Electronic Supplementary Material (ESI) for Chemical Communications.

Bioorthogonal 4*H*-Pyrazole "Click" Reagents

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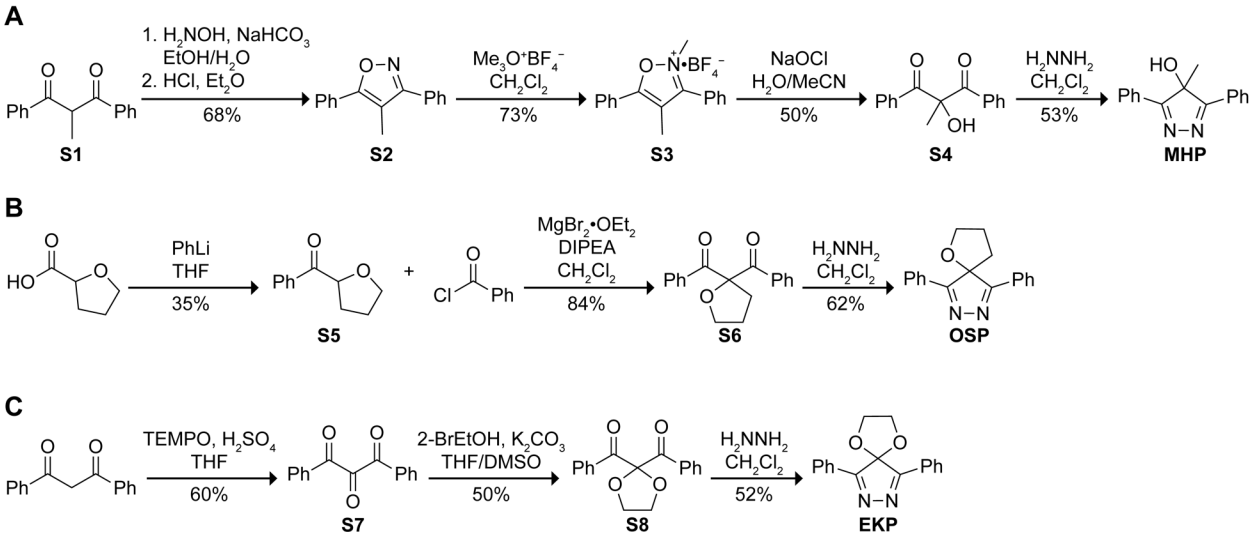


Fig. S1 Synthetic routes for (A) MHP, (B) OSP, and (C) EKP.

Synthesis of Dienes

General. All chemicals were from commercial sources and were used without further purification. NMR spectra were acquired with an Avance Neo 400 spectrometer or Avance Neo 500 spectrometer from Bruker (Billerica, MA, USA). Mass spectra were acquired by using positive ionization with an AccuTOF-DART 4G instrument from JEOL (Tokyo, Japan). HPLC experiments were carried out on a 1200 series HPLC from Agilent Technologies (Santa Clara, CA, USA) equipped with a Varian Microsorb-MV 100-5 C18 250 × 4.6 mm column. Gradients were run with water containing TFA (0.1% v/v) and ACN containing TFA (0.1% v/v). Absorbance was measured at 280 nm. Column chromatography was performed with an Isolera automated purification system from Biotage (Uppsala, Sweden) using prepacked SNAP KP silica gel columns.

The phrase "concentrated under reduced pressure" refers to the removal of solvents and other volatile materials using a rotary evaporator at water aspirator pressure (<20 Torr) while maintaining the water-bath temperature of 40 °C. Residual solvent was removed from samples by the vacuum (<0.1 Torr) achieved by a mechanical belt-drive oil pump.

All procedures were performed in air at ambient temperature (~22 °C) and pressure (1.0 atm) unless indicated otherwise.

2-Methyl-1,3-diphenylpropane-1,3-dione (S1). This compound was synthesized as reported previously.[1]

4-Methyl-3,5-diphenylisoxazole (S2). Compound **S1** (500 mg, 2.1 mmol) and hydroxylamine HCl (452 mg 6.5 mmol) were dissolved in a mixture of saturated aqueous $NaHCO_3$ (11 mL) and ethanol (11 mL) and stirred for 30 minutes to allow CO_2(g) to vent. The solution was subsequently heated to 70 °C and stirred overnight. The solution was diluted with water then extracted 3× with ethyl acetate. The combined organic extracts were washed with brine then dried over Na_2SO_4(s), filtered, and concentrated under reduced pressure. The residue was dissolved in 100 mL $CHCl_3$, 2 mL of ~1 M HCl in diethyl ether was added, and the resulting solution was stirred for 5 min. The solution was concentrated under reduced pressure, and the residue was redissolved in CH_2Cl_2 and passed through a silica plug to provide compound **S2** (335.8 mg, 1.43 mmol, 68%) as a pale-yellow

solid. **^{1}H NMR** (400 MHz, $CDCl_3$, δ): 7.83–7.76 (m, 2H), 7.76–7.66 (m, 2H), 7.59–7.44 (m, 6H), 2.35 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 165.77, 163.86, 129.62, 129.53, 129.45, 128.87, 128.76, 128.55, 128.45, 127.00, 108.67, 77.34, 77.03, 76.71, 9.36. **HRMS** *m*/*z* calcd for $C_{16}H_{14}NO$ $[M + H]^+$, 236.10754; found, 236.10532.

2,4-Dimethyl-3,5-diphenylisoxazol-2-ium Tetrafluoroborate (S3). Compound **S2** (500 mg, 2.13 mmol) and trimethyloxonium tetrafluoroborate (346 mg, 2.33 mmol) were added to an oven-dried flask, which was then purged 3× with vacuum and filled 3× with N_2(g). CH_2Cl_2 (6 mL) was added, and the resulting solution was stirred at room temperature under N_2(g) for 7 h. The reaction mixture was then diluted with methanol, filtered through celite, and concentrated under reduced pressure. The resulting residue was triturated with diethyl ether to yield compound **S3** (387.5 mg, 1.55 mmol, 73%) as a white solid. **^{1}H NMR** (400 MHz, DMSO, δ): 8.04–7.91 (m, 2H), 7.86–7.70 (m, 8H), 4.32 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, DMSO, δ): 166.31, 159.83, 133.58, 133.38, 130.36, 130.18, 130.10, 128.48, 124.07, 122.50, 115.13, 40.09, 9.10. **HRMS** *m*/*z* calcd for $C_{17}H_{16}NO^+$ $[M]^+$, 250.12319; found, 250.12144.

2-Hydroxy-2-methyl-1,3-diphenylpropane-1,3-dione (S4). Compound **S3** (200 mg, 0.8 mmol) was dissolved in MeCN (8 mL) and H_2O (8 mL), and the resulting solution was cooled to 0 °C. Bleach (8.25% w/v NaOCl, 9.5 mL) was added dropwise, and the solution was stirred for 1 h at 0 °C. The reaction mixture was diluted with H_2O then extracted 3× with ethyl acetate. The combined organic layers were washed with aqueous $Na_2S_2O_3$ (10% w/v) and then with 1 M HCl. The organic layers were dried over Na_2SO_4(s), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide compound **S4** (153.3 mg, 0.604 mmol, 76%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, δ): 8.03–7.89 (m, 4H), 7.56–7.48 (m, 2H), 7.44–7.36 (m, 4H), 5.22 (s, 1H), 1.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 197.88, 133.94, 133.83, 129.75, 128.70, 84.27, 25.68. **HRMS** *m*/*z* calcd for $C_{16}H_{15}O_3$ $[M + H]^+$, 255.10212; found, 255.10110.

4-Methyl-3,5-diphenyl-4*H*-pyrazol-4-ol (MHP). Compound **S4** (20 mg, 0.08 mmol) was dissolved in CH_2Cl_2 (3 mL), and hydrazine monohydrate (0.0121 mL, 12.5 mg, 0.25 mmol) was added to the resulting solution. The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide **MHP** (10.4 mg, 0.0416 mmol, 53%) as a white solid. **^{1}H NMR** (400 MHz, DMSO, δ): 8.21 (dt, J = 6.8, 2.2 Hz, 4H), 7.66–7.46 (m, 6H), 6.95 (s, 1H), 1.56 (s, 3H). **^{13}C NMR** (101 MHz, DMSO, δ): 174.90, 131.78, 129.48, 129.38, 128.08, 88.83, 25.43. **HRMS** *m*/*z* calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$, 251.11844; found, 251.11762.

Phenyl(tetrahydrofuran-2-yl)methanone (S5). Tetrahydrofuran-2-carboxylic acid (1161.2 mg, 0.96 mL, 10 mmol) was added to an oven-dried flask, which was then purged 3× with vacuum and filled 3× with N_2(g). Tetrahydrofuran (25 mL) was added to the flask, and the resulting solution was cooled to 0 °C under N_2(g). Phenyl lithium (1.9 M in dibutyl ether, 13.2 mL, 25 mmol) was added dropwise over 30 min. The resulting solution was allowed to warm to room temperature then stirred for 24 h under N_2(g). The reaction mixture was poured into an ice and dilute HCl bath then extracted 3× with diethyl ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4(s), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide compound **S5** (609.8 mg, 3.5 mmol, 35 %) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$, δ): 8.04–7.98 (m, 2H), 7.62–7.55 (m, 1H), 7.48 (dd, J = 8.5, 7.1 Hz, 2H), 5.27 (dd, J = 8.4, 5.8 Hz, 1H), 4.05 (dt, J = 8.4, 6.8 Hz, 1H), 3.99 (dt, J = 8.3, 6.7 Hz, 1H), 2.36–2.25 (m, 1H), 2.15 (ddt, J = 12.5, 8.1, 6.2 Hz, 1H), 2.03–1.94 (m, 2H). **^{13}C NMR** (126

MHz, $CDCl_3$, δ): 198.78, 135.08, 133.29, 128.72, 128.61, 80.00, 69.39, 29.29, 25.62. **HRMS** *m*/*z* calcd for $C_{11}H_{13}O_2$ $[M + H]^+$, 177.09155; found, 177.09005.

Tetrahydrofuran-2,2-diyl)bis(phenylmethanone) (S6). Magnesium bromide ethyl etherate (1807.6 mg, 7.0 mmol) was added to an oven-dried flask, which was then purged 3× with vacuum and filled 3× with N_2(g). CH_2Cl_2 (20 mL), compound **S5** (500 mg, 2.8 mmol), and benzoyl chloride (435.8 mg, 0.357 mL, 3.1 mmol) were added, and the reaction mixture was stirred for 5 min under N_2(g). *N*,*N*-Diisopropylethylamine (1085 mg, 1.46 mL, 8.4 mmol) was added, and the reaction mixture was stirred for 2 h under N_2(g). The reaction was quenched by the addition of 1 M HCl (50 mL), and the mixture was stirred for 10 min and extracted 3× with CH_2Cl_2. The combined organic extracts were washed with brine, dried on Na_2SO_4(s), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide compound **S6** (655.0 mg, 2.34 mmol, 84%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$, δ): 8.08–7.97 (m, 4H), 7.53–7.44 (m, 2H), 7.38 (dd, J = 8.5, 7.1 Hz, 4H), 4.14 (t, J = 6.7 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 2.08 (q, J = 7.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 196.06, 134.38, 133.36, 129.88, 128.49, 95.53, 70.36, 32.93, 25.95. **HRMS** *m*/*z* calcd for $C_{18}H_{17}O_3$ $[M + H]^+$, 281.11777; found, 281.11836.

