SUPPORTING INFORMATION

for

Real-time spectroscopic analysis enabling the full and safe consumption of fluoroform during nucleophilic trifluoromethylation in flow.

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Numbers of pages: 35

Numbers of figures: 1 (S1) plus 42 figures containing NMR spectra.

Content

S1. General experimental section.

1H-NMR spectra were recorded on a Bruker Avance DRX-600 spectrometer with the residual solvent peak as the internal reference (CHCl3 = 7.26 ppm). 1H resonances are reported to the nearest 0.01 ppm. 13C-NMR spectra were recorded on the same spectrometers with the central resonance of the solvent peak as the internal reference (CDCl3 = 77.16 ppm). All 13C resonances are reported to the nearest 0.1 ppm. The multiplicity of 1 H signals are indicated as: s = singlet, d = doublet, t = triplet, m = multiplet, br. = broad, or combinations of thereof. Coupling constants (J) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. ^{19}F NMR spectra were recorded on a 43 MHz Magritek Spinsolve Spectrometer. Chemical shifts are reported in ppm with $PhCF_3$ as the internal standard ($PhCF_3$: -63.46 ppm). Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. High resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier™ spectrometer using time of flight with positive ESI, or conducted by Mr Paul Skelton on a Bruker BioApex 47e FTICR spectrometer using (positive) ESI or EI at 70 eV within a tolerance of 5 ppm of the theoretically calculated value. LC-MS analysis was performed on an Agilent HP 1100 series chromatography (Mercury Luna 3u C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionization source in ESI mode. Elution was carried out at a flow rate of 0.6 mL min-1 using a reverse phase gradient of acetonitrile and water containing 0.1% formic acid. Retention time (Rt) is given in min to the nearest 0.1 min and the m/z value is reported to the nearest mass unit (m.u.). Unless stated otherwise, reagents were obtained from commercial sources and used without purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. Unless otherwise stated, yields of compounds were calculated based on the isolated compounds estimated. Flash column chromatography was performed using high-purity grade silica gel (Merck grade 9385) with a pore size 60 Å and 230–400 mesh particle size under air pressure. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated glass backed plates and visualized by ultraviolet radiation (254 nm) and/or potassium permanganate solution as appropriate.

All the flow reactions were performed using a Uniqsis FlowSyn module. In-line IR spectroscopy was performed using the Mettler Toledo FlowIR®. The solution of chlorotrimethylsilane was dispensed using a Masterflex peristaltic. Back pressure regulator is indicated as BPR. All gas-flow reactions were performed with a tube-in-tube reactor as described to introduce gases into a continuous flow stream.

S2. Spinsolve Benchtop NMR Spectroscopy: Inline and online monitoring carried with benchtop Magritek Spinsolve©.

1H probe with detection using a solenoid coil at a frequency of 43.62 MHz. 19F probe with detection using a solenoid coil at a frequency of 40.89 MHz. Magnet temperature of 29 °C Resolution at 50% peak height: linewidth < 20Hz. Fast automatic hardware lock using an external lock configuration (allows use of non-deuterated solvent). Automated shimming using a 10% H2O in D2O mixture. NMR data collected automatically with Spinsolve software and processed automatically using MNOVA© software. Reaction Monitoring (RM) protocol, for inline experiment, capture sequence of 1D proton and 1D Fluorine single scans at user selected time intervals. Processing data as stacked spectra in MNOVA. Following the script:

```
TimeStampFolder        = "c:/ReactionMonitor/1H + 19F"
ProtonPhase            = "FirstScan"
FluorinePhase          = "FirstScan"

# Loop
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 RunProtocol("1D EXTENDED+", ["Number=4", "RepetitionTime=10", "PulseAngle=90",
"AcquisitionTime=6.4"])
 wait(00:00:10:000)
 RunProtocol("1D FLUORINE+", ["Number=16", "RepetitionTime=4", "PulseAngle=90",
"AcquisitionTime=1.64"])
endloop

wait(00:00:10:000)
RunMnovaFile("ScriptUtilities/ReactionMonitor.qs", "process", ["1H"])
wait(00:00:10:000)
RunMnovaFile("ScriptUtilities/ReactionMonitor.qs", "process", ["19F"])
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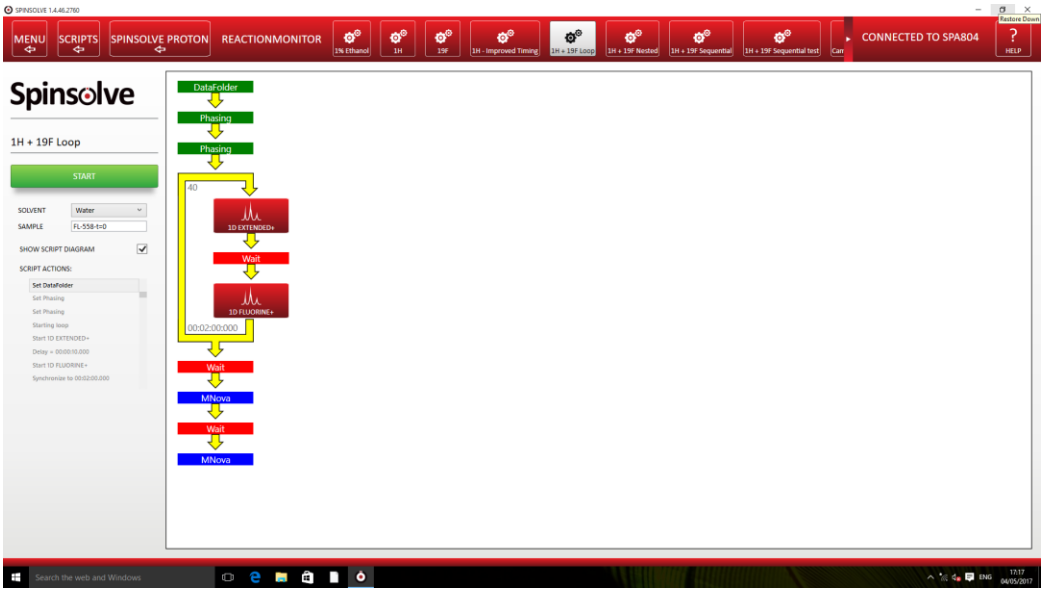


Figure S1. Reaction Monitoring (RM) Script.

S3. General procedure for the preparation of 3a in flow.

A solution of the benzophenone **2a** (2.0 mmol) in THF (2.0 mL) was loaded (0.2 ml/min) into a 2.0 mL PTFE sample loop and a solution of KHMDS (1.0 M) in THF (2.0 mL) was loaded (0.2 ml/min) into a second 2.0 mL PTFE sample loop. A third solvent stream (THF) enriched with CF_3H (3 bar) from the tube-in-tube gas-liquid reactor was pumped (0.2 mL/min). These three streams were mixed at a 4-ways cross connection valve for high pressure. The combined substrate, base and enriched CF_3H streams were directed to the cooling PTFE coil (14 mL, -20 °C) of the Polar Bear Plus system. The total residence time in the cooled flow coil was 23.33 min. On exiting the cooling coil, the product flow stream was directed through the FlowIR device and, next, the benchtop NMR machine. A backpressure regulator (75 psi) was placed immediately after the benchtop NMR instrument to prevent out-gassing of the dissolved CF_3H from the solvent mixture. The product stream was then collected into a round bottom flask, containing a saturated solution of NH_4Cl and extracted with Et_2O (10 mL×3). The combined organic phase was dried over Na_2SO_4, after removing the solvent under vacuum, the residue was purified by column chromatography to give the product.

S4. General procedure for the preparation of 4a-4f in flow.

A solution of the ketone **2** (0.6 mmol) in THF (2.0 mL) was loaded (0.2 ml/min) into a 2.0 mL PTFE sample loop and a solution of KHMDS (1.0 M) in THF (2.0 mL) was loaded(0.2 ml/min) into a second 2.0 mL PTFE sample loop. A third solvent stream (THF) enriched with CF_3H (3 bar) from the tube-in-tube gas-liquid reactor was pumped (0.2 mL/min). These three strams were mixed at a 4-ways cross connection valve for high pressure. The combined substrate, base and enriched CF_3H streams were directed to the cooling PTFE coil (14 mL, -20 °C) of the Polar Bear Plus system. The total residence time in the cooled flow coil was 23.33 min. On exiting the cooling coil, the product flow stream was directed through the FlowIR device and, *via* a T-piece, was mixed with a fourth stream containing a solution of $ClSiMe_3$ in THF (0.3 M) and directed to a second PTFE coil (16 ml, room temperature). On exiting the coil, the product flow stream was directed through the benchtop NMR machine. A backpressure regulator (75 psi) was placed immediately after the benchtop NMR instrument to prevent out-gassing of the dissolved CF_3H from the solvent mixture. The product stream was then collected into a round bottom flask, containing a saturated solution of NH_4Cl and extracted with Et_2O (10 mL×3). The combined organic phase was dried over Na_2SO_4, after removing the solvent under vacuum, the residue was purified by column chromatography to give the product.

S5. General procedure for the preparation of 6a-6g in flow.

A solution of the aldehyde **5** (0.6 mmol) in DMF (2.0 mL) was loaded (0.2 ml/min) into a 2.0 mL PTFE sample loop and a solution of KOtBu (1.0 M) in THF (2.0 mL) was loaded (0.2 ml/min) into a second 2.0 mL PTFE sample loop. A third solvent stream (THF) enriched with CF_3H (3 bar) from the tube-in-

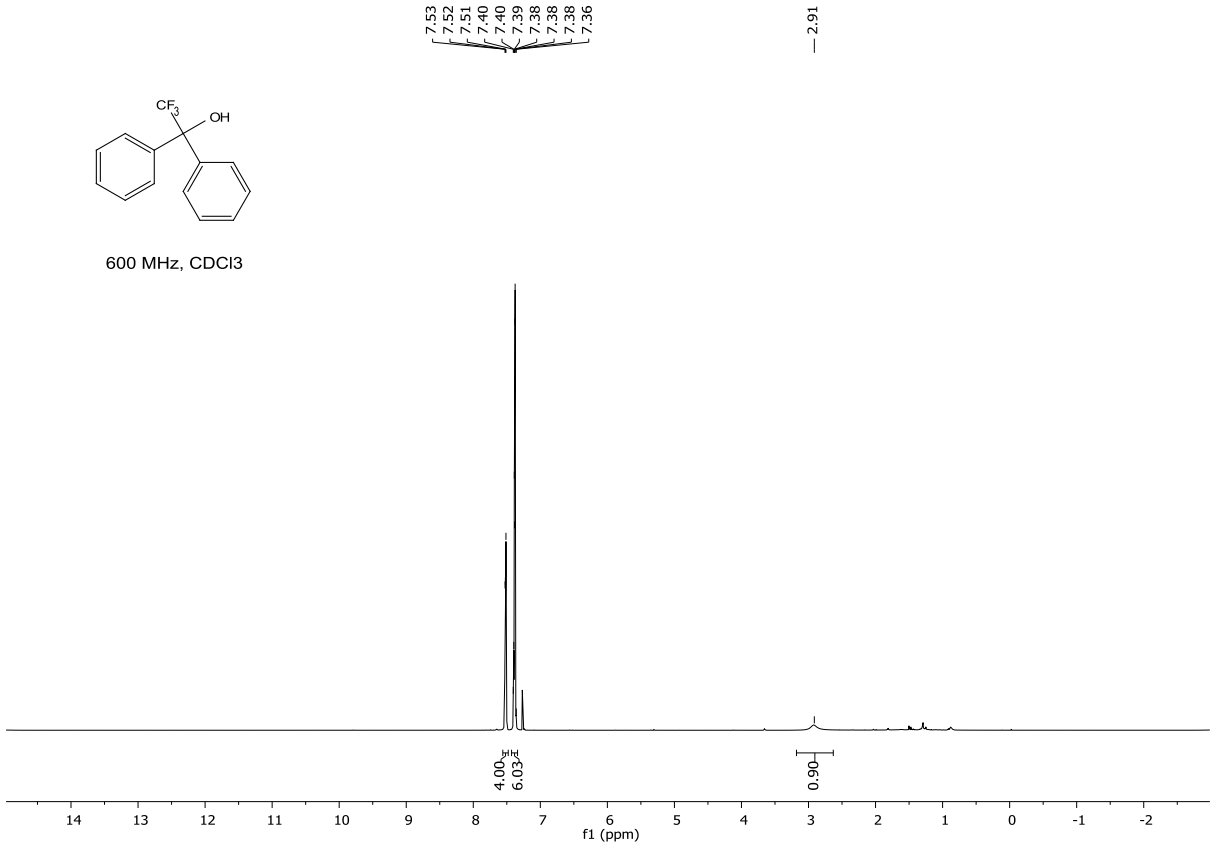
tube gas-liquid reactor was pumped (0.2 mL/min). These three strams were mixed at a 4-ways cross connection valve for high pressure. The combined substrate, base and enriched CF_3H streams were directed to the cooling PTFE coil (16 mL, -20 °C) of the Polar Bear Plus system. The total residence time in the cooled flow coil was 23.33 min. On exiting the cooling coil, the product flow stream was directed through the FlowIR device and, next, the benchtop NMR machine. A backpressure regulator (75 psi) was placed immediately after the benchtop NMR instrument to prevent out-gassing of the dissolved CF_3H from the solvent mixture. The product stream was then collected into a round bottom flask, containing a saturated solution of NH_4Cl and extracted with Et_2O (10 mL×3). The combined organic phase was dried over Na_2SO_4, after removing the solvent under vacuum, the residue was purified by column chromatography to give the product.

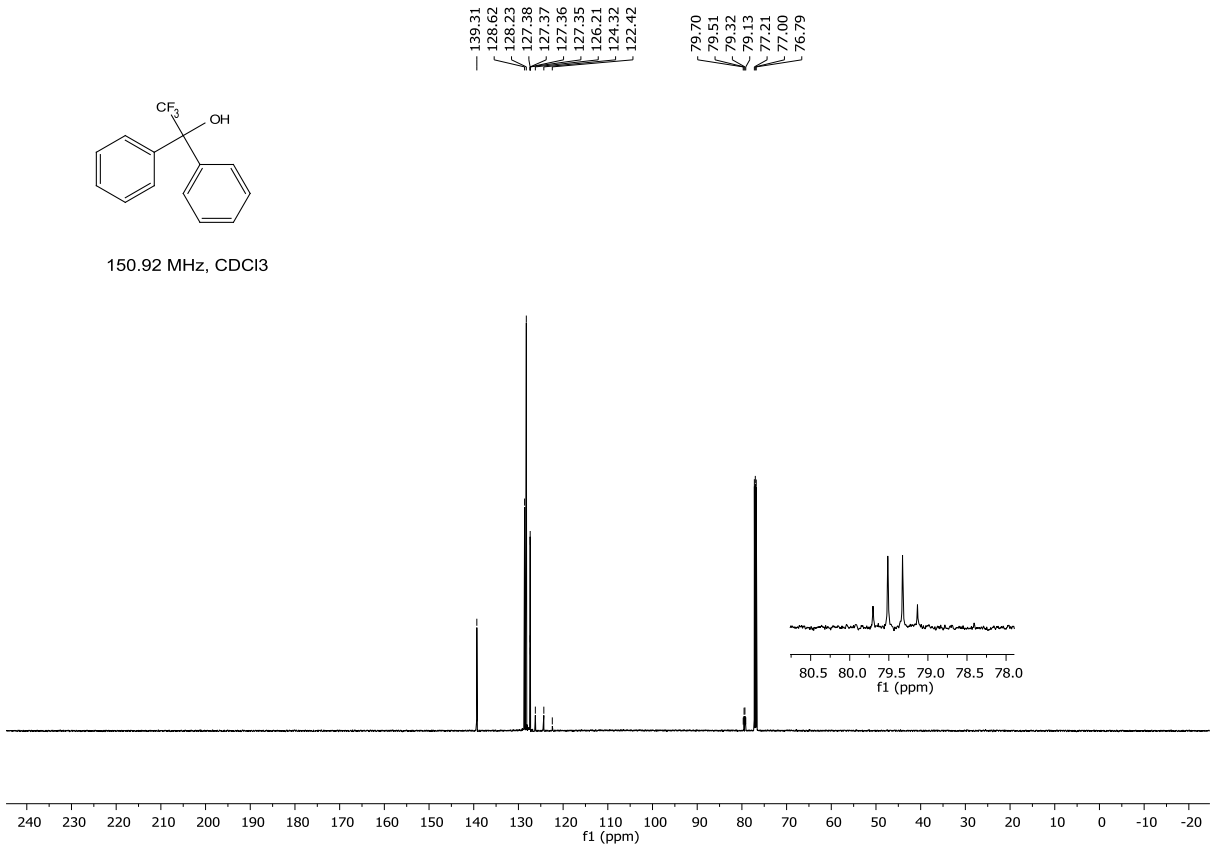
S6. General procedure for the preparation of 8 in flow.

A solution of the Et_3SiCl **7** in THF (2.0 M) was loaded (0.1 ml/min) into a 2.0 mL PTFE sample loop and a solution of KHMDS (1.0 M) in THF (2.0 mL) was loaded (0.1 ml/min) into a second 2.0 mL PTFE sample loop. A third solvent stream (THF) enriched with CF_3H (3 bar) from the tube-in-tube gas-liquid reactor was pumped (0.1 mL/min). These three streams were mixed at a 4-ways cross connection valve for high pressure. The combined substrate, base and enriched CF_3H streams were directed to the cooling PTFE coil (14 mL, -40 °C) of the Polar Bear Plus system. The total residence time in the cooled flow coil was 46.66 min. On exiting the cooling coil, the product flow stream was directed through the FlowIR device and, next, the benchtop NMR machine. A backpressure regulator (75 psi) was placed immediately after the benchtop NMR instrument to prevent out-gassing of the dissolved CF_3H from the solvent mixture. The formation of the product **8** was determined by NMR using $PhCF_3$ as internal standard.

