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The synthesis of tetrasubstituted propargylamines from cyclohexanones by solvent-free copper(II) catalysis

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General reagent information

All reactions were set up in the air and carried out in oven-dried screw-cap test-tubes with Teflon seals under an atmosphere of nitrogen. Flash column chromatography was performed using silica gel purchased from Silicycle. $CuCl_2$ was purchased from Acros and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, or Aldrich and distilled before use. All ketones and alkynes were purchased from Acros Organics, Alfa Aesar or TCI America and were purified by distillation before use.

General analytical information

^1H and ^{13}C NMR spectra were measured on a Varian Inova 400 (400 MHz) spectrometer using $CDCl_3$ as a solvent and trimethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. NMR spectra were acquired at 300 K. Gas chromatography (GC) was carried out on an Agilent Technologies 6850 Network GC System, and dodecane was used as the internal standard. IR spectra were recorded on Perkin Elmer Spectrum One FT-IR Spectrometer. Attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm^{-1}). Mass spectrometric data was collected on a HP 5989A GC/MS quadrupole instrument. Exact masses were recorded on a Waters GCT Premier ToF instrument using direct injection of samples in acetonitrile into the electrospray source.

General procedure

An oven-dried test tube equipped with a magnetic stir bar was charged with 5 mol % $CuCl_2$, capped with a septum, and purged with argon for 5 minutes. Cyclohexanone (1.0 equiv), alkyne (1.0 equiv.), and amine (1.0 equiv) were added, and the septum under Argon pressure was then quickly replaced with a Teflon-seal screw cap. The reaction was stirred at 110 °C for the indicated time. Upon reaction completion as confirmed by GC analysis, the mixture was cooled to room temperature and loaded directly atop a silica gel column. Chromatography with the solvent system indicated as the eluent afforded the desired product.

^1H and ^{13}C NMR Spectra for Compounds from original communication available at: http://dx.doi.org/10.1039/C2GC35713E

Characterization data for new compounds

1-(oct-1-yn-1-yl)-*N*-(4-(trifluoromethyl)benzyl)cyclohexanamine (4c)

Prepared according to the general procedure: 4-(trifluoromethyl)benzylamine (142 μL, 1.0 mmol), cyclohexanone (103 μL, 1.0 mmol), octyne (147 μL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 74% yield (0.270 g, 0.74 mmol) after chromatography on silica gel (20% EtOAc in hexanes). IR (film) 2946, 2853, 2155, 1460, 1325, 1174 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.47 (d, *J*= 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 3.86 (s, 2H), 2.17 (t, J = 6.8 Hz, 2H), 1.75 (d, *J* = 12 Hz, 2H), 1.60-1.12 (m, 17H), 0.81 (t, *J*= 6.8 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 145.8, 128.8, 128.7 (2 overlapping carbons), 125.3 (J= 4.0 Hz), 123.15, 84.9, 83.81, 55.0, 47.6, 38.7, 31.5, 29.3, 28.7, 26.1, 23.1, 22.8, 18.9, 14.2. HRMS (ESI) *m*/*z* calcd for $[M+H]^+$ requires 366.2403, found 366.2420.

4*N*-(4-(trifluoromethyl)benzyl)-1-((triisopropylsilyl)ethynyl) cyclohexanamine (4p)

Prepared according to the general procedure: 4-(trifluoromethyl)-benzylamine (142 μL, 1.0 mmol), cyclohexanone (103 μL, 1.0 mmol), (triisopropylsilyl) acetylene (269 μL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 80% yield (0.350 g, 0.80 mmol) after chromatography on silica gel (20% EtOAc in hexanes). IR (film) 2936, 2863, 2155, 1462, 1323, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.46 (d, *J*= 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 3.90 (s, 2H), 1.78 (d, *J* = 12 Hz, 3H), 1.58 (m, 6H), 1.33 (m, 2H), 1.13 (m, 2H) 1.02 (d, *J*= 4 Hz, 18H).^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 145.5, 128.8 (2 overlapping carbons), 125.3 (J= 4.0 Hz) (2 carbons overlapped), 112.1, 84.4, 55.8, 47.8, 38.4, 26.0, 23.1, 18.8, 11.4. HRMS (ESI) *m*/*z* calcd for $[M+H]^+$ requires 438.2798, found 438.2775.

N-benzyl-1-((triisopropylsilyl)ethynyl)cyclohexanamine (4q)

Prepared according to the general procedure: benzylamine (109 μL, 1.0 mmol), cyclohexanone (103 μL, 1.0 mmol), (triisopropylsilyl) acetylene (269 μL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 75% yield (0.277 g, 0.75 mmol) after chromatography on silica gel (10% EtOAc in hexanes). IR (film) 2931, 2862, 2154, 1461, 1279 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.27 (d, *J*= 7.2 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.13 (t, *J*= 7.2 Hz, 1H), 3.84 (s, 2H), 1.80 (d, *J* = 16 Hz, 3H), 1.59 (m, 6H), 1.34 (m, 2H), 1.17 (m, 2H) 1.03 (d, *J*= 4 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 141.2, 128.8, 128.6, 127.0, 112.5, 84.2, 55.9, 48.4, 38.4, 26.1, 23.3, 18.9, 11.5. HRMS (ESI) *m*/*z* calcd for $[M+H]^+$ requires 370.2925, found 370.2936.

N-benzyl-N-methyl-1-((triisopropylsilyl)ethynyl) cyclohexanamine (4r)

Prepared according to the general procedure: N-methyl-benzylamine (129 μL, 1.0 mmol), cyclohexanone (103 μL, 1.0 mmol), (triisopropylsilyl) acetylene (269 μL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 76% yield (0.291 g, 0.76 mmol) after chromatography on silica gel (10% EtOAc in hexanes). IR (film) 2932, 2863, 2153, 1462, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.24 (d, *J*= 8 Hz, 2H), 7.20 (t, *J* = 8 Hz, 2H), 7.11 (t, *J*= 8 Hz, 1H), 3.53 (s, 2H), 2.06 (s, 3H), 1.96 (d, *J* = 12 Hz, 3H), 1.64 (m, 2H), 1.54 (t, *J*= 9.6 Hz, 2H), 1.45 (t, *J*= 12 Hz, 2H), 1.18 (m, 4H) 1.03 (d, *J*= 4 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 141.2, 128.9, 128.2, 126.6, 109.0, 84.7, 59.6, 56.0, 36.98, 35.3, 25.9, 23.1, 18.9, 11.4. HRMS (ESI) *m*/*z* calcd for $[M+H]^+$ requires 384.3081, found 384.3089.

4-methyl-1-(1-((triisopropylsilyl)ethynyl)cyclohexyl) piperidine (4t)

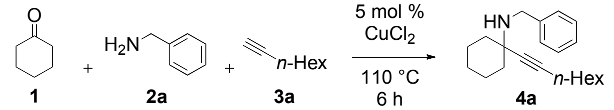
Prepared according to the general procedure: 4-methyl-piperidine (117 μL, 1.0 mmol), cyclohexanone (103 μL, 1.0 mmol), (triisopropylsilyl) acetylene (269 μL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 98% yield (0.354 g, 0.98 mmol) after chromatography on silica gel (20% EtOAc in hexanes). IR (film) 2926, 2863, 2154, 1462, 1258 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 2.96 (d, *J*= 16 Hz, 2H), 2.14 (t, *J* = 12 Hz, 2H), 1.96 (d, *J*= 16 Hz, 3H), 1.58 (m, 7H), 1.30 (t, *J* = 12.4 Hz, 3H), 1.13 (m, 5H), 1.01 (d, *J*= 4 Hz,18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 108.9, 85.19, 59.4, 46.4, 36.3, 35.0, 31.1, 25.8, 23.2, 21.8, 18.8, 11.4. HRMS (ESI) *m*/*z* calcd for $[M+H]^+$ requires 362.3238, found 362.3226.

1-methyl-4-(1-((triisopropylsilyl)ethynyl)cyclohexyl) piperazine (4u)

Prepared according to the general procedure: 1-methyl-piperazine (110 μL, 1.0 mmol), cyclohexanone (103 μL, 1.0 mmol), (triisopropylsilyl) acetylene (269 μL, 1.2 mmol), and $CuCl_2$ (6.7 mg, 0.05 mmol) afford the title compound as a yellow oil in 70% yield (0.253 g, 0.70 mmol) after column chromatography on silica gel (25% methanol in CH_2Cl_2). IR (film) 2932, 2863, 2155, 1456, 1283 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 2.65 (bs, 4H), 2.46 (bs, 4H), 2.22 (s, 3H), 1.91 (d, *J*= 16 Hz, 3H), 1.56 (m, 6H), 1.32 (t, *J*= 12 Hz, 2H), 1.12 (m, 2H), 1.00 (d, *J*= 4 Hz,18H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 108.0, 86.2, 58.9, 55.6, 45.8, 45.7, 35.9, 25.6, 22.9, 18.7, 11.3. HRMS (ESI) *m*/*z* calcd for $[M+H]^+$ requires 363.3190, found 363.3203.

