Selenium-Epoxy 'Click' Reaction and Se-Alkylation: Efficient Access to Organo-Selenium and Selenonium Compounds

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General Methods and Materials

Glycidol, glycidyl methacrylate, allyl glycidyl ether, glycidyl propargyl ether, epichlorohydrin, aniline, benzoic acid, phenol, thiophenol, benzeneselenol, lithium hydroxide monohydrate (LiOH), 1,8,-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine (TEA), acetic anhydride, 3-bromopropane-1,2-diol, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), 4-dimethylaminopyridine (DMAP), acetic acid, iodomethane, silver tetrafluoroborate ($AgBF_4$), red blood cells (sterile defibrinated sheep's blood, RBC), were purchased from commercial sources. NMR spectra were recorded on a Varian NMR system 500 MHz spectrometer, using $CDCl_3$, DMSO-d_6 and D_2O as the solvents. HRMS was carried out on a JMS-700 from JEOL in EI and FAB mode. FT-IR spectrometer with ATR (attenuated total reflection) was carried out on Agilent Cary 630 FTIR. Hemolysis assay were performed using a microplate reader (Spectra Max 340, Molecular Devices, Sunnyvale, CA USA).

Synthesis of **3** in water: To a solution of freshly obtained benzeneselenol **1** (471 mg, 3.0 mmol) and glycidol **2** (222 mg, 3.0 mmol) in 3 mL water was added TEA, DBU, or LiOH (0.01, 0.03 or 0.05 eq., respectively, per selenol unit) at 0 °C. The cooling was removed and the reaction mixture was stirred at room temperature for time shown in Table 2. After this time, 100 μL of the reaction mixture was removed and diluted with 1 mL of $CDCl_3$, dried over sodium sulfate, and studied with the help of NMR spectroscopies.

Synthesis of **3** in chloroform: To a solution of freshly obtained benzeneselenol **1** (471 mg, 3.0 mmol) and glycidol **2** (222 mg, 3.0 mmol) in 3 mL chloroform was added TEA, DBU, or LiOH (0.01, 0.03 or 0.05 eq., respectively, per selenol unit) at 0 °C. The cooling was removed and the reaction mixture was stirred at room temperature for time shown in Table 1. After this time, 100 μL of the reaction mixture was removed and diluted with 1 mL of $CDCl_3$, and studied with the help of NMR spectroscopies.

Synthesis of **3** via **6**: To a solution of 3-bromopropane-1,2-diol **6** (1.0 g, 6.45 mmol) and benzeneselenol **1** (2.03 g, 12.9 mmol) in 6 mL MeCN was added TEA (5.22 g, 51.6 mmol) and the reaction mixture was stirred at 75 °C for 6 h. After this time, the reaction mixture was

cooled to room temperature, diluted with DCM and washed with water. The organic solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (eluent = DCM/MeOH 95:5) which gave about 1.31 g of **3** as a white powder (yield = 88%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.50 – 7.44 (m, 2H), 7.35 – 7.15 (m, 3H), 4.98 (d, J = 5.1 Hz, 1H), 4.65 (t, J = 5.5 Hz, 1H), 3.74 – 3.56 (m, 1H), 3.44 – 3.33 (m, 2H), 3.17 – 2.85 (m, 2H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 131.22, 130.94, 129.15, 126.19, 70.88, 65.01, 31.59. ^{77}Se NMR (95 MHz, DMSO-D_6) δ 262.59. HRMS (EI+) m/z calcd for $C_9H_{12}O_2Se$ $[M]^+$: 232.0003, observed: 231.9997. IR (cm^{-1}): 3324, 3194, 3054, 2944, 2925, 1576, 1487, 1474, 1448, 1435, 1412, 1375, 1321, 1295, 1244, 1200, 1181, 1164, 1134, 1095, 1017, 1041, 1026, 1017, 984, 896, 872, 836, 803, 724, 687, 670.

Synthesis of **7**: A suspension of compound **3** (500 mg, 2.16 mmol), acetic acid (649 mg, 10.8 mmol), EDCI (2.07 g, 10.8 mmol), and DMAP (132 mg, 1.08 mmol) was stirred at 0 °C in 10 mL DMF for 1 hr. Then the reaction mixture was stirred at room temperature for overnight. After this time, the reaction was diluted with DCM and washed with water, 0.1 M HCl solution, followed by saturated $NaHCO_3$. The organic solvent was removed under reduced pressure which gave about 552 mg of the product as a colorless oil (yield = 81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 – 7.42 (m, 2H), 7.40 – 7.19 (m, 3H), 5.10 (dtd, J = 7.0, 6.1, 3.3 Hz, 1H), 4.30 – 4.05 (m, 2H), 3.24 – 3.12 (m, 2H), 1.98 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 170.22, 169.82, 131.94, 129.57, 129.42, 127.13, 70.76, 64.06, 26.68, 20.69, 20.61. ^{77}Se NMR (95 MHz, DMSO-D_6) δ 272.87. HRMS (EI+) m/z calcd for $C_{13}H_{16}O_4Se$ $[M]^+$: 316.0214, observed: 316.0211. IR (cm^{-1}): 3054, 2950, 1735, 1578, 1477, 1436, 1367, 1220, 1108, 1041, 1021, 998, 961, 943, 872, 836, 803, 736, 691, 669.

Synthesis of **12**-**15**: To a solution of **8**, **9**, **10**, or **11** (3.0 mmol) and freshly obtained benzeneselenol **1** (471 mg, 3.0 mmol) in 3 mL water was added LiOH (0.03 eq. per selenol unit) at 0 °C. The cooling was removed and the reaction mixture was stirred at room temperature for 15 mins. After this time, 100 μL of the reaction mixture was added to 1 mL $CDCl_3$, dried over sodium sulfate, and studied with the help of NMR spectroscopies.

12: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.47 (m, 2H), 7.29 – 7.20 (m, 3H), 4.12 (dd, J = 2.4, 0.9 Hz, 2H), 3.96 – 3.87 (m, 1H), 3.67 – 3.52 (m, 2H), 3.12 – 2.97 (m, 2H), 2.73 (d, J = 4.4 Hz, 1H), 2.43 (t, J = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.97, 129.56, 129.32, 127.35, 79.43, 75.06, 72.71, 69.37, 58.65, 31.93. ^{77}Se NMR (95 MHz, $CDCl_3$) δ 244.31. HRMS (EI+) m/z calcd for $C_{12}H_{14}O_2Se$ $[M]^+$: 270.0159, observed: 270.0156. IR (cm^{-1}): 3408,

3283, 3054, 2901, 2855, 2115, 1578, 1477, 1436, 1356, 1263, 1205, 1095, 1071, 1021, 946, 909, 734, 689, 699.

13: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.29 – 7.19 (m, 3H), 5.85 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.28 – 5.14 (m, 2H), 3.95 (dt, *J* = 5.7, 1.5 Hz, 2H), 3.94 – 3.86 (m, 1H), 3.55 – 3.43 (m, 2H), 3.12 – 2.97 (m, 2H), 2.75 (d, *J* = 4.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.43, 132.90, 129.68, 129.27, 127.28, 117.48, 72.90, 72.37, 69.52, 31.97. ^{77}Se NMR (95 MHz, $CDCl_3$) δ 245.11. HRMS (EI+) m/z calcd for $C_{12}H_{16}O_2Se$ $[M]^+$: 272.0316, observed: 272.0313. IR (cm^{-1}): 3412, 3067, 2896, 2855, 1647, 1578, 1477, 1436, 1420, 1345, 1265, 1203, 1099, 1071, 1021, 997, 924, 799, 732, 689, 699.

14: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.47 (m, 2H), 7.25 (m, 3H), 6.09 (p, *J* = 1.1 Hz, 1H), 5.57 (p, *J* = 1.6 Hz, 1H), 4.28 – 4.16 (m, 2H), 4.02 – 3.94 (m, 1H), 3.15 – 2.96 (m, 2H), 2.88 – 2.78 (s, 1H), 1.91 (t, *J* = 1.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.40, 135.95, 133.19, 129.42, 127.63, 126.29, 68.74, 67.29, 32.44, 18.40. ^{77}Se NMR (95 MHz, $CDCl_3$) δ 243.31. HRMS (EI+) m/z calcd for $C_{13}H_{16}O_3Se$ $[M]^+$: 300.0265, observed: 300.0262. IR (cm^{-1}): 3431, 3056, 2980, 2950, 2925, 2892, 1701, 1636, 1578, 1477, 1451, 1436, 1420, 1401, 1377, 1317, 1293, 1157, 1101, 1071, 1021, 943, 812, 734, 689, 699.

15: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.48 (m, 2H), 7.27 (m, 3H), 3.97 – 3.88 (m, 1H), 3.70 – 3.60 (m, 2H), 3.16 – 3.02 (m, 2H), 2.76 (d, *J* = 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.18, 129.46, 128.95, 127.69, 70.19, 48.44, 32.44. ^{77}Se NMR (95 MHz, $CDCl_3$) δ 247.43. HRMS (EI+) m/z calcd for $C_9H_{11}ClOSe$ $[M]^+$: 249.9664, observed: 249.9661. IR (cm^{-1}): 3390, 3052, 2948, 1654, 1576, 1476, 1436, 1339, 1297, 1261, 1209, 1181, 1157, 1131, 1066, 1034, 1021, 998, 982, 943, 909, 883, 851, 808, 732, 689, 699.

Reaction with aniline, phenol, benzoic acid, or thiophenol: To a solution of glycidol **2** (3.0 mmol), freshly obtained benzeneselenol **1** (3.3 mmol) and any one of the nucleophile (3.3 mmol) in 3 mL water added LiOH (0.03 eq. per selenol units) at 0 °C. The cooling was removed and the reaction mixture was stirred at room temperature for 15 mins. After this time, 100 μL of the reaction mixture was added in 1 mL $CDCl_3$, dried over sodium sulfate, and studied with the help of NMR spectroscopy.

Reaction between thiophenol and glycidol in the absence of **1**: To a solution of glycidol (222 mg, 3.0 mmol), thiophenol (330 mg, 3 mmol) in 3 mL water added LiOH (2 mg, 0.09 mmol) at 0 °C. The cooling was removed and the reaction mixture was stirred at room temperature for 15 mins. After this time, 100 μL of the reaction mixture was added in 1 mL $CDCl_3$, dried over sodium sulfate, and studied with the help of NMR spectroscopy.

Synthesis of **16/17**: To a solution of selenide **3** or **7** (100 mg/mL) and $AgBF_4$ (1.25 eq. per selenide) in MeCN was added iodomethane (4 eq. per selenol unit) and the reaction mixture was stirred under an inert atmosphere in the dark at 50 °C for 24 hr. After this time, AgI was removed by syringe filter and the filtrate was precipitated into diethyl ether thrice and then dried under high vacuum conditions.

16: ^{1}H NMR (500 MHz, DMSO-D_6) δ 7.97 – 7.90 (m, 2H), 7.74 – 7.59 (m, 3H), 5.81 – 5.74 (m, 1H), 5.15 (t, J = 5.5 Hz, 0.5H), 5.09 (t, J = 5.6 Hz, 0.5H), 3.95 (ddq, J = 7.8, 5.9, 4.7 Hz, 0.5H), 3.77 – 3.56 (m, 2.5H), 3.52 – 3.37 (m, 2H), 3.07 (d, J = 1.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 132.62, 132.38, 130.97, 130.72, 130.52, 130.41, 127.72, 126.55, 67.29, 66.95, 64.89, 48.89, 48.60, 23.34, 22.99. ^{77}Se NMR (95 MHz, DMSO-D_6) δ 377.97. HRMS (FAB+) m/z calcd for $C_{10}H_{15}O_2Se^+$ $[M]^+$: 247.0237, observed: 247.0235. IR (cm^{-1}): 3507, 3054, 2952, 2884, 1636, 1578, 1582, 1483, 1446, 1416, 1285, 995, 937, 877, 743, 683.

