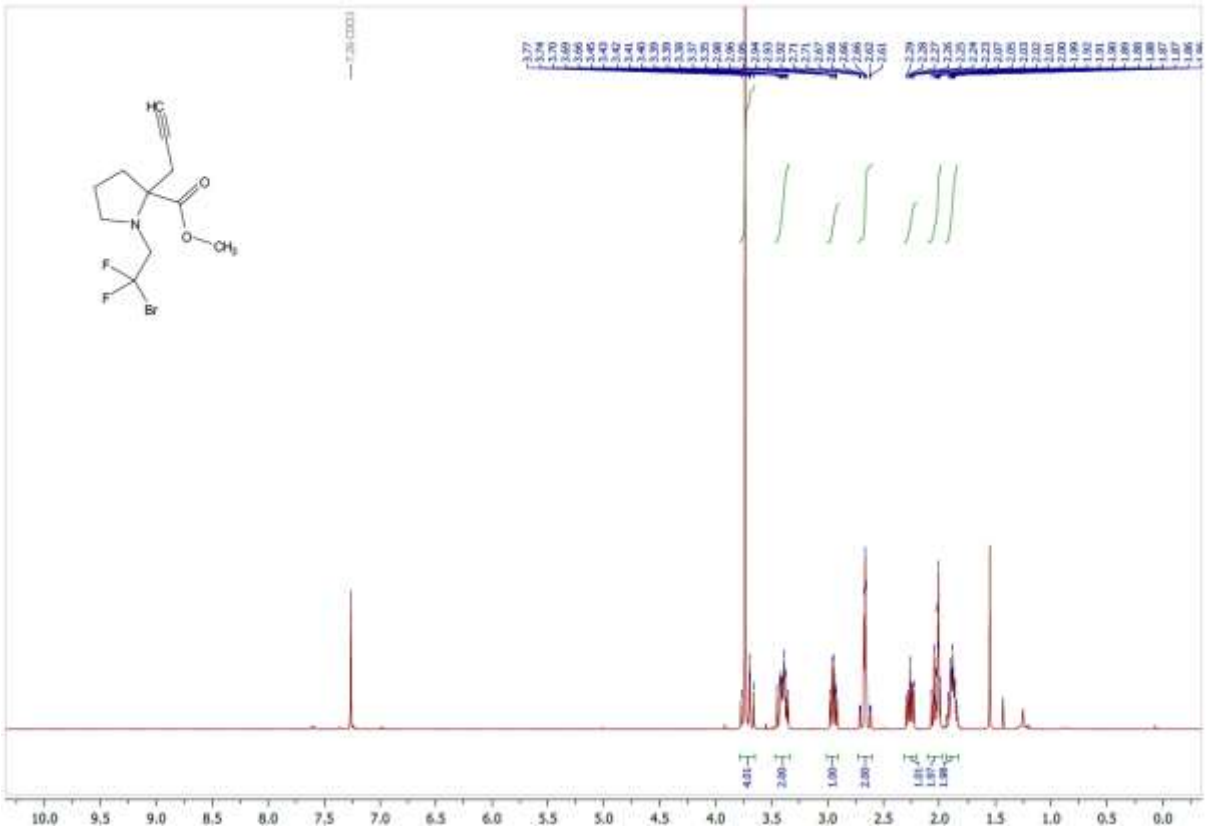
Supplementary Figure 63. ^{1}H NMR Methyl 2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate hydrochloride **51**



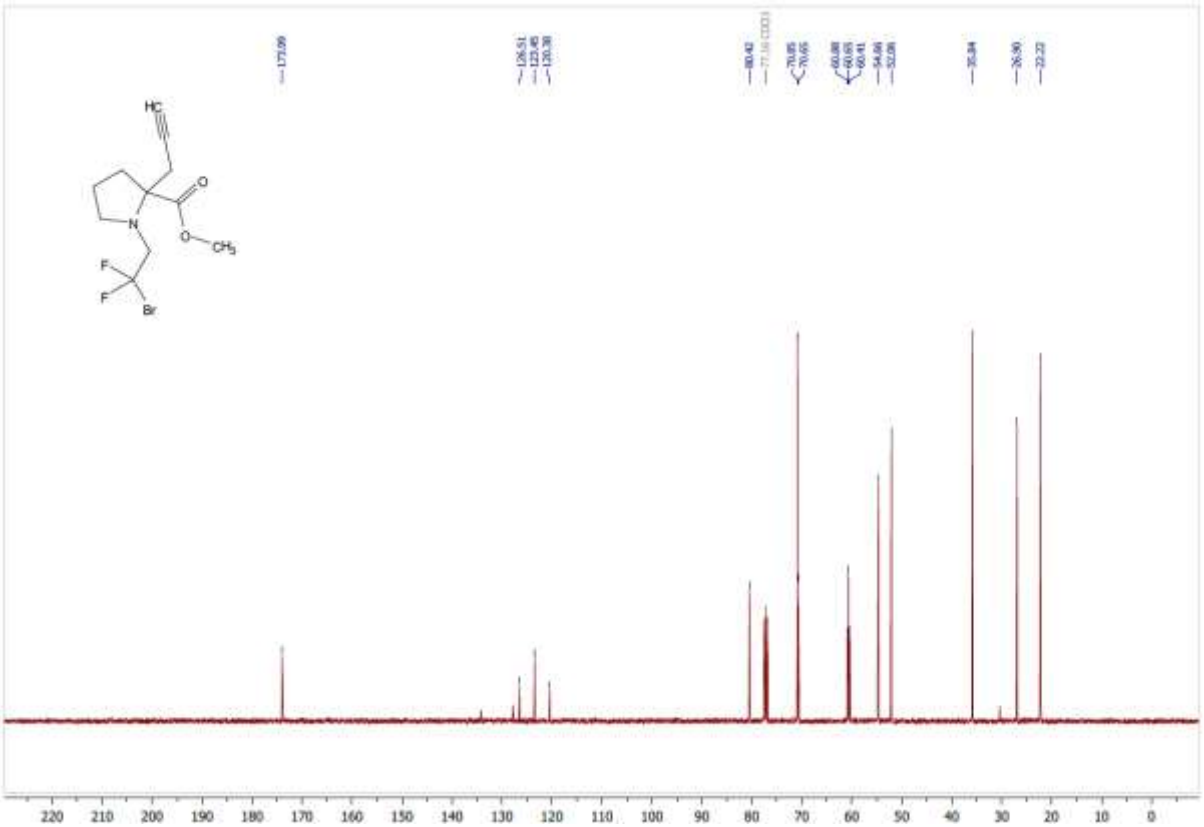
Supplementary Figure 64. ^{13}C NMR Methyl 2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate hydrochloride **51**



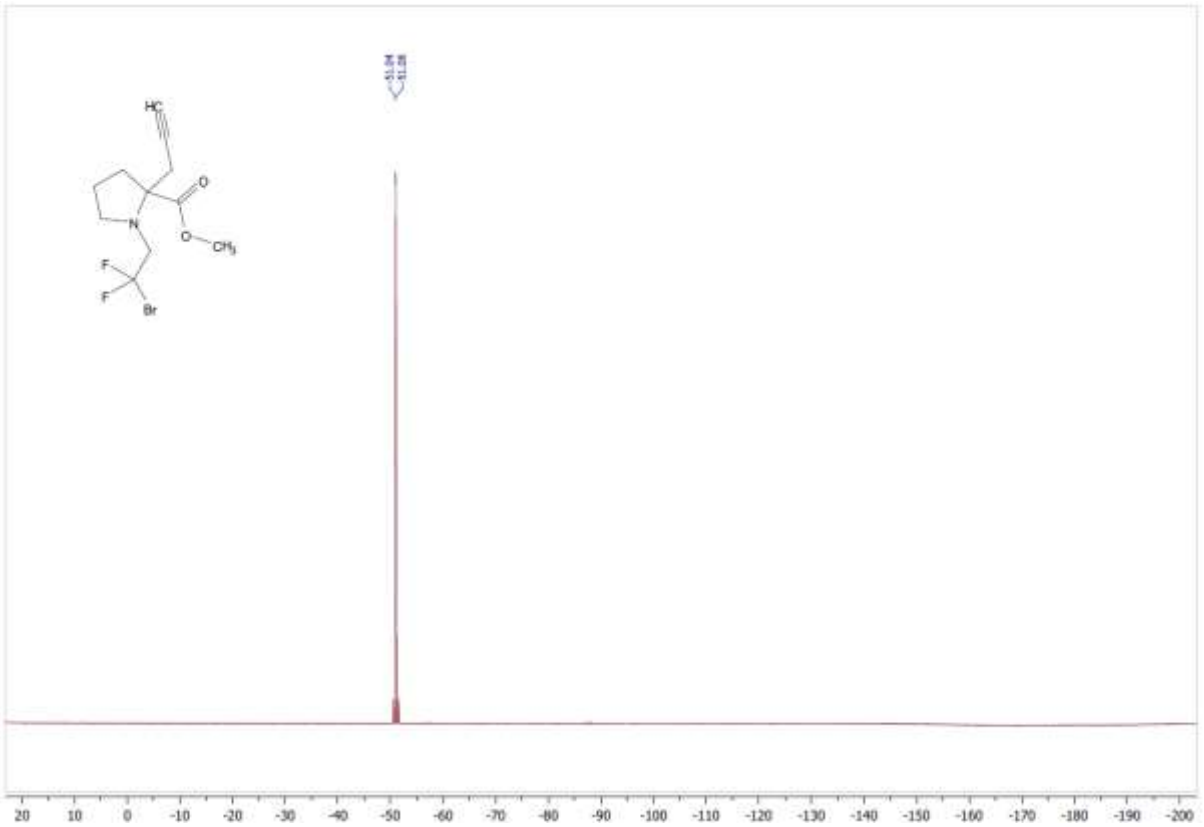
Supplementary Figure 65. ^{1}H NMR Methyl 1-(2-bromo-2,2-difluoroethyl)-2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **52**



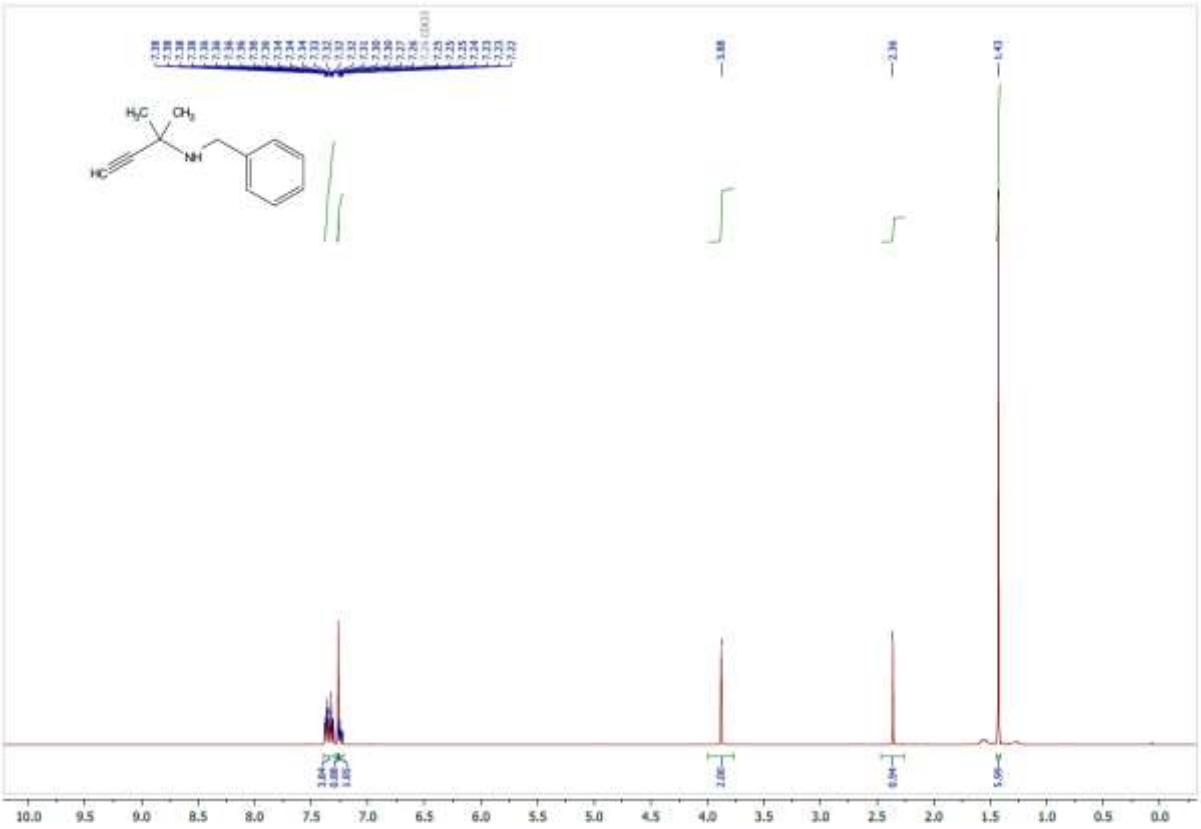
Supplementary Figure 66. ^{13}C NMR Methyl 1-(2-bromo-2,2-difluoroethyl)-2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **52**



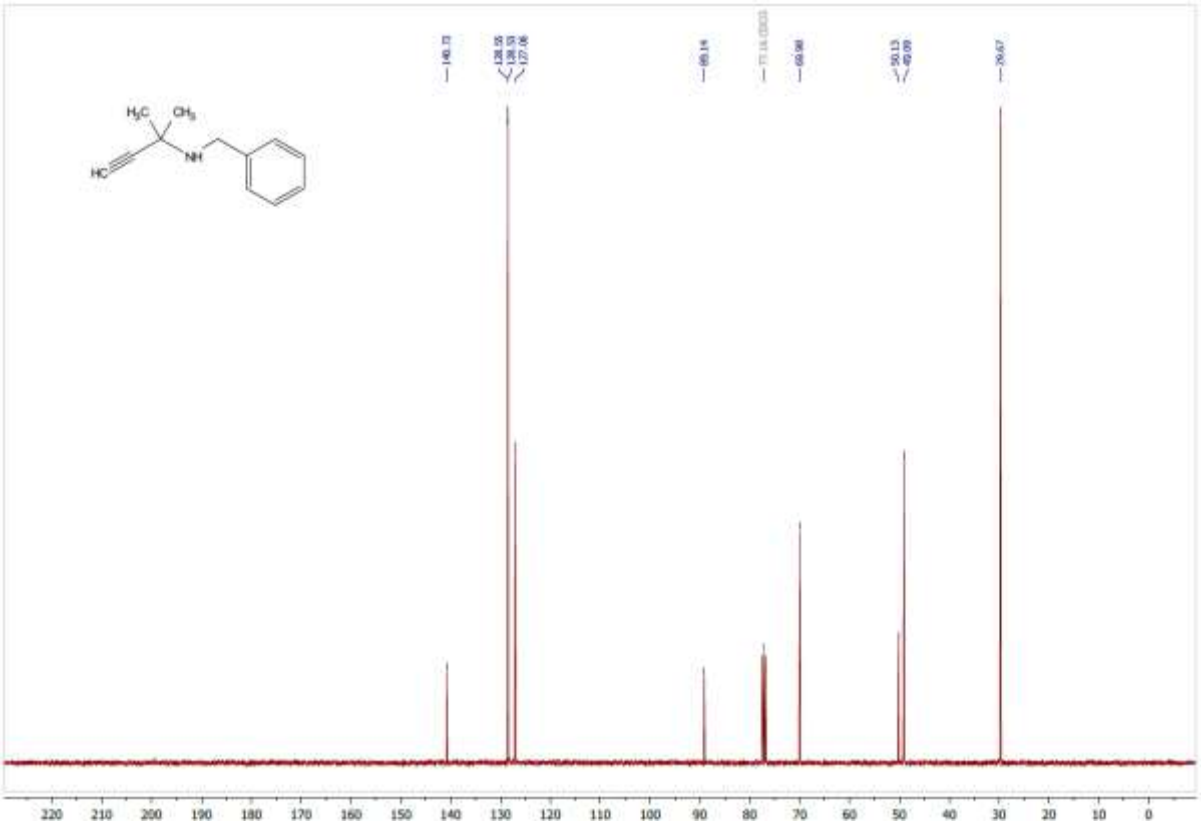
Supplementary Figure 67. ^{19}F NMR Methyl 1-(2-bromo-2,2-difluoroethyl)-2-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate **52**



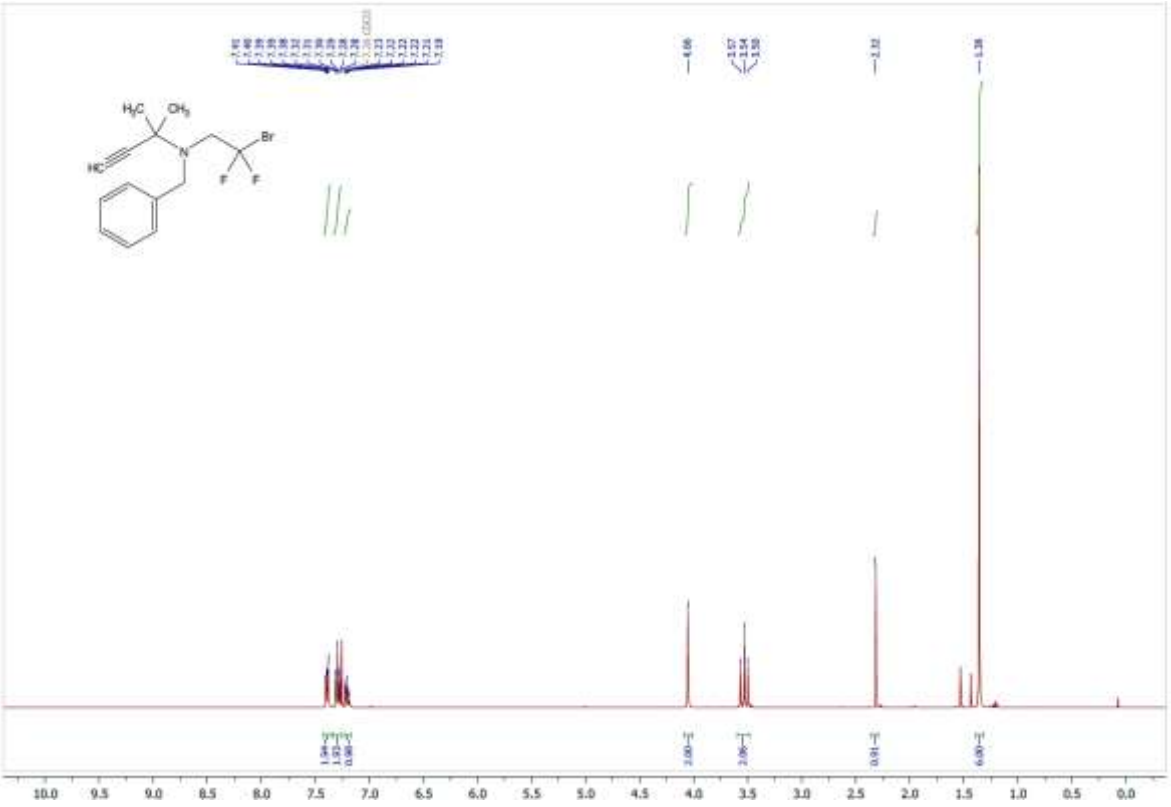
Supplementary Figure 68. ^{1}H NMR *N*-Benzyl-2-methylbut-3-yn-2-amine **53**



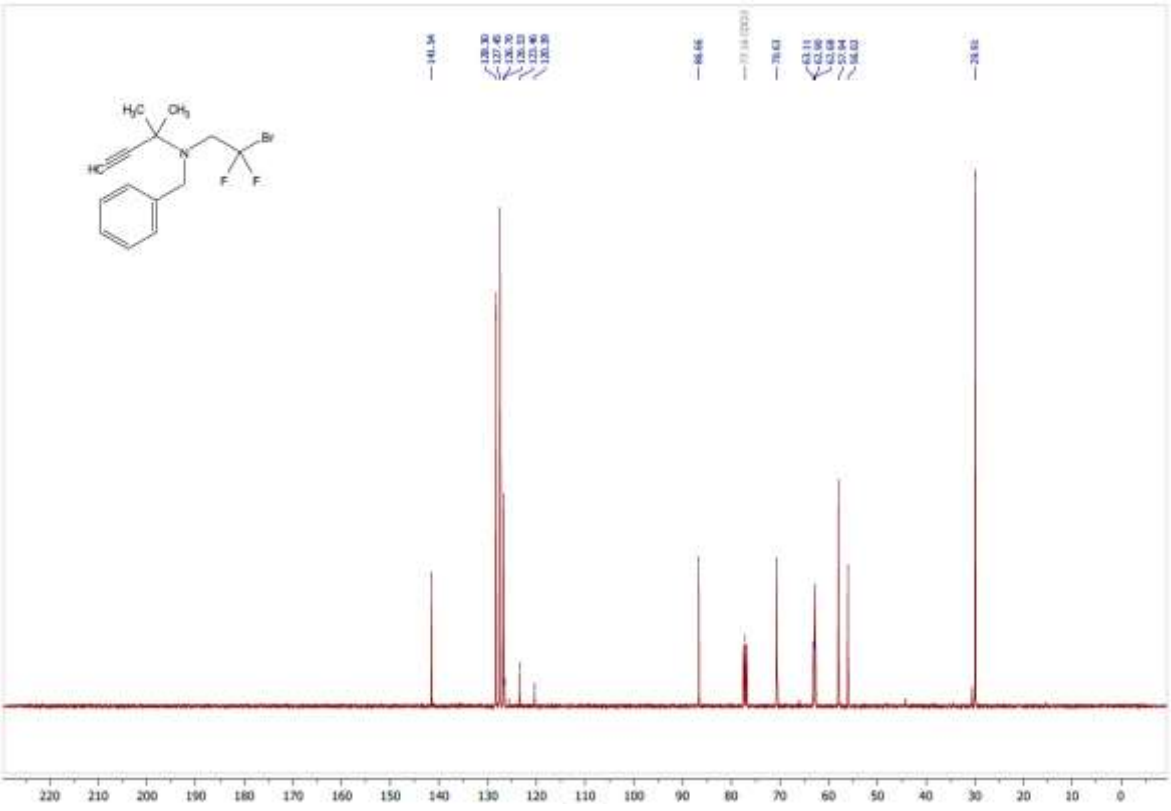
Supplementary Figure 69. ^{13}C NMR *N*-Benzyl-2-methylbut-3-yn-2-amine **53**



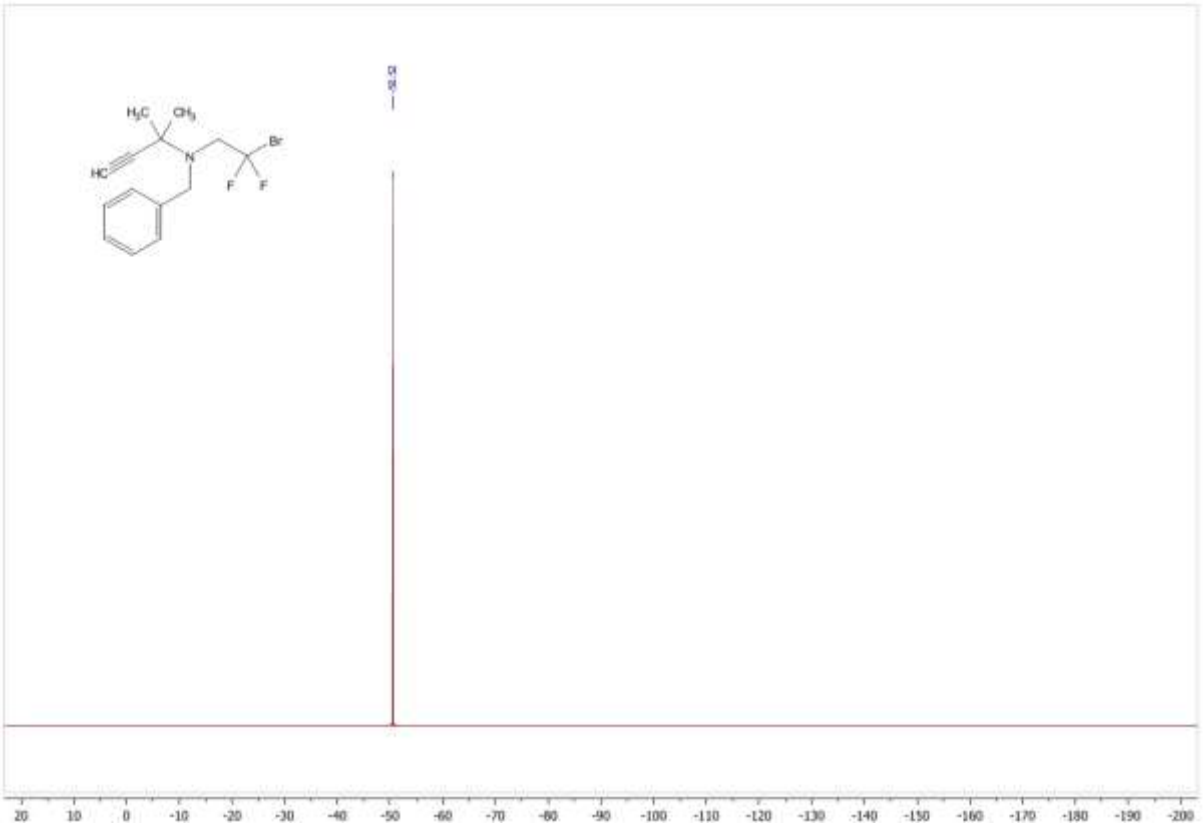
Supplementary Figure 70. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-2-methylbut-3-yn-2-amine **54**



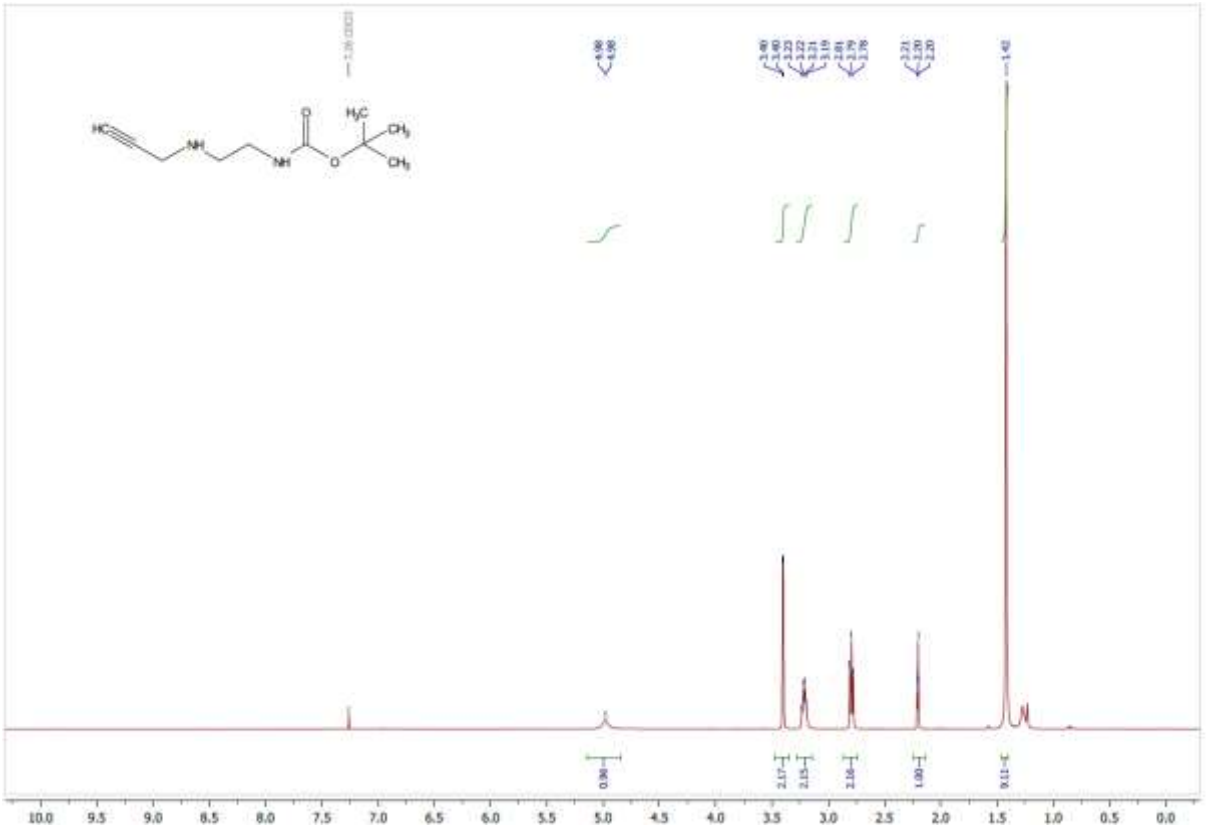
Supplementary Figure 71. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-2-methylbut-3-yn-2-amine **54**



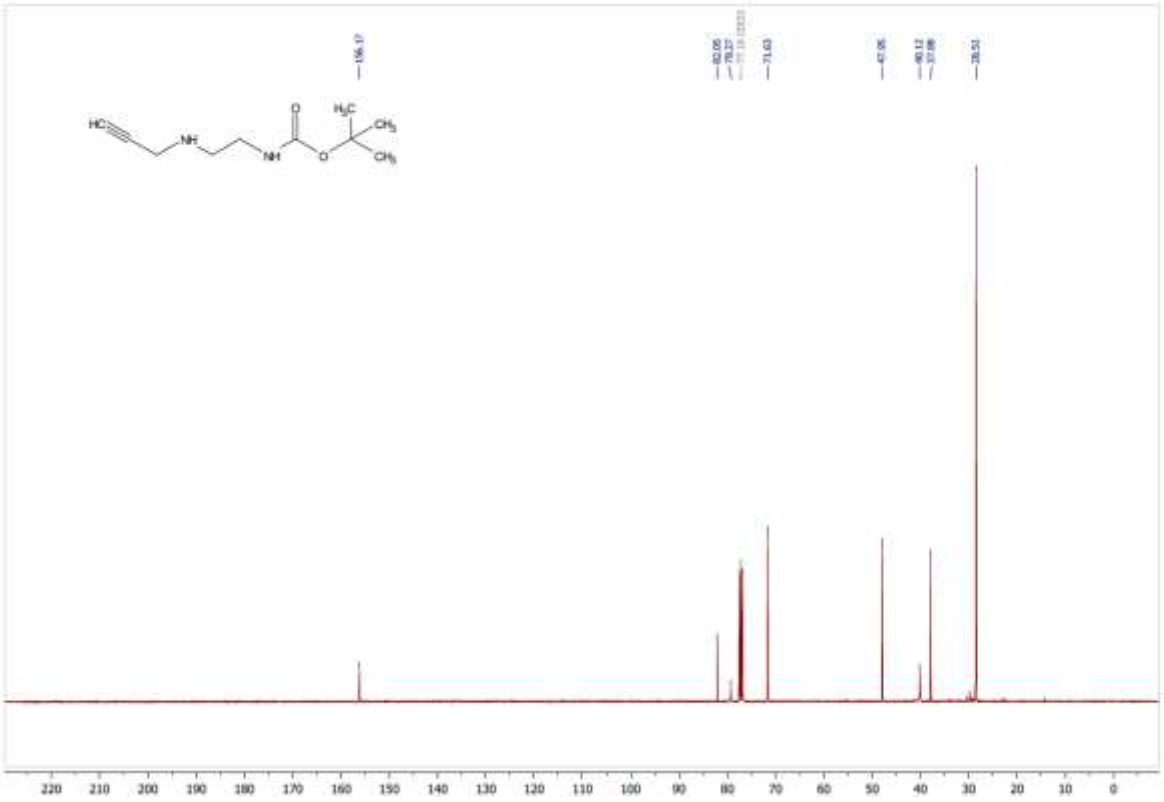
Supplementary Figure 72. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-2-methylbut-3-yn-2-amine **54**



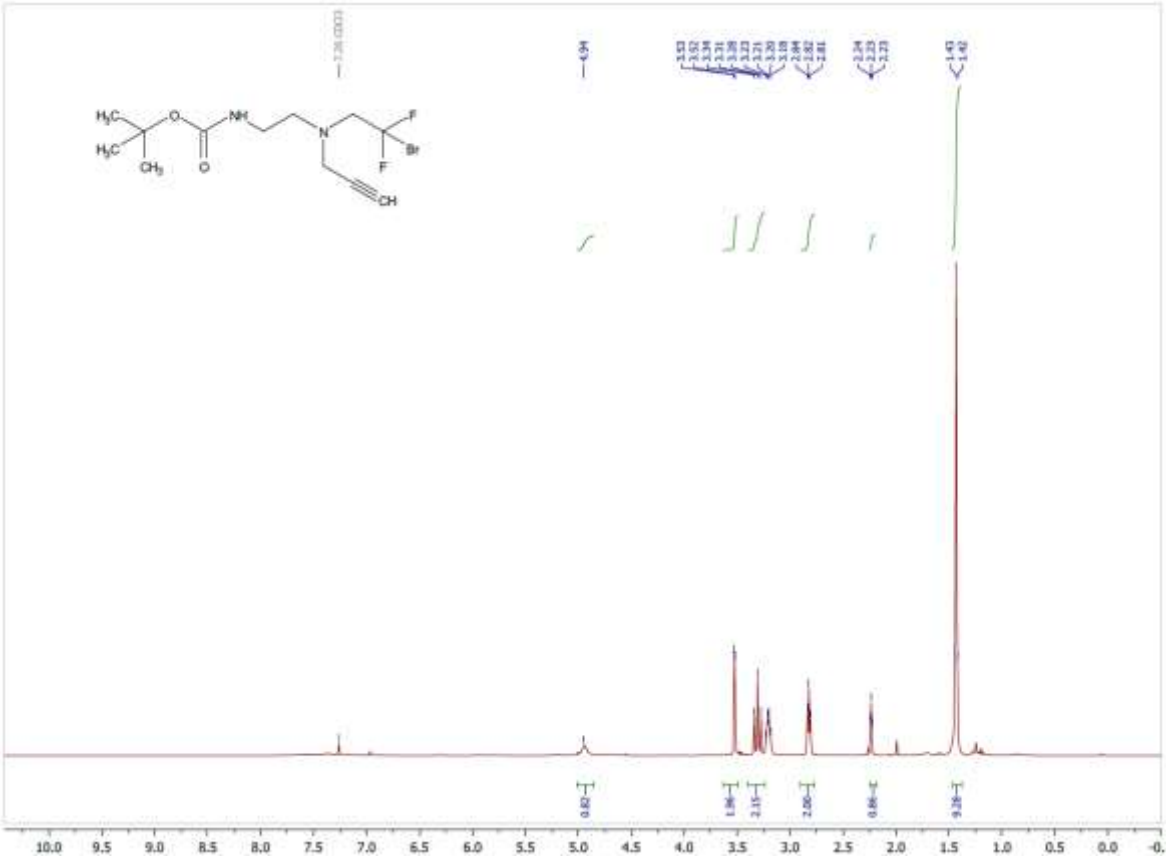
Supplementary Figure 73. ^{1}H NMR *tert*-Butyl (2-(prop-2-yn-1-ylamino)ethyl)carbamate **55**



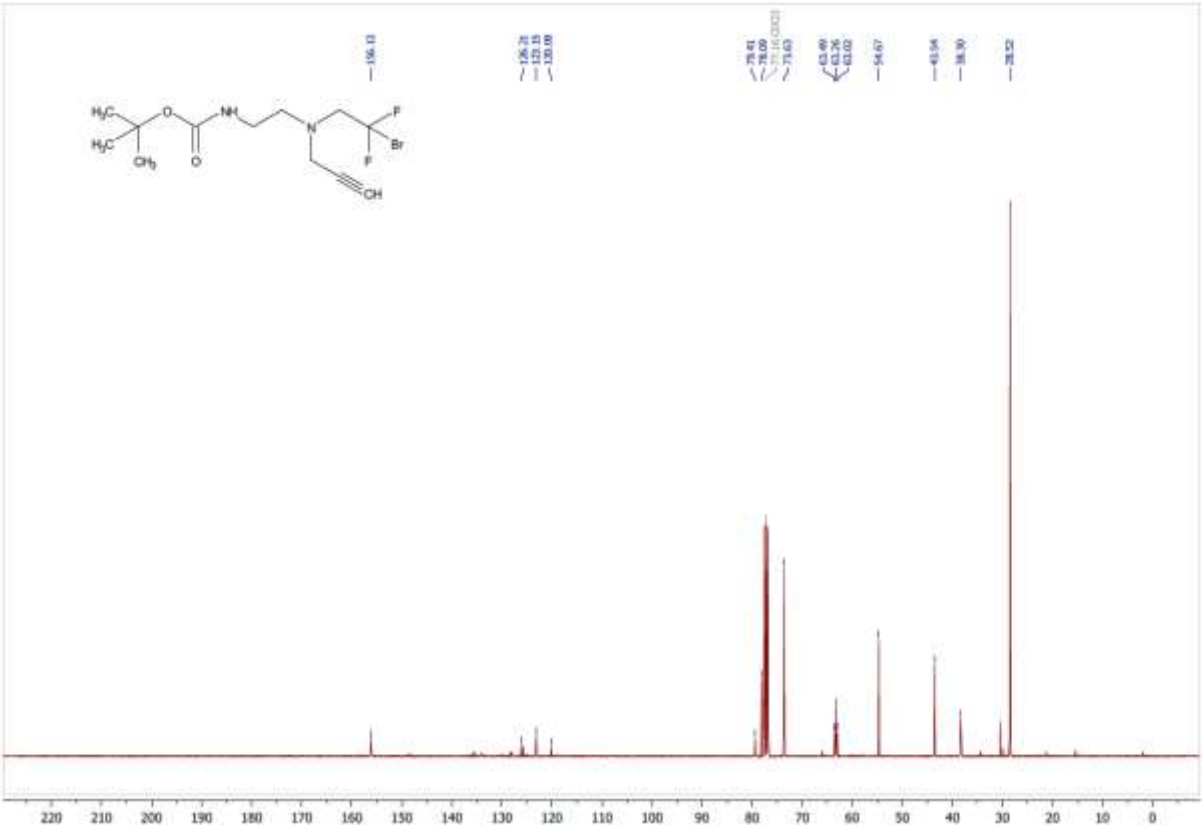
Supplementary Figure 74. ^{13}C NMR *tert*-Butyl (2-(prop-2-yn-1-ylamino)ethyl)carbamate **55**



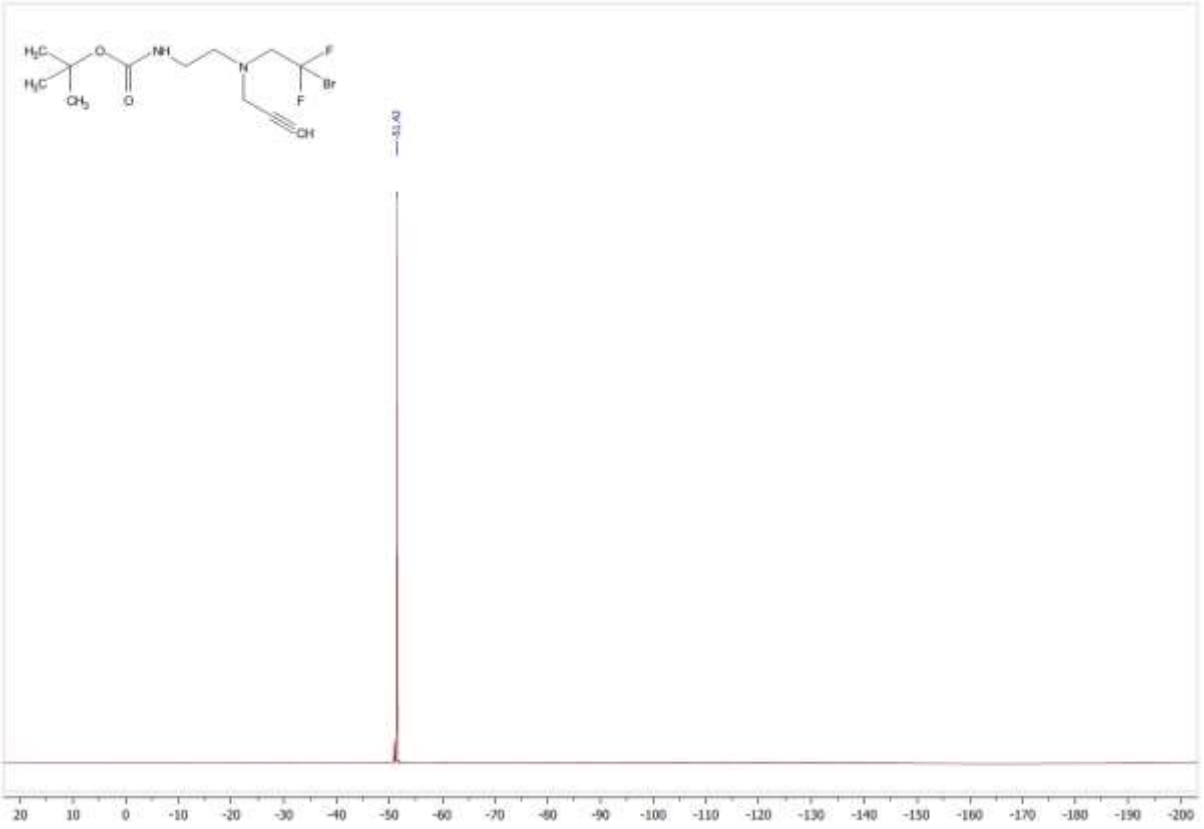
Supplementary Figure 75. ^{1}H NMR *tert*-Butyl (2-((2-bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethyl)carbamate **56**



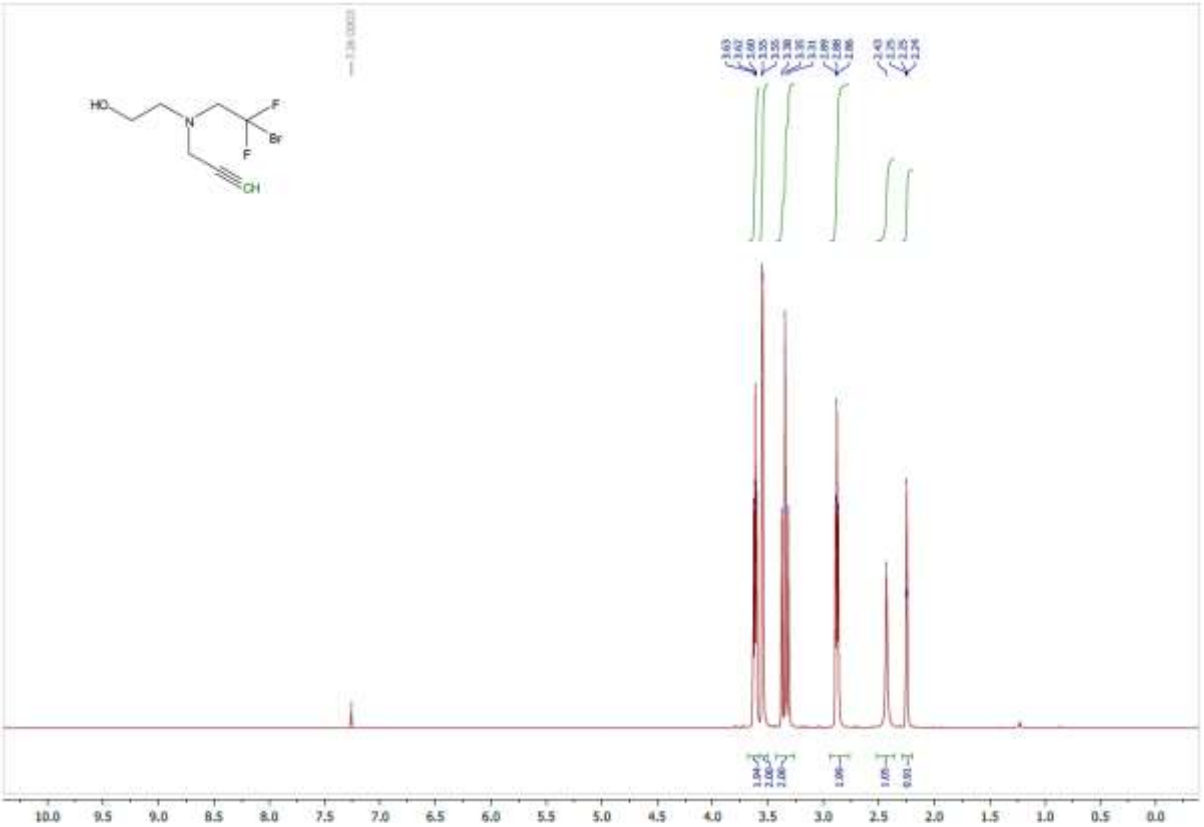
Supplementary Figure 76. ^{13}C NMR *tert*-Butyl (2-((2-bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethyl)carbamate **56**



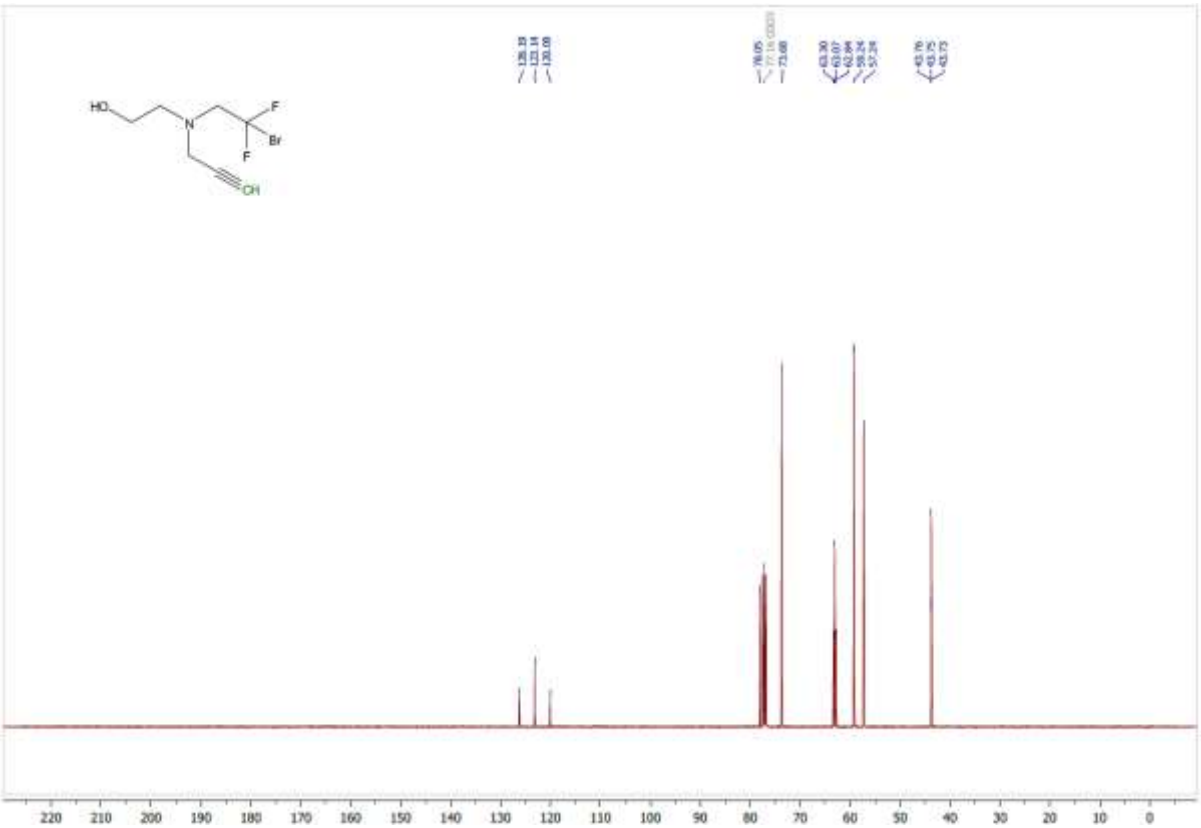
Supplementary Figure 77. ^{19}F NMR *tert*-Butyl (2-((2-bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethyl)carbamate **56**



