Supplementary Information (SI) for RSC Mechanochemistry.

Sustainable mechanochemical synthesis of functionalisable fluorinated scaffolds for drug discovery using green LAG

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Supporting information

Contents

General Methods

All reactants, reagents and solvents were bought from commercial suppliers and used as received without further purification unless stated. Column chromatography was carried out using a stationary phase of silica gel 60, 40-60 µm. Analytical thin-layer chromatography was performed using precoated aluminium silica gel plates. Organic extracts during were dried using magnesium sulfate. The yields reported are isolated yields. The milling devices used were a YKL-0.4L Planetary Ball Mill (manufactured by Changsha Yonglekang Equipment Co., Ltd (https://www.csyonglekang.com/), and a Fritsch Pulverisette 7 Micro Mill (manufactured by Fritsch International (https://www.fritsch-international.com/). NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 400, 500 or 600 MHz (^{1}H NMR), 376, 470 or 564 MHz (^{19}F NMR) and 100, 125 or 150 MHz (^{13}C NMR) on Jeol ECS 400, ECZ 500 or ECZ 600 spectrometers. Chemical shifts, δ, are reported in parts per million (p.p.m), referenced to tetramethylsilane for ^{1}H and ^{13}C spectra. ^{19}F NMR spectra are referenced to $CFCl_3$ or hexafluorobenzene. Coupling constants, *J*, are reported in hertz (Hz). Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q) or multiplet (m). High resolution mass spectrometry (HRMS) was carried out on a ThermoFisher Exactive (Orbitrap) instrument with an ESI probe and a max ion source. Elemental analysis (EA) was carried out using a Perkin-Elmer 2400 analyser. Melting points were determined using open-ended capillaries in a Stuart Scientific SMP10 melting point instrument at a ramping rate of 1 °C/min, and are uncorrected. IR spectra were recorded using a Thermo Scientific Nicolet FTIR spectrometer.

Method Optimisation Experiments

The optimum size and number of milling balls, and optimum grinding agent were identified from milling experiments conducted in 100 ml steel milling jars in the Changsha Yonglekang YKL-0.4L mill. The use of different sizes of milling balls was found to be superior to the use of balls of the same size, giving a more homogeneous mixture after milling for 20 min. (Table 1). The highest recovery of organic material was obtained using balls of mass (number), 5.68 g (3), 3.28 g (2) and 2.14 g (5) (Entry 5). This combination was used for all further experiments. The agate milling balls available for use in the Fritsch Pulverisette 7 micro mill were 10 mm diameter and six were employed for reactions in this mill

Entry	**Mass of steel balls /g**	**Quantity of steel balls**	**Appearance of resulting mixture**	**Recovery /%**
1	5.68	6	Heterogeneous	32
2	0.45	24	Heterogeneous	24
3	5.68 2.14	3 4	Homogeneous	52
4	3.28 2.14	4 8	Homogeneous	61
5	5.68 3.28 2.14	3 2 5	Homogeneous	90

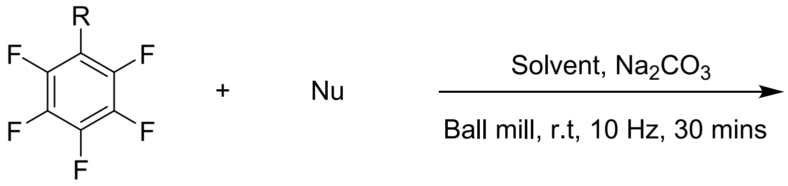
Table 1: Variation of mass and number of milling balls employed for grinding.

The effect of different milling aids was tested using:

- Anhydrous sodium carbonate
- Sodium fluoride
- Potassium carbonate
- Aluminium oxide / potassium fluoride

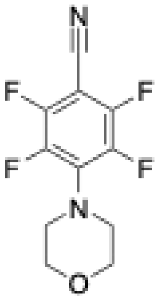
Sodium carbonate was found the cheapest and most effective milling agent with 1.0 g employed for 5 mmol scale reactions. The amount was adjusted depending on the mass of other reagents to ensure milling jars had the same overall mass to ensure balanced rotation during operation of the mill.

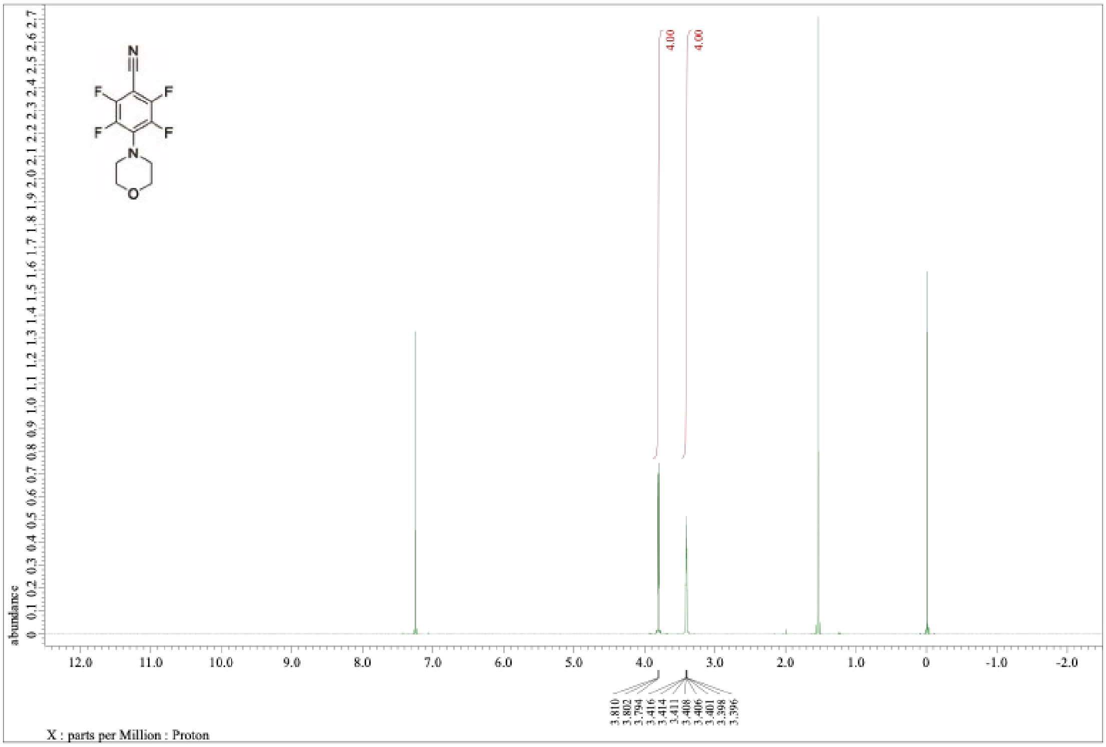
General Reaction Procedure



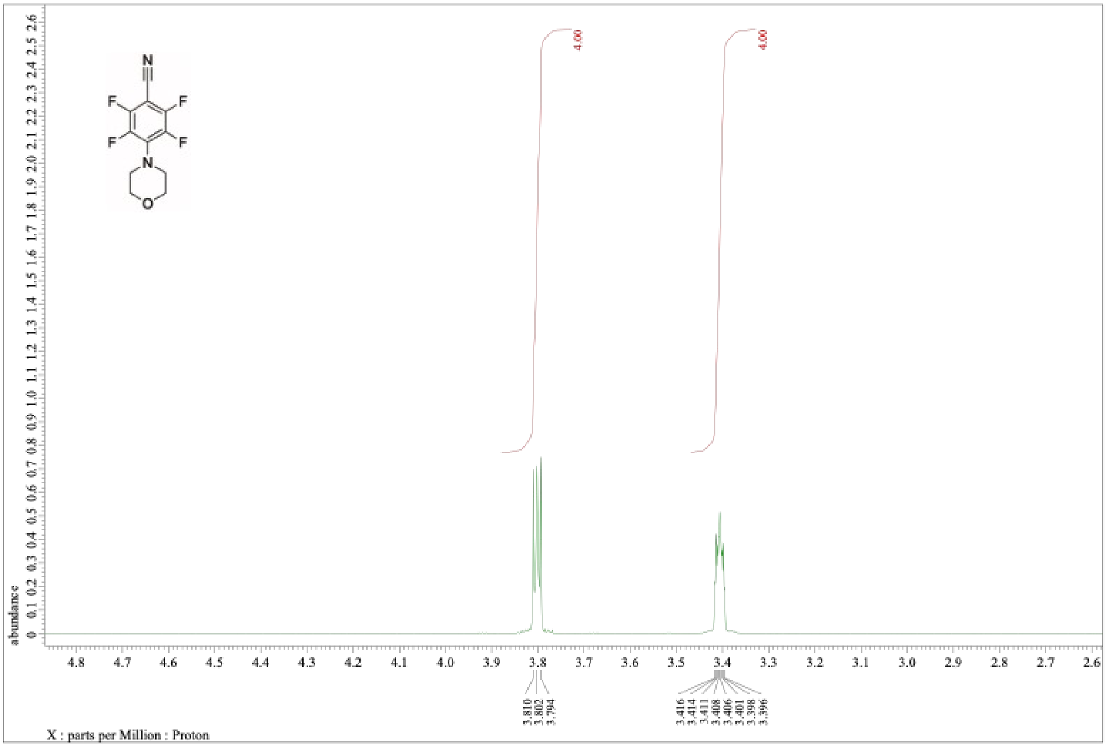
The chosen fluoroarene (5 mmol), the chosen nucleophile (5 mmol) and sodium carbonate (1.0 g, 9.4 mmol) were added to a 100 ml stainless milling jar along with 5.68 g (3), 3.28 g (2) and 2.14 g (5) steel milling balls, and the chosen solvent (0.25 ml) added. The jars were spun at 600 rpm for 30 minutes. Water was then added to dissolve the precipitate and the mixture extracted with ethyl acetate. The organic extracts were combined, dried with magnesium sulfate and the solvent removed *in vacuo* to give the crude product which was then purified by column chromatography.

2,3,5,6-Tetrafluoro-4-morpholinobenzonitrile (8aa)

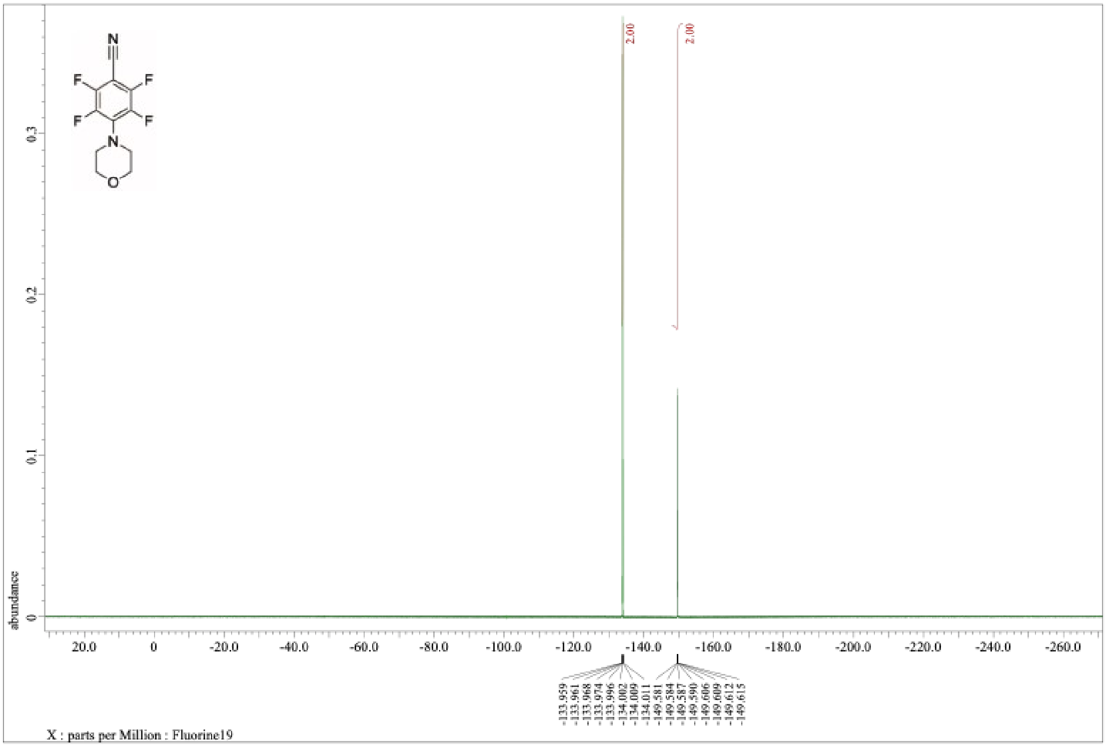
	Prepared from pentafluorobenzonitrile (0.63 mL, 5.0 mmol) and morpholine (0.43 mL, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 5:1) to form compound **8aa** as a white solid (1.18 g, 91 %, 4.6 mmol). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 3.81-3.79 (m, 4H), 3.42-3.40 (m, 4H); **^{19}F NMR (564 MHz, CDCl$_3$)** δ -134.0 (m, 2F), -149.6 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 148.2 (ddd, *J* 258, 11, 3), 140.6 (ddd, *J* 246, 13, 2), 135.4 (tt, *J* 10, 3), 108.3 (t, *J* 4), 84.6 (t, *J* 17), 67.1, 51.0; **IR ν_{max} /cm^{-1}**: 2858 (C-H, alkane), 2235 (CΞN), 1647 (C=C, cyclic alkene), 1171 (C-F), 1066 (C-N); **HRMS** calculated for $C_{11}H_8F_4N_2ONa^+$ 283.0465, found 283.0464; **EA** Found: C 50.5, H 3.09, N 10.6. $C_{11}H_8F_4N_2O$ requires C 50.8, H 3.10, N, 10.8; **mp** 79.1 – 80.2 °C (lit.,[1] 78-79 °C). The yields were 73% and 78% respectively with water or DMF as solvent. Data in agreement with litearature values.[1]



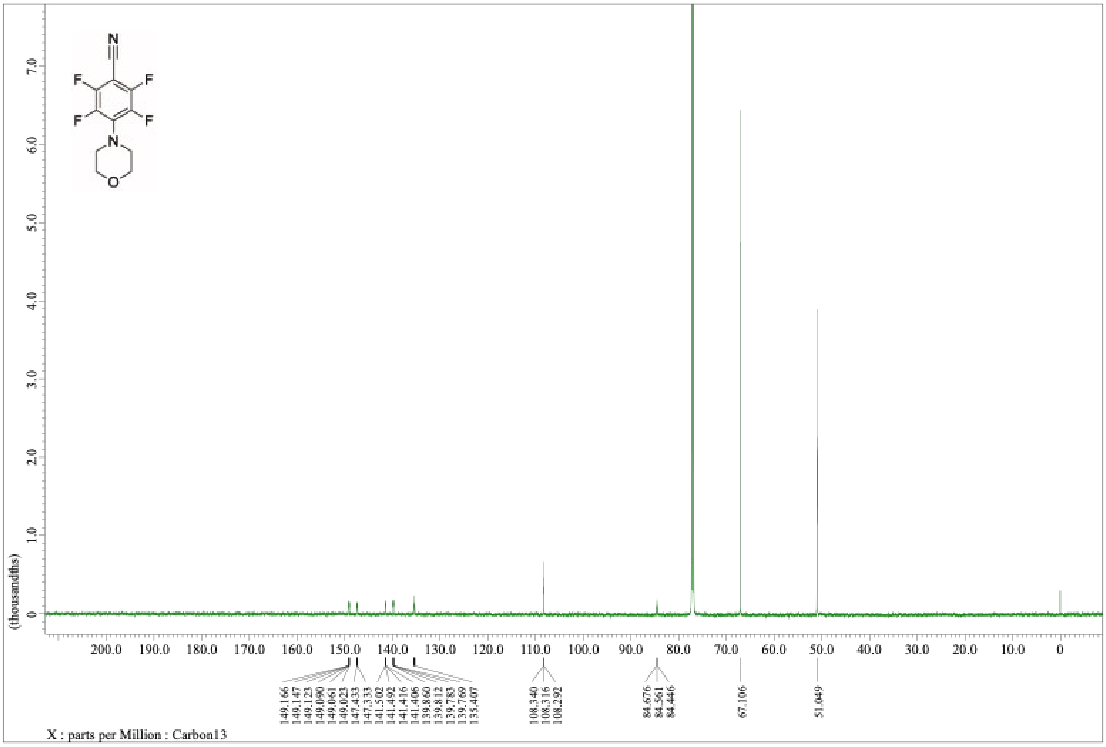
8aa ^{1}H NMR spectrum (600 MHz, $CDCl_3$)



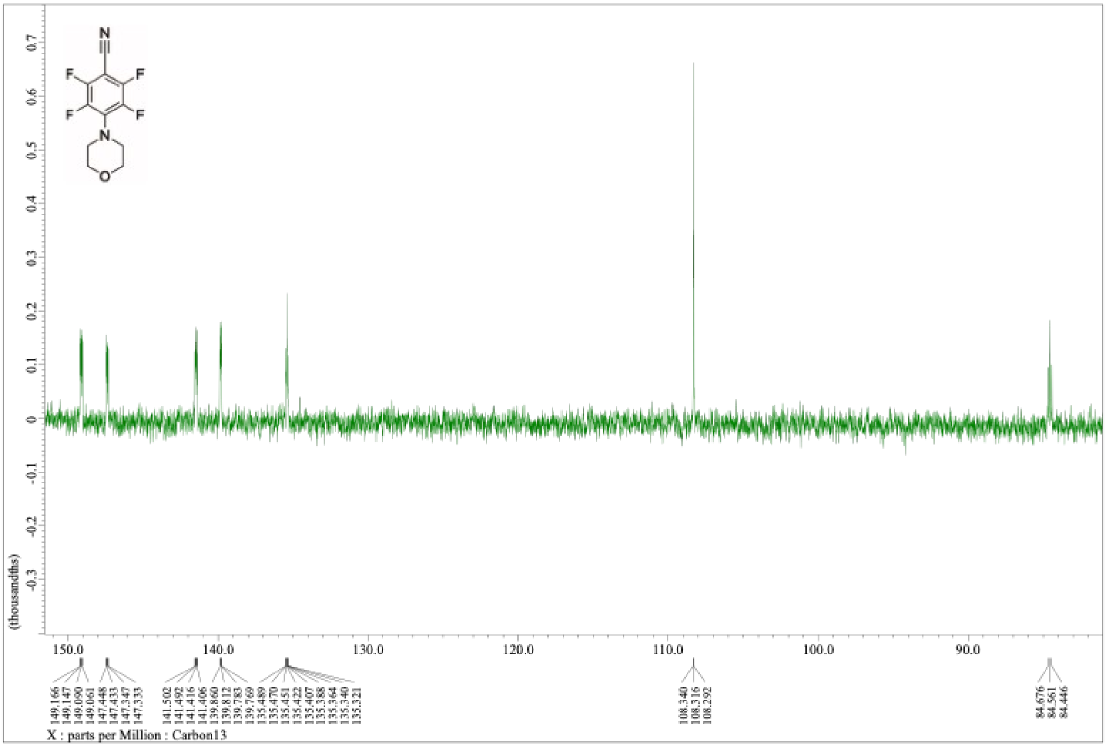
8aa ^{1}H NMR spectrum expansion (600 MHz, $CDCl_3$)



8aa ^{19}F NMR spectrum (564 MHz, CDCl$_3$)

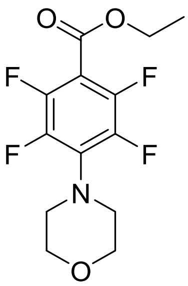


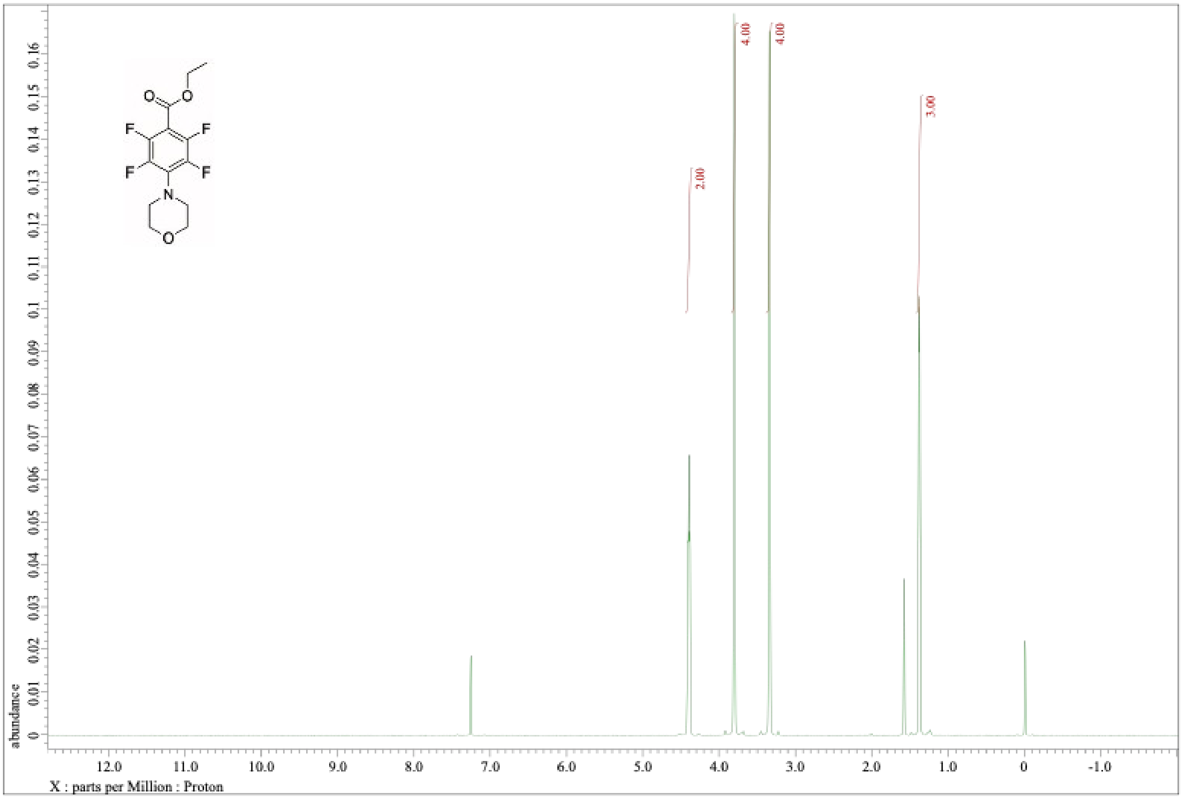
8aa ^{13}C NMR spectrum (150 MHz, CDCl$_3$)



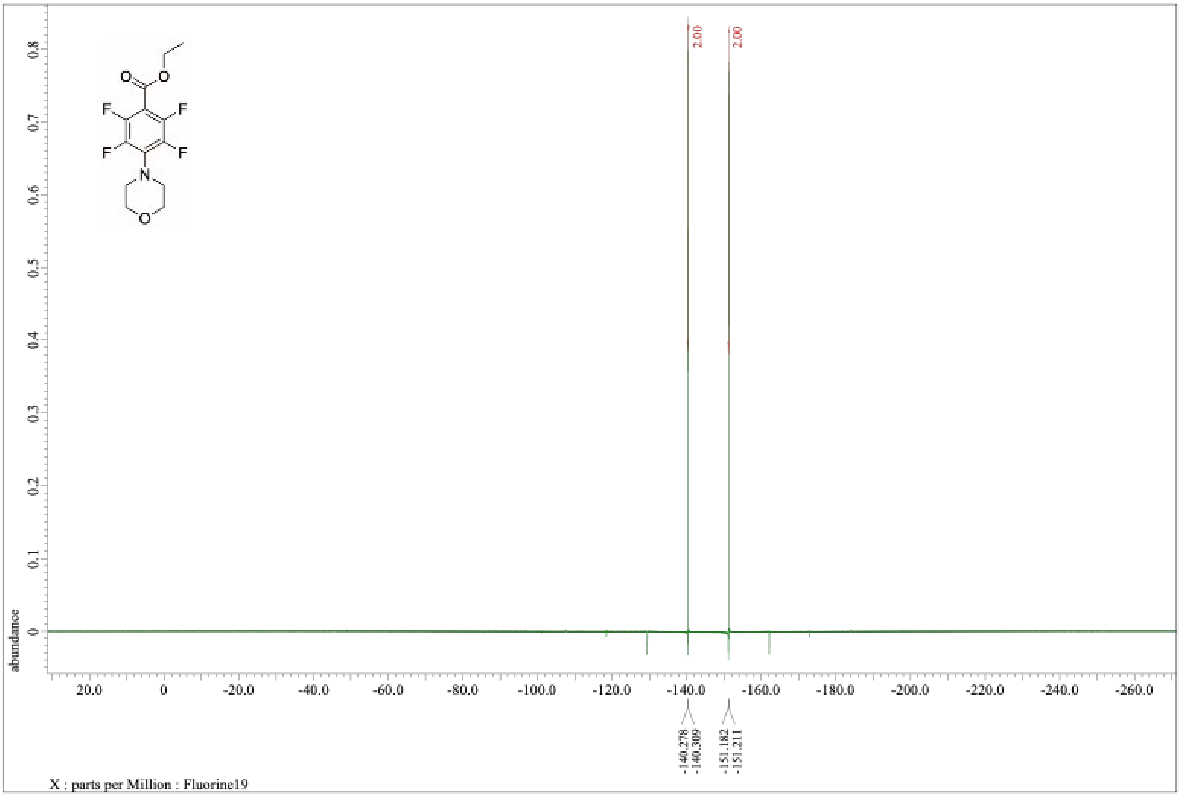
8aa ^{13}C NMR spectrum expansion (150 MHz, $CDCl_3$)

Ethyl 2,3,5,6-tetrafluoro-4-morpholinobenzoate (8ba)

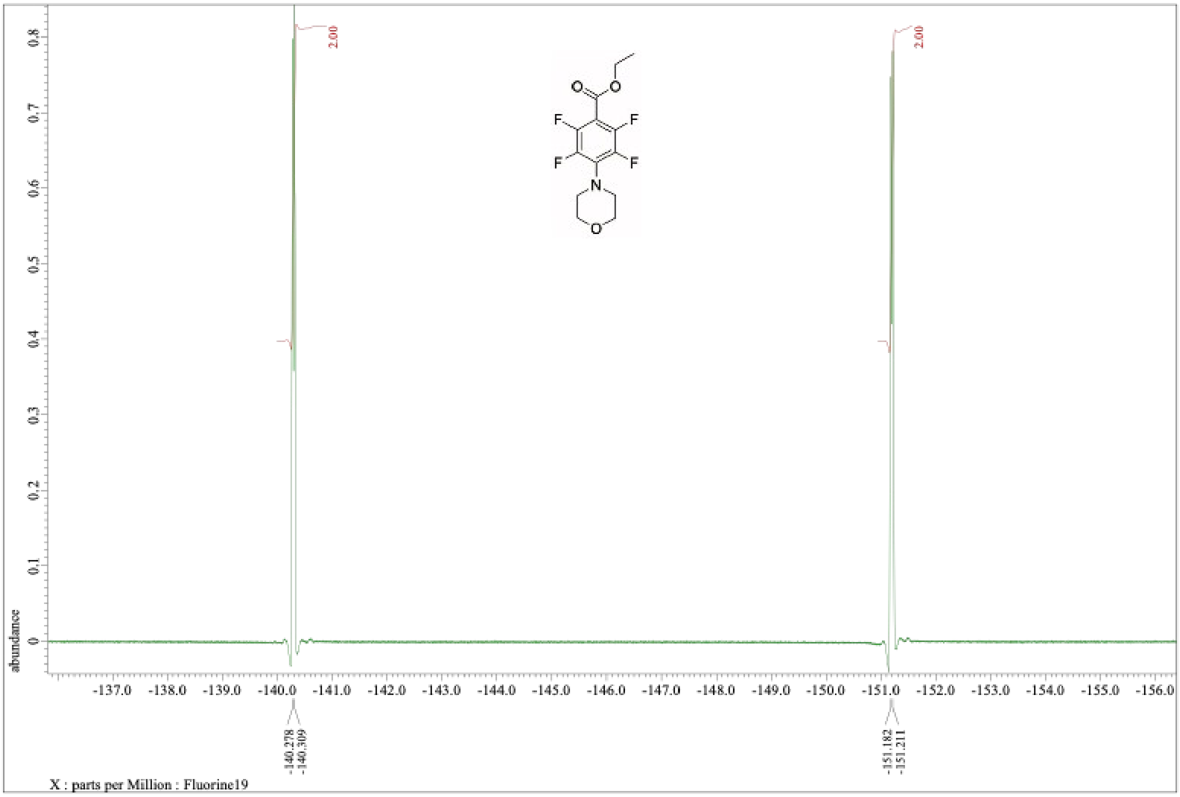
	Prepared from ethyl pentafluorobenzoate (0.84 mL, 5.0 mmol) and morpholine (0.43 mL, 5.0 mmol) using water (0.25 mL) as solvent. The crude product was then purified via column chromatography over silica gel (elution with hexane: ethyl acetate 1:1) to give compound **8ba** as a white solid (1.08 g, 70%, 3.5 mmol). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 4.39 (q, *J* 7, 2H), 3.82-3.78 (m, 4H), 3.36-3.32 (m, 4H), 1.37 (t, *J* 7, 3H); **^{19}F NMR (564 MHz, $CDCl_3$)** δ 21.53 (m, 2F), 10.61 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 160.2, 146.1 (dd, *J* 251, 24), 141.4 (dd, *J* 244, 19), 132.9 (t, *J* 10), 104.6 (t, *J* 15), 67.3, 62.2, 51.0, 14.2; **IR ν_{max} /cm^{-1}**: 2862 (C-H, alkane), 1732 (C=O, ester), 1648 (C=C, cyclic alkene), 1450 (C-H, methyl), 1290 (C-N, aromatic amine), 1225 (C-O, ester), 1009 (C-F); **HRMS** calculated for $C_{13}H_{13}F_4NO_3K^+$ 346.0463 found 346.0578; **mp** 81.0 – 81.9 °C. The yields were 59% and 66% respectively with Cyrene or DMF as solvent.



