C2-Alkenylation of *N*-Heteroaromatic Compounds *via* Brønsted Acid Catalysis

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Supporting Information

Table of Contents

General Experimental Details

All materials were purchased from commercial sources (Acros, Aldrich, Alfa Aesar, Fluorochem and Strem) and used without any further treatment. Reagents requiring purification were purified using standard laboratory techniques according to methods published by Perrin, Armarego, and Perrin (Pergamon Press, 1966). Catalytic reactions were carried out in Young-type re-sealable tubes. Anhydrous solvents were obtained by distillation using standard procedures or by passage through drying columns supplied by Anhydrous Engineering Ltd. Anhydrous DMSO and NMP employed in the catalytic reactions were purchased form Aldrich and they were employed in a 50:1 v/v mixture with deionized water, in order to maintain the water amount constant. High-boiling solvents were removed from the reaction crudes employing rotary evaporators connected with high-vacuum pumps. Heteroarene N-oxides were stored and handled under inert atmosphere (glovebox), due to their hygroscopicity, to facilitate their use. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). Thin layer chromatography was performed using aluminium backed 60 F_{254} silica plates. Visualization was achieved by UV fluorescence or a basic $KMnO_4$ solution and heat. Proton nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz or 500 MHz. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz as stated. Chemical shifts (δ) are given in parts per million (ppm). Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m) and broad (br.). Coupling constants (*J*) are quoted to the nearest 0.5 Hz. All assignments of NMR spectra were based on 2D NMR data ($DEPT^{135}$, COSY, HSQC and HMBC). *In situ* yields were determined by employing 1,3,5-trimethoxybenzene as internal standard. Mass spectra were recorded using a VG Autospec (CI^+ mode), a Brüker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS (ESI^+ mode) and Shimadzu GCMS QP2010+ (EI^+ mode). Infrared spectra were recorded on a Perkin Elmer Spectrum Two FTIR spectrometer as thin films or solids compressed on a diamond plate. Melting points were determined using Stuart SMP30 melting point apparatus and are reported uncorrected. Enantiomeric excess was determined by integration of chromatograms peaks. Chiral HPLC was performed on an Agilent 1260 Infinity SFC Control Module system equipped with a quaternary pump, diode array detector and column thermostat under the conditions specified.

Experimental Procedures and Data

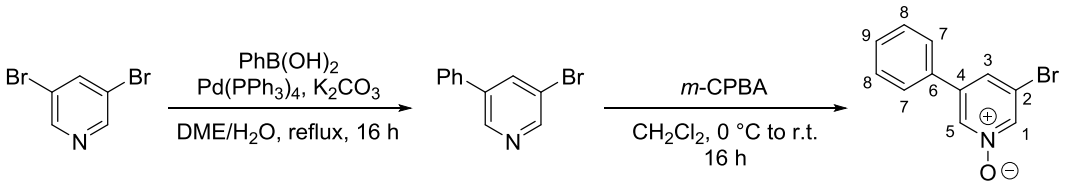
Substrates Synthesis

General Procedure A for the preparation of *N*-oxide substrates employing *m*-CPBA as oxidant: To a stirred, ice-cooled (0 °C) solution of heteroarene derivate (100 mol%) in CH_2Cl_2 (0.2 M) was added portion-wise *m*-CPBA (130 mol%). The reaction was warmed to room temperature and stirred overnight. Saturated aq. $NaHCO_3$ (5 mL/mmol) was slowly added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL/mmol). The organic extracts were combined, washed with brine (2 mL/mmol), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product. Purification by FCC (EtOAc → 10% MeOH/EtOAc) afforded pure *N*-oxide product.

General Procedure B for the preparation of *N*-oxide substrates employing hydrogen peroxide-urea adduct as oxidant: To a stirred solution of heteroarene derivate (100 mol%) in CH_2Cl_2 (0.3 M) was added portion-wise hydrogen peroxide-urea adduct (300 mol%). The mixture was cooled to 0 °C and trifluoroacetic anhydride (270 mol%) was added dropwise. The reaction was warmed to room temperature and stirred for 3 hours. The reaction was quenched with a 1M aq. solution of $Na_2S_2O_3$ (5 mL/mmol) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL/mmol). The organic portions were combined, washed with brine (2 mL/mmol), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product. Purification by FCC (EtOAc → 5% MeOH/EtOAc) afforded pure *N*-oxide product.

*Substrates **1a** (83% yield), **1b** (48% yield), **1c** (90% yield), **1d** (85% yield), **1e** (85% yield), **1f** (86% yield), **1g** (42% yield), **1h** (86% yield), **1i** (78% yield), **1j** (80% yield), **1l** (91% yield) and **1n** (84% yield) were synthesized according to **General Procedure A** from the corresponding commercially available quinoline, isoquinoline and pyridine precursors (yields reported in parenthesis for each compound). Substrates **1k** (87% yield) and **1o** (58% yield) were synthesized according to **General Procedure B** from the corresponding commercially available pyridine precursors (yields reported in parenthesis for each compound). The spectroscopic proprieties of all compounds were consistent with the data available in literature.[1] Substrates **1q** and **1r** were purchased from commercial sources (Aldrich, Alfa-Aesar) and used without any further treatment.*

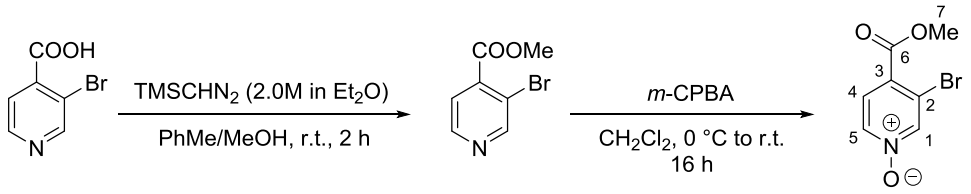
3-Bromo-5-phenylpyridine *N*-oxide (1m)



Step 1: The title compound was prepared following a literature procedure.[2] To a solution of 3,5-dibromopyridine (1.00 g, 4.22 mmol, 110 mol%) in DME (13 mL) was added $Pd(PPh_3)_4$ (125 mg, 0.08 mmol, 2 mol%) and the mixture was stirred for 10 minutes. A solution of potassium carbonate (1.75 g, 12.7 mmol, 330 mol%) in water (7 mL) was added, followed by phenylboronic acid (463 mg, 3.79 mmol, 100 mol%), and the mixture was heated at reflux for 4 hours. The reaction was cooled to room temperature and quenched with 1M aq. NaOH (6 mL). The mixture was extracted with Et_2O (3 × 20 mL). The organic portions were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by FCC (10% EtOAc/hexane) afforded 3-bromo-5-phenylpyridine (586 mg, 66% yield) as a colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.76 (1H, d, *J* = 2.0 Hz), 8.65 (1H, d, *J* = 2.0 Hz), 8.02 (1H, dd, *J* = 2.0, 2.0 Hz), 7.60-7.53 (2H, m), 7.53-7.46 (2H, m), 7.46-7.40 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.3, 146.4, 138.3, 136.9, 136.3, 129.2, 128.7, 127.2, 120.9. *The spectroscopic proprieties were consistent with the data available in literature.*[2]

Step 2: To a stirred, ice-cooled (0 °C) solution of 3-bromo-5-phenylpyridine (580 mg, 2.48 mmol, 100 mol%) in CH_2Cl_2 (15 mL) was added portion-wise *m*-CPBA (556 mg, 3.22 mmol, 130 mol%). The reaction was warmed to room temperature and stirred overnight. Saturated aq. $NaHCO_3$ (10 mL) was slowly added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product. Purification by FCC (EtOAc → 10% MeOH/EtOAc) afforded 3-bromo-5-phenylpyridine *N*-oxide (580 mg, 94% yield) as a colorless solid; m.p. = 114-116 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3098 (m), 3048 (s), 2922 (s), 2852 (m), 1591 (s), 1543 (s), 1397 (s), 1191 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.40-8.34 (1H, m, C**5**-H), 8.34-8.28 (1H, m, C**1**-H), 7.62-7.55 (1H, m, C**3**-H), 7.55-7.41 (5H, m, 2 × C**7**-H, 2 × C**8**-H and C**9**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.6 (C**4**), 138.9 (C**1**), 136.4 (C**5**), 134.0 (C**6**), 129.9 (C**9**), 129.5 (C**8**), 127.5 (C**3**), 126.9 (C**7**), 120.4 (C**2**); HRMS: (ESI^+) Calculated for $C_{11}H_8(^{79}Br)NNaO$: 271.9681. Found $[M+Na]^+$: 271.9677.

Methyl 3-bromoisonicotinate *N*-oxide (1p)



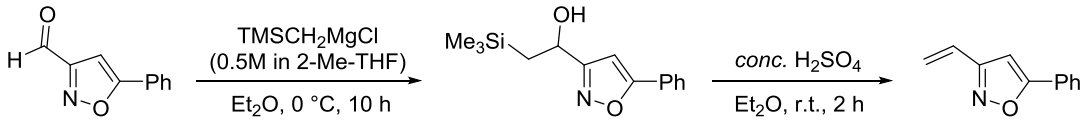
To a stirred solution of 3-bromoisonicotinic acid (250 mg, 1.24 mmol, 100 mol%) in toluene (5 mL) and MeOH (2 mL) was added dropwise a solution of (trimethylsilyl)diazomethane (2.0 M in Et_2O, 1.24 mL, 2.47 mmol, 200 mol%). The mixture was stirred for 2 hours at room temperature. The volatiles were removed under reduced pressure and the crude material was re-disolved in in CH_2Cl_2 (7 mL). The solution was cooled to 0 °C and *m*-CPBA (278 mg, 1.61 mmol, 130 mol%) was added portion-wise. The reaction was warmed to room temperature and stirred overnight. Saturated aq. $NaHCO_3$ (5 mL) was slowly added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product. Purification by FCC (EtOAc → 10% MeOH/EtOAc) afforded methyl 3-bromoisonicotinate N-oxide (185 mg, 64% yield) as a colorless solid; m.p. = 134-135 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3105 (m), 3065 (m), 3027 (s), 2922 (s), 2851 (m), 1724 (s), 1596 (s), 1438 (s), 1244 (s), 1149 (s), 1052 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43 (1H, d, *J* = 2.0 Hz, C**1**-H), 8.11 (1H, dd, *J* = 2.0, 7.0 Hz, C**5**-H), 7.80 (1H, d, *J* = 7.0 Hz, C**4**-H), 3.94 (3H, s, C**7**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9 (C**6**), 142.7 (C**1**), 137.9 (C**5**), 127.3 (C**4**), 126.9 (C**3**), 120.8 (C**2**), 53.0 (C**7**); HRMS: (ESI^+) Calculated for $C_7H_6(^{79}Br)NNaO_3$: 253.9423. Found $[M+Na]^+$: 253.9416.

Alkene Synthesis

General Procedure C for the preparation of alkene partner from aldehydes: To a stirred, ice-cooled (0 °C) solution of the appropriate aldehyde (100 mol%) in anhydrous Et_2O (1 M) was added dropwise a solution of (trimethylsilyl)methylmagnesium chloride (0.5 M in 2-Me-THF, 110 mol%). The reaction was maintained stirring at 0 °C for 10 hours. Saturated aq. NH_4Cl (5 mL/mmol) was slowly added and the mixture was extracted with Et_2O (3 × 5 mL/mmol). The organic extracts were combined, washed with saturated aq. $NaHCO_3$. (2 mL/mmol), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the corresponding 2-(trimethylsilyl)ethanol. The crude material was re-dissolved in Et_2O (1 M) and stirred with 1M aq. HCl (1.3 mL/mmol) at room temperature, monitoring the reaction by TLC. The mixture was extracted with Et_2O (3 × 5 mL/mmol). The organic extracts were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure [*N.B. many alkenes tent to be really volatile, pay attention before putting the flask into the heating-bath of the rotary evaporator or on the high-vacuum line*]. Purification by either distillation or FCC (10%EtOAc/hexane) afforded pure terminal olefins.

4-Vinylthiazole *(34% yield),* ***2-vinylfuran*** *(61% yield) and* ***3-vinylthiophene*** *(51% yield) were synthesized according to* ***General Procedure C*** *from the corresponding commercially available aldehyde precursors (yields reported in parenthesis for each compound). The spectroscopic proprieties of all compounds were consistent with the data available in literature.*[3] *All the other olefinic partners were purchased from commercial sources (Aldrich, Alfa-Aesar) and used without any further treatment.*

5-Phenyl-3-vinylisoxazole



To a stirred, ice-cooled (0 °C) solution of 5-phenylisoxazole-3-carboxaldehyde (210 mg, 1.21 mmol, 100 mol%) in anhydrous Et_2O (2 mL) was added dropwise a solution of (trimethylsilyl)methylmagnesium chloride (0.5 M in 2-Me-THF, 2.67 mL, 1.33 mmol, 110 mol%). The reaction was maintained stirring at 0 °C for 10 hours. Saturated aq. NH_4Cl (5 mL/mmol) was slowly added and the mixture was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with saturated aq. $NaHCO_3$. (1 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the corresponding 2-(trimethylsilyl)ethanol. The crude material was re-dissolved in Et_2O (1.5 mL) and stirred with conc. H_2SO_4 (0.1 mL) at room temperature, monitoring the reaction by TLC. The mixture was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification by FCC (20% EtOAc/hexane → 30% EtOAc/hexane) afforded 5-phenyl-3-vinylisoxazole (182 mg, 92% yield) as a colorless solid; m.p. = 49-51 °C [hexane/CH_2Cl_2] (Lit.[4] 55-56 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85-7.73 (2H, m), 7.55-7.39 (4H, m), 6.82 (1H, dd, *J* = 11.0, 18.0 Hz), 5.93 (1H, dd, *J* = 1.0, 18.0 Hz), 5.65 (1H, dd, *J* = 1.0, 11.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 184.8, 169.8, 162.3, 130.2, 128.9, 126.0, 125.8, 121.4, 96.2. *The spectroscopic proprieties were consistent with the data available in literature.*[5]

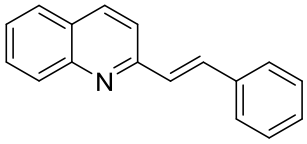
C2-Alkenylation Reactions

<u>General Procedure D</u> for Brønsted-acid catalysed C2-alkenylation reactions:

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with *N*-oxide substrate (0.143 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of the appropriate alkene (300-500 mol%) and acid catalyst (5 mol%) in the appropriate solvent (50:1 v/v mixture with H_2O, 1.5 M concentration with respect to substrate) was added *via* syringe and the tube was sealed with a Young's tap. The reaction vessel was placed into a pre-heated heating block at 120-140 °C and stirred for 24-48 hours. The reaction mixture was cooled to room

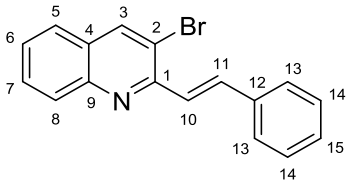
temperature and concentrated *in vacuo*. Purification of the residue by FCC (10% EtOAc/hexane → 30% EtOAc/hexane) afforded pure (*E*)-2-alkenylated heteroaromatic product.

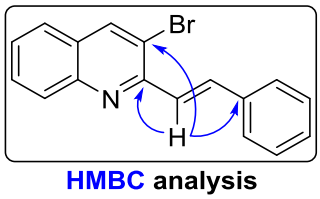
(*E*)-2-Styrylquinoline (2a)



General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (450 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **2a** (31.8 mg, 96% yield) as an off-white solid; m.p. = 99-100 °C [hexane/CH_2Cl_2] (Lit.[6] 98-100 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (1H, d, *J* = 8.5 Hz), 8.07 (1H, d, *J* = 8.5 Hz), 7.78 (1H, d, *J* = 8.0 Hz), 7.72-7.63 (5H, m), 7.49 (1H, dd, *J* = 7.5, 7.5 Hz), 7.43-7.38 (3H, m), 7.34-7.32 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0, 148.3, 136.5, 136.3, 134.4, 129.7, 129.2, 129.0, 128.8, 128.6, 127.5, 127.3, 127.2, 126.1, 119.2. *The spectroscopic proprieties were consistent with the data available in literature.*[7]

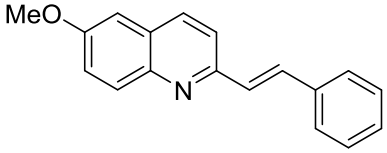
(*E*)-3-Bromo-2-styrylquinoline (2b)





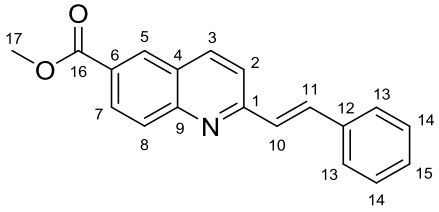
General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (300 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **2b** (30.2 mg, 68% yield) as a yellow solid; m.p. = 125-126 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3055 (m), 3026 (m), 2922 (s), 2851 (m), 1726 (s), 1631 (s), 1575 (s), 1484 (s), 1309 (s), 1017 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (1H, s, C**3**-H), 8.13-8.01 (2H, m, C**8**-H and C**11**-H), 7.82 (1H, d, *J* = 16.0 Hz, C**10**-H), 7.75-7.65 (4H, m, C**5**-H, C**7**-H and 2 × C**13**-H), 7.54-7.46 (1H, m, C**6**-H), 7.42 (2H, dd, *J* = 7.5, 7.5 Hz, 2 × C**14**-H), 7.35 (1H, t, *J* = 7.5 Hz, C**15**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.9 (C**1**), 146.9 (C**9**), 139.3 (C**3**), 137.1 (C**11**), 136.7 (C**12**), 130.1 (C**7**), 129.4 (C**8**), 129.0 (C**15**), 128.9 (C**14**), 128.5 (C**4**), 127.8 (C**13**), 127.0 (C**6**), 126.6 (C**5**), 125.1 (C**10**), 118.6 (C**2**); HRMS: (ESI$^+$) Calculated for $C_{17}H_{13}(^{79}Br)N$: 310.0226. Found $[M+H]^+$: 310.0224. *The regiochemistry of compound **2b** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C**10**-H [J = 16.0 Hz].*

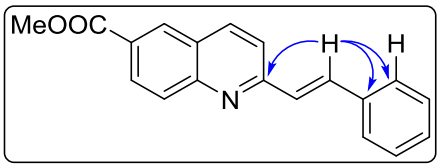
(*E*)-6-Methoxy-2-styrylquinoline (2c)



General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded quinoline **2c** (28.2 mg, 76% yield) as a yellow solid; m.p. = 147-149 °C [hexane/CH_2Cl_2] (Lit.[8] 147-149 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-7.96 (2H, m), 7.66-7.58 (4H, m), 7.43-7.28 (5H, m), 7.05 (1H, d, *J* = 2.5 Hz), 3.93 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8, 153.8, 144.4, 136.8, 135.2, 133.3, 130.8, 129.2, 128.9, 128.5, 128.4, 127.2, 122.4, 119.7, 105.4, 55.7. *The spectroscopic proprieties were consistent with the data available in literature.*[7]

Methyl (*E*)-2-styrylquinoline-6-carboxylate (2d)

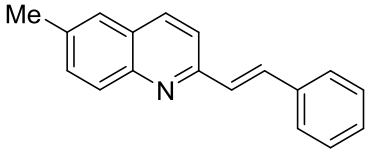




HMBC analysis

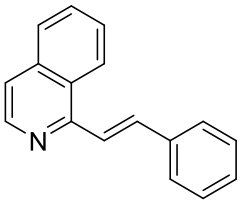
General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **2d** (37.7 mg, 91% yield) as an off-white solid; m.p. = 185-186 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3027 (m), 3003 (m), 2952 (s), 2922 (s), 2850 (m), 1709 (s), 1590 (s), 1269 (s), 1186 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.52 (1H, d, *J* = 2.0 Hz, C**5**-H), 8.28 (1H, dd, *J* = 2.0, 9.0 Hz, C**7**-H), 8.19 (1H, d, *J* = 8.5 Hz, C**3**-H), 8.09 (1H, d, *J* = 9.0 Hz, C**8**-H), 7.75 (1H, d, *J* = 16.5 Hz, C**11**-H), 7.71-7.60 (3H, m, C**2**-H and 2 × C**13**-H), 7.47-7.30 (4H, m, C**10**-H, 2 × C**14**-H and C**15**-H), 3.98 (3H, s, C**17**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.8 (C**16**), 158.1 (C**1**), 150.3 (C**9**), 137.6 (C**3**), 136.3 (C**12**), 135.9 (C**11**), 130.7 (C**5**), 129.5 (C**8**), 129.4 (C**7**), 129.1 (C**15**), 129.0 (C**14**), 128.6 (C**10**), 127.6 (*2 signals*, C**4** and C**13**), 126.5 (C**6**), 120.3 (C**2**), 52.5 (C**17**); HRMS: (ESI$^+$) Calculated for $C_{19}H_{16}NO_2$: 290.1176. Found [M+H]$^+$: 290.1190. *The regiochemistry of compound **2d** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C**11**-H [J = 16.5 Hz].*

(*E*)-6-Methyl-2-styrylquinoline (2e)



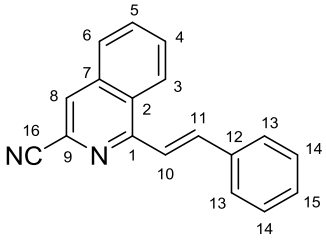
General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **2e** (28.6 mg, 82% yield) as an off-white solid; m.p. = 136-137 °C [hexane/CH_2Cl_2] (Lit.[6] 136-138 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06-7.95 (2H, m), 7.69-7.59 (4H, m), 7.56-7.51 (2H, m), 7.44-7.36 (3H, m), 7.36-7.29 (1H, m), 2.53 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.2, 146.9, 136.7, 136.2, 135.8, 134.0, 132.1, 129.2, 129.0, 128.9, 128.6, 127.5, 127.3, 126.5, 119.3, 21.7. *The spectroscopic proprieties were consistent with the data available in literature.*[7]

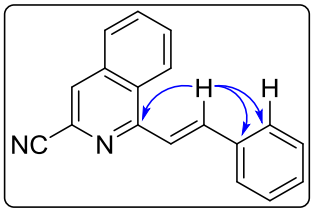
(*E*)-1-Styrylisoquinoline (2f)



General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of styrene (300 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded isoquinoline **2f** (20.5 mg, 62% yield) as a yellow solid; m.p. = 102-103 °C [hexane/CH_2Cl_2] (Lit.[8] 107-109 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (1H, d, *J* = 5.5 Hz), 8.38 (1H, dd, *J* = 1.0, 8.5 Hz), 8.06-7.96 (2H, m), 7.83 (1H, dd, *J* = 1.5, 8.0 Hz), 7.77-7.60 (4H, m), 7.57 (1H, dd, *J* = 1.0, 5.5 Hz), 7.48-7.39 (2H, m), 7.39-7.31 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5, 142.5, 136.9, 136.7, 135.8, 129.9, 128.8, 128.6, 127.4, 127.3, 127.2, 126.7, 124.4, 122.8, 120.0. *The spectroscopic proprieties were consistent with the data available in literature.*[7]

(*E*)-1-Styrylisoquinoline-3-carbonitrile (2g)



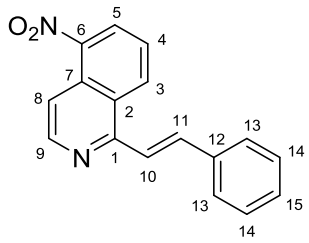


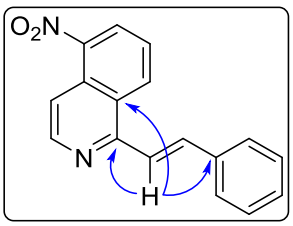
HMBC analysis

General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of styrene (300 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24

hours and afforded isoquinoline **2g** (27.6 mg, 75% yield) as an off-white solid; m.p. = 126-128 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3060 (m), 3024 (m), 2922 (s), 2852 (m), 2228 (s), 1629 (s), 1550 (s), 1360 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.46-8.36 (1H, m, C**3**-H), 8.09 (1H, d, *J* = 15.5 Hz, C**11**-H), 7.98 (1H, s, C**8**-H), 7.94-7.85 (2H, m, C**6**-H and C**10**-H), 7.85-7.77 (2H, m, C**4**-H and C**5**-H), 7.74-7.65 (2H, m, 2 × C**13**-H), 7.48-7.35 (3H, m, 2 × C**14**-H and C**15**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.4 (C**1**), 138.7 (C**11**), 136.3 (C**12**), 135.9 (C**7**), 131.5 (C**5**), 130.3 (C**4**), 129.4 (C**15**), 129.0 (C**14**), 128.0 (C**6**), 127.9 (C**13**), 127.5 (C**2**), 126.6 (C**9**), 126.3 (C**8**), 124.9 (C**3**), 121.0 (C**10**), 118.5 (C**16**); HRMS: (ESI^+) Calculated for $C_{18}H_{13}N_2$: 257.1073. Found $[M+H]^+$: 257.1066. *The regiochemistry of compound **2g** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C**11**-H [J = 15.5 Hz].*

(*E*)-5-Nitro-1-styrylisoquinoline (2h)

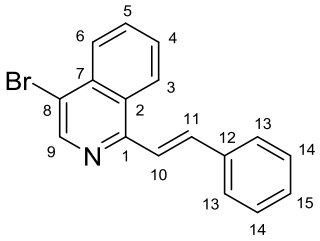


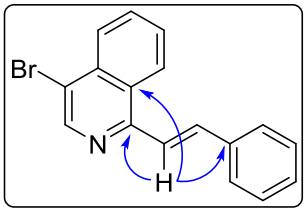


HMBC analysis

General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded isoquinoline **2h** (23.1 mg, 59% yield) as a yellow solid; m.p. = 117-119 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3056 (m), 2922 (s), 2855 (m), 1629 (s), 1517 (s), 1313 (s), 1033 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.77-8.68 (2H, m, C**3**-H and C**9**-H), 8.46 (1H, dd, *J* = 1.0, 8.0 Hz, C**5**-H), 8.30 (1H, dd, *J* = 1.0, 6.0 Hz, C**8**-H), 8.04 (1H, d, *J* = 15.5 Hz, C**11**-H), 7.94 (1H, d, *J* = 15.5 Hz, C**10**-H), 7.74-7.65 (3H, m, C**4**-H and 2 × C**13**-H), 7.48-7.33 (3H, m, 2 × C**14**-H and C**15**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5 (C**1**), 145.8 (C**9**), 145.7 (C**6**), 138.1 (C**11**), 136.4 (C**12**), 131.4 (C**3**), 129.3 (*2 signals*, C**7** and C**15**), 129.0 (C**14**), 127.8 (C**5**), 127.7 (C**13**), 127.2 (C**2**), 125.5 (C**4**), 122.0 (C**10**), 114.5 (C**8**); HRMS: (ESI^+) Calculated for $C_{17}H_{13}N_2O_2$: 277.0972. Found $[M+H]^+$: 277.0977. *The regiochemistry of compound **2h** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**10**-H and C**11**-H [J = 15.5 Hz].*

(*E*)-4-Bromo-1-styrylisoquinoline (2i)

