Electronic Supplementary Information

Deep Eutectic Solvents Meet Safe, Scalable and Sustainable Hydrogenations Enabled by Aluminum Powder and Pd/C

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1 General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer and chemical shifts are reported in parts per million (δ). Dimethyl sulfone has been used as the internal standard for yield determination by ^{1}H NMR analysis of the crude reaction mixtures. FT-IR spectra were recorded on a Perkin-Elmer 681 spectrometer. Analytical thin-layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 mL 17.6 % (w/v) aq. sulphuric acid and heating to 473 K until blue spots appeared. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 ASTM. GC-MS analyses were performed on HP 5995C model. High-resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI). ICP-OES analyses were performed with a ThermoFisher iCAP 6500 duo spectrometer. Melting points were determined with an Electrothermal melting point apparatus. Reagents and solvents, unless otherwise specified, were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) and used without any further purification. Aluminum powder was purchased from Alfa Aesar (Thermo Fisher, Kandel, GmbH, Germany), with the following features: -325 mesh, 99.5%, APS 7–15 μm. Petroleum ether refers to the 40–60 °C boiling fraction. The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, br = broad. Deep Eutectic Solvents [K_2CO_3/glycerol (Gly) (1:5 mol/mol); $ZnCl_2$/urea (1:3.5 mol/mol); tetrabutylammonium bromide (TBAB)/ethylene glycol (EG) (1:4 mol/mol); cholinium chloride (ChCl)/urea (1:2 mol/mol); ChCl/Gly (1:2 mol/mol)] were prepared by heating under stirring at 60–80 °C for 10–30 min the corresponding individual components until a clear solution was obtained. Fully characterization data, including HRMS and copies of ^{1}H and ^{13}C NMR spectra, have been reported for all the synthetized compounds. The fractional factorial design of experiments (DOE) was planned with the software Umetrics MODDE PRO (version 12.1).

2 Experimental Procedures for hydrogenations in Deep Eutectic Solvents

2.1 General hydrogenation procedure for the synthesis of products 2a-o

CAUTION: The addition of KOH to the reaction mixture, composed of Al, Pd/C and substrate in DES/H_2O, must be done at 25 °C (or lower) because of an exothermic reaction between aluminum and KOH/H_2O.

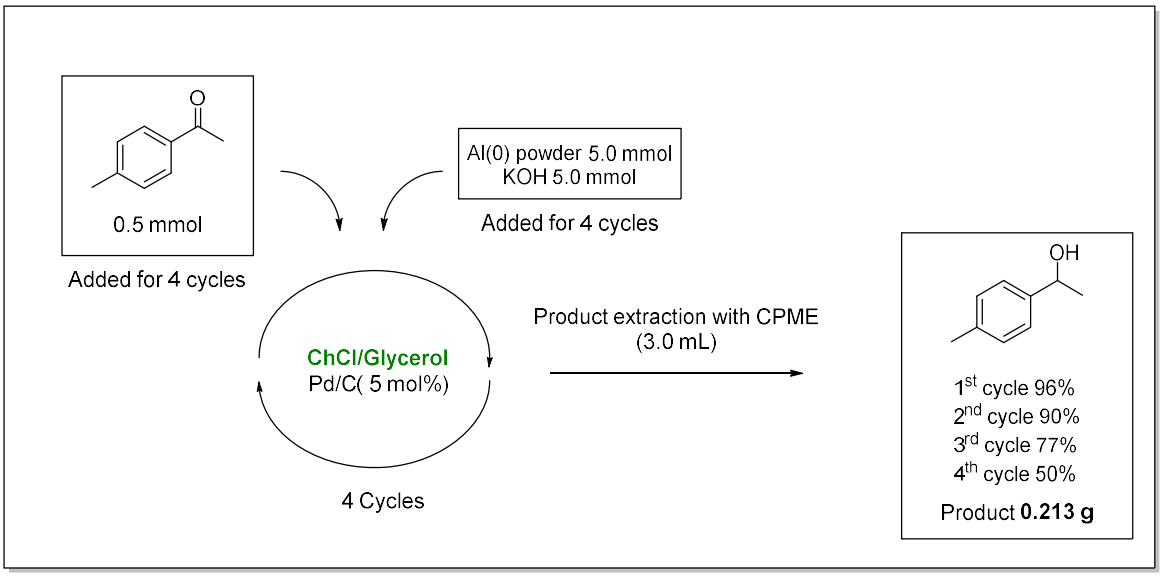
In a 10 mL round bottom flask substrate (0.5 mmol), Pd/C (5.0 mol%, 0.025 mmol, 26.5 mg), Al(0) powder (10.0 equiv., 5.0 mmol, 134 mg), ChCl/Gly (2.0 g) and distilled water (400 μL) were sequentially added. The mixture was stirred until it was homogeneous. Then, KOH (10.0 equiv., 5.0 mmol, 280 mg) was carefully added to the mixture at 25 °C and the flask was quickly closed with a

rubber stopper equipped with a balloon to prevent the H_2 overpressure. The reaction was stirred for 8 h at 40 °C. After this time, the reaction mixture was cooled down to room temperature and water (5 mL) was added. The reaction mixture was extracted with CPME (3 mL x 3). The reunited organic phases were dried over anhydrous Na_2SO_4, filtered through a celite pad, and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (petroleum ether/AcOEt 90:10 to petroleum ether/AcOEt 60:40) to obtain the desired reduction product.

2.2 Recycling procedure of both DES and catalyst for the synthesis of 1-(*p*-tolyl)ethan-1-ol (2a)

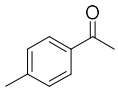
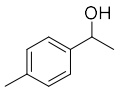
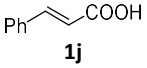
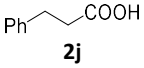
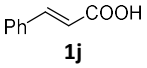
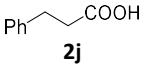
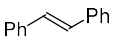
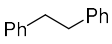
CAUTION: The addition of KOH to the reaction mixture, composed of Al, Pd/C and **1a** in DES/H_2O, must be done at 25 °C (or lower) because of an exothermic reaction between aluminum and KOH/H_2O.

In a 10 mL round bottom flask 1-(*p*-tolyl)ethan-1-one **1a** (0.5 mmol, 67.0 mg, 65 µL), Pd/C (5.0 mol%, 0.025 mmol, 26.5 mg), Al(0) powder (10 equiv., 5.0 mmol, 134 mg), ChCl/Gly (2.0 g) and distilled water (400 µL) were sequentially added. The mixture was stirred until it was homogeneous. Then, KOH (10.0 equiv., 5.0 mmol, 280 mg) was carefully added to the mixture at 25 °C and the flask was quickly closed with a rubber stopper equipped with a balloon to prevent H_2 overpressure. The reaction was stirred for 8 h at 40 °C, then cooled to room temperature and finally extracted with 3 mL of CPME. This process leaves the catalytic system in the eutectic mixture. The organic layer was filtered through a Celite pad and evaporated under reduced pressure to afford the crude product. The latter was then analyzed by ^{1}H NMR to determine the yield of **2a** (dimethyl sulfone was used as the internal standard). Upon adding new, fresh reagents **1a** (0.5 mmol), Al(0) powder (5.0 mmol) and KOH (5.0 mmol), the catalyst and DES could be successfully re-used over four cycles.



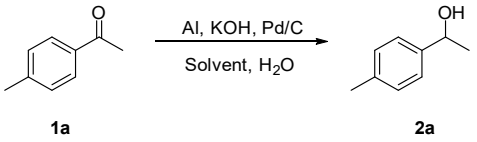
2.3 Hydrogenation of compounds 1a,d,j,i in the absence of KOH

Table S1: *Al-promoted hydrogenation of compound* ***1a,d,i,j*** *in the absence of KOH*[a]

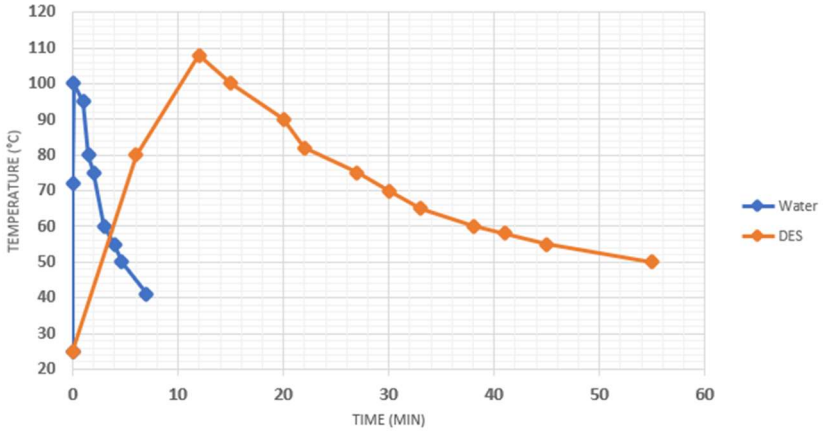
entry	Substrate 1	Product 2	Solvent	1 Conversion (%)[b]	2 Yield (%)[b]
1	 **1a**	 **2a**	ChCl/Gly	92	**4**[c]
2	 **1j**	 **2j**	ChCl/Gly	98	**70**
3	 **1j**	 **2j**	H_2O	<2	**<2**
4	 **1d**	 **2d**	ChCl/Gly	95	**32**[d]
5	 **1i**	 **2i**	ChCl/Gly	50	**43**

[a] **Reaction conditions: 1** (0.5 mmol), Al (5.0 mmol), H_2O (400 μL), Pd/C (5 mol%), solvent (2.0 g), under vigorous magnetic stirring at 40 °C for 8 hours. [b] Calculated via ^1H NMR analysis of the crude reaction mixture using dimethyl sulfone as the internal standard. [c] A mixture of acetals derived from **1a** and glycerol were detected by LC-MS analysis on the crude reaction mixture. [d] A complex mixture of by-products had formed beside the expected aniline **2d**.

2.4 Temperature variation during the hydrogenation reaction of 1a in water and in DES.



1a **2a**



Graph S1. Temperature vs time in the hydrogenation of 1a in pure water (blu line) or DES (orange line)

Water			DES (ChCl/Gly)	
time (s)	Temp. (°C)		time (min)	Temp. (°C)
0	25		0	25
2	72		6	80
4	100		12	108
60	95		15	100
90	80		20	90
120	75		22	82
180	60		27	75
240	55		30	70
280	50		33	65
420	41		38	60
			41	58
			45	55
			55	50

Experimental procedure: In a three necked 250 mL round bottom flask, equipped with an internal thermometer and a balloon to prevent the H_2 overpressure, **1a** (6.25 mmol, 838 mg), Pd/C (5.0 mol%, 0.31 mmol, 329 mg), Al(0) powder (10.0 equiv., 62.5 mmol, 1.688 g), water (5.0 mL in the case of ChCl/Gly) and the solvent (25 mL) were sequentially added. The mixture was stirred at 25 °C for 1 minute until it was homogeneous. After this time, KOH (10.0 equiv., 62.5 mmol, 3.500 g) was added to the mixture and the flask was quickly closed. The temperature of the reaction mixture was then recorded until it returned to values close to 40 °C.

When the reduction was performed in pure water (blue line) the temperature of the medium reached its maximum value (100 °C) in only 4 seconds after the addition of last reagent (KOH). Such

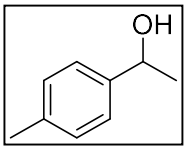
a violent boiling of the solvent combined with a fast hydrogen evolution caused a hazardous and undesirable bumping of the reaction mixture. When the same reduction was performed in ChCl/Gly deep eutectic solvent (orange line) the temperature of the medium raised very slowly and reached the maximum value (108 °C) after 12 minutes. The negligible volatility of the ionic solvent and its low thermal conductivity ensured a somewhat safe reaction.

2.5 Solubility of Al_2O_3 in Cholinium Chloride/Glycerol (1/2 mol/mol)

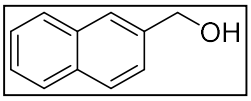
A commercially available sample of Al_2O_3 (25.5 mg, 0.25 mml) was suspended in 2.0 g of ChCl/Gly and stirred at 40 °C for 8 hours. After this time the DES was centrifuged, and the supernatant filtered over a cellulose acetate membrane with a pore size of 0.45 μm. The filtrate was then analyzed by ICP-OES. The experiment was similarly performed in pure water at 40 °C for 8 hours.

Solvent	**Solubility of Al_2O_3 [ppm]**
Cholinium Chloride/Glycerol	0.72
Water	0.16

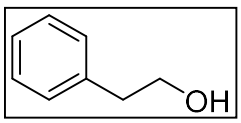
3 Spectroscopic data of reduction products 2a-o



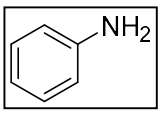
1-(*p*-tolyl)ethan-1-ol (2a):[1] colorless oil, 96%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.28–7.26 (m, 2H), 7.18–7.16 (m, 2H), 4.85 (q, *J* = 6.4 Hz, 1H), 2.36 (s, 3H), 2.16 (br s, 1H), 1.49 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 142.9, 137.0, 129.1, 125.3, 70.1, 25.0, 21.0. FT-IR (Film, cm^{-1}): 3332, 2969, 1513, 1369, 1201, 1074, 814. GC/MS (70 eV) m/z (%):136 (M^+, 40), 121 (100), 93 (78), 91 (65), 77 (37). HRMS (ESI) m/z calcd. for $[C_9H_{12}O + Na]^+$: 159.0780; found: 159.0782.



Naphthalen-2-ylmethanol (2b):[2] white solid, m.p. 81–83 °C, 95%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.82–7.77 (m, 4H), 7.47–7.43 (m, 3H), 4.81 (s, 2H), 2.01 (br s, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 138.3, 133.3, 132.9, 128.3, 127.8, 127.7, 126.1, 125.8, 125.4, 125.1, 65.4. FT-IR (KBr, cm^{-1}): 2953, 2925, 1512, 1464, 1158, 738, 687. GC/MS (70 eV) m/z (%):158 (M^+, 63), 141 (12), 129 (100), 115 (10), 77 (9). HRMS (ESI) m/z calcd. for $[C_{11}H_{10}O + Na]^+$: 181.0624; found: 181.0626.



2-phenylethan-1-ol (2c):[3] colorless oil, 76%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.35–7.31 (m, 2H), 7.27–7.22 (m, 3H), 3.85 (t, *J* = 6.6 Hz, 2H), 2.87 (t, *J* = 6.6 Hz, 2H), 1.84 (s, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 138.5, 129.0, 128.5, 126.4, 63.6, 39.1. FT-IR (Film, cm^{-1}): 3402, 3100, 3021, 2944, 2880, 1492, 1453, 1063, 710. GC/MS (70 eV) m/z (%): 122 (M^+, 40), 92 (60), 91 (100), 77 (10), 39 (10). HRMS (ESI) m/z calcd. for $[C_8H_{10}O + Na]^+$: 145.0624, found: 145.0626.



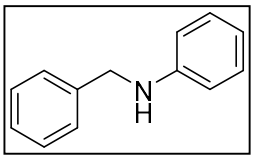
Aniline (2d):[4] pale yellow oil, 99%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.27–7.22 (m, 2H), 6.87–6.83 (m, 1H), 6.76–6.72 (m, 1H), 3.59 (s, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 146.5, 129.3, 118.5, 115.2. FT-IR (Film, cm^{-1}): 3480, 3395, 3041, 1500, 1340, 690. GC/MS (70 eV) m/z (%): 93 (M^+, 100), 66 (54). HRMS (ESI) m/z calcd. for $[C_6H_7N + H]^+$: 94.0651; found: 94.0658.

[1] I. Khan, B. G. Reed-Berendt, R. L. Melen and L. C. Morrill *Angew. Chem. Int. Ed.,* **2018**, *57*, 12356 –12359

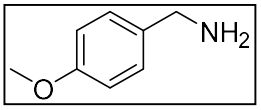
[2] T. Kawamoto, T. Okada, D. P. Curran, I. Ryu, *Organic Letters,* **2013**, *15*(9), 2144–2147.

[3] Y. Wang, X. Cao, L. Zhao, C. Pi, J. Ji, X. Cui, Y. Wu, *Adv. Synth. Catal.*, **2020**, *362*, 4119–4129.

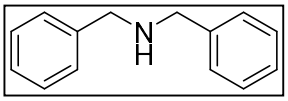
[4] S. Sharma, Yamini, P. Das, *New J. Chem.*, **2019**,*43*, 1764–1769.



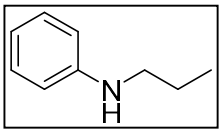
***N*-benzylaniline (2e):**[5] pale yellow solid, m.p. 36–38 °C, 97%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.47–7.35 (m, 5H), 7.29–7.25 (m, 2H), 6.84–6.79 (m, 1H), 6.73–6.70 (m, 2H), 4.40 (s, 2H), 4.05 (br s, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 148.2, 139.5, 129.3, 128.7, 127.5, 127.2, 117.6, 112.9, 48.3. FT-IR (KBr, cm^{-1}): 3414, 3034, 2848, 1665, 2320, 2102, 1897, 1598, 1500, 1318, 1264, 1174, 1083, 984, 864, 741. GC/MS (70 eV) m/z (%): 183 (M+, 97), 106 (34), 91 (100), 77 (32). HRMS (ESI) m/z calcd. for $[C_{13}H_{13}N + H]^+$ 184.1121, found: 184.1119.



(4-methoxyphenyl)methanamine (2f):[6] pale yellow oil, 68%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.23–7.20 (m, 2H), 6.89–6.85 (m, 2H), 3.79–3.78 (m, 5H), 2.24 (br s, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.4, 135.1, 128.2, 113.8, 55.2, 45.6. FT-IR (Film, cm^{-1}): 3366, 3294, 2954, 2929, 2869, 1611, 1513, 1033, 812. GC/MS (70 eV) m/z (%): 137 (M^+, 45), 136 (100), 121 (40), 106 (41), 77 (20). HRMS (ESI) m/z calcd. for $[C_8H_{11}NO + H]^+$: 138.0913, found: 138.0918.



Dibenzylamine (2g):[7] colorless oil, 86%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.39–7.33 (m, 8H), 7.30–7.25 (m, 2H), 3.84 (s, 4H), 1.63 (br s, 1H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 140.3, 128.3, 128.1, 126.9, 53.1. FT-IR (Film, cm^{-1}): 3428, 3032, 2923, 2825, 1650, 1489, 1458. GC/MS (70 eV) m/z (%): 197 (M^+, 37), 106 (86), 91 (100). HRMS (ESI) m/z calcd. for $[C_{14}H_{15}N + H]^+$: 198.1277, found: 198.1273.



