Electronic Supplementary Information

Efficient, continuous *N*-Boc deprotection of amines using solid acid catalysts

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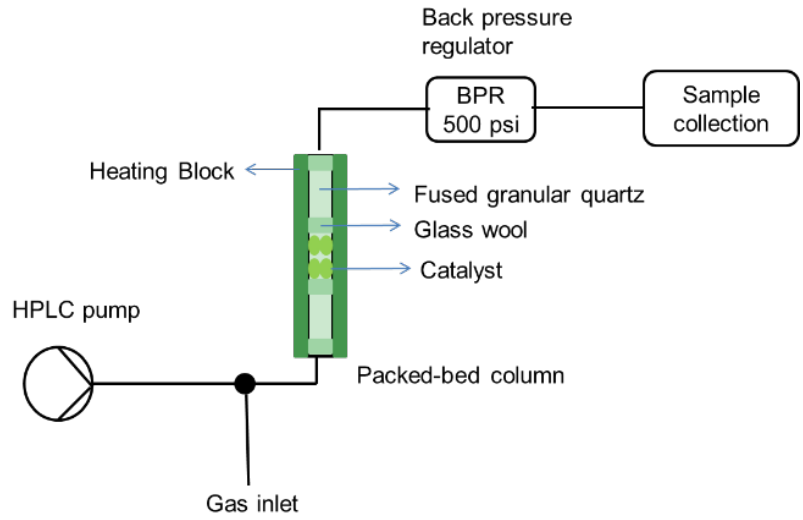
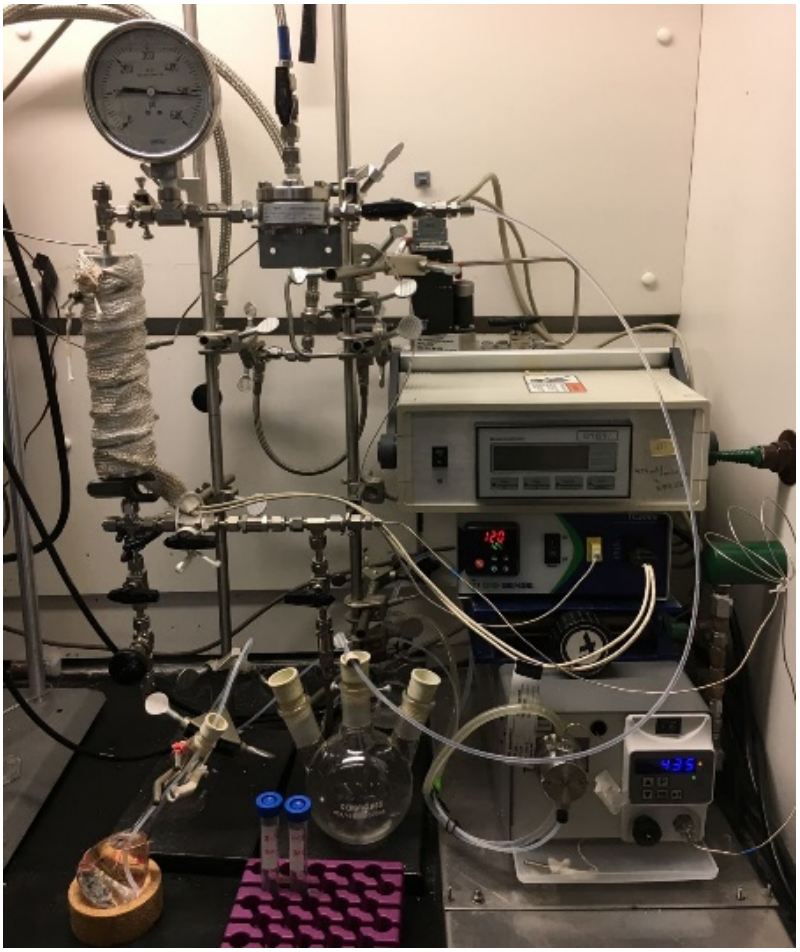


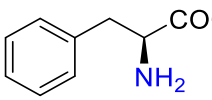
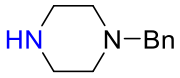
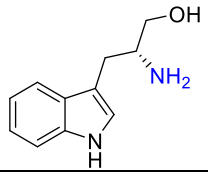


Scheme S1. Schematic (top) and photograph (bottom) of continuous flow reactor.

Residence time calculation

The nominal residence time τ was calculated as follows: a precisely weighed amount of H-BEA zeolite (80-100 mesh, 1.0 g) was centrifuged at 4000 rpm for 30 min. Its volume in the centrifuge tube was 1.60 mL, giving the density as 0.62 g mL^{-1}. The framework density of HBEA (15.3 T sites/1000 $Å^3$) corresponds to a bulk density of 1.52 g mL^{-1}. The intercrystalline void volume is therefore 1.60 – $(1.52)^{-1}$ = 0.94 mL g^{-1}. The nominal residence time is the product of the intercrystalline void volume and the catalyst loading, divided by the flow rate.

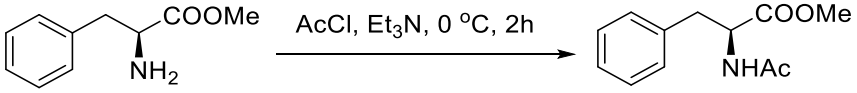
Table S1. Effect of anisole cosolvent on continuous flow deBoc reaction[a]

Designation [b]	Product[c]	Cat. mass g	Temp. °C	10% anisole	Flow rate mL min^{-1}	Res. Time[d] min	Yield[e] %
H		0.300	180	Yes	0.04	7.05	88
			200	No			75
J[f]		0.300	200	Yes	0.05	5.6	86
			180	No			12[g]
K[f]		0.500	200	Yes	0.04	11.75	85
				No			65[h]

[a] Reactions were conducted with 0.050 M substrate in a packed-bed reactor at 500 psi. [b] Letters correspond to Table 4 in the main text. [c] The deprotected amine site is indicated in blue. [d] Nominal residence time = volume of intercrystalline void × catalyst loading/flow rate. [e] NMR yield, using 20 mol% 1,3,5-trimethoxybenzene relative to the starting material as internal standard. [f] Reaction conducted under N_2 protection. [g] 10% 1-benzylpiperazine-2,5-dione (oxidized side-product) was formed according to GC-MS. [h] 20% N-tBu-tryptophanol (tert-butylation side-product) was formed according to GC-MS.

Stereochemistry retention during catalytic deprotection

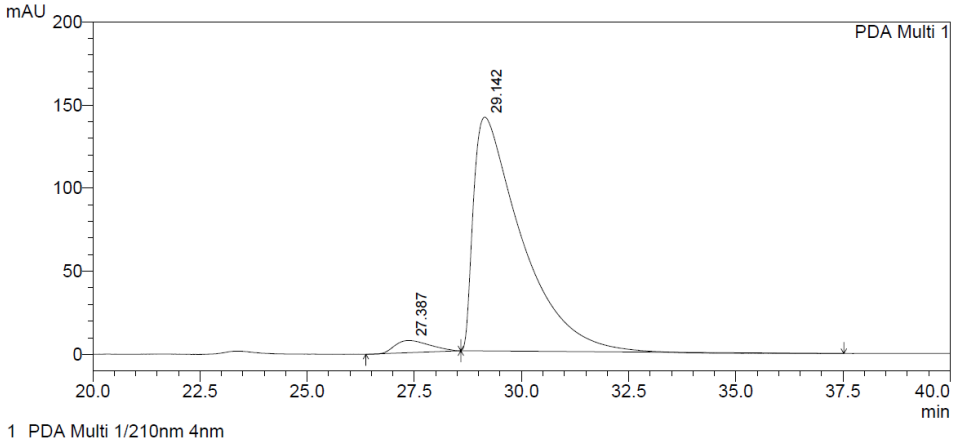
Due to the low solubility of methyl-(2*S*)-2-amino-3-phenylpropanoate (**H**) in the HPLC solvent (iPrOH), as well as difficulties in achieving baseline separation of the stereoisomers by chiral HPLC, the amine group was protected by an acetyl group to form (*S*)-*N*-acetylphenylalanine, eq 1, following a literature procedure.[1]



(1)

Characterization of (*S*)-*N*-acetylphenylalanine: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 (dd, *J* = 7.1, 1.2 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.19 – 5.98 (m, 1H), 4.88 (d, *J* = 7.8 Hz, 1H), 3.72 (s, 3H), 3.13 (d, *J* = 5.9 Hz, 1H), 3.09 (d, *J* = 5.9 Hz, 1H), 1.97 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.15, 169.64, 135.90, 129.23, 128.56, 127.11, 77.30, 77.09, 76.88, 53.16,

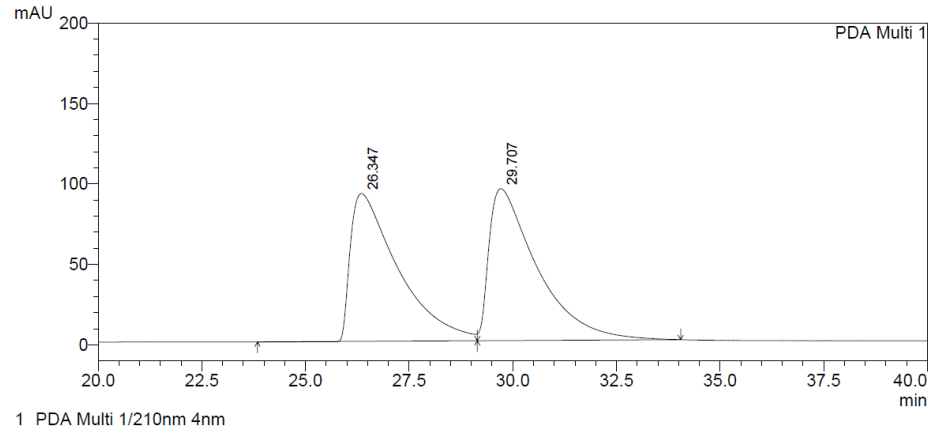
53.15, 37.86, 23.07, 0.00. The ee value of the product (93 %)was determined by HPLC on a Chiralcel IB column, Figure S2.



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.387	409397	7316	3.600	4.945
2	29.142	10963510	140623	96.400	95.055
Total		11372907	147940	100.000	100.000



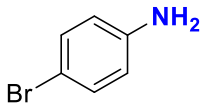
PeakTable

PDA Ch1 210nm 4nm

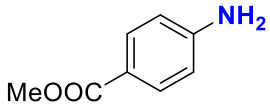
Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.347	7351219	91862	49.031	49.308
2	29.707	7641694	94442	50.969	50.692
Total		14992913	186304	100.000	100.000

Figure S1. Chiral HPLC of (*S*)-*N*-acetylphenylalanine from deprotection of **H** (top) and standard racemic mixture (bottom). Conditions: hexane/iPrOH = 95 : 5; flow rate = 1.0 mL/min; UV detection at 220 nm; tR = 27.387 min (minor), 29.142 min (major), ee = 93%.

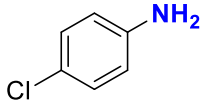
Characterization data for deprotected amines



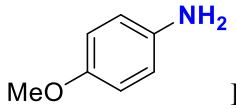
A was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 140 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as white solid (95% yield). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.53, 132.07, 116.79, 110.22.



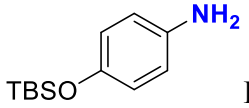
B was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 140 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as white solid (>95% yield).^{1}H NMR (500 MHz, methanol-d_4) δ 6.37 (d, *J* = 8.7 Hz, 2H), 5.27 (d, *J* = 8.8 Hz, 2H), 3.45 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ 166.44, 151.79, 129.65, 115.75, 111.51.



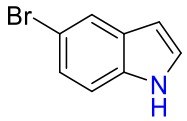
C was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 140 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as yellow solid (>95% yield).^{1}H NMR (500 MHz, chloroform-*d*) δ 6.59 (dd, *J* = 8.8, 2.3 Hz, 2H), 3.66 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.08, 129.15, 123.12, 116.30.



