Supporting Information

Modular synthesis of aryl amines from 3-alkynyl-2-pyrones

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1 General Considerations

1.1 Experimental Procedures

Unless otherwise noted, all reactions were performed in flame or oven-dried glassware fitted with rubber septa under a positive pressure of nitrogen using standard Schlenk techniques. Air and moisture sensitive liquids were transferred using a syringe or stainless-steel cannula through rubber septa. Solids were added under inert gas or were dissolved in appropriate solvents. Reaction temperatures above 23 ˚C were conducted in an oil bath or in a heated metal block (reactions conducted in tightly capped vials sealed with Teflon tape). Reaction mixtures were magnetically stirred and monitored by NMR spectroscopy, liquid chromatography–mass spectrometry (LC–MS) or analytical thin-layer chromatography (TLC), using glass plates precoated with silica gel (Silicycle Siliaplates, glass backed, extra hard layer 60 Å, 250 μm thickness, F254 indicator) or aluminum plates precoated with silica gel (Macherey-Nagel, aluminum backed, 0.20 mm silica gel 60, fluorescent indicator). TLC plates were visualized by exposure to ultraviolet light (254 nm) or were stained by submersion in aqueous potassium permanganate solution ($KMnO_4$) and developed by heating with a heat gun. Flash-column chromatography was performed as described by Still et al.,[1] employing silica gel (Silicycle silica gel, 40–63 μm particle size). Organic solutions were concentrated under reduced pressure on a Büchi temperature-controlled rotary evaporator equipped with a dry ice/isopropanol cold finger. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

1.2 Materials

Unless noted below, commercial reagents were purchased from Sigma Aldrich, Acros Organics, ChemImpex, Oakwood Chemical, Combi-blocks, TCI, and/or Alfa Aesar, and used without additional purification. Solvents were purchased from Fisher Scientific, Acros Organics, Alfa Aesar, or Sigma Aldrich. Tetrahydrofuran (THF), diethyl ether (Et_2O), acetonitrile (CH_3CN), benzene, toluene (PhMe), methanol (MeOH), and triethylamine (Et_3N) were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2, DCM) was freshly distilled over calcium hydride under a N_2 atmosphere prior to each use.

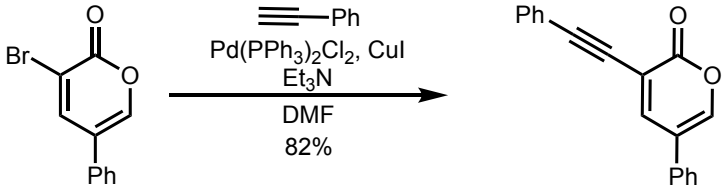
1.3 NMR Spectroscopy

NMR spectral data were obtained using deuterated solvents, obtained from Cambridge Isotope Laboratories, Inc. ^{1}H NMR and ^{13}C NMR data were recorded on Bruker AVB-400, AVQ-400, JEOL-400 NEO-500, NEO-501 or AV-600 spectrometers operating at 400 MHz, 400 MHz, 400 500 MHz, or 600 MHz for proton nuclei (100 MHz, 100 MHz, 100 MHz, 125 MHz, 126 MHz, or 150 MHz for carbon nuclei), respectively. The reported ^{13}C spectra are decoupled. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26). Carbon chemical shifts are expressed in parts per million (δ scale, assigned carbon atom) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.16). ^{19}F NMR spectra were acquired on an AVQ-400, JEOL-400 or NEO-500 spectrometer and internally referenced to $CFCl_3$ (δ 0.00). ^{1}H NMR spectroscopic data are reported as follows: Chemical shift in ppm (multiplicity, coupling constants J (Hz), integration) (e.g., “5.21

(t, 3 J = 7.3 Hz, 1H)"). The multiplicities are abbreviated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), se (sextet), h (heptet), m (multiplet) and app (apparent multiplet). In cases of overlapping multiplets, the multiplicity with the larger coupling constant is stated first. With the exception of multiplets, the chemical shift of all signals, as well as for centrosymmetric multiplets, is reported as the center of the resonance range. Data for ^{13}C, and ^{19}F NMR spectroscopy are reported in terms of chemical shift. All raw FID files were processed, and the spectra analyzed using the program MestReNOVA 11.0 from Mestrelab Research S. L. Note: Instruments in the Berkeley College of Chemistry NMR facility are supported in part by NIH S10OD024998.

2 Preparative Procedures to Access the Alkynyl 2-Pyrones

2.1 Synthesis of phenyl alkynyl pyrone 7a



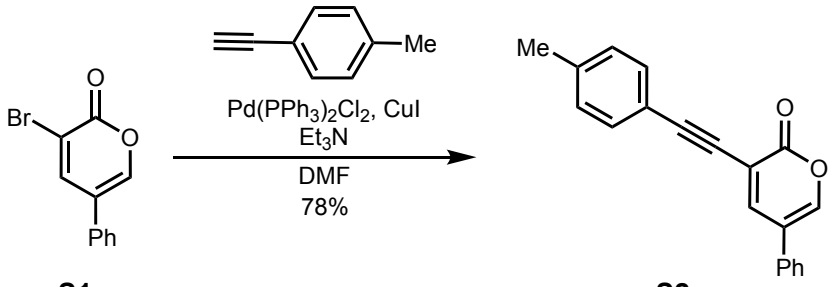
S1 **7a**

We have previously reported a synthesis of **7a**.[1] This procedure is reproduced here for convenience as subsequent procedures reported here rely on this protocol.

All alkynyl pyrones were prepared following the procedure developed by Cho et al.[2] as reported previously by our group. To a yellow solution of 3-bromo-5-phenyl-2-pyrone (**S1**, 214 mg, 0.852 mmol, 1 equiv)[3], $Pd(PPh_3)_2Cl_2$ (29.9 mg, 0.0426 mmol, 5 mol %), and CuI (16.2 mg, 0.0852 mmol, 10 mol %) in *N*,*N*-dimethylformamide (DMF) (12 mL) in an oven-dried 30 mL vial was sequentially added NEt_3 (140 µL, 1.00 mmol, 1.2 equiv) and phenyl acetylene (110 µL, 1.02 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C. After 16 h, the mixture was diluted with Et_2O (50 mL) and washed with water (50 mL) and brine (50 mL). The resulting organic phase was dried over $MgSO_4$, filtered, and the filtrate concentrated *in vacuo*. The brown residue was purified by flash column chromatography using 12:1 hexanes:EtOAc to provide diphenyl alkynyl pyrone **7a** (190 mg, 0.699 mmol, 82%) as a brown solid. The ^1H NMR spectrum was fully consistent with that reported in the literature.[1]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.6 Hz, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.48 – 7.44 (m, 2H), 7.41 (dt, *J* = 5.8, 1.4 Hz, 3H), 7.39 – 7.33 (m, 3H).

2.2 Synthesis of 4-methylphenyl alkynyl pyrone (S2)

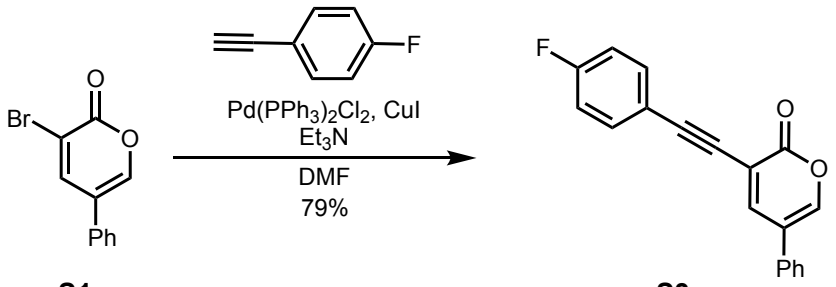


S1 **S2**

Following the procedure for the preparation of **7a**, to a mixture of **S1** (50.0 mg, 0.199 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (7.00 mg, 0.098 mmol, 5 mol %), and CuI (3.8 mg, 0.020 mmol, 10 mol %) in DMF (2.8 mL) in a 20 mL vial was sequentially added NEt_3 (40 µL, 0.287 mmol, 1.2 equiv) and 1-ethynyl-4-methoxybenzene (38 µL, 0.290 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 21 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to give 4-methylphenyl alkynyl pyrone **S2** (44.8 mg, 0.156 mmol, 78% yield) as a yellow-brown solid.

R_f = 0.38 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.6 Hz, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.48 – 7.43 (m, 4H), 7.40 (ddd, *J* = 9.4, 3.5, 2.5 Hz, 3H), 7.16 (d, *J* = 7.9 Hz, 2H), 2.37 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 160.18, 147.40, 145.13, 139.60, 133.21, 132.00, 129.42, 129.31, 128.67, 126.18, 121.24, 119.22, 113.60, 96.93, 82.74, 21.72.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{20}H_{15}O_2$: 287.1067, found 287.1065.

2.3 Synthesis of 4-fluorophenyl alkynyl pyrone (S3)



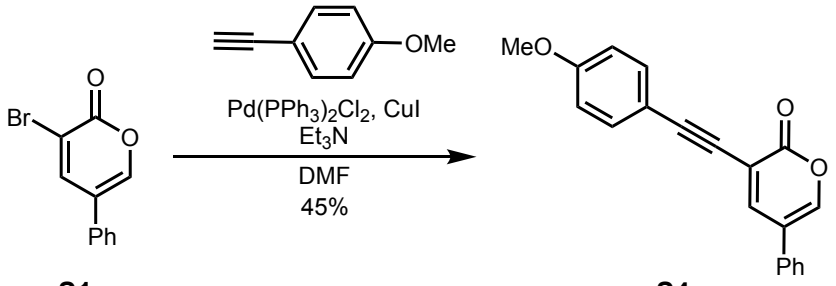
S1 **S3**

Following the procedure for the preparation of **7a**, to a mixture of **S1** (50.0 mg, 0.199 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (7.00 mg, 0.098 mmol, 5 mol %), and CuI (3.8 mg, 0.020 mmol, 10 mol %) in DMF (2.8 mL) in a 20 mL vial was sequentially added NEt_3 (40 µL, 0.287 mmol, 1.2 equiv) and 1-ethynyl-4-methoxybenzene (38 µL, 0.290 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 4.5 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to give 4-fluorophenyl alkynyl pyrone **S3** (45.9 mg, 0.158 mmol, 79% yield) as a yellow-brown solid.

R_f = 0.26 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.6 Hz, 1H), 7.69 (d, *J* = 2.6 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.45 (dd, *J* = 8.5, 6.6 Hz, 2H), 7.43 – 7.36 (m, 3H), 7.05 (t, *J* = 8.6 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.11 (d, J = 251.1 Hz), 160.02, 147.67, 145.45, 134.06 (d, J = 8.4 Hz), 133.07, 129.43, 128.71, 126.15, 121.20, 118.40 (d, J = 3.4 Hz), 115.90 (d, J = 22.3 Hz), 113.22, 95.40, 83.01.
^{19}F NMR (565 MHz, $CDCl_3$) δ -109.24.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{19}H_{12}O_2F$: 291.0816, found 291.0820.

2.4 Synthesis of 4-methoxyphenyl alkynyl pyrone (S4)

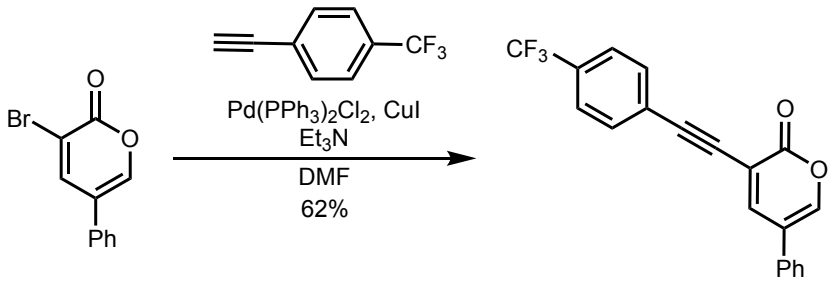


S1 **S4**

Following the procedure for the preparation of **7a**, to a mixture of **S1** (60.0 mg, 0.239 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (8.40 mg, 0.012 mmol, 5 mol %), and CuI (4.6 mg, 0.024 mmol, 10 mol %) in DMF (3.4 mL) in a 20 mL vial was sequentially added NEt_3 (40 µL, 0.287 mmol, 1.2 equiv) and 1-ethynyl-4-methoxybenzene (38 µL, 0.290 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 4.5 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc to 5:1 hexanes:EtOAc) to give 4-methoxyphenyl alkynyl pyrone **S4** (32.8 mg, 0.108 mmol, 45% yield) as a bright yellow solid.

R_f = 0.41 (3:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 2.6 Hz, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.49 – 7.42 (m, 2H), 7.42 – 7.36 (m, 3H), 6.91 – 6.84 (m, 2H), 3.83 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 160.45, 160.24, 147.21, 144.74, 133.67, 133.26, 129.41, 128.65, 126.18, 121.24, 114.36, 114.22, 113.72, 96.90, 82.25, 55.46.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{20}H_{15}O_3$: 303.1016, found 303.1019.

2.5 Synthesis of 4-trifluoromethylphenyl alkynyl pyrone (S5)



S1 **S5**

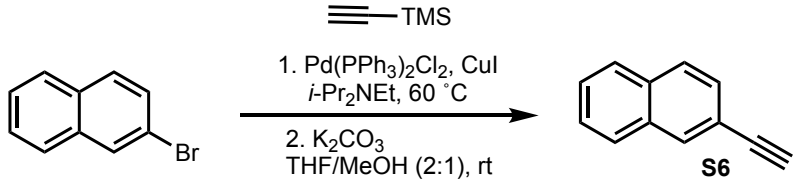
Following the procedure for the preparation of **7a**, to a mixture of **S1** (100.0 mg, 0.398 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (14.00 mg, 0.020 mmol, 5 mol %), and CuI (7.60 mg, 0.040 mmol, 10 mol %) in DMF (5.7 mL) in a 20 mL vial was sequentially added NEt_3 (67 µL, 0.478 mmol, 1.2

equiv) and 1-ethynyl-4-methoxybenzene (78 μL, 0.478 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 20 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to give 4-trifluoromethylphenyl alkynyl pyrone **S5** (83.6 mg, 0.246 mmol, 62% yield) as a pale yellow solid.

R_f = 0.35 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.6 Hz, 1H), 7.73 (d, *J* = 2.6 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.42 (ddt, *J* = 7.4, 6.3, 1.6 Hz, 3H).
^{13}C NMR{^{19}F, ^{1}H decoupled} (101 MHz, $CDCl_3$) δ 159.86, 148.23, 146.32, 132.98, 132.33, 130.93, 129.52, 128.86, 126.22, 126.09, 125.52, 123.95, 121.31, 112.85, 94.77, 85.39.
^{19}F NMR (471 MHz, $CDCl_3$) δ -62.91.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{20}H_{12}O_2F_3$: 341.0784, found 341.0786.

2.6 Synthesis of 2-naphthyl alkynyl pyrone (S7)

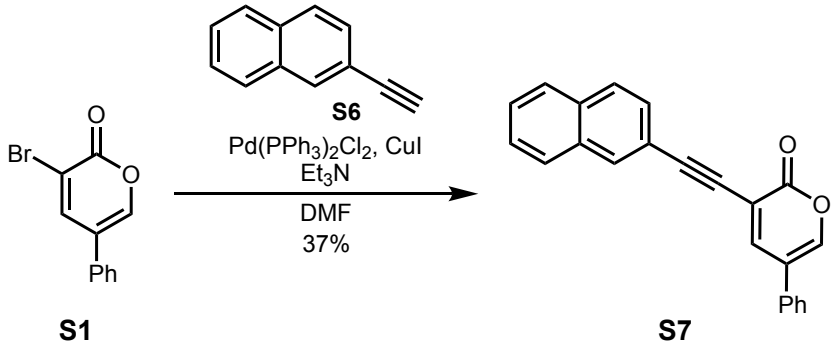
Procedure for 2-napthyl alkyne S6 synthesis



2-Napthyl alkyne (**S6**) was prepared in a two-step sequence from 2-bromonaphthalene. Following a modified procedure,[4] to a solution of 2-bromonapthalene (542 mg, 2.62 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (220 mg, 0.314 mmol, 12 mol %) and CuI (99.7 mg, 0.523 mmol, 20 mol %) in THF (4.3 mL) was sequentially added Hünig's base (1.79 mL, 10.5 mmol, 4 equiv) and ethynyltrimethylsilane (10.5 mmol, 1.49 mL, 4 equiv). The resulting solution turned red and then dark brown, and the reaction mixture was heated in an oil bath at 60 ˚C. After 24 h, the reaction mixture was diluted with diethyl ether and the organic layer washed with water, sat. aq. $NaHCO_3$, and brine, dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to give trimethyl(naphthalene-2-ylethynyl)silane (503 mg, 2.24 mmol, 86%) as a brown-orange oil. The TMS group was cleaved following a known procedure.[5] To the resulting yellow solution of trimethyl(naphthalene-2-ylethynyl)silane (200 mg, 0.891 mmol, 1 equiv) in a 2:1 mixture of THF:MeOH (15:7.5 mL), K_2CO_3 (493 mg, 3.57 mmol, 4 equiv) was added and the reaction mixture was stirred at room temperature. After full consumption of SM as judged by TLC (3 h), the reaction mixture was concentrated *in vacuo*. The resulting residue was diluted with water (40 mL), extracted into Et_2O (3 x 40 mL), and the resulting organic layer was dried over $MgSO_4$, filtered, and concentrated to give the desired 2-naphthyl alkyne **S6** (131 mg, 0.861 mmol, 97% yield) as a brown solid. The ^{1}H NMR spectrum was fully consistent with that reported in the literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.91 – 7.72 (m, 3H), 7.52 (ddd, *J* = 9.6, 7.3, 2.5 Hz, 3H), 3.15 (s, 1H).

Procedure for alkynyl pyrone S7 synthesis

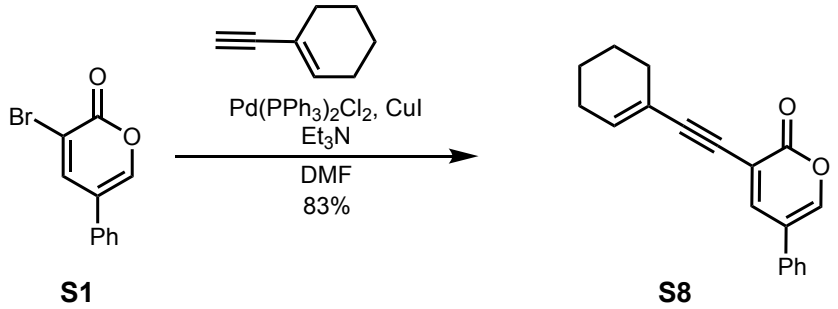


S1 **S7**

Following the procedure for the preparation of **7a**, to a mixture of **S1** (85.0 mg, 0.339 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (11.9 mg, 0.017 mmol, 5 mol %), CuI (6.45 mg, 0.034 mmol, 10 mol %), and **S6** (61.8 mg, 0.406 mmol, 1.2 equiv) in DMF (4.8 mL) in a 20 mL vial was added NEt_3 (60 µL, 0.430 mmol, 1.3 equiv). The resulting dark brown solution was stirred at 23 ˚C for 20 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to give 2-naphthyl alkynyl pyrone **S7** (40.0 mg, 0.120 mmol, 37% yield) as a yellow-orange solid.

R_f = 0.21 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.5 Hz, 1H), 7.91 (d, *J* = 2.6 Hz, 1H), 7.83 (dd, *J* = 9.3, 4.4 Hz, 3H), 7.72 (d, *J* = 2.6 Hz, 1H), 7.60 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.49 – 7.41 (m, 5H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.18, 147.64, 145.49, 133.35, 133.20, 133.02, 132.49, 129.48, 128.75, 128.38, 128.27, 128.13, 127.97, 127.30, 126.87, 126.23, 121.33, 119.56, 113.50, 97.08, 83.61.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{15}O_2$: 323.1067, found 323.1064.

2.7 Synthesis of cyclohexenyl alkynyl pyrone (S8)



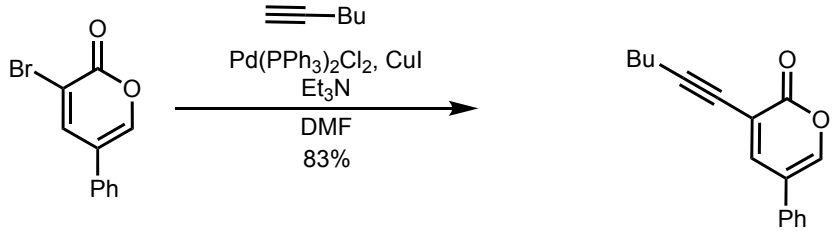
S1 **S8**

Following the procedure for the preparation of **7a**, to a mixture of **S1** (50.0 mg, 0.199 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.010 mmol, 5 mol %), and CuI (3.79 mg, 0.199 mmol, 10 mol %) in 1,4-dioxane (2.9 mL) in a 20 mL vial was sequentially added NEt_3 (35 µL, 0.255 mmol, 1.3 equiv) and 1-ethynylcyclohex-1-ene (30 uL, 0.260 mmol, 1.3 equiv). The resulting dark

brown solution was stirred at 23 ˚C for 24 h. The crude residue was purified by flash-column chromatography on silica gel (12:1 hexanes:EtOAc) to give cyclohexenyl alkynyl pyrone **S8** (40.0 mg, 0.120 mmol, 37% yield) as an orange oil.

R_f = 0.48 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 2.6 Hz, 1H), 7.43 (dd, *J* = 8.6, 6.3 Hz, 2H), 7.41 – 7.36 (m, 3H), 6.31 (tt, *J* = 4.1, 1.9 Hz, 1H), 2.23 (tq, *J* = 5.3, 2.3 Hz, 2H), 2.15 (tq, *J* = 6.0, 2.9 Hz, 2H), 1.67 (qd, *J* = 7.8, 6.3, 4.0 Hz, 2H), 1.61 (qd, *J* = 9.3, 7.7, 4.2 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 160.27, 147.04, 144.57, 137.77, 133.30, 129.38, 128.60, 126.15, 121.17, 120.32, 113.83, 98.72, 80.81, 28.94, 25.99, 22.30, 21.49.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{19}H_{17}O_2$: 277.1223, found 277.1222.

2.8 Synthesis of butyl alkynyl pyrone (S9)

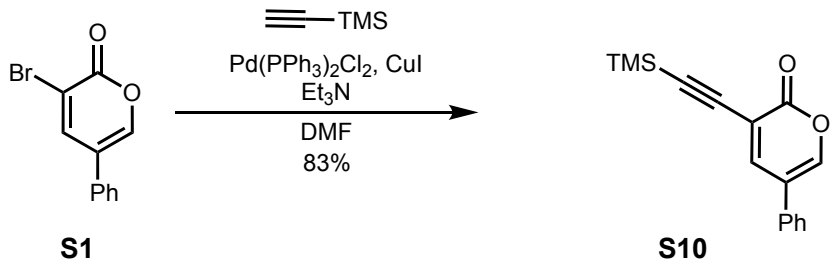


S1 **S9**

Following the procedure for the preparation of **7a**, to a mixture of **S1** (50.0 mg, 0.199 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 0.010 mmol, 5 mol %), and CuI (3.79 mg, 0.199 mmol, 10 mol %) in 1,4-dioxane (2.9 mL) in a 20 mL vial was sequentially added NEt_3 (35 µL, 0.255 mmol, 1.3 equiv) and hex-1-yne (30 uL, 0.260 mmol, 1.3 equiv). The resulting dark brown solution was stirred at 23 ˚C for 24 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hex:EA) to give butyl alkynyl pyrone **S8** (36.1 mg, 0.143 mmol, 72% yield) as a clear oil.

R_f = 0.39 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.6 Hz, 1H), 7.64 (d, *J* = 2.6 Hz, 1H), 7.47 – 7.37 (m, 4H), 7.37 (q, *J* = 1.8, 1.2 Hz, 1H), 2.47 (t, *J* = 7.1 Hz, 2H), 1.65 – 1.59 (m, 2H), 1.48 (qd, *J* = 7.5, 2.5 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.80, 146.94, 145.02, 133.32, 129.40, 128.61, 126.18, 121.11, 113.98, 98.77, 74.63, 30.59, 22.19, 19.62, 13.75.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{17}H_{17}O_2$: 253.1223, found 253.1222.

2.9 Synthesis of TMS alkynyl pyrone (S10)

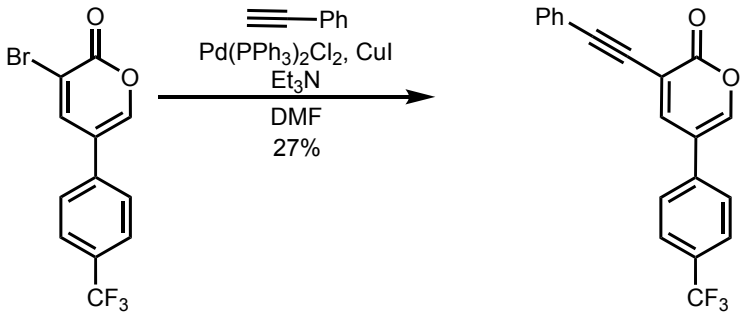


S1 **S10**

Following the procedure for the preparation of **7a**, to a mixture of **S1** (240 mg, 0.956 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (33.5 mg, 0.048 mmol, 5 mol %), and CuI (18.2 mg, 0.096 mmol, 10 mol %) in DMF (13.7 mL) in a 50 mL round-bottomed flask was sequentially added NEt_3 (163 µL, 1.15 mmol, 1.3 equiv) and TMS acetylene (µL, 1.15 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 24 h. The crude residue was purified by flash-column chromatography on silica gel (8:1 hexanes:EtOAc) to give TMS alkynyl pyrone **S9** (170.8 mg, 0.636 mmol, 67% yield) as an orange oil.

R_f = 0.52 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 1H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.50 – 7.33 (m, 5H), 0.26 (d, *J* = 1.2 Hz, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.03, 147.92, 146.65, 133.06, 129.43, 128.71, 126.17, 121.08, 113.13, 102.97, 98.02, -0.14 (s).
HRMS (ESI): $[M+H]^+$ cal'd for $C_{16}H_{17}O_2Si_1$: 269.0992, found 269.0994.

2.10 Synthesis of 5-(4-trifluoromethylphenyl)-3-phenyl alkynyl pyrone (S12)



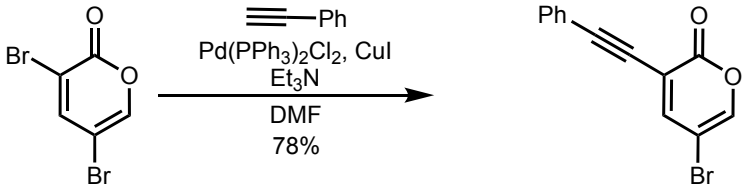
S11 **S12**

Following the procedure for the preparation of **7a**, to a mixture of **S11** (62.1 mg, 0.195 mmol, 1 equiv)[6], $Pd(PPh_3)_2Cl_2$ (6.83 mg, 0.01 mmol, 5 mol %), and CuI (3.71 mg, 0.019 mmol, 10 mol %) in DMF (2.7 mL) in a 8 mL vial was added NEt_3 (33.0 µL, 0.24 mmol, 1.2 equiv) and phenyl acetylene (26 uL, 0.24 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 24 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 to 5:1 hexanes:EtOAc) to give 5-(4-trifluoromethylphenyl)-3-phenyl alkynyl pyrone **S12** (17.8 mg, 0.052 mmol, 27% yield) as an off-white solid.

R_f = 0.30 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.6 Hz, 1H), 7.75 (d, *J* = 2.6 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.58 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.36 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.64, 148.23, 144.43, 136.82, 132.14, 130.91 (q, J = 33.1 Hz), 129.48, 128.60, 126.54, 126.49 (q, J = 3.7 Hz), 122.10, 120.08, 113.95, 97.18, 82.97. *Note: CF_3 is not observed here, likely due to ^{13}C-^{19}F splitting which reduces signal intensity. However, ^{19}F NMR clearly shows evidence for CF_3 group).*
^{19}F NMR (471 MHz, $CDCl_3$) δ -62.70.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{20}H_{12}O_2F_3$: 341.0784, found 341.0790.

2.11 Synthesis of 5-Br-3-phenyl alkynyl pyrone (S14)

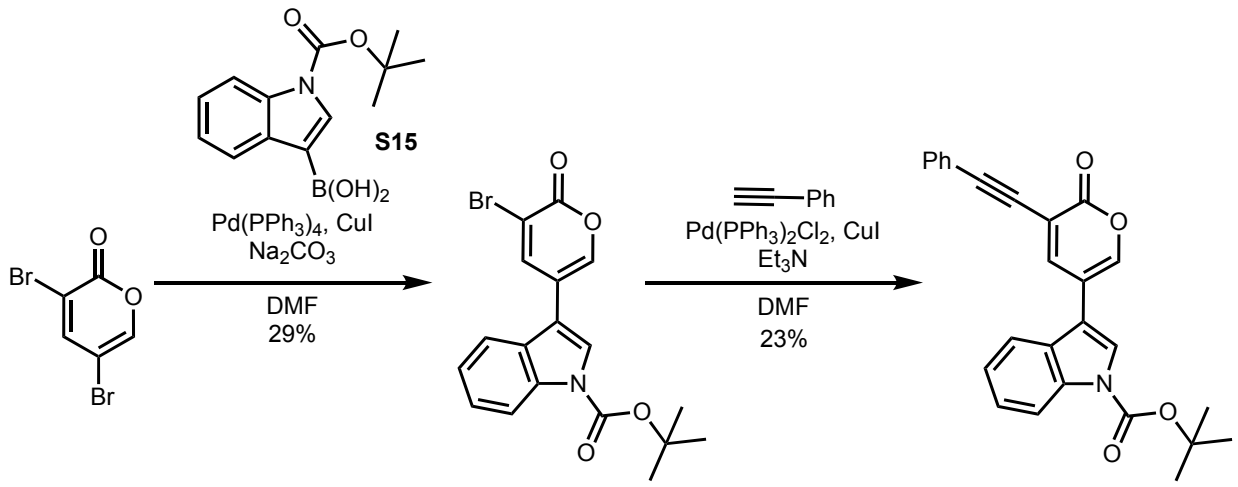


S13 **S14**

Following the procedure for the preparation of **7a**, to a mixture of **S13** (200 mg, 0.788 mmol, 1 equiv),[7] $Pd(PPh_3)_2Cl_2$ (27.6 mg, 0.039 mmol, 5 mol %), and CuI (15.0 mg, 0.079 mmol, 10 mol %) in DMF (11.2 mL) in a 30 mL vial was added NEt_3 (132 µL, 0.945 mmol, 1.2 equiv) and phenyl acetylene (100 uL, 0.945 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 19 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to give 5-Br-3-phenyl alkynyl pyrone **S12** (169 mg, 0.615 mmol, 78% yield) as a yellow solid. The ^{1}H NMR spectrum was fully consistent with that reported in the literature.[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.49 (m, 4H), 7.45 – 7.32 (m, 3H).

2.12 Synthesis of 5-(3-*N*-Boc-indole)-3-phenyl alkynyl pyrone (S17)



S13 **S16** **S17**

Procedure for 3-bromo-2-pyrone S16 synthesis

An oven-dried vial was charged with a magnetic stir bar, **S13** (100 mg, 0.394 mmol, 1 equiv), boronic acid **S15** (123 mg, 0.423 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (45.5 mg, 0.039 mmol, 10 mol %), CuI (75.0 mg, 0.39 mmol, 1 equiv), and Na_2CO_3 (84.0 mg, 0.79 mmol, 2 equiv) in DMF (4 mL) was heated to 50 ˚C in a heating block. After 24 h, the mixture was cooled to 23 ˚C and diluted with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NH_4Cl (~2 mL). The aqueous layer was extracted with ethyl acetate (4 x 20 mL) and the combined organic extracts were washed with water and saturated aqueous NaCl solution. The washed organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (10:1 hexanes:EtOAc) to provide **S16** (45.0 mg, 0.115 mmol, 29%) as a bright yellow solid.

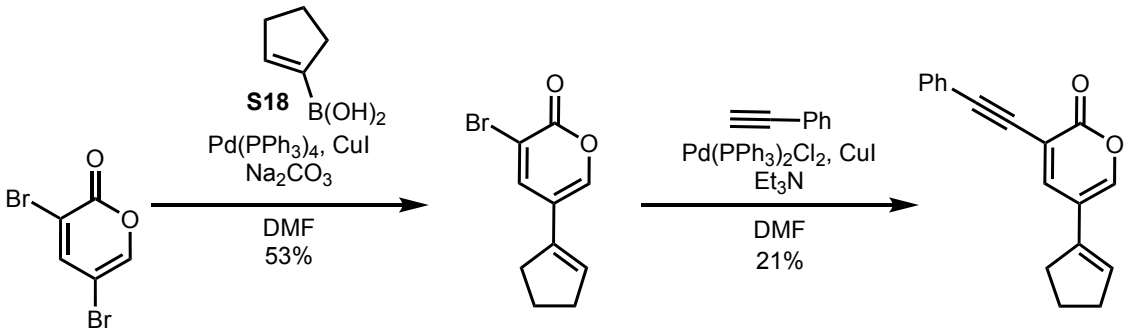
R_f = 0.42 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 2.3 Hz, 1H), 7.79 (d, *J* = 2.3 Hz, 1H), 7.67 (s, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.36 – 7.30 (m, 1H), 1.70 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.82, 149.35, 147.34, 145.66, 135.80, 127.82, 125.52, 123.63, 123.60, 119.05, 115.90, 114.50, 113.01, 84.81, 60.51, 28.29.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{18}H_{17}O_4NBr$: 390.0335, found 390.0342.

Procedure for alkynyl pyrone S17 synthesis

Following the procedure for the preparation of **7a**, to a mixture of **S16** (45.0 mg, 0.115 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (4.1 mg, 0.006 mmol, 5 mol %), and CuI (2.20 mg, 0.012 mmol, 10 mol %) in DMF (1.7 mL) in a 20 mL vial was added NEt_3 (20.0 µL, 0.143 mmol, 1.2 equiv) and phenyl acetylene (20 µL, 0.18 mmol, 1.6 equiv). The resulting dark brown solution was stirred at 23 ˚C for 72 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to give 5-(3-*N*-Boc-indole)-3-phenyl alkynyl pyrone **S17** (10.9 mg, 0.027 mmol, 23% yield) as sticky orange solid.

R_f = 0.41 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 2.5 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.69 (s, 1H), 7.62 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.41 (ddd, *J* = 8.5, 7.2, 1.2 Hz, 1H), 7.39 – 7.30 (m, 4H), 1.70 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 160.05, 149.44, 147.74, 145.89, 135.87, 132.12, 129.34, 128.55, 128.05, 125.45, 123.55, 123.45, 122.24, 119.24, 115.89, 114.16, 113.84, 113.75, 96.79, 84.71, 83.15, 28.33.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{22}H_{22}O_4N$: 412.1543, found 412.1549.

2.13 Synthesis of 5-cyclopentenyl-3-phenyl alkynyl pyrone (S20)



Procedure for 3-bromo-2-pyrone S19 synthesis

Following the procedure for the preparation of **S16**, **S13** (50.0 mg, 0.197 mmol, 1 equiv), boronic acid **S18** (26.5 mg, 0.236 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (22.8 mg, 0.020 mmol, 10 mol %), CuI (37.5 mg, 0.197 mmol, 1 equiv), and Na_2CO_3 (41.7 mg, 0.394 mmol, 2 equiv) in DMF (2 mL) was heated to 55 ˚C in a heating block for 72 h. The crude residue was purified by flash column chromatography on silica gel (10:1 hexanes:EtOAc) to provide **S19** (25.2 mg, 0.105 mmol, 53%) as a pale orange solid.

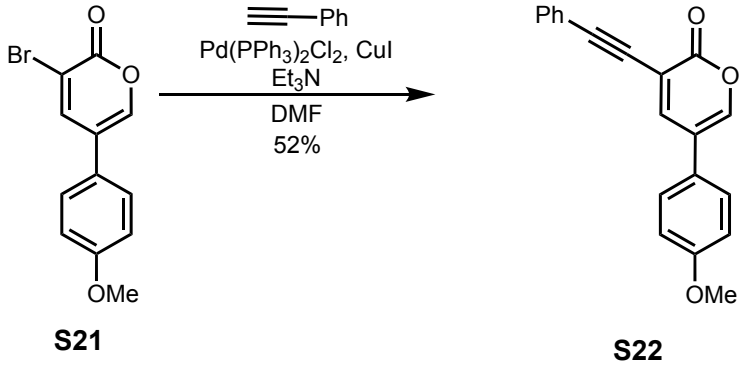
R_f = 0.48 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.3 Hz, 2H), 7.37 (d, *J* = 2.3 Hz, 2H), 6.03 (p, *J* = 2.2 Hz, 2H), 2.49 (dddd, *J* = 19.2, 10.1, 4.6, 2.2 Hz, 9H), 2.02 (p, *J* = 7.5 Hz, 5H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 158.01, 145.90, 143.77, 134.19, 128.80, 117.66, 112.62, 33.23, 32.23, 23.30.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{12}H_{10}O_2Br$: 240.9859, found 240.9859.

Procedure for alkynyl pyrone S20 synthesis

Following the procedure for the preparation of the preparation of **7a**, to a mixture of **S19** (36.0 mg, 0.149 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (5.24 mg, 0.007 mmol, 5 mol %), and CuI (2.84 mg, 0.015 mmol, 10 mol %) in DMF (2.1 mL) in a 20 mL vial was added NEt_3 (25.0 µL, 0.179 mmol, 1.2 equiv) and phenyl acetylene (20 µL, 0.179 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 23 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hexanes:EtOAc) to provide 5-cyclopentenyl-3-phenyl alkynyl pyrone **S20** (8.4 mg, 0.032 mmol, 21% yield) as a red-orange solid.

R_f = 0.39 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.5 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.37 – 7.33 (m, 3H), 6.07 (t, *J* = 2.1 Hz, 1H), 2.51 (dqd, *J* = 10.3, 4.2, 2.1 Hz, 4H), 2.03 (p, *J* = 7.5 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 160.25, 146.36, 144.07, 134.70, 132.08, 129.21, 128.51, 128.31, 122.36, 117.09, 113.16, 95.99, 83.27, 33.28, 32.25, 23.32.
HRMS (EI): $[M]^+$ cal'd for $C_{18}H_{14}O_2$: 262.0994, found 262.0993.

2.14 Synthesis of 5-(4-methoxyphenyl)-3-phenyl alkynyl pyrone (S21)



S21 **S22**

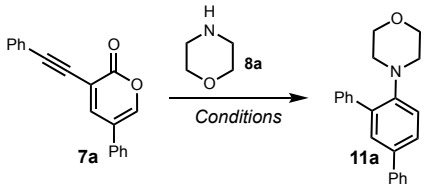
Following the procedure for the preparation of **7a**, to a mixture of **S21** (117 mg, 0.416 mmol, 1 equiv),[8] $Pd(PPh_3)_2Cl_2$ (14.6 mg, 0.021 mmol, 5 mol %), and CuI (7.93 mg, 0.042 mmol, 10 mol %) in DMF (5.9 mL) in a 20 mL vial was added NEt_3 (70.0 µL, 0.502 mmol, 1.2 equiv) and phenyl acetylene (55 uL, 0.502 mmol, 1.2 equiv). The resulting dark brown solution was stirred at 23 ˚C for 24 h. The crude residue was purified by flash-column chromatography on silica gel (10:1 hex:EA) to give 5-(4-methoxyphenyl)-3-phenyl alkynyl pyrone **S22** (65.5 mg, 0.217 mmol, 52% yield) as bright yellow solid.

R_f = 0.29 (3:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.6 Hz, 1H), 7.63 (d, *J* = 2.6 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.39 – 7.35 (m, 3H), 7.35 – 7.30 (m, 2H), 7.00 – 6.93 (m, 2H), 3.85 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 160.19, 160.11, 146.89, 145.69, 132.08, 129.24, 128.52, 127.44, 125.47, 122.34, 120.94, 114.86, 113.27, 96.43, 83.35, 55.55.
HRMS (ESI): $[M]^+$ cal'd for $C_{16}H_{14}O_3$: 325.0835, found 325.0839.

3 Optimization of the Ring-opening/Annulation Reaction

The development and subsequent attempts to optimize this annulation reaction were carried out first by varying equivalents of **8a,** temperature, and solvent. These variations in reagent quantity and conditions are outlined in Table S1.

Table S1. Initial screen of solvent, temperature, and amount of **8a**. All reactions (unless otherwise noted): under N_2, anhydrous, 5.0 mg of **7a**, 0.025 M, 16 h, isolated yields listed.

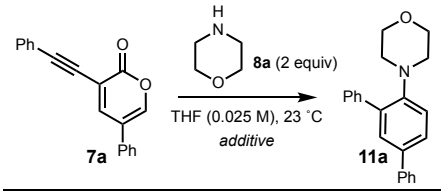


entry	equiv **8a**	solvent	temp.	yield
1	1.5	THF (0.05 M)	60 ˚C	28%
2	2	THF	60 ˚C	38%
3	**2**	**THF**	**23 ˚C**	**61%**
4	5	THF	23 ˚C	62%
5	2	DMF	23 ˚C	40%
6	2	PhMe	23 ˚C	51%
7	2	DCM	23 ˚C	45%
8	2	dioxane	23 ˚C	49%
9	2	Et_2O	23 ˚C	51%
10	2	HFIP	23 ˚C	SM + decomp

We initially observed formation of aryl amine **11a** when **7a** was treated with 1.5 equivalents of **8a** in THF at 60 ˚C (entry 1), which were conditions previously reported by our group for another substituted pyrone.[9] We observed a slight increase in yield (entry 2) by decreasing the concentration from 0.05 M to 0.025 M to prevent undesired intermolecular side reactions. A key change to the reaction conditions was lowering the temperature from 60˚C to 23˚C (entry 3), which we predicted would further inhibit undesired side reactions. We found that there was no difference in reaction efficiency in using 2 equivalents or 5 equivalents of **8a**, and upon a solvent screen (entries 4–10), identified THF as the optimal solvent.

We then explored various additives to see if we could further improve the reaction efficiency, as shown in Table S2.

Table S2. Additive Screen. All reactions (unless otherwise noted): under N_2, anhydrous, 5.0 mg of **7a**, 2 equiv of **8a**, 0.025 M, 16 h, isolated yields listed. *a.* reaction run on 0.05 mmol scale. *b.* reaction run on 1 mmol scale under air with non-flame dried glassware.

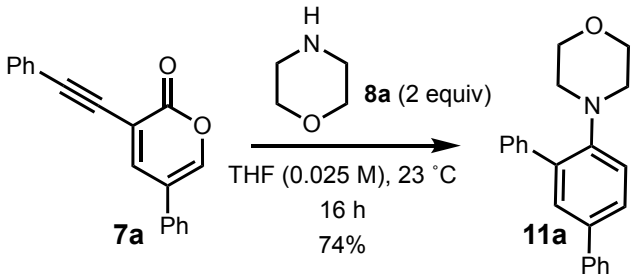


entry	additive	yield
1	10 mol % $[Rh(CO)_2Cl]_2$	20%
2	10 mol % acetic acid	45%
3	40 mol % acetic acid	44%
4	10 mol % PPh_3	55%
5	10 mol % K_2CO_3	47%
6	10 mol % DBU	49%
7	10 mol% NEt_3	54%
8	no celite filtration	74%[a]
9	no celite filtration	52%[b]

Initially, on the basis of our prior work of a Rh-mediated cyclization to access substituted benzoates,[1] we added 10 mol % of $[Rh(CO)_2Cl]_2$ as a potential Lewis acid to assist in the cyclization reaction. However, we only isolated **11a** in 20% yield. We added PPh_3 to aid in E/Z isomerization of the ring opened intermediate accessed through a 1,6 addition (entry 4), acid to aid in proton transfers (entries 2 & 3), or base to increase nucleophilicity of **8a** (entries 5–7), but these additives did not improve the reaction efficiency. Because typical reaction conditions involve filtration over a short celite plug (with EtOAc as the eluent) before concentration of the reaction mixture, and terphenyl systems are known to not be very soluble in ethereal solvents or ethyl acetate,[10] we postulated that direct concentration of the reaction mixture may increase the yield of this transformation. We observed a large increase in yield, as shown in entry 8. We subsequently ran this reaction on 1 mmol scale in a non-flame-dried flask, open to air, and isolated the desired product in 52% yield.

4. Substrate Scope for Ring-opening/Annulation Reaction

4.1 Synthesis of aryl amine 11a

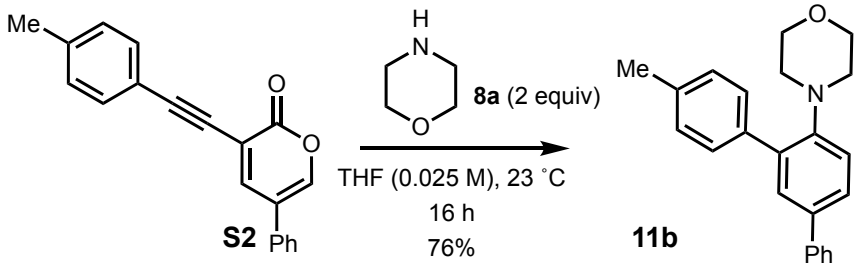


To a vial charged with phenyl alkynyl pyrone **7a** (14.1 mg, 0.052 mmol, 1 equiv) in THF (2.1 mL) was added morpholine **8a** as a solution in THF (50 µL in 500 µL THF, transferred 100 µL, 0.104 mmol, 2 equiv), and the resulting red reaction mixture was left to stir at room temperature.

After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography with 10:1 hexanes:EtOAc to yield the desired aryl amine **11a** (12.0 mg, 0.038 mmol, 74%) as an off-white solid.

R_f = 0.45 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H), 7.56 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.50 (dt, *J* = 8.2, 2.1 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.38 (tt, *J* = 7.8, 2.4 Hz, 4H), 7.28 (dt, *J* = 9.1, 6.5 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 3.65 – 3.54 (m, 4H), 2.83 (dd, *J* = 5.4, 3.4 Hz, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.50, 141.13, 140.78, 135.77, 135.30, 130.55, 128.97, 128.86, 128.45, 127.14, 127.00, 126.95, 126.89, 118.48, 67.06, 51.57.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{22}H_{22}ON$: 316.1696, found 316.1693.
Mp: 130–133 ˚C

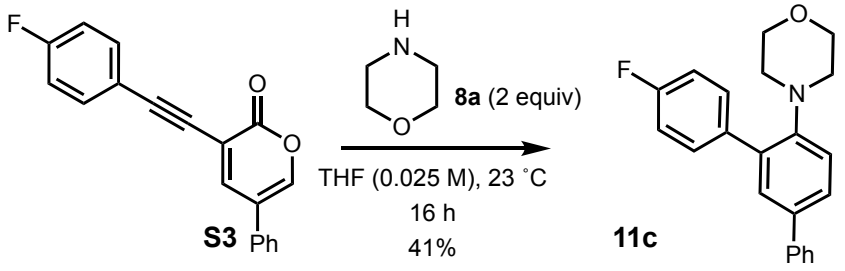
4.2 Synthesis of 4-tolyl aryl amine 11b



Compound **11b** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S2** (20.0 mg, 0.698 mmol, 1 equiv) in THF (3.0 mL) was added **8a** as a solution in THF (100 µL in 500 µL THF, transferred 70 µL, 0.140 mmol, 2 equiv) and the reaction mixture left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash-column chromatography on silica gel (12:1 hexanes:EtOAc) to provide 4-tolyl aryl amine **11b** (17.4 mg, 0.528 mmol, 76% yield) as a yellow solid.

R_f = 0.41 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.4, 2.7 Hz, 4H), 7.54 – 7.49 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 3.69 – 3.62 (m, 4H), 2.92 – 2.85 (m, 4H), 2.41 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.50, 140.87, 138.16, 136.81, 135.77, 135.25, 130.56, 129.18, 128.85, 128.80, 126.97, 126.91, 126.73, 118.45, 67.13, 51.54, 21.38.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{24}ON$: 330.1852, found 330.1851.

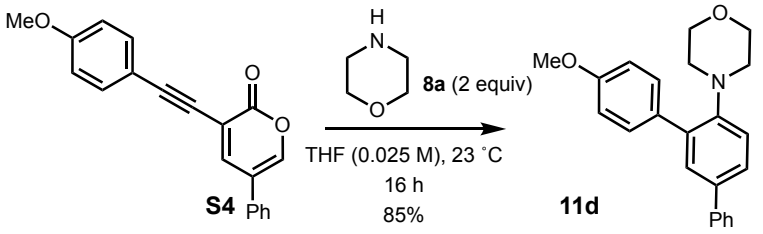
4.3 Synthesis of 4-fluoro aryl amine 11c



Compound **11c** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S3** (18.0 mg, 0.620 mmol, 1 equiv) in THF (2.5 mL) was added **8a** as a solution in THF (110 µL in 900 µL THF, transferred 100 µL, 0.124 mmol, 2 equiv) and the reaction mixture left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (3:1 hexanes:EtOAc) to provide 4-fluoro aryl amine **11c** (8.5 mg, 0.25 mmol, 41% yield) as a yellow solid.

R_f = 0.45 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (ddd, *J* = 8.3, 5.6, 2.0 Hz, 2H), 7.61 – 7.56 (m, 2H), 7.54 (dt, *J* = 8.3, 2.2 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.42 (td, *J* = 7.7, 1.9 Hz, 2H), 7.36 – 7.28 (m, 1H), 7.16 – 7.06 (m, 3H), 3.63 (dq, *J* = 4.7, 2.1 Hz, 4H), 2.86 (dq, *J* = 4.6, 2.1 Hz, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 162.13 (d, *J* = 246.2 Hz), 149.47, 140.68, 136.98 (d, *J* = 3.5 Hz), 136.07, 134.46, 130.64, 130.59, 130.44, 128.91, 127.13, 126.93, 118.77, 115.38 (d, *J* = 21.1 Hz), 67.09, 51.64.
^{19}F NMR (470 MHz, $CDCl_3$) δ -115.31.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{22}H_{21}ONF$: 334.1602, found 334.1599.

4.4 Synthesis of 4-methoxy aryl amine 11d

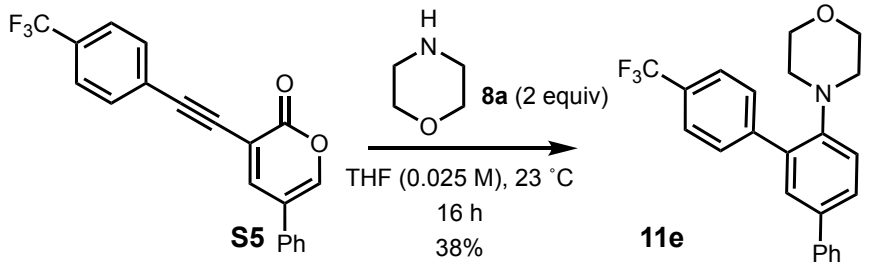


Compound **11d** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S4** (32.0 mg, 0.106 mmol, 1 equiv) in THF (4.0 mL) was added **8a** as a solution in THF (50 µL in 450 µL THF, transferred 170 µL, 0.212 mmol, 2 equiv) and the reaction mixture was stirred at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica (3:1 hexanes:EtOAc) to provide 4-methoxy aryl amine **11d** (30.9 mg, 0.895 mmol, 85% yield) as a bright yellow solid.

R_f = 0.35 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 8.9, 3.0 Hz, 2H), 7.64 – 7.57 (m, 2H), 7.52 (ddq, *J* = 9.3, 5.9, 2.2 Hz, 2H), 7.44 (td, *J* = 7.7, 2.6 Hz, 2H), 7.38 – 7.30 (m, 1H), 7.10 (dt, *J* = 8.3, 2.2 Hz, 1H), 6.99 (dt, *J* = 8.9, 2.8 Hz, 2H), 3.88 (t, *J* = 1.9 Hz, 3H), 3.66 (dq, *J* = 7.6, 2.7 Hz, 4H), 2.89 (dq, *J* = 7.3, 2.5 Hz, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 158.80, 149.49, 140.85, 135.77, 134.93, 133.43, 130.40, 130.01, 128.84, 126.95, 126.88, 126.55, 118.45, 113.85, 67.14, 55.37, 51.48.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{24}O_2N$: 346.1802, found 346.1799.

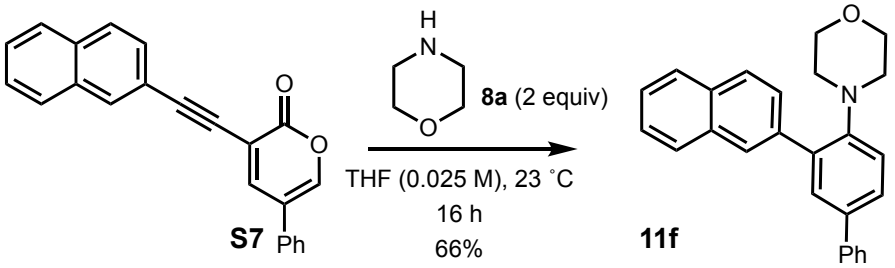
4.5 Synthesis of 4-CF_3 aryl amine 11e



Compound **11e** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S5** (25.0 mg, 0.074 mmol, 1 equiv) in THF (2.9 mL) was added **8a** (12.9 µL, 0.147 mmol, 2 equiv) *via* microsyringe and the reaction mixture left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1 hexanes:EtOAc x 2) to provide 4-CF_3 aryl amine **11e** (10.8 mg, 0.028 mmol, 38% yield) as a white solid.

R_f = 0.41 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.63 – 7.54 (m, 3H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 3.66 – 3.58 (m, 4H), 2.91 – 2.81 (m, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.54, 144.88, 140.49, 136.24, 134.02, 130.44, 129.26 (q, *J* = 32.4 Hz), 129.33, 128.96, 127.81, 127.25, 126.92, 125.42 (q, *J* = 3.7 Hz), 124.42 (q, *J* = 271.8 Hz), 118.95, 67.00, 51.78.
^{19}F NMR (565 MHz, $CDCl_3$) δ -62.39.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{21}ONF_3$: 384.1570, found 384.1571.

4.6 Synthesis of 2-napthyl aryl amine 11f

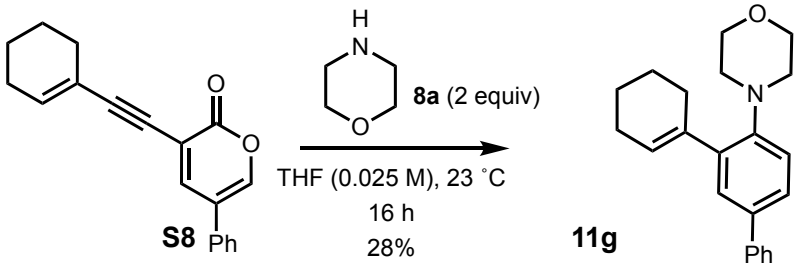


Compound **11f** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S7** (31.0 mg, 0.096 mmol, 1 equiv) in THF (4.0 mL) was added **8a** as a solution in THF (100 µL in 500 µL THF, transferred 100 µL, 0.19 mmol, 2 equiv) and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in*

vacuo. The crude residue was purified by flash column chromatography (12:1 hexanes:EtOAc) to provide 2-napthyl aryl amine **11f** (23.3 mg, 0.064 mmol, 66% yield) as a fluffy yellow solid.

R_f = 0.41 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.00 – 7.94 (m, 1H), 7.89 (d, *J* = 8.0 Hz, 3H), 7.67 – 7.61 (m, 3H), 7.59 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.51 (p, *J* = 5.1 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 3.61 (t, *J* = 4.5 Hz, 4H), 2.94 – 2.86 (m, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.63, 140.80, 139.04, 135.99, 135.06, 133.91, 132.66, 130.92, 128.91, 128.13, 127.82, 127.59, 127.35, 127.17, 127.06, 126.95, 126.17, 126.04, 118.61, 67.14, 51.60.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{26}H_{24}ON$: 366.1852, found 366.1856.

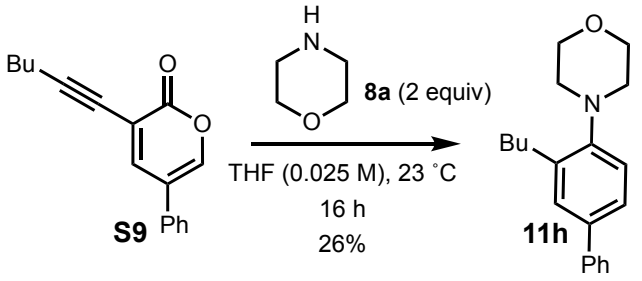
4.7 Synthesis of cyclohexenyl aryl amine 11g



Compound **11g** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S8** (15.1 mg, 0.055 mmol, 1 equiv) in THF (2.2 mL) was added **8a** (10.0 µL, 0.114 mmol, 2.1 equiv) via microsyringe and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1 hexanes:EtOAc) to provide cyclohexenyl aryl amine **11g** (4.9 mg, 0.015 mmol, 28% yield) as a white solid.

R_f = 0.48 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 – 7.54 (m, 2H), 7.45 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.34 (d, *J* = 2.3 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 5.82 (tt, *J* = 3.7, 1.7 Hz, 1H), 3.90 – 3.78 (m, 4H), 3.14 – 3.02 (m, 4H), 2.53 (tq, *J* = 6.2, 2.3 Hz, 2H), 2.20 (tq, *J* = 6.0, 2.6 Hz, 2H), 1.75 (tdd, *J* = 8.2, 5.1, 2.6 Hz, 2H), 1.69 (dtt, *J* = 9.3, 6.0, 2.7 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.11, 141.02, 140.62, 138.75, 135.52, 129.56, 128.79, 126.95, 126.85, 126.17, 126.09, 118.18, 67.52, 51.75, 27.63, 26.01, 23.41, 22.57.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{22}H_{26}ON$: 320.2009, found 320.2013.

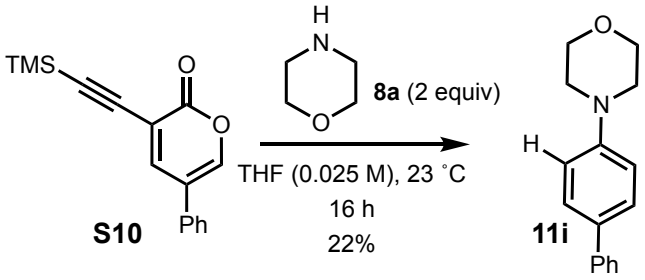
4.8 Synthesis of *n*-Bu aryl amine 11h



Compound **11h** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S9** (16.5 mg, 0.065 mmol, 1 equiv) in THF (3.0 mL) was added **8a** as a solution in THF (100 µL in 600 µL THF, transferred 100 µL, 0.163 mmol, 2.5 equiv) and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (3:1 hexanes:EtOAc) to provide *n*-Bu aryl amine **11h** (5.0 mg, 0.017 mmol, 26% yield) as a brown solid.