6,9-Diphenyl-1-oxa-7,8-diazaspiro[4.4]nona-6,8-diene (OSP). Compound **S6** (400 mg, 1.4 mmol) was dissolved in CH_2Cl_2 (10 mL), and hydrazine monohydrate (1.0 mL, 1032 mg, 20.6 mmol) was added. The reaction was stirred overnight then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide OSP (238.8 mg, 0.865 mmol, 62%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, δ): 8.05–7.89 (m, 4H), 7.59–7.40 (m, 6H), 4.46 (t, J = 6.9 Hz, 2H), 2.24 (t, J = 7.3 Hz, 2H), 2.15–1.96 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 174.66, 131.13, 130.00, 128.74, 128.06, 99.33, 71.84, 35.33, 25.59. **HRMS** *m*/*z* calcd for $C_{18}H_{17}N_2O$ $[M + H]^+$, 277.13409; found, 277.13460.

1,3-Diphenylpropane-1,2,3-trione (S7). 1,3-Diphenyl-1,3-propanedione (5000 mg, 22.3 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (3484 mg, 22.3 mmol) were dissolved in ethyl acetate (150 mL), and the resulting solution was stirred at 60 °C for 2 h. Sulfuric acid (4375 mg, 2.4 mL, 44.6 mmol) was added to the stirring solution, and the reaction mixture was allowed to stir overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 and filtered through celite. The filtrate was washed with water, dried on Na_2SO_4(s), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide compound **S7** (3209.7 mg, 13.5 mmol, 60%) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$, δ): 8.13–8.07 (m, 4H), 7.77–7.70 (m, 2H), 7.59 (t, J = 7.8 Hz, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$, δ): 194.05, 192.45, 188.26, 135.41, 132.14, 130.26, 130.23, 129.11. **HRMS** *m*/*z* calcd for $C_{15}H_{11}O_3$ $[M + H]^+$, 239.07082; found, 239.07069.

(1,3-Dioxolane-2,2-diyl)bis(phenylmethanone) (S8). Compound **S7** (2500 mg, 10.5 mmol) and potassium carbonate (1451 mg, 10.5 mmol) were added to an oven-dried flask, which was then purged 3× with vacuum and filled 3× with N_2(g). Tetrahydrofuran (5 mL) and dimethyl sulfoxide (5 mL) were added to the flask, followed by 2-bromoethanol (1312 mg, 0.744 mL, 10.5 mmol), and the resulting solution was heated to 40 °C and stirred for 24 h. The reaction mixture was diluted with water and extracted 2× with diethyl ether. The combined organic layers were washed with water, dried on Na_2SO_4(s), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide compound **S8** (1470.8 mg, 5.21 mmol, 50%) as a pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.15–8.00 (m, 4H), 7.59–7.46 (m, 2H), 7.40 (dd, J = 8.5, 7.1 Hz, 4H), 4.25 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 192.70, 133.90, 133.39, 130.19, 128.54, 108.66, 66.52. **HRMS** *m*/*z* calcd for $C_{17}H_{15}O_4$ $[M + H]^+$, 283.09703; found, 283.09873.

6,9-Diphenyl-1,4-dioxa-7,8-diazaspiro[4.4]nona-6,8-diene (EKP). Compound **S8** (500 mg, 1.77 mmol) was added to an oven-dried flask, which was then purged 3× with vacuum and filled 3× with N_2(g). CH_2Cl_2 (10 mL) and hydrazine monohydrate (133.2 mg, 0.129 mL, 2.66 mmol) were added, and the resulting solution was stirred under N_2(g) overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (100:0→80:20 hexanes/EtOAc) to provide **EKP** (255.0 mg, 0.92 mmol, 52%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$, δ): 7.95–7.86 (m, 4H), 7.53–7.46 (m, 4H), 7.39 (dt, J = 5.0, 2.5 Hz, 2H), 4.34 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$, δ): 168.76, 131.49, 128.74, 128.10, 127.34, 97.58, 66.25. **HRMS** *m*/*z* calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$, 279.11335; found, 279.11521.

Kinetic Analyses

Stock solutions of diene and dienophile (2 mM in 9:1 MeOH/H_2O) were prepared for each diene and dienophile. Aliquots (0.5 mL) of diene and dienophile were mixed, and reactions were monitored by HPLC with aliquots injected at the timepoints shown in the kinetic traces below. Each reaction was carried out in triplicate. The concentration of remaining diene was obtained from its corresponding peak in the chromatogram monitored at 280 nm. Second-order rate constants were calculated from the slope of a plot of $[diene]^{-1}$ versus time.

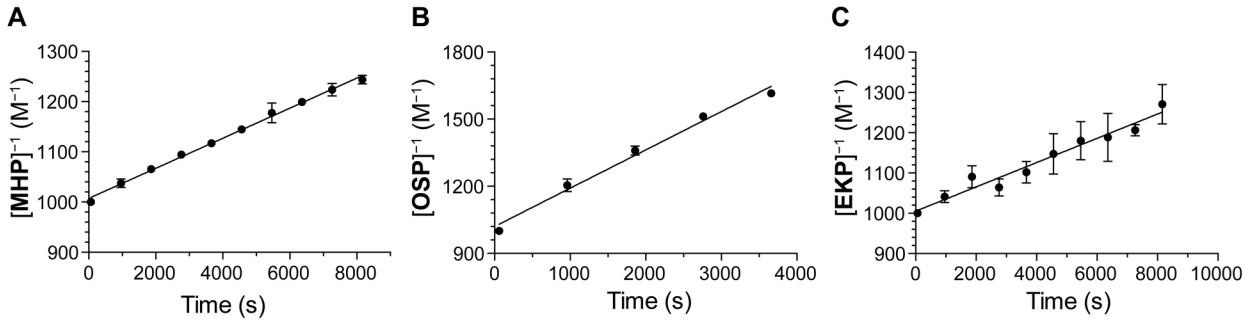


Fig. S2 Kinetic data for the reactions of **BCN** with (A) **MHP**, (B) **OSP**, and (C) **EKP**. All reactions were carried out in 9:1 methanol/water at 26 °C and were monitored by HPLC. Values are the mean ± SD for triplicate experiments. Second-order rate constants derived from these data are listed in Figure 1.

Stability of Dienes in the Presence of Glutathione

A solution of each diene (25 μM) was prepared in Dulbecco's phosphate-buffered saline (DPBS) containing reduced glutathione (1.0 mM), oxidized glutathione (0.2 mM), and DMSO (2% v/v for solubility). The solutions were incubated at 37 °C for 8 h and HPLC analyses were performed to determine the remaining concentration of diene after incubation to yield the "% Remaining 4*H*-Pyrazole" shown in Figure 2.

Stability of OSP in Cell Culture Medium

The stability of OSP was assessed in Dulbecco's modified Eagle's medium (DMEM; ThermoFisher #11995065) that was supplemented with FBS (10% v/v), penicillin (100 units/mL), and streptomycin (100 μg/mL). To 1.496 mL of full medium was added 4 μL of a 20 mM solution of OSP in DMSO (final concentrations: OSP, 50 μM; DMSO, 2.5% v/v). As an initial time point, a 500-μL aliquot was removed and diluted with 500 μL of a 50 μM solution of naphthalene in MeCN as an internal standard, then subjected to centrifugation for 10 min at 10,000*g* and analyzed by HPLC. The reaction mixture was incubated at 37 °C for 24 h. Then, a final aliquot was removed and treated as previously. The procedure was performed in triplicate, and the "% Remaining 4*H*-Pyrazole" was determined by the area of the OSP peak at 280 nm compared to the internal standard. After the 24-h incubation, 95.9 ± 0.7% of the OSP remained intact (mean ± SD).

Mammalian Cell Culture

HeLa cells (ATCC #CCL-2) were cultured according to ATCC guidelines in DMEM that was supplemented with FBS (10% v/v), penicillin (100 units/mL), and streptomycin (100 μg/mL). Cells were cultured in an incubator maintained at 37 °C in the presence of CO_2 (5% v/v).

Preparation of HeLa Cell Lysate

HeLa cells (ATCC # CCL-2) were grown in three T75 flasks to >85% confluency. Cells were washed with DPBS (2 × 5 mL; ThermoFisher #14190144), released from the plate by treatment with trypsin (0.25% v/v; ThermoFisher #25200056), combined, and pelleted by centrifugation at 1000 rpm for 5 min at 4 °C. Cells were subsequently resuspended in DPBS (10 mL) and pelleted again. The pellet was flash-frozen in liquid nitrogen and permitted to warm on ice until thawed. The thawed pellet was resuspended in ice-cold DPBS (1 mL), and flash-frozen again. This freeze-thaw cycle was performed three additional times. After the final thaw, cellular debris was removed via centrifugation at 14,000*g* for 15 min at 4 °C. The resultant supernatant was isolated as clarified lysate and stored at −70 °C. The protein concentration in the lysate was determined to be 1.96 mg/mL by using a bicinchoninic acid (BCA) assay (ThermoFisher #23225) according to the manufacturer's instructions and measuring absorbance at 562 nm with a Tecan Spark plate reader (Männedorf, Switzerland).

Stability of OSP in HeLa Cell Lysate

To each of two 49-μL aliquots of a HeLa cell lysate (*vide supra*) was added 1 μL of a 100 mM solution of OSP in DMSO (final concentrations: OSP, 2 mM; DMSO, 2% v/v). For an initial timepoint, one mixture was diluted with 950 μL of MeCN. Then, 500 μL of this mixture was diluted further with 500 μL of a 50 μM solution of naphthalene in MeCN as an internal standard. The resulting solution was subjected to centrifugation at 10,000*g* for 10 min and analyzed by HPLC. The second reaction mixture was incubated at 37 °C for 24 h, then diluted and analyzed in the same manner. The reaction was performed in triplicate, and the "% Remaining

4*H*-Pyrazole"was determined by the area of the OSP peak at 280 nm compared to the internal standard. After the 24-h incubation, 84 ± 1% of the OSP remained intact (mean ± SD).

Cytotoxicity of OSP

The toxicity of OSP towards HeLa cells (ATCC #CCL-2) was assessed by using the CellTiter 96® AQueous One Solution Cell Proliferation Assay kit from Promega (Madison, WI; #G3580). This colorimetric assay leverages the metabolic activity of viable cells to convert a tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium, inner salt; MTS] into a colored, soluble formazan having absorbance in the visible range. The absorbance of the formazan product is directly proportional to the living cell count.

