Supplementary Data

Supplementary Data For Expanding the Utility of Flow Hydrogenation – A Robust Protocol Restricting Hydrodehalogenation

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Abstract

A commonly observed limitation of conducting hydrogenations under flow chemistry conditions is hydrodehalogenation. In a bid to circumvent this limitation a series of hydrogenation catalysts were screened, with 5 % Pt/C (sulfided) catalyst identified as an effective catalyst to selectively effect reductive aminations, nitro reduction, and alkene reductions in the presence of halogen atoms. Additionally the optimised protocol to effect reductive aminations, which utilised the ThalesNano H-cube pro™, cleanly reduced an imine functionality in the presence of furan moiety indicating potential amenability with other labile functionalities.

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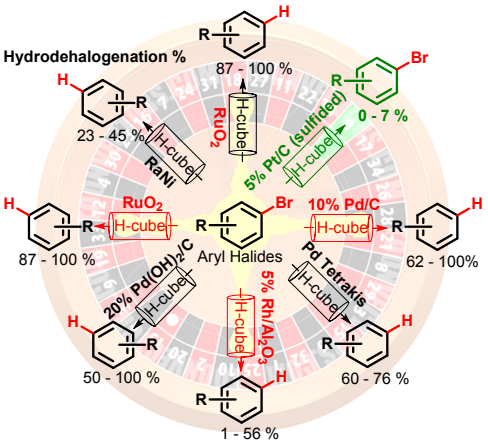
GRAPHICAL ABSTRACT



Supporting Information

1. GCMS Data

Gas chromatography-mass spectrometry (GC-MS) was performed using a Schimadzu GC-MS QF2010 EI/NCI System fitted with a ZB-5MS column [30 m x 0.25 mm], 5% phenyl-arylene stationary phase. The injector temperature was set at 250 °C and an oven program starting at 160 °C, with a hold time of 1 min. The temperature was then rapidly increased to 230 °C (35 °C/min) and it was held for 18.5 – 22 min. The flow rate was set at 23mL/min, with a column flow rate of 0.95 mL/min.

Table S1: Details of compounds including molecular weight and retention times observed in GC-MS traces (A – K, Table S2).

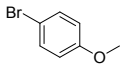
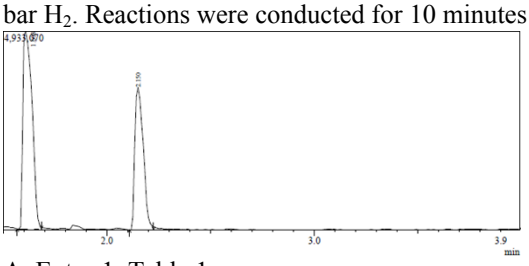
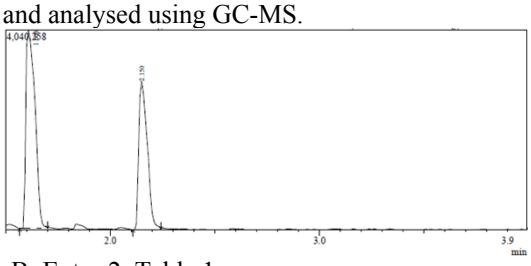
Compound	Structure	Retention Time (mins)
7	 Chemical Formula: C_7H_7BrO Molecular Weight: 187.03	2.15
10	 Chemical Formula: C_7H_8O Molecular Weight: 108.14	1.61

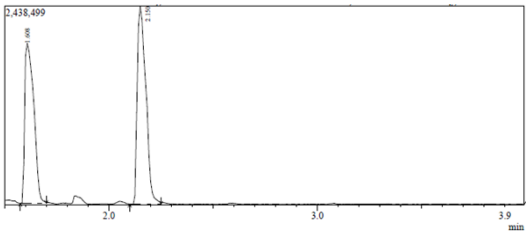
Table S2: Evaluation of commercially available catalysts for the hydrogenation of **7** at 1.0 mL.min^{-1} flow rate, 50 °C, 50 bar H_2. Reactions were conducted for 10 minutes and analysed using GC-MS.



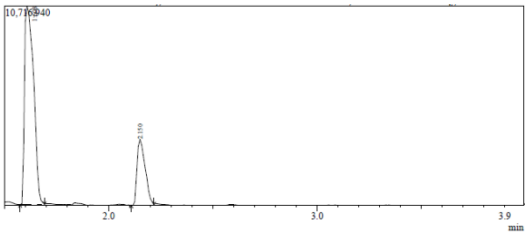
A. Entry 1, Table 1



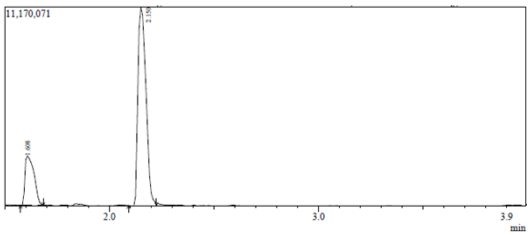
B. Entry 2, Table 1



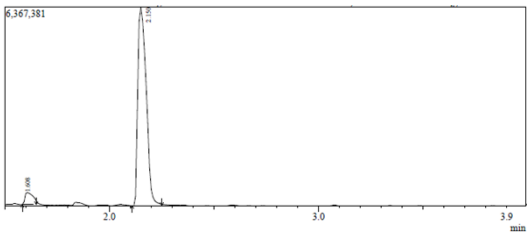
C. Entry 3, Table 1



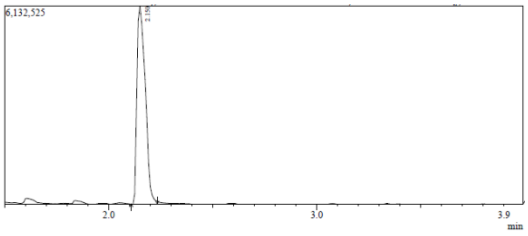
D. Entry 4, Table 1



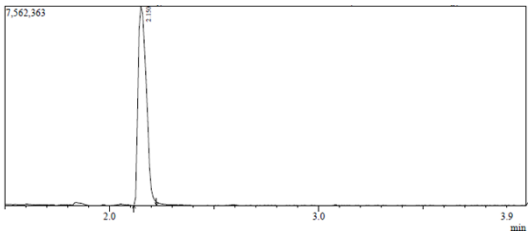
E. Entry 5, Table 1



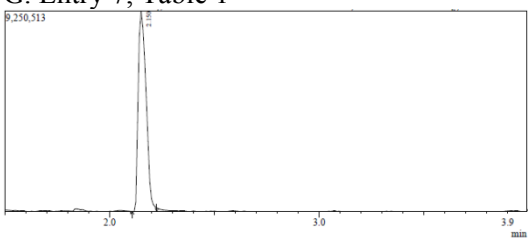
F. Entry 6, Table 1



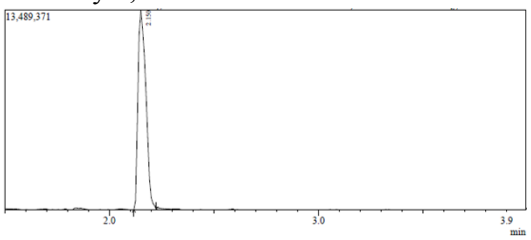
G. Entry 7, Table 1



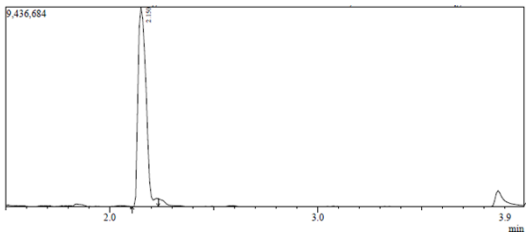
H. Entry 8, Table 1



I. Entry 9, Table 1



J. Entry 10, Table 1



K. Entry 11, Table 1

Table S3: Details of compounds including molecular weight and retention times observed in GC-MS traces (A-K, Table S4).

