Supplementary Information for:

Intramolecular Asymmetric Propargylation of Esters and Imides: C–H Functionalisation Enables Stereocontrolled Access to UCS1025A

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Contents

1. General information

General reagent information:

Anhydrous THF was dried and deoxygenated by passage through packed columns of alumina and Q5 copper catalyst, respectively, and dispensed from a solvent purification system. Other anhydrous solvents were purchased from Acros (AcroSeal packaging) or Sigma Aldrich (Sure/Seal packaging) and were sparged with argon and transferred into an argon-filled glovebox before use. Bis(1,5-cyclooctadiene)diiridium(I) dichloride was purchased from Sigma Aldrich and was used as received. 2,2,6,6-Tetramethylpiperidine (TMPH) was purchased from Sigma Aldrich and vacuum distilled from CaH_2. (*Note*: Distilled TMPH should be stored under inert atmosphere.) All other reagents were purchased from TCI, Strem, Oakwood, Acros, Alfa Aesar, or Sigma Aldrich and used as received. Compounds were purified by preparative thin-layer chromatography (prep TLC) on SiliCycle 1000 μm plates, or by flash column chromatography using SiliCycle SiliaFlash® F60 silica gel. Analytical thin-layer chromatography (TLC) was performed using SiliCycle 250 μm plates. Compounds were visualised by irradiation with UV (254 nm), or by staining with iodine/silica gel or potassium permanganate. Yields refer to isolated compounds, unless otherwise indicated.

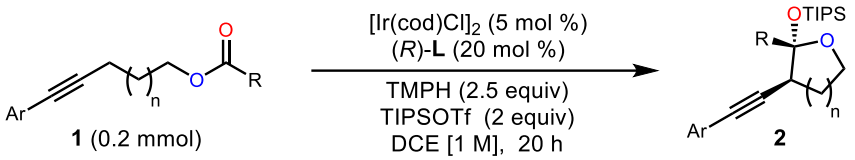
General analytical information:

All new compounds (starting materials and products) were characterised by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry. All ^{1}H NMR data are reported in δ units, parts per million (ppm), and were measured relative to the residual proton signal in the deuterated solvent at 7.26 ppm ($CDCl_3$). Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), integration, and coupling constant (Hz). All ^{13}C NMR spectra are ^{1}H decoupled and reported in ppm relative to the solvent signal at 77.16 ppm ($CDCl_3$). Enantiomeric excesses (ee) were determined by HPLC (high performance liquid chromatography) analysis using a chiral stationary phase. Specific columns and analytical methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analyses are provided with the associated chromatograms. High-resolution mass spectra were obtained on a Bruker Daltonics, Inc. APEXIII 7.0 TESLA FTMS instrument (ESI) or Waters Micromass GCT Premier instrument (EI). Specific optical rotation was collected on a Jacso P-2000 Digital Polarimeter.

2. Procedures and characterisation data

2.1 Cyclisation of esters and imides to cyclic acetals and hemiaminals

General Procedure A for the synthesis of cyclic silyl acetals from alkyne-tethered esters

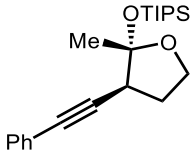


Preparation of the Ir complex solution: A reaction tube (13 mm by 100 mm, Fisherbrand part # 14-959-35C) equipped with a magnetic stir bar was flame dried and transferred into an argon-filled glovebox. In the glovebox, $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 5 mol %) and phosphoramidite (*R*)-**L** (20.3 mg, 0.04 mmol, 20 mol %) were added. (In some cases, noted below, 2.5 mol % $[Ir(cod)Cl]_2$ and 10 mol % (*R*)-**L** were used instead.) 1,2-Dichloroethane (0.2 mL) was added by syringe. The reaction tube was capped, and the solution was stirred at room temperature for 1 h to give a dark red solution.

Ir-catalyzed cyclisation reaction: To the solution prepared above were added **1** (0.2 mmol, 1.0 equiv), distilled 2,2,6,6-tetramethylpiperidine (TMPH) (85 µL, 0.5 mmol, 2.5 equiv), and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) (108 µL, 0.4 mmol, 2.0 equiv) in succession. The tube was again capped and removed from the glovebox and stirred for 20 hours at 50 °C, unless another temperature is specified. The reaction mixture was quenched by adding Et_3N (50 µL, 0.36 mmol, 1.8 equiv) and CH_2Cl_2 (ca. 1 mL). The diluted mixture was flushed through a short plug of silica (ca. 1 g) by eluting with CH_2Cl_2 (ca. 10 mL). The solution was concentrated *in vacuo* and dissolved in $CDCl_3$ (ca. 0.5 mL). ^{1}H NMR spectroscopy was used to determine crude diastereomeric ratio (dr). The solution was then concentrated *in vacuo* and purified by preparative thin layer chromatography (Prep TLC) to afford the isolated major diastereomer. (Preparative TLC plates were developed through multiple runs in succession until the desired degree of separation was achieved, with the plate removed from the developing chamber and dried thoroughly under a stream of air between runs.) For HPLC analysis, racemic samples were prepared by mixing equal amounts of samples prepared following general procedure A using (*S*)- and (*R*)-**L**.

The relative configurations of the 5-membered products were assigned by analogy to **2b**, whose relative configuration was determined based on ^{1}H NMR coupling constants. The relative configurations were determined separately for 6 membered products **2c**, **2g, and 2h,** each based on its own ^{1}H NMR coupling constants**.** The absolute configuration of all products was assigned by analogy to **4b** and **4db**. See section 4 for details.

Triisopropyl(((2*S*,3*S*)-2-methyl-3-(phenylethynyl)tetrahydrofuran-2-yl)oxy)silane (2a)



Prepared following general procedure A at a reaction temperature of 35 °C. The dr of the crude material was determined to be >20:1. The reaction mixture was purified by preparative TLC, developing 3 times in 99:1 hexanes/EtOAc to afford the title compound (major diastereomer) as a colorless oil (57.2 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.31 – 7.26 (m, 3H), 4.11 – 3.99 (m, 2H), 3.18 (dd, *J* = 7.5, 4.1 Hz, 1H), 2.52 (dq, *J* = 12.3, 7.7 Hz, 1H), 2.09 (tt, *J* = 7.6, 4.6 Hz, 1H), 1.71 (s, 3H), 1.09 – 1.05 (m, 21H).

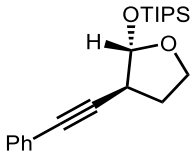
^{13}C NMR (126 MHz, $CDCl_3$) δ 131.7, 128.4, 127.9, 123.8, 107.5, 89.8, 83.7, 66.6, 44.3, 32.7, 25.5, 18.3, 13.2.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 99:1, 0.8 mL/min, r.t., λ = 242 nm) indicated a 99% ee: t_R (major) = 4.16 min, t_R (minor) = 4.44 min.

Specific rotation $[\alpha]_D^{25} = -109.2$ (*c* 0.545, $CHCl_3$).

HRMS (ESI) calcd. for $C_{22}H_{35}O_2Si$ $[M+H]^+$: 359.2401, Found: 359.2398.

Triisopropyl(((2*S*,3*S*)-3-(phenylethynyl)tetrahydro-2H-pyran-2-yl)oxy)silane (2b)



Prepared following general procedure A at room temperature, but with precatalyst and ligand loading reduced to: $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol %) and (*R*)-**L** (10.2 mg, 0.02 mmol, 10 mol %). The dr of the crude material was determined to be 11:1. The reaction mixture was purified by preparative TLC, developing 4 times in hexanes/EtOAc = 99:1 to afford the title compound (major diastereomer) as a colorless oil (39.4 mg, 57%). The relative configuration was assigned based on ^{1}H NMR coupling constants. See section 4 for details.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, *J* = 6.0, 3.2 Hz, 2H), 7.31 – 7.26 (m, 3H), 5.57 (br. s, 1H), 4.13 – 4.04 (m, 2H), 3.11 (dd, *J* = 7.5, 3.3 Hz, 1H), 2.42 (dq, *J* = 12.0, 7.7 Hz, 1H), 2.06 (dddd, *J* = 10.9, 7.0, 5.2, 3.9 Hz, 1H), 1.16 – 1.05 (m, 21H).

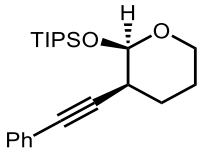
^{13}C NMR (126 MHz, $CDCl_3$) δ 131.8, 128.3, 128.0, 123.6, 102.6, 89.6, 82.5, 67.0, 40.6, 31.3, 18.0, 17.9, 12.2.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 99.5:0.5, 0.8 mL/min, r.t., λ = 243 nm) indicated a 99% ee: t_R (major) = 5.16 min, t_R (minor) = 5.67 min.

Specific rotation $[\alpha]_D^{25} = -108.4$ (*c* 0.59, $CHCl_3$).

HRMS (ESI) calcd. for $C_{21}H_{33}O_2Si$ $[M+H]^+$: 345.2244, Found: 345.2241.

Triisopropyl(((2*S*,3*S*)-3-(phenylethynyl)tetrahydro-2H-pyran-2-yl)oxy)silane (2c)



Prepared following general procedure A, but with precatalyst and ligand loading reduced to: $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol %) and (*R*)-**L** (10.2 mg, 0.02 mmol, 10 mol %). The dr of the crude material was determined to be >10:1. The reaction mixture was purified by prep TLC, developing 3 times in hexanes/EtOAc = 49:1 to afford the title compound (major diastereomer) as a colorless oil (43.9 mg, 61%). The relative configuration was assigned based on ^{1}H NMR coupling constants. See section 4 for details.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.30 – 7.26 (m, 3H), 4.95 (d, *J* = 4.9 Hz, 1H), 4.01 (ddd, *J* = 10.9, 6.8, 3.7 Hz, 1H), 3.54 (ddd, *J* = 11.1, 7.3, 3.5 Hz, 1H), 2.69 (dt, *J* = 8.0, 4.5 Hz, 1H), 2.20 (ddt, *J* = 12.1, 7.8, 3.9 Hz, 1H), 1.82 (dtt, *J* = 14.5, 7.4, 3.7 Hz, 1H), 1.73 (dtd, *J* = 12.3, 8.1, 3.9 Hz, 1H), 1.52 (dtt, *J* = 12.1, 7.7, 3.8 Hz, 1H), 1.14 – 1.06 (m, 21H).

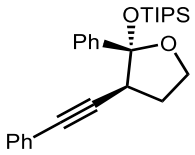
^{13}C NMR (126 MHz, $CDCl_3$) δ 131.8, 128.3, 127.8, 124.0, 96.1, 90.6, 82.4, 63.3, 36.5, 26.7, 23.4, 18.1, 18.0, 12.4.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 99.5:0.5, 0.5 mL/min, r.t., λ = 241 nm) indicated a 95% ee: t_R (major) = 8.61 min, t_R (minor) = 8.24 min.

Specific rotation $[\alpha]_D^{25} = -61.3$ (*c* 0.185, $CHCl_3$).

HRMS (ESI) calcd. for $C_{22}H_{35}O_2Si$ $[M+H]^+$: 359.2401, Found: 359.2396.

Triisopropyl(((2*R*,3*S*)-2-phenyl-3-(phenylethynyl)tetrahydrofuran-2-yl)oxy)silane (2d)



Prepared following general procedure A. The dr of the crude reaction mixture was determined to be 3.8:1. The reaction mixture was purified by prep TLC, developing 3 times in hexanes/EtOAc = 99:1 to afford the title compound (major diastereomer) as a colorless oil (43.0 mg, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 2H), 7.35 – 7.27 (m, 3H), 7.21 – 7.11 (m, 3H), 7.01 – 6.93 (m, 2H), 4.36 – 4.24 (m, 2H), 3.49 (dd, *J* = 7.0, 4.3 Hz, 1H), 2.60 (dq, *J* = 12.0, 7.8 Hz, 1H), 2.16 (ddt, *J* = 11.1, 6.5, 4.6 Hz, 1H), 1.00 – 0.92 (m, 21H).

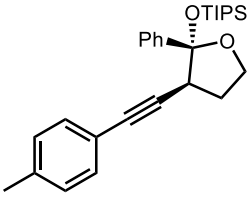
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 131.5, 128.1, 127.8, 127.7, 127.3, 127.1, 123.6, 109.4, 89.0, 85.0, 68.5, 46.6, 32.4, 18.3, 18.2, 13.2.

HPLC analysis (IB column, hexanes/i-PrOH = 99.9:0.1, 0.2 mL/min, r.t., λ = 246 nm) indicated a 99% ee: t_R (major) = 20.44 min, t_R (minor) = 20.72 min.

Specific rotation $[\alpha]_D^{25} = -54.4$ (*c* 0.68, $CHCl_3$).

HRMS (ESI) calcd. for $C_{27}H_{37}O_2Si$ $[M+H]^+$: 421.2557, Found: 421.2571.

Triisopropyl(((2*R*,3*S*)-2-phenyl-3-(p-tolylethynyl)tetrahydrofuran-2-yl)oxy)silane (2e)



Prepared following general procedure A, but with the reaction time increased to 3 days. The dr of the crude reaction mixture was determined to be 3.0:1. The reaction mixture was purified by prep TLC, developing 4 times in hexanes/EtOAc = 99:1 to afford the title compound (major diastereomer) as a colorless oil (45.3 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.33 – 7.27 (m, 3H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 4.34 – 4.24 (m, 2H), 3.47 (dd, *J* = 6.9, 4.4 Hz, 1H), 2.59 (dq, *J* = 12.0, 7.8 Hz, 1H), 2.27 (s, 3H), 2.14 (ddt, *J* = 11.2, 6.5, 4.5 Hz, 1H), 0.97 – 0.93 (m, 21H).

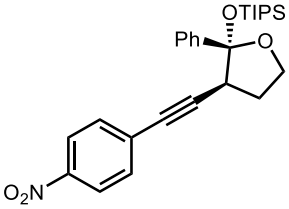
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 137.7, 131.3, 128.8, 127.8, 127.3, 127.1, 120.5, 109.4, 88.2, 85.0, 68.5, 46.6, 32.4, 21.5, 18.3, 18.2, 13.2.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 99.9:0.1, 0.8 mL/min, r.t., λ = 243 nm) indicated a 98% ee: t_R (major) = 6.43 min, t_R (minor) = 7.78 min.

Specific rotation $[\alpha]_D^{25} = -122.2$ (*c* 0.13, $CHCl_3$).

HRMS (ESI) calcd. for $C_{28}H_{39}O_2Si$ $[M+H]^+$: 435.2714, Found: 435.2713

Triisopropyl(((2*R*,3*S*)-3-((4-nitrophenyl)ethynyl)-2-phenyltetrahydrofuran-2-yl)oxy)silane (2f)



Prepared following general procedure A . The dr of the crude reaction mixture was determined to be 8.1:1. The reaction mixture was purified by prep TLC, developing 3 times in hexanes/EtOAc = 49:1 to afford the title compound (major diastereomer) as a yellow oil (39.7 mg, 43%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 2H), 7.61 – 7.57 (m, 2H), 7.36 – 7.27 (m, 3H), 7.05 (d, *J* = 8.9 Hz, 2H), 4.35 – 4.28 (m, 2H), 3.53 (dd, *J* = 7.2, 4.3 Hz, 1H), 2.63 (dq, *J* = 12.1, 7.8 Hz, 1H), 2.18 (ddt, *J* = 11.3, 6.1, 4.8 Hz, 1H), 1.02 – 0.92 (m, 21H).

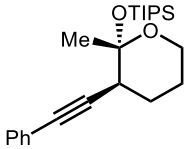
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 143.1, 132.2, 130.6, 128.0, 127.4, 127.0, 123.4, 109.3, 95.2, 83.6, 68.5, 46.8, 32.1, 18.22, 18.20, 13.1.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 99.9:0.1, 1.8 mL/min, r.t., λ = 300 nm) indicated a >99% ee: t_R (major) = 7.48 min, t_R (minor) = 6.89 min.

Specific rotation $[\alpha]_D^{25} = -87.9$ (*c* 0.645, $CHCl_3$).

HRMS (ESI) calcd. for $C_{27}H_{26}NO_4Si$ $[M+H]^+$: 466.2408, Found: 466.2404.

Triisopropyl(((2S,3S)-2-methyl-3-(phenylethynyl)tetrahydro-2*H*-pyran-2-yl)oxy)silane (2g)



Prepared following general procedure A, but with $LiNTf_2$ (5.7 mg, 0.02 mmol, 10 mol %) used as an additive. The dr of the crude reaction mixture was determined to be 5.3:1. The reaction mixture was purified by prep TLC, developing 2 times in hexanes/EtOAc = 99:1 to afford the title compound (major diastereomer) as a yellow oil (36.5 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.30 – 7.23 (m, 3H), 3.96 (td, *J* = 11.1, 3.1 Hz, 1H), 3.63 (dt, *J* = 7.8, 3.7 Hz, 1H), 2.82 (t, *J* = 4.4 Hz, 1H), 2.26 (tt, *J* = 12.5, 4.0 Hz, 1H), 2.07 – 1.92 (m, 1H), 1.83 – 1.71 (m, 1H), 1.43 (qd, *J* = 7.5, 3.7 Hz, 1H), 1.20 – 1.04 (m, 21H).

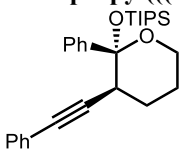
13C NMR (101 MHz, CDCl3) δ 131.8, 128.3, 127.7, 97.4, 91.1, 61.7, 39.5, 26.9, 25.6, 21.9, 18.5, 13.5.

HPLC analysis (IB column, hexanes/i-PrOH = 99.9:0.1, 2.0 mL/min, r.t., λ = 242 nm) indicated a 94% ee: t_R (major) = 1.87 min, t_R (minor) = 2.12 min.

Specific rotation $[\alpha]_D^{25}$ = −63.4 (*c* 0.50, $CHCl_3$).

HRMS (ESI) calcd. for $C_{23}H_{37}O_2Si$ $[M+H]^+$: 373.2557, Found: 373.2558.

Triisopropyl(((2S,3S)-2-phenyl-3-(phenylethynyl)tetrahydro-2*H*-pyran-2-yl)oxy)silane (2h)



Prepared following general procedure A, but with $LiNTf_2$ (5.7 mg, 0.02 mmol, 10 mol %) used as an additive. The dr of the crude reaction mixture was determined to be 5.3:1. The reaction mixture was purified by prep TLC, developing 3 times in hexanes/EtOAc = 99:1 to afford the title compound (mixture of diastereomers) as a yellow oil (47.7 mg, 55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 6.7 Hz, 2H'), 7.62 (d, *J* = 7.3 Hz, 2H*), 7.39 – 7.36 (m, 2H'), 7.35 – 7.30 (m, 2H*+1H'), 7.30 – 7.26 (m, 1H*+5H'), 7.18 – 7.11 (m, 3H*), 7.01 (dd, *J* = 7.5, 1.9 Hz, 2H*), 4.16 – 4.03 (m, 1H*+1H'), 3.92 – 3.82 (m, 1H*+1H'), 3.32 (t, *J* = 3.4 Hz, 1H*), 2.66 (dd, *J* = 12.2, 4.0 Hz, 1H'), 2.45 (tt, *J* = 13.0, 4.0 Hz, 1H*), 2.29 – 2.12 (1H*+1H'), 2.05 – 1.96 (m, 1H'), 1.97 – 1.88 (m, 1H*), 1.80 – 1.67 (m, 2H'), 1.49 (br. d, *J* = 13.3 Hz, 1H*), 1.09 – 1.07 (m, 9H'), 1.02 (d, *J* = 6.0 Hz, 9H*), 0.96 – 0.88 (m, 12H*+12H').

H* indicates the major diastereomer, while H' indicates the minor diastereomer.

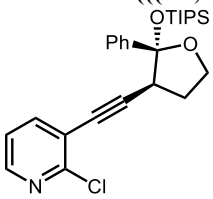
^{13}C NMR ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1, 144.7, 131.6, 128.3, 128.0, 127.9, 127.9, 127.6, 127.5, 127.4, 127.3, 127.0, 126.5, 124.0, 97.9, 91.7, 90.8, 83.2, 61.6, 61.4, 43.2, 40.2, 27.5, 25.2, 24.8, 21.2, 18.4, 18.3, 18.2, 18.2, 14.1, 13.7.

HPLC analysis (OD3 column, hexanes/i-PrOH = 99.9:0.1, 0.4 mL/min, **r.t. and 40 °C separately** , λ = 243 nm) Major diastereomer: indicated a >90 % ee: t_R (major) = 10.01 min, t_R (minor) = 9.74 min; Minor diastereomer: indicated a >90 % ee: t_R (major) = 11.03 min, t_R (minor) = 10.43 min.

Specific rotation $[\alpha]_D^{25}$ = −74.9 (*c* 0.515, $CHCl_3$).

HRMS (ESI) calcd. for $C_{28}H_{39}O_2Si$ $[M+H]^+$: 435.2714, Found: 435.2714.

2-Chloro-3-(((2*R*,3*S*)-2-phenyl-2-((triisopropylsilyl)oxy)tetrahydrofuran-3-yl)ethynyl)pyridine (2i)



Prepared following general procedure A, but with precatalyst and ligand loading increased to: $[Ir(cod)Cl]_2$ (13.4 mg, 0.02 mmol, 10 mol %), phosphoramidite (*R*)-**L** (40.6 mg, 0.08 mmol, 40 mol %), and with the reaction time increased to 3 days. The dr of the crude reaction mixture was determined to be >20:1. The reaction mixture was purified by prep TLC, developing 2 times in hexanes/EtOAc = 9:1 to afford the title compound (major diastereomer) as a yellow oil (51.1 mg, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.3 Hz, 2H), 7.33 – 7.23 (m, 3H), 7.17 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.02 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.38 – 4.29 (m, 2H), 3.57 (dd, *J* = 7.0, 3.8 Hz, 1H), 2.66 (ddd, *J* = 15.5, 12.0, 8.0 Hz, 1H), 2.22 (ddt, *J* = 8.0, 6.5, 4.1 Hz, 1H), 0.99 – 0.93 (m, *J* = 5.3 Hz, 21H)

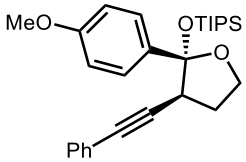
^{13}C NMR (126 MHz, $CDCl_3$) δ 152.1, 147.8, 143.0, 141.5, 128.0, 127.5, 127.1, 121.7, 120.7, 109.2, 97.2, 80.1, 68.5, 46.8, 32.3, 18.22, 18.20, 13.2.

HPLC analysis (OD3 column, hexanes/i-PrOH = 99:1, 1.0 mL/min, r.t., λ = 250 nm) indicated a 98% ee: t_R (major) = 5.09 min, t_R (minor) = 4.85 min.

Specific rotation $[\alpha]_D^{25} = -90.9$ (*c* 0.37, $CHCl_3$).

HRMS (ESI) calcd. for $C_{26}H_{35}O_2SiNCl$ $[M+H]^+$: 456.2120, Found: 456.2117.

Triisopropyl(((2*R*,3*S*)-2-(4-methoxyphenyl)-3-(phenylethynyl)tetrahydrofuran-2-yl)oxy)silane (2j)



Prepared following general procedure A, but with precatalyst and ligand loading reduced to: $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol %) and (*R*)-**L** (10.2 mg, 0.02 mmol, 10 mol %). The dr of the crude reaction mixture was determined to be 6.8:1. The reaction mixture was purified by prep TLC, developing 2 times in hexanes/Et_2O = 39:1 to afford the title compound (major diastereomer) as a colorless oil (53.7 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.15 (m, 3H), 7.05 – 7.00 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.32 – 4.24 (m, 2H), 3.81 (s, 3H), 3.45 (dd, *J* = 6.8, 4.7 Hz, 1H), 2.57 (dq, *J* = 12.1, 7.5 Hz, 1H), 2.13 (td, *J* = 11.5, 4.8 Hz, 1H), 0.98 – 0.96 (m, *J* = 2.3 Hz, 21H).

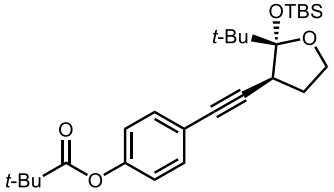
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 135.8, 131.5, 128.4, 128.1, 127.7, 123.7, 112.6, 109.3, 89.2, 84.9, 68.3, 55.4, 46.6, 32.5, 18.28, 18.25, 13.2.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 99.9:0.1, 0.4 mL/min, r.t., λ = 237 nm) indicated a >99% ee: t_R (major) = 15.40 min, t_R (minor) = 17.53 min.

Specific rotation $[\alpha]_D^{25} = -86.1$ (*c* 0.275, $CHCl_3$).

HRMS (ESI) calcd. for $C_{28}H_{39}O_3Si$ $[M+H]^+$: 451.2663, Found: 451.2658.

4-(((2*R*,3*S*)-2-(*tert*-Butyl)-2-((*tert*-butyldimethylsilyl)oxy)tetrahydrofuran-3-yl)ethynyl)phenyl pivalate (2k)



Prepared following general procedure A, but with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (92 μL, 0.4 mmol, 2 equiv) instead of TIPSOTf, and with the reaction time increased to 36 h. The dr of the crude reaction mixture was determined to be 3.6:1. The reaction mixture was purified by prep TLC, initially developing a first plate 5 times in hexanes/EtOAc = 99:1. After recovering only partially purified product from the first plate due to partial overlap of the diastereomer bands, a second prep TLC plate was used to further purify the major diastereomer. The second plate was also developed 5 times in hexanes/EtOAc = 99:1. This afforded the major diastereomer as a colorless oil (36.3 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.10 – 3.94 (m, 2H), 3.25 (dd, *J* = 9.8, 7.8 Hz, 1H), 2.39 (dddd, *J* = 12.0, 7.7, 6.4, 4.2 Hz, 1H), 2.15 (ddt, *J* = 12.2, 9.7, 8.6 Hz, 1H), 1.35 (s, 9H), 1.17 (s, 9H), 0.91 (s, 9H), 0.14 (s, 6H).

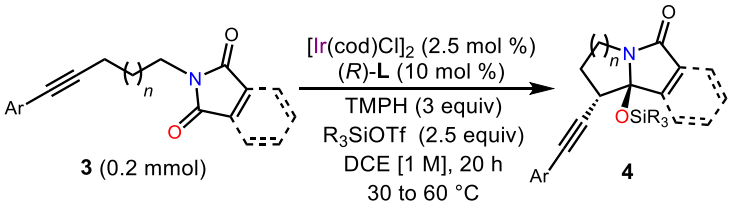
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 150.8, 132.4, 121.7, 121.4, 113.0, 89.9, 84.4, 67.3, 43.5, 41.0, 39.3, 34.8, 27.3, 26.2, 26.0, 18.4, -24, -2.9.

HPLC analysis (IB column, hexanes/i-PrOH = 99.9:0.1, 2.0 mL/min, r.t., λ = 250 nm) indicated a 97% ee: t_R (major) = 2.17 min, t_R (minor) = 2.37 min.

Specific rotation $[\alpha]_D^{25} = -91.23$ (*c* 0.70, $CHCl_3$).

HRMS (ESI) calcd. for $C_{27}H_{43}O_4Si$ $[M+H]^+$: 459.2925, Found: 458.2935.

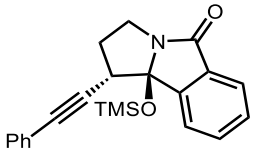
General Procedure B for the synthesis of cyclic silyl hemiaminals from alkyne-tethered imides



Preparation of the Ir complex solution: A reaction tube (13mm x 100mm, Fisherbrand part # 14-959-35C) equipped with a magnetic stir bar was flame dried and transferred into an argon-filled glovebox. In the glovebox, $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 2.5 mol %) and phosphoramidite (*R*)-**L** (10.2 mg, 0.02 mmol, 10 mol %) were added, unless another quantity is noted below. 1,2-dichloroethane (0.2 mL) was added by syringe. The reaction tube was capped, and the solution was stirred at room temperature for 1 h to give a dark red solution.

Ir-catalyzed cyclisation reaction: To the solution were added **1** (0.2 mmol, 1.0 equiv), distilled 2,2,6,6-tetramethylpiperidine (TMPH) (102 µL, 0.6 mmol, 3.0 equiv), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (90 µL, 0.5 mmol, 2.5 equiv). The tube was again capped and removed from the glovebox, then stirred at the specified temperature for 20 hours. To the crude reaction mixture were added Et_3N (50 µL, 0.36mmol, 1.8 equiv) and CH_2Cl_2 (ca. 1 mL). The diluted mixture was flushed through a short plug of silica (ca. 1 g) eluting with CH_2Cl_2 (ca. 10 mL). The solution was concentrated *in vacuo* and dissolved in $CDCl_3$ (ca. 0.5 mL). ^1H NMR spectroscopy was used to determine crude diastereomeric ratio (dr). The solution was concentrated *in vacuo* and purified by preparative TLC or column chromatography afford the isolated major diastereomer. Preparative TLC plates were developed only once. Exact conditions are listed below. For HPLC analysis, racemic samples were prepared by mixing equal amounts of samples prepared following general procedure B using (*S*)- and (*R*)-**L**.

(1*S*,9b*R*)-1-(Phenylethynyl)-9b-((trimethylsilyl)oxy)-1,2,3,9b-tetrahydro-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (4a)



Prepared following general procedure B at a reaction temperature of 60 °C. The dr of the crude reaction mixture was determined to be 11:1. The reaction mixture was purified by prep TLC in hexanes/EtOAc = 9:1 to afford the title compound (major diastereomer) as a clear oil (46.0 mg, 64%). The absolute and relative configurations were assigned by analogy to **4b**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.52 – 7.46 (m, 1H), 7.15 (ddd, *J* = 6.3, 3.6, 1.3 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.87 – 6.81 (m, 2H), 3.89 (td, *J* = 10.7, 7.9 Hz, 1H), 3.47 (ddd, *J* = 10.7, 8.9, 1.2 Hz, 1H), 3.39 (d, *J* = 6.1 Hz, 1H), 2.88 (dddd, *J* = 12.3, 10.2, 9.0, 6.2 Hz, 1H), 2.48 (dd, *J* = 12.4, 7.7 Hz, 1H), -0.10 (s, 9H).

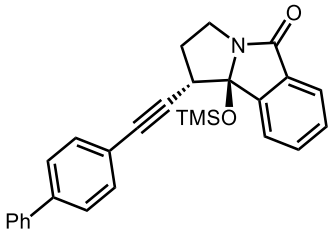
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 146.5, 133.1, 132.7, 131.4, 129.9, 128.1, 128.0, 123.2, 123.1, 122.7, 100.2, 86.7, 85.3, 41.6, 41.1, 34.4, 0.8.

HPLC analysis (AD-3 column, hexanes/i-PrOH = 90:10, 0.4 mL/min, r.t., λ = 241 nm) indicated a 99% ee: t_R (major) = 12.60 min, t_R (minor) = 11.92 min.

Specific rotation $[\alpha]_D^{25}$ = −83.1 (*c* 1.35, $CHCl_3$).

HRMS (ESI) calcd. for $C_{22}H_{24}NO_2Si$ $[M+H]^+$: 362.1571, Found: 362.1568.

(1*S*,9b*R*)-1-([1,1'-Biphenyl]-4-ylethynyl)-9b-((trimethylsilyl)oxy)-1,2,3,9b-tetrahydro-5*H*-pyrrolo[2,1-*a*]isoindol-5-one (4b)



Prepared following general procedure B at a reaction temperature of 60 °C. The dr of the crude reaction mixture was determined to be 14:1. The reaction mixture was purified by column chromatography in hexanes/EtOAc = 9:1 to afford the title compound (major diastereomer) as a white solid (51.0 mg, 58%). The connectivity and stereochemistry were determined by X-ray crystallography.

m.p. 163.4 – 170.8 °C (dec.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.54 – 7.46 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.29 (m, 3H), 6.92 (d, *J* = 8.3 Hz, 2H), 3.91 (td, *J* = 10.7, 8.0 Hz, 1H), 3.49 (ddd, *J* = 10.6, 9.0, 0.9 Hz, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 2.90 (dddd, *J* = 12.3, 10.0, 9.1, 6.3 Hz, 1H), 2.50 (dd, *J* = 12.4, 7.7 Hz, 1H), -0.09 (s, 9H).

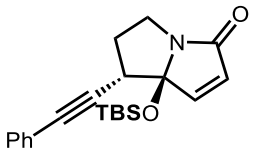
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 146.5, 140.8, 140.5, 133.1, 132.7, 131.8, 129.9, 128.9, 127.6, 127.1, 126.8, 123.2, 123.1, 121.6, 100.2, 87.4, 85.2, 41.6, 41.2, 34.5, 0.8.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 90:10, 0.8 mL/min, r.t., λ = 295 nm) indicated a >99% ee: t_R (major) = 6.17 min, t_R (minor) = 5.31 min.

Specific rotation $[\alpha]_D^{25}$ = −102.9 (*c* 0.54, $CHCl_3$).

HRMS (ESI) calcd. for $C_{28}H_{28}NO_2Si$ $[M+H]^+$: 438.1884, Found: 438.1896.

(7*S*,7a*S*)-7a-((*tert*-Butyldimethylsilyl)oxy)-7-(phenylethynyl)-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one (4c)



Small scale: Prepared following general procedure B at a reaction temperature of 40 °C, but with precatalyst and ligand loading increased to: $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 5 mol %), phosphoramidite (*R*)-**L** (20.3 mg, 0.04 mmol, 20 mol %); and with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (115 µL, 0.5 mmol, 2.5 equiv) used instead of TMSOTf. The dr of the crude reaction mixture was determined to be >20:1. The crude reaction mixture was purified by flash column chromatography (hexanes/Et_3N 9:1) to afford the title compound as a yellow solid (43.2 mg, 61%).

Large Scale: In an argon-filled glovebox, a pressure vessel (Synthware part #P160020) was charged with $[Ir(cod)Cl]_2$ (101 mg, 0.15 mmol, 5 mol %), phosphoramidite (*R*)-**L** (305 mg, 0.6 mmol, 20 mol %), and 1,2-dichloroethane (3.0 mL). The reaction mixture was stirred for 1 h. To the reaction tube were added 1-(5-phenylpent-4-yn-1-yl)-1*H*-pyrrole-2,5-dione (**3c**, 718 mg, 3.0 mmol, 1.0 equiv), distilled TMPH (1.53 mL, 9.0 mmol, 3 equiv), and TBSOTf (1.72 mL, 7.5 mmol, 2.5 equiv). The vessel was sealed, removed from the glovebox, and stirred at 40 °C for 20 h. To the crude reaction mixture was added Et_3N (1.0 mL, 7.2 mmol, 2.4 equiv) and CH_2Cl_2 (ca. 3 mL). The diluted mixture was flushed through a pad of silica with CH_2Cl_2 (ca. 100 mL) and solution was concentrated *in vacuo*. The dr of the crude reaction mixture was determined to be >20:1. The crude mixture was purified by column chromatography, first with hexanes/Et_3N = 9:1. A second column was run with hexanes/EtOAc = 9:1 to remove a pink-colored impurity from the product. This was presumed to be an iridium complex. Previously, after a single column, visibly pink samples of **4c** appeared to undergo semi-hydrogenation to **5** with poor selectivity. Performing column chromatography in both eluents successively afforded **4c** as a yellow solid (658 mg, 62%). Stereochemical configuration was confirmed through the synthesis of **7**, whose properties matched those previously reported.[1]

m.p. 73.1 – 76.0 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 5H), 7.02 (d, *J* = 5.8 Hz, 1H), 6.07 (d, *J* = 5.8 Hz, 1H), 3.68 (td, *J* = 10.7, 7.7 Hz, 1H), 3.31 (ddd, *J* = 10.5, 8.6, 1.3 Hz, 1H), 3.18 (d, *J* = 6.0 Hz, 1H), 2.78 (dddd, *J* = 12.4, 10.5, 8.6, 6.2 Hz, 1H), 2.41 (dd, *J* = 12.5, 7.6 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).

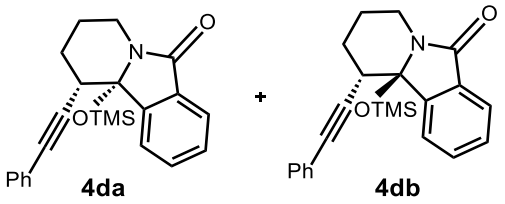
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 149.2, 131.6, 128.4, 128.3, 128.0, 122.9, 101.9, 86.5, 86.2, 41.4, 40.6, 35.0, 25.6, 18.0, -3.4, -4.0.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 90:10, 0.8 mL/min, r.t., λ = 246 nm) indicated a 99% ee: t_R (major) = 5.19 min, t_R (minor) = 4.77 min.

Specific rotation $[\alpha]_D^{25}$ = +83.9 (*c* 0.46, $CHCl_3$).

HRMS (ESI) calcd. for $C_{21}H_{28}NO_2Si$ $[M+H]^+$: 354.1884, Found: 354.1895.

(1*S*,10b*S*)-1-(Phenylethynyl)-10b-((trimethylsilyl)oxy)-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2H)-one (4da) and **(1*S*,10b*R*)-1-(phenylethynyl)-10b-((trimethylsilyl)oxy)-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (4db)**



Prepared following general procedure B at a reaction temperature of 30 °C. Crude dr = 1.3:1. The reaction mixture was purified by prep TLC in hexanes/EtOAc = 6:1 to afford both diastereomers separately. The *cis*-configured product **4da** was obtained as a colorless oil that crystalised on standing (37.6 mg, 50%). The *trans*-configured product **4db** was also obtained as a colorless solid (29.8 mg, 40%). The connectivity and stereochemistry of **4db** were determined by X-ray crystallography.