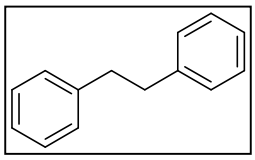
***N*-propylaniline (2h):**[8] light brown oil, 87%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.22–7.16 (m, 2H), 6.72–6.67 (m, 1H), 6.63–6.60 (m, 2H), 3.51 (br s, 1H) 3.10 (t, *J* = 7.2 Hz, 2H), 1.66 (sext, *J* = 7.2 Hz, 2H), 1.02 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 148.5, 129.2, 117.0, 112.6, 45.8, 22.7, 11.6. FT-IR (Film, cm^{-1}): 3412, 2958, 1600, 1505, 1320, 1176, 746. GC/MS (70 eV) m/z (%):136 (M+, 10), 106 (100), 77 (40), 51 (15). HRMS (ESI) m/z calcd. for $[C_9H_{13}N + H]^+$: 136.1121, found: 136.1123.

[5] M. Rauser, R. Eckert, M. Gerbershagen, M. Niggemann, *Angew. Chem. Int. Ed.*, **2019**, *58*, 6713–6717.

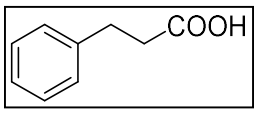
[6] M. Szostak, B. Sautier, M. Spain, D. J. Procter, *Org. Lett.*, **2014**, *16 (4)*, 1092–1095.

[7] O. Lee, K. Law, D. Yang, *Organic Letters,* **2009**, *11* (15), 3302–3305.

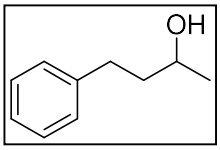
[8] M. Warsitz, S. Doye, *Chem. Eur. J.*, **2020**, *26*, 15121–15125.



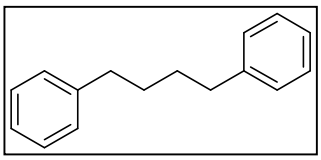
1,2-diphenylethane (2i):[9] white solid, m.p. 49–51 °C, 95% [from stilbene (*E*)-**1i**] and 99% [from stilbene (*Z*)-**1i**]. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.41–7.37 (m, 4H), 7.32–7.28 (m, 6H), 3.04 (s, 4H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 141.8, 128.5, 128.4, 126.0, 38.0. FT-IR (KBr, cm^{-1}): 3033, 2971, 2874, 1796, 1722, 1483, 1397, 1370, 1347, 1334, 1281, 1234, 1206, 1044. GC/MS (70 eV) m/z (%): 182 (M^+, 30), 91 (100), 65 (30), 63 (10), 51 (10). HRMS (ESI) m/z calcd. for $[C_{14}H_{14} + H]^+$: 183.1168, found: 183.1165.



3-phenylpropanoic acid (**2j**)**:** [10] white solid, m.p. 45–47 °C, 99%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.34–7. 29 (m, 2H), 7.25–7.21 (m, 3H), 2.97 (t, *J* = 7.9 Hz, 2H), 2.70 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 179.0, 140.1, 128.5, 128.2, 126.3, 35.6, 30.0. FT-IR (KBr, cm^{-1}): 3030, 2982, 2938, 1710, 1599, 1498, 1412, 1377, 1286, 1182, 1067, 933, 859, 761. GC/MS (70 eV) m/z (%): 150 (M^+, 45), 104 (60), 91 (100), 77 (22), 51 (11). HRMS (ESI) m/z calcd. for $[C_9H_{10}O_2 + Na]^+$: 173.0573, found: 173.0577.



4-phenylbutan-2-ol (2k):[11] colorless oil, 96%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.21–7.14 (m, 3H), 3.82 (dq, *J* = 12.4, 6.2 Hz, 1H), 2.79–2.62 (m, 2H), 1.91 (br s, 1H) 1.83–1.70 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 142.0, 128.3 (2C), 125.8, 67.5, 40.8, 32.1, 23.5. FT-IR (Film, cm^{-1}): 3342, 3025, 2963, 2924, 1602, 1497, 1455, 1372, 1307, 1178, 1128, 1079, 1052, 1030. GC/MS (70 eV) m/z (%):150 (M^+, 9), 132 (62), 117 (100), 91 (80), 77 (23). HRMS (ESI) m/z calcd. for $[C_{10}H_{14}O + Na]^+$: 173.0937; found: 173.0944.



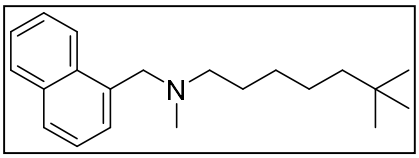
1,4-diphenylbutane (2l):[12] white solid, m.p. 50–51 °C, 99%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.39–7.35 (m, 4H), 7.29–7.25 (m, 6H), 2.75–2.72 (m, 4H), 1.79–1.75 (m, 4H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 142.6, 128.4, 128.3, 125.7, 35.8, 31.1. FT-IR (KBr, cm^{-1}): 2936, 1490, 1464, 1455, 749, 695. GC/MS (70 eV) m/z (%): 210 (M^+, 72), 117 (21), 91 (100), 77 (10), 65 (34). HRMS (ESI) m/z calcd. for $[C_{16}H_{19} + H]^+$: 211.1481, found: 211.1479.

[9] A. J. Smith, A. Young, S. Rohrbach, E. F. O'Connor, M. Allison, H.-S. Wang, D. L. Poole, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed*., **2017**, *56*, 13747–13751.

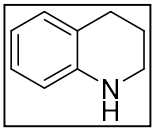
[10] M. Lamani, R. S. Guralamatta, K. R. Prabhu, *Chem. Commun*., **2012**,48, 6583–6585.

[11] S. Alazet, M. S. West, P. Patel, S. A. L. Rousseaux, *Angew. Chem. Int. Ed.,* **2019**, *58*, 10300–10304.

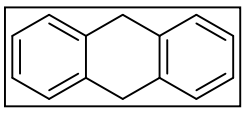
[12] Y. Zhu, T. Xiong, W. Han, Y. Shi, *Organic Letters*, **2014**, *16* (23), 6144–6147.



***N*,6,6-trimethyl-*N*-(naphthalen-1-ylmethyl)heptan-1-amine (2m)**: pale yellow oil, 92%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.33–8.30 (m, 1H), 7.86–7.84 (m, 1H), 7.79–7.77 (m, 1H), 7.56–7.39 (m, 4H), 3.92 (s, 2H), 2.50 (dd, *J* = 8.4, 6.6 Hz, 2H), 2.23 (s, 3H), 1.61 (p, *J* = 7.4 Hz, 2H), 1.34–1.13 (m, 6H), 0.87 (s, 9H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 134.8, 133.8, 132.5, 128.3, 127.8, 127.4, 125.7, 125.5, 125.0, 124.6, 60.5, 58.0, 44.2, 42.1, 29.7, 29.4, 28.3, 27.2, 24.4. FT–IR (Film, cm^{-1}): 3046, 2949, 2934, 2906, 2861, 2787, 1509, 1464, 1362, 1017, 970, 790, 774. GC/MS (70 eV) *m/z* (%): 297 (M^+, 9), 282 (6), 184 (78), 141 (100), 115 (27), 57 (10). HRMS (ESI) *m/z* calcd. for $[C_{21}H_{31}N + H]^+$:298.2529, found: 298.2532.



1,2,3,4-tetrahydroquinoline (2n):[13] pale yellow oil, 75%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 6.99–6.95 (m, 2H), 6.64–6.60 (m, 1H), 6.50–6.48 (m, 1H), 3.86 (br s, 1H), 3.30 (t, *J* = 5.5 Hz, 2H), 2.77 (t, *J* = 5.7 Hz, 2H), 1.98–1.92 (m, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 144.7, 129.4, 126.6, 121.4, 116.9, 114.2, 41.9, 26.9, 22.1. FT-IR (Film, cm^{-1}): 3405, 3050, 3019, 2931, 2867, 1600, 1510, 1310, 747. GC/MS (70 eV) m/z (%): 132 (M^+, 100), 118 (20), 104 (8), 91 (6), 77 (12), 65 (6). HRMS (ESI) m/z calcd. for $[C_9H_{11}N + H]^+$: 134.0964, found: 134.0961.



9,10-dihydroanthracene (2o):[14] white solid, m.p. 110–113 °C, 60%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.32–7.29 (m, 4H), 7.23–7.19 (m, 4H), 3.96 (s, 4H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 136.7, 127.4, 126.1, 36.1. FT-IR (KBr, cm^{-1}): 3026, 2955, 2926, 1430, 758, 728. GC/MS (70 eV) m/z (%): 180 (M^+, 100), 179 (95), 165 (40) 89 (40), 77 (20). HRMS (ESI) m/z calcd. for $[C_{14}H_{12} + H]^+$: 181.1012, found: 181.1014.

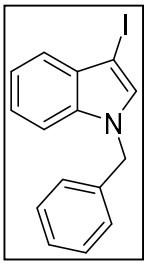
[13] R. Adam, J. R. Cabrero-Antonino, A. Spannenberg, K. Junge, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.,* **2017**, *56*, 3216–3220.

[14] B. Huang, L. Guo, W. Xia, *Green Chem.*, **2021**, *23*, 2095–2103.

4 Experimental Procedures for the synthesis of Benzindopyrine

4.1 Multigram Synthesis of *N*-benzyl-3-iodo indole (4)

In a 250 mL round bottomed flask, equipped with mechanical stirrer, indole was added (0.040 mol, 4.73 g) and suspended in 100 mL of ChCl/EG. Subsequentially KOH (0.116 mol, 6.50 g) and I_2 (0.060 mol, 15.20 g) were added. The reaction was heated to 40 °C under mechanical stirring (300 rpm). After two hours, the reaction was quenched with 100 mL of H_2O and extracted with CPME (50 mL x 3). The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude reaction mixture was then analyzed by ^1H NMR in the presence of dimethylsulfone as the internal standard: the product **3** was formed in 90% yield (8.74 g).
The crude was used without further purification for the next step. A solution of the crude mixture containing **3** in 100 mL of 2-MeTHF was added in a 250 mL round bottomed flask, then KOH (0.108 mol, 6.05 g) and benzyl bromide (0.036 mol, 6.16 g, 4.3 mL) were subsequentially added. The rection was mixed under mechanical stirring (250 rpm) for 6 hours at room temperature. The solvent was evaporated under reduced pressure and the product, *N*-benzyl-3-iodo indole (**4**), was obtained by crystallization from hexane/AcOEt in 93% yield (11.15 g).

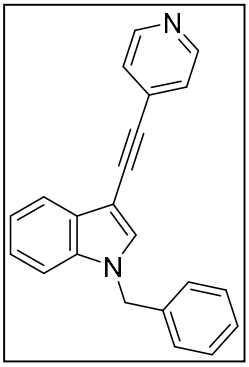


1-benzyl-3-iodo-1*H*-indole (4):[15] white solid, m.p. 60 °C (decomposition), 93%. ^1H NMR (400.12 MHz, $CDCl_3$): δ 7.48–7.43 (m, 1H), 7.32–7.17 (m, 7H), 7.13–7.10 (m, 2H), 5.29 (s, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 136.7, 136.3, 132.0, 130.6, 128.8, 127.9, 126.9, 122.8, 121.2, 120.5, 109.8, 55.9, 50.3. FT-IR (KBr, cm^{-1}): 3113, 3058, 3031, 2926, 1583, 1450, 1320, 1192, 1159, 943, 726. GC/MS (70 eV) m/z (%): 333 (M^+, 87), 206 (7), 115 (8), 91 (100), 65 (9). HRMS (ESI) m/z calcd. for $[C_{15}H_{12}IN + H]^+$: 334.0087, found: 334.0091.

4.2 Multigram Synthesis of 1-benzyl-3-(pyridin-4-ylethynyl)-1*H*-indole (5) *via* Sonogashira-Hagihara Coupling

In a 2 L round bottomed flask equipped with mechanical stirrer, **4** (0.033 mol, 11.15 g), 4-ethynylpyridine (2.5 equiv., 0.083 mol, 8.50 g), $Pd(PPh_3)_2Cl_2$ (2.5 mol%, 0.8 mmol, 0.58 g), CuI (15.0 mol%, 0.005 mol, 0.94 g), Et_3N (3.5 equiv., 0.116 mol, 11.70 g, 16.1 mL) and ChCl/Gly (0.5 L) were sequentially added. The reaction mixture was stirred (300 rpm) at 40°C for 4.5 h. Then, the reaction was cooled to room temperature, quenched with H_2O (0.5 L) and filtered over a filer paper. The crude was extracted with CPME (3 x 250 mL) and the reunited organic phases were dried over Na_2SO_4 and filtered over celite pad. The solvent was removed under reduced pressure and the product 1-benzyl-3-(pyridin-4-ylethynyl)-1*H*-indole (**5**) was isolated by crystallization from MeOH in 96% yield (9.76 g).

[15] P. Barbie, U. Kazmaier, *Org. Biomol. Chem.*, **2015**, *13*, 9267–9275.

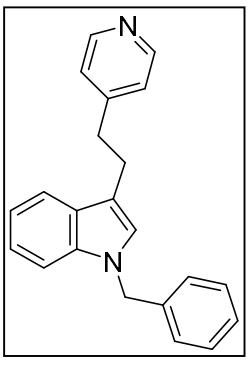


1-benzyl-3-(pyridin-4-ylethynyl)-1*H*-indole (5): light brown solid, m.p. 96-98 °C, 96%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.60 (br s, 2H), 7.85–7.81 (m, 1H), 7.46 (s, 1H), 7.39–7.24 (m, 8H), 7.17–7.15 (m, 2H), 5.33 (s, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 149.6, 136.2, 135.9, 132.6, 132.4, 129.1, 128.9, 128.0, 127.0, 124.5, 123.2, 121.0, 120.1, 110.2, 96.7, 89.2, 88.6, 50.4. FT-IR (KBr, cm^{-1}): 3427, 3062, 3030, 2924, 2200, 1593, 1537, 1386, 1167, 818, 732; GC/MS (70 eV) *m/z* (%): 308 (M^+, 95), 91 (100), 65 (10). HRMS (ESI) *m/z* calcd. for $[C_{22}H_{16}N_2 + H]^+$ 309.1386, found: 309.1389.

4.3 Multigram Reduction of 1-benzyl-3-(pyridin-4-ylethynyl)-1*H*-indole (5) to Benzindopyrine (6)

CAUTION: The addition of H_2O to the reaction mixture, composed of Al, KOH, Pd/C and substrate in DES, must be done at 0 °C because of an exothermic reaction between aluminum and water.

In a 500 mL round bottomed flask, equipped with mechanical stirrer, 1-benzyl-3-(pyridin-4-ylethynyl)-1*H*-indole (**5**) (0.032 mol, 9.76 g), Pd/C 10% w/w (5.0 mol%, 0.002 mol, 1.70 g), Al(0) powder (10.0 equiv., 0.320 mol, 8.64 g) and ChCl/Gly (200 mL) were sequentially added. The mixture was stirred (300 rpm) until it was homogeneous. Then, KOH (10.0 equiv., 0.320 mmol, 17.90 g) and distilled water (25.6 mL) were carefully added to the mixture at 0 °C and the flask was quickly closed with a rubber stopper equipped with a balloon to prevent H_2 overpressure. The reaction was stirred for 8 h at 40 °C. After this time, the reaction mixture was cooled down to room temperature and water (200 mL) was added. The reaction mixture was extracted with CPME (100 ml x 3) and the reunited organic phases were dried over anhydrous Na_2SO_4, filtered through a celite pad, and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (hexane/AcOEt 8:2) to obtain Benzindopyrine (**5**) in 97% yield (9.68 g).



1-benzyl-3-(2-(pyridin-4-yl)ethyl)-1*H*-indole (Benzindopyrine, 6): pale yellow waxy solid, 97%. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.43–8.42 (m, 2H), 7.61–7.59 (m, 1H), 7.28–7.09 (m, 6H), 7.05–7.01 (m, 4H), 6.74 (s, 1H), 5.19 (s, 2H), 3.09–3.05 (m, 2H), 3.00–2.96 (m, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 151.1, 149.3, 137.5, 136.6, 128.6, 127.7, 127.5, 126.6, 125.7, 124.0, 121.8, 119.0, 118.8, 114.0, 109.7, 49.7, 35.6, 26.0. FT–IR (KBr, cm^{-1}): 3055, 3026, 2923, 2854, 1599, 1465, 1453, 1327, 1177, 1013, 808, 745, 697. GC/MS (70 eV) *m/z* (%): 312 (M^+, 27), 220 (98), 129 (7), 91 (100), 65 (24). HRMS (ESI) *m/z* calcd. for $[C_{22}H_{20}N_2 + H]^+$:313.1699, found: 313.1702.

5 Design of Experiments (DoE) approach for the optimization of multigram scale synthesis of 1-benzyl-3-(pyridin-4-ylethynyl)-1*H*-indole (5)

A Fractional Factorial (Res IV) Design was planned and performed to study the effect of eight factors (described below) on reaction yield (%) for the Sonogashira cross-coupling between 1-benzyl-3-iodo-1H-indole (**4**) and 4-ethynylpyridine. Investigated factors and related ranges of variation are shown in Table S2.

Table S2: Factors and corresponding variability intervals

Name	Abbr.	Units	Settings
4-ethynylpyridine (equiv.)	Py	eq	1 to 4
Temperature (°C)	T	°C	25 to 55
Time (h)	Tim	h	1 to 8
msub/mDES (g/g)	DES	g/g	0,03 to 0,2
Rotation (rpm)	Vel	rpm	150 to 450
Triethylamine (equiv.)	TEA	eq	2 to 5
Pd load (mol%)	Pd	mol%	0,1 to 5
CuI Load (mol %)	CuI	mol%	0 to 30

Data Analysis and Comments

Data analysis was performed with the support of the software Umetrics MODDE PRO (ver. 12.1). The response, Yield (%), was measured and evaluated in the light of the corresponding desired values reported in Table S3

Table S3: Responses and corresponding desired values

Name	Abbr.	Units	Type	Min	Target	Max
5 Yield%	5	%	Regular	70	-	100

A Fractional Factorial (Res IV) design was planned: 16 tests at different experimental conditions and 3 tests at the center point were carried out according to the Worksheet (Table S4).