Concentrated solvent screen study:

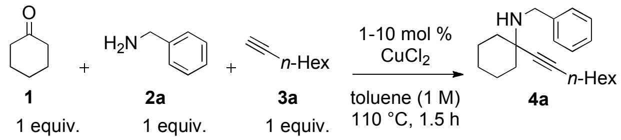
Carried out under the general procedure except with an added 1 mL solvent as indicated in entries 2-4: benzylamine (110 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), $CuCl_2$ (6.8 mg, 0.05 mmol), and dodecane internal standard (20 μl). GC aliquots were flushed through a silica gel pipette plug with diethyl ether.

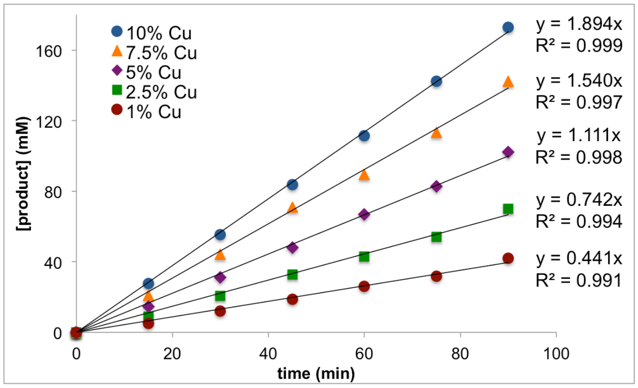


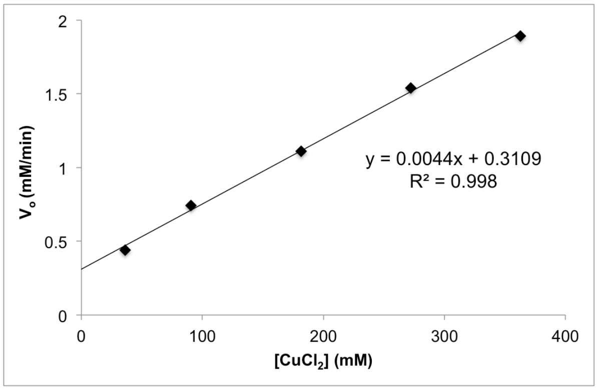
Entry	Solvent	GC yield (%)
1	none	90
2	hexanes	5
3	toluene	52
4	acetonitrile	18

Catalyst ($CuCl_2$) loading study:

At each catalyst loading, a set of identical reactions was set up; each data point represents the sole sample taken from a reaction. An oven-dried test tube equipped with a magnetic stir bar was charged with $CuCl_2$ (1–10 mol %, 1.3mg–13.4mg), capped with a septum, and purged with argon for 5 minutes. Cyclohexanone (103 μL, 1.0 mmol), octyne (147 μL, 1.0 mmol), benzylamine (109 μL, 1.0 mmol), dodecane internal standard (20 μl), and toluene (1 mL) were added via syringe. Under argon pressure, the septum was then quickly replaced with a Teflon-seal screw cap. The reaction was stirred at 110 °C for 90 minutes. GC aliquots at each time point were flushed through a silica gel pipette plug with diethyl ether.

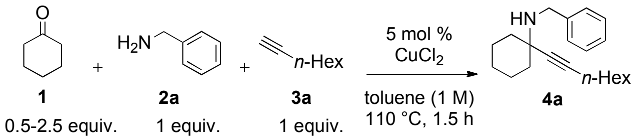


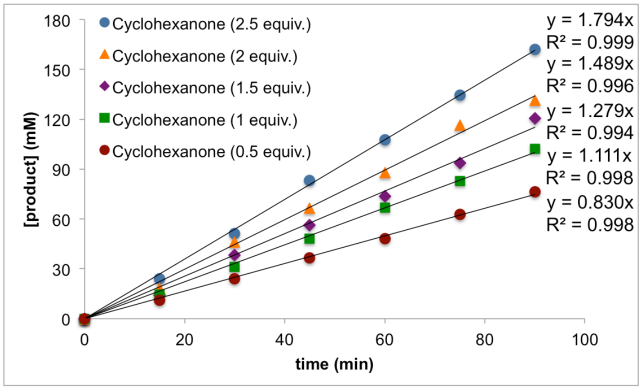


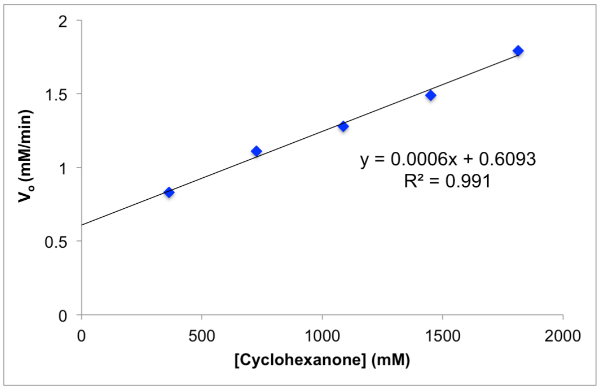


Cyclohexanone Concentration Study:

At each concentration of cyclohexanone, a set of identical reactions was set up; each data point represents the sole sample taken from a reaction. An oven-dried test tube equipped with a magnetic stir bar was charged with $CuCl_2$ (5 mol %, 6.7 mg), capped with a septum, and purged with argon for 5 minutes. Toluene (1051 μL - 846 μL) was added such that the total reaction volume remained constant. The dodecane internal standard (20 μL) was added, followed by cyclohexanone (51 μL – 257 μL, 0.5 – 2.5 mmol), benzylamine (109 μL, 1.0 mmol) and octyne (147 μL, 1.0 mmol). Under argon pressure, the septum was then quickly replaced with a Teflon-seal screw cap. The reaction was stirred at 110 °C for 90 minutes. GC aliquots at each time point were flushed through a silica gel pipette plug with diethyl ether.

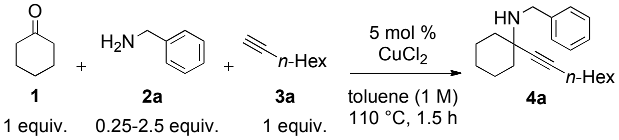


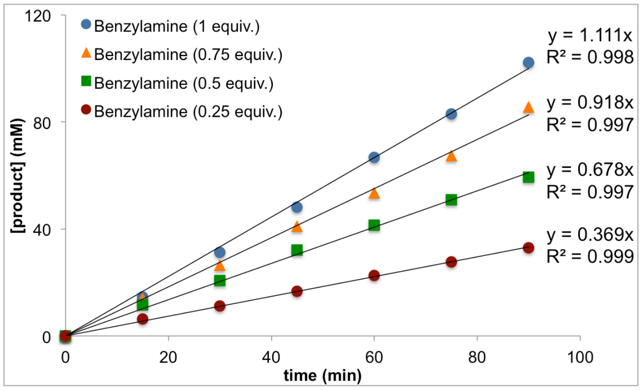


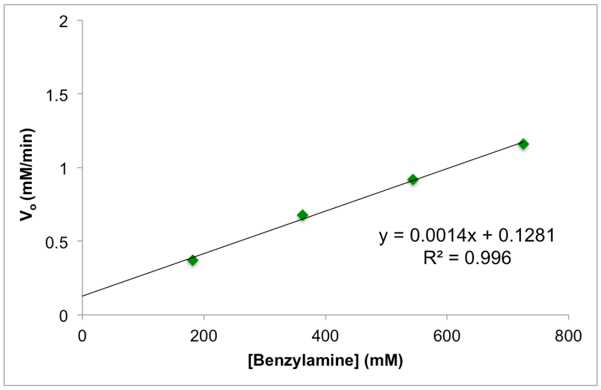


Benzylamine Concentration Study:

At each concentration of benzylamine, a set of identical reactions was set up; each data point represents the sole sample taken from a reaction. An oven-dried test tube equipped with a magnetic stir bar was charged with $CuCl_2$ (5 mol %, 6.7 mg), capped with a septum, and purged with argon for 5 minutes. Toluene (1081 μL - 837 μL) was added such that the overall concentration was kept constant. The dodecane internal standard (20 µL) was added, followed by cyclohexanone (103 µL, 1.0 mmol), benzylamine (27 µL – 272 µL, 0.25 – 2.5 mmol), and octyne (147 µL, 1.0 mmol). Under argon pressure, the septum was then quickly replaced with a Teflon-seal screw cap. The reaction was stirred at 110 °C for 90 minutes. GC aliquots at each time point were flushed through a silica gel pipette plug with diethyl ether.

