ortho-Directed C–H Borylation/Suzuki Coupling Sequence in the Formation of Biphenylbenzylic Amines

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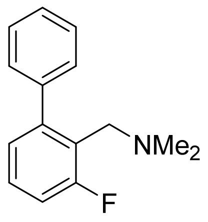
Supporting Information

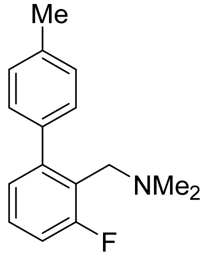
Contents:



1

2-Fluoro-6-phenyl-*N*,*N*-dimethylbenzylamine (1)

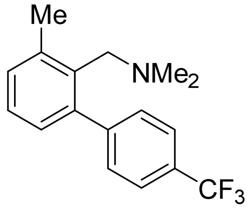
The general procedure was followed using 2-fluoro-*N*,*N*-dimethylbenzylamine (0.154 g, 1.00 mmol) and iodobenzene (0.120 mL, 1.07 mmol). The coupling reaction was heated to 100 °C for 5 h. The crude product was purified by flash column chromatography (23:77 ethyl acetate:hexanes) to give **1** as a yellow oil (0.156 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.42–7.36 (m, 3H), 7.29 (m, 1H), 7.07 (m, 2H), 3.38 (d, *J* = 2.2 Hz, 2H), 2.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1 (d, *J* = 246.6 Hz), 145.7 (d, *J* = 3.6 Hz), 140.4 (d, *J* = 2.8 Hz), 129.8, 128.3 (d, *J* = 9.7 Hz), 127.9, 127.2, 125.9 (d, *J* = 2.8 Hz), 123.9 (d, *J* = 14.2 Hz) 114.2 (d, *J* = 23.4 Hz), 53.3, 45.0; IR (neat) 2819, 2773, 1570, 1464, 1366, 1234, 1018, 760, 703, 566 cm^{-1}; HRMS (CI) calcd for $(C_{15}H_{16}FN + H)^+$ 230.1345, found 230.1341.



2

2-Fluoro-6-(4’-methylphenyl)-*N*,*N*-dimethylbenzylamine (**2**)

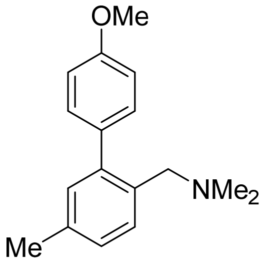
The general procedure was followed using 2-fluoro-*N*,*N*-dimethylbenzylamine (0.308 g, 2.01 mmol) and 4-bromotoluene (0.382 g, 2.23 mmol). The coupling reaction was heated to 100 °C for 5 h. The crude product was purified by flash column chromatography (25:75 ethyl acetate:hexanes) to give **2** as a yellow oil (0.255 g, 52%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.26 (m, 1H), 7.21 (d, *J* = 7.1 Hz, 2H), 7.06 (m, 2H), 3.38 (s, 2H), 2.41 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, *J* = 246.3 Hz), 145.6 (d, *J* = 3.6 Hz), 137.5 (d, *J* = 2.9 Hz), 136.8, 129.7, 128.6, 128.2 (d, *J* = 9.6 Hz), 125.8 (d, *J* = 2.9 Hz), 123.8 (d, *J* = 14.8 Hz), 113.9 (d, *J* = 23.5 Hz), 53.3, 45.0, 21.1; IR (neat) 2818, 1611, 1453, 1234, 1017, 820, 782, 570 cm^{-1}; HRMS (CI) calcd for $(C_{16}H_{18}FN + H)^+$ 244.1501, found 244.1508.



3

2-Methyl-6-(4’-trifluoromethylphenyl)-*N,N*-dimethylbenzylamine (3)

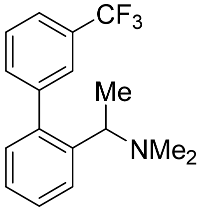
The general procedure was followed using 2-methyl-*N*,*N*-dimethylbenzylamine (0.300 g, 2.01 mmol) and 4-trifluoromethyliodobenzene (0.340 mL, 2.31 mmol). The coupling reaction was heated to 100 °C for 16 h. The crude product was purified by flash column chromatography (20:80 to 25:75 ethyl acetate:hexanes) to give **3** as a pale brown solid (0.367 g, 59%): mp 32–39 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.22 (m, 2H), 7.01 (m, 1H), 3.33 (s, 2H), 2.51 (s, 3H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 142.2, 139.2, 134.6, 130.34, 130.25, 128.8 (q, *J* = 32.4 Hz), 127.5, 126.8, 124.5 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 272.0 Hz), 57.2, 45.0, 20.0; IR (thin film) 2941, 2816, 1617, 1466, 1325, 1125, 848, 743 cm^{-1}; HRMS (CI) calcd for $(C_{17}H_{18}F_3N + H)^+$ 294.1470, found 294.1473.



4

2-(4'-Methoxyphenyl)-4-methyl-*N*,*N*-dimethylbenzylamine (4)

The general procedure was followed using 4-methyl-*N*,*N*-dimethylbenzylamine (0.300 g, 2.01 mmol) and 4-bromoanisole (0.276 mL, 2.20 mmol). The coupling reaction was heated to 100 °C for 17 h. The crude product was purified by flash column chromatography (75:25 ethyl acetate:hexanes to 99.5:0.5 ethyl acetate:methanol) to give **4** as a yellow oil (0.279 g, 55%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 6.96 (d, *J* = 8.1 Hz, 2H), 3.89 (s, 3H), 3.35 (s, 2H), 2.39 (s, 3H), 2.18 (s, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 158.5, 141.9, 136.2, 134.0, 133.4, 130.8, 130.7, 129.9, 127.7, 113.2, 60.7, 55.3, 45.3, 21.0; IR (neat) 2942, 2816, 1681, 1605, 1267, 1045, 836, 722 cm^{-1}; HRMS (CI) calcd for $(C_{17}H_{21}NO + H)^+$ 256.1701, found 256.1705.

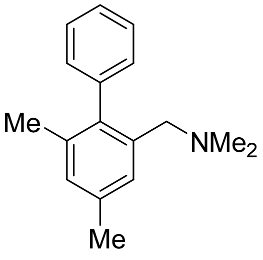


5

***N*,*N*-Dimethyl-2-(3'-trifluoromethylphenyl)-phenylethylamine (5)**

The general procedure was followed using *N*,*N*-dimethylphenylethylamine (0.299 g, 2.00 mmol) and 3-trifluoromethyliodobenzene (0.320 mL, 2.22 mmol). The coupling reaction was heated to

100 °C for 16 h. The crude product was purified by flash column chromatography (20:80 ethyl acetate:hexanes) to give **5** as a yellow oil (0.336 g, 57%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 2H), 7.57 (s, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.40 (m, 1H), 7.28 (m, 1H), 7.16 (m, 1H) , 3.20 (q, *J* = 6.6 Hz, 1H), 2.10 (s, 6H), 1.27 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 142.5, 139.9, 132.8, 130.3 (q, *J* = 32.4 Hz) , 129.7, 128.4, 128.3, 127.0, 126.4, 126.3 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 272.7 Hz), 123.6 (q, *J* = 3.7 Hz), 61.1, 43.4, 20.7; IR (neat) 2979, 2815, 2767, 1427, 1332, 1124, 804, 705, 621 cm^{-1}; HRMS (CI) calcd for $(C_{17}H_{18}F_3N + H)^+$ 294.1470, found 294.1472.

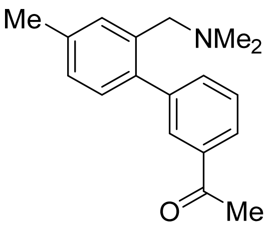


6

2-Phenyl-3,5-dimethyl-*N*,*N*-dimethylbenzylamine (6)

The general procedure was followed using 3,5-dimethyl-*N*,*N*-dimethylbenzylamine (0.327 g, 2.00 mmol) and iodobenzene (0.245 mL, 2.20 mmol). The coupling reaction was heated to 100 °C for 17 h. The crude product was purified by flash column chromatography (85:15 ethyl acetate:hexanes) to give **6** as a pale brown oil (0.380 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.24 (s, 1H), 7.11 (d, *J* = 6.8 Hz, 2H), 6.99 (s, 1H), 3.08 (s, 2H), 2.36 (s, 3H), 2.11 (s, 6H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 139.1, 137.1, 136.8, 135.9, 129.8, 129.2, 128.3, 127.2, 126.7, 61.4, 45.7, 21.3, 21.0; IR (neat)

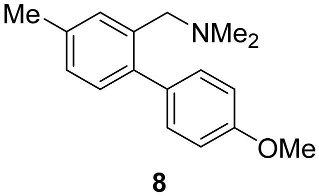
3057, 3022, 2970, 2940, 2853, 2813, 2765, 1612, 1455, 1039, 1010, 860, 768 cm^{-1}; HRMS (CI) calcd for $(C_{17}H_{21}N + H)^+$ 240.1752, found 240.1761.



7

3-(4'-Methyl-2'-(*N*,*N*-dimethylaminomethyl))acetophenone (7)

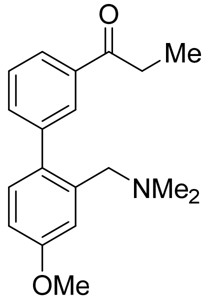
The general procedure was followed using 3-methyl-*N*,*N*-dimethylbenzylamine (0.298 g, 2.00 mmol) and 3-bromoacetophenone (0.291 mL, 2.20 mmol). The coupling reaction was heated to 100 °C for 16 h. The crude product was purified by flash column chromatography (100% ethyl acetate) to give **7** as a pale brown oil (0.449 g, 84%); ^{1}H NMR (500 MHz, C_6D_6) δ 8.24 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.37 (s, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 6.5 Hz, 1H), 3.19 (s, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 2.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 141.8, 138.6, 137.4, 136.7, 136.0, 134.3, 130.7, 129.9, 129.8, 128.1, 127.7, 126.5, 61.0, 45.3, 26.7, 21.1; IR (neat) 3023, 2941, 2814, 2764, 1685, 1600, 1358, 1231 cm^{-1}; HRMS (CI) calcd for $(C_{18}H_{21}NO + H)^+$ 268.1701, found 268.1692.



8

5-Methyl-2-(4'-methoxyphenyl)-*N*,*N*-dimethylbenzylamine (8)

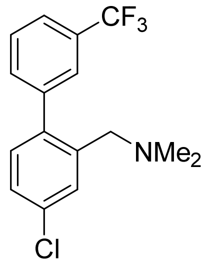
The general procedure was followed using 3-methyl-*N*,*N*-dimethylbenzylamine (0.413 g, 1.5 mmol) and 4-bromoanisole (0.207 mL, 1.65 mmol). The coupling reaction was heated to 100 °C for 17 h. The crude product was purified by flash column chromatography (73:27 ethyl acetate:hexanes) to give **8** as a pale brown oil (0.153 g, 40%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (s, 1H), 7.27 (d, *J* = 8.7, 2H), 7.12 (m, 2H), 6.94 (d, *J* = 8.8, 2H), 3.86 (s, 3H), 3.33 (s, 2H), 2.39 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.5, 139.2, 137.0, 136.7, 133.9, 130.8, 130.3, 130.0, 129.7, 127.9, 127.5, 113.3, 60.9, 55.3, 45.4, 21.2 ; IR (thin film) 2940, 2855, 2814, 2765, 1610, 1490, 1456, 1245, 1177, 1041, 820 cm^{-1}; HRMS (CI) calcd for (C$_{17}$H$_{21}$NO + H)$^+$ 256.1701, found 256.1698.