Cells were seeded at 5,000 cells/well in a tissue culture-treated, flat black, clear-bottomed 96-well plate (Corning #3603) 24 h prior to the start of the experiment. The confluency at the time of the experiment was determined to be 10%, which is appropriate for assays of proliferating cells. A 100-mM stock solution of OSP was prepared in DMSO. A dilution series was prepared, and samples were sterile-filtered with a sterile 0.22 μm Corning® Costar® Spin-X® centrifuge tube filter (Millipore Sigma #CLS8160). Cells were treated with OSP (0.1 μM–1 mM) such that the DMSO concentration was always ≤1% v/v, which minimizes membrane permeabilization. The working volume of each treatment was 100 μL. The OSP-treated cells were incubated for either 24 or 48 h at 37 °C in the presence of CO_2 (5% v/v). The cells were then treated with 20 μL of the MTS reagent and incubated for 1.5 h at 37 °C in the presence of CO_2 (5% v/v). The absorbance of the solution was measured at 490 nm with a Tecan Spark plate reader. Values represent data collected from biological duplicates with three technical replicates and are normalized to the average background absorbance signal from the formazan in DMEM alone and from cells treated with DMSO (1% v/v). Values were plotted as the mean ± SE with GraphPad Prism software (La Jolla, CA).

Computational Methods

Calculations were performed at the M06-2X/def-2tzp-SMD(H2O)//M06-2X/6-31+G(d)-SMD(H2O) level of theory.

Reference

1. N. S. Abularrage, B. J. Levandowski and R. T. Raines. *Int. J. Mol. Sci.*, 2020, **21**, 3964.

Computational Energetic Data and Coordinates

	G (energy)
OSP	879.9419126
EKP	915.8727705
MHP	802.5769521
DFP	886.5802445
DMP	766.6311152
MFP	826.6059328

	H (Enthalpy)
H_2	−688.0215959
CH_4	−40.44787025
EKP	−915.8105195
EKP − CH_2	−268.2492375
OSP	−879.8794496
OSP − CH_2	−232.3100974
MHP	−802.5172551
MHP − CH_2	−154.9485591
DFP	−886.5215535
DFP − CH_2	−238.9682471
DMP	766.5701412
DMP − CH_2	118.9990524
MFP	−826.5465398
MFP − CH_2	−178.9830678

MFP

C	-1.19904400	0.10420300	0.23582500
C	1.03608000	0.65301500	0.23679000
C	-0.29402900	1.24479500	-0.19318300
C	4.83453600	2.57537100	-0.01926700
C	3.66688200	3.32117400	-0.16976400
C	2.42251100	2.69762400	-0.09297500
C	2.33966300	1.31699800	0.13762900
C	3.52029200	0.57175800	0.28984400
C	4.75780100	1.19868300	0.21091400
H	5.80314200	3.06251600	-0.08221100
H	3.72066200	4.39100300	-0.34700300
H	1.52112900	3.29207300	-0.20284100
H	3.45965900	-0.49799000	0.46369400
H	5.66588000	0.61441500	0.32553300
C	-5.45618900	0.05335500	-0.01880900
C	-4.76465400	1.25180500	-0.18538100
C	-3.37290300	1.27439700	-0.10893500
C	-2.66193500	0.09102900	0.13717700
C	-3.36535200	-1.11287800	0.30559000
C	-4.75248900	-1.12923400	0.22708500
H	-6.54034100	0.03749100	-0.08108000
H	-5.30624500	2.17364900	-0.37451100
H	-2.84924400	2.21716400	-0.23124100
H	-2.81757700	-2.03127400	0.49195400
H	-5.28807400	-2.06516800	0.35474200
N	0.88296400	-0.55742400	0.64824000
N	-0.50334700	-0.89762900	0.64831500
F	-0.58641500	2.42698300	0.48438400
C	-0.35066500	1.48082900	-1.69429000
H	0.37696200	2.24447200	-1.98028500
H	-0.11361900	0.55039900	-2.21940700
H	-1.35364300	1.80519300	-1.98313200

DMP

C	0.99329200	0.75235400	-0.39295900
C	-1.25321900	0.38271100	-0.30005300
C	-0.28182900	1.53643800	-0.16836700
C	-5.52638900	0.37801700	0.07824400
C	-4.83185300	1.58380800	0.13050000
C	-3.44206400	1.60350800	0.00986900
C	-2.72370100	0.41228300	-0.16759200
C	-3.43714400	-0.79914400	-0.21697400
C	-4.82115900	-0.81569100	-0.09616300
H	-6.60813600	0.36505500	0.17413000
H	-5.36781300	2.51841800	0.26634800
H	-2.93748900	2.56068100	0.05558800

H	-2.89538500	-1.72978100	-0.34831000
H	-5.35241800	-1.76208500	-0.13570700
C	5.04784100	2.14939800	-0.47264100
C	4.74524400	0.81381900	-0.75091500
C	3.42747400	0.37453500	-0.72243200
C	2.37935900	1.26049300	-0.41383200
C	2.69503100	2.59848400	-0.13716900
C	4.01918200	3.03673800	-0.16671000
H	6.07785300	2.49287000	-0.49601200
H	5.53968100	0.11377700	-0.99229400
H	3.19923400	-0.66303800	-0.94179200
H	1.92157100	3.31678700	0.10531000
H	4.24086600	4.07724300	0.05098800
N	-0.63758900	-0.73006700	-0.53904000
N	0.74908000	-0.50180500	-0.59737200
H	-1.32836600	2.56257400	1.44394200
C	-0.48031700	2.57785500	-1.28857600
H	-1.42456900	3.11156000	-1.16575600
H	0.32518100	3.31532600	-1.27370200
H	-0.48239100	2.08887100	-2.26781400
C	-0.34078900	2.13776300	1.24998800
H	-0.14322500	1.36592100	2.00046100
H	0.39595500	2.93432300	1.36891400

DFP

C	-1.18595100	-0.04465200	0.00076700
C	1.08338600	0.48447100	-0.00201200
C	-0.27328700	1.17283600	0.00131800
C	4.81382900	2.52361900	-0.00338500
C	3.62448400	3.25007700	-0.00226800
C	2.39986100	2.58533500	-0.00174600
C	2.36458300	1.18372800	-0.00246400
C	3.56536600	0.45552900	-0.00352700
C	4.78169400	1.12539300	-0.00397300
H	5.76725600	3.04346500	-0.00375400
H	3.64630800	4.33539600	-0.00178700
H	1.48076700	3.16358000	-0.00082700
H	3.53632400	-0.62966700	-0.00390800
H	5.70823500	0.55957400	-0.00473200
C	-5.43379200	0.12834200	0.00754300
C	-4.69053000	1.30724800	0.00782400
C	-3.29810300	1.25489800	0.00564200
C	-2.64445000	0.01454400	0.00312800
C	-3.39723500	-1.17086100	0.00285500
C	-4.78448000	-1.11040100	0.00509100
H	-6.51895200	0.17096400	0.00924100
H	-5.19173300	2.27009900	0.00971800

H	-2.73062100	2.18042300	0.00589600
H	-2.88933200	-2.13018900	0.00095400
H	-5.36420300	-2.02829800	0.00492300
N	0.92377300	-0.78855200	-0.00383800
N	-0.47966400	-1.11576400	-0.00215200
F	-0.45406800	1.95690400	1.09539000
F	-0.45786300	1.96055900	-1.08951600

MHP

C	-1.21607900	0.43665800	-0.58660900
C	1.03967600	0.85653900	-0.63699600
C	-0.21243600	1.39174000	0.04345700
C	5.01393900	2.33932400	-0.13899100
C	3.93186100	3.08091300	0.33144400
C	2.63129800	2.60321300	0.17362600
C	2.40338600	1.37370400	-0.46114300
C	3.49942900	0.63251300	-0.93324200
C	4.79352800	1.11282300	-0.77226100
H	6.02628300	2.71195900	-0.01271600
H	4.09646900	4.03504100	0.82312600
H	1.79601200	3.19326900	0.53515700
H	3.32905700	-0.32310000	-1.41905400
H	5.63369900	0.52943200	-1.13714400
C	-5.44089200	0.42438400	0.04129800
C	-4.67633000	1.50280900	0.48229500
C	-3.29584600	1.51250500	0.28534500
C	-2.66757500	0.43742100	-0.35972900
C	-3.44527500	-0.64629900	-0.80060700
C	-4.82048500	-0.65129400	-0.60056400
H	-6.51570100	0.41828900	0.19744100
H	-5.15242900	2.34205100	0.98042300
H	-2.71245700	2.36211100	0.62341200
H	-2.96325400	-1.48427700	-1.29413000
H	-5.41134700	-1.49593500	-0.94235500
N	0.77269800	-0.17430500	-1.36265000
N	-0.62766100	-0.43469400	-1.33173000
O	-0.47270800	2.76373200	-0.17437800
H	-0.53057500	2.93105200	-1.13104400
C	-0.13332200	1.15079600	1.55171300
H	0.07309000	0.09618000	1.75602100
H	0.66769700	1.75901200	1.98048300
H	-1.08235000	1.42443300	2.02050100

OSP

C	-1.29124700	2.59428000	-0.64102600
C	-1.51872800	0.31328500	-0.67516500
C	-0.41737600	1.35259400	-0.57610100

C	1.70105400	1.84710600	0.42947200
H	2.47993400	1.47648600	1.09961400
H	1.69489200	2.93965800	0.47040000
C	-1.02576800	-3.92846200	-0.82422500
C	0.08505700	-3.09599700	-0.94383100
C	-0.06755100	-1.71089100	-0.89358900
C	-1.33817300	-1.14448600	-0.72338300
C	-2.45286700	-1.99107200	-0.60347000
C	-2.29619500	-3.37096400	-0.65364800
H	-0.90514900	-5.00715300	-0.86231500
H	1.07520800	-3.52117000	-1.07762700
H	0.80699700	-1.07843300	-0.99587100
H	-3.43951000	-1.55984700	-0.46750600
H	-3.16514900	-4.01514700	-0.55767800
C	-0.00524300	6.66573400	-0.58914800
C	-1.12608200	6.27203400	0.14415000
C	-1.53883200	4.94253000	0.12843700
C	-0.82930600	3.99136200	-0.61891300
C	0.29745100	4.39125800	-1.35147800
C	0.70243300	5.72439500	-1.33730700
H	0.31604400	7.70309700	-0.57623200
H	-1.67640900	7.00033300	0.73244900
H	-2.40388500	4.63047500	0.70615000
H	0.84503500	3.66685200	-1.94621600
H	1.57161400	6.02734300	-1.91351600
N	-2.68202900	0.86603400	-0.64749600
N	-2.54066800	2.28714300	-0.62731900
C	1.89967700	1.35698800	-0.99771400
H	2.35242900	0.35937900	-1.02583300
H	2.49065900	2.03414300	-1.61914400
O	0.57738900	1.27533000	-1.57890300
C	0.32567100	1.27818300	0.78459800
H	0.40894800	0.23132900	1.09248800
H	-0.19502500	1.83467100	1.56739700