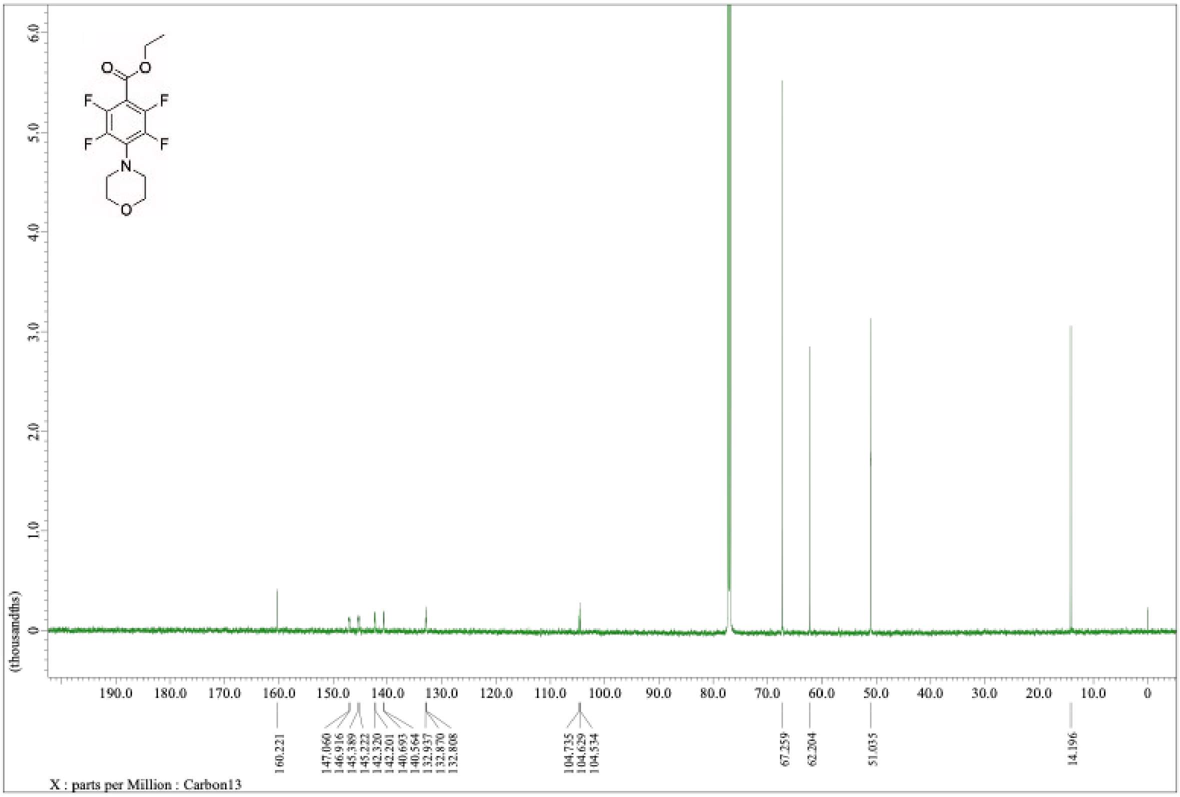
8ba ^{1}H NMR spectrum (600 MHz, $CDCl_3$)



8ba ^{19}F NMR spectrum (564 MHz, $CDCl_3$)

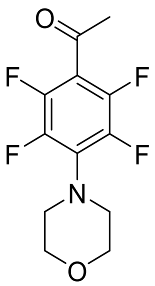


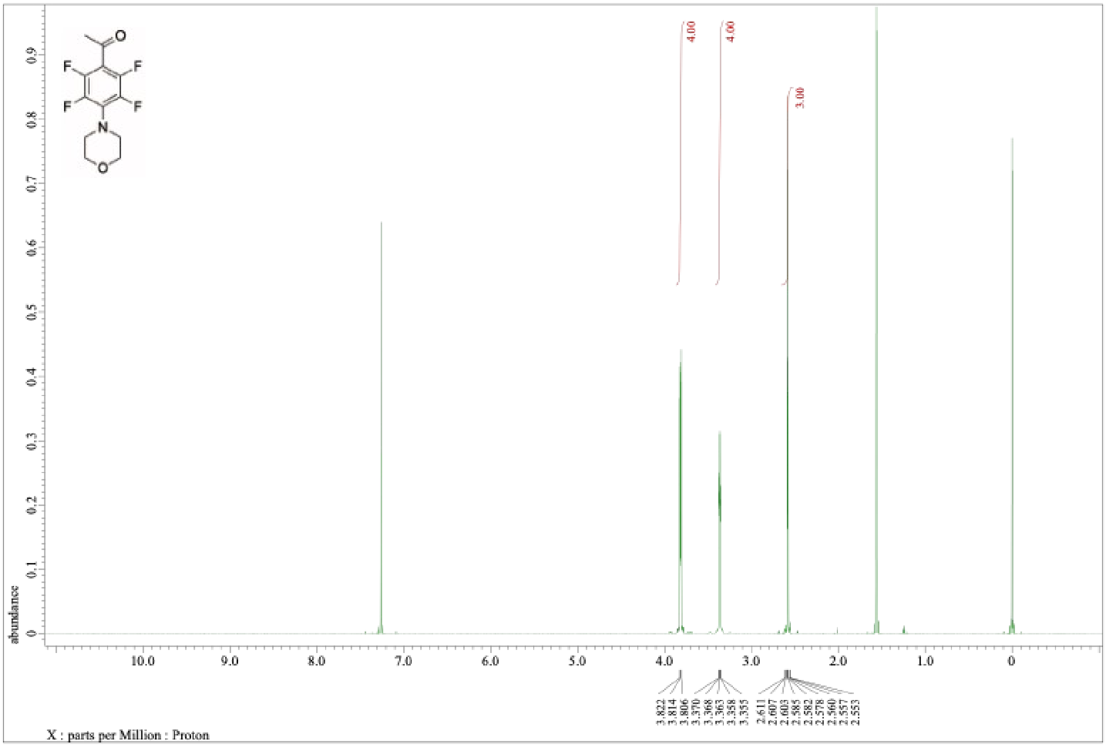
8ba ^{19}F NMR spectrum expansion (564 MHz, $CDCl_3$)



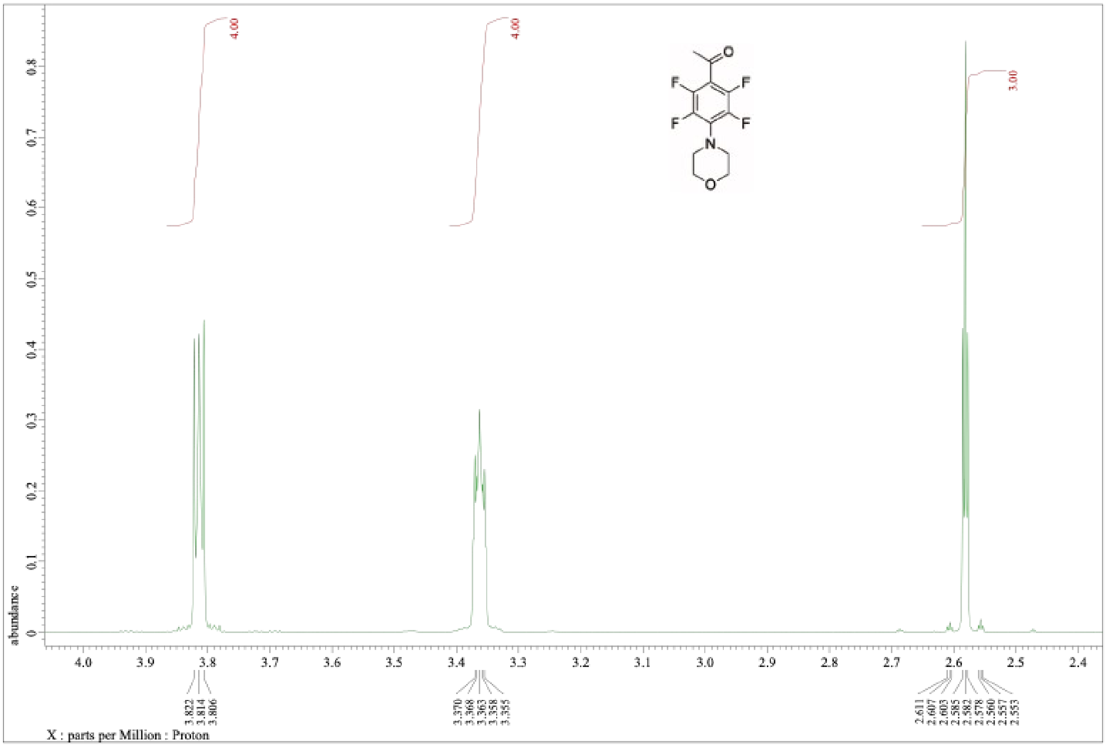
8ba ^{13}C NMR spectrum (150 MHz, $CDCl_3$)

2,3,5,6-Tetrafluoro-4-morpholinoacetophenone (8ca)

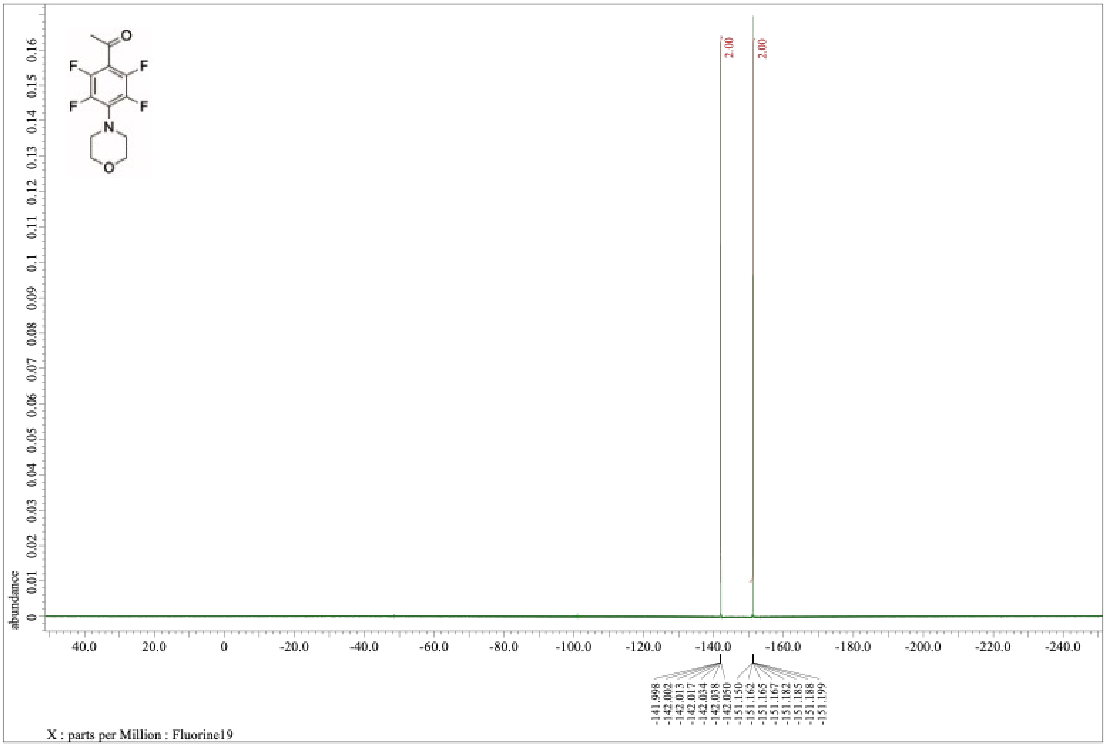
	Prepared from pentafluoroacetophenone (0.71 mL, 5.0 mmol) and morpholine (0.43 mL, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was taken without purification as compound **8ca** as a white solid (1.10 g, 79%, 4.0 mmol). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 3.82-3.81 (m, 4H), 3.37-3.36 (m, 4H), 2.58 (t, *J* 2, 3H); **^{19}F NMR (564 MHz, $CDCl_3$)** δ -142.0 (m, 2F), -151.2 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 191.8, 147.8, 141.3, 132.9, 111.4, 67.2, 51.0, 32.6 ; **IR ν_{max} /cm^{-1}**: 2918 (C-H, alkane), 1687 (C=O), 1629 (C=C, cyclic alkene), 1265 (C-N, aromatic amine), 1005 (C-F); **HRMS** calculated for $C_{12}H_{11}F_4NO_2H^+$ 278.0799, found 278.045; **mp** 73.6 – 74.9 °C. The yields were 41% and 35% respectively with water or DMF as solvent.



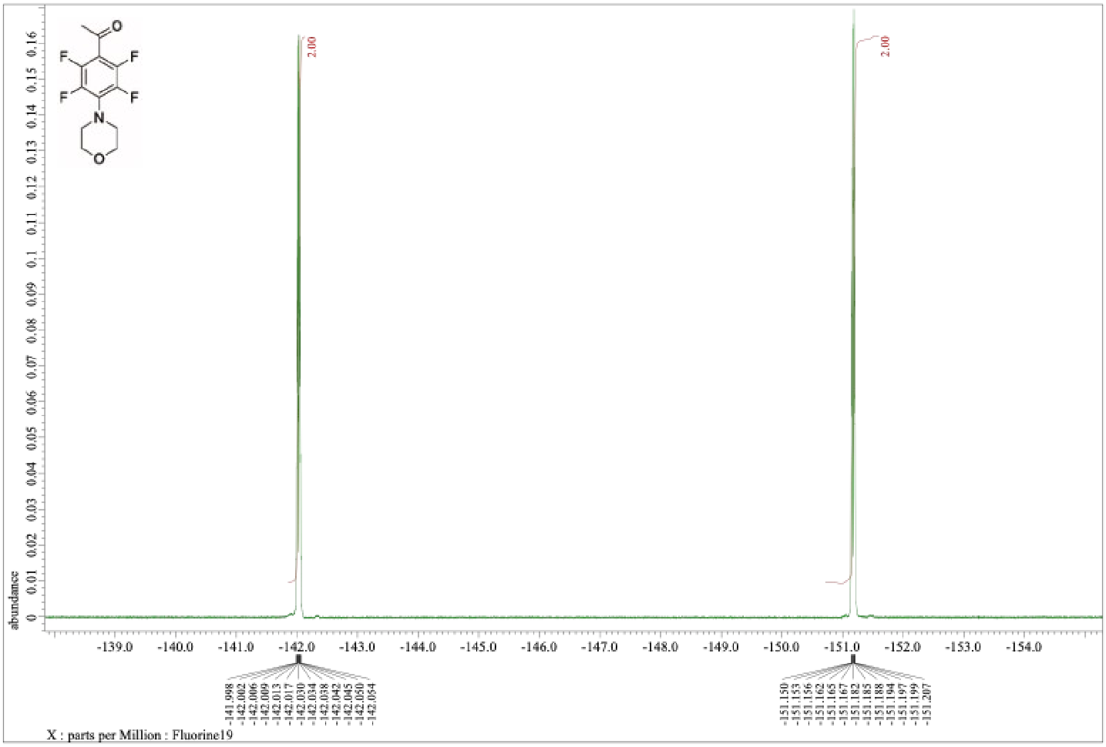
8ca ^{1}H NMR spectrum (600 MHz, $CDCl_3$)



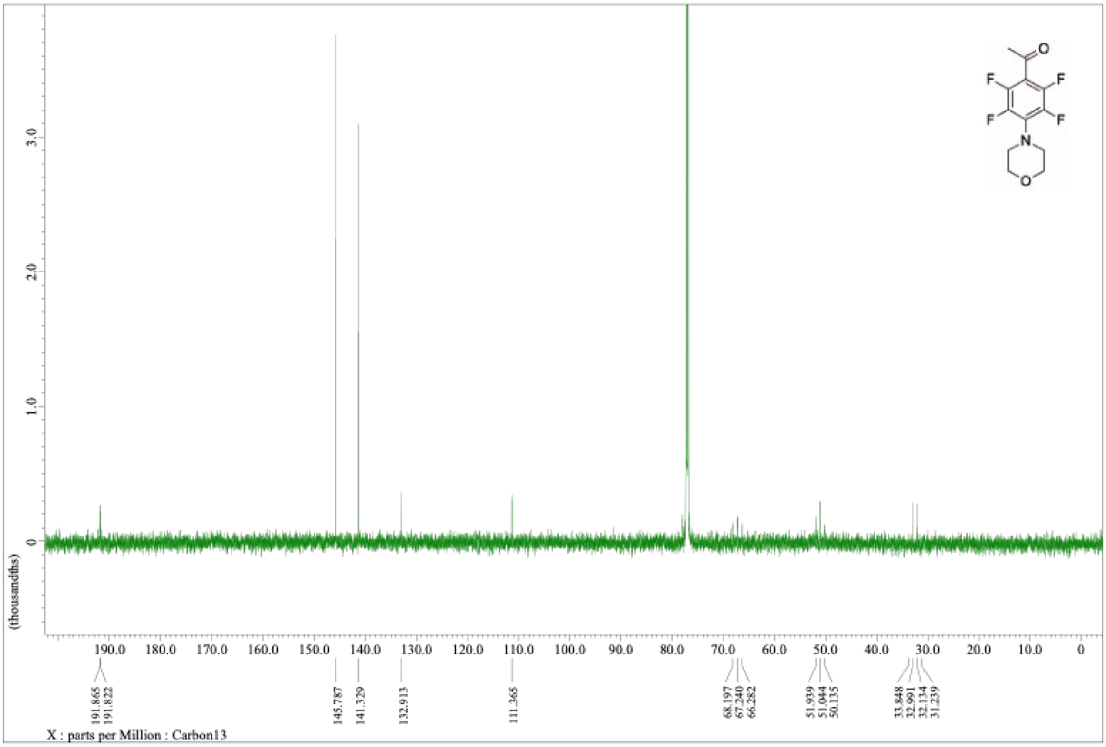
8ca ^{1}H NMR spectrum expansion (600 MHz, $CDCl_3$)



8ca ^{19}F NMR spectrum (564 MHz, $CDCl_3$)

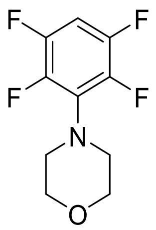


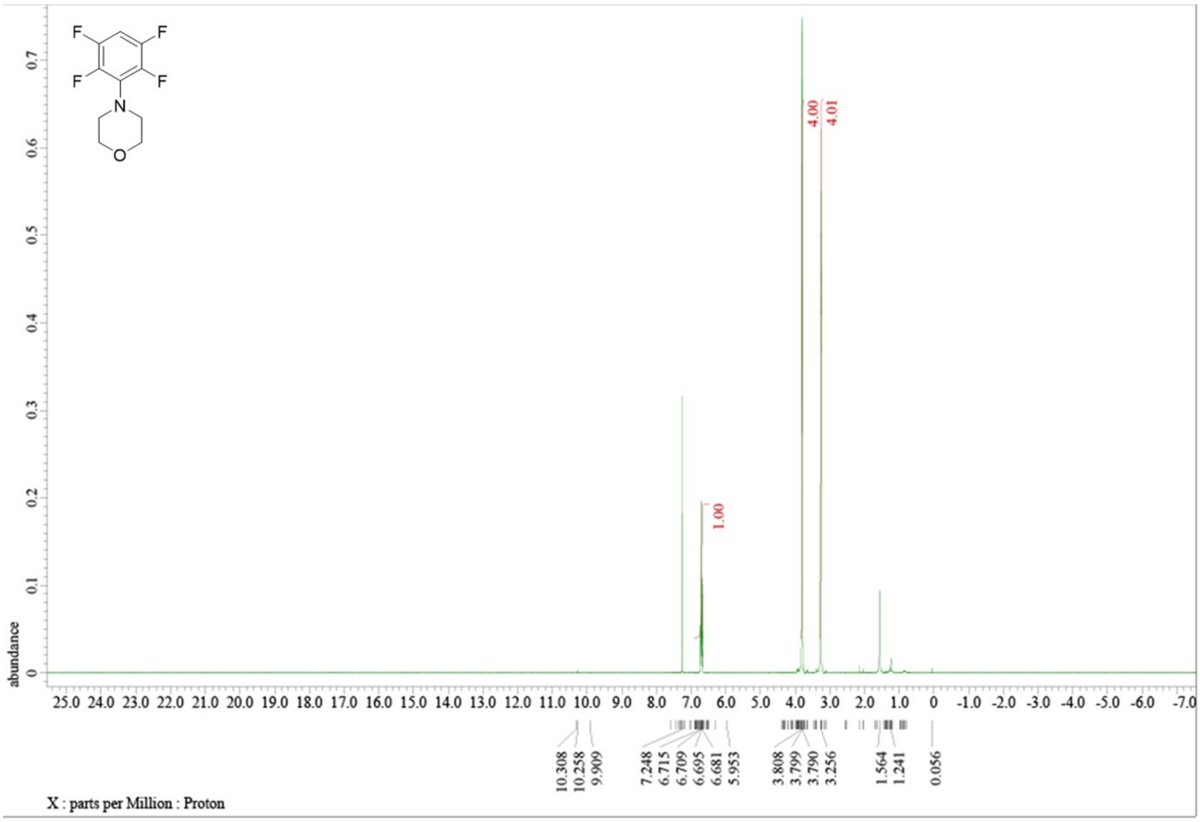
8ca ^{19}F NMR spectrum expansion (564 MHz, $CDCl_3$)



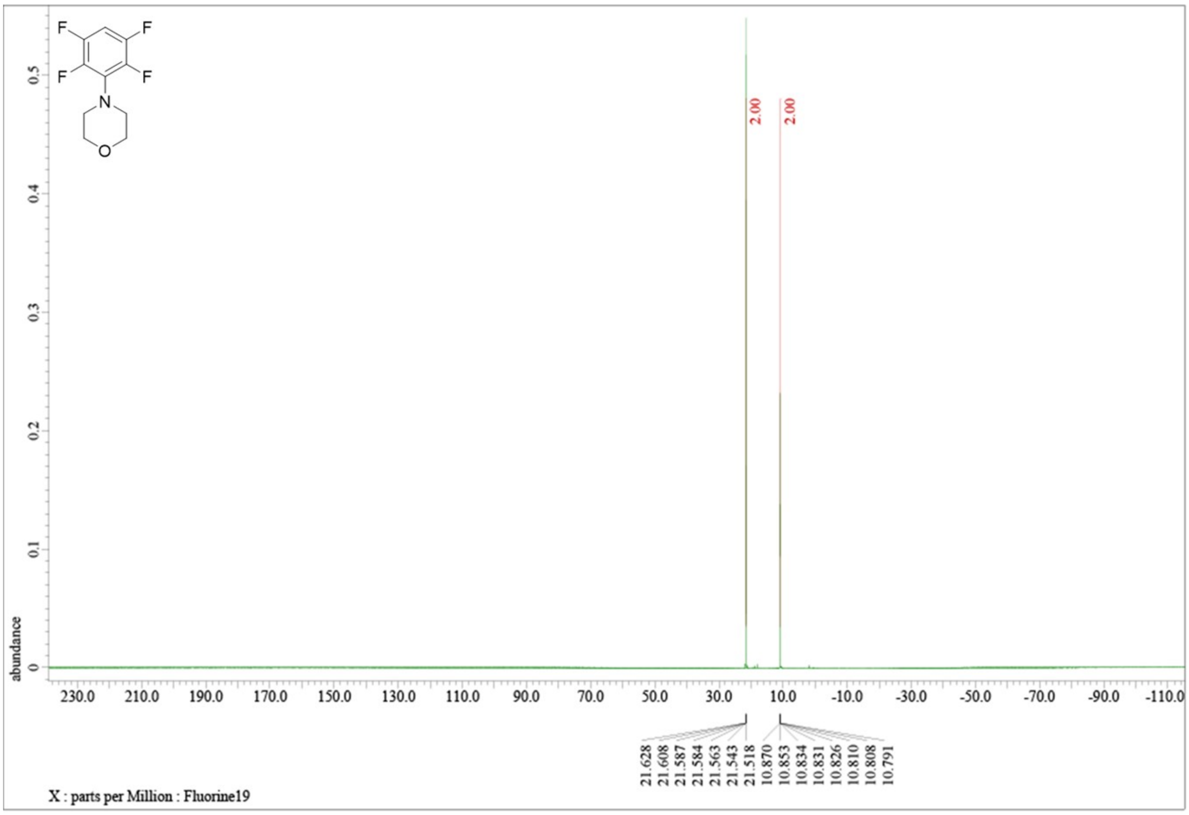
8ca ^{13}C{^{19}F} NMR spectrum (150 MHz, CDCl$_3$)

4-(2,3,5,6-Tetrafluorophenyl)morpholine (8da)

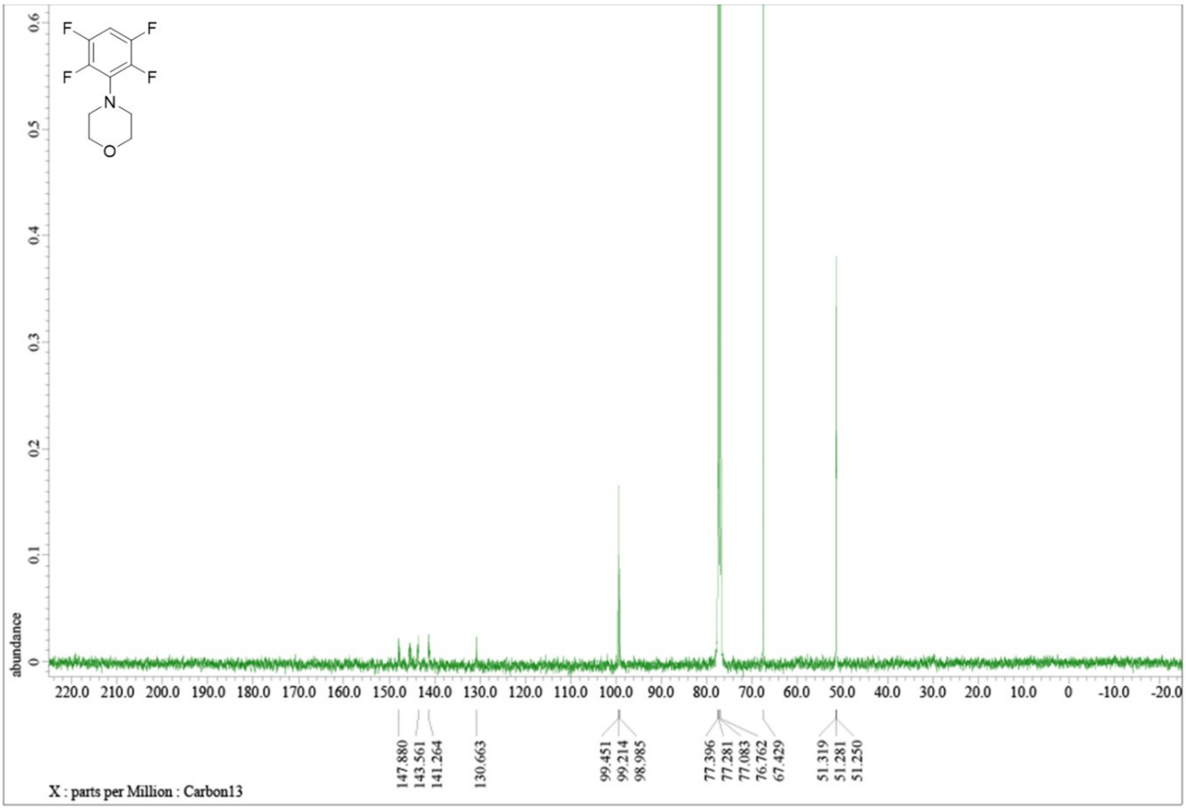
	Prepared from pentafluorobenzaldehyde (0.62 mL, 5.0 mmol) and morpholine (0.43 mL, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was then purified via column chromatography over silica gel (elution with hexane: ethyl acetate 2:1) to give compound **8da** as a white solid (0.16 g, 12 %, 0.6 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 6.70 (tt, *J* 10, 3, 1H), 3.80 (m, 4H), 3.26 (m, 4H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 21.6 (m, 2F), 10.8 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 146.6 (d, *J* 240), 142.4 (d, *J* 230), 130.7, 99.2 (t, *J* 23), 67.4, 51.3 ; **IR ν_{max} /cm^{-1}** 2832 (C-H, alkane), 1853 (C-H, aromatic), 1117 (C-F); **HRMS** calculated for $C_{10}H_9F_4NOH^+$ 236.0716 found 236.0693; **mp** 132.1 – 133.0 °C. The yields were 10% and 8% respectively with water or DMF as solvent.



8da ^{1}H NMR spectrum (500 MHz, $CDCl_3$)

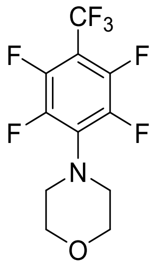


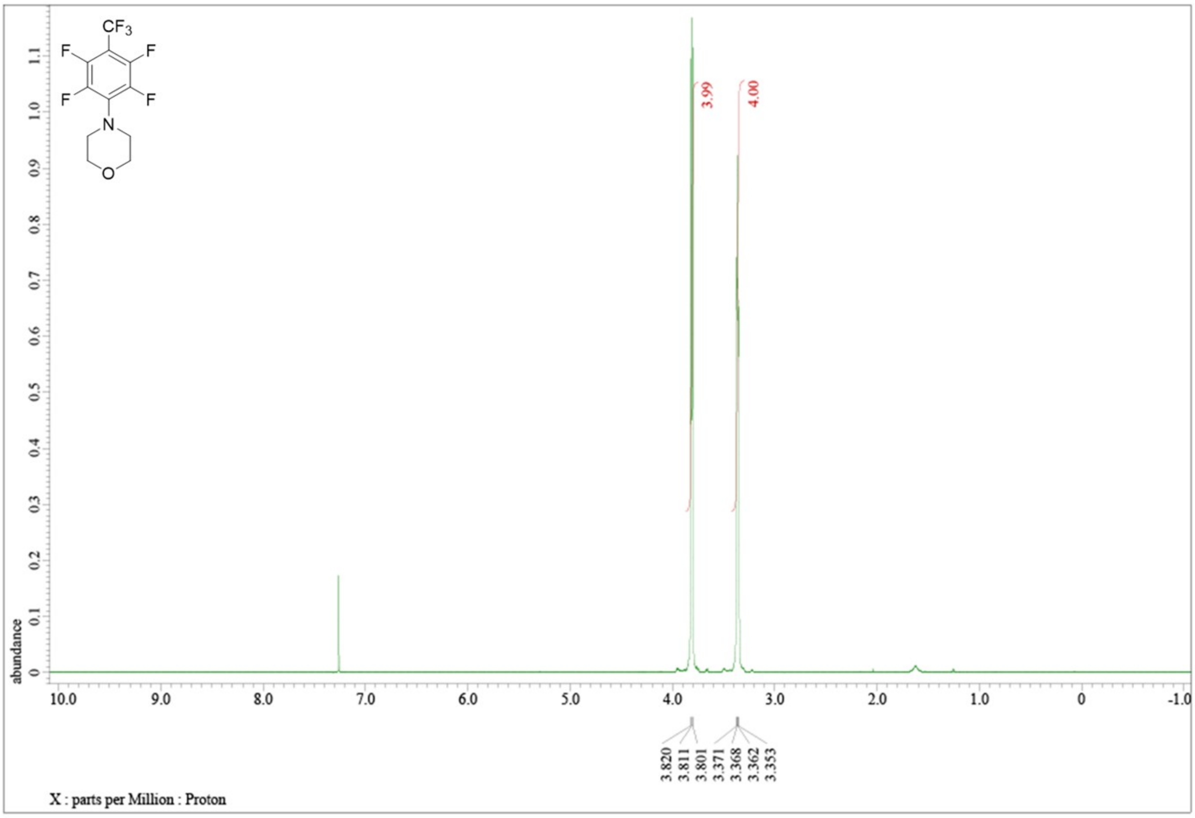
8da ^{19}F NMR spectrum (470 MHz, $CDCl_3$)



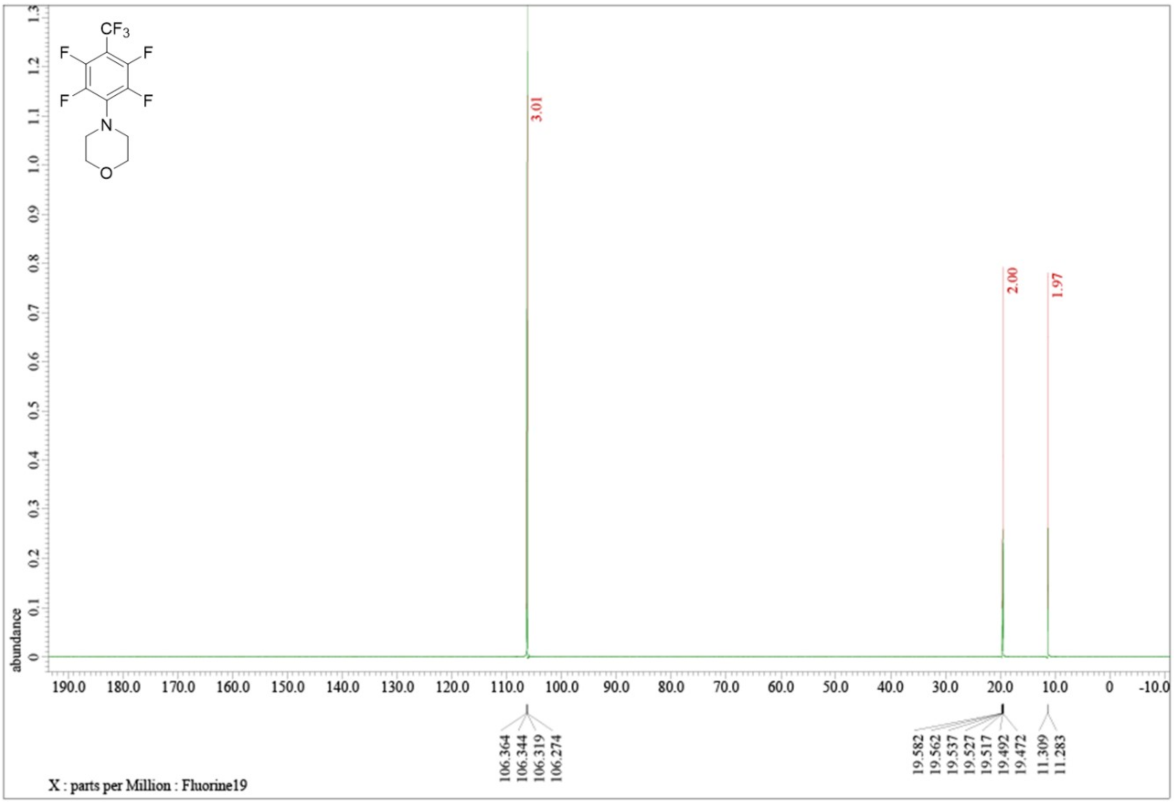
8da ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

4-[2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl]morpholine (8ea)

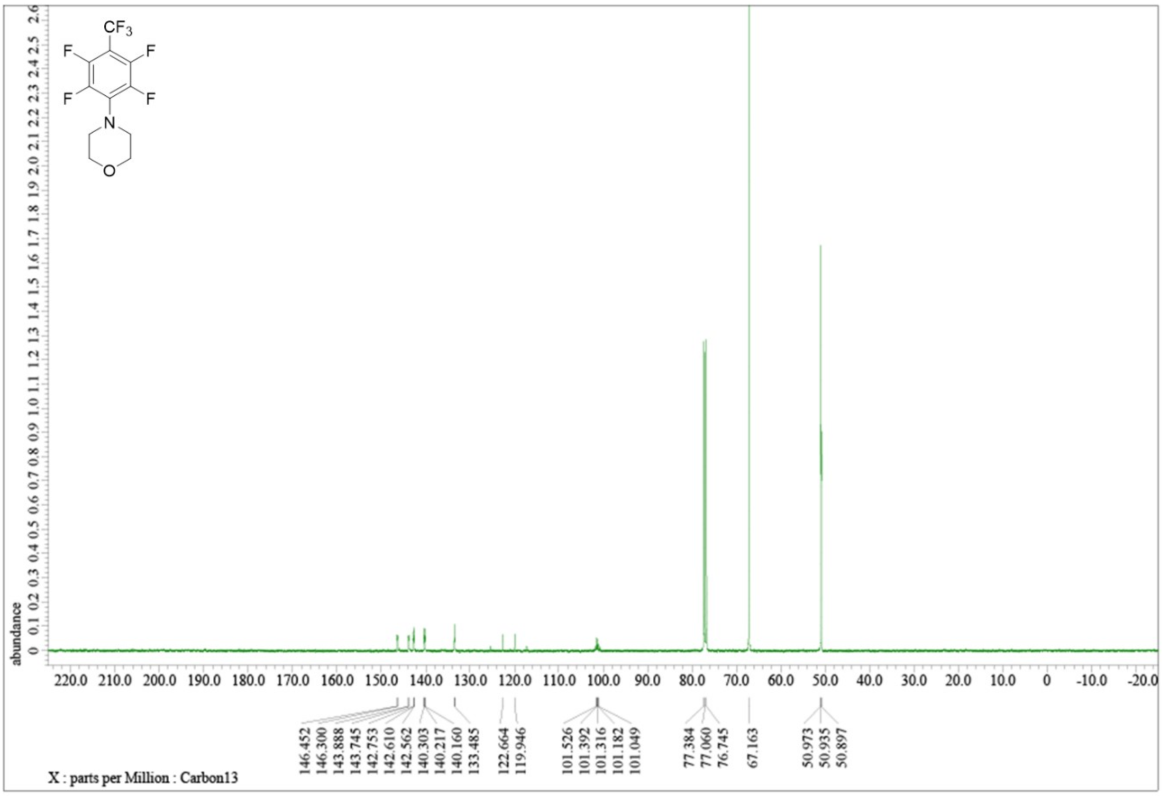
	Prepared from octafluorotoluene (0.71 mL, 5.0 mmol) and morpholine (0.43 mL, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was then purified by column chromatography (elution with hexane: ethyl acetate 5:1) to give compound **8ea** as a white solid (1.32 g, 87%, 4.4 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 3.82-3.80 (m, 4H), 3.37-3.35 (m, 4H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 106.3 (m, 3F), 19.6 (m, 2F), 11.3 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 144.6 (dd, *J* 256, 15), 141.5 (d, *J* 245), 133.5, 121.3 (q, *J* 272), 101.3 (m), 67.2, 51.0; **IR ν_{max} /cm^{-1}**: 2856 (C-H, alkane), 1656 (C=C, cyclic alkene), 1342 (C-N, aromatic amine), 1116, 980 (C-F), 712 (benzene); **HRMS** calculated for $C_{11}H_8F_7NOK^+$ 342.0126, found 342.0523; **EA** Found: C 43.7, H 2.61, N 4.64. $C_{11}H_8F_7NO$ requires C 43.6, H 2.64, N, 4.62; **mp** 61.3 – 62.1 °C. NMR spectroscopic data in agreement with literature values.[2] The yields were 35% and 83% respectively with water or DMF as solvent.



