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SUPPLEMENTARY INFORMATION FOR:

Comparison of Free-Radical Inhibiting Antioxidant Properties of Carvedilol and its Phenolic Metabolites

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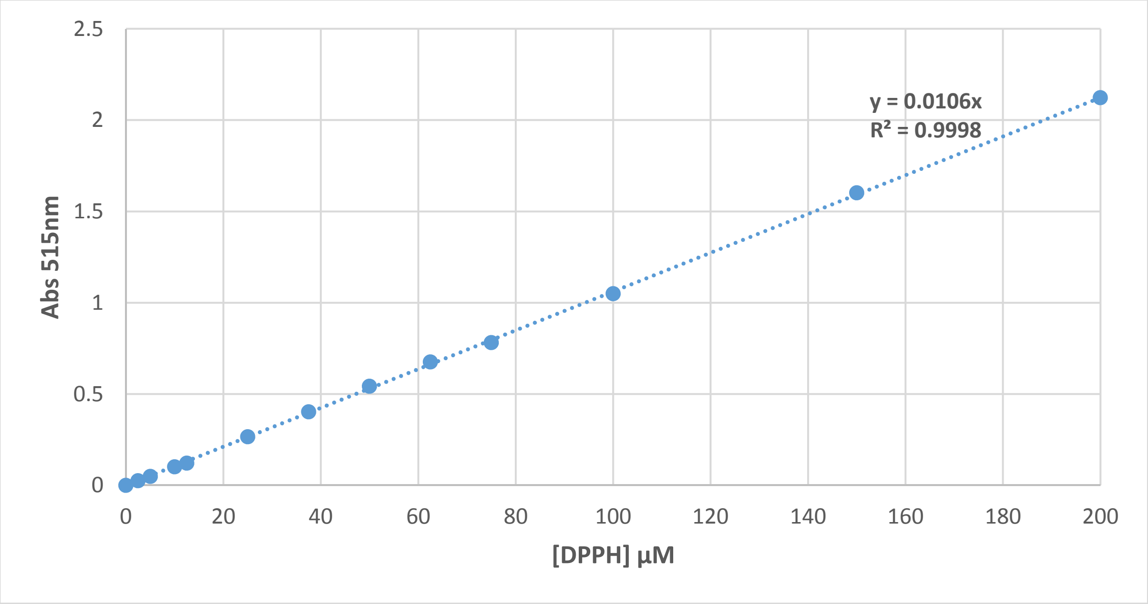


Figure S1. Calibration curve of absorbance of DPPH at 515 nm vs. concentration.