S7. Spectral characterization of compounds 3a, 4a-4f, 6a-6g.

2,2,2-trifluoro-1,1-diphenylethanol, 3a. Isolated by flash chromatography (pentane/acetone 95/5), 97% yield. The NMR spectra are in accordance with the reported data.[1]

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79.13
77.21
77.00
76.79
CF3
OH
150.92 MHz, CDCl3
80.5 80.0 79.5 79.0 78.5 78.0
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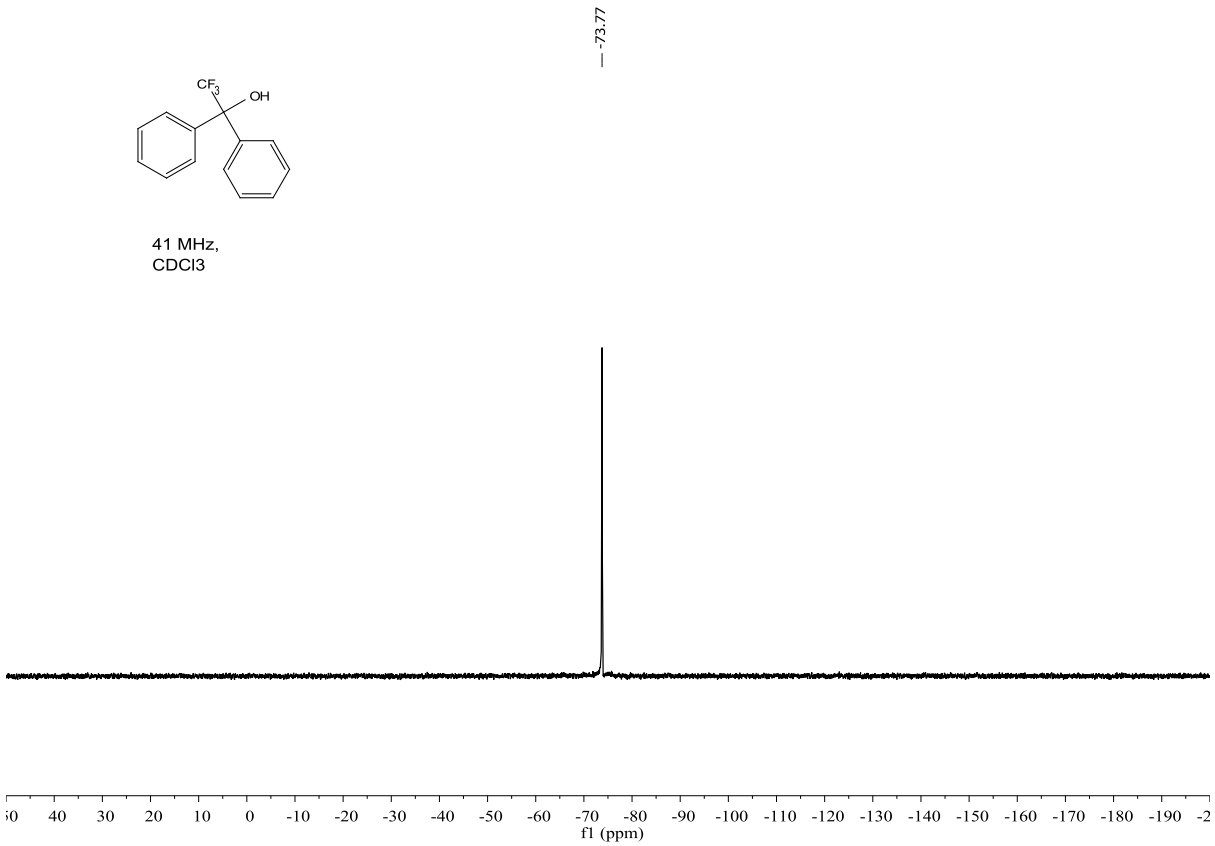
f1 (ppm)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41 MHz,
CDCl3
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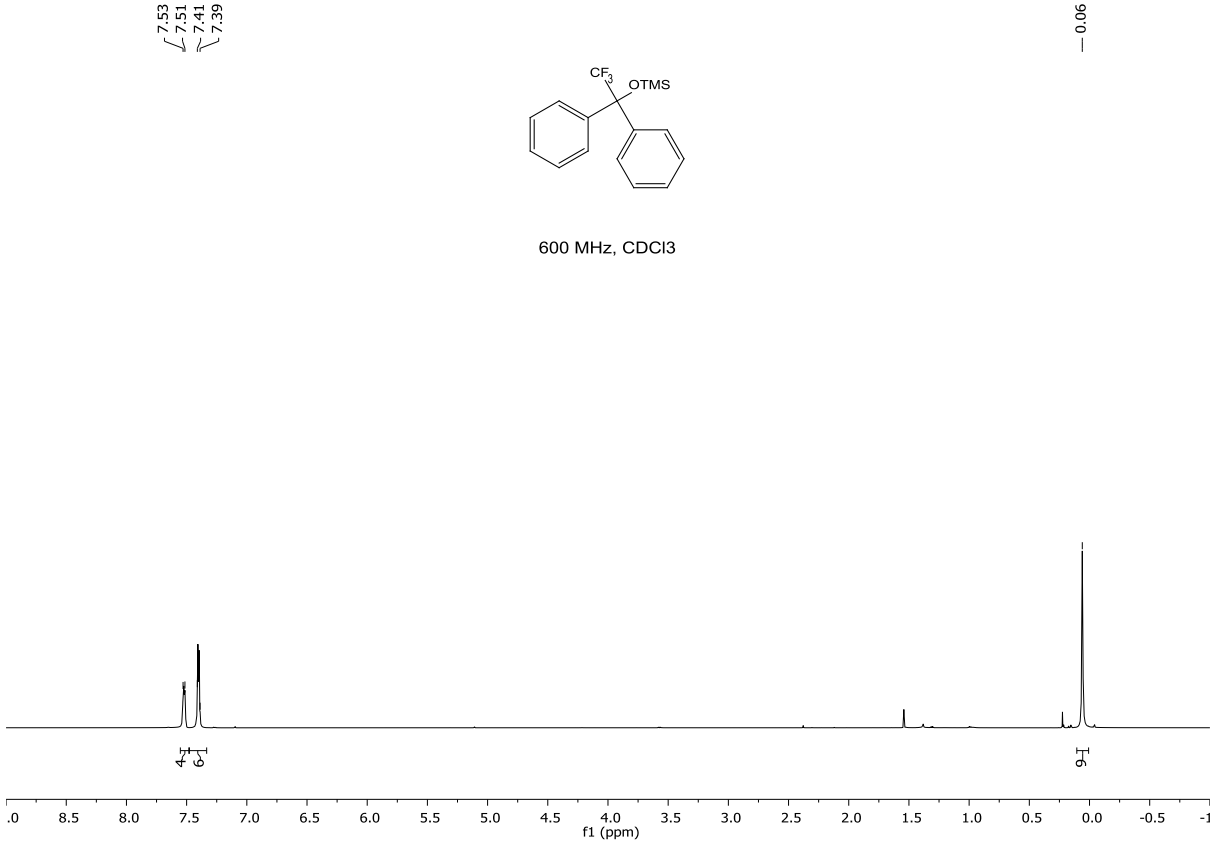
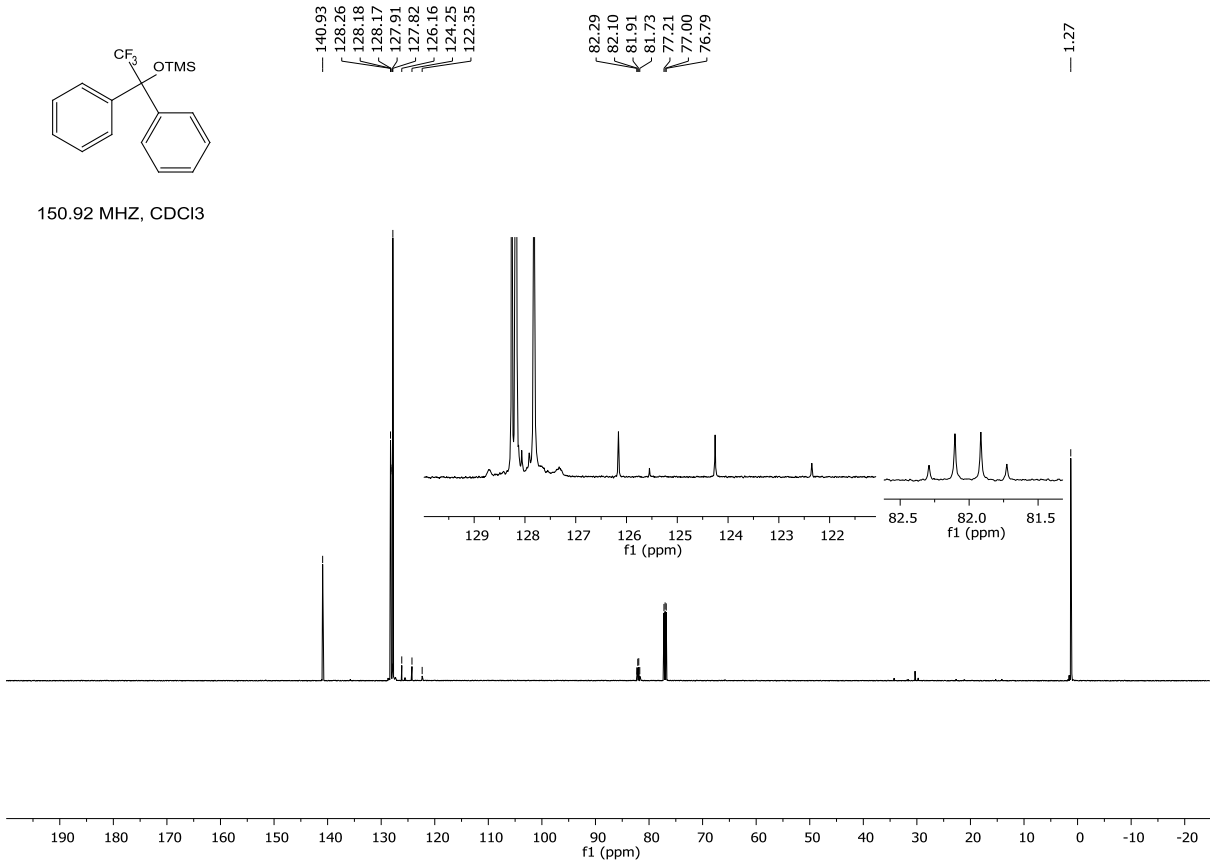
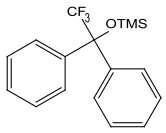
f1 (ppm)

(2,2,2-Trifluoro-1,1-diphenylethoxy)trimethylsilane, 4a. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 95% yield. The NMR spectra are in accordance with the reported data.[2]



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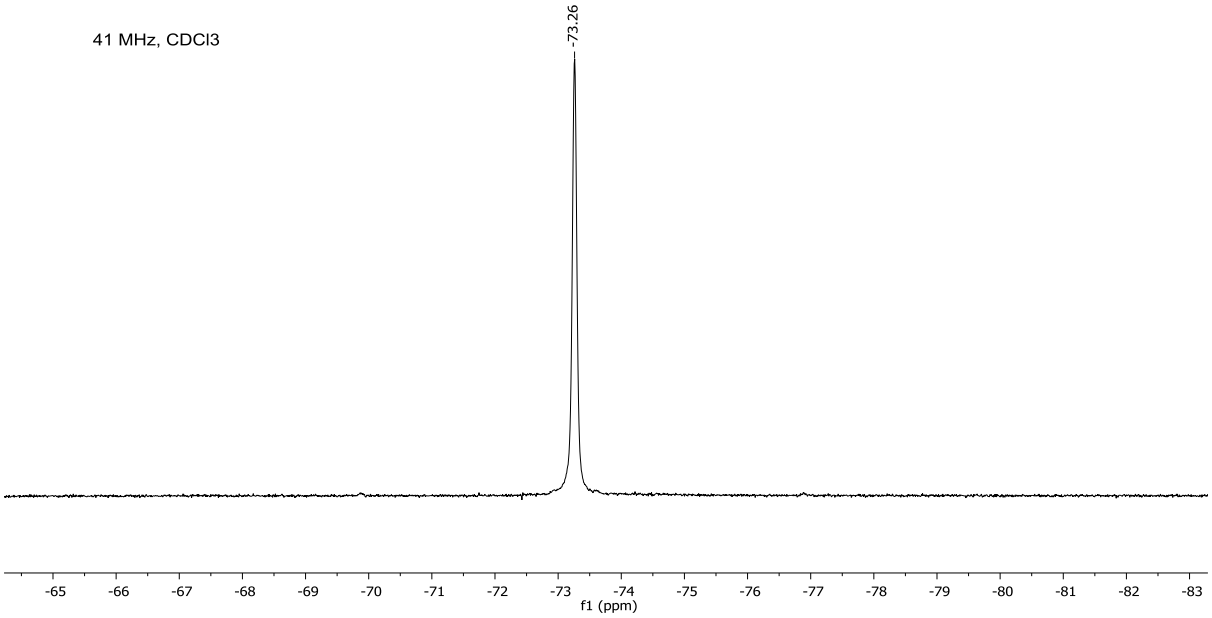
41 MHz, CDCl3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-71
-72
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-74
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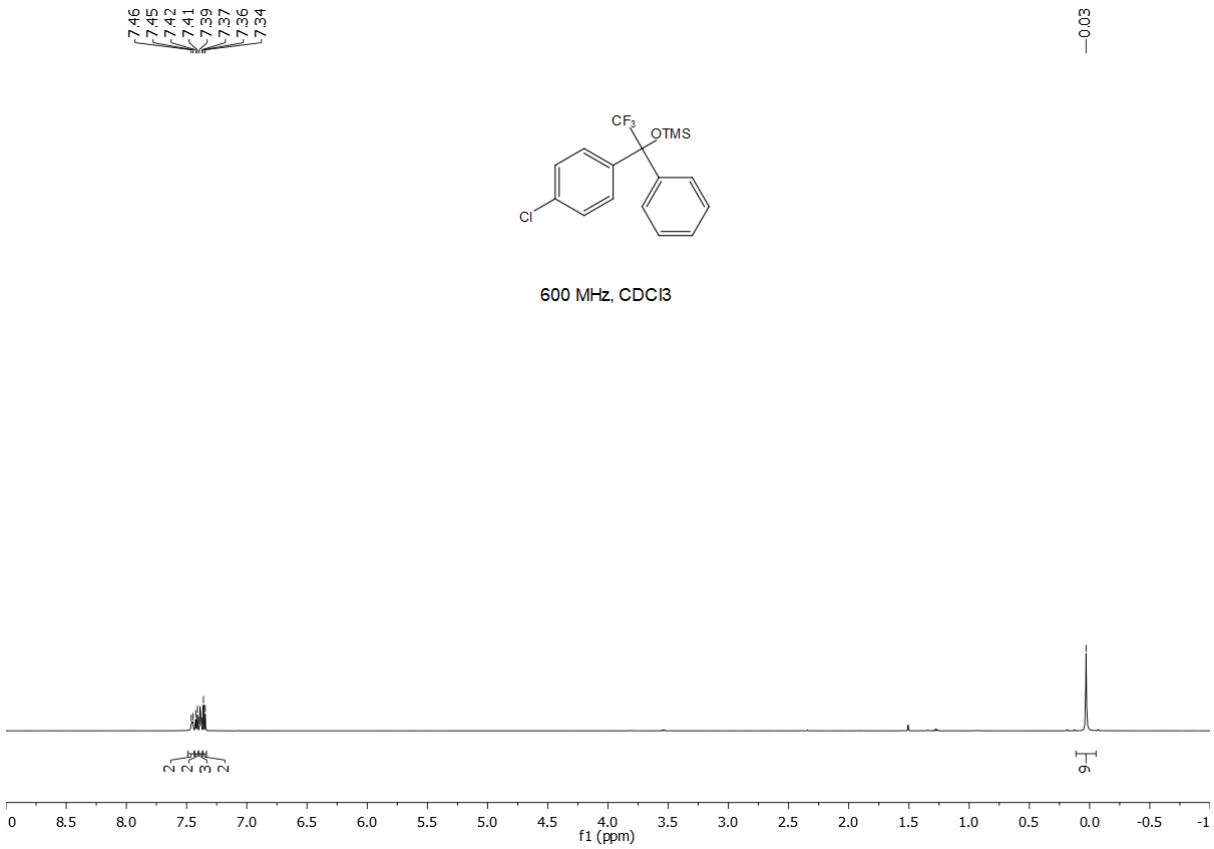
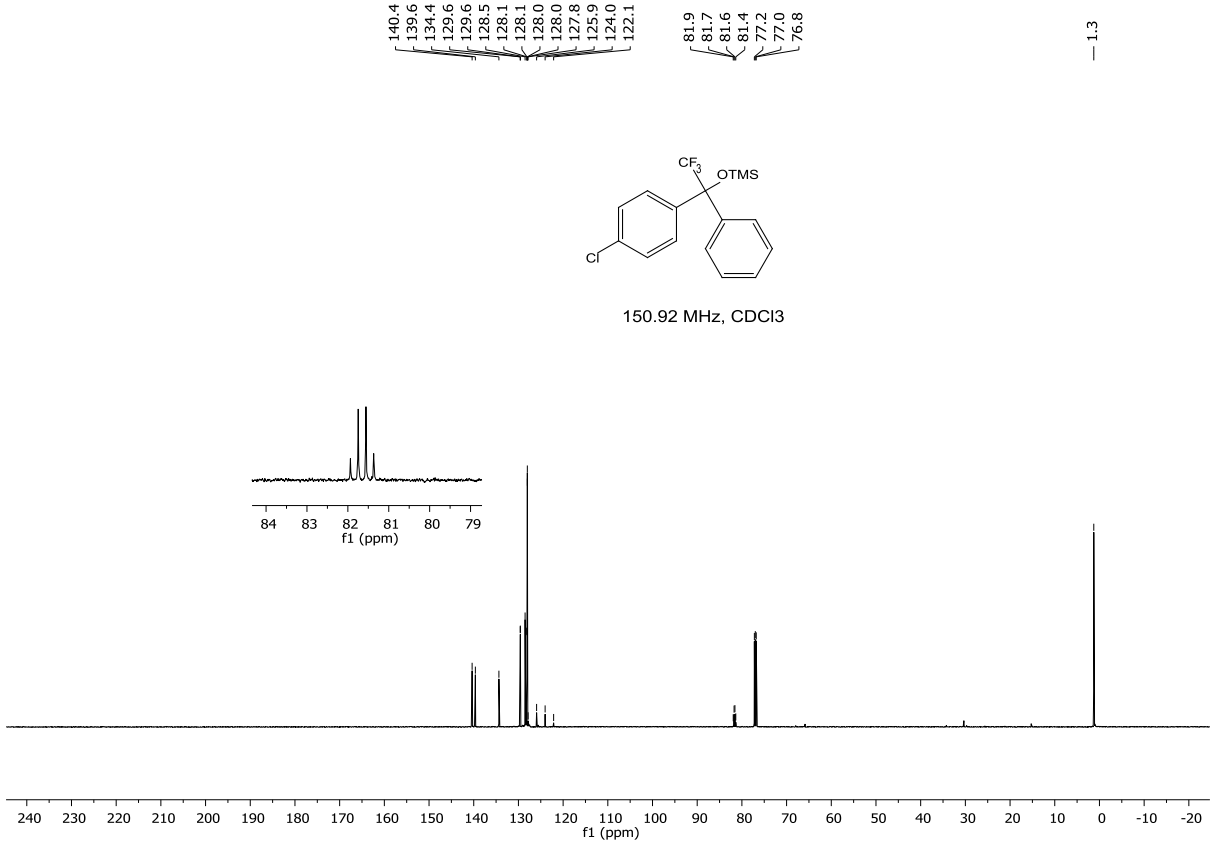
-76
-77
-78
-79
-80
-81
-82
-83
f1 (ppm)