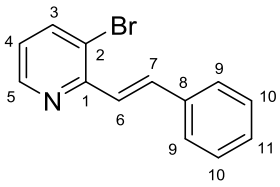


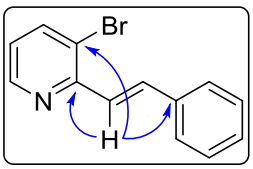


HMBC analysis

General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded isoquinoline **2i** (32.4mg, 73% yield) as a yellow solid; m.p. = 88-90 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3057 (m), 3025 (m), 2923 (s), 2856 (m), 1681 (s), 1625 (s), 1446 (s), 1383 (s), 1225 (s), 1032 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.73 (1H, s, C**9**-H), 8.35 (1H, dd, *J* = 1.0, 8.5 Hz, C**3**-H), 8.19 (1H, dd, *J* = 1.5, 8.5 Hz, C**6**-H), 7.99 (1H, d, *J* = 15.5 Hz, C**11**-H), 7.92 (1H, d, *J* = 15.5 Hz, C**10**-H), 7.79 (1H, ddd, *J* = 1.0, 7.0, 8.5 Hz, C**5**-H), 7.75-7.64 (3H, m, C**4**-H and 2 × C**13**-H), 7.43 (2H, dd, *J* = 7.5, 7.5 Hz, 2 × C**14**-H), 7.39-7.33 (1H, m, C**15**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.0 (C**1**), 144.2 (C**9**), 136.7 (C**12**), 136.6 (C**11**), 135.2 (C**7**), 131.1 (C**5**), 128.8 (*2 signals*, C**14** and C**15**), 128.0 (C**4**), 127.8 (C**2**), 127.5 (C**13**), 126.6 (C**6**), 124.8 (C**3**), 122.1 (C**10**), 118.3 (C**8**); HRMS: (ESI^+) Calculated for $C_{17}H_{13}(^{79}Br)N$: 310.0226. Found $[M+H]^+$: 310.0213. *The regiochemistry of compound **2i** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**10**-H and C**11**-H [J = 15.5 Hz].*

(*E*)-3-Bromo-2-styrylpyridine (2j)



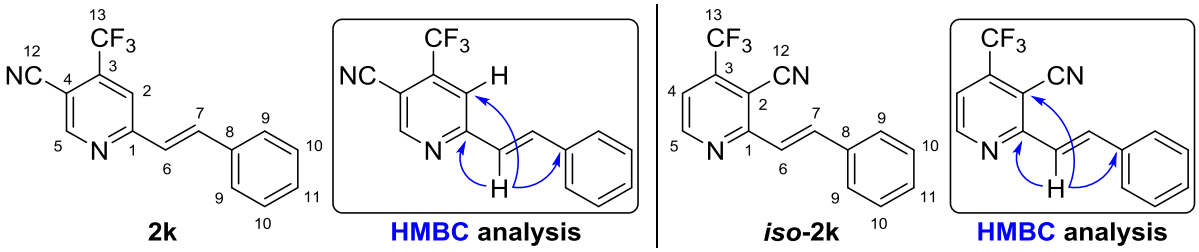


HMBC analysis

General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine **2j** (16.8 mg, 45% yield) as a yellow oil; ν_{max} / cm^{-1}: 3051 (m), 2926 (s), 1631 (s), 1418 (s), 1264 (s), 1021 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (1H, dd, *J* = 1.5, 4.5 Hz, C**5**-H), 7.89-7.80 (2H, m, C**3**-H and C**7**-H), 7.68-7.56 (3H, m, C**6**-H and 2 × C**9**-H), 7.39 (2H, dd, *J* = 6.5, 8.0 Hz, 2 × C**10**-H), 7.36-7.30 (1H, m, C**11**-H), 7.03 (1H, dd, *J* = 4.5, 8.0 Hz, C**4**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.4 (C**1**), 148.2 (C**5**), 140.9 (C**3**), 136.6 (C**8**), 136.0 (C**7**), 128.9 (*2 signals*, C**10** and C**11**), 127.7 (C**9**), 124.9 (C**6**), 123.2 (C**4**), 121.2 (C**2**); HRMS: (ESI^+) Calculated for

$C_{13}H_{11}(^{79}Br)N$: 260.0069. Found $[M+H]^+$: 260.0066. *The regiochemistry of compound* ***2j*** *was confirmed by HMBC analysis (as indicated above).*

(*E*)-6-Styryl-4-(trifluoromethyl)nicotinonitrile (2k) and *iso*-2k isomer

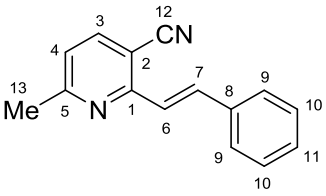


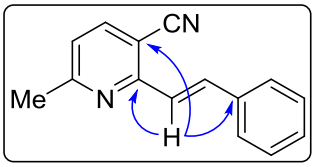
General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours. Purification by FCC afforded pyridine **2k** (14.8 mg, 38% yield) as an off-white solid. Continued elution provided regioisomer ***iso*-2k** (9.2 mg, 23% yield) as an off-white solid.

Data for **2k**: m.p. = 107-109 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3060 (m), 3026 (m), 2923 (s), 2855 (m), 2231 (s), 1591 (s), 1384 (s), 1291 (s), 1144 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.99 (1H, s, C**5**-H), 7.93 (1H, d, *J* = 16.0 Hz, C**7**-H), 7.66 (1H, s, C**2**-H), 7.63 (2H, dd, *J* = 1.5, 8.0 Hz, 2 × C**9**-H), 7.47-7.38 (3H, m, 2 × C**10**-H and C**11**-H), 7.22 (1H, d, *J* = 16.0 Hz, C**6**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.4 (C**1**), 154.6 (C**5**), 140.6 (q, $^2J_{C\text{-}F}$ = 34.0 Hz, C**3**), 139.5 (C**7**), 135.3 (C**8**), 130.2 (C**11**), 129.2 (C**10**), 128.1 (C**9**), 125.2 (C**6**), 121.4 (q, $^1J_{C\text{-}F}$ = 275.0 Hz, C**13**), 118.1 (q, $^3J_{C\text{-}F}$ = 4.5 Hz, C**2**), 114.2 (C**12**), 103.3 (q, $^3J_{C\text{-}F}$ = 2.0 Hz, C**4**); HRMS: (ESI^+) Calculated for $C_{15}H_9F_3N_2Na$: 297.0610. Found $[M+Na]^+$: 297.0609. *The regiochemistry of compound* ***2k*** *was confirmed by HMBC analysis (as indicated above) and by the multiplicity of C**5**-H and C**2**-H signals in ^1H NMR (singlets). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 16.0 Hz].*

Data for ***iso*-2k**: m.p. = 86-88 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3024 (m), 2922 (s), 2855 (m), 2230 (s), 1632 (s), 1397 (s), 1338 (s), 1179 (s), 1138 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.93 (1H, d, *J* = 5.0 Hz, C**5**-H), 8.14 (1H, d, *J* = 15.5 Hz, C**7**-H), 7.71-7.67 (2H, m, 2 × C**9**-H), 7.64 (1H, d, *J* = 15.5 Hz, C**6**-H), 7.50 (1H, d, *J* = 5.0 Hz, C**4**-H), 7.47-7.38 (3H, m, C**2**-H, 2 × C**10**-H and C**11**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.5 (C**1**), 153.2 (C**5**), 141.3 (q, $^2J_{C\text{-}F}$ = 34.0 Hz, C**3**), 140.3 (C**7**), 135.2 (C**8**), 130.1 (C**11**), 129.0 (C**10**), 128.2 (C**9**), 121.6 (C**6**), 121.4 (q, $^1J_{C\text{-}F}$ = 275.0 Hz, C**2**), 117.5 (q, $^3J_{C\text{-}F}$ = 4.5 Hz, C**4**), 113.4 (C**12**), 103.2 (q, $^3J_{C\text{-}F}$ = 2.0 Hz, C**2**); HRMS: (ESI^+) Calculated for $C_{15}H_{10}F_3N_2$: 275.0791. Found $[M+H]^+$: 275.0801. *The regiochemistry of compound iso-**2k** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 15.5 Hz].*

(*E*)-6-Methyl-2-styrylnicotinonitrile (2l)

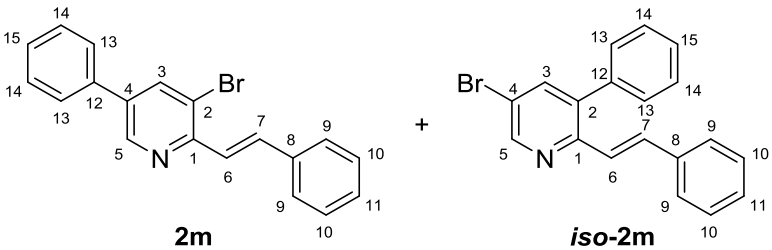




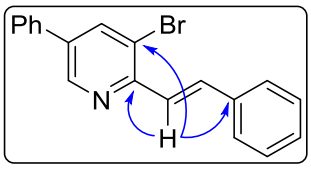
HMBC analysis

General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine **2l** (16.7 mg, 53% yield) as a yellow oil; ν_{max} / cm^{-1}: 3053 (m), 2982 (s), 2921 (m), 2225 (s), 1581 (s), 1494 (s), 1264 (s), 1053 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (1H, d, *J* = 15.5 Hz, C**7**-H), 7.79 (1H, d, *J* = 8.0 Hz, C**3**-H), 7.69-7.63 (2H, m, 2 × C**9**-H), 7.50 (1H, d, *J* = 15.5 Hz, C**6**-H), 7.45-7.33 (3H, m, 2 × C**10**-H and C**11**-H), 7.09 (1H, d, *J* = 8.0 Hz, C**4**-H), 2.66 (3H, s, C**13**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6 (C**5**), 156.8 (C**1**), 140.3 (C**3**), 137.4 (C**7**), 135.8 (C**8**), 129.3 (C**11**), 128.8 (C**10**), 127.8 (C**9**), 123.0 (C**6**), 121.3 (C**4**), 117.2 (C**12**), 104.5 (C**2**), 25.3 (C**13**); HRMS: (ESI^+) Calculated for $C_{15}H_{13}N_2$: 221.1073. Found $[M+H]^+$: 221.1070. *The regiochemistry of compound **2l** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 15.5 Hz].*

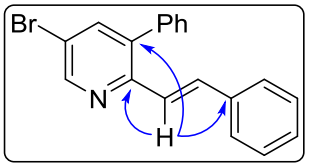
(*E*)-3-Bromo-5-phenyl-2-styrylpyridine (2m) and *iso*-2m isomer



2m + ***iso*-2m**



HMBC analysis

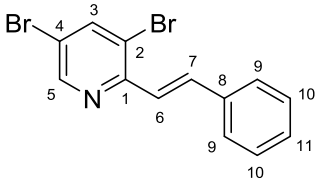


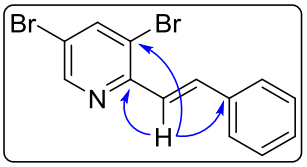
HMBC analysis

General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded a 0.8:0.2 mixture of pyridine **2m** and *iso*-**2m** (25.8 mg, 54% yield) as a yellow solid; ν_{max} / cm^{-1}: 3055 (m), 3025 (m), 2922 (m), 2845 (m), 1628 (s), 1576 (s), 1448 (s), 1440 (s), 1033 (s), 1013 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.79 (0.8H, d, *J* = 2.0 Hz, C**5**-H, **2m**), 8.67 (0.2H,

d, *J* = 2.0 Hz, C**5**-H, *iso*-**2m**), 8.07 (0.8H, d, *J* = 2.0 Hz, C**3**-H, **2m**), 7.89 (0.8H, d, *J* = 15.5 Hz, C**7**-H, **2m**), 7.82 (0.2H, d, *J* = 15.5 Hz, C**7**-H, *iso*-**2m**), 7.75 (0.2H, d, *J* = 2.0 Hz, C**3**-H, *iso*-**2m**), 7.70-7.24 (10.8H, m, C**6**-H for **2m** and C_{Ar}-H *for* **2m** *and iso*-**2m**), 7.11 (0.2H, d, *J* = 15.5 Hz, C**6**-H, *iso*-**2m**); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.7 (C**1**, **2m**), 151.0 (C**1**, *iso*-**2m**), 149.3 (C**5**, *iso*-**2m**), 146.4 (C**5**, **2m**), 140.0 (C**3**, *iso*-**2m**), 138.6 (C**3**, **2m**), 137.6 (*2 signals*, C**2** and C**12**, *iso*-**2m**), 136.7 (C**8**, *iso*-**2m**), 136.5 (C**8**, **2m**), 136.2 (C**4**, **2m**), 136.1 (C**12**, **2m**), 135.7 (C**7**, **2m**), 134.2 (C**7**, *iso*-**2m**), 129.5 (C_{Ar}-H, *iso*-**2m**), 129.2 (C_{Ar}-H, **2m**), 128.8 (C_{Ar}-H, **2m**), 128.7 (C_{Ar}-H, **2m**), 128.6 (*2 signals*, C_{Ar}-H, *iso*-**2m**), 128.5 (C_{Ar}-H, **2m**), 128.4 (C_{Ar}-H, *iso*-**2m**), 128.2 (C_{Ar}-H, *iso*-**2m**), 127.5 (C_{Ar}-H, **2m**), 127.3 (C_{Ar}-H, *iso*-**2m**), 126.9 (C_{Ar}-H, **2m**), 124.4 (*2 signals*, C**6**, **2m** and *iso*-**2m**), 121.1 (C**2**, **2m**), 118.3 (C**4**, *iso*-**2m**); HRMS: (ESI$^+$) Calculated for $C_{19}H_{15}(^{79}Br)N$: 336.0382. Found [M+H]$^+$: 336.0382. *The regiochemistry of compounds* ***2m*** *and iso-****2m*** *was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**7**-H [J = 15.5 Hz] for* ***2m*** *and for C**6**-H and C**7**-H [J = 15.5 Hz] for iso-****2m****.*

(*E*)-3,5-Dibromo-2-styrylpyridine (2n)

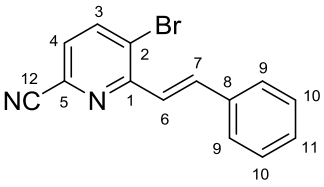


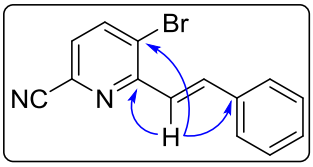


HMBC analysis

General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine **2n** (33.2 mg, 69% yield) as an off-white solid; m.p. = 112-113 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3080 (m), 3056 (m), 3025 (s), 2853 (s), 1628 (s), 1429 (s), 1207 (s), 1020 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (1H, d, *J* = 2.0 Hz, C**5**-H), 8.01 (1H, d, *J* = 2.0 Hz, C**3**-H), 7.84 (1H, d *J* = 15.5 Hz, C**7**-H), 7.65-7.59 (2H, m, 2 × C**9**-H), 7.52 (1H, d *J* = 15.5 Hz, C**6**-H), 7.43-7.30 (3H, m, 2 × C**10**-H and C**11**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.0 (C**1**), 149.1 (C**5**), 142.5 (C**3**), 136.6 (C**7**), 136.4 (C**8**), 129.1 (C**11**), 128.9 (C**10**), 127.7 (C**9**), 123.7 (C**6**), 120.8 (C**2**), 118.1 (C**4**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{10}(^{79}Br)_2N$: 337.9180. Found [M+H]$^+$: 337.9127. *The regiochemistry of compound* ***2n*** *was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 15.5 Hz].*

(*E*)-5-Bromo-6-styrylpicolinonitrile (2o)

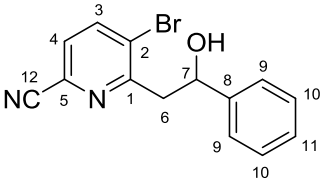


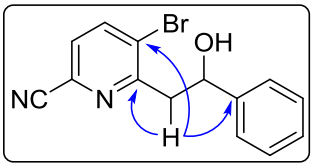


HMBC analysis

An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with 5-bromo-2-cyanopyridine *N*-oxide (28.4 mg, 0.143 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of styrene (82.1 µL, 0.710 mmol, 500 mol%) and TsOH·H_2O (1.36 mg, 7.14 µmol, 5 mol%) in 0.1 mL of a 50:1 v/v mixture of DMSO and H_2O was added *via* syringe and the tube was sealed with a Young's tap. The reaction vessel was placed into a pre-heated heating block at 120 °C and stirred for 16 hours. The tube was cooled to room temperature and the tap was replaced with a rubber septum. Acetic anhydride (13.5 µL, 0.143 mmol, 100 mol%) was added to the solution and the vessel was re-sealed with the tap. The reaction was stirred for further 16 hours at 120 °C. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification of the residue by FCC (10% EtOAc/hexane → 30% EtOAc/hexane) afforded pyridine **2o** (27.3 mg, 67% yield) as a yellow solid; m.p. = 147-148 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3026 (m), 3054 (m), 2922 (s), 2851 (m), 2238 (s), 1624 (s), 1549 (s), 1418 (s), 1012 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (1H, d, *J* = 8.0 Hz, C**3**-H), 7.96 (1H, d, *J* = 15.5 Hz, C**7**-H), 7.67-7.63 (2H, m, 2 × C**9**-H), 7.55 (1H, d, *J* = 15.5 Hz, C**6**-H), 7.45-7.34 (4H, m, C**4**-H, 2 × C**10**-H and C**11**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3 (C**1**), 141.7 (C**3**), 138.9 (C**7**), 135.7 (C**8**), 132.1 (C**5**), 129.5 (C**11**), 128.9 (C**10**), 127.9 (C**9**), 126.4 (C**4**), 124.2 (C**2**), 122.6 (C**6**), 116.8 (C1**2**); HRMS: (ESI$^+$) Calculated for $C_{14}H_{10}(^{79}Br)N_2$: 285.0022. Found $[M+H]^+$: 285.0024. *The regiochemistry of compound **2o** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 15.5 Hz].*

Data for **5-Bromo-6-(2-hydroxy-2-phenylethyl)picolinonitrile** *intermediate*



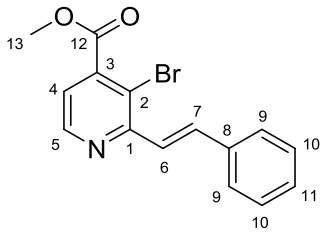


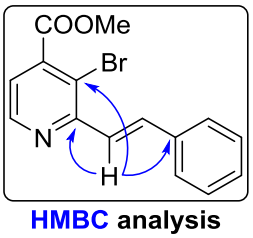
HMBC analysis

When the Ac_2O step was omitted, this compound was isolated by FCC (10% EtOAc/hexane → 30% EtOAc/hexane) as a yellow oil; ν_{max} / cm^{-1}: 3326 (s), 2942 (s), 2831 (m), 2222 (s), 1451 (s), 1270 (s), 1023 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, d, *J* = 8.0 Hz, C**3**-H), 7.50-7.43 (3H, m, C**4**-H and 2 × C**9**-H), 7.43-7.35 (2H, m, 2 × C**10**-H), 7.35-7.28 (1H, m, C**11**-H), 5.34 (1H, dt, *J* = 3.0, 6.5 Hz, C**7**-H), 3.71 (1H, d, *J* = 3.0 Hz, OH), 3.36 (2H, d, *J* = 6.5 Hz, C**6**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5 (C**1**), 143.0 (C**8**), 141.4 (C**3**), 131.3 (C**5**), 128.6 (C**10**), 127.8 (C**11**), 127.2 (C**4**), 126.6 (C**2**), 125.8 (C**9**), 116.5 (C1**2**), 71.8 (C**7**), 45.6 (C6); HRMS: (ESI$^+$) Calculated for $C_{14}H_{11}(^{79}Br)N_2NaO$:

324.9947. Found $[M+Na]^+$: 324.9954. *The regiochemistry of the isolated compound was confirmed by HMBC analysis (as indicated above).*

Methyl (*E*)-3-bromo-2-styrylisonicotinate (2p)

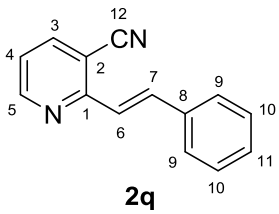




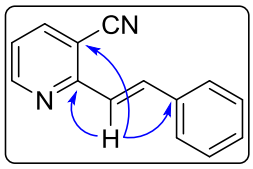
HMBC analysis

General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours and afforded pyridine **2p** (21.9 mg, 48% yield) as a yellow oil; ν_{max} / cm^{-1}: 3053 (m), 2986 (s), 1739 (s), 1629 (s), 1577 (s), 1264 (s), 1111 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.59 (1H, d, *J* = 4.5 Hz, C**5**-H), 7.87 (1H, d, *J* = 15.5 Hz, C**7**-H), 7.75 (1H, d, *J* = 15.5 Hz, C**6**-H), 7.67-7.61 (2H, m, 2 × C**9**-H), 7.44-7.37 (2H, m, 2 × C**10**-H), 7.37-7.32 (1H, m, C**11**-H), 7.30 (1H, d, *J* = 4.5 Hz, C**4**-H), 3.98 (3H, s, C**13**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.1 (C**12**), 155.0 (C**1**), 147.9 (C**5**), 142.1 (C**3**), 137.1 (C**7**), 136.3 (C**8**), 129.0 (C**11**), 128.8 (C**10**), 127.6 (C**9**), 124.5 (C**6**), 121.6 (C**4**), 117.6 (C**2**), 53.0 (C**13**); HRMS: (ESI^+) Calculated for $C_{15}H_{13}(^{79}Br)NO_2$: 318.0124. Found $[M+H]^+$: 318.0125. *The regiochemistry of compound **2p** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 15.5 Hz].*

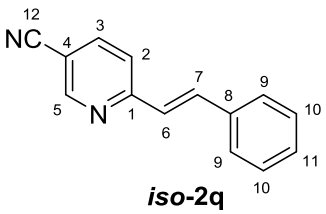
(*E*)-2-Styrylnicotinonitrile (2q) and *iso*-2q isomer



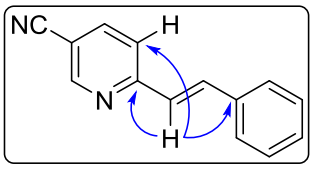
2q



HMBC analysis



***iso*-2q**



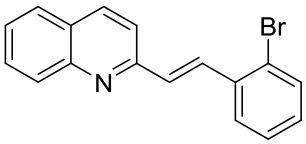
HMBC analysis

General Procedure D: $TsOH \cdot H_2O$ was employed as the catalyst. A solution of styrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 140 °C for 24 hours. Purification by FCC afforded pyridine *iso*-**2q** (6.3 mg, 21% yield) as an off-white solid. Continued elution provided regioisomer **2q** (18.7 mg, 64% yield) as an off-white solid.

Data for **2q**: m.p. = 99-101 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3057 (m), 3024 (m), 2922 (s), 2845 (m), 2222 (s), 1632 (s), 1573 (s), 1425 (s), 1032 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (1H, dd, *J* = 2.0, 5.0 Hz, C**3**-H), 8.04 (1H, d, *J* = 15.5 Hz, C**7**-H), 7.92 (1H, dd, *J* = 2.0, 8.0 Hz, C**5**-H), 7.69-7.63 (2H, m, 2 × C**9**-H), 7.53 (1H, d, *J* = 15.5 Hz, C**6**-H), 7.47-7.32 (3H, m, 2 × C**10**-H and C**11**-H), 7.25 (1H, dd, *J* = 5.0, 8.0 Hz, C**4**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4 (C**1**), 152.7 (C**3**), 140.5 (C**5**), 138.0 (C**7**), 135.6 (C**8**), 129.5 (C**11**), 128.9 (C**10**), 127.9 (C**9**), 122.6 (C**6**), 121.3 (C**4**), 116.7 (C**12**), 107.5 (C**2**); HRMS: (ESI^+) Calculated for $C_{14}H_{11}N_2$: 207.0917. Found $[M+H]^+$: 207.0914. *The regiochemistry of compound* ***2q*** *was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 15.5 Hz].*

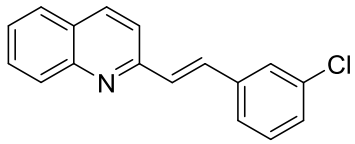
*Data for iso-***2q**: m.p. = 102-104 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3024 (m), 2921 (s), 2845 (m), 2221 (s), 1582 (s), 1475 (s), 1033 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.84 (1H, d, *J* = 2.0 Hz, C**5**-H), 7.90 (1H, dd, *J* = 8.0, 2.0 Hz, C**3**-H), 7.81 (1H, d, *J* = 16.0 Hz, C**7**-H), 7.61 (2H, dd, *J* = 7.5, 2.0 Hz, 2 × C**9**-H), 7.47-7.33 (4H, m, C**2**-H, 2 × C**10**-H and C**11**-H), 7.17 (1H, d, *J* = 16.0 Hz, C**6**-H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1 (C**1**), 152.6 (C**5**), 139.8 (C**3**), 137.2 (C**7**), 135.8 (C**8**), 129.6 (C**11**), 129.1 (C**10**), 127.8 (C**9**), 126.3 (C**6**), 121.8 (C**2**), 117.3 (C**12**), 107.4 (C**4**); HRMS: (ESI^+) Calculated for $C_{14}H_{11}N_2$: 207.0917. Found $[M+H]^+$: 207.0912. *The regiochemistry of compound iso-****2q*** *was confirmed by HMBC analysis (as indicated above) and by the multiplicity of C**5**-H signal in ^{1}H NMR (doublet, J = 2.0 Hz). The geometry of the double bond was confirmed by the coupling constants observed for C**6**-H and C**7**-H [J = 16.0 Hz].*

(*E*)-2-(2-Bromostyryl)quinoline (3a)



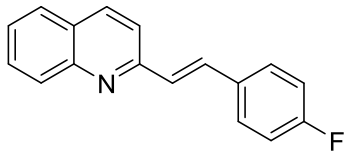
General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of 2-bromostyrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3a** (35.2 mg, 80% yield) as an off-white solid; m.p. = 58-60 °C [hexane/CH_2Cl_2]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (1H, d, *J* = 8.5 Hz), 8.10 (1H, dd, *J* = 1.0, 8.5 Hz), 7.99 (1H, d, *J* = 16.5 Hz), 7.83-7.74 (3H, m), 7.71 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz), 7.62 (1H, dd, *J* = 1.5, 8.5 Hz), 7.51 (1H, ddd, *J* = 1.0, 7.0, 8.0 Hz), 7.41-7.30 (2H, m), 7.17 (1H, ddd, *J* = 1.5, 7.0, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.8, 148.3, 136.5, 136.4, 133.3, 133.0, 132.1, 129.9, 129.8, 129.4, 127.8, 127.6, 127.5, 127.3, 126.5, 124.8, 119.0. *The spectroscopic proprieties were consistent with the data available in literature.*[9]

(*E*)-2-(3-Chlorostyryl)quinoline (3b)



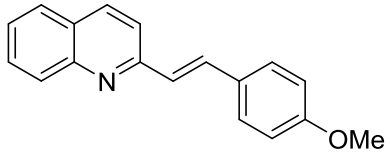
General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of 3-chlorostyrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3b** (38.3 mg, quantitative yield) as an off-white solid; m.p. = 91-93 °C [hexane/CH_2Cl_2] (Lit.[9] 96-99 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (1H, d, *J* = 8.5 Hz), 8.09 (1H, dd, *J* = 1.0, 8.5 Hz), 7.78 (1H, dd, *J* = 1.0, 8.5 Hz), 7.75-7.67 (1H, m), 7.66-7.58 (3H, m), 7.54-7.46 (2H, m), 7.38 (1H, d, *J* = 16.5 Hz), 7.35-7.26 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 148.4, 138.6, 136.6, 134.9, 132.9, 130.4, 130.1, 130.0, 129.4, 128.6, 127.6 (*2 signals*), 127.2, 126.5, 125.5, 119.6. *The spectroscopic proprieties were consistent with the data available in literature.*[9]