8ea ^{1}H NMR spectrum (500 MHz, $CDCl_3$)

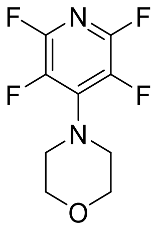


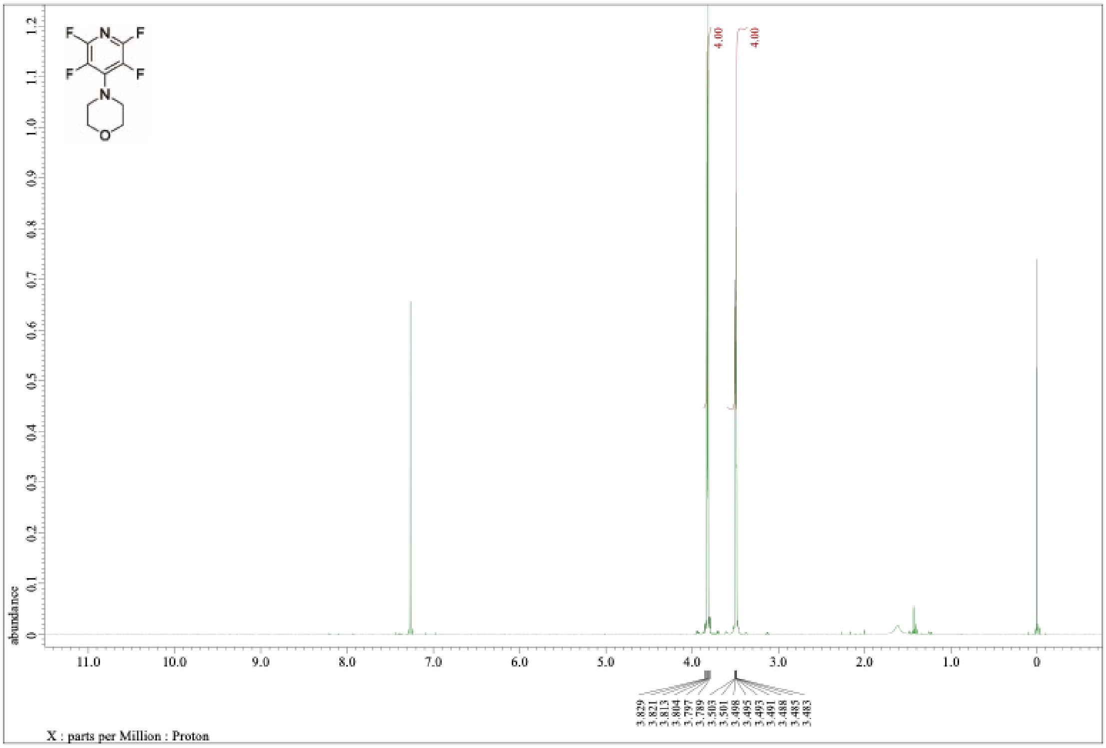
8ea ^{19}F NMR spectrum (470 MHz, $CDCl_3$)



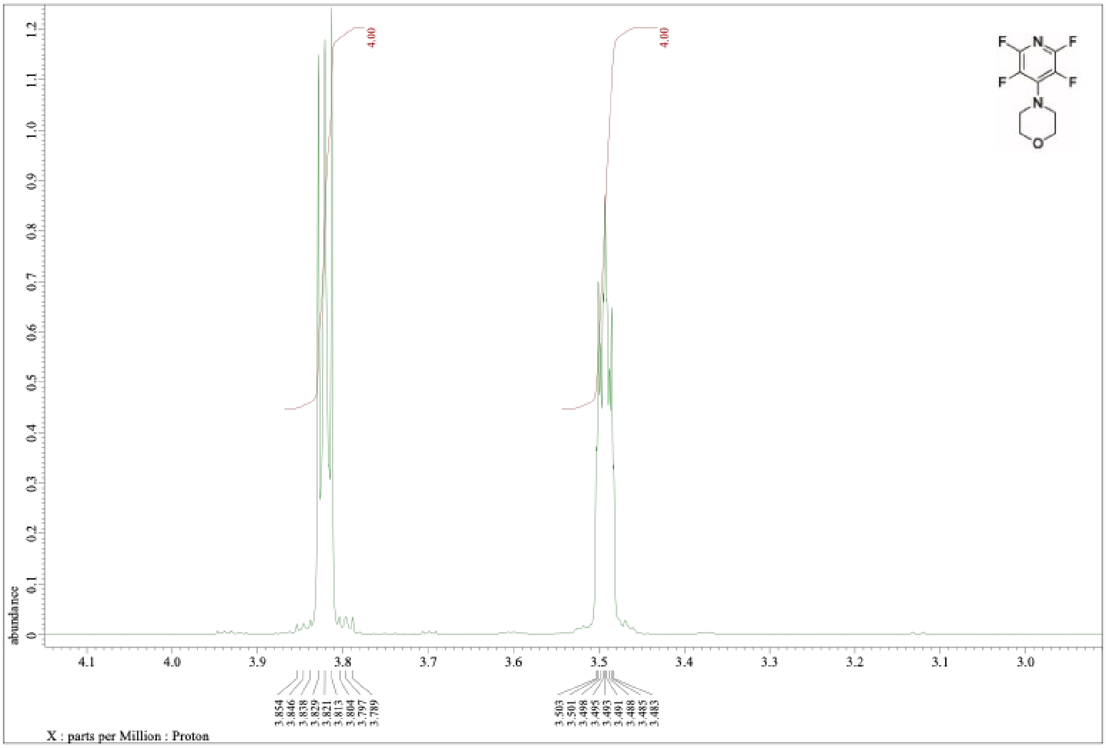
8ea ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

2,3,5,6-Tetrafluoro-4-morpholinopyridine (12a)

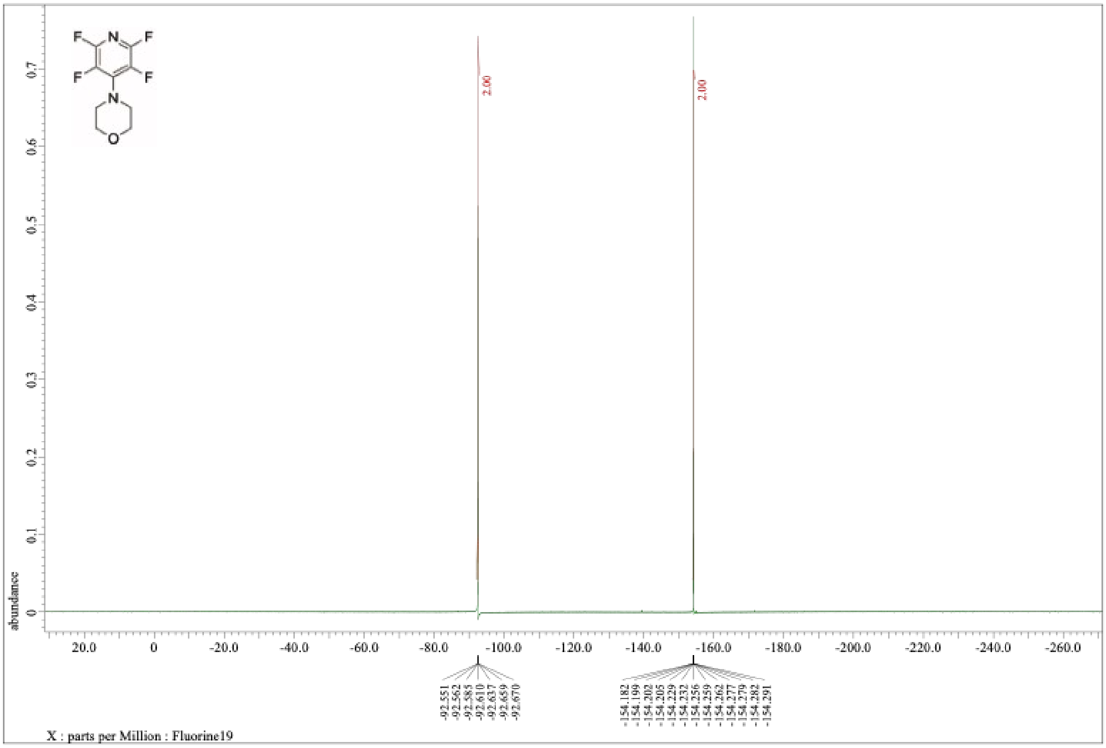
	Prepared from pentafluoropyridine (0.55 mL, 5.0 mmol) and morpholine (0.43 mL, 5.0 mmol) using water (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 4:1) to give compound **12a** as a white solid (0.85 g, 72%, 3.6 mmol). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 3.83-3.79 (m, 4H), 3.50-3.48 (m, 4H); **^{19}F NMR (564 MHz, CDCl$_3$)** δ -92.7, (m, 2F), -154.3 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 144.9 (dt, *J* 239, 15), 139.9 – 138.8 (m), 135.1 (dd, *J* 252, 7), 67.0, 50.5; **IR ν$_{max}$ /cm^{-1}**: 2854 (C-H, alkane), 1631 (C=C, cyclic alkene), 1146 (C-O-C), 963 (C-F); **HRMS** calculated for $C_9H_8F_4N_2O$ 236.0567, found 236.0715; **EA** Found: C 45.6, H 3.34. $C_9H_8F_4N_2O$ requires C 45.8, H 3.41; **mp** 52.2 – 52.8 °C (lit.,[3] 51-53 °C). Data in agreement with literature values.[3] The yields were 59% and 0% respectively with Cyrene or DMF as solvent.



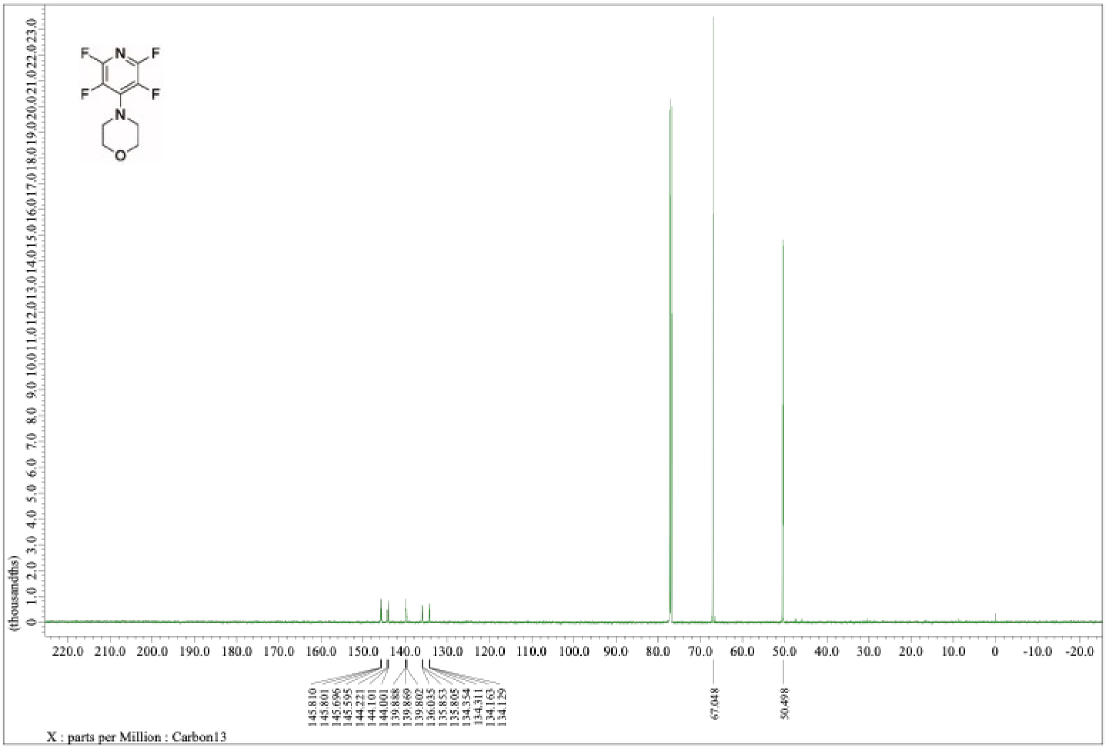
12a ^{1}H NMR spectrum (600 MHz, CDCl$_3$)



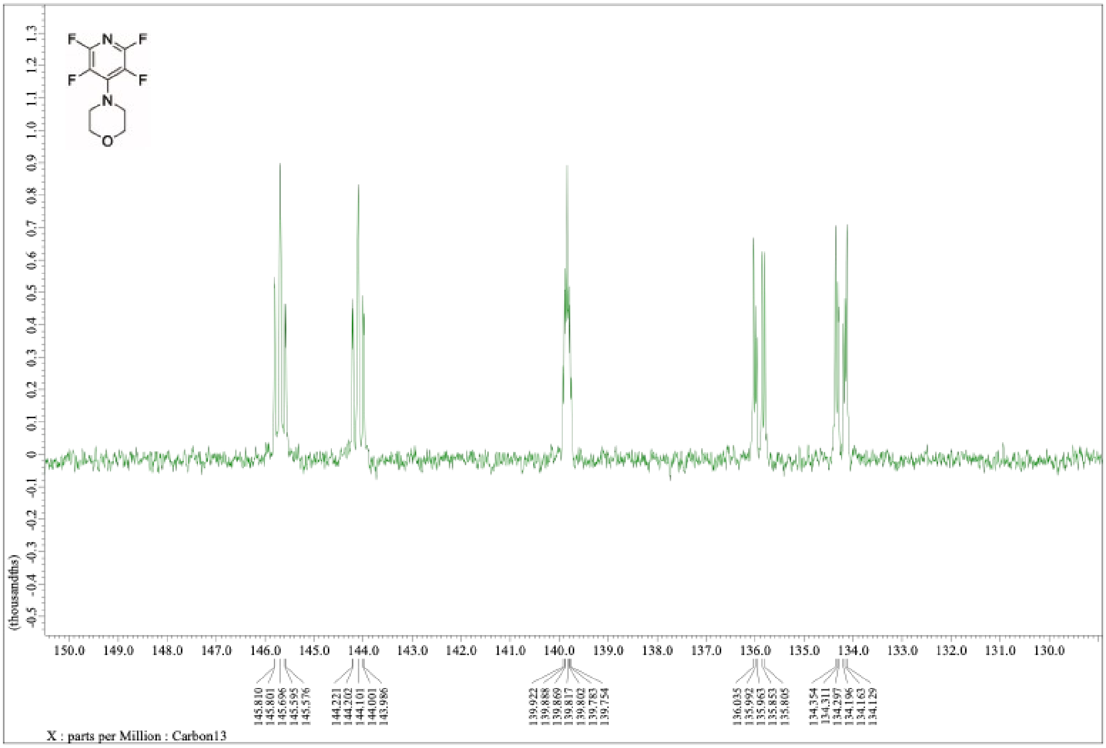
12a ^{1}H NMR spectrum expansion (600 MHz, CDCl$_3$)



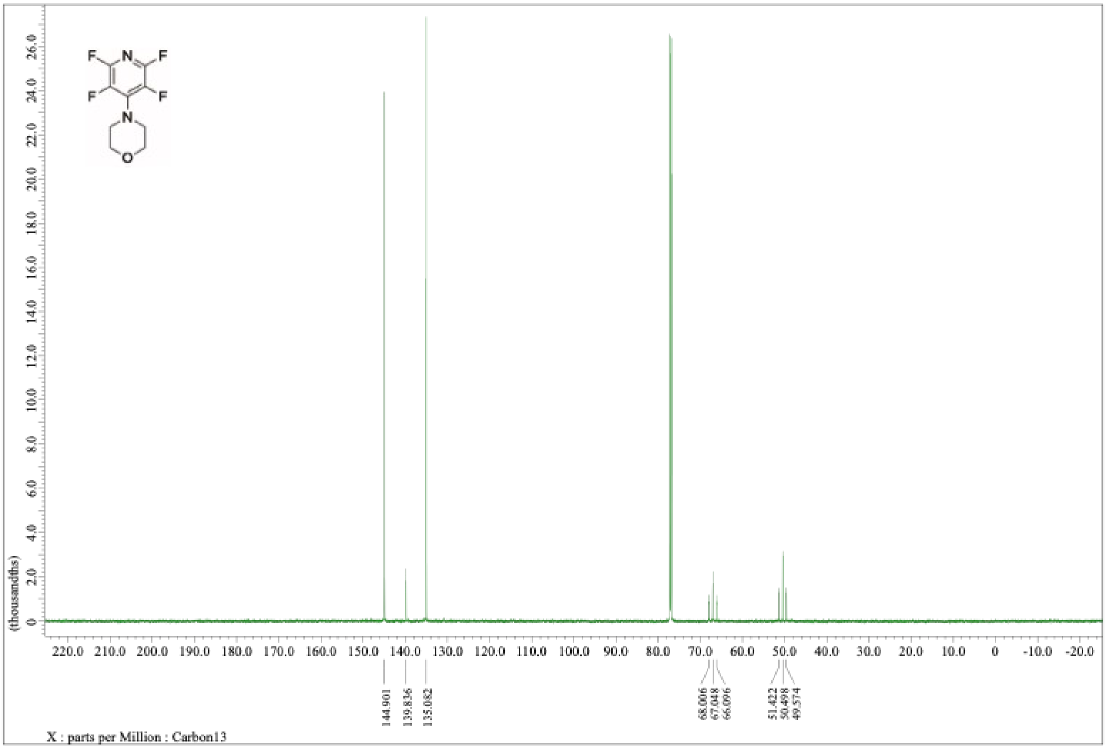
12a ^{19}F NMR spectrum (564 MHz, $CDCl_3$)



12a ^{13}C NMR spectrum (150 MHz, $CDCl_3$)

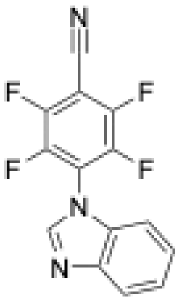


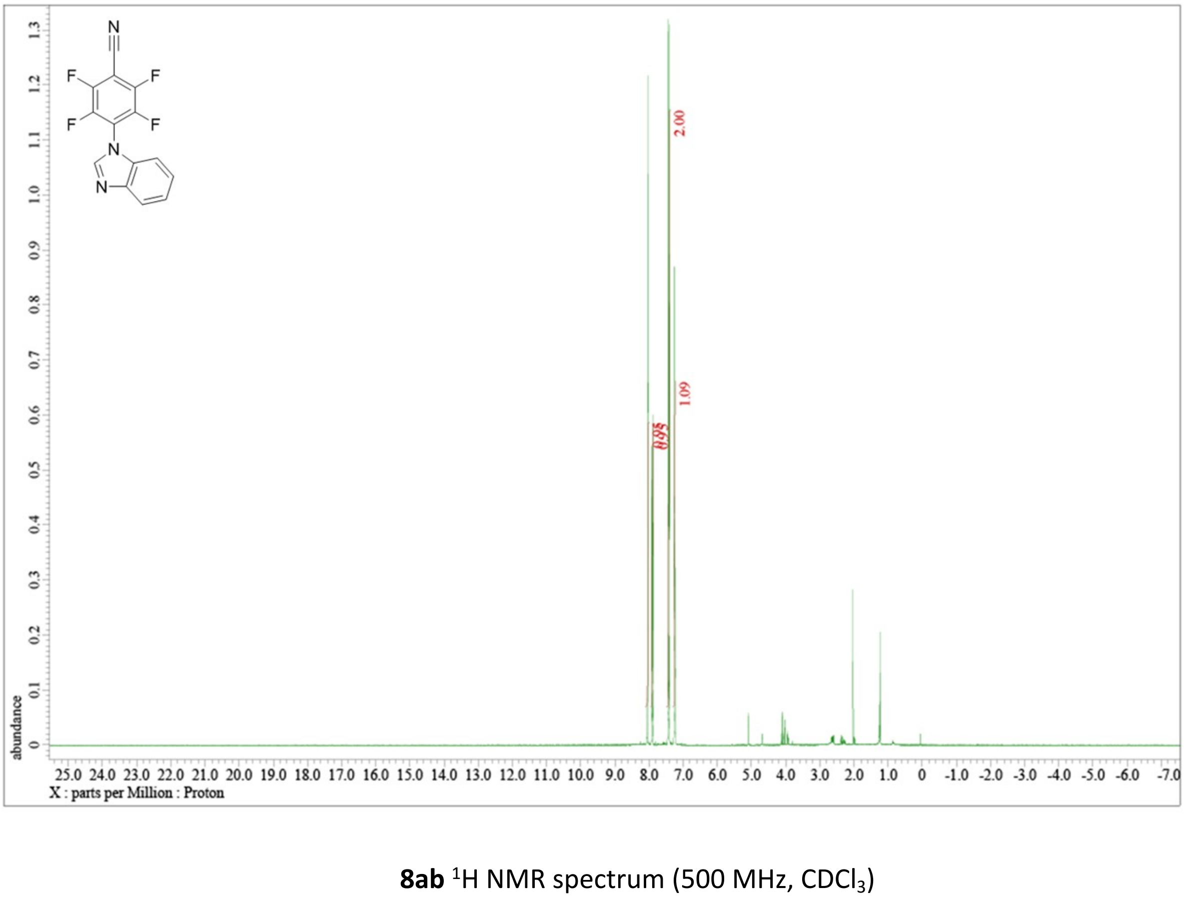
12a ^{13}C NMR spectrum expansion (150 MHz, CDCl$_3$)



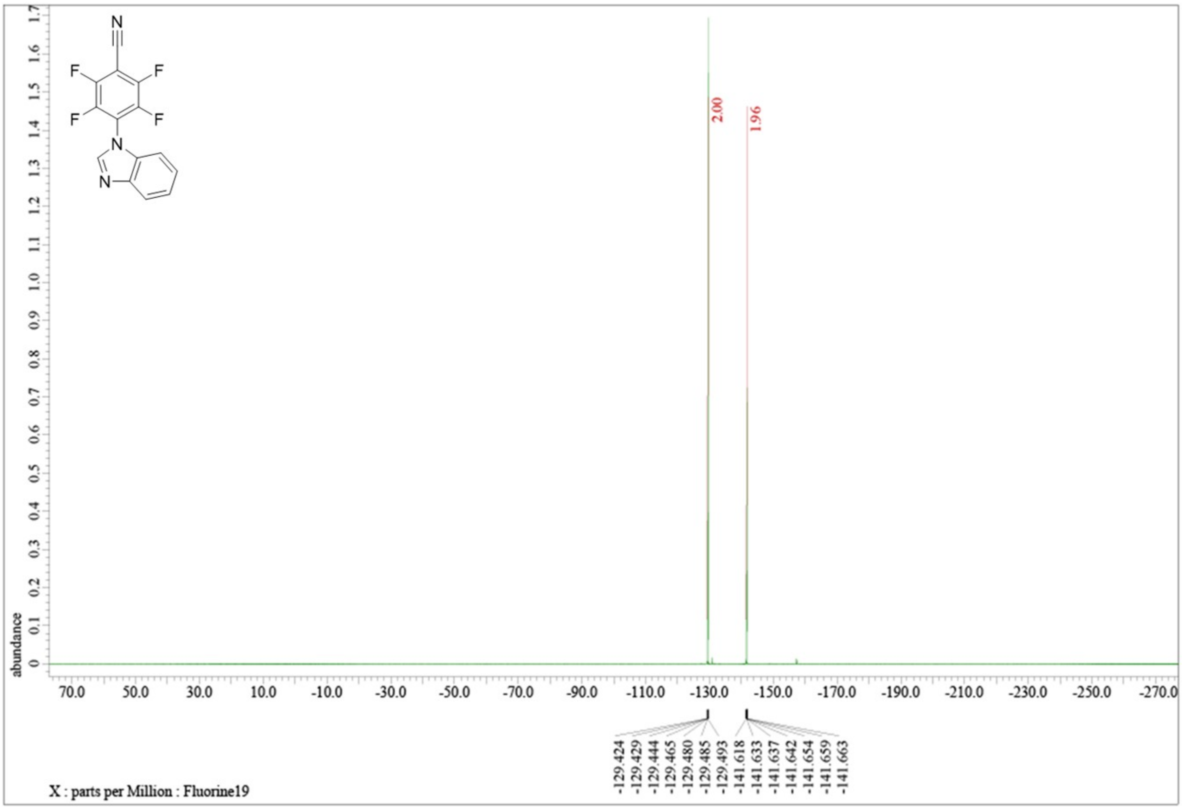
12a ^{13}C{^{19}F} NMR spectrum (150 MHz, CDCl$_3$)

4-(1*H*-Benzimidazol-1-yl)-2,3,5,6-tetrafluorobenzonitrile (8ab)

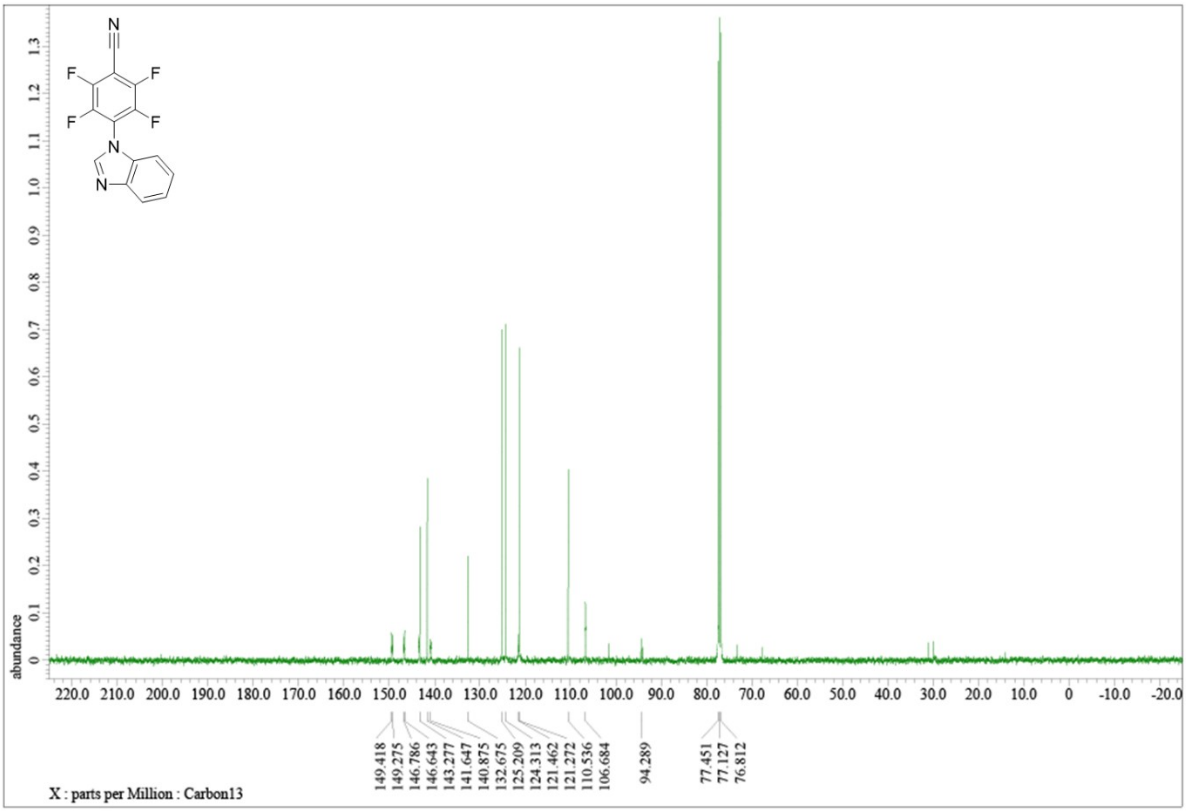
	Prepared from pentafluorobenzonitrile (0.63 mL, 5.0 mmol) and benzimidazole (0.59 g, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 4:1) to give compound **8ab** as an off-white solid (0.83 g, 57 %, 2.85 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.05 (s, 1H), 7.90 (m, 1H), 7.42 (m, 2H), 7.25 (m, 1H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ -129.4 (m, 2F), -141.6 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 148.0 (dd, *J* 263, 14), 143.3, 142.0 (d, *J* 240), 141.6 132.7, 125.2, 124.3, 121.5, 121.3, 110.5, 106.7, 94.3 (t, *J* 20); **IR ν_{max} /cm^{-1}**: 2242 (C≡N), 1651 (C-H, aromatic), 1609 (C=C, cyclic alkene), 1264 (C-N, aromatic amine), 982 (C-F); **HRMS** calculated for $C_{14}H_5F_4N_3H^+$ 292.0492, found 292.0492; **mp** 183.1 – 184.4 °C. Data in agreement with literature values.[4] The yields were 42% and 52% respectively with water or DMF as solvent.



