Micelle-enabled Bromination of α-Oxo Ketene Dithioacetals: Mild and Scalable Approach via Enzymatic Catalysis

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Electronic Supplementary Information

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Experimental Section

Materials and methods

All chemicals and solvents were obtained from commercially available suppliers such as Sigma-Aldrich and TCI (Japan) and were used without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed with precoated Merck silica gel 60 F254 plates (0.25 mm for thick layer) and visualized at 254 nm using an ultraviolet lamp. Column chromatography was performed with Silicycle silica gel 60-200 μm (70-230 mesh). ^{1}H- and ^{13}C-NMR spectra were obtained with JEOL JNM-ECZ500R/S1 NMR spectrometers operating at 500 MHz for ^{1}H or 125 MHz for ^{13}C nuclei. High-resolution electrospray ionization mass spectrometry (HR-ESIMS) was performed by using an ESI QTOF 6540 Agilent Tecnologies.

Protein overexpression and purification

Ten milliliters of an overnight culture of *E. coli* BL21(DE3) containing the overexpression plasmid pET30-*Ci*VCPO were inoculated into 1 liter of Luria-Bertani (LB) broth containing a final concentration of 50 μg/mL kanamycin. The culture was incubated at 37 °C with shaking at 200 rpm until the OD600 reached approximately 0.6. The protein overexpression was induced by adding isopropyl-*β*-D-1-thiogalactopyranoside (IPTG) to a final concentration of 200 μM. The protein was overexpressed as a fusion protein with an *N*-terminal His tag. The culture was then incubated at 20 °C with shaking at 200 rpm for an additional 16 h. The cells were harvested by centrifugation at 5000 rpm at 8 °C for 25 min. The pellet was resuspended in lysis buffer (300 mM NaCl, 50 mM Na_2HPO_4, and 10 mM imidazole, pH 8.0). The cells in the ice bath were lysed by sonication (1.5 s cycle, 50 % duty) for 30 seconds three times. The lysate was clarified by centrifugation at 12,000 rpm and 4 °C for 40 min. The supernatant was applied to a Ni-NTA column (QIAGEN), and the protein were purified according to the manufacturer's instructions. The purified protein was incubated with two equivalents of Na_3VO_4. Finally, the protein was desalted using a 10-DG column (BioRad) pre-equilibrated with the desalting buffer (100 mM potassium phosphate buffer, 20% glycerol, pH 7.5). The purified proteins were aliquoted and stored at -80 ºC.

Amino acid sequence of *Ci*VCPO (The His-tag sequence is underlined.):

<u>MSSHHHHHHSSGENLYFQGGG</u>MGSVTPIPLPKIDEPEEYNTNYILFWNHVGLELNRV
THTVGGPLTGPPLSARALGMLHLAIHDAYFSICPPTDFTTFLSPDTENAAYRLPSPNG
ANDARQAVAGAALKMLSSLYMKPVEQPNPNPGANISDNAYAQLGLVLDRSVLEAP
GGVDRESASFMFGEDVADVFFALLNDPRGASQEGYHPTPGRYKFDDEPTHPVVLIPV
DPNNPNGPKMPFRQYHAPFYGKTTKRFATQSEHFVADPPGLRSNADETAEYDDAVR
VAIAMGGAQALNSTKRSPWQTAQGLYWAYDGSNLIGTPPRFYNQIVRRIAVTYKKE
EDLANSEVNNADFARLFALVDVACADAGIFSWKEKWEFEFWRPLSGVRDDGRPDH
GDPFWLTLGAPATNTNDIPFKDPFPAYPSGHATFGGAVFQMVRRYYNGRVGTWKD
DEPDNIAIDMMISEELNGVNRDLRQPYDPTAPIEDQPGIVRTRIVRHFDSAWELMFEN
AISRIFLGVHWRFDAAAARDILIPTTTKDVYAVDNNGATVFQNVEDIRYTTRGTRED
PEGLFPIGGVPLGIEIADEIFNNGLKPTPPEIQPMPQETPVQKPVGQQPVKGMWEEEQ
APVVKEAP

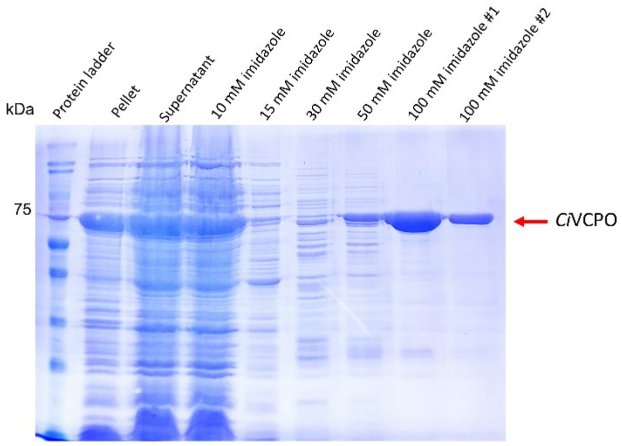


Figure S1. 10% SDS-PAGE analysis of *Ci*VCPO purification.

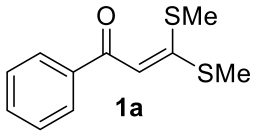
Starting materials preparation

General procedure for synthesis of α-oxo ketene dithioacetals 1a-1t (General Procedure A)

The synthesis of compounds **1a-1t** followed the previous report with some modifications[1]. To a stirred suspension of freshly prepared potassium *tert*-butoxide (3.4 eq.) in dry THF (3.5 mL) at 0 °C, a solution of aryl ketones (1.0 eq.) and carbon disulfide (1.5 eq.) in dry THF (5 mL) was added, and the mixture was vigorously stirred at 0 °C for 120 min. The color of the reaction was changed to reddish after the addition of aryl ketone and carbon disulfide indicating the formation of disodium salt of 1-aryl-3,3-bissulfanyl-2-propen-1-ones. To this suspension, a solution of methyl iodide (2.4 eq.) in dry THF (2.5 mL) was added, and the reaction mixture was stirred at 0 °C for 120 min. After completion of the reaction, the mixture was transferred into a 100 mL beaker containing 50 g of crushed ice, and the resulting solution was continually stirred. A light yellow colored solid formed, filtered, and washed with water (20 mL × 3). The crude solid was recrystallized from 5% DCM in EtOH.

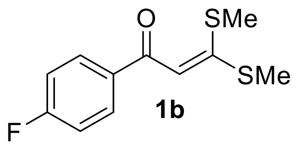
General procedure for synthesis of α-oxo ketene dithioacetals 1u-1w (General Procedure B)

The synthesis of compounds **1u-1w** followed the previous report with some modifications[1]. To a stirred suspension of freshly prepared potassium *tert*-butoxide (3.4 eq.) in dry THF (3.5 mL) at 0 °C, a solution of ketone (1.0 eq.) and carbon disulfide (1.5 eq.) in dry THF (5 mL) was added, and the mixture was vigorously stirred at 0 °C for 120 min. The color of the reaction was changed to reddish after the addition of ketone and carbon disulfide indicated the formation of disodium salt of 1-aryl-3,3-bissulfanyl-2-propen-1-ones. To this suspension, a solution of methyl iodide or ethyl bromide or 1,3-dibromopropane (2.4 eq.) in dry THF (2.5 mL) was added, and the reaction mixture continued to stir at 0 °C to room temperature (28-32 °C) overnight. After completion of the reaction, the mixture was transferred into a 100 mL beaker containing 50 g of crushed ice, and the resulting solution was continually stirred. Then, the solution was extracted with EtOAc (50 mL x 3), evaporated the solvent, and performed column chromatography (H:EA 9:1, v/v) to obtain the desired products.



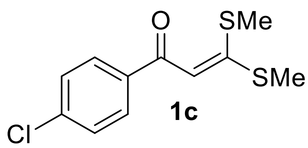
1a

3,3-bis(methylthio)-1-phenylprop-2-en-1-one (**1a**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), acetophenone (540.7 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1a** (735.8 mg, 73%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.92-7.91 (m, 2H), 7.50-7.48 (m, 1H), 7.45-7.42 (m, 2H), 6.77 (s, 1H), 2.56 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 185.8, 166.6, 139.5, 131.9, 128.6, 127.9, 109.6, 17.5, 15.2.



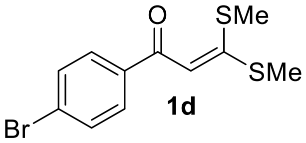
1b

1-(4-fluorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**1b**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-fluoroacetophenone (621.6 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1b** (764.1 mg, 70%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.94-7.90 (m, 2H), 7.12-7.07 (m, 2H), 6.70 (s, 1H), 2.56 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.3, 167.2, 166.0, 164.0, 135.7, 130.3, 130.2, 115.7, 115.5, 109.0, 17.5, 15.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ -107.5.



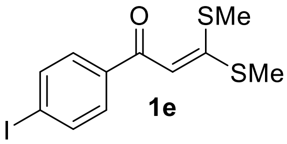
1c

1-(4-chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**1c**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-chloroacetophenone (695.7 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1c** (923.0 mg, 79%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (d, J = 8.6, 2H), 7.39 (d, J = 8.6, 2H), 6.69 (s, 1H), 2.55 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.3, 167.7, 138.1, 137.7, 129.2, 128.8, 108.9, 17.5, 15.2.



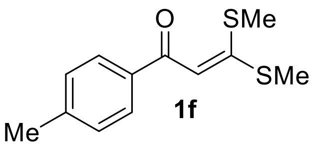
1d

1-(4-bromophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**1d**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-bromoacetophenone (895.7 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1d** (703.4 mg, 52%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.77 (d, J = 8.6, 2H), 7.56 (d, J = 8.3, 2H), 6.88 (s, 1H), 2.56 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.5, 167.9, 138.2, 131.8, 129.4, 126.7, 108.8, 17.5, 15.2.



1e

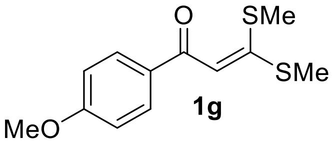
1-(4-iodophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**1e**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-iodoacetophenone (1107.2 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1e** (815.0 mg, 52%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 (d, J = 8.6, 2H), 7.62 (d, J = 8.6, 2H), 6.67 (s, 1H), 2.55 (s, 3H), 2.52 (s, 3H) .^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.7, 167.9, 138.8, 137.8, 129.4, 108.8, 99.3, 17.5, 15.2.



1f

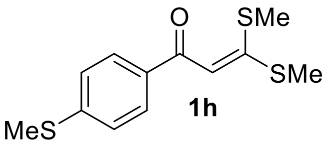
3,3-bis(methylthio)-1-(p-tolyl)prop-2-en-1-one (**1f**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-methylacetophenone

(603.8 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1f** (728.6 mg, 68%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.82 (d, J = 8.3, 2H), 7.23 (d, J = 8.6, 2H), 6.75 (s, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.39 (s, 3H) .^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 185.6, 165.8, 142.5, 136.8, 129.3, 128.0, 109.6, 21.7, 17.5, 15.2.



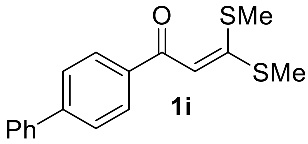
1g

1-(4-methoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (1g) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-methoxylacetophenone (675.8 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1g** (276.5 mg, 24%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.91 (d, J = 9.1, 2H), 6.92 (d, J = 8.9, 2H), 6.74 (s, 1H), 3.85 (s, 3H), 2.55 (s, 3H), 2.51 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.7, 165.1, 162.6, 132.2, 130.0, 113.8, 109.5, 55.5, 17.4, 15.2.



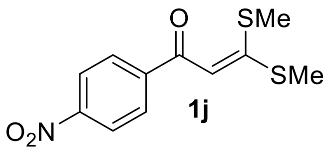
1h

3,3-bis(methylthio)-1-(4-(methylthio)phenyl)prop-2-en-1-one (1h) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(4-(methylthio)phenyl)ethan-1-one (485.0 mg, 2.9 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1h** (628.5 mg, 80%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (d, J = 8.6, 2H), 7.25 (d, J = 8.6, 2H), 6.73 (s, 1H), 2.55 (s, 3H), 2.52 (s, 3H), 2.50 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.8, 166.2, 144.1, 135.7, 128.3, 125.2, 109.3, 17.5, 15.2, 15.0.



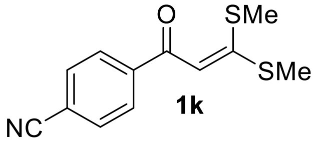
1i

1-([1,1'-biphenyl]-4-yl)-3,3-bis(methylthio)prop-2-en-1-one (**1i**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-([1,1'-biphenyl]-4-yl)ethan-1-one (883.1 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1i** (955.2 mg, 71%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.99 (d, J = 8.6, 2H), 7.67 (d, J = 8.6, 2H), 7.63 (d, J = 8.6, 2H), 7.46 (t, J = 7.2, 2H), 7.38 (t, J = 7.5, 1H), 6.81 (s, 1H), 2.58 (s, 3H), 2.54 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 185.3, 166.6, 144.5, 140.2, 138.2, 129.0, 128.4, 128.1, 127.3 (x2), 109.5, 17.5, 15.2.



1j

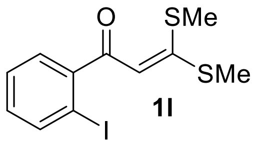
3,3-bis(methylthio)-1-(4-nitrophenyl)prop-2-en-1-one (**1j**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-nitroacetophenone (743.2 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1j** (635.7 mg, 53%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.28 (d, J = 8.9, 2H), 8.03 (d, J = 8.9, 2H), 6,71 (s, 1H), 2.6 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 183.4, 170.7, 149.5, 144.6, 128.7, 123.8, 108.5, 17.6, 15.3.



1k

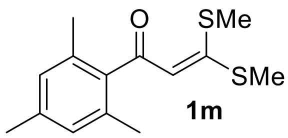
4-(3,3-bis(methylthio)acryloyl)benzonitrile (**1k**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 4-acetylbenzonitrile (653.0 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1k** (249 mg, 74%) as yellow solid: ^{1}H NMR (500 MHz, DMSO) δ ppm 8.1 (d,

J = 8.6, 2H), 7.97 (d, J = 8.3, 2H), 6.87 (s, 1H), 2.68 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, DMSO): δ ppm 182.8, 169.0, 142.3, 132.7, 128.4, 118.4, 114.0, 108.9, 16.9, 14.5.



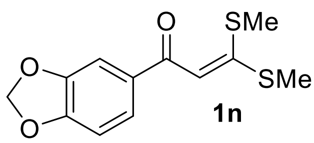
1l

1-(2-iodophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**1l**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(2-iodophenyl)ethan-1-one (1107.2 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1l** (921.1 mg, 58%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.87 (d, J = 8.9, 1H), 7.41-7.38 (m, 2H), 7.09-7.06 (m, 1H), 6.37 (s, 1H), 2.54 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 189.0, 167.3, 146.4, 140.1, 131.0, 128.7, 128.2, 112.2, 92.4, 17.4 15.1.



1m

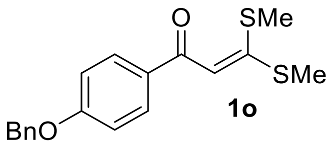
1-mesityl-3,3-bis(methylthio)prop-2-en-1-one (**1m**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-mesitylethan-1-one (730.0 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1m** (533.1 mg, 45%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.84 (s, 2H), 6.15 (s, 1H), 2.53 (s, 3H), 2.40 (s, 3H), 2.28 (s, 3H), 2.23 (s, 6H) .^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 193.2, 165.1, 140.3, 138.1, 133.8, 128.5, 114.3, 21.2, 19.6, 17.4 15.0.



1n

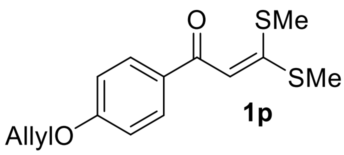
1-(benzo[d][1,3]dioxol-5-yl)-3,3-bis(methylthio)prop-2-en-1-one (**1n**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(benzo[d][1,3]dioxol-5-yl)ethan-1-one (738.7 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5

mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1n** (827.1 mg, 66%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.48 (dd, J = 8.0, 1.7, 1H), 7.42 (d, J = 1.8, 1H), 6.83 (d, J = 8.3, 1H), 6.67 (s, 1H), 6.02 (s, 2H), 2.54 (s, 3H), 2.51 (s, 3H) . ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.1, 165.7, 150.8, 148.1, 134.1, 123.3, 109.3, 108.1, 107.9, 101.7, 17.5, 15.2.



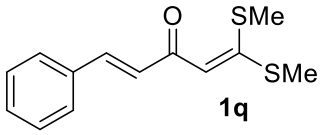
1o

1-(4-(benzyloxy)phenyl)-3,3-bis(methylthio)prop-2-en-1-one (**1o**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(4-(benzyloxy)phenyl)ethan-1-one (766.0 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1q** (422 mg, 34%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.91 (d, J = 8.9, 2H), 7.44-7.34 (m, 5H), 7.00 (d, J = 8.9, 2H), 6.74 (s, 1H), 5.12 (s, 2H), 2.55 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.7, 165.2, 161.8, 136.5, 132.4, 130.0, 128.8, 128.3, 127.6, 114.7, 109.6, 70.2, 17.5, 15.2.



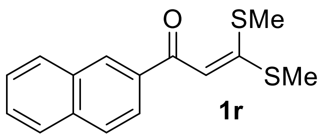
1p

1-(4-(allyloxy)phenyl)-3,3-bis(methylthio)prop-2-en-1-one (**1p**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(4-(allyloxy)phenyl)ethan-1-one (510.9 mg, 3.0 mmol), carbon disulfide (342.7 mg, 4.5 mmol), methyl iodide (1.021 g, 7.2 mmol) to afford **1p** (403.2 mg, 48%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.90 (d, J = 8.9, 2H), 6.94 (d, J = 8.9, 2H), 6.75 (s, 1H), 6.09-6.02 (m, 1H), 5.45-5.40 (m, 1H), 5.33-5.30 (m, 1H), 4.60-4.58 (m, 2H), 2.56 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 184.9, 165.1, 161.7, 132.8, 132.3, 130.0, 118.3, 114.5, 109.6, 69.0, 17.5, 15.2.



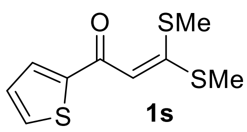
1q

(*E*)-1,1-bis(methylthio)-5-phenylpenta-1,4-dien-3-one (**1q**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), (*E*)-4-phenylbut-3-en-2-one (657.9 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1q** (358.2 mg, 32%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (d, J = 15.8, 1H), 7.57-7.55 (m, 2H), 7.38-7.36 (m, 3H), 6.83 (d, J = 15.8, 1H), 6.24 (s, 1H), 2.53 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 183.9, 165.7, 141.2, 135.3, 129.9, 128.9, 128.2, 127.4, 113.3, 17.4, 15.2.



1r

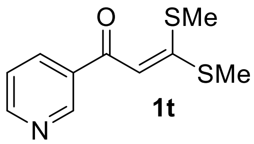
3,3-bis(methylthio)-1-(naphthalen-2-yl)prop-2-en-1-one (**1r**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(naphthalen-2-yl)ethan-1-one (766.0 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1r** (422 mg, 34%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.4 (s, 1H), 8.02 (dd, J = 8.3, 1.7, 1H), 7.95 (d, J = 8.0, 1H), 7.90-7.85 (m, 2H), 7.58-7.51 (m, 2H), 6.92 (s, 1H), 2.62 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 185.7, 166.7, 136.8, 135.1, 132.8, 129.5, 128.6, 128.4, 127.9, 126.7, 124.5, 109.7, 17.6, 15.3.



1s

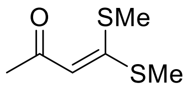
3,3-bis(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (**1s**) Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(thiophen-2-yl)ethan-1-one (567.8 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1s** (514.2 mg, 50%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$)

δ ppm 7.64-7.63 (m, 1H), 7.53-7.52 (m, 1H), 7.09-7.07 (m, 1H), 6.60 (s, 1H), 2.54 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 178.3, 166.1, 146.3, 132.1, 129.6, 128/0, 109.2, 17.4, 15.2.



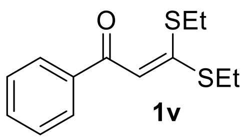
1t

3,3-bis(methylthio)-1-(pyridin-3-yl)prop-2-en-1-one (**1t)** Synthesized according to the General procedure A using potassium *tert*-butoxide (3.479 g, 31 mmol), 1-(pyridin-3-yl)ethan-1-one (545.1 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1t** (605.7 mg, 60%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.1 (d, J = 2.3, 1H), 8.69 (dd, J = 4.9, 1.8, 1H), 8.22-8.19 (m, 1H), 7.40-7.37 (m, 1H), 6.70 (s, 1H), 2.57 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 183.6, 169.2, 152.2, 148.9, 135.6, 134.7, 123.8, 108.5, 17.5, 15.2.



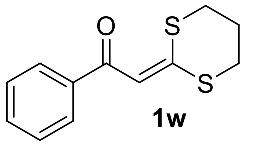
1u

4,4-bis(methylthio)but-3-en-2-one (**1u**) Synthesized according to the General procedure B using potassium *tert*-butoxide (3.479 g, 31 mmol), acetone (261.0 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), methyl iodide (1.532 g, 10.8 mmol) to afford **1u** (373.7 mg, 51%) as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.02 (s, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 192.9, 163.5, 113.0, 30.5, 17.2, 14.8.



1v

3,3-bis(ethylthio)-1-phenylprop-2-en-1-one (**1v**) Synthesized according to the General procedure B using potassium *tert*-butoxide (3.479 g, 31 mmol), acetophenone (540.7 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), ethyl bromide (1.177 g, 10.8 mmol) to afford **1u** (747.5 mg, 66%) as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.02 (s, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 192.9, 163.5, 113.0, 30.5, 17.2, 14.8.



1w

2-(1,3-dithian-2-ylidene)-1-phenylethan-1-one (**1w**) Synthesized according to the General procedure B using potassium *tert*-butoxide (3.479 g, 31 mmol), acetophenone (261.0 mg, 4.5 mmol), carbon disulfide (1.027 g, 13.5 mmol), 1,3-dibrompropanoe (1.532 g, 10.8 mmol) to afford **1u** (370.3 mg, 35%) as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.02 (s, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 192.9, 163.5, 113.0, 30.5, 17.2, 14.8.

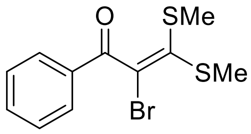
Enzymatic bromination of α-oxo ketene dithioacetals

General procedure for the enzymatic bromination of α-oxo ketene dithioacetals under on-water process (General Procedure C)

The α-oxo ketene dithiolacetals (**1a-1w**, 20 mM) were freshly dissolved in DMSO (1.0 mL, 20% v/v), then KBr (80 mM), 400 nM enzyme *Ci*VCPO, and H_2O_2 (85 mM) were added in sequence in a 100 mM citrate buffer solution (100 mM, pH 5.0) to obtain the final reaction volume of reaction solution 5.0 mL. The above-mentioned concentration represents the final concentration of each ingredient. Then, the mixture was allowed to stir at the speed of 1000 rpm at room temperature (28-32 ºC) for 24 h. After the reaction, the crude mixture was extracted with water and ethyl acetate. The organic layer was evaporated under reduced pressure to give the crude product, which was further purified by column chromatography (eluted with ethyl acetate/hexane) to afford the desired compoundproduct.

General procedure for the enzymatic bromination of *α*-oxo ketene dithioacetals under in-water process (General Procedure D)

The *α*-oxo ketene dithiolacetal (**1a**-**1w**, 20 mM) freshly dissolved in acetone (500 *μ*L,), KBr (80 mM), 400 nM *Ci*VCPO, and H_2O_2 (85 mM) were added in sequence in a 2%wt TPGS-750-M/citrate buffer solution (100 mM, pH 5.0) to obtain the final reaction volume of 5.0 mL. The above-mentioned concentration represents the final concentration of each ingredient. Then, the mixture was allowed to stir at the speed of 1000 rpm at room temperature (28-32 °C) for 24 h. After the reaction, the crude mixture was extracted with water and ethyl acetate. The organic layer was evaporated under reduced pressure to give the crude product, which was further purified by column chromatography (eluted with ethyl acetate/hexane) to afford the product.

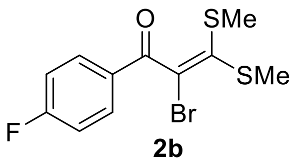


2a

2-bromo-3,3-bis(methylthio)-1-phenylprop-2-en-1-one (**2a**) Synthesized according to the General procedure C using **1a** (22.4 mg, 0.1 mmol) to afford **2a** (30.0mg, 99%) and General procedure D using **1a** (22.4 mg, 0.1 mmol) to afford **2a** (30.0mg, 99%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) *δ* ppm 7.91-7.89 (m, 2H), 7.60-7.57 (m, 1H), 7.49-7.46 (m, 2H), 2.47 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* ppm 189.4, 138.5, 134.8, 134.0, 129.9, 128.9, 118.0, 19.0, 16.4. ESI-MS: m/z: 302.9501 $[M+H]^+$ (calcd for $[C_{11}H_{12}BrOS_2]^+$ 302.9513).

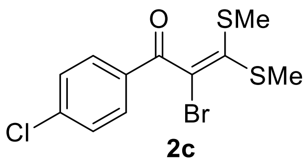
For gram-scale synthesis of **2a**: *α*-oxo ketene dithiolacetals **1a** (1.12g, 50 mM) were freshly dissolved in acetone (10 mL, 10% v/v), then KBr (1.19 g, 2.0 eq.), 400 nM enzyme *Ci*VCPO, and H_2O_2 (1.086 mL, 2.1 eq.) were added in sequence in a 2%wt TPGS-750-M/citrate buffer solution (100mM, pH 5.0) to obtain the final volume of reaction solution 100.0

mL. The above-mentioned concentration represents the final concentration of each ingredient. Then, the mixture was allowed to stir at room temperature at the speed 1000 rpm for 36h. After the reaction, the crude mixture was extracted with water and ethyl acetate. The organic layer was evaporated under reduced pressure to give the crude product, which was further purified by column chromatography (eluted with ethyl acetate/hexane) to afford the desired compound **2a** (1.422 g, 94%).



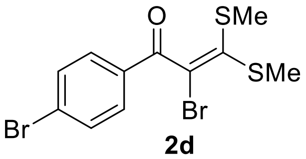
2b

2-bromo-1-(4-fluorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**2b**) Synthesized according to the General procedure C using **1b** (24.2 mg, 0.1 mmol) to afford **2b** (28.8 mg, 90%) and General procedure D using **1b** (24.2 mg, 0.1 mmol) to afford **2b** (31.9 mg, 99%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.95-7.91 (m, 2H), 7.18-7.14 (m, 2H), 2.48 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 187.8, 167.3, 165.3, 138.7, 132.6, 132.5, 131.3, 117.4, 116.3, 116.1, 19.0, 16.4. ^{19}F NMR (470 MHz, $CDCl_3$) δ -103.2 ESI-MS: m/z: 320.9385 $[M+H]^+$, 322. 9368 $[M+H+2]^+$ (calcd for $[C_{11}H_{11}BrFOS_2]^+$ 320.9419).



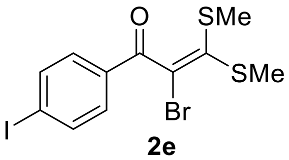
2c

2-bromo-1-(4-chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**2c**) Synthesized according to the General procedure C using **1c** (25.9 mg, 0.1 mmol) to afford **2c** (32.8 mg, 97%) and General procedure D using **1c** (25.9 mg, 0.1 mmol) to afford **2c** (27.7 mg, 82%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.86-7.83 (m, 2H), 7.47-7.45 (m, 2H), 2.48 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.2, 140.5, 139.1, 133.2, 131.2, 129.3, 117.2, 19.1, 16.4. ESI-MS: m/z: 336.9105 $[M+H]^+$, 338.9077 $[M+H+2]^+$, 340.9060 $[M+H+4]^+$ (calcd for $[C_{11}H_{11}BrClOS_2]^+$ 336.9123).



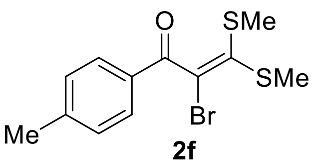
2d

2-bromo-1-(4-bromophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**2d**) Synthesized according to the General procedure C using **1d** (30.3 mg, 0.1 mmol) to afford **2d** (26.8 mg, 70%) and General procedure D using **1d** (30.3 mg, 0.1 mmol) to afford **2d** (27.8 mg, 73%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78-7.75 (m, 2H), 7.64-7.62 (m, 2H), 2.48 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.4, 139.2, 133.6, 132.3, 131.2, 129.3, 117.1, 19.1, 16.4. ESI-MS: m/z: 402.8431 $[M+H]^+$, 402.8410 $[M+H+2]^+$, 404.8391 $[M+H+4]^+$ (calcd for $[C_{11}H_{11}Br_2OS_2]^+$ 336.9123).



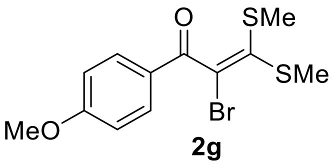
2e

2-bromo-1-(4-iodophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**2e**) Synthesized according to the General procedure D using **1e** (35.0 mg, 0.1 mmol) to afford **2e** (24.3 mg, 57%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.87-7.84 (m, 2H), 7.62-7.59 (m, 2H), 2.48 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.6, 139.2, 138.3, 134.2, 131.1, 117.1, 102.3, 19.1, 16.4. ESI-MS: m/z: 428.8448 $[M+H]^+$, 430.8421 $[M+H+2]^+$(calcd for $[C_{11}H_{11}BrIOS_2]^+$ 428.8479).



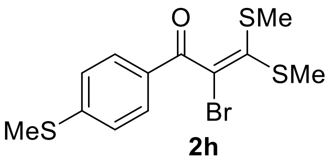
2f

2-bromo-3,3-bis(methylthio)-1-(p-tolyl)prop-2-en-1-one (**2f**) Synthesized according to the General procedure C using **1f** (23.8 mg, 0.1 mmol) to afford **2f** (23.6 mg, 74%) and General procedure D using **1f** (23.8 mg, 0.1 mmol) to afford **2f** (31.5 mg, 99%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.81 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 2.47 (s, 3H), 2.43 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 189.0, 145.2, 137.8, 132.1, 130.1, 129.7, 118.3, 22.0, 19.0, 16.4. ESI-MS: m/z: 338.9485 $[M+H]^+$, 340. 9469 $[M+H+2]^+$ (calcd for $[C_{12}H_{14}BrOS_2]^+$ 320.9419).



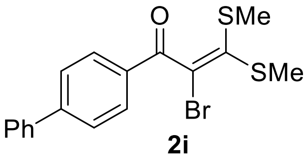
2g

2-bromo-1-(4-methoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (**2g**) Synthesized according to the General procedure C using **1g** (25.4 mg, 0.1 mmol) to afford **2g** (28.5 mg, 86%) and General procedure D using **1g** (25.4 mg, 0.1 mmol) to afford **2g** (33.1 mg, 99%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.90-7.88 (m, 2H), 6.98-6.95 (m, 2H), 3.88 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.3, 164.4, 137.4, 132.4, 127.4, 118.4, 114.3, 55.7, 19.0, 16.4. ESI-MS: m/z: 322.9613 $[M+H]^+$, 324. 9596 $[M+H+2]^+$ (calcd for $[C_{12}H_{14}BrO_2S_2]^+$ 322.9619).



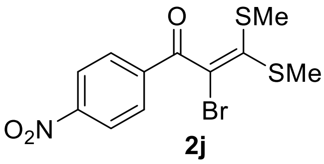
2h

2-bromo-3,3-bis(methylthio)-1-(4-(methylthio)phenyl)prop-2-en-1-one (**2h**) Synthesized according to the General procedure C using **1h** (27.0 mg, 0.1 mmol) to afford **2h** (23.5 mg, 67%) and General procedure D using **1h** (27.0 mg, 0.1 mmol) to afford **2h** (13.9 mg, 40%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.83-7.80 (m, 2H), 7.29-7.26 (m, 2H), 2.53 (s, 3H), 2.47 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.4, 150.9, 147.5, 138.0, 130.8, 130.3, 125.1, 118.0, 19.0, 16.4, 14.8. ESI-MS: m/z: 348.9378 $[M+H]^+$, 350. 9337 $[M+H+2]^+$ (calcd for $[C_{12}H_{14}BrOS_3]^+$ 348.9390).



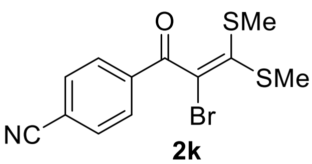
2i

1-([1,1'-biphenyl]-4-yl)-2-bromo-3,3-bis(methylthio)prop-2-en-1-one (**2i**) Synthesized according to the General procedure C using **1i** (30.0 mg, 0.1 mmol) to afford **2i** (8.1 mg, 21%) and General procedure D using **1i** (30.0 mg, 0.1 mmol) to afford **2i** (27.2 mg, 72%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.00-7.98 (m, 2H), 7.73-7.70 (m, 2H), 7.65-7.63 (m, 2H), 7.50-7.46 (m, 2H), 7.43-7.40 (m, 1H), 2.50 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 189.0, 146.7, 139.9, 138.3, 133.4, 130.5, 129.1, 128.6, 127.6, 127.5, 118.1, 19.1, 16.4. ESI-MS: m/z: 378.9834 $[M+H]^+$, 380. 9817 $[M+H+2]^+$ (calcd for $[C_{17}H_{16}BrOS_2]^+$ 378.9826).



2j

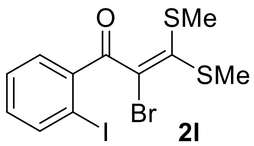
2-bromo-3,3-bis(methylthio)-1-(4-nitrophenyl)prop-2-en-1-one (**2j**) Synthesized according to the General procedure D using **1j** (26.9 mg, 0.1 mmol) to afford **2j** (15.1 mg, 43%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.34-8.32 (m, 2H), 8.06-8.03 (m, 2H), 2.50 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 187.5, 150.7, 141.1, 130.5, 124.1, 116.2, 19.1, 16.6. ESI-MS: m/z: 347.9357 $[M+H]^+$, 349. 9338 $[M+H+2]^+$ (calcd for $[C_{11}H_{10}BrNO_3S_2]^+$ 347.9364).



2k

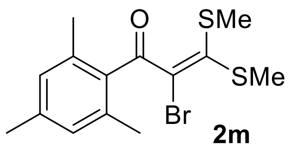
4-(2-bromo-3,3-bis(methylthio)acryloyl)benzonitrile (**2k**) Synthesized according to the General procedure C using **1k** (24.9 mg, 0.1 mmol) to afford **2k** (5.6 mg, 99%) and General procedure D using **1k** (24.9 mg, 0.1 mmol) to afford **2k** (9.3 mg, 28%) as a yellow oil: ^{1}H NMR

(500 MHz, $CDCl_3$) δ ppm 7.97 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 2.49 (s, 3H0, 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 187.7, 141.0, 138.5, 132.7, 130.0, 118.0, 116.9, 116.3, 19.1, 16.5. ESI-MS: m/z: 327.9443 $[M+H]^+$, 329. 9432 $[M+H+2]^+$ (calcd for $[C_{12}H_{11}BrNOS_2]^+$ 327.9465).



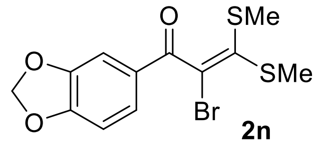
2l

2-bromo-1-(2-iodophenyl)-3,3-bis(methylthio)prop-2-en-1-one (**2l**) Synthesized according to the General procedure D using **1l** (35.0 mg, 0.1 mmol) to afford **2l** (34.3 mg, 99%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.97 (dd, J = 8.1, 1.2, 1H), 7.51 (dd, J = 7.8, 1.7, 1H), 7.39 (dt, J = 7.5, 1.2, 1H), 7.12 (dt, J = 7.8, 1.8, 1H), 2.50 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 139.7, 146.8, 142.2, 141.3, 132.3, 130.5, 127.8, 119.0, 94.2, 18.9, 17.1. ESI-MS: m/z: 428.8436 $[M+H]^+$, 430. 8354 $[M+H+2]^+$ (calcd for $[C_{11}H_{11}BrIOS_2]^+$ 320.9419).



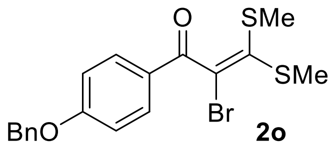
2m

2-bromo-1-mesityl-3,3-bis(methylthio)prop-2-en-1-one (**2m**) Synthesized according to the General procedure C using **1m** (26.6 mg, 0.1 mmol) to afford **2m** (6.8 mg, 20%) and General procedure D using **1m** (26.6 mg, 0.1 mmol) to afford **2m** (31.9 mg, 93%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.82 (s, 2H), 2.51 (s, 3H), 2.28 (s, 3H), 2.24 (s, 6H), 2.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 193.0, 150.1, 139.2, 135.4, 131.0, 128.7, 123.2, 21.3, 20.2, 18.9, 17.8. ESI-MS: m/z: 366.9797 $[M+Na]^+$, 368. 9775 $[M+Na+2]^+$ (calcd for $[C_{14}H_{17}BrOS_2Na]^+$ 320.9419).



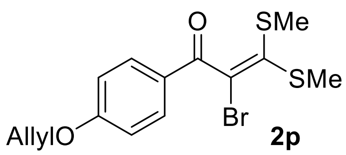
2n

1-(benzo[*d*][1,3]dioxol-5-yl)-2-bromo-3,3-bis(methylthio)prop-2-en-1-one (2n) Synthesized according to the General procedure C using **1n** (26.8 mg, 0.1 mmol) to afford **2n** (11.1 mg, 32%) and General procedure D using **1n** (26.8 mg, 0.1 mmol) to afford **2n** (20.5 mg, 59%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.48 (dd, J = 8.0, 1.7 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.07 (s, 2H), 2.47 (s, 3H), 2.18 (s, 3H) . ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 187.8, 152.8, 148.6, 137.8, 129.3, 127.0, 118.1, 109.1, 108.3, 102.3, 19.1, 16.4. ESI-MS: m/z: 346.9406 $[M+H]^+$, 348. 9385 $[M+H+2]^+$ (calcd for $[C_{12}H_{12}BrO_3S_2]^+$ 346.9411).



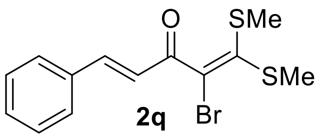
2o

1-(4-(benzyloxy)phenyl)-2-bromo-3,3-bis(methylthio)prop-2-en-1-one (2o) Synthesized according to the General procedure C using **1o** (33.0 mg, 0.1 mmol) to afford **2o** (9.9 mg, 24%) and General procedure D using **1o** (33.0 mg, 0.1 mmol) to afford **2o** (12.8 mg, 31%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.91-7.88 (m, 2H), 7.44-7.35 (m, 5H), 7.05-7.02 (m, 2H), 5.14 (s, 2H), 2.47 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.1, 163.5, 137.5, 136.1, 132.3, 128.8, 128.4, 127.6 (x2), 118.4, 115.0, 70.4, 19.0, 16.4. ESI-MS: m/z: 408.9928 $[M+H]^+$, 410. 9858 $[M+H+2]^+$ (calcd for $[C_{18}H_{18}BrO_2S_2]^+$ 408.9932).



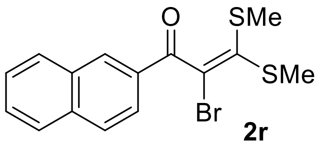
2p

1-(4-(allyloxy)phenyl)-2-bromo-3,3-bis(methylthio)prop-2-en-1-one (2p) Synthesized according to the General procedure C using **1p** (28.0 mg, 0.1 mmol) to afford **2p** (24.0 mg, 67%) and General procedure D using **1p** (28.0 mg, 0.1 mmol) to afford **2p** (20.0 mg, 56%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.89-7.86 (m, 2H), 6.89-6.85 (m, 2H), 6.09-6.01 (m, 1H), 5.45-5.41 (m, 1H), 5.34-5.31 (m, 1H), 4.62-4.61 (m, 2H), 2.47 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.1, 163.4, 134.5, 132.5, 132.3, 127.5, 118.5, 118.4, 114.9, 69.1, 19.0, 16.4. ESI-MS: m/z: 320.9385 $[M+H]^+$, 322. 9368 $[M+H+2]^+$ (calcd for $[C_{14}H_{15}BrO_2S_2]^+$ 320.9419).



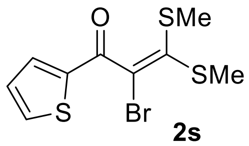
2q

(*E*)-2-bromo-1,1-bis(methylthio)-5-phenylpenta-1,4-dien-3-one (**2q**) Synthesized according to the General procedure C using **1q** (25.0 mg, 0.1 mmol) to afford **2q** (12.2 mg, 37%) and General procedure D using **1q** (25.0 mg, 0.1 mmol) to afford **2q** (25.8 mg, 78%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.58-7.55 (m, 3H), 7.42-7.40 (m, 3H), 6.93 (d, J = 16.1, 1H), 2.49 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.3, 145.7, 140.9, 134.4, 131.0, 129.1, 128.7, 124.8, 119.4, 19.5, 16.8. ESI-MS: m/z: 350.9501 $[M+Na]^+$, 352. 9420 $[M+Na+2]^+$ (calcd for $[C_{13}H_{14}BrOS_2Na]^+$ 350.9489).



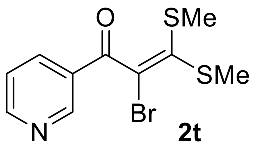
2r

2-bromo-3,3-bis(methylthio)-1-(naphthalen-2-yl)prop-2-en-1-one (**2r**) Synthesized according to the General procedure C using **1r** (27.4 mg, 0.1 mmol) to afford **2r** (10.0 mg, 28%) and General procedure D using **1r** (27.4 mg, 0.1 mmol) to afford **2r** (23.4 mg, 66%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.38 (s, 1H), 8.00-7.96 (m, 2H), 7.93-7.87 (m, 2H), 7.63-7.60 (m, 1H), 7.57-7.54 (m, 1H), 2.50 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 189.4, 138.6, 136.1, 132.6, 132.2, 132.1, 129.9, 129.1, 129.0, 128.1, 127.1, 124.8, 118.1, 19.1, 16.5. ESI-MS: m/z: 352.9662 $[M+H]^+$, 354. 9650 $[M+H+2]^+$ (calcd for $[C_{15}H_{14}BrOS_2]^+$ 352.9669).



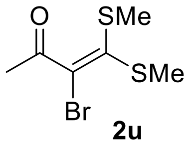
2s

2-bromo-3,3-bis(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (**2s**) Synthesized according to the General procedure C using **1s** (23.0 mg, 0.1 mmol) to afford **2s** (30.6 mg, 99%) and General procedure D using **1s** (23.0 mg, 0.1 mmol) to afford **2s** (30.7 mg, 99%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.74-7.72 (m, 1H), 7.66-7.65 (m, 1H), 7.15-7.14 (m, 1H), 2.47 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 182.0, 141.8, 139.1, 135.7, 134.9, 128.5, 117.0, 19.3, 16.5. ESI-MS: m/z: 308.9071 $[M+H]^+$, 310. 9044 $[M+H+2]^+$ (calcd for $[C_9H_{10}BrOS_3]^+$ 308.9077).



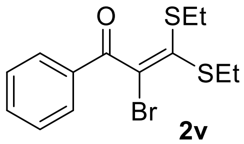
2t

2-bromo-3,3-bis(methylthio)-1-(pyridin-3-yl)prop-2-en-1-one (**2t**) Synthesized according to the General procedure C using **1t** (22.5 mg, 0.1 mmol) to afford **2t** (28.4 mg, 94%) and General procedure D using **1t** (22.5 mg, 0.1 mmol) to afford **2t** (24.5 mg, 81%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.05-9.04 (m, 1H), 8.80-8.78 (m, 1H), 8.21-8.18 (m, 1H), 7.46-7.43 (m, 1H), 2.49 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.1, 154.0, 151.1, 140.7, 136.8, 130.7, 123.9, 116.4, 19.0, 16.5. ESI-MS: m/z: 303.9446 $[M+H]^+$, 305. 9421 $[M+H+2]^+$ (calcd for $[C_{10}H_{11}BrNOS_2]^+$ 303.9465).