R_f = 0.58 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 2H), 7.45 (d, *J* = 2.3 Hz, 1H), 7.42 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.42 – 7.40 (m, 1H), 7.35 – 7.28 (m, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 3.92 – 3.82 (m, 4H), 2.98 – 2.89 (m, 4H), 2.77 – 2.65 (m, 2H), 1.75 – 1.61 (m, 2H), 1.42 (h, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 150.69, 141.26, 138.69, 137.13, 128.82, 128.80, 127.10, 127.00, 125.36, 120.56, 67.68, 53.38, 33.26, 30.55, 23.01, 14.19.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{20}H_{26}ON$: 296.2009, found 296.2007.

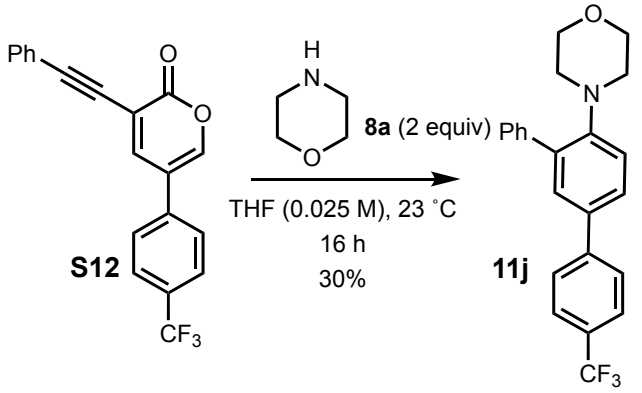
4.9 Synthesis of aryl amine 11i



Compound **11i** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S10** (8.9 mg, 0.033 mmol, 1 equiv) in THF (1.4 mL) was added **8a** as a solution in THF (50 µL in 1650 µL THF, transferred 200 µL, 0.066 mmol, 2.0 equiv) and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (3:1 hexanes:EtOAc x 3) to provide aryl amine **11i** (1.8 mg, 0.007 mmol, 22% yield) as an off-white solid. The ^{1}H NMR spectrum was fully consistent with that reported in the literature.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 4H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 3.92 – 3.85 (m, 4H), 3.22 (dd, *J* = 5.8, 3.9 Hz, 4H).

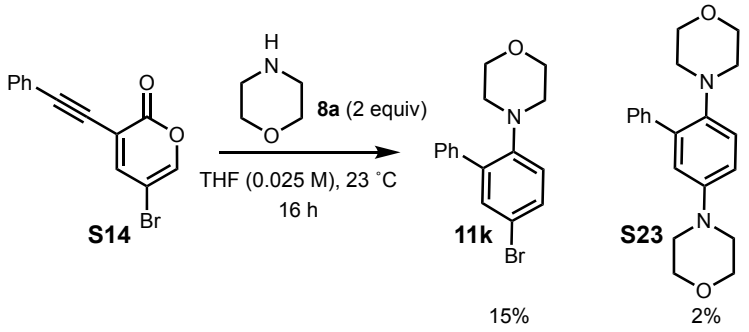
4.10 Synthesis of C5 4-CF_3 aryl amine 11j



Compound **11j** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S12** (17.8 mg, 0.052 mmol, 1 equiv) in THF (2.1 mL) was added **8a** as a solution in THF (100 µL in 1000 µL THF, transferred 100 µL, 0.105 mmol, 2 equiv) and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (3:1 hexanes:EtOAc) to provide 4-CF_3 aryl amine **11j** (6.0 mg, 0.016 mmol, 30% yield) as a yellow solid.

R_f = 0.44 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 6H), 7.55 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.29 (m, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 3.62 (dd, *J* = 5.8, 3.3 Hz, 4H), 2.91 – 2.83 (m, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 150.21, 144.14, 140.75, 135.32, 133.95, 130.55, 129.14 (app d, *J* = 32.5 Hz), 128.81 – 128.67 (m), 128.47, 127.24, 127.02, 126.91, 125.70 (q, *J* = 3.7 Hz), 124.36 (app d, *J* = 271.8 Hz), 118.48, 66.88, 51.33.
^{19}F NMR (471 MHz, $CDCl_3$) δ -62.33.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{21}ONF_3$: 384.1570, found 384.1574.

4.11 Synthesis of 4-Br aryl amine 11k and S23



Compounds **11k and S22** were prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S14** (25.0 mg, 0.091 mmol, 1 equiv) in THF (3.6 mL) was added **8a** (16 µL, 0.182 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified using preparative TLC (5:1 hexanes:EtOAc) to give 4-Br-aryl amine **11k** (4.3 mg, 0.014 mmol, 15%) as a pale yellow oil and a second fraction (as identified by TLC). This latter fraction was repurified on another preparative TLC (3:1 hexanes:EtOAc) to give bis-morpholine aryl amine **S23** (0.6 mg, 0.002 mmol, 2% yield) as an off-white solid.

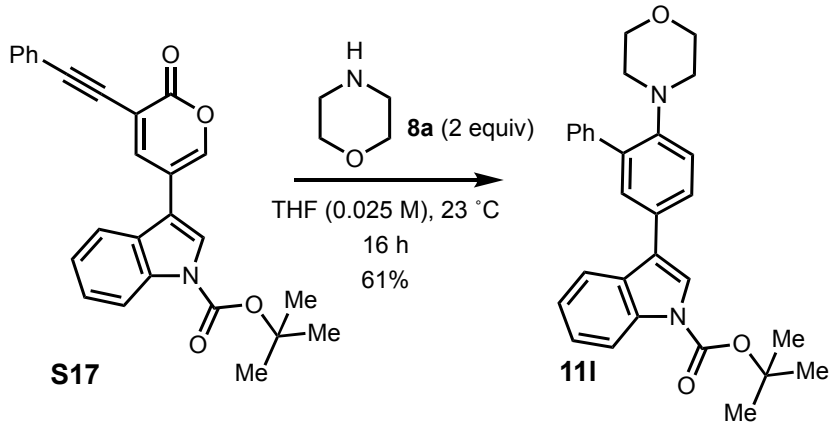
Characterization for **11k**:

R_f = 0.58 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 2H), 7.44 – 7.36 (m, 4H), 7.35 – 7.28 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 3.63 – 3.54 (m, 4H), 2.83 – 2.74 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.20, 139.76, 137.10, 134.32, 131.15, 128.79, 128.56, 127.59, 120.00, 115.86, 66.93, 51.51.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{16}H_{17}ONBr$: 318.0488, found 318.0487.

Characterization for **S23**:

R_f = 0.16 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.41 – 7.36 (m, 2H), 7.33 – 7.27 (m, 1H), 7.02 – 6.97 (m, 1H), 6.87 (d, *J* = 7.1 Hz, 2H), 3.88 – 3.83 (m, 4H), 3.59 – 3.55 (m, 4H), 3.15 – 3.10 (m, 4H), 2.78 – 2.73 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 147.41, 143.59, 141.19, 136.49, 129.17, 128.24, 127.03, 119.84, 119.27, 115.63, 67.24, 67.16, 52.04 50.19.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{20}H_{25}O_2N_2$: 325.1911, found 325.1913.

4.12 Synthesis of *N*-Boc Indole aryl amine 11l

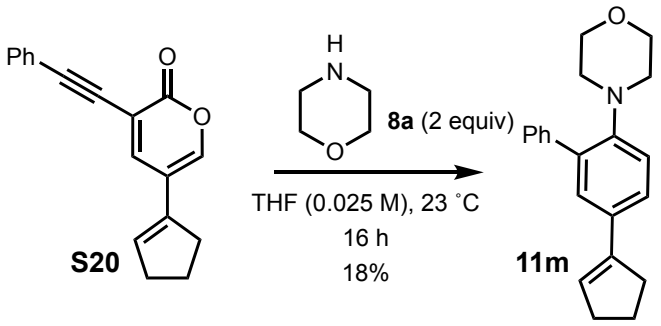


Compound **11l** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S17** (7.3 mg, 0.018 mmol, 1 equiv) in THF (0.7 mL) was added **8a** as a solution in THF (50 µL in 1500 µL THF, transferred 100 µL, 0.035 mmol, 2 equiv) and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in*

vacuo. The crude residue was purified using preparative TLC (5:1 hexanes:EtOAc) to give *N*-Boc indole aryl amine **11l** (4.9 mg, 0.011 mmol, 61%) as a pale yellow solid.

R_f = 0.66 (3:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.68 (s, 1H), 7.59 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.31 (m, 2H), 7.32 – 7.27 (m, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 3.70 – 3.58 (m, 4H), 2.96 – 2.81 (m, 4H), 1.69 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.92, 149.35, 141.00, 136.04, 135.49, 131.25, 129.22, 129.01, 128.54, 128.50, 127.86, 127.21, 124.69, 123.02, 122.56, 121.85, 120.13, 118.59, 115.58, 83.92, 67.11, 51.61, 28.39.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{29}H_{31}O_3N_2$: 455.2329, found 455.2333.

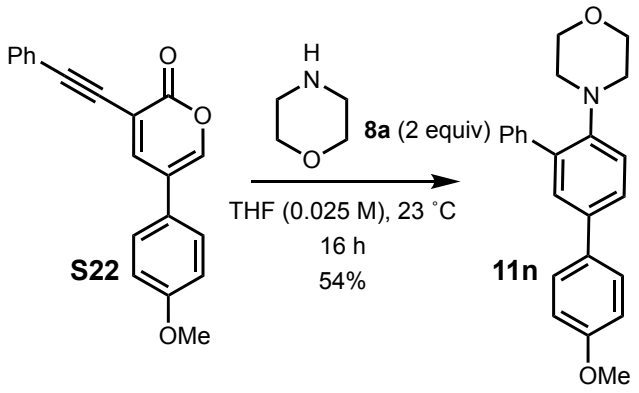
4.13 Synthesis of cyclopentenyl aryl amine 11m



Compound **11m** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S20** (8.4 mg, 0.032 mmol, 1 equiv) in THF (1.3 mL) was added **8a** (5.6 µL, 0.064 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1 hexanes:EtOAc) to isolate cyclopentenyl aryl amine **11m** (1.8 mg, 0.006 mmol, 18%) as a white solid.

R_f = 0.57 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.36 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.10 (t, *J* = 2.4 Hz, 1H), 3.62 – 3.52 (m, 4H), 2.86 – 2.74 (m, 4H), 2.75 – 2.63 (m, 2H), 2.61 – 2.48 (m, 2H), 2.01 (p, *J* = 7.4 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 148.99, 141.97, 141.30, 134.88, 131.80, 129.10, 129.04, 128.39, 127.03, 125.60, 124.99, 118.01, 67.09, 51.62, 33.50, 33.42, 23.57.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{21}H_{24}ON$: 306.1852, found 306.1856.

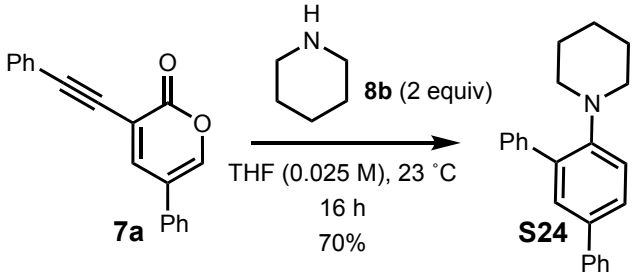
4.14 Synthesis of 4-methoxy aryl amine 11n



Compound **11n** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **S22** (19.8 mg, 0.066 mmol, 1 equiv) in THF (2.6 mL) was added **8a** as a solution in THF (50 µL in 500 µL THF, transferred 140 µL, 0.131 mmol, 2 equiv) and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (12:1 hexanes:EtOAc) to isolate 4-methoxy aryl amine **11n** (12.3 mg, 0.036 mmol, 54%) as a yellow solid.

R_f = 0.30 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.56 – 7.50 (m, 2H), 7.49 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.01 – 6.93 (m, 2H), 3.84 (s, 3H), 3.65 – 3.58 (m, 4H), 2.86 (app dd, *J* = 5.5, 3.6 Hz, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 159.04, 148.92, 141.17, 135.61, 135.39, 133.40, 130.18, 129.03, 128.44, 127.93, 127.14, 126.55, 118.58, 114.34, 67.09, 55.49, 51.68.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{24}O_2N$: 346.1802, found 346.1805.

4.15 Synthesis of piperidine aryl amine S24

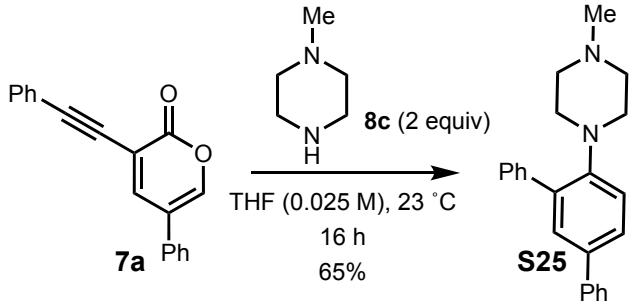


Compound **S24** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14 mg, 0.05 mmol, 1 equiv) in THF (2.0 mL) was added **8b** (10 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (6:1 hexanes:EtOAc) to give piperidine aryl amine **S24** (11.0 mg, 0.035 mmol, 70%) as a white solid.

R_f = 0.81 (5:1 hexanes:EtOAc, UV/$KMnO_4$)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.8, 2.0 Hz, 2H), 7.63 – 7.57 (m, 2H), 7.53 – 7.47 (m, 2H), 7.41 (tdd, *J* = 8.1, 3.4, 1.5 Hz, 4H), 7.34 – 7.27 (m, 2H), 7.10 (dd, *J* = 8.3, 1.4 Hz, 1H), 2.82 (t, *J* = 4.2 Hz, 4H), 1.47 (d, *J* = 5.3 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 151.21, 141.64, 141.07, 135.35, 134.97, 130.36, 128.99, 128.82, 128.29, 126.87, 126.82, 126.79, 126.78, 118.90, 52.74, 26.16, 24.35.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{24}N$: 314.1903, found 314.1907.

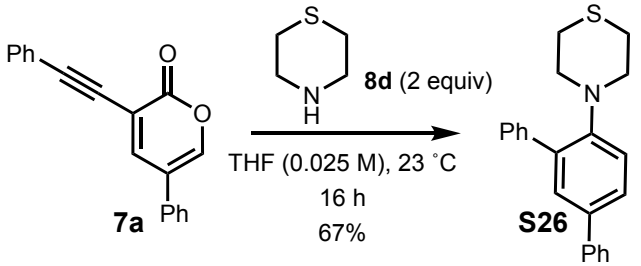
4.16 Synthesis of *N*-methyl piperazine aryl amine S25



Compound **S25** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (27 mg, 0.10 mmol, 1 equiv) in THF (4.0 mL) was added **8c** (22 µL, 0.20 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by a short silica plug (5% MeOH in DCM) to isolate *N*-methyl piperazine aryl amine **S25** (21.5 mg, 0.066 mmol, 65%) as a bright yellow solid.

R_f = 0.19 (10:1 DCM:MeOH, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.59 (d, *J* = 7.7 Hz, 2H), 7.55 – 7.48 (m, 2H), 7.42 (td, *J* = 7.5, 4.5 Hz, 4H), 7.32 (q, *J* = 7.5 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 1H), 2.98 (d, *J* = 5.0 Hz, 4H), 2.62 – 2.42 (m, 4H), 2.37 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.18, 141.12, 140.75, 135.82, 135.29, 130.44, 128.97, 128.84, 128.42, 127.09, 126.98, 126.94, 126.87, 118.82, 54.98, 50.40, 45.66.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{25}N_2$: 329.2012, found 329.2012.

4.17 Synthesis of thiomorpholine aryl amine S26



Compound **S26** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14 mg, 0.05 mmol, 1 equiv) in THF (2.0 mL) was added **8d** (10 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC

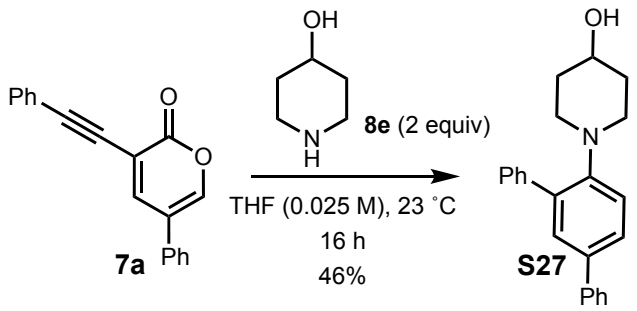
(3:1 hexanes:EtOAc) to give thiomorpholine aryl amine **S26** (11.1 mg, 0.034 mmol, 67%) as an off-white solid.

R_f = 0.44 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H), 7.61 – 7.57 (m, 2H), 7.53 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.42 (q, *J* = 7.6 Hz, 4H), 7.36 – 7.29 (m, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 3.15 (dd, *J* = 6.1, 3.8 Hz, 4H), 2.58 – 2.50 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 139.93, 139.76, 135.17, 129.41, 128.31, 127.88, 127.41, 126.15, 126.08, 125.97, 125.95, 118.90, 53.05, 26.91.

In $CDCl_3$, two carbons in the aromatic region are missing, so we have also included NMR data in acetone:

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.72 – 7.65 (m, 4H), 7.60 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.45 (dt, *J* = 15.6, 7.7 Hz, 4H), 7.33 (dt, *J* = 13.4, 7.5 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 1H), 3.16 – 3.06 (m, 4H), 2.56 – 2.44 (m, 4H).
^{13}C NMR (126 MHz, Acetone-d_6) δ 151.91, 141.83, 141.42, 136.93, 136.54, 130.55, 130.05, 129.68, 129.12, 127.80, 127.77, 127.55, 127.41, 120.84, 54.79, 28.20.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{22}H_{22}NS$: 332.1467, found 332.1466.

4.18 Synthesis of piperidine-4-ol aryl amine S27



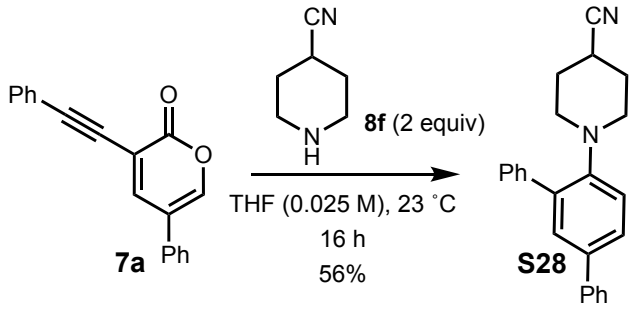
Compound **S27** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.4 mg, 0.053 mmol, 1 equiv) in THF (2.1 mL) was added **8e** (10.7 mg, 0.106 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (1:1 hexanes:EtOAc) to give piperidine-4-ol aryl amine **S27** (8.0 mg, 0.024 mmol, 46%) as a white solid.

R_f = 0.23 (3:1 hexanes:EtOAc, UV/$KMNO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.61 – 7.57 (m, 2H), 7.53 – 7.48 (m, 2H), 7.41 (td, *J* = 7.7, 4.5 Hz, 4H), 7.35 – 7.28 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 3.72 (tt, *J* = 8.9, 4.2 Hz, 1H), 3.18 – 3.05 (m, 2H), 2.67 (ddd, *J* = 12.3, 9.8, 2.8 Hz, 2H), 1.86 – 1.70 (m, 2H), 1.49 (dt, *J* = 6.7, 3.5 Hz, 1H), 1.48 – 1.44 (m, 1H), 1.40 (s, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 150.13, 141.39, 140.92, 135.43, 130.39, 128.90, 128.85, 128.42, 126.99, 126.91, 126.89, 126.81, 119.00, 68.16, 49.25, 34.75.

In chloroform, a carbon in the aromatic region is missing, so we have also included NMR data in acetone:

^{1}H NMR (600 MHz, Acetone-d_6) δ 7.77 – 7.72 (m, 2H), 7.69 – 7.65 (m, 2H), 7.57 (dd, J = 8.3, 2.3 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.44 (dt, J = 11.2, 7.7 Hz, 4H), 7.37 – 7.28 (m, 2H), 7.18 (d, J = 8.3 Hz, 1H), 3.64 (d, J = 11.4 Hz, 2H), 3.15 – 3.03 (m, 2H), 2.66 (ddd, J = 12.2, 9.9, 2.8 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.49 – 1.45 (m, 1H), 1.45 – 1.42 (m, 1H).
^{13}C NMR (151 MHz, Acetone-d_6) δ 151.50, 142.48, 141.69, 136.24, 135.86, 130.66, 129.76, 129.68, 129.23, 127.77, 127.71, 127.50, 127.43, 120.03, 50.17, 35.60, 20.93.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{24}NO$: 330.1852, found 330.1855.

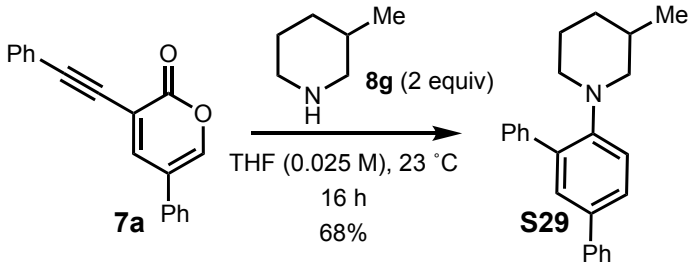
4.19 Synthesis of piperidine-4-carbonitrile aryl amine S28



Compound **S28** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.9 mg, 0.055 mmol, 1 equiv) in THF (2.2 mL) was added **8f** (12 µL, 0.11 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (3:1 hexanes:EtOAc) to give piperidine-4-carbonitirle aryl amine **S28** (10.4 mg, 0.031 mmol, 56%) as a yellow solid.

R_f = 0.31 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 2H), 7.61 – 7.56 (m, 2H), 7.53 (dd, J = 8.2, 2.4 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.43 (td, J = 7.6, 5.3 Hz, 4H), 7.33 (dt, J = 9.3, 7.5 Hz, 2H), 7.10 (d, J = 8.2 Hz, 1H), 3.09 (ddd, J = 10.9, 6.5, 3.4 Hz, 2H), 2.77 (ddd, J = 11.9, 8.2, 3.0 Hz, 2H), 2.64 (dp, J = 8.6, 4.3 Hz, 1H), 1.91 – 1.78 (m, 2H), 1.75 (ddt, J = 12.2, 8.2, 4.1 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.62, 140.98, 140.72, 136.12, 135.72, 130.43, 128.95, 128.89, 128.49, 127.20, 127.09, 126.94, 126.92, 121.83, 119.09, 49.89, 28.98, 26.19.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{24}H_{23}N_2$: 339.1856, found 339.1854.

4.20 Synthesis of 3-methylpiperidine aryl amine S29



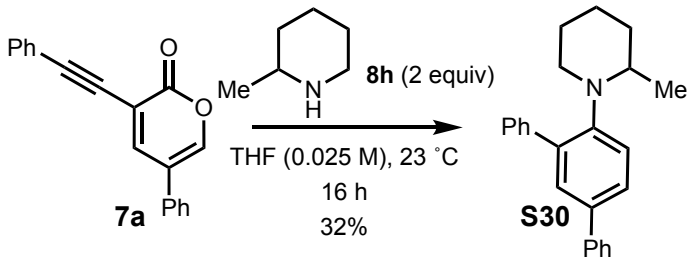
Compound **S29** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.1 mL) was added **8g** (12 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (12:1 hexanes:EtOAc) to isolate 3-methylpiperidine aryl amine **S29** (10.4 mg, 0.031 mmol, 56%) as a clear oil.

R_f = 0.69 (10:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.54 – 7.48 (m, 2H), 7.41 (td, *J* = 7.8, 2.3 Hz, 4H), 7.33 – 7.27 (m, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 3.06 (t, *J* = 11.1 Hz, 2H), 2.46 (td, *J* = 11.4, 2.8 Hz, 1H), 2.21 (t, *J* = 10.6 Hz, 1H), 1.68 (dt, *J* = 12.7, 4.0 Hz, 1H), 1.59 (tt, *J* = 14.3, 10.8, 4.8 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.47 – 1.37 (m, 1H), 0.91 (qd, *J* = 12.0, 4.1 Hz, 1H), 0.77 (d, *J* = 6.6 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 150.98, 141.63, 141.07, 135.43, 134.92, 130.33, 129.03, 128.82, 128.26, 126.87, 126.80, 126.78, 118.95, 59.67, 52.40, 32.86, 31.26, 25.54, 19.50.

In $CDCl_3$, a carbon in the aromatic region is missing, so we have also included NMR data in acetone:

^{1}H NMR (600 MHz, acetone-d_6) δ 7.74 – 7.69 (m, 2H), 7.69 – 7.63 (m, 2H), 7.57 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.43 (td, *J* = 7.6, 5.0 Hz, 4H), 7.31 (dt, *J* = 10.0, 7.4 Hz, 2H), 7.15 (s, 1H), 3.13 – 3.00 (m, 2H), 2.47 (td, *J* = 11.4, 2.8 Hz, 1H), 2.19 (t, *J* = 10.6 Hz, 1H), 1.68 (dt, *J* = 12.8, 4.0 Hz, 1H), 1.58 (dtp, *J* = 13.6, 6.4, 3.6 Hz, 1H), 1.51 (dp, *J* = 10.9, 3.6 Hz, 1H), 1.44 (ddt, *J* = 16.3, 12.3, 6.1 Hz, 1H), 0.91 (pd, *J* = 11.1, 10.2, 5.6 Hz, 1H), 0.75 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (151 MHz, acetone-d_6) δ 151.90, 142.57, 141.78, 136.42, 135.80, 130.70, 129.85, 129.82, 129.21, 127.75, 127.58, 127.49, 120.09, 120.08, 60.53, 53.08, 33.56, 32.09, 26.32, 19.76.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{24}H_{26}N$: 328.2060, found 328.2058.

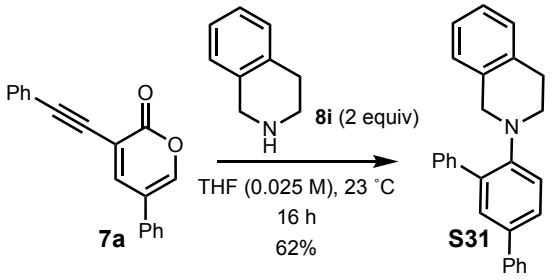
4.21 Synthesis of 2-methylpiperidine aryl amine S30



Compound **S30** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.2 mg, 0.052 mmol, 1 equiv) in THF (2.1 mL) was added **8h** (12 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1 hexanes:EtOAc) to give 2-methylpiperidine aryl amine **S30** (5.5 mg, 0.017 mmol, 32%) as a white solid.

R_f = 0.38 (hexanes, UV/$KMnO_4$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.63 – 7.57 (m, 2H), 7.52 (dq, *J* = 5.2, 2.5 Hz, 2H), 7.41 (q, *J* = 7.8 Hz, 4H), 7.34 – 7.27 (m, 2H), 7.20 – 7.12 (m, 1H), 3.08 (pd, *J* = 6.5, 2.8 Hz, 1H), 2.98 (ddd, *J* = 11.2, 6.8, 3.1 Hz, 1H), 2.65 (ddd, *J* = 11.5, 7.7, 3.3 Hz, 1H), 1.59 (qd, *J* = 7.9, 6.7, 2.9 Hz, 2H), 1.51 – 1.45 (m, 1H), 1.39 (ddtd, *J* = 20.3, 11.6, 7.6, 3.8 Hz, 2H), 1.24 – 1.16 (m, 1H), 0.92 (d, *J* = 6.3 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.96, 141.35, 141.04, 137.96, 135.89, 129.96, 129.41, 128.82, 127.94, 126.94, 126.90, 126.66, 126.45, 122.56, 53.41, 51.20, 33.10, 26.51, 22.29, 16.96.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{24}H_{26}N$: 328.2060, found 328.2056.

4.22 Synthesis of tetrahydroisoquinoline aryl amine S31

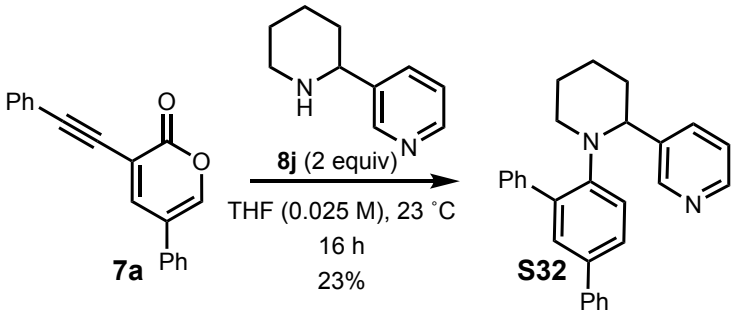


Compound **S31** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.0 mL) was added **8i** (13.0 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (10:1 hexanes:EtOAc) to give tetrahydroisoquinoline aryl amine **S31** (11.5 mg, 0.032 mmol, 62%) as a pale yellow oil.

R_f = 0.55 (10:1 hexanes:EtOAc, UV/$KMnO_4$)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.63 – 7.60 (m, 2H), 7.55 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.15 (dd, *J* = 5.7, 3.3 Hz, 2H), 7.07 (dt, *J* = 5.3, 3.5 Hz, 2H), 4.22 (s, 2H), 3.08 (t, *J* = 5.8 Hz, 2H), 2.59 (t, *J* = 5.8 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.61, 141.58, 140.90, 135.26, 135.24, 135.16, 134.89, 130.75, 128.97, 128.95, 128.87, 128.55, 126.99, 126.92, 126.89, 126.80, 126.59, 126.26, 125.78, 118.60, 52.65, 50.56, 29.10.
HRMS (ESI): $[M–H]^+$ cal'd for $C_{27}H_{22}N$: 360.1747, found 360.1744.
HRMS (ESI): $[M–3H]^+$ cal'd for $C_{27}H_{20}N$: 358.1590, found 358.1587. Fully aromatized compound formed upon ionization.

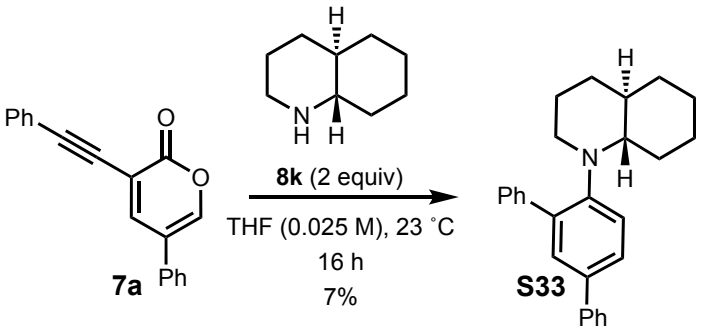
4.23 Synthesis of anabasine aryl amine S32



Compound **S32** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.4 mg, 0.053 mmol, 1 equiv) in THF (2.1 mL) was added **8j** (16.0 µL, 0.11 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1 hexanes:EtOAc) to give anabasine aryl amine **S32** (4.7 mg, 0.012 mmol, 23%) as a pale yellow oil.

R_f = 0.17 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.32 (d, *J* = 4.8 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.37 (q, *J* = 8.1 Hz, 3H), 7.34 – 7.29 (m, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.05 – 7.02 (m, 1H), 4.03 (dd, *J* = 10.6, 2.7 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.64 (td, *J* = 11.5, 2.6 Hz, 1H), 1.86 – 1.78 (m, 2H), 1.64 – 1.58 (m, 1H), 1.47 (t, *J* = 9.2 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.43, 148.88, 148.03, 140.98, 140.59, 140.00, 138.57, 136.72, 135.24, 130.01, 129.58, 128.78, 128.05, 127.08, 126.99, 126.92, 126.35, 123.73, 123.39, 63.39, 56.65, 36.83, 26.02, 24.89.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{28}H_{27}N_2$: 391.2169, found 391.2172.

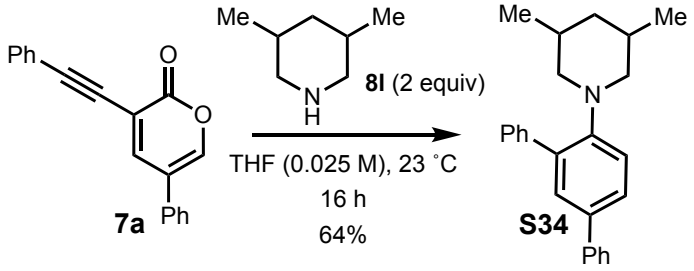
4.24 Synthesis of decahydroisoquinoline aryl amine S33



Compound **S33** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.1 mL) was added **8k** (14.3 mg, 0.10 mmol, 2 equiv) and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1 hexanes:EtOAc) to give decahydroisoquinoline aryl amine **S33** (1.3 mg, 0.004 mmol, 7%) as a clear oil.

R_f = 0.20 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.60 (m, 2H), 7.60 – 7.57 (m, 2H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.53 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 1H), 2.83 (d, *J* = 11.5 Hz, 1H), 2.52 – 2.42 (m, 2H), 1.88 (d, *J* = 13.0 Hz, 1H), 1.64 (d, *J* = 9.2 Hz, 2H), 1.48 – 1.38 (m, 1H), 1.32 (ddd, *J* = 18.4, 13.7, 10.0 Hz, 3H), 1.14 – 0.99 (m, 2H), 0.97 – 0.82 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.31, 141.04, 140.85, 140.61, 137.22, 130.05, 129.60, 128.83, 127.59, 127.09, 127.07, 126.58, 126.47, 124.29, 64.83, 56.87, 42.66, 33.09, 32.64, 31.10, 26.45, 26.29, 25.69.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{27}H_{30}N$: 368.2373, found 368.2371.

4.25 Synthesis of 3,5-dimethylpiperidine aryl amine S34



Compound **S34** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.0 mL) was added **8l** (14.0 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (12:1 hexanes:EtOAc) to isolate 3,5-dimethylpiperidine aryl amine **S34** (11.2 mg, 0.033

mmol, 64%) as a clear oil and a 1:0.2 mixture of cis/trans isomers (from amine **8l** starting material).

R_f = 0.78 (10:1 hexanes:EtOAc, UV/$KMnO_4$)

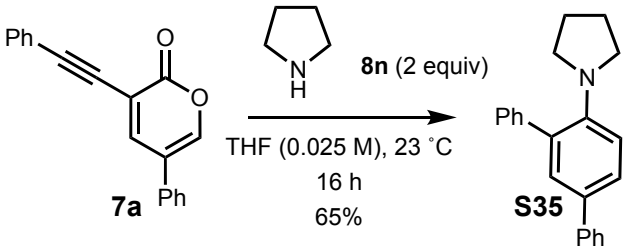
The sets of peaks for the two isomers are reported together in the ^{1}H NMR spectra. For minor isomer, the carbon peaks are starred:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.63 – 7.58 (m, 2H), 7.54 – 7.47 (m, 2H), 7.40 (dt, *J* = 9.1, 7.7 Hz, 4H), 7.30 (td, *J* = 7.3, 1.5 Hz, 2H), 7.11 (dd, *J* = 17.6, 8.2 Hz, 1H), 3.12 – 2.77 (m, 2H), 2.54 – 1.97 (m, 2H), 1.86 – 1.65 (m, 1H), 1.64 – 1.52 (m, 2H), 0.76 (dd, *J* = 29.3, 6.7 Hz, 6H), 0.54 (q, *J* = 12.2 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 151.53*, 150.61, 141.65*, 141.61, 141.08, 141.03*, 136.47*, 135.31, 135.06*, 134.83, 130.33*, 130.29, 129.42*, 129.00, 128.82, 128.23, 128.20*, 126.90*, 126.82*, 126.78, 126.73*, 119.22*, 118.94, 59.42, 59.25*, 42.20, 38.98*, 31.35, 27.58*, 19.44, 19.06*.

In $CDCl_3$, carbons in the aromatic region are missing, so we have also included NMR data in acetone:

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.73 – 7.68 (m, 2H), 7.68 – 7.61 (m, 2H), 7.57 (ddd, *J* = 8.3, 5.1, 2.4 Hz, 1H), 7.48 (dd, *J* = 14.0, 2.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 4H), 7.36 – 7.27 (m, 2H), 7.16 (dd, *J* = 14.0, 8.4 Hz, 1H), 3.18 – 2.83 (m, 2H), 2.50 – 2.43 (m, 0.5H), 1.79 (dt, *J* = 6.5, 3.3 Hz, 0.5H), 1.69 (ddq, *J* = 12.7, 3.5, 1.8 Hz, 1H), 1.58 (dddt, *J* = 17.6, 10.4, 6.8, 3.4 Hz, 2H), 0.76 (dd, *J* = 29.1, 6.8 Hz, 6H), 0.56 (p, *J* = 12.1, 11.7 Hz, 1H).
^{13}C NMR (126 MHz, Acetone-d_6) δ 152.24*, 151.35, 142.44*,142.37, 141.60, 141.56*, 137.26*, 136.09, 135.74*, 135.53, 130.52*, 130.48, 130.05, 129.65, 129.02, 128.97*, 127.61*, 127.57, 127.55, 127.49*, 127.43*, 127.40, 127.34*, 127.30, 120.18, 119.90*, 60.01, 59.84*, 42.71, 39.46*, 31.99, 28.22*, 19.52, 19.24*.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{25}H_{28}N$: 342.2216, found 342.2213.

4.26 Synthesis of pyrrolidine aryl amine S35



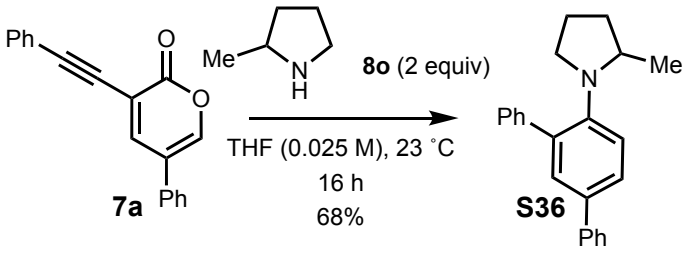
Compound **S35** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.0 mL) was added **8n** (8.2 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (6:1 hexanes:EtOAc) to give pyrrolidine aryl amine **S35** (9.8 mg, 0.033 mmol, 65%) as a sticky yellow oil.

$\mathbf{R_f}$ = 0.76 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 3H), 7.47 (t, *J* = 2.0 Hz, 1H), 7.45 – 7.36 (m, 4H), 7.34 – 7.30 (m, 1H), 7.30 – 7.27 (m, 1H), 6.98 (dd, *J* = 8.5, 1.5 Hz, 1H), 2.98 (dt, *J* = 6.5, 3.4 Hz, 4H), 1.80 (tt, *J* = 4.0, 2.3 Hz, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 147.42, 143.36, 141.15, 131.17, 130.81, 130.26, 129.36, 128.77, 128.08, 126.53, 126.42, 126.29, 114.92, 51.17, 25.61.

In $CDCl_3$, a carbon in the aromatic region is missing, so we have also included NMR data in acetone:

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.65 – 7.61 (m, 2H), 7.51 (ddd, *J* = 10.0, 8.3, 1.8 Hz, 3H), 7.43 – 7.36 (m, 5H), 7.34 – 7.28 (m, 1H), 7.28 – 7.21 (m, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 2.98 – 2.87 (m, 4H), 1.84 – 1.70 (m, 4H).
^{13}C NMR (126 MHz, Acetone-d_6) δ 148.30, 144.10, 141.75, 131.56, 131.34, 131.23, 129.86, 129.59, 128.91, 127.22, 127.02, 126.93, 126.88, 116.12, 51.61, 25.91.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{22}H_{22}N$: 300.1747, found 300.1750.

4.27 Synthesis of 2-methylpyrrolidine aryl amine S36



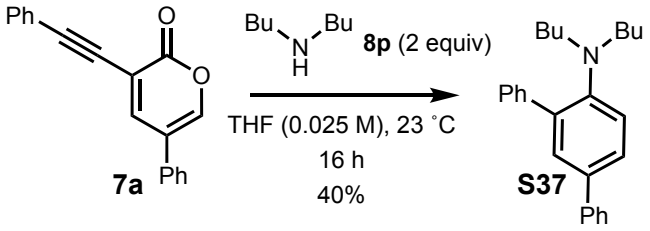
Compound **S36** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.4 mg, 0.053 mmol, 1 equiv) in THF (2.1 mL) was added **8o** (11 µL, 0.11 mmol, 2 equiv) *via* microsyringe and the reaction left to stir at 23˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (15:1 hexanes:EtOAc) to give 2-methylpyrrolidine aryl amine **S36** (9.8 mg, 0.033 mmol, 65%) as a sticky white solid.

$\mathbf{R_f}$ = 0.33 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H), 7.57 – 7.52 (m, 2H), 7.50 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.40 (td, *J* = 7.6, 4.9 Hz, 4H), 7.29 (ddt, *J* = 8.9, 7.4, 1.6 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 3.63 (dp, *J* = 8.2, 6.1 Hz, 1H), 2.99 (td, *J* = 9.4, 6.8 Hz, 1H), 2.73 (ddd, *J* = 10.0, 8.2, 2.7 Hz, 1H), 2.07 (dtd, *J* = 12.1, 6.6, 2.7 Hz, 1H), 1.70 (dddd, *J* = 14.4, 7.0, 5.1, 2.8 Hz, 1H), 1.68 – 1.56 (m, 1H), 1.52 – 1.41 (m, 1H), 1.15 (d, *J* = 5.9 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 146.64, 143.02, 141.16, 132.69, 131.96, 130.86, 129.10, 128.77, 128.28, 126.61, 126.40, 126.25, 116.79, 53.99, 53.28, 34.33, 24.47, 19.45.

In $CDCl_3$, a carbon in the aromatic region is missing, so we have also included NMR data in acetone:

^{1}H NMR (600 MHz, Acetone-d_6) δ 7.67 – 7.63 (m, 2H), 7.58 – 7.55 (m, 2H), 7.53 (dd, J = 8.5, 2.4 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.41 (d, J = 15.3 Hz, 4H), 7.32 – 7.28 (m, 1H), 7.28 – 7.24 (m, 1H), 7.08 (d, J = 8.5 Hz, 1H), 3.66 – 3.57 (m, 1H), 3.03 (td, J = 9.2, 6.9 Hz, 1H), 2.74 – 2.66 (m, 1H), 2.11 – 2.05 (m, 1H), 1.69 (ddt, J = 14.6, 6.7, 3.3 Hz, 1H), 1.66 – 1.57 (m, 1H), 1.46 (ddt, J = 12.0, 10.1, 7.9 Hz, 1H), 1.09 (d, J = 6.0 Hz, 3H).
^{13}C NMR (151 MHz, Acetone-d_6) δ 147.37, 143.70, 141.76, 133.87, 132.88, 130.97, 129.67, 129.61, 129.09, 127.24, 127.19, 127.02, 126.86, 118.16, 54.49, 53.51, 34.68, 24.69, 19.49.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{23}H_{24}N$: 314.1903, found 314.1903.

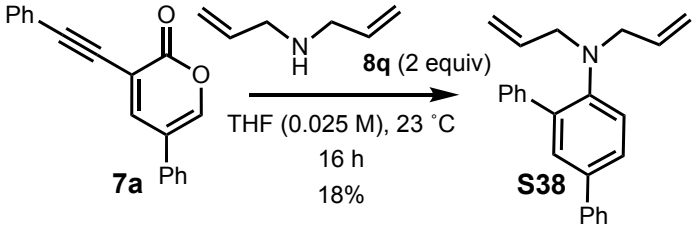
4.28 Synthesis of dibutyl aryl amine S37



Compound **S37** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.1 mL) was added **8p** (17 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (10:1 hexanes:EtOAc) to give dibutyl aryl amine **S37** (7.4 mg, 0.021 mmol, 40%) as a clear oil.

$\mathbf{R_f}$ = 0.43 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 2H), 7.58 – 7.54 (m, 2H), 7.50 (dd, J = 8.3, 2.4 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 7.40 (td, J = 7.6, 5.0 Hz, 4H), 7.29 (dt, J = 9.0, 7.5 Hz, 2H), 7.13 (d, J = 8.3 Hz, 1H), 2.90 – 2.79 (m, 4H), 1.35 (tt, J = 7.6, 6.4 Hz, 4H), 1.15 (h, J = 7.4 Hz, 4H), 0.81 (t, J = 7.4 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.08, 142.23, 141.00, 136.52, 134.29, 130.50, 129.19, 128.80, 128.28, 126.78, 126.71, 126.64, 126.20, 120.81, 52.29, 29.23, 20.58, 14.07.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{26}H_{22}N$: 358.2529, found 358.2527.

4.29 Synthesis of diallyl aryl amine S38

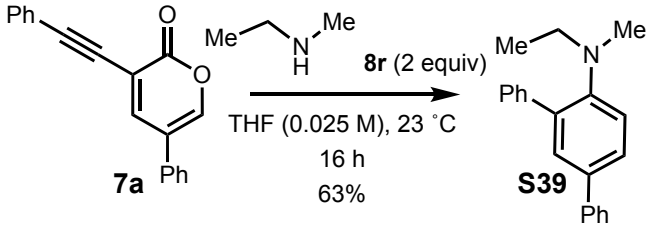


Compound **S38** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.1 mL) was added **8p** (13 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16

h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (9:1 hexanes:EtOAc) to give diallyl aryl amine **S38** (3.0 mg, 0.009 mmol, 18%) as a clear oil.

R_f = 0.35 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (td, *J* = 8.5, 1.4 Hz, 4H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.41 (td, *J* = 7.7, 6.0 Hz, 4H), 7.34 – 7.27 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 5.67 (ddt, *J* = 16.7, 10.2, 6.3 Hz, 2H), 5.10 (q, *J* = 1.6 Hz, 1H), 5.07 (dq, *J* = 3.2, 1.5 Hz, 2H), 5.06 (q, *J* = 1.4 Hz, 1H), 3.50 (dt, *J* = 6.3, 1.4 Hz, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 148.16, 141.68, 140.88, 136.22, 135.17, 135.08, 130.50, 129.20, 128.82, 128.44, 126.90, 126.87, 126.85, 126.23, 121.51, 117.42, 54.91.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{24}H_{24}N$: 326.1903, found 326.1901.

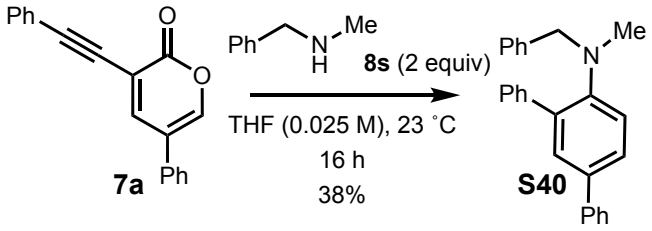
4.30 Synthesis of *N*-methylethyl aryl amine S39



Compound **S39** was prepared according to the procedure described for the synthesis of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.1 mL) was added **8r** (8.0 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (8:1 hexanes:EtOAc) to give *N*-methylethyl aryl amine **S39** (9.1 mg, 0.032 mmol, 63%) as a clear oil.

R_f = 0.33 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 4H), 7.51 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.47 (d, *J* = 2.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 4H), 7.30 (q, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 1H), 2.84 (q, *J* = 7.0 Hz, 2H), 2.63 (s, 3H), 0.89 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 150.29, 142.08, 141.01, 135.36, 134.41, 130.55, 129.03, 128.82, 128.37, 126.82, 126.75, 126.72, 126.51, 119.40, 49.87, 39.75, 12.14.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{24}H_{24}N$: 288.1747, found 288.1744.

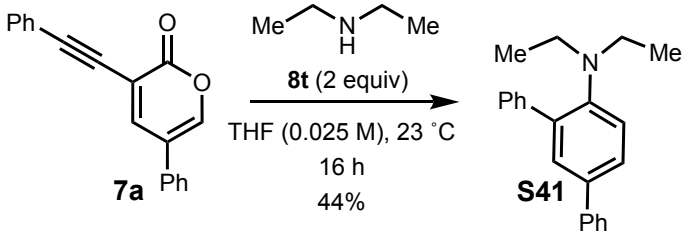
4.31 Synthesis of *N*-methyl-benzyl aryl amine S40



Compound **S40** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.1 mL) was added **8s** (13.0 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (5:1 hexanes:EtOAc) to give *N*-methyl-benzyl aryl amine **S40** (6.9 mg, 0.020 mmol, 38%) as a clear oil.

R_f = 0.77 (10:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.67 – 7.62 (m, 2H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.50 – 7.41 (m, 4H), 7.38 – 7.30 (m, 2H), 7.29 – 7.25 (m, 2H), 7.25 – 7.20 (m, 1H), 7.20 – 7.14 (m, 1H), 7.12 – 7.06 (m, 2H), 3.97 (s, 2H), 2.54 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 150.40, 141.81, 140.87, 138.58, 135.74, 135.01, 130.60, 129.31, 128.85, 128.68, 128.51, 128.23, 127.04, 126.92, 126.88, 126.86, 126.71, 119.96, 60.28, 40.14.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{26}H_{24}N$: 350.1903, found 350.1902.

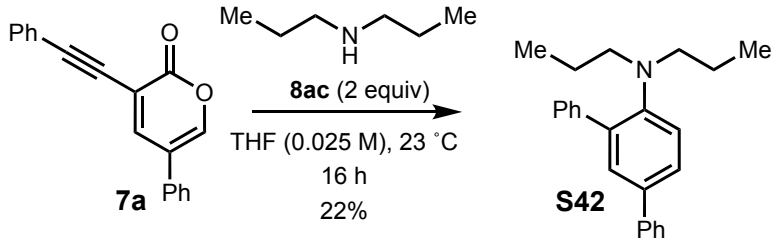
4.32 Synthesis of diethyl aryl amine S41



Compound **S41** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.0 mg, 0.051 mmol, 1 equiv) in THF (2.1 mL) was added **8t** (10.0 µL, 0.10 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (8:1 hexanes:EtOAc) to give diethyl aryl amine **S41** (6.6 mg, 0.022 mmol, 44%) as a clear oil.

R_f = 0.23 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (dt, *J* = 8.0, 1.3 Hz, 4H), 7.50 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.43 – 7.36 (m, 4H), 7.30 (tt, *J* = 7.3, 3.3 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 1H), 2.92 (q, *J* = 7.1 Hz, 4H), 0.94 (t, *J* = 7.0 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 148.31, 142.02, 141.02, 137.01, 134.79, 130.43, 129.19, 128.81, 128.24, 126.83, 126.78, 126.66, 126.20, 121.41, 46.18, 12.18.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{22}H_{24}N$: 302.1903, found 302.1900.

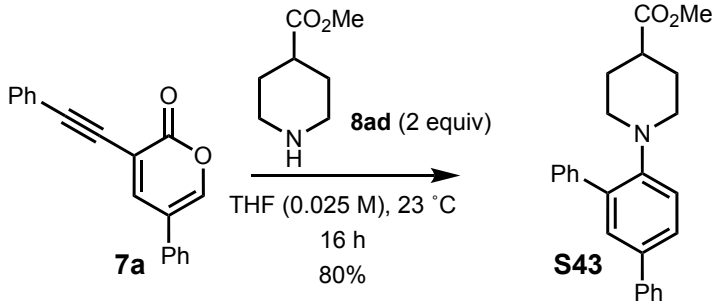
4.33 Synthesis of dipropyl aryl amine S42



Compound **S42** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.8 mg, 0.054 mmol, 1 equiv) in THF (2.2 mL) was added **8ac** (15.0 µL, 0.11 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (10:1 hexanes:EtOAc) to give dipropyl aryl amine **S42** (4.0 mg, 0.012 mmol, 22%) as a clear oil.

R_f = 0.48 (hexanes, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 2H), 7.58 – 7.53 (m, 2H), 7.49 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.39 (td, *J* = 7.7, 4.6 Hz, 4H), 7.33 – 7.26 (m, 2H), 7.14 (d, *J* = 8.3 Hz, 1H), 2.85 – 2.75 (m, 4H), 1.42 – 1.36 (m, 4H), 0.73 (t, *J* = 7.4 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.07, 142.24, 141.02, 136.60, 134.37, 130.50, 129.23, 128.80, 128.26, 126.79, 126.72, 126.65, 126.24, 120.92, 54.47, 20.30, 11.85.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{24}H_{28}N$: 330.2216, found 330.2218.

4.34 Synthesis of methyl pipperidine-4-carboxylate aryl amine S43



Compound **S43** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.8 mg, 0.054 mmol, 1 equiv) in THF (2.2 mL) was added **8ad** (15.0 µL, 0.11 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (10:1 hexanes:EtOAc) to give methyl piperidine-4-carboxylate aryl amine **S43** (16.2 mg, 0.044 mmol, 80%) as a pale orange solid.

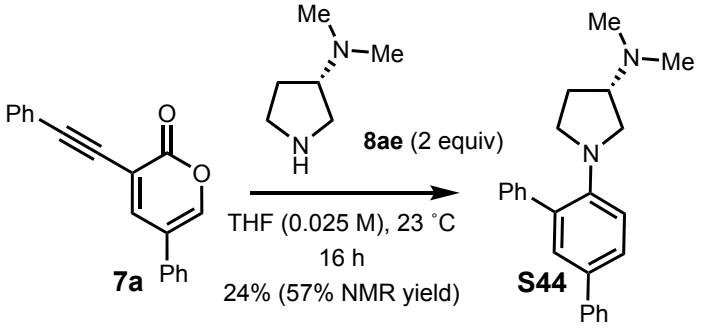
R_f = 0.65 (5:1 hexanes:EtOAc, UV/$KMnO_4$)
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 2H), 7.62 – 7.57 (m, 2H), 7.54 – 7.48 (m, 2H), 7.42 (td, *J* = 7.7, 6.0 Hz, 4H), 7.35 – 7.28 (m, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 3.68 (s, 3H), 3.18

(dt, *J* = 12.0, 3.8 Hz, 2H), 2.59 (td, *J* = 11.7, 2.4 Hz, 2H), 2.32 (tt, *J* = 11.4, 4.0 Hz, 1H), 1.84 – 1.77 (m, 2H), 1.64 (dtd, *J* = 12.9, 11.4, 3.8 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.72, 150.25, 141.29, 140.91, 135.48, 130.42, 128.90, 128.84, 128.45, 127.02, 126.92, 126.89, 126.80, 118.90, 51.78, 51.20, 41.02, 28.49.

In $CDCl_3$, a carbon in the aromatic region is missing, so we have also included NMR data in acetone:

^{1}H NMR (600 MHz, Acetone-d_6) δ 7.74 – 7.69 (m, 2H), 7.69 – 7.64 (m, 2H), 7.57 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.47 – 7.40 (m, 4H), 7.36 – 7.28 (m, 2H), 7.17 (d, *J* = 8.3 Hz, 1H), 3.62 (s, 3H), 3.17 – 3.11 (m, 2H), 2.62 (td, *J* = 11.6, 2.5 Hz, 2H), 2.34 (tt, *J* = 11.4, 4.0 Hz, 1H), 1.81 – 1.74 (m, 2H), 1.59 (dtd, *J* = 12.8, 11.3, 3.8 Hz, 2H).
^{13}C NMR (151 MHz, Acetone-d_6) δ 175.54, 151.26, 142.21, 141.52, 136.28, 136.00, 130.59, 129.66, 129.62, 129.15, 127.73, 127.66, 127.44, 127.35, 119.95, 51.78, 51.71, 41.33, 29.20.
HRMS (ESI): $[M+H]^+$ cal'd for $C_{25}H_{26}NO_2$: 372.1958, found 372.1961.

4.35 Synthesis of *N,N*-dimethylamino-3-pyrrolidine aryl amine S44



Compound **S44** was prepared according to the procedure described for the preparation of **11a**. To a vial charged with **7a** (14.4 mg, 0.053 mmol, 1 equiv) in THF (2.1 mL) was added **8ae** (13.0 µL, 0.11 mmol, 2 equiv) *via* microsyringe and the reaction mixture was left to stir at 23 ˚C. After 16 h, the reaction mixture was concentrated *in vacuo*. The crude residue was purified by preparative TLC (20:1 DCM:MeOH) to give *N,N*-dimethylamino-3-pyrrolidine aryl amine **S44** (4.4 mg, 0.013 mmol, 24%) as an orange solid. The NMR yield was determined using trimethoxybenzene as an internal standard.

R_f = 0.07 (10:1 DCM:MeOH, UV/$KMnO_4$)
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.60 – 7.53 (m, 2H), 7.49 (ddd, *J* = 9.9, 8.2, 1.8 Hz, 3H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.38 (q, *J* = 7.5 Hz, 4H), 7.31 – 7.23 (m, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 3.05 (ddd, *J* = 9.1, 5.9, 3.7 Hz, 3H), 2.88 (t, *J* = 8.7 Hz, 1H), 2.64 (p, *J* = 7.3 Hz, 1H), 2.16 (s, 6H), 2.02 – 1.91 (m, 1H), 1.73 – 1.69 (m, 1H).
^{13}C NMR (151 MHz, Chloroform-*d*) δ 146.99, 142.93, 141.06, 131.45, 131.08, 130.64, 129.33, 128.80, 128.21, 126.61, 126.59, 126.48, 126.42, 115.04, 65.59, 55.63, 50.26, 44.14, 30.13.

In $CDCl_3$, a proton in the aromatic region overlaps with the resonance peaks from residual $CHCl_3$, so we have also included ^{1}H NMR data in acetone, although we observed some decomposition of the material in acetone.

^{1}H NMR (600 MHz, Acetone-d_6) δ 7.64 (p, J = 1.4 Hz, 1H), 7.63 (dd, J = 2.0, 1.1 Hz, 1H), 7.53 (dd, J = 8.5, 2.4 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.44 – 7.37 (m, 5H), 7.32 (ddt, J = 7.8, 6.9, 1.3 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.00 (d, J = 8.5 Hz, 1H), 3.08 – 3.00 (m, 3H), 2.65 (s, 1H), 2.11 (s, 6H), 2.07 – 2.06 (m, 1H), 2.00 – 1.95 (m, 1H), 1.72 – 1.66 (m, 1H).
HRMS (ESI): $[M+H]^+$ cal'd for $C_{24}H_{27}N_2$: 343.2169, found 343.2170.

5. DFT Mechanistic Calculations

5.1 Computational details

The range separated dispersion-corrected ωB97X-D[12,13] functional and the 6-31+G(d,p)[14–18] basis set was used to optimize all stationary point geometries.[19]8/25/24 11:51:00 AM Harmonic vibrational frequency calculations were used to confirm stationary points as minima or first-order saddle points on the potential energy surface (PES) and to obtain quasi-harmonic rigid-rotor/harmonic oscillator thermochemistry values with the GoodVibes[20] program. Where possible, intrinsic reaction coordinate (IRC) calculations were carried out to ensure that the intermediates (**Int**) of the different pathways connected to their corresponding transition structure (**TS**).

Energies were refined with single-point energy calculations at the ωB97X-D /def2-TZVP level. In all cases, the calculations included the integral equation formalism variant of the polarizable continuum model (IEF-PCM)[21–25] with the SMD[26] solvation model (solvent=tetrahydrofuran) to account for solvent effects.