9

3-(4'-Methoxy-2'-(*N*,*N*-dimethylaminomethyl))propiophenone (**9**)

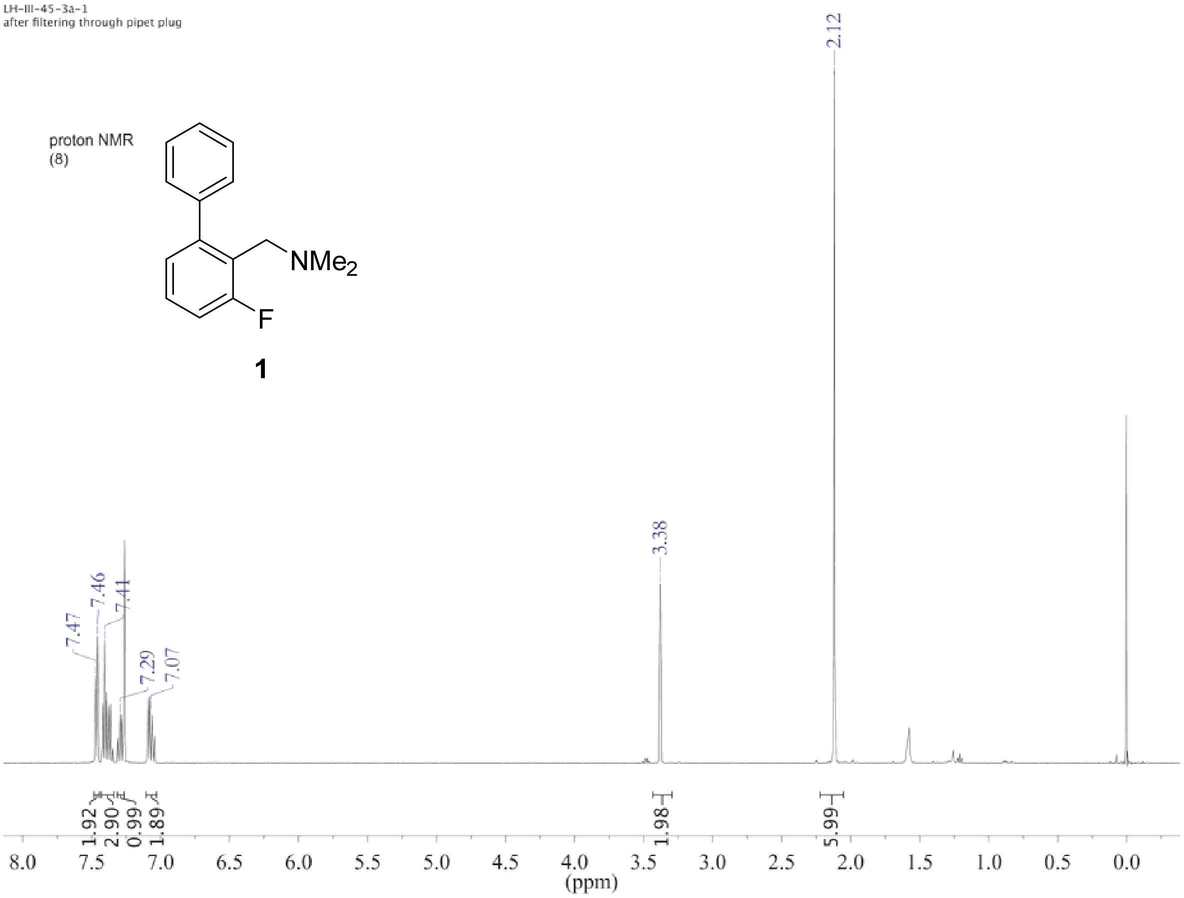
The general procedure was followed using 3-methoxy-*N*,*N*-dimethylbenzylamine (0.582 g, 2.00 mmol) and 3-bromopropiophenone (0.469 g, 2.20 mmol). The coupling reaction was heated to 100 °C for 18 h. The crude product was purified by flash column chromatography (90:10 ethyl acetate:hexanes) to give **9** as a pale yellow solid (0.471 g, 79%): mp 64–72 °C; ^{1}H NMR (500 MHz, CDCl$_3$) 7.99 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.2, 2H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 2.6, 1H), 6.87 (dd, *J* = 2.7 Hz, 1H), 3.86 (s, 3H), 3.31 (s, 2H), 3.06 (q, *J* = 7.2 Hz, 2H), 2.15 (s, 6H), 1.26 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 200.6, 159.33, 146.2, 137.9, 135.1, 133.8, 130.9, 130.0, 127.7, 114.8, 112.7, 61.2, 55.4, 45.3, 31.8, 8.4 ; IR (neat) 2818, 1611, 1453, 1234, 1017, 820, 782, 570 cm^{-1}; HRMS (CI) calcd for $(C_{19}H_{23}NO_2 + Na)^+$ 320.1627, found 320.1616.



10

5-Chloro-2-(3'-trifluoromethylphenyl)-*N*,*N*-dimethylbenzylamine (10)