(*E*)-2-(4-Fluorostyryl)quinoline (3c)



General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of 4-fluorostyrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3c** (32.6 mg, 92% yield) as an off-white solid; m.p. = 121-123 °C [hexane/CH_2Cl_2] (Lit.[10] 123-125 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (1H, d, *J* = 8.5 Hz), 8.08 (1H, d, *J* = 8.5 Hz), 7.77 (1H, dd, *J* = 1.0, 8.0 Hz), 7.74-7.56 (5H, m), 7.49 (1H, ddd, *J* = 1.0, 7.0, 8.0 Hz), 7.31 (1H, d, *J* = 16.0 Hz), 7.15-7.02 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0 (d, $^1J_{C\text{-}F}$ = 248.5 Hz), 155.9, 148.4, 136.5, 133.2, 132.8 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 129.9, 129.3, 128.9 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 128.8 (d, $^5J_{C\text{-}F}$ = 2.5 Hz), 127.6, 127.4, 126.3, 119.4, 115.9 (d, $^2J_{C\text{-}F}$ = 21.5 Hz). *The spectroscopic proprieties were consistent with the data available in literature.*[10]

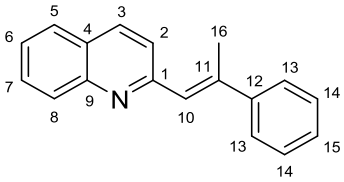
(*E*)-2-(4-Methoxystyryl)quinoline (3d)

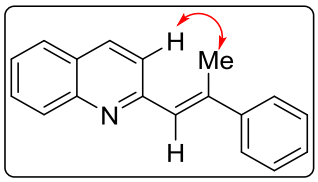


General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of 4-methoxystyrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3d** (29.1 mg, 78% yield) as an off-white solid; m.p. = 120-122 °C [hexane/CH_2Cl_2] (Lit.[6] 125-127 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10-8.03

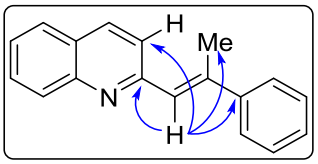
(2H, m), 7.75 (1H, dd, *J* = 1.5, 8.0 Hz), 7.71-7.54 (5H, m), 7.46 (1H, ddd, *J* = 1.0, 7.0, 8.0 Hz), 7.27 (1H, d, *J* = 16.5 Hz), 6.95-6.89 (2H, m), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 156.4, 148.4, 136.3, 134.2, 129.8, 129.4, 129.2, 128.7, 127.6, 127.3, 126.9, 126.0, 119.2, 114.4, 55.4. *The spectroscopic proprieties were consistent with the data available in literature.*[7]

(*E*)-2-(2-Phenylprop-1-en-1-yl)quinoline (3e)





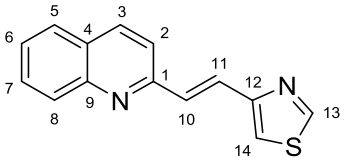
nOe analysis

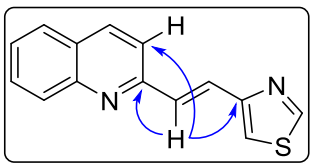


HMBC analysis

General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of α-methylstyrene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3e** (9.5 mg, 27% yield) as off-white solid; m.p. = 96-98 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3053 (m), 2922 (s), 2863 (m), 2845 (m), 1594 (s), 1444 (s), 1032 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17-8.08 (2H, m, C**3**-H and C**8**-H), 7.80 (1H, dd, *J* = 1.5, 8.0 Hz, C**5**-H), 7.71 (1H, ddd, *J* = 1.5, 7.0, 8.0 Hz, C**7**-H), 7.65-7.59 (2H, m, 2 × C**13**-H), 7.55-7.48 (1H, m, C**6**-H), 7.46 (1H, d, *J* = 8.5 Hz, C**2**-H), 7.41 (2H, dd, *J* = 7.0, 8.0 Hz, 2 × C**14**-H), 7.37-7.31 (1H, m, C**15**-H), 7.02 (1H, s, C**10**-H), 2.65 (3H, s, C**16**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4 (C**1**), 148.0 (C**9**), 143.9 (C**11**), 143.6 (C**12**), 135.8 (C**3**), 129.5 (C**7**), 129.3 (C**8**), 128.4 (C**14**), 127.8 (C**15**), 127.4 (C**5**), 127.1 (C**10**), 126.4 (C**4**), 126.2 (C**13**), 126.1 (C**6**), 123.0 (C**2**), 18.0 (C**16**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{16}N$: 246.1277. Found $[M+H]^+$: 246.1273. *The regiochemistry of compound **3e** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by 1D gradient nOe analysis (as shown above). Selective irradiation of signal for C**16**-H_3 revealed a positive peak for C**2**-H signal.*

(*E*)-4-(2-(Quinolin-2-yl)vinyl)thiazole (3f)



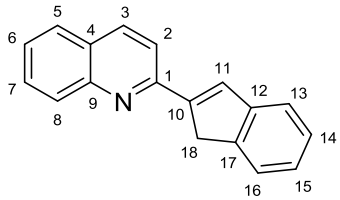


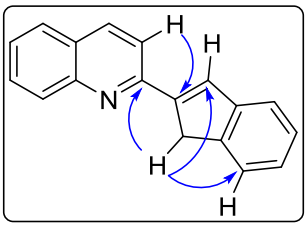
HMBC analysis

General Procedure D: TFA was employed as the catalyst. A solution of 4-vinylthiazole (500 mol%) in NMP/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3f** (19.3 mg, 57% yield) as off-white solid; m.p. = 81-82 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3062 (m), 3045 (m), 2965 (s), 2922 (s), 2844 (m), 1595 (s), 1503 (s), 1428 (s), 1315 (s),

1033 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.85 (1H, d, *J* = 2.0 Hz, C**13**-H), 8.12 (1H, d, *J* = 8.5 Hz, C**3**-H), 8.09 (1H, d, *J* = 8.5 Hz, C**8**-H), 7.87 (1H, d, *J* = 16.0 Hz, C**11**-H), 7.78 (1H, dd, *J* = 1.5, 8.0 Hz, C**5**-H), 7.75-7.66 (2H, m, C**7**-H and C**10**-H), 7.57 (1H, d, *J* = 8.5 Hz, C**2**-H), 7.49 (1H, dd, *J* = 7.0, 8.0 Hz, C**6**-H), 7.42 (1H, d, *J* = 2.0 Hz, C**14**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.4 (C**1**), 154.5 (C**12**), 153.2 (C**13**), 148.3 (C**9**), 136.4 (C**3**), 131.2 (C**10**), 129.7 (C**7**), 129.3 (C**8**), 127.5 (*2 signals*, C**4** and C**5**), 126.4 (C**11**), 126.2 (C**6**), 120.6 (C**2**), 117.1 (C**14**); HRMS: (ESI$^+$) Calculated for $C_{14}H_{11}N_2S$: 239.0637. Found $[M+H]^+$: 239.0635. *The regiochemistry of compound **3f** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C**11**-H [J = 16.0 Hz].*

2-(1*H*-Inden-2-yl)quinoline (3g)

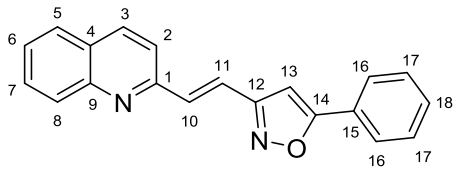


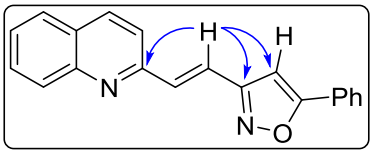


HMBC analysis

General Procedure D: TFA was employed as the catalyst. A solution of indene (500 mol%) in NMP/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3g** (13.6 mg, 39% yield) as off-white solid; m.p. = 133-135 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3057 (m), 3038 (m), 2922 (s), 2844 (m), 1596 (s), 1427 (s), 1203 (s), 1149 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14-8.07 (2H, m, C**3**-H and C**8**-H), 7.83 (1H, d, *J* = 8.5 Hz, C**2**-H), 7.78 (1H, dd, *J* = 1.5, 8.0 Hz, C**5**-H), 7.74-7.66 (2H, m, C**7**-H and C**11**-H), 7.57 (1H, dd, *J* = 1.5, 7.0 Hz, C**16**-H), 7.54-7.46 (2H, m, C**6**-H and C**13**-H), 7.36-7.25 (2H, m, C**14**-H and C**15**-H), 4.12 (2H, d, *J* = 1.5 Hz, C**18**-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.4 (C**1**), 148.3 (C**9**), 147.7 (C**10**), 144.7 (C**12**), 144.4 (C**17**), 135.9 (C**3**), 131.8 (C**11**), 129.6 (C**8**), 129.5 (C**7**), 127.4 (C**5**), 127.2 (C**4**), 126.6 (C**14**), 126.1 (C**15**), 125.9 (C**6**), 124.0 (C**16**), 121.9 (C**13**), 118.8 (C**2**), 39.1 (C**18**); HRMS: (ESI$^+$) Calculated for $C_{18}H_{14}N$: 244.1121. Found $[M+H]^+$: 244.1123. *The regiochemistry of compound **3g** was confirmed by HMBC analysis (as indicated above).*

(*E*)-5-Phenyl-3-(2-(quinolin-2-yl)vinyl)isoxazole (3h)



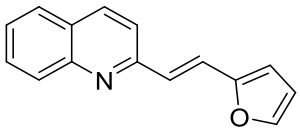


HMBC analysis

General Procedure D: TFA was employed as the catalyst. A solution of 5-phenyl-3-vinylisoxazole (500 mol%) in NMP/H_2O mixture was added to the reaction tube. The reaction was conducted at 120

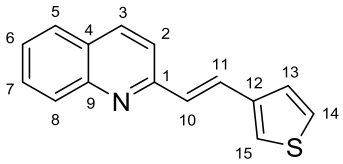
°C for 24 hours and afforded quinoline **3h** (24.4 mg, 63% yield) as a colourless solid; m.p. = 175-176 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 2981 (m), 2938 (s), 2922 (s), 2844 (m), 2253 (s), 1615 (s), 1574 (s), 1430 (s), 1033 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.17 (1H, d, *J* = 8.5 Hz, C**3**-H), 8.09 (1H, d, *J* = 8.5 Hz, C**8**-H), 7.85-7.77 (3H, m, C**5**-H and 2 × C**16**-H), 7.77-7.64 (3H, m, C**2**-H, C**7**-H and C**11**-H), 7.58-7.41 (5H, m, C**6**-H, C**10**-H, 2 × C**17**-H and C**18**-H), 6.84 (1H, s, C**13**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1 (C**14**), 161.9 (C**12**), 154.5 (C**1**), 148.2 (C**9**), 136.7 (C**3**), 136.3 (C**10**), 130.3 (C**18**), 130.0 (C**7**), 129.5 (C**8**), 129.0 (C**17**), 127.7 (C**4**), 127.6 (C**5**), 127.2 (C**15**), 126.9 (C**6**), 125.9 (C**16**), 121.6 (C**11**), 118.9 (C**2**), 96.7 (C**13**); HRMS: (ESI^+) Calculated for $C_{20}H_{15}N_2O$: 299.1179. Found $[M+H]^+$: 299.1184. *The regiochemistry of compound **3h** was confirmed by HMBC analysis (as indicated above).*

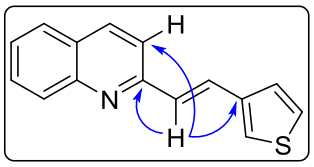
(*E*)-2-(2-(Furan-2-yl)vinyl)quinoline (3i)



General Procedure D: TFA was employed as the catalyst. A solution of 4-vinylfuran (500 mol%) in NMP/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3i** (15.9 mg, 50% yield) as a yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (1H, d, *J* = 8.5 Hz), 8.06 (1H, d, *J* = 8.5 Hz), 7.76 (1H, dd, *J* = 1.5, 8.0 Hz), 7.69 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz), 7.61-7.44 (4H, m), 7.28 (1H, d, *J* = 16.0 Hz), 6.54 (1H, d, *J* = 3.5 Hz), 6.47 (1H, dd, *J* = 2.0, 3.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 152.8, 148.3, 143.2, 136.3, 129.7, 129.2, 127.5, 127.3, 126.8, 126.0, 121.7, 119.9, 112.0, 111.1. *The spectroscopic proprieties were consistent with the data available in literature.*[7]

(*E*)-2-(2-(Thiophen-3-yl)vinyl)quinoline (3j)



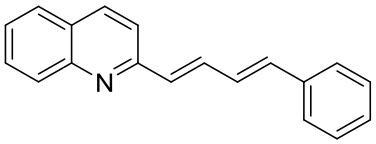


HMBC analysis

General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of 3-vinylthiophene (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3j** (27.3 mg, 80% yield) as brown solid; m.p. = 125-127 °C [hexane/CH_2Cl_2]; ν_{max} / cm^{-1}: 3104 (m), 3007 (m), 2922 (s), 2865 (m), 1590 (s), 1550 (s), 1412 (s), 1116 (s), 1055 (s); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (1H, d, *J* = 8.5 Hz, C**3**-H), 8.06 (1H, d, *J* = 8.5 Hz, C**8**-H), 7.76 (1H, dd, *J* = 1.5, 8.0 Hz, C**5**-H), 7.73-7.65 (2H, m, C**7**-H and C**11**-H), 7.62 (1H, d, *J* = 8.5 Hz, C**2**-H), 7.53-7.41 (3H, m, C**6**-H, C**14**-H and C**15**-H), 7.35 (1H, dd, *J* = 3.0, 5.0 Hz, C**13**-H),

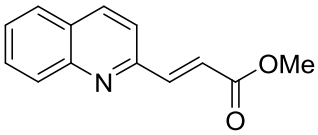
7.24 (1H, d, *J* = 16.0 Hz, C**10**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.1 (C**1**), 148.2 (C**9**), 139.5 (C**12**), 136.3 (C**3**), 129.7 (C**7**), 129.1 (C**8**), 128.9 (C**10**), 128.4 (C**11**), 127.5 (C**5**), 127.3 (C**4**), 126.5 (C**13**), 126.1 (C**6**), 125.1 (C**14**), 124.7 (C**15**), 119.0 (C**2**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{12}NS$: 238.0685. Found $[M+H]^+$: 238.0682. *The regiochemistry of compound **3j** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constant observed for C**10**-H [J = 16.0 Hz]*.

2-((1*E*,3*E*)-4-Phenylbuta-1,3-dien-1-yl)quinoline (3k)



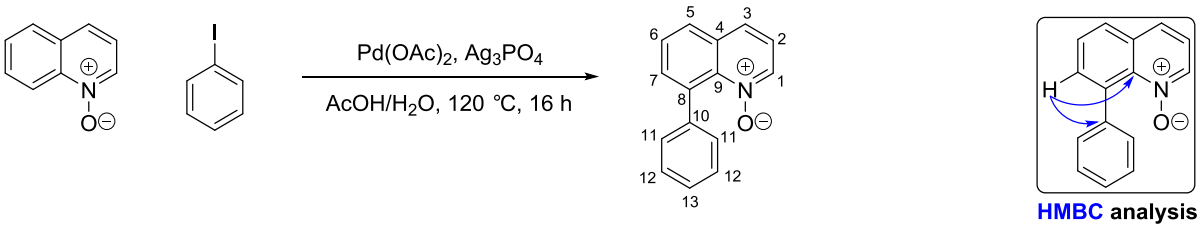
General Procedure D: TFA was employed as the catalyst. A solution of *trans*-1-phenyl-1,3-butadiene (500 mol%) in NMP/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3k** (18.7 mg, 51% yield) as an off-white solid; m.p. = 107-109 °C [hexane/CH_2Cl_2] (Lit.[8] 110-112 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12-8.02 (2H, m), 7.76 (1H, dd, *J* = 1.5, 8.0 Hz), 7.69 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz), 7.61-7.43 (5H, m), 7.41-7.32 (2H, m), 7.32-7.24 (1H, m), 7.06 (1H, ddd, *J* = 1.0, 10.5, 15.5 Hz), 6.96 (1H, d, *J* = 15.5 Hz), 6.86 (1H, d, *J* = 15.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.0, 148.3, 136.9, 136.2, 136.0, 134.9, 132.8, 129.7, 129.2, 128.7, 128.6, 128.1, 127.5, 127.3, 126.8, 126.1, 119.4. *The spectroscopic proprieties were consistent with the data available in literature.*[7]

Methyl (*E*)-3-(quinolin-2-yl)acrylate (3l)



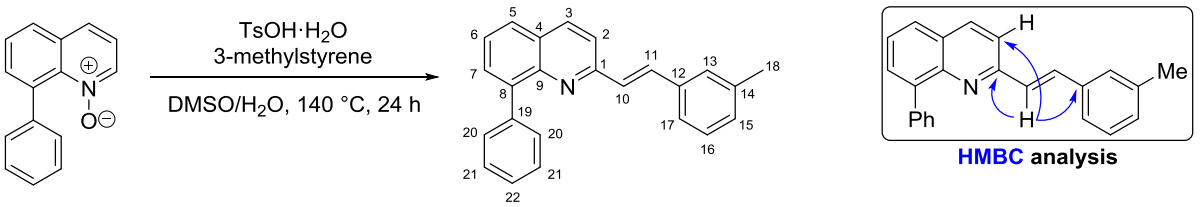
General Procedure D: TsOH·H_2O was employed as the catalyst. A solution of methyl acrylate (500 mol%) in DMSO/H_2O mixture was added to the reaction tube. The reaction was conducted at 120 °C for 24 hours and afforded quinoline **3l** (5.1 mg, 17% yield) as an yellow solid; m.p. = 75-76 °C [hexane/CH_2Cl_2] (Lit.[11] 79-80 °C [*no solvent quoted*] [MeOH]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (1H, d, *J* = 8.5 Hz), 8.11 (1H, d, *J* = 8.0 Hz), 7.91 (1H, d, *J* = 16.0 Hz), 7.85-7.80 (1H, m), 7.74 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz), 7.62 (1H, d, *J* = 8.5 Hz), 7.57 (1H, ddd, *J* = 1.0, 7.0, 8.0 Hz), 7.01 (d, *J* = 16.0 Hz), 3.86 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.0, 153.1, 148.3, 144.3, 136.8, 130.1, 129.9, 128.1, 127.5, 127.3, 123.2, 120.4, 51.9. *The spectroscopic proprieties were consistent with the data available in literature.*[12]

8-Phenylquinoline *N*-oxide (4)



The title compound was prepared following a literature procedure.[13] An oven-dried sealed tube was charged with quinoline *N*-oxide (145 mg, 1.00 mmol, 100 mol%), Ag_3PO_4 (dried overnight at 90 °C under high-vacuum, 209 mg, 0.50 mmol, 50 mol%) and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%). The vessel was fitted with a rubber septum and flushed with argon. Degassed glacial acetic acid (1.72 mL, 30.0 mmol, 3000 mol%) and degassed deionized water (0.720 mL, 40.0 mmol, 4000 mol%) were added to the vessel followed by iodobenzene (0.336 mL, 3.00 mmol, 300 mol%). The tube was sealed with a Young's tap, placed into a pre-heated heating-block at 120 °C and stirred for 16 hours. The reaction was then cooled to room temperature and diluted with 5 mL of a 1:3 v/v mixture of 30% aq. NH_3 and saturated aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The organic portions were combined, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification of the crude material by FCC (EtOAc → 10% MeOH/EtOAc) afforded quinoline *N*-oxide **4** (222 mg, quantitative yield) as a brown wax; ν_{max} / cm^{-1}: 3054 (m), 2981 (s), 2922 (s), 2844 (m), 1569 (s), 1421 (s), 1306 (s), 1264 (s), 1033 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 (1H, dd, *J* = 1.0, 6.0 Hz, C**1**-H), 7.88 (1H, dd, *J* = 1.5, 7.5 Hz, C**5**-H), 7.76 (1H, dd, *J* = 1.0, 8.5 Hz, C**3**-H), 7.61 (1H, dd, *J* = 7.5, 7.5 Hz, C**6**-H), 7.53 (1H, dd, *J* = 1.5, 7.5 Hz, C**7**-H), 7.42-7.25 (6H, m, C**2**-H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.7 (C**10**), 139.2 (C**9**), 136.9 (C**1**), 136.4 (C**8**), 134.2 (C**7**), 132.0 (C**4**), 128.4 (C**5**), 128.0 (C**12**), 127.6 (C**6**), 126.9 (C**11**), 126.2 (C**3**), 125.9 (C**13**), 121.2 (C**2**); HRMS: (ESI^+) Calculated for $C_{15}H_{12}NO$: 222.0913. Found $[M+H]^+$: 222.0920. *The regiochemistry of compound **4** was confirmed by HMBC analysis (as indicated above). The product structure was further confirmed by the presence of the characteristic C**1**-H peak at 136.9 ppm in ^{13}C-NMR spectrum.*

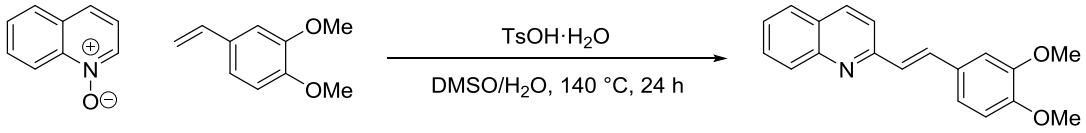
(*E*)-2-(3-Methylstyryl)-8-phenylquinoline (5)



An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with 8-Phenylquinoline *N*-oxide **4** (74.4 mg, 0.336 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of 3-methylstyrene (0.223 mL, 1.68 mmol, 500 mol%) and $TsOH·H_2O$ (3.19 mg, 0.0168 mmol, 5 mol%) in 0.2 mL of a 50:1 v/v mixture of DMSO and H_2O was added *via* syringe and

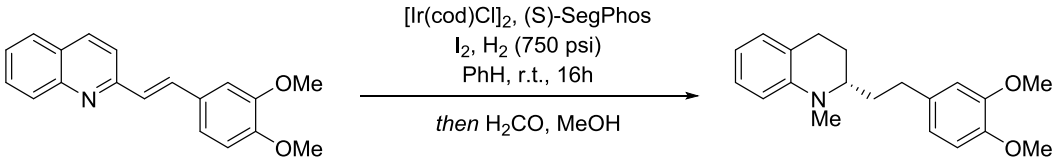
the tube was sealed with a Young's tap. The reaction vessel was placed into a pre-heated heating block at 140 °C and stirred for 24 hours. Purification of the residue by FCC (10% EtOAc/hexane → 30% EtOAc/hexane) afforded quinoline **5** (69.8 mg, 65% yield) as a brown wax; ν_{max} / cm^{-1}: 2981 (m), 2973 (m), 2938 (s), 2922 (s), 2865 (m), 2844 (m), 1598 (s), 1499 (s), 1379 (s), 1033 (s); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (1H, d, *J* = 8.5 Hz, C**3**-H), 7.93-7.87 (2H, m, 2 × C**20**-H), 7.82-7.76 (2H, m, C**5**-H and C**7**-H), 7.66 (1H, d, *J* = 16.0 Hz, C**11**-H), 7.64 (1H, d, *J* = 8.5 Hz, C**2**-H), 7.61-7.54 (3H, m, C**6**-H and 2 × C**21**-H), 7.52-7.46 (1H, m, C**22**-H), 7.46-7.39 (2H, m, C**13**-H and C**17**-H), 7.35 (1H, d, *J* = 16.0 Hz, C**10**-H), 7.30 (1H, dd, *J* = 7.5, 7.5 Hz, C**16**-H), 7.19-7.13 (1H, m, C**15**-H), 2.42 (3H, s, C**18**-H_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5 (C**1**), 145.7 (C**9**), 140.3 (C**8**), 139.5 (C**19**), 138.3 (C**14**), 136.6 (C**12**), 136.5 (C**3**), 134.3 (C**11**), 131.2 (C**20**), 130.5 (C**7**), 129.3 (C**15**), 129.2 (C**10**), 128.6 (C**16**), 127.9 (C**13**), 127.8 (C**4**), 127.7 (C**21**), 127.2 (*2 signals*, C**5** and C**22**), 125.9 (C**6**), 124.6 (C**17**), 119.5 (C**2**), 21.5 (C**18**); HRMS: (ESI^+) Calculated for $C_{24}H_{20}N$: 322.1590. Found $[M+H]^+$: 322.1595. *The regiochemistry of compound **5** was confirmed by HMBC analysis (as indicated above). The geometry of the double bond was confirmed by the coupling constants observed for C**10**-H and C**11**-H [J = 16.0 Hz].*

(*E*)-2-(3,4-Dimethoxystyryl)quinoline (7)



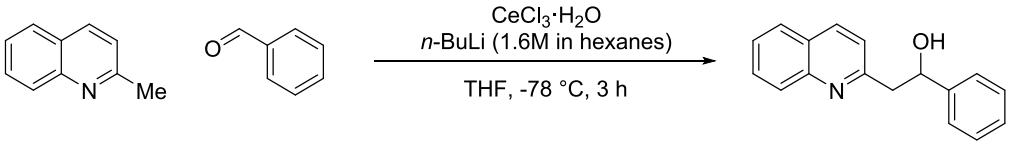
An oven-dried re-sealable tube, fitted with a magnetic stirrer, was charged with quinoline *N*-oxide (88.4 mg, 0.609 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with nitrogen. A solution of 3,4-dimethoxystyrene (0.298 mL, 2.03 mmol, 330 mol%) and $TsOH·H_2O$ (8.69 mg, 0.0457 mmol, 7.5 mol%) in 0.5 mL of a 50:1 v/v mixture of DMSO and H_2O was added *via* syringe and the tube was sealed with a Young's tap. The reaction vessel was placed into a pre-heated heating block at 140 °C and stirred for 24 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification of the residue by FCC (10% EtOAc/toluene → 30% EtOAc/toluene) afforded quinoline **7** (160 mg, 90% yield) as an orange solid; m.p. = 101-102 °C [hexane/CH_2Cl_2] (Lit.[14] 104-105 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (1H, d, *J* = 8.5 Hz), 8.06 (1H, d, *J* = 8.5 Hz), 7.78 (1H, dd, *J* = 1.5, 8.0 Hz), 7.73-7.66 (2H, m), 7.61 (1H, d, *J* = 16.5 Hz), 7.49 (1H, ddd, *J* = 1.0, 7.0, 8.0 Hz), 7.30 (1H, d, *J* = 16.5 Hz), 7.24 (1H, d, *J* = 2.0 Hz), 7.17 (1H, dd, *J* = 2.0, 8.5 Hz), 6.90 (1H, d, *J* = 8.5 Hz), 3.96 (3H, s), 3.93 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.3, 149.8, 149.2, 148.2, 136.3, 134.2, 129.7, 129.6, 129.0, 127.5, 127.2, 127.1, 126.0, 121.3, 118.9, 111.1, 108.8, 55.9 (*2 signals*). *The spectroscopic proprieties were consistent with the data available in literature.*[14]