8ab ^{1}H NMR spectrum (500 MHz, CDCl$_3$)

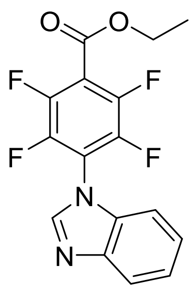


8ab ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



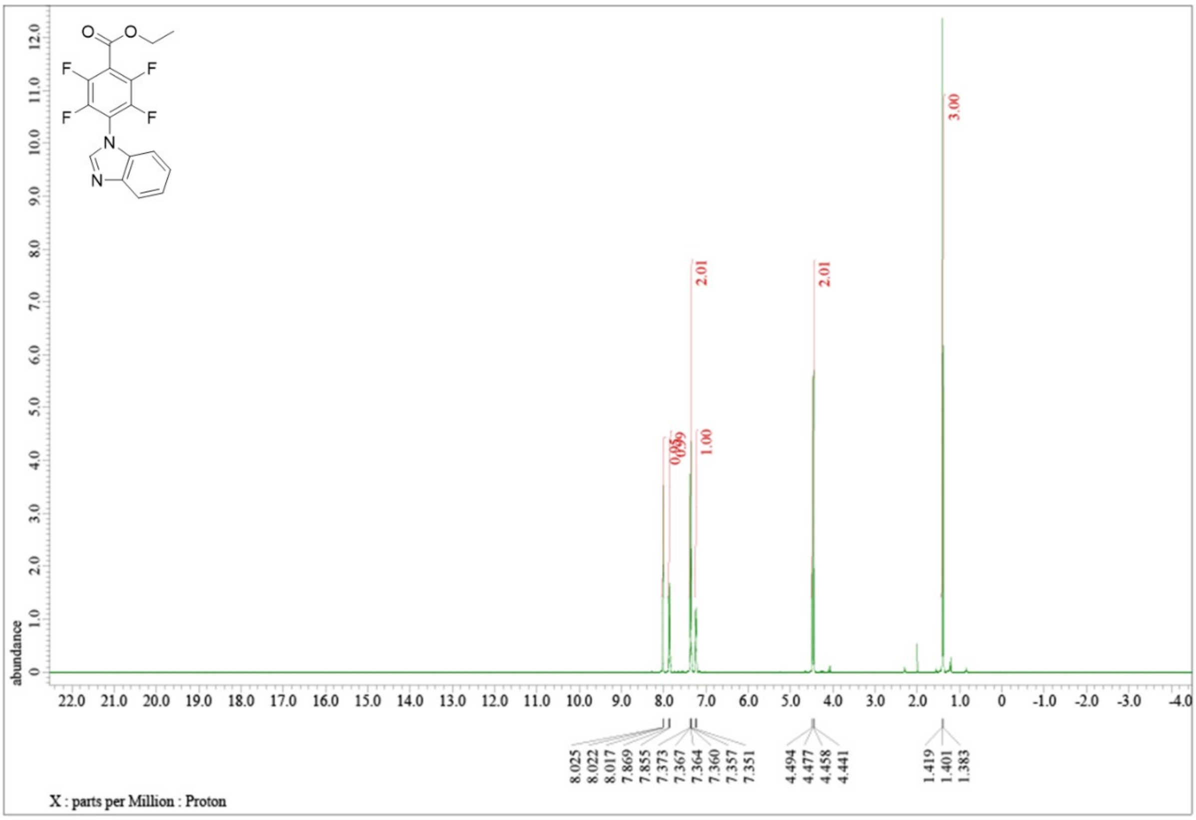
8ab ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

Ethyl 4-(1*H*-benzimidazol-1-yl)-2,3,5,6-tetrafluorobenzoate (8bb)

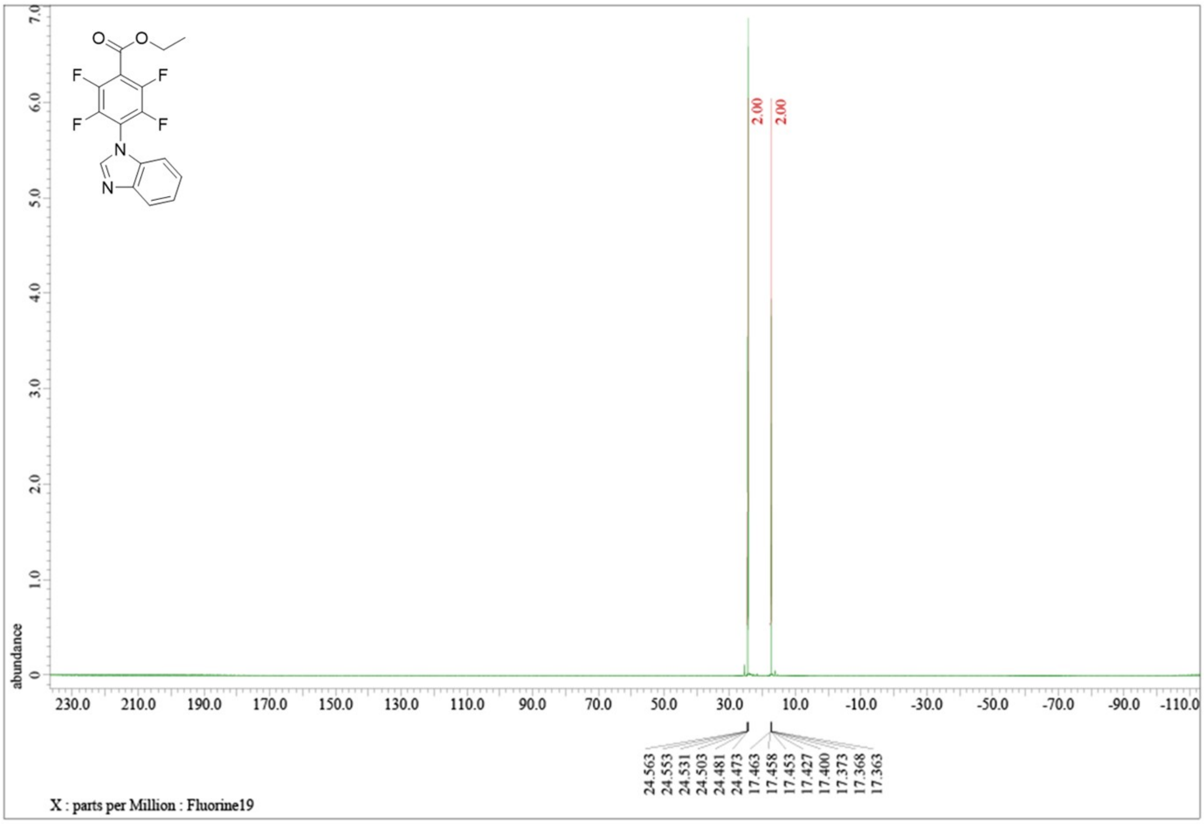


Prepared from ethyl pentafluorobenzoate (0.84 mL, 5.0 mmol), benzimidazole (0.59 g, 5.0 mmol) using water (0.25 mL) as solvent. The crude product was then purified via column chromatography over silica gel (elution with hexane: ethyl acetate 1:1) to give compound **8bb** as a white solid (0.95 g, 56%, 2.8 mmol). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.02 (s, 1H), 7.87-7.86 (m, 1H), 7.37-7.36 (m, 2H), 7.35-7.34 (m, 1H), 4.47 (q, *J* 7, 2H), 1.40 (t, *J* 7, 3H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 24.6-24.5 (m, 2F), 17.5-17.4 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 158.8, 145.2 (d, *J* 244), 143.2, 142.2 (d, *J* 260), 142.1, 133.1, 124.8, 123.8, 121.0, 118.1, 113.2, 110.5, 63.3, 14.1; **IR ν_{max} /cm^{-1}**: 2856 (C-H, alkane), 1735 (C=O, ester), 1653 (C=C, cyclic alkene), 1455 (C-H, methyl group), 1270 (C-O, aromatic ester), 1229 (C-F), 743 (C-H, benzene derivative); **HRMS** calculated for $C_{16}H_{10}F_4N_2O_2H^+$ 339.0751 found 339.0750; **mp** 168.7 – 170.5 °C.

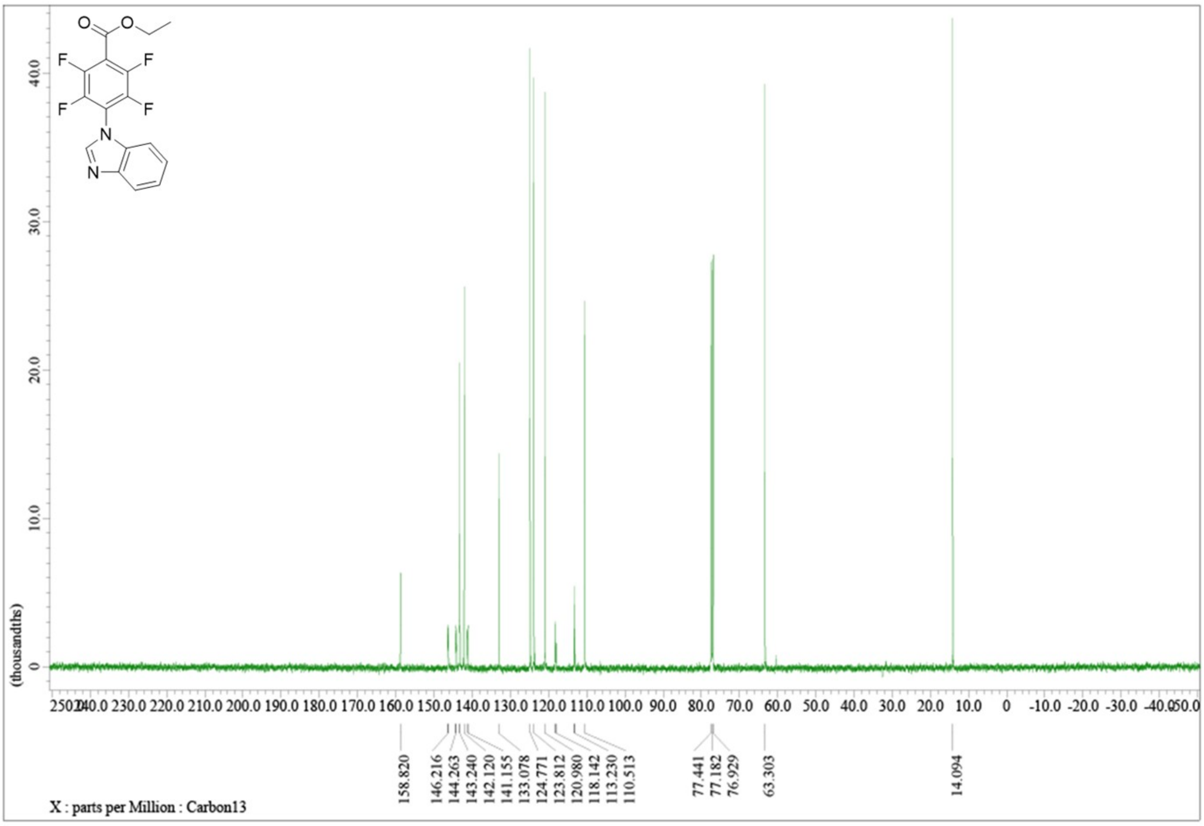
The yields were 28% and 21% respectively with Cyrene or DMF as solvent.



8bb ^{1}H NMR spectrum (400 MHz, CDCl$_3$)

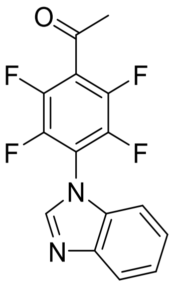


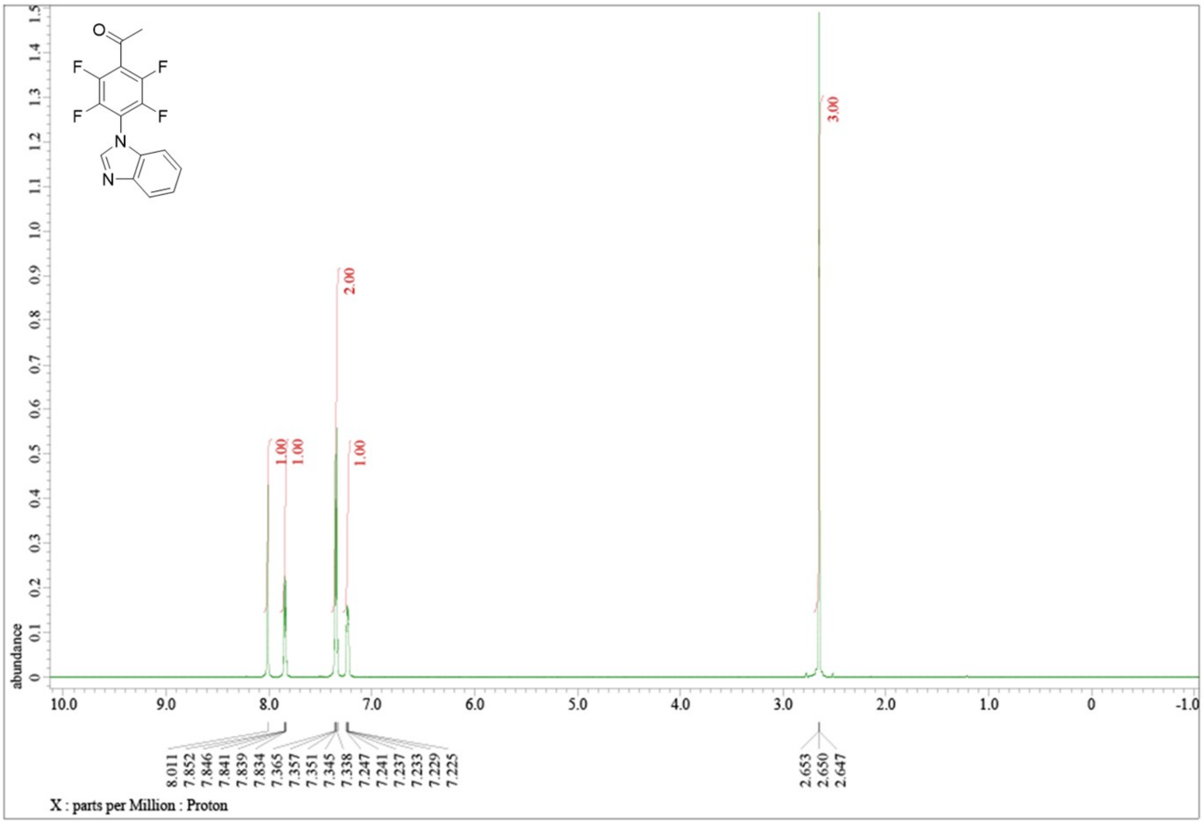
8bb ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



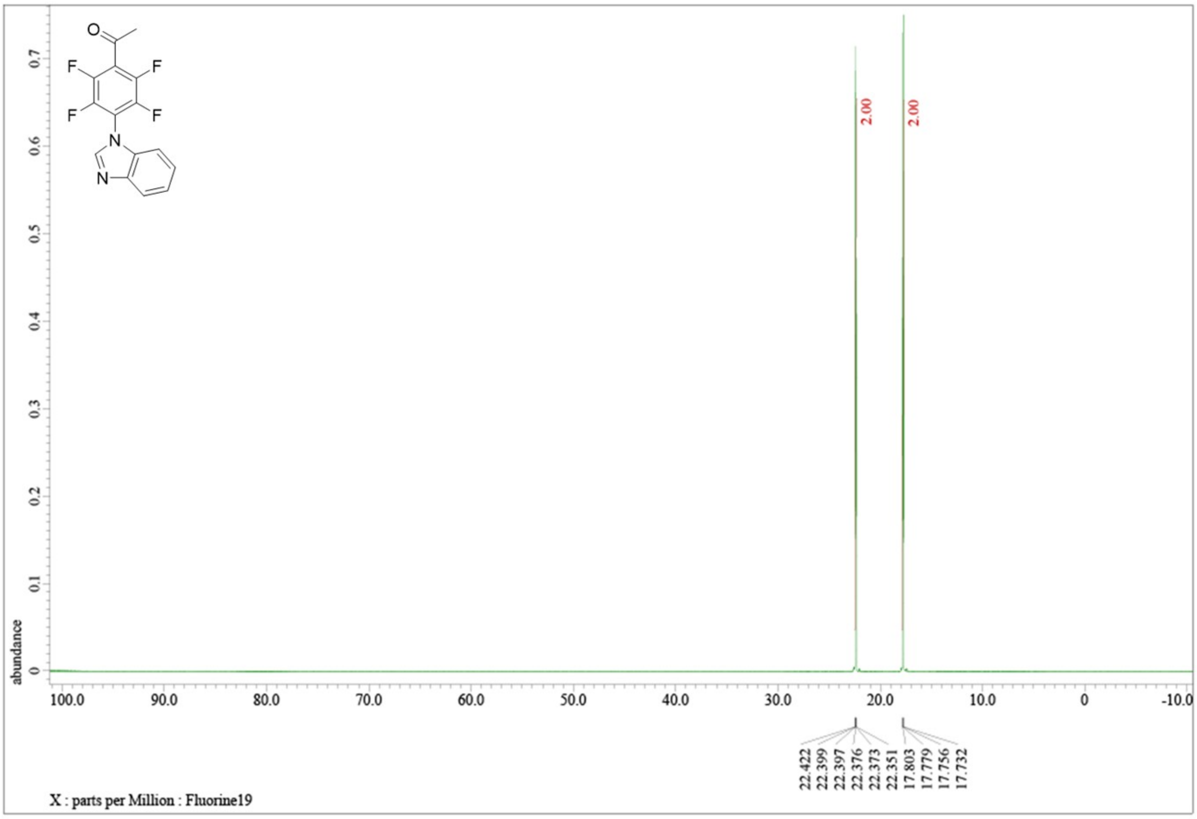
8bb ^{13}C NMR spectrum (125 MHz, CDCl$_3$)

4-(1*H*-Benzimidazol-1-yl)-2,3,5,6-tetrafluoroacetophenone (8cb)

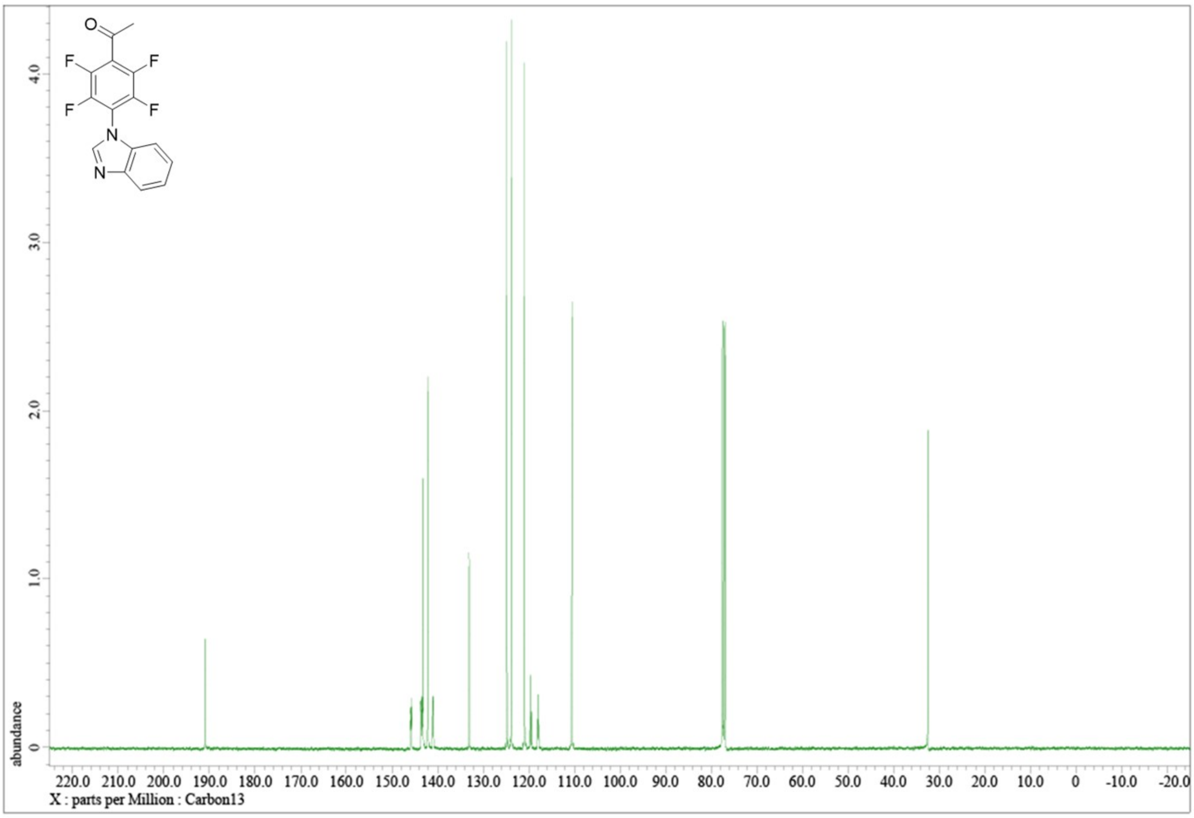
	Prepared from pentafluoroacetophenone (0.71 mL, 5.0 mmol), benzimidazole (0.59 g, 5.0 mmol) using water (0.25 mL) as solvent. The crude product was then purified via column chromatography over silica gel (elution with hexane: ethyl acetate 4:1) to give compound **8cb** as a white solid (0.43 g, 28%, 1.4 mmol**). ^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.01 (s, 1H), 7.85-7.83 (m, 1H), 7.36-7.34 (m, 2H), 7.25-7.23 (m, 1H), 2.66 (t, *J* 2, 3H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 22.4 (m, 2F), 17.8 (m, 2F) (AA’BB’ spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 191.0, 144.6 (d, *J* 250), 142.2 (d, *J* 250), 142.1, 141.1, 133.1, 124.8, 123.8, 120.9, 119.5 (t, *J* 20), 117.9 (t, *J* 20), 110.5, 32.4. **IR ν_{max} /cm^{-1}**: 2937 (C-H, alkane), 1771 (C=O), 1587 (C=C, cyclic alkene), 1271 (C-N, aromatic amine), 1243 (C-F), 743 (C-H, benzene); **HRMS** calculated for $C_{15}H_8F_4N_2OK^+$ 347.0204 found 347.0098; **mp** 170.0 – 171.5 °C. The yields were 0% and 25% respectively with Cyrene or DMF as solvent.



8cb ^{1}H NMR spectrum (500 MHz, CDCl$_3$)

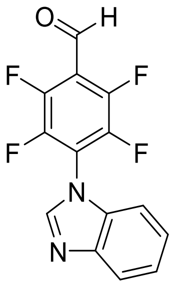


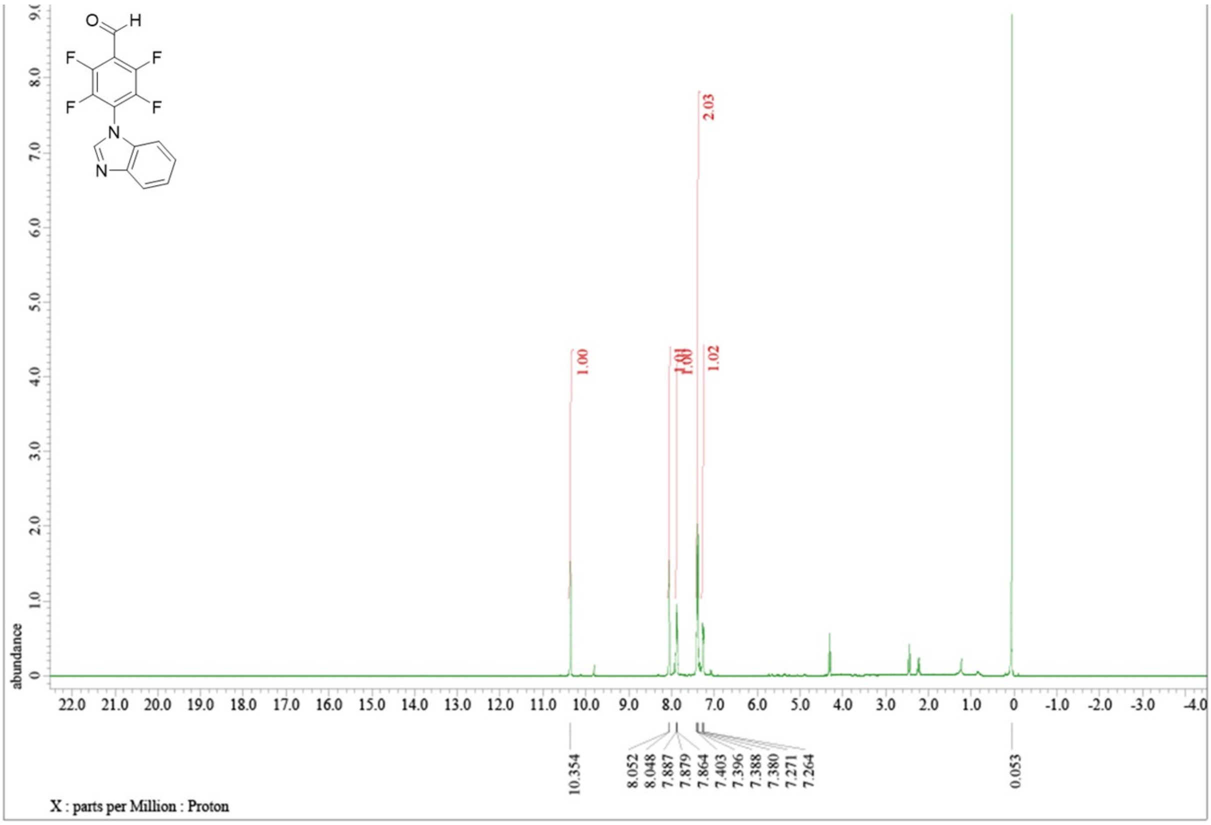
8cb ^{19}F NMR spectrum (470 MHz, $CDCl_3$)



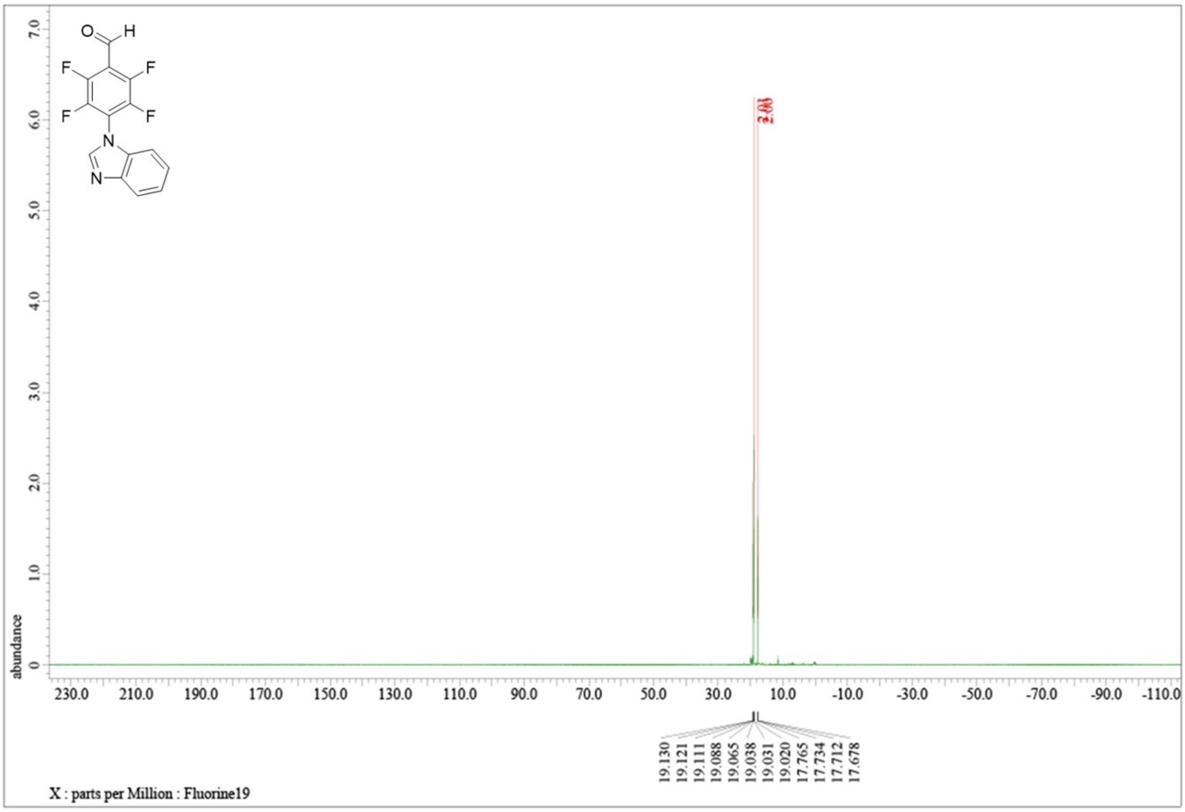
8cb ^{13}C NMR spectrum (100 MHz, $CDCl_3$)

4-(1*H*-Benzimidazol-1-yl)-2,3,5,6-tetrafluorobenzaldehyde (8db)

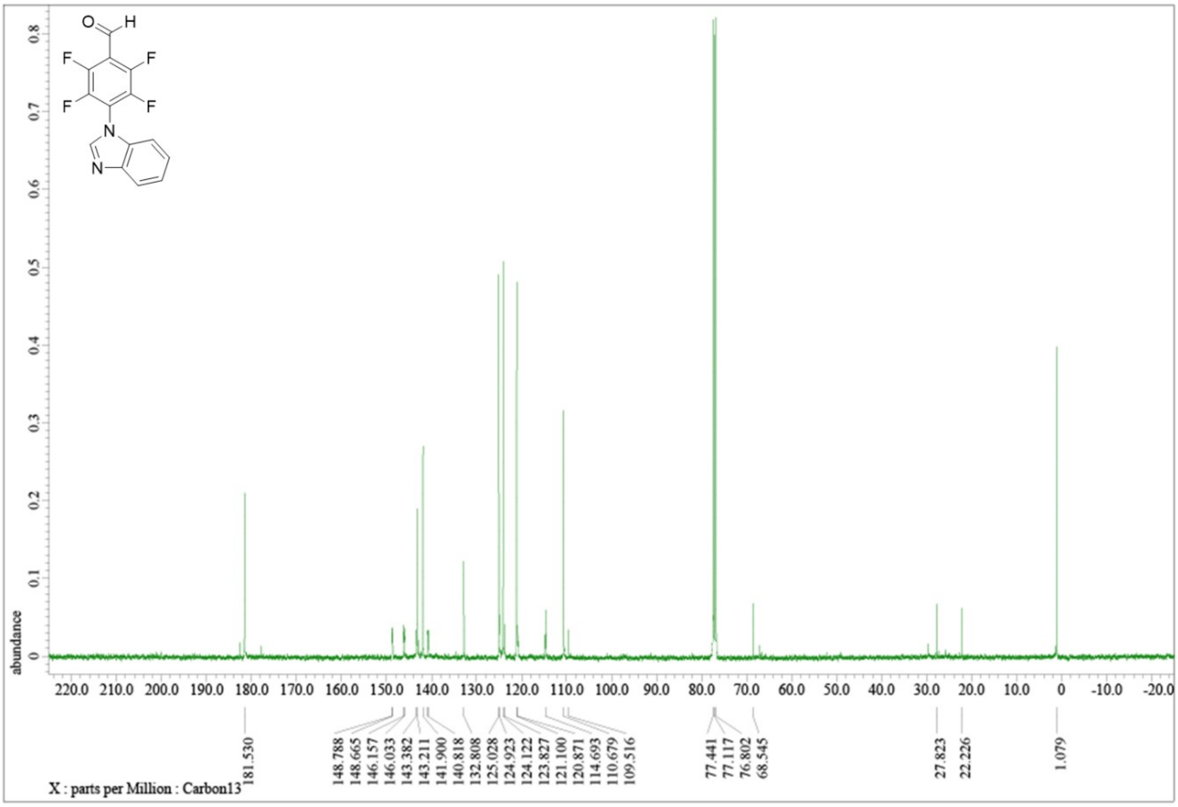
	Prepared from pentafluorobenzaldehyde (0.62 mL, 5.0 mmol) and benzimidazole (0.59 g, 5.0 mmol) using water (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 2:1) to give compound **8db** as an off-white solid (1.10 g, 75 %, 3.8 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 10.35 (s, 1H), 8.05 (s, 1H), 7.87 (m, 1H), 7.38 (m, 2H), 7.26 (m, 1H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 19.08 (m, 2F), 17.72 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 181.5, 147.4 (d, *J* 263), 143.2, 142.1 (d, *J* 256), 141.9, 132.8, 125.0, 124.1, 121.1, 114.7, 110.7, 109.5; **IR ν_{max} /cm^{-1}**: 1704 (C=O, aldehyde), 1648 (C=C, cyclic alkene), 1454 (C-H), 1404 (C-H, aldehyde), 1263 (C-N, aromatic amine), 1208 (C-F), 752 (benzene derivative); **HRMS** calculated for $C_{14}H_6F_4N_2OH^+$ 295.0488, found 295.0489; **mp** 161.5 – 162.7 °C (lit.,[5] 160-162 °C). Data in agreement with literature values.[5] The yields were 42% and 0% respectively with Cyrene or DMF as solvent.