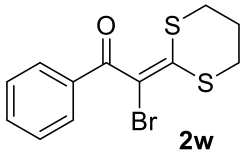
2u

3-bromo-4,4-bis(methylthio)but-3-en-2-one (**2u**) Synthesized according to the General procedure C using **1u** (16.2 mg, 0.1 mmol) to afford **2u** (13.3 mg, 99%) and General procedure D using **1u** (16.2 mg, 0.1 mmol) to afford **2u** (5.4 mg, 22%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.49 (s, 3H), 2.46 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 195.0, 142.5, 120.5, 29.5, 19.8, 17.2.



2v

2-bromo-3,3-bis(ethylthio)-1-phenylprop-2-en-1-one (**2v**) Synthesized according to the General procedure C using **1v** (25.2 mg, 0.1 mmol) to afford **2v** (26.0 mg, 79%) and General procedure D using **1v** (25.2 mg, 0.1 mmol) to afford **2v** (33.6 mg, 96%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.92-7.90 (m, 2H), 7.61-7.58 (m, 1H), 7.50-7.46 (m, 2H), 2.98 (q, J = 7.2 Hz, 2H), 2.67 (q, J = 7.4 Hz, 2H), 1.35 (t, J = 7.5 Hz, 3H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 189.6, 136.1, 134.7, 133.9, 129.9, 128.9, 120.0, 30.1, 28.0, 15.4, 14.2. ESI-MS: m/z: 330.9819 $[M+H]^+$, 332. 9790 $[M+H+2]^+$ (calcd for $[C_{13}H_{16}BrOS_2]^+$ 330.9826).

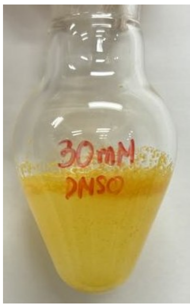


2w

2-bromo-2-(1,3-dithian-2-ylidene)-1-phenylethan-1-one (**2w**) Synthesized according to the General procedure C using **1w** (23.6 mg, 0.1 mmol) to afford **2w** (26.1 mg, 83%) and General procedure D using **1w** (23.6 mg, 0.1 mmol) to afford **2w** (29.3 mg, 93%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.85-7.82 (m, 2H), 7.55-7.52 (m, 1H), 7.46-7.43 (m, 2H), 3.10

(t, J = 6.6 Hz, 2H), 2.85 (t, J = 6.9 Hz, 2H), 2.18 (quin, J = 6.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 188.8, 149.3, 137.0, 132.9, 129.7, 128.4, 109.1, 29.8, 29.6, 23.4. ESI-MS: m/z: 336.9332 $[M+Na]^+$, 338. 9321 $[M+Na+2]^+$ (calcd for $[C_{12}H_{11}BrOS_2Na]^+$ 336.9332).

Experiment set up

a) 

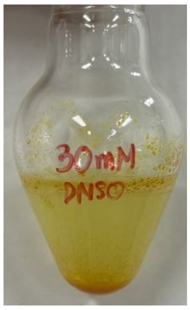
b) 

Figure S2. On-water reaction flask at 30 mM of **1a** a) before the reaction and b) after the reaction

a) 

b) 

Figure S3. In-water reaction flask at 20 mM of **1a** a) before the reaction and b) after the reaction

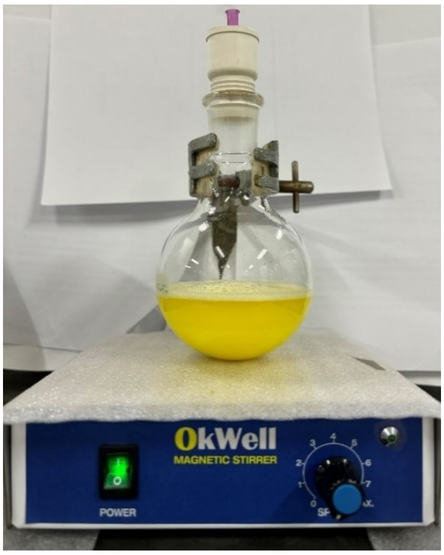


Figure S4. Gram-scale set up

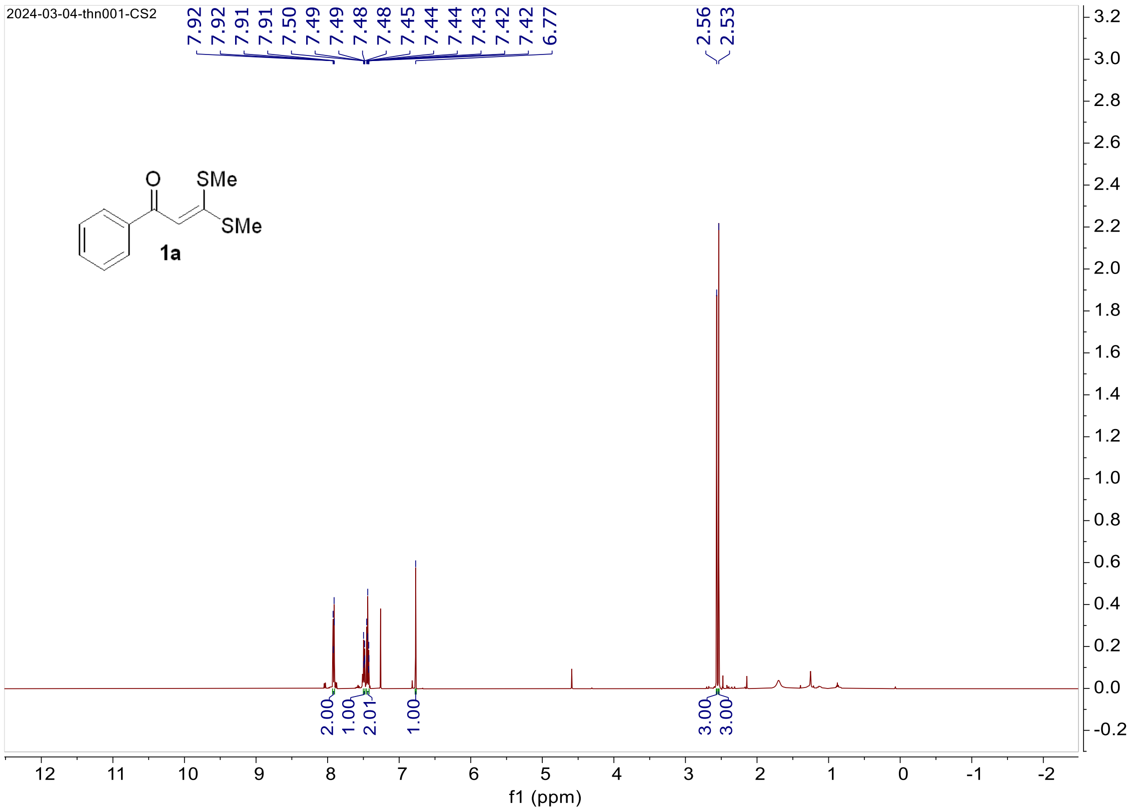


Figure S5 ^{1}H NMR spectra of **1a** ($CDCl_3$, 500 MHz)

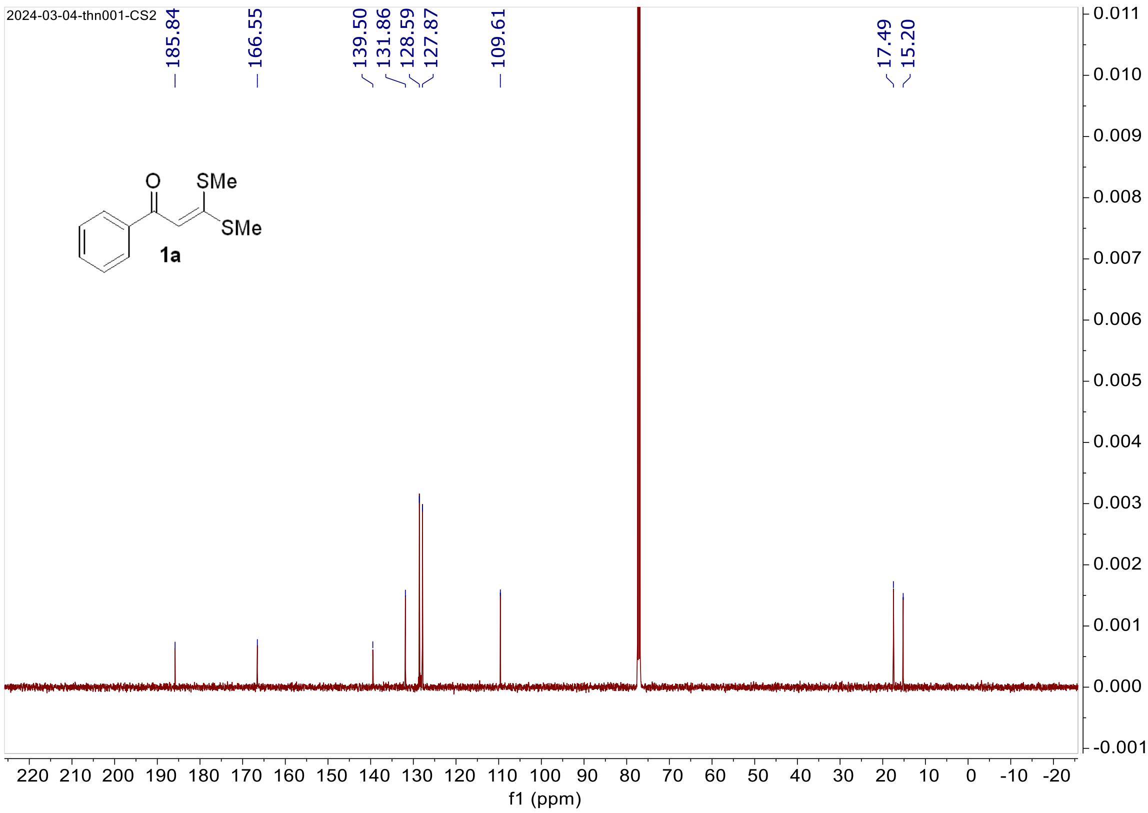


Figure S6 ^{13}C NMR spectra of **1a** ($CDCl_3$, 125 MHz)

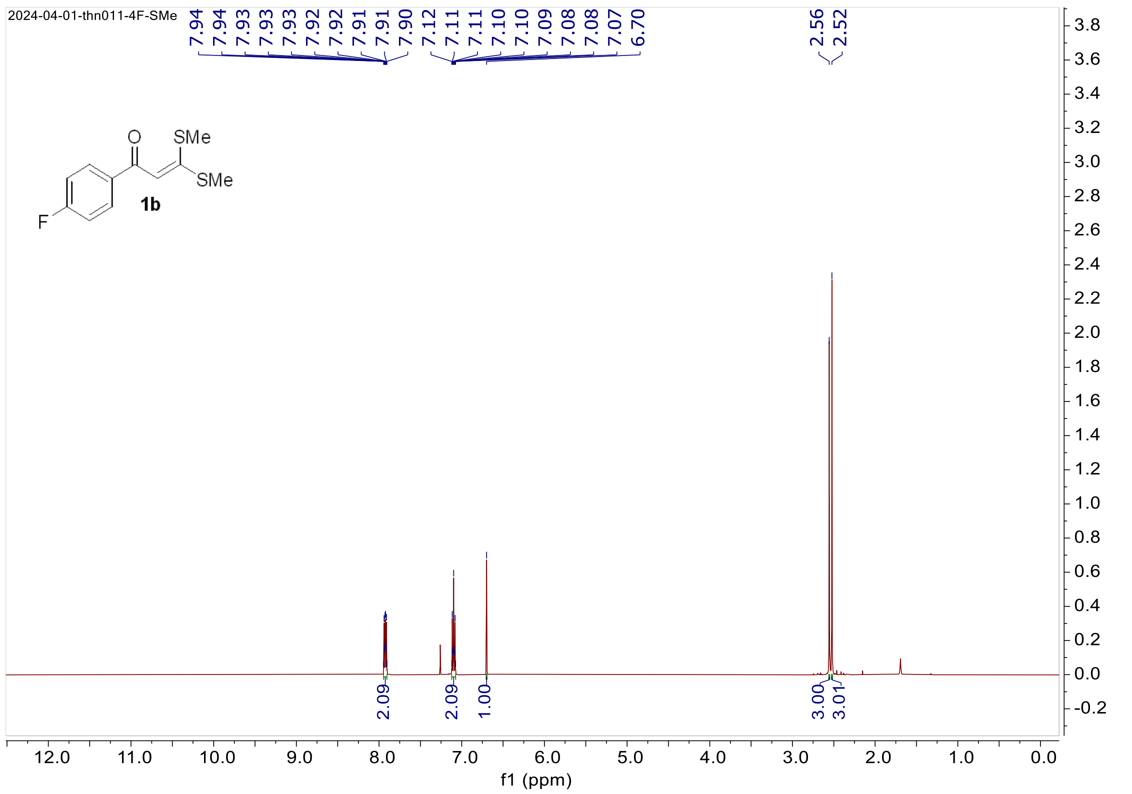


Figure S7 ^{1}H NMR spectra of **1b** ($CDCl_3$, 500 MHz)

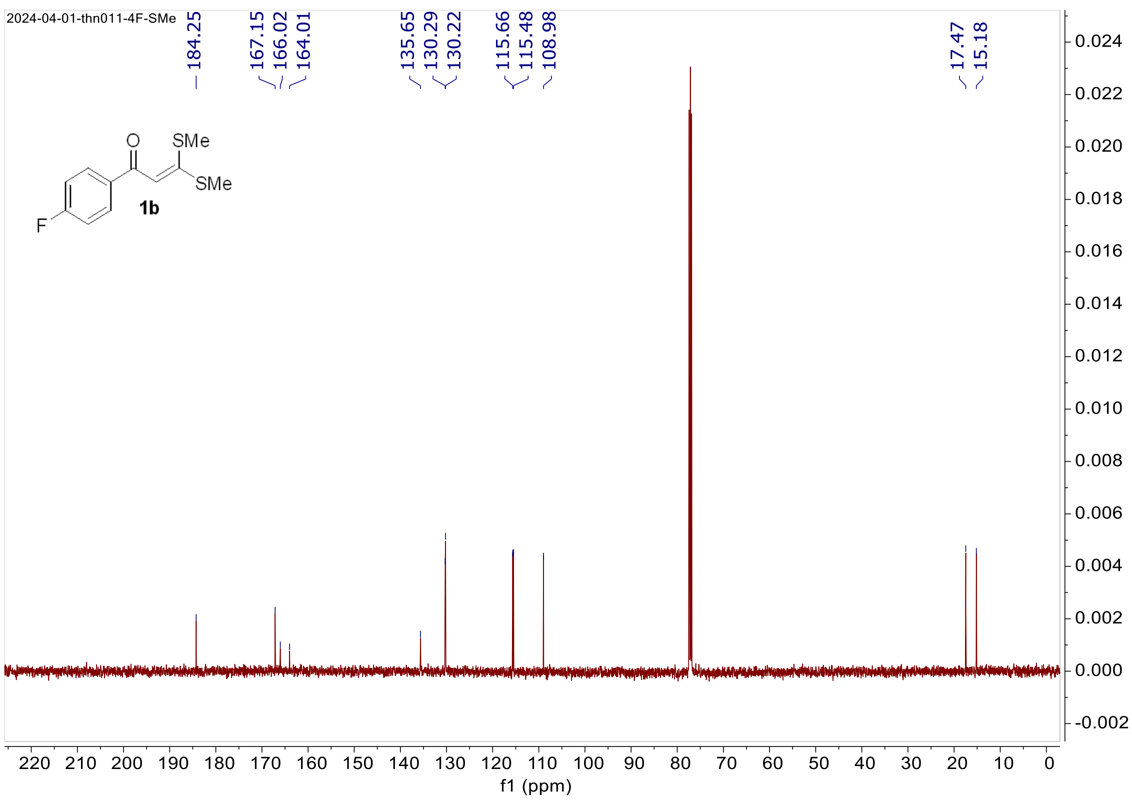


Figure S8 ^{13}C NMR spectra of **1b** ($CDCl_3$, 125 MHz)

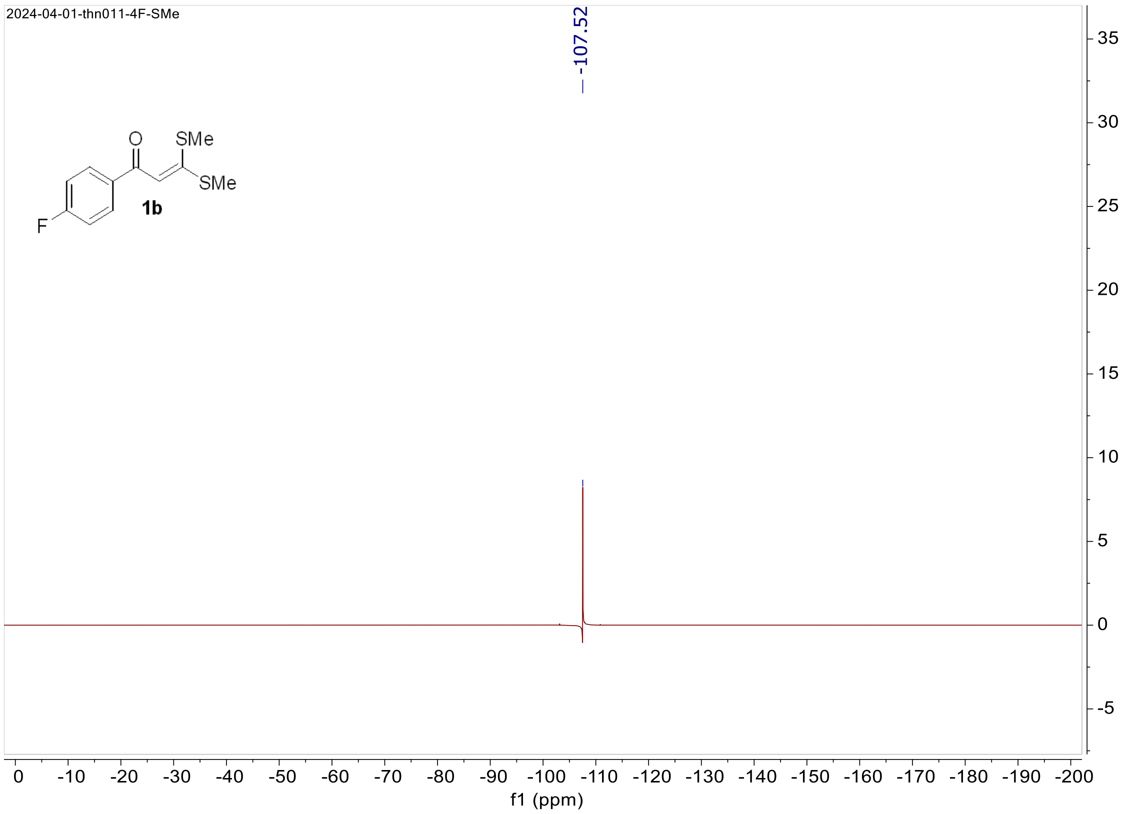


Figure S9 ^{19}F NMR spectra of **1b** ($CDCl_3$, 470 MHz)

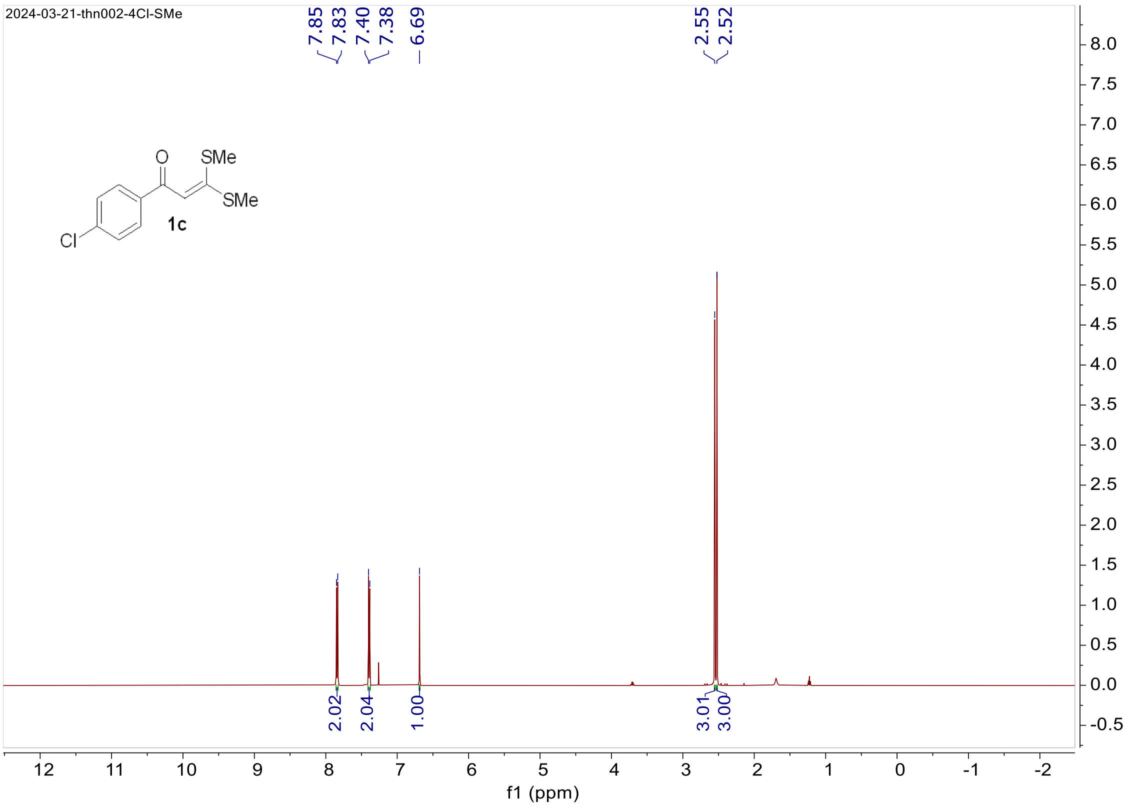


Figure S10 [1]H NMR spectra of **1c** ($CDCl_3$, 500 MHz)

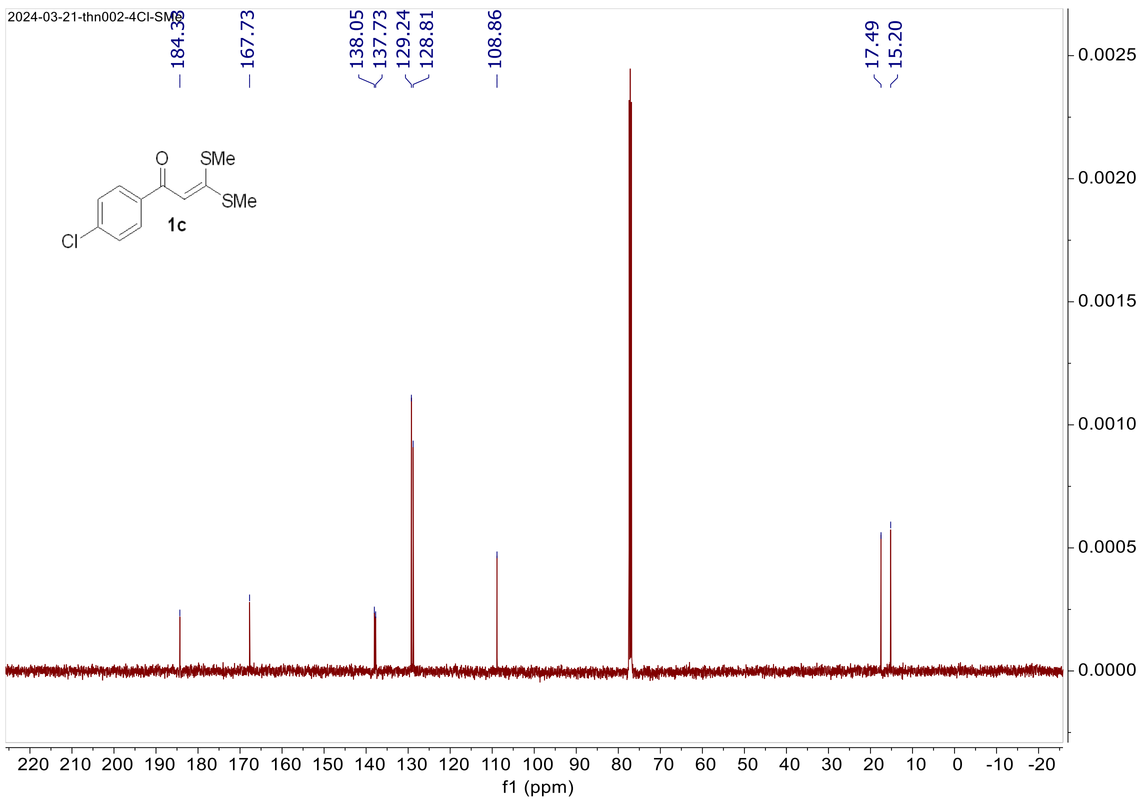


Figure S11 [13]C NMR spectra of **1c** ($CDCl_3$, 125 MHz)

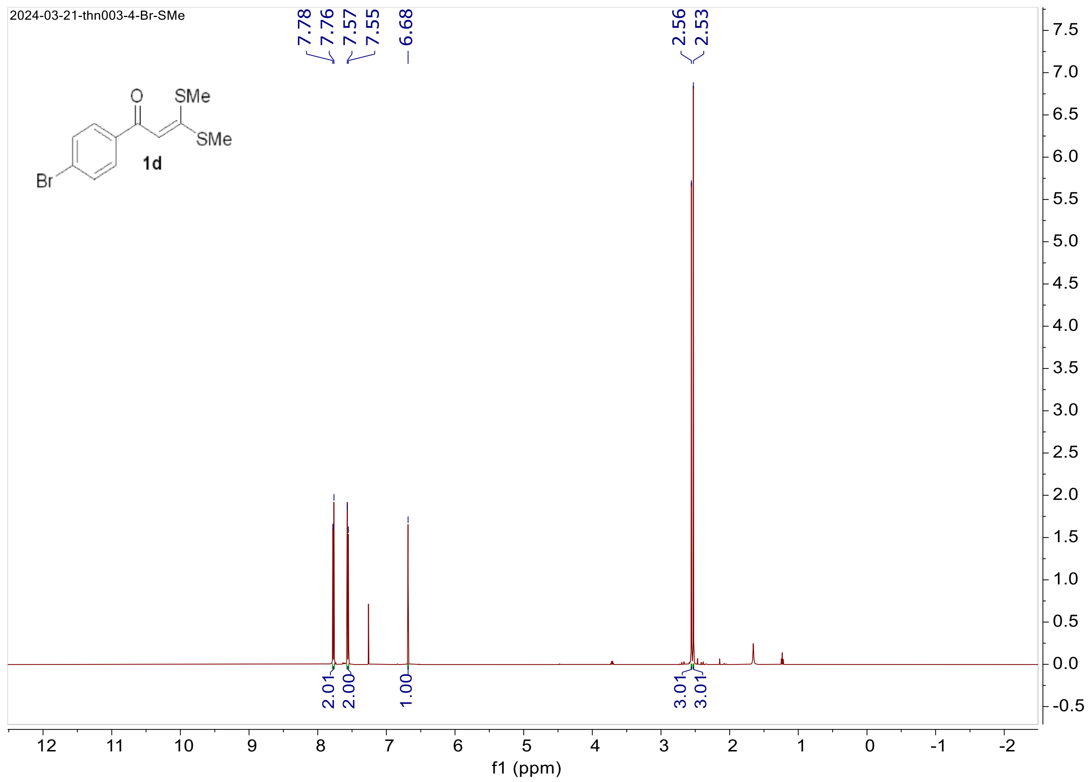


Figure S12 ^{1}H NMR spectra of **1d** ($CDCl_3$, 500 MHz)

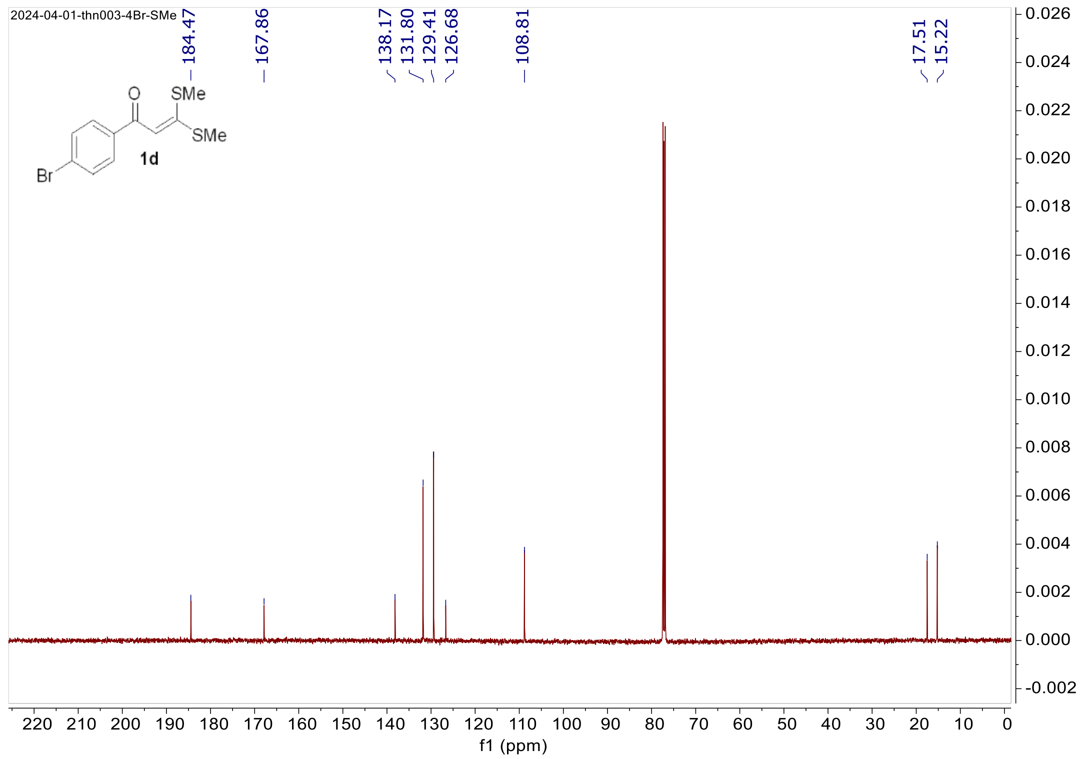


Figure S13 ^{13}C NMR spectra of **1d** ($CDCl_3$, 125 MHz

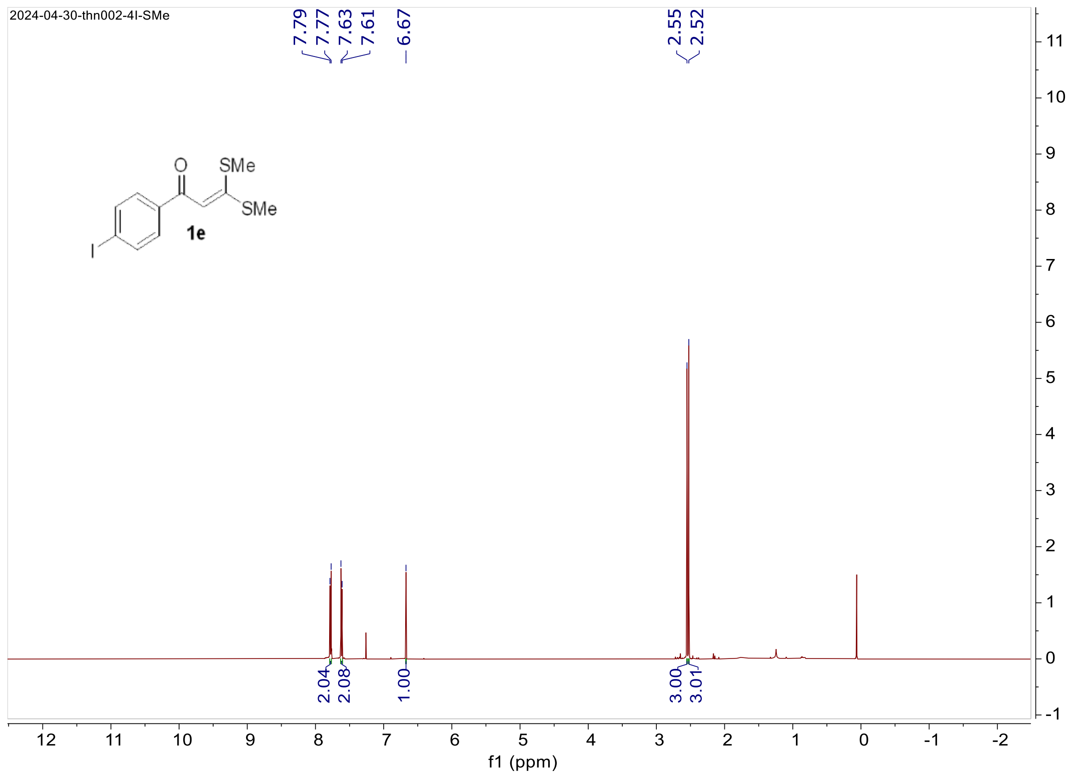


Figure S14 ^{1}H NMR spectra of **1e** ($CDCl_3$, 500 MHz)

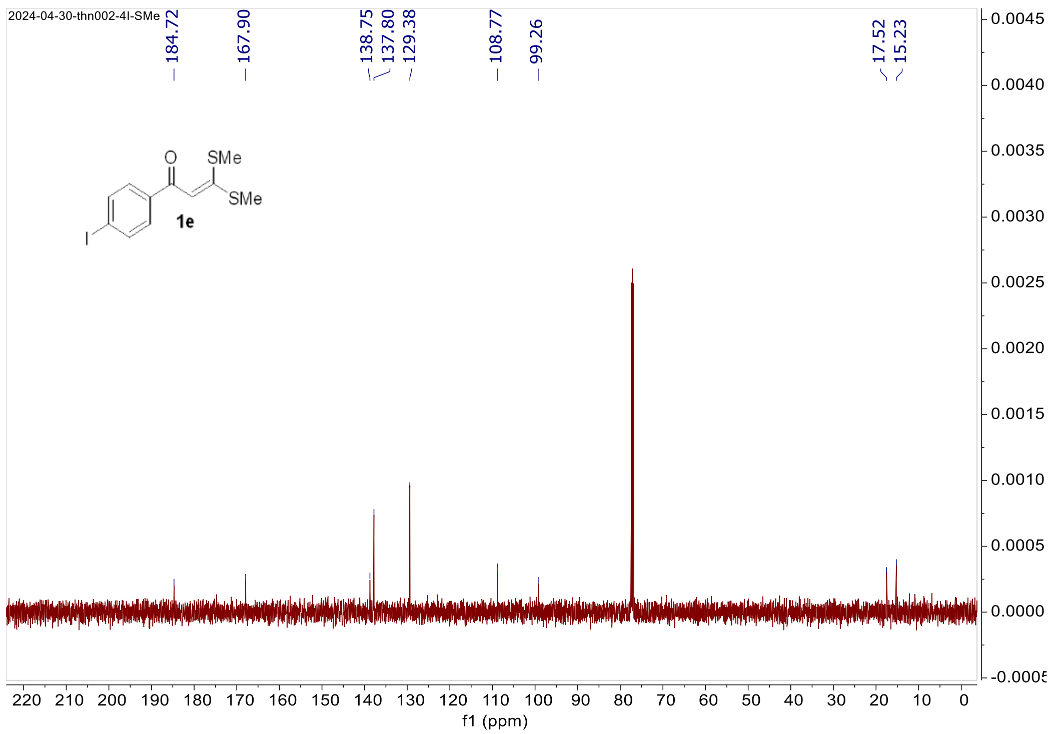


Figure S15 ^{13}C NMR spectra of **1e** ($CDCl_3$, 125 MHz)

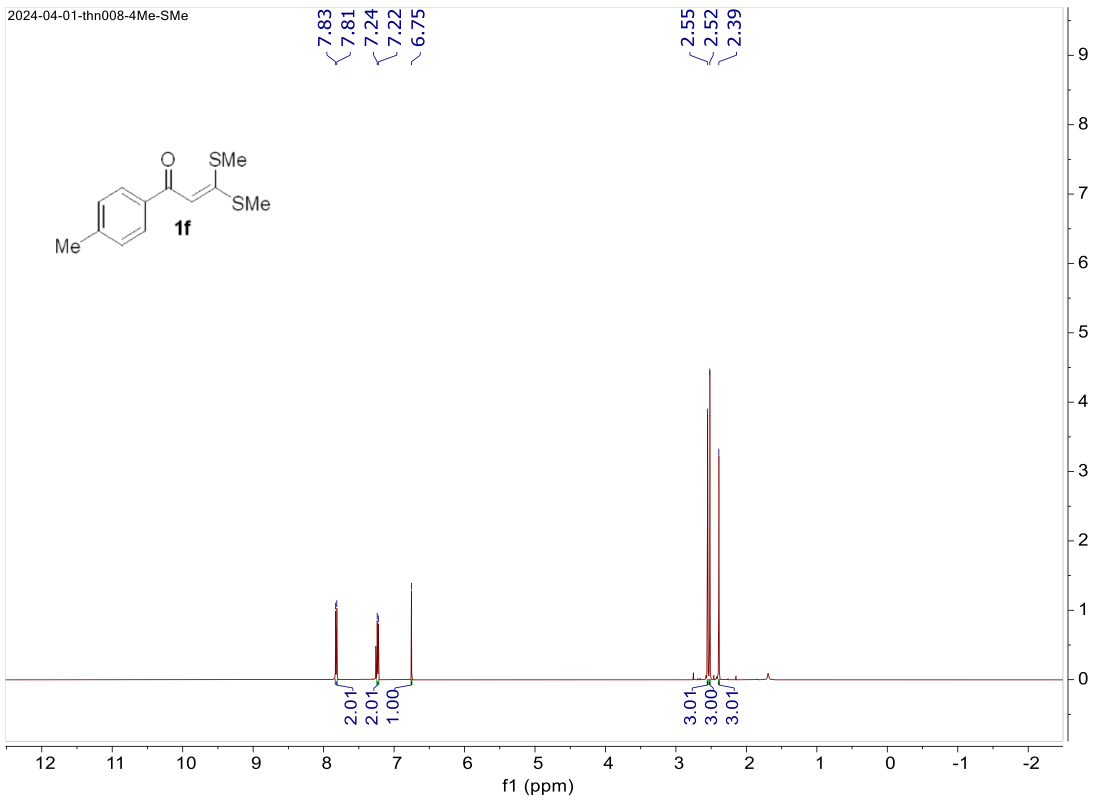


Figure S16 ^{1}H NMR spectra of **1d** ($CDCl_3$, 500 MHz)

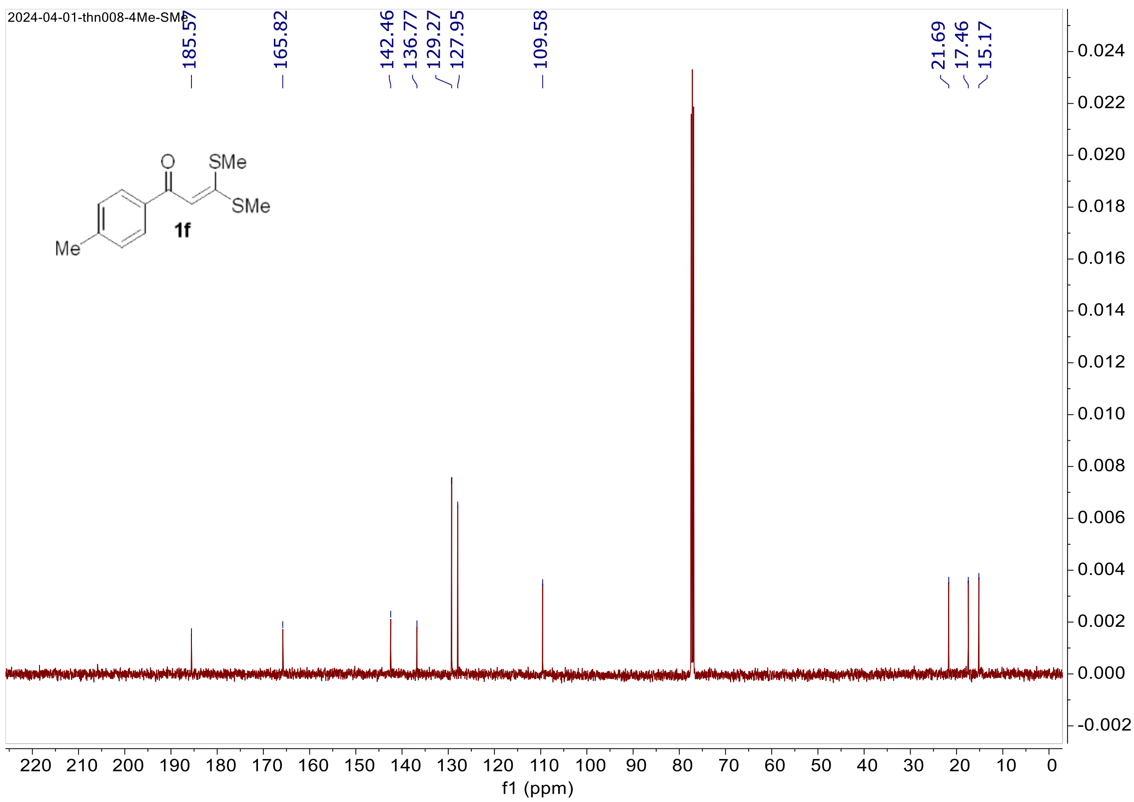


Figure S17 ^{13}C NMR spectra of **1f** ($CDCl_3$, 125 MHz)

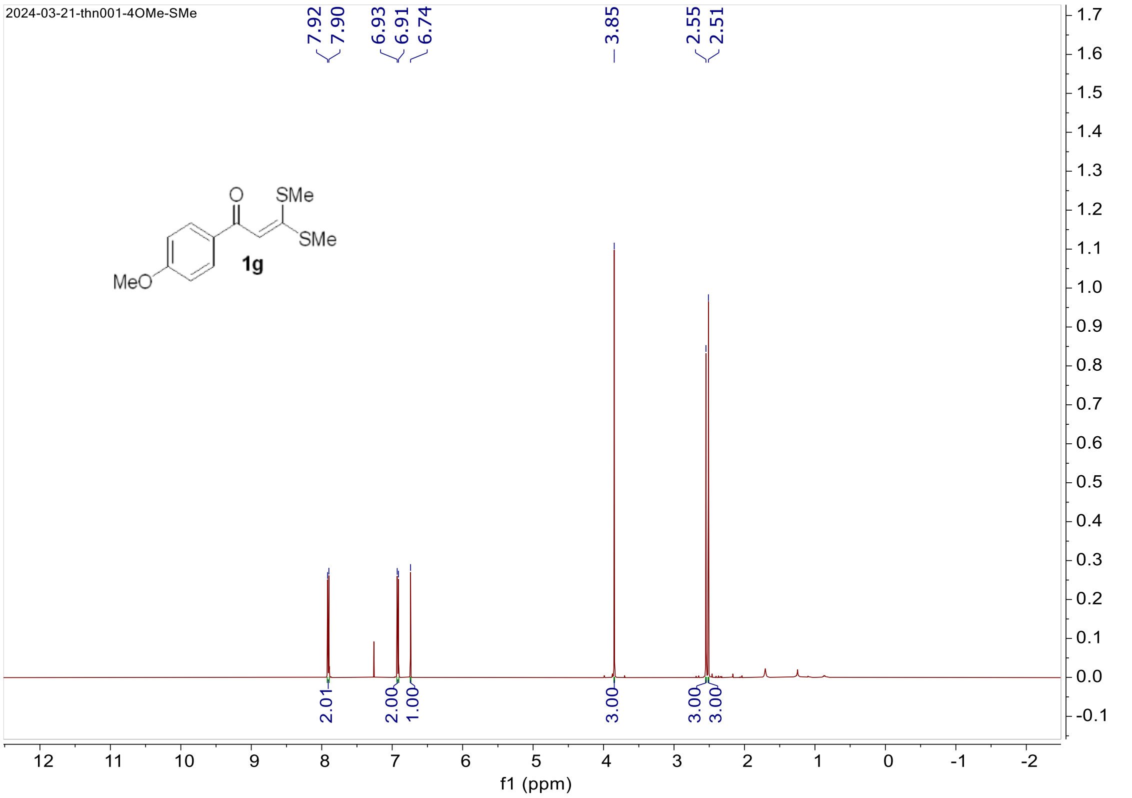


Figure S18 ^{1}H NMR spectra of **1g** ($CDCl_3$, 500 MHz)