(1-(4-Chlorophenyl)-2,2,2-trifluoro-1-phenylethoxy)trimethylsilane, 4b. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 90% yield. The NMR spectra are in accordance with the reported data.[3]

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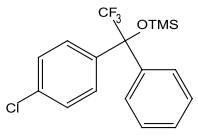
122.1
81.9
81.7
81.6
81.4
77.2
77.0
76.8
1.3
CF3
OTMS
Cl
150.92 MHz, CDCl3
84 83 82 81 80 79
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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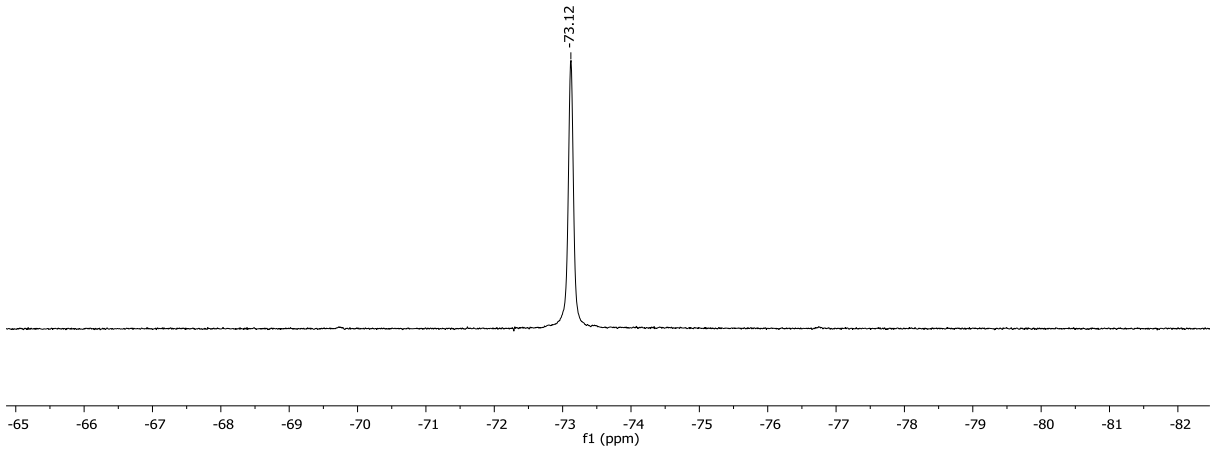
OTMS
Cl

41 MHz, CDCl3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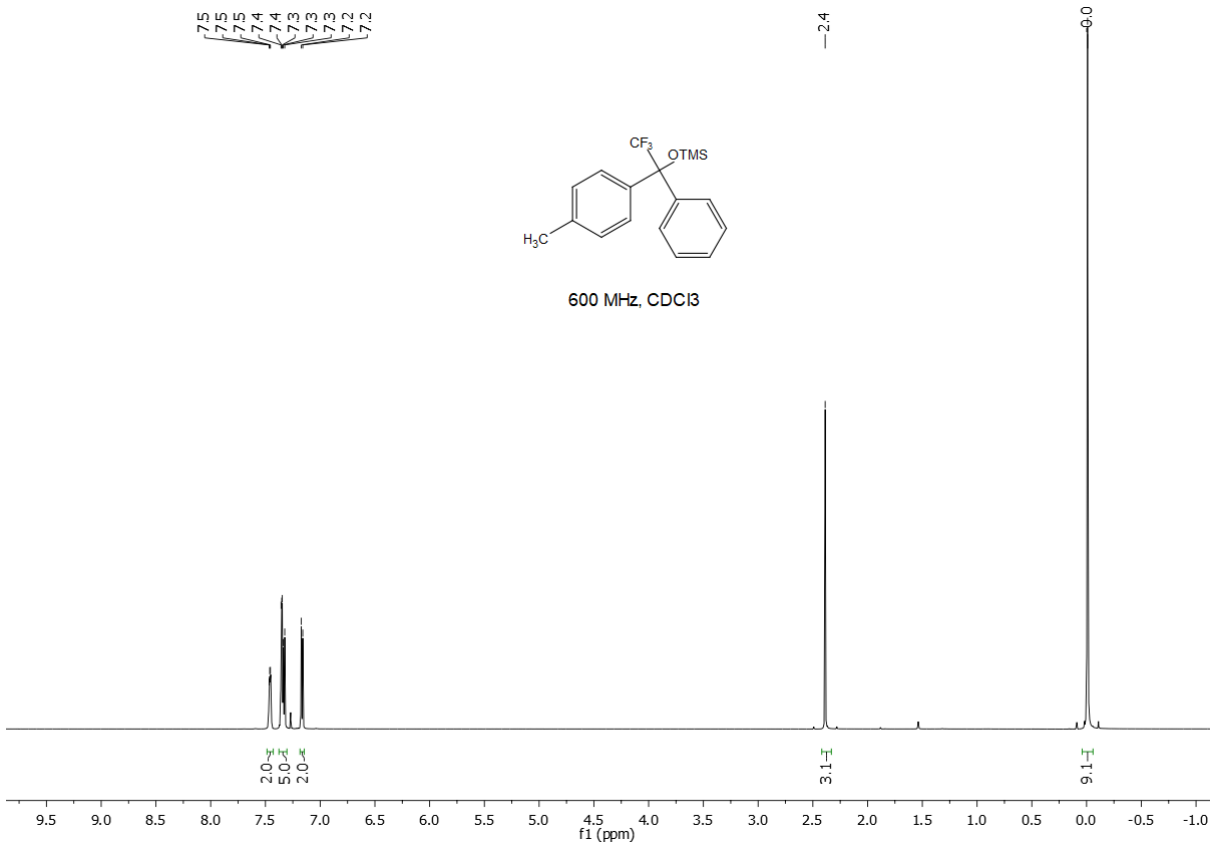
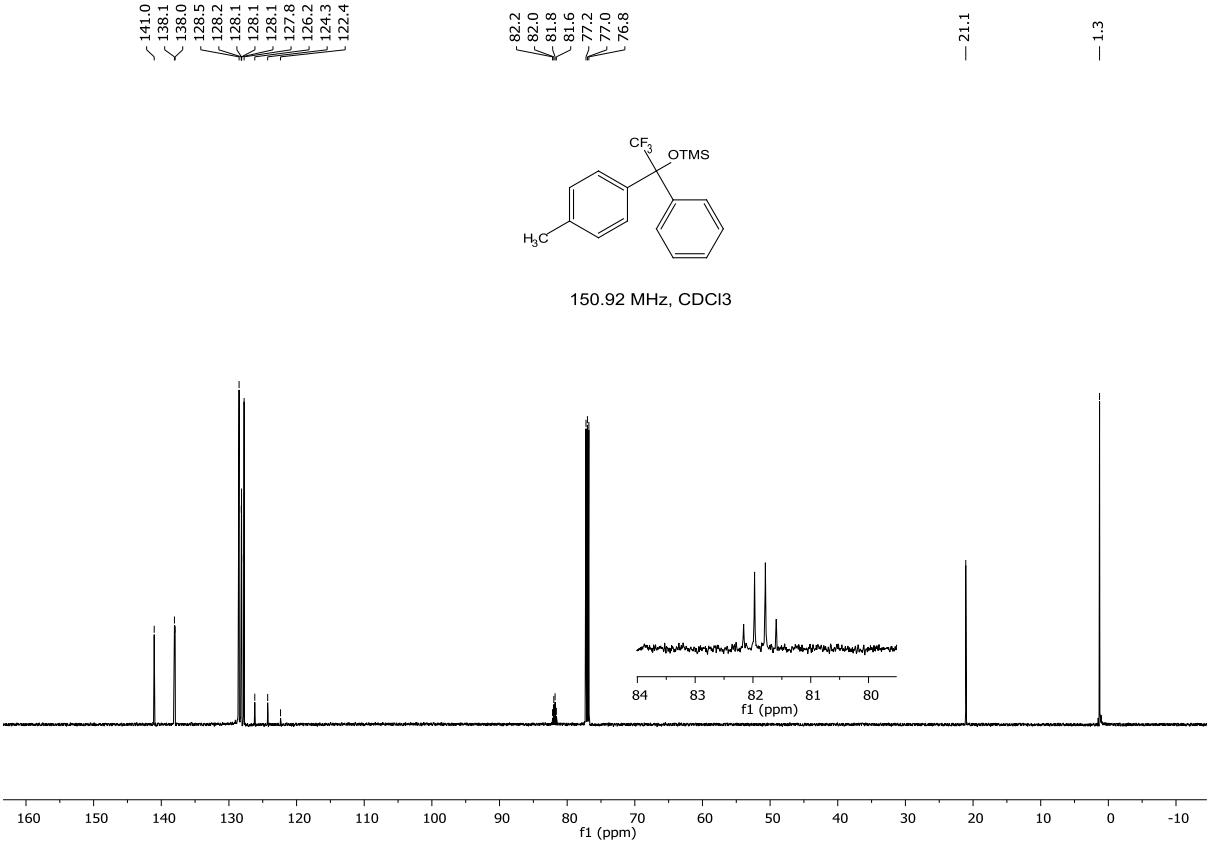
-65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82
f1 (ppm)

(2,2,2-Trifluoro-1-phenyl-1-*p*-tolylethoxy)trimethylsilane, 4c. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 88% yield. The NMR spectra are in accordance with the reported data.[2]

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82.0
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81.6
77.2
77.0
76.8
21.1
1.3
CF3
OTMS
H3C
150.92 MHz, CDCl3
84
83
82
81
80
f1 (ppm)
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140
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80
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60