17: ^{1}H NMR (500 MHz, DMSO-D_6) δ 7.98 (m, 2H), 7.74 – 7.63 (m, 3H), 5.38 – 5.30 (m, 0.5H), 5.06 (ddt, J = 7.4, 5.0, 3.6 Hz, 0.5H), 4.28 – 4.10 (m, 2H),.1 Hz, 2H), 3.92 (dd, J = 12.7, 3.6 Hz, 1H), 3.87 – 3.78 (m, 2H), 3.11 (d, J = 11.9 Hz, 3H), 2.03 (d, J = 8.1 Hz, 3H), 1.82 (d, J = 6.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-D_6) δ 170.17, 170.15, 170.12, 169.93, 132.89, 132.77, 131.04, 130.83, 130.58, 130.49, 127.04, 126.21, 67.83, 67.33, 63.77, 63.69, 43.61, 43.53, 24.26, 23.83, 20.57, 20.52, 20.37, 20.25. ^{77}Se NMR (95 MHz, DMSO-D_6) δ 380.59, 379.13. HRMS (FAB+) m/z calcd for $C_{14}H_{19}O_4Se^+$ $[M]^+$: 331.0449, observed: 331.0449. (cm^{-1}): 3507, 3050, 2948, 1735, 1645, 1513, 1483, 1446, 1420, 1373, 1231, 1017, 939, 877, 840, 742, 685.

Hemolysis assay

Hemolytic activity of the crosslinked micelles was determined using sheep's red blood cells (RBCs). RBCs were pelletized by centrifuging 1 mL of the blood and then washing the RBCs at 4 times with PBS buffer (pH 7.4) solution. The crosslinked micelles were re-dispersed in PBS buffer. Then, 1mL of samples and 25 μL of the RBCs were mixed and incubated at room temperature for 2h. After incubation, the mixtures were re-pelletized by centrifuging and 200 μL of the supernatant of each sample were put into wells in a 96-well plate. The absorbance at 540 nm was measured with a microplate reader. The percent hemolysis was calculated by following equation.

$I=\{(A_i-A_{negative})/(A_{positive}-A_{negative})\}$x100 %

(A_i = the absorbance of samples solution, $A_{negative}$ = the absorbance of PBS solution, $A_{positive}$ = the absorbance of DI.)

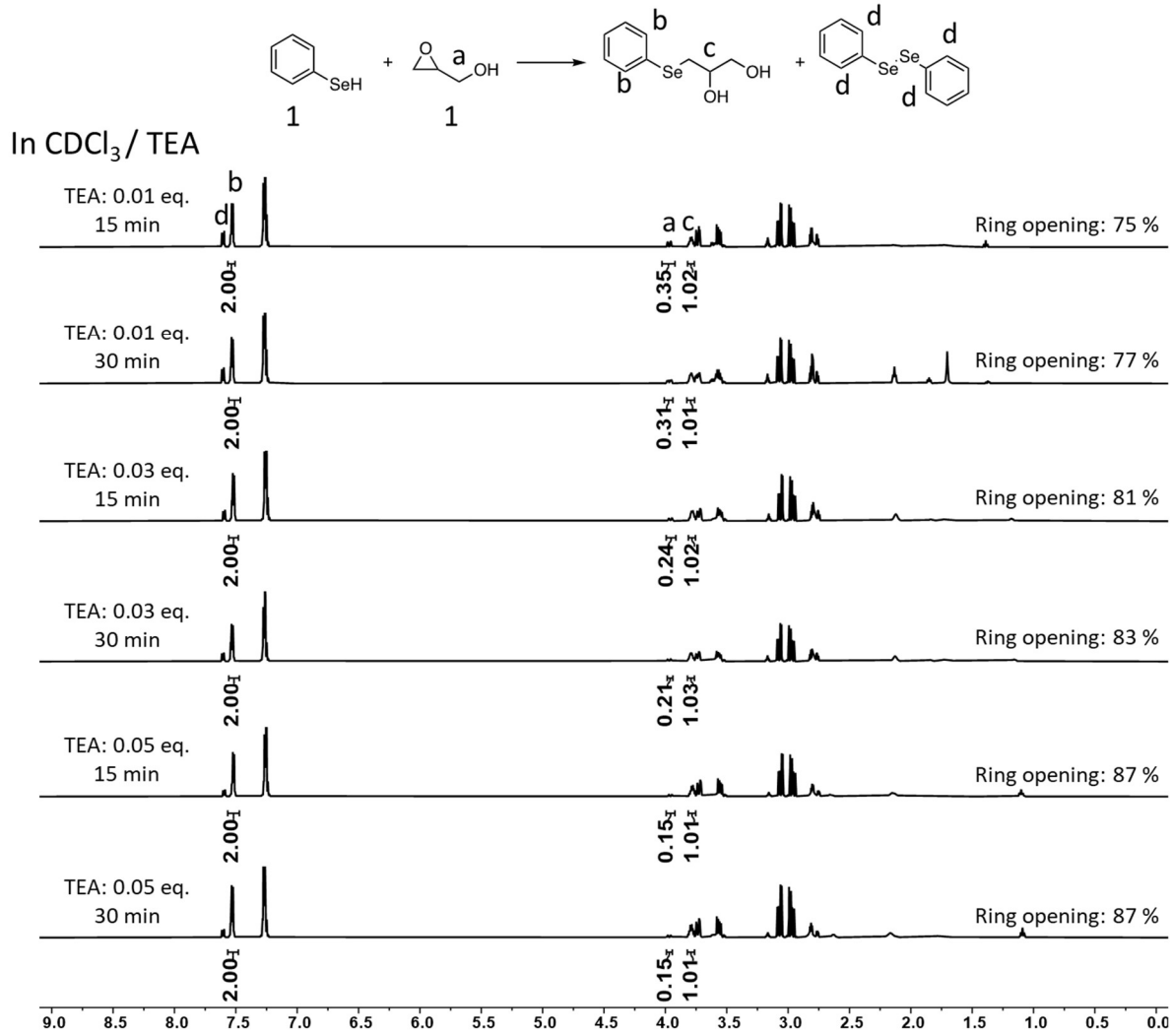

Figure S1. Crude ^{1}H-NMR ($CDCl_3$) from ring opening reaction in chloroform under TEA catalysis.

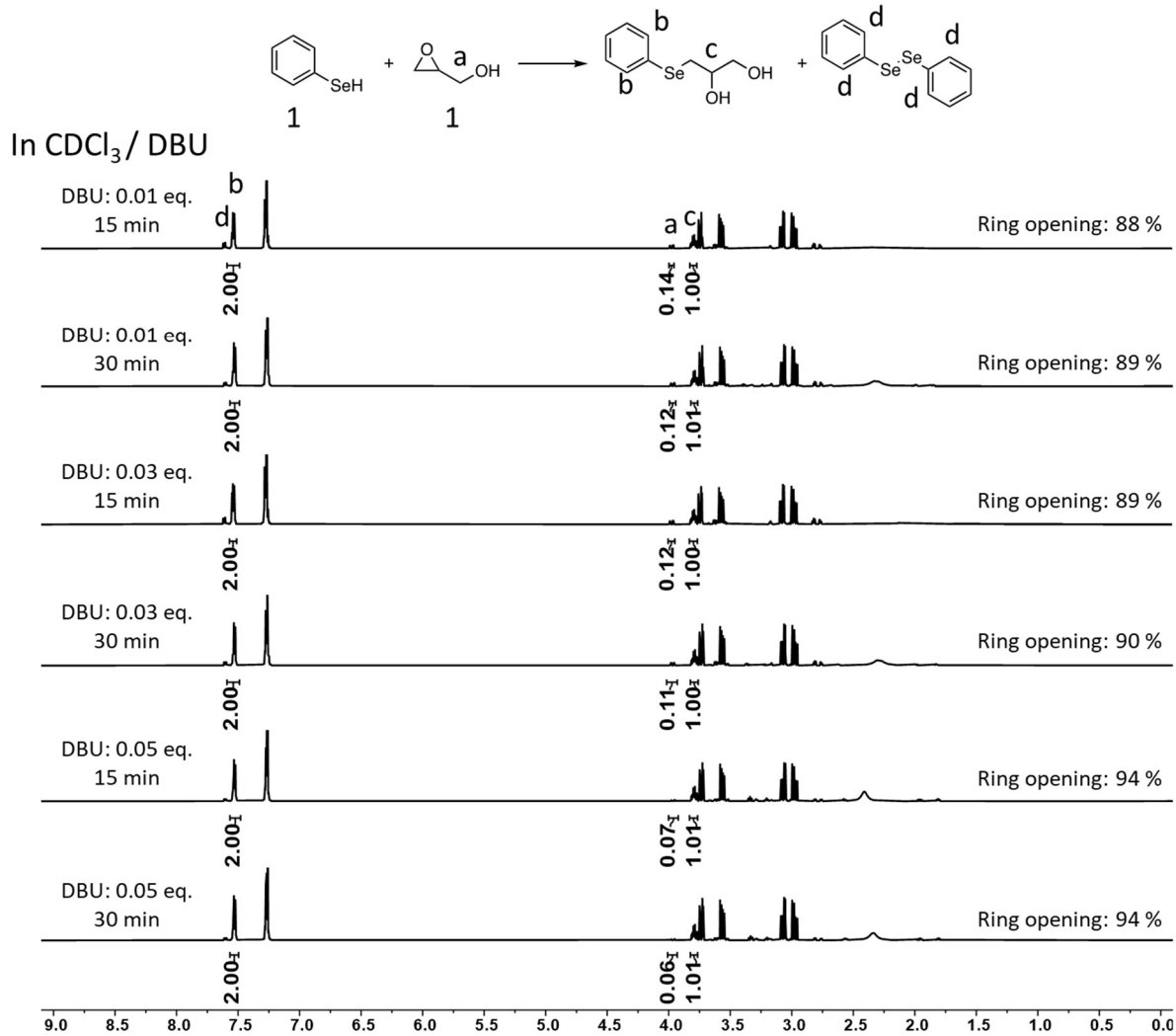

Figure S2. Crude ^{1}H-NMR ($CDCl_3$) from ring opening reaction in chloroform under DBU catalysis.

