Electronic Supplementary Informations

A Phosphonium-Based Deep Eutectic Solvent Promotes the Stereoselective Semi-Reduction of Internal Alkynes to (*Z*)-Alkenes

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1 General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 600 or 400.12 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. 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. 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; visualisation 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). 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 TCI (Tokyo Chemical Industry, Europe, N. V.) 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. Deep Eutectic Solvents (DES) [cholinium chloride (ChCl)/glycerol (Gly) (1:2 mol/mol); ChCl/ethylene glycol (EG) (1:2 mol/mol); $MePh_3PBr$ (MTPBr)/EG DES (1:5 or 1:4 mol/mol); ChCl/urea (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 eutectic mixture was obtained. Particularly, for the preparation of dry MTPBr/EG DES (1:5 mol/mol), freshly distilled EG over anhydrous Na_2SO_4, under reduced pressure and N_2 atmosphere, was used. Full characterization data, including copies of ^{1}H NMR and ^{13}C NMR spectra, have been reported for all the synthesized compounds.

2 Synthesis of Internal Alkynes (1)

For the preparation of non-commercially available alkynes (**1**), unless specified otherwise, a known palladium catalysed Sonogashira cross-coupling reaction in DES was used.[1] To a suspension of aryl iodide (0.5 mmol) in 2.0 g of degassed Gly/ChCl (2:1 mol/mol), aryl-substituted terminal alkyne (1.0 mmol), Et_3N (0.2 mL, 1.5 mmol), and Pd/C 10 wt % (2.0 mol%, 10 mg), were sequentially added. The

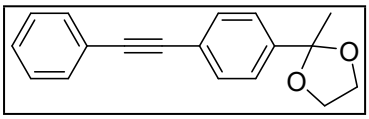
reaction mixture was stirred at 60 °C for 3 h until complete consumption of the starting material (monitored by TLC), then cooled to room temperature, and finally extracted with CPME (2.0 mL x 3). The organic layer was filtered through a celite pad and evaporated under reduced pressure to afford the crude mixture. The latter was purified by column chromatography on silica gel (petroleum ether/EtOAc 70:30 ÷ 80:20) to provide the desired alkyne.

Internal alkyne **1o** was prepared by reacting (phenylethynyl)lithium with cyclohexanone, using a known literature method.[2]

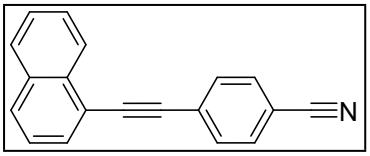
The internal alkynes **1g**, **1i** and **1k** were prepared following a modified literature procedure, reacting iodobenzene and 2-(4-ethynylphenyl)-2-methyl-1,3-dioxolane for **1g**, 1-iodonaphtalene and 4-ethynylbenzonitrile for **1i** and 1-iodonaphthalene and 4-ethynylpyridine for **1k**, and.[3] Particularly in a 50 mL round bottom flask, aryl Iodide (1.0 mmol), *i*-Pr_2NH (2.0 mmol, 118.0 mg, 170.0 µL), terminal alkyne (1.0 mmol) were added to a solution of $Pd(PPh_3)_2Cl_2$ (4.0 mol%, 0.04 mmol, 28.0 mg) and CuI (2 mol%, 0.02 mmol, 3.8 mg) in dry THF (3.0 mL), at room temperature. After 20–30 min of stirring, the mixture was filtered through a short celite pad and washed with petroleum ether and AcOEt (2:1). The combined eluents were concentrated to afford a crude mixture, which was purified by flash silica gel column chromatography (petroleum ether/EtOAc 70:30 ÷ 80:20) obtaining the desired internal alkyne.

Characterization data for unknown alkynes **1g**, **1i**, **1k** have been reported below.

2.1 Characterization Data for the Alkynes 1g, 1i, 1k

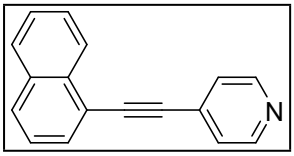


2-Methyl-2-(4-(phenylethynyl)phenyl)-1,3-dioxolane (1g): brown solid, 85% (225 mg), m.p. 80-83 °C. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.58–7.34 (m, 9H), 4.09–4.00 (m, 2H), 3.82–3.74 (m, 2H), 1.66 (s, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 143.4, 131.6, 131.4, 128.4, 128.3, 128.2, 125.3, 123.2, 122.7, 108.6, 89.4, 89.1, 64.4, 27.4; FT–IR (KBr, cm^{-1}): 3056, 2987, 2887, 2217, 1249, 1195, 1118, 836; GC/MS (70 eV) *m/z* (%): 264 [M^+, 10], 249 (100), 205 (35), 176 (18), 151 (12), 88 (95); HRMS (ESI) *m/z* calcd for $[C_{18}H_{16}O_2 + H]^+$ 265.1223; found: 265.1229.



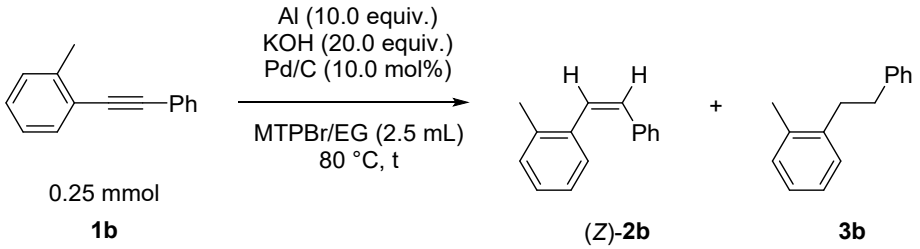
4-(Naphthalen-1-ylethynyl)benzonitrile (1i): pale yellow solid, 96% (243 mg), m.p. 116–119 °C. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.40–8.38 (m, 1H), 7.91–7.89 (m, 2H), 7.80–7.78 (m, 1H), 7.71–7.61 (m, 5H),

7.59–7.55 (m, 1H), 7.51–7.47 (m, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 133.1, 133.08, 132.03, 132.02, 131.0, 129.7, 128.5, 128.2, 127.1, 126.6, 125.8, 125.2, 119.8, 118.5, 111.5, 92.5, 92.0; FT–IR (KBr, cm^{-1}):3389, 3087, 3062, 2226, 2205, 1648, 840, 799, 736; GC/MS (70 eV) *m/z* (%): 253 [M^+, 100], 252 (45), 251 (60), 225 (15), 126 (20), 112 (15); HRMS (ESI) *m/z* calcd for $[C_{19}H_{11}N + H]^+$ 254.0964 ; found: 254.0969.



4-(Naphthalen-1-ylethynyl)pyridine (1k): brown oil, 70% (161 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.66–8.64 (m, 2H), 8.40–8.37 (m, 1H), 7.91–7.88 (m, 2H), 7.81–7.79 (m, 1H), 7.64–7.61 (m, 1H), 7.58–7.54 (m, 1H), 7.50–7.46 (m, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 149.7, 133.12, 133.10, 131.5, 131.1, 129.8, 128.4, 127.1, 126.6, 125.8, 125.5, 125.2, 119.6, 92.2, 91.4; FT–IR (Film, cm^{-1}): 3420, 3055, 3046, 2213, 1593, 1399, 818, 772; GC/MS (70 eV) *m/z* (%): 229 [M^+, 100], 228 (63), 200 (35), 176 (15), 150 (14), 114 (15), 88 (22); HRMS (ESI) *m/z* calcd for $[C_{17}H_{11}N + H]^+$ 230.0964; found: 230.0972.

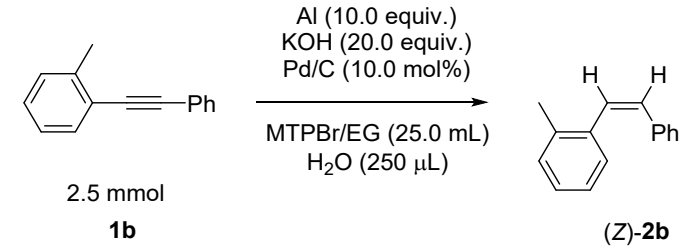
3 Table S1: Supplementary Details for the Investigation of Reaction Time in the Semi-reduction of Alkyne 1b to Alkene (*Z*)-2b.



Entry	t (h)	**1b** Conv. (%)[a]	(*Z*)-**2b** Yield (%)[a]	**3b** Yield (%)[a]
1	1	18	10	ND
2	5	49	44	ND
3	12	99	63	29
4	16	98	64	31

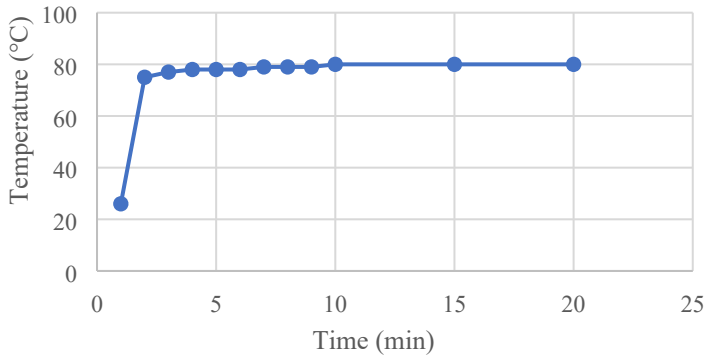
ND = not detected. [a] Calculated *via* ^{1}H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone).

4 Graph S1: Temperature Variation During the Semi-reduction of Alkyne 1b to (*Z*)-Alkene 2b.



2.5 mmol
1b

(*Z*)-**2b**

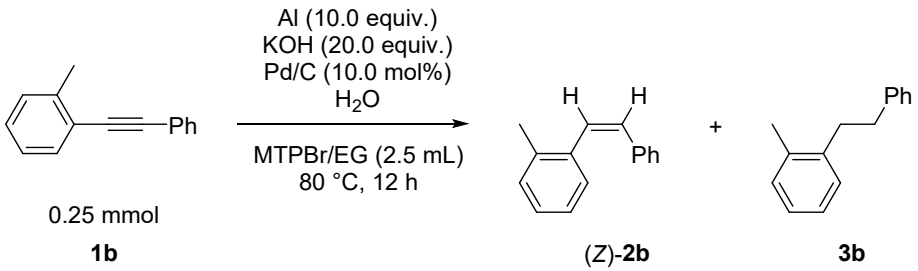


Time (min)	**Temp.** (° C)
1	26
2	75
3	77
4	78
5	78
6	78
7	79
8	79
9	79
10	80
15	80
20	80

Experimental procedure: In a three necked 250 mL round bottom flask, equipped with an internal thermometer, MTPBr (17.1 g, 48.0 mmol) and freshly distilled dry EG (14.8 g, 13.3 mL, 240 mmol) were added and gently heated up to 80 °C until 25.0 mL of a clear DES mixture was formed. After cooling the DES to r.t., internal alkyne **1b** (2.5 mmol, 480 mg), distilled water (250 µL), Pd/C 10 wt % (10.0 mol%, 0.25 mmol, 265 mg) and Al(0) powder (10.0 equiv., 25.0 mmol, 675 mg) were

sequentially added. The mixture was stirred for about 1 min. then, KOH (20.0 equiv., 50.0 mmol, 2.800 g) was carefully added to the mixture, and the flask was quickly closed. The temperature of the reaction mixture was then recorded until it reached the value of 80 °C.

5 Table S2: Supplementary Details for the Investigation of Water Influence in the Semi-reduction of Alkyne 1b to Alkene (*Z*)-2b.



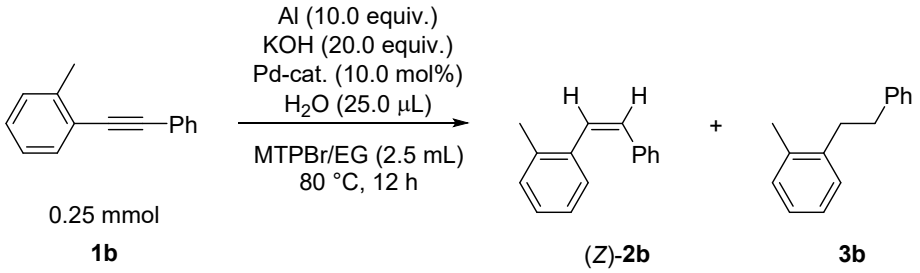
0.25 mmol

1b (*Z*)-**2b** **3b**

Entry	H_2O (µL)	**1b** Conv. (%)[a]	(*Z*)-**2b** Yield (%)[a]	**3b** Yield (%)[a]
1	-	48	40	<2
2	10	55	47	<2
3	25	99	91	<2
4	100	99	53	42
5	250	99	11	81
6	500	99	<2	95

[a] Calculated *via* ^{1}H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone).

6 Table S3: Supplementary Details for the Influence of Palladium Heterogeneous Catalysts on the Semi-reduction of Alkyne 1b to Alkene (*Z*)-2b.



0.25 mmol **1b** (*Z*)-**2b** **3b**

Entry	Pd-cat.	**1b** Conv. (%)[a]	(*Z*)-**2b** Yield (%)[a]	**3b** Yield (%)[a]
1	$Pd/BaSO_4$	31	31	ND
2	Pd/Al_2O_3	58	57	ND
4	$Pd/CaCO_3/Pb(AcO)_2$	80	77	ND
5[b]	$Pd/CaCO_3/Pb(AcO)_2$	99	84	8

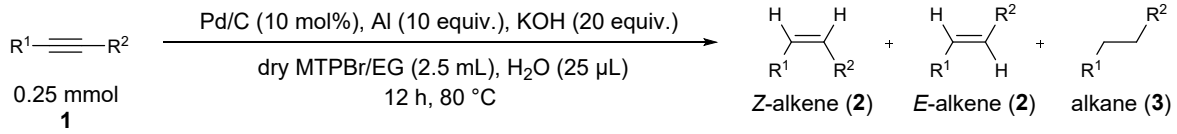
ND = not detected. [$Pd/CaCO_3/Pb(AcO)_2$] = Lindlar's catalyst. [a] Calculated via ^1H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone). [b] Reaction performed in ChCl/urea (1:2 mol/mol).

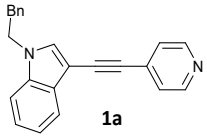
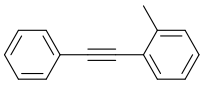
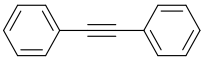
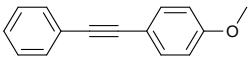
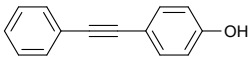
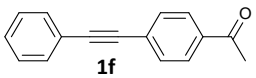
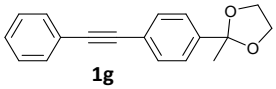
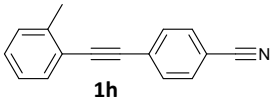
7 Experimental Procedure for the Stereoselective Semi-reduction of Internal Alkynes to *Z*-Alkenes.

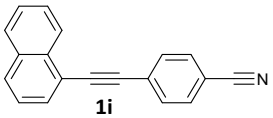
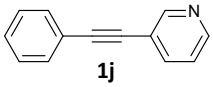
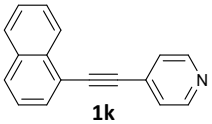
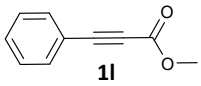
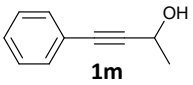
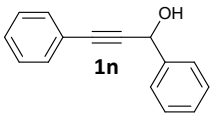
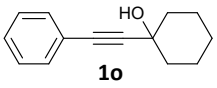
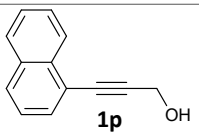
In a 50 mL round bottom flask, MTPBr (1.71 g, 4.8 mmol) and freshly distilled dry EG (1.48 g, 1.33 mL, 24.0 mmol) were added and gently heated up to 80 °C until 2.5 mL of a clear DES mixture was formed. After cooling the DES to r.t., internal alkyne (0.25 mmol), distilled water (25.0 μL), Pd/C 10 wt % (10.0 mol%, 0.025 mmol, 26.5 mg), Al(0) powder (10.0 equiv., 2.5 mmol, 67.5 mg) were sequentially added. The mixture was stirred for about 1 min. then, KOH (20.0 equiv., 5.0 mmol, 280 mg) was carefully added to the mixture, 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 12 hours at 80°C. After this time, the reaction mixture was cooled to room temperature and water (5.0 ml) was added. For alkenes with an acidic functional group (**2e, l**) after the water addition, HCl 10% v/v solution was added up to pH = 2. The reaction mixture was then extracted with AcOEt (5 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 flash chromatography column on silica gel (using as eluent petroleum ether/AcOEt 100/0 to petroleum ether/AcOEt 80/20; for

compounds **2l-p**, petroleum ether/acetone 70/30 with 5 gtt of acetic acid for 10.0 mL of eluent was used) to obtain the desired *Z*-alkene.

7.1 Table S4: Supplementary Details for the Stereoselective Semi-reduction of Internal Alkyne to *Z*-Alkenes in MTPBr/EG DES.

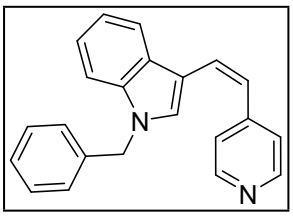


Entry	Alkyne (**1**)	**1** Conv. (%)	(*Z*)-**2** Yield[a] (%)	*Z/E* ratio[b]	**3** Yield[c] (%)
1 [d,e,f]	 **1a**	99	92	>99/1	6
2	 **1b**	99	91	>99/1	<2
3	 **1c**	100	80	80/20	ND
4	 **1d**	90	88	>99/1	ND
5	 **1e**	93	85	91/9	ND
6	 **1f**	85	81	99/1	ND
7	 **1g**	99	95	>99/1	ND
8 [d,e]	 **1h**	100	60	75/25	20

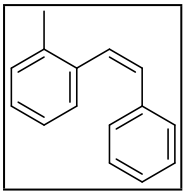
9 [d,e]	 **1i**	100	88	93/7	5
10[d,e]	 **1j**	100	80	>99/1	18
11 [d,g]	 **1k**	100	55	63/37	13
12	 **1l**	100	70[h]	99/1	ND
13 [g]	 **1m**	100	87	87/13	ND
14 [e]	 **1n**	100	97	>99/1	ND
15 [e]	 **1o**	87	83	>99/1	ND
16	 **1p**	100	99	>99/1	ND

ND = not detected. [a] Isolated yields. [b] Calculated *via* ^{1}H NMR analysis of the crude reaction mixture. [c] Calculated *via* ^{1}H NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: dimethyl sulfone). [d] Reaction performed with Pd/C 5.0 mol%. [e] Reaction performed at 40 °C. [f] Reaction time: 8 h. [g] Reaction performed at r.t. [h] (*Z*)-cinnamic acid was isolated.

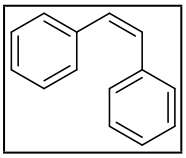
7.2 Characterization Data for the *Z*-Alkenes 2a-p.



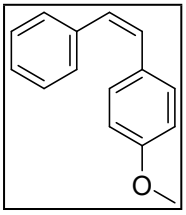
(*Z*)-1-Benzyl-3-(2-(pyridin-4-yl)vinyl)-1*H*-indole (2a): pale orange oil, 92% (71 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.43–8.41 (m, 2H), 7.44–7.42 (m, 1H), 7.33–7.27 (m, 6H), 7.22–7.18 (m, 1H), 7.13–7.06 (m, 4H), 6.92 (d, *J* = 12.1, Hz, 1H), 6.40 (d, *J* = 12.1 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 149.5, 147.0, 136.8, 136.2, 128.8, 127.9, 127.8, 127.3, 126.9, 125.3, 124.0, 122.4, 120.2, 119.7, 111.5, 109.9, 104.2, 50.1; FT–IR (Film, cm^{-1}): 3053, 3025, 2960, 1585, 1564, 1446, 1025, 810; GC/MS (70 eV) *m/z* (%): 310 [M$^+$, 100], 219 (25), 191 (10), 91 (95), 65 (15); HRMS (ESI) *m/z* calcd for $[C_{22}H_{18}N_2 + H]^+$ 311.1543; found: 311.1547.



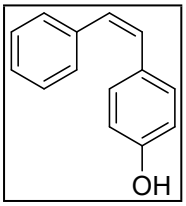
(*Z*)-1-Methyl-2-styrylbenzene (2b):[4] pale yellow oil, 91% (44 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$) δ 7.22–7.10 (m, 8H), 7.07–7.03 (m, 1H), 6.66 (d, *J* = 12.0 Hz, 1H), 6.62 (d, *J* = 12.0 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 137.05, 137.03, 136.0, 130.4, 130.0, 129.5, 128.83, 128.81, 128.0, 127.1, 127.0, 125.6, 19.8; FT–IR (Film, cm^{-1}): 3056, 3020, 2920, 1492, 1445, 1105, 734; GC/MS (70 eV) *m/z* (%): 194 [M$^+$, 81], 179 (100), 178 (74), 115 (20), 89 (13), 77 (9); HRMS (ESI) *m/z* calcd for $[C_{15}H_{14} + H]^+$ 195.1168; found: 195.1172.