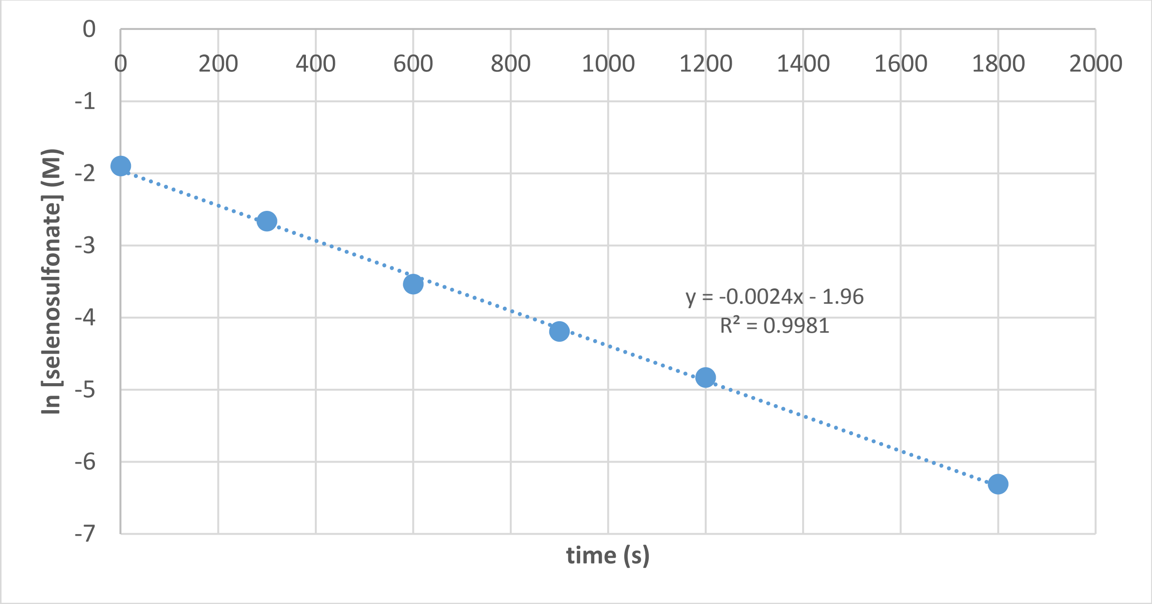


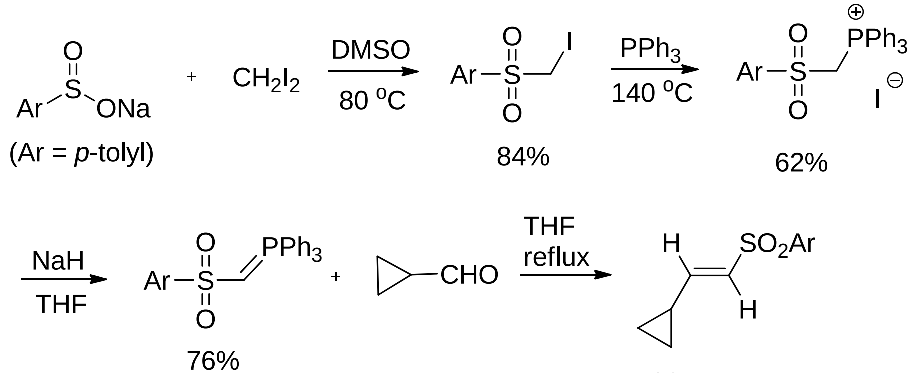
Figure S2. Kinetic plot for photolysis of Se-phenyl *p*-tolueneselenosulfonate (12) performed in the presence of cyclopropylacetylene and the absence of an antioxidant in $CDCl_3$.

Preparation of 1-{[(1E)-2-cyclopropyl-2-(phenylseleno)ethenyl]sulfonyl}-4-methylbenzene (14) and 1-methyl-4-{[5-(phenylseleno)-1,2-pentadien-1-yl]sulfonyl}benzene (16).

The products were obtained by a variation of our previous procedure.[1] Selenosulfonate **12** (468 mg, 1.50 mmol) and cyclopropylacetylene (99 mg, 1.5 mmol) in chloroform (10 mL) were irradiated with UV light (254 nm) for 4 h. The crude mixture was then subjected to flash chromatography using hexanes-ethyl acetate (4:1) as eluent to obtain **14** (363 mg, 64%) as a white solid; mp 113-114 ºC; IR (film) 1598, 1564, 1311, 1276, 1141, 1080, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (crude d, *J* = 8.3 Hz, 2 H), 7.50 – 7.34 (m, 5 H), 7.31 (crude d, *J* = 8.0 Hz, 2 H), 5.91 (d, *J* = 0.8 Hz, 1 H), 2.97 – 2.88 (m, 1 H), 2.46 (s, 3 H), 1.02 – 0.96 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 143.7, 139.7, 136.3, 130.1, 129.7, 129.6, 126.9, 125.9, 125.8, 21.6, 14.7, 9.3; HRMS (EI-TOF) *m/z* $[M]^+$ calcd for $C_{18}H_{18}O_2SSe$: 376.0201; found: 376.0213.

