Electronic Supplementary Information

Programmable Chemical Switch based on Triggerable Michael Acceptors

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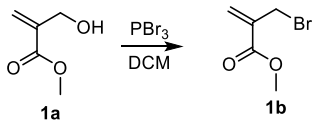
Materials and Instrumentation

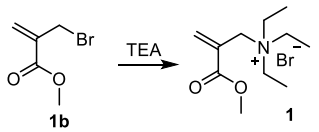
All reagents were used as received from commercial sources unless otherwise mentioned. ^{1}H NMR, ^{13}C NMR spectra were recorded on a Brucker 400 MHz NMR spectrometer. UV-Vis spectra were recorded on PerkinElmer Lambda 35 UV/Vis spectrometer. Fluorescent spectra were obtained from PerkinElmer LS 55 fluorescence spectrometer. Protein labeling and quantification were carried out on Biodrop microvolume UV-Vis spectrophotometer. Mass spectra were recorded on a Bruker AmaZon quadrupole ion trap mass spectrometer coupled with electrospray ionization source or a Thermo Orbitrap Fusion tribrid (quadrupole, orbitrap, and ion trap) mass spectrometer coupled with Easy nLC 1000 nanoLC system. Rheological measurements were performed by a Malvern Kinexus Pro rheometer.

Synthesis of compound 1 to 38

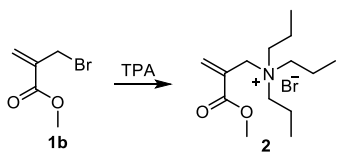
Synthesis of compound **1b:** Compound **1b** was synthesized followed the reported procedure.[1] Briefly, compoud **1a** (2.0 g, 17.23 mmol) was dissolved in 20 mL of dry DCM and cooled to 0 ^{o}C in ice bath. PBr_3 (2.332 g, 8.615 mmol) was added slowly to the solution. Then the reaction mixture was stirred at room temperature. The completion of reaction was monitored by TLC. The reaction was then quenched by the addition of ice. The reaction solution was neutralized by sodium bicarbonate solution and then extracted with DCM three times. Organic layers were collected and dried over anhydrous sodium sulfate, then concentrated. Compound **1b** was obtained by flash chromatography. Yield: 2.52 g, 82%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.34 (s, 1H), 5.96 (s, 1H), 4.18 (s, 2H), 3.82(s, 3H).



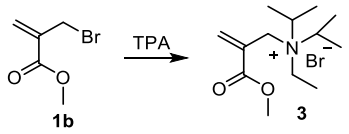
Synthesis of compound **1:** Compound **1b** (50 mg, 0.28 mmol) was dissolved in 200 uL of dry THF. To the solution, triethylamine (57 mg, 0.56 mmol) was added. The reaction was allowed to stirred at room temperature for 2 hours. Then mixture was concentrated and precipitated in dry diethyl ether for 3 times. The precipitate was collected and dried to afford compound **1**. Yield: 65 mg, 83%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 6.90 (s, H), 6.40 (s, H), 4.23 (s, 2H), 3.85(s, 3H), 3.30 (q, 6H), 1.37 (t, 9H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 167.42, 140.52, 130.66, 56.97, 54.30, 53.44, 8.08. MS (m/z): $[M]^+$ calcd. for $C_{11}H_{22}BrNO_2$, 279.08; found, 200.4 for $[M\text{-}Br]^+$



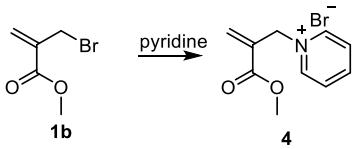
Synthesis of compound **2.** Compound **1b** (25 mg, 0.14 mmol) was weighed to glass vial. To the vial, tripropylamine (40 mg, 0.28 mmol) was added. The reaction was kept for 2 hours at room temperature. Then the white precipitate was washed with diethyl ether for three times. The precipitate was collected and dried to achieve compound **2**. Yield: 32.1 mg, 71%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 6.90 (s, 1H), 6.36 (s, 1H), 4.27 (s, 2H), 3.85(s, 3H), 3.15 (p, 6H), 1.81 (m, 6H), 0.99 (t, 9H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 166.04, 139.16, 129.44, 60.00, 57.31, 52.09, 15.27, 9.31. MS (m/z): $[M]^+$ calcd. for $C_{14}H_{28}BrNO_2$, 321.13; found, 242.3 for $[M\text{-}Br]^+$.



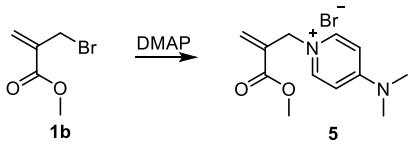
Synthesis of compound **3.** Compound **1b** (25 mg, 0.14 mmol) was weighed to glass vial. To the vial, N, N-diisopropylethylamine (36.2 mg, 0.28 mmol) was added. The reaction was kept for 2 hours at room temperature. Then the white precipitate was washed with diethyl ether for three times. The precipitate was collected and dried to achieve compound **3**. Yield: 35.7, 83%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 6.83 (s, 1H), 6.46 (s, 1H), 4.23 (s, 2H), 4.16 (m, 2H), 3.87 (s, 3H), 3.46 (q, 2H), 1.51 (q, 12 H), 1.40 (t, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 166.48, 138.62, 131.19, 62.66, 57.00, 52. 16, 17.65, 17.21, 8.76. MS (m/z): $[M]^+$ calcd. for $C_{13}H_{26}BrNO_2$, 307.11; found, 228.4 for $[M-Br]^+$



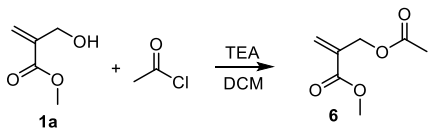
Synthesis of compound **4.** Compound **1b** (25 mg, 0.14 mmol) was weighed to glass vial. To the vial, pyridine (22.1 mg, 0.28 mmol) was added. The reaction was kept for 2 hours at room temperature. Then the white precipitate was washed with diethyl ether for three times. The precipitate was collected and dried to achieve compound **4**. Yield: 30.1 mg, 83%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 9.06 (d, J=5.6 Hz, 2H), 8.63 (t, J=7.8 Hz, 1H), 8.14 (t, 2H), 6.67(s, 1H), 6.36 (s, 1H), 5.53(s, 2H) 3.75 (s, 1H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 166.29, 147.56, 146.52, 134.89, 134.83, 62.94, 53.03. MS (m/z): $[M]^+$ calcd. for $C_{10}H_{12}BrNO_2$, 257.01; found, 178.4 for $[M-Br]^+$.



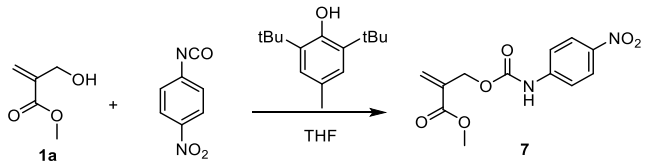
Synthesis of compound **5.** 4-(dimethylamino) pyridine (24.4 mg, 0.2 mmol) was dissolved in 100 uL of dry THF. To the solution, compound **1b** (50 mg, 0.28 mmol) was added. The reaction was kept for 2 hours at room temperature. Then the white precipitate was washed with diethyl ether for three times. The precipitate was collected and dried to achieve compound **5**. Yield: 53.2 mg, 89%. ^{1}H-NMR (400 MHz, MeOH-d4): δ 8.16 (d, 2H), 6.99 (d, 2H), 6.52(s, 1H), 6.08(s, 1H), 5.02(s, 2H), 3.76(s, 3H), 3.26 (s, 6H).13C-NMR (100 MHz, MeOH-d4): δ(ppm) 166.53, 158.10, 143.43, 136.17, 132.28, 108.76, 58.93, 52.87, 40.36. MS (m/z): $[M]^+$ calcd. for $C_{12}H_{17}BrNO_2$, 300.05; found, 221.3 for $[M-Br]^+$.



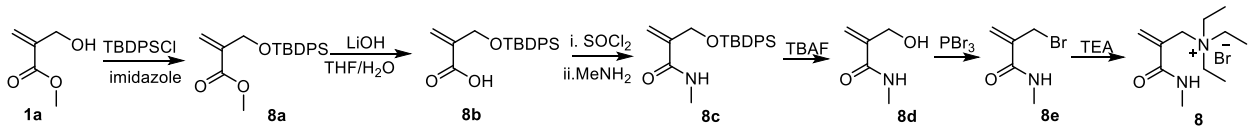
Synthesis of compound **6.** Compound **1b** (232 mg, 2 mmol) was dissolved in 5 mL of DCM with TEA (220 mg, 2 mmol) and cooled to 0 ^{o}C. To the solution, acetyl chloride (157 mg, 2 mmol) was added dropwise. The reaction mixture was stirred at room temperature after addition. After reaction, the reaction solution was collected by filtration and extracted with water for three times. The organic layers was collected and dried over anhydrous sodium sulfate. The solution was further filtered and concentrated to afford crude product which was subjected to flash chromatography to obtain pure compound **6**. Yield: 224.4 mg, 71%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.36 (s, 1H), 5.85 (s, 2H), 4.81 (s, 2H), 3.79 (s, 3H), 2.10 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 170.41, 165.68, 135.21, 127.60, 62.47, 52.06, 20.88. The compound was previously reported.[2]



Synthesis of compound **7.** Compound **1b** (116 mg, 1 mmol) was dissolved in 5 mL of THF with 4-nitrophenyl isocyanate (164.1 mg, 1 mmol) and 2,6-Di-tert-butyl-4-methylphenol (2.2 mg, 0.01 mmol). The reaction mixture was heated at 60 ^{o}C under argon atmosphere. The completion of reaction was followed by TLC. Compound **7** was obtained by flash chromatography. Yield: 134 mg, 48%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 8.19 (d, 2H), 7.67 (d, 2H), 6.37(d, 1H), 5.98(d, 1H), 4.91 (s, 2H), 3.79 (s, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 165.71, 153.21, 145.29, 142.54, 135.75, 126.75, 124.45, 117.50, 62.88, 51.13. MS (m/z): $[M]^{+}$ calcd. for $C_{12}H_{12}N_2O_6$, 280.07; found, 303.1 for $[M+Na]^{+}$.



Synthesis of compound **8, 9, 10.**



Synthesis of compound ***8a***. Compound **1a** (3.48 g, 30 mmol) was dissolved in 50 mL of dry THF with imidazole (2.250 g, 33 mmol). TBDPSCl (9.070 g, 33 mmol) was added to the solution dropwise at 0 ^{o}C. The reaction was stirred overnight at room temperature. Then, precipitate was removed by filtration to achieve clear solution which was further extracted with saturated sodium bicarbonate solution, water and brine. The organic layers were combined and dried over anhydrous sodium sulfate. The solution was collected, concentrated and subjected to flash chromatography to afford compound **8a**. Yield, 6.99 g, 66%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.64-7.69 (m, 4H), 7.34-7.47 (m, 6H), 6.33(q, 1H), 6.11(q, 1H), 4.42 (t, 2H), 3.70 (s, 3H), 1.08 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 166.25, 139.33, 135.46, 133.24, 129.78, 127.77, 124.09, 62.21, 51.63, 26.82, 19.30. MS (m/z): $[M]^{+}$ calcd. for $C_{21}H_{26}O_3Si$, 354.17; found, 377.1 for $[M+Na]^{+}$.

Synthesis of compound ***8b***. Compound **8b** (5g, 14.15 mmol) was dissolved in 50 mL of THF/H_2O mixture (1:1). Lithium hydroxide (1.015 g, 42.45 mmol) in 2 mL of water was added to the solution. The reaction was stirred overnight. Then, the solution was acidified with 2M HCl solution to pH 3 and extracted with DCM. Organic layers were collected and dried over anhydrous sodium sulfate. The organic layer was further concentrated to obtain crude product, compound **8b** which was subjected for reaction without further purification. Yield: 3.925 g, 82%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.62-7.68 (m, 4H), 7.34-7.46 (m, 6H), 6.43(s, 1H) 6.18(s,1H), 4.40 (q, 0.92Hz, 2H), 1.08 (s, 9H).^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 169.70, 138.42,135.44, 133.00, 129,86, 127.80, 126.47, 62.06, 26.80.19.28. MS (m/z): $[M]^{+}$ calcd. for $C_{20}H_{24}O_3Si$, 340.15; found, 363.1 for $[M+Na]^{+}$.

Synthesis of compound ***8c***. To 50 mL of compound **8b** (2.620 g, 8.13 mmol) solution in THF, thionyl chloride (19.4 g, 160.26 mmol) was added. The mixture was refluxed for 3 hours. Then volatiles were removed under vacuum. The residue was dissolved in 10 mL of dry DCM in a round bottom flask. To the

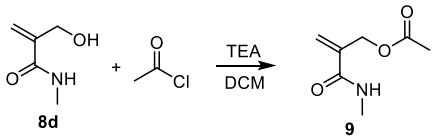
flask, a solution of methylamine (4.13 mL 2M THF solution, 8.13 mmol) and TEA (0.828 g, 8.13 mmol) in 10 mL DCM was added dropwise at 0 ºC. The reaction was stirred overnight at room temperature. The white precipitate was removed by filtration. Solvent was removed and the residue was extracted with sodium bicarbonate, and water using ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate. The solution was collected and dried for flash chromatography. Pure compound **8c** was obtained after purification. Yield: 2.60 g, 95%. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.62-7.69(m, 4H), 7.36-7.48 (m, 6H), 6.84 (bs, NH), 5.98 (s, 1H), 5.36 (d, 1H), 4.41 (s. 2H), 2.89 (d, 3H), 1.07 (s, 9H).

*Synthesis of compound **8d***. To 10 mL of compound **8c** (2.50 g, 7.08 mmol) solution, 7.79 mL of TBAF solution (1M in THF) was added dropwise at 0 ºC. The reaction completed in 20 minutes. Compound 8d was obtained by flash chromatography. Yield: 513 mg, 63%. ^{1}H-NMR (400 MHz, MeOH-d4): 5.80 (d, 1H), 5.58 (d, 1H), 4.27 (s, 2H), 2.79 (s, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): 169.06, 143.76, 118.13, 61.22, 24.94.

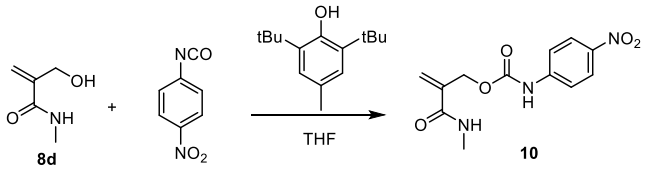
*Synthesis of compound **8e***. To the solution of compound 8d (230 mg, 2 mmol) in 5 mL of dry DCM, PBr_3 (270 mg, 1 mmol) was added slowly at 0 ºC. The reaction was stirred at room temperature after addition. The completion of reaction was followed by TLC. Then reaction was quenched by addition of 2 M sodium bicarbonate solution. The solution was further extracted with DCM and water for two more times, and organic layers were combined and dried over anhydrous sodium sulfate. The solution was collected and dried to afford compound **8e** for further reaction.

*Synthesis of compound **8***. Compound **8e** (35.6 mg, 0.2 mmol) was weighed into a small glass vial. To the vial, triethylamine (44.48 mg, 0.44 mmol) was added. The reaction was kept for 2 hours at room temperature. Then the white precipitate was washed with diethyl ether for three times. The precipitate was collected and dried to achieve compound **8.** Yield: 42 mg, 75%. ^{1}H-NMR (400 MHz, MeOH-d4): 6.24 (s, 1H), 6.07 (s, 1H), 4.19 (s, 2H), 3.26 (q, 6H), 2.83 (s, 3H), 1.34 (t, J=7.20 Hz, 9H). ^{13}C-NMR (100 MHz, MeOH-d4): 168.41, 134.17, 131.35, 56.41, 52.78, 25.18, 6.65. MS (m/z): $[M]^+$ calcd. for $C_{11}H_{23}BrN_2O$, 278.10; found, 199.4 for $[M\text{-}Br]^+$.

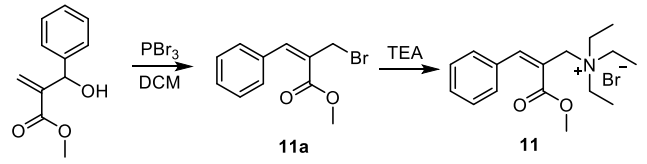
*Synthesis of compound **9***. Compound **8d** (115 mg, 1 mmol) was dissolved in 1 mL of dry DCM with triethyl amine (101 mg, 1 mmol). The reaction mixture was cooled to 0 ºC followed by slow addition of acetyl chloride (78 mg, 1 mmol). Then reaction was stirred at room temperature for 6 hours. The mixture was dried and subjected to flash chromatography to afford pure compound **8d**. Yield: 120 mg, 76%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 6.12 (bs, NH), 5.94 (s, 1H), 5.61 (s, 1H), 4.82 (d, 2H), 2.88 (d, 3H), 2.10 (s, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 170.80, 166.88, 139.39, 122.97, 63.59, 26.61, 21.07. MS (m/z): $[M]^+$ calcd. for $C_7H_{11}NO_3$, 157.07; found, 180.4 for $[M+Na]^+$.



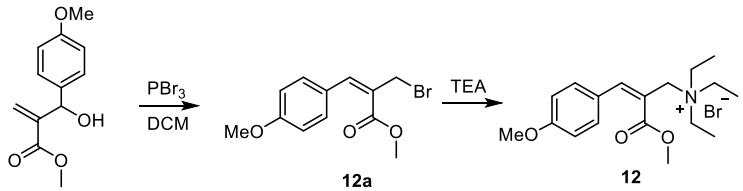
*Synthesis of compound **10***. Compound **8d** (115 mg, 1 mmol) was dissolved in 5 mL of THF with 4-nitrophenyl isocyanate (164.1 mg, 1 mmol) and 2,6-Di-tert-butyl-4-methylphenol (2.2 mg, 0.01 mmol). The reaction mixture was heated at 60 ºC under argon atmosphere. The completion of reaction was followed by TLC. Compound **7** was obtained by flash chromatography. Yield: 166 mg, 59%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 8.18 (m, 2H), 7.67 (m, 2H), 5.91(s, 1H), 5.72 (t, 1H), 4.91 (dd, 2H), 2.80 (s, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 168.09, 153.23, 145.32, 142.52, 139.66, 124.46, 120.84, 117.49, 63.78, 25.09. MS (m/z): $[M]^+$ calcd. for $C_{12}H_{13}N_3O_5$, 279.09; found, 302.1 for $[M+Na]^+$.



*Synthesis of compound **11***. 2-(Hydroxy-phenyl-methyl)-acrylic acid methyl ester (403.4 mg, 2.1 mmol) was dissolved in 5 mL dry DCM and cooled to 0 ^{o}C. To the solution, PBr_3 (285 mg, 1.05 mmol) was added slowly. The solution was quenched by addition of 2 M sodium bicarbonate solution. The mixture was extracted using DCM, then washed with water for 2 more times. The organic layer was collected and dried over anhydrous sodium sulfate. The product was obtained after filtration and concentration followed by drying over vacuum. The product was used for next step without purification. Then compound **11a** (25.5 mg, 0.1 mmol) was weighed into a small vial followed by addition of triethylamine (20.2 mg, 0.2 mmol). The reaction was kept for 2 hours. The white precipitate was washed with diethyl ether for 3 times and dried to afford compound **11**. Yield: 29 mg, 79%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 8.44 (s, 1H), 7.41-7.58 (m, 4H), 4.47 (s, 2H), 3.92 (s, 3H), 3.11 (q, 6H), 1.06 (t, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 168.65, 153.25, 135.49, 130.99, 130.62, 129.66, 123.61, 54.32, 53.61, 51.88, 7.91. MS (m/z): $[M]^+$ calcd. for $C_{11}H_{26}BrO_2$, 355.11; found, 276.2 for $[M\text{-}Br]^+$.

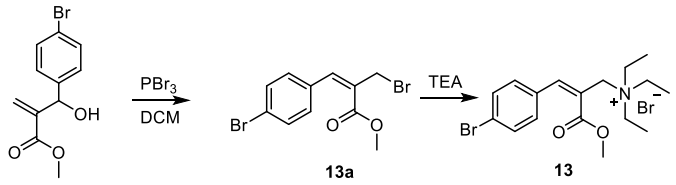


*Synthesis of compound **12***. Methyl 2-[hydroxy (4-methoxyphenyl) methyl]acrylate (222.2 mg, 1.0 mmol) was dissolved in 5 mL dry DCM and cooled to 0 ^{o}C. To the solution, PBr_3 (142 mg, 0.5 mmol) was added slowly. The solution was quenched by addition of 2 M sodium bicarbonate solution. The mixture was extracted using DCM, then washed with water for 2 more times. The organic layer was collected and dried over anhydrous sodium sulfate. The product was obtained after filtration and concentration followed by drying over vacuum. The product was used for next step without purification. Then compound **12a** (28.5 mg, 0.1 mmol) was weighed into a small vial followed by addition of triethylamine (20.2 mg, 0.2 mmol). The reaction was kept for 2 hours. The white precipitate was washed with diethyl ether for 3 times and dried to afford compound **12**. Yield: 29 mg, 75%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 8.35 (s, 1H), 7.45(m, 2H), 7.08(m, 2H), 4.52 (s, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 3.14 (q, 6H), 1.12 (t, Hz, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 168.96, 162.72, 153.01, 131.88, 127.39, 121.51, 116.01, 55.99, 54.31, 53.47, 52.20, 8.05. MS (m/z): $[M]^+$ calcd. for $C_{18}H_{28}BrO_3$, 385.13; found, 306.1 for $[M\text{-}Br]^+$.

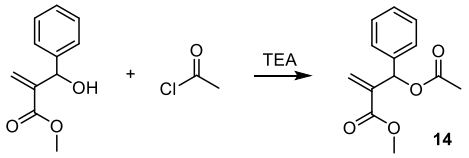


*Synthesis of compound **13***. Methyl 2-[hydroxy (4-bromophenyl) methyl]acrylate (271.1 mg, 1.0 mmol) was dissolved in 5 mL dry DCM and cooled to 0 ^{o}C. To the solution, PBr_3 (142 mg, 0.5 mmol) was added slowly. The solution was quenched by addition of 2 M sodium bicarbonate solution. The mixture was extracted using DCM, then washed with water for 2 more times. The organic layer was collected and dried over anhydrous sodium sulfate. The product was obtained after filtration and concentration followed by

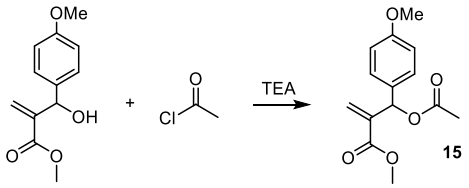
drying over vacuum. The product was used for next step without purification. Then compound **13a** (33.4 mg, 0.1 mmol) was weighed into a small vial followed by addition of triethylamine (20.2 mg, 0.2 mmol). The reaction was kept for 2 hours. The white precipitate was washed with diethyl ether for 3 times and dried to afford compound **11**. Yield: 38 mg, 88%. ^{1}H-NMR (400 MHz, MeOH-d4): δ 8.34 (s, 1H), 7.71 (m, 2H), 7.39 (m, 2H), 4.45 (s, 2H), 3.92 (s, 3.92), 3.13 (q, 6H),1.09 (t, 9H). ^{13}C-NMR (100 MHz, MeOH-d4): 168.48, 151.88, 134.42, 133.81, 131.61, 125.19, 124.13, 54.39, 53.68, 51.93, 7.97. MS (m/z): $[M]^+$ calcd. for $C_{17}H_{25}Br_2NO_2$, 331.90; found, 354.8 for $[M+Na]^+$.



*Synthesis of compound **14.*** 2-(Hydroxy-phenyl-methyl)-acrylic acid methyl ester (192 mg, 1.0 mmol) was dissolved in 1 mL of DCM with triethylamine (101.2 mg, 1.0 mmol) and cooled to 0 °C. Acetyl chloride (78.5 mg, 1.0 mmol) was added to the solution slowly. Completion of reaction was monitored by TLC. The reaction mixture was extracted using DCM and water. The organic layer was collected and dried over anhydrous sodium sulfate followed by filtration. The solution was then concentrated and subjected to flash chromatography to afford compound **14**. Yield:162 mg, 69%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.27-7.41(m, 5H), 6.68(s, 1H), 6.40 (s, 1H), 5.86 (s, 1H), 3.71 (s, 3H), 2.11 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 169.57, 165.57, 139.80, 137.93, 128.61, 128.54, 127.82, 125.93, 73.26, 52.15, 21.25.

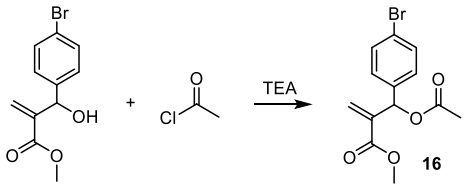


*Synthesis of compound **15.*** Methyl 2-[hydroxy (4-methoxyphenyl) methyl]acrylate (444.4 mg, 2.0 mmol) was dissolved in 4 mL of DCM with triethylamine (202.4 mg, 2.0 mmol) and cooled to 0 °C. Acetyl chloride (157 mg, 2.0 mmol) was added to the solution slowly. Completion of reaction was monitored by TLC. The reaction mixture was extracted using DCM and water. The organic layer was collected and dried over anhydrous sodium sulfate followed by filtration. The solution was then concentrated and subjected to flash chromatography to afford compound **15**. Yield:196 mg, 74%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.30 (d, J=4.85Hz, 2H), 6.86 (d, J=4.85Hz, 2H), 6.63(s, 1H), 6.34 (s, 1H), 5.87 (t, 1H), 3.79 (s, 1H), 3.70 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 169.62, 165.62, 159.78, 139.89, 129.98, 129.32, 125.27, 114.00, 73.00, 55.41, 52.13, 21.30. MS (m/z): $[M]^+$ calcd. for $C_{14}H_{16}O_5$, 264.1; found, 287.1 for $[M+Na]^+$.

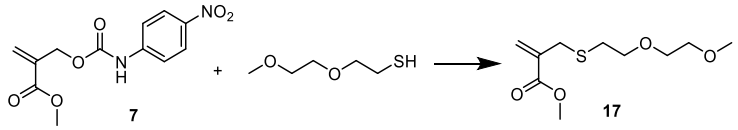


*Synthesis of compound **16.*** Methyl 2-[hydroxy (4-bromophenyl) methyl]acrylate (542 mg, 2.0 mmol) was dissolved in 4 mL of DCM with triethylamine (202.4 mg, 2.0 mmol) and cooled to 0 °C. Acetyl chloride (157 mg, 2.0 mmol) was added to the solution slowly. Completion of reaction was monitored by TLC. The reaction mixture was extracted using DCM and water. The organic layer was collected and dried over anhydrous sodium sulfate followed by filtration. The solution was then concentrated and subjected to flash

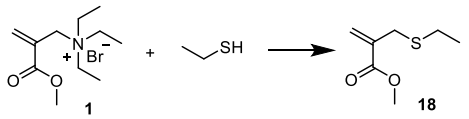
chromatography to afford compound **16**. Yield:197 mg, 63%. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 (m, 2H), 6.86 (m, 2H), 6.63(s, 1H), 6.40 (t, 1H), 5.87 (dd, 1H), 3.79 (s, 1H), 3.70 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 169.45, 165.35, 139.34, 137.08, 131.80, 129.57, 126.06, 122.66, 72.65, 52.22, 21.20. MS (m/z): $[M]^+$ calcd. for $C_{13}H_{13}BrO_4$, 312.00; found, 335.0 for $[M+Na]^+$.



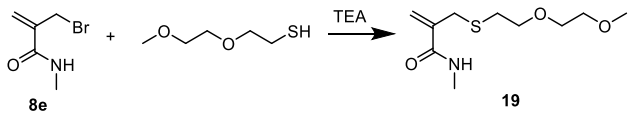
*Synthesis of compound **17.*** Compound **7** (56 mg, 0.2 mmol) was dissolved in 1 mL of MeOH. To the solution, 2-(2-methoxyethoxy) ethanethiol (26 mg, 0.19 mmol) in 0.5 mL water was slowly added. Solvent was removed after reaction. The residue was extracted with DCM for three times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography afford compound **17**. Yield: 40 mg, 90%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 7.98 (m, 2H), 6.62 (m, 2H), 6.15(d, 1H), 5.72 (d, 1H), 3.76 (s, 3H), 3.63 (t, 2H), 3.57-3.61(m, 2H), 3.51-3.56 (m, 2H), 3.44 (d, 2H), 3.36 (s, 3H), 2.63 (t, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 166.46, 136.78, 126.32, 71.94, 70.95, 70.28, 59.09, 52.09, 33.06, 30.66. MS (m/z): $[M]^+$ calcd. for $C_{10}H_{18}O_4S$, 234.09; found, 257.1 for $[M+Na]^+$.



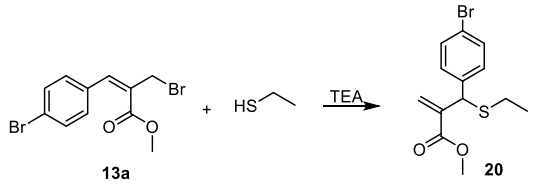
*Synthesis of compound **18.*** Compound **1** (140 mg, 0.5 mmol) was dissolved in 2 mL of water. To the solution, ethanethiol (28.2 mg, 0.45 mmol) was slowly added. Completion of reaction was monitored by TLC. Then the reaction mixture was extracted with DCM for three times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography afford compound **18**. Yield: 72 mg, 50%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 6.20 (d, 1H), 5.65 (q, 1H), 3.79 (s, 3H), 3.40 (s, 2H), 2.48 (q, 2H), 1.24 (t, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 166.71, 136.90, 125.80, 52.08, 32.34, 25.41, 14.28. The compound was previously reported.[3]



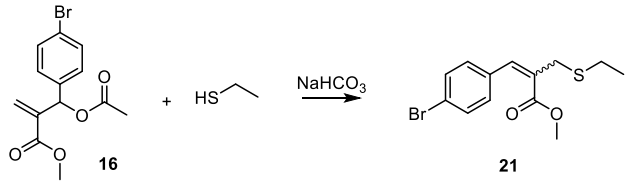
*Synthesis of compound **19.*** Compound **8e** (53.4 mg, 0.3 mmol) and 2-(2-methoxyethoxy) ethanethiol (39.0 mg, 0.29 mmol) was dissolved in 1 mL of DCM. To the solution, triethylamine (30.5 mg, 0.3 mmol) was added. Completion of reaction was monitored by TLC. Then the reaction mixture was extracted using DCM and water for three times. Organic layers were combined Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography afford compound **19**. Yield: 58 mg, 85%. ^{1}H-NMR (400 MHz, D_2O): δ(ppm) 5.74 (s, 1H), 5.54 (s, 1H), 3.58-3.72 (m, 6H), 3.48(s, 2H), 3.39(s, 3H), 2.82 (s, 3H), 2.71 (t, 2H) ^{13}H-NMR(100 MHz, MeOH-d4): δ(ppm) 169.32, 141.14, 119.15, 71.57, 70.60, 69.69, 57.69, 32.86, 29.75, 25.15. MS (m/z): $[M]^+$ calcd. for $C_{10}H_{19}NO_3S$, 233.11; found, 256.1 for $[M+Na]^+$.



*Synthesis of compound **20.*** Compound **13a** (70 mg, 0.21 mmol) and triethylamine (21.2 mg, 0.21mmol) was mixed in a glass vial and kept for 30 minutes.Then ethanethiol (6.8 mg, 0.11 mmol) in 1 mL of MeOH was added to the vial. Completion of reaction was monitored by TLC. Then the reaction mixture was extracted using DCM and water for three times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **20**. Yield: 30 mg, 87%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.43 (m, 2H), 7.25 (m, 2H), 6.45 (s, 1H), 6.04 (s, 1H), 5.03 (s, 1H), 3.72 (s, 3H), 2.42 (q, 2H), 1.21 (t, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 166.36, 140.05, 139.15, 131.60, 130.05, 127.22, 121.21, 62.20, 48.19, 26.43, 14.19. MS (m/z): $[M]^+$ calcd. for $C_{13}H_{15}BrO_2S$, 314.0; found, 336.9 for $[M+Na]^+$.

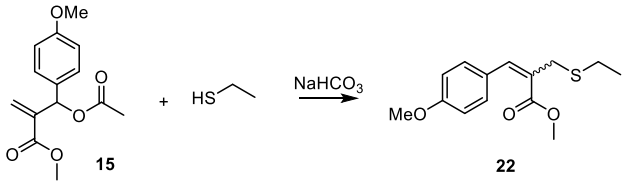


*Synthesis of compound **21.*** MeOH solution (1 mL) of compound **16** (100 mg, 0. 32 mmol) was added with 1 mL of saturate $NaHCO_3$ aqueous solution. To the mixture ethanthiol (19.8 mg, 0.32 mmol) was added. The was stirred at room temperature until reaction completed. MeOH was then removed. The residue was extracted using DCM and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **21**. Yield: 85 mg, 84%. The product contains 13% *cis* and 87% *trans* isomers. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) *trans* isomer: 7.65 (s, 1H), 7.54 (m, 2H), 7.39 (m, 2H), 3.85 (s, 3H), 3.61 (s, 2H), 2.58 (q, 2H), 1.22 (t, 3H). *cis* isomer: 7.44 (m, 2H), 7.14 (m, 2H), 6.67 (s, 1H), 3.70 (s, 3H), 3.51 (d, 2H), 2.54 (q, 2H), 1.27 (t, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) *trans* isomer:167.85, 139.30, 134.01, 131.99, 131.27, 130.36, 123.38, 52.51, 28.43, 27.21, 14.78. MS (m/z): $[M]^+$ calcd. for $C_{13}H_{15}BrO_2S$, 314.0; found, 336.9 for $[M+Na]^+$

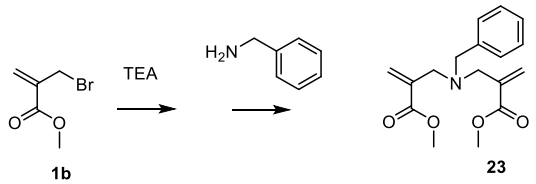


*Synthesis of compound **22.*** MeOH solution (1 mL) of compound **15** (132 mg, 0. 50 mmol) was added with 1 mL of saturate $NaHCO_3$ aqueous solution. To the mixture ethanthiol (31 mg, 0.50 mmol) was added. The was stirred at room temperature until reaction completed. MeOH was then removed. The residue was extracted using DCM and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **22**. Yield: 85 mg, 84%. The product contains 7% *cis* and 93% *trans* isomers. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) *trans* isomer : 7.70 (s, 1H), 7.51 (m, 2H), 6.94 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (s, 2H), 2.62 (q, 2H), 1.25(t, 3H). *cis* isomer: 7.25 (m, 2H), 6.85(m, 2H), 6.67 (s, 1H), 3.81(s, 3H), 3.72 (s, 3H), 3.52 (d, 2H), 2.55 (q, 2H), 1.26 (t, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) *trans* isomer:

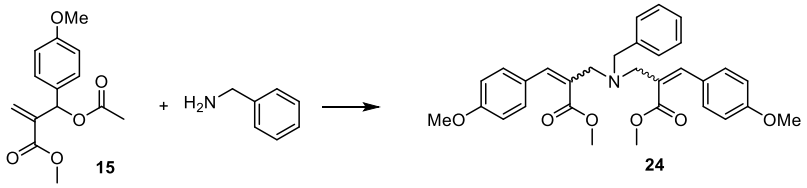
168.39, 160.39, 140.61, 131.75, 127.66, 127.37, 114.26, 55.47, 52.32, 28.68, 27.15, 14.85. MS (m/z): $[M]^+$ calcd. for $C_{13}H_{15}BrO_2S$, 266.1; found, 289.1 for $[M+Na]^+$



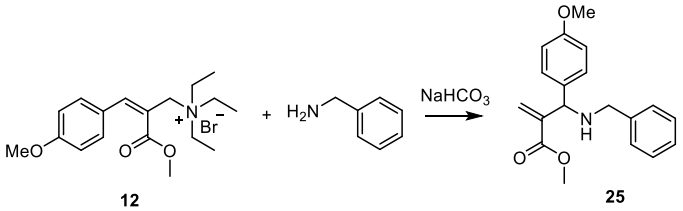
*Synthesis of compound **23.*** Triethylamine (55.7 mg, 0.55 mmol) was added to compound **1b** (89 mg, 0.50 mmol) at room temperature. Then, benzylamine (48.2 mg, 0.45 mmol) in 0.5 mL of THF was added to the reaction mixture followed by the addition of 0.5 mL of water. The reaction mixture was extracted with ethyl acetate for 3 times after reaction completed. Organic layers was collected and dried over anhydrous sodium sulfate. Product, compound 23 was obtained after flash chromatography. Yield: 100.6 mg, 84%. ^{1}H-NMR (400 MHz, MeOH-d4/D_2O(1:1)): δ(ppm):7.21-7.37(m, 5H), 6.20 (s, 1H), 5.86(d, 1H), 3.71(s, 6H), 3.55 (s,2H), 3.25 (s, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 167.31, 139.08, 137.99, 128.54, 128.37, 128.25, 126.99, 126.11, 58.34, 54.26, 51.73. MS (m/z): $[M]^+$ calcd. for $C_{14}H_{18}BrO_3S$, 266.1; found, 289.1 for $[M+Na]^+$



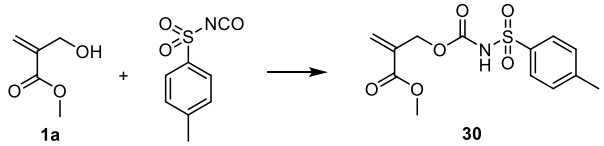
*Synthesis of compound **24.*** Compound **15** (52.8 mg, 0. 20 mmol) was dissolved in 400 uL of MeOH and 200 uL mixture. Benzyl amine (10.7 mg, 0.10 mmol) was added to the mixture. The reaction was kept overnight. MeOH was then removed. The residue was extracted using DCM and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **24**. Yield: 27 mg, 52%. The product contains 87% *trans* isomer. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.78 (s, 2H), 7.56 (m, 4H), 7.19-7.35 (m, 5H), 6.63 (m, 4H), 3.73(s, 3H), 3.72(s, 3H), 3.57(s, 4H), 3.52 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 169. 69, 160.38, 143.09, 138.99, 132.90, 130.24, 128.01, 127.63, 127.04, 126.79, 113.76, 59,45, 55.18, 52.00, 50.63. MS (m/z): $[M]^+$ calcd. for $C_{31}H_{33}NO_6$, 515.2; found, 538.2 for $[M+Na]^+$



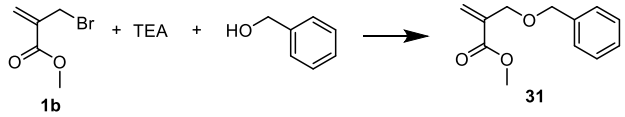
*Synthesis of compound **25.*** MeOH solution (2 mL) of compound **12** (77.2 mg, 0. 20 mmol) was added 1mL of sodium bicarbonate saturated solution followed by the addition of benzyl amine (10.7 mg, 0.10 mmol). The reaction was kept overnight. MeOH was then removed. The residue was extracted using DCM and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **25**. Yield: 23 mg, 73%. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.28-7.34 (m, 6H),7.20-7.26(m, 1H), 6.85(m, 2H), 6.34 (d, 1H), 6.00 (t, 1H), 4.67(s, 1H), 3.79(s, 3H), 3.70 (q, 2H), 3.68(s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.09, 158.96, 142.34, 140.47, 133.72, 128.93, 128.52, 128.28, 127.09, 125.22, 113.90 61.66, 55.38, 51.90, 51.87. MS (m/z): $[M]^+$ calcd. for $C_{19}H_{21}NO_3$, 311.15; found, 334.1 for $[M+Na]^+$



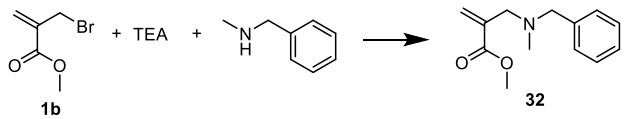
*Synthesis of compound **30.*** Solution of compound **1a** (116.1 mg, 1 mmol) in 2 mL of dry DCM was cooled to 0 ºC. p-Toluenesulfonyl isocyanate (205 mg, 1.05 mmol) was added to the solution. Completion of reaction was monitored by TLC. The residue was subjected subjected to flash chromatography after removing the solvent to afford compound **30**. Yield, 285 mg, 91%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 7.85 (m, 2H),7.39 (m, 2H), 6.28(s, 1H), 5.81 (s, 1H), 4.75 (s, 2H), 3.71(s, 3H), 2.44 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 165.38, 144.71, 136.50, 135.00, 129.19, 127.67, 127.34, 125.76, 63.62, 51.10, 20.13. MS (m/z): $[M]^+$ calcd. for $C_{13}H_{15}NO_6S$, 313.06; found, 336.0 for $[M+Na]^+$



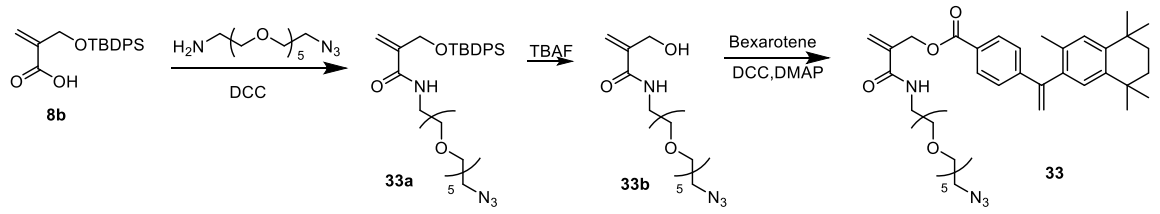
*Synthesis of compound **31.*** Compound 1b (44 mg, 0.25 mmol) was weighed into a glass vial and was added with triethylamine (50 mg, 0.50 mmol). Benzyl alcohol (265 mg, 2.5 mmol) with 100 uL of water was added to the mixture. The reaction was kept for 6 hours. DCM and water were used to extract the reaction mixture. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **31.** Yield: 41mg, 80% ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.33-7.38 (m, 4H), 7.30 (m, 1H), 6.33 (q,1H), 5.94 (s, 1H), 4.59 (s, 2H), 4.24 (t, 2H), 3.77(s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 166.47, 138.16, 137.25, 128.56, 127.84, 127.79, 126.16, 72.87, 68.45, 51.98. MS (m/z): $[M]^+$ calcd. for $C_{12}H_{14}O_3$, 206.09; found, 229.2 for $[M+Na]^+$.



*Synthesis of compound **32.*** Compound **1b** (100 mg, 0.56 mmol) was weighed into a glass vial and was added with triethylamine (62 mg, 0.62 mmol). N-methylbenzylamine (68mg, 0.56 mmol) in 100 uL of THF/H_2O (1:1) mixed solution was added to the vial. The mixture was extracted using DCM and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **32.** Yield: 91 mg, 74%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.28-7.35(m, 4H), 7.20-7.27(m, 1H), 6.27(s, 1H), 5.85(q, 1H), 3.75 (s, 3H), 3.55 (s, 2H), 3.23 (s, 2H), 2.20 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 167.63, 139.22, 138.06, 128.95, 128.33, 127.10, 126.63, 62.21, 57.71, 51.93, 42.31. MS (m/z): $[M]^+$ calcd. for $C_{13}H_{17}NO_2$, 219.13; found, 242.2 for $[M+Na]^+$.



*Synthesis of compound **33.***



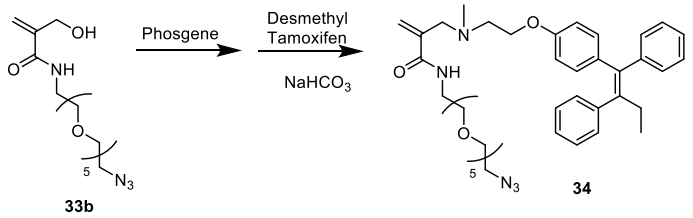
*Synthesis of compound **33a.*** To solution of compound **8b** (630 mg, 1.96 mmol) in 10 ml dry DCM, DCC(404 mg, 1.96 mmol) was added. PEG amine (500 mg, 1.63mmol) was added to the solution after 10 minutes. The reaction was stirred overnight at room temperature. Then the white precipitate was filtered, and the clear solution was subjected to flash chromatography to afford compound **33a.** Yield, 635 mg, 62%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.67 (d, 4H), 7.35-7.47 (m, 6H), 7.08 (t, NH), 5.93(s, 1H), 5.46 (s, 1H), 4.42 (s, 2H), 3.57-3.72 (m, 20H), 3.54 (q, 2H), 3.38 (t, 2H), 1.07 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.05, 142.10, 135.68, 132.99, 130.06, 127.94, 120.80, 70.85, 70.82, 70.77,70.74, 70.72, 70.71, 70.64, 70.42, 70.18, 69.99, 64.30, 50.82, 39.42, 26.94, 19.34. MS (m/z): $[M]^+$ calcd. for $C_{32}H_{48}N_4O_7Si$, 628.33; found, 651.3 for $[M+Na]^+$.

*Synthesis of compound **33b*** To solution of compound **33a** (630 mg, 1.0 mmol) in 2 ml dry THF, 1.15 mL of TBAF solution (1M in THF) was added dropwise at 0 ºC. The reaction mixture was stirred at room temperature until the reaction completed. Reaction mixture was then dried and subjected to flash chromatography to afford compound **33b**. Yield: 296 mg, 76%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.36 (bs, NH), 5.95(s, 1H), 5.53(dd, 1H), 4.34 (d, 2H), 3.56-3.73 (m, 20H), 3.53 (s, 2H), 3.38(t, 2H), 2.62 (bs, OH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 167.51, 142.27, 121.76, 70.80, 70.76, 70.73, 70.70, 70. 63, 70.60, 70.53, 70.17, 69.68, 63.90, 50.81, 39.31. MS (m/z): $[M]^+$ calcd. for $C_{16}H_{30}N_4O_7$, 390.21; found, 413.10 for $[M+Na]^+$.

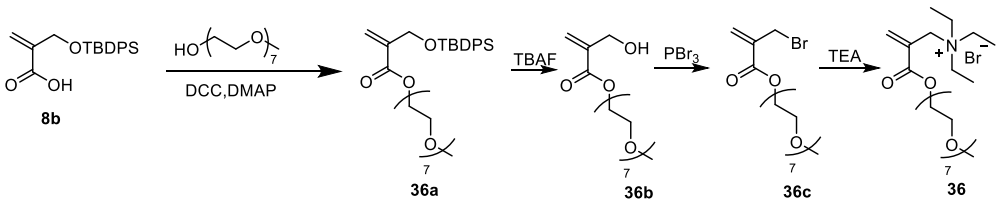
*Synthesis of compound **33*** Bexarotene (34.8 mg, 0.1 mmol) was dissolved in 0.5 mL of DCM. To the solution, DCC (20.6 mg, 0.1 mmol) was added followed by the addition of 1 mL of DCM solution of Compound **33b** (39 mg, 0.1 mmol) and DMAP (12.2 mg, 0.1 mmol) after 10 minutes. The reaction as stirred overnight. The mixture was dried and subjected to flash chromatography to afford compound **33.** Yield: 31 mg, 43%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.96 (d, J=8.44Hz, 2H), 7.34 (d, J=8.44Hz, 2H), 7.12 (s, 1H), 7.07 (s, 1H), 6.74 (t, NH), 5.98 (s), 5.80 (d, 1H), 5.69 (s, 1H), 5.33 (d, 1H), 5.09 (s, 2H), 3.57-3.68 (m, 20H), 3.55(q, 2H). 3.37 (t, 2H), 1.93(s, 3H), 1.70 (s, 4H), 1.30 (s, 6H), 1.27 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 166.36, 166.02, 149.24, 146.04, 144.55, 142.50, 139.58, 138.07, 132.81, 129.93, 128.71, 128.19, 126.77, 121.83, 117.12, 70.83, 70.80, 70.75, 70.70, 70.68, 70.64, 70.41, 70.17, 69.85, 63.83, 50.81, 39.60, 35.32, 34.14, 34.04, 32.07,32.02, 20.07. MS (m/z): $[M]^+$ calcd. for $C_{40}H_{56}N_4O_8$, 720.41; found, 743.4 for $[M+Na]^+$.

*Synthesis of compound **34*** Compound **33b** (39 mg, 0.1mmol) was dissolved in 1 mL of dry THF. To the solution, 135 uL of phosgene (20% in toluene) was added. The reaction was stirred under argon atmosphere for 3 hours. Then, solvent and remaining phosgene was removed by rotovapping (Note: phosgene is highly toxic!!! The receiving flask in evaporator was filled with saturated sodium hydroxide solution and the outlet of the pump was connected to saturated sodium hydroxide to quench the phosgene. The operation was carried in a high hazardous fume hood.) The residue was added with THF solution (1mL) of desmethyl tamoxifen (35.7 mg, 0.1mmol) followed by the addition of aqueous solution (1 mL) of sodium bicarbonate (25.3 mg, 0.3 mmol). Completion of reaction was followed by TLC. The reaction mixture was extracted using DCM and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **34.** Yield: 24 mg, 33%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 7.31-7.40 (m, 2H), 7.07-7.30 (m, 8H), 6.78

(d, 2H), 6.60 (d, 2H), 6.07 (s, 1H), 5.49 (s, 1H), 4.00 (t, 2H), 3.33-3.67(m, 24H), 2.76 (t, 2H), 2.45(q, 2H), 2.28 (s, 3H), 0.91(t, 3H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 168.05, 156.84, 143.69, 142.37, 141.33, 139.05, 138.46, 135.66, 131.58, 129.49, 129.03, 127.83, 127.58, 126.32, 125.81, 124.28, 113.19, 70.24, 70.21, 70.20, 70.18, 70.16, 69.94, 69.74, 69.02, 65.34, 60.40, 55.31, 50.37, 40.66, 38.72, 28.45, 12.43. MS (m/z): $[M]^+$ calcd. for $C_{41}H_{54}N_4O_8$, 730.39; found, 753.2 for $[M+Na]^+$



*Synthesis of compound **36*** :



*Synthesis of compound **36**a*. Solution of compound 8b (400 mg, 1.24 mmol) in 2 mL DCM was added with DCC (256 mg, 1.24 mmol). After 10 minutes, the reaction mixture was added with PEG alcohol (352 mg, 1.0 mmol) and DMAP (152 mg, 1.24 mmol). The reaction was stirred overnight at room temperature. The solution was collected after removal of white precipitate using filtration. Then, the solution was dried and subjected to then subjected to flash chromatography to afford compound **36a.** Yield: 298mg, 45%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.63-7.71(d, 4H), 7.33-7.47(m, 6H), 6.35(q, 1H), 6.12(q, 1H), 4.42(t, 2H), 4.26(t, 2H), 3.69 (t, 2H), 3.58-3.67 (m, 22H), 3.54 (m, 2H), 3.38(s, 3H), 1.08 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 165.81, 139.38, 135.58,133.36, 129.92, 127.90, 124.42, 72.08, 70.76, 70.72, 70.67, 69.16, 63.86, 62.32, 59.18, 26.95, 19.43. MS (m/z): $[M]^+$ calcd. for $C_{35}H_{54}O_{10}Si$, 662.35; found, 685.3 for $[M+Na]^+$

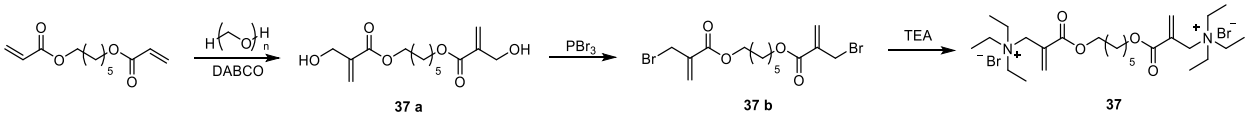
*Synthesis of compound **36b***. Solution of compound **36a** (200 mg, 0.31 mmol) in 1mL of dry THF was added with 340 uL of TBAF solution (1 M in THF) at 0 ^{o}C. After reaction completion, the solution was dried and subjected to flash chromatography to afford compound **36b**. Yield: 125 mg, 94%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 6.29 (s, 1H), 5.84 (q, 1H), 4.30-4.38 (m, 4H), 3.75 (m, 2H), 3.61-3.70 (m, 22H), 3.55 (m, 2H), 3.38 (s, 3H), 2.64 (bs, OH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 166.34, 139.69, 126.28, 72.08, 70.82, 70.78, 70.72, 70.66, 69.07, 64.01, 62.56, 59.18. MS (m/z): $[M]^+$ calcd. for $C_{19}H_{36}O_{10}$, 424.23; found, 447.1 for $[M+Na]^+$

*Synthesis of compound **36c***. Compound **36b** (120 mg, 0.28 mmol) was dissolved in 1 mL of dry DCM and cooled to 0 ^{o}C. PBr_3 (38 mg, 0.14 mmol) was slowly added to the solution. The reaction completed in 30 minutes. The reaction was quenched by adding saturated sodium bicarbonate solution. The reaction mixture was further extracted using DCM and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration to afford compound **36c** which was directly used for next reaction.

*Synthesis of compound **36***. Compound **36c** (24 mg, 0.2 mmol) was weighed to a glass vial. To the vial triethylamine (81 mg, 0.8 mmol) was added. After 4 hours, 3 mL of diethyl ether was added and sonicated for 1 minutes. Then, supernatant was removed. The operation was repeated for 4 times and the viscous solid

was collected and dried to afford compound **36**. Yield: 94 mg, 68%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 6.93(s, 1H), 6.40 (s, 1H), 4.40 (m, 2H), 4.24 (s, 2H), 3.79(m, 2H), 3.60-3.69 (m, 22H), 3.54 (m, 2H), 3.36 (s, 3H), 3.28-3.35 (q, 6H), 1.37(t, 9H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 166.86, 140.63, 130.82, 72.98, 71.57, 71.55,71.36, 69.85, 66.18, 59.09, 57.01, 54.35, 8.12. MS (m/z): $[M]^+$ calcd. for $C_{25}H_{50}BrNO_9$, 587.27; found, 508.3 for $[M-Br]^+$.

*Synthesis of compound **37***



*Synthesis of compound **37a*** DABCO (4.9 g, 44 mmol) were dispersed in 10 mL water followed by the addition of paraformaldehyde (1.98 g, 52 mmol) at 0 °C. Acetonitrile (17.5 mL) and 1,6-hexanediol diacrylate (5 g, 22 mmol) was sequentially added to the reaction after 15 minutes. Then the reaction mixture was heated at 45 °C for 3 hours. The reaction mixture was then cooled and volatiles were removed. The crude was extracted using ethyl acetate and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and then subjected to flash chromatography to afford compound **37a**. Yield: 3.2 g, 51%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 6.23(s, 2H), 5.82(s, 2H), 4.31(s, 4H), 4.17(t, 4H), 2.51(bs, 2H), 1.69 (m, 4H), 1.42(m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.38, 139.49, 125.72, 64.75, 62.62, 28.44, 25.61. MS (m/z): $[M]^+$ calcd. for $C_{14}H_{22}O_6$, 286.14; found, 309.1 for $[M+Na]^+$.

*Synthesis of compound **37b*** To solution of compound **37a** (500 mg, 1.75 mmol) in 10 mL drug DCM, PBr_3 (473 mg, 165 µL) was added at 0 °C. The reaction was stirred at room temperature and completed in 30 minutes. The reaction was quenched by addition of 2 mL of saturated sodium bicarbonate solution. The crude was extracted using ethyl acetate and water for 3 times. Organic layers were combined and dried over anhydrous sodium sulfate. The solution was dried after filtration and further subjected chromatography to afford compound **36c**. Yield: 360 mg, 50%.^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 6.33(s, 2H), 5.94(s, 2H), 4.22(t, 4H), 4.18(s, 4H), 1.73 (m, 4H), 1.46 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) 164.90,137.55, 129.05, 65.20, 28.46, 28.4639, 25.6. MS (m/z): $[M]^+$ calcd. for $C_{14}H_{20}Br_2O_4$, 409.97; found, 433.0 for $[M+Na]^+$.

*Synthesis of compound **37*** Compound **37b** (100 mg, 0.244 mmol) was dissolved in 3 mL of dry DCM. Then triethylamine (247 mg, 345 µL) was added to the solution. The reaction was stirred for 24 hours. Then volatiles were removed, and the residue was added with 5 mL of diethyl ether to precipitate the product. Then the precipitate was re-dissolved in 100 µL of MeOH and precipitated in 5 mL of diethyl ether. The procedure was repeated for two more times. The precipitate was collected and dried to afford compound **37**. Yield: 98 mg, 64%. ^{1}H-NMR (400 MHz, MeOH-d4): δ(ppm) 6.89 (s, 2H), 6.40 (s, 2H), 4.27 (t, 4H), 4.23 (s, 4H), 3.25-3.36 (q, 12H), 1.76 (m, 4H), 1.48 (m, 4H), 1.31-1.42 (t, 18H). ^{13}C-NMR (100 MHz, MeOH-d4): δ(ppm) 165.94, 138.90, 129.46, 65.73, 53.01, 28.13, 28.10, 25.25, 7.98.

*Synthesis of compound **38*** Compound **38** was synthesized following the reported procedures.[4]

Experimental Section

Kinetics study for trigger-to-release process

10 µmol (2 eq.) of **A1** molecules was dissolved in single or mixed deuterated solvents (the volume of solvent depends on the solubility of **A1**). Then, 5 µmol (1 eq.) of 2-(2-Methoxyethoxy) ethanethiol or

benzylamine was added to the solution. The reaction was immediately followed by NMR. The conversion of thiol or amine was calculated from the integration of corresponding peaks by NMR and plotted against reaction time.

Thiol-addition condition:

Compound **1, 2, 3, 4, 5, 8, 11, 12, 13**: 10 μmol (2 eq.) of molecule **1, 2, 3, 4, 5, 8, 11, 12, 13** was dissolved in 1000 μL of MeOH-d4. Then, 5 μmol (1 eq.) of thiol was added to the solution. The reaction was immediately followed by NMR.

Compound **6, 7, 9**: 10 μmol (2 eq.) of molecule **6, 7, 9** was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH 7.4 phosphate buffer. Then, 5 μmol (1 eq.) of thiol or amine was added to the solution. The reaction was immediately followed by NMR.

Compound **10:** 10 μmol (2 eq.) of molecule **10** was dissolved in 1000 μL of DMSO-d6 and 500 μL of 50 mM pH 7.4 phosphate buffer. Then, 5 μmol (1 eq.) of thiol or amine was added to the solution. The reaction was immediately followed by NMR.

Compound **14, 15, 16**:10 μmol (2 eq.) of molecule **14, 15, 16** was dissolved in dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH 6.2 phosphate buffer. Then, 5 μmol (1 eq.) of thiol or amine was added to the solution. The reaction was immediately followed by NMR.

Amine-addition condition:

Compound **1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13:**10 μmol (2 eq.) of molecule **1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13** was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH 7.4 phosphate buffer. Then, 5 μmol (1 eq.) of benzylamine was added to the solution. The reaction was immediately followed by NMR.

Compound **10:**10 μmol (2 eq.) of molecule **10** was dissolved in 1000 μL of DMSO-d6 and 500 μL of 50 mM pH 7.4 phosphate buffer. Then, 5 μmol (1 eq.) of benzylamine was added to the solution. The reaction was immediately followed by NMR.

Compound **14, 15, 16:**10 μmol (2 eq.) of molecule **14, 15, 16** was dissolved in 800 μL of MeOH-d4 and 200 μL of 50 mM pH 7.4 phosphate buffer. Then, 5 μmol (1 eq.) of benzylamine was added to the solution. The reaction was immediately followed by NMR.

Trigger-to-reverse reaction

Typically, product of thiol-**A1** or amine-**A1** addition product was dissolved in single or mixed deuterated solvents (the volume of solvent depends on the solubility of product). Then, thiol was added to the solution. The reaction was immediately followed by NMR. Detailed information is shown below:

Compound **17**: 10 μmol (1 eq.) of **17** was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH6.8 phosphate buffer. Then, 80 μmol (8 eq.) of thiol was added to the solution. Final concentration of **17** is 10 mM.

Compound **18**: 10 μmol (1 eq.) of **18** was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH7.4 phosphate buffer. Then, 5 μmol (0.5 eq.) of thiol was added to the solution. Final concentration of **18** is 10 mM.

Compound **19**: 10 μmol (1 eq.) of **19** was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH7.4 phosphate buffer. Then, 5 μmol (0.5 eq.) of thiol was added to the solution. Final concentration of **19** is 10 mM.

Compound **20:** 10 µmol (1 eq.) of **20** was dissolved in 1000 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 5 µmol (0.5 eq.) of thiol was added to the solution. Final concentration of **20** is 6.67 mM.

Compound **21:** 10 µmol (1 eq.) of **21** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 5 µmol (0.5 eq.) of thiol was added to the solution. Final concentration of **21** is 10 mM.

Compound **22:** 10 µmol (1 eq.) of **22** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 5 µmol (0.5 eq.) of thiol was added to the solution. Final concentration of **22** is 10 mM.

Compound **23**: 10 µmol (1 eq.) of **23** was dissolved in 1000 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 20 µmol (2 eq.) of thiol was added to the solution. Final concentration of **23** is 6.67 mM.

Compound **24:** 10 µmol (1 eq.) of **24** was dissolved in 2000 µL of MeOH-d4 Then, 5 µmol (0.5 eq.) of thiol or amine was added to the solution. Final concentration of **24** is 5 mM.

Compound **25:** 10 µmol (1 eq.) of **25** was dissolved in 1000 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 5 µmol (0.5 eq.) of thiol was added to the solution. Final concentration of **25** is 6.67 mM.

Thiol triggered functionality recovery

*Functionality recovery from small molecules:**1, 4, 6, 7, 17, 30, 31, 32***

Triethylamine recovery: 10 µmol (1 eq.) of **1** was dissolved in 1000 µL of MeOH-d4. Then, 10 µmol (10 eq.) of thiol was added to the solution. The release of triethylamine was followed by NMR.

Pyridine recovery: 10 µmol (1 eq.) of **4** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 10 µmol (1 eq.) of thiol was added to the solution. The release of pyridine was followed by NMR.

Acetic acid recovery: 10 µmol (1 eq.) of **6** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 10 µmol (1 eq.) of thiol was added to the solution. The release of acetic acid was followed by NMR.

4-nitroaniline recovery: 10 µmol (1 eq.) of **7** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 10 µmol (1 eq.) of thiol was added to the solution. The release of 4-nitroaniline was followed by NMR.

2-(2-Methoxyethoxy) ethanethiol recovery: 10 µmol (1 eq.) of **17** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH6.8 phosphate buffer. Then, 10 µmol (8 eq.) of thiol was added to the solution. The release of 2-(2-Methoxyethoxy) ethanethiol was followed by NMR.

Sulfonamide recovery: 10 µmol (1 eq.) of **30** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 10 µmol (1 eq.) of thiol was added to the solution. The release of sulfonamide was followed by NMR.

Benzyl alcohol recovery: 10 µmol (1 eq.) of **31** was dissolved in 500 µL of MeOH-d4 and 500 µL of 50 mM pH7.4 phosphate buffer. Then, 10 µmol (1 eq.) of thiol was added to the solution. The release of benzyl alcohol was followed by NMR.

N-methylbenzylamine recovery: 10 μmol (1 eq.) of **32** was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH7.4 phosphate buffer. Then, 10 μmol (1 eq.) of thiol was added to the solution. The release of N-methylbenzylamine was followed by NMR.

*Functionality recovery from small molecules **33** & **34**:*

Compound **33**:

Procedure A: 5 μmol (1 eq.) of **33** was dissolved in 500 μL of MeOH-d4 followed by addition of 10 mg of Na_2CO_3. 10 μmol (2 eq.) of 2-(2-Methoxyethoxy) ethanethiol was added to solution. The release of Bexarotene was followed by NMR.

Procedure B: To 250 μL of stock solution of compound **33** (1 mM solution in MeOH), 250 μL of 10 mM Glutathione (GSH) solution in 50 mM pH7.4 sodium phosphate buffer was added. The reaction solution was subjected to mass spectral analyses after 6 hours.

Compound **34**: 5 μmol (1 eq.) of **34** was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH7.4 phosphate buffer. 10 μmol (2 eq.) of 2-(2-Methoxyethoxy) ethanethiol was added to solution. The release of Desmethyltamoxifen was followed by NMR.

Aptamer drug conjugation and thiol triggered of Desmethyltamoxifen

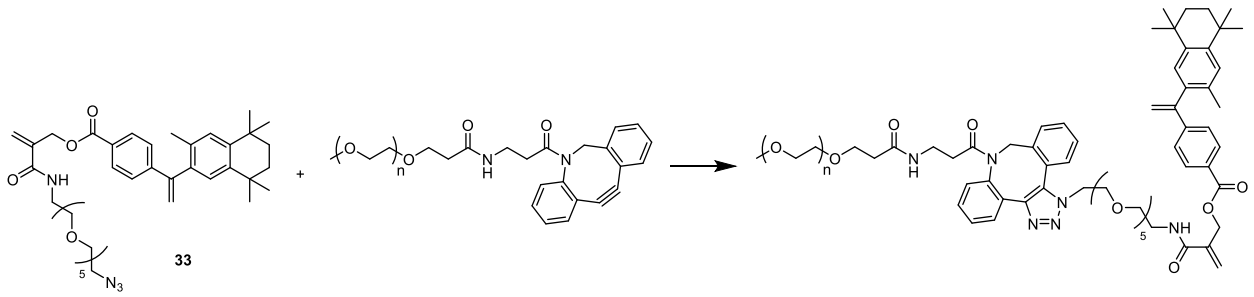
Stock solution of **34** was first prepared in DMSO. 100 μM DNA aptamer (AS1411: 5'-GGT GGT GGT GGT TGT GGT GGT GGT GGT/3DBCO/-3', ordered from Integrated DNA Technologies) solution was incubated with 20 equivalents of **34** in a solvent mixture of H_2O and DMSO (V/V=80:20) for 1 h at room temperature. After reaction, the aptamer was purified using GE PD SpinTrap G-25 column (GE Healthcare Bio-Sciences, Pittsburgh, PA) to remove the excess of **34**. The collected aptamer was characterized by ESI-MS before further experiments. Drug release was performed by incubating 50 μM conjugated aptamer with 10 mM of 2-(2-Methoxyethoxy) ethanethiol at room temperature for 12 h. After reaction, the mixture was injected in a LC-MS system to separate and detect the released drug molecules.