8db ^{1}H NMR spectrum (500 MHz, CDCl$_3$)

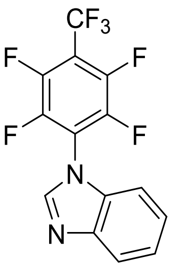


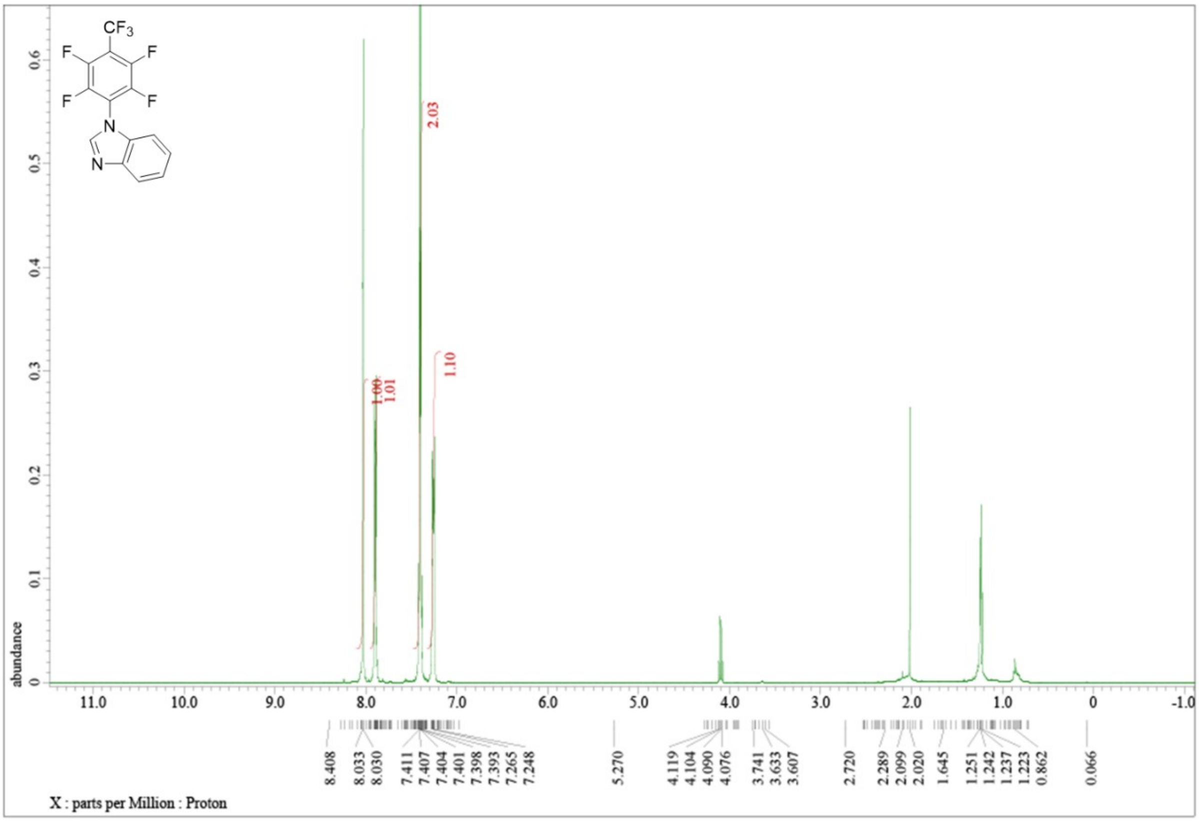
8db ^{19}F NMR spectrum (470 MHz, $CDCl_3$)



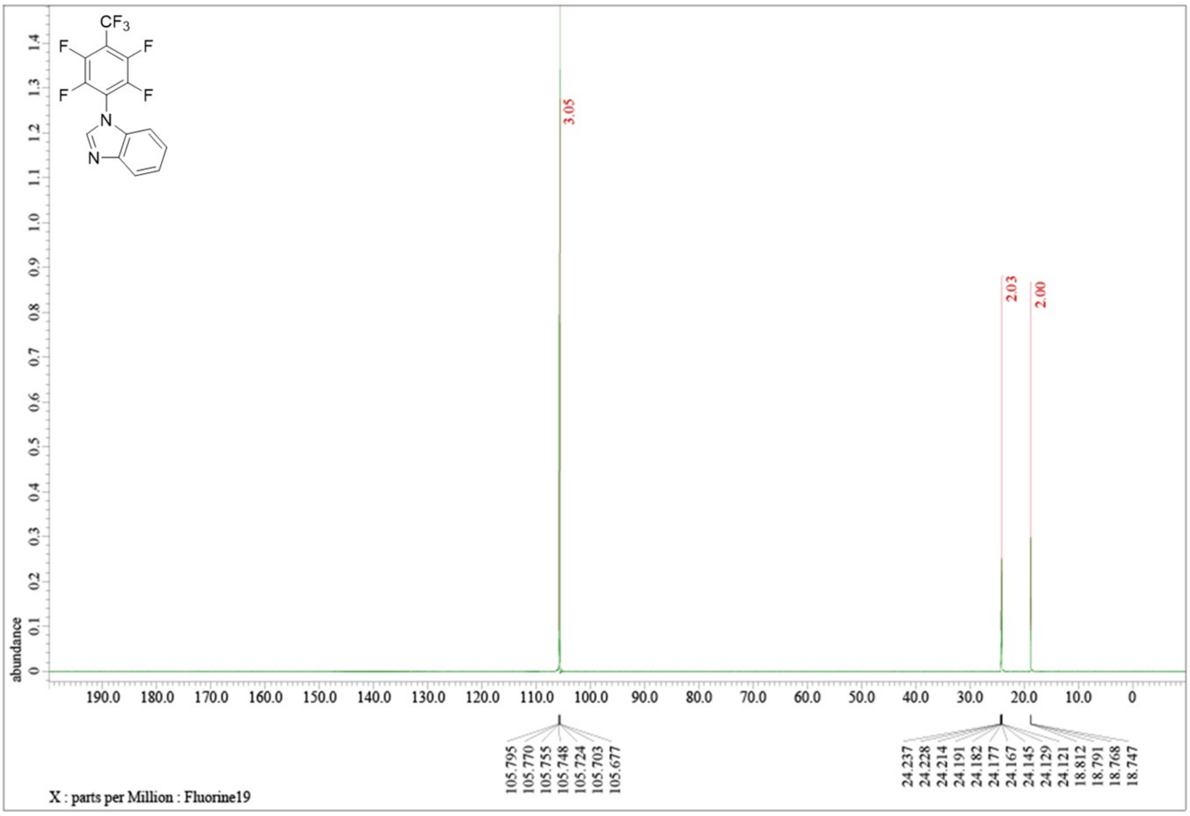
8db ^{13}C NMR spectrum (100 MHz, $CDCl_3$)

1-[2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl]-1*H*-benzimidazole (8eb)

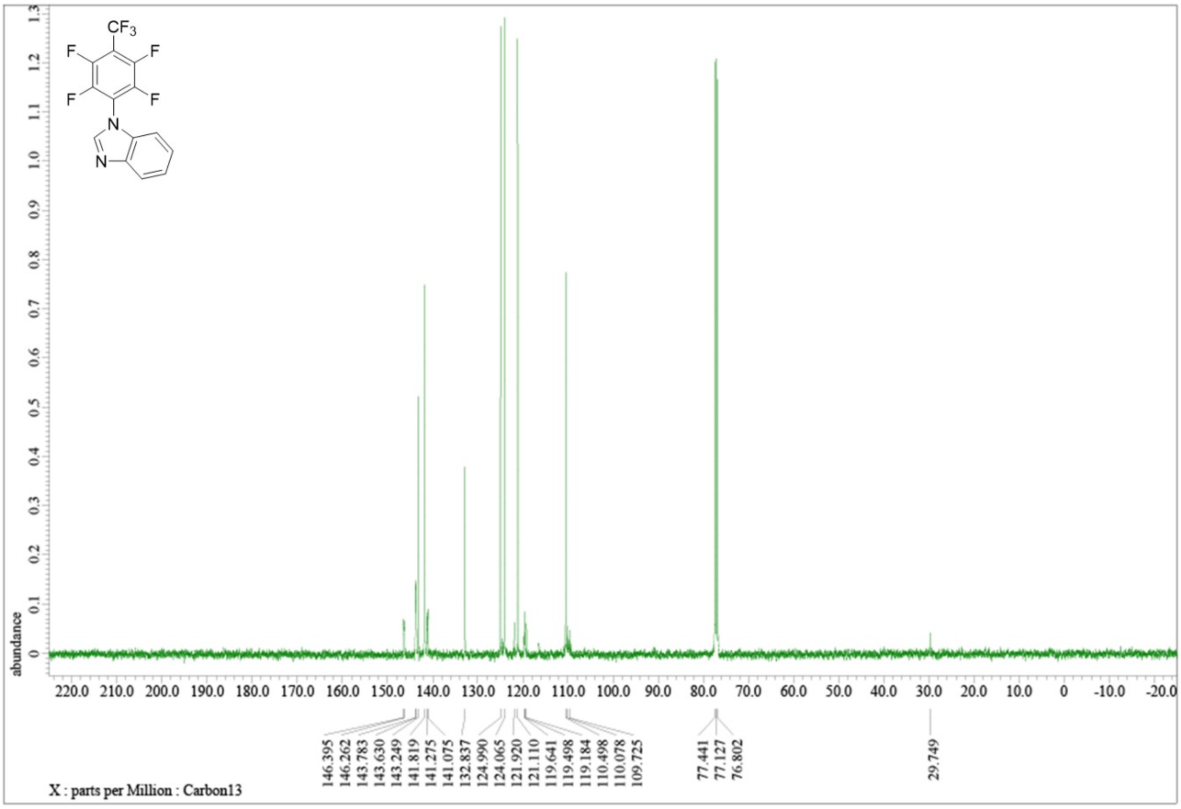
	Prepared from octafluorotoluene (0.71 mL, 5.0 mmol) and benzimidazole (0.59 g, 5.0 mmol) using DMF (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 5:1) to give compound **8eb**[4] as a white solid (1.10 g, 66 %, 3.3 mmol). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.03 (s, 1H), 7.88 (m, 1H), 7.42 (m, 2H), 7.25 (m, 1H); **^{19}F NMR (470 MHz, $CDCl_3$)** δ 105.8 (m, 3F, CF_3), 24.1 (m, 2F), 18.7 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.0 (dd, *J* 262, 13), 143.2, 142.4 (d, *J* 254), 141.8, 132.8, 125.0, 124.1, 121.1, 120.6 (q, *J* 274), 119.5 (t, *J* 14), 110.5, 110.1 (m); **IR ν_{max} /cm^{-1}**: 3092 (C-H, alkene), 1658 (C=C, cyclic alkene), 1266 (C-N, aromatic amine), 1117, 983 (C-F); **HRMS** calculated for $C_{14}H_5F_7N_2H^+$ 335.0414, found 335.0414; **EA** Found: C 50.3, H 1.58, N 8.29. $C_{14}H_5F_7N_2$ requires C 50.3, H 1.50, N, 8.38; **mp** 111.3 – 112.1 °C. The yields were 38% and 25% respectively with Cyrene or water as solvent.



8eb ^{1}H NMR spectrum (500 MHz, $CDCl_3$)

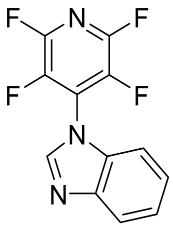


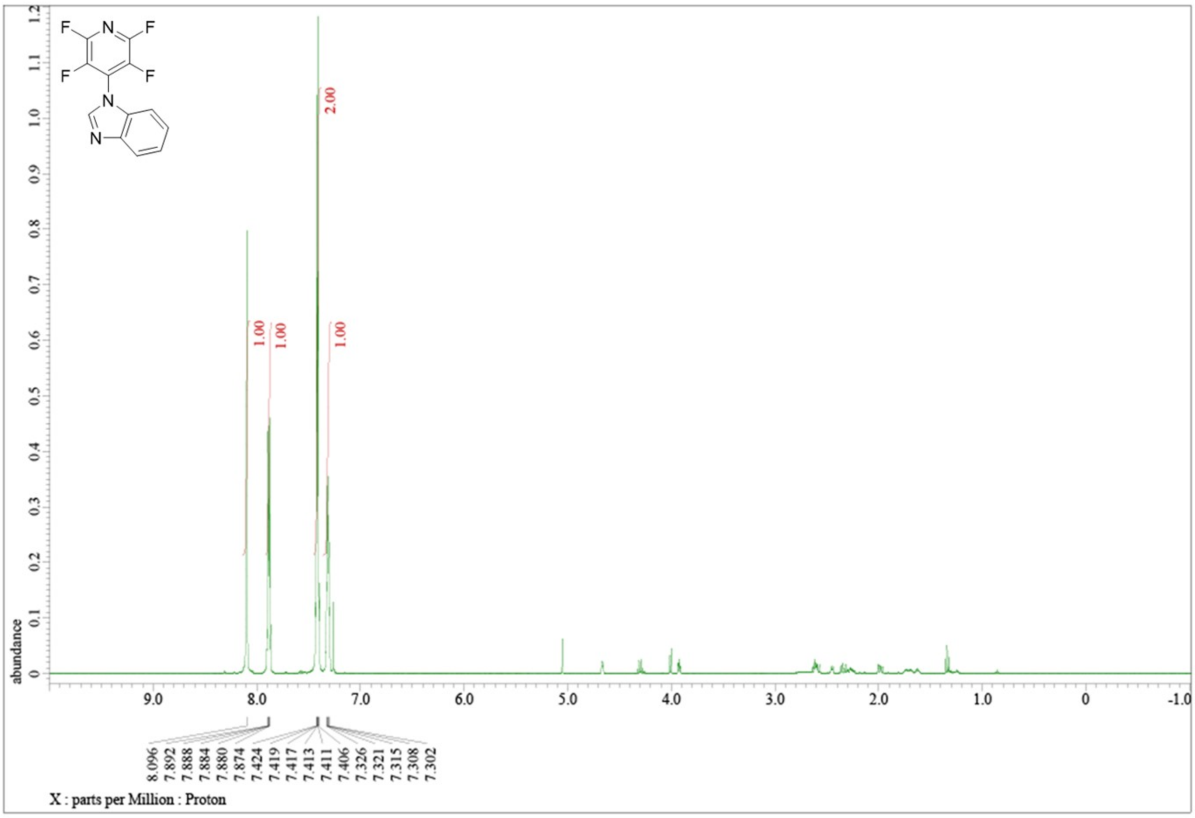
8eb ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



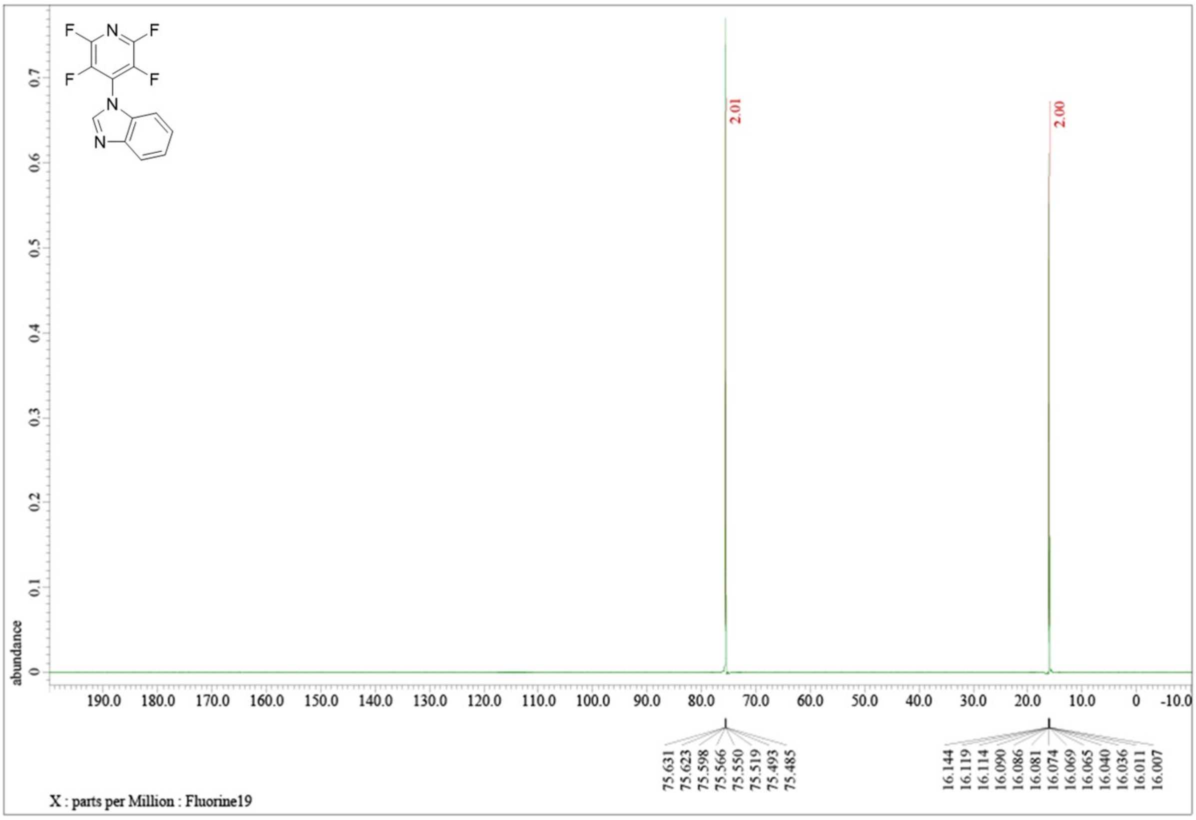
8eb ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

4-(1H-Benzimidazol-1-yl)-2,3,5,6-tetrafluoropyridine (12b)

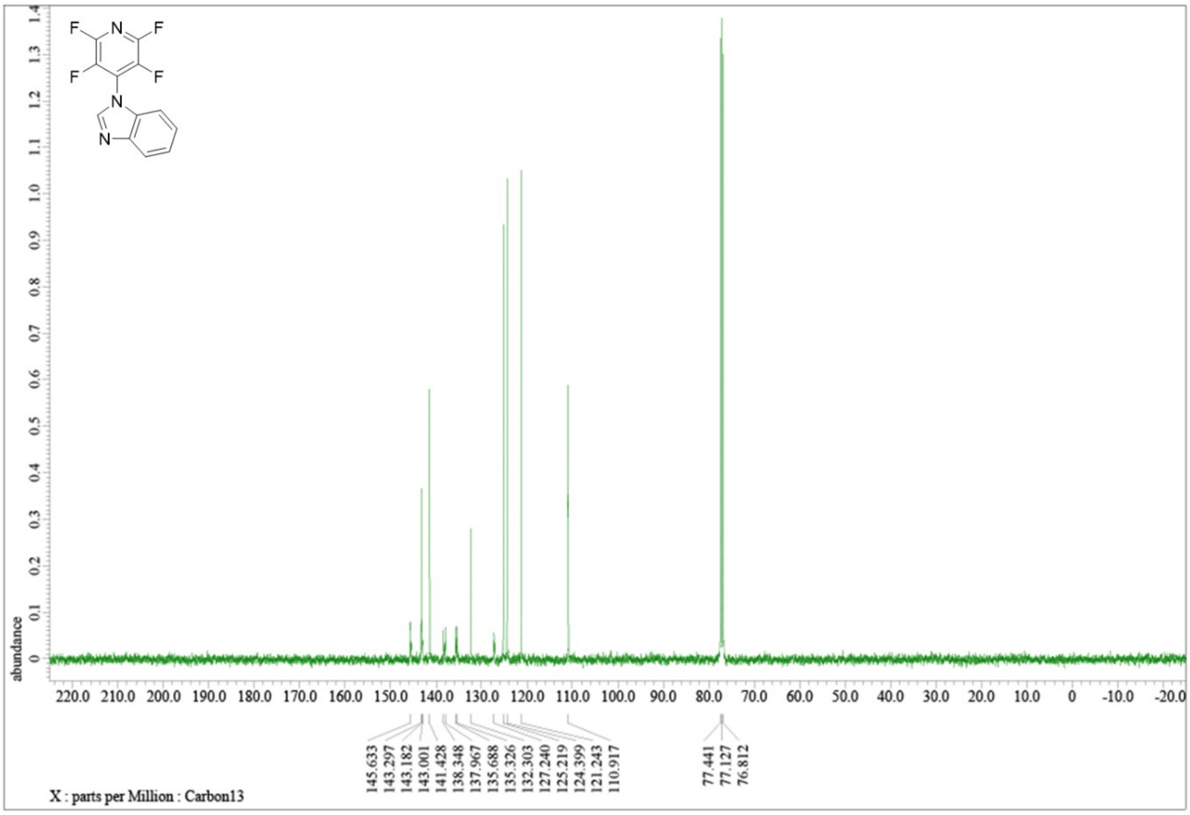
	Prepared from pentafluoropyridine (0.55 mL, 5.0 mmol) and benzimidazole (0.59 g, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 4:1) to give compound **12b**[4] as a white solid (0.96 g, 72%, 3.6 mmol). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.10 (s, 1H), 7.89-7.87 (m, 1H), 7.42-7.40 (m, 2H), 7.33-7.30 (m, 1H) ; **^{19}F NMR (470 MHz, $CDCl_3$)** δ 75.6-75.5 (m, 2F), 16.1-16.0 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.4 (d, *J* 243), 143.0, 141.4, 136.8 (d, *J* 266), 132.3, 127.2, 125.2, 124.4, 121.2, 110.9; **IR ν_{max} /cm^{-1}**: 1632 (C=C, cyclic alkene), 1265 (C-N, aromatic amine), 1014 (C-F); **HRMS** calculated for $C_{12}H_5F_4N_3Na^+$ 290.0312, found 290.0798; **EA** Found: C 53.9, H 1.79, N 15.5. $C_{12}H_5F_4N_3$ requires C 53.9, H 1.87, N, 15.7; **mp** 142.5 – 144.1 °C. The yields were 37% and 0% respectively with water or DMF as solvent.



12b ^{1}H NMR spectrum (500 MHz, $CDCl_3$)

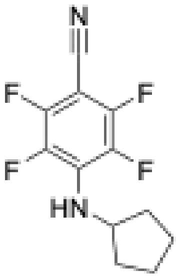


12b ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



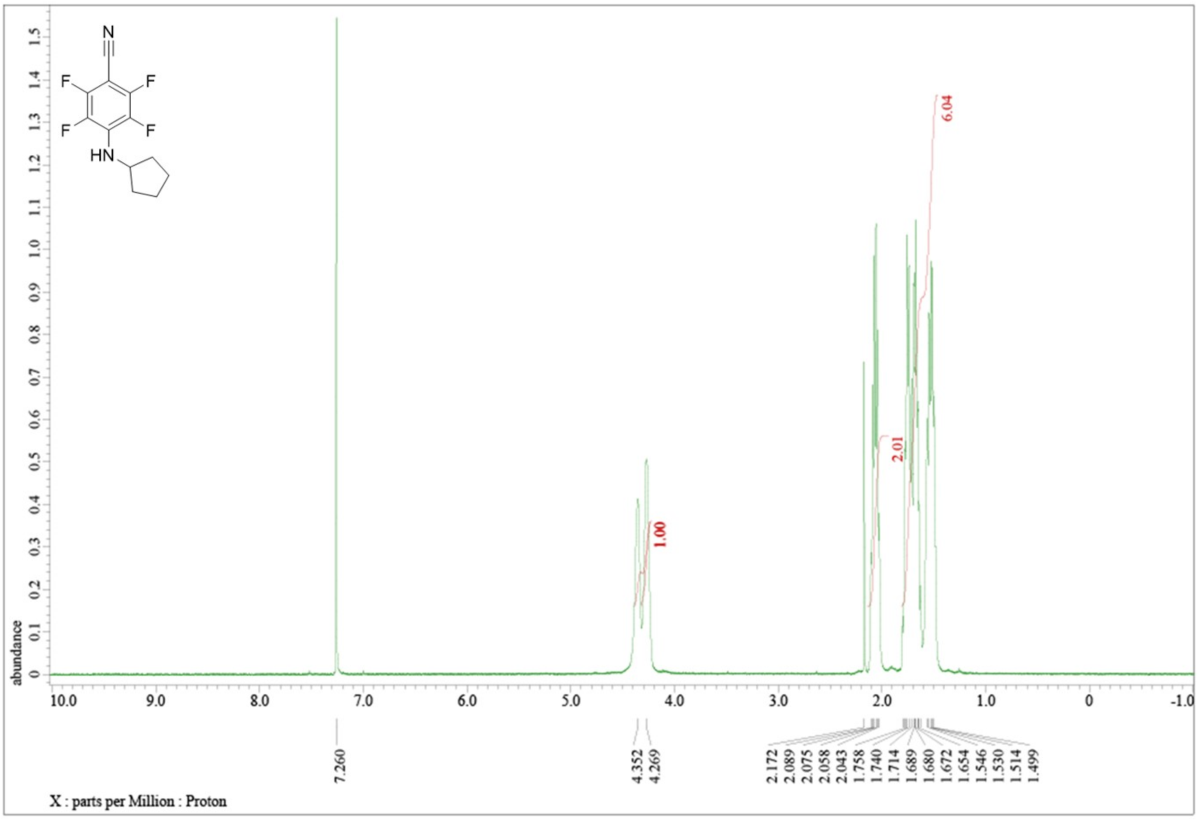
12b ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

4-Cyclopentylamino-2,3,5,6-tetrafluorobenzonitrile (8ac)

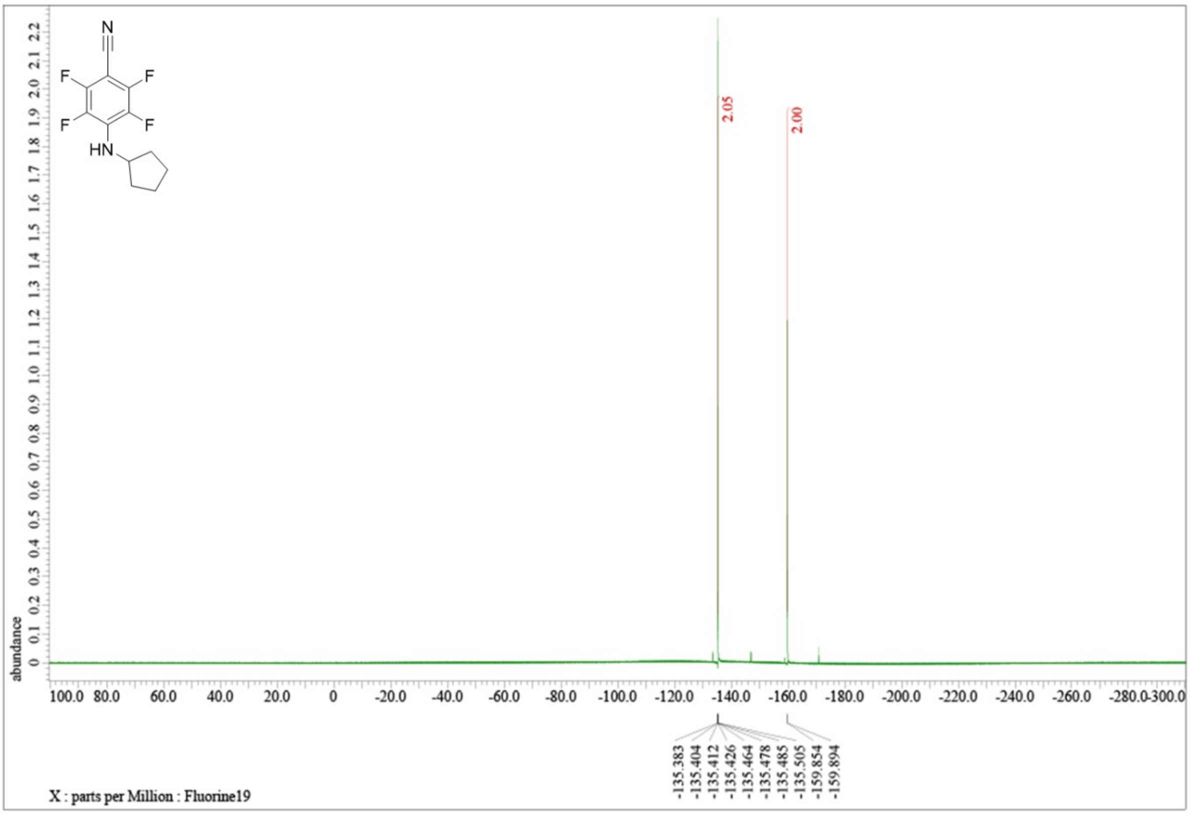


Prepared from pentafluorobenzonitrile (0.63 mL, 5.0 mmol) and cyclopentylamine (0.25 mL, 5.0 mmol) using water (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 1:1) to give compound **8ac** as an off-white solid (0.85 g, 66 %, 3.30 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 4.35 (bs, 1H), 4.27 (bs, 1H), 2.17-2.04 (m, 2H), 1.76-1.50 (m, 6H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ -135.4 (m, 2F), -159.9 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 148.1 (dd, *J* 256, 9), 135.7 (dd, *J* 240, 16), 133.1 (t, *J* 10), 109.1 (t, *J* 4), 78.7 (t, *J* 15), 56.6 (t, *J* 4), 34.8, 23.7; **IR ν_{max} /cm^{-1}**: 3330 (N-H, secondary amine), 2967 (C-H, alkane), 2236 (C≡N), 1651 (C=C, cyclic alkene), 1313 (C-N, aromatic amine), 986 (C-F); **HRMS** calculated for $C_{12}H_{10}F_4N_2H^+$ 259.0853, found 259.0167; **EA** Found: C 55.7, H 3.75, N 10.8. $C_{12}H_{10}F_4N_2$ requires C 55.8, H 3.88, N, 10.9; **mp** 97.4 – 98.8 °C.