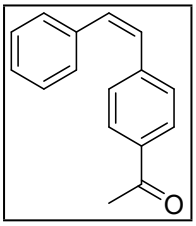
(*Z*)-1,2-Diphenylethene (2c):[5] colourless oil, 80% (36 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.19–7.29 (m, 10H) 6.63 (s, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$): 137.2, 130.2, 128.8, 128.2, 127.0; FT–IR (Film, cm^{-1}): 3079, 3053, 3022, 1946, 1643, 1493, 1446, 781, 697; GC/MS (70 eV) *m/z* (%): 180 [M$^+$, 100], 179 (98), 178 (89), 165 (85), 152 (26), 89 (33), 77 (25); HRMS (ESI) *m/z* calcd for $[C_{14}H_{12} + H]^+$ 181.1012; found: 181.1019. Spectroscopic data for (*E*)-**2c** are in accordance with those reported in the literature.[6]



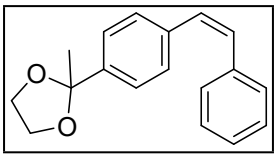
(*Z*)-1-Methoxy-4-styrylbenzene (2d):[4] light yellow oil, 88% (46 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.21–7.10 (m, 7H), 6.70–6.66 (m, 2H), 6.47 (d, *J* = 11.9 Hz, 1H), 6.43 (d, *J* = 11.9Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 158.6, 137.6, 130.1, 129.7, 129.6, 128.8, 128.7, 128.2, 126.9, 113.5, 55.2; FT–IR (Film, cm^{-1}): 3076, 3006, 2952, 2928, 2833, 1604, 1570, 1509, 1296, 1252, 1175, 1032, 830; GC/MS (70 eV) *m/z* (%): 210 [M$^+$, 100], 195 (41), 167 (50), 165 (63), 152 (45), 89 (28), 77 (12); HRMS (ESI) *m/z* calcd for $[C_{15}H_{14} + H]^+$ 211.1117; found: 211.1122.



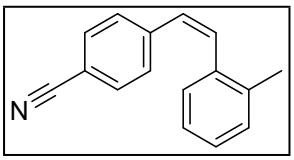
(*Z*)-4-Styrylphenol (2e):[7] pale yellow waxy solid, 85% (42 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ = 7.28–7.22 (m, 5H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 1H), 6.52 (s, 2H) 4.78 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 155.2, 137.5, 130.3, 128.8, 128.27, 128.25, 127.2, 126.8, 126.7, 115.5; FT–IR (KBr, cm^{-1}): 3377 (br), 3022, 1659, 1591, 1235, 1173, 816, 747; GC/MS (70 eV) *m/z* (%): 196 [M^+, 100], 195 (60), 177 (50), 165 (53), 152 (30), 77 (10); HRMS (ESI) *m/z* calcd for $[C_{14}H_{12}O + H]^+$ 197.0961; found: 197.0964.



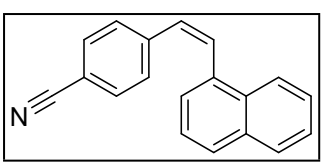
(*Z*)-1-(4-styrylphenyl)ethan-1-one (2f):[8] pale yellow oil, 81% (45 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): 7.75–7.72 (m, 2H), 7.26–7.23 (m, 2H), 7.18–7.13 (m, 5H), 6.64 (d, *J* = 12.2 Hz, 1H), 6.52 (d, *J* = 12.2 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100.62 MHz, CDCl3): 197.6, 142.2, 136.6, 135.5, 132.4, 129.1, 129.0, 128.8, 128.34, 128.32, 127.5, 26.5; FT–IR (Film, cm^{-1}): 3343, 3053, 3012, 2963, 2917, 2849, 1681, 1601, 1357, 1267, 1182; GC/MS (70 eV) *m/z* (%): 222 [M^+, 95], 207 (100), 178 (92), 152 (24), 89 (26), 77 (15); HRMS (ESI) *m/z* calcd for $[C_{16}H_{14}O + H]^+$ 223.1117; found: 223.1122.



(*Z*)-2-Methyl-2-(4–styrylphenyl)-1,3-dioxolane (2g): colourless oil, 95% (62 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.34–7.31 (m, 2H), 7.27–7.16 (m, 7H), 6.60 (d, *J* = 12.3 Hz, 1H), 6.55 (d, *J* = 12.3 Hz, 1H), 4.05–3.96 (m, 2H), 3.81–3.73 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 142.0, 137.2, 136.7, 130.3, 129.8, 128.77, 128.75, 128.2, 127.1, 125.1, 108.7, 64.4, 27.4; FT–IR (Film, cm^{-1}): 3060, 3015, 2970, 2925, 1600, 1510, 1250, 1170, 840, 766, 690; GC/MS (70 eV) *m/z* (%): 266 [M^+, 25], 252 (41), 251 (100), 207 (83), 178 (69), 105 (15), 89 (22); HRMS (ESI) *m/z* calcd for $[C_{18}H_{18}O_2 + H]^+$ 267.1380 ; found: 267.1384.

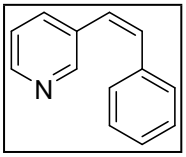


(*Z*)-4-(2–Methylstyryl)benzonitrile (2h): light yellow oil, 60% (33 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.44–7.42 (m, 2H), 7.23–7.17 (m, 4H), 7.08–7.04 (m, 2H), 6.84 (d, *J* = 12.1 Hz, 1H), 6.62 (d, *J* = 12.1 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 141.7, 136.04, 136.03, 133.1, 131.8, 130.3, 129.3, 128.8, 128.6, 127.9, 125.9, 118.9, 110.3, 19.8; FT–IR (Film, cm^{-1}): 3057, 3014, 2967, 2924, 2226, 1603, 1504, 839; GC/MS (70 eV) *m/z* (%): 219 [M^+, 90], 204 (100), 203 (50), 115 (25), 91 (15); HRMS (ESI) *m/z* calcd for $[C_{16}H_{13}N + H]^+$ 220.1121; found: 220.1129. Spectroscopic data for (*E*)-**2h** are in accordance with those reported in the literature.[9]

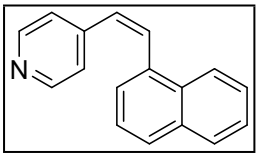


(*Z*)-4-(2-(Naphthalen-1-yl)vinyl)benzonitrile (2i): yellow oil, 88% (56 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.02–7.99 (m, 1H), 7.90–7.88 (m, 1H), 7.81–7.79 (m, 1H), 7.55–7.47 (m, 2H), 7.36–7.32 (m, 3H), 7.28–7.22 (m,

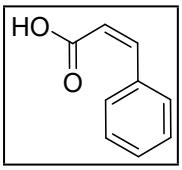
2H), 7.15–7.13 (m, 2H), 6.83 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 141.5, 134.2, 133.8, 132.2, 131.9, 131.3, 130.4, 129.5, 128.7, 128.3, 126.44, 126.42, 126.3, 125.6, 124.6, 118.9, 110.4; FT–IR (Film, cm^{-1}): 3055, 3015, 2224, 1603, 1453, 1265, 851; GC/MS (70 eV) *m/z* (%): 255 [M^+, 100], 254 (98), 153 (28), 152 (30), 127 (22); HRMS (ESI) *m/z* calcd for $[C_{19}H_{13}N + H]^+$ 256.1121 ; found: 256.1126. Spectroscopic data for (*E*)-**2i** are in accordance with those reported in the literature.[10]



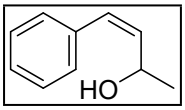
(*Z*)-3-Styrylpyridine (2j):[11] yellow oil, 80% (36 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.40–8.39 (m, 1H), 7.53–7.51 (m, 1H), 7.25–7.17 (m, 5H), 7.14–7.11 (m, 1H), 6.74 (d, *J* = 12.1 Hz, 1H), 6.52 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ 149.6, 147.5, 136.35, 136.32, 133.3, 132.9, 128.6, 128.5, 127.6, 126.1, 123.2; FT–IR (Film, cm^{-1}): 3079, 3053, 3023, 2960, 1585, 1492, 1446, 1024, 808; GC/MS (70 eV) *m/z* (%): 181 [M^+, 100], 180 (98), 152 (55), 127 (22), 77 (34); HRMS (ESI) *m/z* calcd for $[C_{13}H_{11}N + H]^+$ 182.0964; found: 182.0973.



(*Z*)-4-(2-(Naphthalen-1-yl)vinyl)pyridine (2k): colourless oil, 55% (32 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 8.31–8.30 (m, 2H), 8.02–8.00 (m, 1H), 7.91–7.88 (m, 1H), 7.83–7.81 (m, 1H), 7.54–7.50 (m, 2H), 7.37–7.33 (m, 1H), 7.29–7.28 (m, 2H), 6.95–6.93 (m, 2H), 6.77 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 149.2, 144.6, 133.9, 133.6, 133.3, 131.2, 129.5, 128.7, 128.5, 128.3, 126.3, 126.2, 125.5, 124.5, 123.5; FT–IR (Film, cm^{-1}): 3080, 3052, 3023, 2960, 1585, 1564, 1445, 1420, 808; GC/MS (70 eV) *m/z* (%): 231 [M^+, 100], 230 (98), 202 (36), 176 (10), 153 (29), 115 (11), 88 (13); HRMS (ESI) *m/z* calcd for $[C_{17}H_{13}N + H]^+$ 232.1121; found: 232.1126. Spectroscopic data for (*E*)-**2k** are in accordance with those reported in the literature.[12]

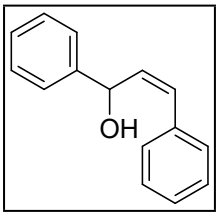


(*Z*)-3-Phenylacrylic acid (2l):[13] colourless solid, m.p. 66–67 °C, 70% (26 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 9.93 (br s, 1H), 7.60–7.57 (m, 2H), 7.37–7.30 (m, 3H), 7.04 (d, *J* = 12.7 Hz, 1H), 5.96 (d, *J* = 12.7 Hz, 1H) ; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 171.3, 145.4, 134.4, 129.9, 129.3, 128.1, 118.9; FT–IR (KBr, cm^{-1}): 3396 (br), 3057, 1694, 1631, 1433, 1228, 764; GC/MS (70 eV) *m/z* (%): 148 [M^+, 81], 147 (100), 131 (19), 103 (54), 77 (42), 51 (25); HRMS (ESI) *m/z* calcd for $[C_9H_8O_2 + Na]^+$ 171.0417; found: 171.0413.

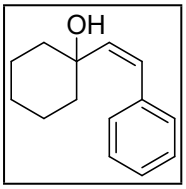


(*Z*)-4-Phenylbut-3-en-2-ol (2m):[14] dark yellow waxy solid, 87% (32 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.37–7.33 (m, 2H), 7.28–7.25 (m, 3H), 6.50 (d, *J* = 11.6 Hz, 1H), 5.70 (dd, *J* = 11.6, 9.1 Hz, 1H), 4.82–4.75 (m, 1H), 1.92 (br s, 1H), 1.36 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100.62 MHz, CDCl3): δ 136.6, 135.7, 129.9, 128.7, 128.2, 127.2, 64.1, 23.5; FT–IR (KBr, cm^{-1}):

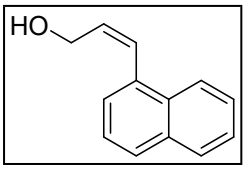
3376 (br), 3022, 3010, 2971, 2926, 1647, 1600, 1111, 734; GC/MS (70 eV) *m/z* (%): 148 [M^+, 55], 133 (39), 115(40) 105 (100), 91 (58), 77 (43), 55 (35); HRMS (ESI) *m/z* calcd for $[C_{10}H_{12}O + H]^+$ 149.0961; found: 149.0965.



(*Z*)-1,3-Diphenylprop-2-en-1-ol (2n):[9] pale yellow waxy solid, 97% (51 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.47–7.45 (m, 2H), 7.41–7.30 (m, 8H), 6.70 (d, *J* = 11.5 Hz, 1H), 5.95 (dd, *J* = 11.5, 9.4 Hz, 1H), 5.66 (d, *J* = 9.4 Hz, 1H), 2.43 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 143.2, 136.4, 133.3, 131.2, 128.8, 128.6, 128.3, 127.7, 127.4, 126.3, 69.9; FT–IR (KBr, cm^{-1}): 3372 (br), 3081, 3058, 3026, 2921, 1642, 1599, 1494, 1445, 1192, 763; GC/MS (70 eV) *m/z* (%): 210 [M^+, 35], 105 (100), 91 (15), 77 (30); HRMS (ESI) *m/z* calcd for $[C_{15}H_{14}O + H]^+$ 211.1117; found: 211.1123.



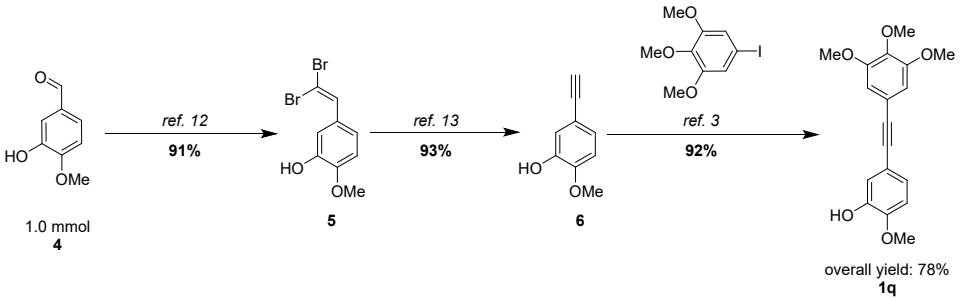
(*Z*)-1-Styrylcyclohexan-1-ol (2o):[15] white solid, 83% (42 mg), m.p. 51–53 °C. ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.40–7.38 (m, 2H), 7.33–7.29 (m, 2H), 7.24–7.21 (m, 1H), 6.49 (d, *J* = 12.7 Hz, 1H), 5.72 (d, *J* = 12.7 Hz, 1H), 1.67–1.55 (m, 6H), 1.53–1.42 (m, 4H), 1.29 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 138.7, 137.7, 129.0, 128.7, 128.0, 126.9, 72.8, 38.9, 25.3, 22.0; FT–IR (KBr, cm^{-1}): 3425 (br), 3057, 3021, 3002, 2931, 2855, 1597, 1492, 1447, 758; GC/MS (70 eV) *m/z* (%): 202 [M^+, 72], 159 (85), 145 (100), 131 (55), 117 (23), 103 (25), 91 (39), 77 (24); HRMS (ESI) *m/z* calcd for $[C_{14}H_{18}O + H]^+$ 203.1430 ; found: 203.1439.



(*Z*)-3-(Naphthalen-1-yl)prop-2-en-1-ol (2p):[10] colourless oil, 99% (46 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): δ 7.98–7.95 (m, 1H), 7.87–7.85 (m, 1H), 7.80–7.78 (m, 1H), 7.52–7.49 (m, 2H), 7.46–7.42 (m, 1H), 7.27–7.25 (m, 1H), 7.09 (d, *J* = 11.5 Hz, 1H), 6.14 (dt, *J* = 11.5, 6.6 Hz, 1H), 4.29 (d, *J* = 6.6 Hz, 1H), 1.52 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 133.42, 133. 40, 132.4, 131.6, 129.3, 128.4, 127.9, 126.5, 126.1, 125.9, 125.1, 124.7, 59.8; FT–IR (Film, cm^{-1}): 3339 (br), 3058, 3014, 2959, 2934, 1374, 1258, 1013, 781; GC/MS (70 eV) *m/z* (%): 184 [M^+, 75], 165 (100), 153 (92), 152 (58), 141 (98), 128 (53), 115 (25), 82 (15); HRMS (ESI) *m/z* calcd for $[C_{13}H_{12}O + H]^+$ 185.0961 ; found: 185.0968.

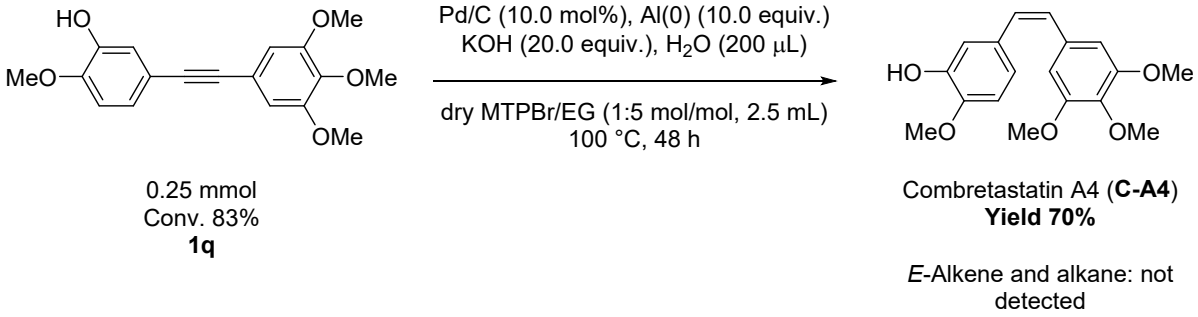
8 Synthesis of the Pharmacologically Active Molecule Combretastatin A4 (C-A4)

8.1 Synthesis of the Internal Alkyne 1q



For the preparation of the internal alkyne **7**, the starting aldehyde isovanilline **4**, was converted to the corresponding *gem*-dibromoolefine **5**, employing a well-known reaction.[16] Subsequently, starting from the alkene **5**, using a literature protocol,[17] the terminal alkyne **6** was obtained. Then, the synthetised **6** underwent a Sonogashira cross-coupling reaction with the 3,4,5-trimethoxy-iodo benzene, according to the procedure described in the Section 2,[3] giving the corresponding internal alkyne **1q**.

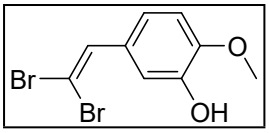
8.2 Semi-reduction of Internal Alkyne 1q to Combretastatin A4 (C-A4)



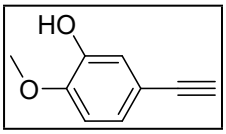
In a 50 mL round bottom flask, MTPBr (1.71 g, 4.8 mmol) and freshly distilled dry EG (1.48 g, 1.33 mL, 24.0 mmol) were added and gently heated up to 80 °C until 2.5 mL of a clear DES mixture was formed. After cooling the DES to r.t., internal alkyne **1q** (0.25 mmol), distilled water (200.0 μL), Pd/C 10 wt % (10.0 mol%, 0.025 mmol, 26.5 mg), Al(0) powder (10.0 equiv., 2.5 mmol, 67.5 mg) were sequentially added. The mixture was stirred for about 1 min. then, KOH (20.0 equiv., 5.0 mmol, 280 mg) was carefully added to the mixture, 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 48 hours at 100 °C. After this time, the reaction mixture was cooled to room temperature, water (5.0 ml) and HCl 10% v/v were added to the mixture up to pH = 4. The reaction mixture was then extracted with

Et_2O (5 ml x 4). 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 flash chromatography column on silica gel (using as eluent petroleum ether/AcOEt 70/30) to obtain the desired combretastatin A4 (**C-A4**) in 70% yield.

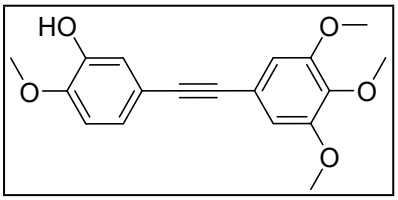
8.3 Characterization Data for the Compounds 5, 6, 1q and Combretastatin A4 (C-A4)



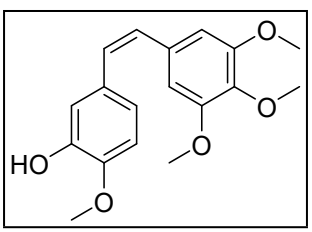
5-(2,2-dibromovinyl)-2-methoxyphenol (5): pale yellow solid, m.p. 92°C, 91% (280 mg).^{1}H NMR (400.12 MHz, $CDCl_3$): 7.36 (s, 1H), 7.23–7.22 (m, 1H), 7.05–7.02 (m, 1H), 6.84–6.82 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): 146.7, 145.2, 136.2, 128.5, 121.1, 114.2, 110.2, 87.6, 55.9; FT–IR (KBr, cm^{-1}): 3510 (br), 1590; GC/MS (70 eV) *m/z* (%): 309 [M^++ 4, 50], 307 [M^++ 2, 100], 305 [M^+, 51], 292 (93), 264 (28), 184 (13), 148 (31), 133 (50), 105 (57), 77 (21), 51 (41); HRMS (ESI) *m/z* calcd for $[C_9H_8Br_2O_2 + H]^+$ 306.8964 ; found: 306.8967.