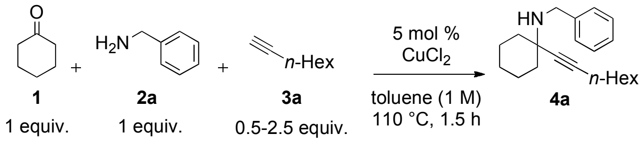


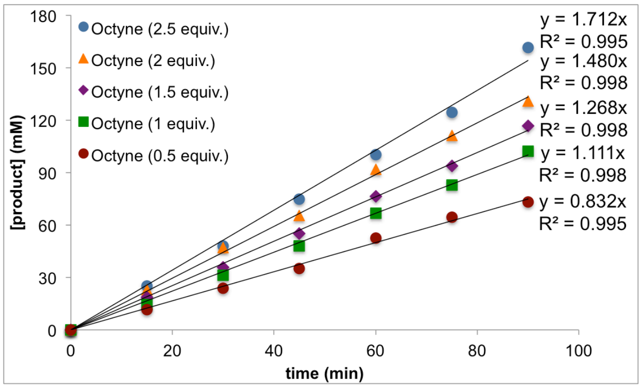


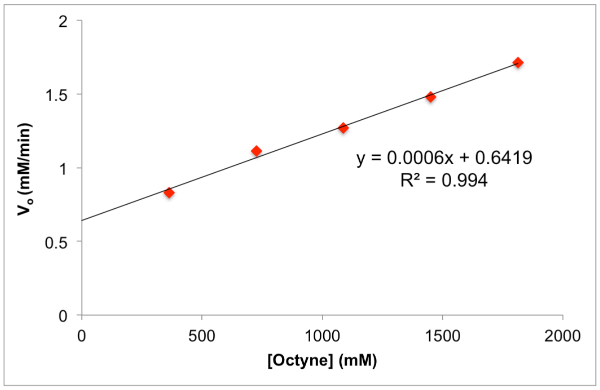


1-Octyne Concentration Study:

At each concentration of 1-octyne, a set of identical reactions was set up; each data point represents the sole sample taken from a reaction. An oven-dried test tube equipped with a magnetic stir bar was charged with $CuCl_2$ (5 mol %, 6.7 mg), capped with a septum, and purged with argon for 5 minutes. Toluene (1073 µL - 780 µL) was added such that the total volume was kept constant. The dodecane internal standard (20 µL) was added, followed by cyclohexanone (103 µL, 1.0 mmol), benzylamine (109 µL, 1.0 mmol), and octyne (73 µL – 367 µL, 0.5 – 2.5 mmol). Under argon pressure, the septum was then quickly replaced with a Teflon-seal screw cap. The reaction was stirred at 110 °C for 90 minutes. GC aliquots at each time point were flushed through a silica gel pipette plug with diethyl ether.

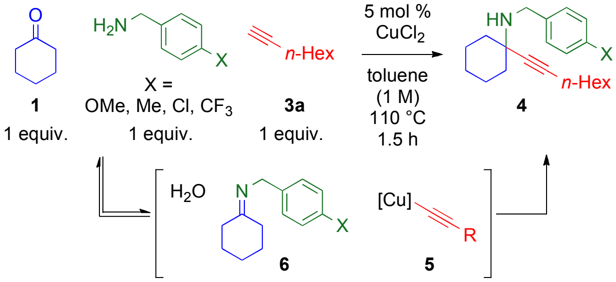


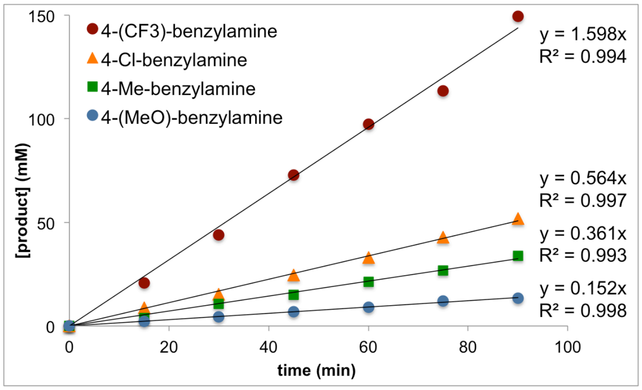


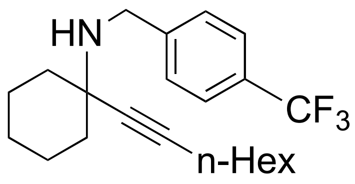


Relative rates of *para*-substituted benzylamines (X = OMe, Me, Cl, or CF_3):

For each substituted benzylamine, a set of identical reactions was set up; each data point represents the sole sample taken from a reaction. An oven-dried test tube equipped with a magnetic stir bar was charged with $CuCl_2$ (5 mol %, 6.7 mg), capped with a septum, and purged with argon for 5 minutes. Toluene (A: 979 μL, B: 982 μL, C: 987 μL D: 967 μL) was added such that the overall concentration was kept constant. The dodecane internal standard (20 μL) was added, followed by cyclohexanone (103 μL, 1.0 mmol), then either 4-methoxybenzylamine (A, 130 μL, 1.0 mmol), 4-methylbenzylamine (B, 127 μL, 1.0 mmol), 4-chlorobenzylamine (C, 122 μL, 1.0 mmol), **<u>or</u>** 4-(trifluoromethyl)benzylamine (D, 142 μL, 1.0 mmol) was added followed by octyne (147 μL, 1.0 mmol). Under argon pressure the septum was then quickly replaced with a Teflon-seal screw cap. The reaction was stirred at 110 °C for 90 minutes. GC aliquots at each time point were flushed through a silica gel pipette plug with diethyl ether.



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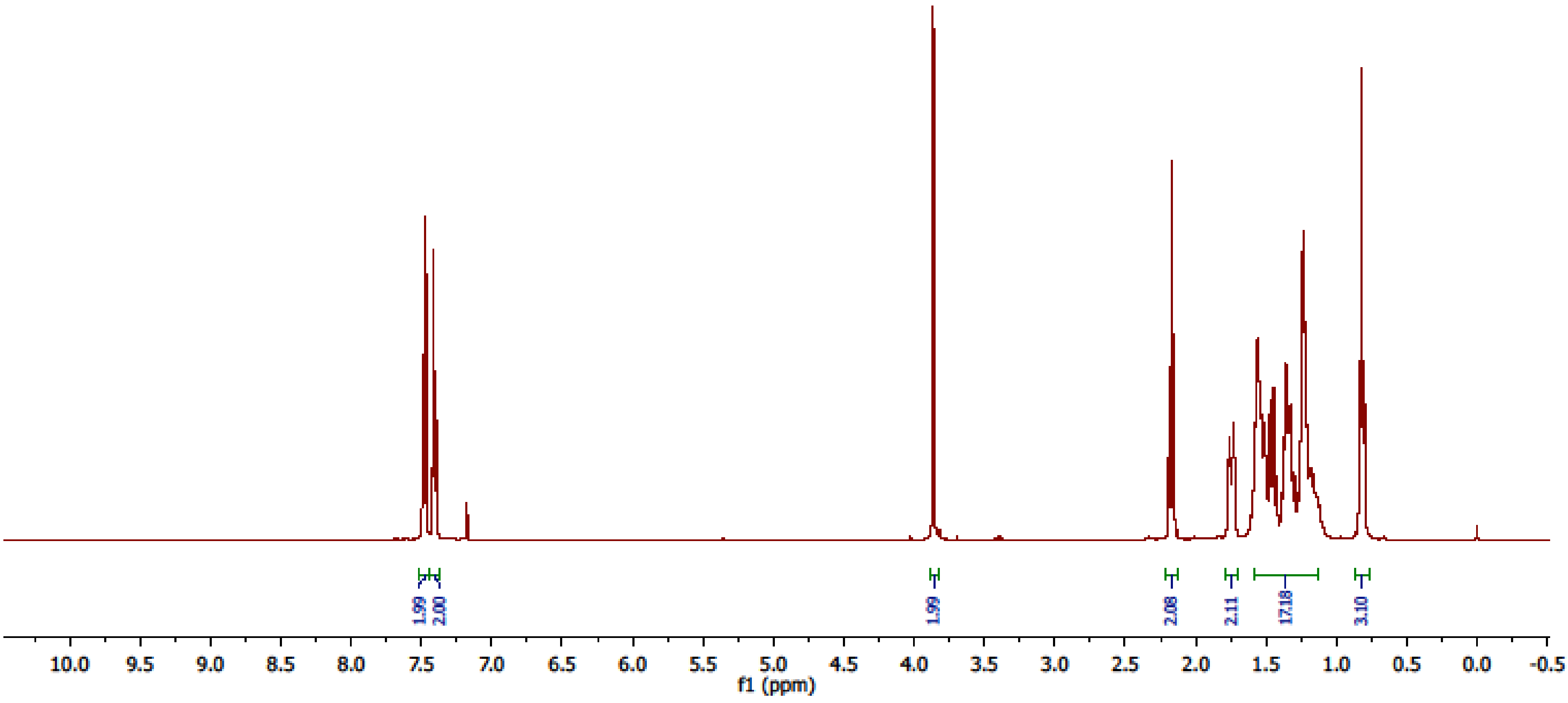
CF3
n-Hex