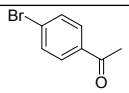
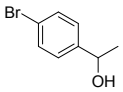
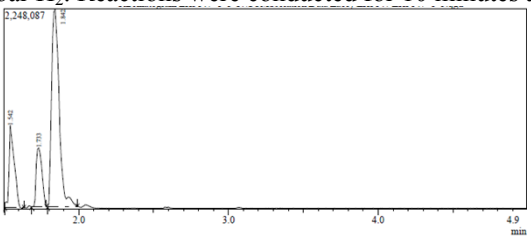
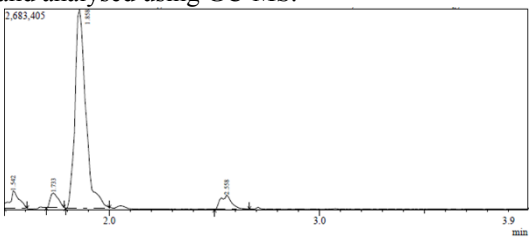
Compound	Structure	Retention Time (mins)
8	 Chemical Formula: C_8H_7BrO Molecular Weight: 199.04	2.54
11	 Chemical Formula: C_8H_9BrO Molecular Weight: 201.06	2.61
12	 Chemical Formula: C_8H_8O Molecular Weight: 120.15	1.86
13	 Chemical Formula: $C_8H_{10}O$ Molecular Weight: 122.16	1.73

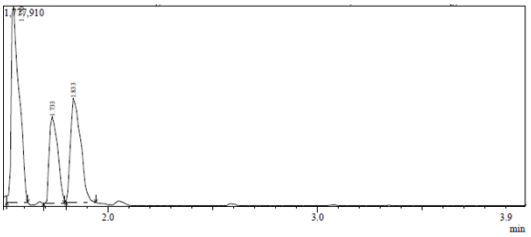
Table S4: Evaluation of commercially available catalysts for the hydrogenation of **8** at 1.0 mL.min^{-1} flow rate, 50 °C, 50 bar H_2. Reactions were conducted for 10 minutes and analysed using GC-MS.



A. Entry 1, Table 2



B. Entry 2, Table 2



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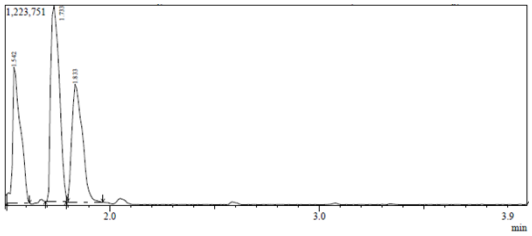
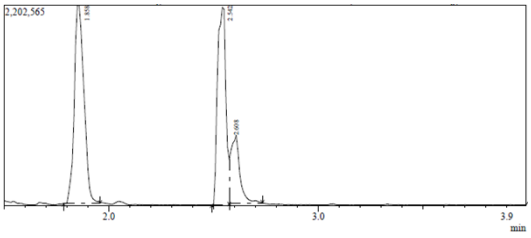
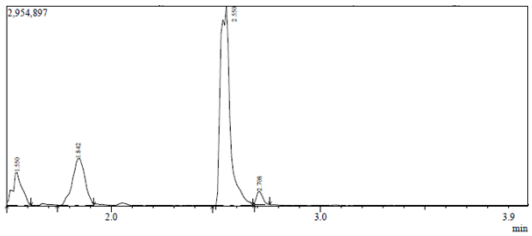


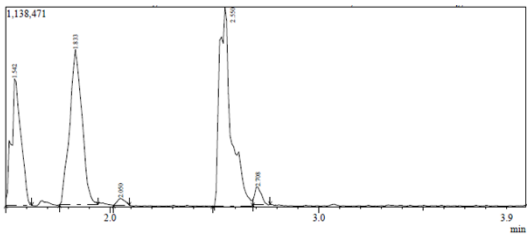
D. Entry 4, Table 2



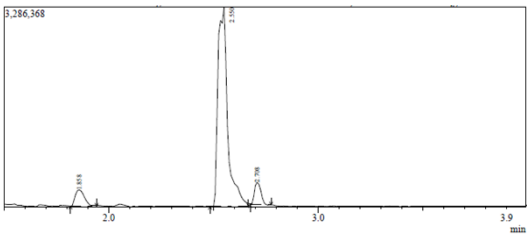
E. Entry 5, Table 2



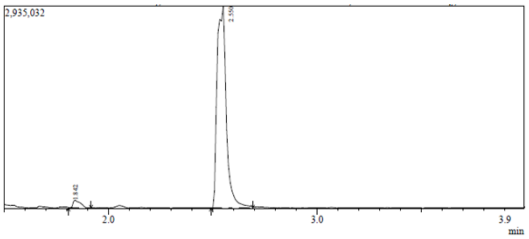
F. Entry 6, Table 2



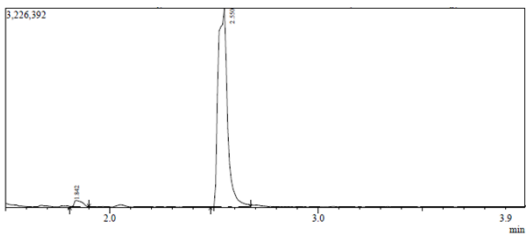
G. Entry 7, Table 2



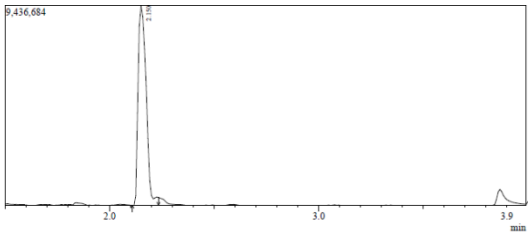
H. Entry 8, Table 2



I. Entry 9, Table 2



J. Entry 10, Table 2



K. Entry 11, Table 2

Table S5: Details of compounds including molecular weight and retention times observed in GC-MS traces (A – K, Table S6).

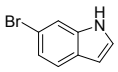
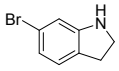
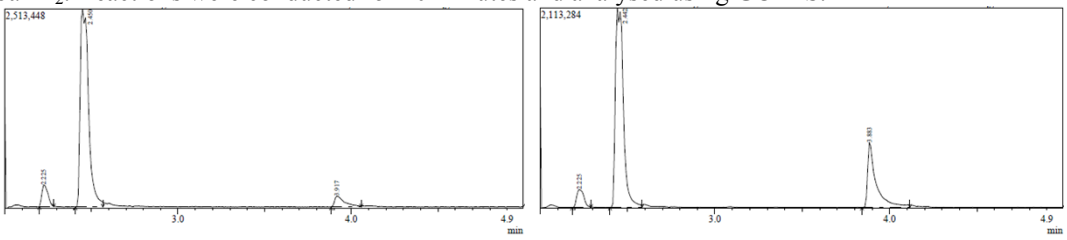
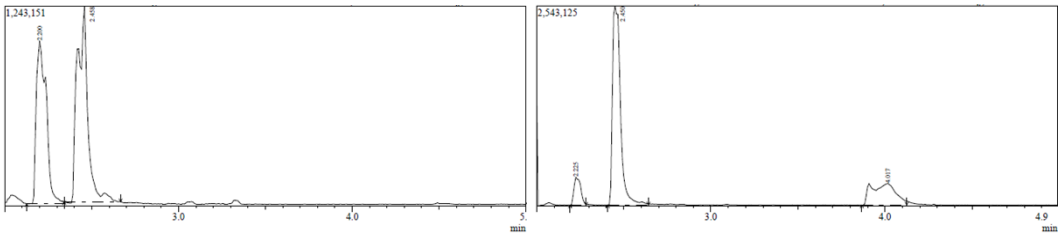
Compound	Structure	Retention Time (mins)
9	 Chemical Formula: C_8H_6BrN Molecular Weight: 196.04	3.88
14	 Chemical Formula: C_8H_8BrN Molecular Weight: 198.06	3.45
15	 Chemical Formula: C_8H_7N Molecular Weight: 117.15	2.47
16	 Chemical Formula: C_8H_{9N} Molecular Weight: 119.16	2.23