Further elution afforded **16** (40 mg, 7%) as a clear oil; IR (film) 1957, 1597, 1582, 1321, 1147, 1085, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (crude d, *J* = 8.3 Hz, 2 H), 7.52 – 7.48 (m, 2 H), 7.33 (crude d, *J* = 8.0 Hz, 2 H), 7.30 – 7.28 (m, 3 H), 6.24 (dt, *J* = 5.8, 2.9 Hz, 1 H), 5.92 (td, *J* = 6.1, 5.9 Hz, 1 H), 2.90 (crude t, *J* = 7.5 Hz, 2 H), 2.55 – 2.48 (m, 2 H), 2.46 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3, 144.5, 138.3, 133.1, 129.8, 129.3, 129.2, 127.7, 127.3, 102.2, 100.1, 28.5, 25.7, 21.6; HRMS (EI-TOF) *m/z* $[M]^+$ calcd for $C_{18}H_{18}O_2SSe$: 376.0201; found: 376.0212.

Preparation of vinyl sulfone 20.



20 32%
E:*Z* = 5:1

Diiodomethane (2.20 mL, 27.3 mmol) was added to a solution of sodium *p*-toluenesulfinate (5.00 g, 28.0 mmol) in DMSO (15 mL) and heated at 80 °C for 4 h. The orange solution was diluted with water (100 mL) and the product precipitated. The crude product was recrystallized from hot ethanol, washed with cold hexanes, and dried *in vacuo* to obtain iodomethyl *p*-tolyl sulfone (6.81 g, 84%) as white crystals; mp 129-130 °C (lit.[2] mp 124-125 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (crude d, J = 8.3 Hz, 2 H), 7.37 (crude d, J = 8.3 Hz, 2 H), 4.44 (s, 2 H), 2.46 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 133.1, 130.1, 129.1, 21.8, 17.1; HRMS (EI-TOF) *m/z* $[M]^+$ calcd for $C_8H_9O_2SI$: 295.9368; found: 295.9374.

The above sulfone (3.00 g, 10.1 mmol) and triphenylphosphine (2.66 g, 10.1 mmol) were heated at 140° C for 2 days. The resulting solid was dissolved in dichloromethane (25 mL) and precipitated by adding toluene (50 mL). The solid was washed with toluene and dried *in vacuo* to yield the corresponding phosphonium salt as a white solid (3.49 g, 62%); mp 240-244 °C (lit.[3] mp 236-238 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.86 (m, 8 H), 7.79 – 7.73 (m, 3 H), 7.67 – 7.60 (m, 6 H), 7.29 (d, J = 8.1 Hz, 2 H), 6.10 (d, J = 12.3 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 136.4, 135.5 (d, J = 3.2 Hz), 134.6 (d, J = 11.1 Hz), 130.2 (d, J = 13.5 Hz,), 130.2, 128.6, 116.6 (d, *J* = 89.1 Hz), 51.0 (d, *J* = 45.7 Hz), 21.8; HRMS (EI-TOF) *m/z* $[M]^+$ calcd for $C_{26}H_{24}O_2PS$: 431.1229; found: 431.1237.