4c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2.11
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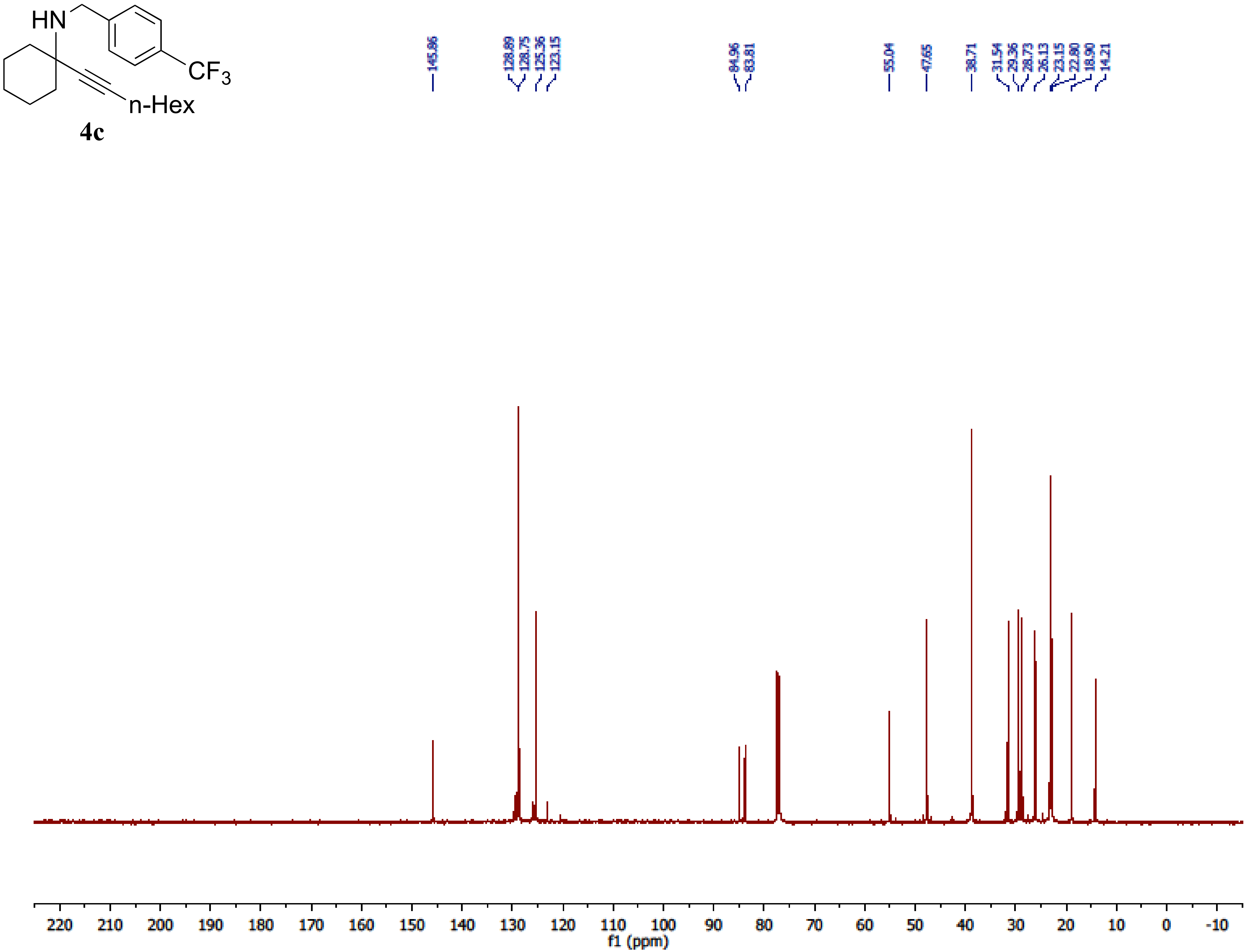
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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22.80
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14.21
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200
190
180
170
160
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140
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100
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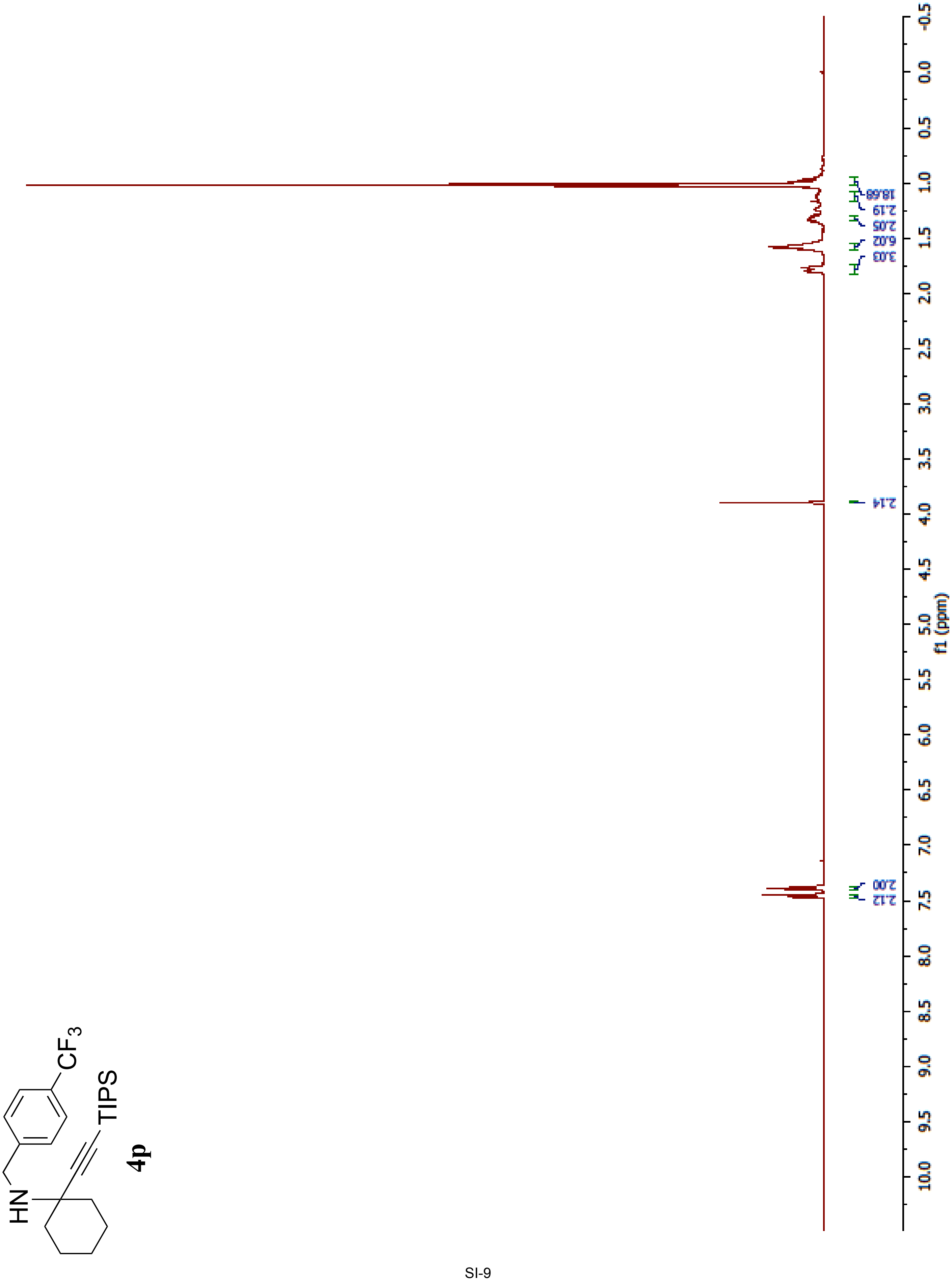
60
50
40
30
20
10
0
-10
f1 (ppm)