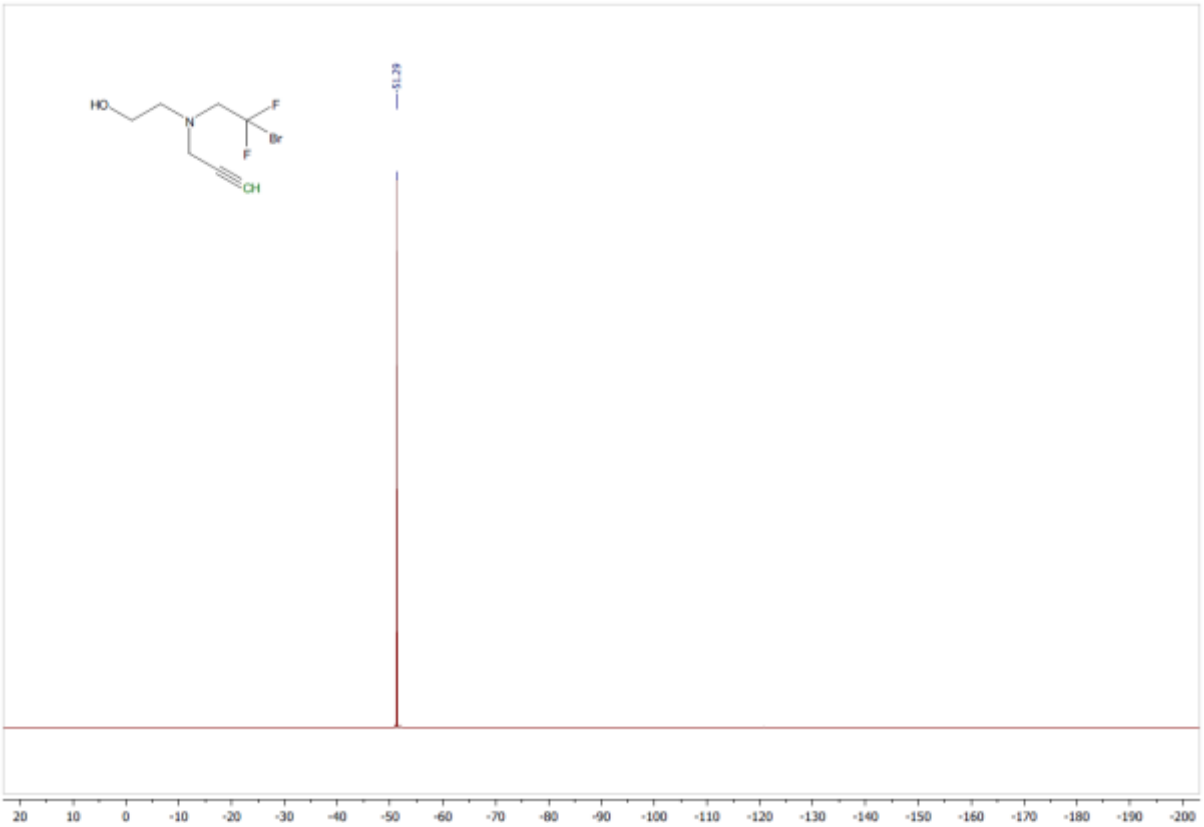
Supplementary Figure 78. ^{1}H NMR 2-((2-Bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethan-1-ol **57**



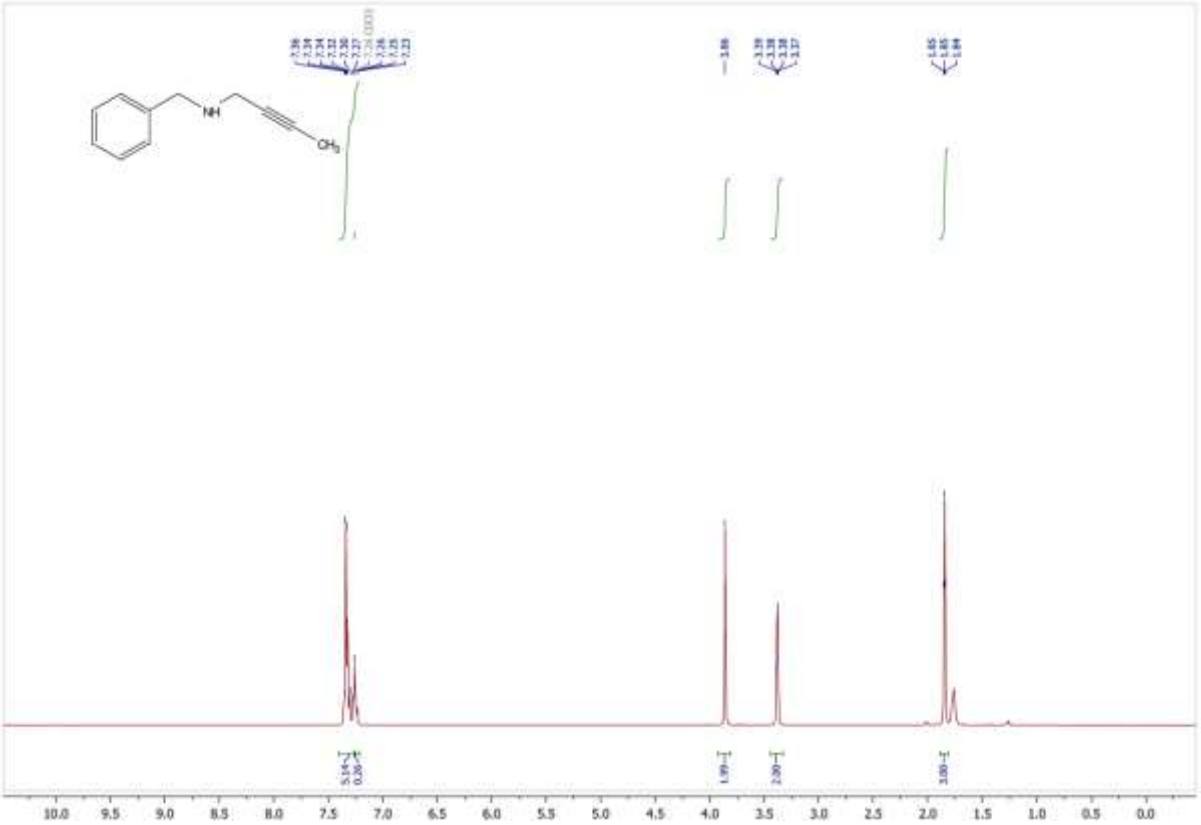
Supplementary Figure 79. ^{13}C NMR2-((2-Bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethan-1-ol **57**



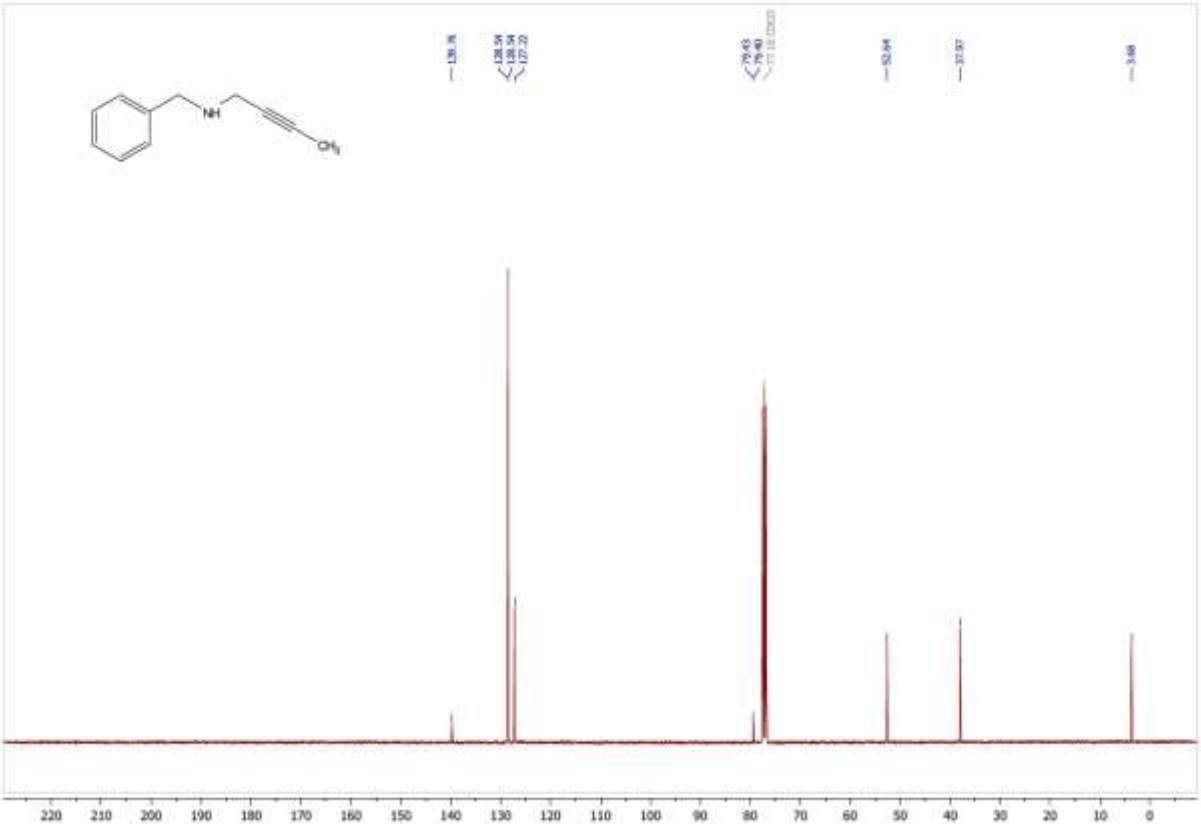
Supplementary Figure 80. ^{19}F NMR 2-((2-Bromo-2,2-difluoroethyl)(prop-2-yn-1-yl)amino)ethan-1-ol **57**



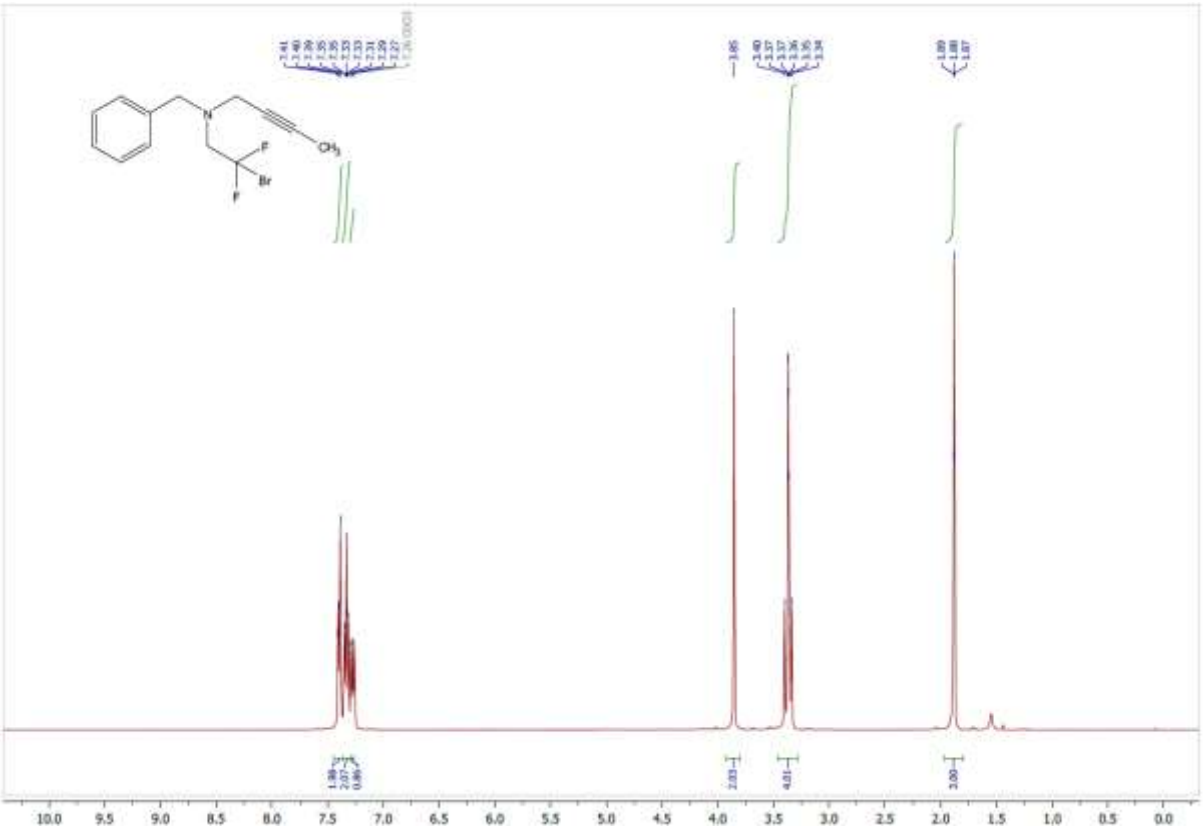
Supplementary Figure 81. ^{1}H NMR *N*-Benzylbut-2-yn-1-amine **58**



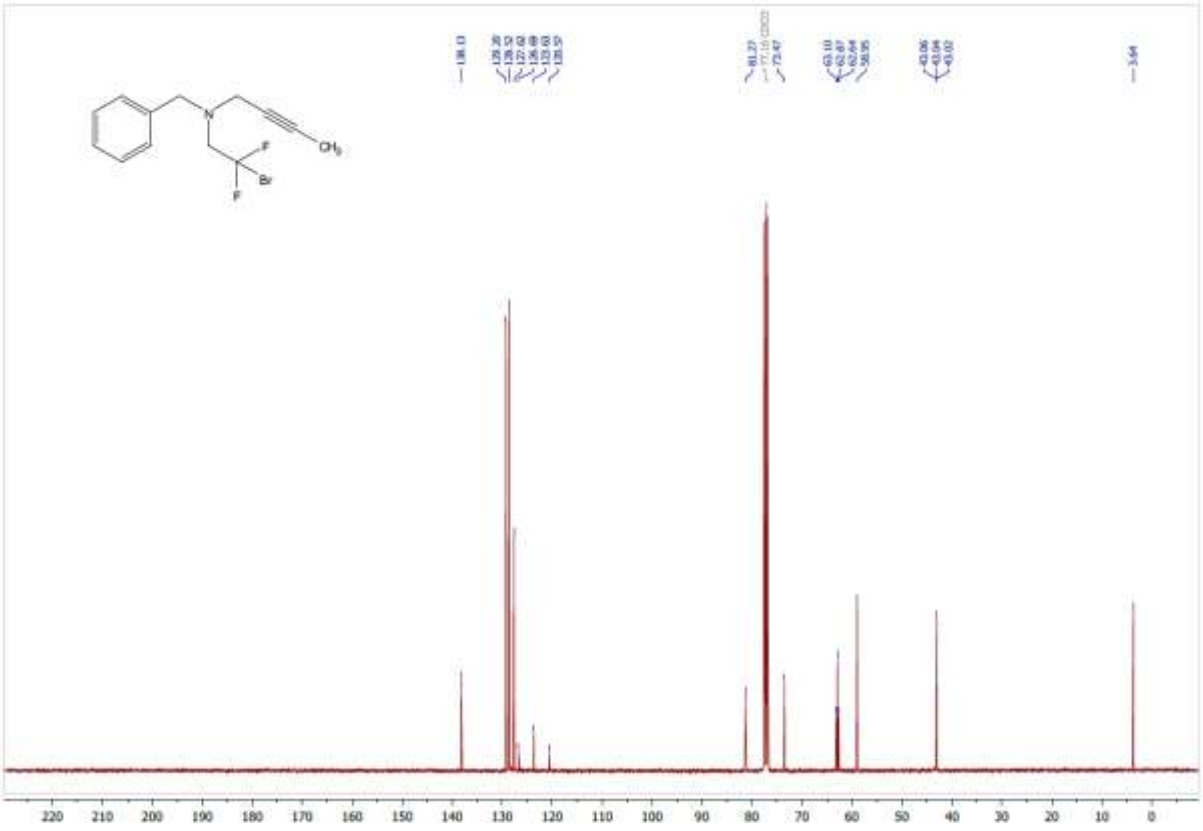
Supplementary Figure 82. ^{13}C NMR *N*-Benzylbut-2-yn-1-amine **58**



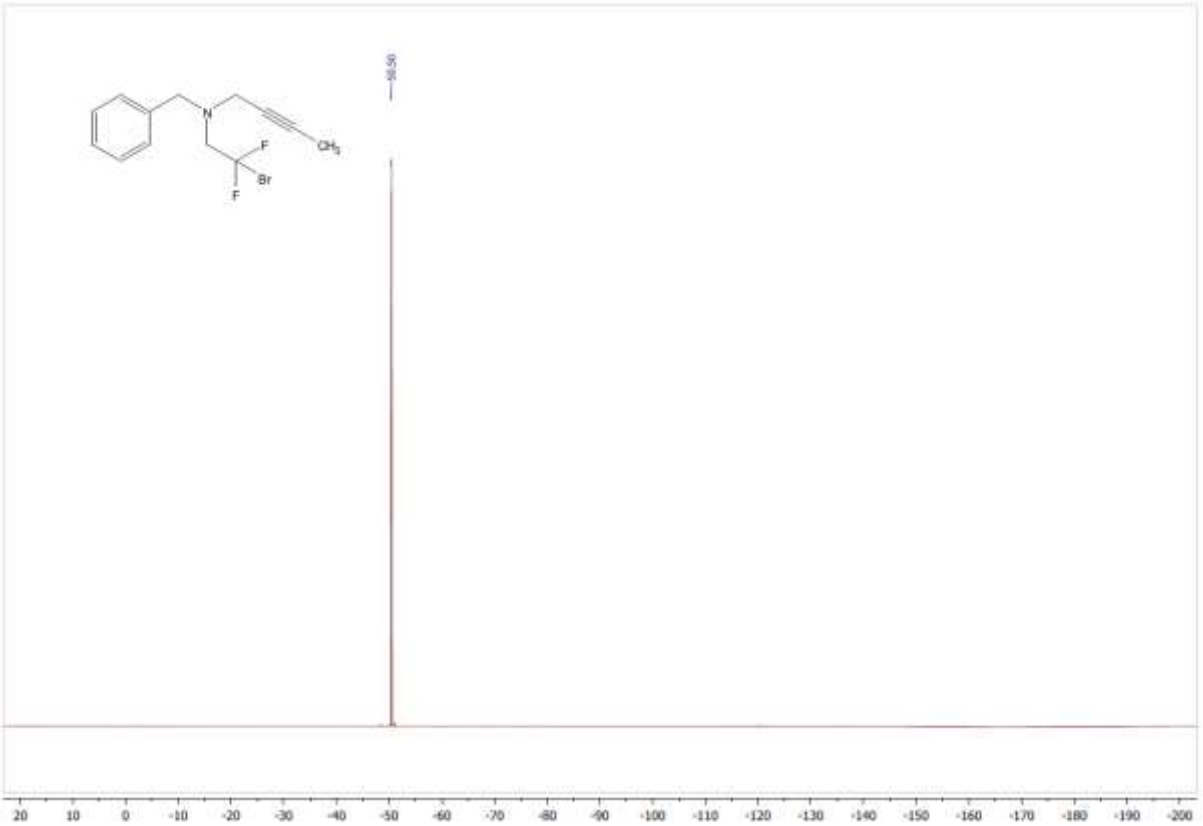
Supplementary Figure 83. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-2-yn-1-amine **59**



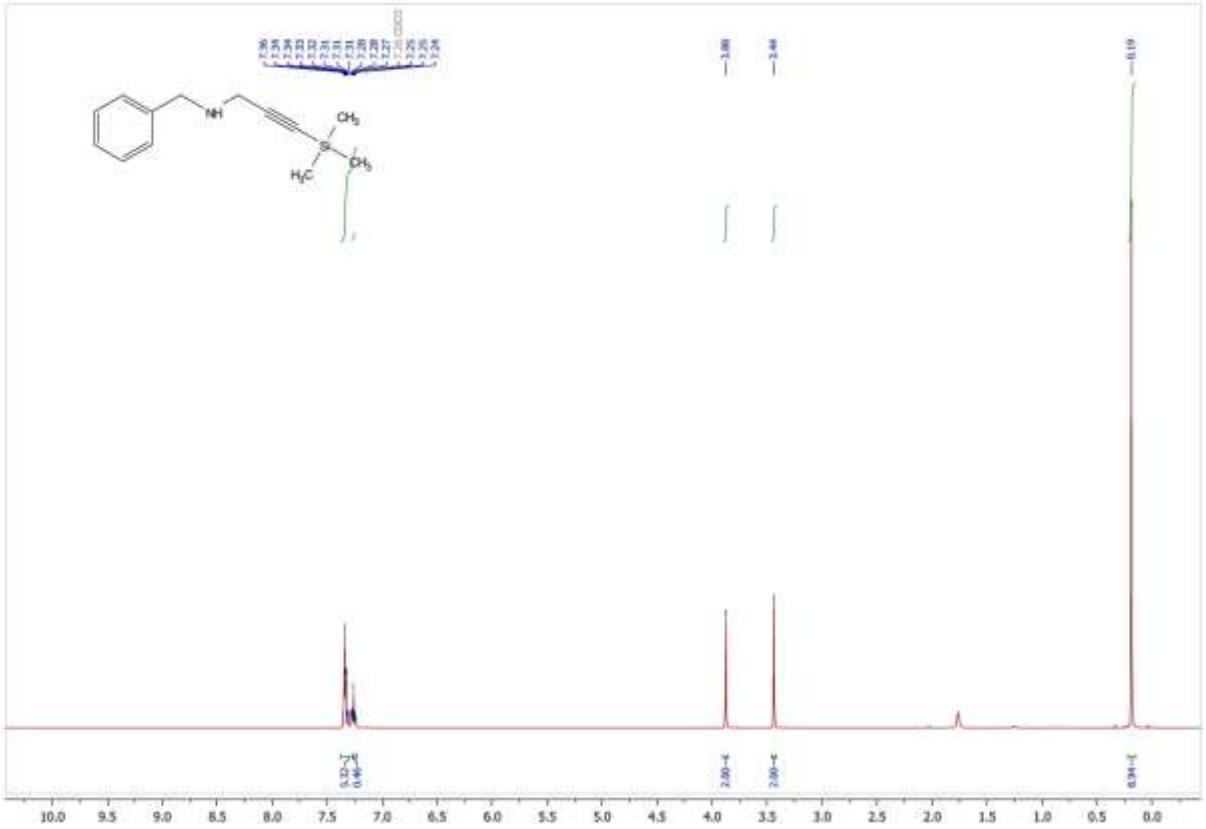
Supplementary Figure 84. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-2-yn-1-amine **59**



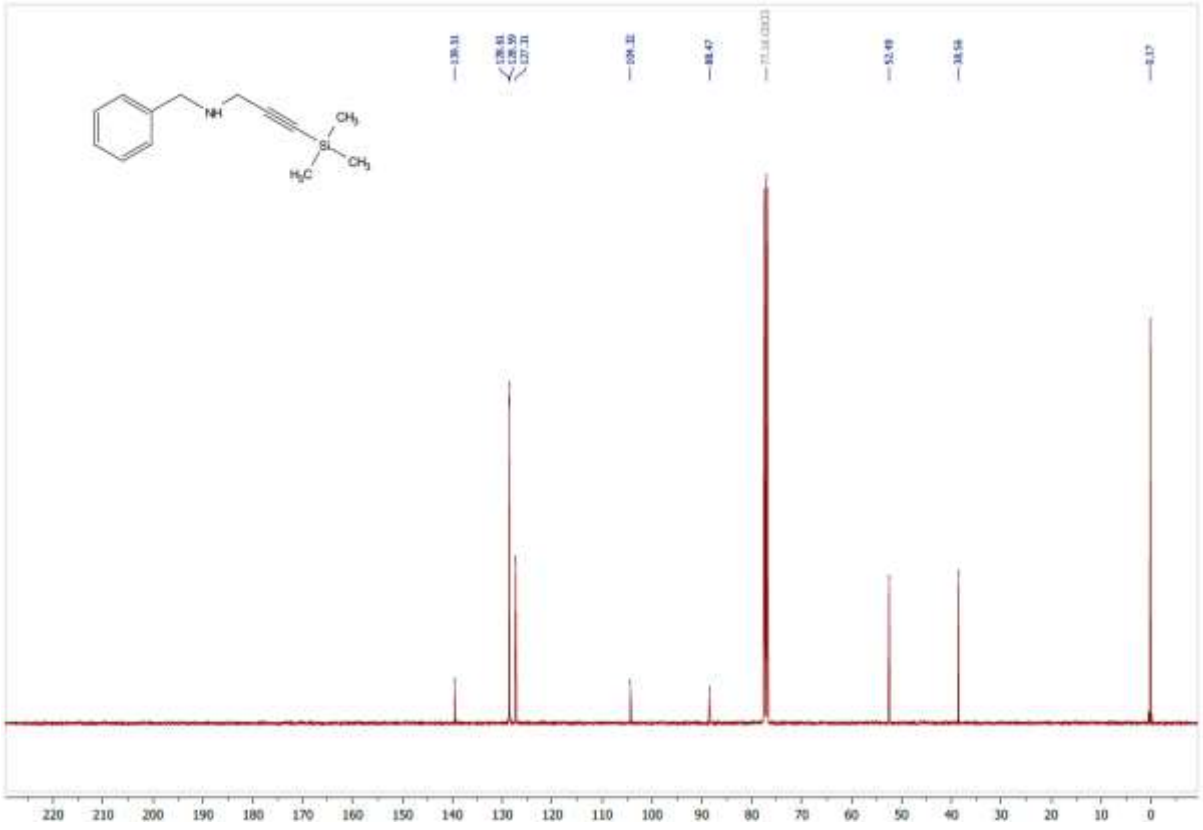
Supplementary Figure 85. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)but-2-yn-1-amine **59**



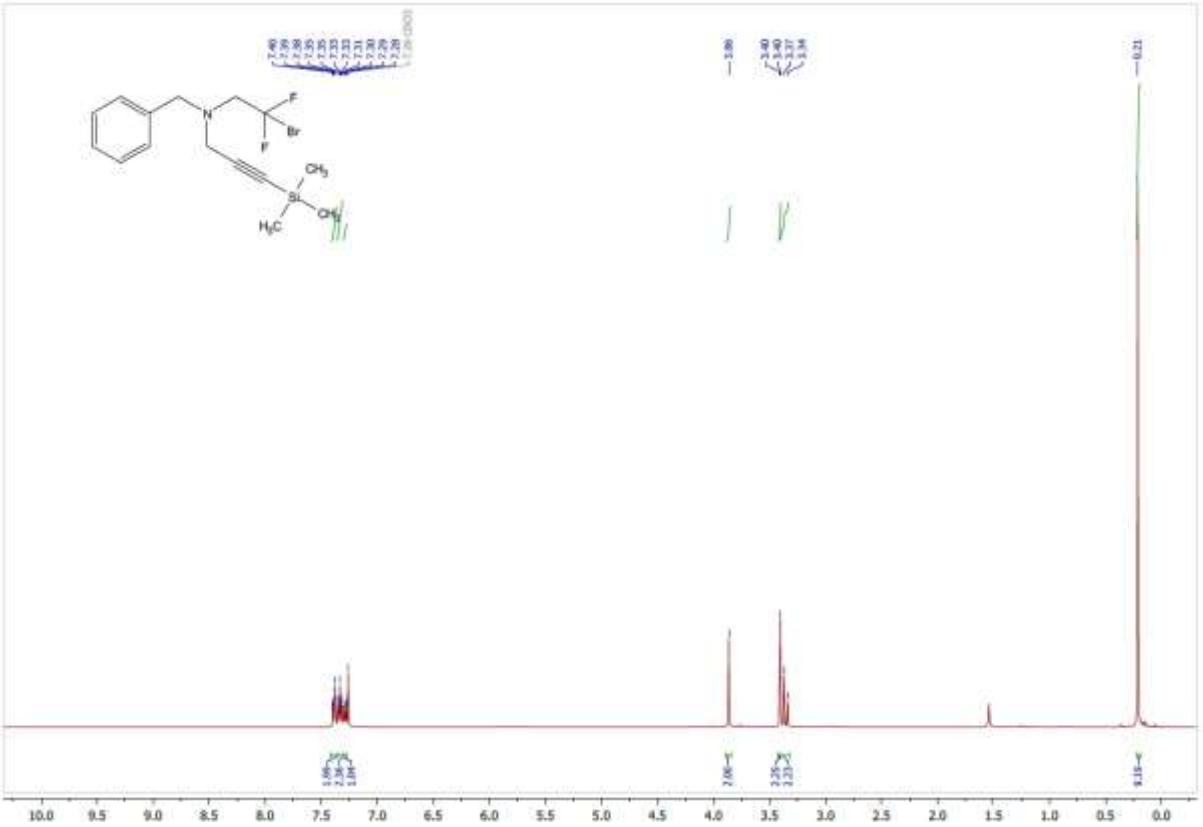
Supplementary Figure 86. ^{1}H NMR *N*-Benzyl-3-(trimethylsilyl)prop-2-yn-1-amine **60**



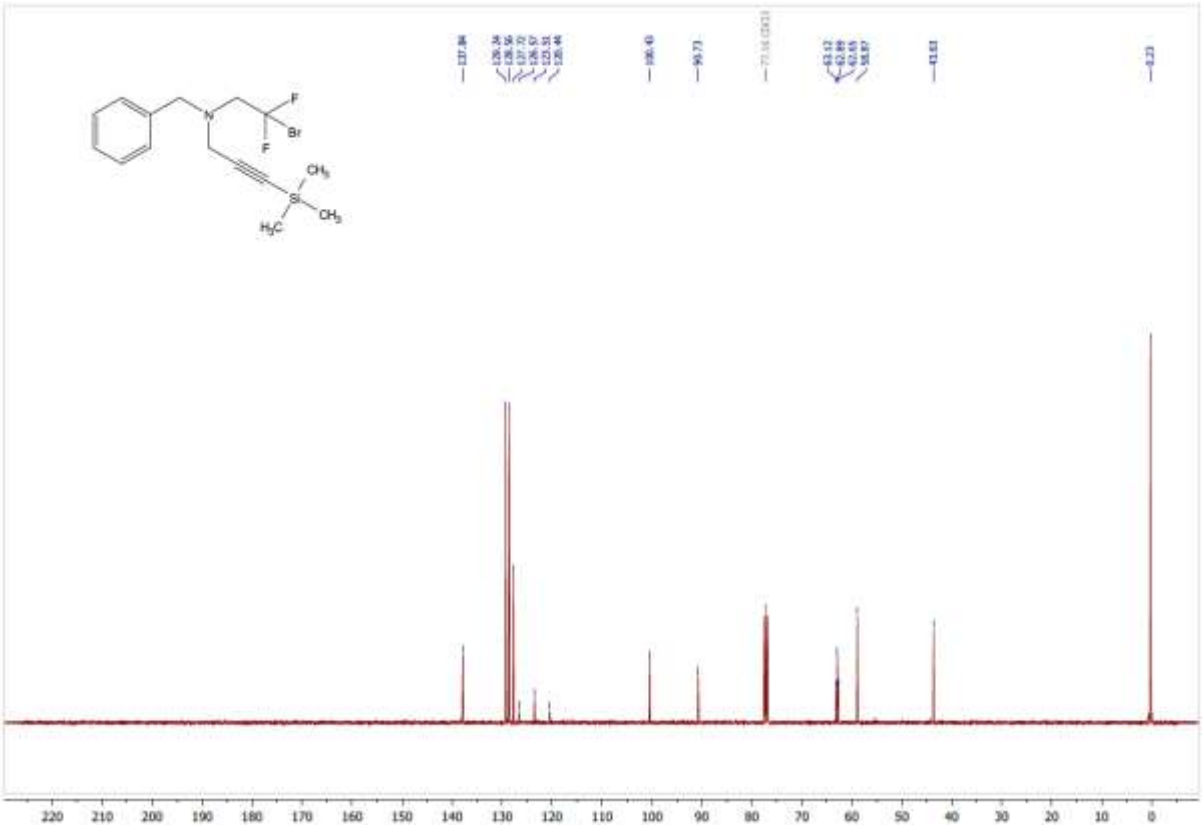
Supplementary Figure 87. ^{13}C NMR *N*-Benzyl-3-(trimethylsilyl)prop-2-yn-1-amine **60**



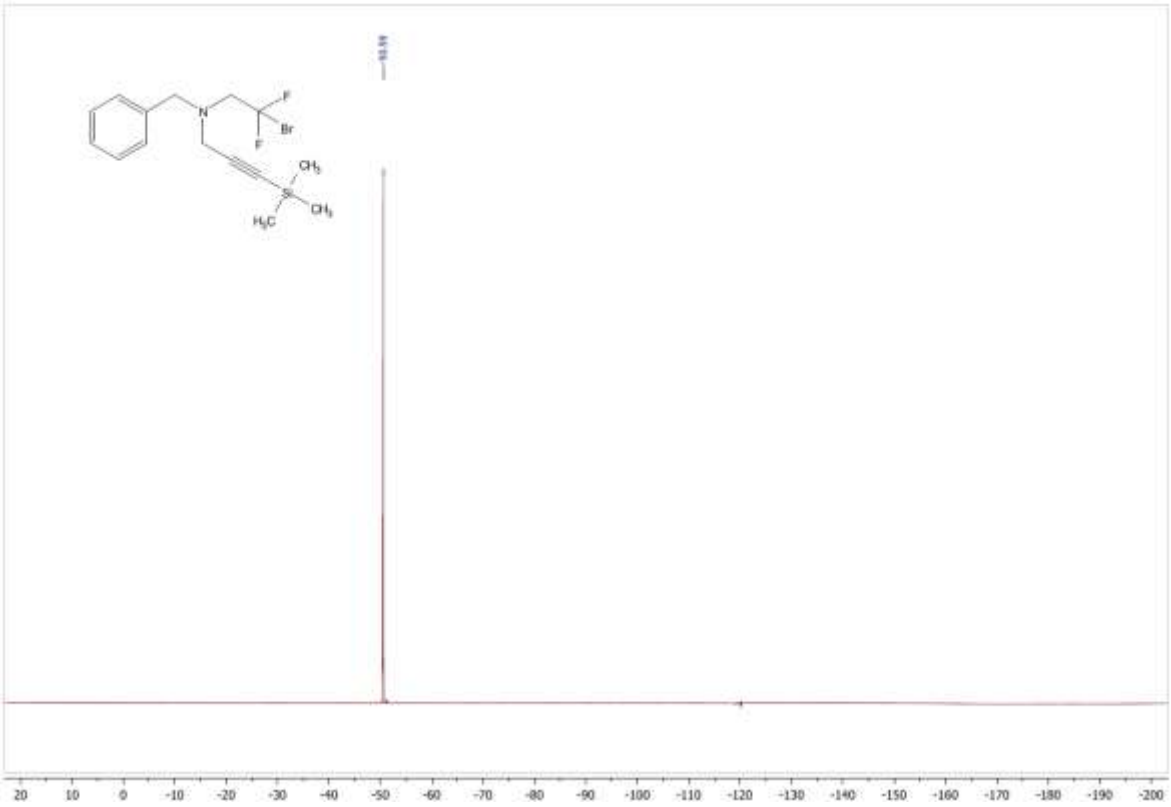
Supplementary Figure 88. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-(trimethylsilyl)prop-2-yn-1-amine **61**



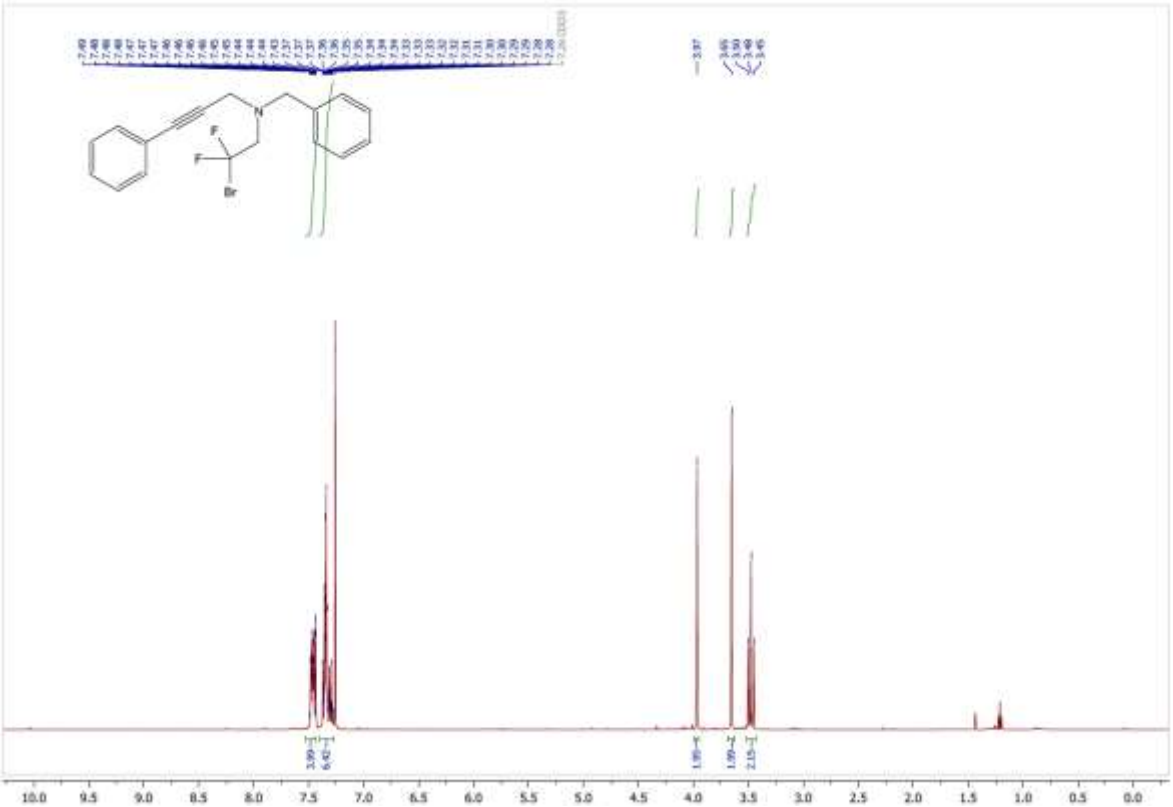
Supplementary Figure 89. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-(trimethylsilyl)prop-2-yn-1-amine **61**



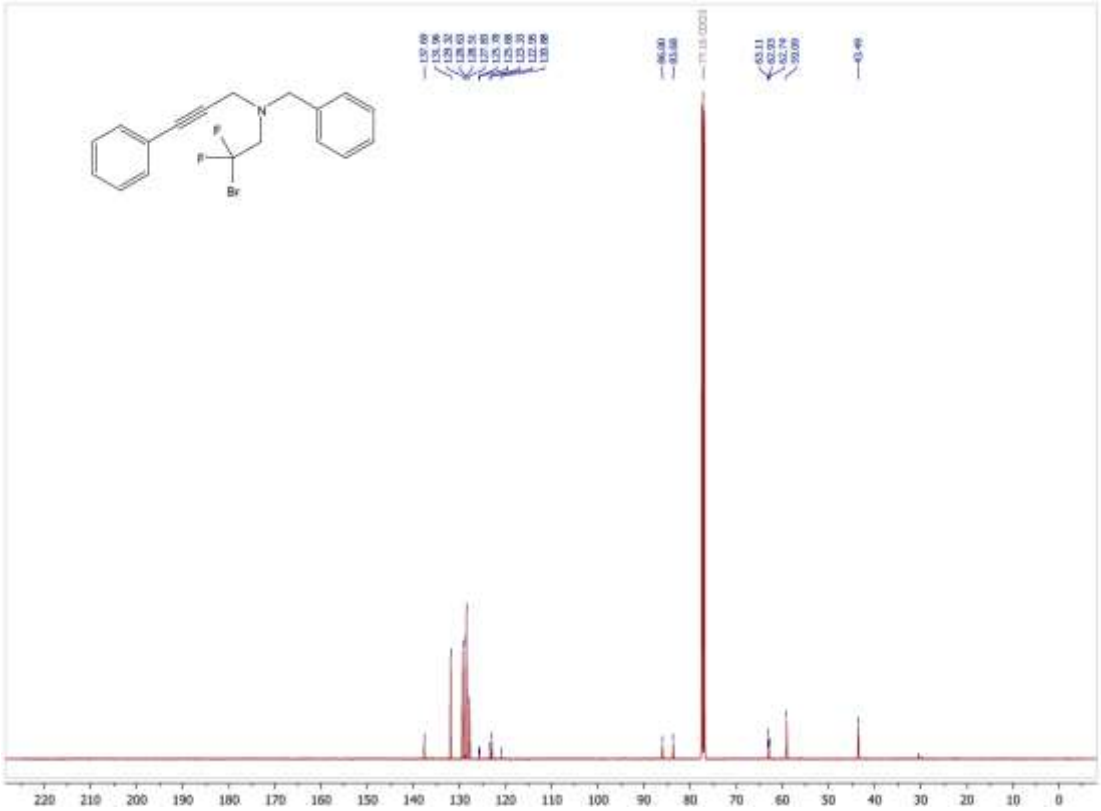
Supplementary Figure 90. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-(trimethylsilyl)prop-2-yn-1-amine **61**



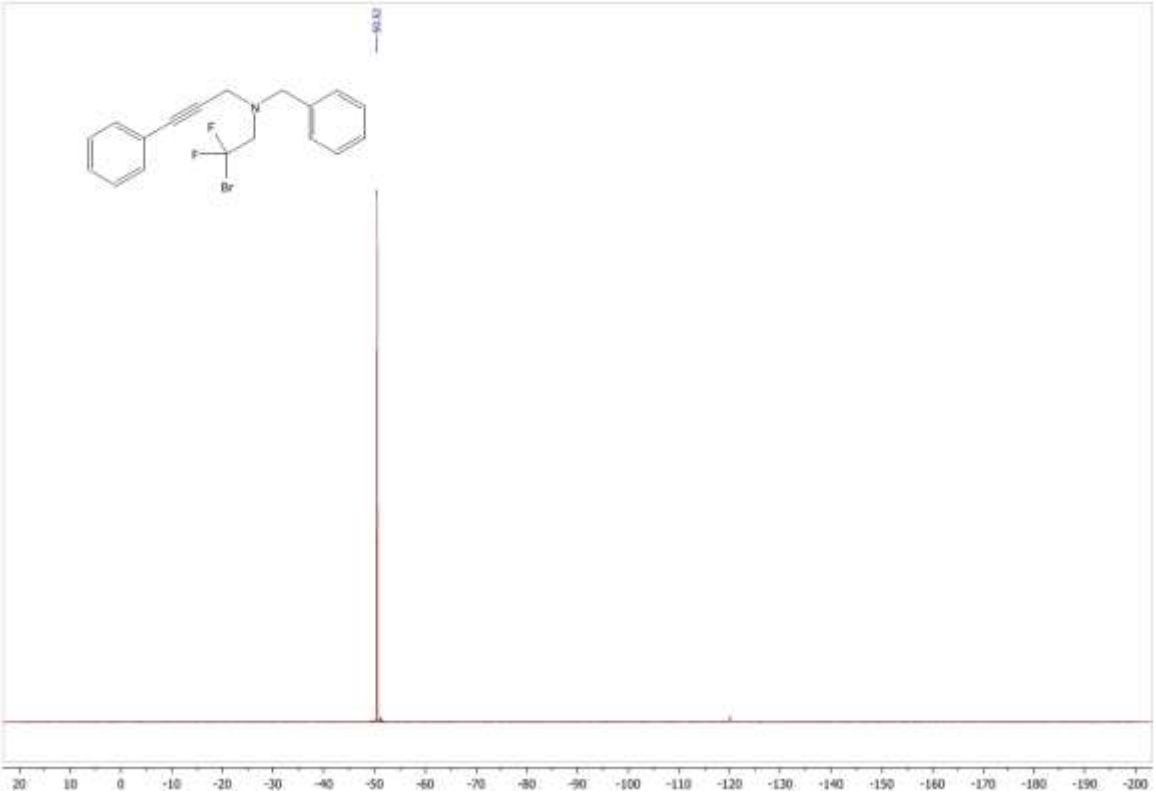
Supplementary Figure 91. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-phenylprop-2-yn-1-amine **62**