Conformational sampling (due to rotations about single bonds) of ground state (**GS**) and transition states (**TS**) structures was performed using a combination of manual sampling and CREST.[27] To enumerate the different conformers, a letter/combination of letters is appended at the end of each name (*e.g.* _a, _b, _c, _ab, _ac, *etc*). Representations in the main text and supporting information refer to the most stable rotameric and isomeric conformation found for each step. Gibbs Free Energies (G) values of all the energy profiles correspond to the Boltzmann weighted G of all the conformers found in each step (G_{av}).

Gaussian 16 was employed for all density functional theory (DFT) calculations, using an "ultrafine" pruned (99,590) grid for numerical integration of the exchange-correlation functional and its derivatives. Visualization settings have been made openly accessible.[29] Atomic charges, Wiberg bond orders[30] and Fukui indices were computed using natural population analysis (NPA) with *NBO 7.0*,[31] interfaced to *Gaussian 16*.

Quasi-harmonic corrections were introduced to the computed vibrational entropies using a frequency cut-off value of 100.0 cm^{-1} with GoodVibes, following the approach proposed by Grimme[32] at 273.15 K. Also, a correction for the change in standard state from gas phase at 1 atm to a 1 M solution was introduced.[33] A few of the GS calculations showed persistent imaginary frequencies lower than 50 cm^{-1}. These imaginary frequencies were inverted to obtain thermochemical contributions.[34] After conformational sampling, duplicate structures at the DFT

level were automatically excluded. Boltzmann weighted Gibbs energies (G_{av}) are quoted throughout, which include considerations of molecular point group and entropies of mixing.[35–38]

All the thermochemical data including absolute energies, zero-point energies (ZPE) and T·S, among other parameters, at the ωB97X-D/6-31+G(d,p) level, as well as the absolute energies, corrected final G and relative G obtained after ωB97X-D/def2-TZVP single point energy calculations, are tabulated in separate files of the ESI labeled with the ".dat" extension.

5.2 Proposed mechanism

Transformation of phenyl alkynyl 2-pyrone **7a** (**S.M.**) into aryl amine **11a** (**Product**) using morpholine is predicted to occur via a ring opening/ ring closing sequence. First, sequential additions of morpholine (via **TS-I-Main** and **TS-III-Main**) generate **Int-IV-Main** (exergonic; –9.3 kcal/mol) with a barrier of 17.5 kcal/mol. Subsequent ring opening of **Int-V-Main** only has a barrier of 5.9 kcal/mol (**TS-V-Main**) to generate triene **Int-VI-Main** (–17.5 kcal/mol). The triene then goes through the highest barrier pericyclic ring closing with an activation energy of 18.0 kcal/mol, followed by a decarboxylation-elimination sequence to generate the final aminated benzene product.

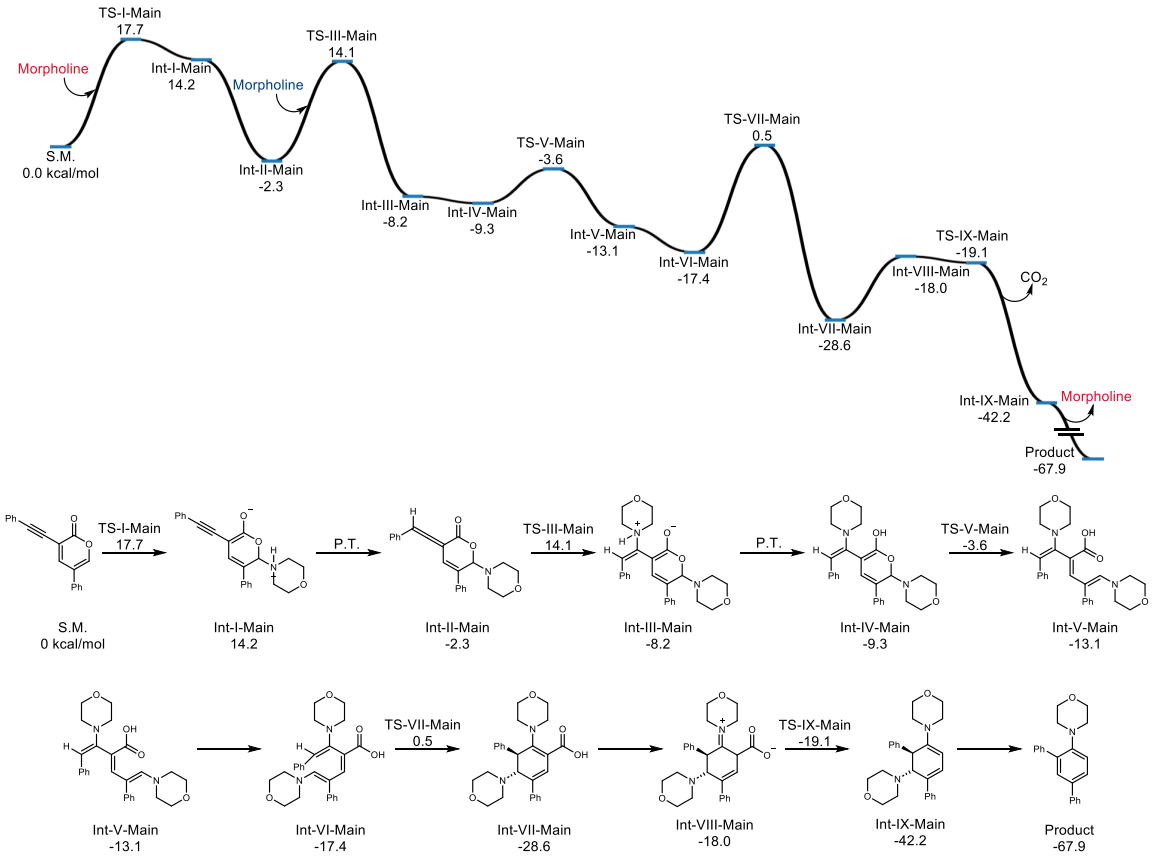


Figure S1. PES of the proposed mechanism for the reaction between morpholine and model pyrone substrate to the product. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p).

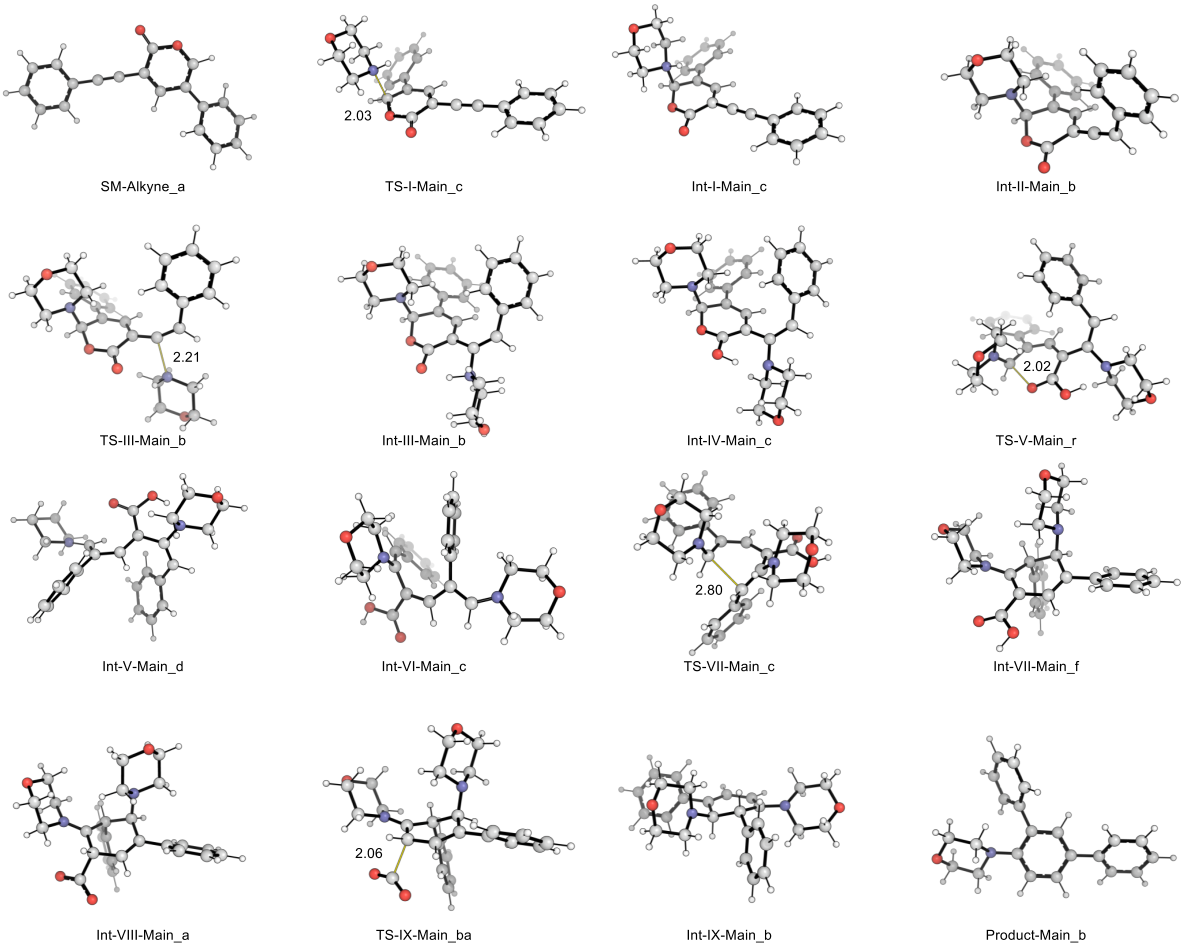


Figure S2. Representation of the most stable conformers in each step for the proposed mechanism in the reaction between morpholine and model pyrone substrate to the product. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p). Key bond forming/breaking distances in Å; all energetic values in kcal/mol.

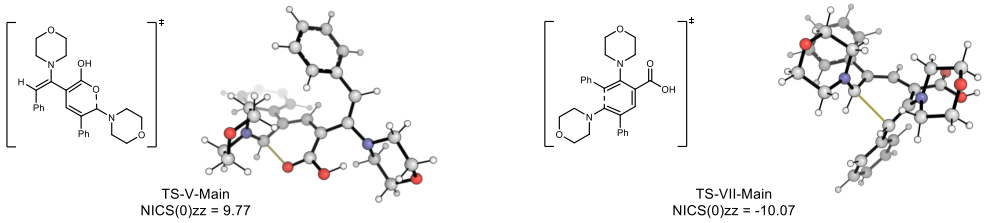


Figure S3. NICS(0)$_{zz}$ calculations for the ring opening steps (**TS-V-Main_r** and **TS-VII-Main_c**) in the main proposed mechanism of morpholine and model pyrone. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p).

5.3 Alternative intermediates in proposed mechanism

The addition of morpholine to the allene (**Int-II-main**) is predicted to occur preferably leading to the E alkene. The addition to form the Z alkene is calculated to have a barrier of 17.7 kcal/mol and form Z alkene **Int-III-Z** located at –4.4 kcal/mol. Additionally, addition of the morpholine after ring opening (**to Int-III-B**) has a barrier of 31.6 kcal/mol (**TS-IV-B**) and thus is disfavored over addition to the ring closed intermediate (**Int-II-Main**) which displays a barrier of 16.4 kcal/mol (**TS-III-Main**). We also investigated different tautomers of **Int-III-Main**, but we believe the proton transfer from **Int-III-Main** to **Int-IV-Main** and subsequent ring opening is too rapid to allow for tautomerization to other tautomers of **Int-III** (e.g., **Int-III-Protomer A–C**) despite them being more stable. Tautomerization would require another molecule to assist in the proton transfer whereas **Int-III-Main** to **INT-IV-Main** is intramolecular.

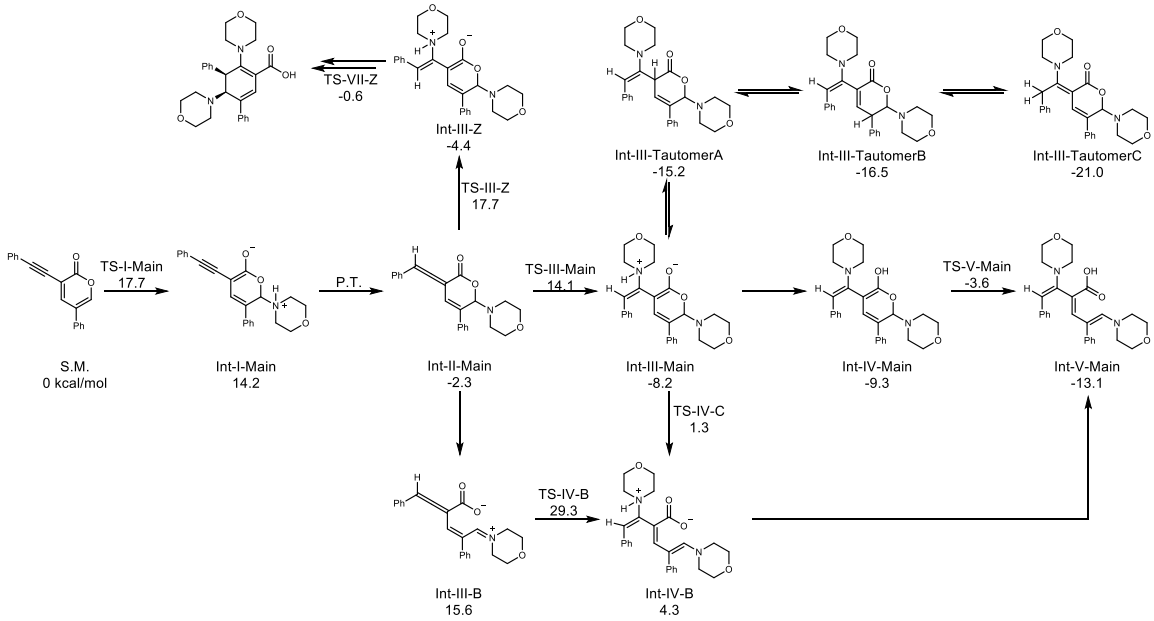


Figure S4. Gibbs free energies relative to starting materials of alternative intermediates in the transformation of **S.M.** to **Int-V-Main**. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p).

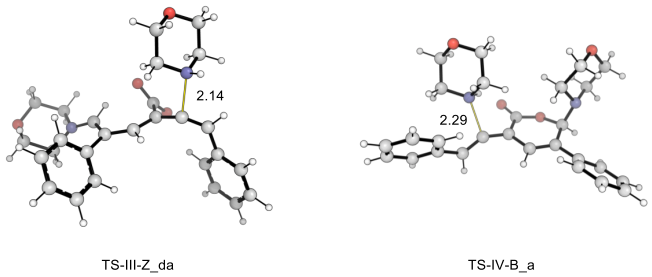


Figure S5. Representation of most stable conformers in the alternative modes of morpholine addition (**TS-III-Z** and **TS-IV-B**). ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p). Key bond forming/breaking distances in Å; all energetic values in kcal/mol.

We investigated whether isomerization of **Int-V-Main** through **Int-VI-TRANS** would provide a lower barrier to cyclization but found that **TS-VII-TRANS** had a barrier of 19.9 kcal/mol higher than the proposed mechanism from **Int-VI-Main** (18.0 kcal/mol). Decarboxylation can also occur prior to ring closing; we investigated the decarboxylation step that results in the E and Z trienes. Decarboxylation to form the E triene via **TS-VI-A** has a barrier of 16.8 kcal/mol and decarboxylation to form the Z triene via **TS-VII-C** has a barrier of 21.6 kcal/mol, these would be followed by a ring closing TS with a barrier of 20.9 kcal/mol. This indicates that decarboxylation could potentially occur via **TS-VI-A** in a competitive manner versus ring closing (**TS-VII-Main**, 20.0 kcal/mol). Alternatively, decarboxylation can occur before the elimination of an equivalent of morpholine, but we found that decarboxylation before elimination (**TS-X-ZwitC**) has a barrier of 28.9 kcal/mol. We also investigated zwitterionic forms of **Int-VII-Main** but these were higher in energy.

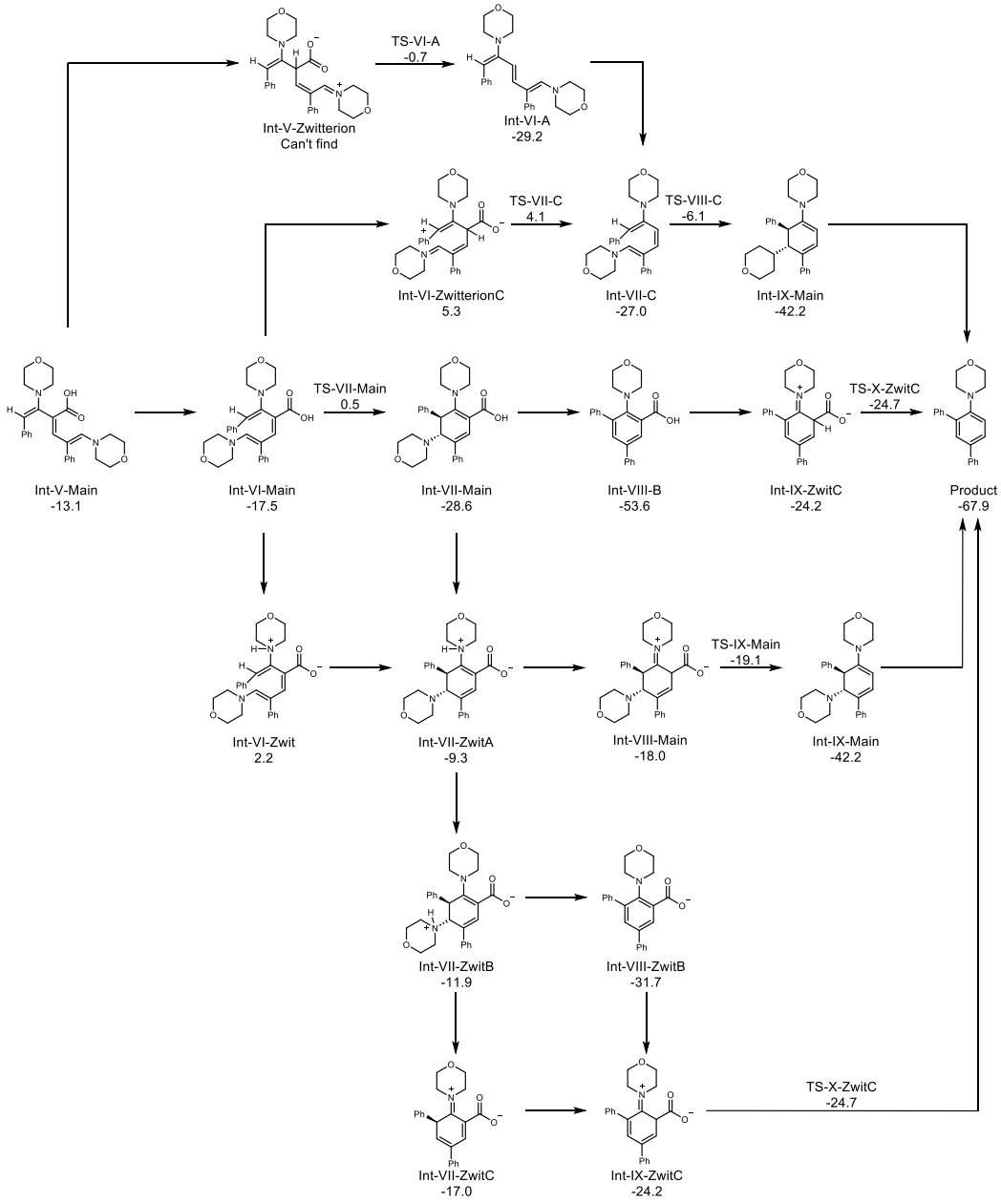


Figure S6. Gibbs free energies relative to starting materials of alternative intermediates in the transformation of **Int-V-Main** to the **Product**. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p).

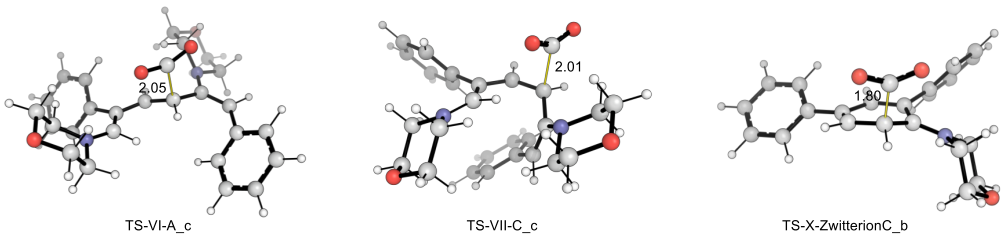


Figure S7. Representation of most stable conformers for transition states in the alternative decarboxylation in the proposed mechanism in the reaction between morpholine and model pyrone substrate. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p). Key forming/breaking distances in Å; all energetic values in kcal/mol.

5.4 Alternative mechanism via a cyclic allene intermediate

We investigated an alternative mechanism through a cyclic allene intermediate. The alternate pathway begins after formation of **Int-I-Main**. Unlike in our proposed mechanism, proton transfer to the oxyanion enables ring opening via **TS-III-Allene** (18.2 kcal/mol) to produce **Int-III-Allene** at 7.2 kcal/mol. Another proton transfer enables decarboxylation via **TS-V-A-Allene** or **TS-V-B-Allene** to yield dienynes **Int-V-A/B-Allene** in a net exergonic fashion (–9.9/–11.4 kcal/mol). **Int-V-A-Allene** is then calculated to undergo ring closing via **TS-VI-Allene** (a barrier of 39.1 kcal/mol) to give cyclic **allene Int-VI-Allene**. The cyclic allene can give product-II through a concerted (**TS-VII-C-Allene**) or stepwise (**TS-VII-H-Allene/TS-VIII-H-Allene**) hydrogen shift. Alternatively, the product might arise through an amine shift (**TS-VII-N-Allene**) or addition/elimination sequence (**TS-VII-S-Allene**). Ultimately, we found the barrier to form the cyclic allene to be prohibitively high for these pathways to be relevant.

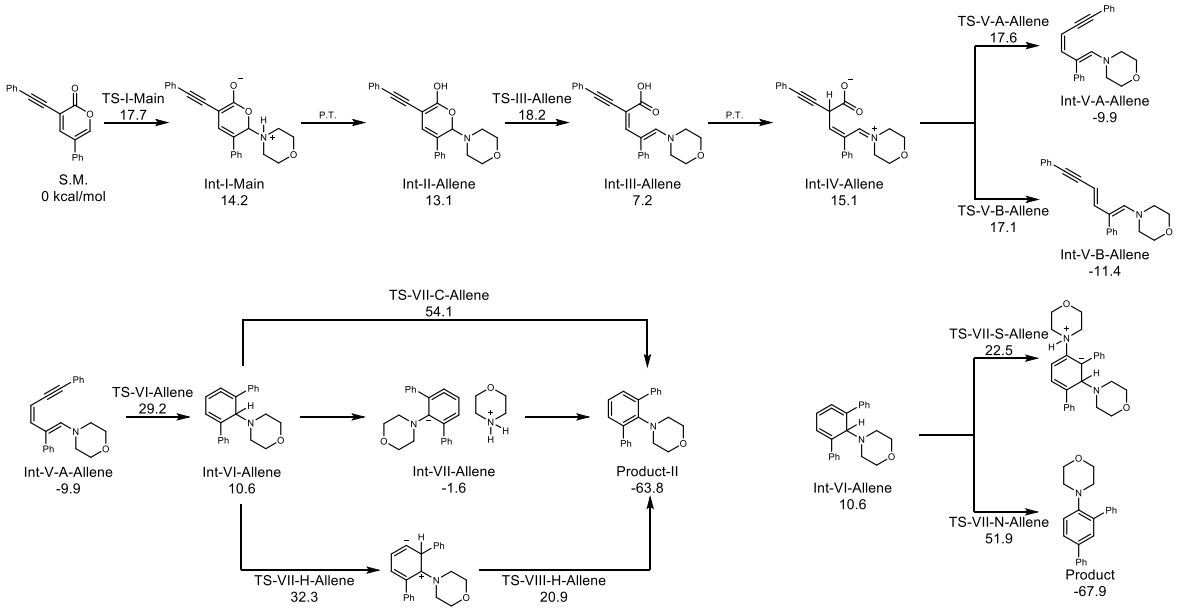


Figure S8. PES of an alternative mechanism in the reaction between morpholine and model pyrone substrate going through a cyclic allene intermediate. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p).

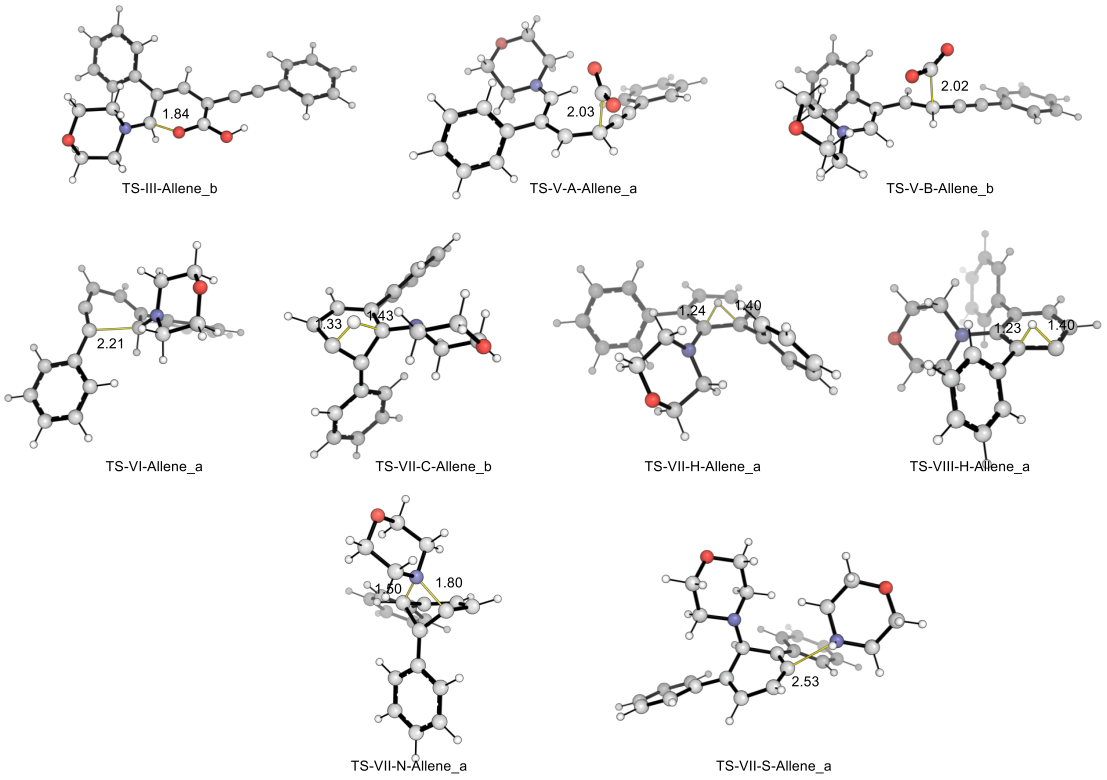


Figure S9. Representation of most stable conformers in key steps for the alternative mechanism in the reaction between morpholine and model pyrone substrate going through a cyclic allene intermediate. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p). Key forming/breaking distances in Å; all energetic values in kcal/mol.

5.5 Barrier for first amine addition and ring closing with other amines

We investigated the effect of different amines on the barrier of amine addition (**TS-I**) and ring closing (**TS-VII**) as the two steps which are likely to be potentially rate determining. Ring closing seems to be more sensitive to increased steric bulk, and barriers for ring closing show good correlation with reactions yields. As shown, amine **8x** as the bulkiest amine does not work experimentally and possesses a TS-VII barrier of 24.2 kcal/mol, amine **8ae** as the least bulky and more electron deficient amines possesses a higher barrier for TS-I (18.3 kcal/mol) over TS-VII (16.3 kcal/mol) and finally amine 8ac as a moderately bulky amine possesses a **TS-VII** barrier of 21.2 kcal/mol.

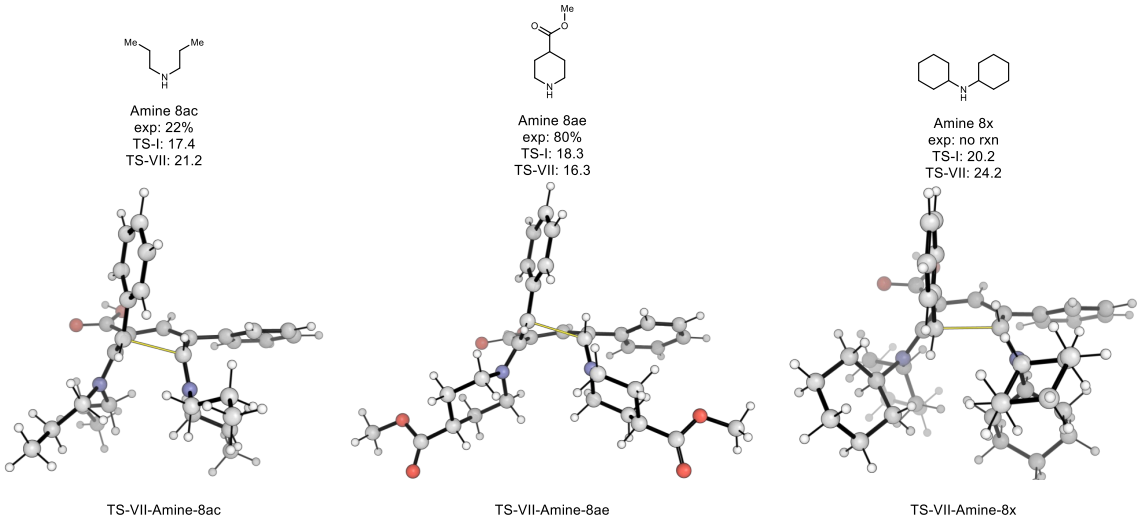


Figure S10. First morpholine attack and ring closing barriers for different amine substrates. ωB97X-D/def2-TZVP//ωB97X-D/6-31+G(d,p). Key forming/breaking distances in Å; all energetic values in kcal/mol.

6. Calculation of Molecular Descriptors and Modeling

6.1 Conformational Searching

Each amine was subjected to a molecular mechanics conformational search using Schrödinger MacroModel and the OPLS4 force field.[39,40] MacroModel conformational searches were conducted in the gas phase, with a maximum of 10,000 interactions, and a convergence threshold of 0.001 au. An ensemble of conformers within 21 kJ/mol (5.02 kcal/mol) of the minimum were collected, excluding mirror-image conformers.

6.2 DFT computations

All quantum mechanical (DFT) geometry optimization and single point calculations were performed using Gaussian 16 (revision C.01).[19] Geometry optimizations and sequent frequency calculations of the selected conformers were performed at the B3LYP-GD3BJ/6-31G(d,p) level of theory with ultrafine integration grid and root mean square (RMS) force criterion of 3 x 10^{-4}. All optimized geometries were verified by frequency computations as minima (zero imaginary frequencies). The resultant geometries were subject to single point calculations at the M062X/def2-TZVP level of theory.[41] Natural bond orbital (NBO) analysis was performed using the NBO program (version 7.0).[31] XYZ coordinates for each conformer in each ensemble are available as Secondary_Amine_Coordinates.xyz

6.3 Featurization

Descriptors were collected using the Get_Properties python scripts.[42]

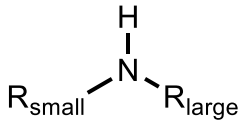


Figure S14. Conserved reactive moiety for which molecular descriptors were collected.

R_Large and R_Small were manually assigned. In cases of symmetrical molecules, large and small were arbitrarily assigned.

6.4 Molecular descriptors:

The M062X/def2-TZVP level of theory was used to calculate the molecular descriptors. Each descriptor was extracted from Gaussian output files (necessary keywords in parentheses) or calculated with the Morfeus python package.[43]

6.5 Global descriptors:

- Frontier Orbitals: E(HOMO), E(LUMO), μ, η, ω
- Polarizability
- Dipole
- Volume
- Solvent accessible surface area, volume, and sphericity (Morfeus)

6.6 Amine-specific descriptors:

- NBO: natural charge from NBO (Gaussian keyword = "pop=nbo7") for N, H, R_{Large} and R_{Small}
- NMR: isotropic NMR shift (Gaussian keyword = "nmr=giao") for N, H, R_{Large} and R_{Small}
- Pyramidalization of N
- Angle (H–N–$R_{large\ or\ small}$)
- NBO Lone pair energy and occupancy of N
- Percent Buried Volume (Morfeus) for N calculated from 2 Å to 6 Å at 0.5 Å steps
- Sterimol B_1, B_5, and L from N to R_{large} and R_{small}

6.7 Calculation of ensemble properties

Individual conformer descriptors collected above were analyzed to determine representative properties for the conformational ensemble. In order to maintain a conformational ensemble of accessible and relevant conformers, any conformers greater than 4 kcal/mol higher in energy than the lowest energy conformer were discarded (as calculated using the relative free energies corrected with the electronic energy from the gas phase single points).[44]

For each property in the revised conformational ensemble, the minimum value of the property (min), the maximum value of the property (max), the value of the property for the lowest energy conformer (LEC), and the Boltzmann-weighted average (Boltz) values were collected. A complete list of these properties is available as a supporting information file (Modeling_Data.xlsx).[42]

6.8 Modeling Yield Data Using Classification and Regression Algorithms

Initial modeling was conducted using the training set as designated in the manuscript (with the exception of compounds **8j**, **8k**, and **8s,** which were selected in the next stage). In the Modeling_Data.xlsx each substrate as well as it's identification in the training set, hand-selected test set, or validation set is denoted. Using the training set, all possible descriptors were analyzed for both univariate classification and multi-variate linear regression.

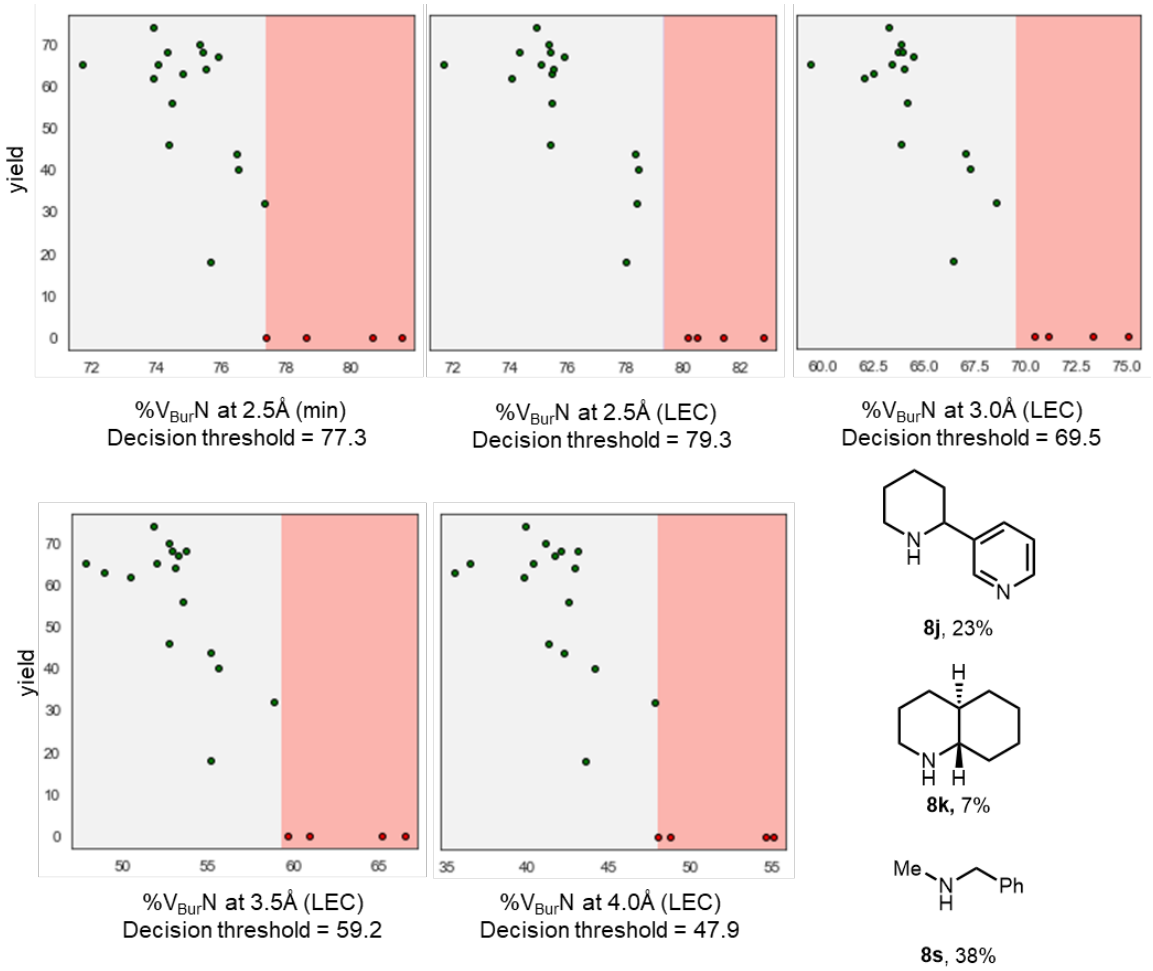


Figure S11. Threshold analysis of the training set identifying multiple models with perfect accuracy using descriptors of the %V$_{Bur}$N.

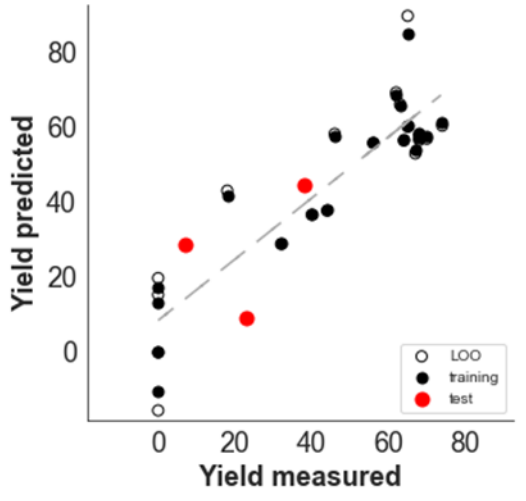
Of note, the training data could be accurately classified by multiple variations of %V$_{Bur}$N, each suggesting that over a certain threshold of steric bulk, no reaction occurs (Figure S15). Notably, we also observed strong univariate correlations in this set, ($R^2 > 0.7$). However, given the sparsity of data for low yields (<40%) of desired products, a test set of additional compounds were selected from in-house secondary amines: **8j**, **8k**, and **8s**. After determining the actual yield for each of these compounds, each of these substrates were active and produced the desired product which was not captured by any of these classification models (Table S3).

%V$_{bur}$N	8j	8k	8s

2.5Å (min)	77.5	78.0	74.7
2.5Å (LEC)	78.4	81.4	78.7
3.0Å (LEC)	68.6	71.8	66.0
3.5Å (LEC)	59.0	62.5	52.7
4.0Å (LEC)	48.9	52.2	39.8
Observed			

Table S3. Computed descriptor values for each relevant descriptor for **8j**, **8k**, and **8s**. Background color indicates whether the corresponding model would predict the compound to be active (green), inactive (red), or if no prediction is available (no color).

While each of the descriptors we investigated gave high univariate correlations (R^2 >0.70), we observed slightly better performance with **%V_{Bur}N at 3.0Å (LEC)** which was used going forward (Figure S12).



45.10 - 23.85 * **V_{bur} of N^1 at 3.0Å (LEC)**

Training R^2 = 0.817
Training Q^2 = 0.767
Training MAE = 9.443
Training K-fold R^2 = 0.758 (+/- 0.001)

Test R^2 = 0.645
Test MAE = 14.077

Figure S12. Univariate model for yield before applying classification to curate the data set.

As described in the main text, we investigated the combination of classification and regression models with this expanded dataset. Penalizing false negatives, the data was split into "reactive and "unreactive" regions at $\%V_{Bur}N_{3.0Å}$(LEC) > 73.3% and the classification was validated with four additional substrates found to be true negatives.

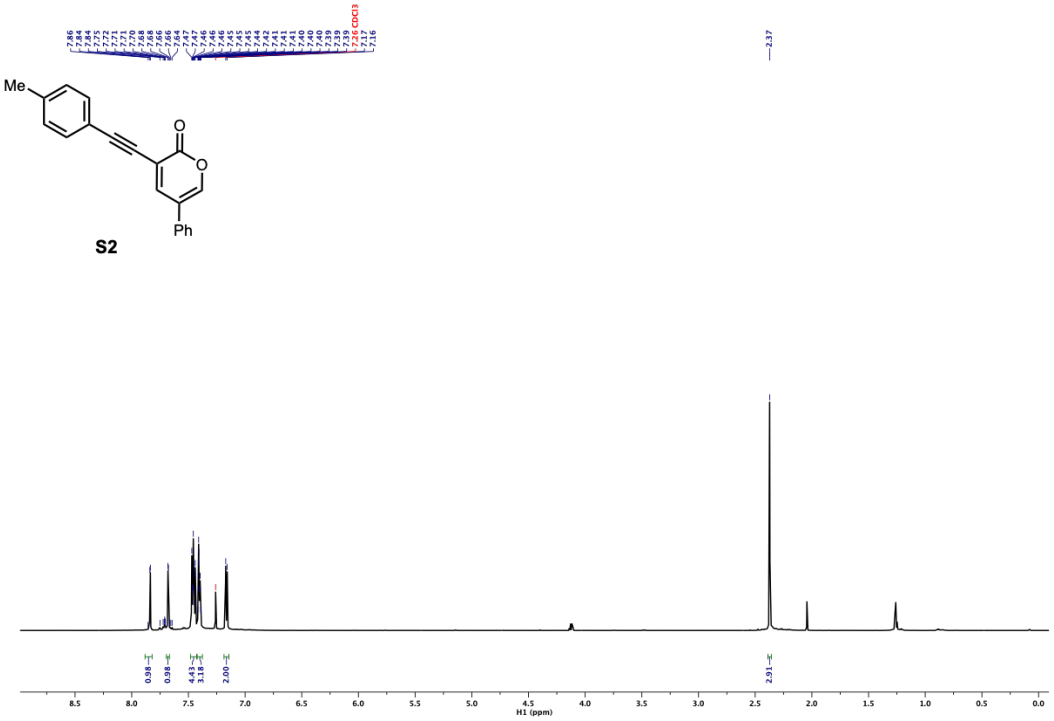
Given the necessity of both positive and negative data for effective modeling, we hypothesized that the inclusion of a single substrate deemed to be "inactive" by the threshold would provide the best results for building predictive models (Available as "Curated_Data_for_Regression" in Modeling_Data.xlsx). Univariate analysis of all descriptors identified the best model as $\%V_{Bur}N_{3.0Å}$ (LEC). Inclusion of additional variables using forward stepwise selection for multivariate linear regression led to bivariate models that were particularly sensitive to internal test/train split leading to overfitting of the data; thus, we proceeded with the univariate model to predict yields for external substrates. Statistics are included in Table S4.

Table S4. Statistics the univariate model using $\%V_{Bur}N_{3.0Å}$ (LEC) for the test set and validation set (with and without outlier **8af**).

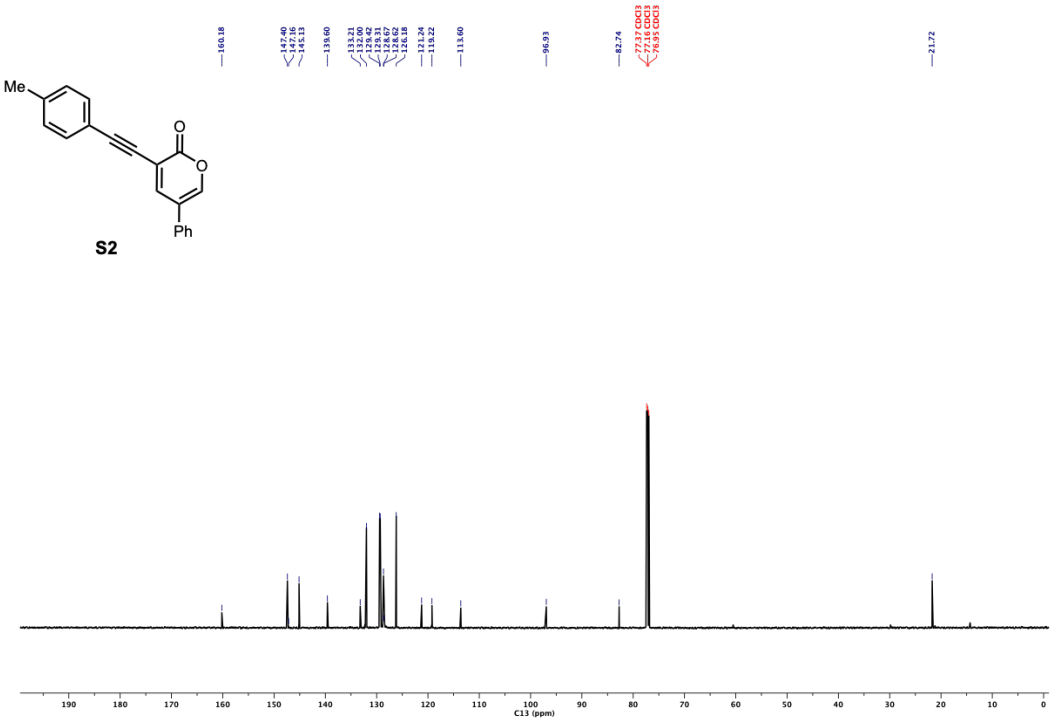
	R^2	Q^2	MAE
Test Set	0.777	0.720	10
Validation Statistics omitting **8af**	0.710	-	15
Validation Statistics with **8ab – 8af**	0.489	-	21

7. NMR Spectra

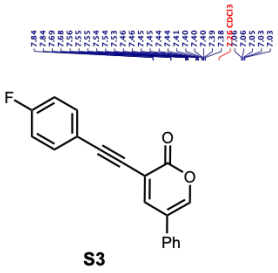
S2 (^{1}H NMR, 600 MHz, $CDCl_3$)



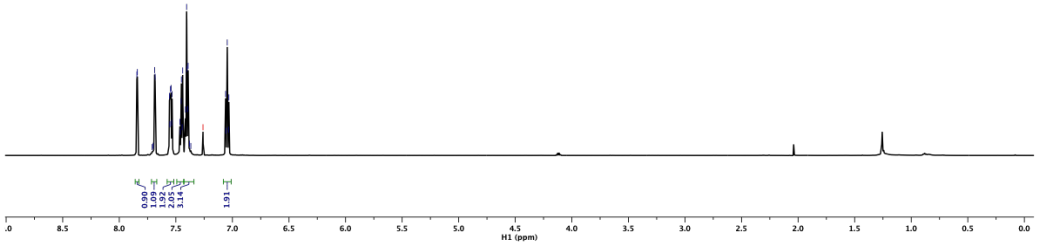
S2 (^{13}C, 151 MHz, $CDCl_3$)



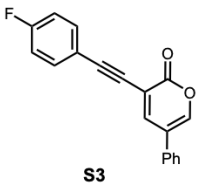
S3 (^{1}H NMR, 600 MHz, $CDCl_3$)



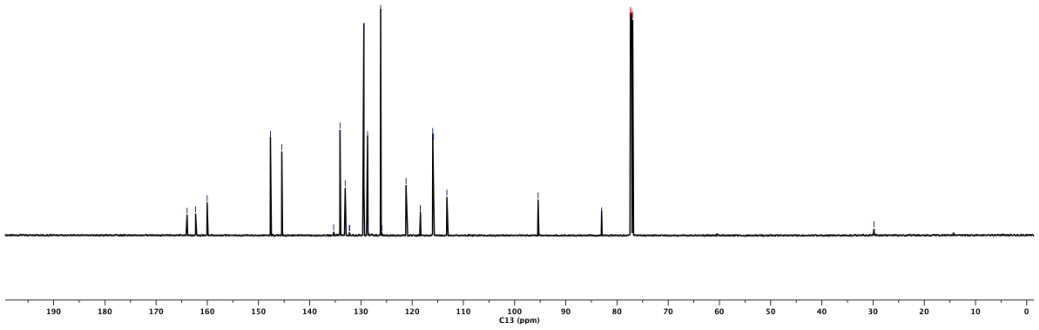
S3



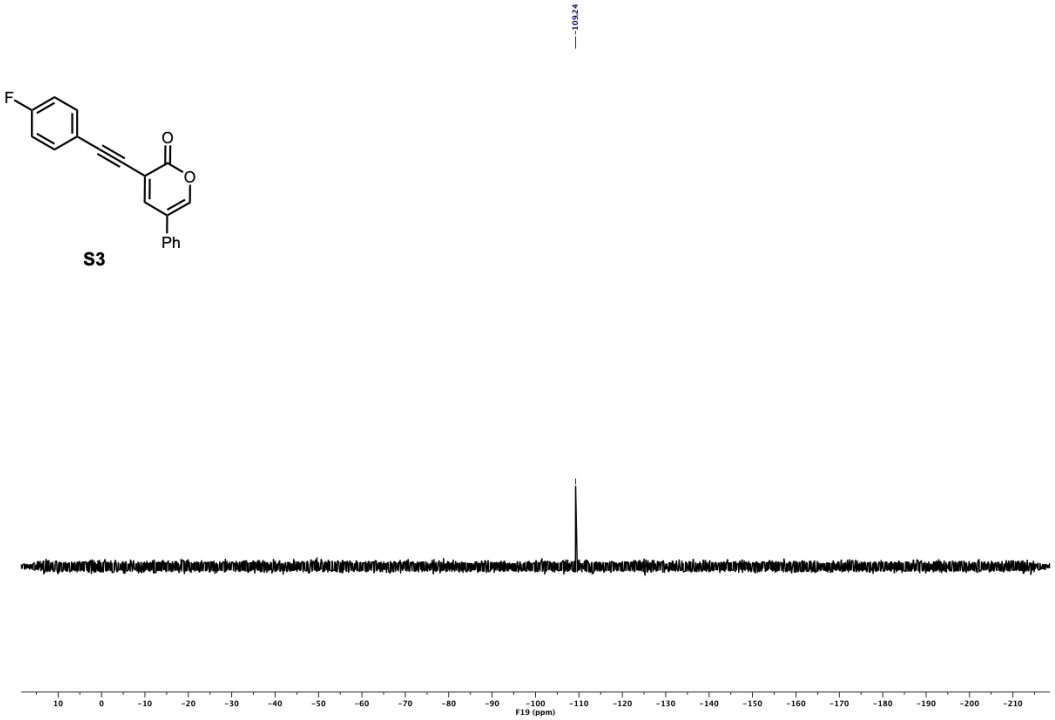
S3 (^{13}C, 151 MHz, $CDCl_3$)



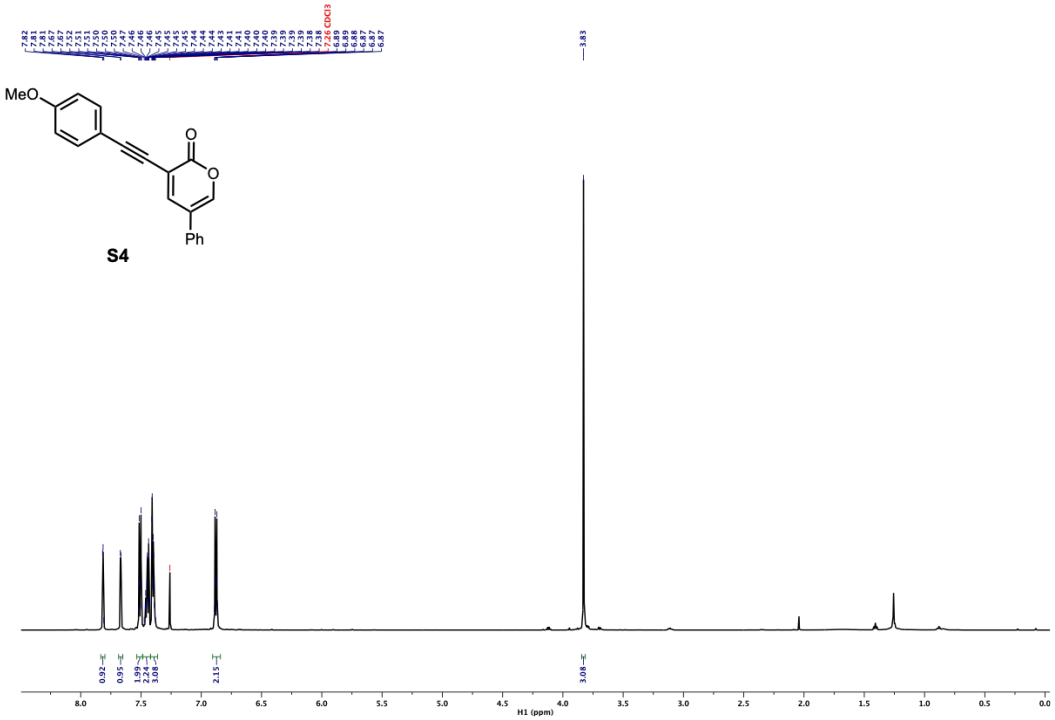
S3



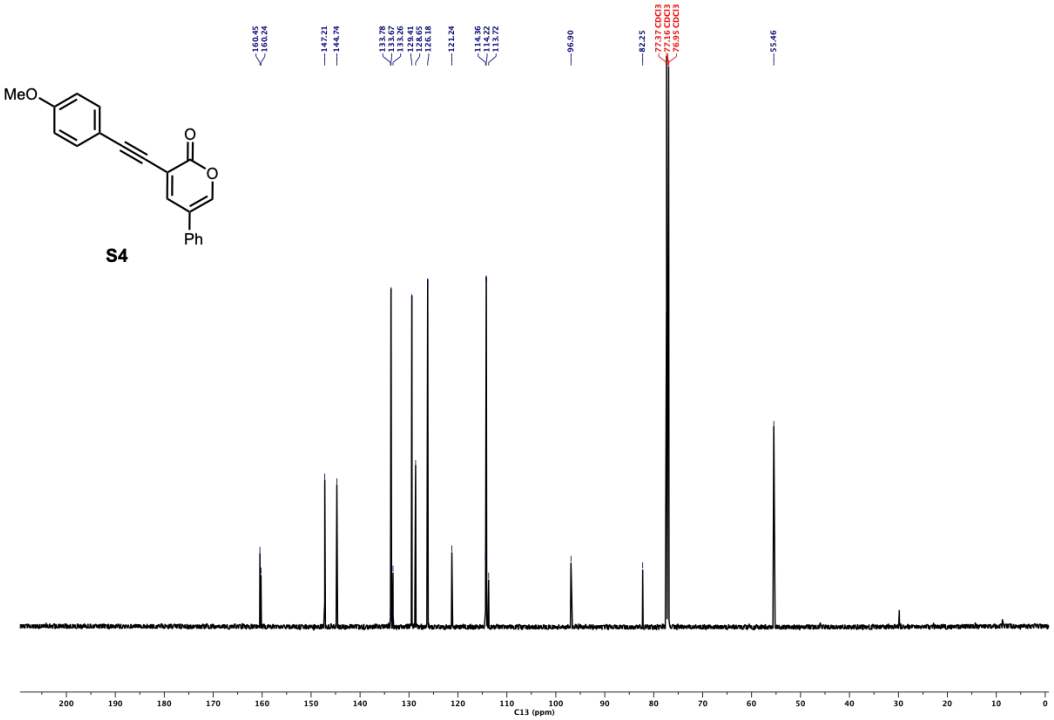
S3 (^{19}F, 565 MHz, $CDCl_3$)



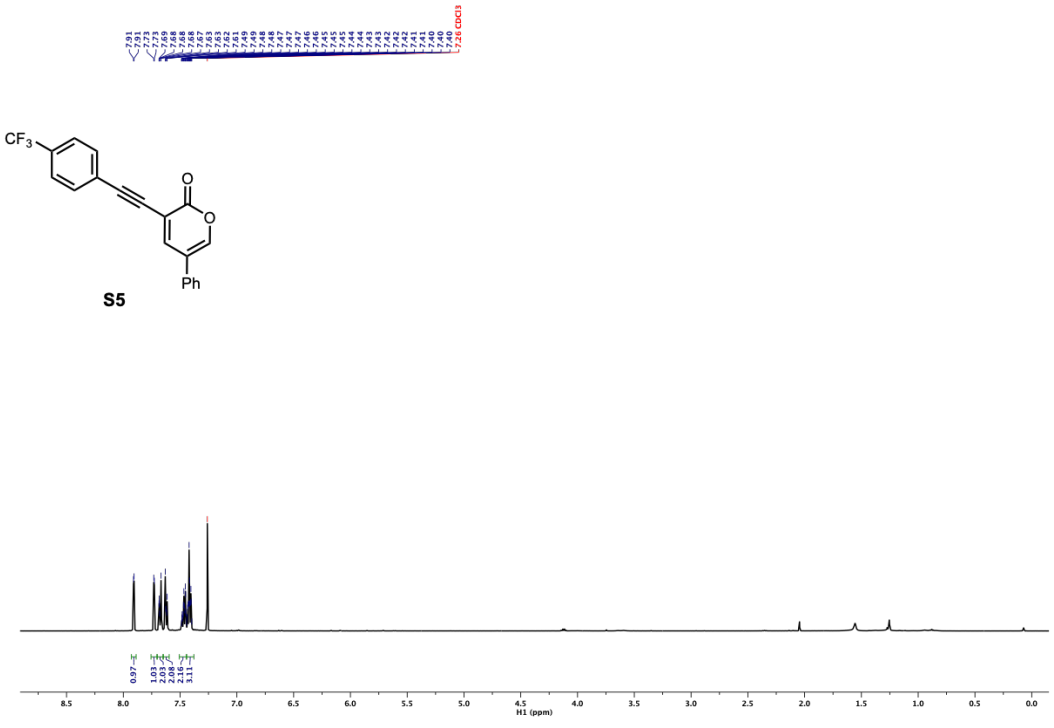
S4 (^{1}H NMR, 600 MHz, $CDCl_3$)