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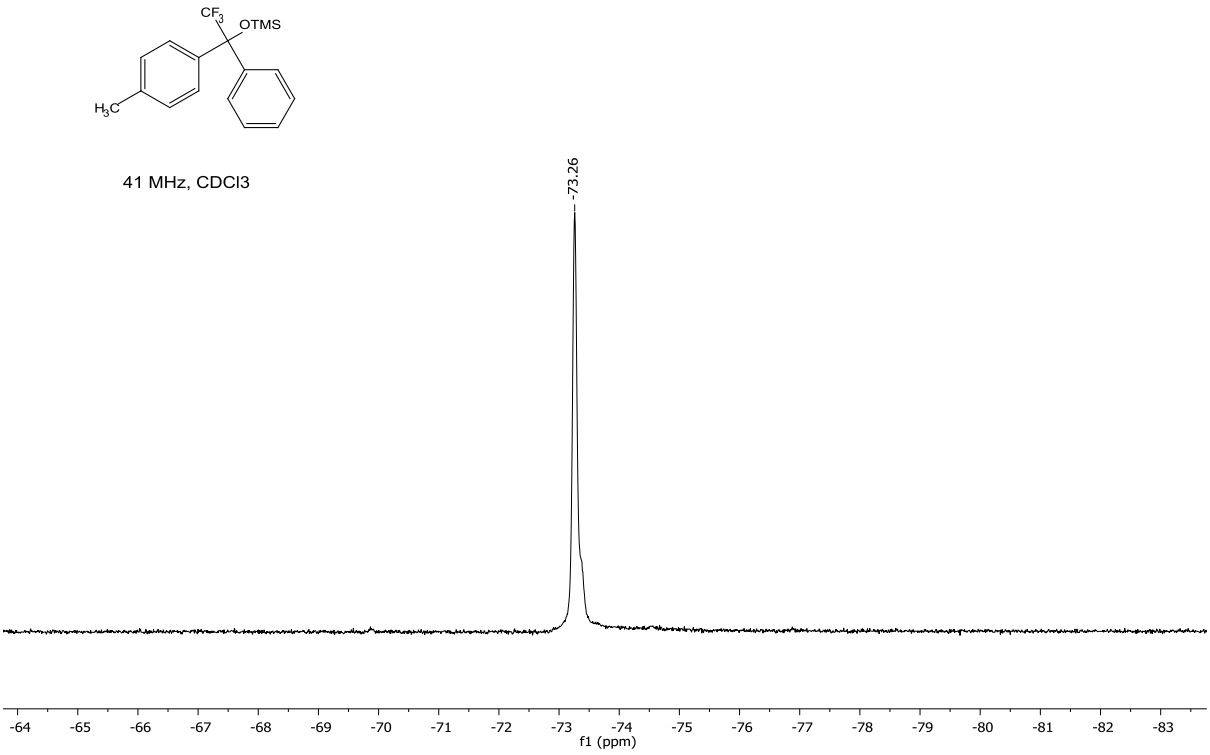
f1 (ppm)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-76
-77
-78
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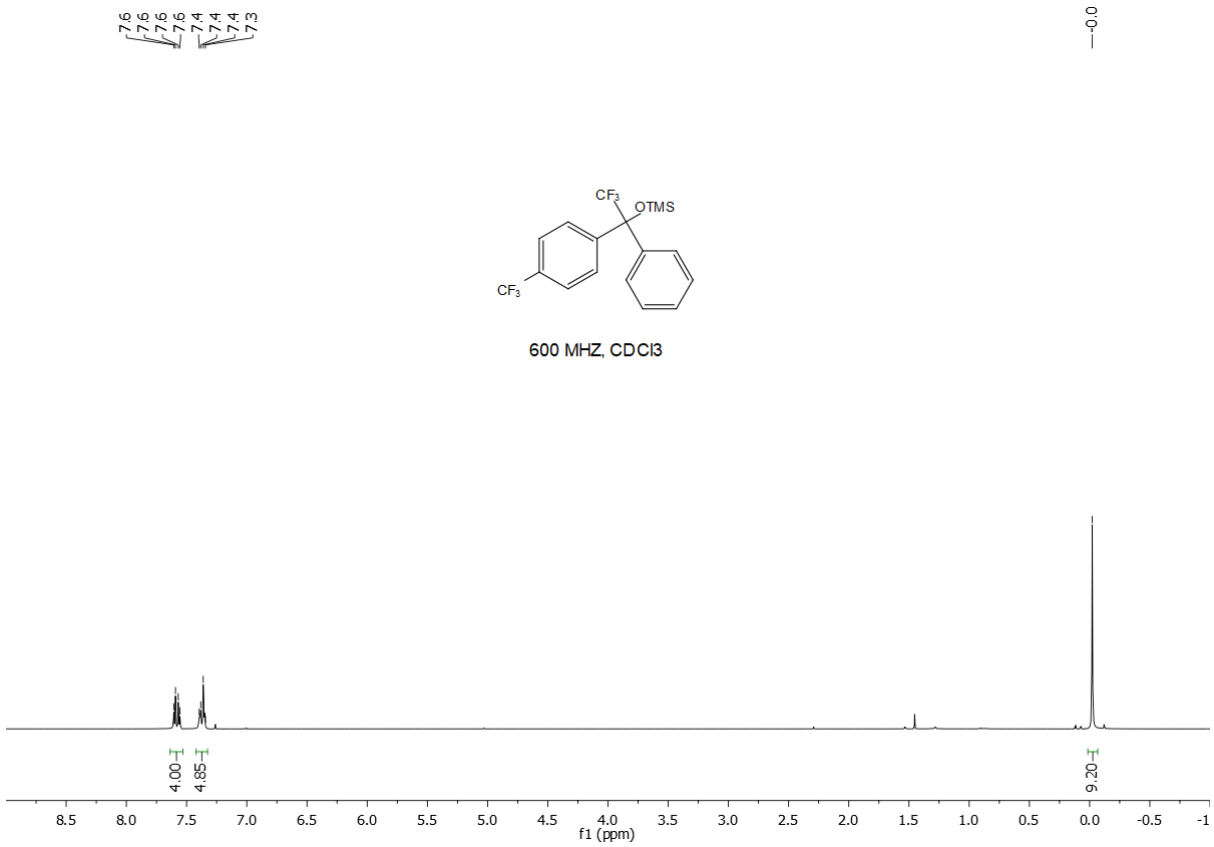
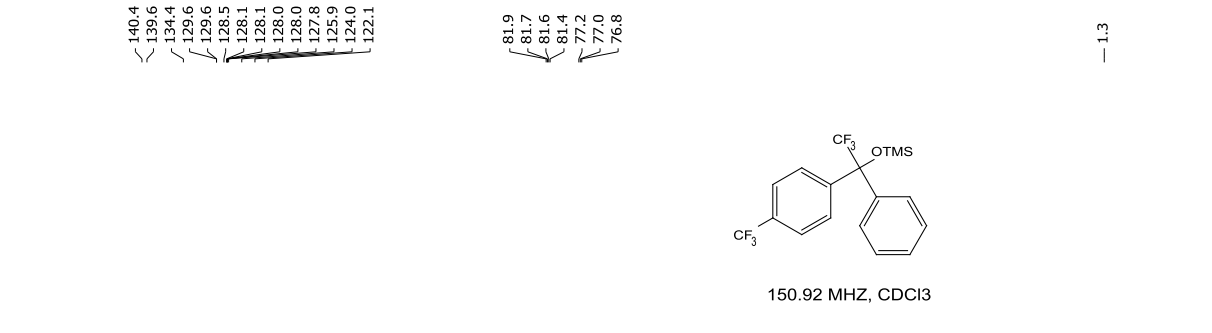
-83
f1 (ppm)

(2,2,2-Trifluoro-1-(4-(trifluoromethyl)phenyl)-1-phenylethoxy)trimethylsilane, 4d. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 71% yield. The NMR spectra are in accordance with the reported data.[2]

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81.4
77.2
77.0
76.8
1.3
CF3
OTMS
CF3
150.92 MHZ, CDCl3
84 83 82 81 80 79
f1 (ppm)
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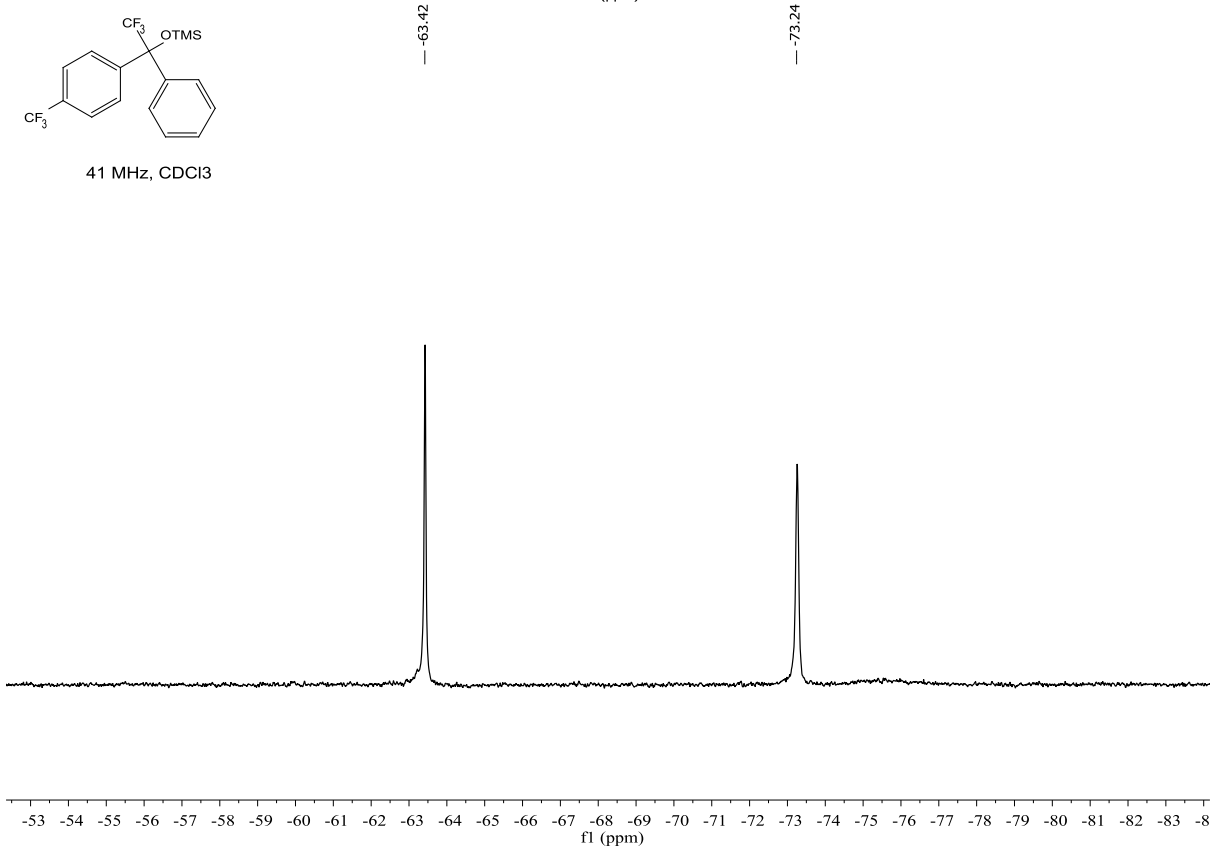
f1 (ppm)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OTMS
CF3
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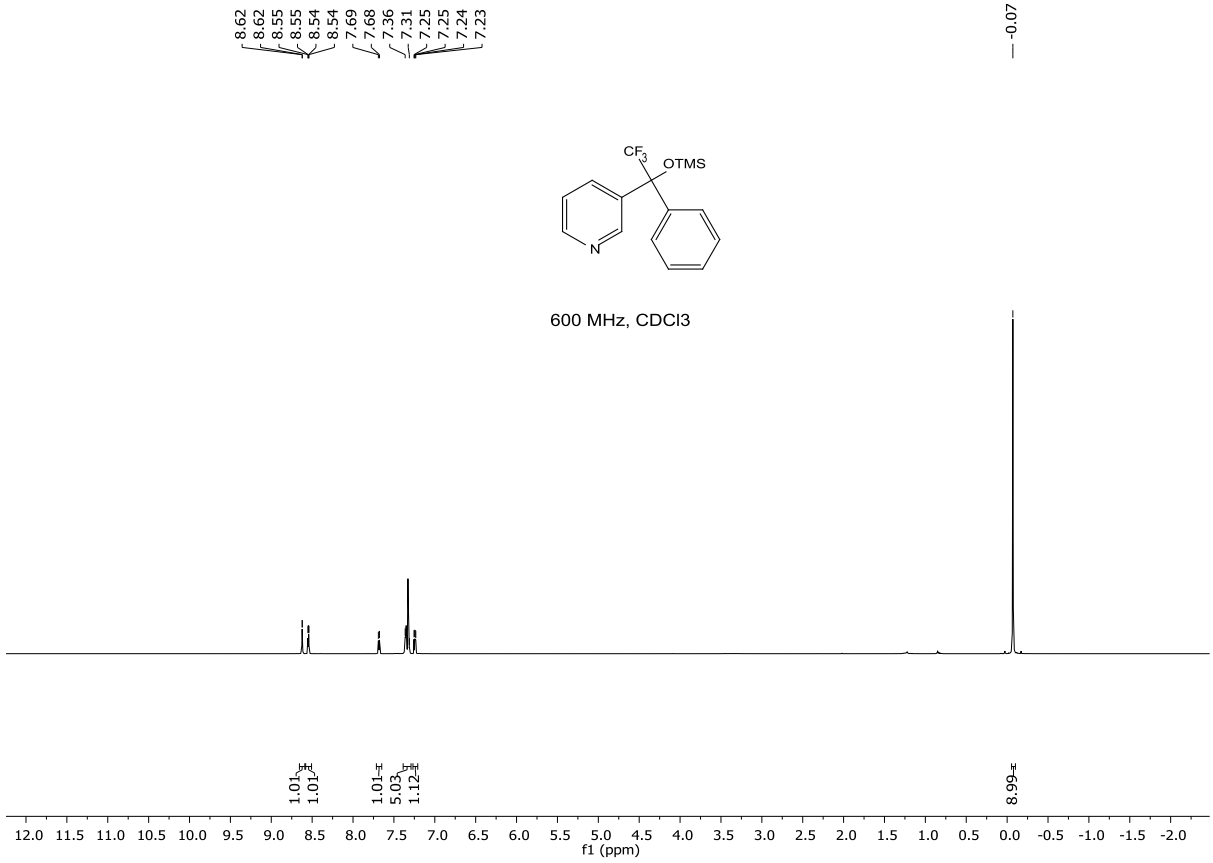
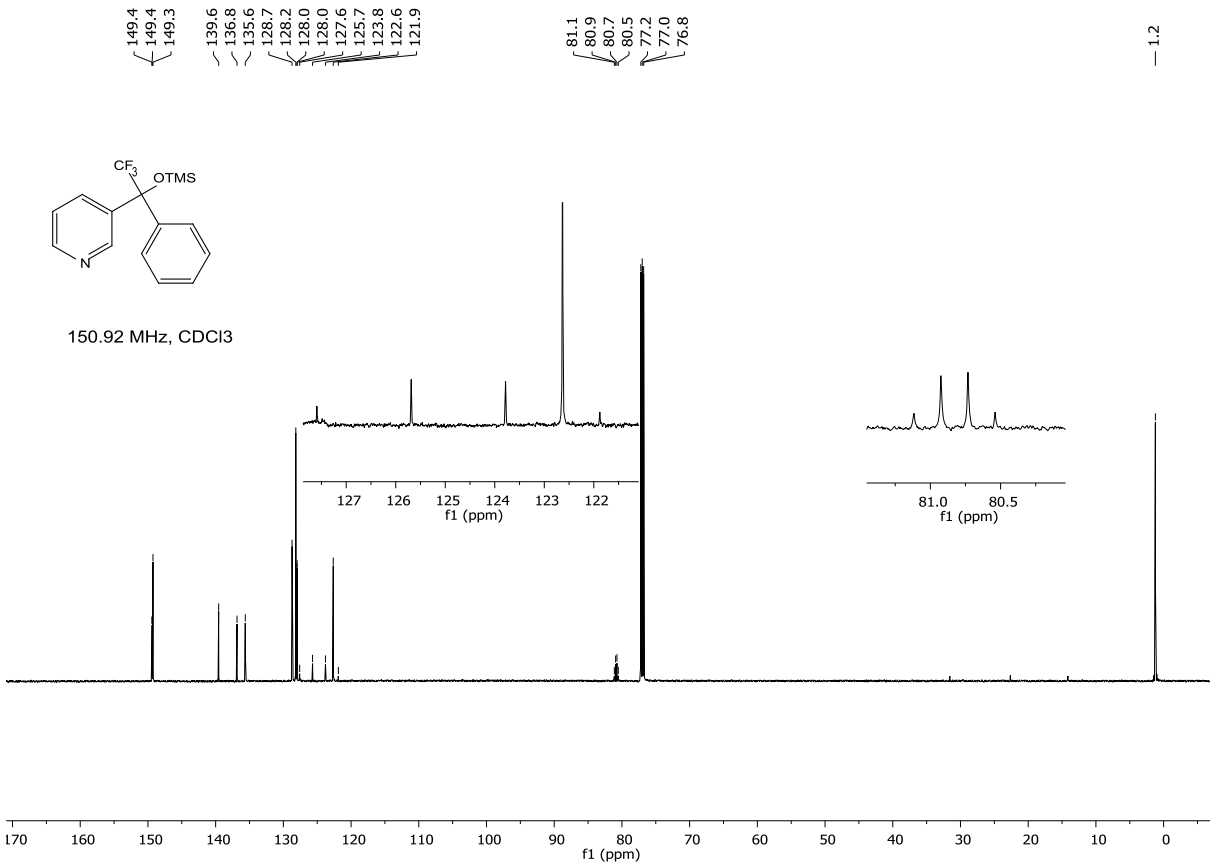
f1 (ppm)

(1-(3-Pyridinyl)-2,2,2-trifluoro-1-phenylethoxy)trimethylsilane, 4e. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 95% yield. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ -0.07 (s, 9H), 7.24 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.31 – 7.36 (m, 5H), 7.68 (d, *J* = 8.1 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.62 (d, *J* = 1.3 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 