4da:

m.p. 115.7 – 118.4 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 6.2, 1.6 Hz, 1H), 7.83 (dd, *J* = 6.2, 1.8 Hz, 1H), 7.54 (qd, *J* = 7.0, 1.3 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.38 – 7.32 (m, 3H), 4.29 (dd, *J* = 13.1, 5.0 Hz, 1H), 3.03 (td, *J* = 13.1, 3.6 Hz, 1H), 2.46 (dd, *J* = 12.3, 3.6 Hz, 1H), 2.23 (qd, *J* = 13.3, 3.6 Hz, 1H), 2.03 (dd, *J* = 13.2, 2.9 Hz, 1H), 1.83 (dd, *J* = 13.4, 1.6 Hz, 1H), 1.46 (qdd, *J* = 13.3, 4.8, 4.0 Hz, 1H), 0.13 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 146.7, 131.74, 131.65, 129.9, 128.5, 128.1, 124.1, 123.8, 123.6, 89.6, 87.6, 82.9, 42.0, 35.8, 27.2, 25.0, 1.1.

HPLC analysis (AD-3 column, hexanes/i-PrOH = 90:10, 0.4 mL/min, r.t., λ = 243 nm) indicated a 95% ee: t_R (major) = 11.32 min, t_R (minor) = 10.57 min.

Specific rotation: $[\alpha]_D^{25}$= −206.1 (*c* 0.95, $CHCl_3$).

HRMS: (ESI) calcd. for $C_{23}H_{26}NO_2Si$ $[M+H]^+$: 376.1727, Found: 376.1724.

4db:

m.p. 92.3 – 94.9 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, *J* = 7.4 Hz, 1H), 7.59 – 7.47 (m, 3H), 7.17 – 7.07 (m, 3H), 6.84 (d, *J* = 6.9 Hz, 2H), 4.32 (dd, *J* = 13.9, 4.5 Hz, 1H), 3.49 (t, *J* = 3.0 Hz, 1H), 3.04 (td, *J* = 12.8, 3.7 Hz, 1H), 2.42 – 2.30 (m, 1H), 2.05 – 1.91 (m, 2H), 1.69 – 1.61 (m, 1H), -0.13 (s, 9H).

^{13}C NMR (126 MHz, CDCl3) δ 165.7, 146.9, 132.8, 131.7, 131.5, 123.0, 128.1, 127.8, 123.2, 123.0, 122.2, 89.2, 87.3, 84.7, 39.3, 36.3, 24.9, 20.4, 1.2.

HPLC analysis (AD-3 column, hexanes/i-PrOH = 90:10, 0.4 mL/min, r.t., λ = 250 nm) indicated a 98% ee: t_R (major) = 12.82 min, t_R (minor) = 12.00 min.

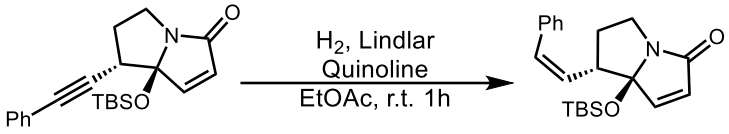
Specific rotation: $[\alpha]_D^{25}$= −147.7 (*c* 0.295, $CHCl_3$).

HRMS: (ESI) calcd. for $C_{23}H_{26}NO_2Si$ $[M+H]^+$: 376.1727, Found: 376.1722.

2.2 Formal synthesis of UCS1025A from 4c

See section 2.1 for **4c** synthesis and section 2.3 for **3c** synthesis

(7*S*,7a*S*)-7a-((*tert*-Butyldimethylsilyl)oxy)-7-((*Z*)-styryl)-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one (5)



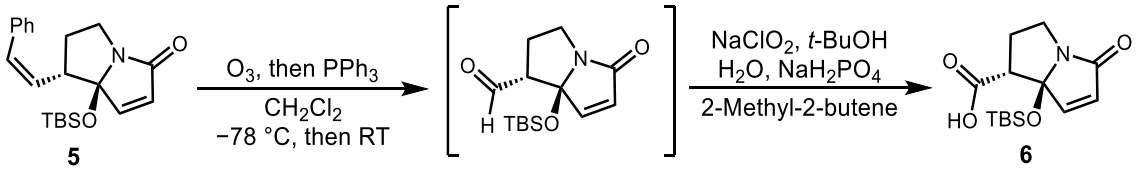
4c **5**

A flask equipped with a magnetic stir bar was charged with Pd (5 wt. %) on $CaCO_3$, Pb-poisoned (Lindlar catalyst) (104.6 mg, 5.0 mol %), followed by the addition of quinoline (67.6 mg, 0.52 mmol, 53 mol %) by syringe. The atmosphere of the reaction vessel was replaced with nitrogen gas, and a solution of 1 (1.0 eq, 0.99 mmol, 349 mg) in EtOAc (7 mL) was added. The atmosphere was then replaced with hydrogen gas (1 atm), and the reaction was made to stir vigorously at r.t. for 1 hour.

The reaction was filtered through a short plug of silica gel, eluting with EtOAc and washed with a 10% aqueous solution of H_3PO_4 (2 x 15 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), the combined organic layer was washed once with a saturated aqueous solution of $NaHCO_3$, dried with anhydrous $MgSO_4$, and concentrated by vacuum. The crude mixture was purified by flash column chromatography using hexanes/EtOAc = 9:1 to yield a white solid (88%, 0.87 mmol, 310 mg).

m.p. 63.2 – 64.8 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 2H), 7.33 – 7.27 (m, 3H), 6.89 (d, *J* = 5.7 Hz, 1H), 6.42 (d, *J* = 11.7 Hz, 1H), 6.01 (d, *J* = 5.7 Hz, 1H), 5.04 (t, *J* = 11.5 Hz, 1H), 3.66 (dt, *J* = 11.3, 8.3 Hz, 1H), 3.45 (ddd, *J* = 9.6, 6.6, 2.5 Hz, 1H), 3.26 (ddd, *J* = 11.6, 8.5, 3.6 Hz, 1H), 2.68 (dtd, *J* = 12.7, 8.5, 6.7 Hz, 1H), 2.07 – 1.97 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 150.1, 136.8, 130.5, 129.0, 128.9, 128.5, 127.7, 127.3, 102.1, 46.2, 41.2, 35.7, 25.7, 18.0, -3.2, -3.8.
HPLC analysis (AD-3 column, hexanes/i-PrOH = 90:10, 0.8 mL/min, r.t., λ = 250 nm) indicated a 99% ee: t_R (major) = 5.06 min, t_R (minor) = 5.49 min.
Specific rotation $[\alpha]_D^{25} = -58.4$ (c 0.645, $CHCl_3$).
HRMS (ESI) calcd. for $C_{21}H_{30}NO_2Si$ $[M+H]^+$: 356.2040, Found: 356.2024.

(1*R*,7a*S*)-7a-((*tert*-Butyldimethylsilyl)oxy)-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylic acid (6)



Ozonolysis: A 50 mL reaction tube equipped with a magnetics stir bar was charged with **5** (177 mg, 0.5 mmol, 1.0 equiv), and dry CH_2Cl_2 (15 mL). The tube was sealed with a septum cap and cooled to −78 °C while stirring under a nitrogen balloon for 5 min. The balloon was removed and replaced with a 21-gauge needle as a gas outlet. An 18-gauge needle was used to make a hole in the septum, removed, and quickly replaced with the thin end of a long Pasteur pipette, connected by tubing to the ozone outlet of a Welsbach T-series ozone generator. The tip of the pipette was submerged in the reaction mixture and ozone was about 1 min, until the mixture turned light blue. The Pipette was removed, and nitrogen was bubbled through the reaction mixture for 1 min. A dry, degassed solution of PPh_3 (392 mg, 1.5 mmol, 3 equiv) was added by syringe, and the reaction was stirred for 45 minutes before removing from the dry ice bath. Stirring was continued at room temperature for 15 minutes. The reaction mixture was added to a pad of silica and flushed with CH_2Cl_2 (200 mL) to remove triphenylphosphine and some benzaldehyde, then the partially purified aldehyde product was eluted from the silica pad with EtOAc (200 mL) and concentrated *in vacuo*.

Pinnick Oxidation: The partially purified aldehyde product and 2-methyl-2-butene (0.83 mL, 7.8 mmol, 16 equiv) were dissolved in *t*-BuOH (7 mL) and stirred at room temperature. A solution of $NaClO_2$ (technical grade, 80%) (108 mg, 0.955 mmol, 1.91 equiv) and NaH_2PO_4•H_2O (83 mg, 0.60 mmol, 1.2 equiv) in water (1.5 mL) was added by syringe. The reaction was stirred at room temperature for 1 hour, then transferred to a separatory funnel with 10% aqueous H_3PO_4 (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford crude **6** as a yellow oil. To avoid apparent product decomposition, which was previously observed in the crude reaction mixture, purification by column chromatography was conducted within 1 hour of concentrating. The crude product was dissolved in of EtOAc/Et_3N = 9:1 (1 mL) and loaded onto a silica gel column approximately 20 cm in height and 1cm in diameter. The column was flushed with (EtOAc/Et_3N = 99:1) (ca. 200 mL) to remove impurities while retaining the desired product near the baseline, then with 100% EtOAc (ca. 30 mL) to remove excess Et_3N. The desired product was eluted with EtOAc/AcOH = 99:1 (ca. 400 mL). Fractions were checked by TLC, spotting aliquots 10-20 times each to ensure visibility on the plate under UV light despite the product's weak chromophore. Fractions containing the largest spot from the acidic eluent were concentrated *in vacuo* to afford a slightly impure white solid. This was purified further by preparative TLC in EtOAc/AcOH = 99:1 to afford pure **6** as a white solid (71.9 mg, 48%), which appeared to be bench-stable if not stored in solution.

m.p. 121.3 –124.1 °C.

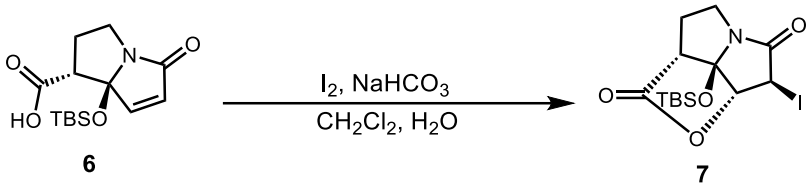
1H NMR (300 MHz, CDCl3) δ 8.63 (bs, 1H), 7.01 (d, *J* = 5.8 Hz, 1H), 5.98 (d, *J* = 5.8 Hz, 1H), 3.75 (dd, *J* = 19.7, 8.8 Hz, 1H), 3.27 (ddd, *J* = 11.1, 8.9, 2.6 Hz, 1H), 3.10 (dd, *J* = 6.3, 1.2 Hz, 1H), 2.69 – 2.45 (m, 2H), 0.86 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 173.9, 148.1, 127.9, 100.8, 52.9, 41.7, 31.0, 25.4, 17.8, -3.5, -4.1.

Specific rotation $[\alpha]_D^{25}$ = −39.1 (*c* 3.08, $CHCl_3$).

HRMS (ESI) calcd. for $C_{14}H_{24}NO_4Si$ $[M+H]^+$: 298.1469, Found: 298.1457.

(2a*R*,6*S*,6a*R*,6b*R*)-6b-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-iodohexahydro-1-oxa-4a-azacyclo-penta[*cd*]pentalene-2,5-dione (7)



Synthesised using a modified literature procedure for an analogous iodolactonisation.[2] **6** (59.4 mg, 0.2 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.7 mL) in a reaction tube and stirred. Aqueous sat. $NaHCO_3$ (0.7 mL) was added dropwise and the reaction mixture was stirred for 20 min. I_2 (53.3 mg, 0.21 mmol, 1.05 eq) was added. The tube was sealed, covered with foil, and stirred 6 h. The reaction was quenched with aqueous sat. $Na_2S_2O_3$ (0.2 mL) and water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give **7** as a light-yellow solid (77.0 mg, 91%), with no need for further purification. For HPLC analysis, the racemic sample was prepared by mixing equal amounts of **7** that had been synthesised using (*R*)- and (*S*)-**L** in the iridium-catalyzed step. The HPLC data matched those reported previously.[1]

m.p. 110.2 –115.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.44 (s, 1H), 3.94 (ddd, *J* = 12.3, 9.5, 5.7 Hz, 1H), 3.32 (ddd, *J* = 12.3, 9.4, 5.9 Hz, 1H), 3.12 (dd, *J* = 9.2, 2.6 Hz, 1H), 2.72 – 2.52 (m, 2H), 0.95 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 172.4, 102.1, 86.1, 49.4, 43.0, 30.0, 25.6, 18.0, 12.7, -3.2, -3.3.

HPLC analysis (OD-3 column, hexanes/i-PrOH = 90:10, 1.0 mL/min, r.t., λ = 240 nm) indicated a 99% ee: t_R (major) = 9.06 min, t_R (minor) = 11.44 min.

Specific rotation $[\alpha]_D^{25} = -29.0$ (*c* 2.935, $CHCl_3$).

HRMS (ESI) calcd. for $C_{14}H_{23}NO_4ISi$ $[M+H]^+$: 424.0436, Found: 424.0432.

2.3 Synthesis of unreported starting materials

5-Phenylpent-4-yn-1-yl 4-methoxybenzoate (1j)

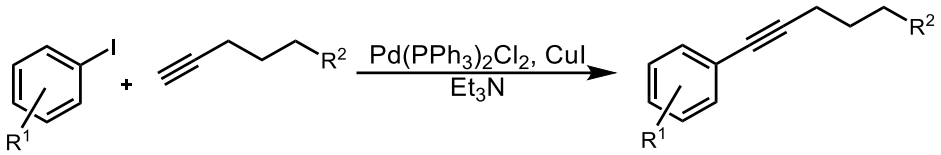
To a stirring solution of 4-methoxybenzoic acid (304 mg, 2.0 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added 5-phenylpent-4-yn-1-ol (336 mg, 2.1 mmol, 1.05 equiv), followed by triethylamine (0.30 mL, 2.1 mmol, 1.05 equiv) and 4-dimethylaminopyridine (36.7 mg, 0.30 mmol, 0.15 equiv). The mixture was stirred overnight at room temperature. The reaction was quenched with HCl (1M, 20 mL) and extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel column chromatography in hexanes/EtOAc = 9:1 to give the title product as a yellow oil (483 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 2H), 7.44 – 7.36 (m, 2H), 7.31 – 7.26 (m, 3H), 6.93 – 6.87 (m, 2H), 4.45 (t, *J* = 6.2 Hz, 2H), 3.86 (s, 3H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.07 (p, *J* = 6.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 163.5, 131.8, 131.7, 128.3, 127.8, 123.8, 122.9, 113.7, 88.9, 81.4, 63.6, 55.6, 28.2, 16.6.

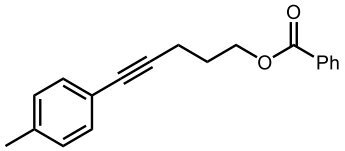
HRMS (ESI) calcd. for $C_{19}H_{19}O_3$ $[M+H]^+$: 295.1329, Found: 295.1329.

General Procedure C for the synthesis of aryl alkynes from terminal alkynes



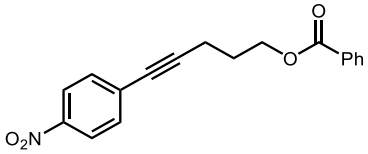
In an argon filled glove box, a 25 mL round bottom flask equipped with a magnetic stir bar was charged with $Pd(PPh_3)_2Cl_2$ (21.1 mg, 0.03 mmol, 1.0 mol%) and CuI (8.6 mg, 0.045 mmol, 1.5 mol%). The flask was sealed and removed. A degassed solution of aryl iodide (3 mmol, 1 equiv) in triethylamine (10 mL) was added by syringe. Terminal alkyne (3 mmol, 1 equiv) was added by syringe. The reaction mixture was stirred at room temperature overnight. Water (20 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 then concentrated *in vacuo.* The crude residue was purified by silica gel column chromatography to afford the title products.

5-(*p*-Tolyl)pent-4-yn-1-yl benzoate (1e)



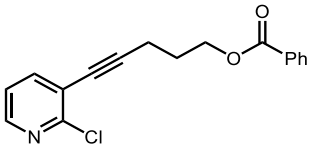
Prepared according to general procedure C. The crude residue was purified by silica gel column chromatography with hexanes/ethyl acetate = 19:1 to give the product as a clear oil. (785 mg, 94%).
^{1}H NMR (300 MHz, CDCl3) δ 8.10 – 8.03 (m, 2H), 7.62 – 7.50 (m, 1H), 7.50 – 7.37 (m, 2H), 7.31 – 7.26 (m, 2H), 7.08 (d, J = 7.9 Hz, 2H), 4.49 (t, *J* = 6.3 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 2.08 (p, *J* = 6.6 Hz, 2H).
^{13}C NMR (126 MHz, CDCl3) δ 166.7, 137.9, 133.1, 131.6, 130.5, 129.8, 129.1, 128.5, 120.7, 88.0, 81.5, 64.0, 28.2, 21.6, 16.6.
HRMS (ESI) calcd. for $C_{19}H_{19}O_2$ $[M+H]^+$: 279.1380, Found: 279.1377.

5-(4-Nitrophenyl)pent-4-yn-1-yl benzoate (1f)



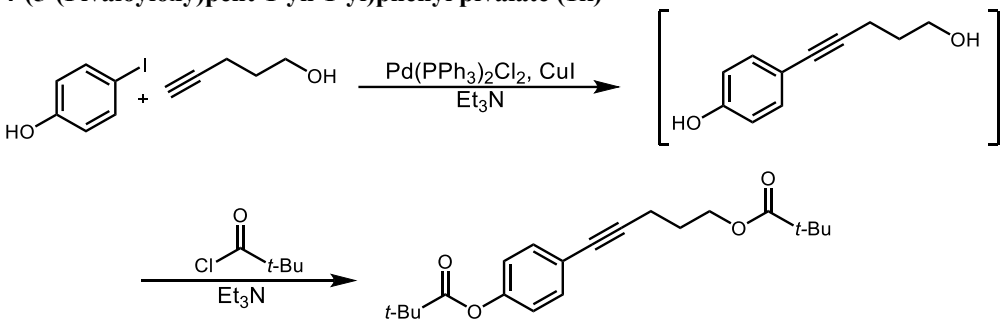
Prepared according to general procedure C. The crude residue was purified by silica gel column chromatography with hexanes/ethyl acetate = 9:1 to give the product as an orange solid. (677 mg, 73%).
m.p. 74.4 – 76.8 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.49 (t, *J* = 6.2 Hz, 2H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.12 (p, *J* = 6.7 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 146.9, 133.2, 132.4, 130.8, 130.3, 129.7, 128.5, 123.6, 94.9, 80.1, 63.7, 27.8, 16.7.
HRMS (ESI) calcd. for $C_{18}H_{16}O_4N$ $[M+H]^+$: 310.1074, Found: 310.1069.

5-(2-Chloropyridin3-yl)pent-4-yn-1-yl benzoate (1i)



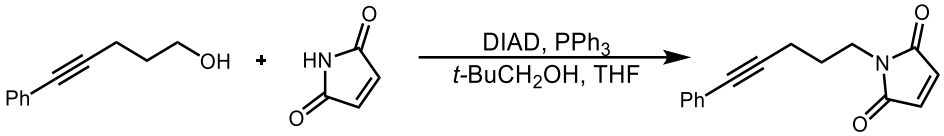
Prepared according to general procedure C. The crude residue was purified by silica gel column chromatography with hexanes/ethyl acetate = 9:1 to give the product as a yellow oil. (669 mg, 79.4%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.06 (d, *J* = 7.1 Hz, 2H), 7.70 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.16 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.52 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.13 (p, *J* = 6.7 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 152.5, 147.9, 141.5, 133.1, 130.3, 129.7, 128.5, 121.9, 121.0, 97.2, 63.7, 27.8, 16.8.
HRMS (ESI) calcd. for $C_{17}H_{15}O_2NCl$ $[M+H]^+$: 300.0786, Found: 300.0786.

4-(5-(Pivaloyloxy)pent-1-yn-1-yl)phenyl pivalate (1k)



In an argon filled glove box, a 25 mL round bottom flask equipped with a magnetic stir bar was charged with $Pd(PPh_3)_2Cl_2$ (35.1 mg, 0.05 mmol, 1.0 mol%) and CuI (14.3 mg, 0.075 mmol, 1.5 mol%). The flask was sealed and removed. A degassed solution of 4-iodophenol (1.10 g, 5 mmol, 1 equiv) in triethylamine (5 mL) and THF (5 mL) was added by syringe. 4-pentyn-1-ol (0.47 mL 5 mmol, 1 equiv) was added by syringe. The reaction mixture was stirred at room temperature for 30 min, at which time the starting material appeared by TLC to have been completely consumed. Pivaloyl chloride (1.60 mL, 13 mmol, 2.6 equiv) was added to the reaction mixture and stirring was continued overnight. Water (20 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 then concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography in hexanes/EtOAc (29:1) to afford to afford the title product as a yellow oil (790 mg, 46%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.20 (t, *J* = 6.3 Hz, 2H), 2.50 (t, *J* = 7.1 Hz, 2H), 1.94 (p, *J* = 6.8 Hz, 2H), 1.35 (s, 9H), 1.21 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 177.0, 150.7, 132.8, 121.6, 121.3, 88.8, 80.6, 63.2, 39.3, 39.0, 28.0, 27.4, 27.3, 16.3.
HRMS (ESI) calcd. for $C_{21}H_{29}O_4$ $[M+H]^+$: 345.2060, Found: 345.2062

1-(5-Phenylpent-4-yn-1-yl)-1*H*-pyrrole-2,5-dione (3c)



Synthesised using a modified literature procedure for the use of maleimide as a nucleophile in the Mitsunobu reaction.[1] A 250mL round bottom flask equipped with a stir bar was charged with a solution of PPh_3 (4.55 g, 17.3 mmol, 1.00 equiv) in 100mL anhydrous THF under nitrogen. The mixture was cooled to −78 °C. DIAD (3.86 mL, 19.6 mmol, 1.13 equiv) was added dropwise by syringe over 2 minutes. After stirring for 5 minutes, the reaction mixture appeared yellow and cloudy. 5-phenyl-pent-4-yn-1-ol (3.22 g, 20.1 mmol, 1.16 equiv) was added dropwise by syringe over 1 minute, then the reaction was allowed to stir for 5 minutes. The septum was briefly removed while neopentyl alcohol (0.880 g, 9.98 mmol, 0.57 equiv) and maleimide (1.95 g, 20.1 mmol, 1.16 equiv) were added sequentially. The septum was replaced, and the reaction flask was evacuated and backfilled with nitrogen 3 times. The mixture was stirred at −78 °C for 5 minutes, then warmed to room temperature and stirred for 18 hours. The crude reaction mixture was reduced to ¼ volume *in vacuo*. The viscous, partially concentrated mixture was purified directly by flash column chromatography in hexanes/EtOAc (9:1 to 4:1) to afford the desired product as a white solid (3.96 g, 96% yield).

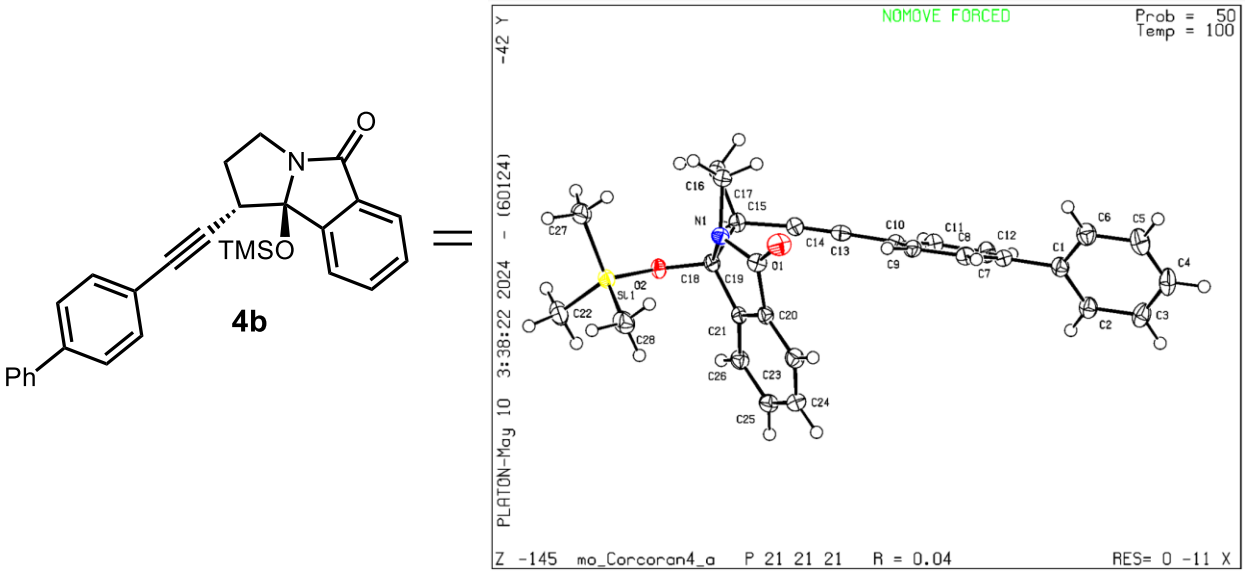
m.p. 46.4 – 48.2 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.30 – 7.26 (m, 3H), 6.67 (s, 2H), 3.69 (t, J = 7.0 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 1.93 (p, J = 7.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 134.3, 131.7, 128.3, 127.8, 123.8, 88.7, 81.5, 37.4, 27.5, 17.3.

HRMS (ESI) calcd. for $C_{15}H_{14}O_2N$ $[M+H]^+$: 240.1019, Found: 240.1018.

3. X-ray Structures



Datablock: mo_Corcoran4_a

Bond precision: C-C = 0.0039 A Wavelength=0.71073

Cell: a=7.4981(5) b=16.7375(12) c=18.9431(13)
alpha=90 beta=90 gamma=90
Temperature: 100 K

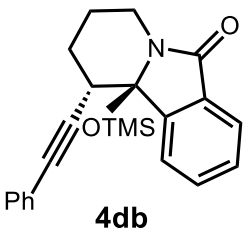
	Calculated	Reported
Volume	2377.4(3)	2377.3(3)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C28 H27 N O2 Si	?
Sum formula	C28 H27 N O2 Si	C28 H27 N O2 Si
Mr	437.60	437.59
Dx,g cm-3	1.223	1.223
Z	4	4
Mu (mm-1)	0.123	0.123
F000	928.0	928.0
F000'	928.67	
h,k,lmax	9,20,23	9,20,23
Nref	4876[2783]	4871
Tmin,Tmax	0.985,0.991	0.610,0.740
Tmin'	0.985	

Correction method= # Reported T Limits: Tmin=0.610 Tmax=0.740
AbsCorr = MULTI-SCAN

Data completeness= 1.75/1.00 Theta(max)= 26.404

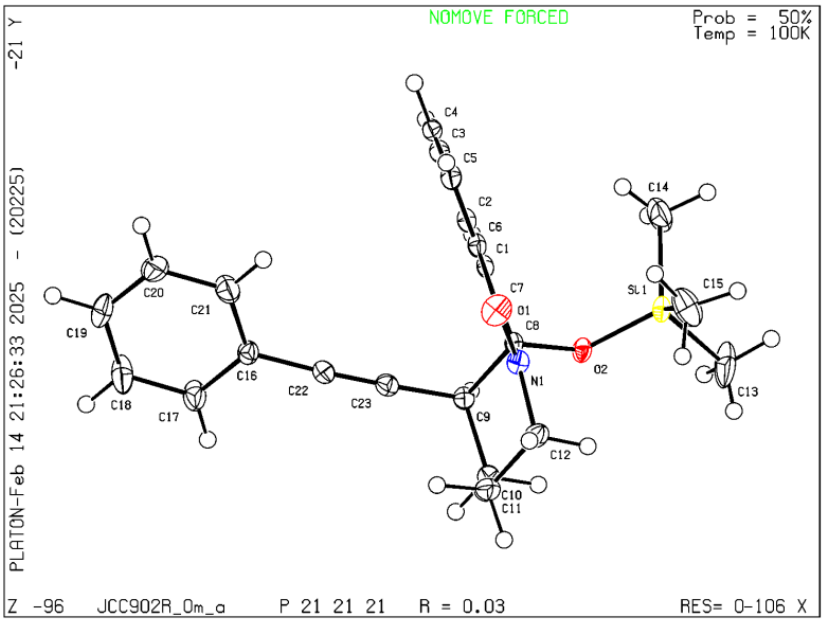
R(reflections)= 0.0371(4278) wR2(reflections)= 0.0893(4871)

S = 1.023 Npar= 293



4db

=



Datablock: JCC902R_0m_a

Bond precision: C-C = 0.0028 A Wavelength=1.54184

Cell: a=10.7177(19) b=11.995(3) c=15.986(3)
alpha=90 beta=90 gamma=90
Temperature: 100 K

	Calculated	Reported
Volume	2055.1(7)	2055.0(7)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C23 H25 N O2 Si	?
Sum formula	C23 H25 N O2 Si	C23 H25 N O2 Si
Mr	375.53	375.53
Dx,g cm-3	1.214	1.214
Z	4	4
Mu (mm-1)	1.136	1.136
F000	800.0	800.0
F000'	803.09	
h,k,lmax	13,14,19	13,14,19
Nref	4055[2309]	4012
Tmin,Tmax	0.897,0.945	0.293,0.754
Tmin'	0.893	

Correction method= # Reported T Limits: Tmin=0.293 Tmax=0.754
AbsCorr = MULTI-SCAN

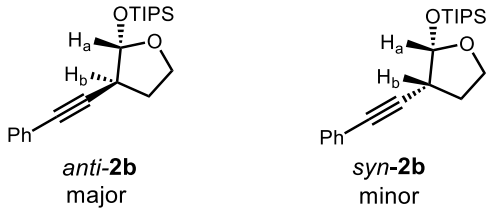
Data completeness= 1.74/0.99 Theta(max)= 72.264

R(reflections)= 0.0277(3948) wR2(reflections)= 0.0748(4012)

S = 1.013 Npar= 248

4. Assignment of relative and absolute configuration for the major and minor diastereomers of 2b and 2c

2b.



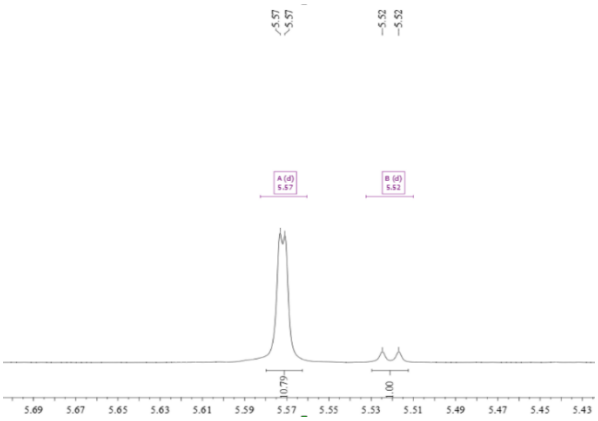
anti-**2b** major *syn*-**2b** minor

For the major diastereomer of **2b**, J_{ab} was determined to be 1.1 Hz based on a doublet signal for H_a which was visible in the ^{1}H NMR spectrum of the crude material at 5.57 ppm, but was not resolved in the NMR of the pure product, instead appearing as a broad singlet. For the minor diastereomer, J_{ab} was determined to be 3.9 Hz, based on a wider doublet attributed to H_a in that stereoisomer, also visible in the spectrum of the crude material at 5.52 ppm. For the major diastereomer, the dihedral angle (φ) between H_a and H_b was assumed to be ~90° based on the small value of J_{ab} (1.1 Hz). MM2 energy minimisation was performed for both possible relative configurations using Chem3D, with the H_a–C–C–H_b dihedral angle (φ) fixed at 90° (clockwise) or –90° (counterclockwise).

H_a-C-C-H_b dihedral angle (φ)	*anti*-2**b** steric *E* (kcal/mol)	*syn*-2**b** steric *E* (kcal/mol)
90° (clockwise)	19.94	29.55
–90° (counterclockwise)	ND	35.71

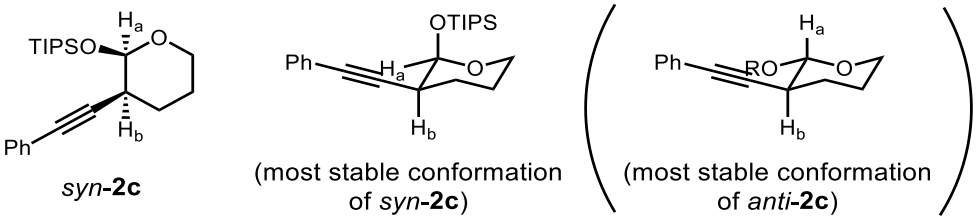
It was shown that *anti*-**2b** where φ = 90° corresponded to a reasonably low-strain conformation. A minimisation did not converge for *anti*-**2b** where φ = –90° (due to high strain energy) and was disregarded. The optimised geometries of *syn*-**2b** with φ fixed at both 90° and –90° both showed significantly greater, and unrealistic, steric energies than in *anti*-**2b** where φ = 90° (higher by ~10 and ~16 kcal/mol, respectively). Subsequent (unconstrained) DFT calculations for *anti*-**2b** and *syn*-**2b** at the RHF/6-31G level of theory optimised to dihedral angles of 90° and 42°, respectively. For these reasons, we assigned the major and minor diastereomers obtained under optimised conditions as *anti*-**2b** and *syn*-**2b**, respectively.

The absolute configuration of the H_b (propargylic) stereocentre was assigned by analogy to the X-ray structures of **4b** and **4cb**, which were in agreement with the assigned geometry of all Ir-catalyzed propargylic C–H functionalisation products previously obtained by our group.[4] The relative configurations of all other 5-membered *O*,*O*-acetal products reported here were assigned by analogy to **2b**, based on comparison of ^{1}H NMR coupling constants for the propargylic signal of **2b** with those seen in the other products.



H_a signals for both diastereomers in the spectrum of **2b** (before purification)

2c.



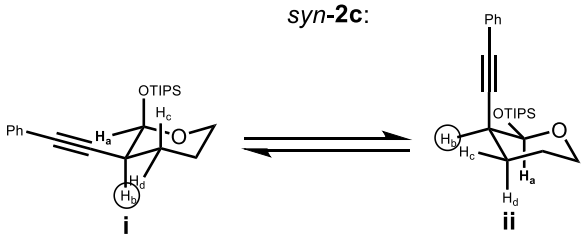
syn-**2c** (most stable conformation of *syn*-**2c**) ((most stable conformation of *anti*-**2c**))

Only a single diastereomer of **2c** could be definitively discerned in the ^{1}H NMR spectrum of the crude material. The signal for H_a was observed at 4.95 ppm as a doublet with J_{ab} = 4.9 Hz. Given the presence of the anomeric effect, the determination of the most stable chair conformation of the *syn*- and *anti*-diastereomers of **2c** is not trivial, and we turned to *ab initio* calculations to determine the relative stabilities of each of the chair conformations of these diastereomers. For the *anti*-diastereomer, the di-equatorial conformation was found to be 0.8 kcal/mol more stable than the di-axial conformation at the RHF/6-31G level of theory, with dihedral angles for H_a–C–C–H_b optimised to 177° (di-equatorial) and 74° (di-axial), respectively. The comparatively weak anomeric effect found computationally (not large enough to compensate for the axial phenylethynyl group) is consistent with previous experimental observations that silyloxy groups give rise to a weaker anomeric effect compared to alkoxy groups.[5] For the *syn*-diastereomer, the (OTIPS axial, phenylethynyl equatorial) conformation was found to be 2.5 kcal/mol more stable than the (OTIPS equatorial, phenylethynyl axial) conformation at the RHF/6-31G level of theory, with dihedral angles optimised to 55° and 56°, respectively. The relatively small value of J_{ab} is less consistent with *anti*-**2c**, given the expected higher population of the di-equatorial conformer compared to the di-axial conformation according to the computational results, and is more consistent with *syn*-**2c**. The absolute configuration of the H_b (propargylic) stereocentre was assigned by analogy to the X-ray structures of **4b** and **4cb**, which were in agreement with the assigned geometry of all Ir-catalyzed propargylic C–H functionalisation products previously obtained by our group.[4]

5. Assignment of relative and absolute configuration for the major diastereomers of 2c and 2g, and 2h

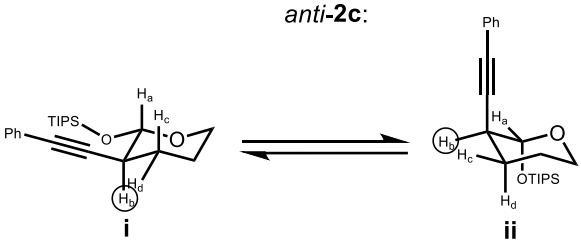
Predicted coupling constants are based on H-C-C-H dihedral angle (φ) anticipated in each possible chair conformer.

syn-**2c**:



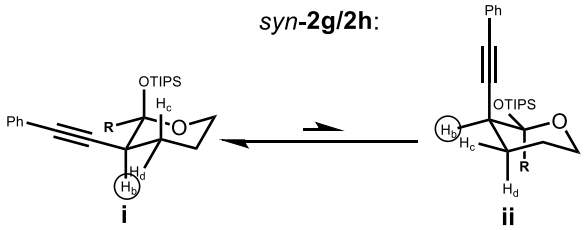
Proposed **2c** assignment, gives dt splitting, significant equilibrium between conformers is likely, based on J_{bc}

anti-**2c**:



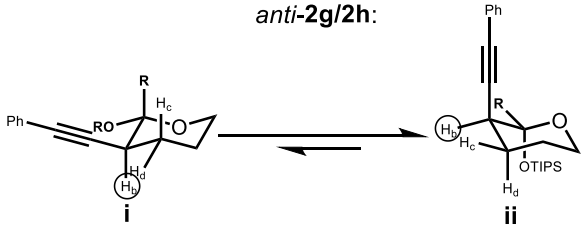
Implausible **2c** assignment. Could give q or td splitting depending on position of equilibrium, but not dt.

syn-**2g/2h**:



Implausible **2g/2h** assignment. Chair **ii** would have to be heavily favoured to give t splitting. The diaxial alkynyl and Me/Ph and lack of anomeric effect should strongly disfavour this conformer.