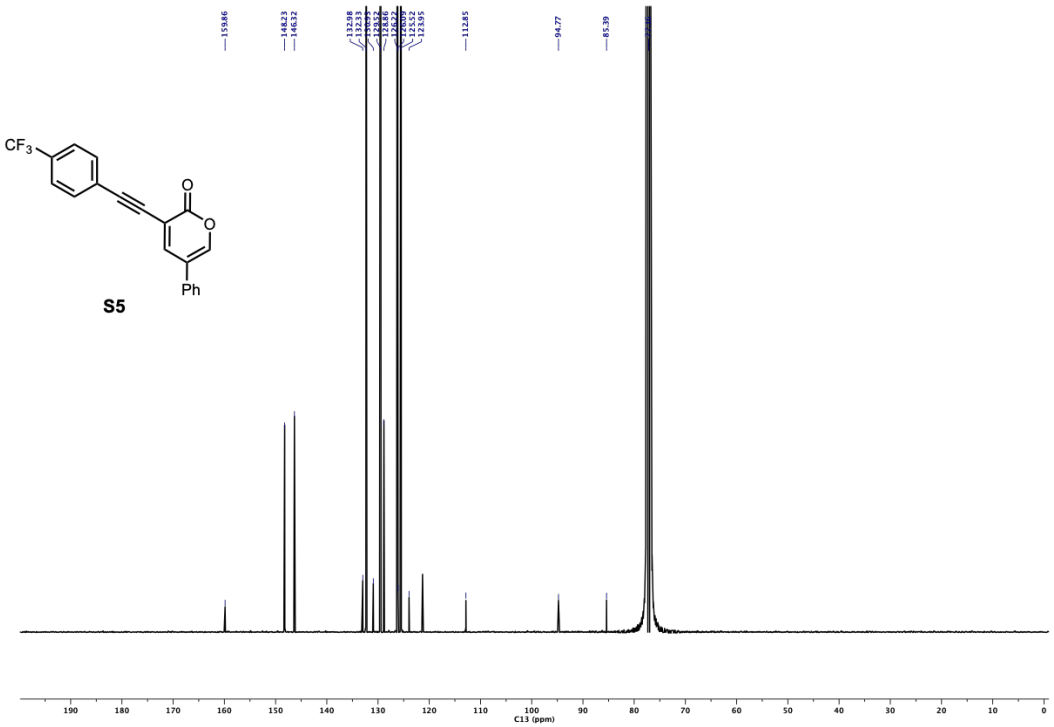
S4 (^{13}C, 151 MHz, $CDCl_3$)



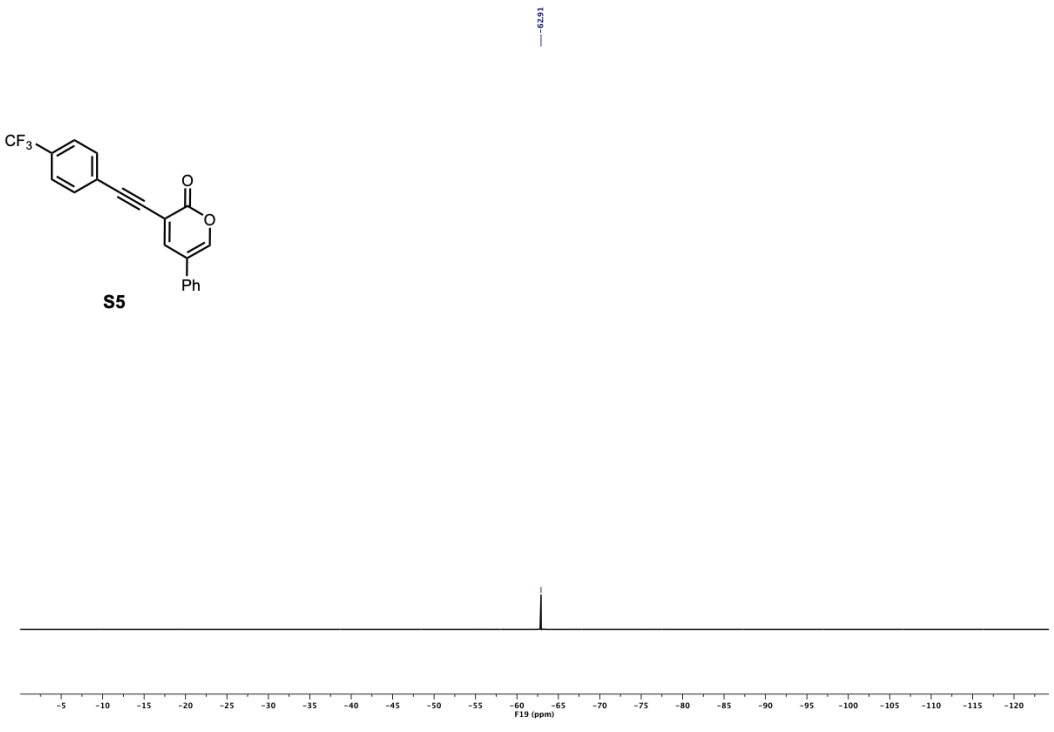
S5 (^{1}H NMR, 500 MHz, $CDCl_3$)



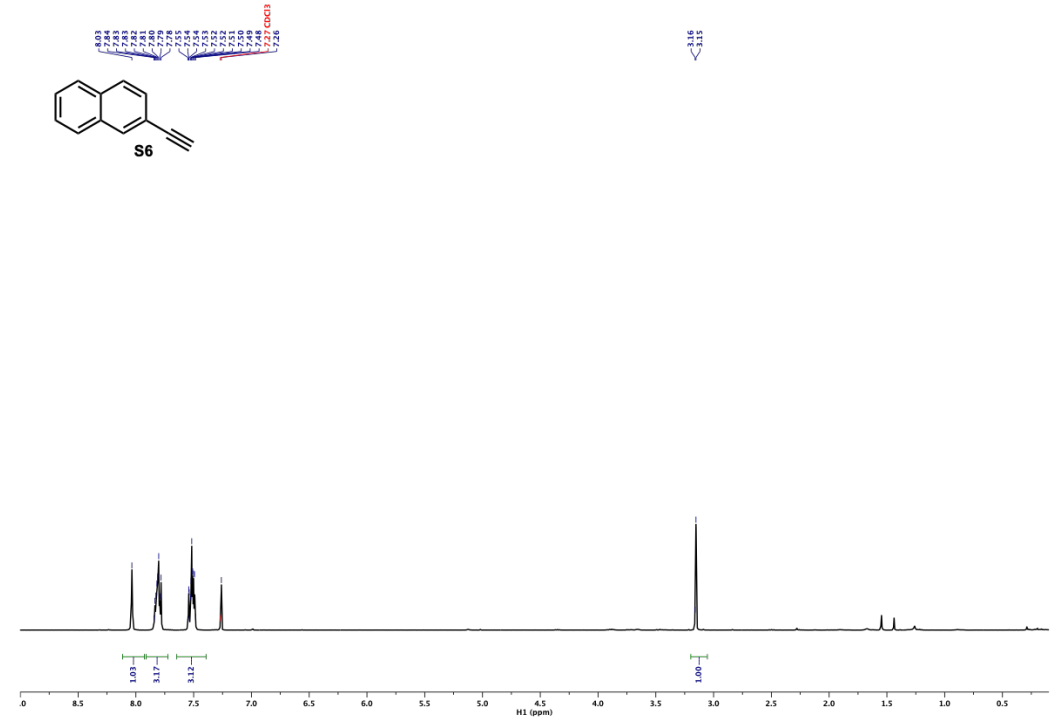
S5 ($^{13}C\{^{19}F, ^{1}H$ decoupled$\}$, 101 MHz, $CDCl_3$)



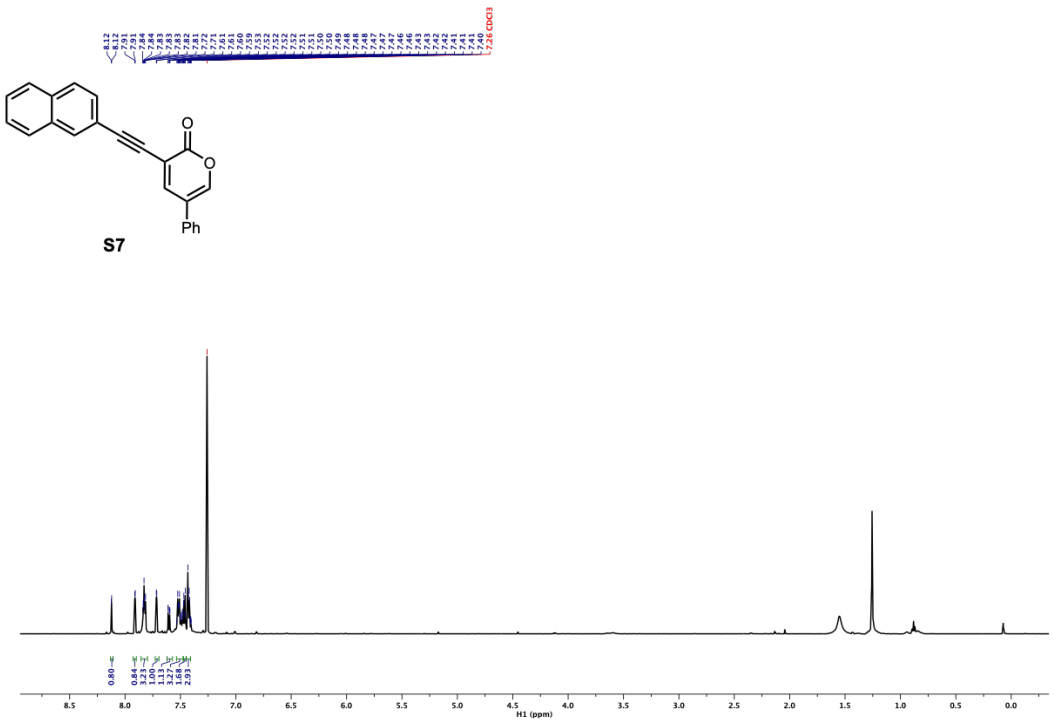
S5 (^{19}F, 471 MHz, $CDCl_3$)



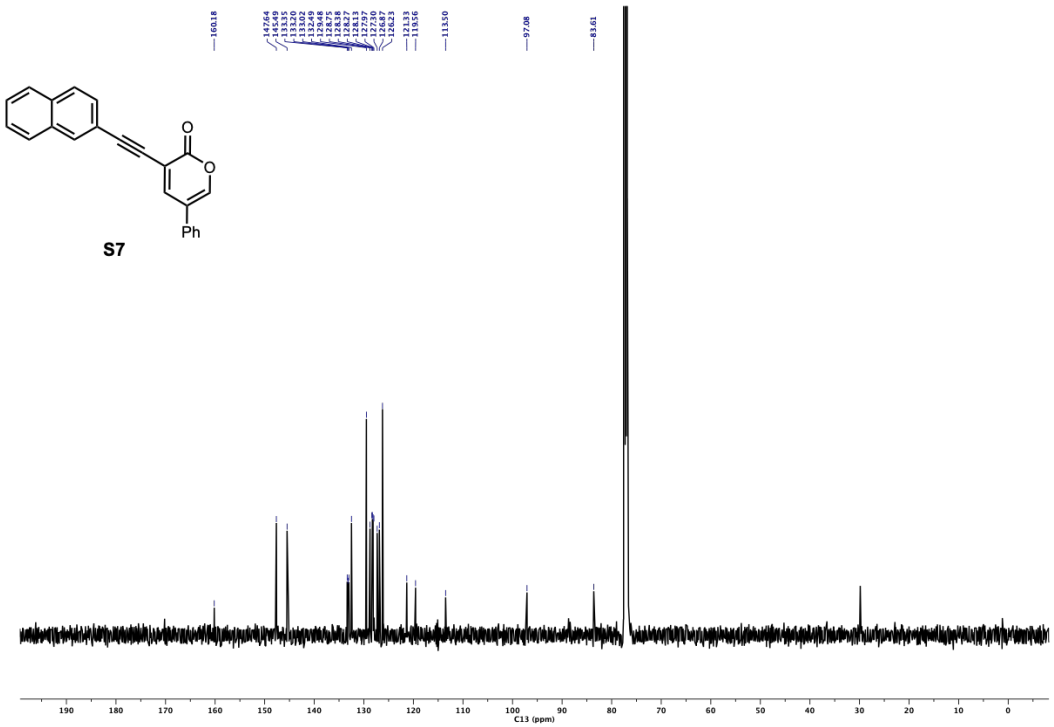
S6 (^{1}H NMR, 400 MHz, $CDCl_3$)



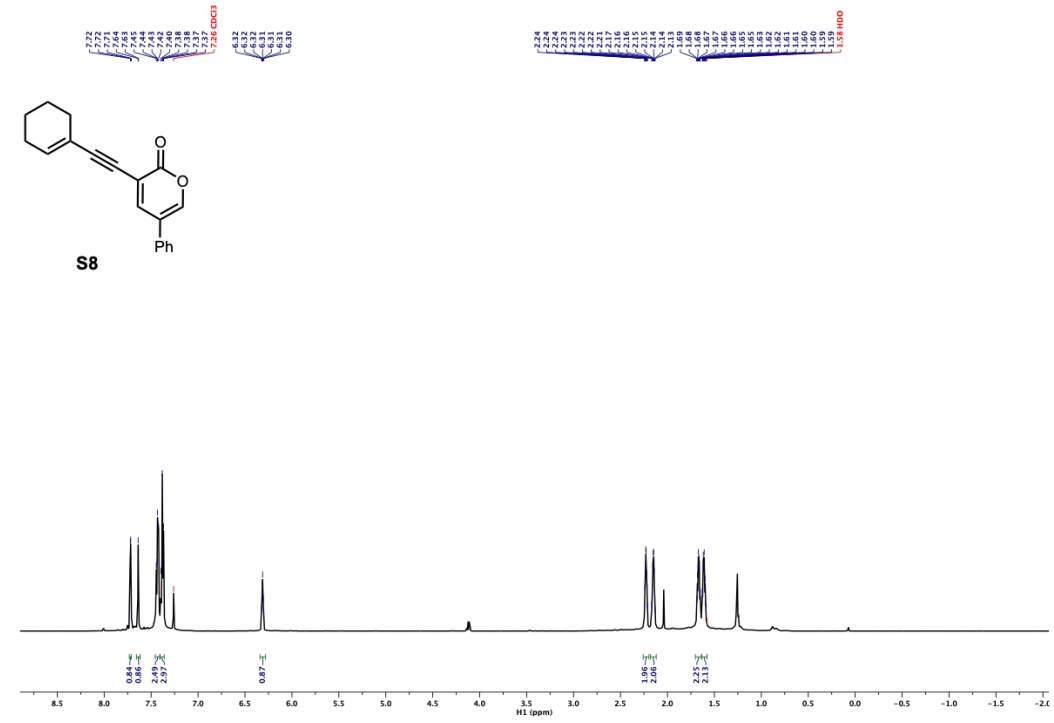
S7 (^{1}H NMR, 500 MHz, $CDCl_3$)



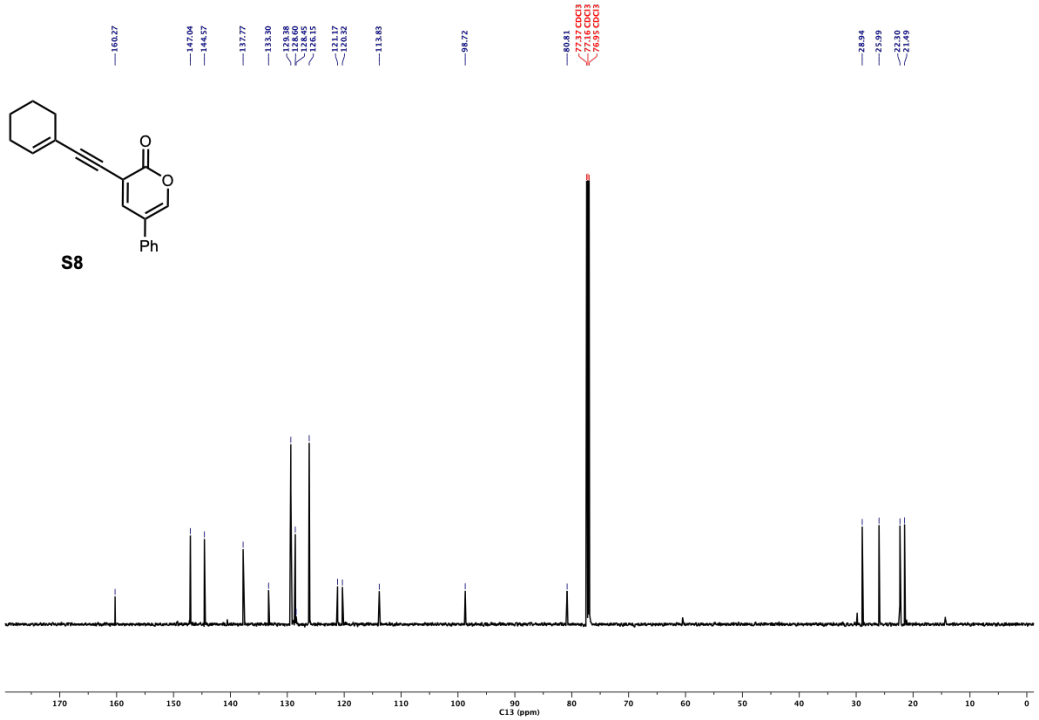
S7 (^{13}C, 126 MHz, $CDCl_3$)



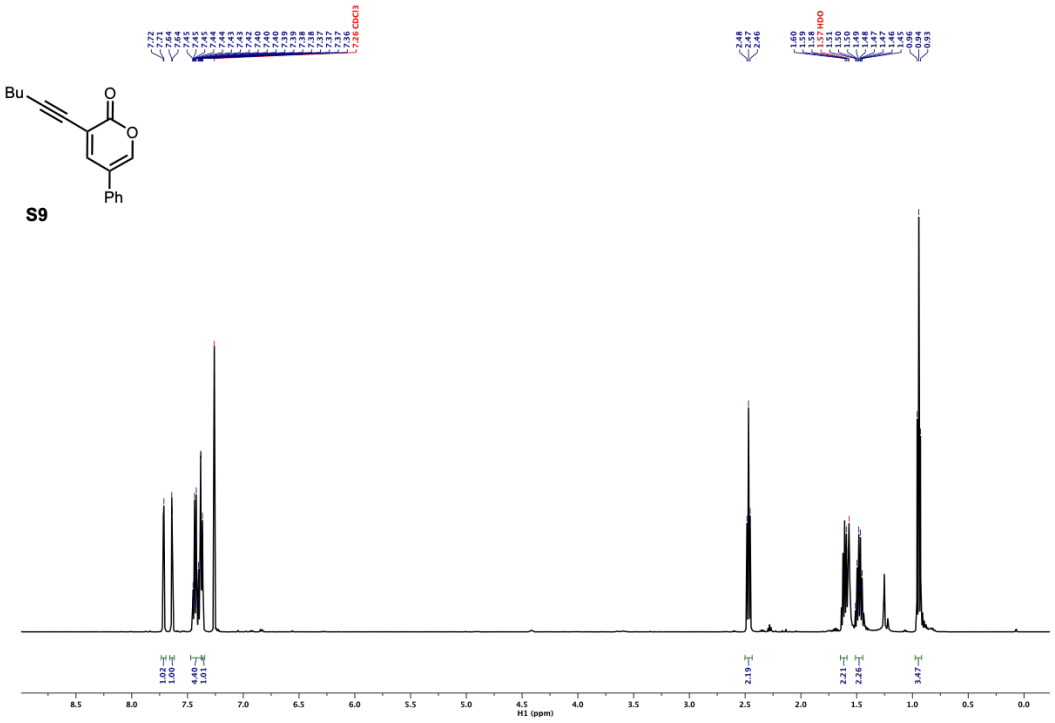
S8 (^{1}H NMR, 600 MHz, $CDCl_3$)



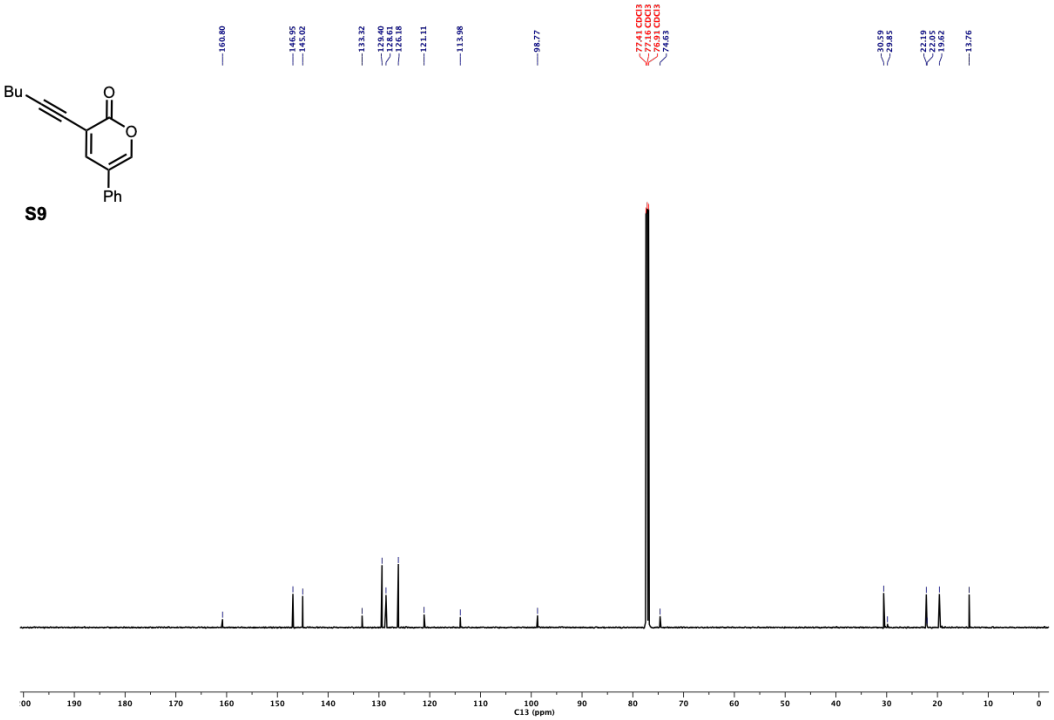
S8 (^{13}C, 151 MHz, $CDCl_3$)



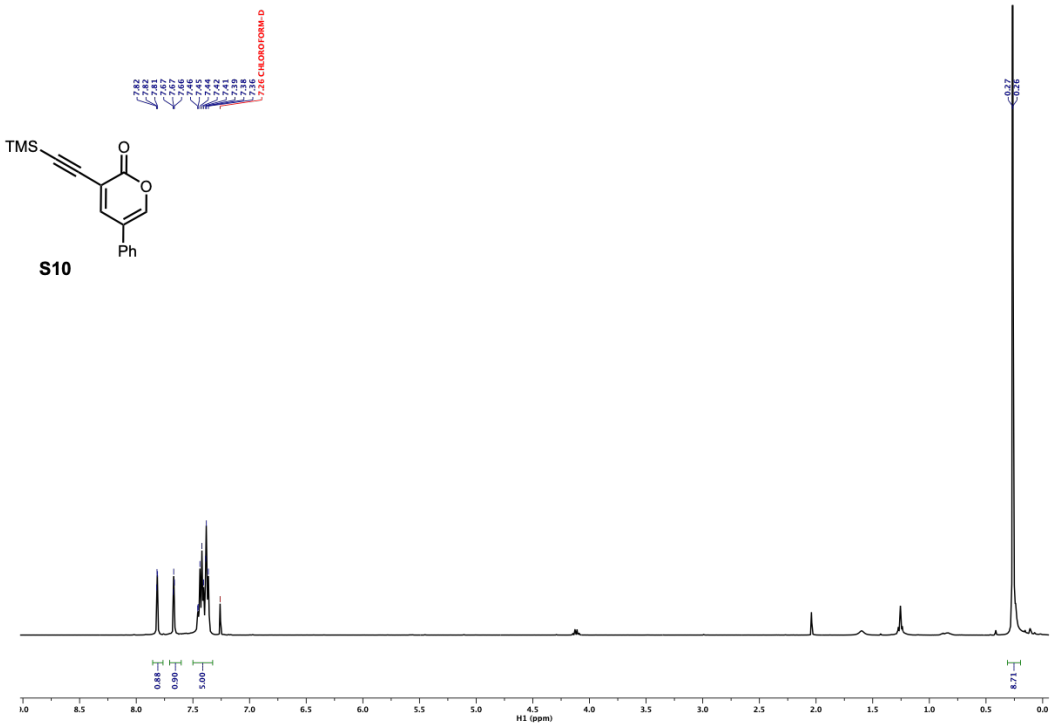
S9 (^{1}H NMR, 500 MHz, $CDCl_3$)



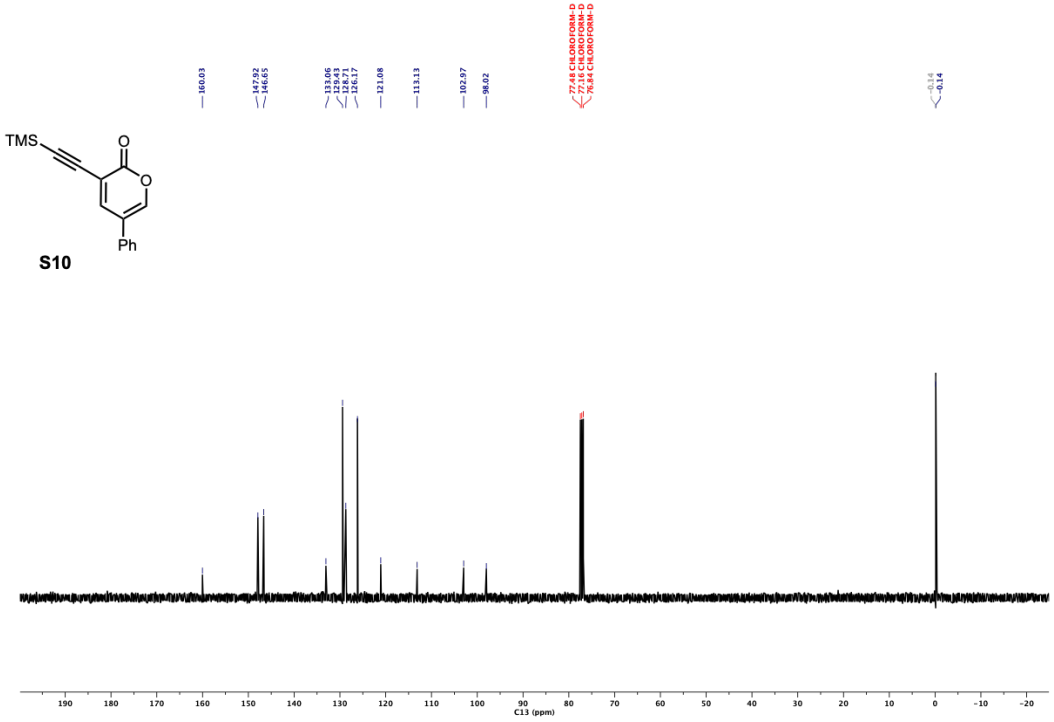
S9 (^{13}C, 126 MHz, $CDCl_3$)



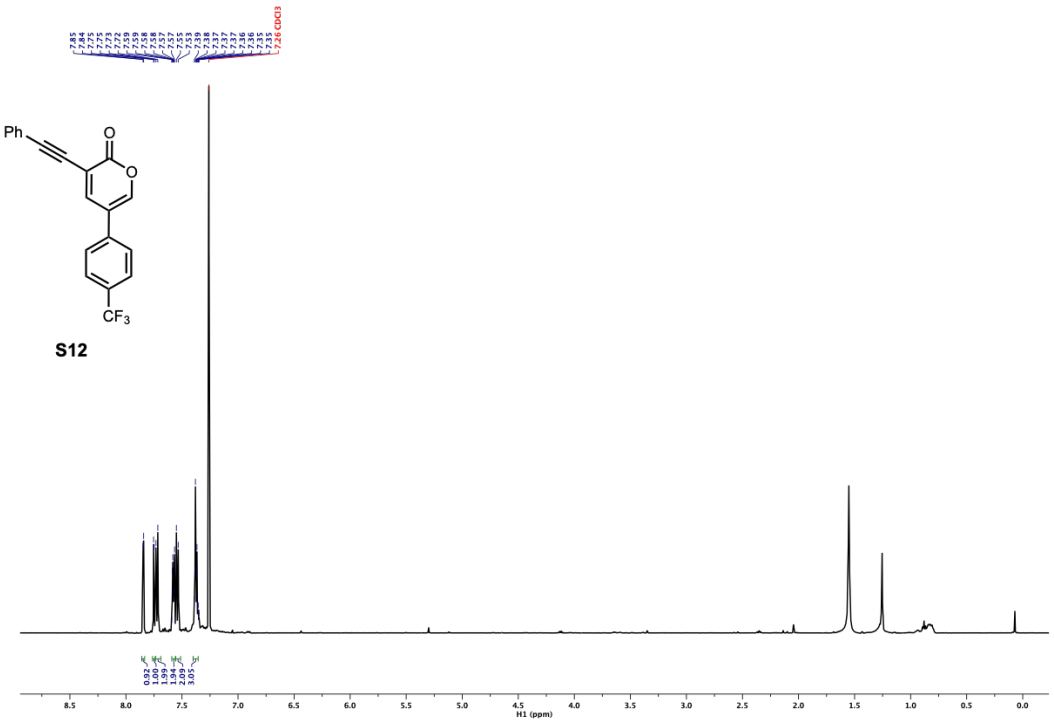
S10 (^{1}H NMR, 400 MHz, $CDCl_3$)



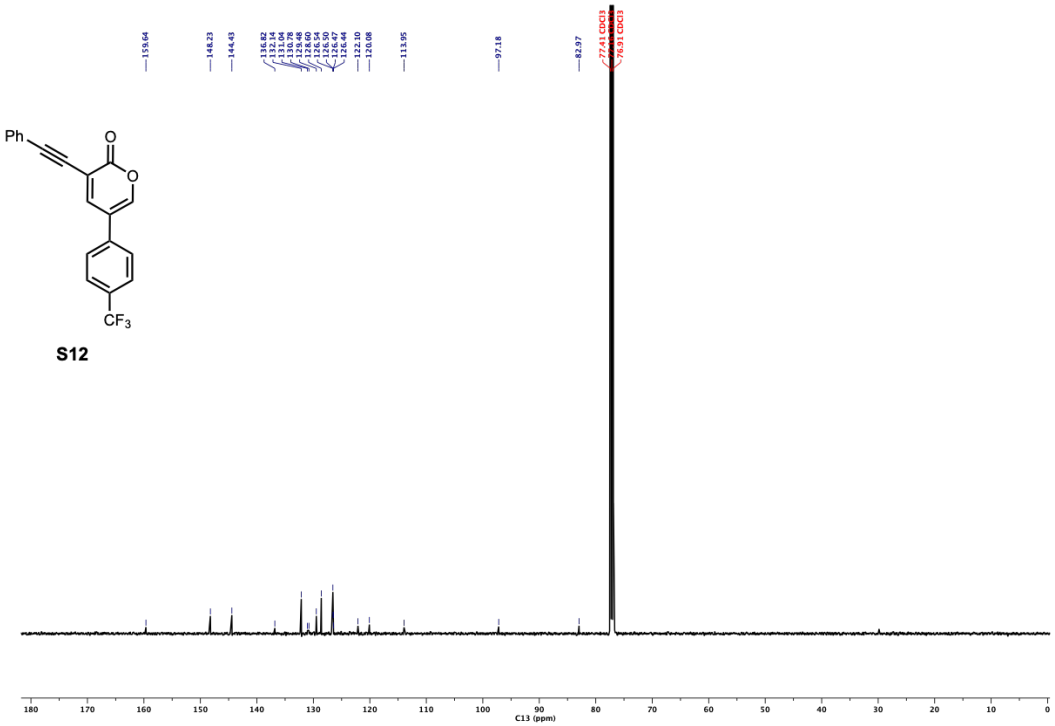
S10 (^{13}C, 101 MHz, $CDCl_3$)



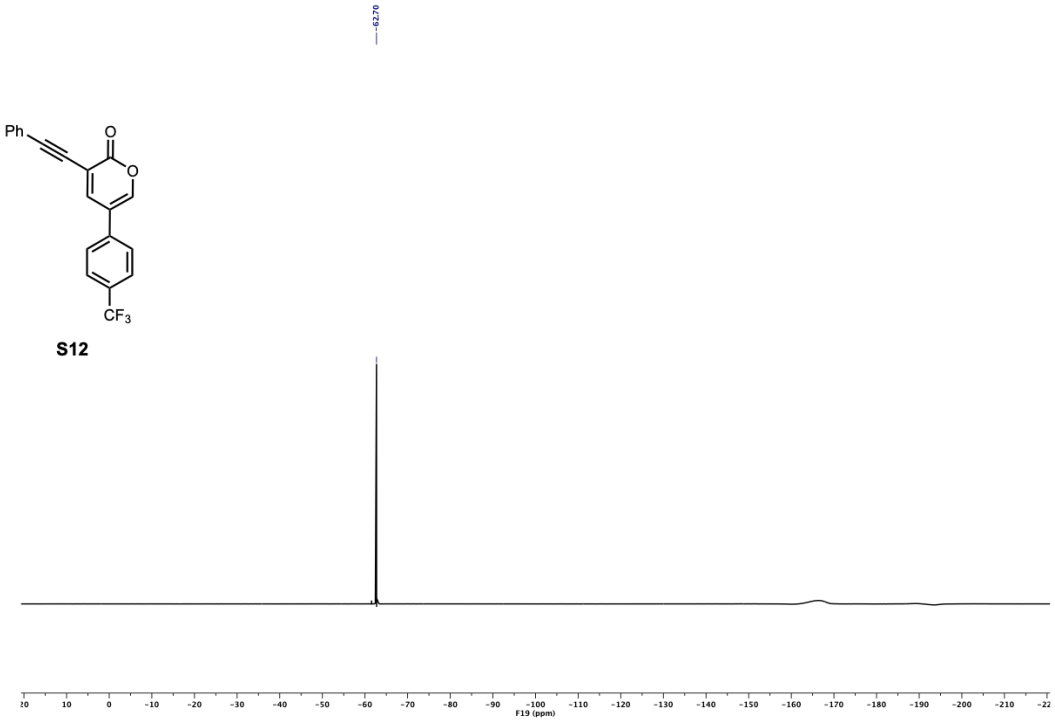
S12 (^{1}H NMR, 500 MHz, $CDCl_3$)



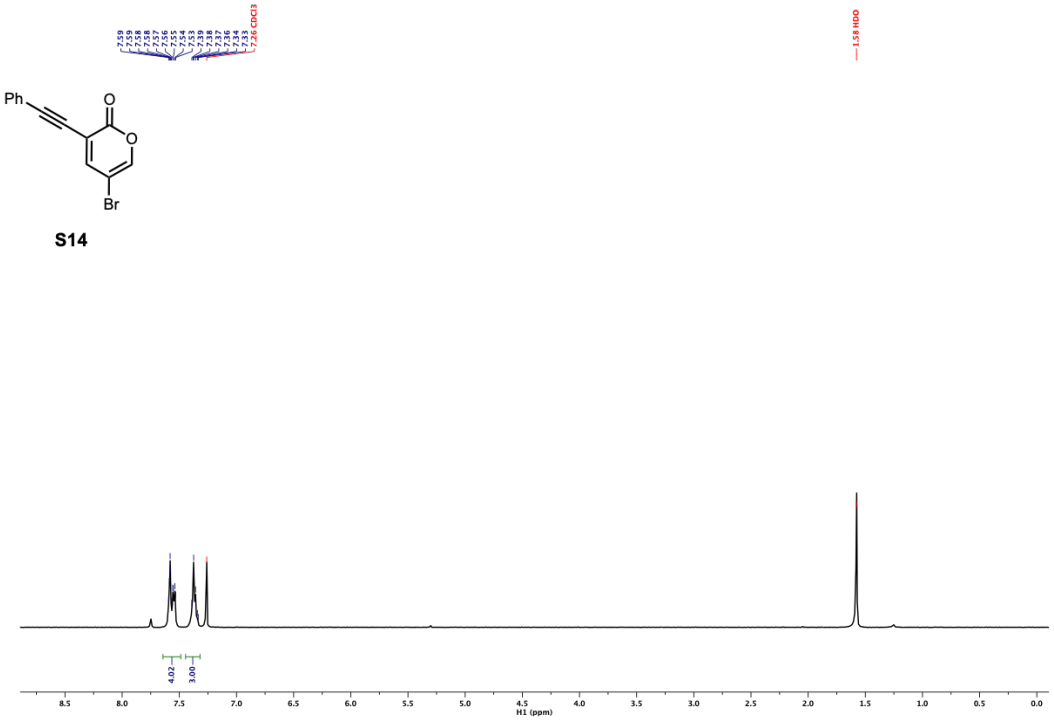
S12 (^{13}C, 151 MHz, $CDCl_3$)



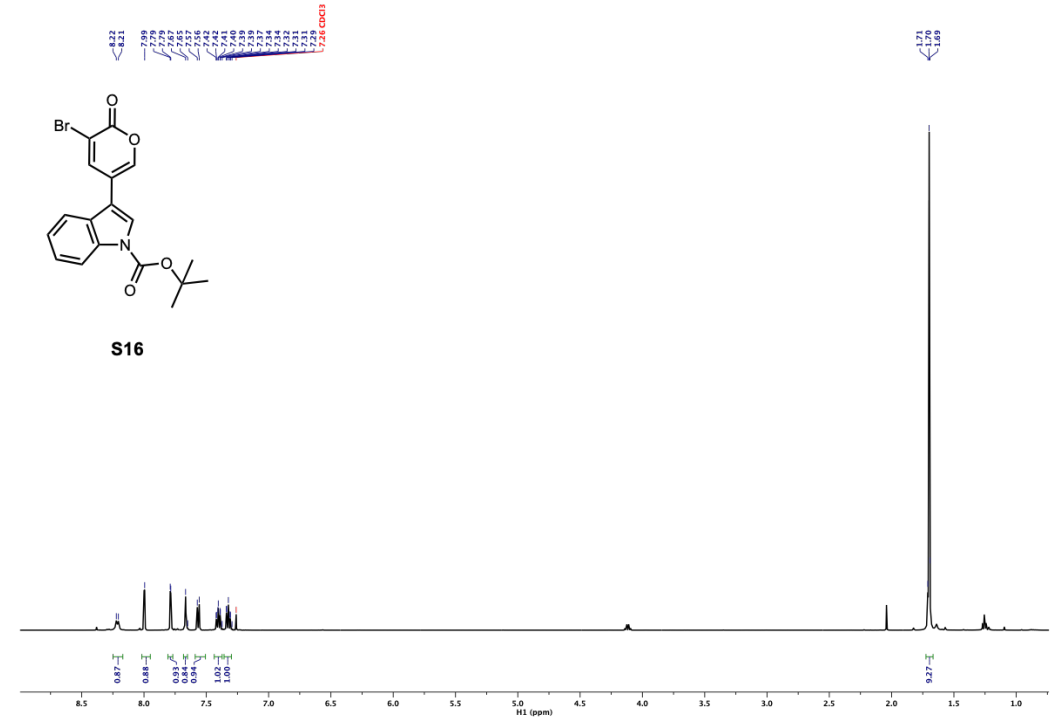
S12 (^{19}F, 471 MHz, $CDCl_3$)



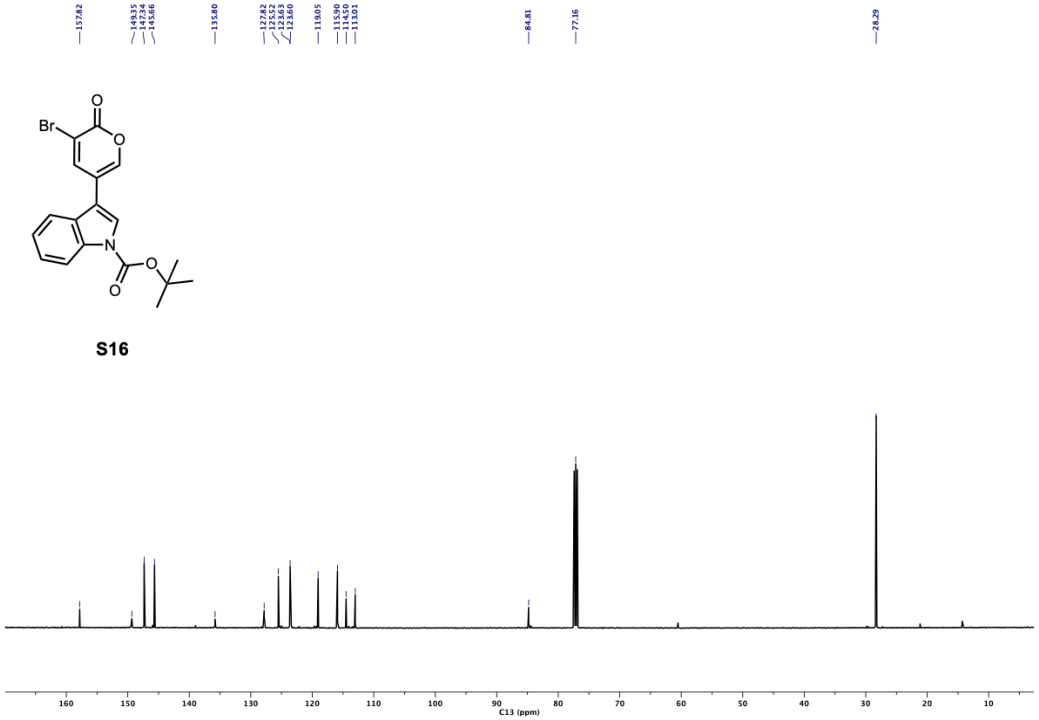
S14 (^{1}H NMR, 400 MHz, $CDCl_3$)



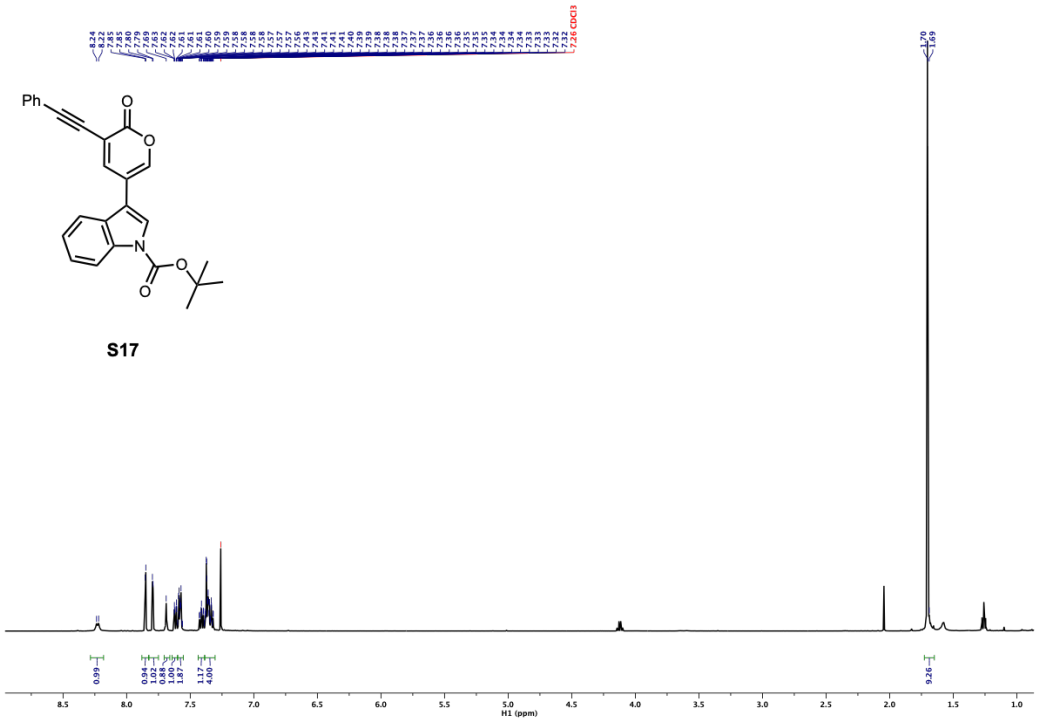
S16 (^{1}H NMR, 500 MHz, $CDCl_3$)



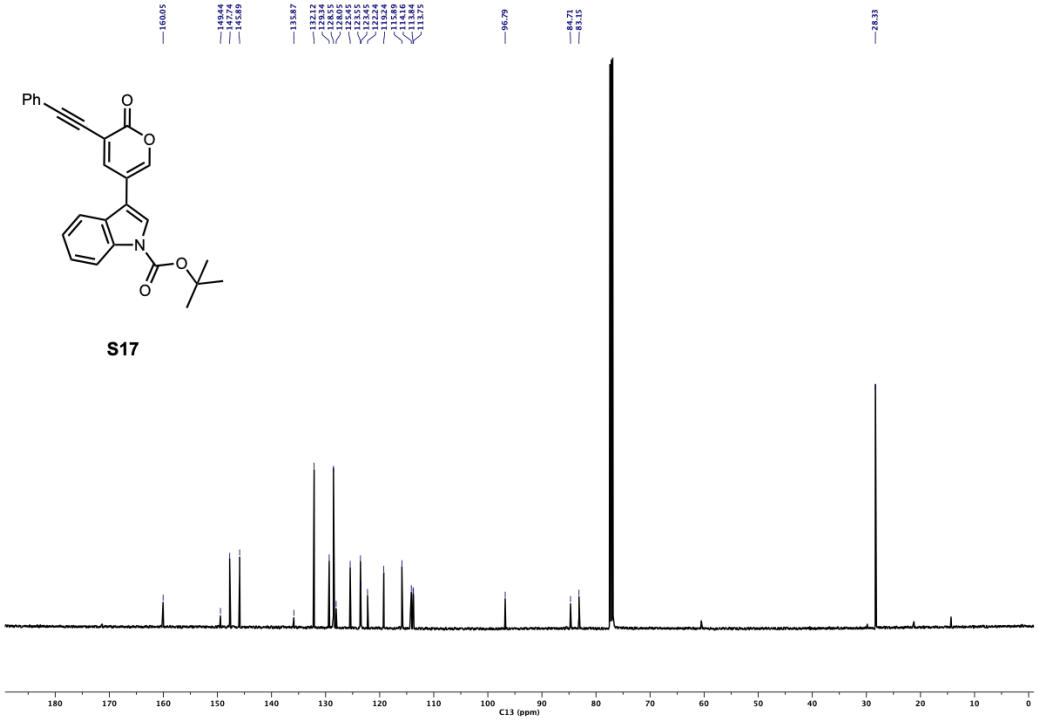
S16 (^{13}C, 126 MHz, $CDCl_3$)



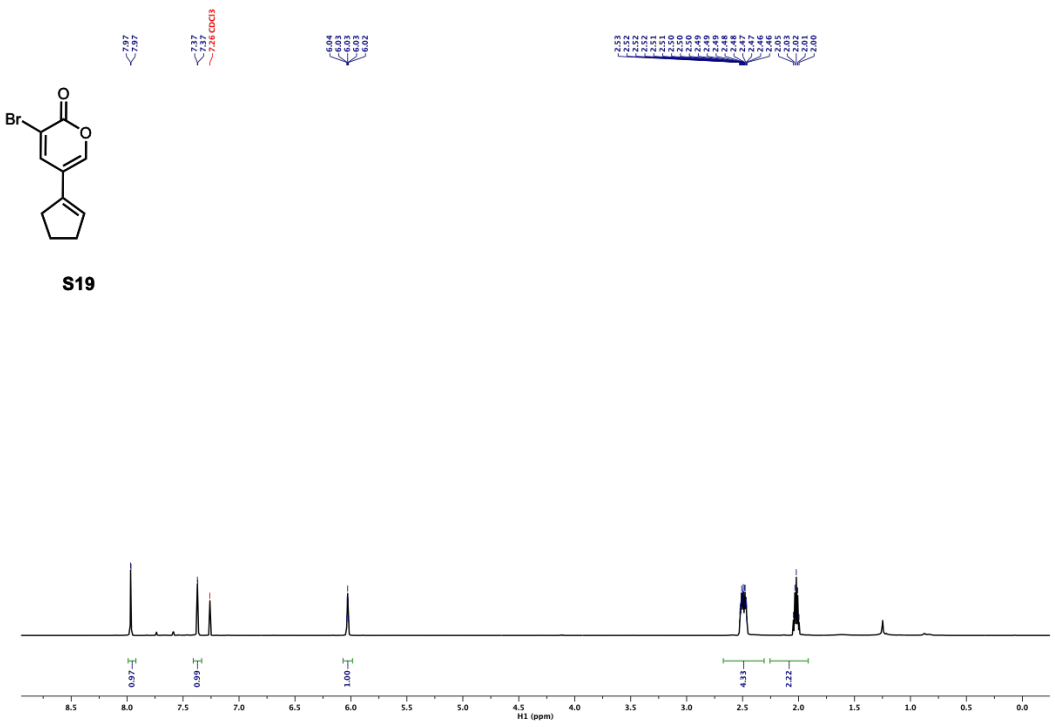
S17 (^{1}H NMR, 500 MHz, $CDCl_3$)



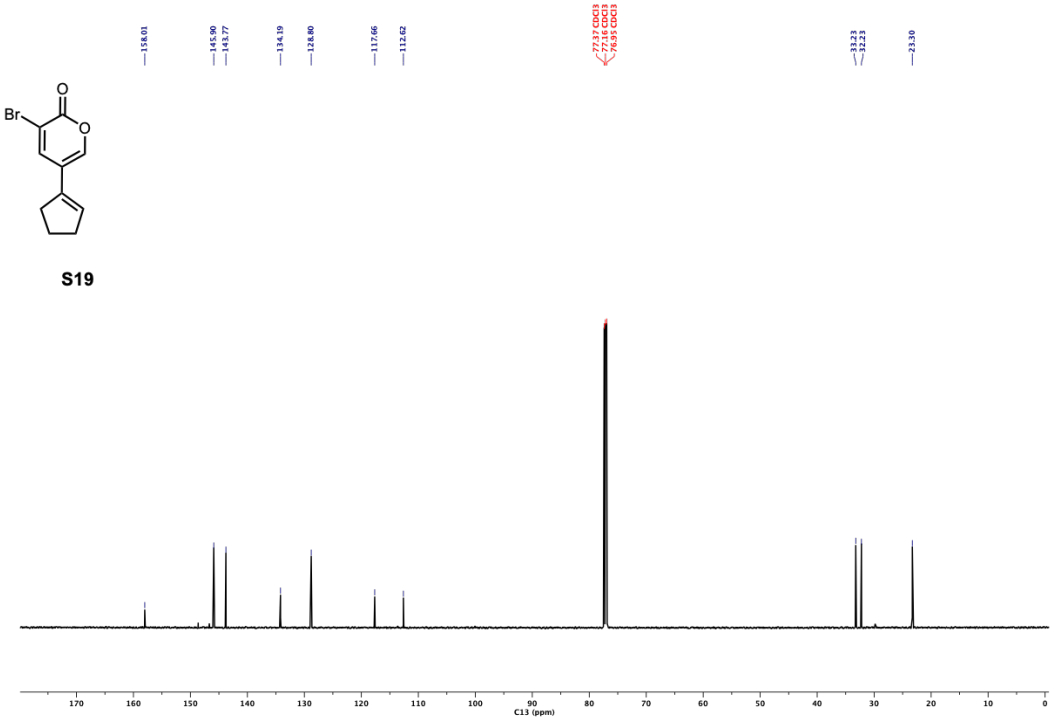
S17 (^{13}C, 126 MHz, $CDCl_3$)



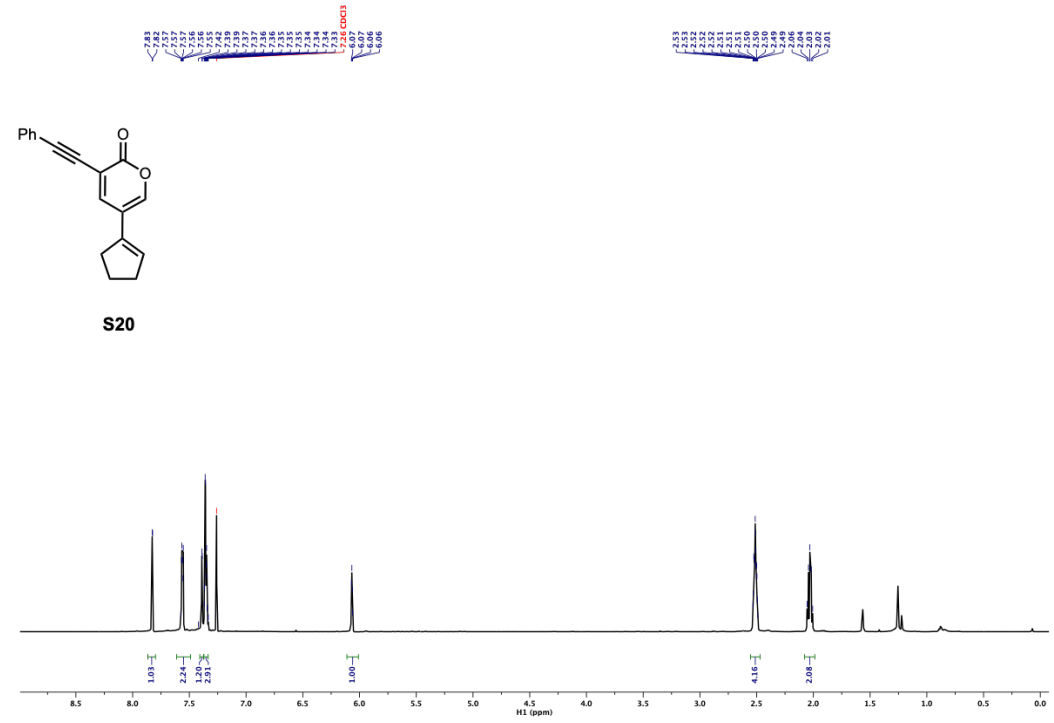
S19 (^{1}H NMR, 600 MHz, $CDCl_3$)



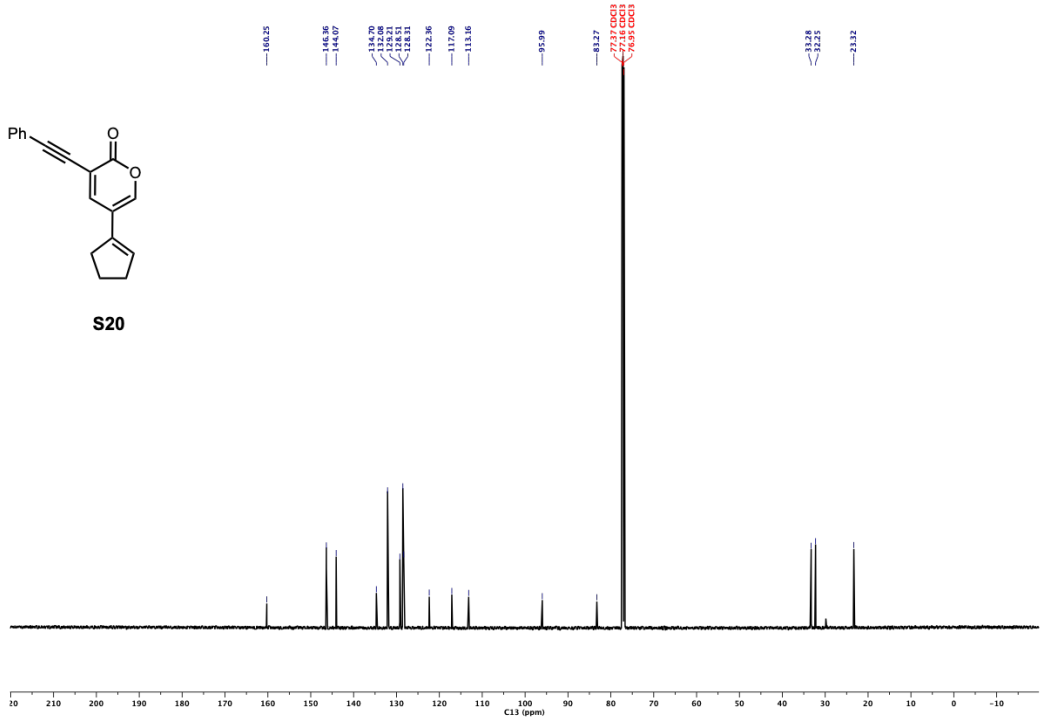
S19 (^{13}C, 151 MHz, $CDCl_3$)



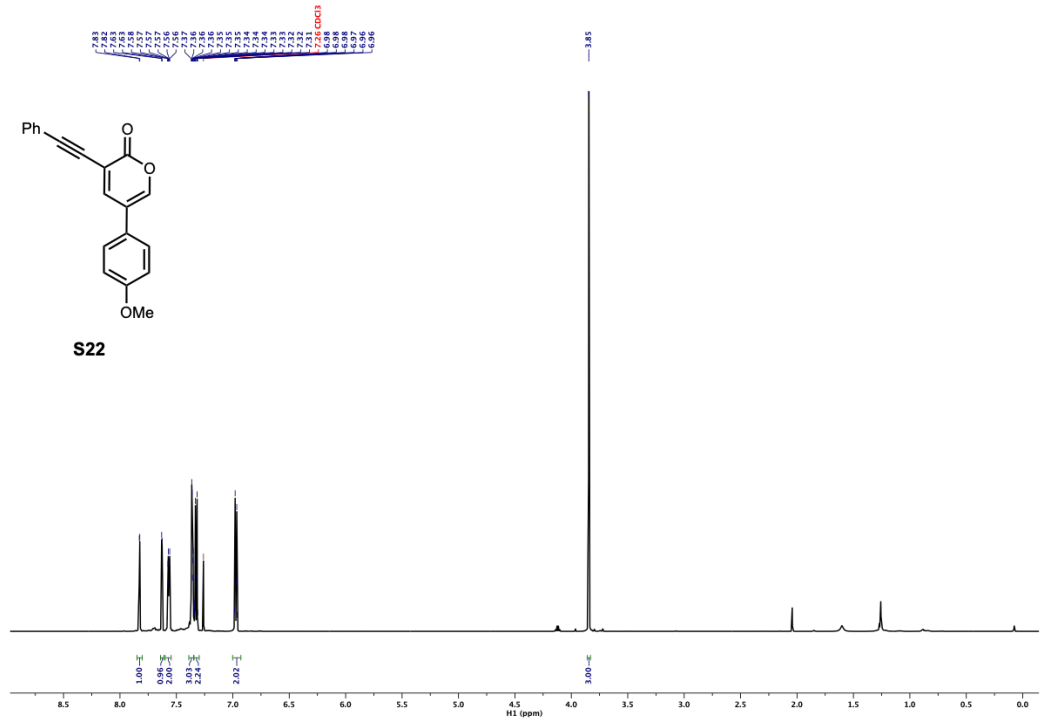
S20 (^{1}H NMR, 600 MHz, $CDCl_3$)