Table S4: Worksheet

4-ethynylpyridine (equiv.)	Temperature (°C)	Time (h)	m_{sub}/m_{DES} (g/g)	Rotation (rpm)	Triethylamine (equiv.)	Pd load (mol%)	CuI Load (mol%)	5 Yield%
1	25	1	0,03	150	2	0,1	0	0
4	25	1	0,03	150	5	5	30	4,6
1	55	1	0,03	450	2	5	30	48,45
4	55	1	0,03	450	5	0,1	0	58,74
1	25	8	0,03	450	5	5	0	0,9
4	25	8	0,03	450	2	0,1	30	0,25
1	55	8	0,03	150	5	0,1	30	10,25
4	55	8	0,03	150	2	5	0	23,13
1	25	1	0,2	450	5	0,1	30	0,98
4	25	1	0,2	450	2	5	0	0,92
1	55	1	0,2	150	5	5	0	52,53
4	56	1	0,2	150	2	0,1	30	65,26
1	27	8	0,2	150	2	5	30	0,46
4	25	8	0,2	150	5	0,1	0	0,13
1	55	8	0,2	450	2	0,1	0	47
4	55	8	0,2	450	5	5	30	0
2,5	40	4,5	0,115	300	3,5	2,55	15	94,98
2,5	40	4,5	0,115	300	3,5	2,55	15	89,62
2,5	40	4,5	0,115	300	3,5	2,55	15	90,52

Response (Yield%)

The data were fitted using partial least squares fitting (PLS) giving a model in which R2 (the goodness of fit of the model) and Q2 (the goodness of prediction of the model) were 0.92 and 0.79 respectively. The low value for Q2 depends to the nonlinear response of the terms but it was not possible to identify with certainty the factor responsible for the second order relation. Figure S1 shows the Replicates Plot. It is clear that a second order equation is necessary to fit the data, that because the Y values of the 16 tests rise to a Yield value lower than the minimum desired level, whereas the center point setting generated a value very close to the

maximum limit. However, the Y values obtained at the center points were a good result of the maximum response affordable in this domain.

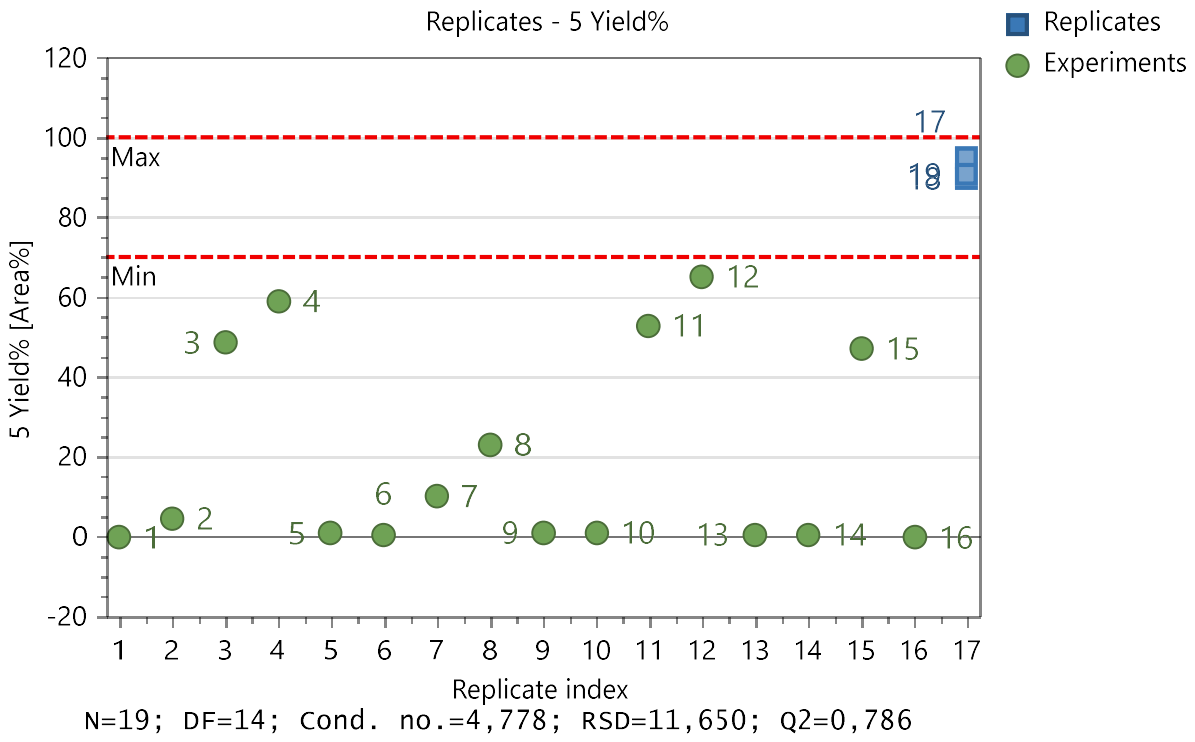


Figure S1: Replicates plot for response Yield with experiment number labels

The software allows to estimate the missing second order terms. In this case, from the Coefficient Plot, Temperature was chosen as the main significant term. Adding the term T*T as Square Term also the Time of Reaction (Tim) become significant, showing an interaction with the Temperature (Figure S2). The coefficients are significant only if the confidence interval does not cross zero. However, the interaction term was highly dependent from the confounding pattern, so the term could be associated to different interaction terms (e.g. [Py*Pd], [DES*Vel], [TEA*CuI]), but was highly probable that this coefficient could be assigned to [T*Tim].

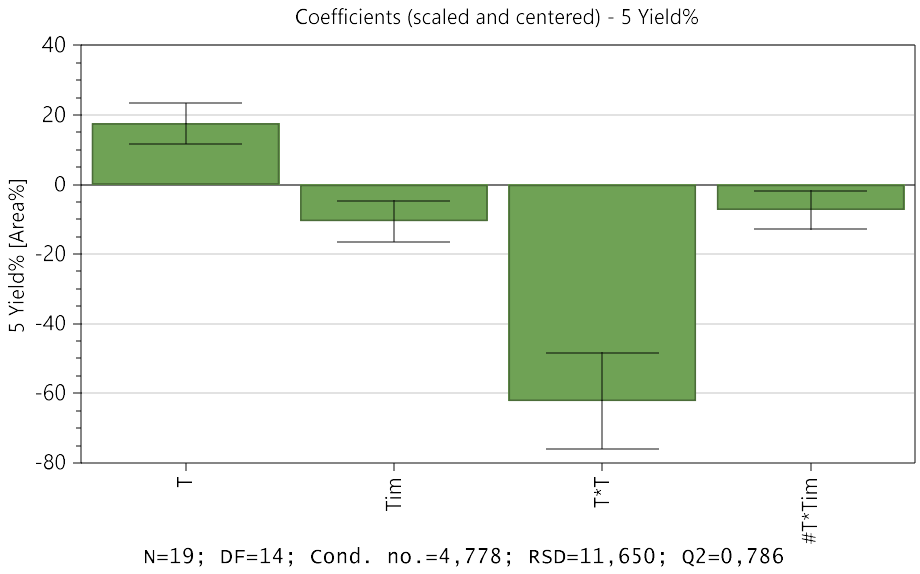


Figure S2: Scaled and centered Coefficients Plot for response Yield[16]

The sign of the factor indicates the type of influence on the response, meanwhile the size of the confidence interval indicates the importance of that factor in the model. From Figure S2 is evident that the key factors are temperature (T) and reaction time (Tim), with a very small influence by 4-ethynylpyridine amount, DES amount and mechanical stirrer speed.

Figure S3 represents the predictions corresponding to experimental conditions within the Yield minimum and maximum set [70%-100%].

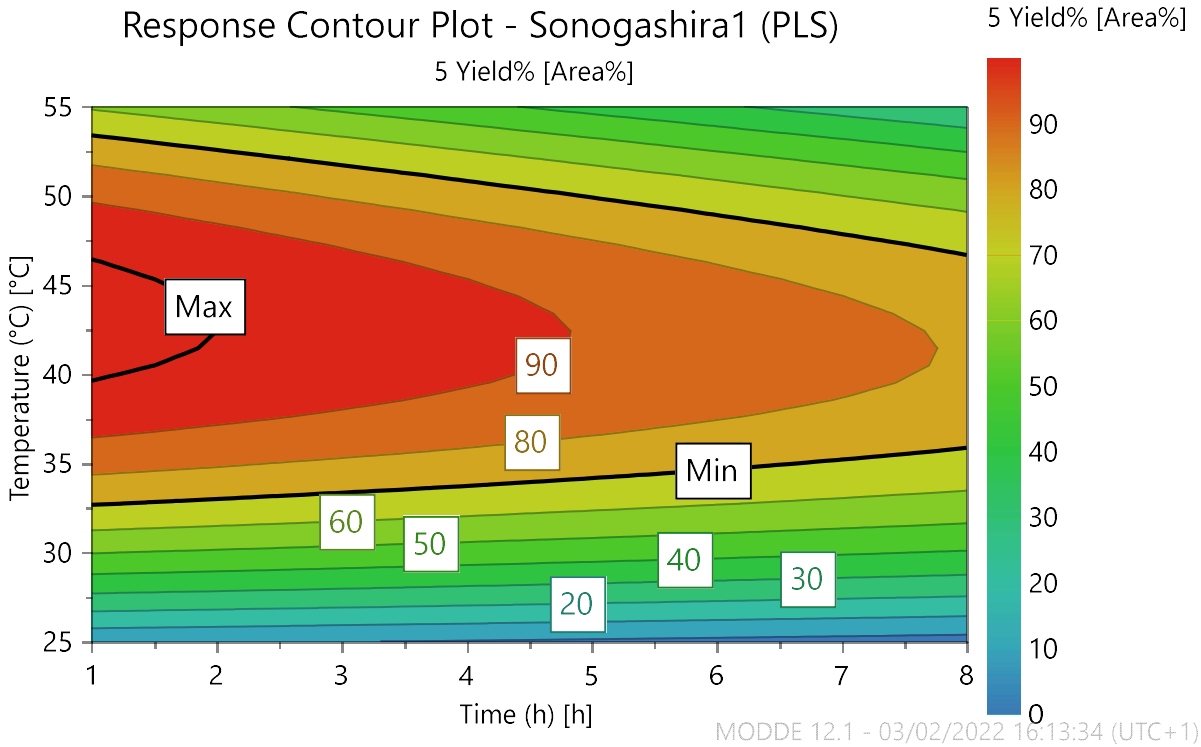


Figure S3. Response surface modeling for response Yield

[16] The model includes only the significant terms

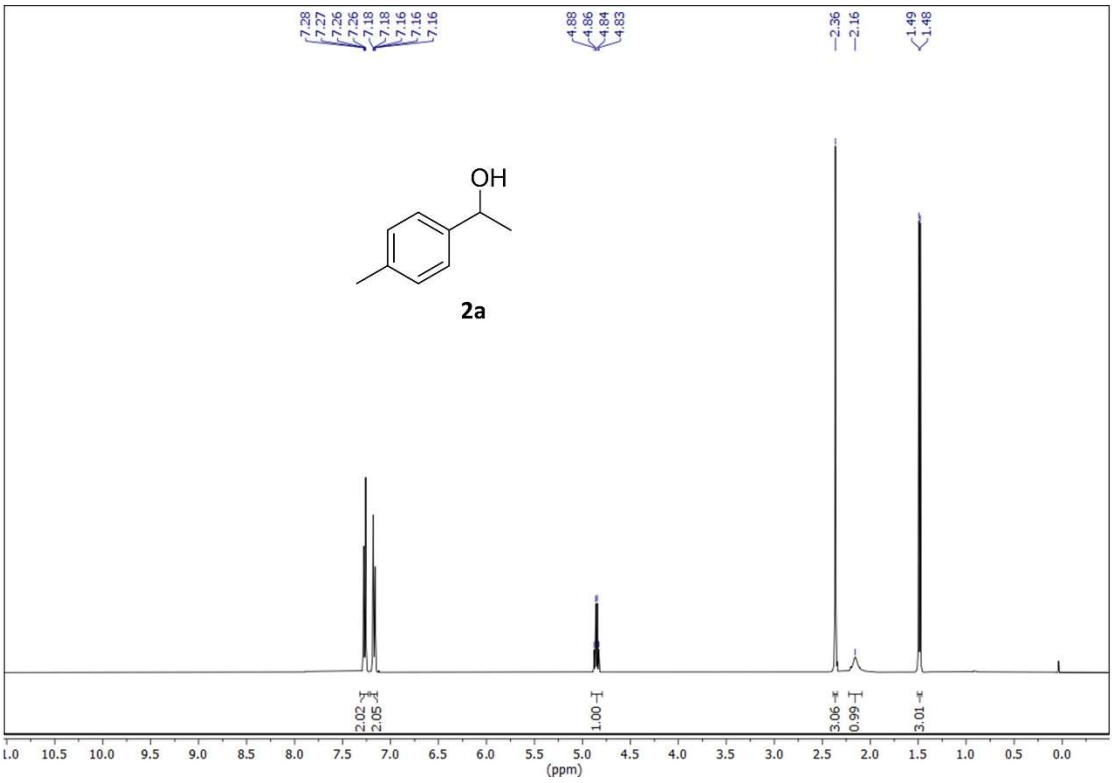
Conclusions

The data analysis highlighted a second order relation between the response, the reaction yield (Yield%) and one or more factors. It was not possible to identify, with certainty, the factors responsible for the second order relation. However, on the bases of the available data, those which show the greatest probability of being involved were Reaction Temperature (T) and Reaction Time (Tim). For a more in-depth evaluation of the second order coefficients, more experiments should be performed but it was not the aim of this work.

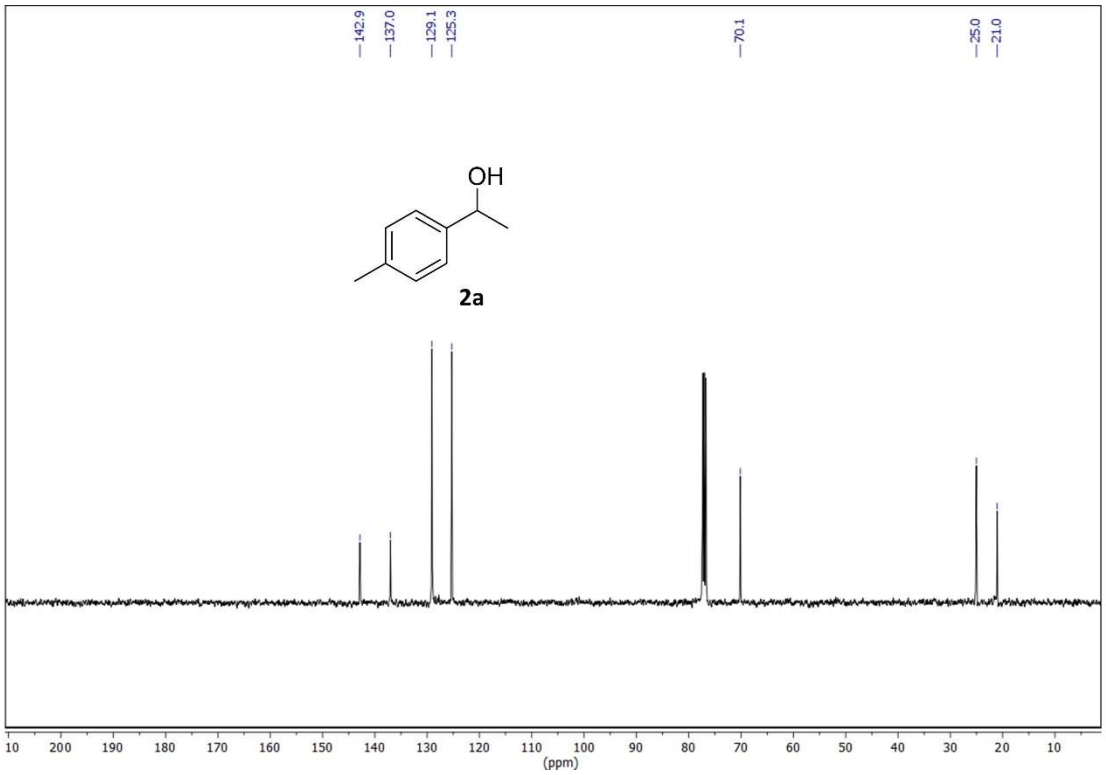
As early assessment results, it was highlighted that the highest response value within the studied experimental domain correspond to the center points.