(-)-Cuspareine



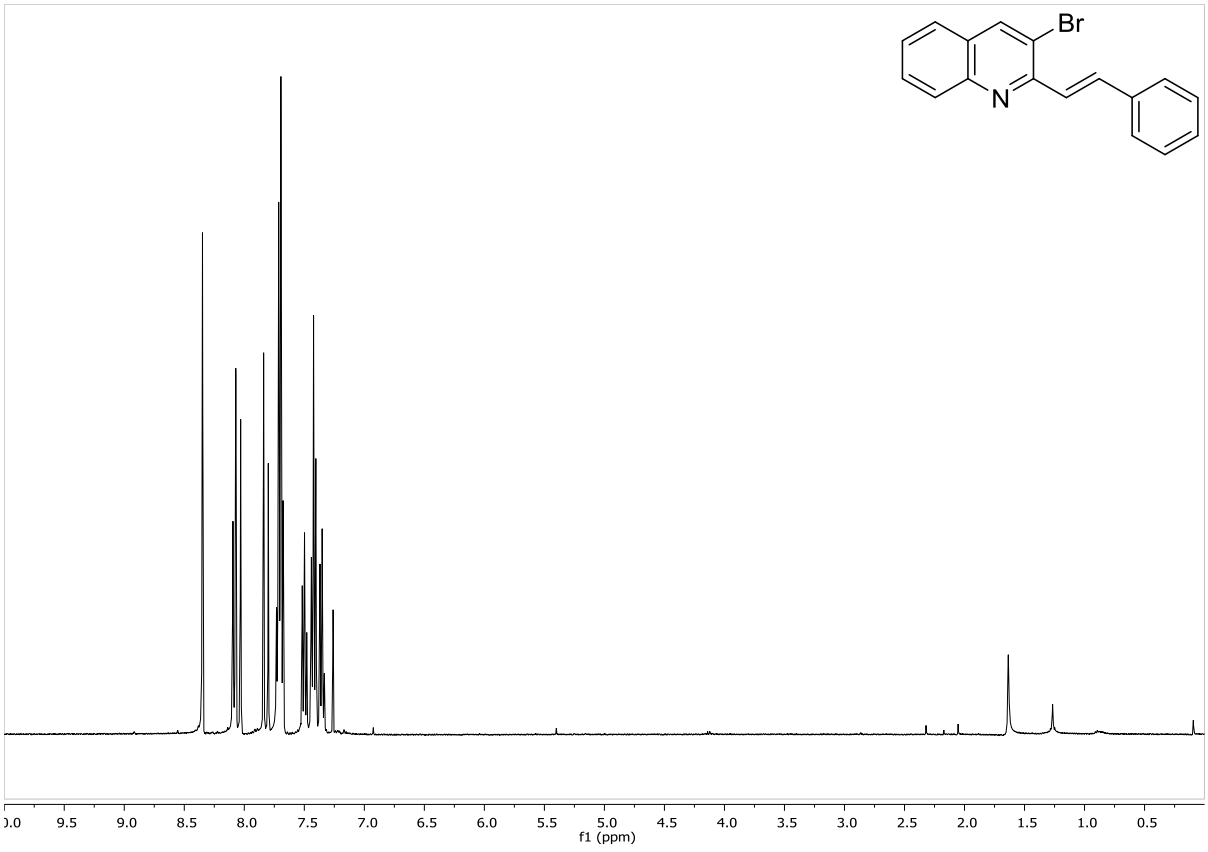
The title compound was prepared following a modified literature procedure.[15] An oven-dried autoclave, equipped with a magnetic follower, was charged with $[Ir(cod)Cl]_2$ (1.68 mg, 2.50 μmol, 1 mol%), (*S*)-SegPhos (3.36 mg, 5.50 μmol, 2.2 mol%) and anhydrous benzene (1 mL) under nitrogen atmosphere. The solution was stirred 10 minutes at room temperature and then a solution of iodine (6.34 mg, 0.025 mmol, 10 mol%) and (*E*)-2-(3,4-dimethoxystyryl)quinoline **7** (72.8 mg, 0.250 mmol, 100 mol%) in anhydrous benzene (2 mL) was added to the vessel in one portion. The reaction was let stir for further 10 minutes at room temperature. The autoclave was pressurised with H_2 (750 psi) and stirred for 16 hours at room temperature. H_2 was carefully released and a solution of formaldehyde (37% wt. sol. in H_2O, 0.609 mL, 7.50 mmol, 3000 mol%) in MeOH (5 mL) was added to the reaction. The autoclave was re-pressurised with H_2 (750 psi) and the reaction was stirred overnight at room temperature. The solvent was then removed *in vacuo*. The crude material was re-suspended in water (2 mL) and washed with CH_2Cl_2 (3 × 5 mL). The organic portions were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by FCC (20% EtOAc/hexane → 30% EtOAc/hexane) afforded enantio-enriched (-)-cuspareine (61.3 mg, 79% yield, 94% *e.e.*) as colourless oil; $[\alpha]_D^{24}$ = -25.6 (*c* 2.0, $CHCl_3$), [Lit.[16] $[\alpha]_D^{24}$ = -30.2 (*c* 0.95, $CHCl_3$), $[\alpha]_D^{25}$ = -22.8 (*c* 1.0, $CHCl_3$), (-)-cuspareine isolated from *Galipea officinalis* (Hancock)].[17] **SFC conditions:** *column*: CHIRALPACK IB, *elute*: 5% MeOH/CO_2, *detector*: 250 nm, *flow rate*: 3.5 mL/min, *temperature*: 40 °C, *retention times*: (*R*) t_1 = 7.86 min, (*S*) t_2 = 8.41 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12-7.07 (1H, m), 6.99 (1H, dd, *J* = 1.5, 7.0 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 6.76-6.70 (2H, m), 6.61 (1H, ddd, *J* = 1.0, 7.5, 7.5 Hz), 6.54 (1H, d, *J* = 8.0 Hz), 3.88 (3H, s), 3.87 (3H, s), 3.30 (1H, dq, *J* = 4.5, 8.5 Hz), 2.93 (3H, s), 2.86 (1H, ddd, *J* = 6.0, 12.0, 17.5 Hz), 2.75-2.63 (2H, m), 2.55 (1H, ddd, *J* = 6.5, 10.0, 14.0 Hz), 2.02-1.87 (3H, m), 1.75 (1H, dddd, *J* = 5.5, 9.0, 10.0, 14.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.9, 147.2, 145.3, 134.6, 128.7, 127.1, 121.7, 120.0, 115.4, 111.6, 111.3, 110.6, 58.4, 55.9 (*2 signals*), 38.1, 33.1, 31.9, 24.4, 23.6. *The spectroscopic proprieties were consistent with the data available in literature.*[16]

1-Phenyl-2-(quinolin-2-yl)ethan-1-ol (9)



The title compound was prepared following a literature procedure.[18] An oven-dried two-necked flask equipped with a magnetic follower was charged with $CeCl_3 \cdot 7H_2O$ (3.73 g, 10.0 mmol, 100 mol%). The solid was heated to 140 °C under high vacuum for 3 hours. The flask was flushed with nitrogen