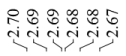
anti-**2g/2h**:



Proposed **2g/2h** assignment. Chair **ii** would give t splitting. This chair should be favoured, considering the anomeric effect and larger A value of Me/Ph groups compared to alkynyl group.

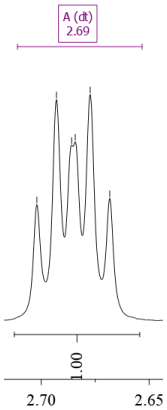
syn-**2c**: proposed assignment

Coupling	**φ (i)**	**J_i** (predicted)	**φ (ii)**	**J_{ii}** (predicted)	**J** (observed)
H_b-H_a	~60°	~4	~60°	~4	4.5
H_b-H_c	~180°	~**13**	~60°	~**4**	**8.0**
H_b-H_d	~60°	~4	~60°	~4	4.5
Observed signal: dt, J = 8.0, 4.5 Hz (2.69 ppm). Best explained as an average of both sets of J values, indicating significant concentrations of both chair conformers. <u>This is the most reasonable assignment for **2c**.</u>					



anti-**2c**: alternate assignment

Coupling	**φ (i)**	**J_i** (predicted)	**φ (ii)**	**J_{ii}** (predicted)	**J** (observed)
H_b-H_a	~180°	~13	~60°	~4	4.5
H_b-H_c	~180°	~13	~60°	~4	8.0
H_b-H_d	~60°	~4	~60°	~4	4.5
Observed signal: dt, J = 8.0, 4.5 Hz (2.69 ppm). Neither set of predicted J values, not any average thereof, can explain the dt splitting pattern. q and td are both possible, but not dt. <u>Not a reasonable assignment for **2c**</u>					



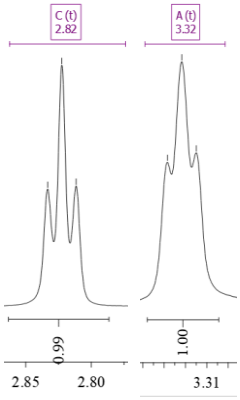
syn-**2g/2h**: alternate assignment

Coupling	**φ (i)**	J_i (predicted)	**φ (ii)**	J_{ii} (predicted)	J (observed)
H_b-H_c	~180°	~13	~60°	~4	4.4/3.4
H_b-H_d	~60°	~4	~60°	~4	4.4/3.4
Observed signals: **2g** (R=Me)**:** t, J = 4.4 Hz (2.82 ppm), **2h** (R=Ph)**:** t, J = 3.4 Hz (3.32 ppm). Observed signals only explicable with conformer **ii** heavily favoured. Unlikely given axial alkynyl and Me/Ph groups and non-anomeric OTIPS. Not a reasonable assignment for **2g/2h**.					

H_b signal for **2g, 2h:**

anti-**2g/2h**: proposed assignment

Coupling	**φ (i)**	J_i (predicted)	**φ (ii)**	J_{ii} (predicted)	J (observed)
H_b-H_c	~180°	~13	~60°	~4	4.4/3.4
H_b-H_d	~60°	~4	~60°	~4	4.4/3.4
Observed signals: **2g** (R=Me)**:** t, J = 4.4 Hz (2.82 ppm), **2h** (R=Ph)**:** t, J = 3.4 Hz (3.32 ppm). Observed signals only explicable with conformer **ii** heavily favoured, as in *syn*-**2g/2h**. More reasonable to favour **ii** here than in *syn* case, in light of anomeric effect and A values. This is the most reasonable assignment for **2g/2h**.					



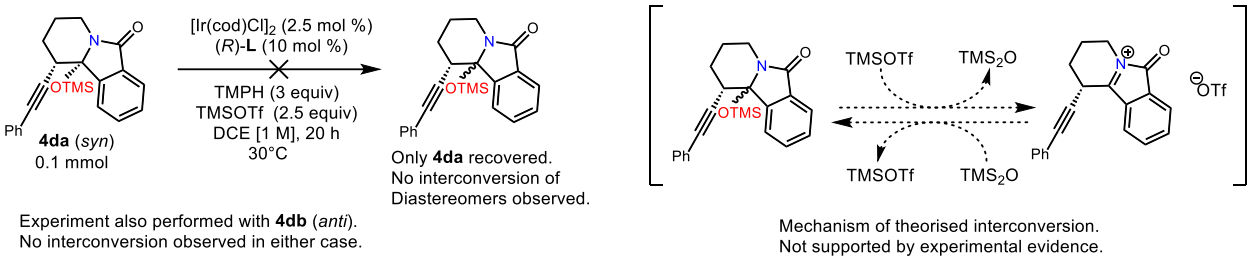
Summary:

The data presented and interpreted above show that based on the ^{1}H NMR for the propargyl H (H_b) signal in product **2c**, the *syn* diastereomer is the only reasonable assignment of the relative configuration. Its dt splitting pattern and J values of 8.0 and 4.5 can be explained as a weighted average of the values expected from contributions of both possible chair conformers (**i** and **ii)**. On the other hand, neither chair conformer of *anti*-**2c** has a set of predicted J values that correspond to the observed signal, nor could the two sets be averaged to give a close match. Conformer **ii** of *anti*-**2c** would likely give a quartet or apparent quartet given its similar, relatively small J values, while conformer **i** or an average of the two chairs would likely give a triplet of doublets (td), the result of two larger J values and one smaller J value. Thus, this diastereomer cannot give rise to a doublet of triplets (dt) for H_b, and so we assign the observed diastereomer as *syn*-**2c** must. This is consistent with the conclusion of the computational analysis of dihedral angles in the section titled "Assignment of relative and absolute configuration of the major and minor diastereomers of 2b and 2c."

For both the *syn*- and *anti*- diastereomers of **2g** (R= Me) and **2h** (R= Ph), any significant contribution from chair conformer **i** would give a doublet of doublets, the product of two very different J values. On the other hand, an equilibrium that heavily favours conformer **ii** would give a triplet with a J value of approximately 4, as is observed for H_b's signal in both products. This suggests that whichever is the major diastereomer for these products must favour chair **ii** heavily. This is implausible for *syn*-**2g/2h**, given the diaxial alkynyl and Me/Ph groups and non-anomeric OTIPS. It is therefore highly unlikely that the *syn* diastereomer is the correct assignment for **2g** and **2h's** major products. On the other hand, it makes sense that *anti*-**2g/2h** would exist predominantly in conformer **ii**, considering the impact of the anomeric effect, and the larger A values of the Me (1.7) and Ph (2.8 to 3.0) groups compared to an alkynyl group (0.5 for ethynyl).

The absolute configuration of the H_b (propargylic) stereocentre in all examples was assigned by analogy to the X-ray structures of **4b** and **4cb**, which were in agreement with the assigned geometry of all Ir-catalyzed propargylic C–H functionalisation products previously obtained by our group.[4]

6. Diastereomer equilibration test

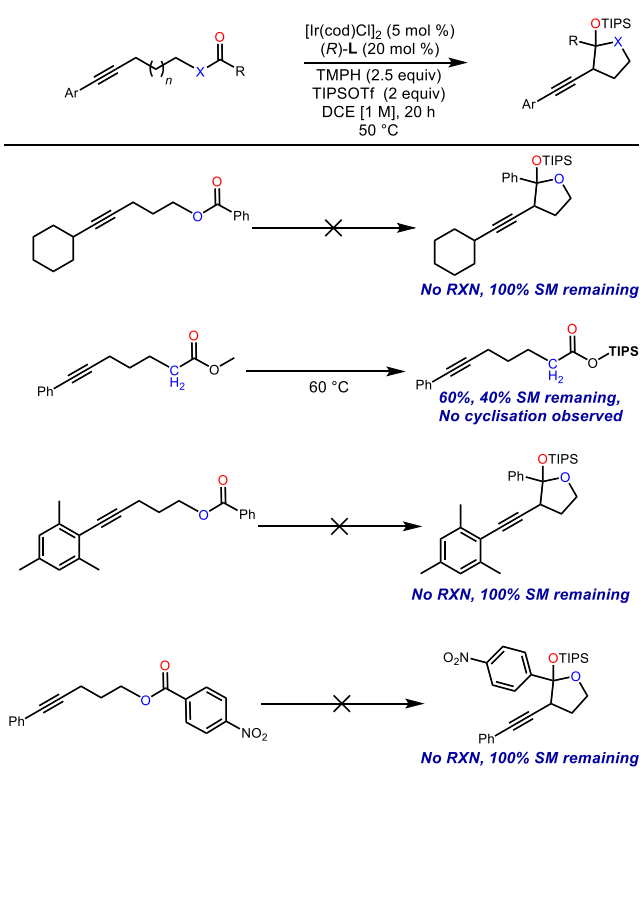


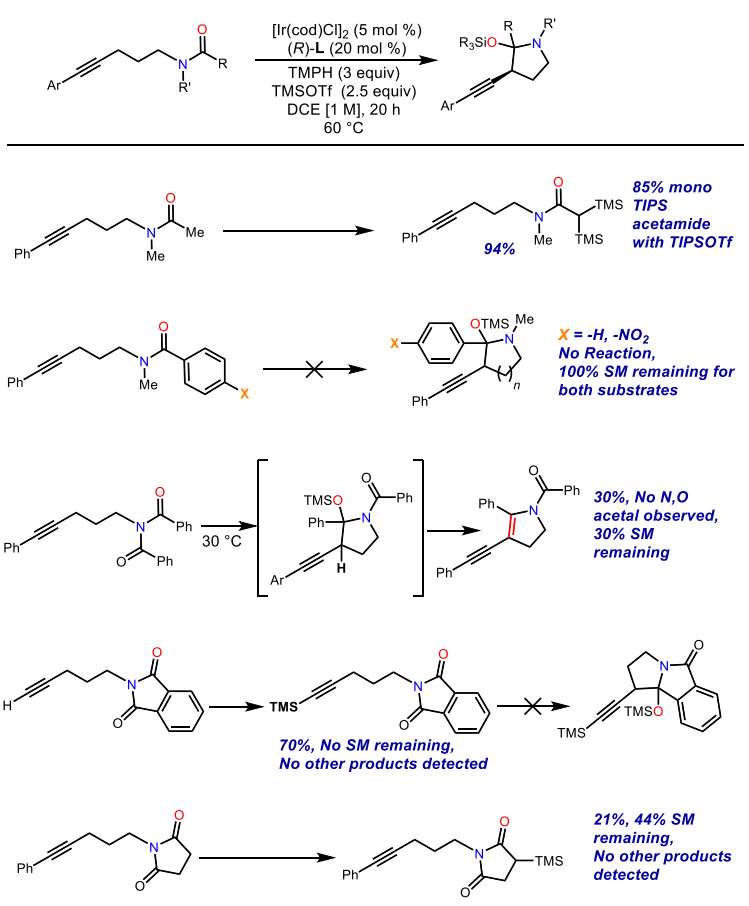
Each separable diastereomer of phthalimide derived product **4d** was independently resubjected to the reaction conditions to examine the possibility that the diastereomeric ratio is controlled thermodynamically, an interconversion of the diastereomers mediated by abstraction and reintroduction of the silyloxy group being hypothesised. If this interconversion were taking place, each purified diastereomer would expected to equilibrate to a mixture containing significant amounts of both diastereomers if resubjected to the reaction conditions. However, no interconversion was observed, and each diastereomer was recovered alone following resubjection. It was concluded that, most likely, the diastereomeric ratios observed for *O*,*O*- and *N*,*O*-acetal products are kinetically controlled by the iridium catalyst.

7. Failed reactions and additional conditions

Listed below are yields and recoveries determined by crude ^{1}H NMR spectroscopy of reaction mixtures for reactions whose outcomes was deemed unsatisfactory and purification of products not pursued. Stereochemistry has been omitted in cases where in cannot be confidently inferred. All yields shown below were determined by ^{1}H NMR relative to 1,1,2,2-tetrachloroethane as the internal standard.

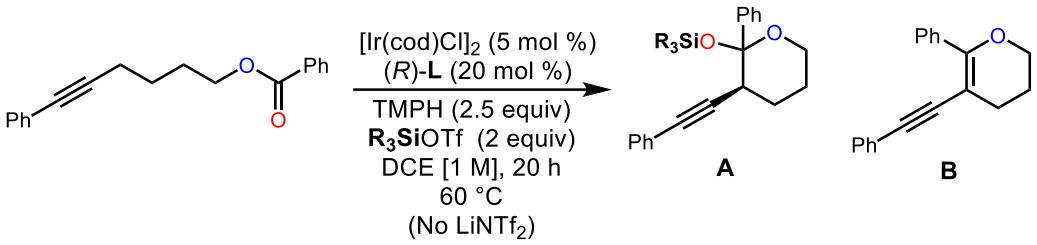
Failed reactions and undesirable reactivity:



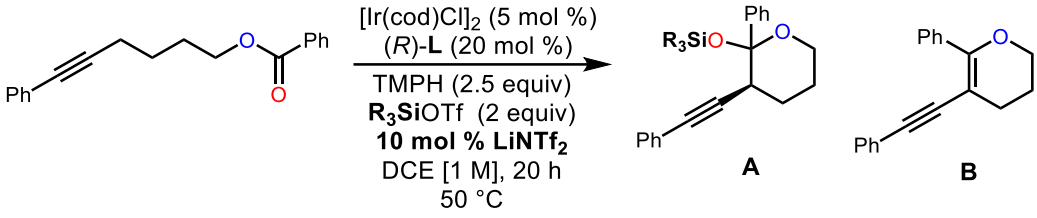


Additional screening of reaction conditions was pursued for the cyclisation of substrates **1g** and **1h**. The results are summarised below. Notably, the addition of $LiNTf_2$ as an additive resulted in improved reactivity in certain cases.

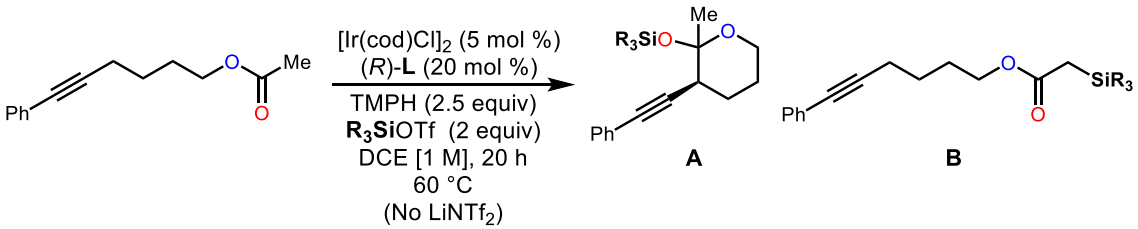
Additional conditions screened for 2g and 2h (or analogues)



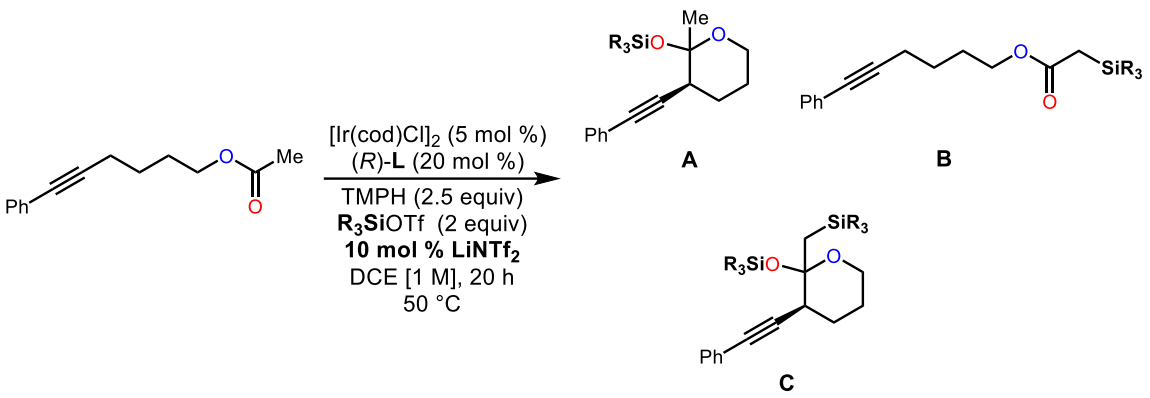
R_3SiOTf	**A** (%)	dr	**B** (%)	SM remaining (%)
TIPSOTf	5	3.6:1	0	90
TESOTf	55	1.4:1	0	45
TMSOTf	40	1.2:1	50	0



R_3SiOTf	**A** (%)	dr	**B** (%)	SM remaining (%)
TIPSOTf (**2h**)	72	5.3:1	0	25
TESOTf	46	1.7:1	0	0
TMSOTf	30	1.3:1	47	0



R_3SiOTf	**A** (%)	dr	**B** (%)	SM remaining (%)
TIPSOTf	29	>5:1	35	14
TESOTf	15	2.0:1	71	0

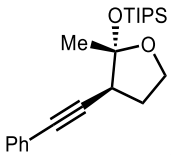


R_3SiOTf	**A** (%)	dr	**B** (%)	**C** (%)	dr
TIPSOTf (**2g**)	76	5.3:1	8	0	N/A
TESOTf	<5%	>20:1	16	76	n.d.

8. References

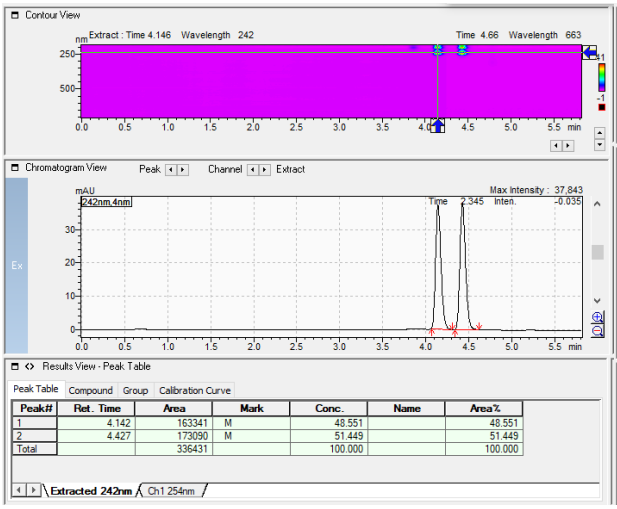
1. T. H. Lambert, S. J. Danishefsky, *J. Am. Chem. Soc.*, 2006, **128**, 426.
2. T. R. Hoye, V. Dvornikovs, *J. Am. Chem. Soc.*, 2006, **128**, 2550.
3. M. A. Walker, *J. Org. Chem.*, 1995, **60**, 5352.
4. (a) J. Zhu, Y. Wang, A. D. Charlack, Y.-M. Wang, *J. Am. Chem. Soc.,* 2022, **144,** 15480; (b) R. Ding, Y. Wang, Y.-M. Wang, *Synthesis,* 2023, **55,** 733; (c) J. Zhu, H. Xiang, H. Chang, J. C. Corcoran, R. Ding, Y. Xia, P. Liu, Y.-M. Wang, *Angew. Chem. Int. Ed.,* 2024, **63,** e202318040; (d) J. Yu, Y. Xia, S. Dey, J. Zhu, K. S. Cheung, S. J. Geib, Y.-M. Wang, *J. Am. Chem. Soc.,* 2024, **146,** 27998.
5. J. P. Praly, R. U. Lemieux, *Can. J. Chem.*, 1987, **65**, 213.

9. Copies of HPLC traces



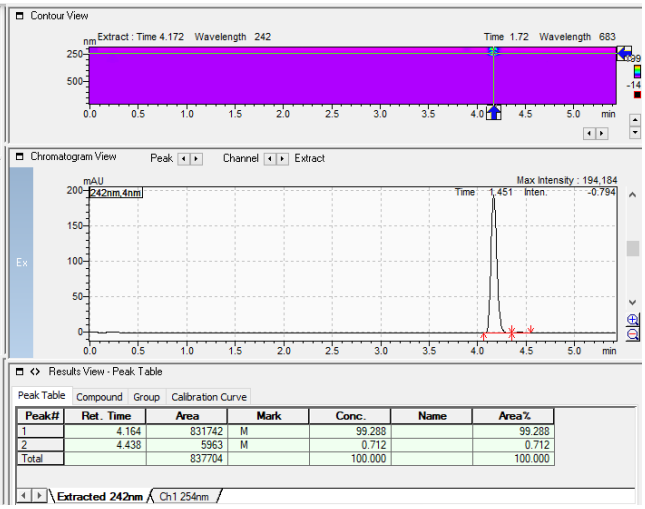
2a

Racemic trace:

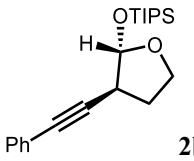


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	4.142	163341	M	48.551		48.551
2	4.427	173090	M	51.449		51.449
Total		336431		100.000		100.000

Enantioenriched trace:

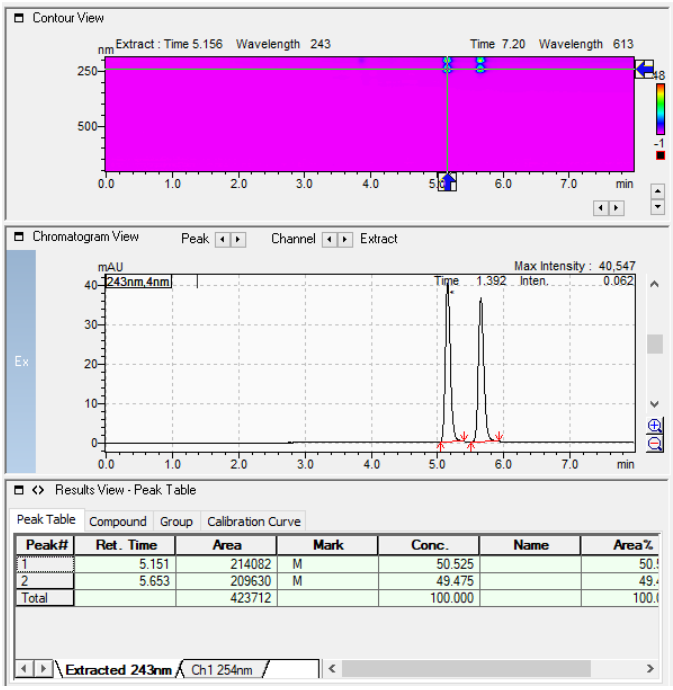


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	4.164	831742	M	99.288		99.288
2	4.438	5963	M	0.712		0.712
Total		837704		100.000		100.000

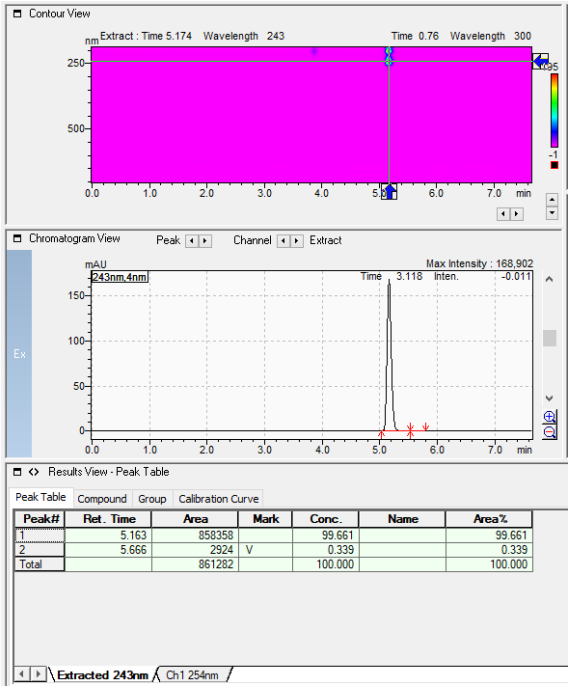


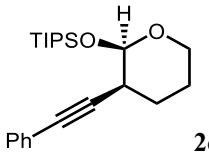
2b

Racemic trace:



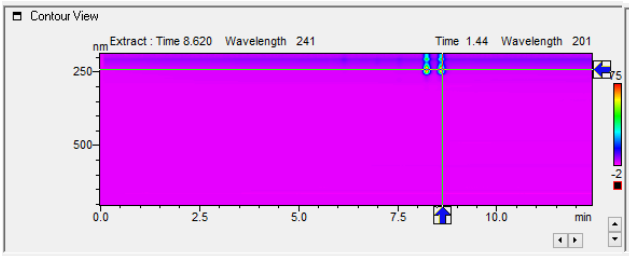
Enantioenriched trace:

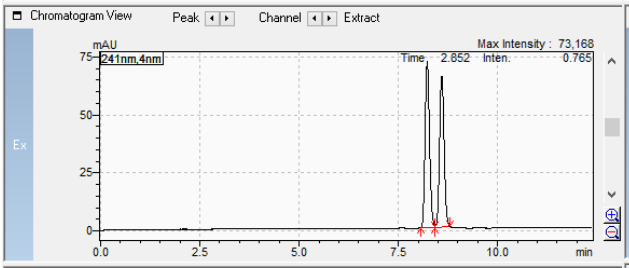


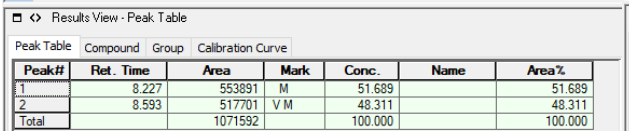


2c

Racemic trace:

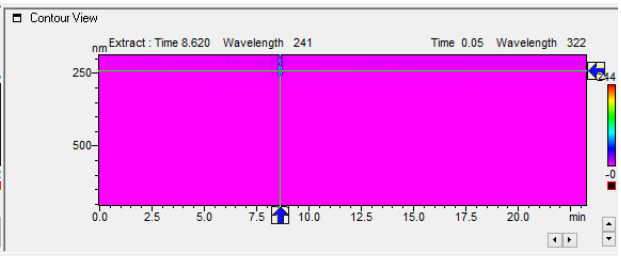


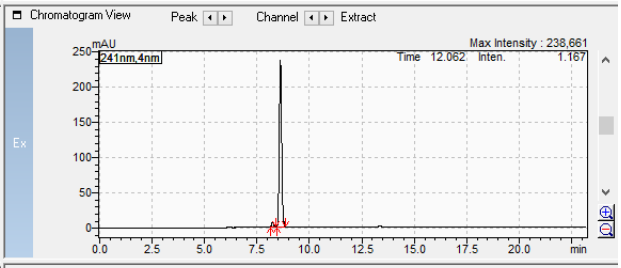


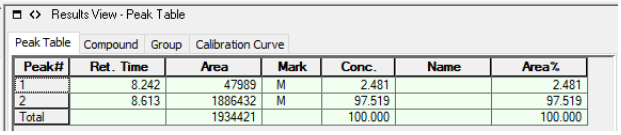


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	8.227	553891	M	51.689		51.689
2	8.593	517701	V M	48.311		48.311
Total		1071592		100.000		100.000

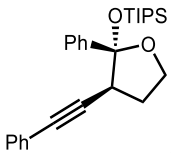
Enantioenriched trace:





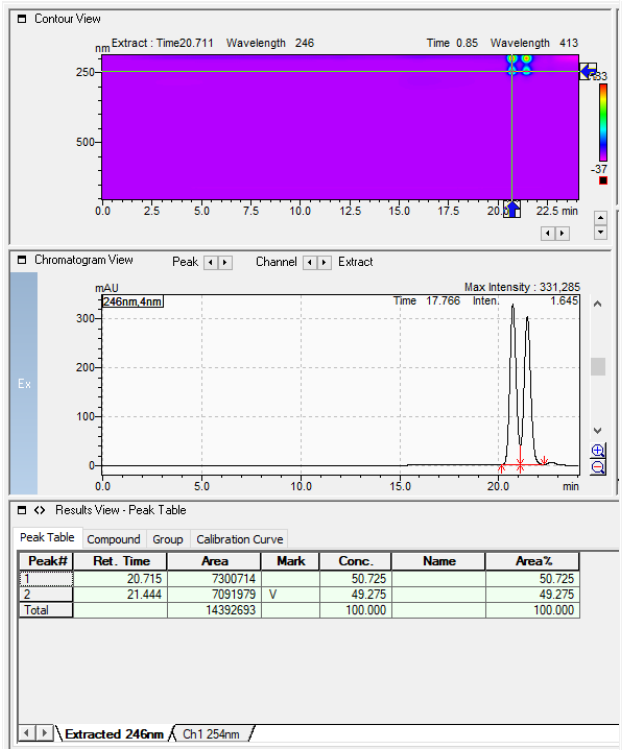


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	8.242	47989	M	2.481		2.481
2	8.613	1886432	M	97.519		97.519
Total		1934421		100.000		100.000

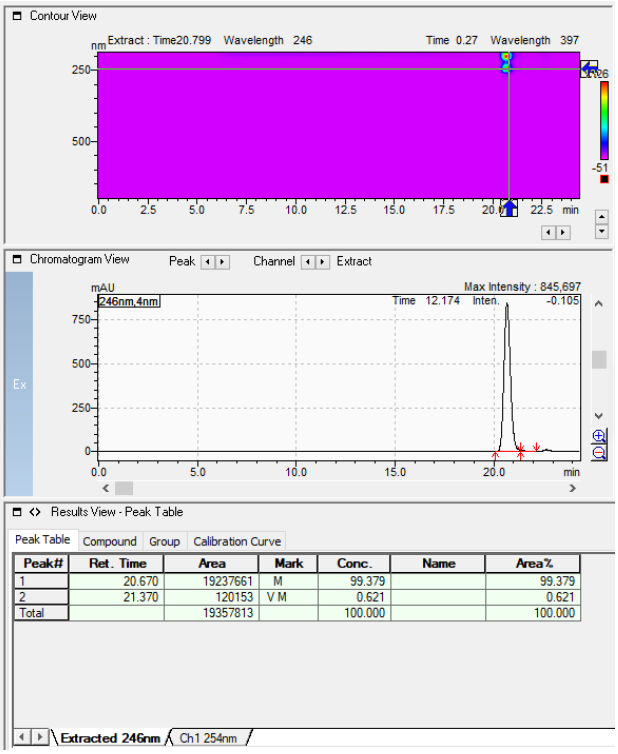


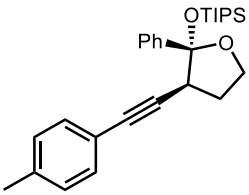
2d

Racemic trace:



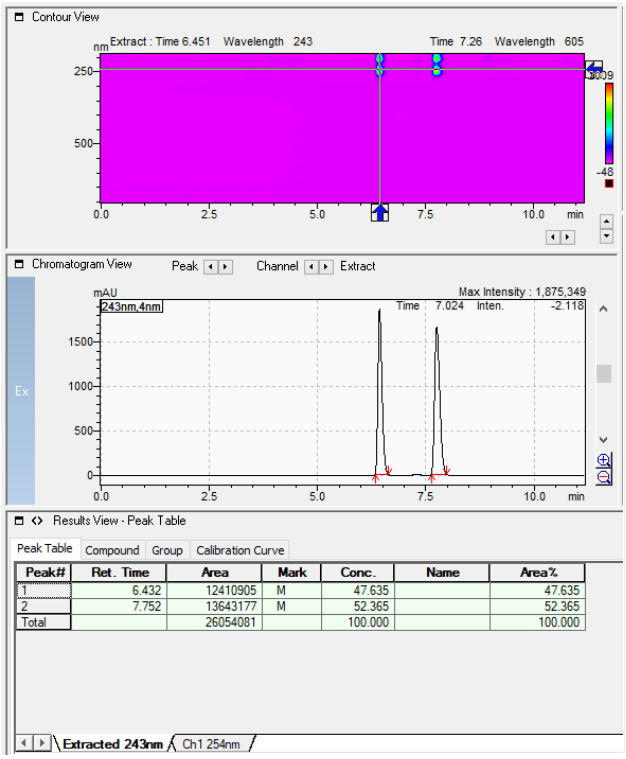
Enantioenriched trace:





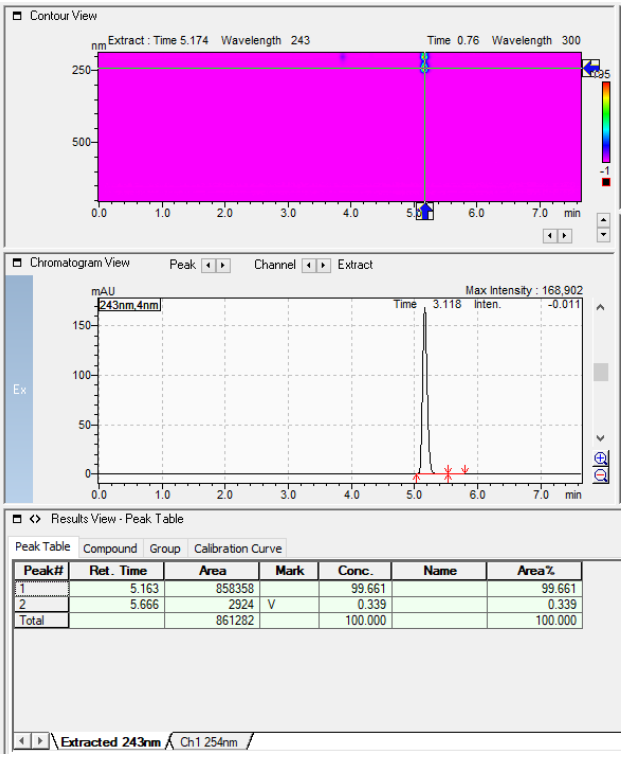
2e

Racemic trace:

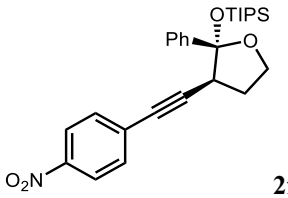


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	6.432	12410905	M	47.635		47.635
2	7.752	13643177	M	52.365		52.365
Total		26054081		100.000		100.000

Enantioenriched trace:

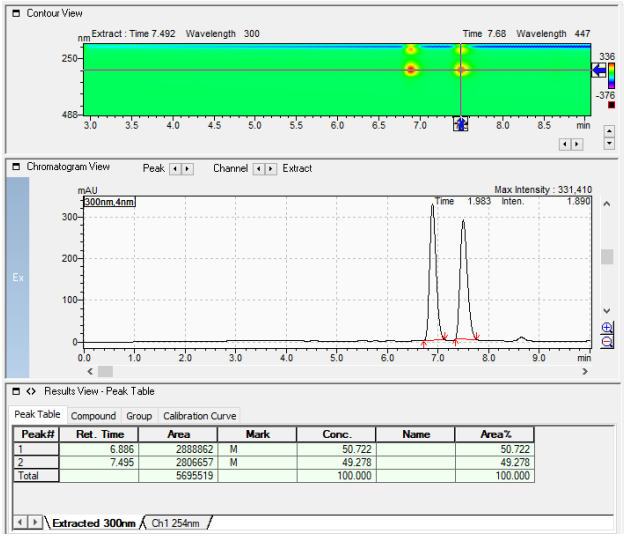


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	5.163	858358		99.661		99.661
2	5.666	2924	V	0.339		0.339
Total		861282		100.000		100.000

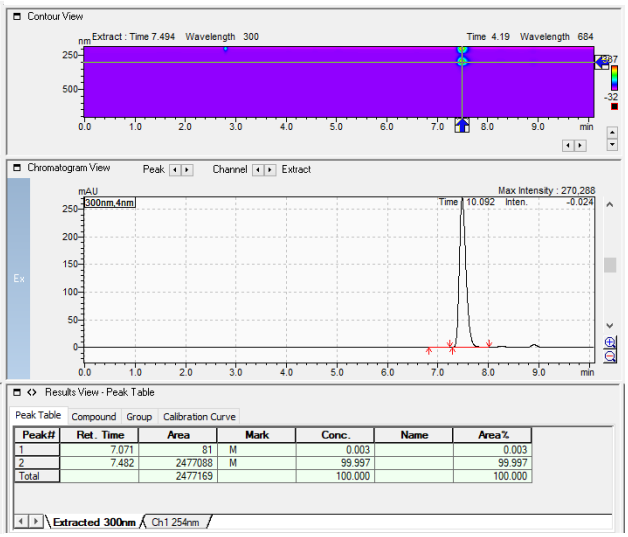


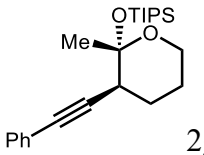
2f

Racemic trace:



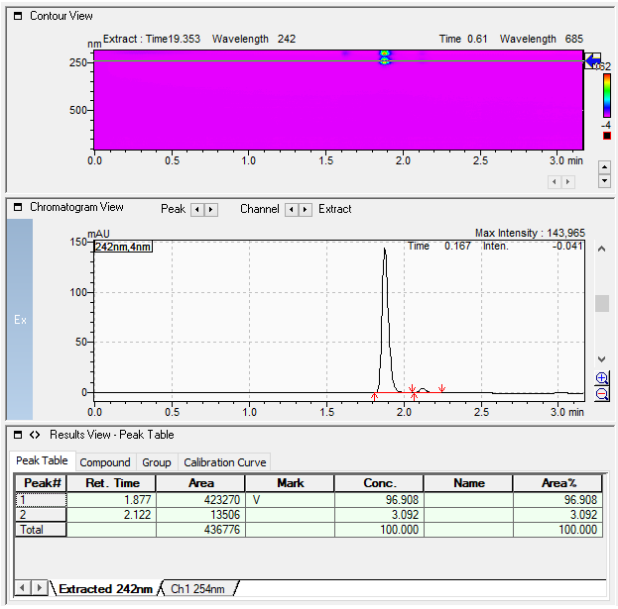
Enantioenriched trace:



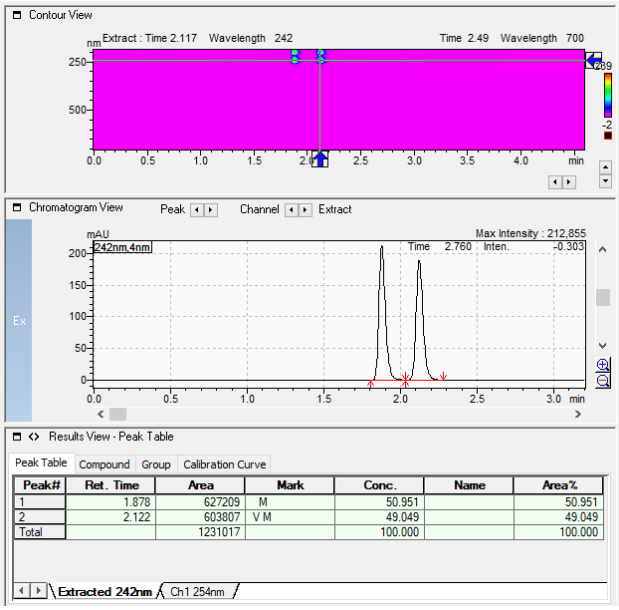


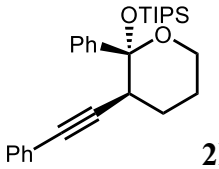
2g

Racemic trace:



Enantioenriched trace:

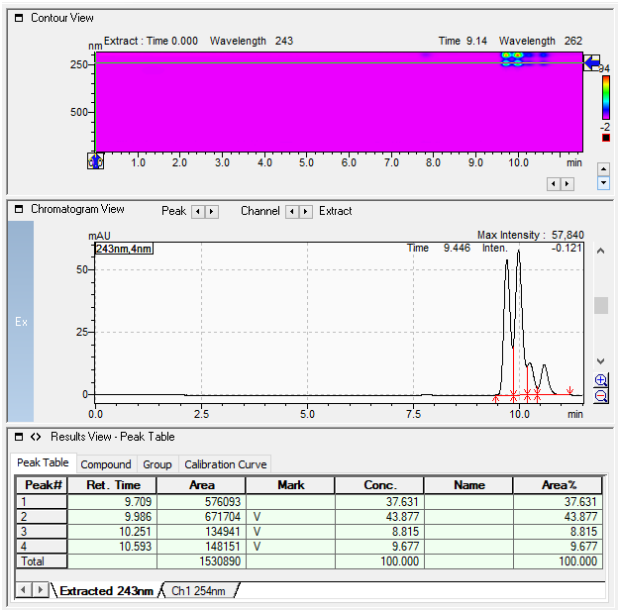




2h

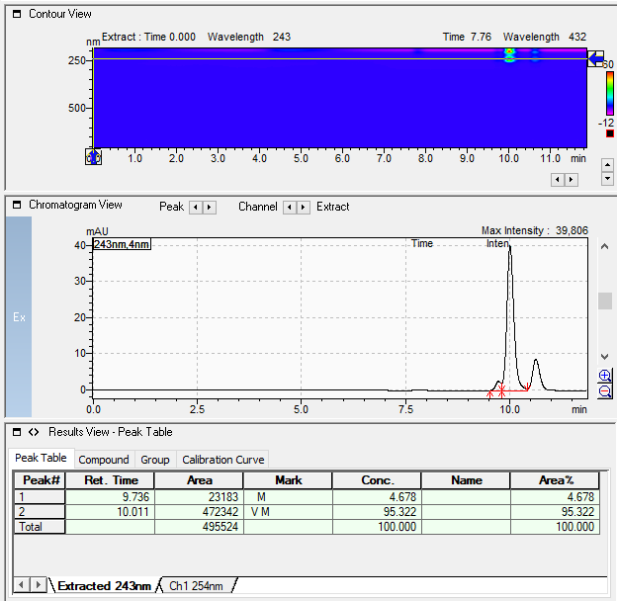
R.t. column oven (major diastereomer peaks resolved):

Racemic trace



Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	9.709	576093		37.631		37.631
2	9.986	671704	V	43.877		43.877
3	10.251	134941	V	8.815		8.815
4	10.593	148151	V	9.677		9.677
Total		1530890		100.000		100.000

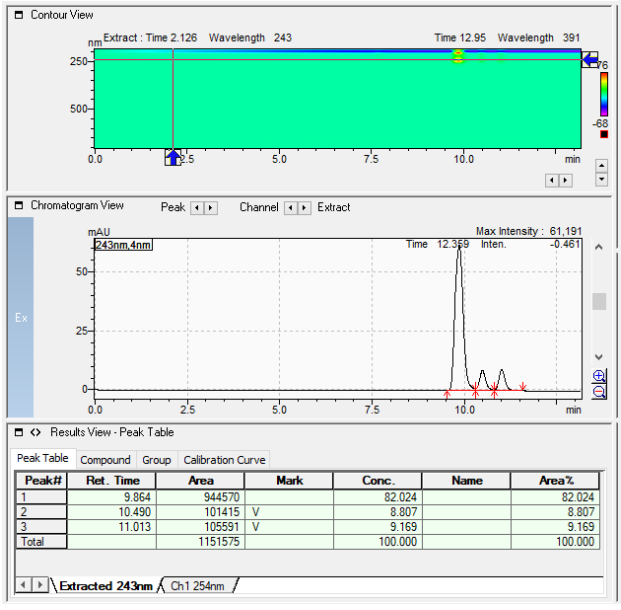
Enantioenriched trace



Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	9.736	23183	M	4.678		4.678
2	10.011	472342	V M	95.322		95.322
Total		495524		100.000		100.000

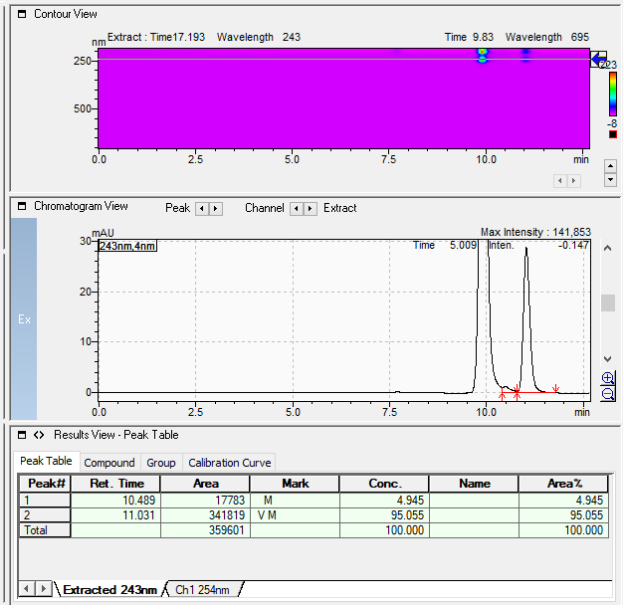
40 °C column oven (minor diastereomer peaks resolved):

Racemic trace

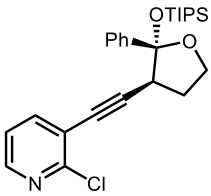


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	9.864	944570		82.024		82.024
2	10.490	101415	V	8.807		8.807
3	11.013	105591	V	9.169		9.169
Total		1151575		100.000		100.000

Enantioenriched trace

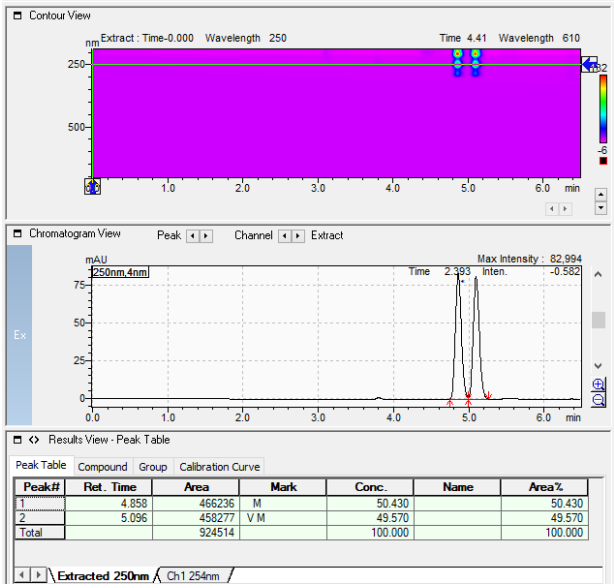


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	10.489	17783	M	4.945		4.945
2	11.031	341819	V M	95.055		95.055
Total		359601		100.000		100.000



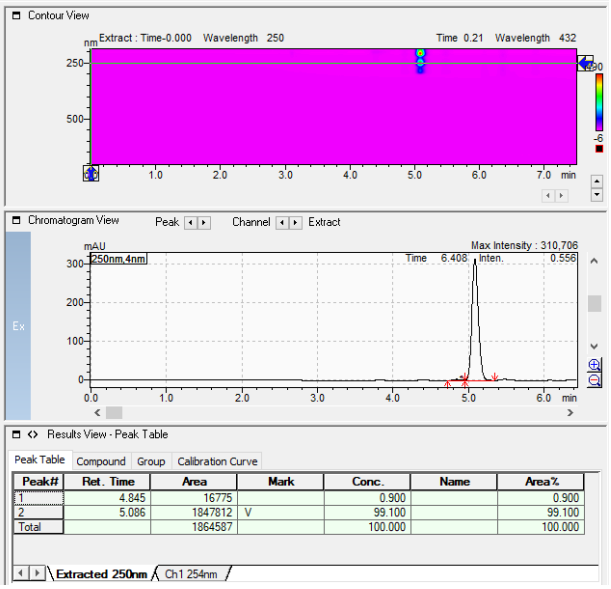
2i

Racemic Trace:

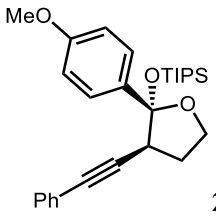


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	4.858	466236	M	50.430		50.430
2	5.096	458277	V M	49.570		49.570
Total		924514		100.000		100.000

Enantioenriched Trace:

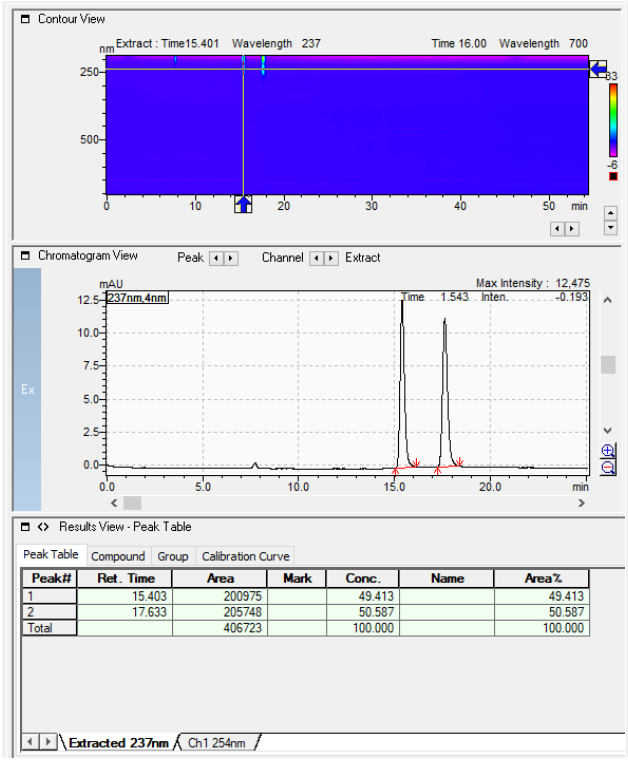


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	4.845	16775		0.900		0.900
2	5.086	1847812	V	99.100		99.100
Total		1864587		100.000		100.000



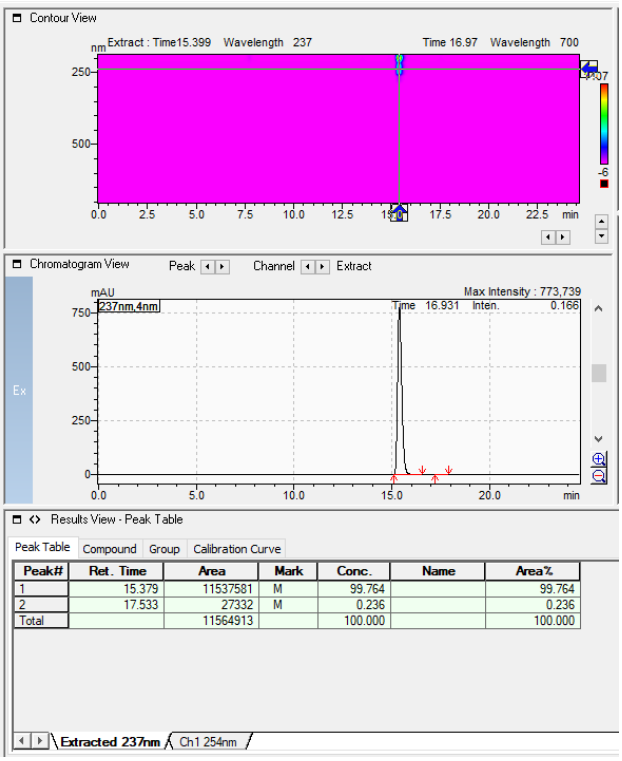
2j

Racemic Trace:

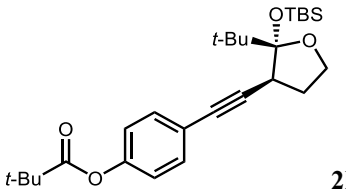


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	15.403	200975		49.413		49.413
2	17.633	205748		50.587		50.587
Total		406723		100.000		100.000

Enantioenriched trace:

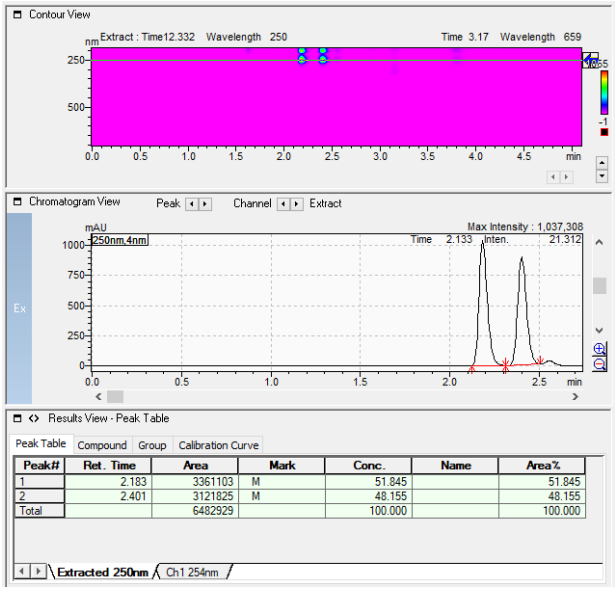


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	15.379	11537581	M	99.764		99.764
2	17.533	27332	M	0.236		0.236
Total		11564913		100.000		100.000

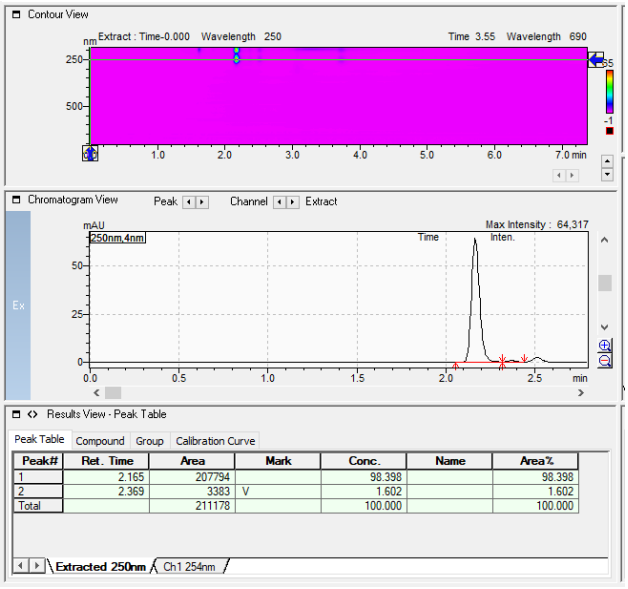


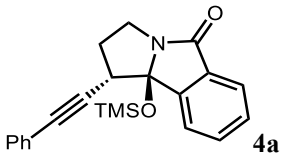
2k

Racemic Trace:



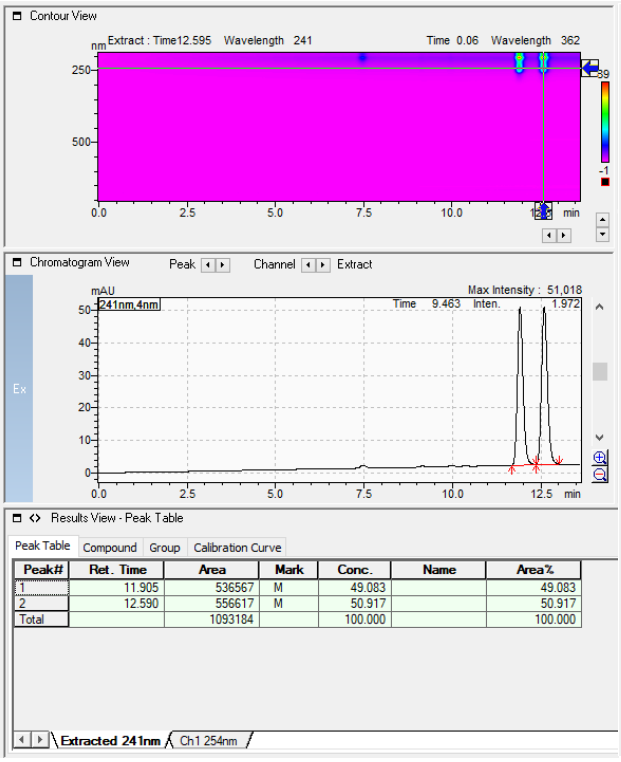
Enantioenriched trace:



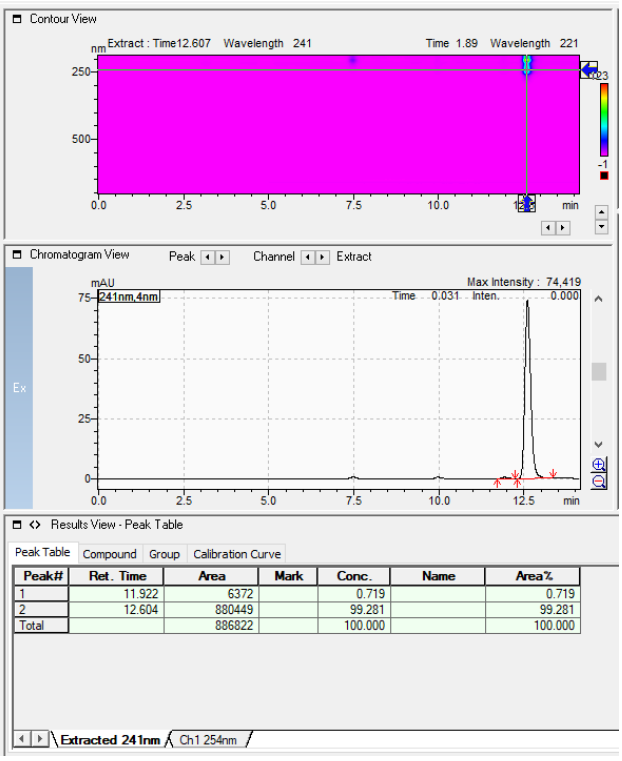


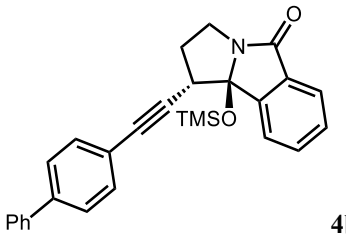
4a

Racemic Trace:



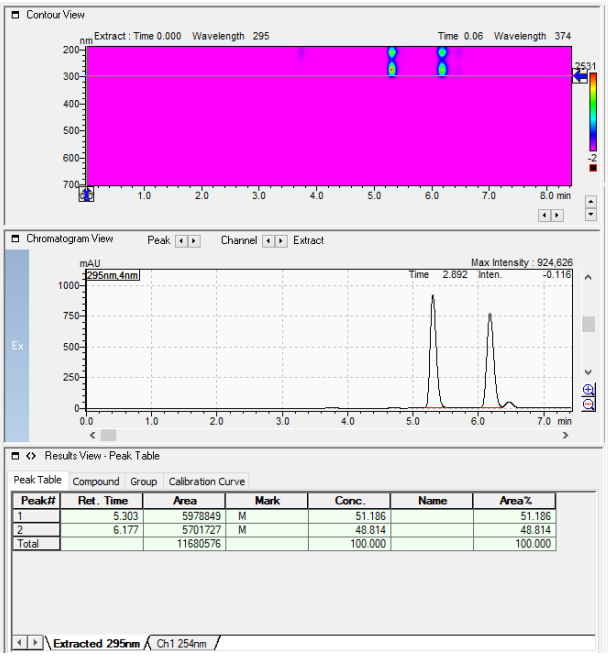
Enantioenriched trace:





4b

Racemic Trace:



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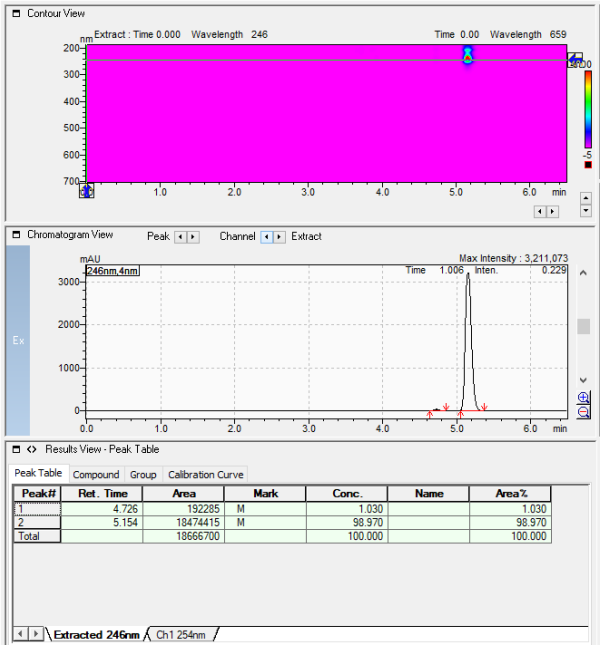
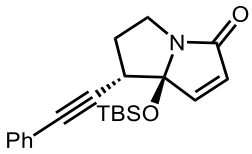
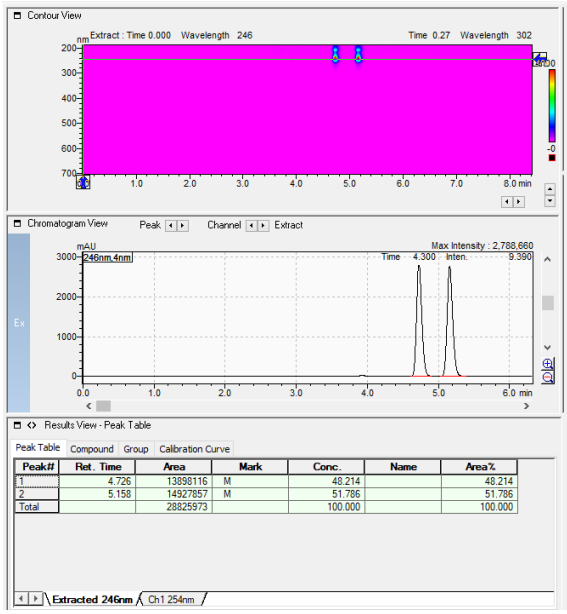




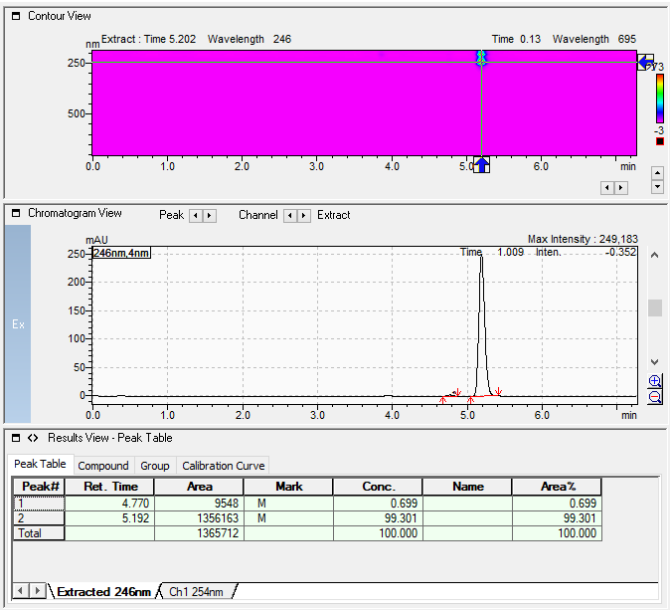
4c

Racemic Trace:

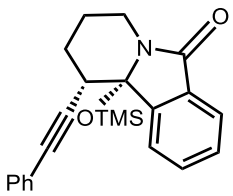


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	4.726	13898116	M	48.214		48.214
2	5.158	14927857	M	51.786		51.786
Total		28825973		100.000		100.000

Enantioenriched trace:

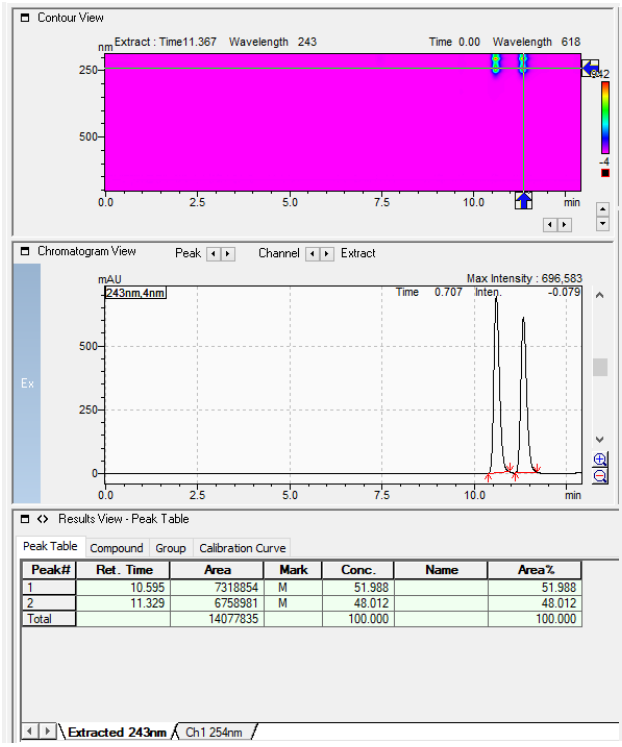


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	4.770	9548	M	0.699		0.699
2	5.192	1356163	M	99.301		99.301
Total		1365712		100.000		100.000



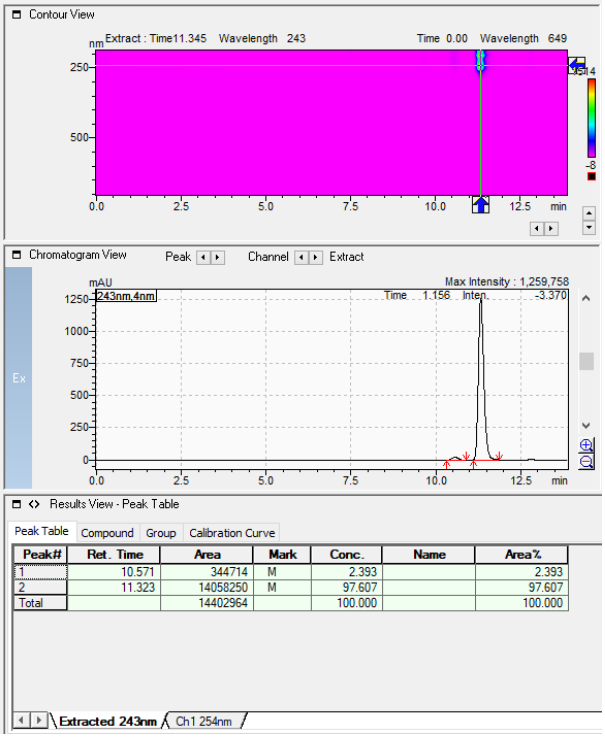
4da

Racemic Trace:

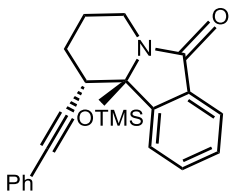


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	10.595	7318854	M	51.988		51.988
2	11.329	6758981	M	48.012		48.012
Total		14077835		100.000		100.000

Enantioenriched trace:

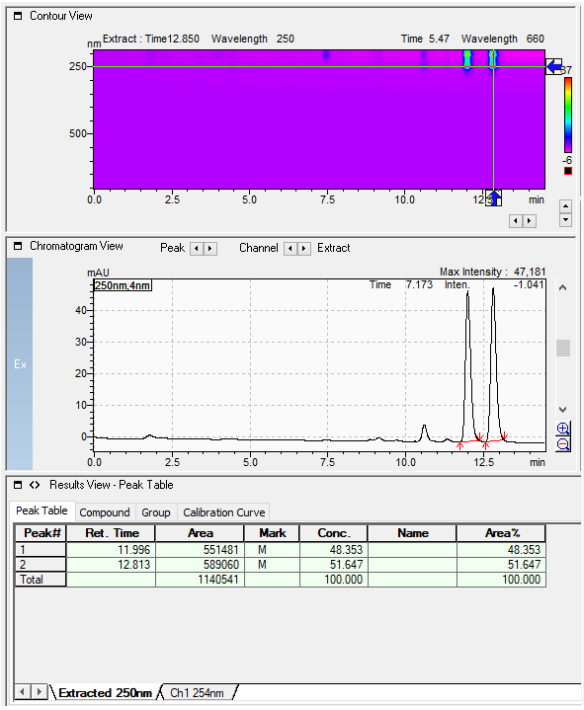


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	10.571	344714	M	2.393		2.393
2	11.323	14058250	M	97.607		97.607
Total		14402964		100.000		100.000

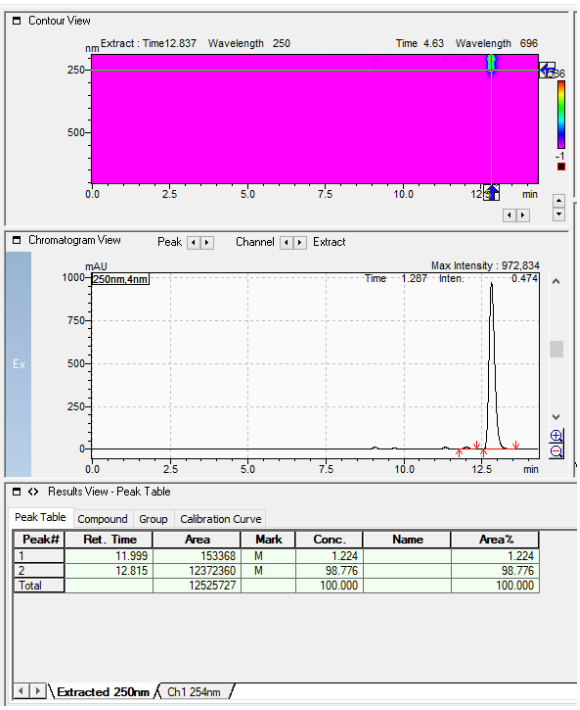


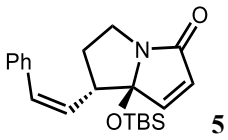
4db

Racemic Trace:



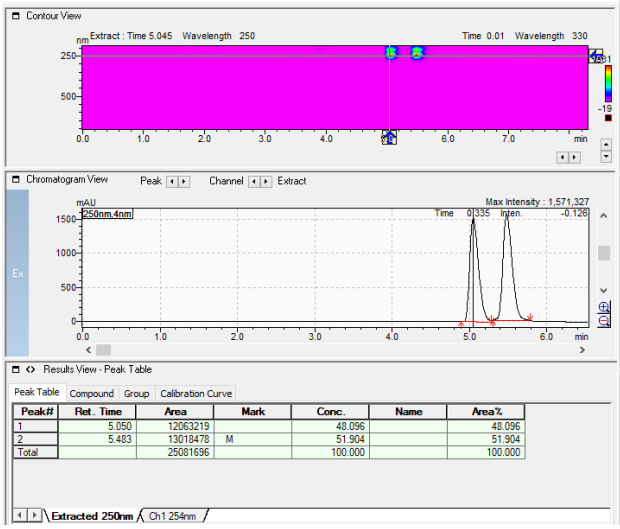
Enantioenriched trace:





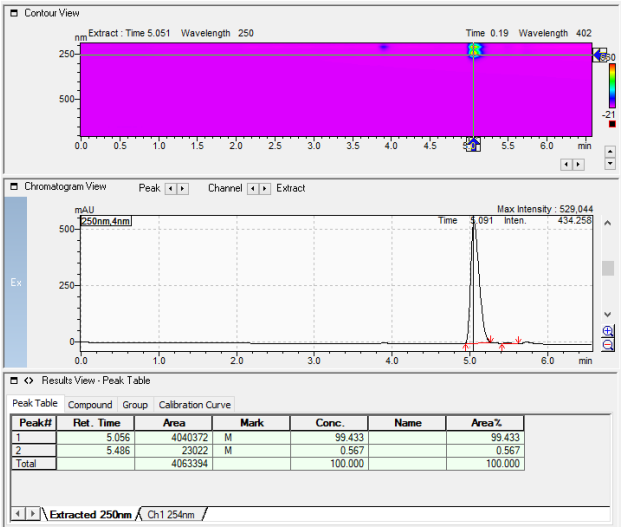
5

Racemic Trace:

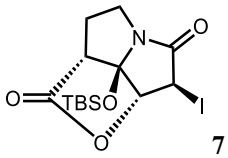


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	5.050	12063219		48.096		48.096
2	5.483	13018478	M	51.904		51.904
Total		25081696		100.000		100.000

Enantioenriched trace:

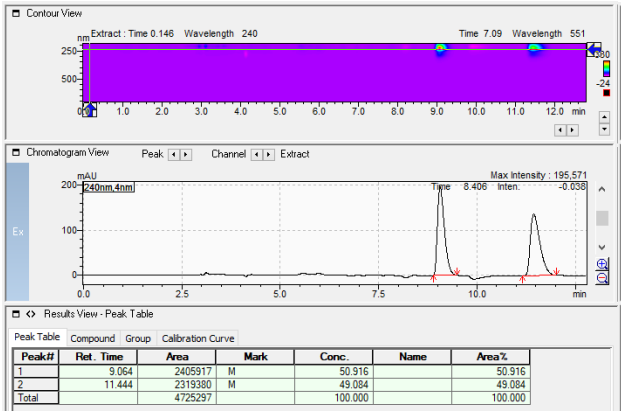


Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	5.056	4040372	M	99.433		99.433
2	5.486	23022	M	0.567		0.567
Total		4063394		100.000		100.000



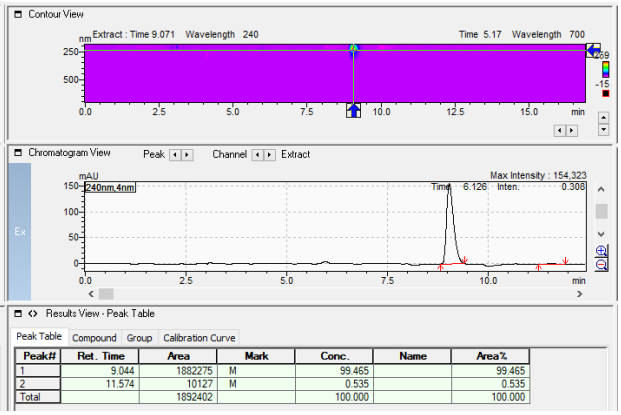
7

Racemic Trace:



Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	9.064	2405917	M	50.916		50.916
2	11.444	2319380	M	49.084		49.084
Total		4725297		100.000		100.000