To separate and detect the released small-molecule drug from the Aptamer solution, a Thermo Scientific Ultimate 3000 HPLC system (Thermo Scientific, Tewksbury, MA) with a Thermo Acclaim PepMap RSLC C18 reverse phase column (300 μM × 15 cm, 2 μm particle size) was used. The small-molecule drug was eluted using an acetonitrile gradient that increases from 5 to 95% over 50 min at a flow rate of 4 μL/min.

Mass spectral analyses of intact DNA aptamers were performed on a Bruker AmaZon (Billerica, MA) quadrupole ion trap mass spectrometer equipped with an electrospray ionization source. Negative mode was used for detection, the capillary voltage was kept at 3.5 kV, and the capillary temperature was set to 300 ℃. The intact aptamer was prepared in a H_2O/ACN (V/V=1:1) buffer containing 25 mM triethylamine and 25 mM imidazole. The solutions were kept at 90 ℃ for 10 min to denature the DNA aptamers before MS detection.

LC-MS detection of the released small-molecule drug from the aptamer drug conjugates was acquired on a Bruker AmaZon (Billerica, MA) quadrupole ion trap mass spectrometer equipped with an electrospray ionization source. The electrospray needle voltage was kept at 4 kV, and the capillary temperature was set to 250 °C.

PEG drug conjugation and thiol triggered release of Bexarotene



Conjugation: mPEG(5000)-DBCO (50mg. 0.01mmol) was dissolved in 1 mL DCM. To the solution, compound **33** (15mg, 0.02 mmol) in 500 uL of DCM was added. The reaction was stirred at room temperature for 2 hours. The reaction mixture was then concentrated and precipitated in diethyl ether for 4 times. The precipitate was collected and dried to afford compound **35**. Yield: 51mg, 89%. The successful conjugation was monitored by NMR.

Bexarotene release: PEG-33 conjugate (5.74 mg, 1 μmol) was dissolved in 500 μL of MeOH-d4 and 500 μL of 50 mM pH7.4 phosphate buffer. Then 4 μmol (2 eq.) of 2-(2-Methoxyethoxy) ethanethiol was added to solution. The release of Bexarotene was followed by NMR.

Protein modification and analysis

Protein modification procedures:

For βLGb labeling reaction, βLGb was first denatured by 8 M of urea to expose the free cysteine. The denatured protein was then diluted with 50 mM pH 8.0 phosphate buffer, which results in a protein solution concentration of 100 μM. This protein solution was incubated with 20 equivalents of **1** for 5 min or with 20 equivalents of **8** for 40 min at room temperature to obtain the fully modified proteins respectively. After labeling, the reaction mixtures were injected immediately into an HPLC to remove excess labeling reagents and phosphate salts and then later analyzed by ESI-MS.

For BCA labeling reaction, BCA was dissolved in 50 mM pH 8.0 phosphate buffer to acquire a 100 μM protein solution. This protein solution was incubated with 20 equivalents of **36** for 1h at room temperature to obtain the modified proteins (>95% of the protein was modified). After labeling, the reaction mixtures were injected immediately into LC-MS for intact protein analyses.

For Myoglobin (Myo) reversible modification reactions, the modified protein solution was prepared by reacting 100 μM of the Myo with 20 equivalents of **1** for 5 min in 50 mM pH 8.0 phosphate buffer at room temperature. The proteins were collected from HPLC purification from previous modification reactions, and the excess labeling reagents were removed from the reaction mixtures. The collected protein solution was characterized by ESI-MS or other biophysical characterizations such as Circular Dichroism (CD) and Ultraviolet-Visible Spectroscopy (UV-Vis). The same protein solution was also buffer-exchanged using 10K NMWL Amicon Ultra centrifugal filters (Millipore, Burlington, MA) with 50 mM pH 7.4 phosphate buffer to yield a 100 μM solution for further reverse reaction. The proteins from previous step were incubated with 10 equivalents of 2-(2-Methoxyethoxy) ethanethiol for 2.5 h at room temperature. After reverse modification reaction, the reaction mixture was injected to a LC-MS system for intact protein analyses.

For kinetic experiments in Figure 4G & 4H, 20 equivalents of **7** were used to react with 100 μM Myo for different time periods. After labeling, the reaction mixtures were injected immediately into an LC-MS for intact protein analyses. The corresponding absorbance spectra of the reaction mixtures were also recorded on a Thermo Scientific NanoDrop 2000c Spectrophotometers (Thermo Scientific, Tewksbury, MA).

Proteolytic digestion:

The labeled βLGb protein samples were first buffer-exchanged using 10K NMWL Amicon Ultra centrifugal filters (Millipore, Burlington, MA) with 100 mM triethylamine acetate (pH 8.0), and reconstituted with 1 M urea before enzymatic digestion. To reduce the disulfide bonds in βLGb, TCEP in water was added at a protein:TCEP molar ratio of 1:20, and the sample was incubated at room temperature for 10 min. To alkylate the reduced cysteines, iodoacetamide in water was added at a protein:iodoacetamide molar ratio of 1:80, and the sample was incubated in the dark at room temperature for 30 min. The denatured, reduced, and alkylated protein samples were then digested with trypsin at an enzyme: substrate ratio of 1:10. After 4 h of digestion at 37 °C, the enzyme was separated from the mixture by centrifugation using a 10K NMWL Microcon filter (Millipore, Burlington, MA). The filtrate was then analyzed by LC-MS and LC-MS/MS.

HPLC separation:

To quench the labeling reaction and to remove excess labeling reagents and buffer salts, a Thermo Scientific Ultimate 3000 HPLC system (Thermo Scientific, Tewksbury, MA) with an OPTI-TRAP C4 reverse phase column (1 × 8 mm) was used. The protein was eluted using an acetonitrile gradient that increases from 1 to 99% over 12 min at a flow rate of 0.2 mL/min. The labeled protein was collected for proteolytic digestion or intact protein MS characterization.

To analyze the Myo digests from the labeling experiments, a Thermo Scientific EASY-nLC 1000 liquid chromatography system (Thermo Scientific, Tewksbury, MA) with an Acclaim PepMap RSLC C18 reverse phase column (75 μm × 15 cm, 2 μm particle size) from Thermo Scientific (Tewksbury, MA) was used. To achieve efficient separation of the proteolytic peptides, a shallow gradient was used where %B (0.1% formic acid in acetonitrile) was increased from 0% to 40% over 45 min. The column was then flushed by increasing to 95% B over 15 min. The column was then cleaned at 95% B for another 20 min. A flow rate of 300 nL/min was used throughout the run.

Mass spectrometry:

Mass spectral analyses of the HPLC separated intact protein samples (Myo and βLGb) from the covalent labeling experiments were acquired on a Bruker AmaZon (Billerica, MA) quadrupole ion trap mass spectrometer equipped with an electrospray ionization source. The electrospray needle voltage was kept at 4 kV, and the capillary temperature was set to 250 °C. Mass spectra of intact BCA protein samples were acquired on a Thermo Orbitrap Fusion Tribrid (Tewksbury, MA) mass spectrometer. The electrospray ionization source was typically operated at a needle voltage of 3800 V, and the ion transfer tube temperature was set to 325 °C.

LC-MS and LC-MS/MS analyses of protein proteolytic fragments were conducted on a Thermo Orbitrap Fusion Tribrid (Tewksbury, MA) mass spectrometer. The electrospray ionization source was typically operated at a needle voltage of 2100 V, and the ion transfer tube temperature was set to 300 °C. Tandem mass spectra were collected using CID with a normalized collision energy of 35%. Due to the large number of detectable peaks, an exclusion limit of 60 s was applied after five spectra had been collected for any given peak. The resolution of the Orbitrap was set to 60000.

Peptide and modification identification:

Raw mass spectral data files were analyzed by Thermo Proteome Discoverer 2.2 software. Spectra were searched against the corresponding protein sequence. Variable modification by certain labeling reagents of the residues and the protein N-terminus was added as a dynamic modification. Other dynamic modifications such as oxidation of methionine and carboxyamidomethylation of cysteine were also used in the searches. Trypsin enzyme cleavage was selected, and a precursor mass tolerance of 10 ppm was used.

Identifications of peptides and modifications at high confidence levels were used and were manually checked in all cases.

Circular dichroism:

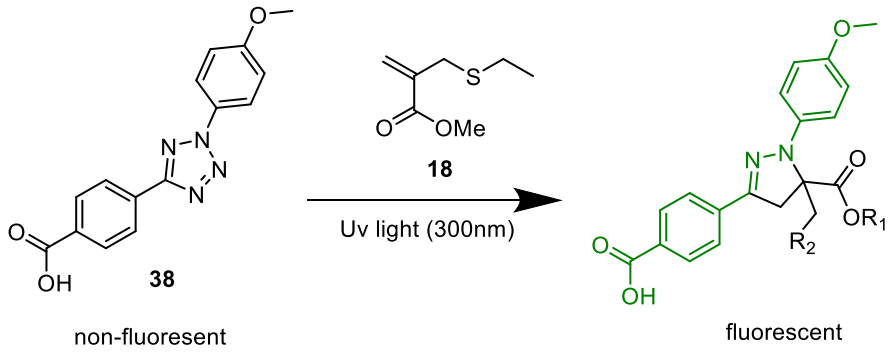
Far-UV CD analyses were performed on a Jasco J-1500 spectropolarimeter. CD spectra were recorded at room temperature over a scan range of 260 to 200 nm. Protein samples were diluted to 0.1 mg/mL in 50 mM pH 7.4 phosphate buffer prior to analysis. The CD spectrometric parameters were set as follows: a scan resolution (data pitch) of 0.5 nm, a scan rate of 20 nm/min, a band width of 2 nm, and a digital integration time of 1 sec. Triplicate measurements were performed for each sample at room temperature.

Temperature dependent CD measurements were also performed for the protein samples to evaluate the thermal stability (melting temperature) of Myo before and after labeling. Ellipticity at 222 nm was recorded every 1 °C from 25 °C to 90 °C. Prior to individual scans, samples were equilibrated at the new temperature for 1 min. Samples were measured in triplicates and the results were shown in average values.

Orthogonal hydrogel manipulation

Hydrogel formation: Compound **37** (24.48 mg, 40 μmol) was dissolved in 2 mL 50 mM sodium phosphate buffer to make stock solution with desired pH. 4 arm PEG10000-thiol (100 mg, 20 μmol) was dissolved in 2 mL 50 mM sodium phosphate buffer with desired pH to make stock solution. Then, 0.75 mL of compound **37** solution was mixed with 0.75 mL of PEG solution.

Hydrogel post-functionalization using small molecule model: Compound **38** (0.4 mg, 2.5 μmol) and compound **18** (0.665 mg, 2.5 μmol) was respectively dissolved in 2 mL of MeOH to prepare the stock solutions. Then, 1 mL of compound **38** and compound **18** solutions was mixed to form reaction solution. 50 μL of the mixed solution was then diluted with 950 μL of MeOH to form final reaction solution, the absorption and emission spectra was measured before and after UV irradiation at λ300nm for 30 seconds.



Hydrogel photo-patterning: Solution of compound **37** (24.48 mg, 40 μmol) in 2 mL 50 mM pH6.8 sodium phosphate buffer and solution of 4 arm PEG10000-thiol (100 mg, 20 μmol) in 2 mL 50 mM pH6.8 sodium phosphate buffer was prepared. 0.75 mL of each solution was mixed in a petri dish and allowed to cure for 30 minutes. The petri dish was placed on the top of a hand-hold UV lamp with a patterned cover in between. Then 1 mL solution of compound **38** with concentration of 1.25 mM in MeOH was added to the middle of the dish followed by the irradiation at λ300nm on the UV lamp. After irradiation, the hydrogel was washed with 2 mL of MeOH for 3 times to remove unreacted compound **38**. A video of the photo-patterning was shown separately.

BSA loading hydrogel formation and thiol triggered BSA release. To a glass vial, 50 μL of 1.0 mg/mL FITC labelled BSA was diluted with 150 μL of 50 mM pH 7.4 sodium phosphate buffer followed by addition of

100 μL of 4-arm PEG10000 thiol (100 mg/mL). Then, 100 μL of compound 37 solution (12.24 mg/mL) in 50 mM pH 7.4 sodium phosphate buffer was added to the vial to form BSA loaded hydrogel in seconds. Two identical hydrogels were prepared using the same procedure at the same time. Then, one of hydrogel was added with 3 mL of 50 mM pH 7.4 sodium phosphate buffer, while the other one was added with 3 mL of 50 mM 2-(2-Methoxyethoxy) ethanethiol solution in 50 mM pH 7.4 sodium phosphate buffer. To monitor the release of BSA, 50 μL of liquid from each hydrogel was sampled and diluted to 1mL and subjected for fluorescence measurement at different interval. Here, we assumed that BSA would diffuse to liquid phase once it is released due to dissolution of hydrogel, while the BSA in intact hydrogel should be entrapped in the solid gel phase.

Hydrogel sample preparation of rheological measurement: Solution of compound **37** (24.48 mg, 40 μmol) in 2 mL 50 mM pH6.8 sodium phosphate buffer and solution of 4 arm PEG10000-thiol (100 mg, 20 μmol) in 2 mL 50 mM pH6.8 sodium phosphate buffer was prepared respectively. 0.75 mL of each solution was mixed in cylinder mode with diameter of 2.5 centimeters. Then hydrogel sample was placed in parallel plate and cut to fit the dimension of the plate.

Hydrogel dissolution for rheological measurement: 10 μL of m-PEG6-thiol (Mw 312.4) was placed and spread in parallel plate. Then hydrogel sample was placed on the top of plate and the measurement was started immediately.

Rheometry: Measurements were performed by using the Malvern Kinexus Pro stress-controlled instrument in a small angle oscillation shear-controlled manner. A stainless parallel plate (20 mm diameter) fixture with a solvent trap was used for all experiments. Sample height was fixed at 1 mm. The shear strain amplitude and angular frequency were 1% and 10 rad/s, respectively. The storage (G') and loss moduli (G'') were measured as a function of time. The transient complex viscosity profile was calculated via the IRIS software package.[5] All experiments were conducted at 25 °C.

Reference

1. P.V. Ramachandran, M. A. Helppi, A. L. Lehmkuhler, J. M. Marchi, C. M. Schmidt, M. T. Yip-Schneider, M.T. *Bioorg Med Chem Lett*, **2015**, 25, 4270-4273.
2. G. Poklukar, M. Stephan, B. Mohar, B. *Adv. Synth. Catal.* **2018**, *360*, 2566-2570.
3. M. L. Quan, C.D. Ellis, A. Y. Liauw, R. S. Alexander, R. M. Knabb, G. Lam, M.R. Wright, P.C. Wong, R.R. Wexler, *J.Med. Chem.* **1999**, *42*, 2760-2773.
4. Y. Fan, C. Deng, R. Cheng, F. Meng, Z. Zhong, *Biomacromolecules* 2013,**148**, 2814-2821.
5. H. H. Winter, M. Mours, *Rheol Acta*, 2006, **45**, 331-338.

Figure S1-S51

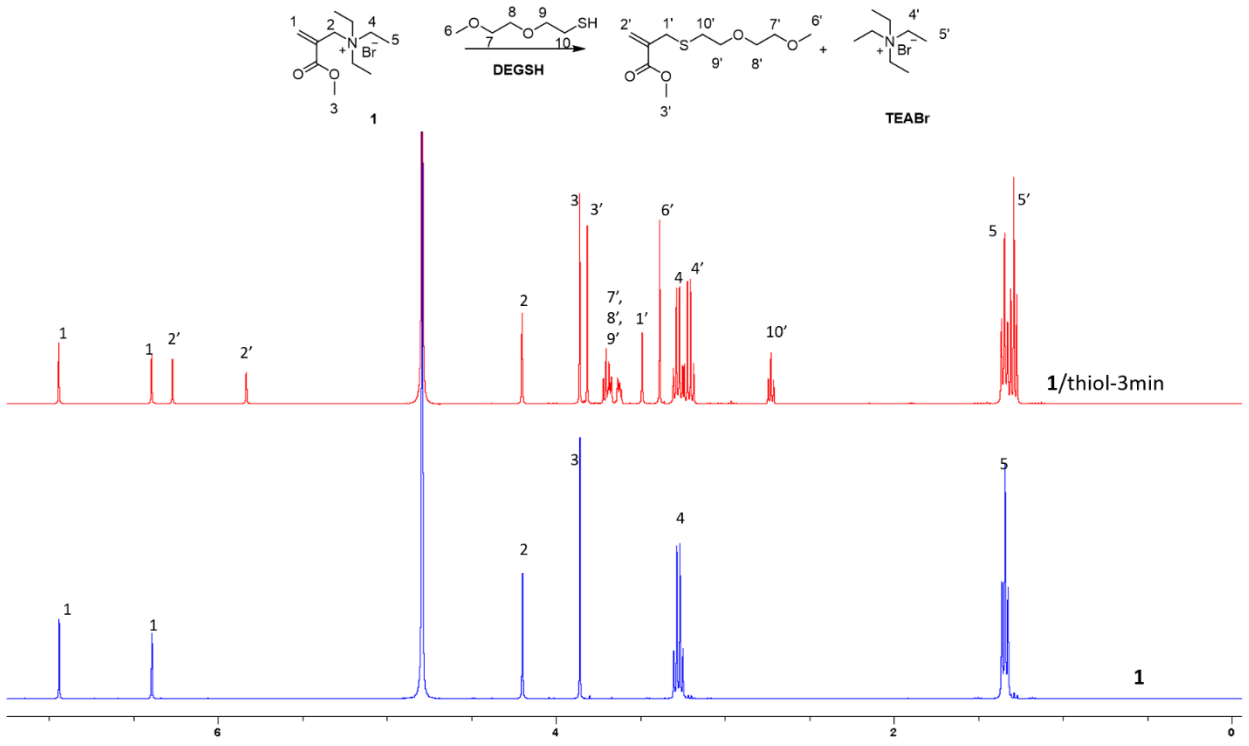


Figure S1 Reaction of DEGSH with **1** followed by NMR. Bottom: compound **1**; top: compound **1** incubated with 0.5 equivalent of thiol for 3 minutes. The reaction was carried out at 50 mM pH 7.4 phosphate buffer.

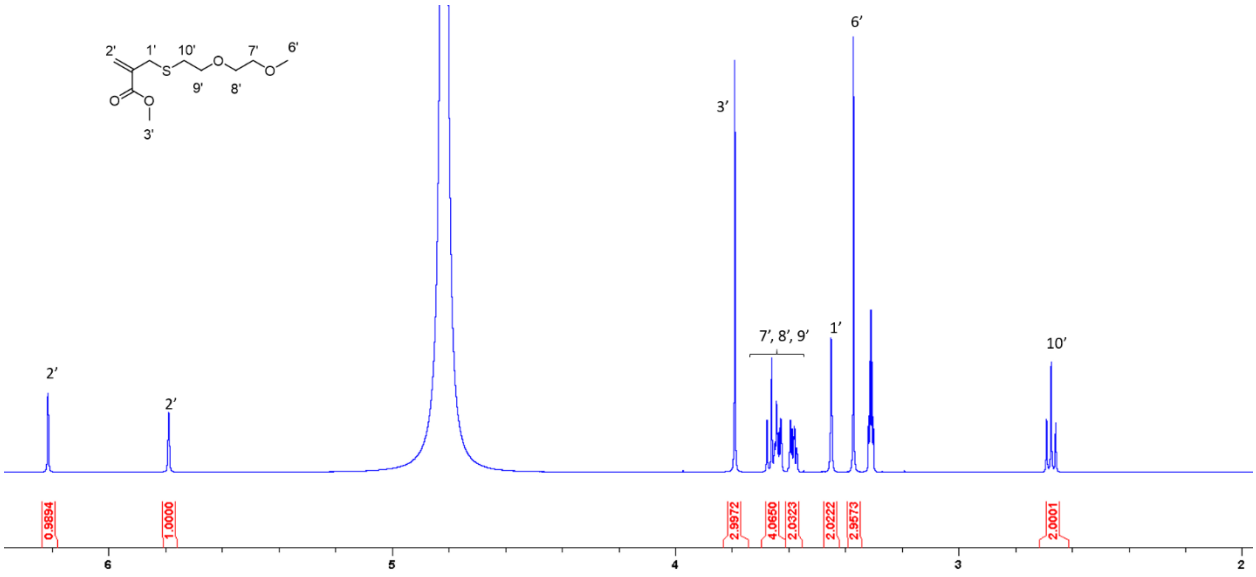


Figure S2 NMR spectrum of isolated product from reaction of DEGSH and compound **1** in MeOH-d4.

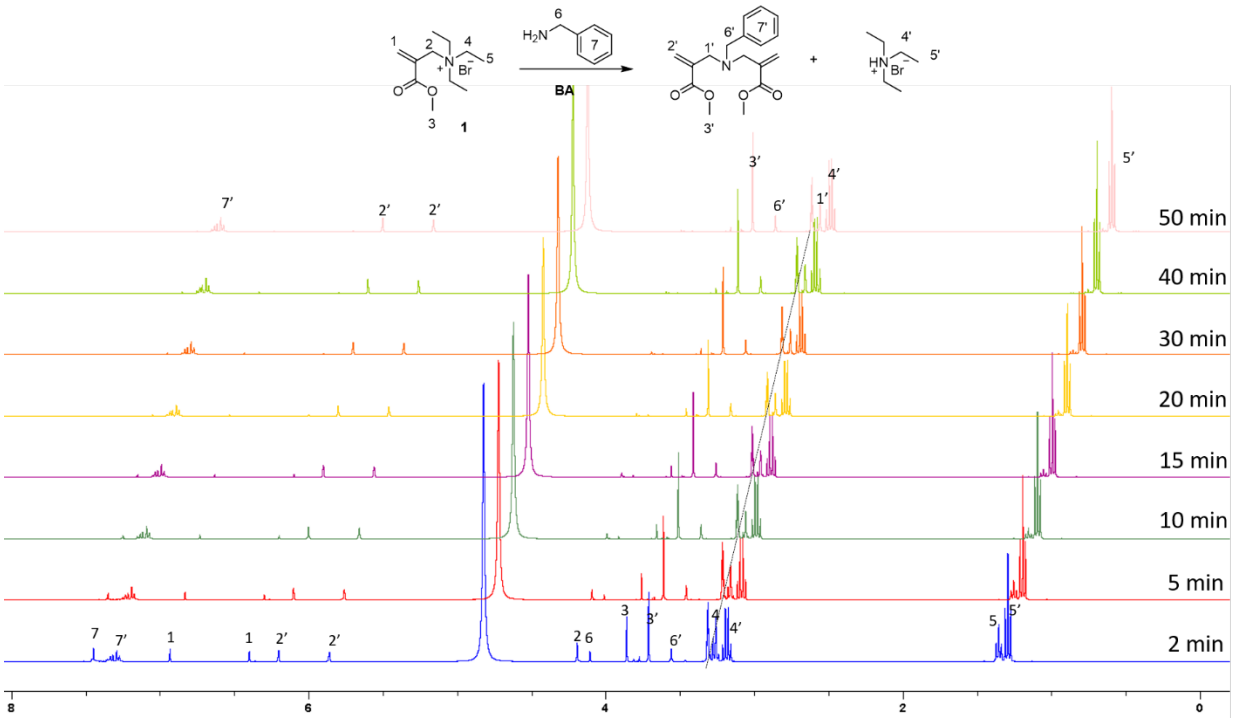


Figure S3 Reaction of benzyl amine with **1** followed by NMR at different timepoints. Compound **1** was incubated 0.5 equivalent of benzyl amine and monitored. The reaction was carried at MeOH-d4 and 50 mM pH 7.4 phosphate buffer mixture (1:1). The spectra were aligned with MeOH-d4 peak. Peak at 4.79 ppm is attributed to H_2O.

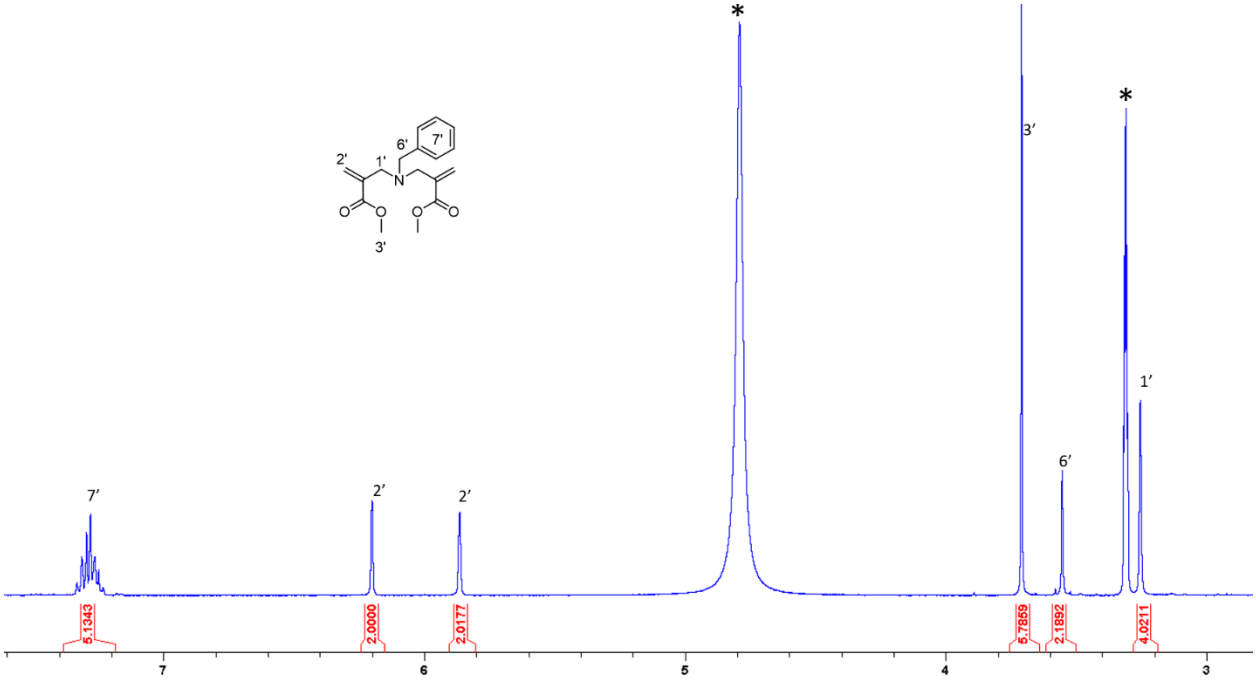


Figure S4 NMR spectrum of isolated product from reaction of benzyl amine and compound **1** in MeOH-d4. " *" indicates solvent peaks.

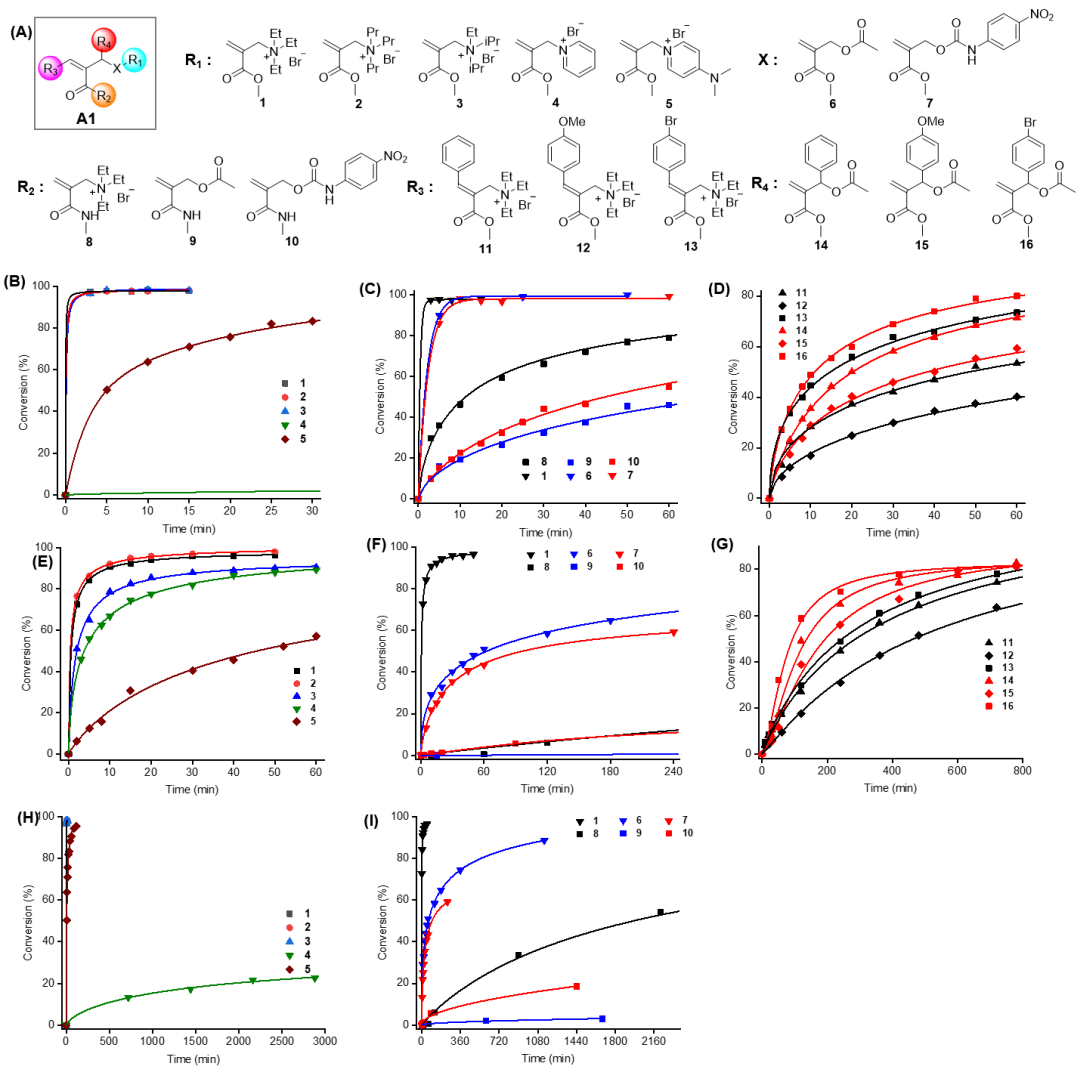


Figure S5 Structure-property relationship investigation on trigger-to-release kinetics for thiol and amine. (A) Structure variations of **A1**. (B) Influence of R^1 substitution on thiol-based trigger-to-release kinetics. Reaction carried out in MeOH-d4 (data points for compound **4** at longer time scales are shown in **Fig S5H**). (C) Influence of X and R^2 substitution on thiol-based trigger-to-release kinetics. Reaction for **1** & **8** was carried out in MeOH-d4, while reaction for **6**, **9**, **7**, & **10** performed in MeOH-d4 and pH7.4 phosphate buffer mixture (1:1). (D) Influence of R^3 and R^4 substitution on thiol-based trigger-to-release kinetics. Reaction for **11**, **12**, **13** was carried out in MeOH-d4, while reaction for **14**, **15**, & **16** performed in MeOH-d4 and pH 6.2 phosphate buffer mixture (1:1). (E) Influence of R^1 substitution amine-based trigger-to-release kinetics. Reaction carried out in MeOH-d4 and pH7.4 phosphate buffer mixture (1:1). (F) Influence of X and R^2 substitution on amine-based trigger-to-release kinetics. Reaction carried out in MeOH-d4 and pH7.4 phosphate buffer mixture (1:1). (data points for compound **9** at longer time scales are shown in **Fig S5I**). G) Influence of R^3 and R^4 substitution on amine-based trigger-to-release kinetics. Reaction carried out in MeOH-d4 and pH 7.4 phosphate buffer. Solvent ratio for **11**, **12**, &**13** was 1:1 while that for **14**, **15**, &**16** was 1:4. (H) Influence of R^1 substitution on thiol-based trigger-to-release kinetics for longer time scale. (I) Influence of X and R^2 substitution on amine-based trigger-to-release kinetics for longer time scale. Note: The original NMR spectra for the kinetics measurement are shown at the end of supplementary information from **Figure S52-S103**.

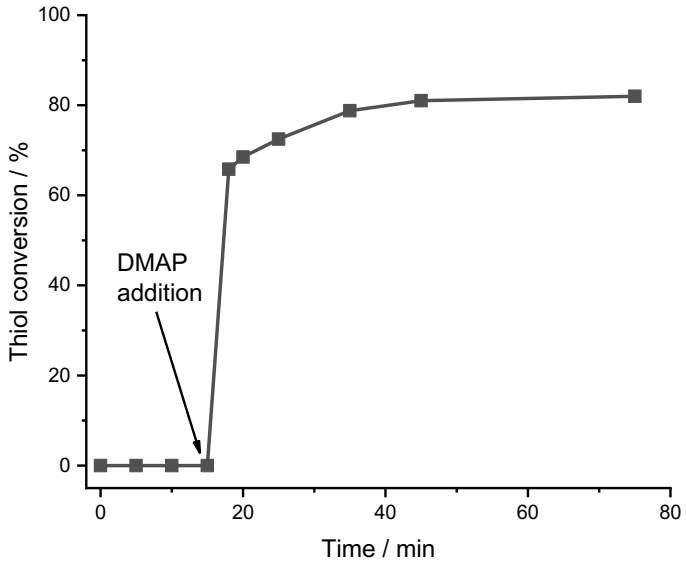


Figure S6. Reaction of thiol with **4** enhanced by the addition of DMAP. The reaction was followed by NMR. NMR spectra can be found in Figure S59 & S60.

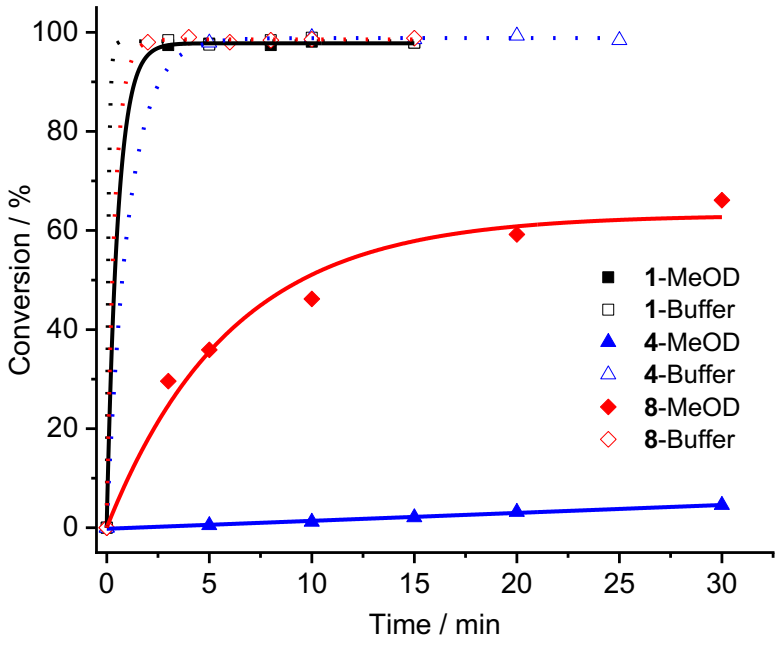


Figure S7 Kinetics of trigger-to-release reaction of **1, 4, 8** with thiol in MeOH-d4 and phosphate buffer.

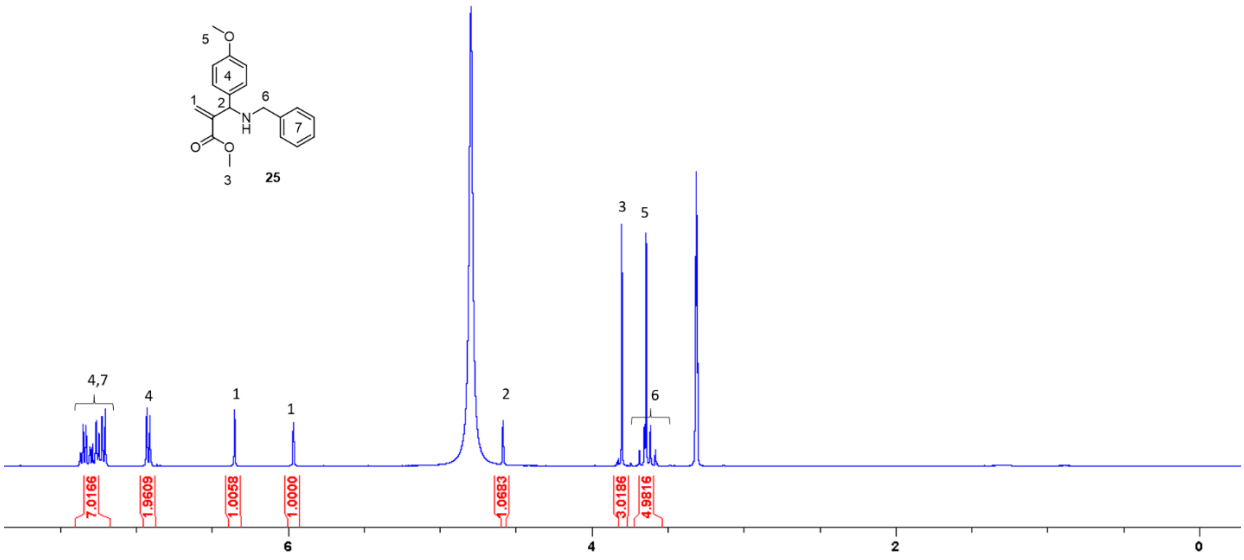


Figure S8 Isolated product from amine-addition of **12** with benzyl amine.

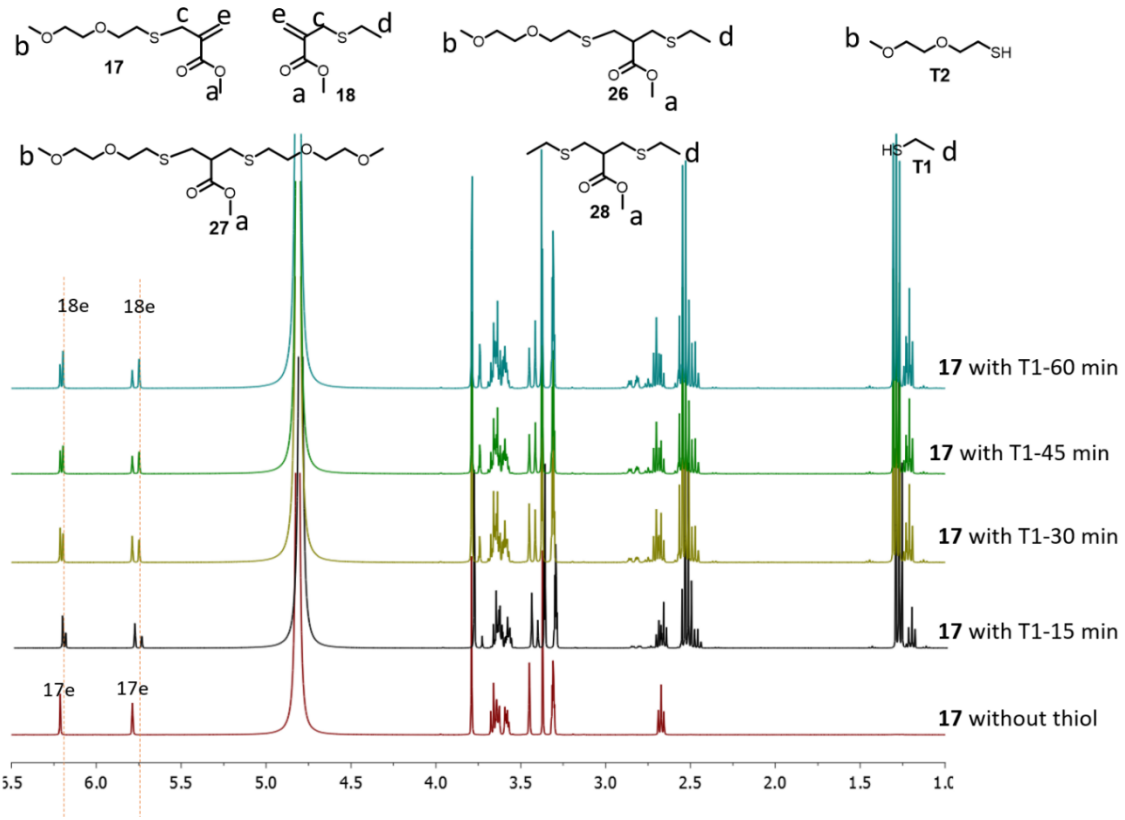


Figure S9 Reversion of thiol-addition product, **17** to **T2** triggered by **T1** followed by NMR. [**T1**]/[**17**]=8/1. The reaction was carried out in mixture of MeOH-d4 and 50 mM pH 6.8 phosphate buffer (1:1).

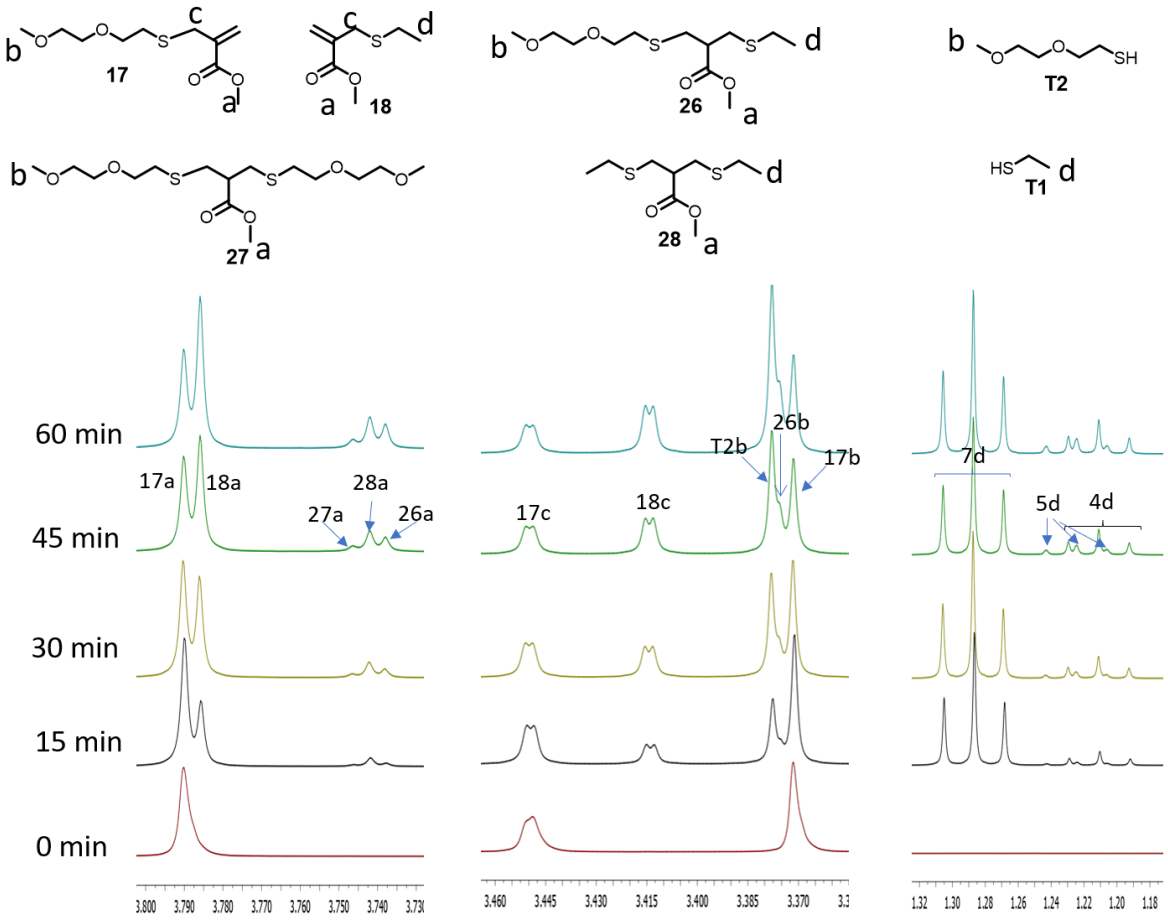


Figure S10 Zoom-in spectra of Figure S9. The integration of the peaks assigned was used to calculate the population of each species.

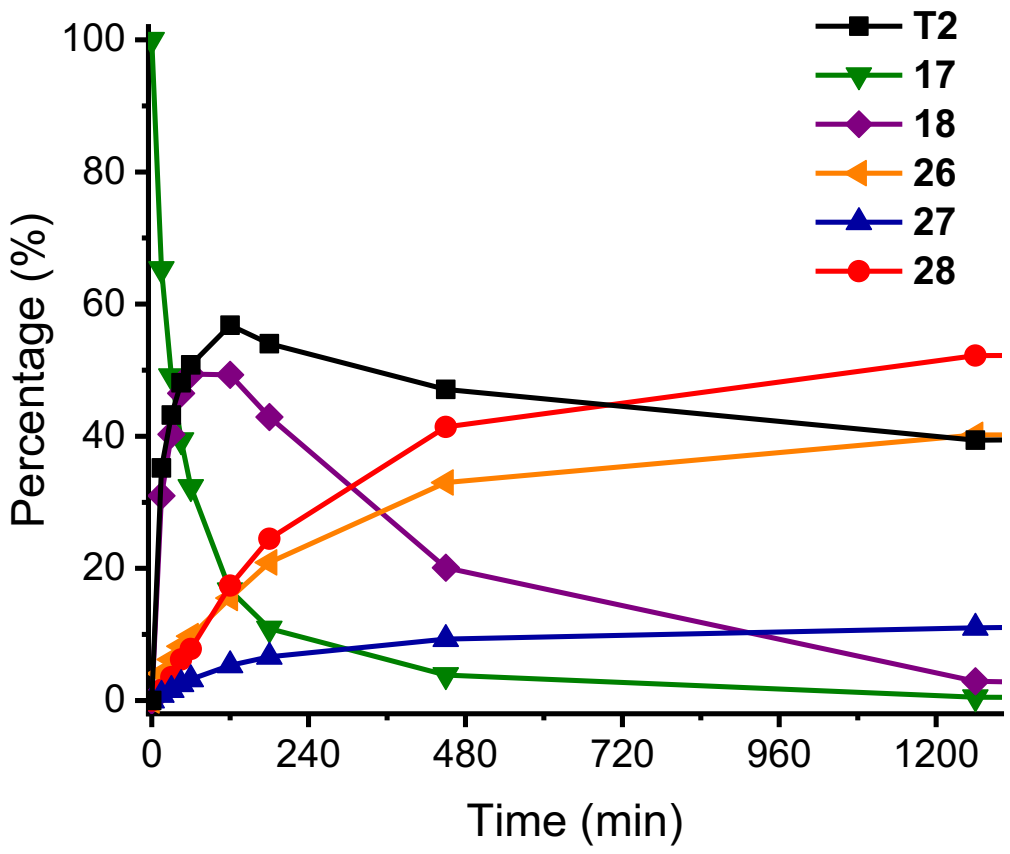


Figure S11 Thiol-triggered reversion of **17**. [**T1**] / [**17**] =3/1. The reaction was carried out in mixture of MeOH-d4 and 50 mM pH 6.8 phosphate buffer (1:1). [**17**] :10 mM.

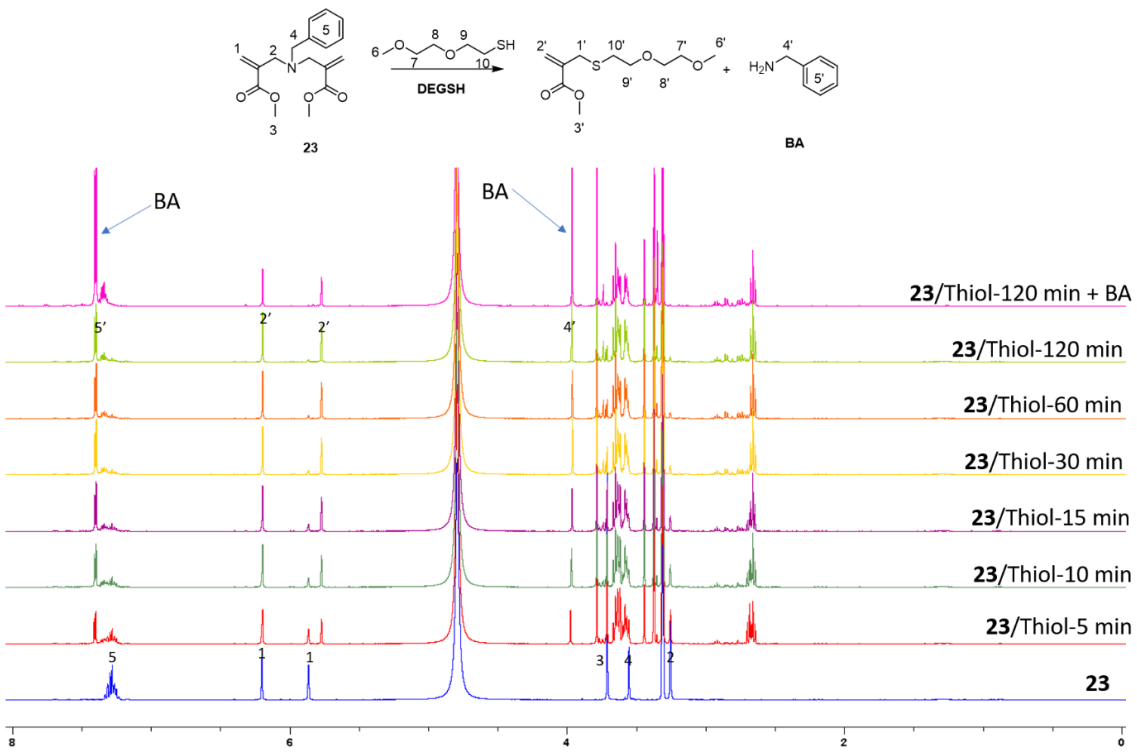


Figure S12 Thiol triggered reversion of amine-addition product, **23**. The progress of the reaction was followed by NMR. After 120 minutes, benzyl amine (BA) was added to the reaction mixture to identify that the released compound is actually benzyl amine. The reaction was carried out in mixture of MeOH-d4 and 50 mM pH 7.4 phosphate buffer (2:1). The ratio between **23** and DEGSH was 1:2. Concentration of **23** was 6.67mM.

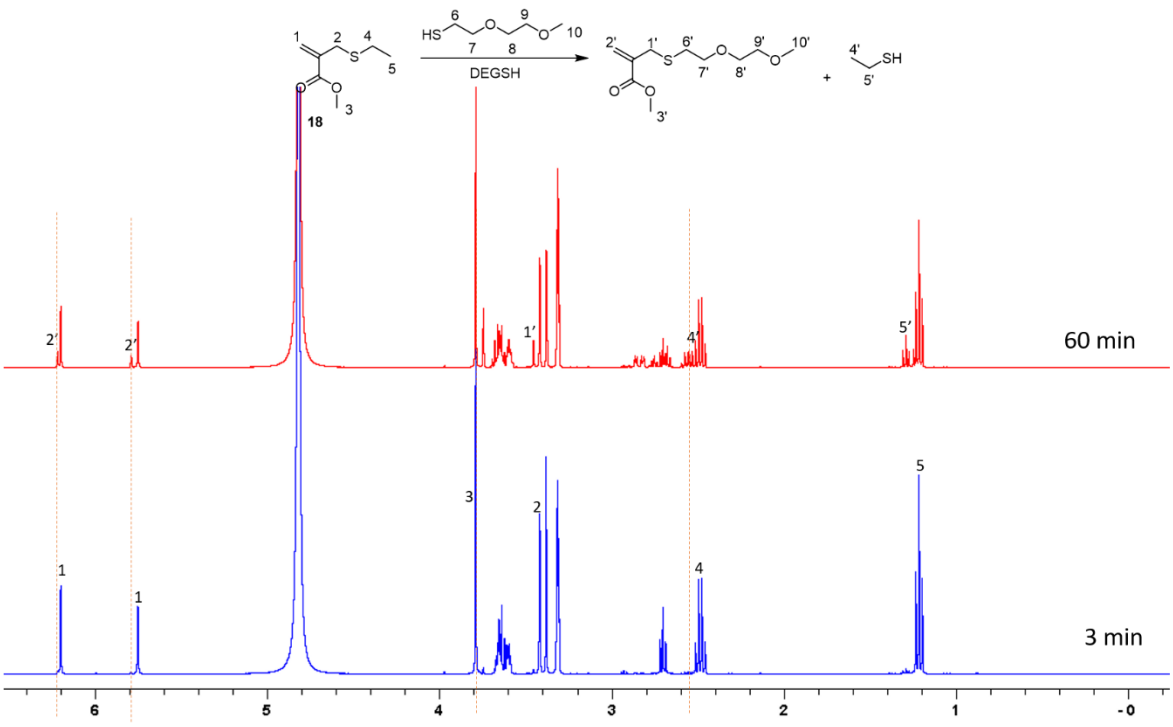


Figure S13 Reversion of thiol-addition product, **18** is triggerable by thiol suggested by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**18**]/[DEGSH]=2. [**18**]: 10 mM. (Reaction at 3 min & 60 min).

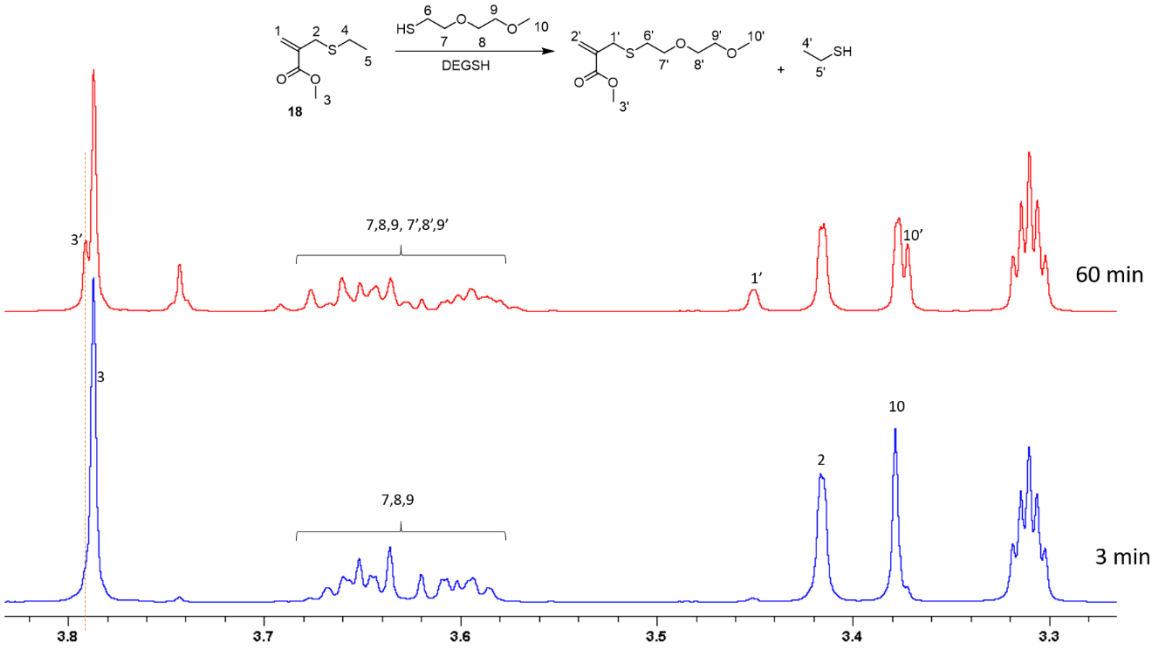


Figure S14 Reversion of thiol-addition product, **18** is triggerable by thiol suggested by NMR. Zoom-in spectra of Figure S13. (Reaction at 3 min & 60 min).

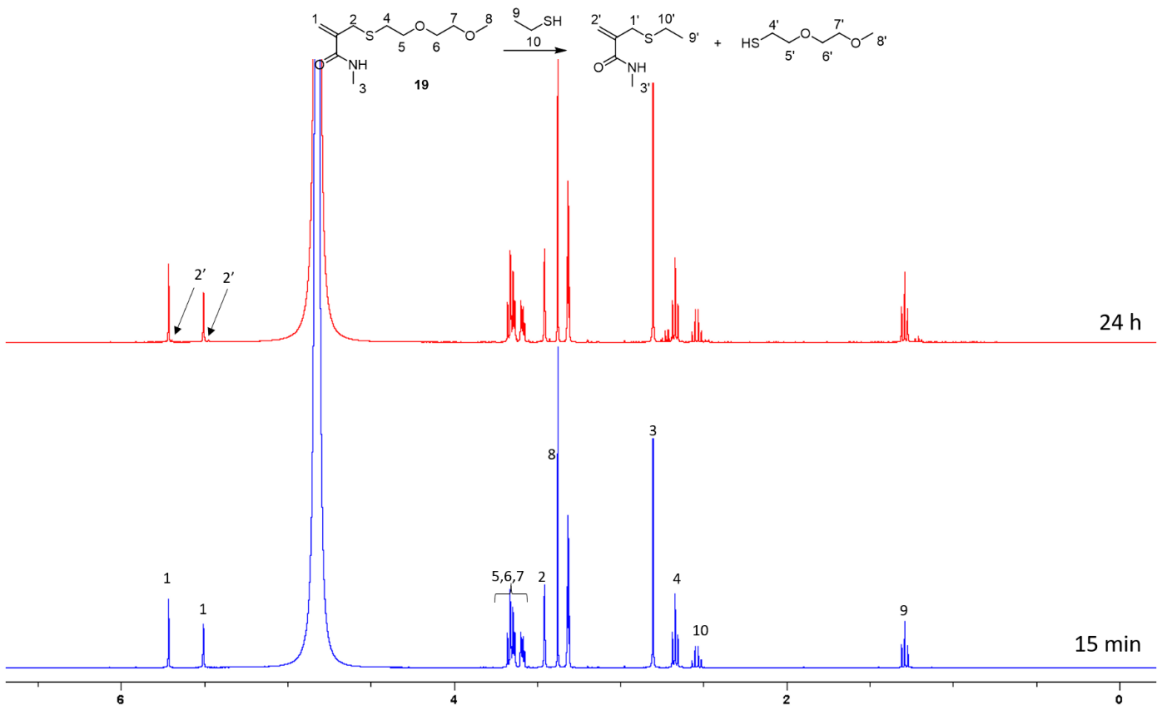


Figure S15 Reversion of thiol-addition product, **19** is triggerable by thiol suggested by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**19**]/[ethanethiol]=2. [**19**]: 10 mM. (Reaction at 15 min & 24 h).

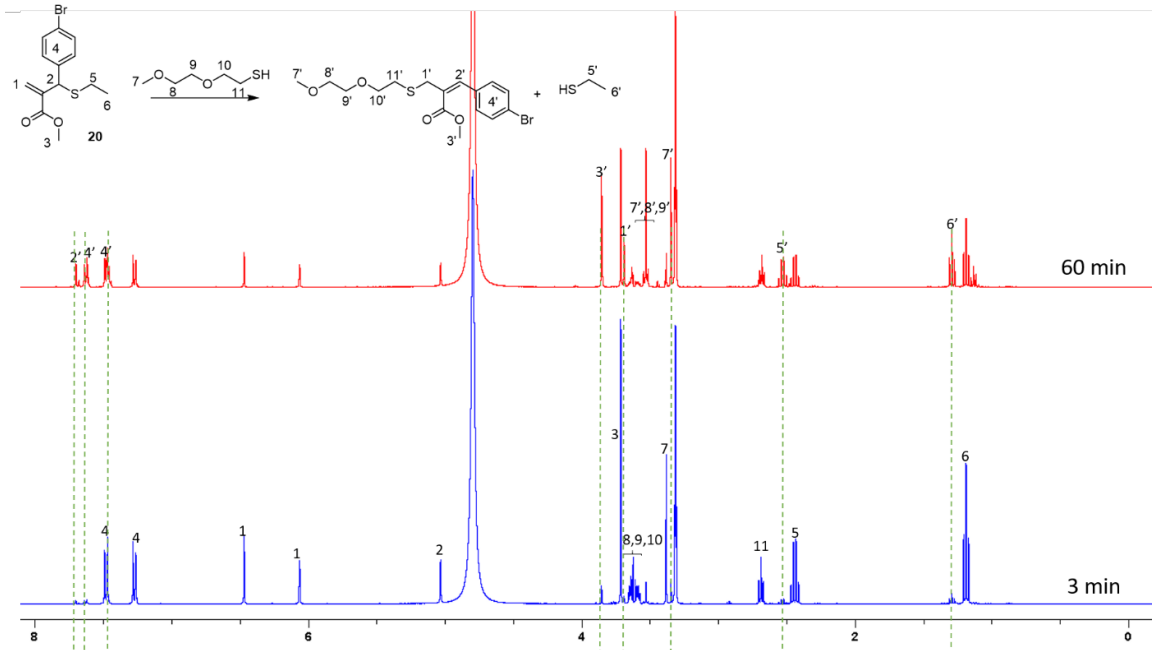


Figure S16 Reversion of thiol-addition product, **20** is triggerable by thiol suggested by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (2:1). [**20**]/[DEGSH]=2. [**20**]:6.67 mM. (Reaction at 3 min & 60 min).

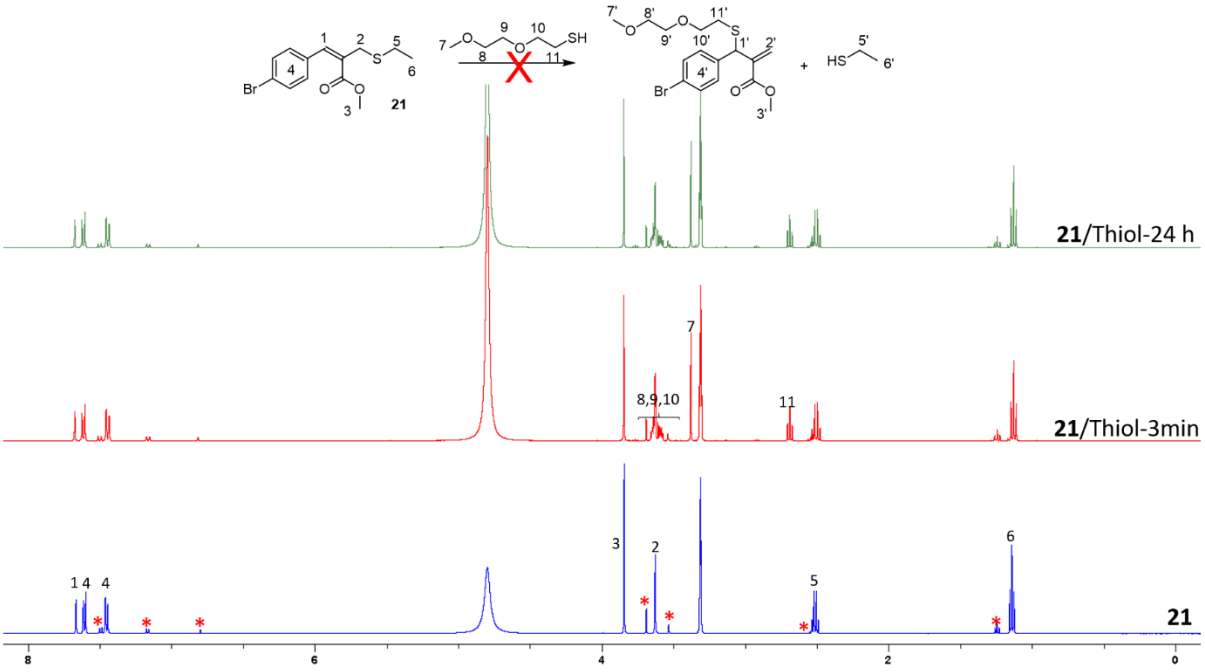


Figure S17 Thiol-addition product, **21** is irreversible in the presence of thiol suggested by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (2:1). [**21**]/[DEGSH]=2. [**21**]:10 mM. (* indicates the isomer of **21**.)

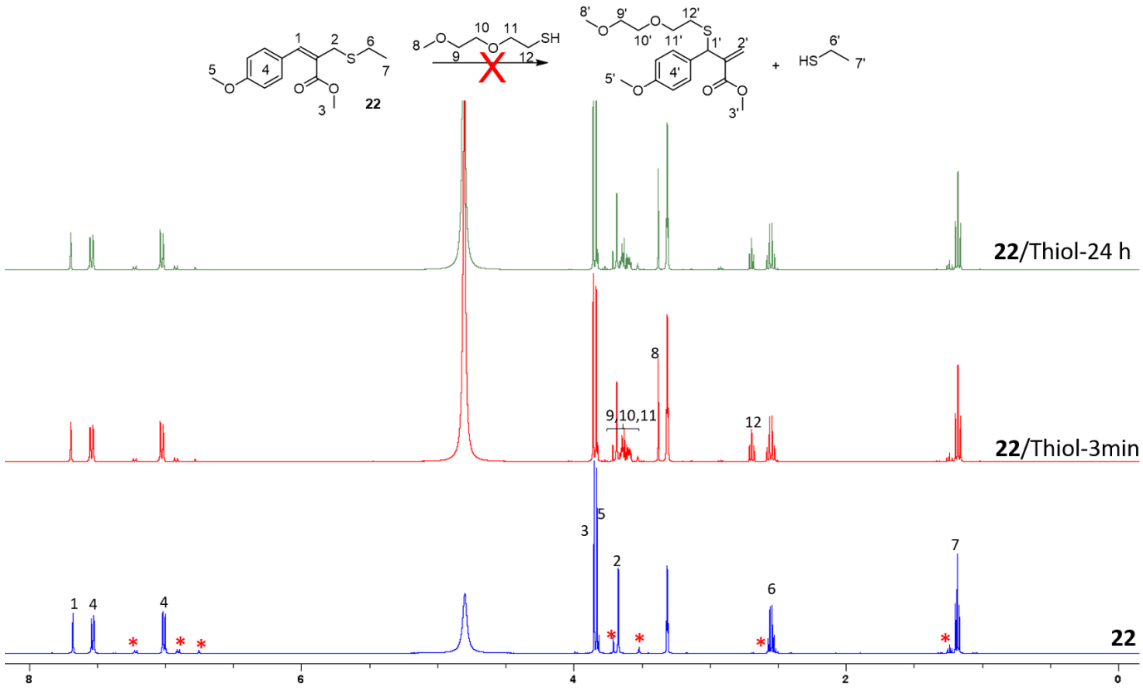


Figure S18 Thiol-addition product, **22** is irreversible in the presence of thiol suggested by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (2:1). [**22**]/[DEGSH]=2. [**22**]: 6.67 mM. (* indicates the isomer of **22**.)