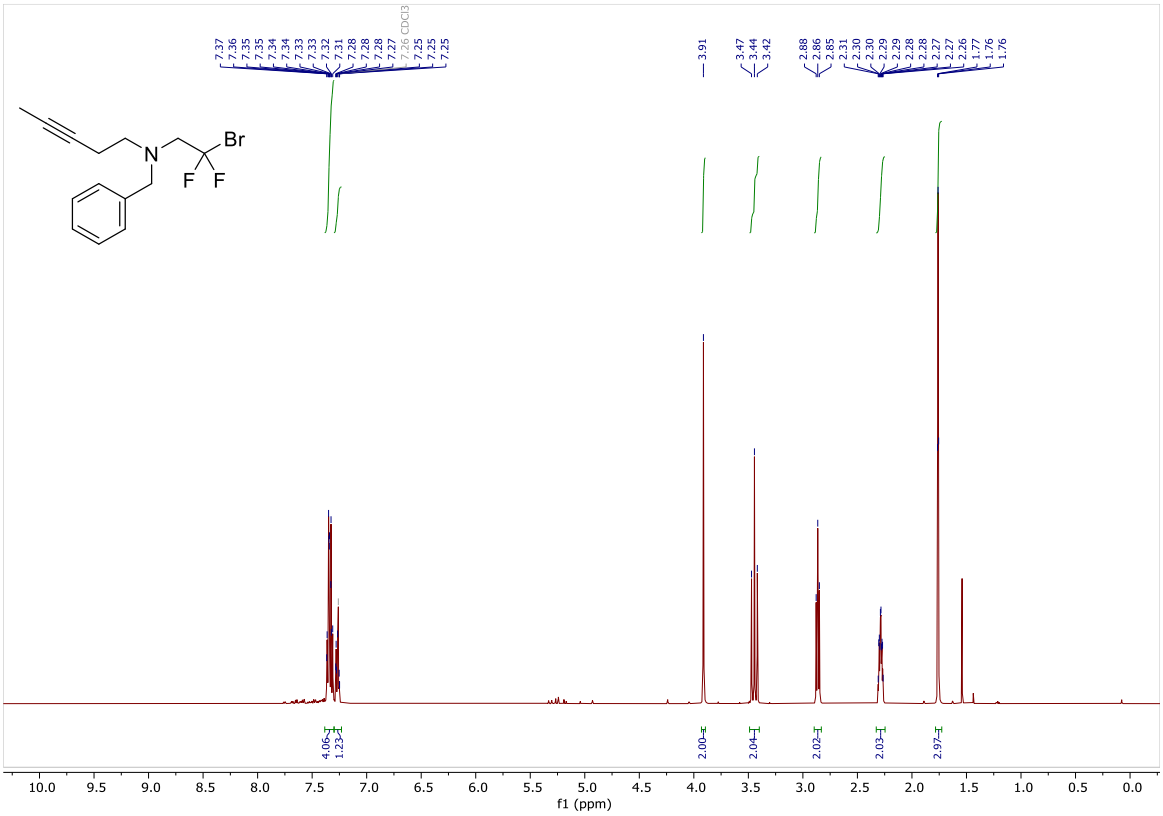
Supplementary Figure 92. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-phenylprop-2-yn-1-amine **62**



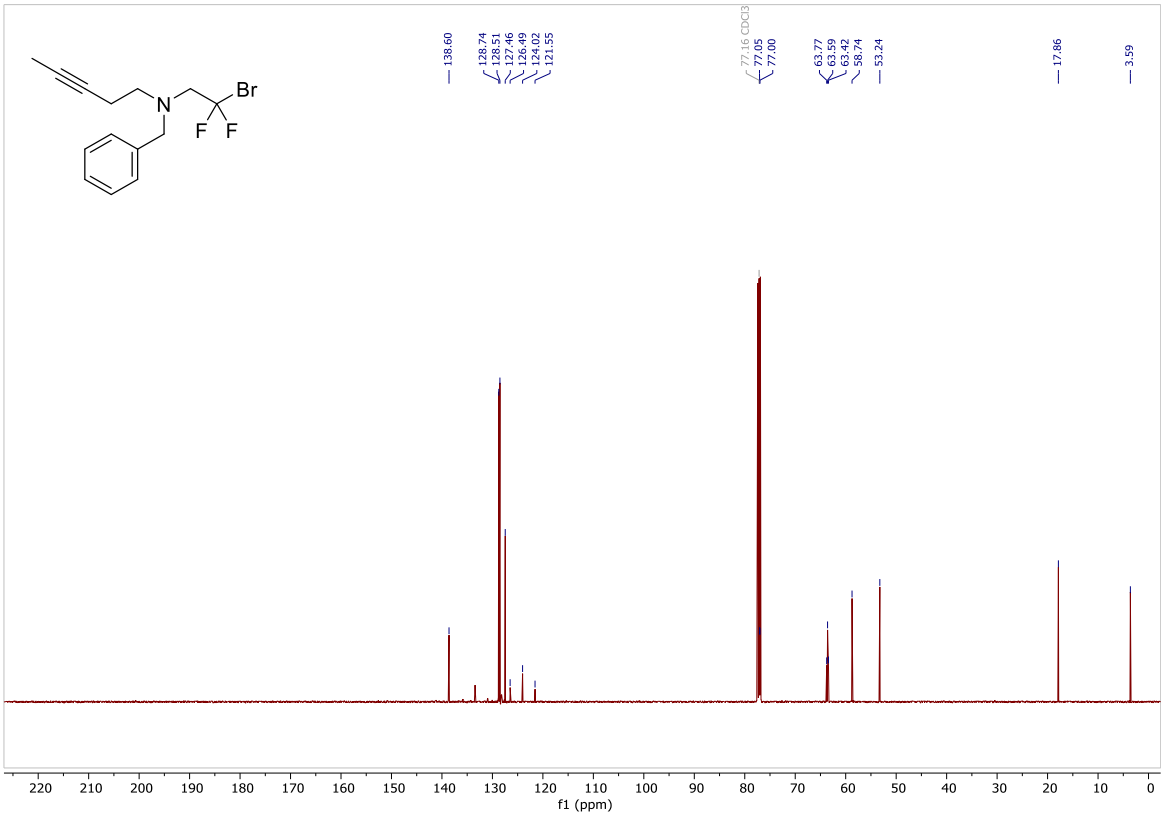
Supplementary Figure 93. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)-3-phenylprop-2-yn-1-amine **62**



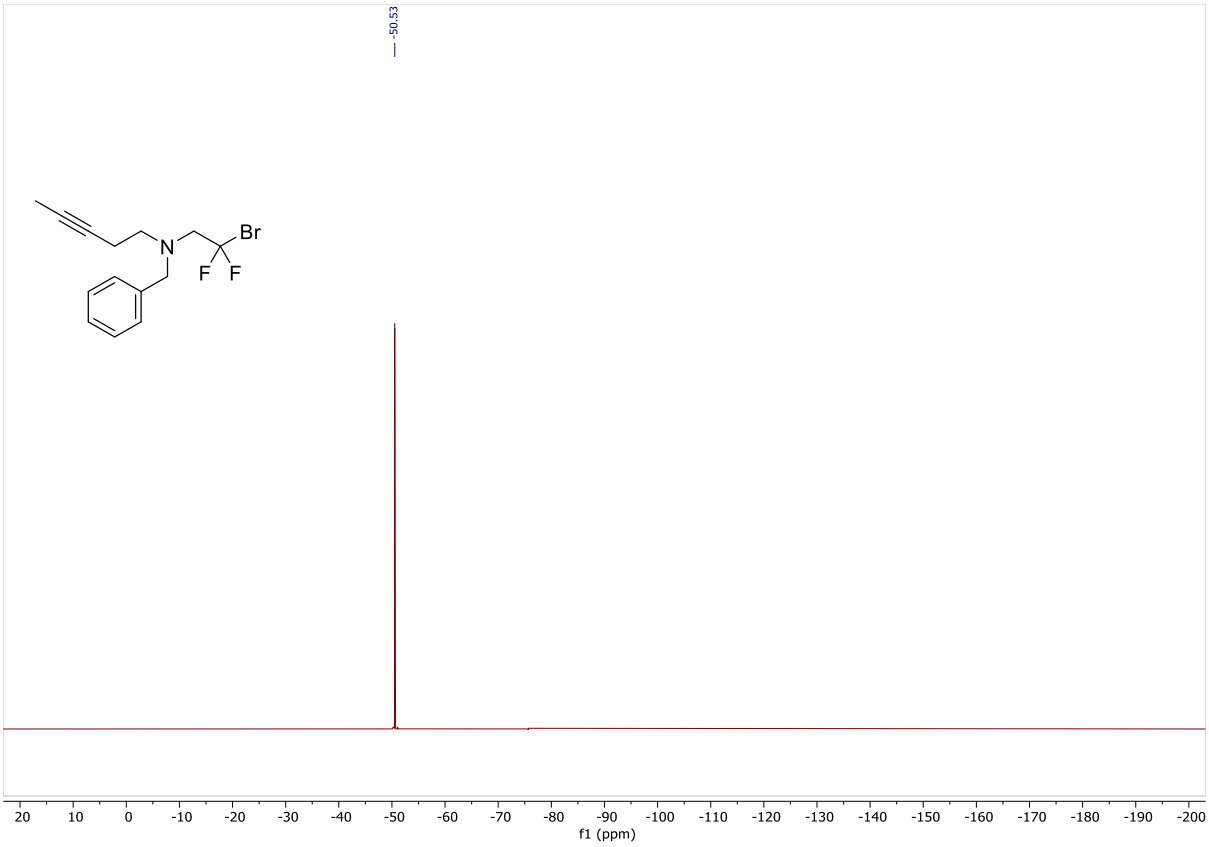
Supplementary Figure 94. ^{1}H NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)pent-3-yn-1-amine **63**



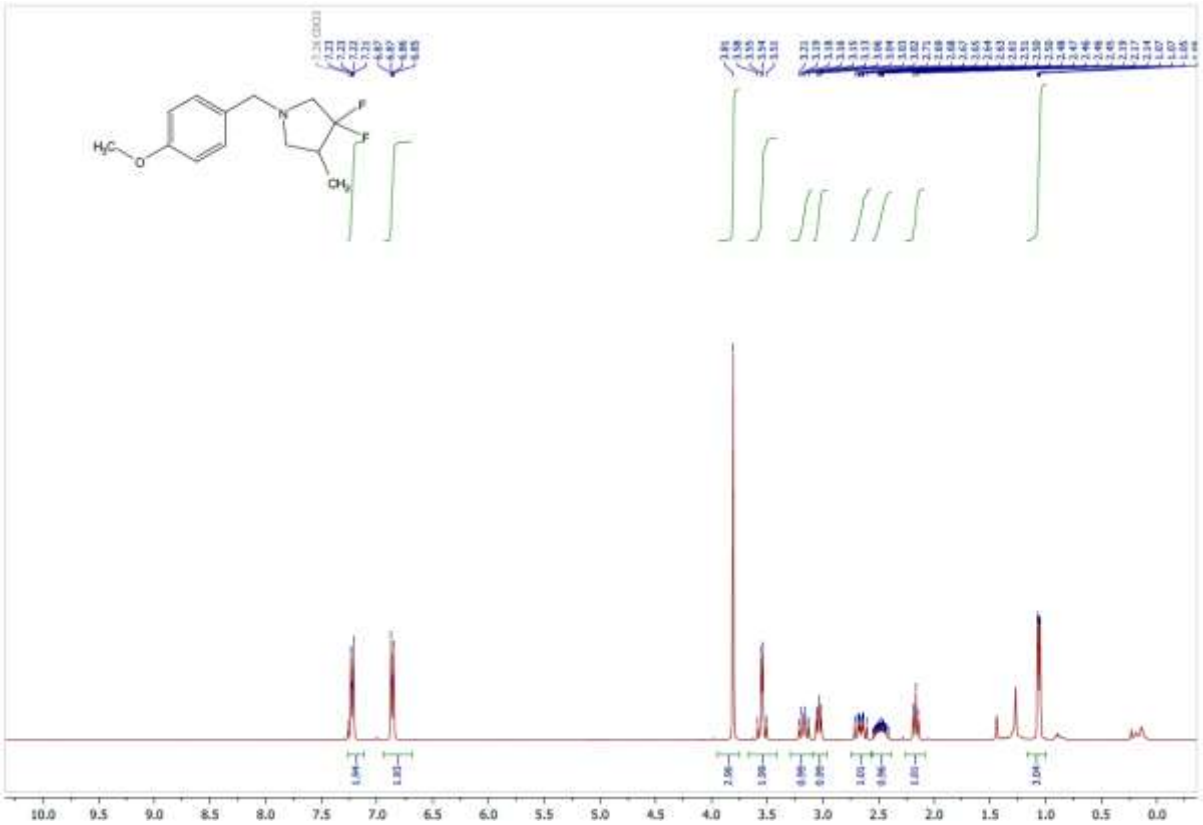
Supplementary Figure 95. ^{13}C NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)pent-3-yn-1-amine **63**



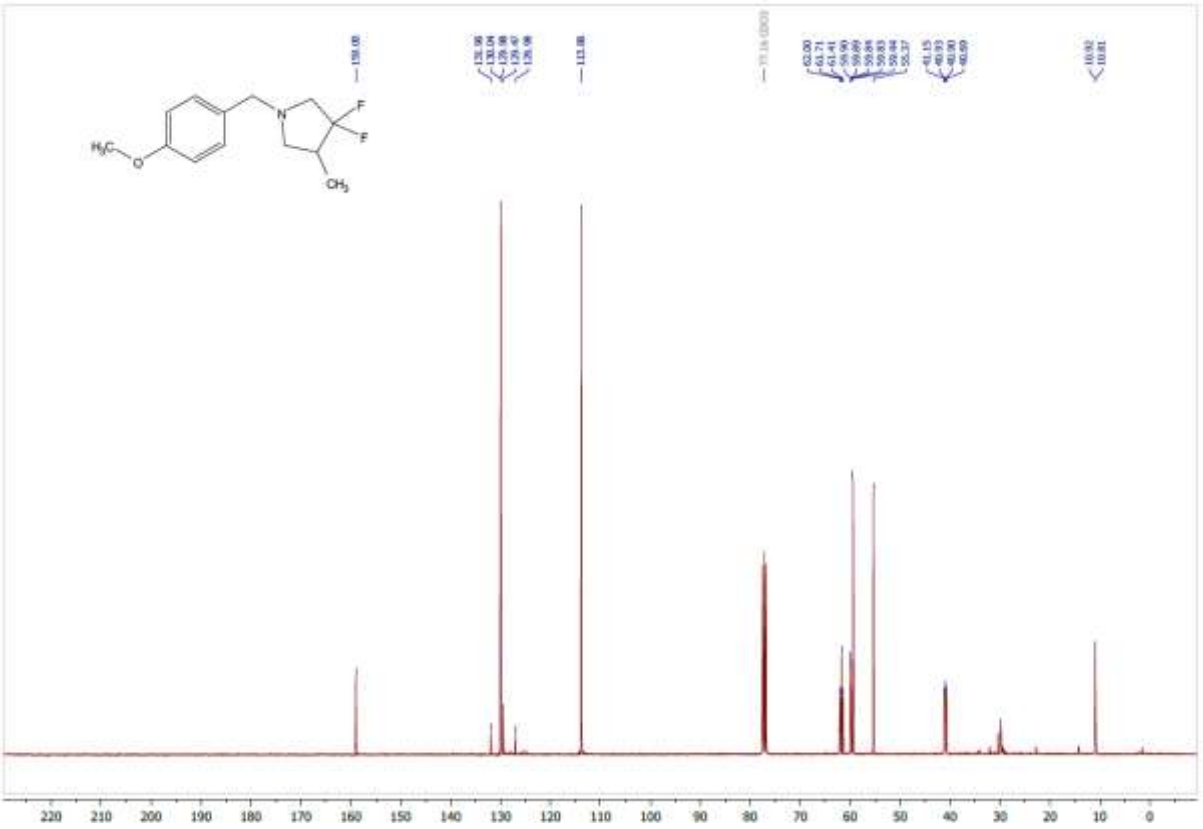
Supplementary Figure 96. ^{19}F NMR *N*-Benzyl-*N*-(2-bromo-2,2-difluoroethyl)pent-3-yn-1-amine **63**



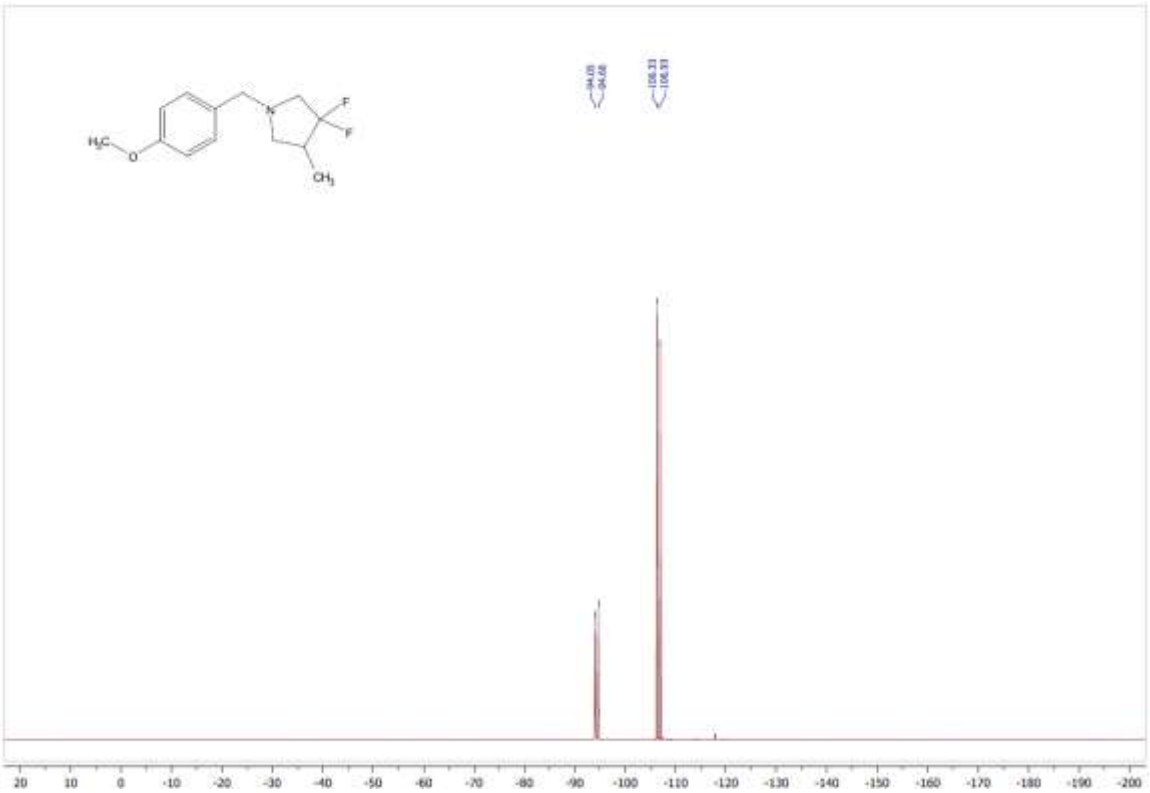
Supplementary Figure 97. ^{1}H NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpyrrolidine **6**



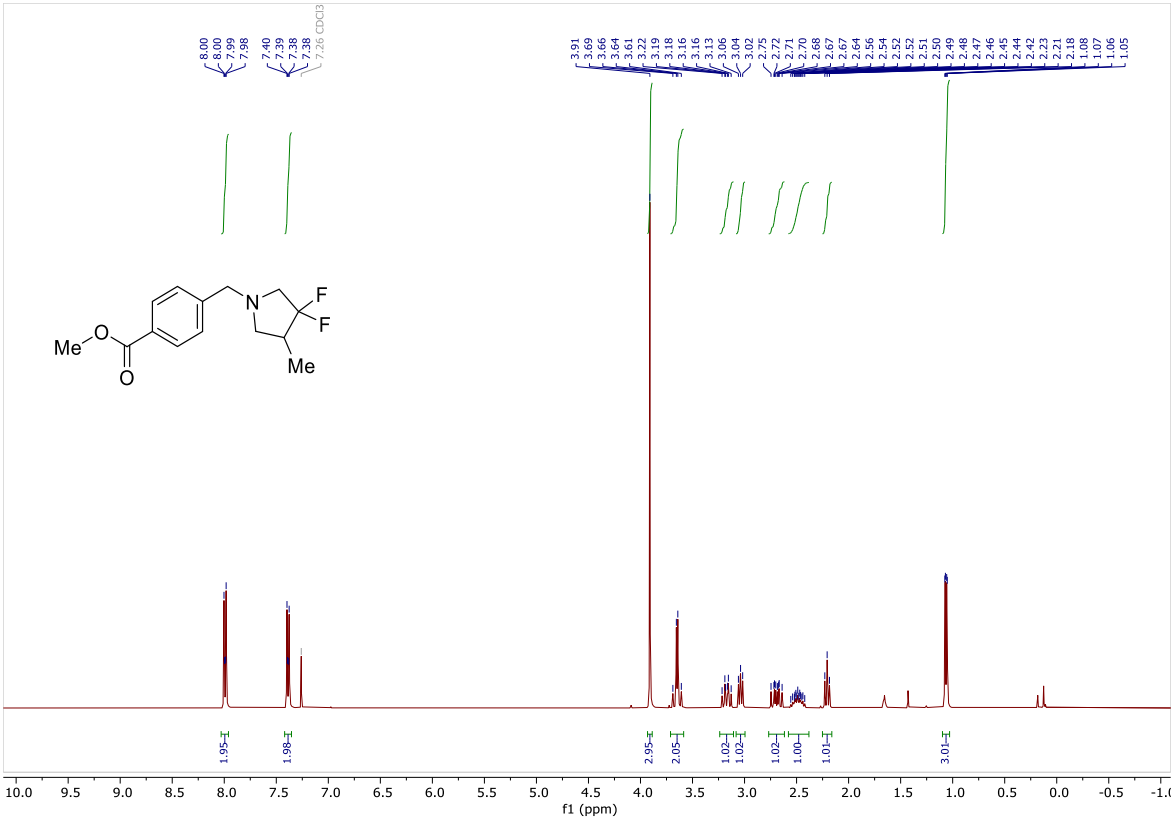
Supplementary Figure 98. ^{13}C NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpyrrolidine **6**



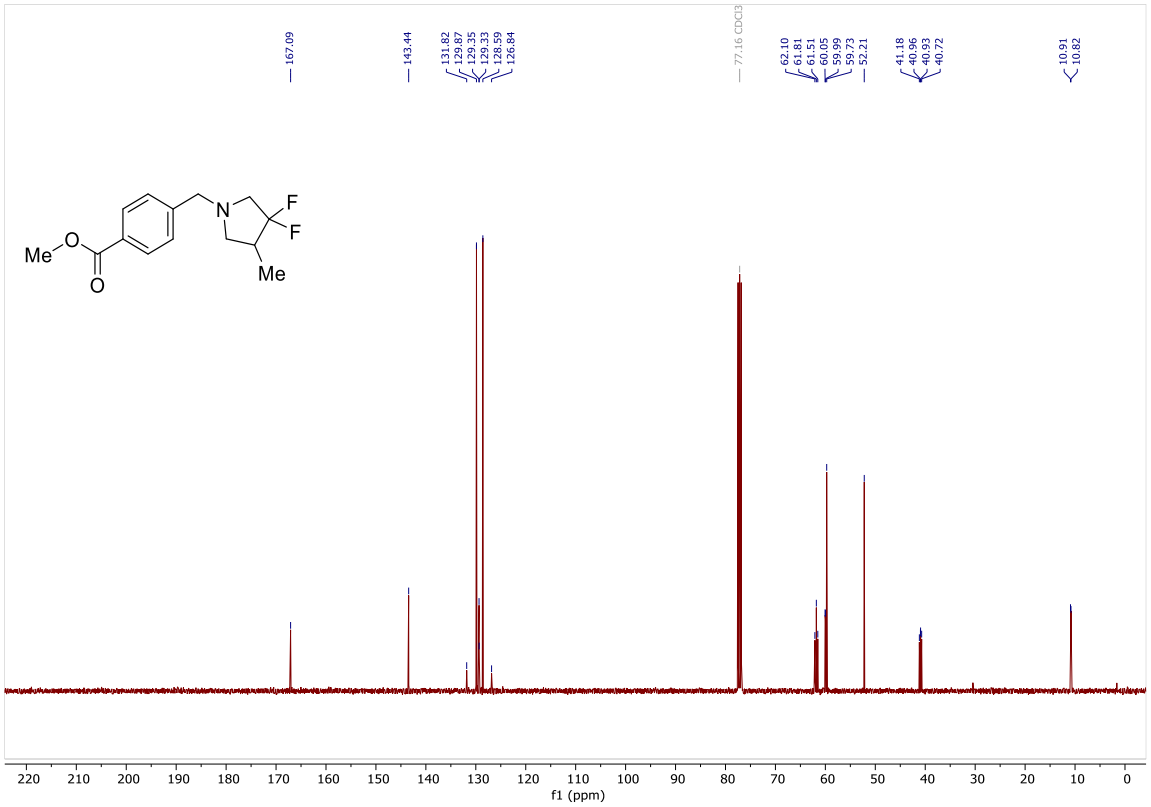
Supplementary Figure 99. ^{19}F NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpyrrolidine **6**



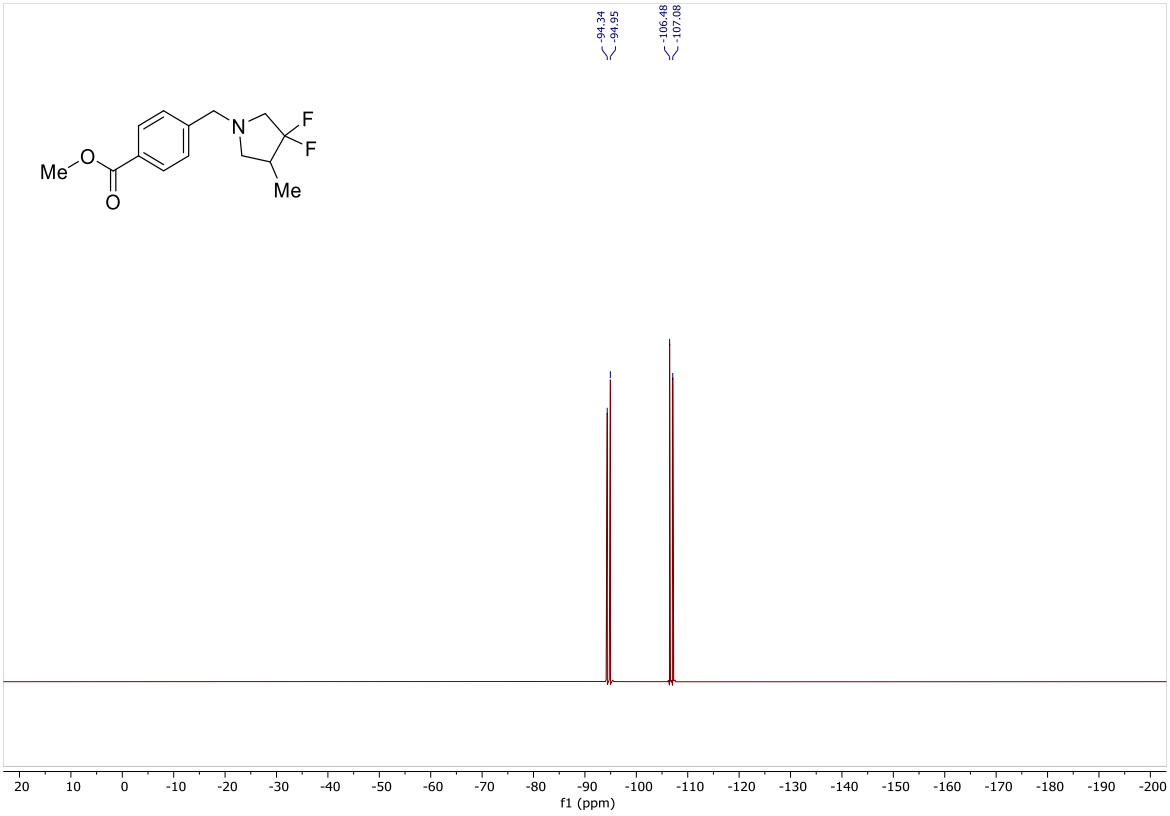
Supplementary Figure 100. ^{1}H NMR Methyl 4-((3,3-difluoro-4-methylpyrrolidin-1-yl)methyl)benzoate **7**



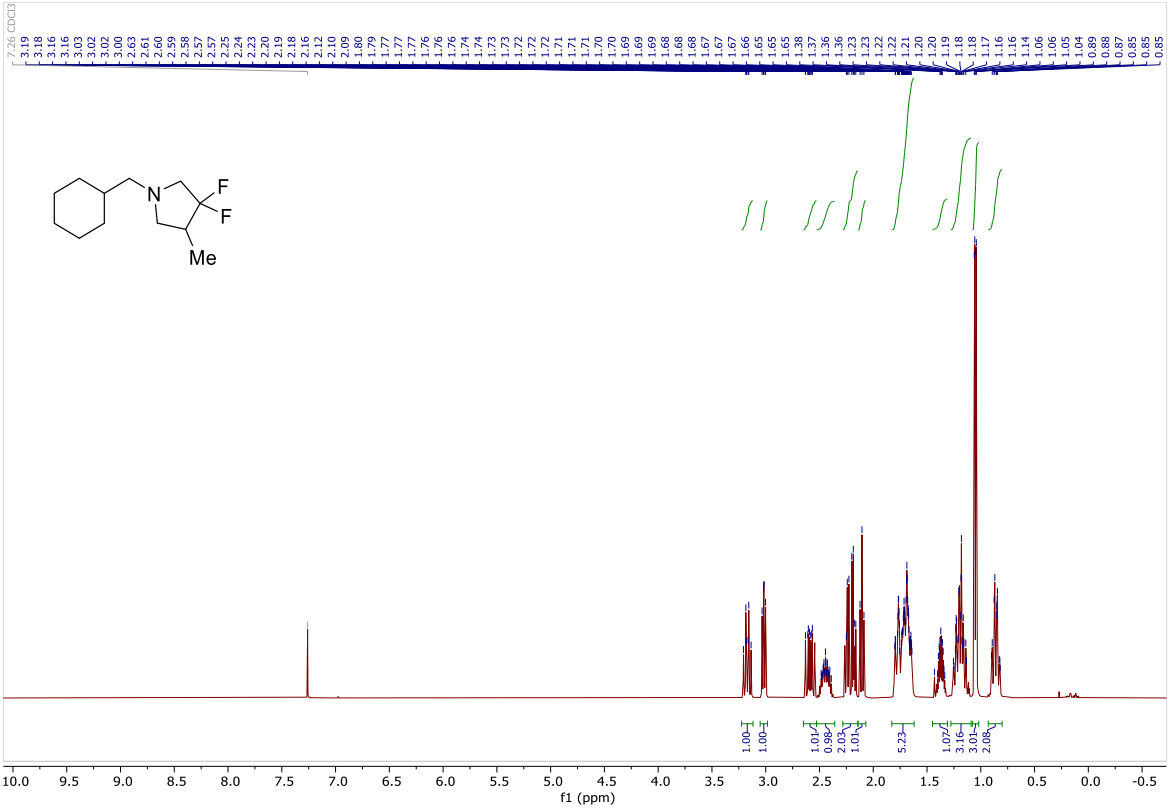
Supplementary Figure 101. ^{13}C NMR Methyl 4-((3,3-difluoro-4-methylpyrrolidin-1-yl)methyl)benzoate **7**



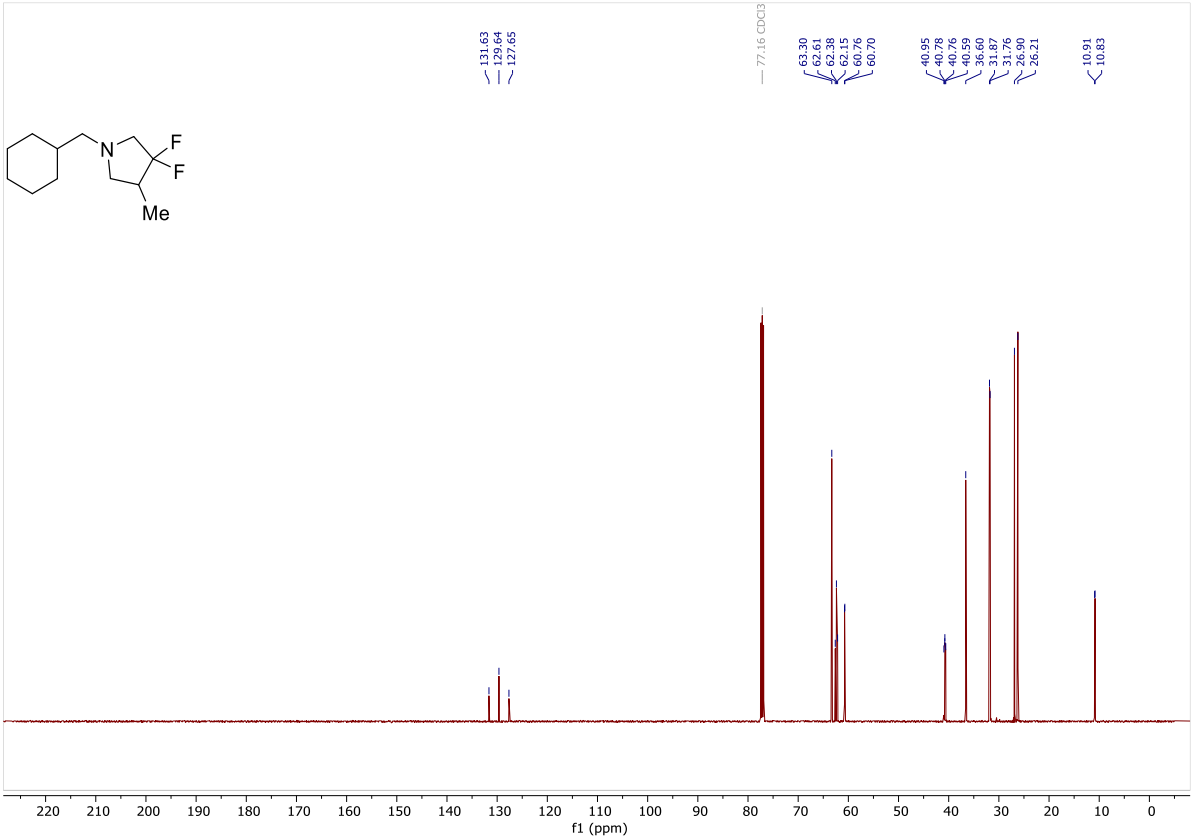
Supplementary Figure 102. ^{19}F NMR Methyl 4-((3,3-difluoro-4-methylpyrrolidin-1-yl)methyl)benzoate **7**



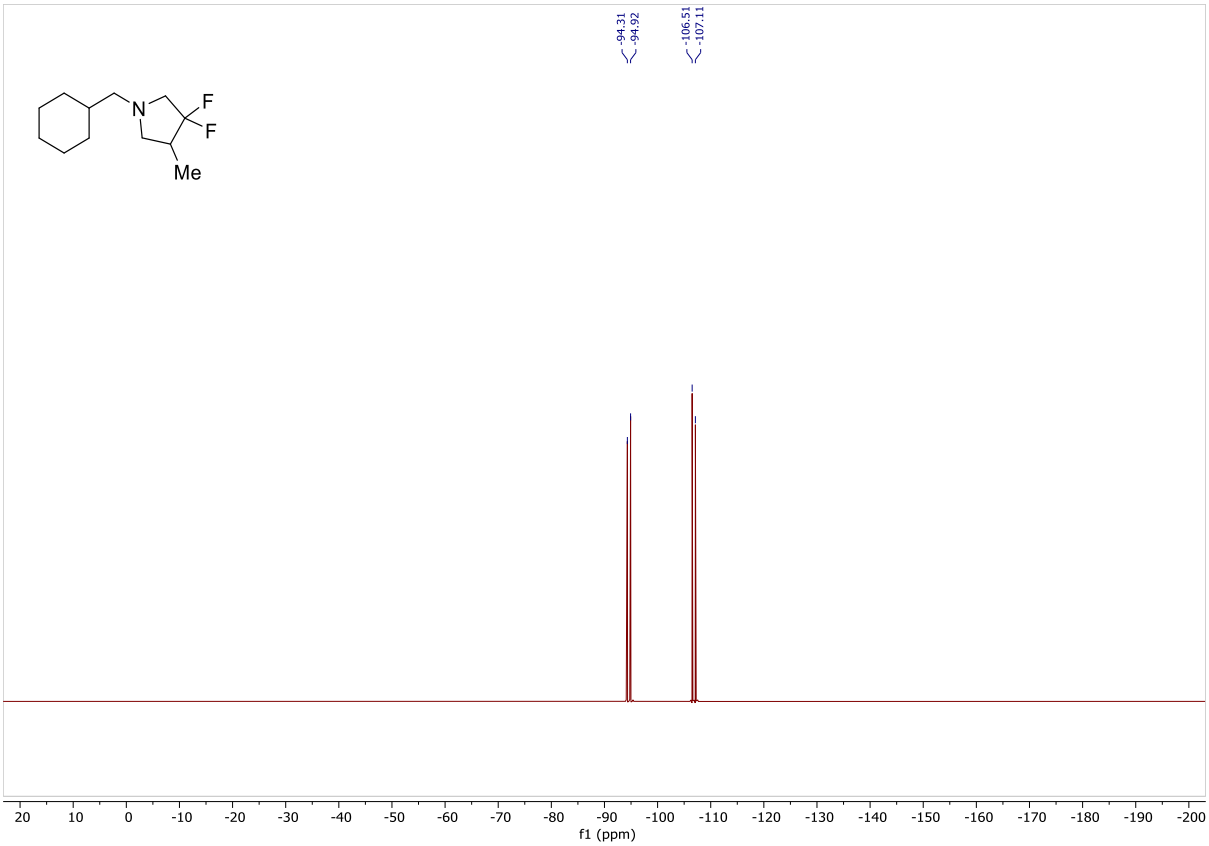
Supplementary Figure 103. ^{1}H NMR 1-(Cyclohexylmethyl)-3,3-difluoro-4-methylpyrrolidine **8**



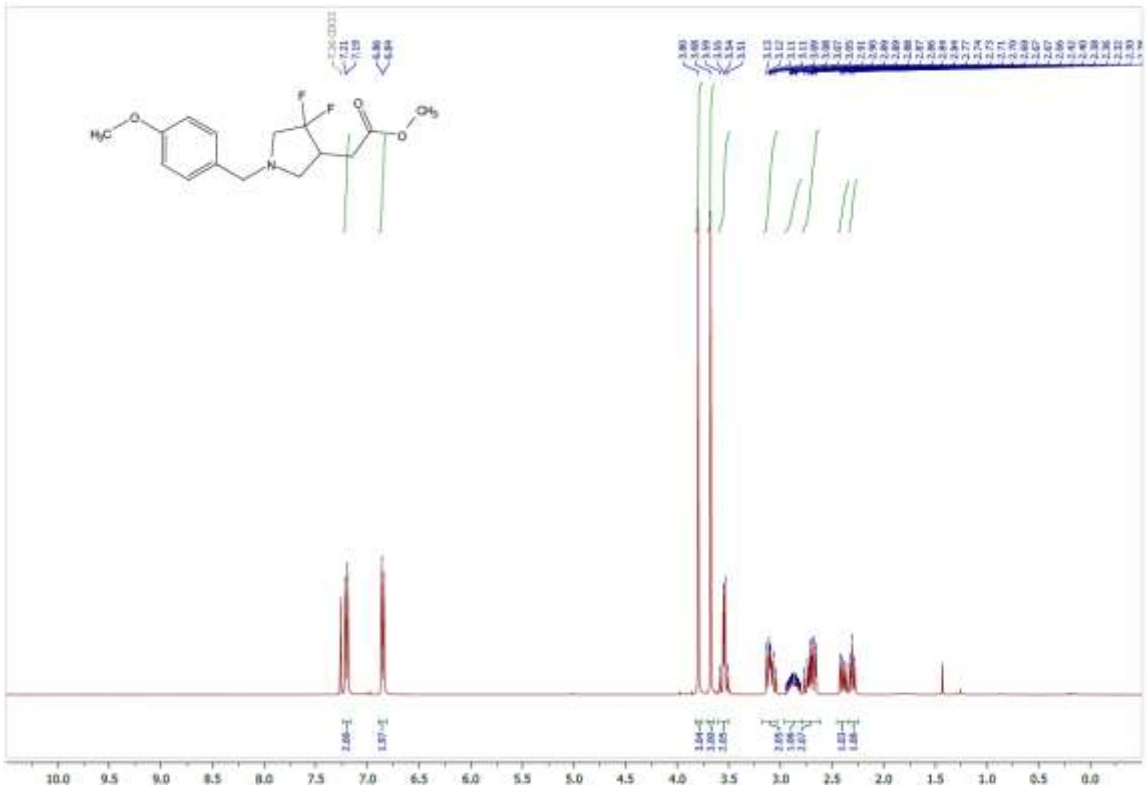
Supplementary Figure 104. ^{13}C NMR 1-(Cyclohexylmethyl)-3,3-difluoro-4-methylpyrrolidine **8**



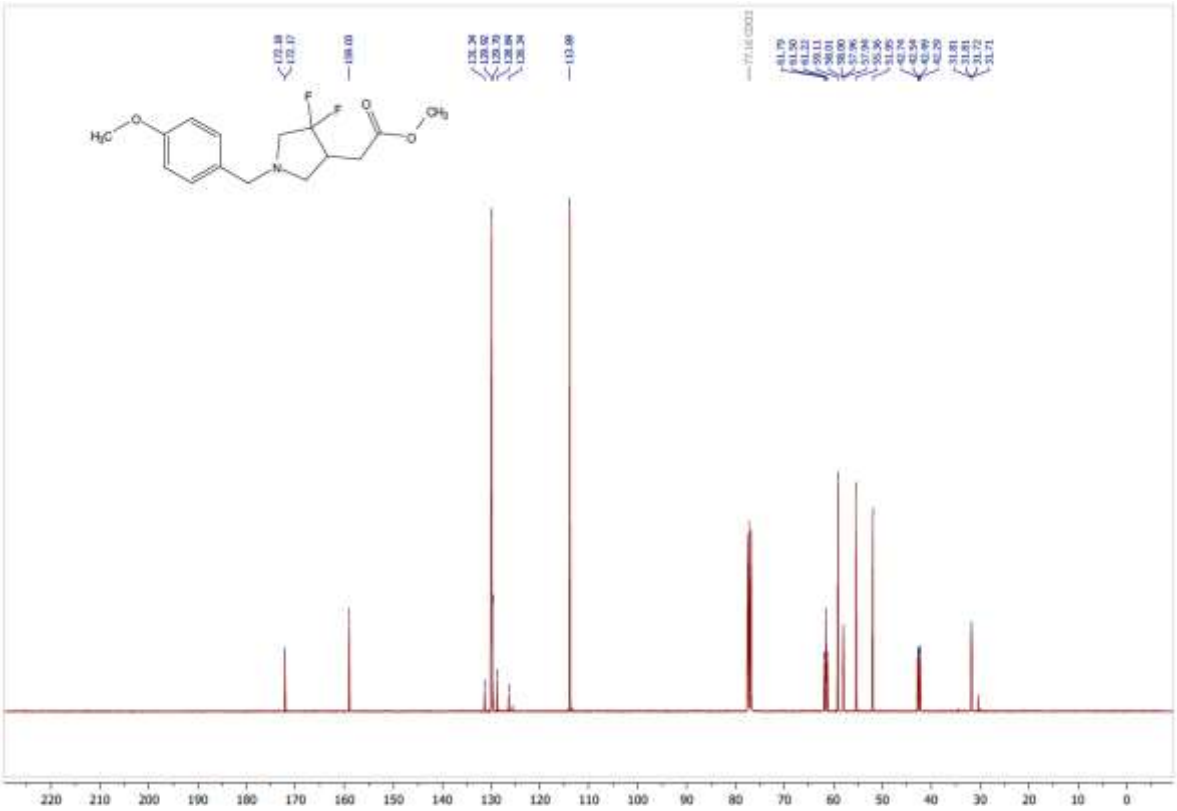
Supplementary Figure 105. ^{19}F NMR 1-(Cyclohexylmethyl)-3,3-difluoro-4-methylpyrrolidine **8**



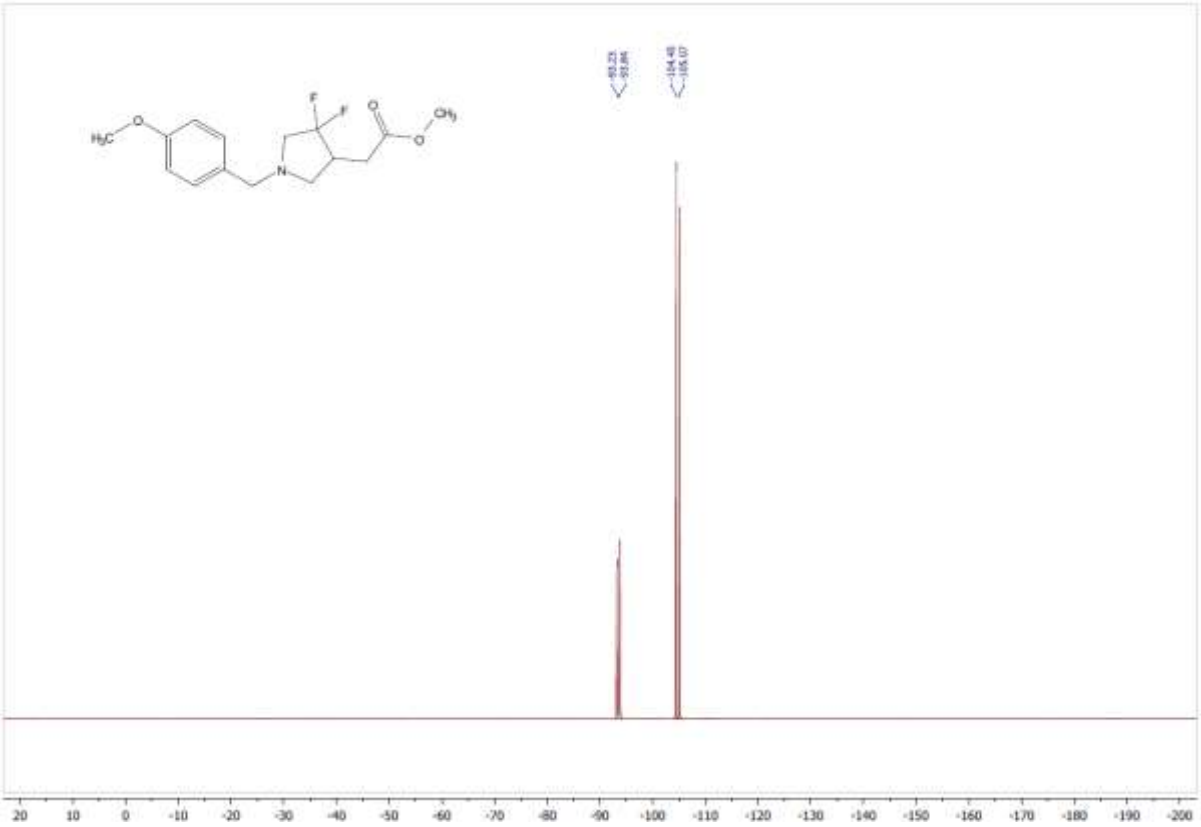
Supplementary Figure 106. ^{1}H NMR Methyl 2-(4,4-difluoro-1-(4-methoxybenzyl)pyrrolidin-3-yl)acetate **9**