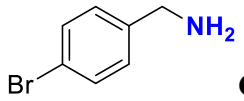
D was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 140 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as white solid (>95% yield). ^{1}H NMR (500 MHz, methanol-d_4) δ 5.21 (d, *J* = 1.8 Hz, 4H), 3.31 (s, 2H), 2.19 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 151.57, 138.67, 115.33, 115.33, 53.26.



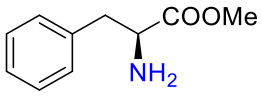
E was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 140 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as yellow solid (>95% yield). ^{1}H NMR (600 MHz, chloroform-*d*) δ 6.69 – 6.65 (m, 2H), 6.59 – 6.55 (m, 2H), 3.36 (s, 3H), 0.99 (s, 10H), 0.17 (s, 6H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 148.23, 140.39, 120.71, 116.37, 116.36, 25.84, 18.26, -4.40.



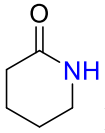
F was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 140 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as yellow solid (91% yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.18 (t, *J* = 2.9 Hz, 1H), 6.50 (s, 1H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 134.52, 129.73, 125.53, 124.87, 123.27, 113.06, 112.58, 102.31.



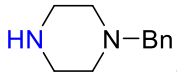
G was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 180 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as yellow oil (>95% yield).^{1}H NMR (500 MHz, chloroform-*d*) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 3.83 (s, 2H), 1.44 (s, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.19, 131.55, 128.82, 120.50, 45.85.



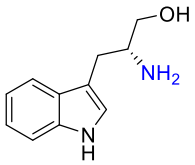
H was prepared in a continuous flow reaction conducted using 0.050 mol/L reactant in THF flowing at 0.04 mL/min at 160 °C with 500 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as white solid (>95% yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 2H), 3.73 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.71 (s, 3H), 3.08 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.85 (dd, *J* = 13.5, 7.9 Hz, 1H), 1.66 (s, 2H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 175.38, 137.21, 129.26, 128.55, 126.82, 77.31, 77.20, 77.10, 76.88, 55.80, 51.94, 41.08.



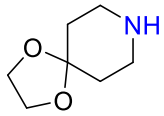
I was prepared in a continuous flow reaction conducted using 0.100 mol/L reactant in THF flowing at 0.5 mL/min at 180 °C with 200 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as white solid (>95% yield). ^{1}H NMR (500 MHz, chloroform-*d*) δ 3.18 (td, *J* = 5.9, 2.2 Hz, 1H), 2.26 – 2.15 (m, 2H), 1.65 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.81, 41.98, 31.36, 22.14, 20.76. ^{1}H NMR (500 MHz, methanol-*d*$_4$) δ 5.27 – 5.08 (m, 1H), 3.32 (s, 1H), 2.19 (s, 1H).



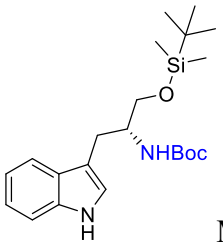
J was prepared in a continuous flow reaction conducted using 0.050 mol/L reactant in THF flowing at 0.04 mL/min at 200 °C with 300 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as yellow oil (86% yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 5H), 7.25 – 7.21 (m, 1H), 3.47 (s, 2H), 2.86 (t, *J* = 4.9 Hz, 4H), 2.43 – 2.35 (m, 4H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 138.08, 129.17, 128.14, 126.95, 63.69, 54.53, 46.10.



K was prepared in a continuous flow reaction conducted using 0.050 mol/L reactant in THF flowing at 0.04 mL/min at 200 °C with 500 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as yellow solid (85% yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.33 (s, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.35 (dd, *J* = 8.3, 4.4 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 5.6 Hz, 1H), 3.68 (dt, *J* = 8.7, 4.3 Hz, 1H), 3.49 – 3.37 (m, 1H), 3.25 (tt, *J* = 8.1, 4.2 Hz, 1H), 2.92 (dt, *J* = 14.7, 4.6 Hz, 1H), 2.69 (ddd, *J* = 13.3, 8.6, 4.3 Hz, 1H), 2.04 (s, 2H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 136.42, 127.56, 122.66, 122.06, 119.37, 118.83, 112.47, 111.24, 66.55, 52.96, 30.13.

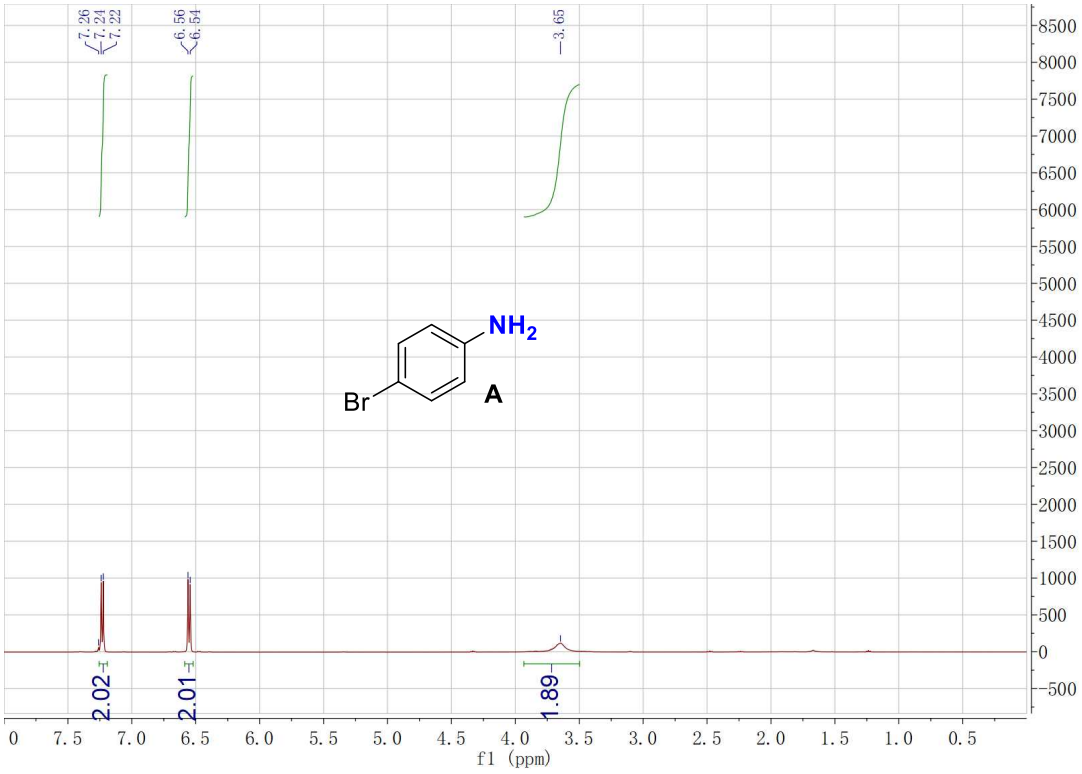


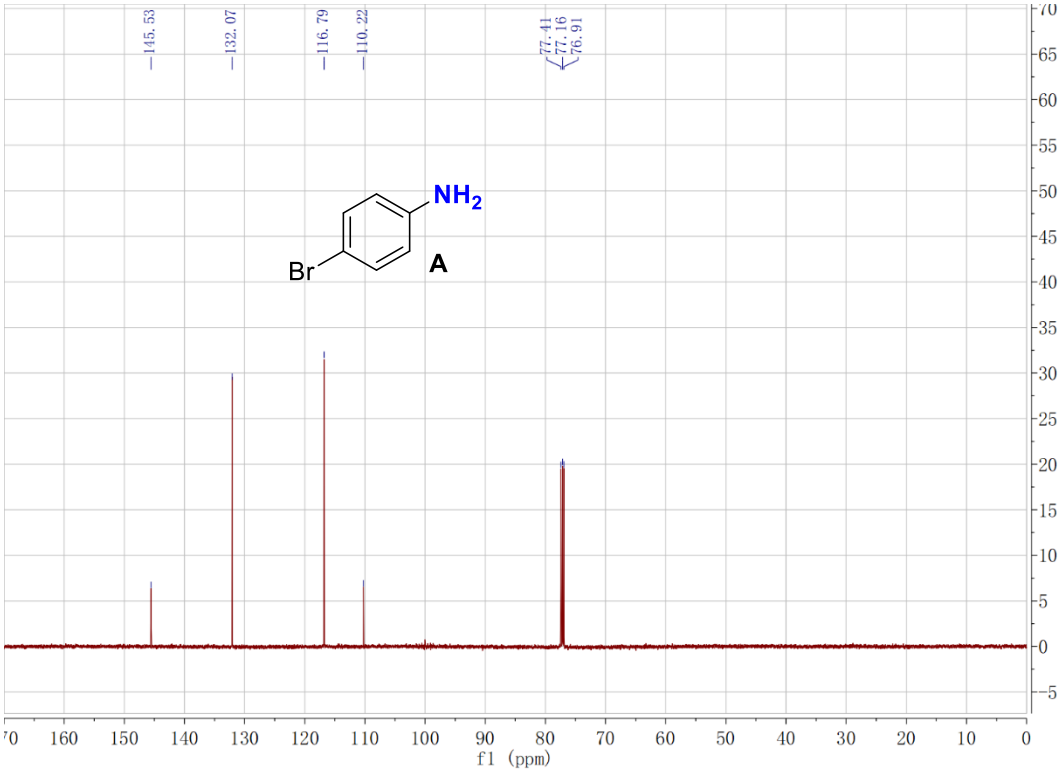
L was prepared in a continuous flow reaction conducted using 0.050 mol/L reactant in THF flowing at 0.04 mL/min at 200 °C with 500 mg HBEA catalyst in a packed-bed column at 500 psi. The product was obtained as colorless oil (92% yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.96 (d, *J* = 5.4 Hz, 4H), 2.92 (t, *J* = 5.8 Hz, 4H), 1.66 (t, *J* = 5.7 Hz, 4H), 1.43 (s, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 107.43, 64.18, 44.58, 36.44.

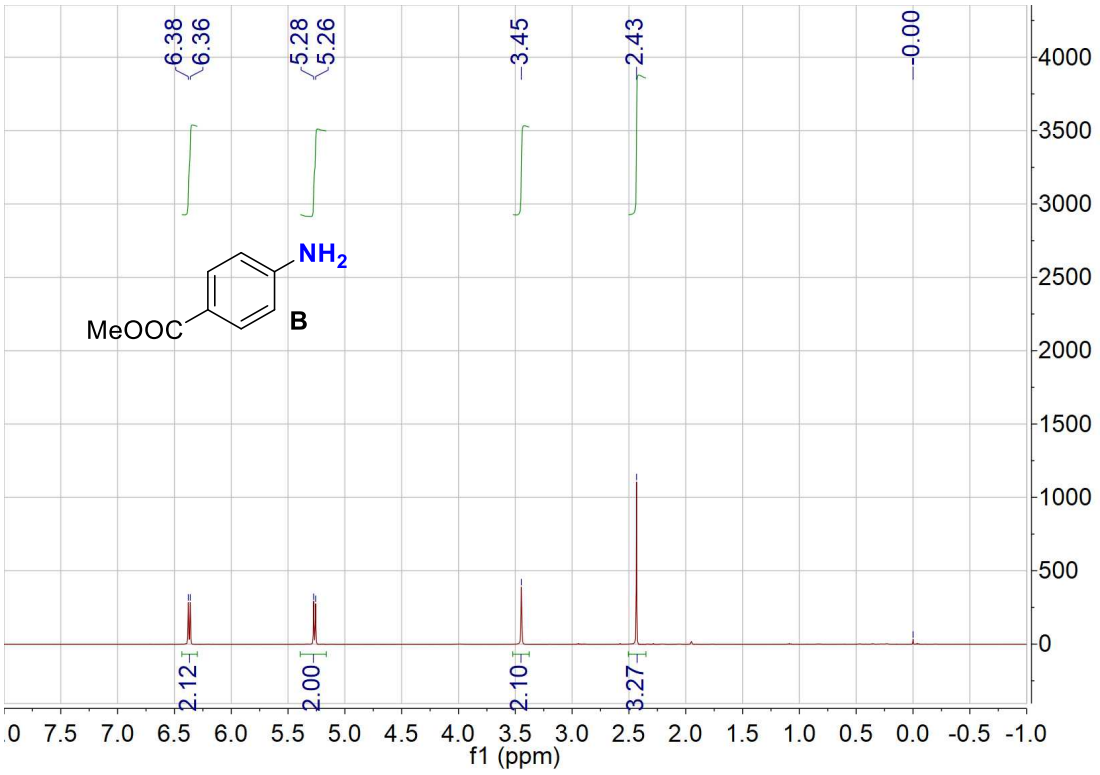


M is synthesized follow the method in the reference.[2] ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.23 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 4.92 – 4.75 (m, 1H), 3.98 (s, 1H), 3.65 – 3.46 (m, 2H), 3.11 – 2.85 (m, 3H), 1.39 (s, 9H), 0.95 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 155.59, 136.23, 127.94, 122.62, 121.89, 119.28, 119.18, 112.36, 110.98, 79.06, 63.24, 52.23, 28.43, 26.74, 25.99, 25.94, 18.30, -5.35, -5.44.