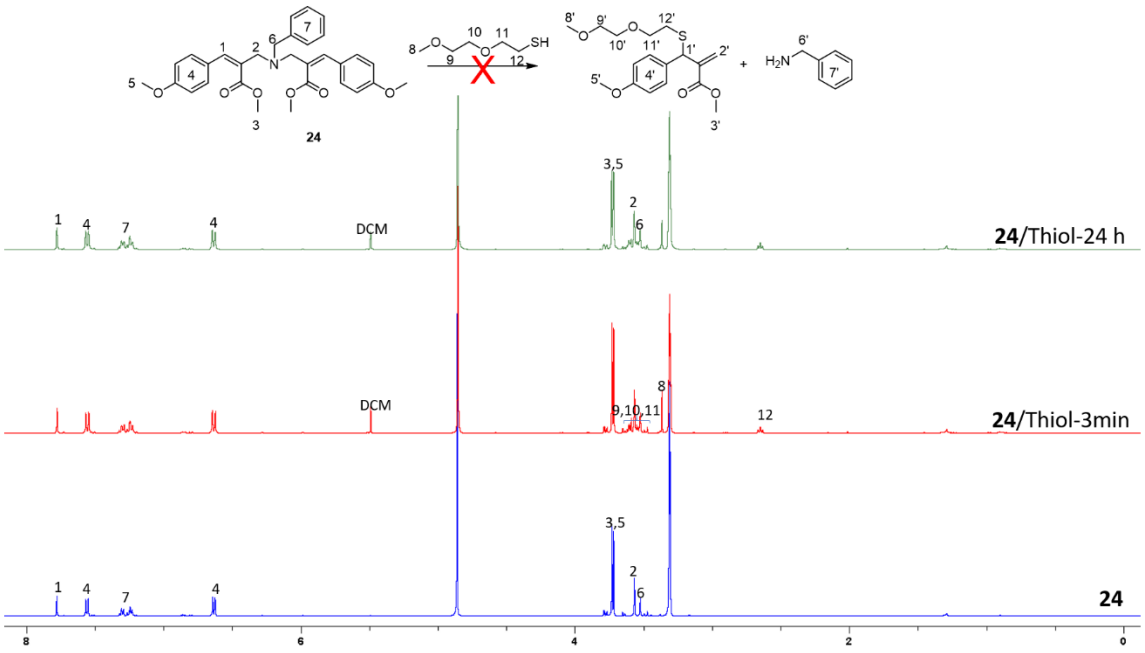


Figure S19 Amine-addition product, **24** is irreversible in the presence of thiol suggested by NMR. The reaction was carried out at MeOH-d4. [**22**]/[DEGSH]=2. [**22**]: 5 mM.

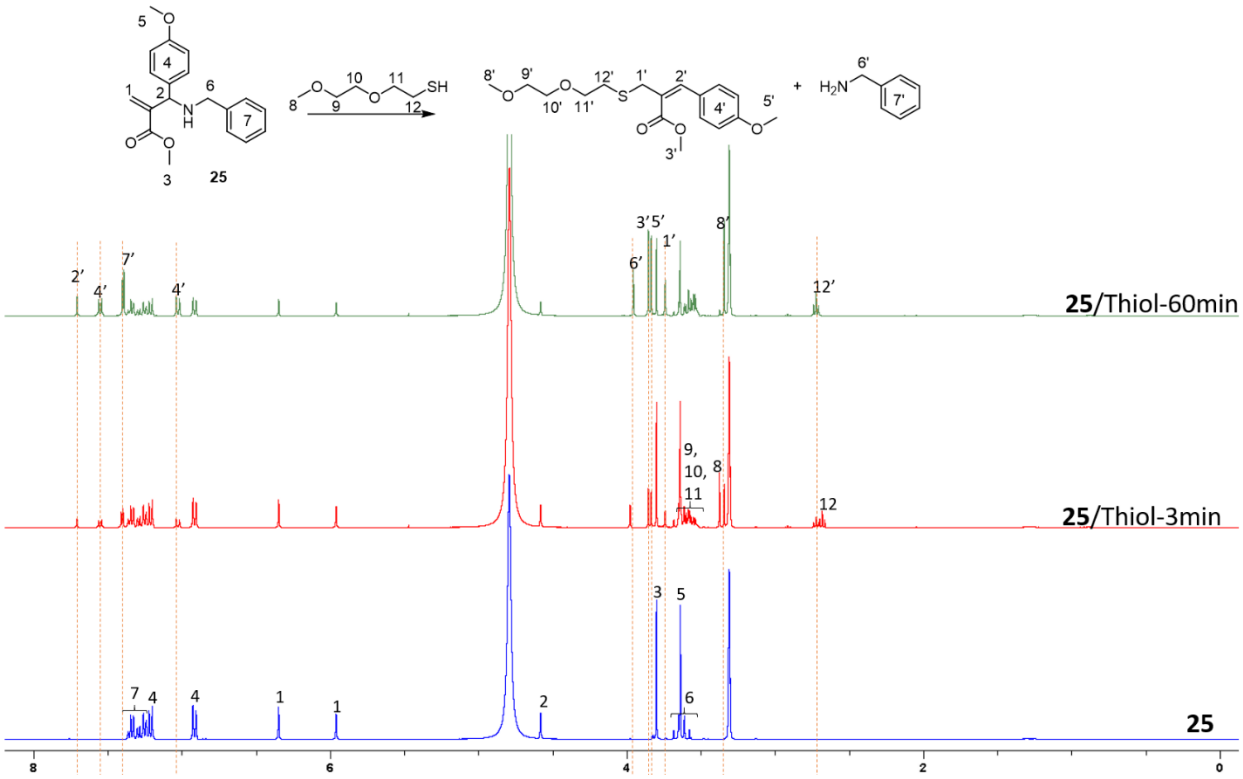


Figure S20 Reversion of amine-addition product, **25** is triggerable by thiol suggested by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (2:1). [**25**]/[DEGSH]=2. [**22**]: 6.67 mM.

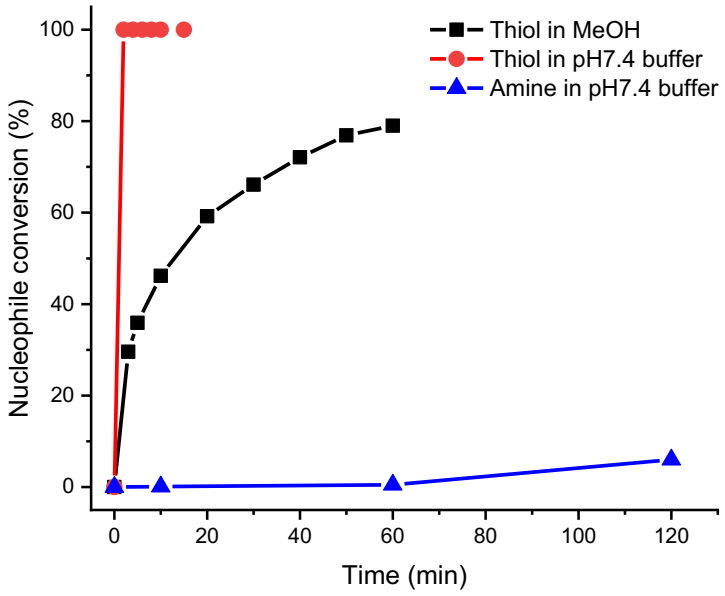


Figure S21 Solvent dependent reactivity of compound **1** toward thiol and amine. Aqueous reaction media drastically accelerates the reaction and improves the selectivity among thiol and amine. [**1**]/[Nucleophile]=2:1.

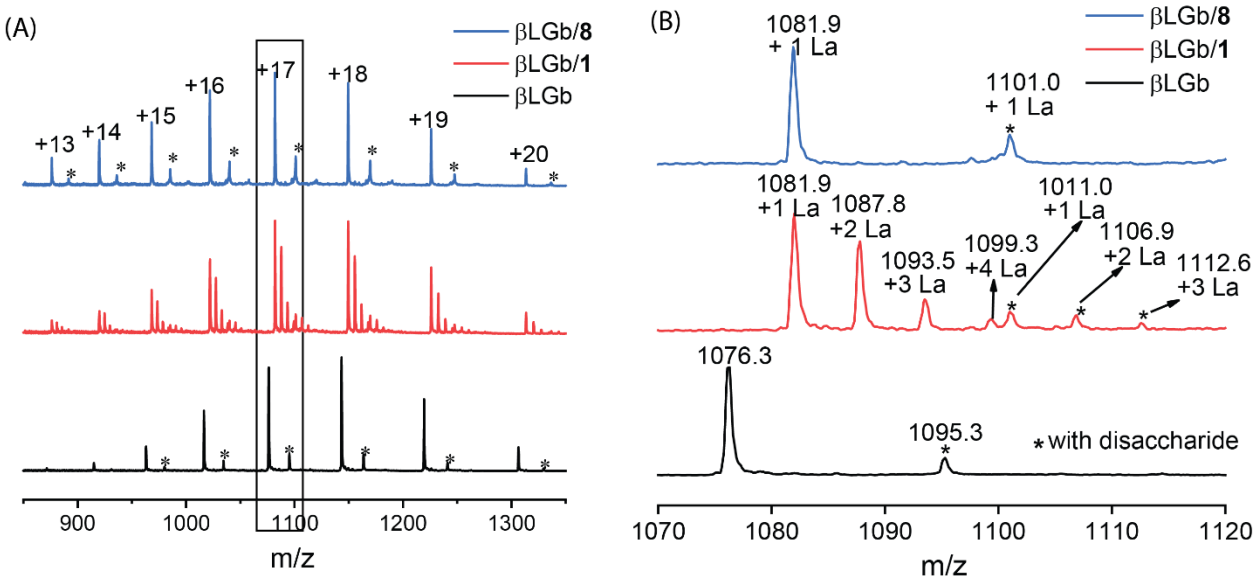


Figure S22 Mass spectra of compound **1** & **8** modified βLGb. (A) Full mass spectra. Top: βLGb modified with **8**. Middle: βLGb modified with **1** Bottom: unmodified βLGb. (B) Corresponding mass spectra of highlighted charge state (+17) in (A). 1 La stands for 1 modification.

Sequence of βLGb:

1-10	11-20	21-30	31-40	41-50
LIVTQTMKGL	DIQKVAGTWY	SLAMAASDIS	LLDAQSAPLR	VYVEELKPTP
51-60	61-70	71-80	81-90	91-100
EGDLEILLQK	WENGECAQKK	IIAEKTKIPA	VFKIDALNEN	KVLVLDTDYK
101-110	111-120	121-130	131-140	141-150
KYLLFCMENS	AEPEQSLACQ	CLVRTPEADD	EALEKFDKAL	KALPMHIRLS
151-160	161-162			
FNPTQLEEQC	HI			

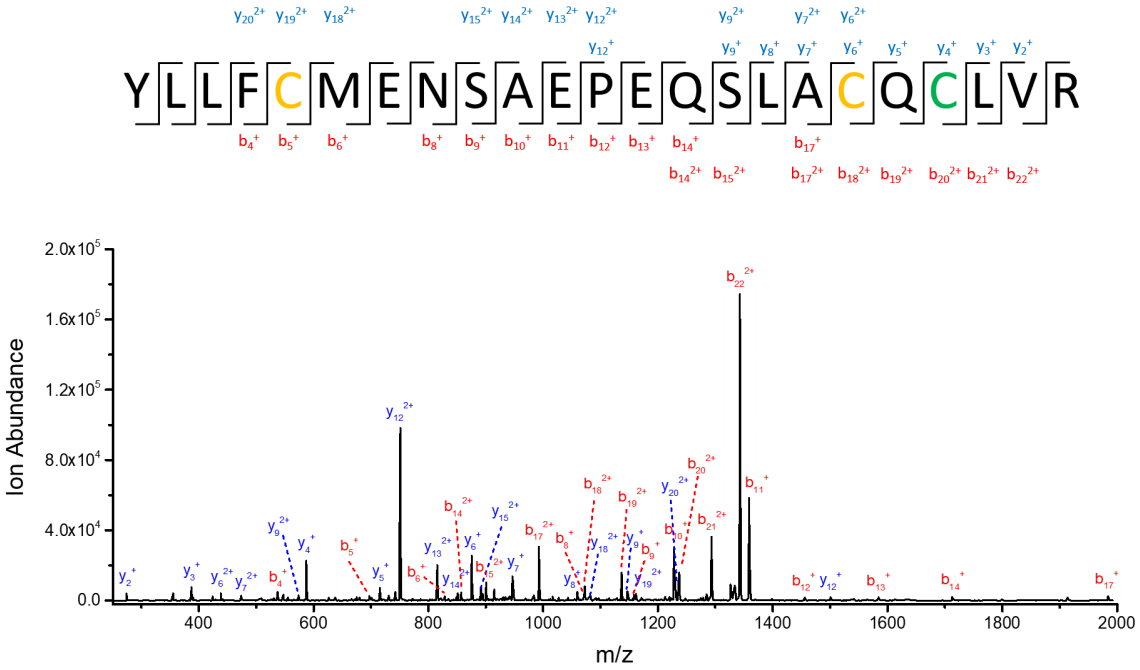


Figure S23 MS/MS of digested βLGb modified with compound **8** shows selective modification on free cysteine, C121 (green coded) while no modifications on cysteines involved in disulfide bond (yellow coded).

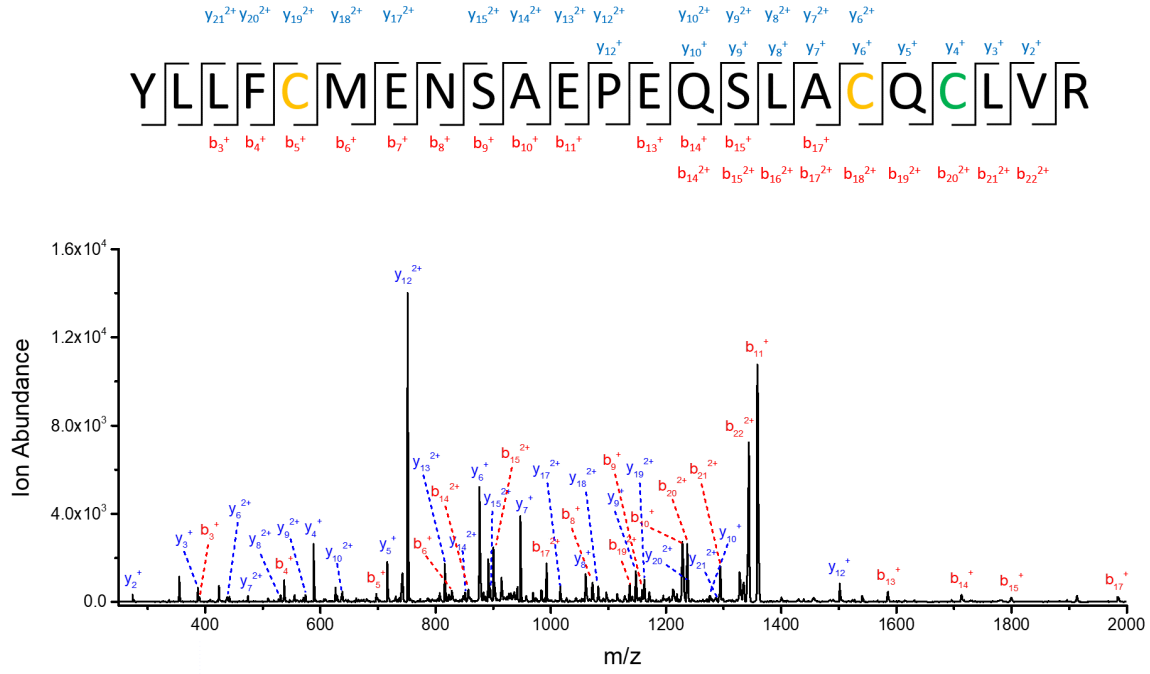


Figure S24 MS/MS of digested βLGb modified with compound **1** shows modification on free cysteine, C121 (green coded) while no modifications on cysteines involved in disulfide bond (yellow coded).

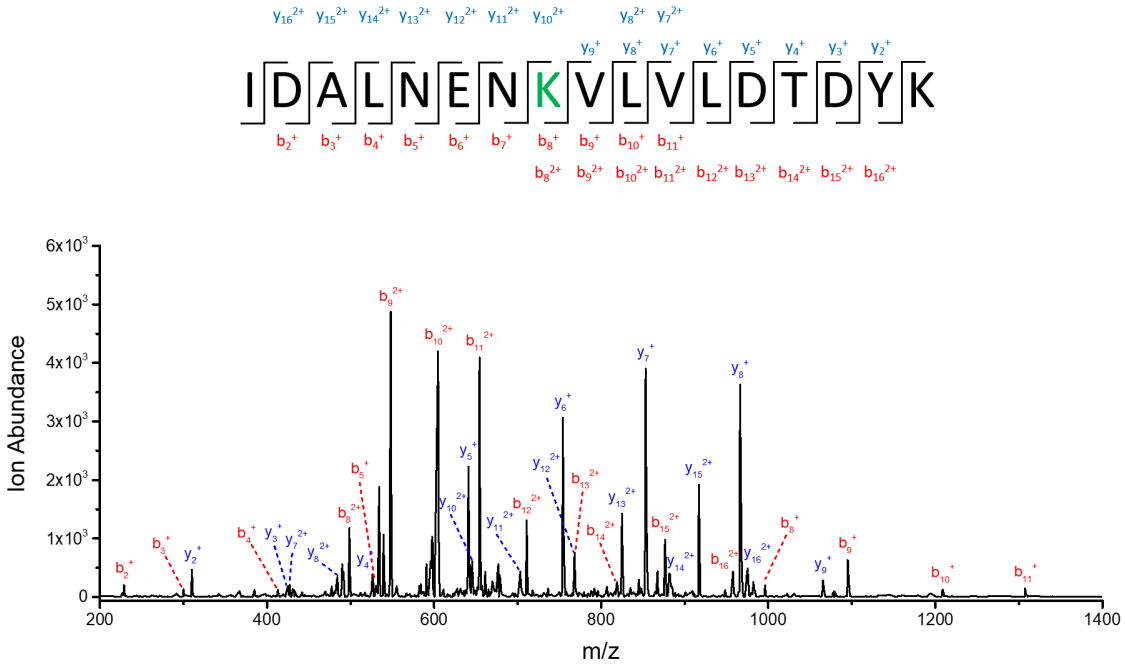


Figure S25 MS/MS of digested βLGb modified with compound **1** shows unselective modification of lysine K91

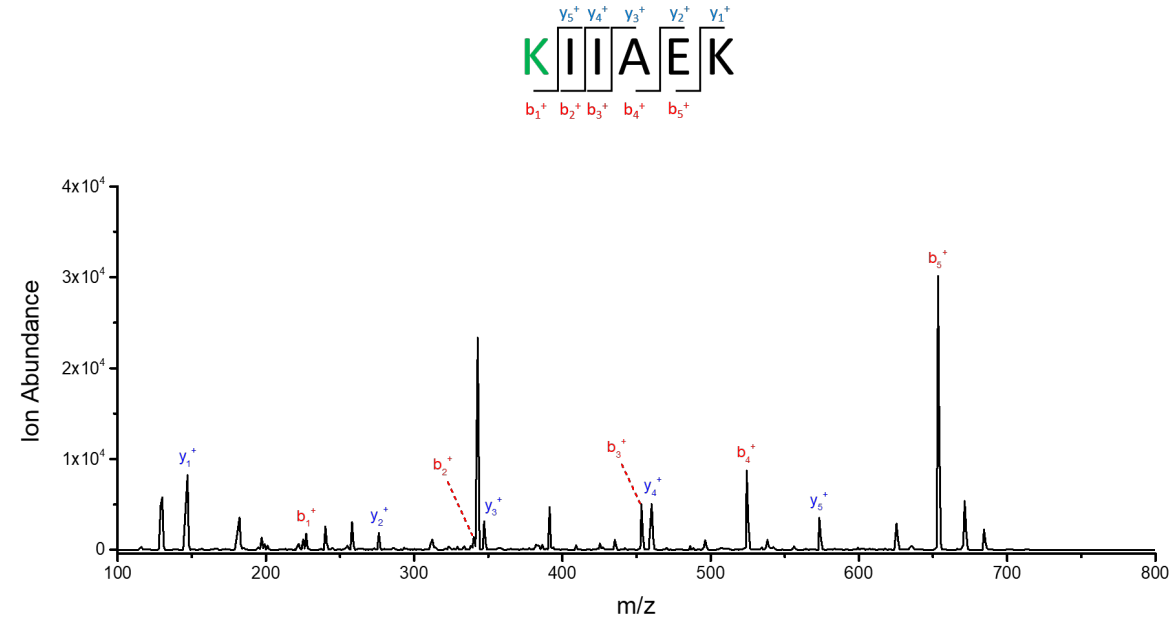


Figure S26 MS/MS of digested βLGb modified with compound **1** shows unselective modification of lysine K70

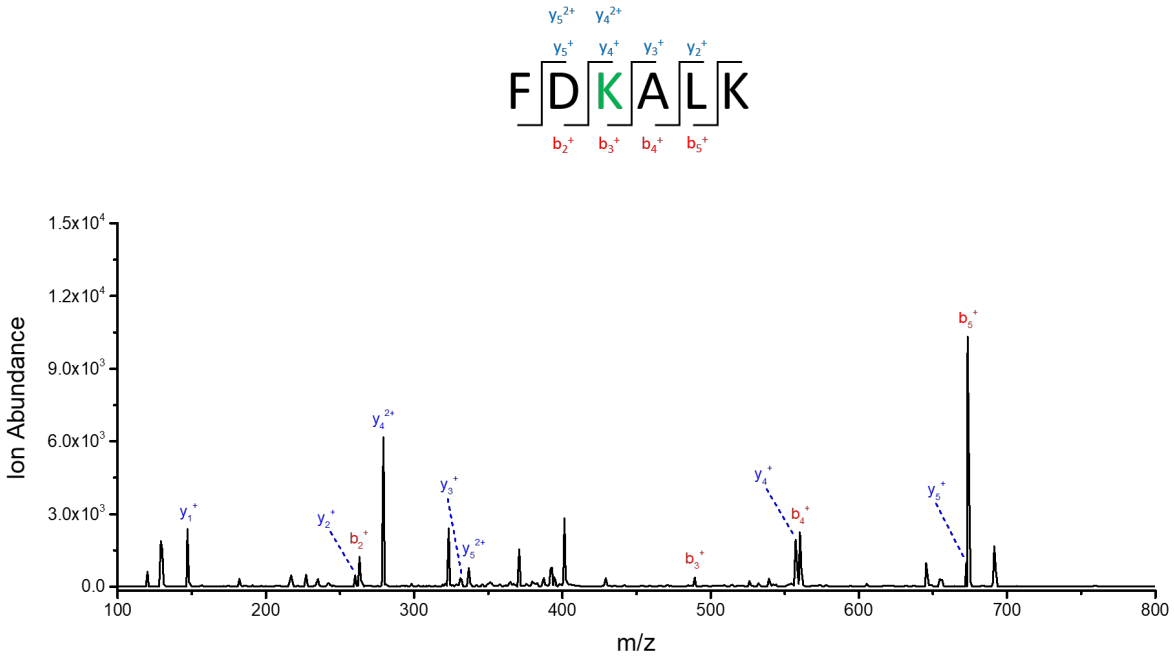


Figure S27 MS/MS of digested βLGb modified with compound **1** shows unselective modification of lysine K138

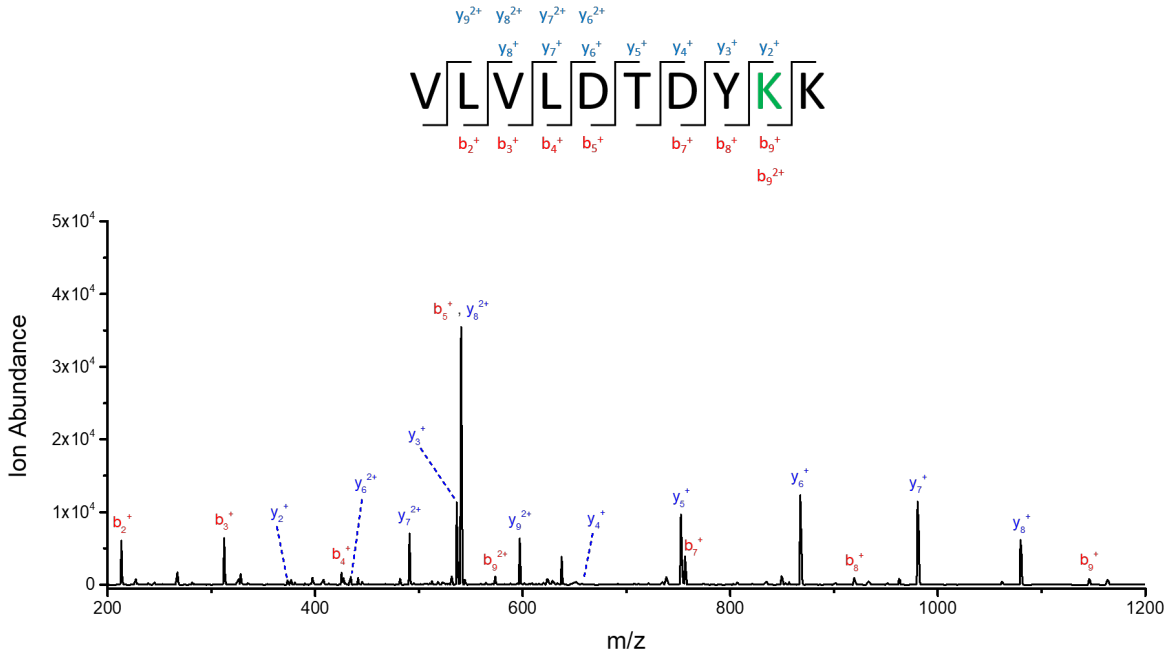


Figure S28 MS/MS of digested βLGb modified with compound **1** shows unselective modification of lysine K100

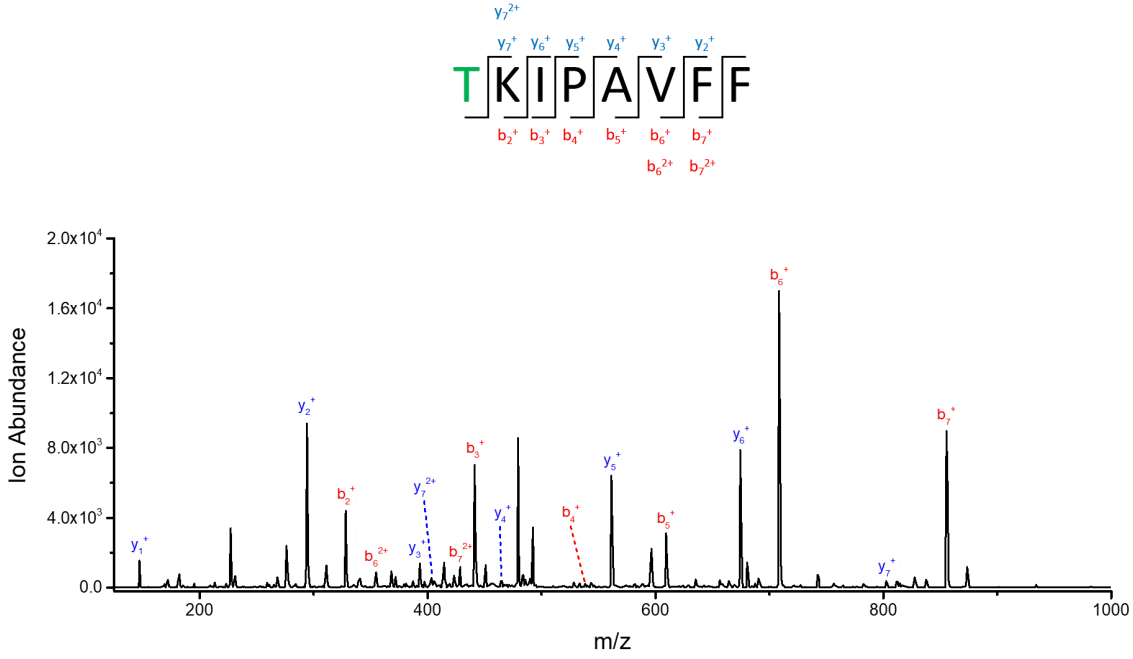


Figure S29 MS/MS of digested βLGb modified with compound **1** shows unselective modification of lysine T76

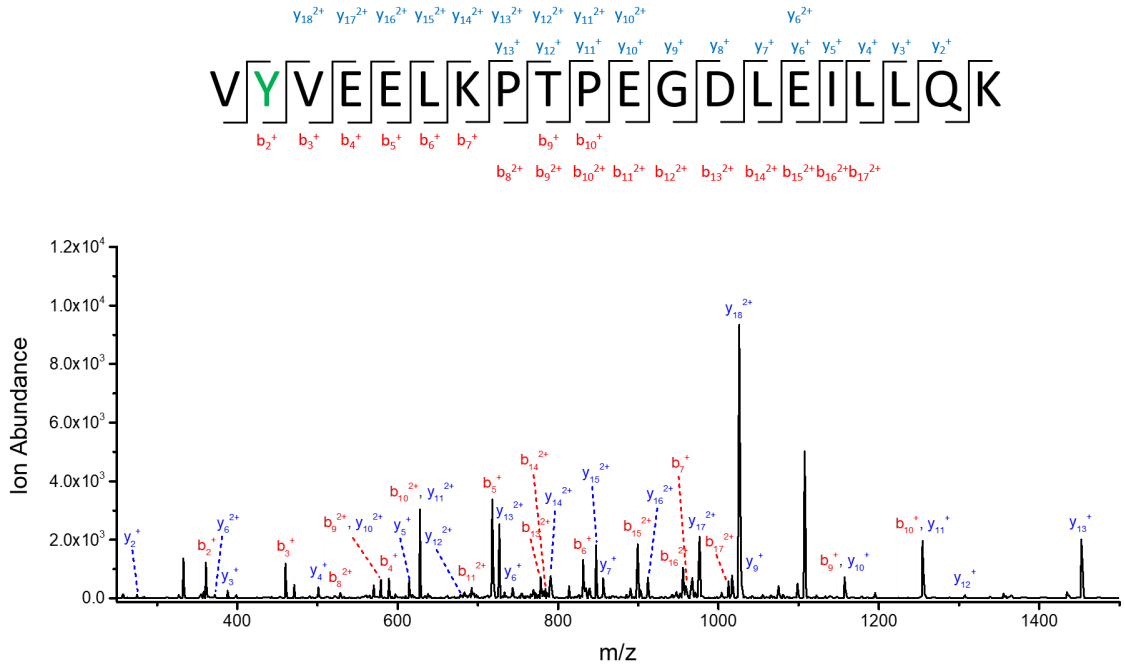


Figure S30 MS/MS of digested βLGb modified with compound **1** shows unselective modification of lysine Y42

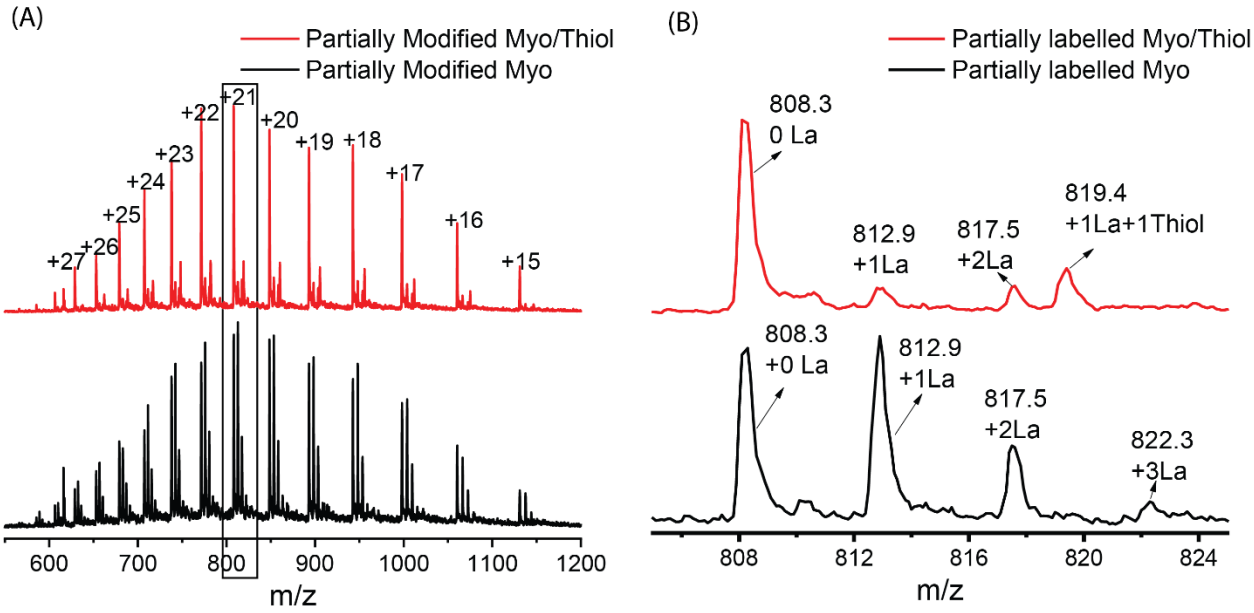


Figure S31 Mass spectra of compound **1** treated myoglobin followed by incubation with and without thiol. (A) Full mass spectra with all charge states. (B) Corresponding mass spectra of highlighted charge state (+21) in (A). 1 La stands for 1 modification.

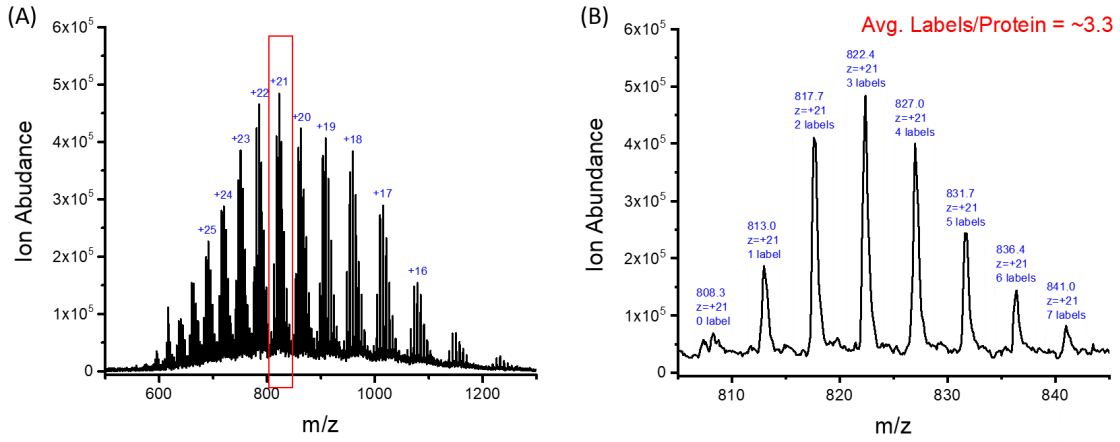


Figure S32 Mass spectra of myoglobin modified with compound **1**. Left: whole mass spectrum. Right: Mass spectrum on +21charge state.

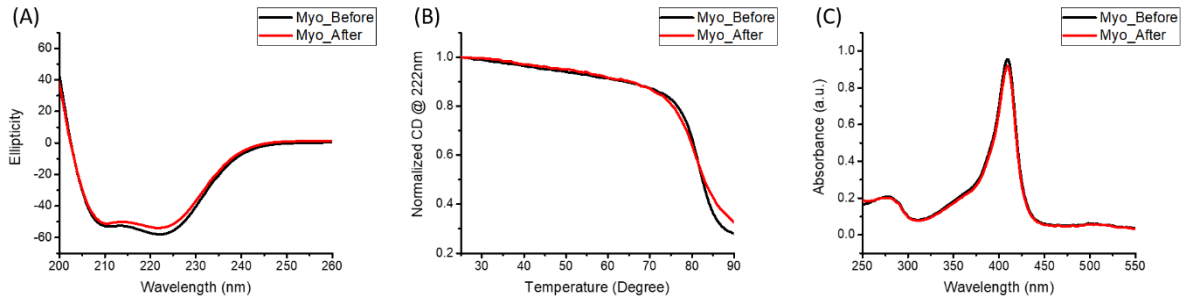


Figure S33 Biophysical characterization of myoglobin before and after modification using **1**. (A) CD, (B) Melting point; (C) UV-visible absorption spectrum of Heme

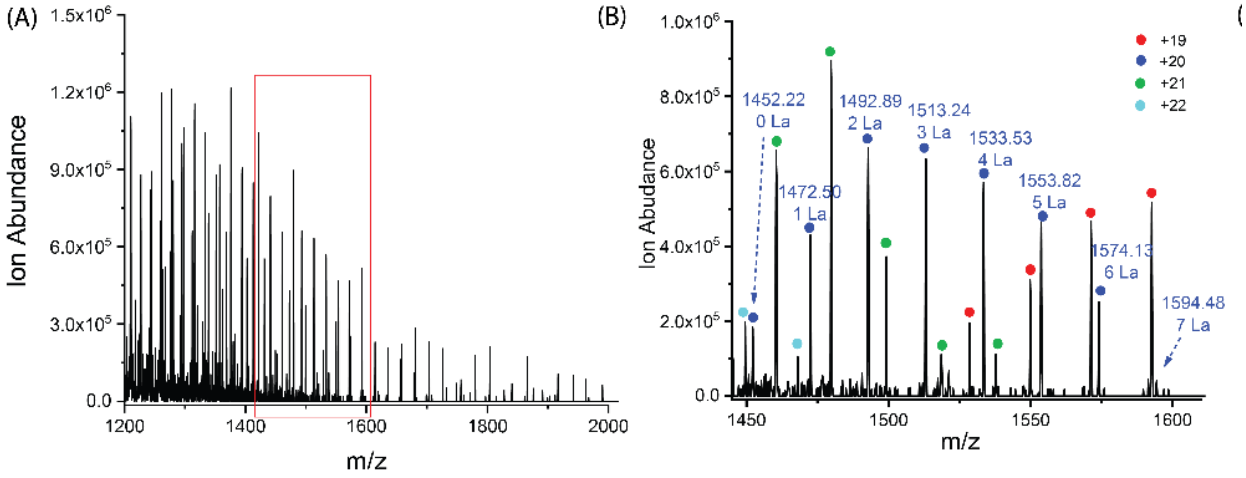


Figure S34 Mass spectrum of bovine carbonic anhydrase (BCA) treated with compound **36**. (A) Full mass spectrum of BCA modified with **36**. (B) Mass spectrum of highlighted m/z region as an example to analyze the modification. Charge states are color coded with the dots. The average modification for each protein is ~ 3.1.

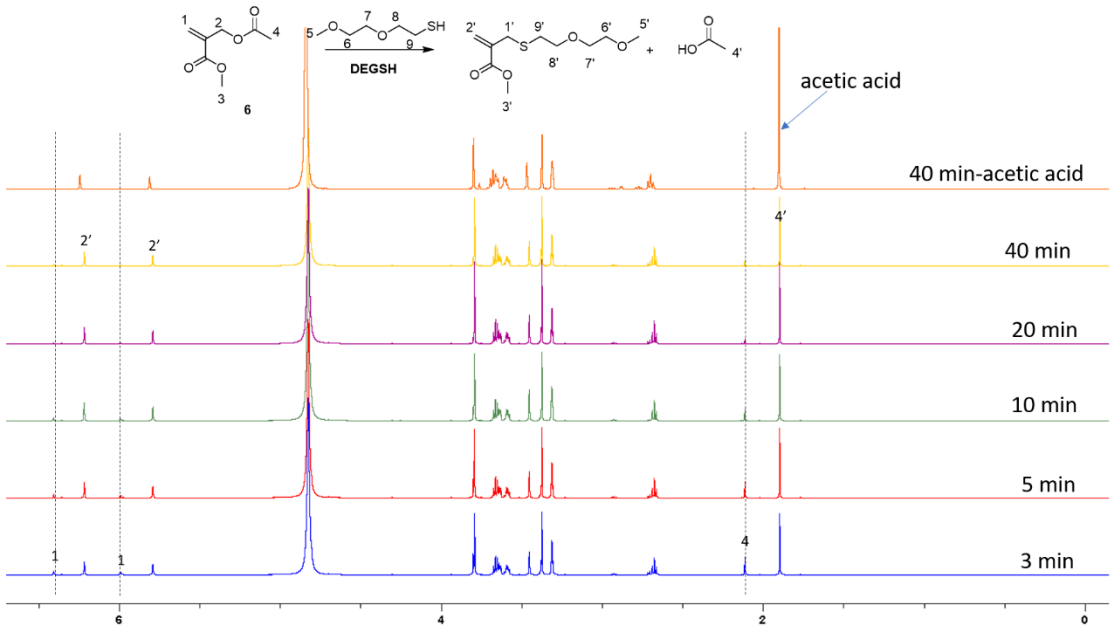


Figure S35 Time-dependent acetic acid recovered from **6** in the presence of thiol monitored by NMR. After 40 minutes, acetic acid was added to the mixture to confirm the identity of released functionality. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**6**]/[DEGSH]=1. [**6**]: 10 mM. Slight shift on peaks were observed due to decreasing pH caused by addition of acetic acid. However, chemical shift of acetic acid is identical to that of released molecule confirming recovery of acetic acid.

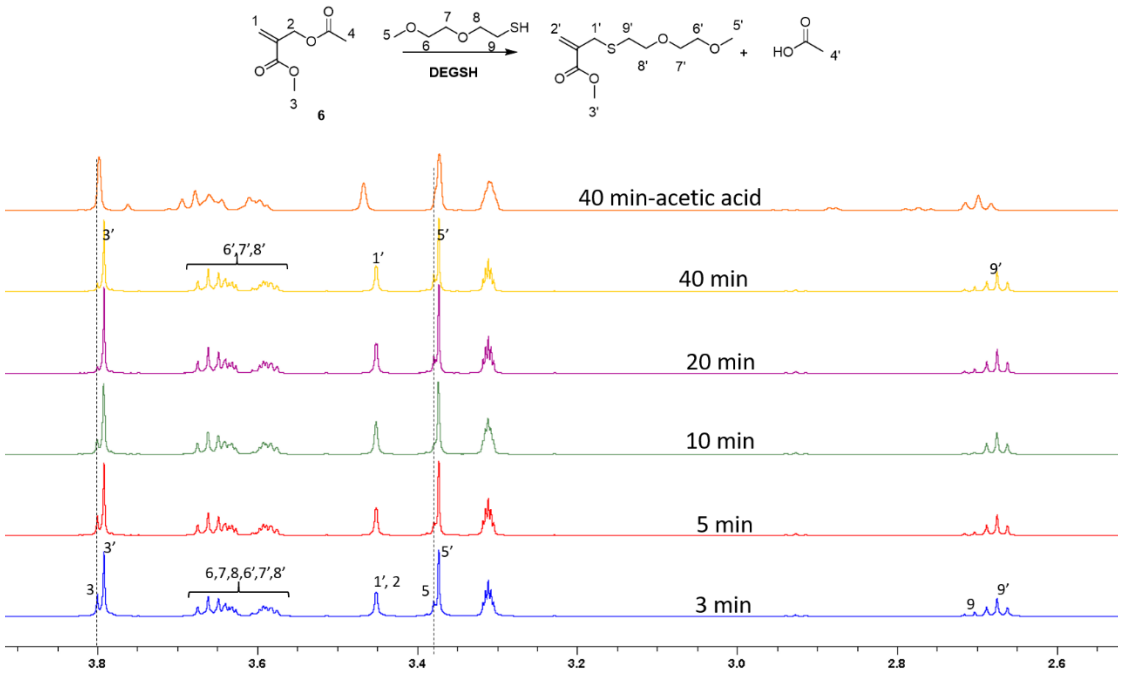


Figure S36 Zoom-in NMR spectra of Figure S35.

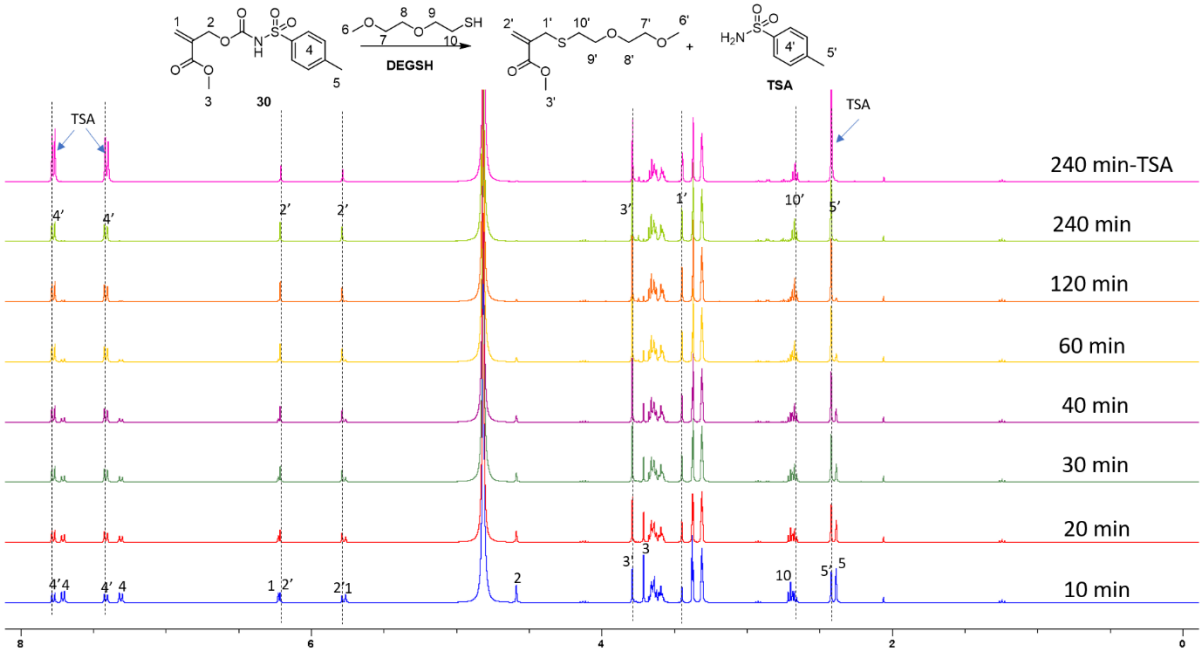


Figure S37 Time-dependent sulfonamide recovered from **30** in the presence of thiol monitored by NMR. After 240 minutes, p-toluene sulfonamide (TSA) was added to the mixture to confirm the identity of released functionality. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**30**]/[DEGSH]=1. [**30**]: 10 mM.

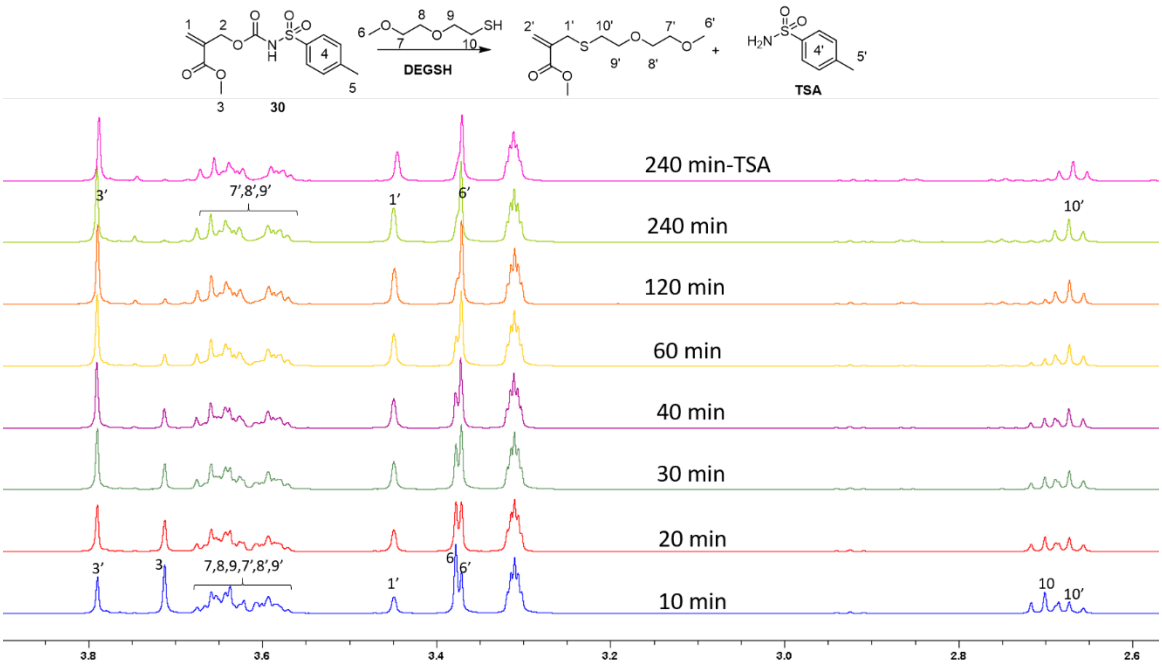


Figure S38 Zoom-in NMR spectra of Figure S37.

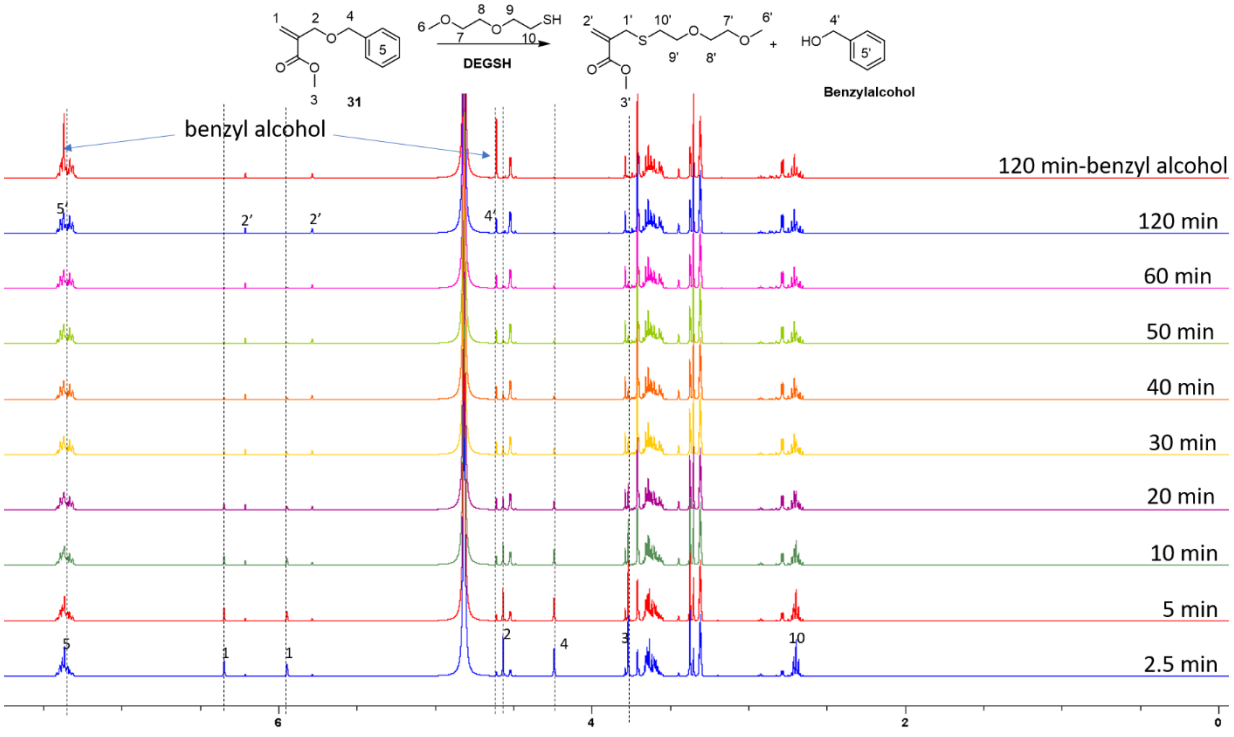


Figure S39 Time-dependent benzyl alcohol recovered from **31** in the presence of thiol monitored by NMR. After 120 minutes, benzyl alcohol was added to the mixture to confirm the identity of released functionality. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**31**]/[DEGSH]=1. [**31**]: 10 mM.

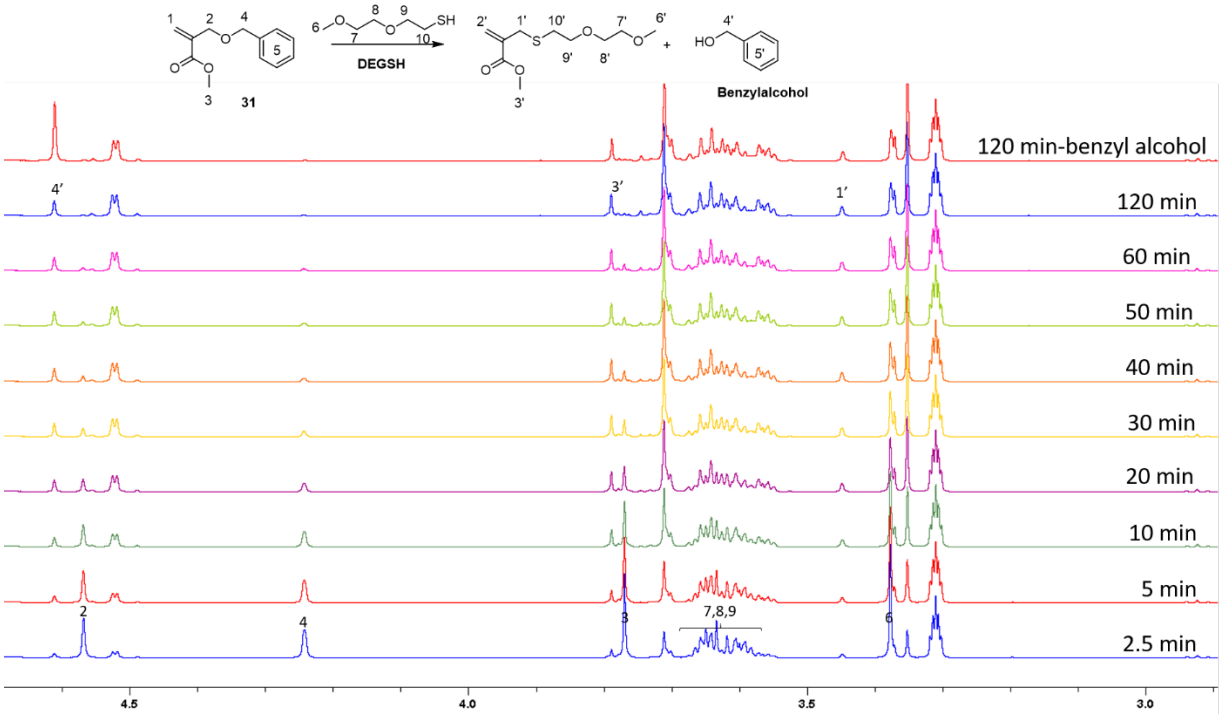


Figure S40 Zoom-in NMR spectra of Figure S39.

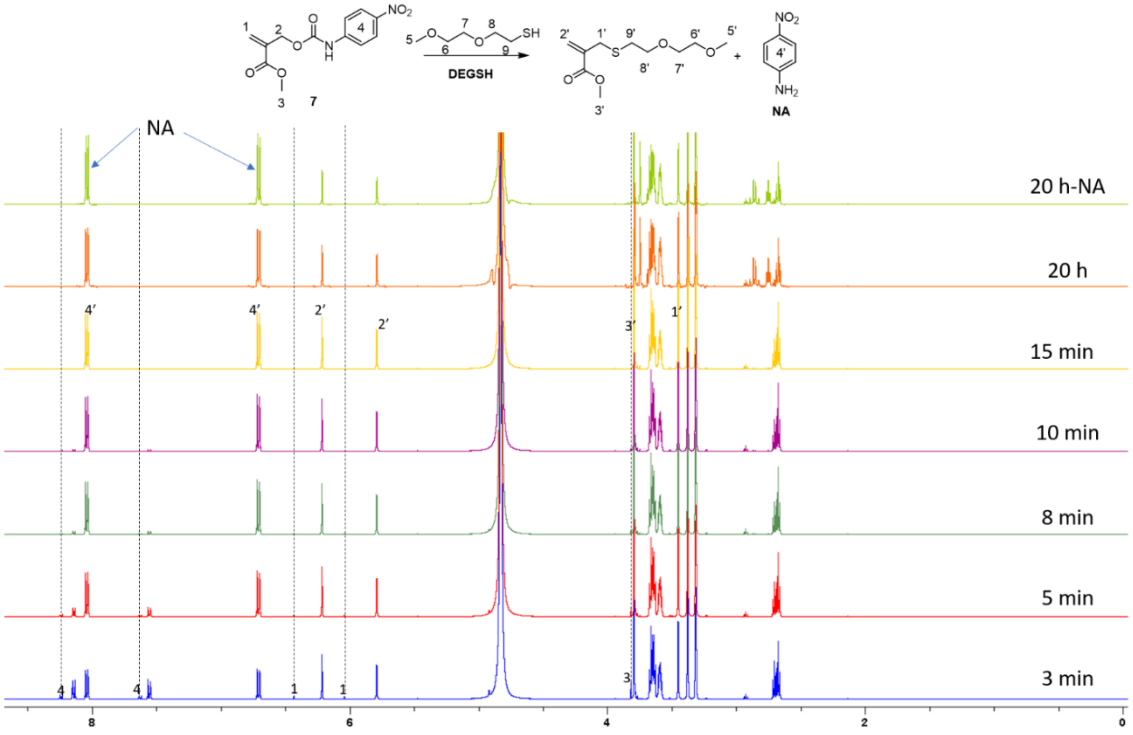


Figure S41 Time-dependent nitroaniline (NA) recovered from **7** in the presence of thiol monitored by NMR. After reaction complete, nitroaniline was added to the mixture to confirm the identity of released functionality. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**7**]/[DEGSH]=1. [**7**]: 10 mM.

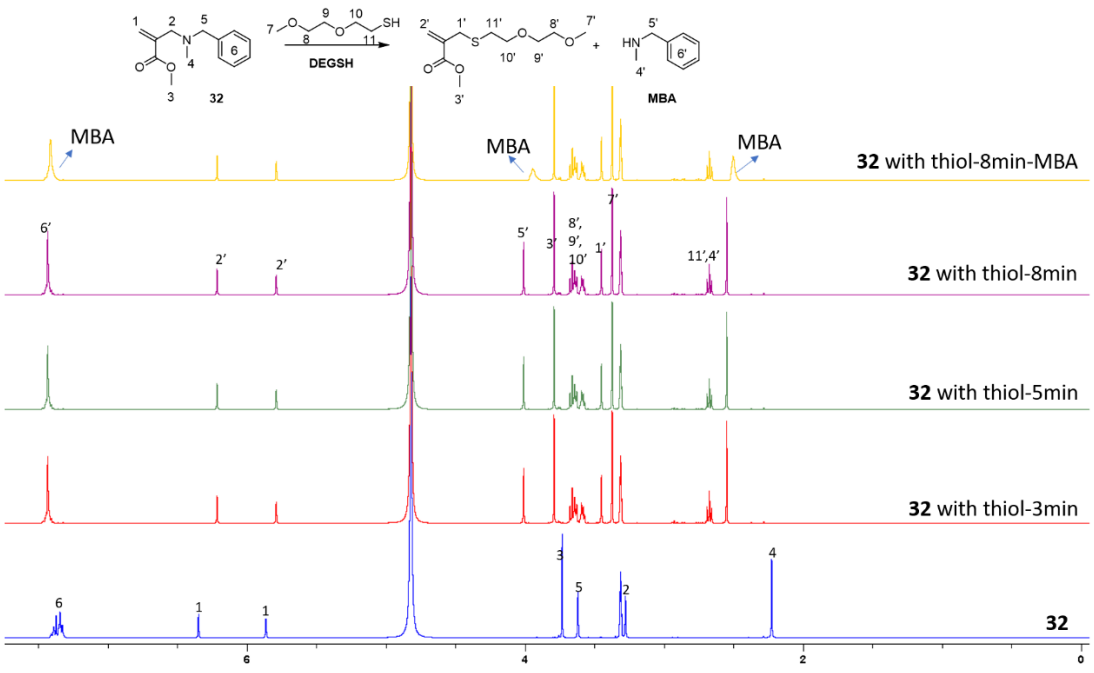


Figure S42 Time-dependent N-methylbenzylamine (MBA) recovered from **32** in the presence of thiol monitored by NMR. After reaction complete, MBA was added to the mixture to confirm the identity of released functionality. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**32**]/[DEGSH]=1. [**32**]: 10 mM.

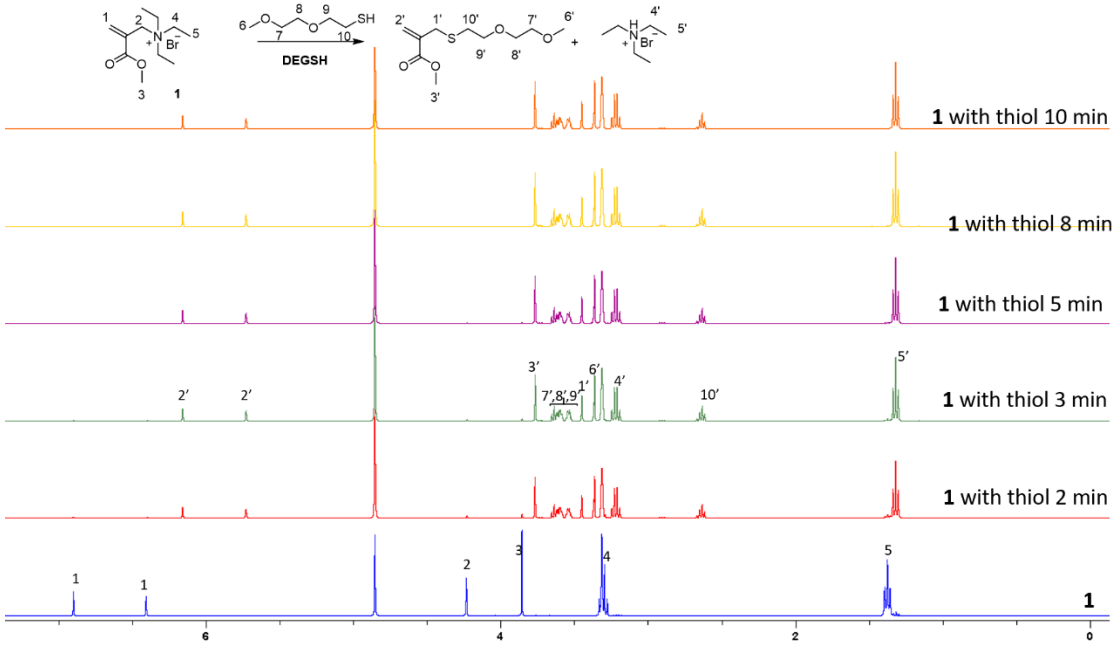


Figure S43 Time-dependent TEA recovered from **1** in the presence of thiol monitored by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**1**]/[DEGSH]=1. [**1**]: 10 mM.

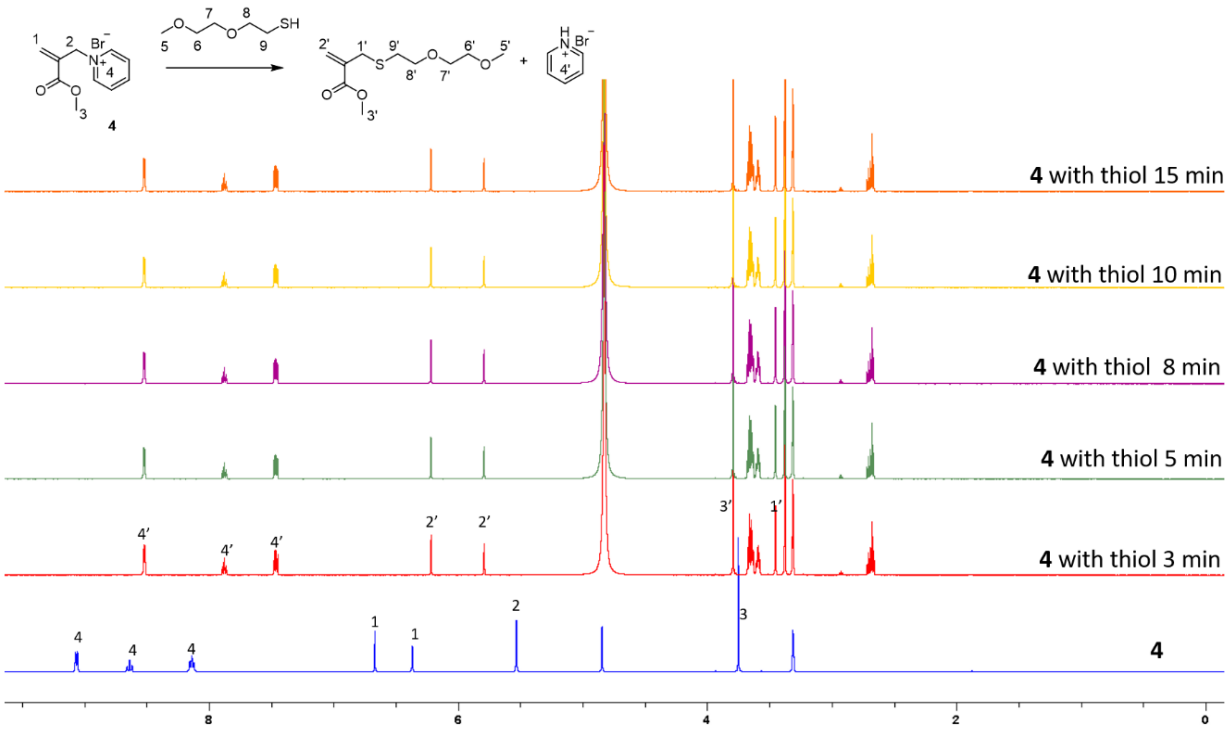


Figure S44 Time-dependent pyridine recovered from **4** in the presence of thiol monitored by NMR. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**4**]/[DEGSH]=1. [**4**]: 10 mM.