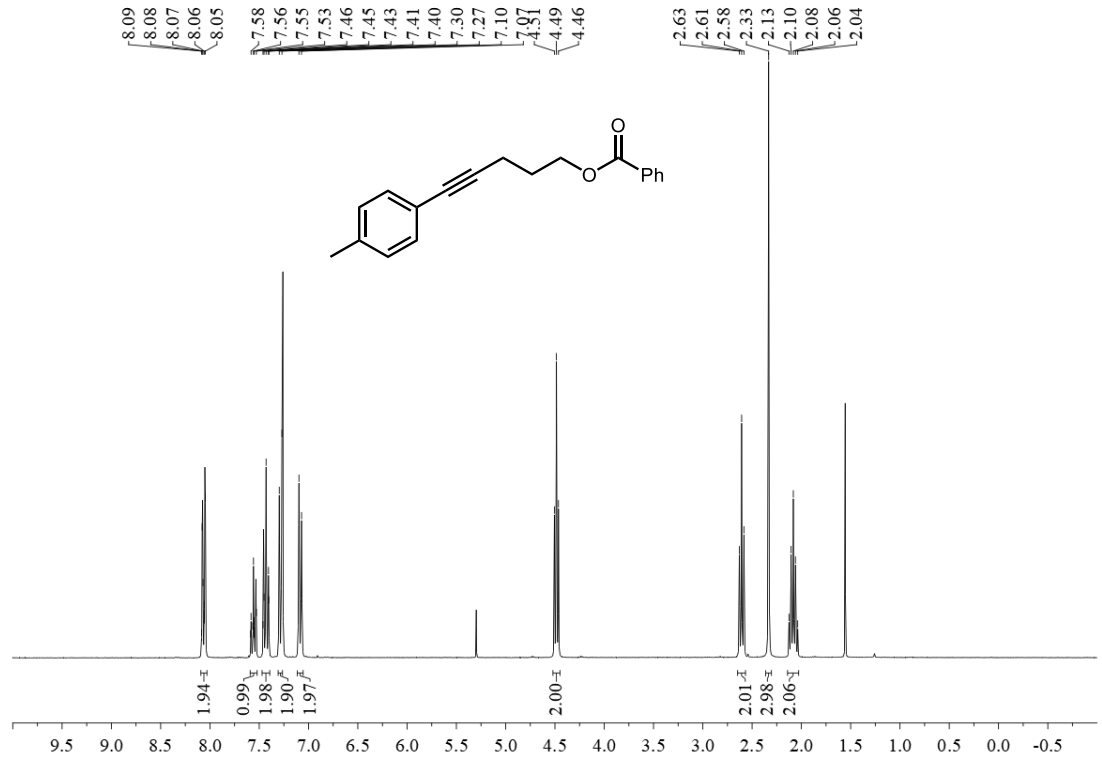
Enantioenriched trace:



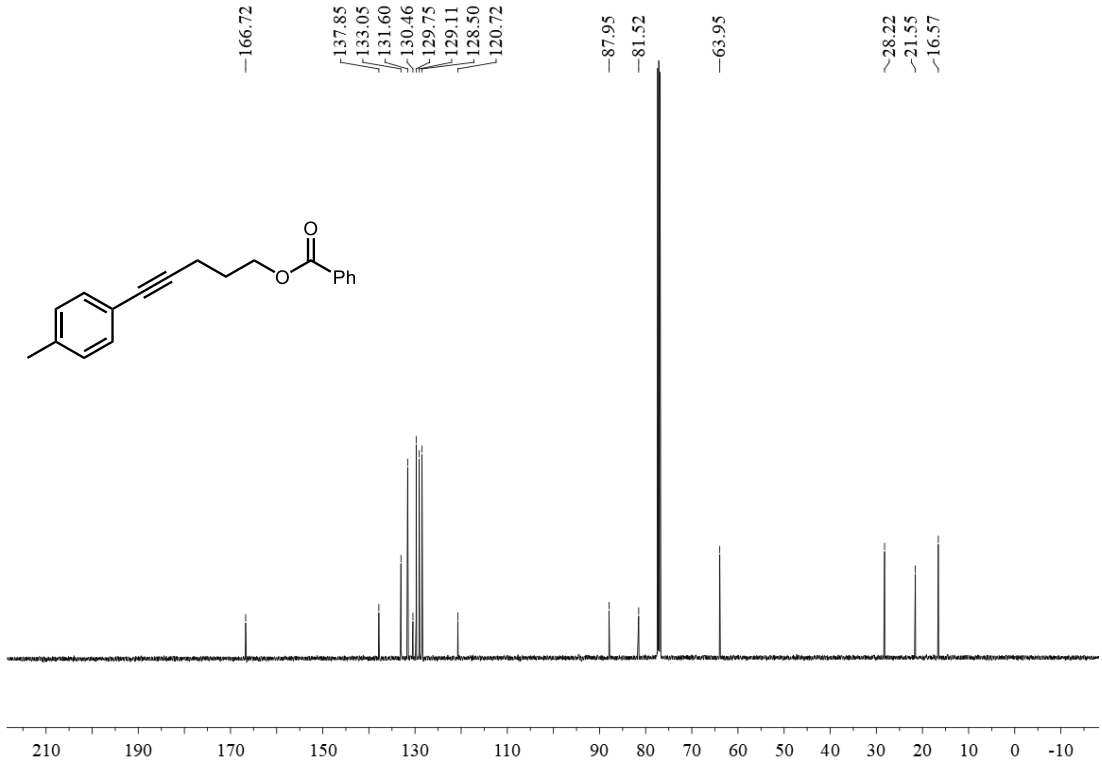
Peak#	Ret. Time	Area	Mark	Conc.	Name	Area%
1	9.044	1882275	M	99.465		99.465
2	11.574	10127	M	0.535		0.535
Total		1892402		100.000		100.000