Representative NMR spectra



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2.10
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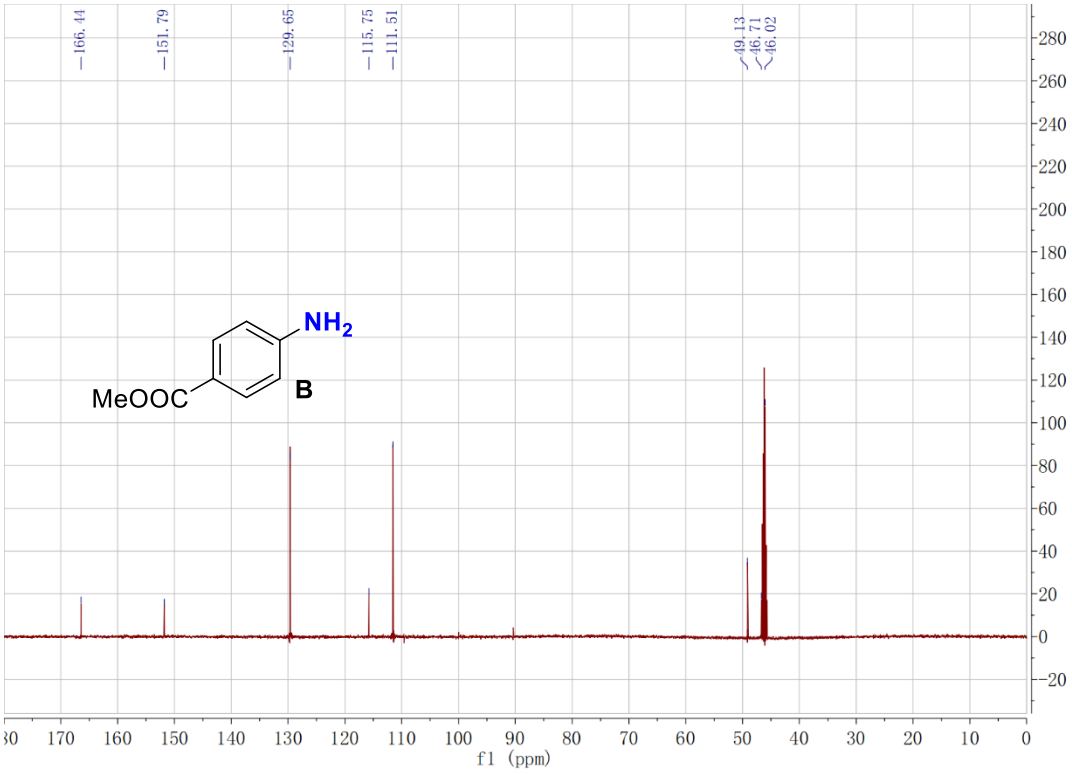
f1 (ppm)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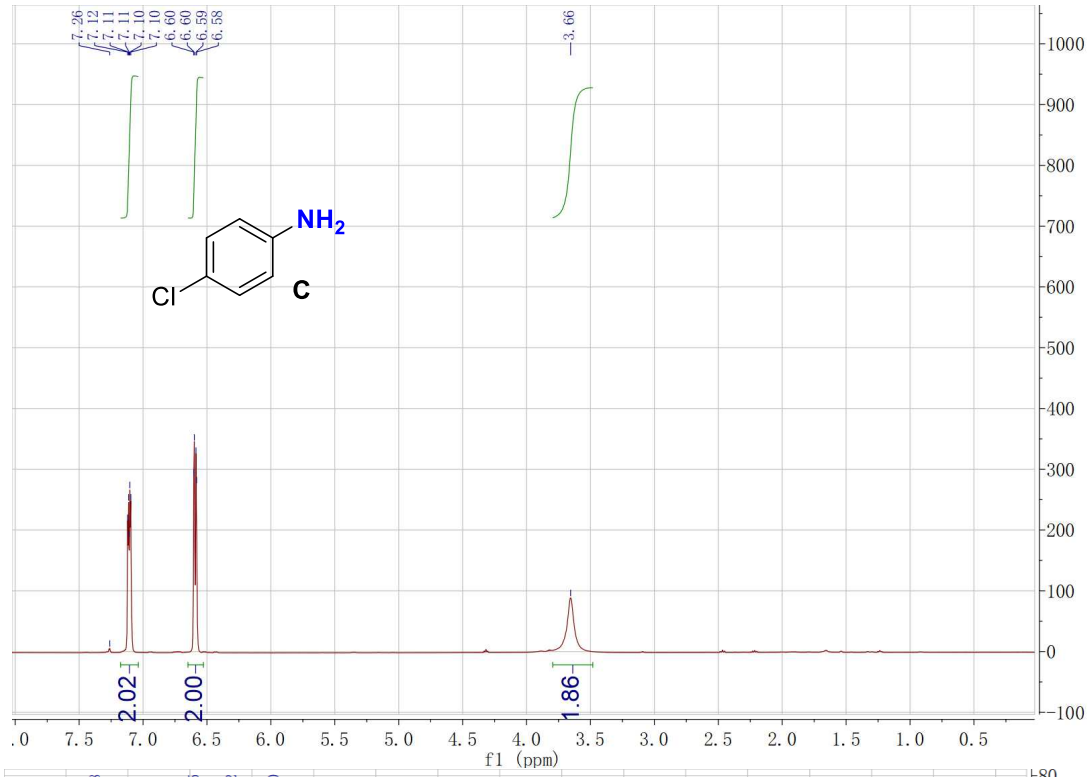
MeOOC
B
f1 (ppm)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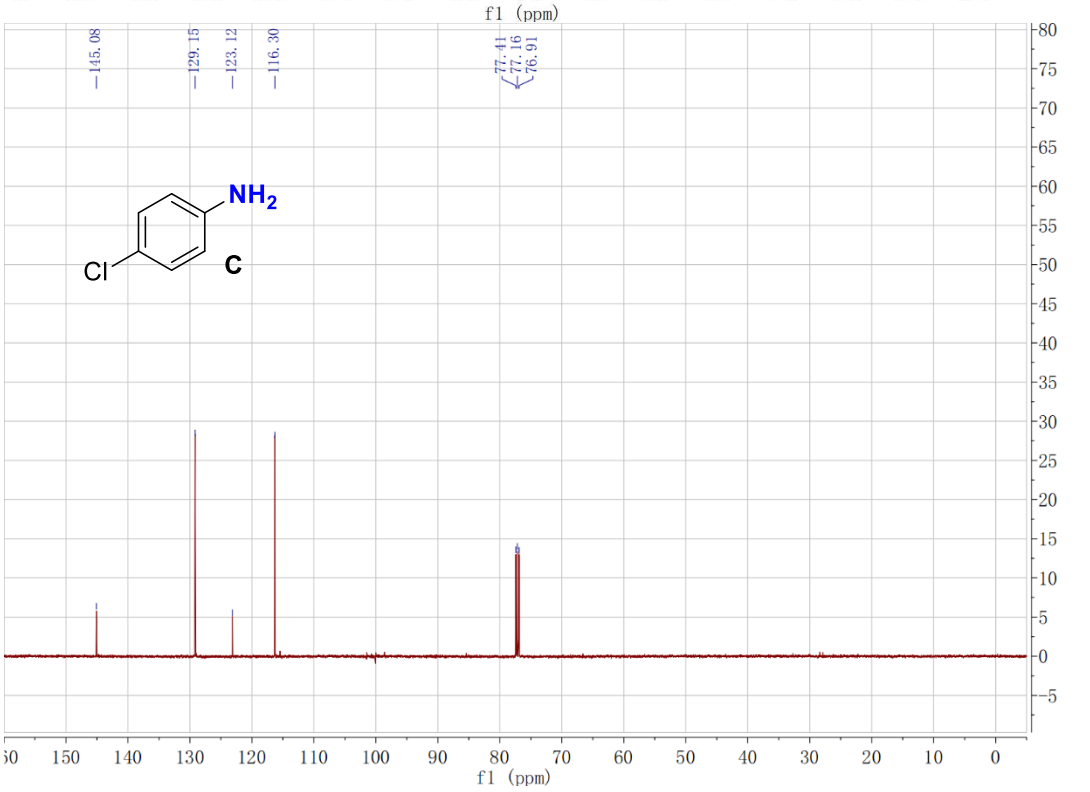