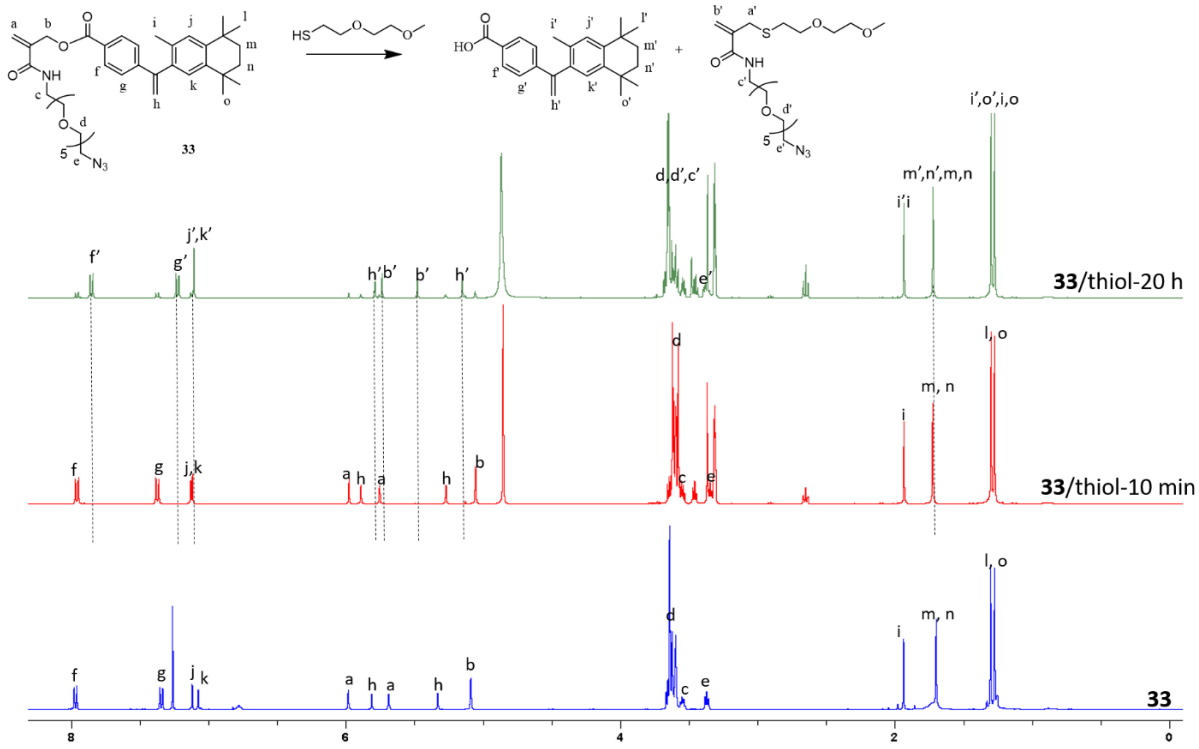


Figure S45 Time-dependent bexarotene released from **33** triggered by thiol and monitored by NMR. The reaction was carried out at MeOH-d4 in the presence of 10 mg of solid Na_2CO_3. Note: NMR of **33** was recorded in $CDCl_3$. [**33**]/[DEGSH]=1/2. [**33**]: 10 mM.

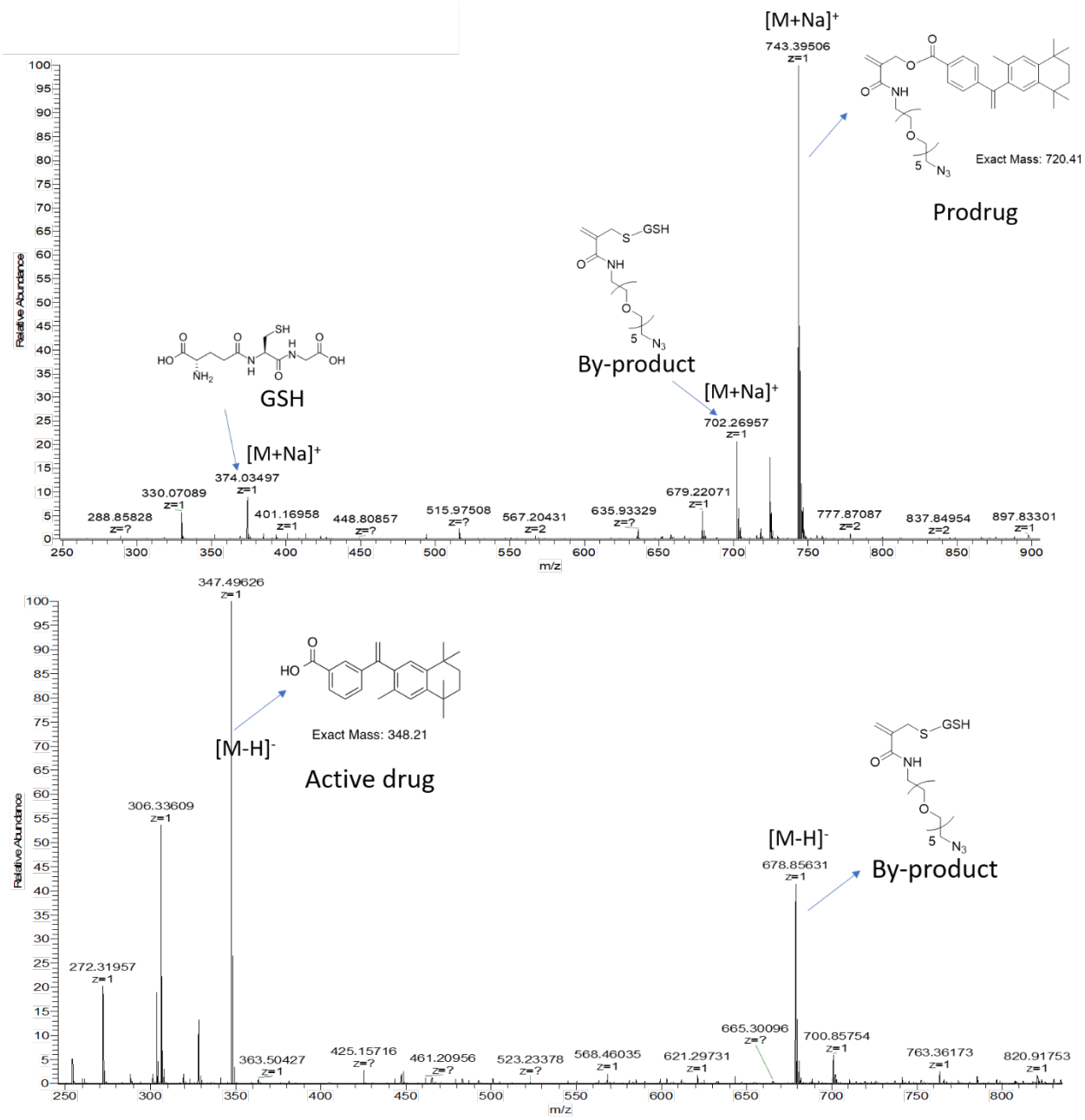


Figure S46 Release of active drug from compound **33** triggered by Glutathione (GSH) followed by mass spectrometry. TOP: Positive mode mass spectrometry analysis; Bottom: negative mode mass spectrometry analysis. Observation of active drug signature suggests the release of drug from the prodrug. The reaction was carried out at MeOH and 50 mM pH 7.4 phosphate buffer mixture (1:1). [**33**] =0.5 mM, [GSH] =5 mM. The sample was analyzed by mass spectrometry after 6-hours incubation.

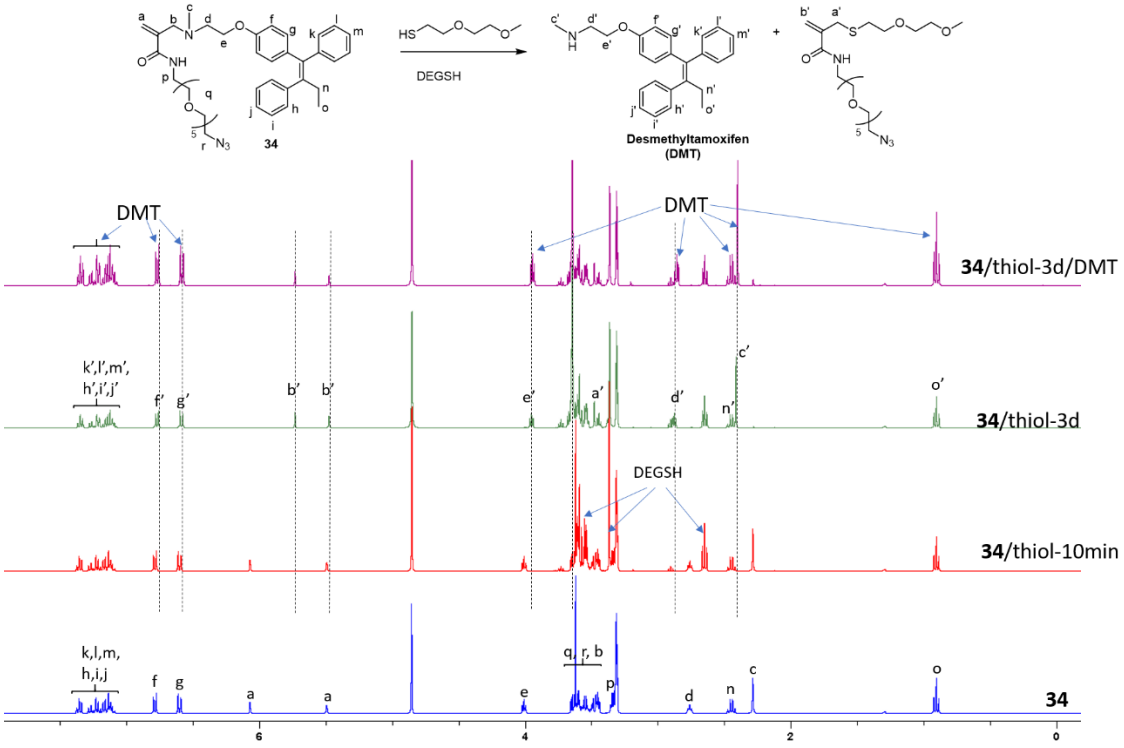


Figure S47 Time dependent desmethyltamoxifen released from **34** in the presence of thiol monitored by NMR. After 3 days, commercial desmethyltamoxifen(DMT) was added to the reaction mixture to validate the identity of released molecule. Observation of identical chemical shifts of both desmethyltamoxifen and released molecules indicates the release of desmethyltamoxifen from **34**. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**34**]/[DEGSH]=1/2. [**34**]: 5 mM.

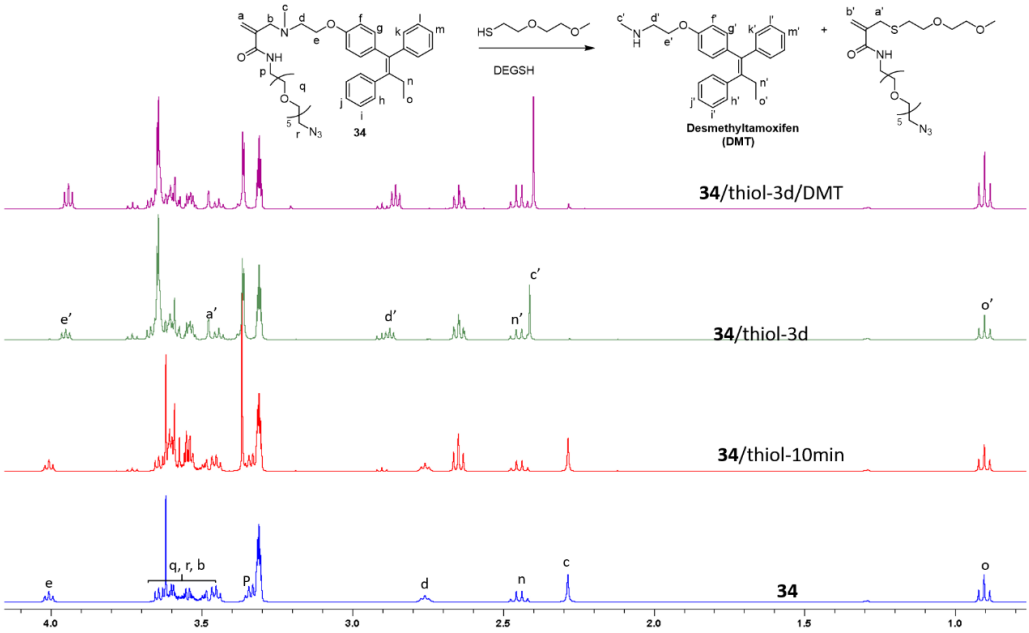


Figure S48 Zoom-in NMR spectra of Figure S47**.**

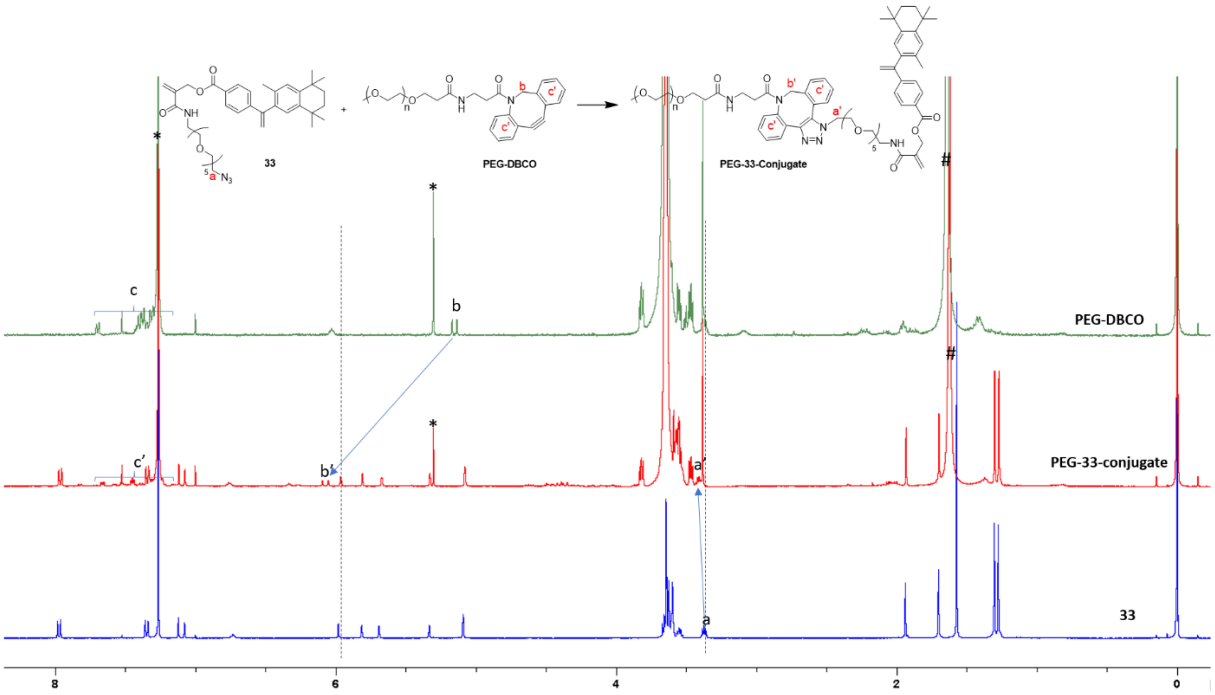


Figure S49 Conjugation of compound **33** to PEG-DBCO followed by NMR in $CDCl_3$. (* and # are attributed to DCM and H_2O). Top: NMR spectrum of PEG-DBCO. Bottom: NMR spectrum of compound 33. Middle: NMR spectrum of PEG-drug conjugate. Observation of chemical shift shifting of a , b and c protons whose chemical shift should be significantly changed after click reaction and signatures from both precursors suggests successful conjugation.

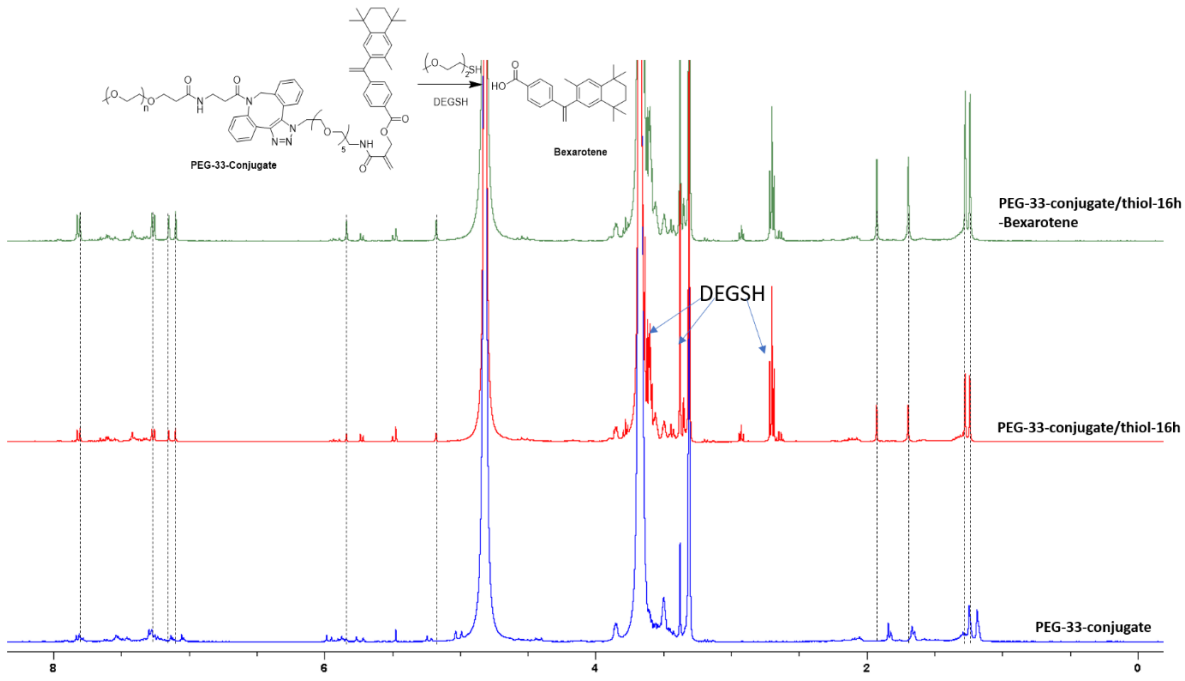


Figure S50 Release of bexarotene from **PEG-33** conjugate in the presence of thiol monitored by NMR. Bottom: PEG-33 conjugate itself. Middle: PEG-33 conjugate treated with thiol for 16 hours. Top: PEG-33 conjugate treated with thiol for 16 hours followed by addition of commercial bexarotene to validate the identity of released molecule. The fact that newly appeared peaks after thiol incubation is identical to bexarotene proves the release of bexarotene from polymer-drug conjugate. The reaction was carried out at MeOH-d4 and 50 mM pH 7.4 phosphate buffer (1:1). [**PEG-33**]/[DEGSH]=1:2. [**PEG-33**]: 1 mM.

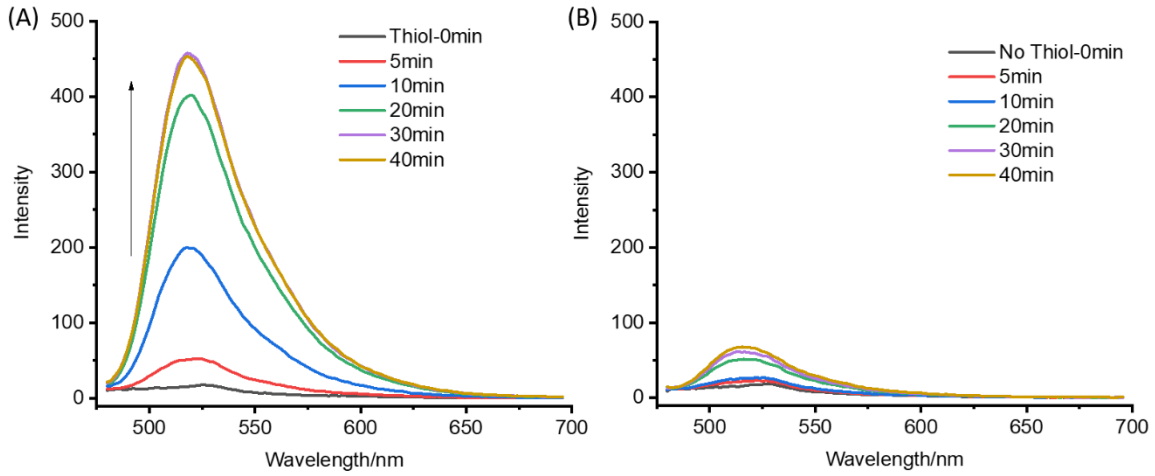


Figure S51 BSA release followed by fluorescence in the presence(A) and absence(B) of thiol.

NMR data for trigger-to-release kinetics measurement (Figure S52-S103)

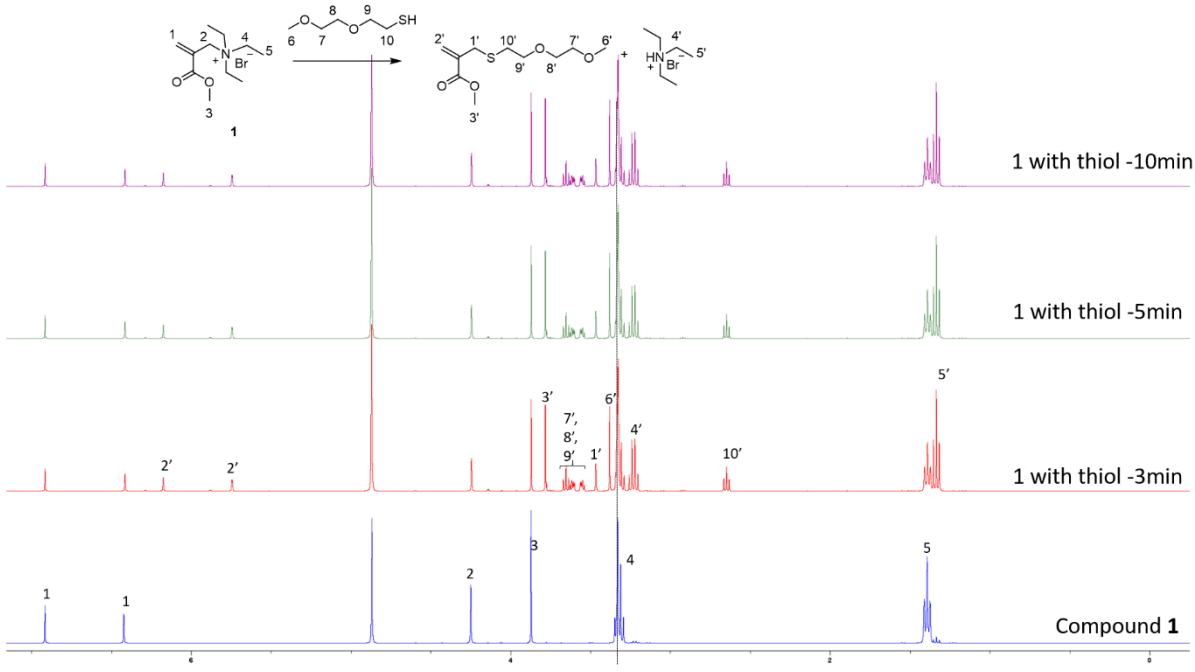


Figure S52 Thiol-addition with **1**.

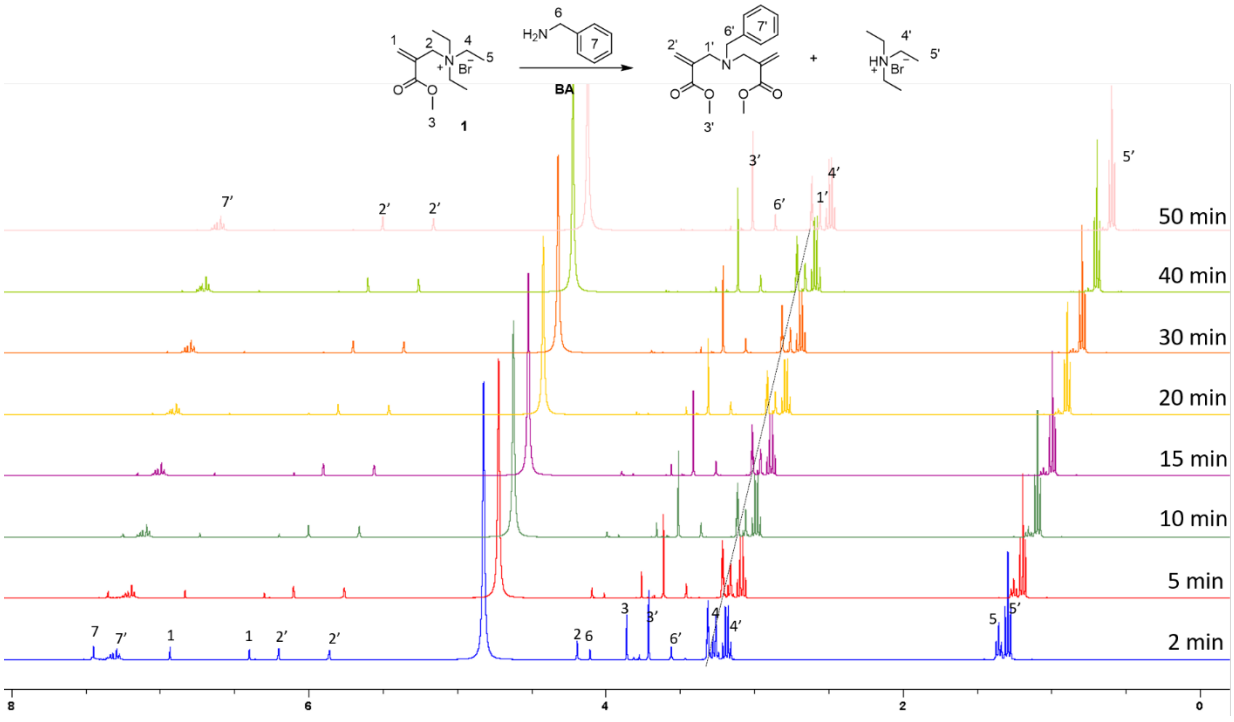


Figure S53 Amine-addition with **1**.

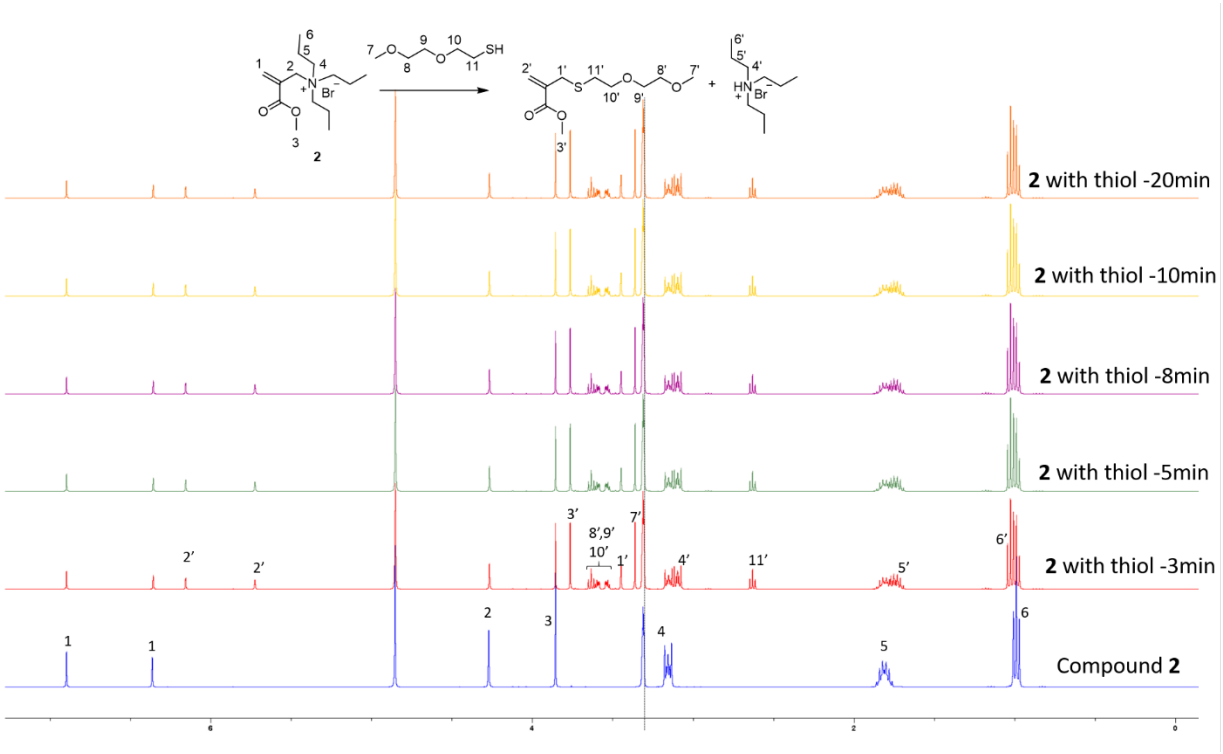


Figure S54 Thiol-addition with **2.**

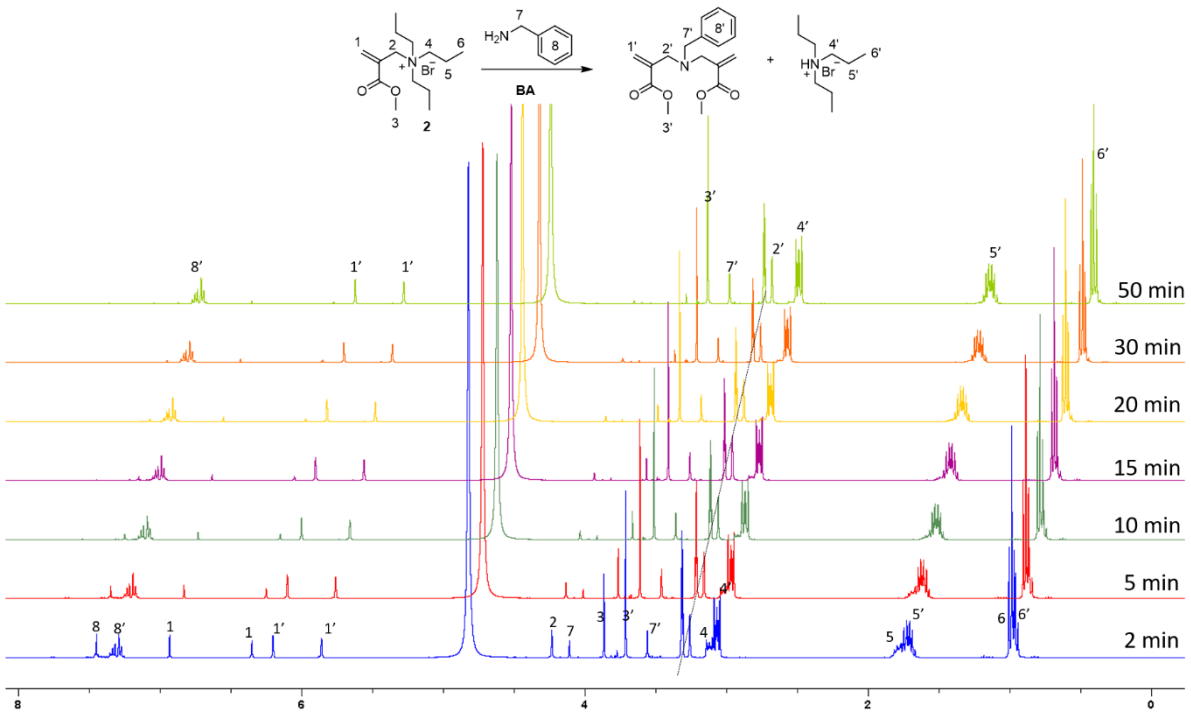


Figure S55 Amine-addition with **2**

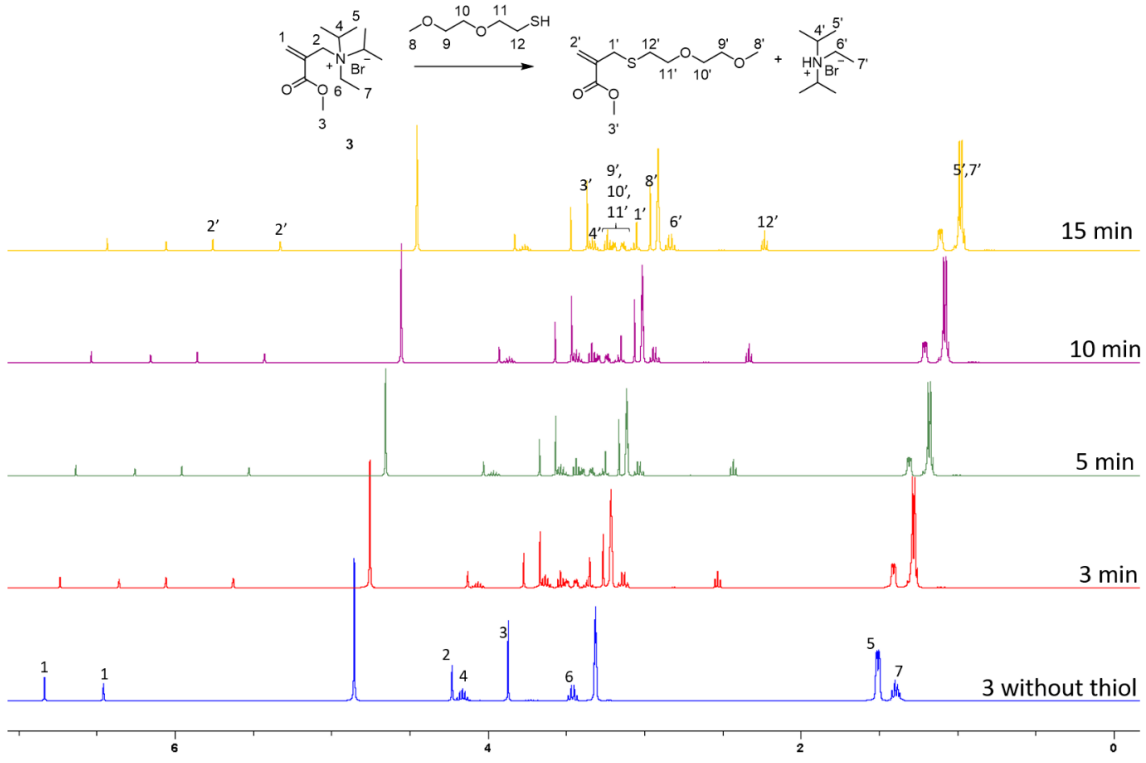


Figure S56 Thiol-addition with **3**.

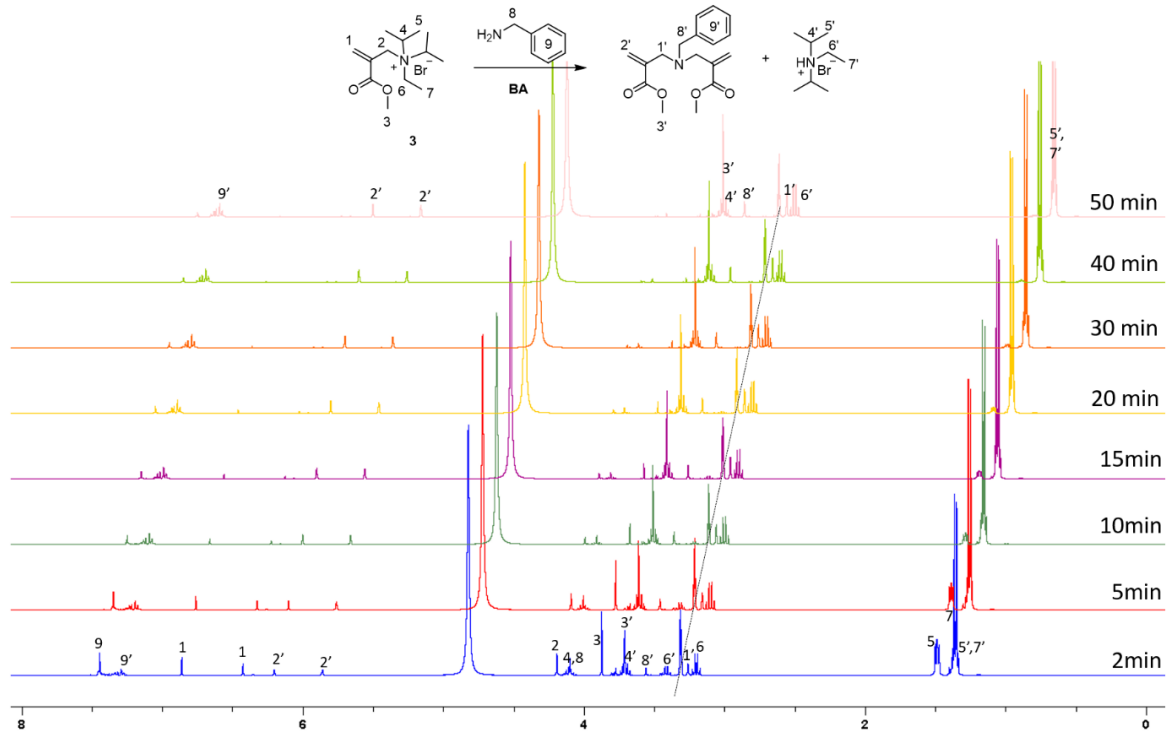


Figure S57 Amine-addition with **3**.

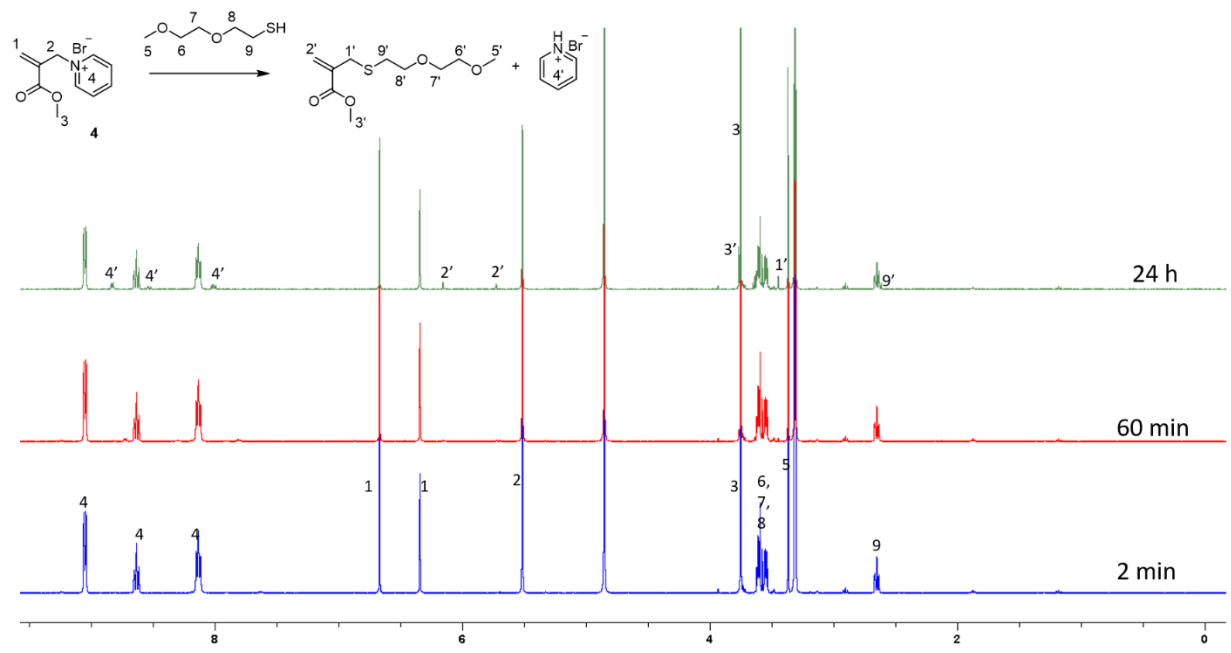


Figure S58 Thiol-addition with **4.**

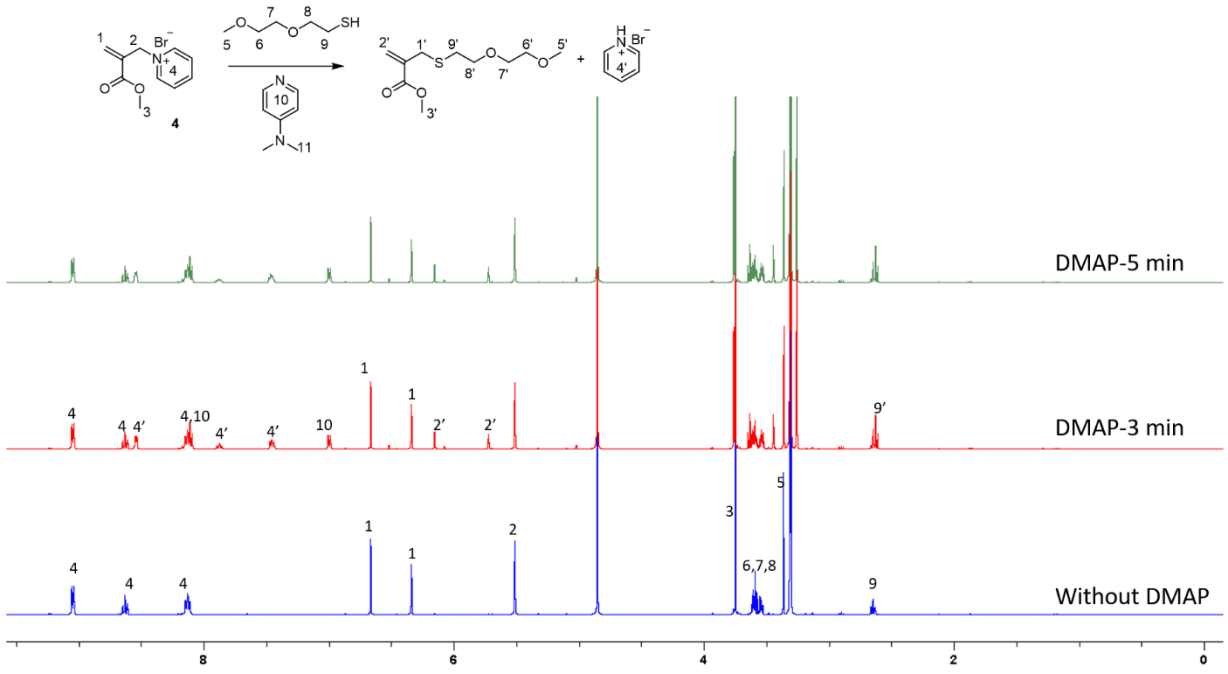


Figure S59 Thiol-addition with **4** accelerated by introduction of DMAP in reaction mixture

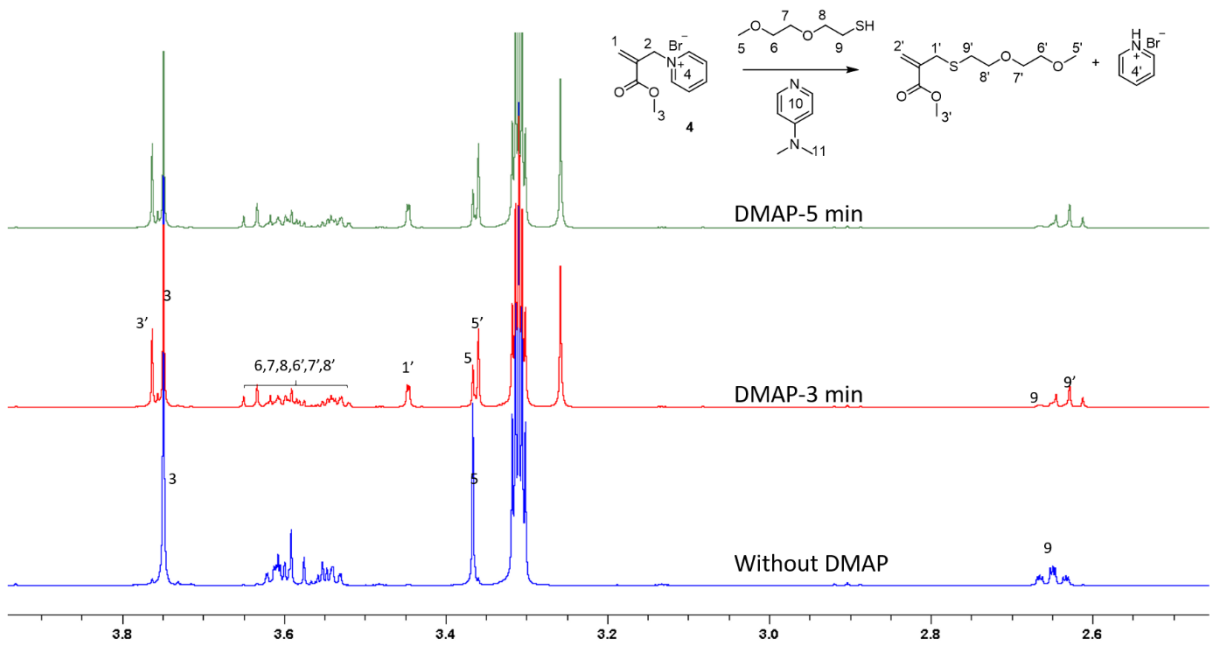


Figure S60. Zoom-in spectra of Figure S59.

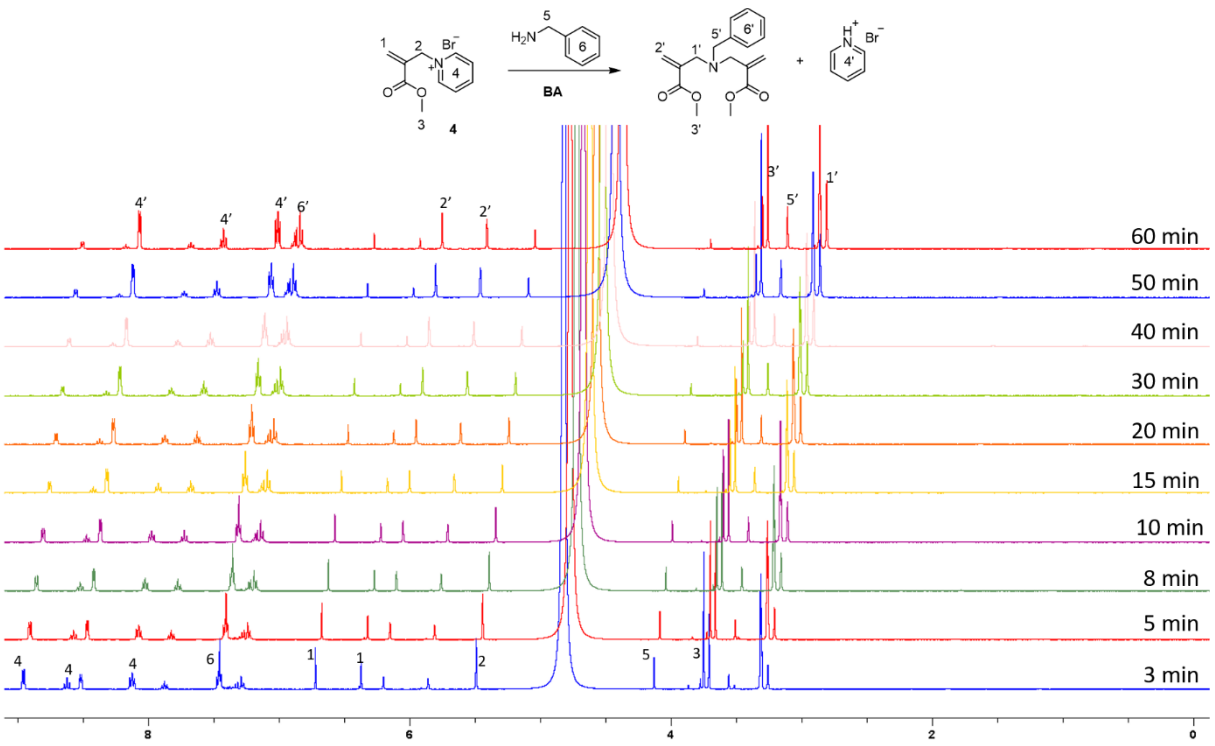


Figure S61 Amine-addition with **4**

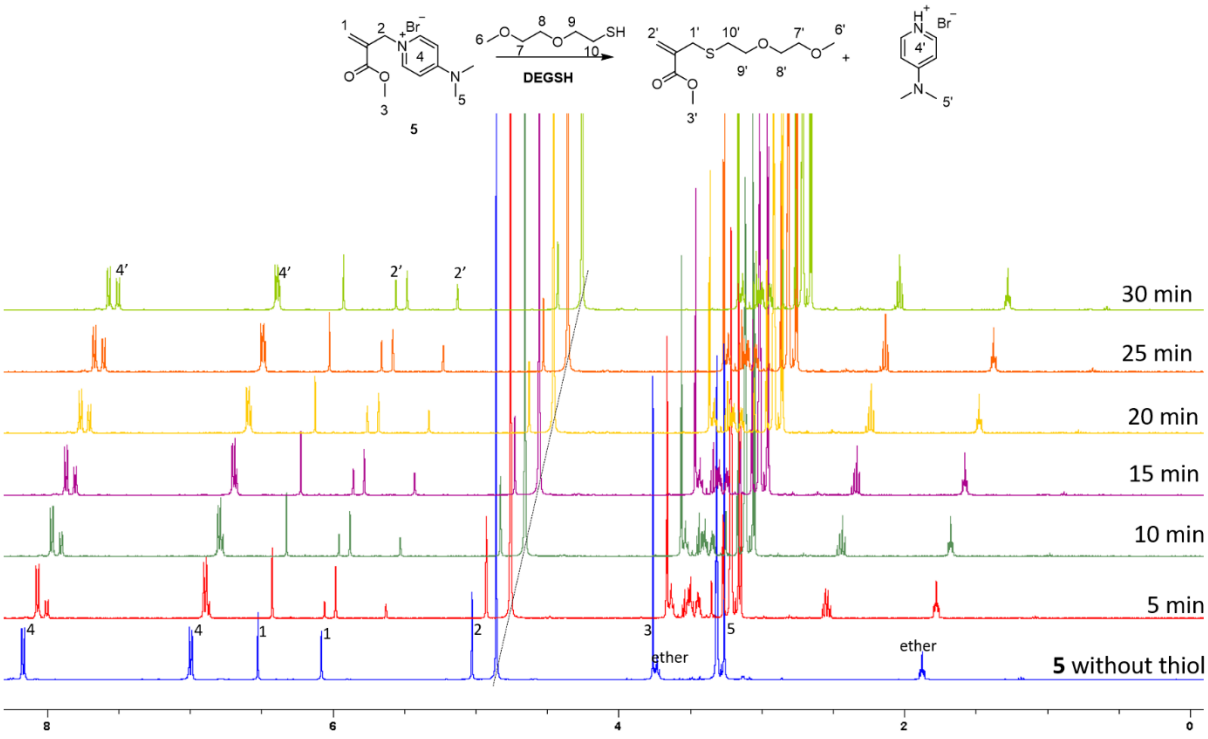


Figure S62 Thiol-addition with **5**

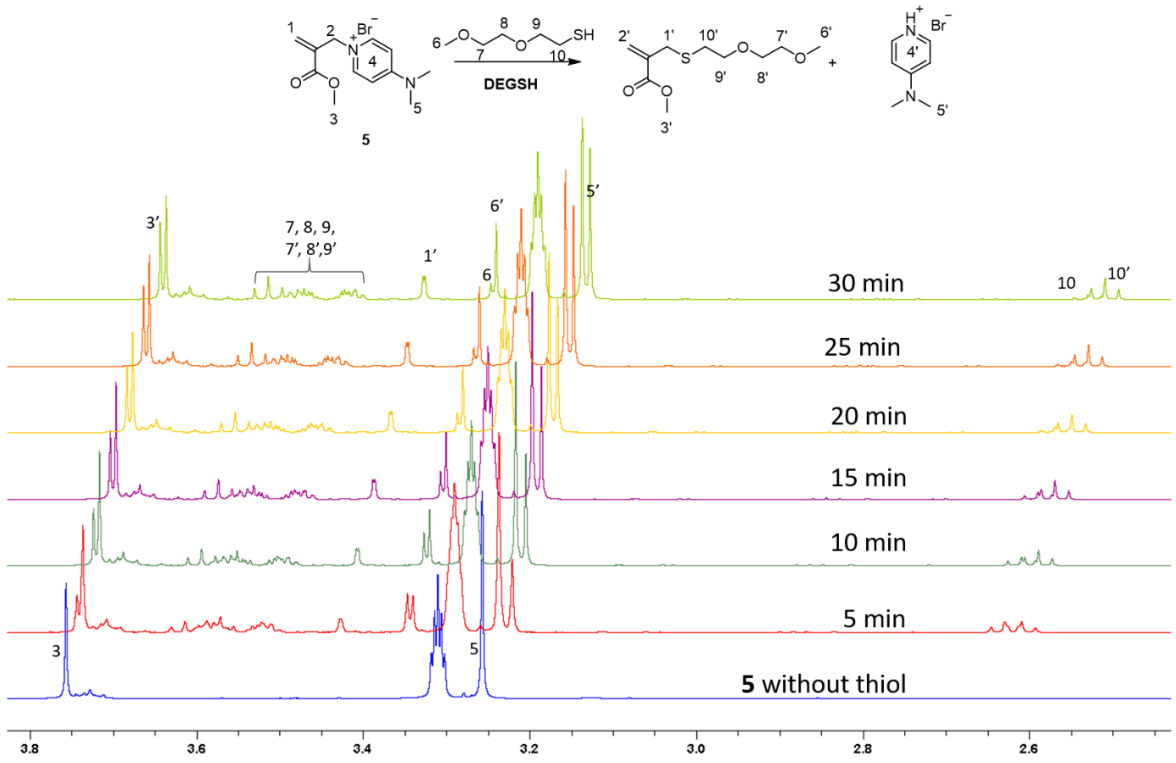


Figure S63 Zoom-in spectra of Figure S62

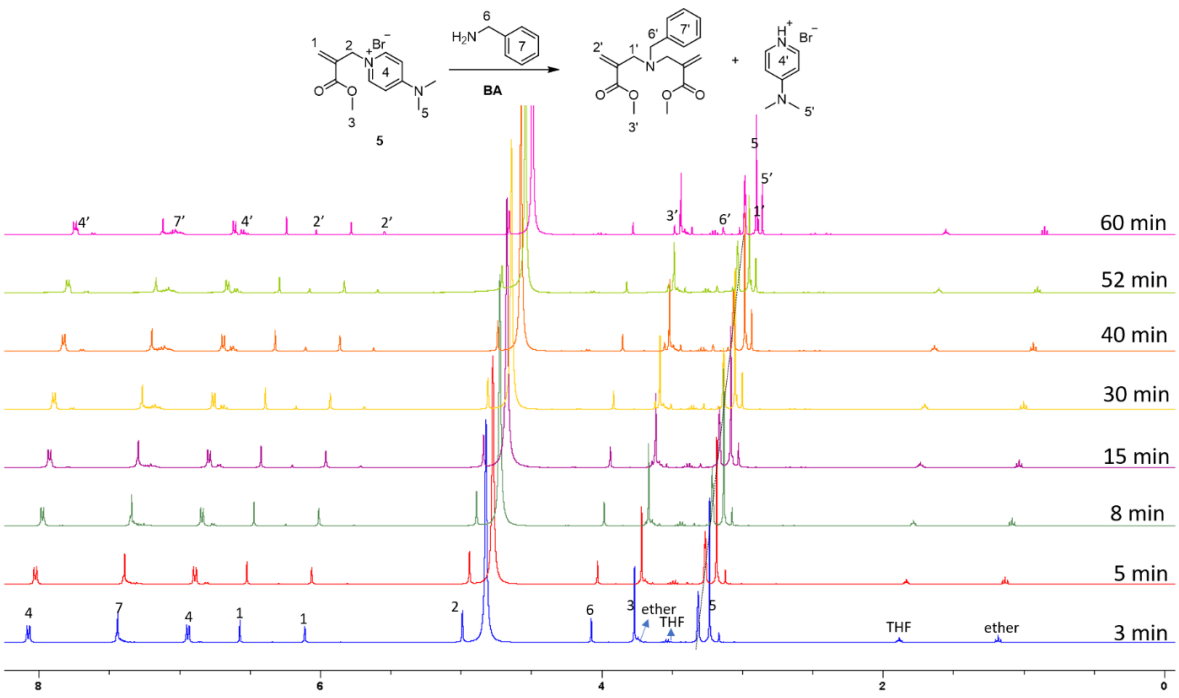


Figure S64 Amine-addition with **5**.

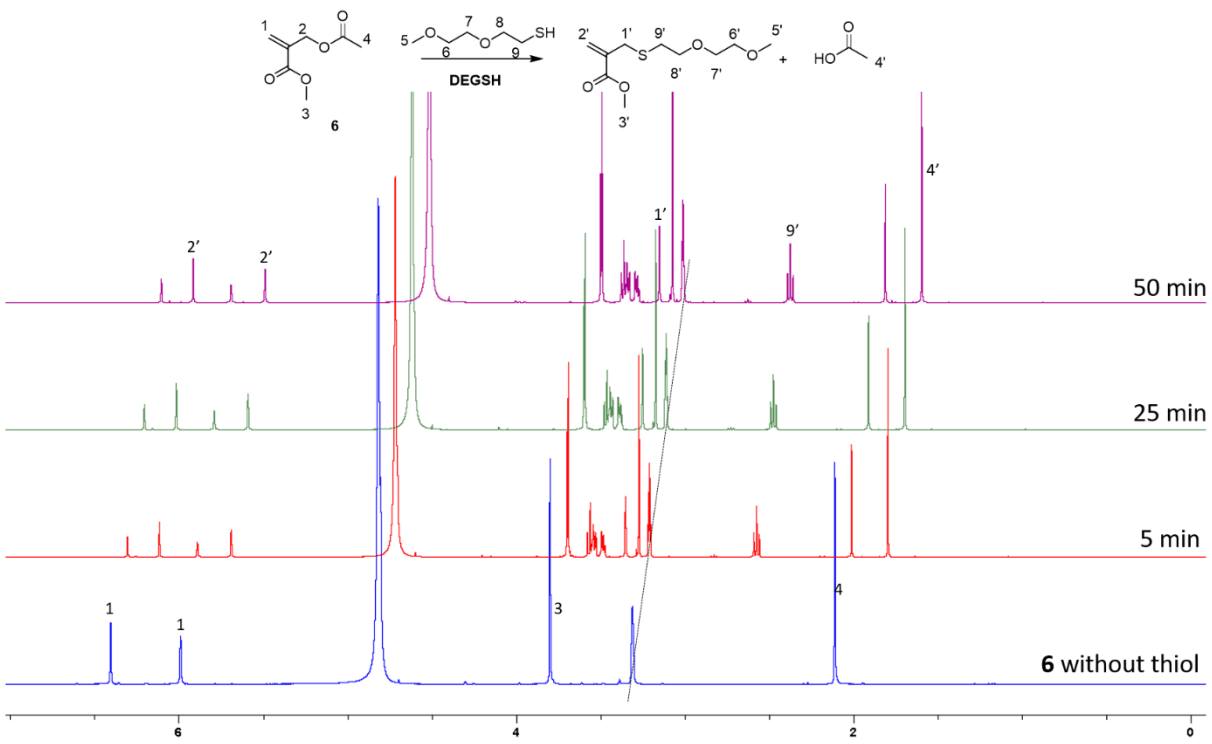


Figure S65 Thiol-addition with **6**.

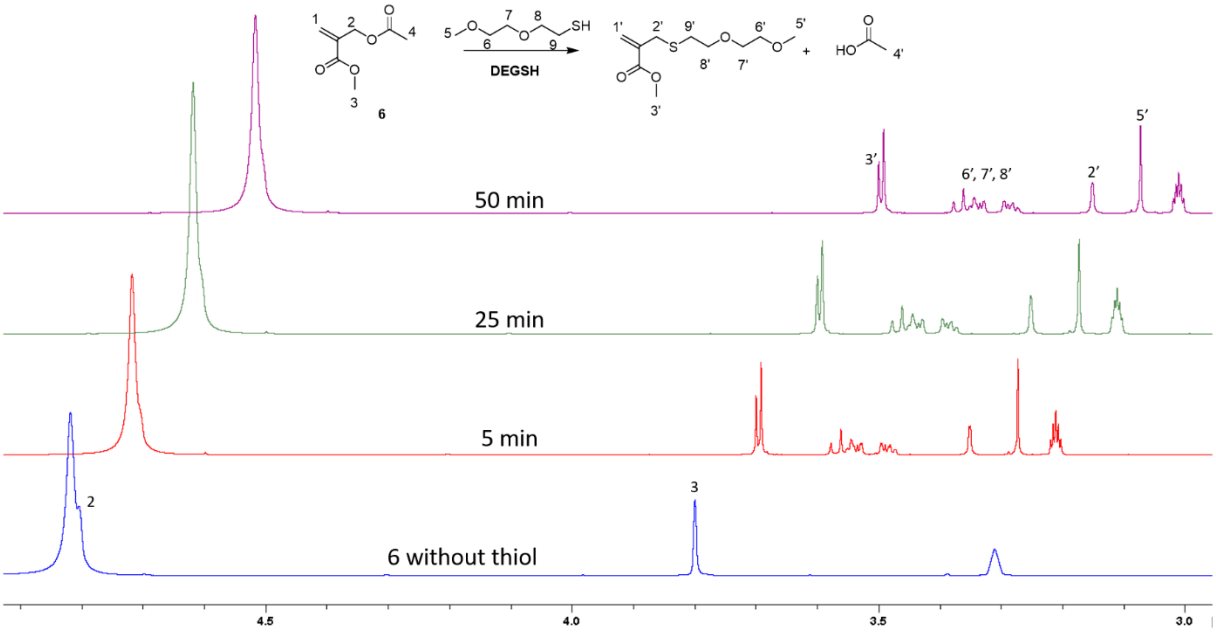


Figure S66 Zoom-in spectra of Figure S65.

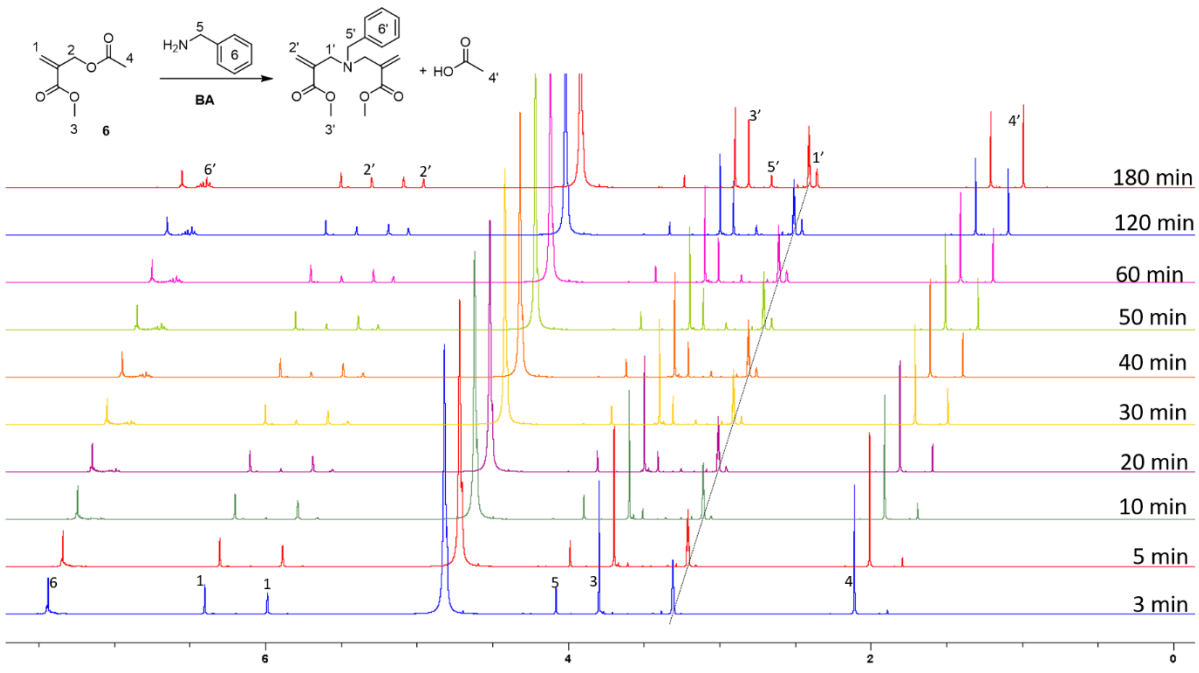


Figure S67 Amine-addition with **6** .

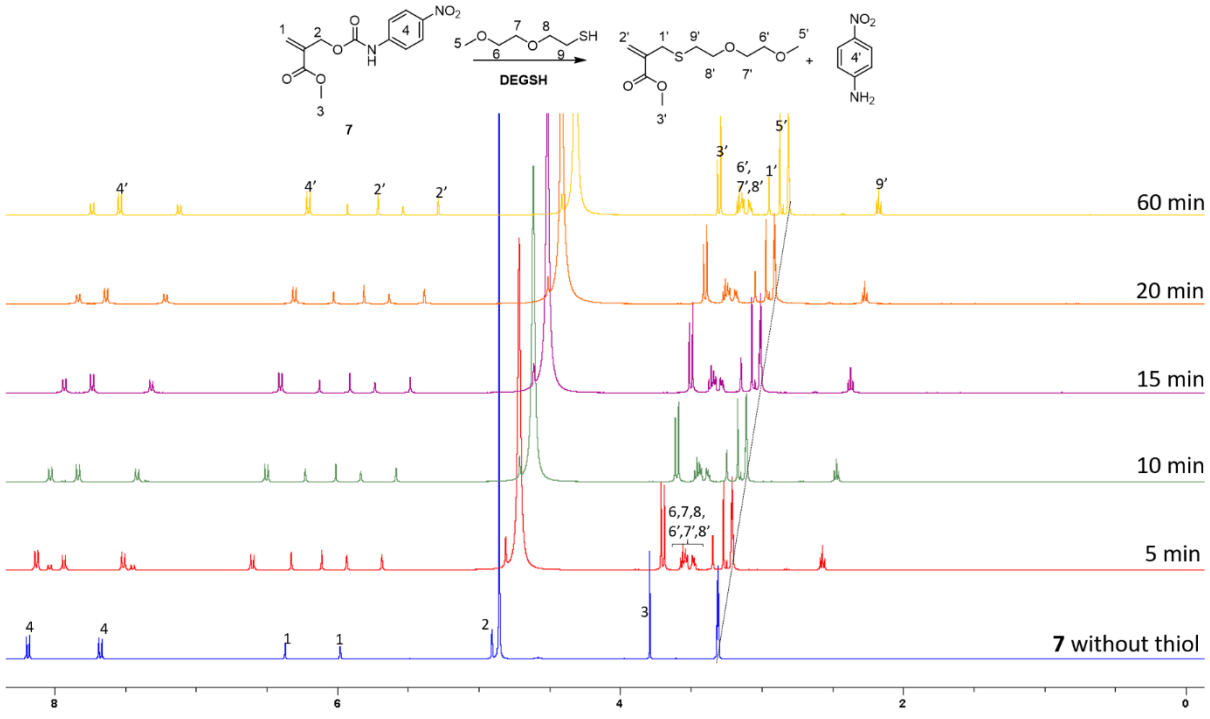


Figure S68 Thiol-addition with **7**.