10. Copies of NMR spectra

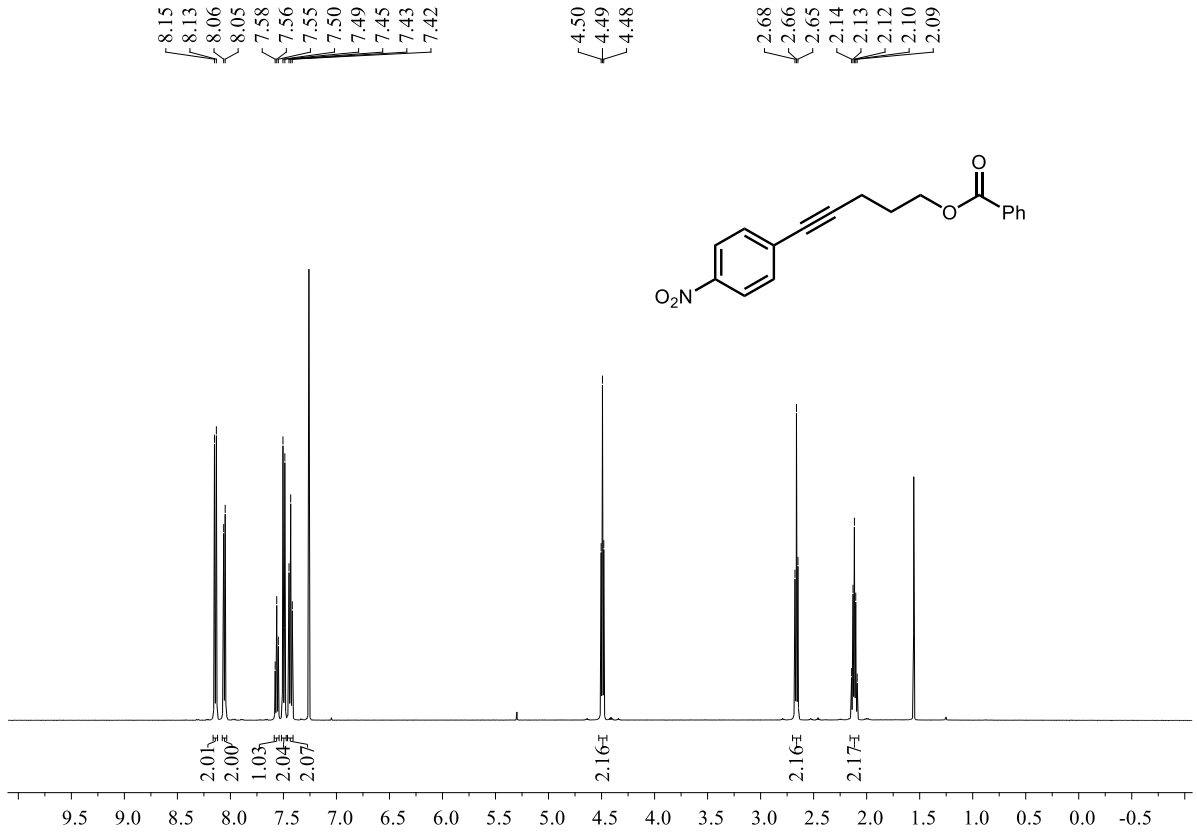
^{1}H NMR (300 MHz, $CDCl_3$) **(1e)**



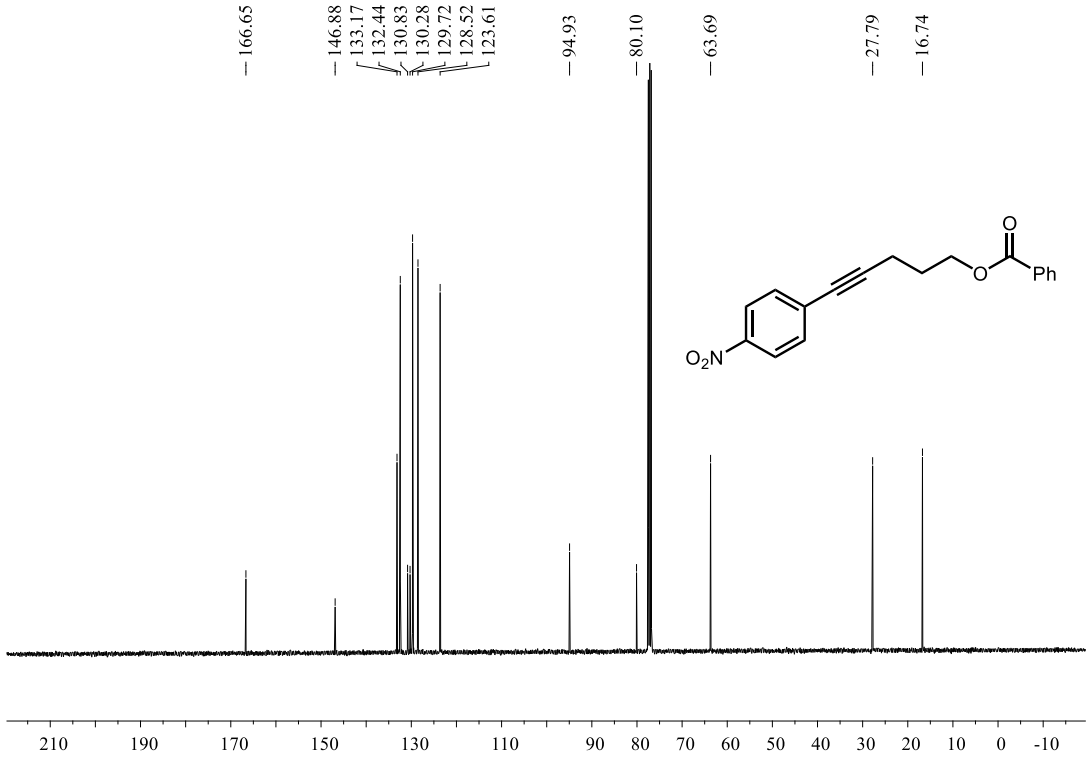
^{13}C NMR (126 MHz, $CDCl_3$) **(1e)**



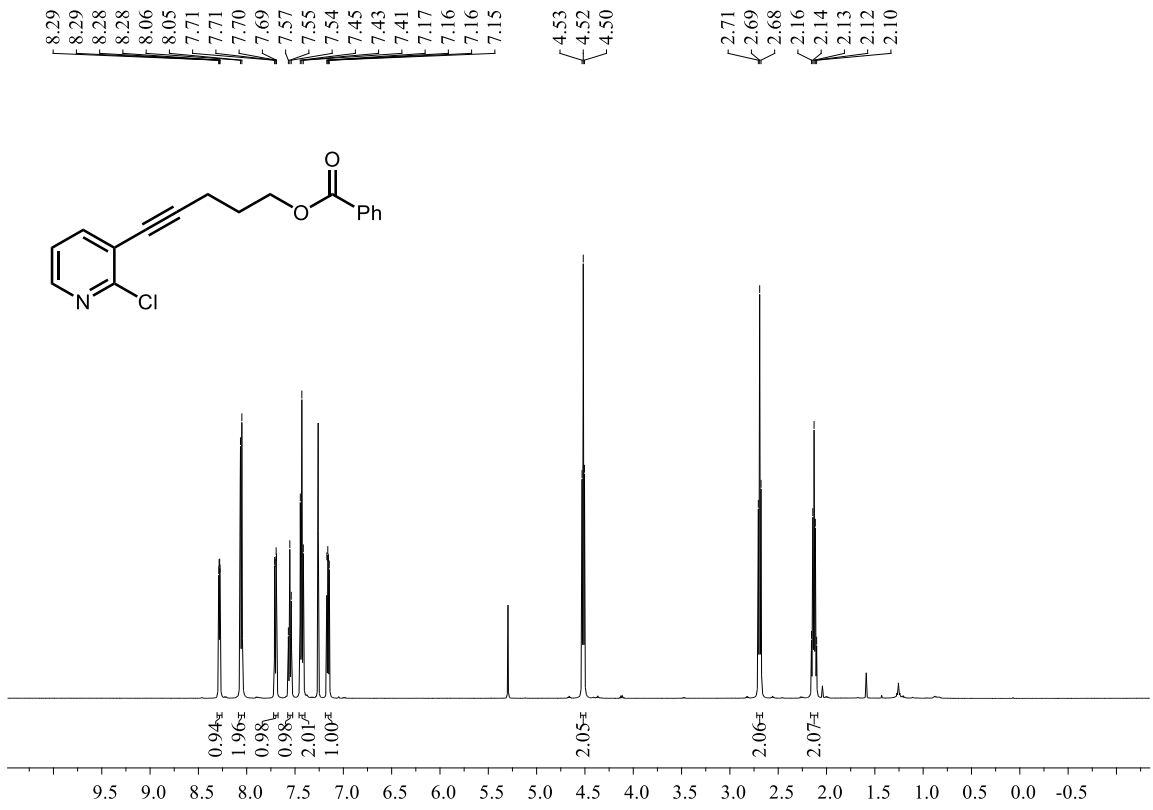
^{1}H NMR (500 MHz, $CDCl_3$) **(1f)**



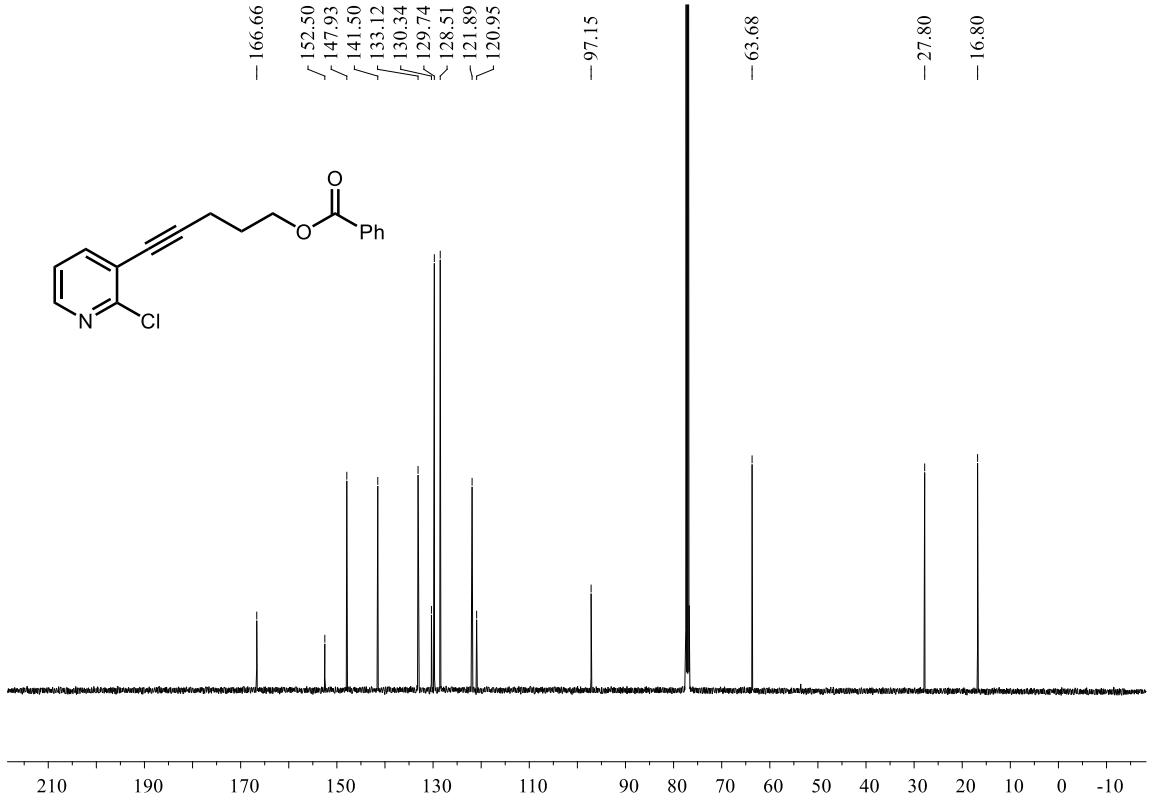
^{13}C NMR (101 MHz, $CDCl_3$) **(1f)**



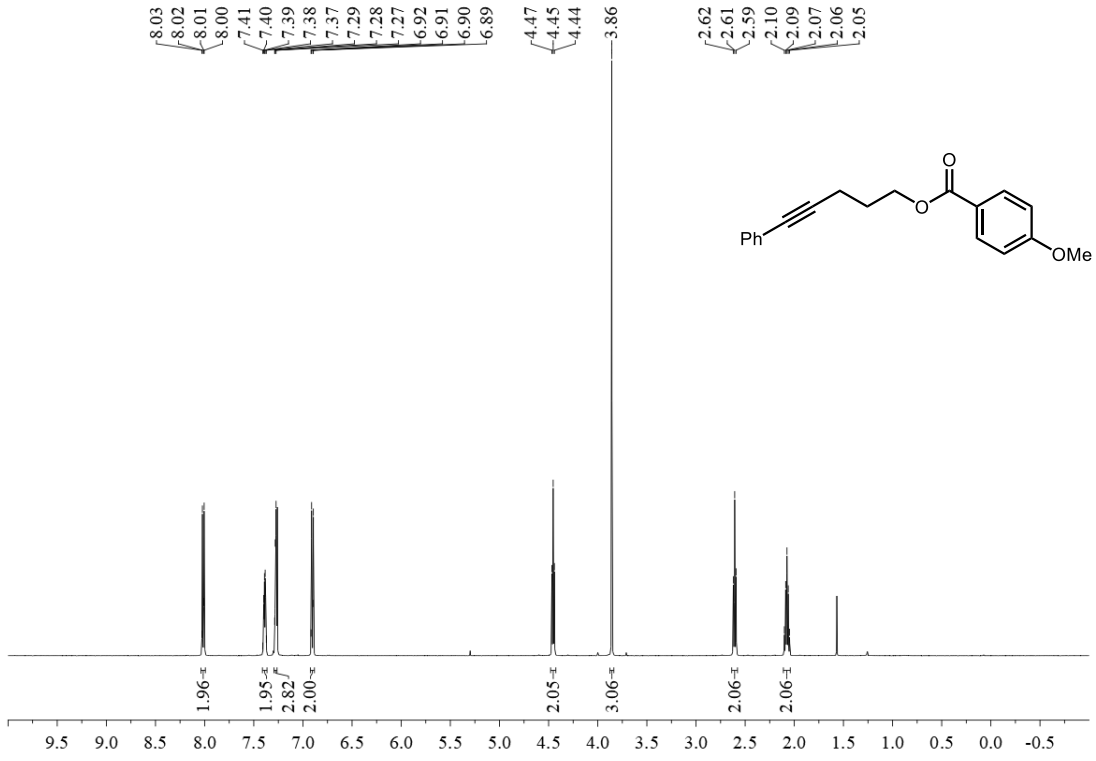
^{1}H NMR (500 MHz, $CDCl_3$) **(1i)**



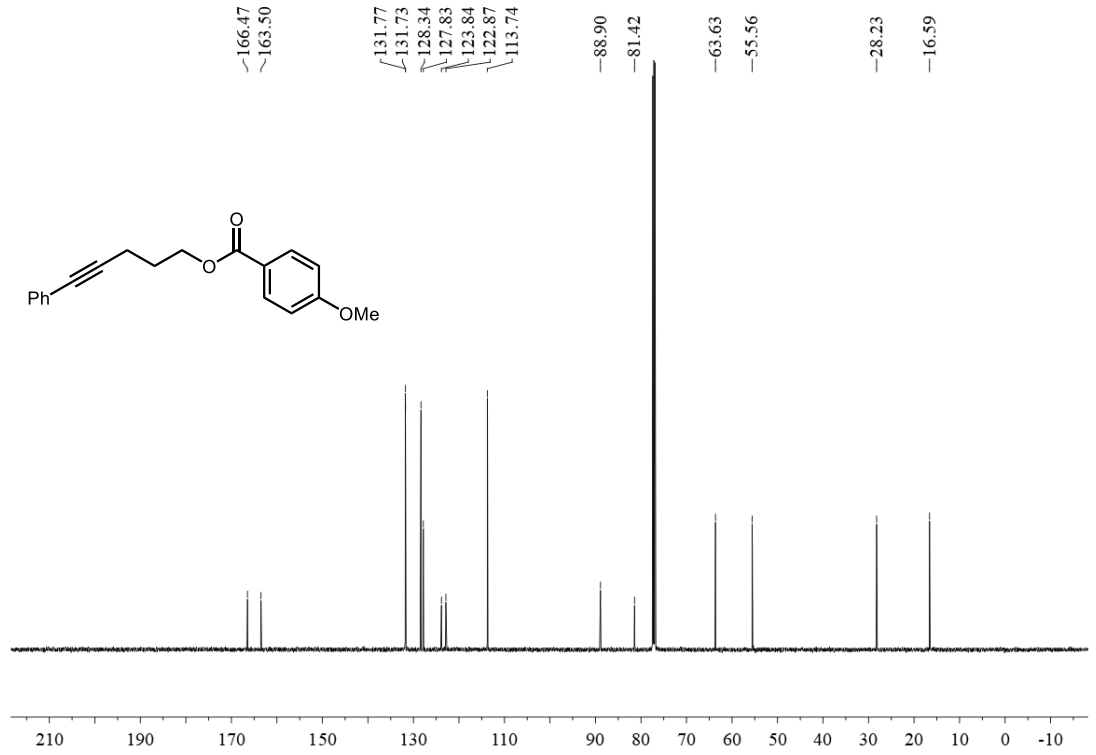
^{13}C NMR (126 MHz, $CDCl_3$) **(1i)**



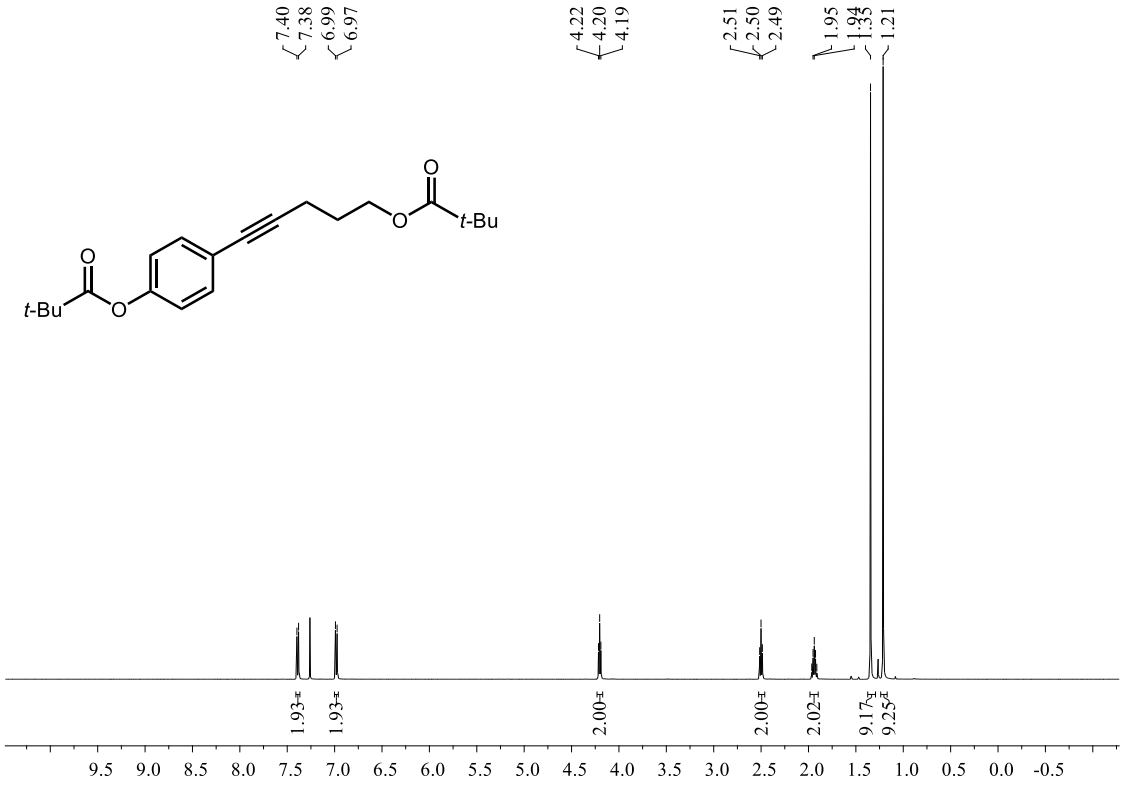
^{1}H NMR (500 MHz, $CDCl_3$) **(1j)**



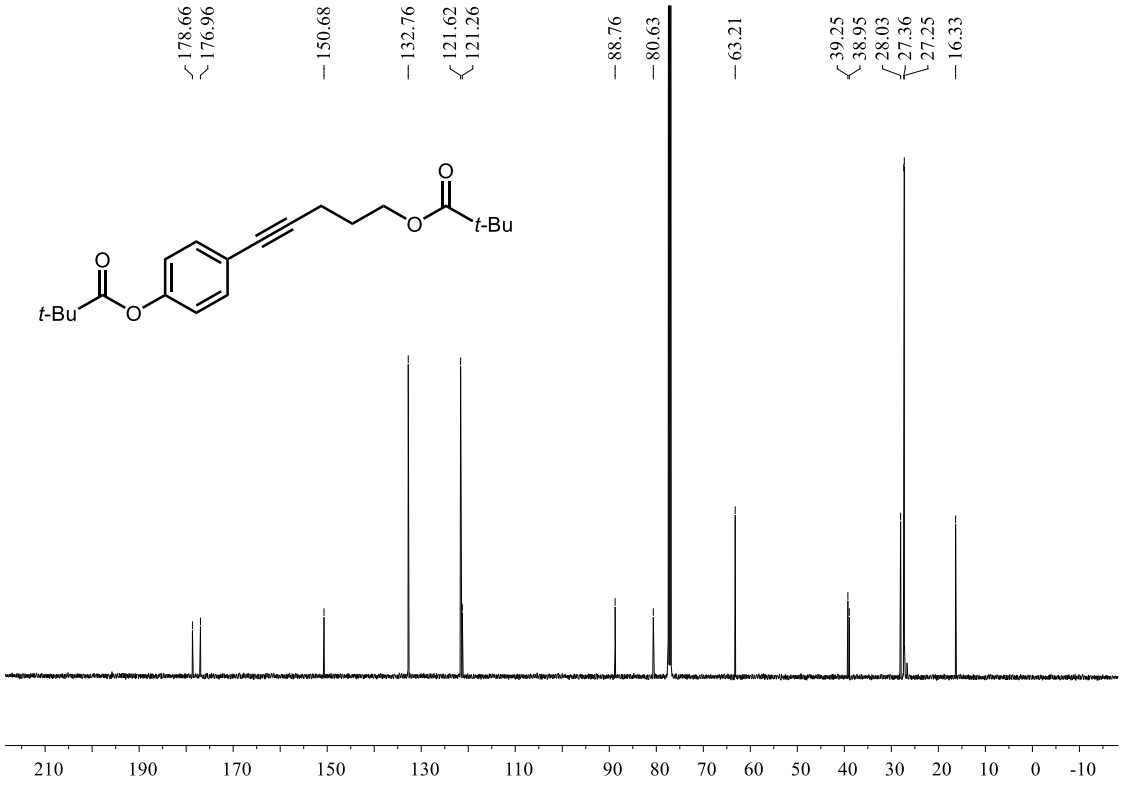
^{13}C NMR (126 MHz, $CDCl_3$) **(1j)**



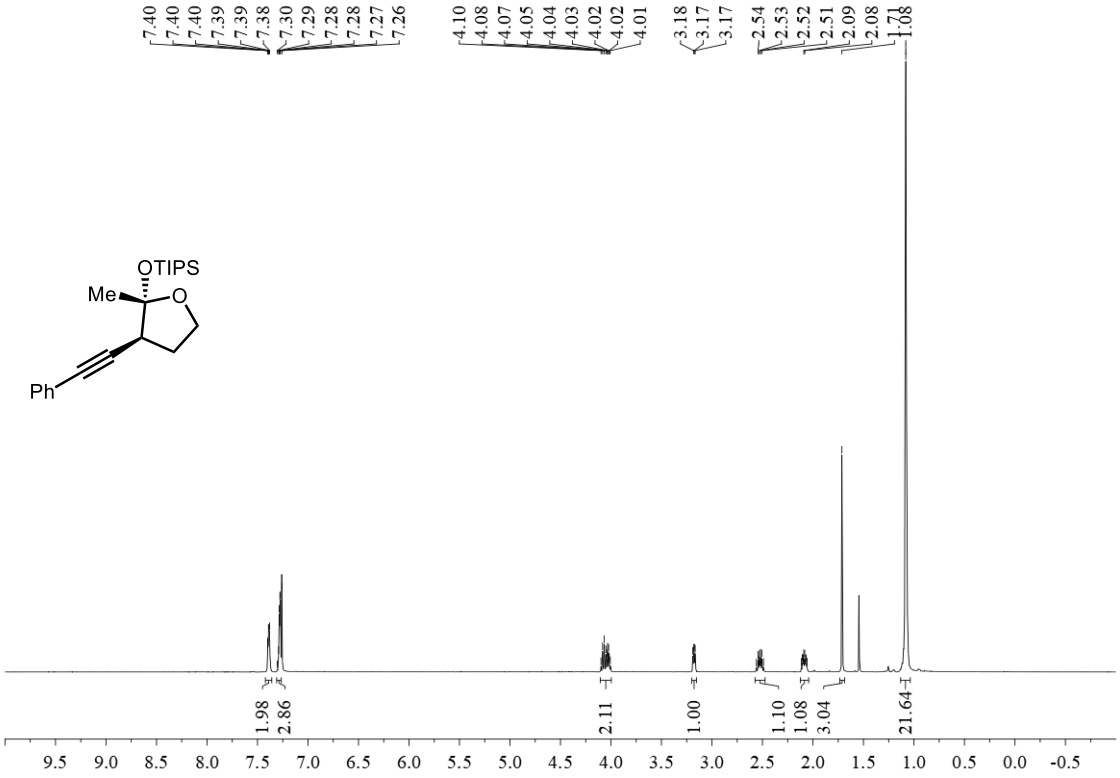
^{1}H NMR (500 MHz, $CDCl_3$) **(1k)**



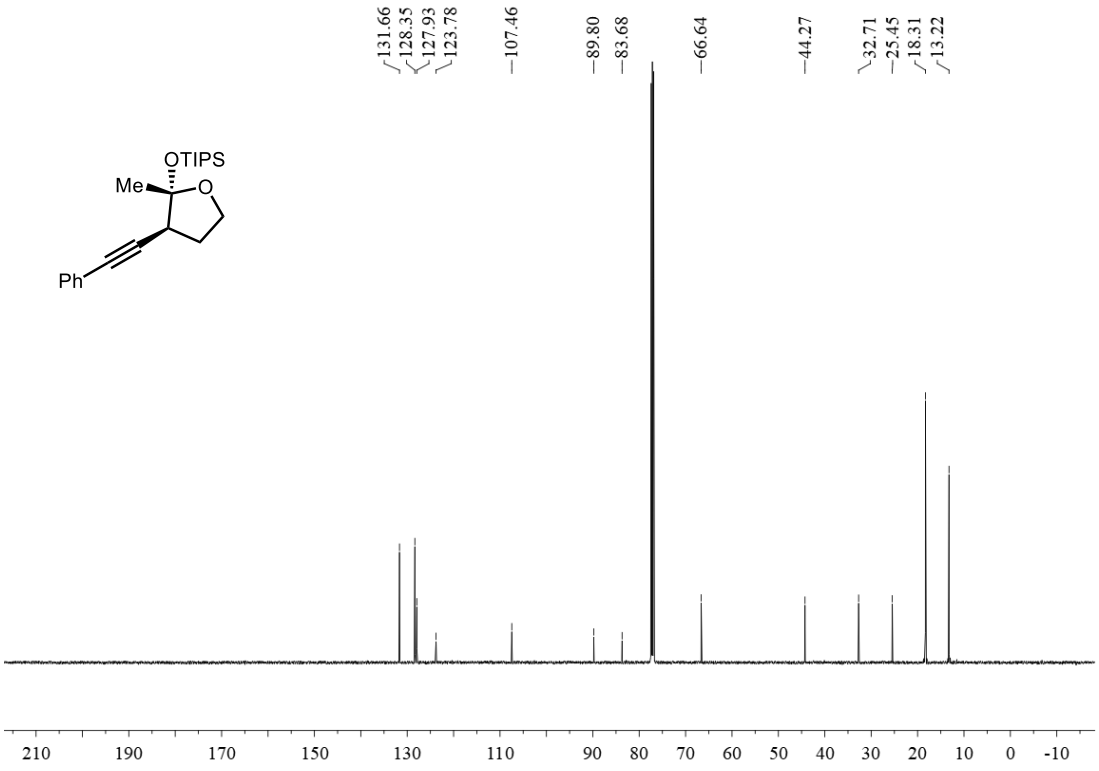
^{13}C NMR (126 MHz, $CDCl_3$) **(1k)**



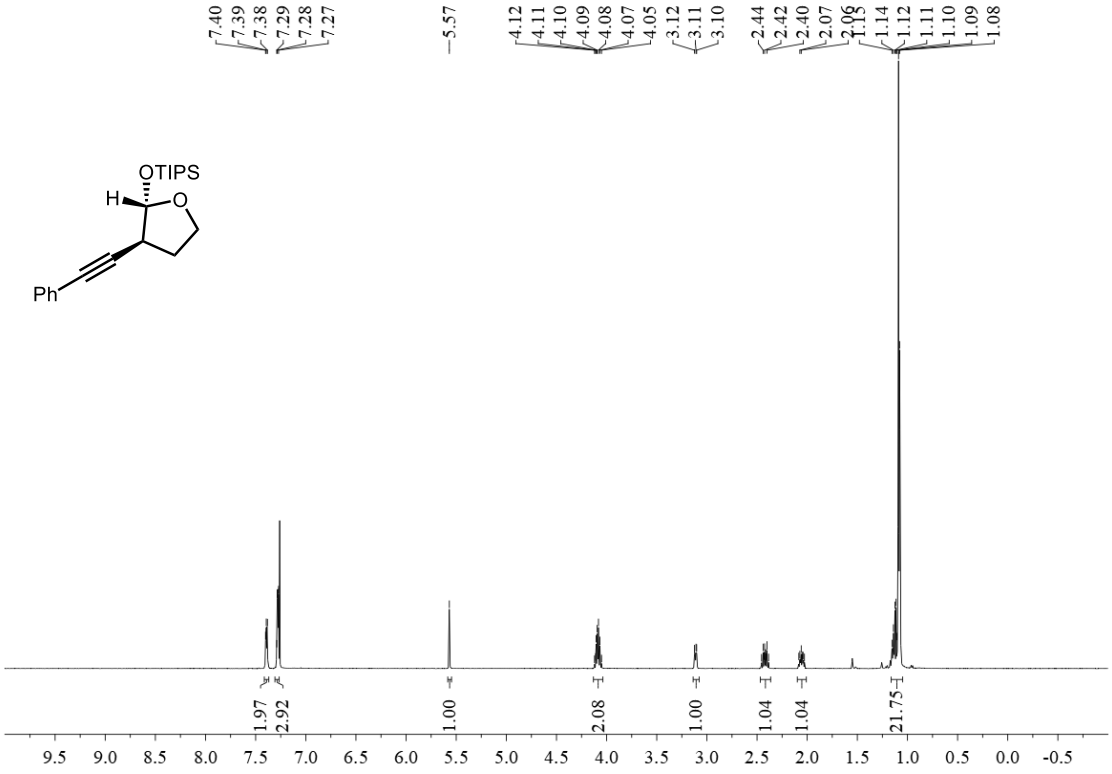
^{1}H NMR (500 MHz, $CDCl_3$) **(2a)**



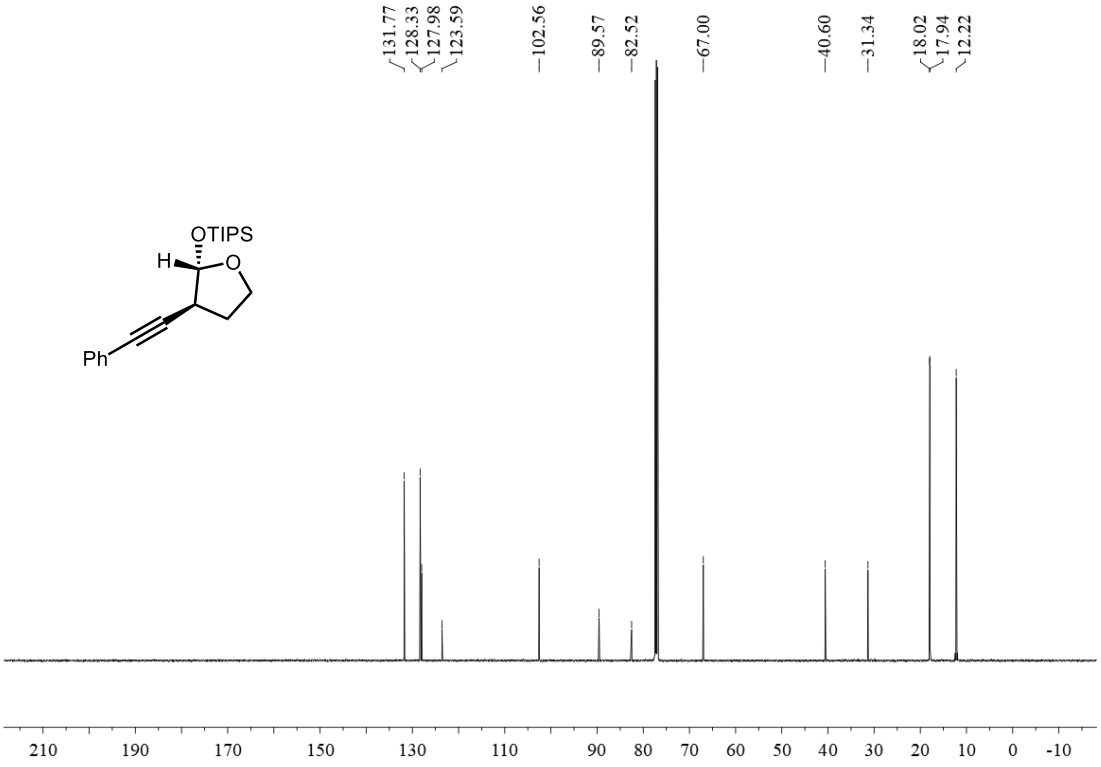
^{13}C NMR (126 MHz, $CDCl_3$) **(2a)**



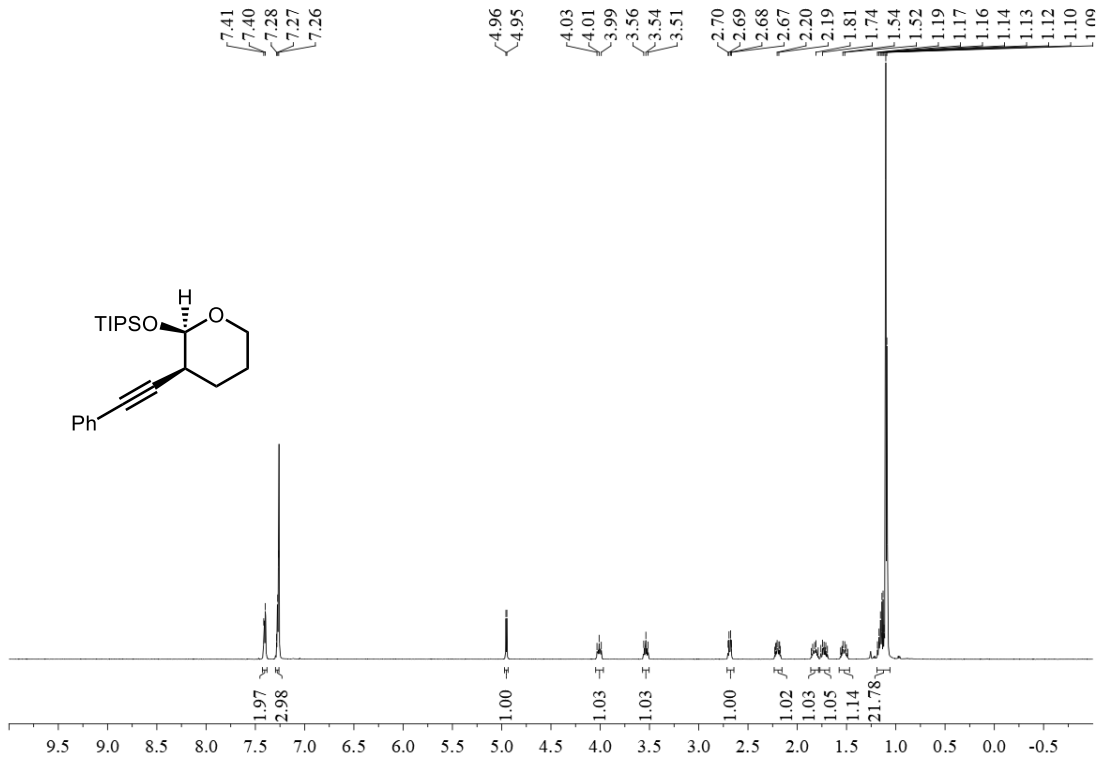
^{1}H NMR (500 MHz, $CDCl_3$) **(2b)**



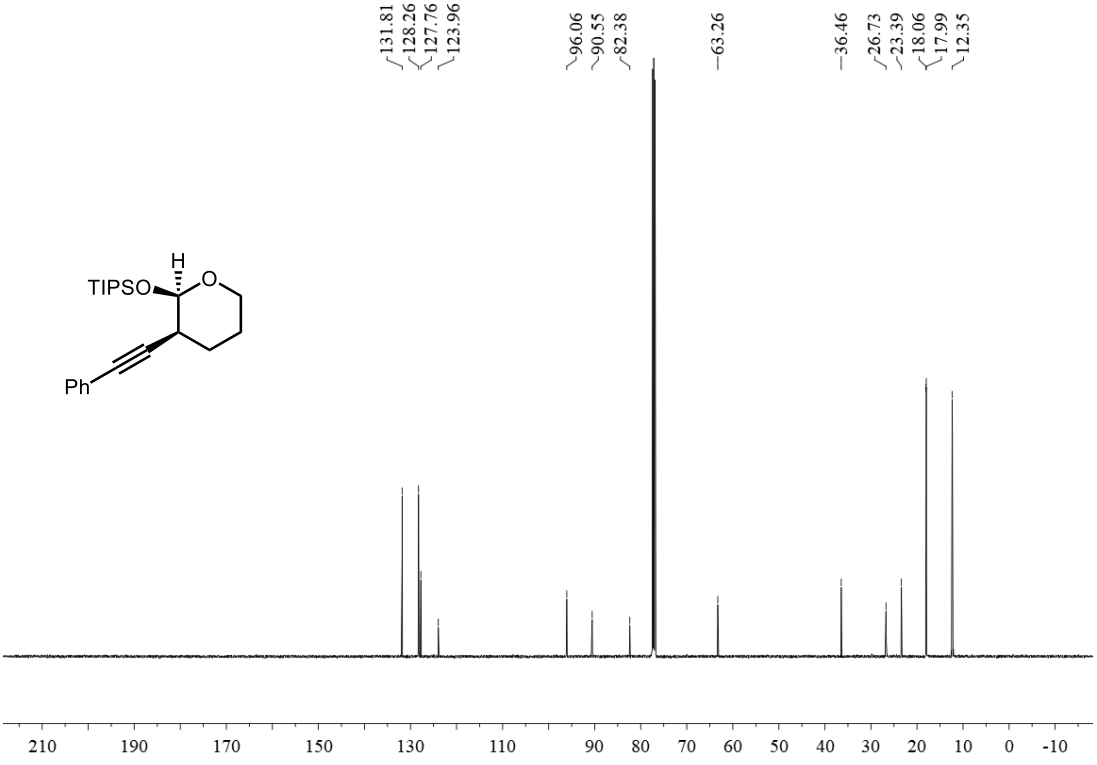
^{13}C NMR (126 MHz, $CDCl_3$) **(2b)**



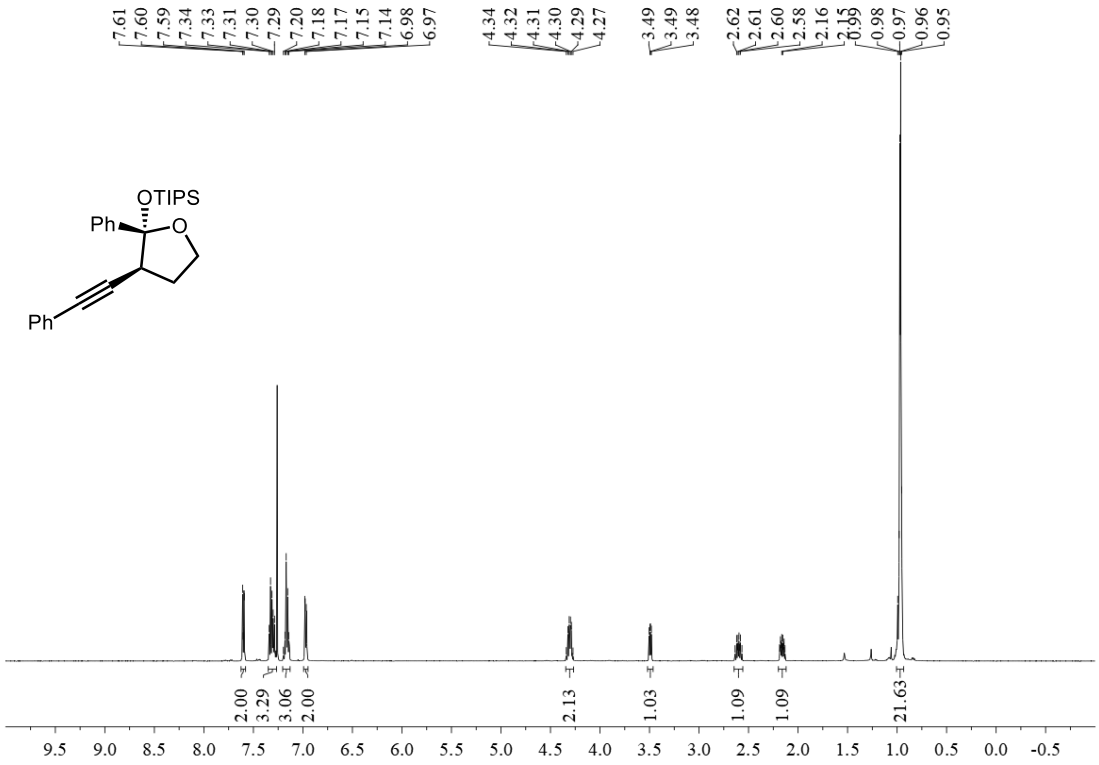
^{1}H NMR (500 MHz, $CDCl_3$) **(2c)**



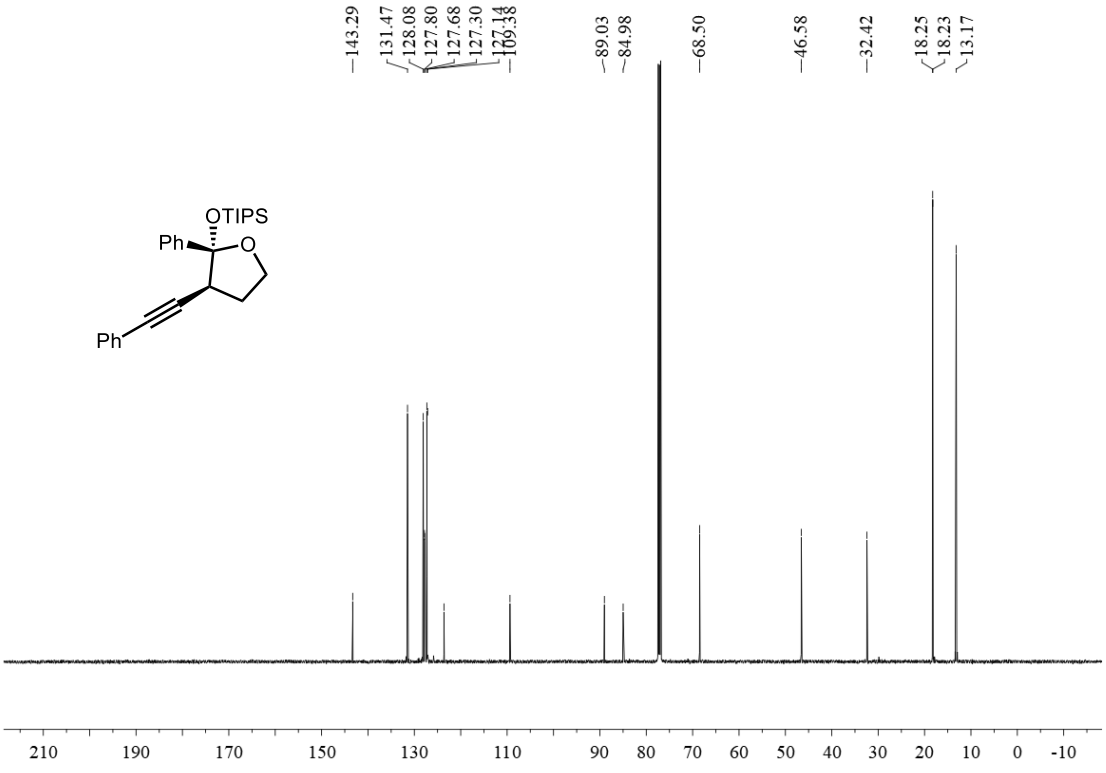
^{13}C NMR (126 MHz, $CDCl_3$) **(2c)**



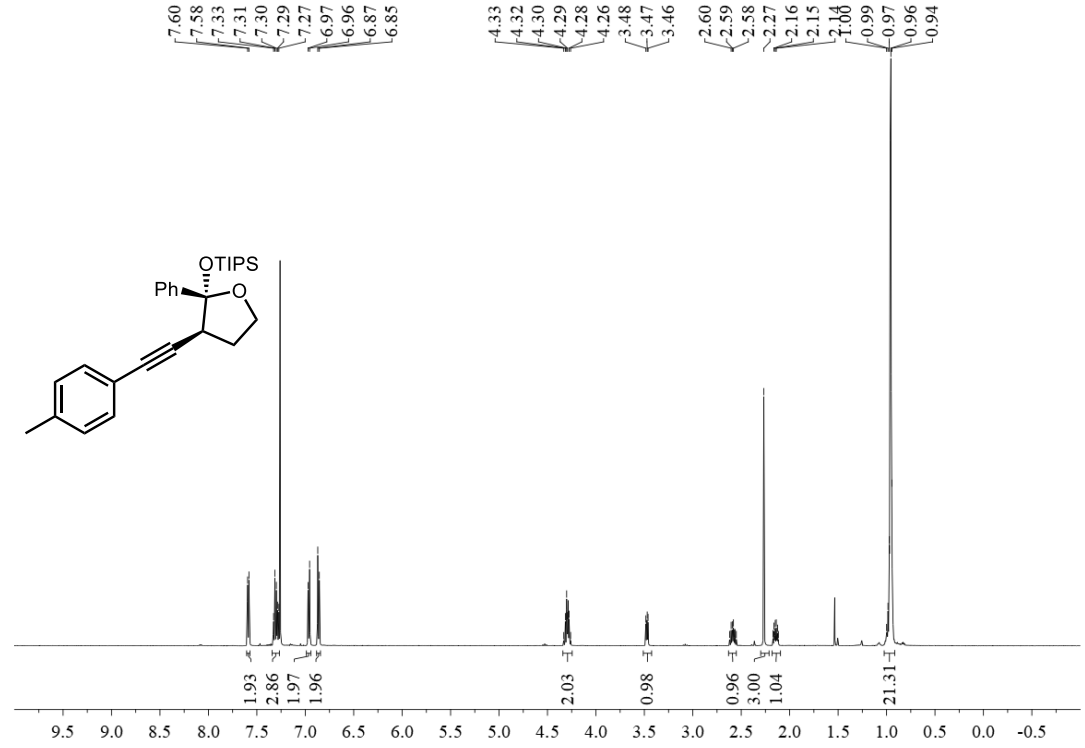
^{1}H NMR (500 MHz, $CDCl_3$) **(2d)**