1.2, 80.8 (q, *J* = 29.07 Hz), 122.6, 124.7 (q, *J* = 287.38 Hz), 127.98 (d, *J* = 1.6 Hz), 128.2, 128.7, 139.5, 149.2, 149.39 (d, *J* = 1.4 Hz). ^{19}F NMR (41 MHz) δ -73.39 (s). HRMS *m/z* calculated for $C_{16}H_{19}F_3NOSi$ $[M + H]^+$ 326.1188 found 326.1173.

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127.6
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123.8
122.6
121.9
81.1
80.9
80.7
80.5
77.2
77.0
76.8
1.2
CF3
OTMS
N
150.92 MHz, CDCl3
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f1 (ppm)
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f1 (ppm)
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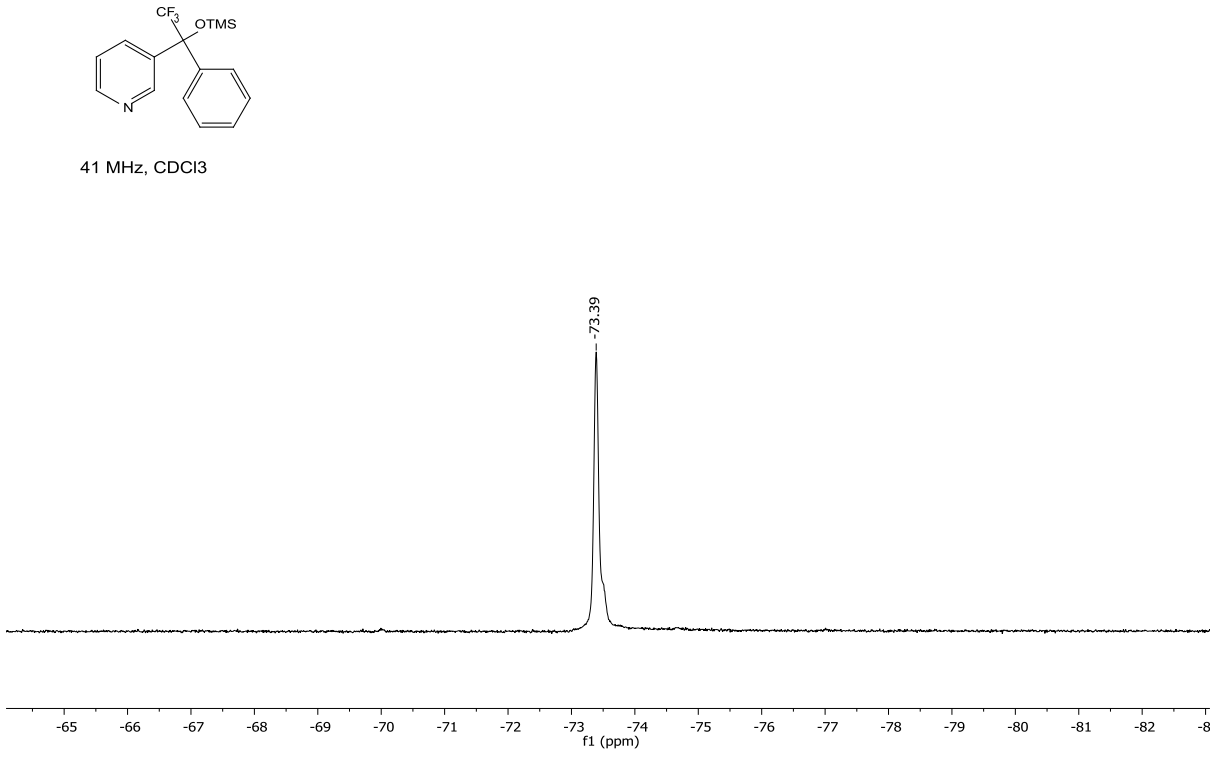
f1 (ppm)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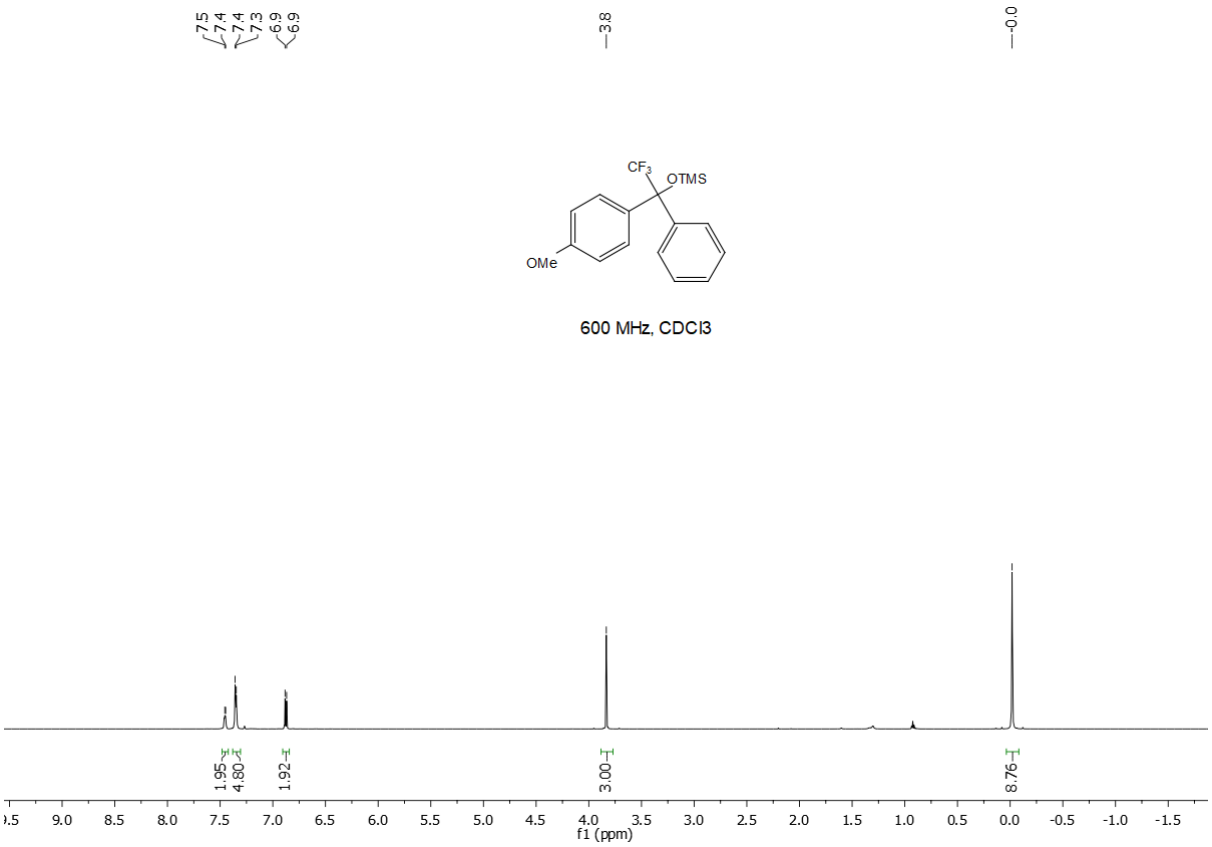
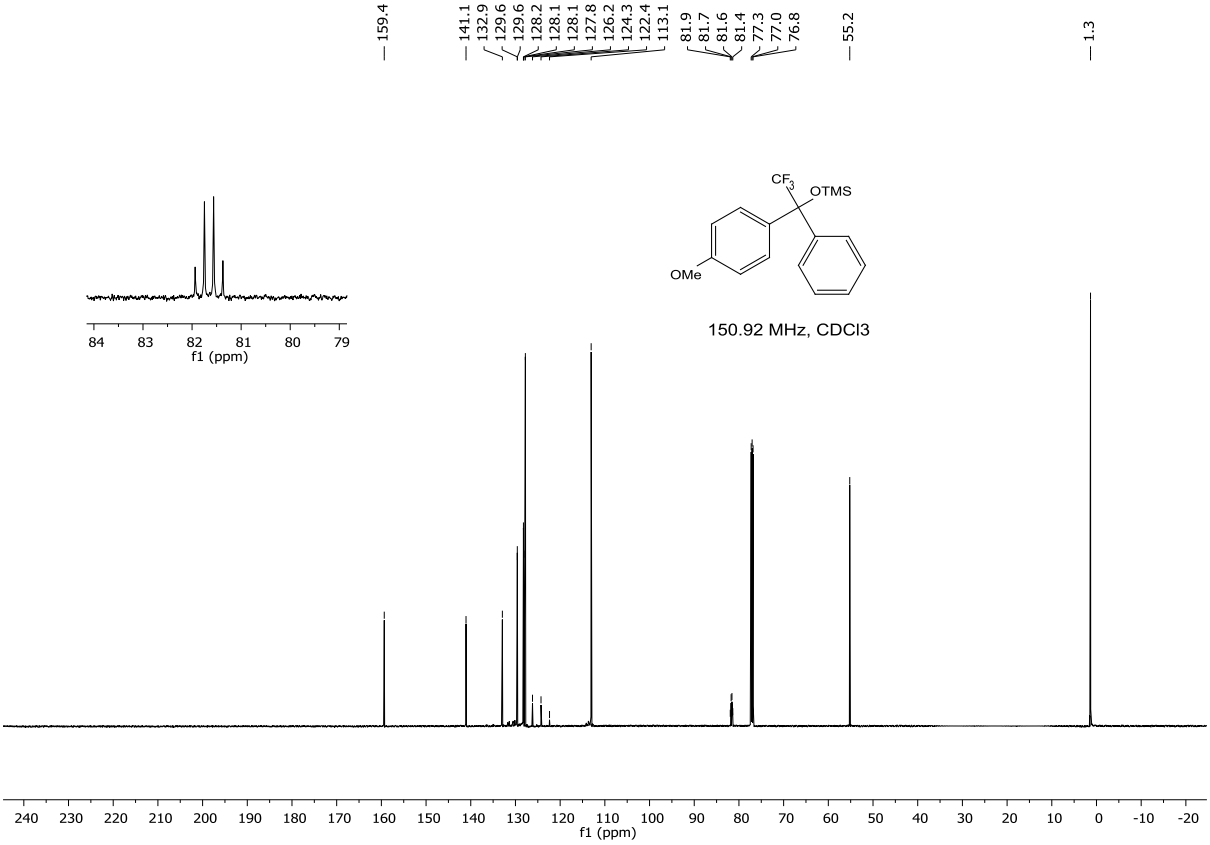
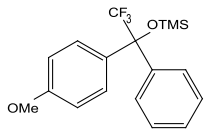
OTMS
N
41 MHz, CDCl3
-73.39
-65 -66 -67 -68 -69 -70 -71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -8
f1 (ppm)

(2,2,2-Trifluoro-1-(4-methoxyphenyl)-1-phenylethoxy)trimethylsilane, 4f. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 95% yield. The NMR spectra are in accordance with the reported data.[2]

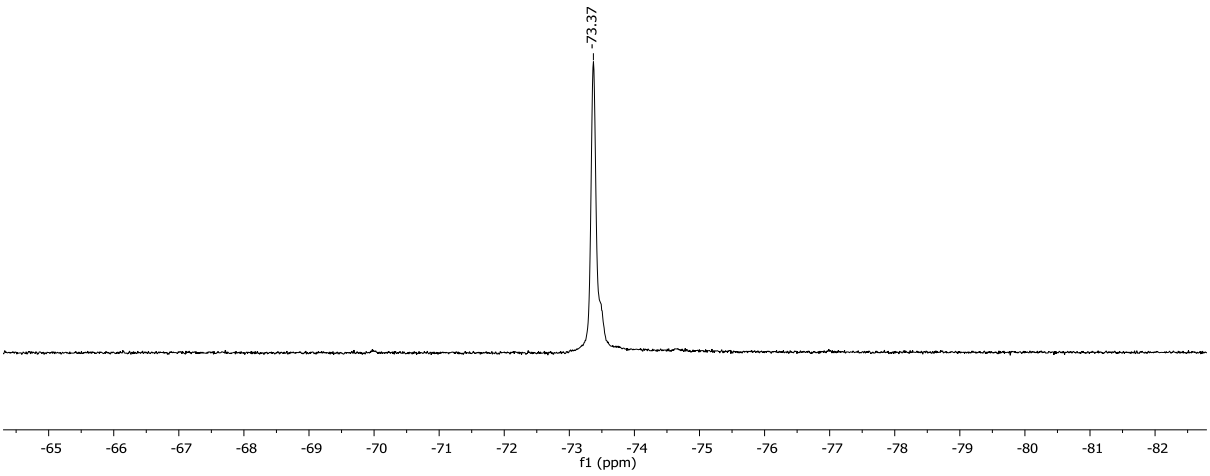




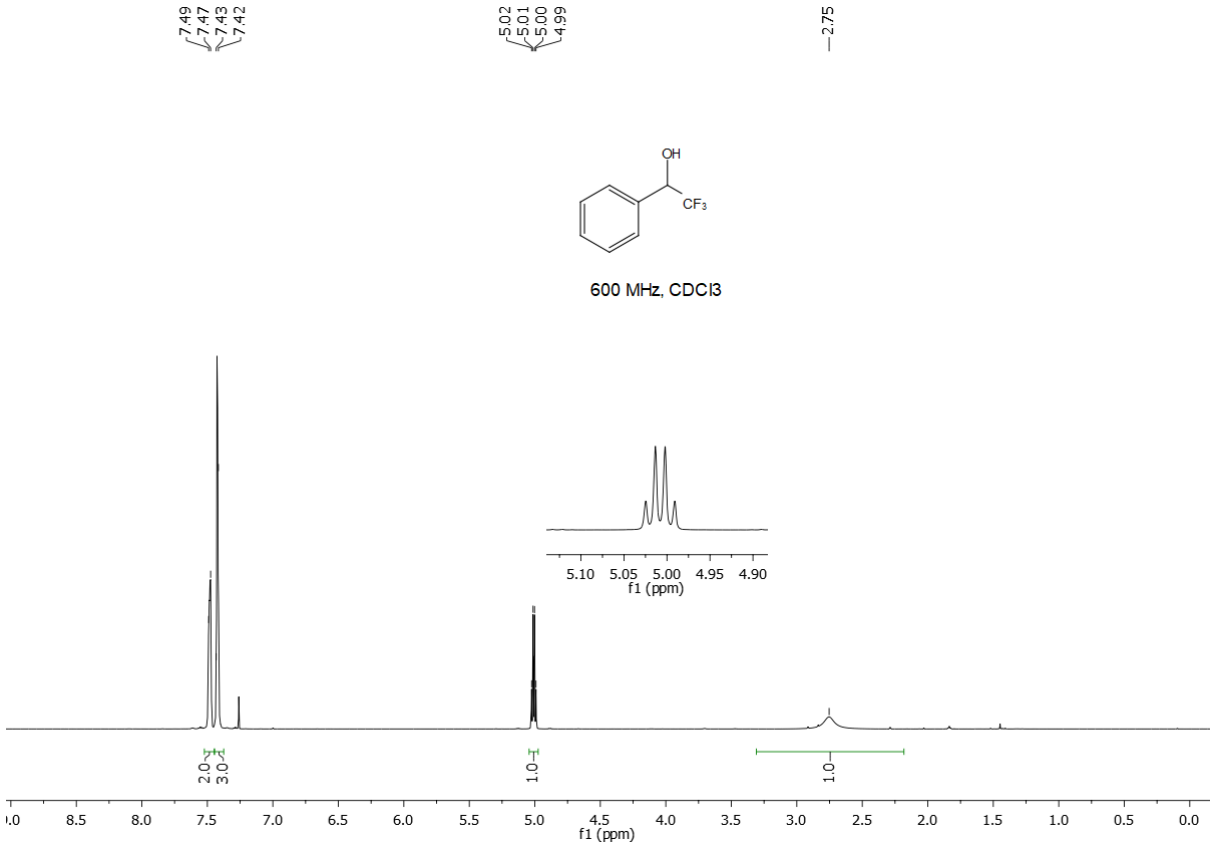
150.92 MHz, CDCl3

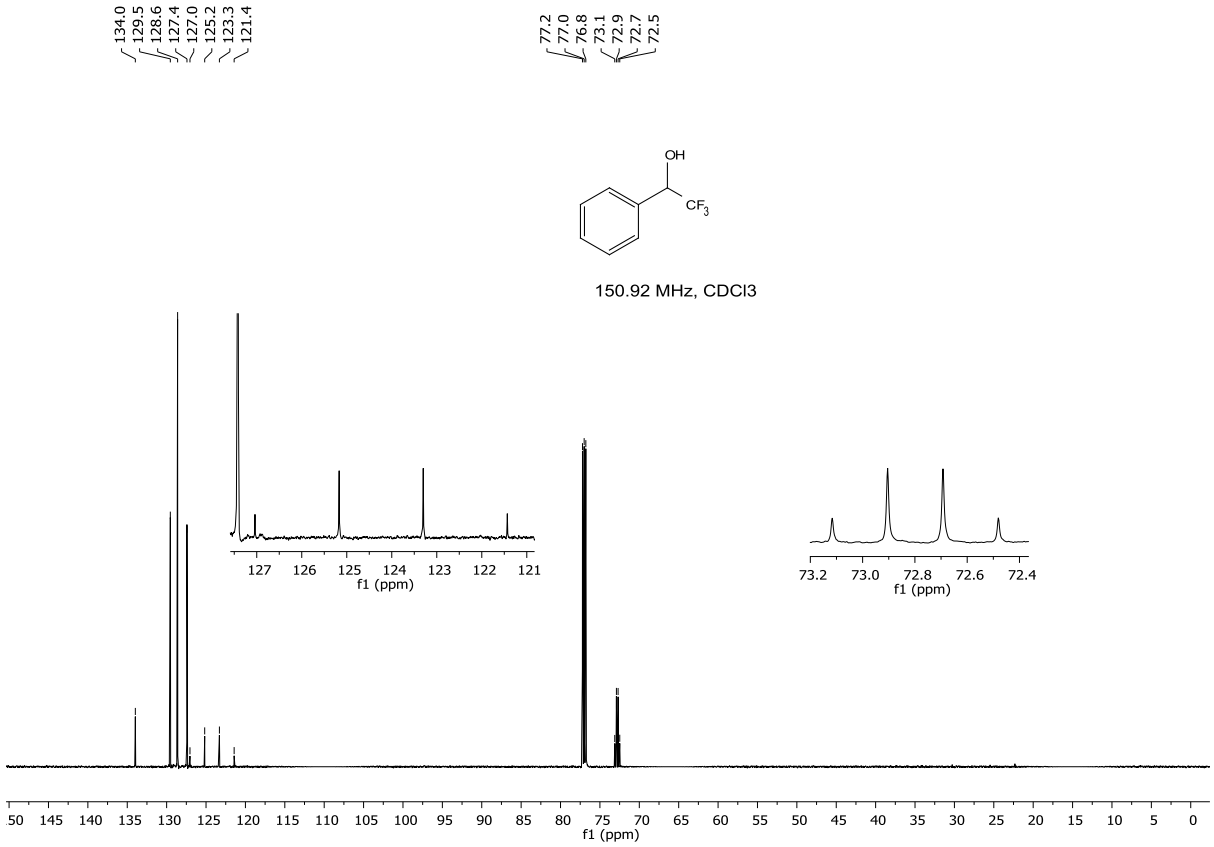