and anhydrous THF was added at -78 °C. The colourless suspension was stirred at the same temperature for 1 hour. A solution of lithiated quinaldine, previously prepared by slow addition of *n*-BuLi (1.6M in hexanes, 6.25 mL, 10.0 mmol, 100 mol%) to a solution of quinaldine (1.35 mL, 10.0 mmol, 100 mol%) in anhydrous THF (20 mL) at -20 °C after stirring for 1 hour, was added in one portion to the mixture at -78 °C and the reaction was maintained stirred at the same temperature for 1 hour. Benzaldehyde (1.21 mL, 12.0 mmol, 120 mol%) was added dropwise to the suspension and the solution was maintained stirring at -78 °C for further 15 minutes. The reaction was quenched with water (50 mL) and Et_2O (20 mL) and 2M HCl *aq. sol.* was added to the mixture to adjust the pH to ≈ 8. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The organic portions were collected, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by FCC (50% Et_2O/hexane → 60% Et_2O/hexane) afforded quinoline **9** (1.85 g, 74% yield) as an off-white solid; m.p. = 125-126 °C [hexane/EtOAc] (Lit.[19] 124-125 °C [*no solvent quoted*]); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17-7.98 (2H, m), 7.89-7.63 (2H, m), 7.60-7.45 (3H, m), 7.45-7.11 (4H, m), 6.24 (1H, br. s), 5.43-5.27 (1H, m), 3.44-3.22 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5, 147.1, 144.0, 136.8, 129.8, 128.7, 128.4, 127.6, 127.3, 126.9, 126.2, 125.9, 122.1, 73.0, 46.2. *The spectroscopic proprieties were consistent with the data available in literature.*[18]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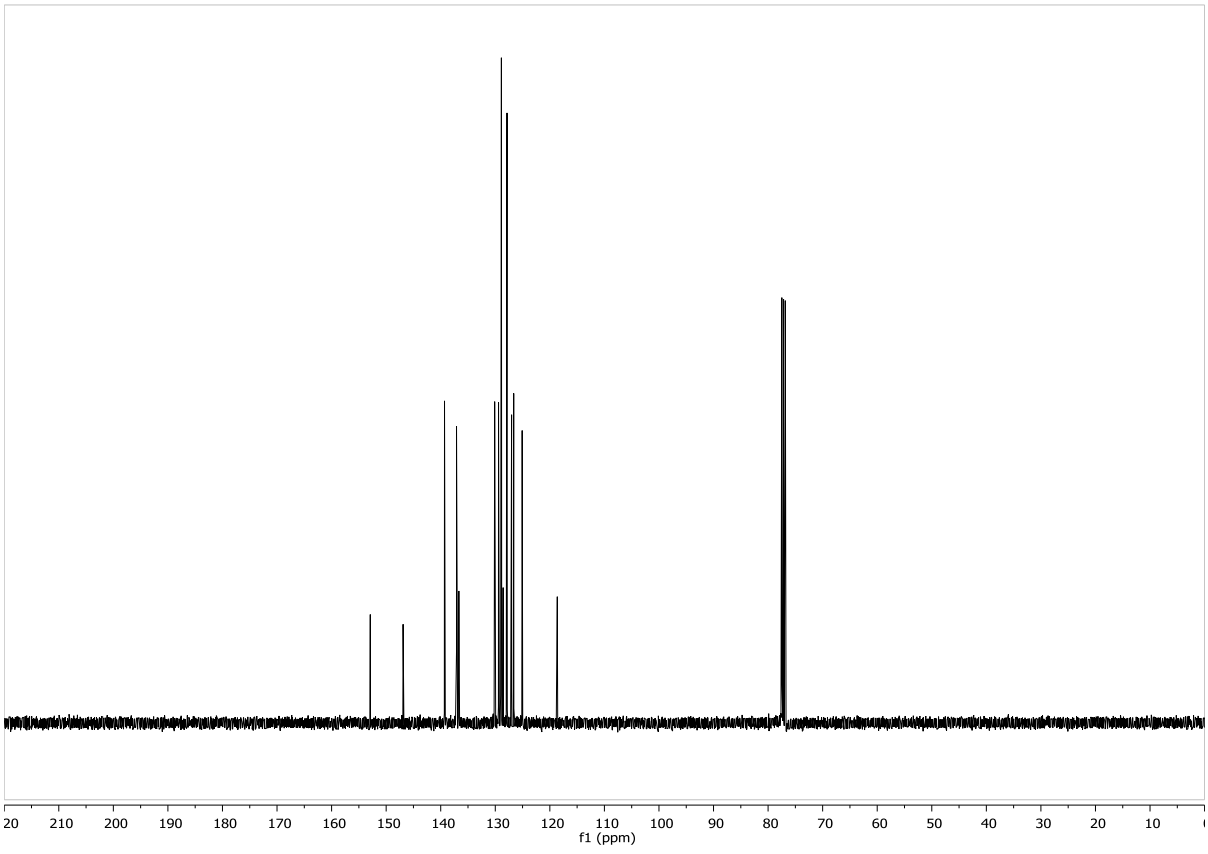
f1 (ppm)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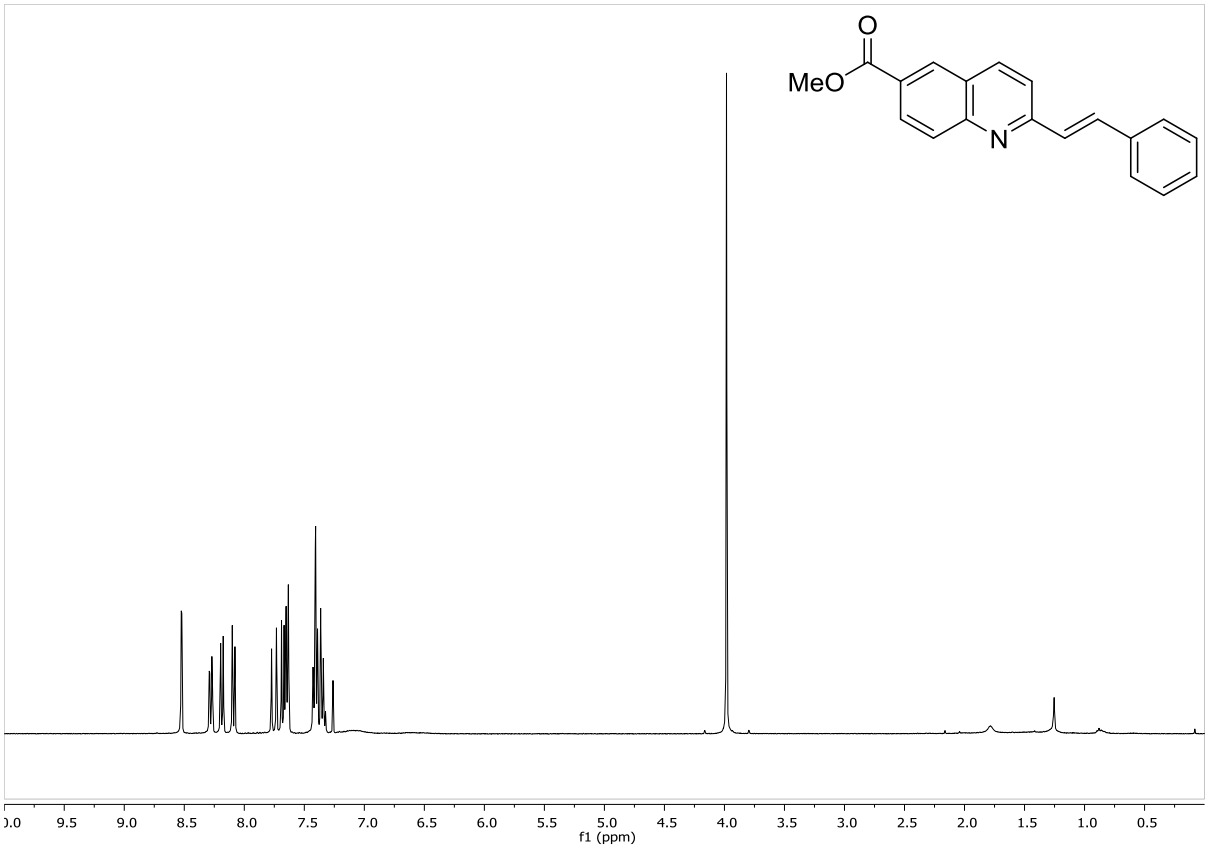
f1 (ppm)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MeO
N
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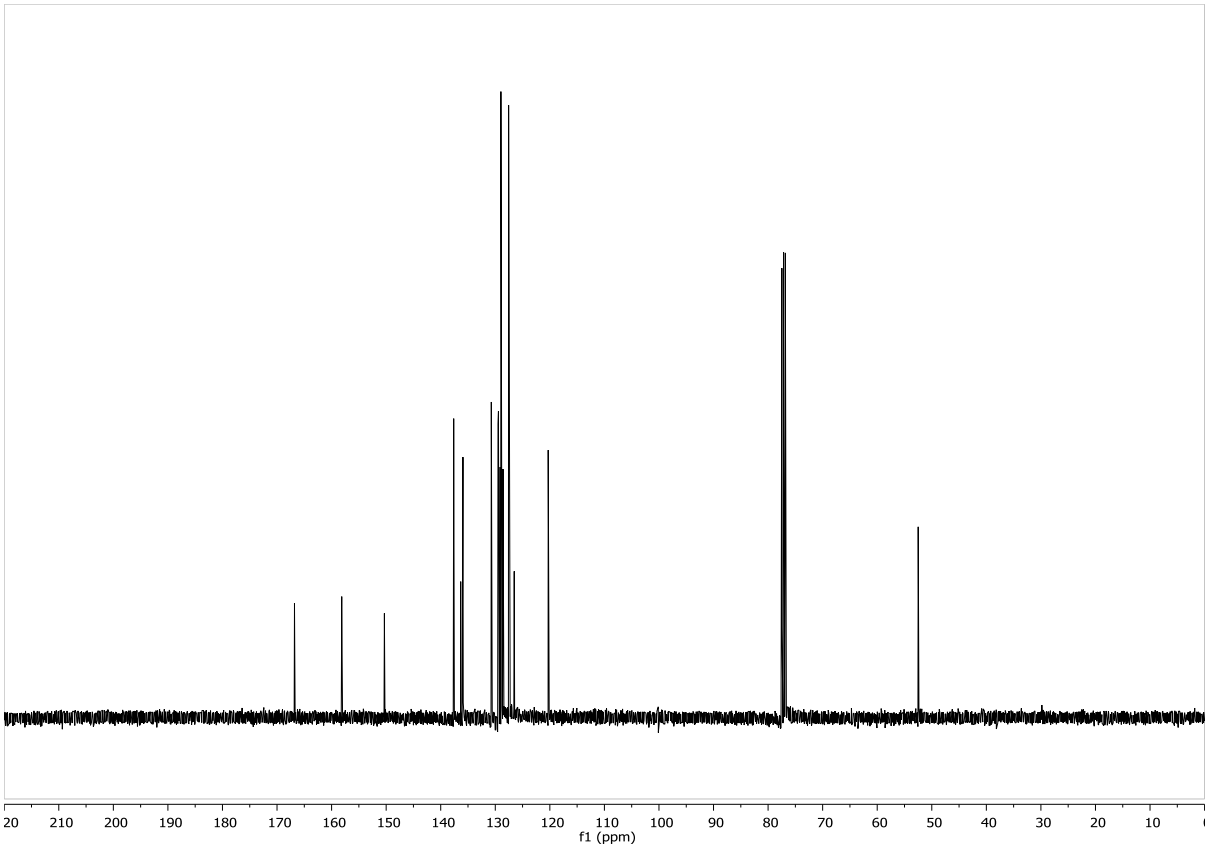
f1 (ppm)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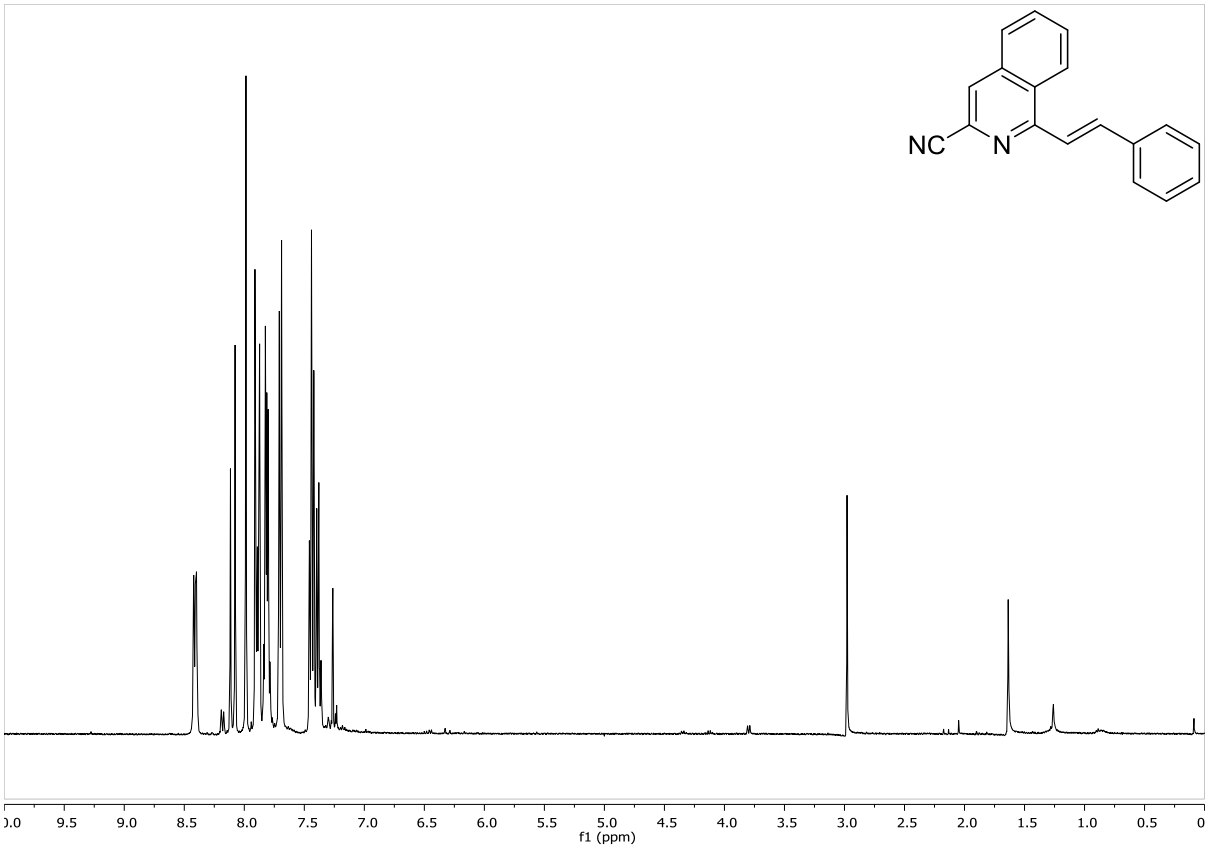
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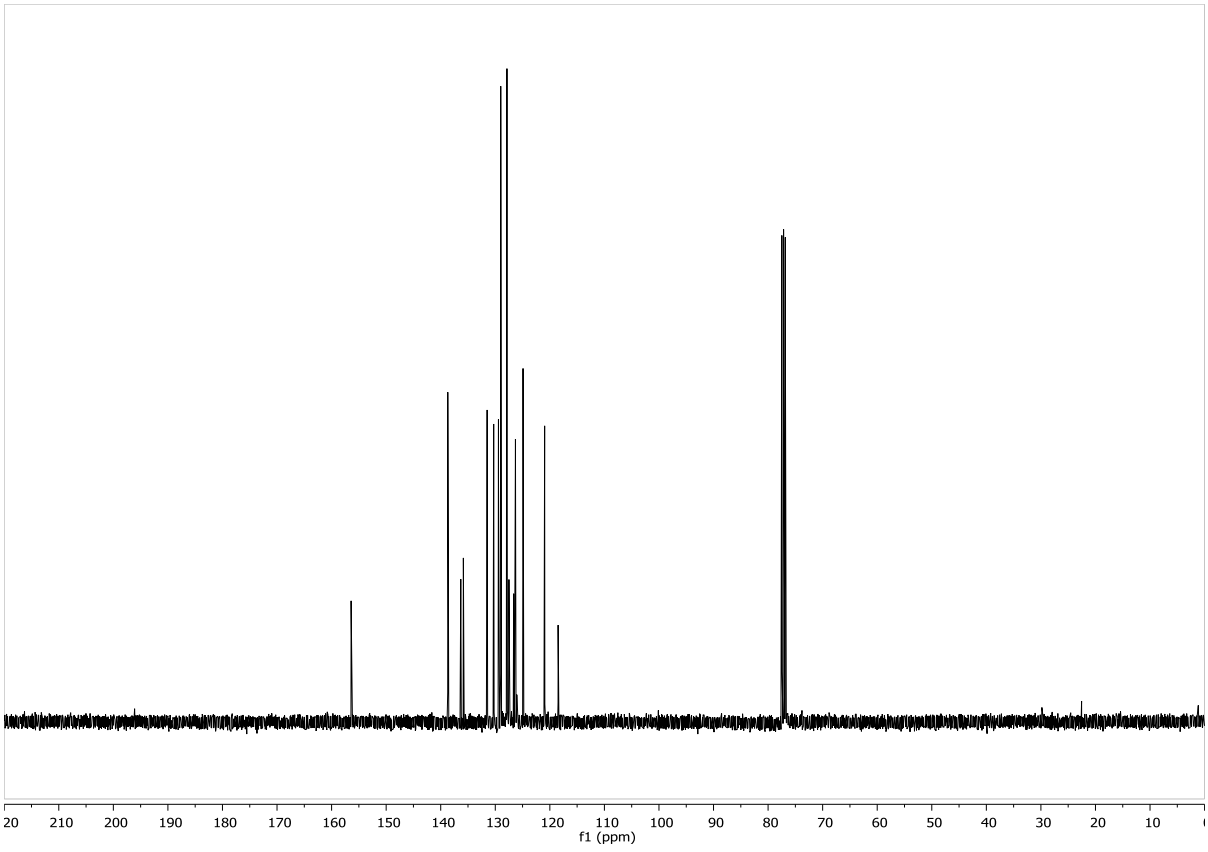
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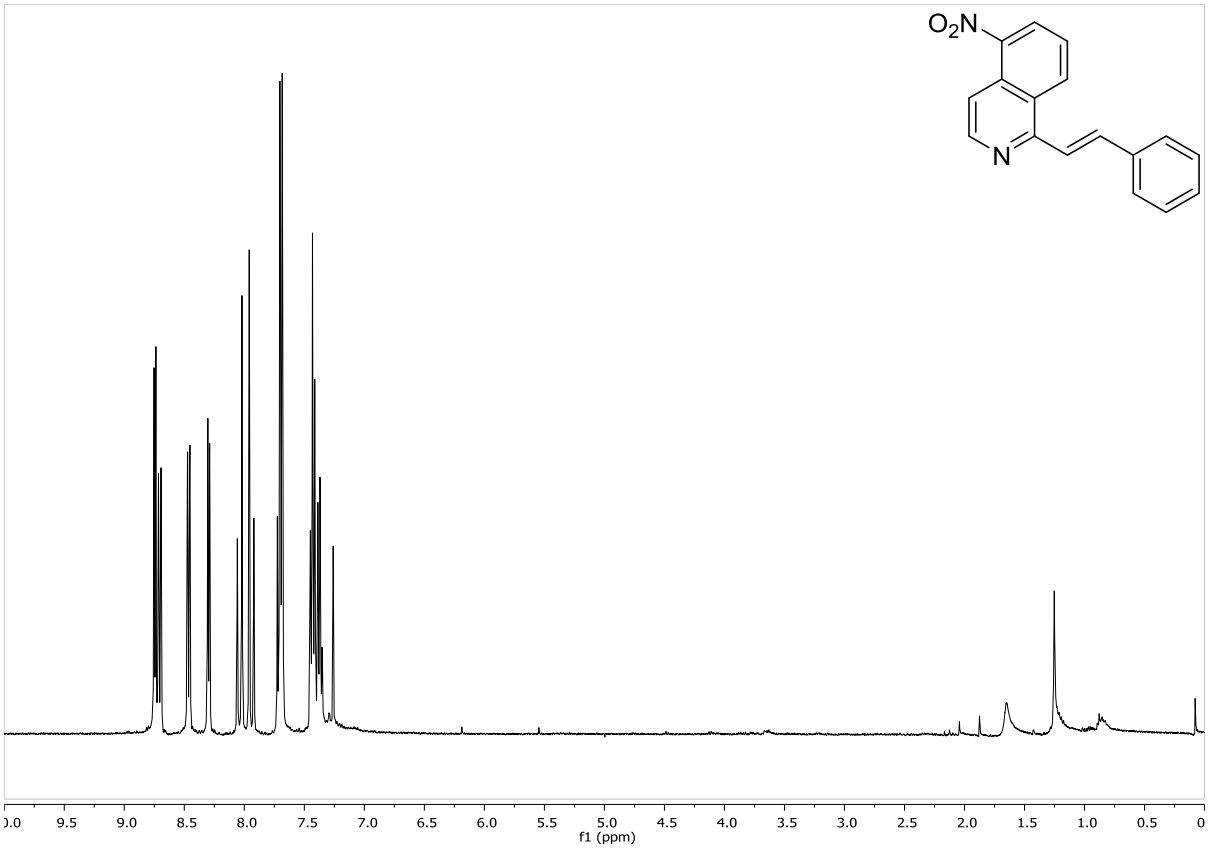
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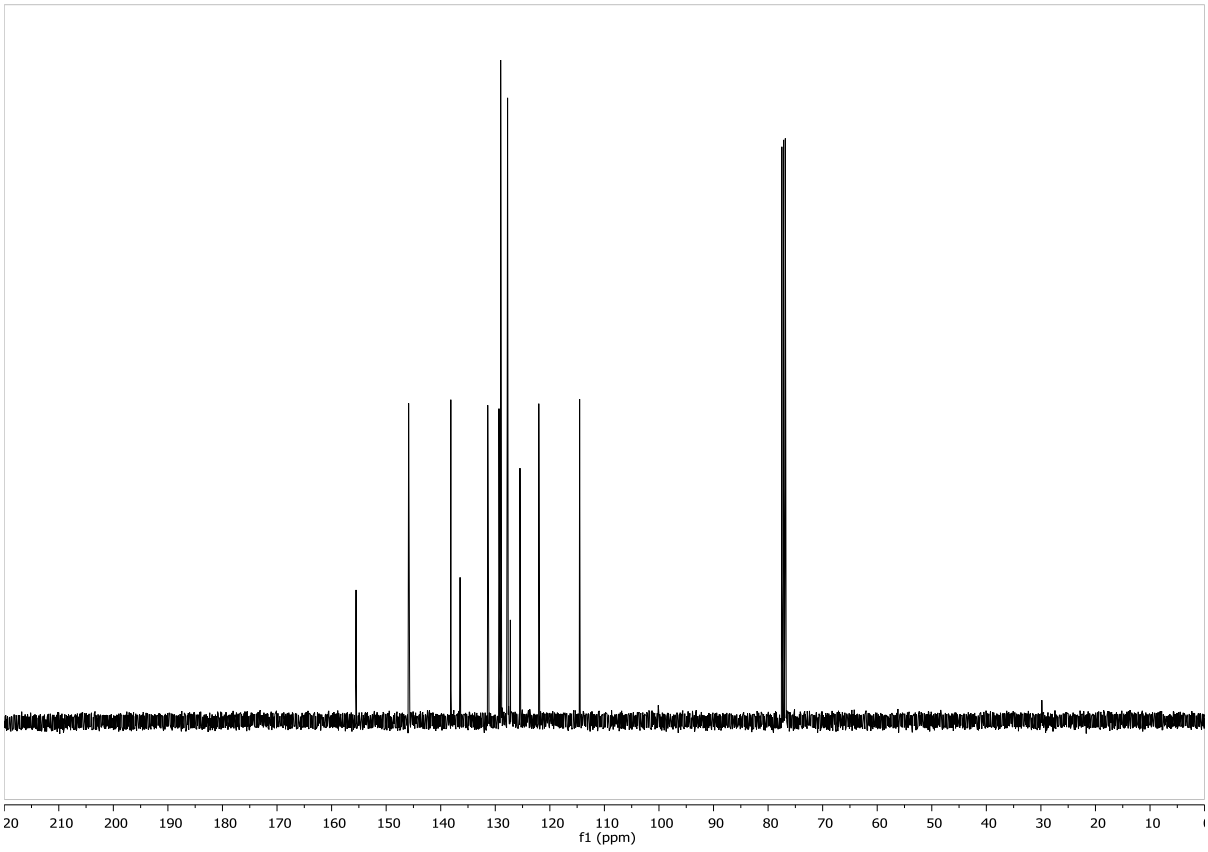
0.5
f1 (ppm)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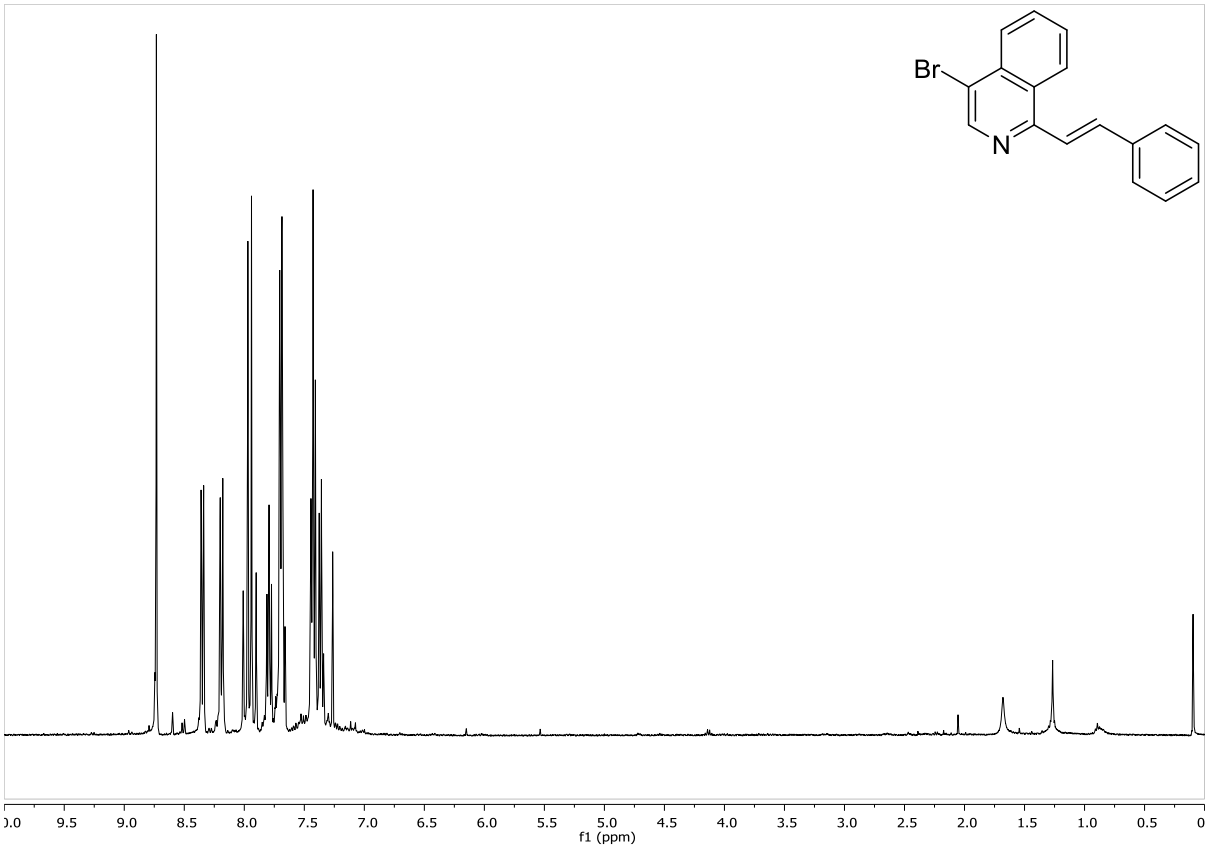
f1 (ppm)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N
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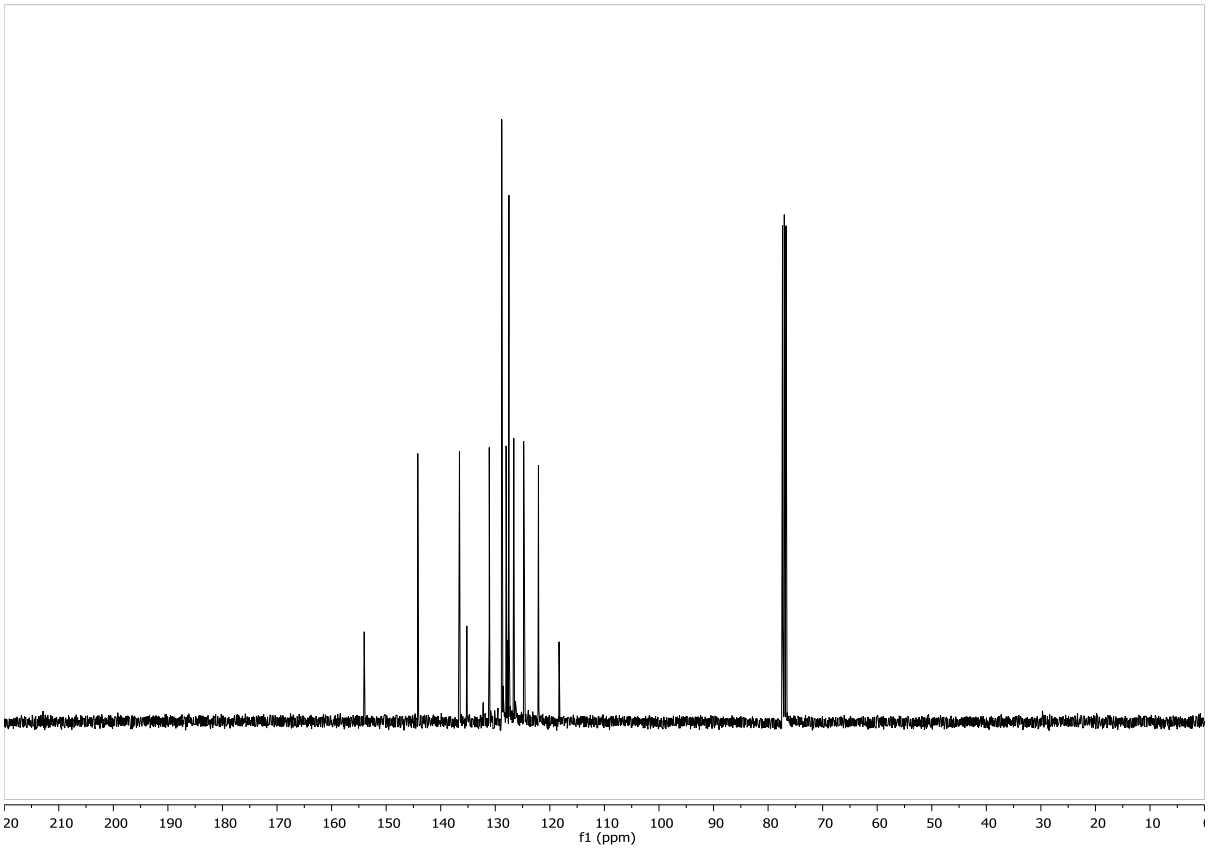
f1 (ppm)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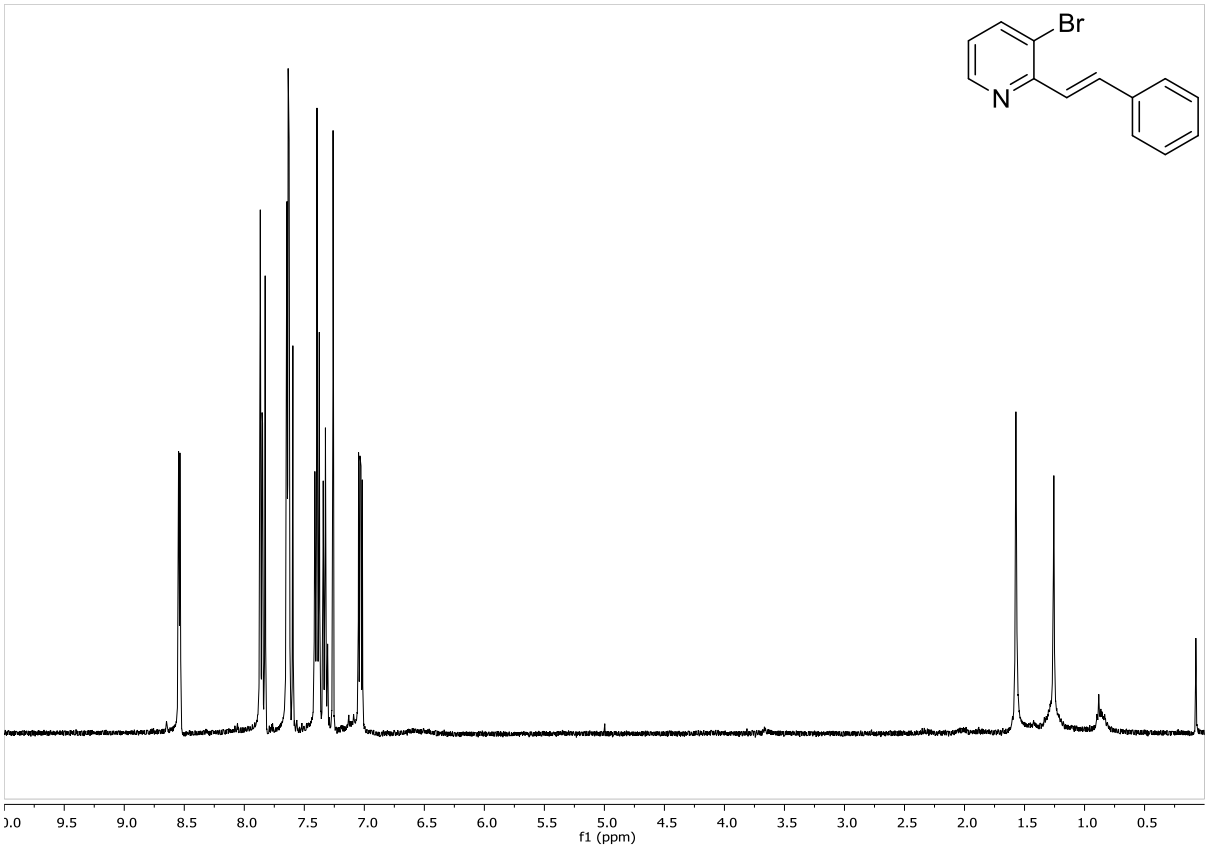
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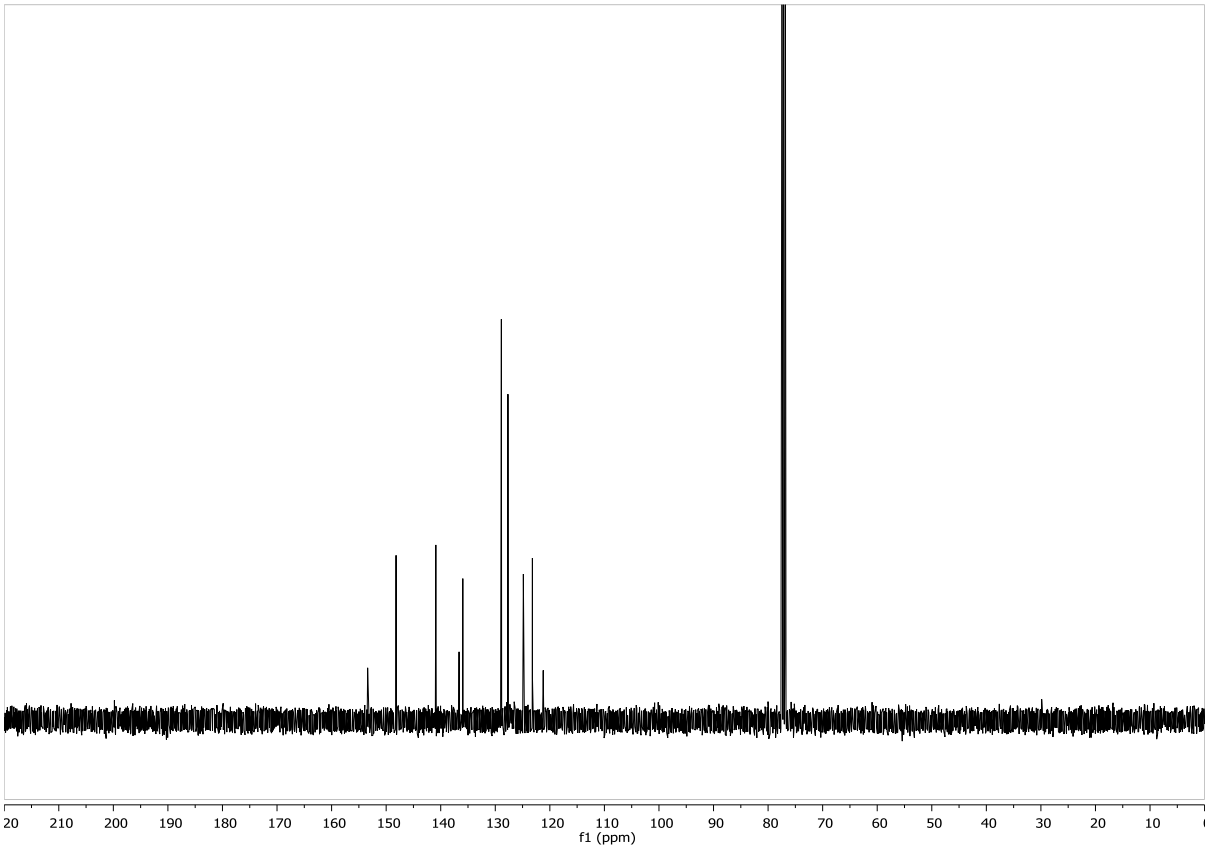
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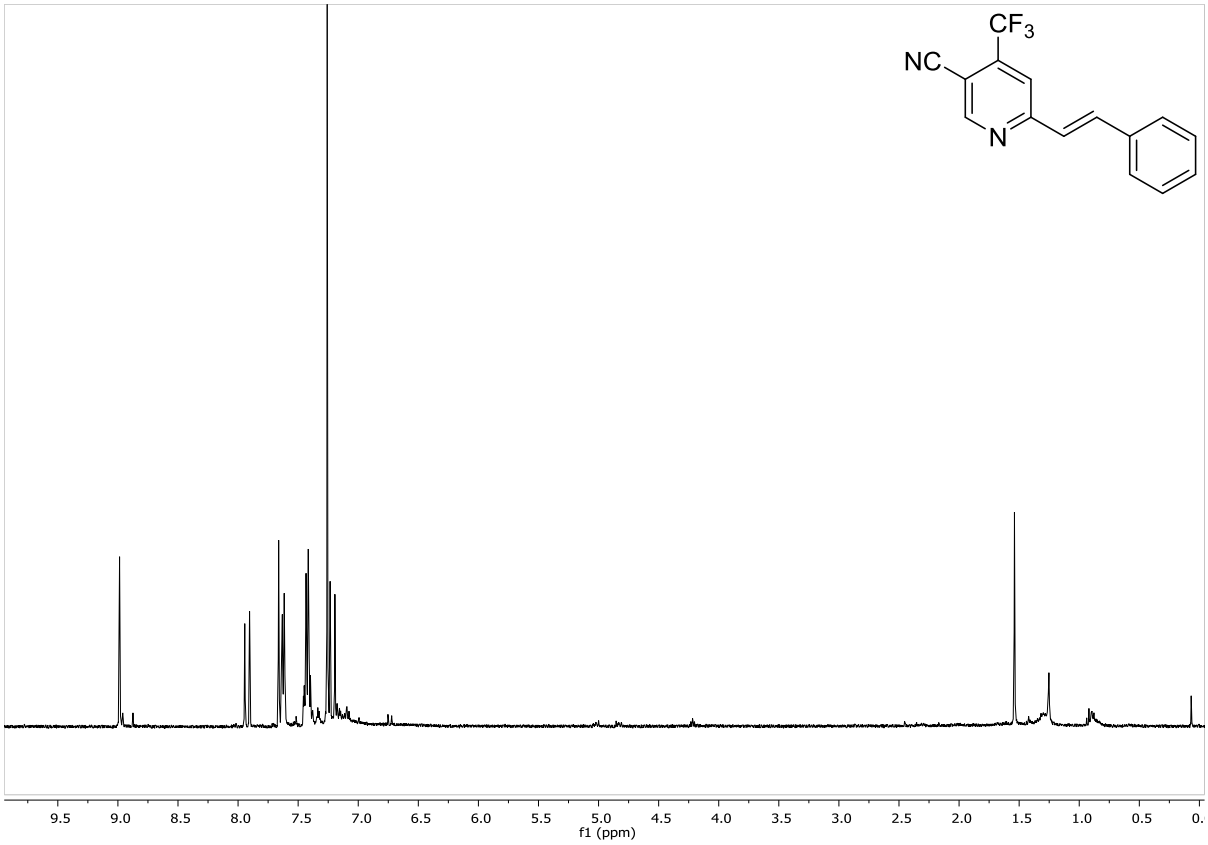
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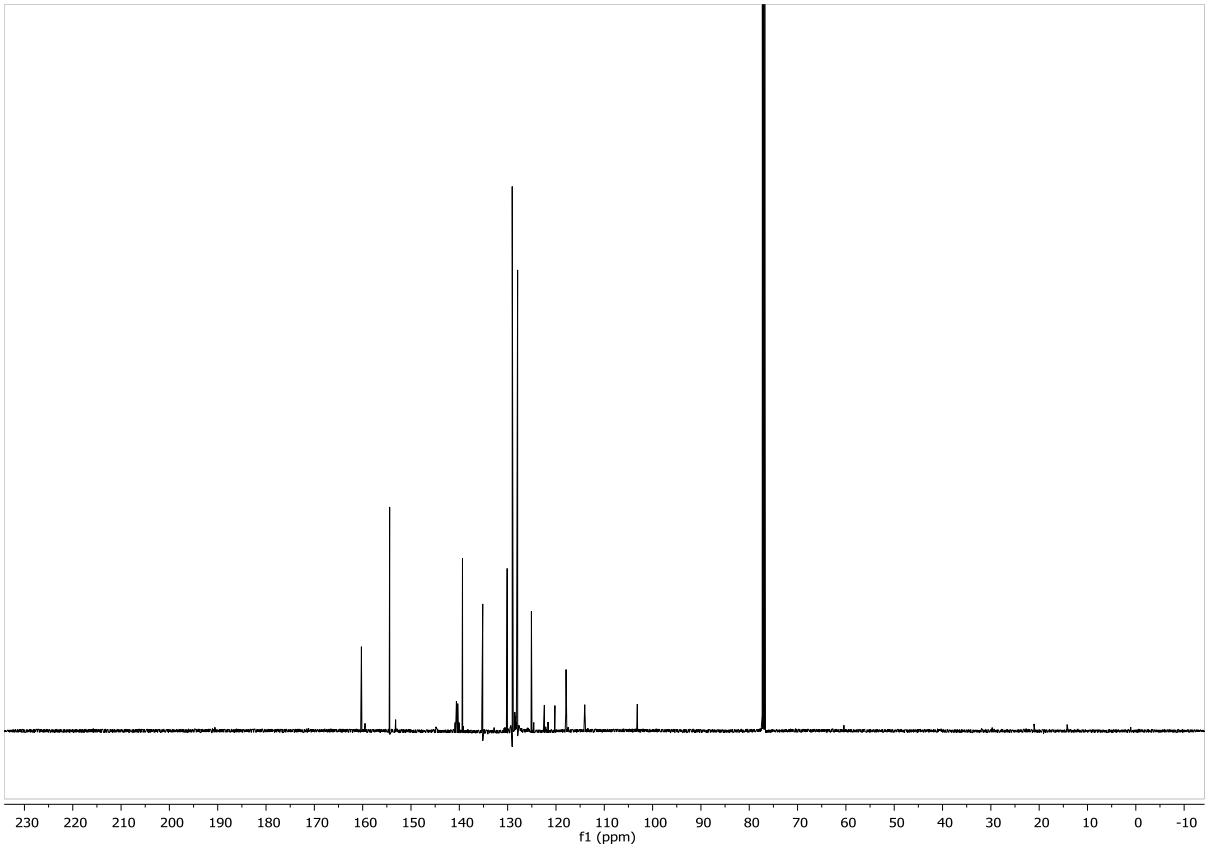
f1 (ppm)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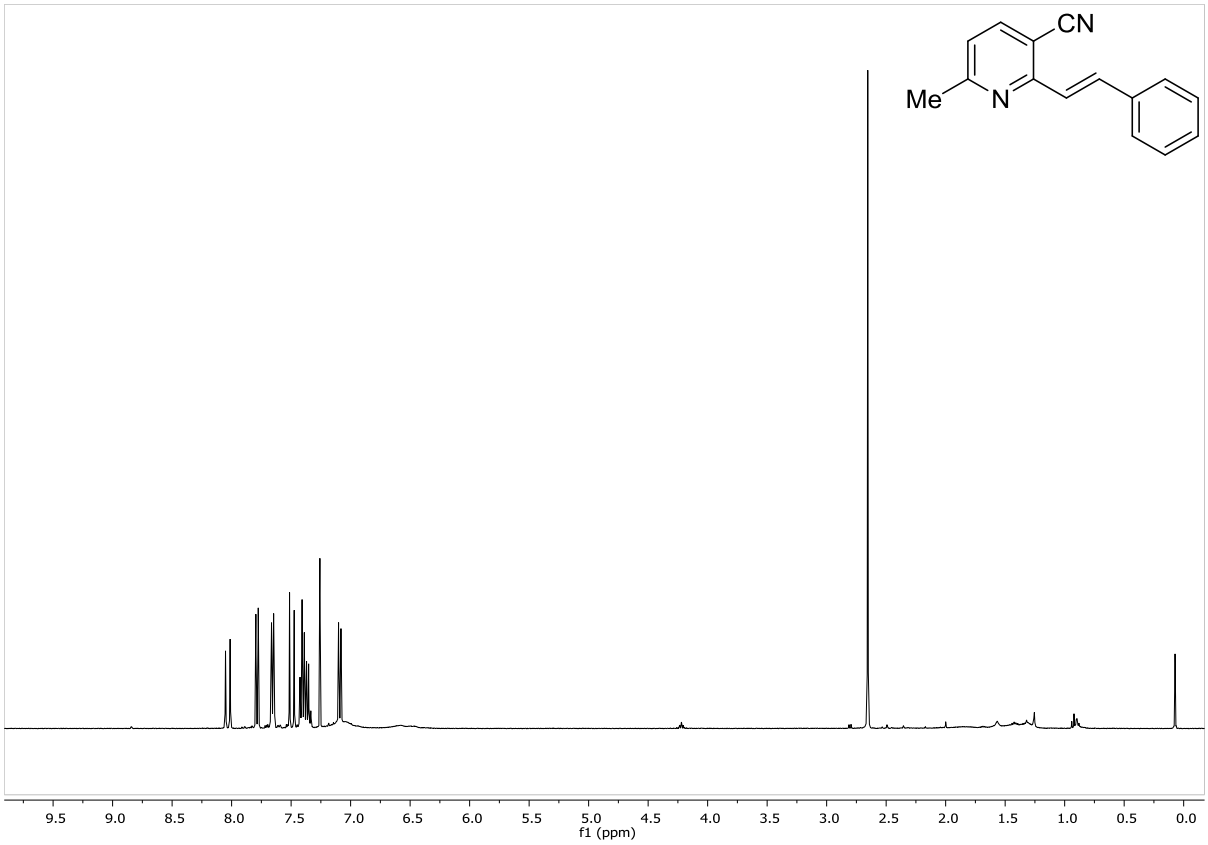
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N
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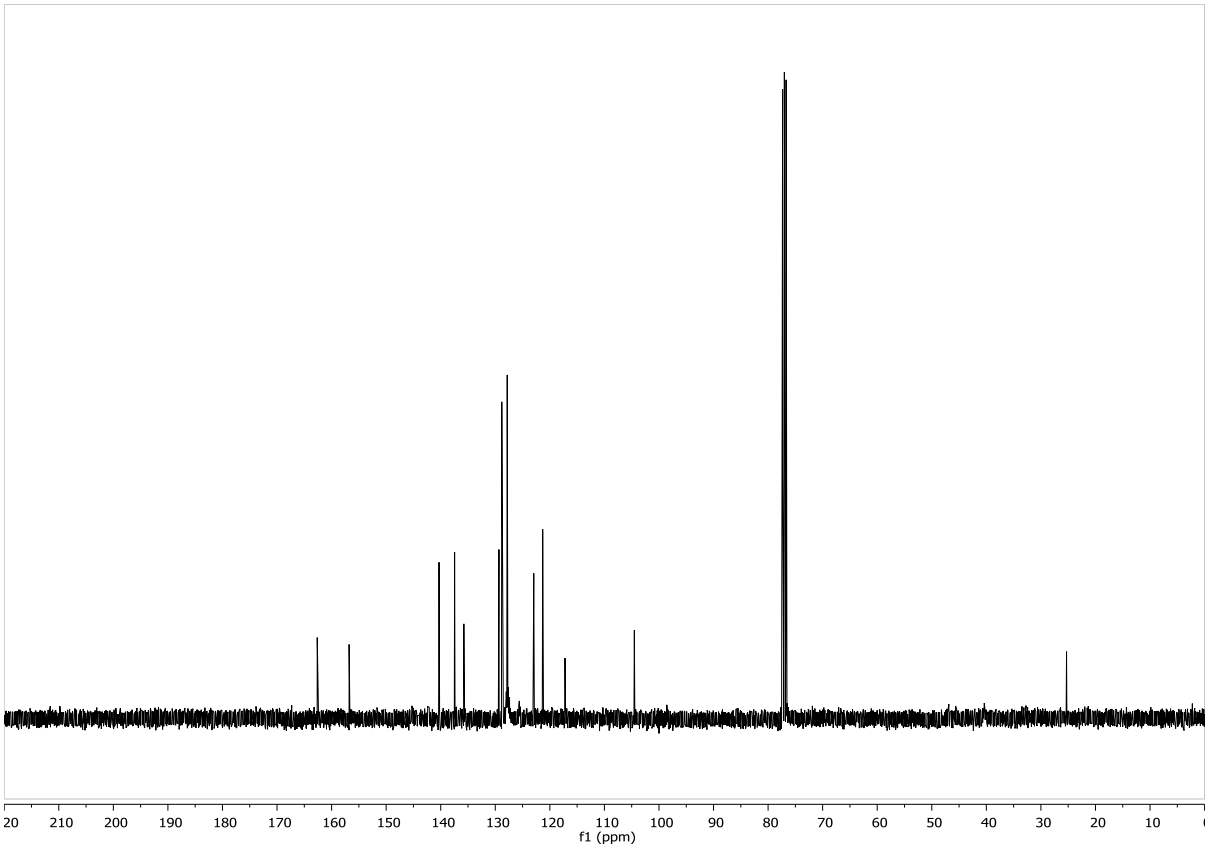
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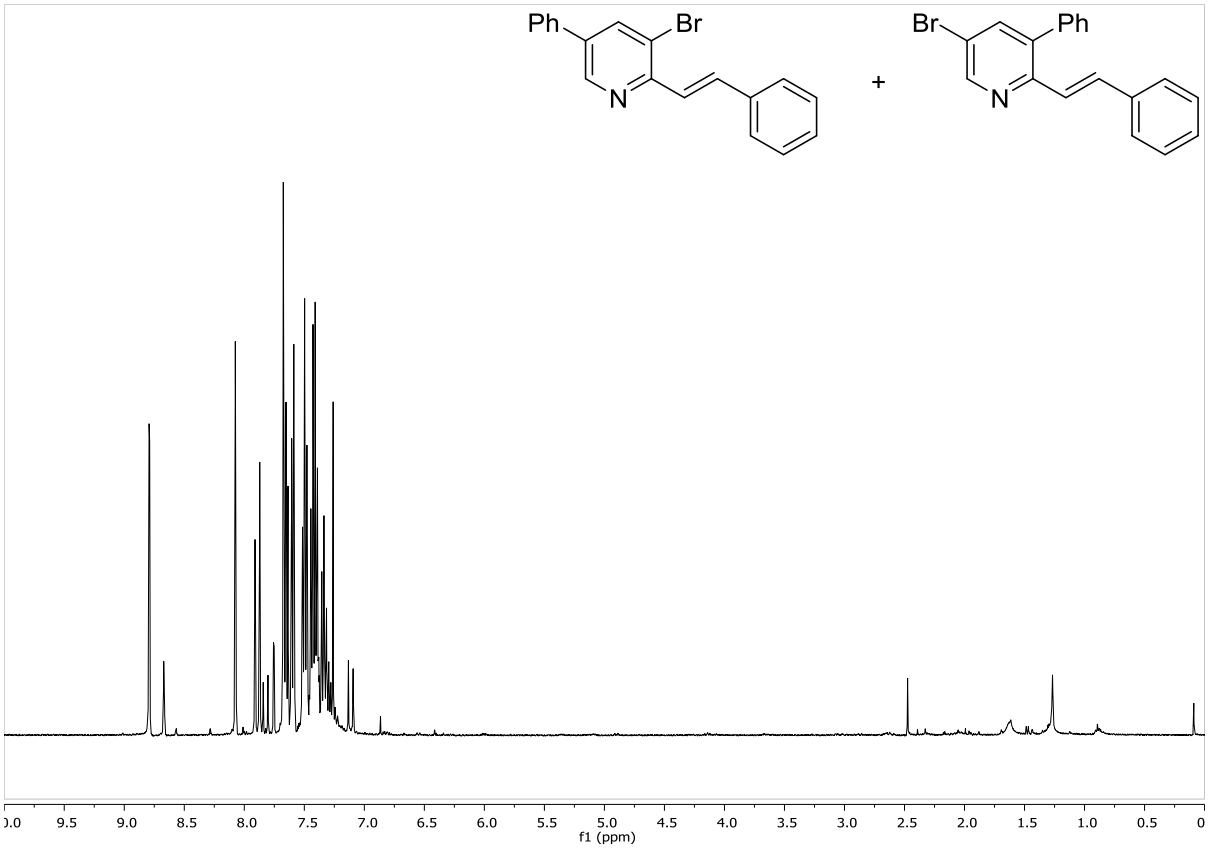
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N
+
Br
Ph
N
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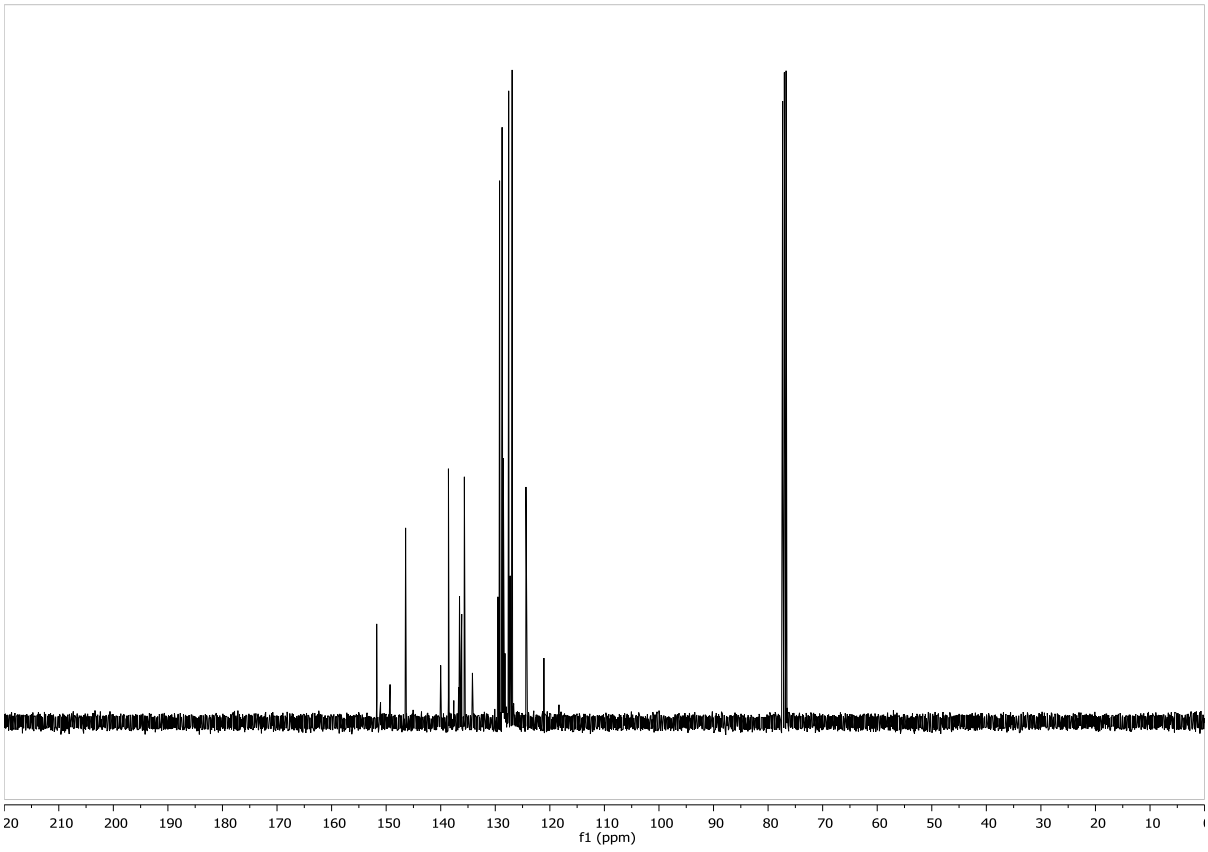
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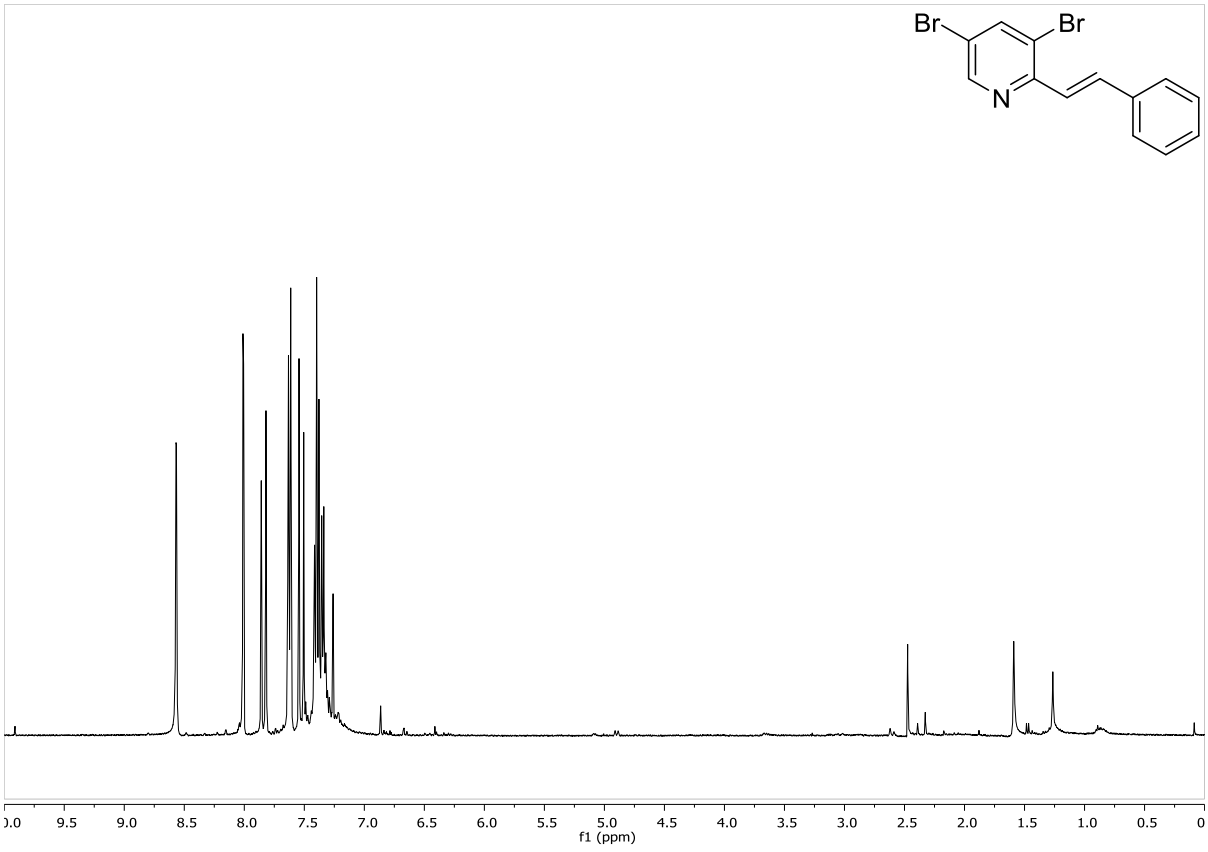
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Br
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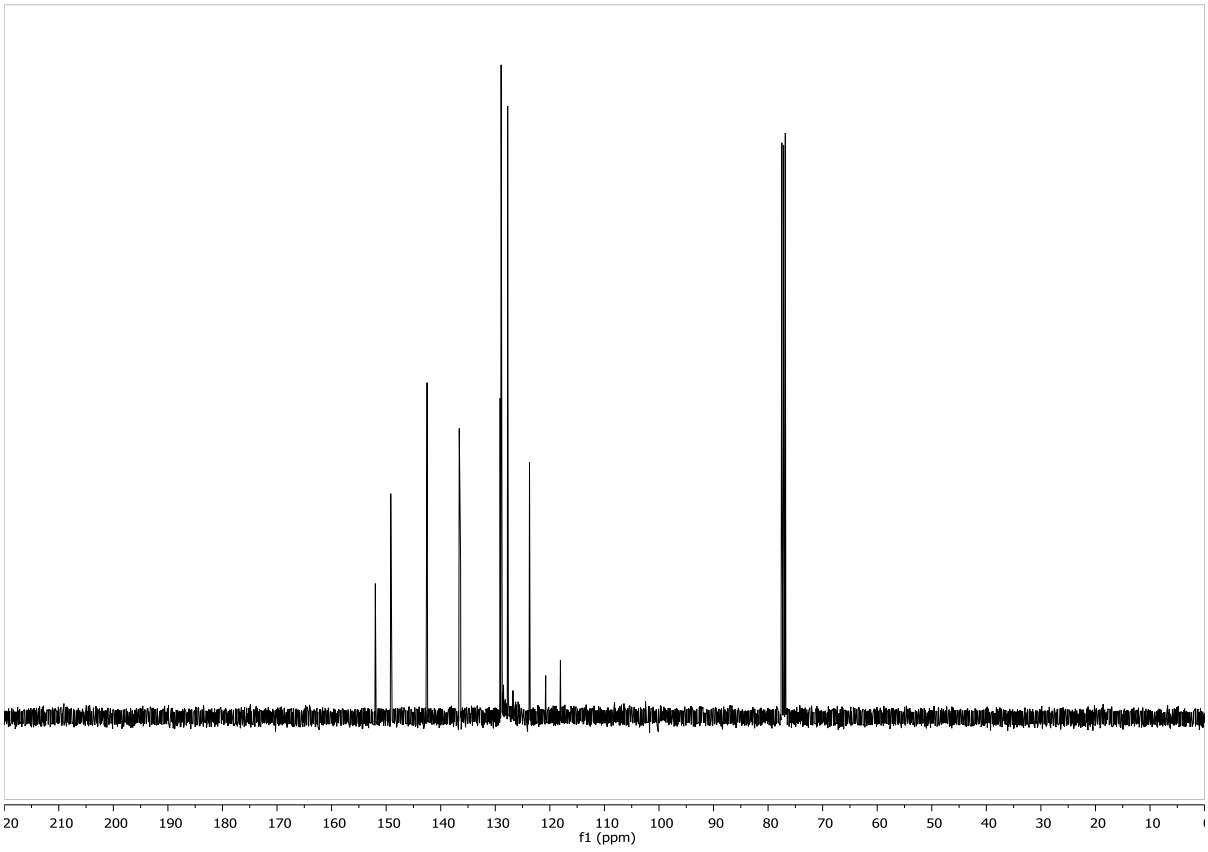
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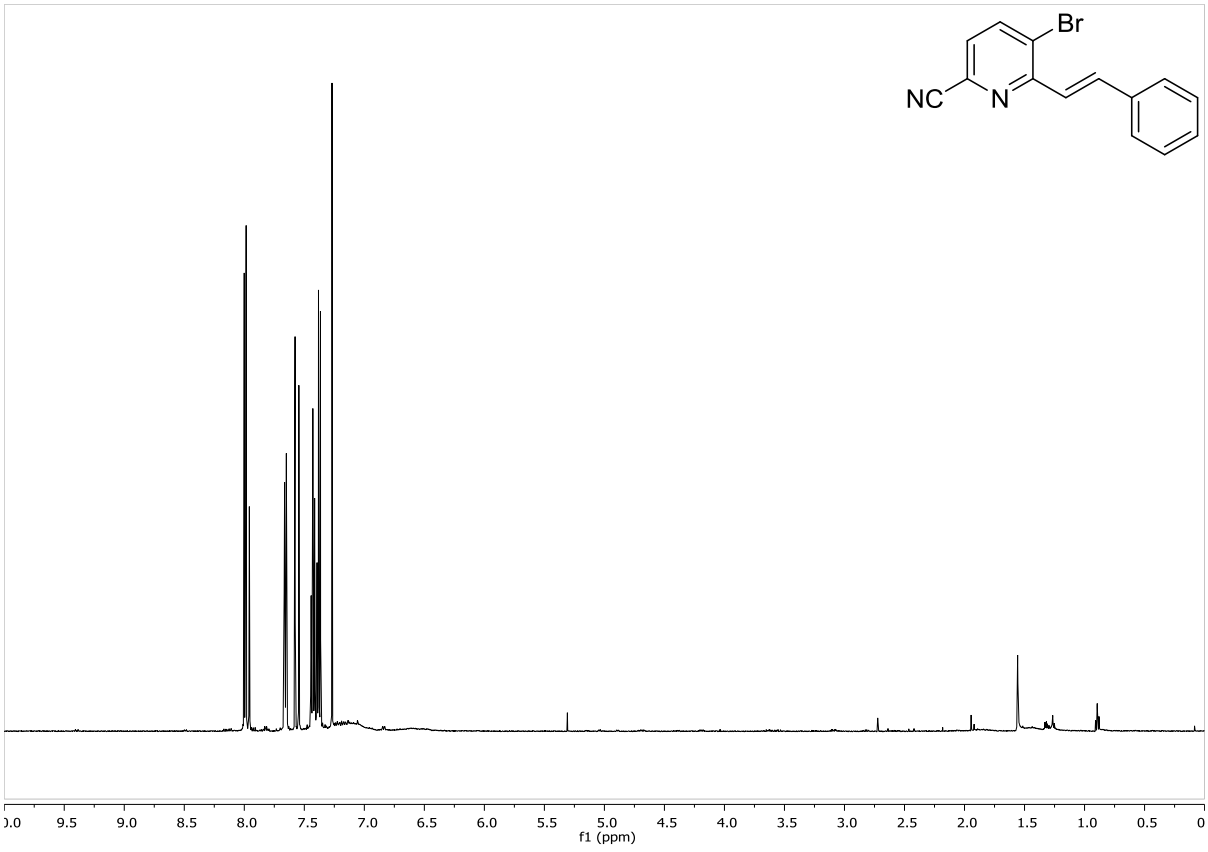
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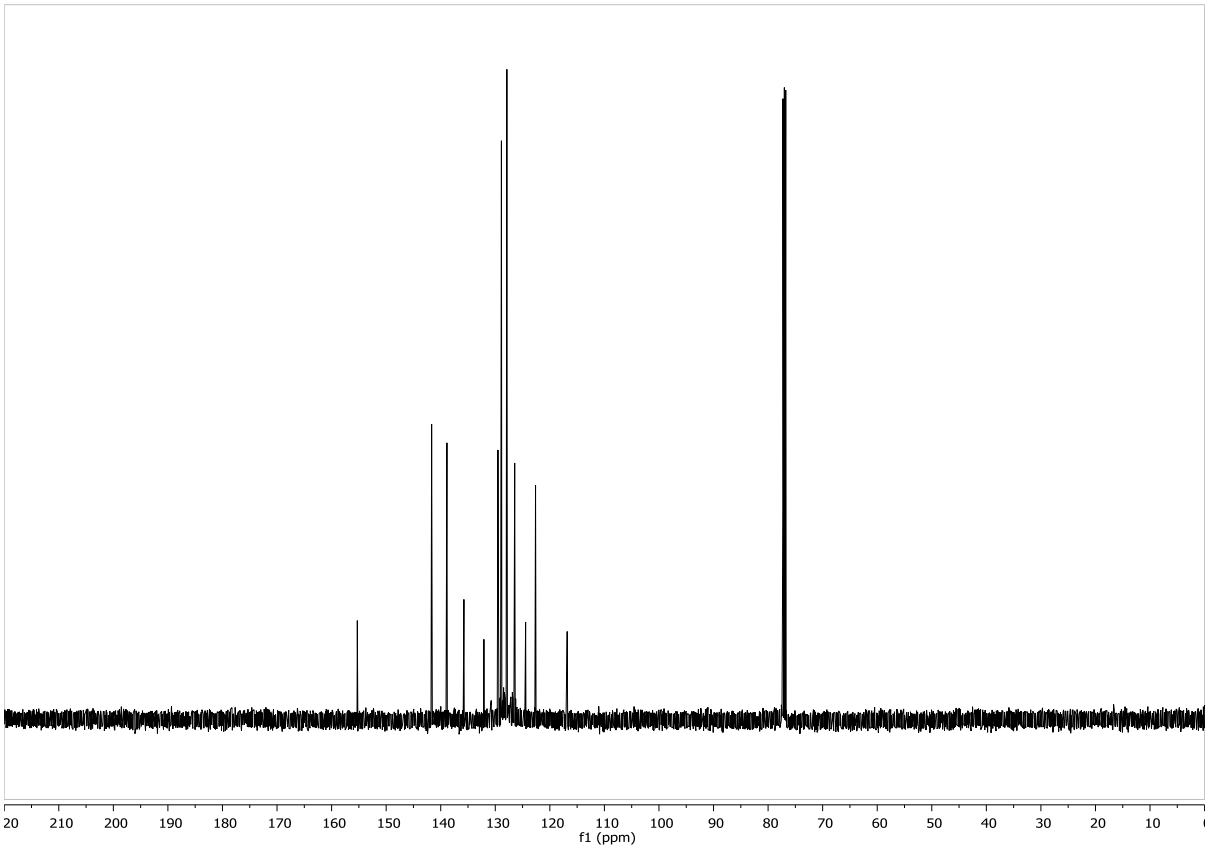
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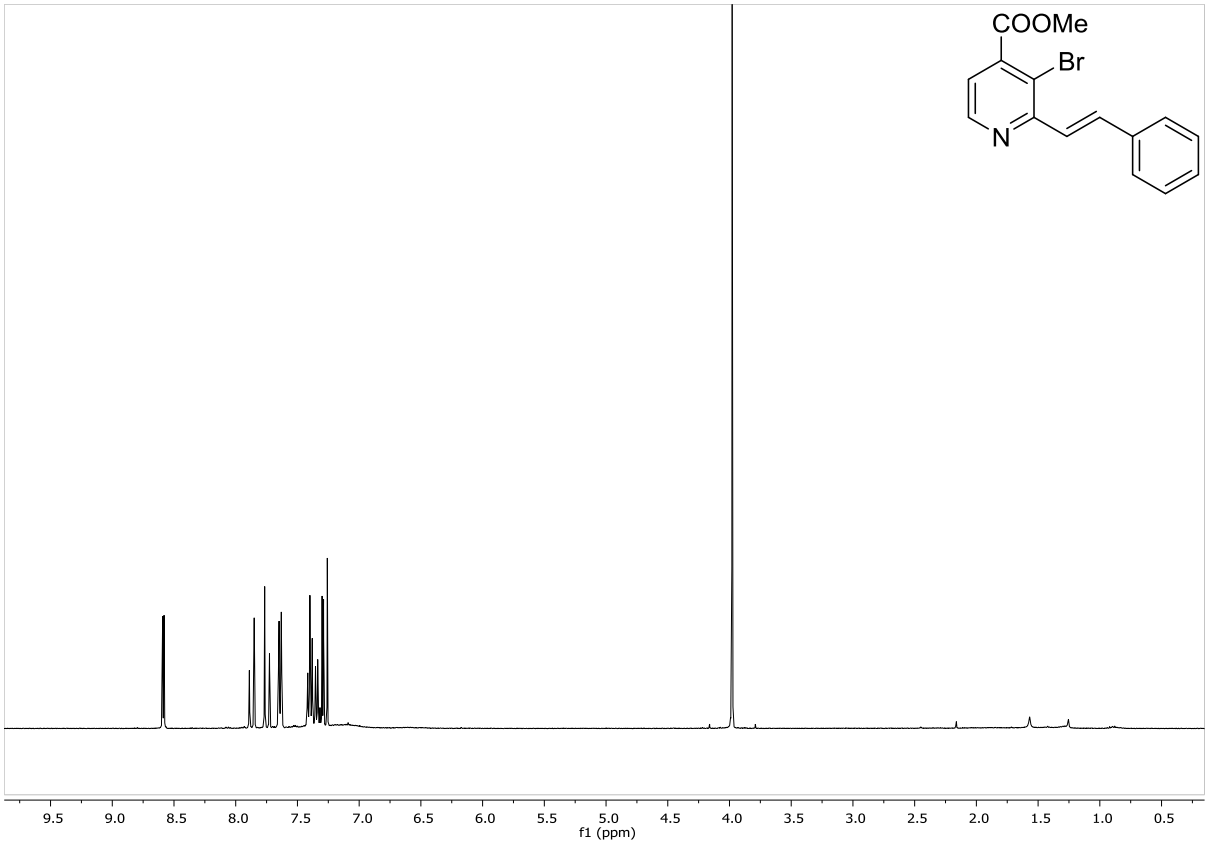
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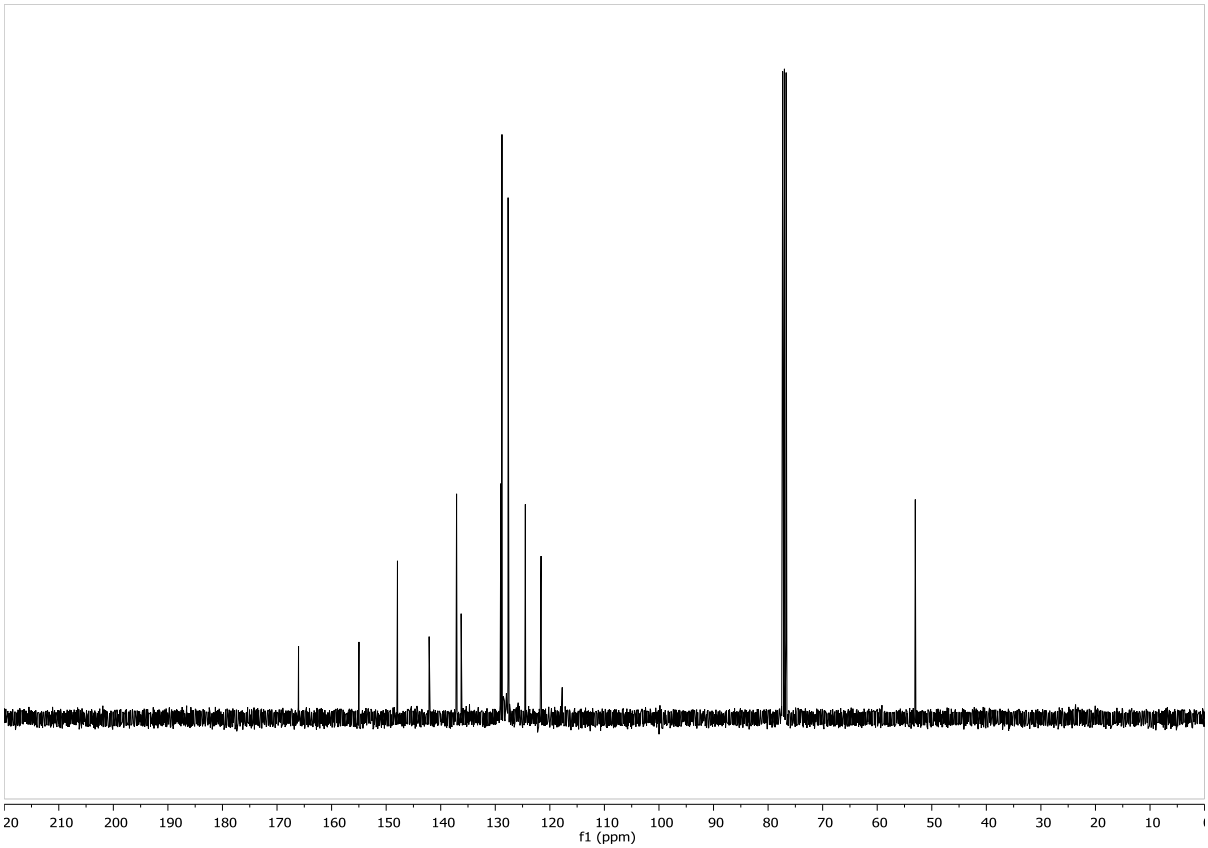
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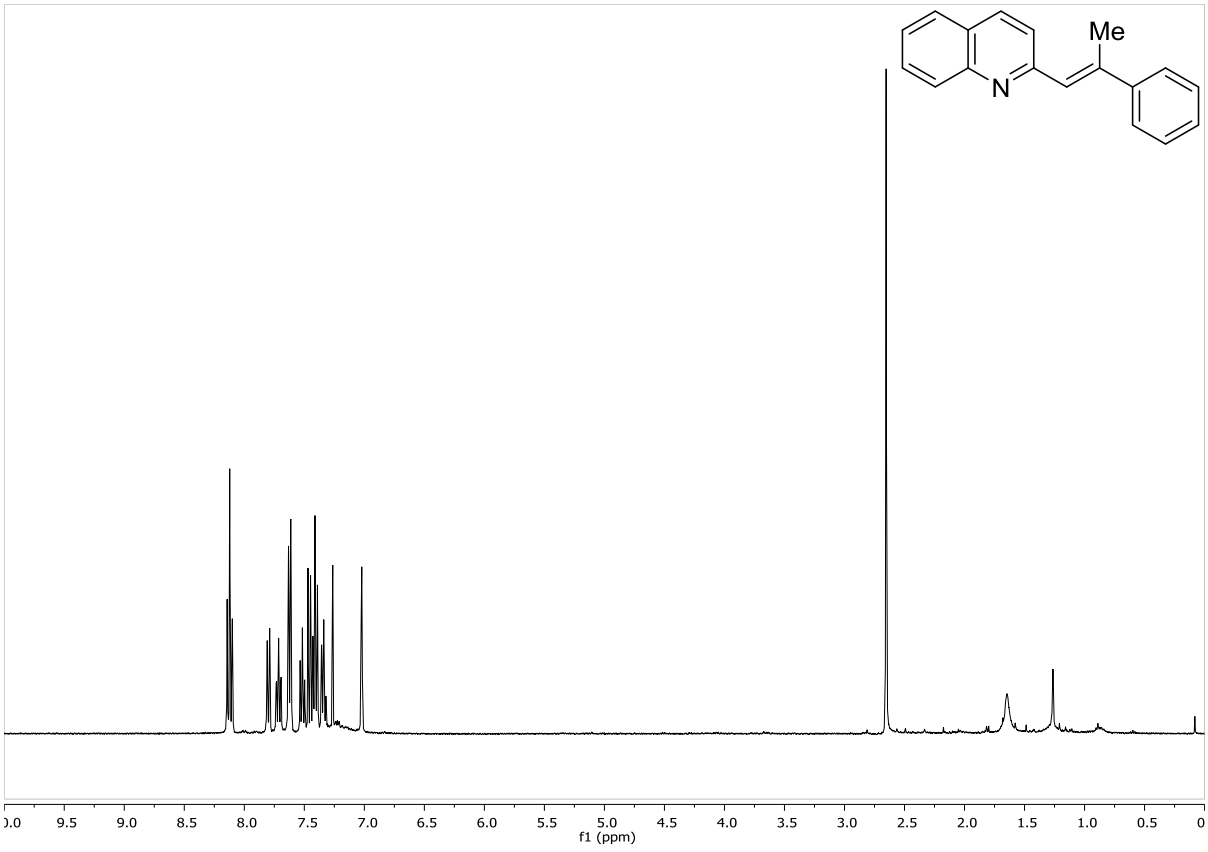
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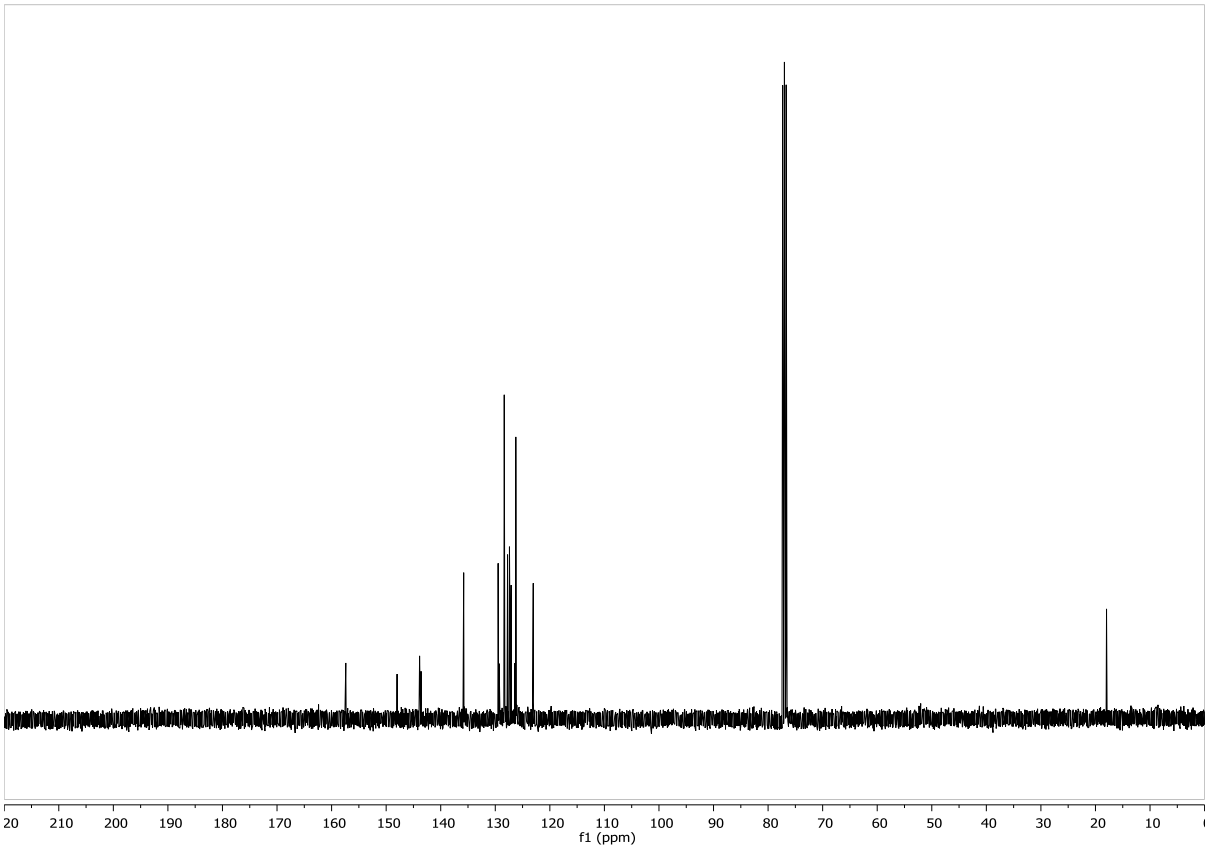
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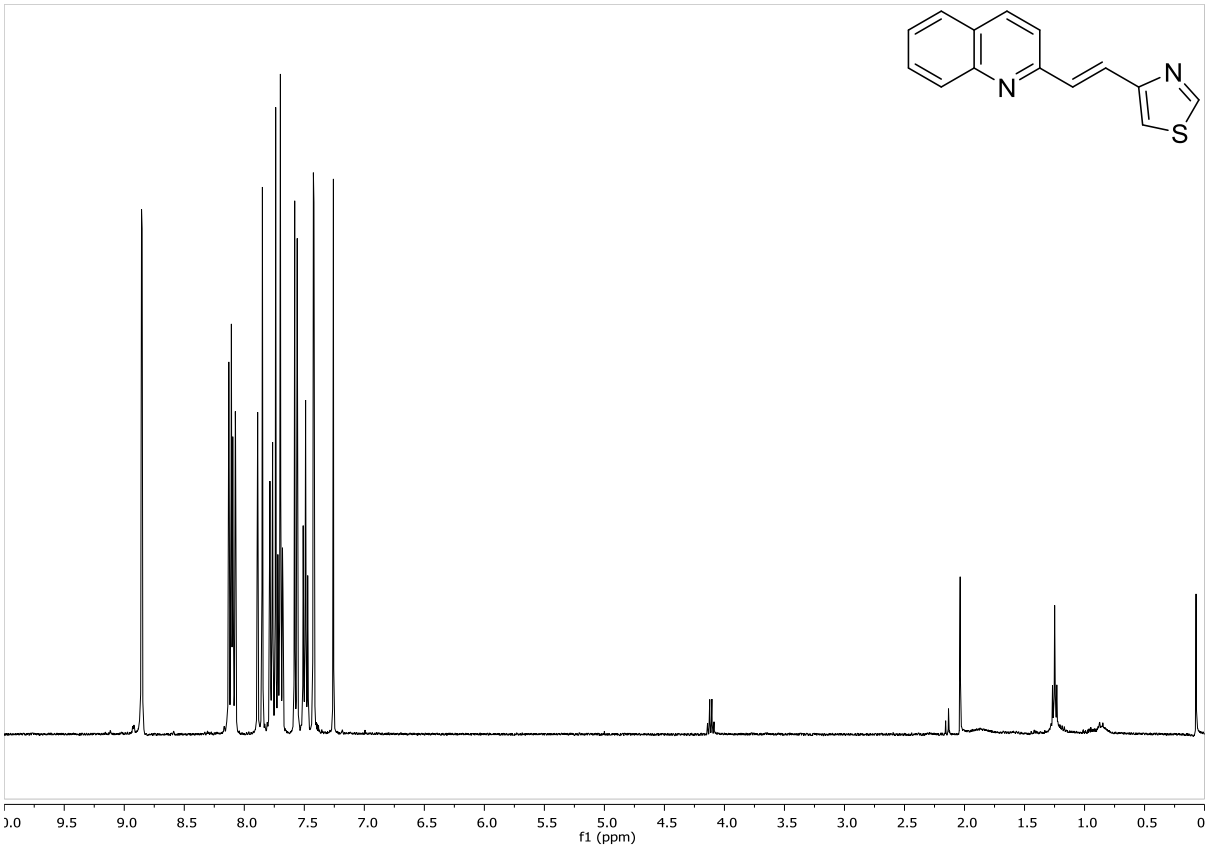
N
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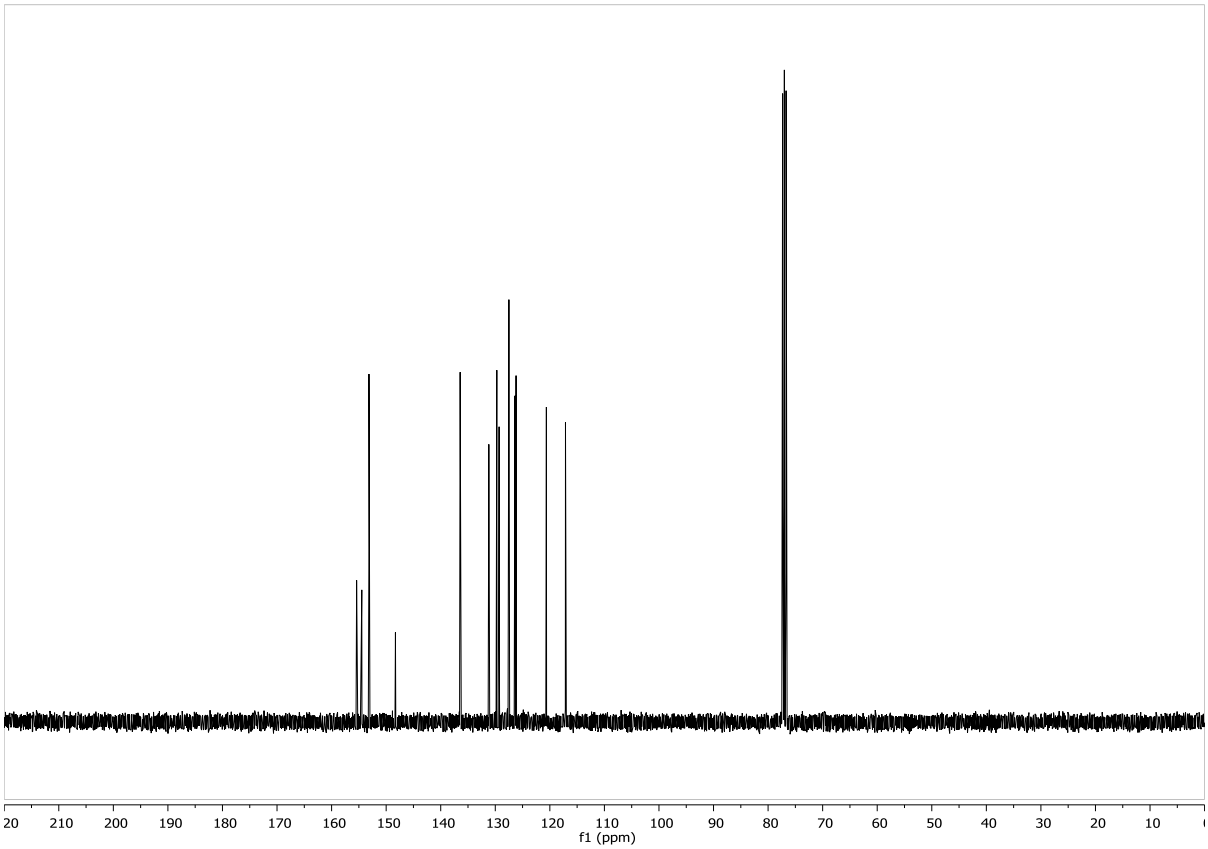
f1 (ppm)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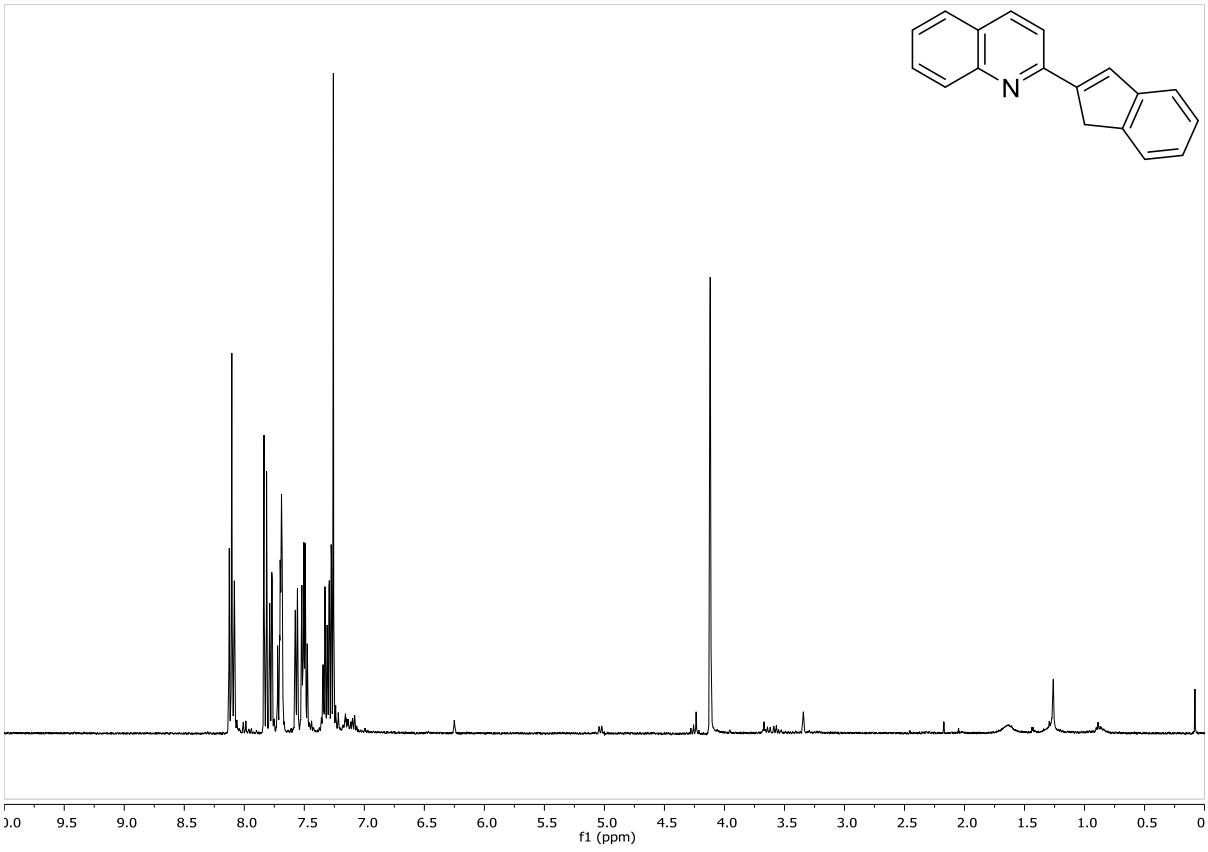
f1 (ppm)