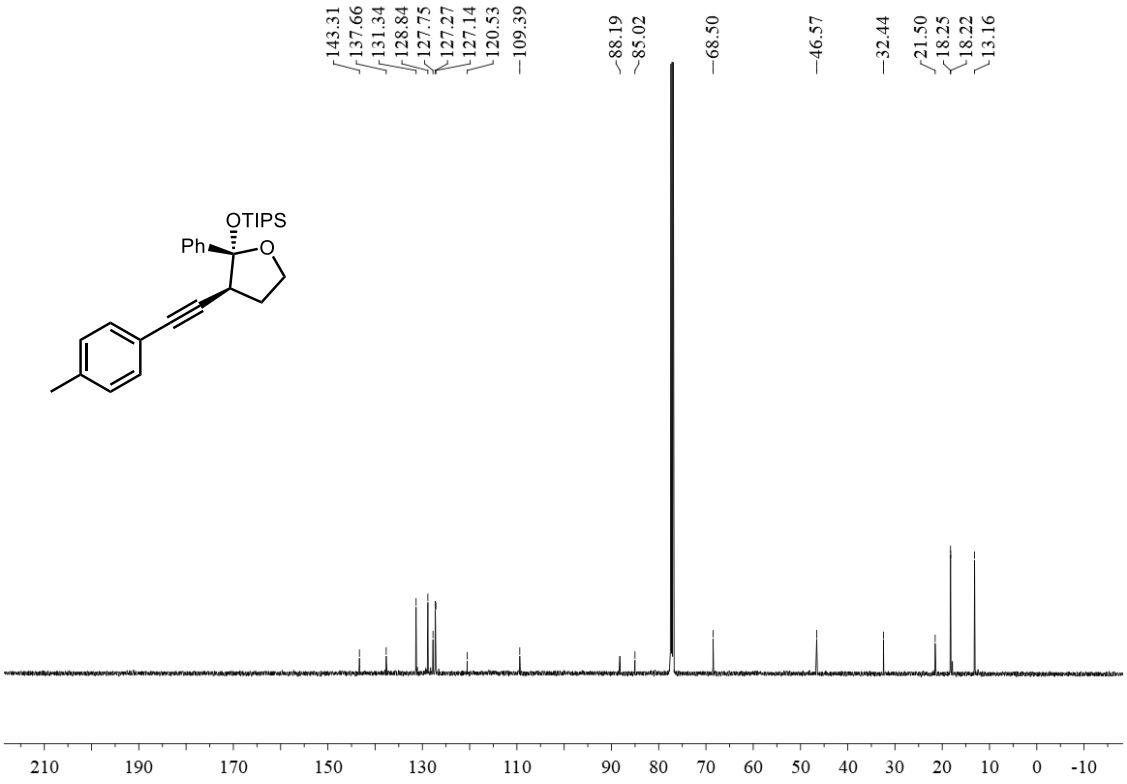
^{13}C NMR (126 MHz, $CDCl_3$) **(2d)**



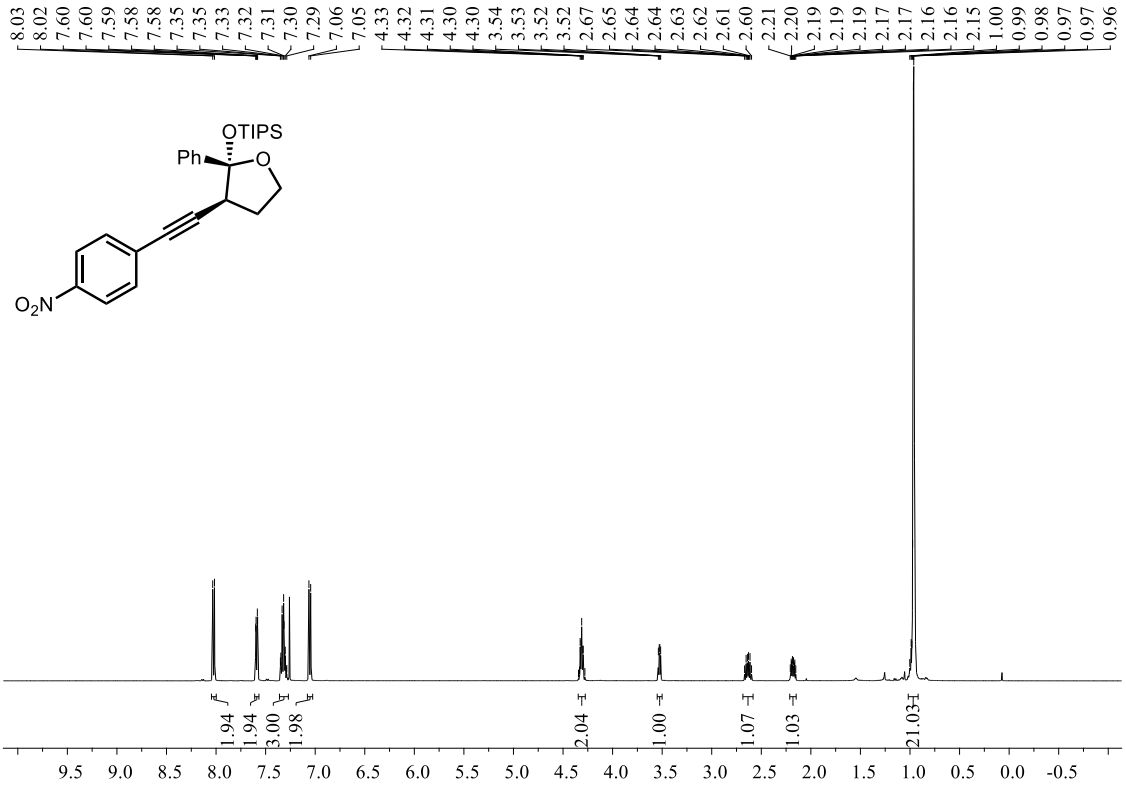
^{1}H NMR (500 MHz, $CDCl_3$) **(2e)**



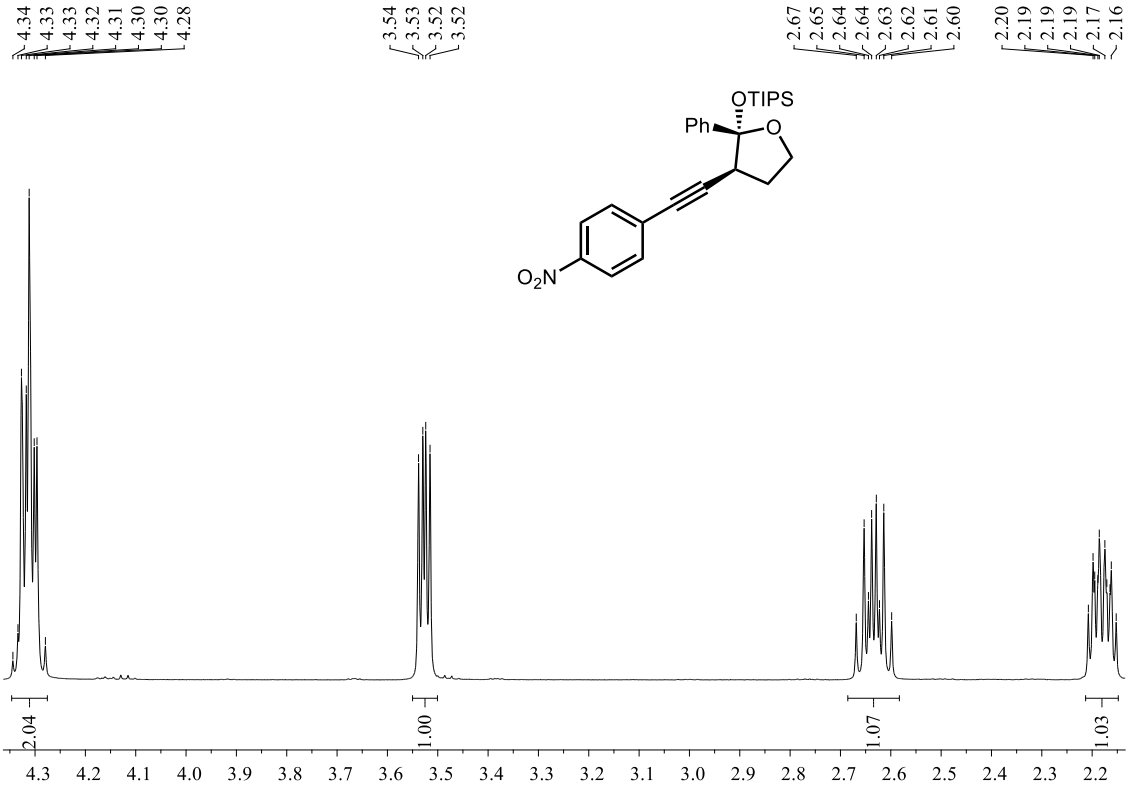
^{13}C NMR (126 MHz, $CDCl_3$) **(2e)**



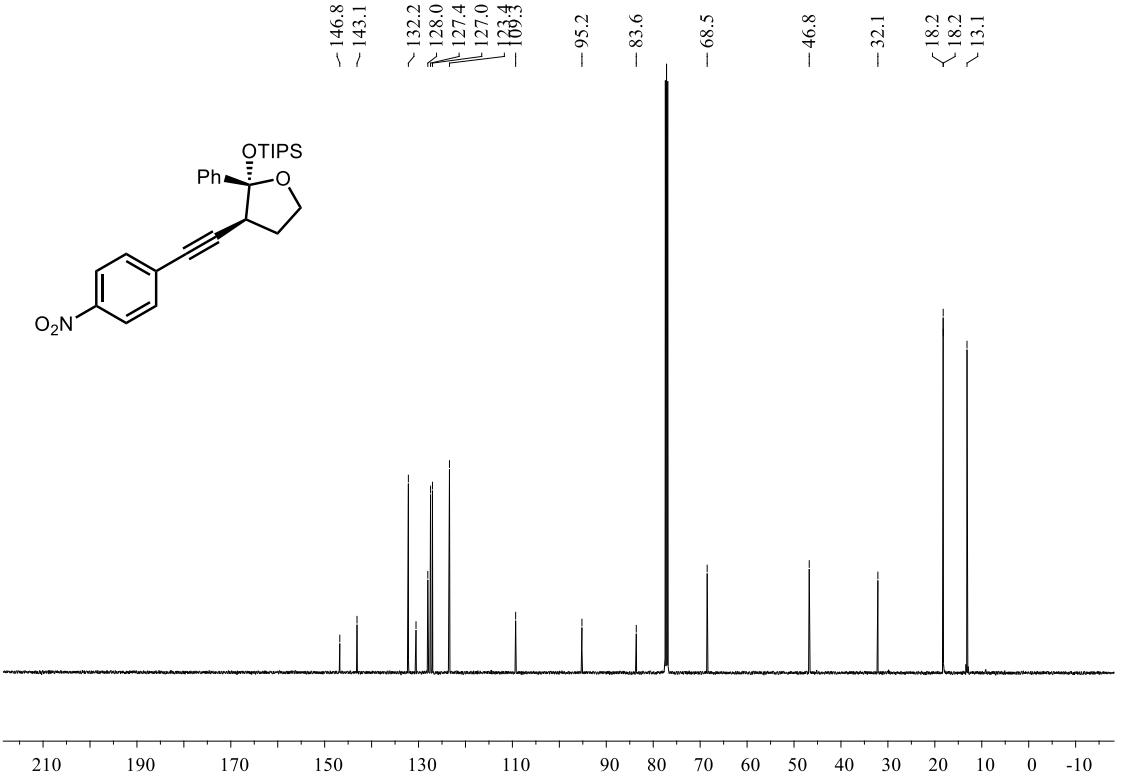
^{1}H NMR (500 MHz, $CDCl_3$) **(2f)**



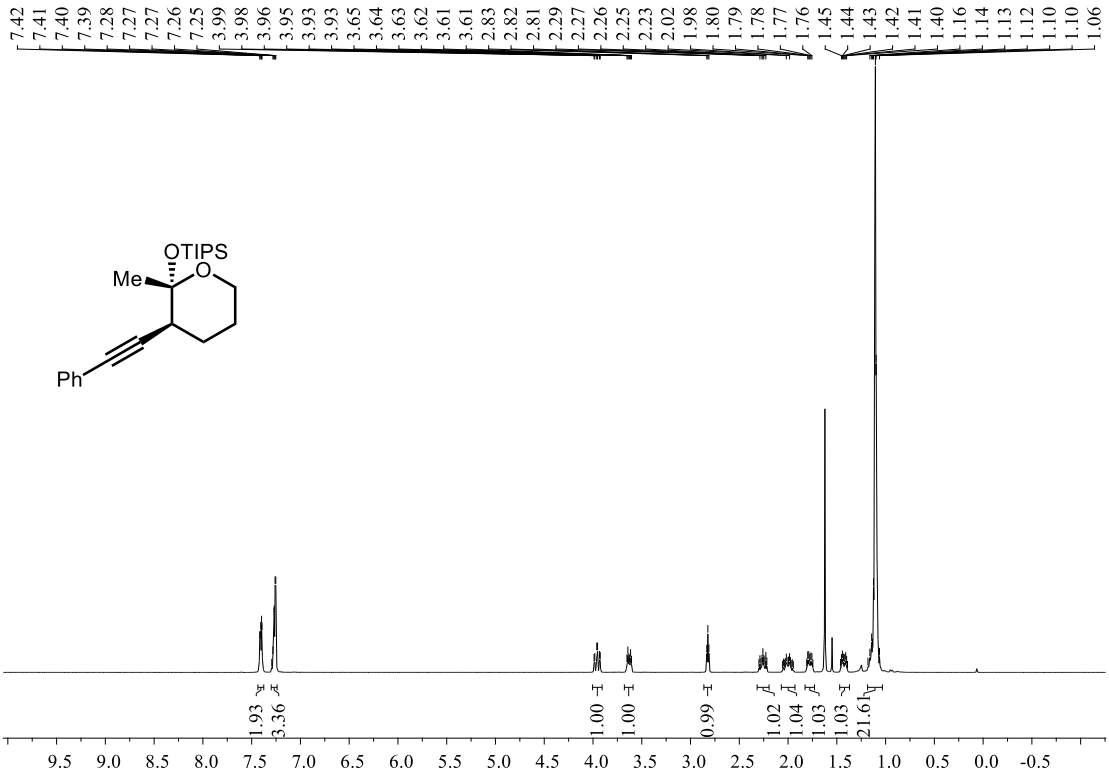
^{1}H NMR (500 MHz, $CDCl_3$) **(2f)**



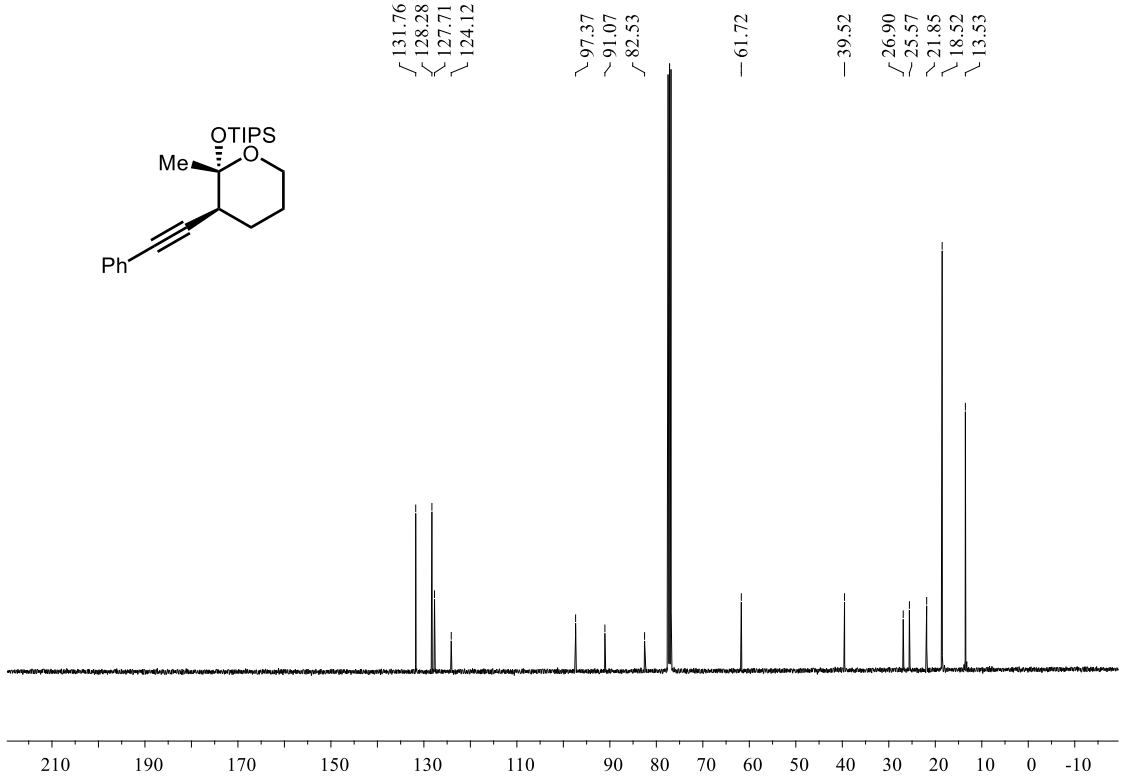
^{13}C NMR (126 MHz, $CDCl_3$) **(2f)**



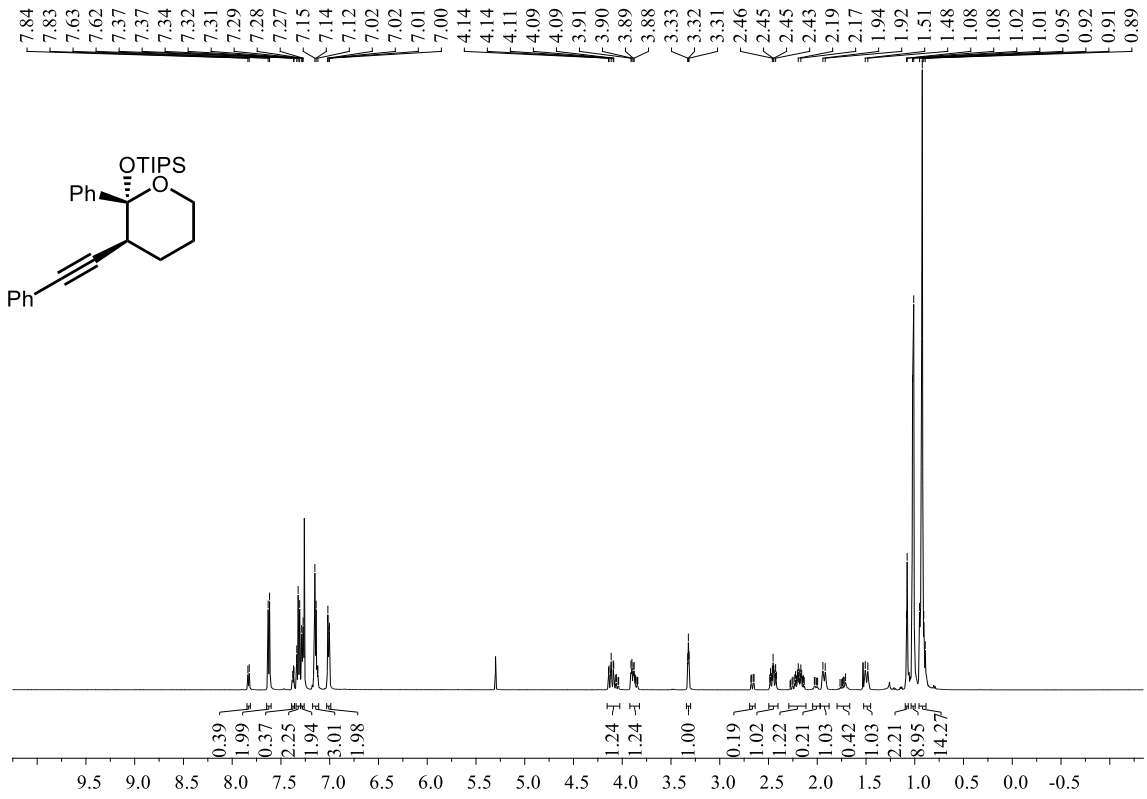
^{1}H NMR (300 MHz, $CDCl_3$) **(2g)**



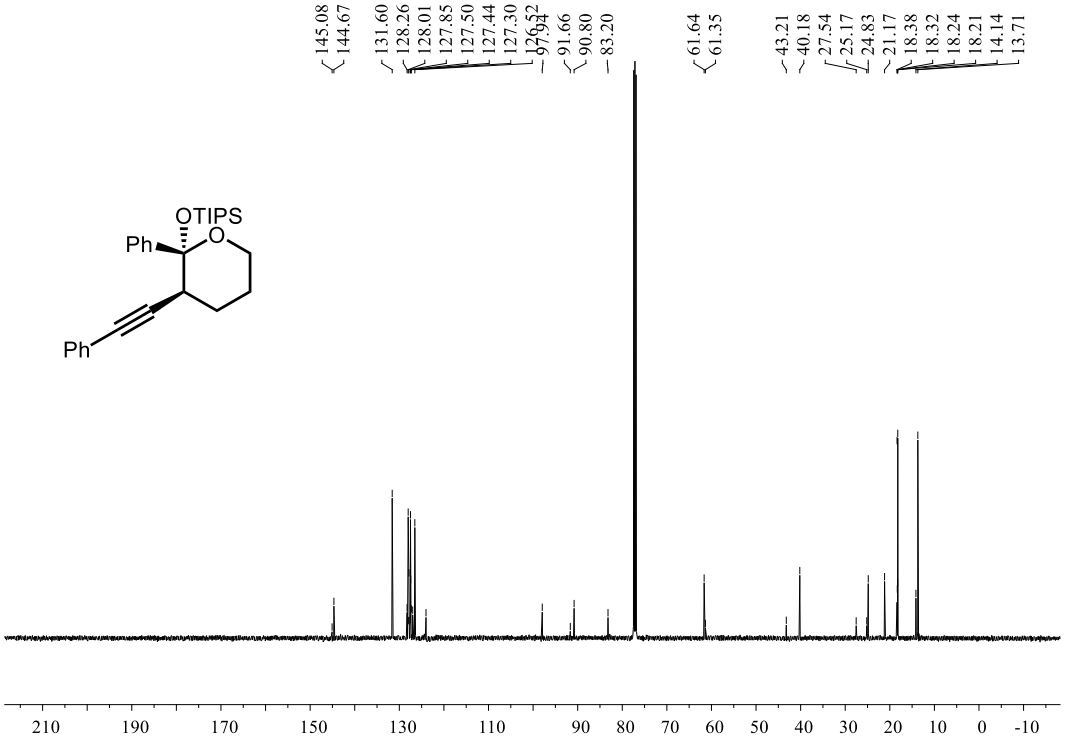
^{13}C NMR (101 MHz, $CDCl_3$) **(2g)**



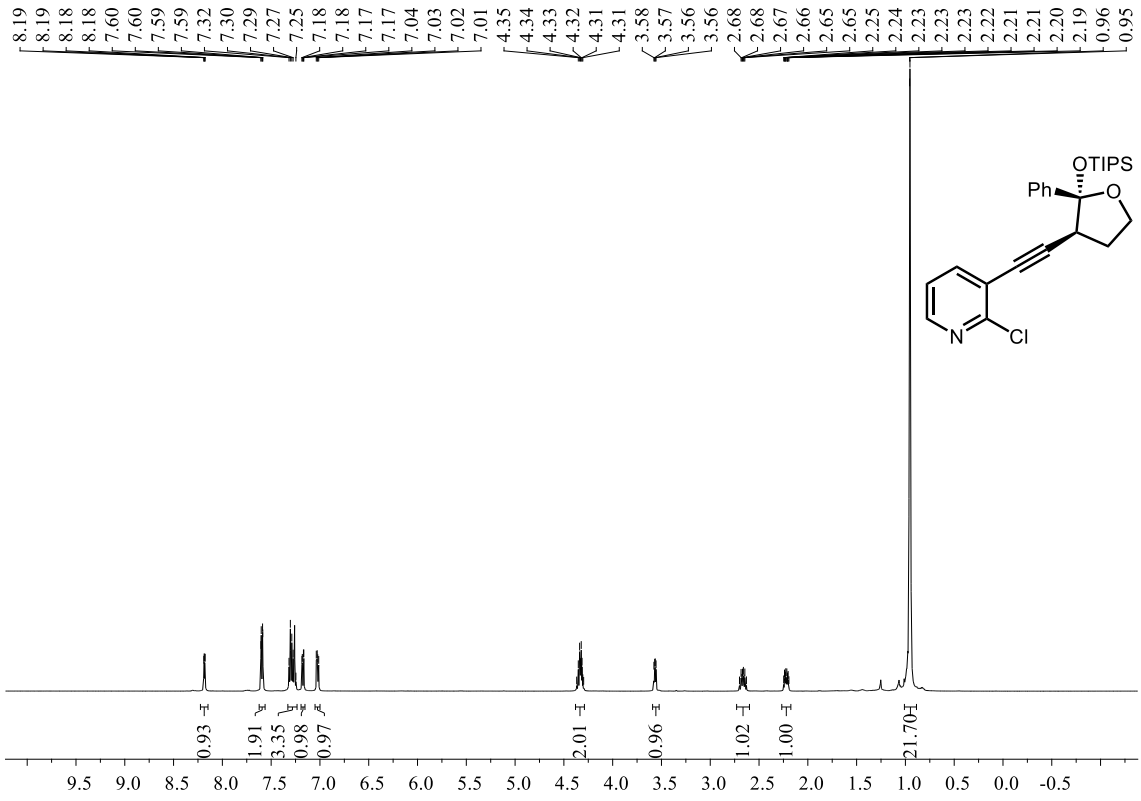
^{1}H NMR (500 MHz, $CDCl_3$) **(2h)**



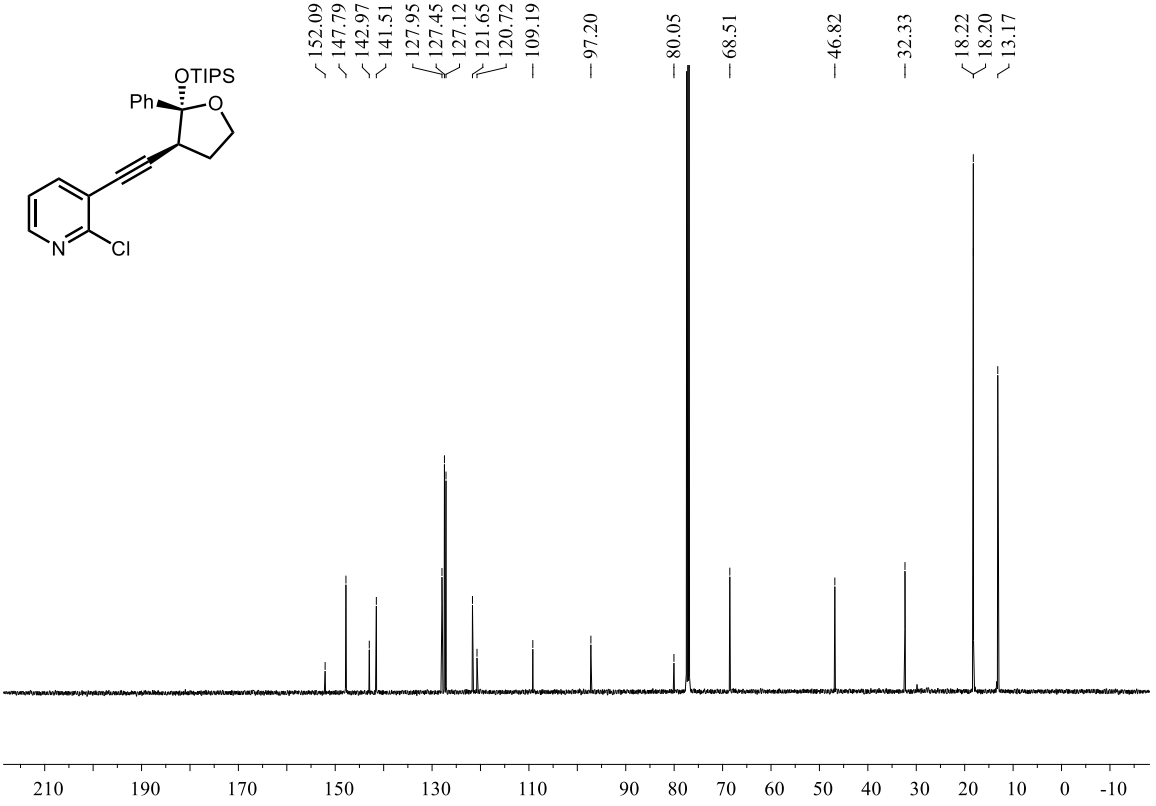
^{13}C NMR (126 MHz, $CDCl_3$) **(2h)**



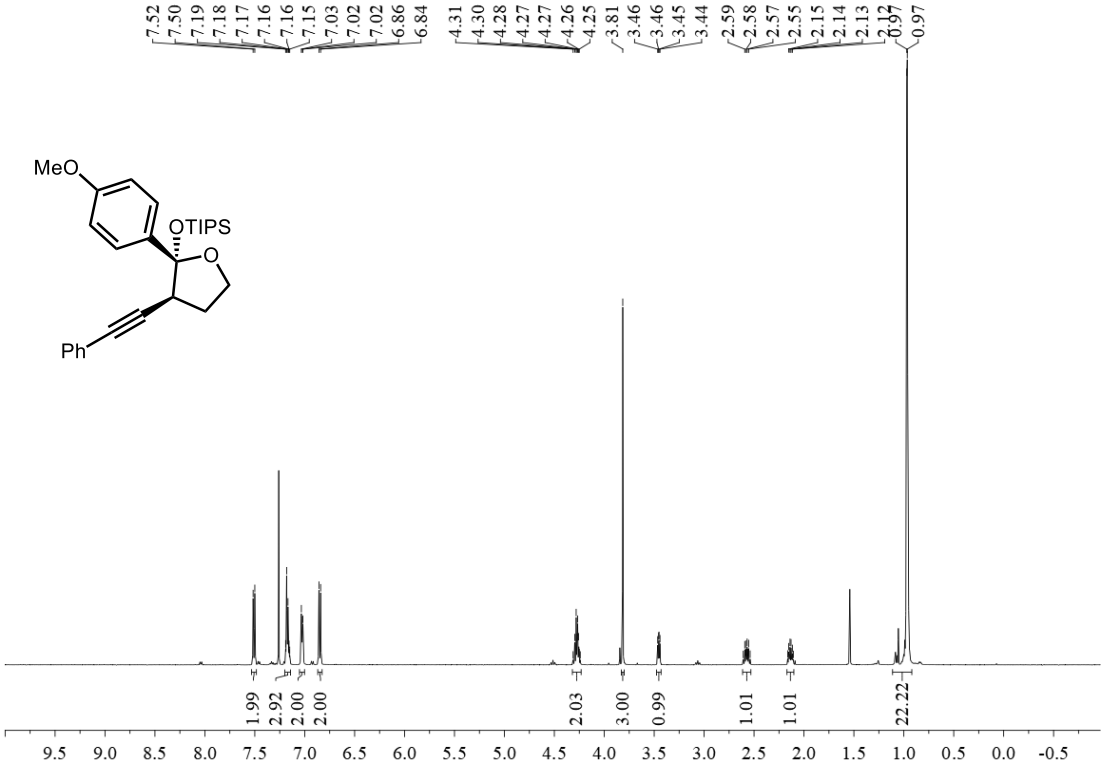
^{1}H NMR (500 MHz, $CDCl_3$) **(2i)**



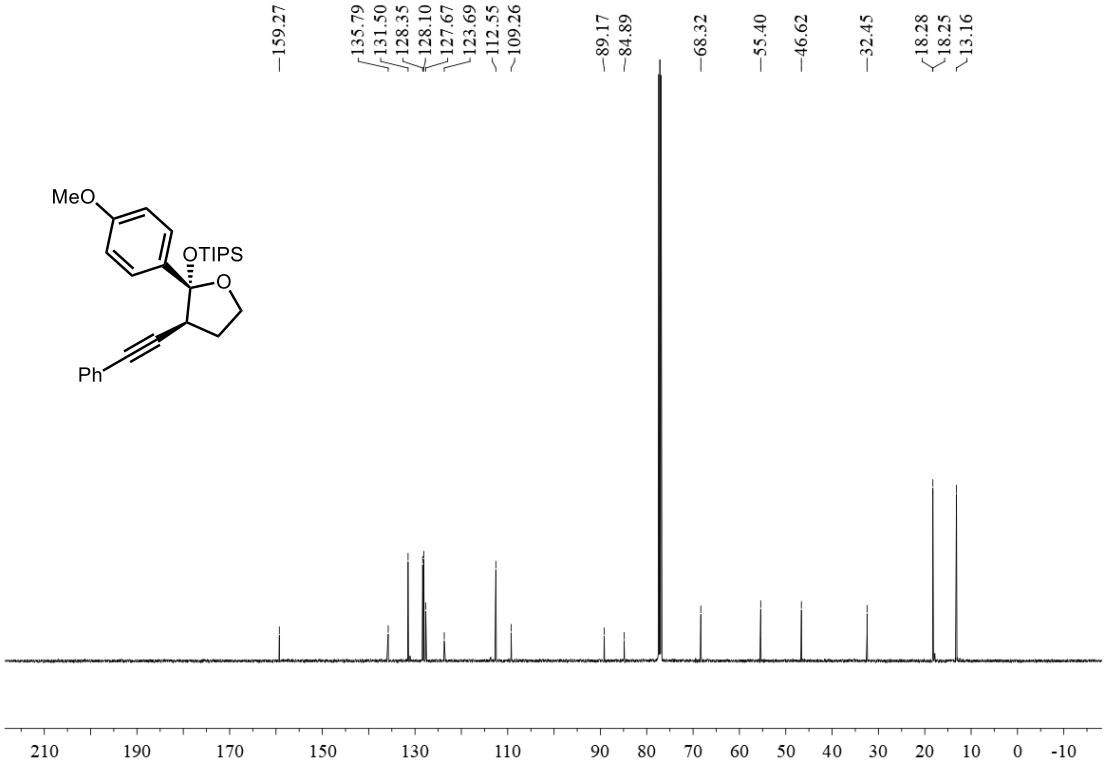
^{13}C NMR (126 MHz, $CDCl_3$) **(2i)**



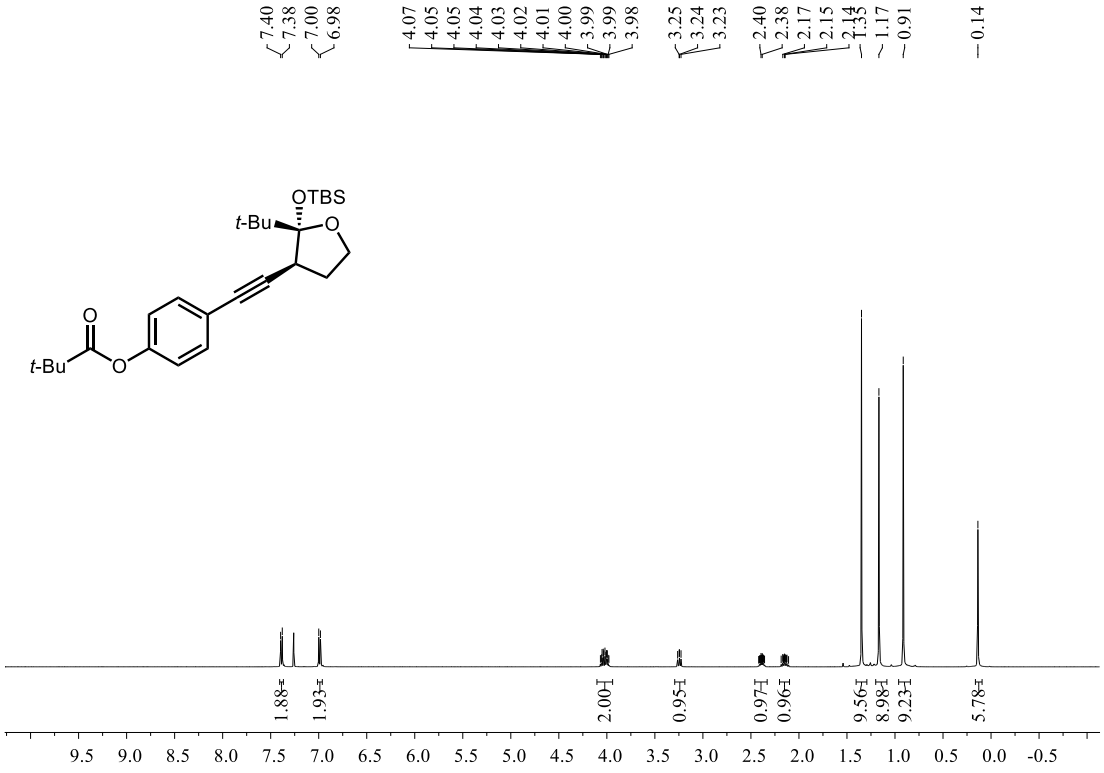
^{1}H NMR (500 MHz, $CDCl_3$) **(2j)**



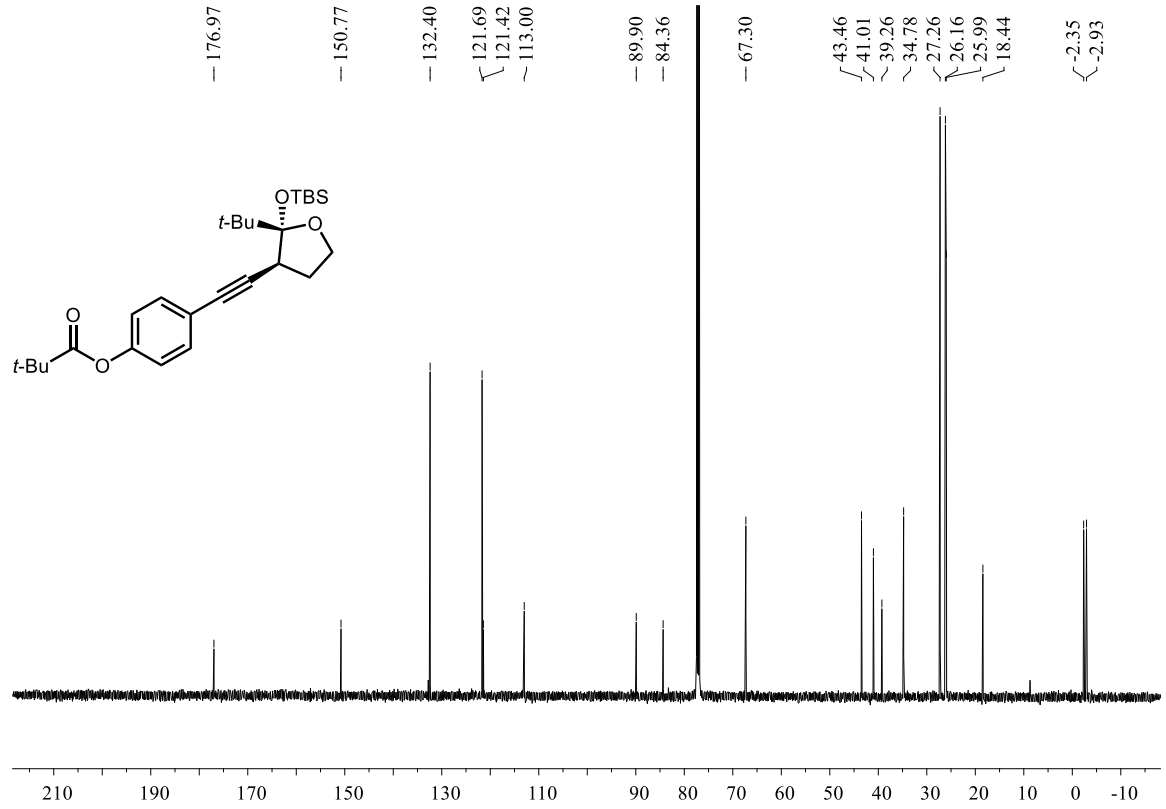
^{13}C NMR (126 MHz, $CDCl_3$) **(2j)**



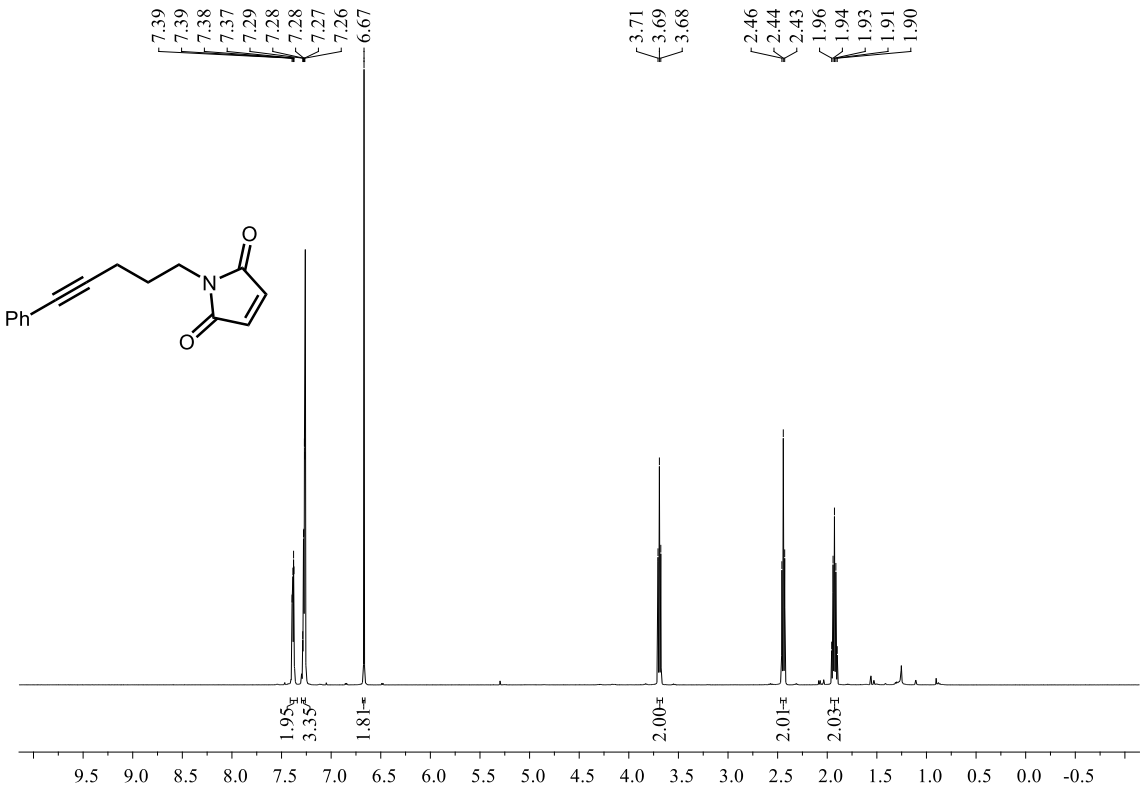
^{1}H NMR (500 MHz, $CDCl_3$) **(2k)**



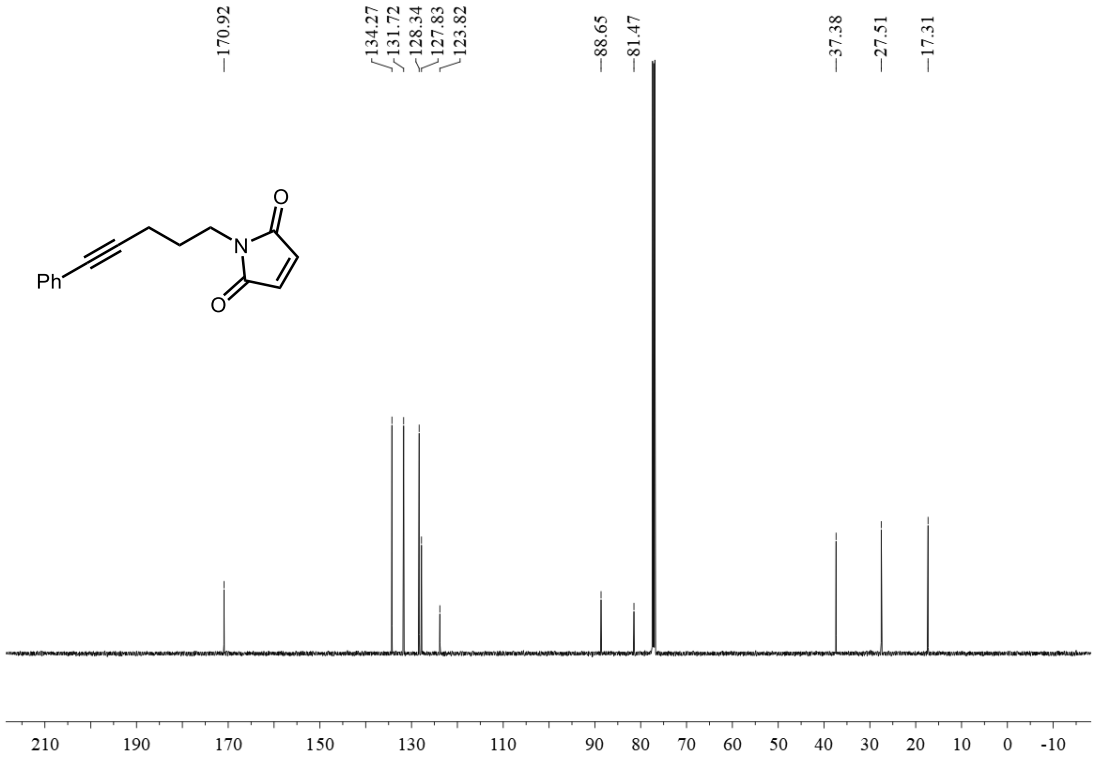
^{13}C NMR (126 MHz, $CDCl_3$) **(2k)**



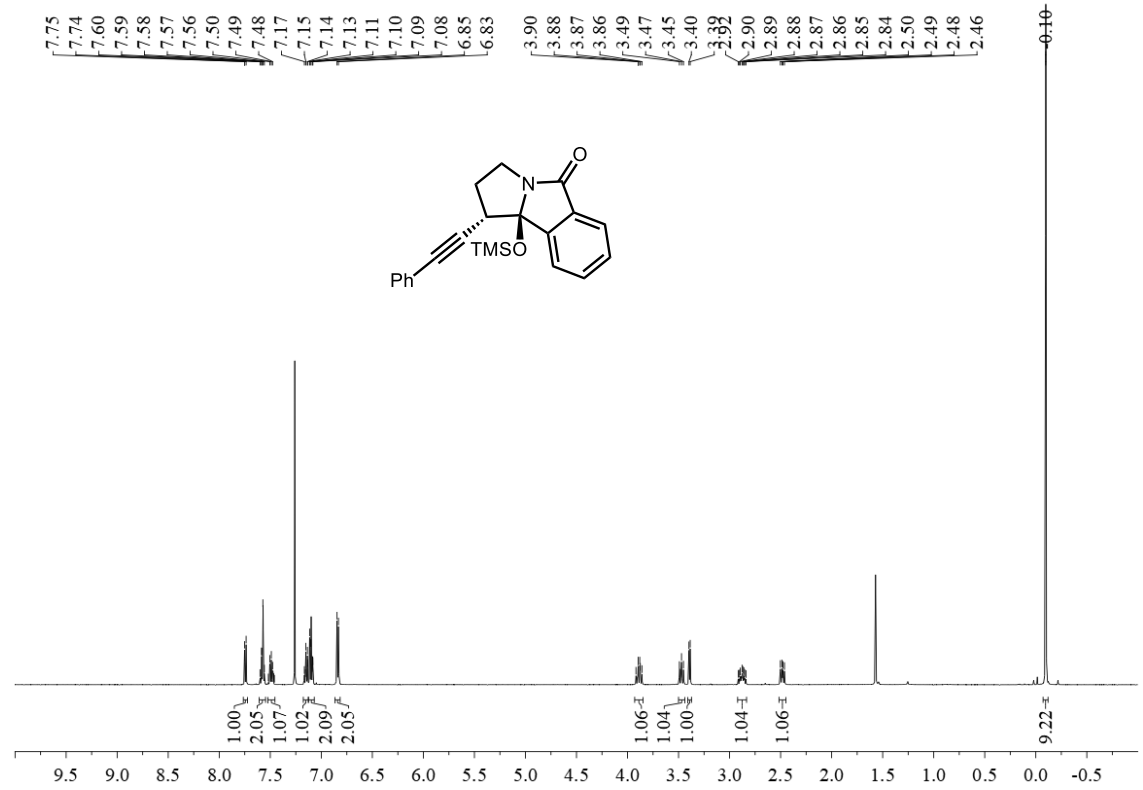
^{1}H NMR (500 MHz, $CDCl_3$) **(3c)**