6 ^{1}H and ^{13}C Spectra

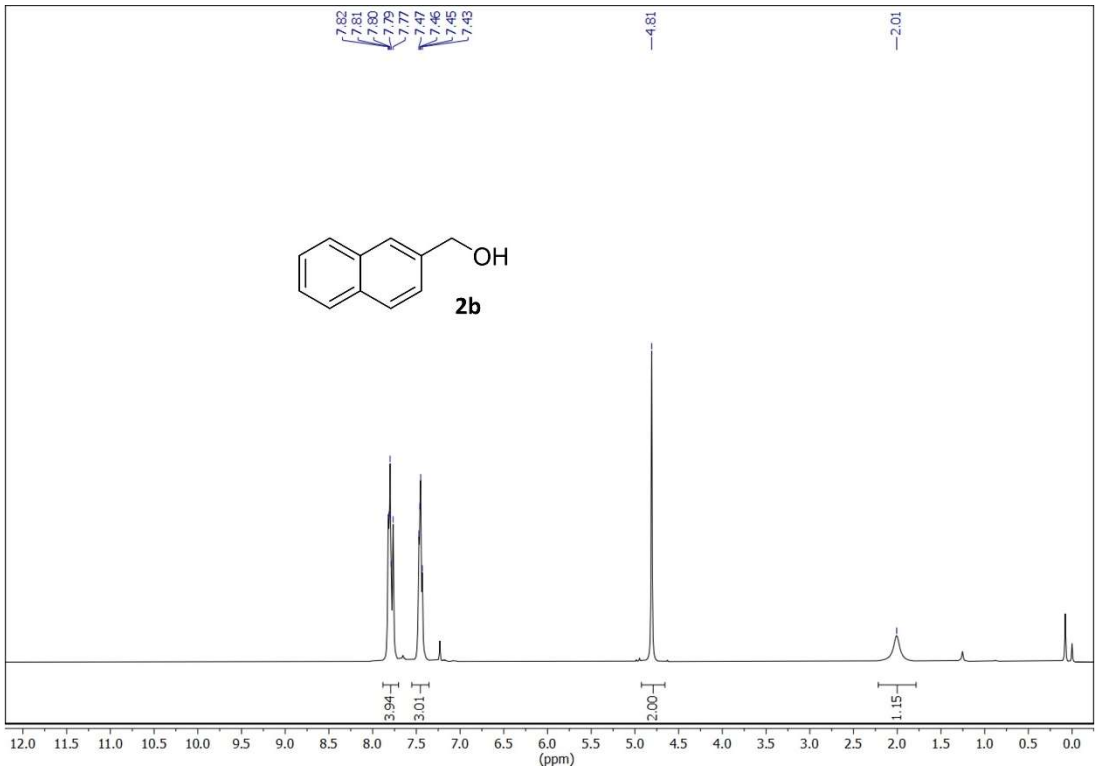
^{1}H NMR 400.12 MHz, $CDCl_3$



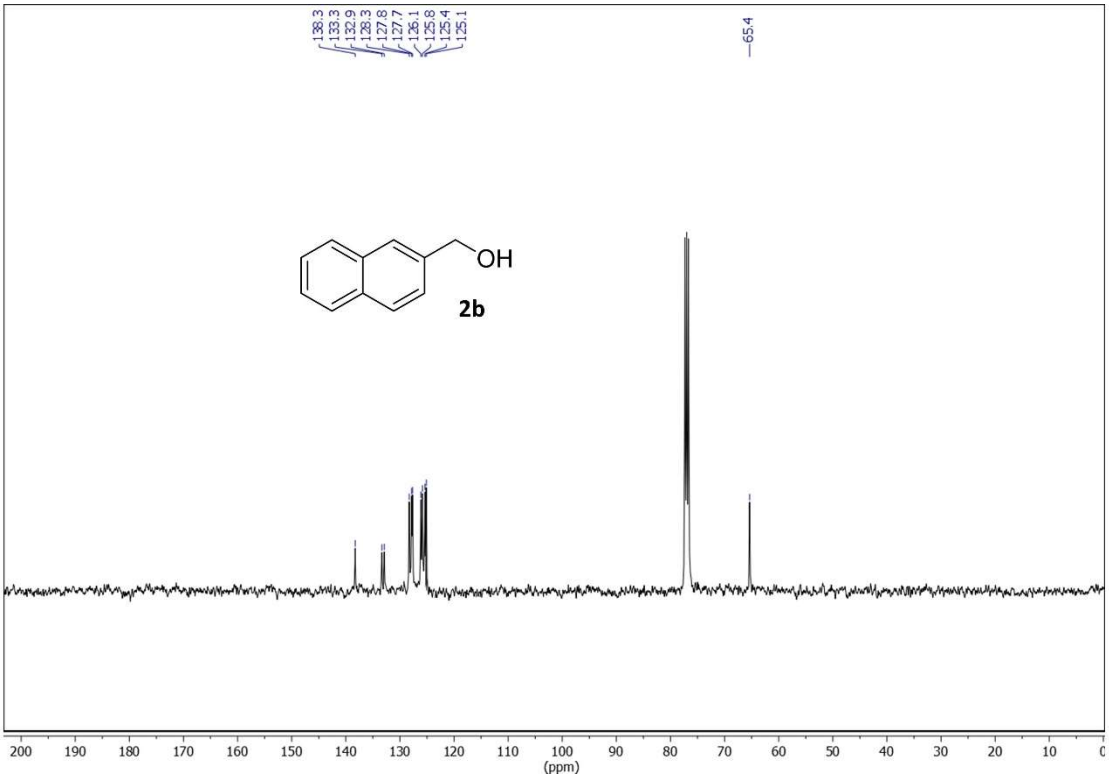
^{13}C NMR 100.62 MHz, $CDCl_3$



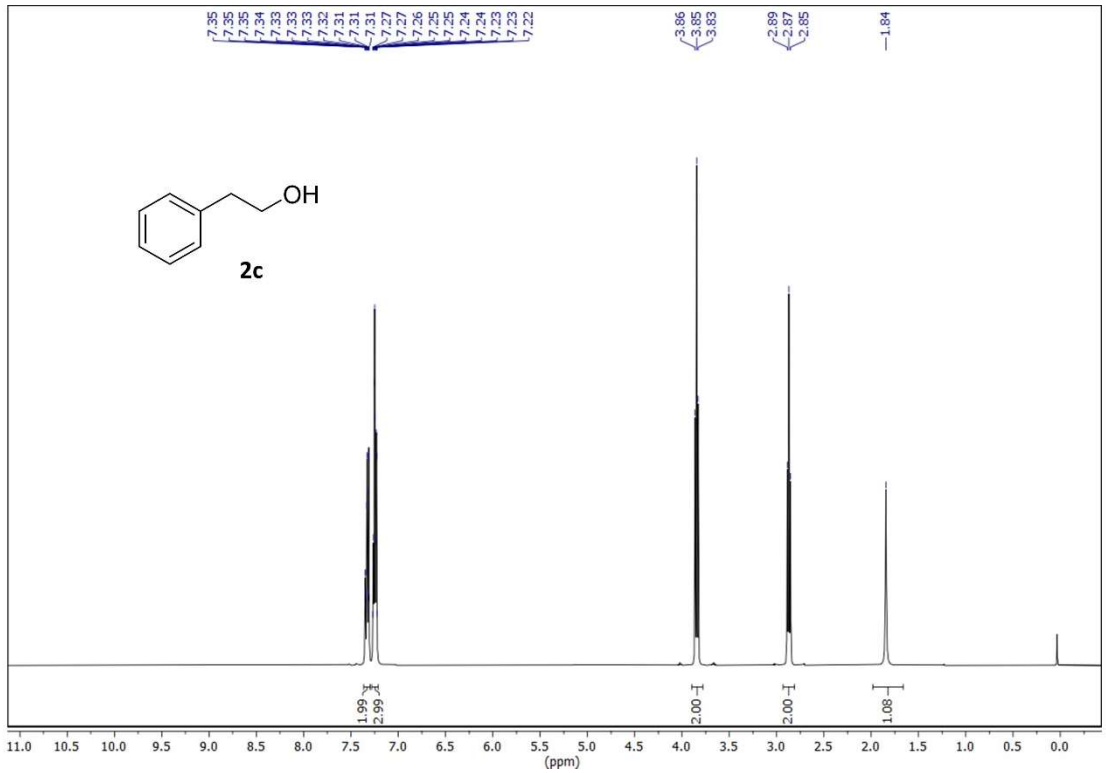
^{1}H NMR 400.12 MHz, $CDCl_3$



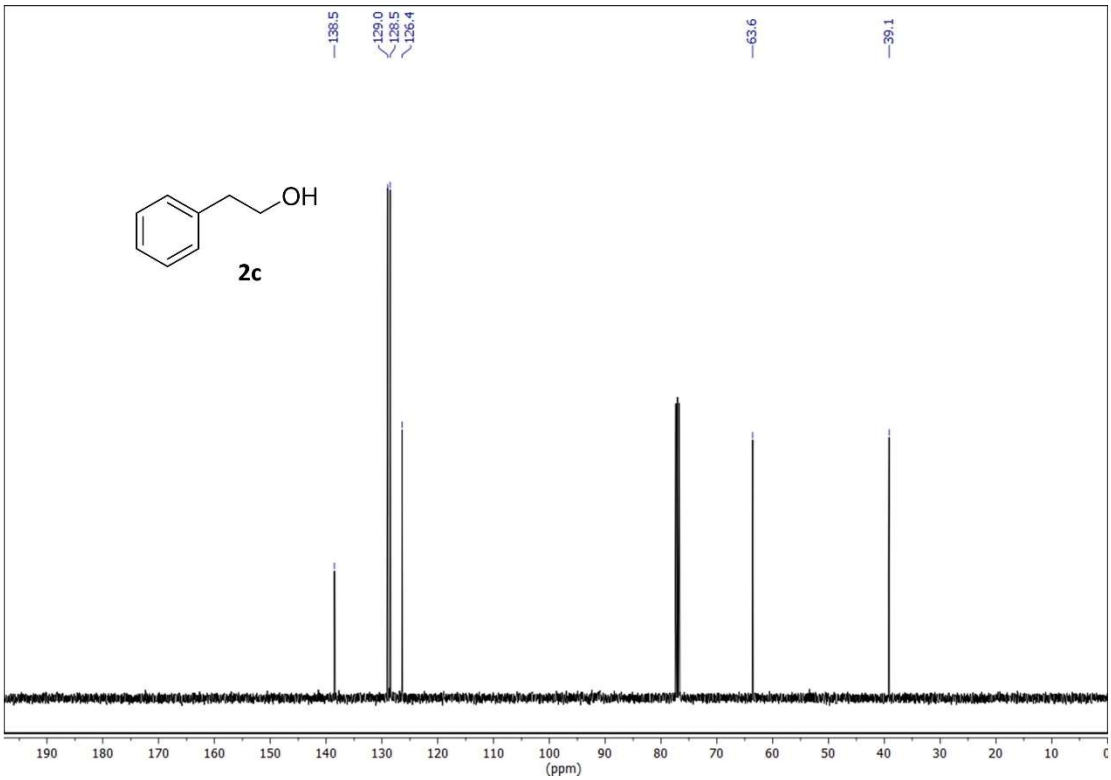
^{13}C NMR 100.62 MHz, $CDCl_3$



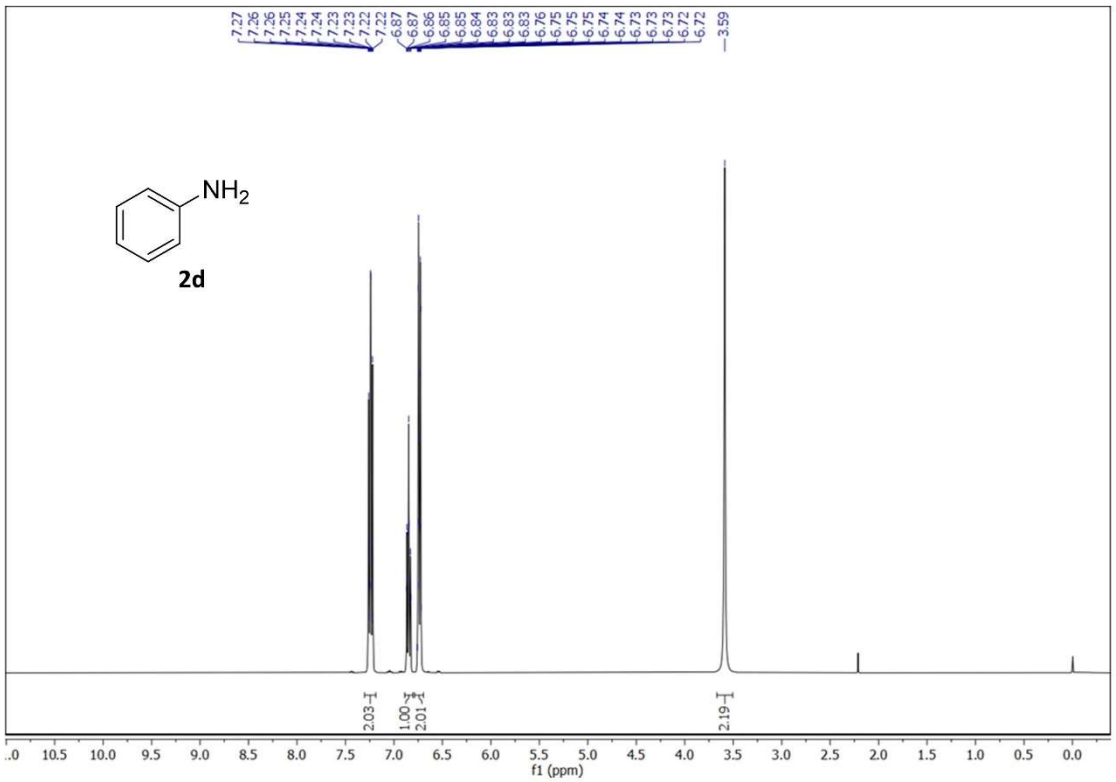
^{1}H NMR 400.12 MHz, $CDCl_3$



^{13}C NMR 100.62 MHz, $CDCl_3$



^{1}H NMR 400.12 MHz, $CDCl_3$



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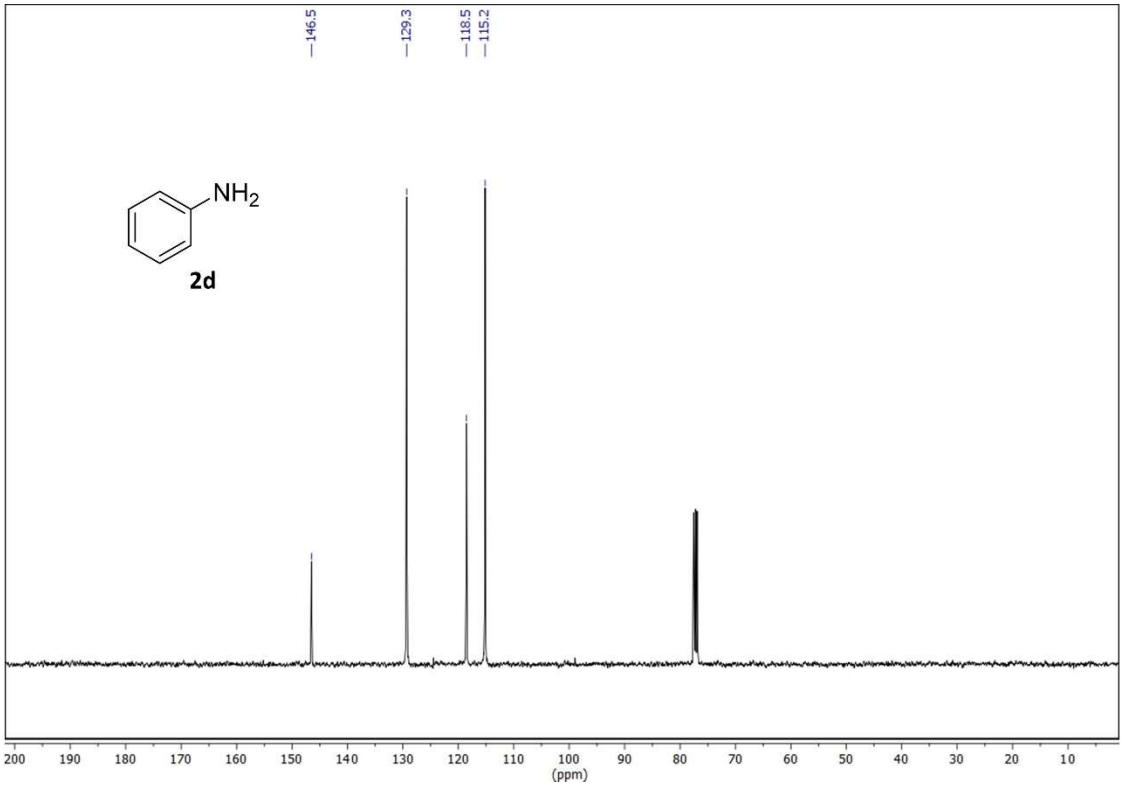
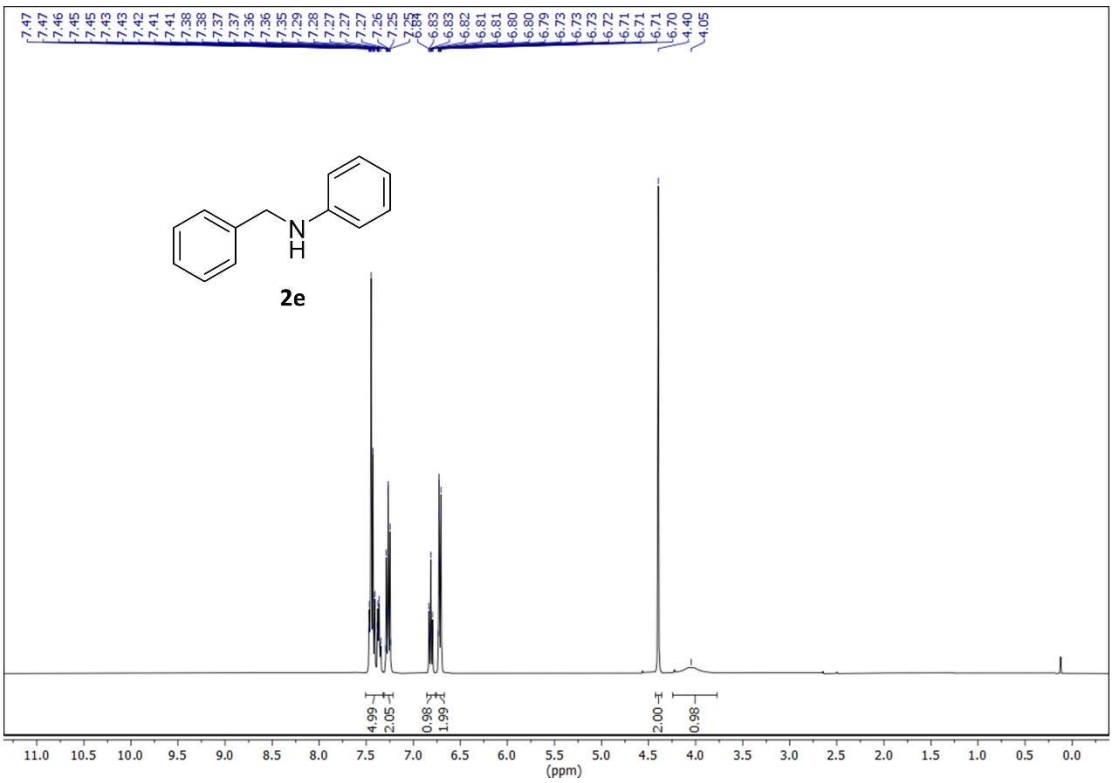