5-ethynyl-2-methoxyphenol (6): white waxy solid, 93% (125 mg). ^{1}H NMR (400.12 MHz, $CDCl_3$): 7.06–7.05 (m, 1H), 7.04–7.02 (m, 1H), 6.79–6.77 (m, 1H), 5.65 (s, 1H), 3.89 (s, 3H), 2.98 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$): 147.3, 145.2, 124.8, 118.0, 114.8, 110.3, 83.5, 75.6, 55.9; FT–IR (KBr, cm^{-1}): 3500 (br), 3104, 2990; GC/MS (70 eV) *m/z* (%): 148 [M^+, 100], 133 (95), 105 (75), 77 (15), 51 (30); HRMS (ESI) *m/z* calcd for $[C_9H_8O_2 + H]^+$ 149.0597; found: 149.0592.



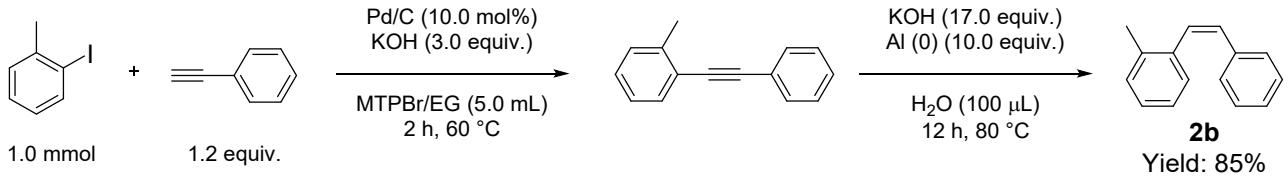
2-methoxy-5-((3,4,5-trimethoxyphenyl)ethynyl)phenol (1q): pale yellow solid, m.p. 94–96 °C, 92% (242 mg).^{1}H NMR (400.12 MHz, $CDCl_3$): 7.09–7.05 (m, 2H), 6.83–6.81 (m, 1H), 6.75 (s, 2H), 5.65 (s, 1H), 3.91 (s, 3H), 3.88 (s, 6H), 3.86 (s, 3H); ^{13}C NMR (100.62 MHz, $CDCl_3$): 153.0, 146.9, 145.3, 138.5, 124.2, 118.5, 117.4, 115.9, 110.4, 108.6, 88.4, 87.8, 60.9, 60.3, 56.1, 55.9; FT–IR (KBr, cm^{-1}): 3480 (br), 2928, 2860, 1675, 1501, 1439, 1390, 1255; GC/MS (70 eV) *m/z* (%): 314 [M^+, 100], 299 (90), 271 (20), 241 (15), 211 (10), 157 (20); HRMS (ESI) *m/z* calcd for $[C_{18}H_{18}O_5 + H]^+$ 315.1227; found: 315.1222.



(*Z*)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol [Combretastatin A4 (C-A4)]: dark yellow solid, m.p. 114-116°C, 70% (55 mg).^{1}H NMR (400.12 MHz, $CDCl_3$): 6.92–6.923 (m, 1H), 6.81–6.78 (m, 1H), 6.74–6.72 (m, 1H), 6.52 (s,

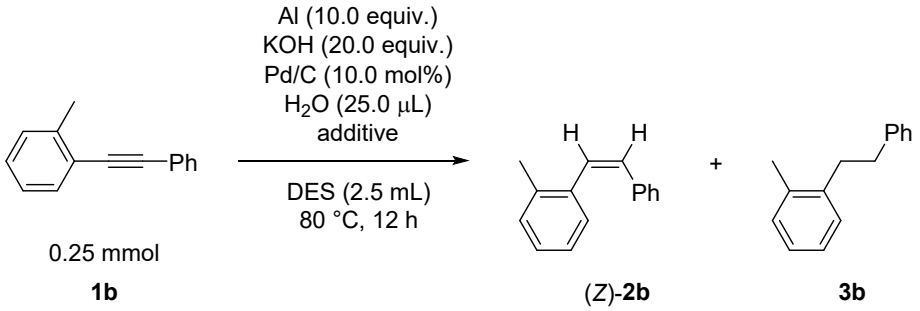
2H), 6.47 (d, *J* = 12.2 Hz, 1H), 6.41 (d, *J* = 12.2 Hz, 1H), 5.56 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.70 (s, 6H); ^{13}C NMR (100.62 MHz, $CDCl_3$): 152.8, 145.7, 145.1, 137.0, 132.6, 130.5, 129.4, 128.9, 121.1, 115.0, 110.2, 105.9, 60.9, 55.87, 55.86.; FT–IR (KBr, cm^{-1}): 3747 (br), 3450, 2918, 2855, 1636, 1579, 1509, 1458, 1270, 1125, 1010, 750; GC/MS (70 eV) *m/z* (%): 316 [M^+, 100], 301 (90), 241 (10), 226 (10), 115 (10); HRMS (ESI) *m/z* calcd for $[C_{18}H_{20}O_5 + H]^+$ 317.1384; found: 317.1387.

9 One-pot Synthesis of (*Z*)-1-Methyl-2-styrylbenzene 2b Starting from 2-Iodotoluene and Phenylacetylene.



In a 50 mL triple-neck round bottomed flask equipped with magnetic stirring**,** MTPBr (3.44 g) and dry EG (2.6 mL) were added. The mixture was heated at 80 °C and stirred until 5 mL of a clear and colourless eutectic mixture was formed. The DES was cooled at r.t. and degassed under vacuum/N_2 atmosphere for 3 times. Afterwards, 2-iodotoluene (1.0 mmol, 218 mg), Pd/C 10% wt (10.0 mol%, 0.1 mmol, 106.4 mg), KOH (3.0 mmol, 168 mg) and phenylacetylene (1.2 mmol, 122.4 mg, 131 µL) were subsequentially added. The mixture was stirred for 2 hours at 60 °C. The reaction was monitored by GC-MS until complete consumption of the starting material. After this time, distilled water (100 µL), aluminum powder (10.0 mmol, 270 mg) and KOH (17.0 mmol, 952 mg) were added to the mixture. The system was quickly sealed with a rubber stopper equipped with a balloon to prevent H_2 overpressure. The reaction mixture was stirred for 12 hours at 80 °C. Then, the mixture was cooled to room temperature and 10 ml of water was added. The mixture was extracted with AcOEt (10 mL x 3). The reunited organic phases were dried over Na_2SO_4, filtered through a celite pad and evaporated under reduced pressure. The crude was purified by flash chromatography column on silica gel using hexane as the eluent to obtain the desired (*Z*)-alkene **2b** in 85% yield (165 mg).

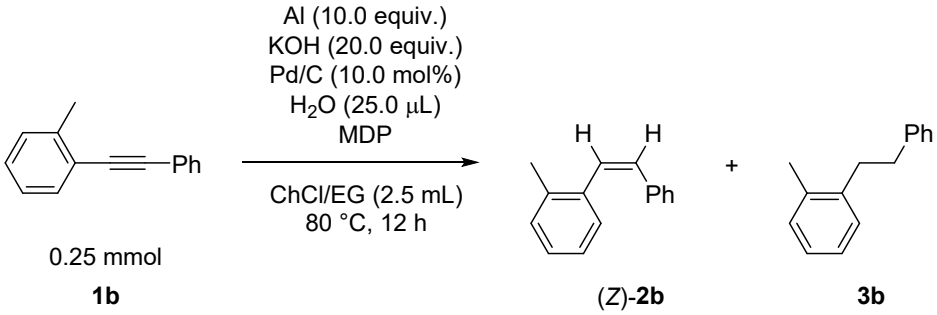
10 Table S5: Supplementary Details for the Influence of DESs and Additives in the Semi-reduction of Alkyne 1b to (*Z*)-Alkene 2b.



Entry	DES (mol/mol)	Additive (equiv.)	**1b** Conv. (%)[a]	(*Z*)-**2b** Yield (%)[a]	**3b** Yield (%)[a]
1	ChCl/urea (1:2)	MDP (0.35)	82	65	17
2	ChCl/EG (1:2)	PPh_3 (0.35)	100	77	20
3	ChCl/EG (1:2)	MTPBr (3.0)	100	ND	99
4	ChCl/EG (1:2)	MDPO (3.0)	100	ND	99

ND = not detected. MDP = methyldiphenylphosphine. MTPBr = methyltriphenylphosphonium bromide. MDPO = methyldiphenylphosphine oxide. [a] Calculated *via* ^{1}H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone).

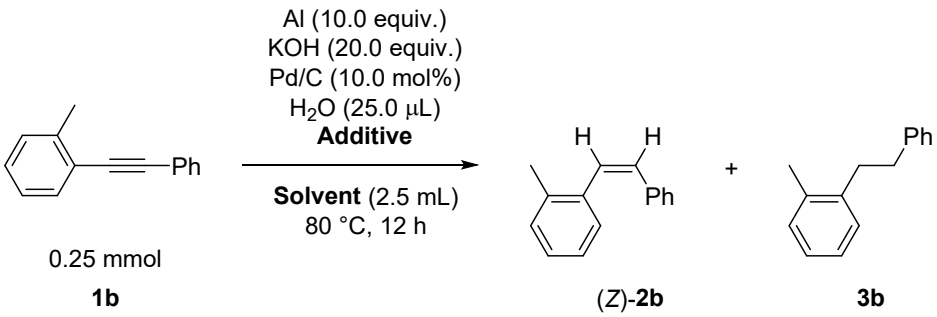
11 Table S6: Supplementary Details for the Influence of MDP in the Semi-reduction of Alkyne 1b to (*Z*)-Alkene 2b in ChCl/EG DES



Entry	MDP (mol%)	**1b** Conv. (%)[a]	(*Z*)-**2b** Yield (%)[a]	**3b** Yield (%)[a]
1	-	>99	ND	98
2	10	>99	30	70
3	20	>99	50	50
4	35	>99	85	15
5	50	55	50	5

ND = not detected. MDP = methyldiphenylphosphine. [a] Calculated *via* ^{1}H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone).

12 Table S7: Supplementary Details for the Influence of EG-based DESs in the Semi-reduction of Alkyne 1b to (*Z*)-Alkene 2b



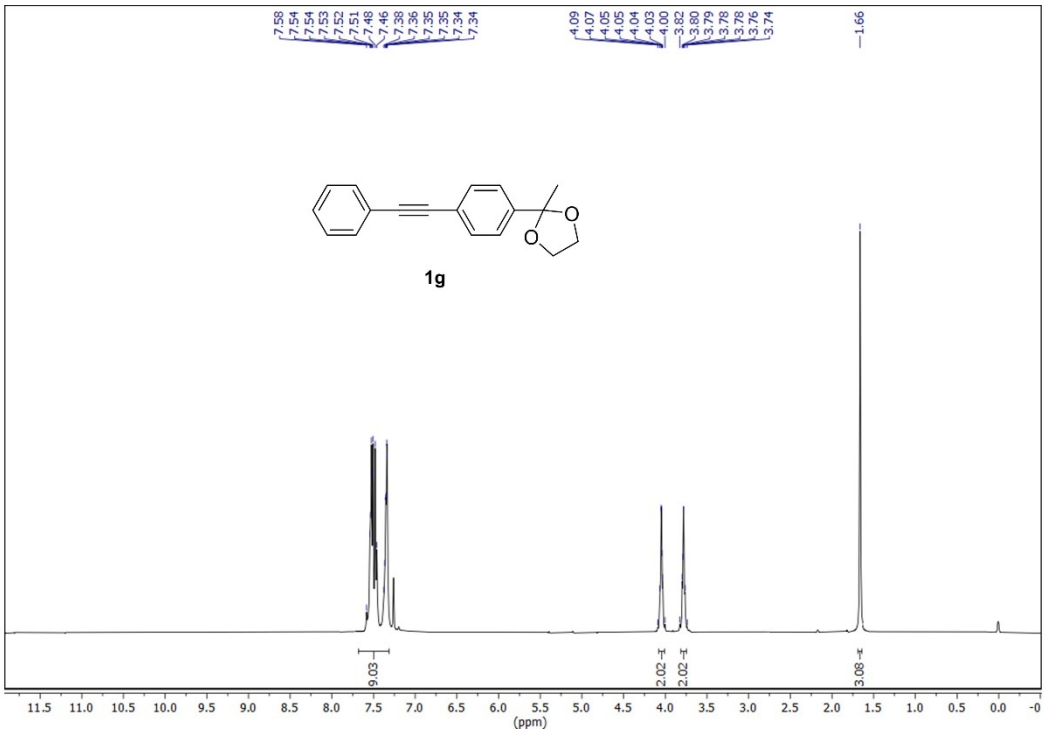
0.25 mmol **1b** (*Z*)-**2b** **3b**

Entry	Solvent	Additive (mol%)	**1b** Conv. (%)a	(*Z*)-**2b** Yield (%)[a]	**3b** Yield (%)[a]
1	EG	-	<5	traces	traces
2	ChCl/gly	MDP (35)[b]	>99	30	70
3	ChCl/urea	MDP (35)[b]	>99	30	70
4[c]	ChCl/EG	Ph_3P	>99	77	20
5	ChCl/EG	MDPO[d] (300)	>99	-	>99

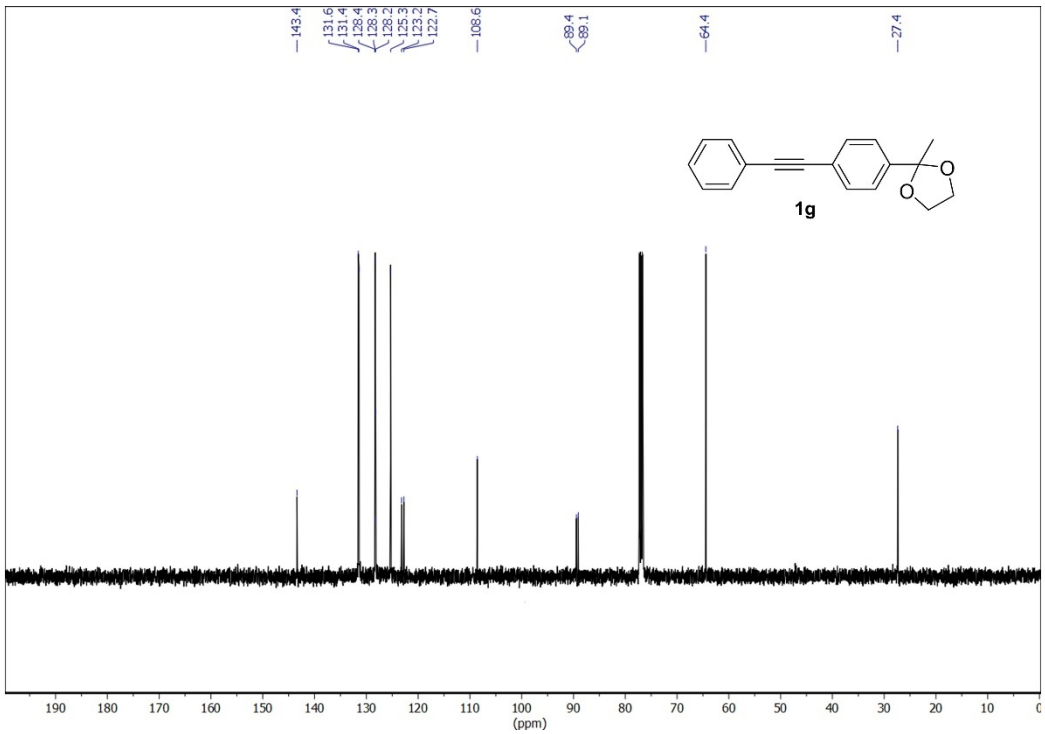
[a] Calculated *via* ^{1}H NMR analysis of the crude reaction mixture using the internal standard technique (NMR internal standard: dimethyl sulfone). [b] MDP = methyldiphenylphosphine. [c] 5% of alkene (*E*)-**2b** were detected in the crude. [d] MDPO = methyldiphenylphosphine oxide