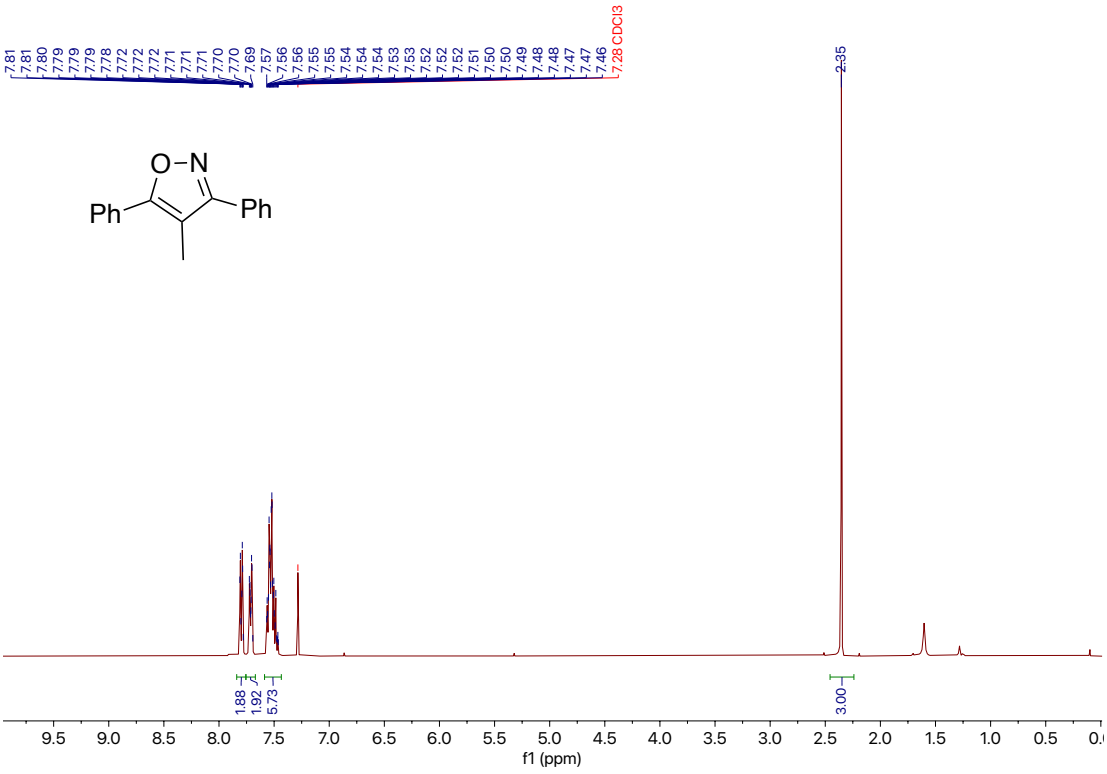
EKP

C	-1.21805400	0.40539600	-0.64616100
C	1.07233200	0.74796100	-0.67128100
C	-0.16890900	1.29081600	0.03921000
C	-0.60191100	3.29577100	1.12068400
H	0.27902100	3.88591600	1.38490000
H	-1.47407600	3.94637900	1.03513600
C	5.05711300	2.16747800	-0.13108800
C	4.04290500	2.60831300	0.71685200
C	2.73757500	2.15012200	0.54507900
C	2.43859700	1.24198800	-0.47948400
C	3.46552500	0.80281800	-1.33126500

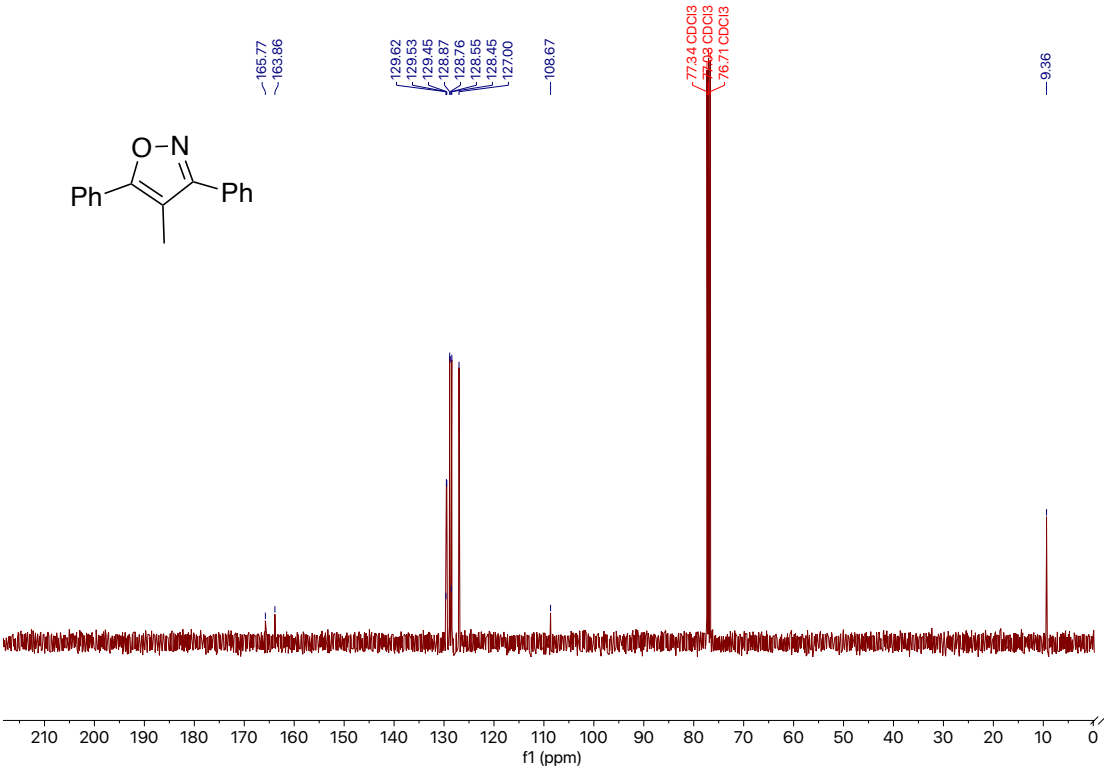
C	4.76462300	1.26306100	-1.15616200
H	6.07323900	2.52672700	0.00292100
H	4.26427900	3.30924100	1.51589800
H	1.96287900	2.49315600	1.22171300
H	3.23608100	0.10673800	-2.13186700
H	5.55180800	0.92006800	-1.82079700
C	-5.41790600	0.35541300	0.09974700
C	-4.73341400	1.57079100	0.08077000
C	-3.36008100	1.59841400	-0.15182900
C	-2.66185400	0.40297400	-0.37380900
C	-3.35557400	-0.81598200	-0.35746300
C	-4.72659200	-0.83765500	-0.11969900
H	-6.48767900	0.33714400	0.28618800
H	-5.26871200	2.50130700	0.24385100
H	-2.84060000	2.55097500	-0.18557400
H	-2.81118500	-1.74219800	-0.51562300
H	-5.25515000	-1.78597000	-0.09973100
N	0.76231700	-0.19550500	-1.48213900
N	-0.66390300	-0.41818400	-1.45712000
C	-0.82439000	2.12148000	2.06318500
H	-0.38571800	2.26794900	3.05017100
H	-1.88050800	1.85226800	2.15412600
O	-0.37391200	2.66660200	-0.15744000
O	-0.09956600	1.05802800	1.42140300

NMR Spectra

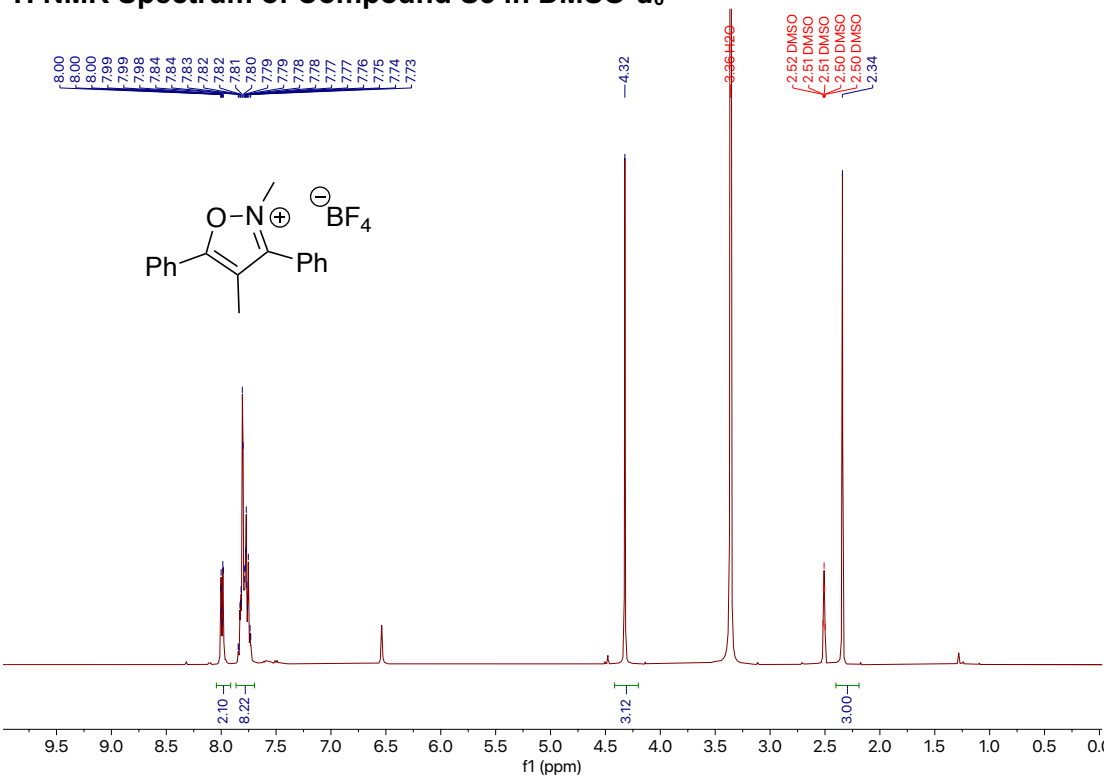
^{1}H NMR Spectrum of Compound S2 in $CDCl_3$