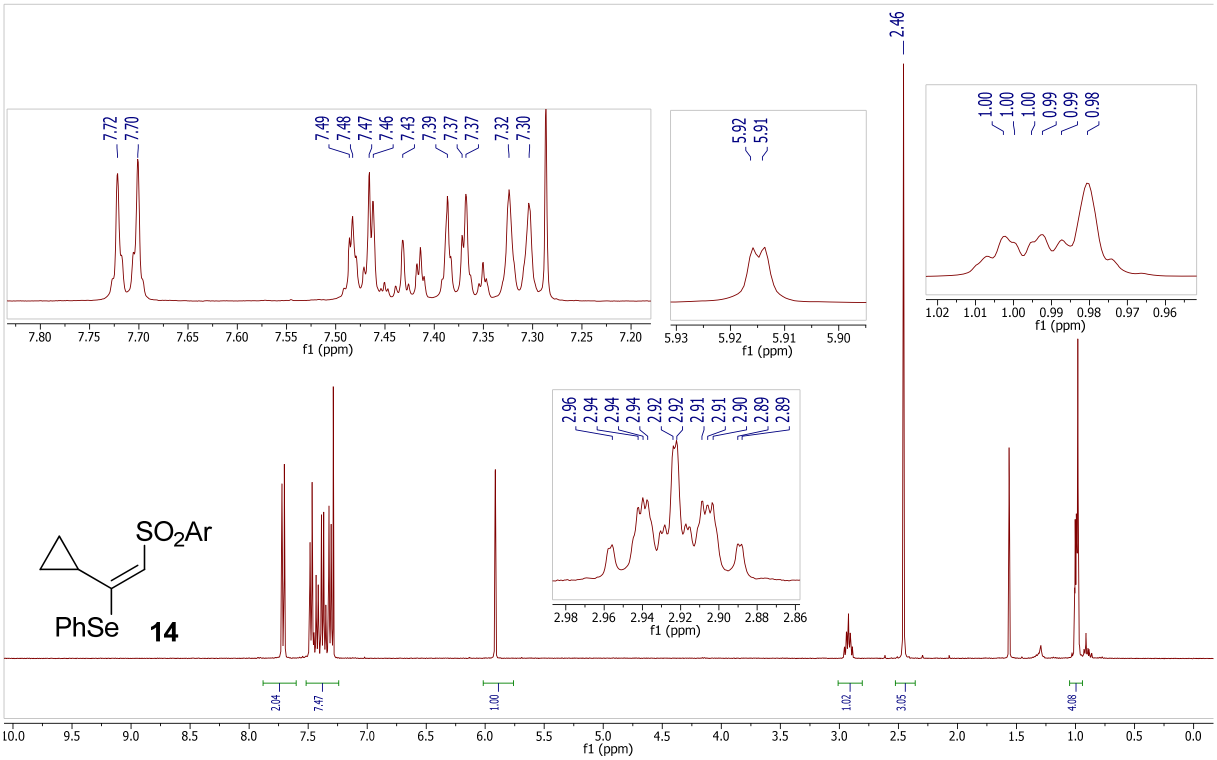
The above phosphonium salt (1.50 g, 2.70 mmol) and 60% sodium hydride in mineral oil (108 mg, 2.70 mmol) were added to THF (12 mL) and stirred for 16 h. The solvent was removed under reduced pressure and the residue was redissolved in dichloromethane and filtered through basic aluminum oxide. The solvent was removed under reduced pressure and the solid was recrystallized from toluene to obtain the corresponding Wittig reagent (882 mg, 76%) as a white solid; mp 181-184 °C (lit.[4] mp 186-187 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 6 H), 7.57 – 7.51 (m, 3 H), 7.46 – 7.39 (m, 6 H), 7.33 (crude d, *J* = 8.2 Hz, 2 H), 6.99 (crude d, *J* = 7.9 Hz, 2 H), 2.96 (d, *J* = 13.9 Hz, 1 H), 2.31 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 139.9, 133.4 (d, *J* = 10.4 Hz), 132.2 (d, *J* = 3.0 Hz), 128.8 (d, *J* = 12.5 Hz), 128.7, 127.3 (d, *J* = 93.2 Hz), 125.1, 34.4 (d, *J* = 123.4 Hz, C-6), 21.4 (C-1); HRMS (EI-TOF) *m/z* $[M]^+$ calcd for $C_{26}H_{23}O_2PS$: 430.1156; found: 430.1158.