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

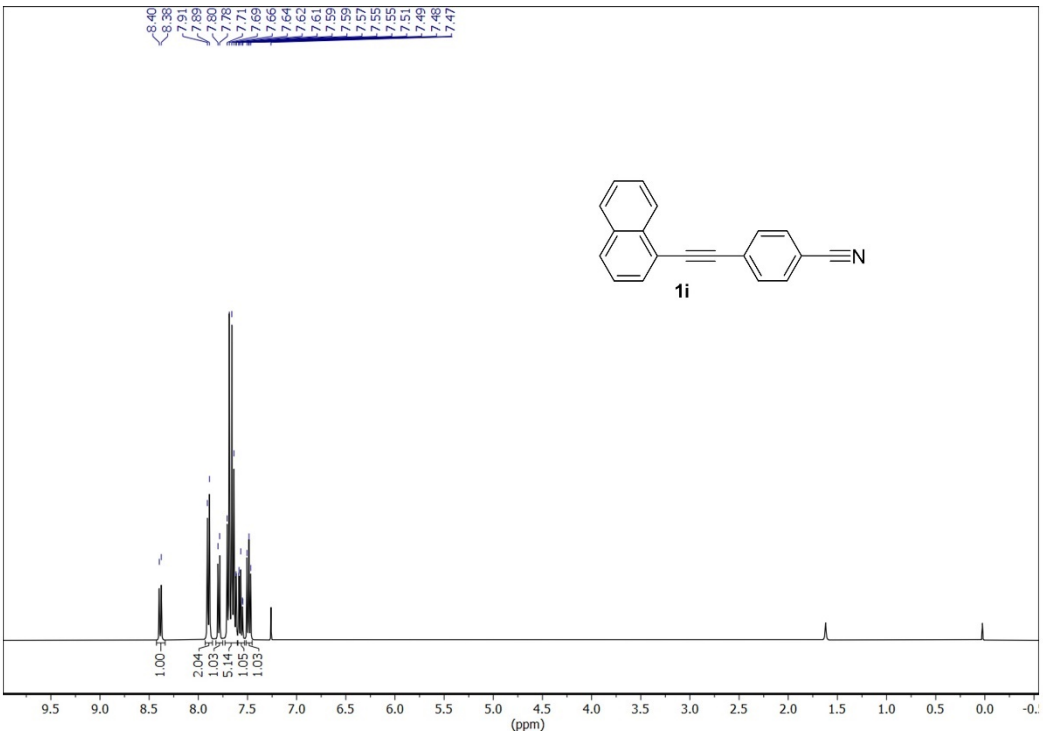
^{1}H NMR 400.12 MHz, $CDCl_3$



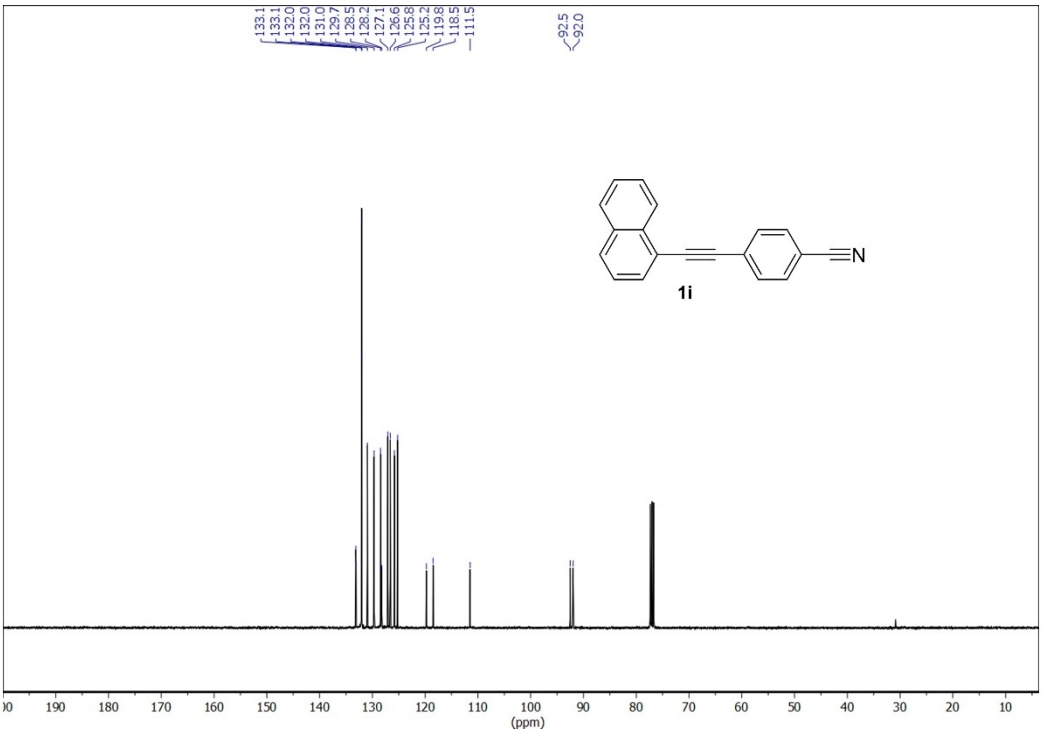
^{13}C NMR 100.62 MHz, $CDCl_3$



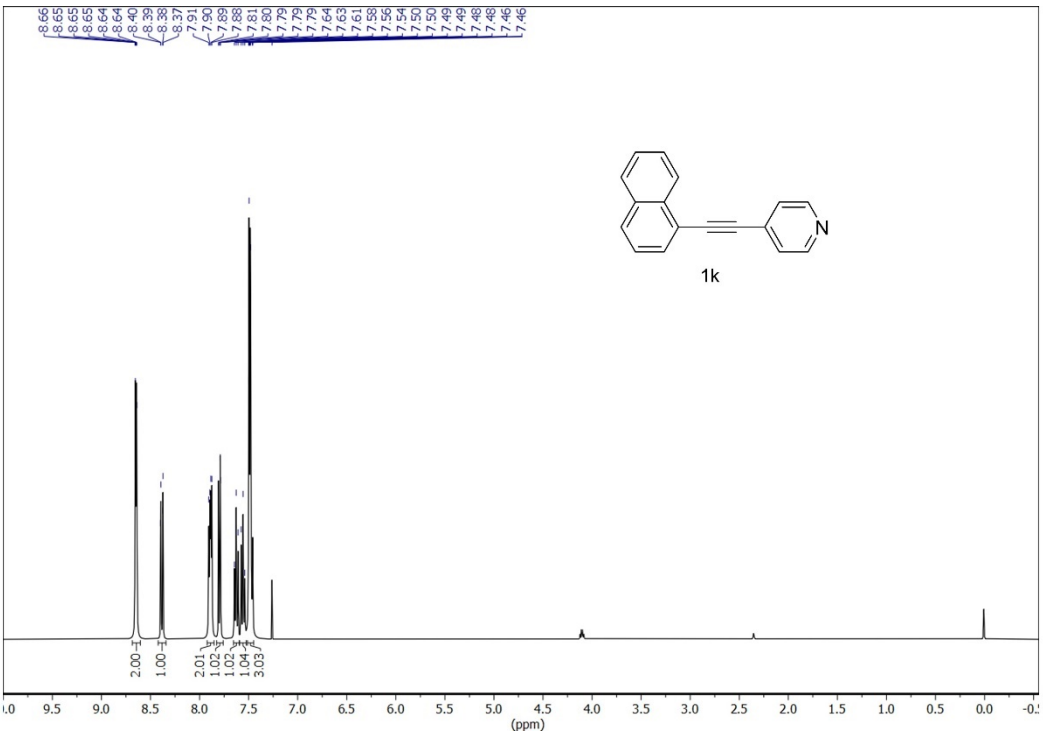
^{1}H NMR 400.12 MHz, $CDCl_3$



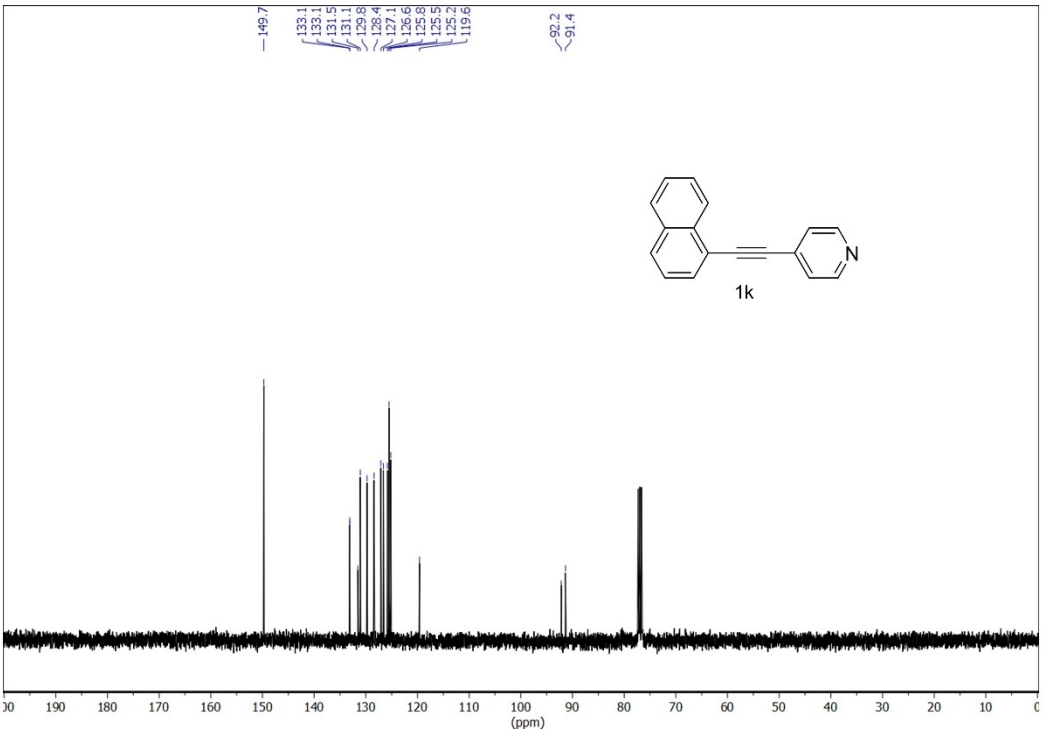
^{13}C NMR 100.62 MHz, $CDCl_3$



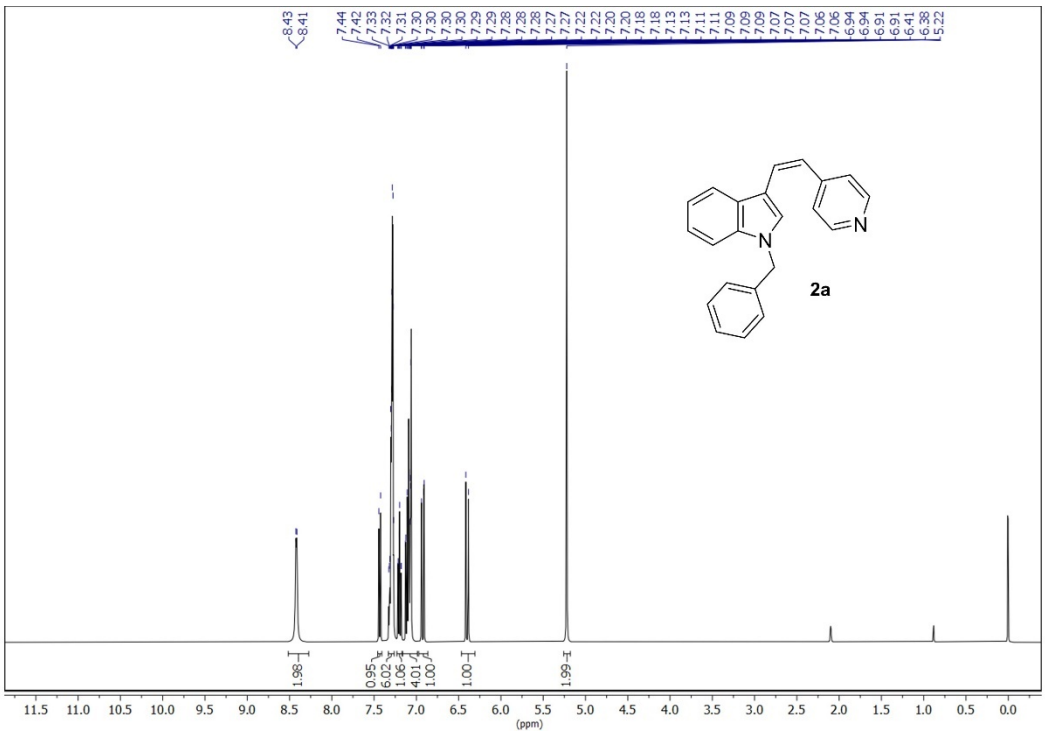
^{1}H NMR 400.12 MHz, $CDCl_3$



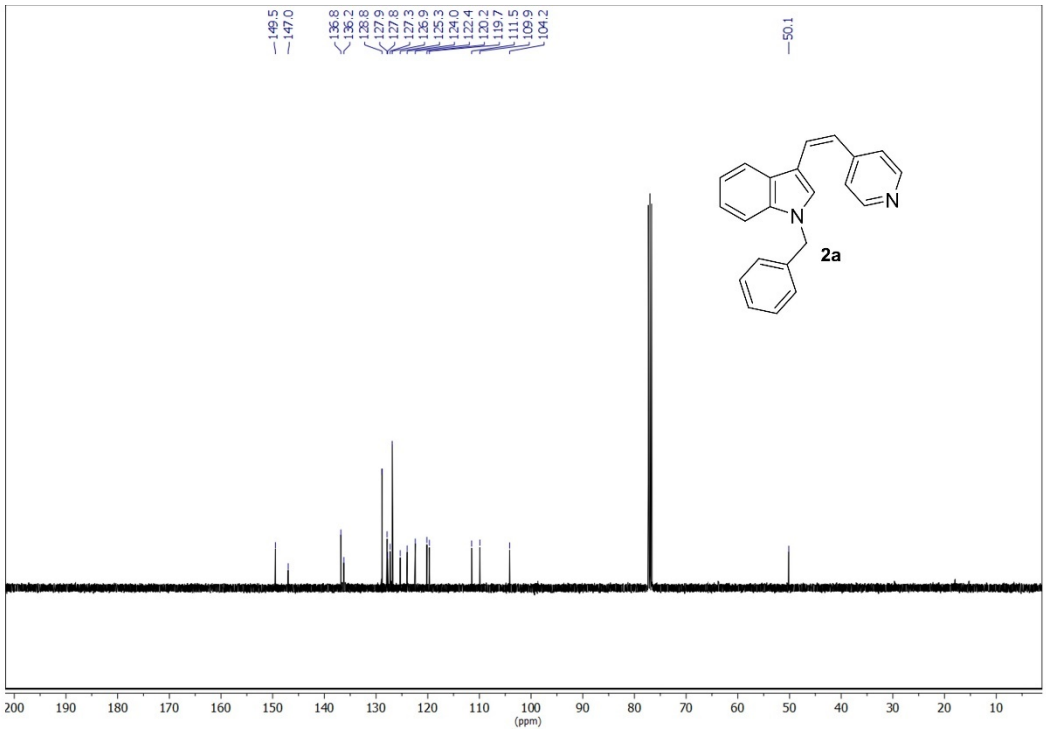
^{13}C NMR 100.62 MHz, $CDCl_3$



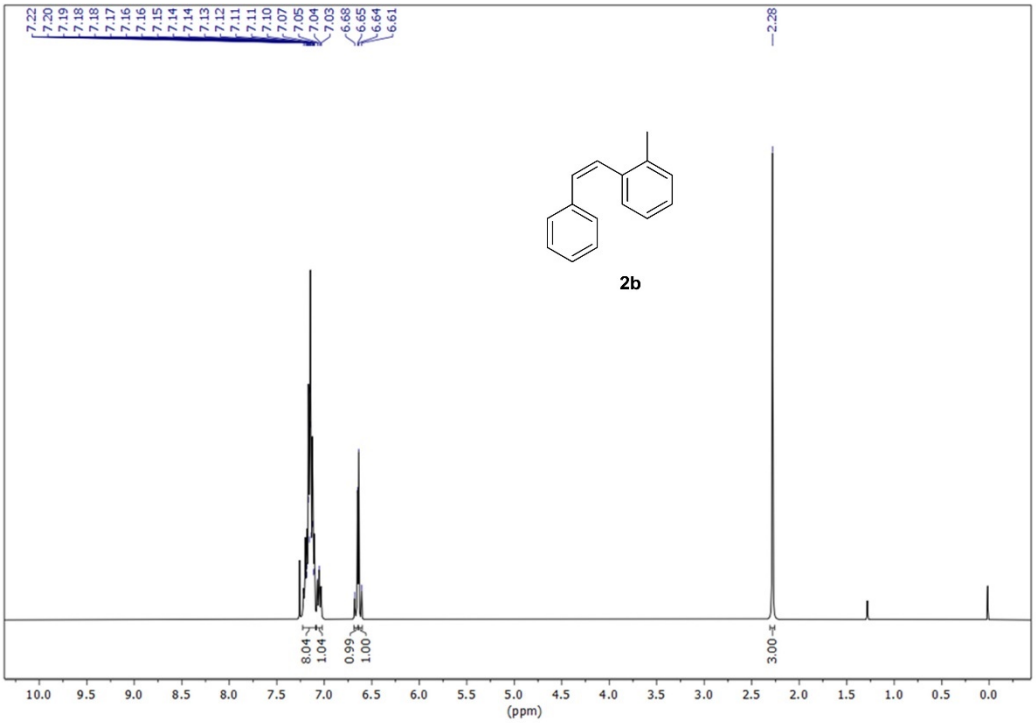
^{1}H NMR 400.12 MHz, $CDCl_3$



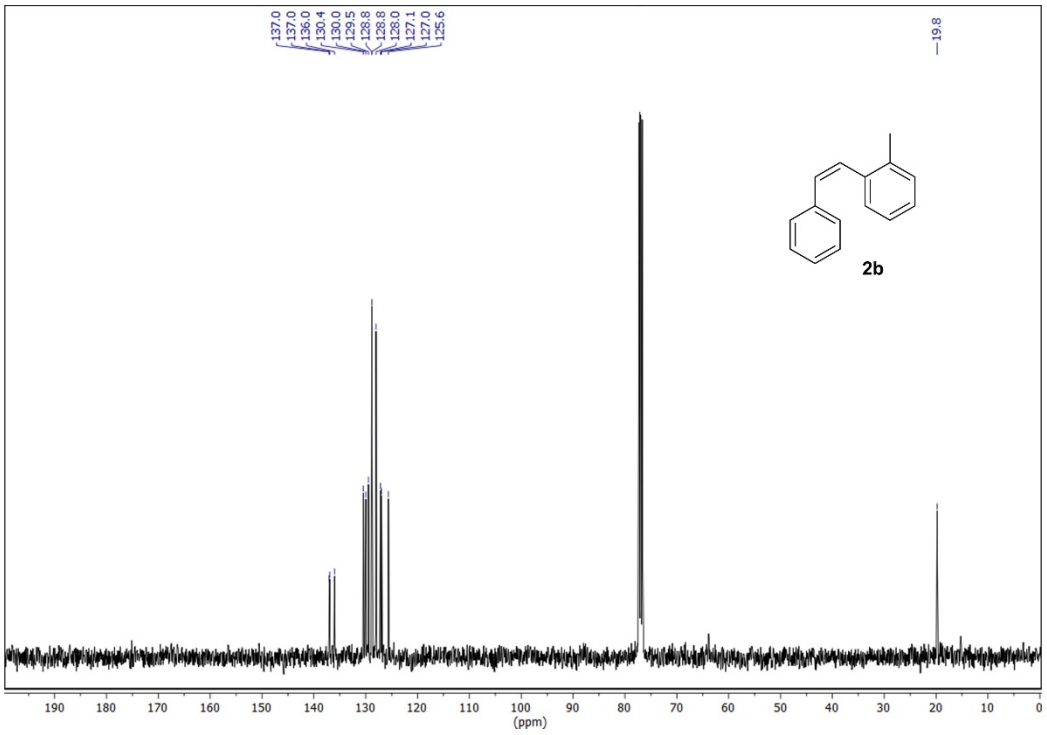
^{13}C NMR 100.62 MHz, $CDCl_3$



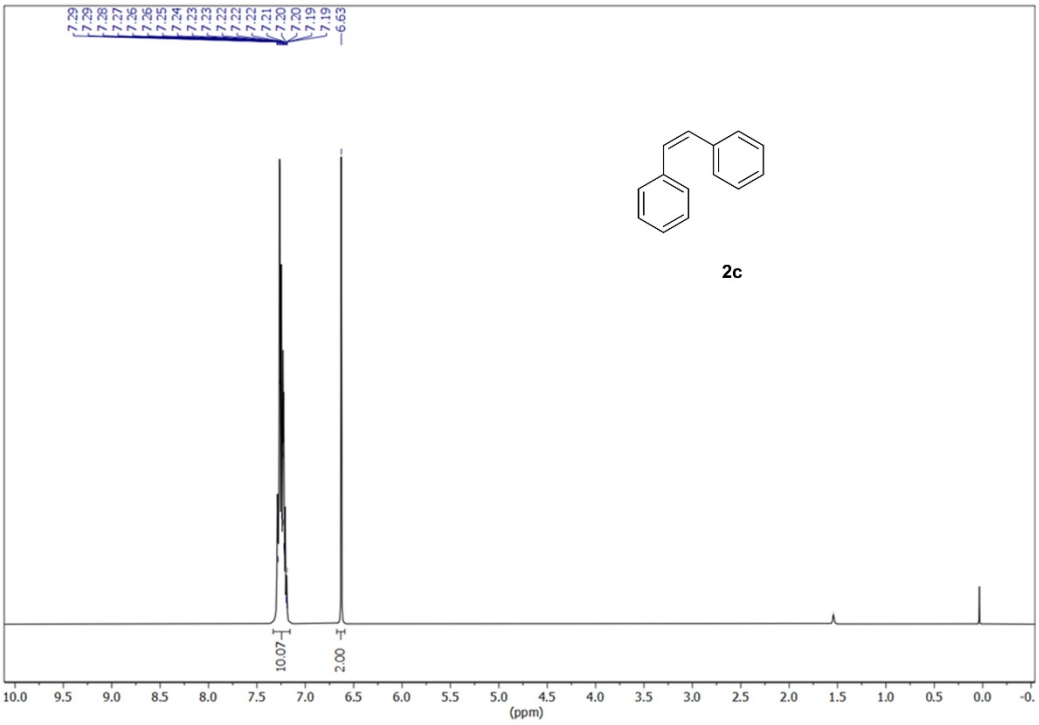
^{1}H NMR 400.12 MHz, $CDCl_3$



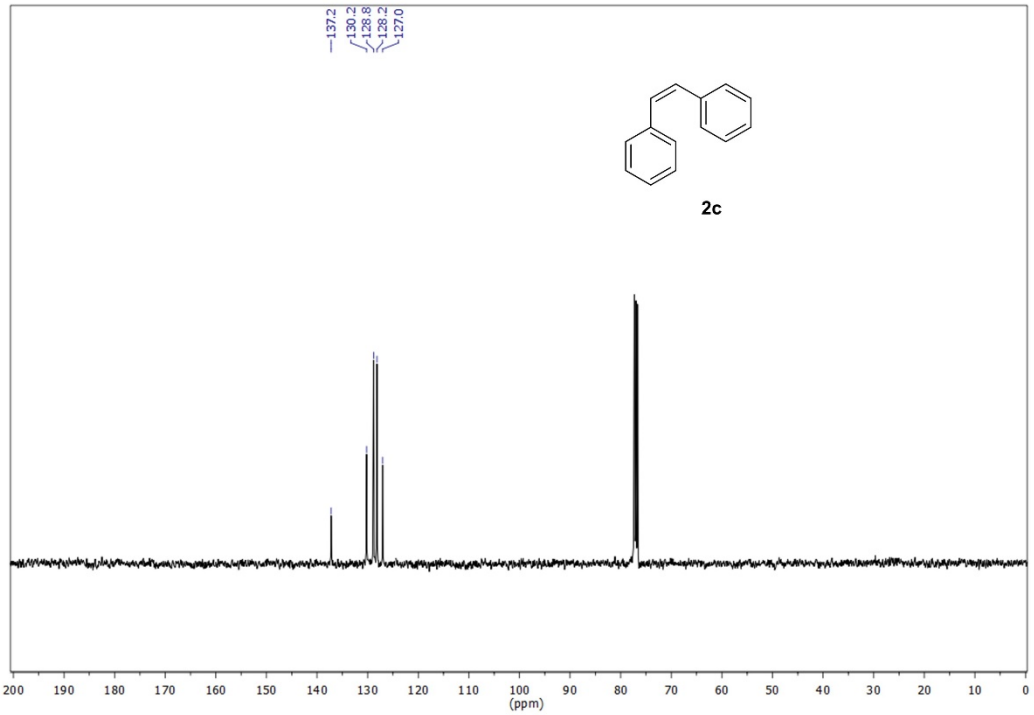