The general procedure was followed using 3-chloro-*N*,*N*-dimethylbenzylamine (0.591 g, 2.00 mmol) and 3-trifluoromethyliodobenzene (0.382 mL, 2.20 mmol). The coupling reaction was heated to 100 °C for 16 h. The crude product was purified by flash column chromatography (10:90 ethyl acetate:hexanes) to give **10** as a pale brown oil (0.392 g, 62%): ^{1}H NMR (500 MHz, $CDCl_3$) 7.72 (s, 1H), 7.62 (m, 1H), 7.53 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 3.22 (s, 2H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 141.1, 139.3, 138.5, 133.8, 132.8, 131.2, 130.4 (q, *J* = 39.4 Hz), 130.0, 128.5, 127.2, 126.4 (q, *J* = 12.2 Hz), 124.2 (q, *J* = 338.8 Hz), 124.0 (q, *J* = 13.8 Hz), 60.8, 45.1; IR (neat) 3060, 2976, 2945, 2860, 2819, 2771, 1594, 1333, 1269, 1167, 1122 cm^{-1}; HRMS (CI) calcd for $(C_{16}H_{15}F_3N + H)^+$ 314.0923, found 314.0923.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7.46
7.41
7.29
7.07
1.92
2.90
0.99
1.89
1.98
5.99
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
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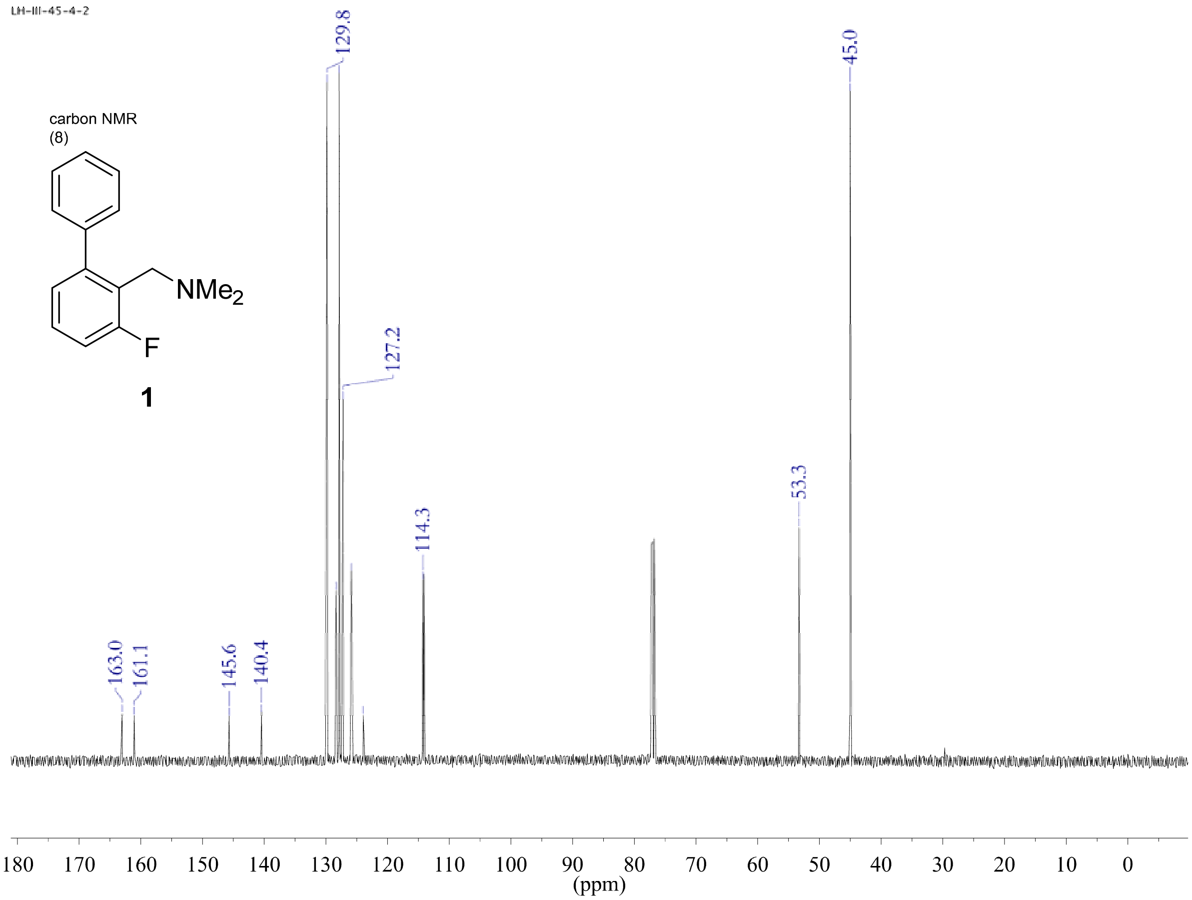
(ppm)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145.6
140.4
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140
130
120
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100
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80
70
60
50
40
30
20
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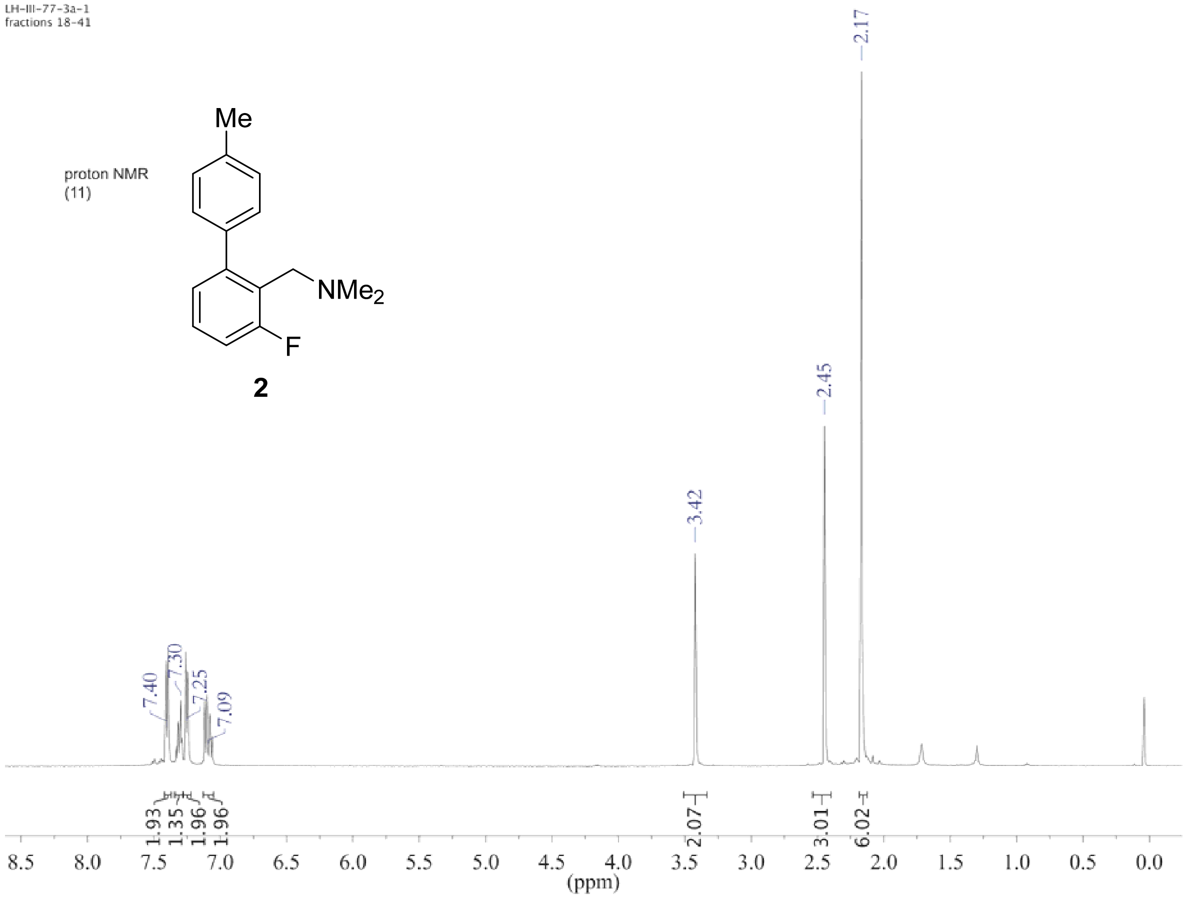
(ppm)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2.45
2.17
1.93
1.35
1.96
1.96
2.07
3.01
6.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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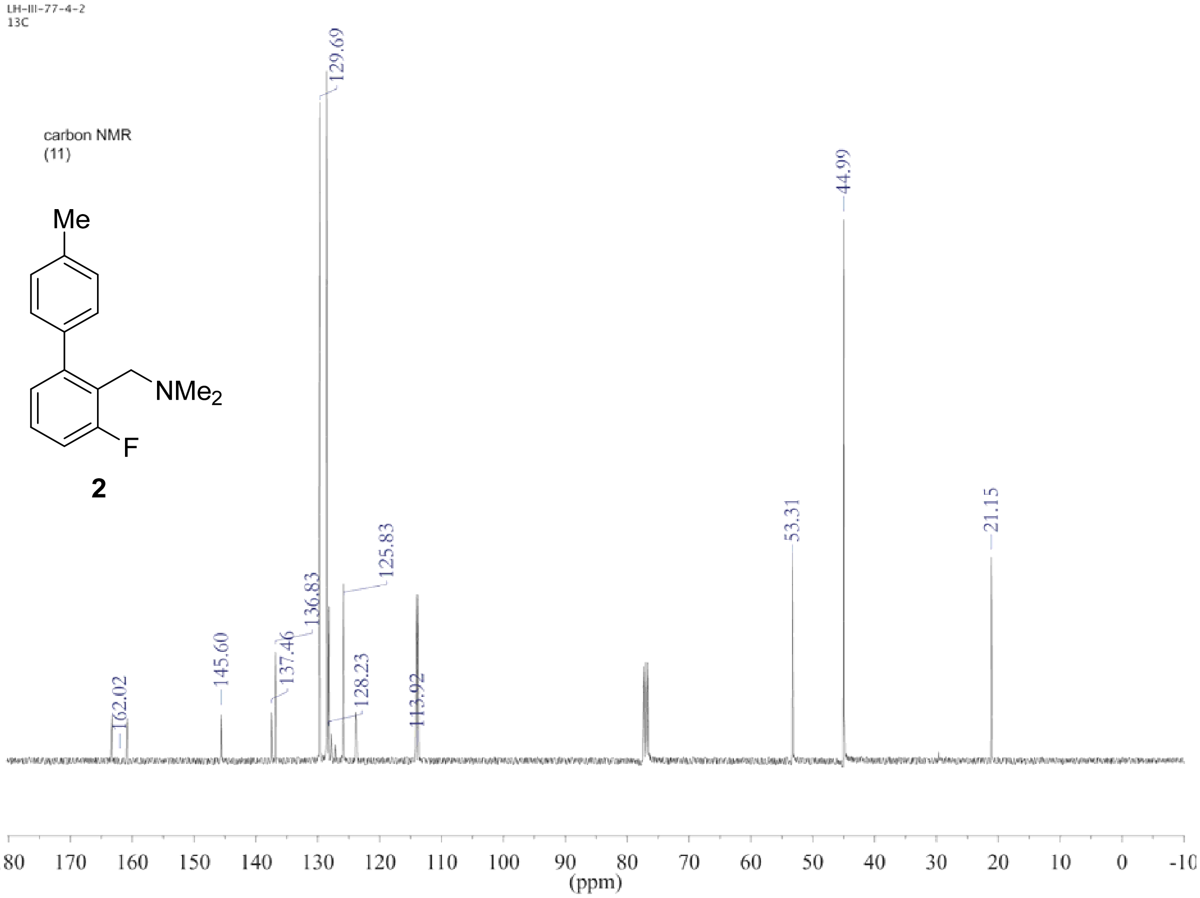
(ppm)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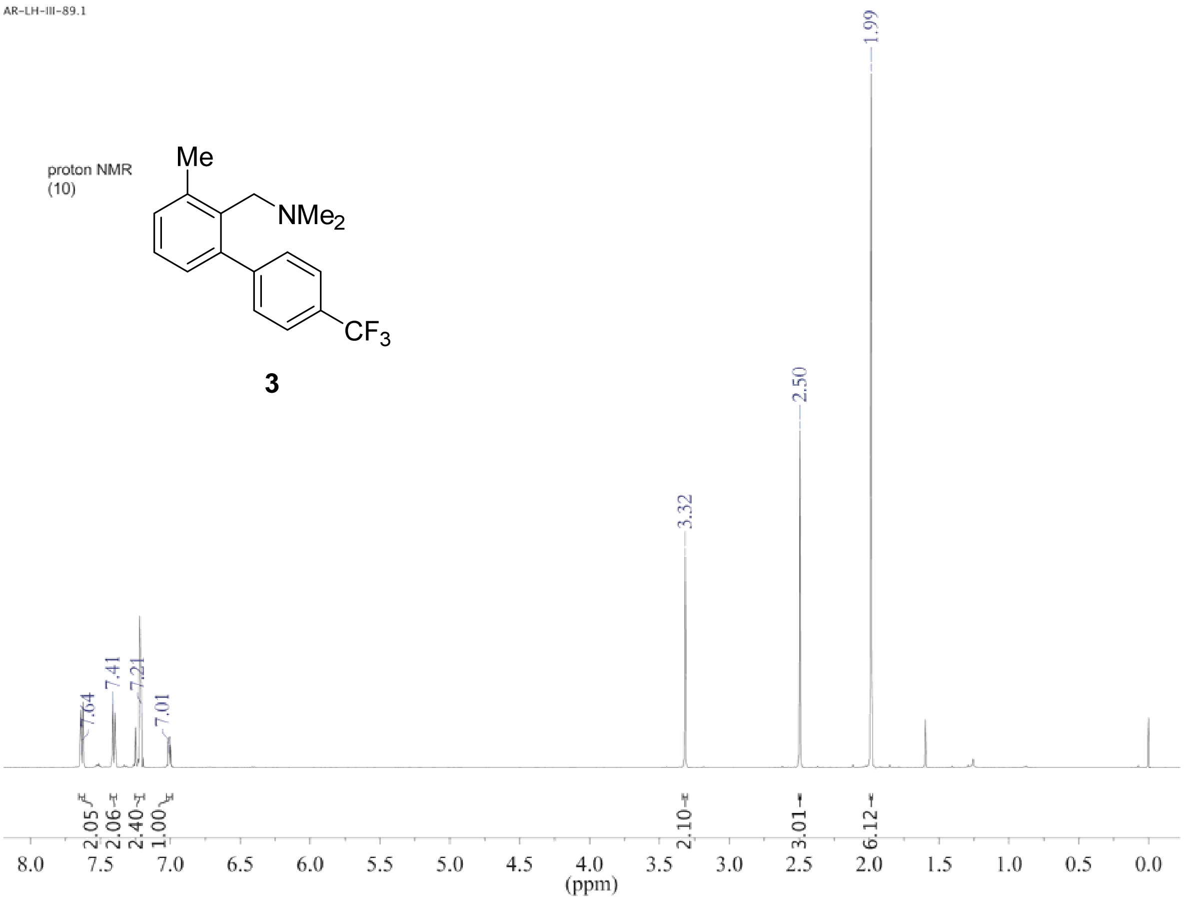
(ppm)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2.05
2.06
2.40
1.00
2.10
3.01
6.12
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7.0
6.5
6.0
5.5
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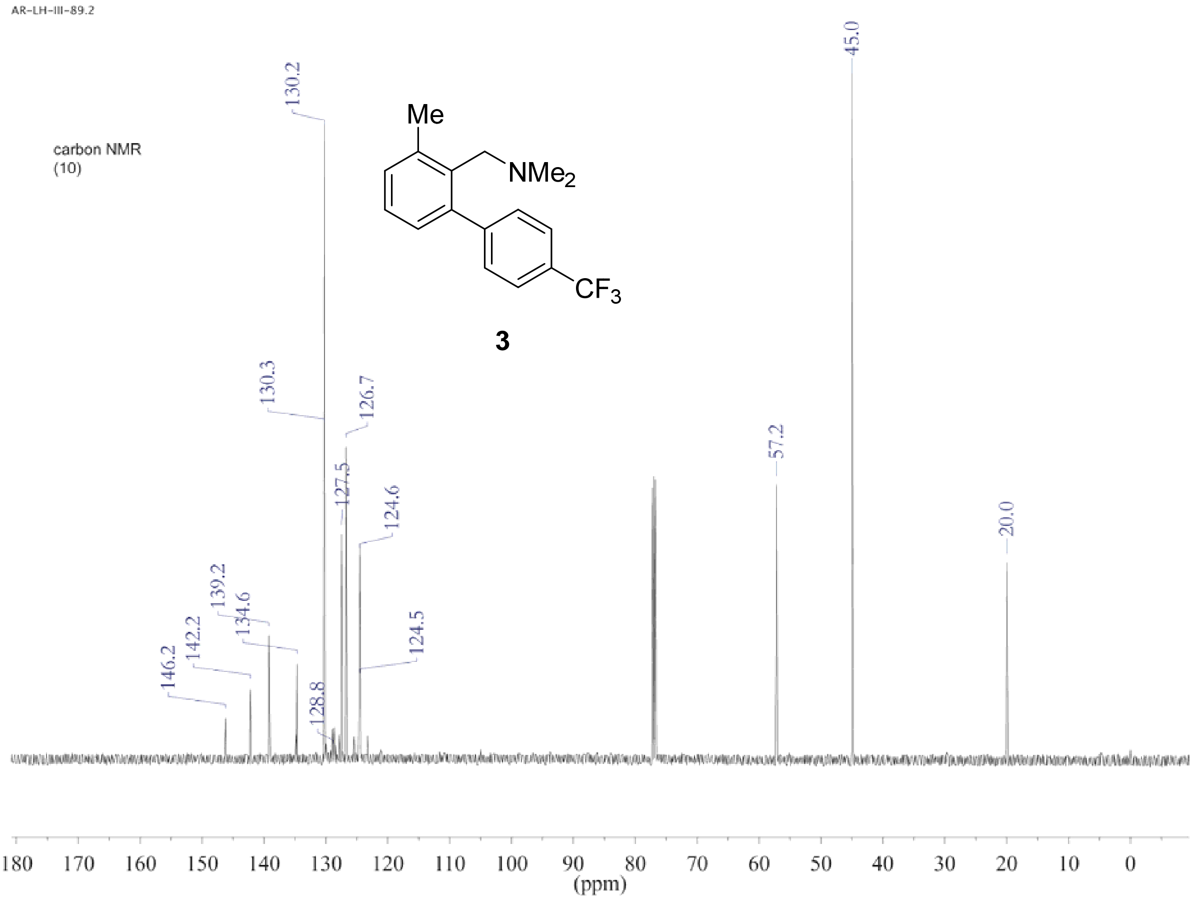
(ppm)