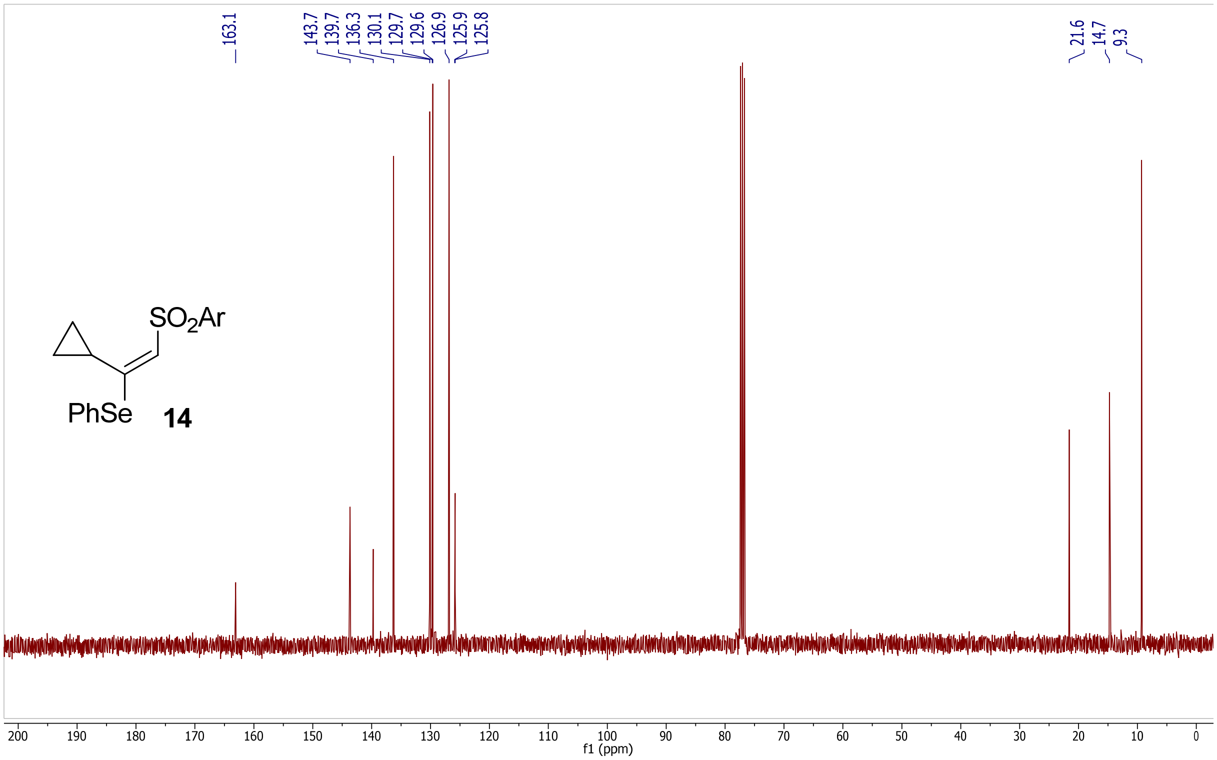
A solution of the above ylide (500 mg, 1.16 mmol) and cyclopropanecarboxaldehyde (105 mg, 1.50 mmol) in THF (5 mL) was refluxed for 12 h. The mixture was concentrated *in vacuo* and subjected to flash chromatography using hexanes-ethyl acetate (4:1) to afford **20** as an inseparable mixture of E/Z isomers (84 mg, 32%) as a white solid; mp 78-84 °C; IR (film) 1621, 1590, 1315, 1301, 1281, 1145 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *E* isomer: δ 7.77 (crude d, *J* = 8.3 Hz, 2 H), 7.34 (crude d, *J* = 8.3 Hz, 2 H), 6.41 (dd, *J* = 14.8, 9.3 Hz, 1 H), 6.35 (d, *J* = 14.8 Hz, 1 H), 2.45 (s, 3 H), 1.62 – 1.53 (m, 1 H), 1.03 – 0.98 (m, 2 H), 0.73 – 0.69 (m, 2 H); *Z* isomer: 7.84 (crude d, *J* = 8.3 Hz, 2 H), 7.36 (crude d, J = 8.3 Hz, 2 H), 6.17 (d, *J* = 11.0 Hz, 1 H), 5.48 (t, *J* = 11.1 Hz, 2.85 – 2.76 (m, 1 H), 2.46 (s, 3 H), 1.10 – 1.04 (m, 2 H), 0.61 – 0.57 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) both isomers δ 151.5, 151.3, 143.9, 139.3, 138.3, 129.79, 129.77, 127.6, 127.5, 127.2, 127.1, 21.58, 21.56, 13.9, 10.8, 9.4, 9.0; HRMS (EI-TOF) *m/z* $[M]^+$ calcd for $C_{12}H_{14}O_2S$: 222.0715; found: 222.0713.