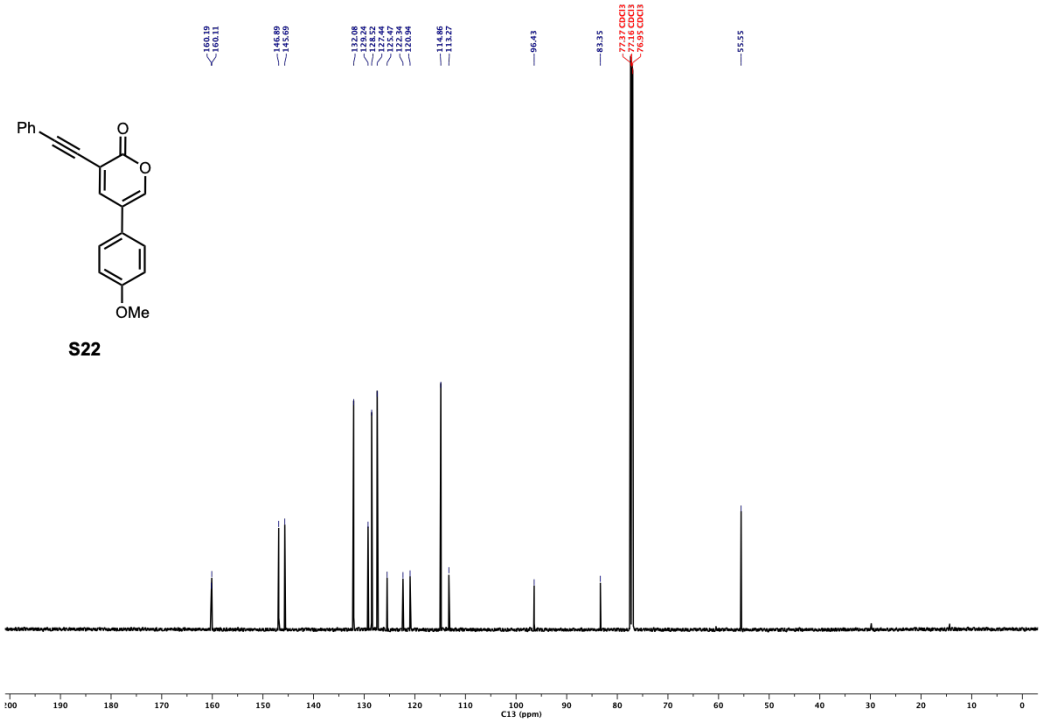
S20 (^{13}C, 151 MHz, $CDCl_3$)



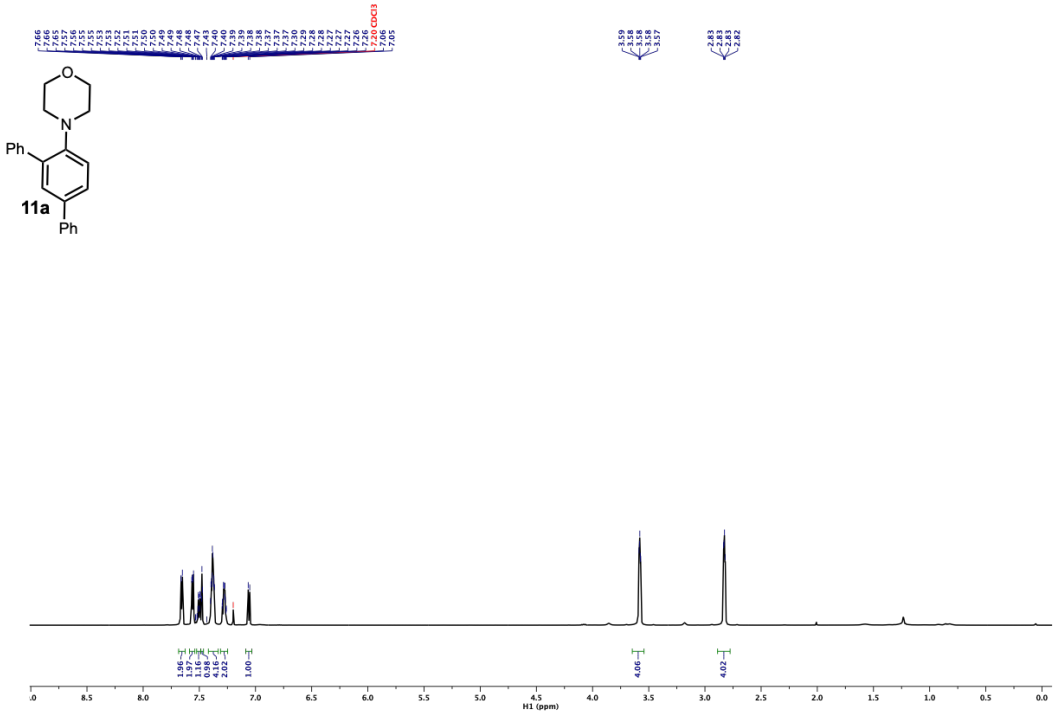
S22 (^{1}H NMR, 600 MHz, $CDCl_3$)



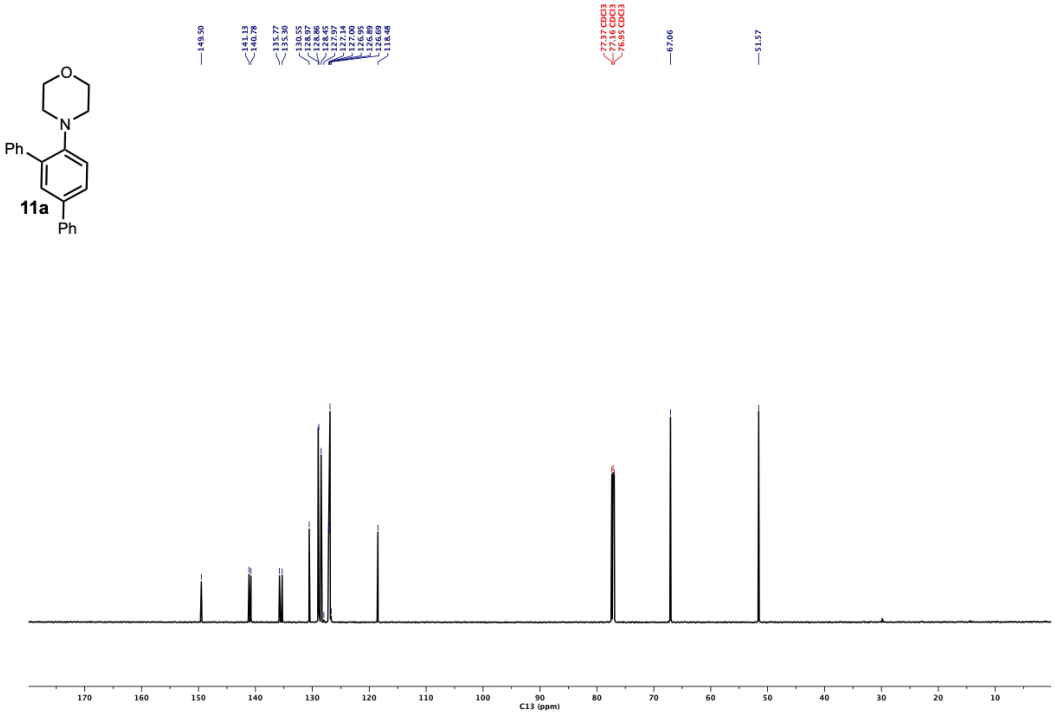
S22 (^{13}C, 151 MHz, $CDCl_3$)



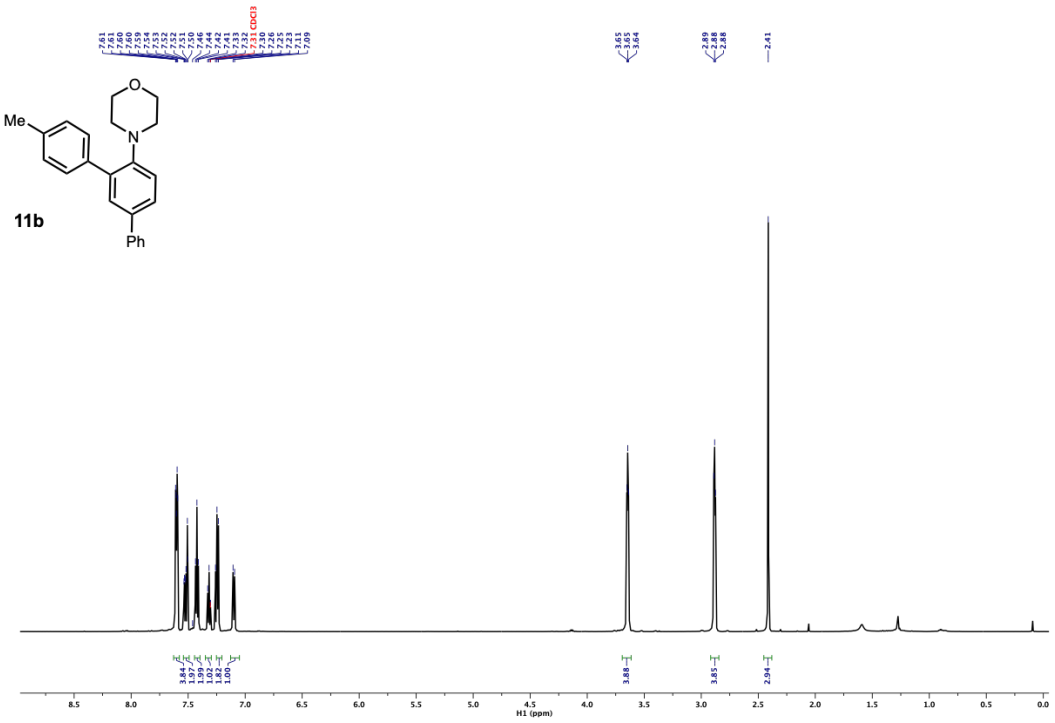
11a (^{1}H NMR, 600 MHz, $CDCl_3$)



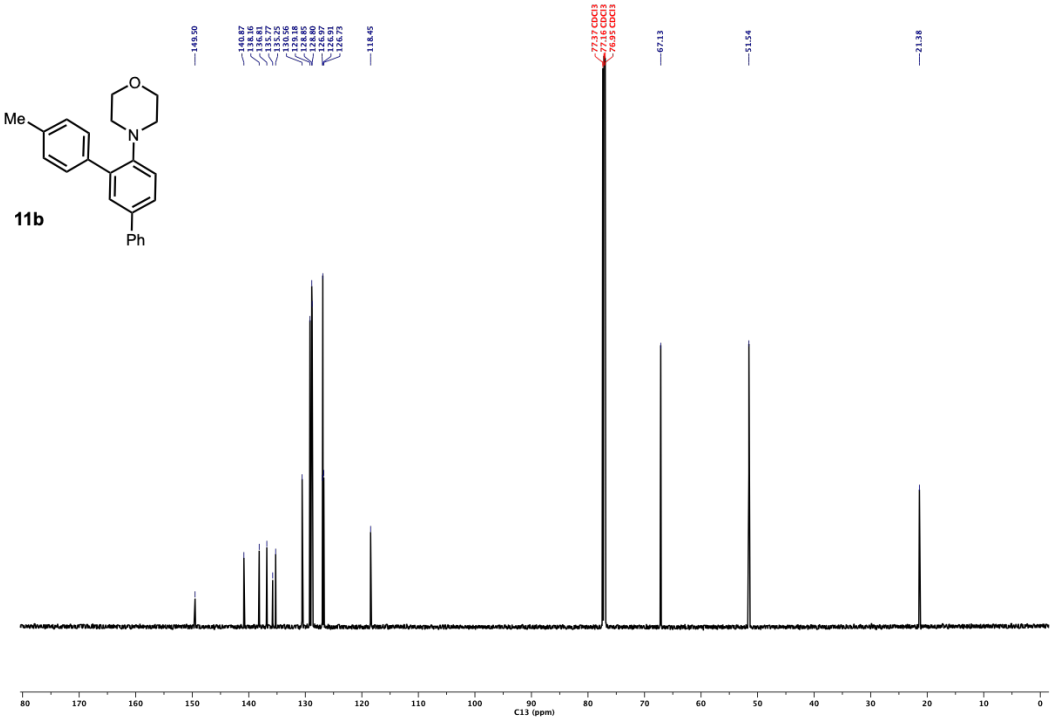
11a (^{13}C, 151 MHz, $CDCl_3$)



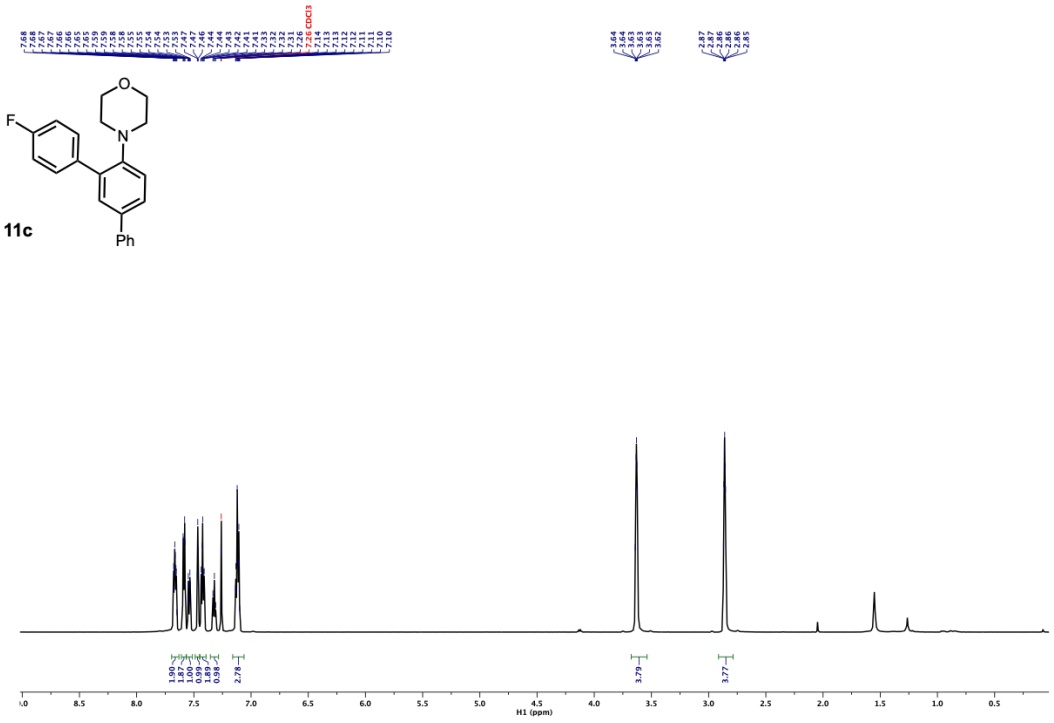
11b (^{1}H NMR, 600 MHz, $CDCl_3$)



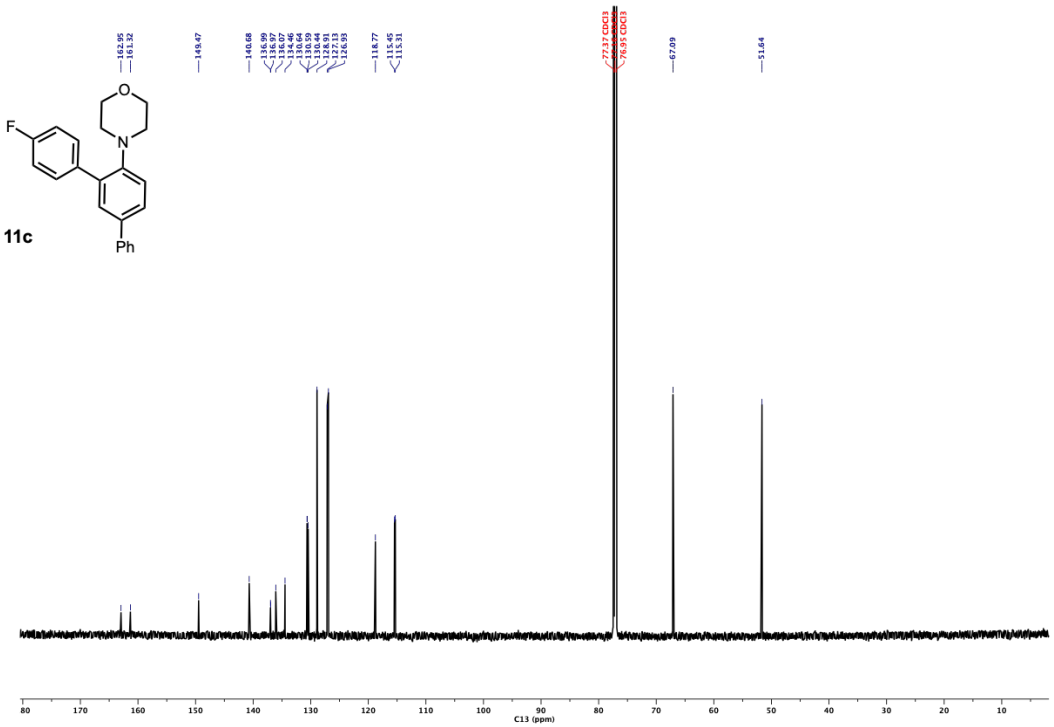
11b (^{13}C, 151 MHz, $CDCl_3$)



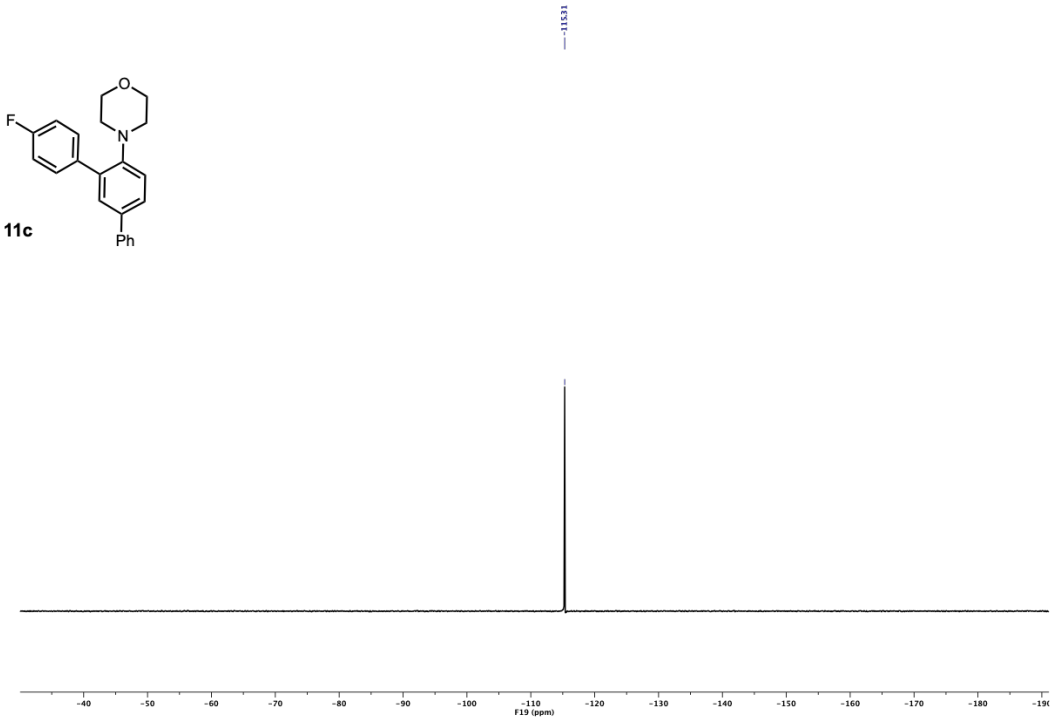
11c (^{1}H NMR, 600 MHz, $CDCl_3$)



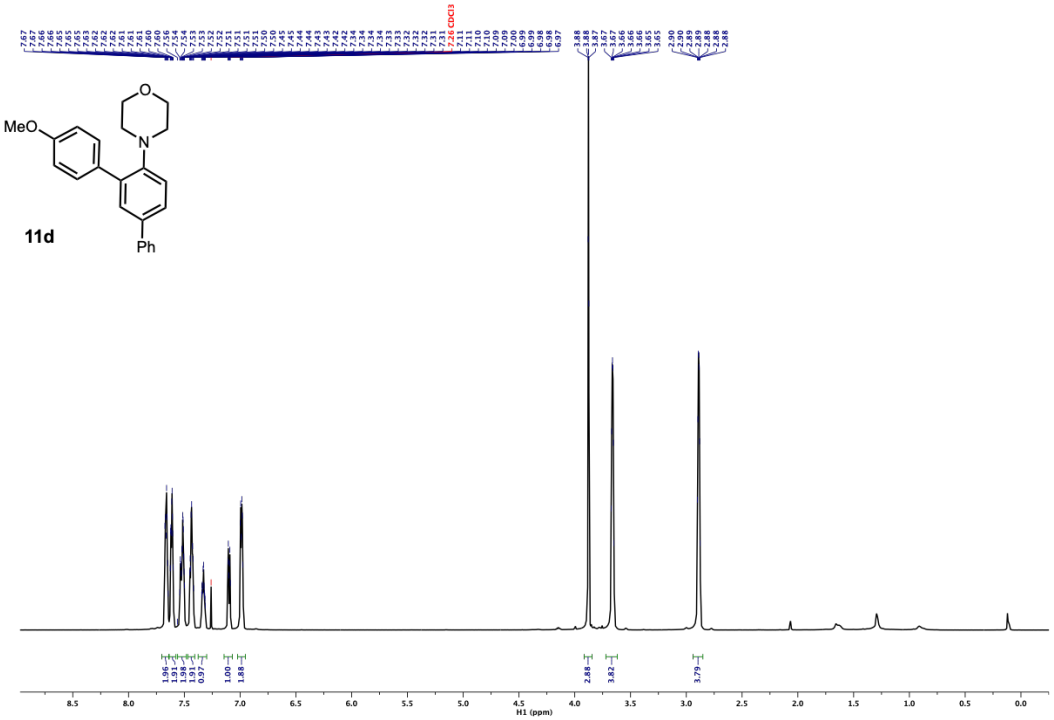
11c (^{13}C, 151 MHz, $CDCl_3$)



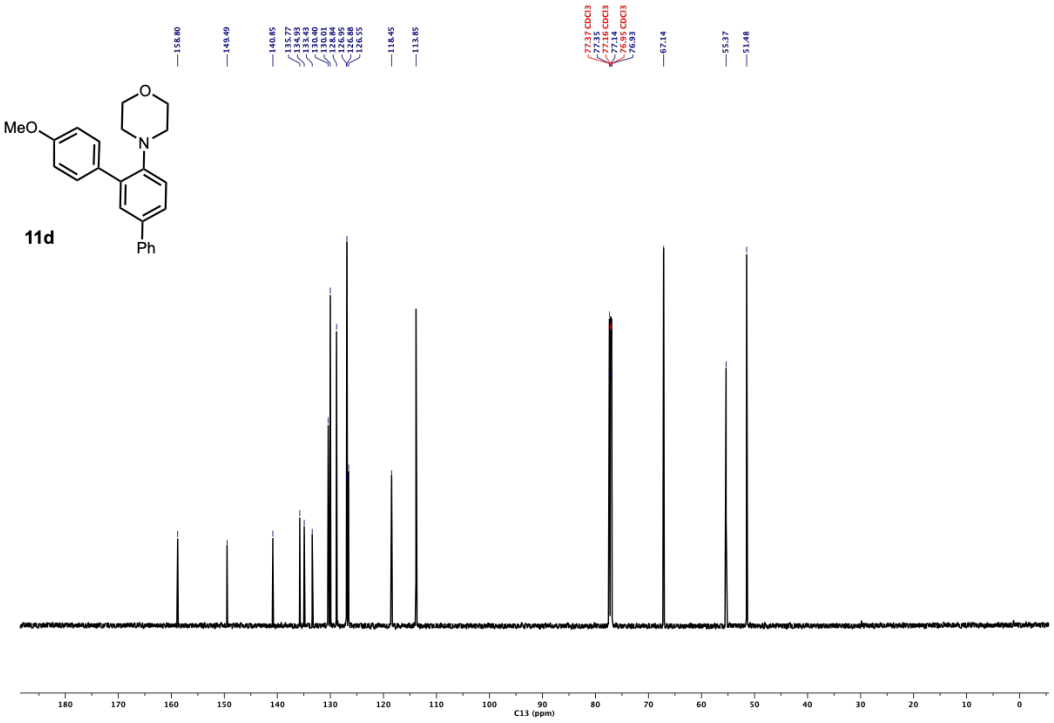
11c (^{19}F, 470 MHz, $CDCl_3$)



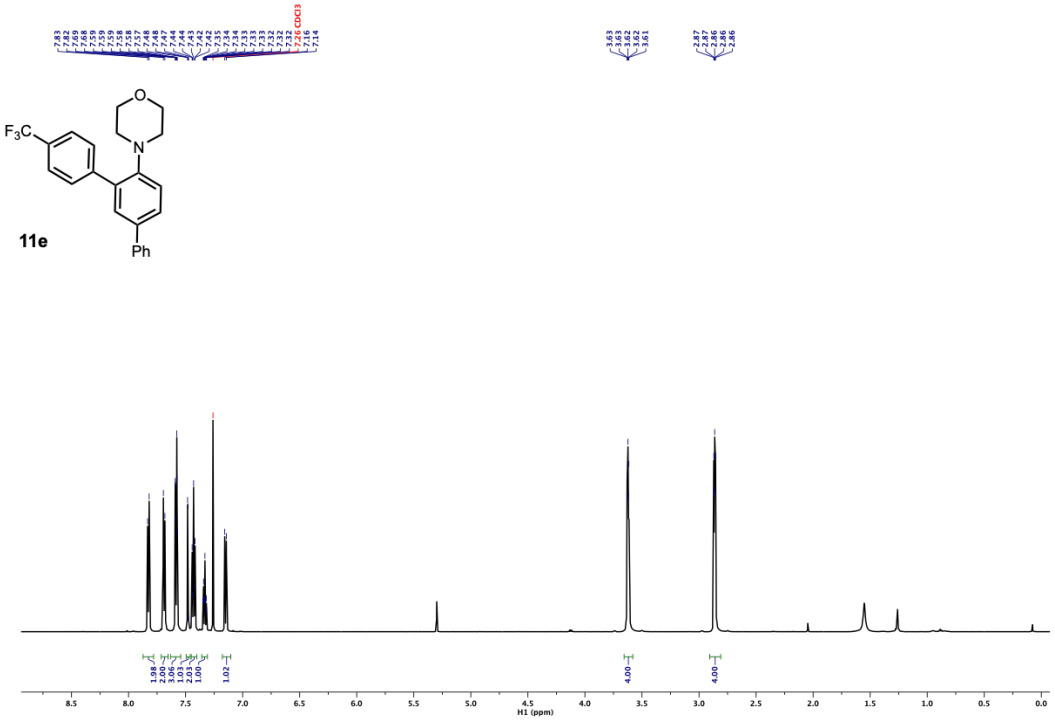
11d (^{1}H NMR, 600 MHz, $CDCl_3$)



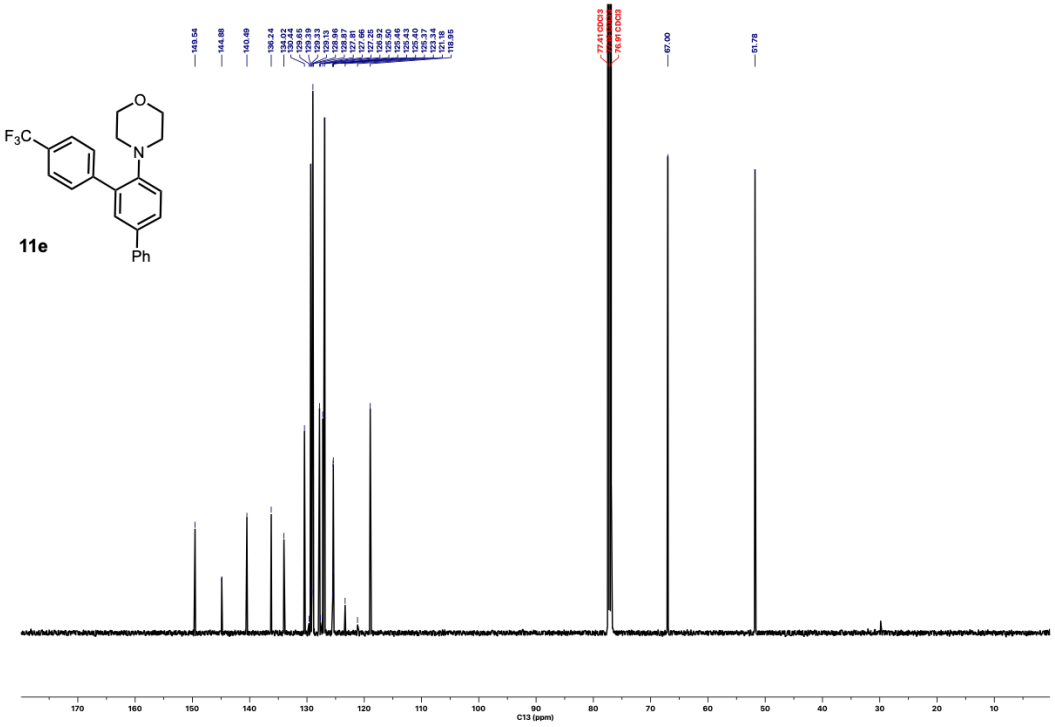
11d (^{13}C, 151 MHz, $CDCl_3$)



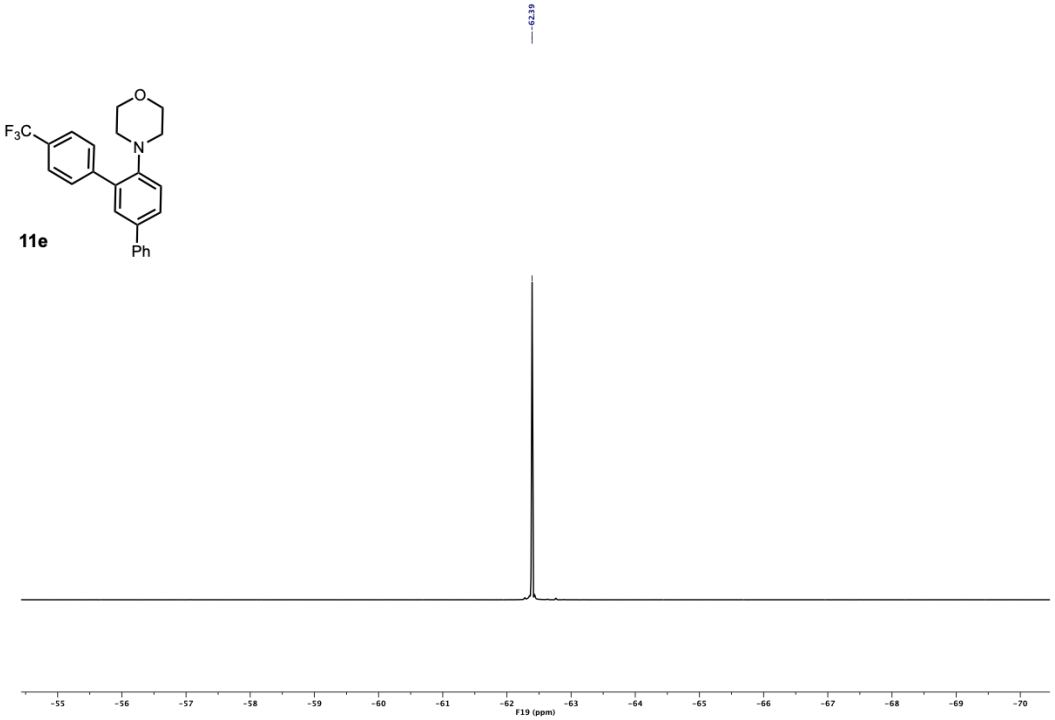
11e (^{1}H NMR, 600 MHz, $CDCl_3$)



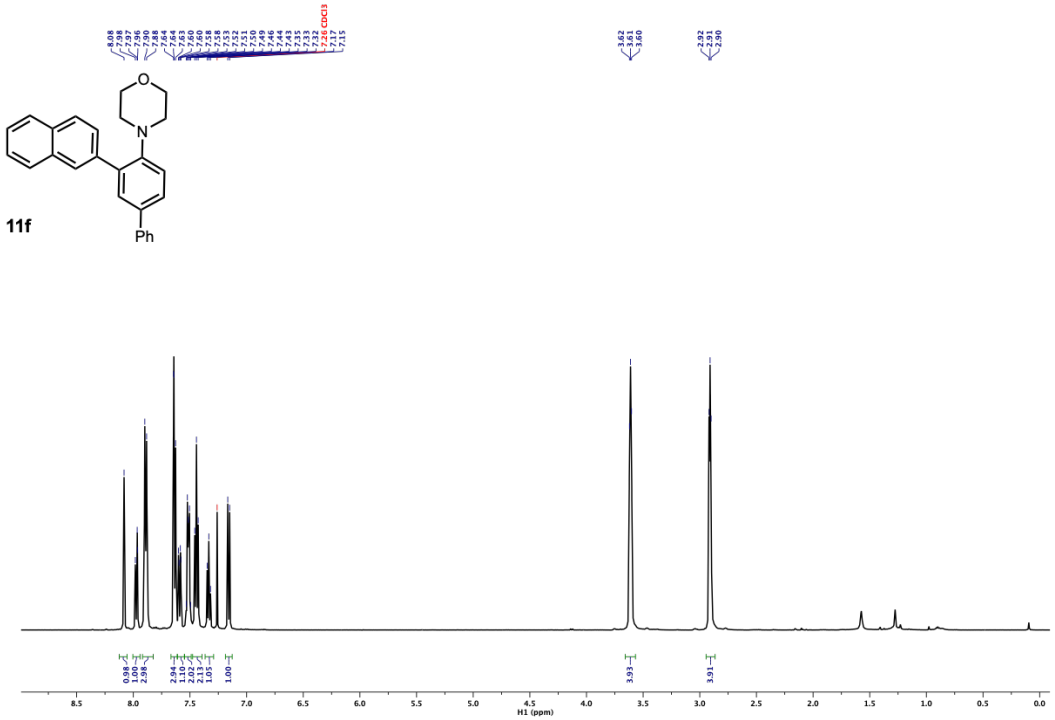
11e (^{13}C, 151 MHz, $CDCl_3$)



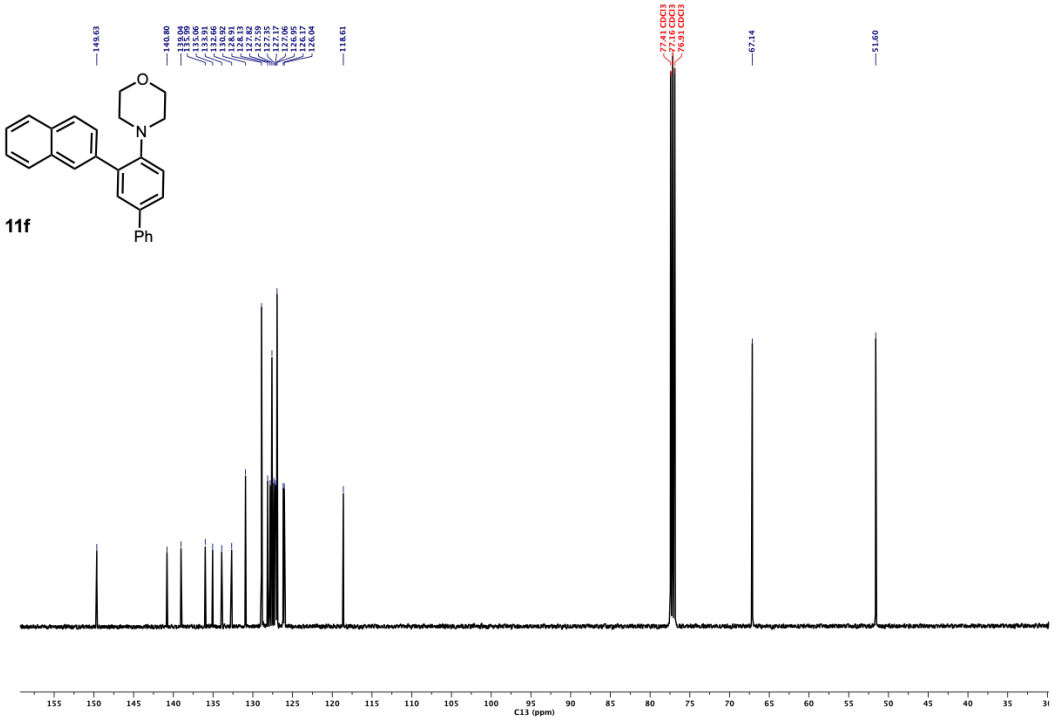
11e (^{19}F, 470 MHz, $CDCl_3$)



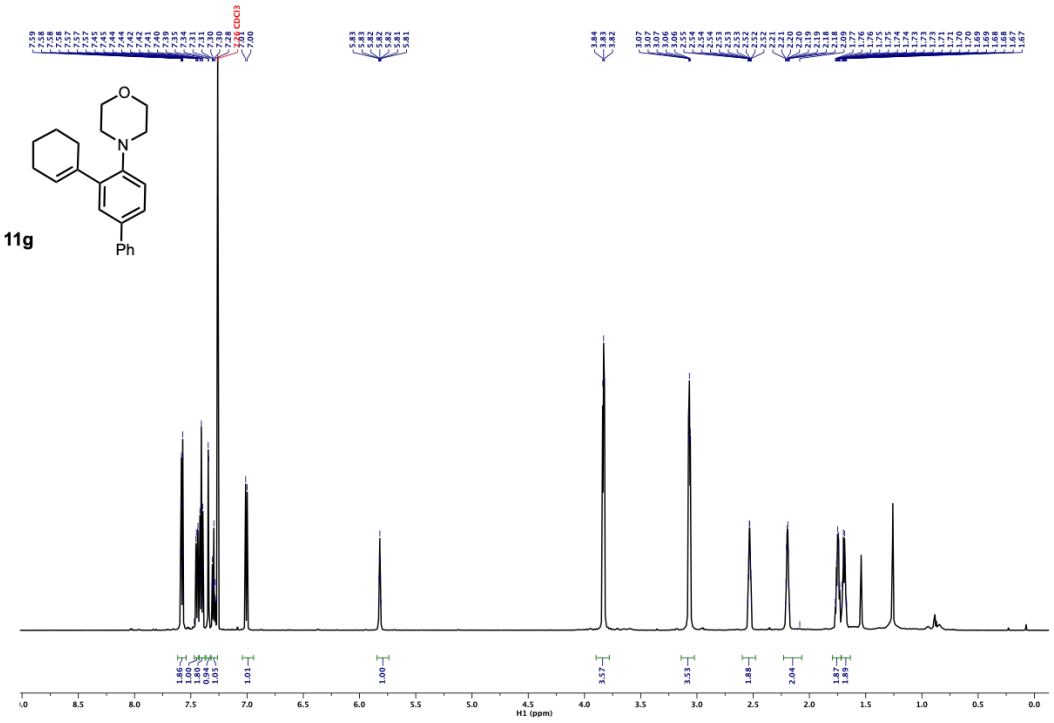
11f (^{1}H NMR, 500 MHz, $CDCl_3$)



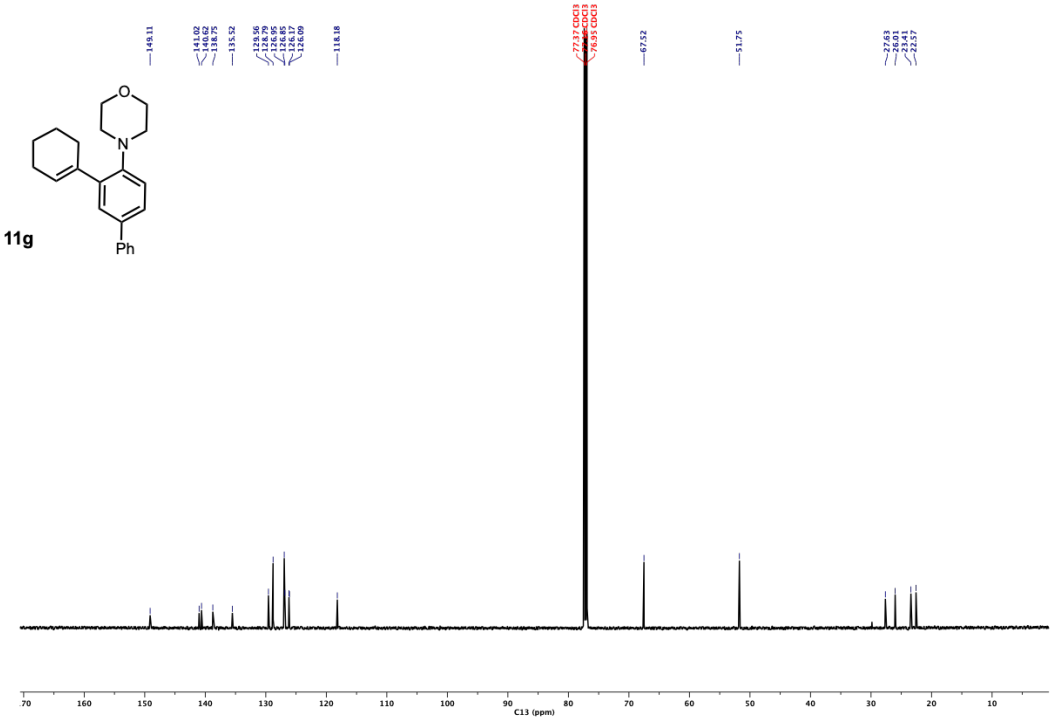
11f (^{13}C, 126 MHz, $CDCl_3$)



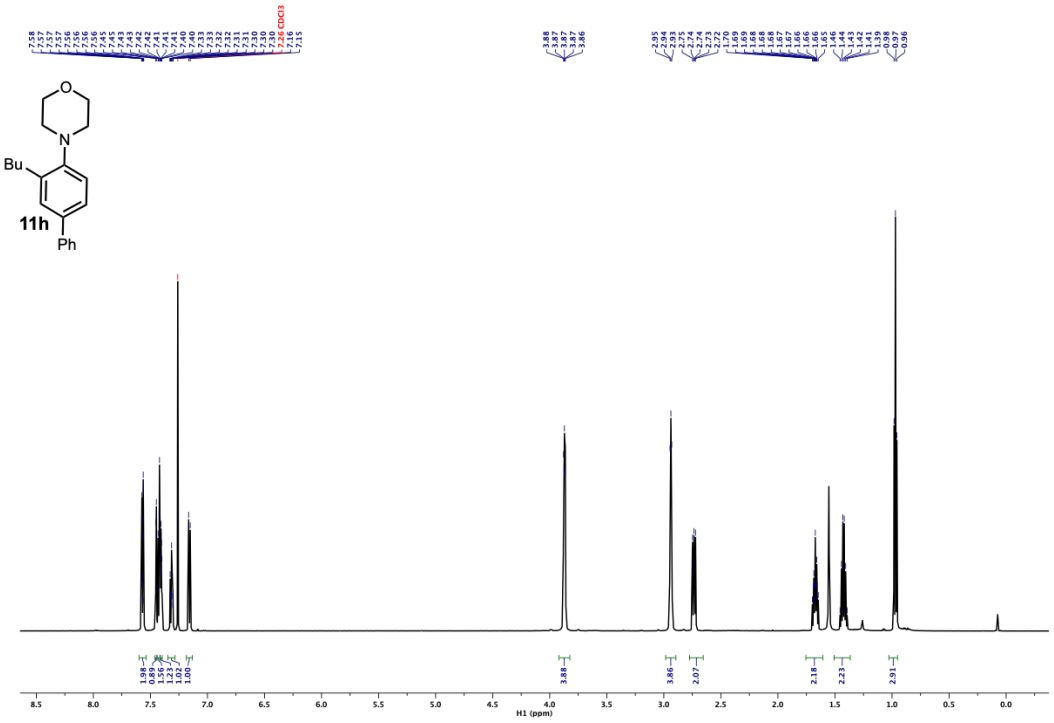
11g (^{1}H NMR, 600 MHz, $CDCl_3$)



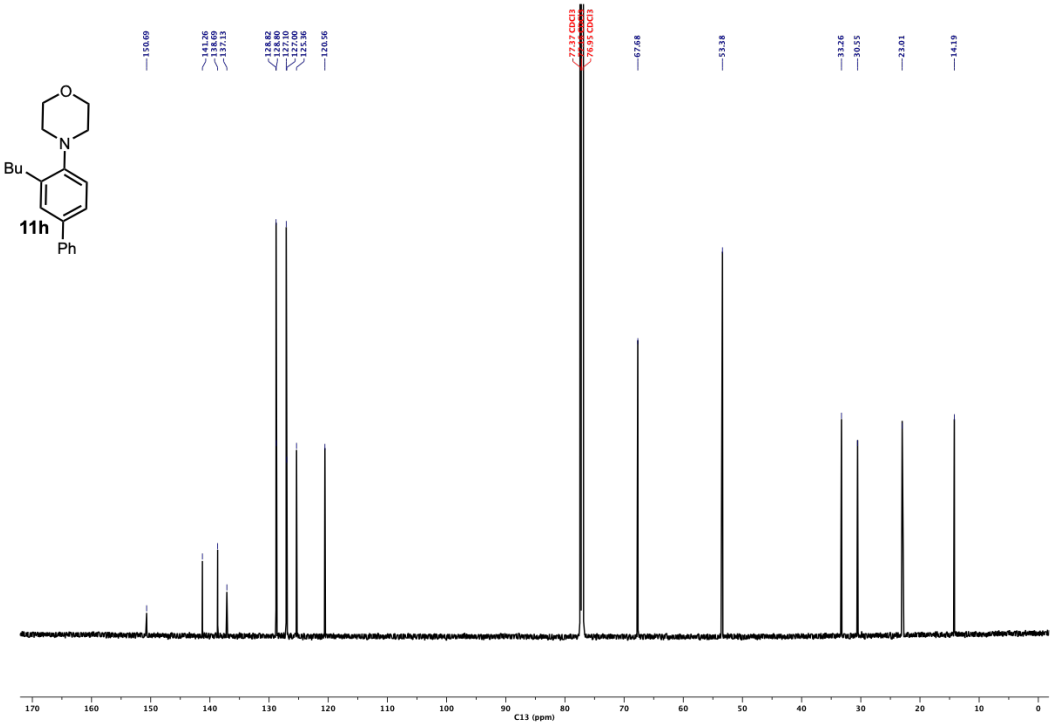
11g (^{13}C, 151 MHz, $CDCl_3$)



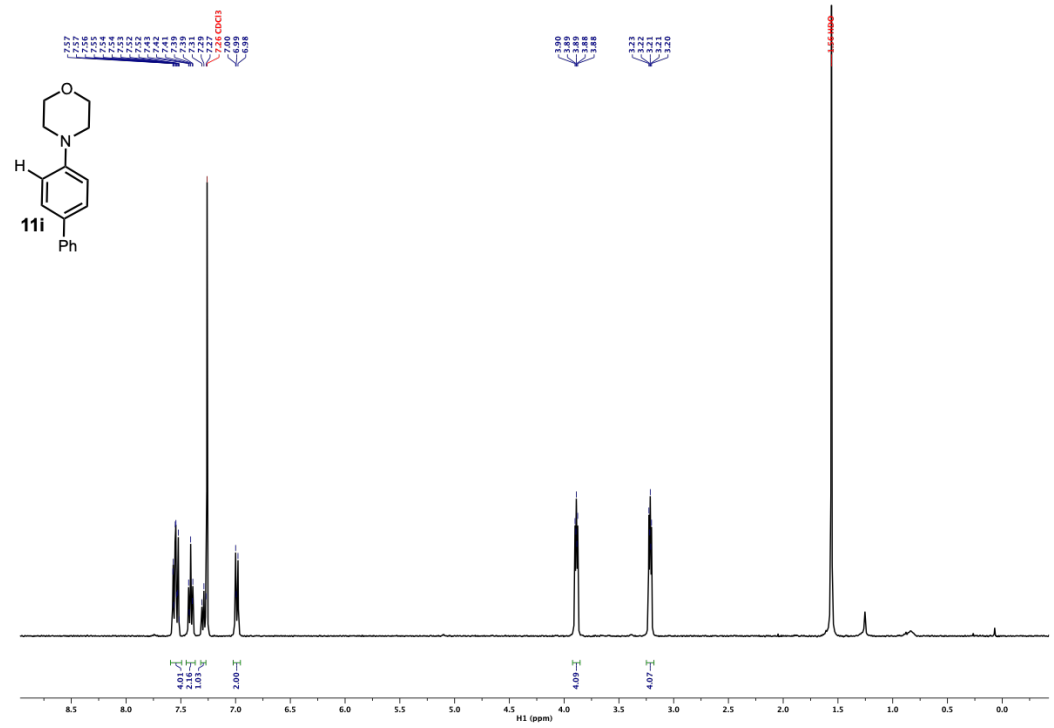
11h (^{1}H NMR, 600 MHz, $CDCl_3$)



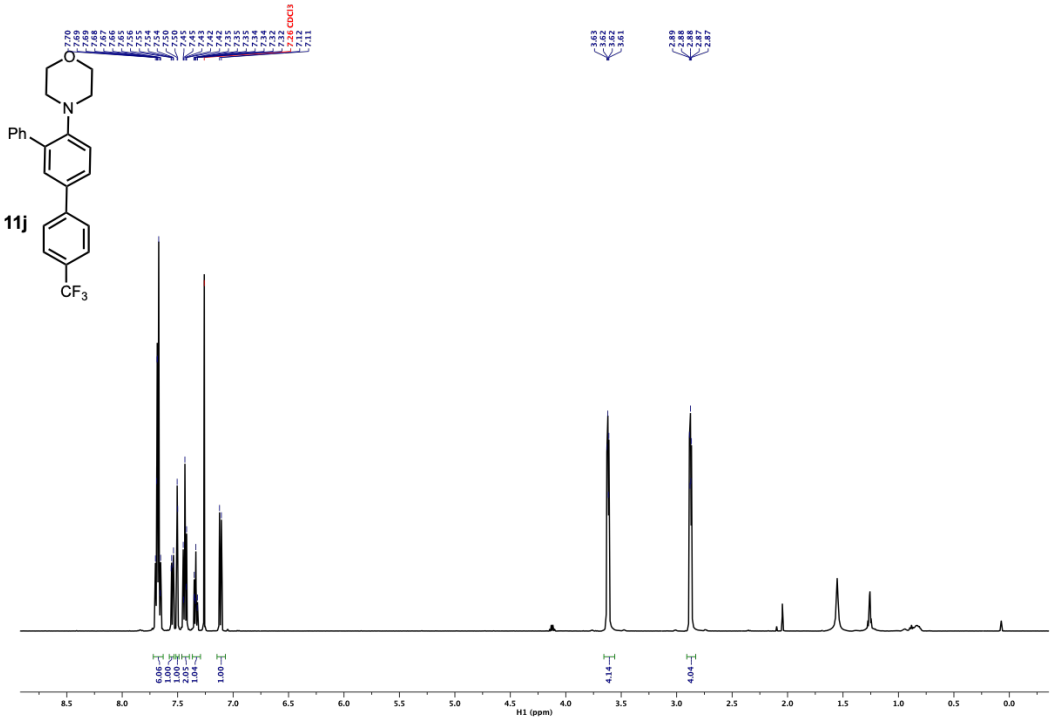
11h (^{13}C, 151 MHz, $CDCl_3$)



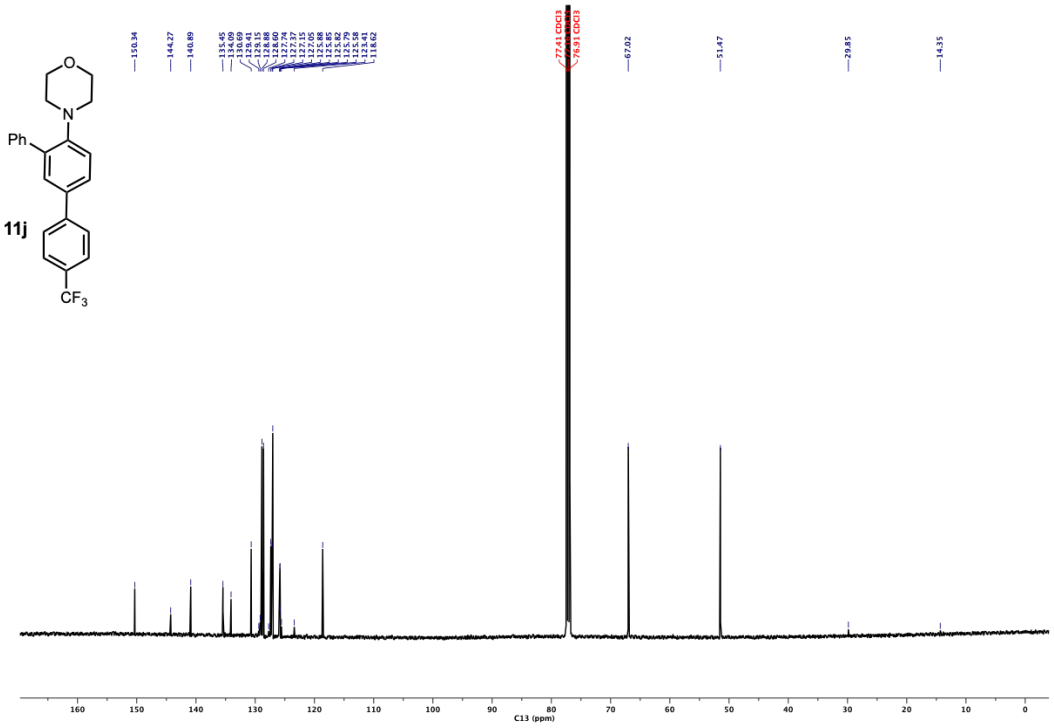
11i (^{1}H NMR, 400 MHz, $CDCl_3$)



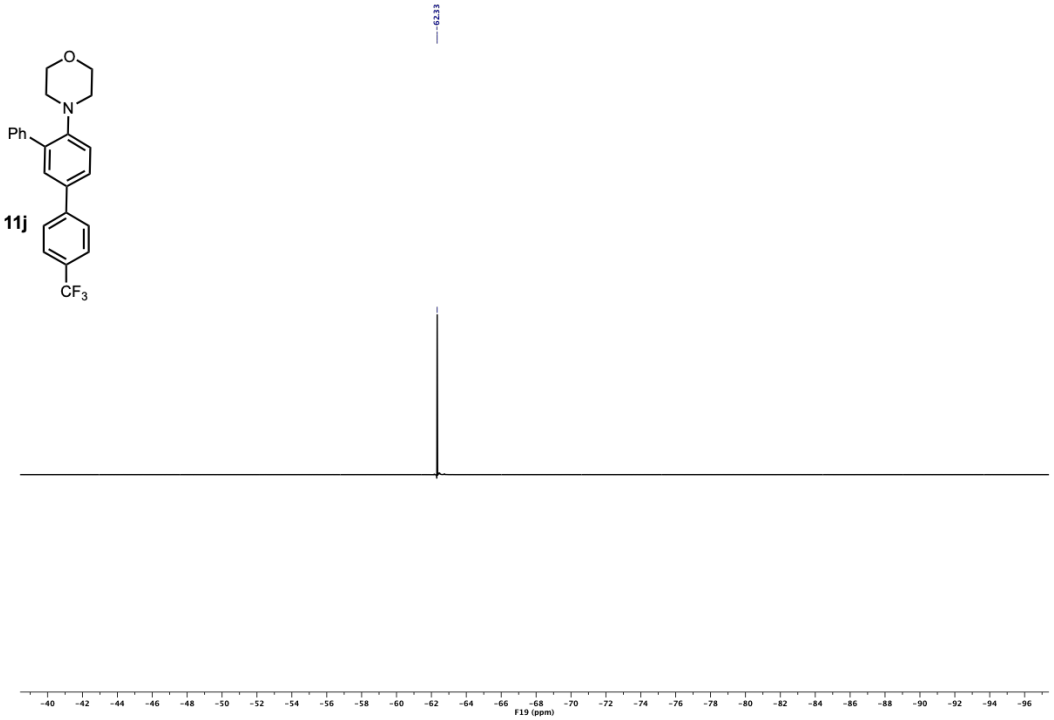
11j (^{1}H NMR, 500 MHz, $CDCl_3$)



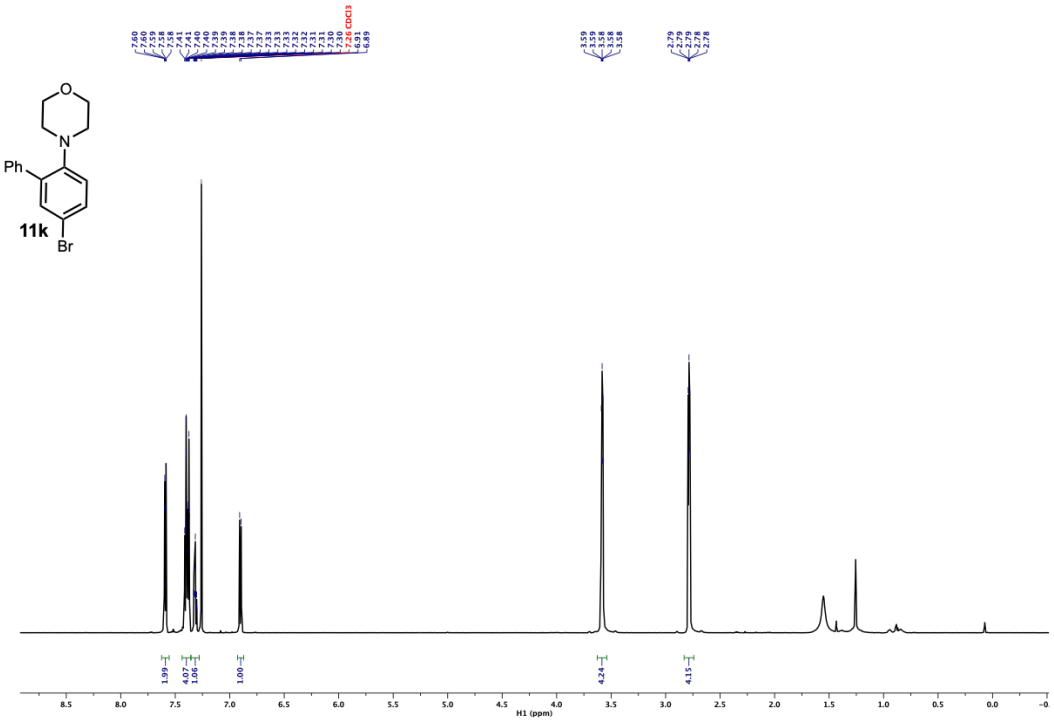
11j (^{13}C, 126 MHz, $CDCl_3$)