3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CF3
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124.6
20.0
139.2
142.2
134.6
146.2
124.5
128.8
180
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120
110
100
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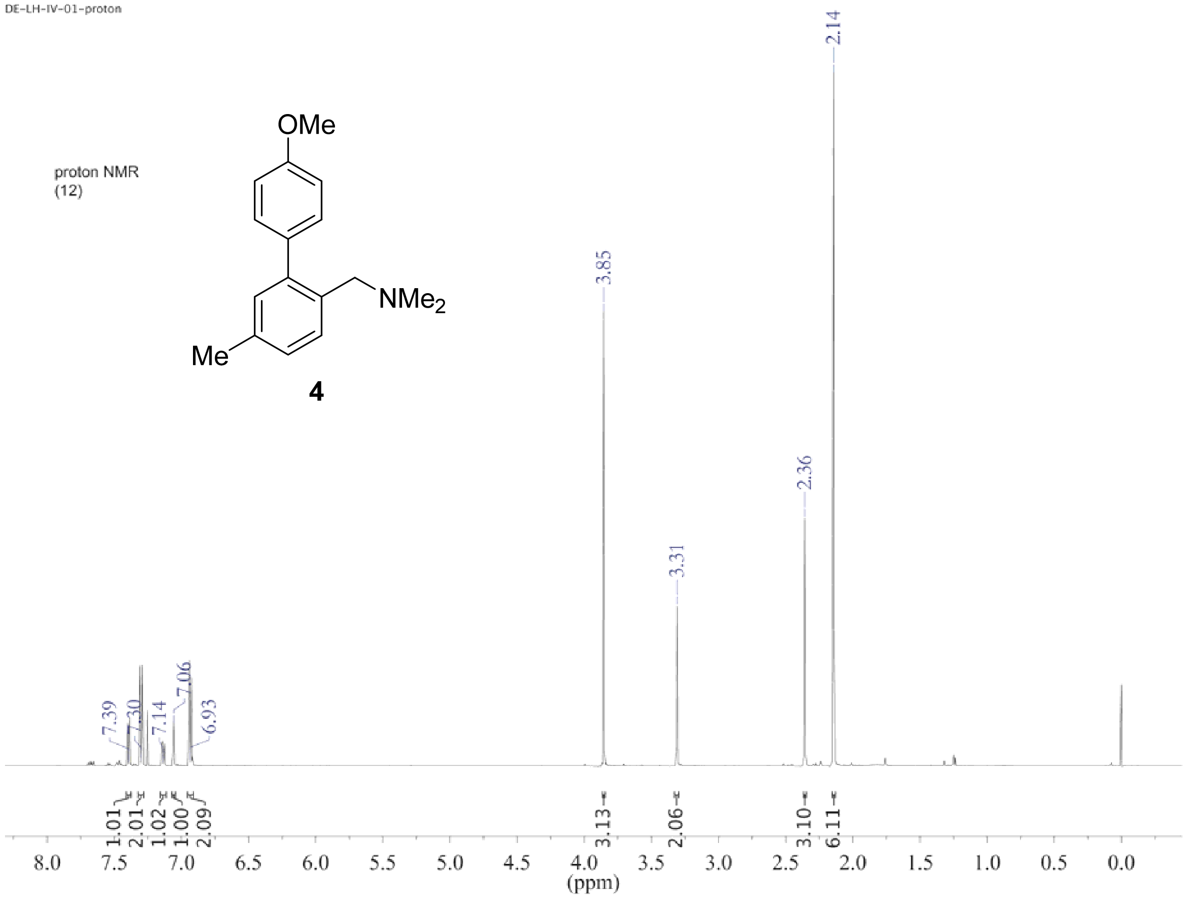
80
70
60
50
40
30
20
10
0
(ppm)