References

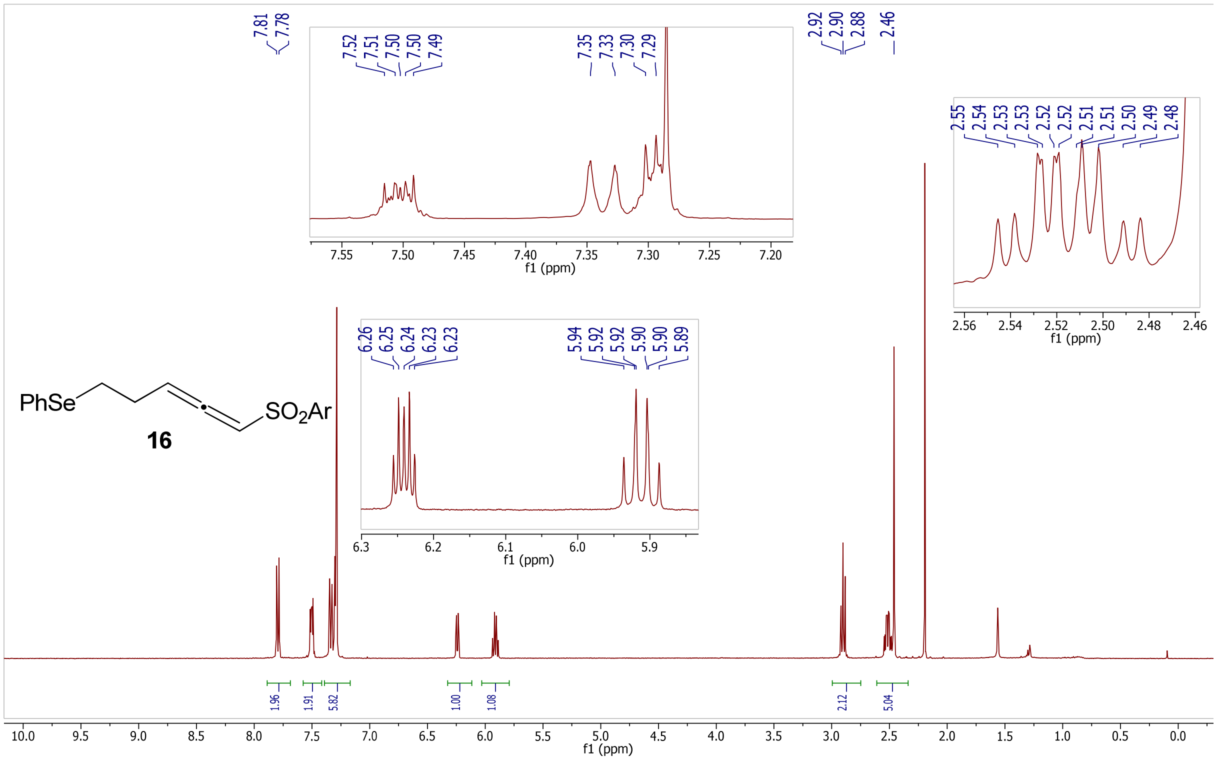
1. T. G. Back and K. R. Muralidharan, *J. Org. Chem.*, 1989, **54**, 121-125.
2. J. K. Crandall and C. Pradat, *J. Org. Chem.*, 1985, **50**, 1327-1329.
3. J. Vicente, A. R. Singhal and P. G. Jones, *Organomet.*, 2002, **21**, 5887-5900.
4. A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, 1965, **87**, 5603-5606.