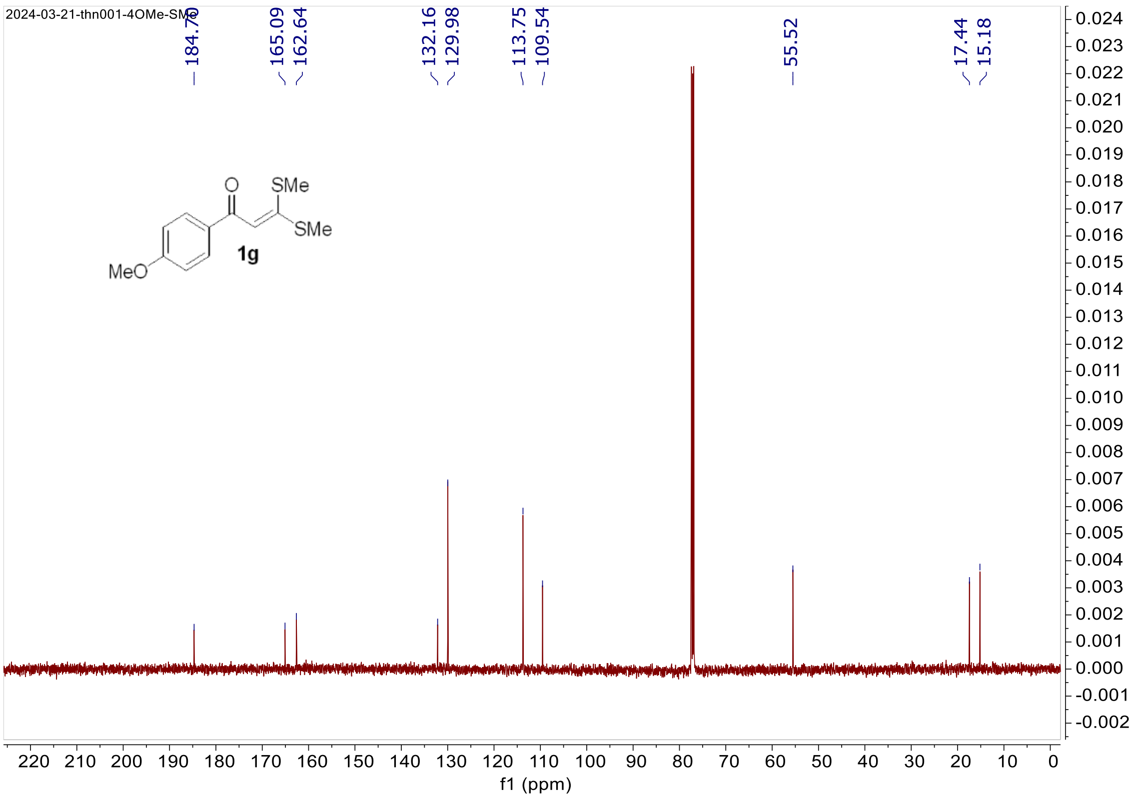


Figure S19 ^{13}C NMR spectra of **1g** ($CDCl_3$, 125 MHz)

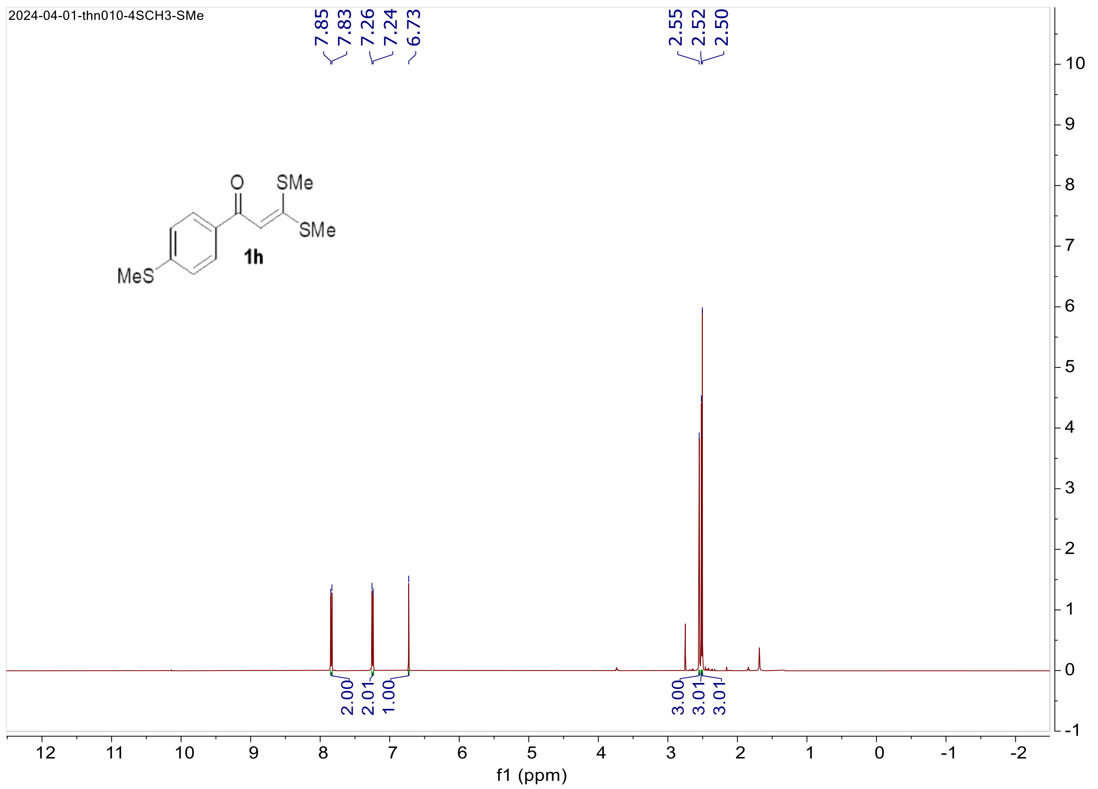


Figure S20 ^{1}H NMR spectra of **1h** ($CDCl_3$, 500 MHz)

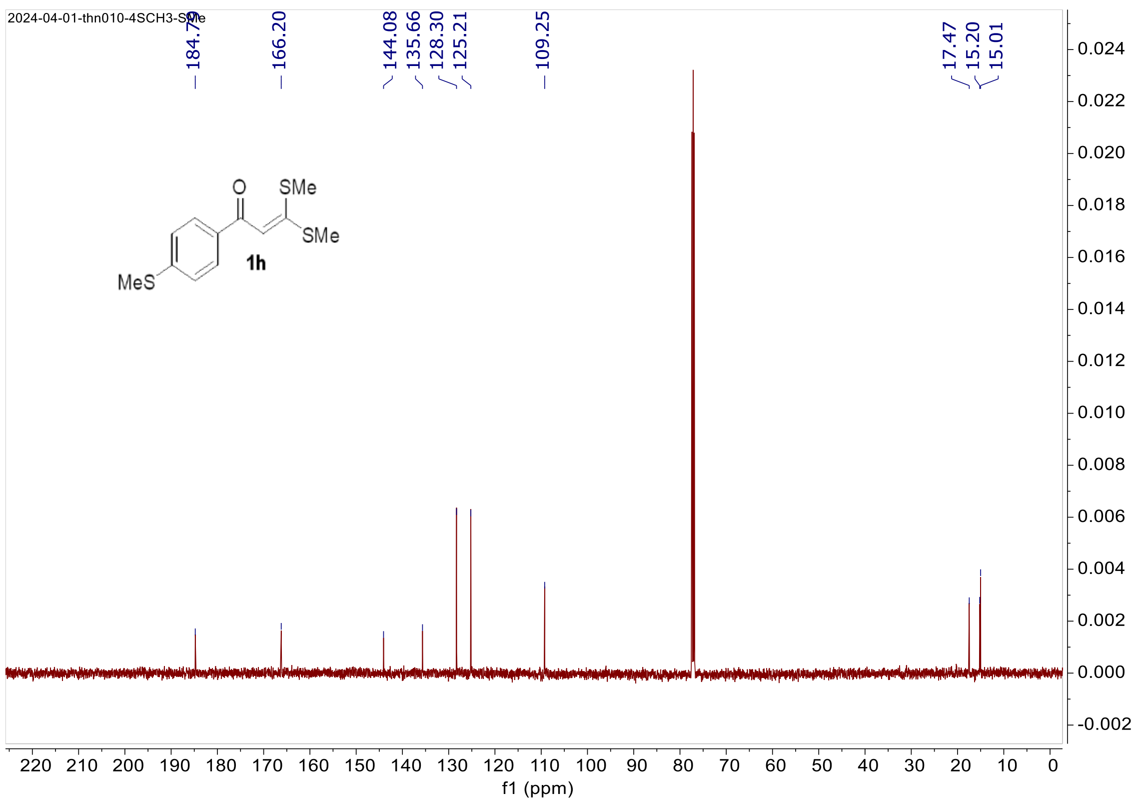


Figure S21 ^{13}C NMR spectra of **1h** ($CDCl_3$, 125 MHz)

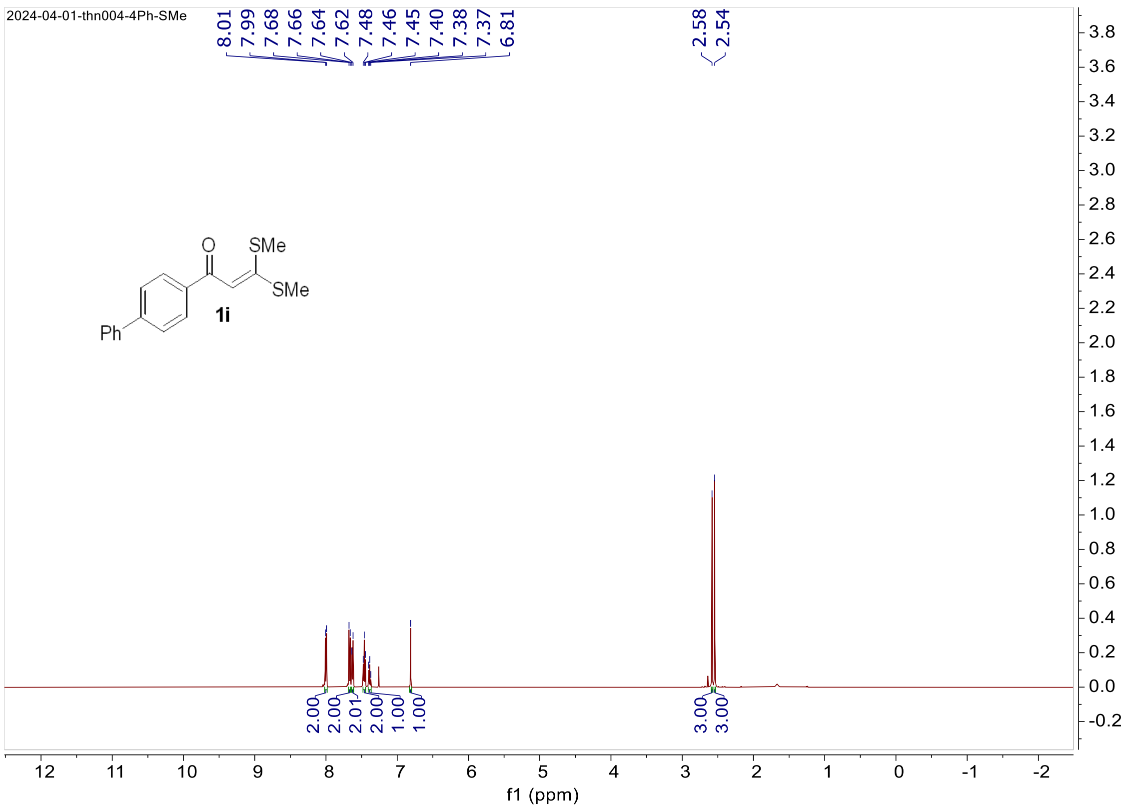


Figure S22 [1]H NMR spectra of **1i** ($CDCl_3$, 500 MHz)

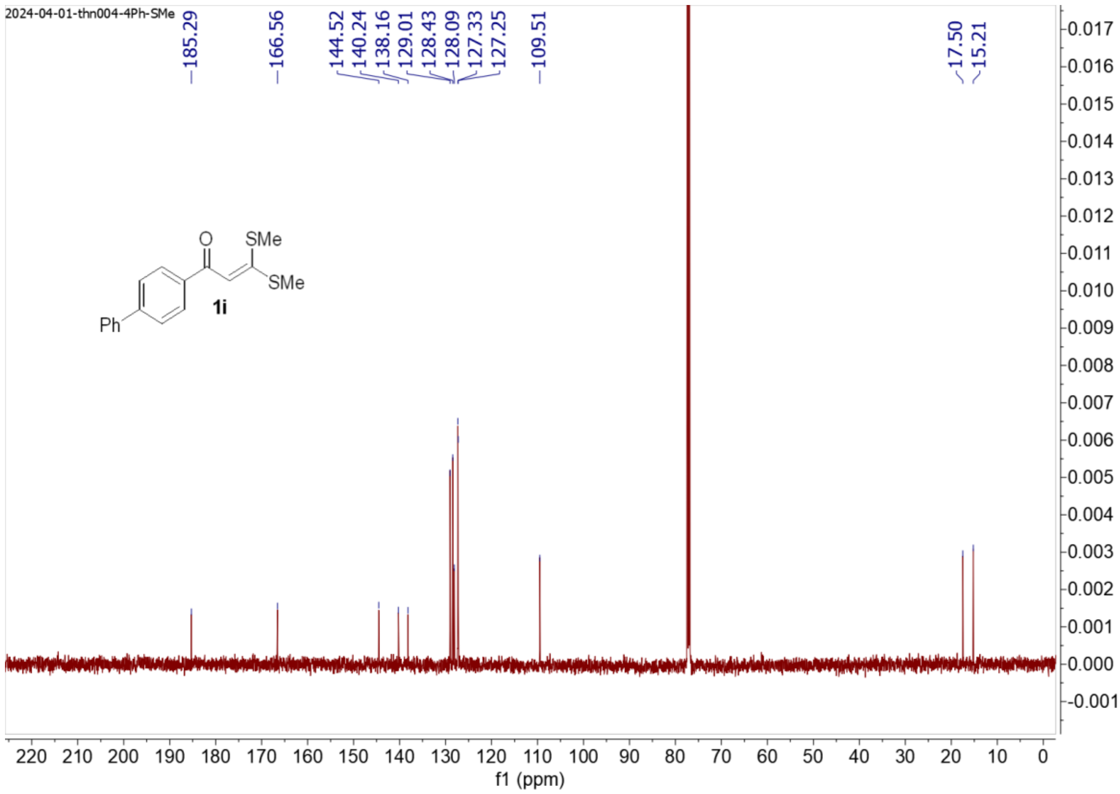


Figure S23 [13]C NMR spectra of **1i** ($CDCl_3$, 125 MHz)

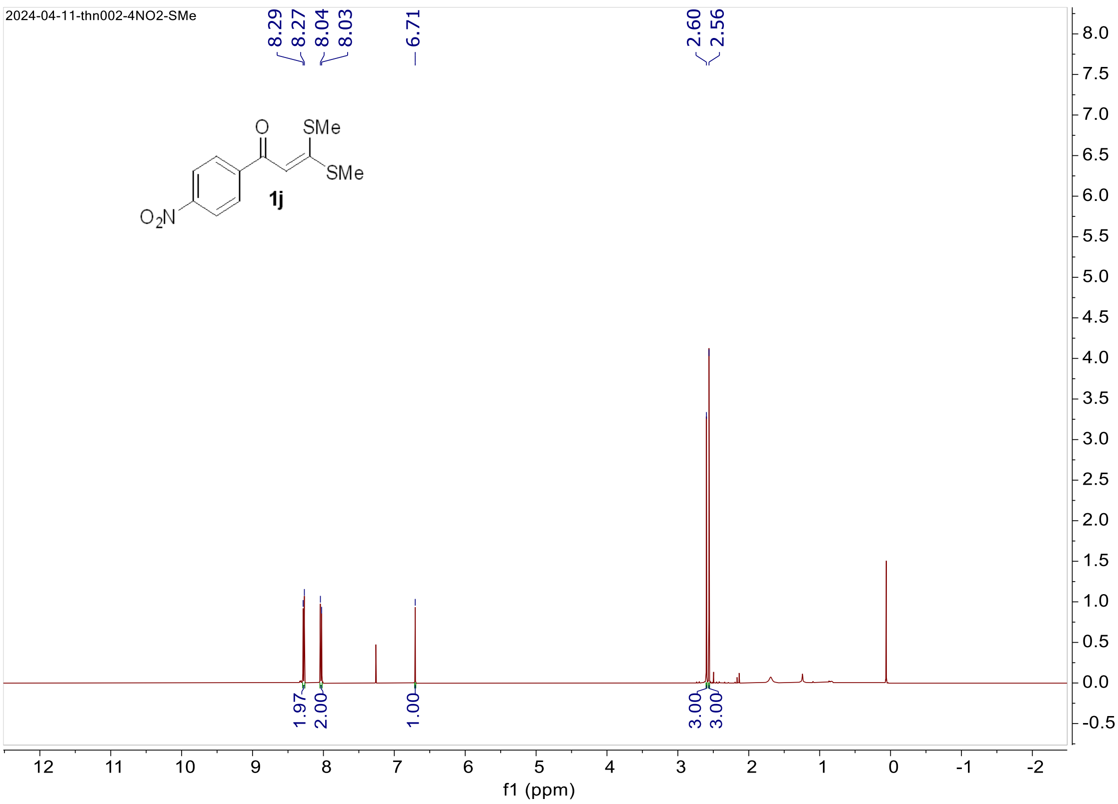


Figure S24 ^{1}H NMR spectra of **1j** ($CDCl_3$, 500 MHz)

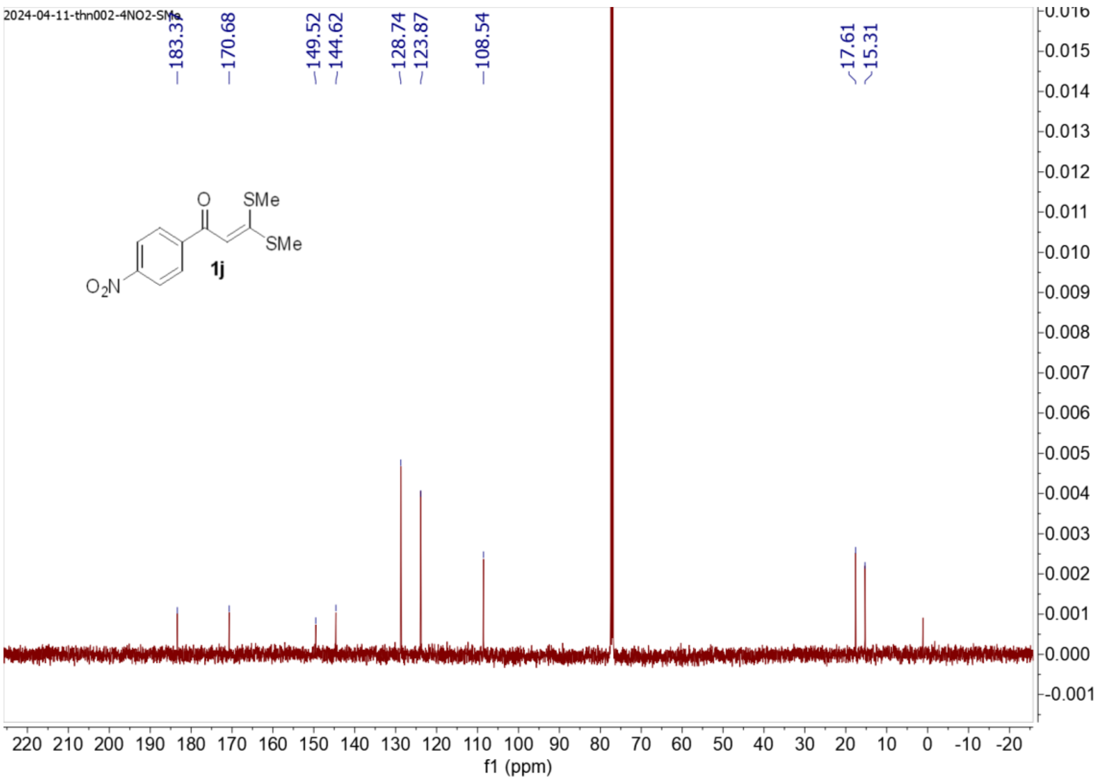


Figure S25 ^{13}C NMR spectra of **1j** ($CDCl_3$, 125 MHz)

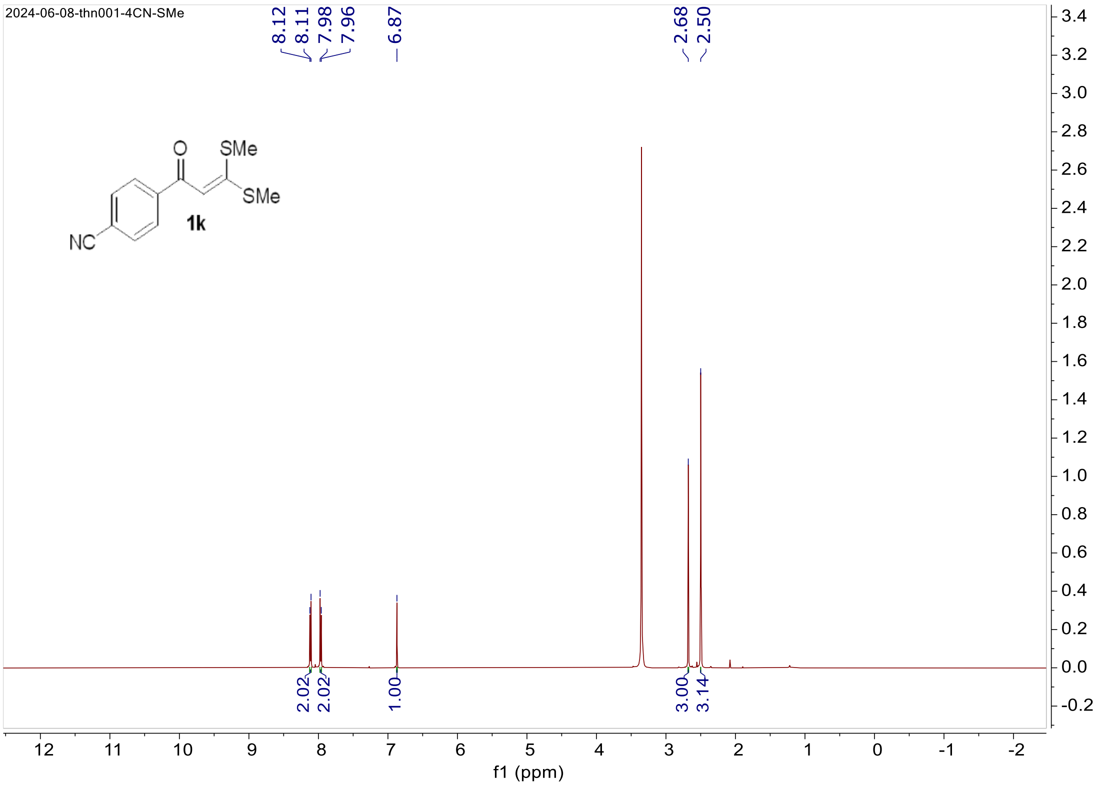


Figure S26 ^{1}H NMR spectra of **1k** (DMSO, 500 MHz)

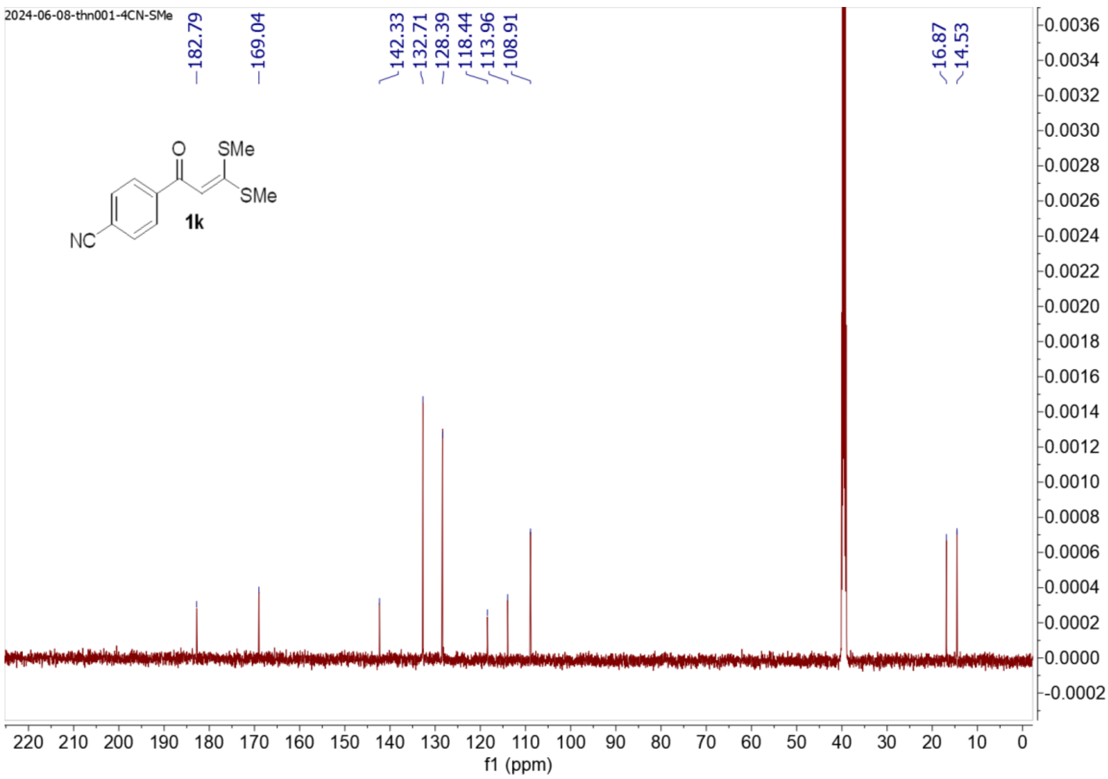


Figure S27 ^{13}C NMR spectra of **1k** (DMSO, 125 MHz)

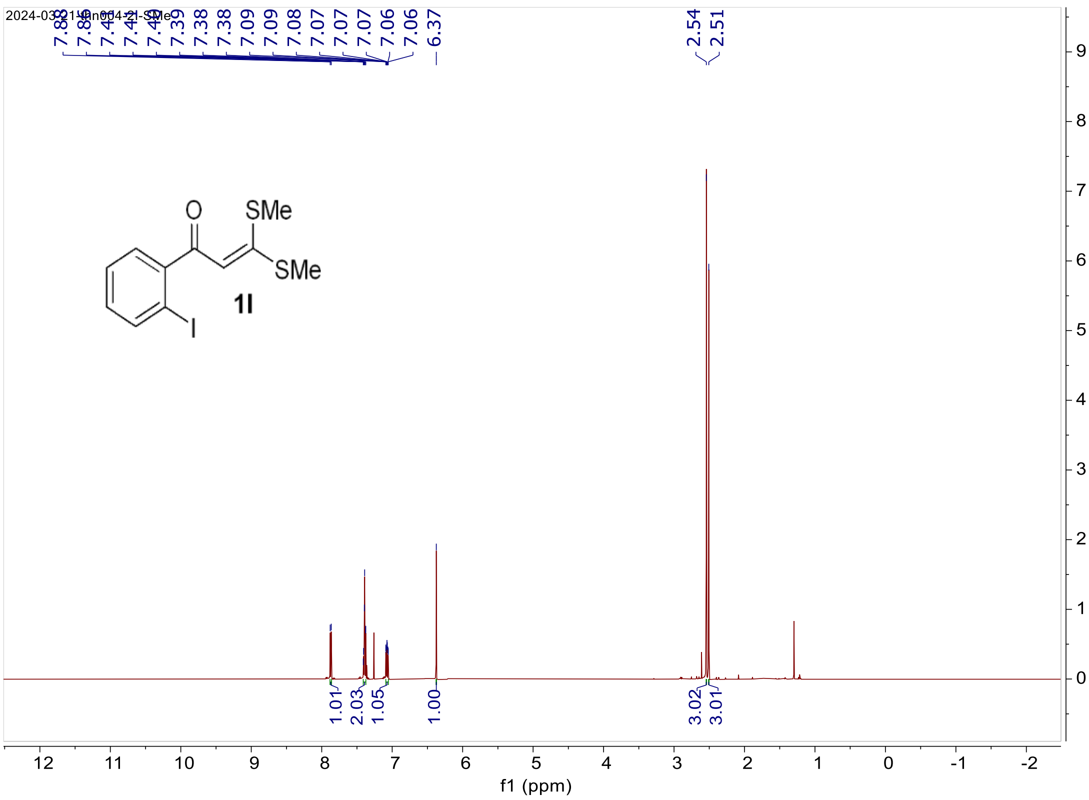


Figure S28 ^{1}H NMR spectra of **1l** ($CDCl_3$, 500 MHz)

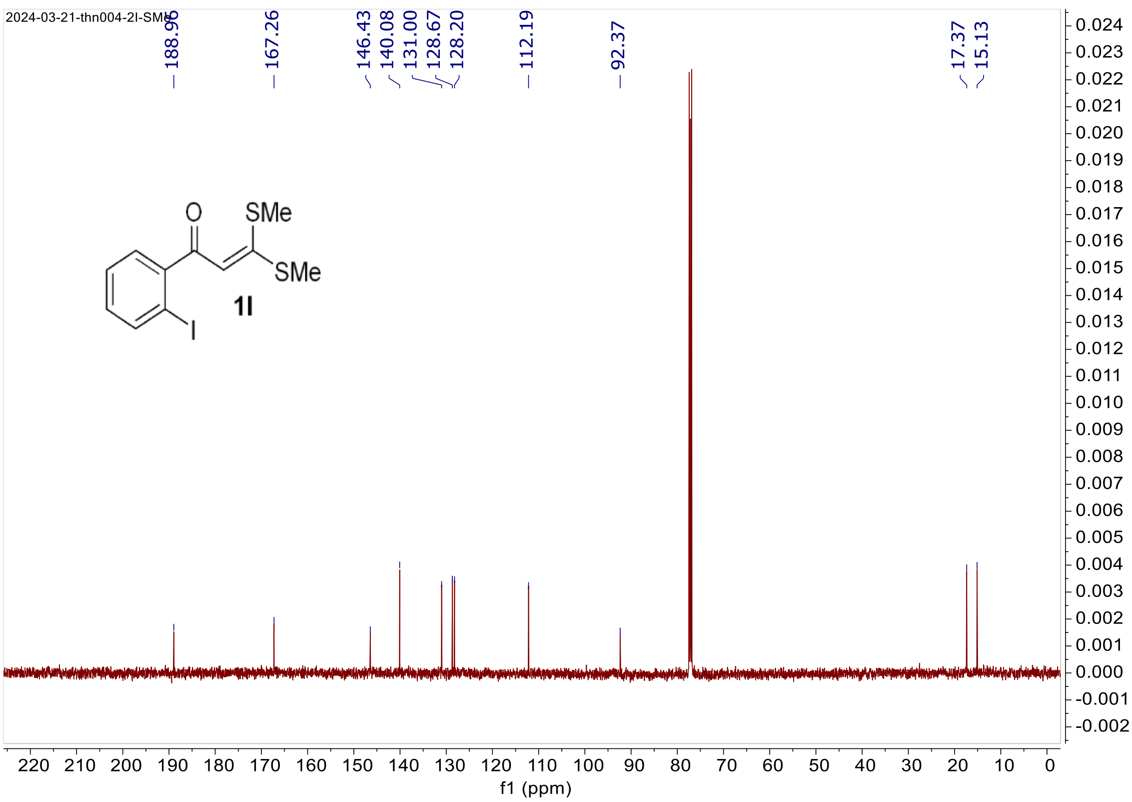


Figure S29 ^{13}C NMR spectra of **1l** ($CDCl_3$, 125 MHz)

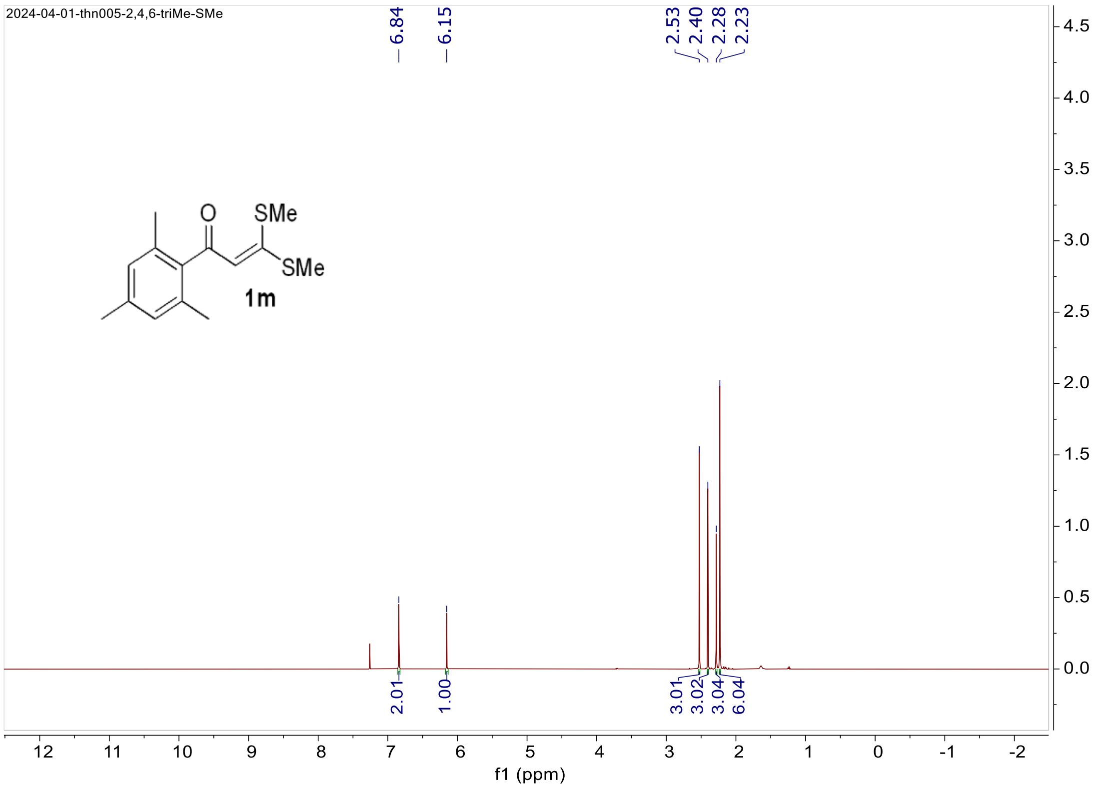


Figure S30 ^{1}H NMR spectra of **1m** ($CDCl_3$, 500 MHz)

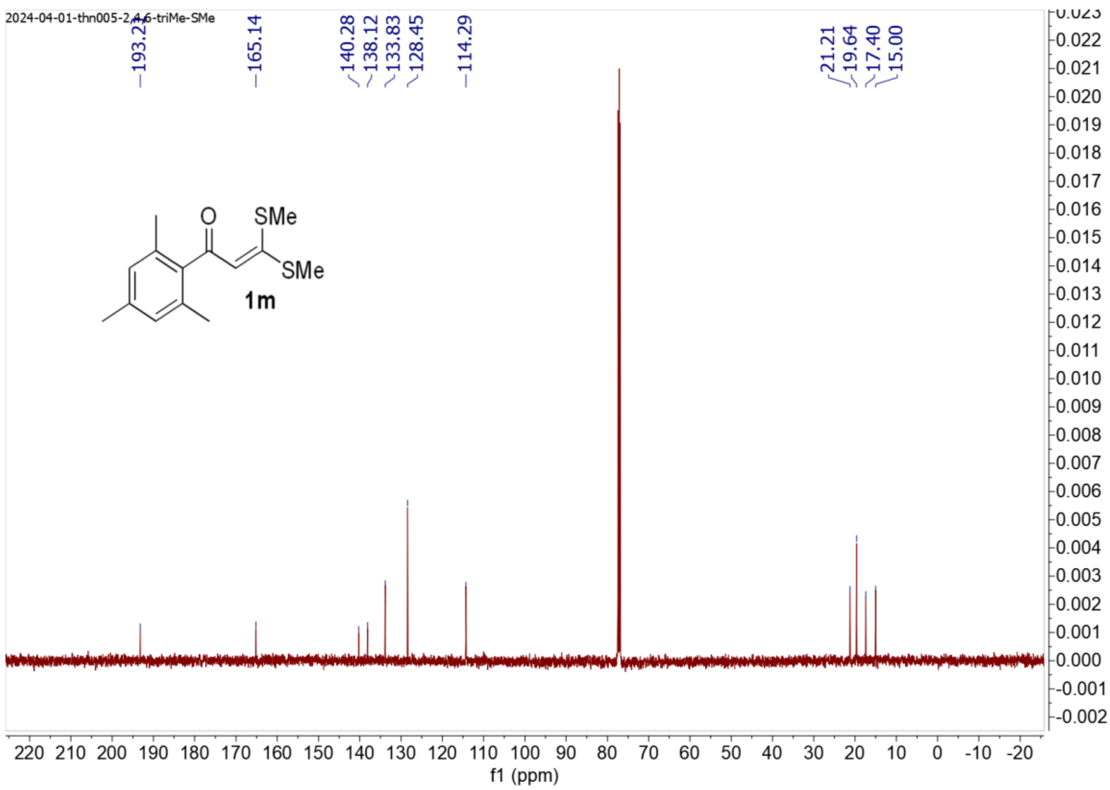


Figure S31 ^{13}C NMR spectra of **1m** ($CDCl_3$, 125 MHz)

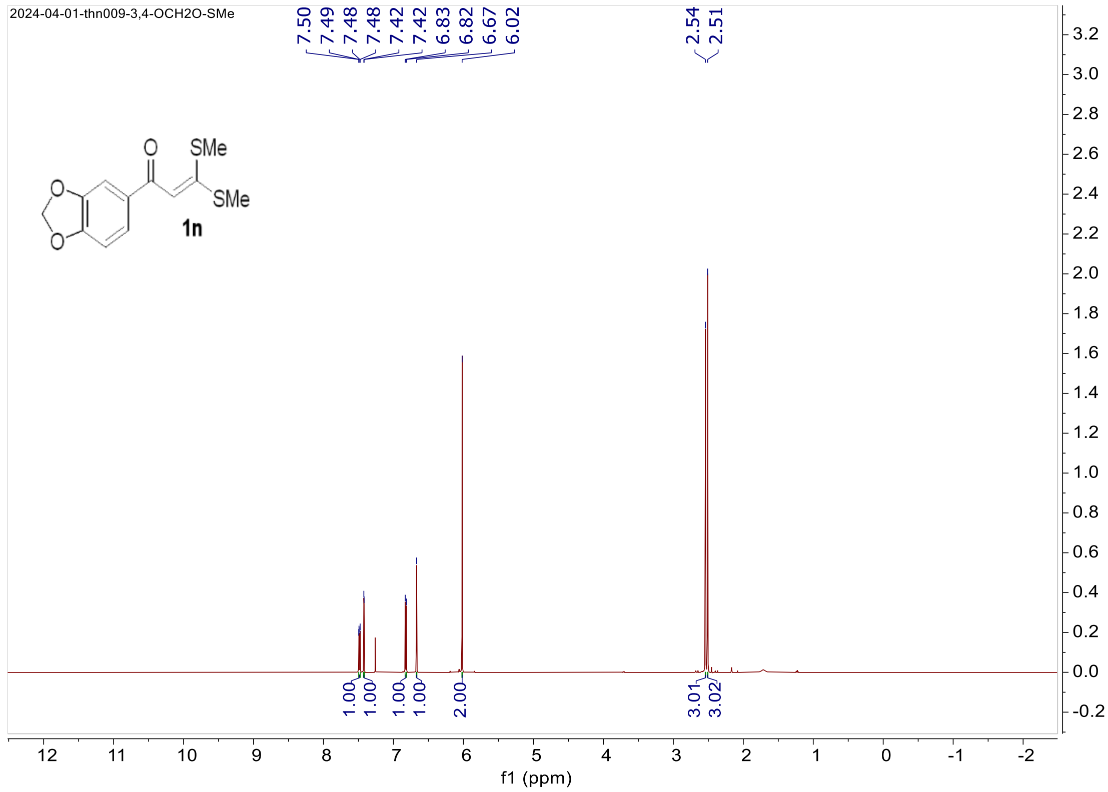


Figure S32 ^{1}H NMR spectra of **1n** ($CDCl_3$, 500 MHz)

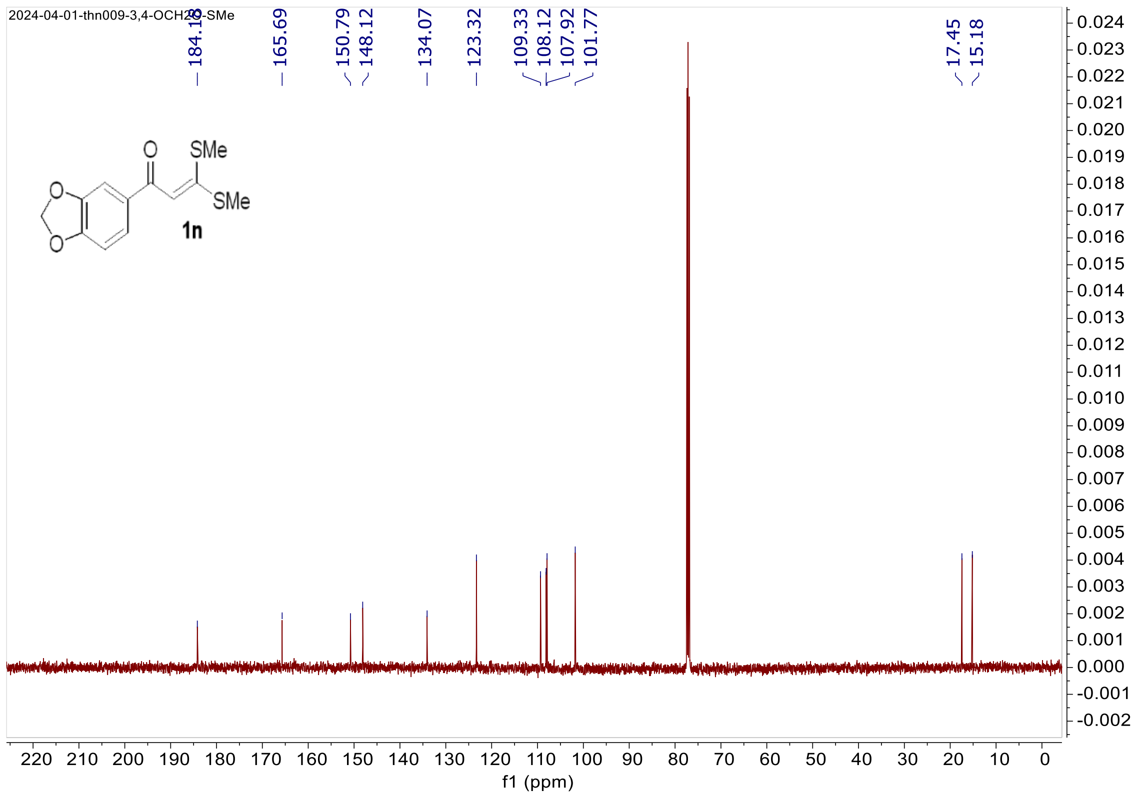


Figure S33 ^{13}C NMR spectra of **1n** ($CDCl_3$, 125 MHz)