4c


HN
CF3
TIPS
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6.02
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2.14
2.00
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1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
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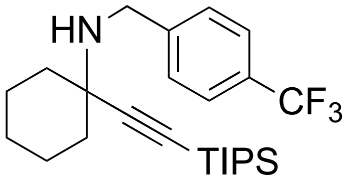
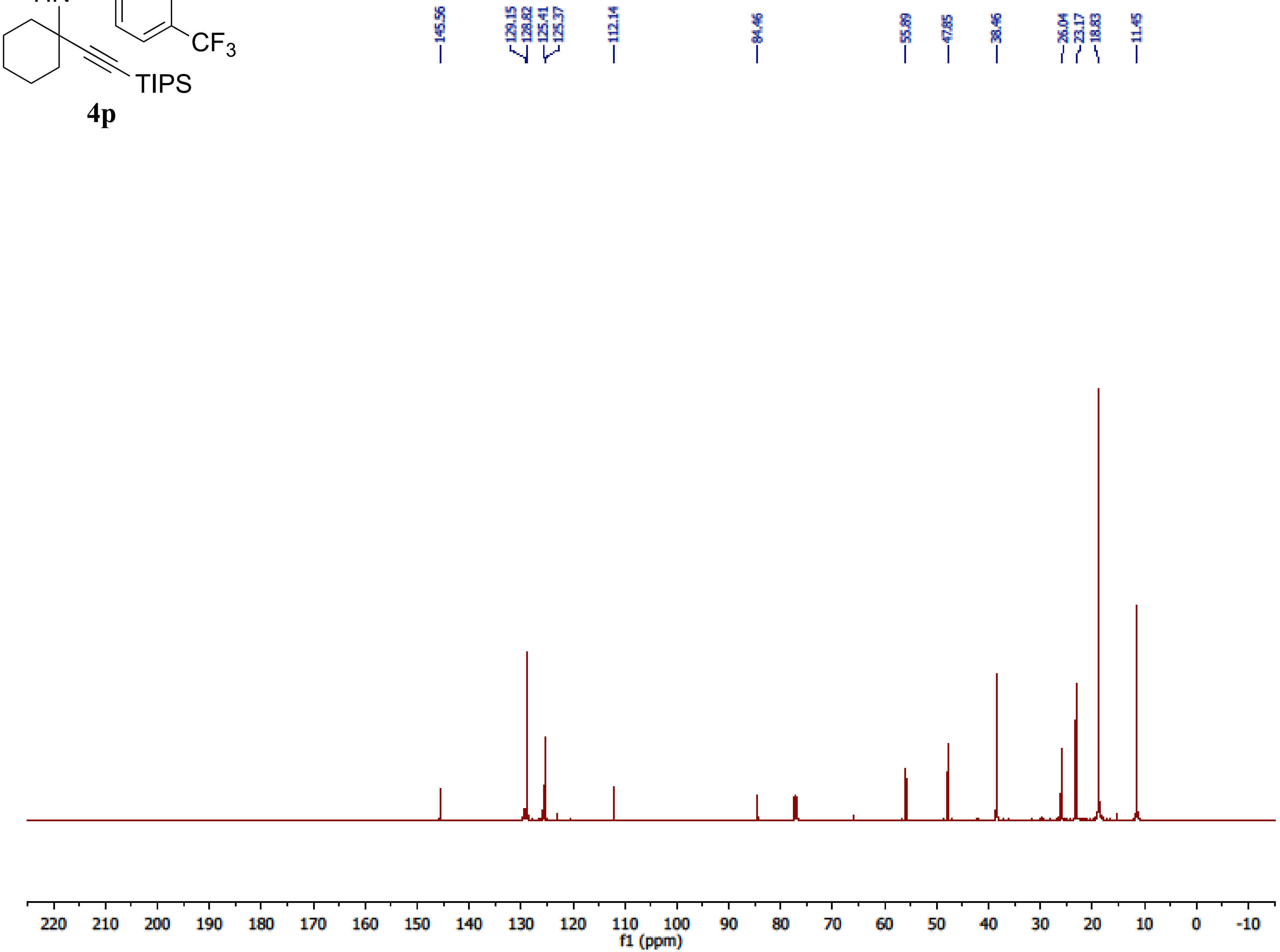
9.0
9.5
10.0
f1 (ppm)

4p


HN
CF3
TIPS

4p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11.45
220
210
200
190
180
170
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30
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10
0
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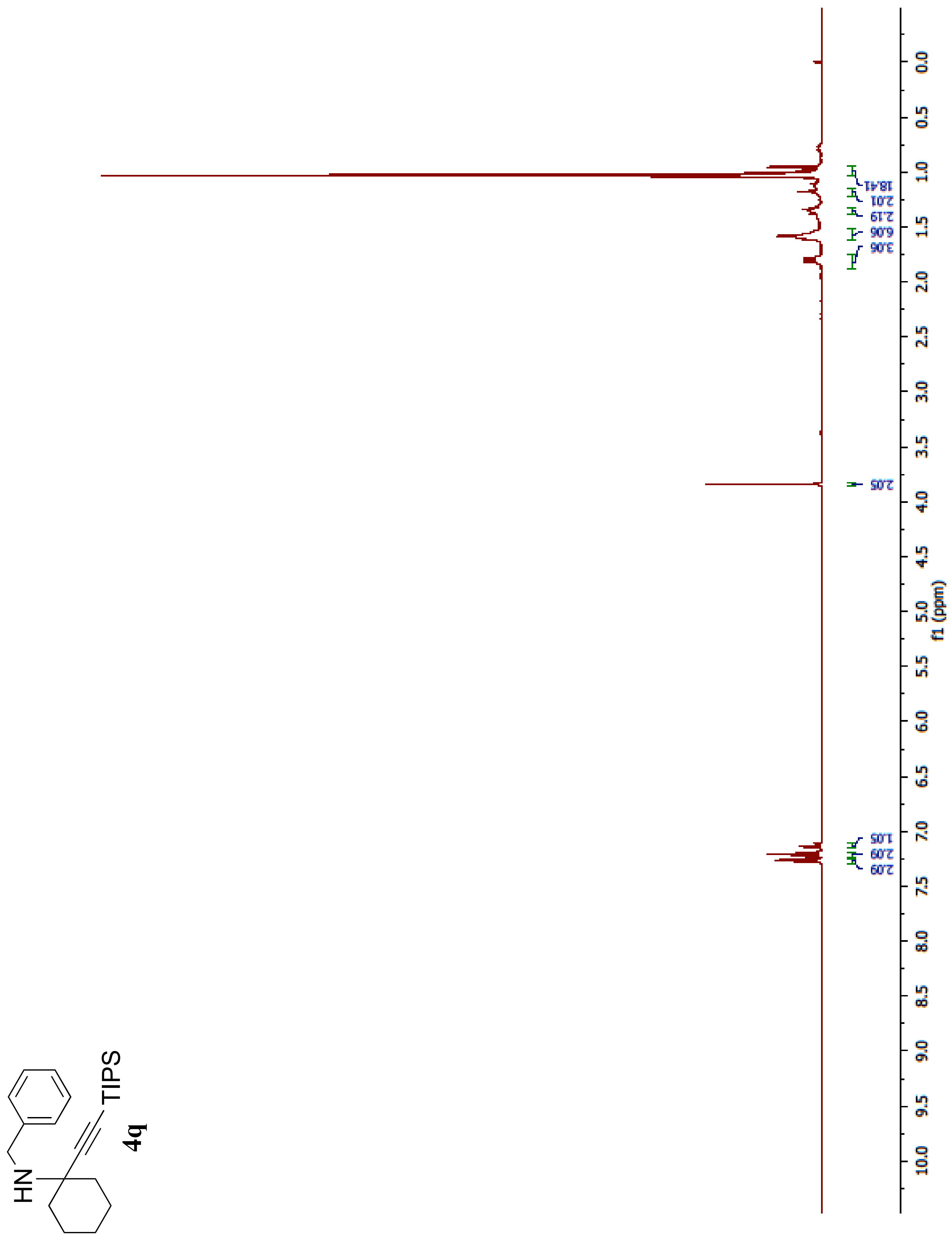
f1 (ppm)