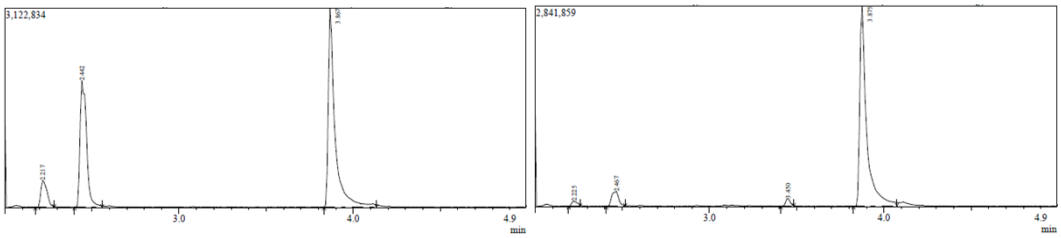
Table S6: Evaluation of commercially available catalysts for the hydrogenation of **9** at 1.0 mL.min^{-1} flow rate, 50 °C, 50 bar H_2. Reactions were conducted for 10 minutes and analysed using GC-MS.



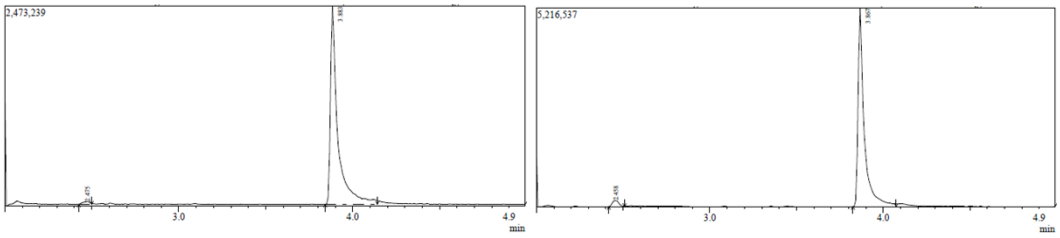
A. Entry 1, Table 3 B. Entry 2, Table 3



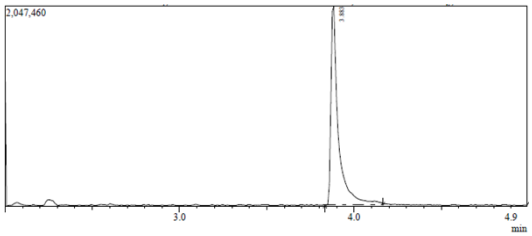
C. Entry 3, Table 3 D. Entry 4, Table 3



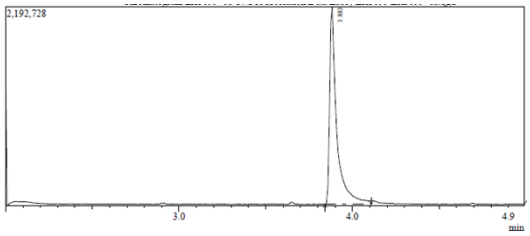
E. Entry 5, Table 3 F. Entry 6, Table 3



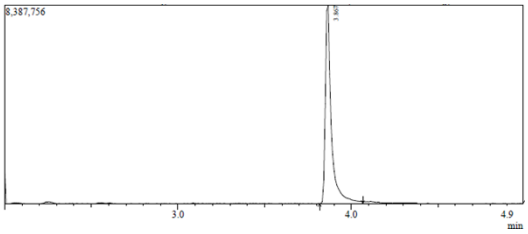
G. Entry 7, Table 3



H. Entry 8, Table 3



I. Entry 9, Table 3



J. Entry 10, Table 3

K. Entry 11, Table 3

Table S7: Details of compounds including molecular weight and retention times observed in GC-MS traces (A – E, Table S8).

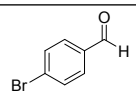
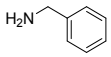
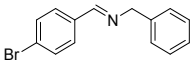
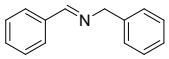
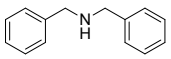
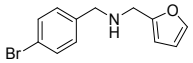
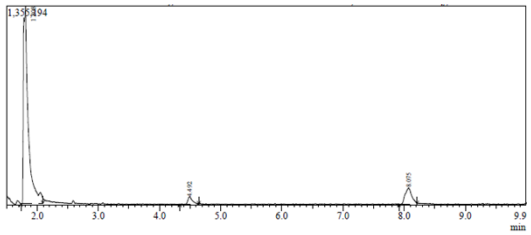
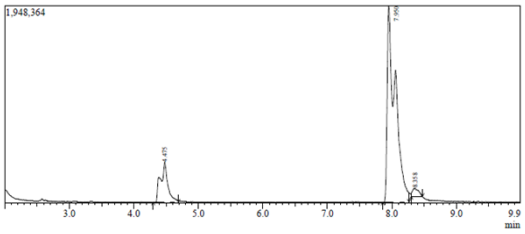
Compound	Structure	Retention Time (mins)
17	 Chemical Formula: C_7H_5BrO Molecular Weight: 185.02	2.61
18	 Chemical Formula: C_7H_9N Molecular Weight: 107.15	1.80
22	 Chemical Formula: $C_{14}H_{12}BrN$ Molecular Weight: 274.16	8.08
21	 Chemical Formula: $C_{14}H_{13}N$ Molecular Weight: 195.26	4.49
24	 Chemical Formula: C_7H_8O Molecular Weight: 108.14	1.81
26	 Chemical Formula: $C_{14}H_{15}N$ Molecular Weight: 197.28	4.33
4	 Chemical Formula: $C_{12}H_{12}BrNO$ Molecular Weight: 266.13	

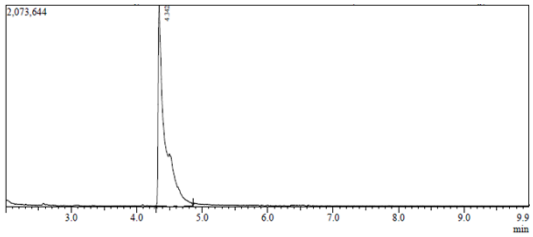
Table S8: Evaluation of hydrogenation reactions in Scheme 3 - 6



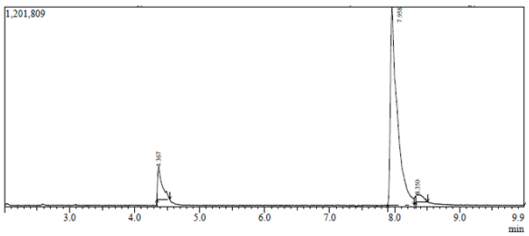
A. Scheme 3 results



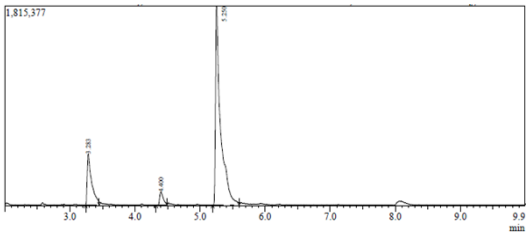
B. Scheme 4 results



C. Scheme 5 – 10% Pd/C



D. Scheme 5 – 5% Pt/C (sulfided)



E. Scheme 6 results

Table S9: Details of compounds including molecular weight and retention times observed in GC-MS traces (A-C, Table S8 and S9).