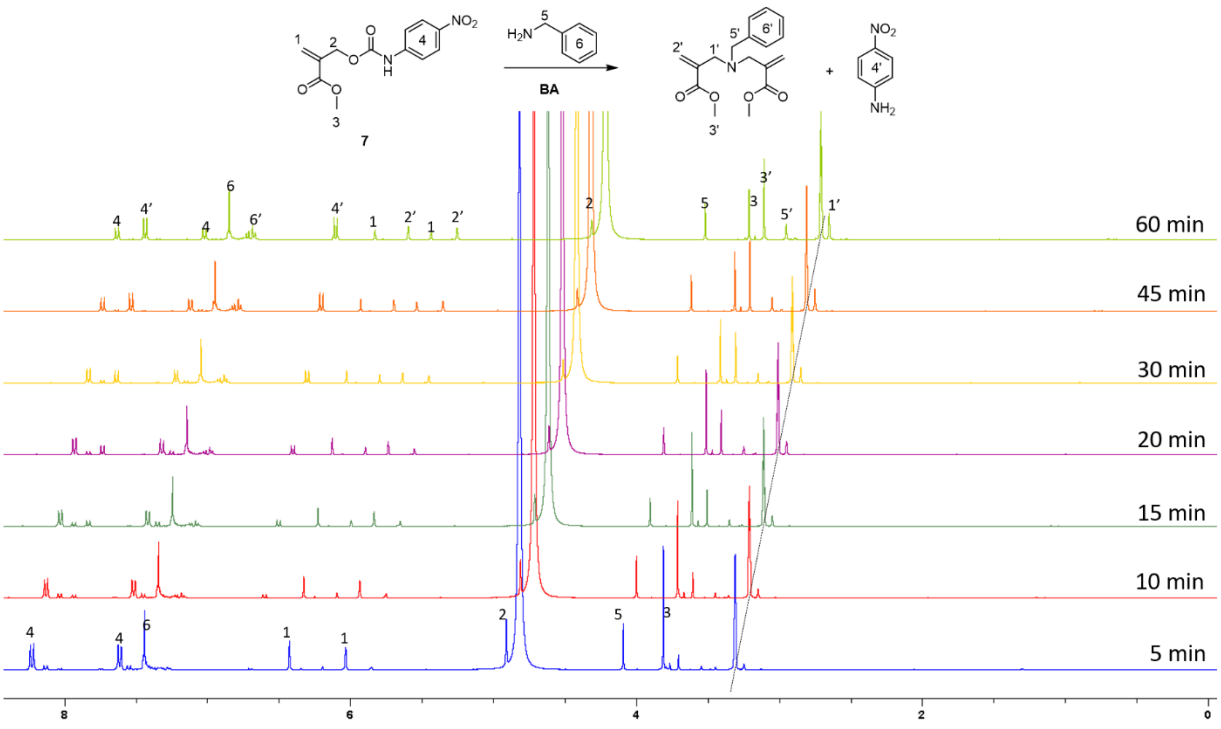


Figure S69 Amine-addition with **7**.

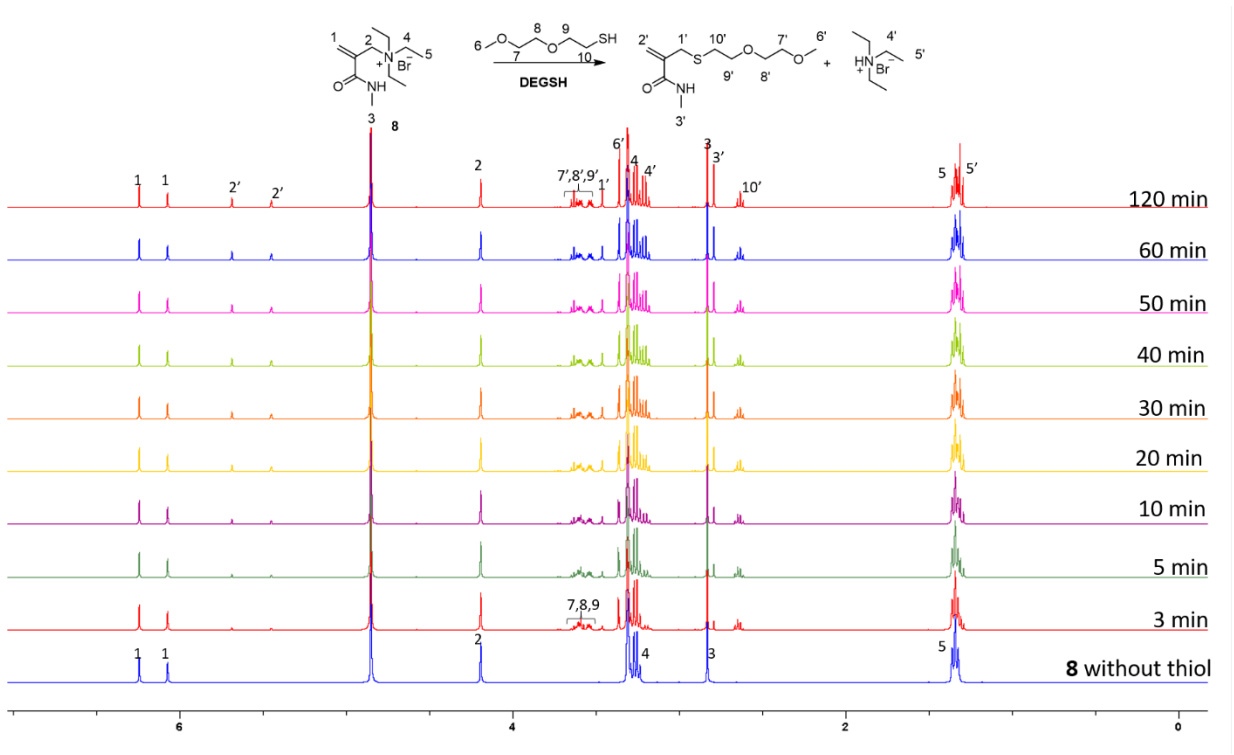


Figure S70 Thiol-addition with **8** .

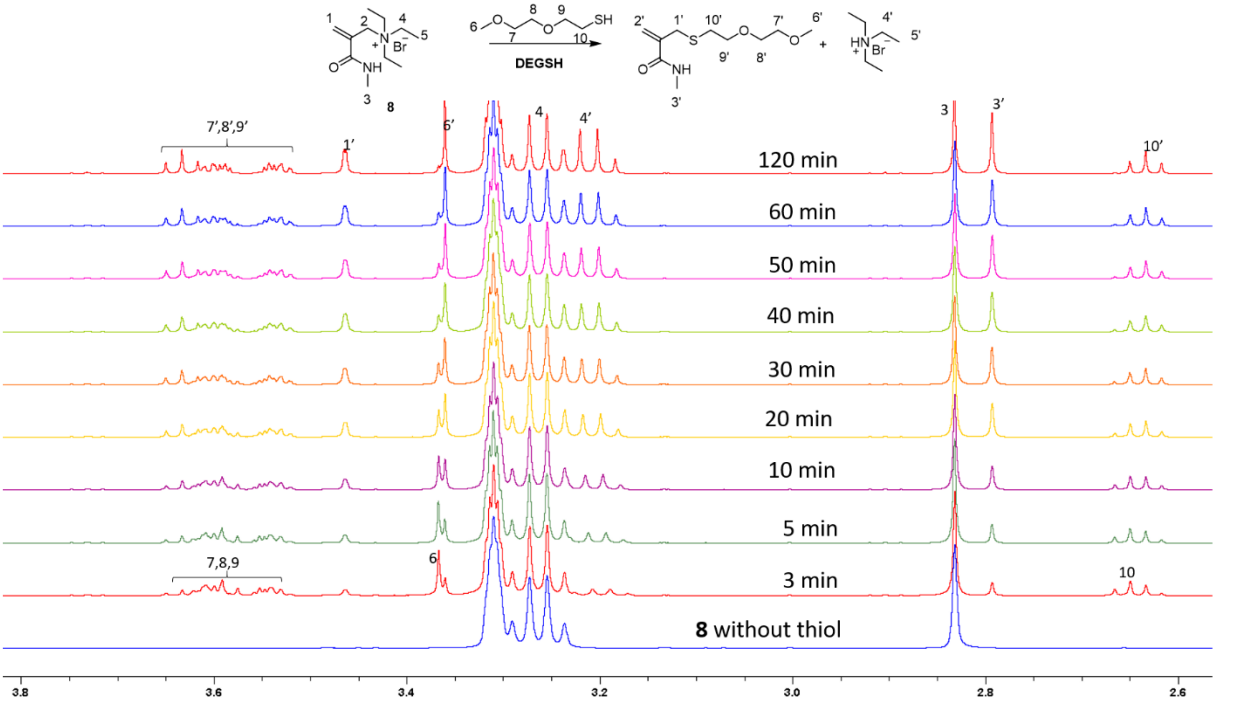


Figure S71 Zoon-in spectra of Figure S70.

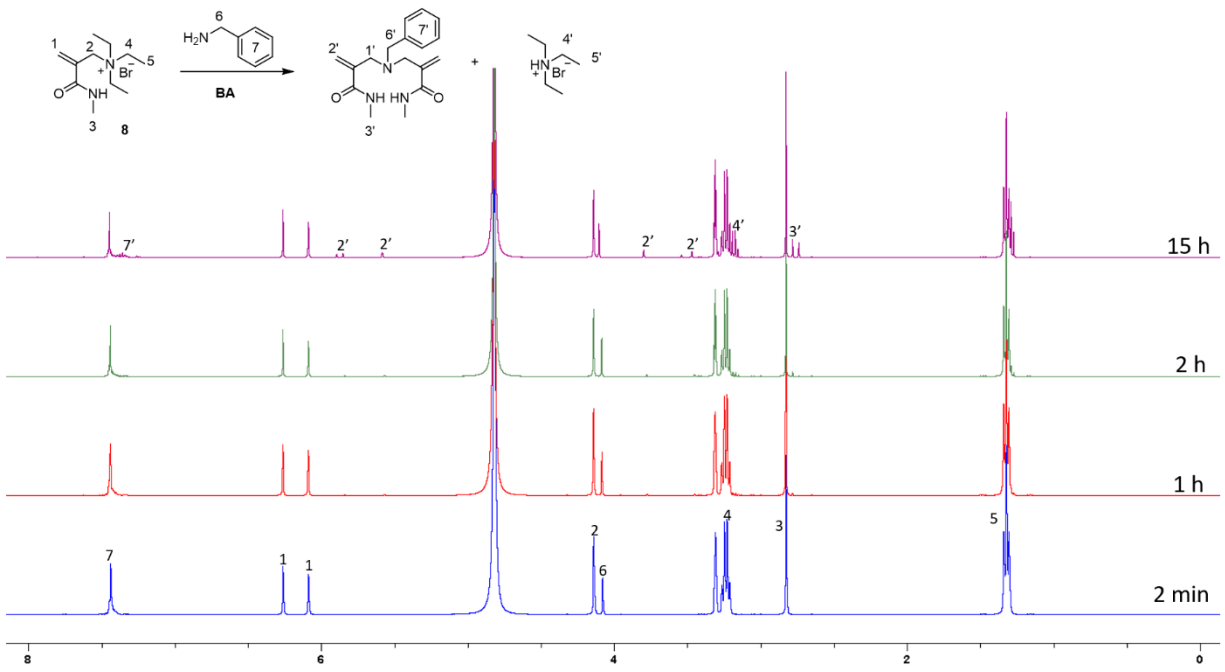


Figure S72 Amine-addition with **8**.

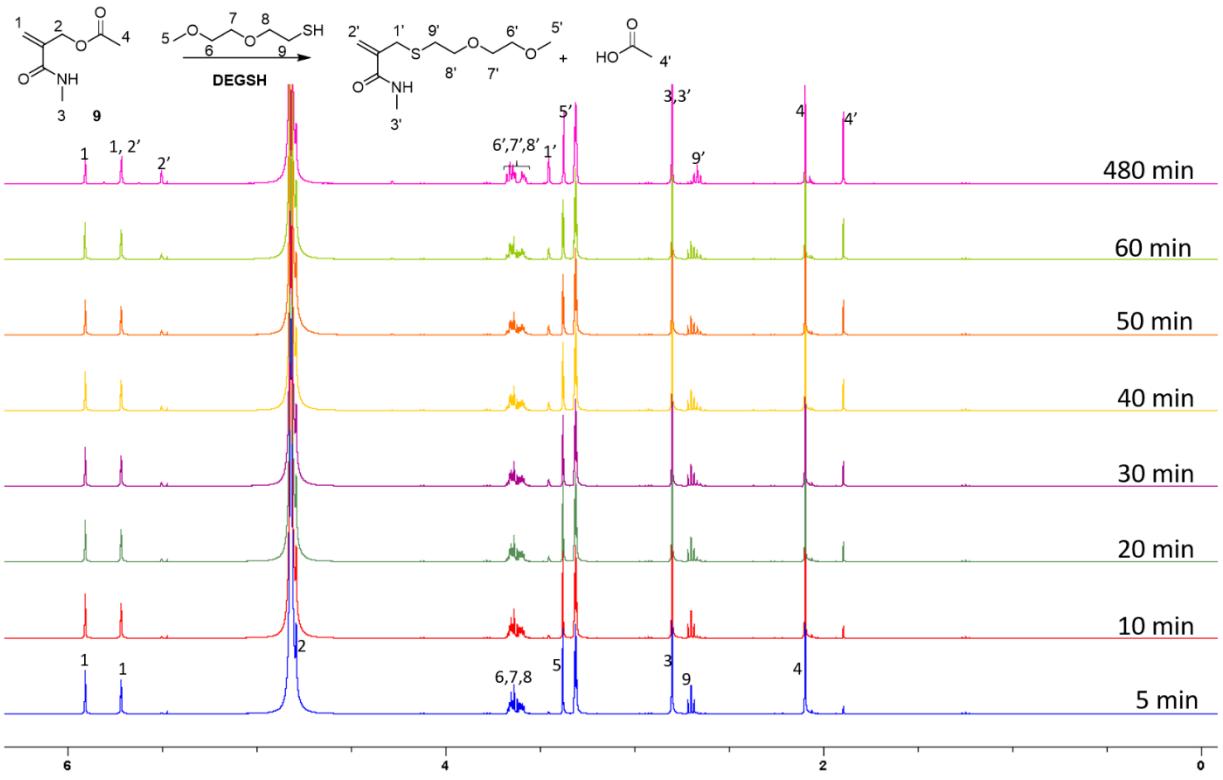


Figure S73 Thiol-addition with **9** .

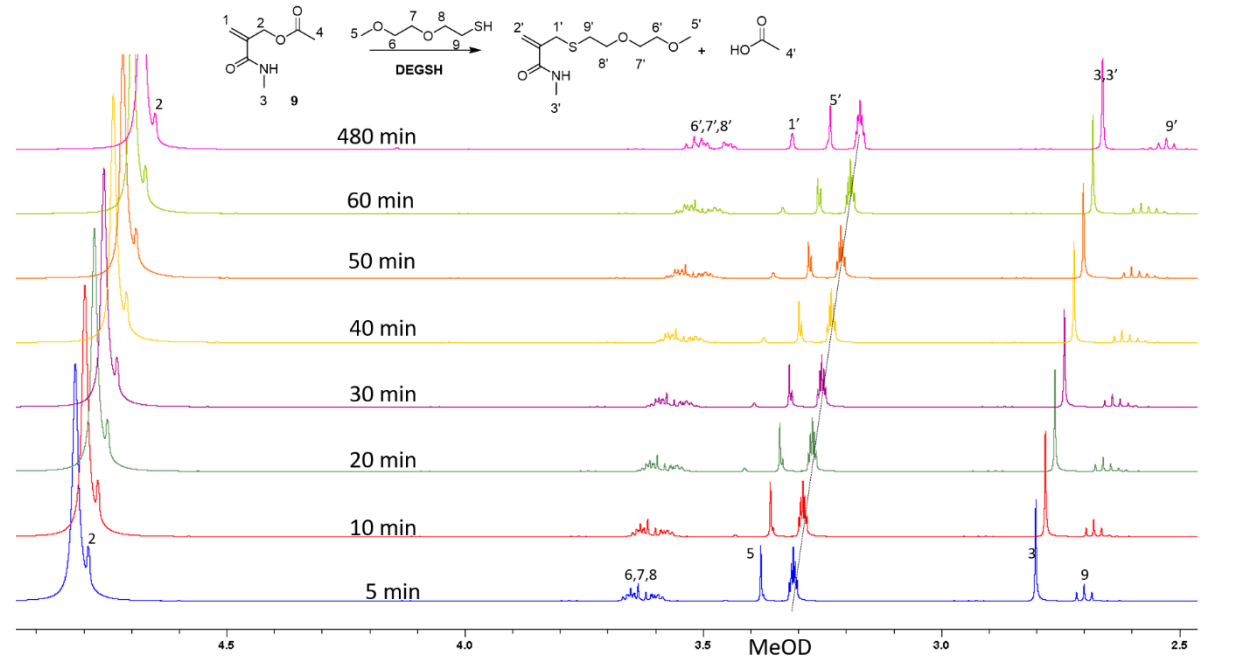


Figure S74 Zoom in spectra of Figure S73.

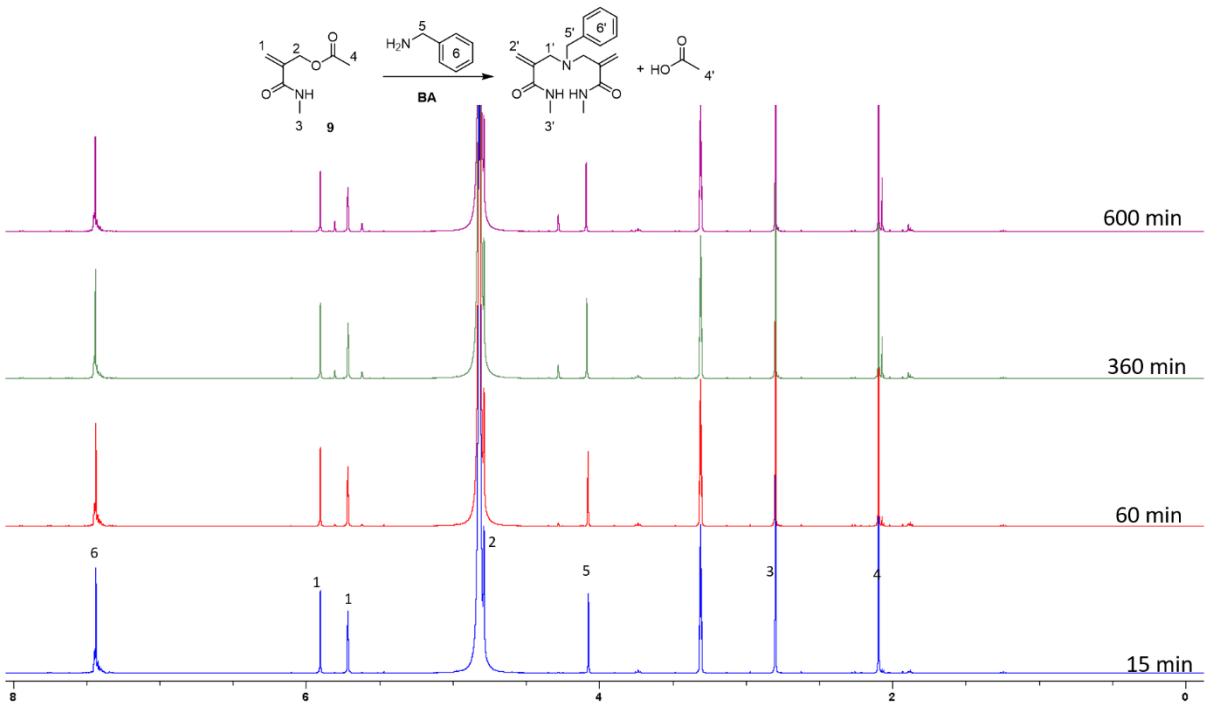


Figure S75 Amine-addition with **9**.

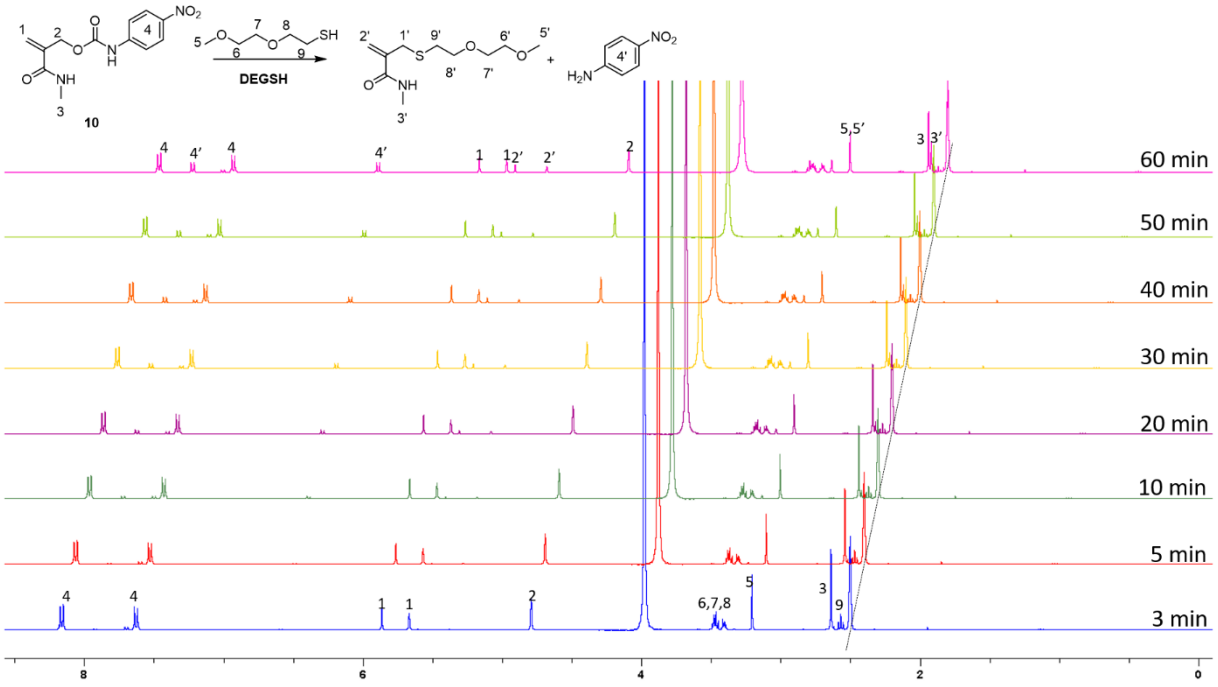


Figure S76 Thiol-addition with **10** .

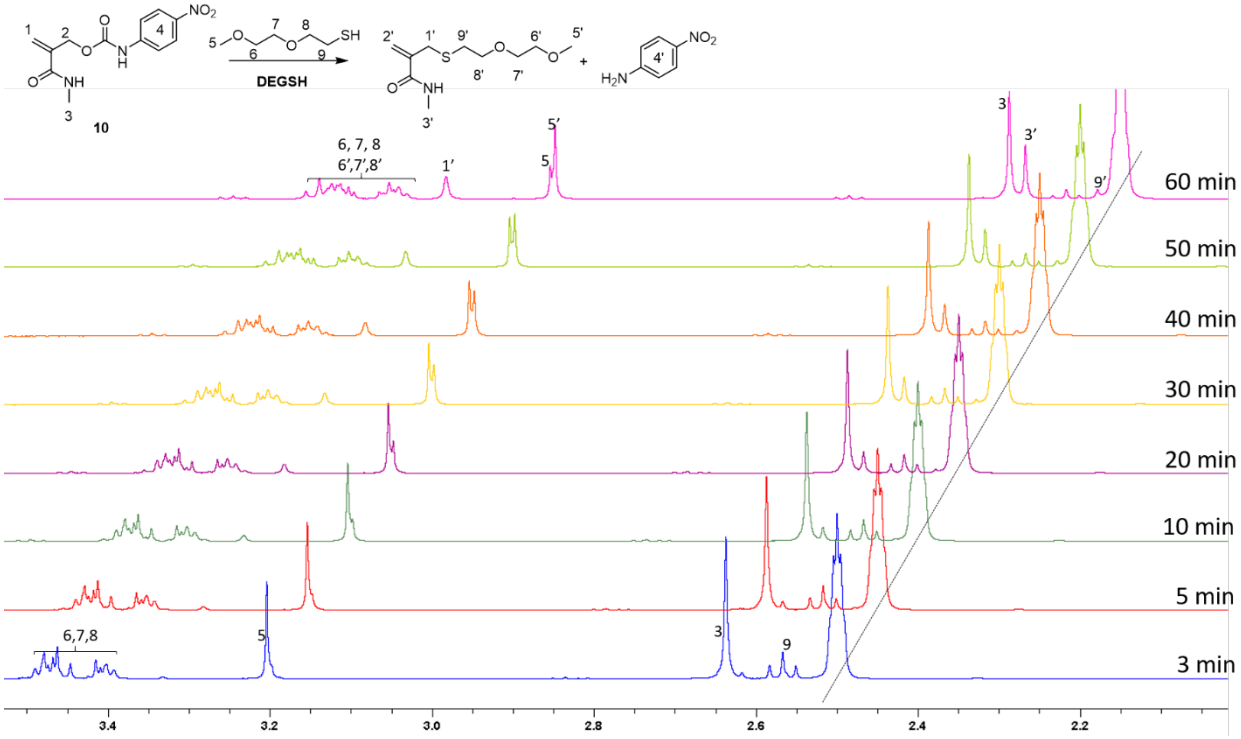


Figure S77 Zoon-in spectra of Figure 76.

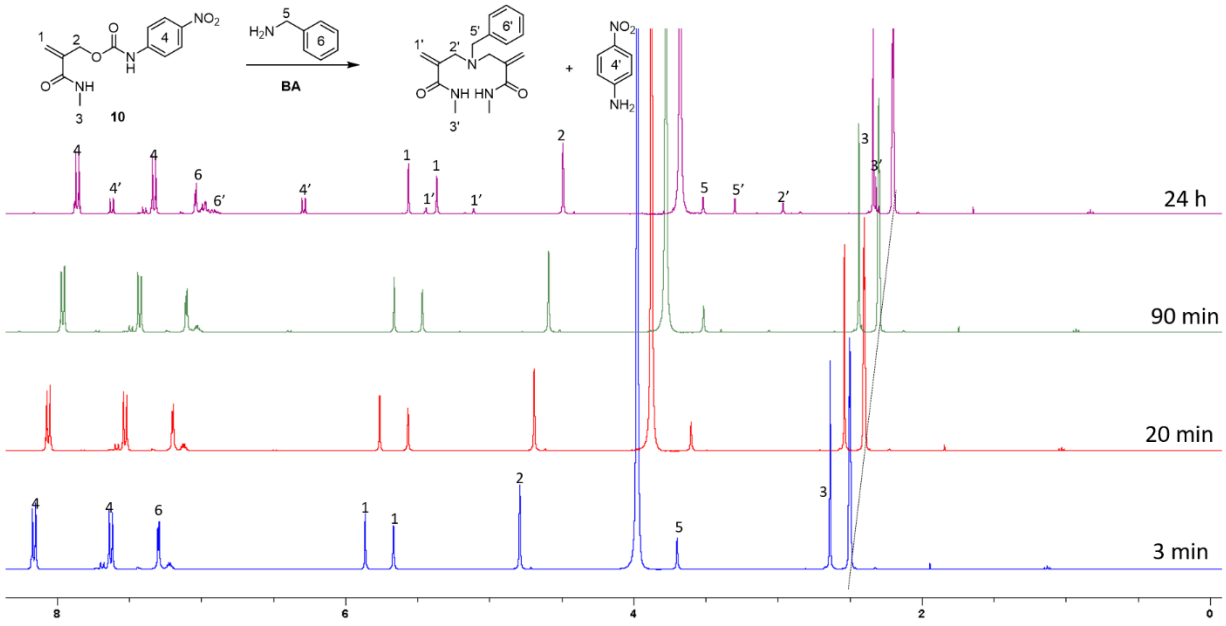


Figure S78 Amine-addition with **10**.

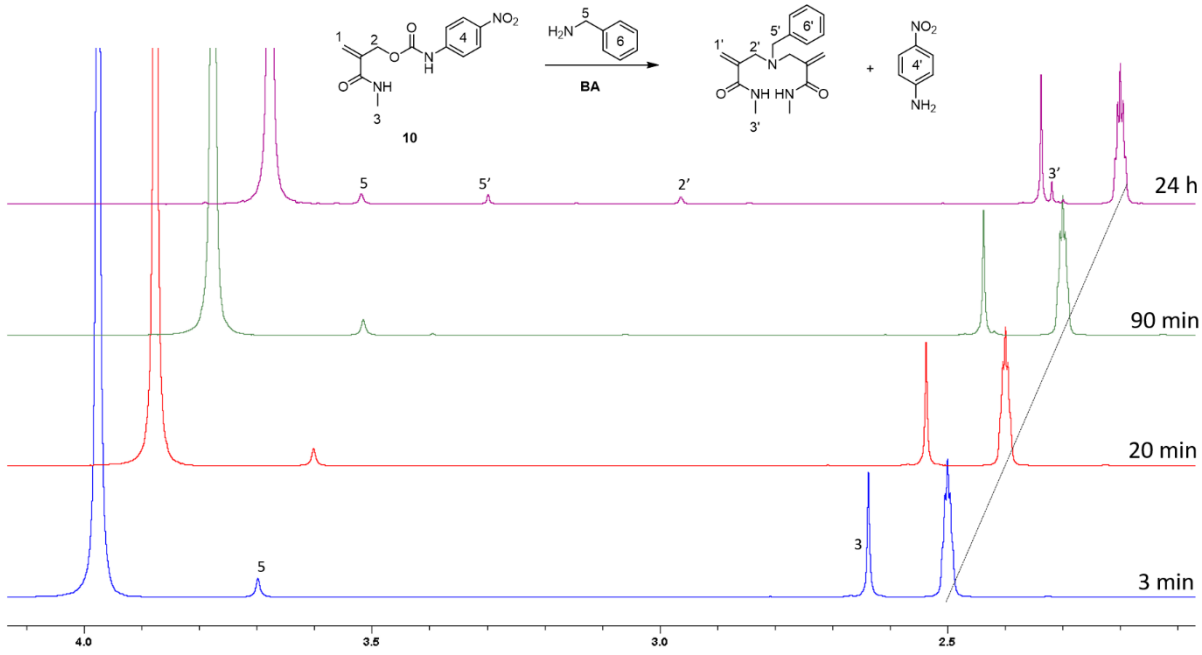


Figure S79 Zoom-in spectra of Figure S78.

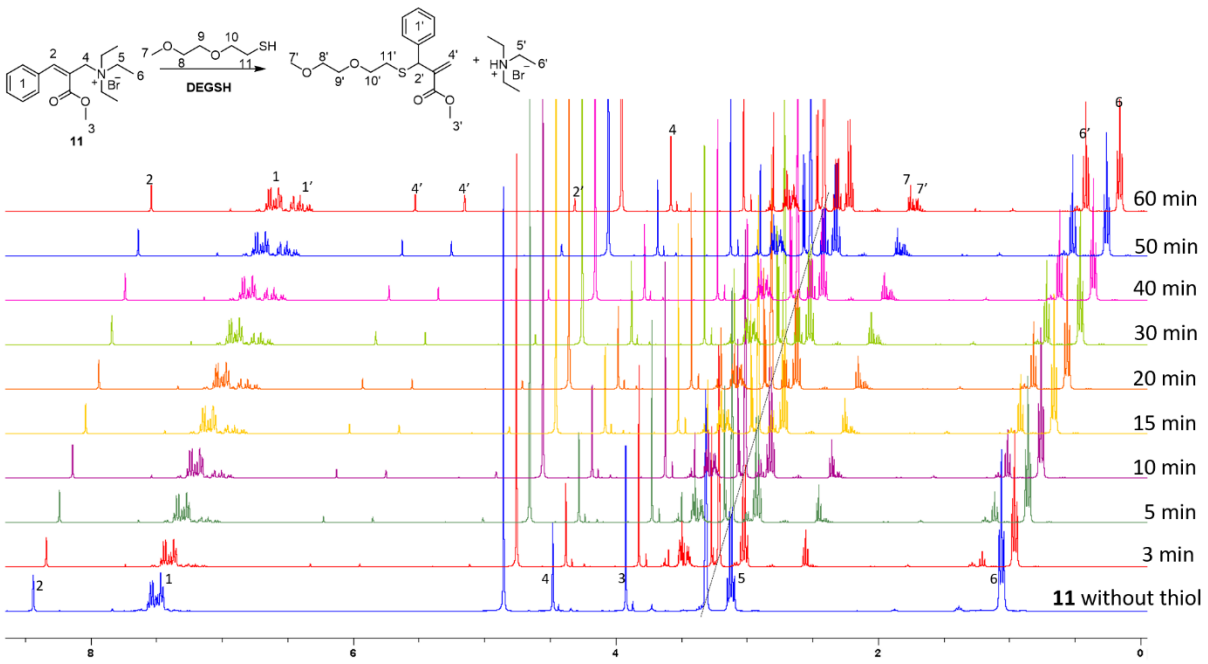


Figure S80 Thiol-addition with **11**.

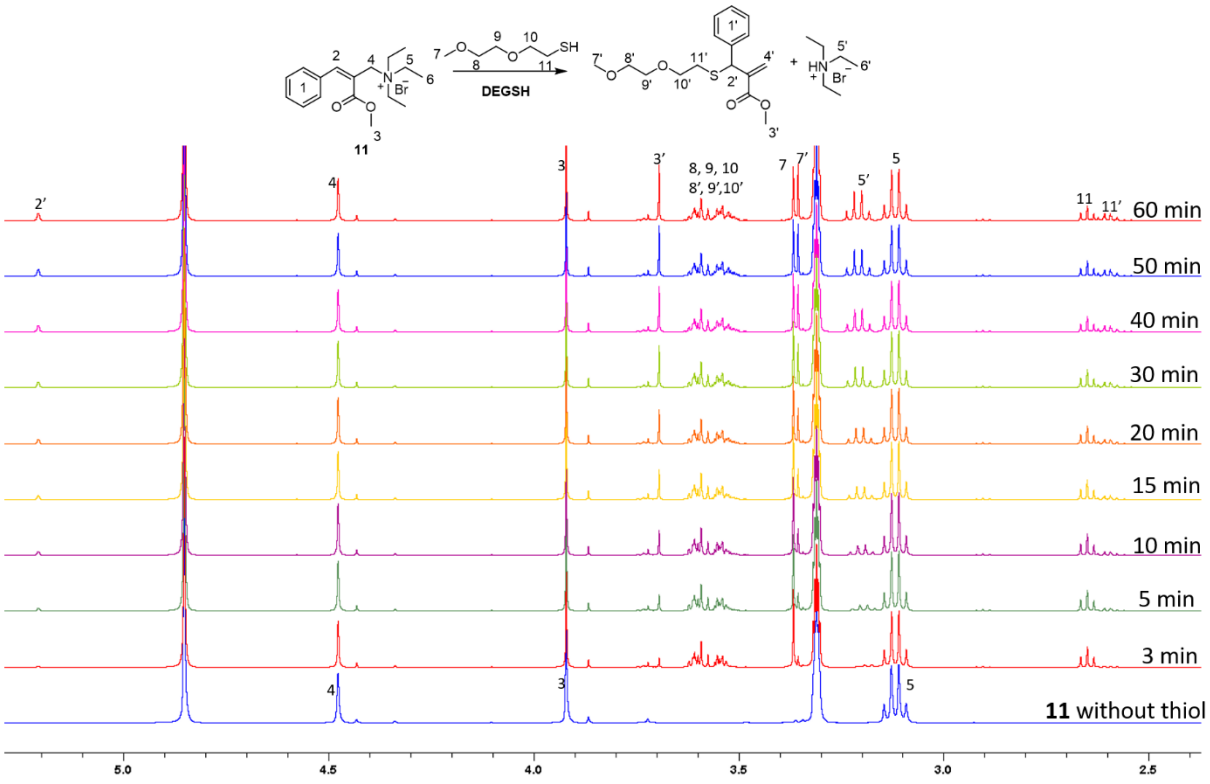


Figure S81 Zoom-in spectra of Figure S80.

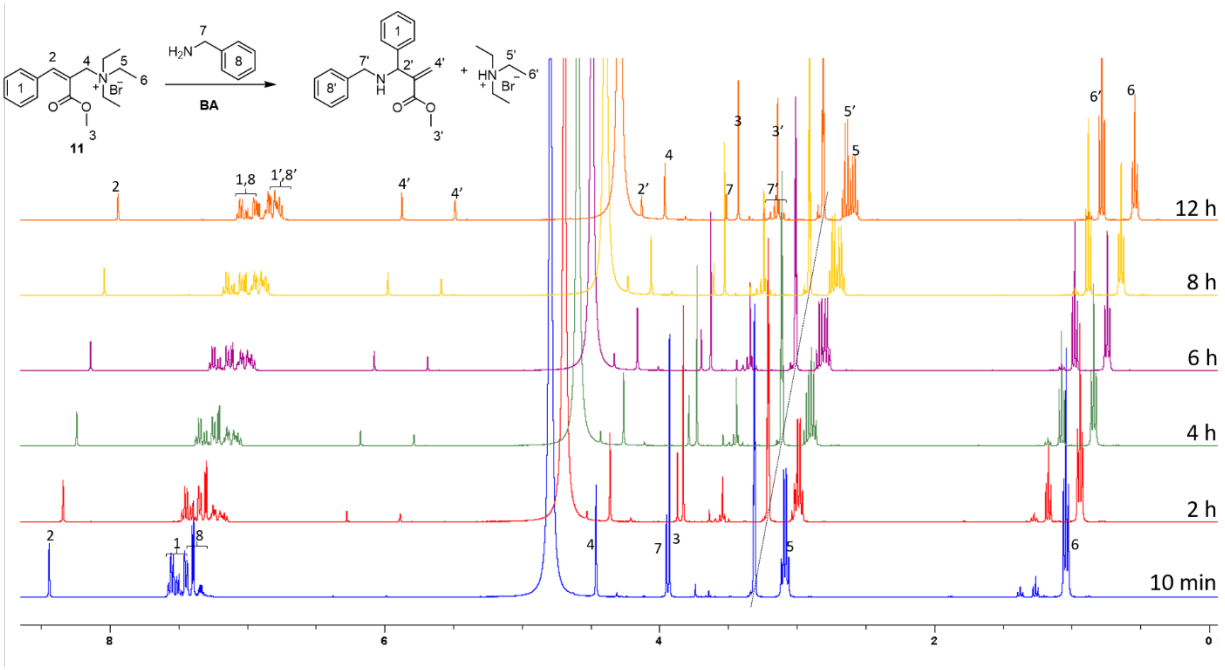


Figure S82 Amine-addition reaction with **11.**

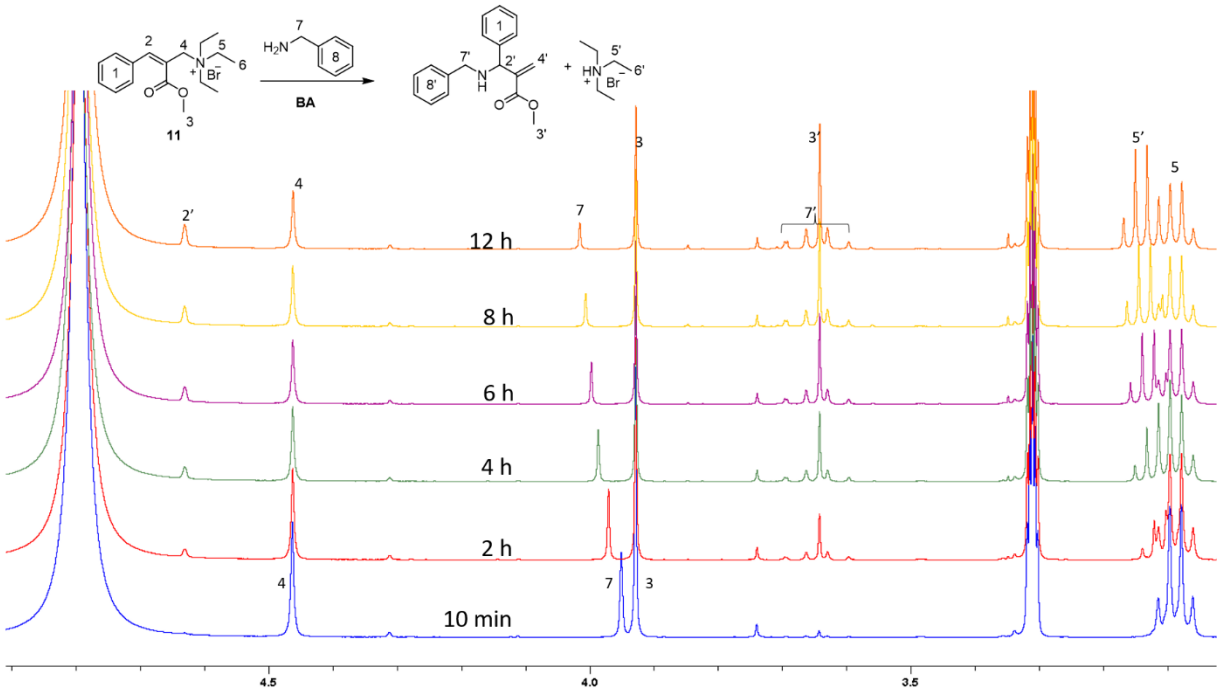


Figure S83 Zoom-in spectra of Figure S82

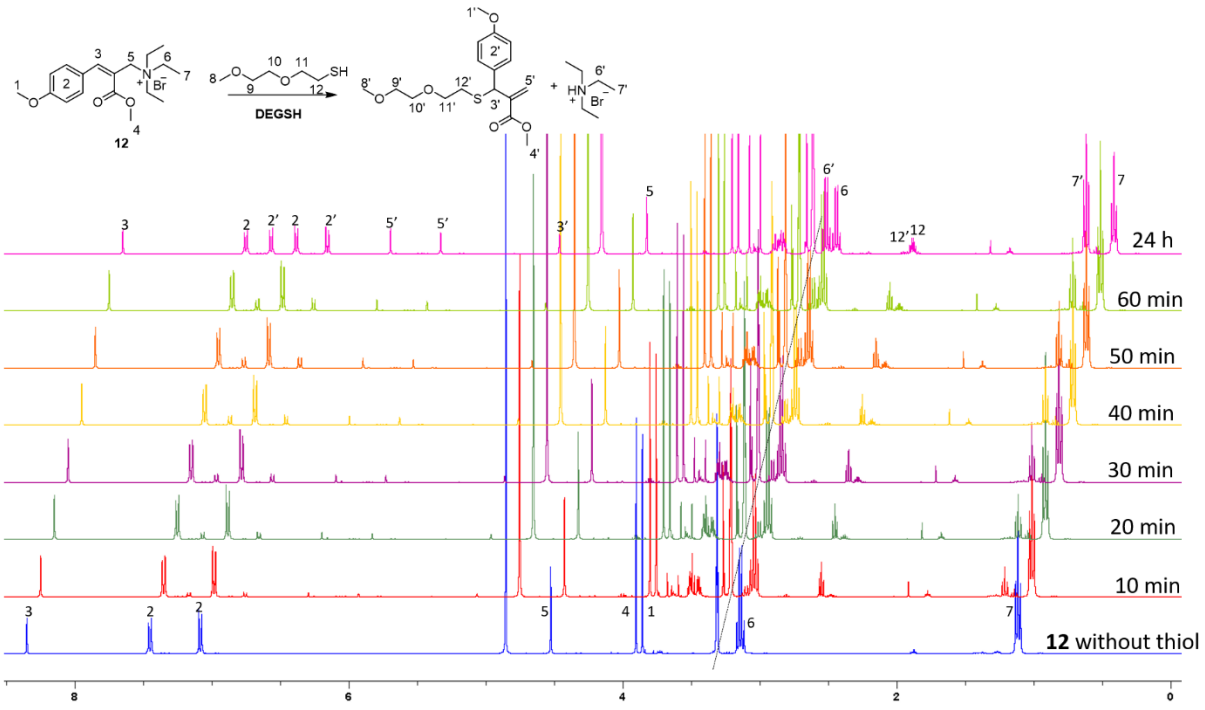


Figure S84 Thiol-addition with **12**.

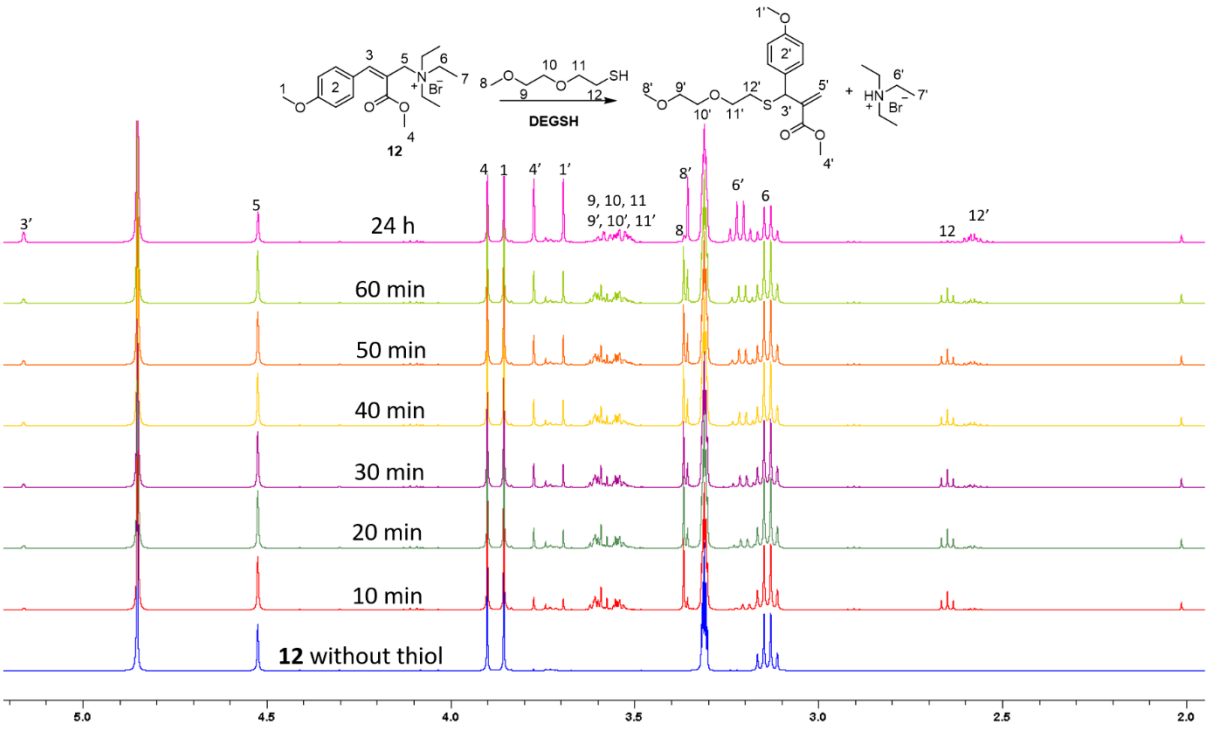


Figure S85 Zoom-in spectra of Figure S84.

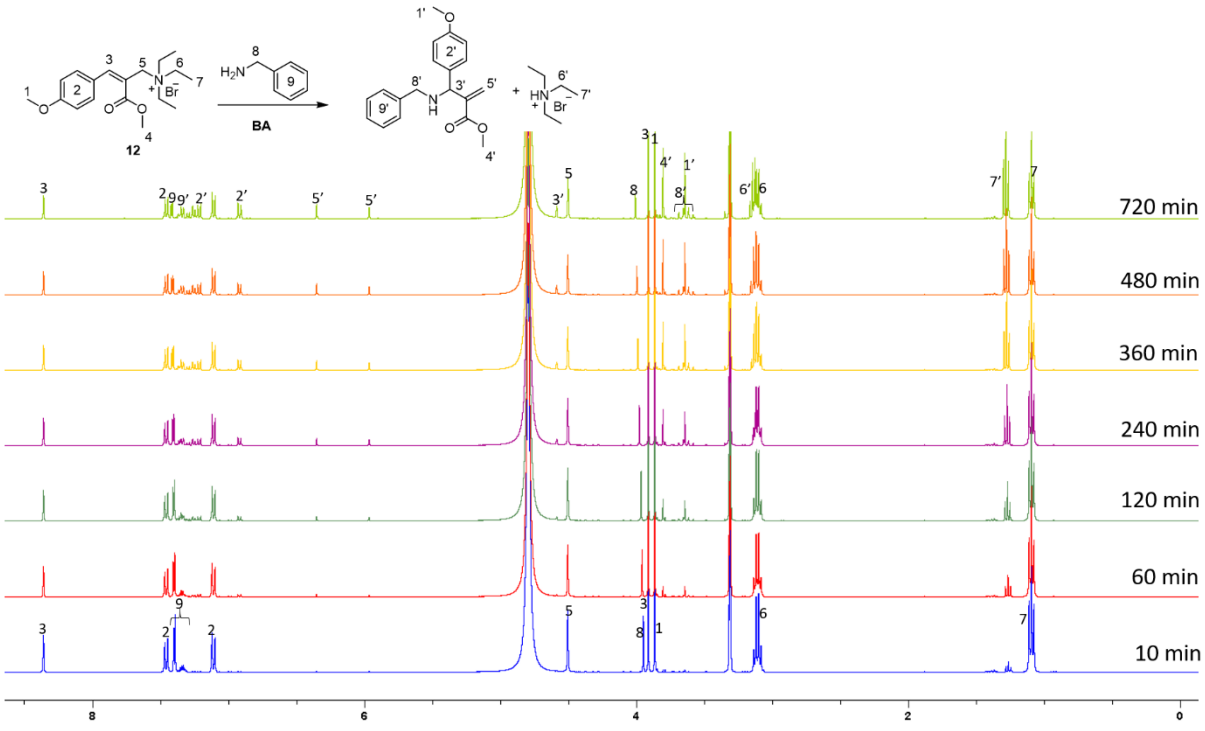


Figure S86 Amine-addition reaction with **12**.

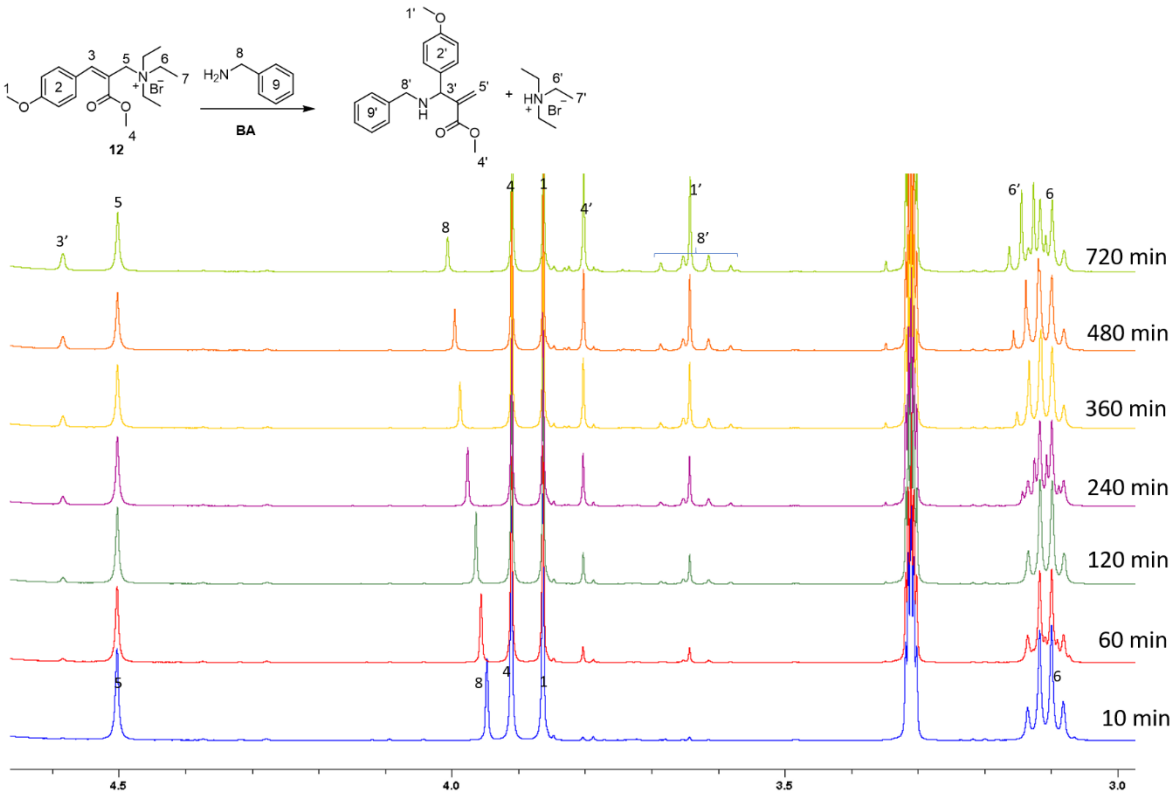


Figure S87 Zoom-in spectra of Figure S86.

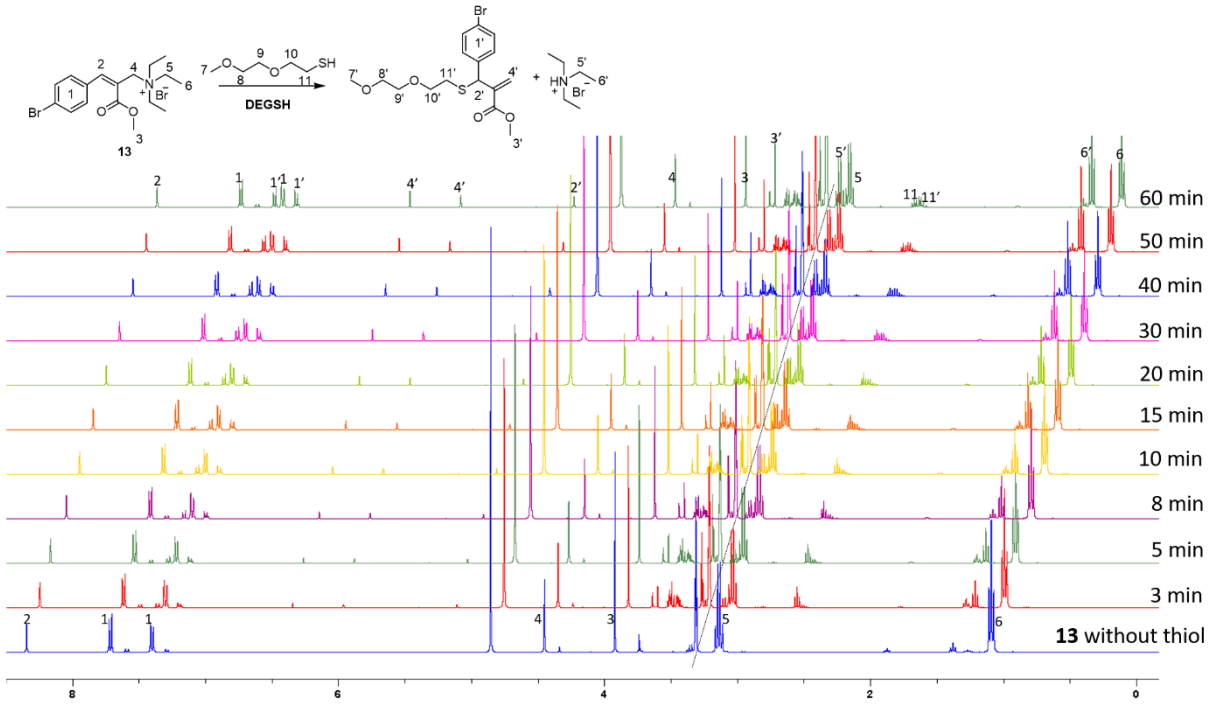


Figure S88 Thiol-addition with **13**.

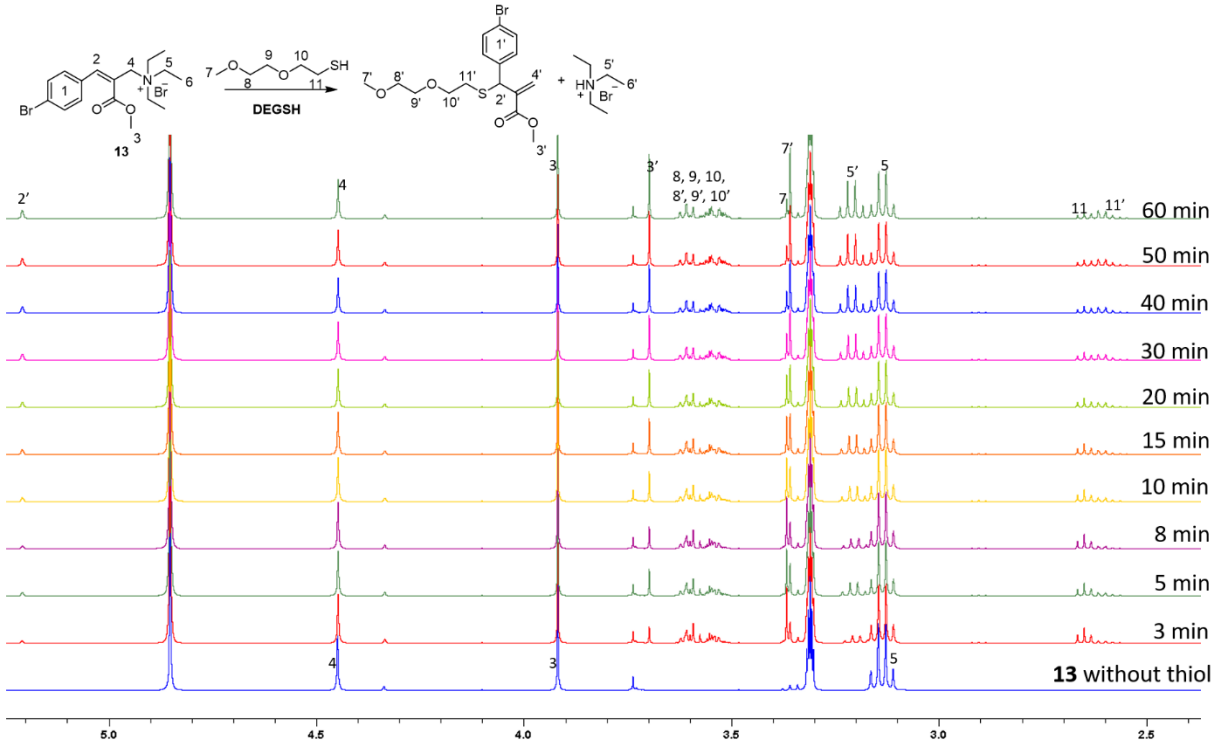


Figure S89 Zoom-in spectra of Figure S88.

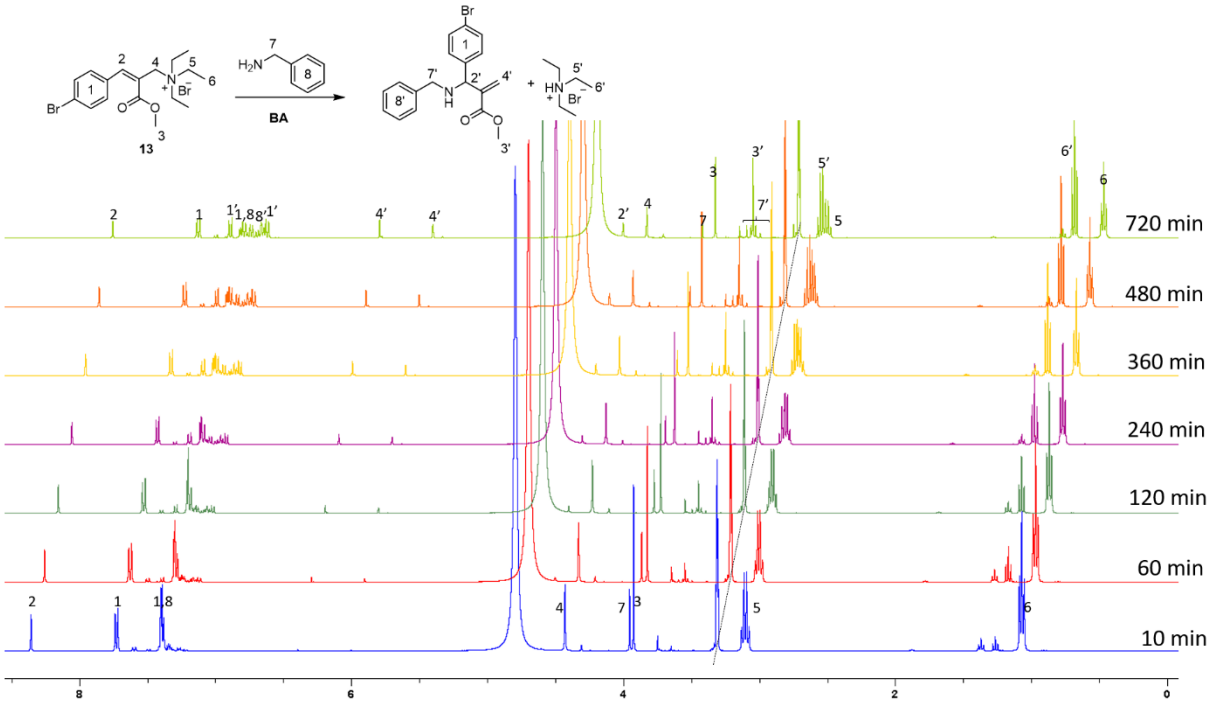


Figure S90 Amine-addition with **13.**

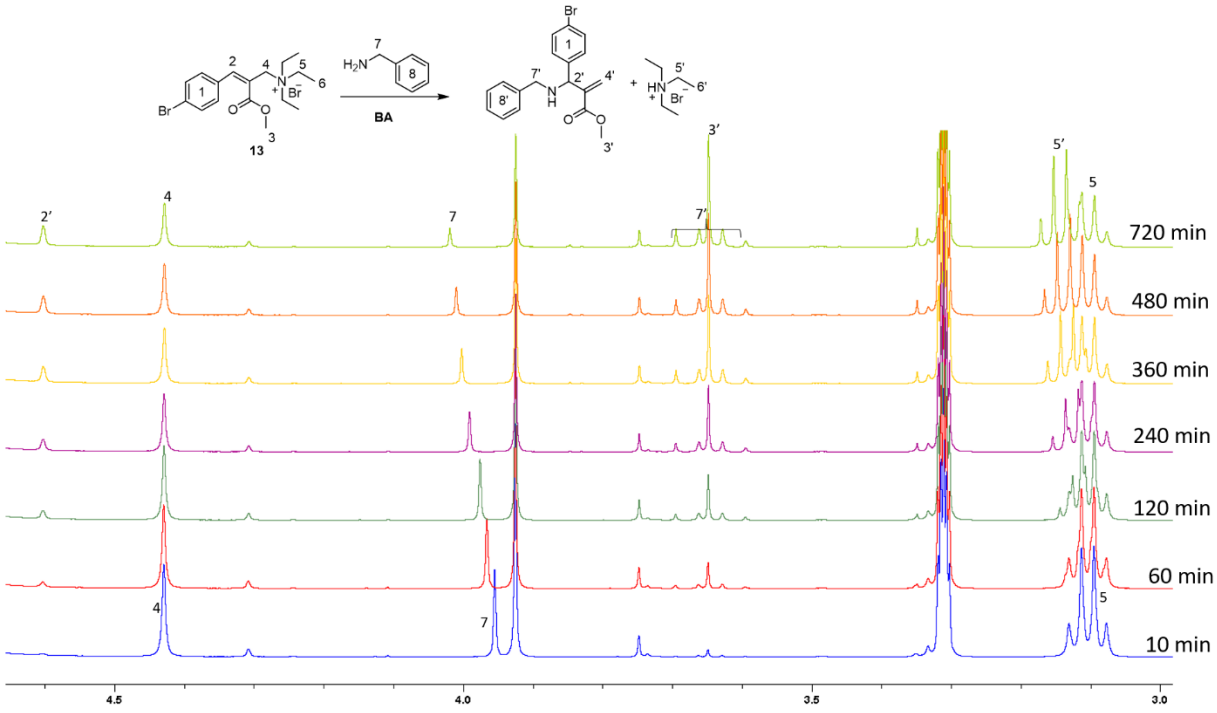


Figure S91 Zoom-in spectra of Figure S90.

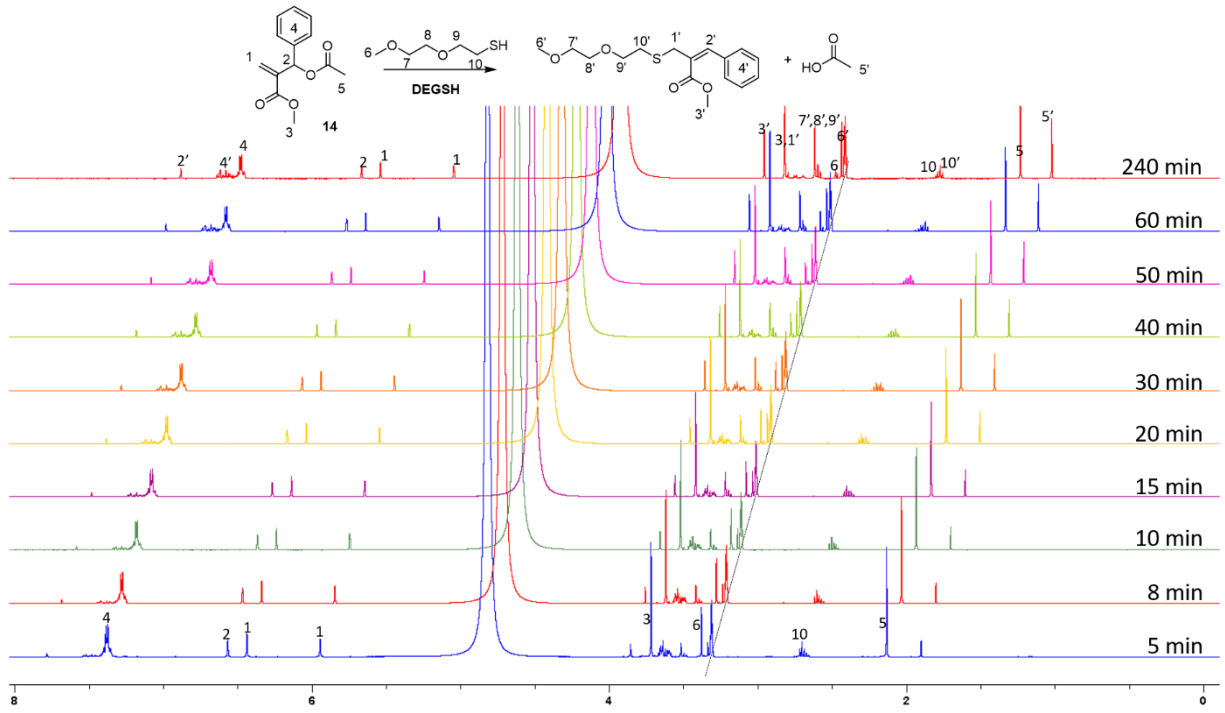


Figure S92 Thiol-addition with **14**.