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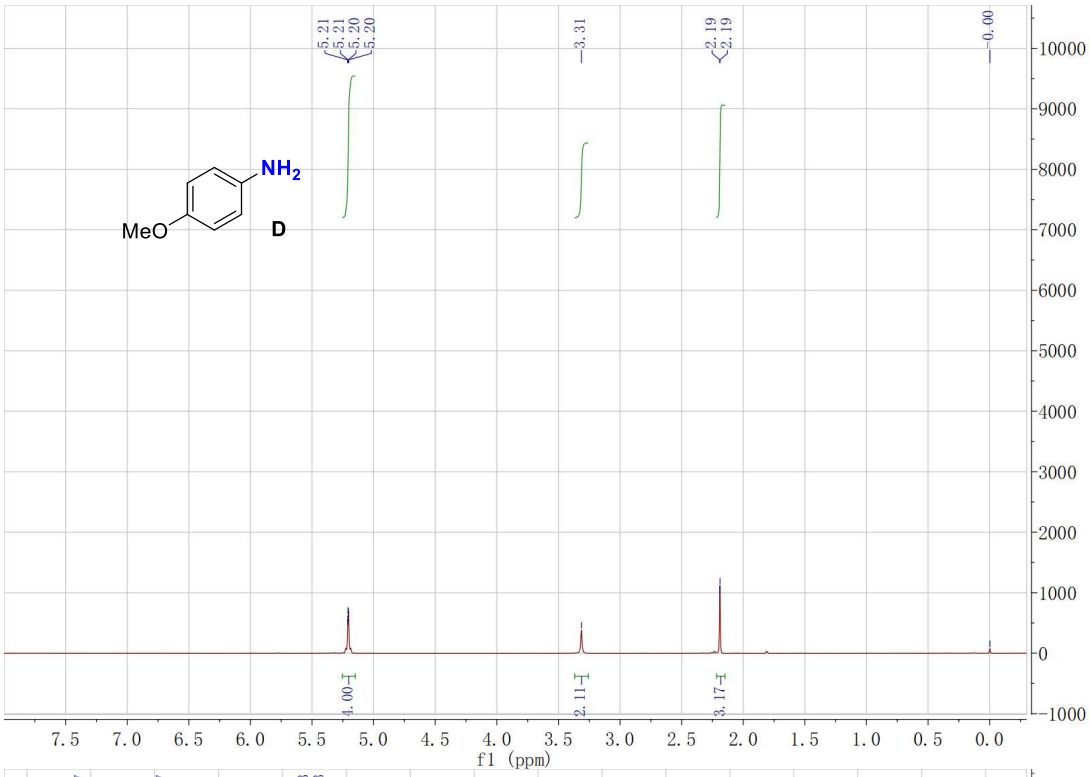
f1 (ppm)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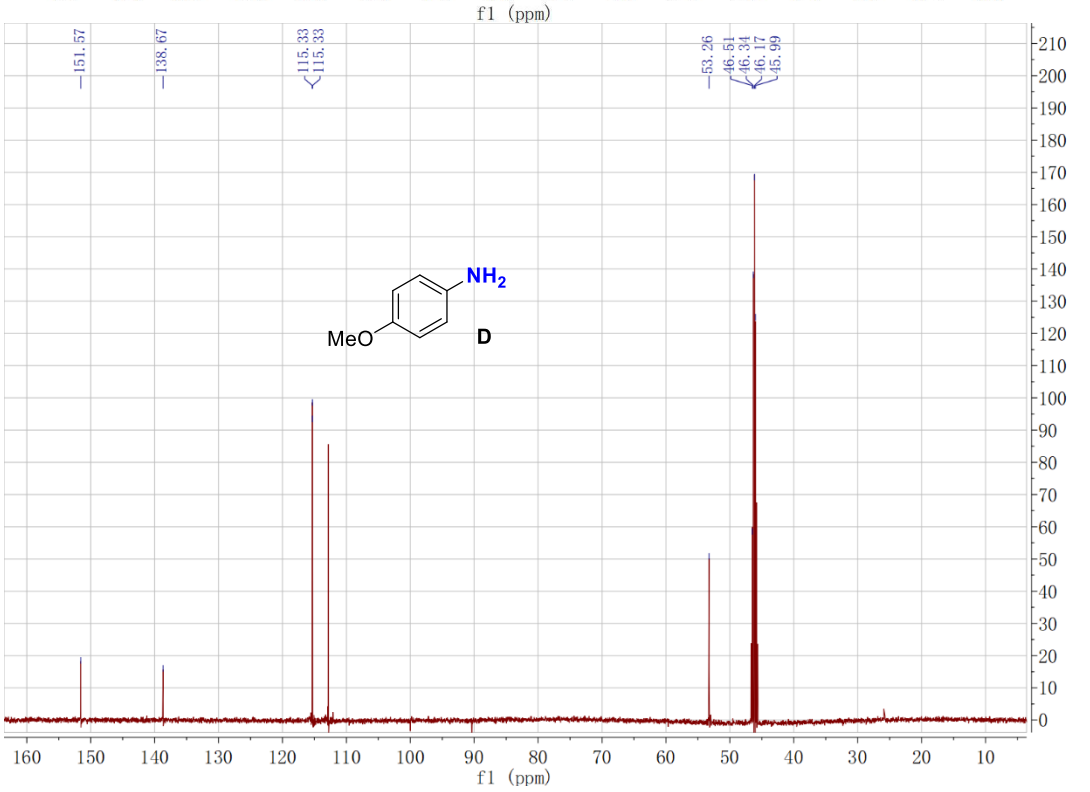
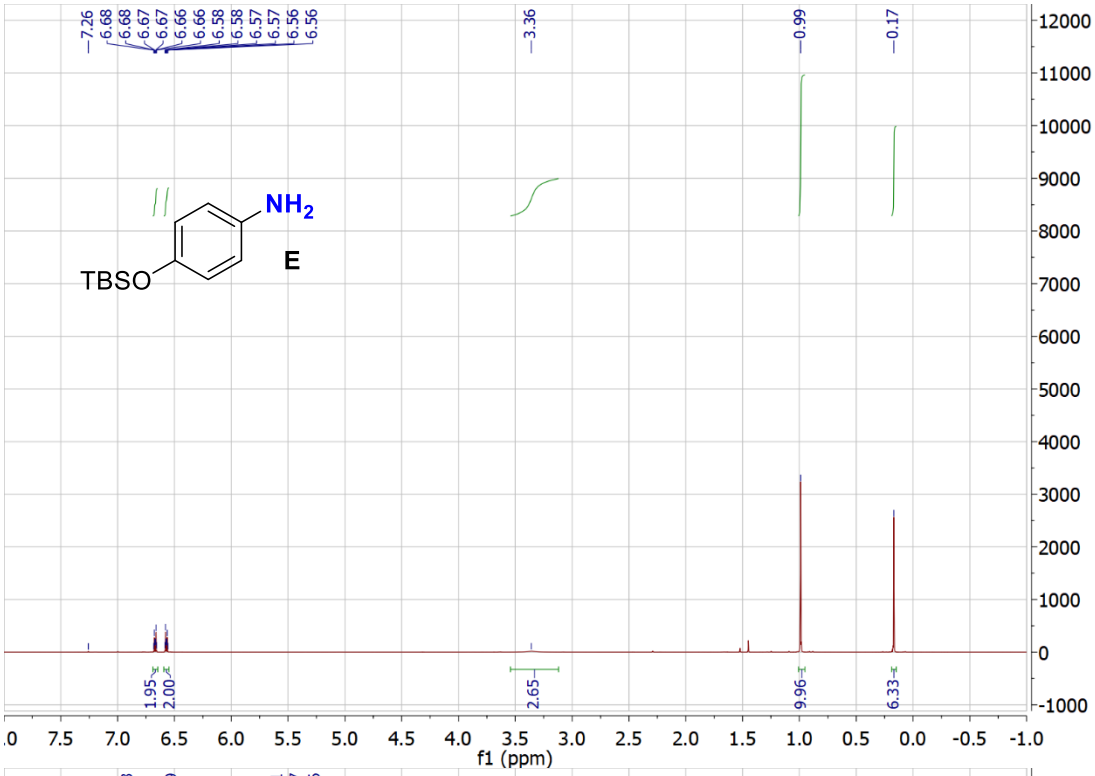
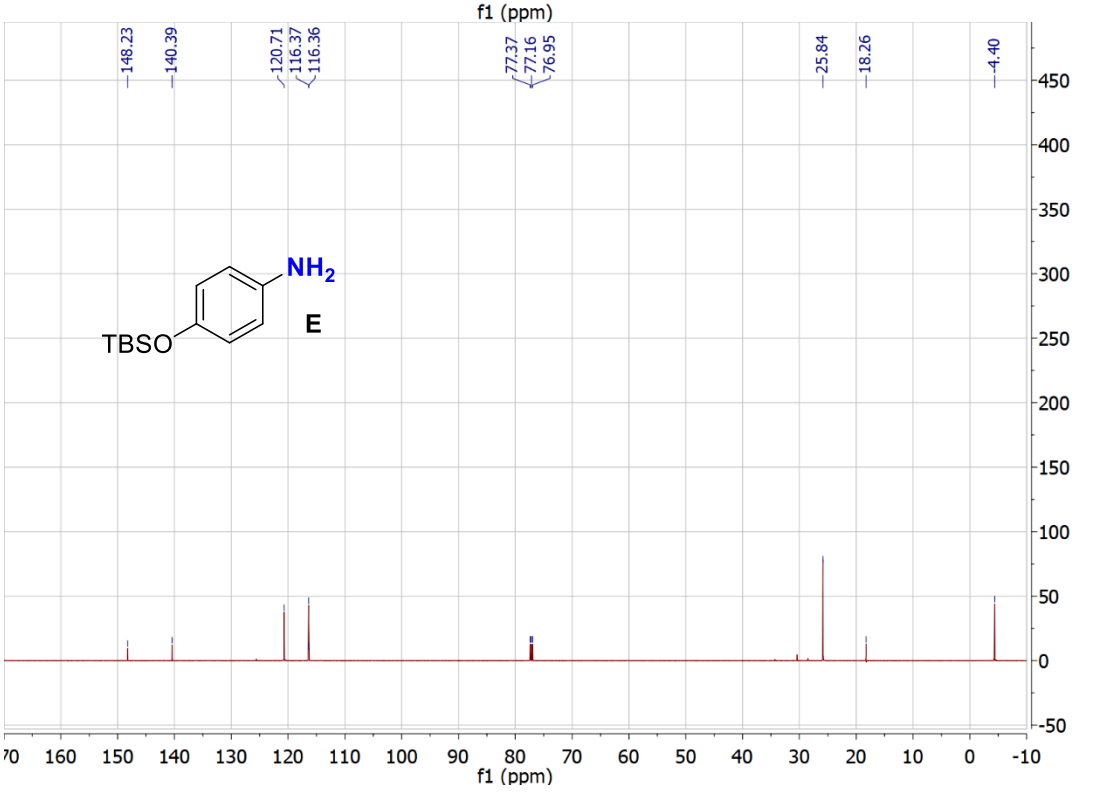
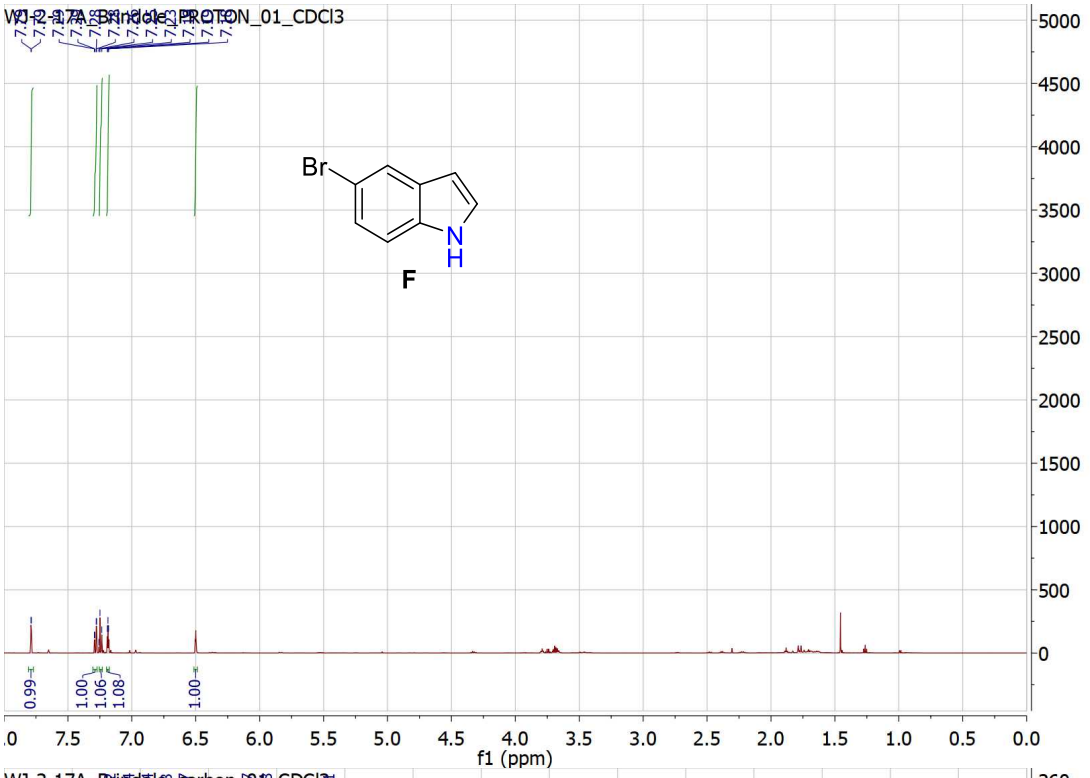
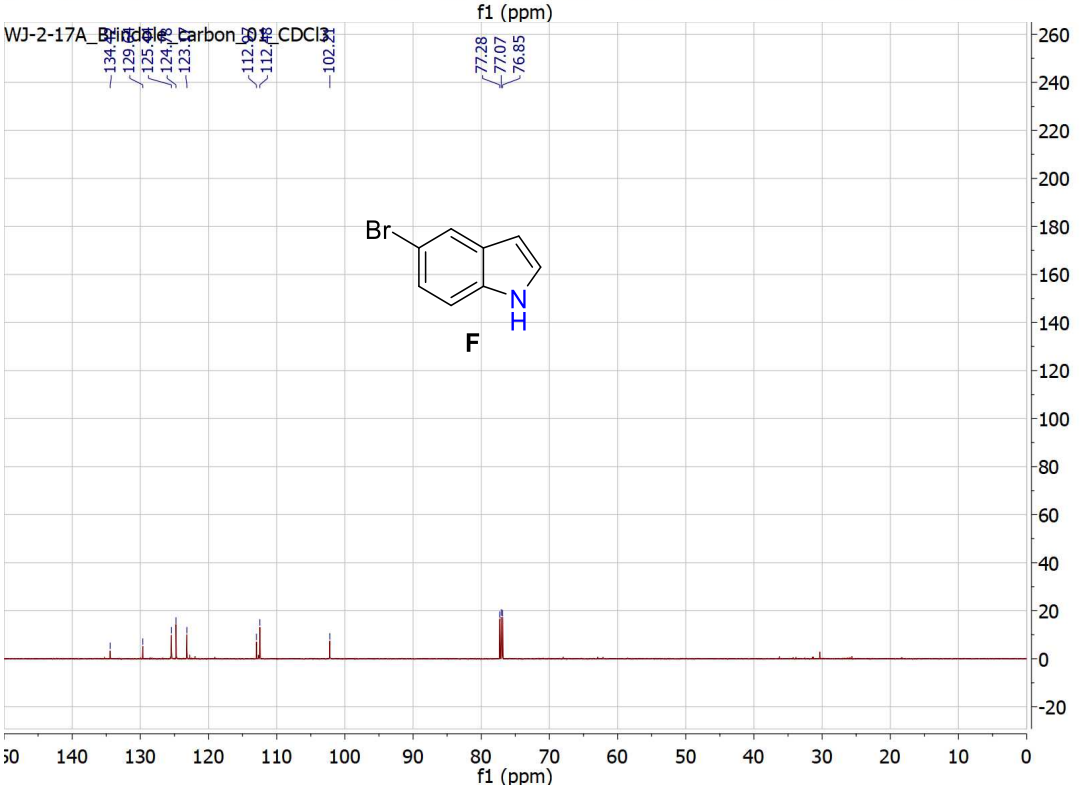
5.21
5.20
5.20
3.31
2.19
2.19
0.00
NH2
MeO
D
4.00
2.11
3.17
f1 (ppm)