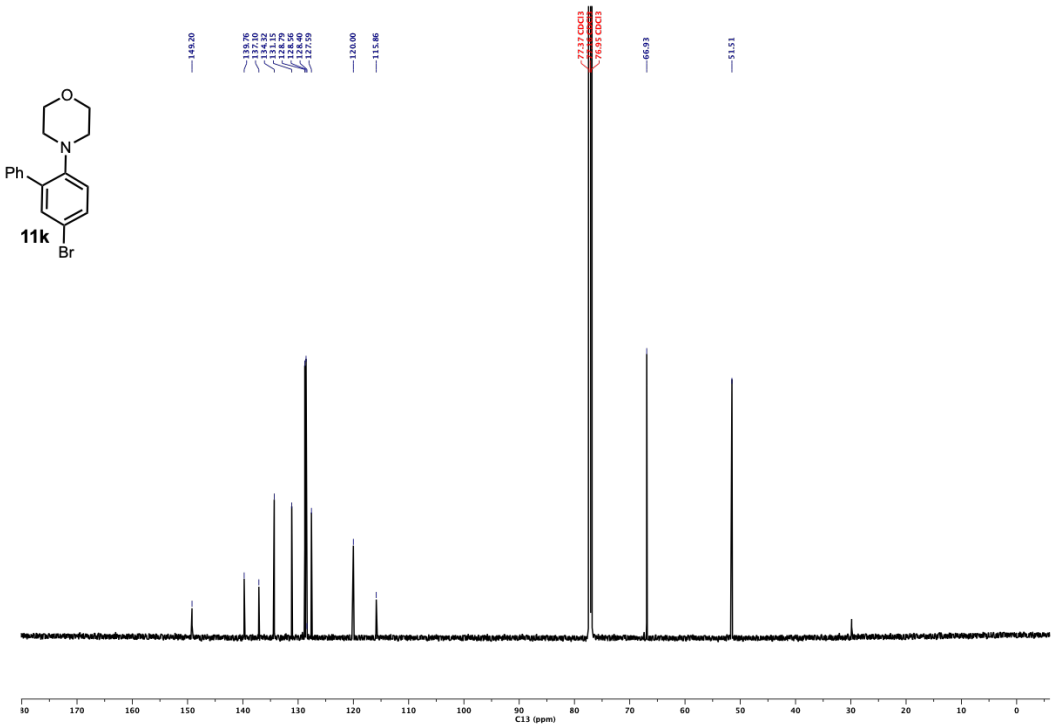
11j (^{19}F, 471 MHz, $CDCl_3$)



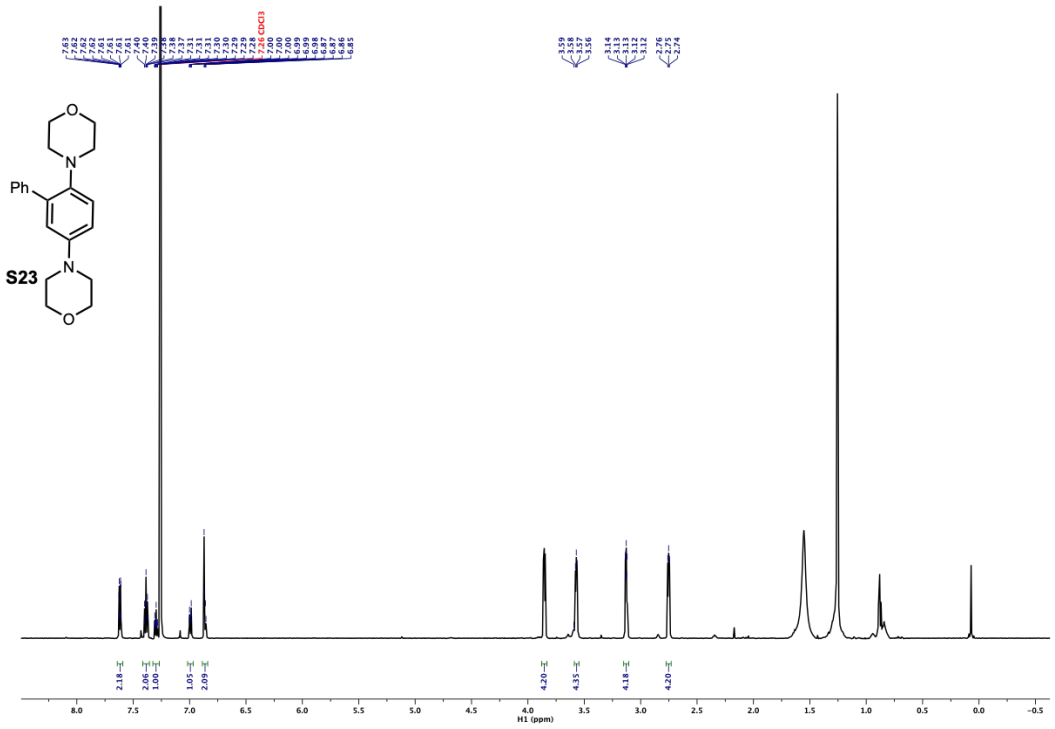
11k (^{1}H NMR, 600 MHz, $CDCl_3$)



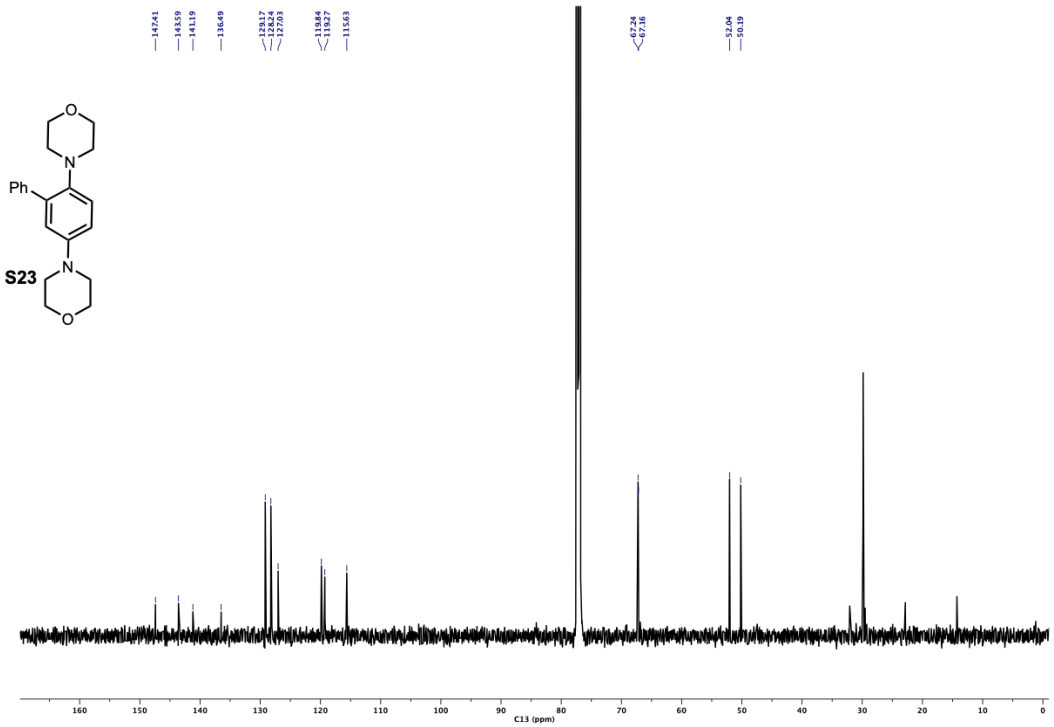
11k (^{13}C, 151 MHz, $CDCl_3$)



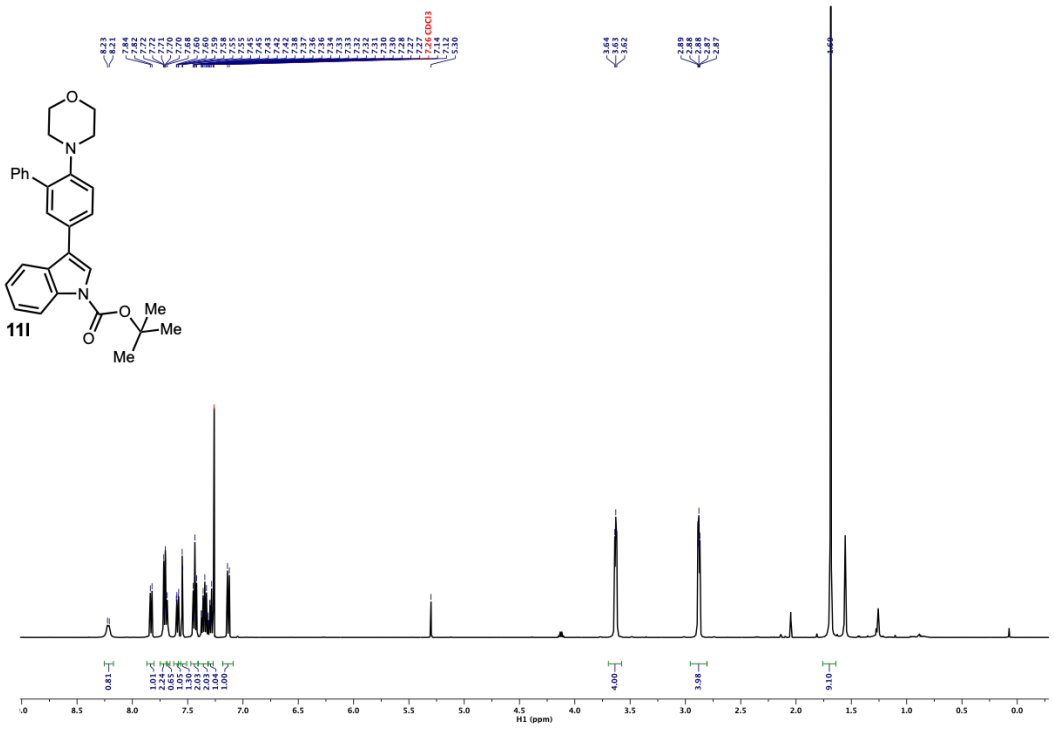
S23 (^{1}H NMR, 600 MHz, $CDCl_3$)



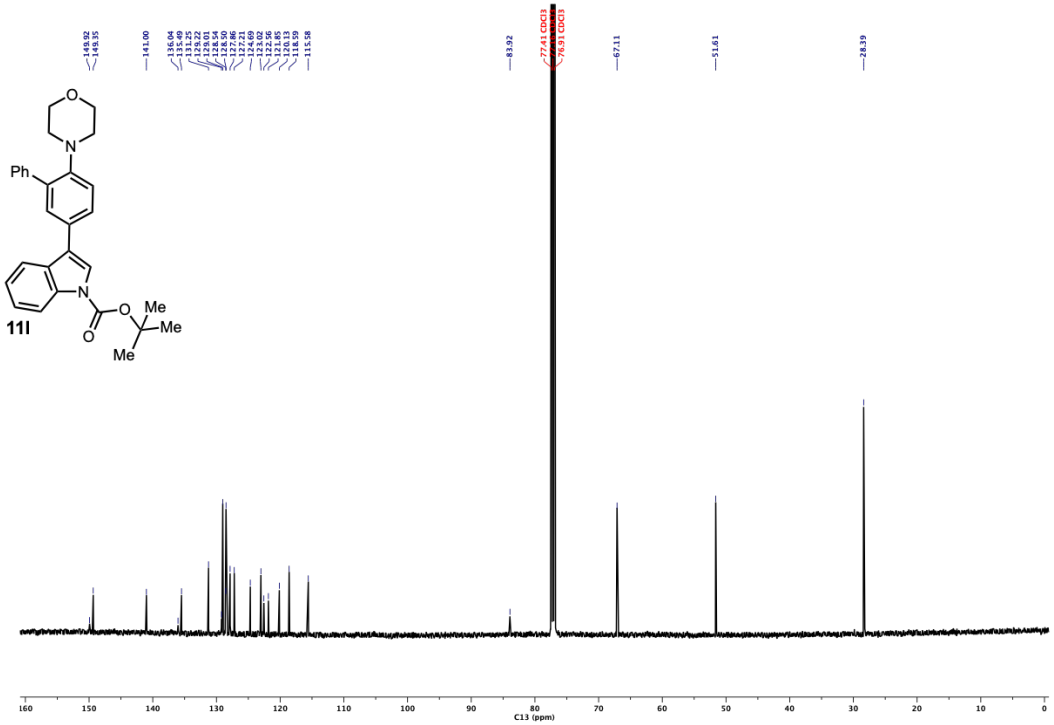
S23 (^{13}C, 151 MHz, $CDCl_3$)



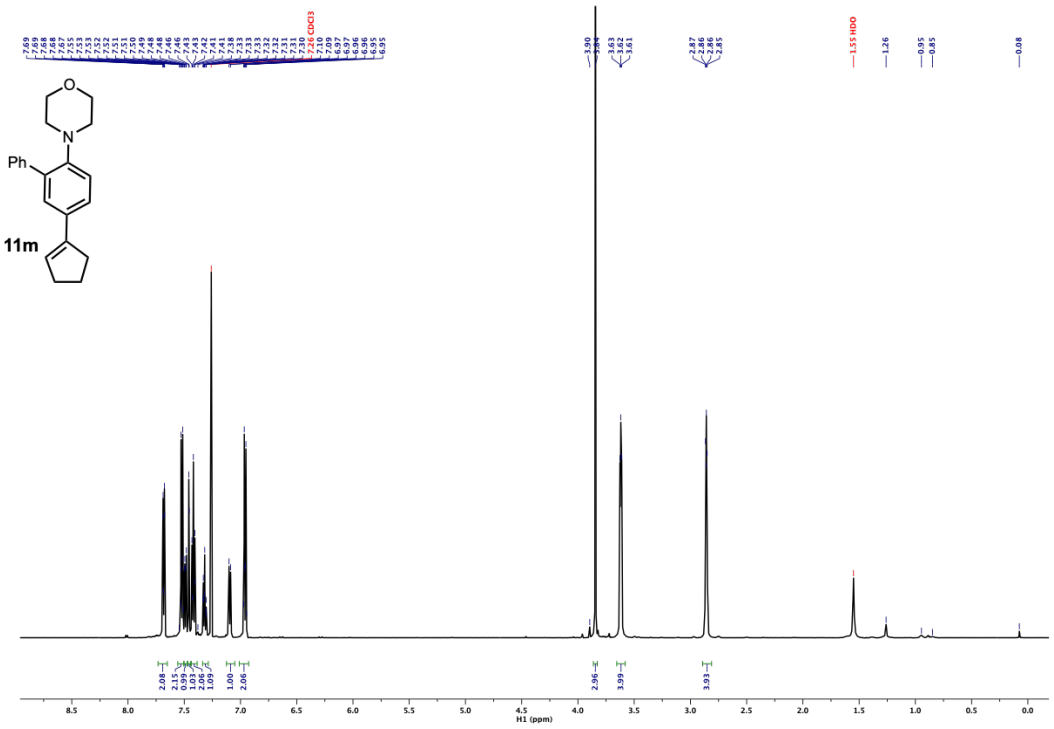
11l (^{1}H NMR, 500 MHz, $CDCl_3$)



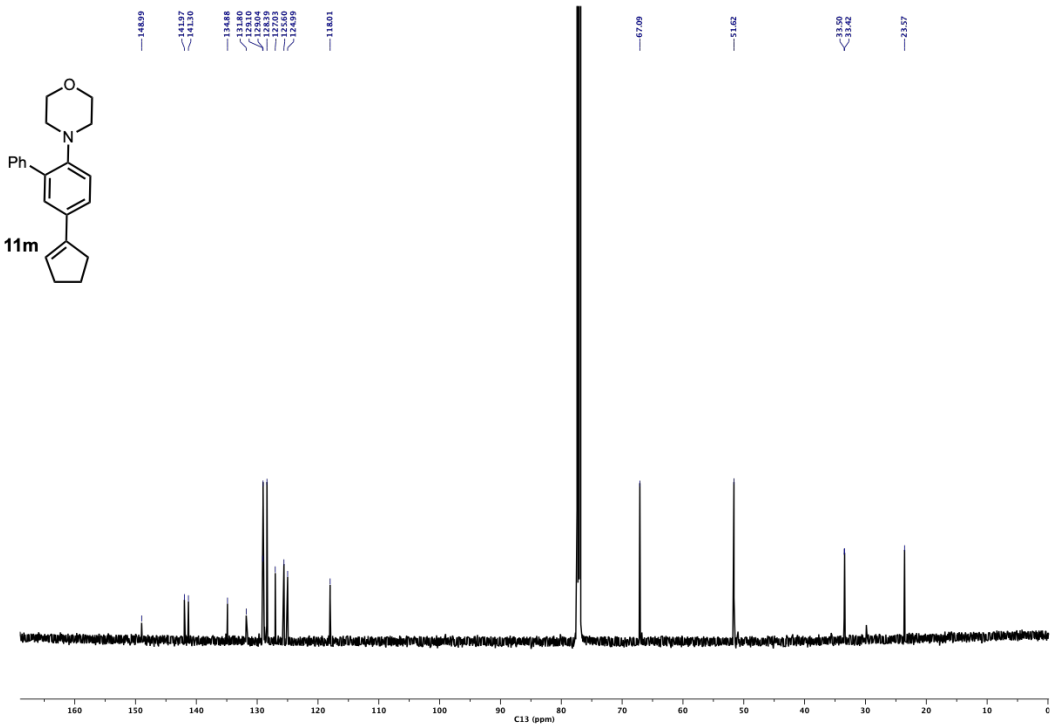
11l (^{13}C, 126 MHz, $CDCl_3$)



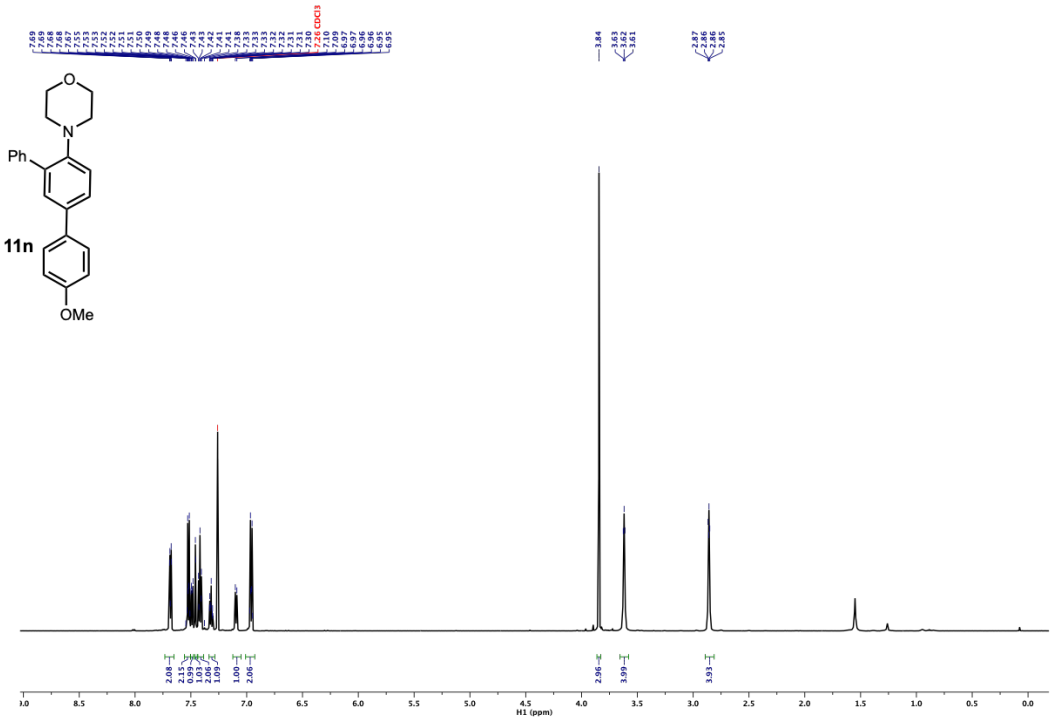
11m (^{1}H NMR, 500 MHz, $CDCl_3$)



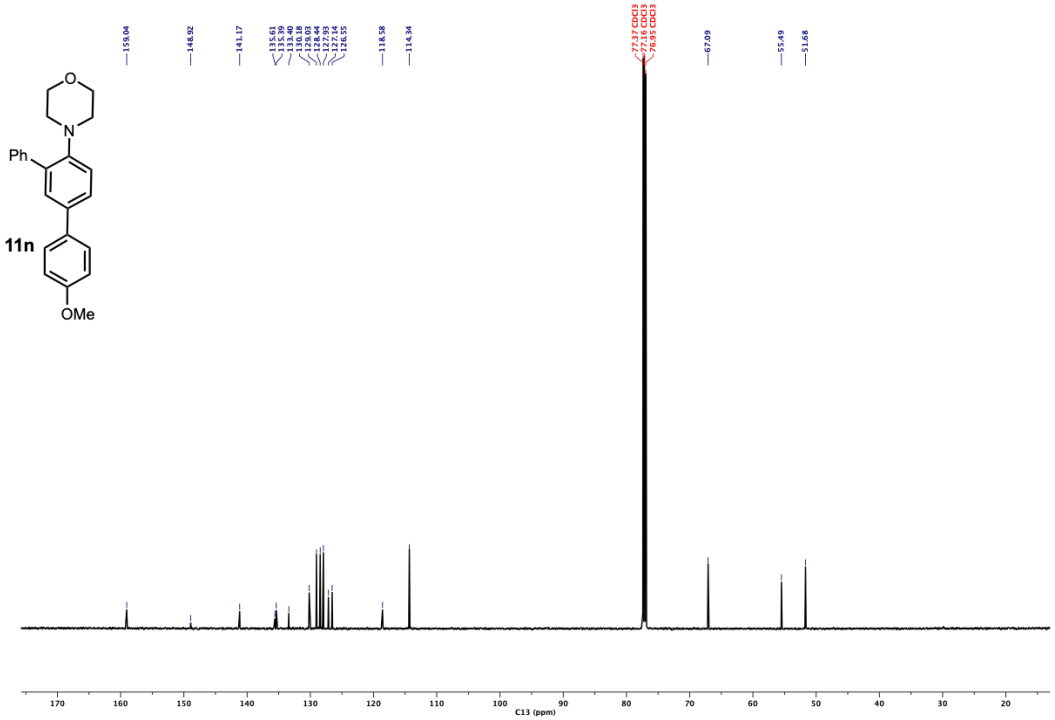
11m (^{13}C, 151 MHz, $CDCl_3$)



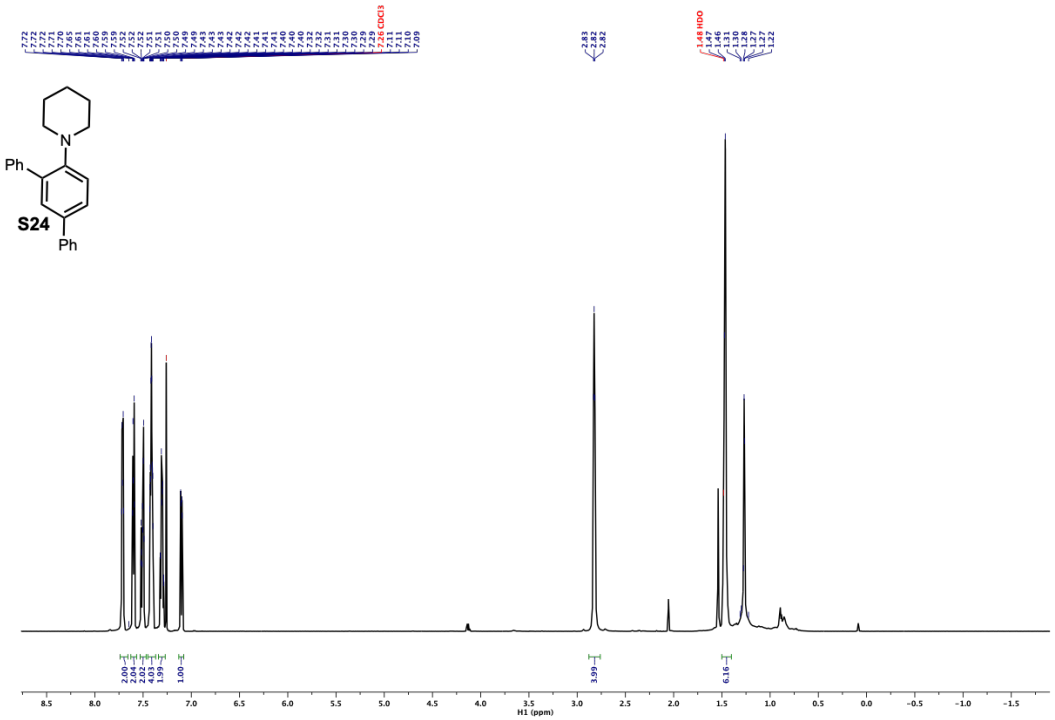
11n (^{1}H NMR, 600 MHz, $CDCl_3$)



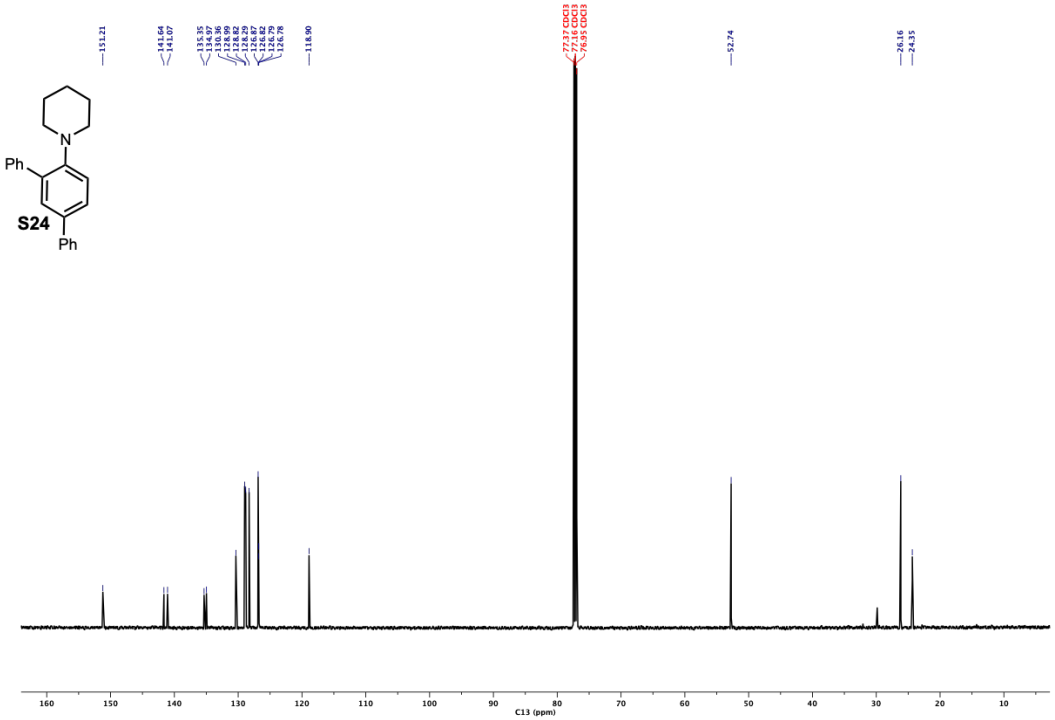
11n (^{13}C, 151 MHz, $CDCl_3$)



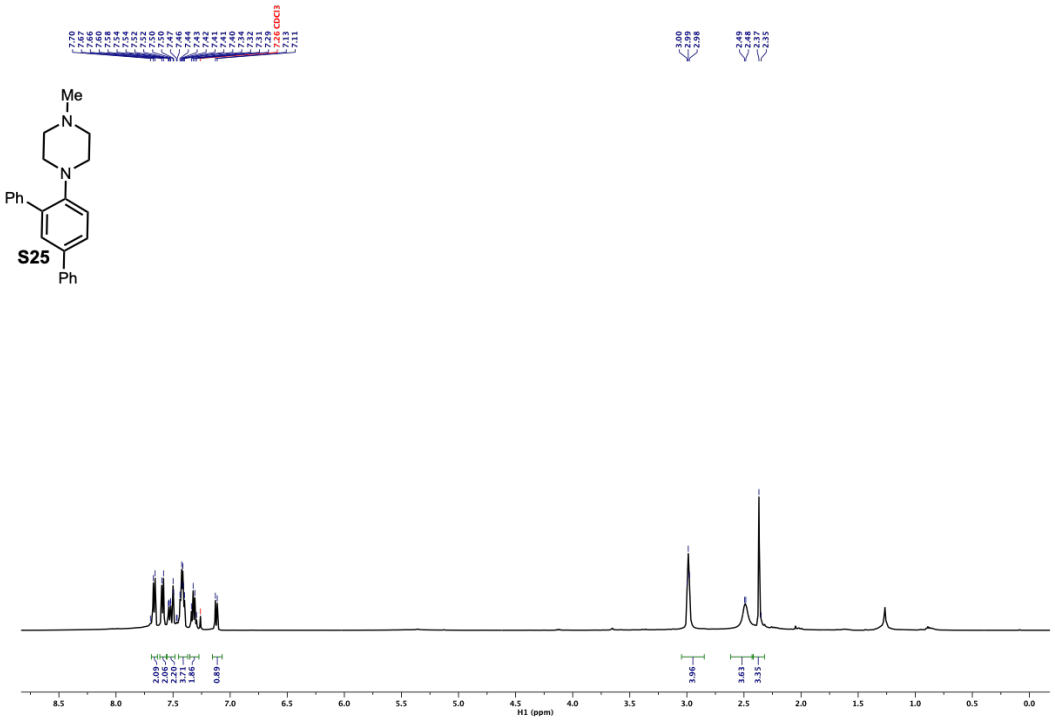
S24 (^{1}H NMR, 600 MHz, $CDCl_3$)



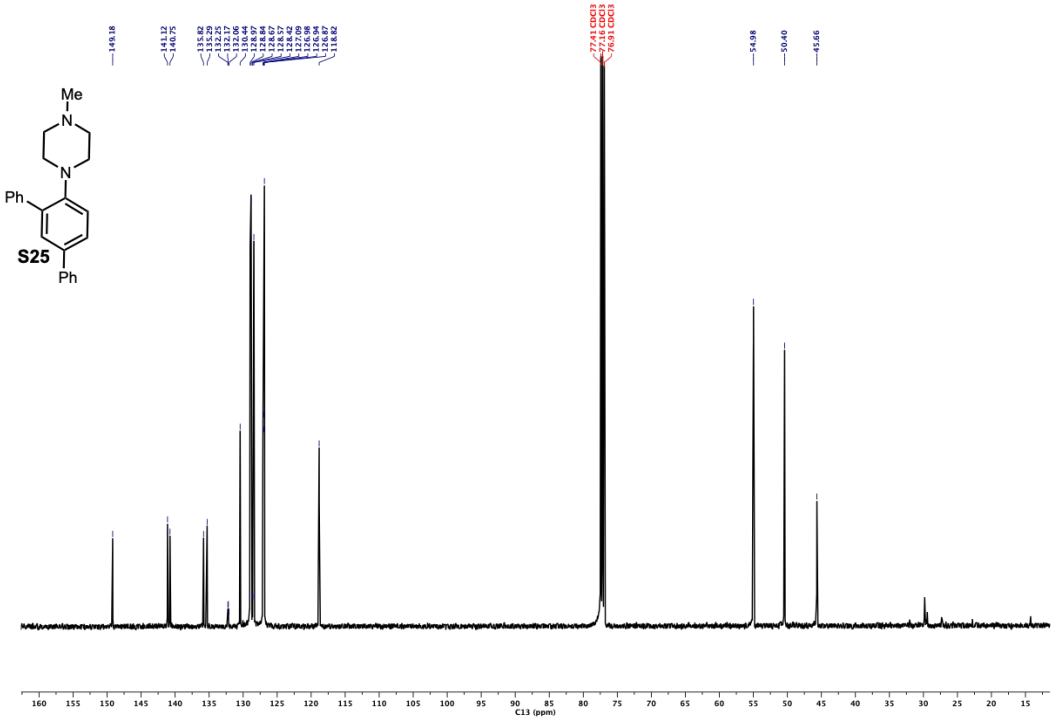
S24 (^{13}C, 151 MHz, $CDCl_3$)



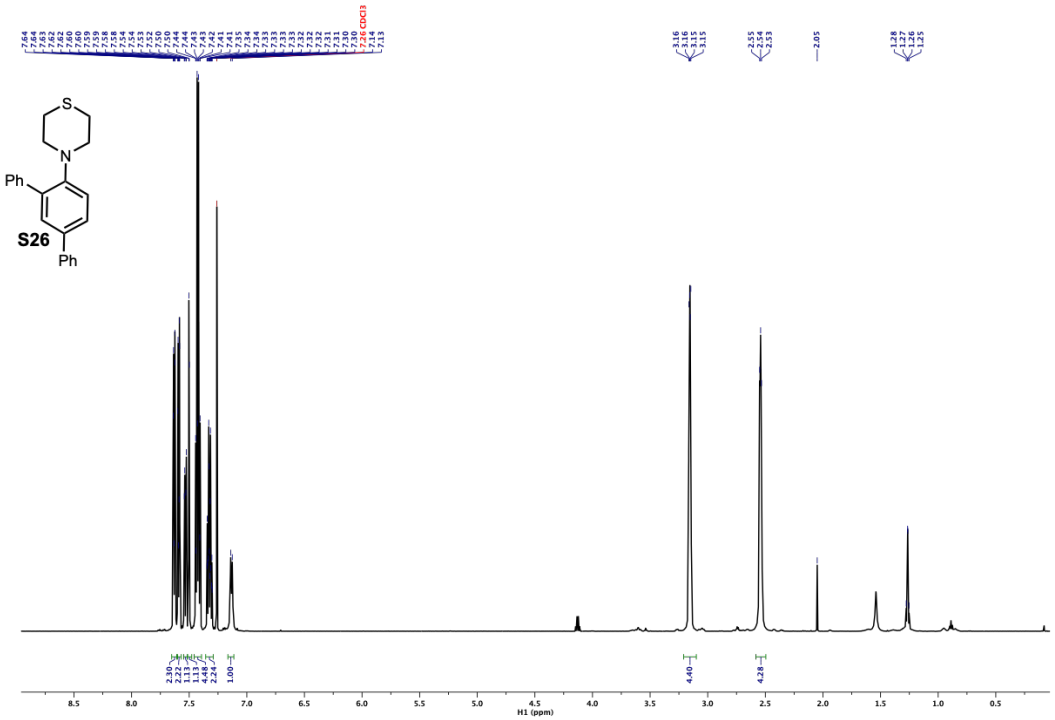
S25 (^{1}H NMR, 500 MHz, $CDCl_3$)



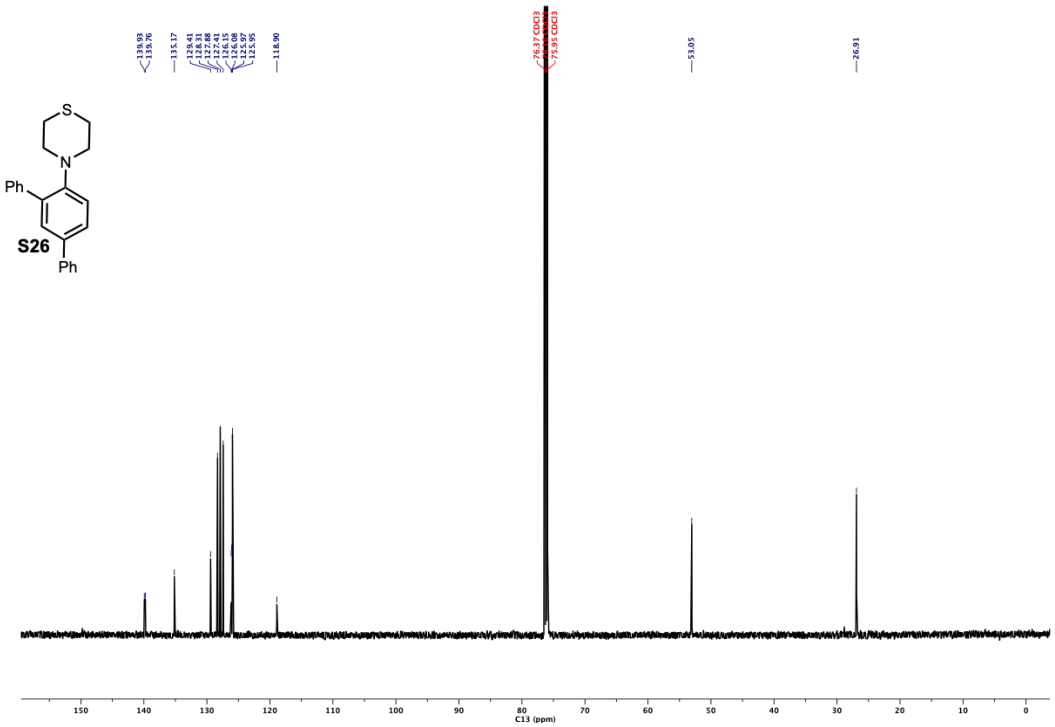
S25 (^{13}C, 126 MHz, $CDCl_3$)



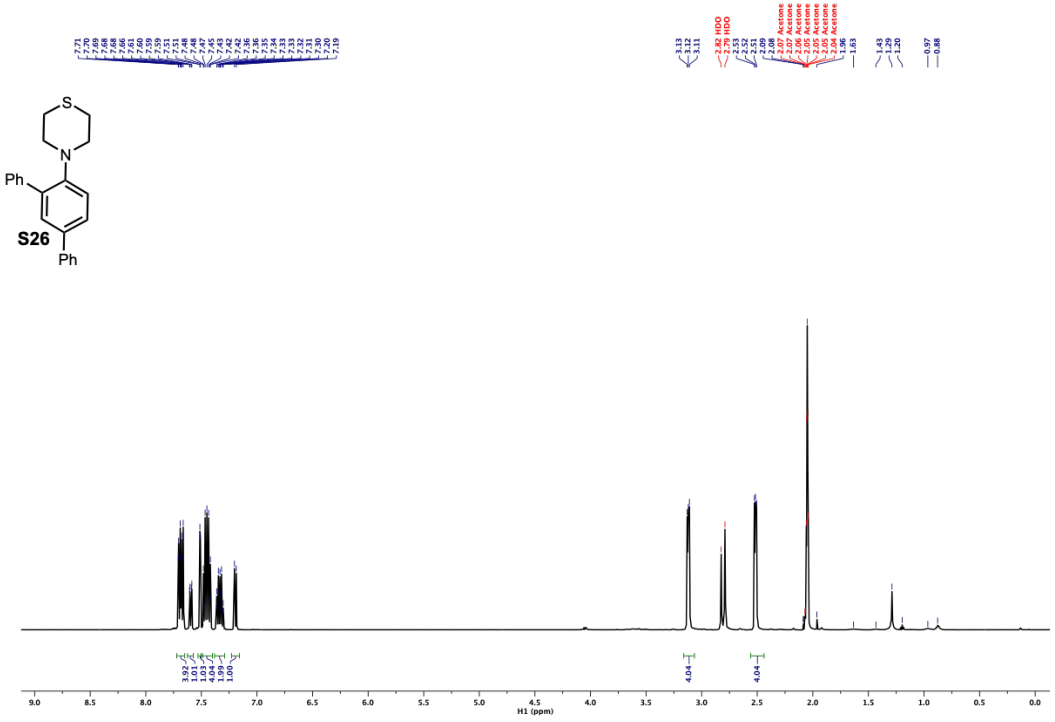
S26 (^{1}H NMR, 600 MHz, $CDCl_3$)



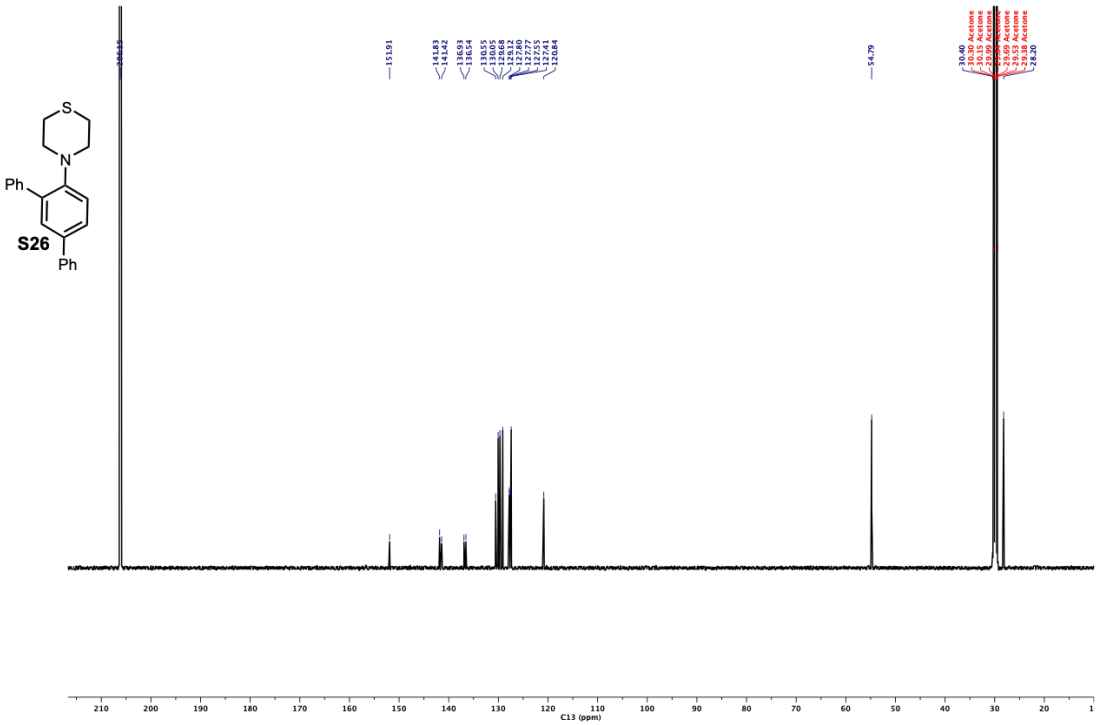
S26 (^{13}C, 151 MHz, $CDCl_3$)



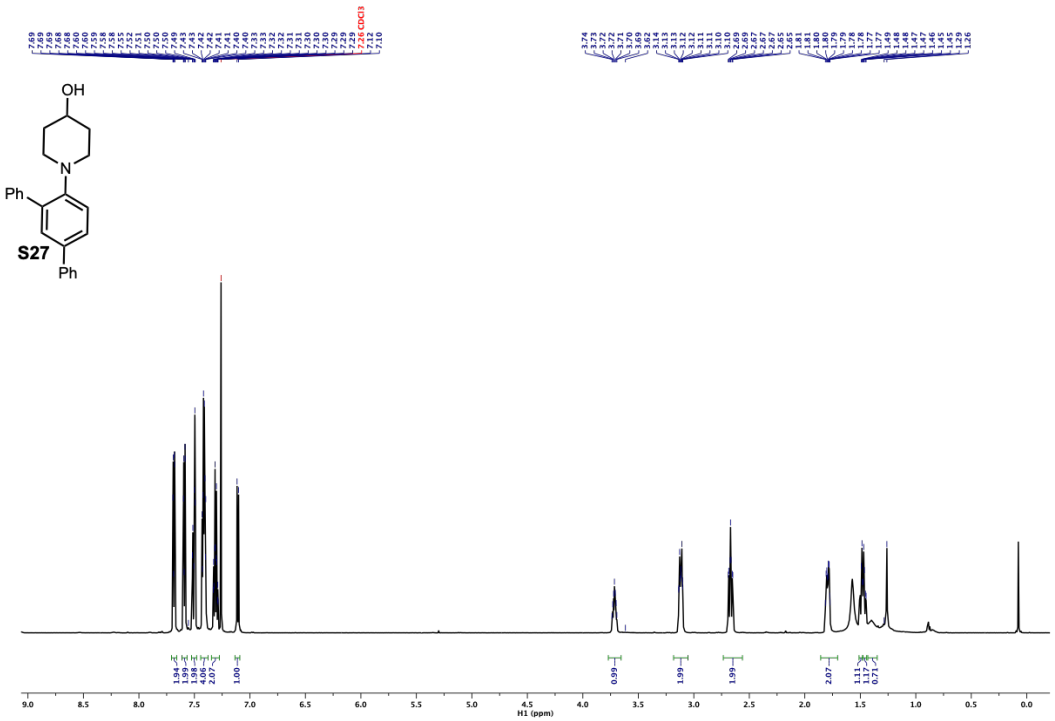
S26 (^{1}H NMR, 500 MHz, Acetone-d_6)



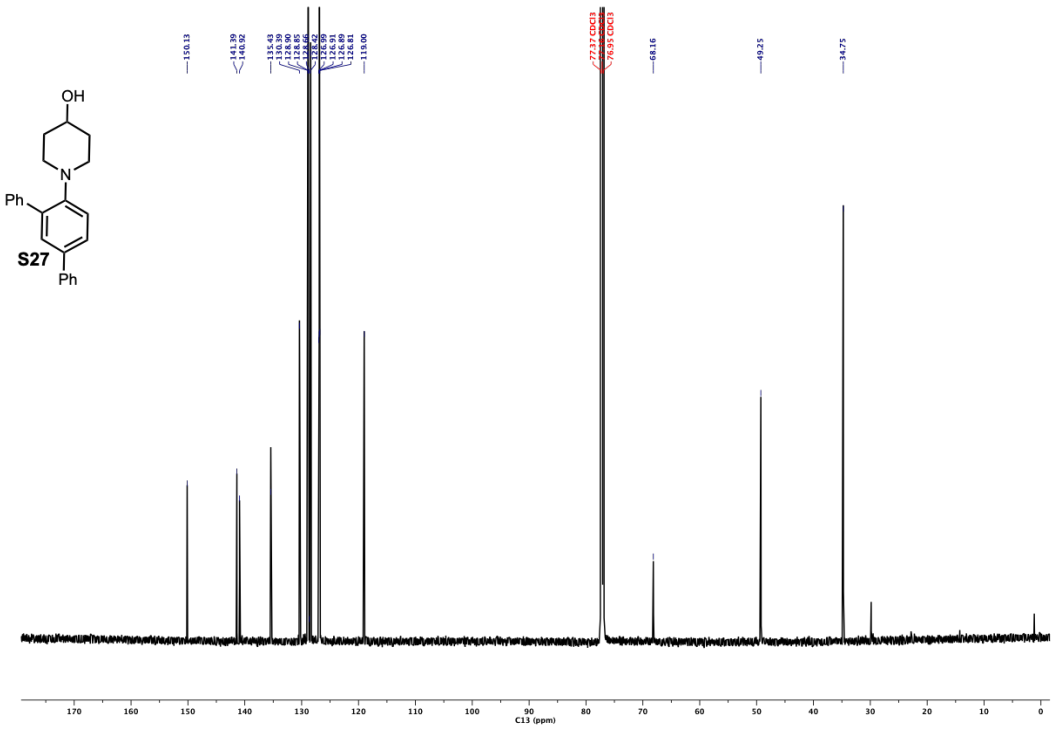
S26 (^{13}C, 126 MHz, Acetone-d_6)



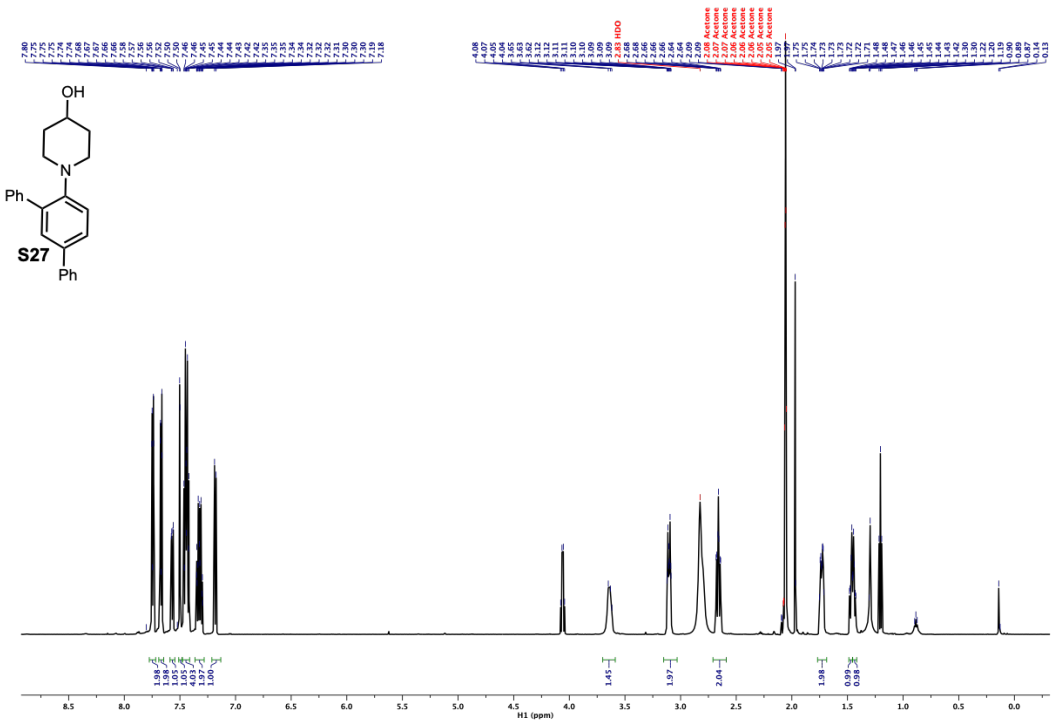
S27 (^{1}H NMR, 600 MHz, $CDCl_3$)



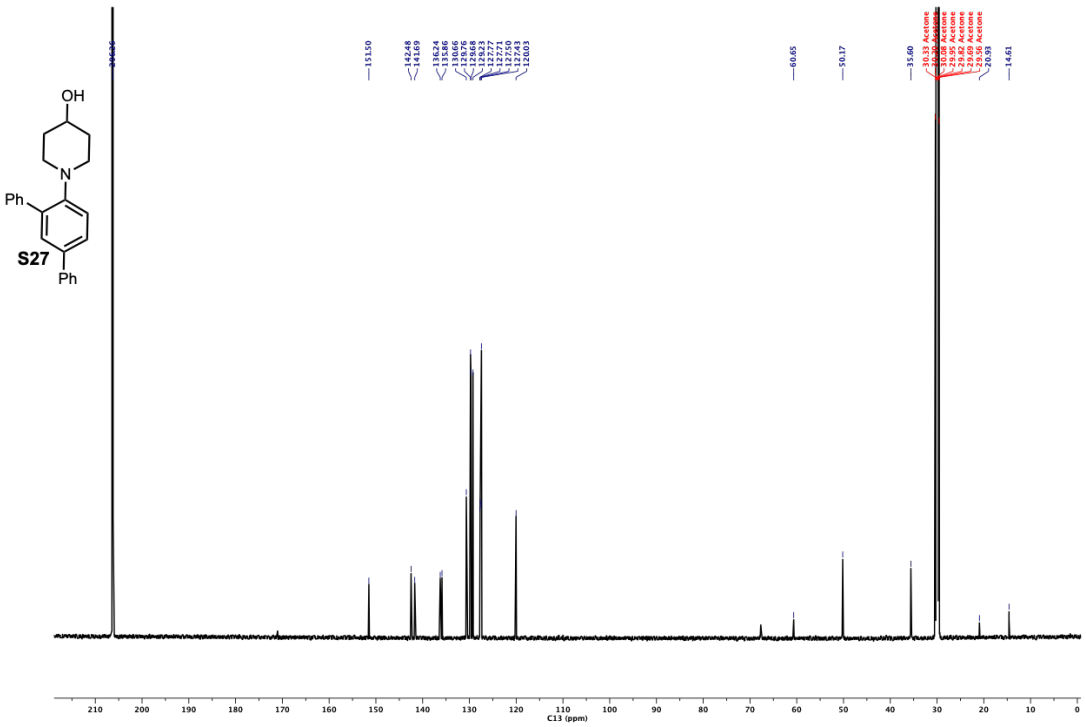
S27 (^{13}C, 151 MHz, $CDCl_3$)



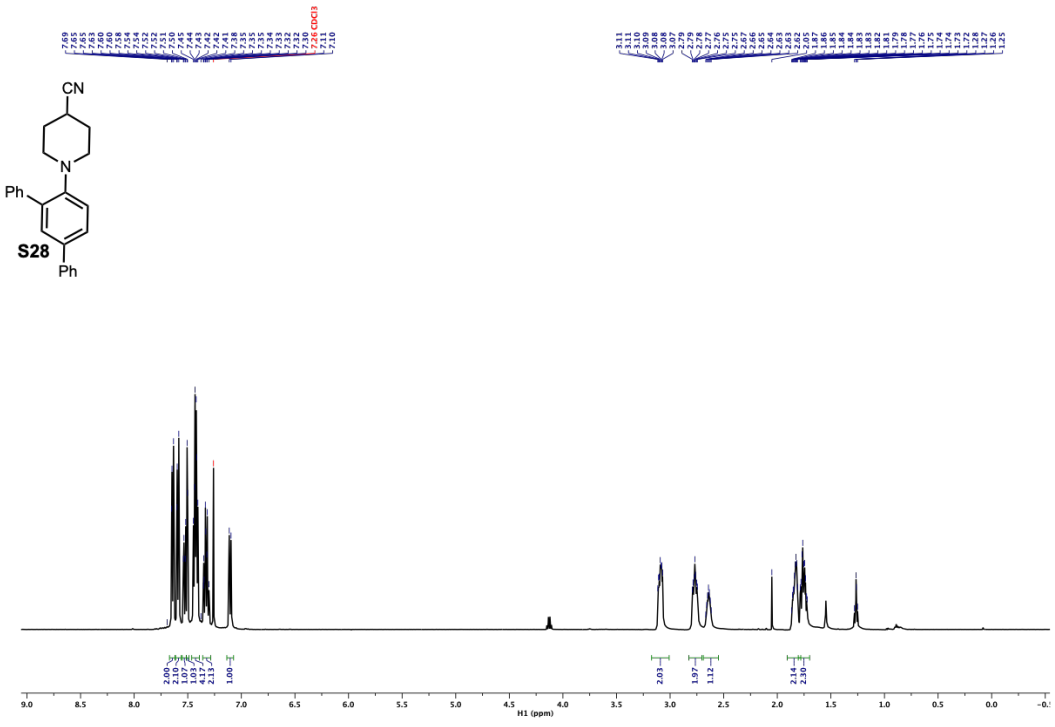
S27 (^{1}H NMR, 600 MHz, Acetone-d_6)



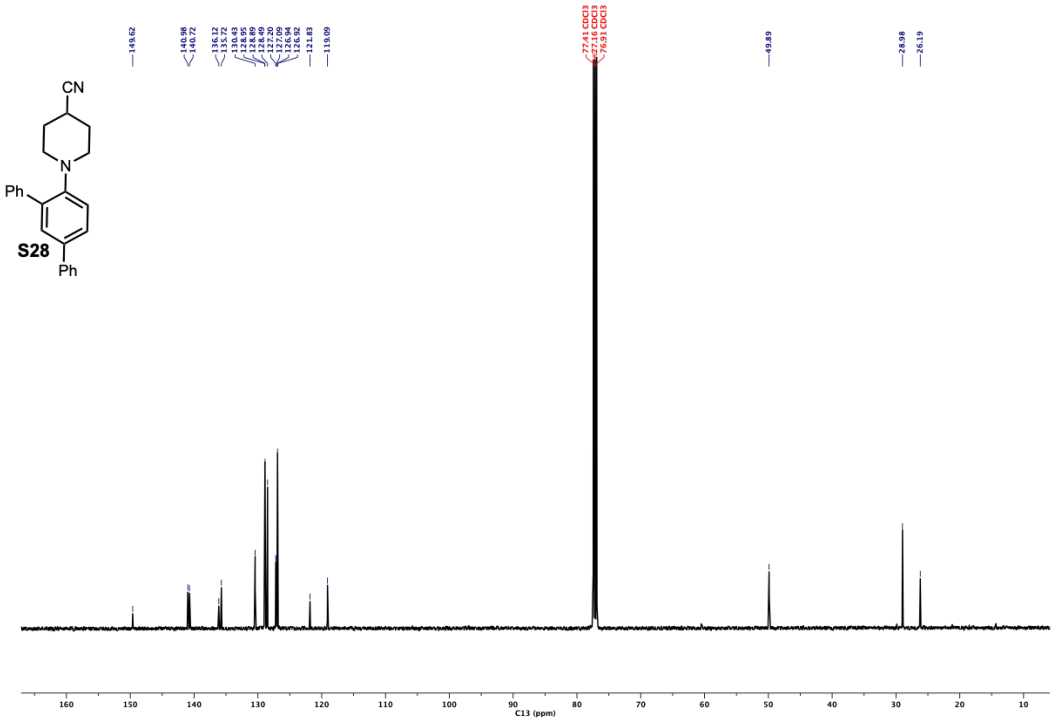
S27 (^{13}C, 151 MHz, Acetone-d_6)



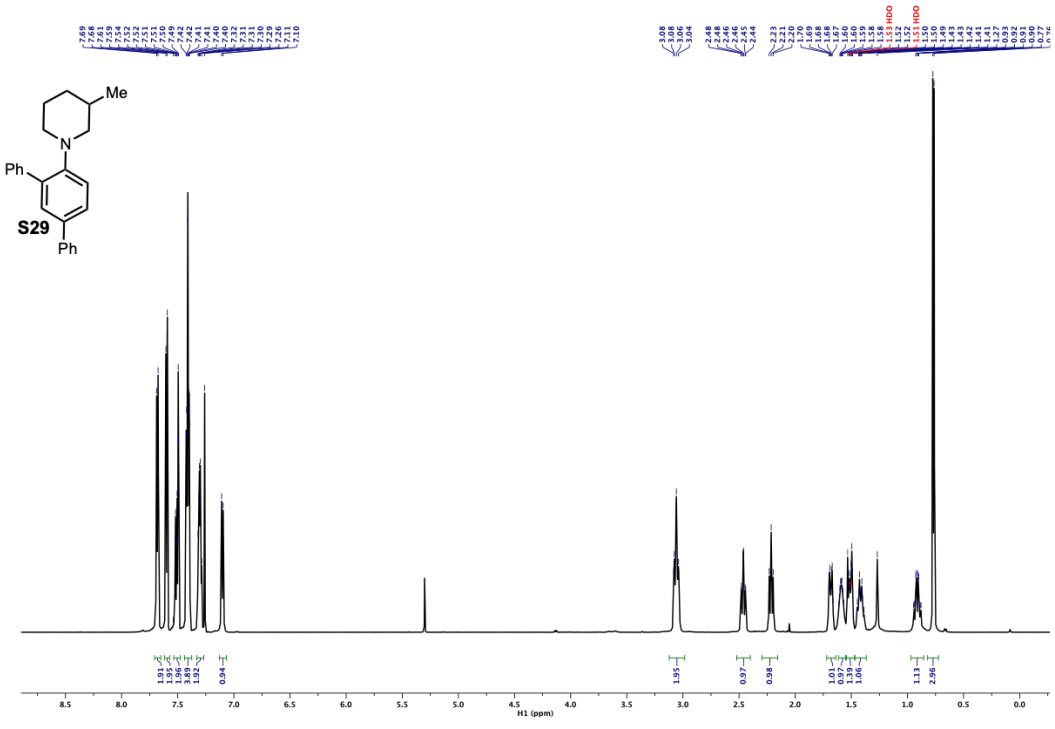
S28 (^{1}H NMR, 500 MHz, $CDCl_3$)