^{1}H NMR 400.12 MHz, $CDCl_3$



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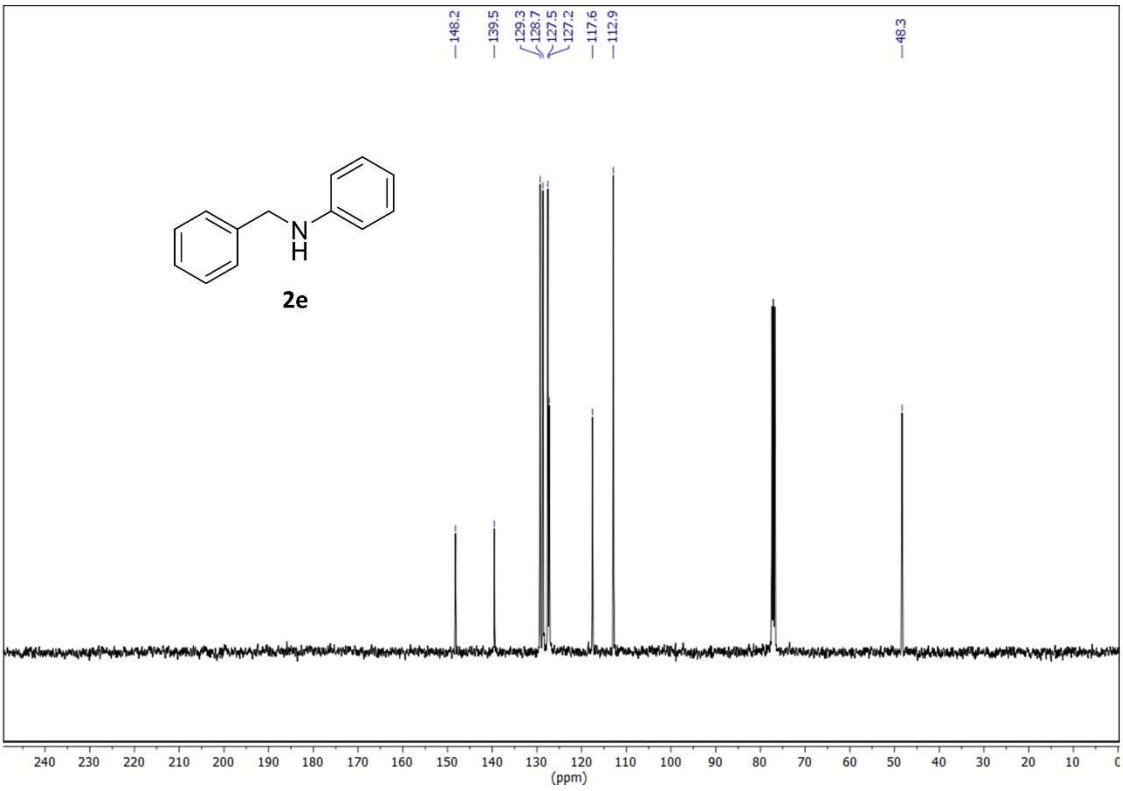

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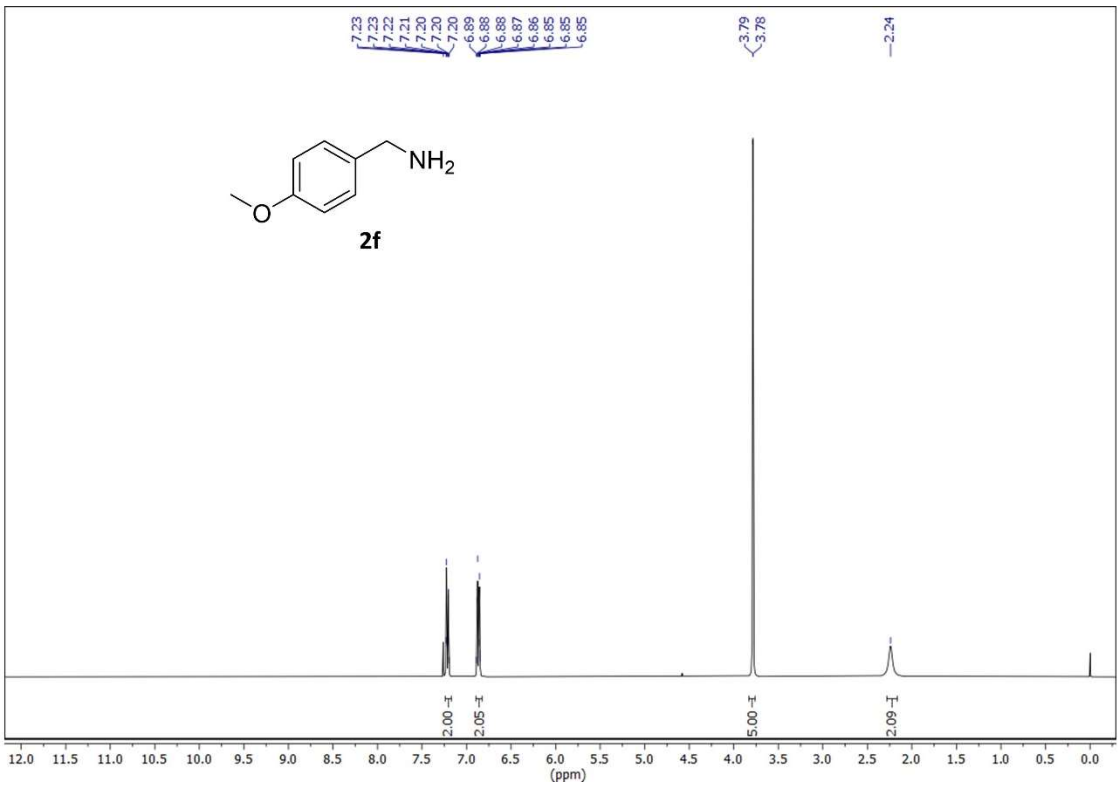

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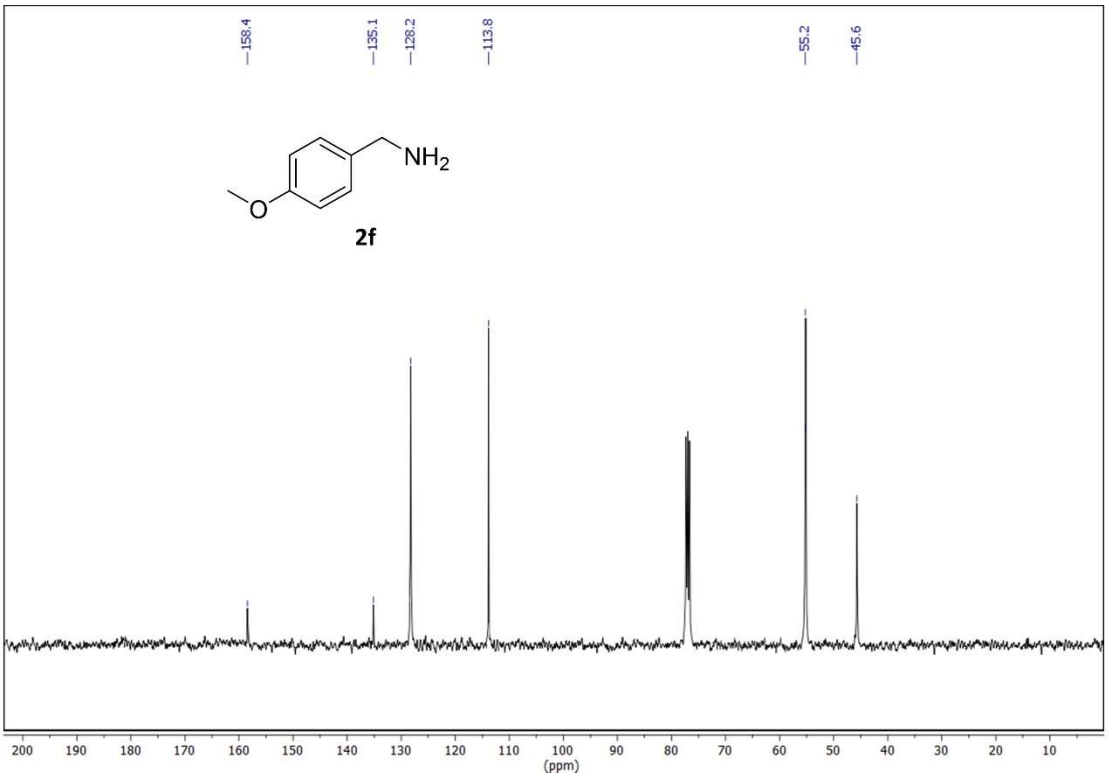

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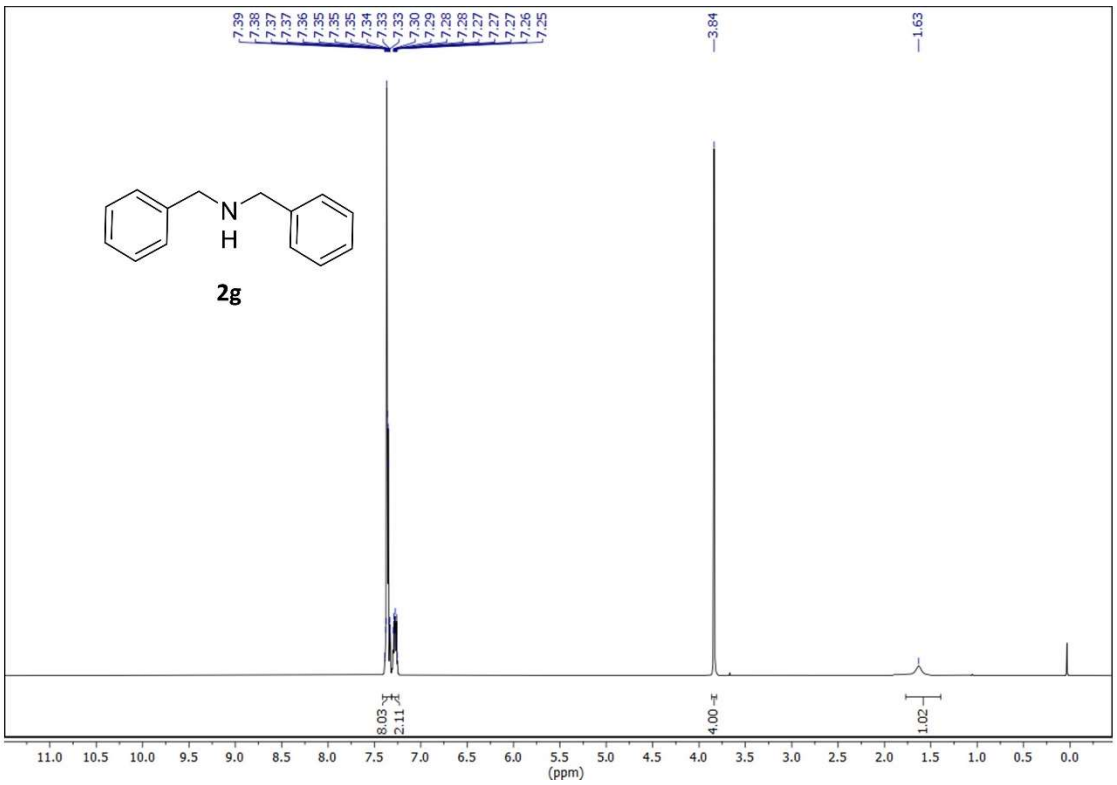

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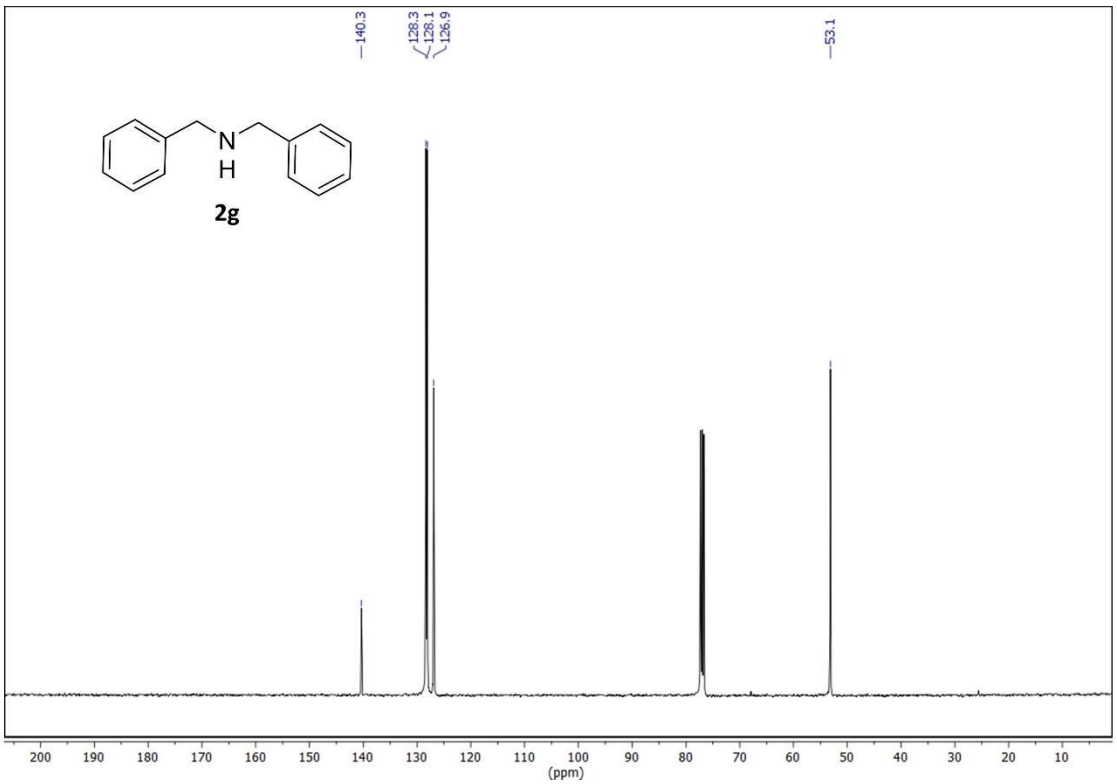

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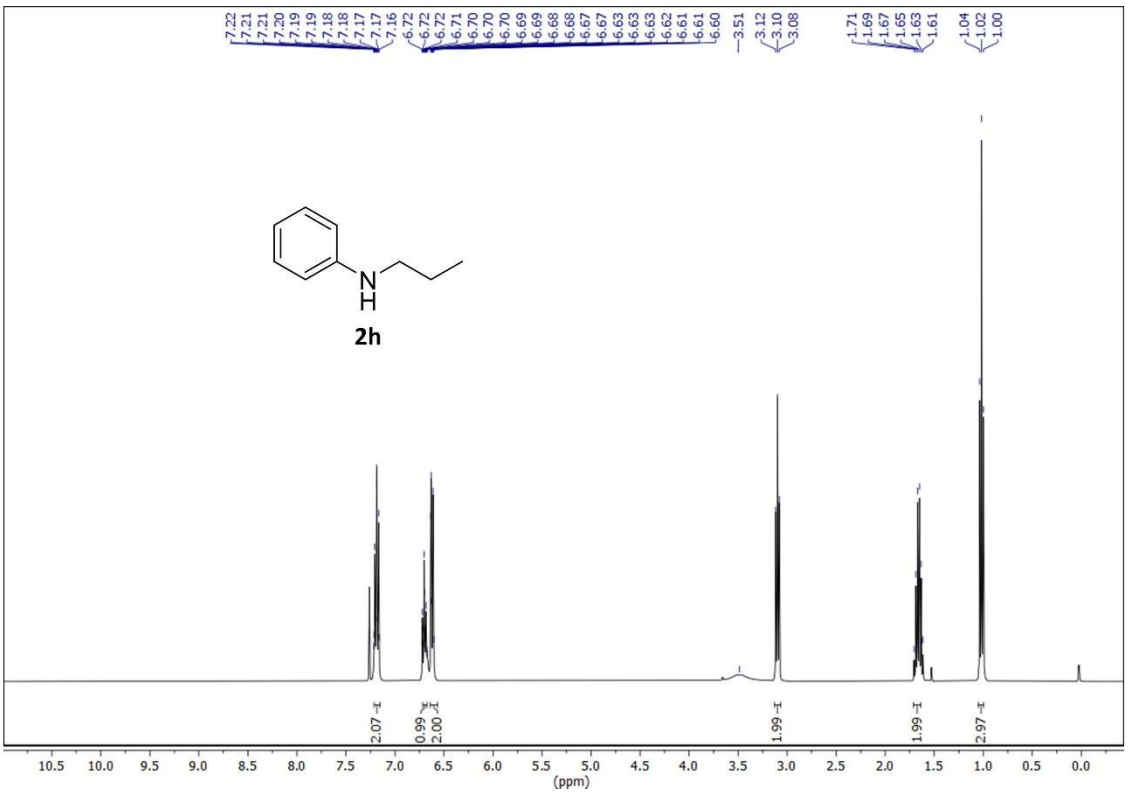