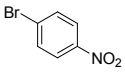
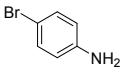
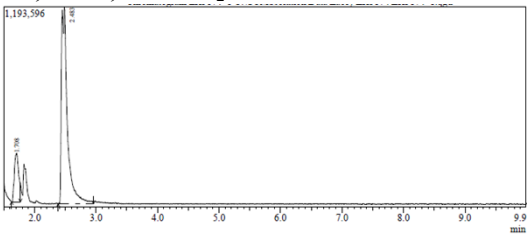
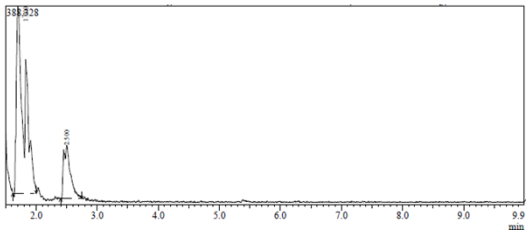
Compound	Structure	Retention Time (mins)
27	 Chemical Formula: $C_6H_4BrNO_2$ Molecular Weight: 202.01	2.57
28	 Chemical Formula: C_6H_6BrN Molecular Weight: 172.02	2.46
29	 Chemical Formula: C_6H_7N Molecular Weight: 93.13	1.71

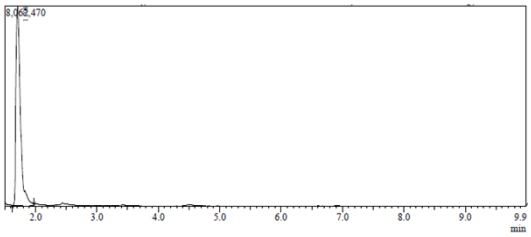
Table S10: Evaluation of hydrogenation catalysts for selective nitro reduction, conditions were set to 1.0 mL.min^{-1} flow rate, 30 °C, 30 bar H_2. Reactions were conducted for 10 minutes and analysed using GC-MS.



A. Entry 1, Table 4

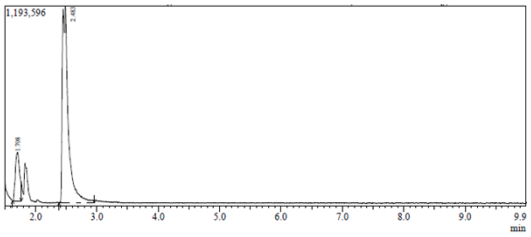


B. Entry 2, Table 4 (10% Pd/C)

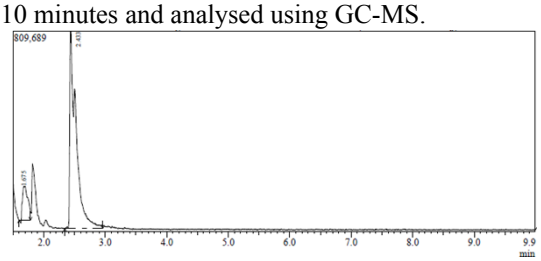


C. Entry 3, Table 4

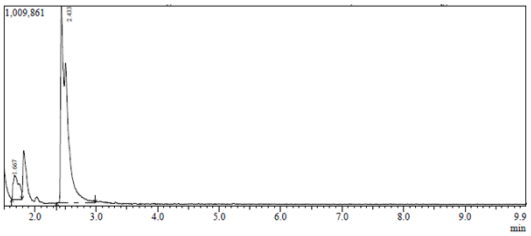
Table S11: Evaluation of residence time for selective nitro reduction, conditions were set to 30 °C, 30 bar H_2 and variable flow rate. Reactions were conducted for 10 minutes and analysed using GC-MS.