3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(12)
OMe
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Me
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3.31
2.36
2.14
1.01
2.01
1.02
1.00
2.09
3.13
2.06
3.10
6.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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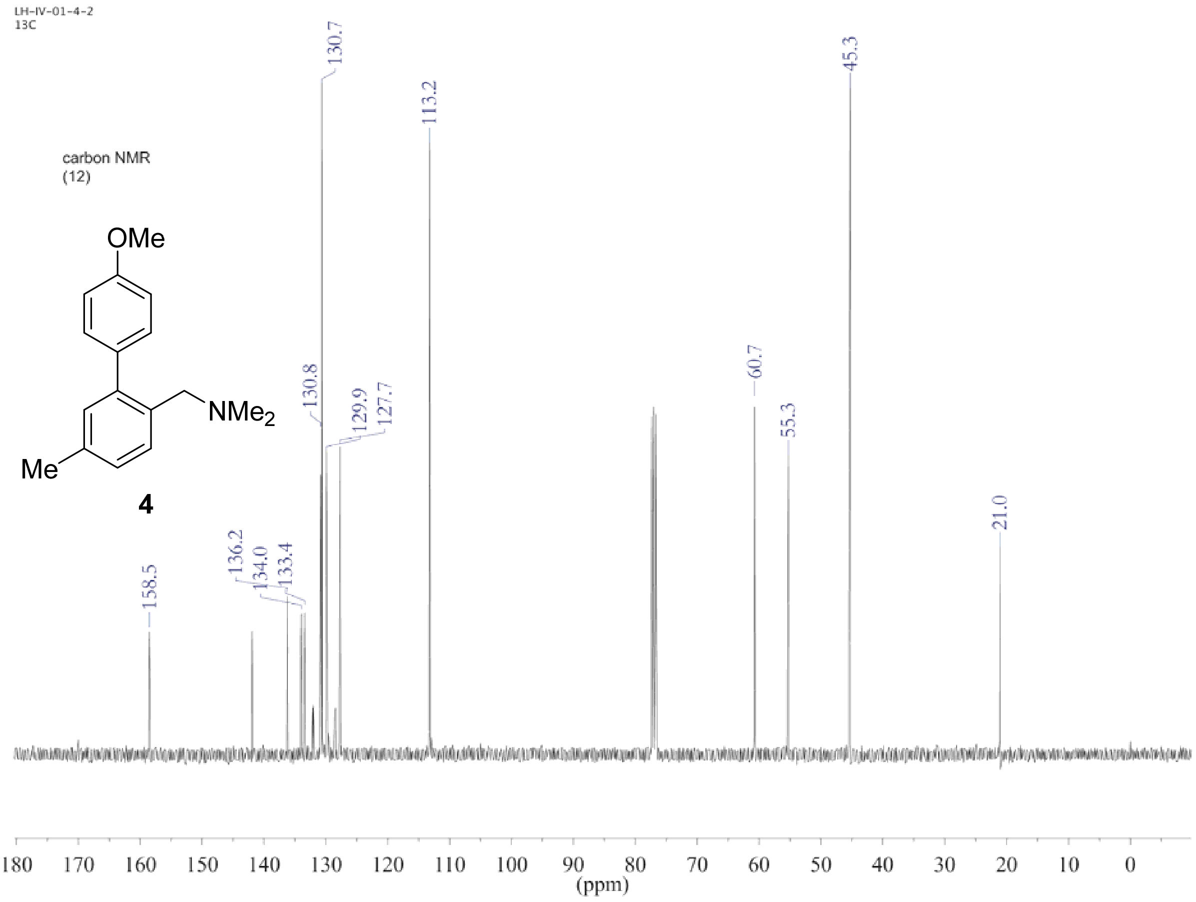
(ppm)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113.2
60.7
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45.3
21.0
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50
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20
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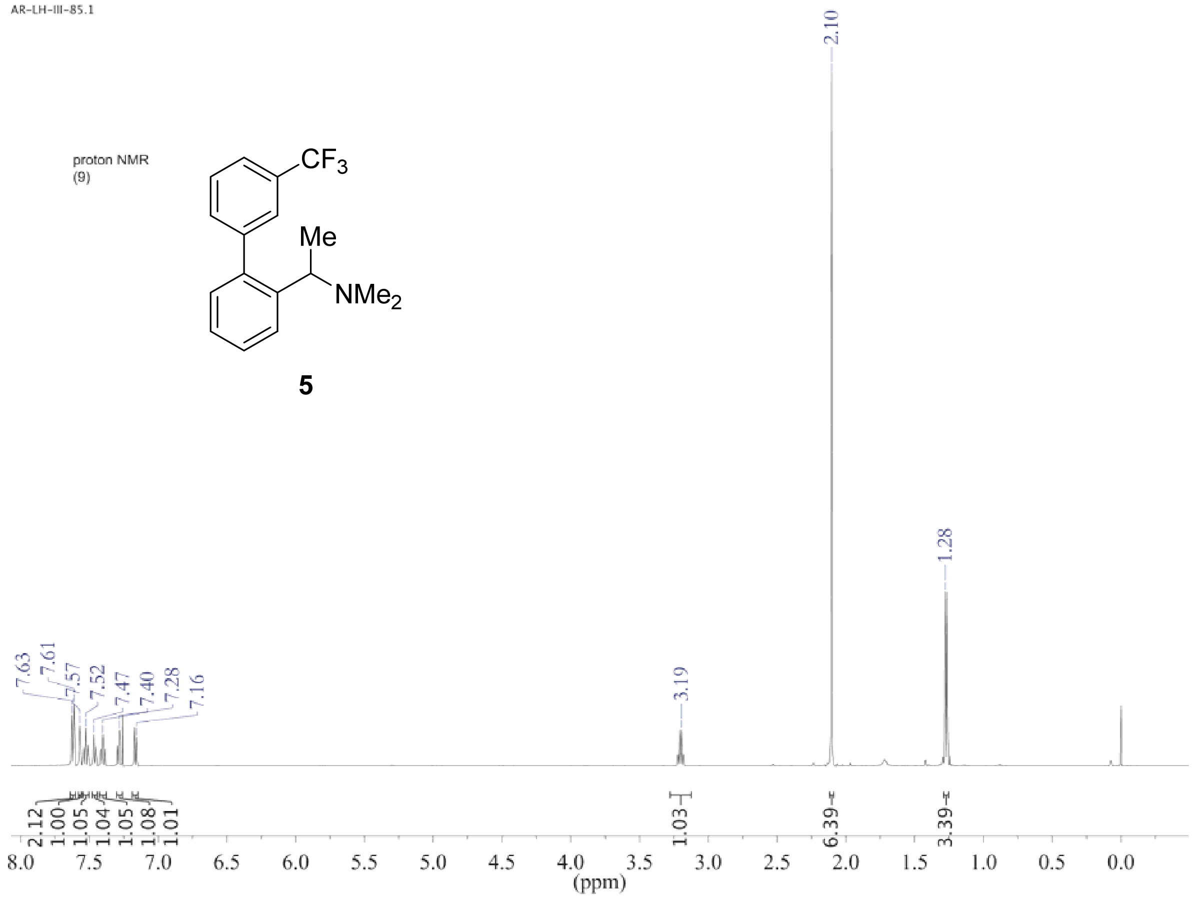