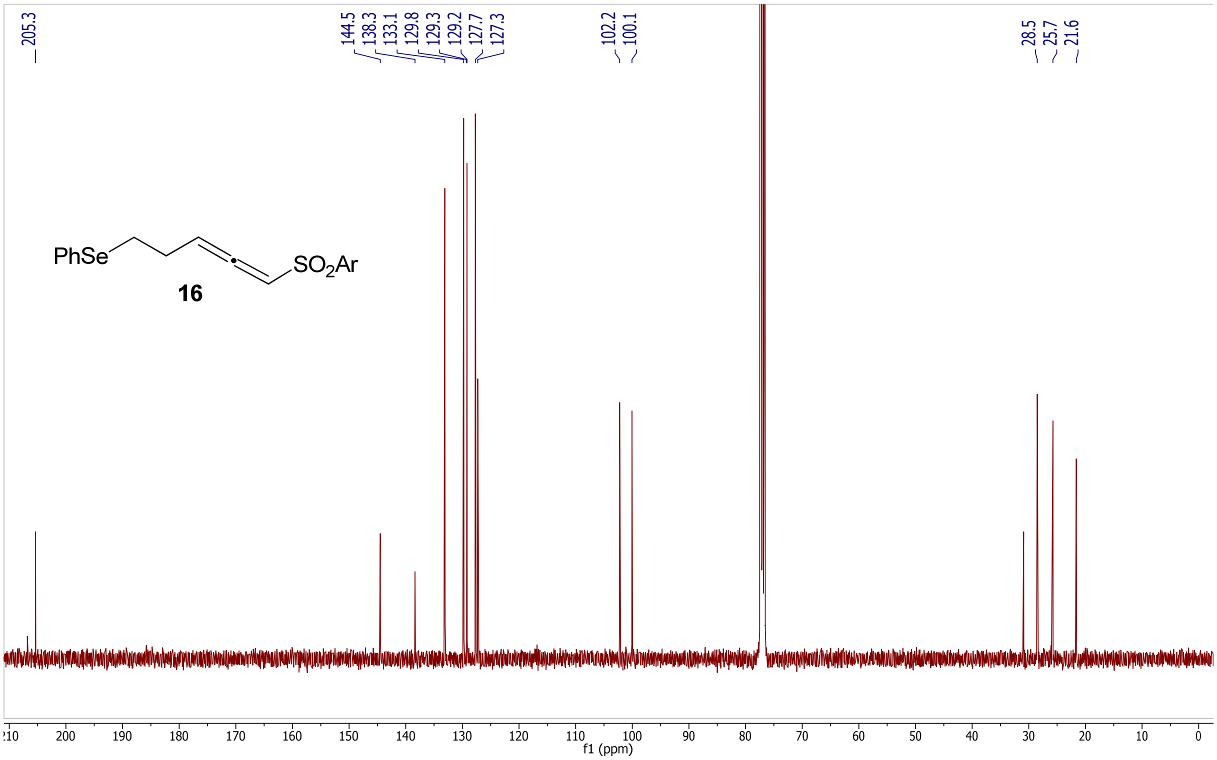
^{1}H and ^{13}C NMR Spectra of 1,2-Addition Product **14** (400 MHz, CDCl$_3$)





^{1}H and ^{13}C NMR Spectra of Allene **16** (400 MHz, CDCl$_3$)





^{1}H and ^{13}C NMR Spectra of (*E*/*Z*)-Vinyl Sulfone **20** (400 MHz, $CDCl_3$)