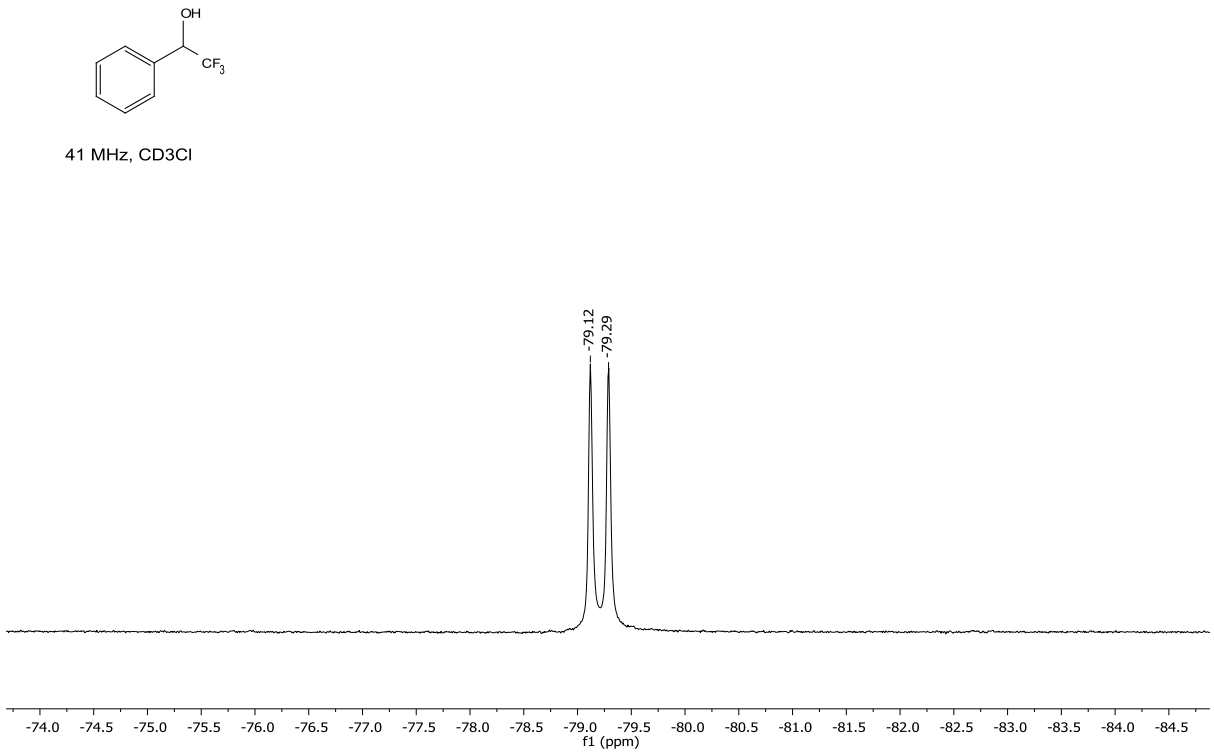
41 MHz, CDCl3



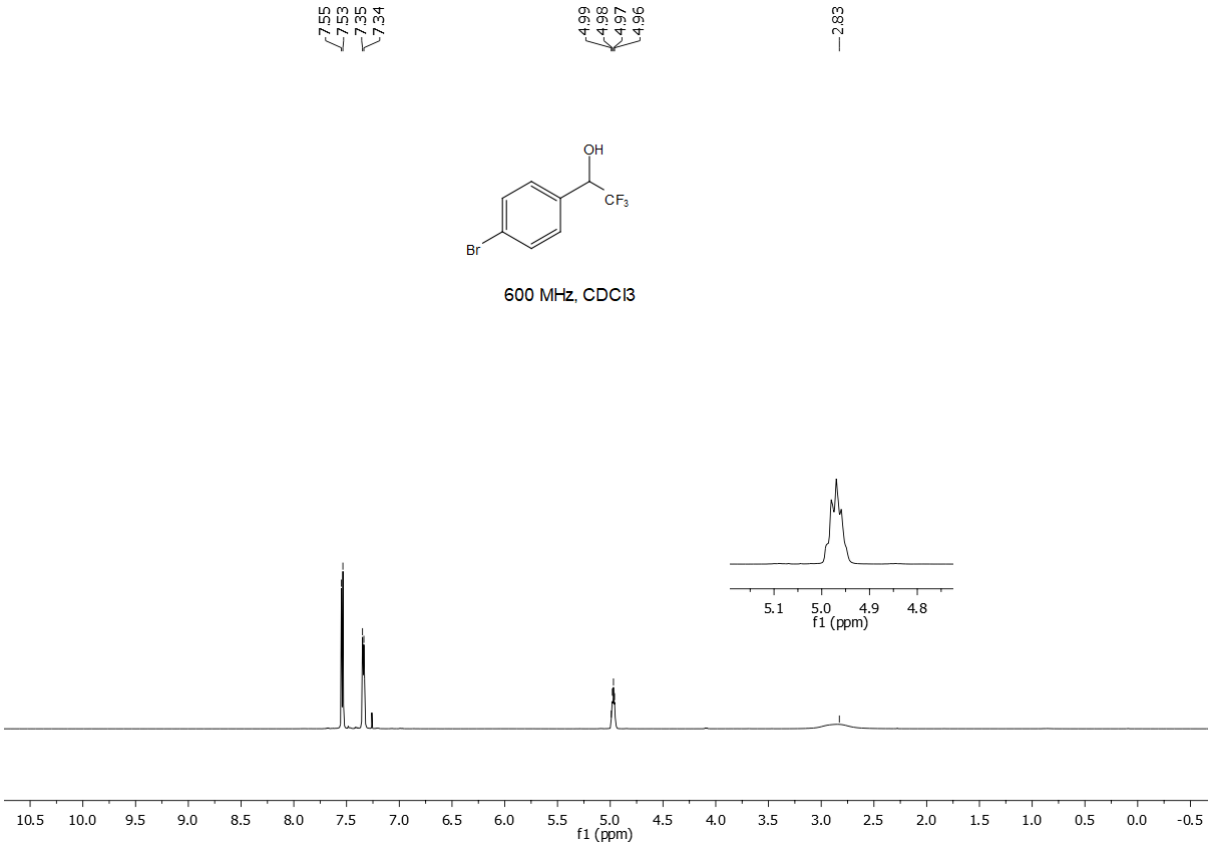
2,2,2-Trifluoro-1-phenylethanol, 6a. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 88% yield. The NMR spectra are in accordance with the reported data.[4]

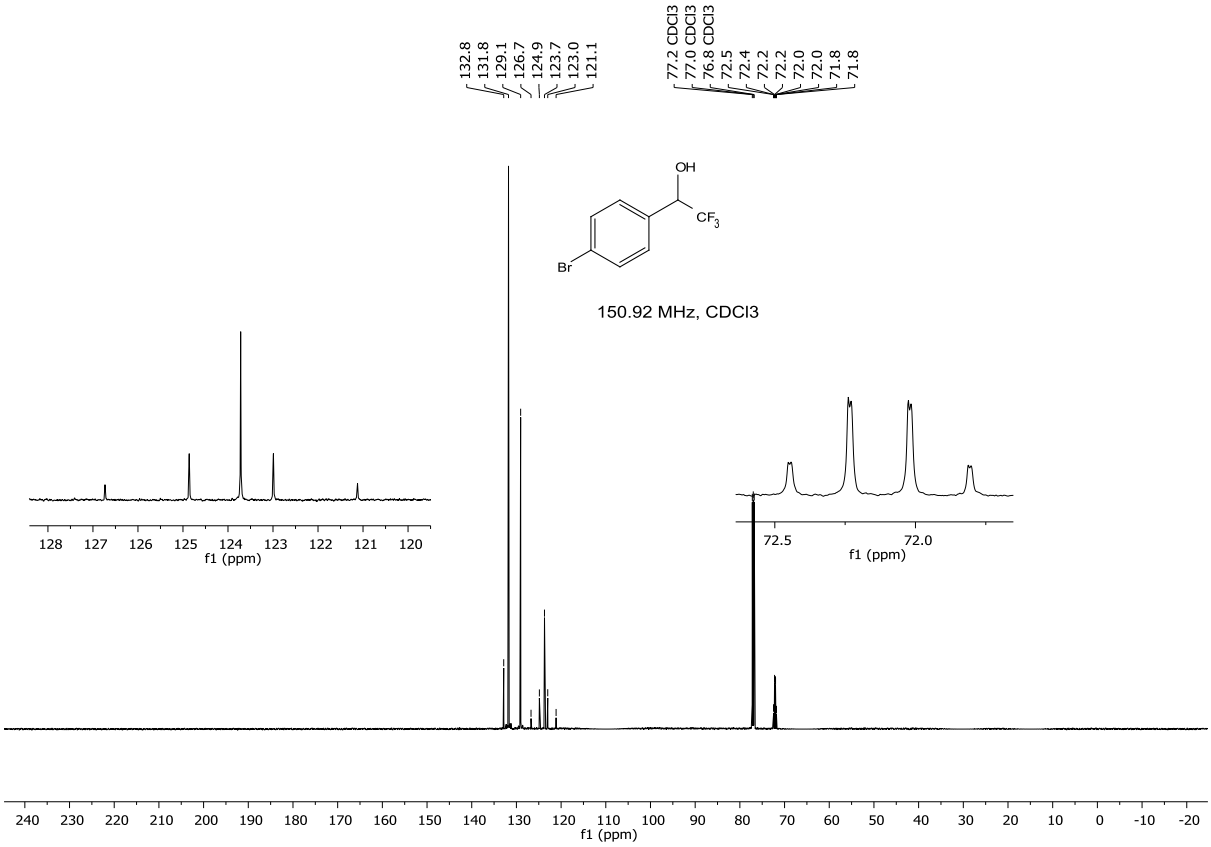


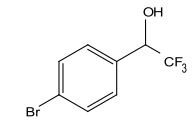

134.0
129.5
128.6
127.4
127.0
125.2
123.3
121.4
77.2
77.0
76.8
73.1
72.9
72.7
72.5
OH
CF3
150.92 MHz, CDCl3
127 126 125 124 123 122 121
f1 (ppm)
73.2 73.0 72.8 72.6 72.4
f1 (ppm)
50 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)


OH
CF3
41 MHz, CD3Cl
-79.12
-79.29
-74.0 -74.5 -75.0 -75.5 -76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5 -80.0 -80.5 -81.0 -81.5 -82.0 -82.5 -83.0 -83.5 -84.0 -84.5
f1 (ppm)

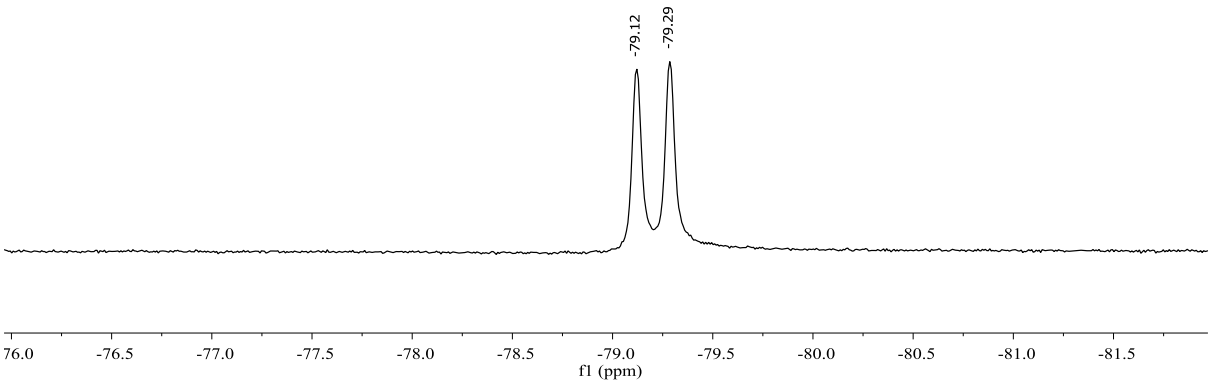
1-(4-Bromophenyl)-2,2,2-trifluoroethanol, 6b. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 88% yield. The NMR spectra are in accordance with the reported data.[5]



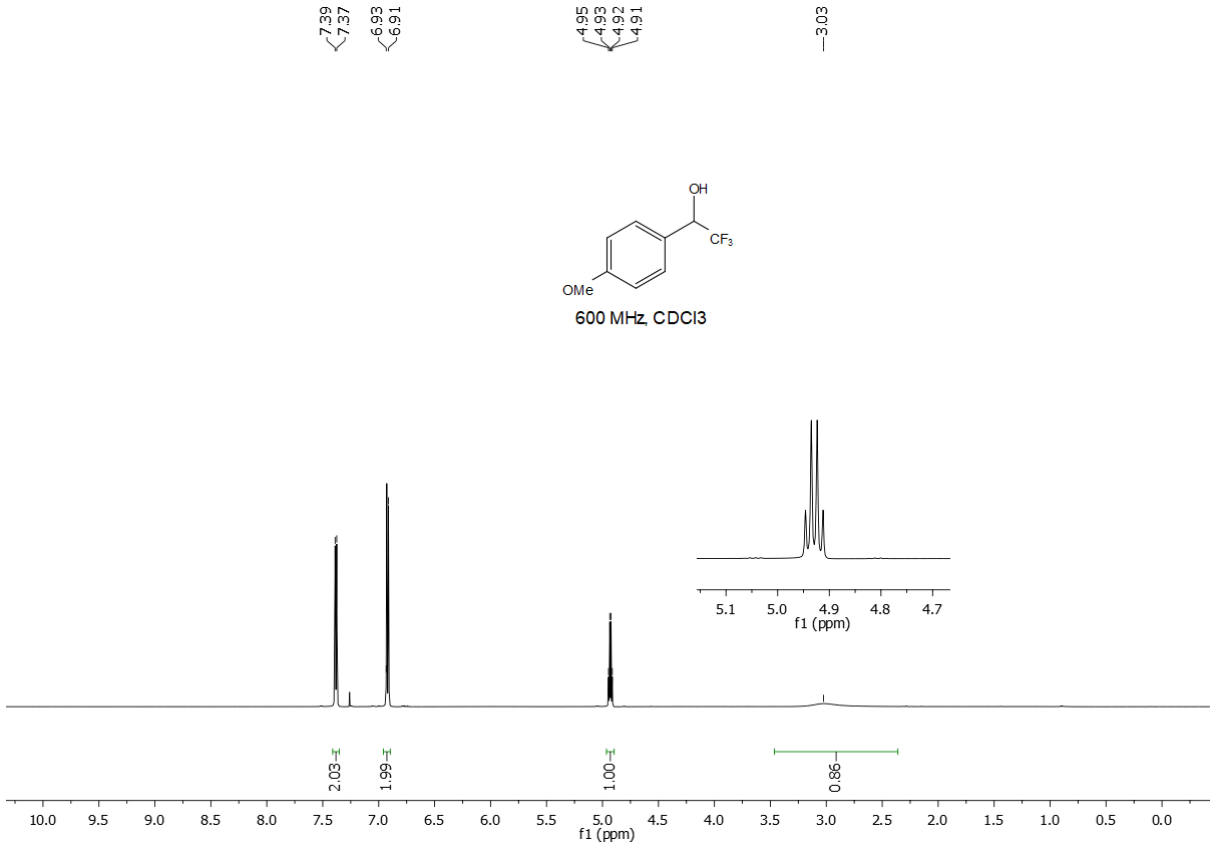

132.8
131.8
129.1
126.7
124.9
123.7
123.0
121.1
77.2 CDCl3
77.0 CDCl3
76.8 CDCl3
72.5
72.4
72.2
72.2
72.0
72.0
71.8
71.8
OH
CF3
Br
150.92 MHz, CDCl3
128 127 126 125 124 123 122 121 120
f1 (ppm)
72.5
72.0
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

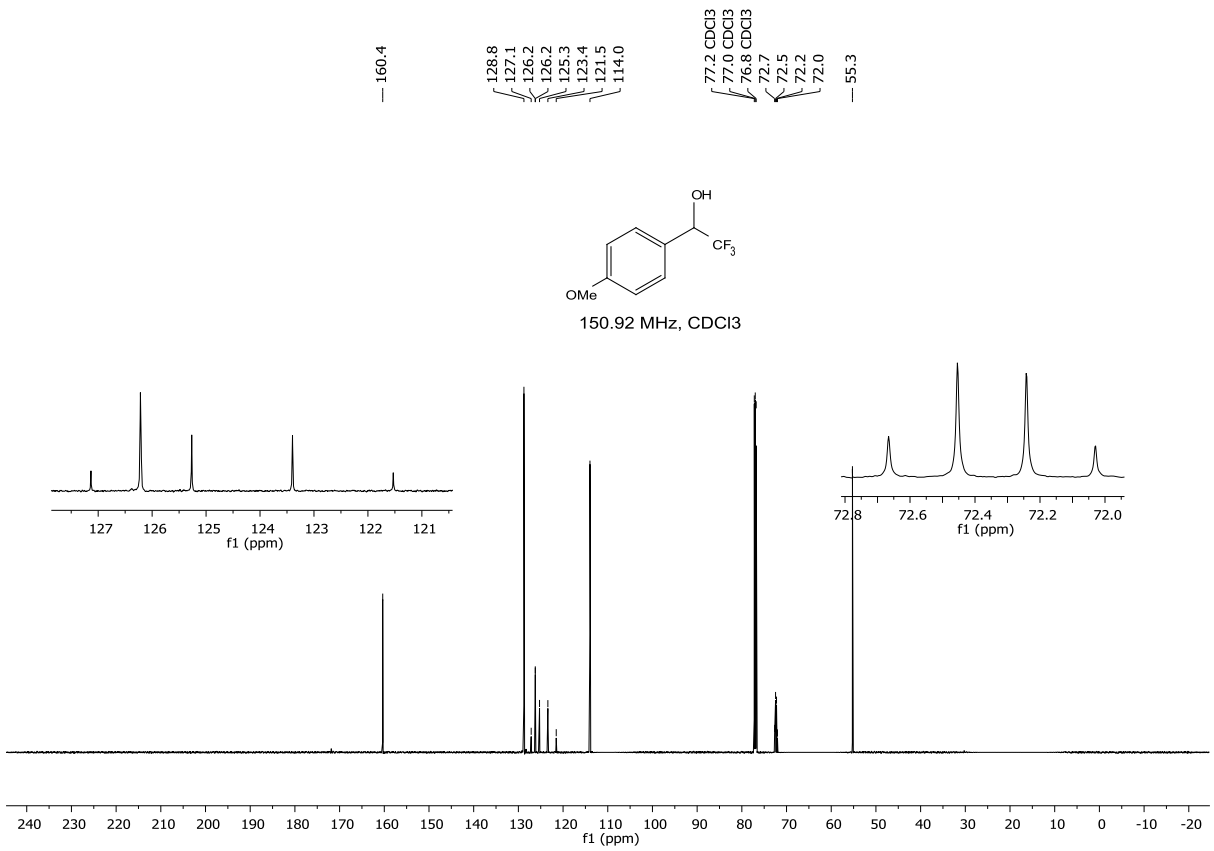