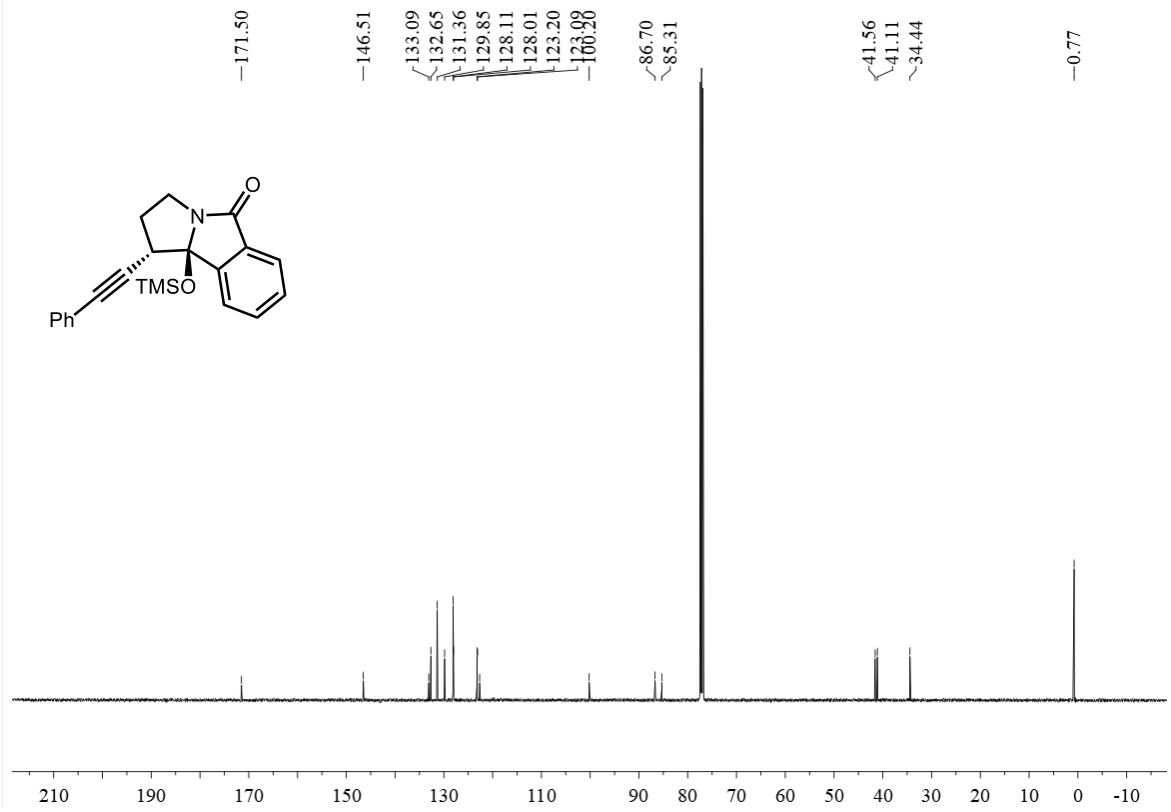
^{13}C NMR (126 MHz, $CDCl_3$) **(3c)**



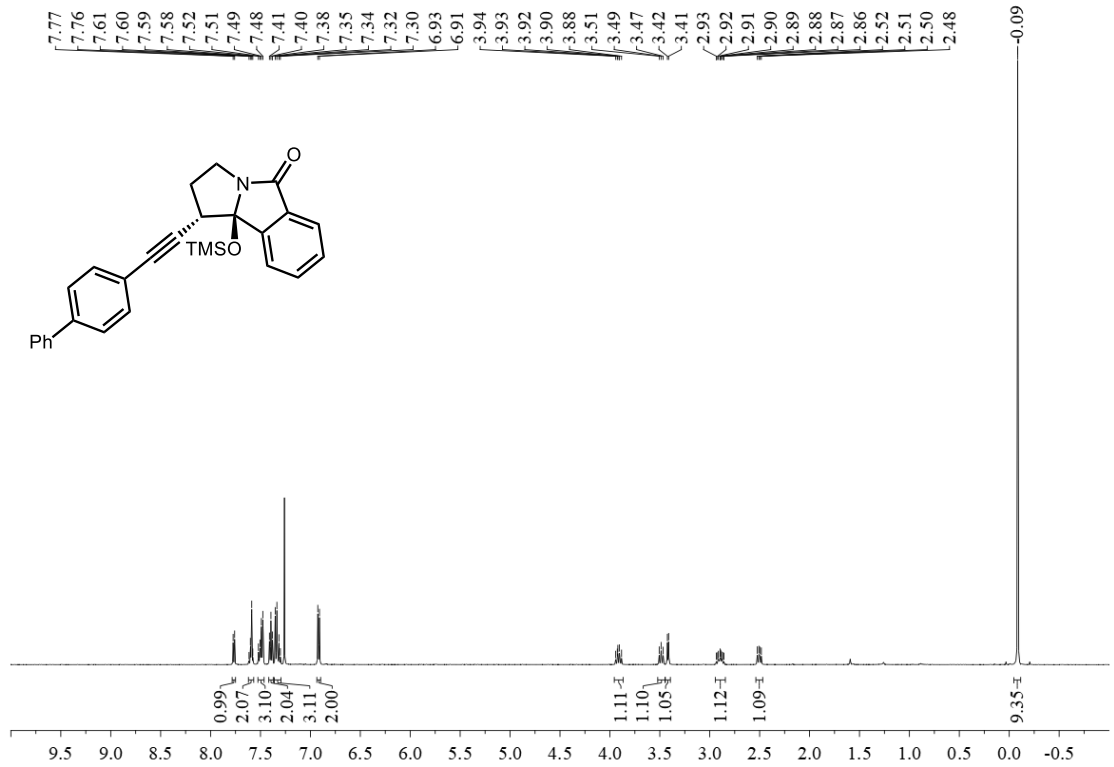
^{1}H NMR (500 MHz, $CDCl_3$) **(4a)**



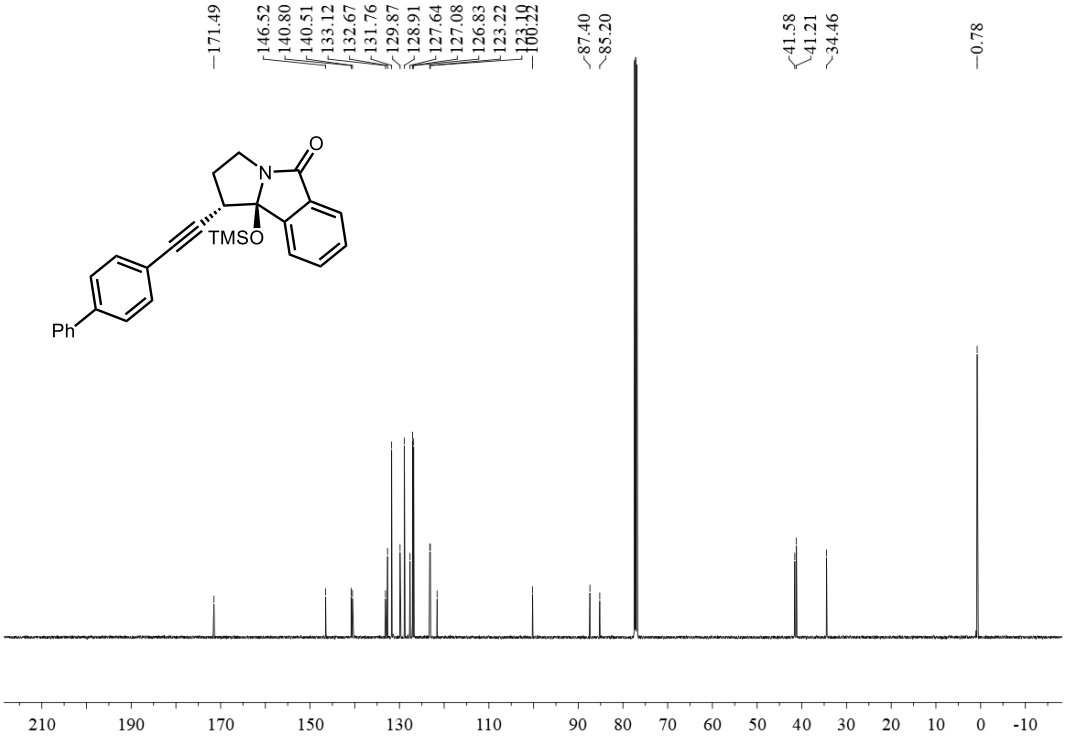
^{13}C NMR (126 MHz, $CDCl_3$) **(4a)**



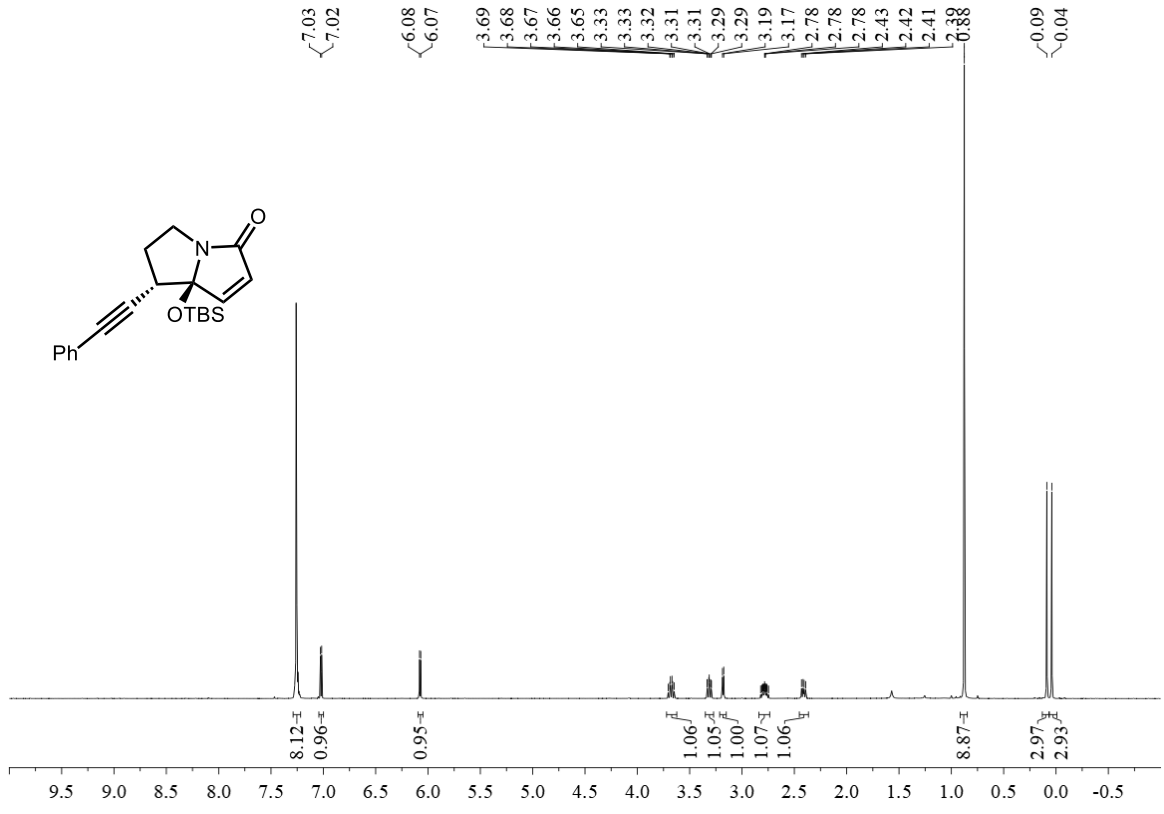
^{1}H NMR (500 MHz, $CDCl_3$) **(4b)**



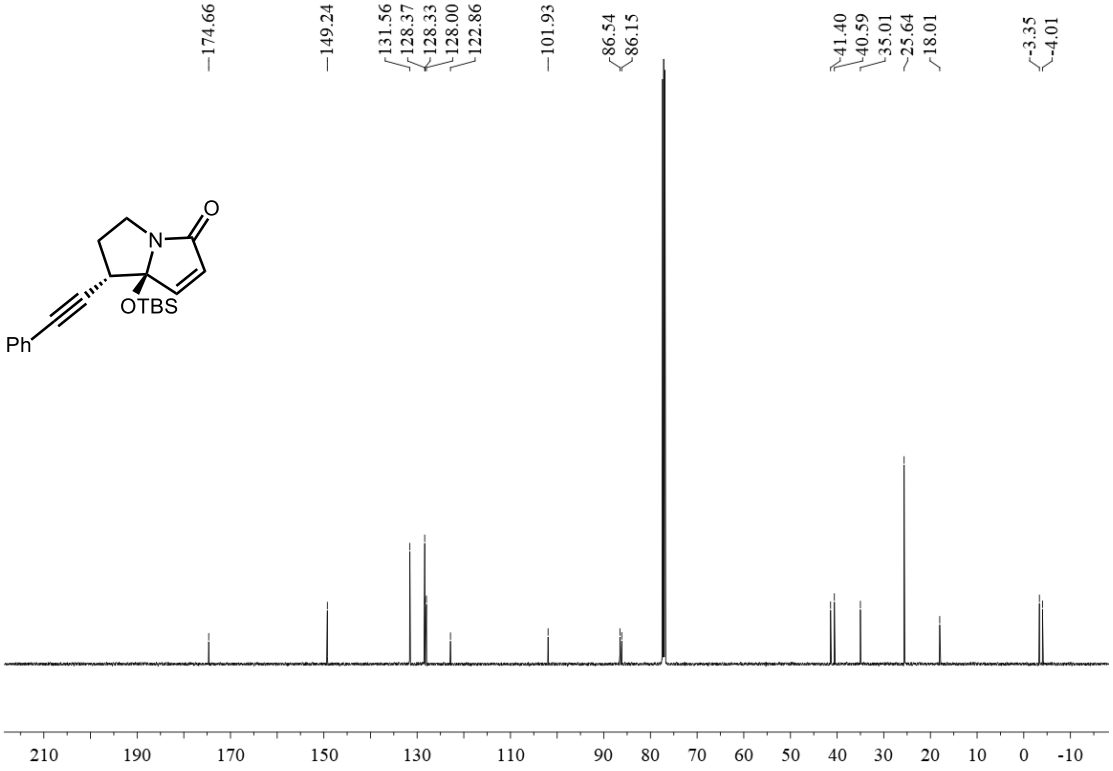
^{13}C NMR (126 MHz, $CDCl_3$) **(4b)**



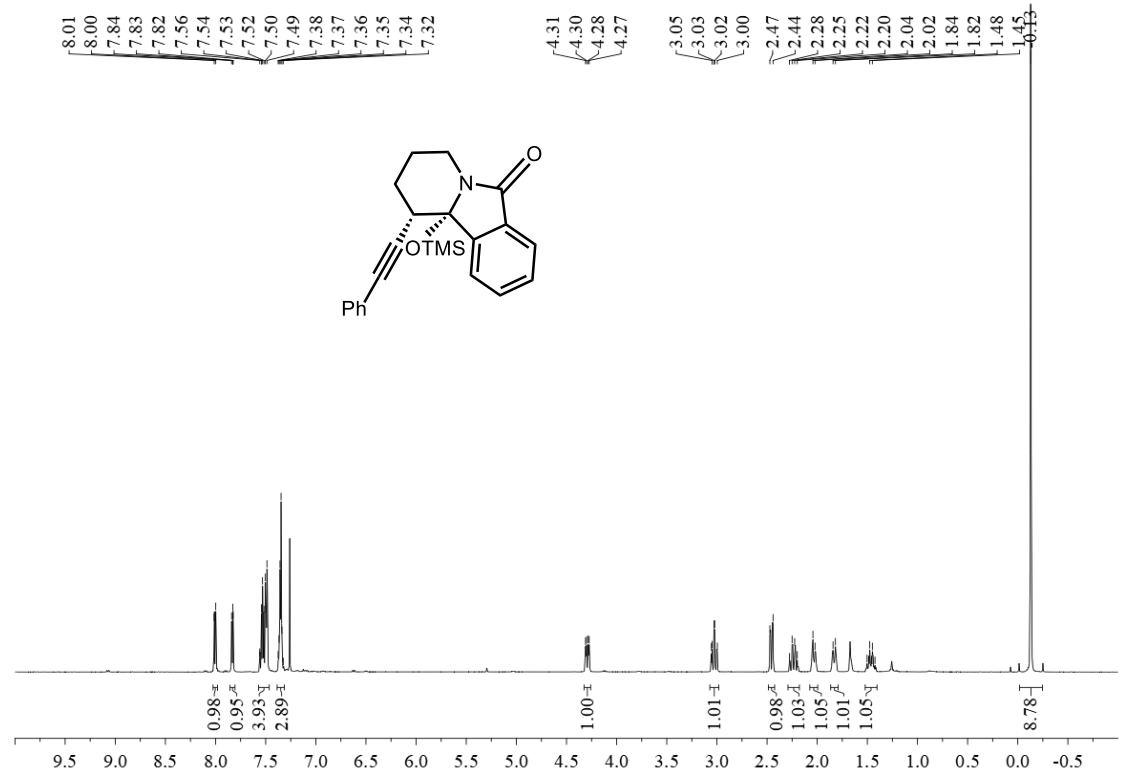
^{1}H NMR (500 MHz, $CDCl_3$) **(4c)**



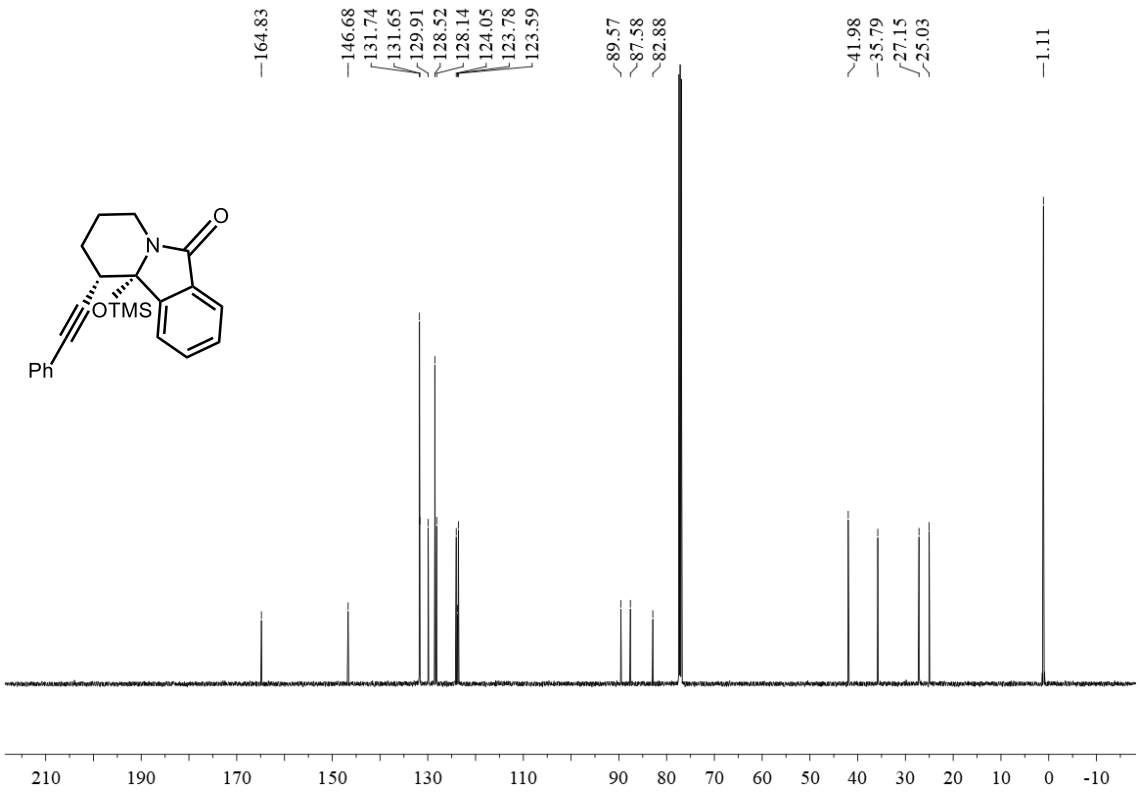
^{13}C NMR (126 MHz, $CDCl_3$) **(4c)**



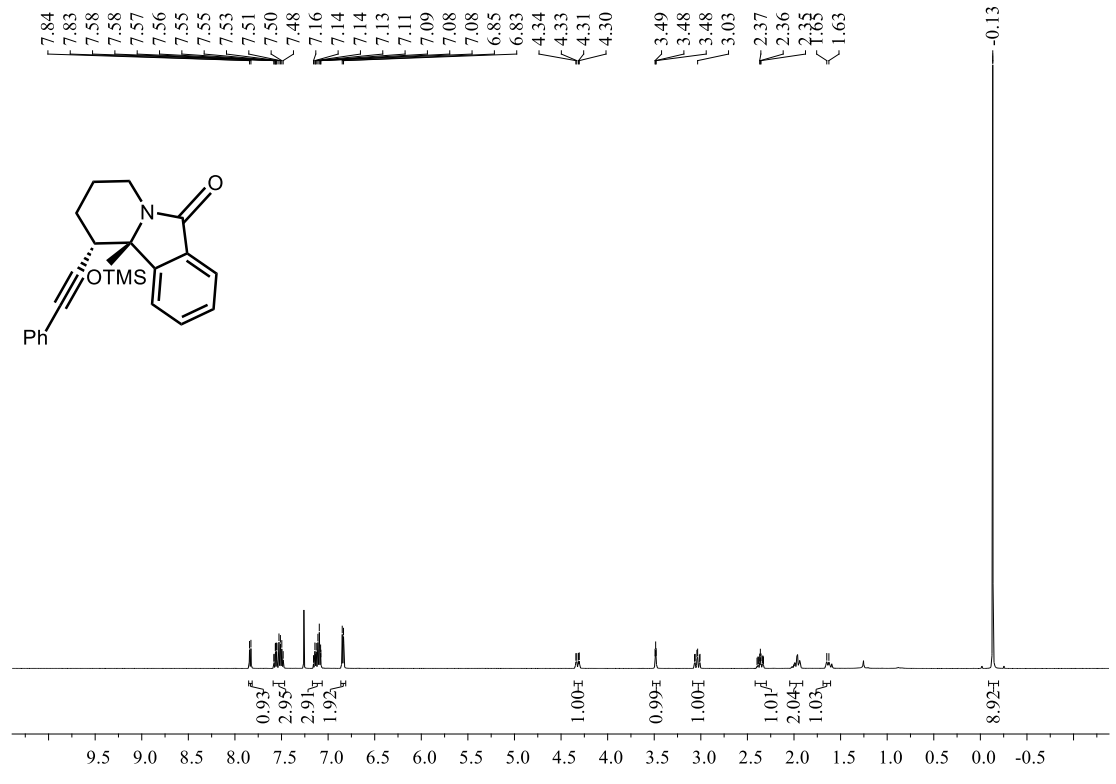
^{1}H NMR (500 MHz, $CDCl_3$) **(4da)**



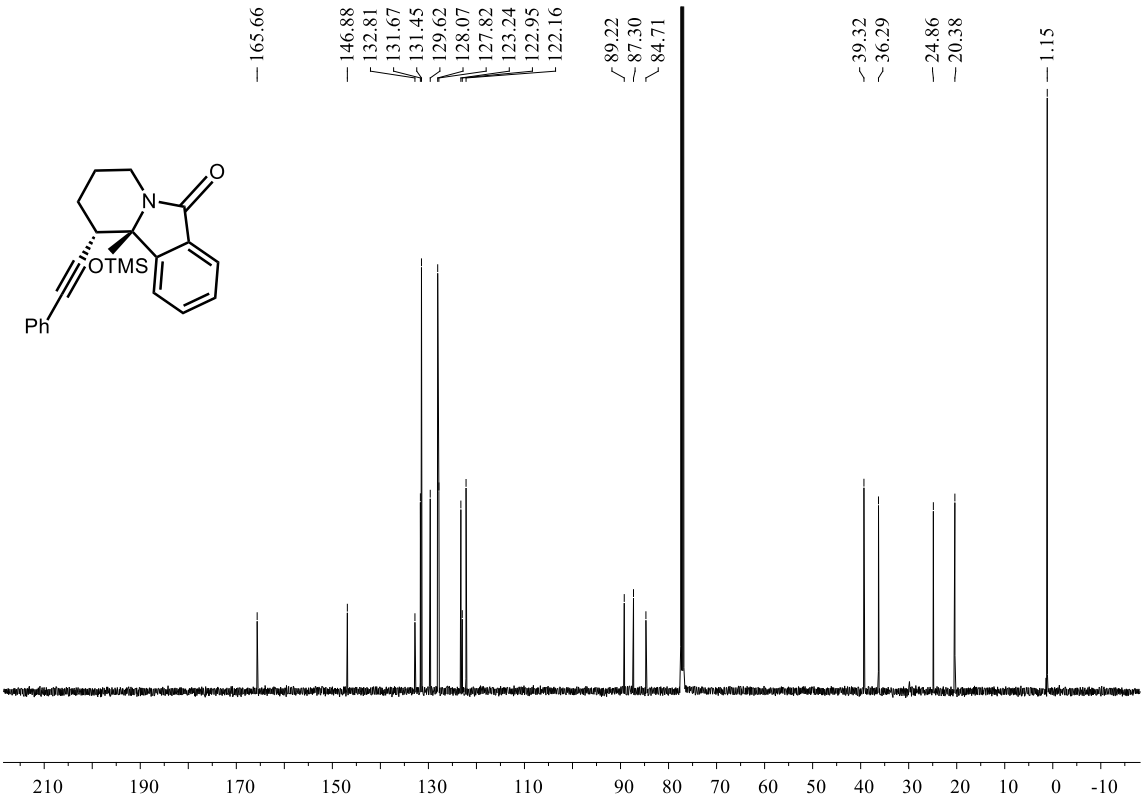
^{13}C NMR (126 MHz, $CDCl_3$) **(4da)**



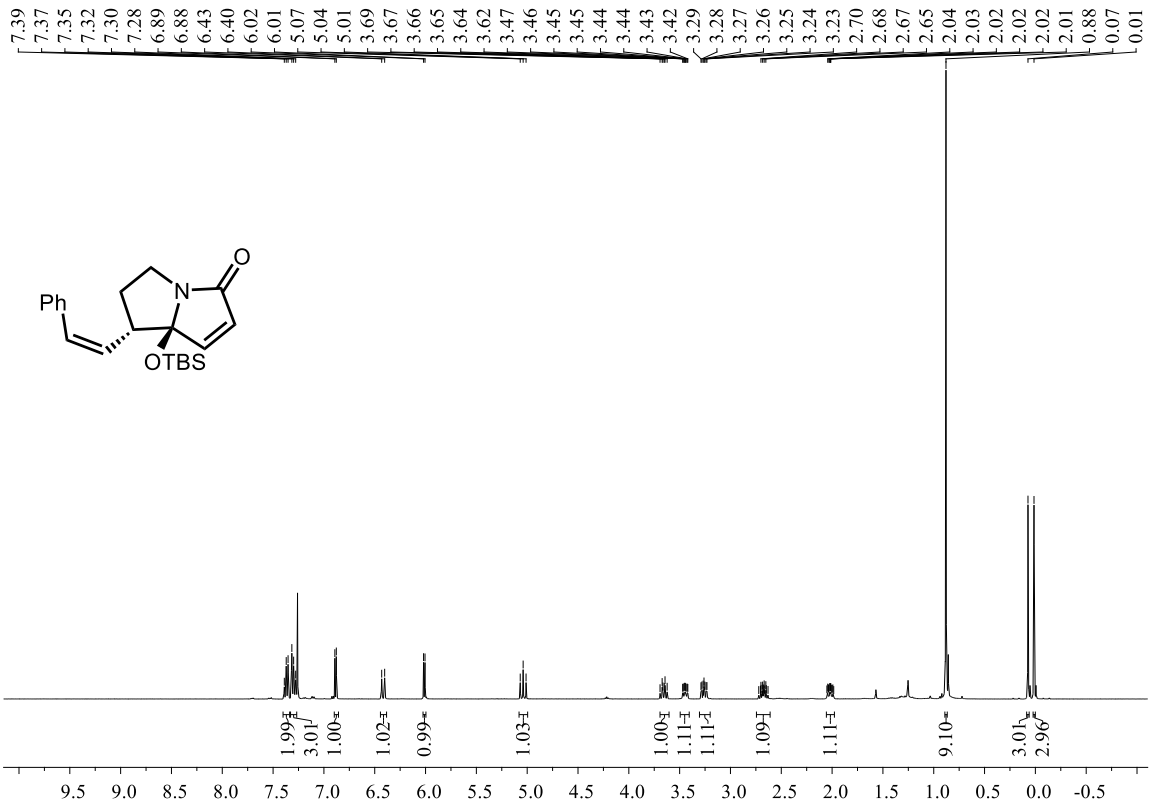
^{1}H NMR (500 MHz, $CDCl_3$) **(4db)**



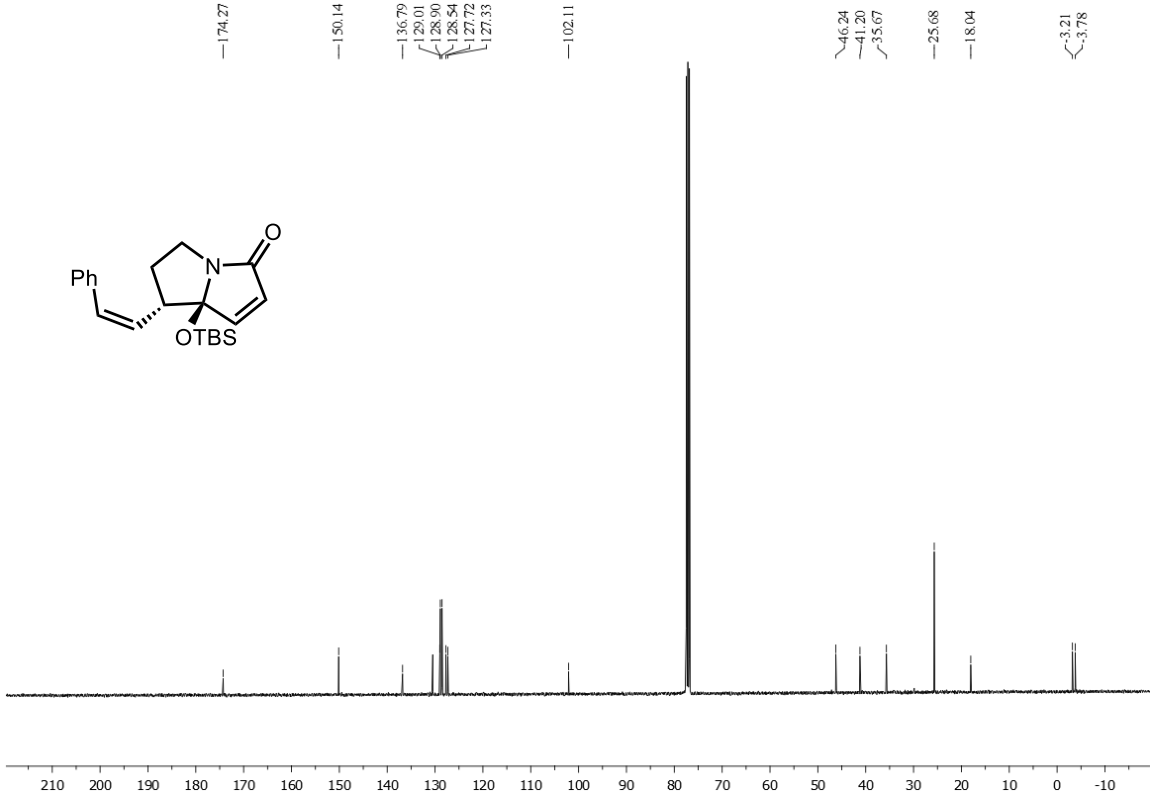
^{13}C NMR (126 MHz, $CDCl_3$) **(4db)**



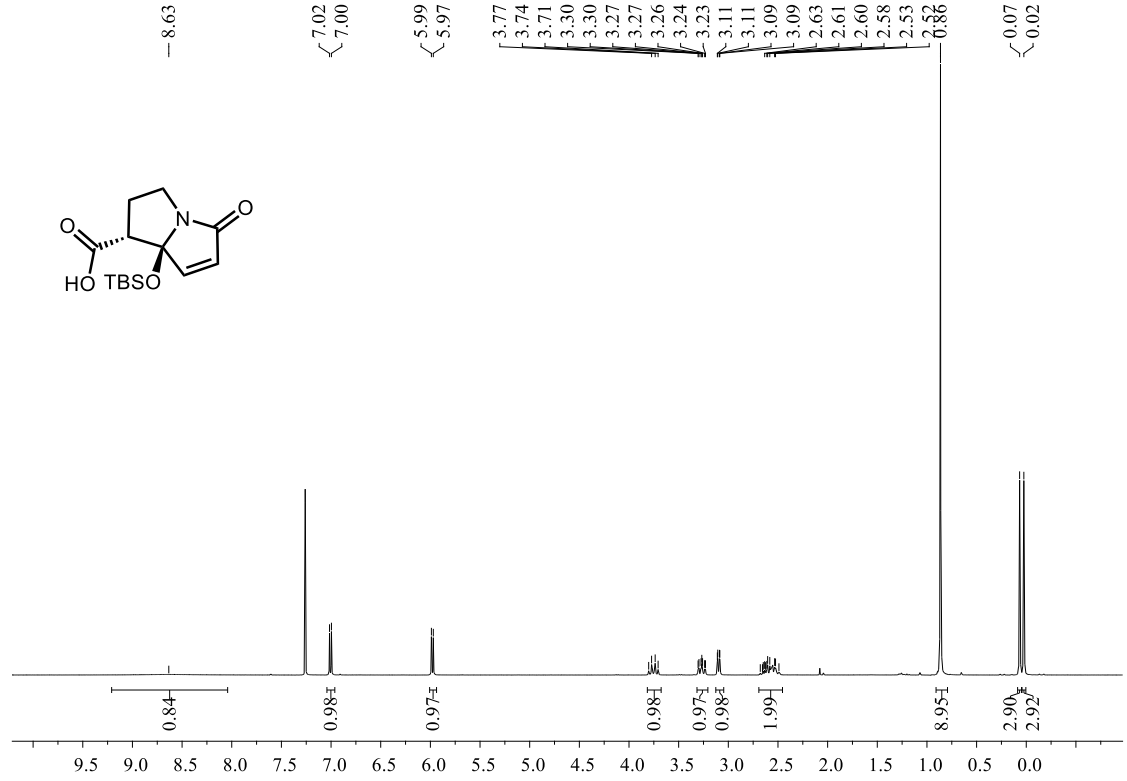
^{1}H NMR (400 MHz, $CDCl_3$) **(5)**



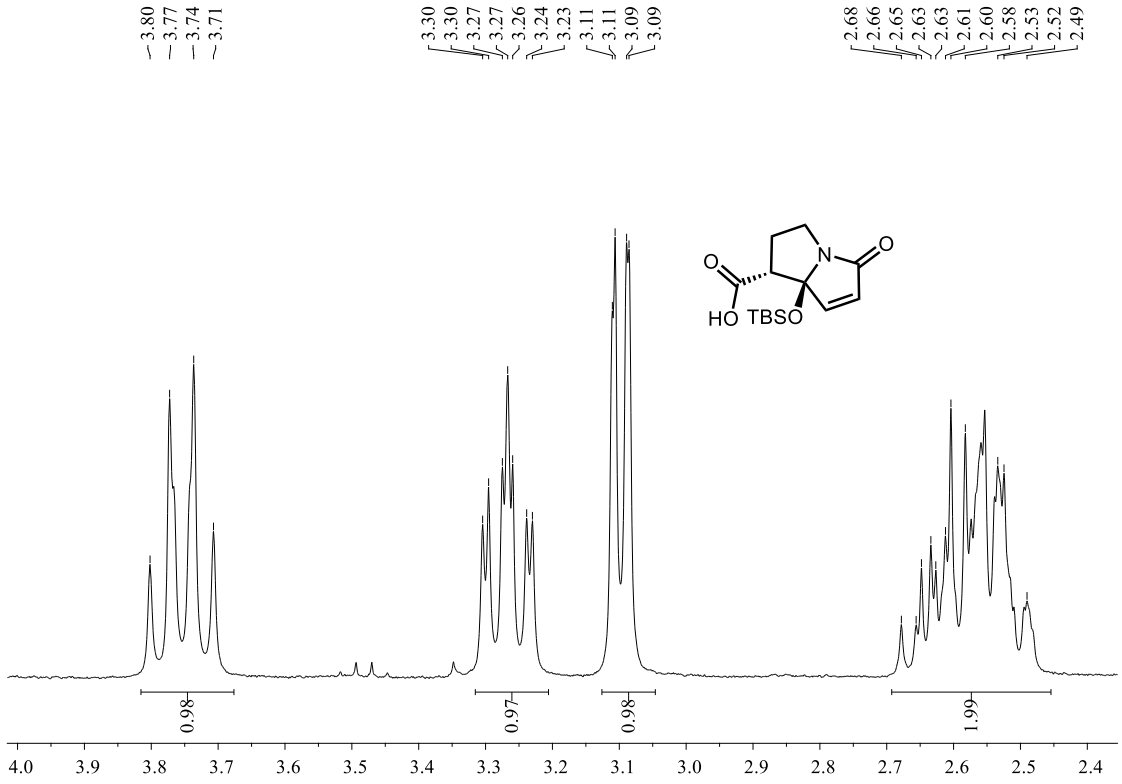
^{13}C NMR (101 MHz, $CDCl_3$) **(5)**



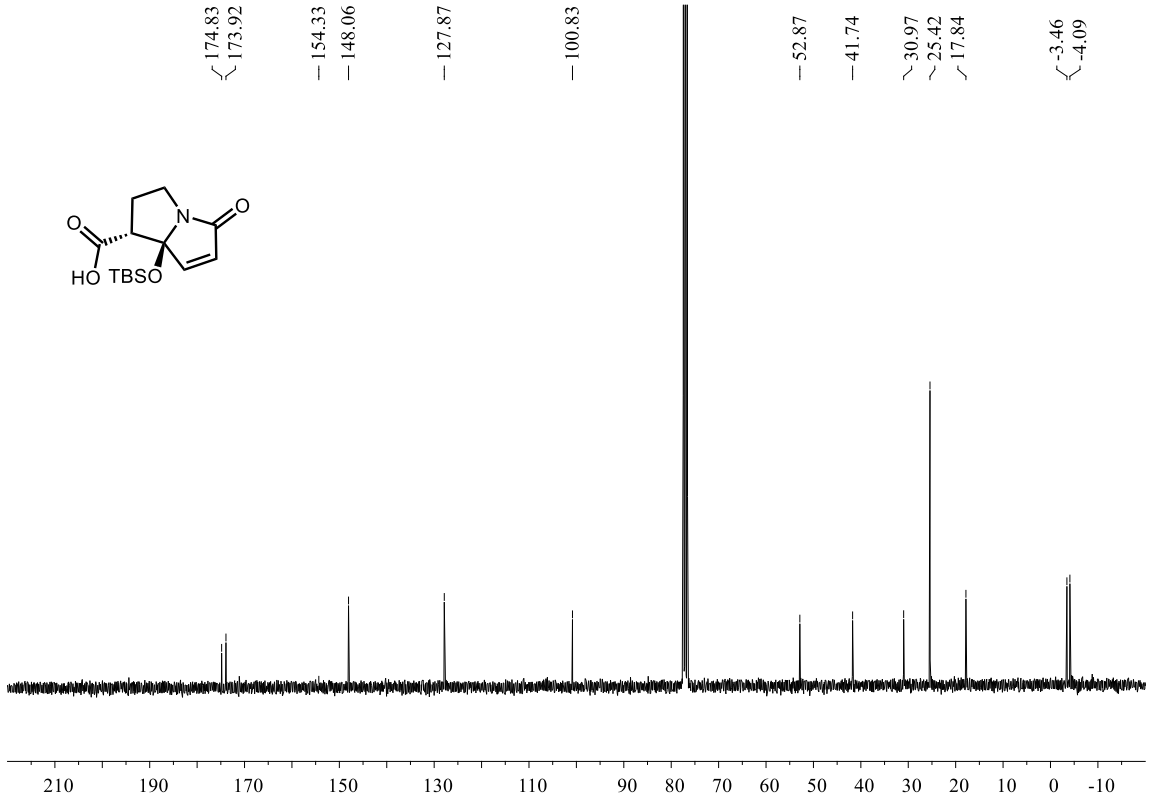
1H NMR (300 MHz, CDCl3) **(6)**



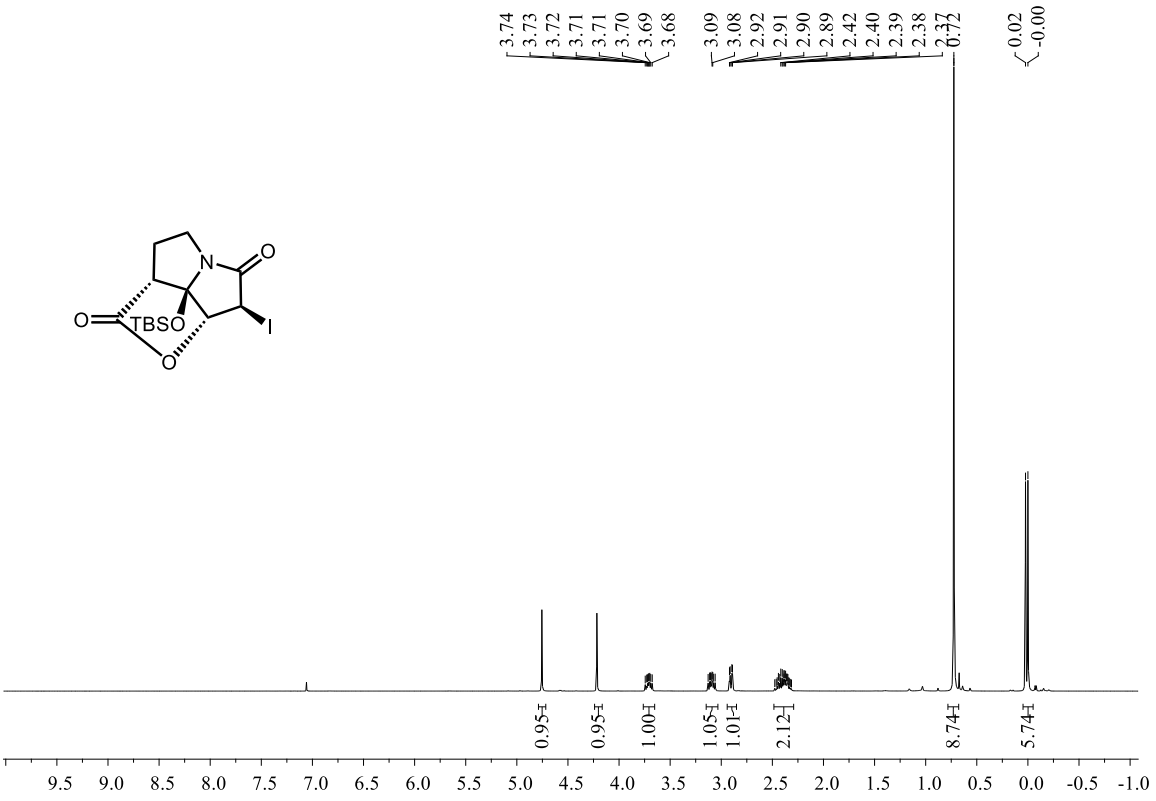
1H NMR (300 MHz, CDCl3) **(6)**



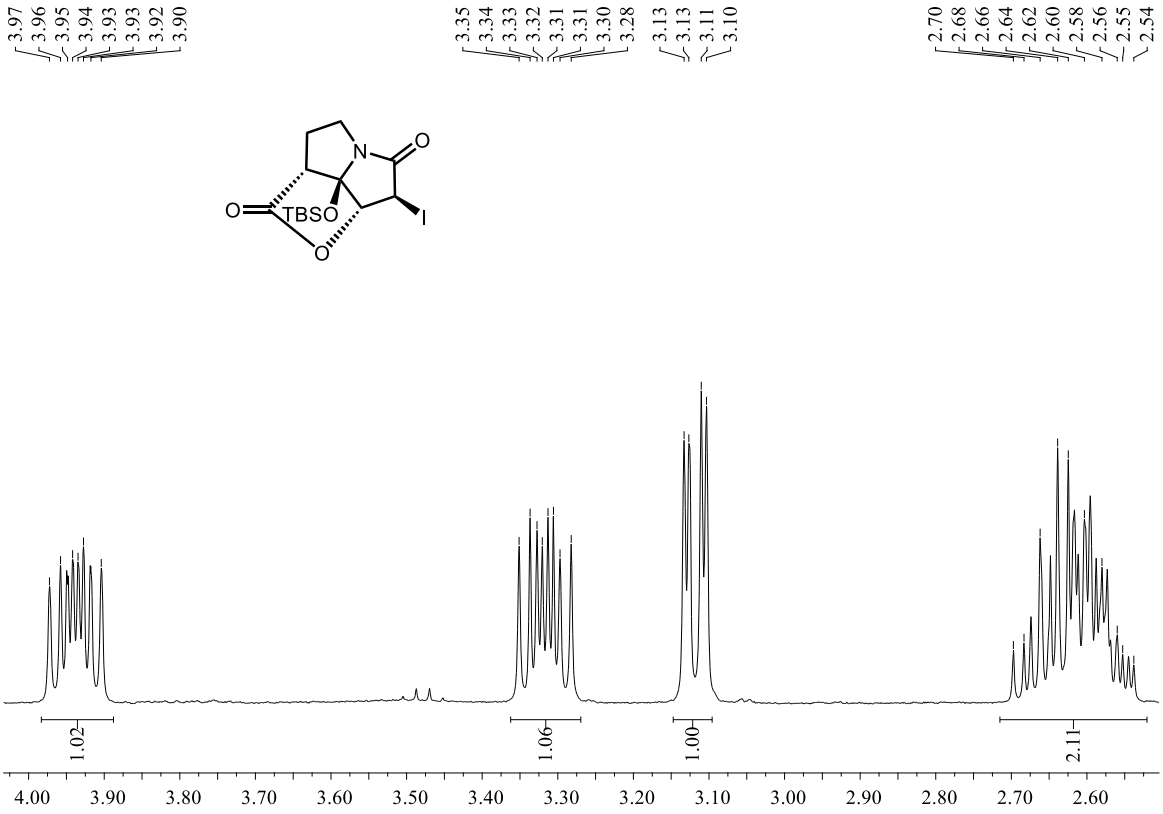
^{13}C NMR (75 MHz, $CDCl_3$) **(6)**



^{1}H NMR (400 MHz, $CDCl_3$) **(7)**



^{1}H NMR (400 MHz, $CDCl_3$) **(7)**



^{13}C NMR (101 MHz, $CDCl_3$) **(7)**