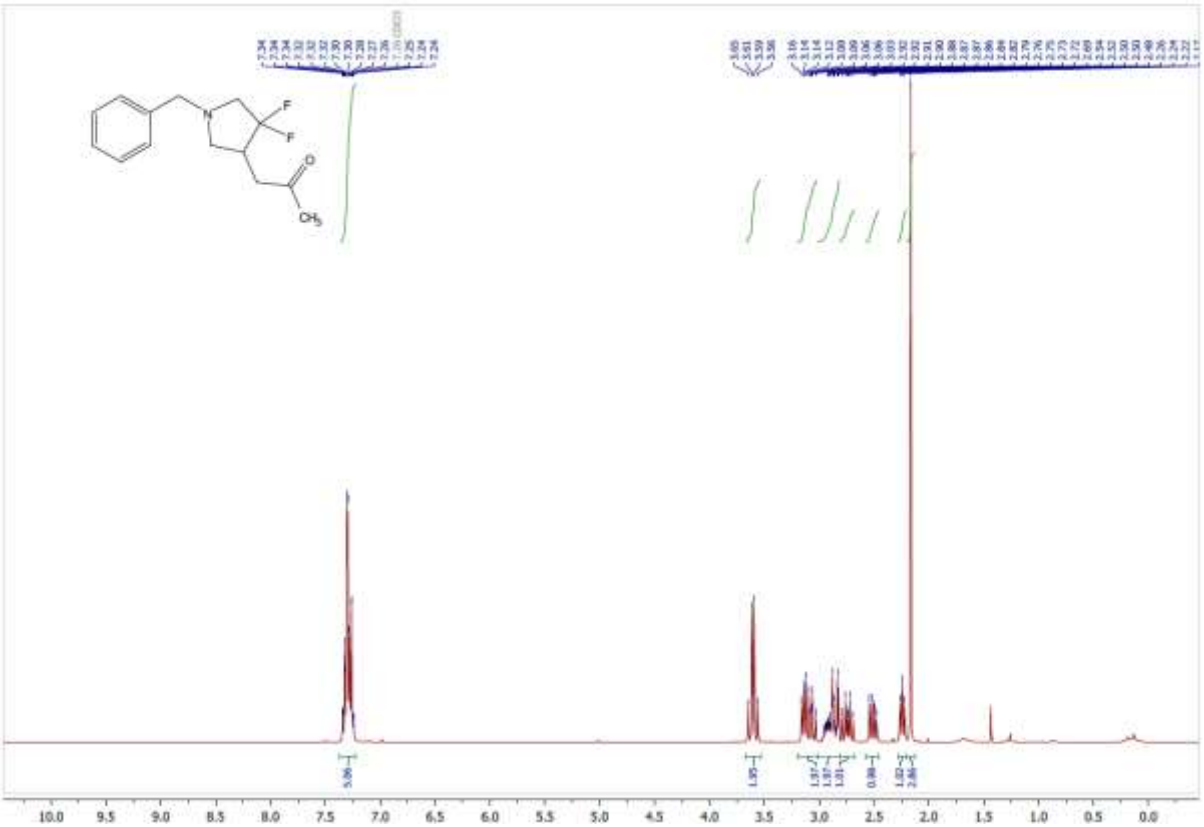
Supplementary Figure 107. ^{13}C NMR Methyl 2-(4,4-difluoro-1-(4-methoxybenzyl)pyrrolidin-3-yl)acetate **9**



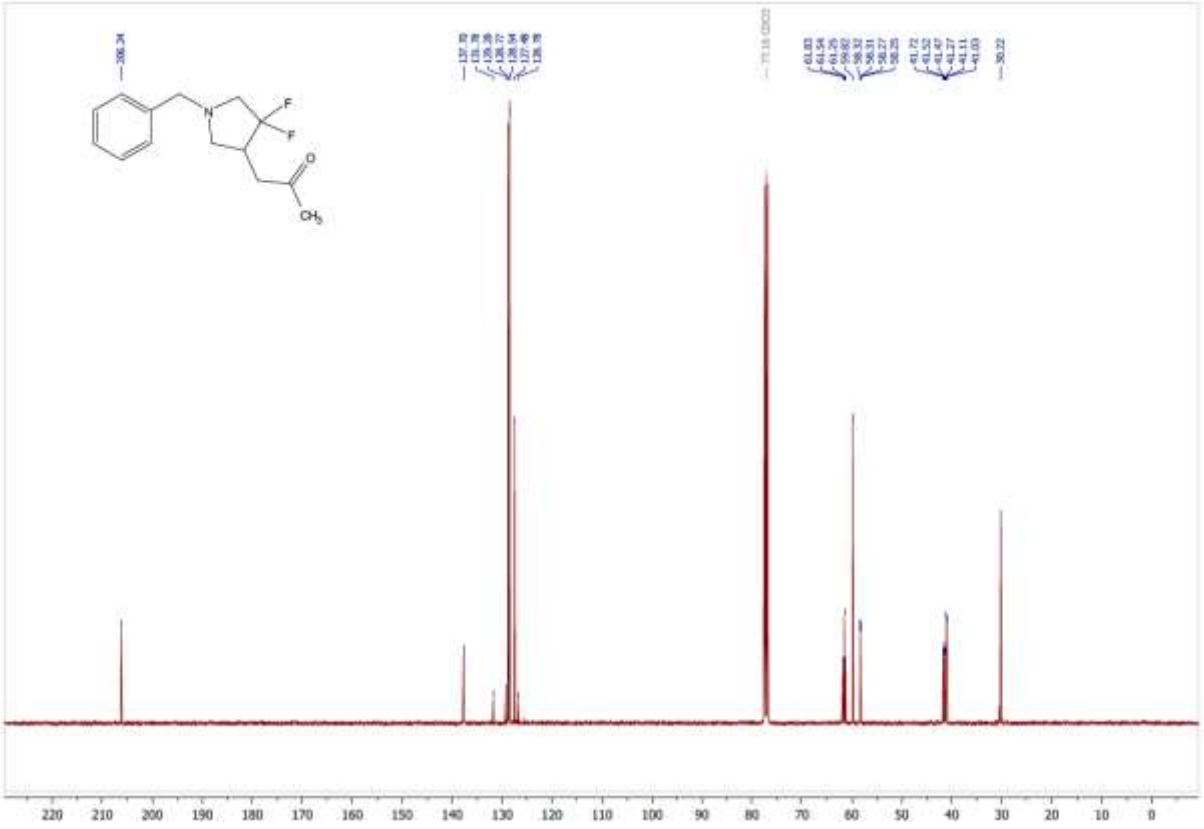
Supplementary Figure 108. ^{19}F NMR Methyl 2-(4,4-difluoro-1-(4-methoxybenzyl)pyrrolidin-3-yl)acetate **9**



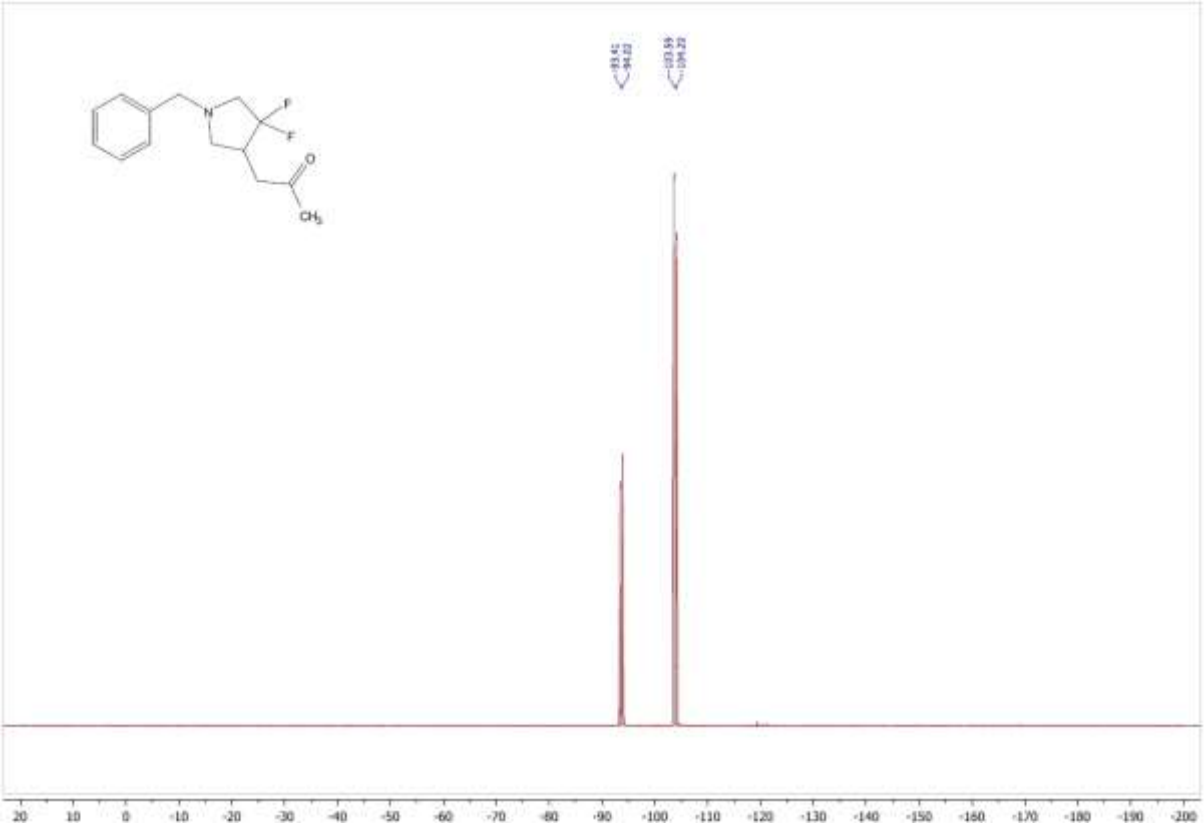
Supplementary Figure 109. ^{1}H NMR 1-(1-Benzyl-4,4-difluoropyrrolidin-3-yl)propan-2-one **10**



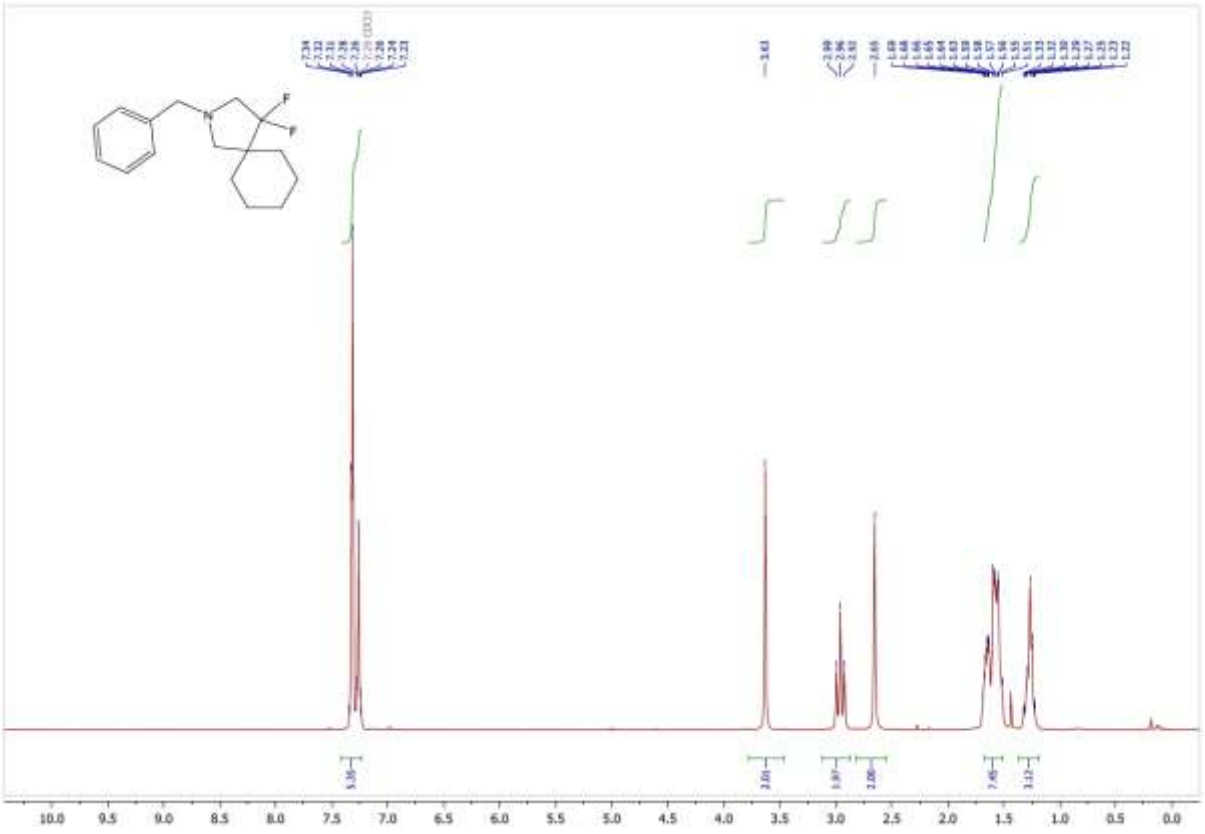
Supplementary Figure 110. ^{13}C NMR 1-(1-Benzyl-4,4-difluoropyrrolidin-3-yl)propan-2-one **10**



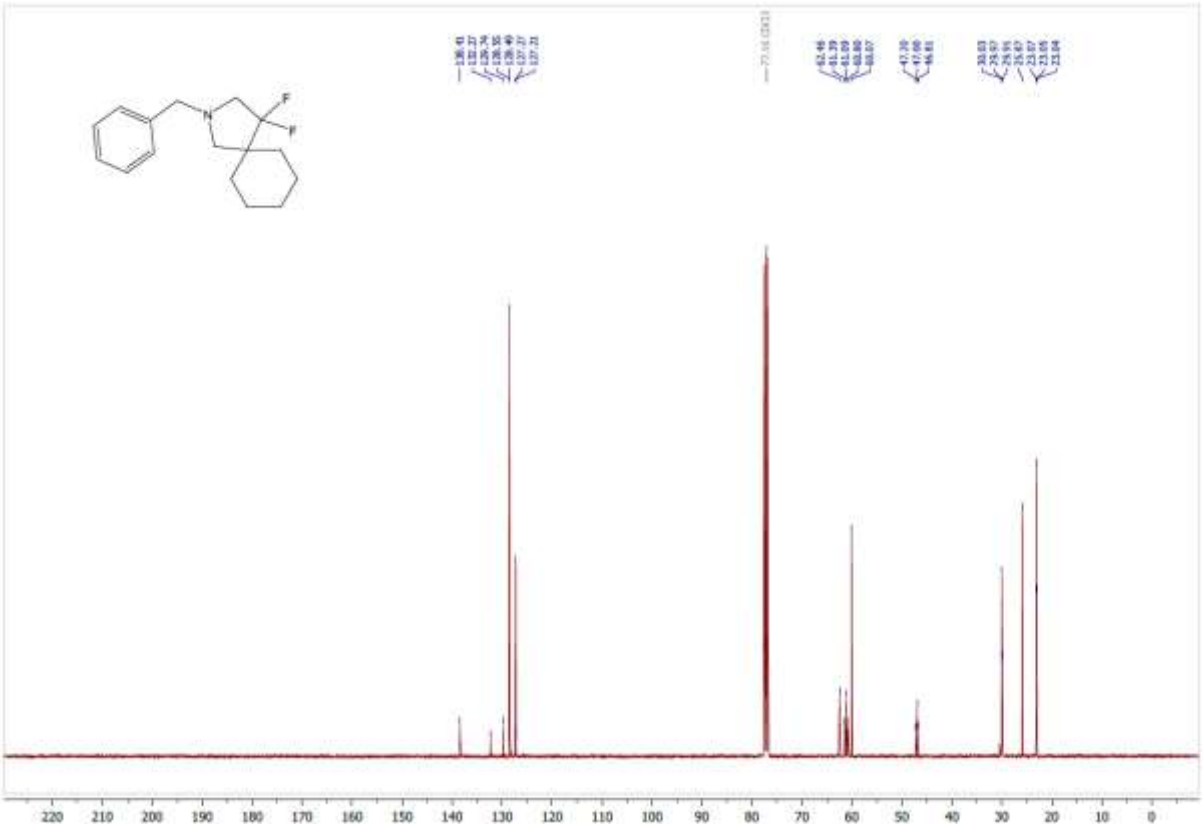
Supplementary Figure 111. ^{19}F NMR 1-(1-Benzyl-4,4-difluoropyrrolidin-3-yl)propan-2-one **10**



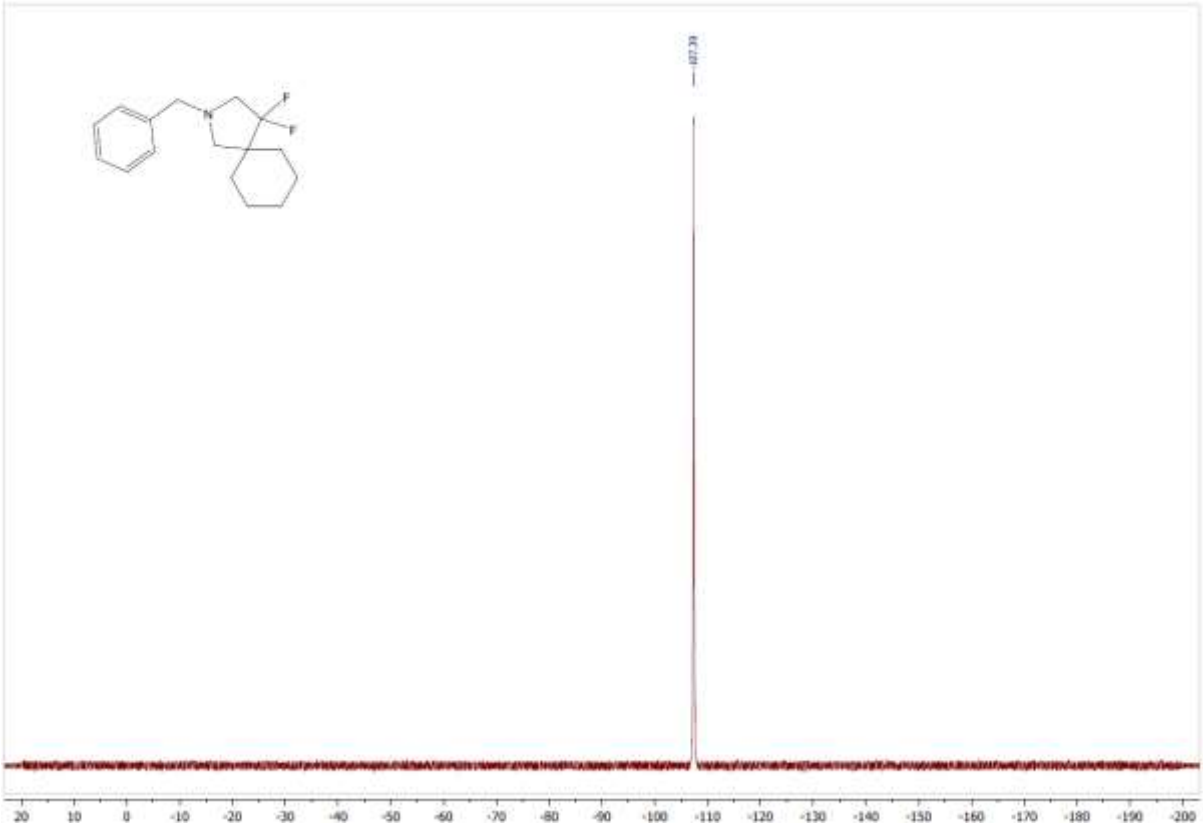
Supplementary Figure 112. ^{1}H NMR 2-Benzyl-4,4-difluoro-2-azaspiro[4.5]decane **11**



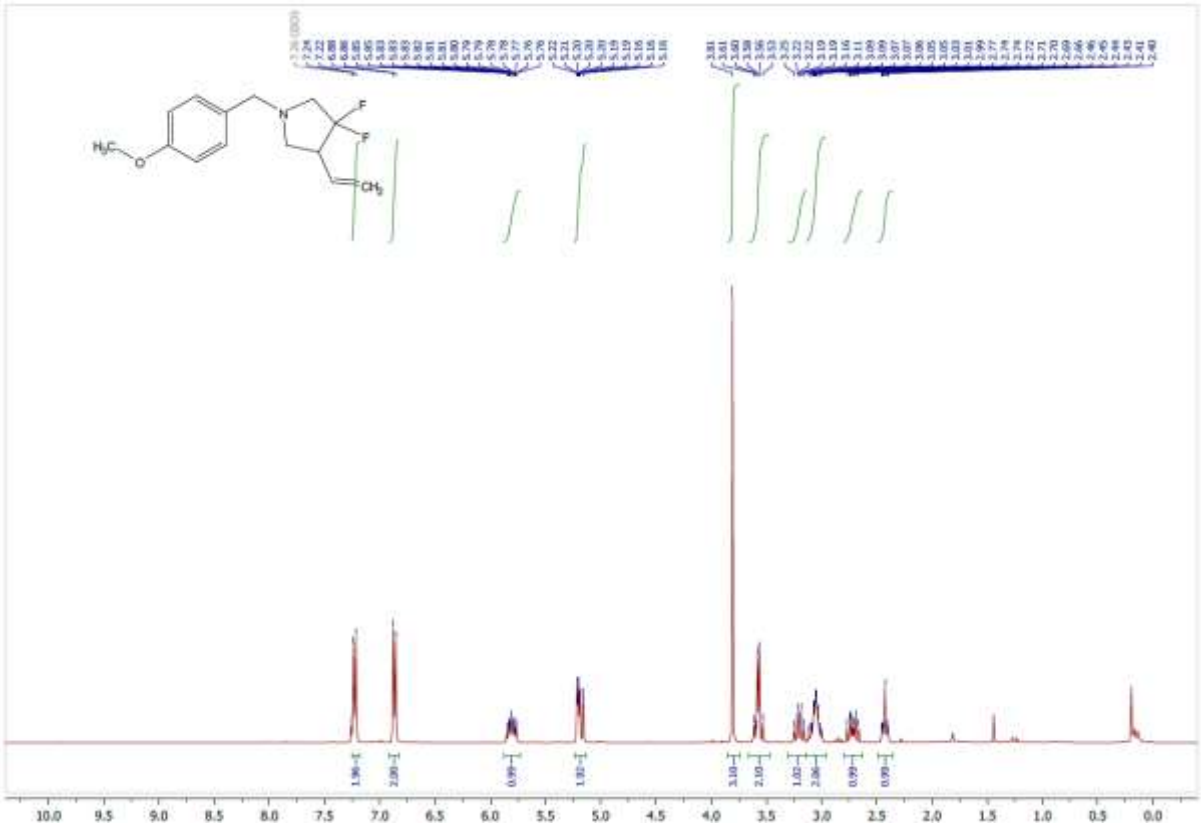
Supplementary Figure 113. ^{13}C NMR 2-Benzyl-4,4-difluoro-2-azaspiro[4.5]decane **11**



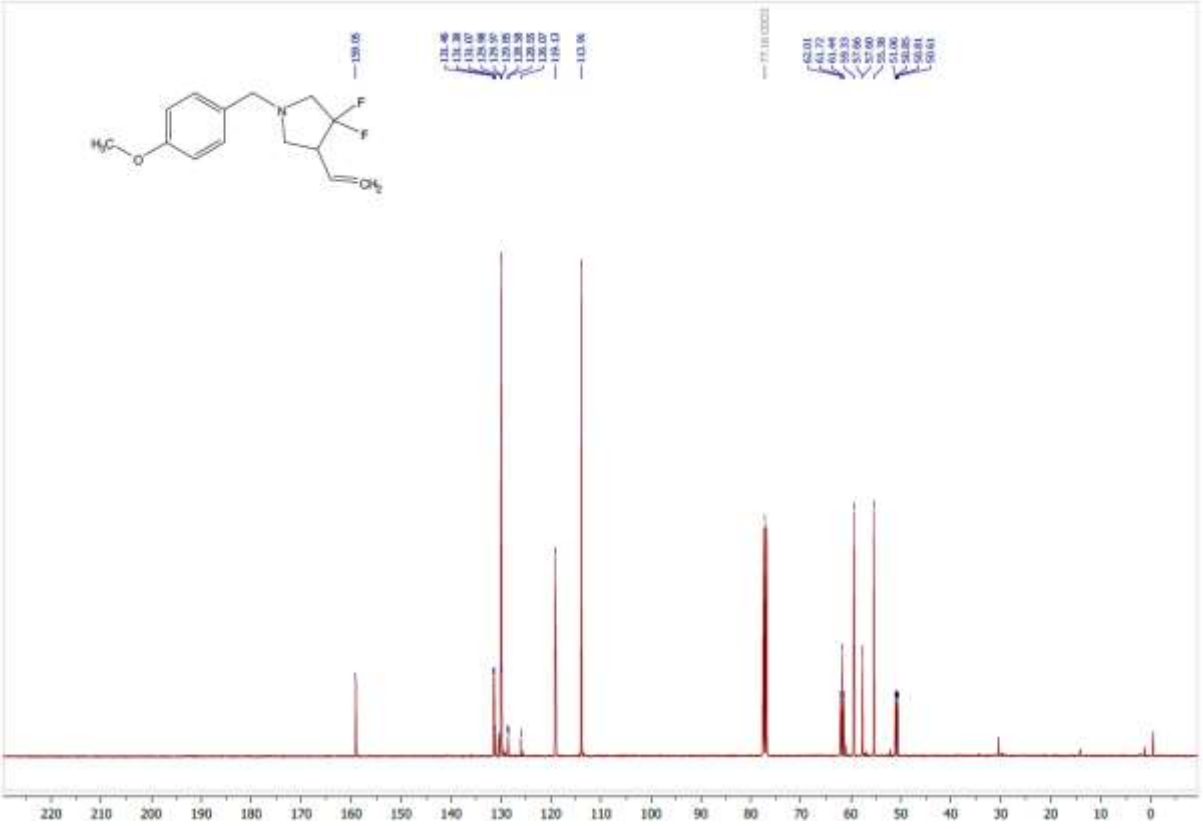
Supplementary Figure 114. ^{19}F NMR 2-Benzyl-4,4-difluoro-2-azaspiro[4.5]decane **11**



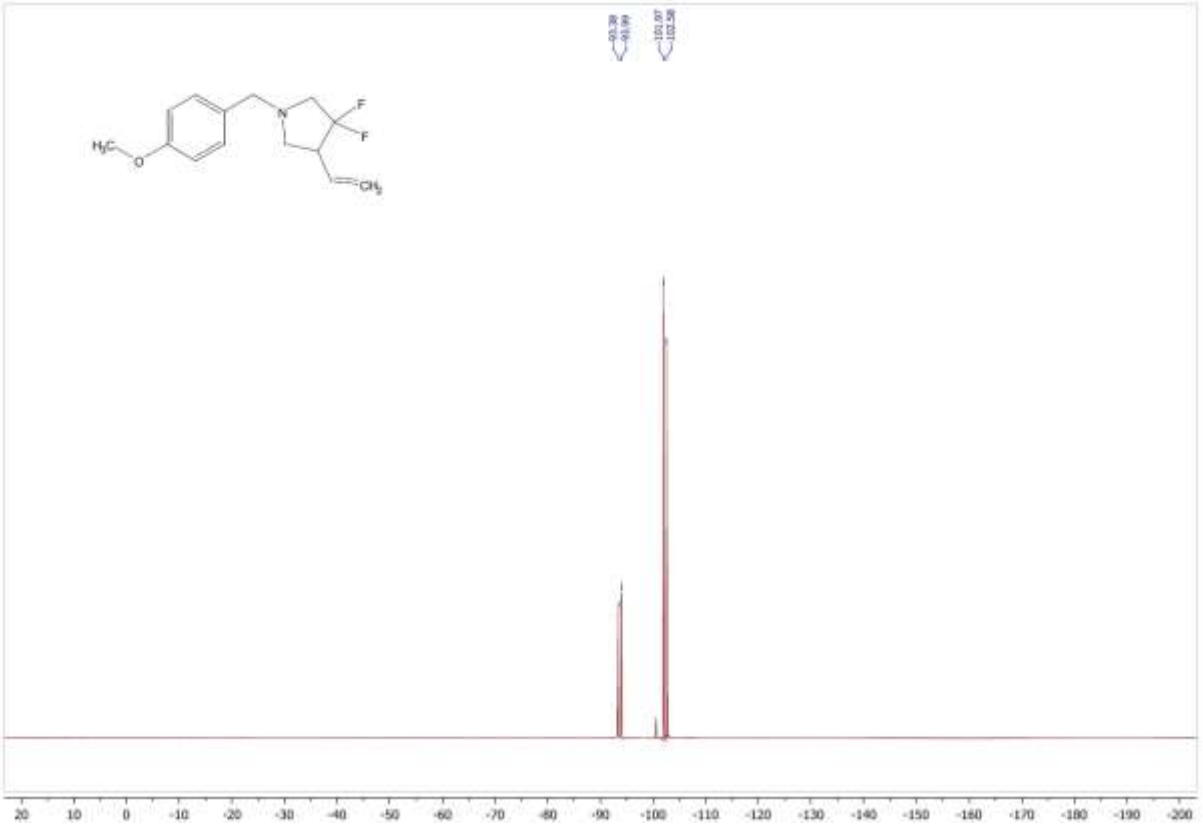
Supplementary Figure 115. ^{1}H NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-vinylpyrrolidine **12**



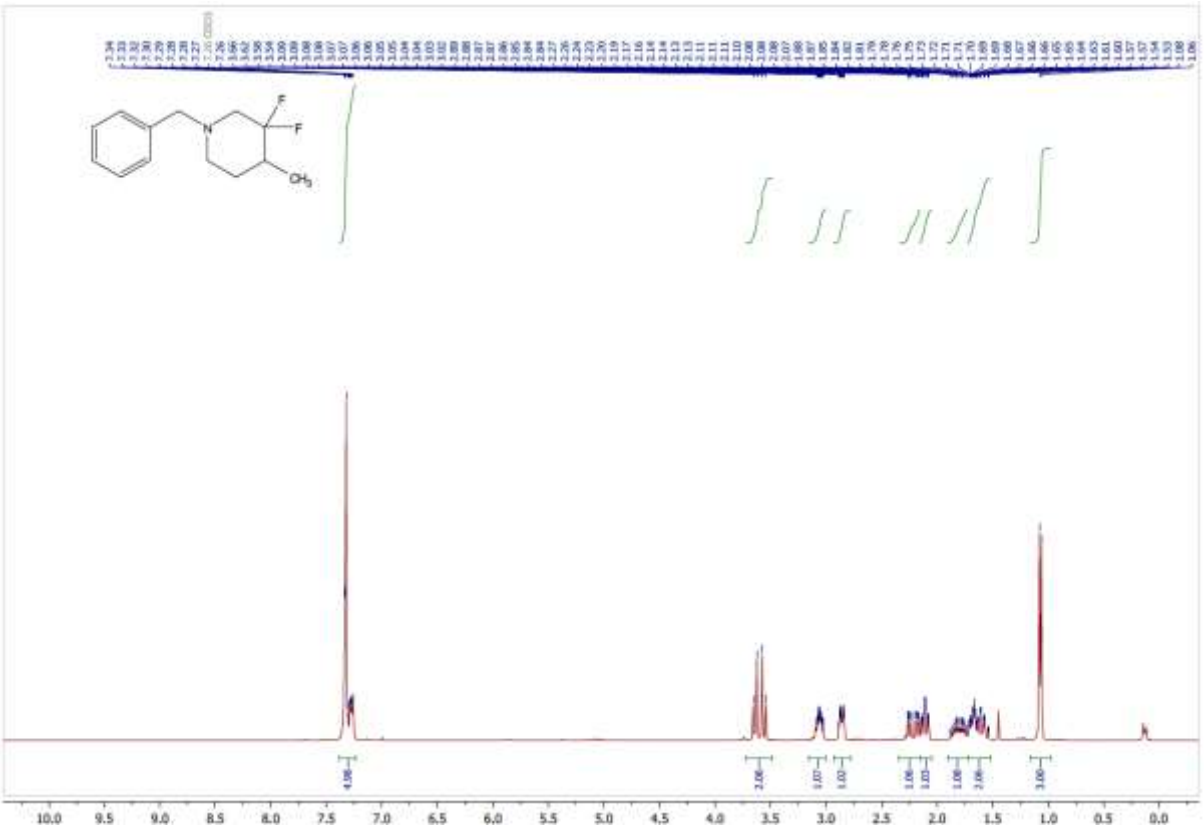
Supplementary Figure 116. ^{13}C NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-vinylpyrrolidine **12**



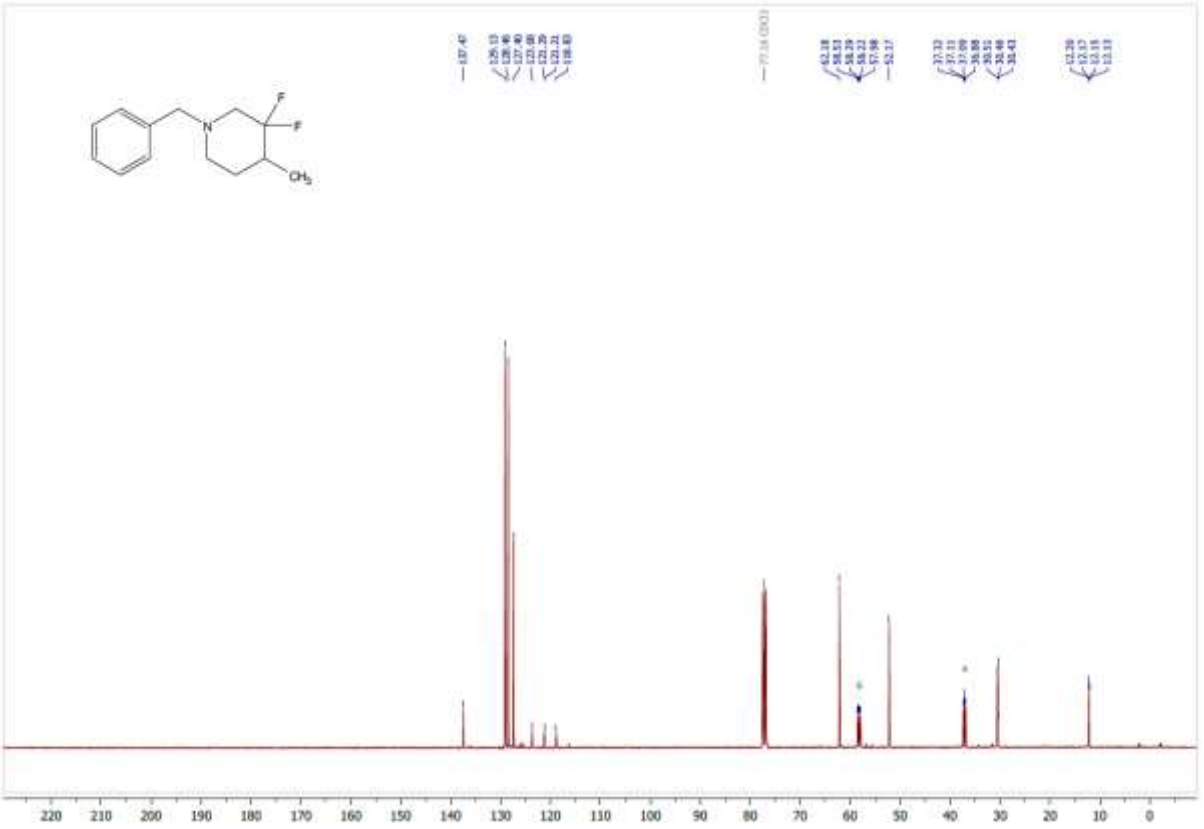
Supplementary Figure 117. ^{19}F NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-vinylpyrrolidine **12**



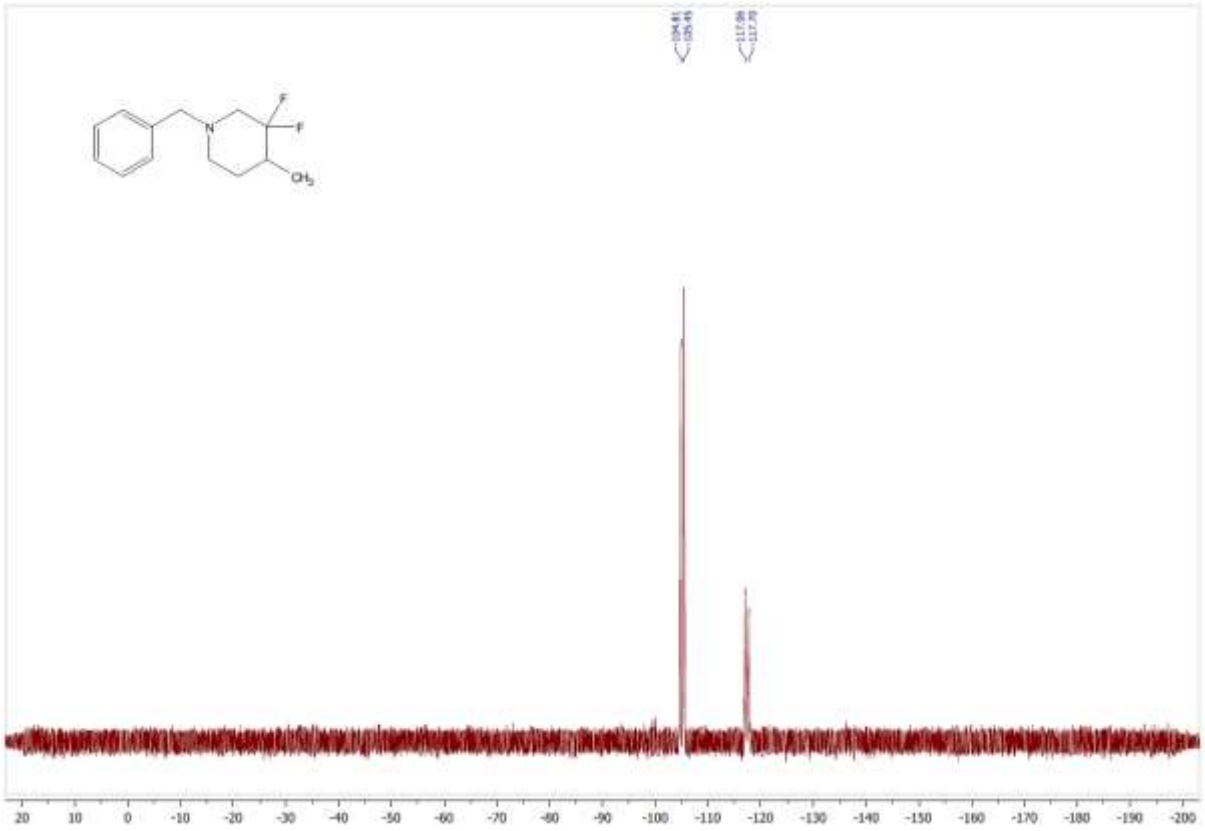
Supplementary Figure 118. ^{1}H NMR 1-Benzyl-3,3-difluoro-4-methylpiperidine **1213**



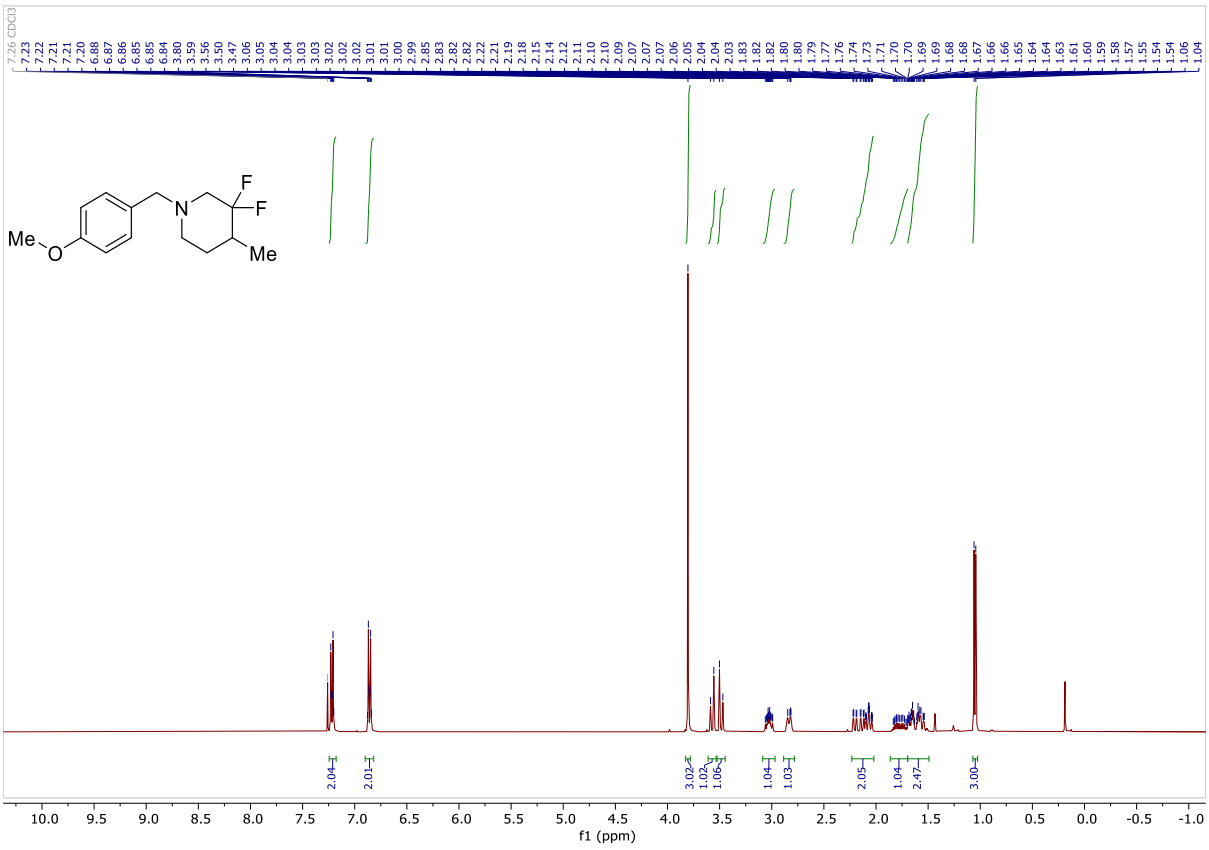
Supplementary Figure 119. ^{13}C NMR 1-Benzyl-3,3-difluoro-4-methylpiperidine **13**



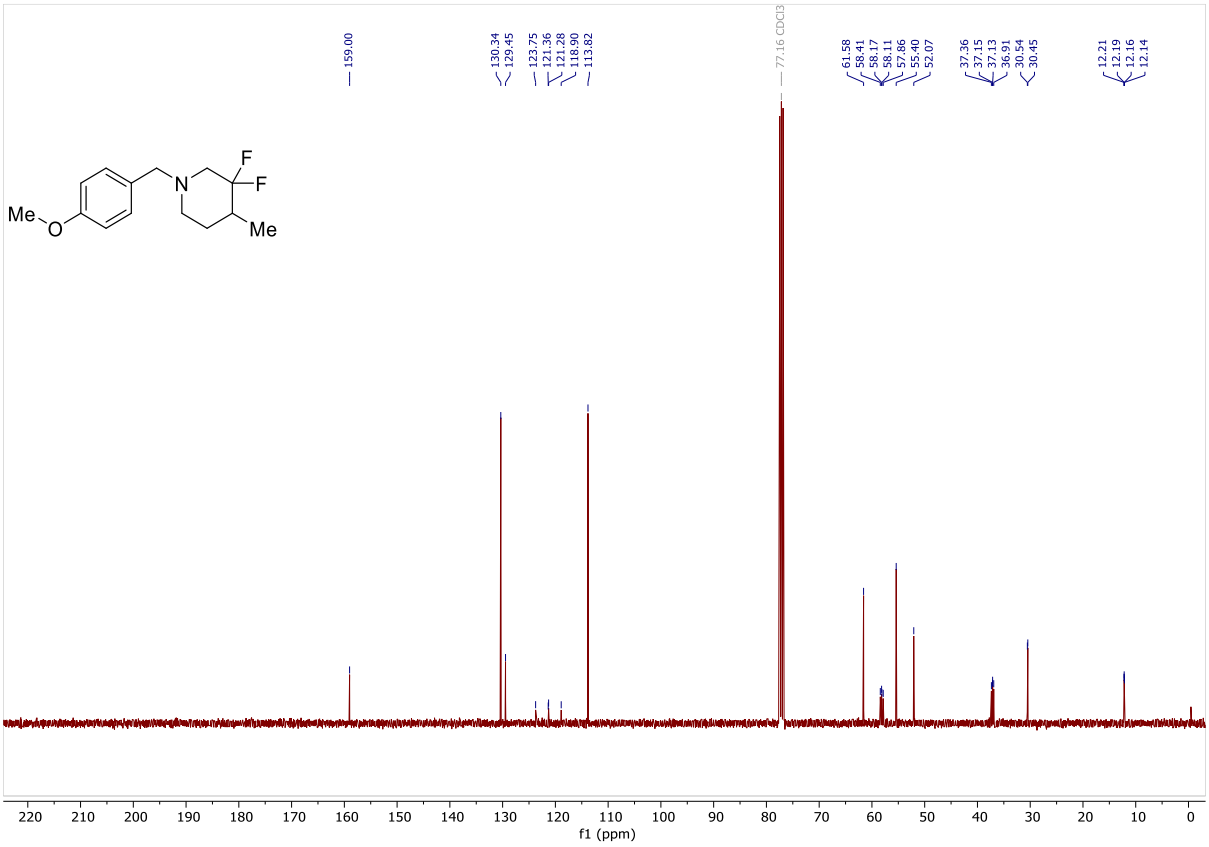
Supplementary Figure 120. ^{19}F NMR 1-Benzyl-3,3-difluoro-4-methylpiperidine **13**