A. Entry 1, Table 5

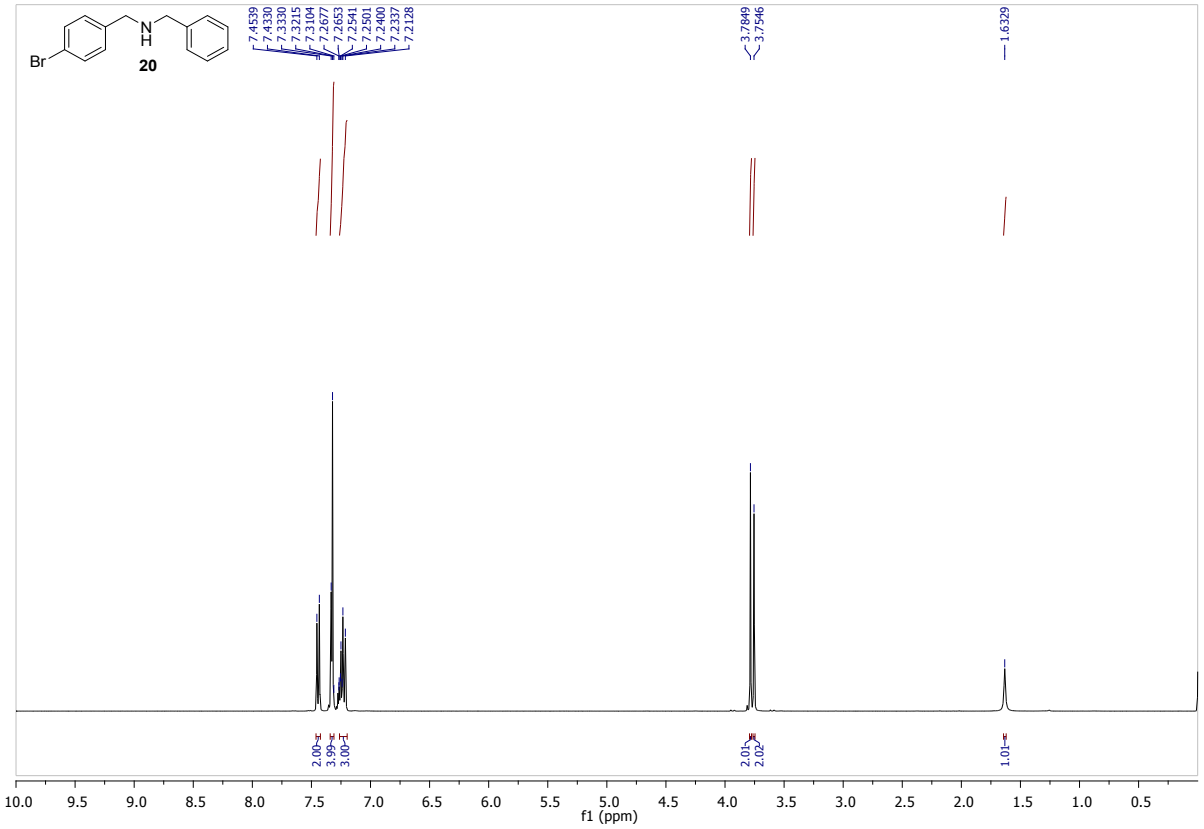


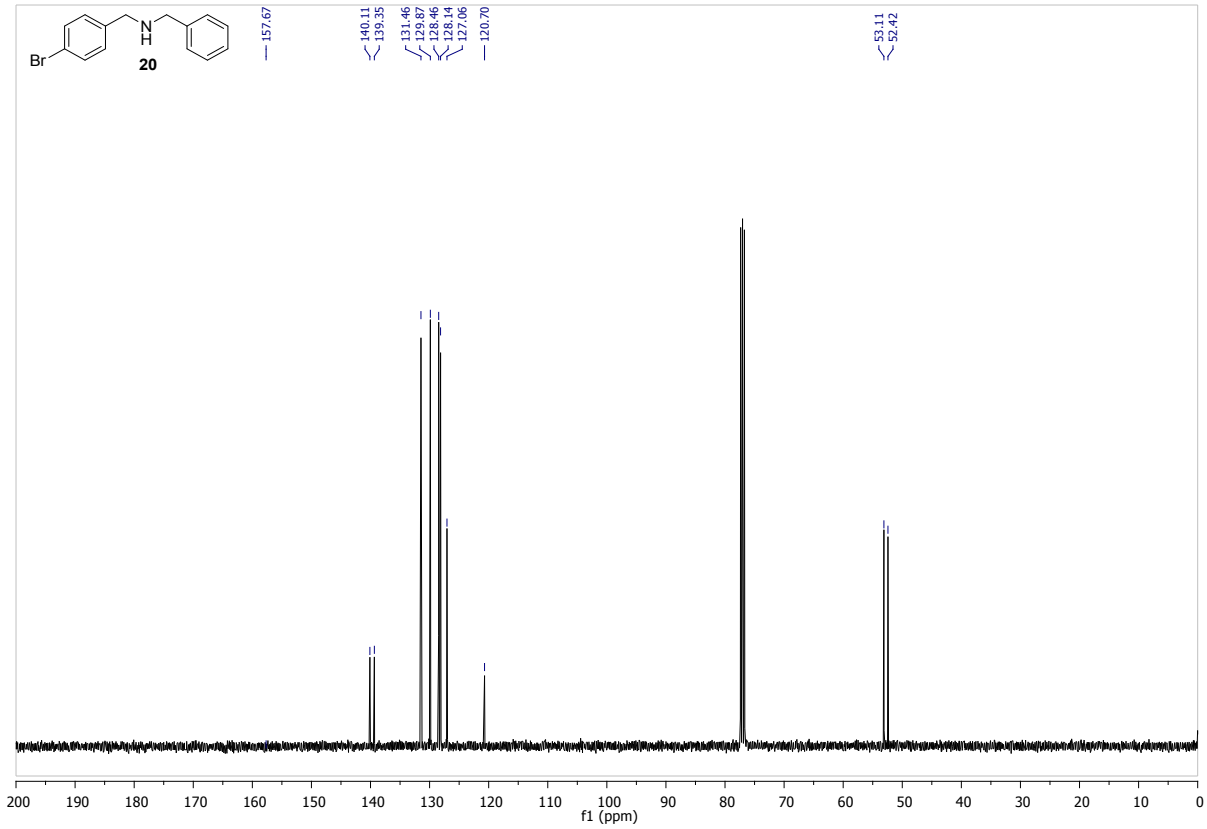
B. Entry 2, Table 5

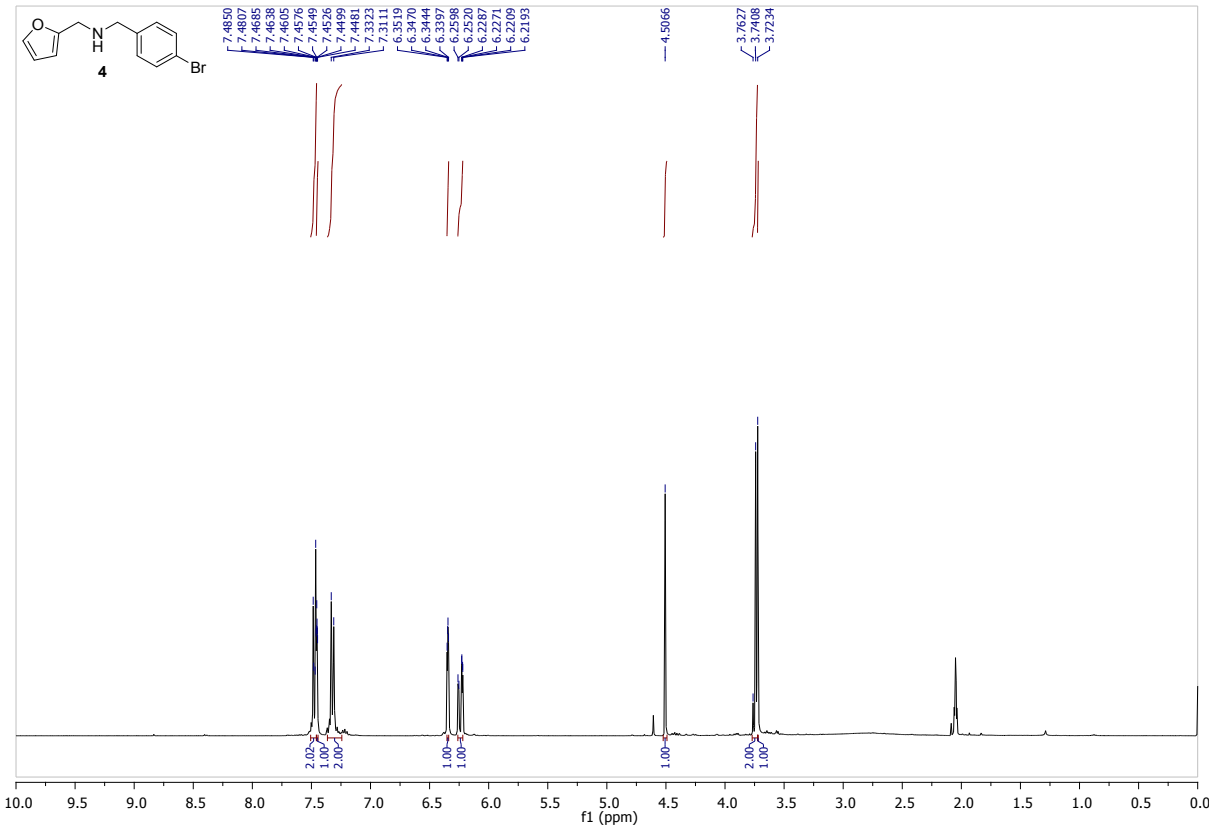


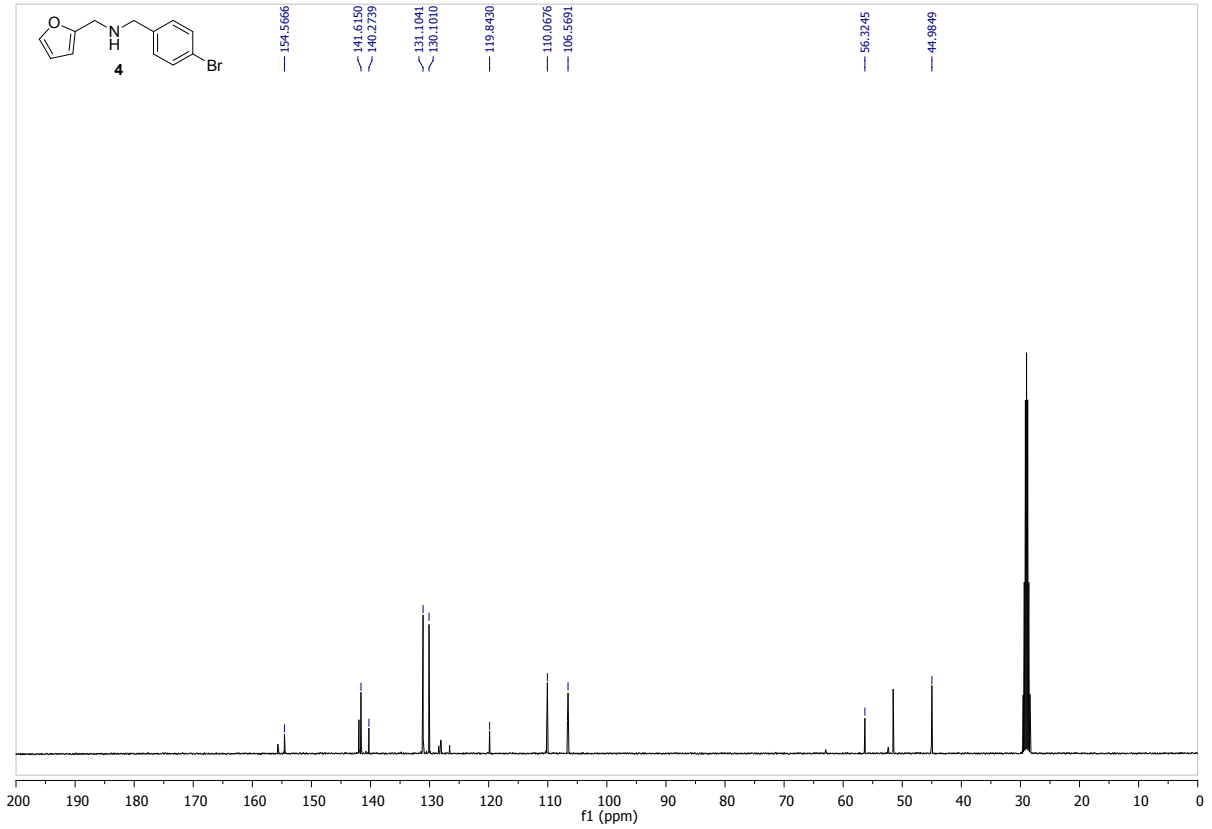