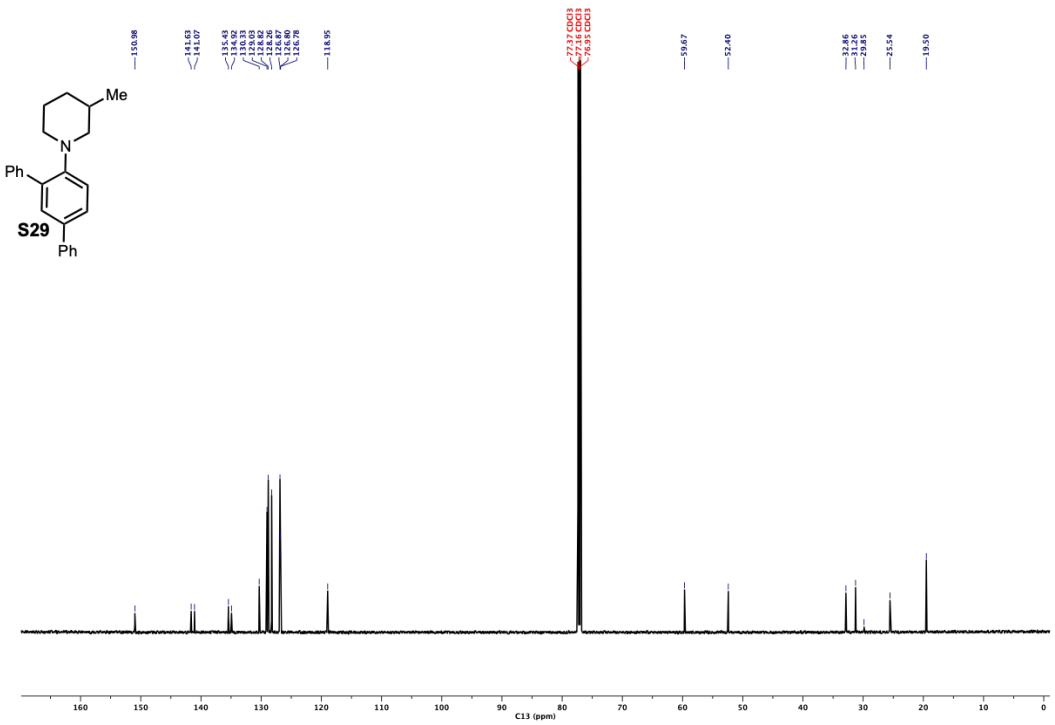
S28 (^{13}C, 126 MHz, $CDCl_3$)



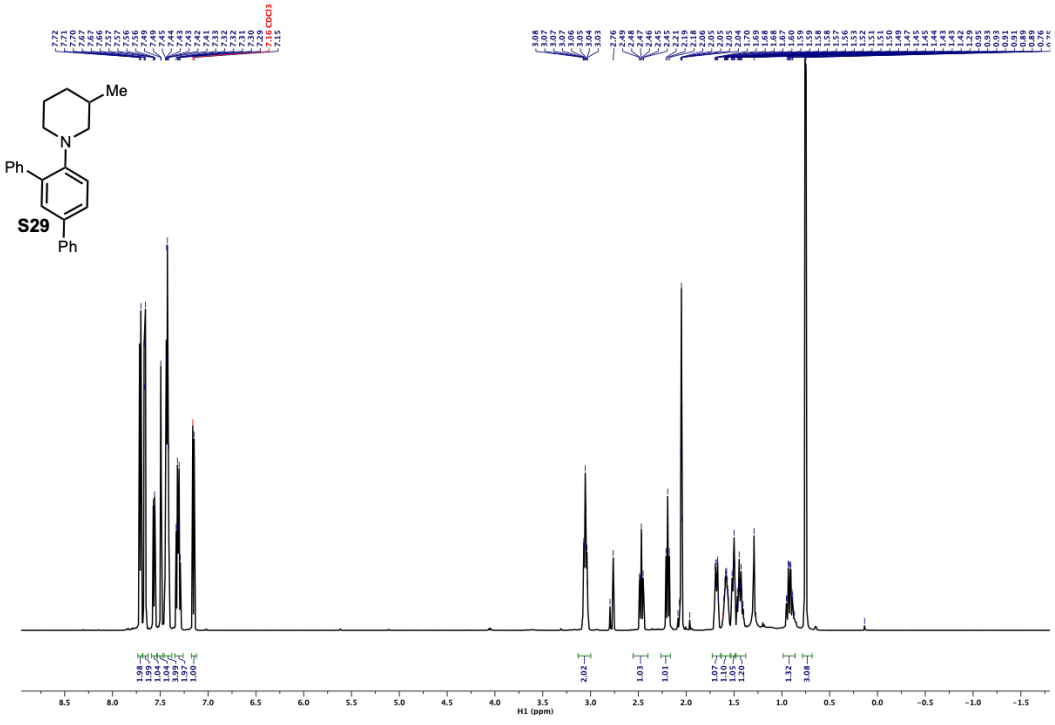
S29 (^{1}H NMR, 600 MHz, $CDCl_3$)



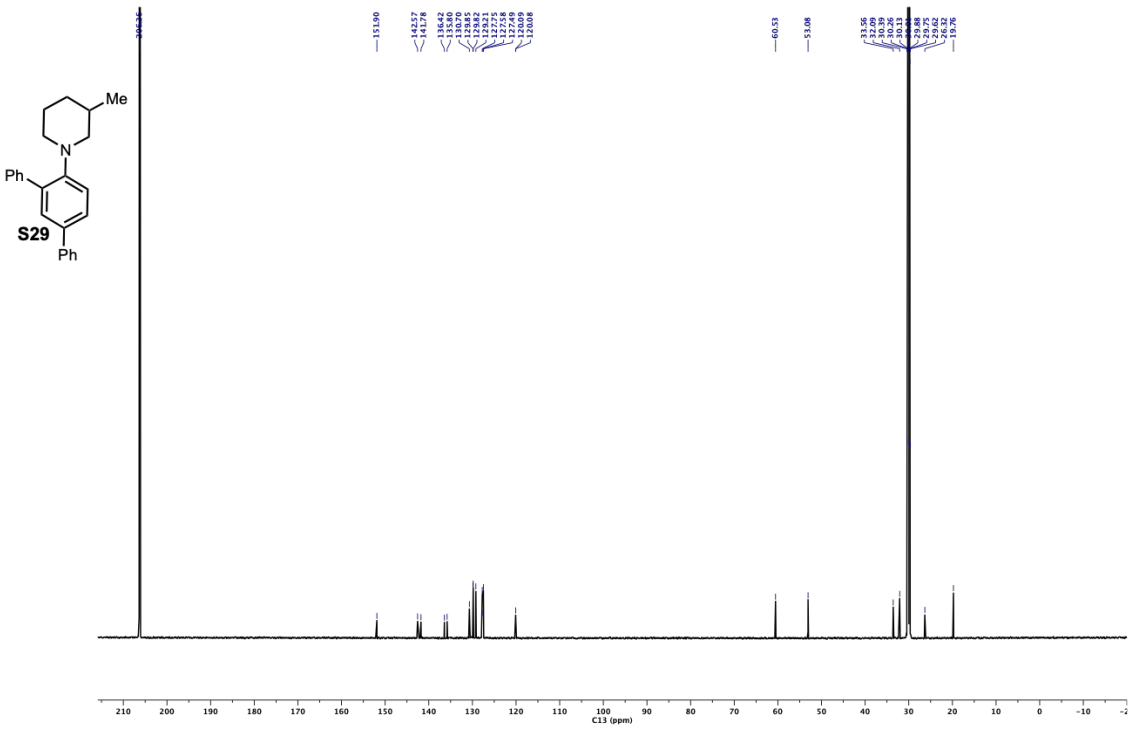
S29 (^{13}C, 151 MHz, $CDCl_3$)



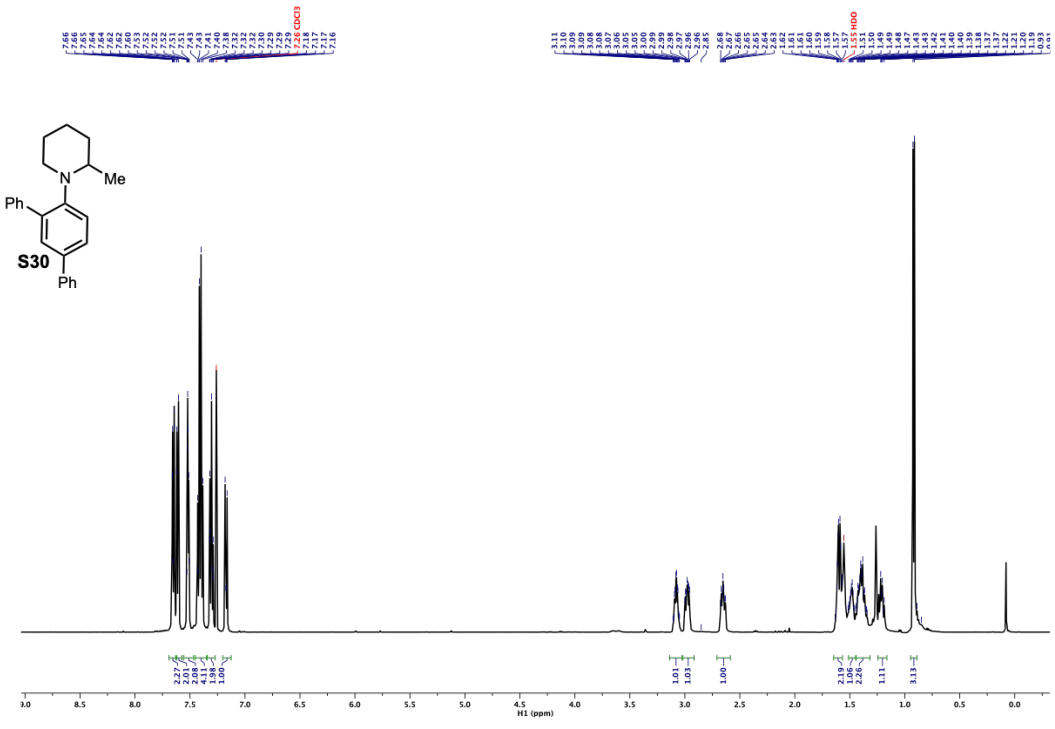
S29 (^{1}H NMR, 600 MHz, Acetone-d_6)



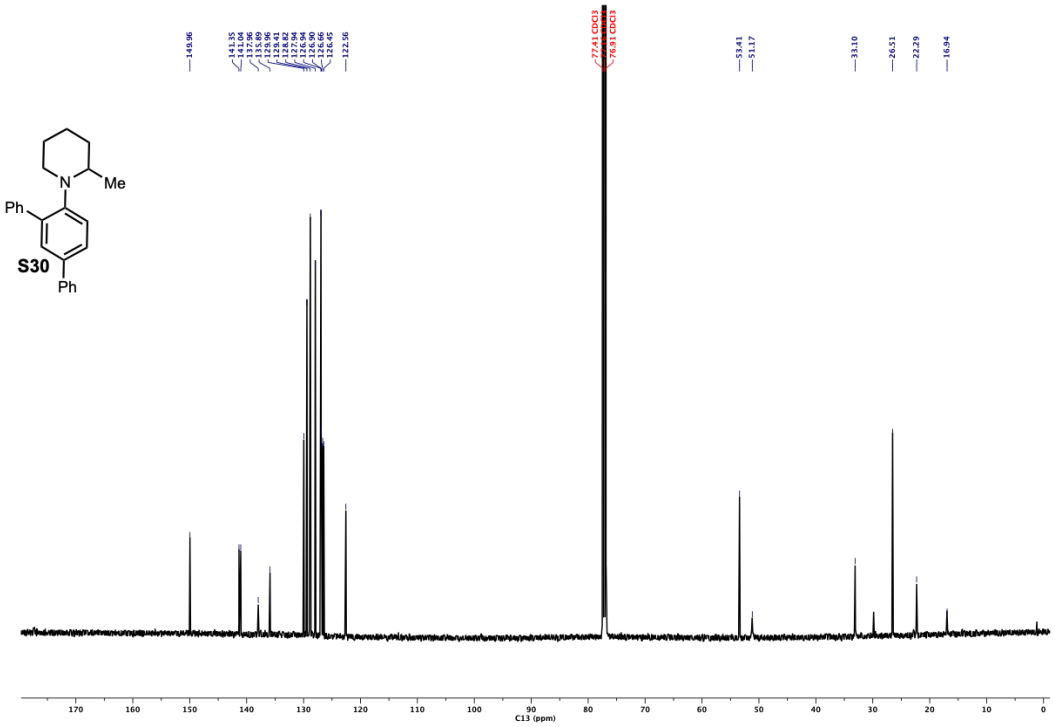
S29 (^{13}C, 151 MHz, Acetone-d_6)



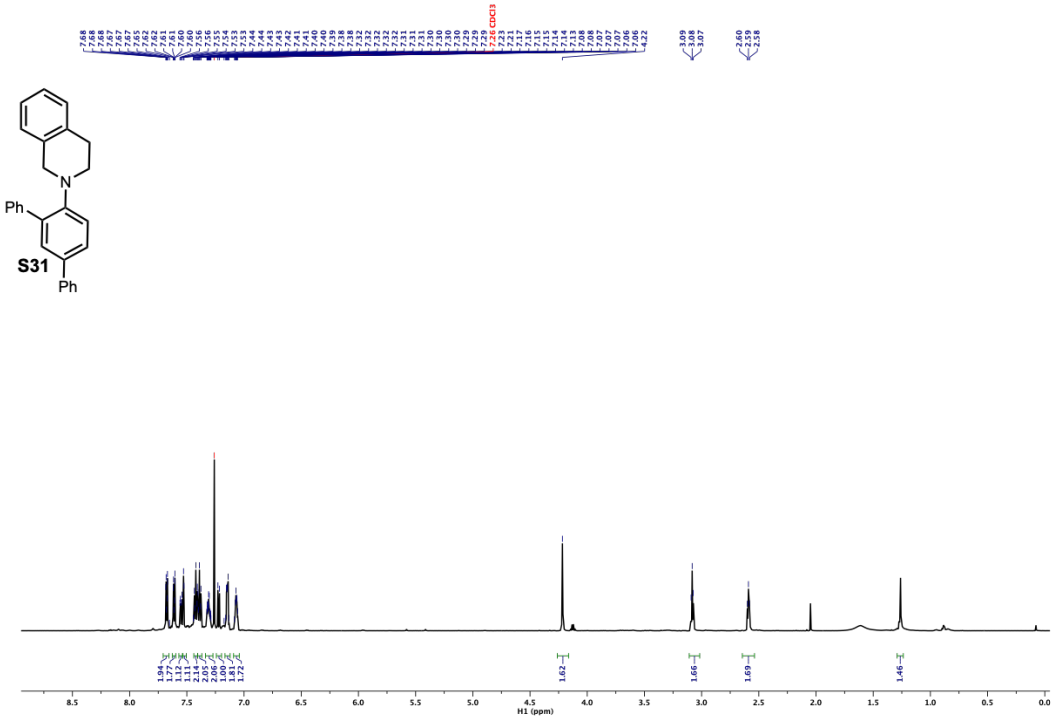
S30 (^{1}H NMR, 500 MHz, $CDCl_3$)



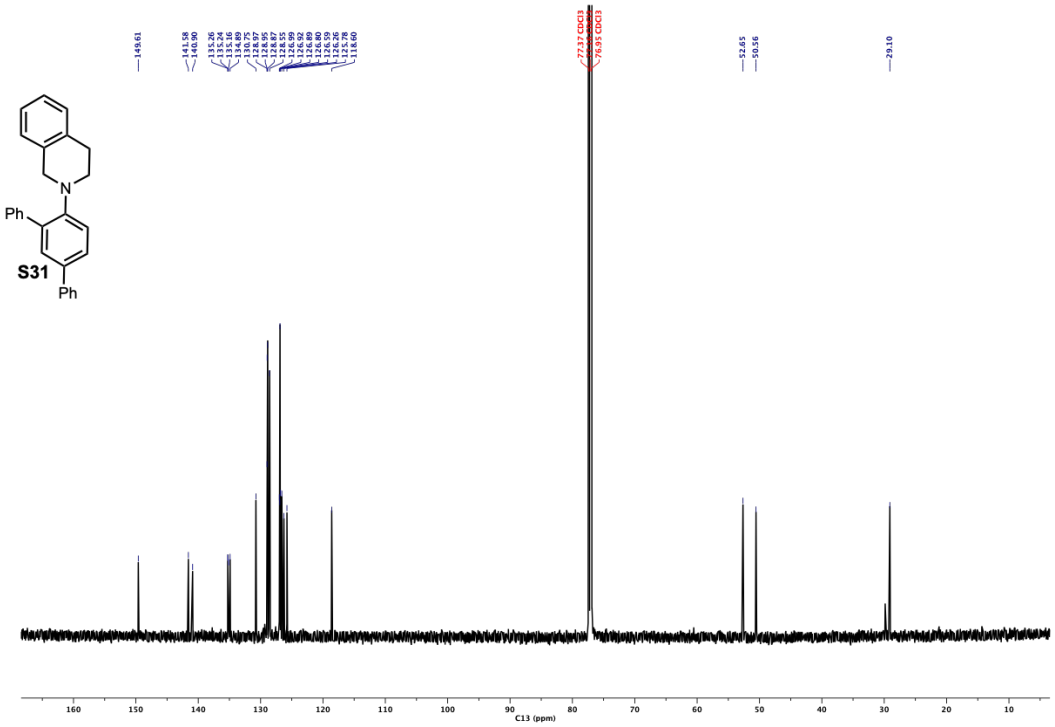
S30 (^{13}C, 126 MHz, $CDCl_3$)



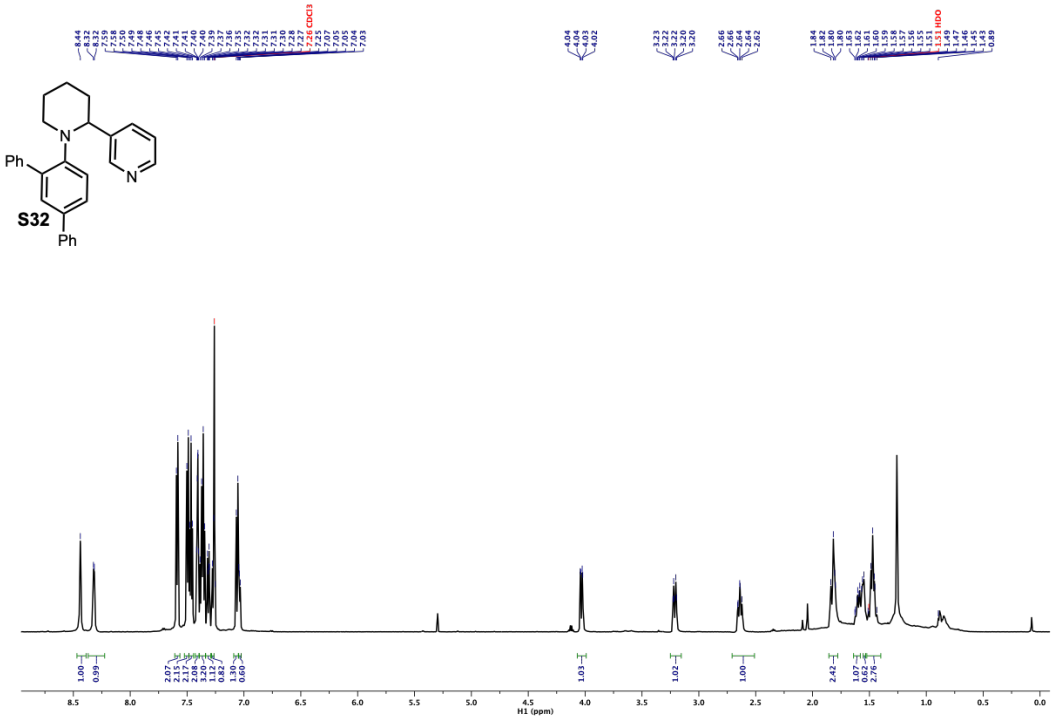
S31 (^{1}H NMR, 600 MHz, $CDCl_3$)



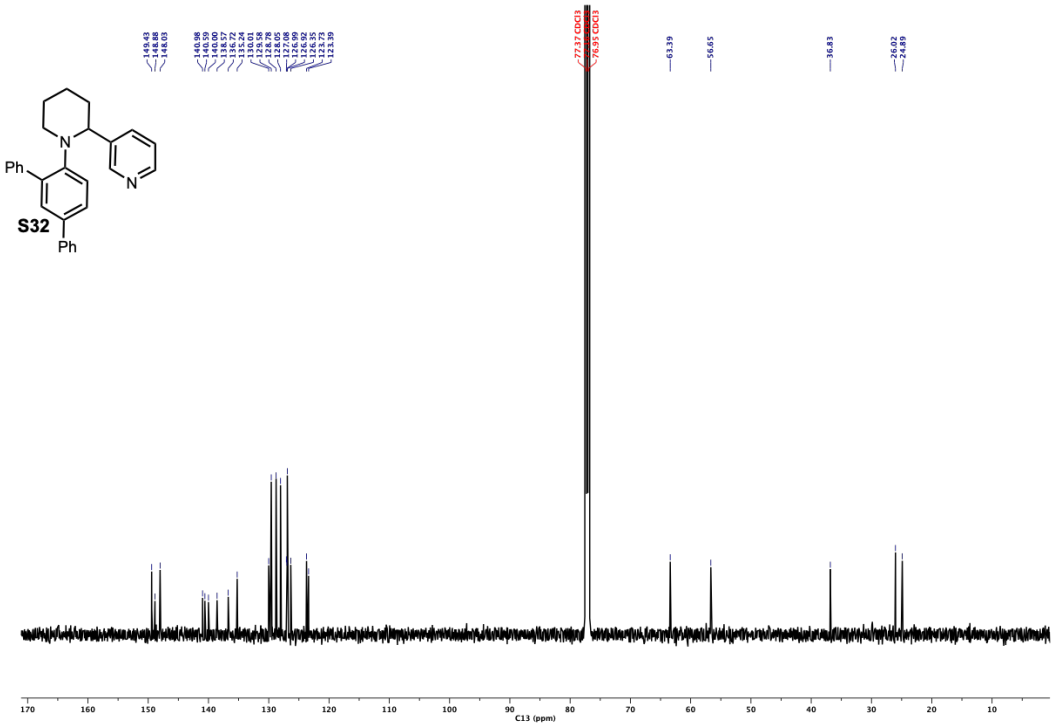
S31 (^{13}C, 151 MHz, $CDCl_3$)



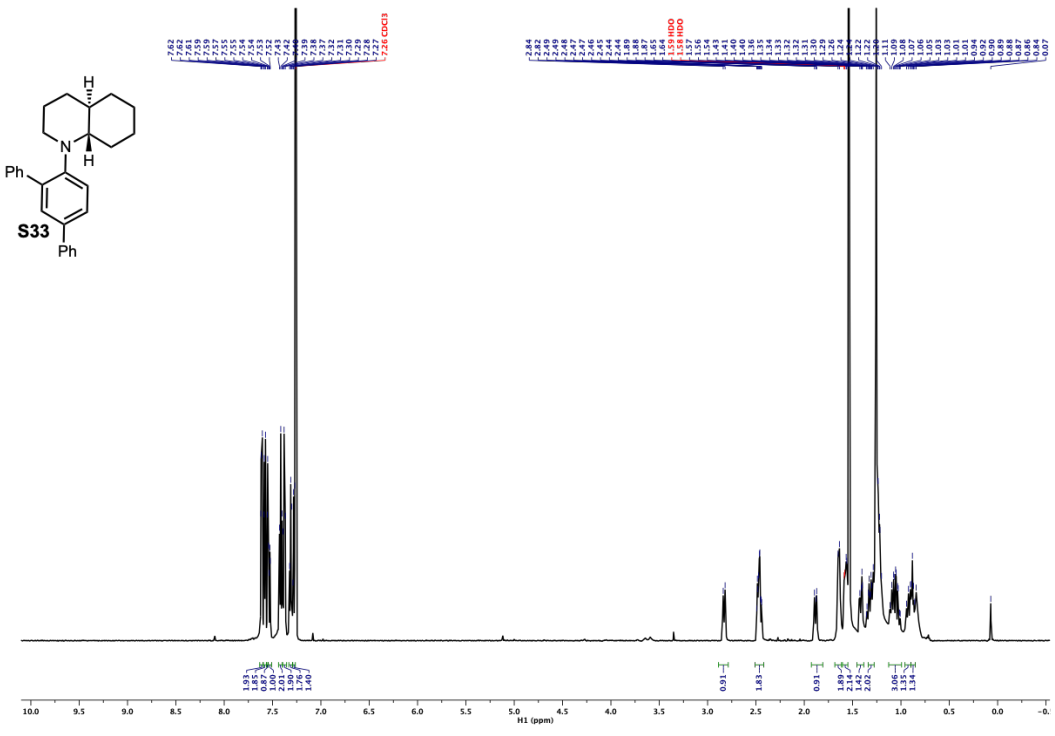
S32 (^{1}H NMR, 600 MHz, $CDCl_3$)



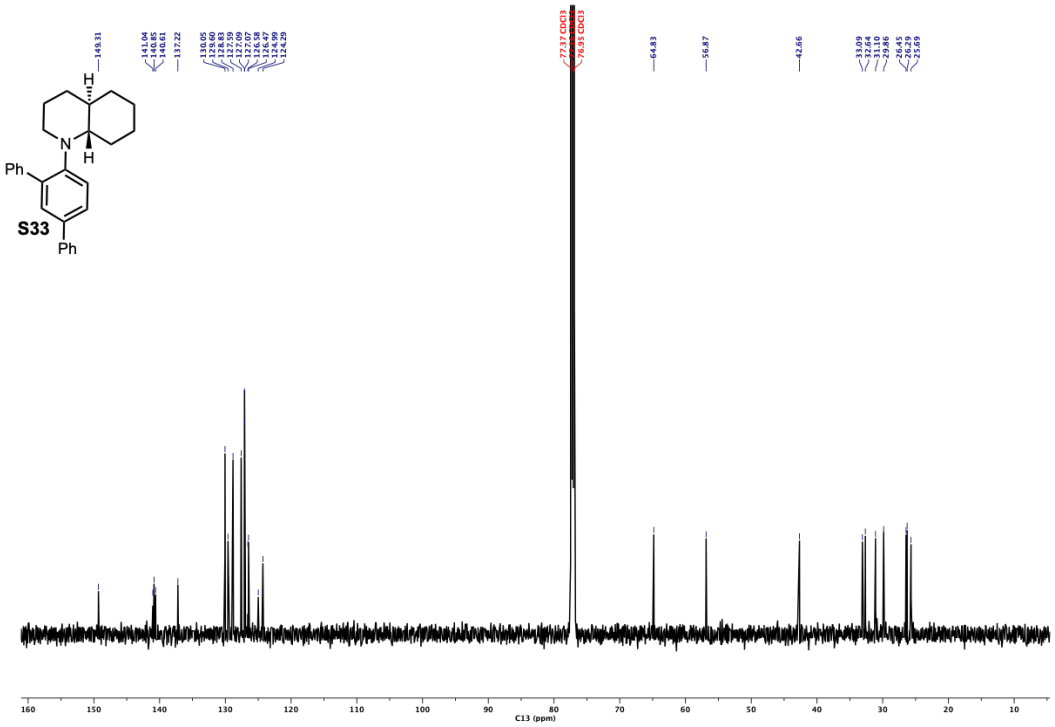
S32 (^{13}C, 151 MHz, $CDCl_3$)



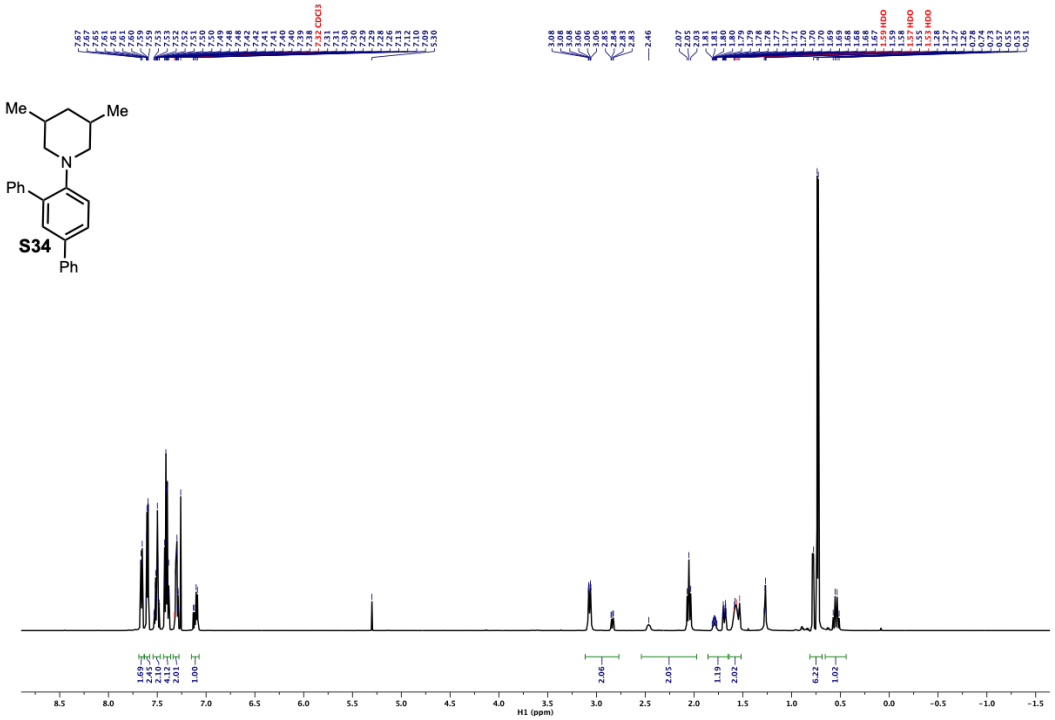
S33 (^{1}H NMR, 600 MHz, $CDCl_3$)



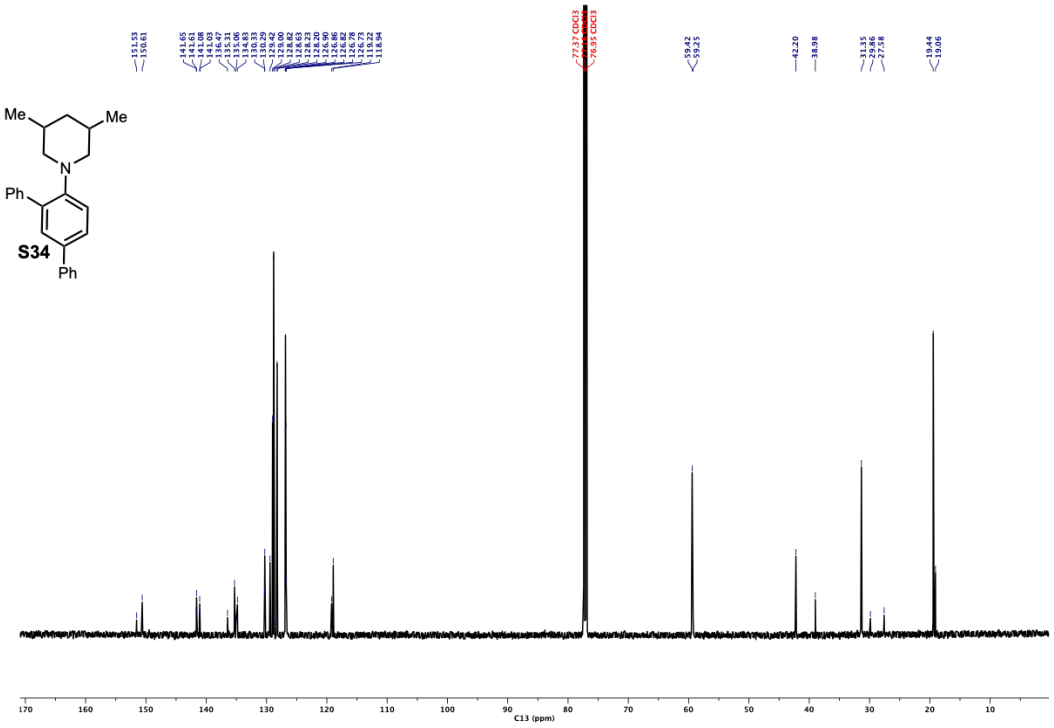
S33 (^{13}C, 151 MHz, $CDCl_3$)



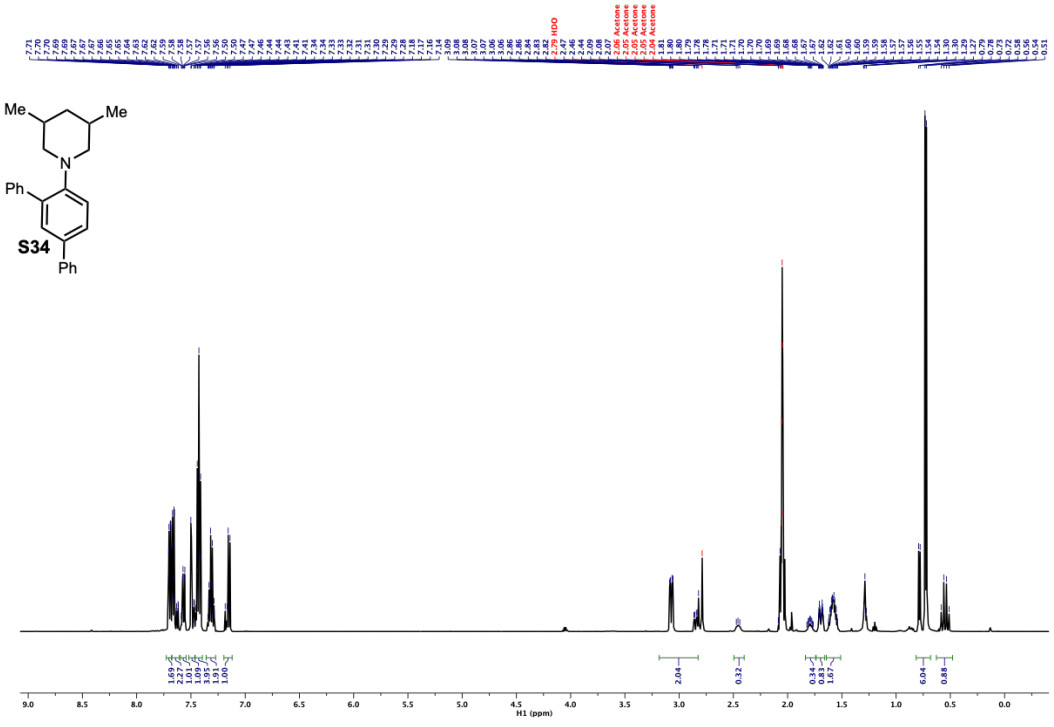
S34 (^{1}H NMR, 600 MHz, $CDCl_3$)



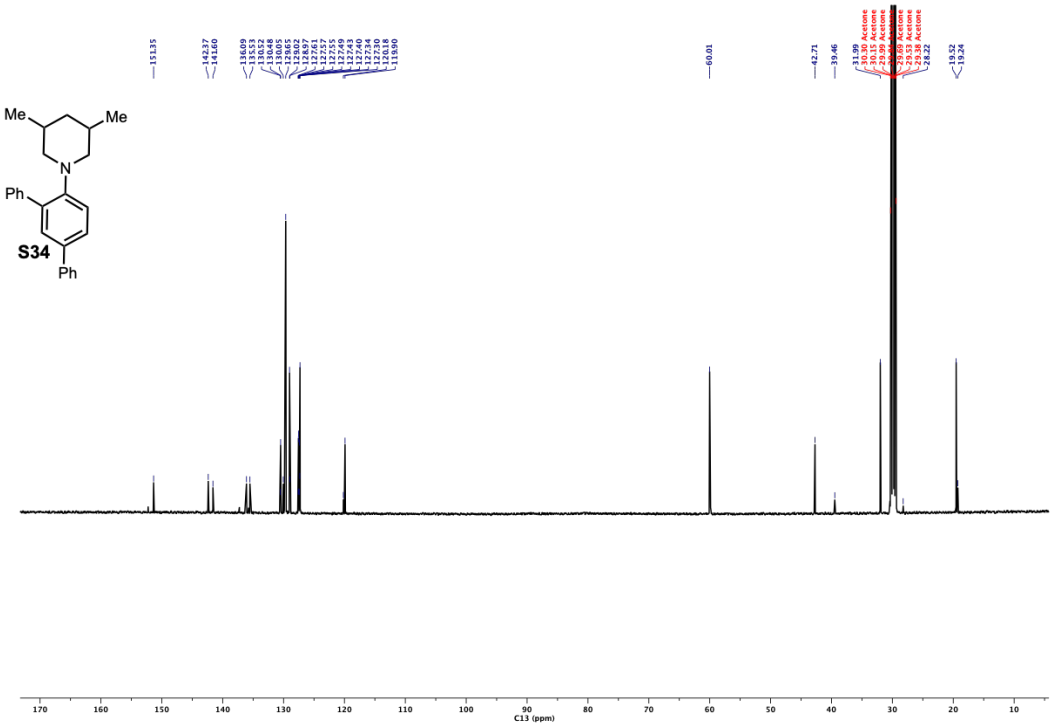
S34 (^{13}C, 151 MHz, $CDCl_3$)



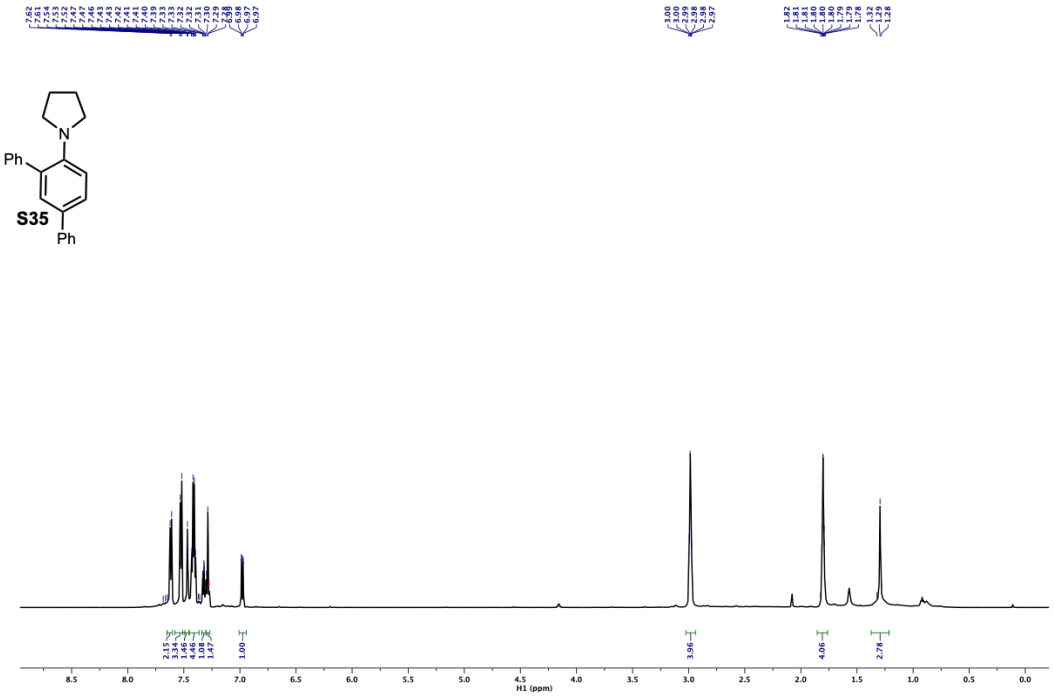
S34 (^{1}H NMR, 500 MHz, Acetone-d_6)



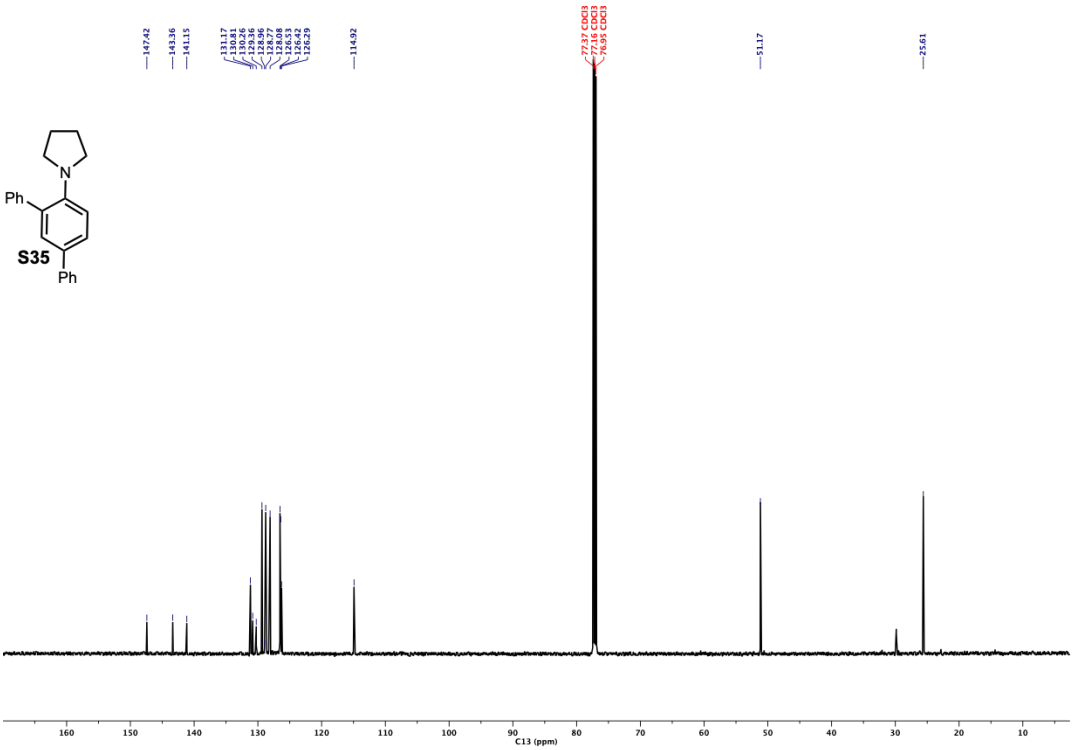
S34 (^{13}C, 126 MHz, Acetone-d_6)



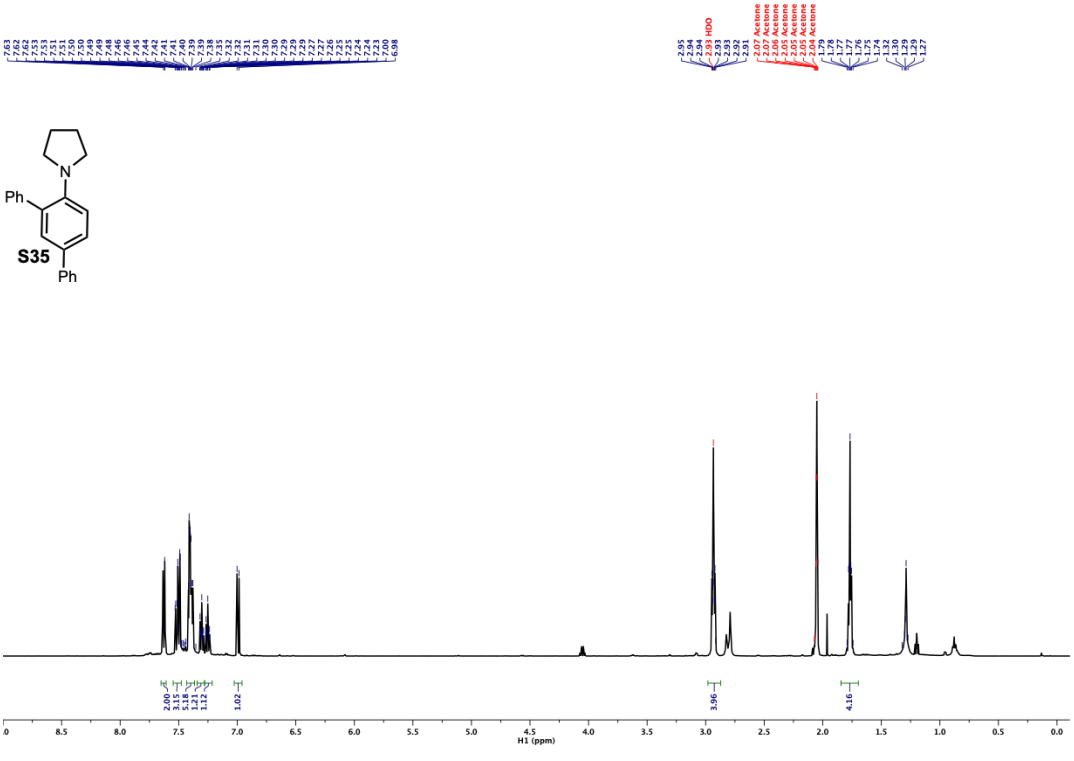
S35 (^{1}H NMR, 600 MHz, $CDCl_3$)



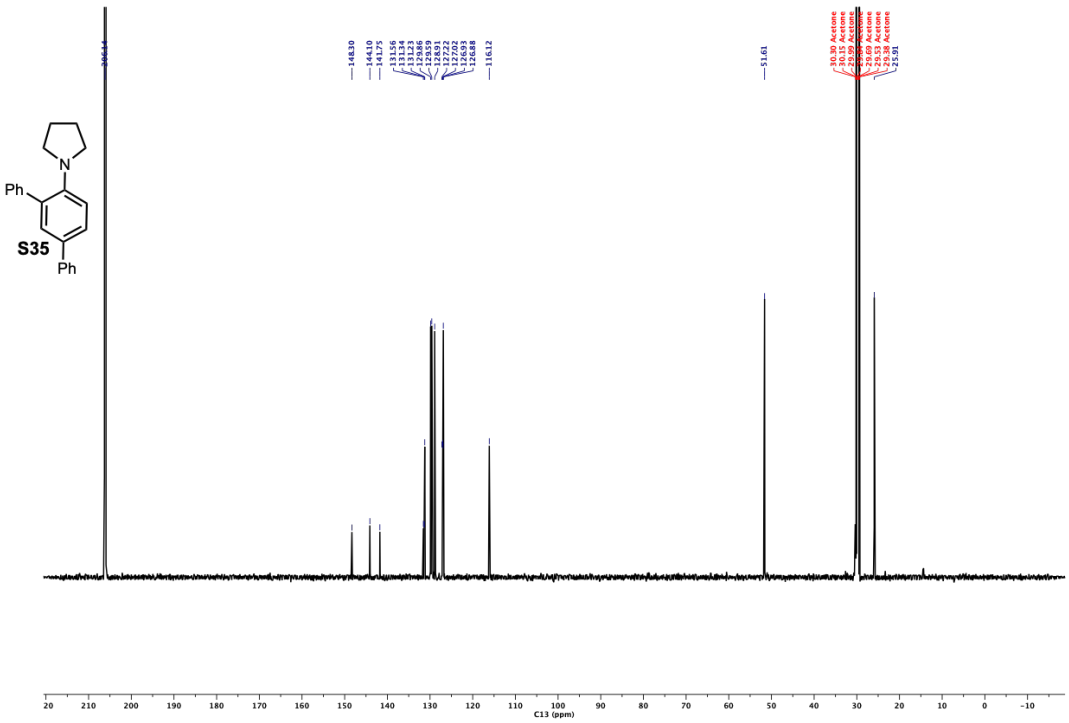
S35 (^{13}C, 151 MHz, $CDCl_3$)



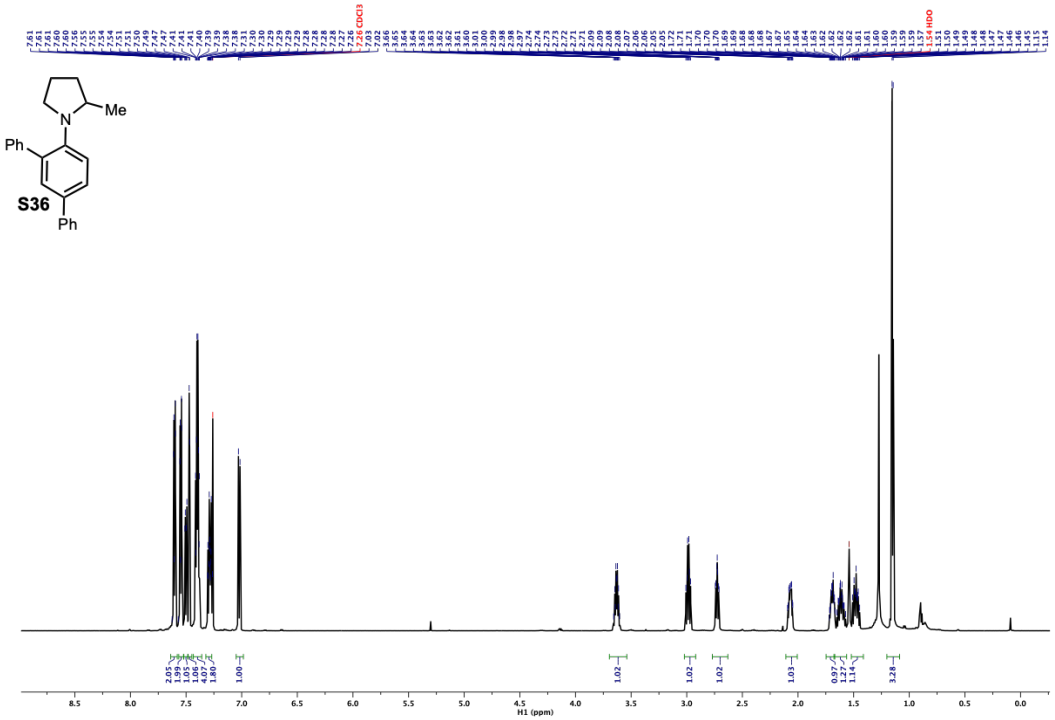
S35 (^{1}H NMR, 500 MHz, Acetone-d_6)



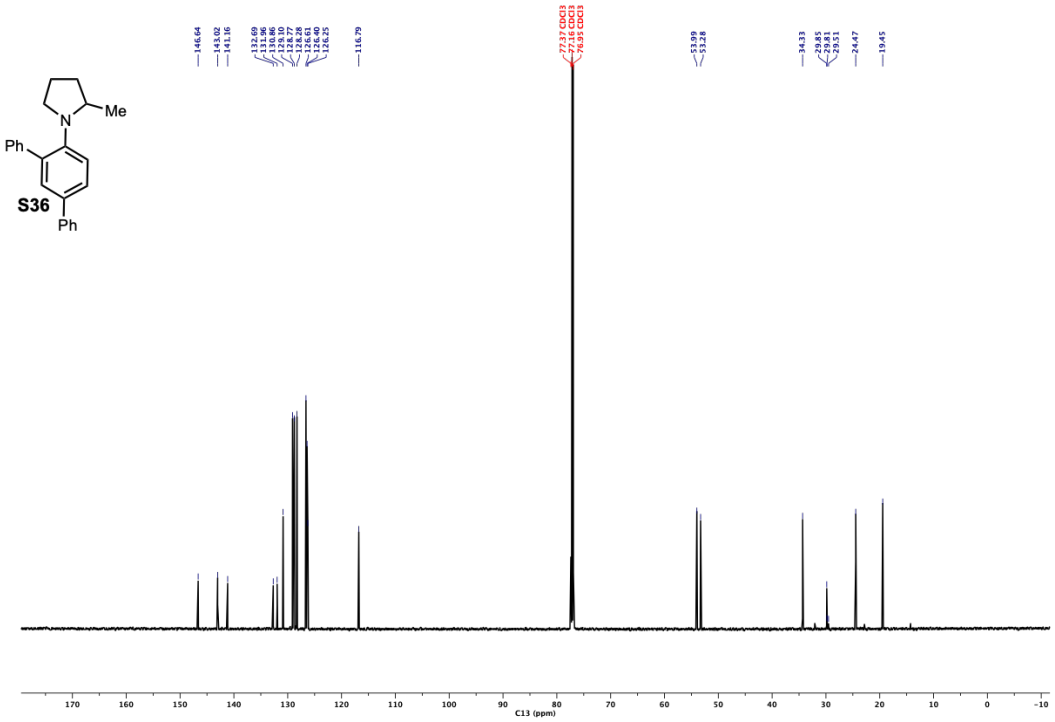
S35 (^{13}C, 126 MHz, Acetone-d_6)



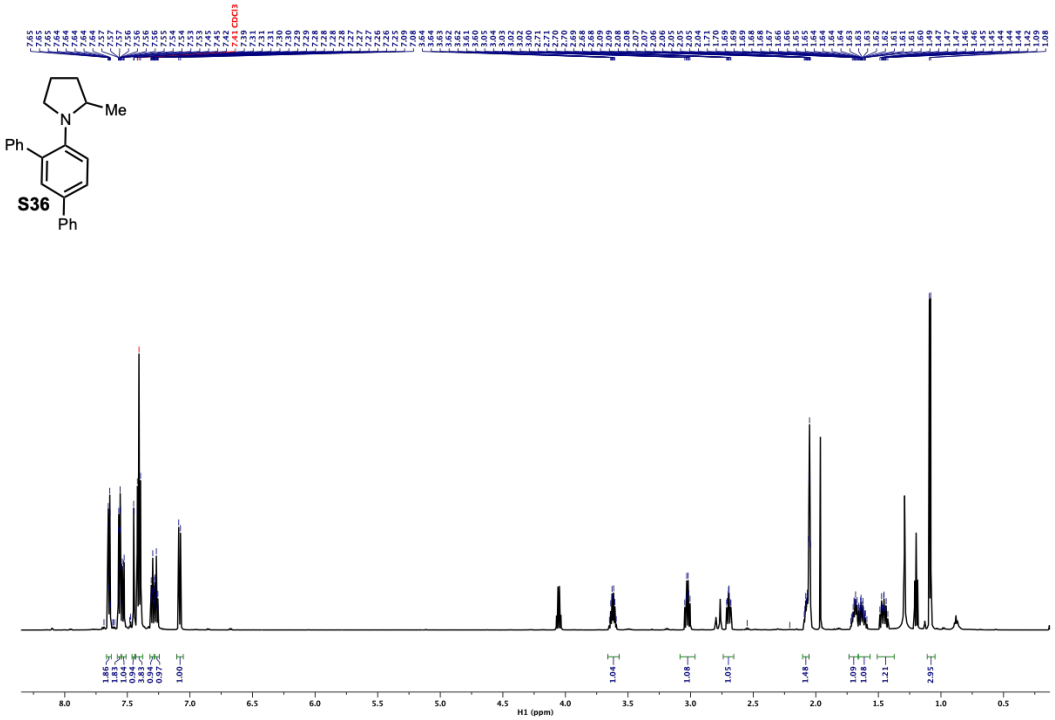
S36 (^{1}H NMR, 600 MHz, $CDCl_3$)



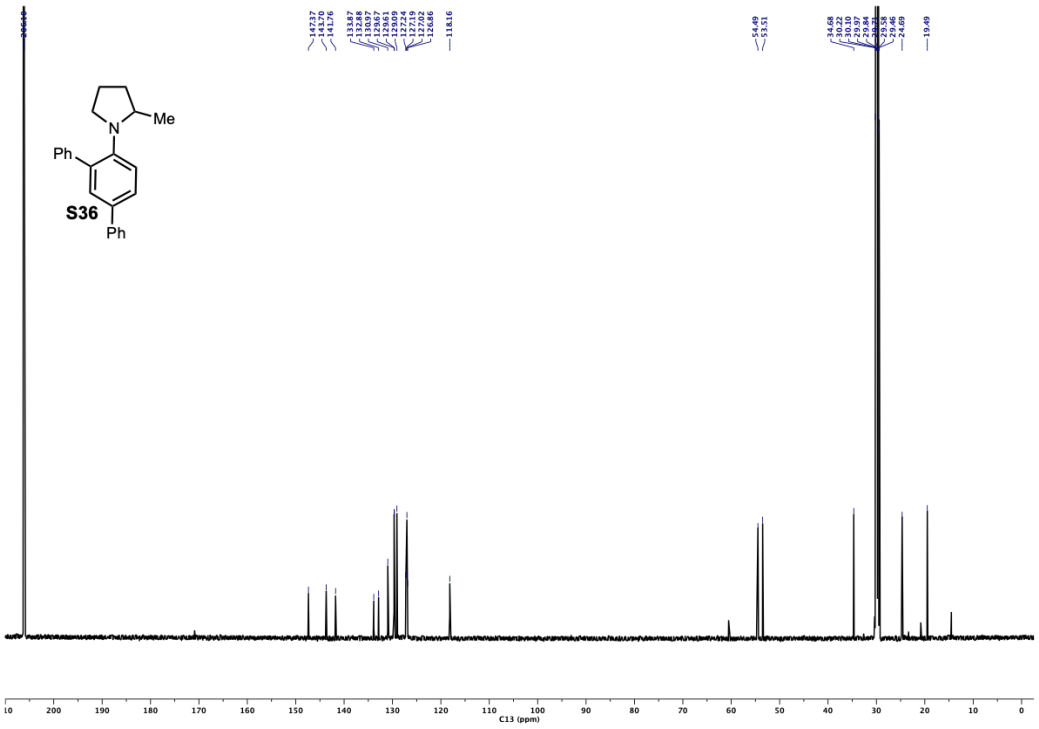
S36 (^{13}C, 151 MHz, $CDCl_3$)



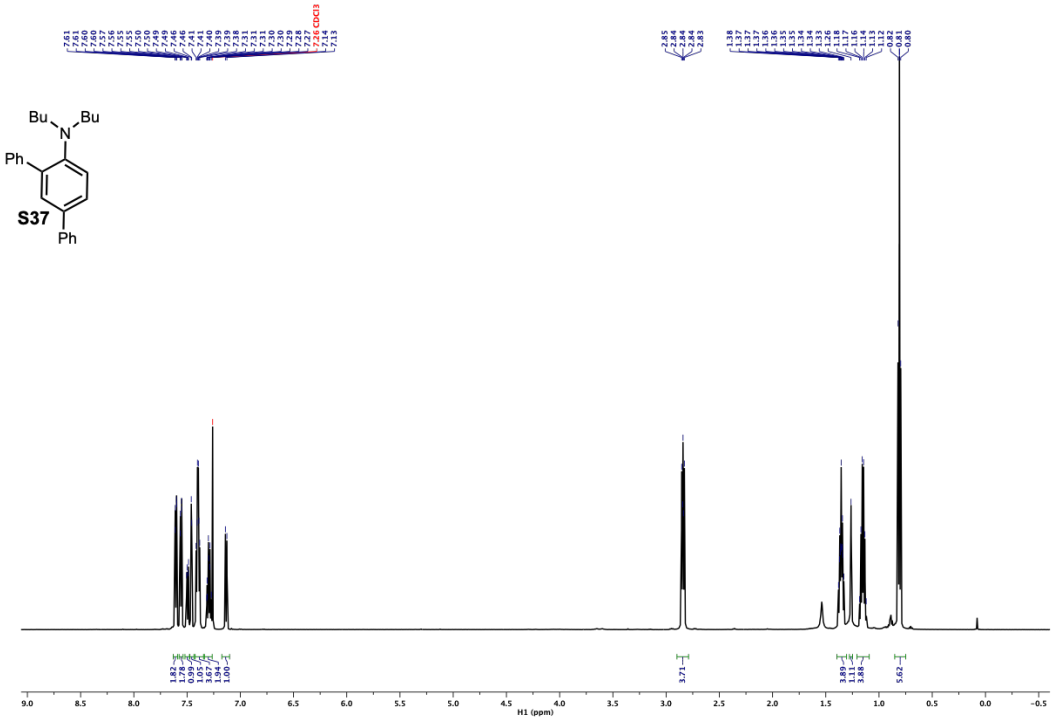
S36 (^{1}H NMR, 500 MHz, Acetone-d_6)