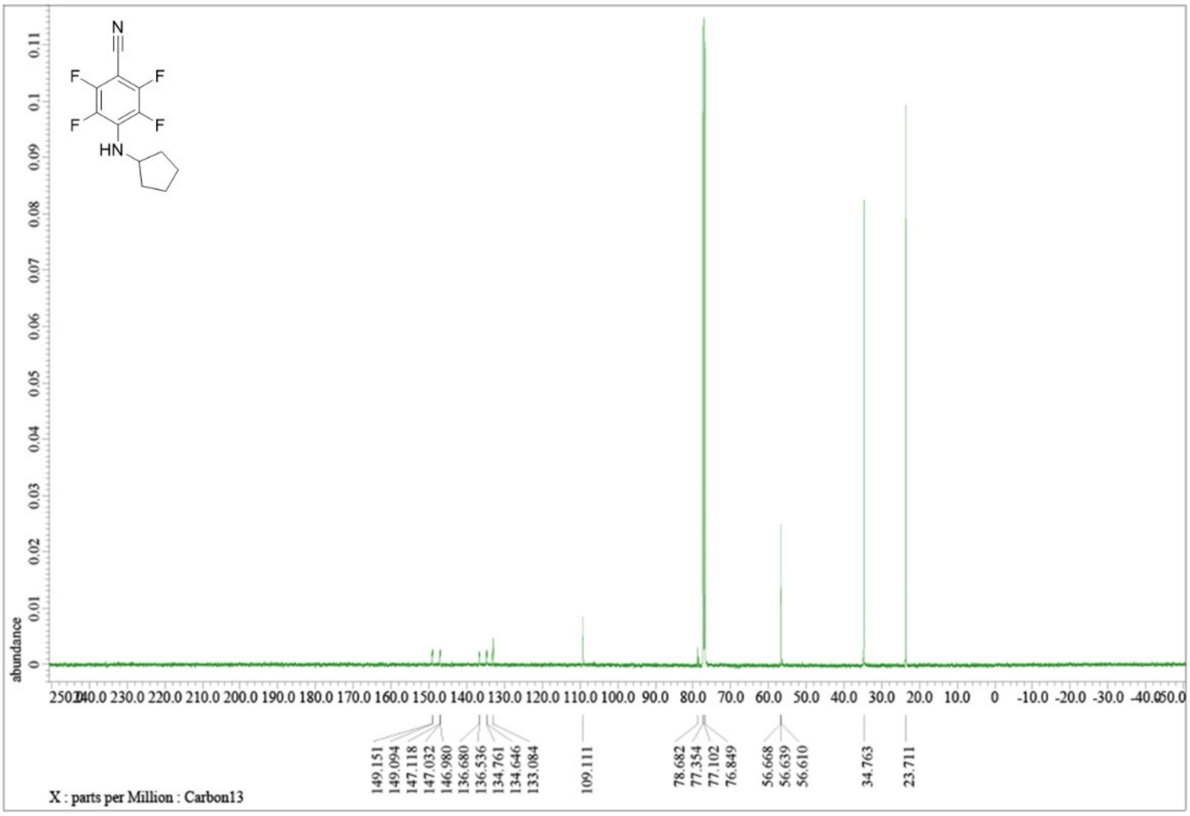
The yields were 62% and 52% respectively with Cyrene or DMF as solvent.



8ac ^{1}H NMR spectrum (500 MHz, CDCl$_3$)

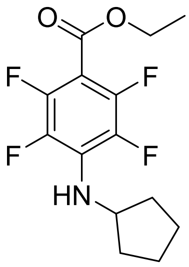


8ac ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



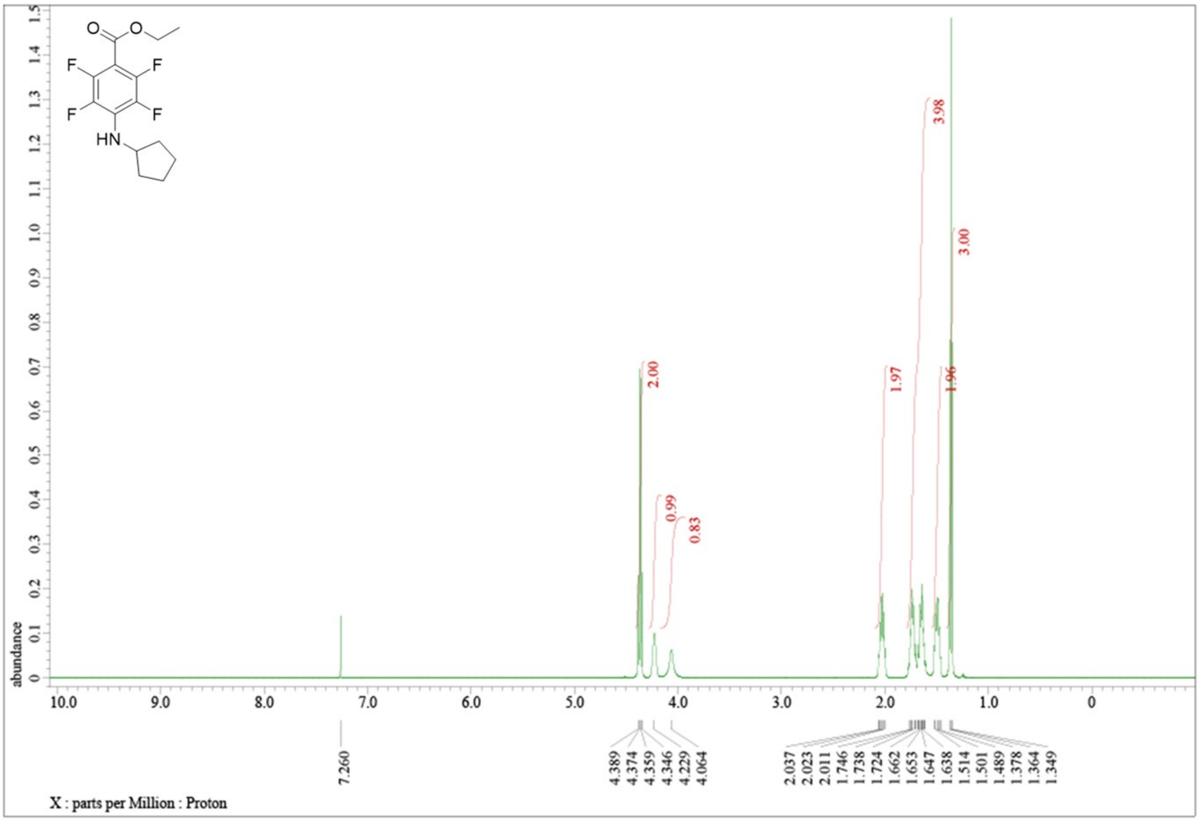
8ac ^{13}C NMR spectrum (125 MHz, CDCl$_3$)

Ethyl 4-cyclopentylamino-2,3,5,6-tetrafluorobenzoate (8bc)

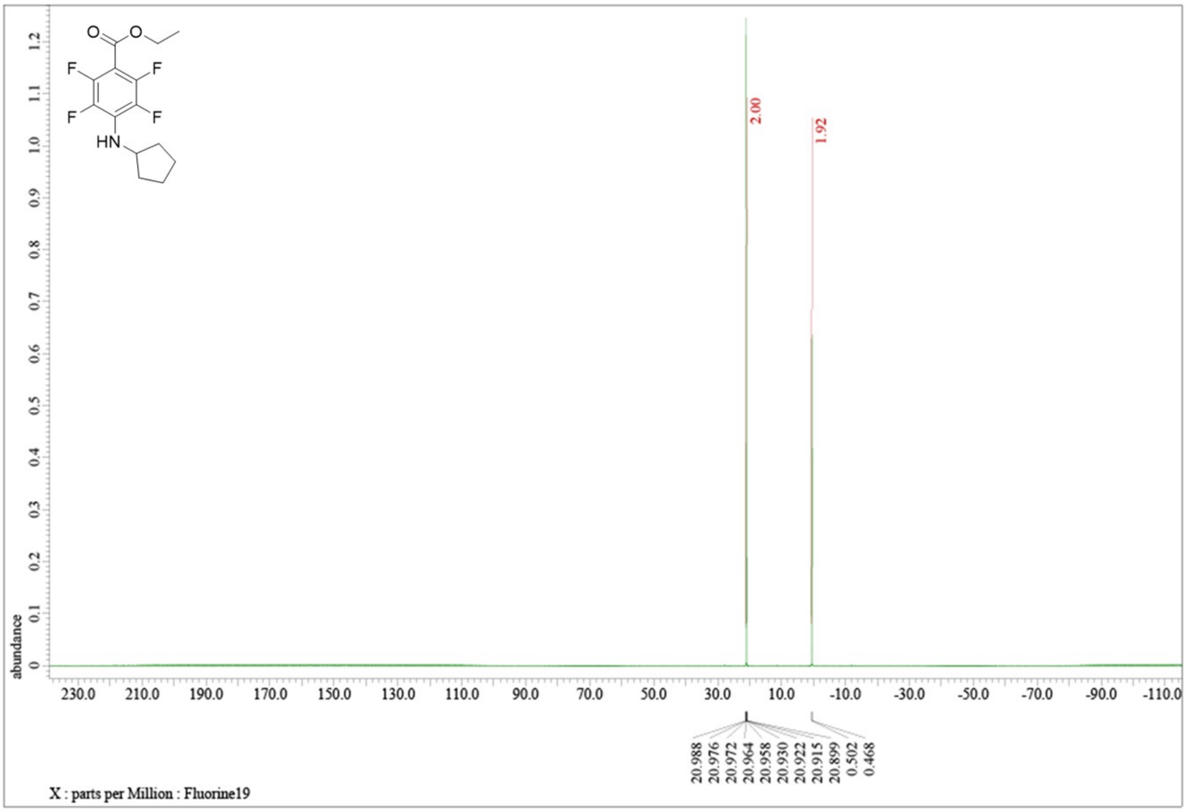


Prepared from ethyl pentafluorobenzoate (0.84 mL, 5.0 mmol) and cyclopentylamine (0.25 mL, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 4:1) to give compound **8bc** as a white solid (1.34 g, 88%, 4.4 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 4.37 (q, *J* 7, 2H), 4.23 (bs, 1H), 4.06 (bs, 1H), 2.04-2.01 (m, 2H), 1.75-1.64 (m, 4H), 1.51-1.49 (m, 2H), 1.36 (t, *J* 7, 3H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 20.9 (m, 2F), 0.48 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 160.8 (C^3), 146.6 (dd, *J* 251, 4), 136.4 (dd, *J* 237, 14), 130.8 (t, *J* 12), 98.4 (t, *J* 14), 61.6, 56.6 (t, *J* 4), 34.6, 23.7, 14.2; **IR ν_{max} /cm^{-1}**: 3348 (N-H, secondary amine), 2982 (C-H, alkane), 1709 (C=O, ester), 1639 (C=C, cyclic alkene), 1466 (C-H, alkane), 1305 (C-N, aromatic ester), 1295 (C-O, aromatic ester), 1225 (C-F); **HRMS** calculated for $C_{14}H_{15}F_4NO_2H^+$ 306.1112, found 306.1112; **EA** Found C 55.1 %, H 4.89 %, N 4.54, $C_{14}H_{15}F_4NO_2$ requires C 55.1 %, H 4.92 %, N 4.59; **mp** 47.3 – 47.4 °C.

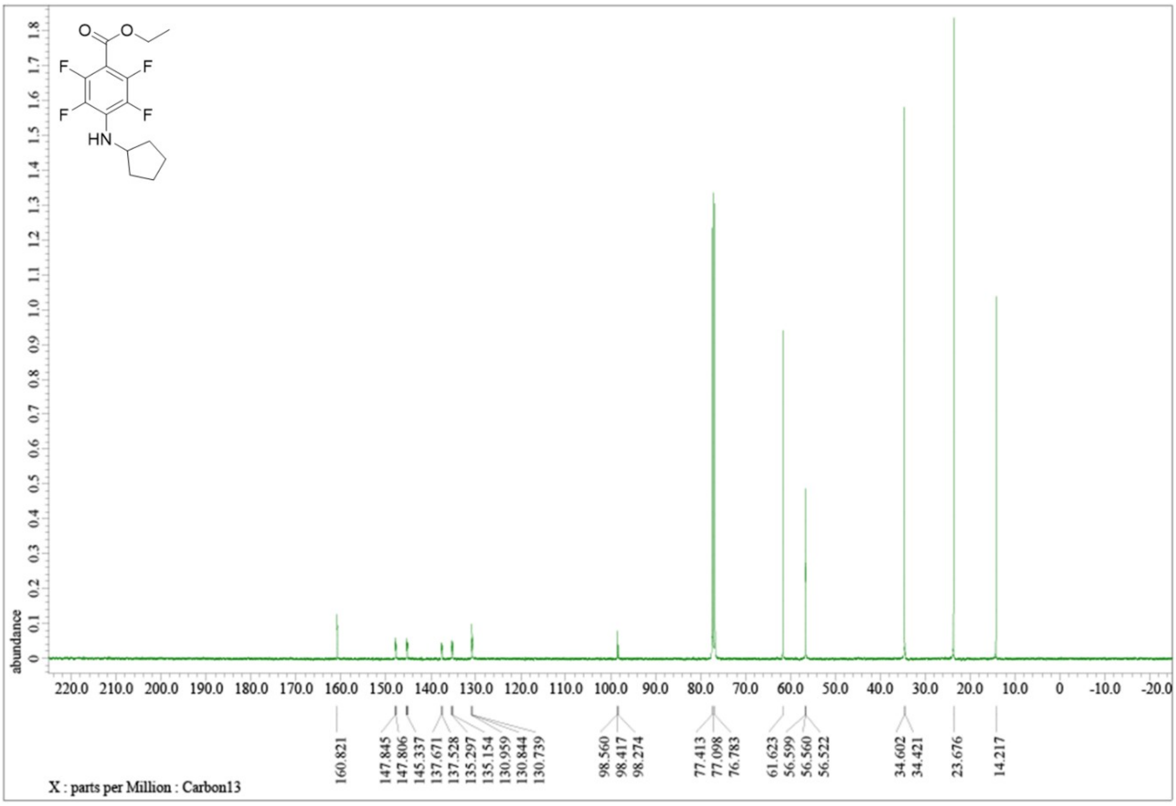
The yields were 0% and 26% respectively with water or DMF as solvent.



8bc ^{1}H NMR spectrum (500 MHz, CDCl$_3$)

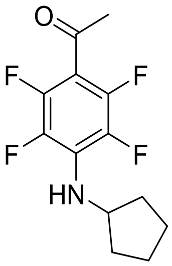


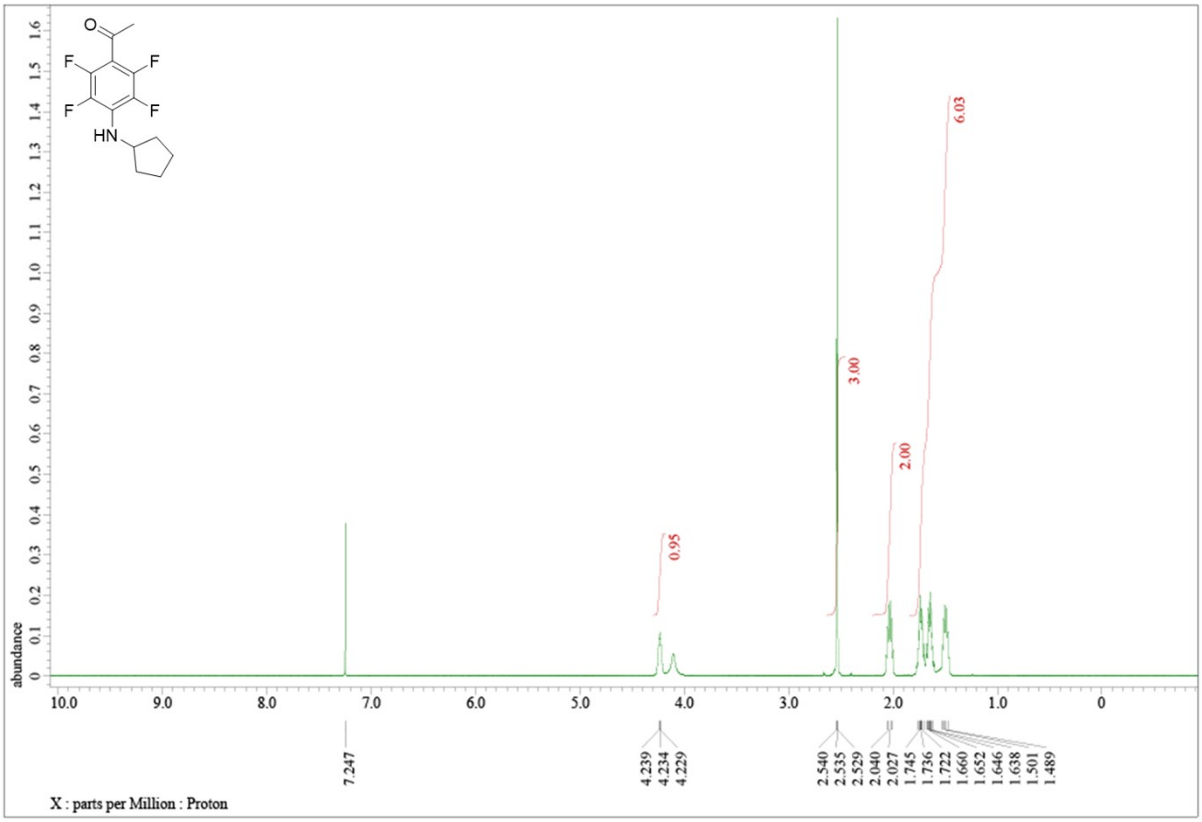
8bc ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



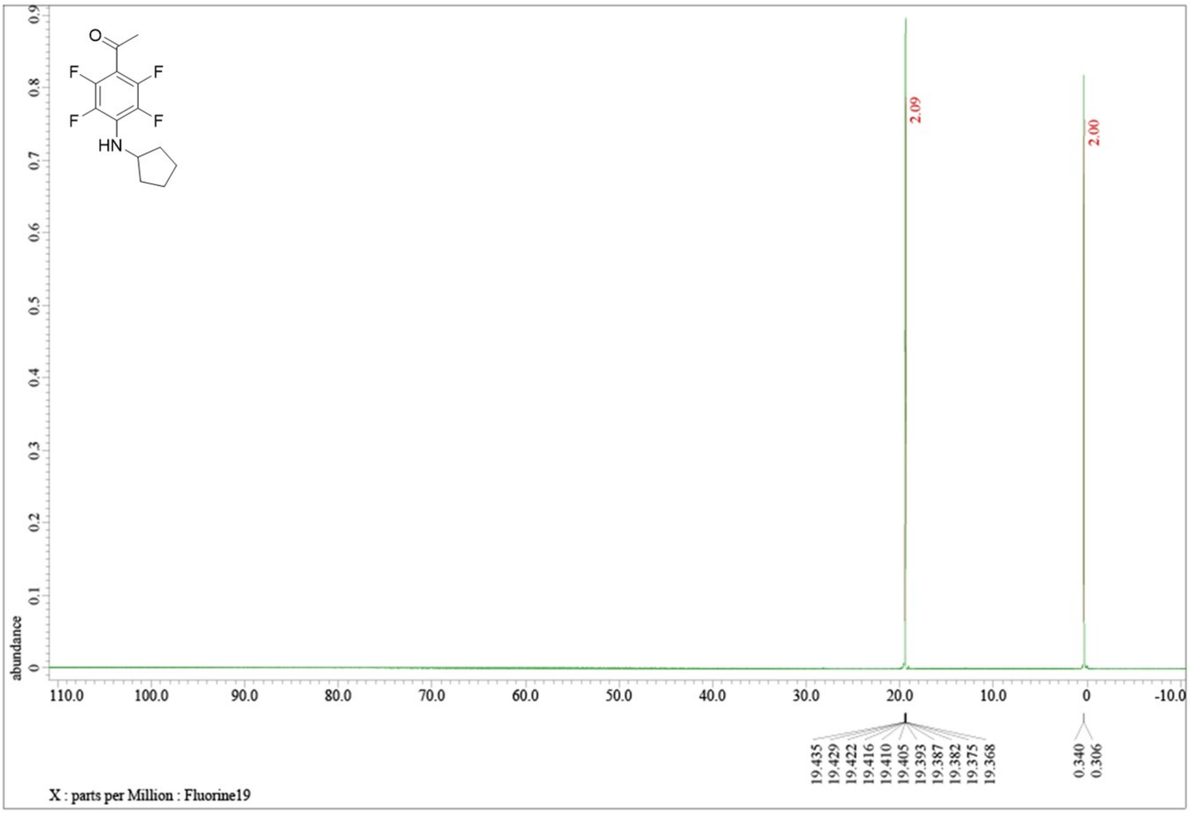
8bc ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

4-Cyclopentylamino-2,3,5,6-tetrafluoroacetophenone (8cc)

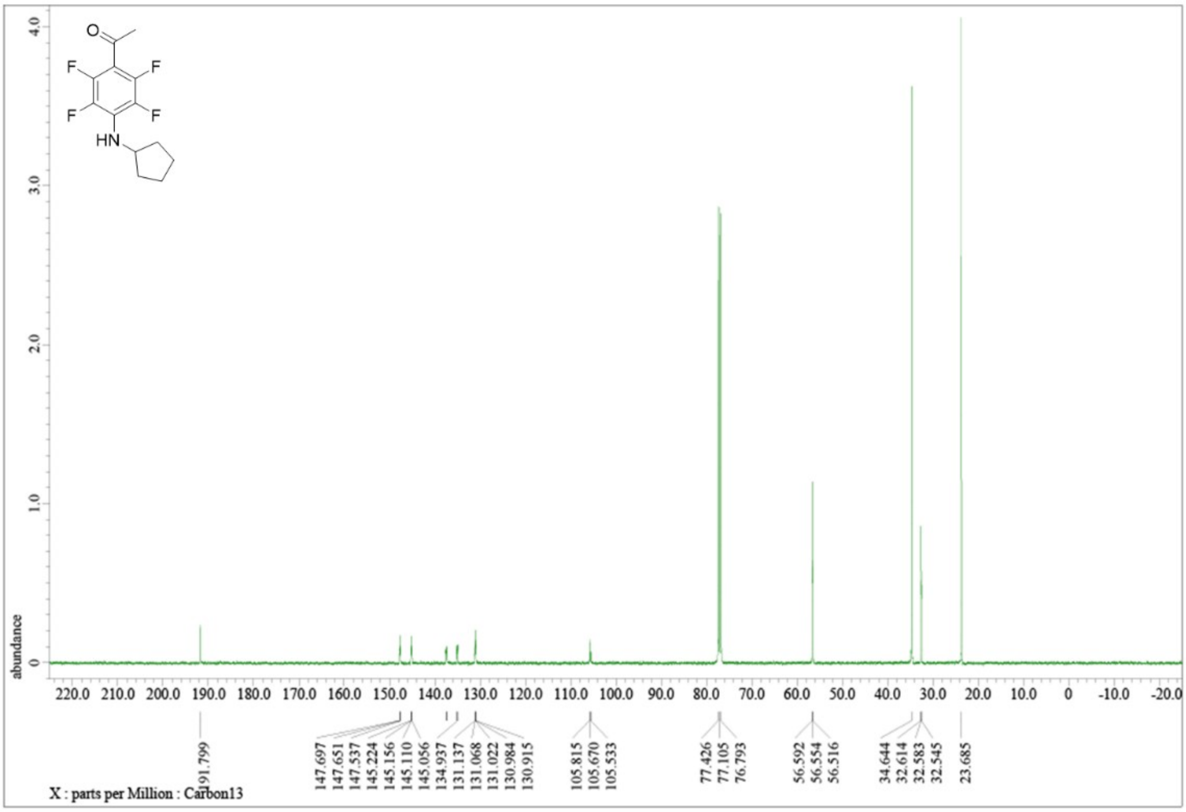
	Prepared from pentafluoroacetophenone (0.71 mL, 5.0 mmol) and cyclopentylamine (0.25 mL, 5.0 mmol) using water (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 2:1) to give compound **8cc** as a white solid (0.96 g, 70%, 3.5 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 4.24-4.33 (m, 1H), 4.12 (bs, 1H), 2.55 (t, *J* 2.5, 3H), 2.04-2.03 (m, 2H), 1.75-1.72 (m, 2H), 1.66-1.64 (m, 2H), 1.511.49 (m, 2H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 19.4 (m, 2F), 0.32 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 191.8, 146.4 (dt, *J* 245, 7), 136.2 (d, *J* = 222), 131.0 (t, *J* 7), 105.7 (t, *J* 15), 56.6 (t, *J* 4), 34.6, 32.6 (t, *J* 4), 23.7; **IR ν$_{max}$ /cm^{-1}**: 3356 (N-H, secondary amine) 2959 (C-H, alkane), 1685 (C=O), 1663 (C=C, cyclic alkene), 1304 (C-N, aromatic amine), 1209 (C-F); **HRMS** calculated for $C_{13}H_{13}F_4NOH^+$ 276.1006, found 276.1006; **EA** Found: C 56.6, H 4.65, N 5.09. $C_{13}H_{13}F_4NO$ requires C 56.7, H 4.72, N, 5.09; **mp** 48.5 – 50.4 °C. The yields were 42% and 59% respectively with Cyrene or DMF as solvent.



8cc ^{1}H NMR spectrum (500 MHz, CDCl$_3$)

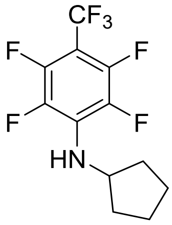


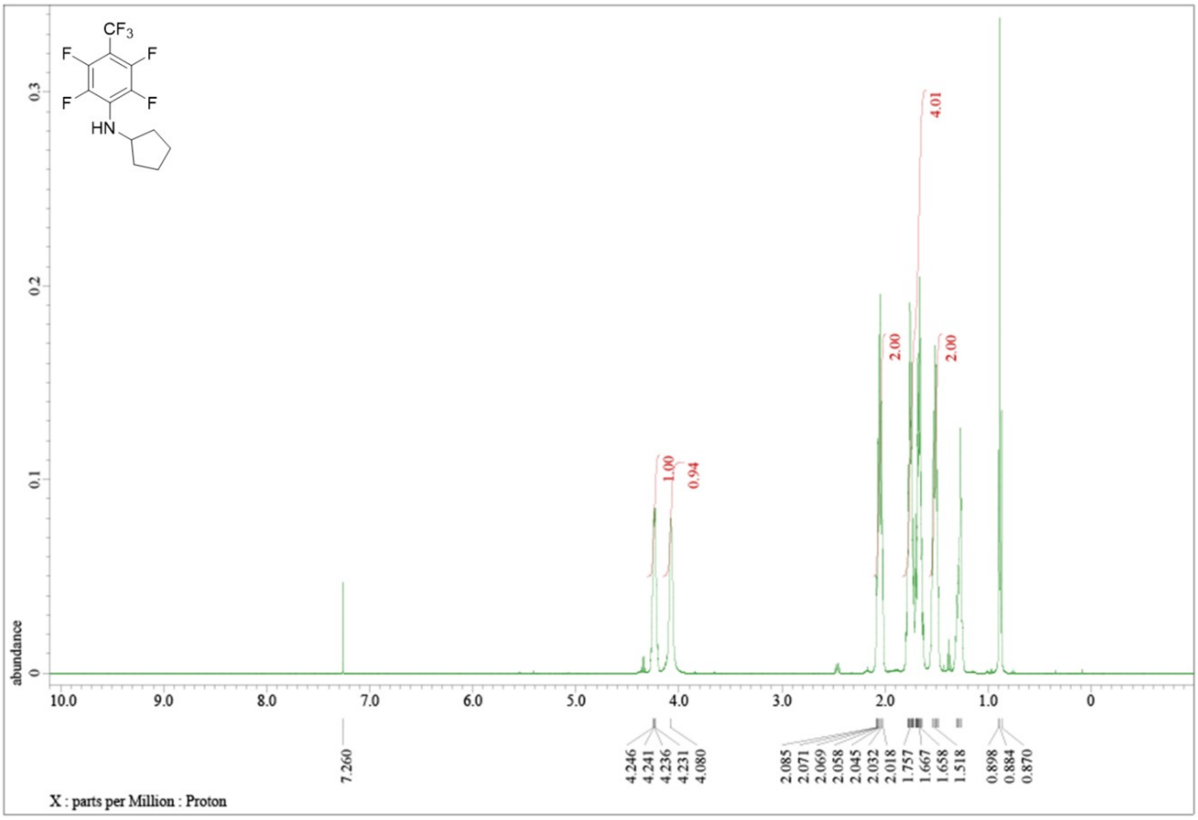
8cc ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



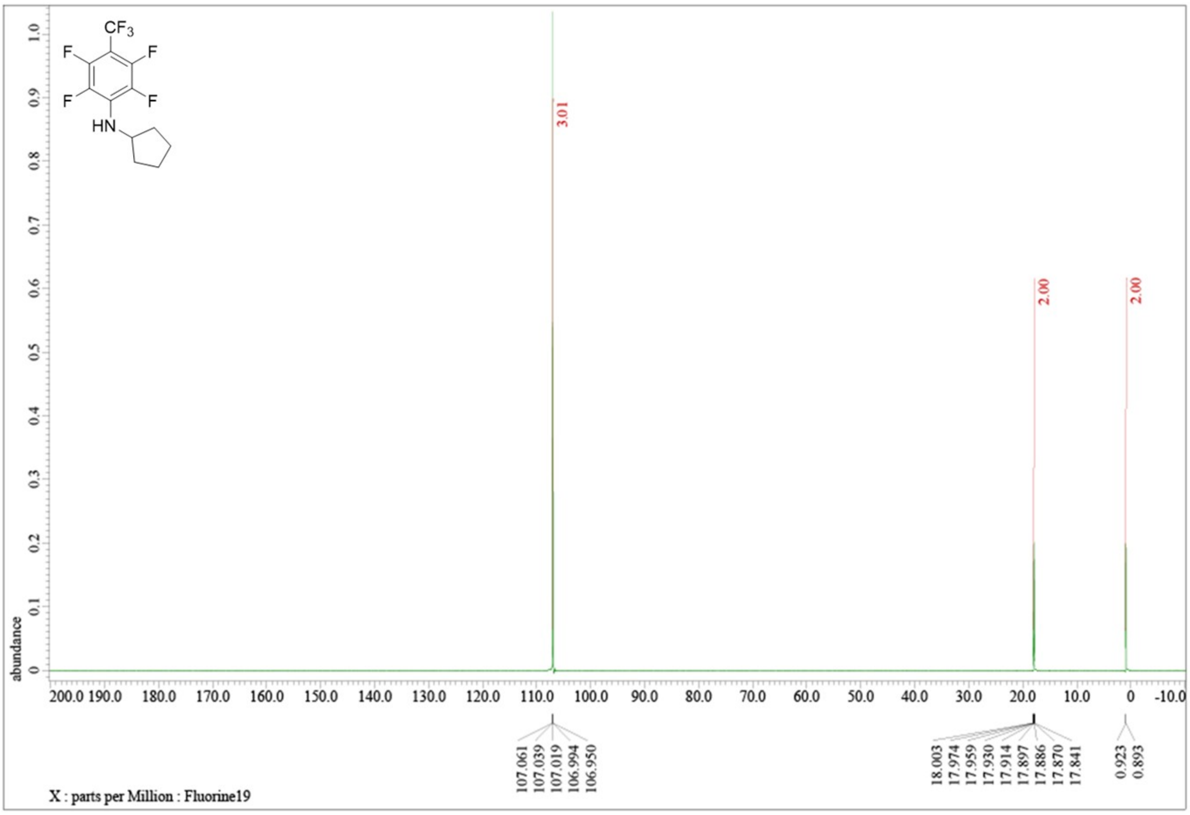
8cc ^{13}C NMR spectrum (100 MHz, $CDCl_3$)

N-[2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl]cyclopentylamine (8ec)

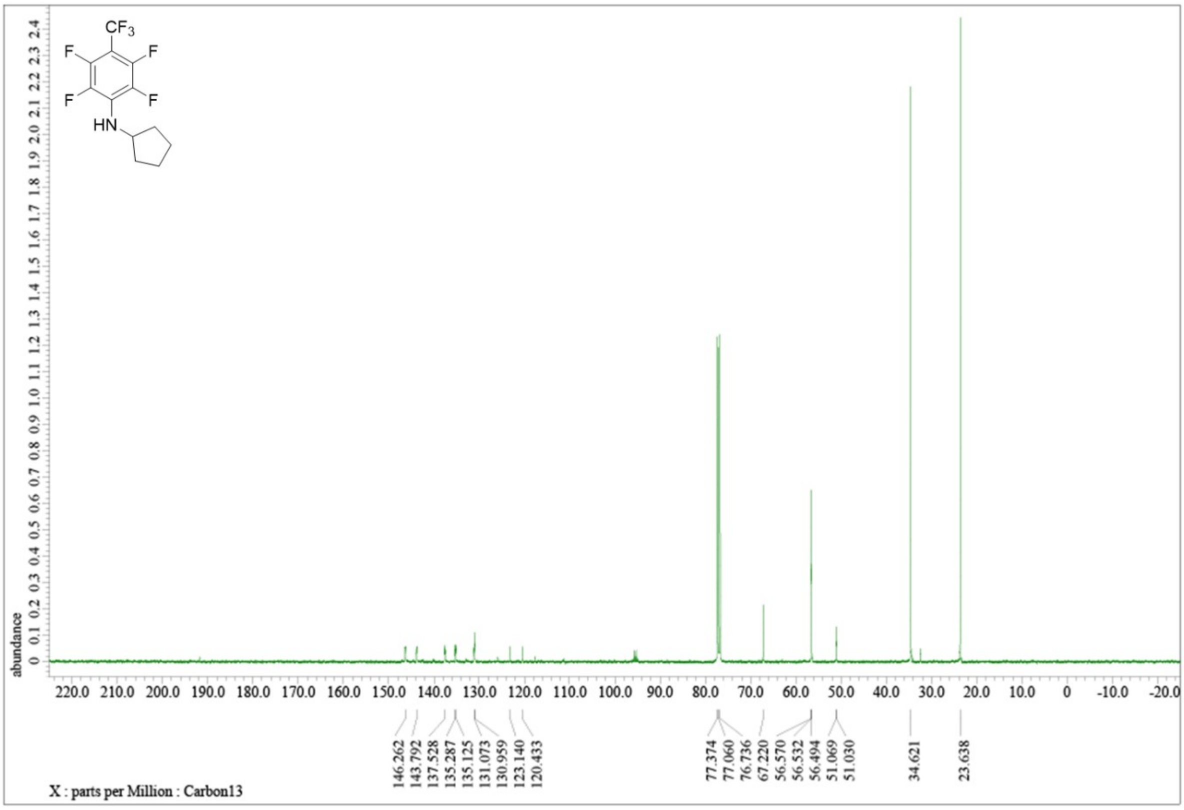
	Prepared from octafluorotoluene (0.71 mL, 5.0 mmol) and cyclopentylamine (0.25 mL, 5.0 mmol) using Cyrene (0.25 mL) as solvent. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 5:1) to give compound **8ec** as a colourless oil (1.31 g, 87%, 4.4 mmol). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 4.25-4.23 (m, 1H), 4.08 (bs, 1H), 2.09-2.02 (m, 2H), 1.76-1.66 (m, 4H), 1.56-1.47 (m, 2H); **^{19}F NMR (470 MHz, $CDCl_3$)** δ 107.0 (m, 3F, CF_3), 18.0-17.8 (m, 2F), 0.92-0.89 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 145.0 (d, *J* 247), 136.3 (dd, *J* 240, 16), 131.1 (t, *J* 11), 121.8 (q, *J* = 271), 95.4 (m), 56.5 (t, *J* 4), 34.6, 23.6; **IR ν_{max} /cm^{-1}**: 3000 (N-H), 2934 (C-H, alkane); **HRMS** calculated for $C_{12}H_{10}F_7N$ 301.0696, found 301.1410; **EA** Found C 46.7, H 3.19, N 4.56, $C_{12}H_{10}F_7N.½H_2O$ requires C 46.5 %, H 3.55 %, N 4.52. The yields were 80% and 85% respectively with water or DMF as solvent.