C. Entry 3, Table 5

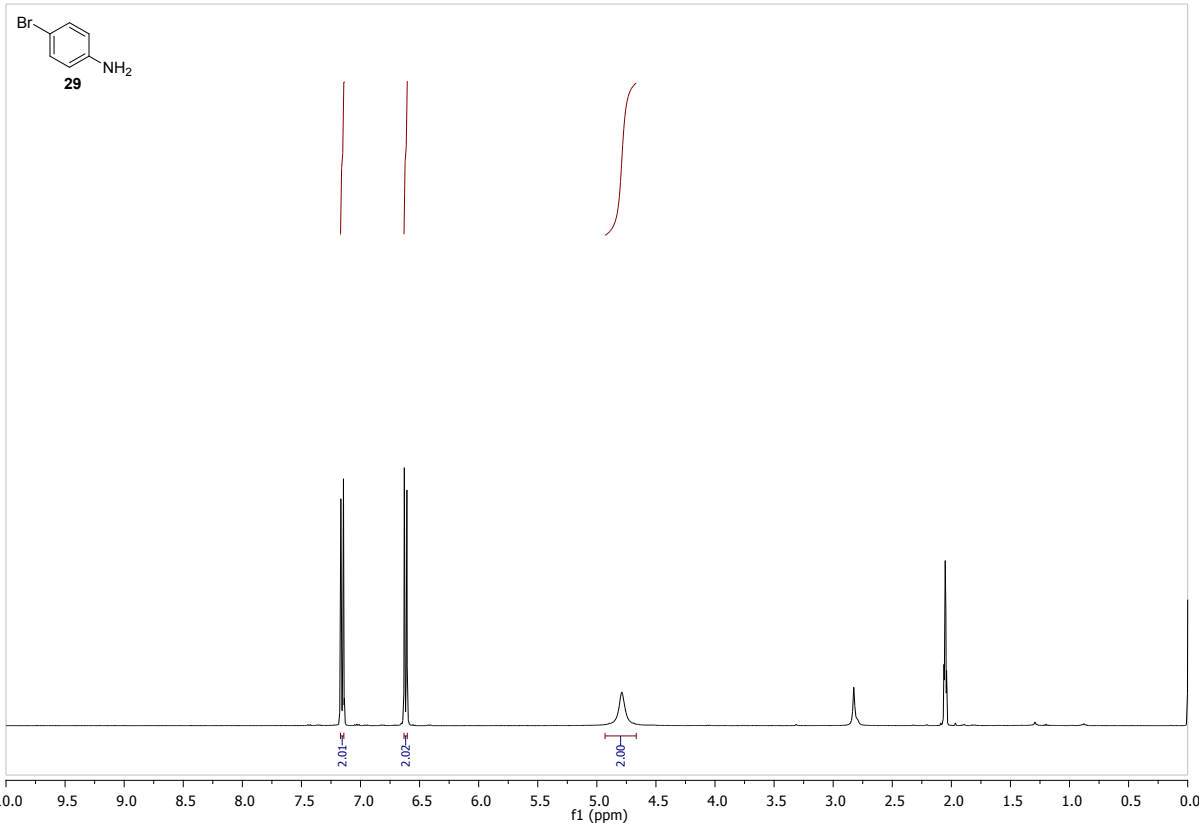
2. NMR Spectra

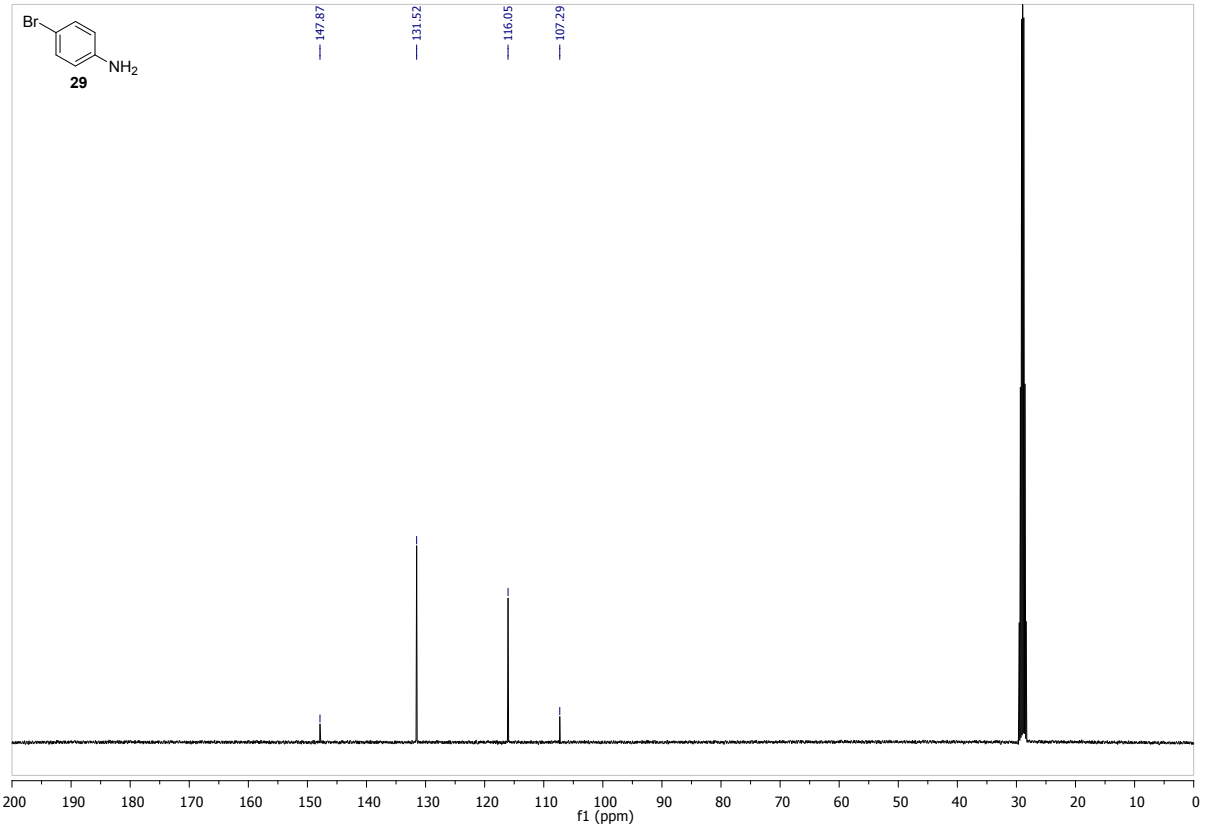


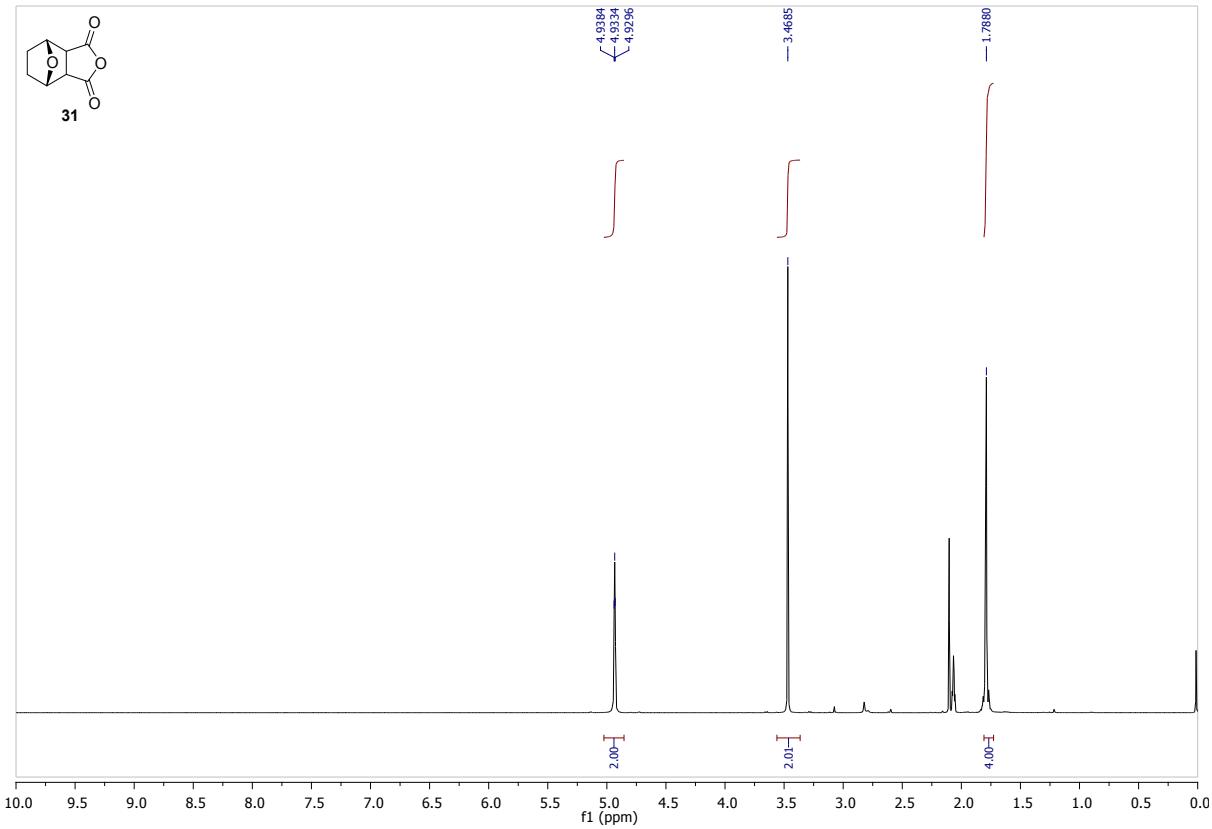


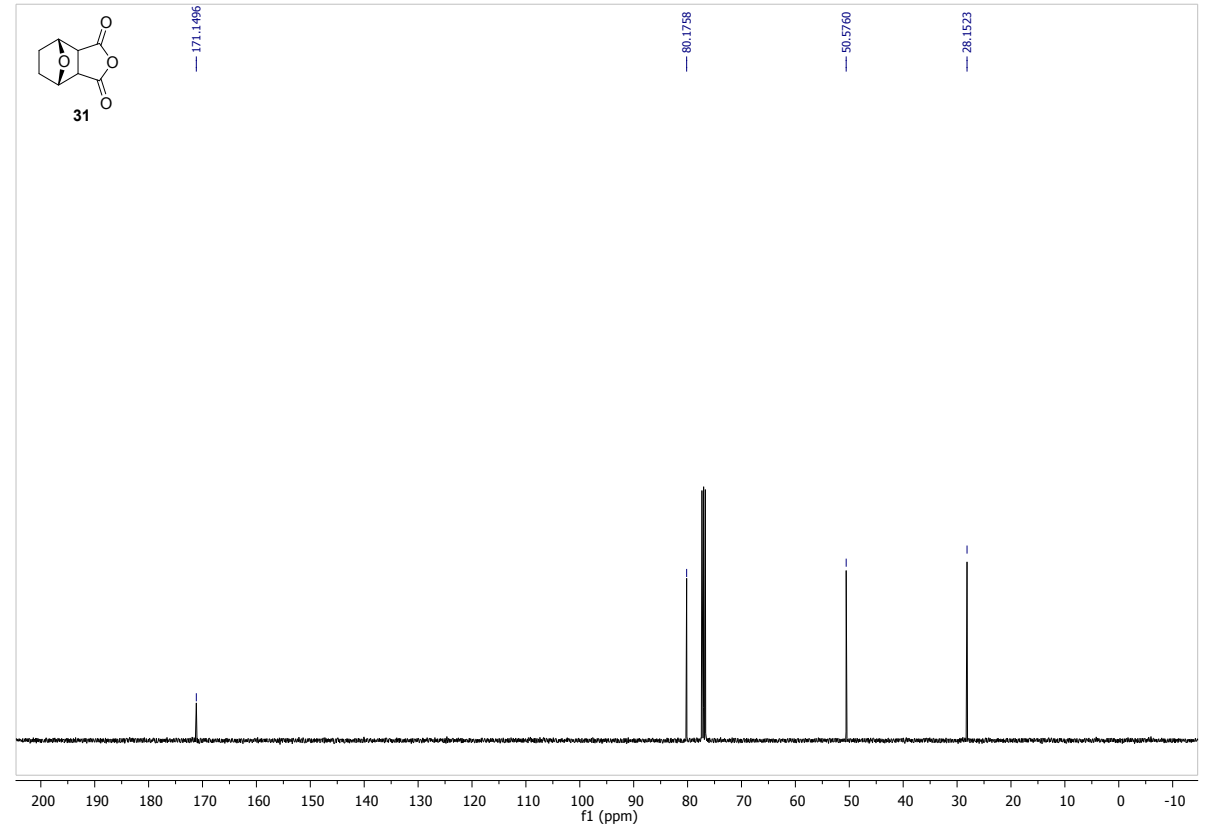

4
Br
7.4850
7.4807
7.4685
7.4638
7.4605
7.4576
7.4549
7.4526
7.4499
7.4481
7.3323
7.3111
6.3519
6.3470
6.3444
6.3397
6.2598
6.2520
6.2287
6.2271
6.2209
6.2193
4.5066
3.7627
3.7408
3.7234
2.02
1.00
2.00
1.00
1.00
1.00
2.00
1.00
f1 (ppm)