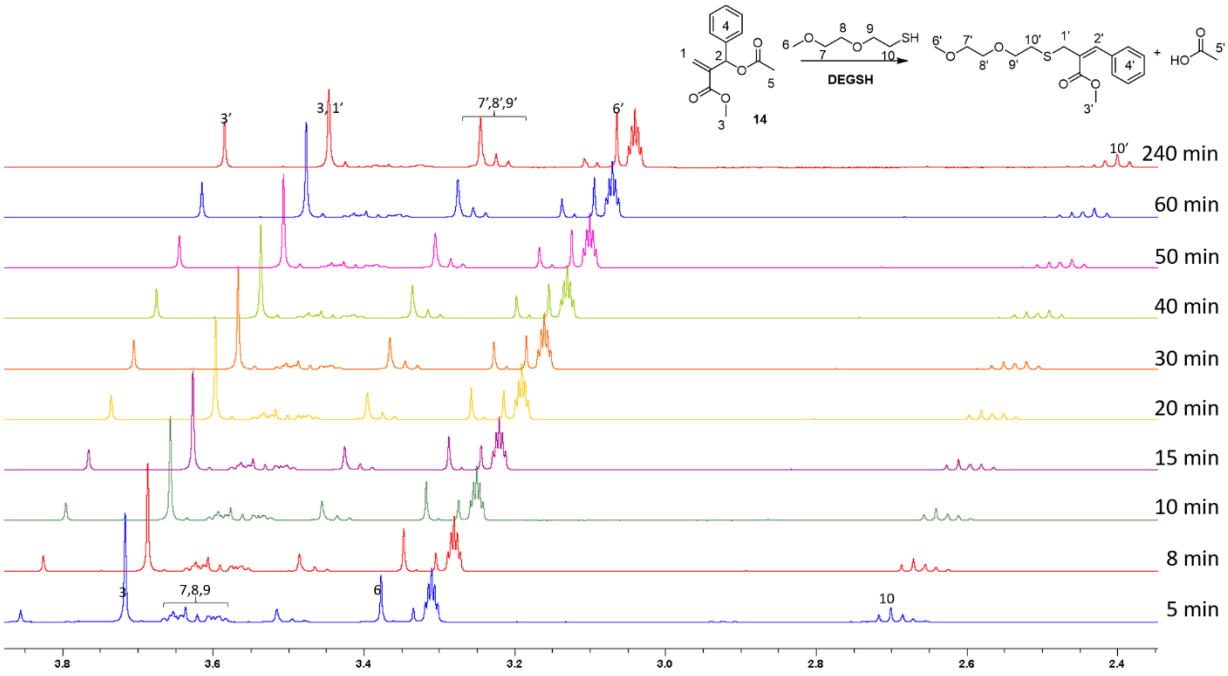


Figure S93 Zoom-in spectra of Figure S92.

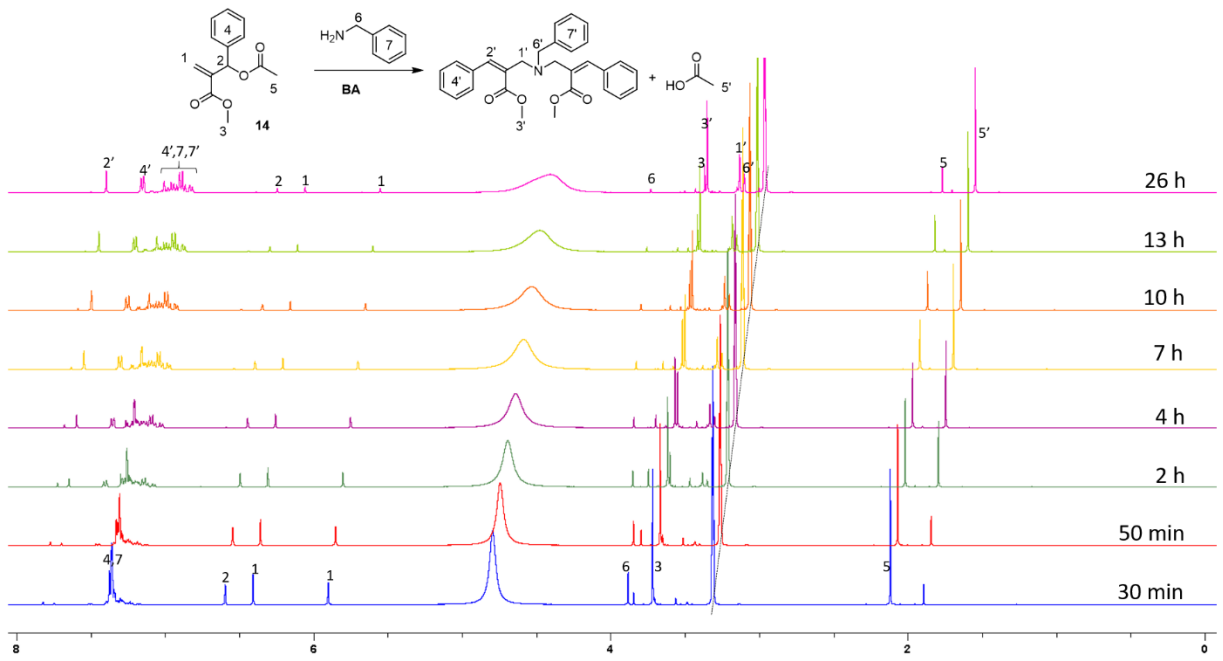


Figure S94 Amine-addition with **14** .

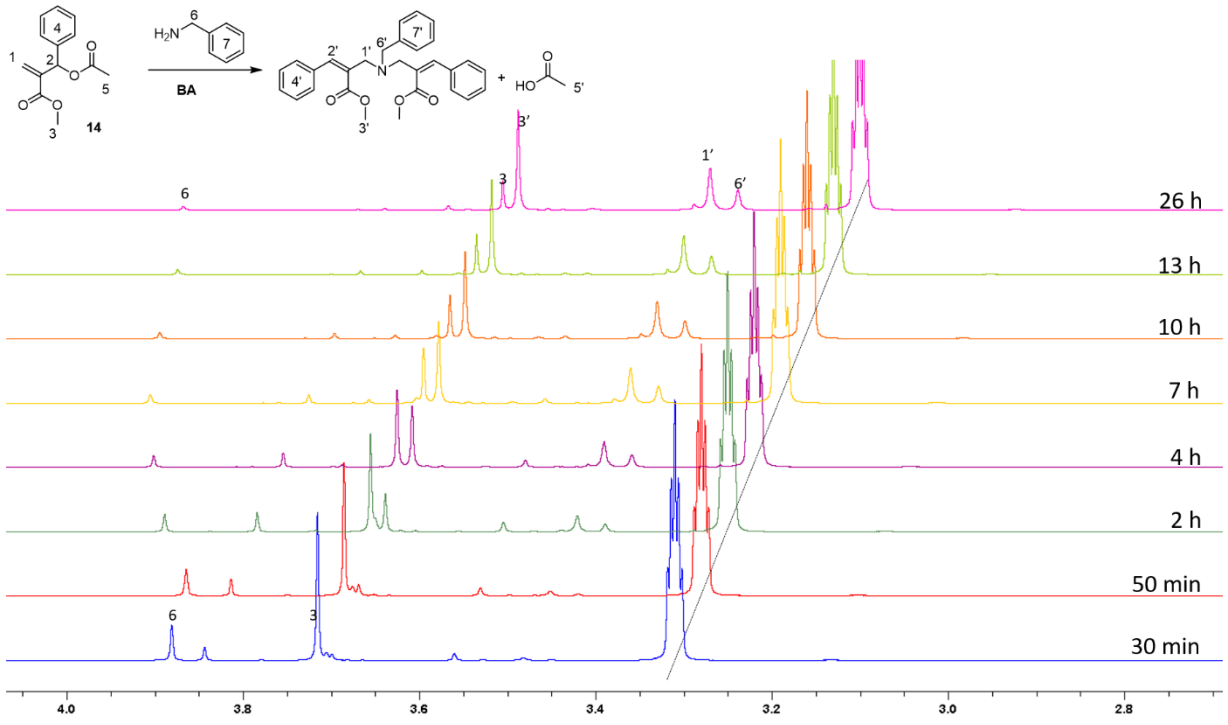


Figure S95 Zoom-in spectra of Figure S94.

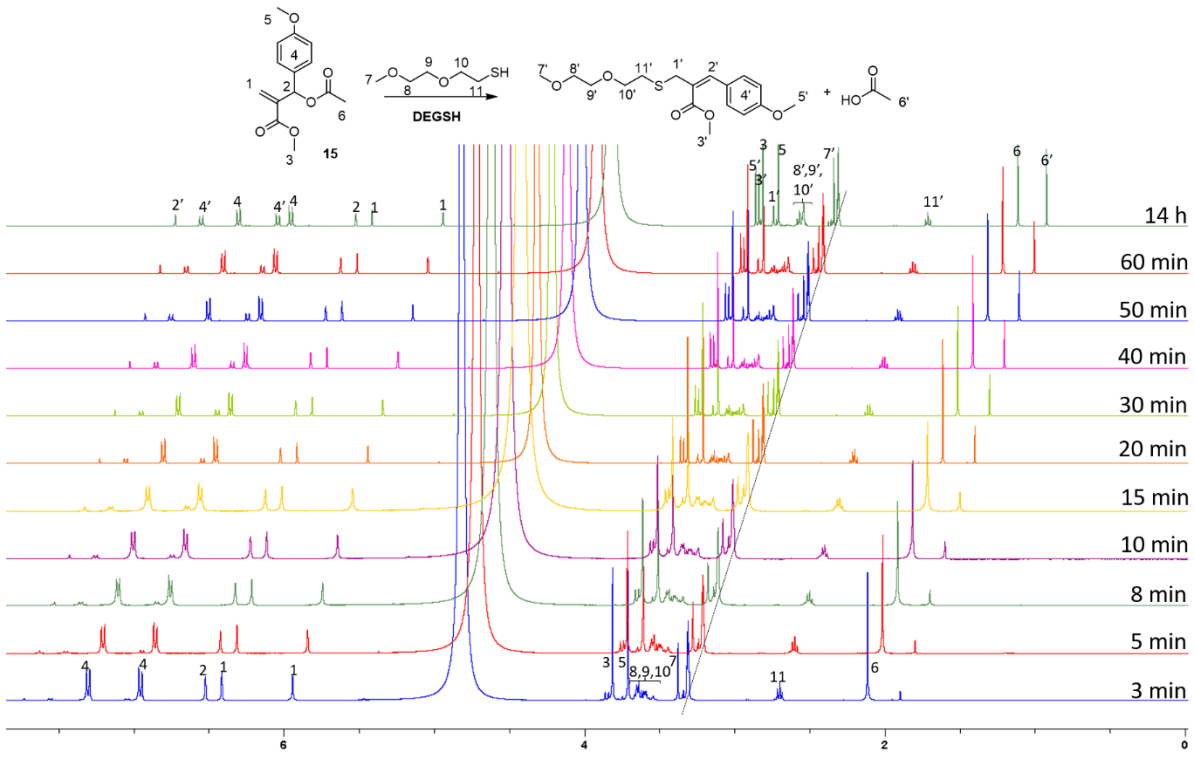


Figure S96 Thiol-addition with **15.**

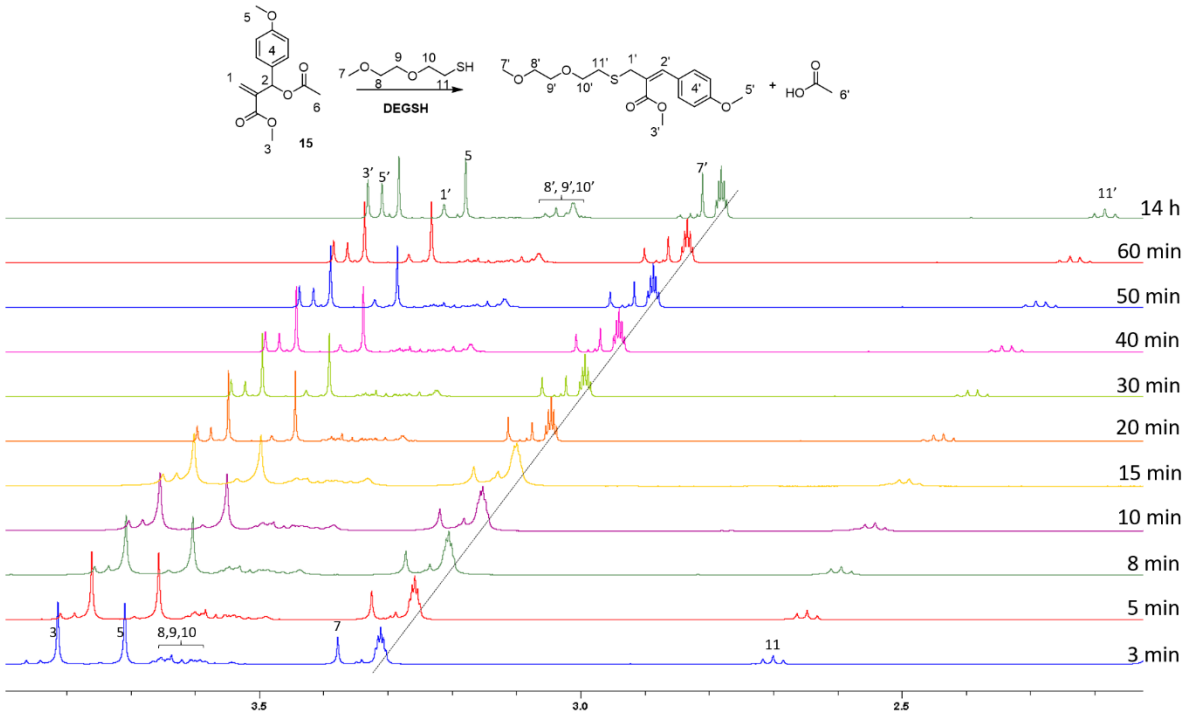


Figure S97 Zoom-in spectra of Figure S96.

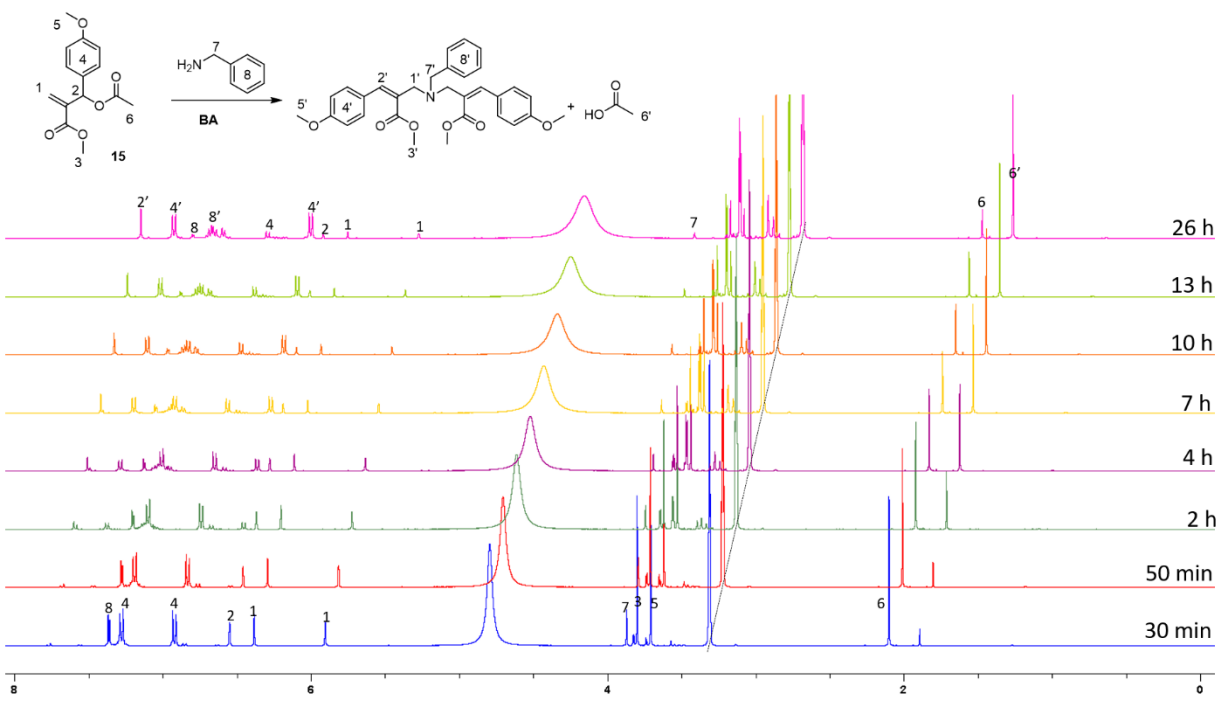


Figure S98 Amine-addition with **15** .

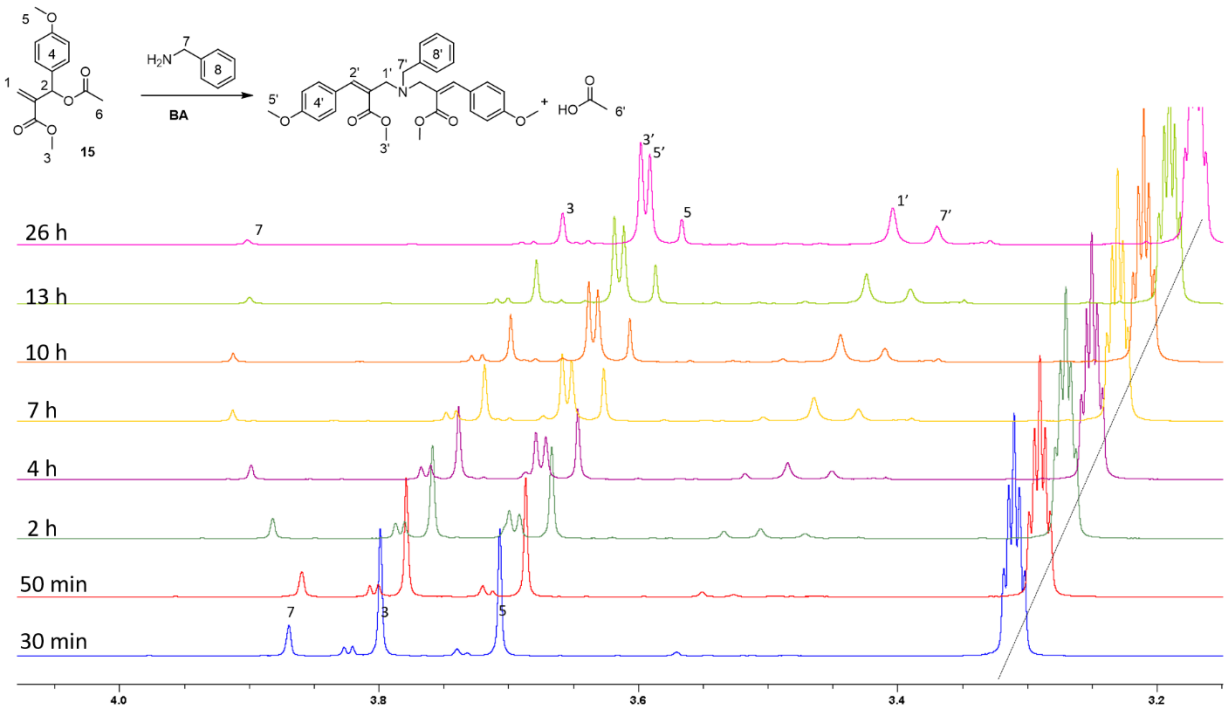


Figure S99 Zoom-in spectra of Figure S98.

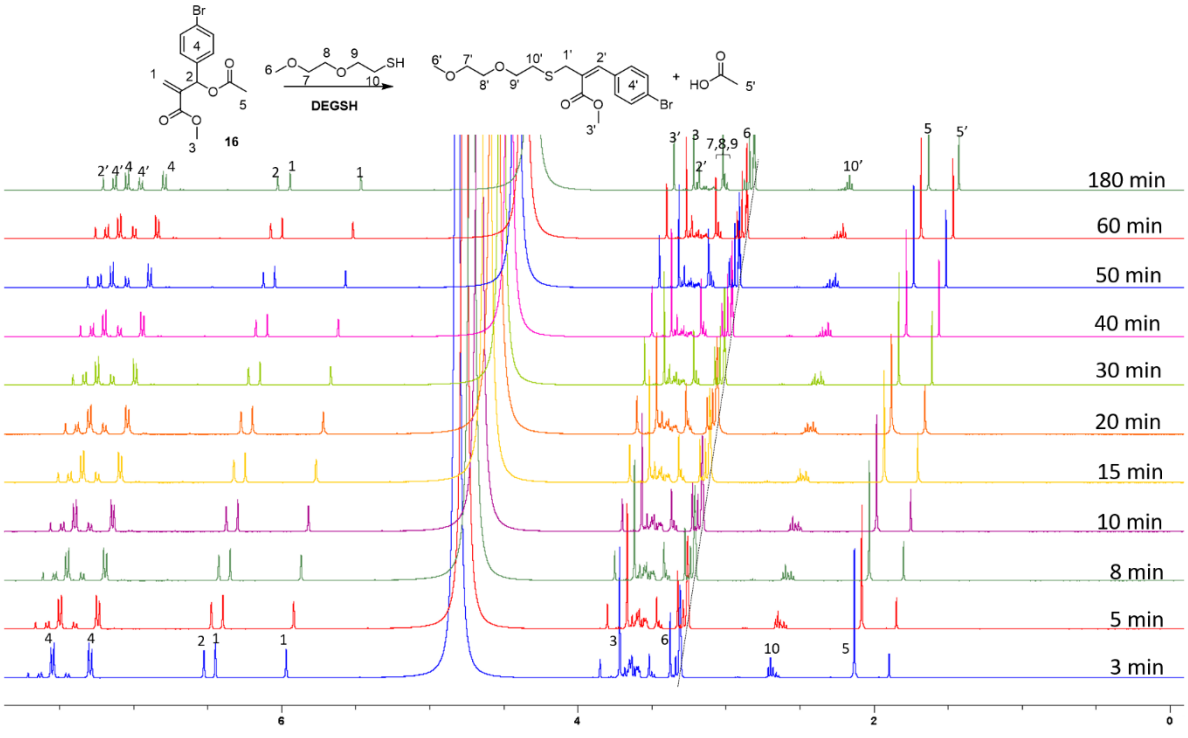


Figure S100 Thiol-addition with **16** .

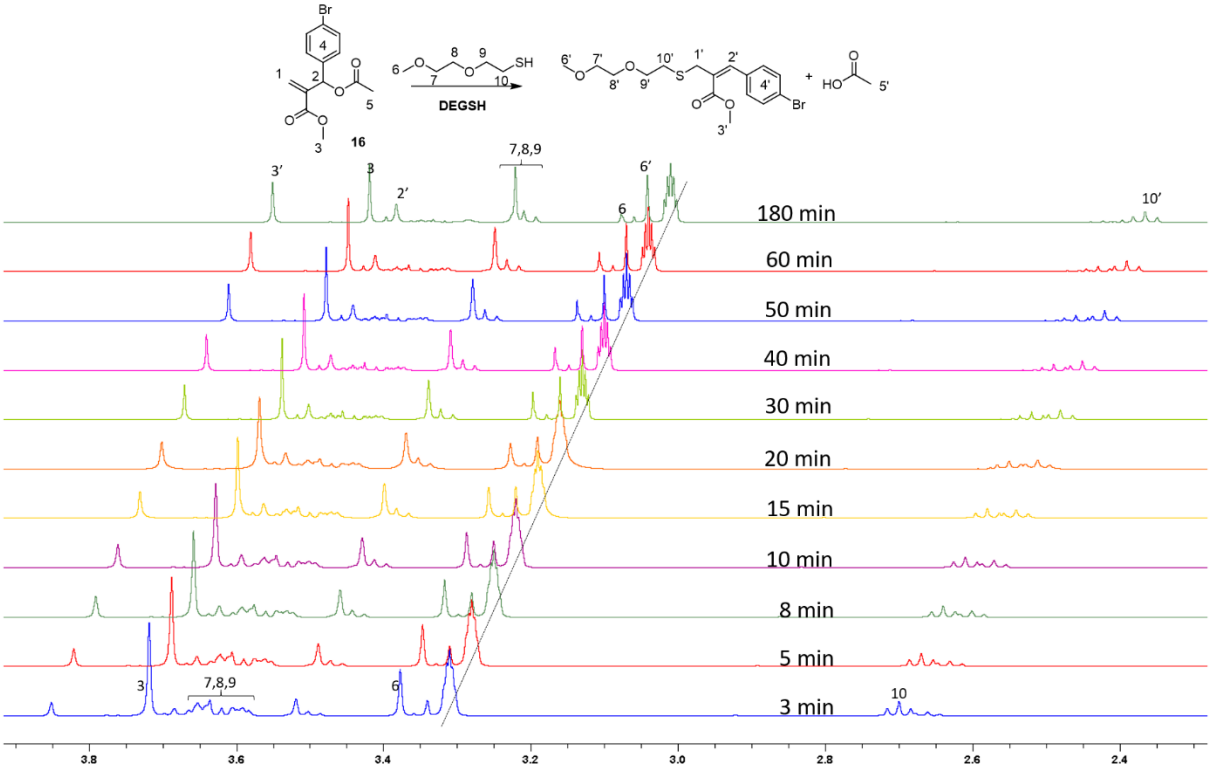


Figure S101 Zoom-in spectra of Figure S100.

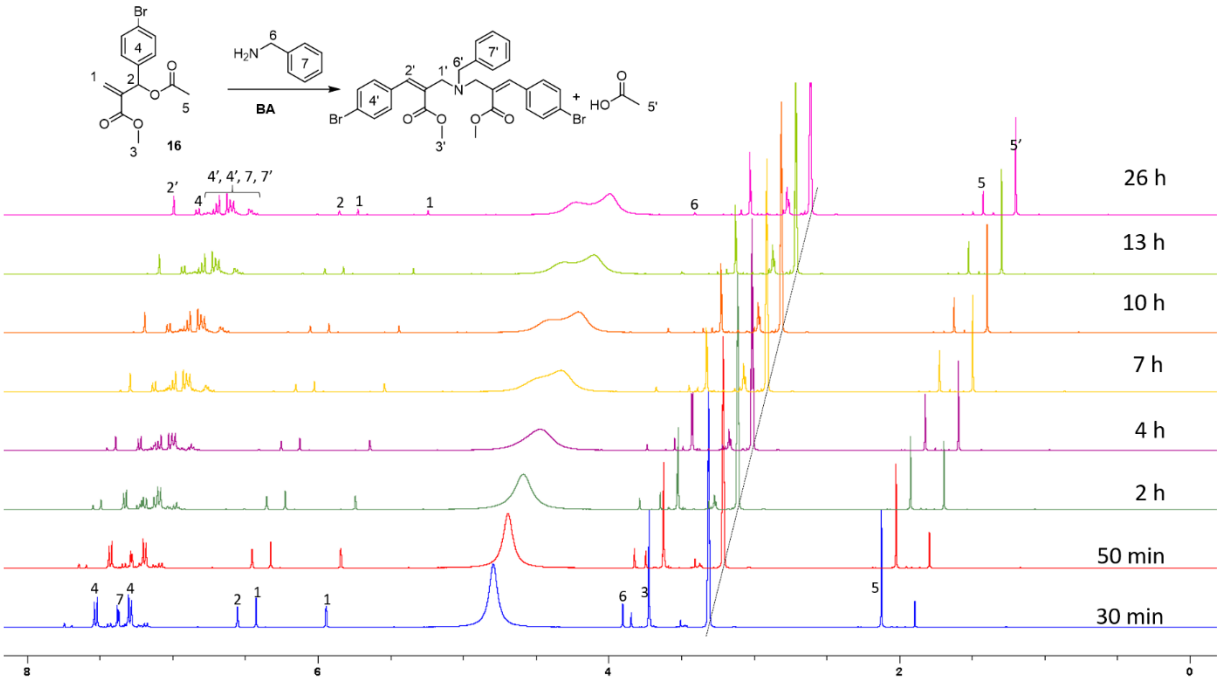


Figure S102 Amine-addition with **16**.

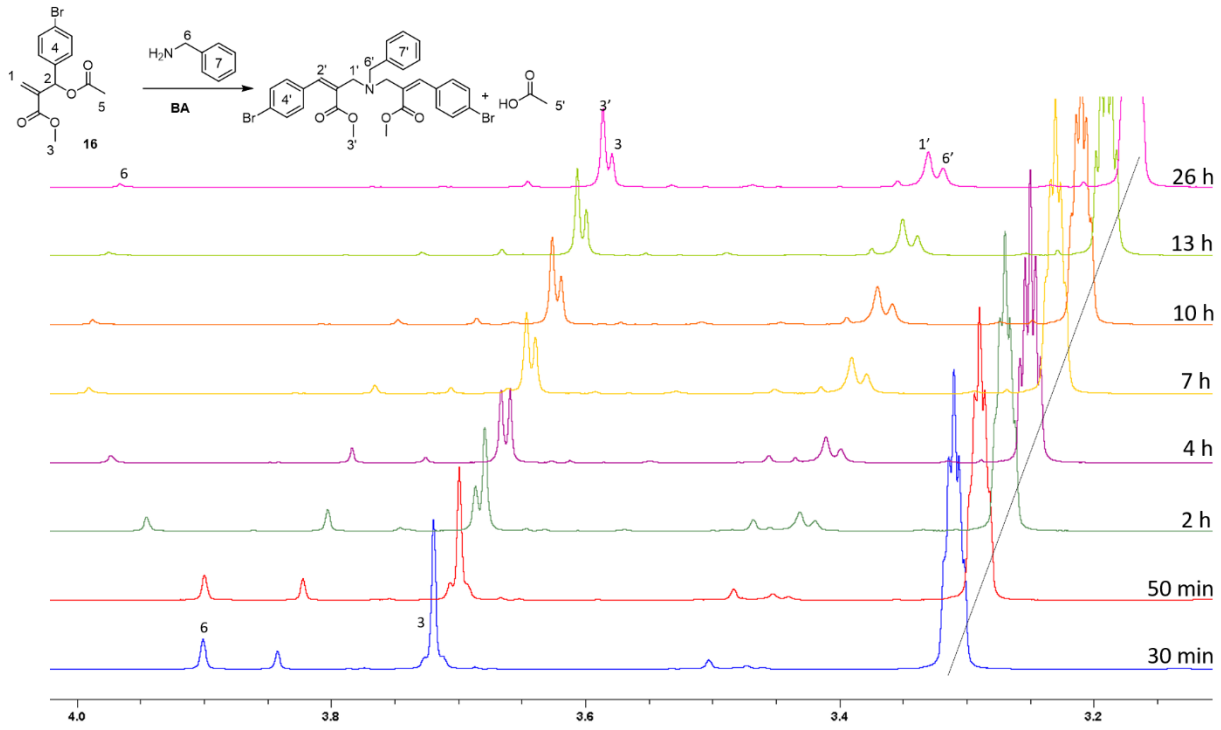


Figure S103 Zoom-in spectra of Figure S102.

Stability of ammonium compound 1(Figure S104)

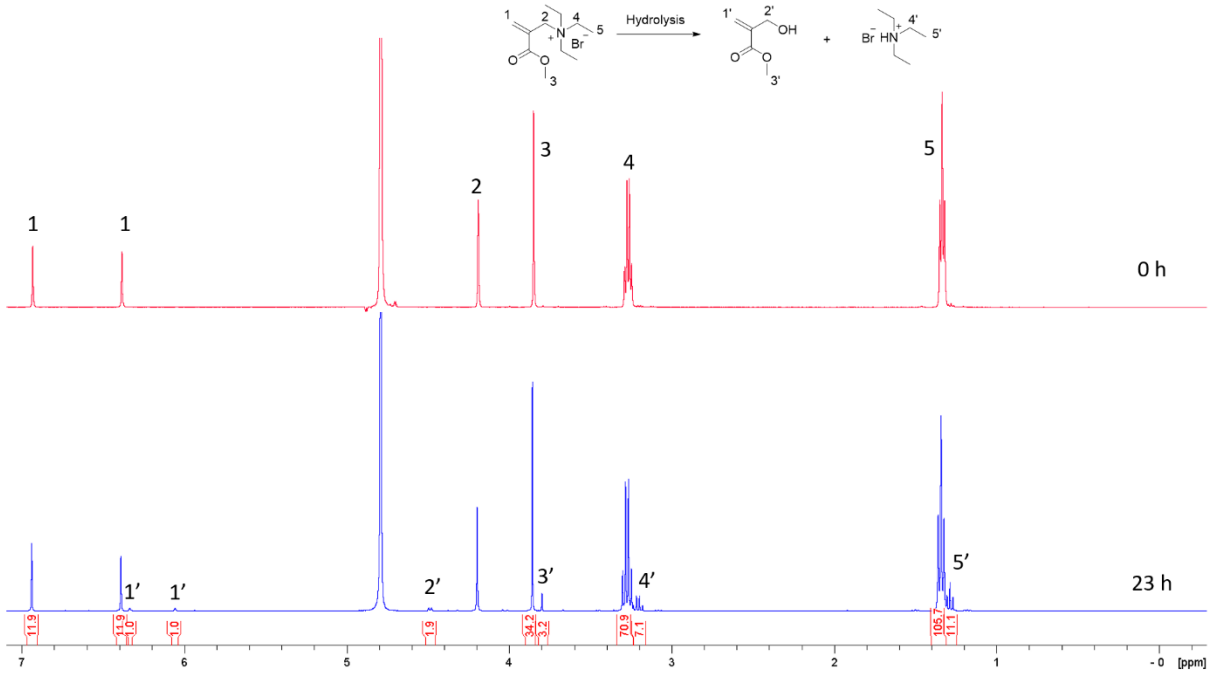


Figure S104 Hydrolytic stability of compound **1** at 50 mM pH7.4 phosphate buffer followed by NMR at 0 hour and 23 hours. The integration ratio between 4' and 4 suggests that 9% of compound **1** hydrolyzes in 23 hours.

Thiol oxidation

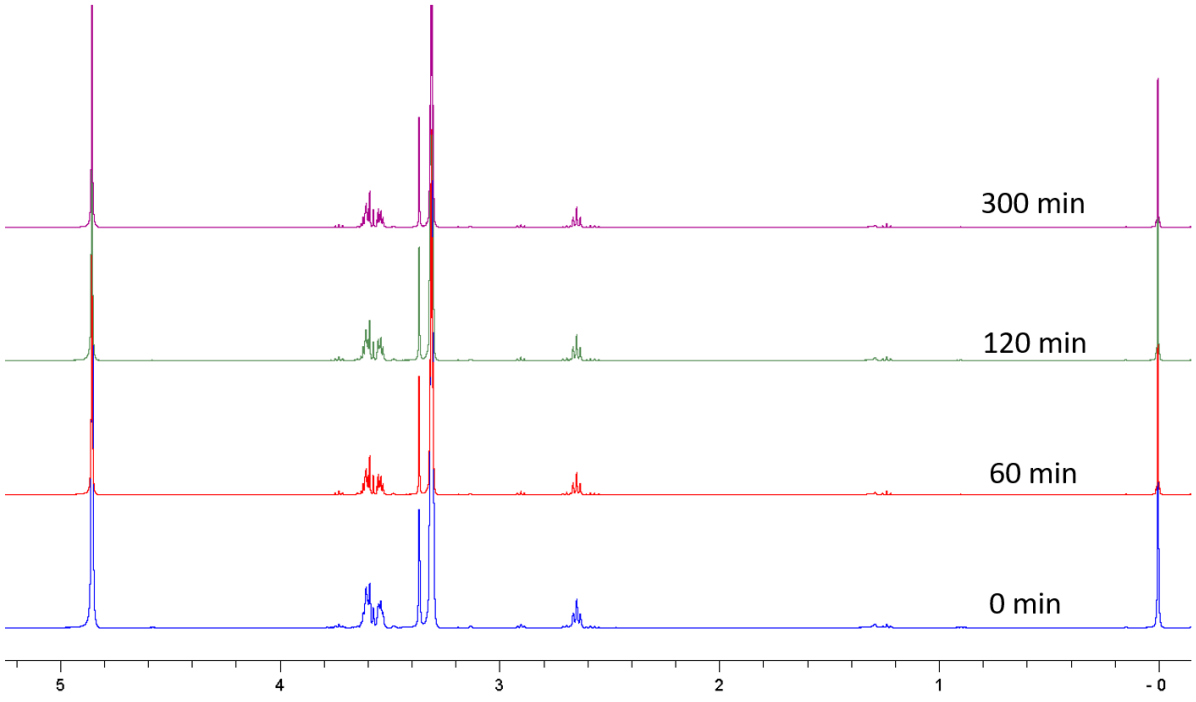


Figure S105. Time dependent NMR of PEG2-SH measured in MeOD.

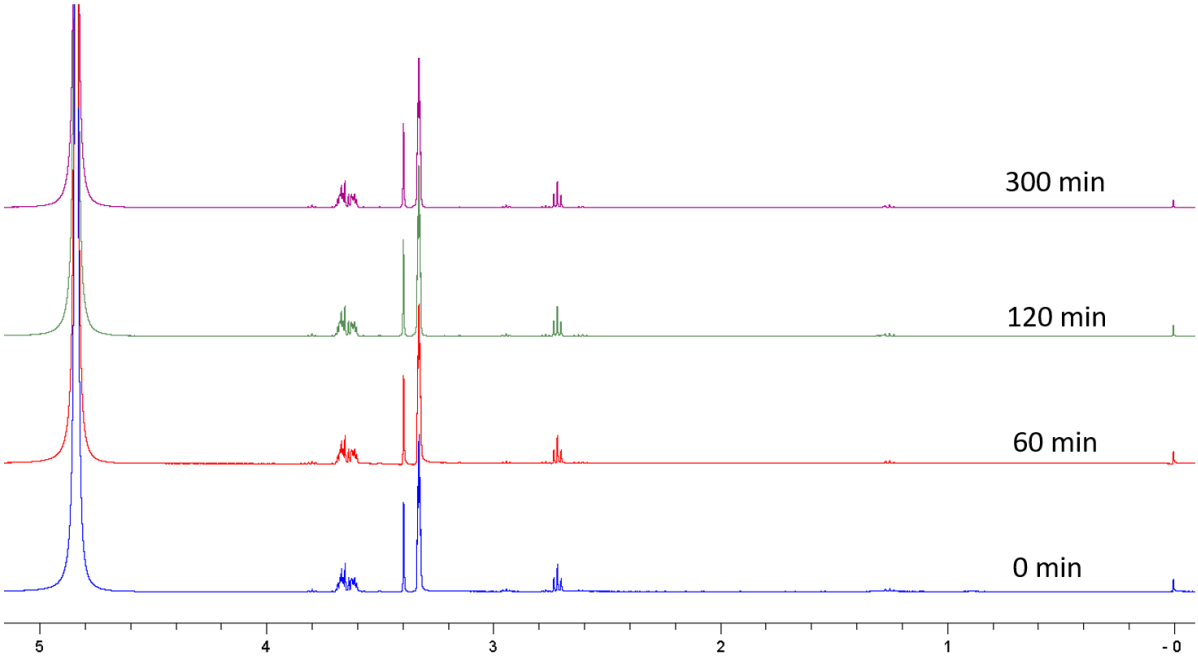


Figure S106. Time dependent NMR of DEGSH measured in MeOH-d4 and pH 7.4 phosphate buffer mixture

Influence of solvent polarity on trigger-to-reverse process

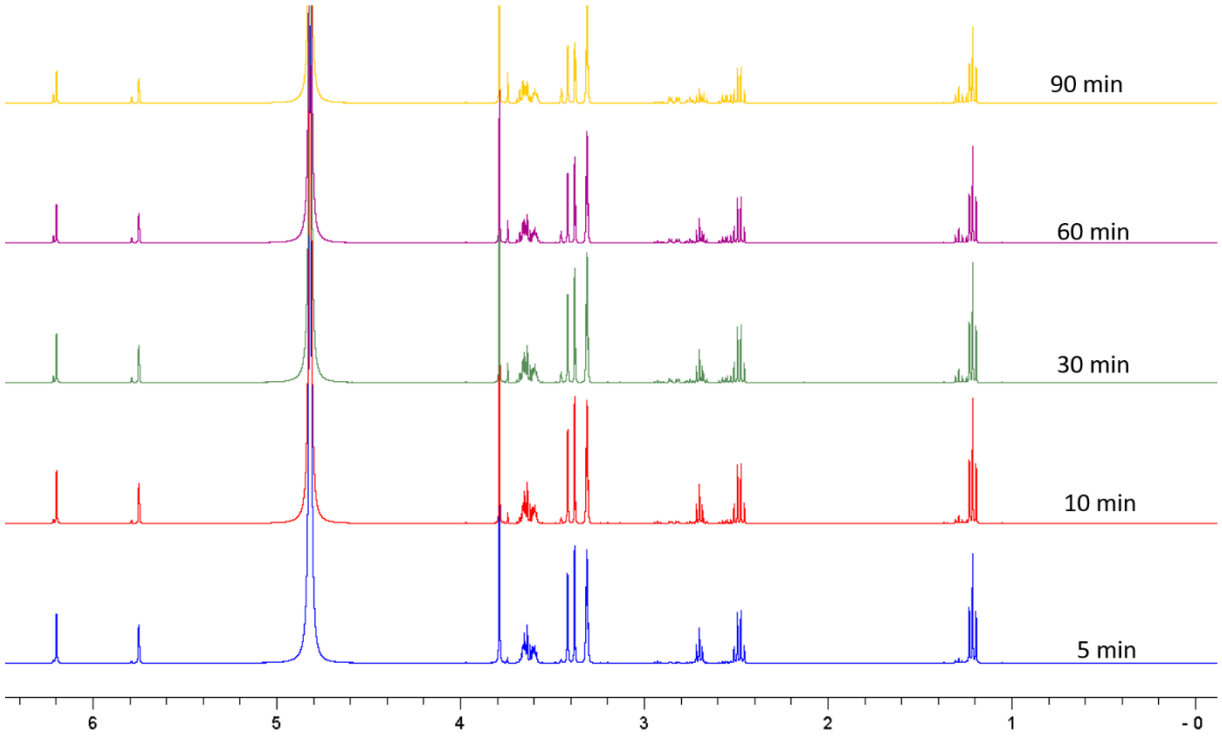


Figure S107. Trigger-to-reverse of compound **18** in pH 7.4 phosphate buffer and MeOH-d4 mixture. [DEGSH]/[**18**] = 1:2.

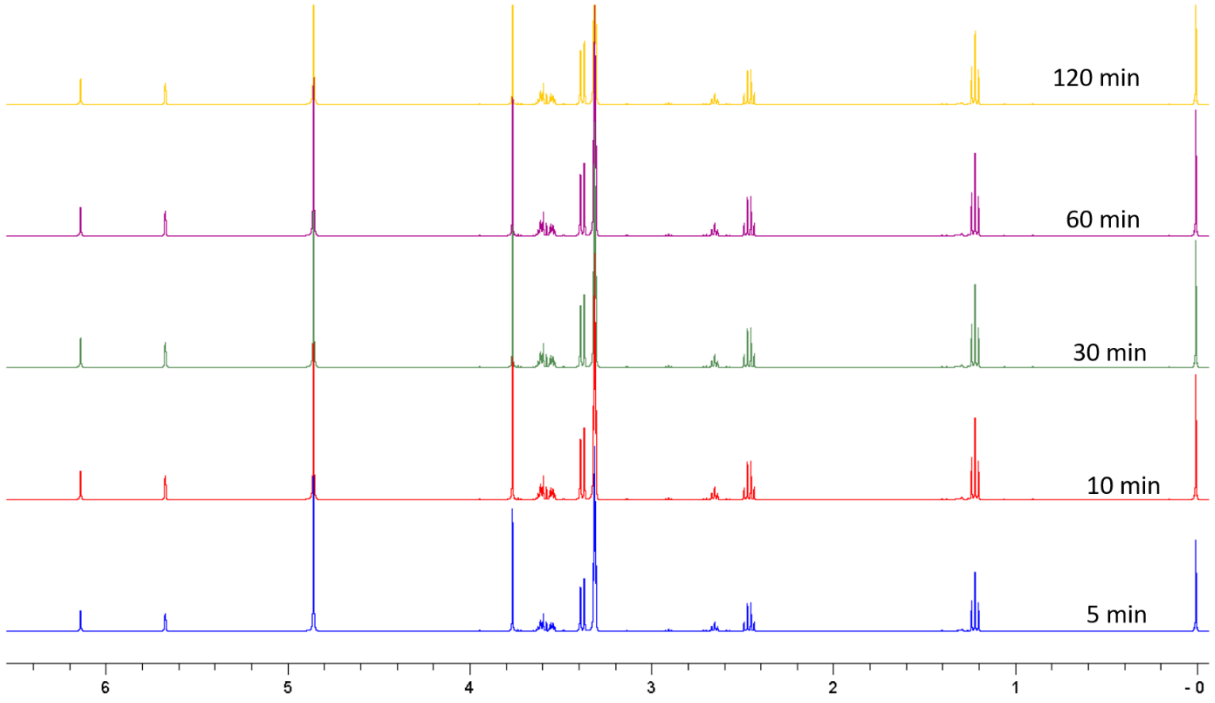
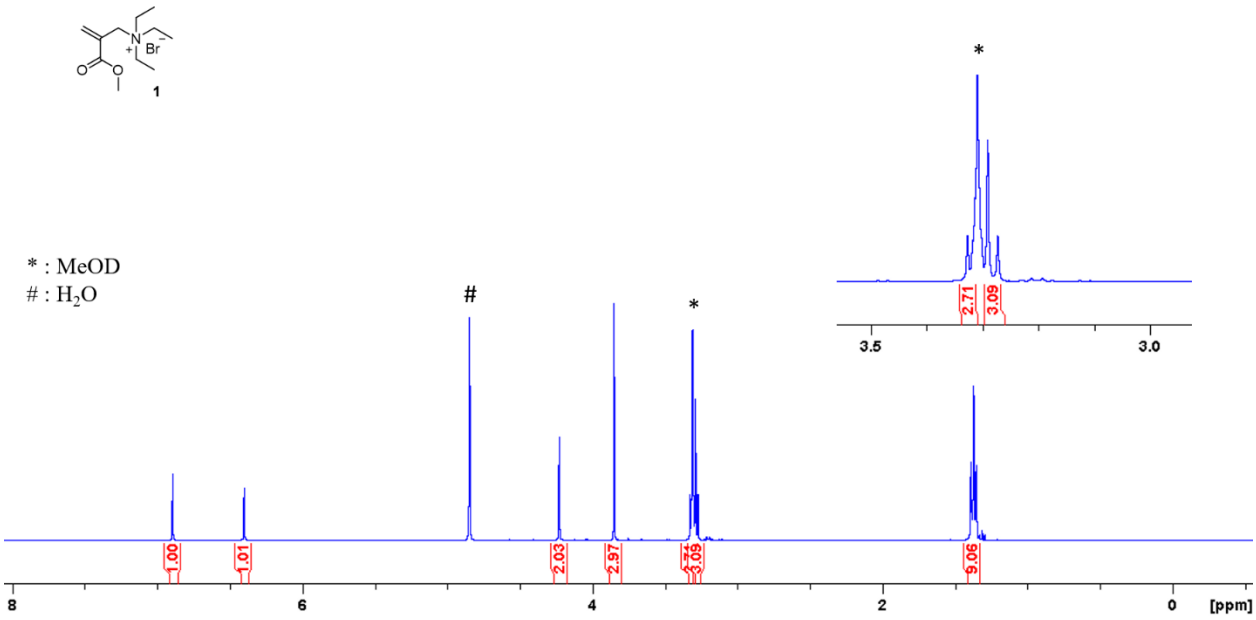
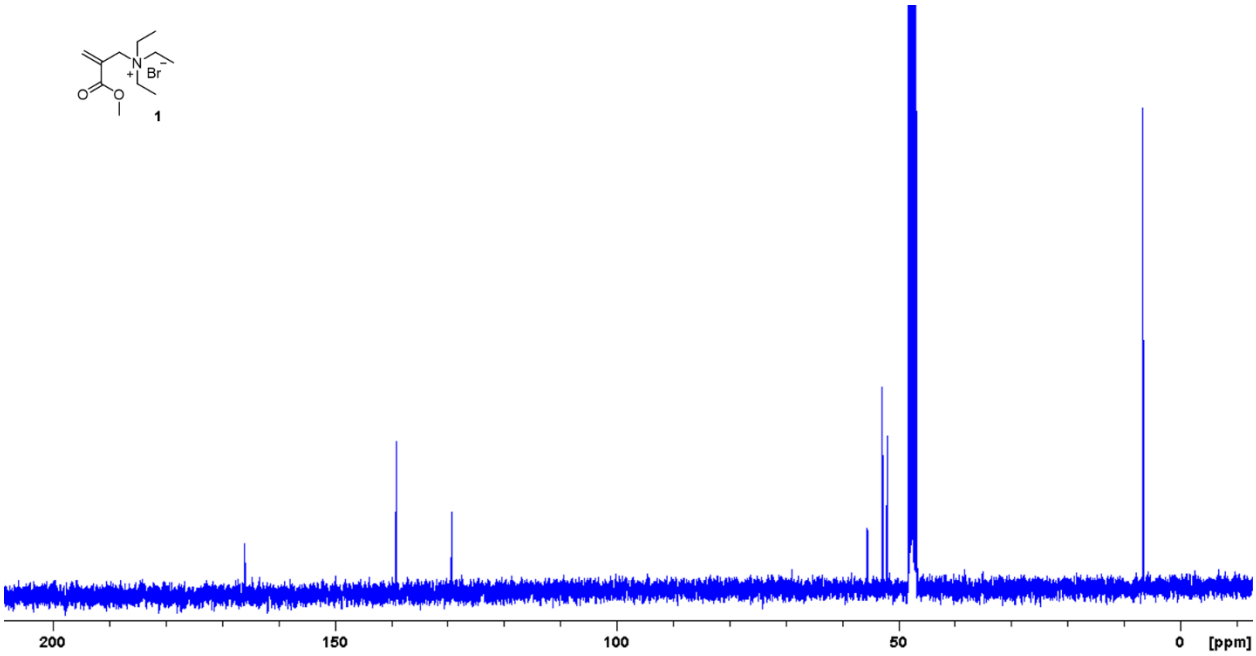
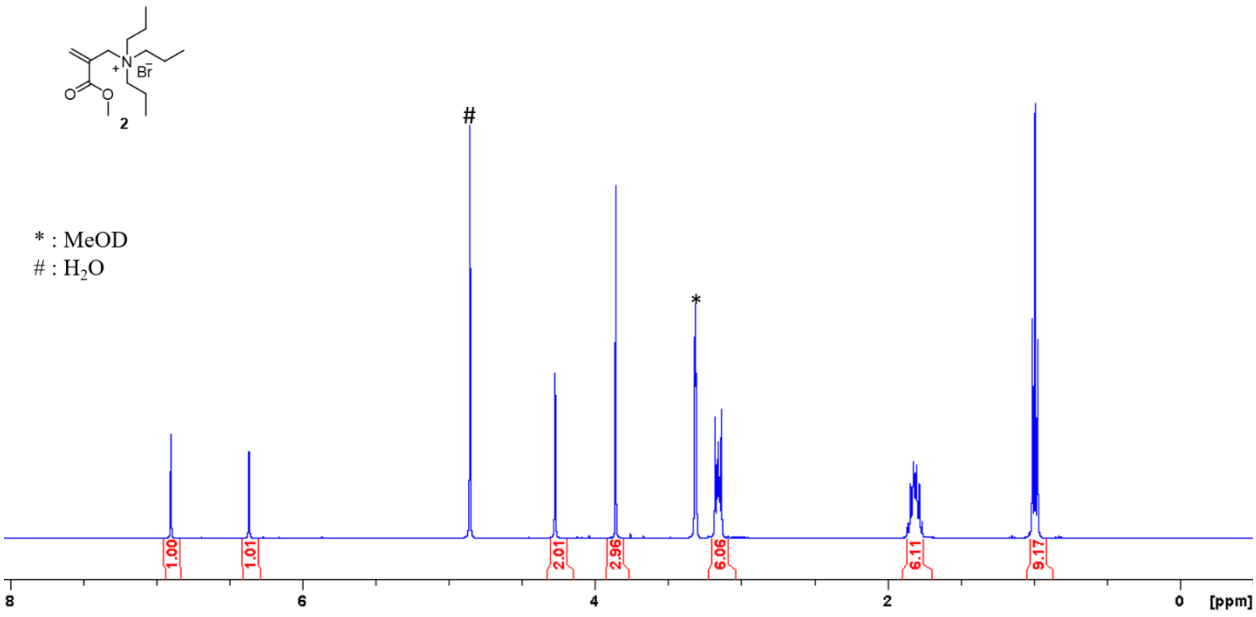


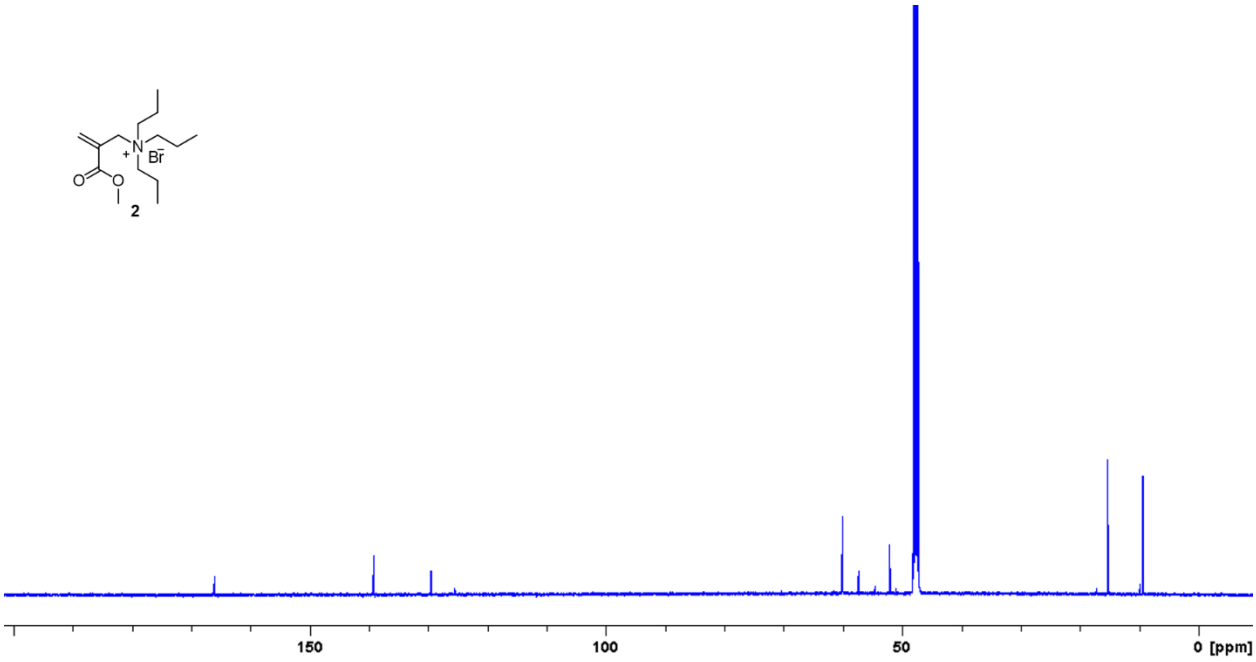
Figure S108. Trigger-to-reverse of compound **18** in MeOH-d4 mixture. [DEGSH]/[**18**] = 1:2.

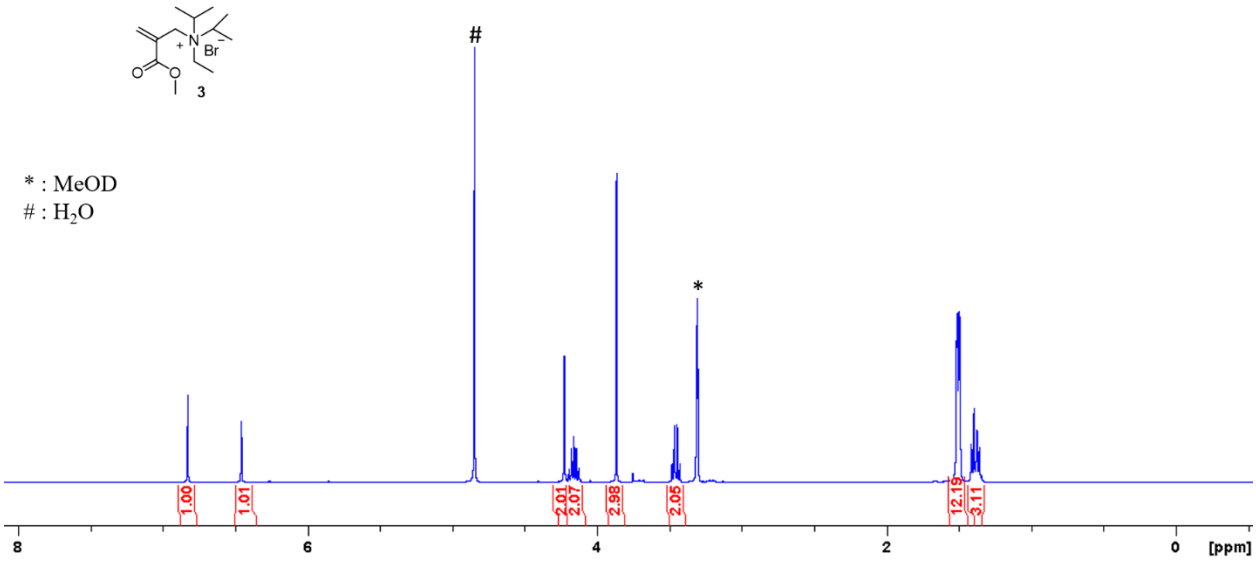
^{1}H NMR and ^{13}C NMR spectra of all synthesized compounds

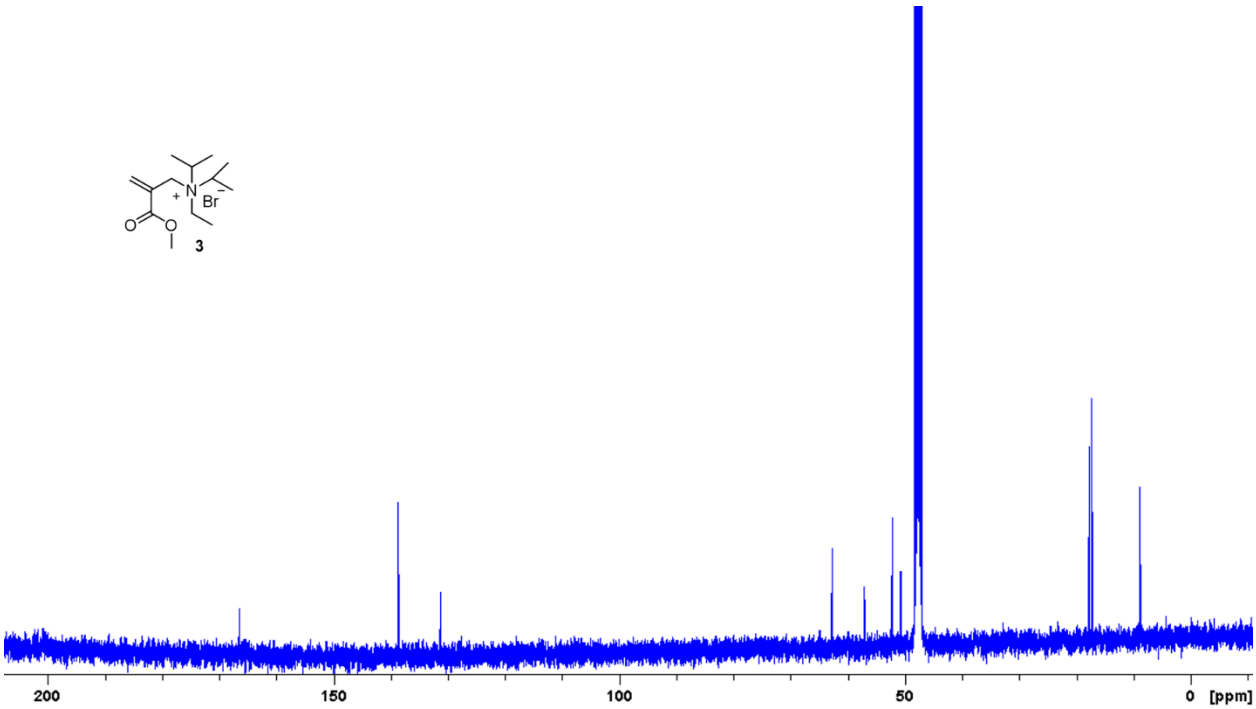


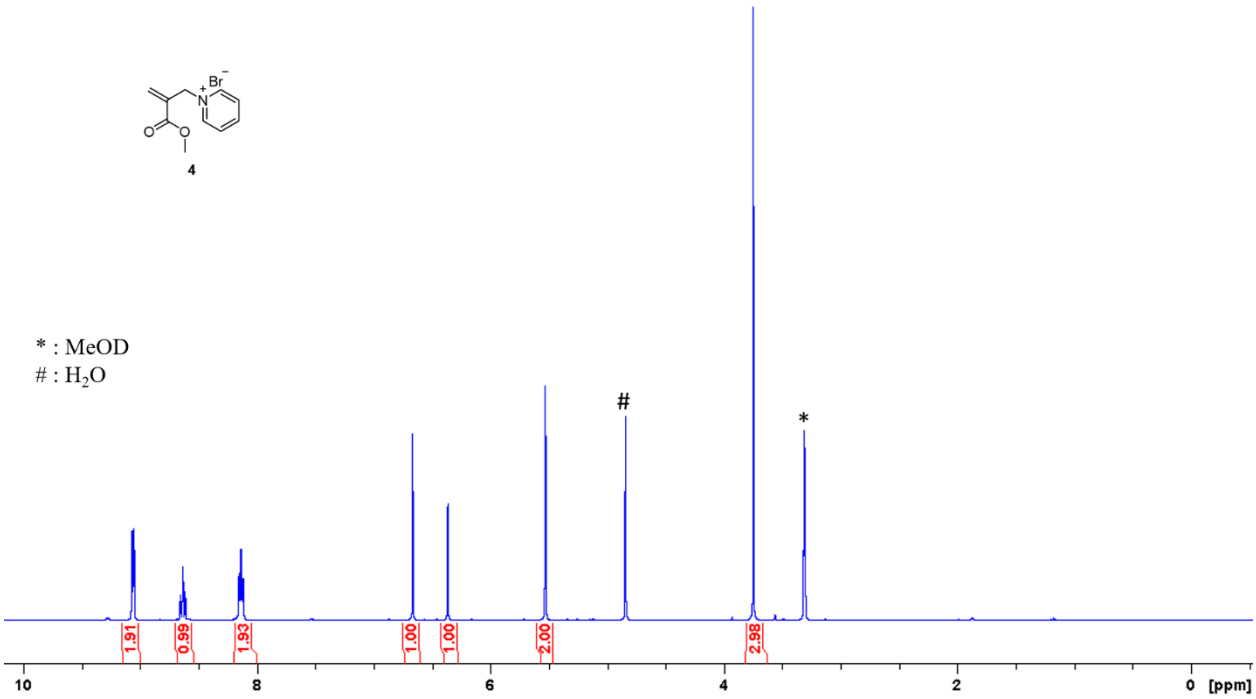


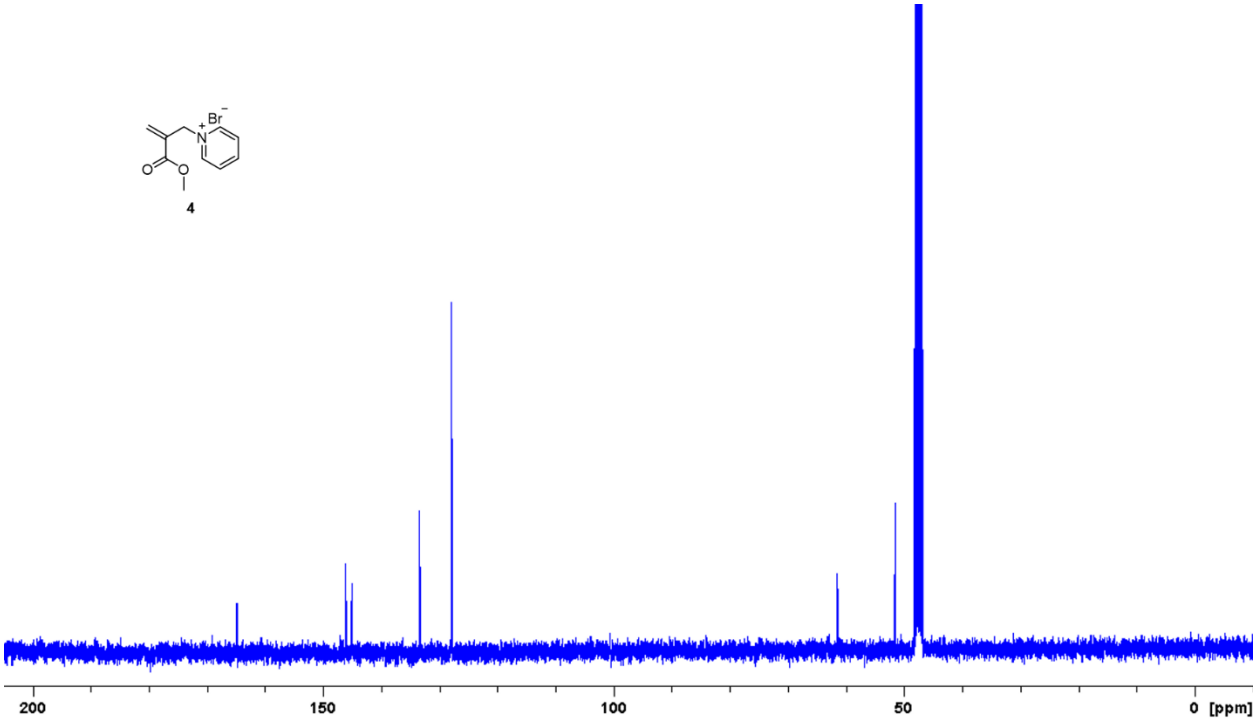

2
* : MeOD
# : H2O
#
*
1.00
1.01
2.01
2.96
6.06
6.11
9.17
8
6
4
2
0
[ppm]