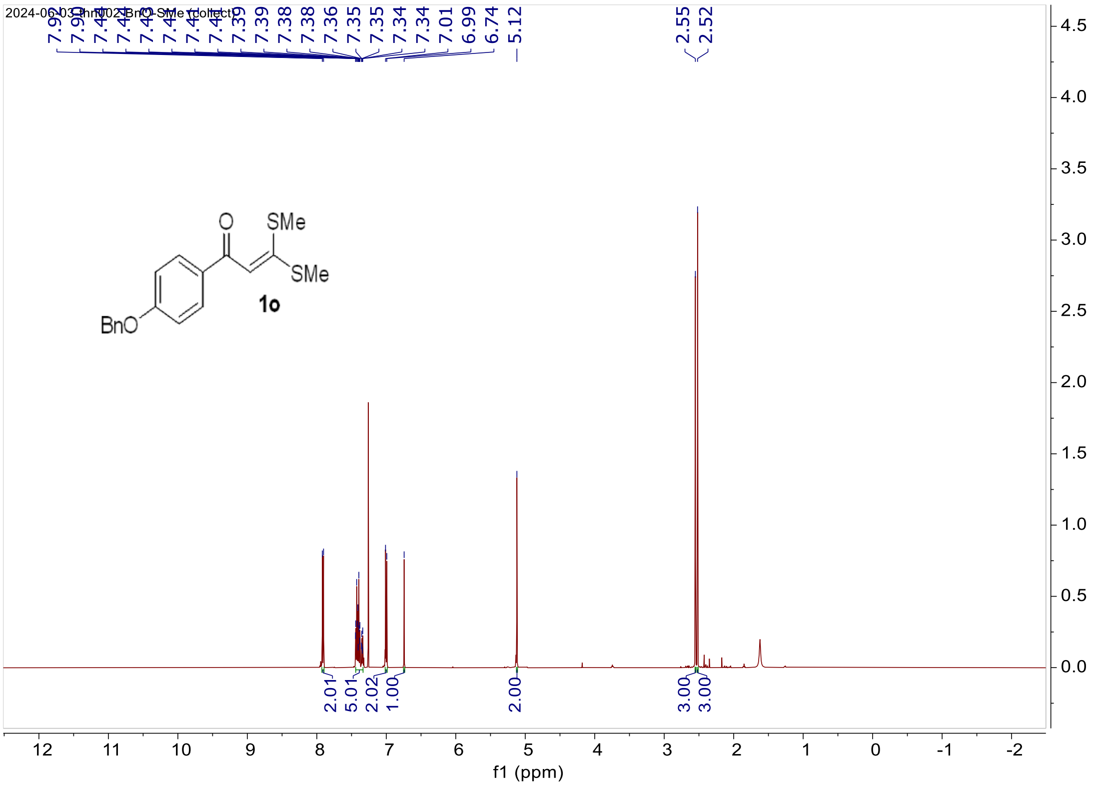


Figure S34 [1]H NMR spectra of **1o** ($CDCl_3$, 500 MHz)

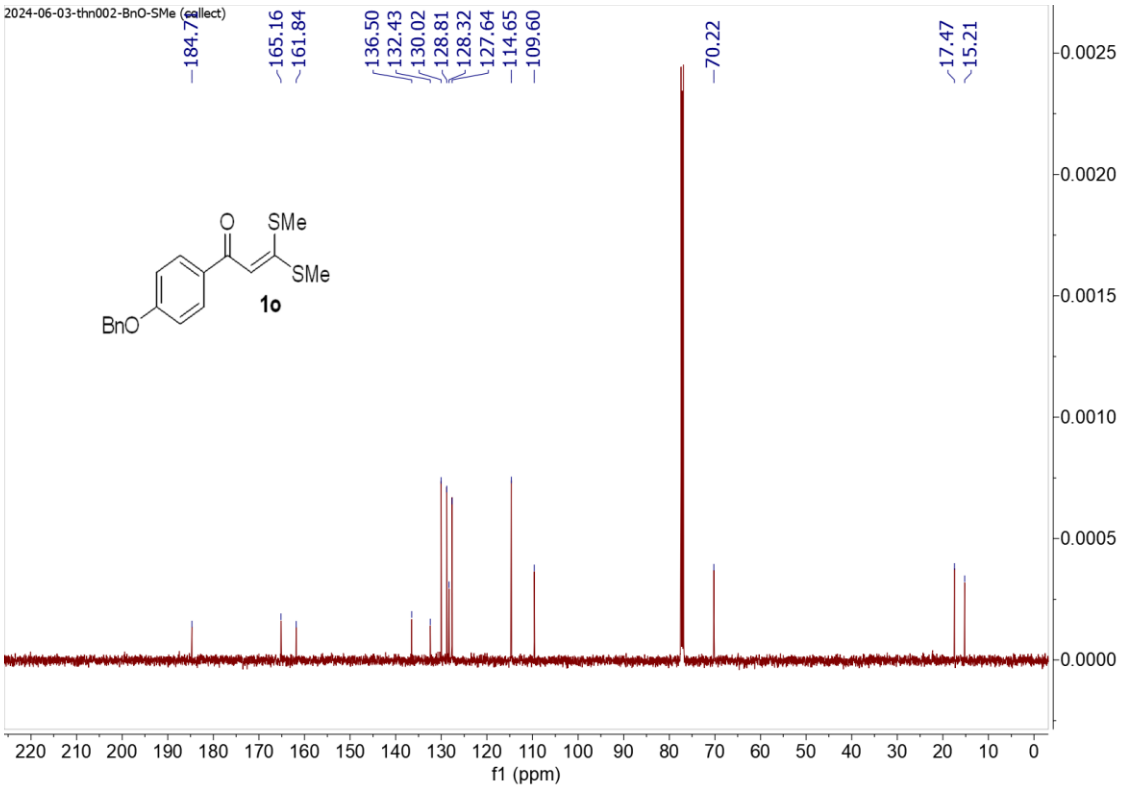


Figure S35 [13]C NMR spectra of **1o** ($CDCl_3$, 125 MHz)

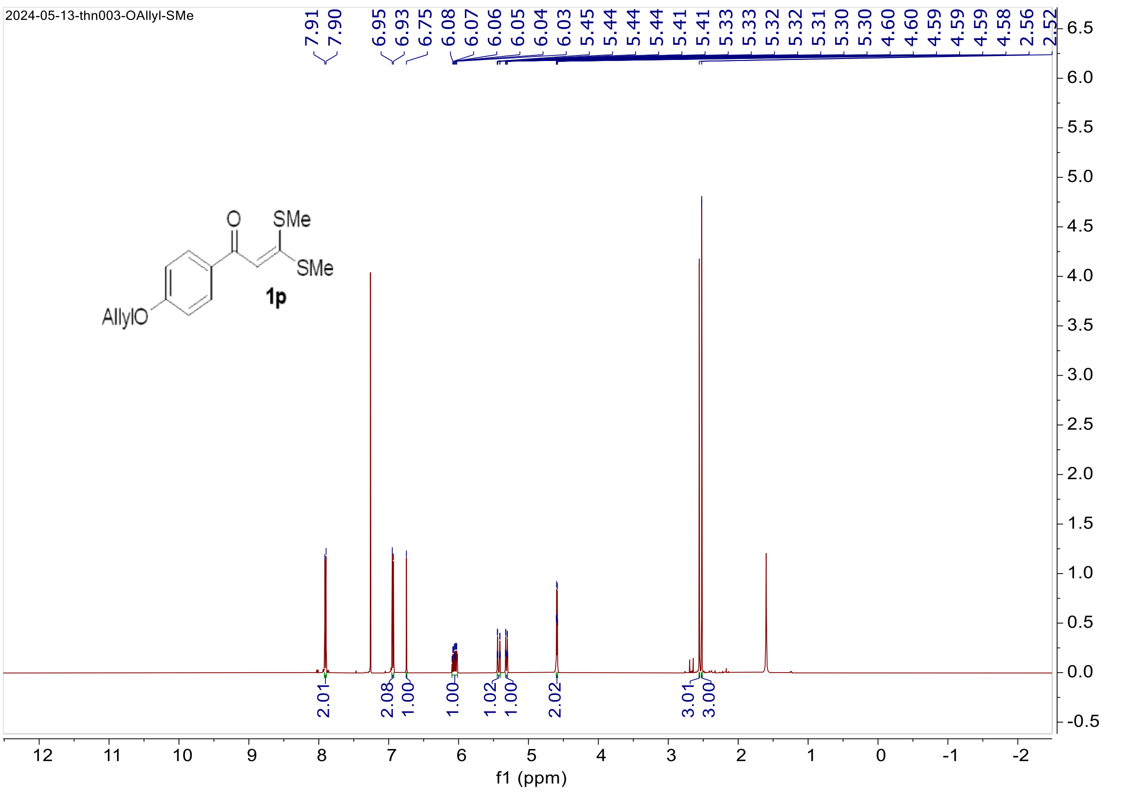


Figure S36 ^{1}H NMR spectra of **1p** ($CDCl_3$, 500 MHz)

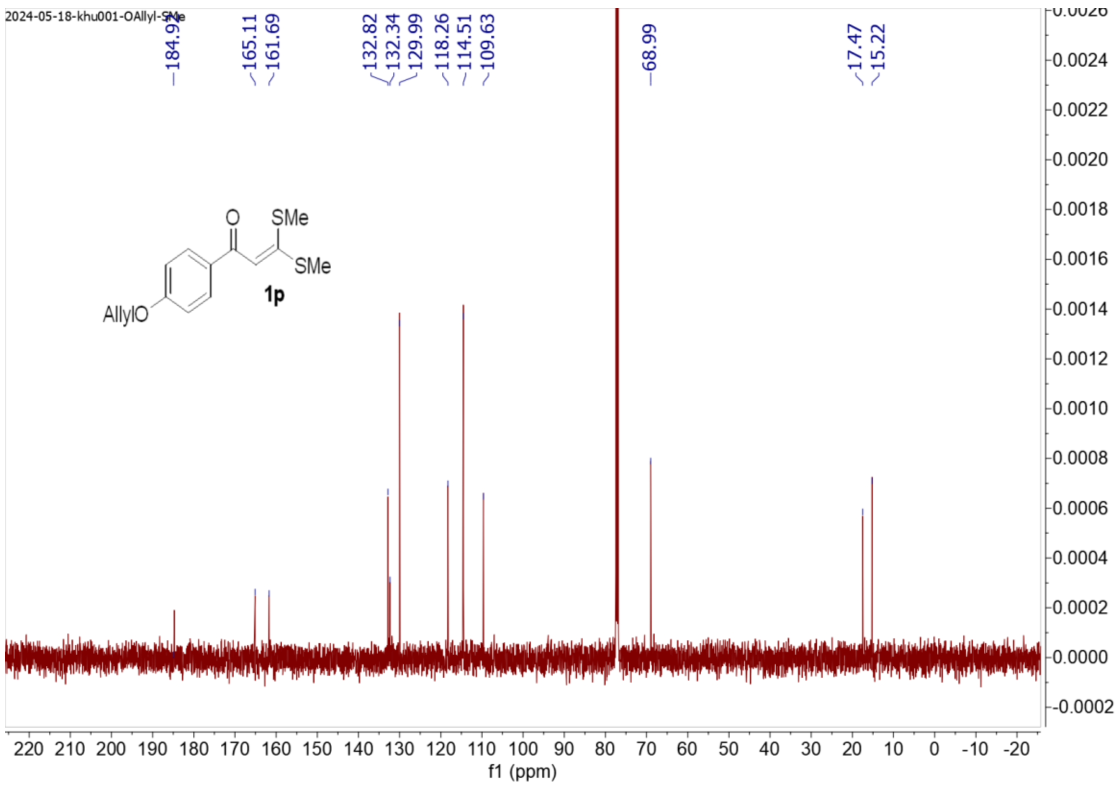


Figure S37 ^{13}C NMR spectra of **1p** ($CDCl_3$, 125 MHz)

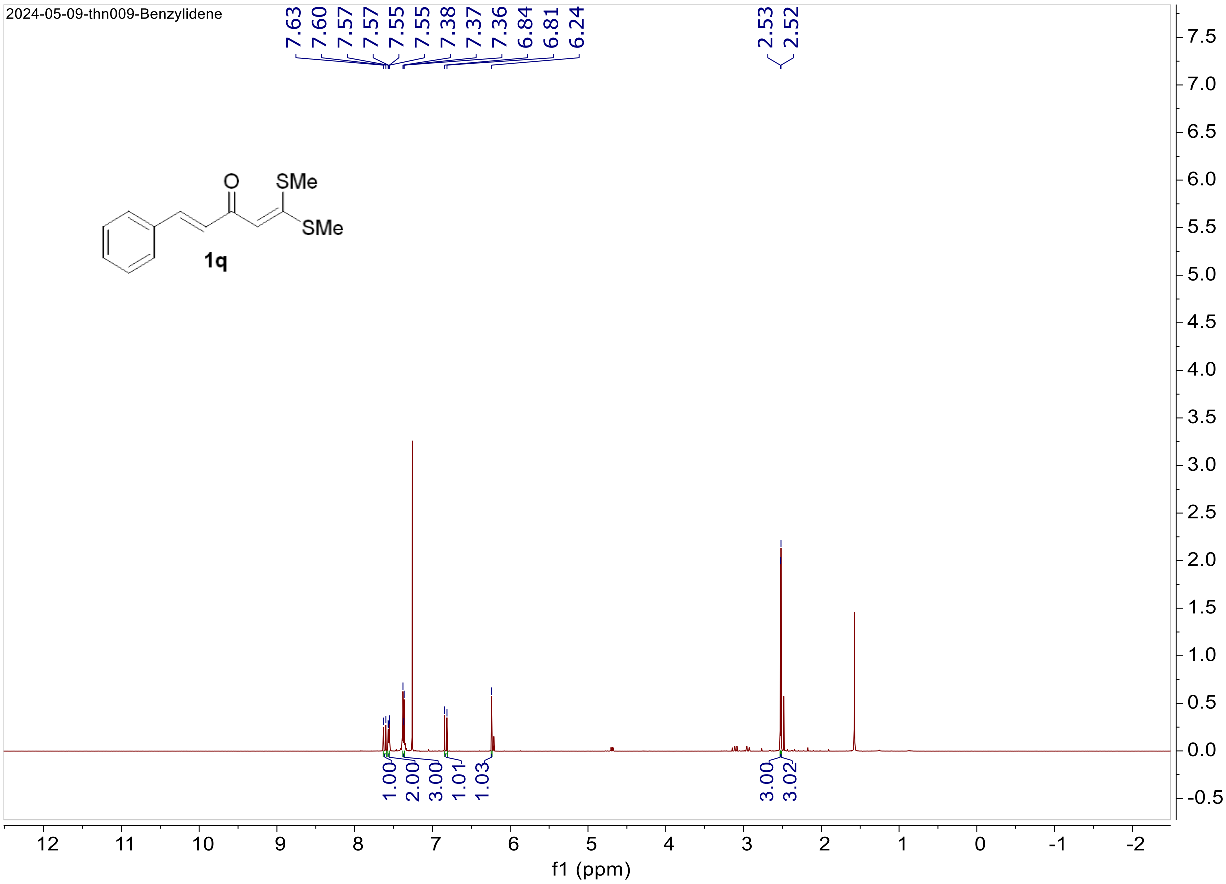


Figure S38 ^{1}H NMR spectra of **1q** ($CDCl_3$, 500 MHz)

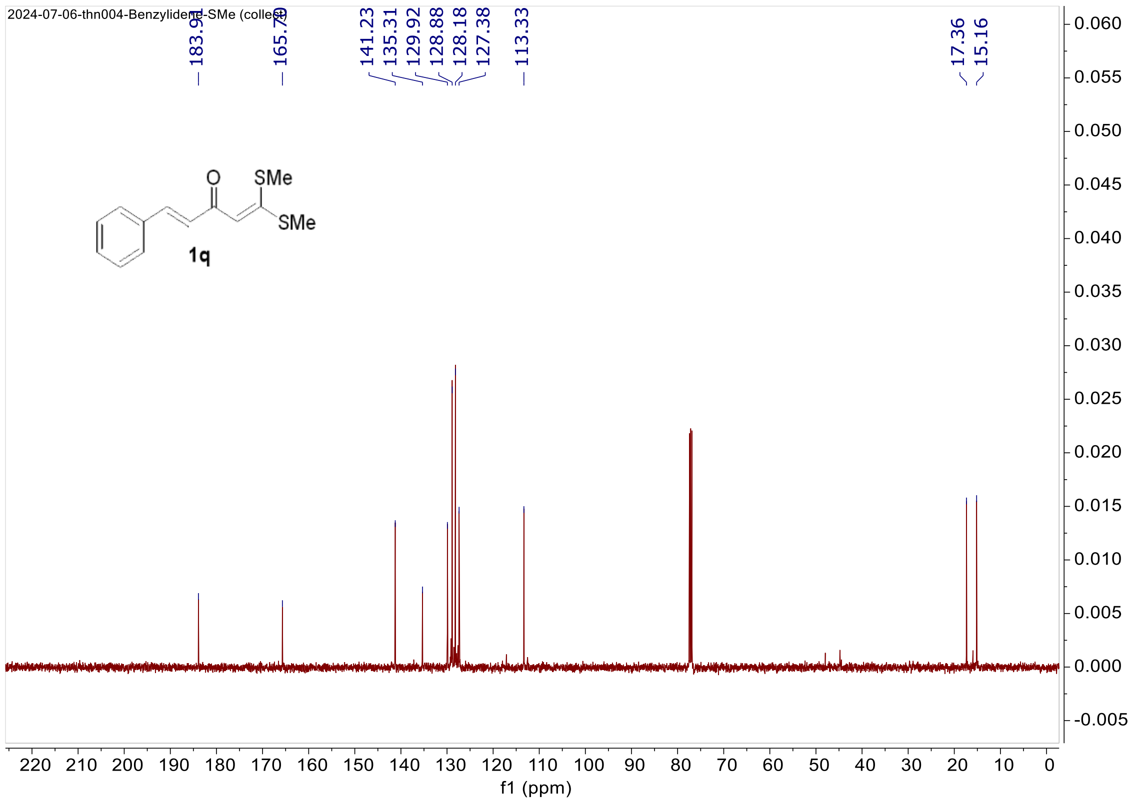


Figure S39 ^{13}C NMR spectra of **1q** ($CDCl_3$, 125 MHz)

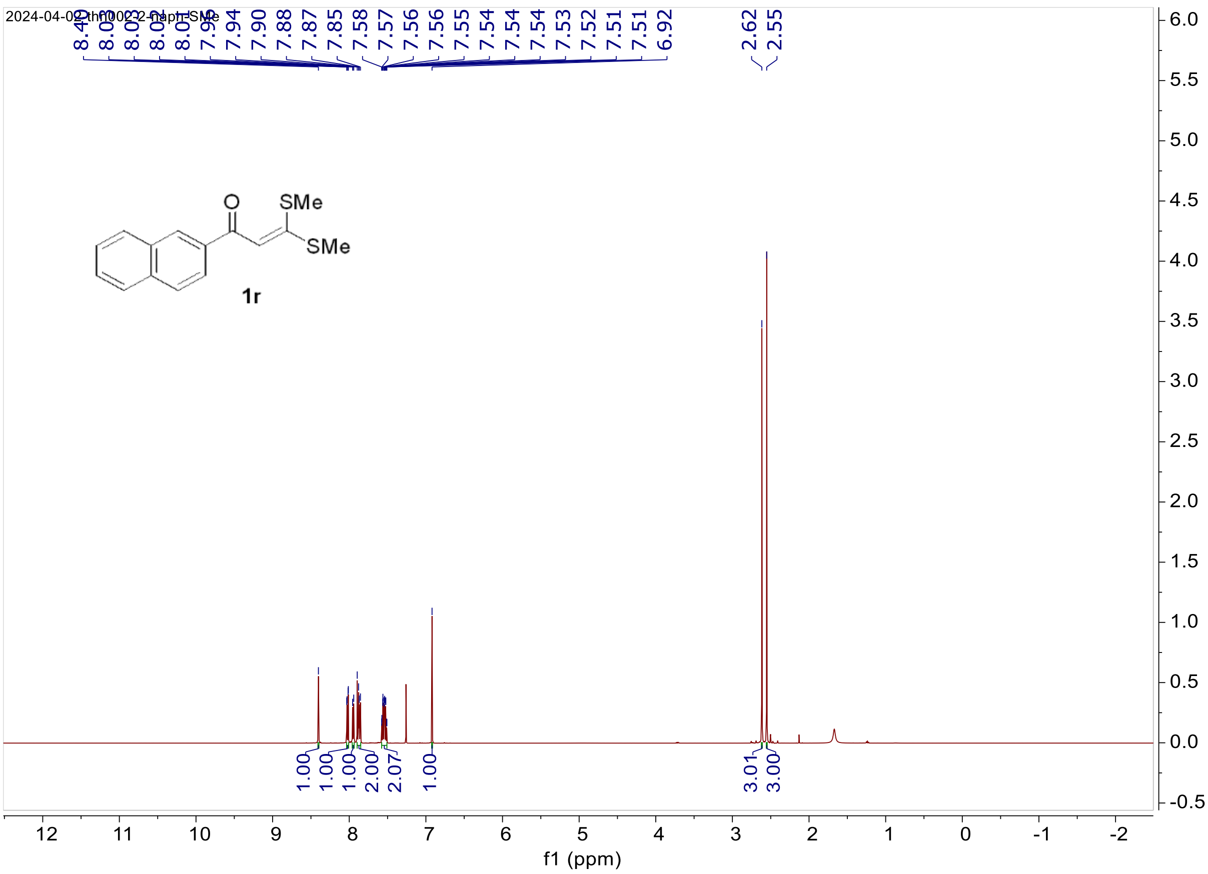


Figure S40 ^{1}H NMR spectra of **1r** ($CDCl_3$, 500 MHz)

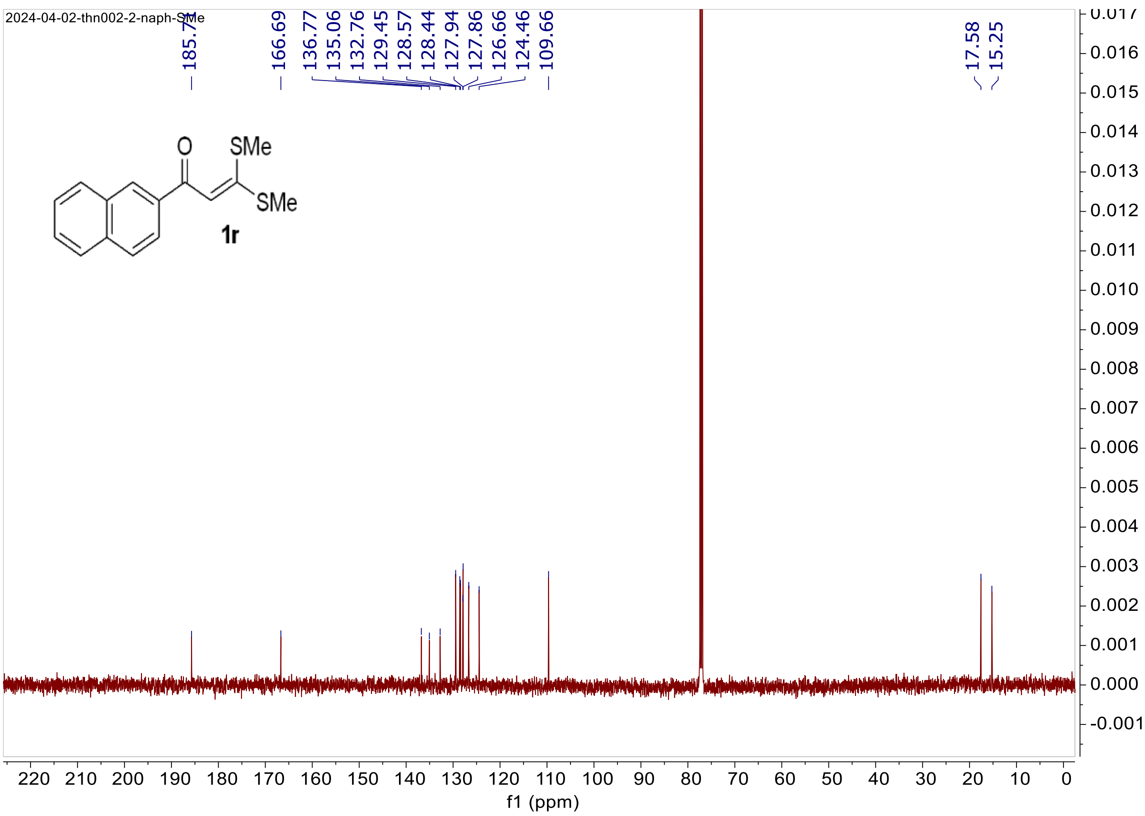


Figure S41 ^{13}C NMR spectra of **1r** ($CDCl_3$, 125 MHz)

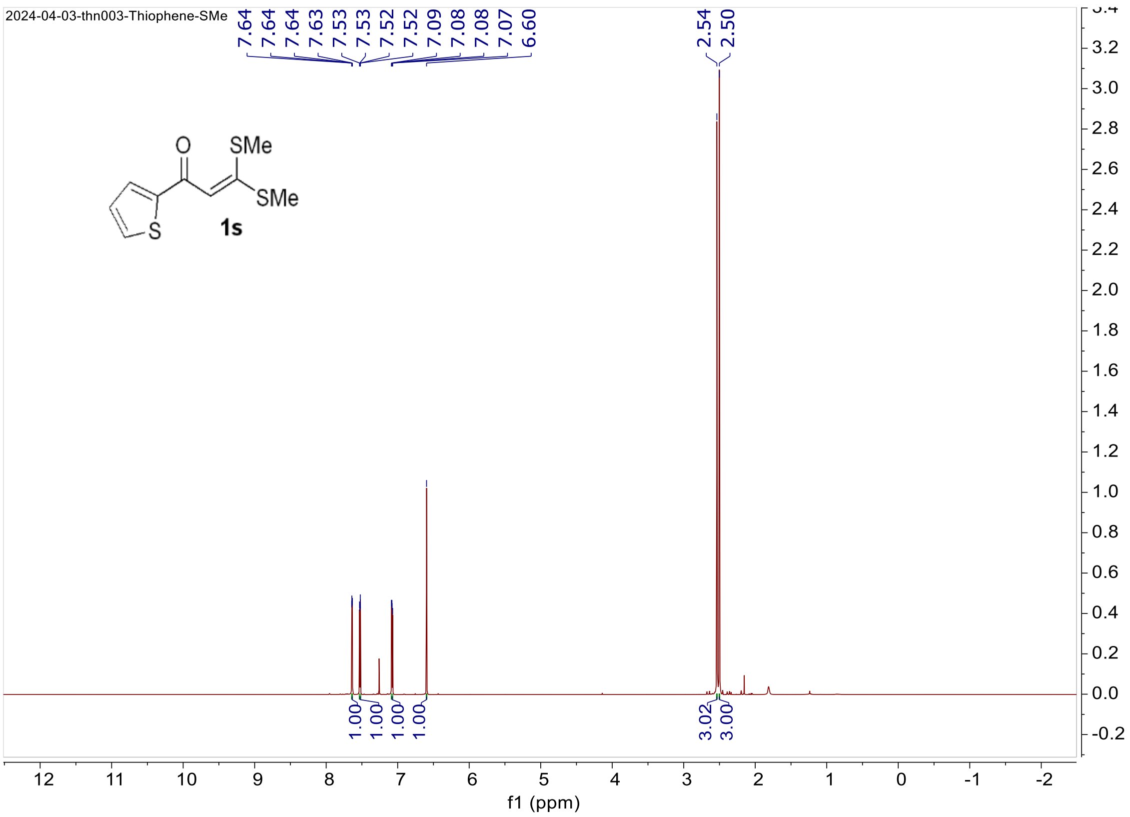


Figure S42 ^{1}H NMR spectra of **1s** (CDCl$_3$, 500 MHz)

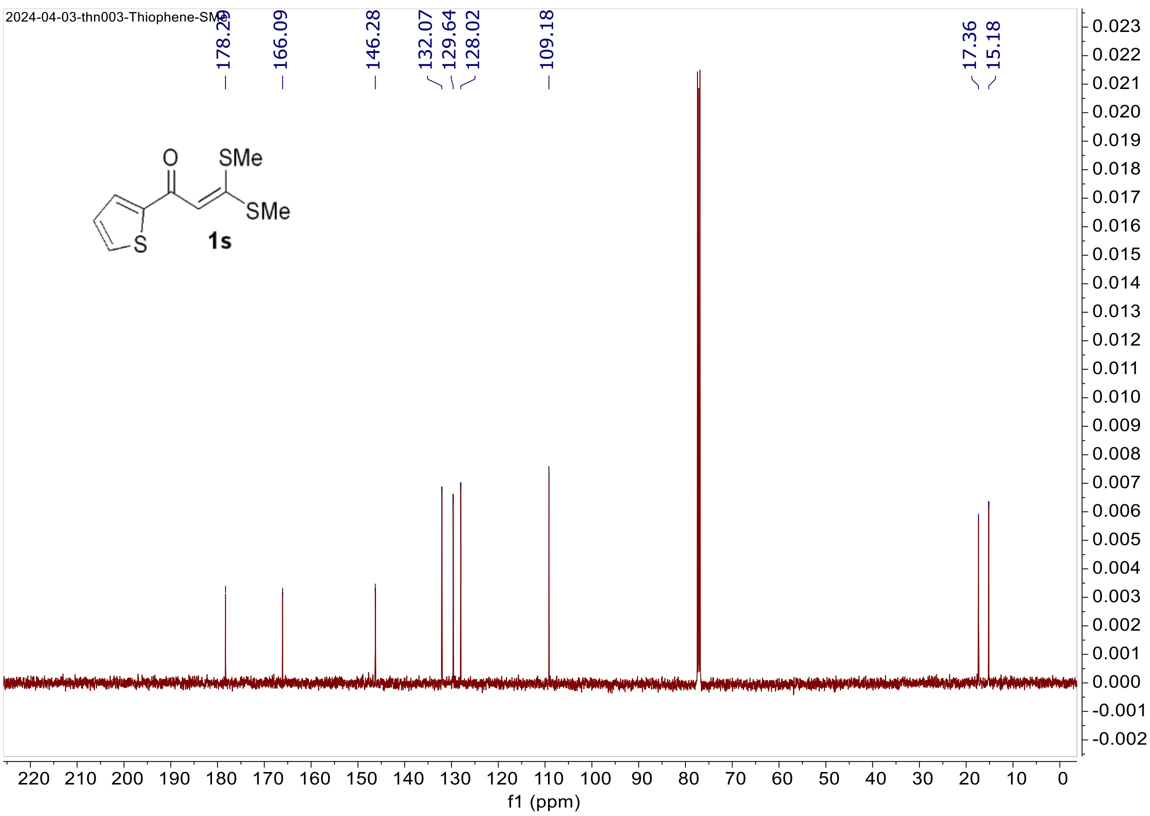


Figure S43 ^{13}C NMR spectra of **1r** (CDCl$_3$, 125 MHz)

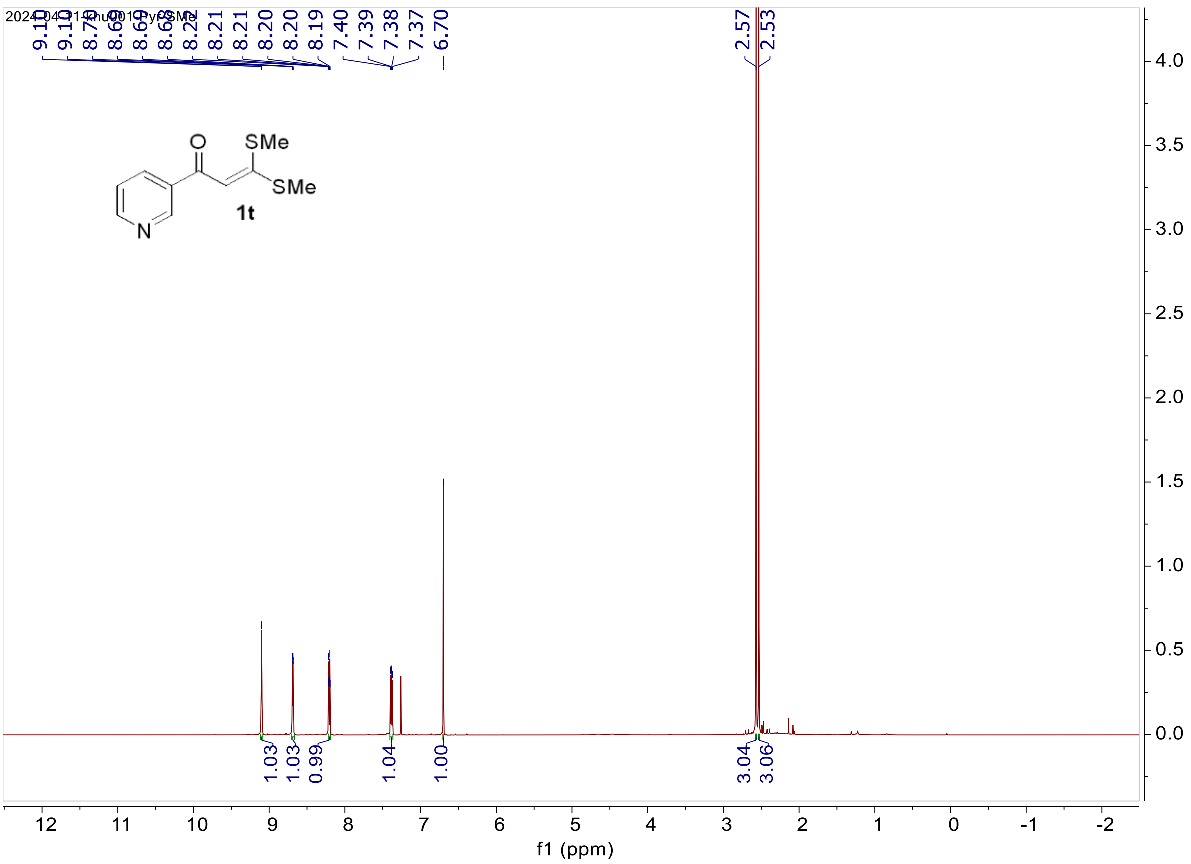


Figure S44 ^{1}H NMR spectra of **1t** ($CDCl_3$, 500 MHz)

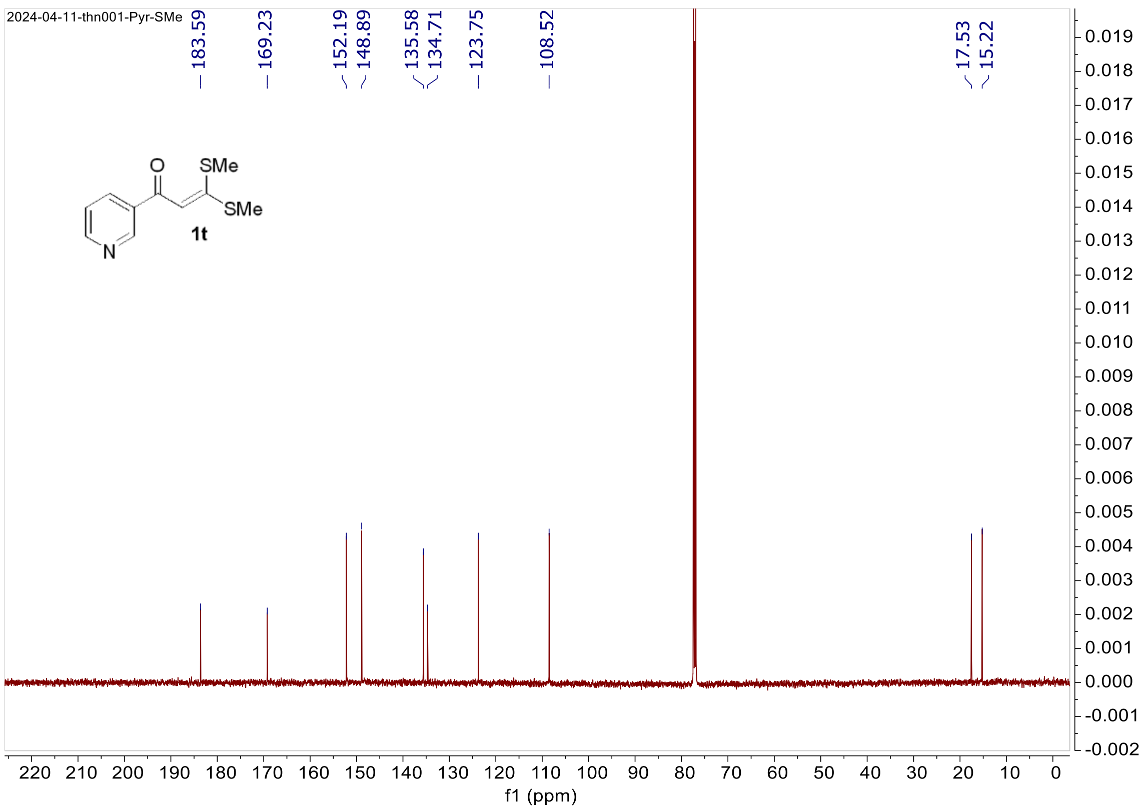


Figure S45 ^{13}C NMR spectra of **1t** ($CDCl_3$, 125 MHz)

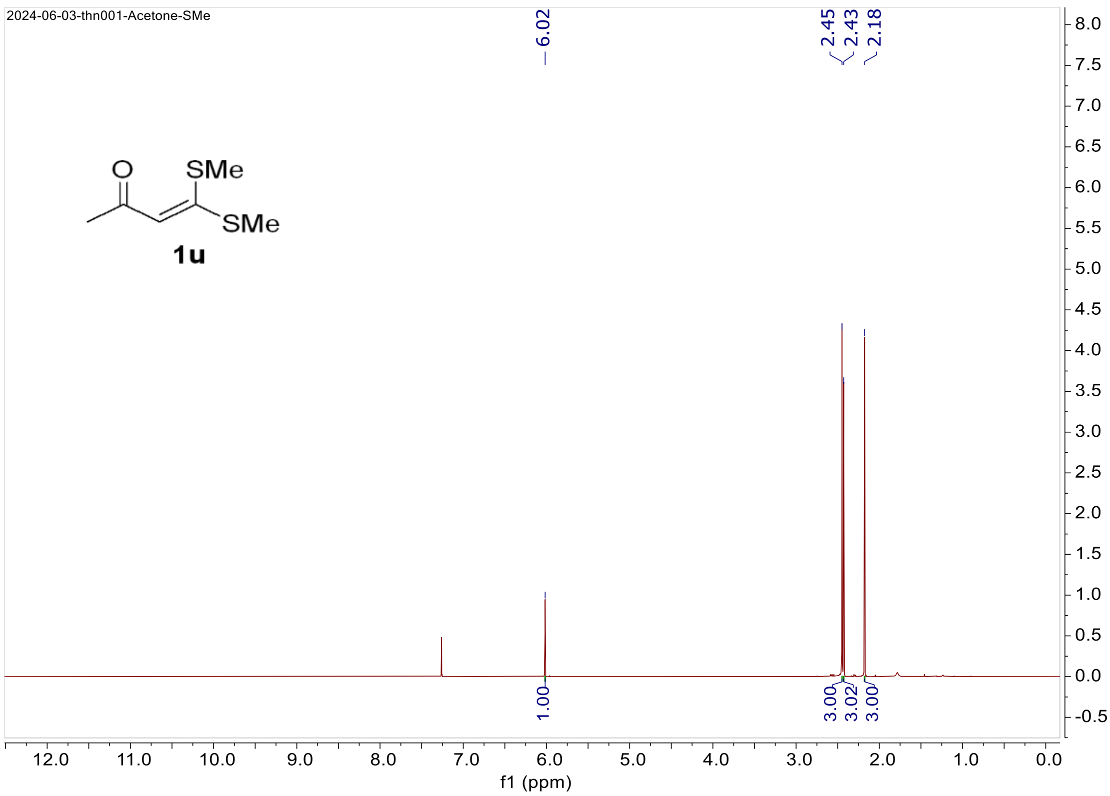


Figure S46 ^{1}H NMR spectra of **1u** ($CDCl_3$, 500 MHz)

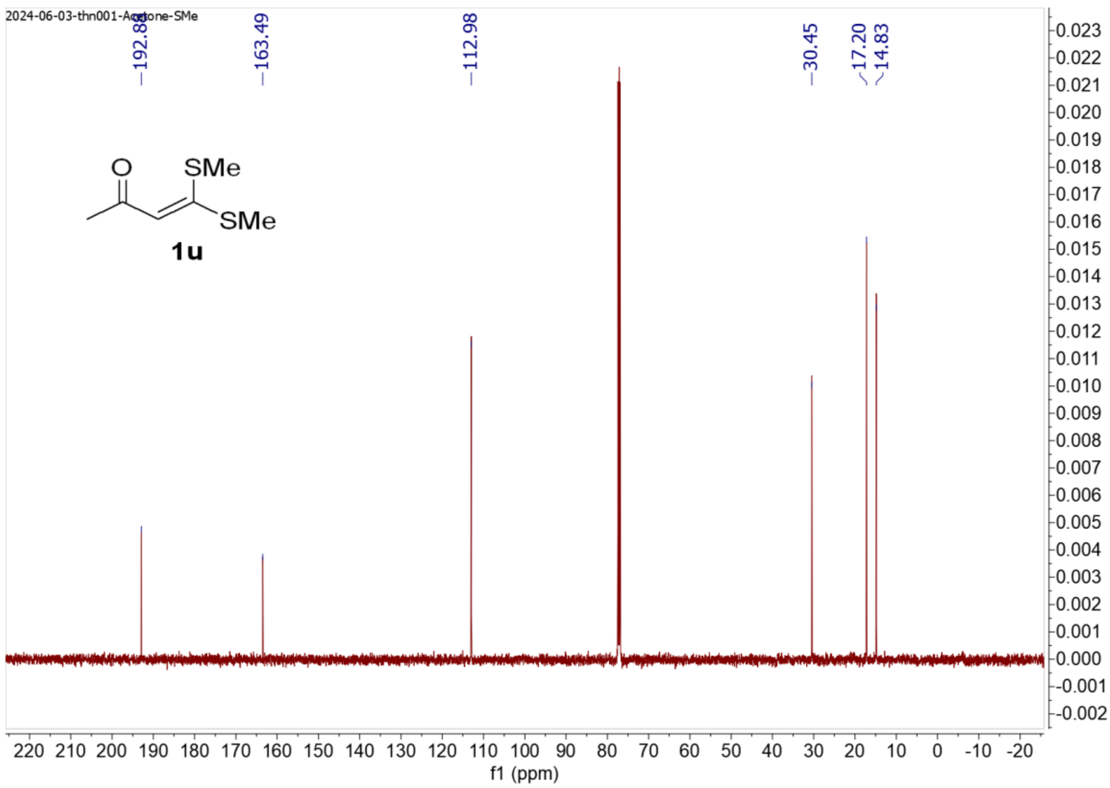


Figure S47 ^{13}C NMR spectra of **1u** ($CDCl_3$, 125 MHz)

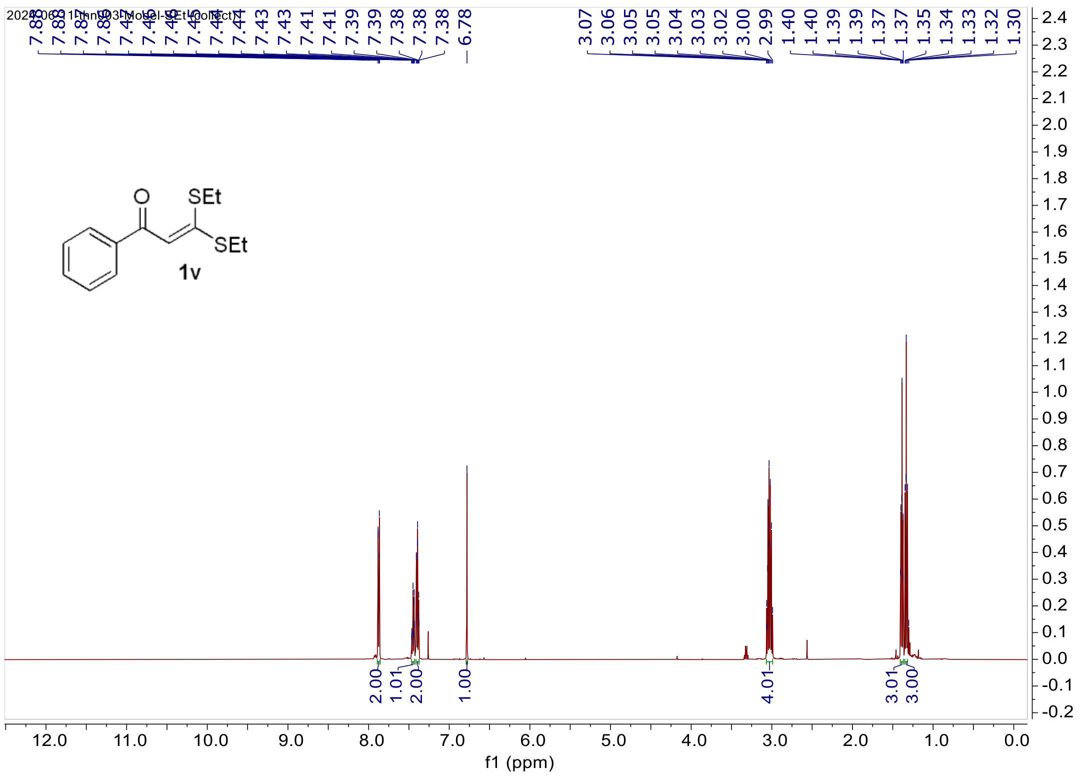


Figure S48 ^{1}H NMR spectra of **1v** ($CDCl_3$, 500 MHz)