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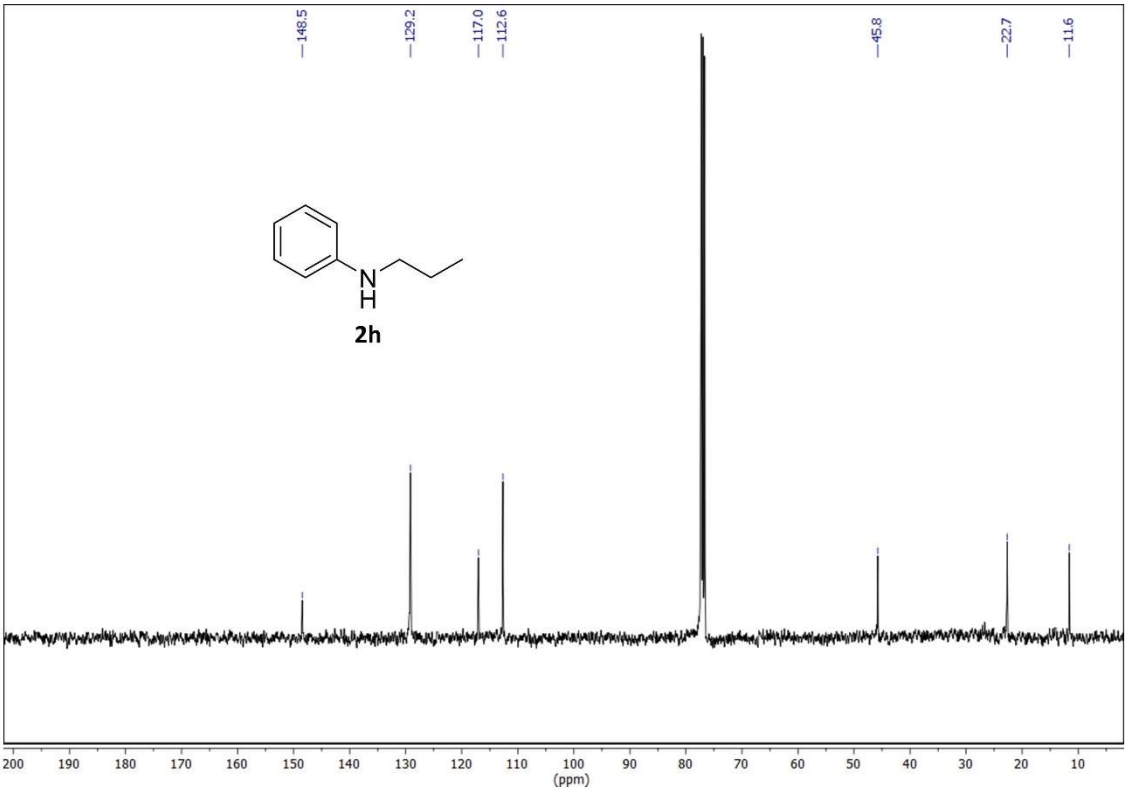
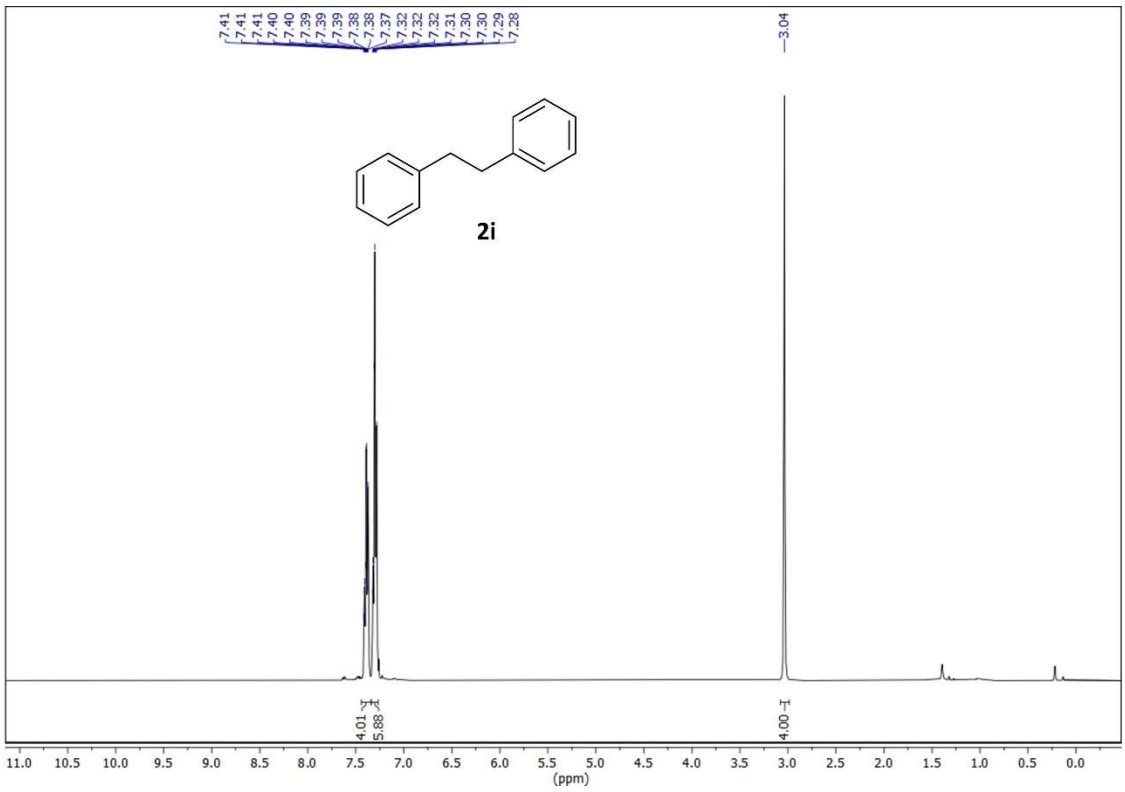


^{1}H NMR 400.12 MHz, $CDCl_3$



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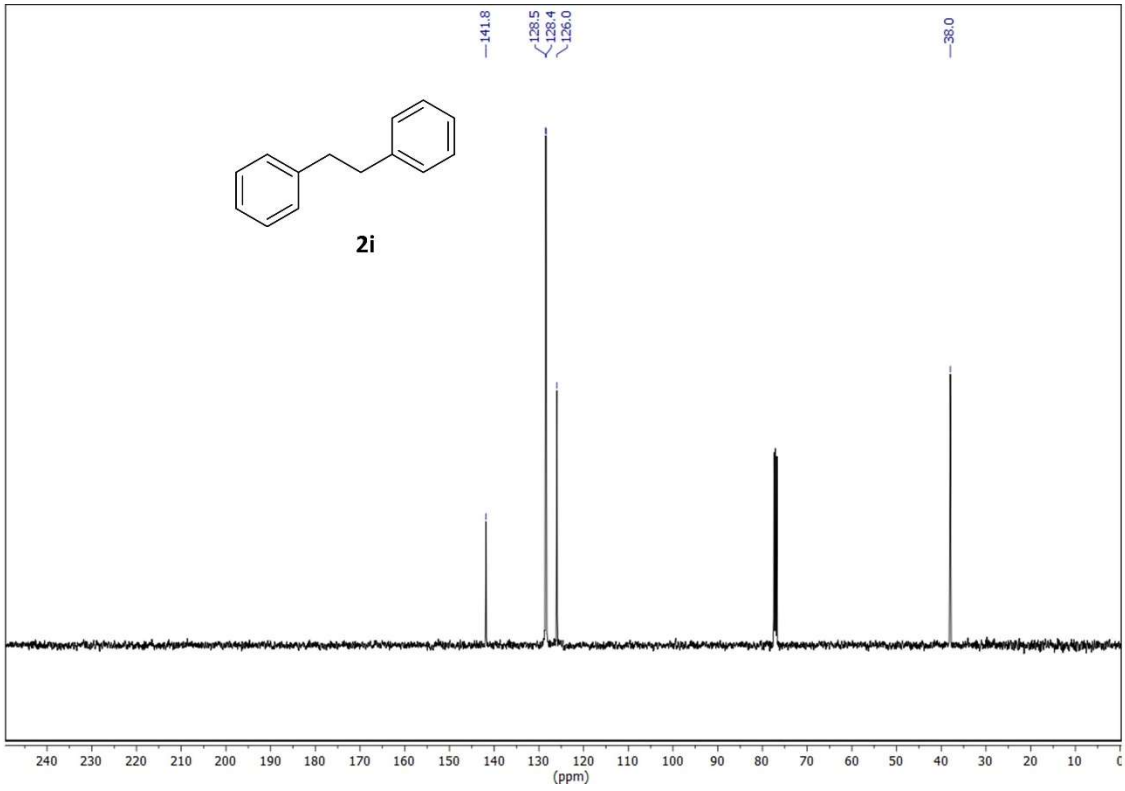

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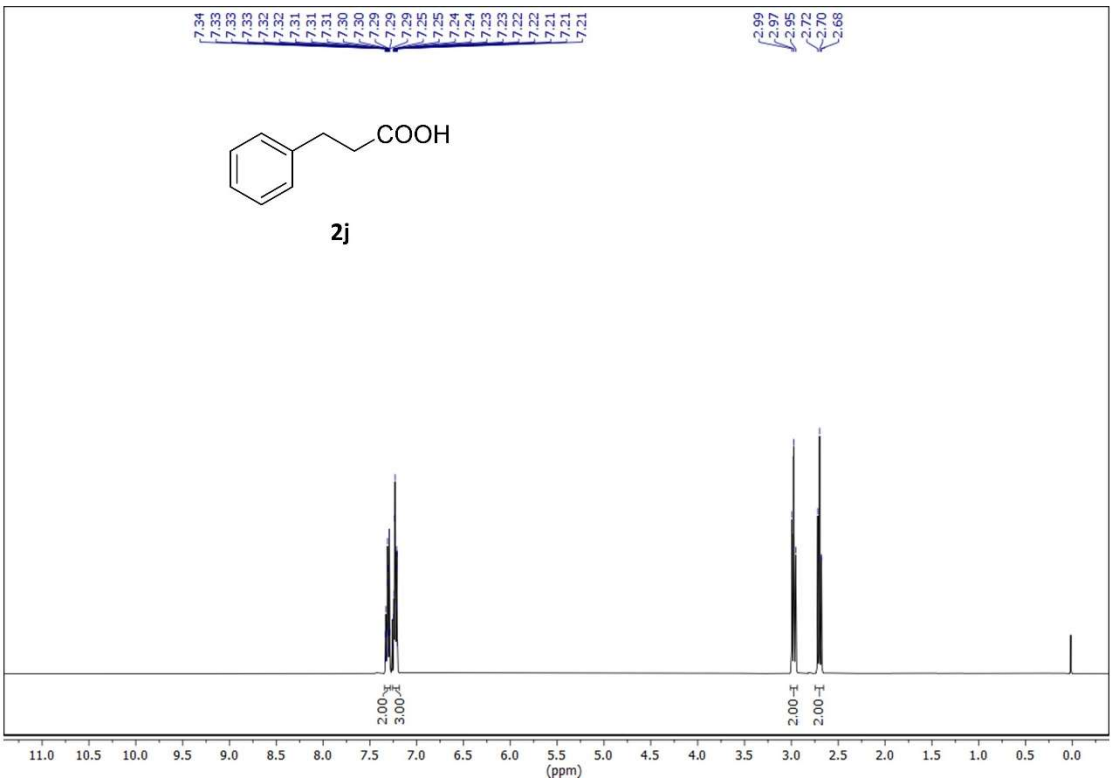

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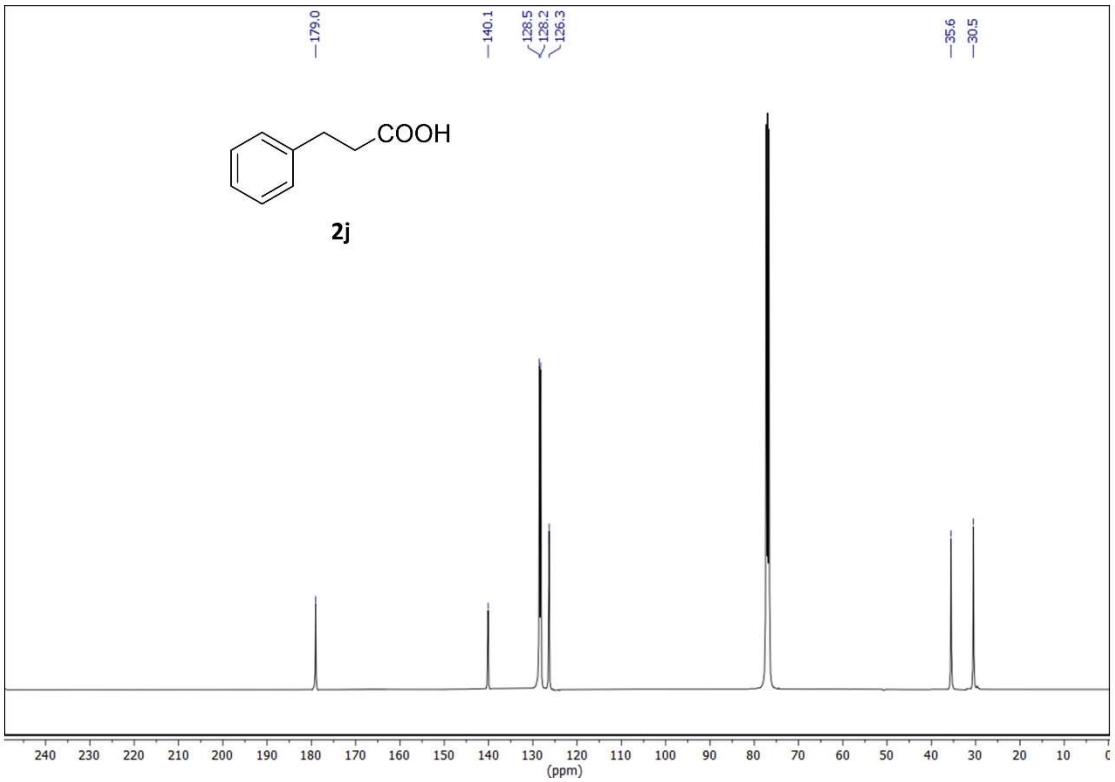

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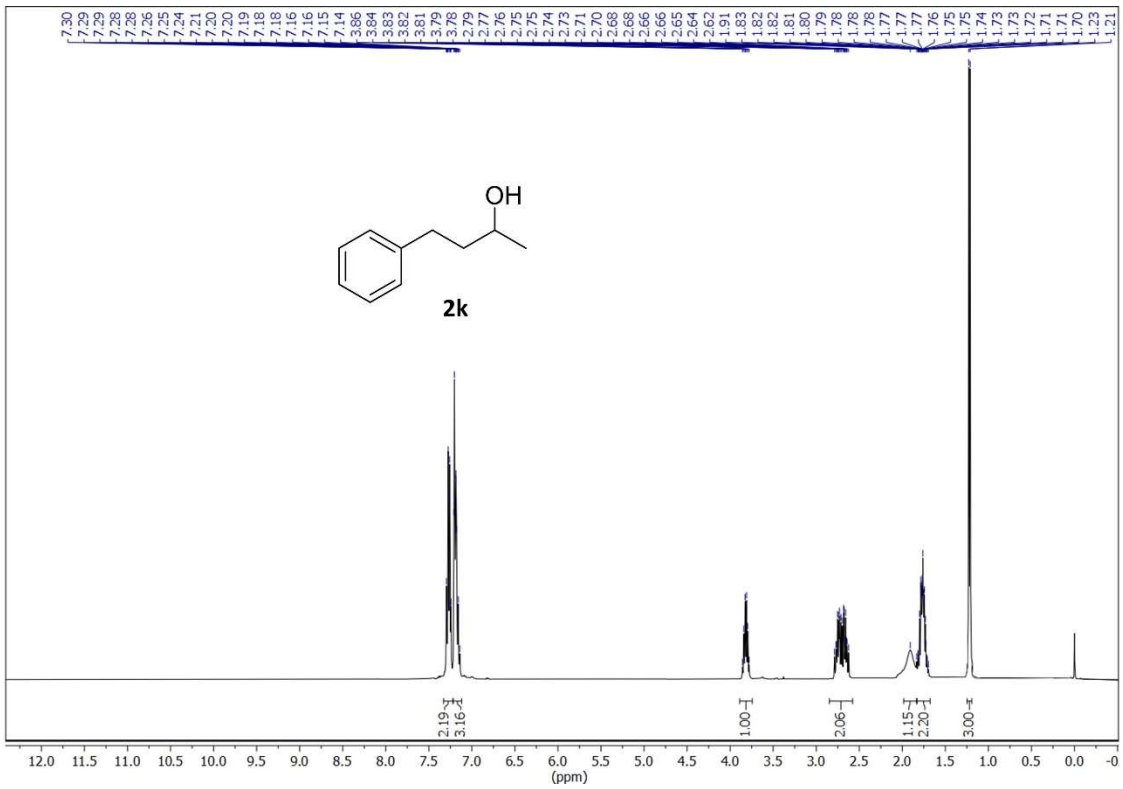

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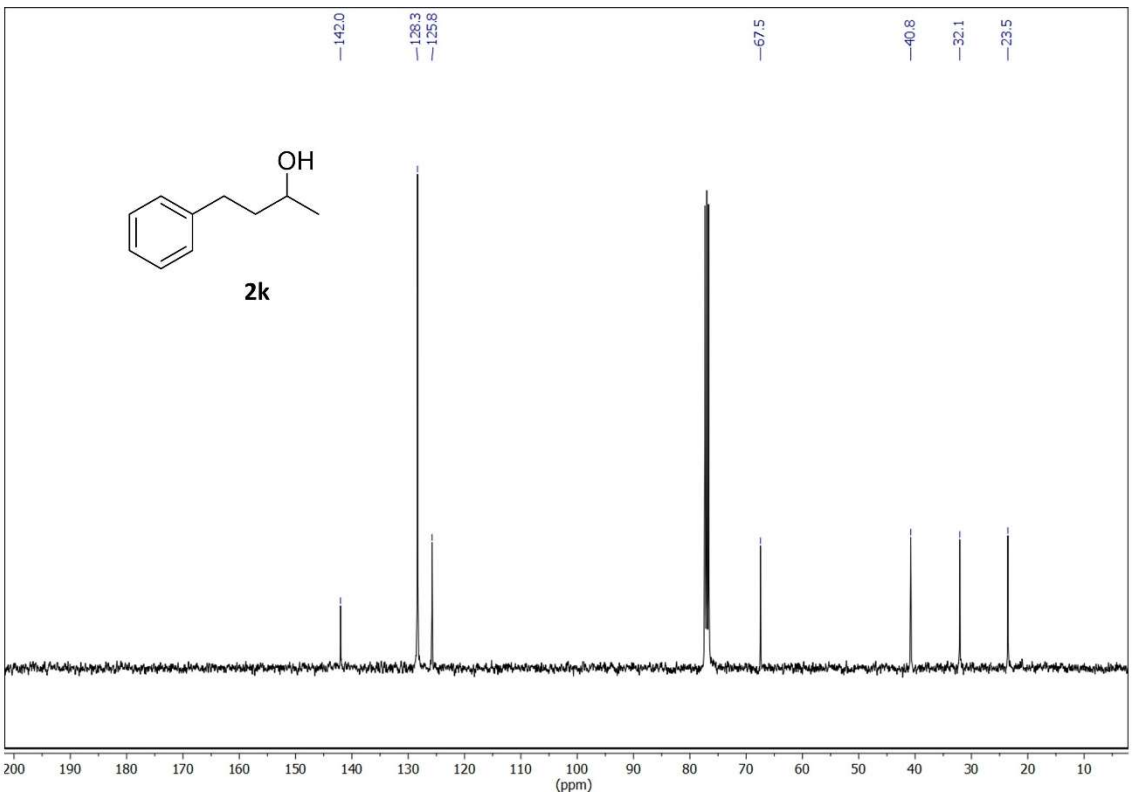