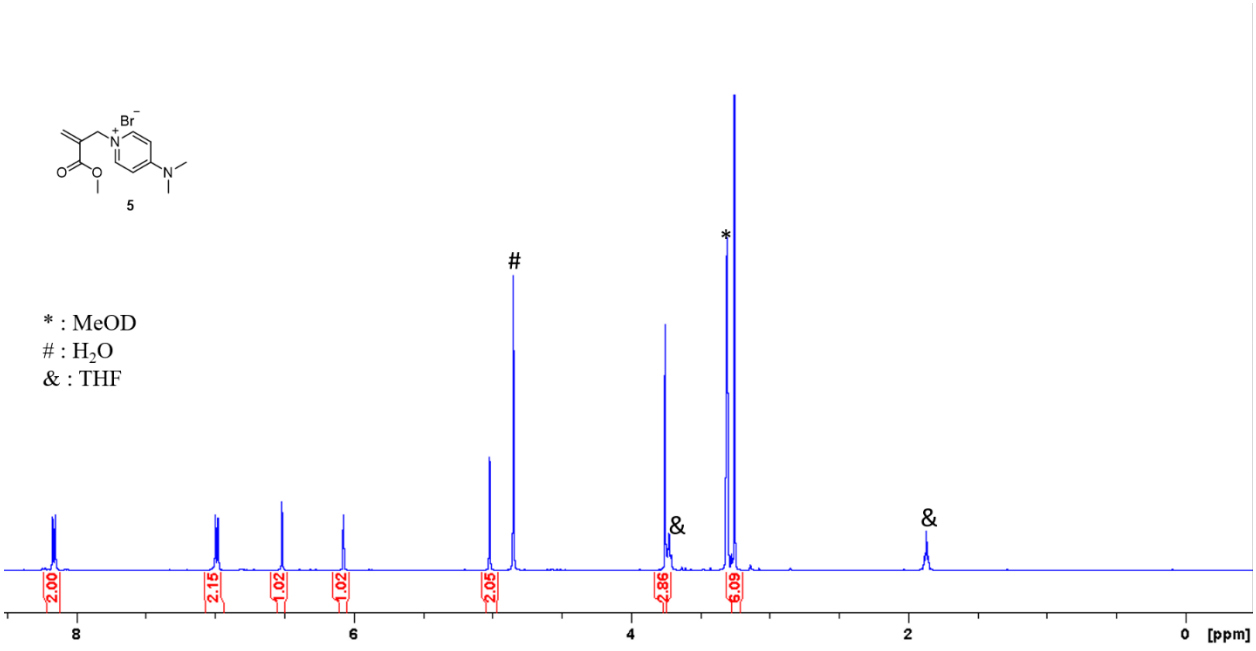

2
150
100
50
0
[ppm]


3
* : MeOD
# : H2O
#
*
1.00
1.01
2.01
2.07
2.98
2.05
12.19
3.11
8
6
4
2
0
[ppm]


3
200
150
100
50
0
[ppm]


4
* : MeOD
# : H2O
#
*
1.91
0.99
1.93
1.00
1.00
2.00
2.98
10
8
6
4
2
0 [ppm]


4
200
150
100
50
0 [ppm]


5
* : MeOD
# : H2O
& : THF
#
*
&
&
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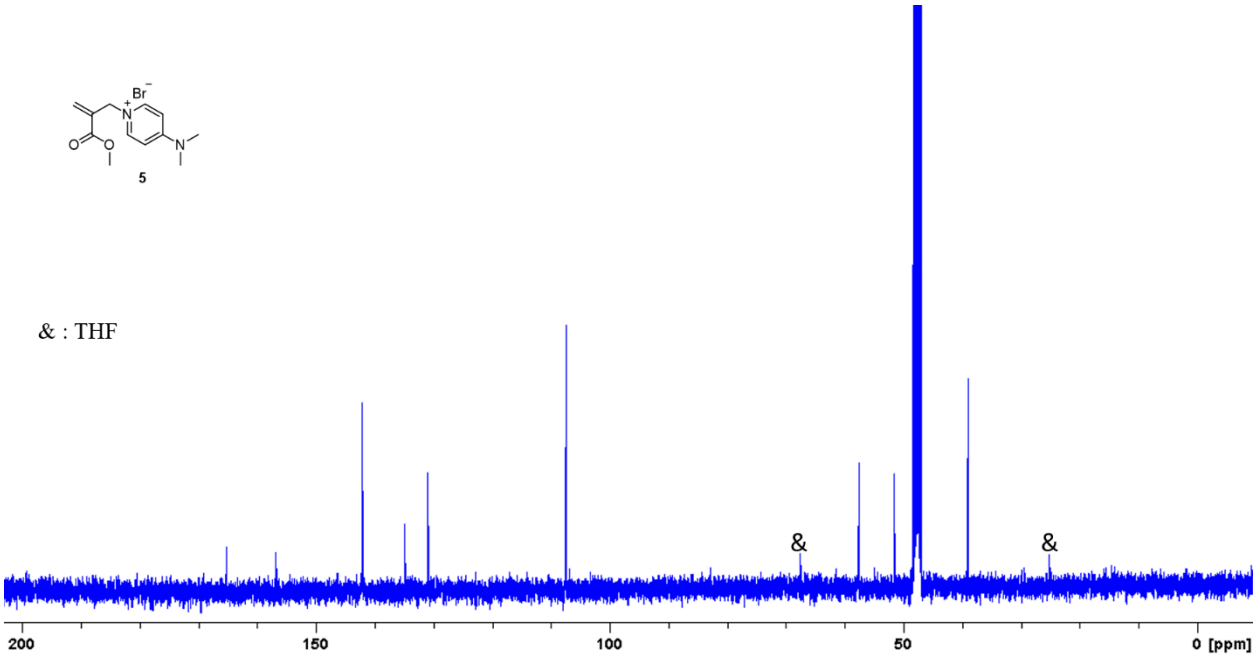
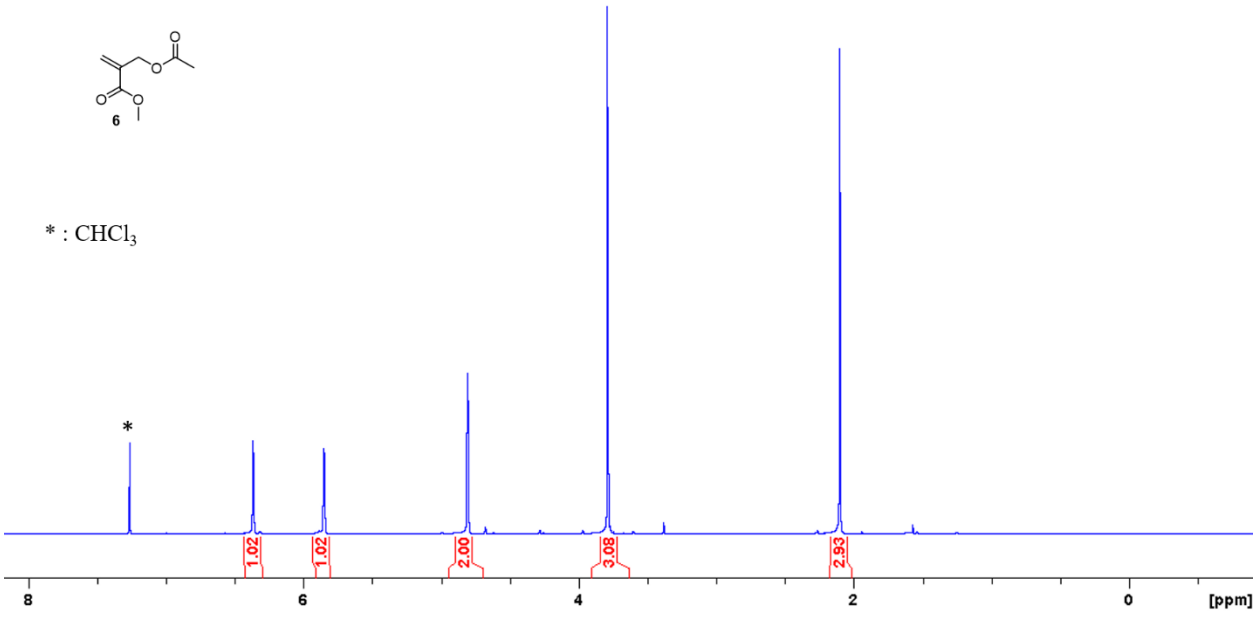
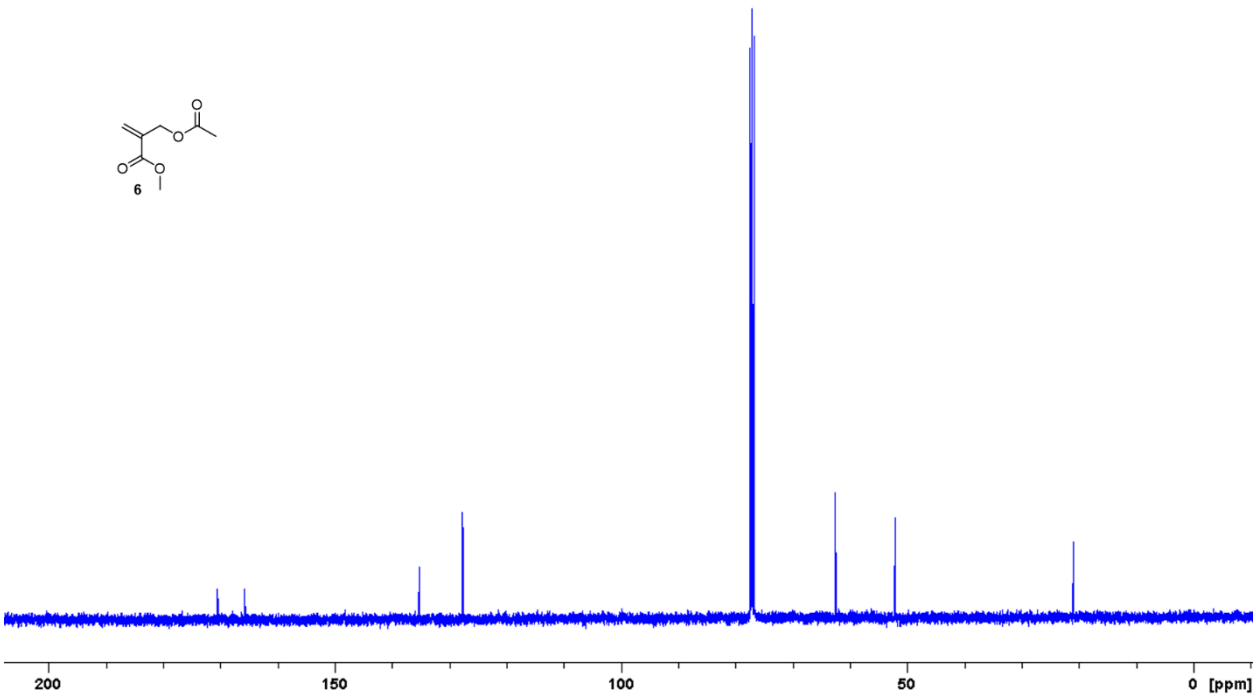
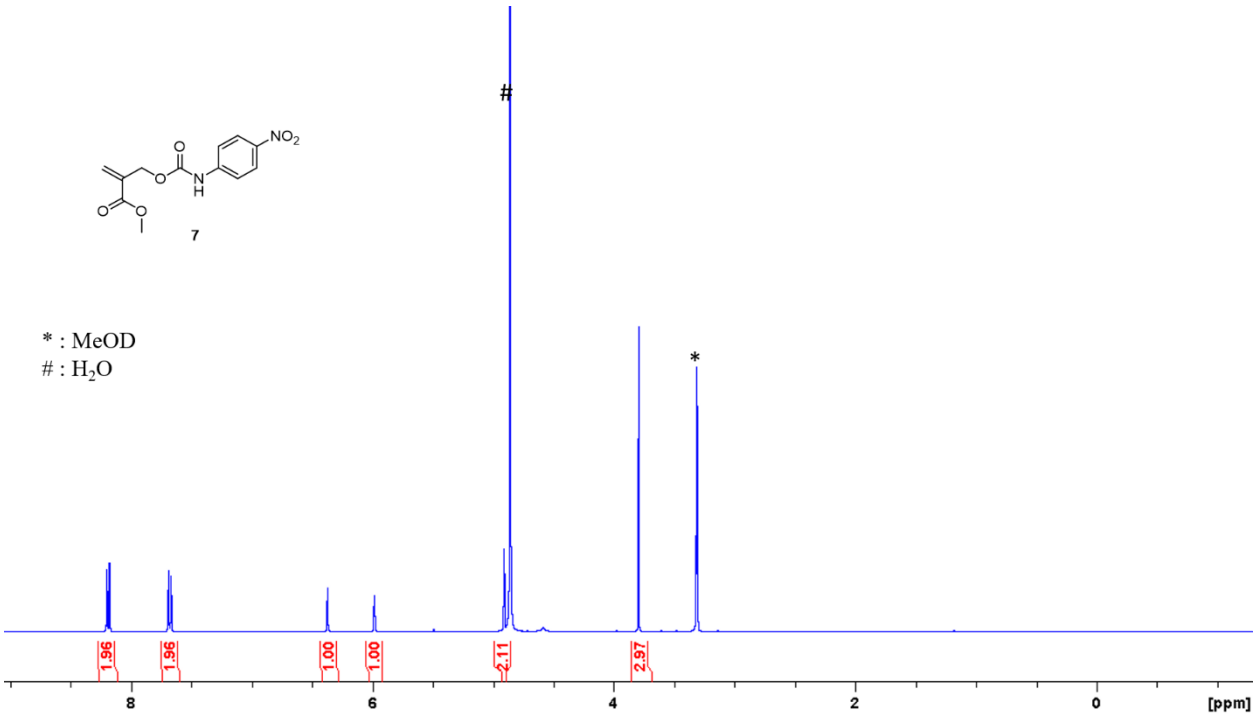
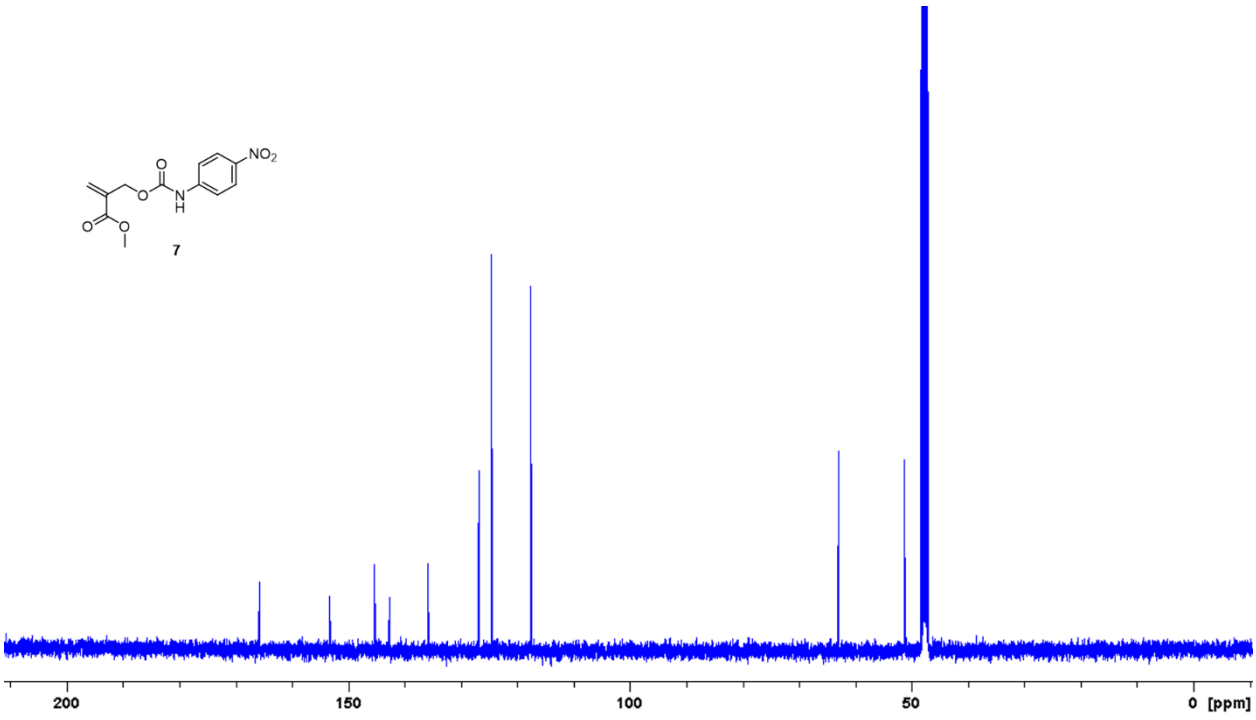
2.15
1.02
1.02
2.05
2.86
6.09
8
6
4
2
0 [ppm]

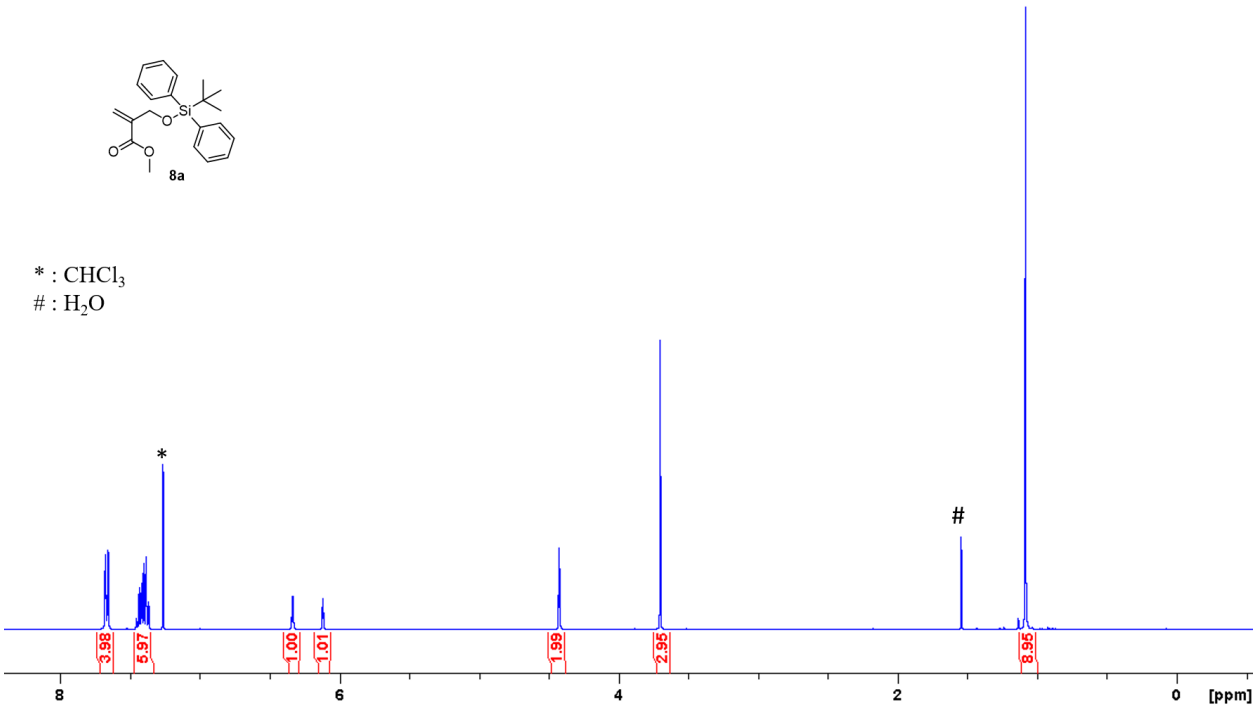

5
& : THF
&
&
200
150
100
50
0 [ppm]

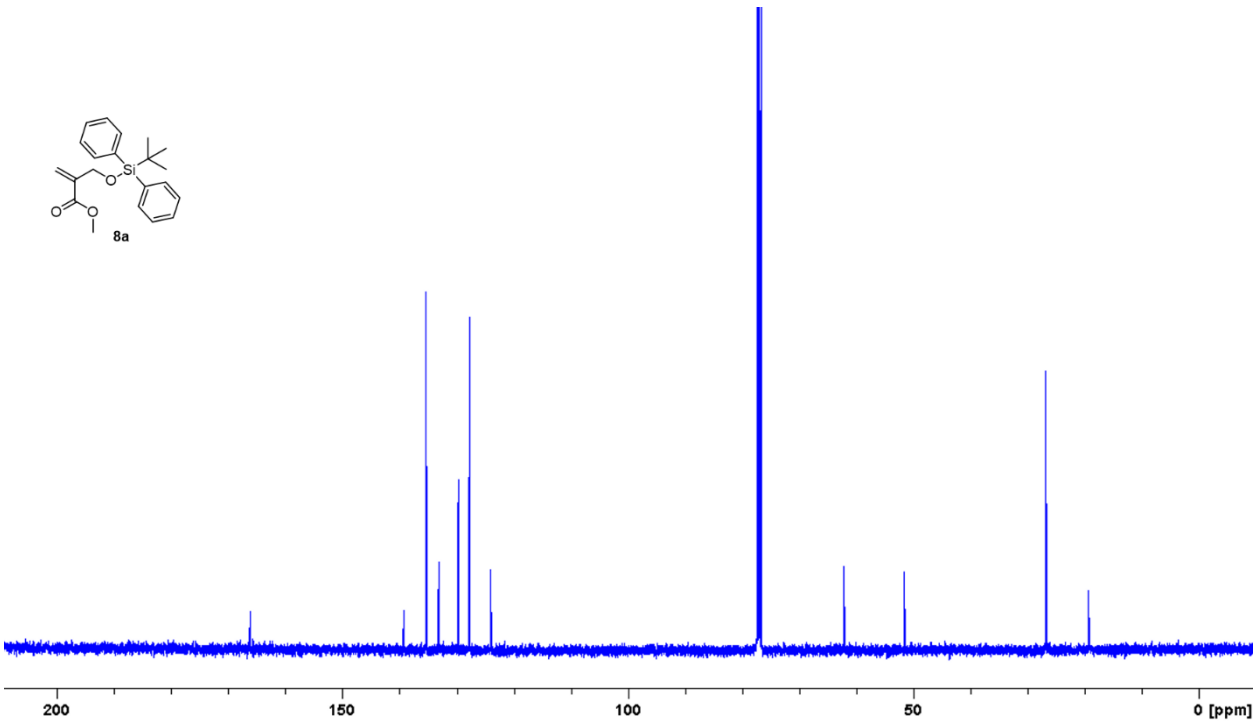

6
* : CHCl3
*
1.02
1.02
2.00
3.08
2.93
8
6
4
2
0
[ppm]

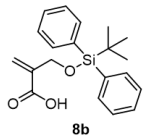

6
200
150
100
50
0
[ppm]


#
*
7
* : MeOD
# : H2O
1.96
1.96
1.00
1.00
2.11
2.97
8
6
4
2
0
[ppm]


7
200
150
100
50
0
[ppm]


8a
* : CHCl3
# : H2O
*
#
3.98
5.97
1.00
1.01
1.99
2.95
8.95
8
6
4
2
0
[ppm]

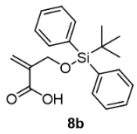

8a
200
150
100
50
0 [ppm]


Si
O
O
OH

8b

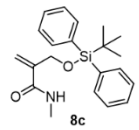
* : $CHCl_3$

*
4.02
6.00
1.00
1.00
2.00
9.19
8
6
4
2
0
[ppm]


Si
O
O
OH

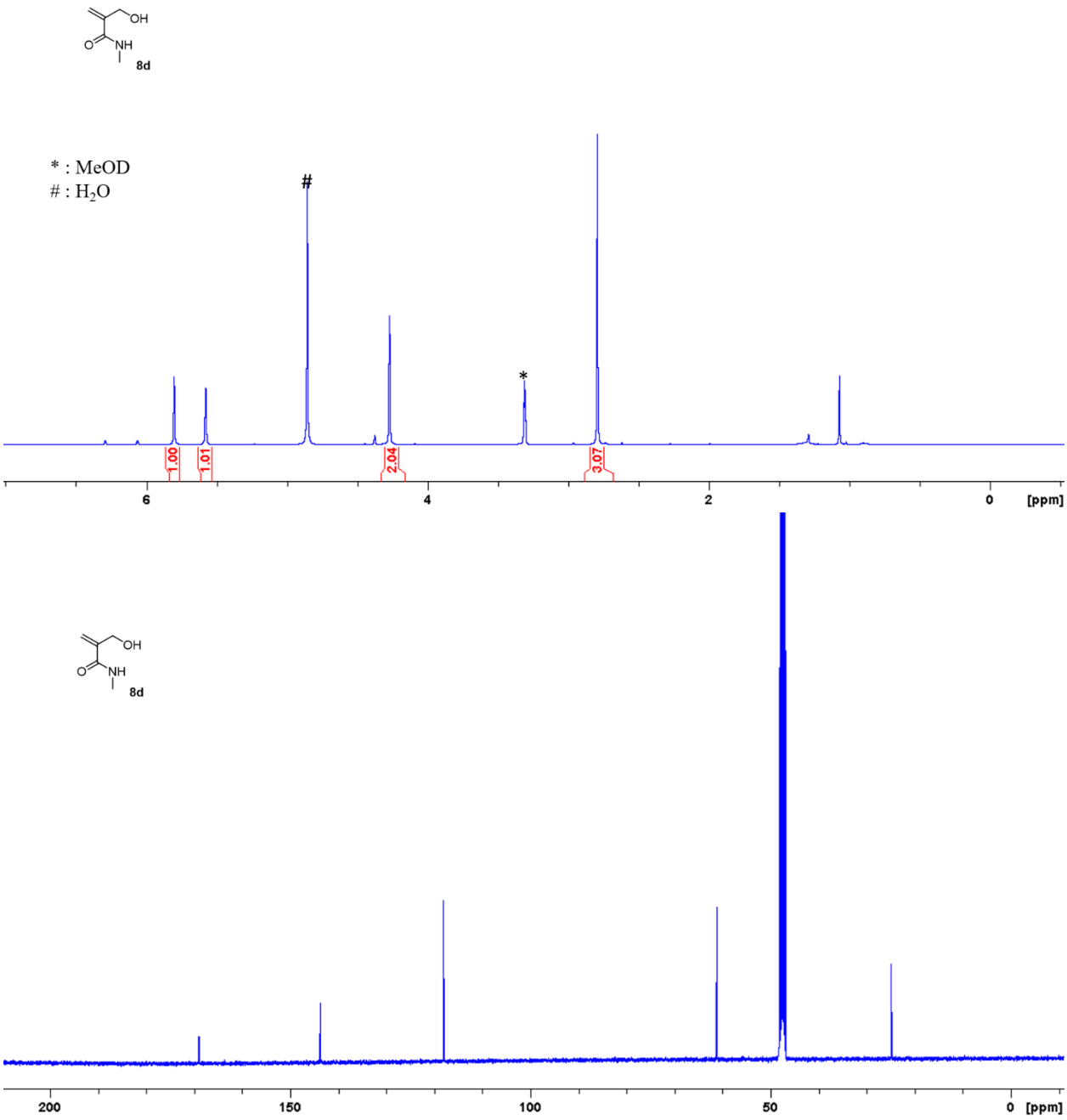
8b

200
150
100
50
0
[ppm]



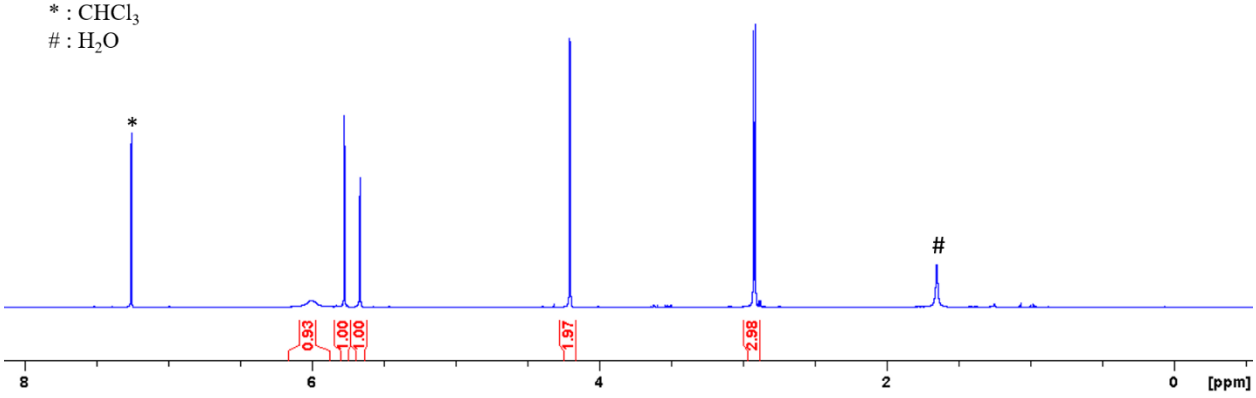
8c

* : $CHCl_3$
\# : H_2O


OH
NH
8d
* : MeOD
# : H2O
#
*
1.00
1.01
2.04
3.07
6
4
2
0
[ppm]
OH
NH
8d
200
150
100
50
0
[ppm]

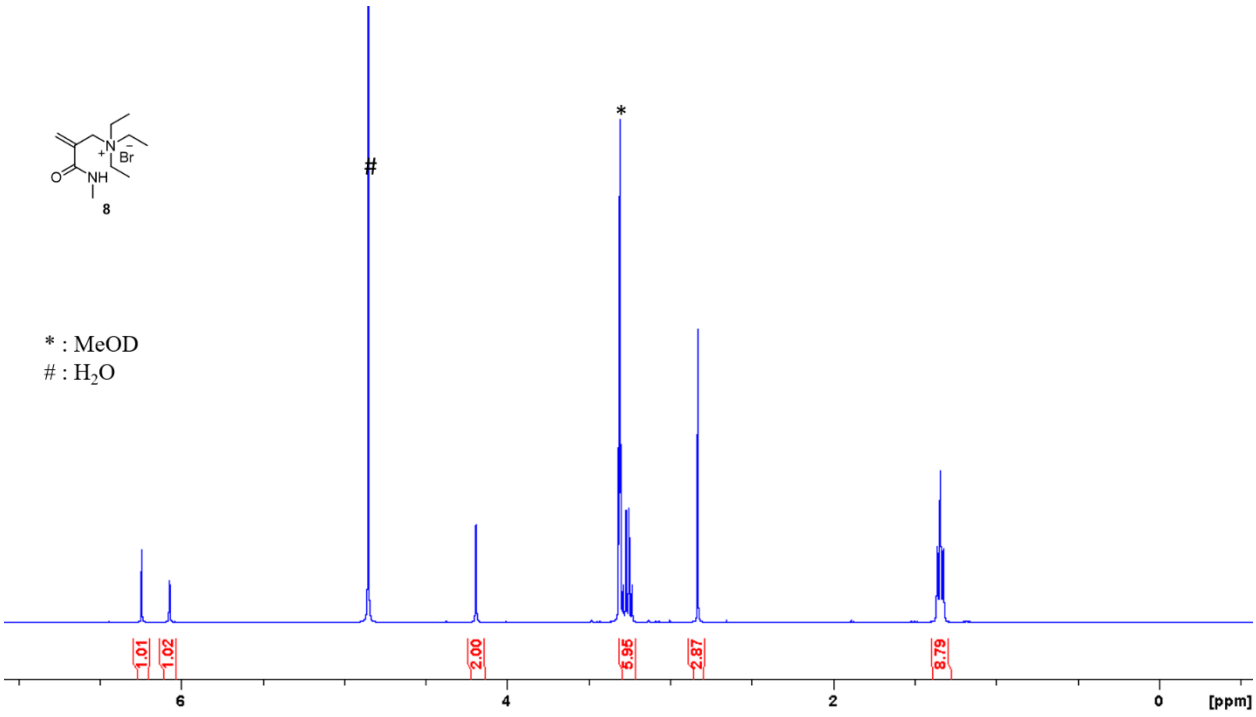

Br
NH
8e

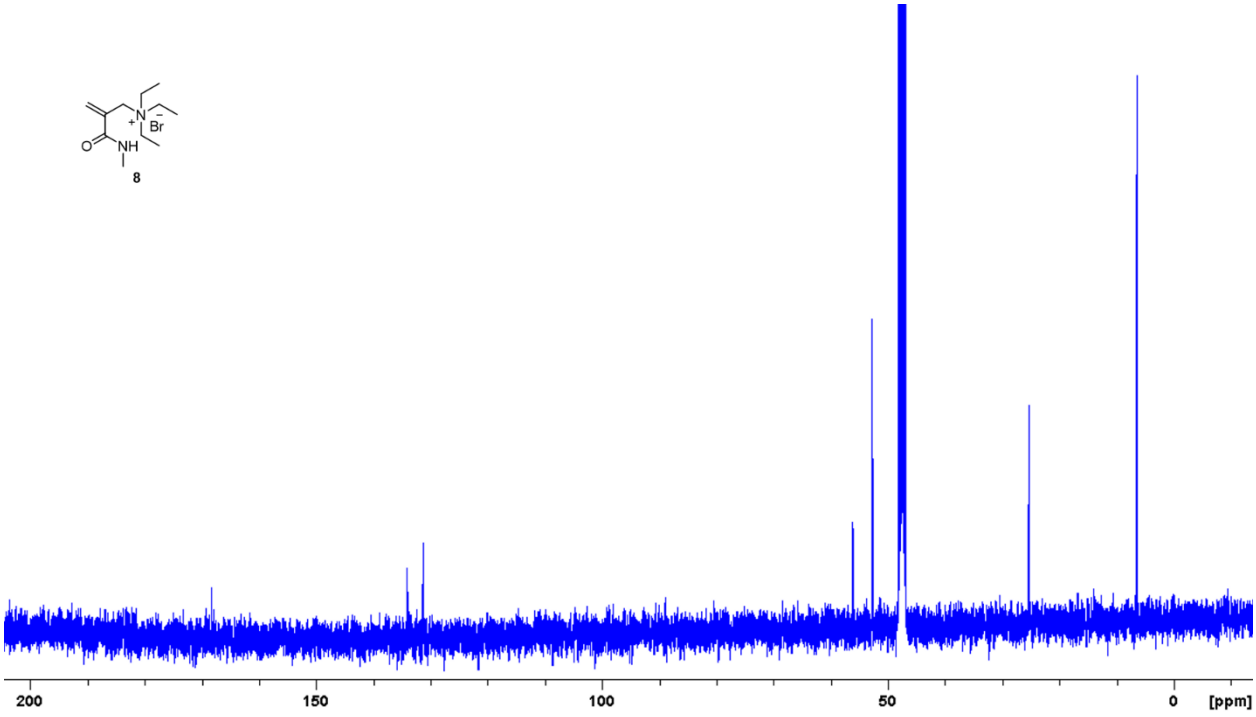
* : $CHCl_3$
\# : H_2O

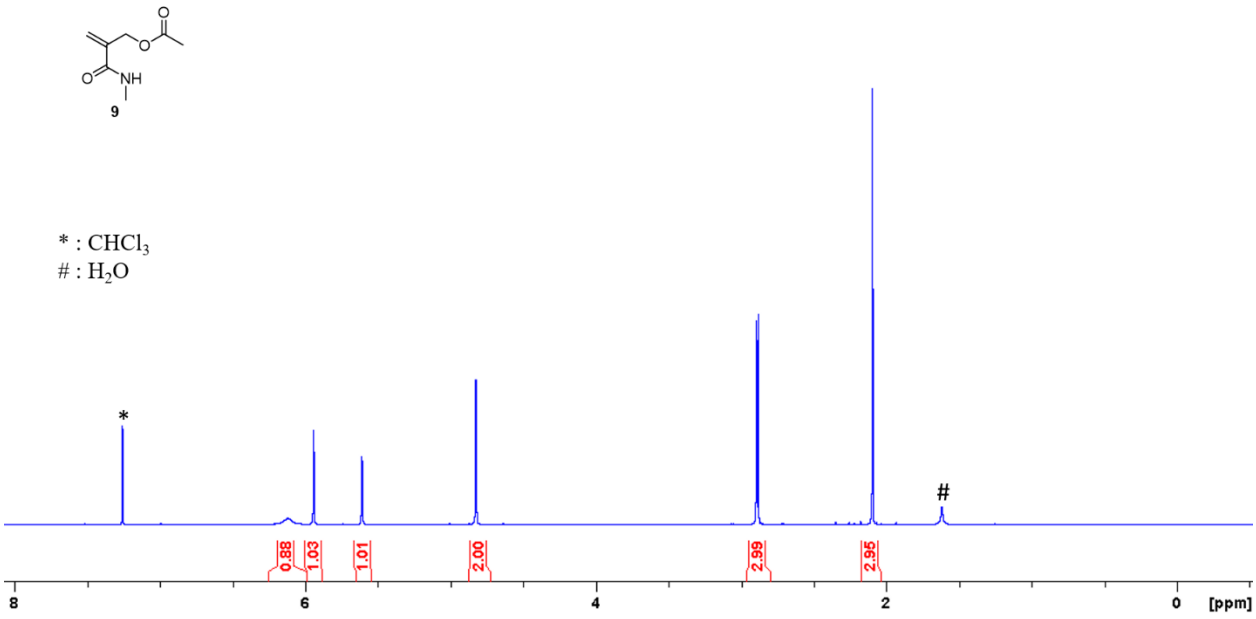

*
#
0.93
1.00
1.00
1.97
2.98
8
6
4
2
0
[ppm]

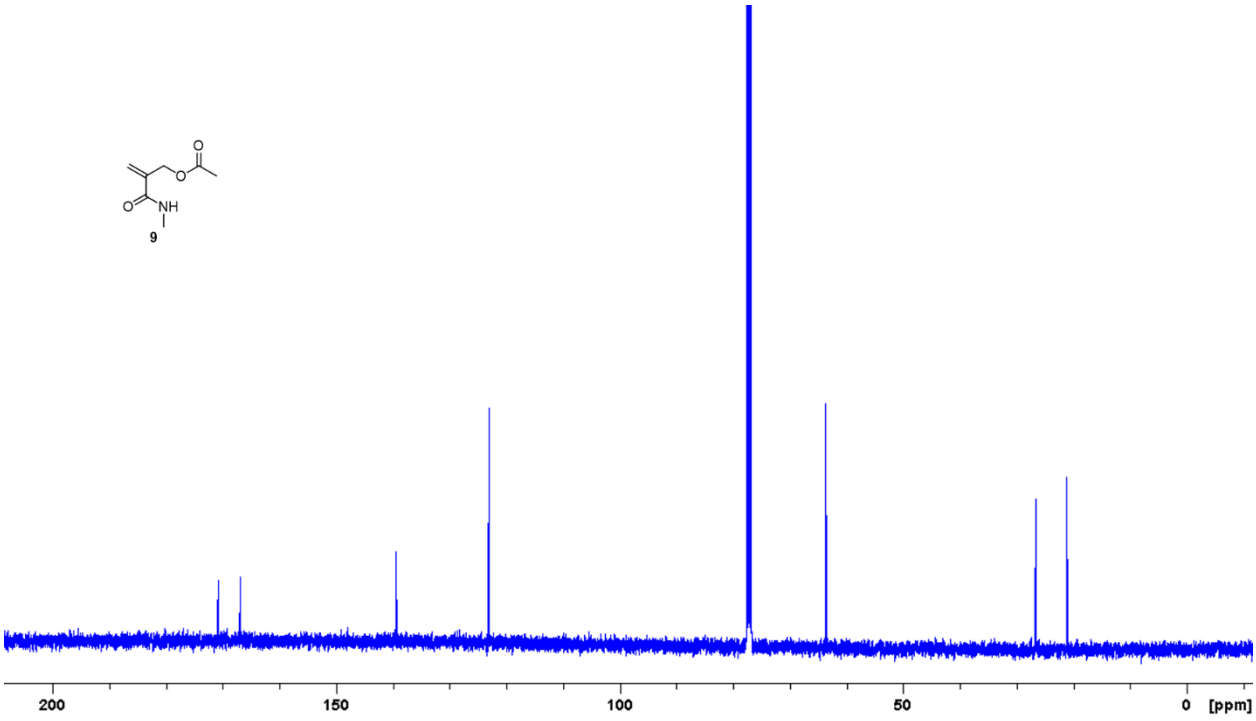

Br
NH
8e

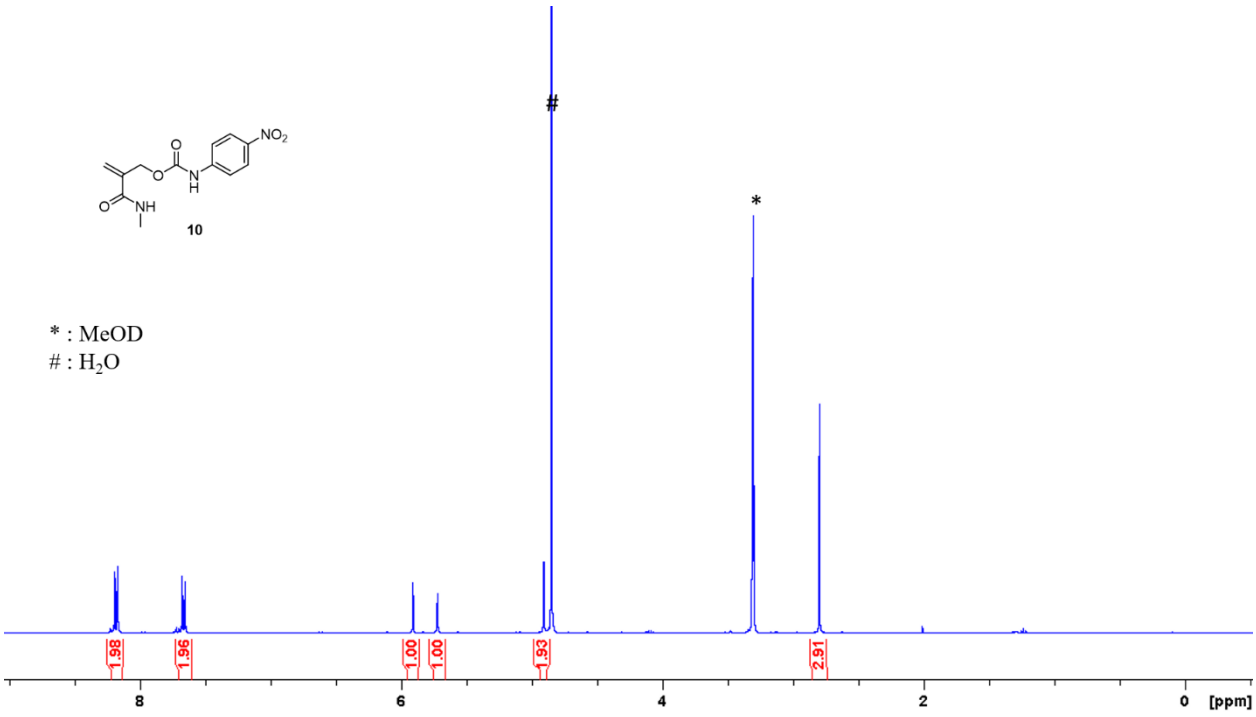
200
150
100
50
0 [ppm]

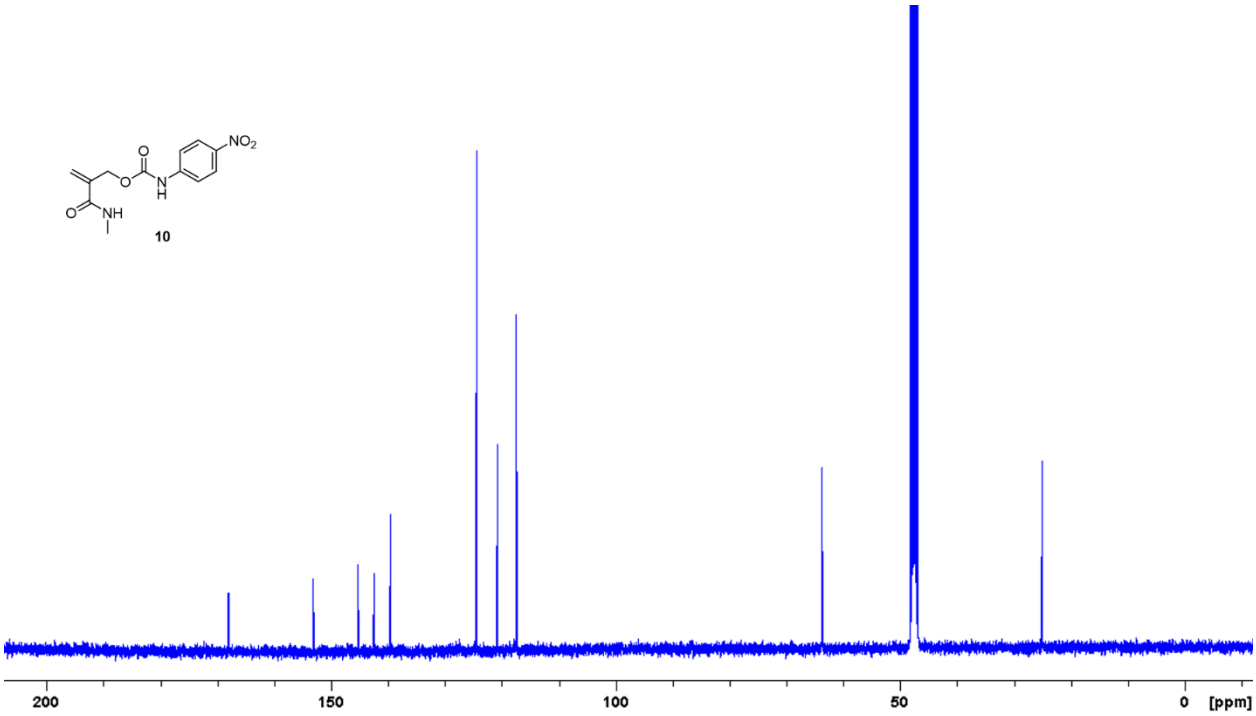

8
#
*
* : MeOD
# : H2O
1.01
1.02
2.00
5.95
2.87
8.79
6
4
2
0
[ppm]

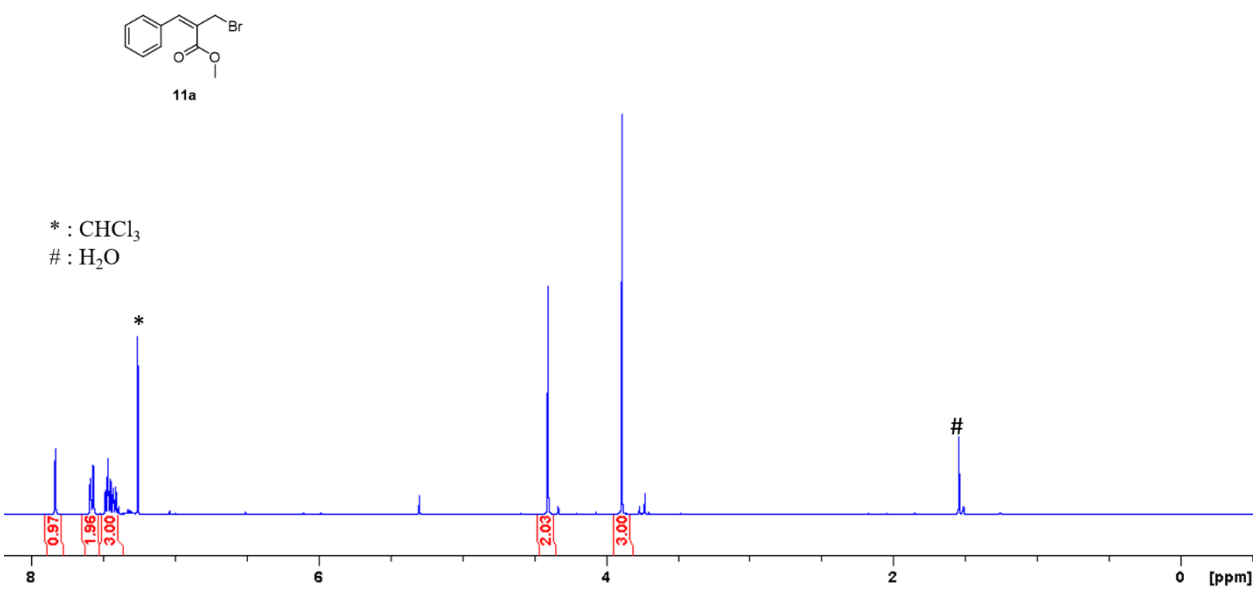

8
200
150
100
50
0
[ppm]

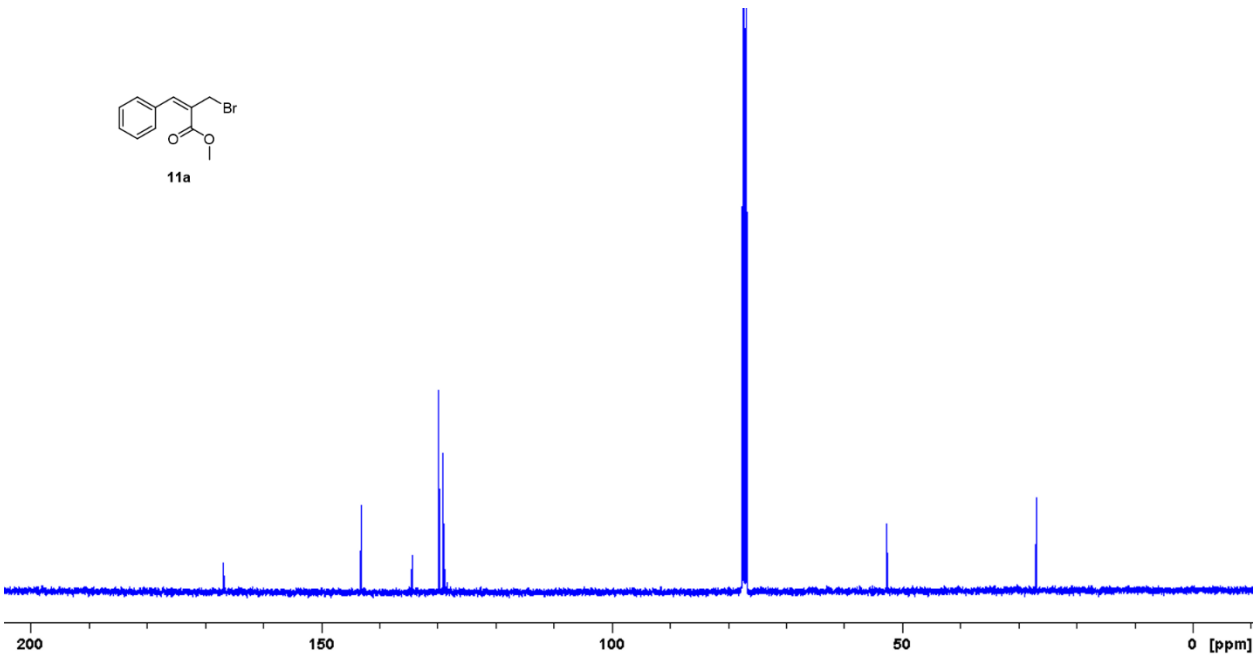

O
O
NH
9
* : CHCl3
# : H2O
*
#
0.88
1.03
1.01
2.00
2.99
2.95
8
6
4
2
0
[ppm]

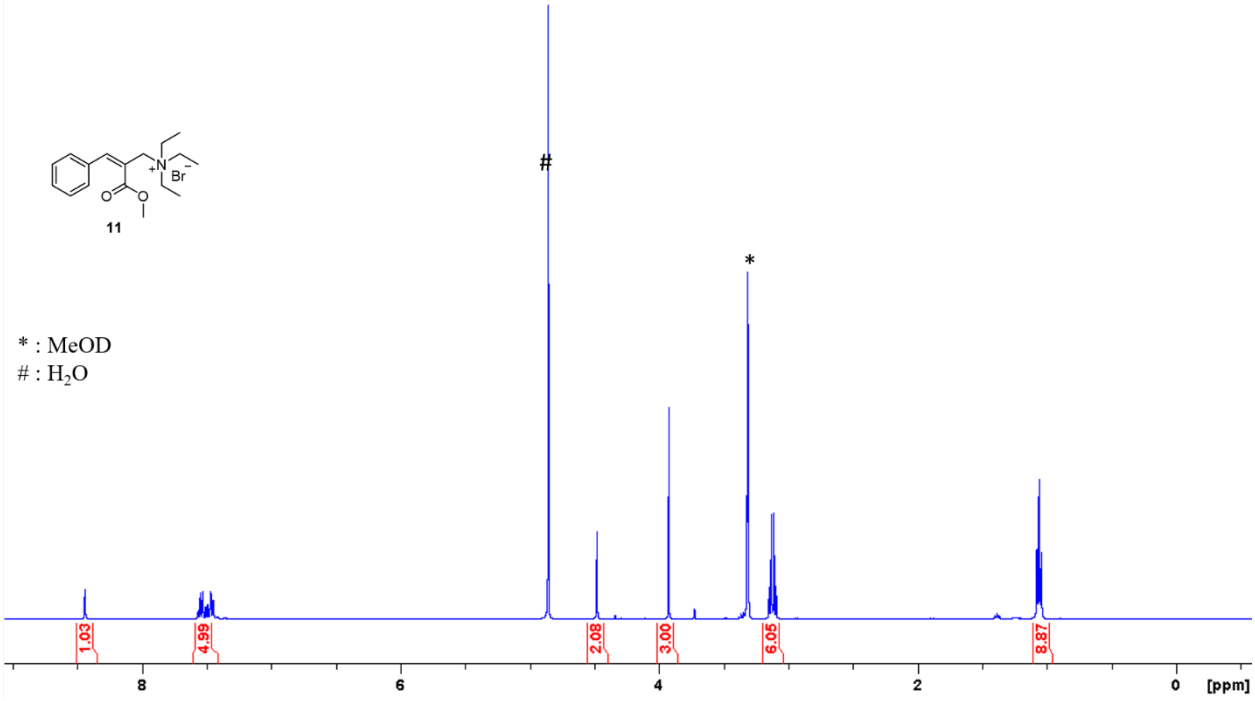

O
O
NH
9
200
150
100
50
0
[ppm]

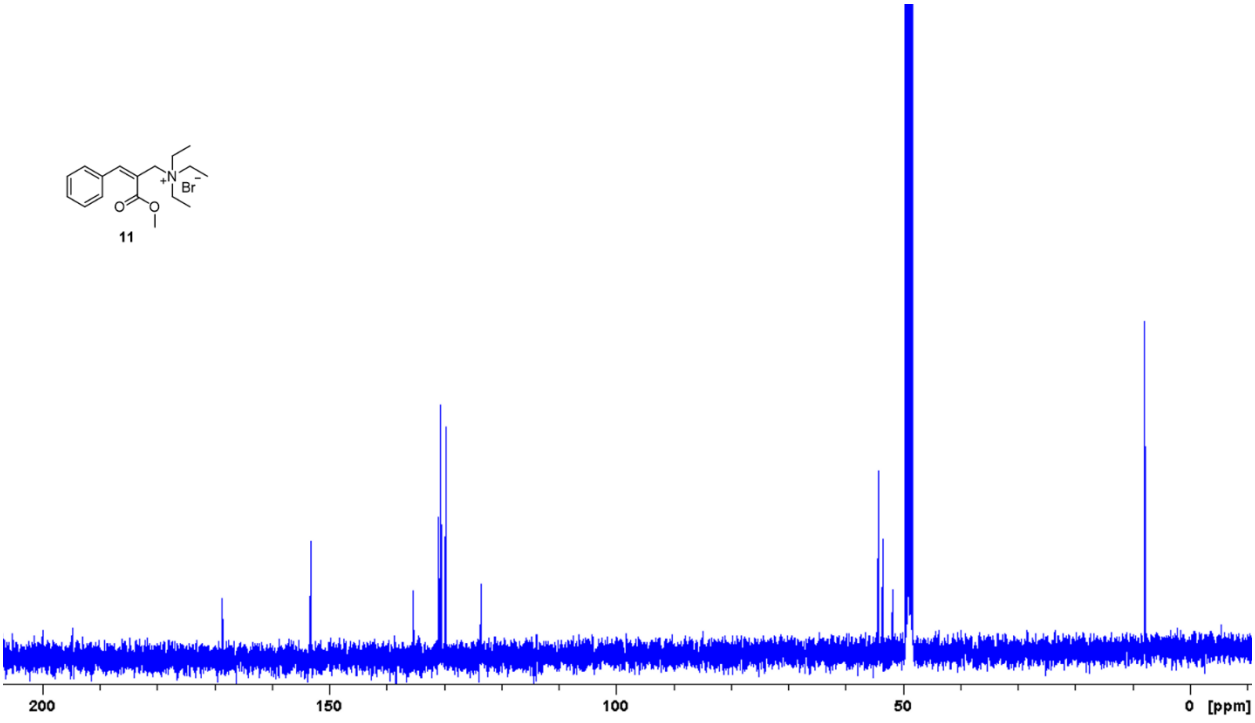

10
* : MeOD
# : H2O
#
*
1.98
1.96
1.00
1.00
1.93
2.91
8
6
4
2
0
[ppm]

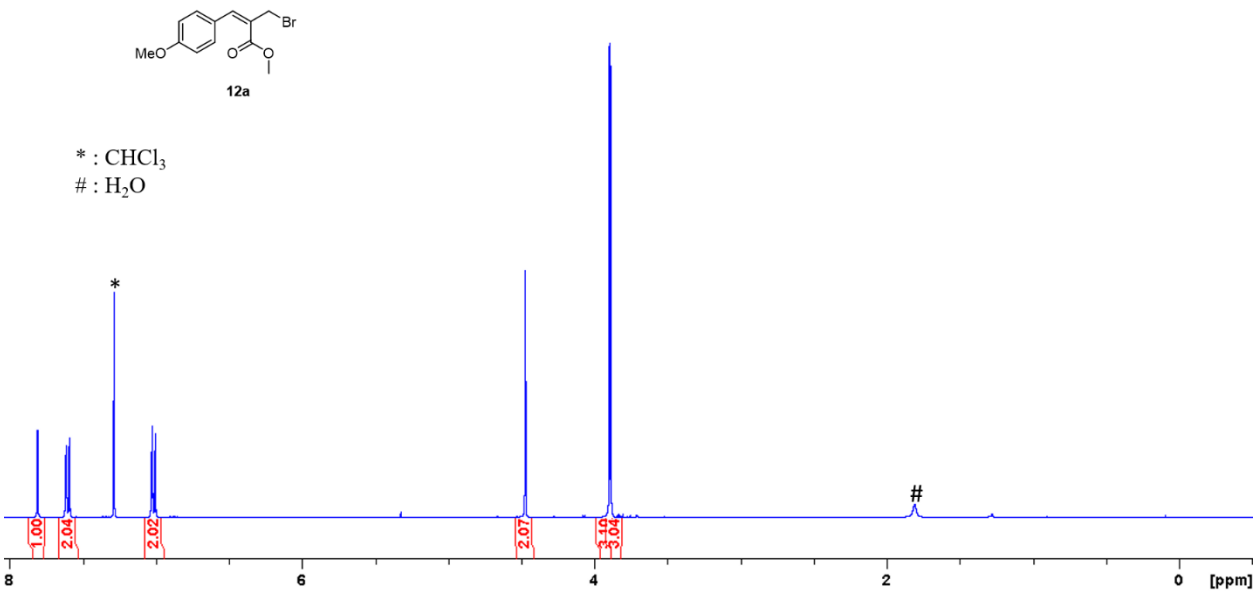

10
200
150
100
50
0
[ppm]

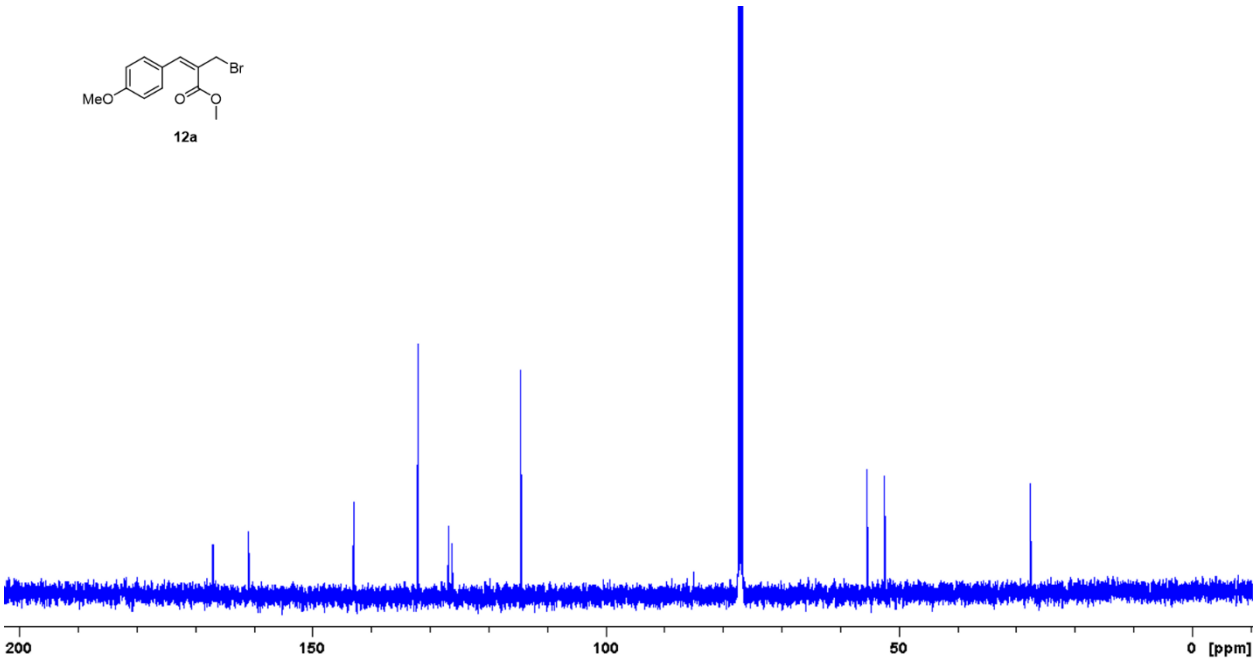

Br
O
O
11a
* : CHCl3
# : H2O
*
#
0.97
1.96
3.00
2.03
3.00
8
6
4
2
0
[ppm]

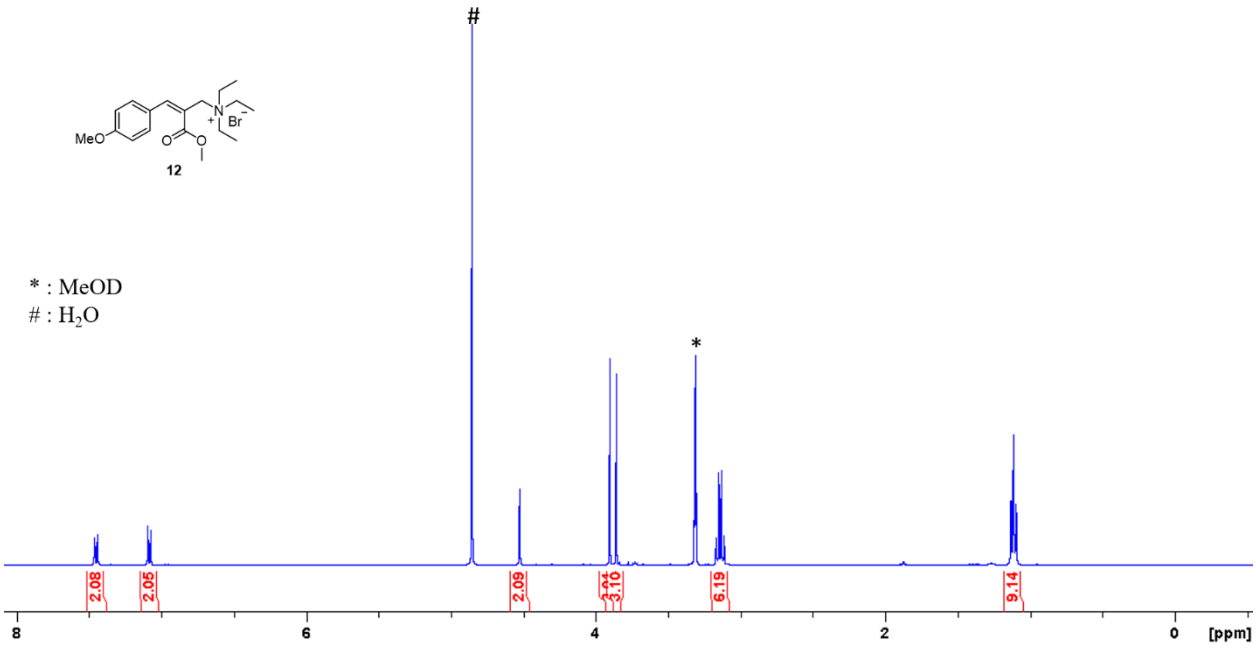

Br
O
O
11a
200
150
100
50
0
[ppm]

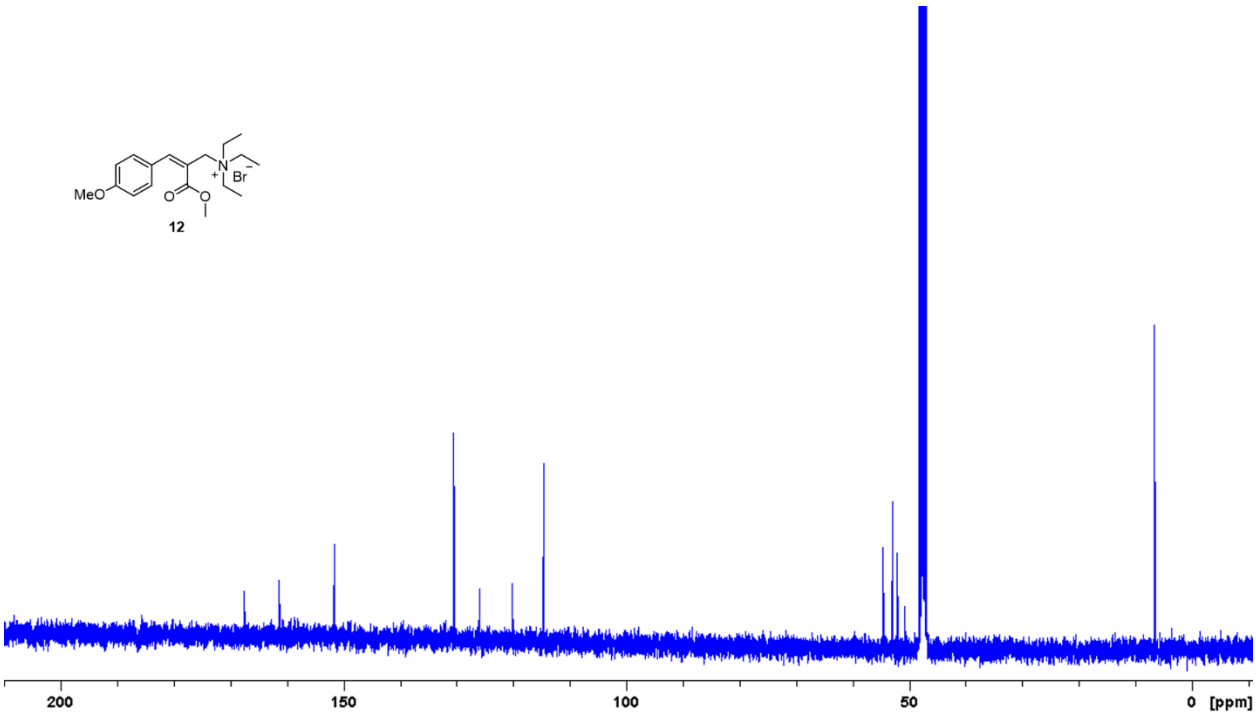

11
#
*
* : MeOD
# : H2O
1.03
4.99
2.08
3.00
6.05
8.87
8
6
4
2
0
[ppm]