HN
TIPS
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2.09
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0.5
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1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
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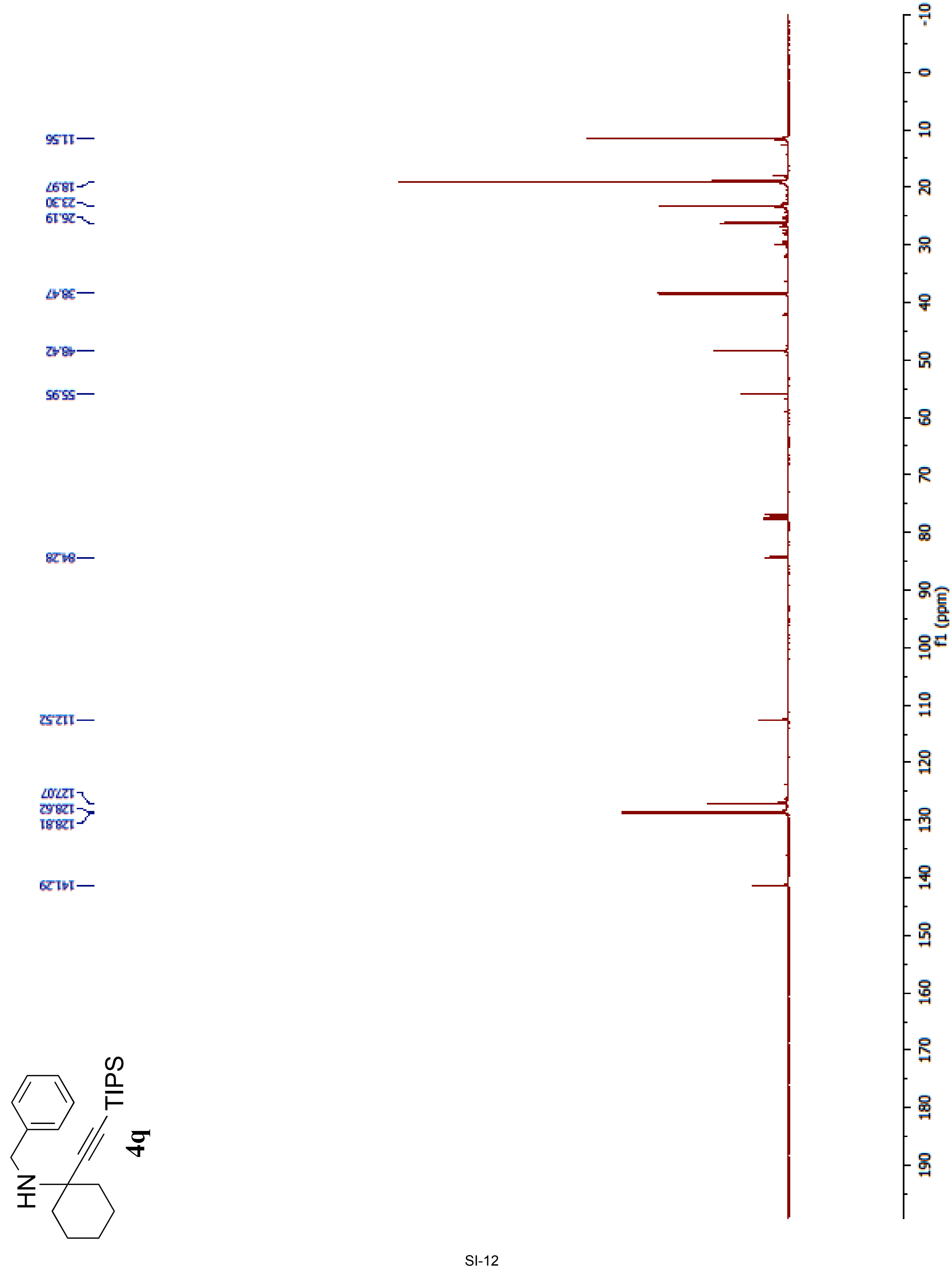
9.0
9.5
10.0
f1 (ppm)

4q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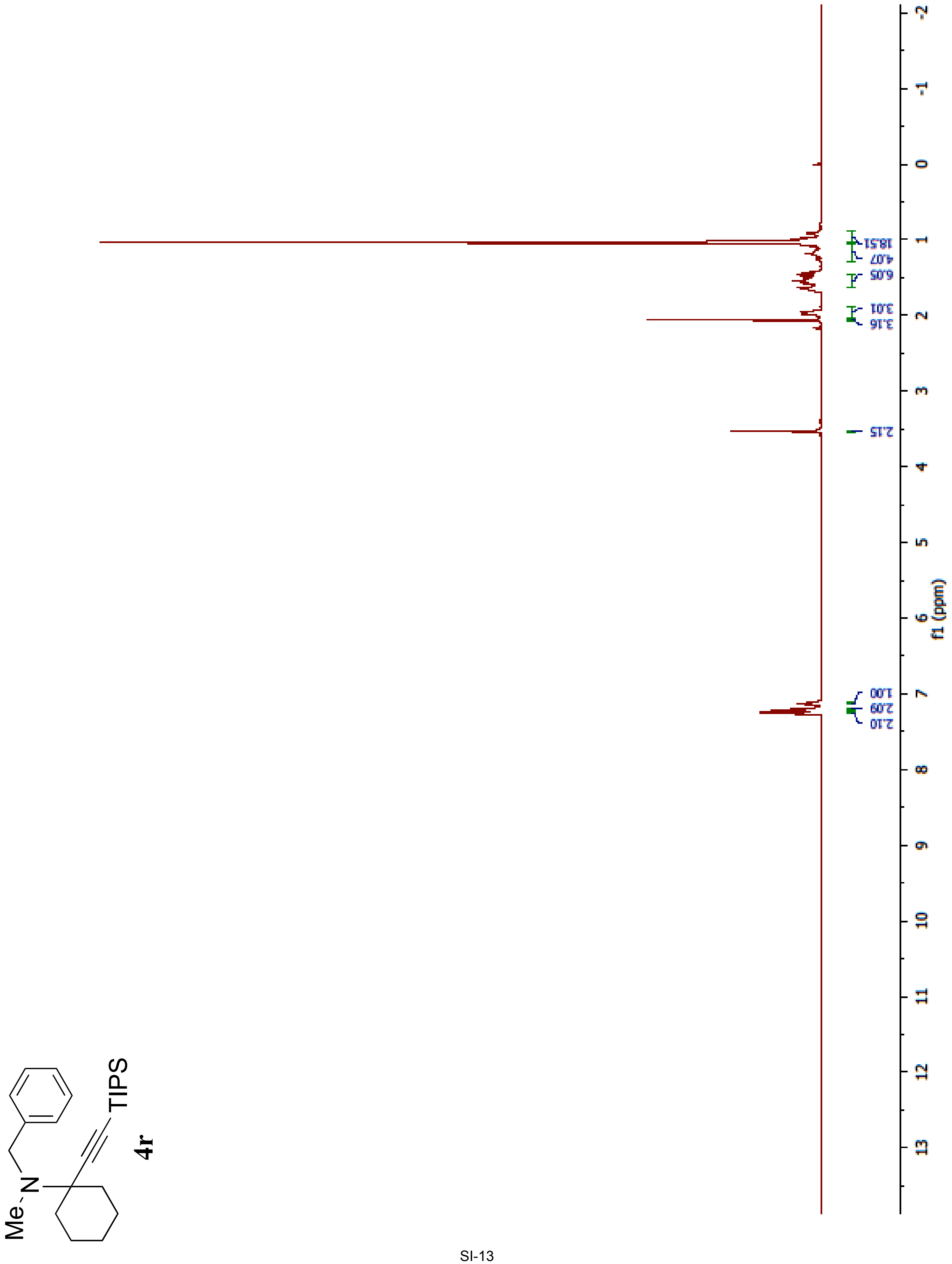
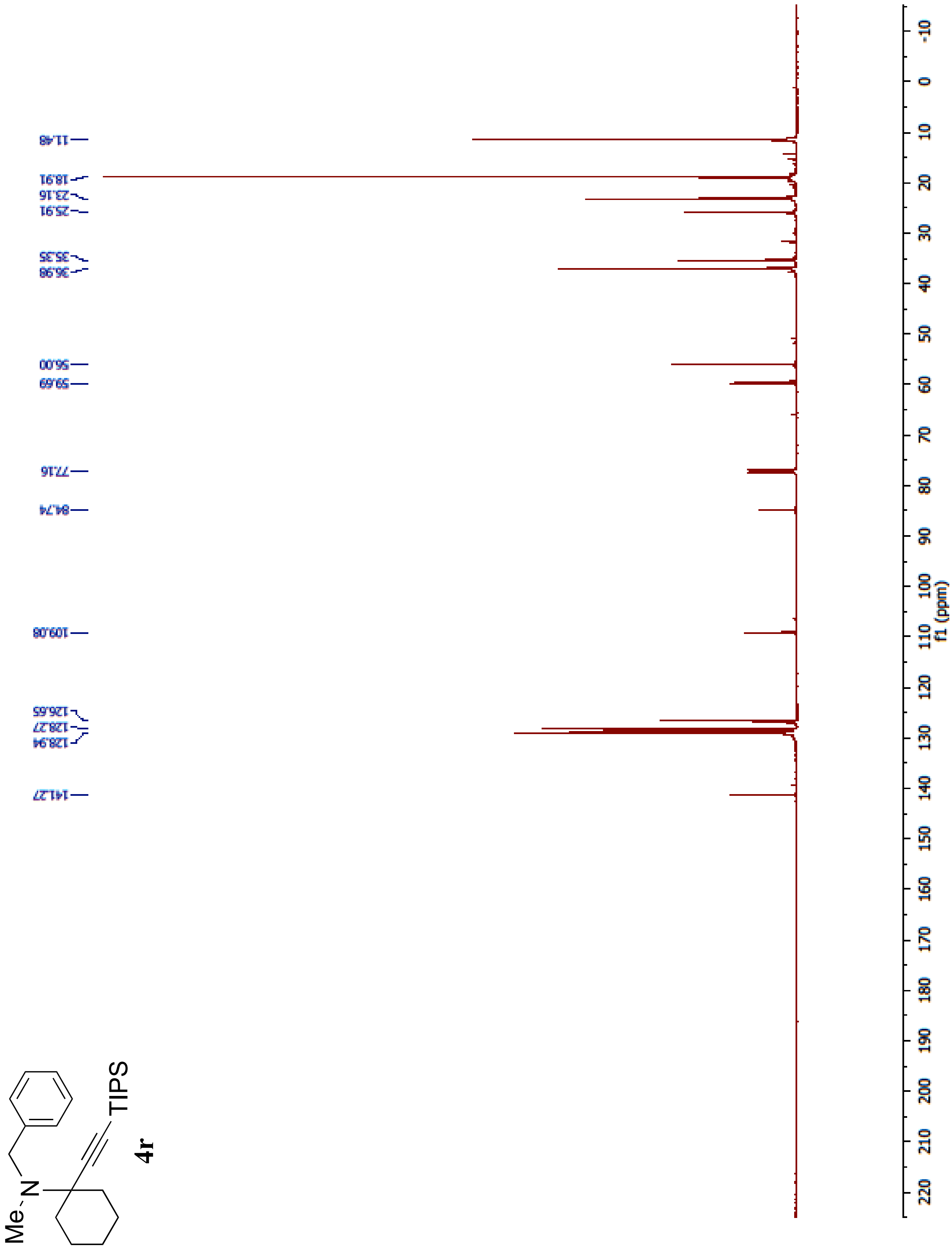
26.19
38.47
48.42
55.95
84.28
112.52
127.07
128.62
128.81
141.29
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)
HN
TIPS