^{13}C NMR 100.62 MHz, $CDCl_3$



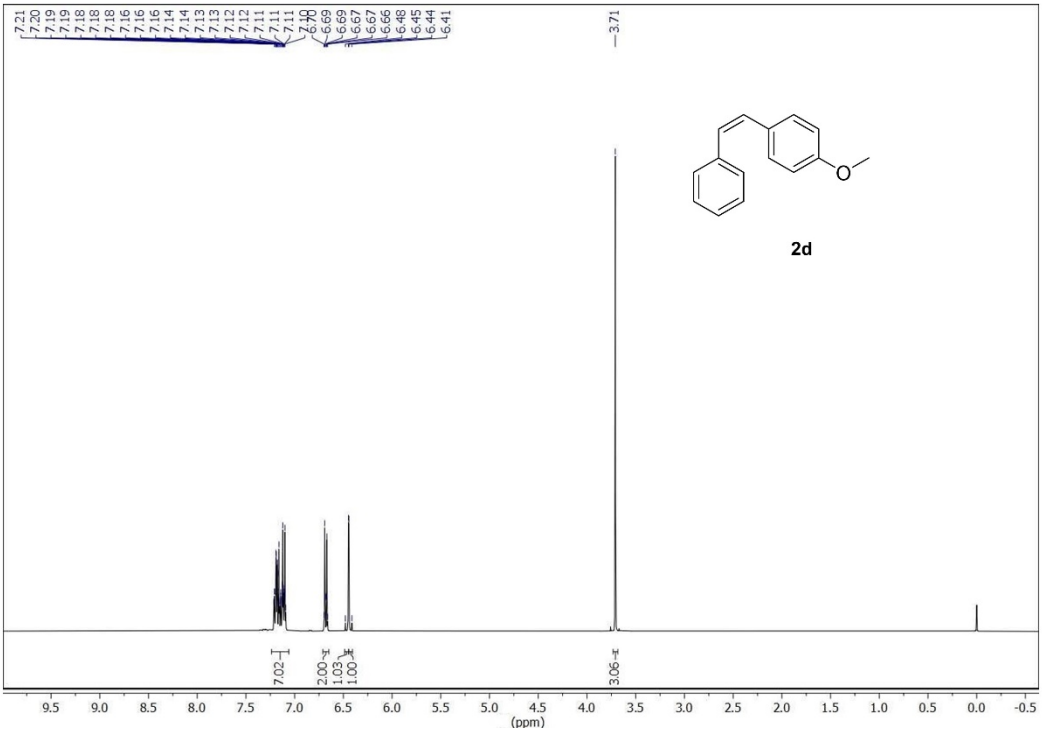
^{1}H NMR 400.12 MHz, $CDCl_3$



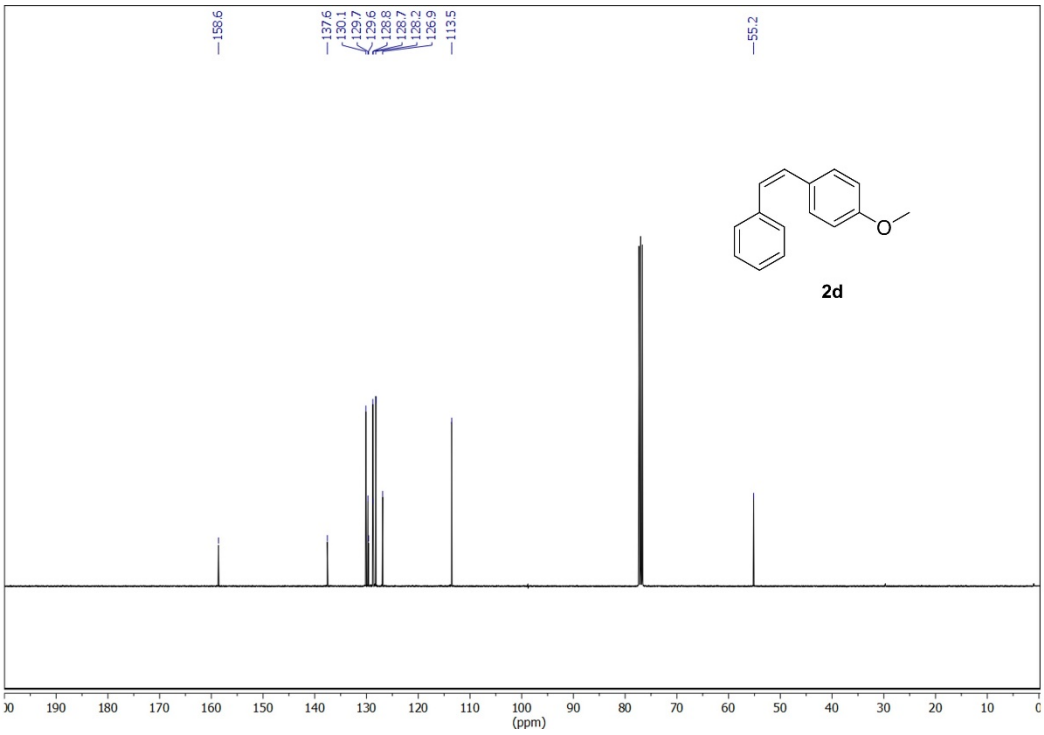
^{13}C NMR 100.62 MHz, $CDCl_3$



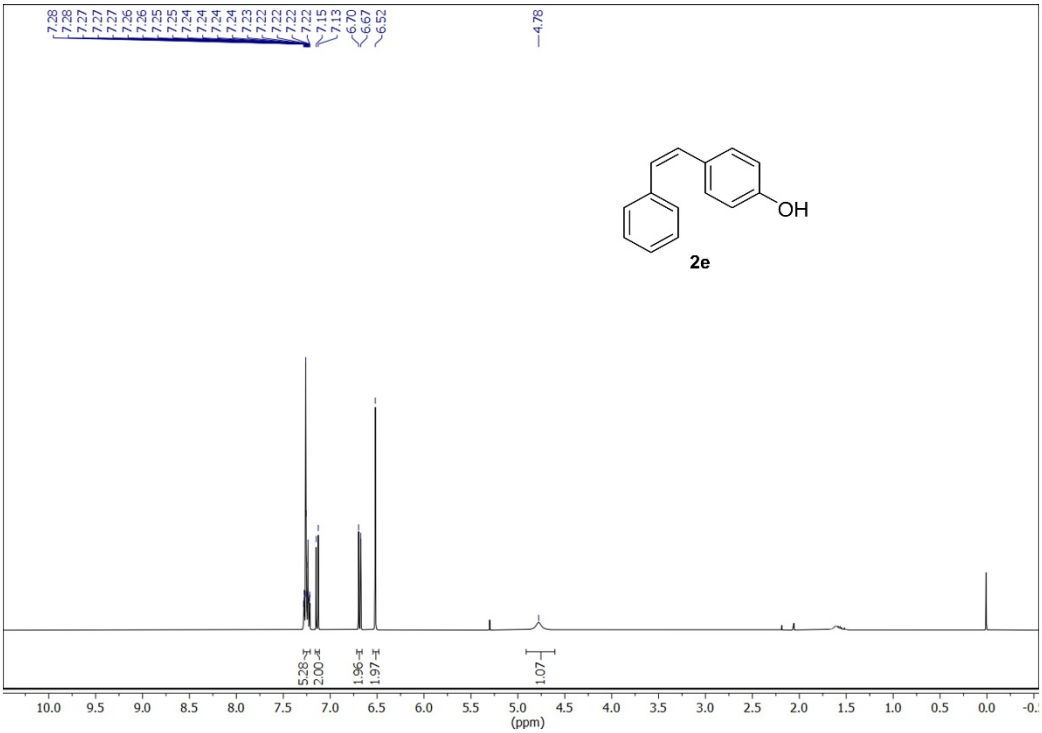
^{1}H NMR 400.12 MHz, $CDCl_3$



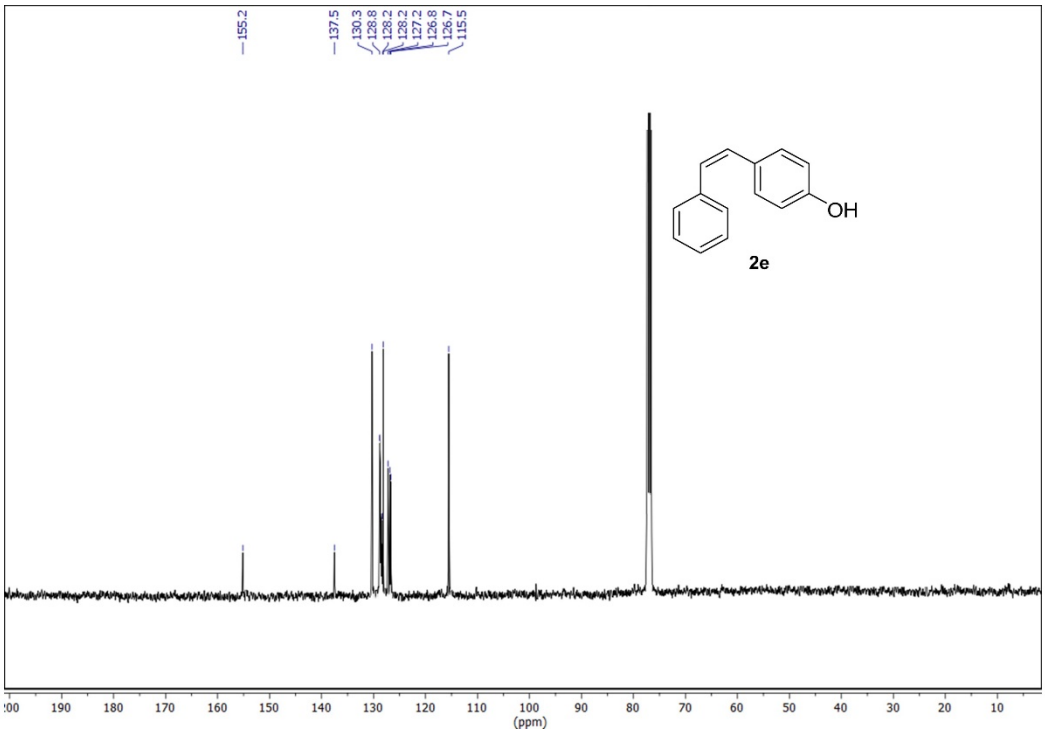
^{13}C NMR 100.62 MHz, $CDCl_3$



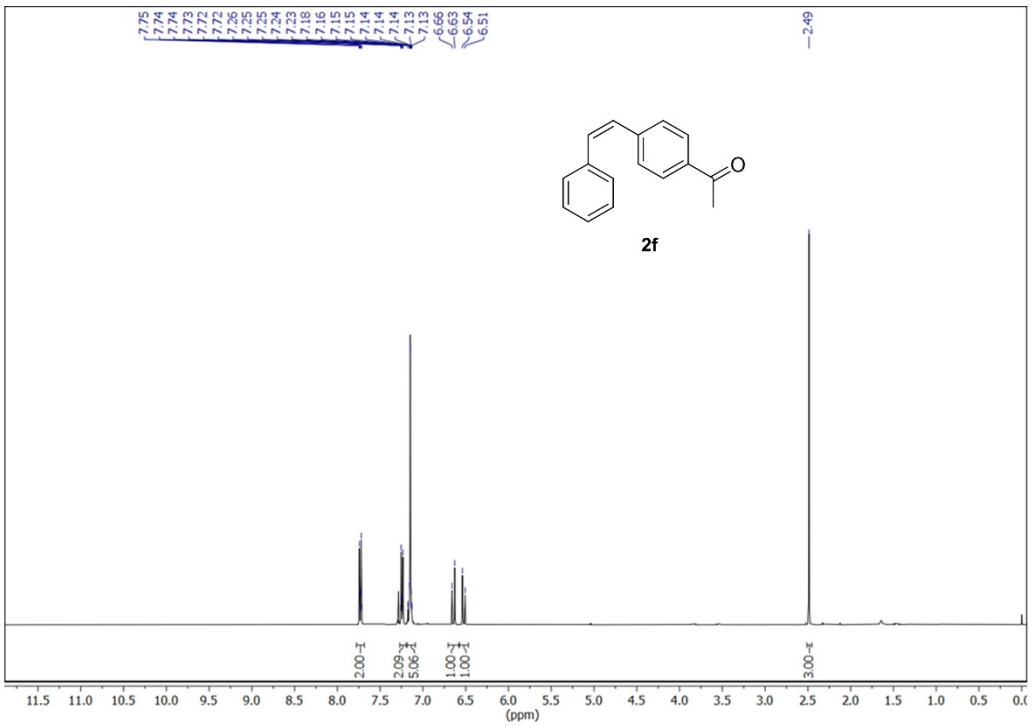
^{1}H NMR 400.12 MHz, $CDCl_3$



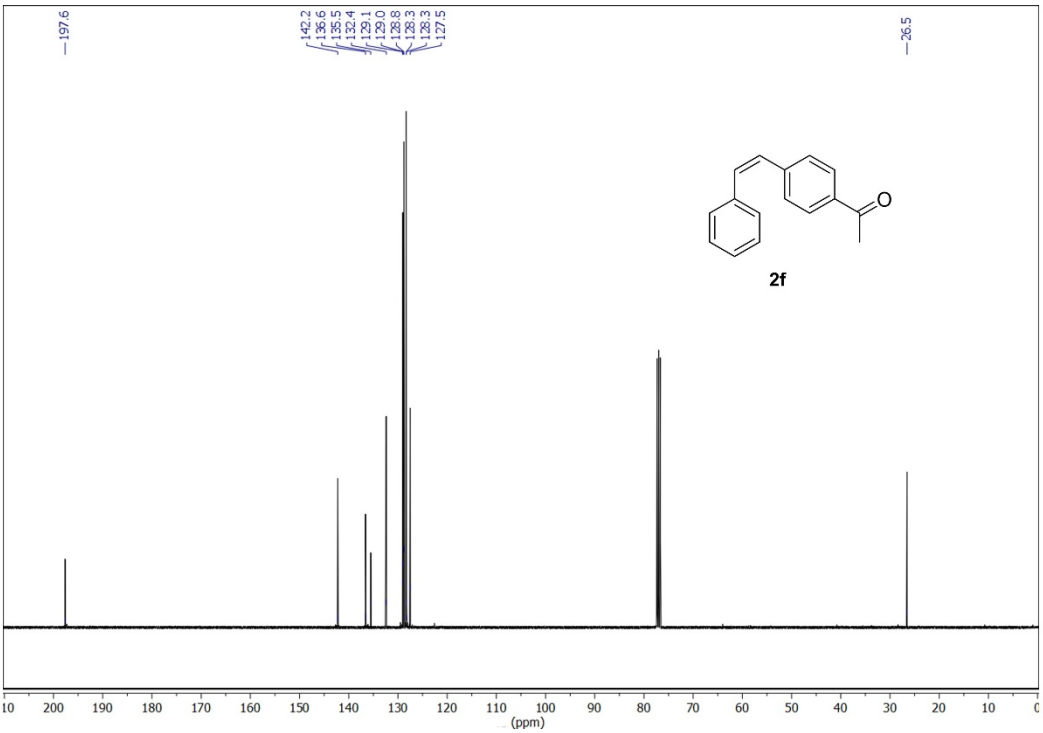
^{13}C NMR 100.62 MHz, $CDCl_3$



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



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



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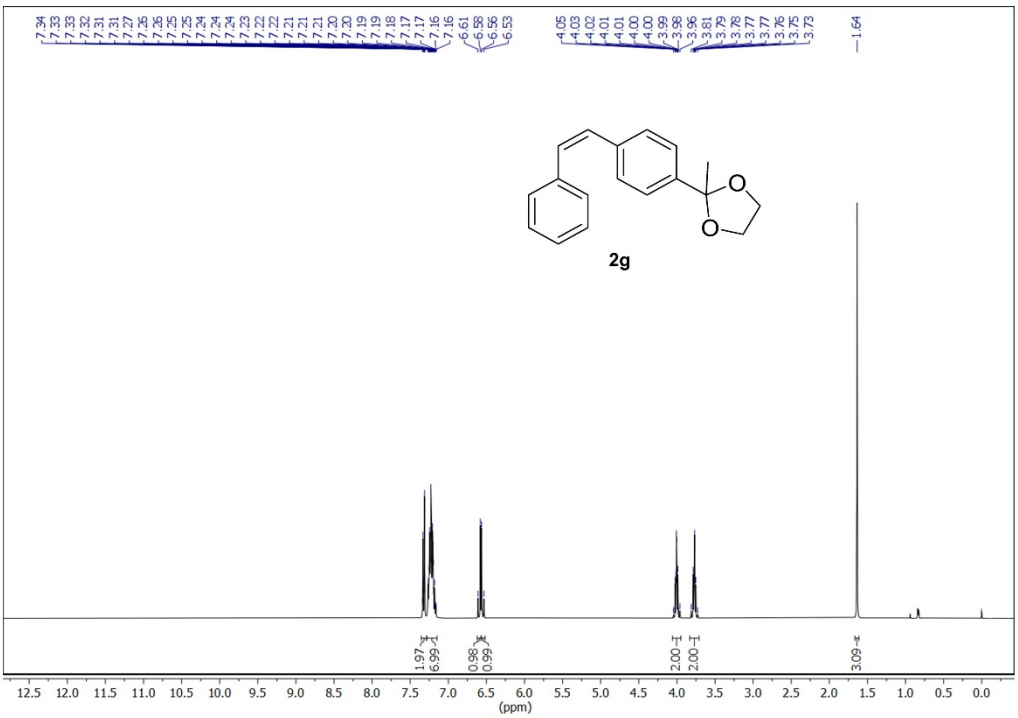
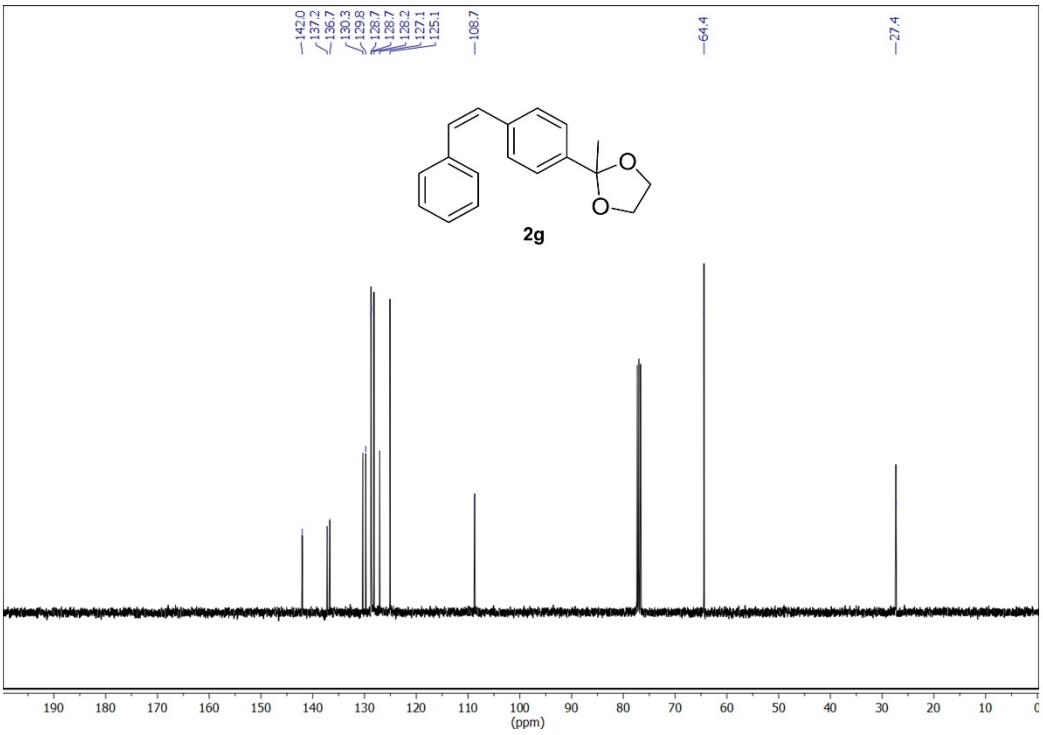