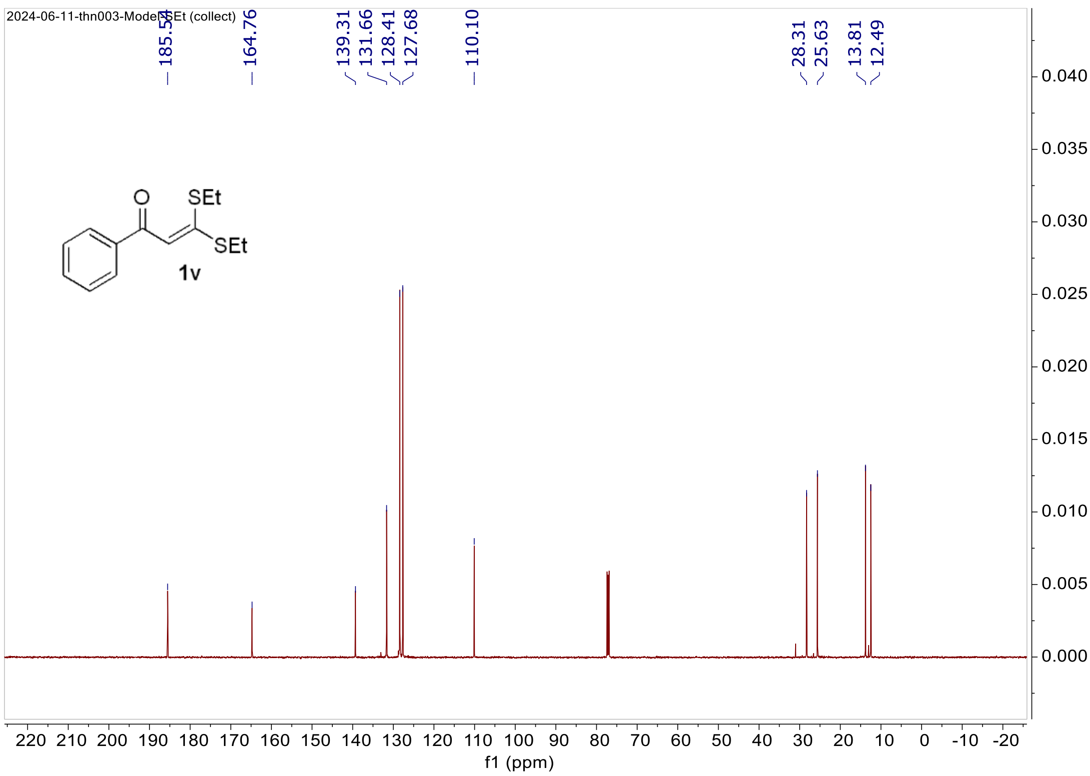


Figure S49 ^{13}C NMR spectra of **1v** ($CDCl_3$, 125 MHz)

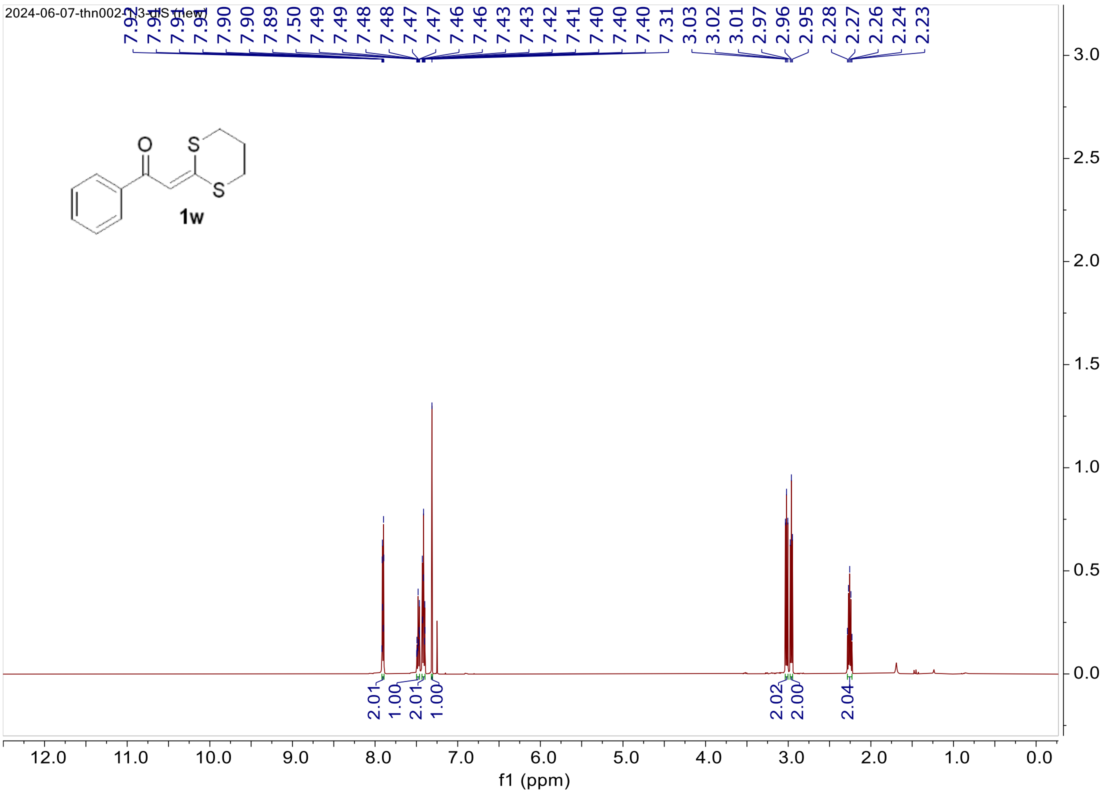


Figure S50 ^{1}H NMR spectra of **1w** ($CDCl_3$, 500 MHz)

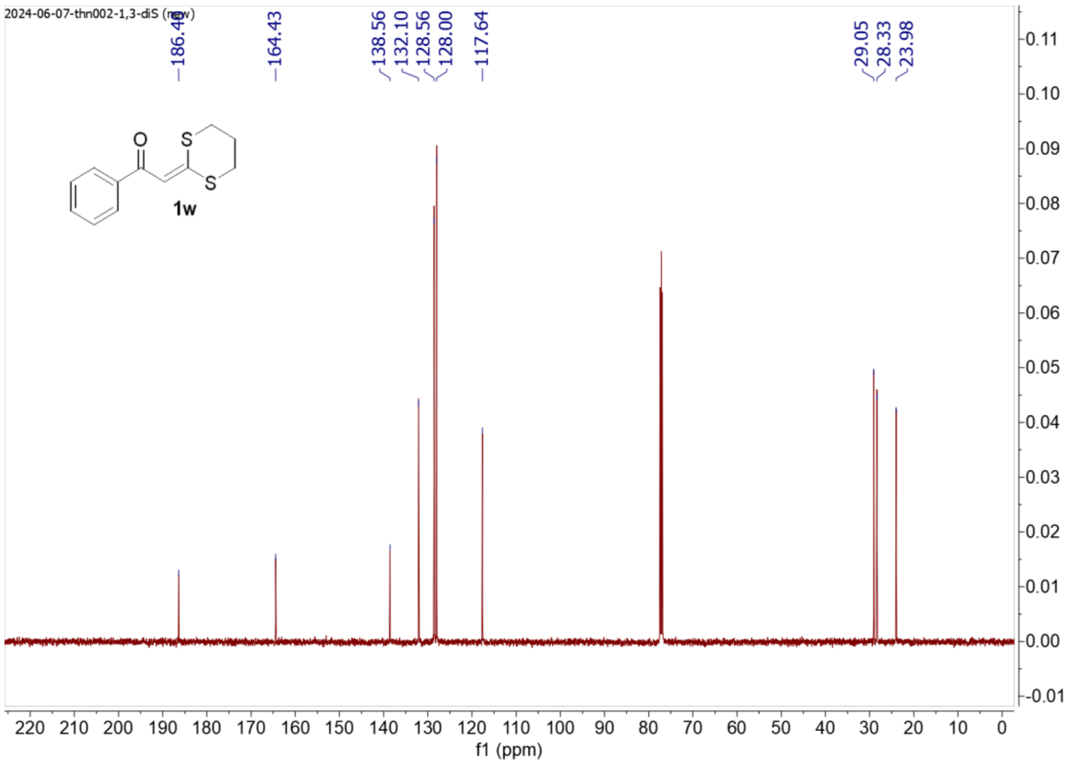


Figure S51 ^{13}C NMR spectra of **1w** ($CDCl_3$, 125 MHz)

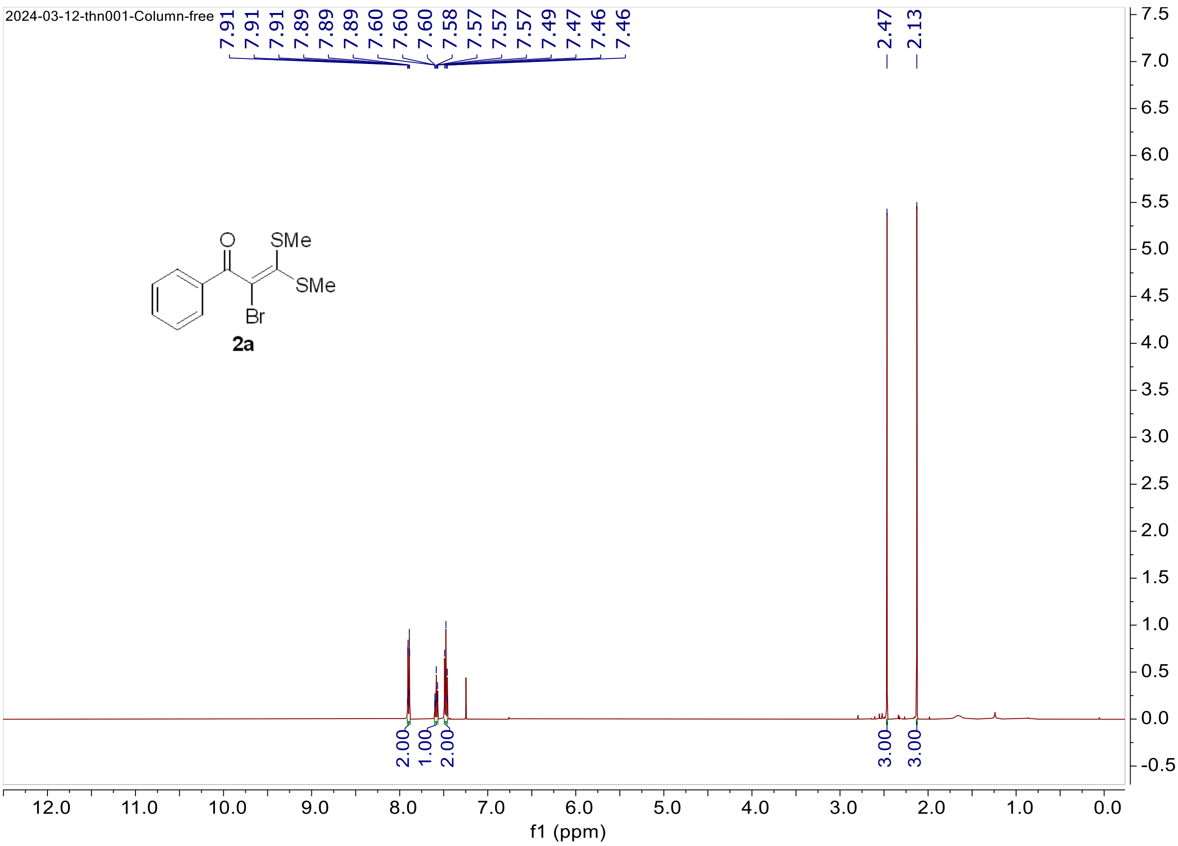


Figure S52 ^{1}H NMR spectra of **2a** ($CDCl_3$, 500 MHz)

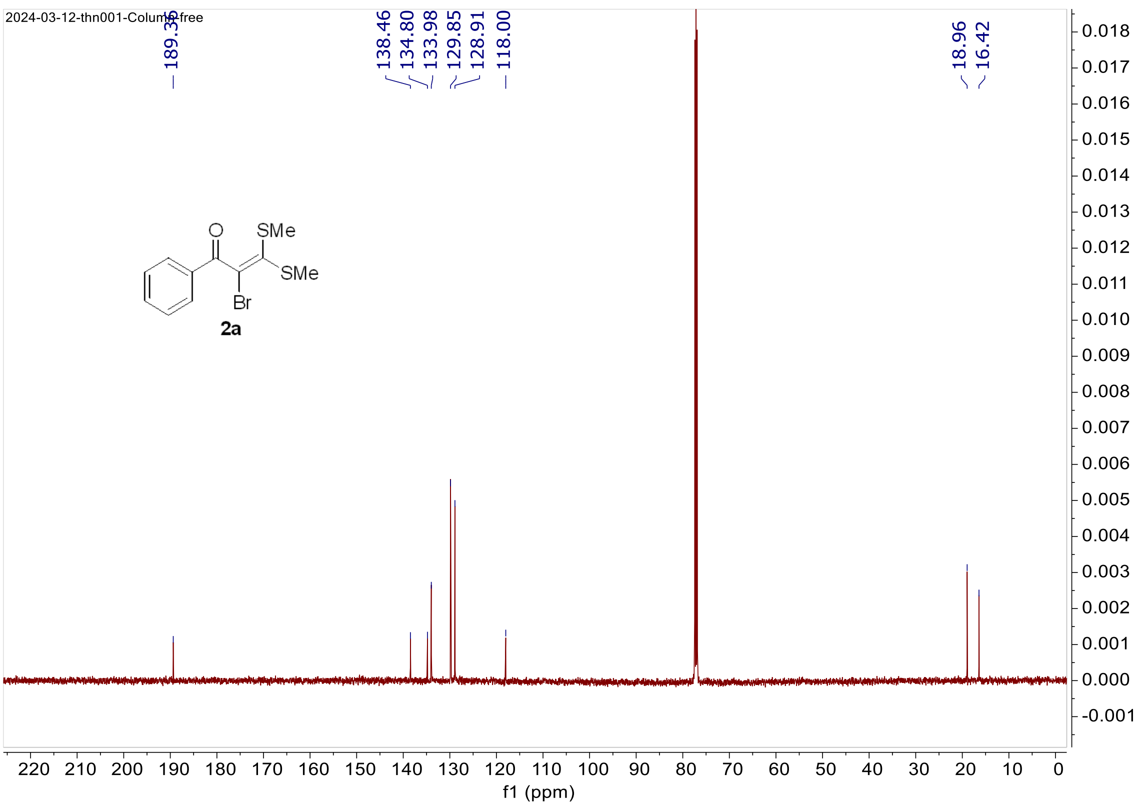


Figure S53 ^{13}C NMR spectra of **2a** ($CDCl_3$, 125 MHz)

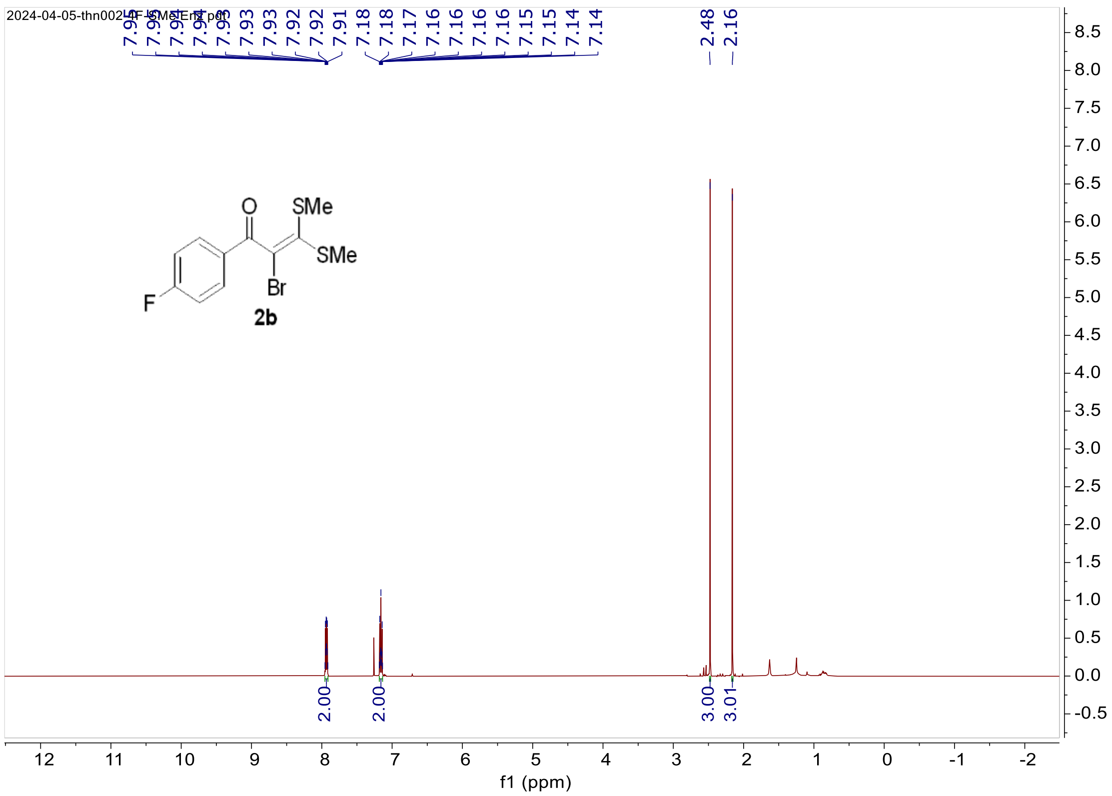


Figure S54 ^{1}H NMR spectra of **2b** ($CDCl_3$, 500 MHz)

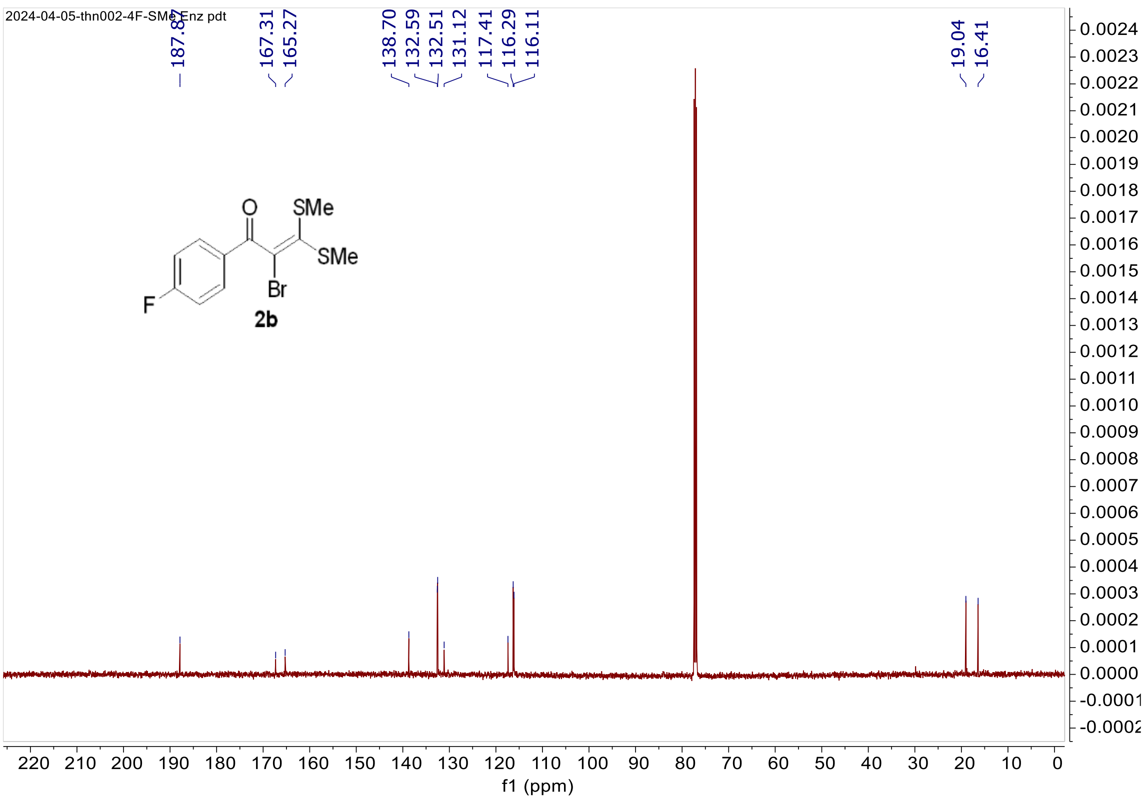


Figure S55 ^{13}C NMR spectra of **2b** ($CDCl_3$, 125 MHz)

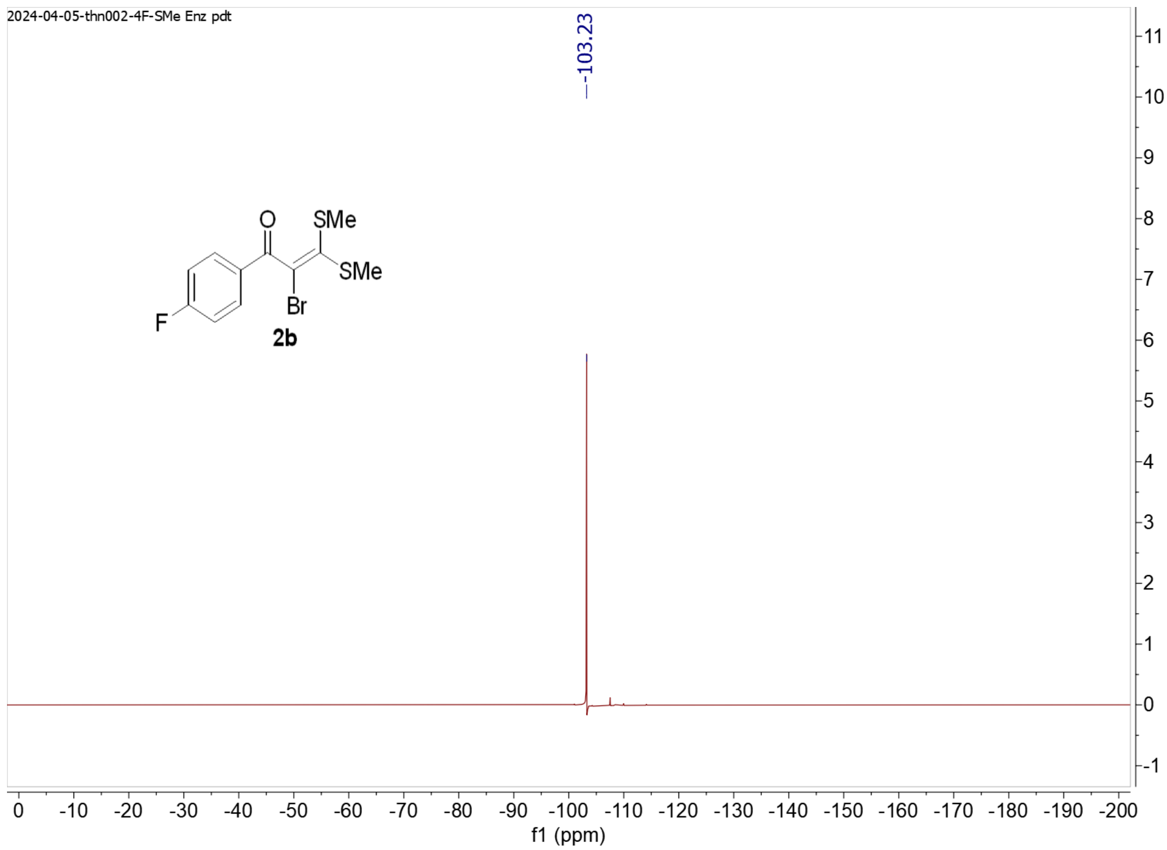


Figure S56 ^{19}F NMR spectra of **2b** ($CDCl_3$, 470 MHz)

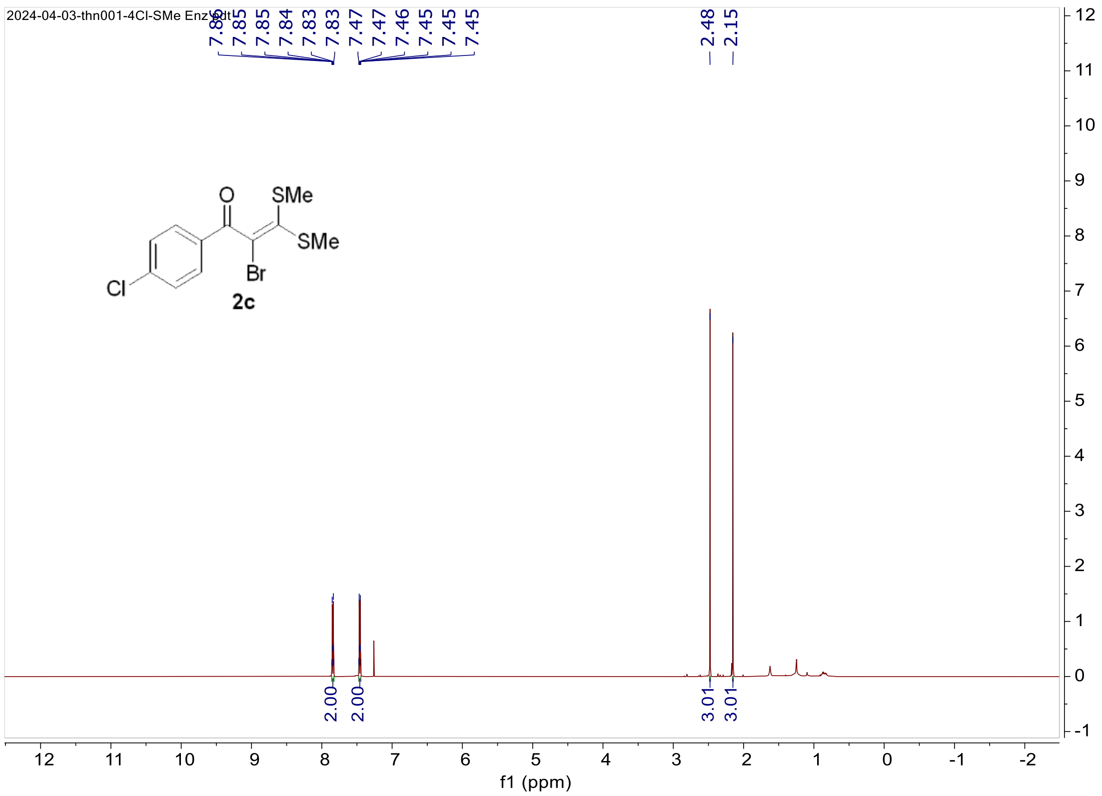


Figure S57 [1]H NMR spectra of **2c** ($CDCl_3$, 500 MHz)

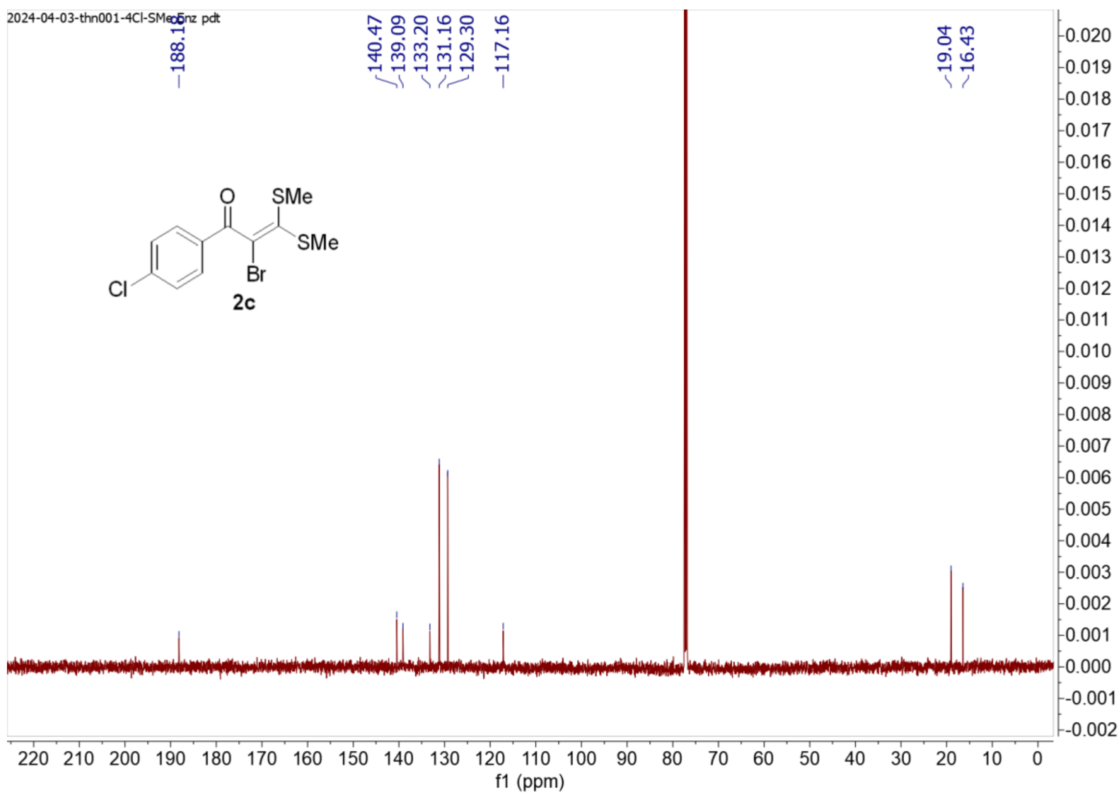


Figure S58 [13]C NMR spectra of **2c** ($CDCl_3$, 125 MHz)

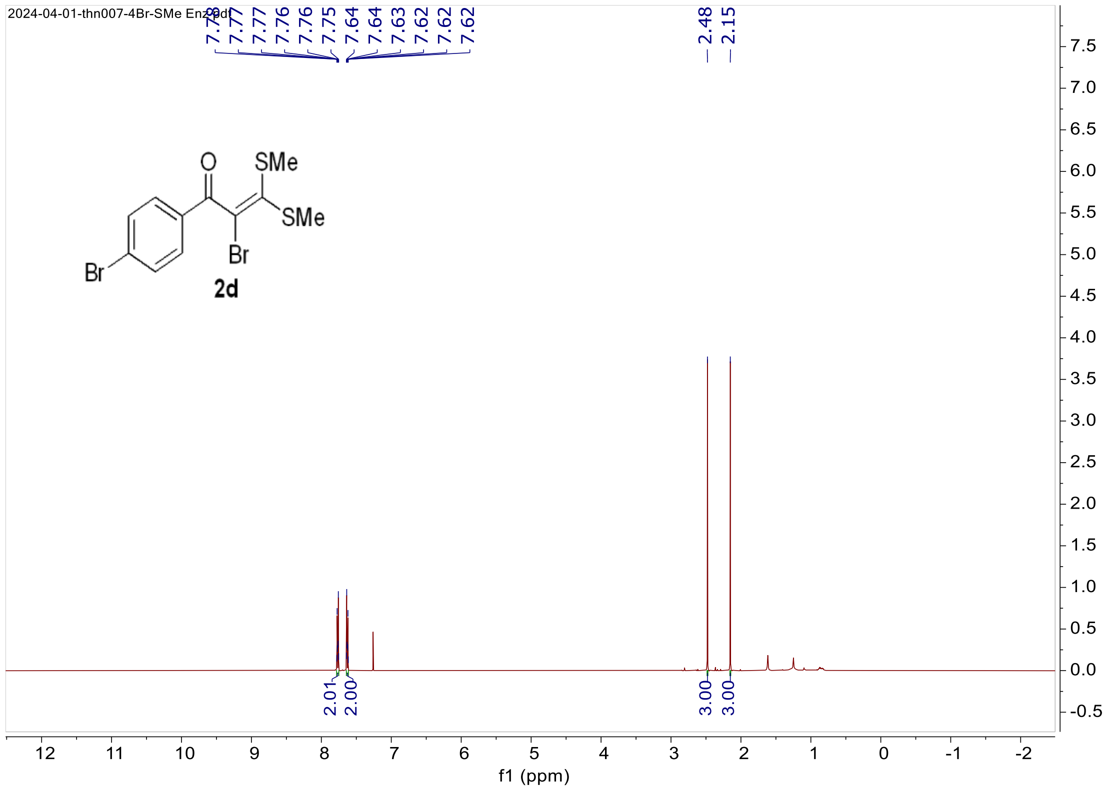


Figure S59 ^{1}H NMR spectra of **2d** ($CDCl_3$, 500 MHz)

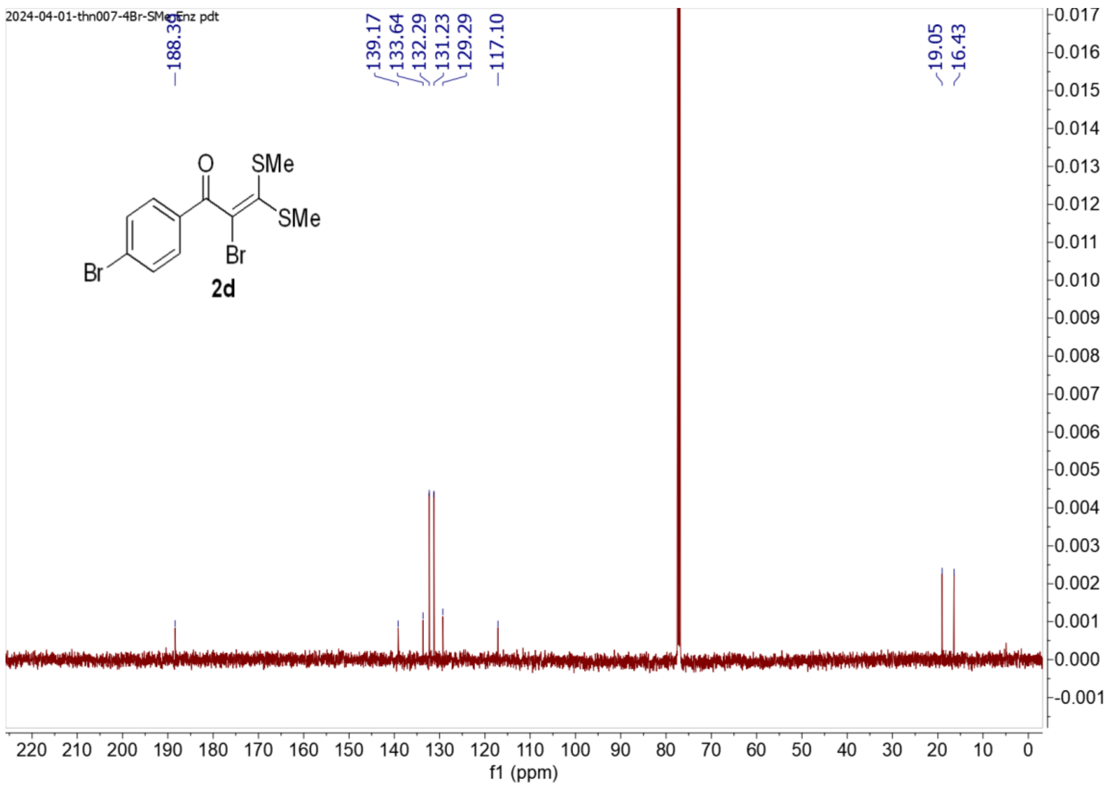


Figure S60 ^{13}C NMR spectra of **2d** ($CDCl_3$, 125 MHz)

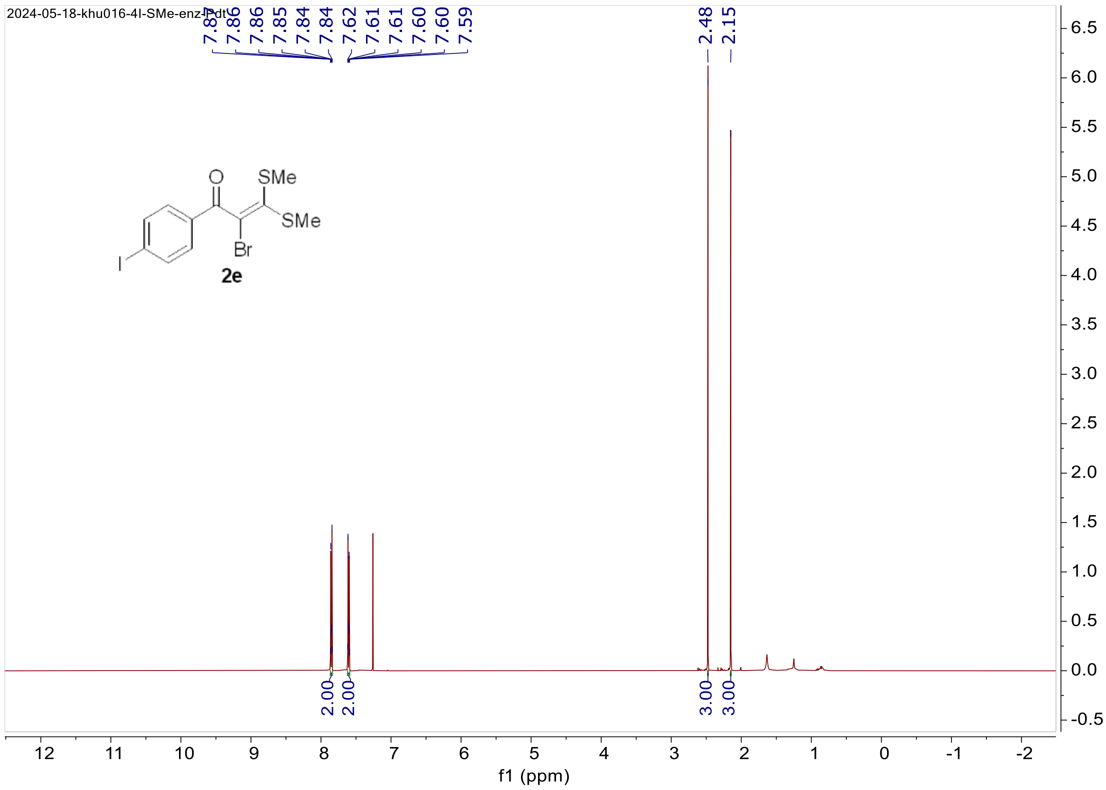


Figure S61 [1]H NMR spectra of **2e** ($CDCl_3$, 500 MHz)

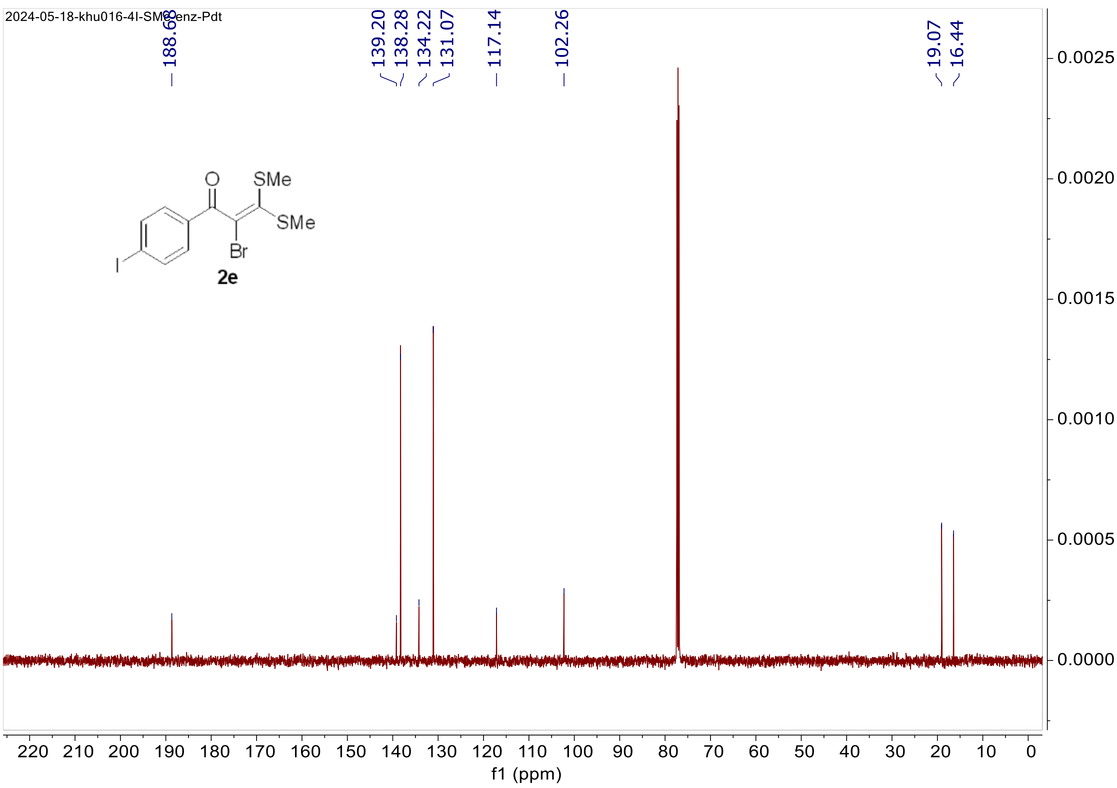


Figure S62 [13]C NMR spectra of **2e** ($CDCl_3$, 125 MHz)

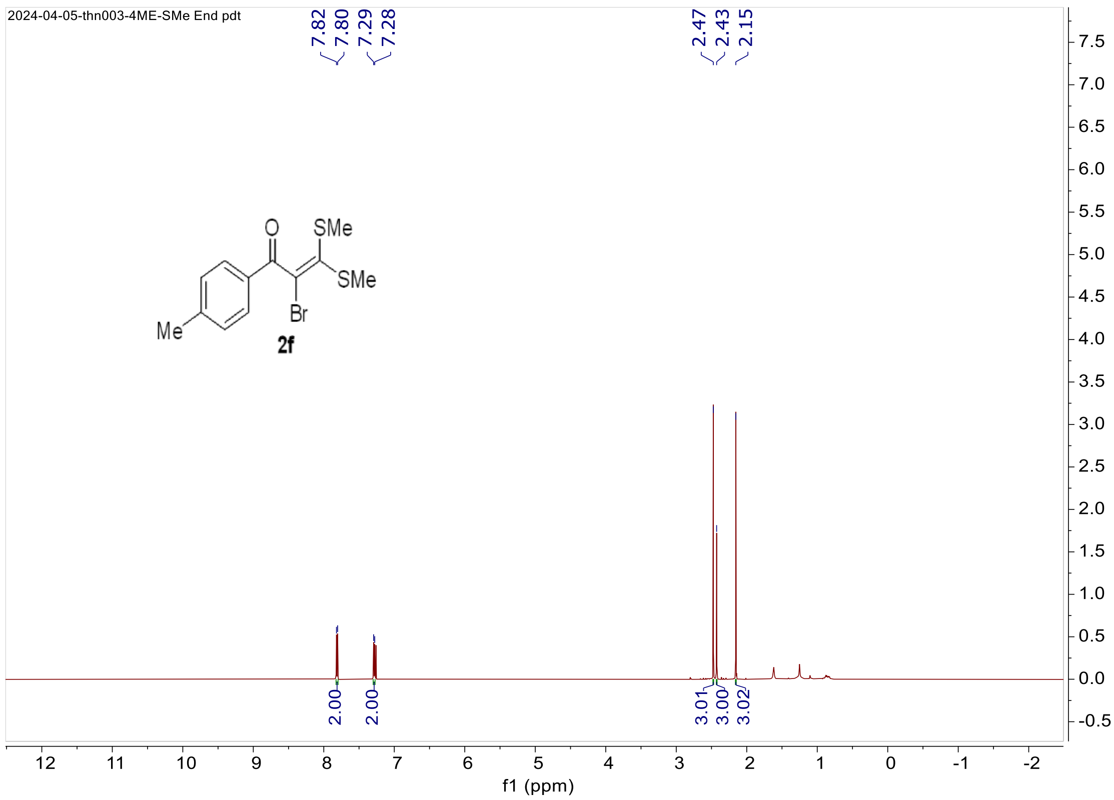


Figure S63 ^{1}H NMR spectra of **2f** ($CDCl_3$, 500 MHz)