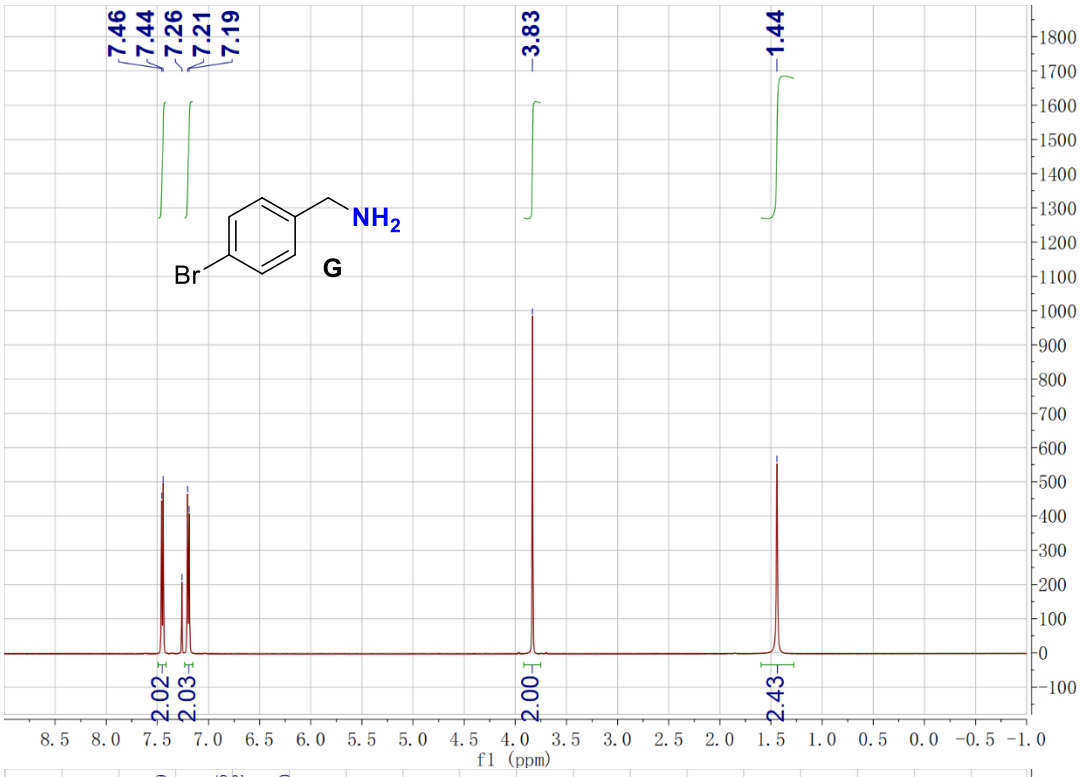

151.57
138.67
115.33
115.33
53.26
46.51
46.34
46.17
45.99
NH2
MeO
D
f1 (ppm)

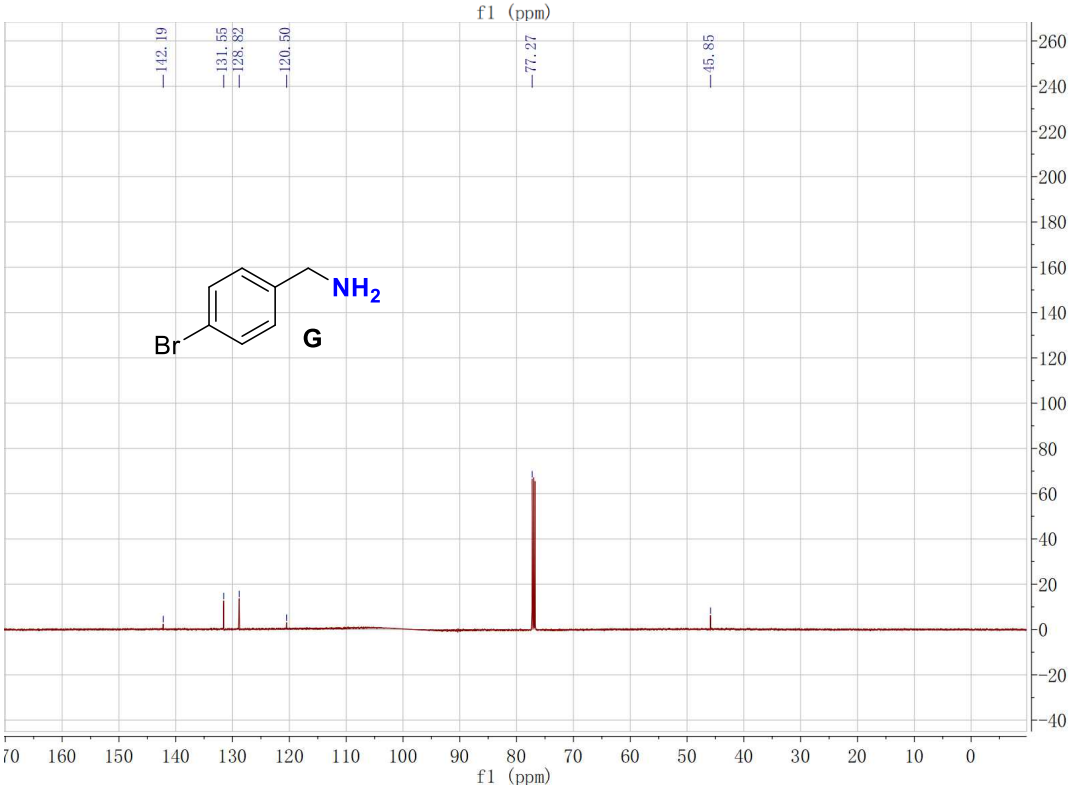

7.26
6.68
6.68
6.67
6.67
6.66
6.66
6.58
6.58
6.57
6.57
6.56
6.56
3.36
0.99
0.17
NH2
TBSO
E
1.95
2.00
2.65
9.96
6.33
f1 (ppm)

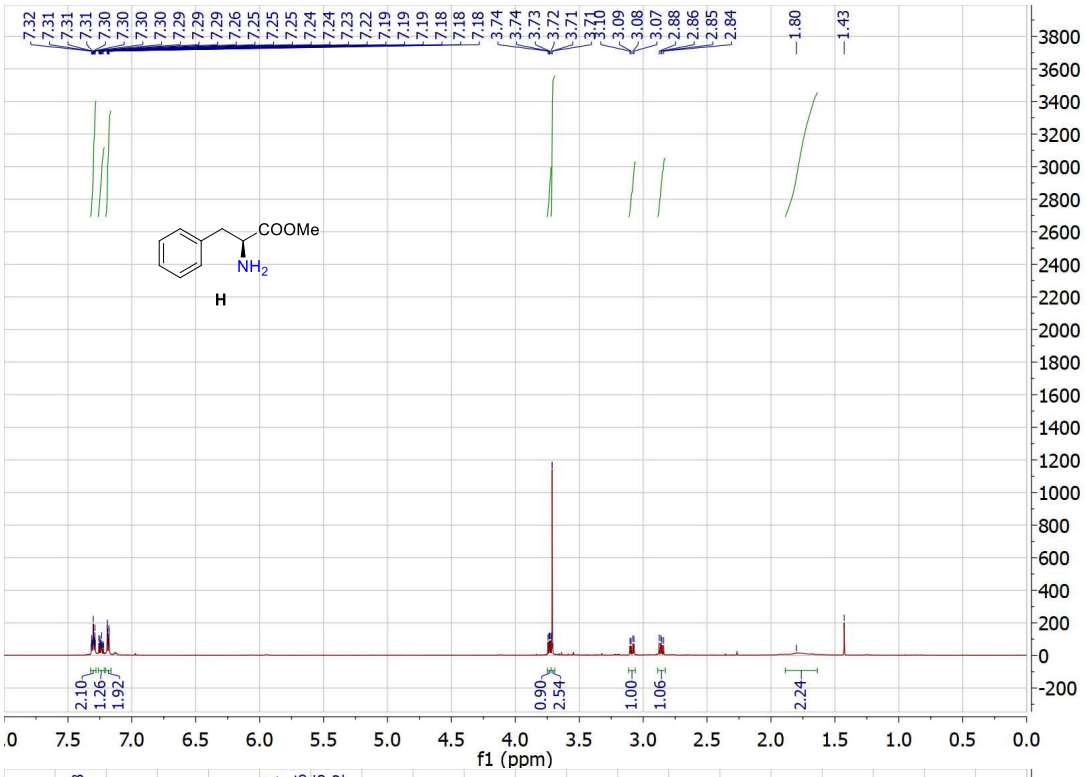

148.23
140.39
120.71
116.37
116.36
77.37
77.16
76.95
25.84
18.26
4.40
NH2
TBSO
E
f1 (ppm)

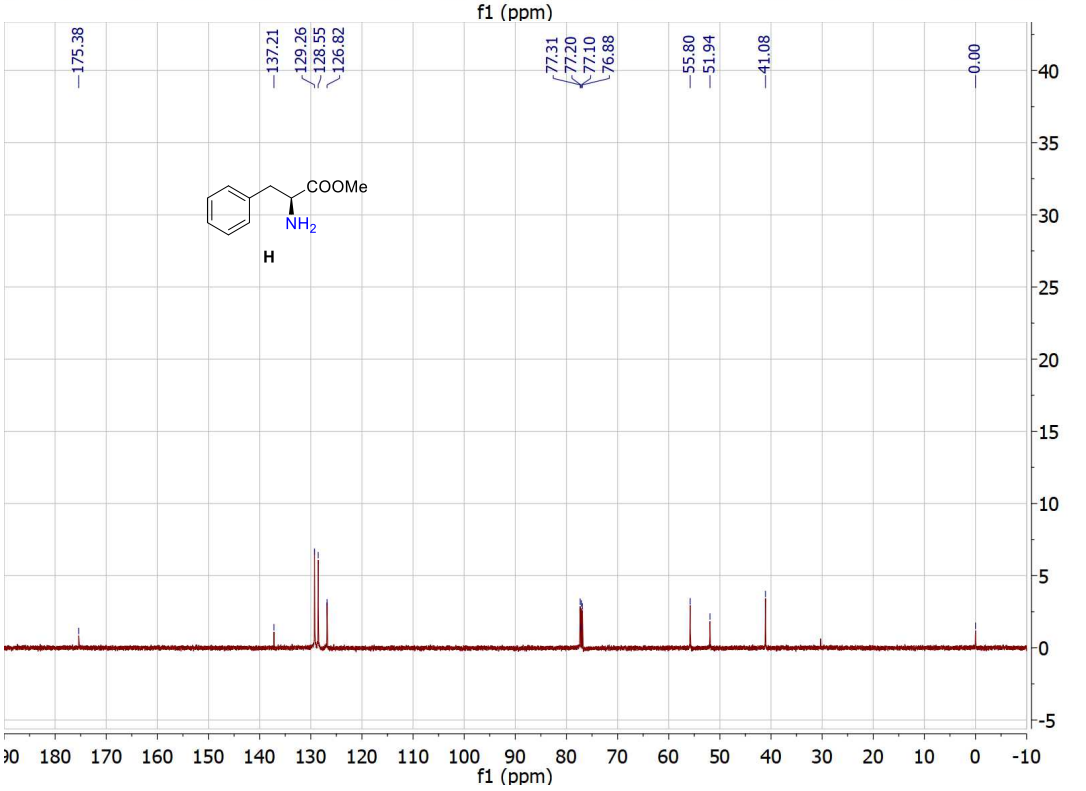

WJ-2-17A_Brindole_PROTON_01_CDCl3
Br
N
H
F
f1 (ppm)