^{13}C NMR 100.62 MHz, $CDCl_3$



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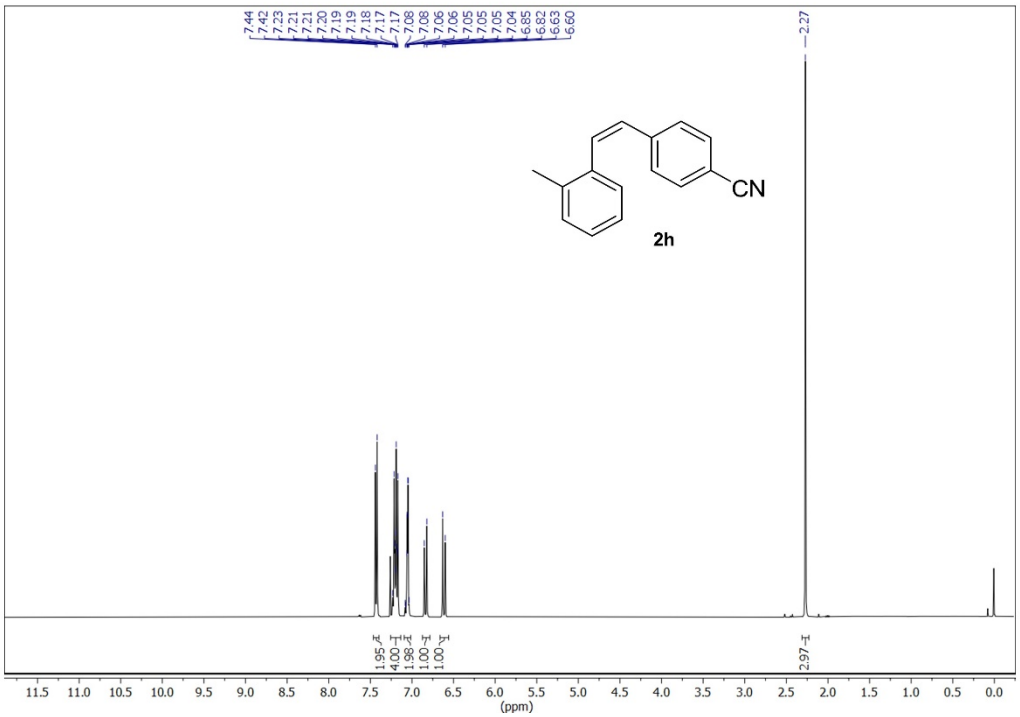
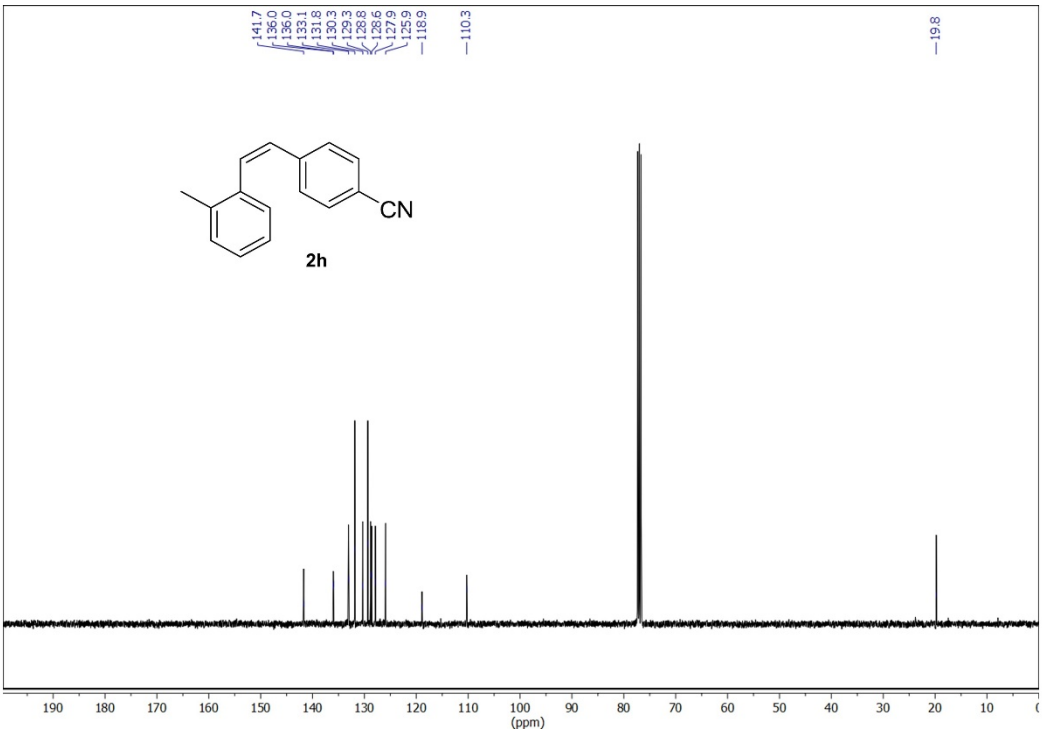
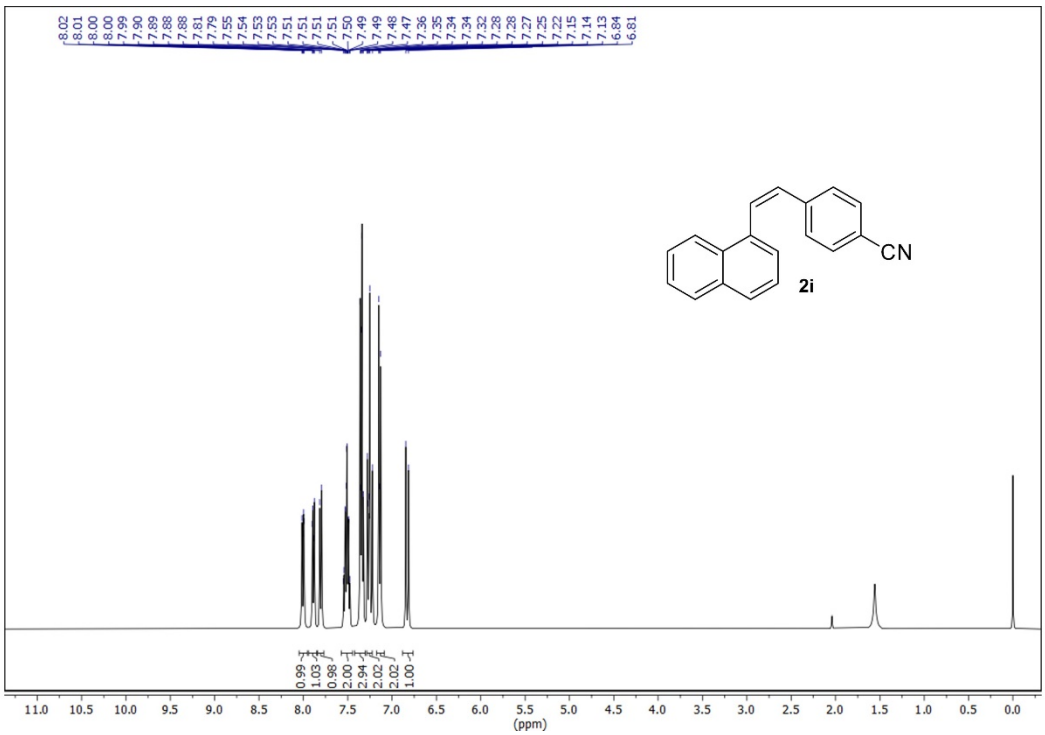


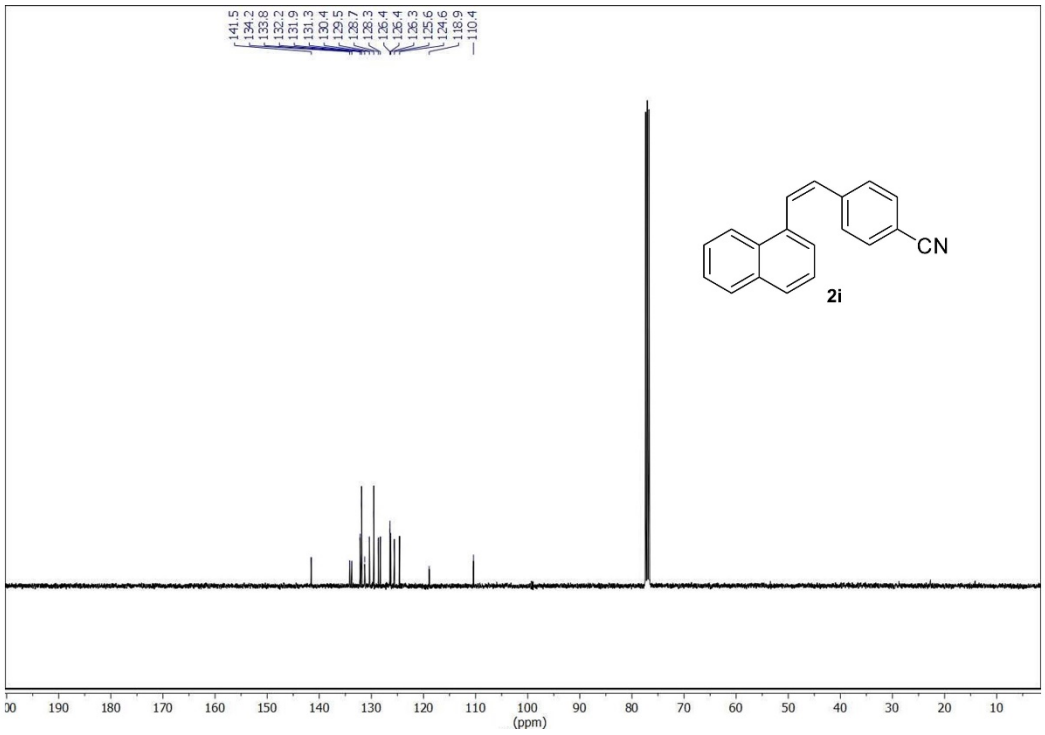
^{13}C NMR 100.62 MHz, $CDCl_3$



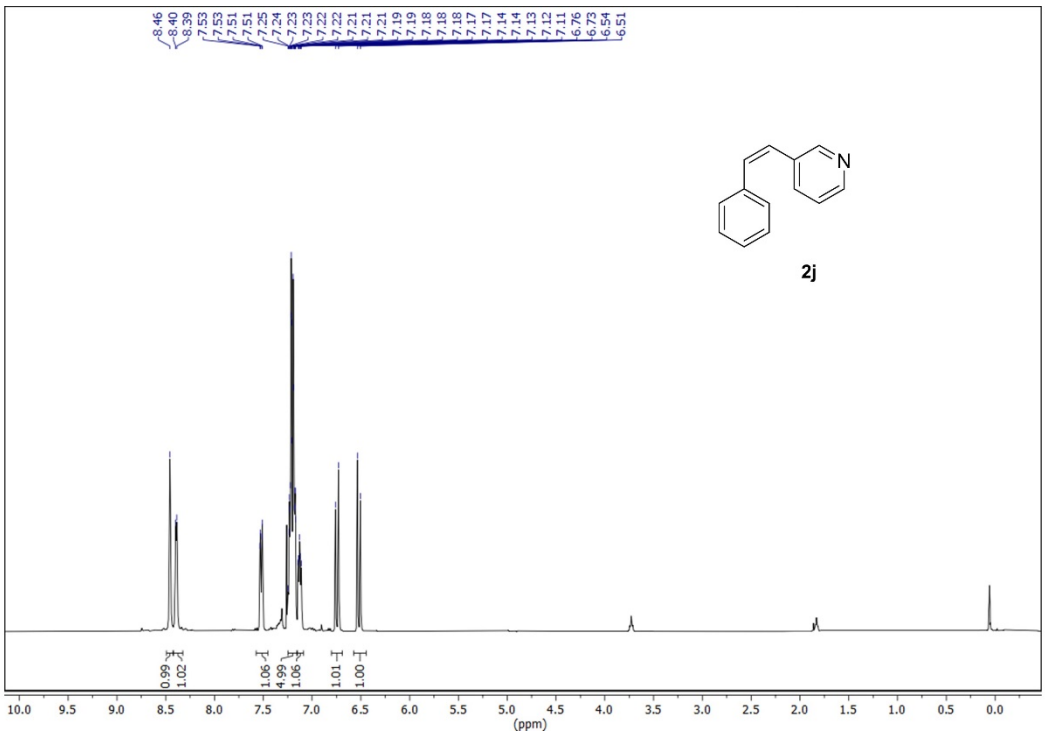
^{1}H NMR 400.12 MHz, $CDCl_3$



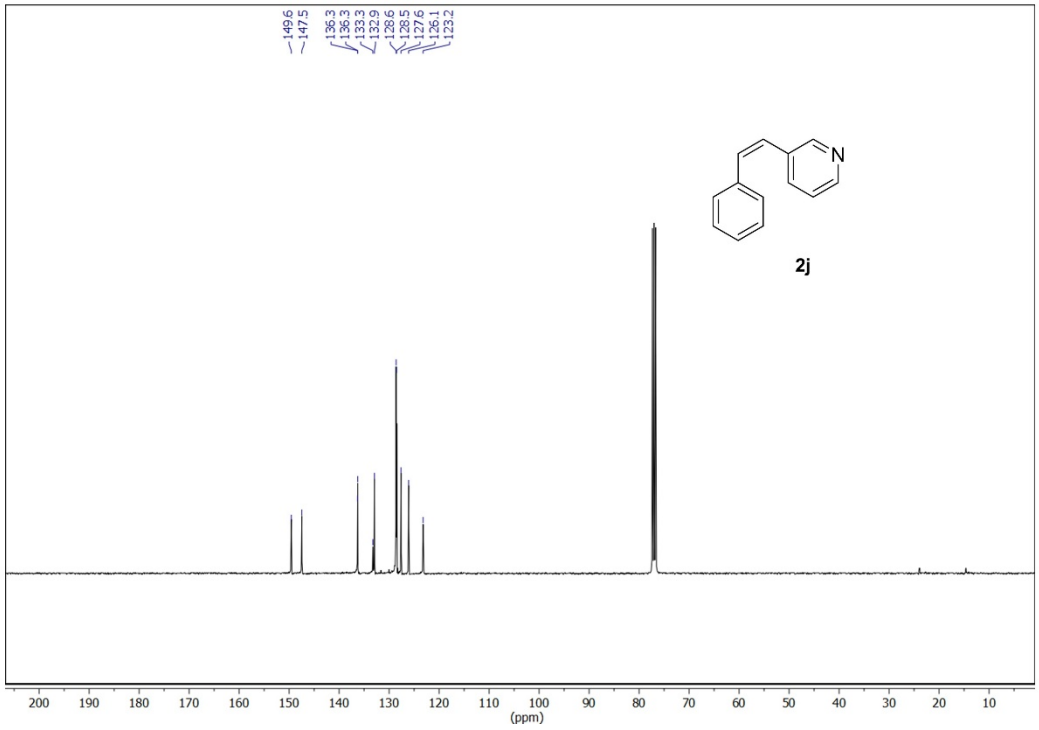
^{13}C NMR 100.62 MHz, $CDCl_3$



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



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



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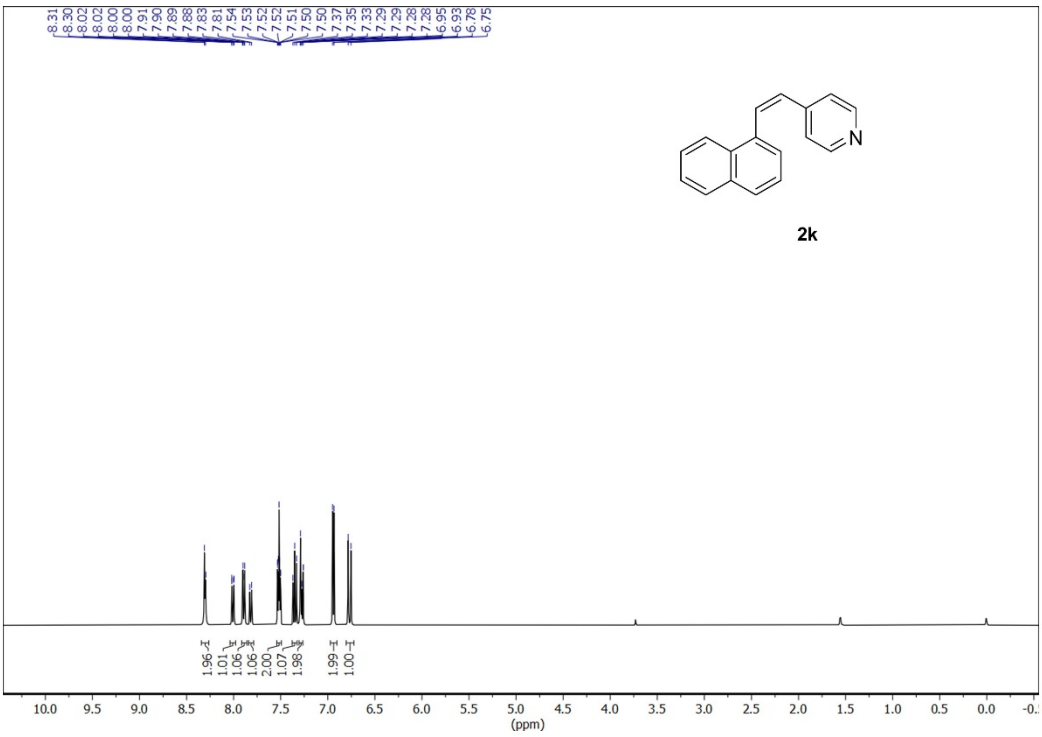

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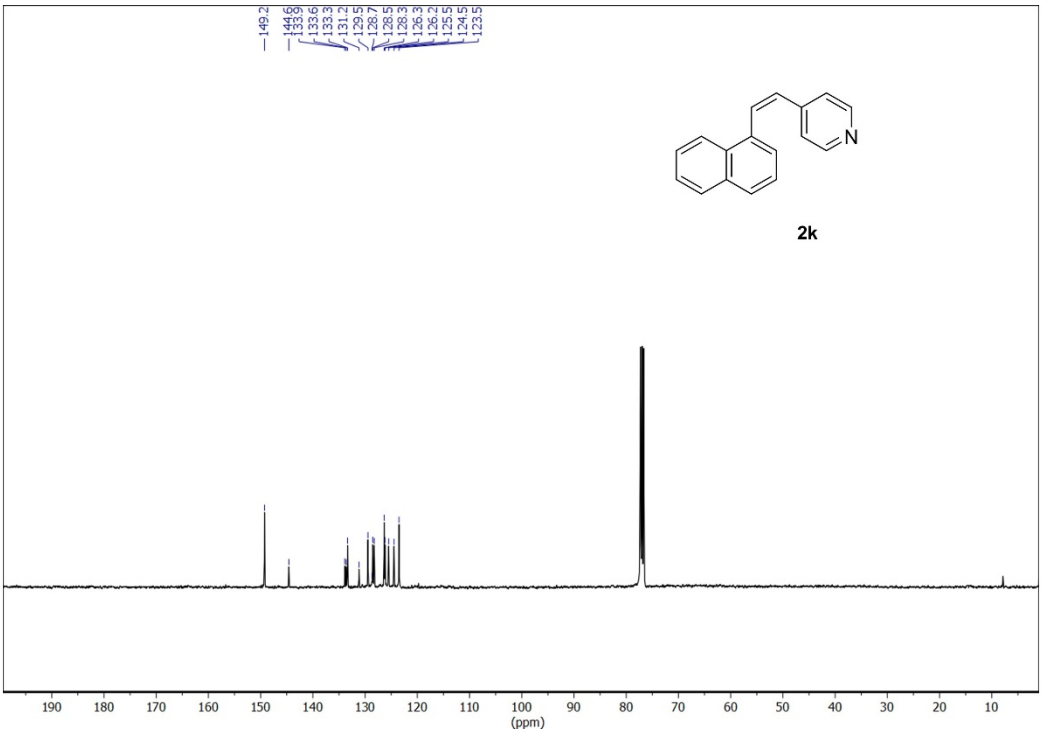

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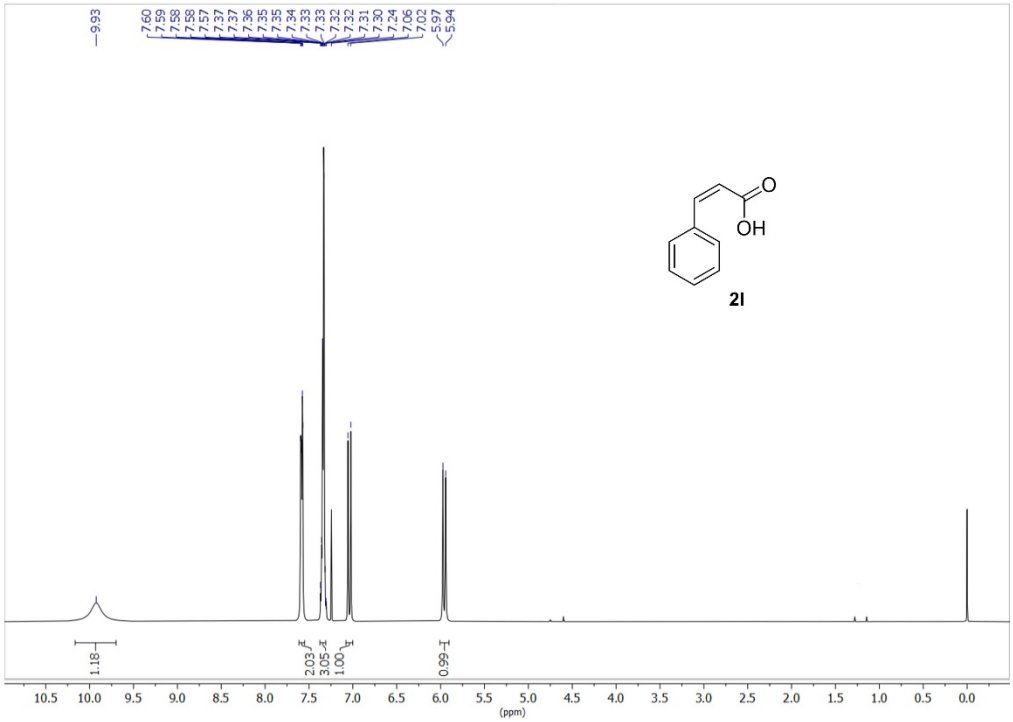