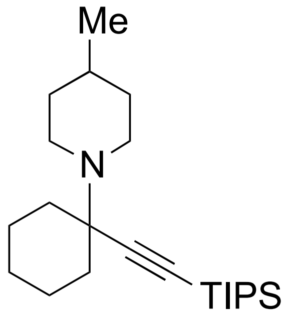
4q



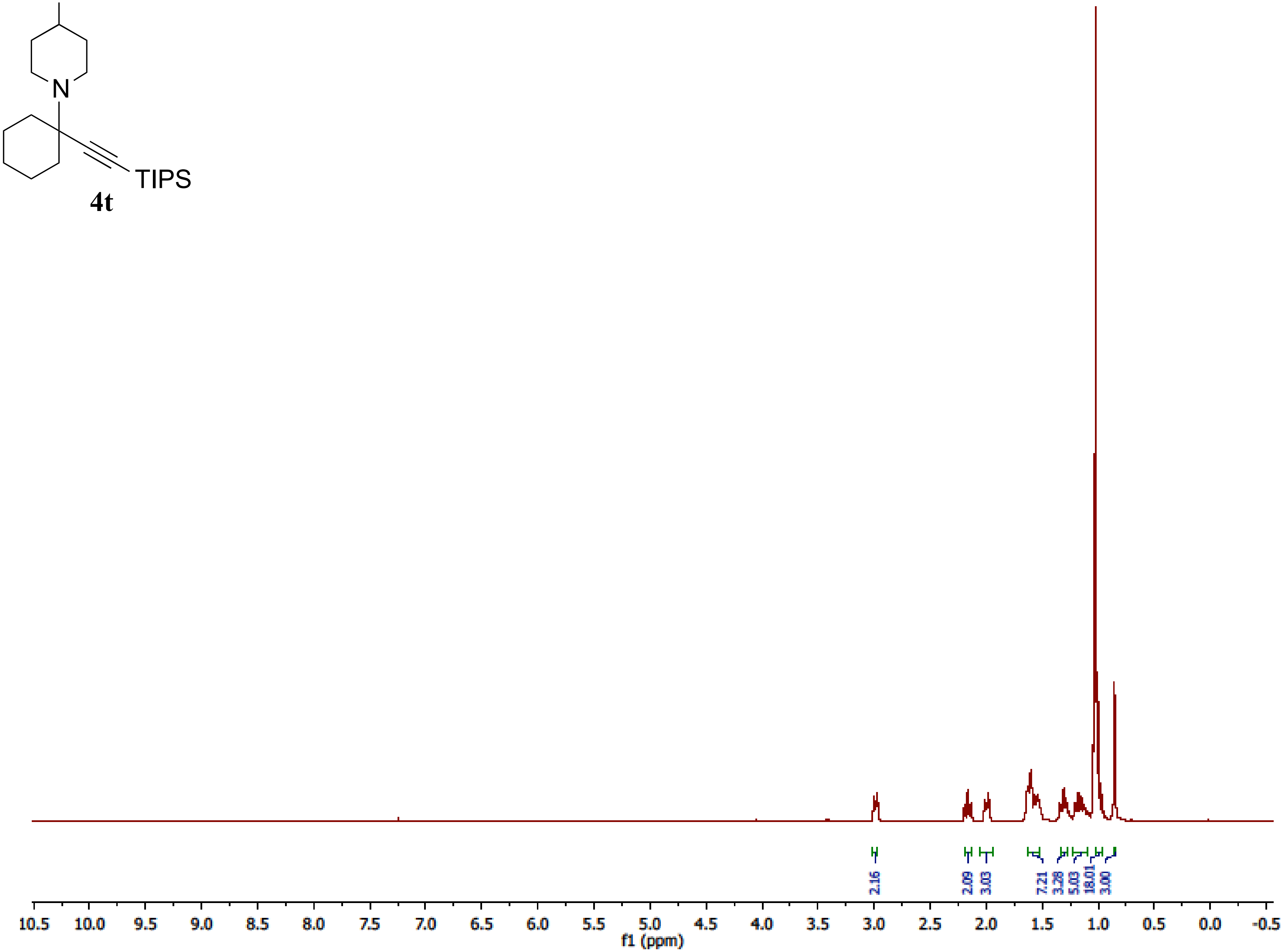
Me
N
TIPS
18.51
4.07
6.05
3.01
3.16
2.15
1.00
2.09
2.10
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
f1 (ppm)