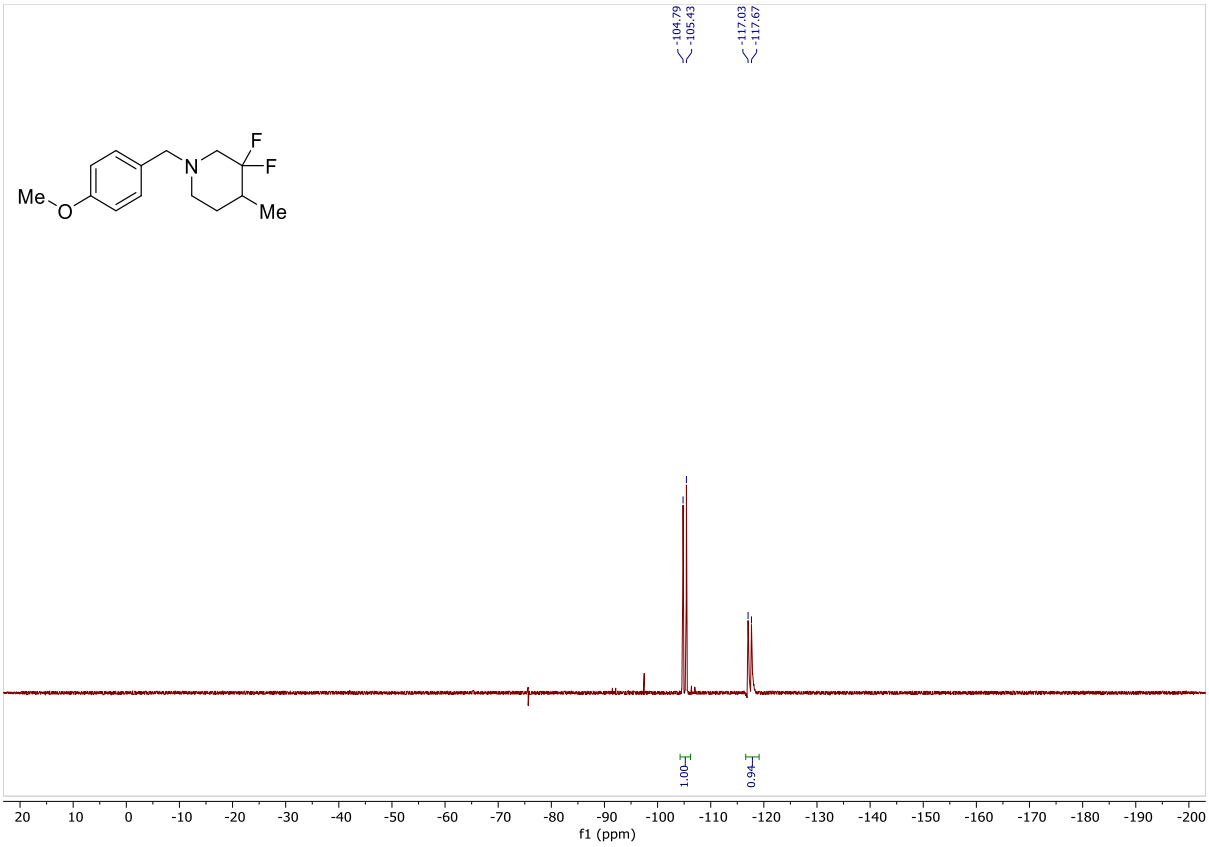
Supplementary Figure 121. ^{1}H NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpiperidine **14**



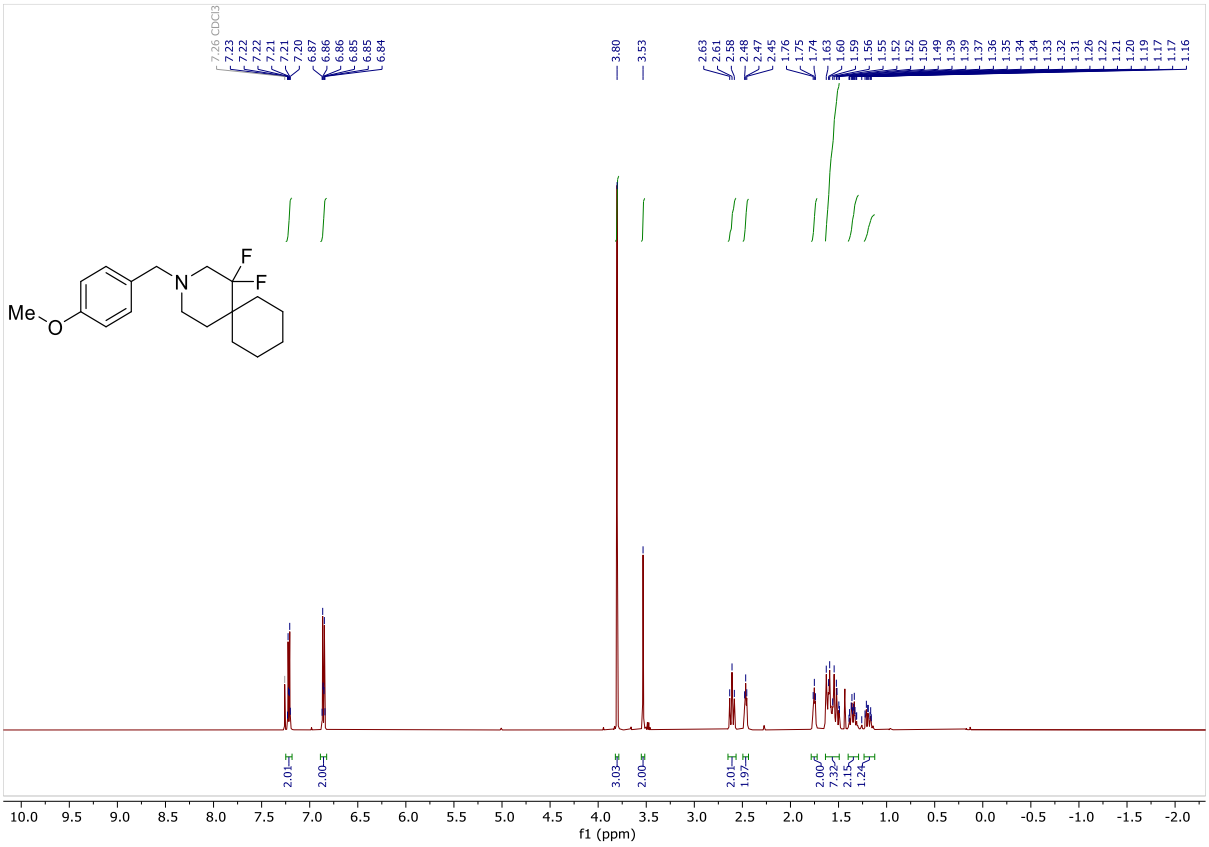
Supplementary Figure 122. ^{13}C NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpiperidine **14**



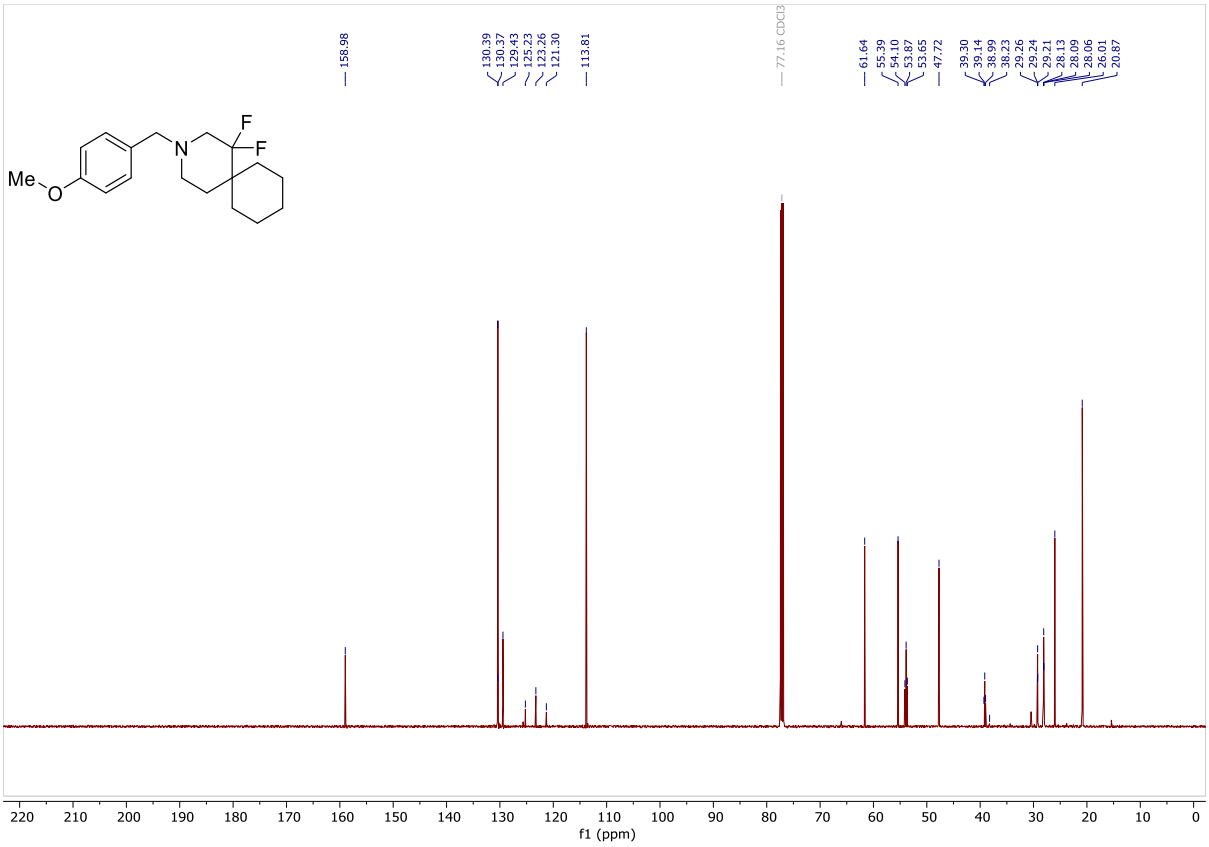
Supplementary Figure 123. ^{19}F NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylpiperidine **14**



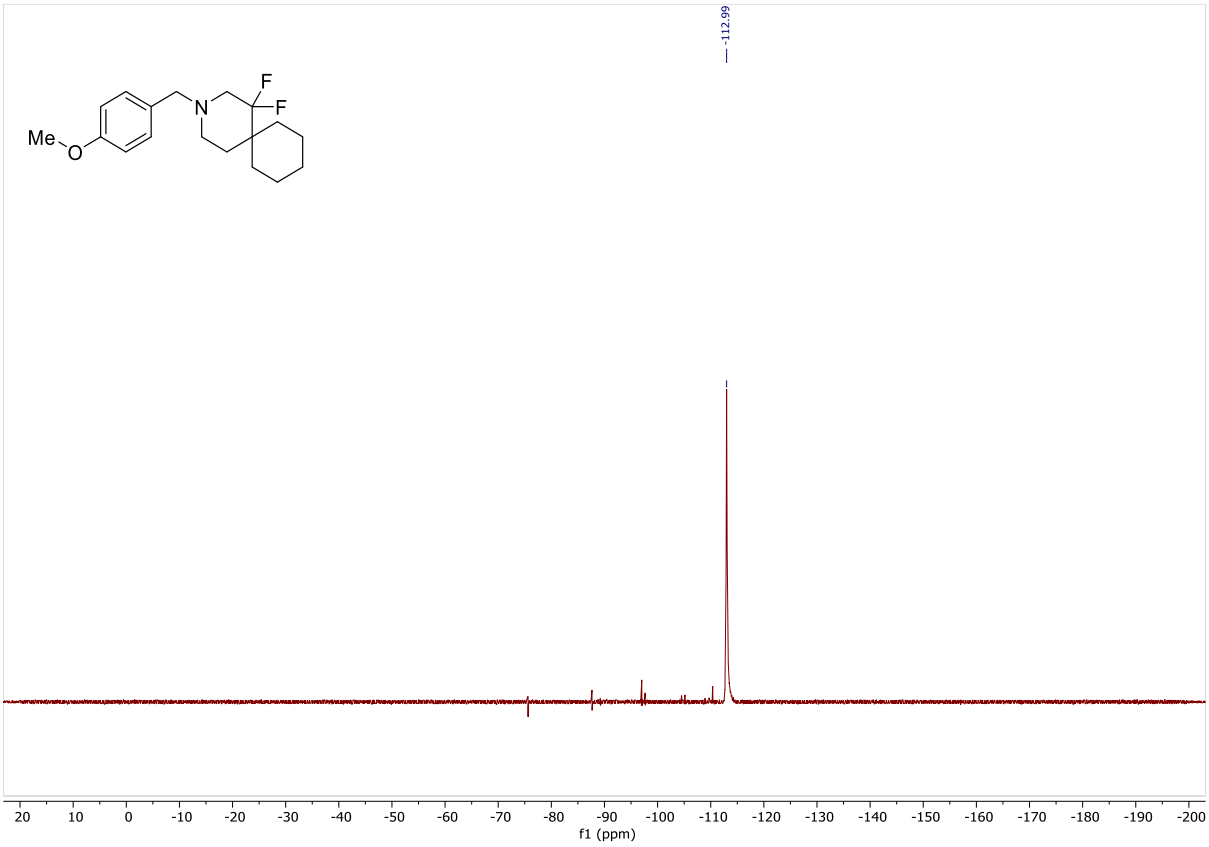
Supplementary Figure 124. ^{1}H NMR 5,5-Difluoro-2-(4-methoxybenzyl)-2-azaspiro[5.5]undecane **15**



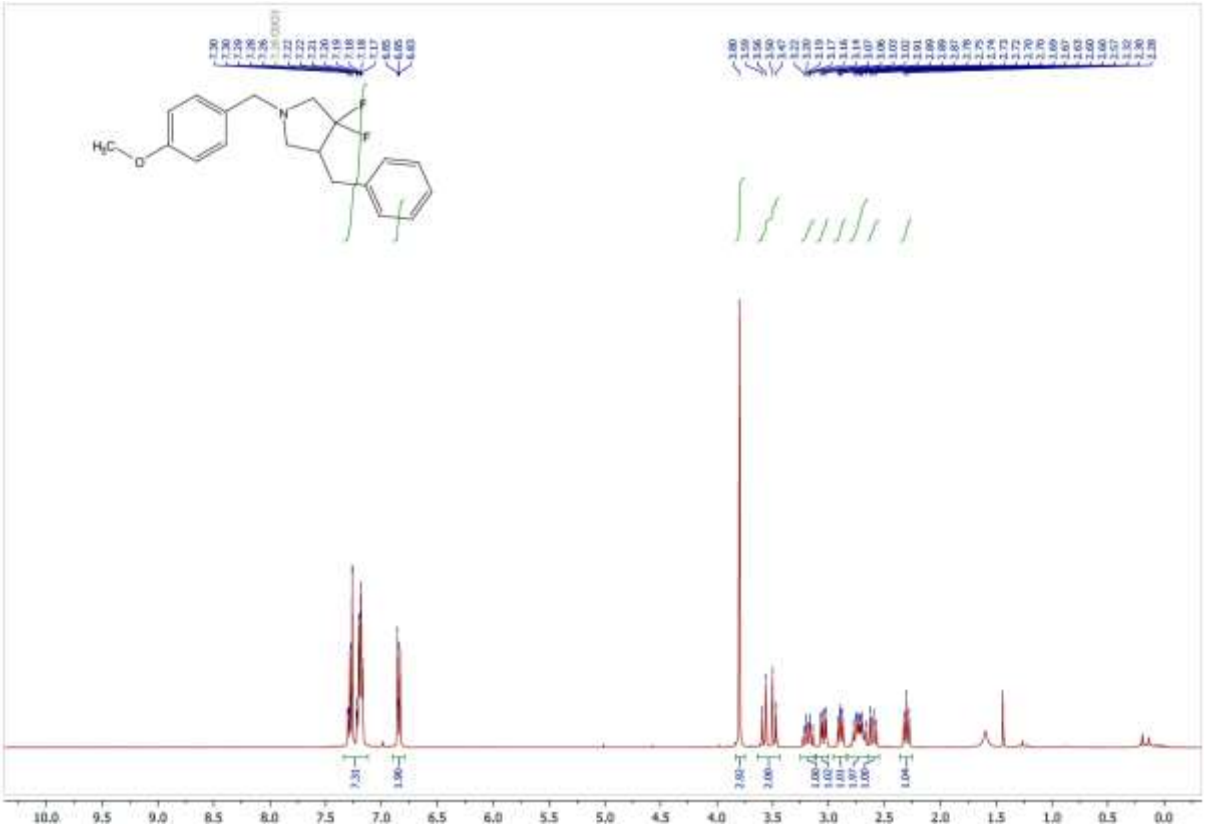
Supplementary Figure 125. ^{13}C NMR 5,5-Difluoro-2-(4-methoxybenzyl)-2-azaspiro[5.5]undecane **15**



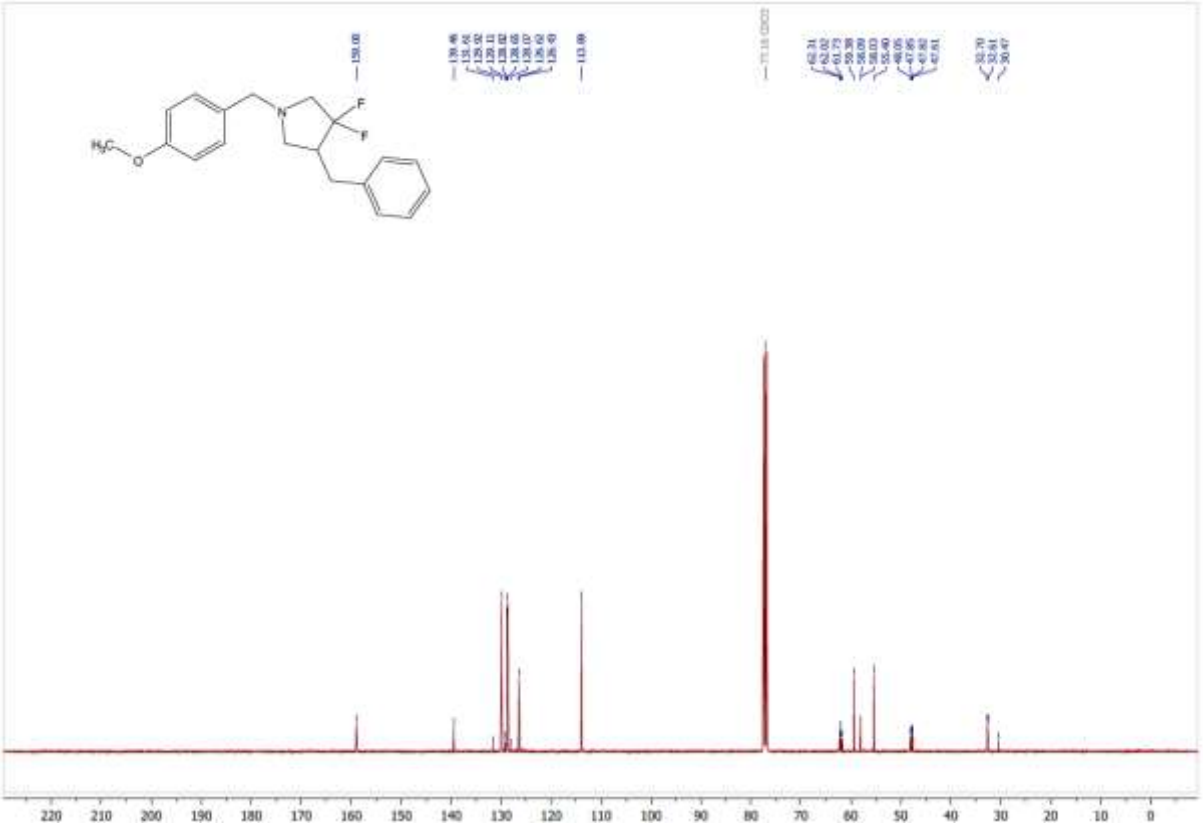
Supplementary Figure 126. ^{19}F NMR 5,5-Difluoro-2-(4-methoxybenzyl)-2-azaspiro[5.5]undecane **15**



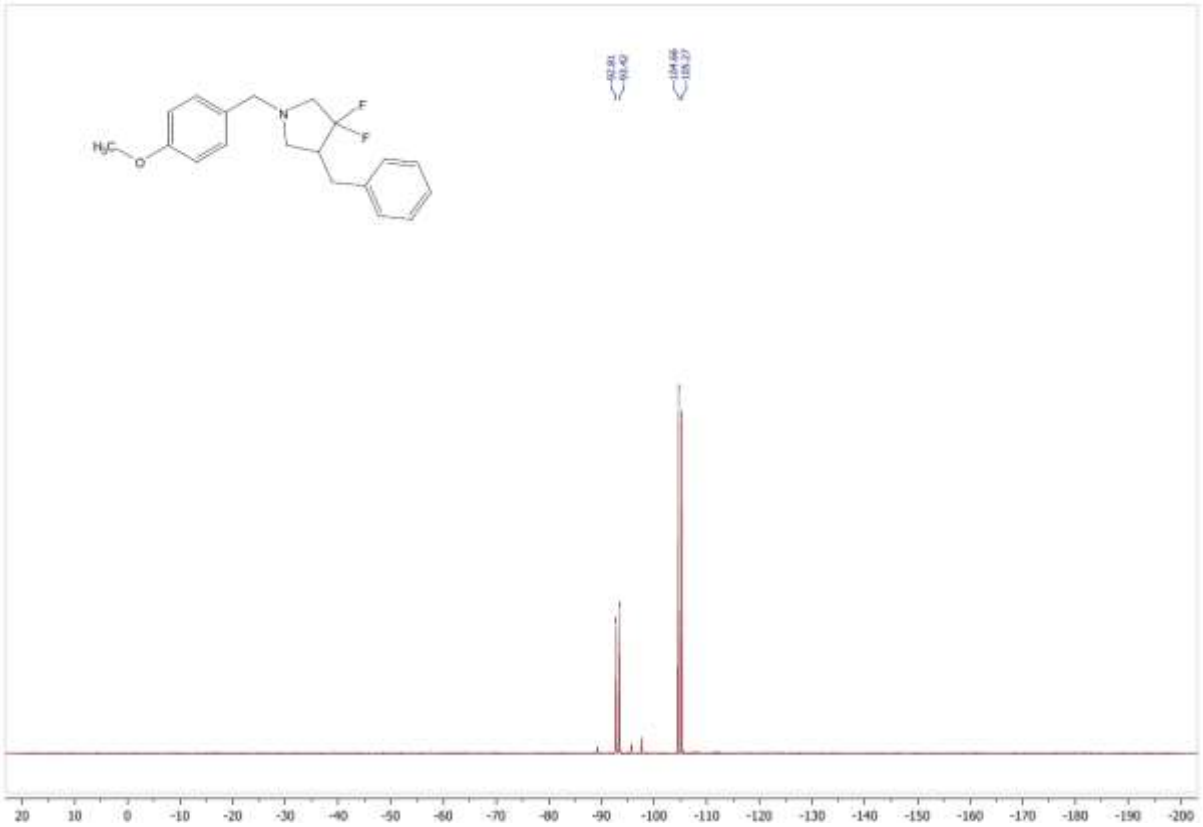
Supplementary Figure 126. ^{1}H NMR 4-Benzyl-3,3-difluoro-1-(4-methoxybenzyl)pyrrolidine **16**



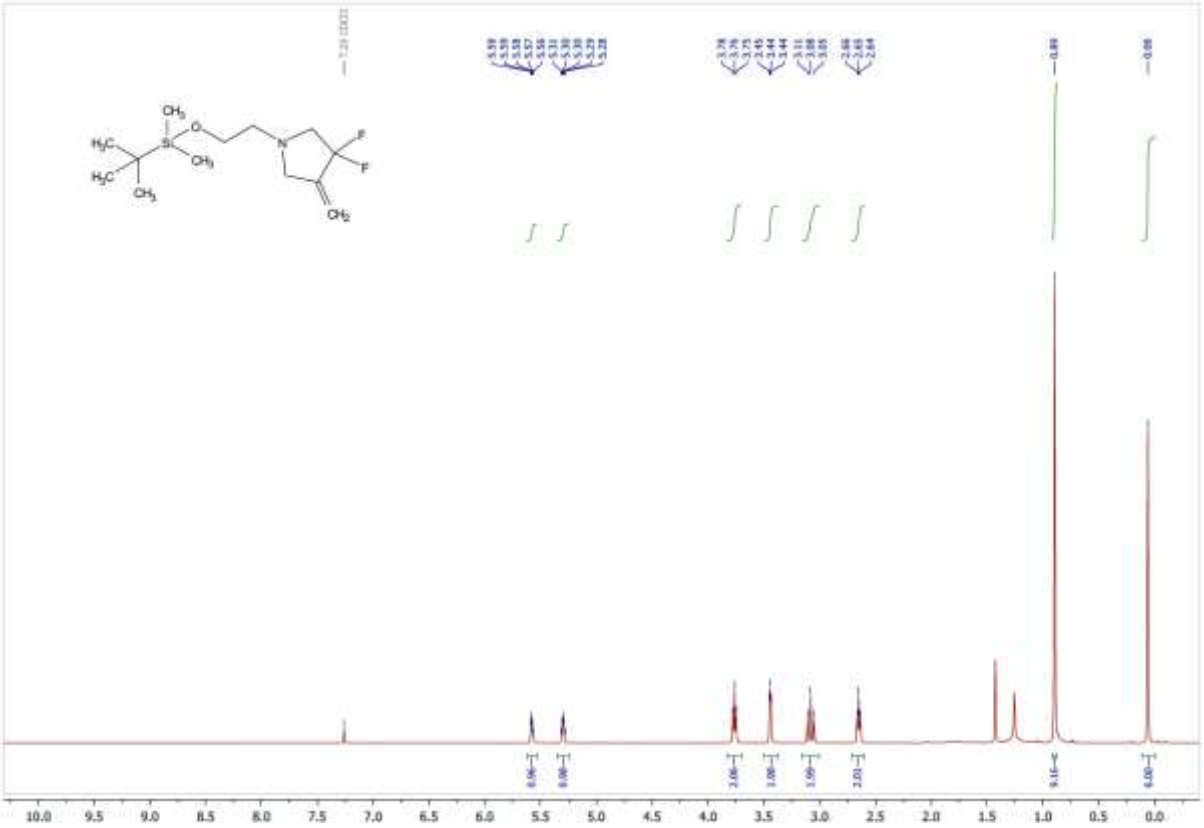
Supplementary Figure 128. ^{13}C NMR 4-Benzyl-3,3-difluoro-1-(4-methoxybenzyl)pyrrolidine **16**



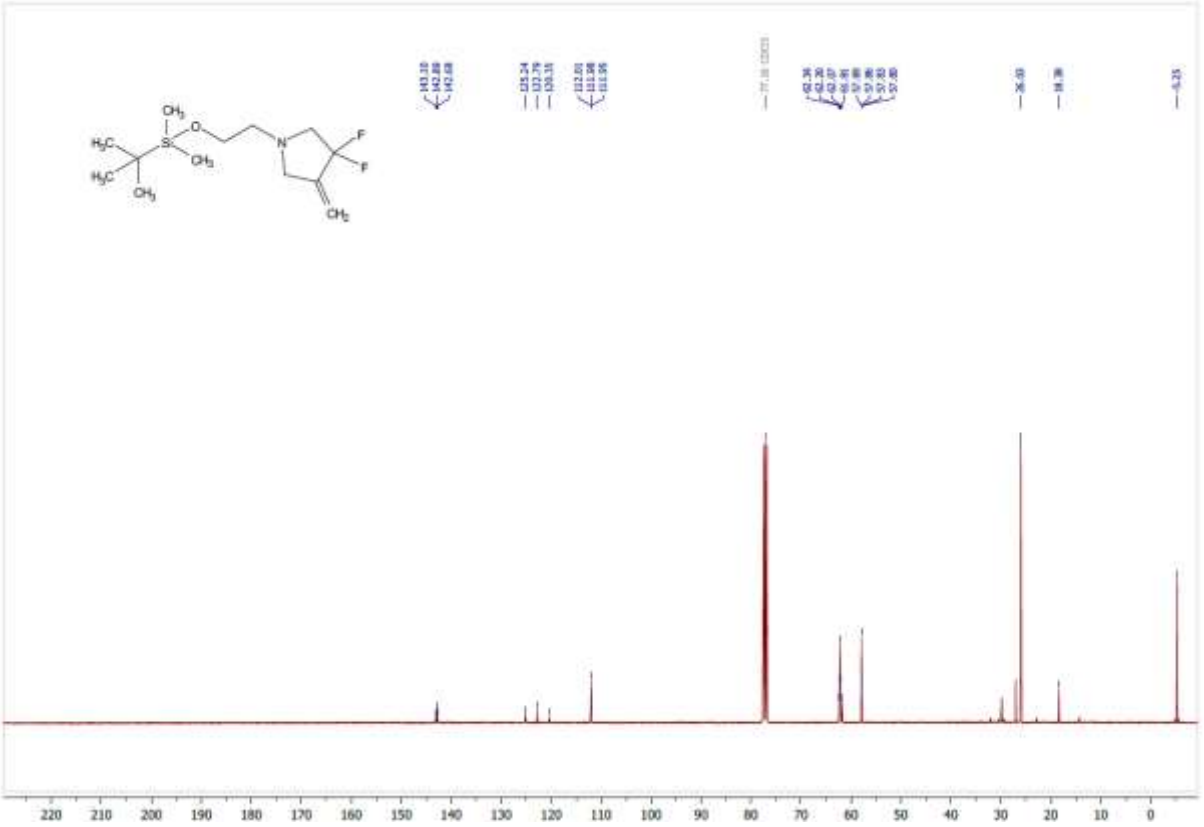
Supplementary Figure 129. ^{19}F NMR 4-Benzyl-3,3-difluoro-1-(4-methoxybenzyl)pyrrolidine **16**



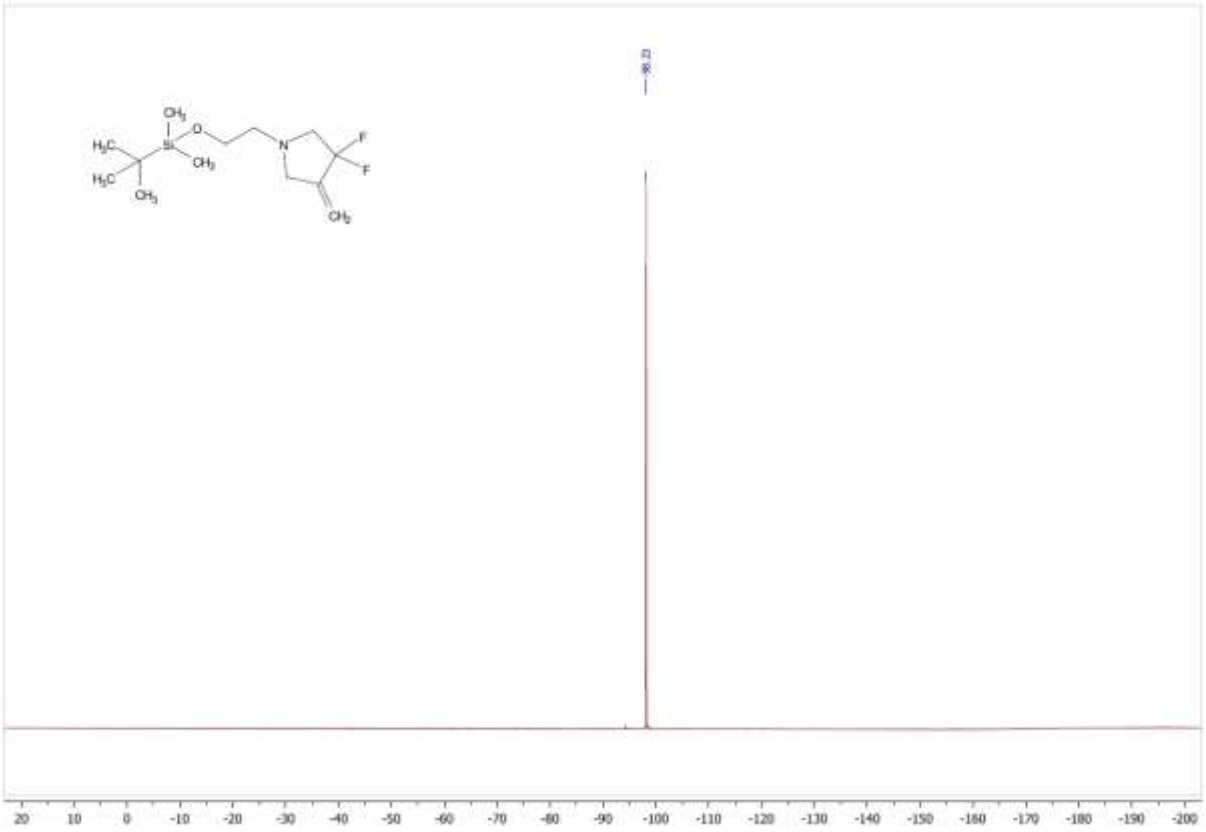
Supplementary Figure 130. ^{1}H NMR 1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3,3-difluoro-4-methylenepyrrolidine **4**



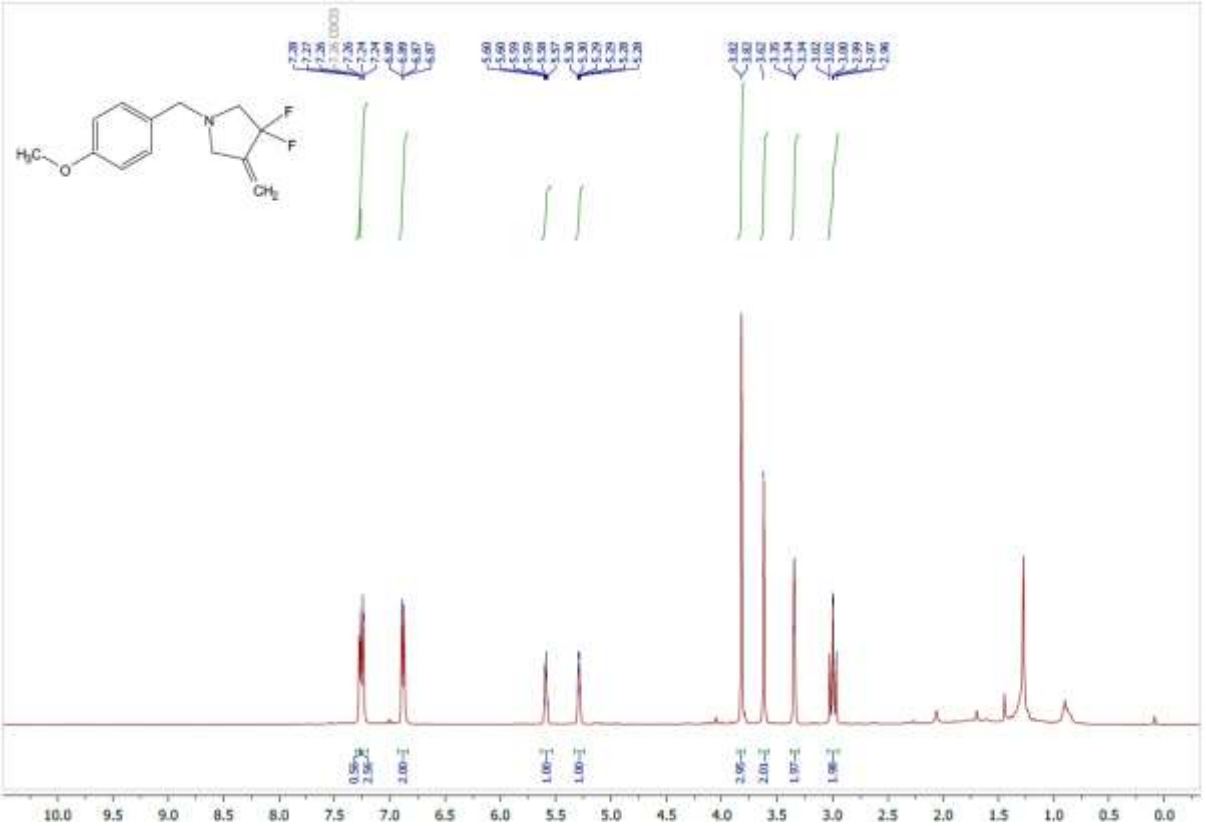
Supplementary Figure 131. ^{13}C NMR 1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3,3-difluoro-4-methylenepyrrolidine **4**



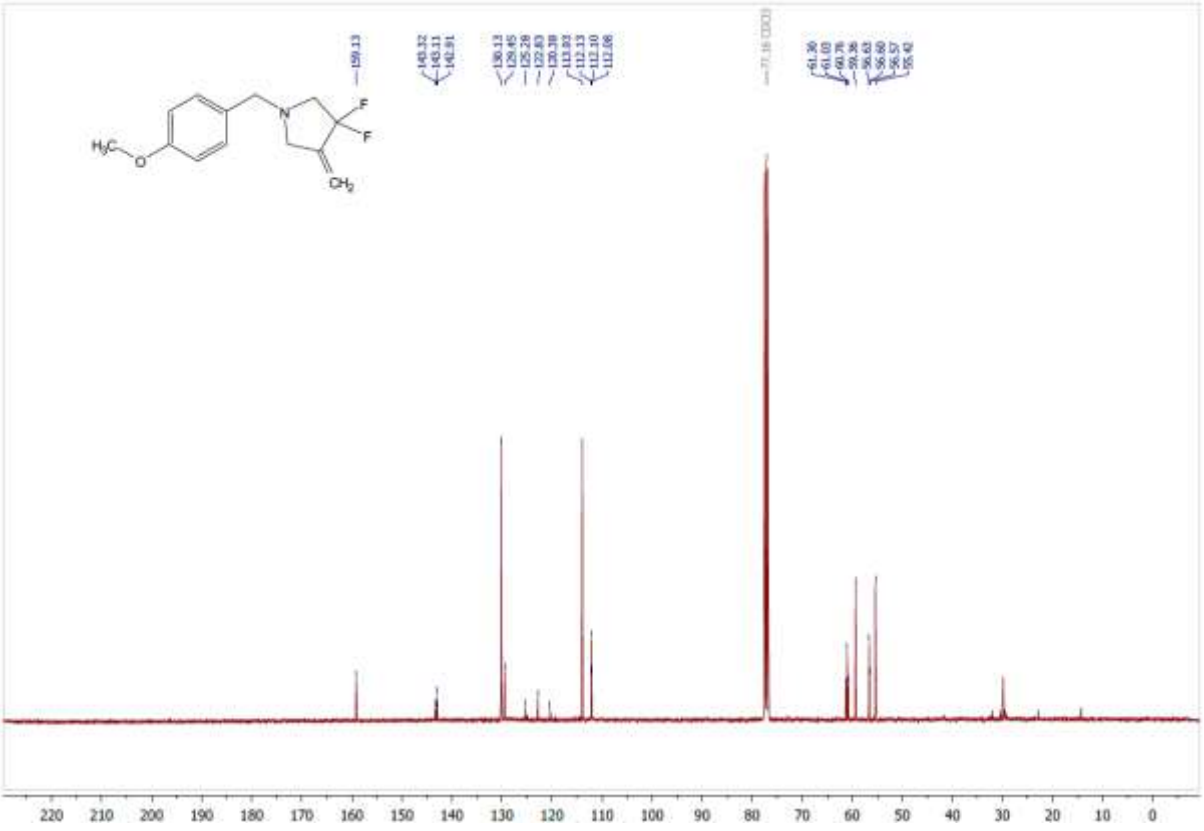
Supplementary Figure 132. ^{19}F NMR 1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3,3-difluoro-4-methylenepyrrolidine **4**



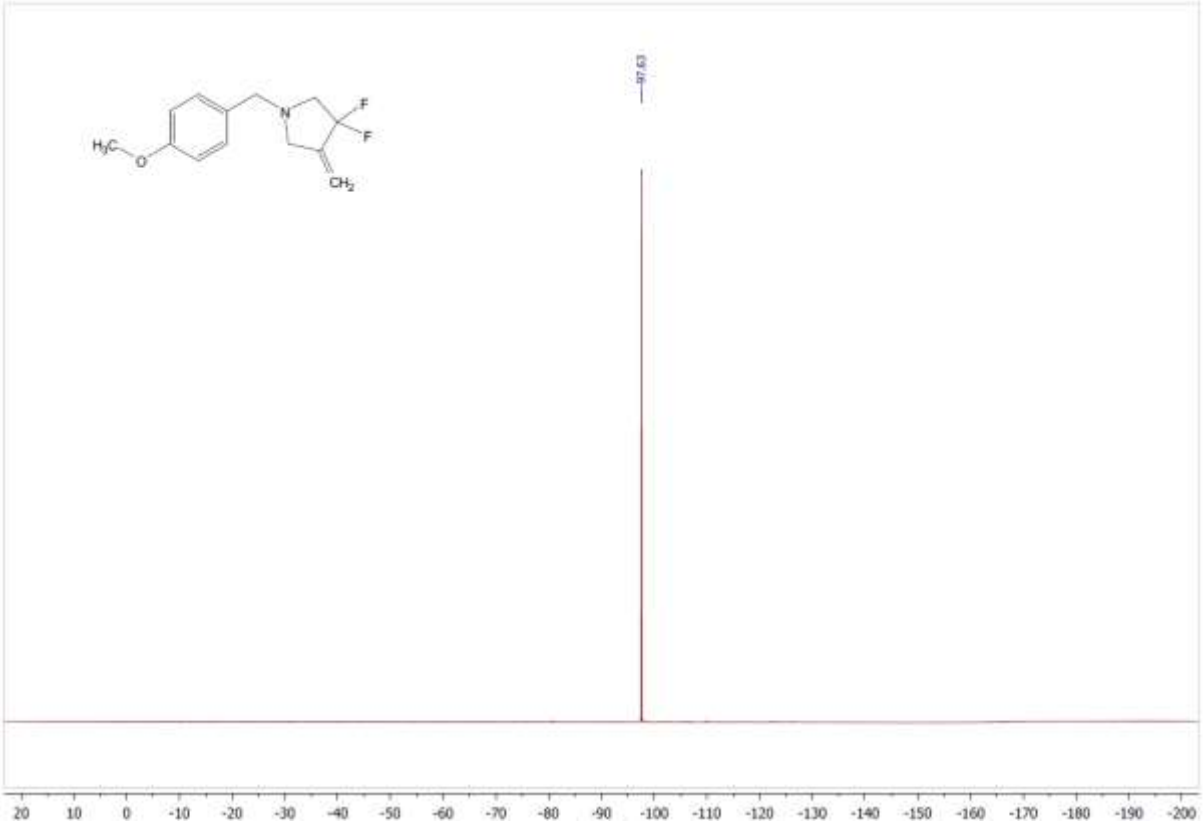
Supplementary Figure 133. ^{1}H NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine **17**



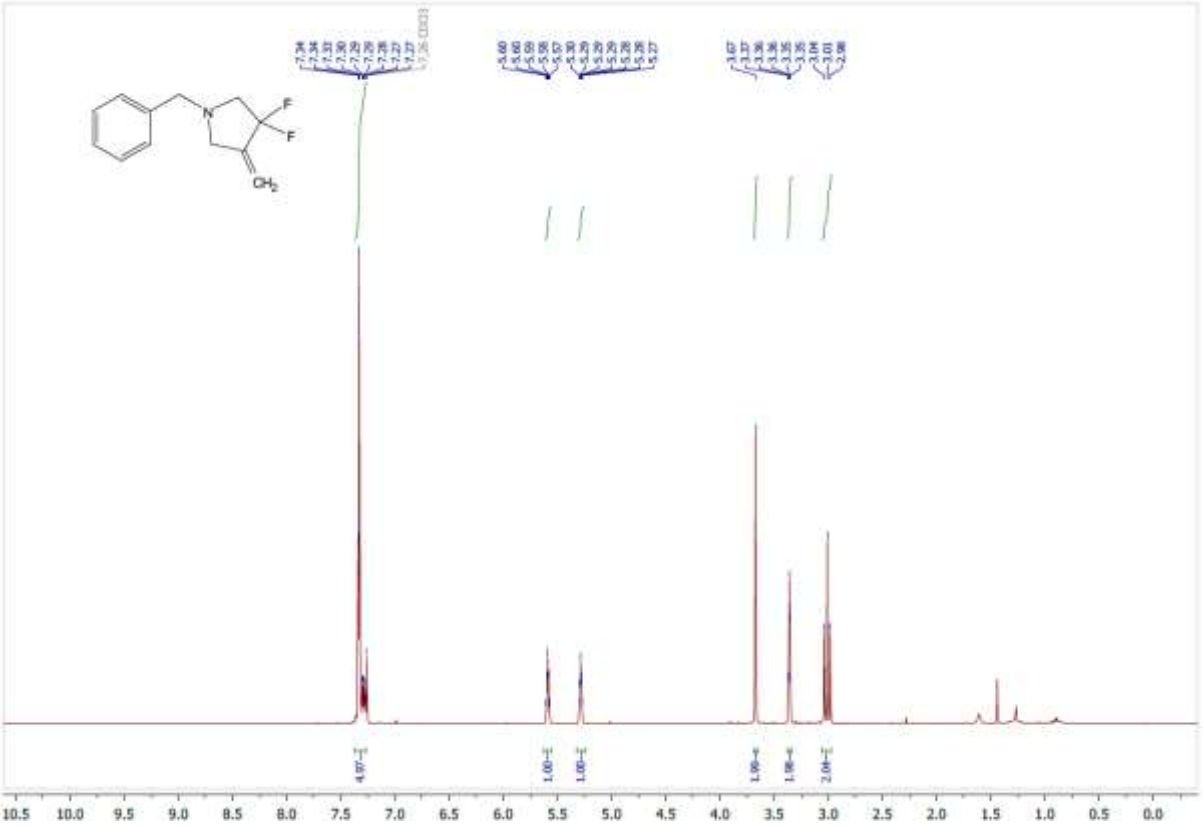
Supplementary Figure 134. ^{13}C NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine **17**