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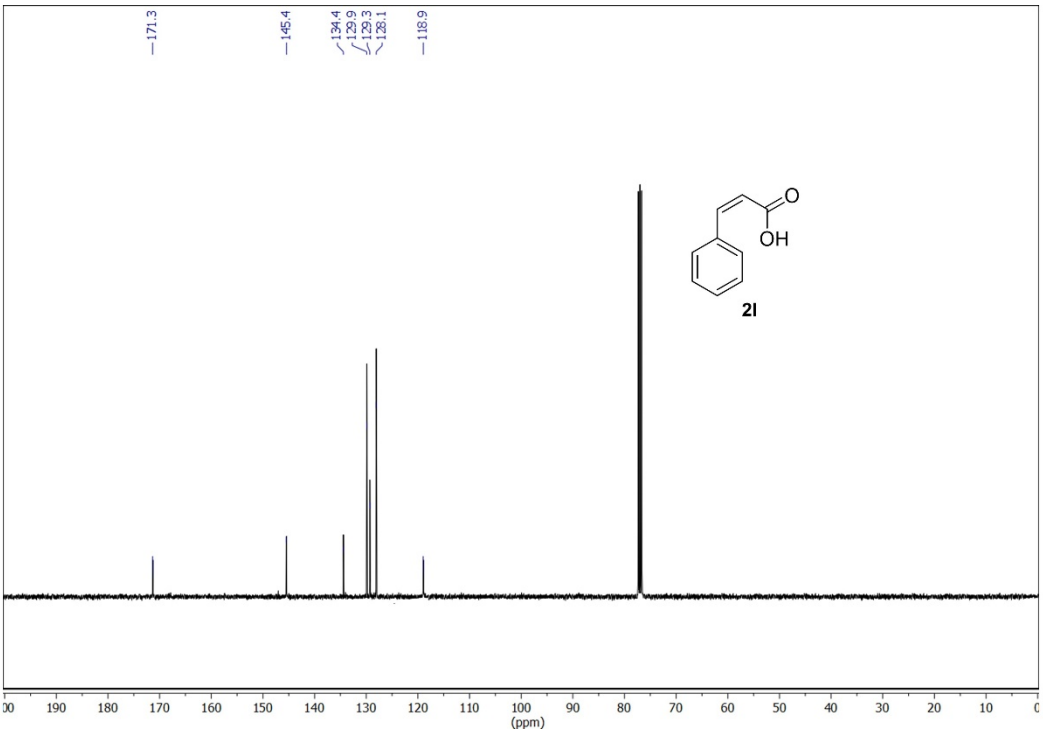

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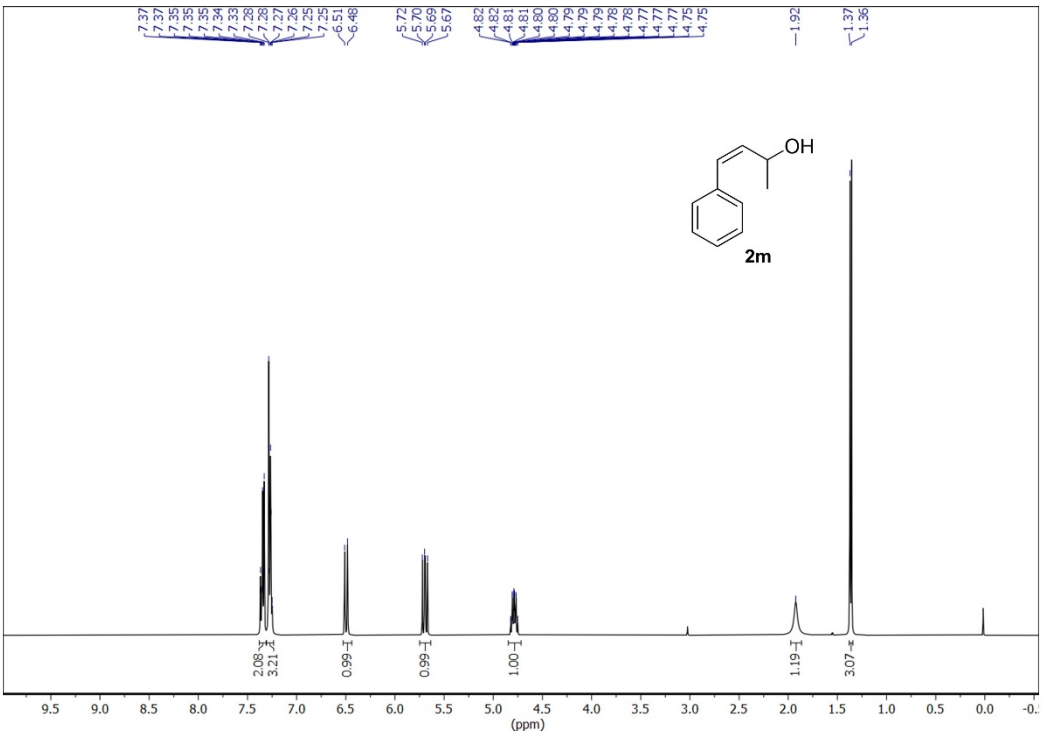

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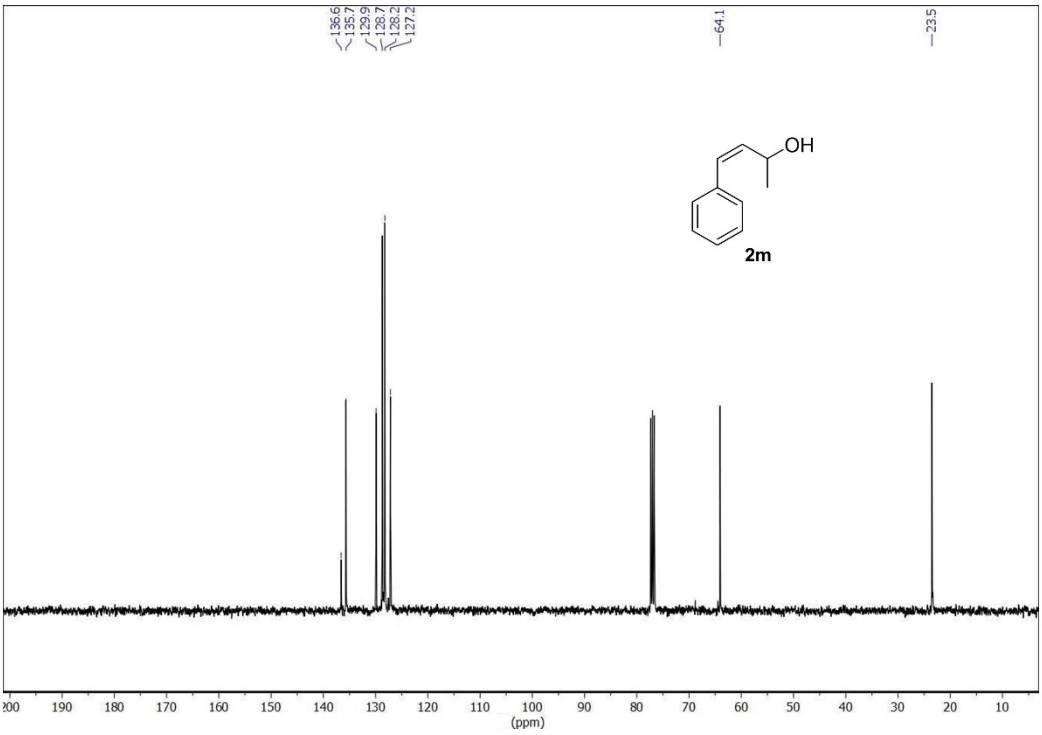

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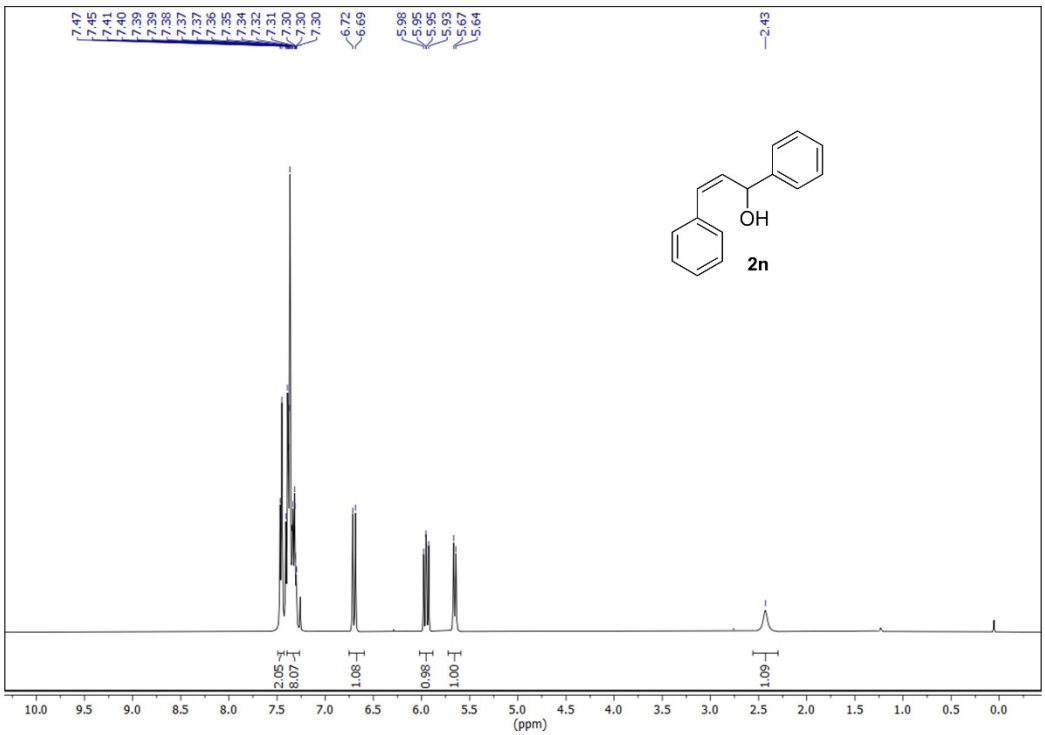

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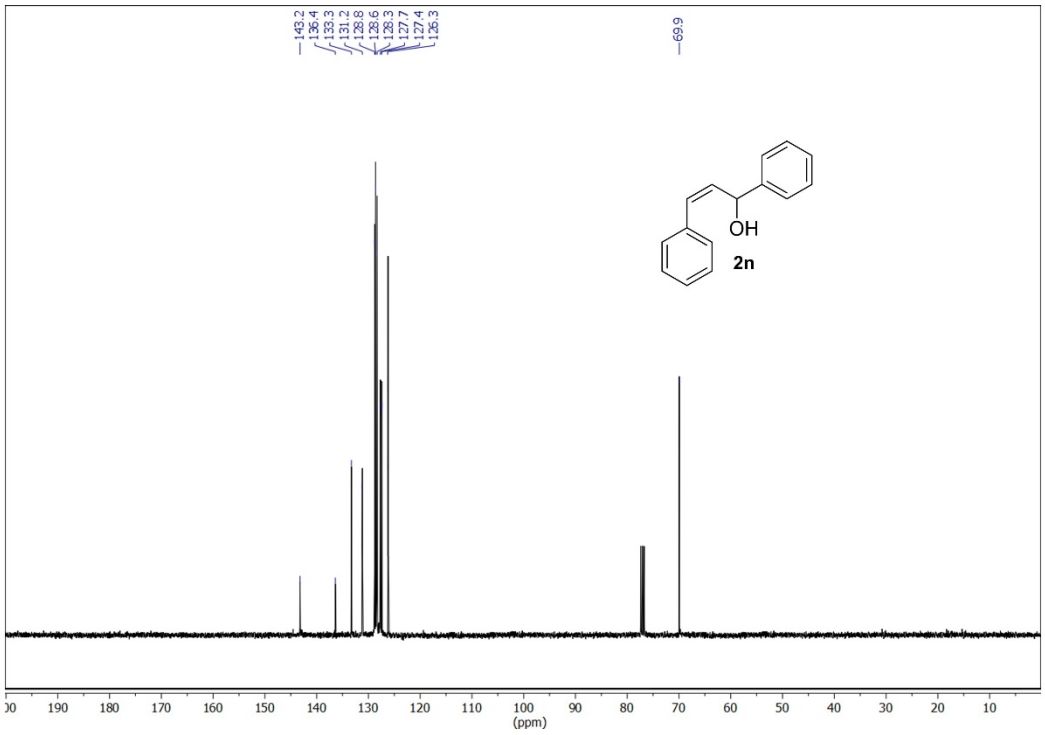

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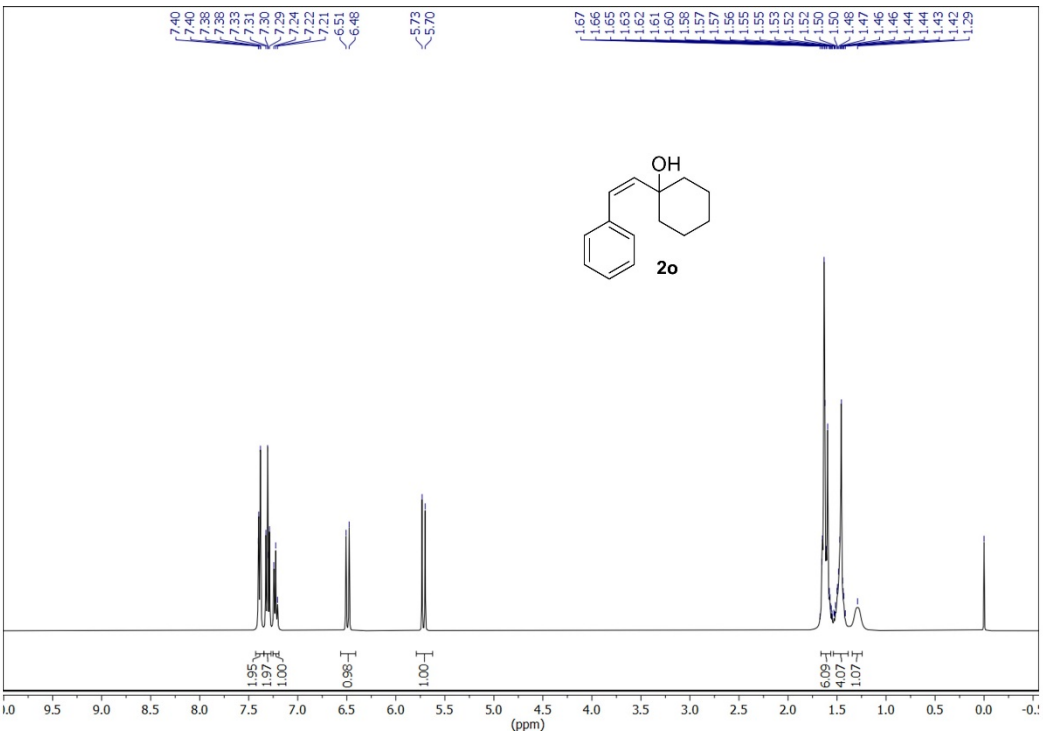

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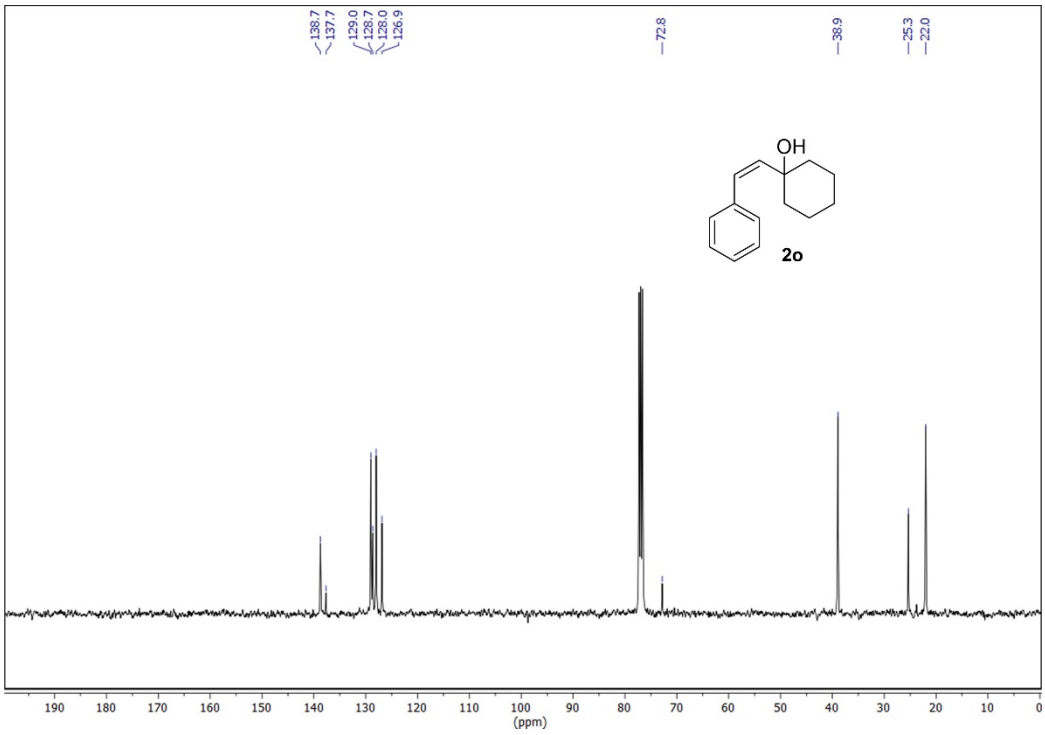

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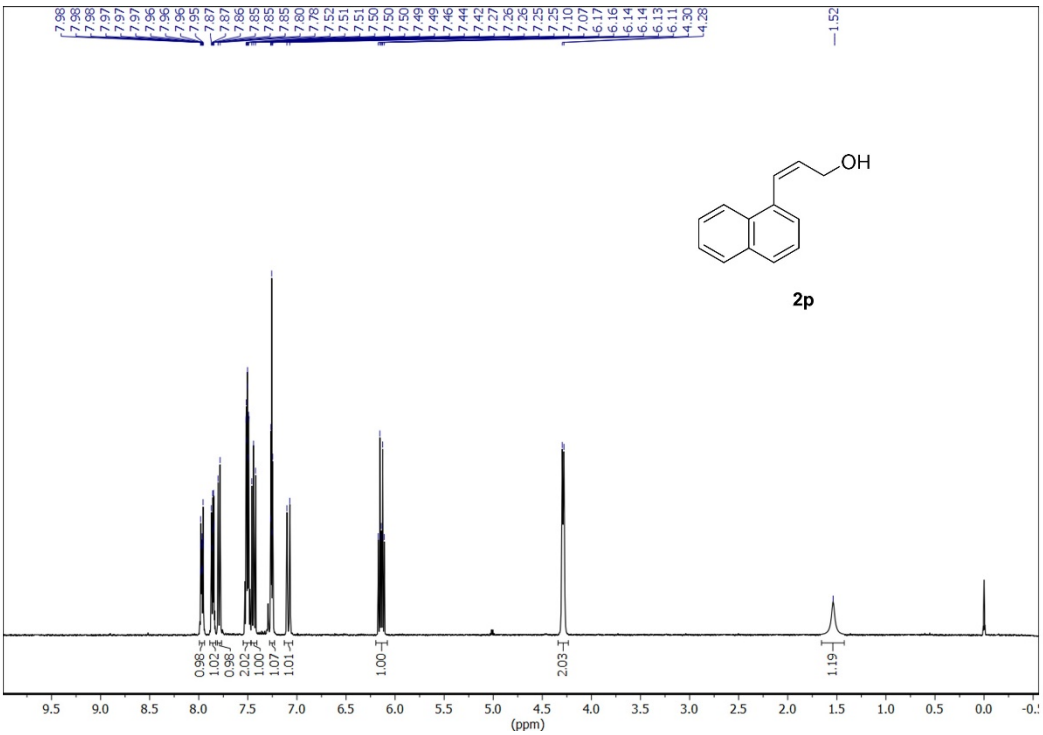

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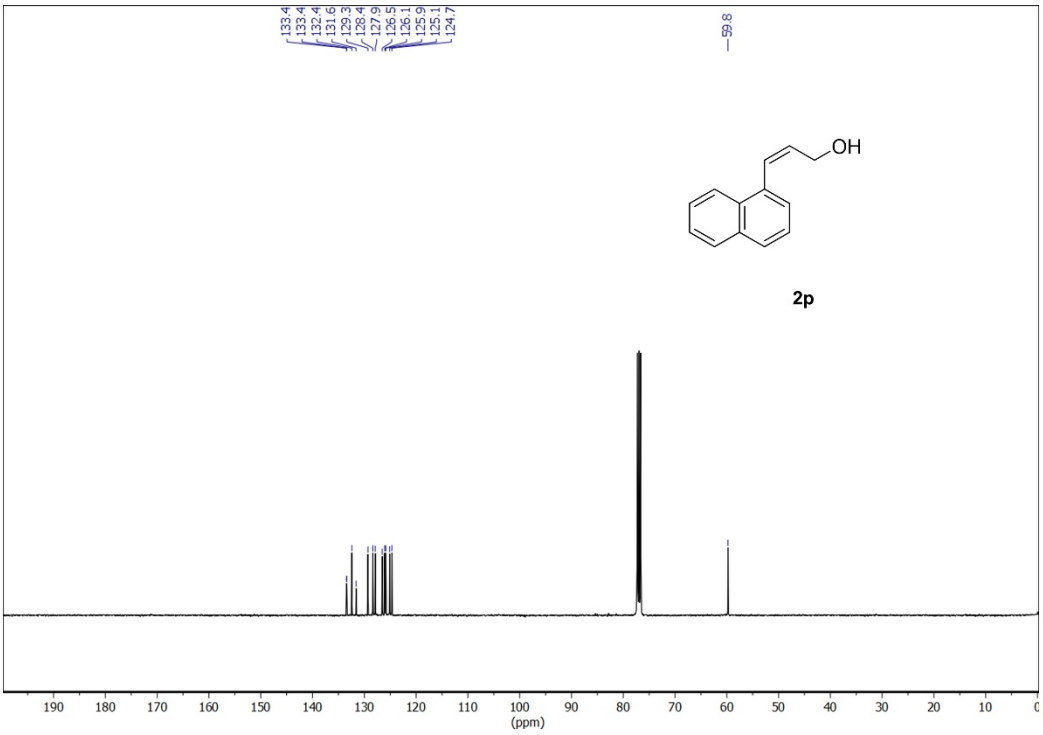