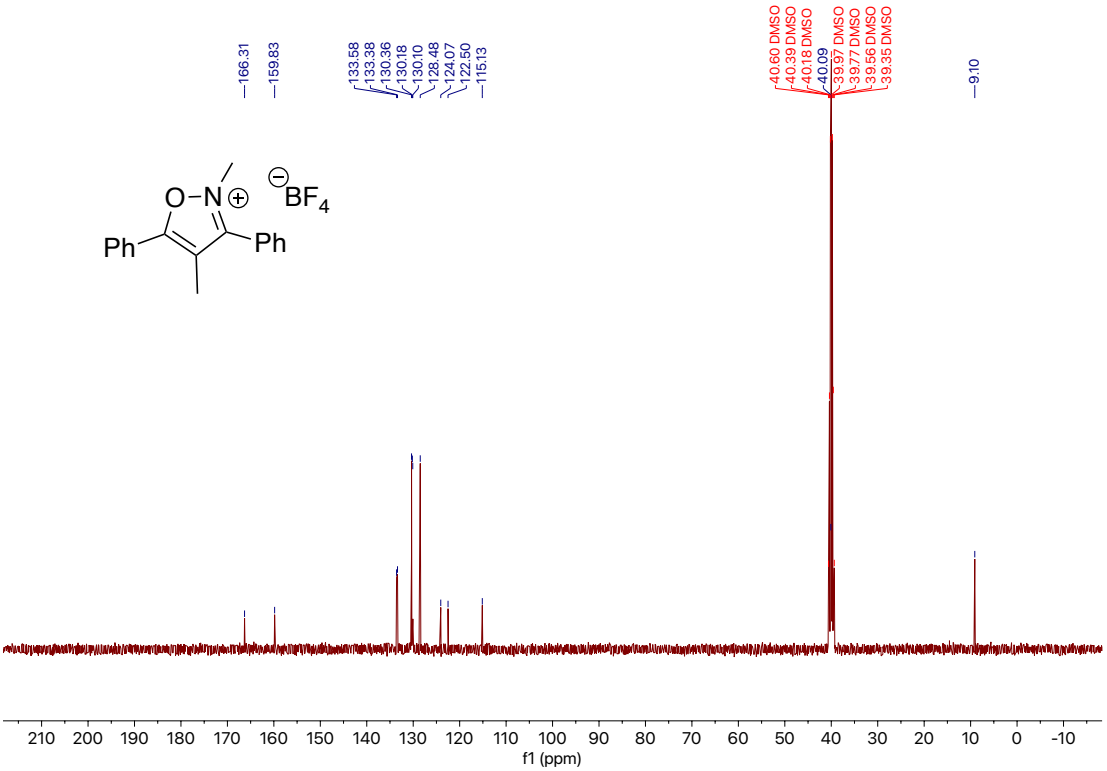
^{13}C NMR Spectrum of Compound S2 in $CDCl_3$



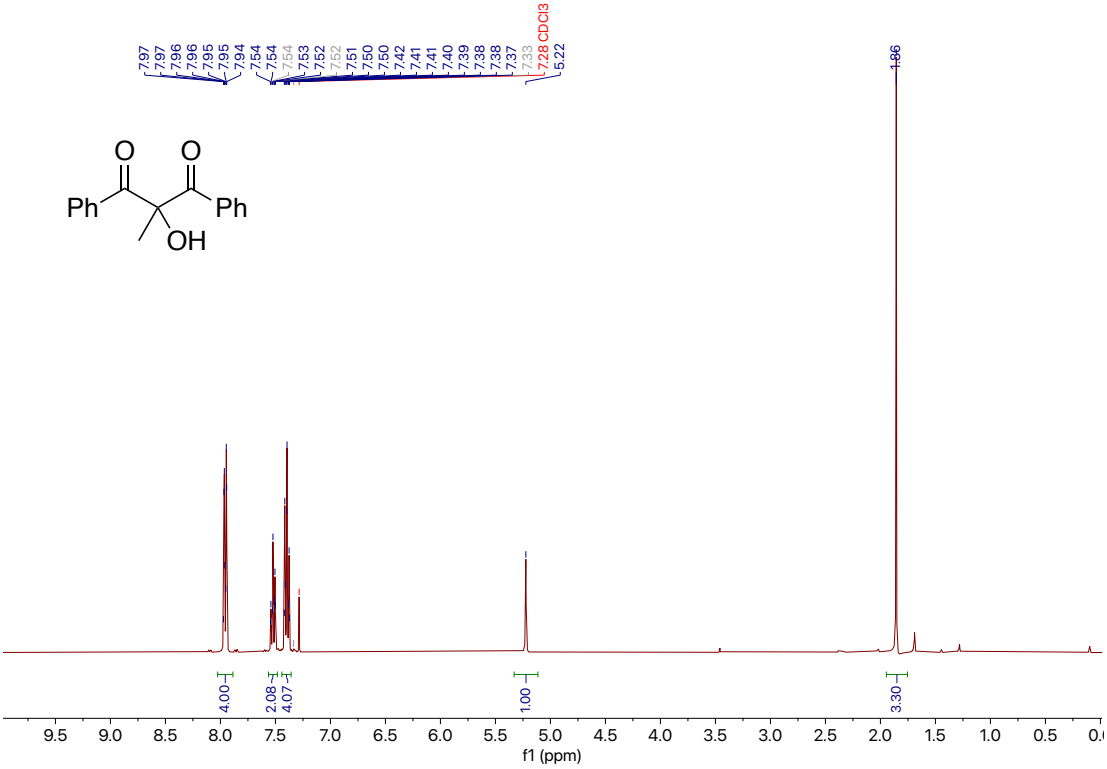
^{1}H NMR Spectrum of Compound S3 in DMSO-d_6



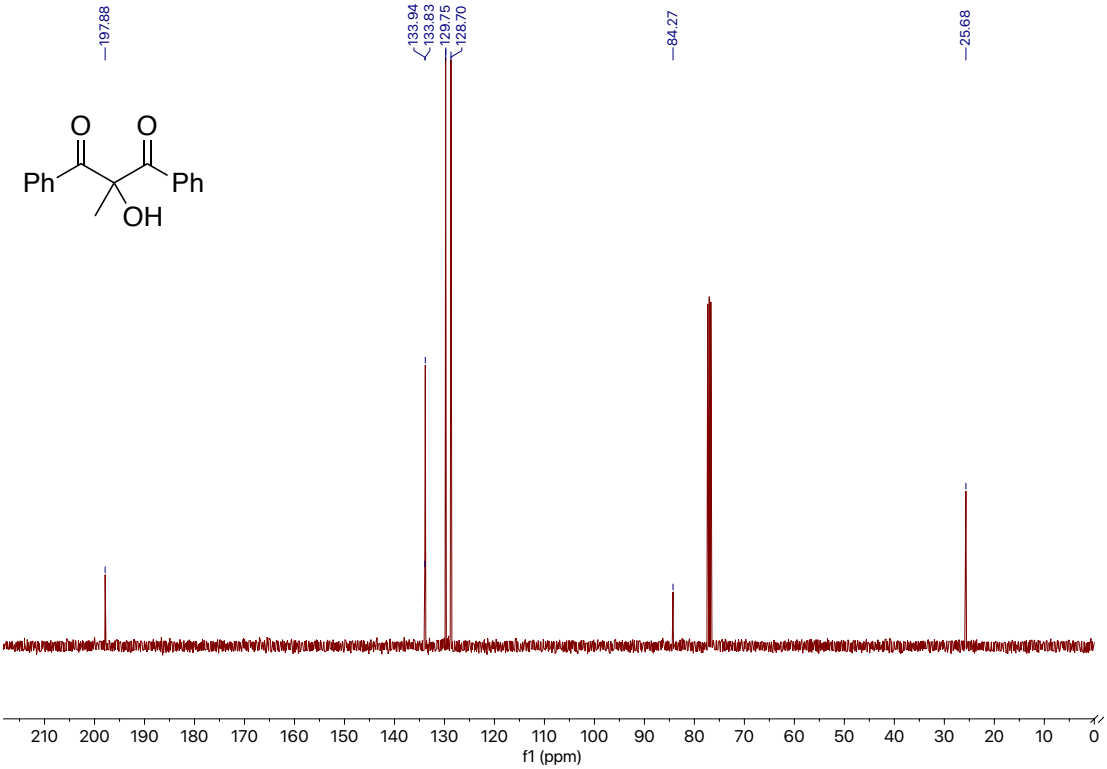
^{13}C NMR Spectrum of Compound S3 in DMSO-d_6



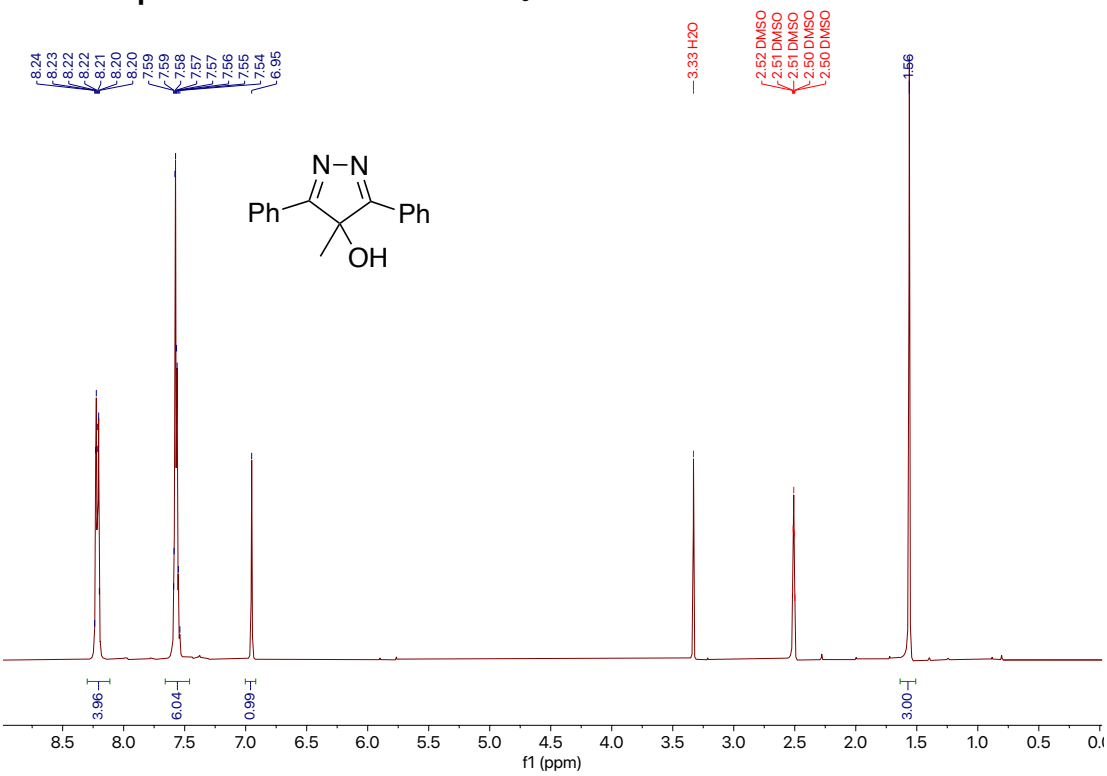
^{1}H NMR Spectrum of Compound S4 in $CDCl_3$