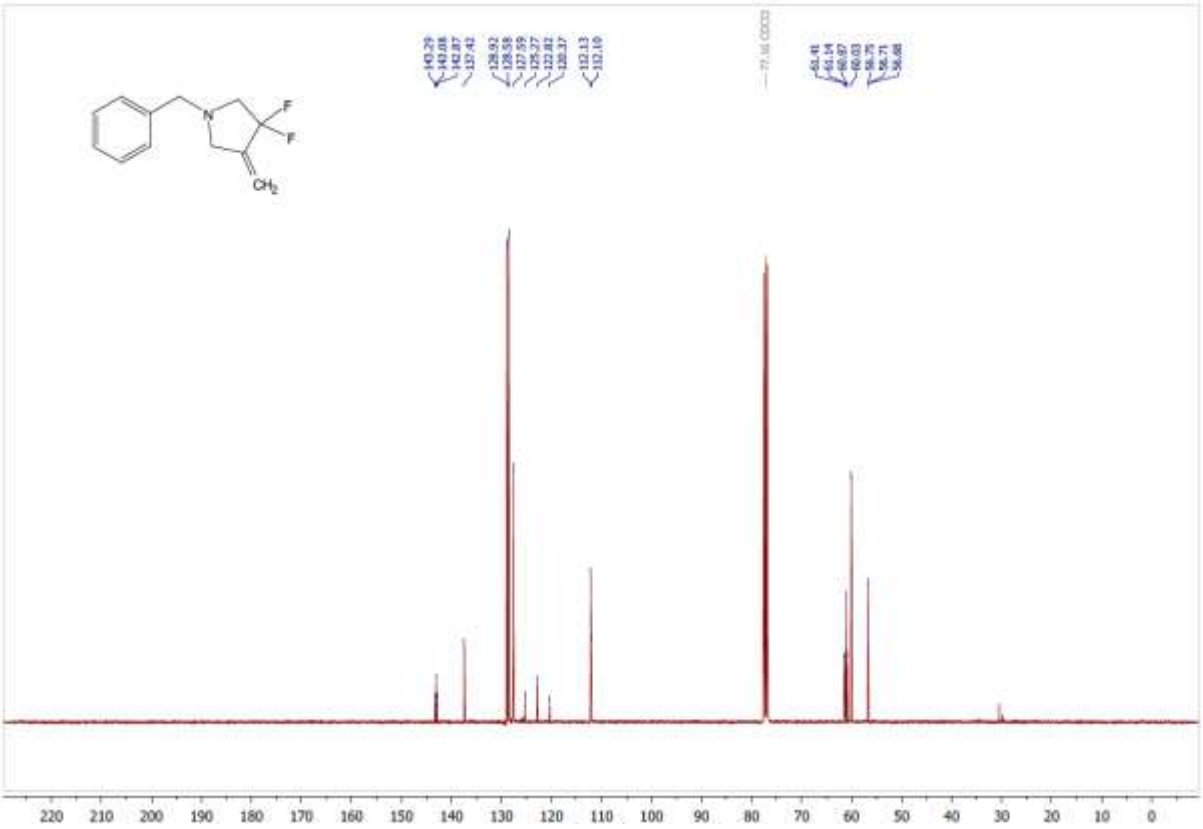
Supplementary Figure 135. ^{19}F NMR 3,3-Difluoro-1-(4-methoxybenzyl)-4-methylenepyrrolidine **17**



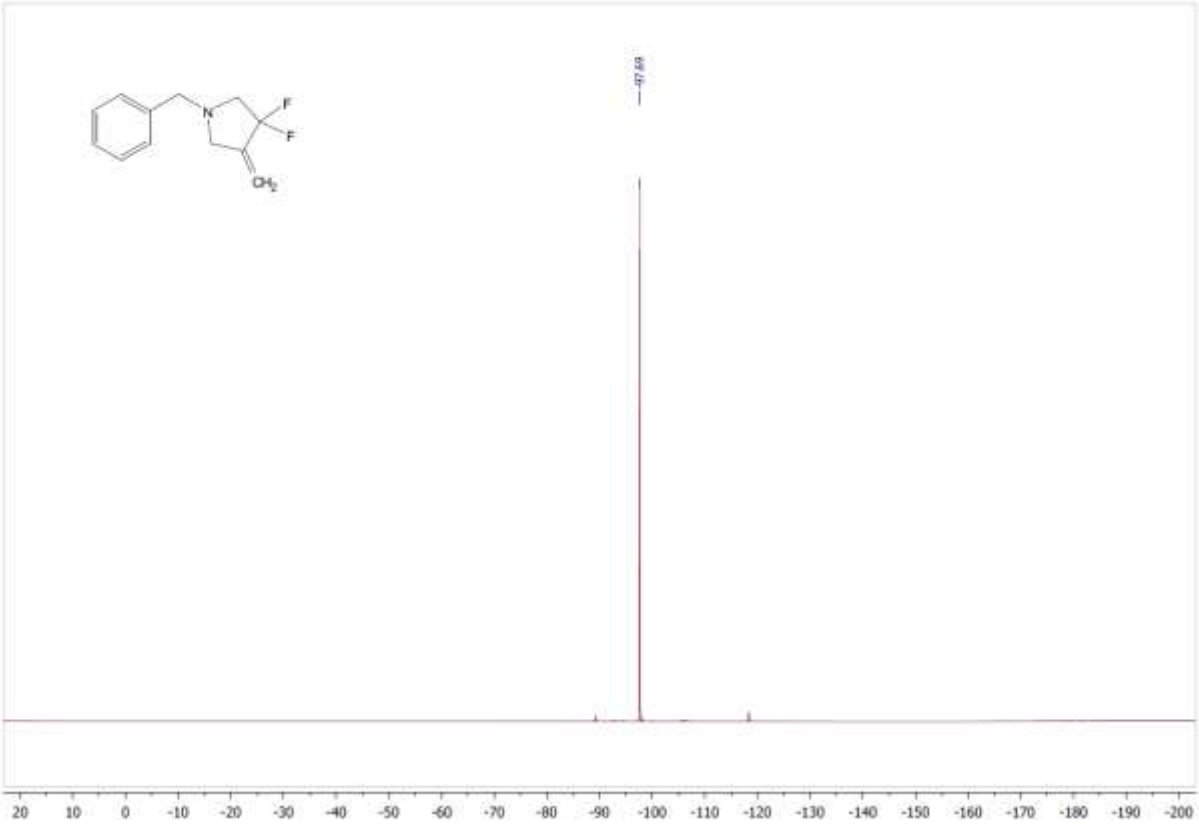
Supplementary Figure 136. ^{1}H NMR 1-Benzyl-3,3-difluoro-4-methylenepyrrolidine **18**



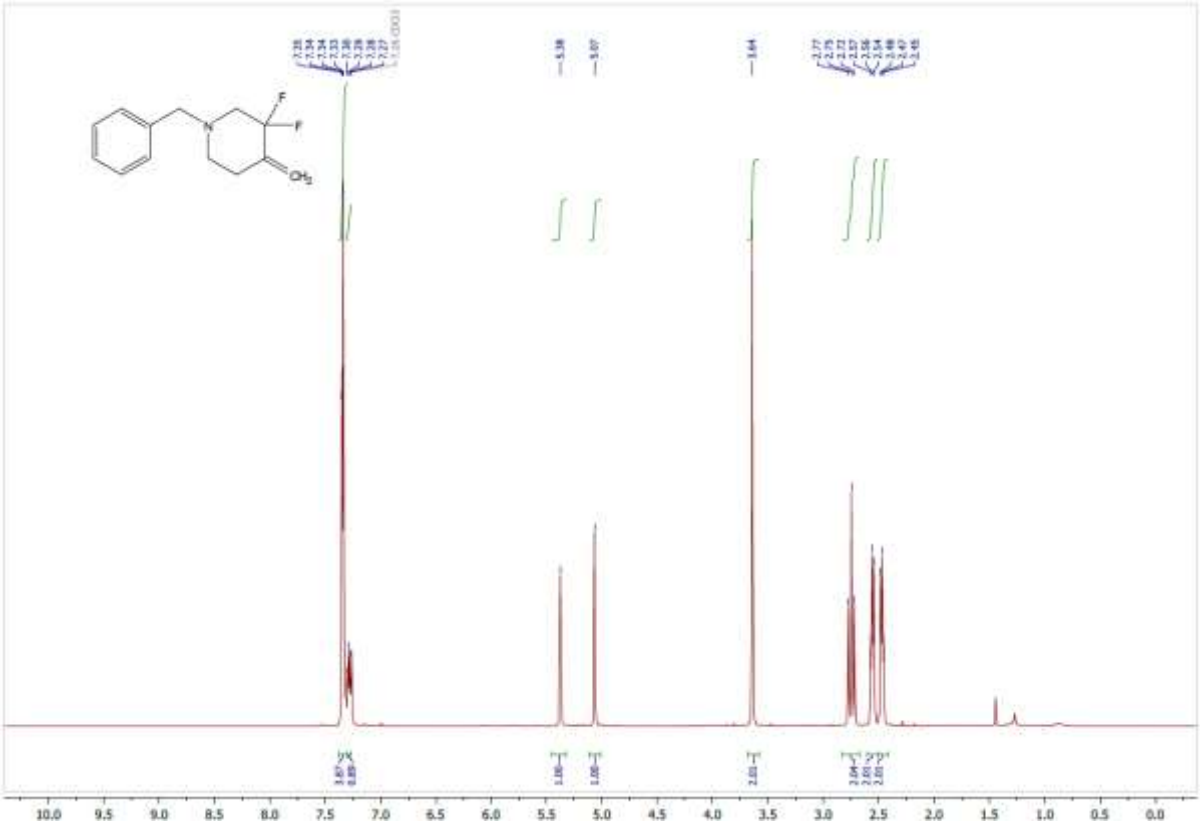
Supplementary Figure 137. ^{13}C NMR 1-Benzyl-3,3-difluoro-4-methylenepyrrolidine **18**



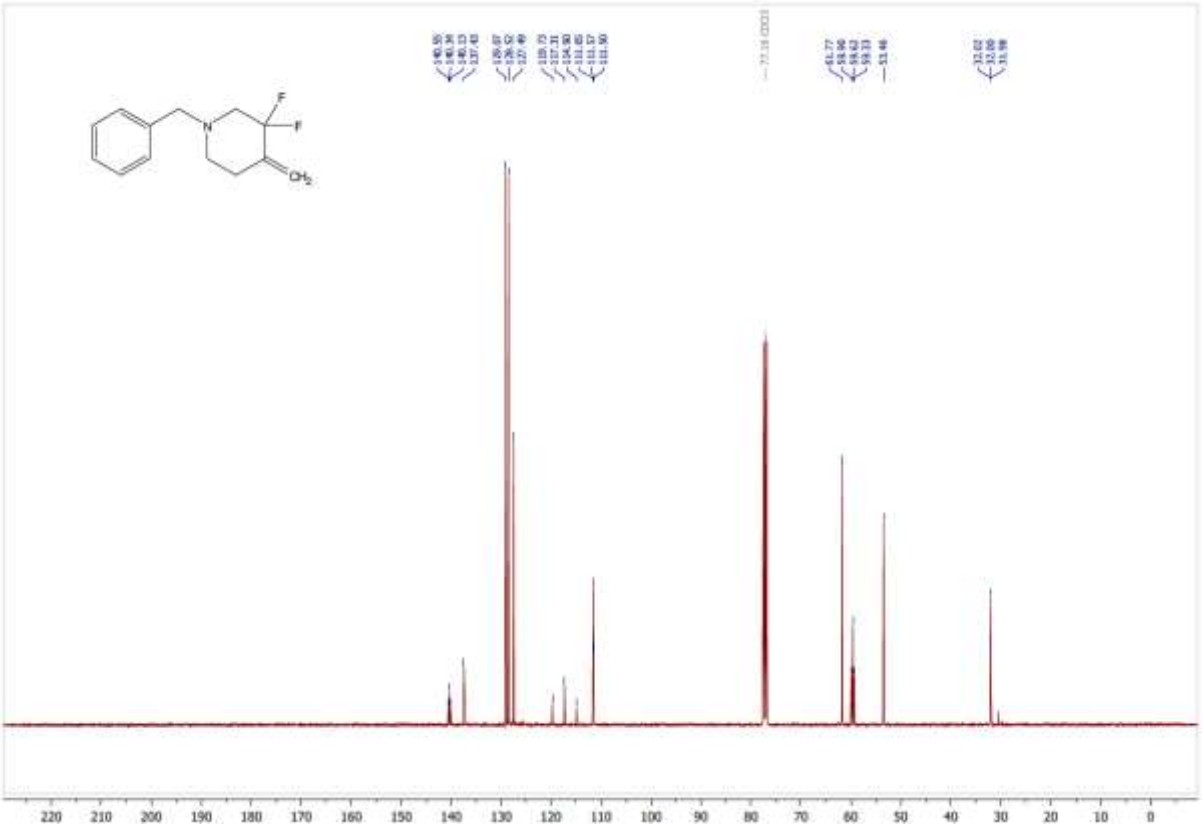
Supplementary Figure 138. ^{19}F NMR 1-Benzyl-3,3-difluoro-4-methylenepyrrolidine **18**



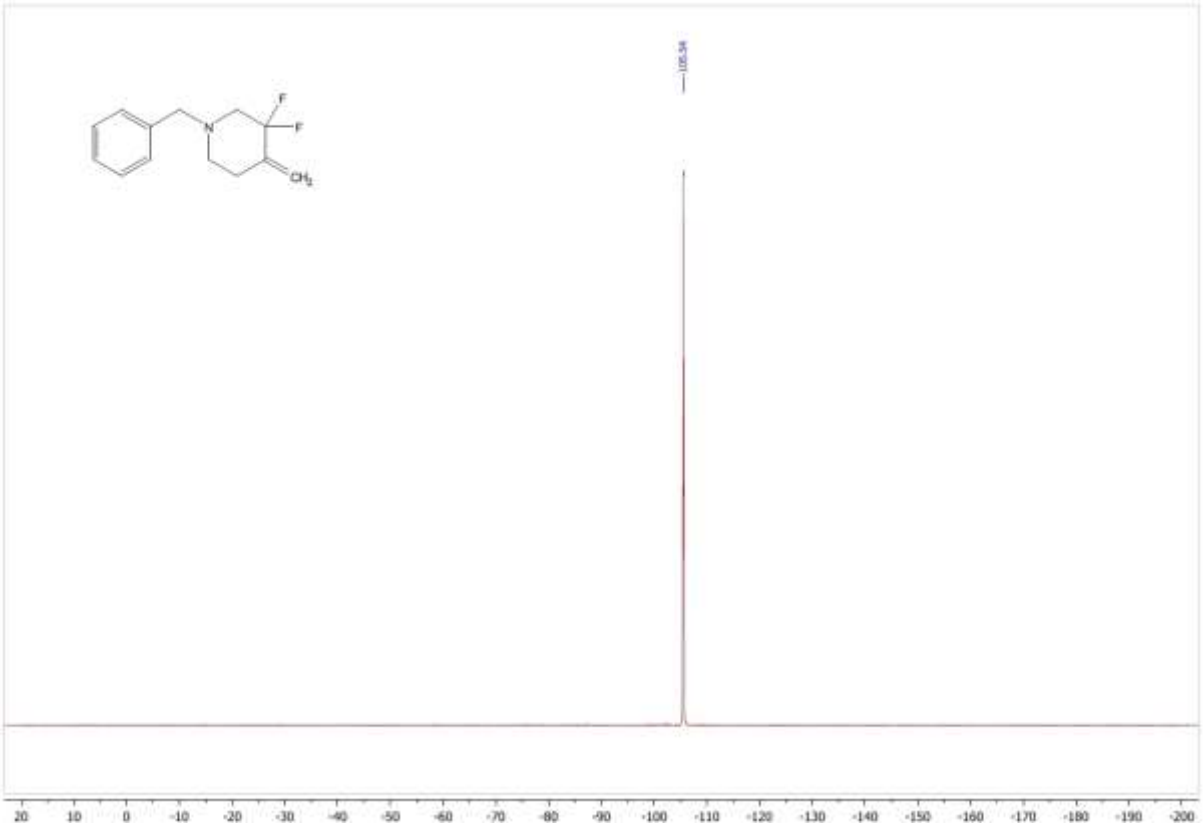
Supplementary Figure 139. ^{1}H NMR 1-Benzyl-3,3-difluoro-4-methylenepiperidine **19**



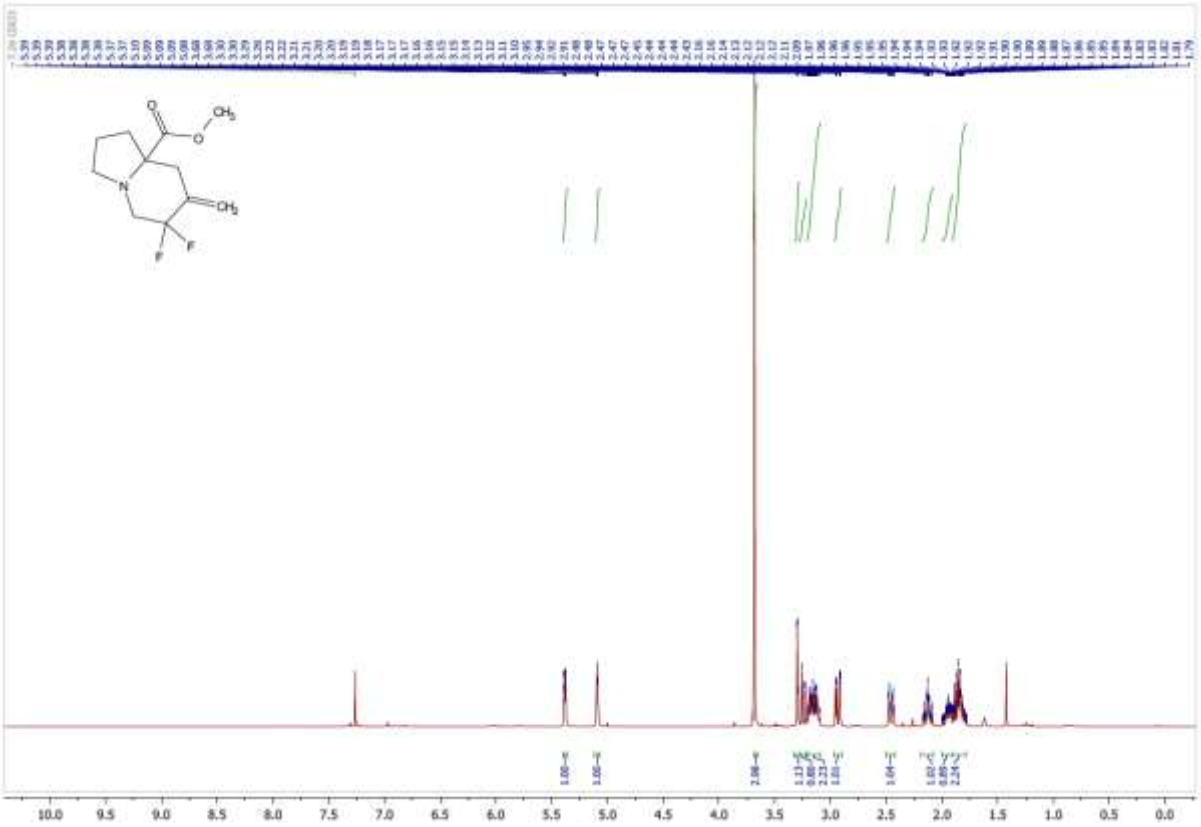
Supplementary Figure 140. ^{13}C NMR 1-Benzyl-3,3-difluoro-4-methylenepiperidine **19**



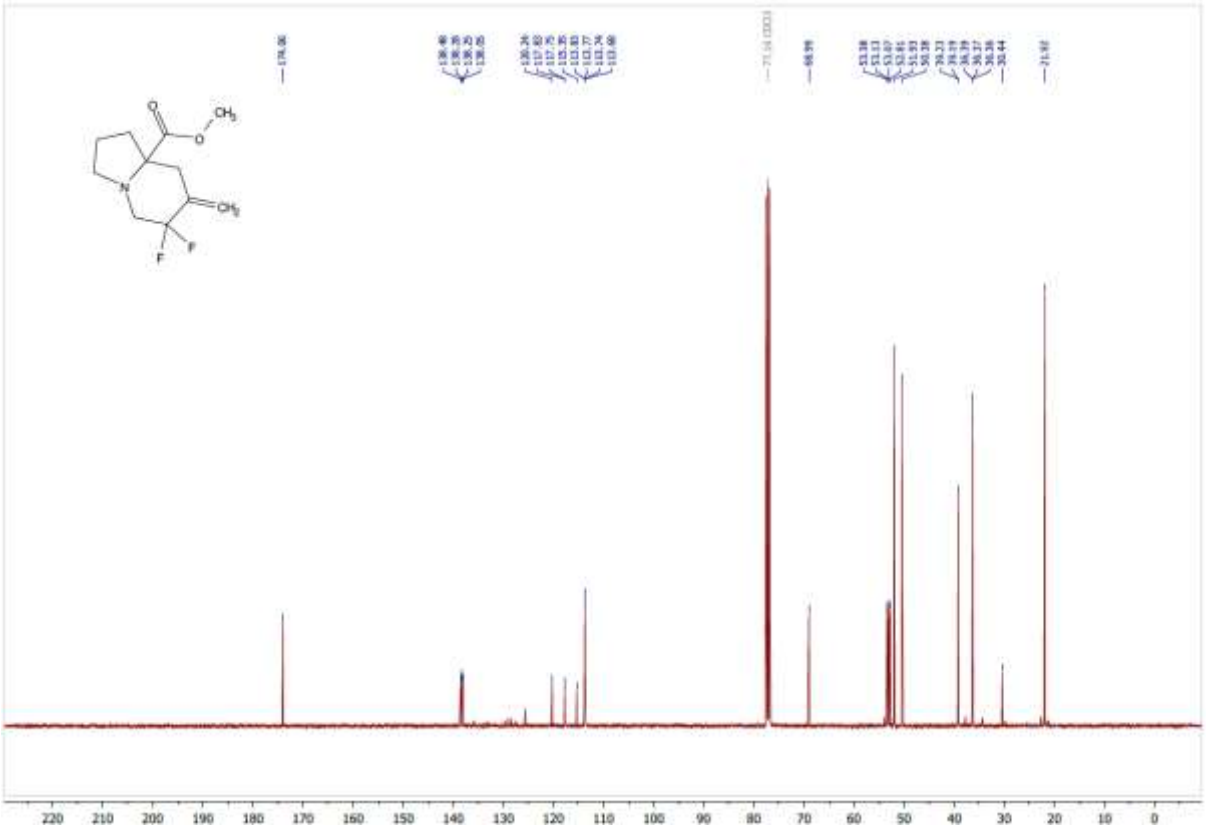
Supplementary Figure 141. ^{19}F NMR 1-Benzyl-3,3-difluoro-4-methylenepiperidine **19**



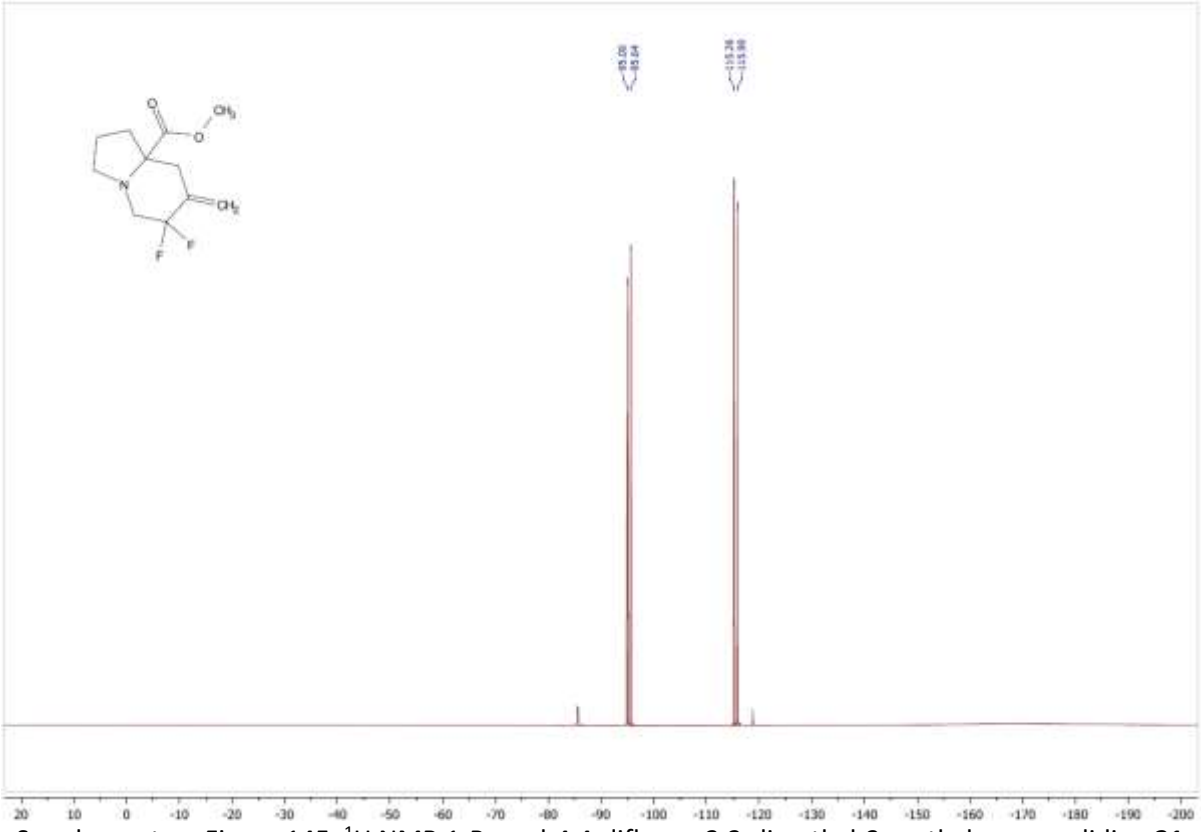
Supplementary Figure 142. ^{1}H NMR Methyl 6,6-difluoro-7-methylenehexahydroindolizine-8a(1*H*)-carboxylate **20**



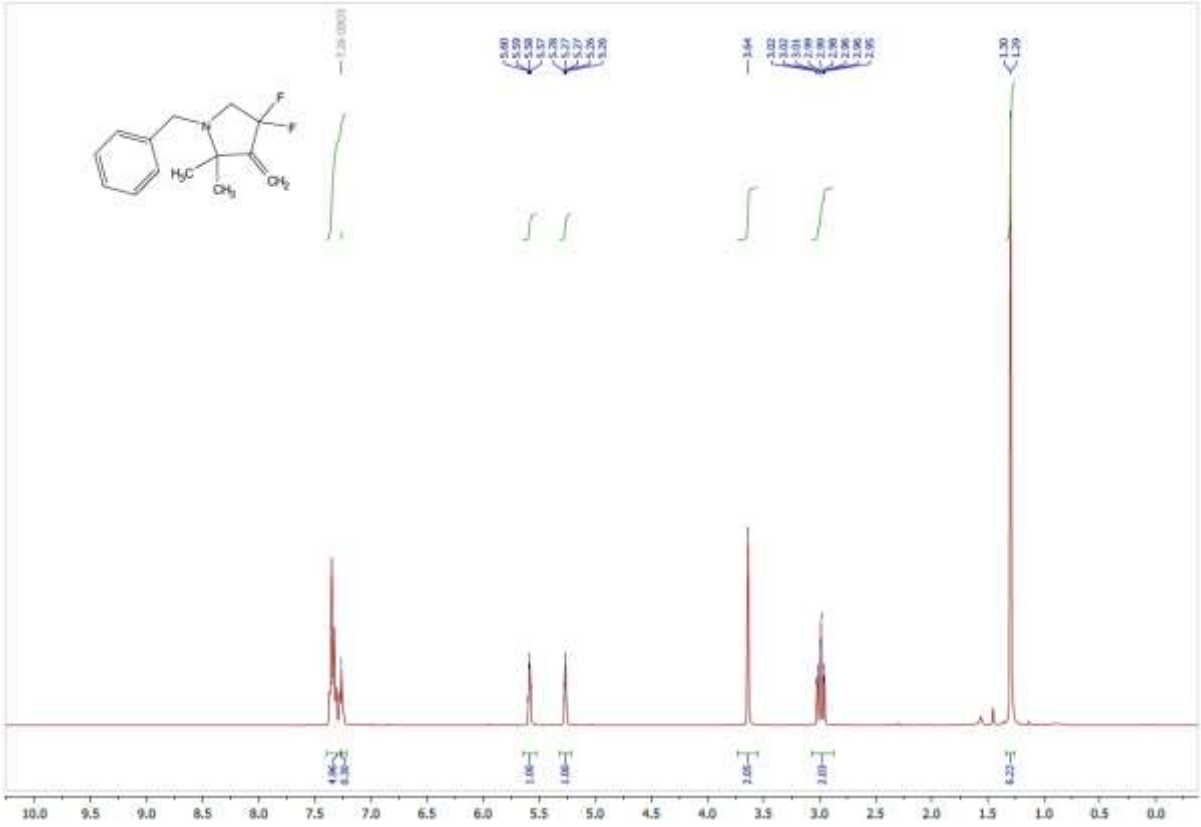
Supplementary Figure 143. ^{13}C NMR Methyl 6,6-difluoro-7-methylenehexahydroindolizine-8a(1*H*)-carboxylate **20**



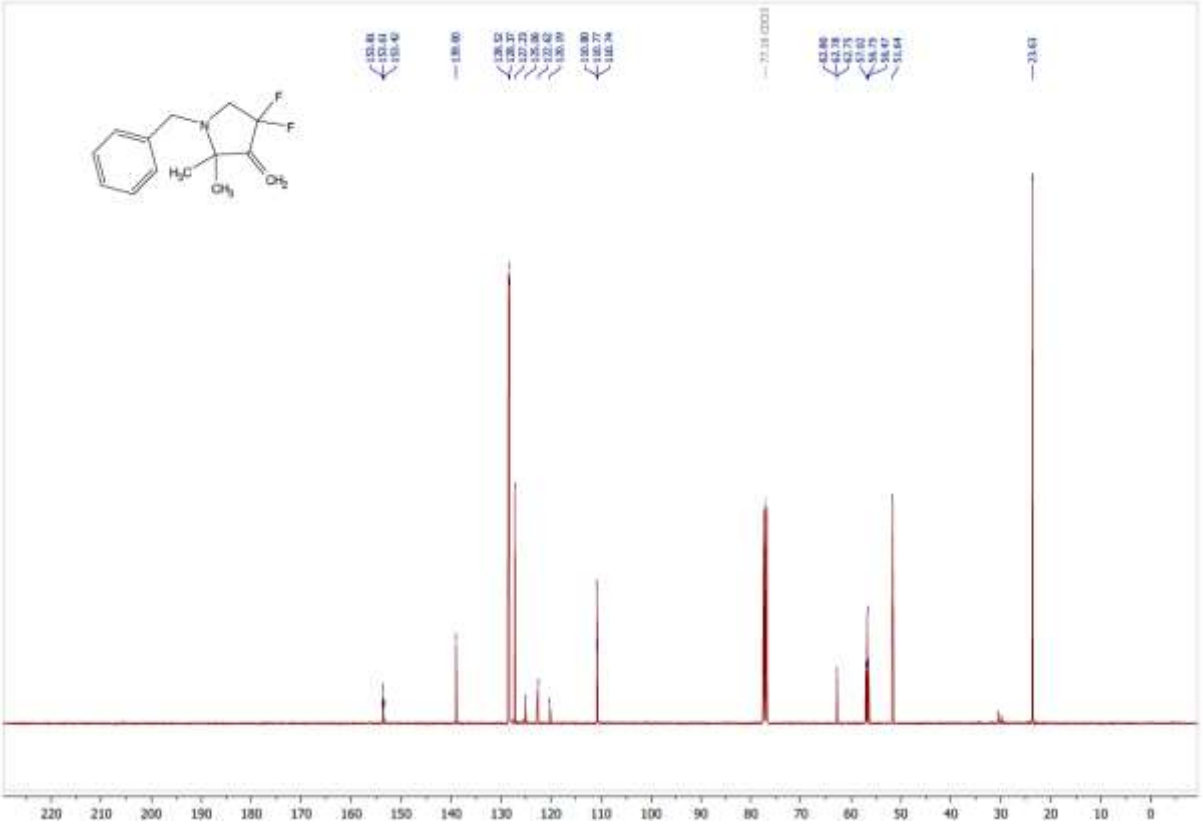
Supplementary Figure 144. ^{19}F NMR Methyl 6,6-difluoro-7-methylenehexahydroindolizine-8a(1*H*)-carboxylate **20**



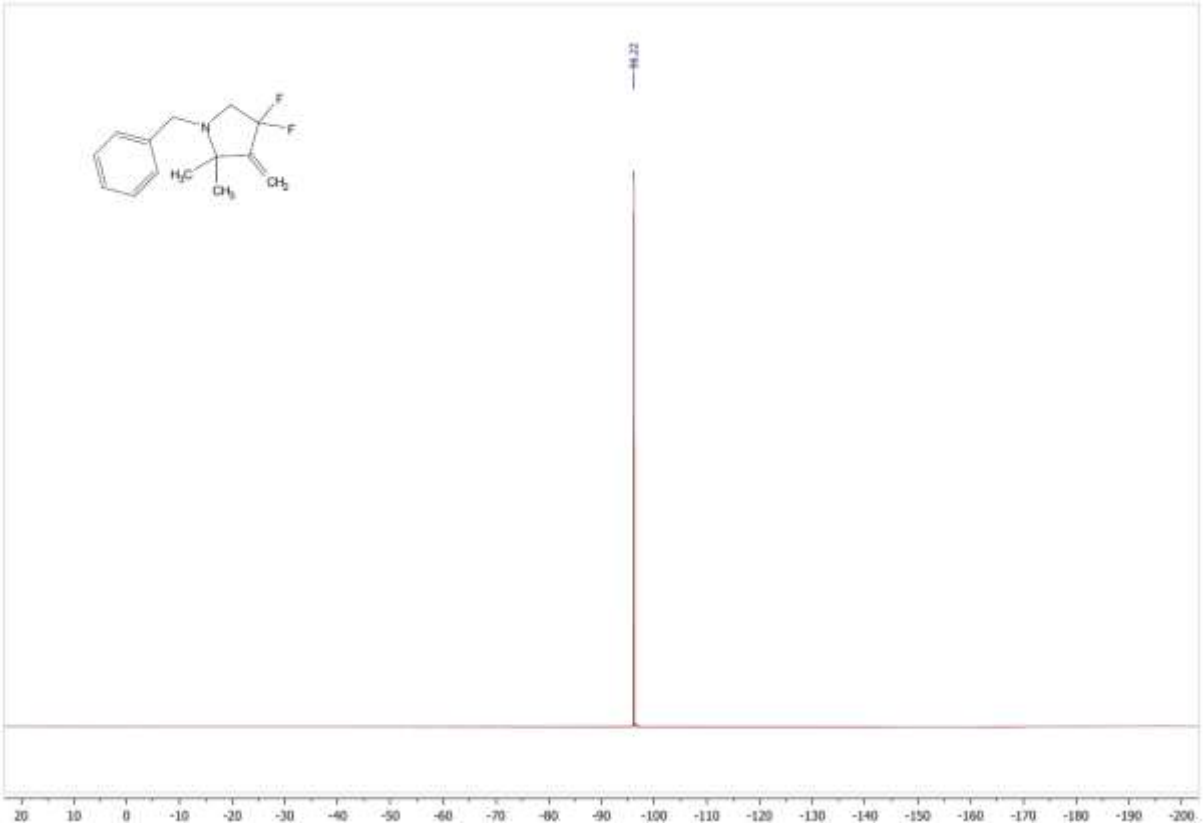
Supplementary Figure 145. ^{1}H NMR 1-Benzyl-4,4-difluoro-2,2-dimethyl-3-methylenepyrrolidine **21**



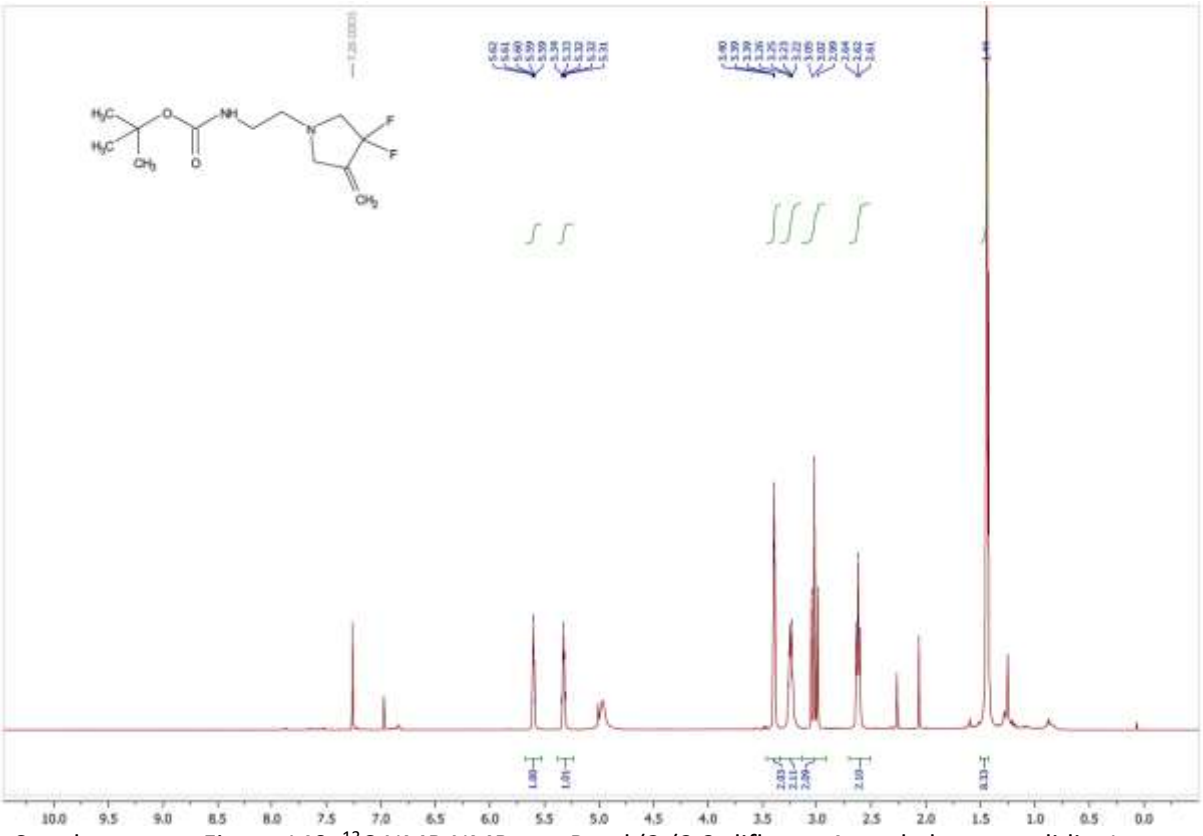
Supplementary Figure 146. ^{13}C NMR 1-Benzyl-4,4-difluoro-2,2-dimethyl-3-methylenepyrrolidine **21**



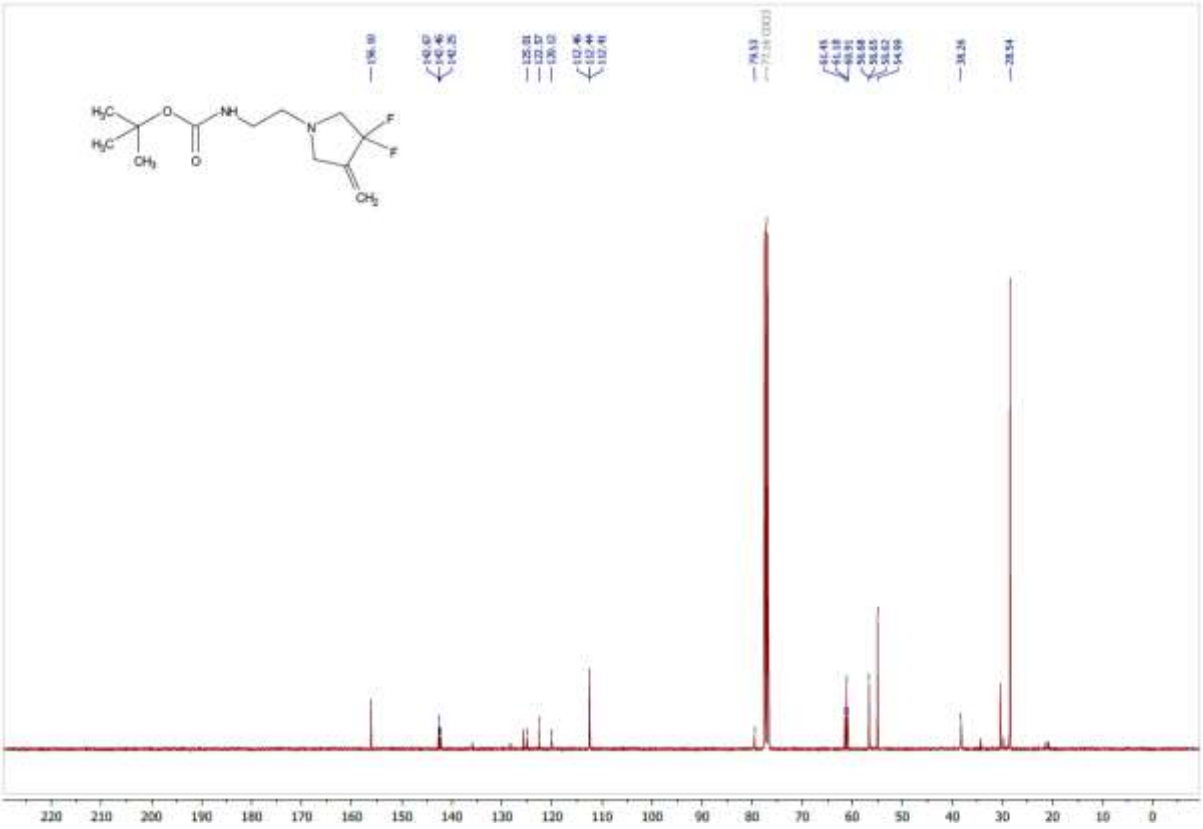
Supplementary Figure 147. ^{19}F NMR 1-Benzyl-4,4-difluoro-2,2-dimethyl-3-methylenepyrrolidine **21**



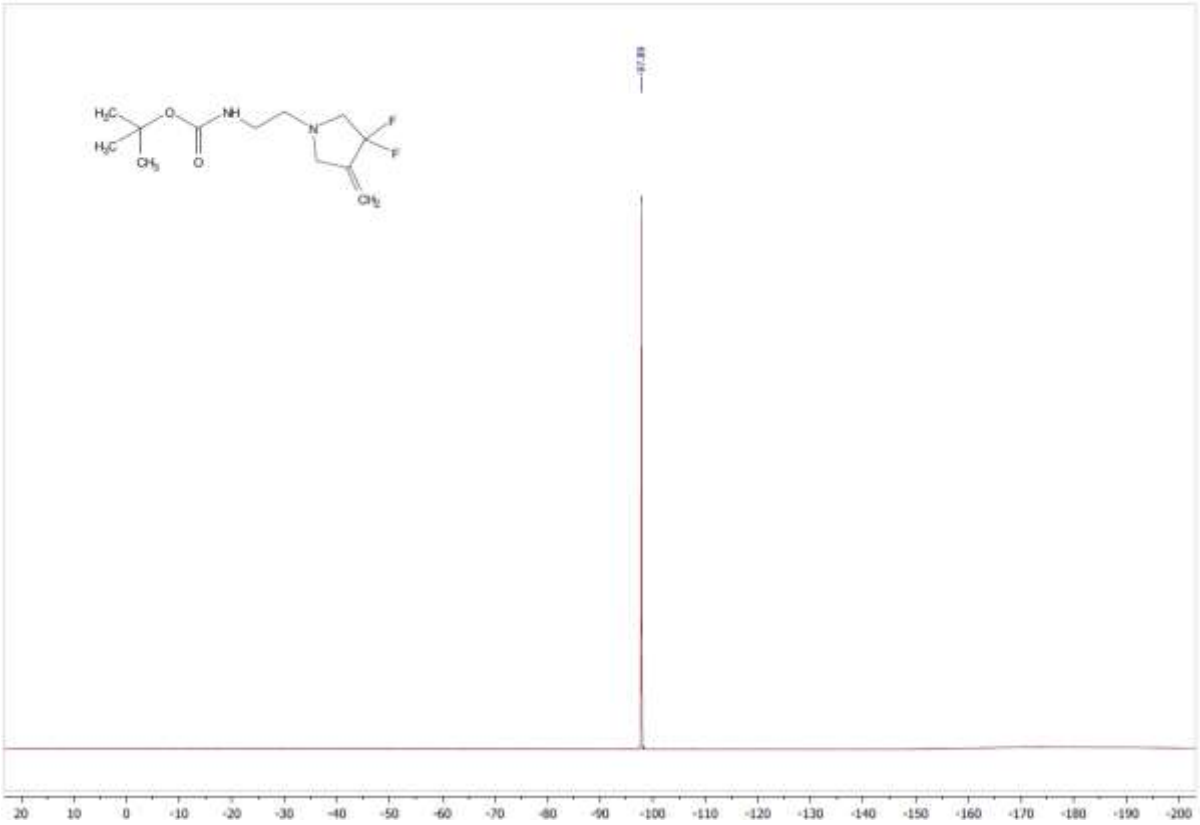
Supplementary Figure 148. ^{1}H NMR *tert*-Butyl (2-(3,3-difluoro-4-methylenepyrrolidin-1-yl)ethyl)carbamate **22**



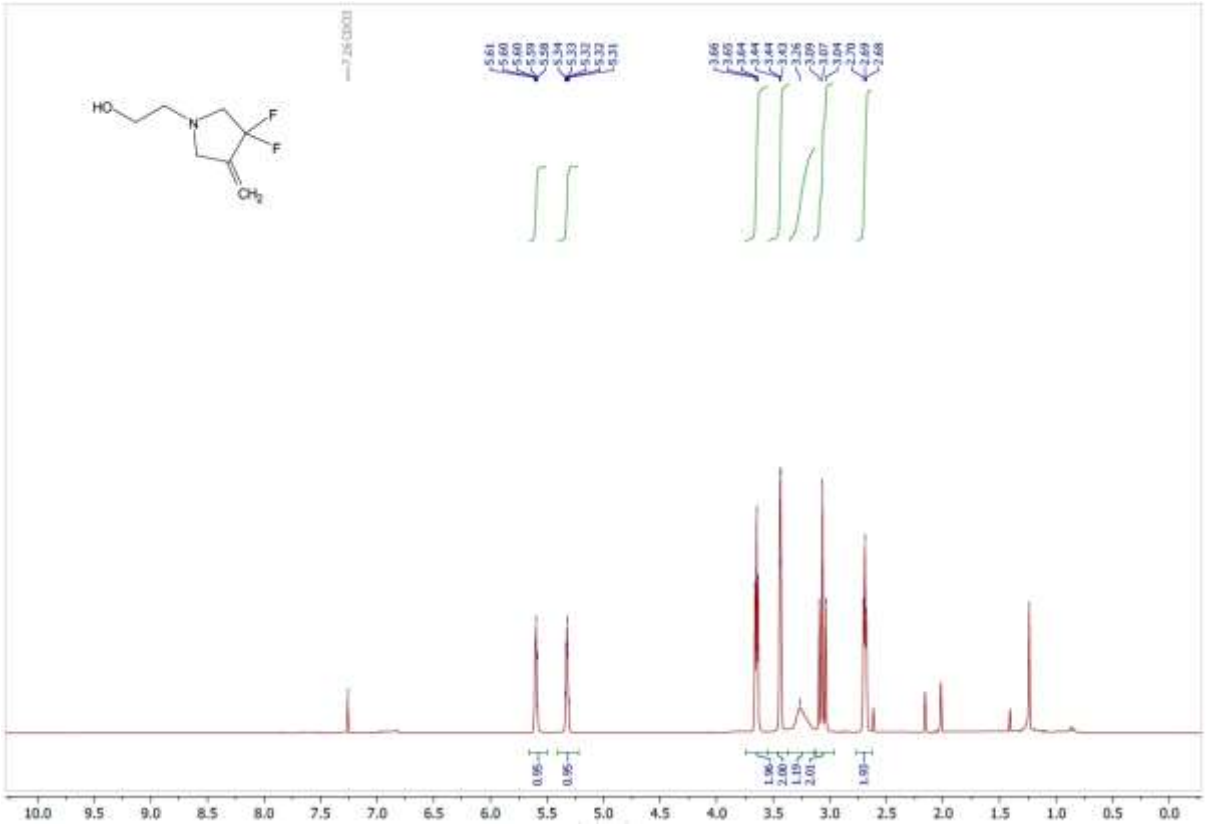
Supplementary Figure 149. ^{13}C NMR NMR *tert*-Butyl (2-(3,3-difluoro-4-methylenepyrrolidin-1-yl)ethyl)carbamate **22**