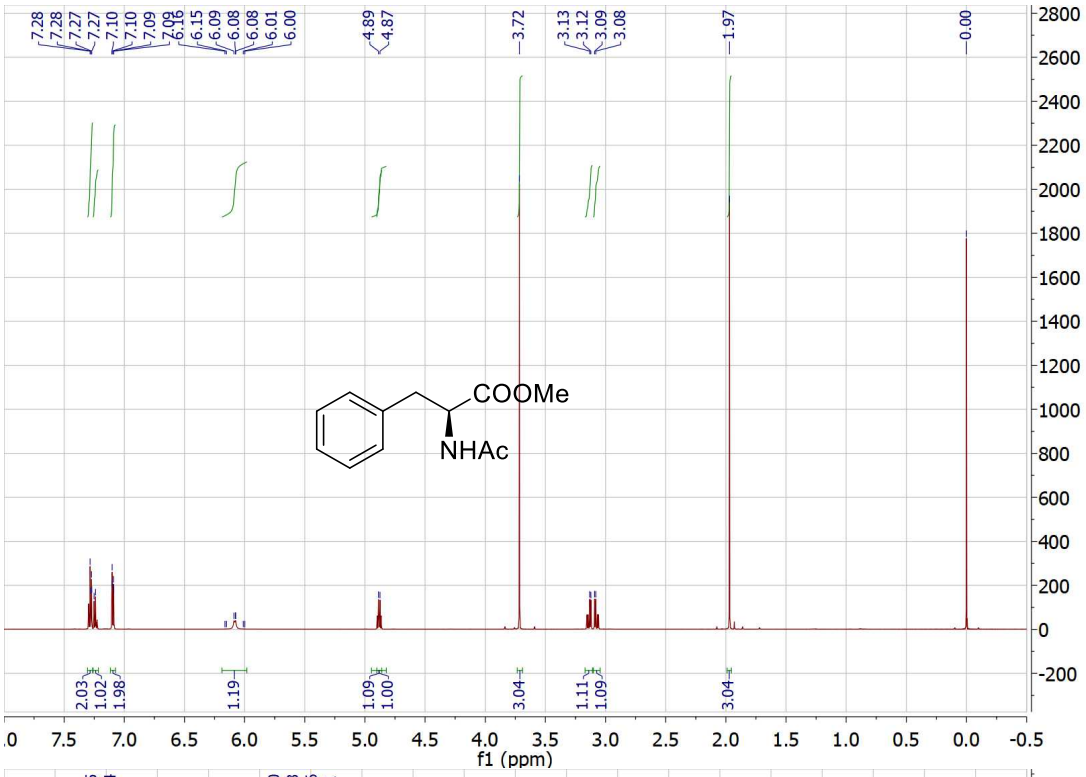

WJ-2-17A_Brindole_carbon_01_CDCl3
77.28
77.07
76.85
Br
N
H
F
f1 (ppm)

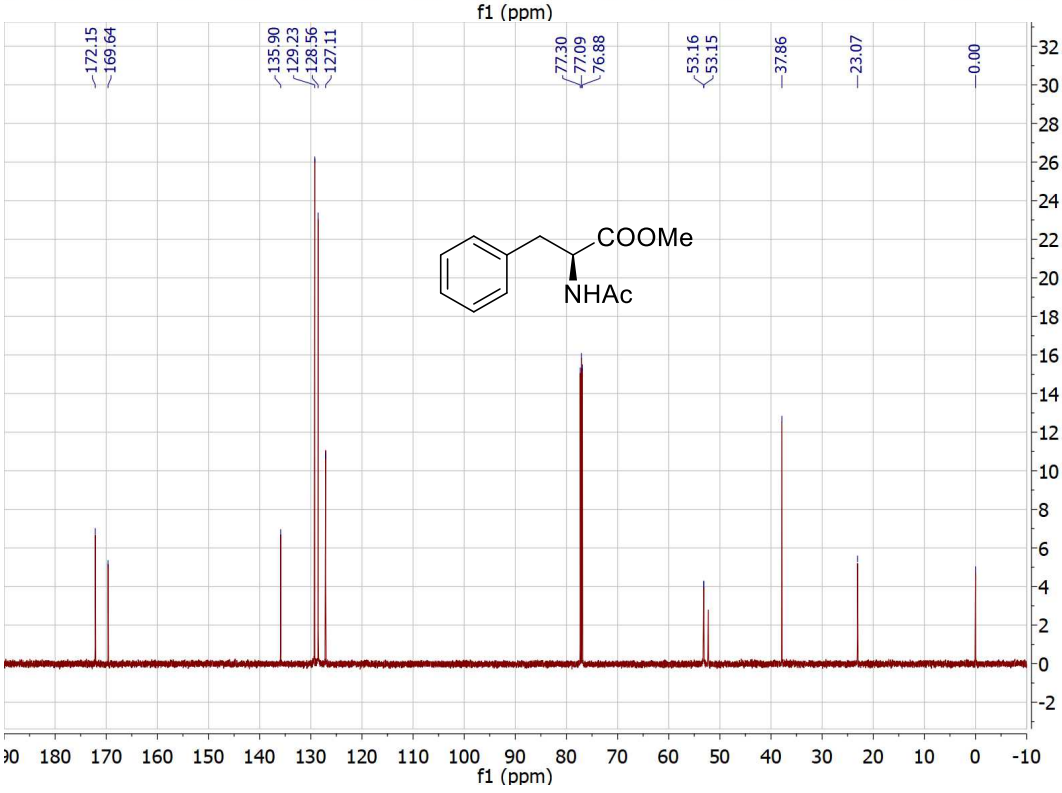

7.46
7.44
7.26
7.21
7.19
3.83
1.44
NH2
Br
G
2.02
2.03
2.00
2.43
f1 (ppm)

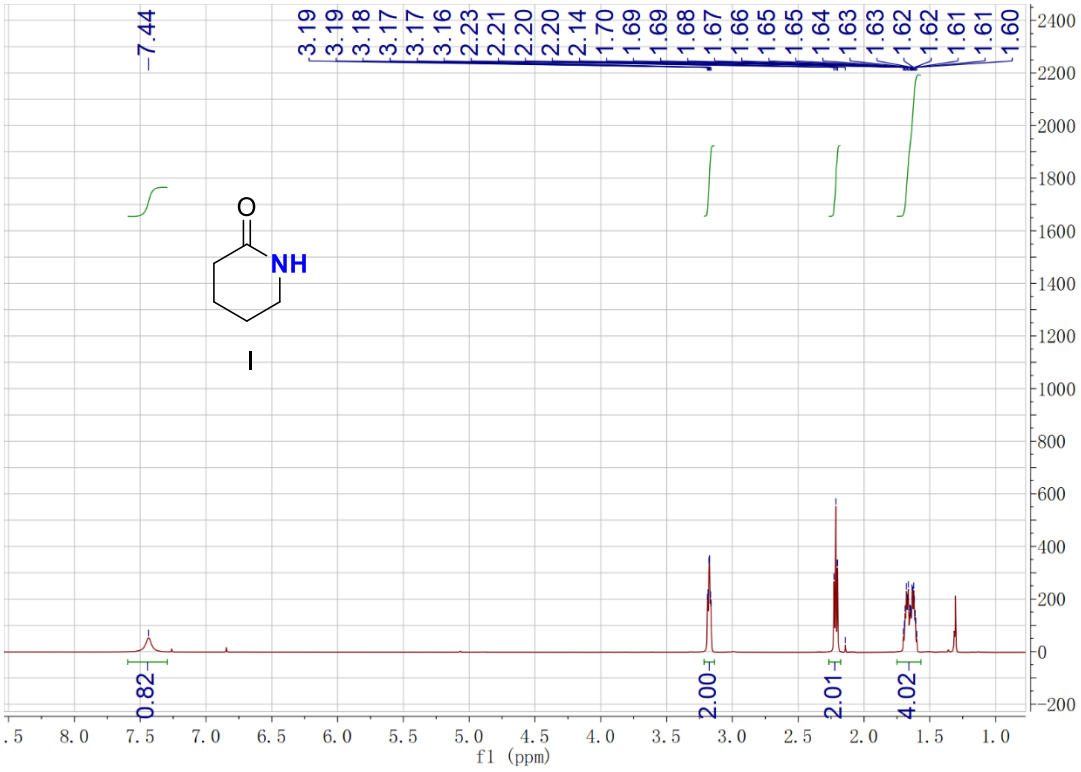

142.19
131.55
128.82
120.50
77.27
45.85
NH2
Br
G
f1 (ppm)

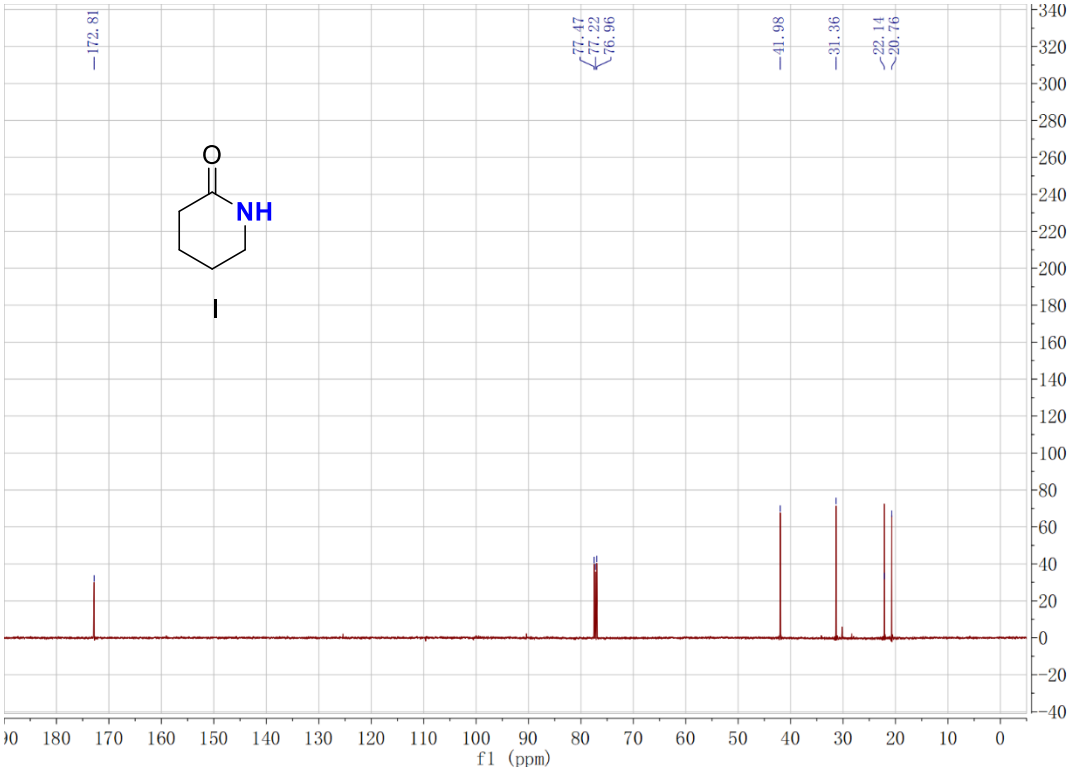

7.32 7.31 7.31 7.31 7.30 7.30 7.30 7.30 7.29 7.29 7.29 7.26 7.25 7.25 7.24 7.24 7.24 7.23 7.22 7.19 7.19 7.19 7.18 7.18 7.18 3.74 3.74 3.73 3.72 3.71 3.71 3.10 3.09 3.08 3.07 2.88 2.86 2.85 2.84 1.80 1.43
COOMe
NH2
H
2.10 1.26 1.92 0.90 2.54 1.00 1.06 2.24
f1 (ppm)