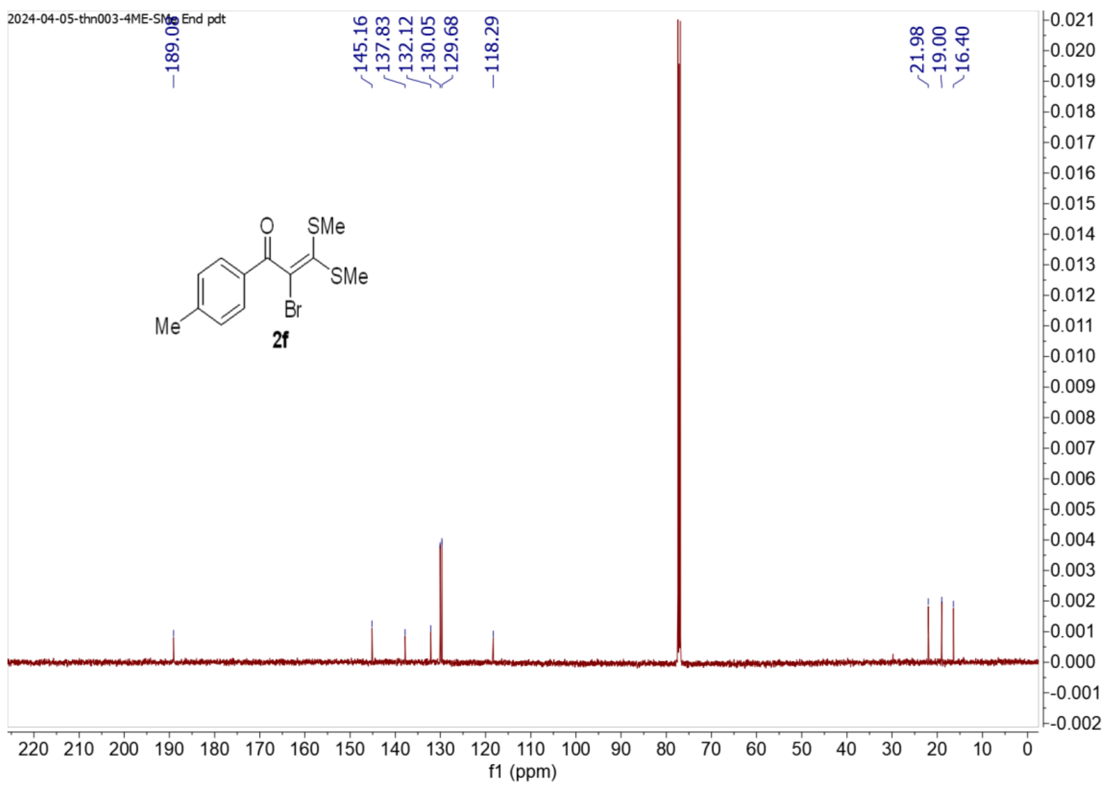


Figure S64 ^{13}C NMR spectra of **2f** ($CDCl_3$, 125 MHz)

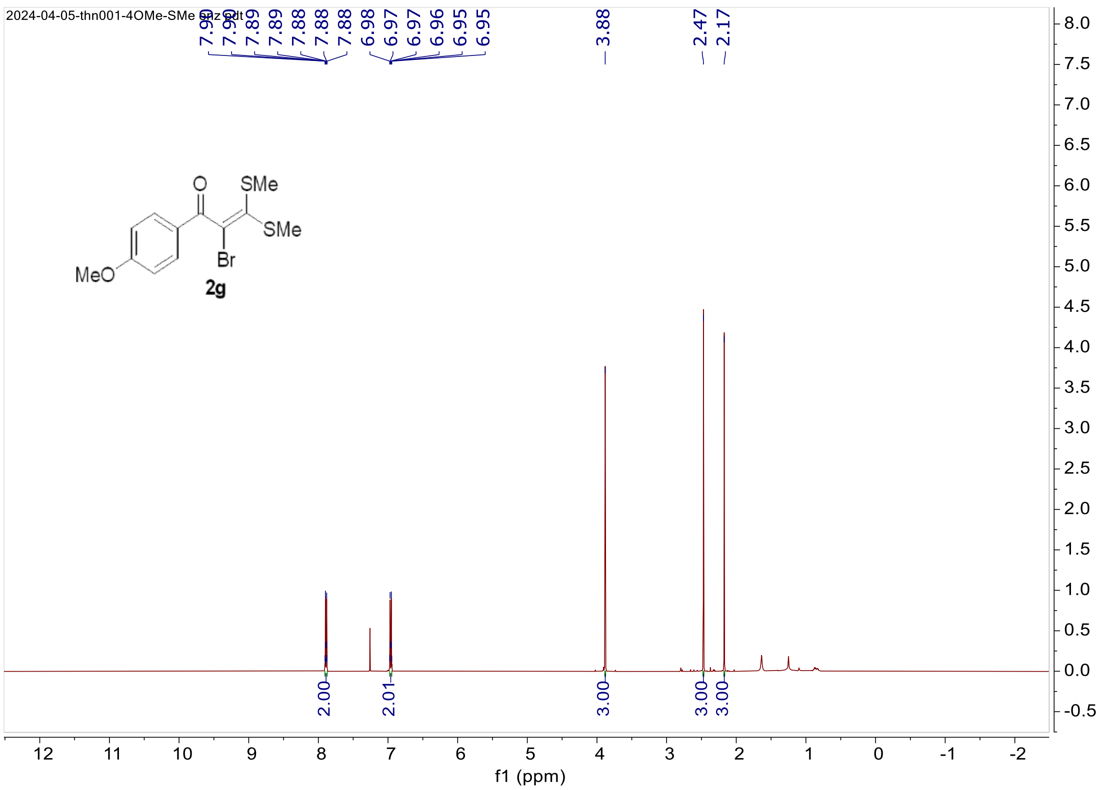


Figure S65 ^{1}H NMR spectra of **2g** ($CDCl_3$, 500 MHz)

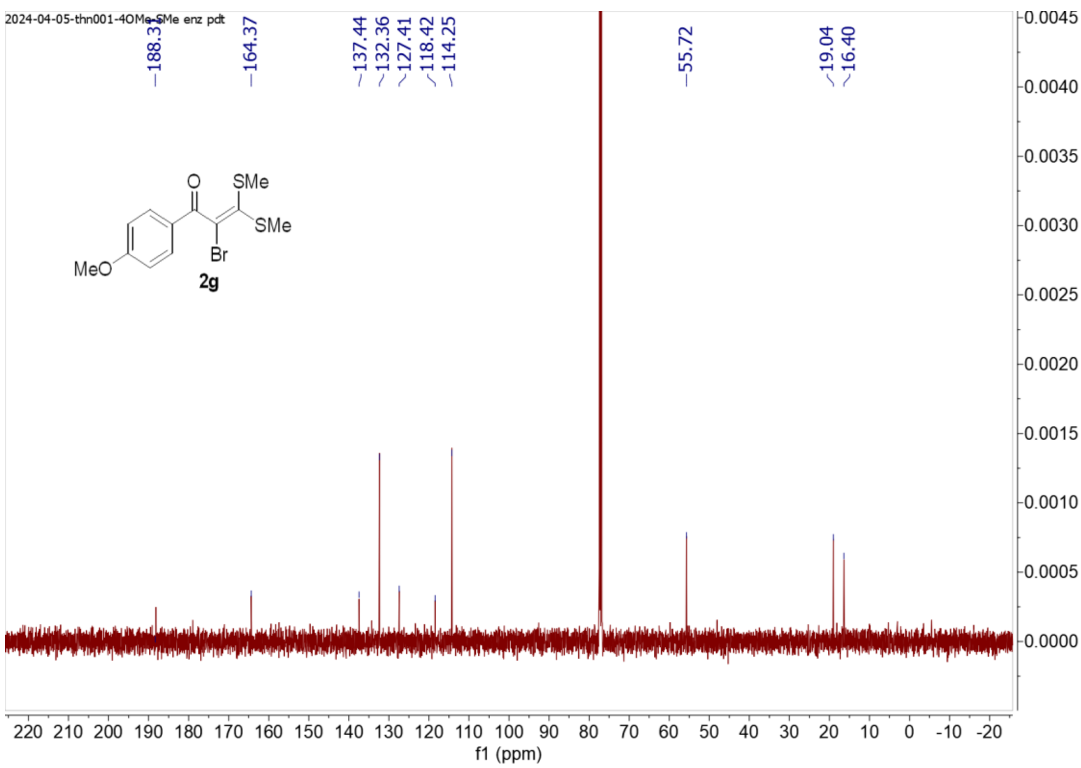


Figure S66 ^{13}C NMR spectra of **2g** ($CDCl_3$, 125 MHz)

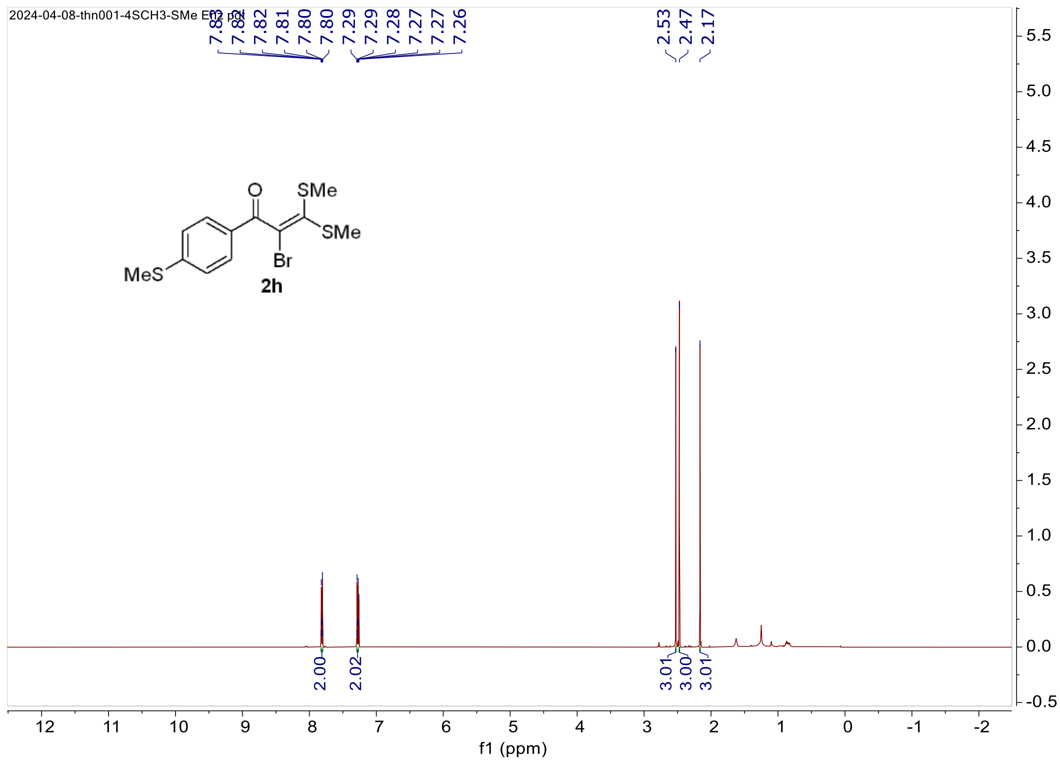


Figure S67 ^{1}H NMR spectra of **2h** ($CDCl_3$, 500 MHz)

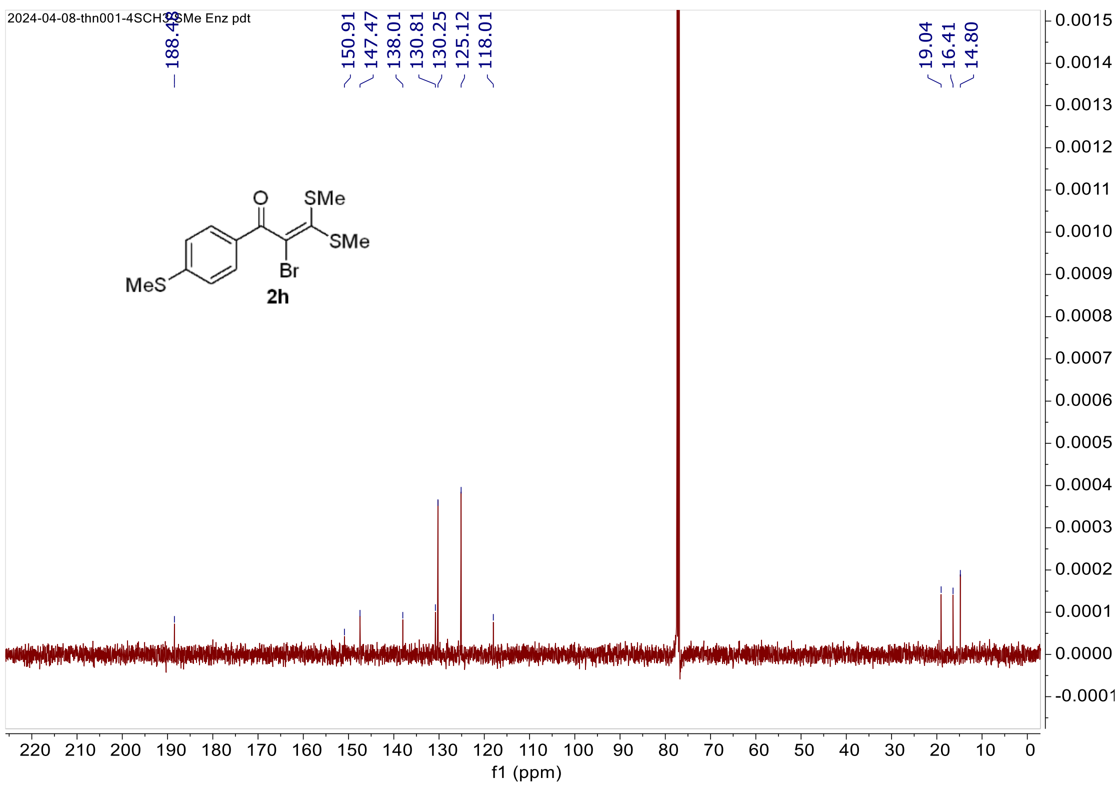


Figure S68 ^{13}C NMR spectra of **2h** ($CDCl_3$, 125 MHz)

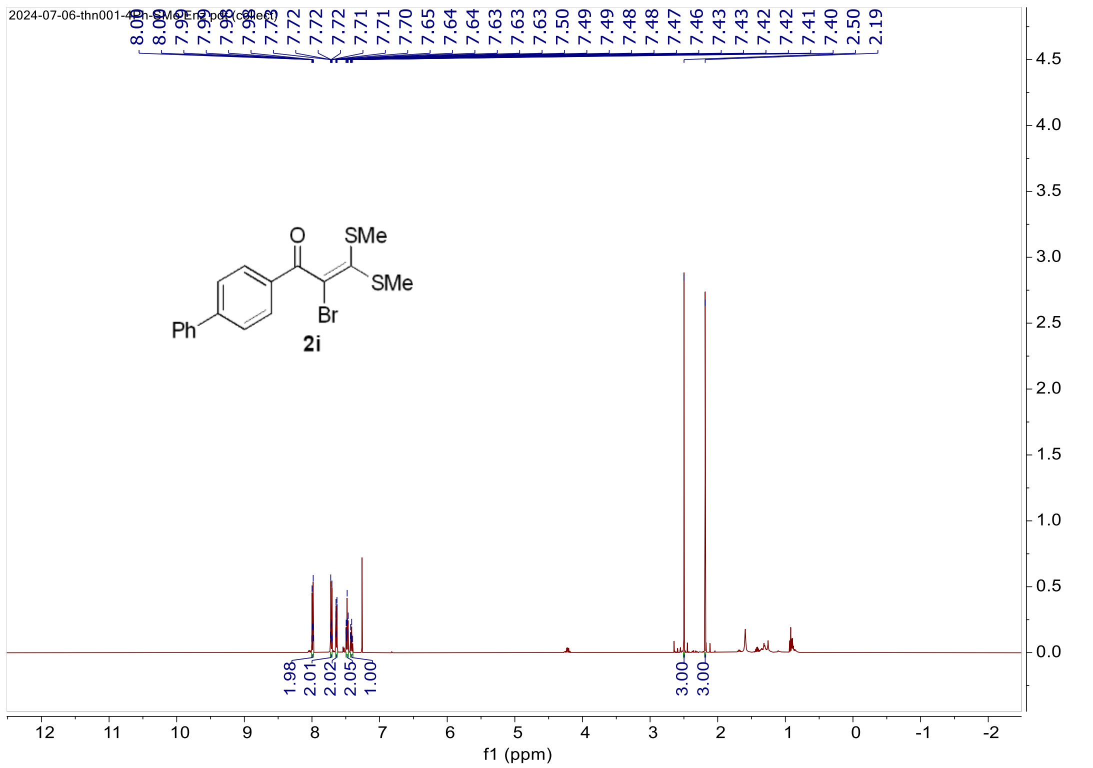


Figure S69 ^{1}H NMR spectra of **2i** ($CDCl_3$, 500 MHz)

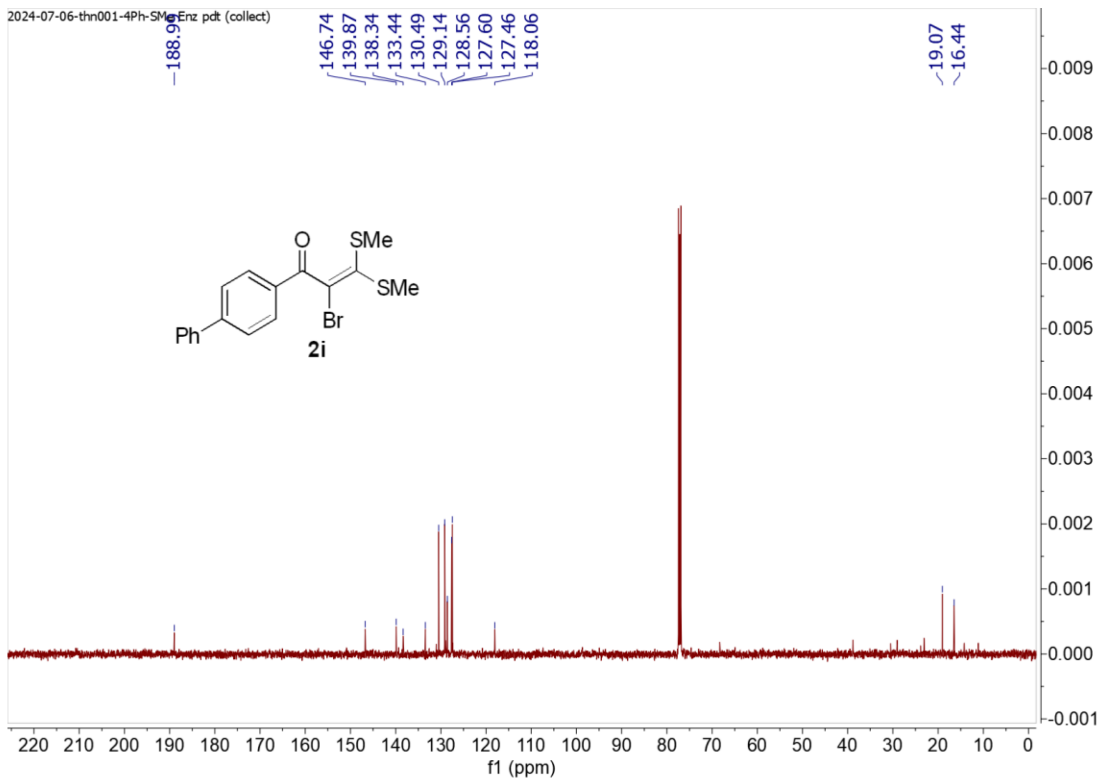


Figure S70 ^{13}C NMR spectra of **2i** ($CDCl_3$, 125 MHz)

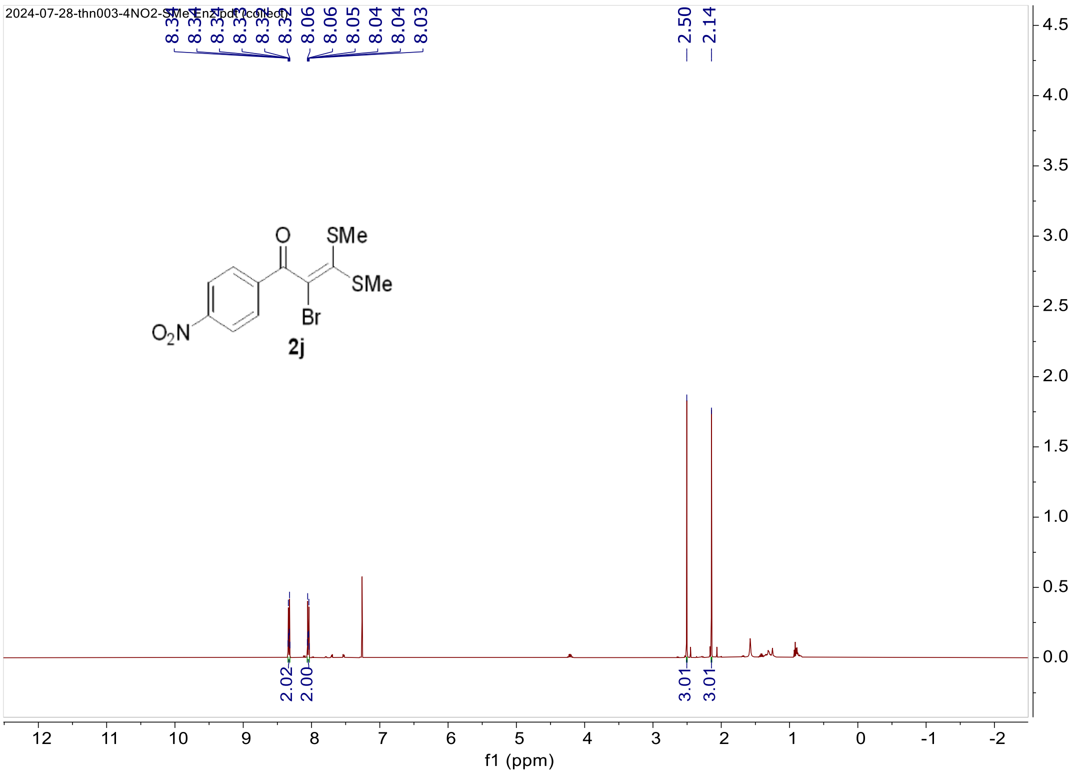


Figure S71 ^{1}H NMR spectra of **2j** ($CDCl_3$, 500 MHz)

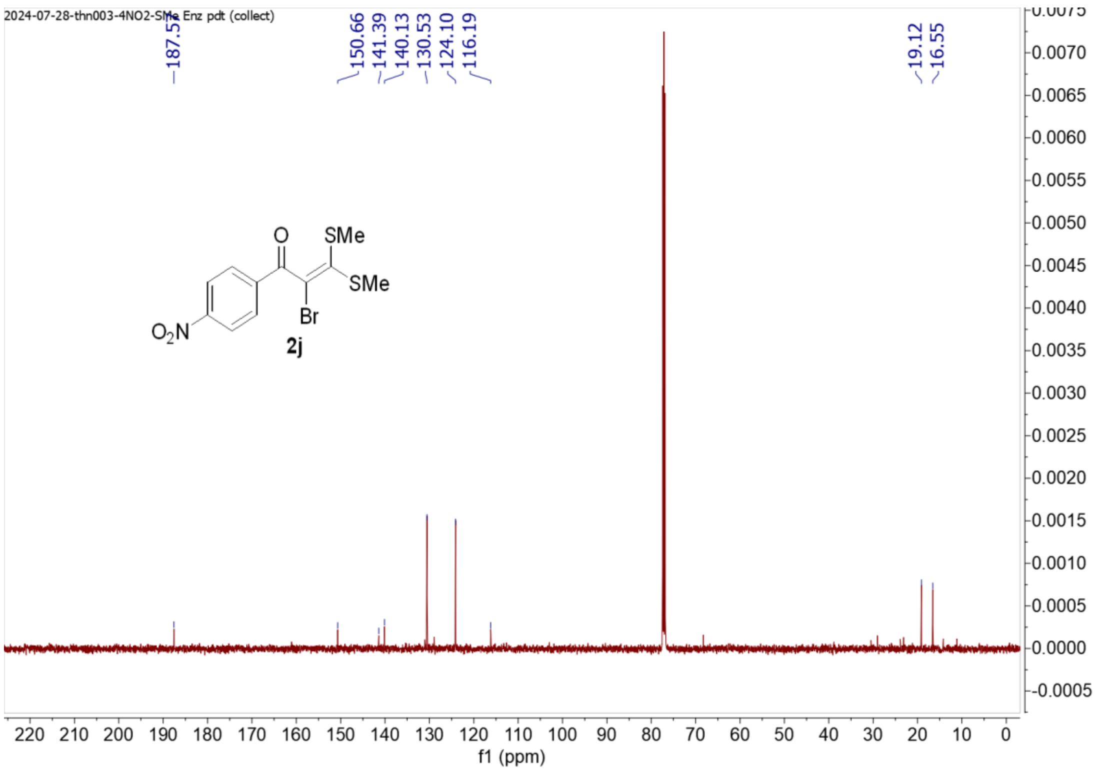


Figure S72 ^{13}C NMR spectra of **2j** ($CDCl_3$, 125 MHz)

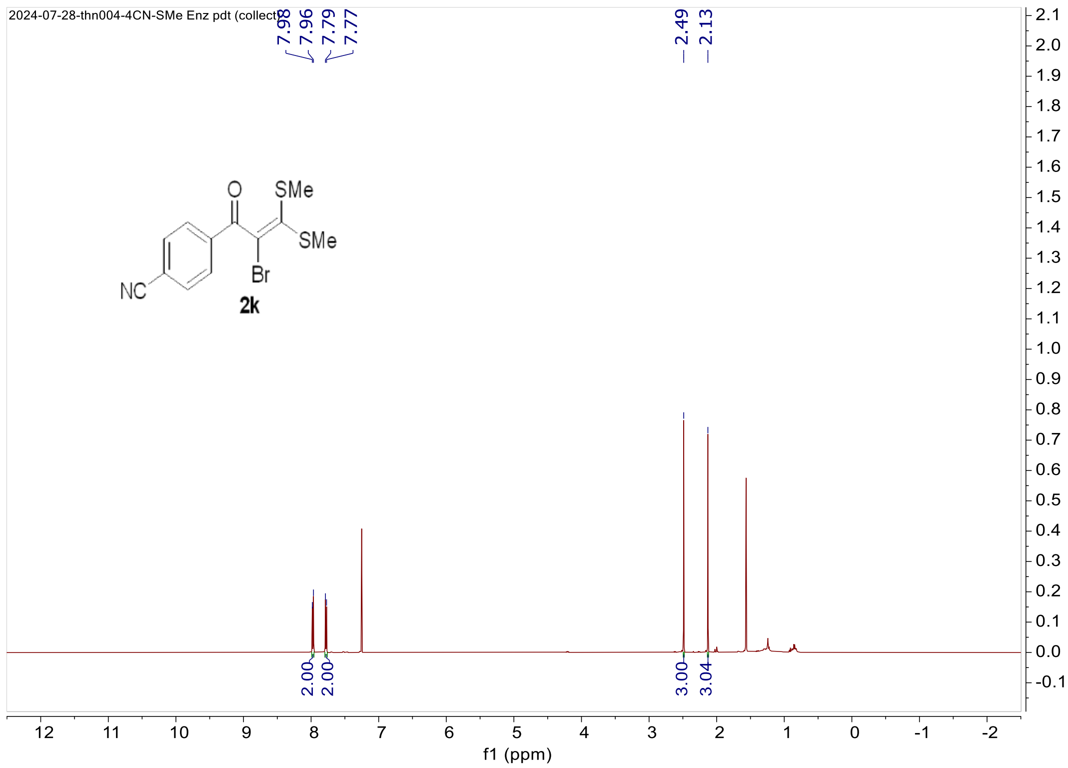


Figure S73 [1]H NMR spectra of **2k** ($CDCl_3$, 500 MHz)

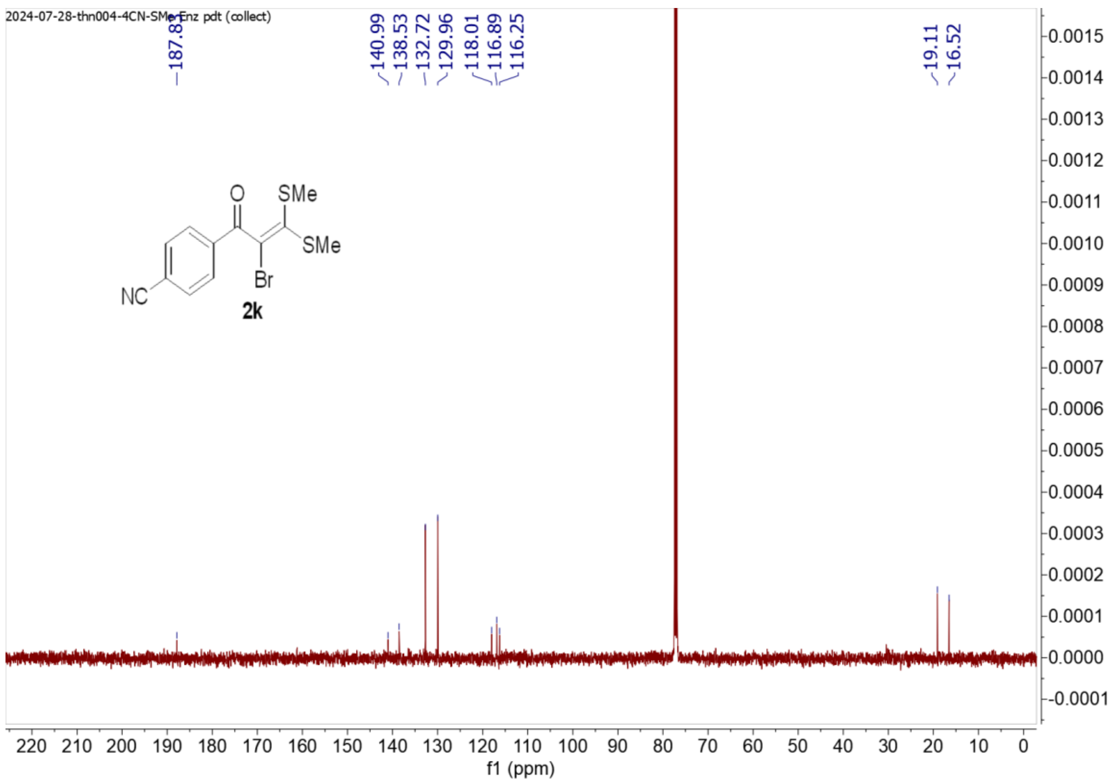


Figure S74 [13]C NMR spectra of **2k** ($CDCl_3$, 125 MHz)

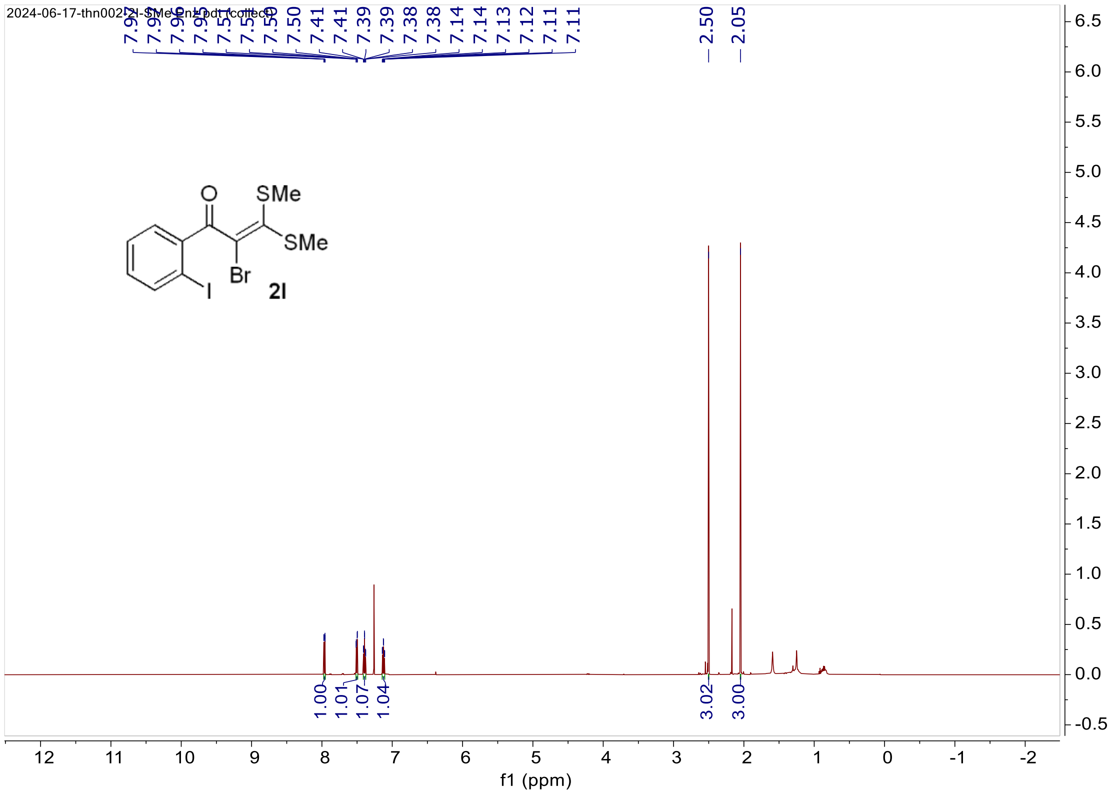


Figure S75 ^{1}H NMR spectra of **2l** ($CDCl_3$, 500 MHz)

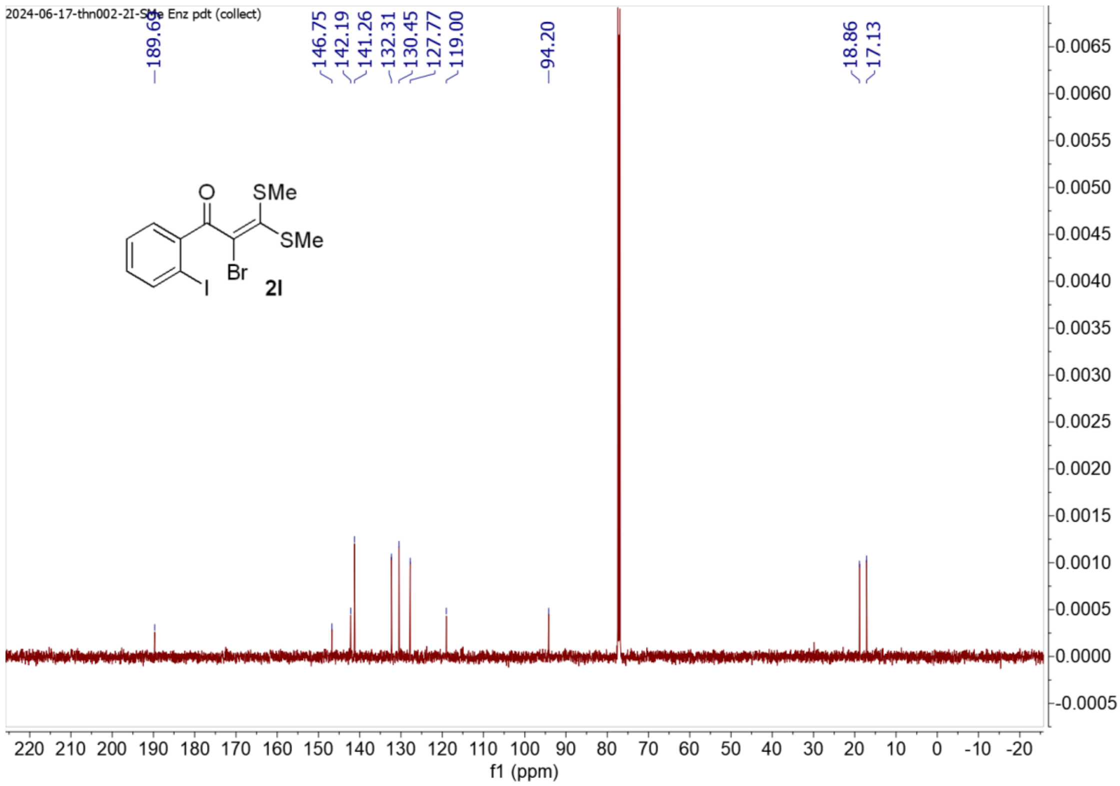


Figure S76 ^{13}C NMR spectra of **2l** ($CDCl_3$, 125 MHz)

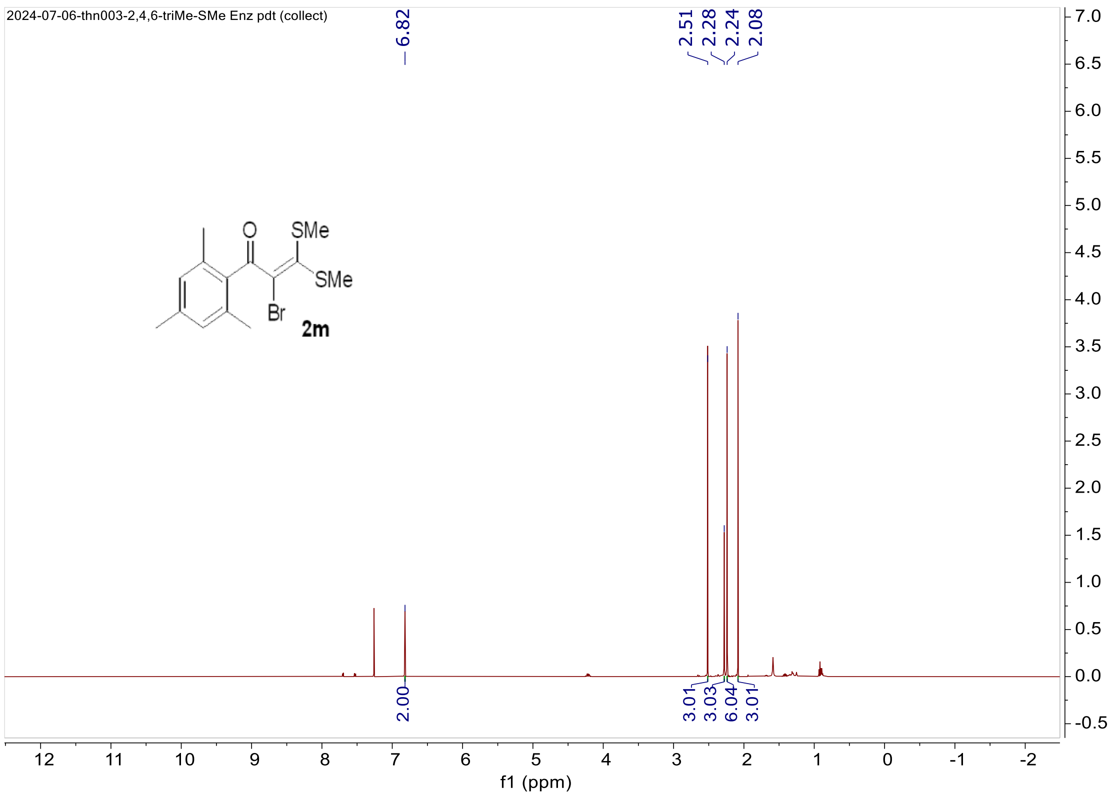


Figure S77 ^{1}H NMR spectra of **2m** ($CDCl_3$, 500 MHz)

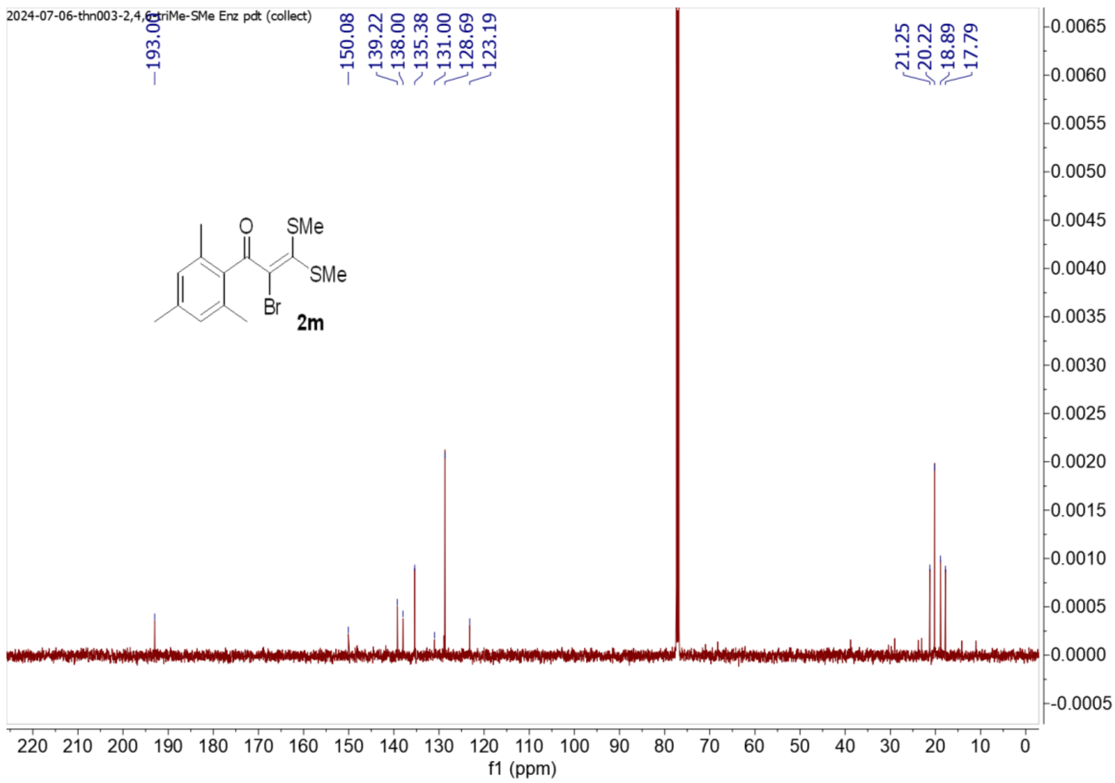


Figure S78 ^{13}C NMR spectra of **2m** ($CDCl_3$, 125 MHz)

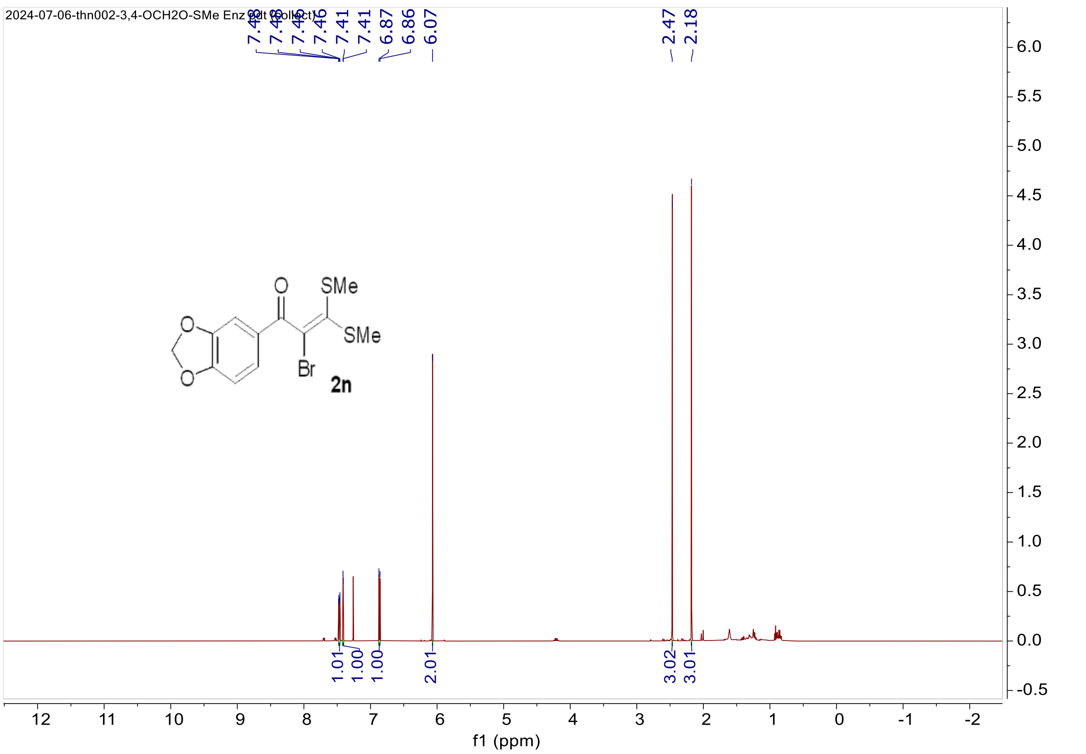


Figure S79 ^{1}H NMR spectra of **2n** ($CDCl_3$, 500 MHz)