N
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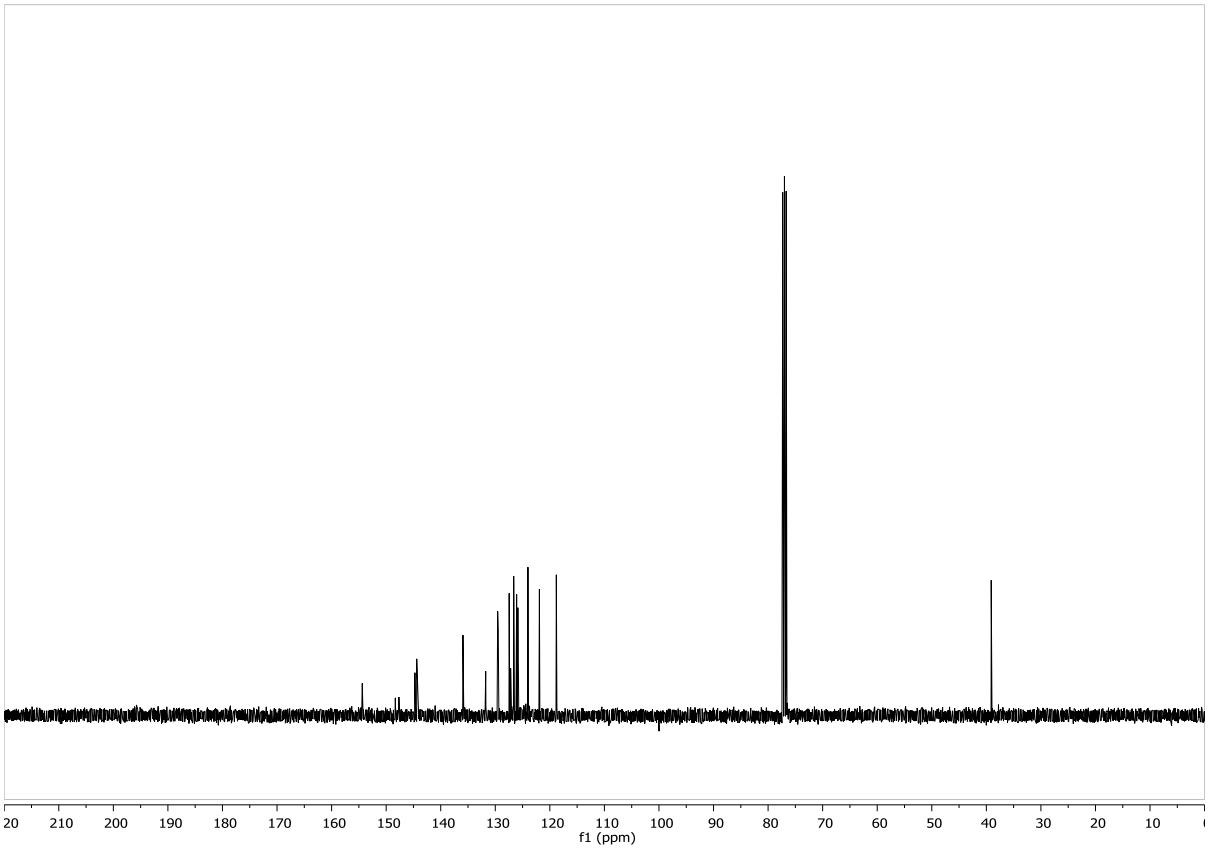
f1 (ppm)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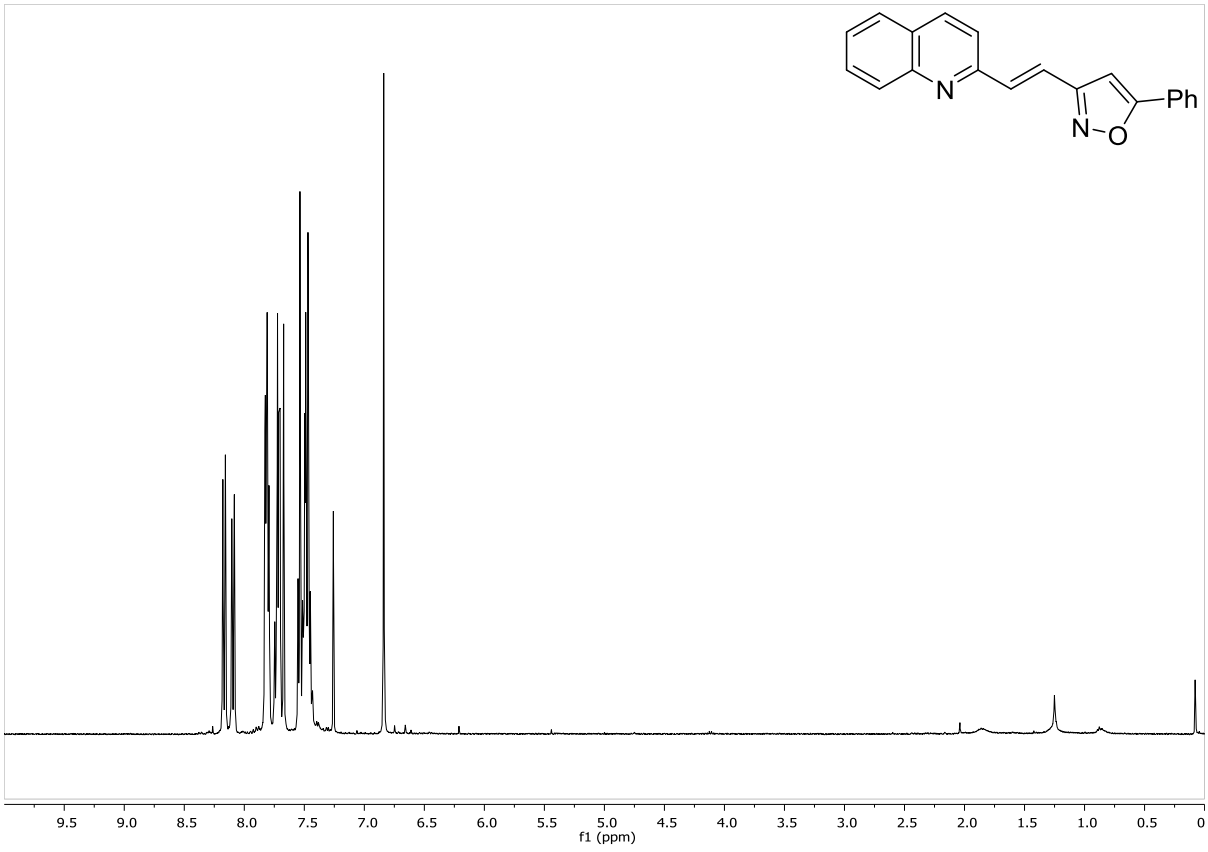
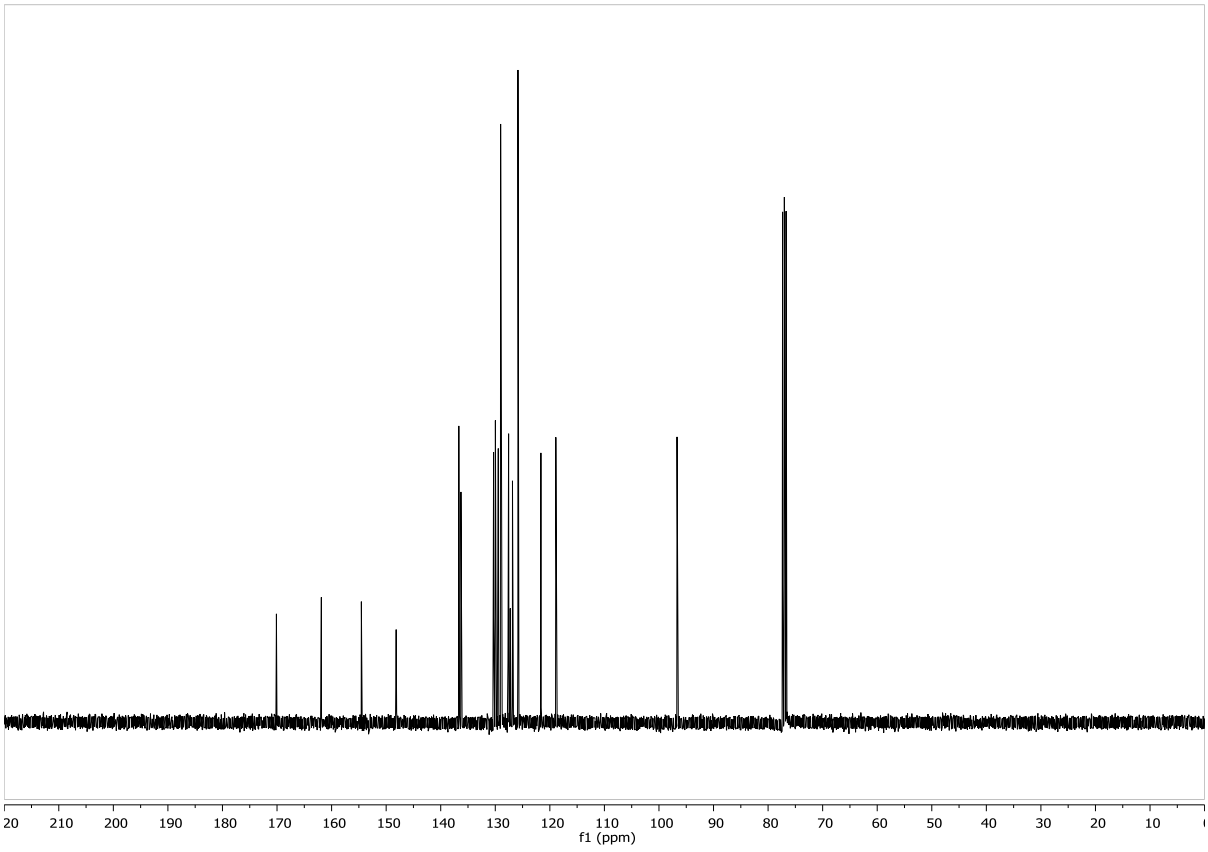
f1 (ppm)