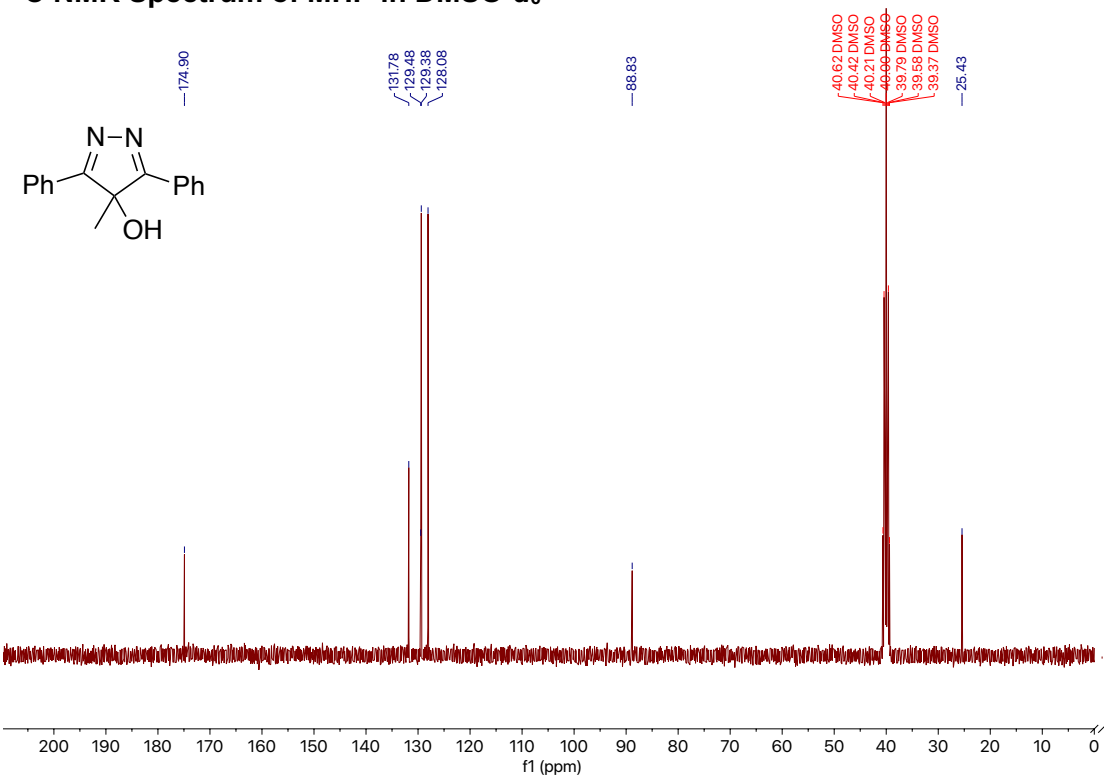
^{13}C NMR Spectrum of Compound S4 in $CDCl_3$



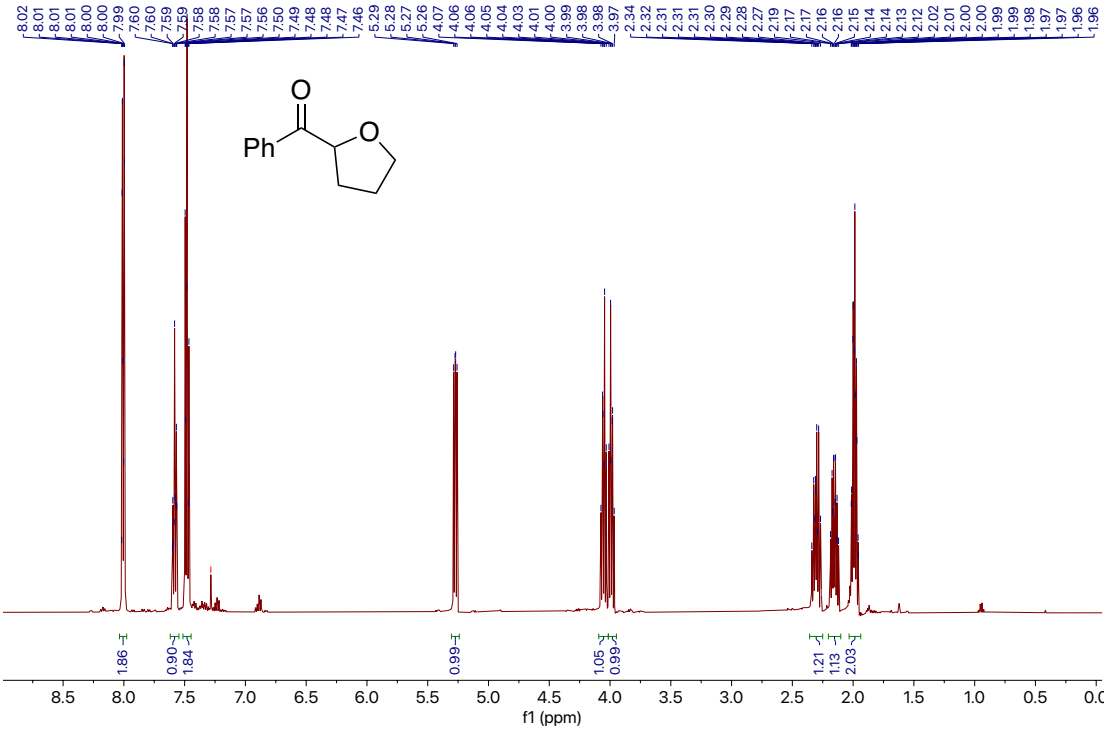
^{1}H NMR Spectrum of MHP in DMSO-d_6



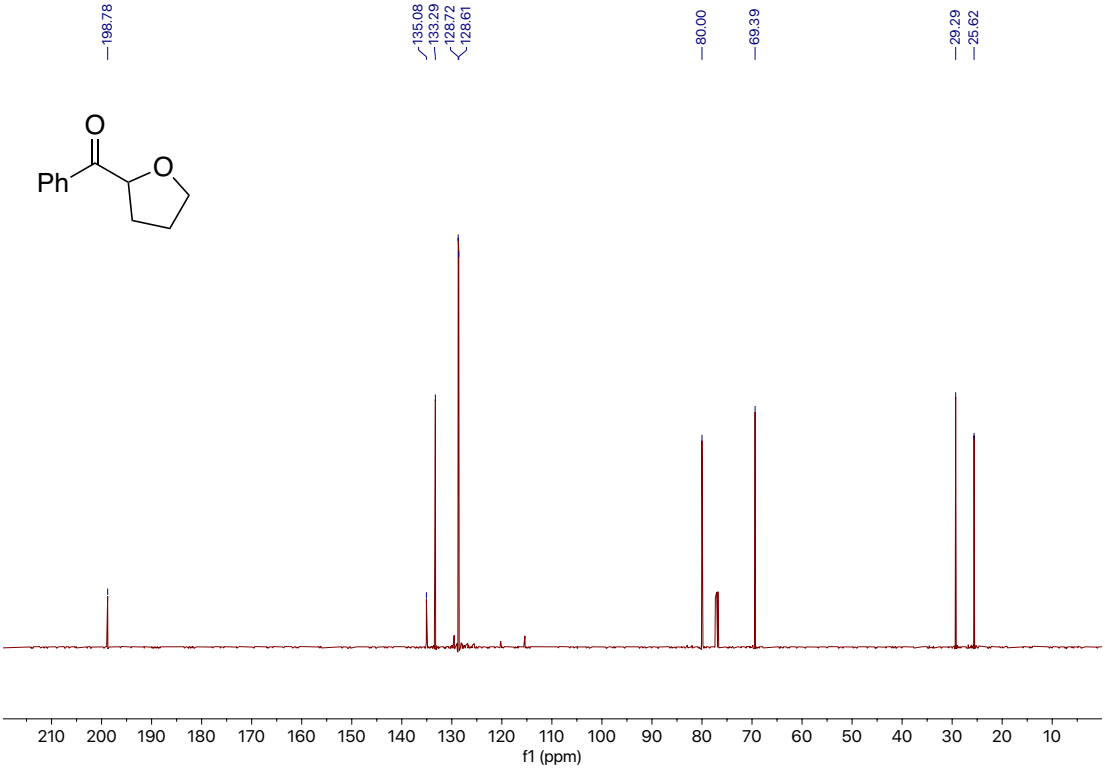
^{13}C NMR Spectrum of MHP in DMSO-d_6



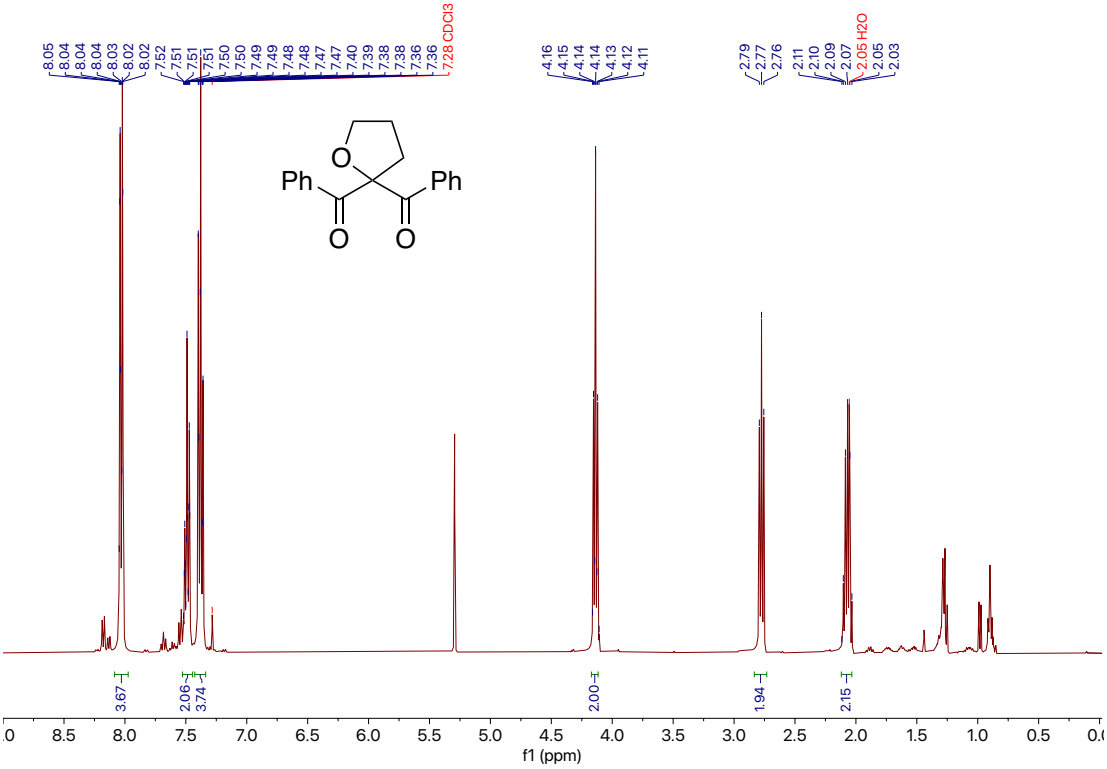
^{1}H NMR Spectrum of Compound S5 in $CDCl_3$