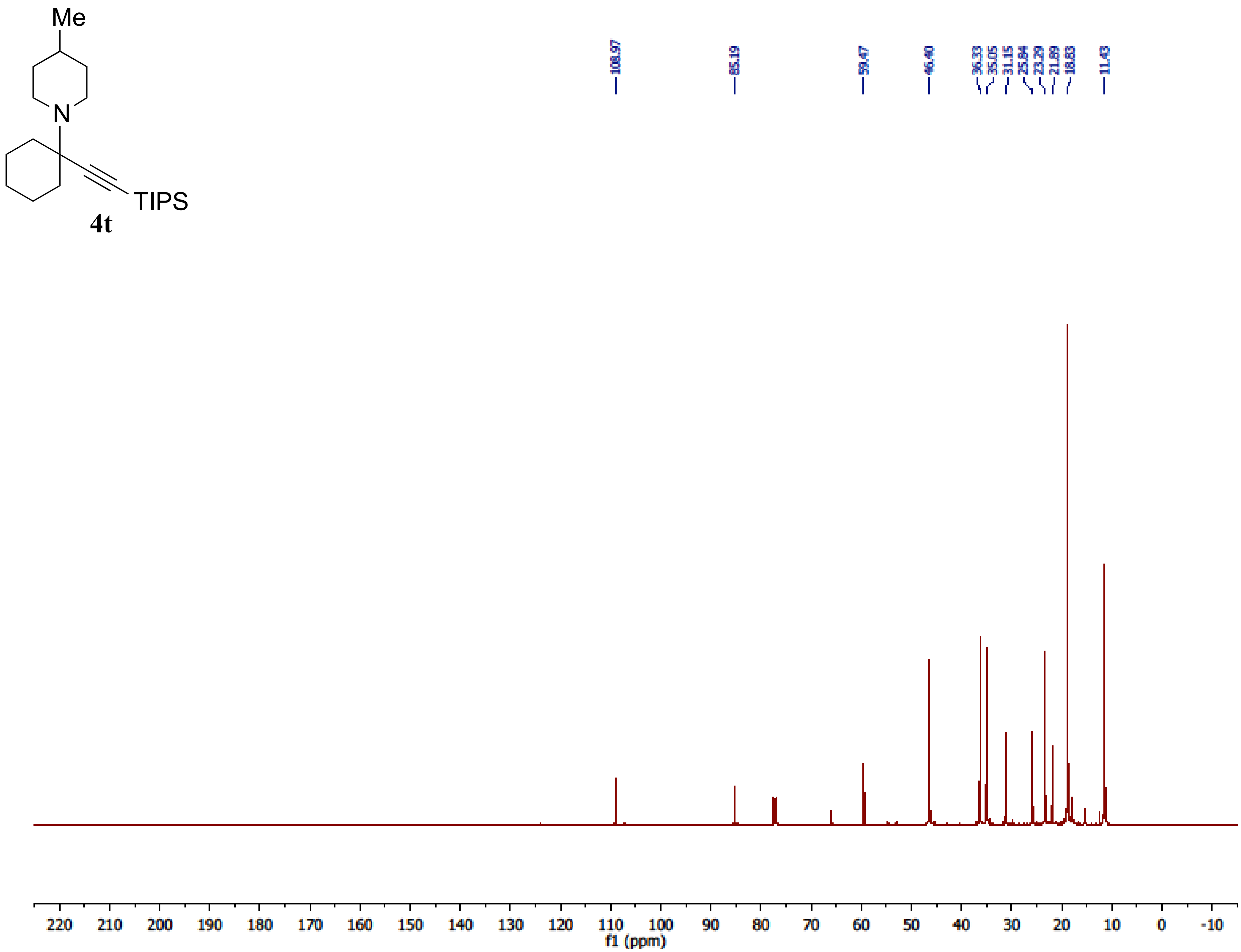
4r

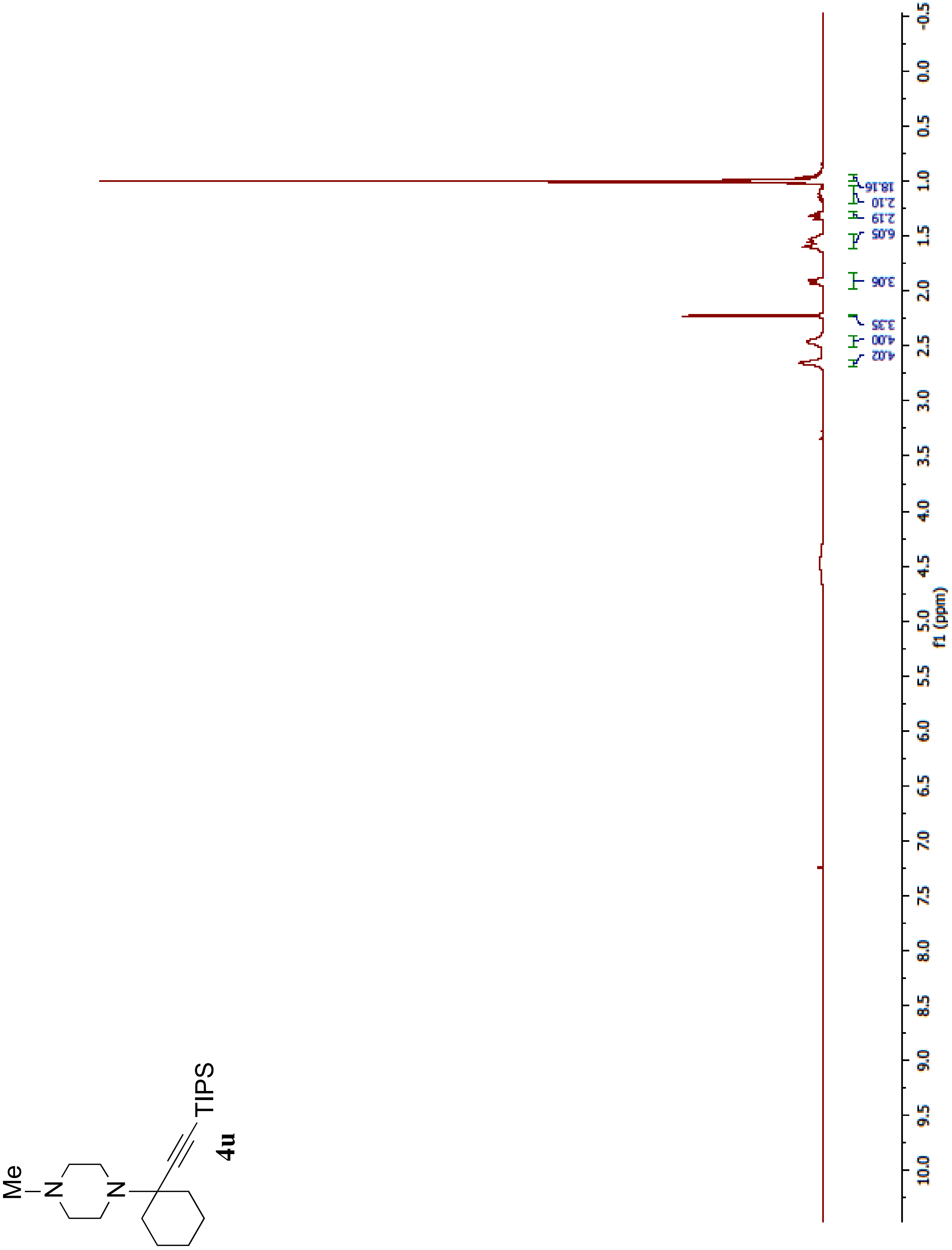

141.27
128.94
128.27
126.65
109.08
84.74
77.16
59.69
56.00
36.98
35.35
25.91
23.16
18.91
11.48
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)
Me
N
TIPS
4r


Me
N
TIPS

4t

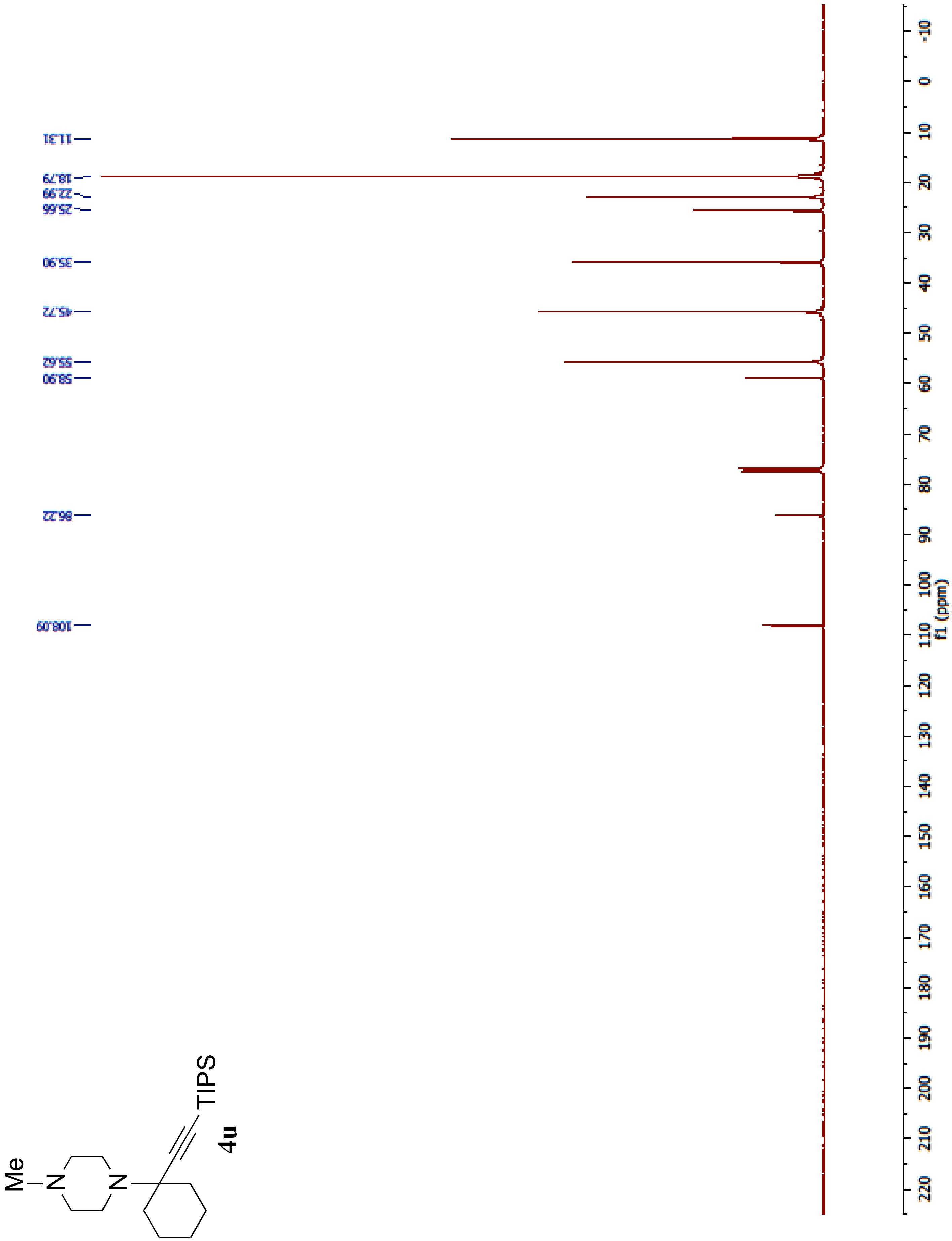

2.16
2.09
3.03
7.21
3.28
5.03
18.01
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


Me
N
TIPS
4t
108.97
85.19
59.47
46.40
36.33
35.05
31.15
25.84
23.29
21.89
18.83
11.43
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Me
N
N
TIPS

4u

18.16
2.10
2.19
6.05
3.06
3.35
4.00
4.02
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
f1 (ppm)


11.31
18.79
22.99
25.66
35.90
45.72
55.62
58.90
86.22
108.09
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)
Me
N
N
TIPS

4u