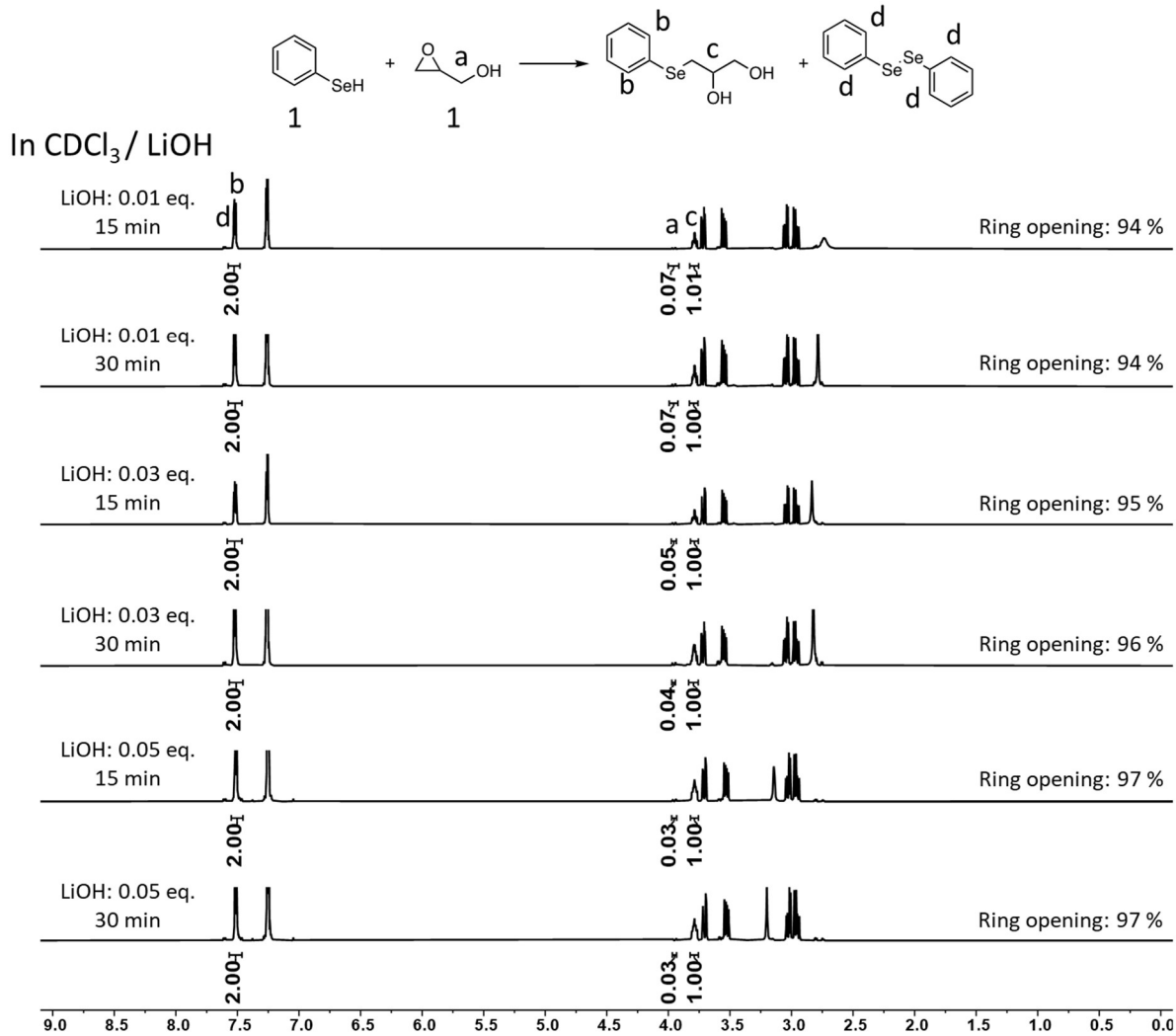

Figure S3. Crude ^{1}H-NMR ($CDCl_3$) from ring opening reaction in chloroform under LiOH catalysis.

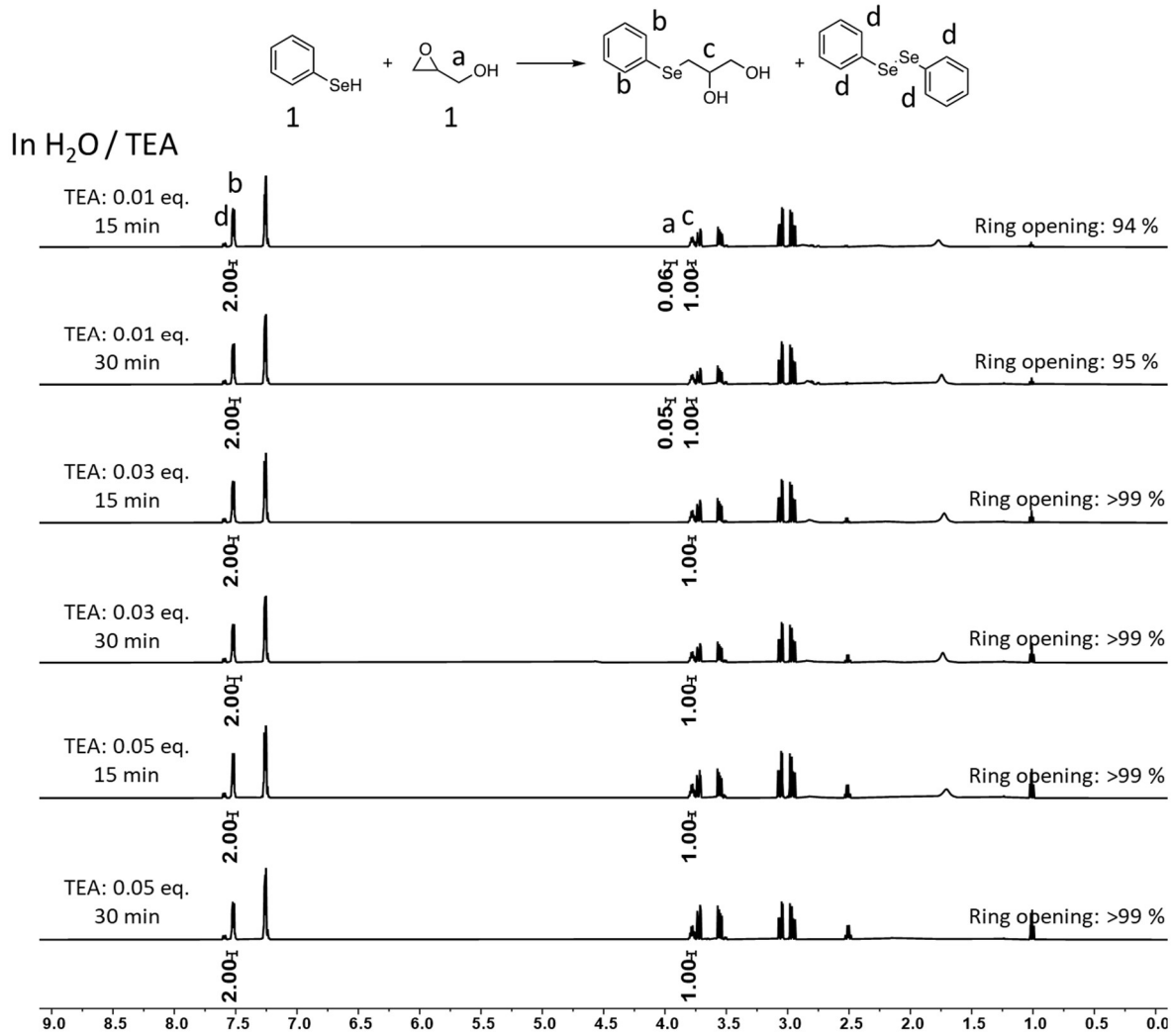

Figure S4. Crude ^{1}H-NMR ($CDCl_3$) from ring opening reaction in water under TEA catalysis.

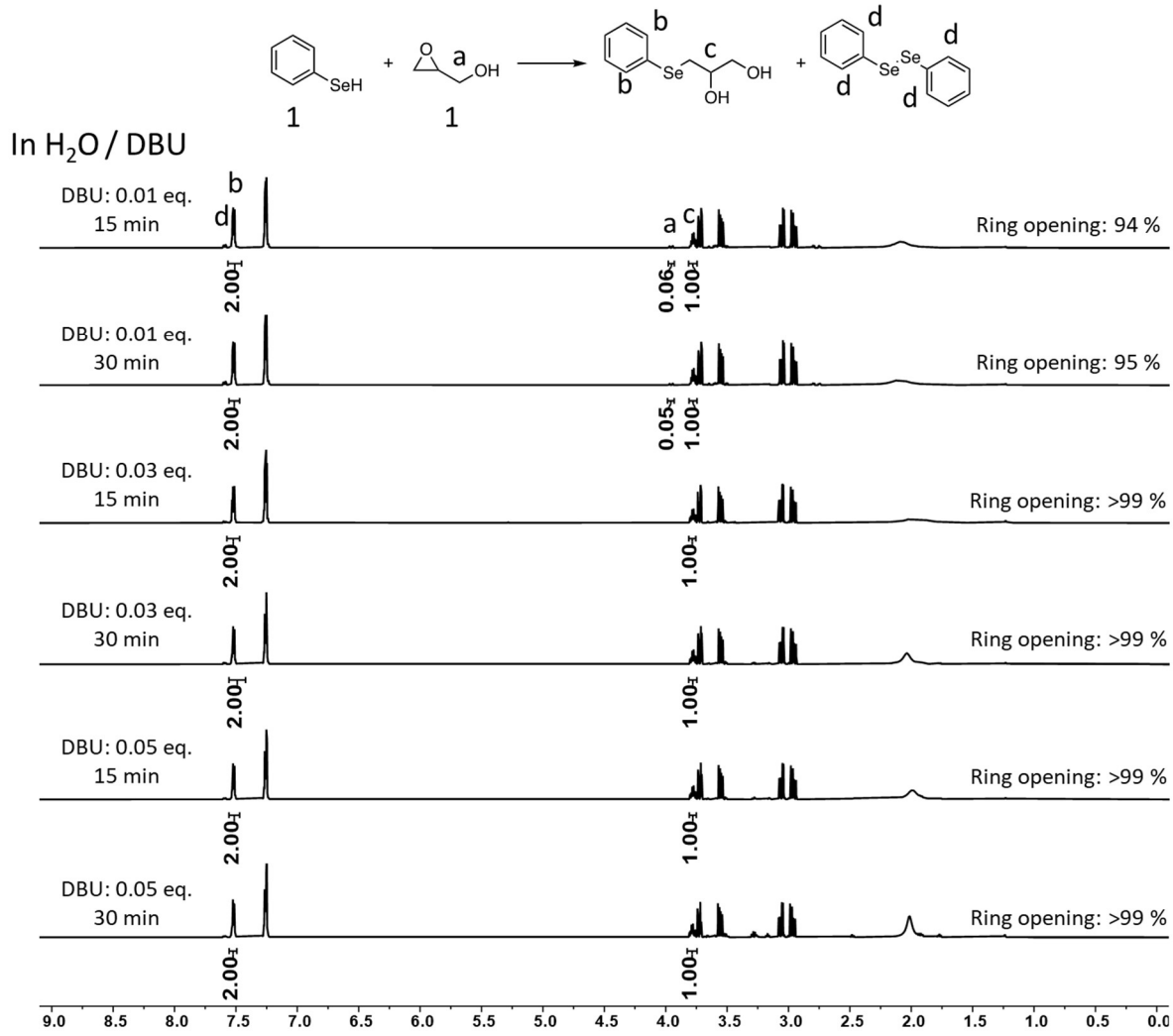

Figure S5. Crude ^{1}H-NMR ($CDCl_3$) from ring opening reaction in water under DBU catalysis.