N
N
O
Ph
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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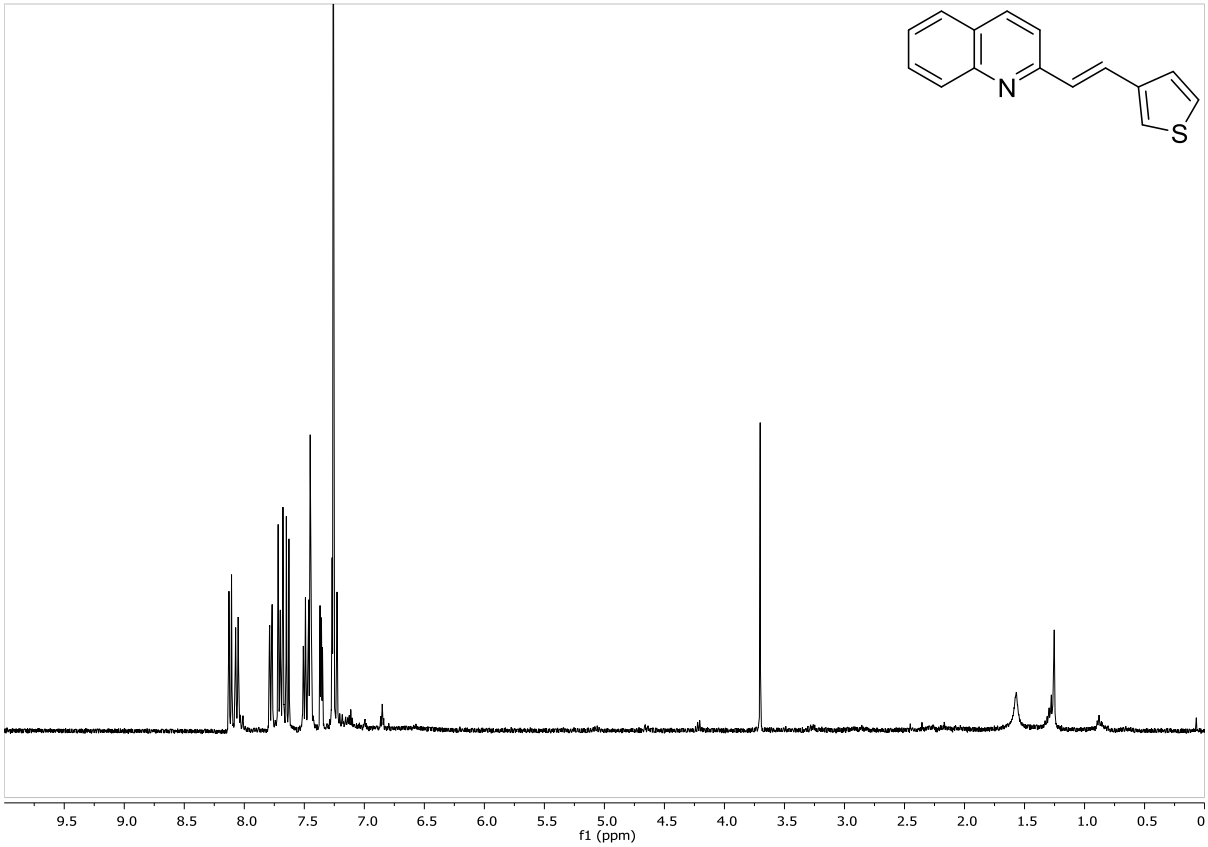
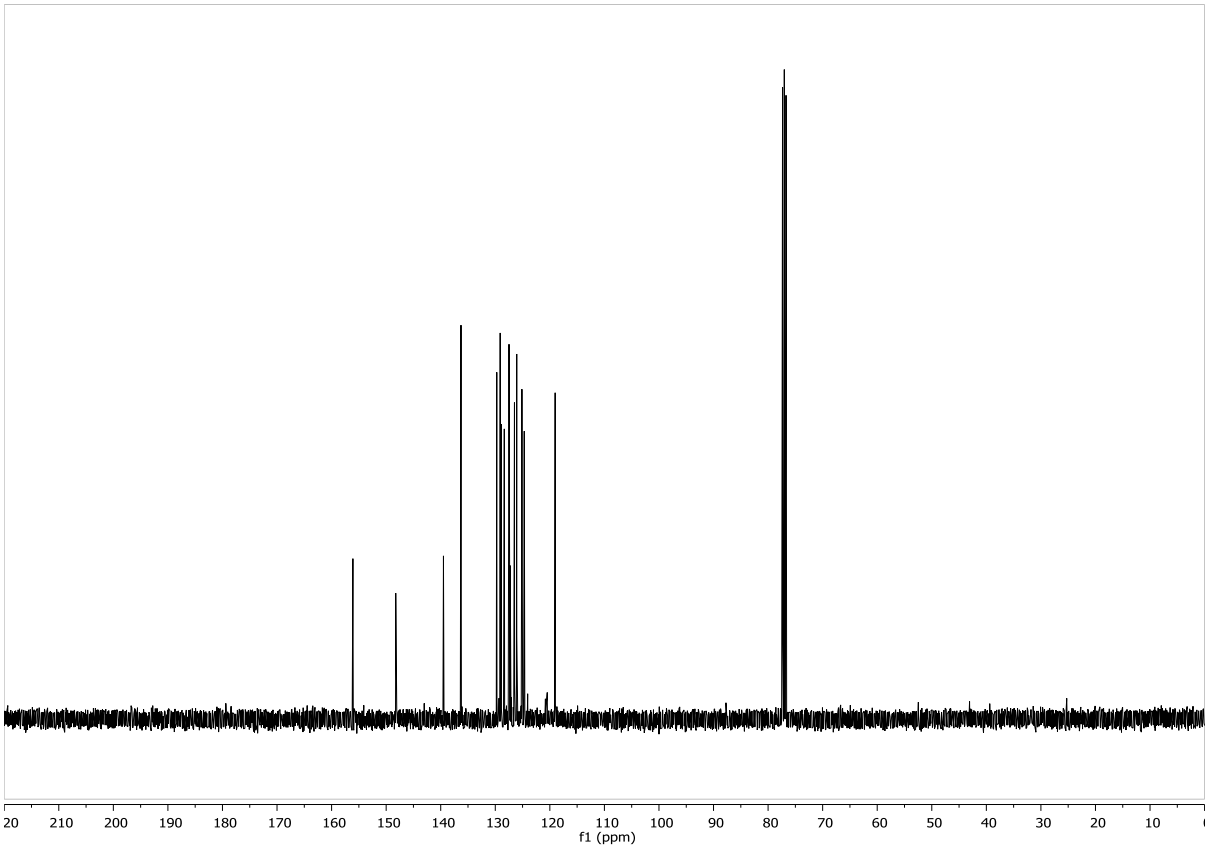
f1 (ppm)