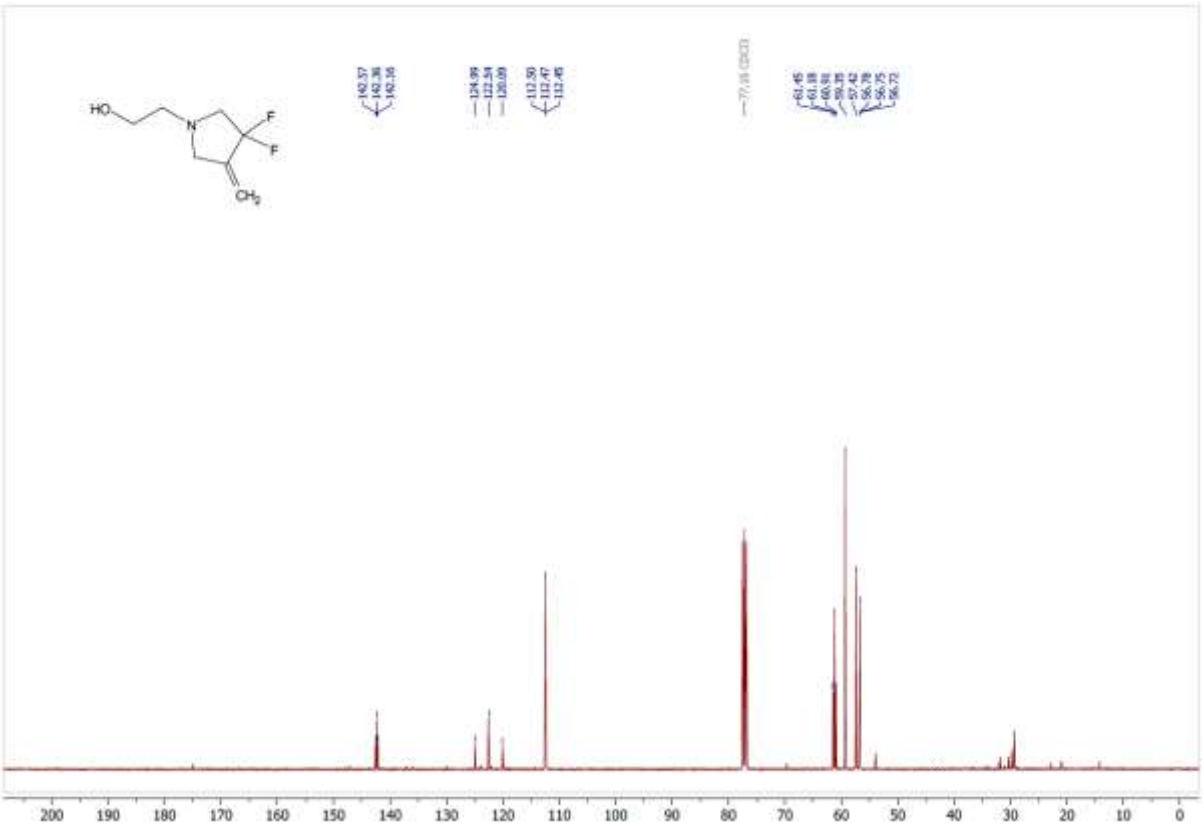
Supplementary Figure 150. ^{19}F NMR NMR *tert*-Butyl (2-(3,3-difluoro-4-methylenepyrrolidin-1-yl)ethyl)carbamate **22**



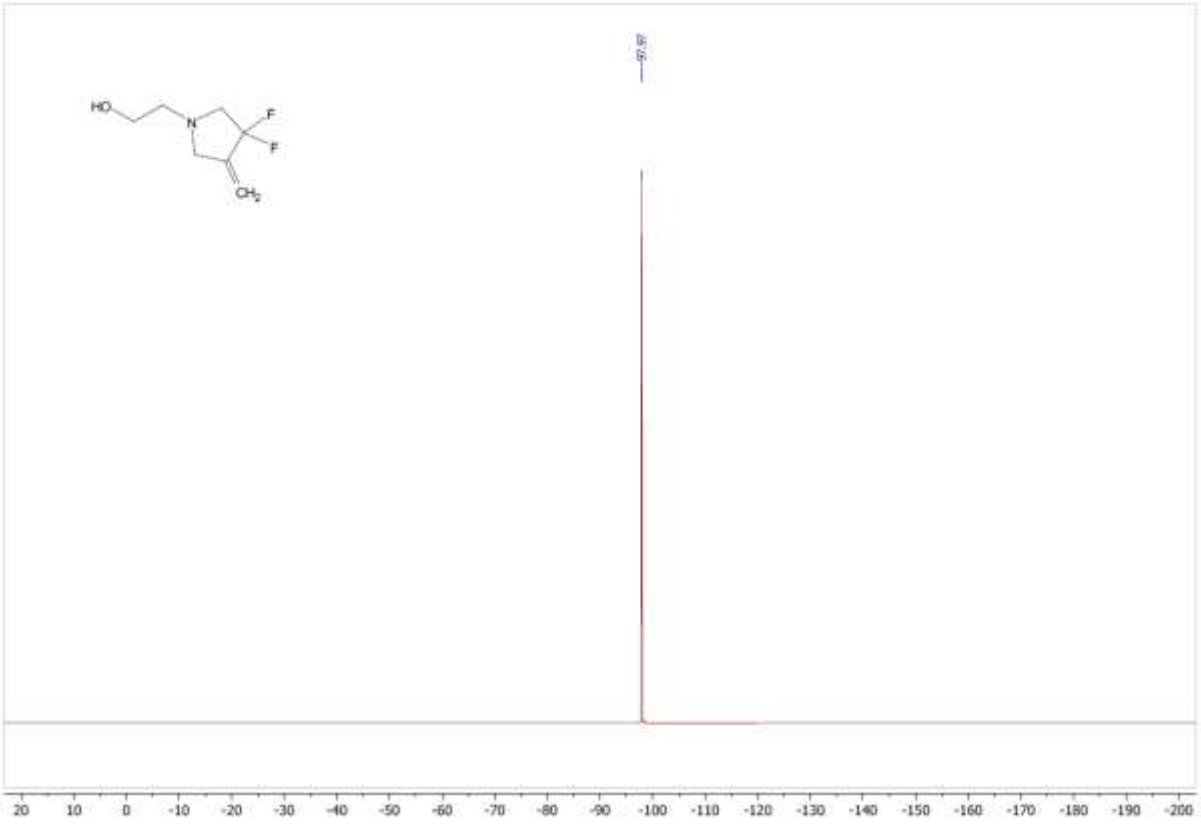
Supplementary Figure 151. ^{1}H NMR 2-(3,3-Difluoro-4-methylenepyrrolidin-1-yl)ethan-1-ol **23**



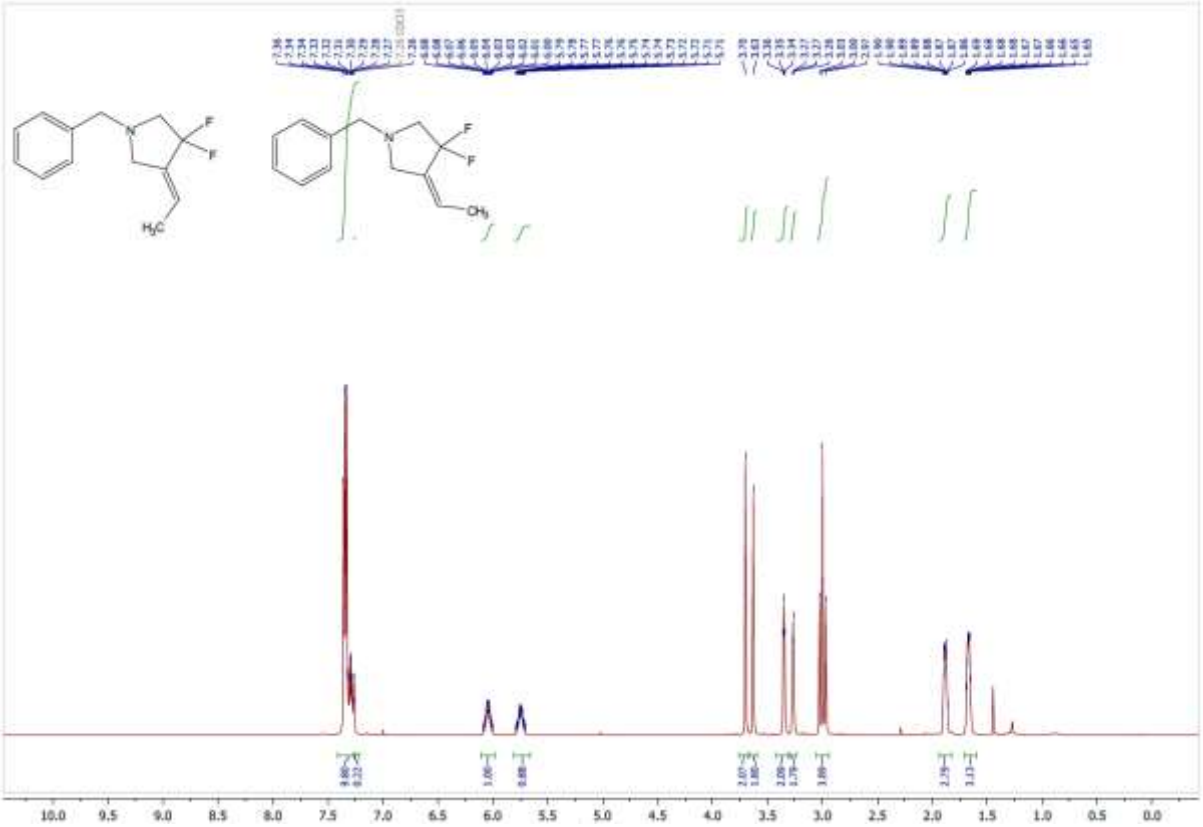
Supplementary Figure 152. ^{13}C NMR 2-(3,3-Difluoro-4-methylenepyrrolidin-1-yl)ethan-1-ol **23**



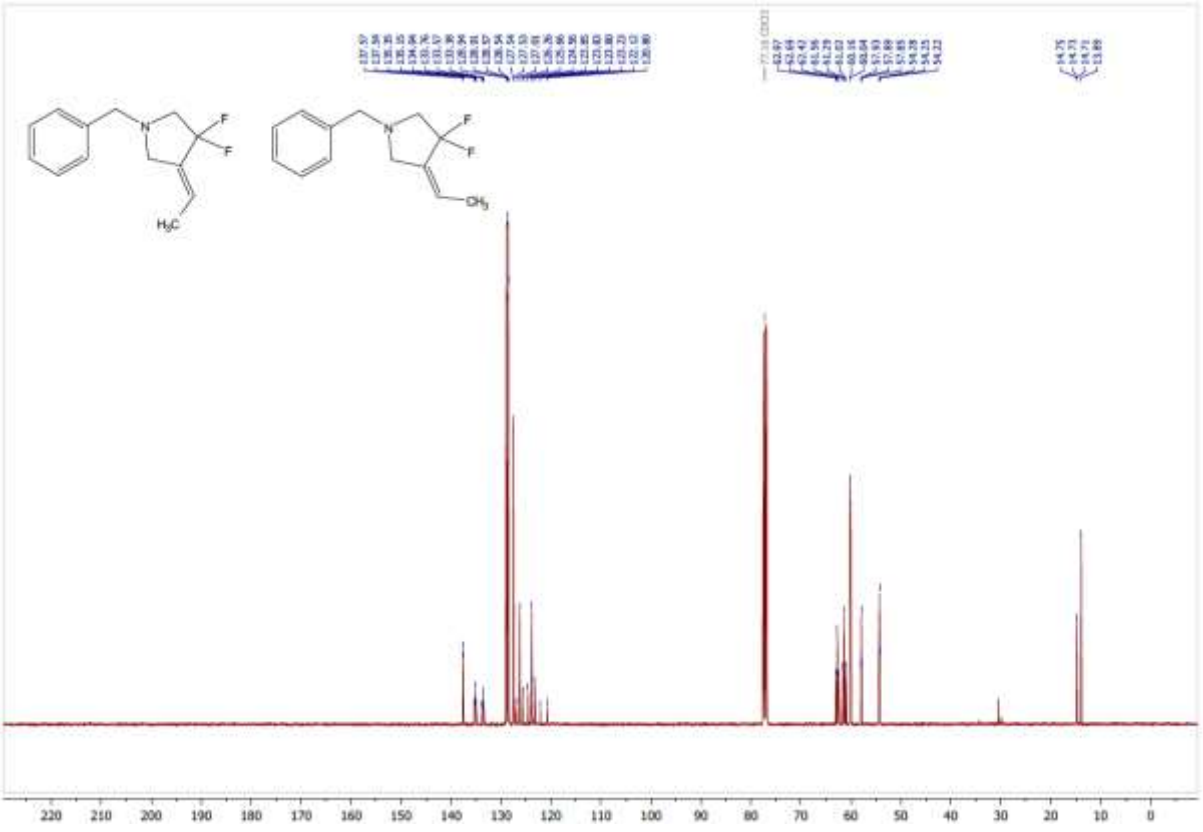
Supplementary Figure 153. ^{19}F NMR 2-(3,3-Difluoro-4-methylenepyrrolidin-1-yl)ethan-1-ol **23**



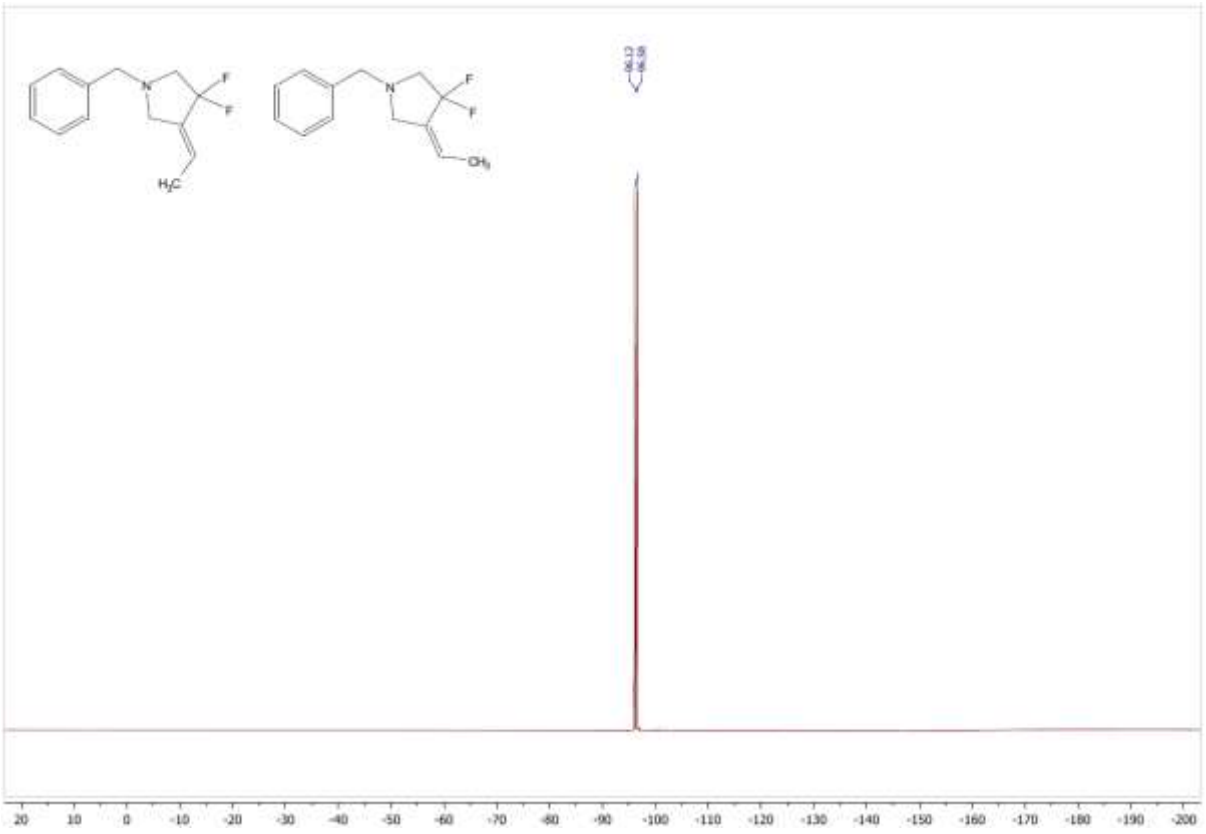
Supplementary Figure 154. ^{1}H NMR 1-Benzyl-4-ethylidene-3,3-difluoropyrrolidine **24**



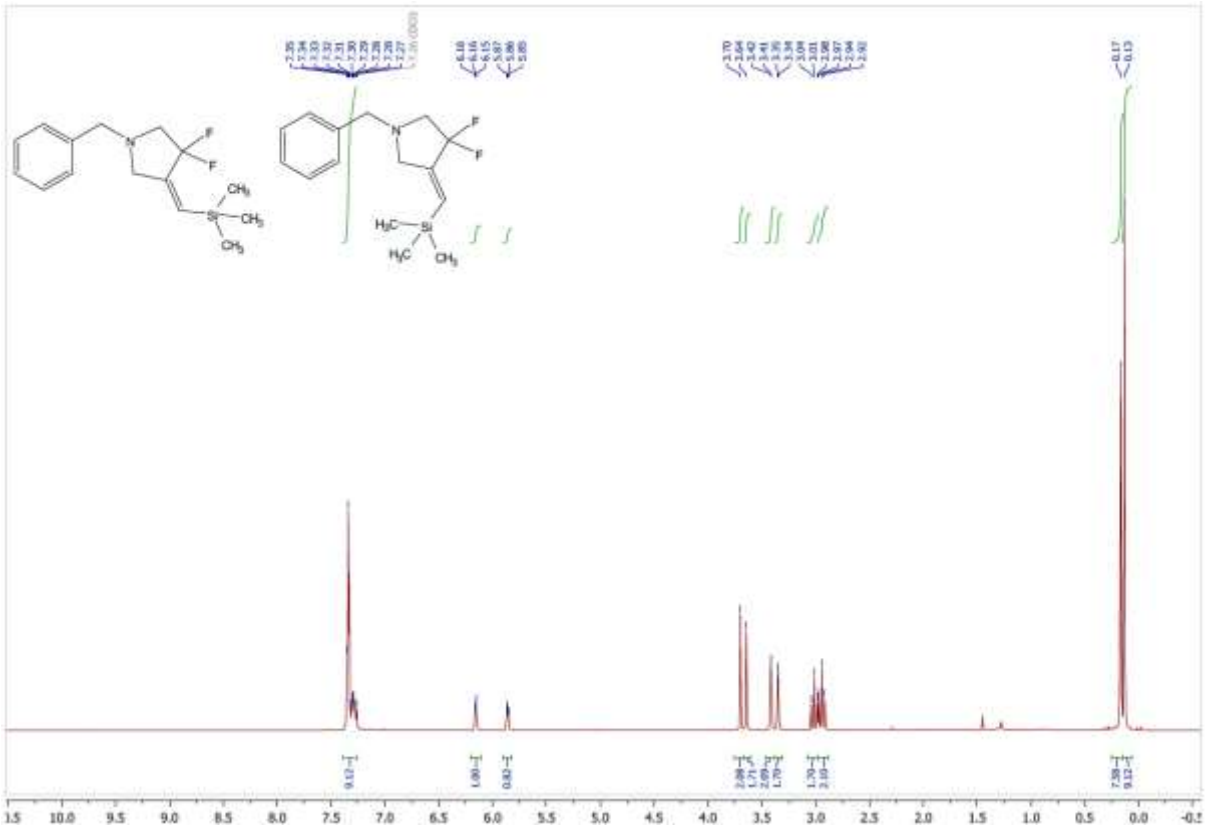
Supplementary Figure 155. ^{13}C NMR 1-Benzyl-4-ethylidene-3,3-difluoropyrrolidine **24**



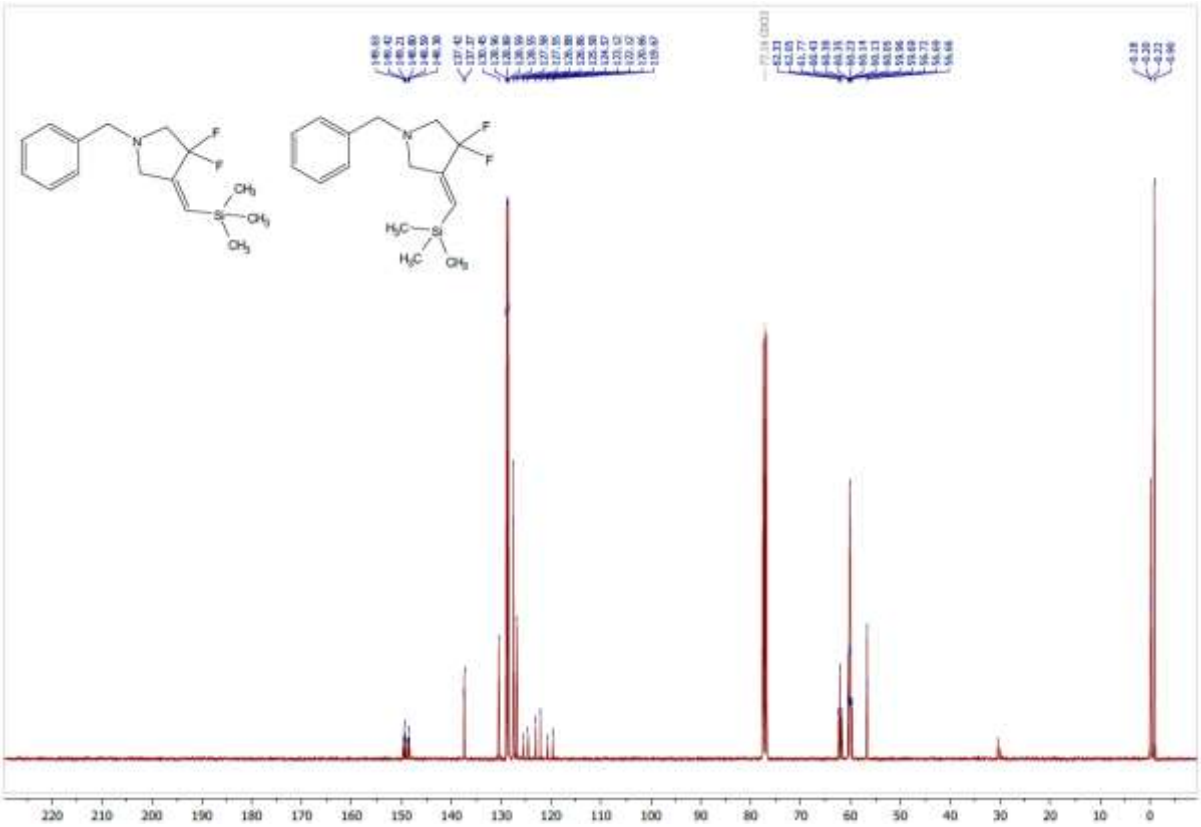
Supplementary Figure 156. ^{19}F NMR 1-Benzyl-4-ethylidene-3,3-difluoropyrrolidine **24**



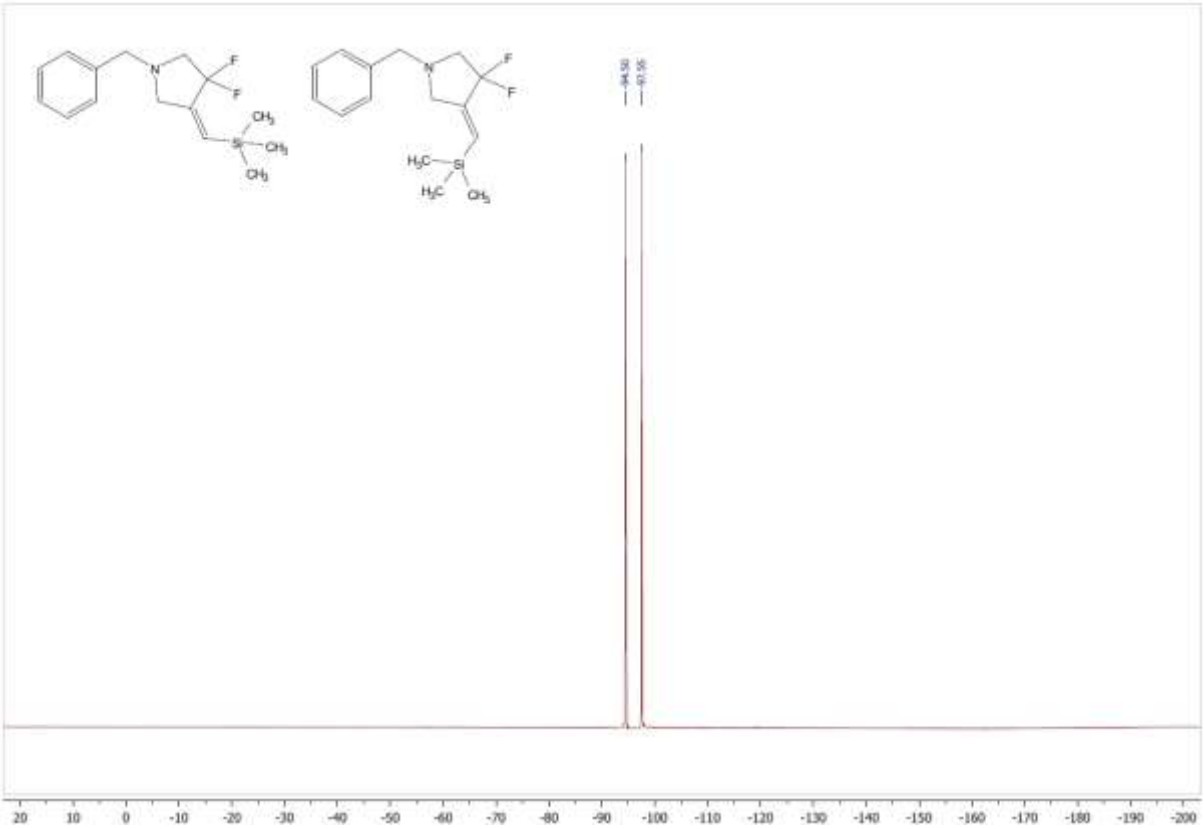
Supplementary Figure 157. ^{1}H NMR 1-Benzyl-3,3-difluoro-4-((trimethylsilyl)methylene)pyrrolidine **25**



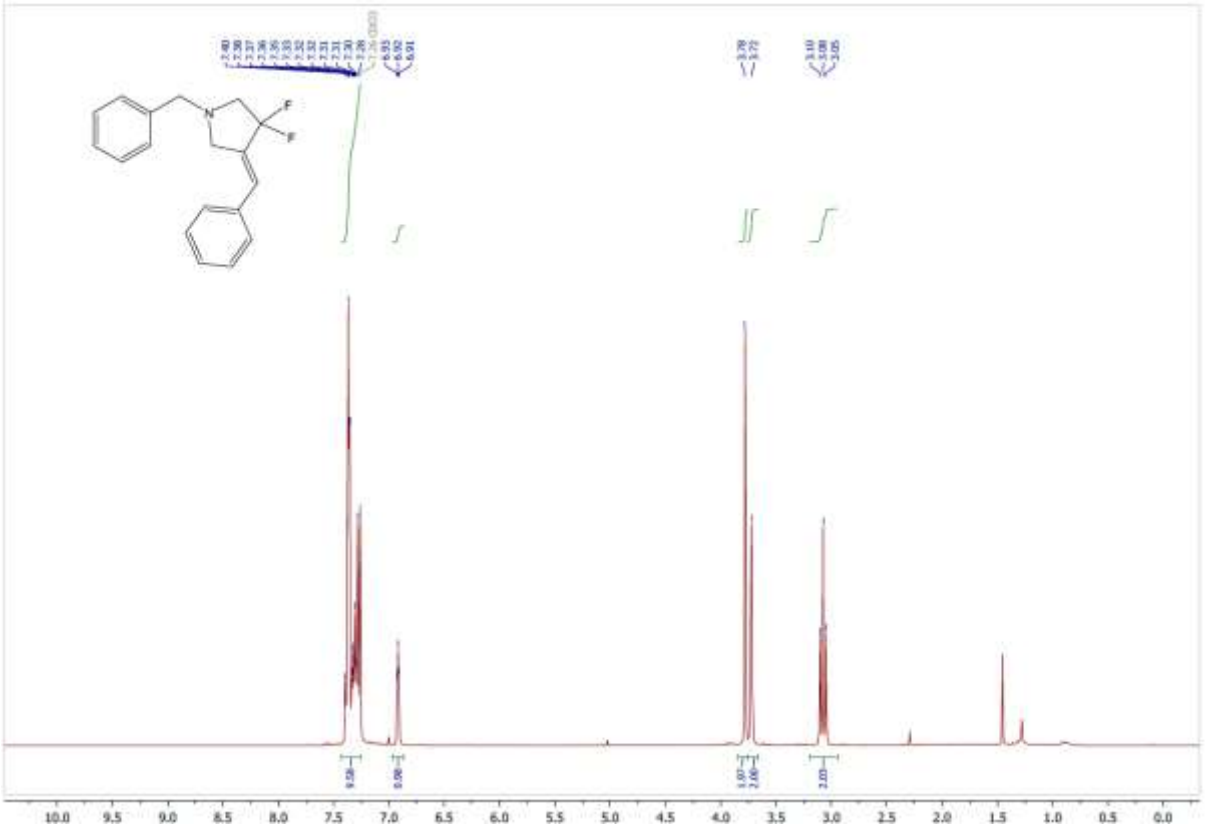
Supplementary Figure 158. ^{13}C NMR 1-Benzyl-3,3-difluoro-4-((trimethylsilyl)methylene)pyrrolidine **25**



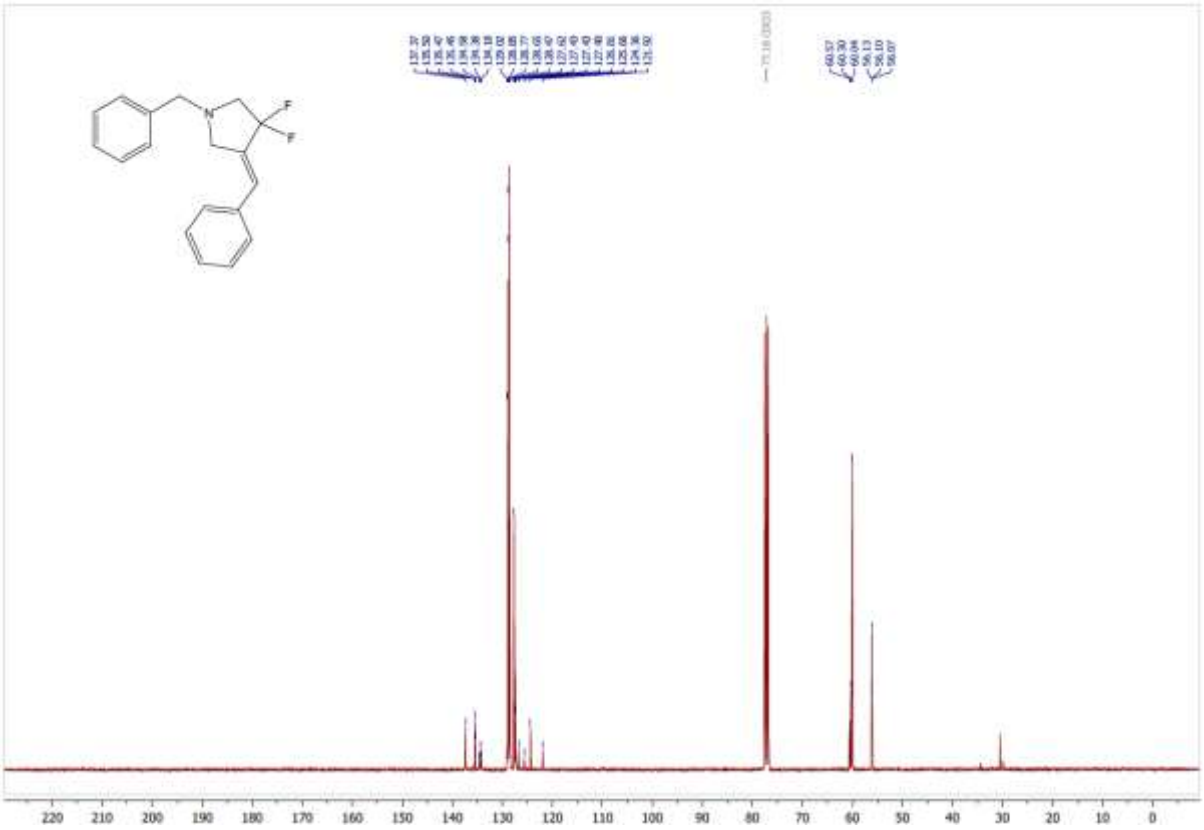
Supplementary Figure 159. ^{19}F NMR 1-Benzyl-3,3-difluoro-4-((trimethylsilyl)methylene)pyrrolidine **25**



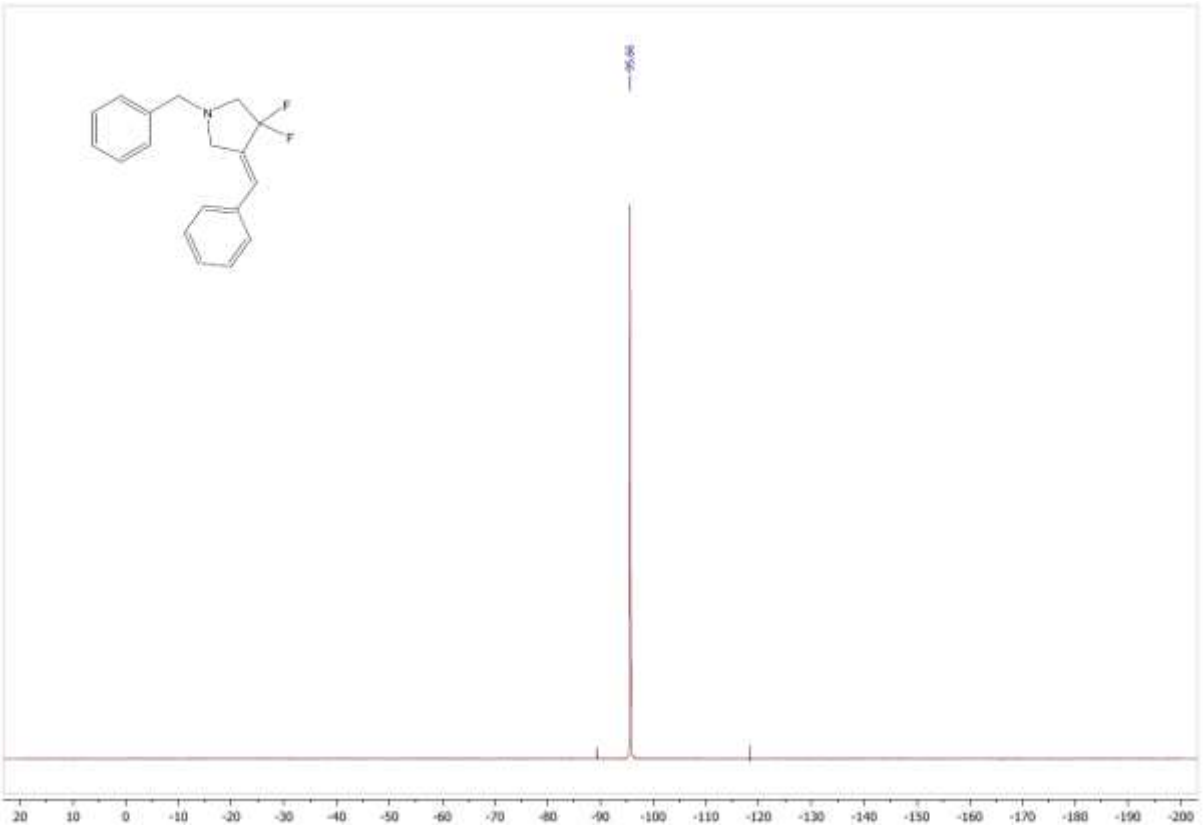
Supplementary Figure 160. ^{1}H NMR (*E*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine **26**



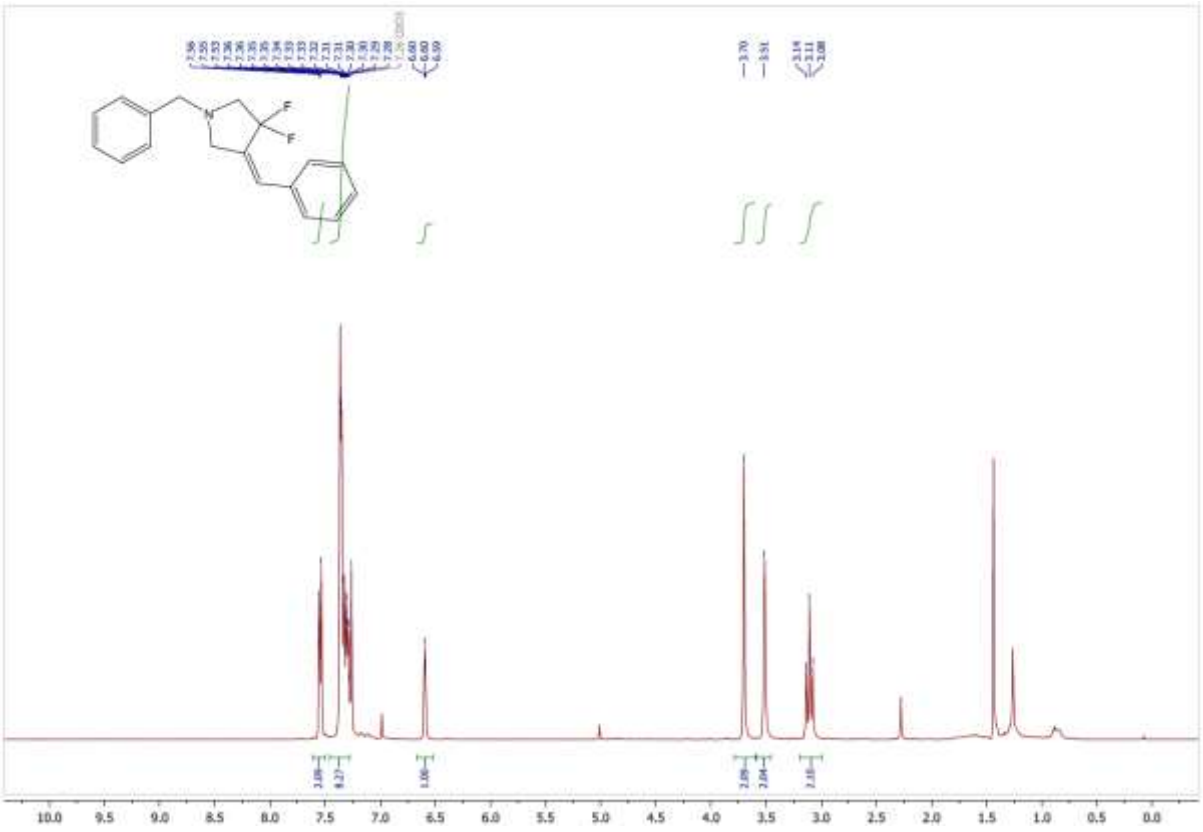
Supplementary Figure 161. ^{13}C NMR (*E*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine **26**



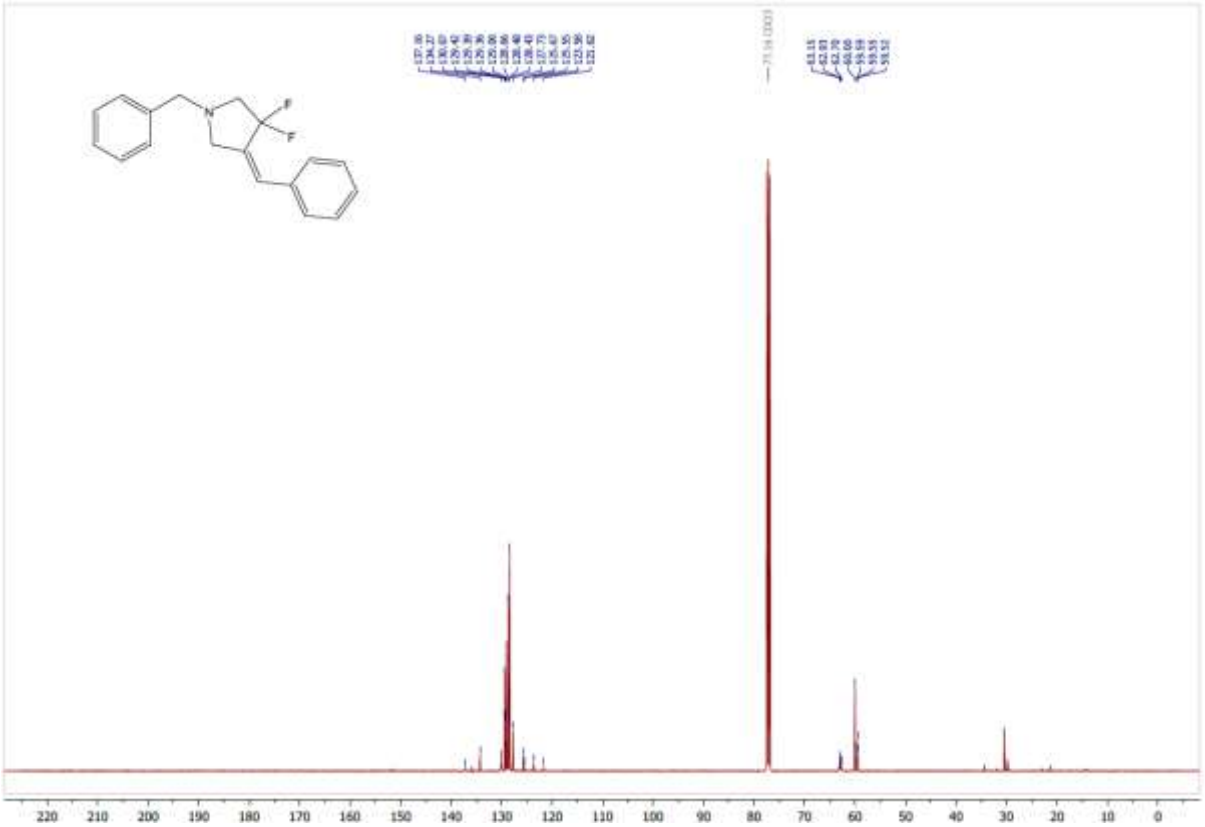
Supplementary Figure 162. ^{19}F NMR (*E*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine **26**



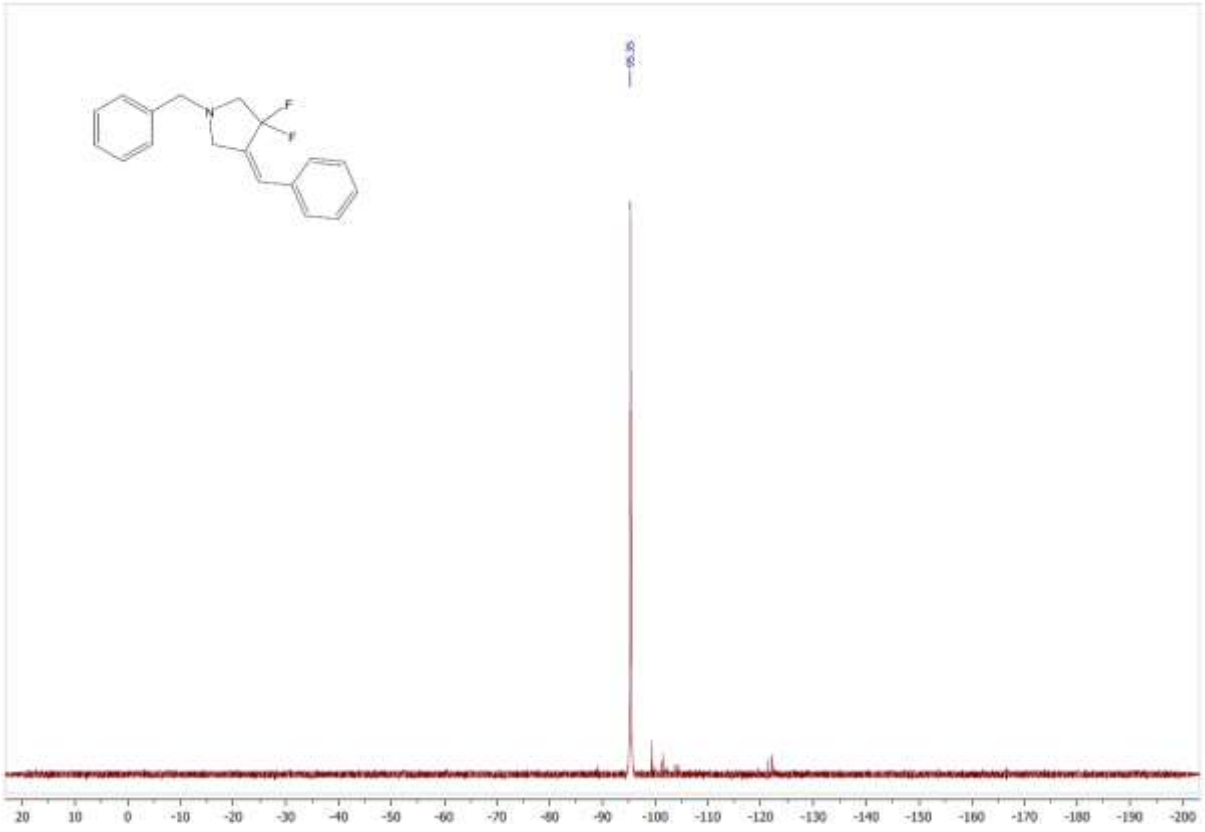
Supplementary Figure 163. ^{1}H NMR (*Z*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine **27**