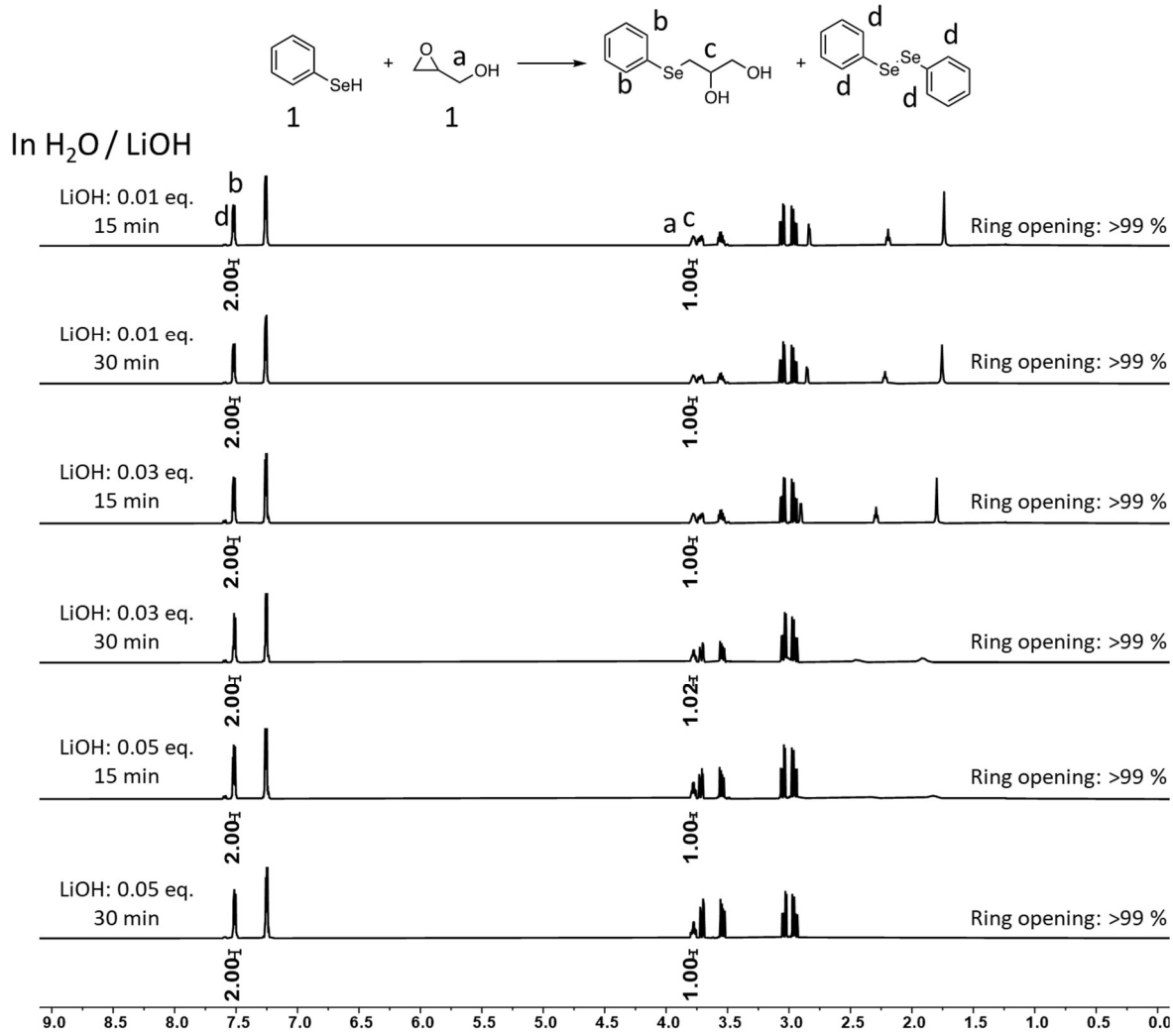

Figure S6. Crude ^{1}H-NMR ($CDCl_3$) from ring opening reaction in water under LiOH catalysis.

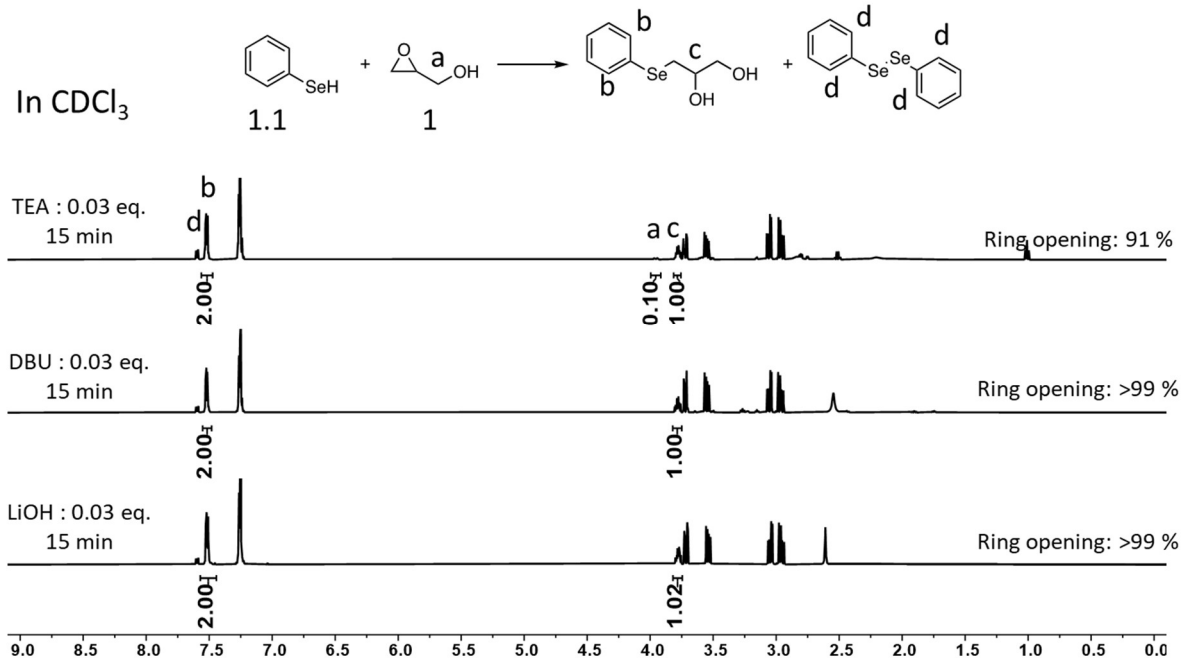

Figure S7. Crude ^{1}H-NMR ($CDCl_3$) from non-stoichiometric ring opening reaction in chloroform.

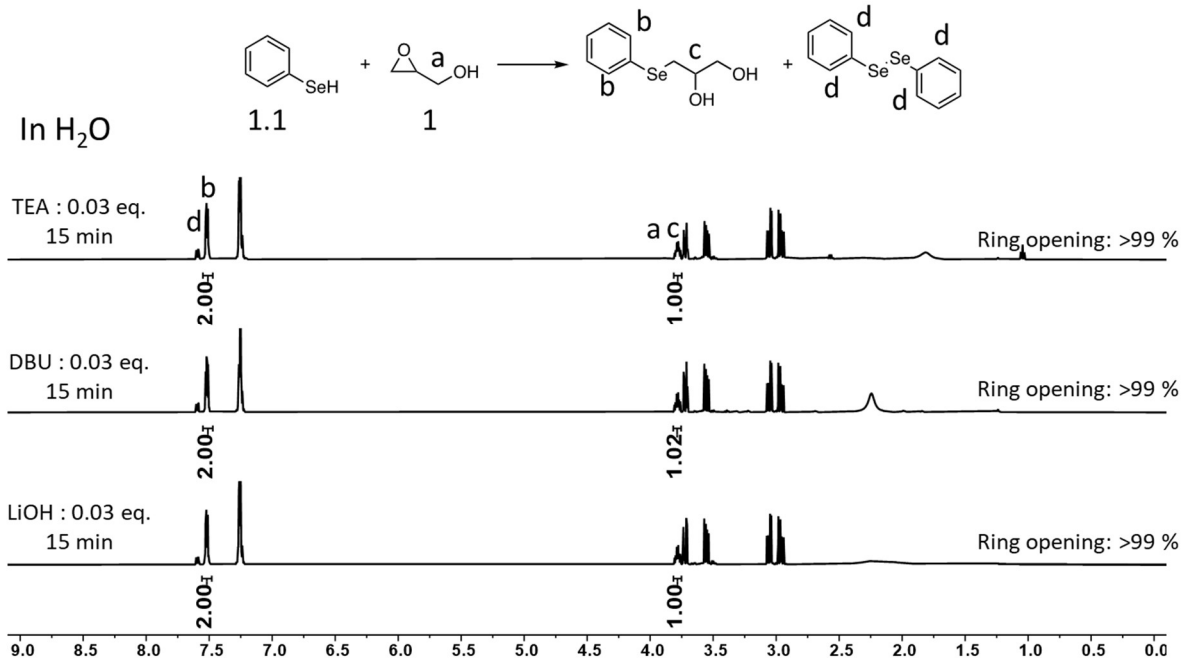

Figure S8. Crude ^{1}H-NMR ($CDCl_3$) from non-stoichiometric ring opening reaction in water.

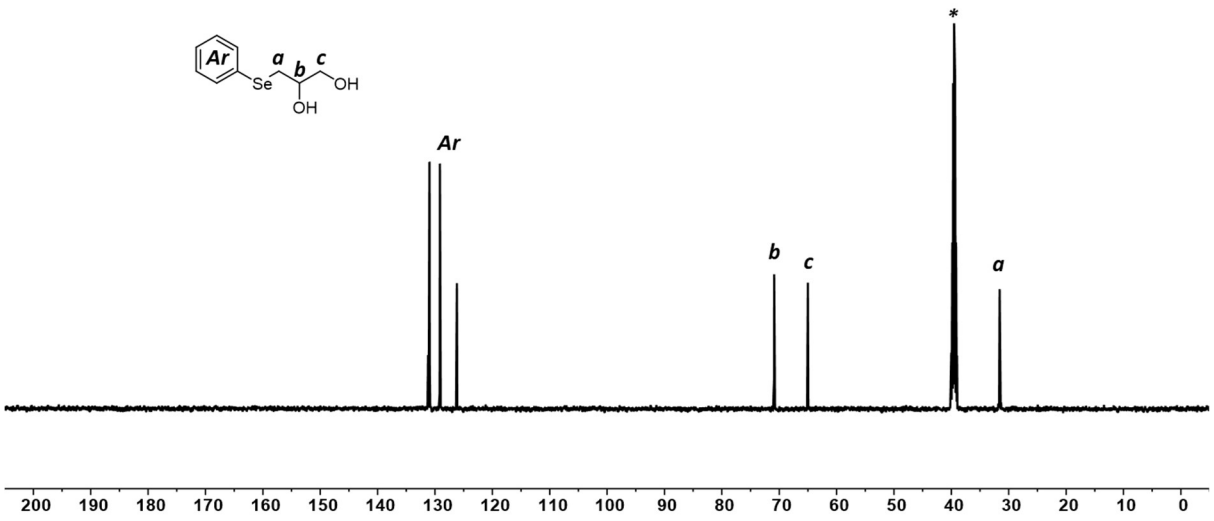

Figure S9. ^{13}C-NMR (DMSO-d_6) of **3**.

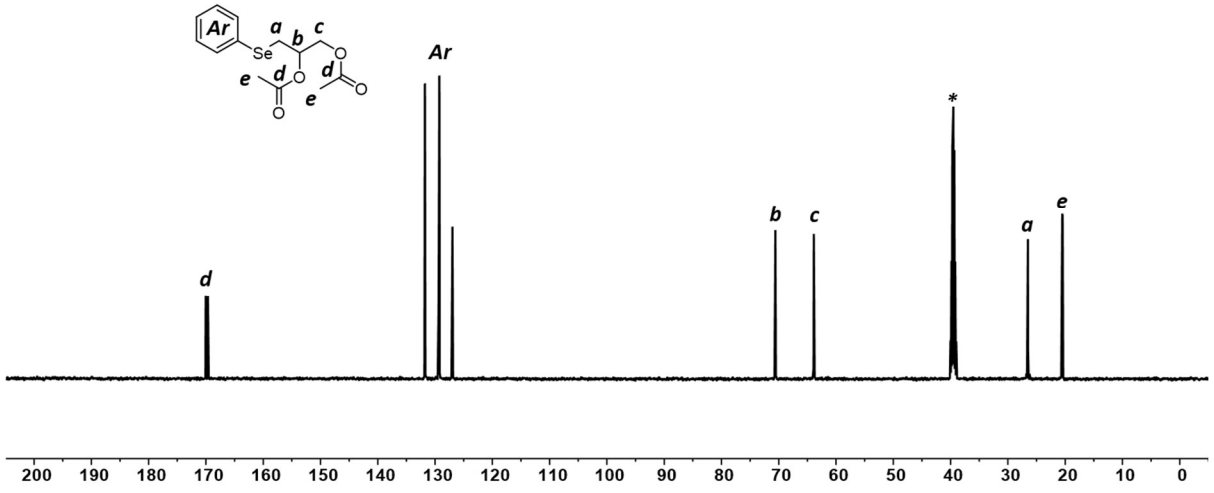

Figure S10. ^{13}C-NMR (DMSO-d_6) of **7**.