(ppm)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(9)
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1.28
2.12
1.00
1.05
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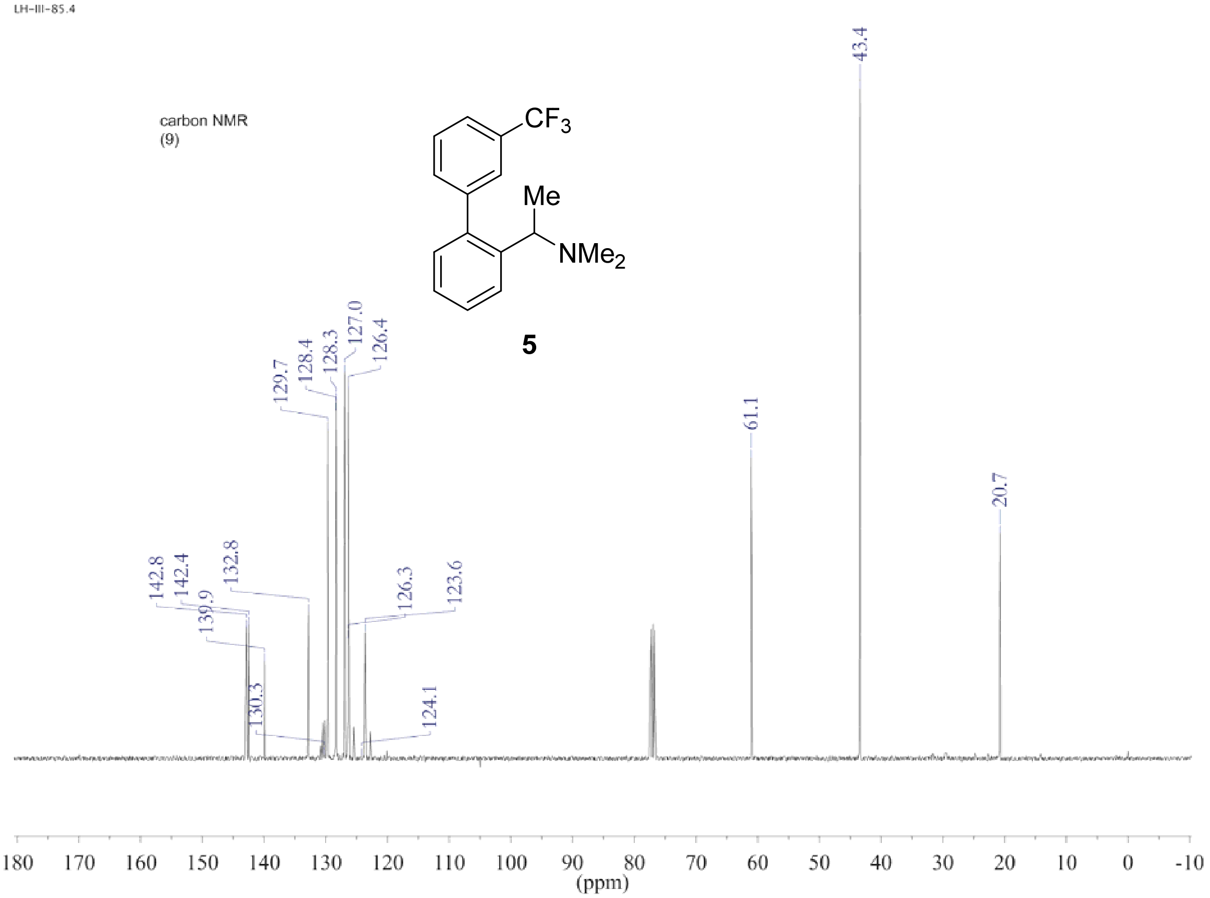
1.05
1.08
1.01
1.03
6.39
3.39
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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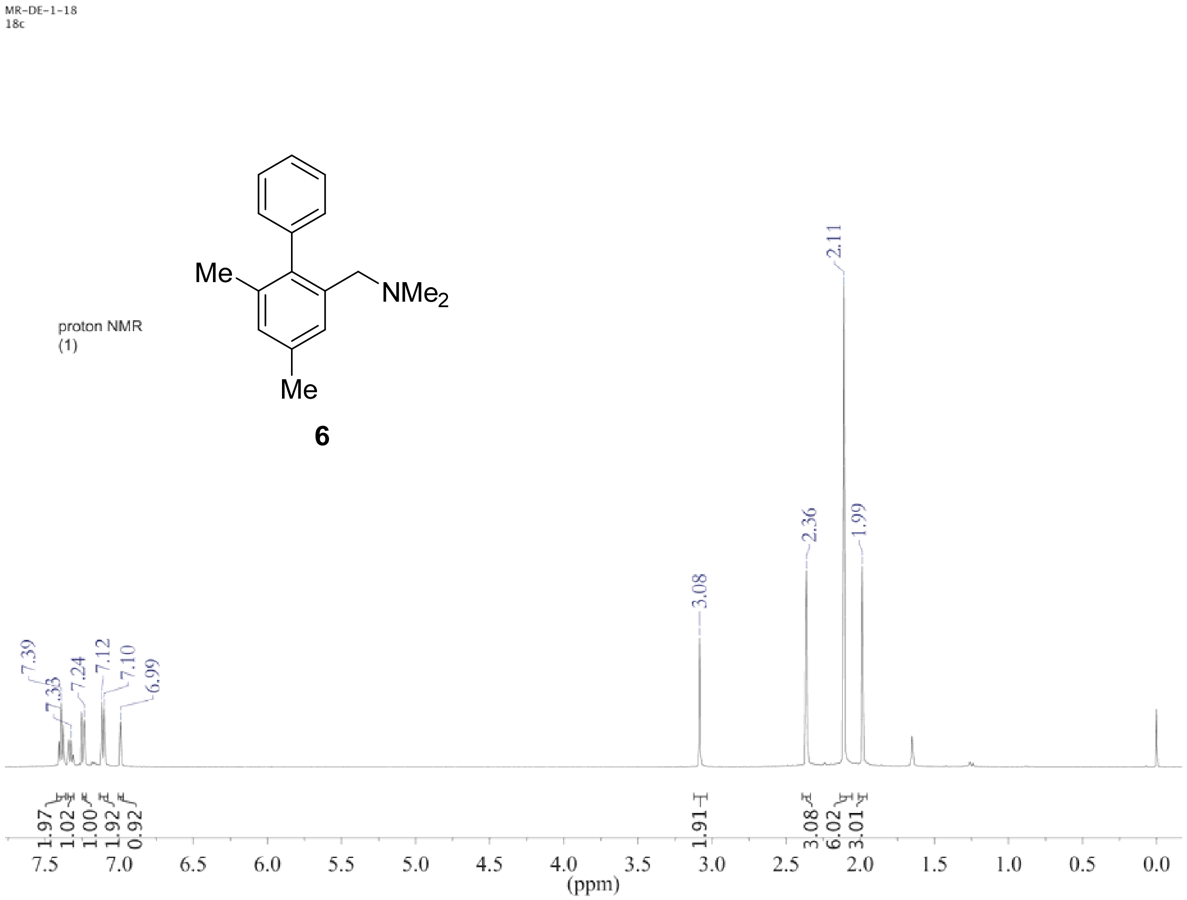
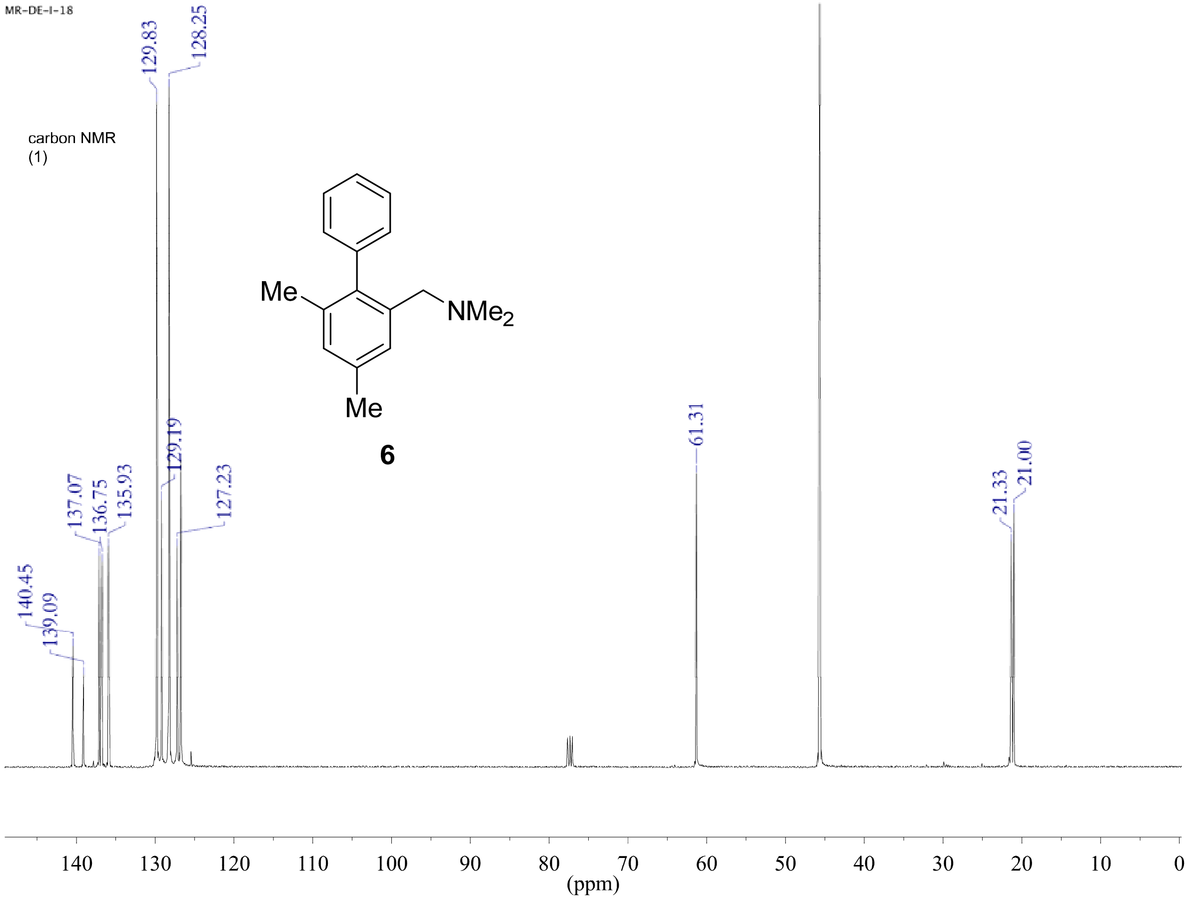
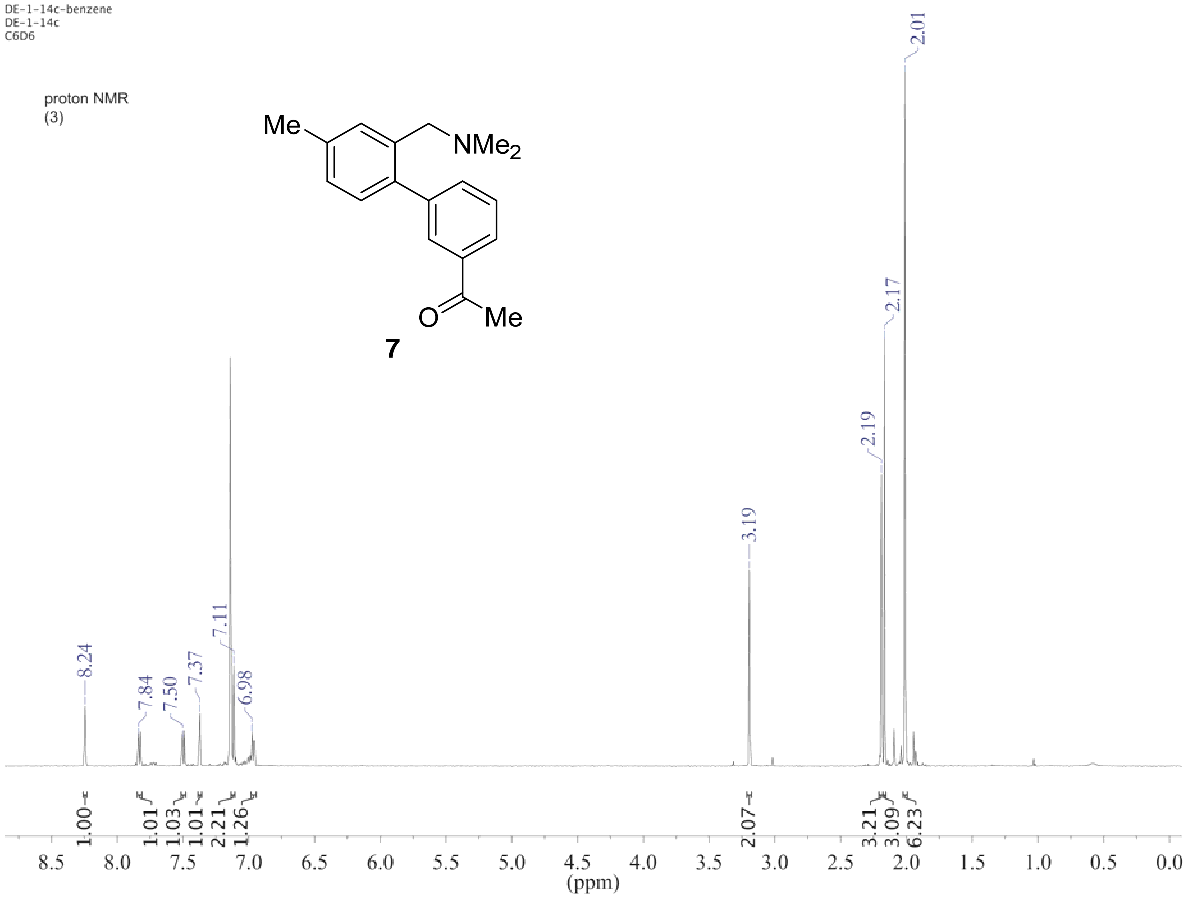
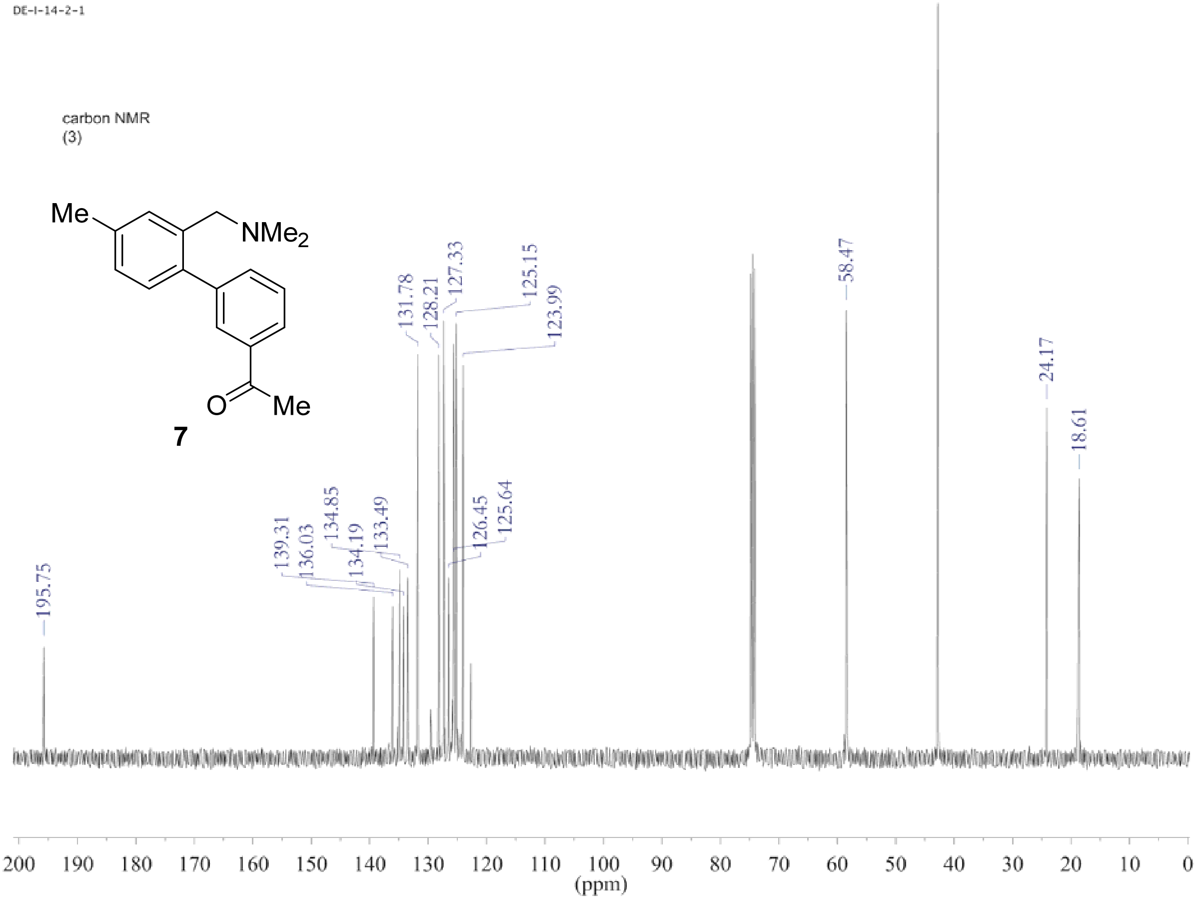
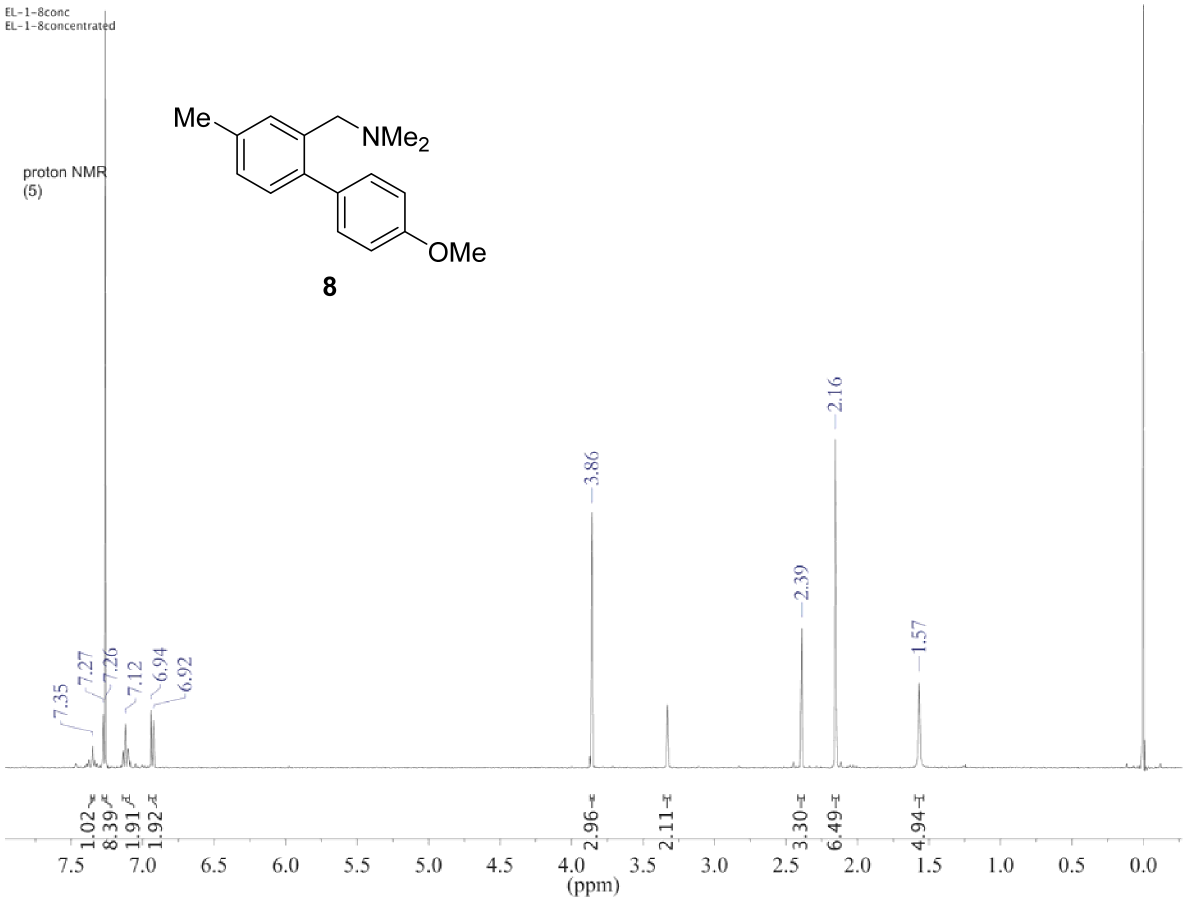
carbon NMR
(9)
CF3
Me
NMe2
5
142.8
142.4
139.9
132.8
130.3
129.7
128.4
128.3
127.0
126.4
126.3
124.1
123.6
61.1
43.4
20.7
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