N
S
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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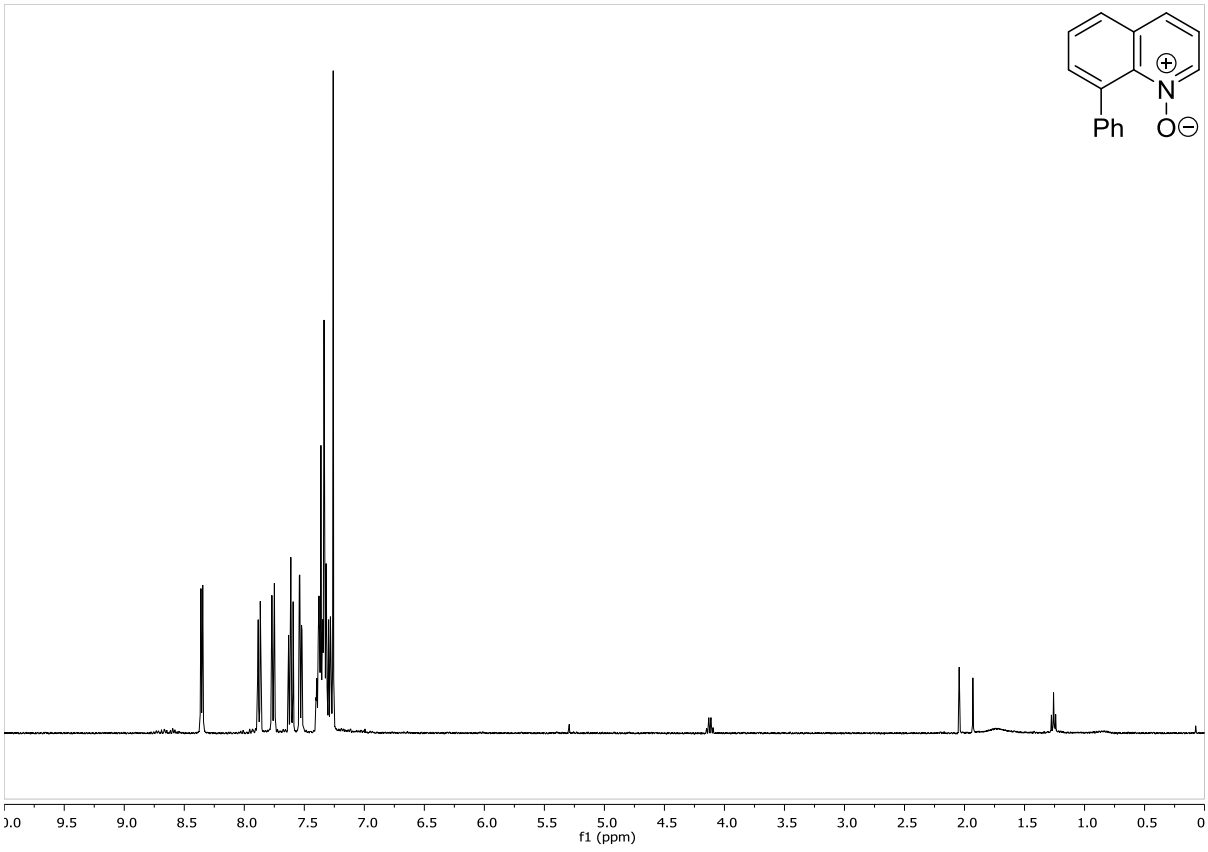
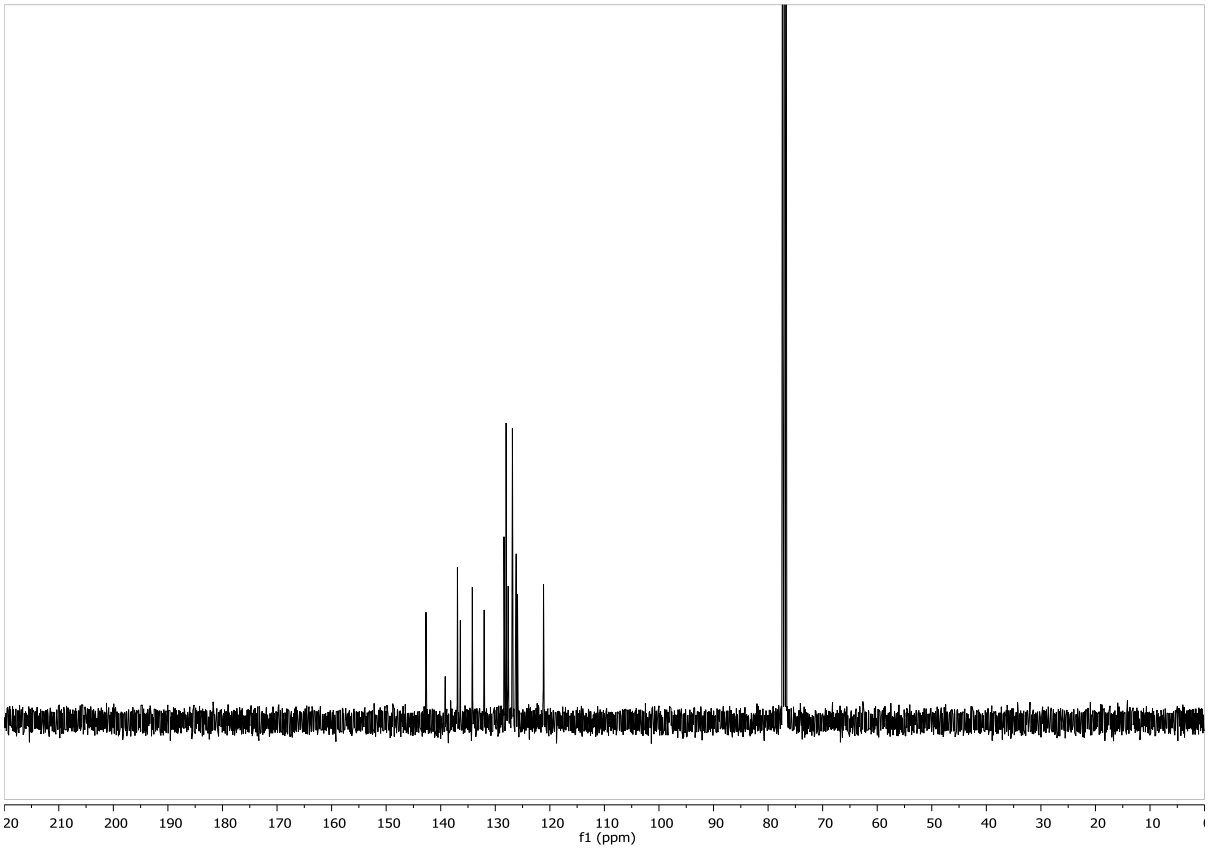
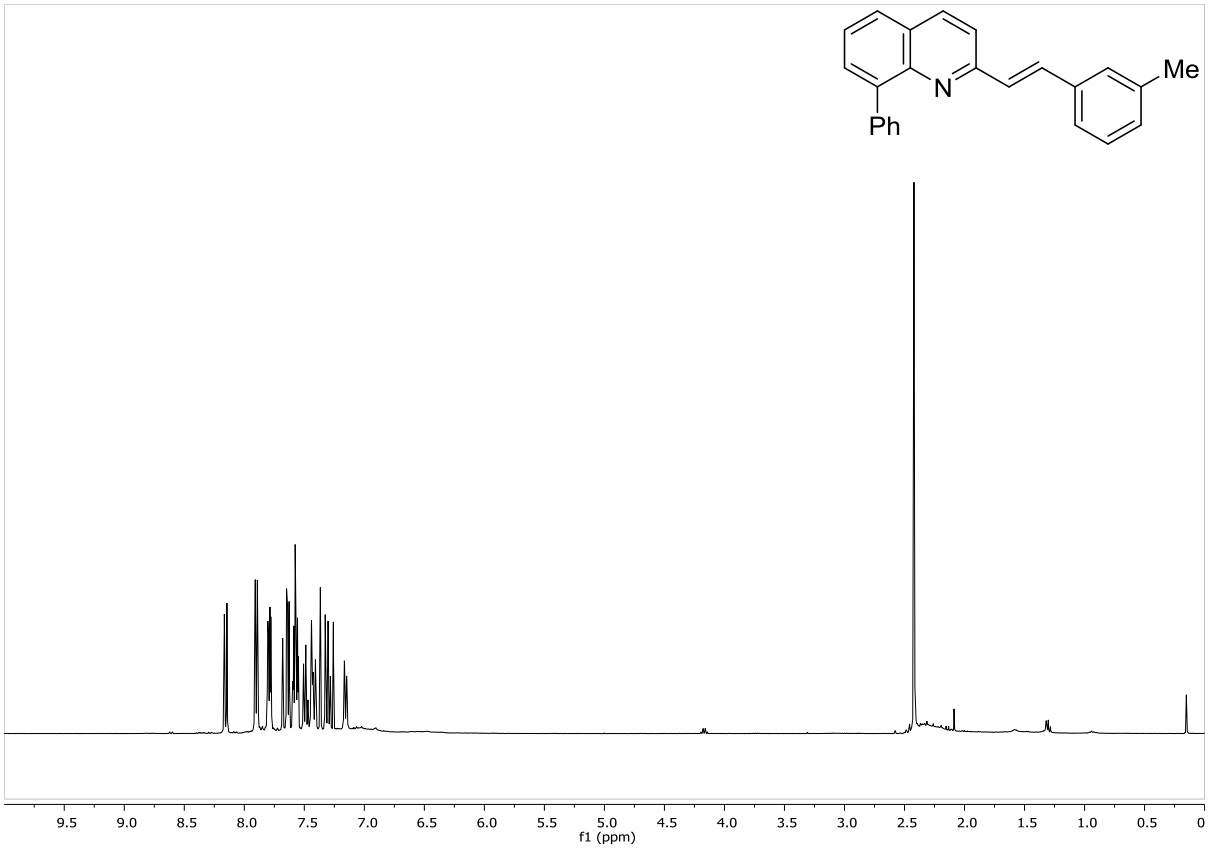
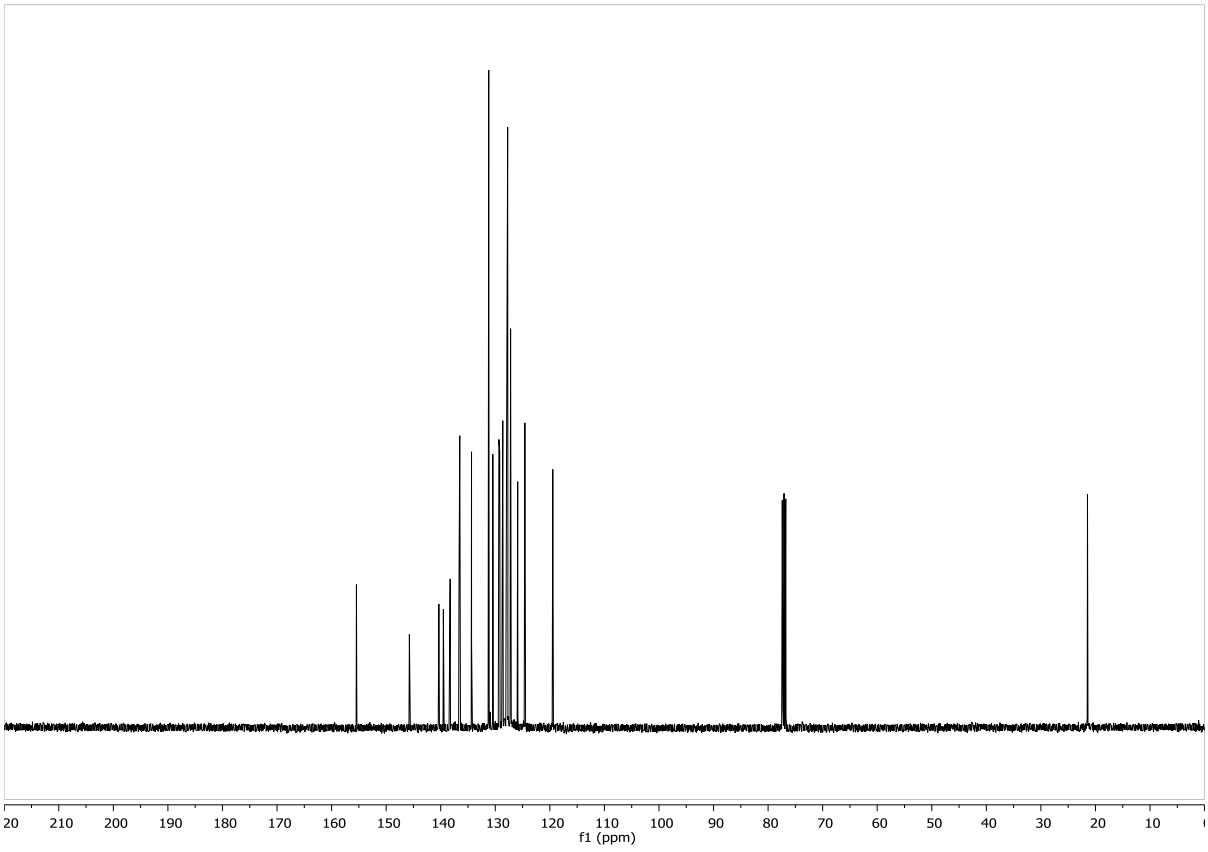
f1 (ppm)


Ph
N
O
f1 (ppm)


f1 (ppm)


N
Ph
Me
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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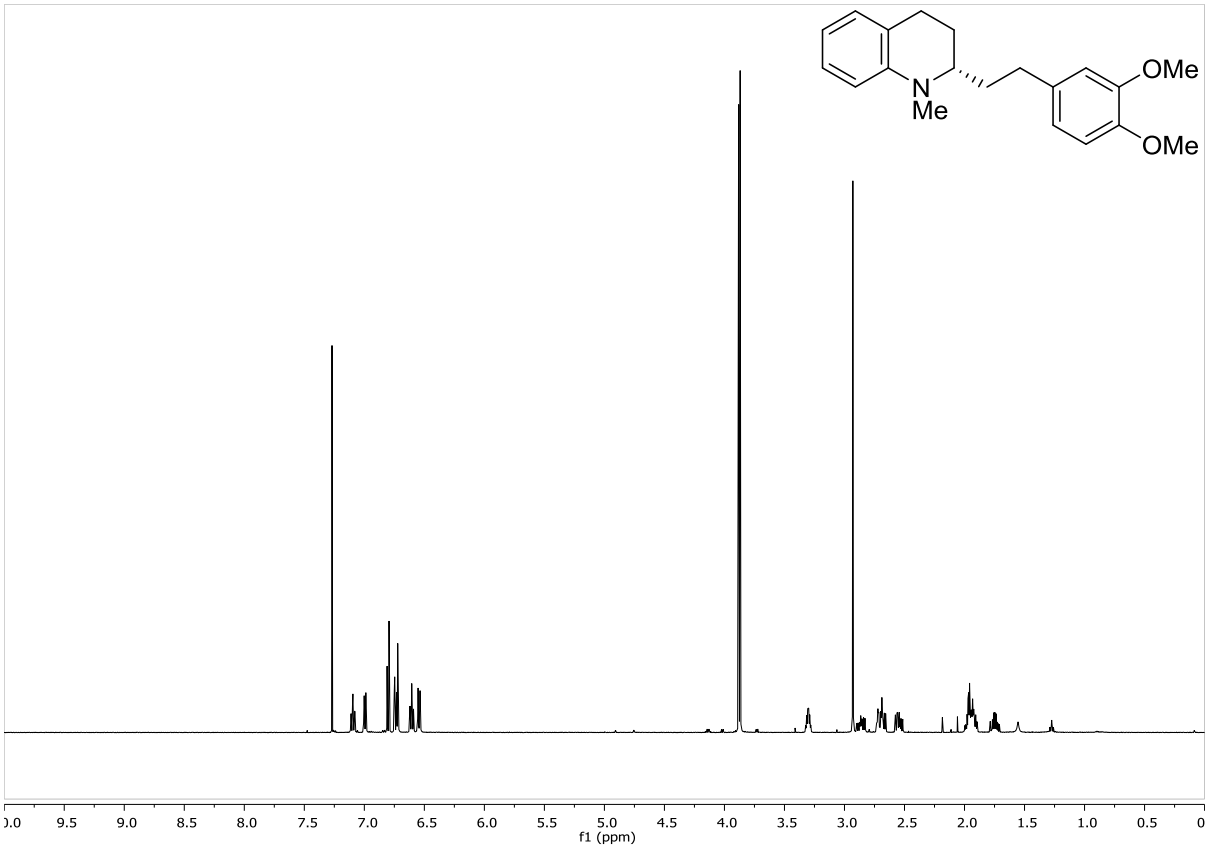
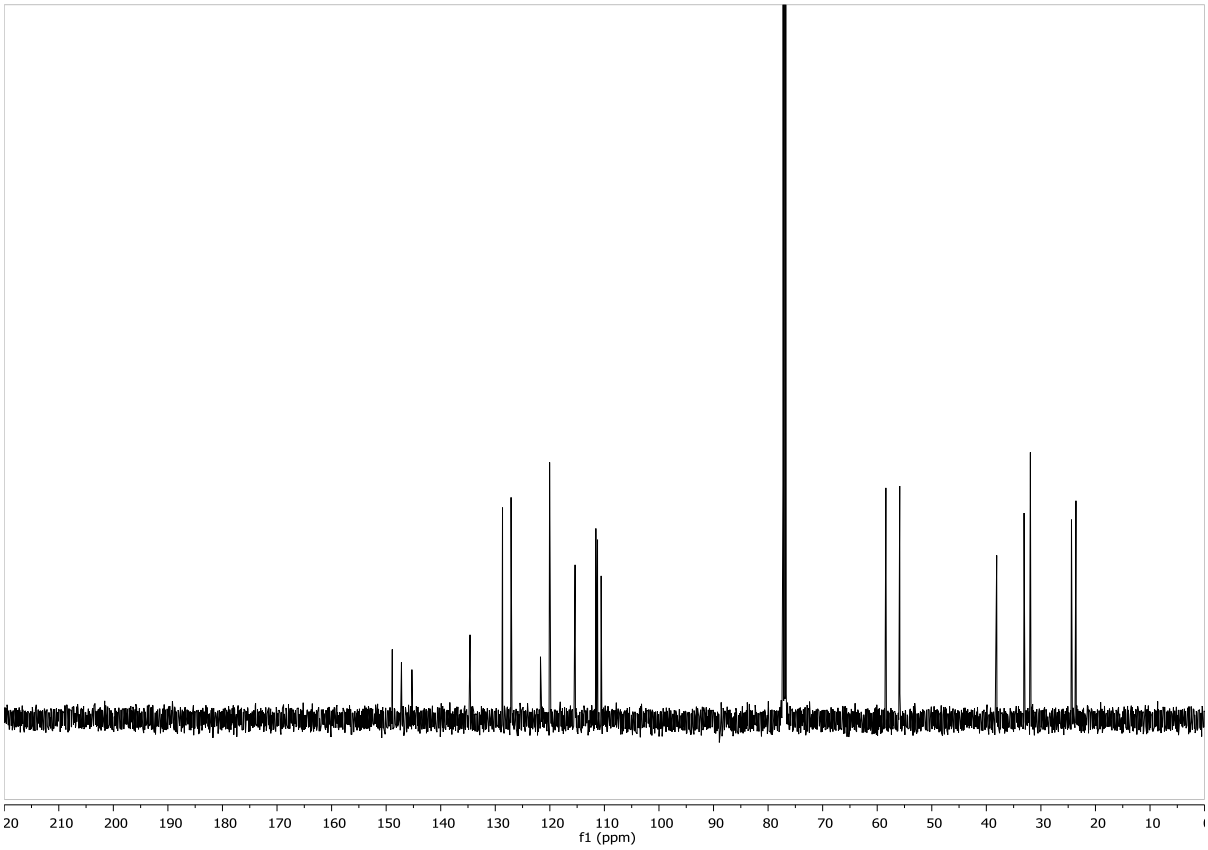

N
Me
OMe
OMe
f1 (ppm)


f1 (ppm)

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