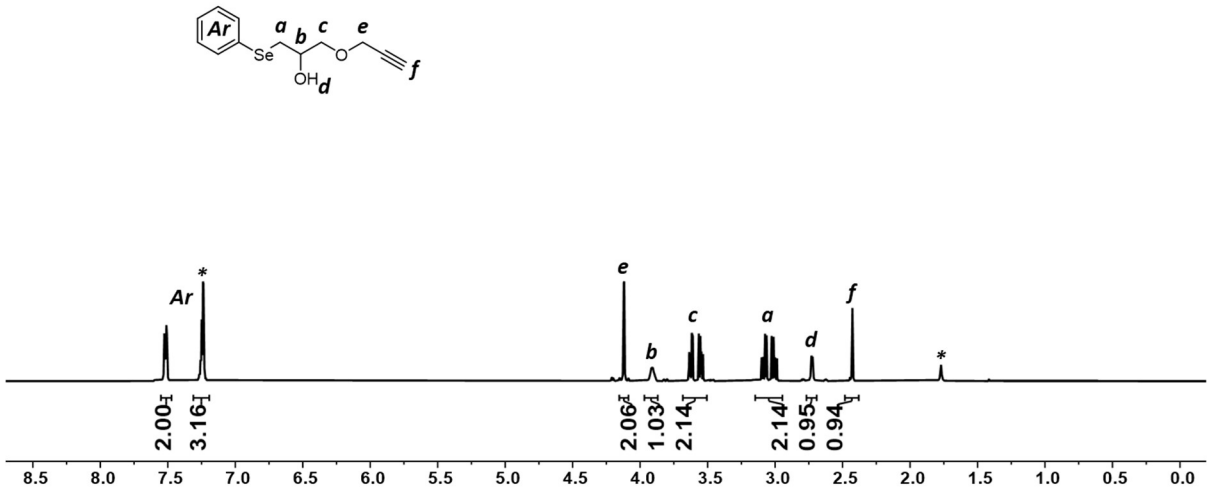

Figure S11. Crude ^{1}H-NMR ($CDCl_3$) of **12**.

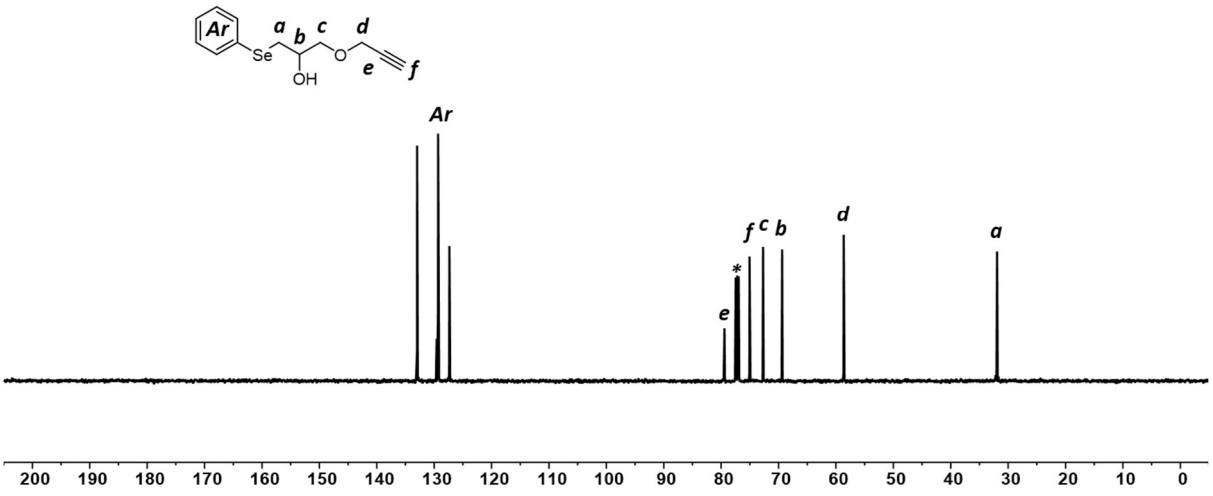

Figure S12. Crude ^{13}C-NMR ($CDCl_3$) of **12**.

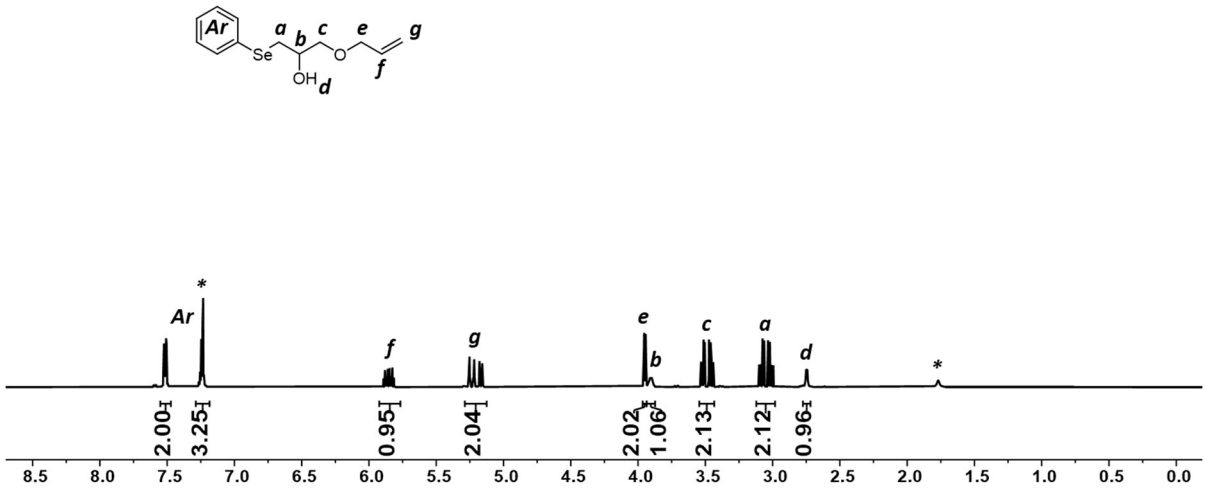

Figure S13. Crude ^{1}H-NMR ($CDCl_3$) of **13**.

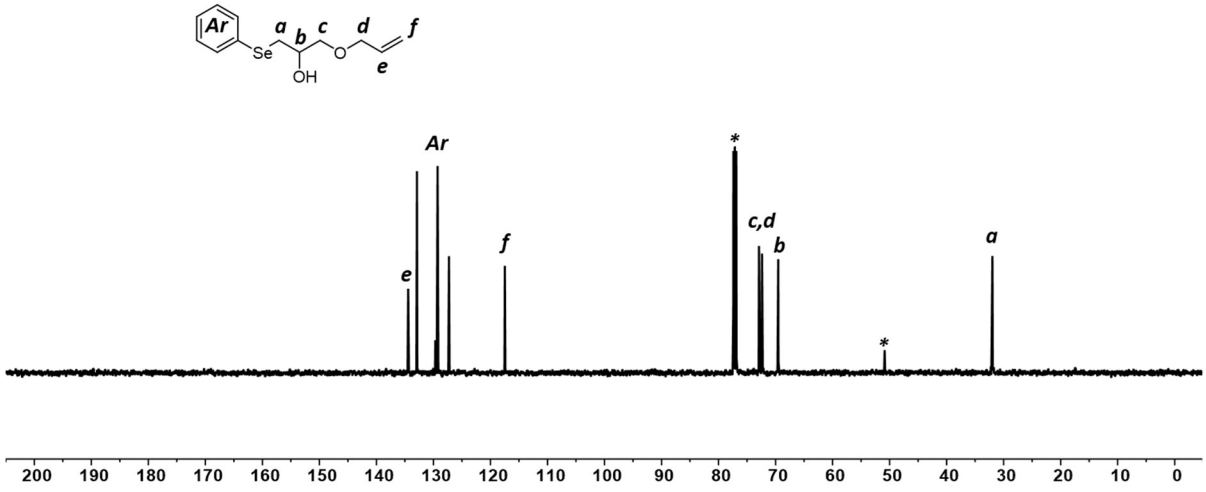

Figure S14. Crude ^{13}C-NMR ($CDCl_3$) of **13**. The signal from methanol is shown with an asterisk.

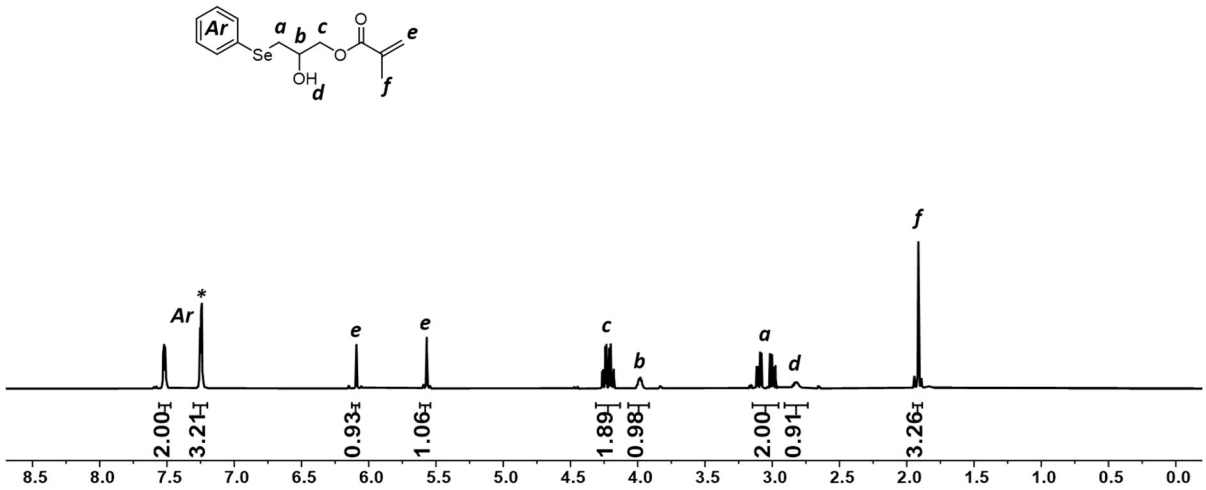

Figure S15. Crude ^{1}H-NMR ($CDCl_3$) of **14**.

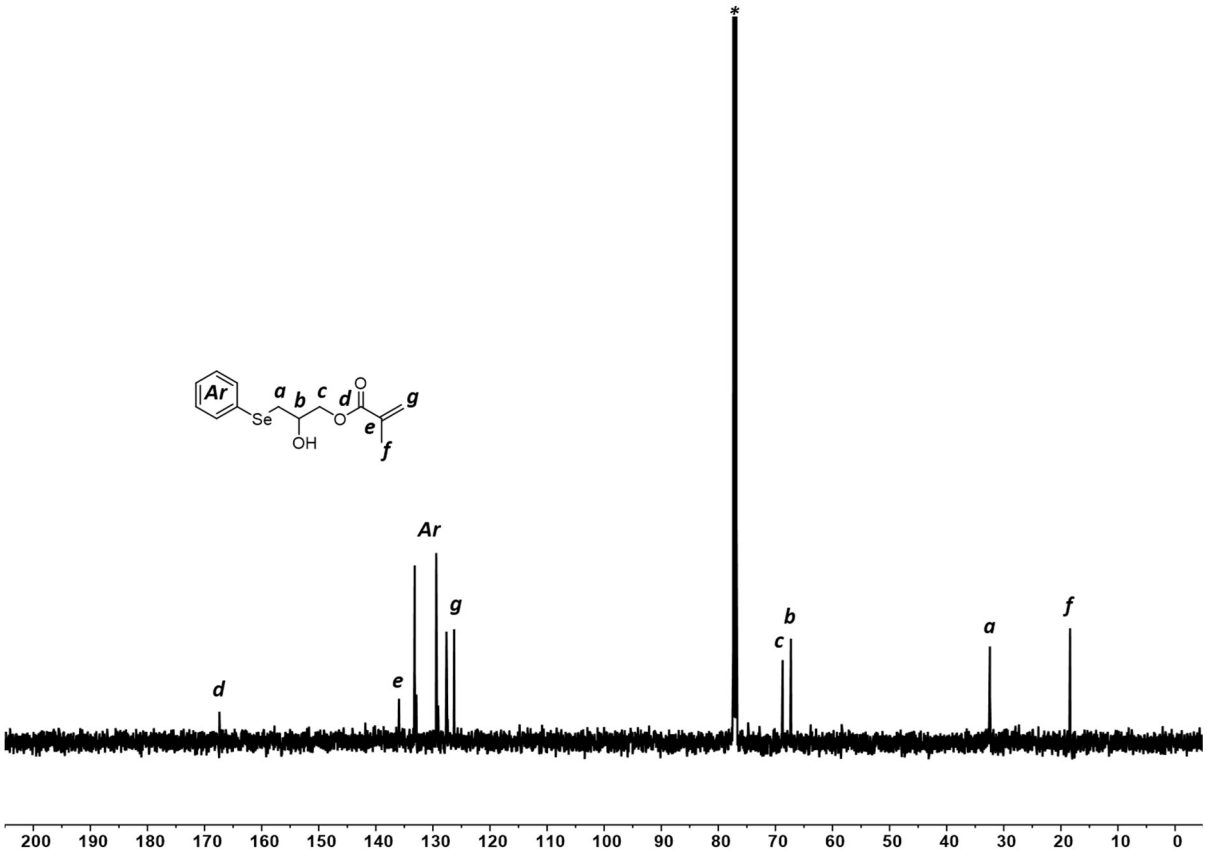

Figure S16. Crude ^{13}C-NMR ($CDCl_3$) of **14**.