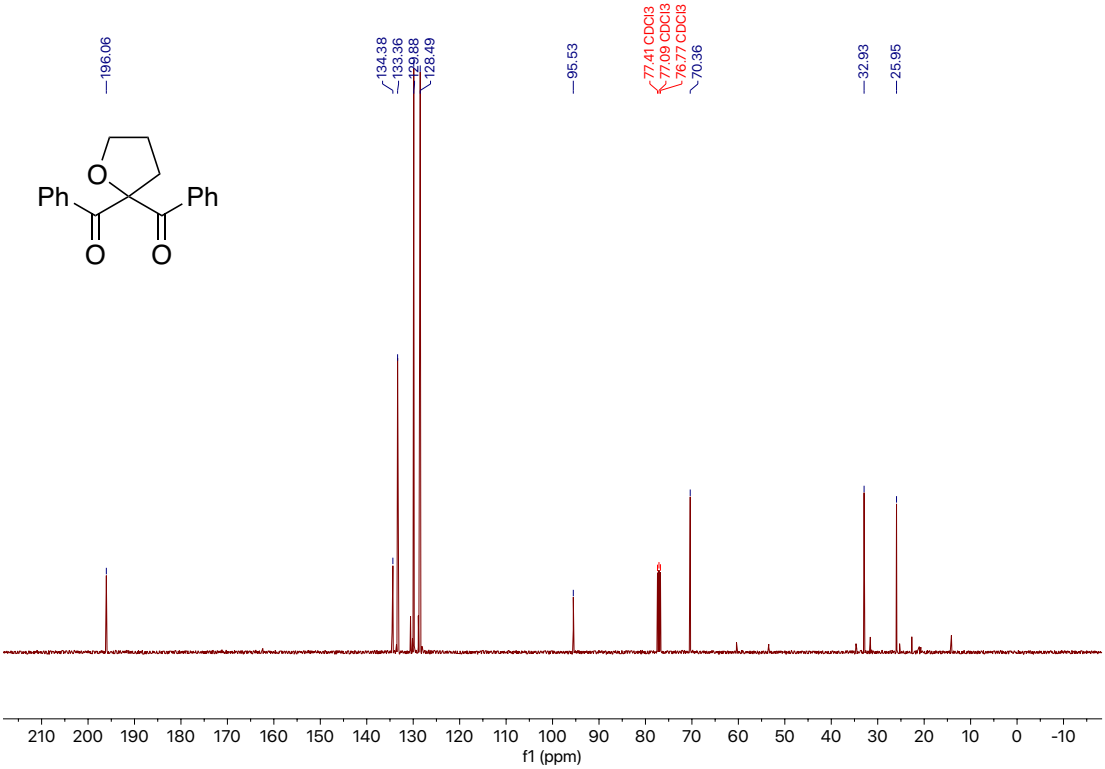
^{13}C NMR Spectrum of Compound S5 in $CDCl_3$



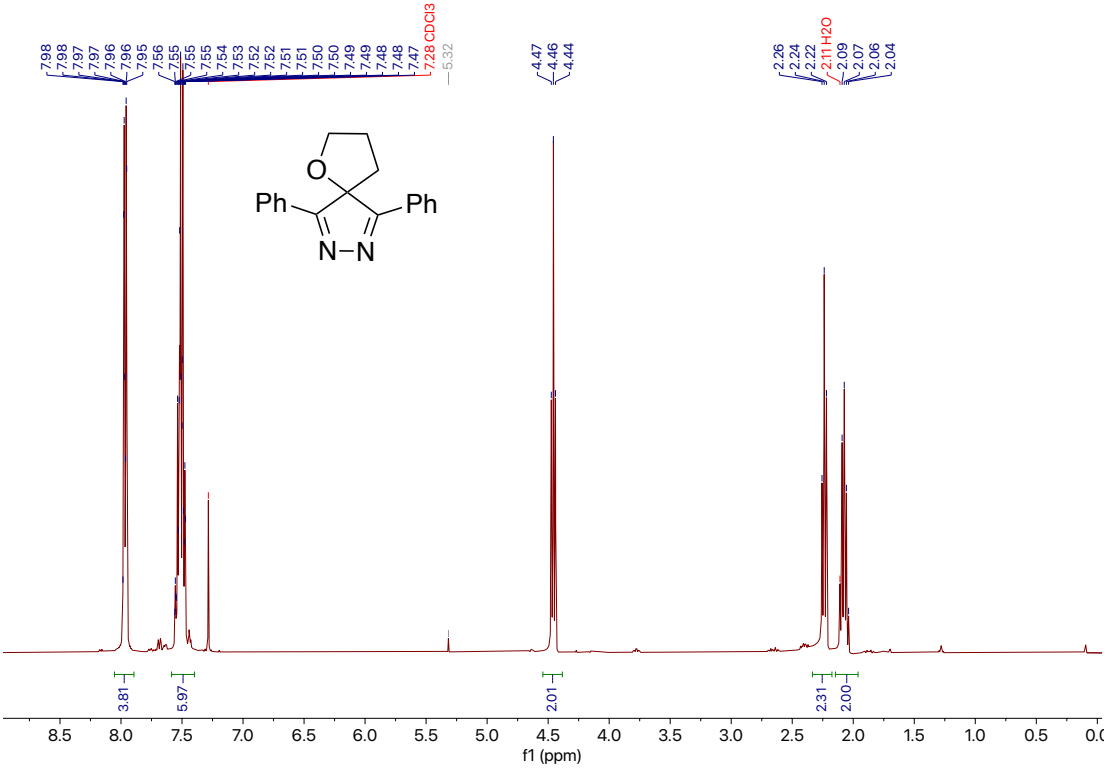
^{1}H NMR Spectrum of Compound S6 in $CDCl_3$



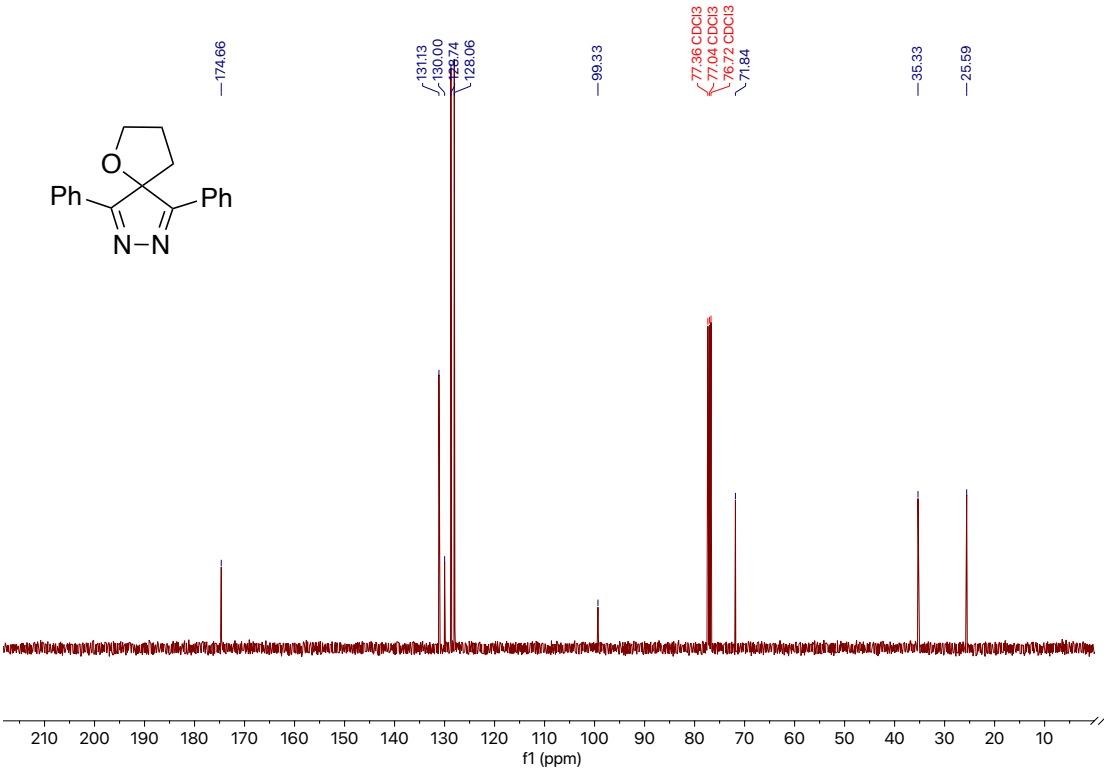
^{13}C NMR Spectrum of Compound S6 in $CDCl_3$