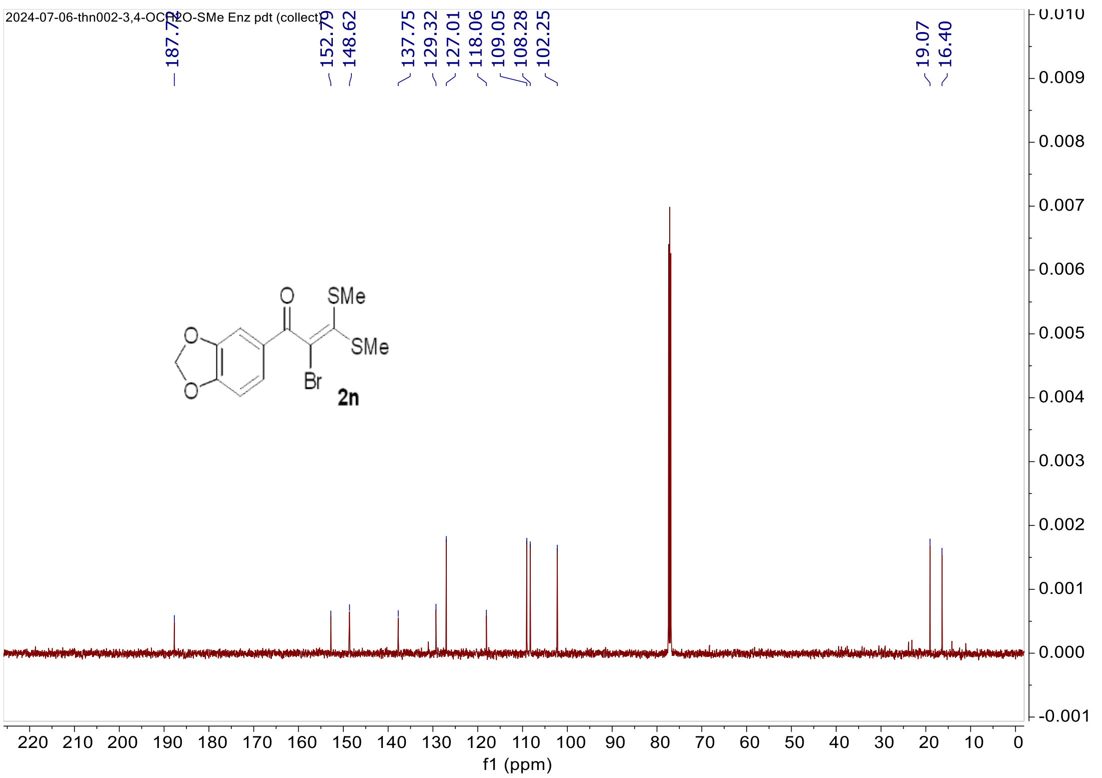


Figure S80 ^{13}C NMR spectra of **2n** ($CDCl_3$, 125 MHz)

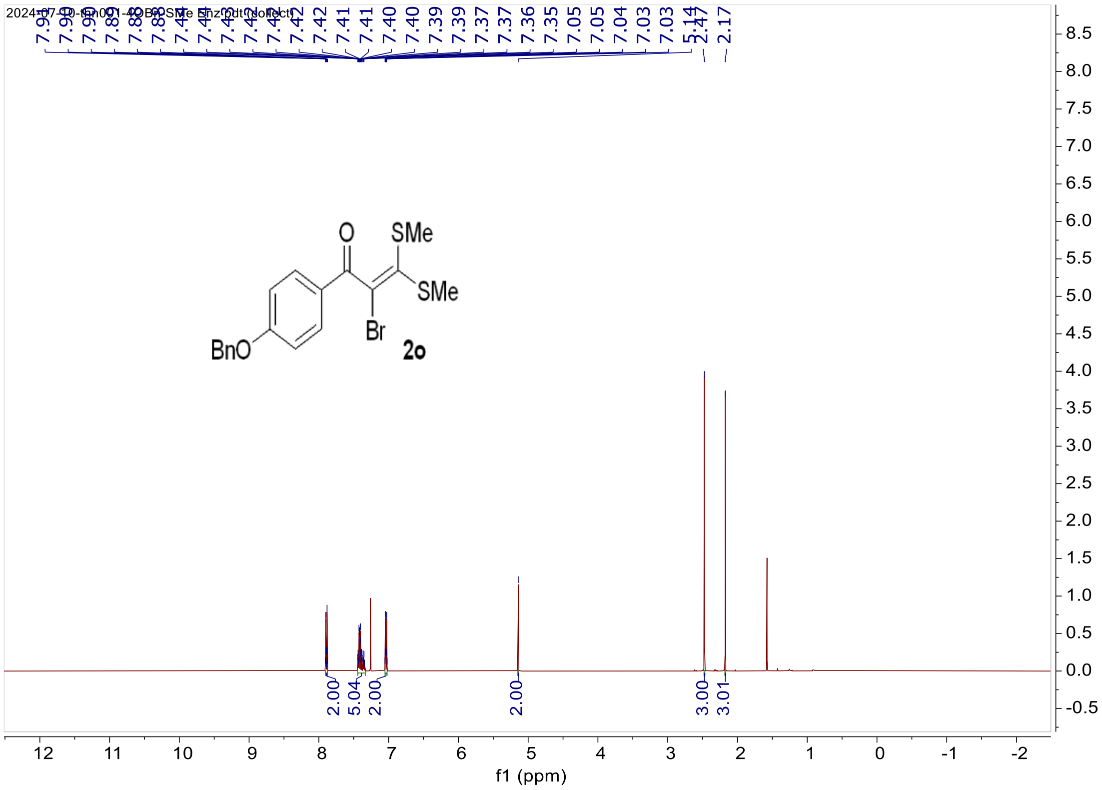


Figure S81 ^{1}H NMR spectra of **2o** ($CDCl_3$, 500 MHz)

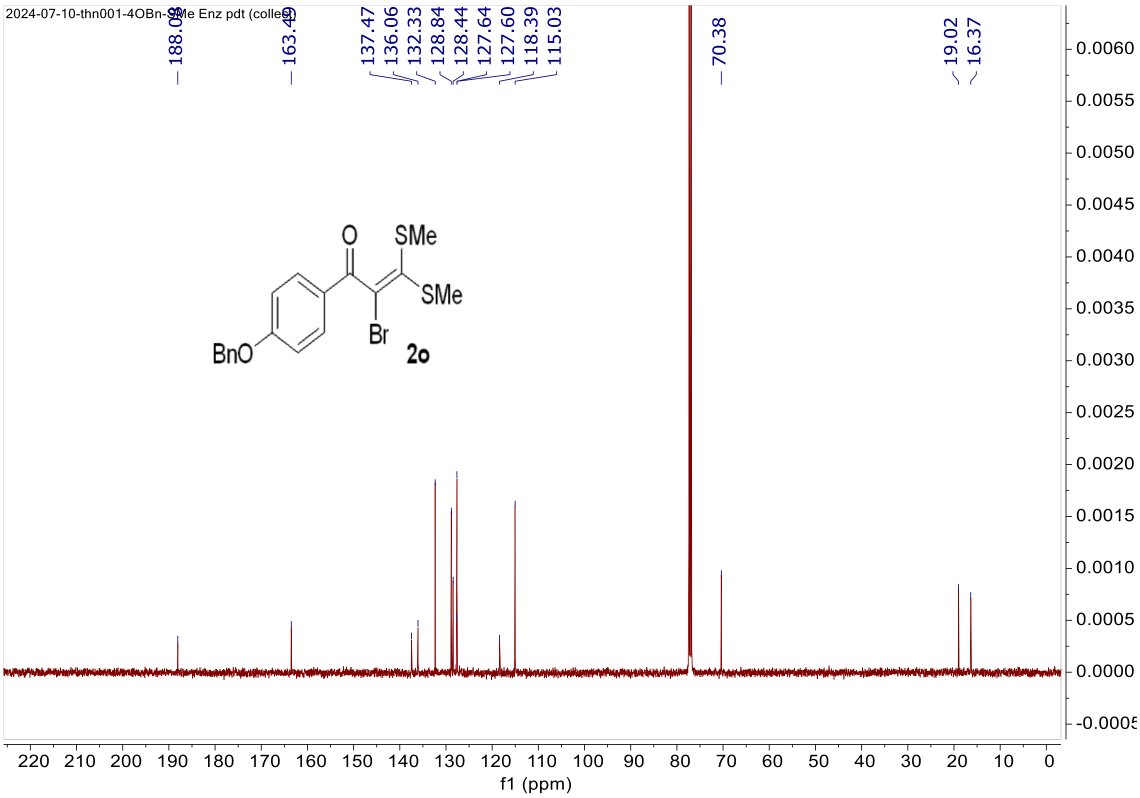


Figure S82 ^{13}C NMR spectra of **2o** ($CDCl_3$, 125 MHz)

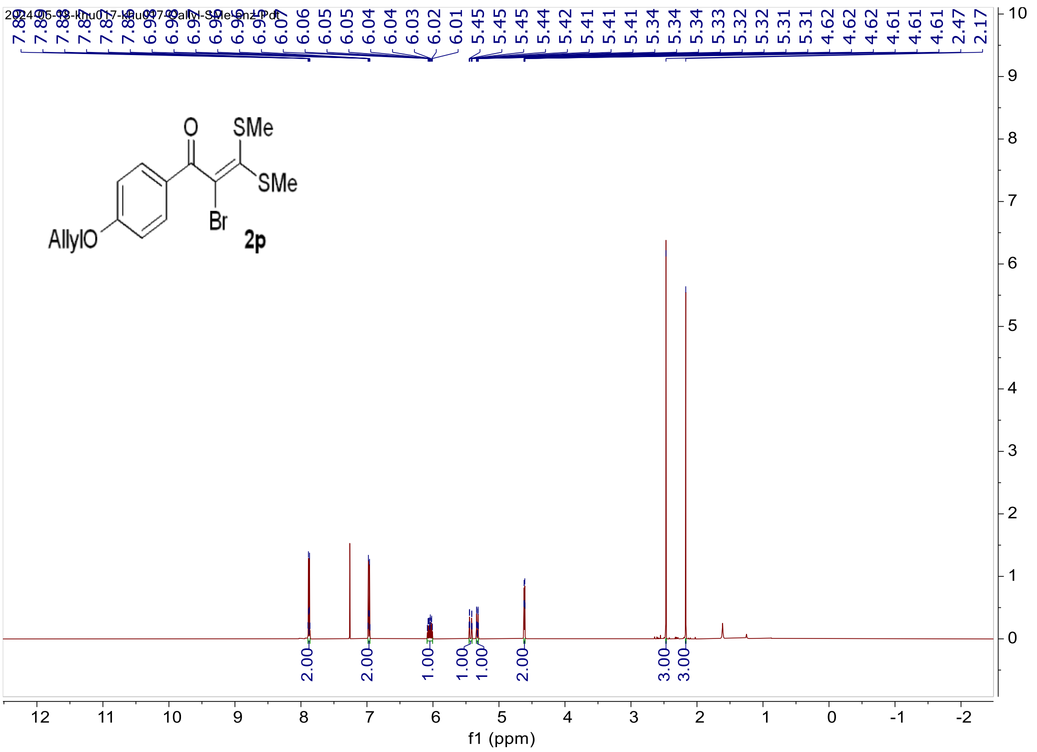


Figure S83 ^{1}H NMR spectra of **2p** ($CDCl_3$, 500 MHz)

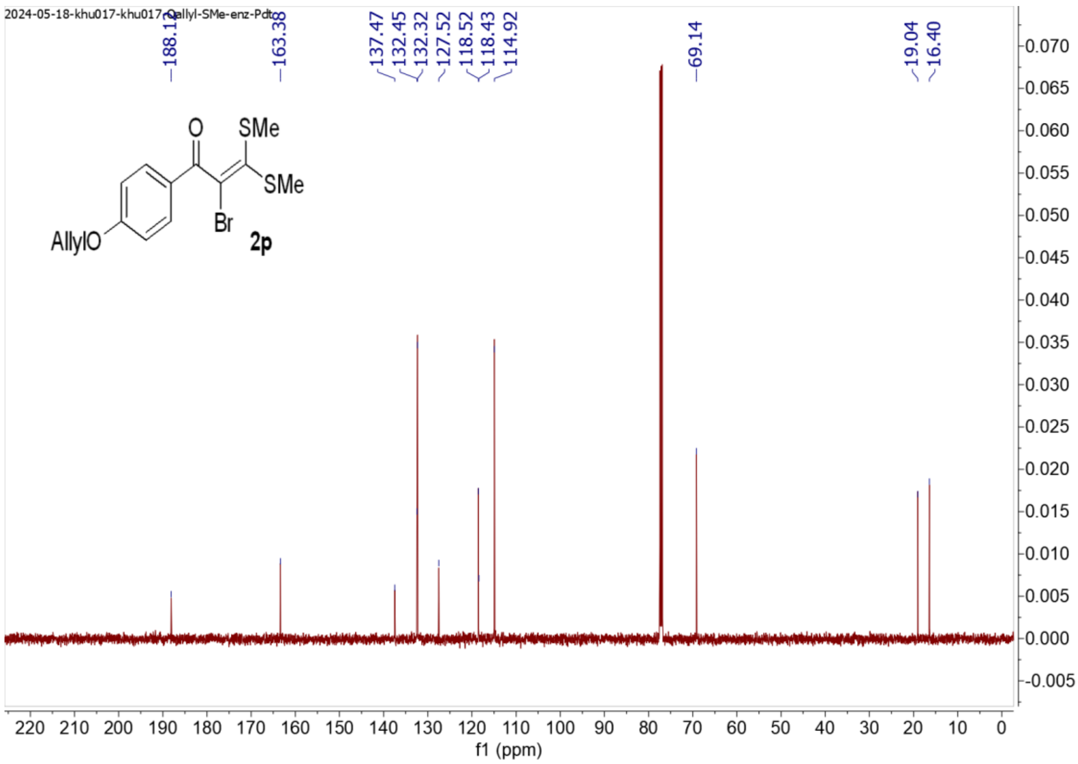


Figure S84 ^{13}C NMR spectra of **2p** ($CDCl_3$, 125 MHz)

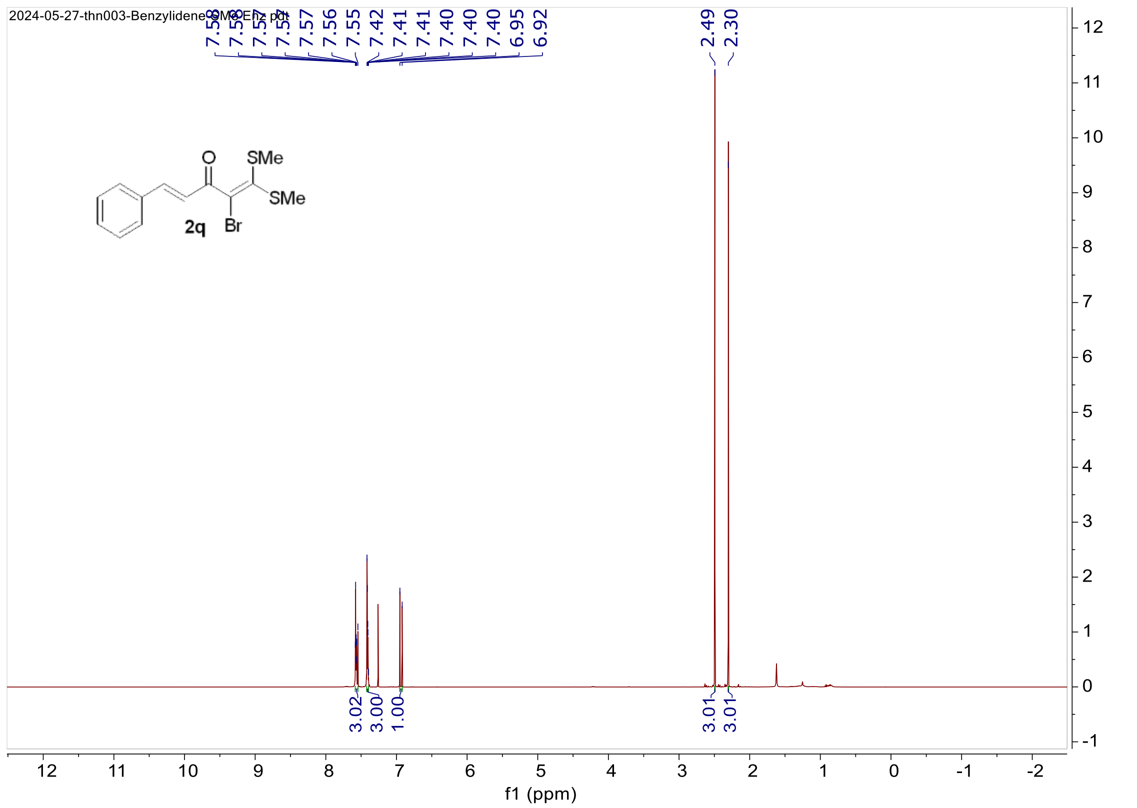


Figure S85 [1]H NMR spectra of **2q** ($CDCl_3$, 500 MHz)

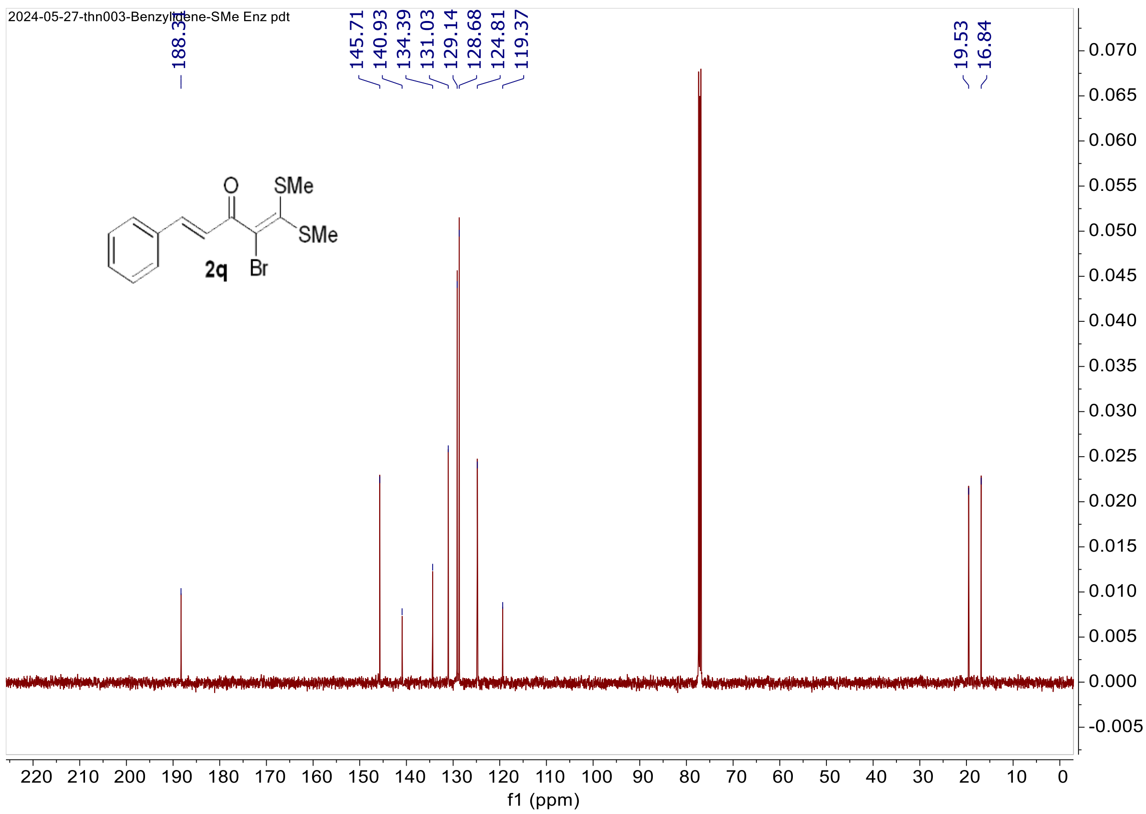


Figure S86 [13]C NMR spectra of **2q** ($CDCl_3$, 125 MHz)

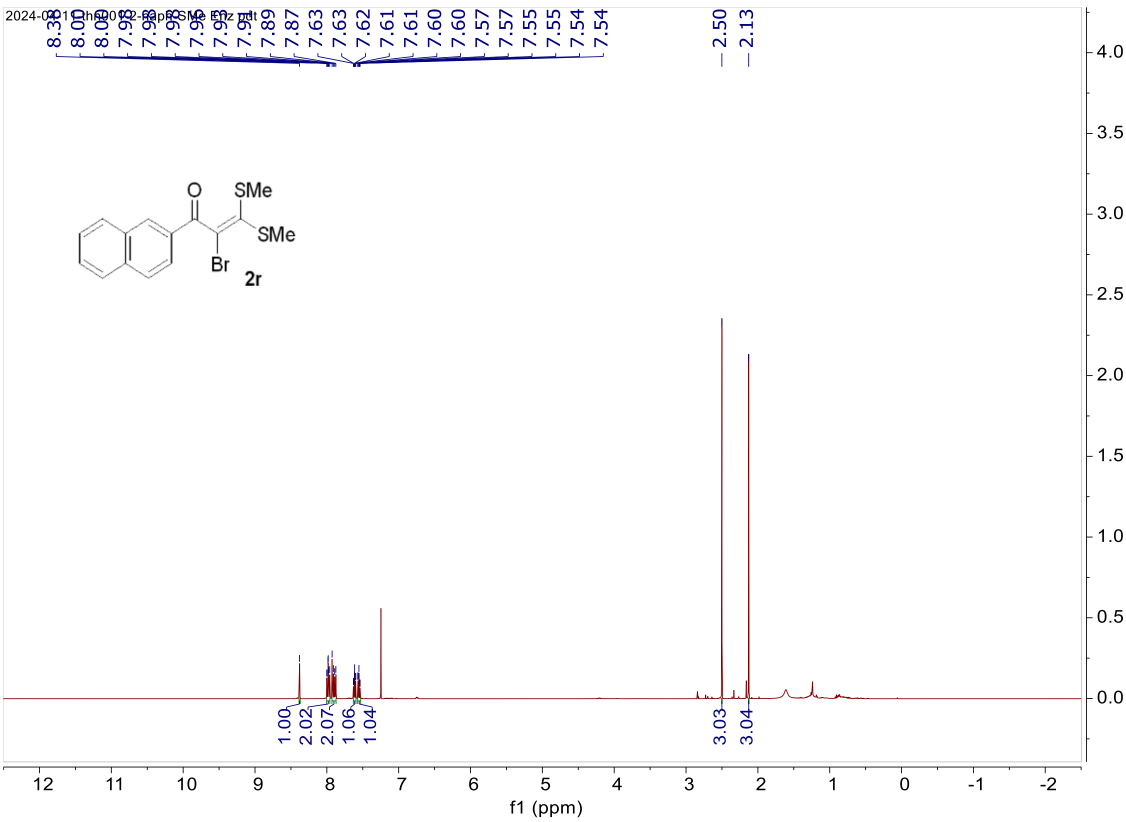


Figure S87 ${}^{1}H$ NMR spectra of **2r** ($CDCl_3$, 500 MHz)

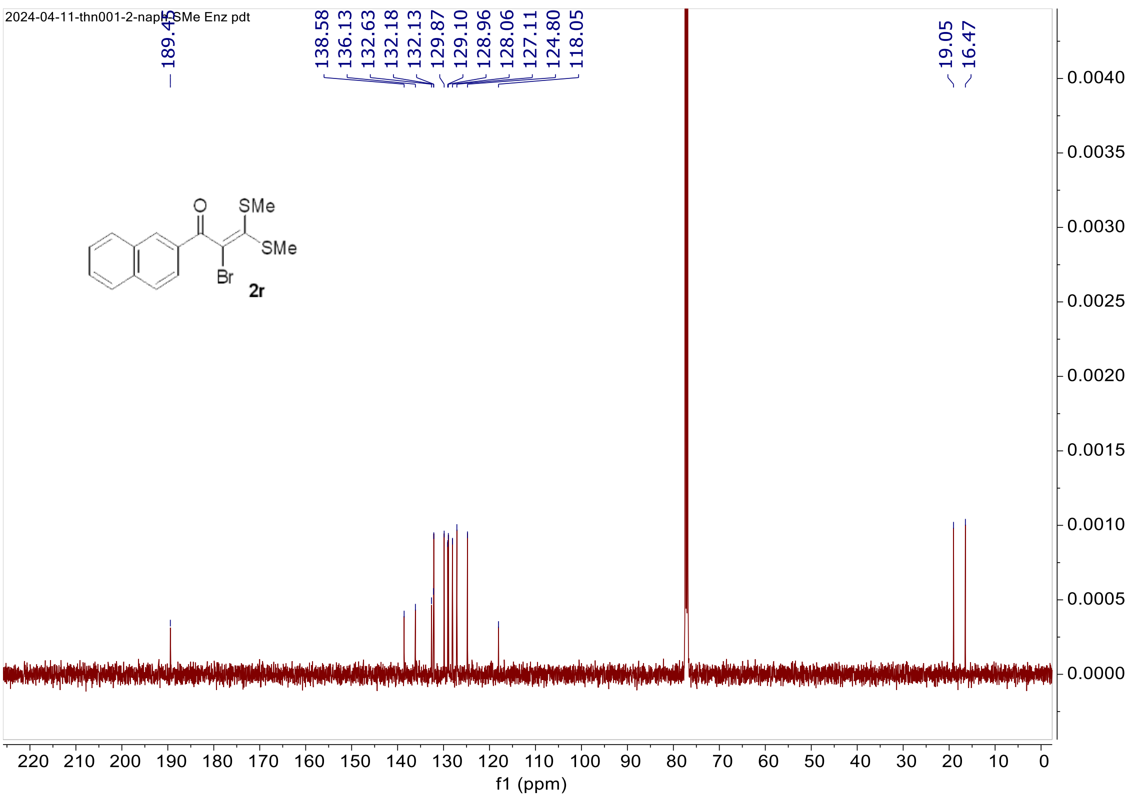


Figure S88 ${}^{13}C$ NMR spectra of **2r** ($CDCl_3$, 125 MHz)

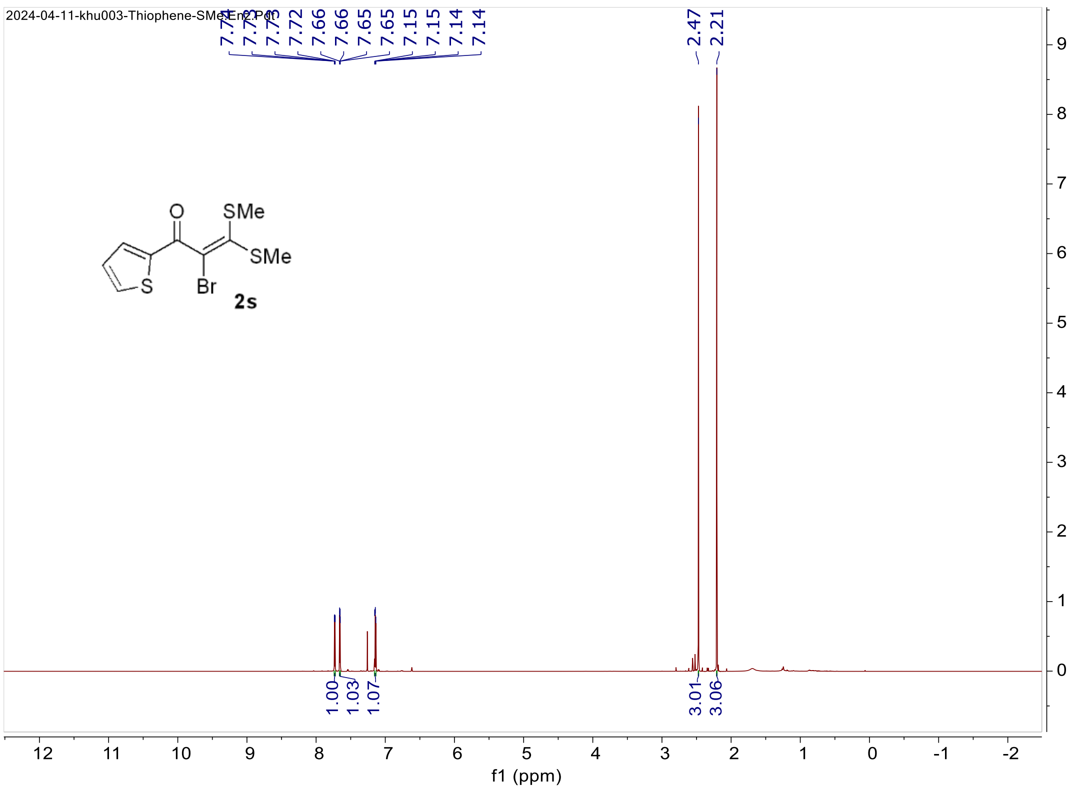


Figure S89 ^{1}H NMR spectra of **2s** ($CDCl_3$, 500 MHz)

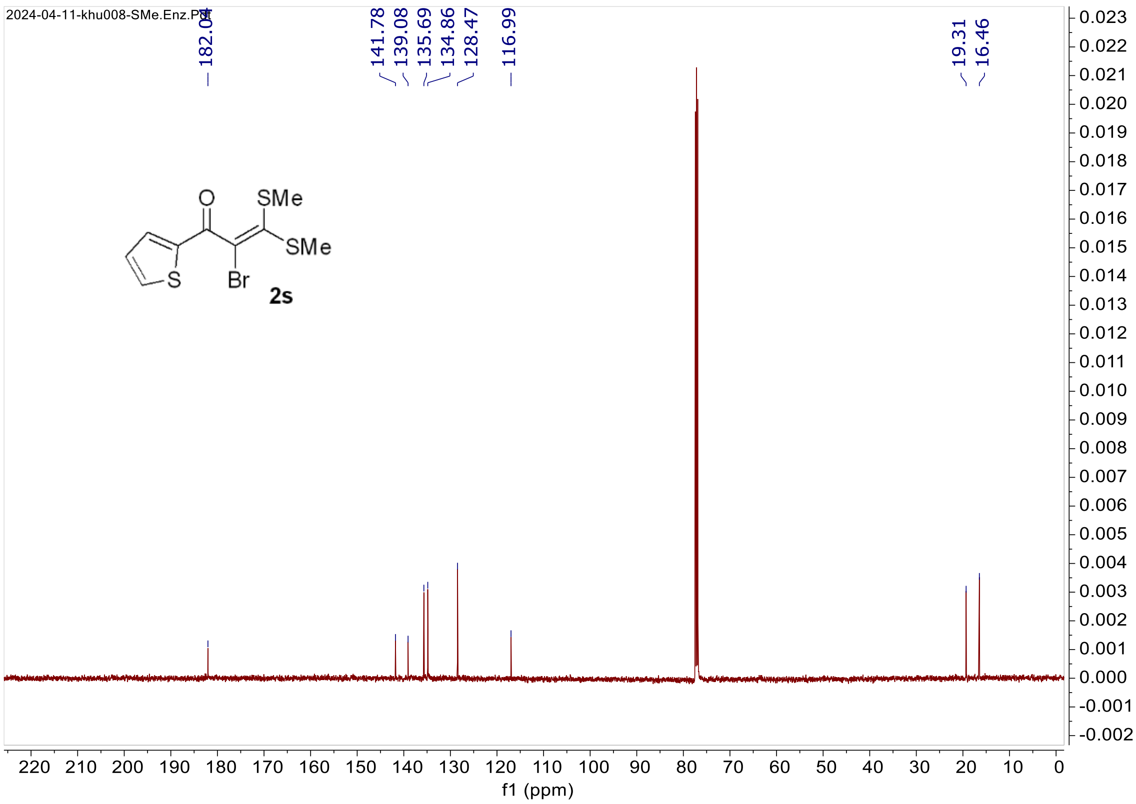


Figure S90 ^{13}C NMR spectra of **2s** ($CDCl_3$, 125 MHz)

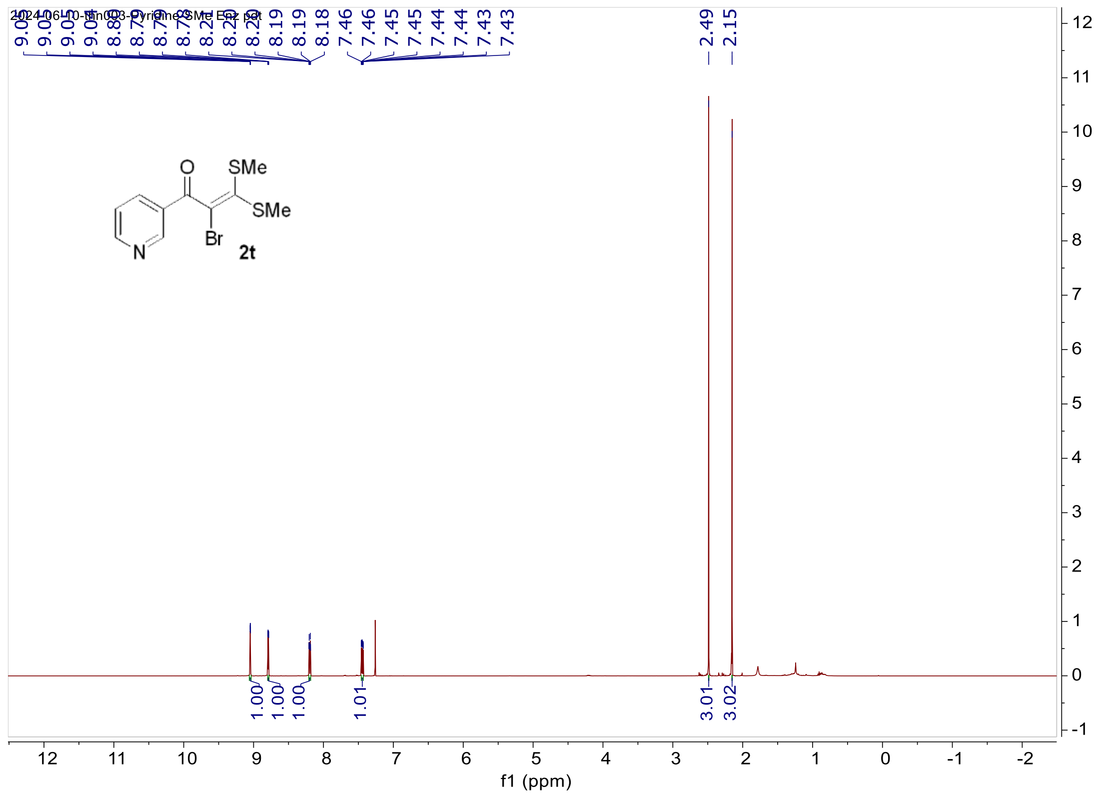


Figure S91 [1]H NMR spectra of **2t** ($CDCl_3$, 500 MHz)

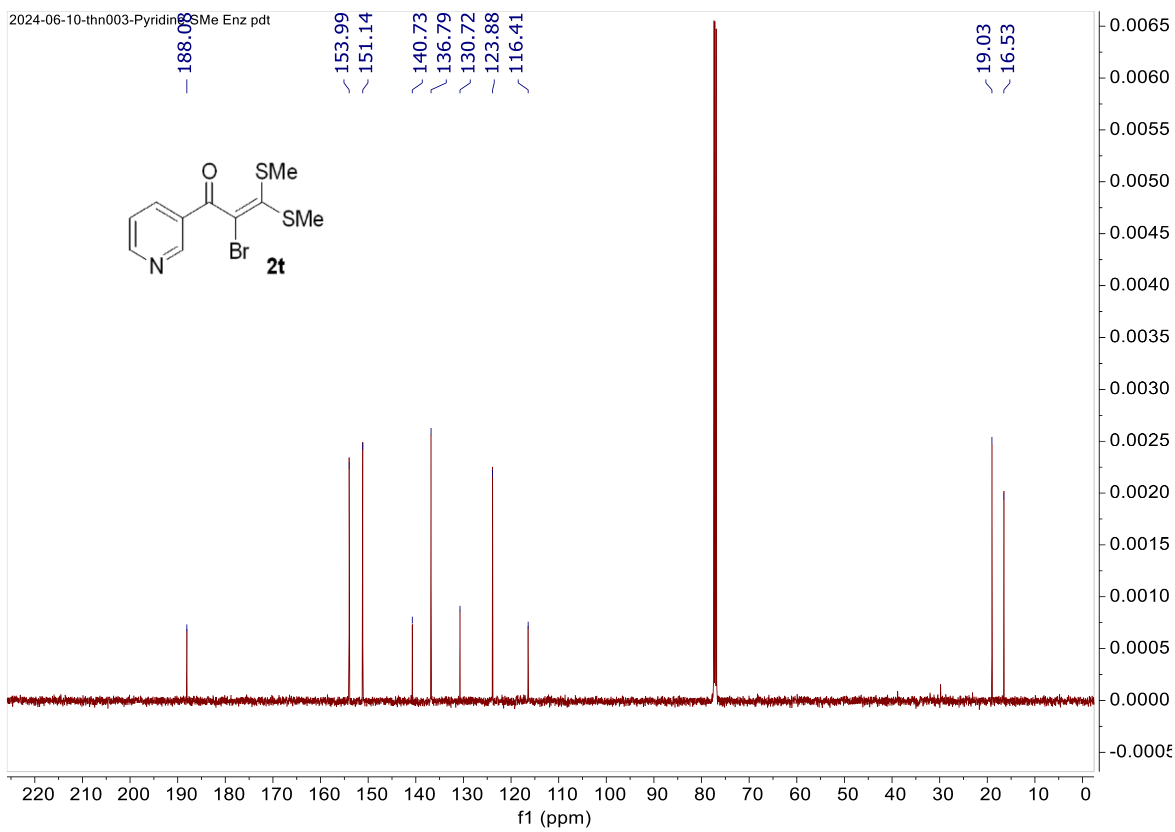


Figure S92 [13]C NMR spectra of **2t** ($CDCl_3$, 125 MHz)

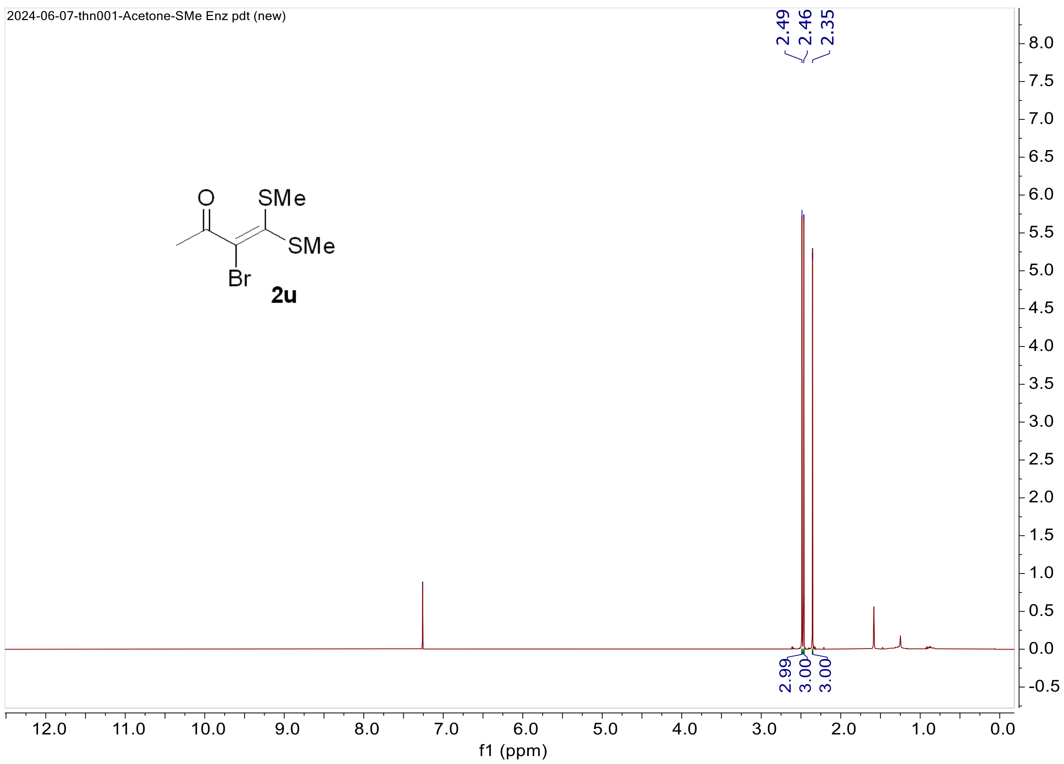


Figure S93 ^{1}H NMR spectra of **2u** ($CDCl_3$, 500 MHz)

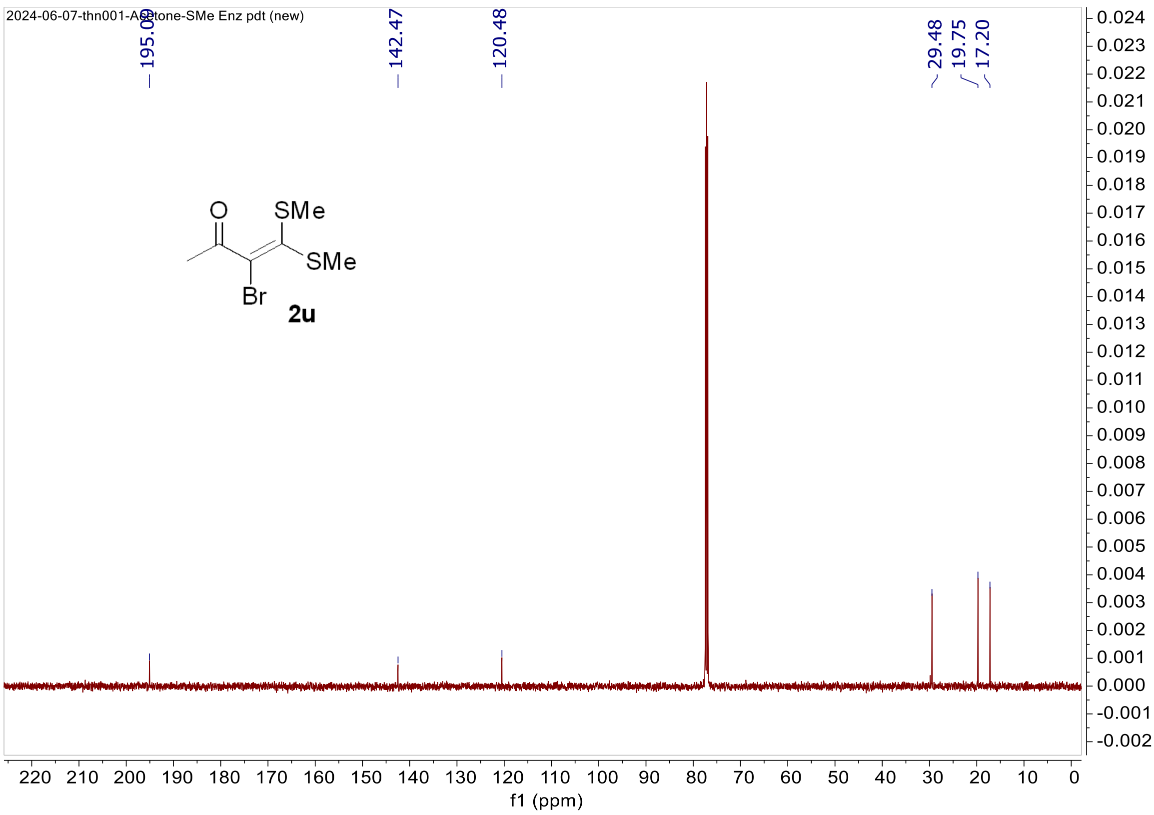


Figure S94 ^{13}C NMR spectra of **2u** ($CDCl_3$, 125 MHz)