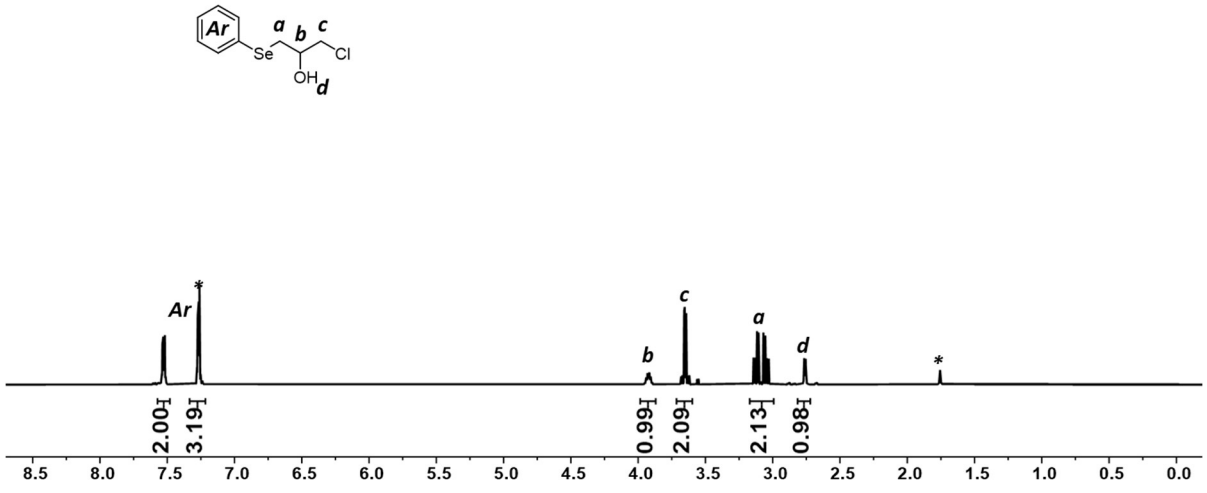

Figure S17. Crude ^{1}H-NMR ($CDCl_3$) of **15**.

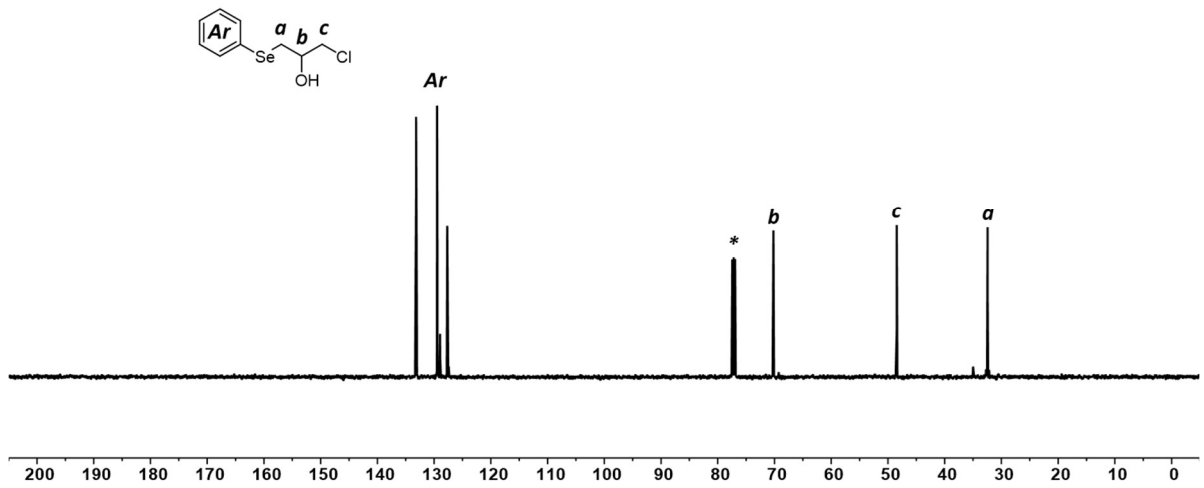

Figure S18. Crude ^{13}C-NMR ($CDCl_3$) of **15**.

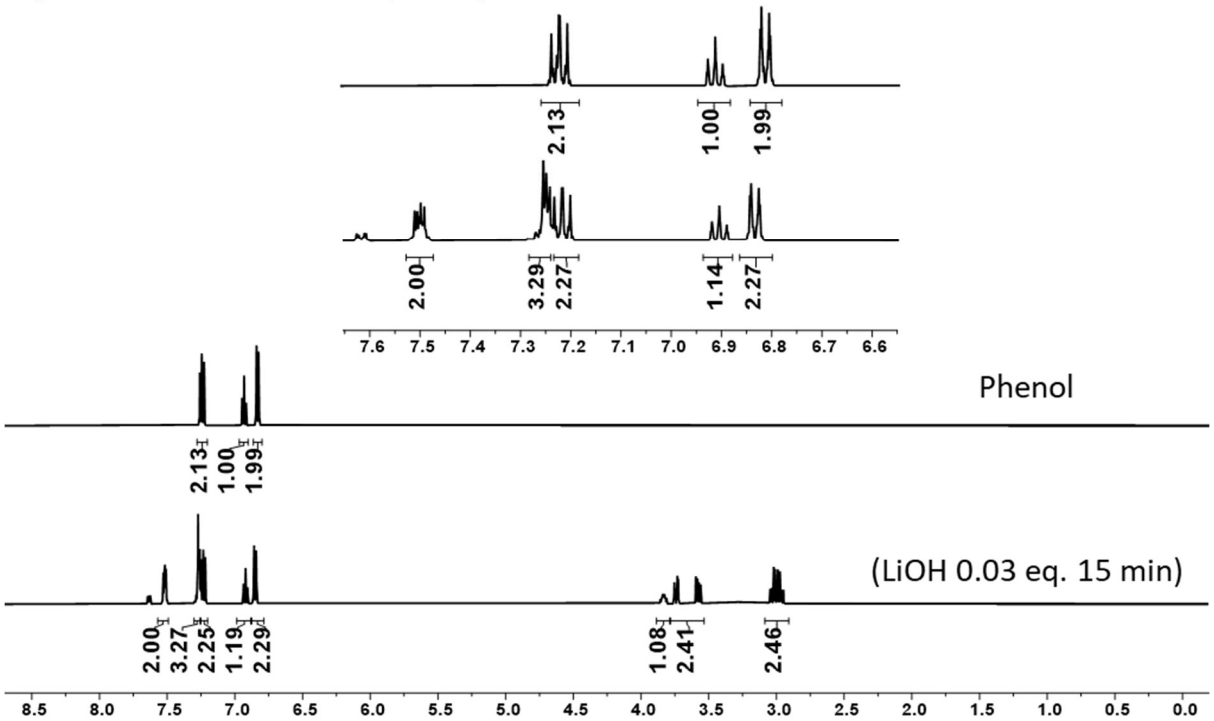

Figure S19. ^{1}H-NMR ($CDCl_3$) of phenol (top) and the reaction mixture (bottom). The signals from phenol remains unchanged.

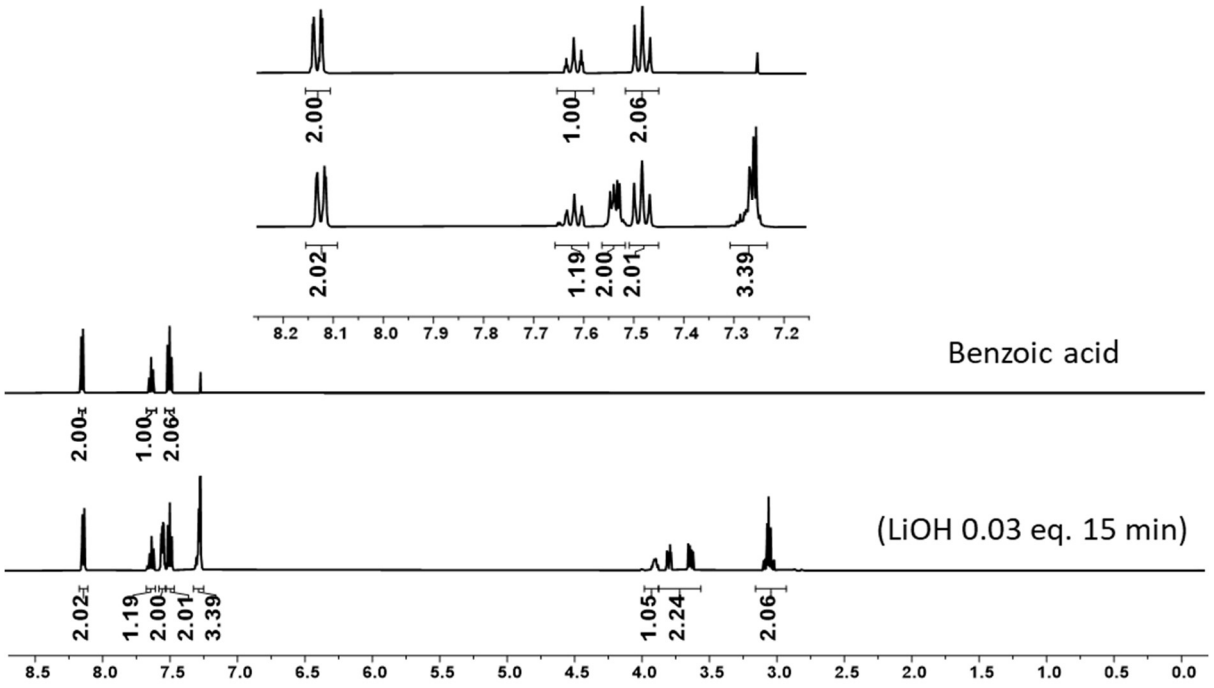

Figure S20. ^{1}H-NMR ($CDCl_3$) of benzoic acid (top) and the reaction mixture (bottom). The signals from benzoic acid remains unchanged.