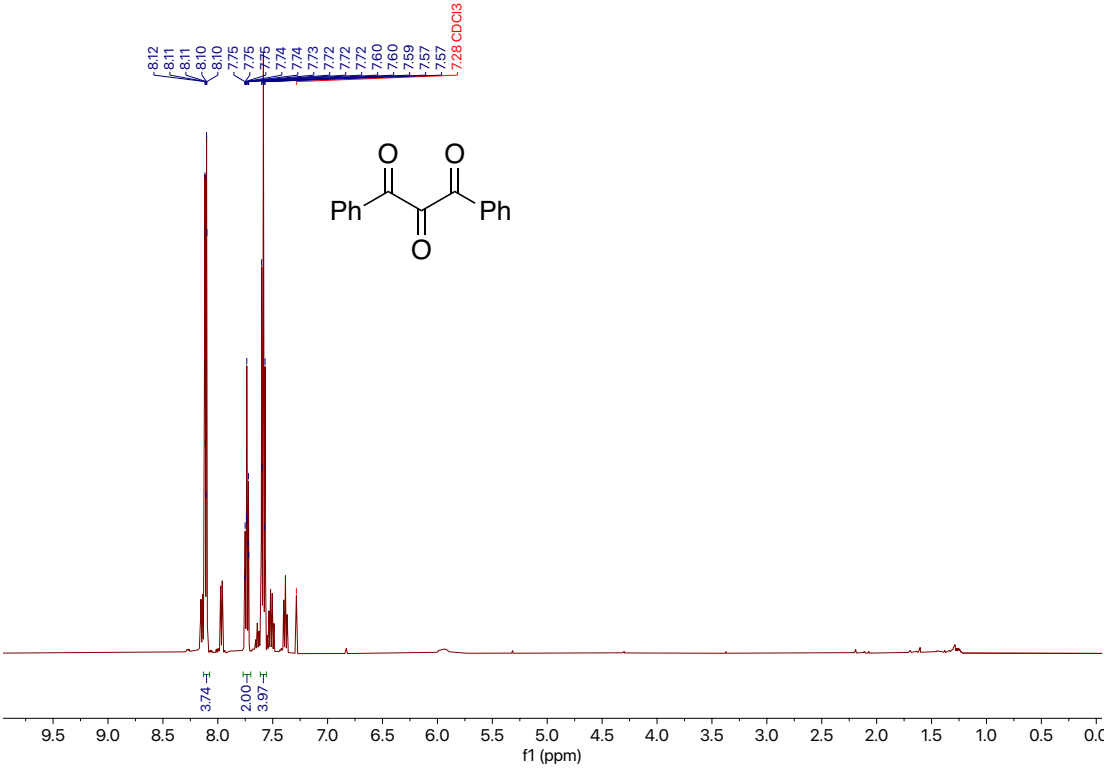
^{1}H NMR Spectrum of OSP in $CDCl_3$



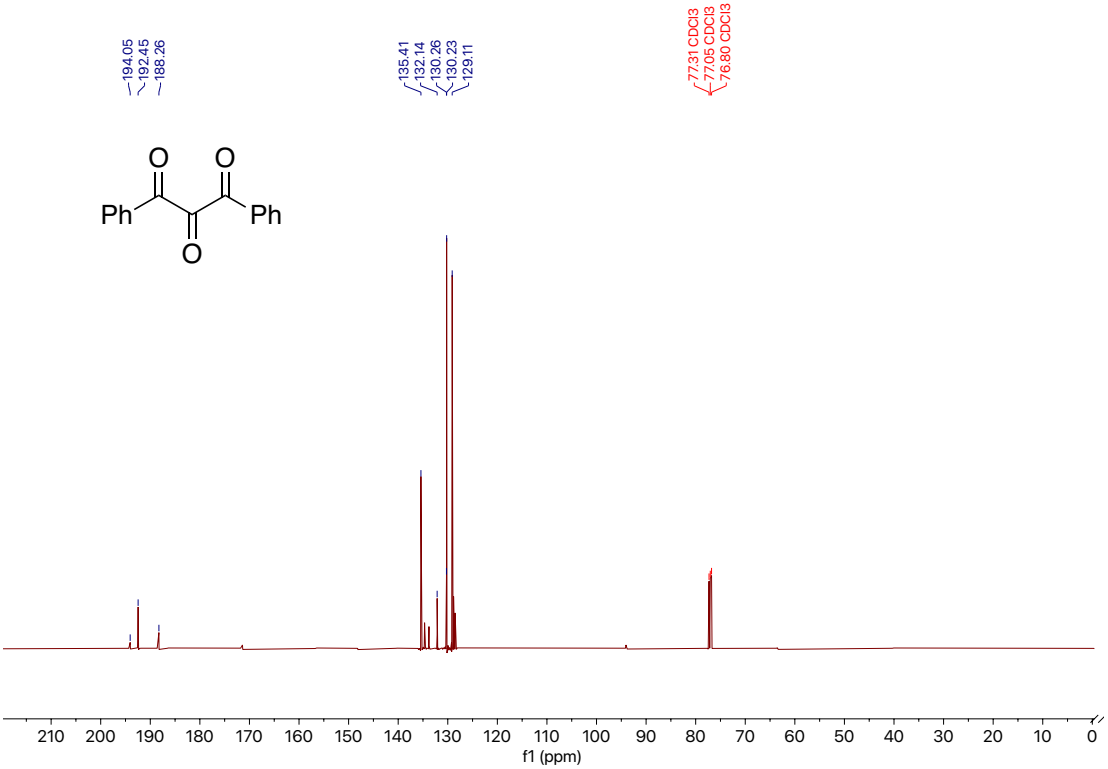
^{13}C NMR Spectrum of $CDCl_3$



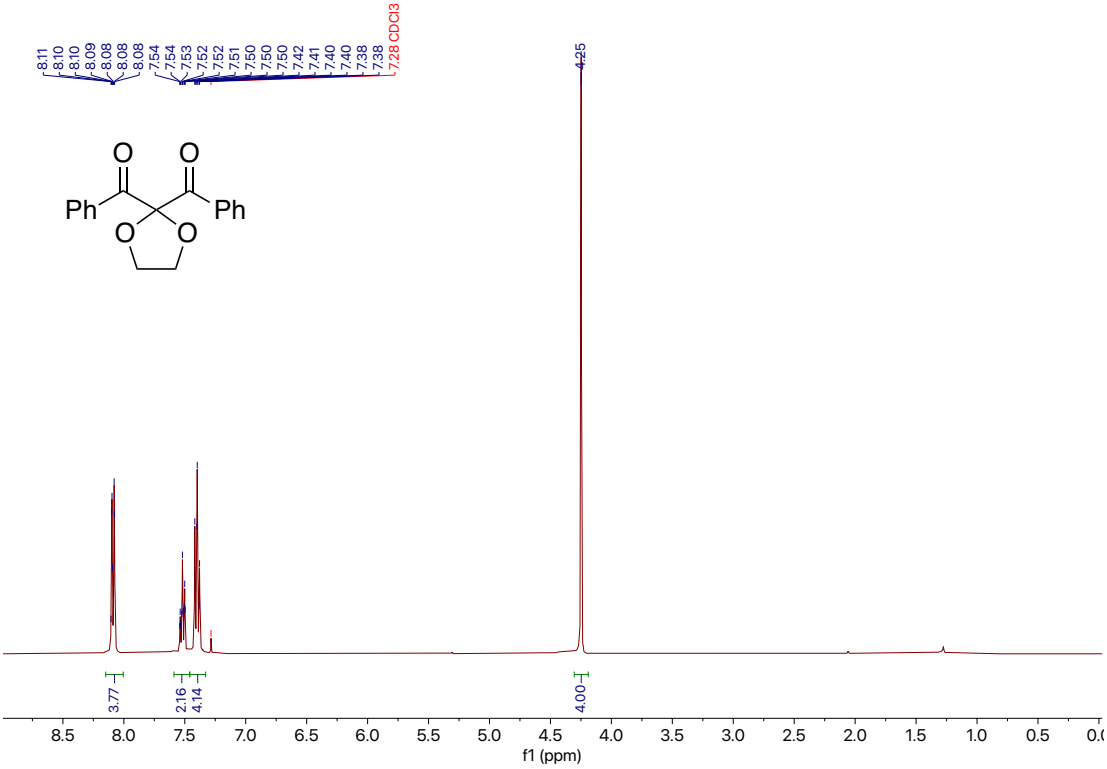
^{1}H NMR Spectrum of Compound S7 in $CDCl_3$



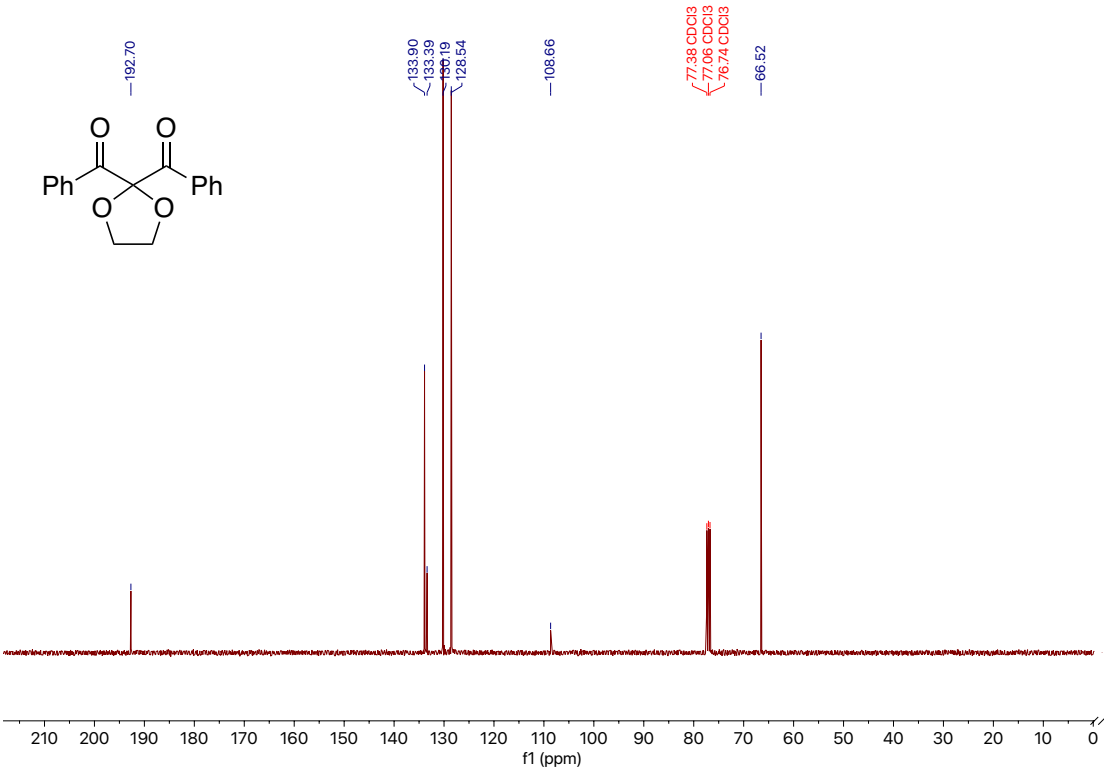
^{13}C NMR Spectrum of Compound S7 in $CDCl_3$



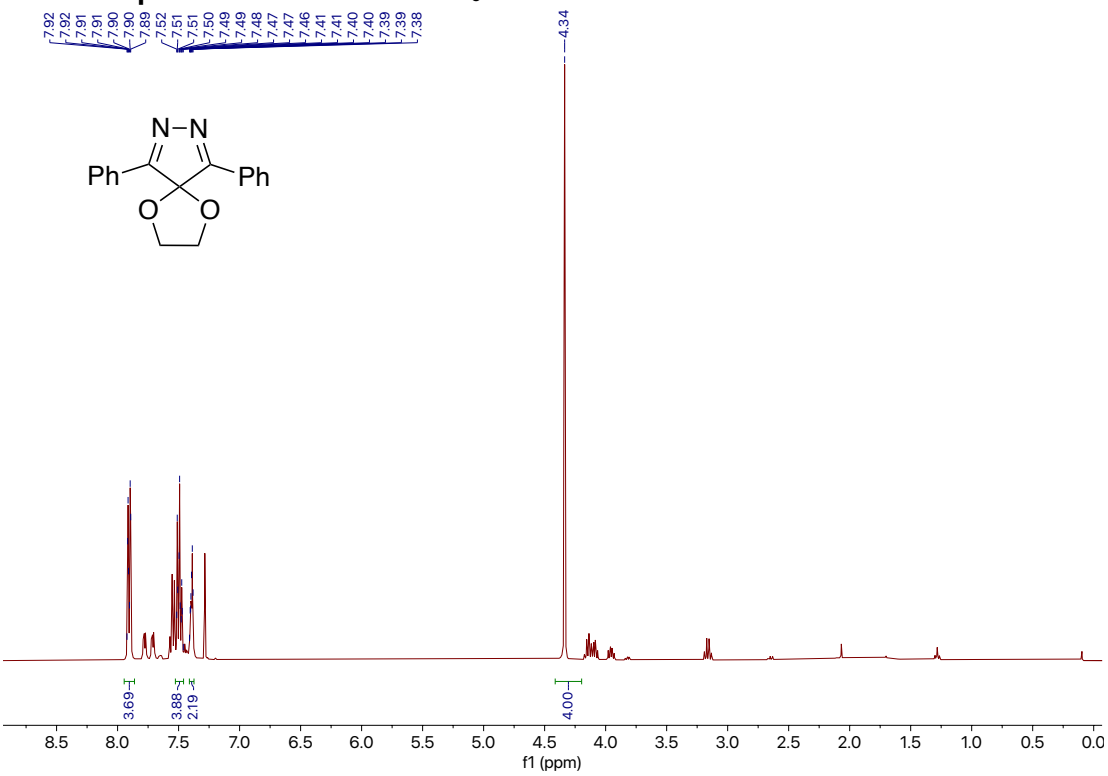
^{1}H NMR Spectrum of Compound S8 in $CDCl_3$



^{13}C NMR Spectrum of Compound S8 in $CDCl_3$



^{1}H NMR Spectrum of EKP in $CDCl_3$



^{13}C NMR Spectrum of EKP in $CDCl_3$