OH
CF3
Br

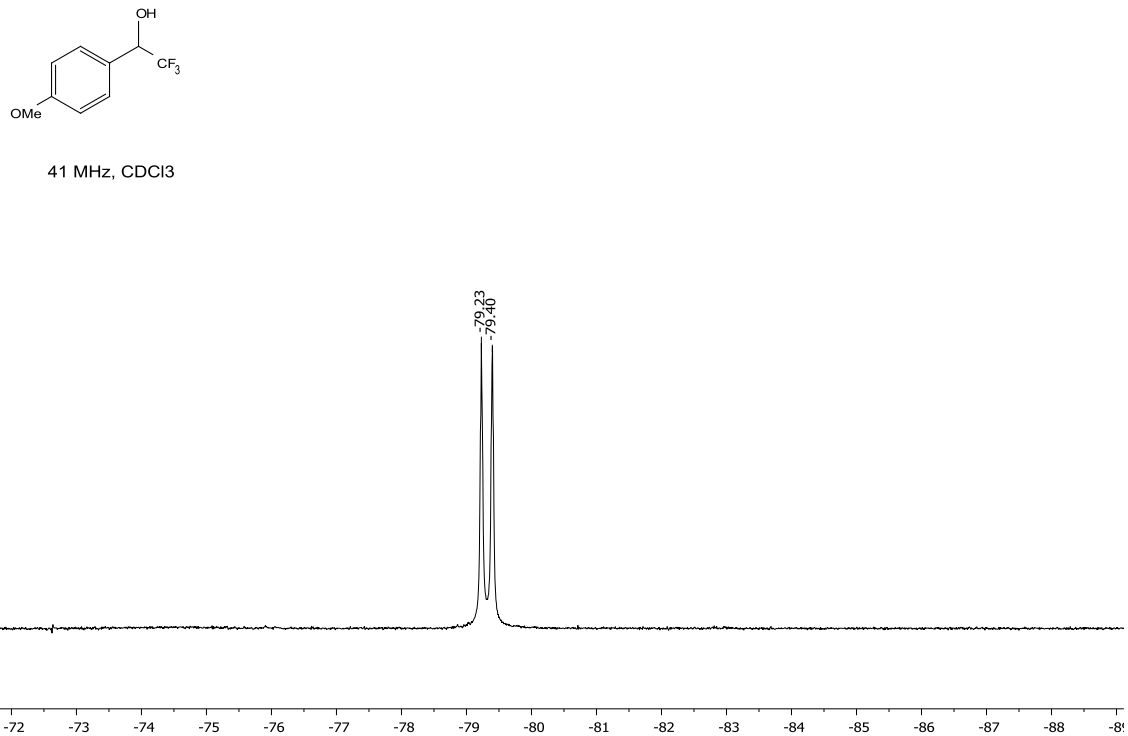
41 MHz, CDCl3


-79.12
-79.29
76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5 -80.0 -80.5 -81.0 -81.5
f1 (ppm)

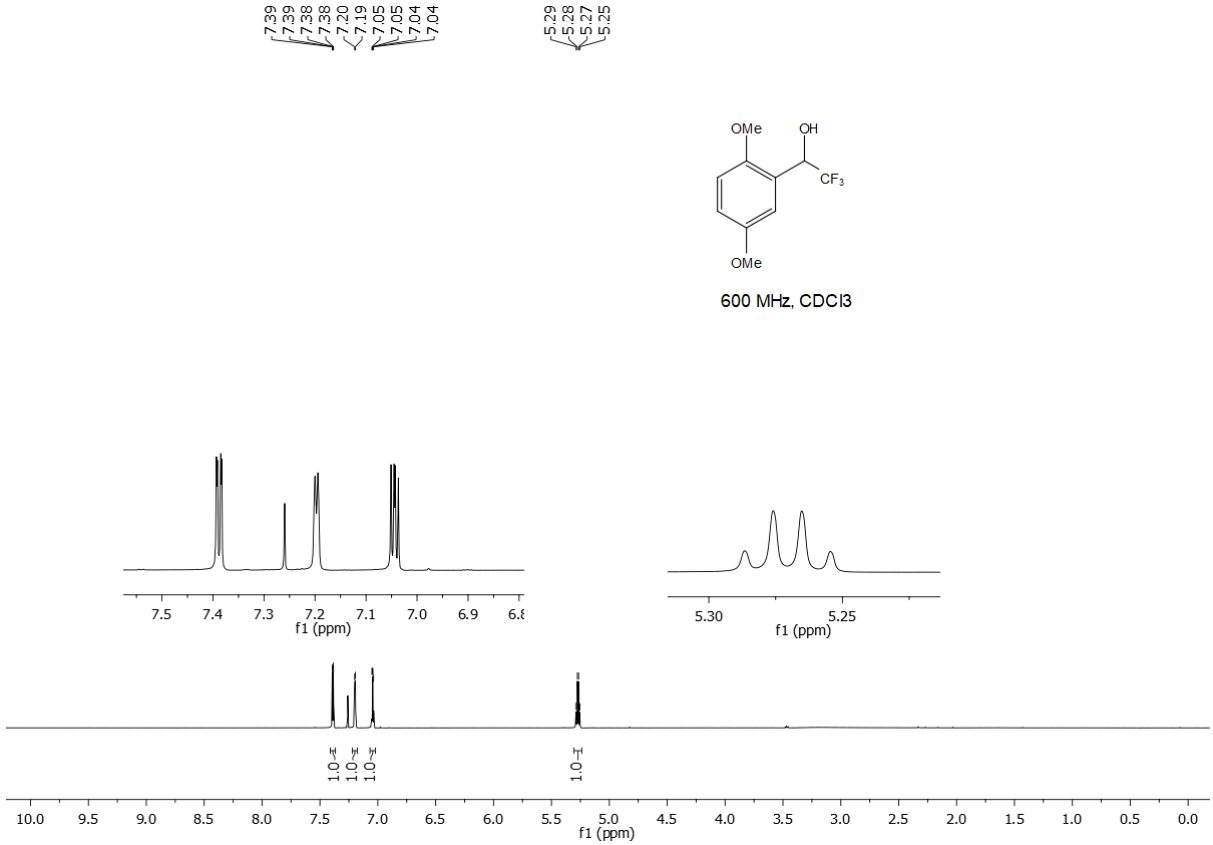
2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol, 6c. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 95% yield. The NMR spectra are in accordance with the reported data.[6]

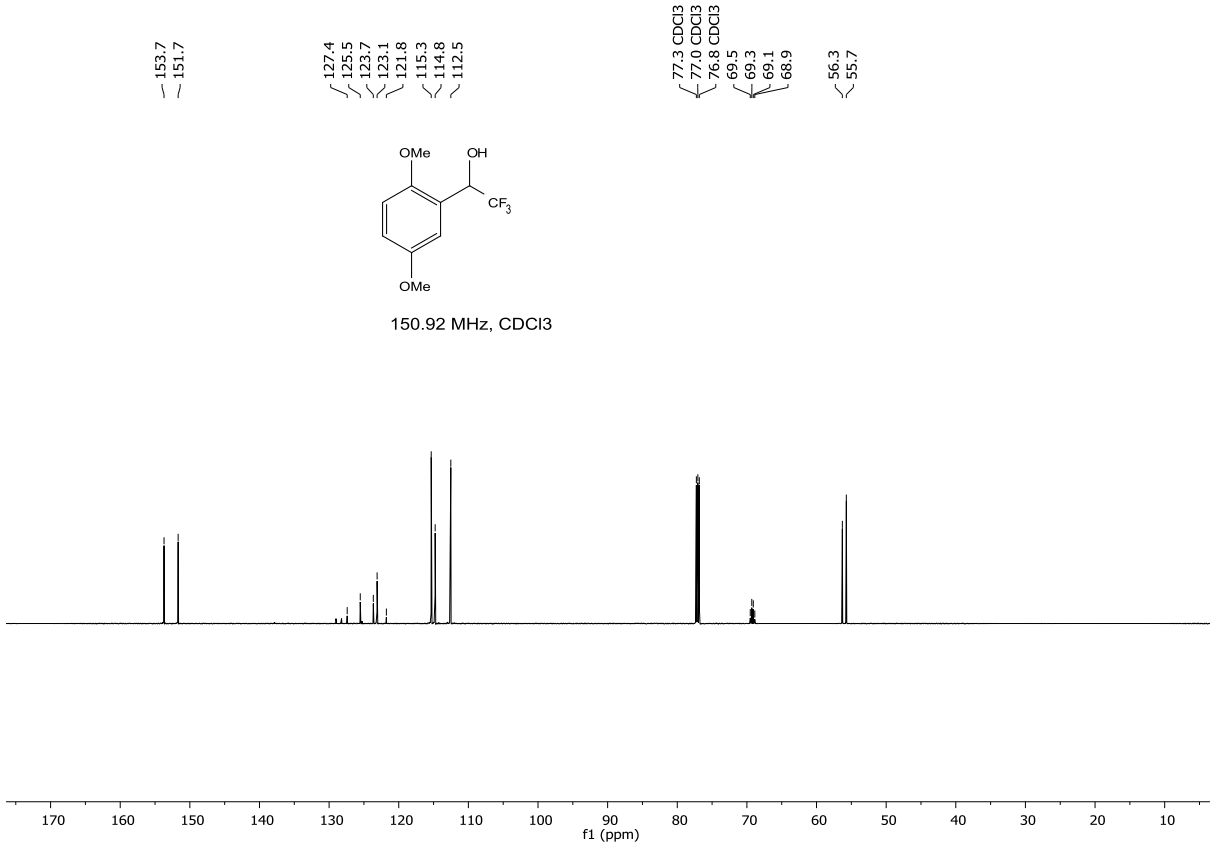


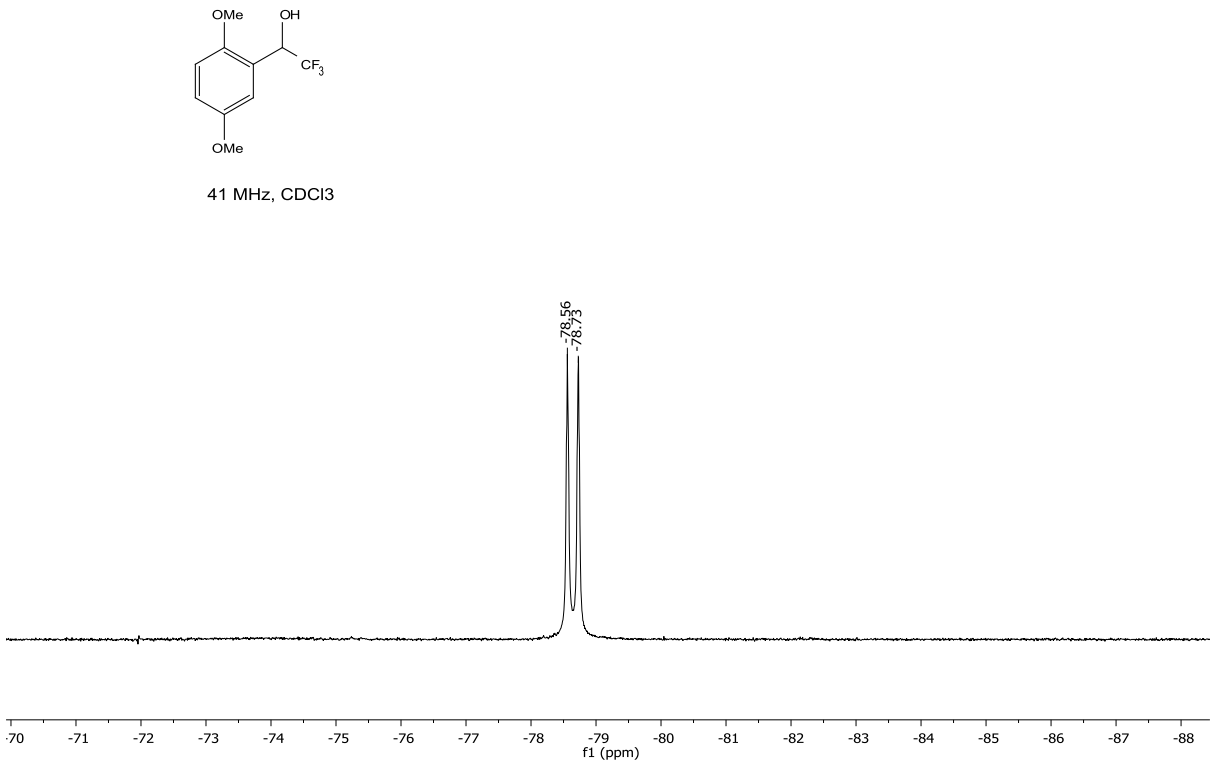

160.4
128.8
127.1
126.2
126.2
125.3
123.4
121.5
114.0
77.2 CDCl3
77.0 CDCl3
76.8 CDCl3
72.7
72.5
72.2
72.0
55.3
OH
CF3
OMe
150.92 MHz, CDCl3
f1 (ppm)


OH
CF3
OMe
41 MHz, CDCl3
-79.23
-79.40
f1 (ppm)

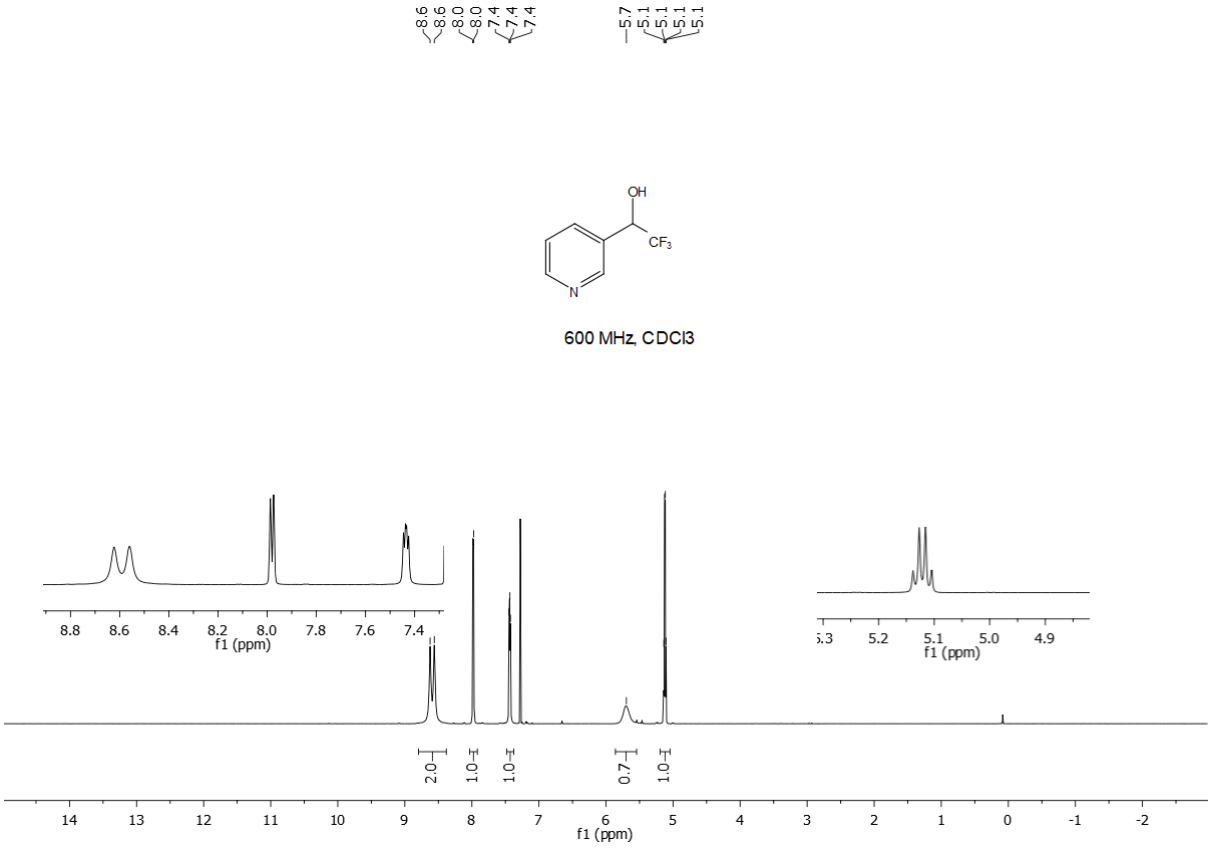
2,2,2-Trifluoro-1-(2,5-dimethoxyphenyl)ethanol, 6d. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 96% yield. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27 (q, *J* = 6.4 Hz, 1H), 7.04 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.20 (d, *J* = 3.5 Hz, 1H), 7.39 (dd, *J* = 5.1, 1.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.7, 56.3, 69.2 (q, *J* = 32.64 Hz), 112.5, 114.8, 115.3, 123.1, 124.6 (q, *J* = 283.07 Hz),151.7, 153.7. ^{19}F NMR (41 MHz) δ -78.64 (d, *J* = 6.9 Hz). HRMS *m/z* calculated for $C_{10}H_{12}F_3NO_3$ [M + H]$^+$ 237.0738 found 237.0746.