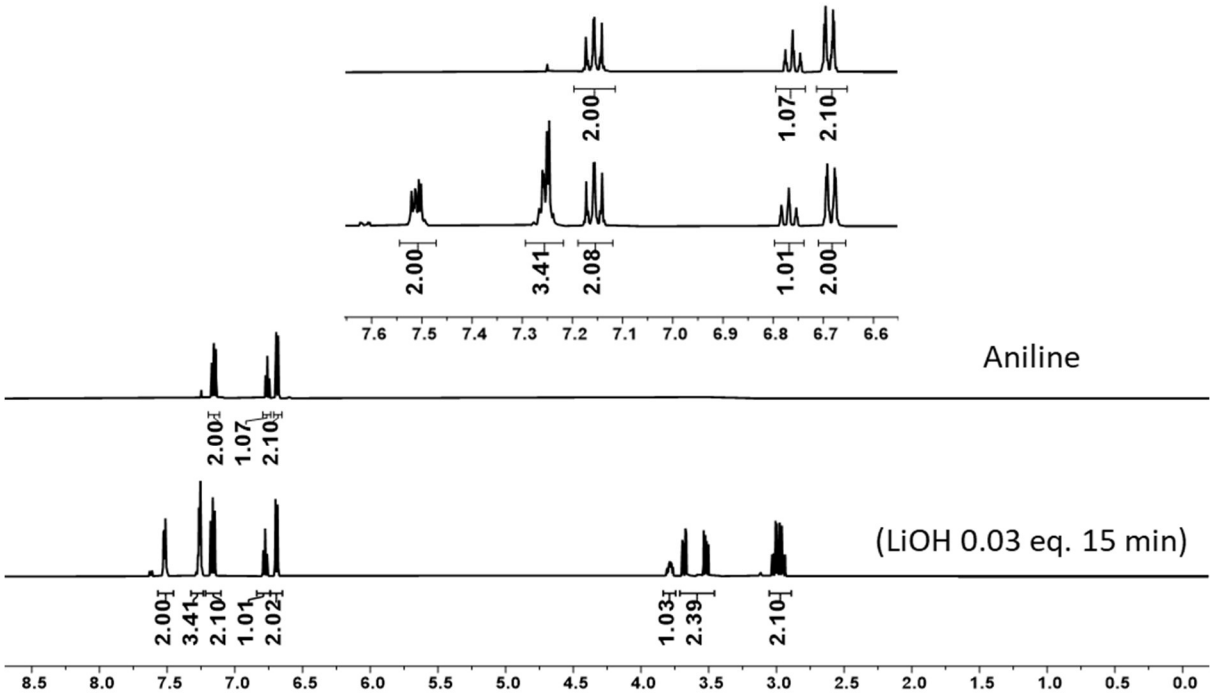

Figure S21. ^{1}H-NMR ($CDCl_3$) of aniline (top) and the reaction mixture (bottom). The signals from aniline remains unchanged.

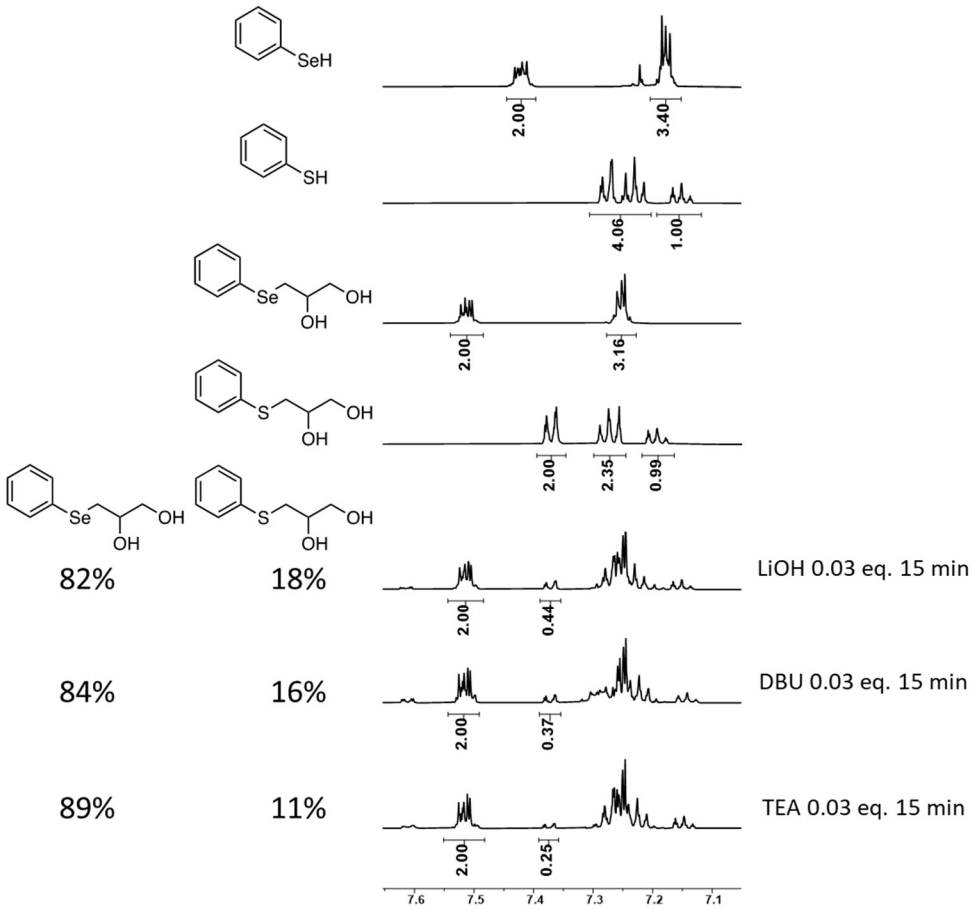

Figure S22. ^{1}H-NMR ($CDCl_3$) of reactants, products, and the crude reaction mixtures in thiol/selenium-based reactions.

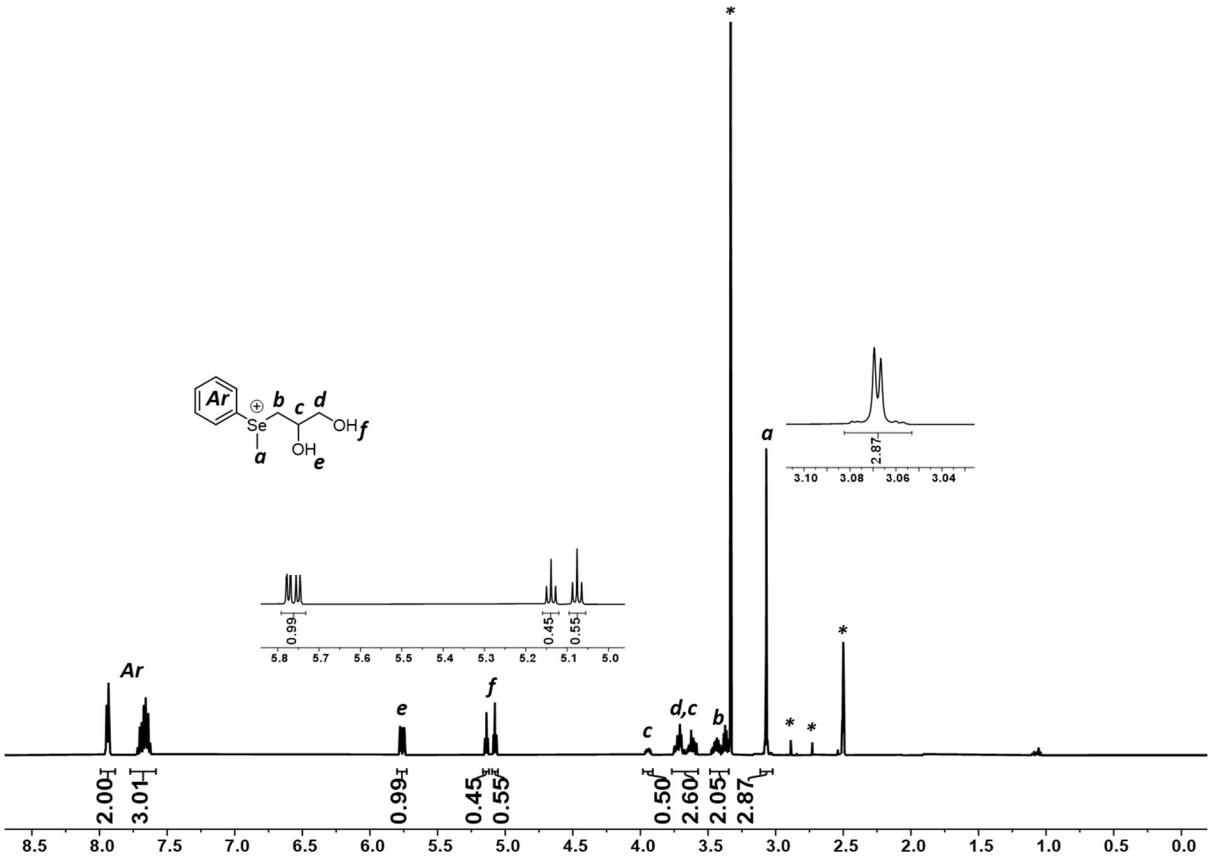

Figure S23. ^{1}H-NMR (DMSO-d_6) of **16**. The signals from DMF is shown with an asterisk.

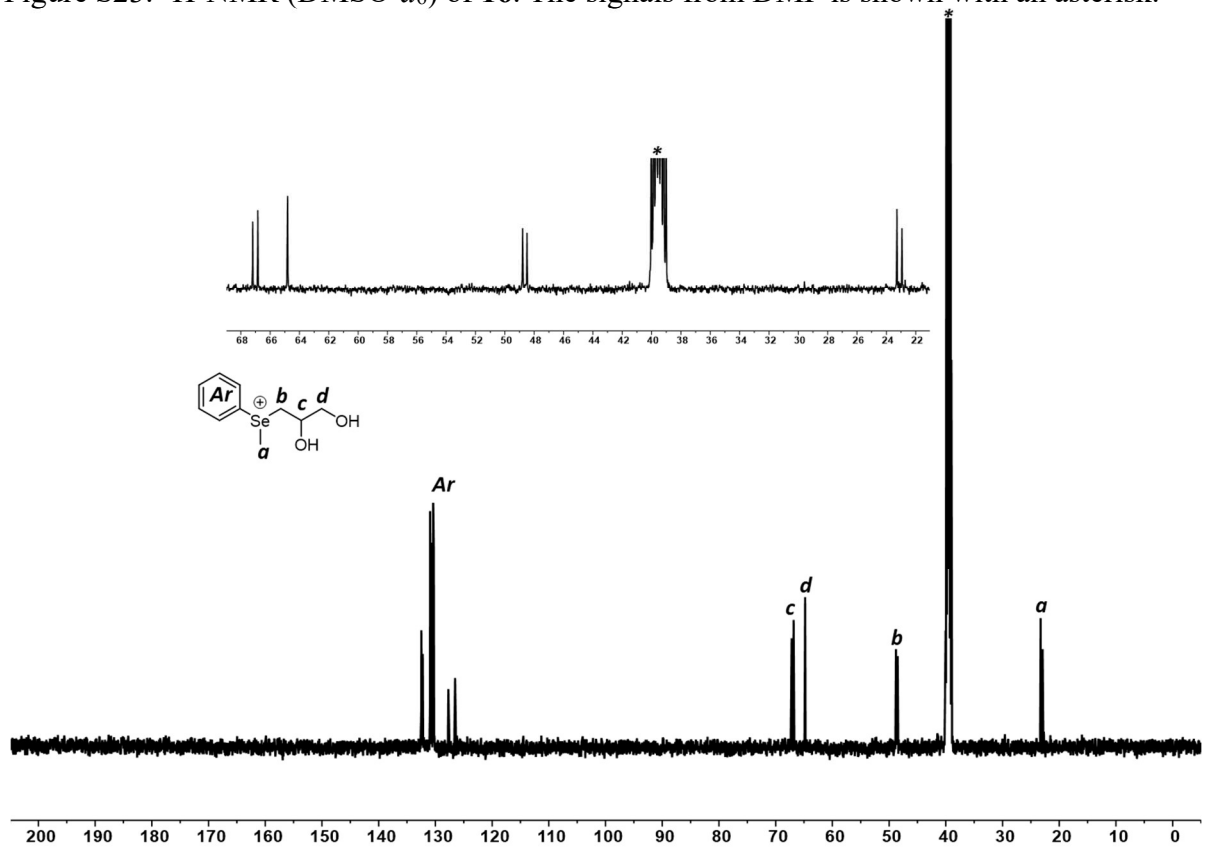

Figure S24. ^{13}C-NMR (DMSO-d_6) of **16**.