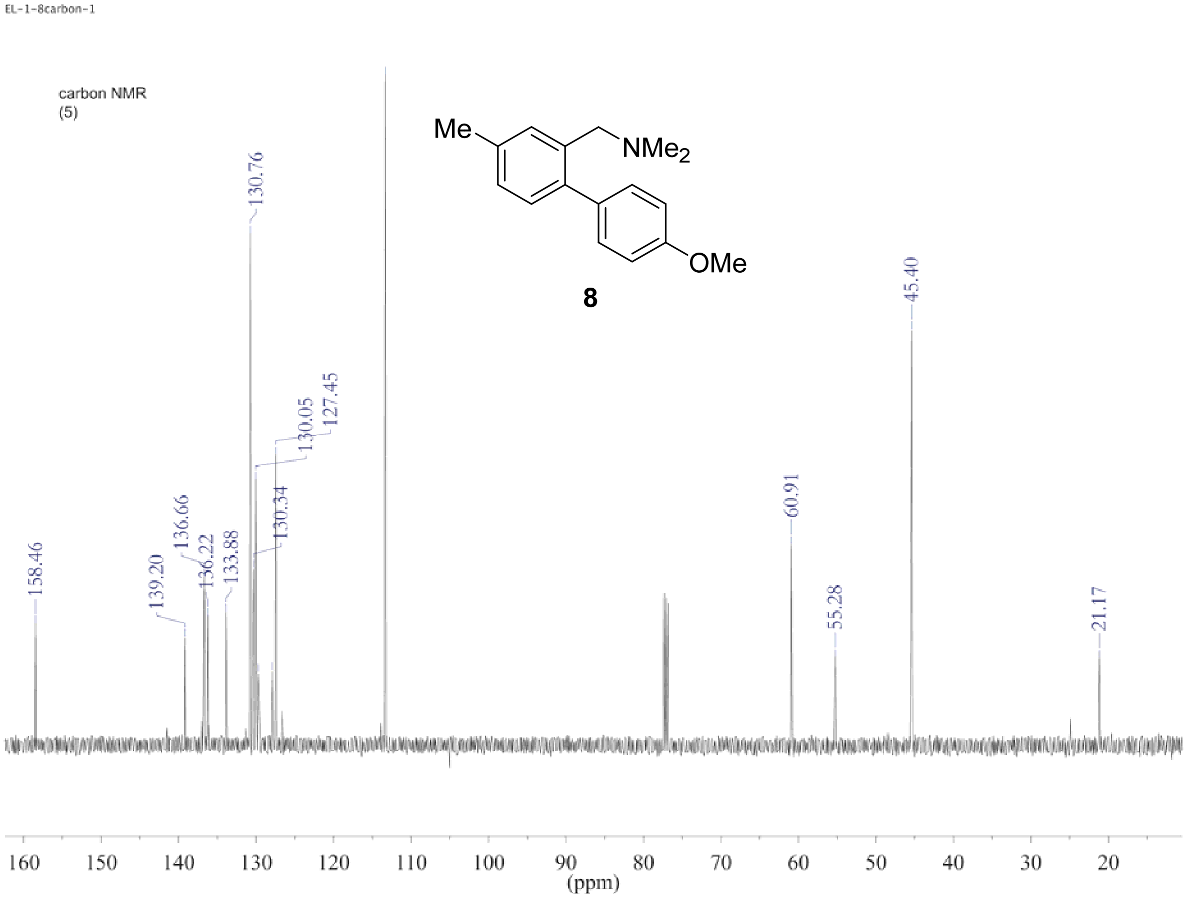

MR-DE-1-18
18c
proton NMR
(1)
Me
NMe2
Me
6
7.39
7.33
7.24
7.12
7.10
6.99
3.08
2.36
2.11
1.99
1.97
1.02
1.00
1.92
0.92
1.91
3.08
6.02
3.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

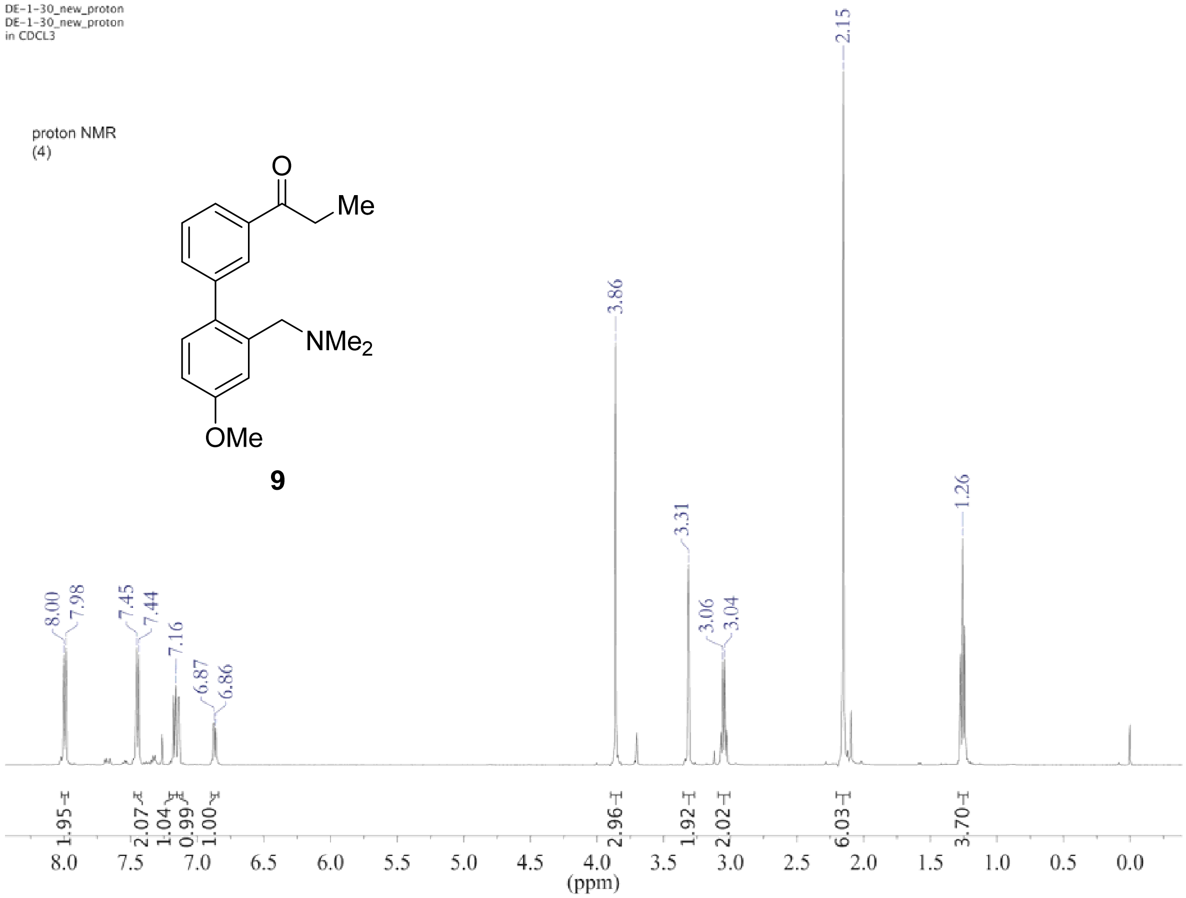

MR-DE-I-18
carbon NMR
(1)
Me
NMe2
Me
6
129.83
128.25
140.45
139.09
137.07
136.75
135.93
129.19
127.23
61.31
21.33
21.00
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