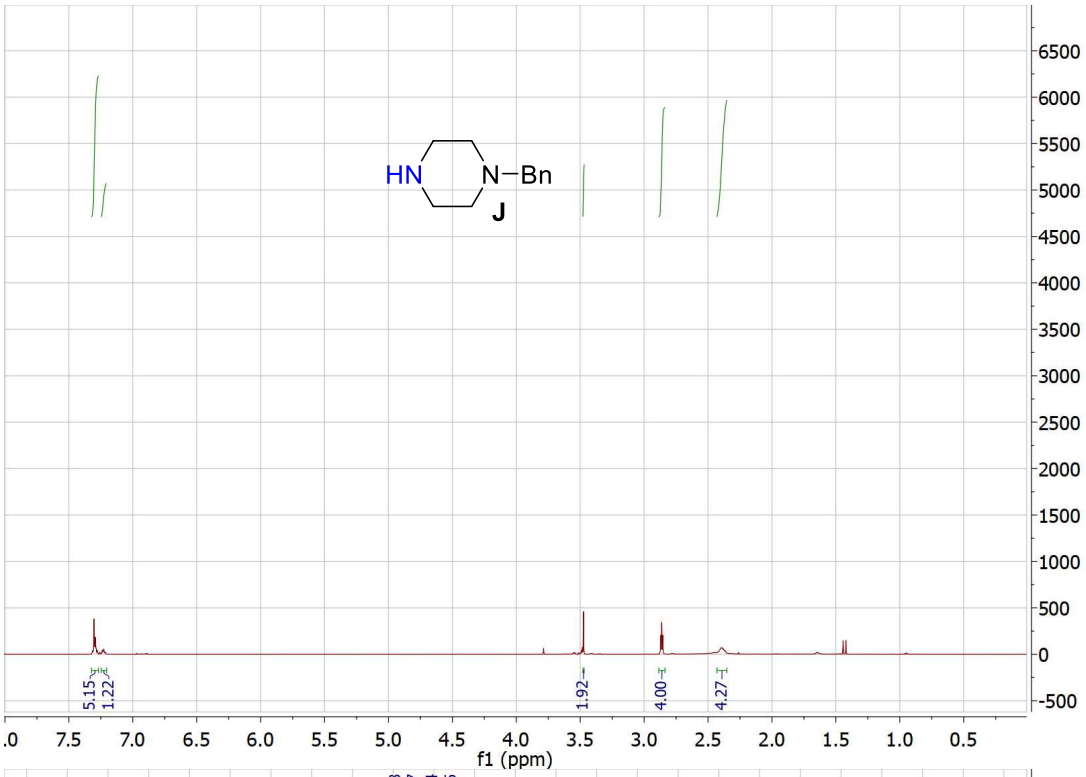

175.38 137.21 129.26 128.55 126.82 77.31 77.20 77.10 76.88 55.80 51.94 41.08 0.00
COOMe
NH2
H
f1 (ppm)

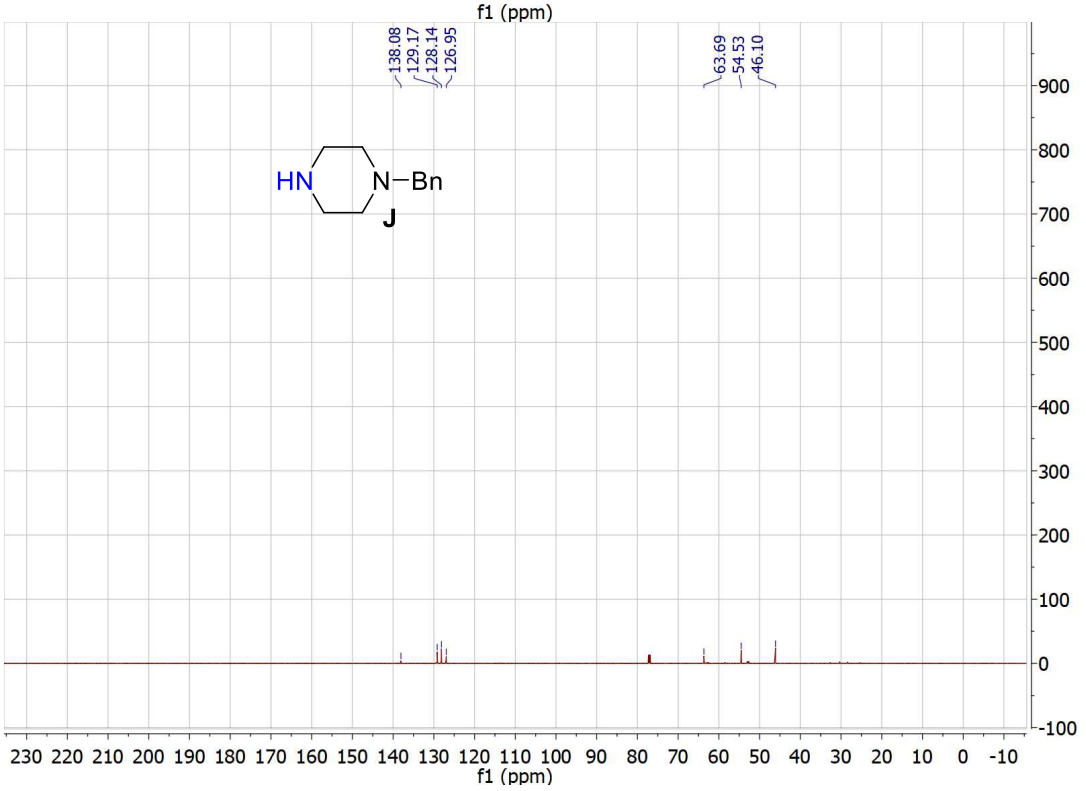

7.28
7.28
7.27
7.27
7.10
7.10
7.09
7.09
6.16
6.15
6.09
6.08
6.08
6.01
6.00
4.89
4.87
3.72
3.13
3.12
3.09
3.08
1.97
0.00
COOMe
NHAc
2.03
1.02
1.98
1.19
1.09
1.00
3.04
1.11
1.09
3.04
f1 (ppm)

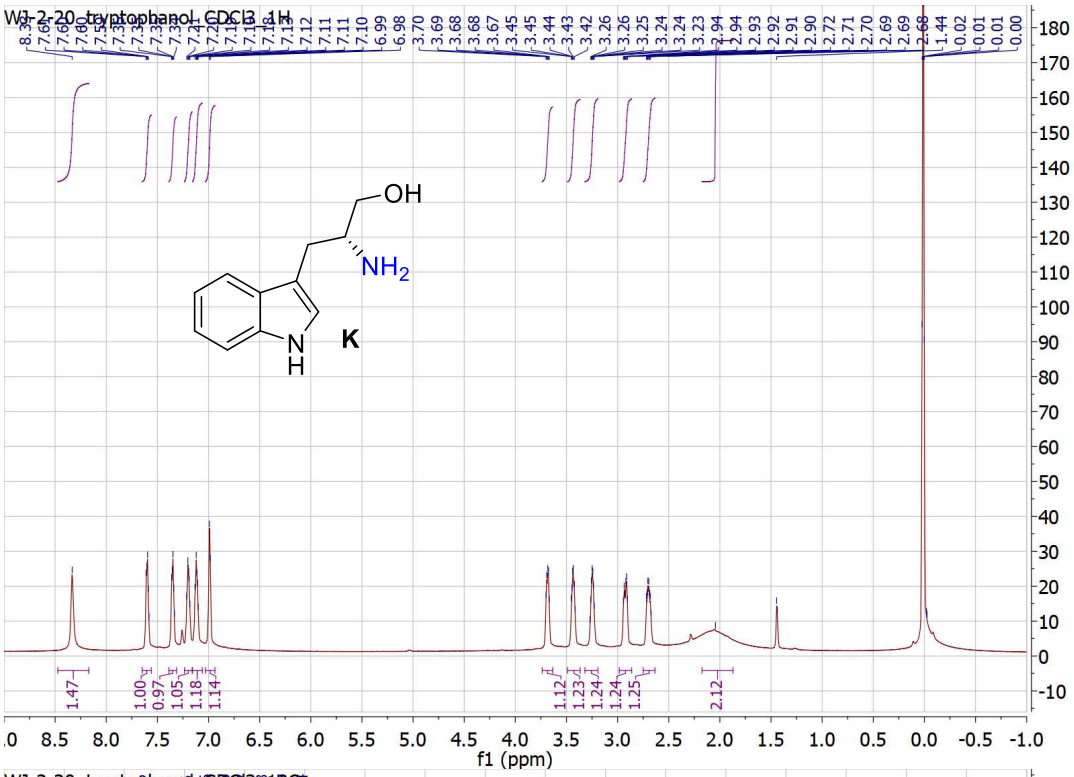

172.15
169.64
135.90
129.23
128.56
127.11
77.30
77.09
76.88
53.16
53.15
37.86
23.07
0.00
COOMe
NHAc
f1 (ppm)

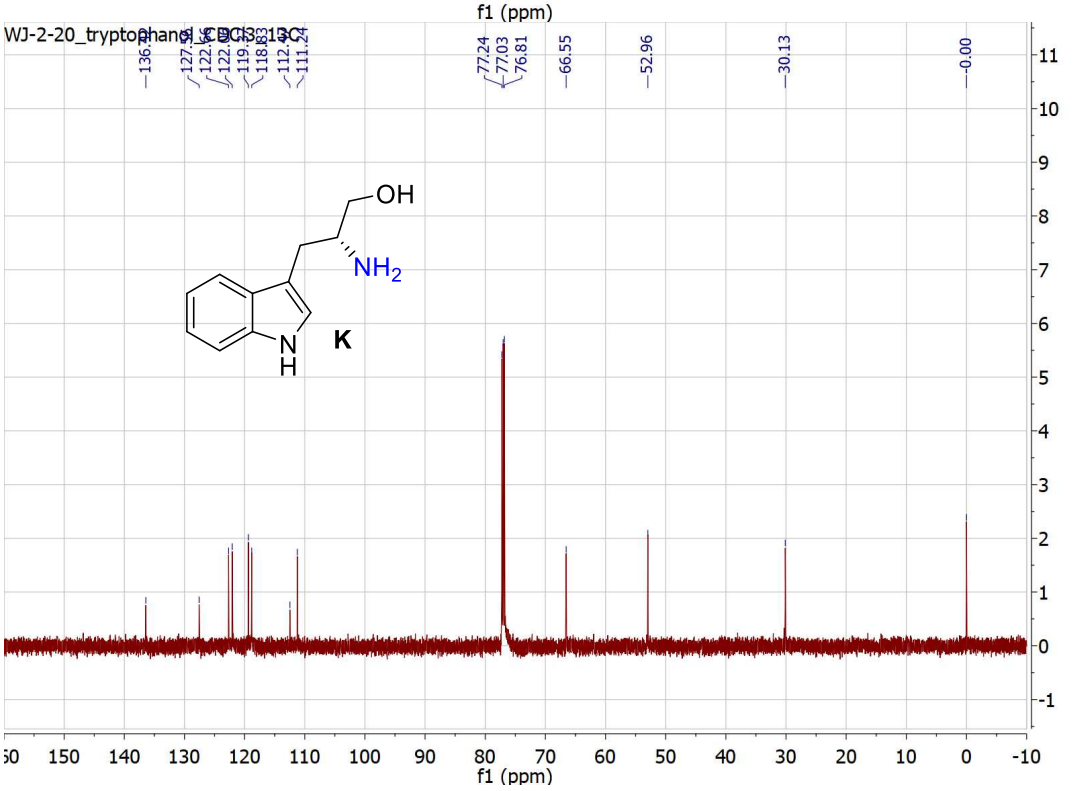

7.44
3.19
3.19
3.18
3.17
3.17
3.16
2.23
2.21
2.20
2.20
2.14
1.70
1.69
1.69
1.68
1.67
1.66
1.65
1.65
1.64
1.63
1.63
1.62
1.62
1.61
1.61
1.60
O
NH
I
0.82
2.00
2.01
4.02
f1 (ppm)