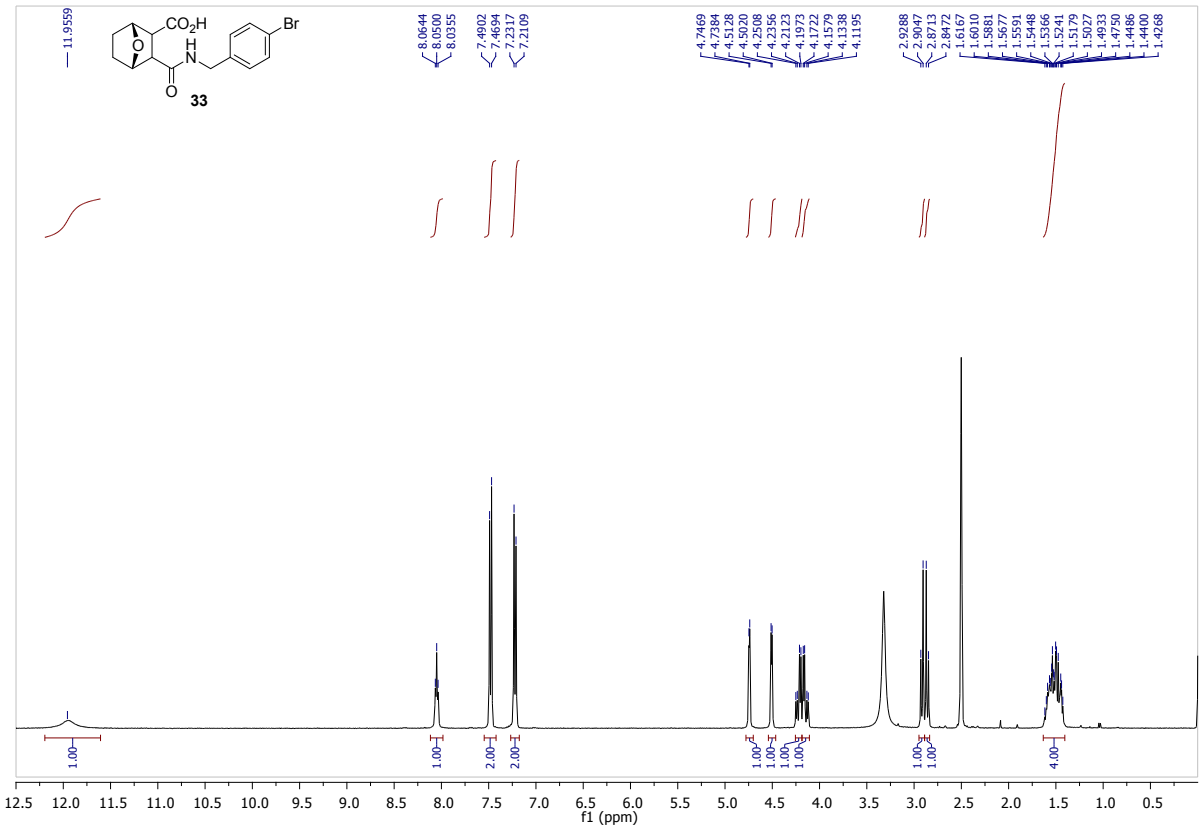

4
Br
154.5666
141.6150
140.2739
131.1041
130.1010
119.8430
110.0676
106.5691
56.3245
44.9849
f1 (ppm)

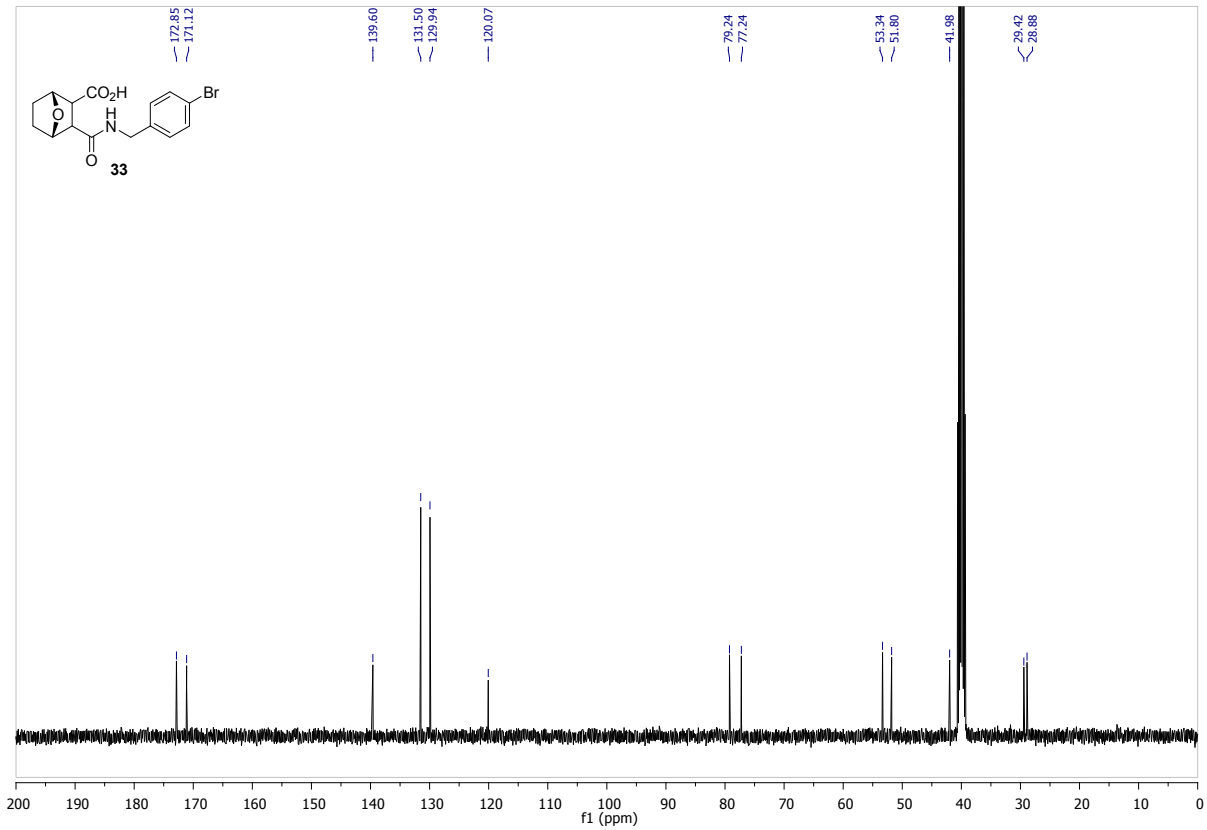

Br
NH2
29
2.01
2.02
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Br
NH2
29
147.87
131.52
116.05
107.29
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


31
4.9384
4.9334
4.9296
3.4685
1.7880
2.00
2.01
4.00
f1 (ppm)


31
171.1496
80.1758
50.5760
28.1523
f1 (ppm)


11.9559
8.0644
8.0500
8.0355
7.4902
7.4694
7.2317
7.2109
4.7469
4.7394
4.5128
4.5020
4.2508
4.2356
4.2123
4.1973
4.1722
4.1579
4.1338
4.1195
2.9288
2.9047
2.8713
2.8472
1.6167
1.6010
1.5881
1.5677
1.5591
1.5448
1.5366
1.5241
1.5179
1.5027
1.4933
1.4750
1.4486
1.4400
1.4268
CO2H
Br
O
H
N
O
33
1.00
1.00
2.00
2.00
1.00
1.00
1.00
1.00
1.00
1.00
4.00
f1 (ppm)


172.85
171.12
139.60
131.50
129.94
120.07
79.24
77.24
53.34
51.80
41.98
29.42
28.88
CO2H
Br
O
H
N
O
33
f1 (ppm)