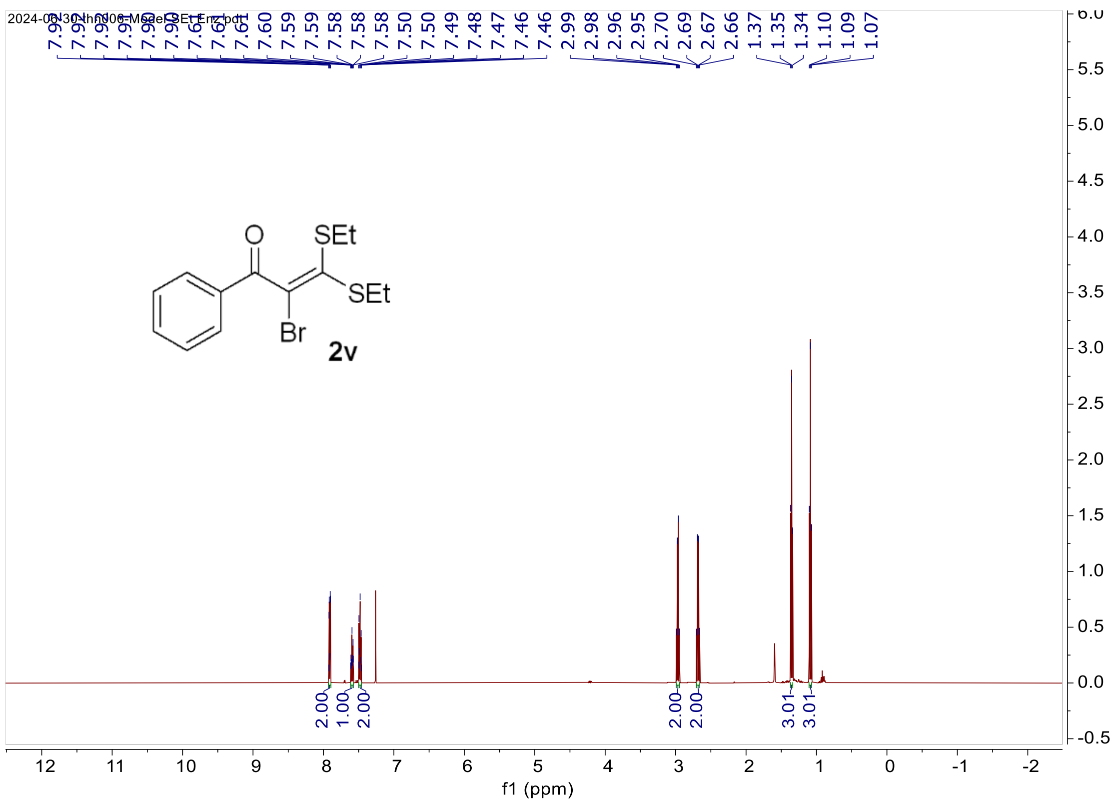


Figure S95 ^{1}H NMR spectra of **2v** ($CDCl_3$, 500 MHz)

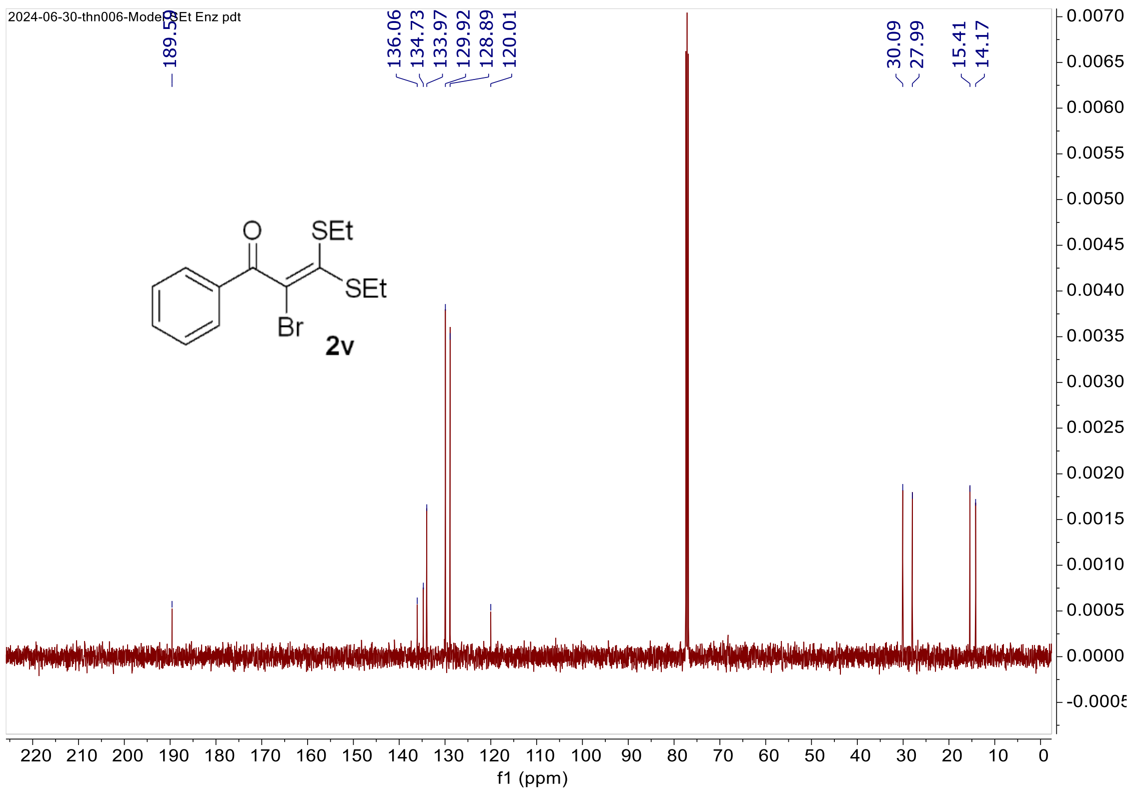


Figure S96 ^{13}C NMR spectra of **2v** ($CDCl_3$, 125 MHz)

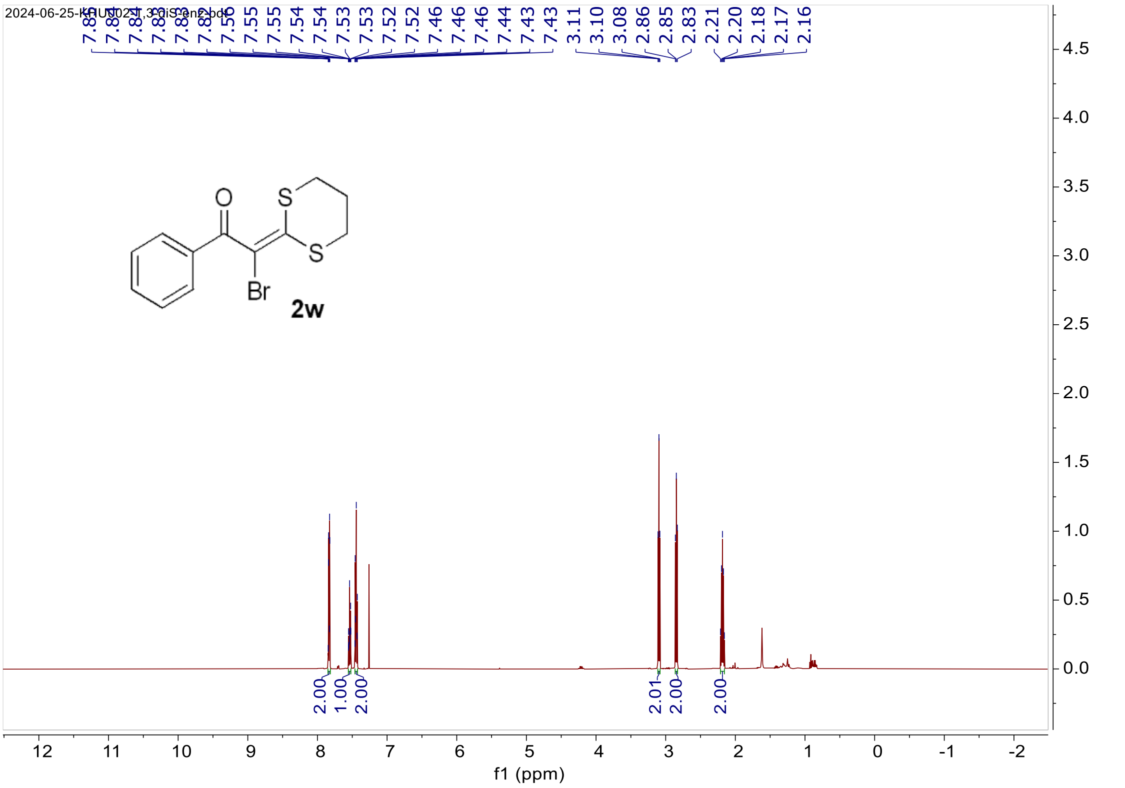


Figure S97 ^{1}H NMR spectra of **2w** ($CDCl_3$, 500 MHz)

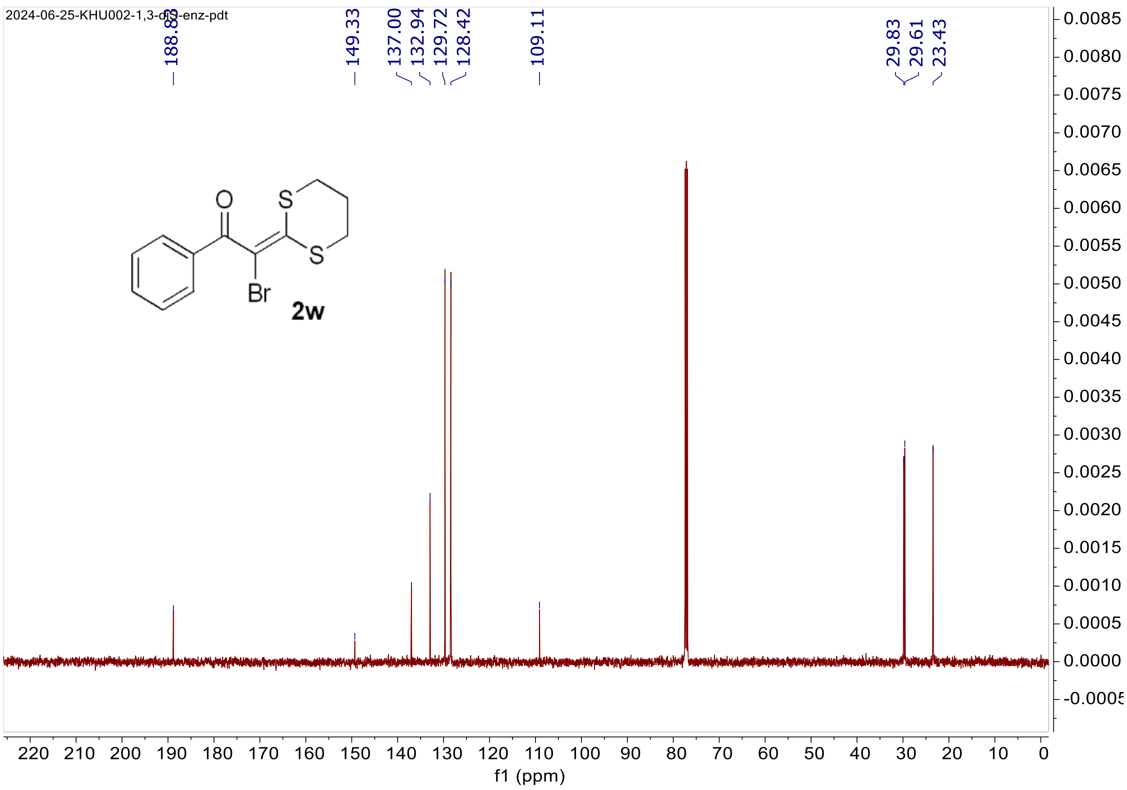


Figure S98 ^{13}C NMR spectra of **2w** ($CDCl_3$, 125 MHz)

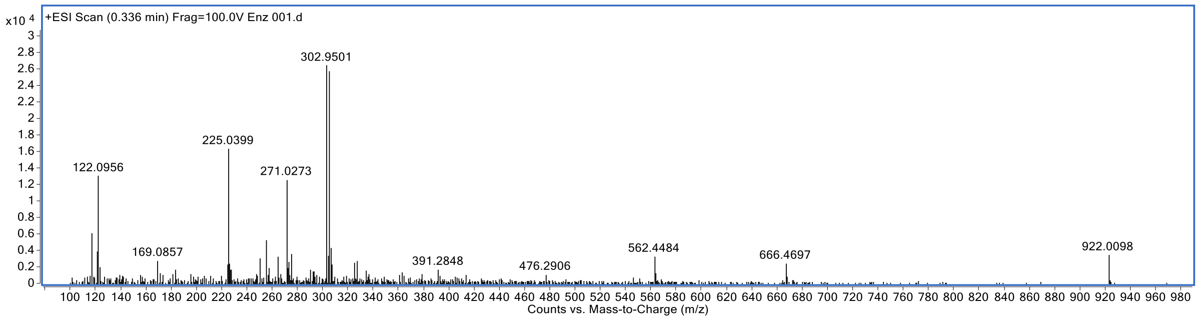


Figure S99 Mass spectrum of **2a**

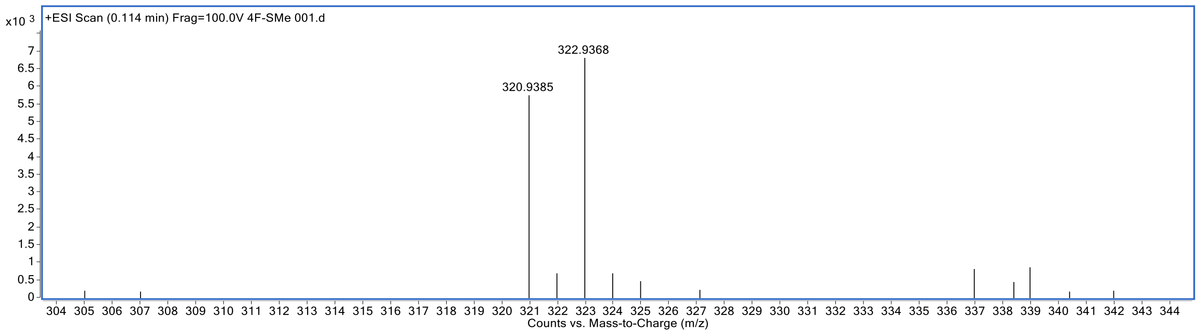


Figure S100 Mass spectrum of **2b**

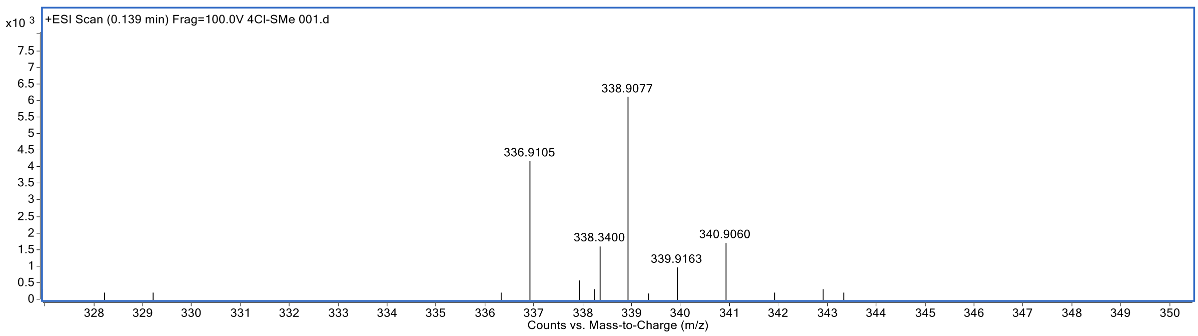


Figure S101 Mass spectrum of **2c**

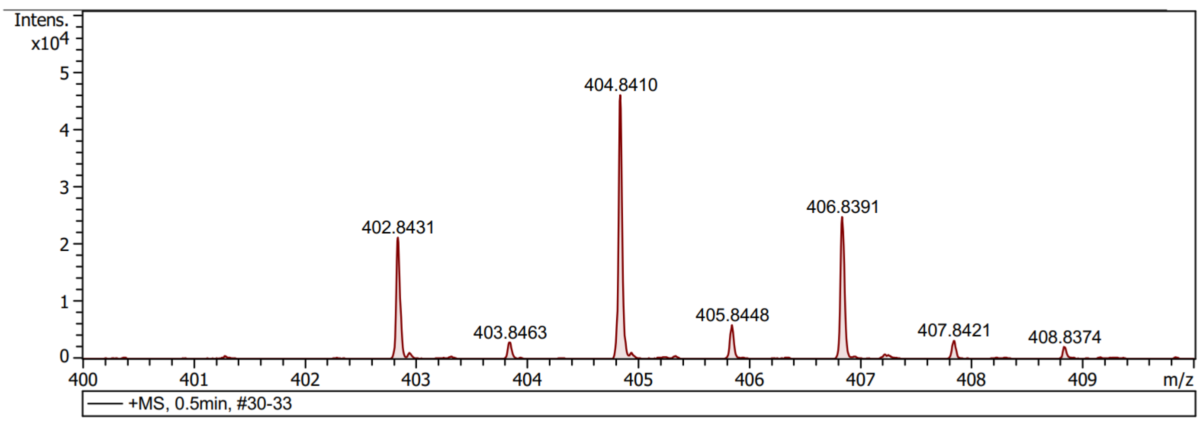


Figure S102 Mass spectrum of **2d**

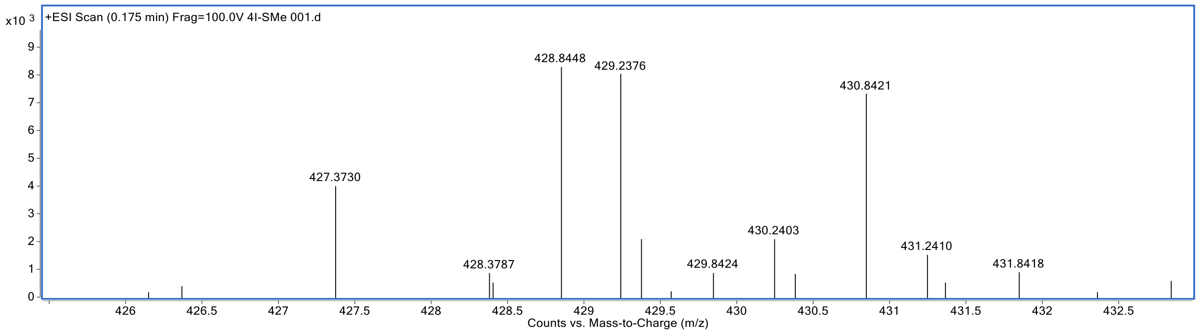


Figure S103 Mass spectrum of **2e**

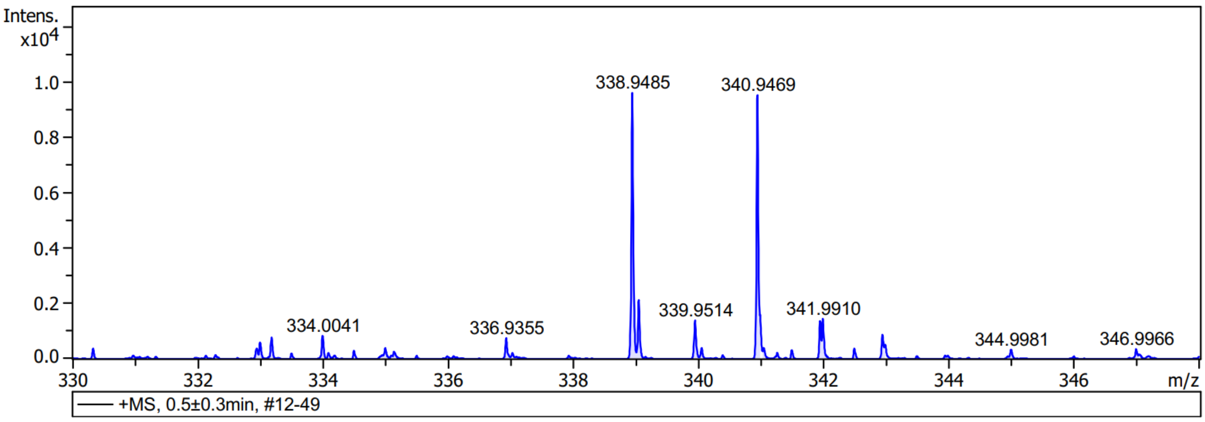


Figure S104 Mass spectrum of **2f**

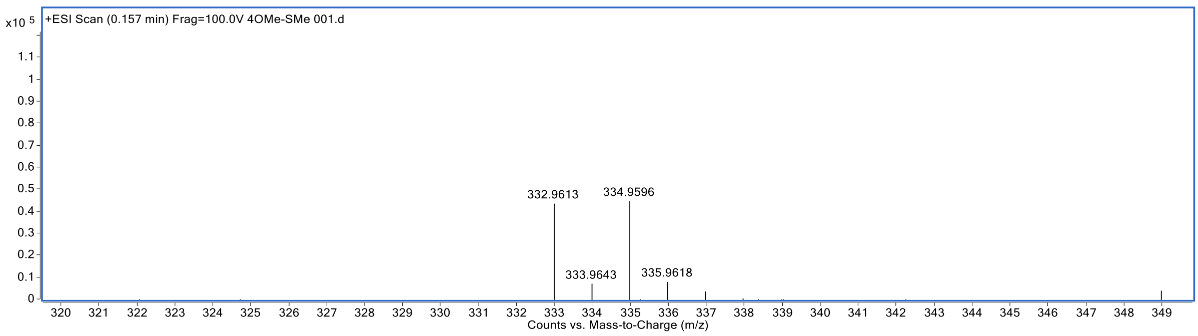


Figure S105 Mass spectrum of **2g**

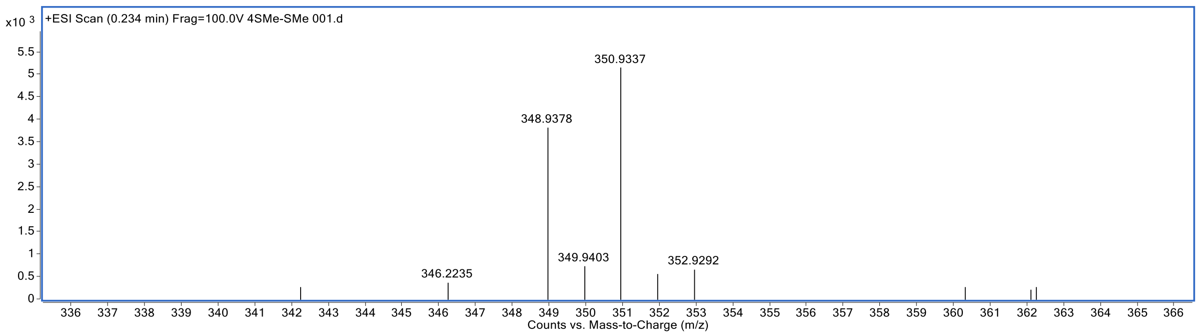


Figure S106 Mass spectrum of **2h**

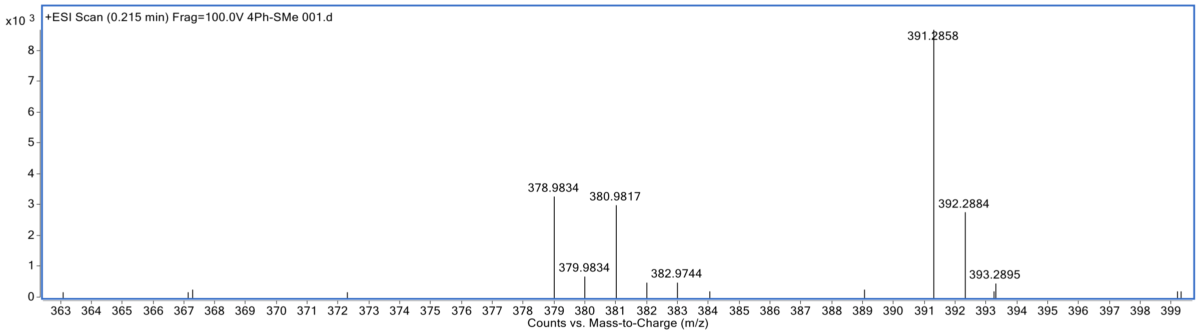


Figure S107 Mass spectrum of **2i**

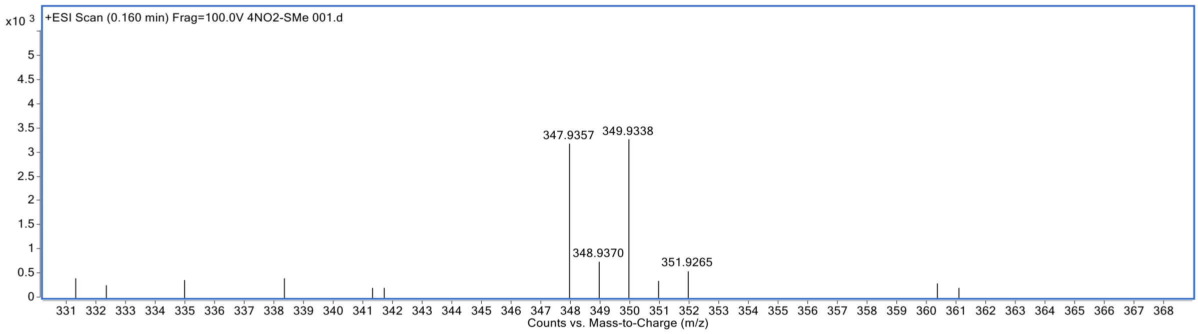


Figure S108 Mass spectrum of **2j**

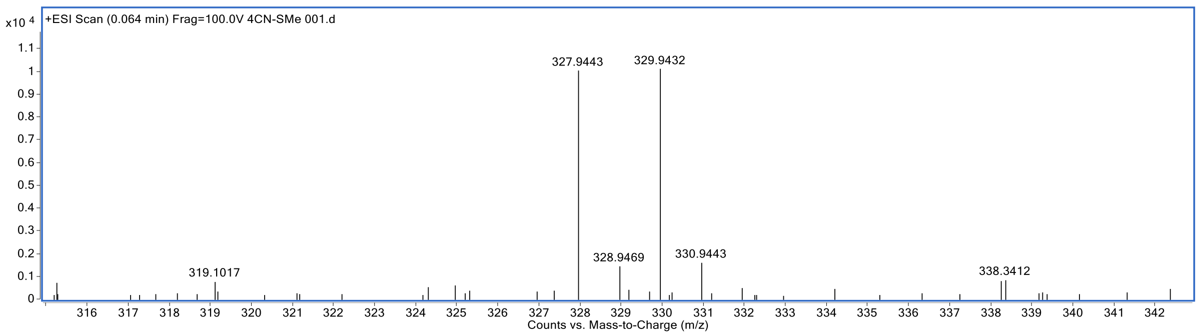


Figure S109 Mass spectrum of **2k**

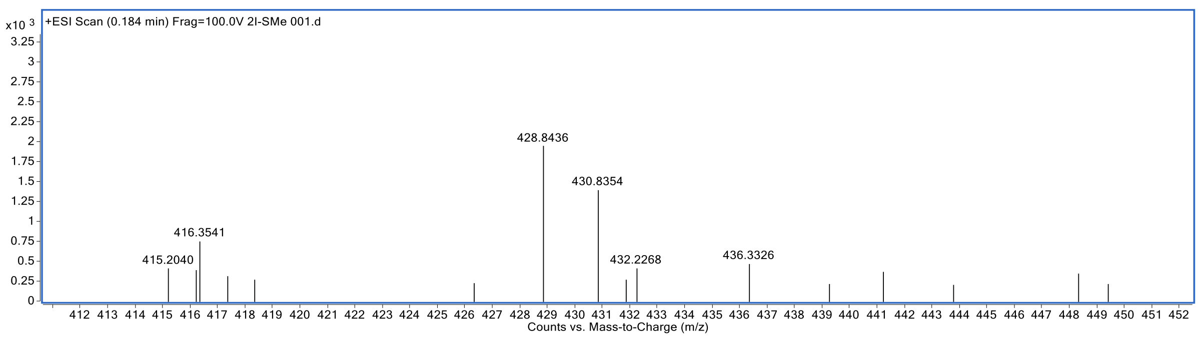


Figure S110 Mass spectrum of **2l**

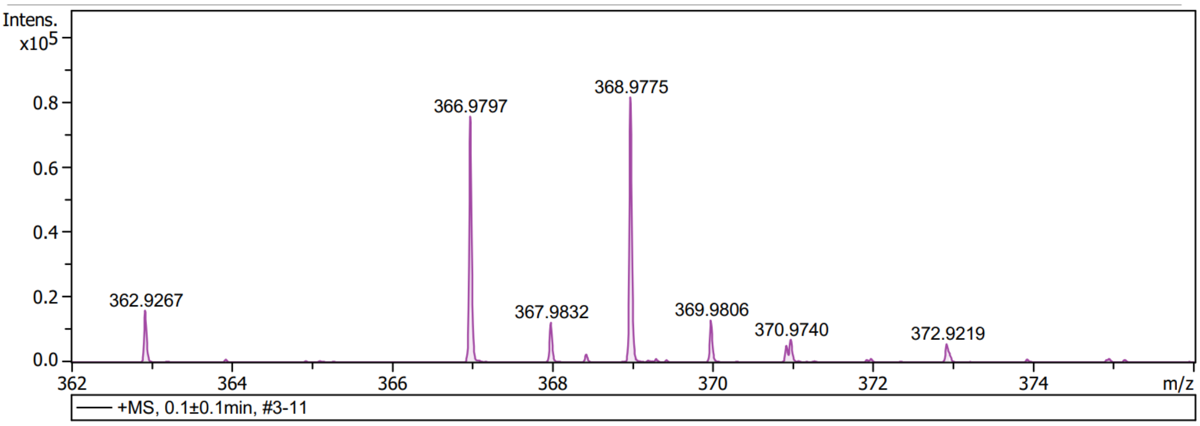


Figure S111 Mass spectrum of **2m**

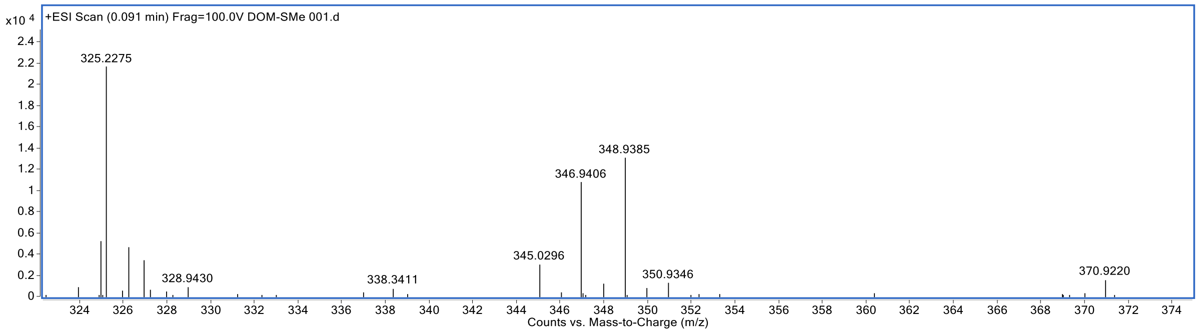


Figure S112 Mass spectrum of **2n**

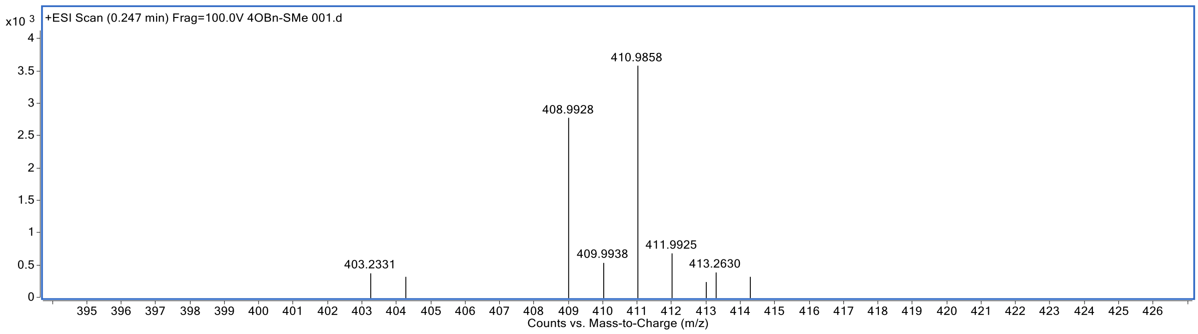
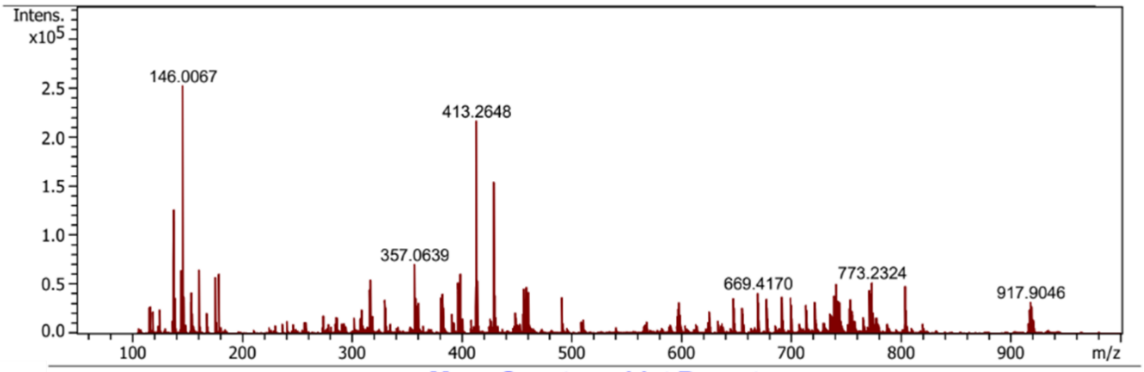


Figure S113 Mass spectrum of **2o**



Mass Spectrum List Report

#	m/z	Res.	S/N	I	I %	FWHM
29	358.3667	11153	313.9	35590	14.1	0.0321
30	358.9766	10739	249.1	28395	11.2	0.0334
31	360.9743	10790	268.8	30813	12.2	0.0335
32	380.9582	10915	281.4	36397	14.4	0.0349
33	382.9558	11293	308.3	40123	15.9	0.0339
34	391.2834	11084	141.9	19258	7.6	0.0353
35	396.9322	11375	365.5	51587	20.4	0.0349
36	398.9313	10440	426.1	60750	24.0	0.0382

Figure S114 Mass spectrum of **2p**

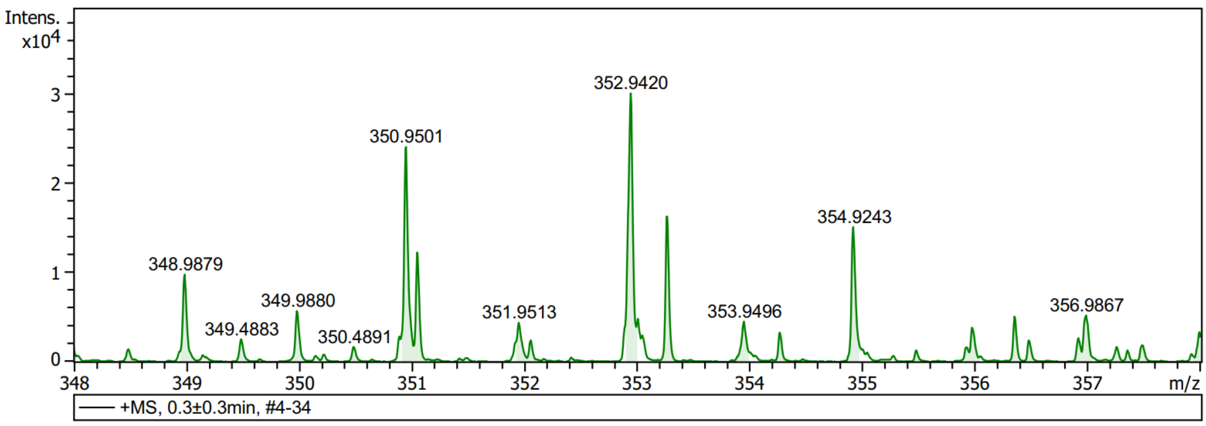


Figure S115 Mass spectrum of **2q**

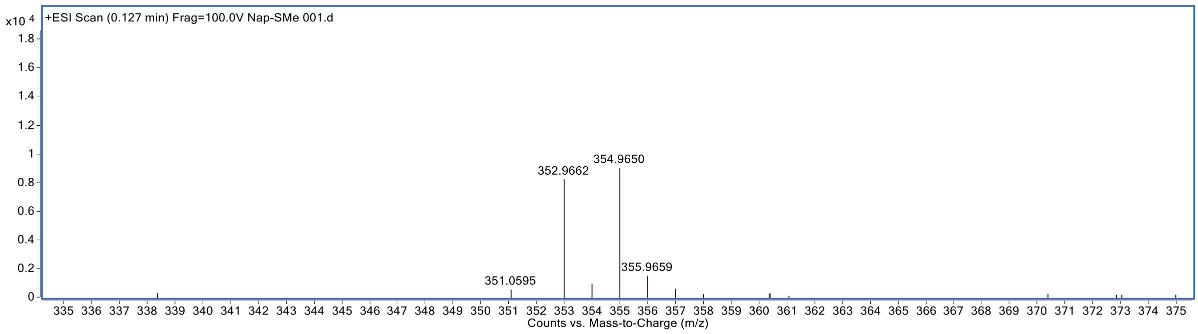


Figure S116 Mass spectrum of **2r**

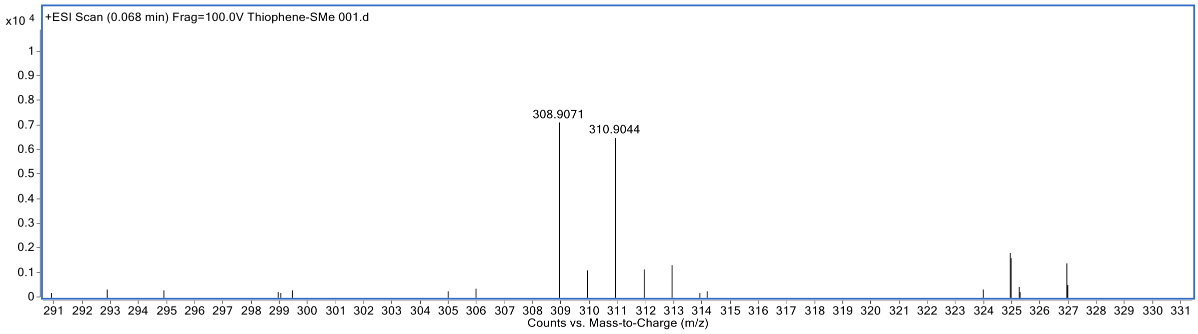


Figure S117 Mass spectrum of **2s**

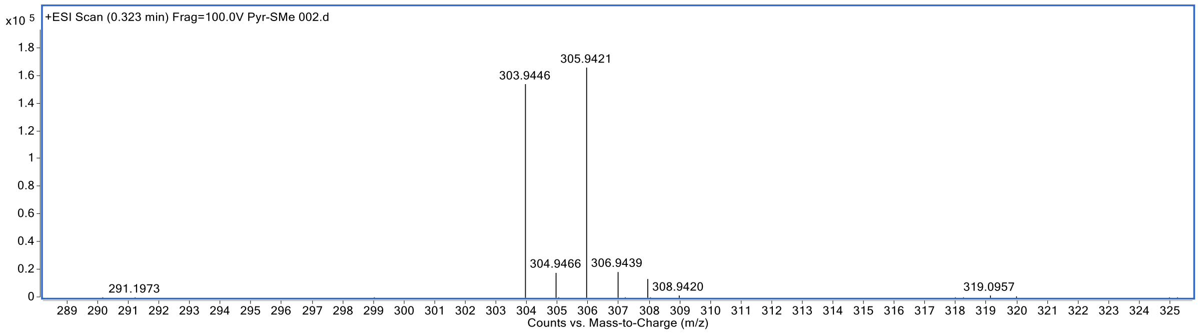


Figure S118 Mass spectrum of **2t**

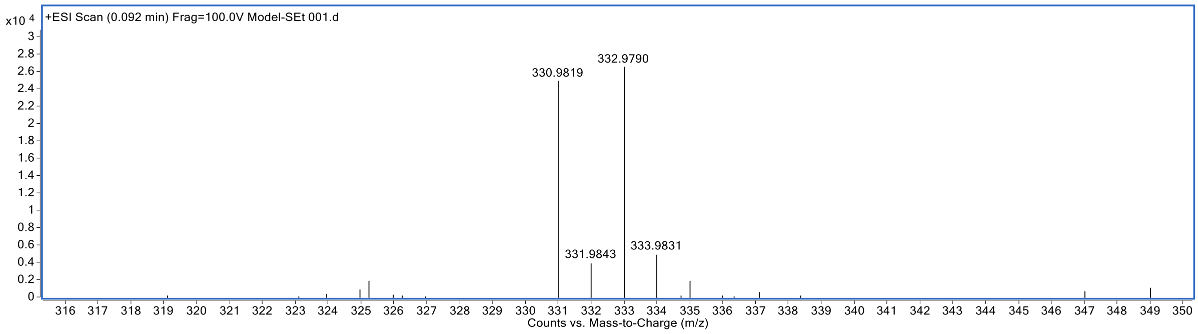
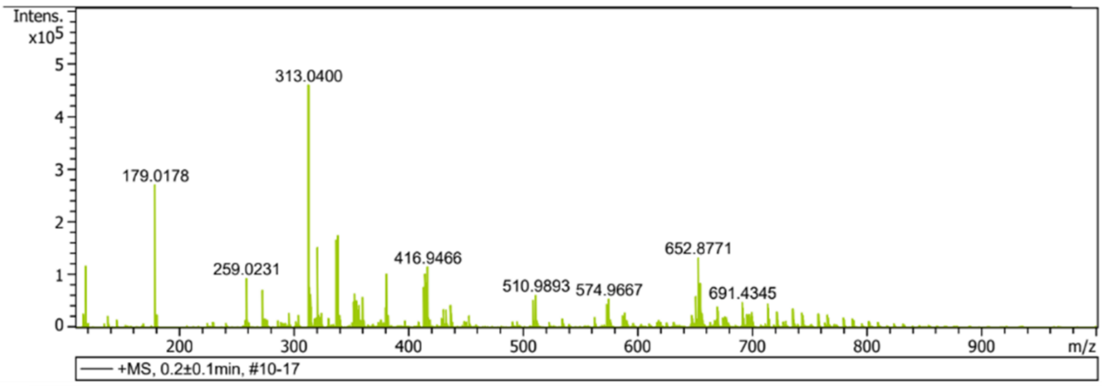


Figure S119 Mass spectrum of **2v**



Mass Spectrum List Report

#	m/z	Res.	S/N	I	I %	FWHM
29	336.9342	10837	1866.6	166617	4.0	0.0311
30	337.0367	9459	188.9	16857	0.4	0.0356
31	337.9374	10917	246.0	22028	0.5	0.0310
32	338.9321	10844	1937.4	175009	4.1	0.0313
33	339.9354	10743	252.9	23015	0.5	0.0316
34	352.3204	11053	489.5	48926	1.2	0.0319

Figure S120 Mass spectrum of **2w**

Reference

1. Rao, H. S. P.; Sivakumar, S., Condensation of a-aroylketene dithioacetals and 2-hydroxyarylaldehydes results in facile synthesis of a combinatorial library of 3-aroylcoumarins. *J. Org. Chem.* **2006**, **71**, 8715-8723.