8ec ^{1}H NMR spectrum (500 MHz, $CDCl_3$)

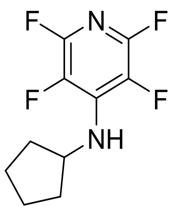


8ec ^{19}F NMR spectrum (470 MHz, CDCl$_3$)



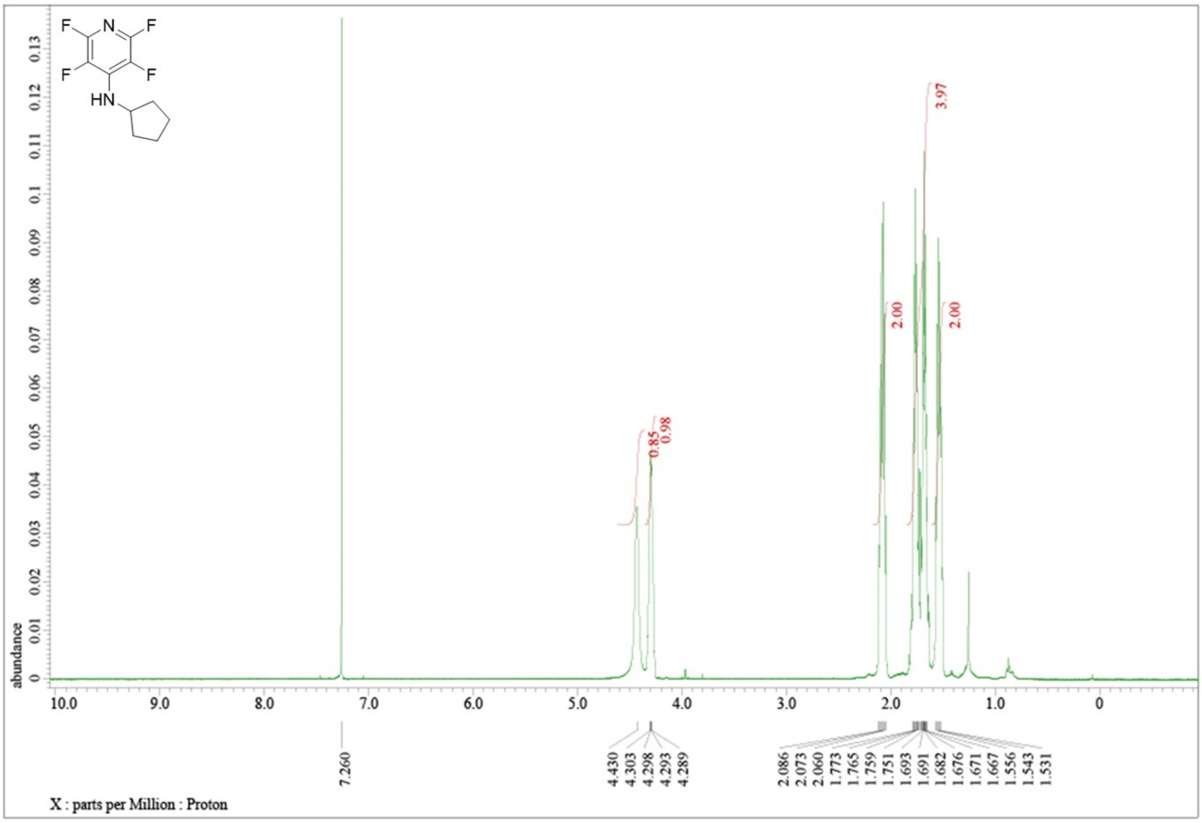
8ec ^{13}C NMR spectrum (600 MHz, CDCl$_3$)

4-Cyclopentylamino-2,3,5,6-tetrafluoropyridine (12c)

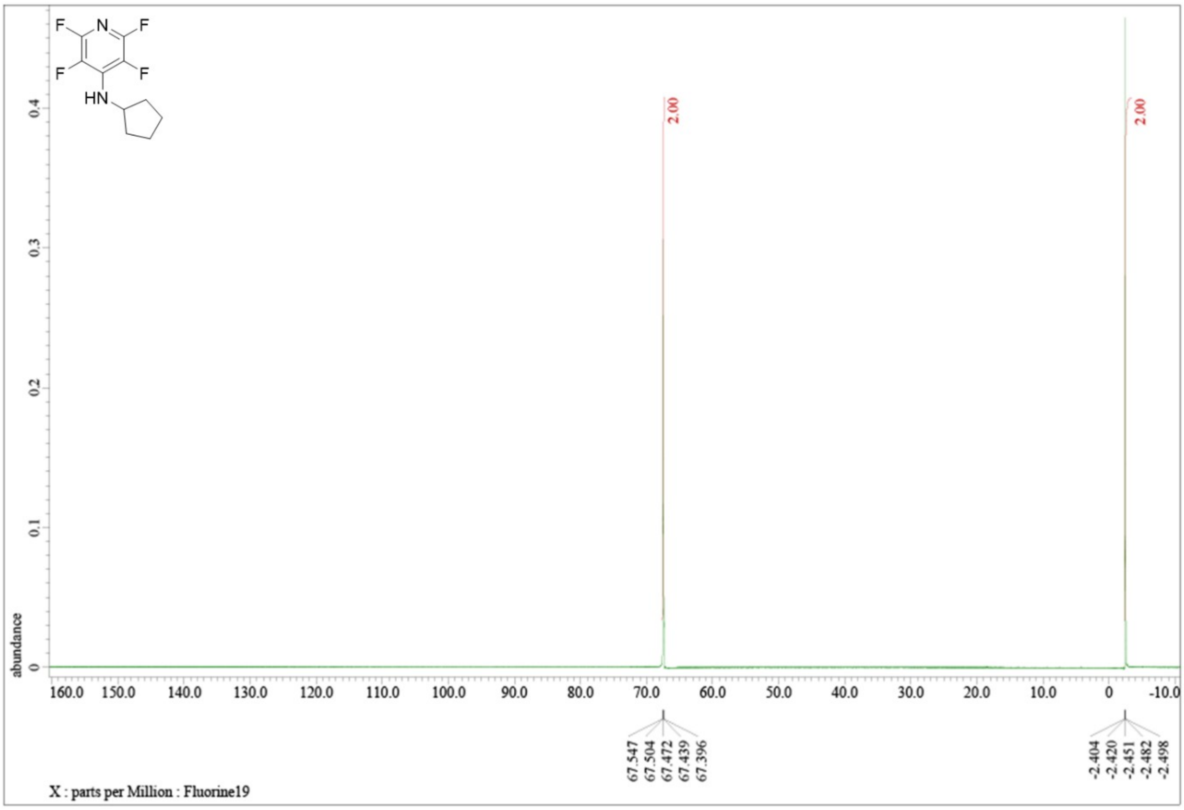


Prepared from pentafluoropyridine (0.55 mL, 5.0 mmol) and cyclopentylamine (0.25 mL, 5.0 mmol) using the general procedure. The crude product was then purified by column chromatography over silica gel (elution with hexane: ethyl acetate 1:1) to give compound **12c** as an orange oil (0.59 g, 50%, 2.5 mmol). **^{1}H NMR (500 MHz, CDCl$_3$)** δ 4.30 (bs, 1H), 4.29 (m, 1H), 2.09-2.06 (m, 2H), 1.77-1.67 (m, 4H), 1.56-1.53 (m, 2H); **^{19}F NMR (470 MHz, CDCl$_3$)** δ 67.5 (m, 2F), -2.45 (m, 2F) (AA'BB' spin pattern); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 144.3 (dt, *J* 236, 17), 137.3, 130.9 (dd, *J* 236, 35), 56.2 (t, *J* 3), 34.7, 23.7; **IR ν$_{max}$ /cm^{-1}**: 3426 (N-H, secondary amine), 2951, (C-H), 1645 (C-N, aromatic amine), 1476 (C-H), 1141 (C-F); **HRMS** calculated for $C_{10}H_{10}F_4N_2H^+$ 235.0853, found 235.0853.

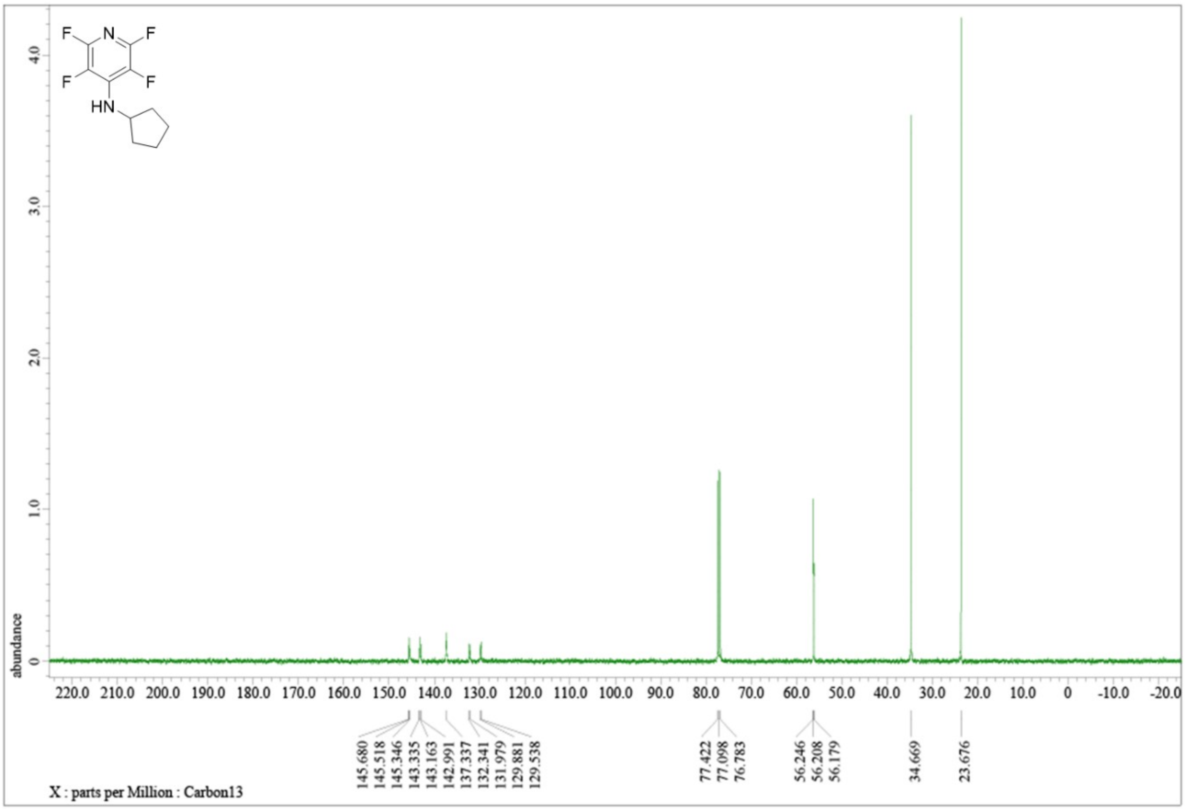
The yields were 38% and 31% respectively with Cyrene or DMF as solvent.



12c ^{1}H NMR spectrum (500 MHz, CDCl$_3$)



12c ^{19}F NMR spectrum (470 MHz, CDCl$_3$)

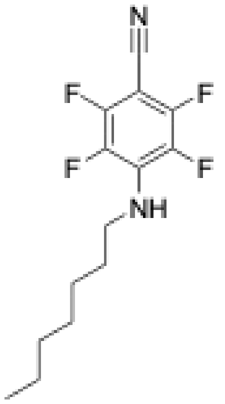


12c ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

Synthesis of Compounds 8ad-8ag

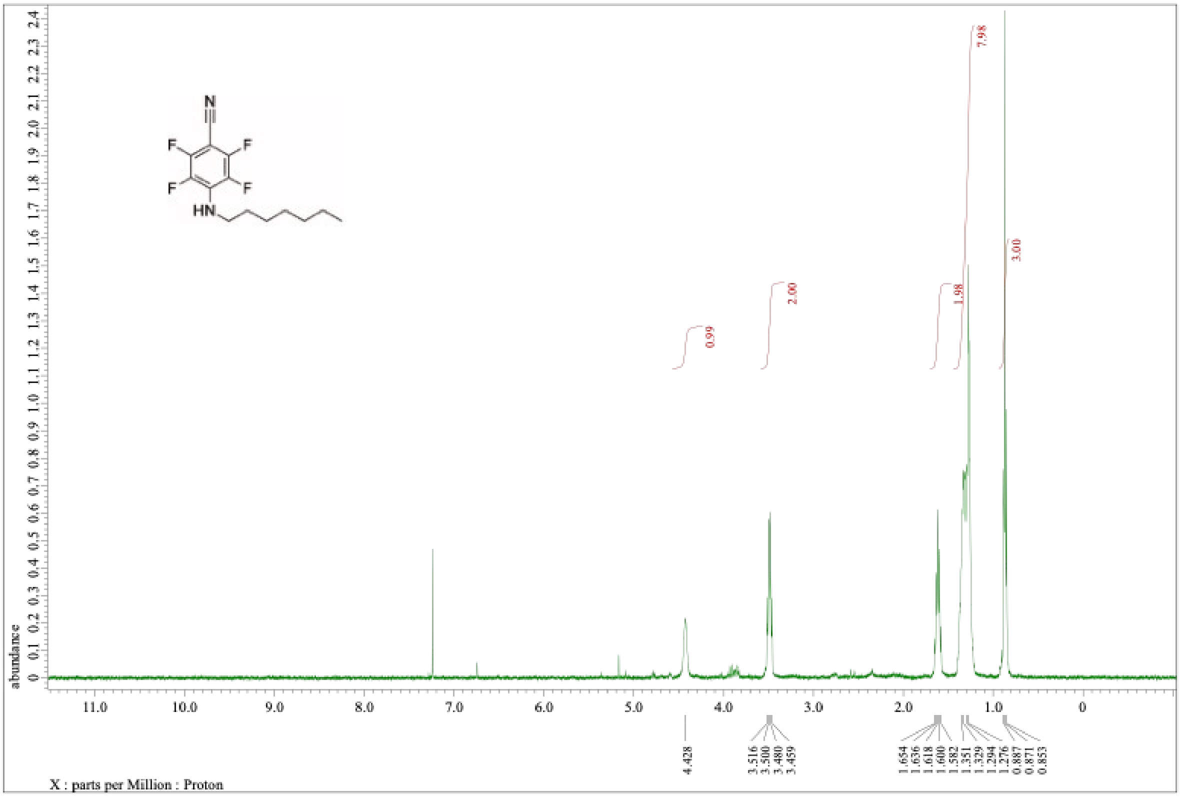
Compounds **8ad**-**8ag** were prepared using a Fritsch Pulverisette 7 micro mill with 12 mL agate jars. Fluoroarene (2 mmol), the nucleophile (2 mmol) and sodium carbonate (0.50 g, 4.7 mmol) were added to a 12 mL agate milling jar along with Cyrene (0.1 ml). Six 10 mm diameter agate milling balls were added and the jars were spun at 600 rpm with 30 repetitions of 1 min milling and 1 min pause. The reaction mixture was then treated with water and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, washed with brine and dried over magnesium sulfate and the solvent was removed *in vacuo* to give the crude product. The product was then purified by column chromatography or crystallisation.

2,3,5,6-Tetrafluoro-4-hexylaminobenzonitrile **8ad**

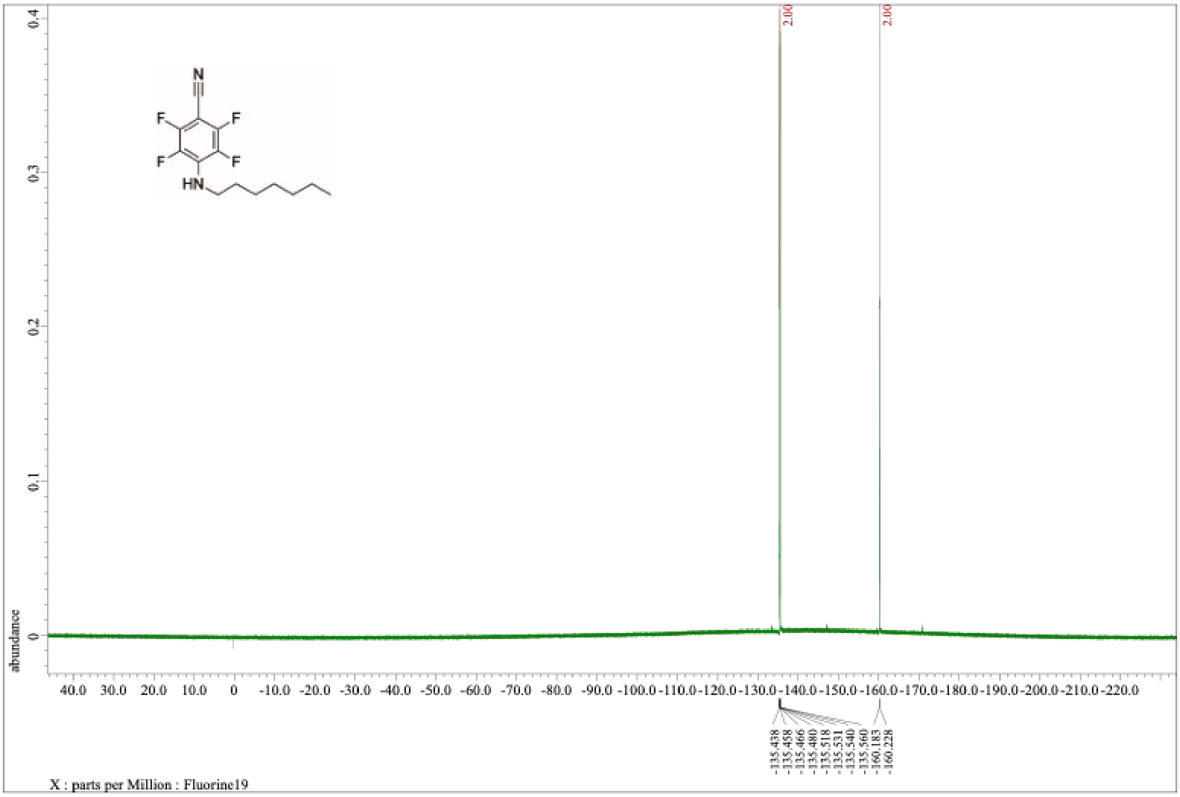


Prepared from pentafluorobenzonitrile (0.25 mL, 2.0 mmol) and hexylamine (0.30 mL, 2 mmol) using Cyrene (0.1 mL) as LAG agent. Solid was formed after aqueous work-up which was recrystallized from ethanol to give **8ad** as a yellow solid (0.45 g, 78%).

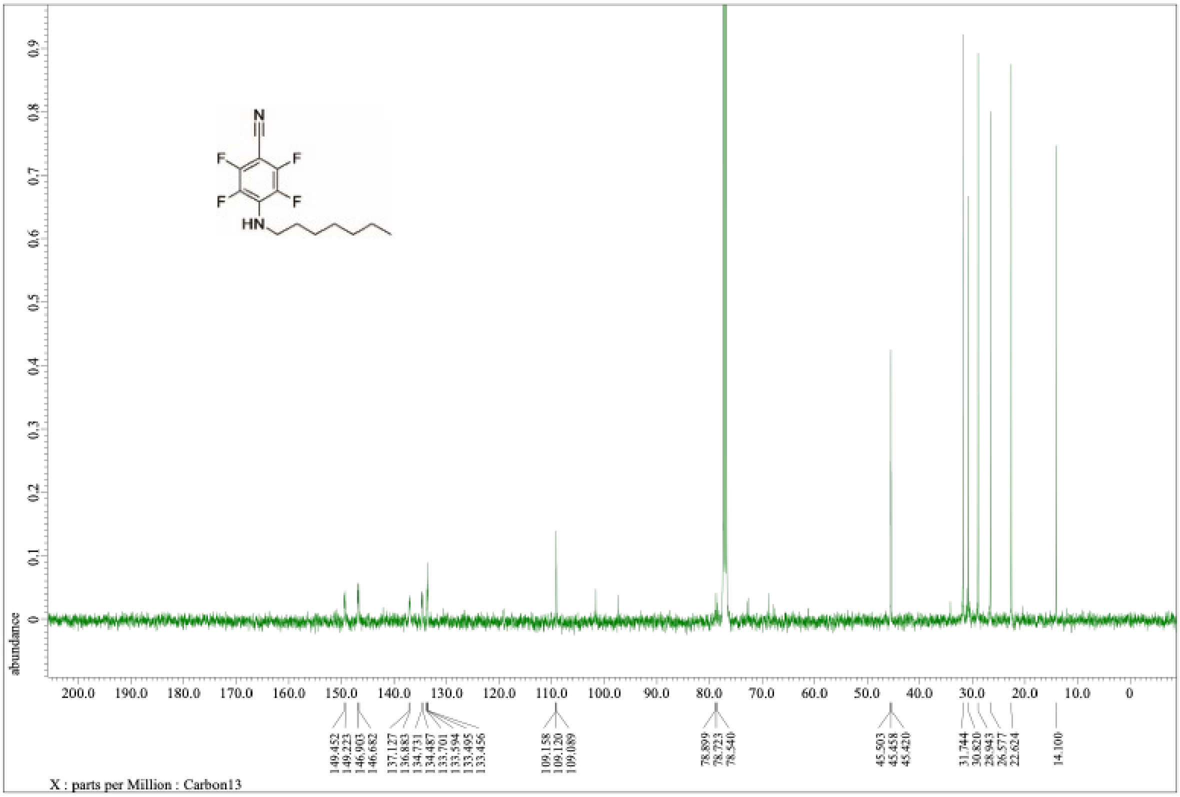
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (1H, bs), 3.49 (2H, q, *J* 8), 1.62 (2H, qn, *J* 7), 1.35-1.28 (8H, m), 0.87 (3H, t, *J* 7), ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.44 – -135.56 (2F, AA'm), -160.18 – -160.22 (2F, BB'm), ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (dm, *J* 255), 135.8 (dm, *J* 240), 133.6 (tt, *J* 11, 5), 109.1 (t, *J* 4), 78.7 (t, *J* 18), 45.5 (t, *J* 4), 31.7, 30.8, 28.9, 26.6, 22.6, 14.1.



18ad ^{1}H NMR spectrum (400 MHz, $CDCl_3$)

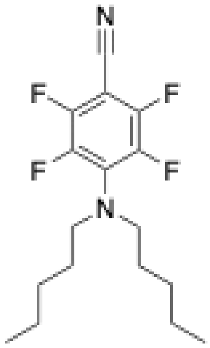


18ad ^{19}F NMR spectrum (376 MHz, CDCl$_3$)



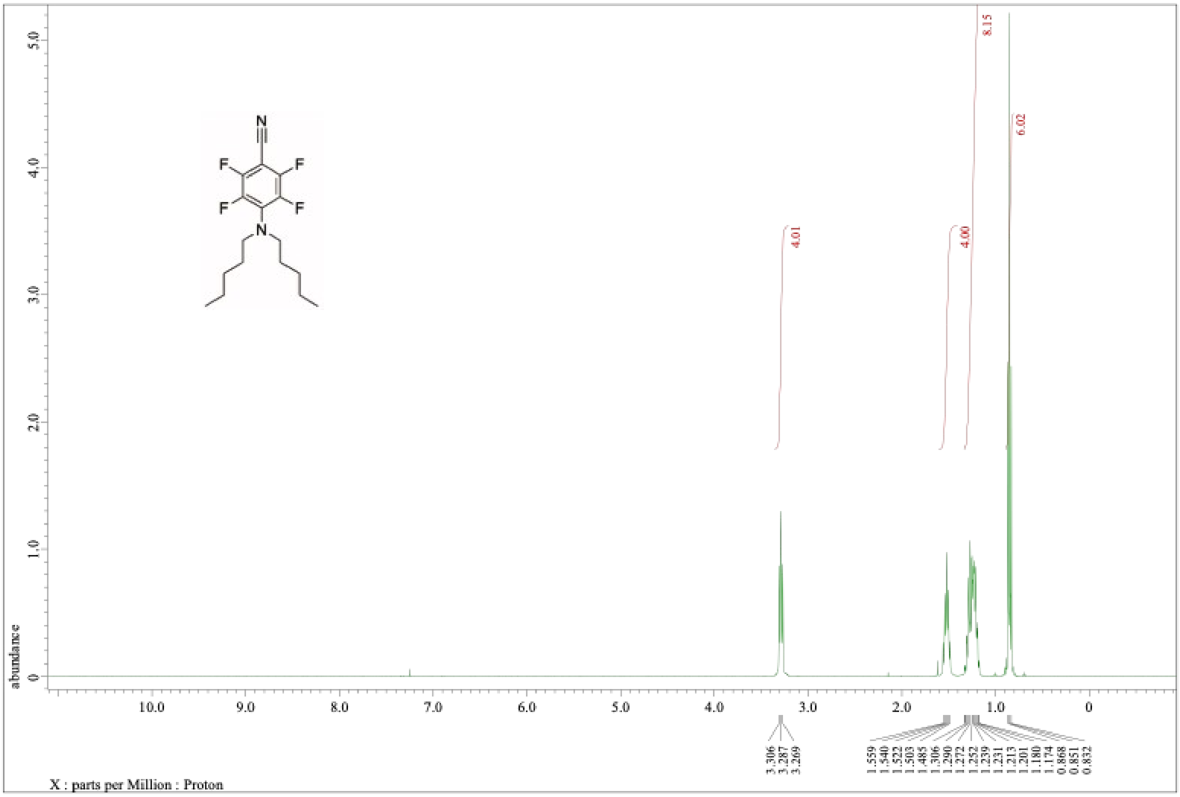
18ad ^{13}C NMR spectrum (100 MHz, CDCl$_3$)

2,3,5,6-Tetrafluoro-4-dipentylaminobenzonitrile **8ae**

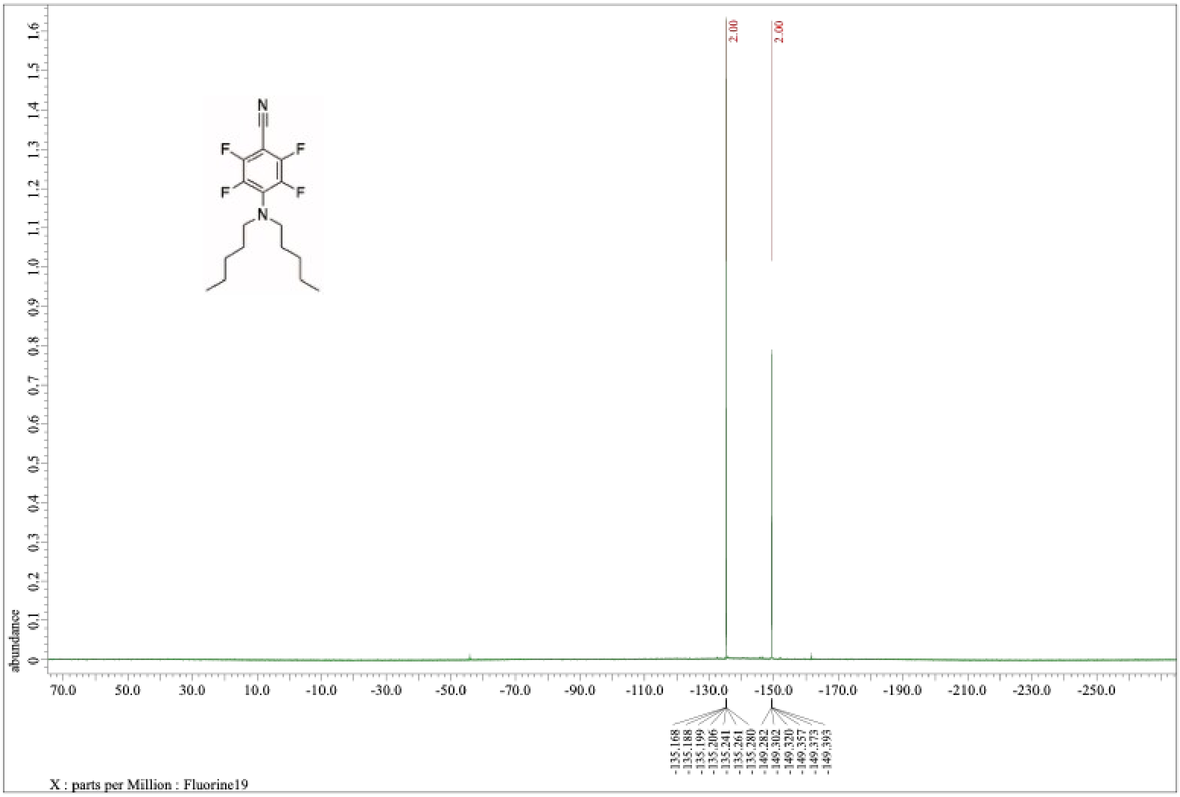


Prepared from pentafluorobenzonitrile (0.25 mL, 2.0 mmol) and dipentylamine (0.27 ml, 2.0 mmol) using Cyrene (0.1 mL) as LAG agent. The crude product (0.54 g, 82% before purification) was chromatographed over silica gel (elution with hexane) to give compound **8ae** as a colourless oil (0.382 g, 58%, 1.2 mmol).