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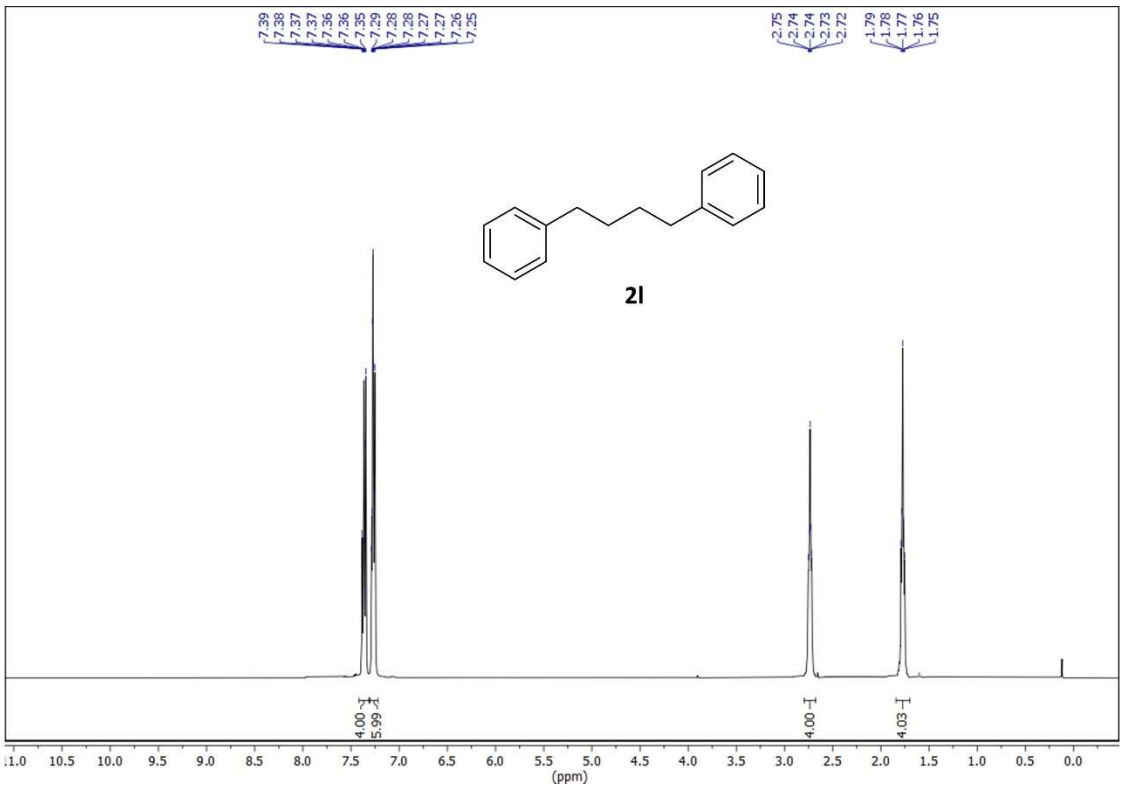

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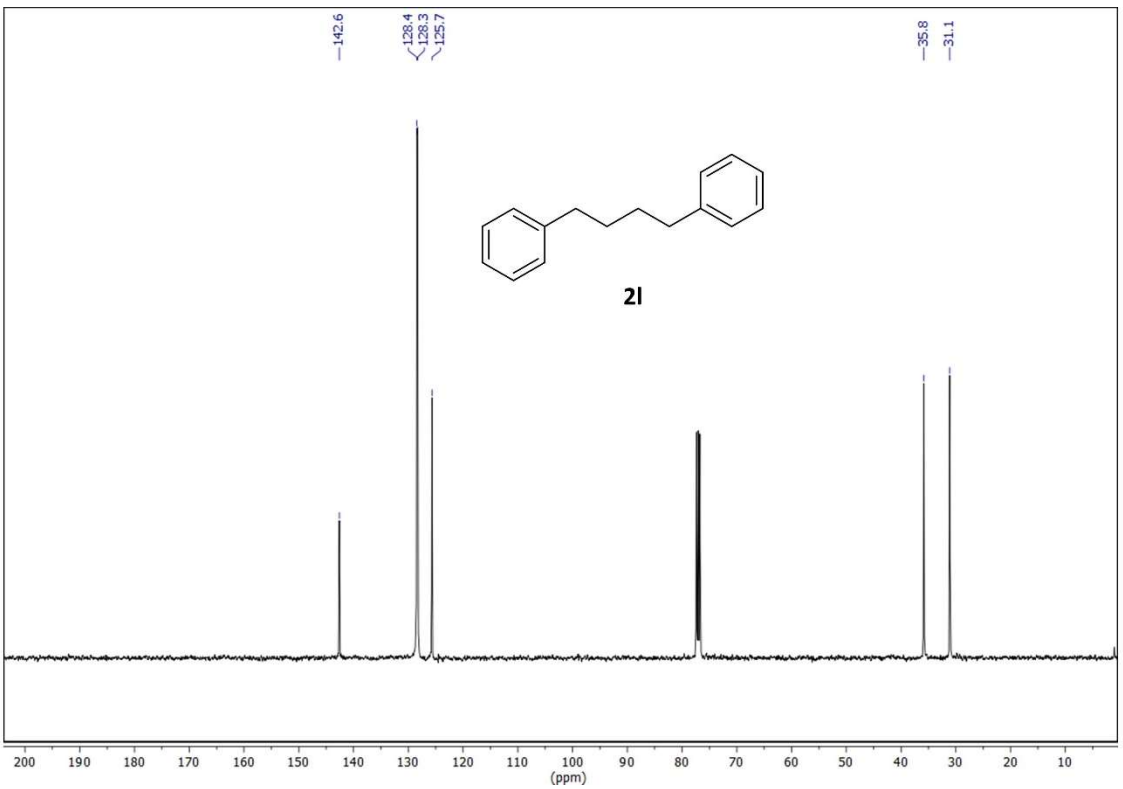
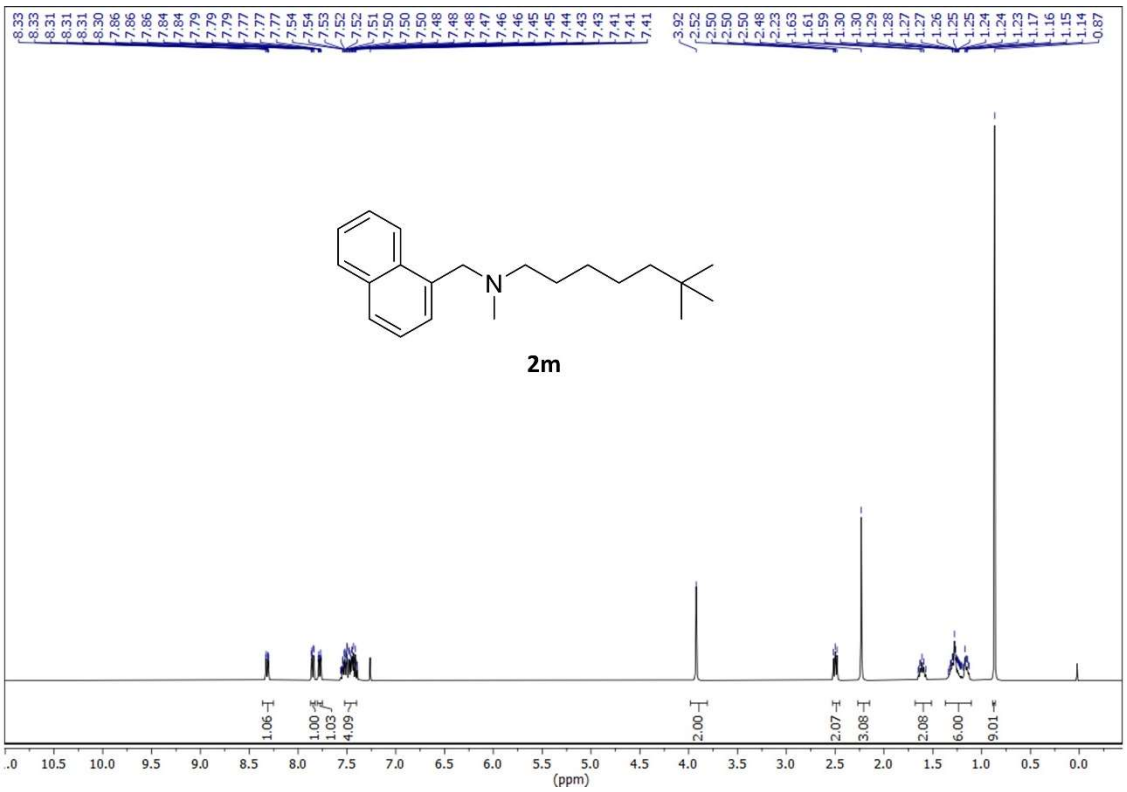


^{1}H NMR 400.12 MHz, $CDCl_3$



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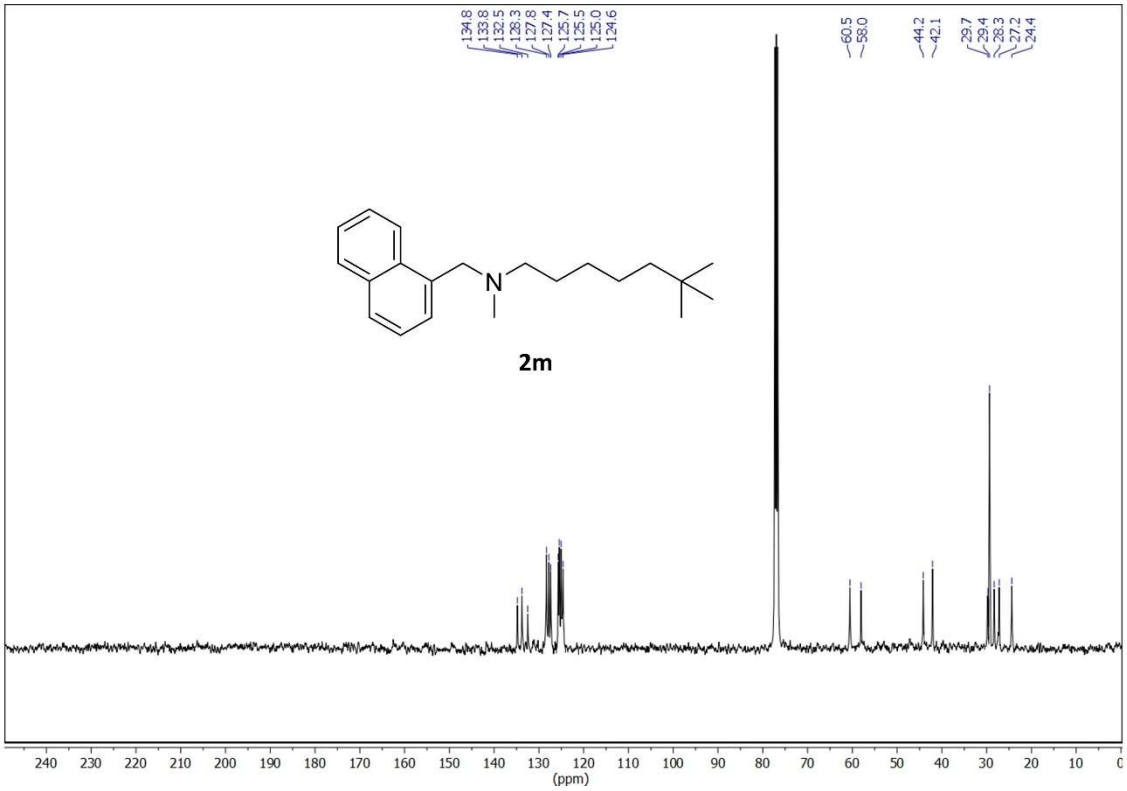

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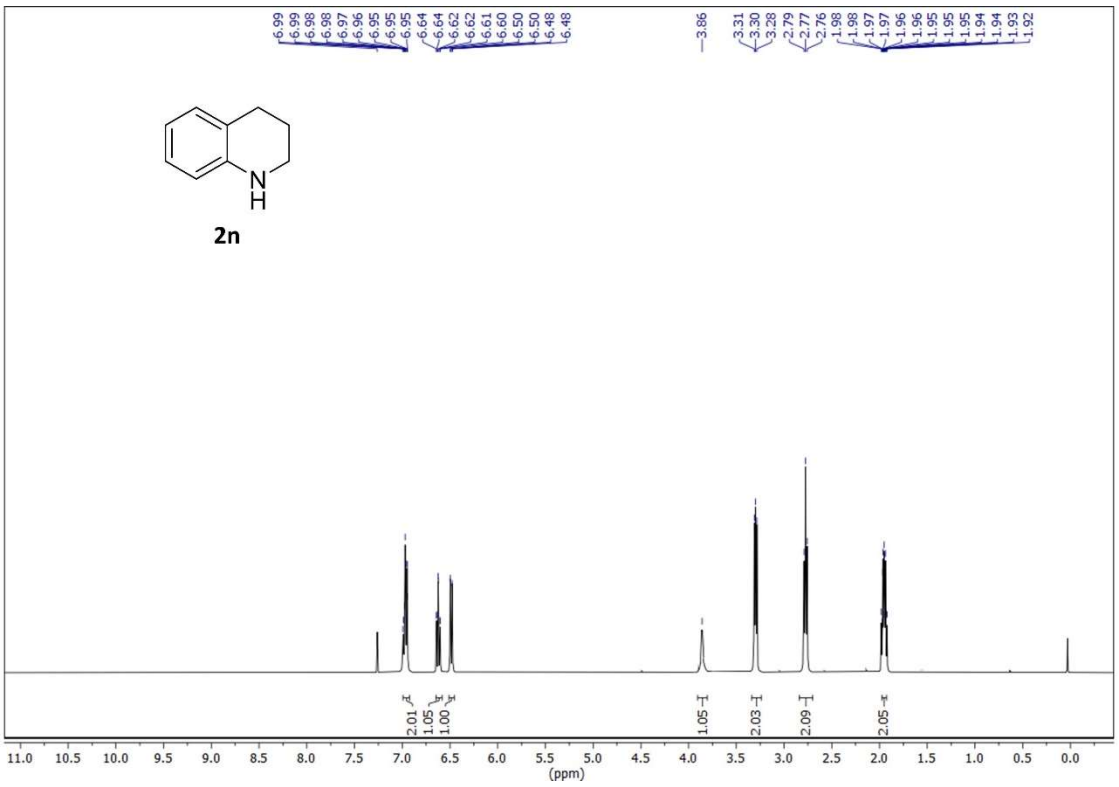

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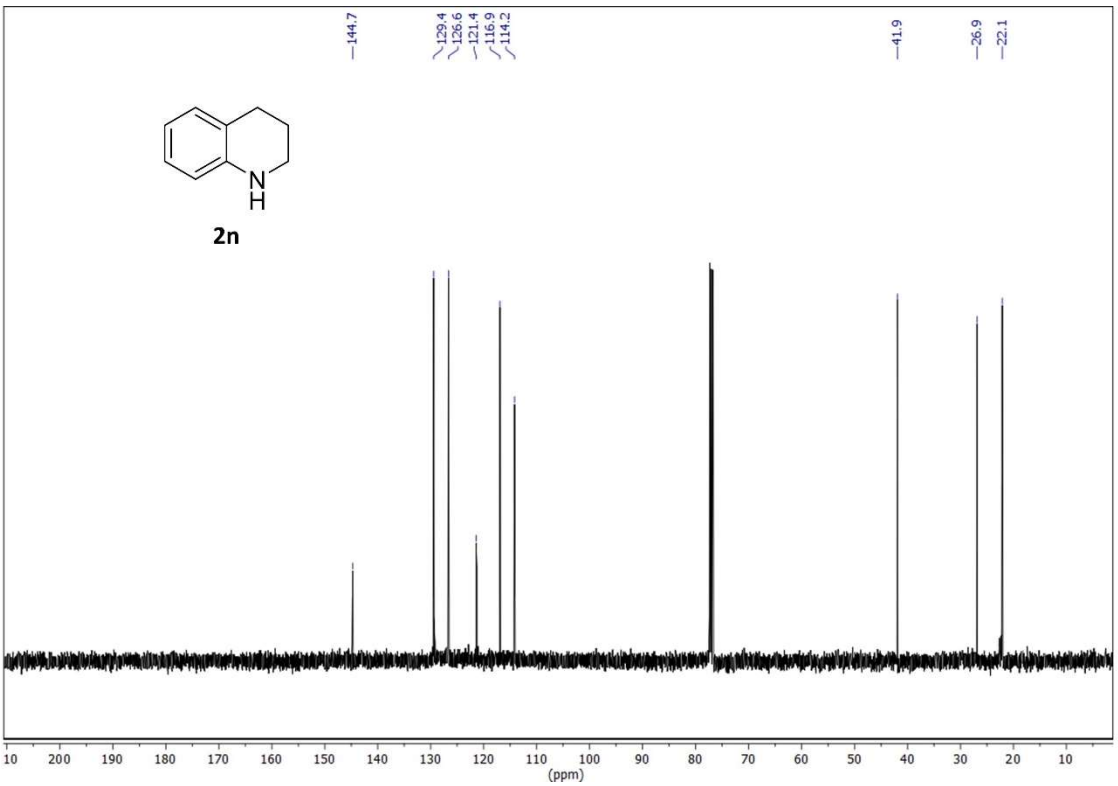

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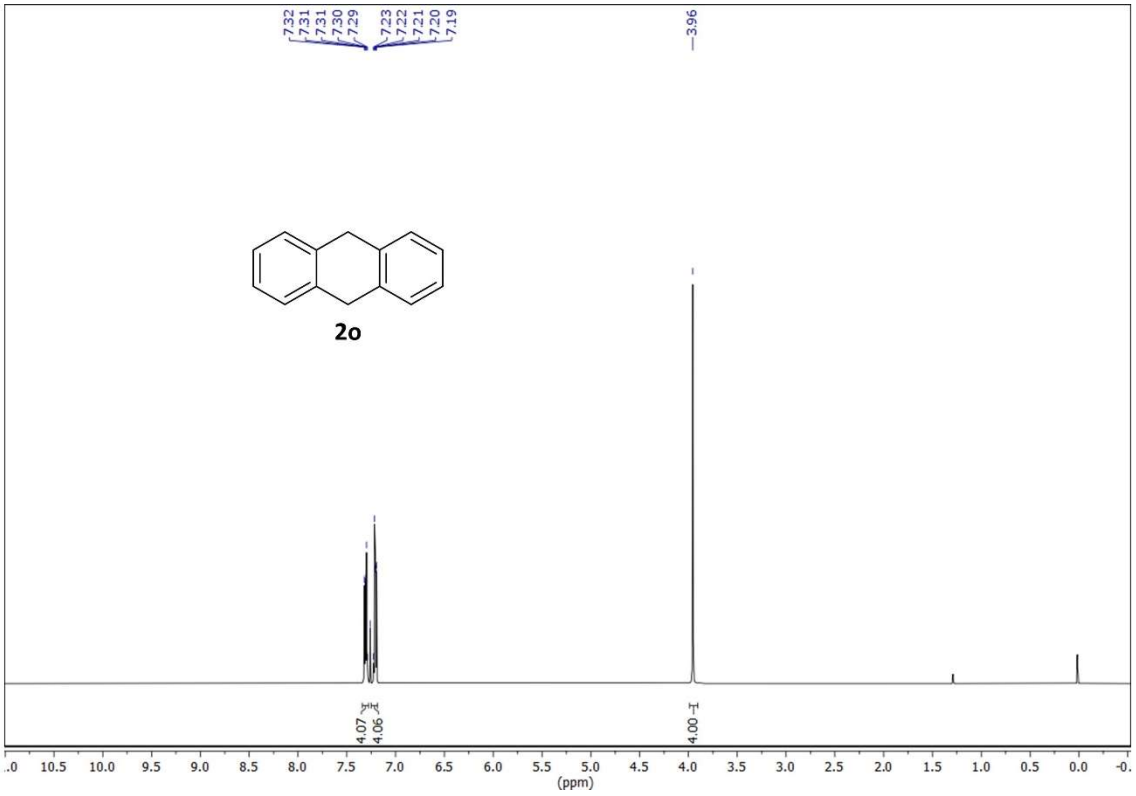