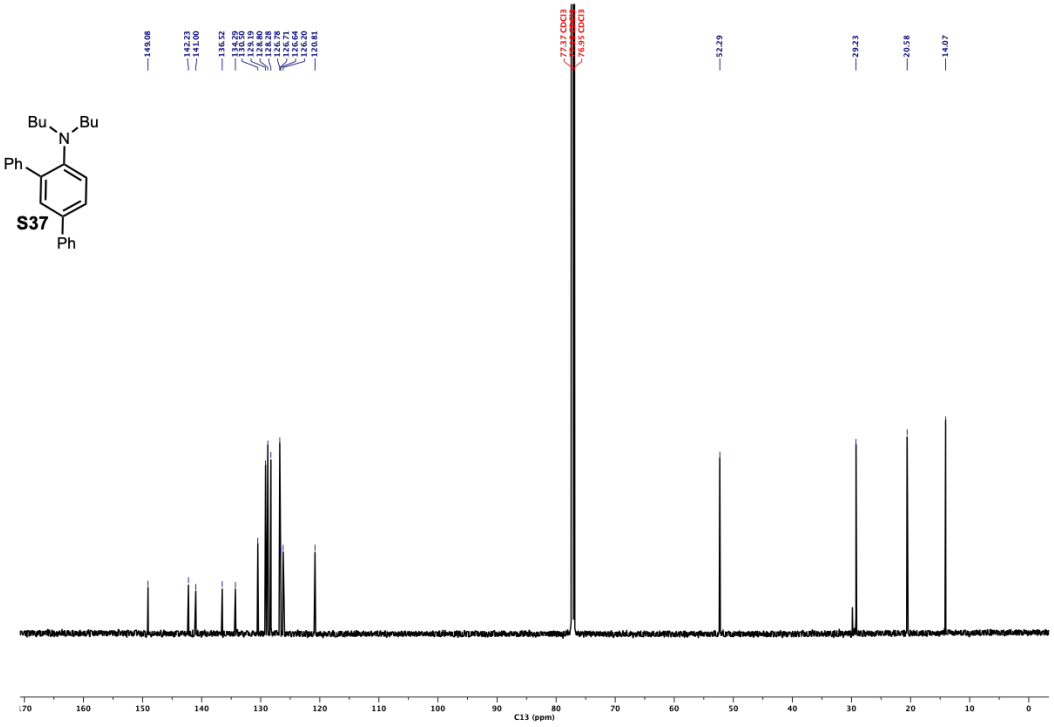
S36 (^{13}C, 126 MHz, Acetone-d_6)



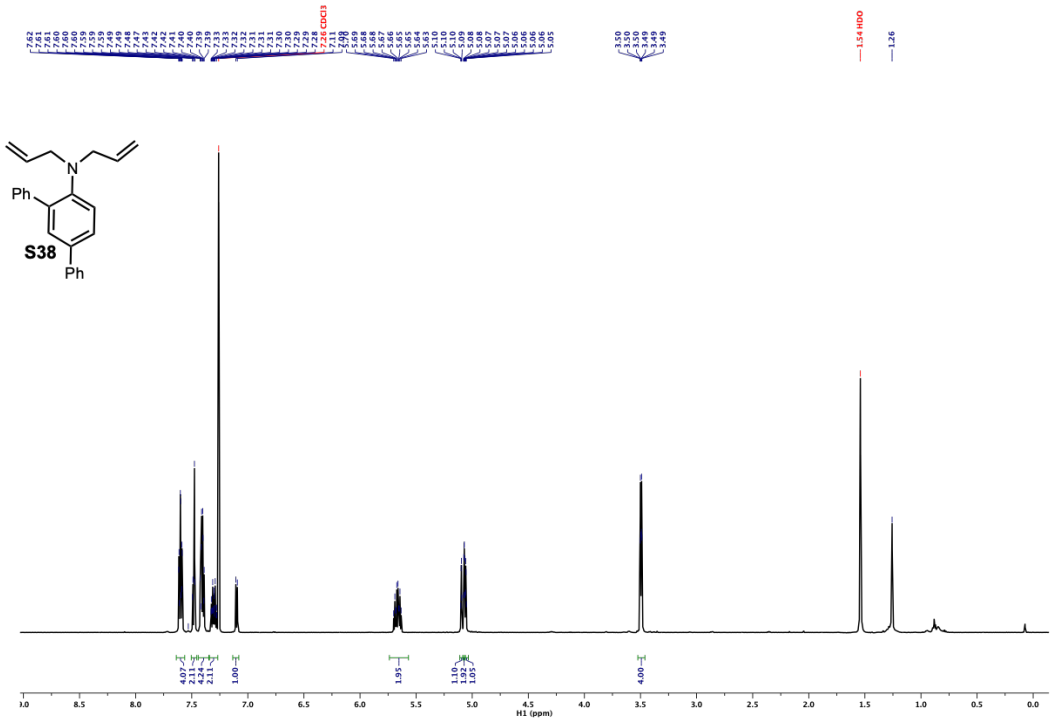
S37 (^{1}H NMR, 600 MHz, $CDCl_3$)



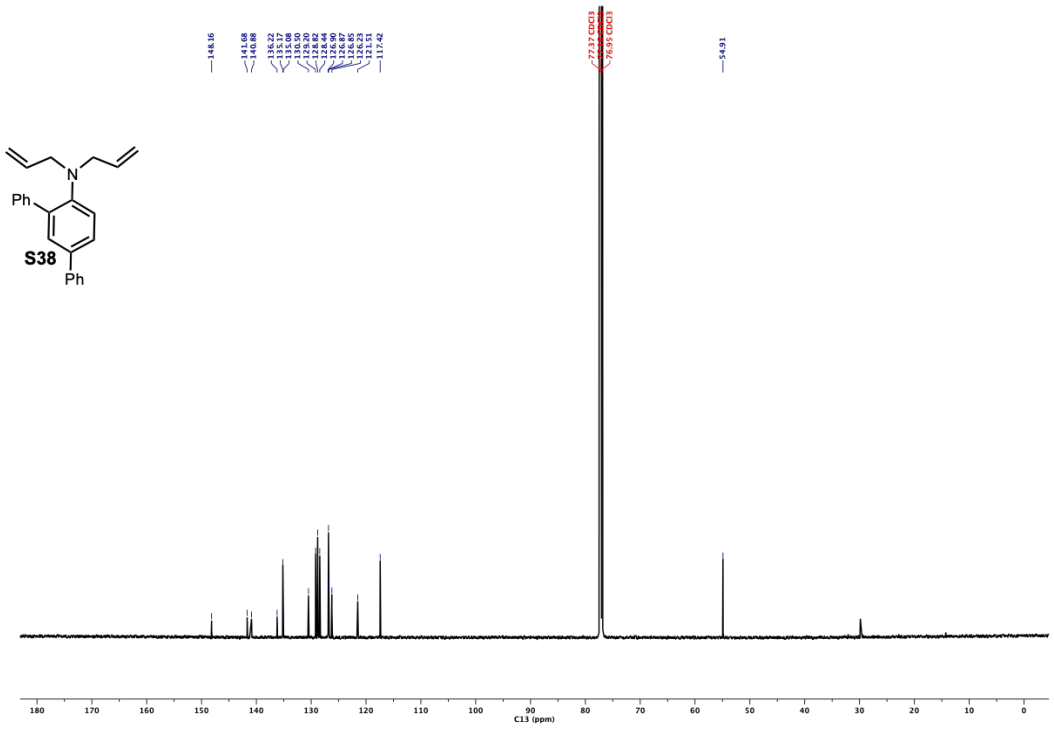
S37 (^{13}C, 151 MHz, $CDCl_3$)



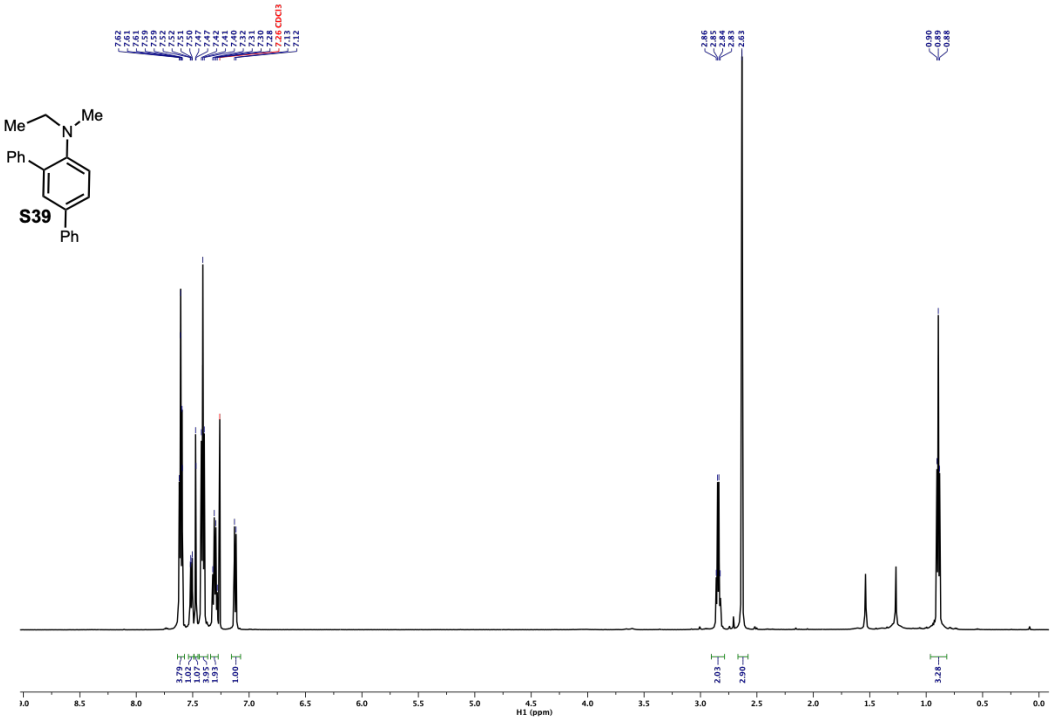
S38 (^{1}H NMR, 600 MHz, $CDCl_3$)



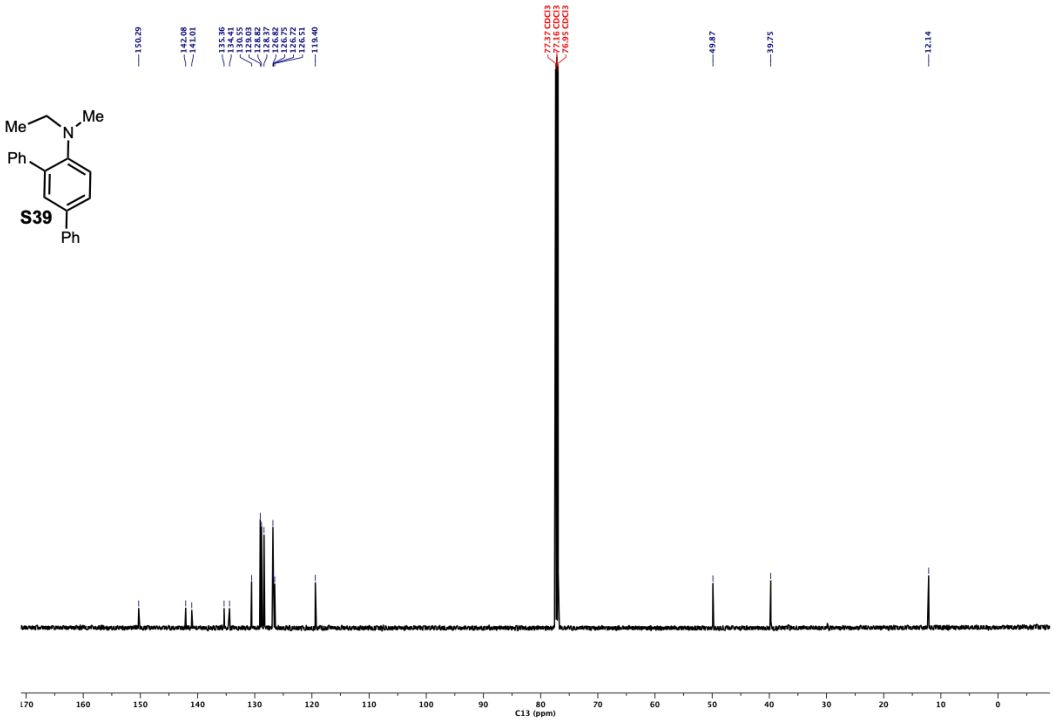
S38 (^{13}C, 151 MHz, $CDCl_3$)



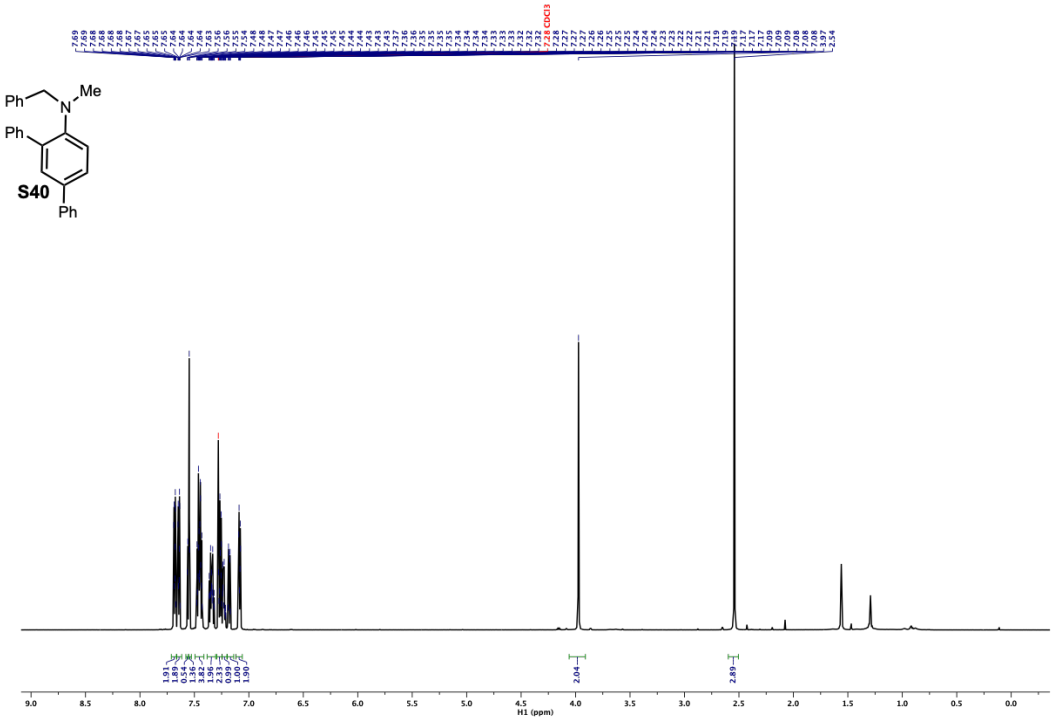
S39 (^{1}H NMR, 600 MHz, $CDCl_3$)



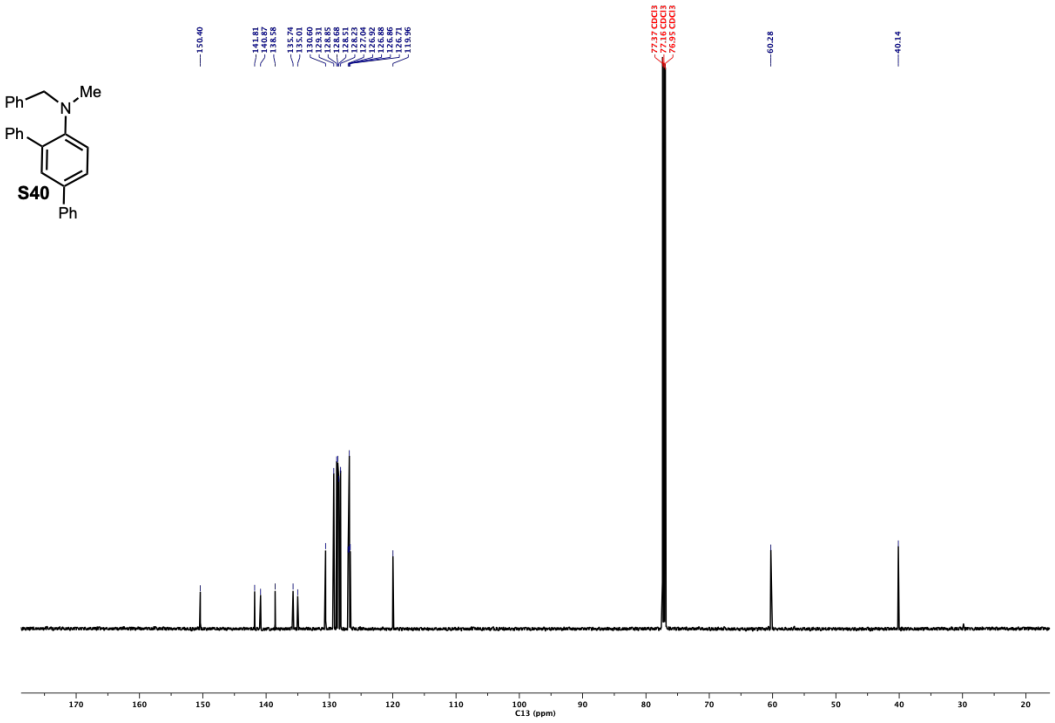
S39 (^{13}C, 151 MHz, $CDCl_3$)



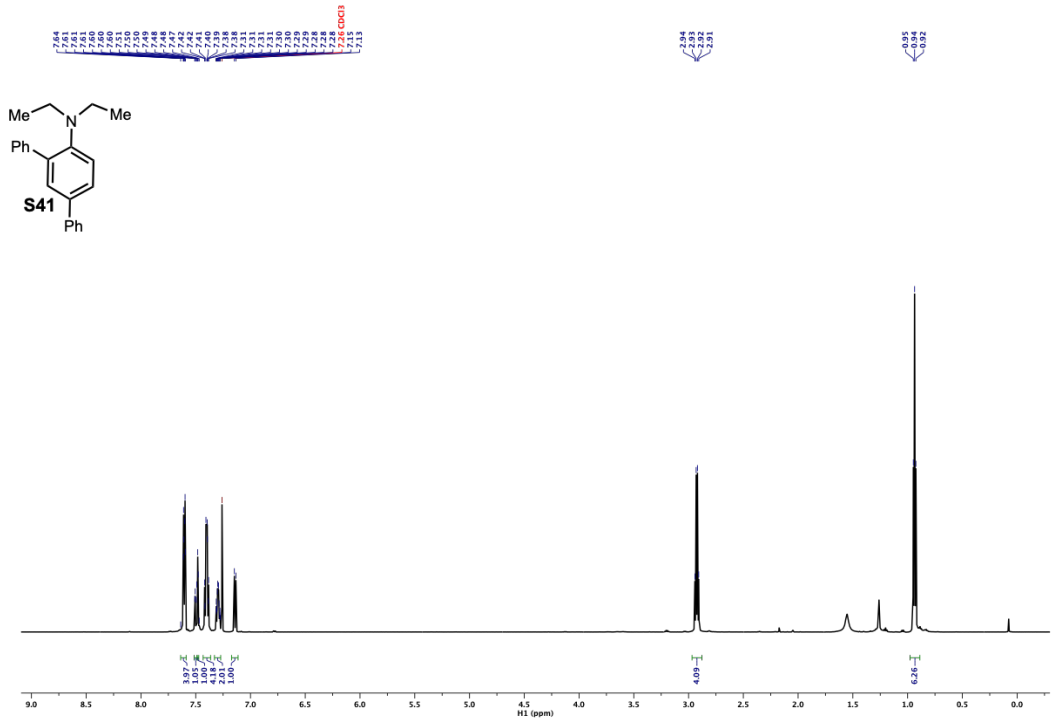
S40 (^{1}H NMR, 600 MHz, $CDCl_3$)



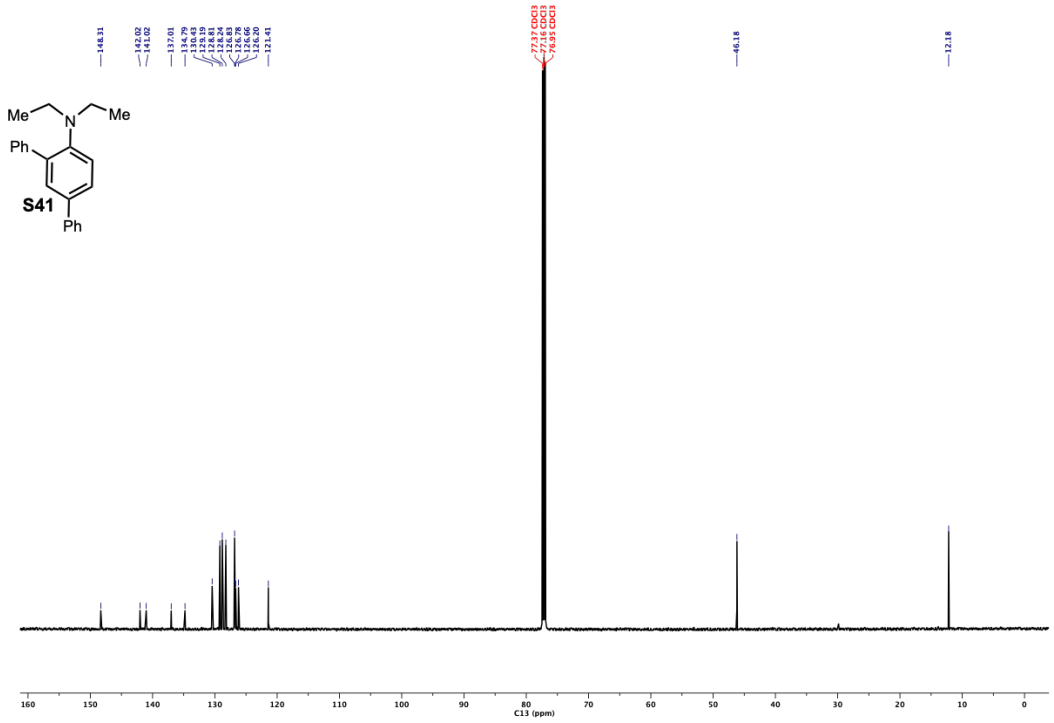
S40 (^{13}C, 151 MHz, $CDCl_3$)



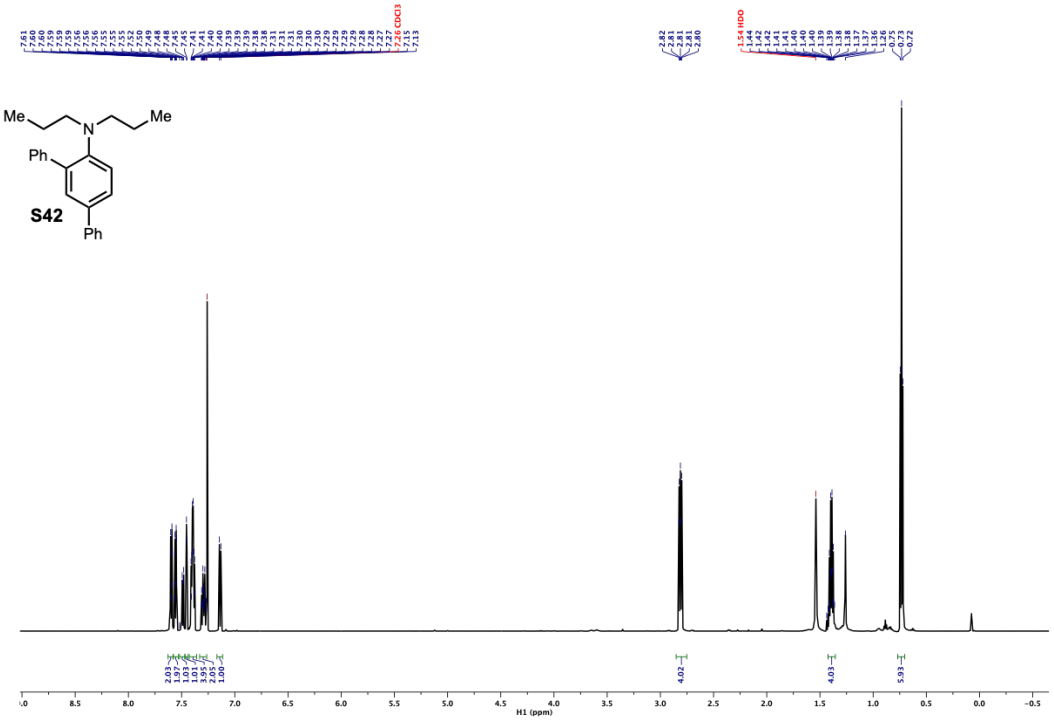
S41 (^{1}H NMR, 600 MHz, $CDCl_3$)



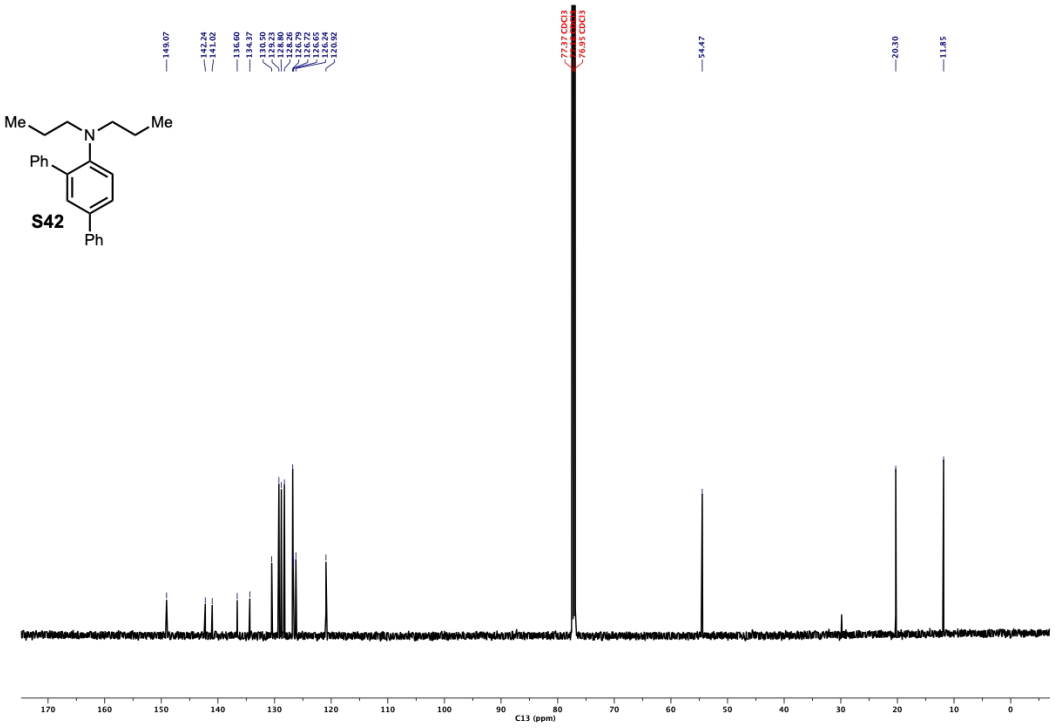
S41 (^{13}C, 151 MHz, $CDCl_3$)



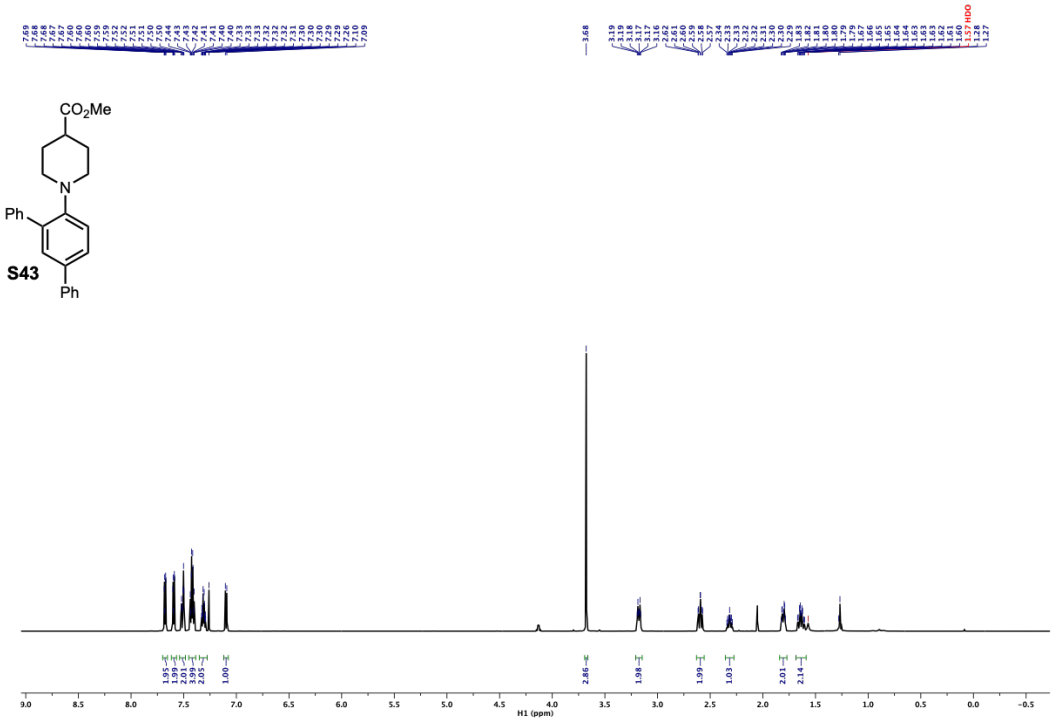
S42 (^{1}H NMR, 600 MHz, $CDCl_3$)



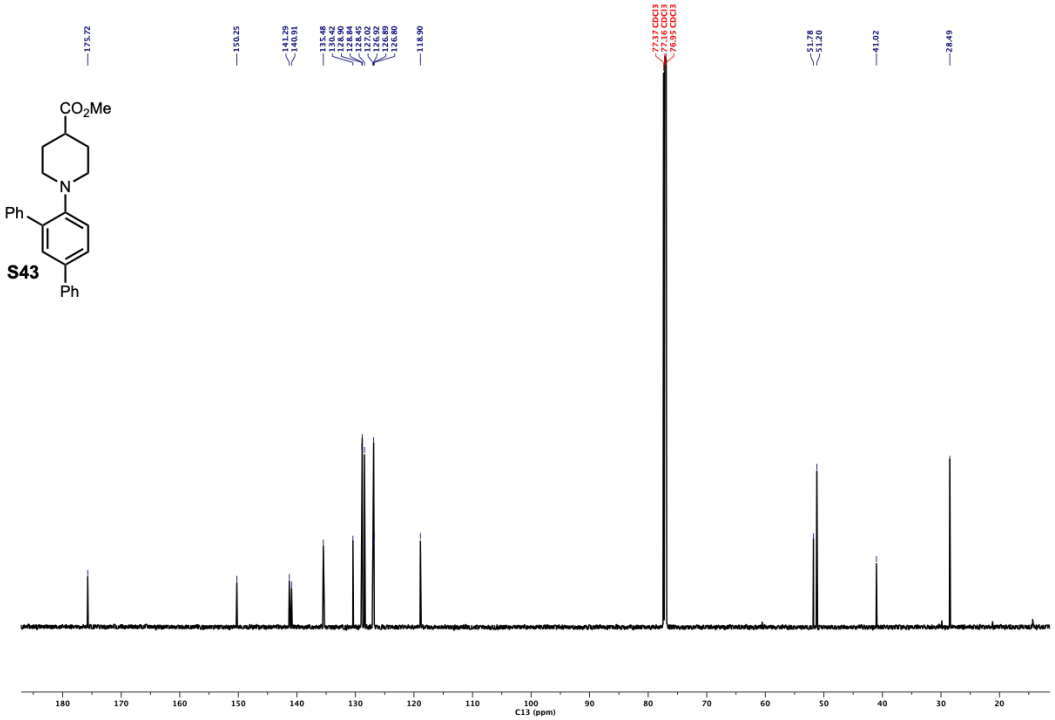
S42 (^{13}C, 151 MHz, $CDCl_3$)



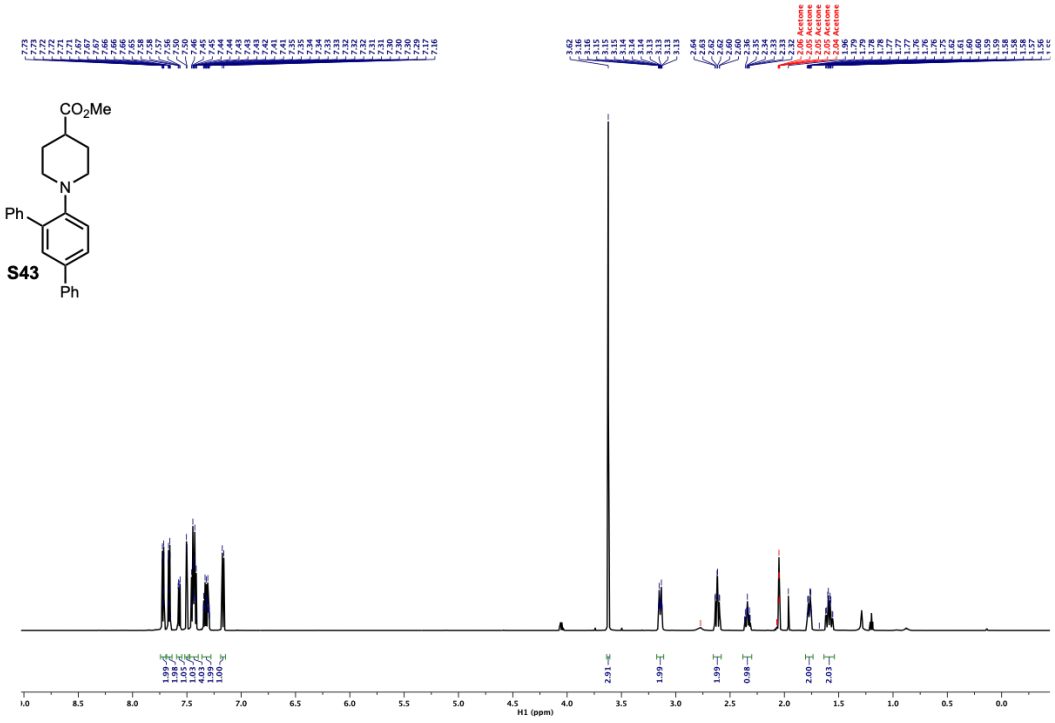
S43 (^{1}H NMR, 600 MHz, $CDCl_3$)



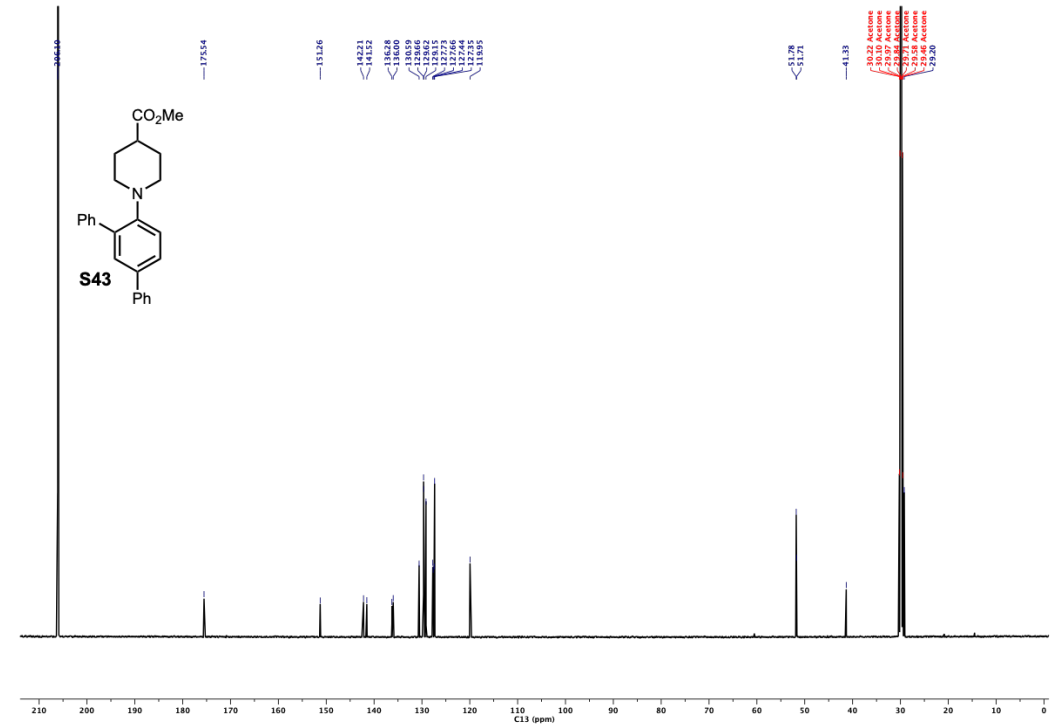
S43 (^{13}C, 151 MHz, $CDCl_3$)



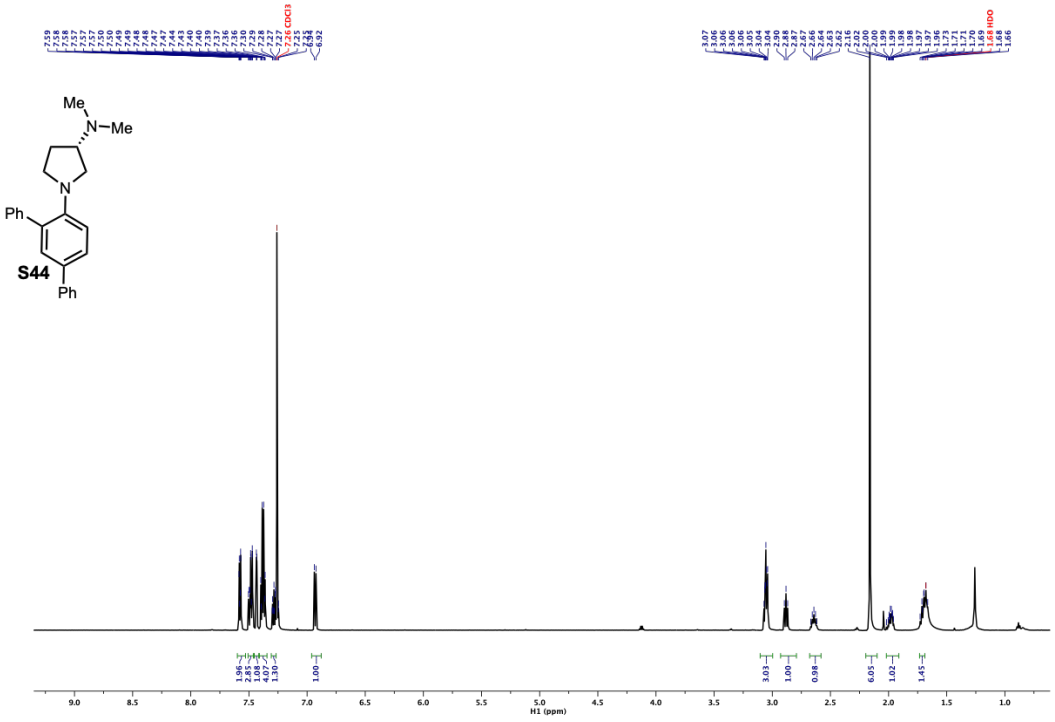
S43 (^{1}H NMR, 600 MHz, Acetone-d_6)



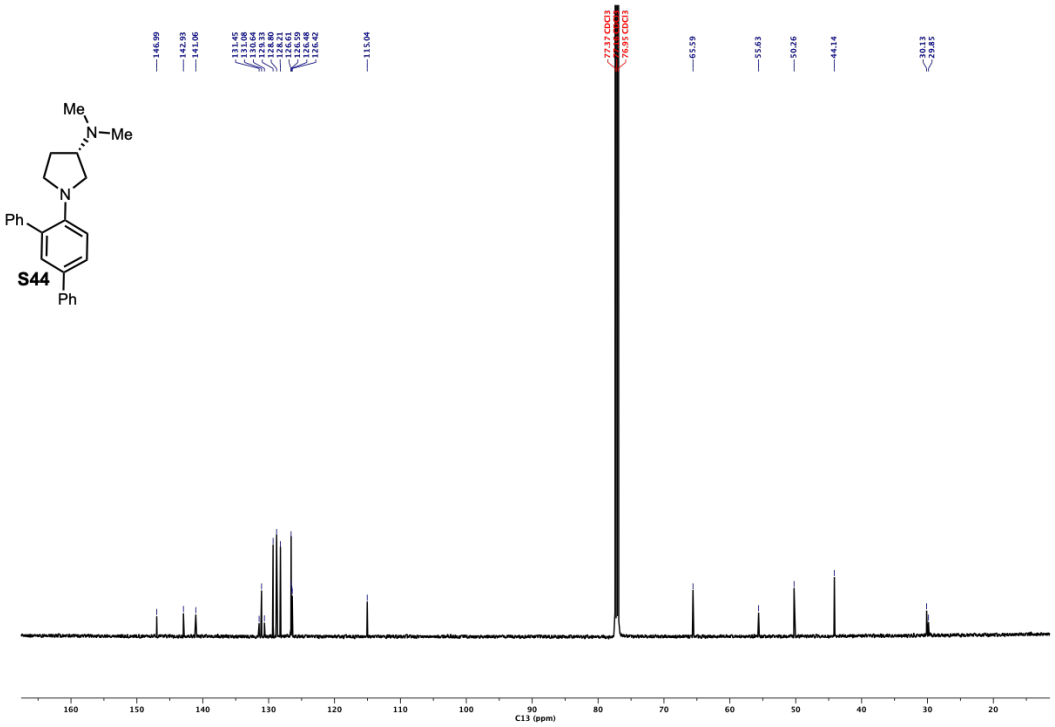
S43 (^{13}C, 151 MHz, Acetone-d_6)



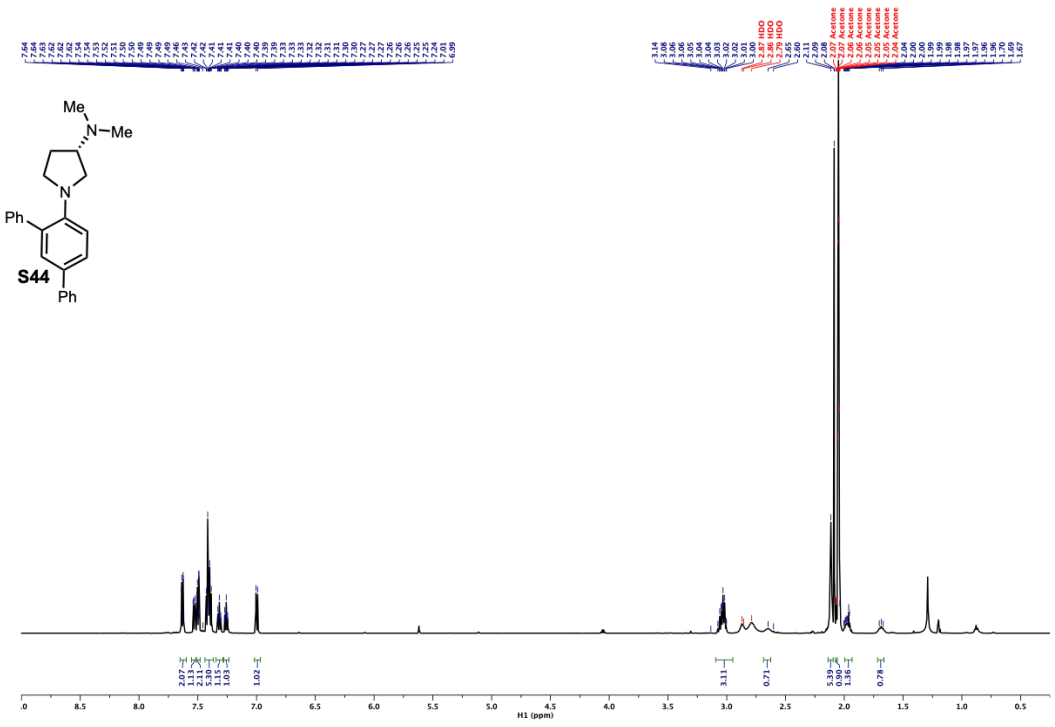
S44 (^{1}H NMR, 600 MHz, $CDCl_3$)



S44 (^{13}C, 151 MHz, $CDCl_3$)



S44 (^{1}H NMR, 600 MHz, Acetone-d_6)



8. X-Ray Crystallographic Information

A colorless block 0.27 x 0.17 x 0.11 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.25 mm and exposure time was 0.50 seconds per frame using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 19025 reflections were collected covering the indices -14<=h<=9, -17<=k<=17, -12<=l<=12. 3443 reflections were founded to be symmetry independent, with an R_{int} of 0.0375. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the CrysAlis^{Pro} 1.171.41.109a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

[*Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172.]*

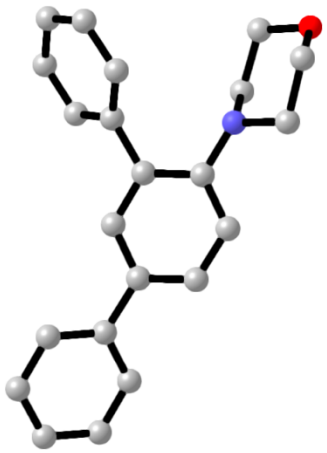


Figure S13. CYLview representation of **11a**.[45]

This crystal structure has been deposited at Cambridge Crystallographic Data Center under CDCC 2339055.

Table S5. Crystal data and structure refinement for KGardner01_Sarpong.

Identification code	KGardner01_Sarpong	
Empirical formula	C22 H21 N O	
Formula weight	315.40	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 11.86970(10) Å	a= 90°.
	b = 14.3822(2) Å	b= 95.7760(10)°.
	c = 9.93520(10) Å	g = 90°.
Volume	1687.45(3) $Å^3$	
Z	4	
Density (calculated)	1.241 Mg/m^3	
Absorption coefficient	0.585 mm^{-1}	
F(000)	672	
Crystal size	0.270 x 0.170 x 0.110 mm^3	
Theta range for data collection	3.743 to 74.445°.	
Index ranges	-14<=h<=9, -17<=k<=17, -12<=l<=12	
Reflections collected	19025	
Independent reflections	3443 [R(int) = 0.0375]	
Completeness to theta = 74.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.74274	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3443 / 0 / 217	
Goodness-of-fit on F^2	1.029	
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.0970	
R indices (all data)	R1 = 0.0412, wR2 = 0.0983	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.218 and -0.266 $e.Å^{-3}$	

Table S6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for kgardner01_sarpong. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1368(1)	2605(1)	6824(1)	26(1)
N(1)	2985(1)	3083(1)	5035(1)	18(1)
C(1)	2866(1)	3649(1)	6239(1)	21(1)
C(2)	1663(1)	3556(1)	6612(1)	24(1)
C(3)	1508(1)	2070(1)	5640(1)	26(1)
C(4)	2720(1)	2113(1)	5286(1)	21(1)
C(5)	3922(1)	3278(1)	4310(1)	17(1)
C(6)	3977(1)	4142(1)	3640(1)	17(1)
C(7)	3062(1)	4855(1)	3616(1)	17(1)
C(8)	1918(1)	4615(1)	3327(1)	19(1)
C(9)	1087(1)	5297(1)	3238(1)	22(1)
C(10)	1374(1)	6227(1)	3445(1)	22(1)
C(11)	2503(1)	6469(1)	3751(1)	21(1)
C(12)	3339(1)	5788(1)	3828(1)	19(1)
C(13)	4909(1)	4327(1)	2932(1)	18(1)
C(14)	5784(1)	3686(1)	2842(1)	18(1)
C(15)	6763(1)	3905(1)	2076(1)	19(1)
C(16)	6611(1)	4345(1)	817(1)	23(1)
C(17)	7519(1)	4494(1)	61(1)	27(1)
C(18)	8600(1)	4209(1)	560(1)	26(1)
C(19)	8768(1)	3786(1)	1819(1)	23(1)
C(20)	7861(1)	3640(1)	2576(1)	21(1)
C(21)	5701(1)	2827(1)	3477(1)	20(1)
C(22)	4787(1)	2630(1)	4205(1)	19(1)

Table S7. Bond lengths [Å] and angles [°] for kgardner01_sarpong.

O(1)-C(3)	1.4292(15)
O(1)-C(2)	1.4325(14)
N(1)-C(5)	1.4124(13)
N(1)-C(4)	1.4578(14)
N(1)-C(1)	1.4661(14)
C(1)-C(2)	1.5169(15)
C(3)-C(4)	1.5161(15)
C(5)-C(22)	1.3988(15)
C(5)-C(6)	1.4135(15)
C(6)-C(13)	1.3958(14)
C(6)-C(7)	1.4918(14)
C(7)-C(12)	1.3930(15)
C(7)-C(8)	1.4030(14)
C(8)-C(9)	1.3875(15)
C(9)-C(10)	1.3912(16)
C(10)-C(11)	1.3877(16)
C(11)-C(12)	1.3915(15)
C(13)-C(14)	1.3982(15)
C(14)-C(21)	1.3947(15)
C(14)-C(15)	1.4859(14)
C(15)-C(16)	1.3969(16)
C(15)-C(20)	1.4003(15)
C(16)-C(17)	1.3907(16)
C(17)-C(18)	1.3897(17)
C(18)-C(19)	1.3879(17)
C(19)-C(20)	1.3900(15)
C(21)-C(22)	1.3917(15)

C(3)-O(1)-C(2)	110.04(8)
C(5)-N(1)-C(4)	118.17(8)
C(5)-N(1)-C(1)	116.83(8)
C(4)-N(1)-C(1)	110.61(8)
N(1)-C(1)-C(2)	108.72(9)
O(1)-C(2)-C(1)	111.73(9)

O(1)-C(3)-C(4)	111.20(9)
N(1)-C(4)-C(3)	107.70(9)
C(22)-C(5)-N(1)	121.81(9)
C(22)-C(5)-C(6)	118.79(9)
N(1)-C(5)-C(6)	119.38(9)
C(13)-C(6)-C(5)	118.75(9)
C(13)-C(6)-C(7)	118.28(9)
C(5)-C(6)-C(7)	122.94(9)
C(12)-C(7)-C(8)	118.52(10)
C(12)-C(7)-C(6)	119.98(9)
C(8)-C(7)-C(6)	121.45(10)
C(9)-C(8)-C(7)	120.38(10)
C(8)-C(9)-C(10)	120.61(10)
C(11)-C(10)-C(9)	119.35(10)
C(10)-C(11)-C(12)	120.22(10)
C(11)-C(12)-C(7)	120.91(10)
C(6)-C(13)-C(14)	122.58(10)
C(21)-C(14)-C(13)	117.89(10)
C(21)-C(14)-C(15)	120.95(9)
C(13)-C(14)-C(15)	121.14(10)
C(16)-C(15)-C(20)	118.22(10)
C(16)-C(15)-C(14)	121.19(10)
C(20)-C(15)-C(14)	120.54(10)
C(17)-C(16)-C(15)	121.10(10)
C(18)-C(17)-C(16)	119.94(11)
C(19)-C(18)-C(17)	119.68(10)
C(18)-C(19)-C(20)	120.32(10)
C(19)-C(20)-C(15)	120.71(10)
C(22)-C(21)-C(14)	120.65(10)
C(21)-C(22)-C(5)	121.30(10)

Symmetry transformations used to generate equivalent atoms:

Table S8. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for kgardner01_sarpong. The anisotropic
displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	29(1)	28(1)	5(1)	11(1)	1(1)
N(1)	18(1)	17(1)	20(1)	0(1)	5(1)	0(1)
C(1)	21(1)	22(1)	19(1)	0(1)	4(1)	2(1)
C(2)	23(1)	26(1)	25(1)	3(1)	7(1)	4(1)
C(3)	22(1)	27(1)	29(1)	3(1)	6(1)	-4(1)
C(4)	21(1)	20(1)	24(1)	3(1)	5(1)	-1(1)
C(5)	15(1)	19(1)	17(1)	-1(1)	1(1)	-1(1)
C(6)	16(1)	18(1)	17(1)	-1(1)	1(1)	-1(1)
C(7)	17(1)	19(1)	15(1)	2(1)	3(1)	1(1)
C(8)	18(1)	19(1)	20(1)	1(1)	2(1)	-2(1)
C(9)	15(1)	24(1)	26(1)	1(1)	1(1)	0(1)
C(10)	20(1)	21(1)	26(1)	2(1)	3(1)	5(1)
C(11)	22(1)	17(1)	23(1)	1(1)	2(1)	-1(1)
C(12)	16(1)	21(1)	19(1)	2(1)	2(1)	-1(1)
C(13)	18(1)	17(1)	19(1)	0(1)	2(1)	-1(1)
C(14)	17(1)	20(1)	19(1)	-2(1)	2(1)	-1(1)
C(15)	18(1)	16(1)	23(1)	-4(1)	5(1)	-1(1)
C(16)	20(1)	24(1)	25(1)	0(1)	3(1)	-1(1)
C(17)	27(1)	30(1)	24(1)	3(1)	7(1)	-4(1)
C(18)	22(1)	28(1)	31(1)	-3(1)	11(1)	-6(1)
C(19)	17(1)	22(1)	31(1)	-5(1)	4(1)	-2(1)
C(20)	19(1)	20(1)	23(1)	-2(1)	3(1)	-1(1)
C(21)	17(1)	19(1)	23(1)	-2(1)	3(1)	2(1)
C(22)	19(1)	17(1)	22(1)	1(1)	2(1)	0(1)

Table S9. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for kgardner01_sarpong.

	x	y	z	U(eq)
H(1A)	3032	4309	6052	25
H(1B)	3407	3435	6999	25
H(2A)	1583	3916	7447	29
H(2B)	1133	3822	5878	29
H(3A)	995	2311	4872	31
H(3B)	1300	1415	5796	31
H(4A)	3242	1865	6042	26
H(4B)	2805	1734	4470	26
H(8)	1710	3981	3191	23
H(9)	315	5127	3034	26
H(10)	803	6693	3377	27
H(11)	2705	7102	3908	25
H(12)	4110	5962	4028	23
H(13)	4951	4911	2494	21
H(16)	5876	4545	472	27
H(17)	7401	4791	-796	32
H(18)	9220	4303	41	32
H(19)	9507	3595	2166	28
H(20)	7987	3357	3442	25
H(21)	6274	2372	3413	23
H(22)	4750	2044	4638	23

Table S10. Torsion angles [°] for kgardner01_sarpong.

C(5)-N(1)-C(1)-C(2)	162.48(9)
C(4)-N(1)-C(1)-C(2)	-58.46(11)
C(3)-O(1)-C(2)-C(1)	-57.32(12)
N(1)-C(1)-C(2)-O(1)	56.62(12)
C(2)-O(1)-C(3)-C(4)	59.23(12)
C(5)-N(1)-C(4)-C(3)	-161.57(9)
C(1)-N(1)-C(4)-C(3)	59.99(11)
O(1)-C(3)-C(4)-N(1)	-60.33(12)
C(4)-N(1)-C(5)-C(22)	-20.52(14)
C(1)-N(1)-C(5)-C(22)	115.39(11)
C(4)-N(1)-C(5)-C(6)	157.80(10)
C(1)-N(1)-C(5)-C(6)	-66.29(12)
C(22)-C(5)-C(6)-C(13)	-1.87(15)
N(1)-C(5)-C(6)-C(13)	179.76(9)
C(22)-C(5)-C(6)-C(7)	176.01(9)
N(1)-C(5)-C(6)-C(7)	-2.36(15)
C(13)-C(6)-C(7)-C(12)	-45.86(14)
C(5)-C(6)-C(7)-C(12)	136.25(11)
C(13)-C(6)-C(7)-C(8)	131.45(11)
C(5)-C(6)-C(7)-C(8)	-46.44(15)
C(12)-C(7)-C(8)-C(9)	0.87(15)
C(6)-C(7)-C(8)-C(9)	-176.48(10)
C(7)-C(8)-C(9)-C(10)	-0.55(17)
C(8)-C(9)-C(10)-C(11)	-0.39(17)
C(9)-C(10)-C(11)-C(12)	1.00(17)
C(10)-C(11)-C(12)-C(7)	-0.68(16)
C(8)-C(7)-C(12)-C(11)	-0.26(15)
C(6)-C(7)-C(12)-C(11)	177.13(10)
C(5)-C(6)-C(13)-C(14)	0.94(15)
C(7)-C(6)-C(13)-C(14)	-177.04(9)
C(6)-C(13)-C(14)-C(21)	0.81(15)
C(6)-C(13)-C(14)-C(15)	179.80(10)
C(21)-C(14)-C(15)-C(16)	136.38(11)
C(13)-C(14)-C(15)-C(16)	-42.57(15)

C(21)-C(14)-C(15)-C(20)	-41.03(15)
C(13)-C(14)-C(15)-C(20)	140.02(11)
C(20)-C(15)-C(16)-C(17)	1.74(17)
C(14)-C(15)-C(16)-C(17)	-175.73(10)
C(15)-C(16)-C(17)-C(18)	-0.42(18)
C(16)-C(17)-C(18)-C(19)	-0.74(18)
C(17)-C(18)-C(19)-C(20)	0.53(18)
C(18)-C(19)-C(20)-C(15)	0.85(17)
C(16)-C(15)-C(20)-C(19)	-1.95(16)
C(14)-C(15)-C(20)-C(19)	175.53(10)
C(13)-C(14)-C(21)-C(22)	-1.63(16)
C(15)-C(14)-C(21)-C(22)	179.39(10)
C(14)-C(21)-C(22)-C(5)	0.70(16)
N(1)-C(5)-C(22)-C(21)	179.42(10)
C(6)-C(5)-C(22)-C(21)	1.09(16)

Symmetry transformations used to generate equivalent atoms:

9. References

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