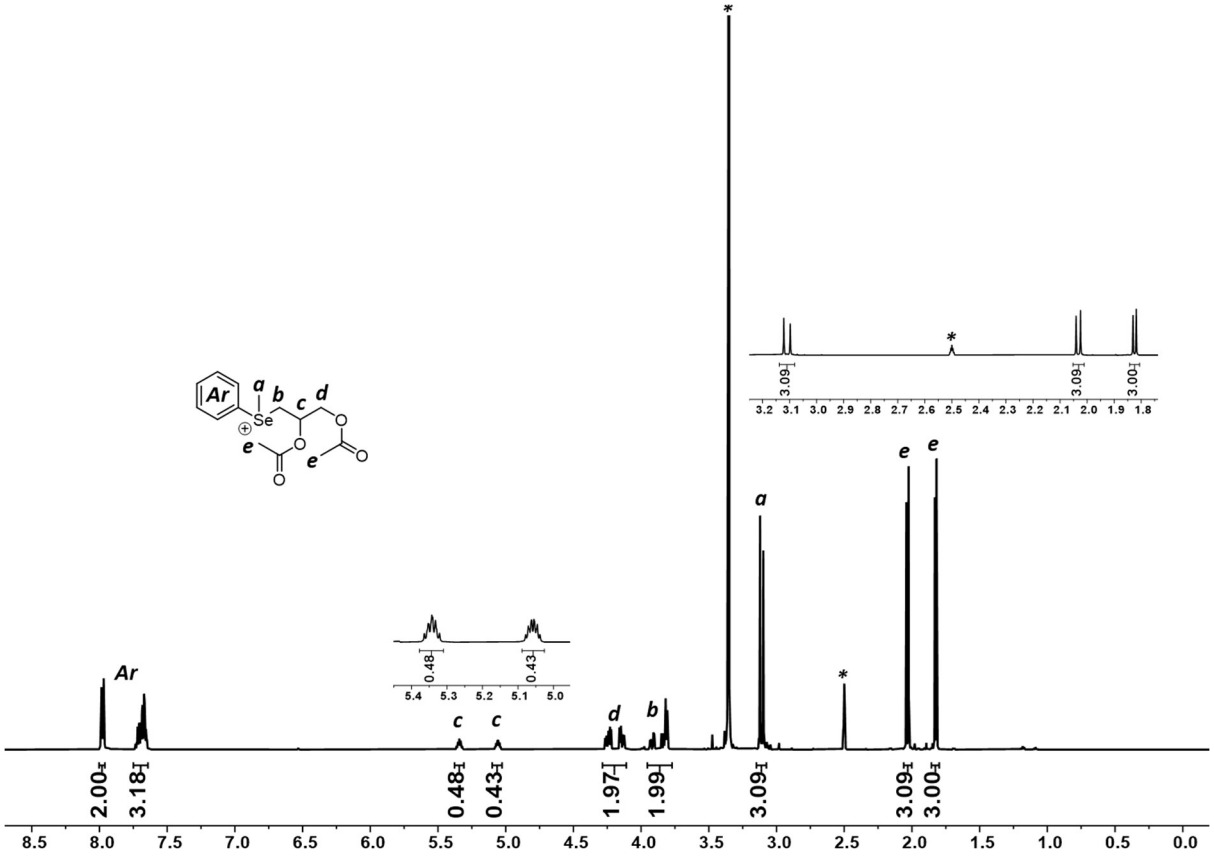

Figure S25. ^{1}H-NMR (DMSO-d_6) of **17**.

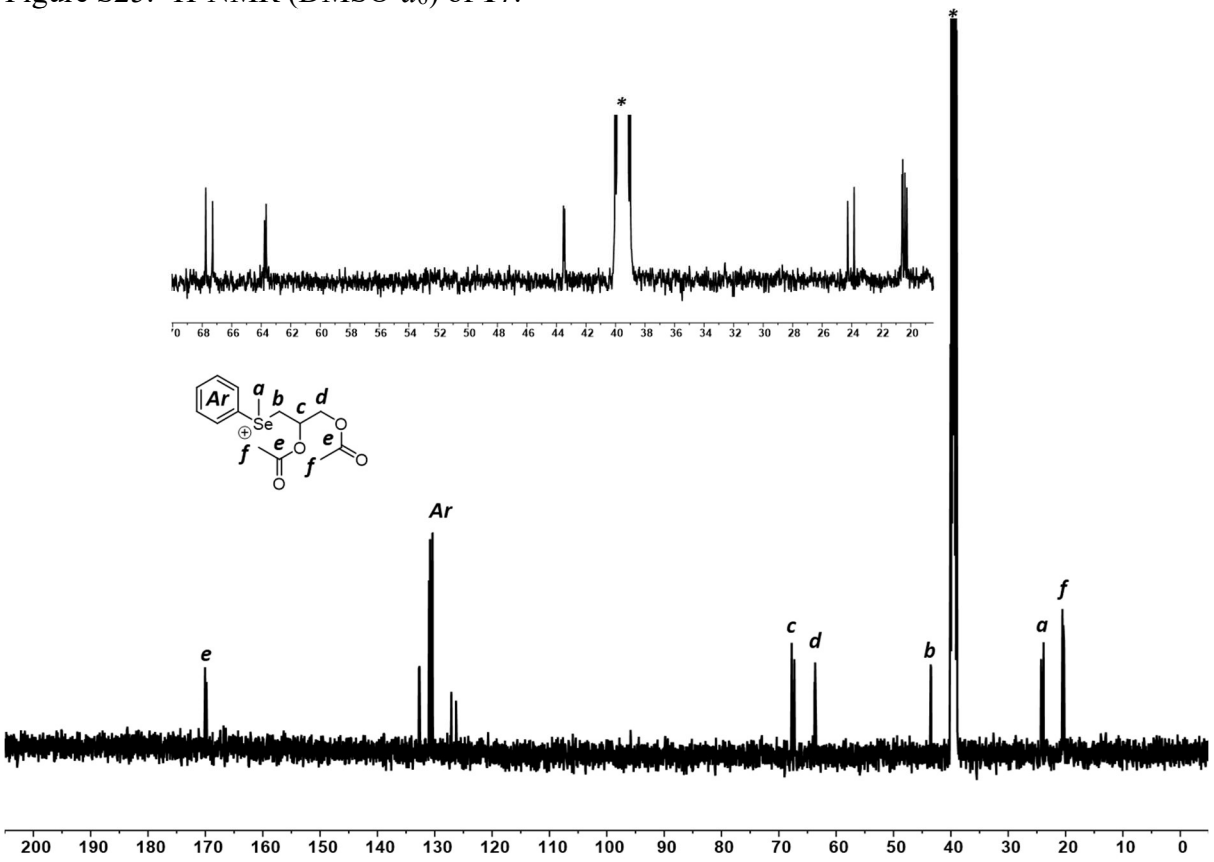

Figure S26. ^{13}C-NMR (DMSO-d_6) of **17**.

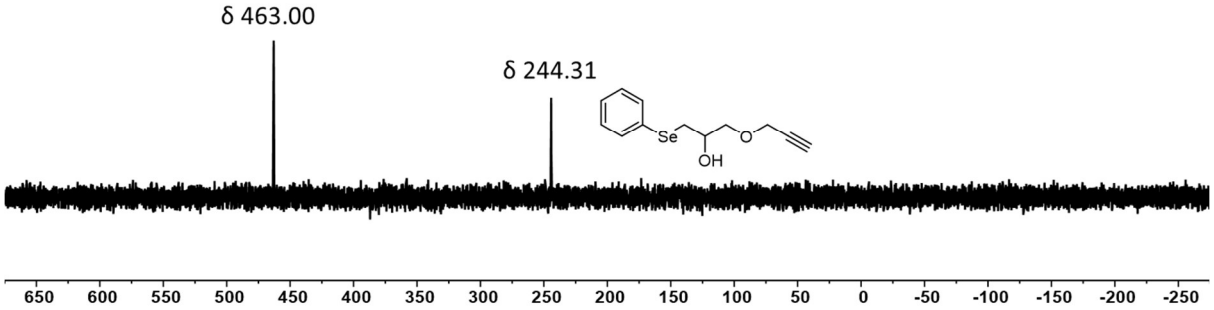

Figure S27. ^{77}Se-NMR ($CDCl_3$) of **12**.

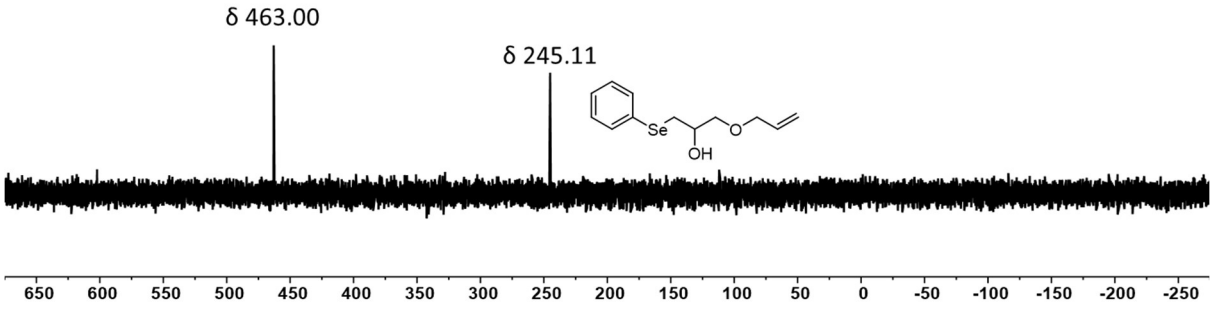

Figure S28. ^{77}Se-NMR ($CDCl_3$) of **13**.

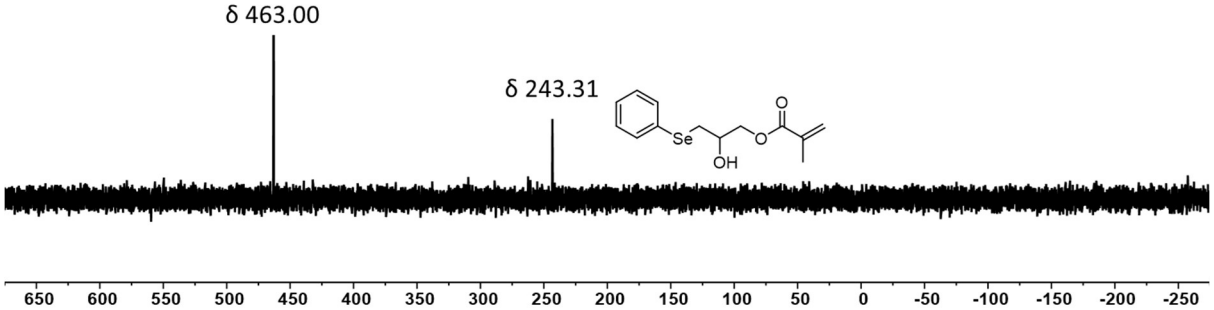

Figure S29. ^{77}Se-NMR ($CDCl_3$) of **14**.

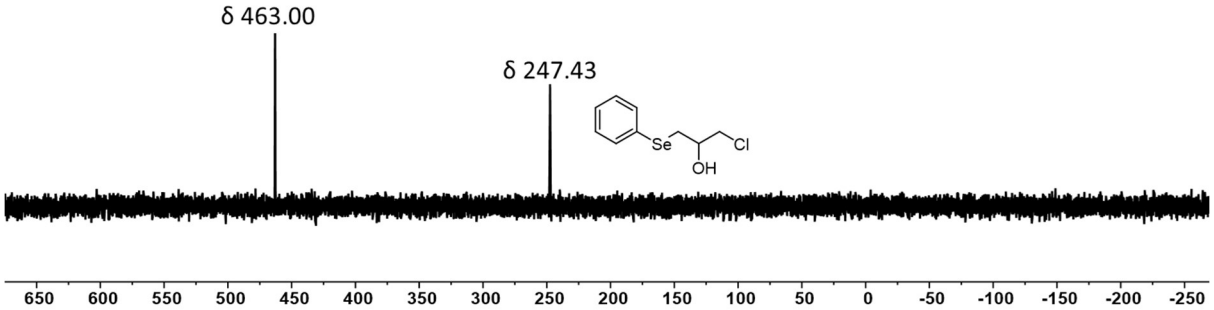

Figure S30. ^{77}Se-NMR ($CDCl_3$) of **15**.