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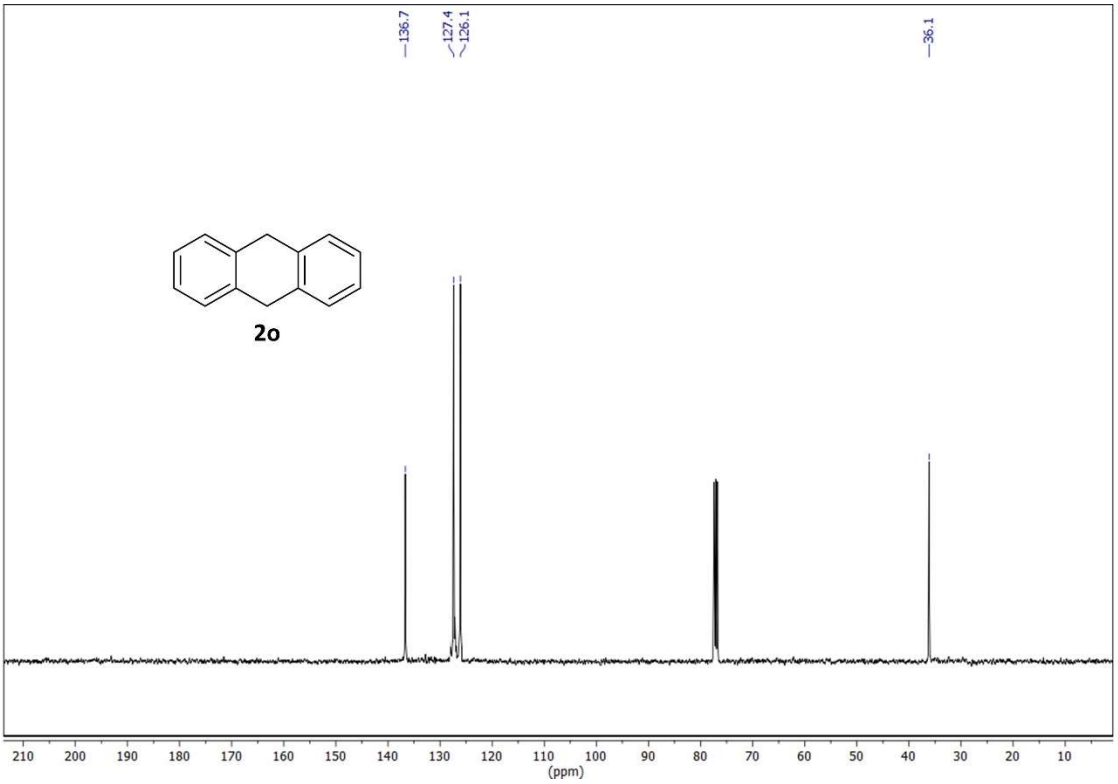

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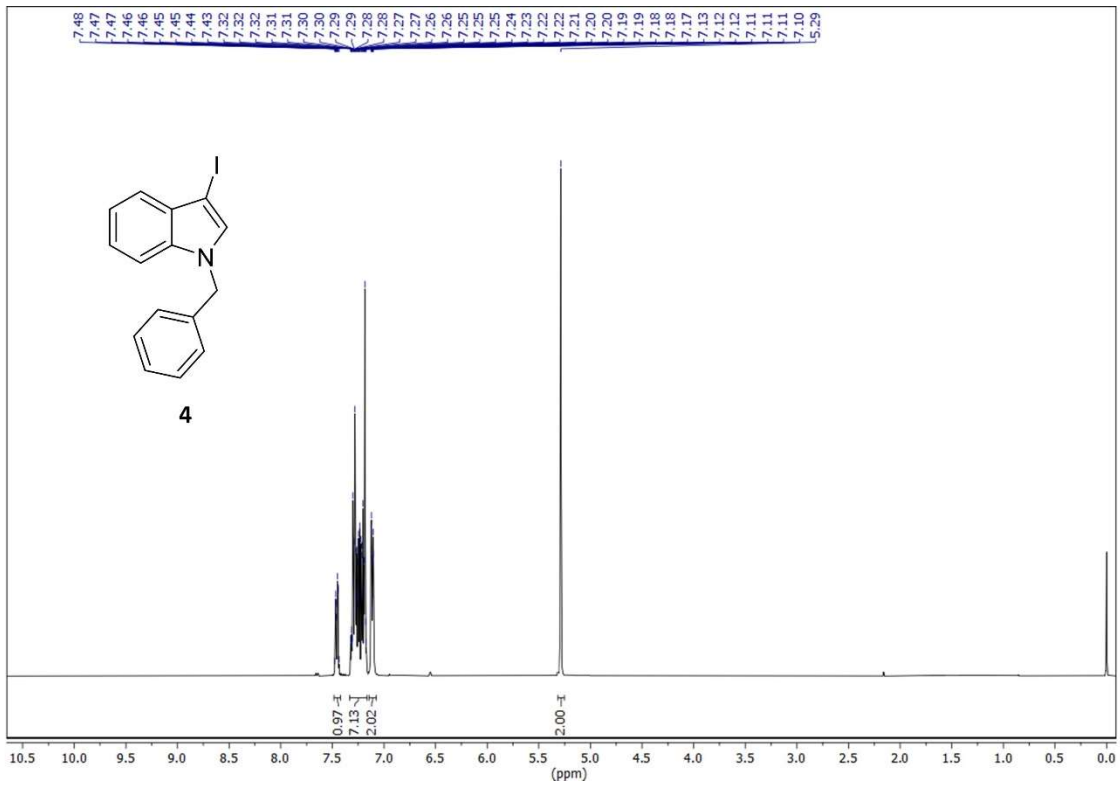

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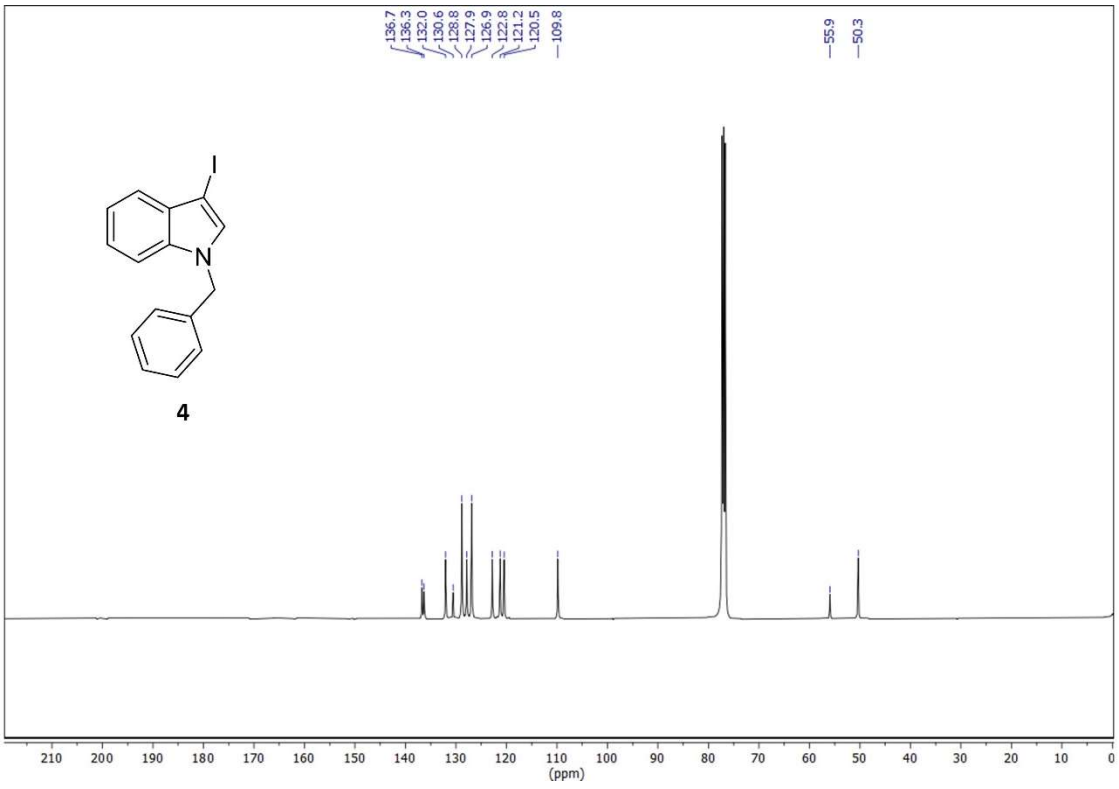

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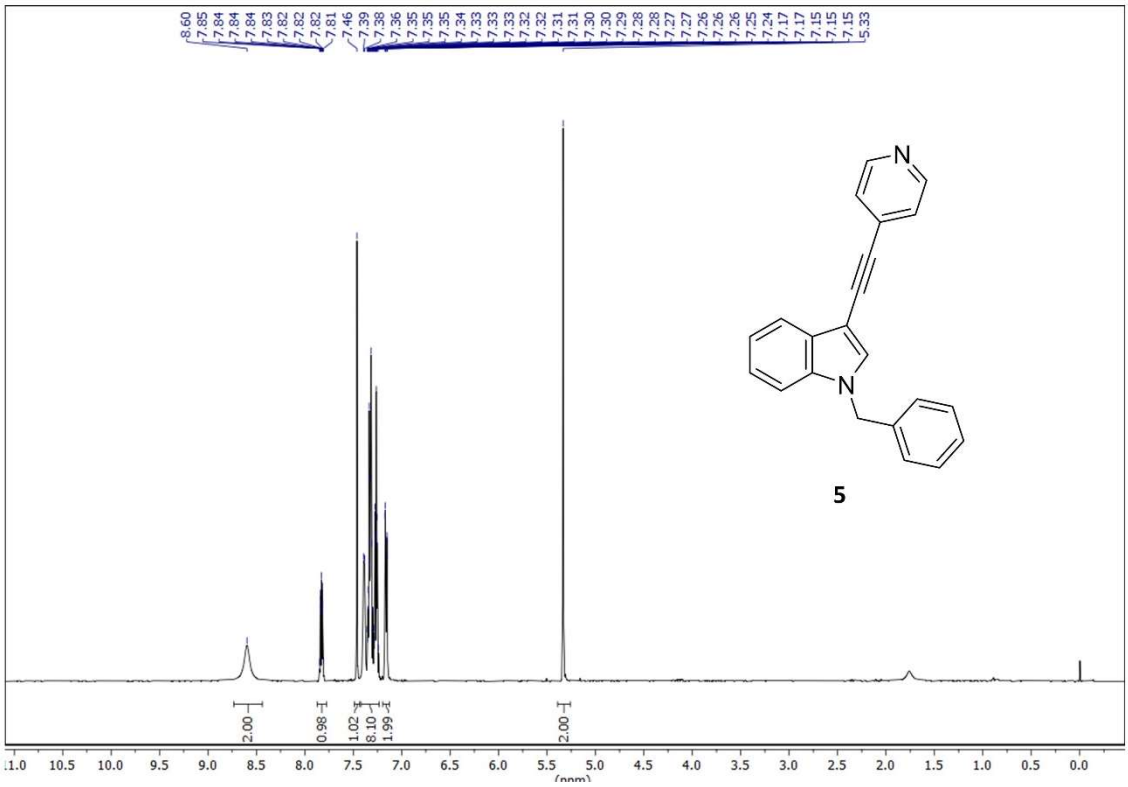

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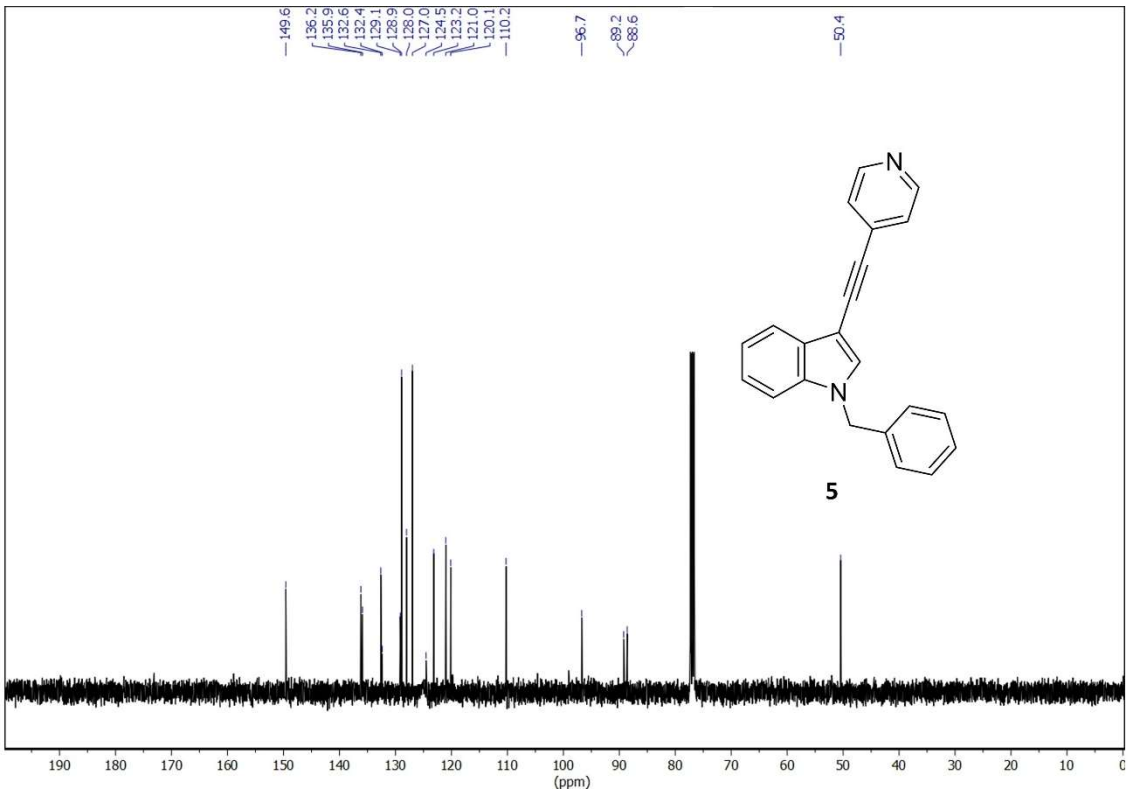

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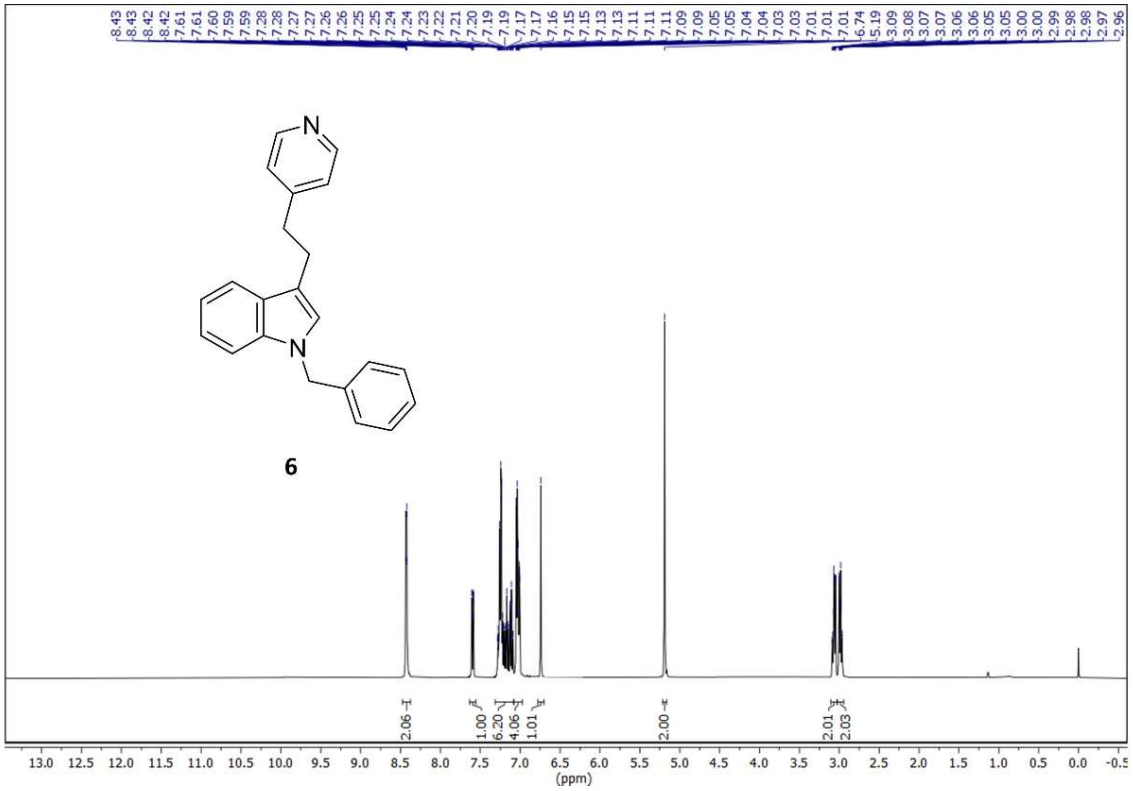

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