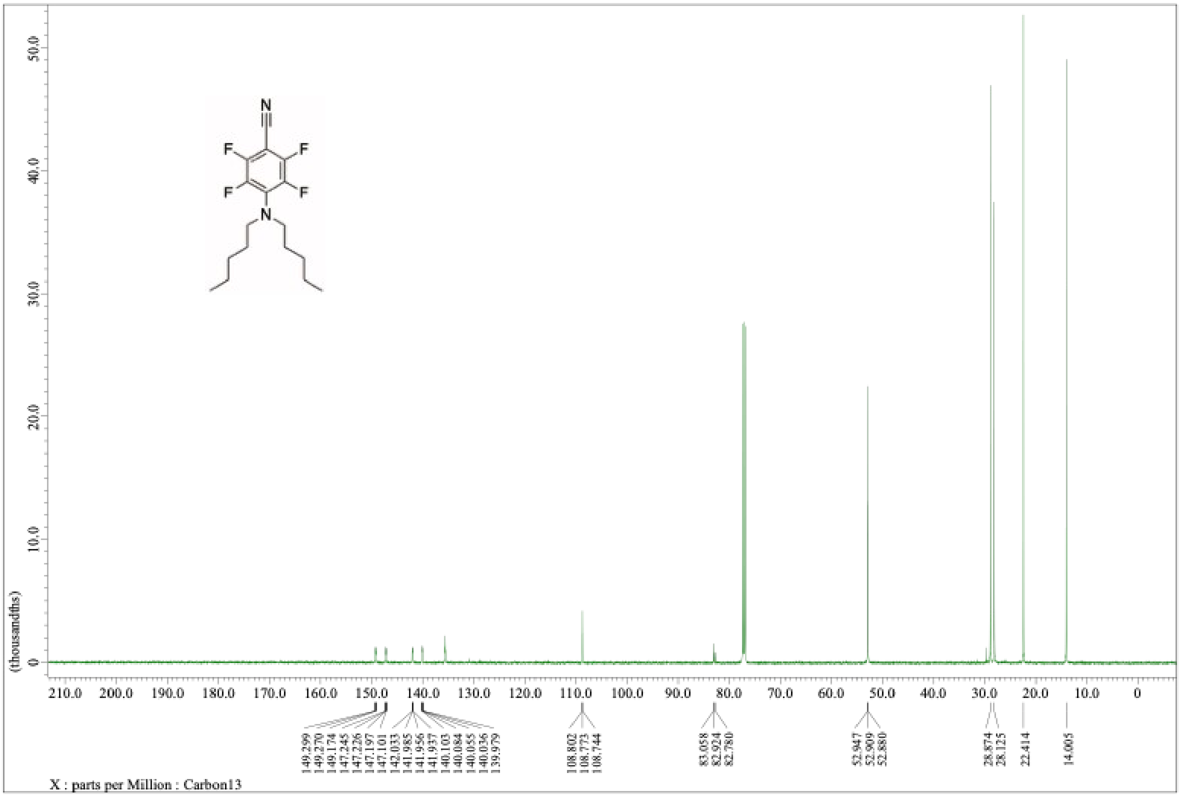
^{1}H NMR (400 MHz, CDCl$_3$) δ 3.29 (4H, t, *J* 7), 1.52 (4H, qn, *J* 7), 1.35 – 1.18 (8H, m), 0.87 (6H, t, *J* 7), ^{19}F NMR (376 MHz, CDCl$_3$) δ -135.16 – -135.30 (2F, AA'm), -149.26 – -149.43 (2F, BB'm), ^{13}C NMR (125 MHz, CDCl$_3$) δ 149.3 (dm, *J* 256), 135.6 (dm, *J* 238), 135.6 (tt, *J* 10, 3), 108.8 (t, *J* 3), 82.9 (t, *J* 17), 52.9 (t, *J* 3), 28.9, 28.1, 22.4, 14.0.



18ae ^{1}H NMR spectrum (400 MHz, $CDCl_3$)

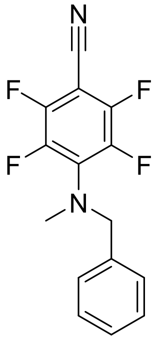


18ae ^{19}F NMR spectrum (376 MHz, CDCl$_3$)



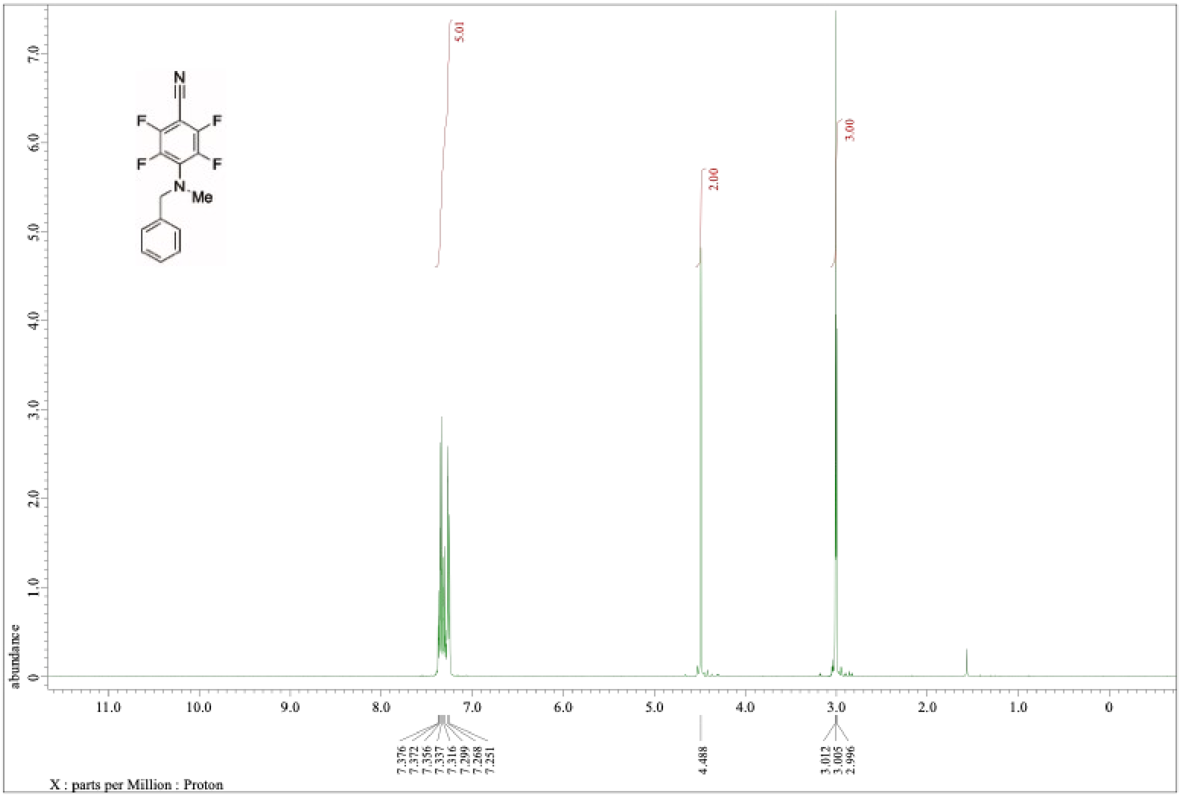
18ae ^{13}C NMR spectrum (125 MHz, CDCl$_3$)

4-(*N*-Benzyl-*N*-methylamino)-2,3,5,6-tetrafluorobenzonitrile **8af**

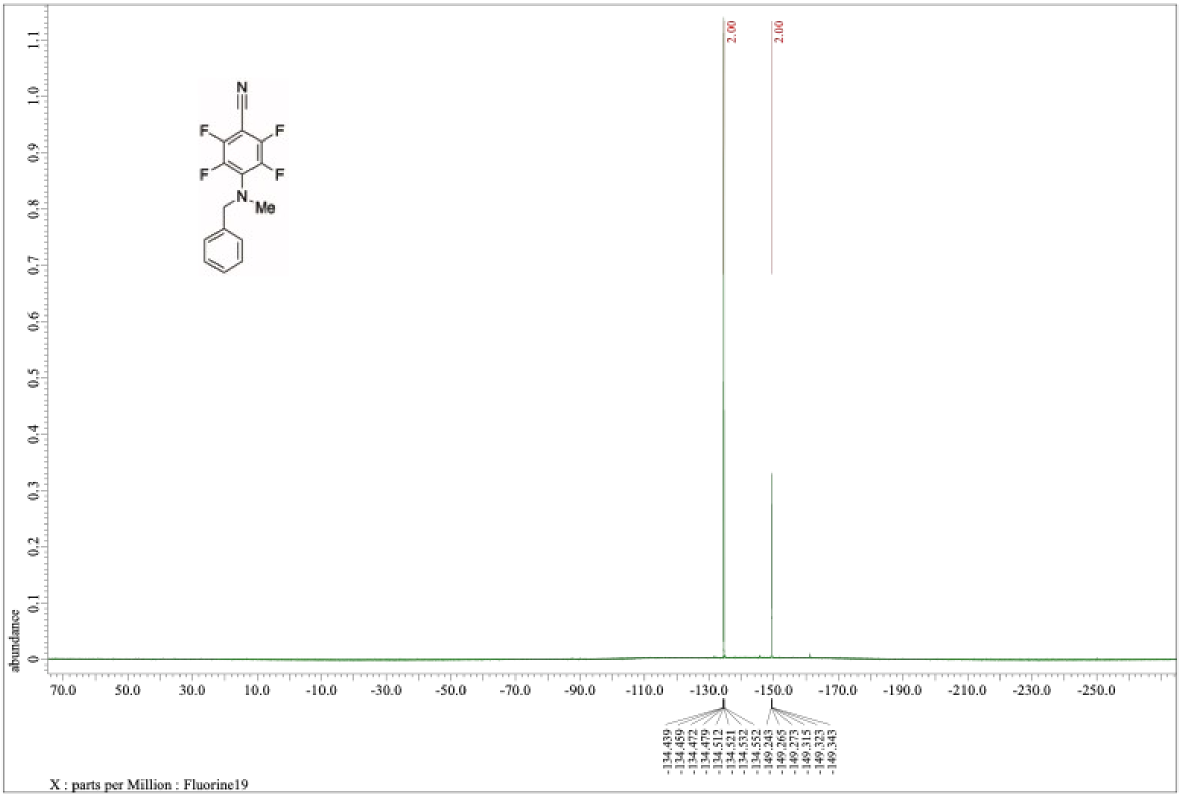


Prepared from pentafluorobenzonitrile (0.25 mL, 2.0 mmol) and *N*-benzylmethylamine (0.26 mL, 2.0 mmol) using Cyrene (0.1 mL) as LAG agent. The crude product (0.55 g, 93 %) was purified by column chromatography over silica gel (elution with hexane: ethyl acetate 20:1) to give compound **8af** as a colourless oil (0.36 g, 62 %, 1.2 mmol).

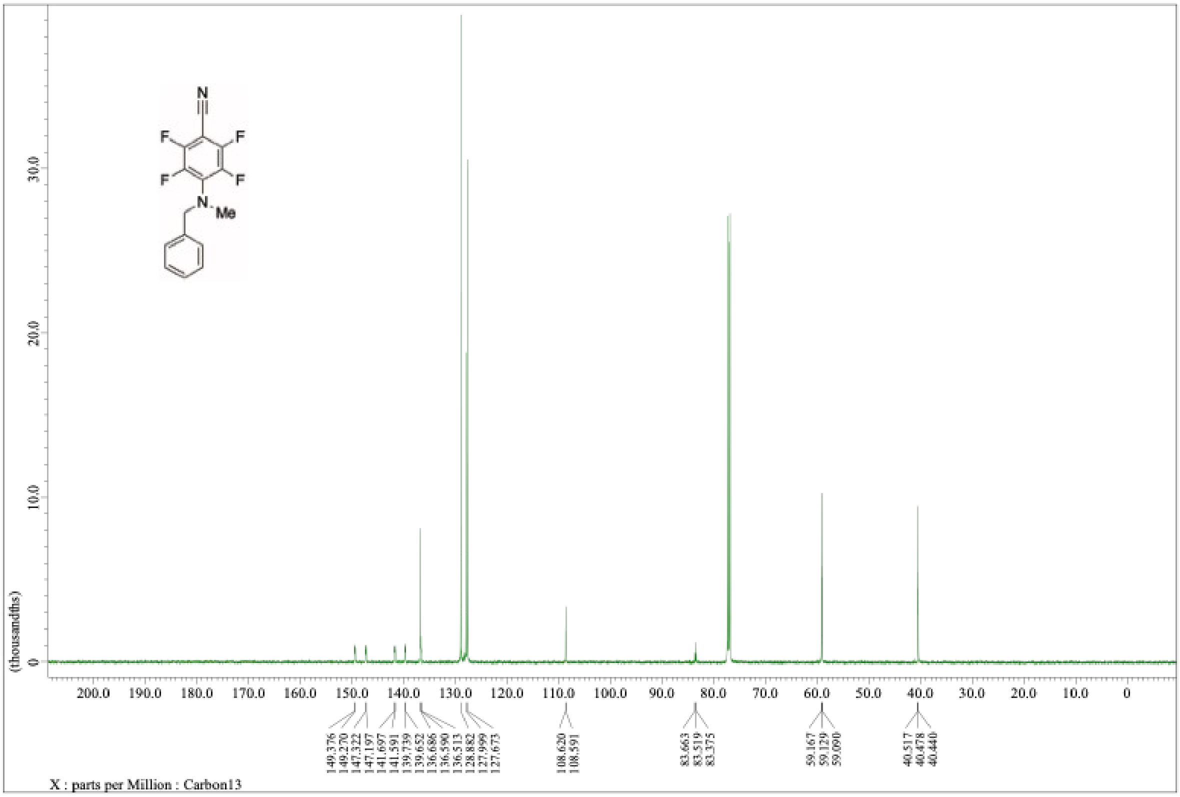
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.25 (5H, m), 4.50 (2H, s), 3.01 (3H, t, *J* 3). ^{19}F NMR (376 MHz, CDCl$_3$) δ -134.42 – -134.57 (2F, AA'm), -149.21 – -149.38 (2F, BB'm), ^{19}F NMR (125 MHz, CDCl$_3$) δ -135.16 – -135.30 (2F, AA'm), -149.26 – -149.43 (2F, BB'm), ^{13}C NMR (125 MHz, CDCl$_3$) δ 148.3 (dm, *J* 258), 140.7 (dm, *J* 245), 136.7, 136.6 (tt, *J* 10, 4), 128.9, 128.0, 127.7, 108.6 (t, *J* 4), 83.5 (t, *J* 18), 59.1 (t, *J* 5), 40.5 (t, *J* 5).



18af ^{1}H NMR spectrum (400 MHz, $CDCl_3$)

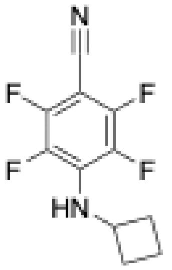


18af ^{19}F NMR spectrum (376 MHz, $CDCl_3$)



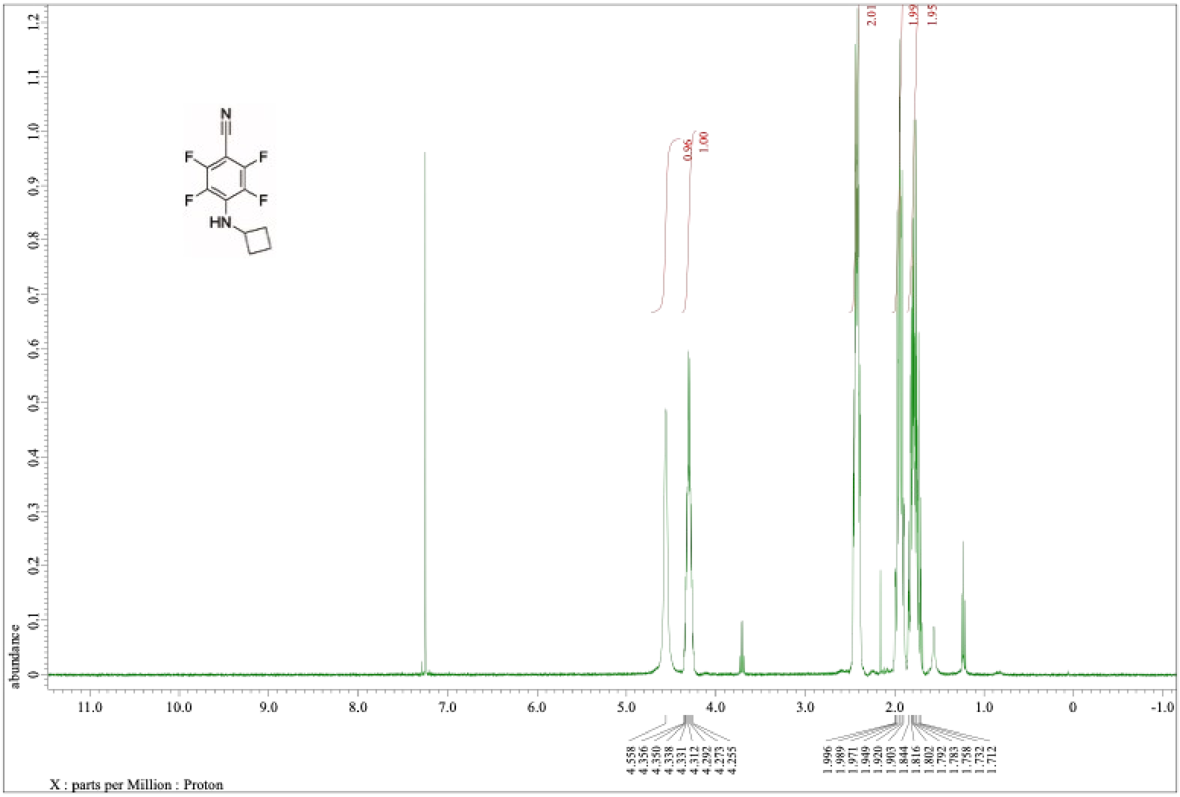
18af ^{13}C NMR spectrum (125 MHz, $CDCl_3$)

4-Cyclobutylamino-2,3,5,6-tetrafluorobenzonitrile **8ag**

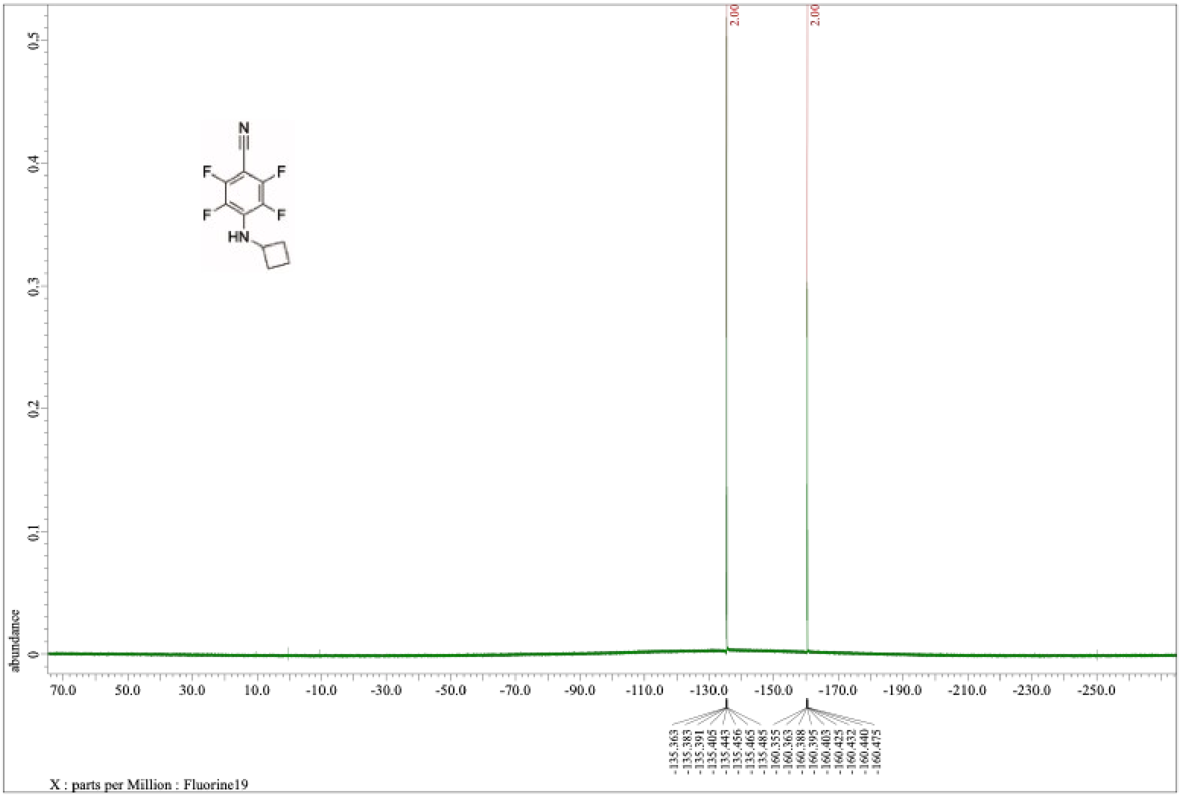


Prepared from pentafluorobenzonitrile (0.25 mL, 2.0 mmol) and cyclobutylamine (0.17 mL, 2 mmol) using Cyrene (0.1 mL) as LAG agent. Solid was formed after aqueous work-up which was recrystallized from ethanol to give **8ag** as colourless crystals (0.35 g, 72%).

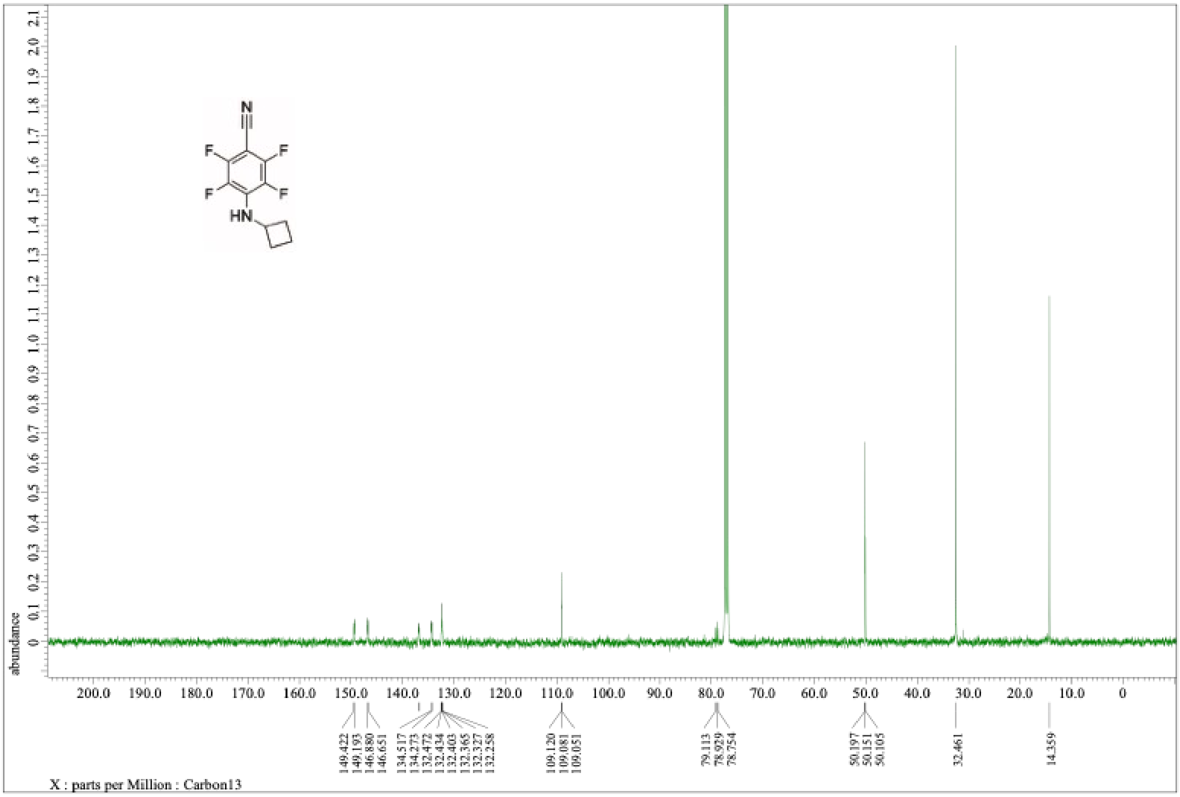
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (1H, bs), 4.36-4.26 (1H, m), 2.50-2.34 (2H, m), 2.00-1.90 (2H, m), 1.84-1.71 (2H, m), ^{19}F NMR (376 MHz, $CDCl_3$) δ -135.36 – -135.49 (2F, AA'm), -160.36 – -160.48 (2F, BB'm), ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0 (dm, *J* 254), 135.6 (dm, *J* 240), 132.4 (tt, *J* 11, 4), 109.1 (t, *J* 4), 78.9 (t, *J* 18), 50.2 (t, *J* 5), 32.5, 14,4.



18ag ^{1}H NMR spectrum (400 MHz, CDCl$_3$)



8ag ^{19}F NMR spectrum (376 MHz, $CDCl_3$)



18ag ^{13}C NMR spectrum (100 MHz, $CDCl_3$)

Reaction of 7a with morpholine without LAG agent

2,3,5,6-Tetrafluoro-4-morpholinobenzonitrile **8aa**

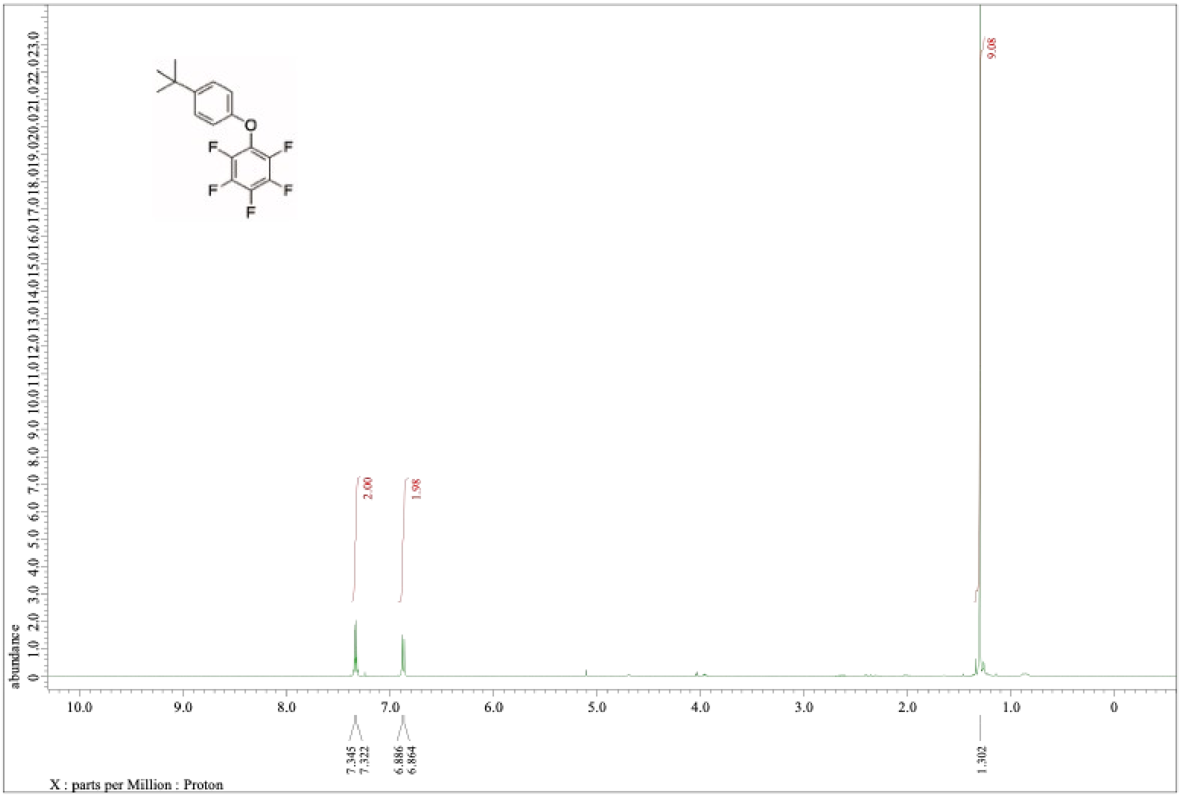
Prepared from pentafluorobenzonitrile (0.25 mL, 2.0 mmol) and morpholine (0.17 mL, 2.0 mmol) without LAG agent. The crude product was purified by column chromatography over silica gel (elution with hexane: ethyl acetate 5:1) to give compound **8aa** as a white solid (0.27 g, 52 %, 1.0 mmol), identical to a sample prepared previously.

^{1}H NMR (400 MHz,) δ 3.84 – 3.77 (4H, m), 3.43 – 3.40 (4H, m),^{19}F NMR (376 MHz,) δ -134.03 – -134.17 (2F, AA'm), -149.54 – -149.68 (2F, BB'm).

Attempted reaction of 4-(*t*-butylphenoxy)pentafluorobenzene 7f with morpholine

4-(*t*-Butylphenoxy)pentafluorobenzene **7f** (0.57 mL, 1.8 mmol) and morpholine (0.16 mL, 1.8 mmol) were milled using Cyrene (0.1 mL) as LAG agent following the general procedure above. Only 4-(*t*-butylphenoxy)pentafluorobenzene was recovered, (0.43 g, 76%, 1.4 mmol) without purification, after work-up.

^{1}H NMR (400 MHz,) δ 7.35-7.32 (2H, AA'm), 6.88-6.86 (2H, BB'm), 1.30 (9H, s).



7f ^{1}H NMR spectrum (400 MHz, $CDCl_3$)

Comparison Solution Phase Reactions

Fluoroarenes **7b**, **7c** or **11** were stirred with 1 eq. of morpholine and 2.5 eq. of triethylamine in THF at room temperature for 75 h. After aqueous work-up and crystallisation from ethanol compounds **8b**, **8c** and **12a** were obtained in 36, 52 and 19% yields respectively, identified by comparison with authentic samples as described above. Reaction of **7b** with benzimidazole with stoichiometric sodium hydride as base afforded **8bb** in a higher yield (77%) than by ball milling, but required refluxing in THF for 24 h.

Energy Usage Comparison

The ball milling method was shown to be more energy efficient than conventional thermal methods. In terms of energy used directly for conducting reaactions, the YKL-0.4L ball mill had a power rating of 750 W and was used for 30 minutes allowing four reactions to be conducted simultaneously giving an energy consumption of 0.75 kW x 0.5 h ÷ 4 = 0.09 kWh (337.5 kJ) per reaction. The hotplates stirrers used had a power rating of 550 W when heating and could be employed for typically 12 h for a single reaction conducted under reflux (some requiring longer) giving an energy consumption of 0.55 kW x 12 h = 6.6 kWh (23760 kJ) per reaction. Other energy usage during work-up, isolation and purification has not been considered.

References

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2. L. Bole, L. Davin, A. Kennedy, R. McLellan and E. Hevia, *Chem. Commun.*, 2019, **55**, 4339-4342.
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4. H. Althagbi, J. Lane, G. Saunders and S. Webb, *J. Fluorine Chem.*, 2014, **166**, 88-95.

5. A. S. Bhambra, M. Edgar, M. R.J. Elsegood, Y. Li, G. W. Weaver, R. R.J. Arroo, V. Yardley, H. Burrell-Saward, V. Krystof, *Euro. J. Med. Chem*., 2016, **108**, 347-353.