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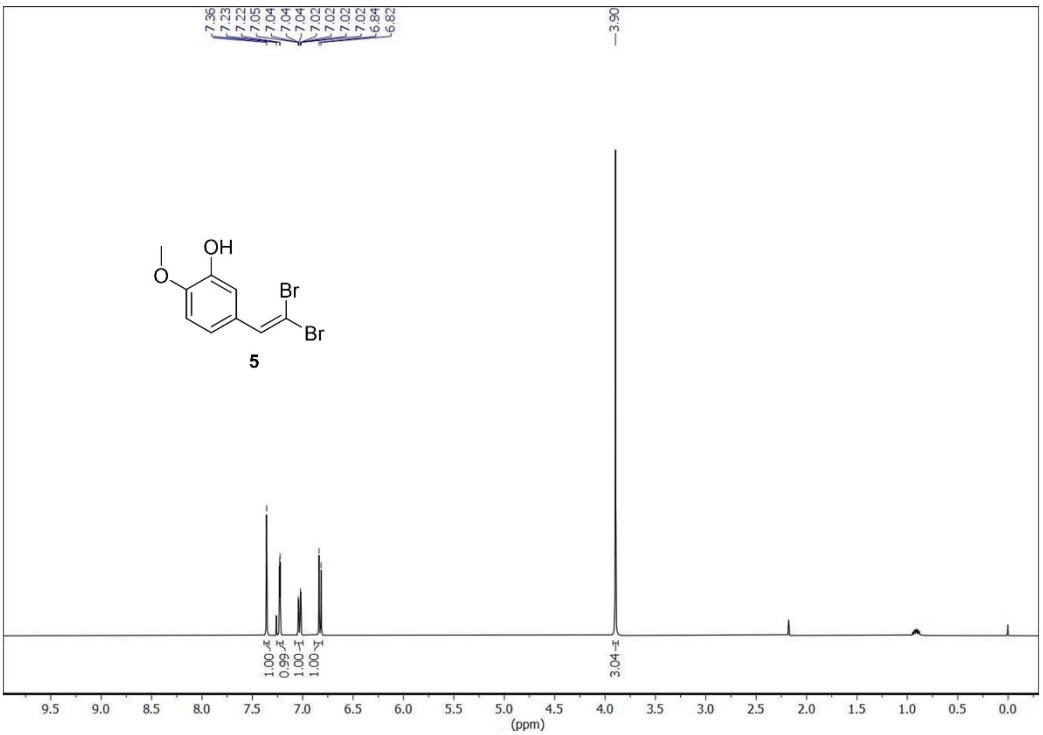

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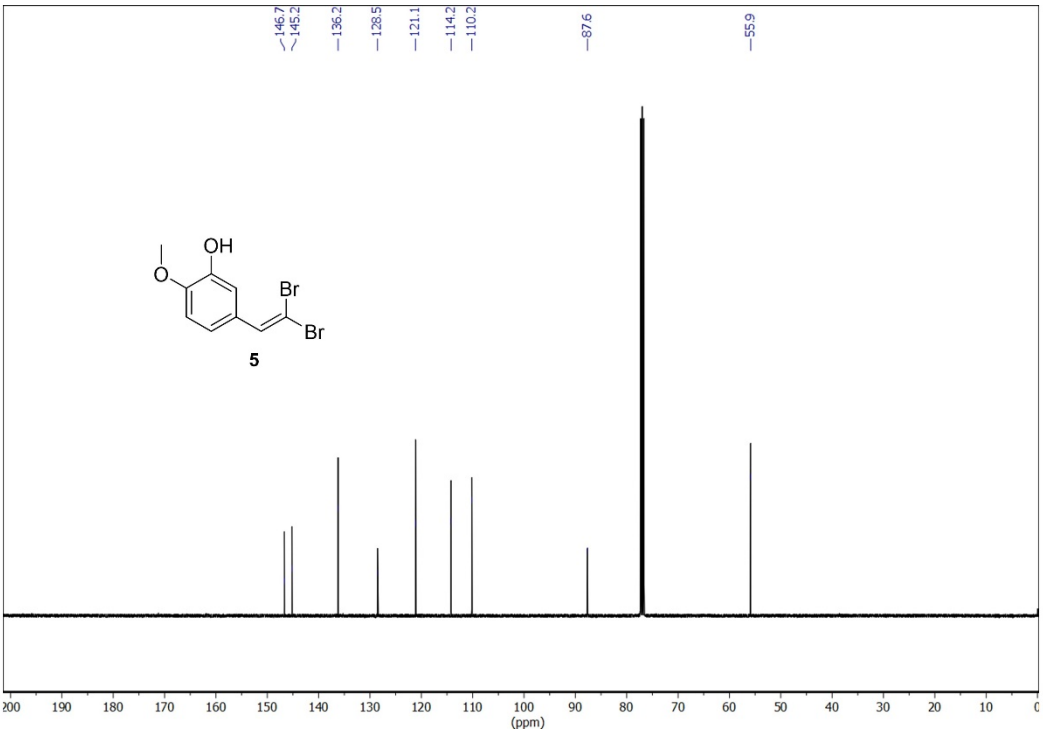

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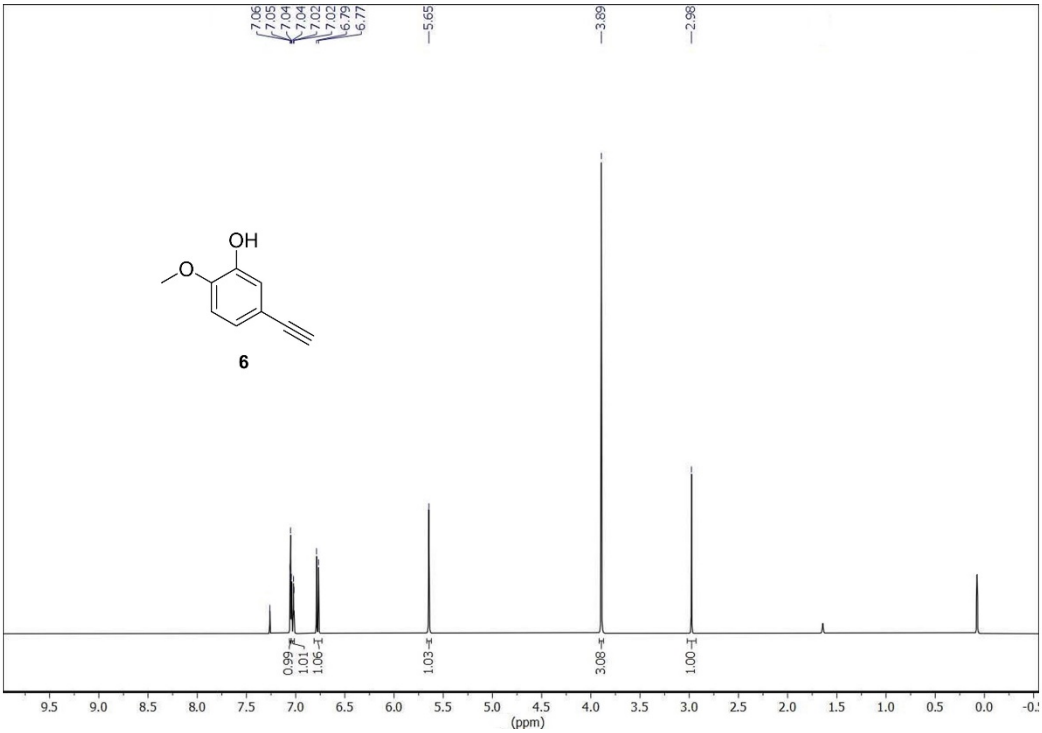

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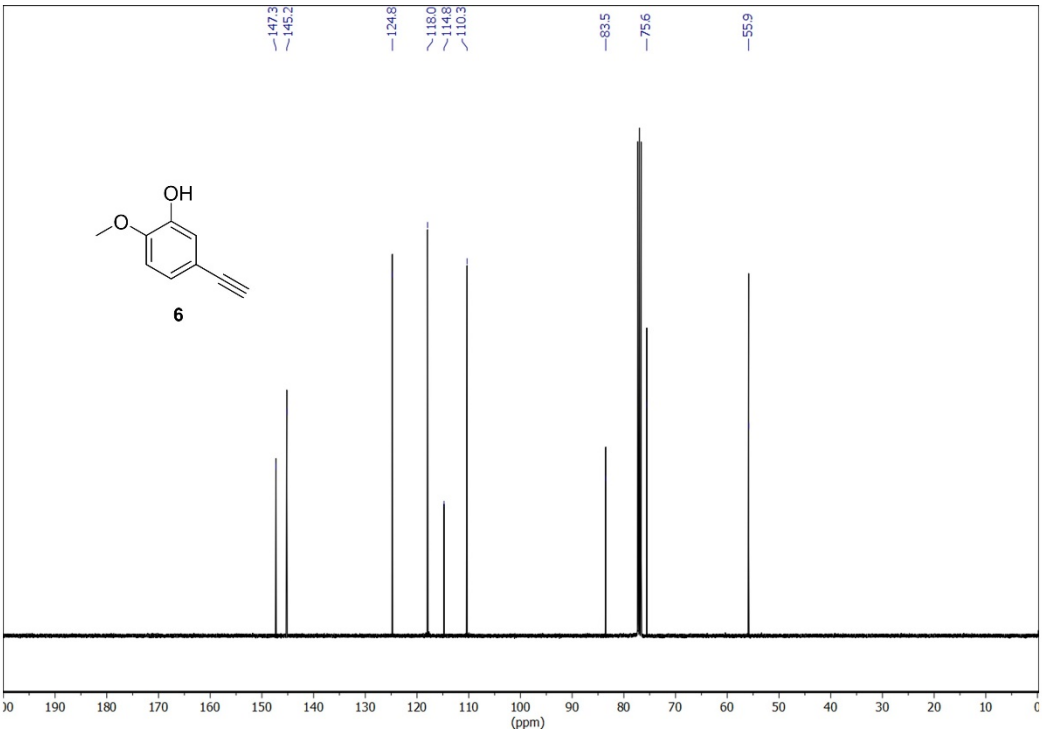

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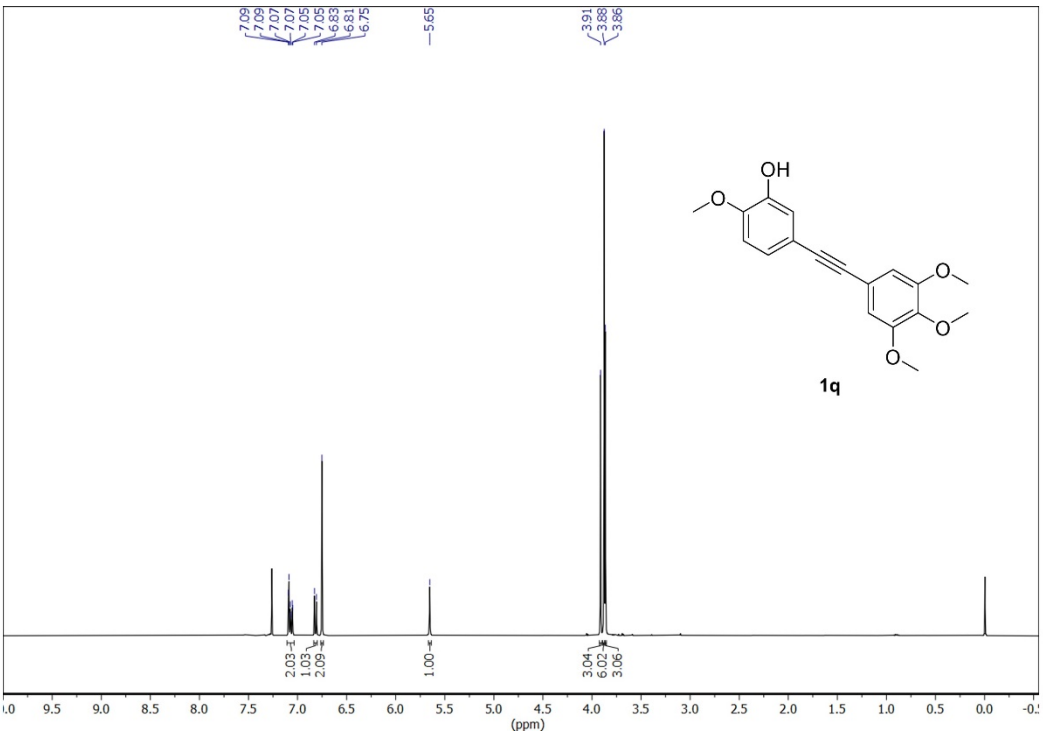

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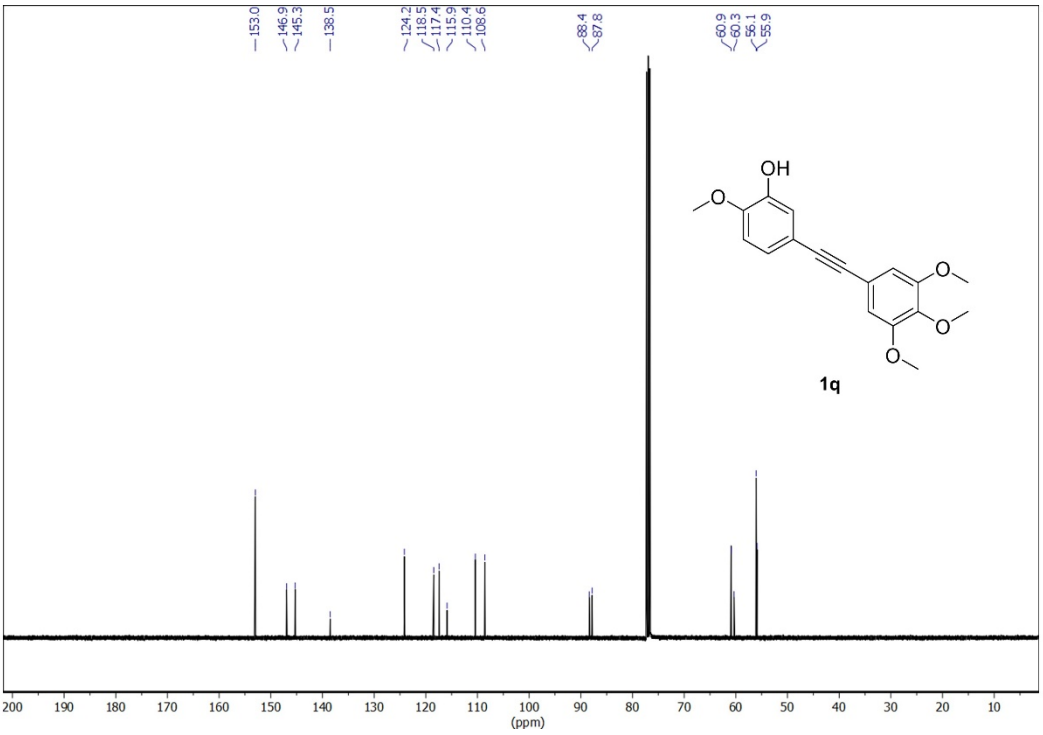

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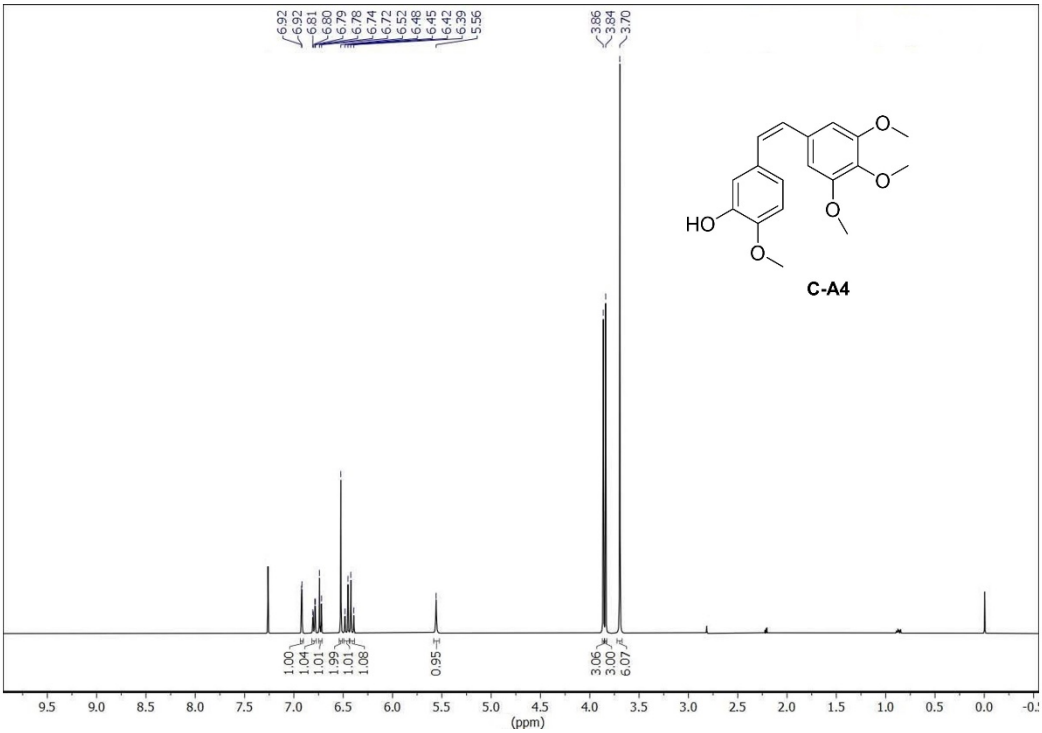

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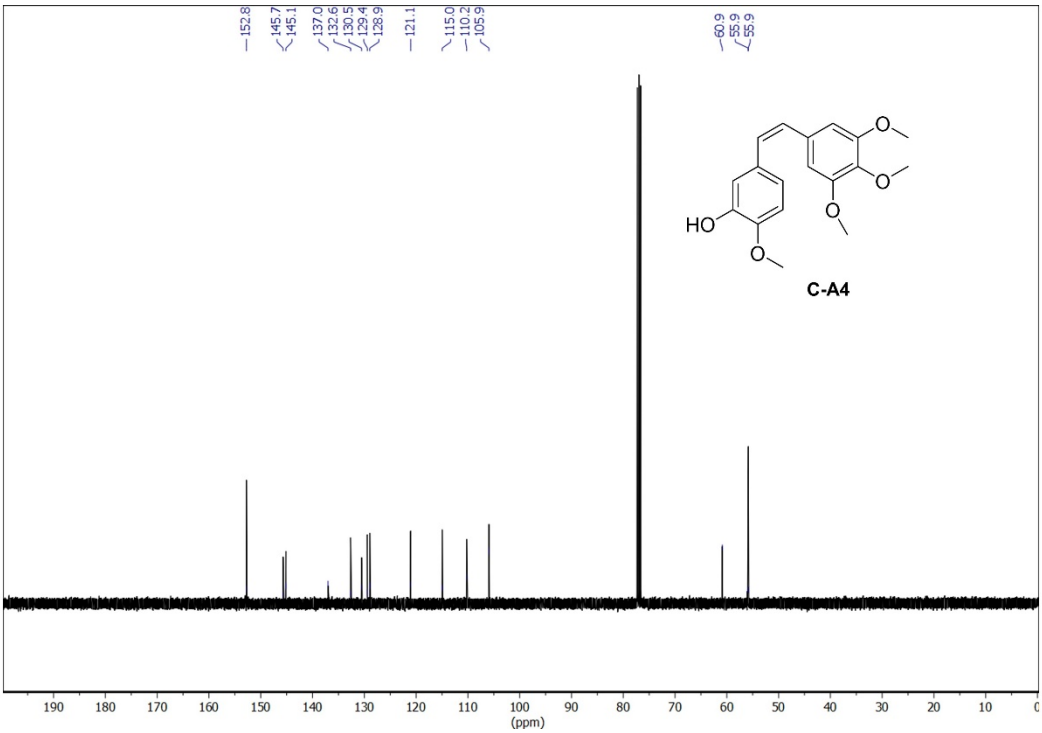

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