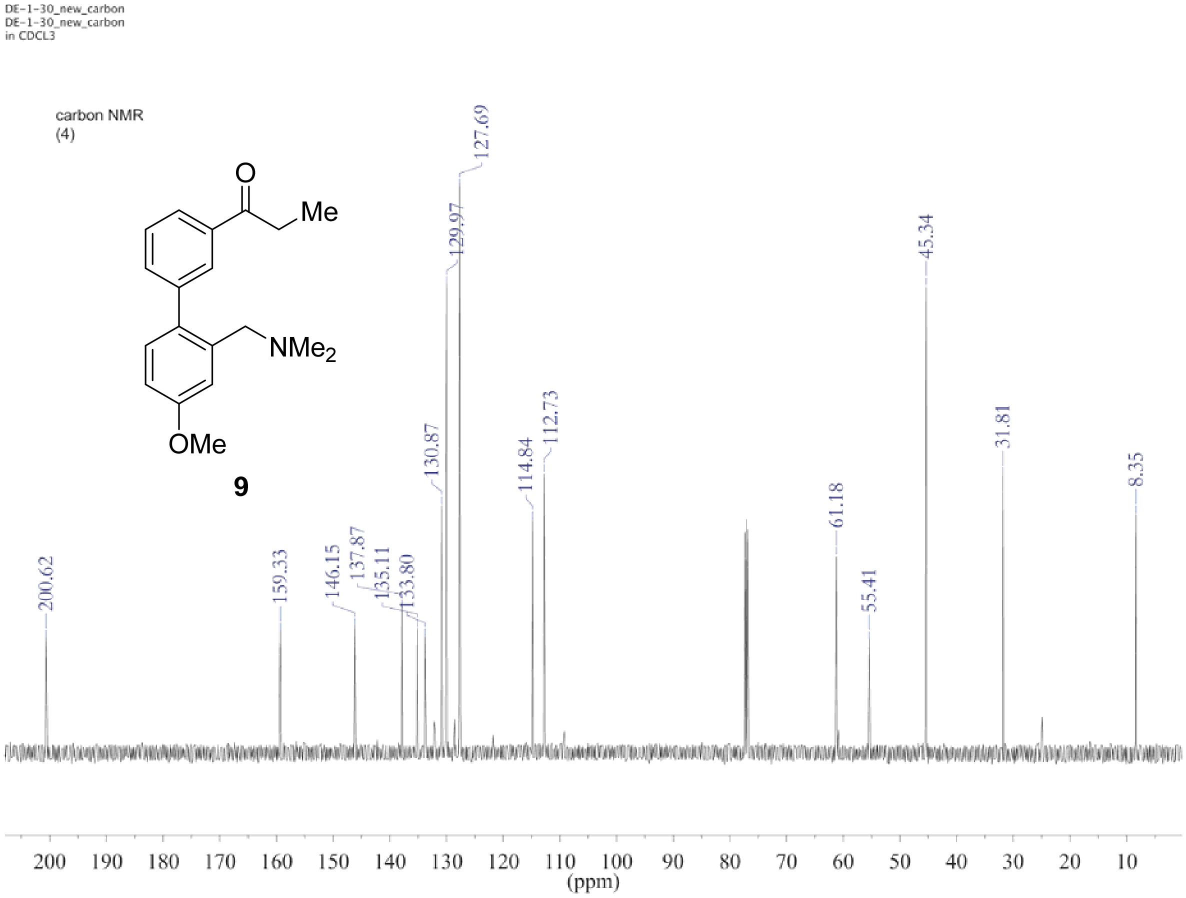

DE-1-14c-benzene
DE-1-14c
C6D6
proton NMR
(3)
Me
NMe2
O
Me
7
8.24
7.84
7.50
7.37
7.11
6.98
3.19
2.19
2.17
2.01
1.00
1.01
1.03
1.01
2.21
1.26
2.07
3.21
3.09
6.23
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

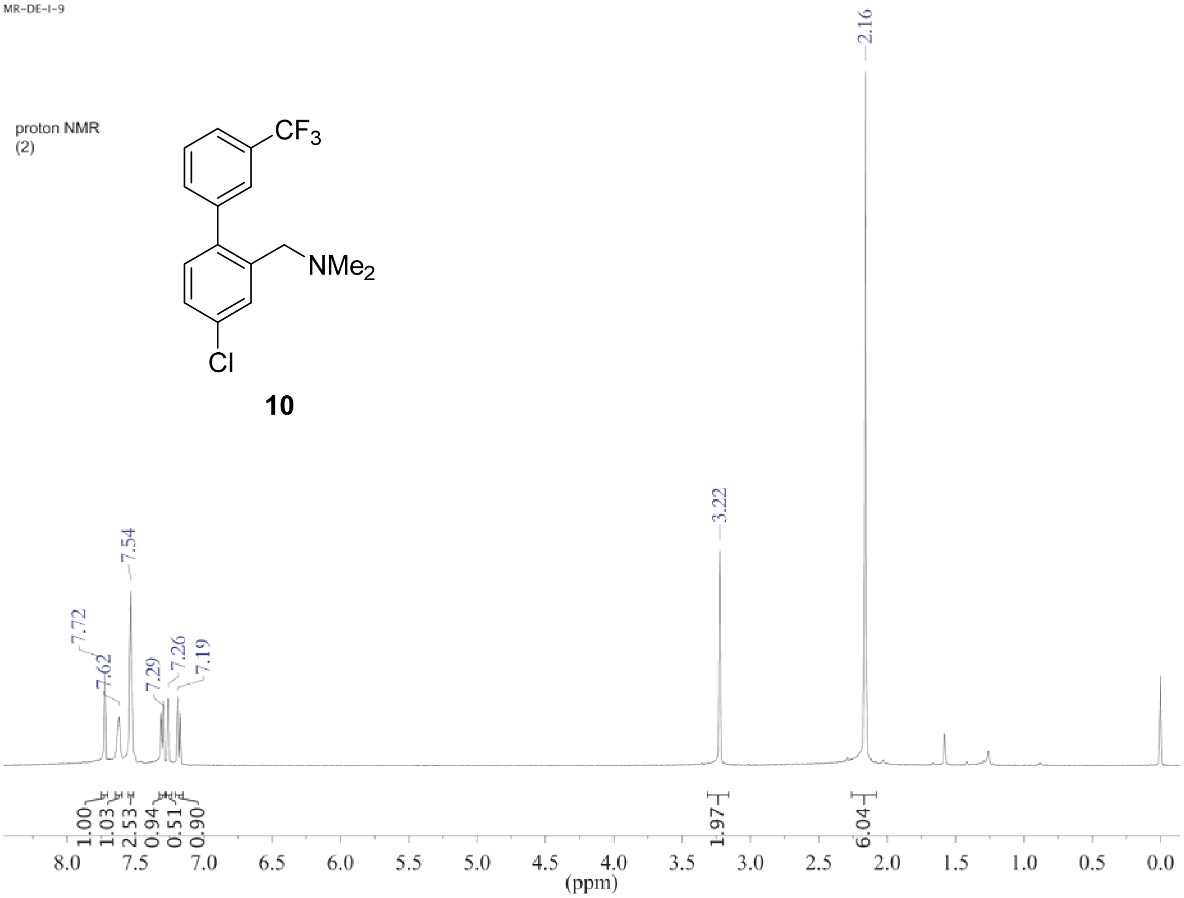

DE-I-14-2-1
carbon NMR
(3)
Me
NMe2
O
Me
7
195.75
139.31
136.03
134.85
134.19
133.49
131.78
128.21
127.33
126.45
125.64
125.15
123.99
58.47
24.17
18.61
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

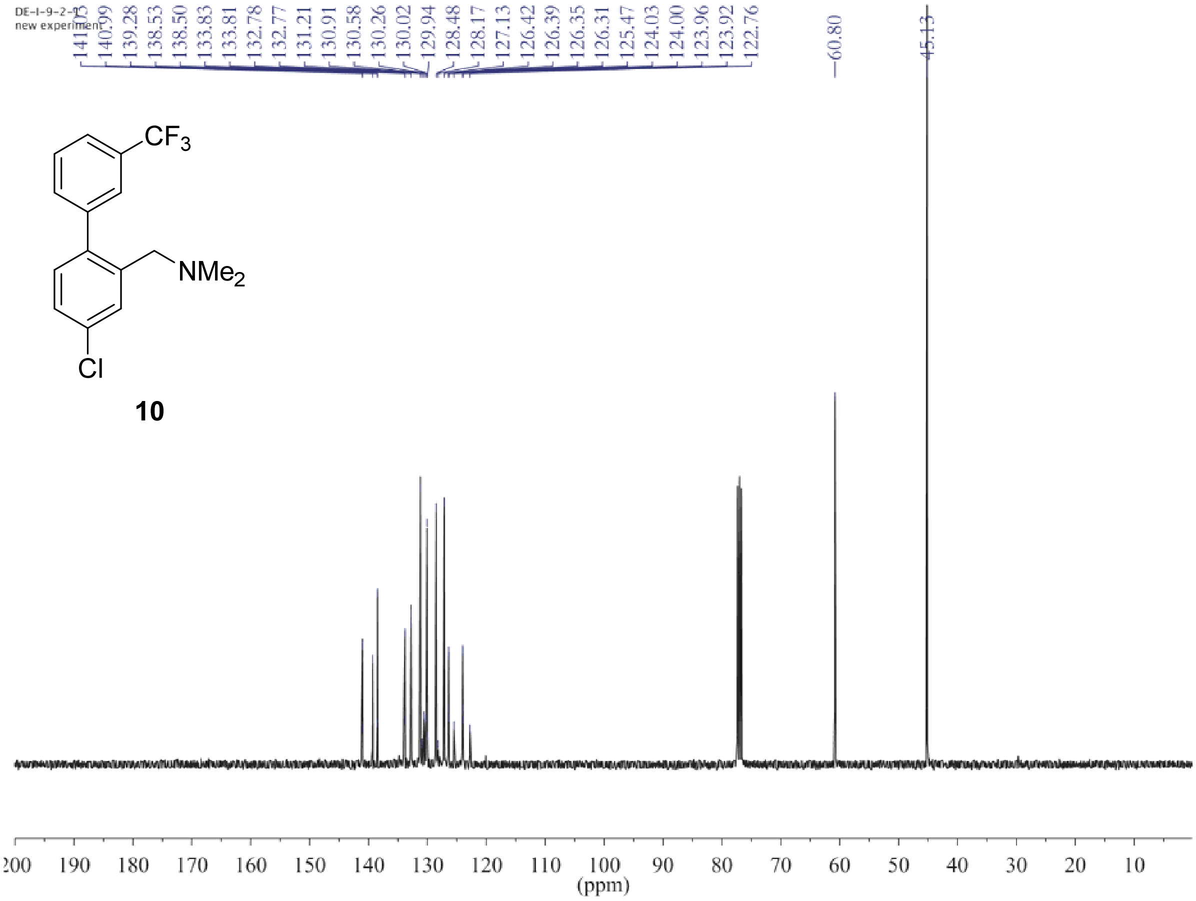

EL-1-8conc
EL-1-8concentrated
proton NMR
(5)
Me
NMe2
OMe
8
7.35
7.27
7.26
7.12
6.94
6.92
3.86
2.39
2.16
1.57
1.02
8.39
1.91
1.92
2.96
2.11
3.30
6.49
4.94
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


EL-1-8carbon-1
carbon NMR
(5)
Me
NMe2
OMe
8
158.46
139.20
136.66
136.22
133.88
130.76
130.34
130.05
127.45
60.91
55.28
45.40
21.17
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


DE-1-30_new_proton
DE-1-30_new_proton
in CDCL3
proton NMR
(4)
O
Me
NMe2
OMe
9
8.00
7.98
7.45
7.44
7.16
6.87
6.86
3.86
3.31
3.06
3.04
2.15
1.26
1.95
2.07
1.04
0.99
1.00
2.96
1.92
2.02
6.03
3.70
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


DE-1-30_new_carbon
DE-1-30_new_carbon
in CDCL3
carbon NMR
(4)
O
Me
NMe2
OMe
9
200.62
159.33
146.15
137.87
135.11
133.80
130.87
129.97
127.69
114.84
112.73
61.18
55.41
45.34
31.81
8.35
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


MR-DE-I-9
proton NMR
(2)
CF3
NMe2
Cl
10
7.72
7.62
7.54
7.29
7.26
7.19
3.22
2.16
1.00
1.03
2.53
0.94
0.51
0.90
1.97
6.04
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


DE-I-9-2-1
new experiment
141.05
140.99
139.28
138.53
138.50
133.83
133.81
132.78
132.77
131.21
130.91
130.58
130.26
130.02
129.94
128.48
128.17
127.13
126.42
126.39
126.35
126.31
125.47
124.03
124.00
123.96
123.92
122.76
60.80
45.13
CF3
NMe2
Cl
10
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)