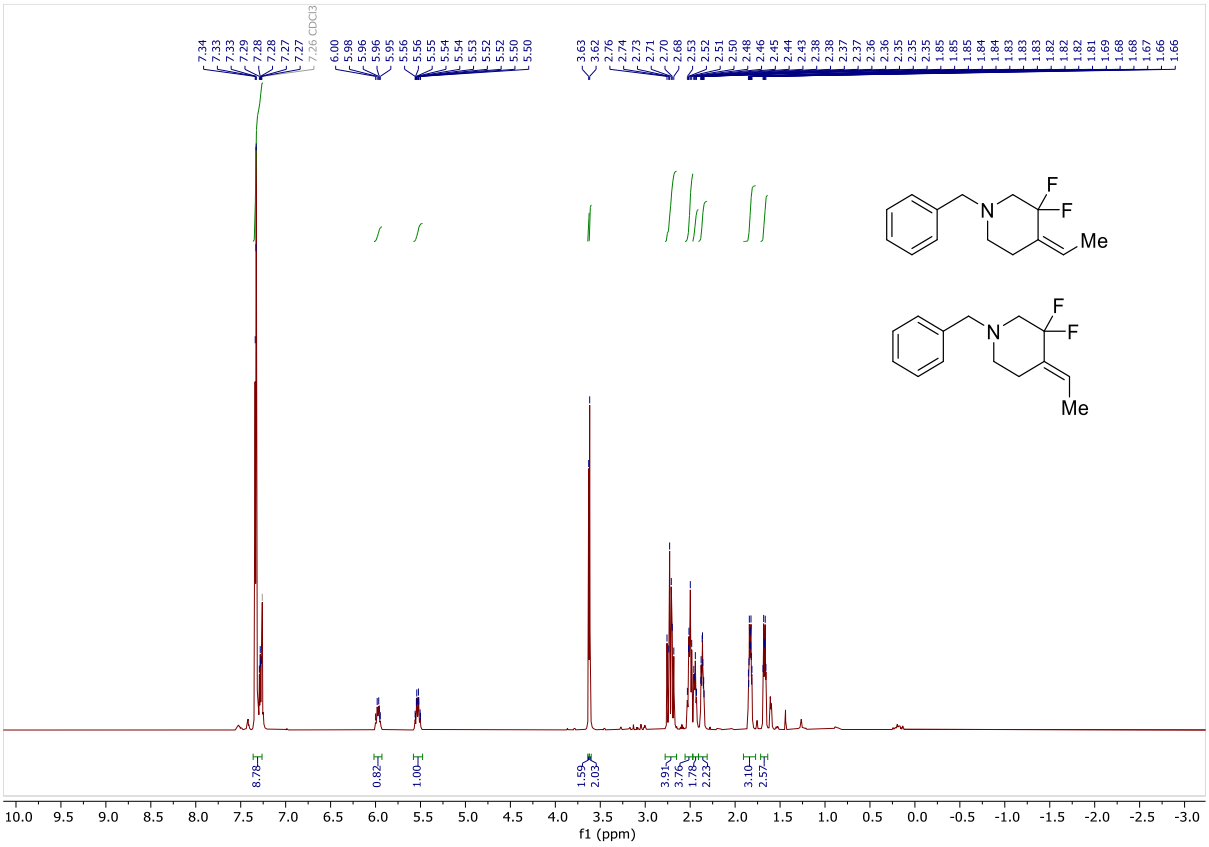
Supplementary Figure 164. ^{13}C NMR (*Z*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine **27**



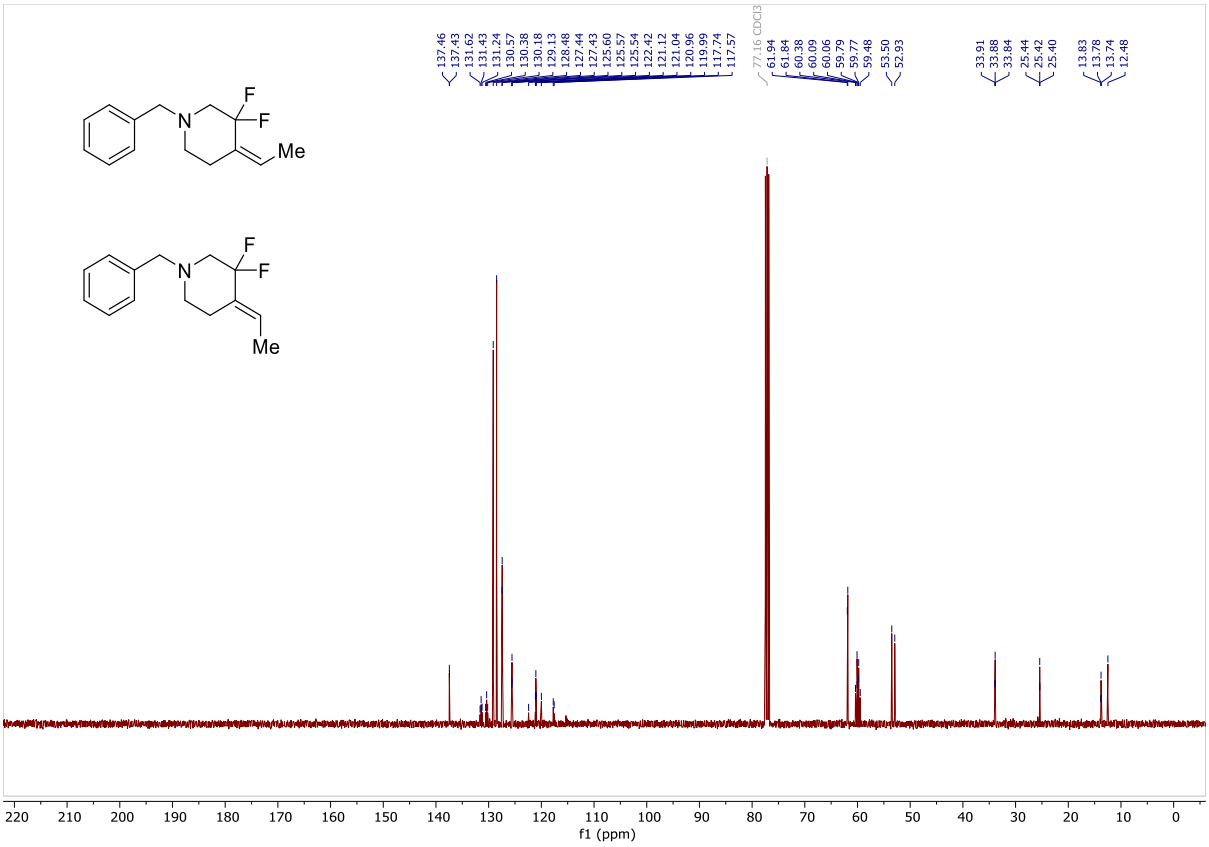
Supplementary Figure 165. ^{19}F NMR (*Z*)-1-Benzyl-4-benzylidene-3,3-difluoropyrrolidine **27**



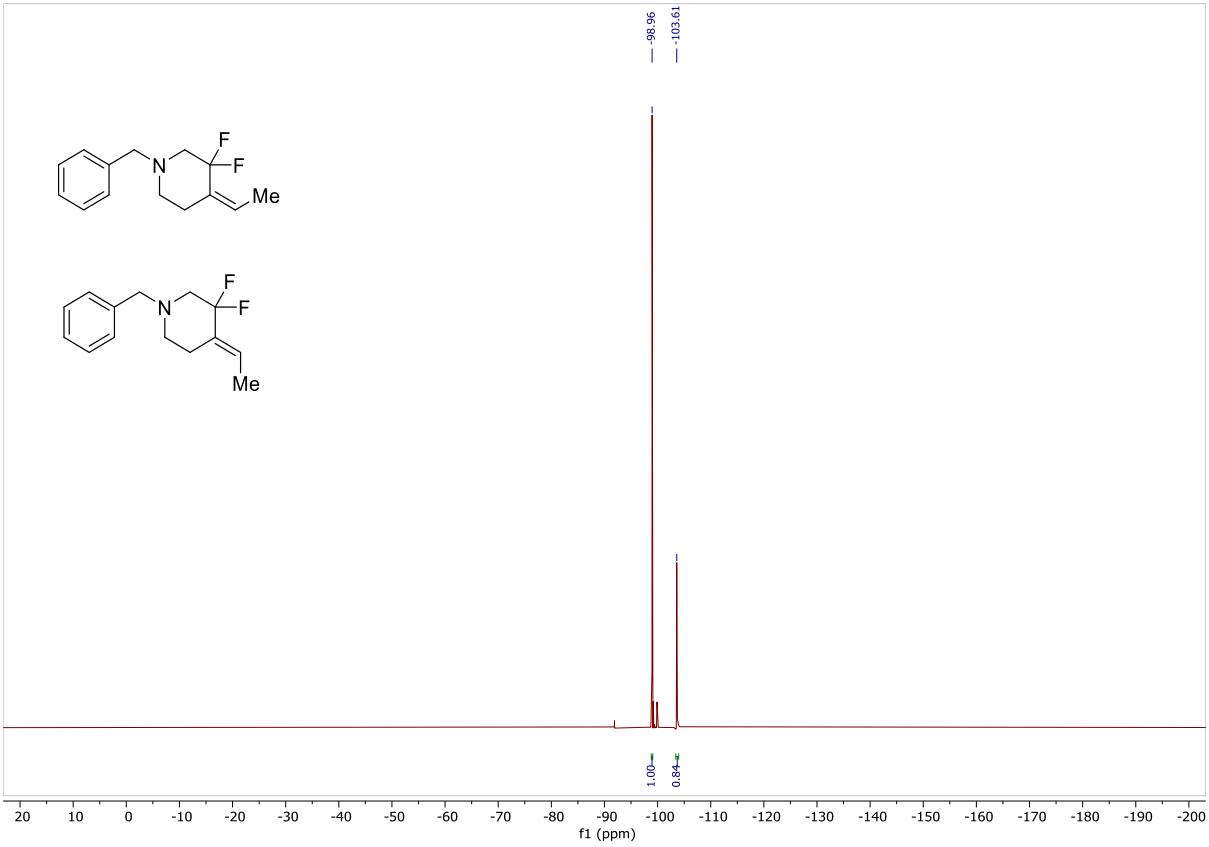
Supplementary Figure 166. ^{1}H NMR 1-Benzyl-4-ethylidene-3,3-difluoropiperidine **28**



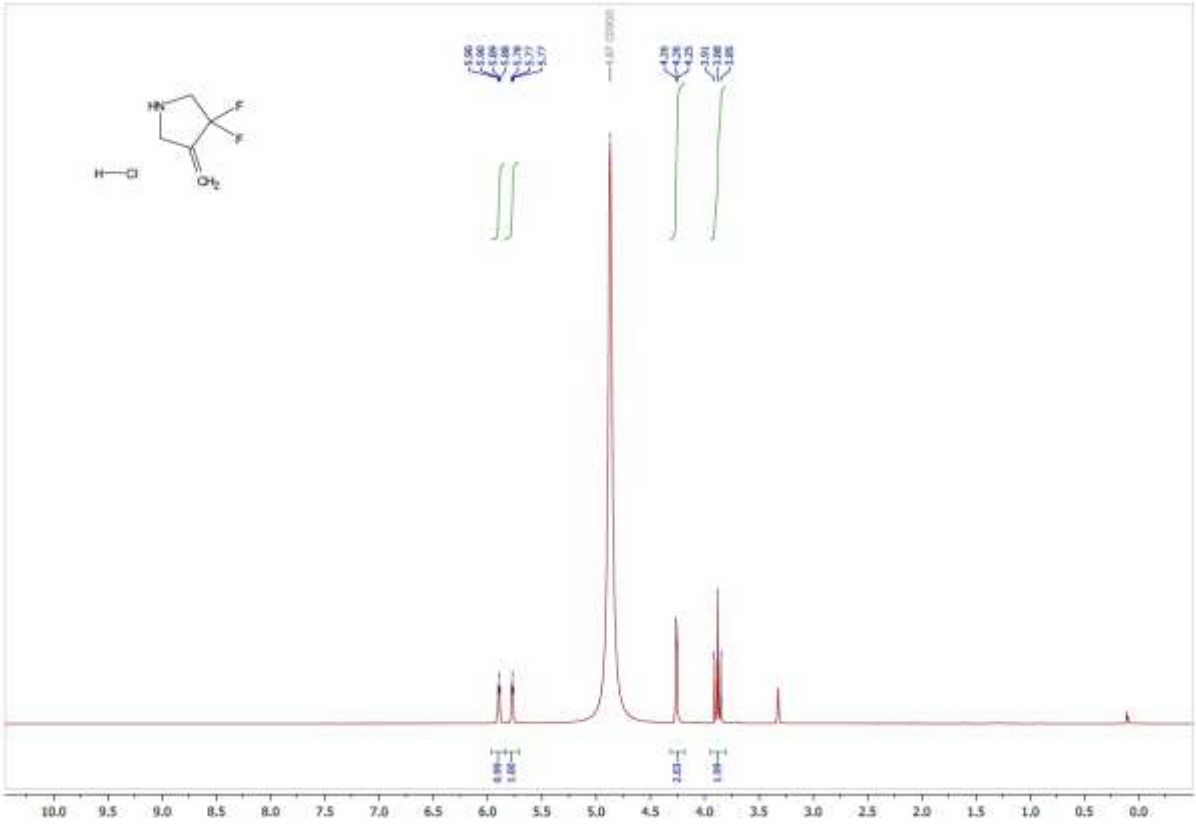
Supplementary Figure 167. ^{13}C NMR 1-Benzyl-4-ethylidene-3,3-difluoropiperidine **28**



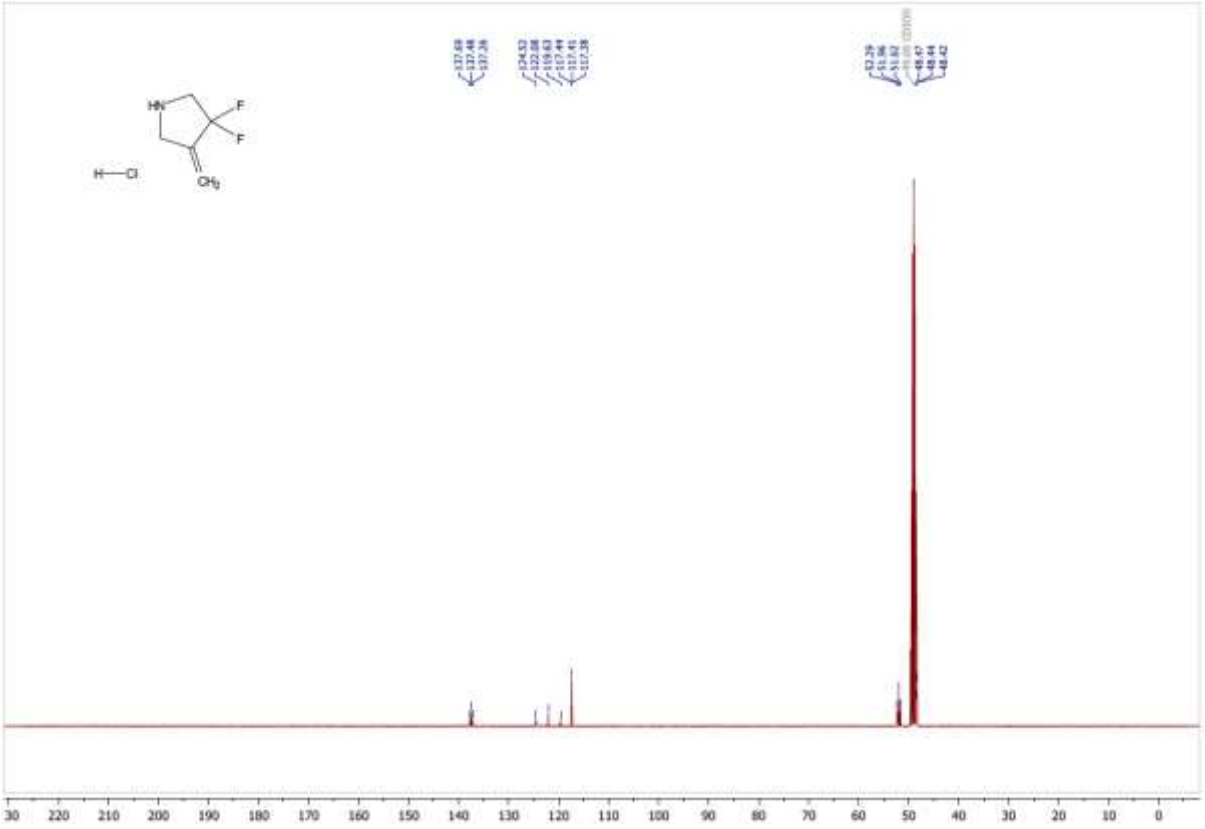
Supplementary Figure 168. ^{19}F NMR 1-Benzyl-4-ethylidene-3,3-difluoropiperidine **28**



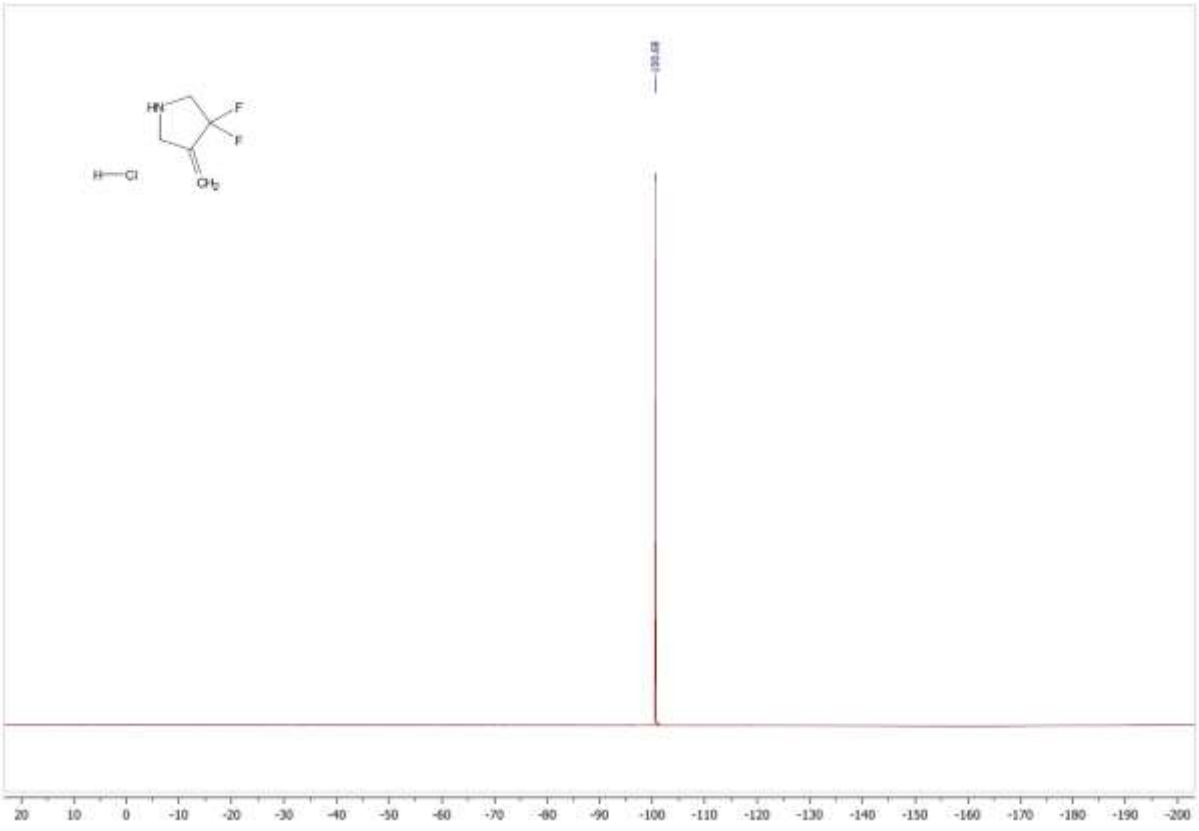
Supplementary Figure 169. ^{1}H NMR 3,3-Difluoro-4-methylenepyrrolidine hydrochloride **30**



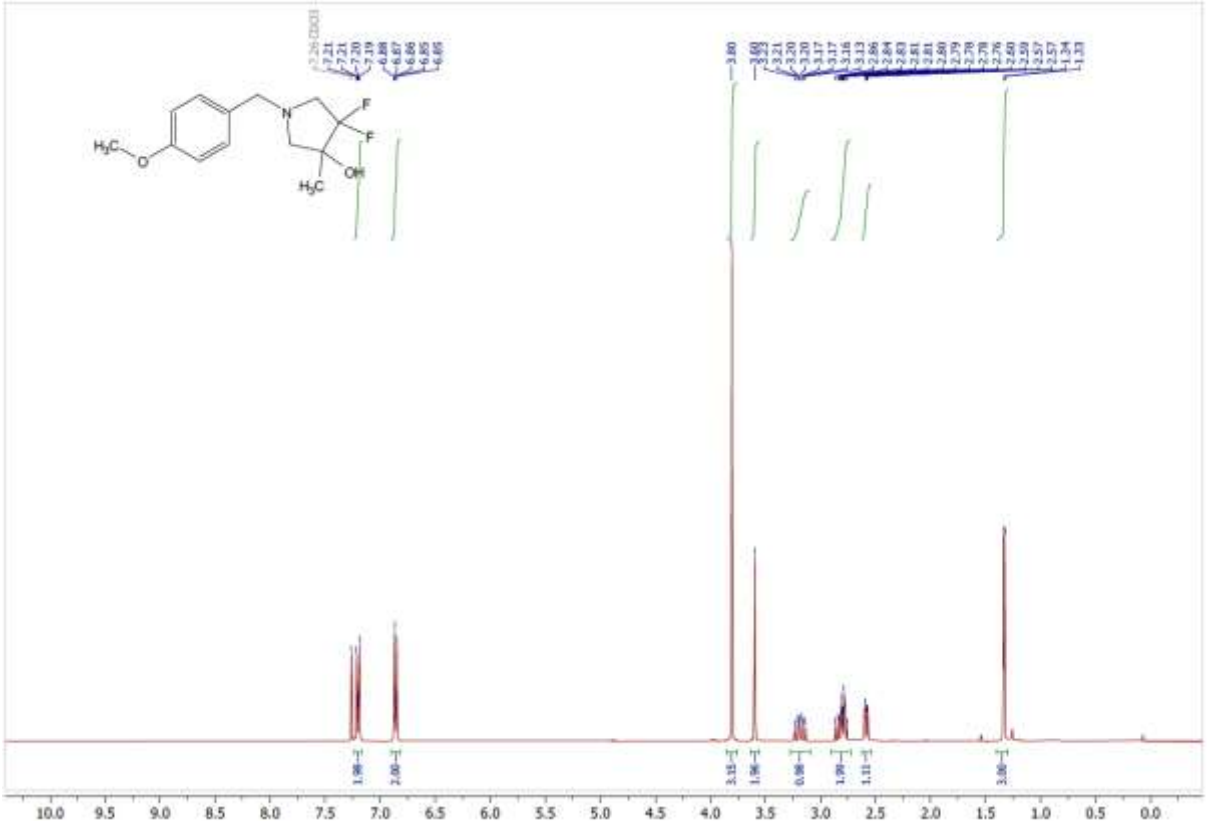
Supplementary Figure 170. ^{13}C NMR 3,3-Difluoro-4-methylenepyrrolidine hydrochloride **30**



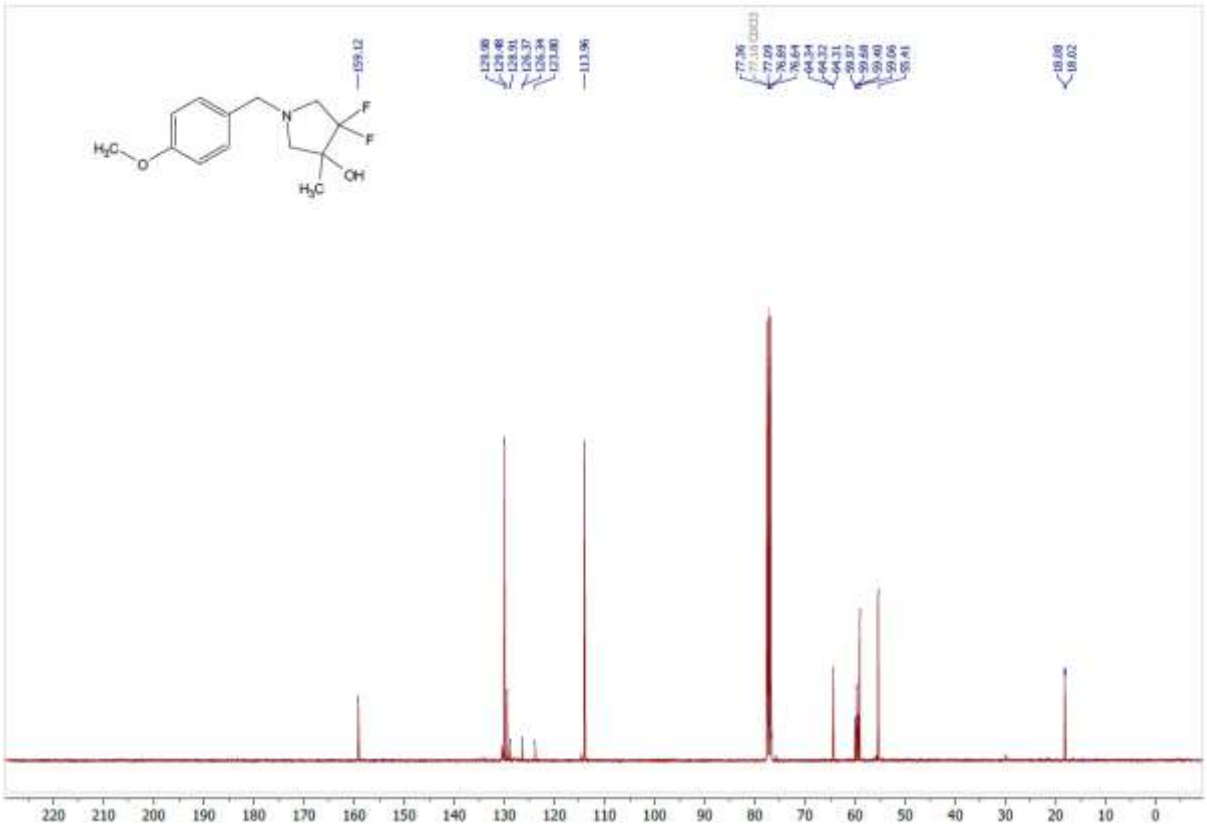
Supplementary Figure 171. ^{19}F NMR 3,3-Difluoro-4-methylenepyrrolidine hydrochloride **30**



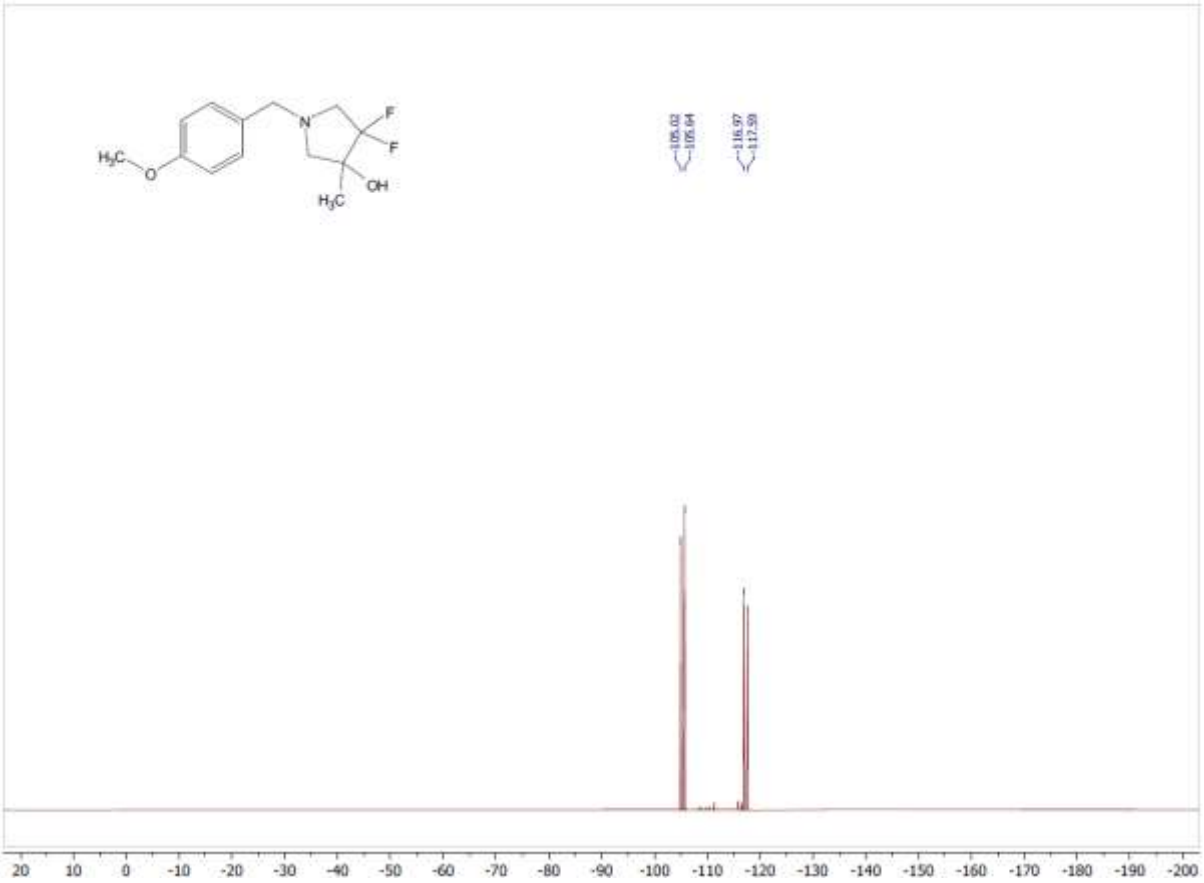
Supplementary Figure 172. ^{1}H NMR 4,4-Difluoro-1-(4-methoxybenzyl)-3-methylpyrrolidin-3-ol **31**



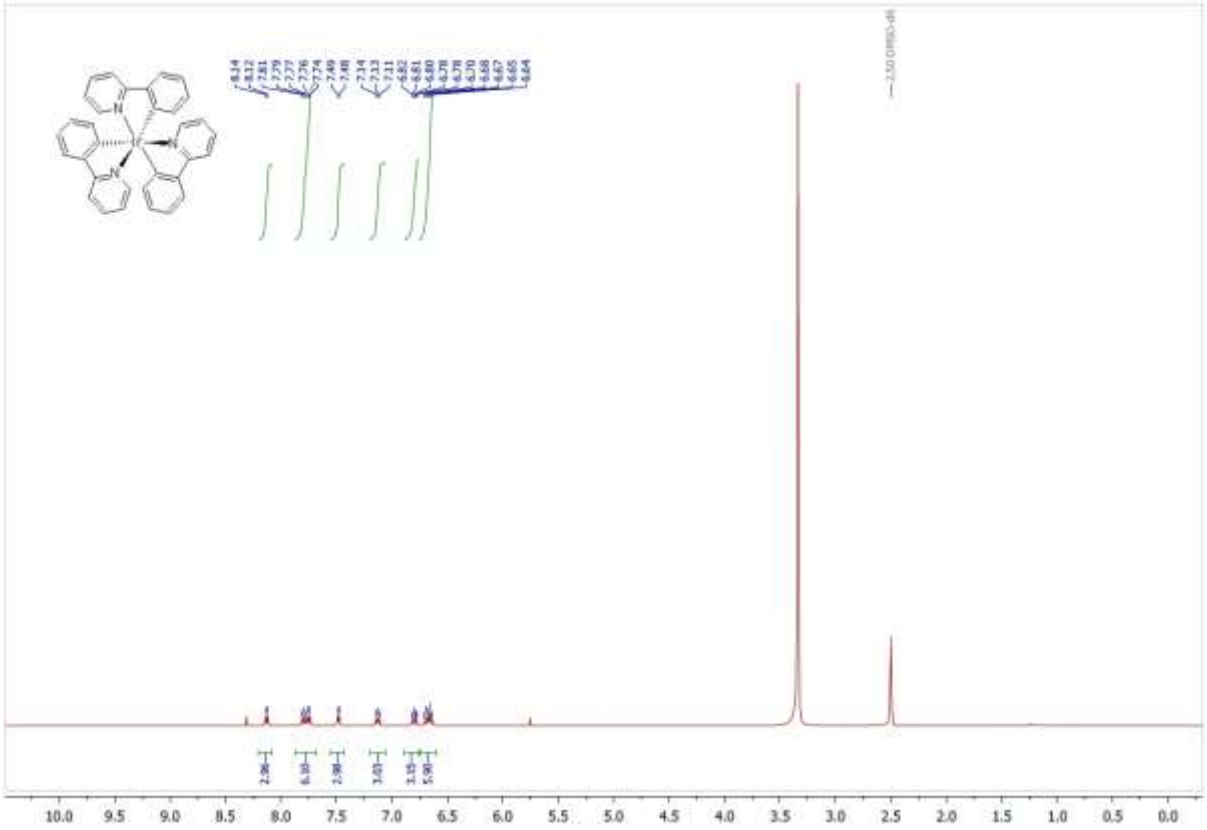
Supplementary Figure 173. ^{13}C NMR 4,4-Difluoro-1-(4-methoxybenzyl)-3-methylpyrrolidin-3-ol **31**



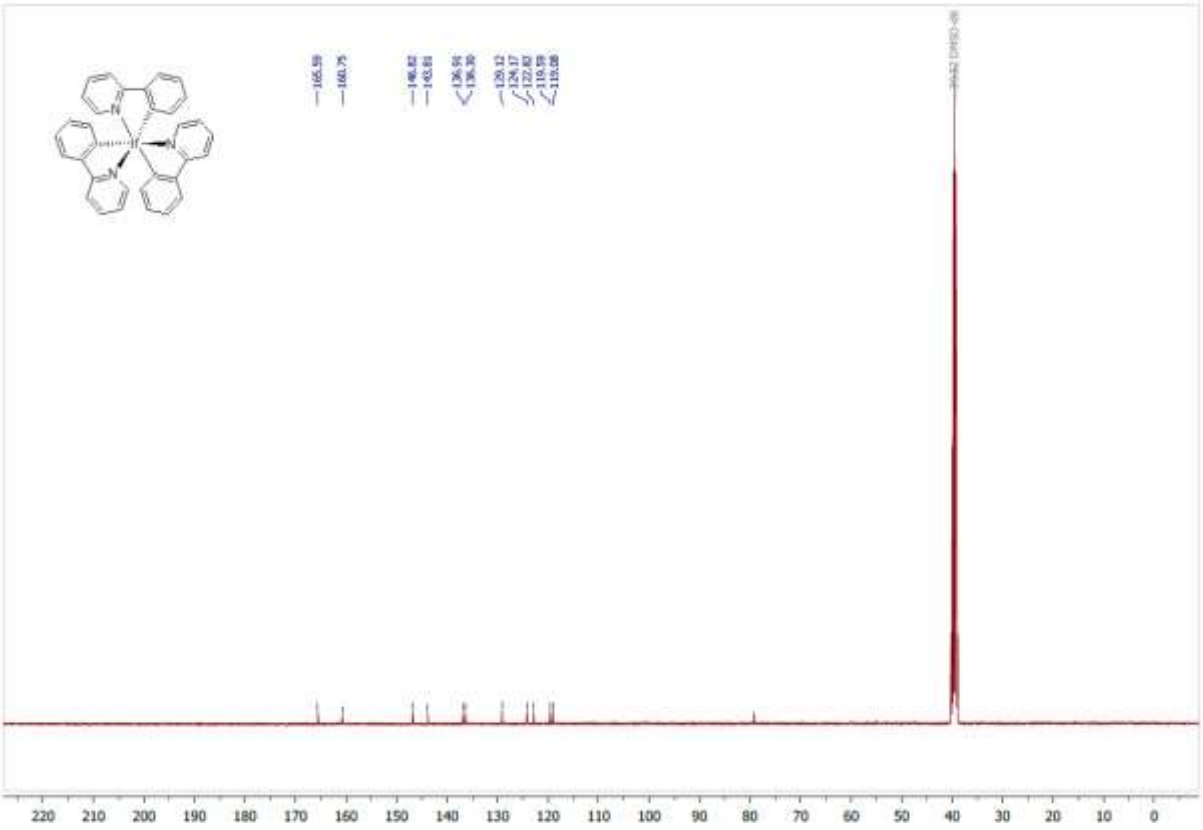
Supplementary Figure 174. ^{19}F NMR 4,4-Difluoro-1-(4-methoxybenzyl)-3-methylpyrrolidin-3-ol **31**



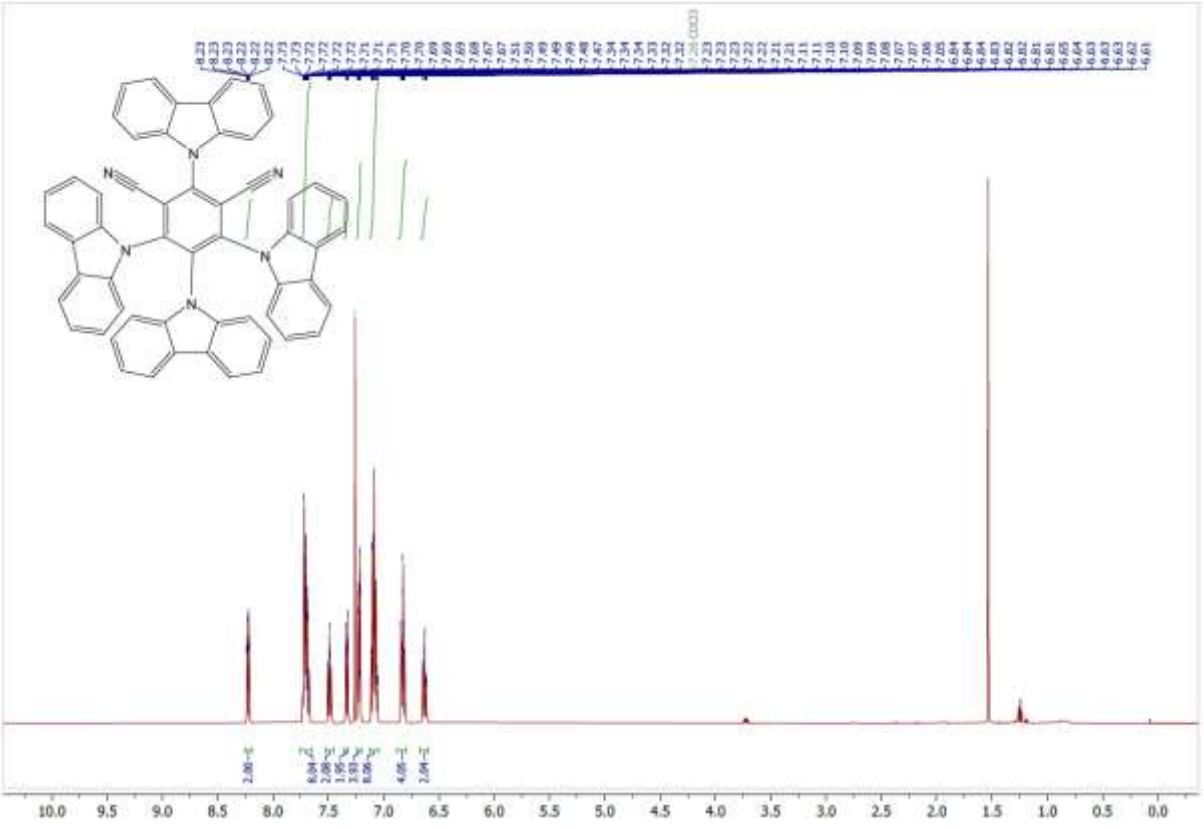
Supplementary Figure 175. ^{1}H NMR *fac*-Ir(ppy)$_3$ **65**



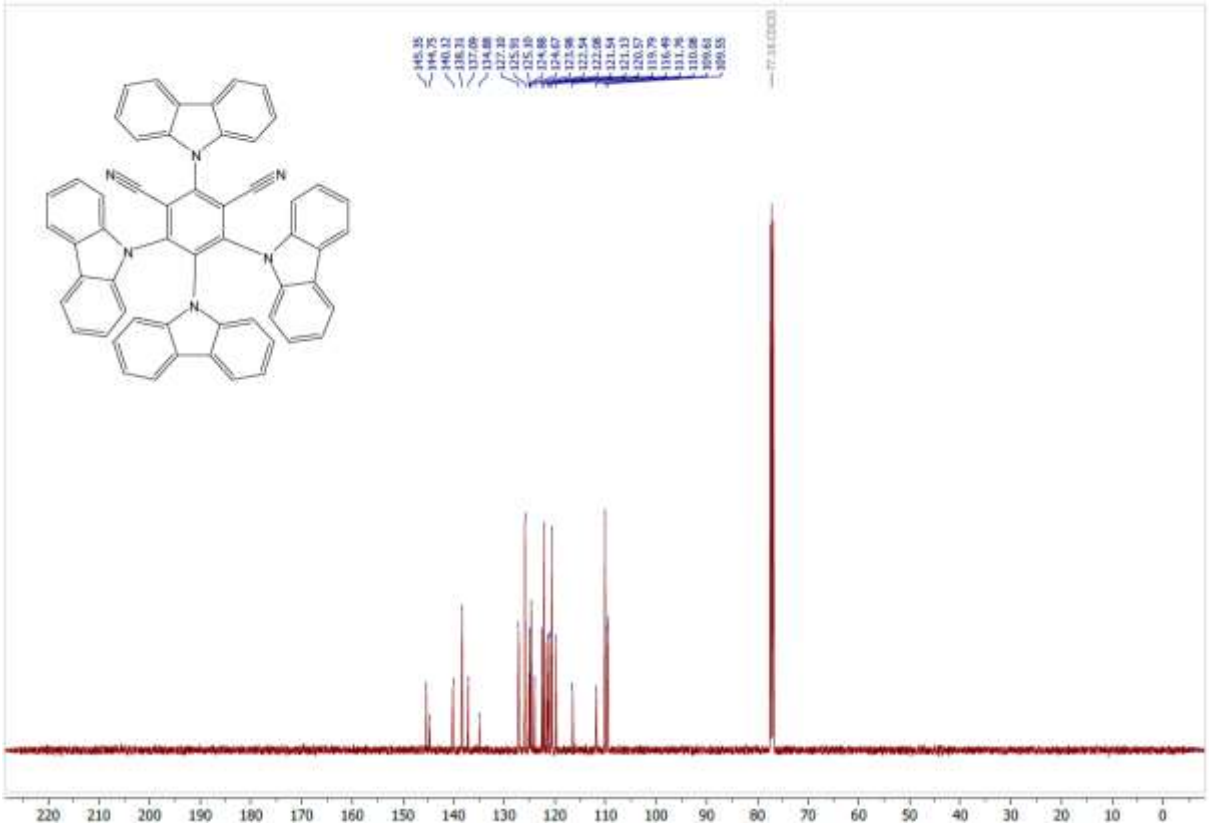
Supplementary Figure 176. ^{13}C NMR *fac*-Ir(ppy)$_3$ **65**



Supplementary Figure 177. ^{1}H NMR 4CzIPN **66**



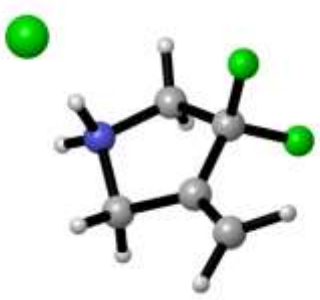
Supplementary Figure 178. ^{13}C NMR 4CzIPN **66**

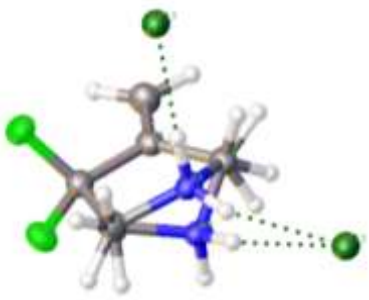


8 X-ray crystallography

The structure is disordered over a mirror plane where the ring carbon atoms lie on the plane and the nitrogen and fluorine lie above it. For clarity only one structure from the mirror plane is depicted in the manuscript.

Supplementary Table 7. Crystal data and structure refinement for **30**





Empirical formula	$C_5H_8ClF_2N$
Formula weight	155.57
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	Pnma

a/Å	10.0074(7)
b/Å	7.0673(5)
c/Å	9.5009(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	671.95(8)
Z	4
ρ_{calc}g/cm^3	1.538
μ/mm^{-1}	4.681
F(000)	320.0
Crystal size/mm^3	0.24 × 0.04 × 0.023
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	12.848 to 145.26
Index ranges	-12 ≤ h ≤ 12, -7 ≤ k ≤ 8, -11 ≤ l ≤ 11
Reflections collected	4429
Independent reflections	714 [R_{int} = 0.0526, R_{sigma} = 0.0265]
Data/restraints/parameters	714/2/61
Goodness-of-fit on F^2	1.084
Final R indexes [I>=2σ (I)]	R_1 = 0.0318, wR_2 = 0.0811
Final R indexes [all data]	R_1 = 0.0331, wR_2 = 0.0819
Largest diff. peak/hole / e Å^{-3}	0.34/-0.26
CCDC Deposit Number	2083564

Single crystal X-ray diffraction measurement and refinement of 30

A single crystal of **30** was selected and mounted using Fomblin® (YR-1800 perfluoropolyether oil) on a polymer-tipped MiTeGen MicroMountTM and cooled rapidly to 120 K in a stream of cold N_2 using an Oxford Cryosystems open flow cryostat.[11] Single crystal X-ray diffraction data were collected on an Oxford Diffraction GV1000 (TitanS2 CCD area detector, mirror-monochromated Cu-Kα radiation source; λ = 1.54184 Å, ω scans). Cell parameters were refined from the observed positions of all strong reflections and absorption corrections were applied using a Gaussian numerical method with beam profile correction (CrysAlisPro).[12] Structures were solved within Olex2[13] by dual space iterative methods (SHELXT)[14] and all non-hydrogen atoms refined by full-matrix least-squares on all unique F2 values with anisotropic displacement parameters (SHELXL).[15] Structures were checked with checkCIF.[16] CCDC-2083564 contains the supplementary data for this compound. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Ammonium nitrogen atom N8 is disordered across a mirror plane which is coincident with the ring system of the main residue. It has been placed in disorder "part -1" to prevent a bond in the connectivity list between the symmetrically equivalent counterparts.

All hydrogen atoms were observed in the electron density map. Hydrogen atoms on the carbon atoms were geometrically placed and refined with a riding model. The two hydrogen atoms on nitrogen atom N8 are refined with the N-H bond distances restrained to target values of 0.91 Å, and their isotropic displacement parameters fixed at 1.2 time Ueq of the parent nitrogen atom.

9 References

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