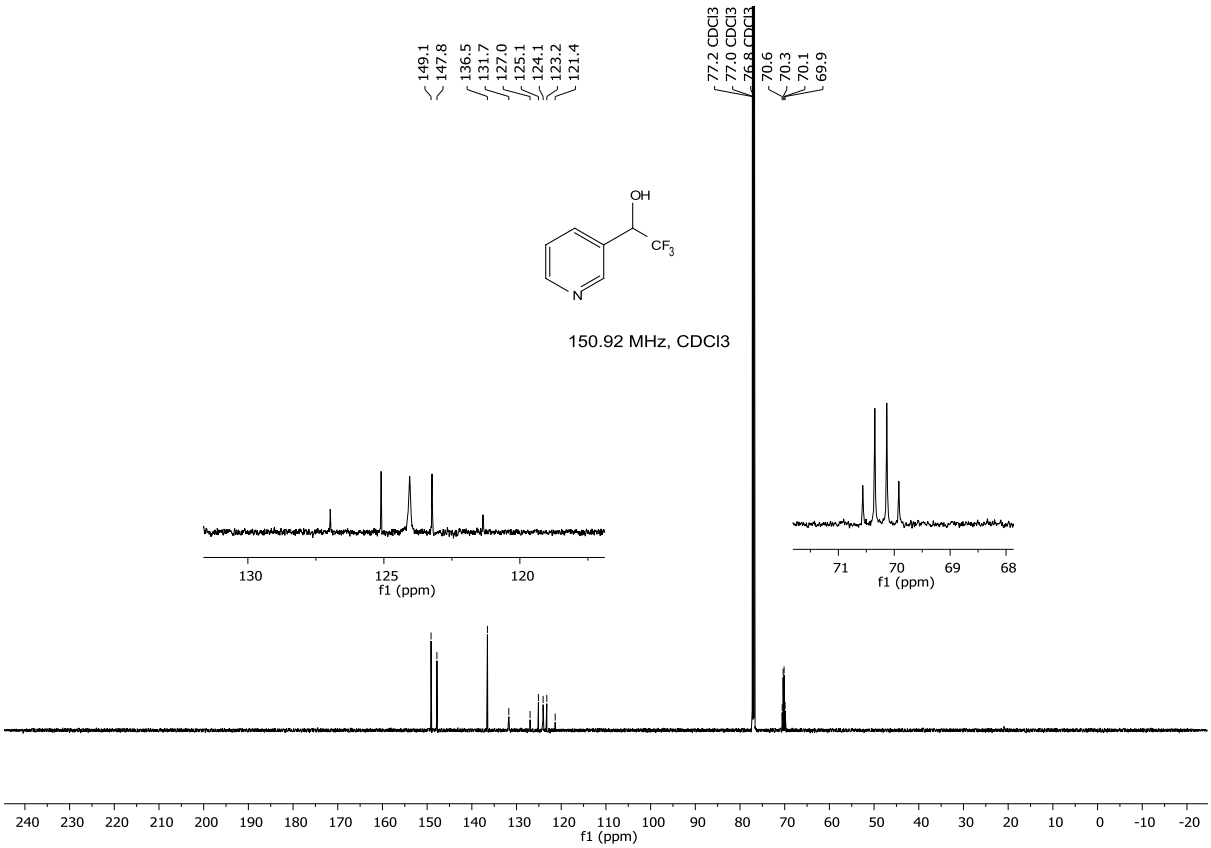


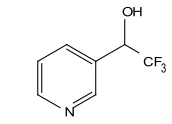

153.7
151.7
127.4
125.5
123.7
123.1
121.8
115.3
114.8
112.5
77.3 CDCl3
77.0 CDCl3
76.8 CDCl3
69.5
69.3
69.1
68.9
56.3
55.7
OMe
OH
CF3
OMe
150.92 MHz, CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OMe
OH
CF3
OMe
41 MHz, CDCl3
-78.56
-78.73
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
-86
-87
-88
f1 (ppm)

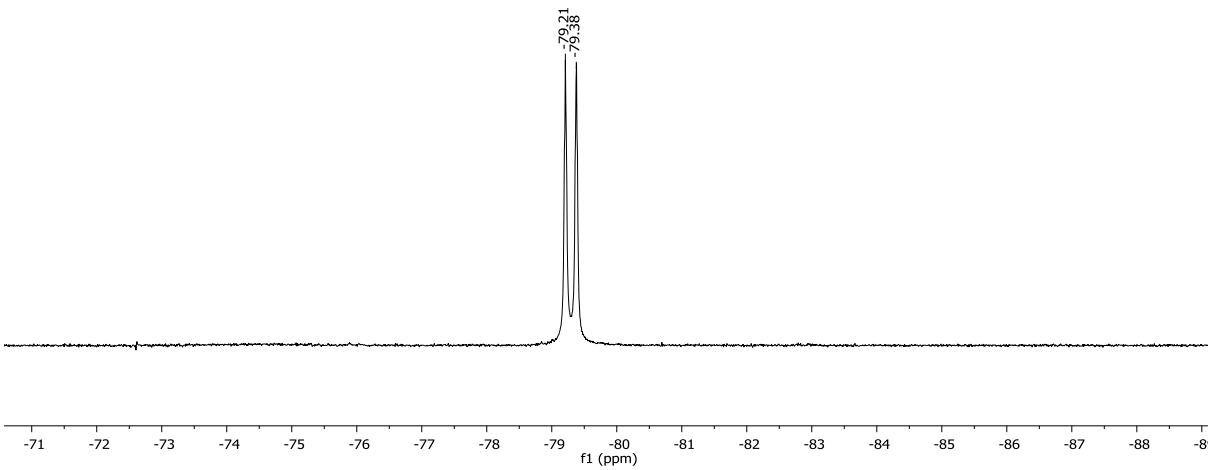
2,2,2-Trifluoro-1-(pyridin-3-yl)ethanol, 6e. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 97% yield. The NMR spectra are in accordance with the reported data.[7]



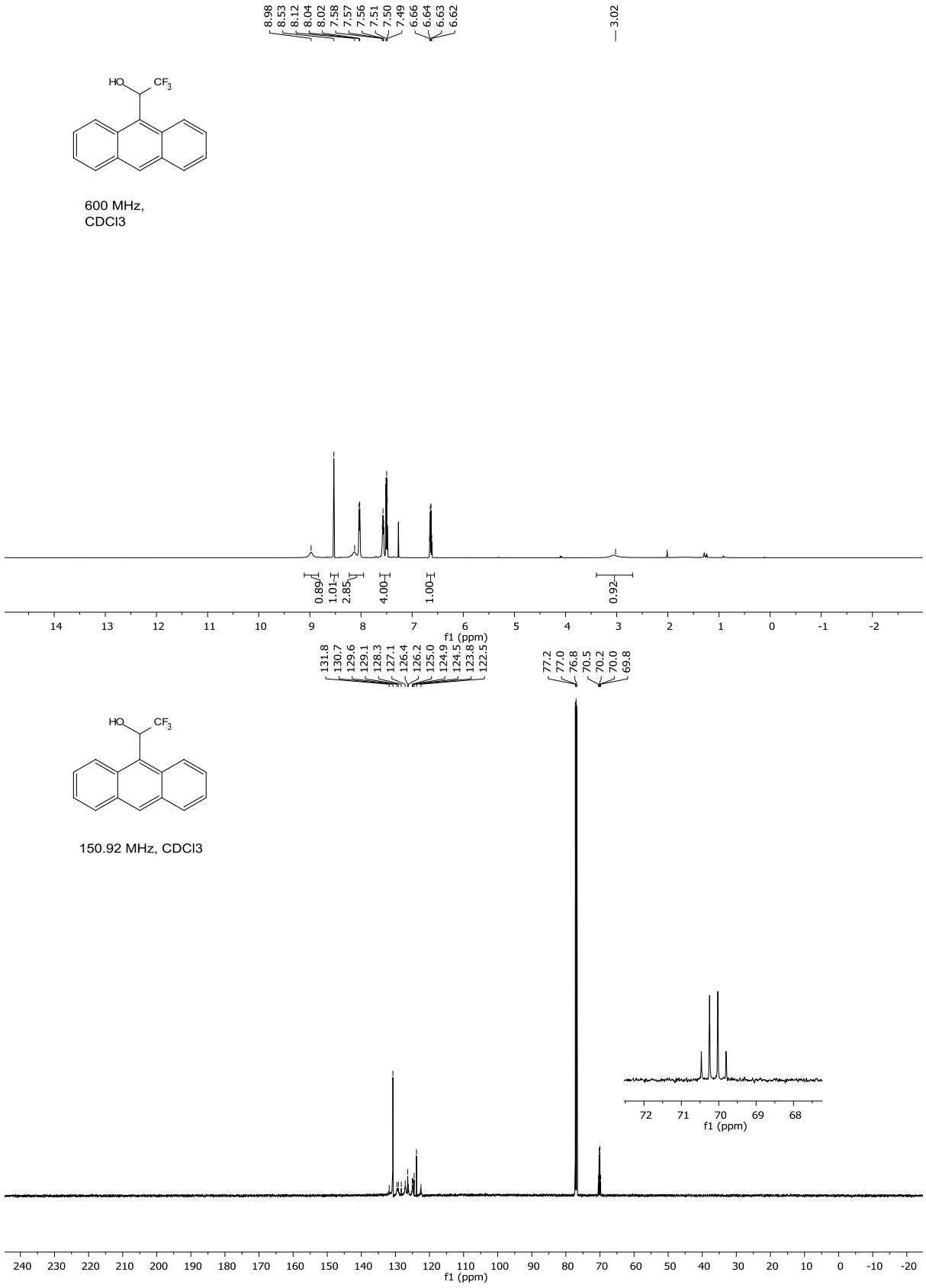

149.1
147.8
136.5
131.7
127.0
125.1
124.1
123.2
121.4
77.2 CDCl3
77.0 CDCl3
76.8 CDCl3
70.6
70.3
70.1
69.9
OH
CF3
N
150.92 MHz, CDCl3
130
125
120
f1 (ppm)
71
70
69
68
f1 (ppm)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

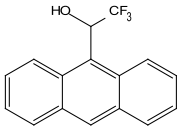

OH
CF3
N

41 MHz, CDCl3

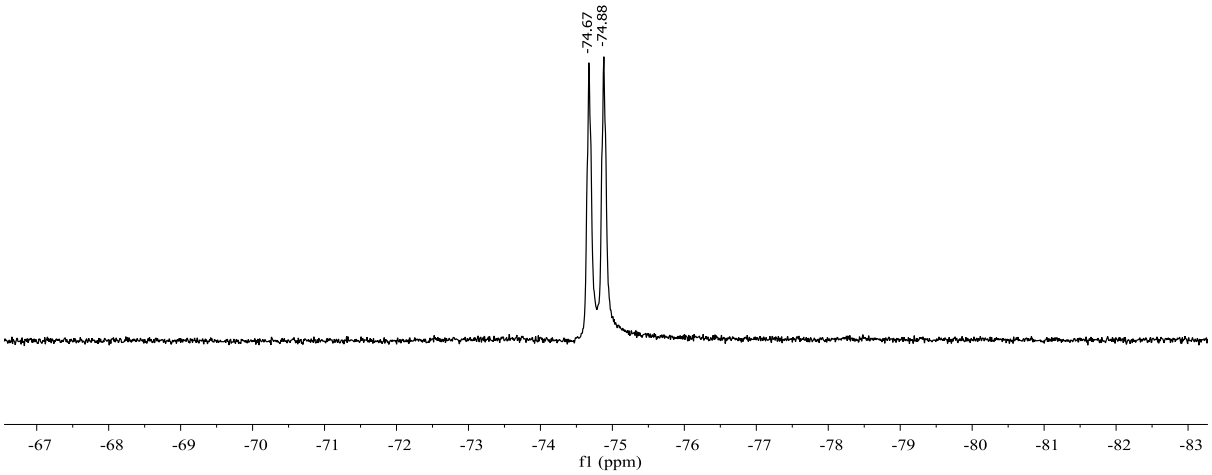

-79.21
-79.38
-71 -72 -73 -74 -75 -76 -77 -78 -79 -80 -81 -82 -83 -84 -85 -86 -87 -88
f1 (ppm)

1-(Anthracen-10-yl)-2,2,2-trifluoroethanol, 6f. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 75% yield. The NMR spectra are in accordance with the reported data.[5]

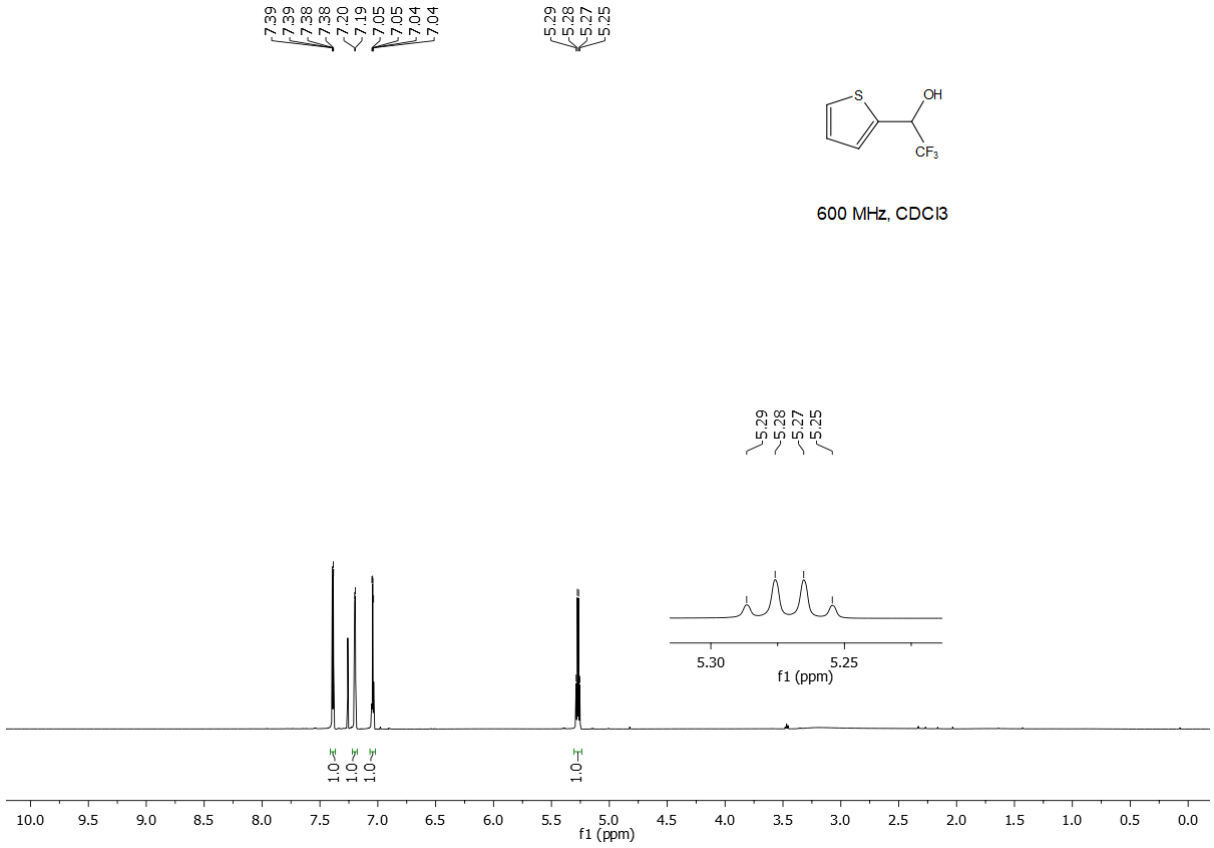


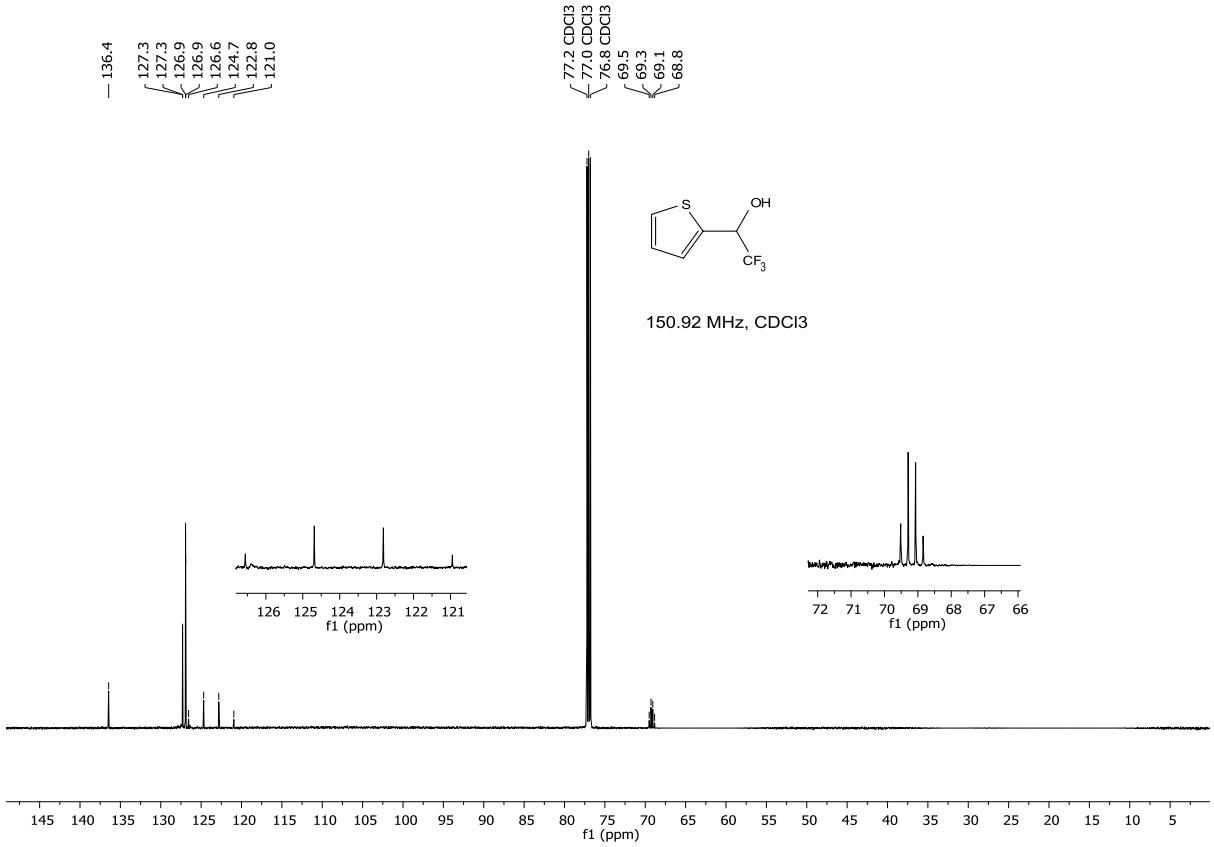

HO
CF3

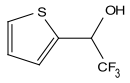
41 MHz, CDCl3


-74.67
-74.88
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
f1 (ppm)

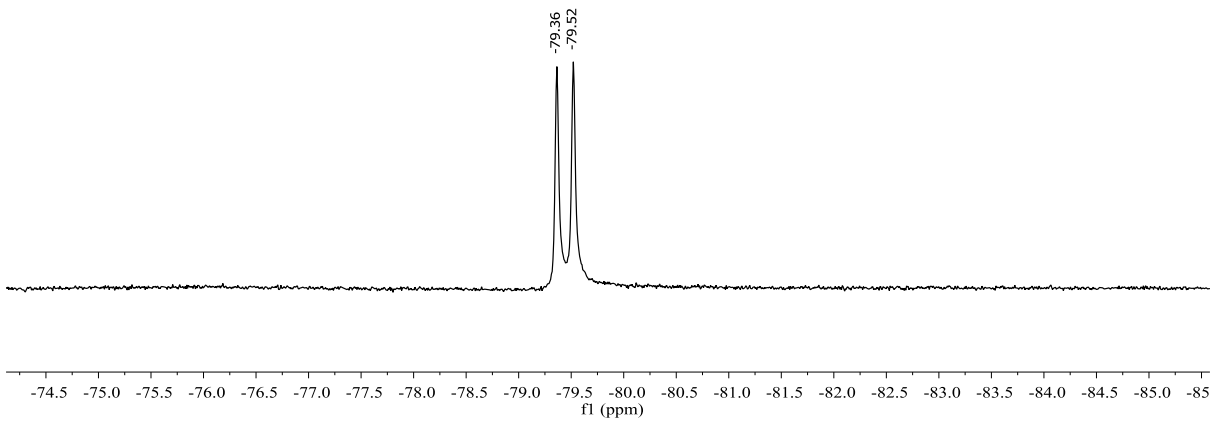
2,2,2-Trifluoro-1-(thiophen-2-yl)ethanol, 6g. Isolated by flash chromatography (hexane/ethyl acetate 90/10), 88% yield. The NMR spectra are in accordance with the reported data.[8]




136.4
127.3
127.3
126.9
126.9
126.6
124.7
122.8
121.0
77.2 CDCl3
77.0 CDCl3
76.8 CDCl3
69.5
69.3
69.1
68.8
S
OH
CF3
150.92 MHz, CDCl3
126 125 124 123 122 121
f1 (ppm)
72 71 70 69 68 67 66
f1 (ppm)
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5
f1 (ppm)


S
OH
CF3

41 MHz, CDCl3


-79.36
-79.52
-74.5 -75.0 -75.5 -76.0 -76.5 -77.0 -77.5 -78.0 -78.5 -79.0 -79.5 -80.0 -80.5 -81.0 -81.5 -82.0 -82.5 -83.0 -83.5 -84.0 -84.5 -85.0 -85
f1 (ppm)

S8. References

(1) Prakash, G. K. S.; Jog, P. V; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338*, 1324–1327.

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(6) Aikawa, K.; Toya, W.; Nakamura, Y.; Mikami, K. *Org. Lett.* **2015**, *17* (20), 4996–4999.

(7) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. *Tetrahedron* **2009**, *65* (33), 6611–6625.

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