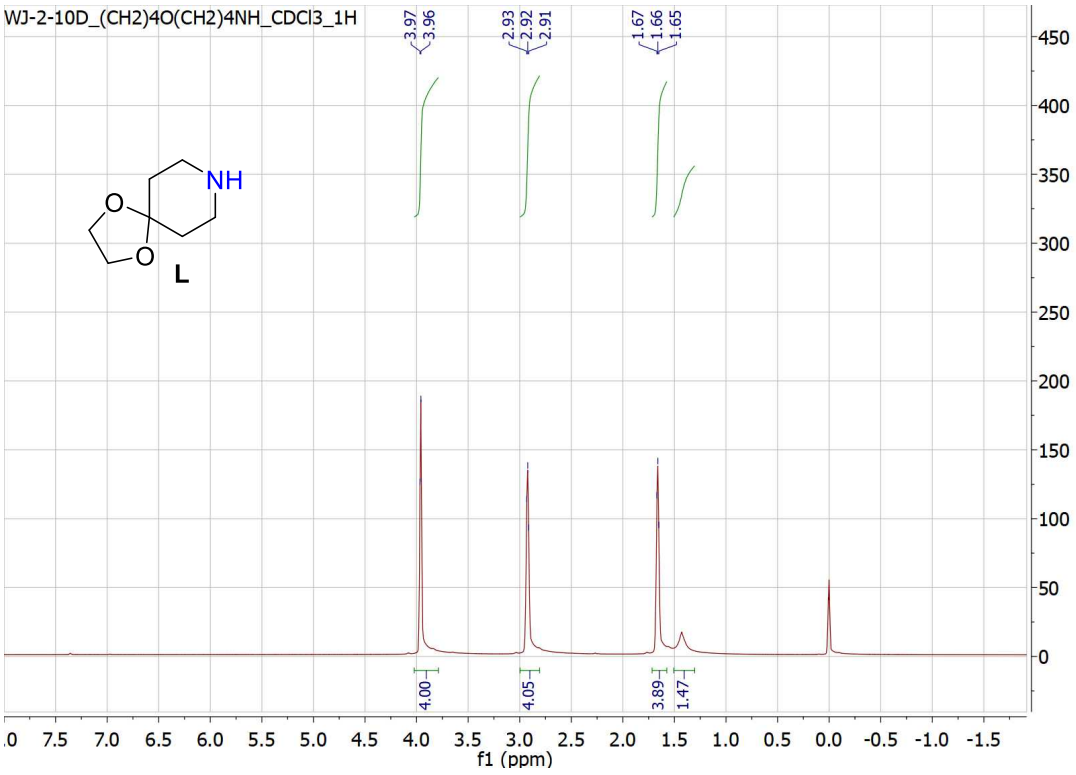

172.81
77.47
77.22
76.96
41.98
31.36
22.14
20.76
O
NH
I
f1 (ppm)

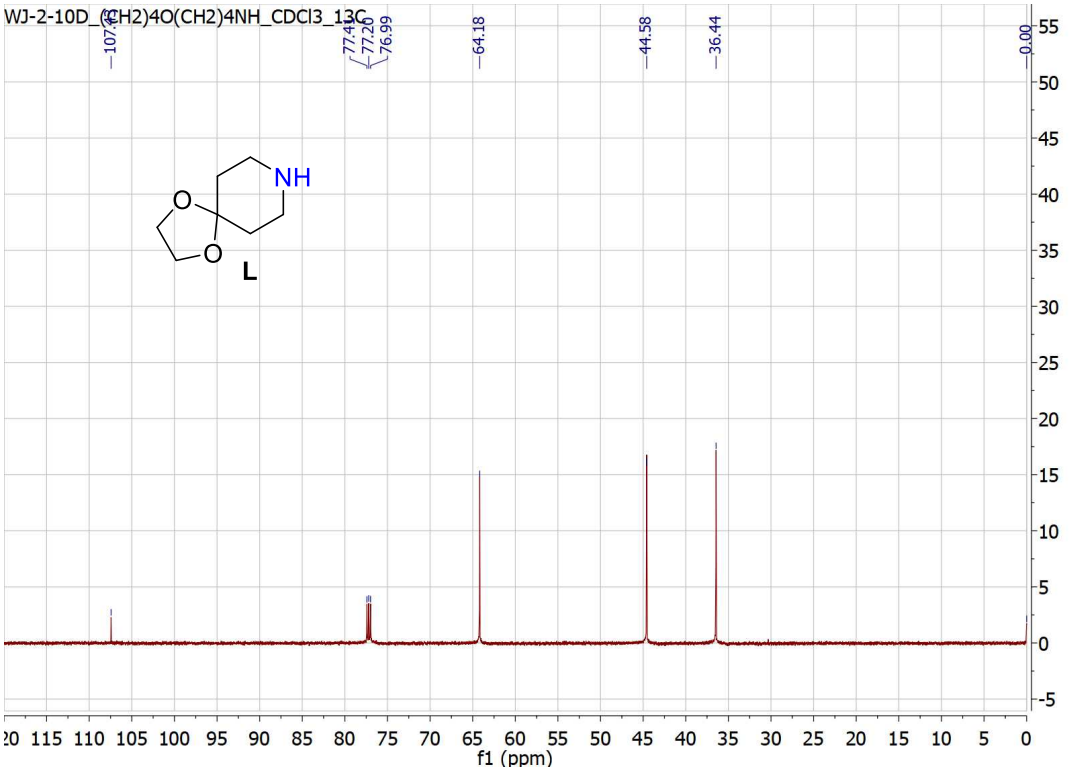

HN
N–Bn
J
5.15
1.22
1.92
4.00
4.27
f1 (ppm)

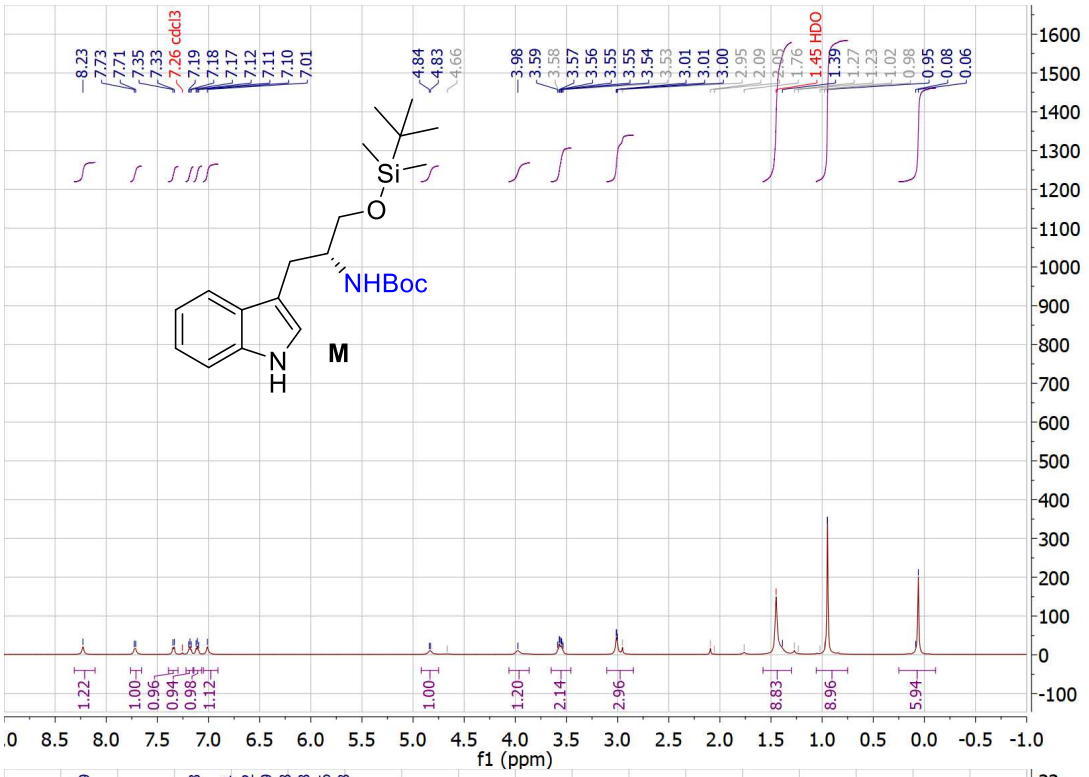

138.08
129.17
128.14
126.95
63.69
54.53
46.10
HN
N–Bn
J
f1 (ppm)

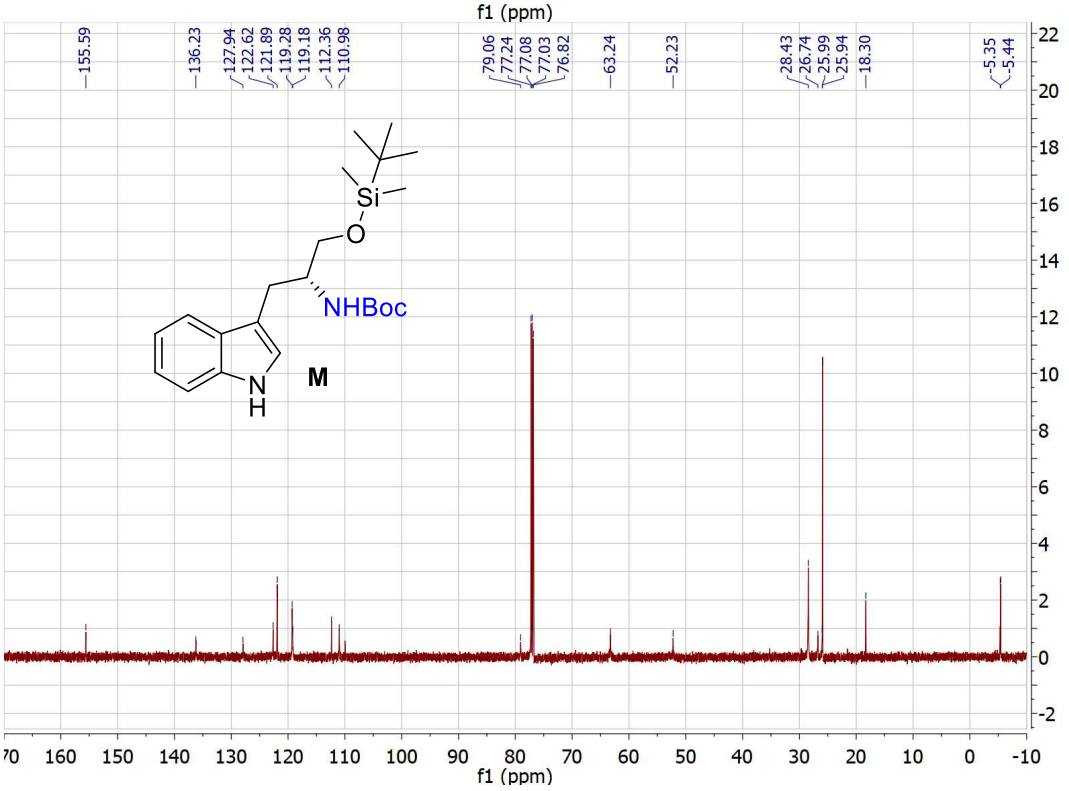

WJ-2-20_tryptophanol_CDCl3_1H
OH
NH2
N
H
K
f1 (ppm)


WJ-2-20_tryptophanol_CDCl3_13C
OH
NH2
N
H
K
f1 (ppm)


WJ-2-10D_(CH2)4O(CH2)4NH_CDCl3_1H
3.97
3.96
2.93
2.92
2.91
1.67
1.66
1.65
NH
O
O
L
4.00
4.05
3.89
1.47
f1 (ppm)


WJ-2-10D_(CH2)4O(CH2)4NH_CDCl3_13C
77.41
77.20
76.99
64.18
44.58
36.44
0.00
NH
O
O
L
f1 (ppm)





Additional References

1. X. Pan and Z. Liu, *Tetrahedron*, 2014, **70**, 4602-4610.
2. A. R. Bogdan, M. Charaschanya, A. W. Dombrowski, Y. Wang and S. W. Djuric, *Org. Lett.*, 2016, **18**, 1732-1735.