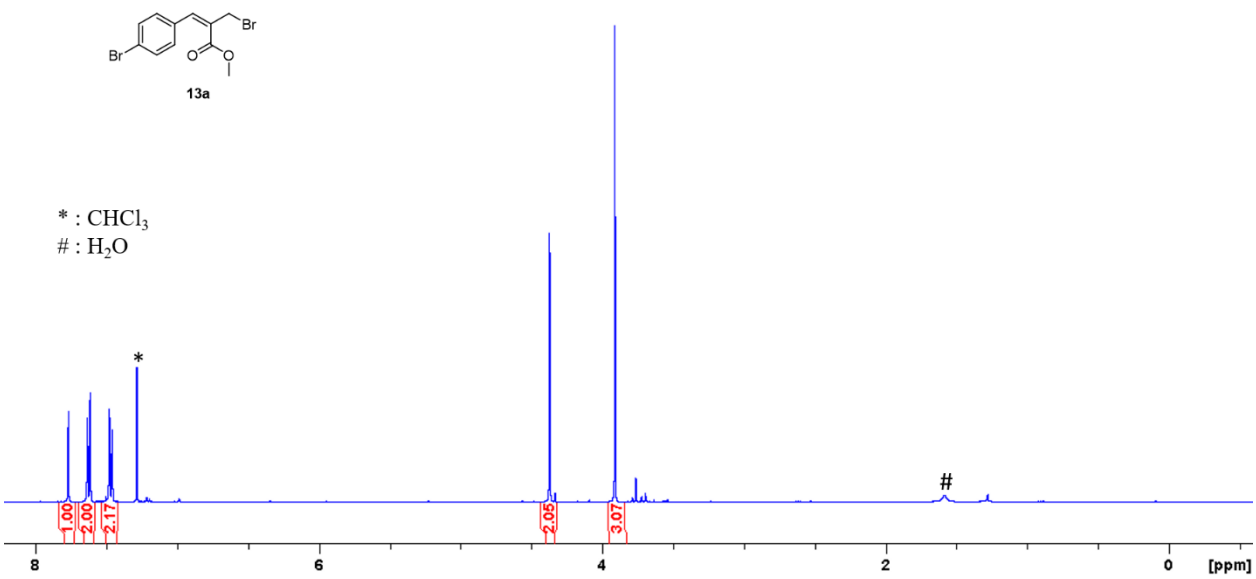

11
200
150
100
50
0
[ppm]

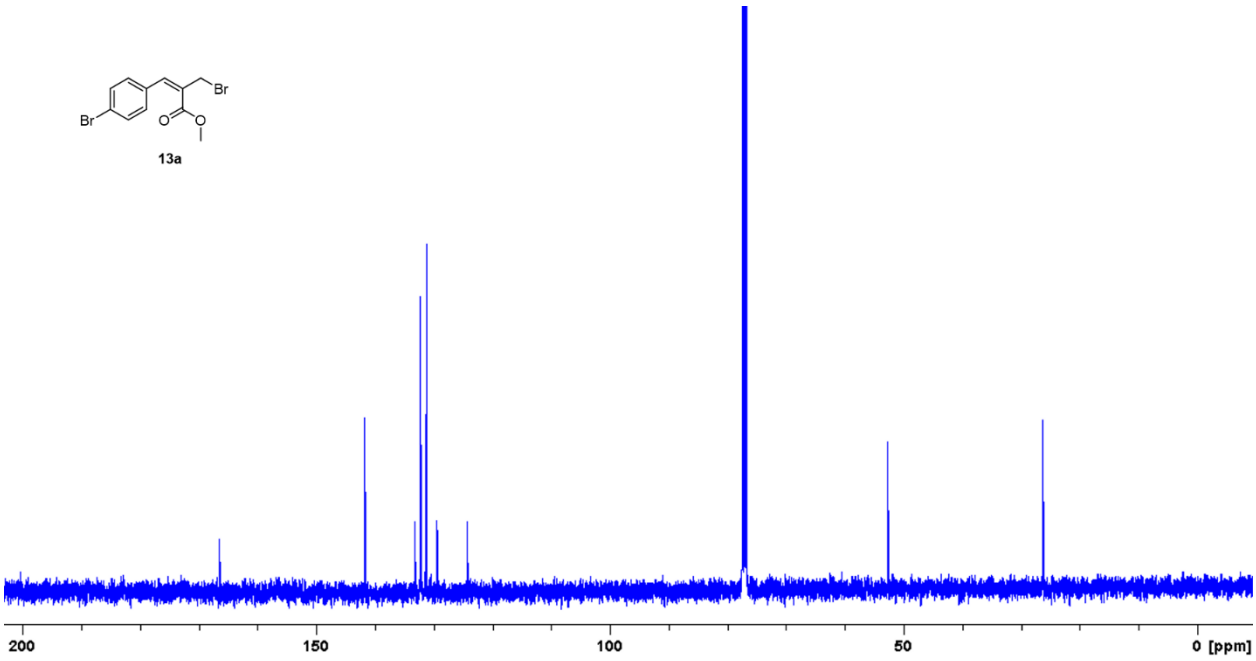

MeO
Br
O
O
12a
* : CHCl3
# : H2O
*
#
1.00
2.04
2.02
2.07
3.10
3.04
8
6
4
2
0
[ppm]

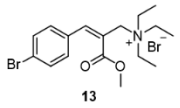

MeO
Br
O
O
12a
200
150
100
50
0
[ppm]


#
MeO
Br
12
* : MeOD
# : H2O
*
2.08
2.05
2.09
3.04
3.10
6.19
9.14
8
6
4
2
0
[ppm]

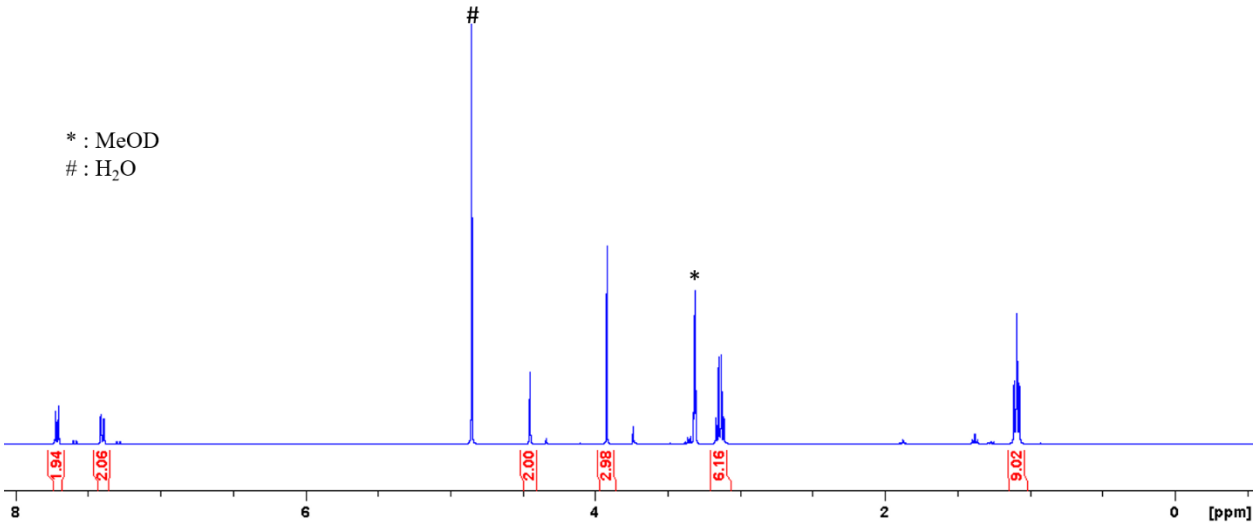

MeO
Br
12
200
150
100
50
0
[ppm]


13a
* : CHCl3
# : H2O
*
#
1.00
2.00
2.17
2.05
3.07
8
6
4
2
0
[ppm]

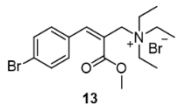

13a
200
150
100
50
0 [ppm]



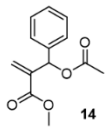
13

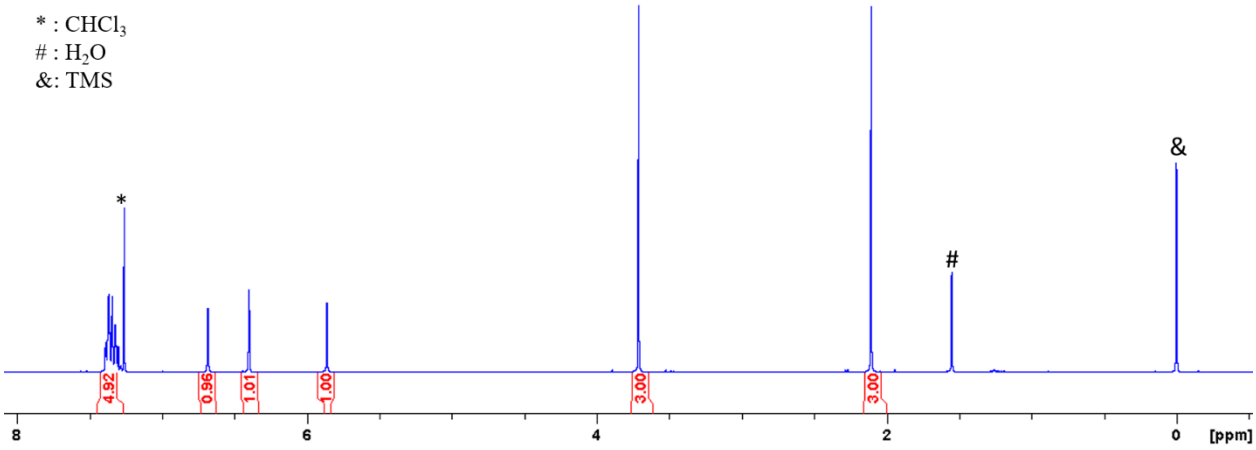


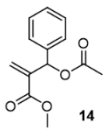
* : MeOD
# : H_2O



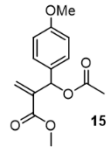
13

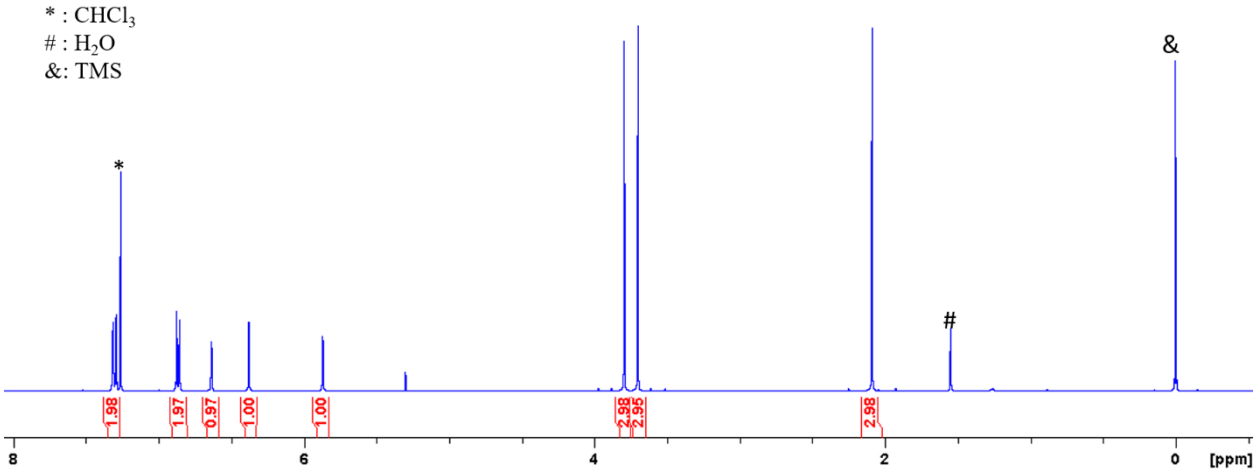

14

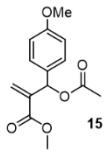

* : CHCl3
# : H2O
&: TMS
*
#
&
4.92
0.96
1.01
1.00
3.00
3.00
8
6
4
2
0
[ppm]


14

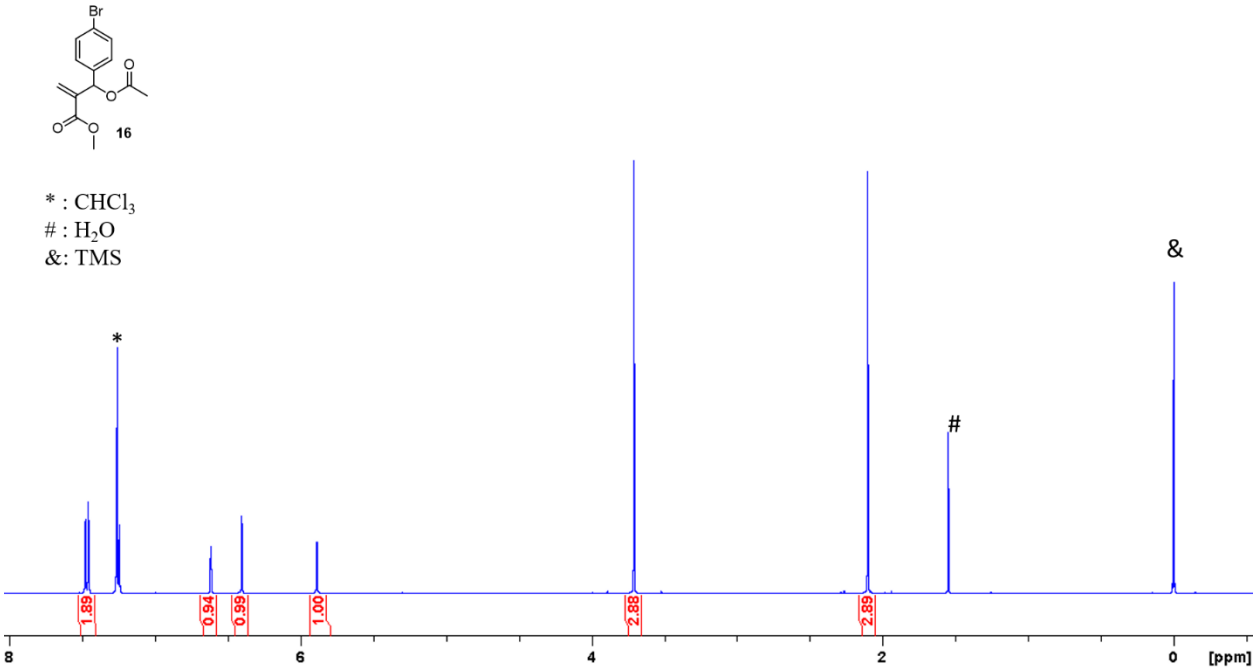
&: TMS
&
200
150
100
50
0
[ppm]

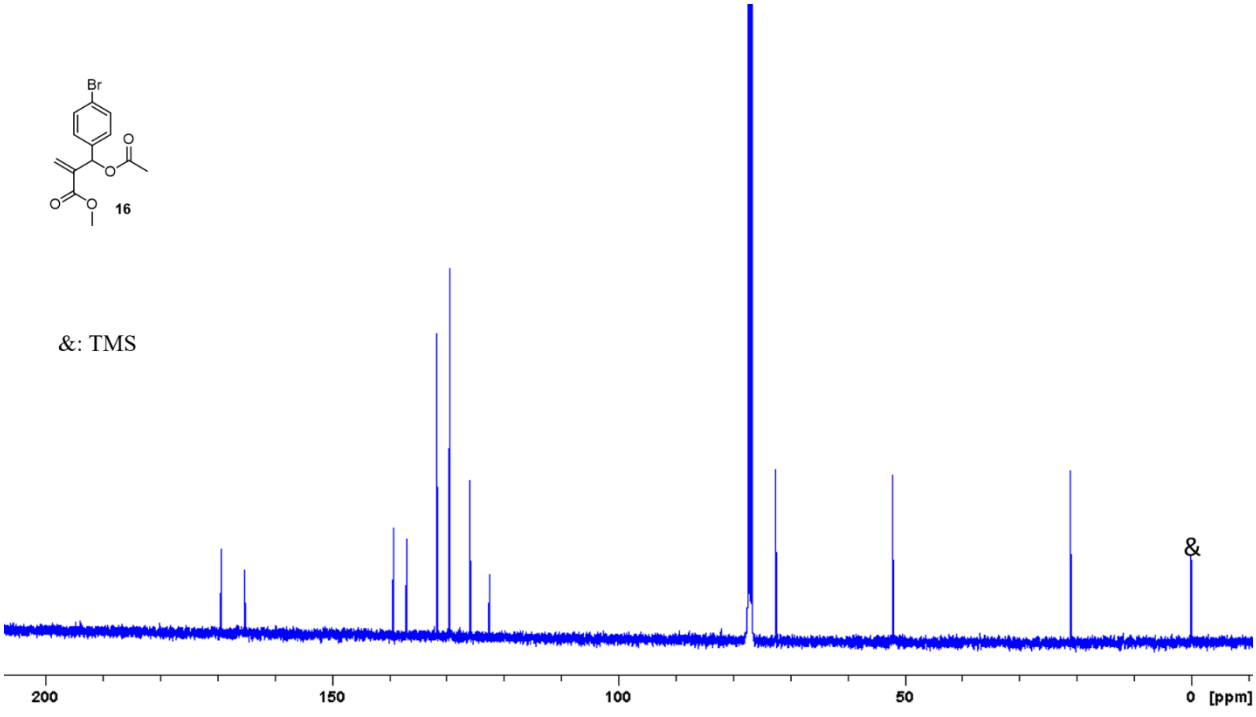

OMe
O
O
O
O
15

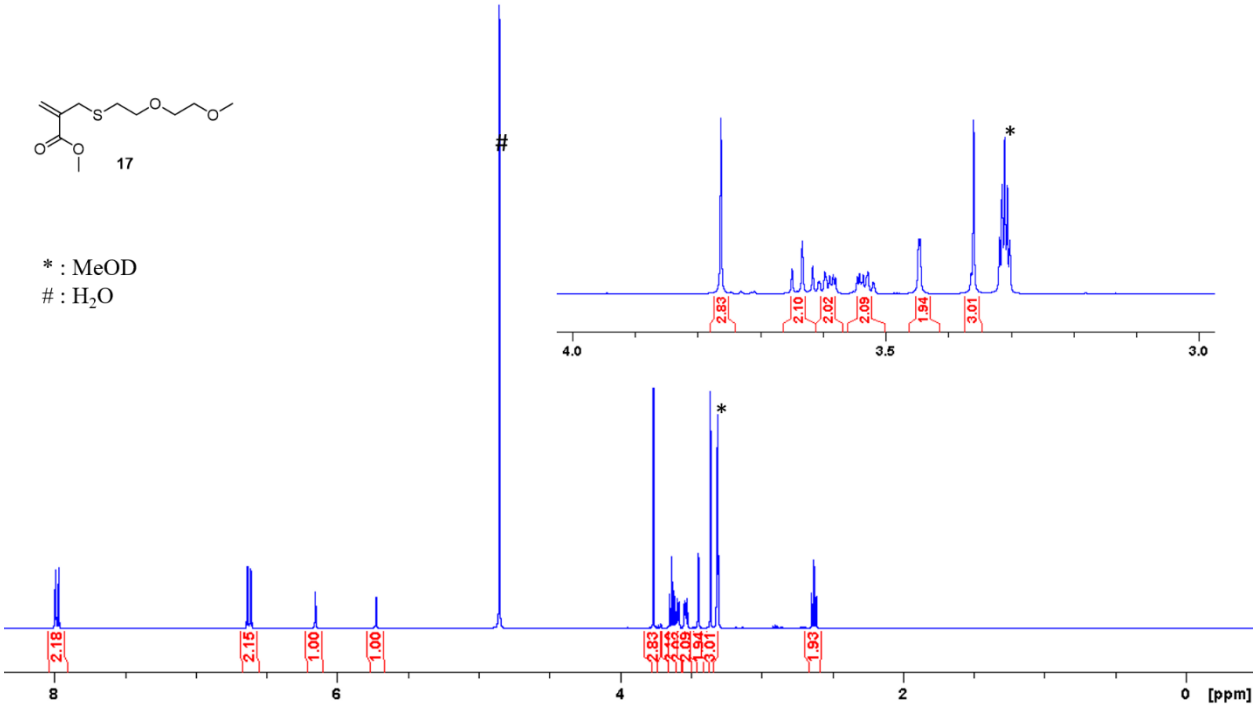

* : CHCl3
# : H2O
&: TMS
*
#
&
1.98
1.97
0.97
1.00
1.00
2.98
2.95
2.98
8
6
4
2
0
[ppm]

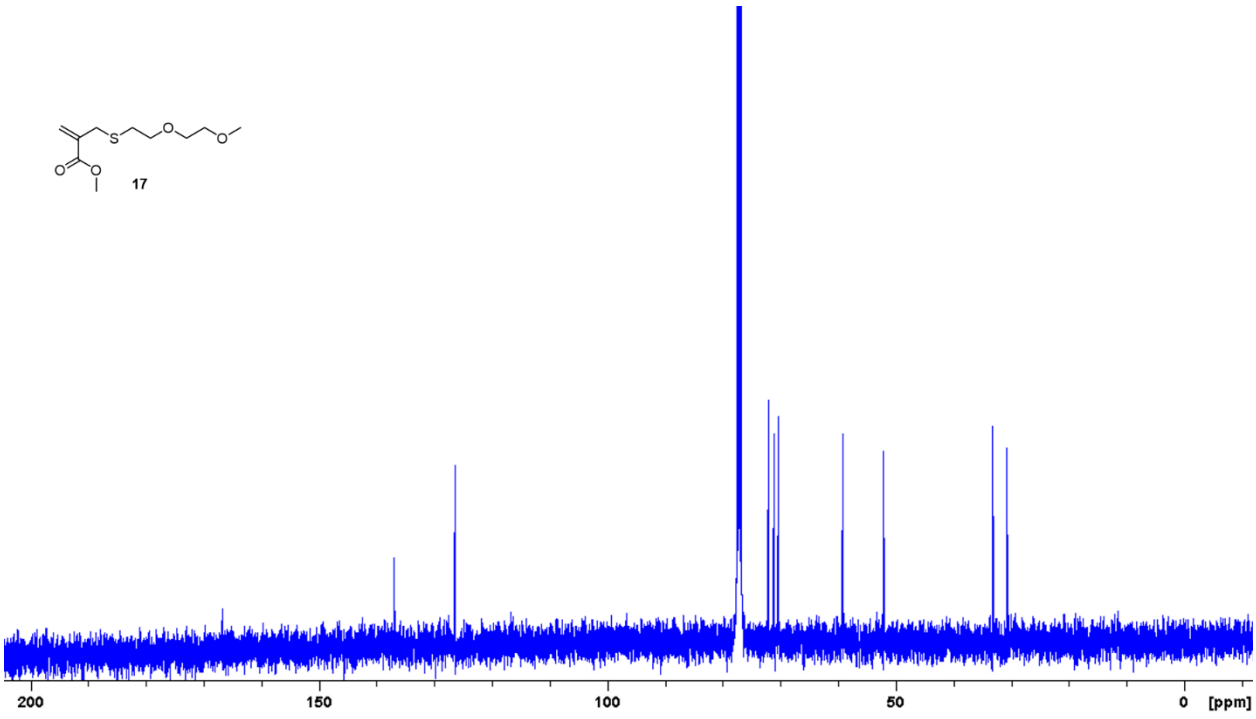

OMe
O
O
O
O
15

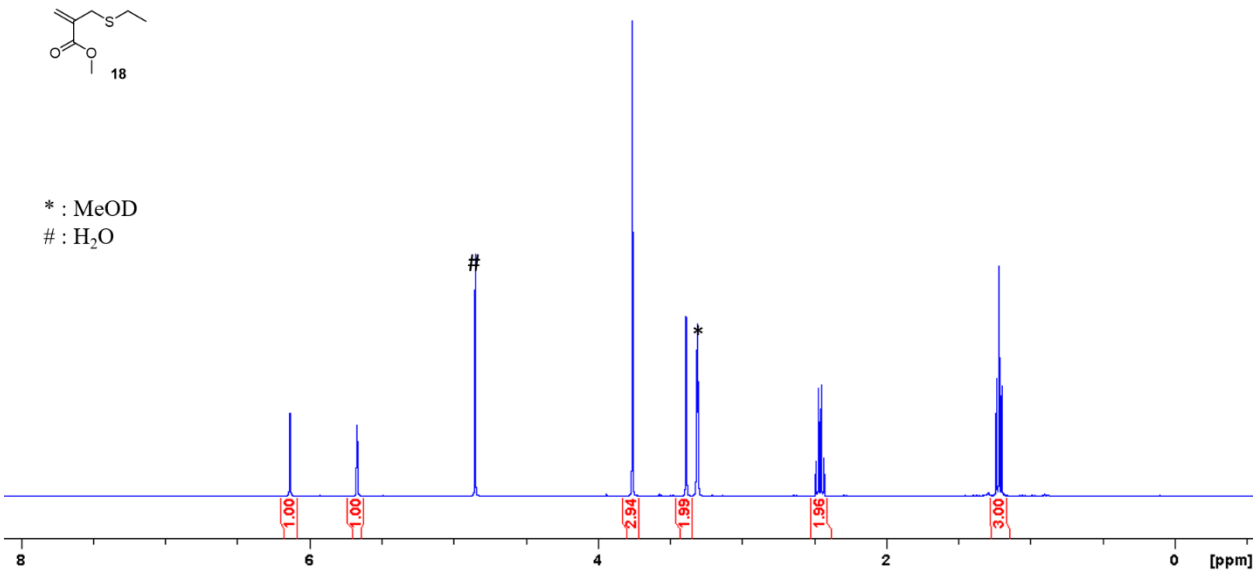
&: TMS
&
200
150
100
50
0
[ppm]

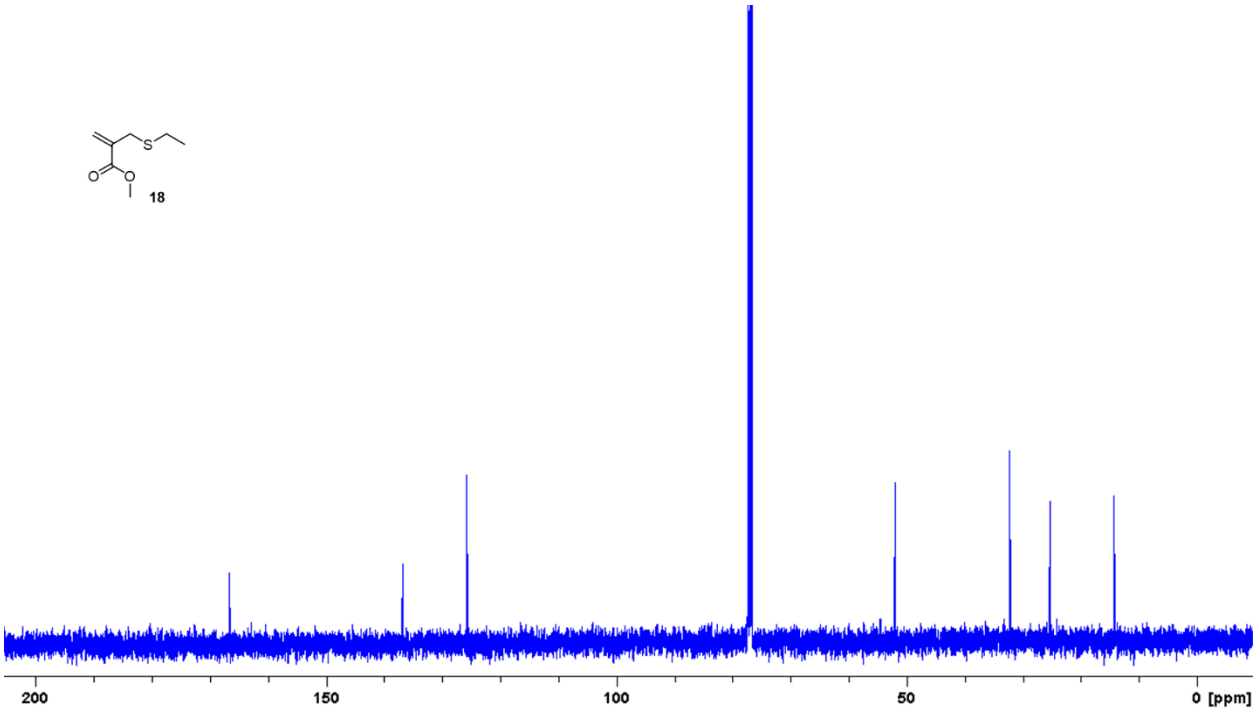

Br
O
O
O
O
16
* : CHCl3
# : H2O
&: TMS
*
#
&
1.89
0.94
0.99
1.00
2.88
2.89
8
6
4
2
0
[ppm]

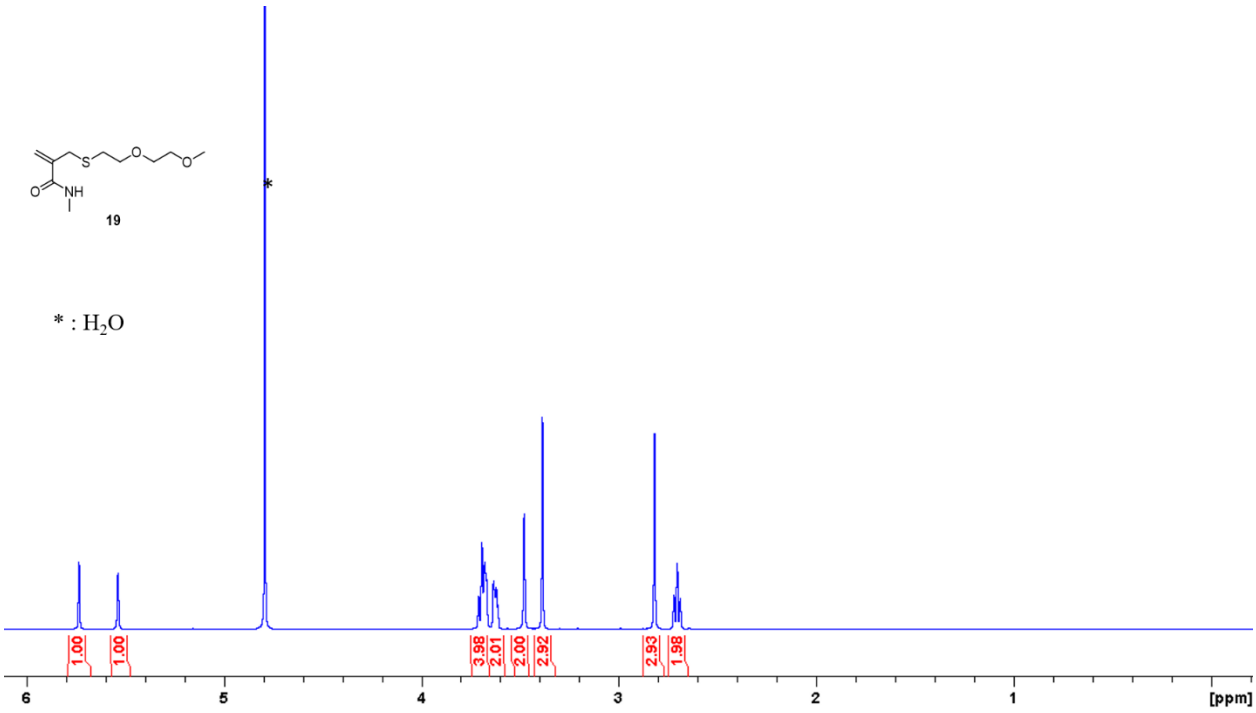

Br
O
O
O
O
16
&: TMS
&
200
150
100
50
0
[ppm]

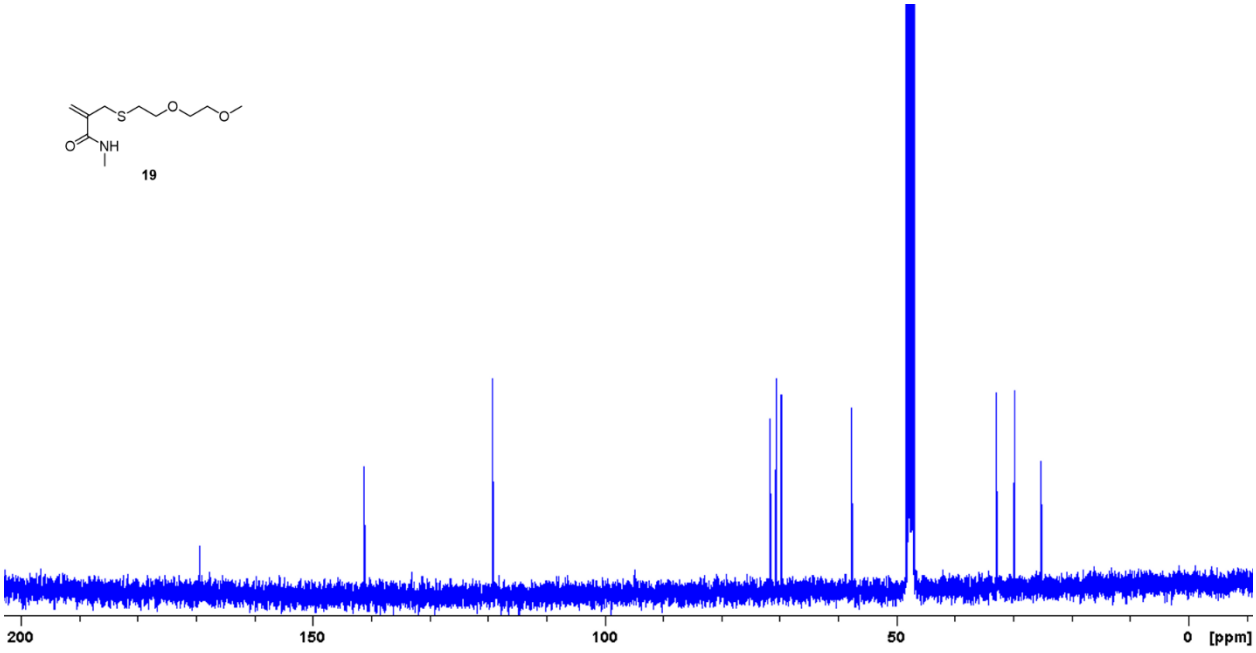

17
* : MeOD
# : H2O
#
*
2.18
2.15
1.00
1.00
2.83
2.10
2.02
2.09
1.94
3.01
1.93
8
6
4
2
0
[ppm]
4.0
3.5
3.0

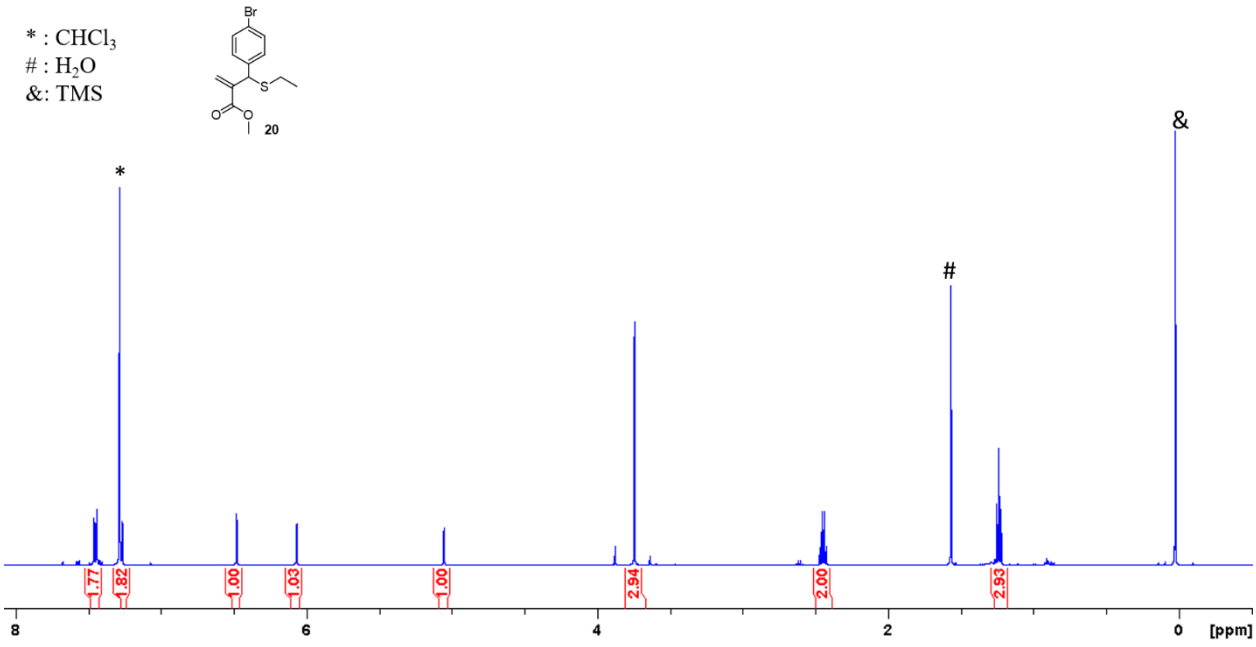

17
200
150
100
50
0
[ppm]

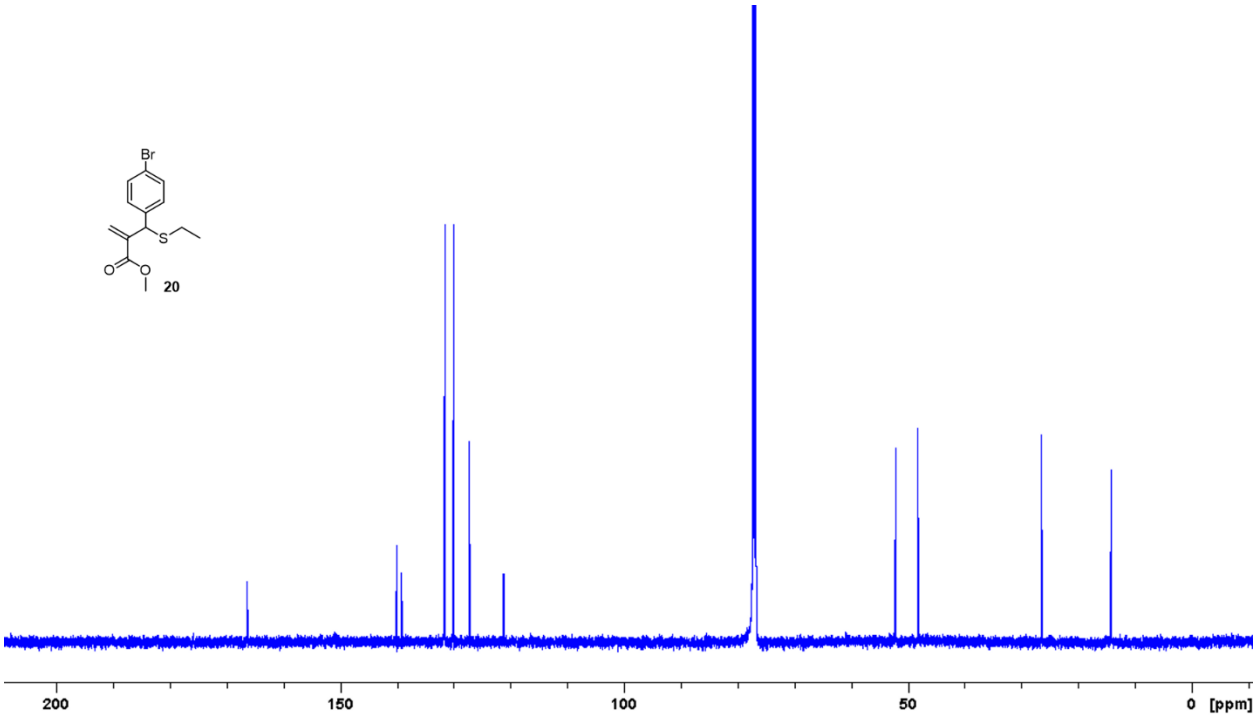

18
* : MeOD
# : H2O
#
*
1.00
1.00
2.94
1.99
1.96
3.00
8
6
4
2
0
[ppm]

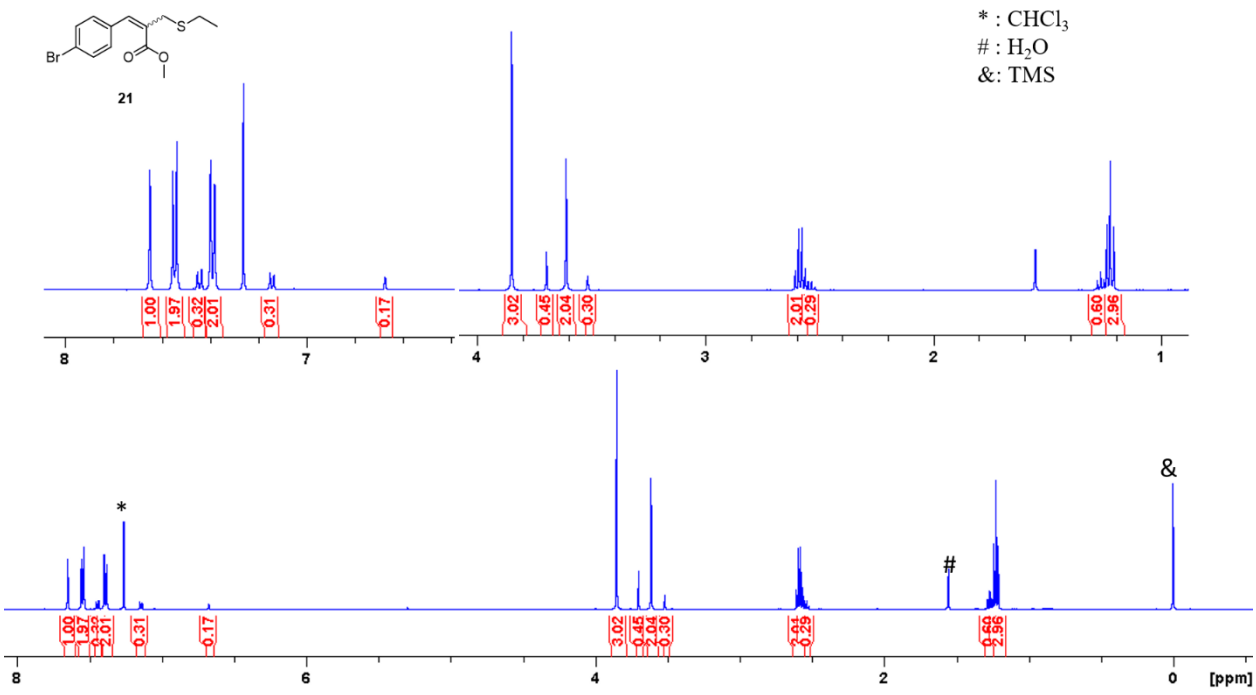

18
200
150
100
50
0 [ppm]

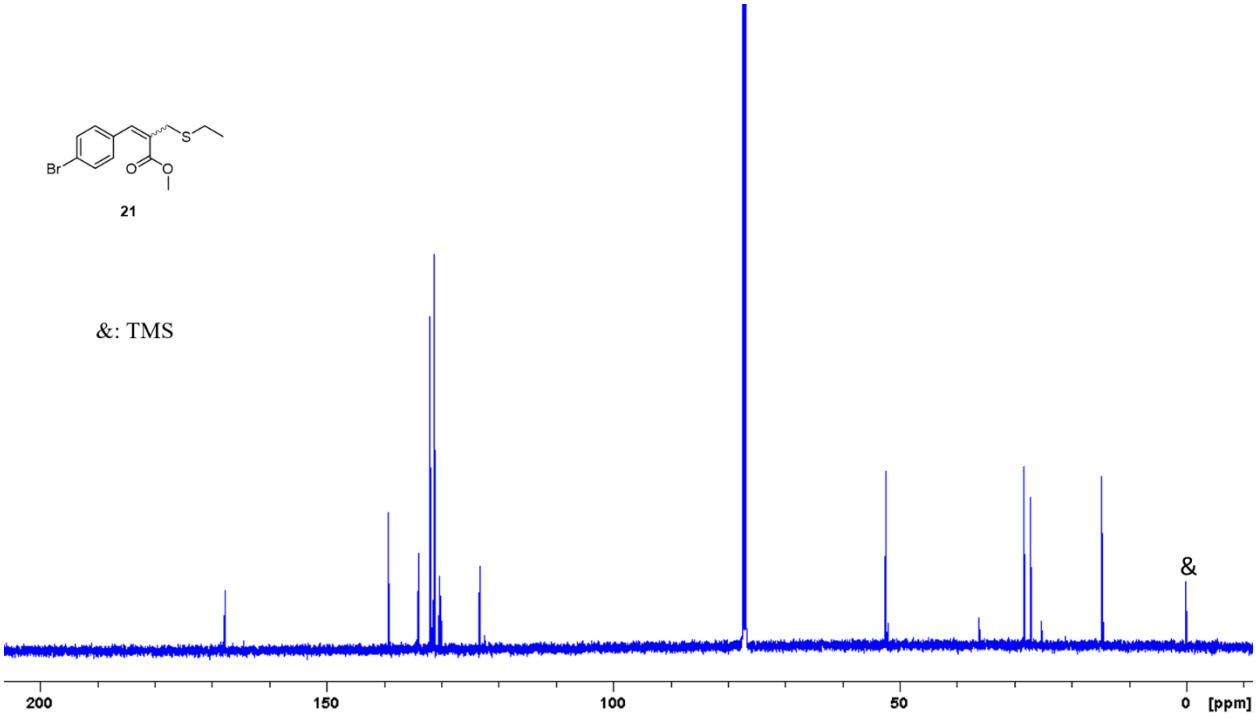

19
* : H_2O
1.00
1.00
3.98
2.01
2.00
2.92
2.93
1.98
6
5
4
3
2
1
[ppm]

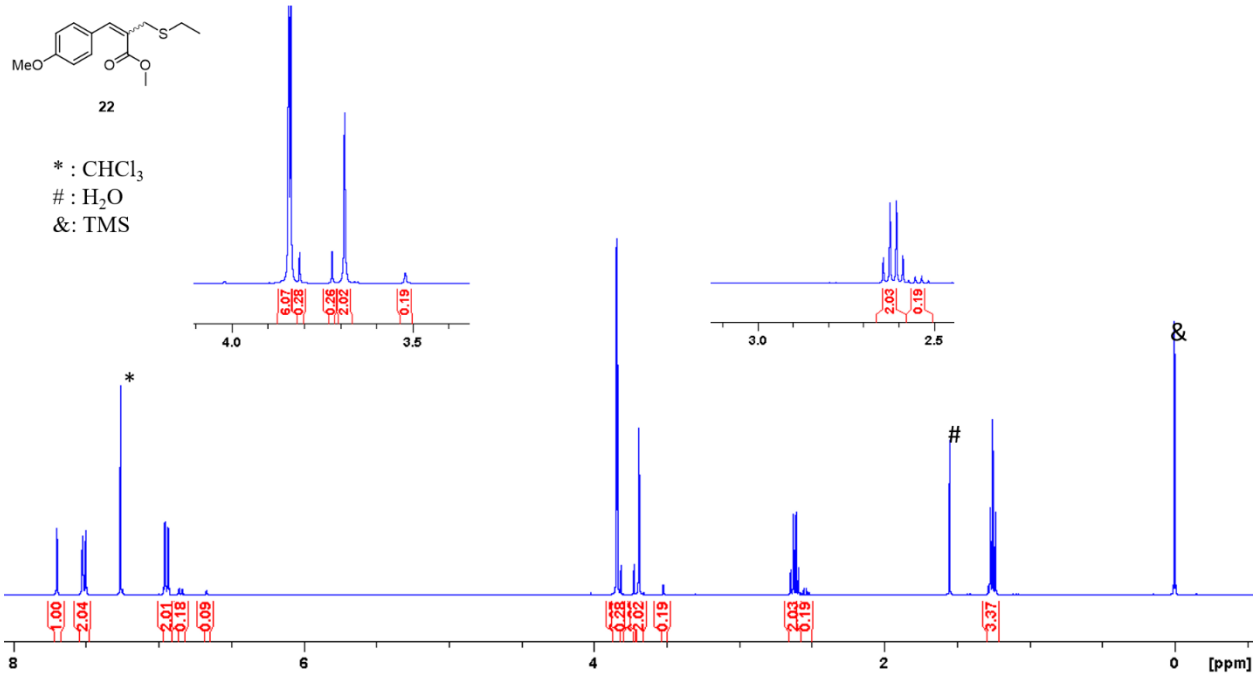

19
200
150
100
50
0
[ppm]

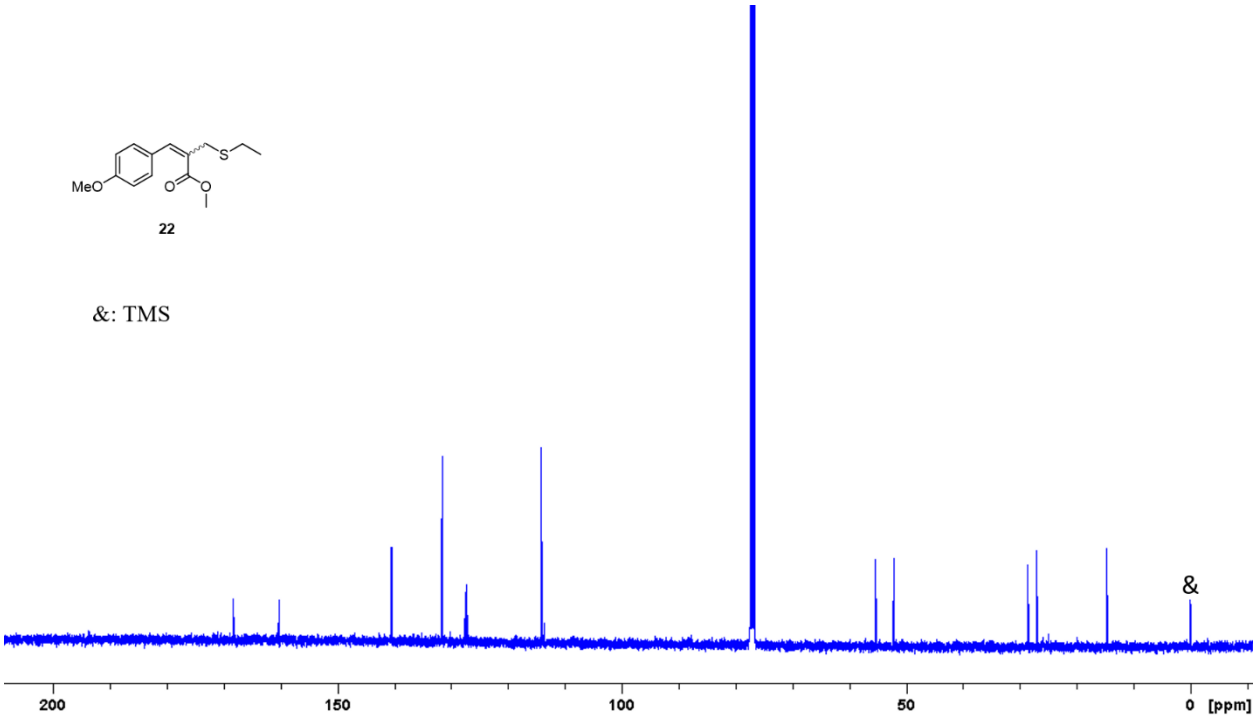

* : CHCl3
# : H2O
&: TMS
Br
S
O
O
20
*
#
&
1.77
1.82
1.00
1.03
1.00
2.94
2.00
2.93
8
6
4
2
0
[ppm]

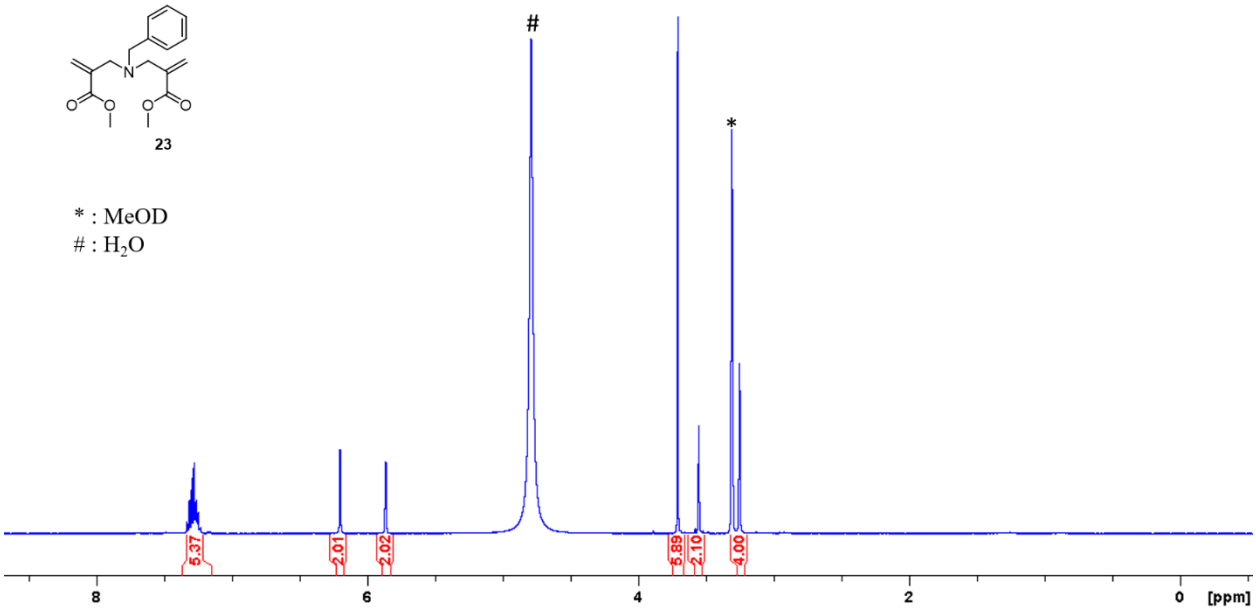

Br
S
O
O
20
200
150
100
50
0
[ppm]

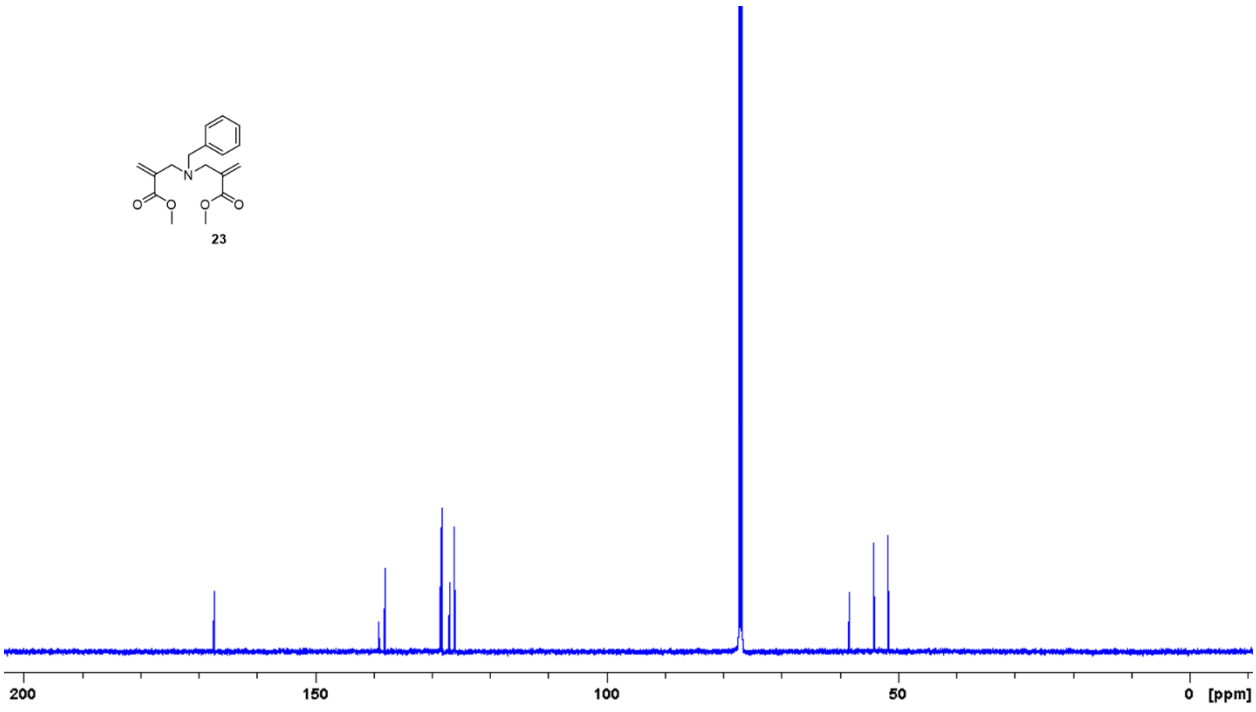

21
* : CHCl3
# : H2O
&: TMS
1.00
1.97
0.32
2.01
0.31
0.17
3.02
0.45
2.04
0.30
2.01
0.29
0.60
2.96
[ppm]

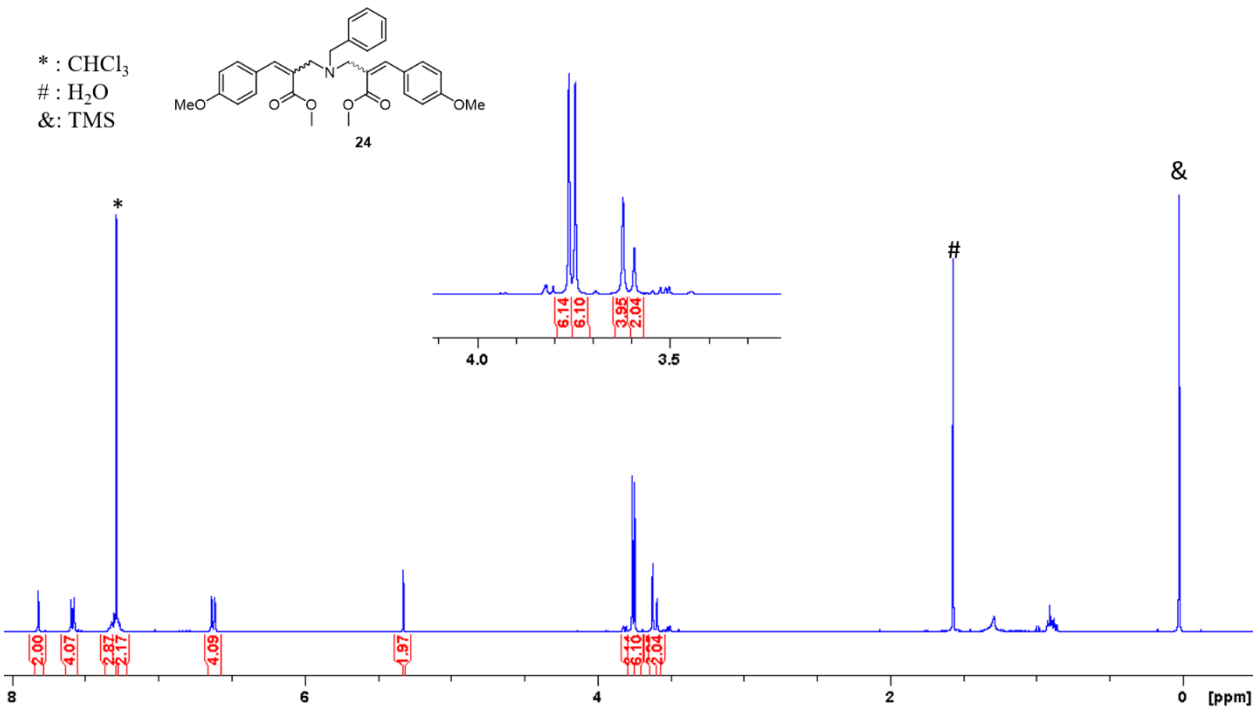

21
&: TMS
[ppm]

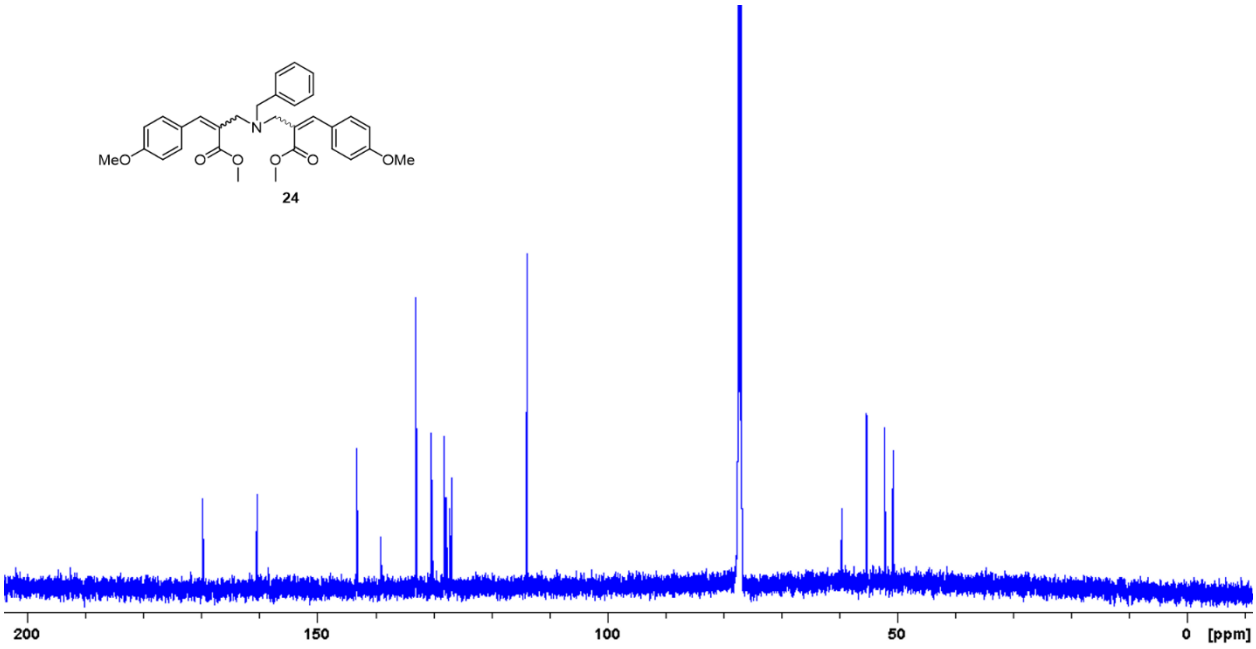

MeO
S
O
O
22
* : CHCl3
# : H2O
&: TMS
6.07
0.28
0.26
2.02
0.19
2.03
0.19
*
#
&
1.00
2.04
2.01
0.18
0.09
0.28
0.15
2.02
0.19
2.03
6.19
3.37
8
6
4
2
0
[ppm]

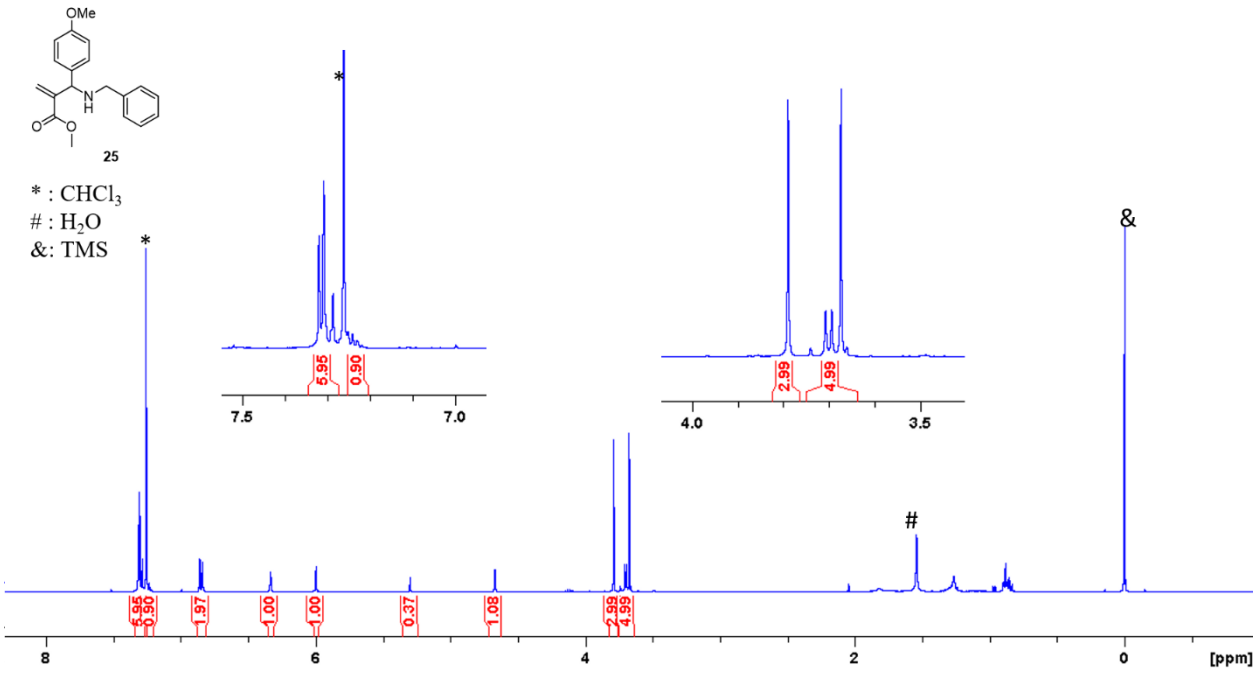

MeO
S
O
O
22
&: TMS
&
200
150
100
50
0
[ppm]

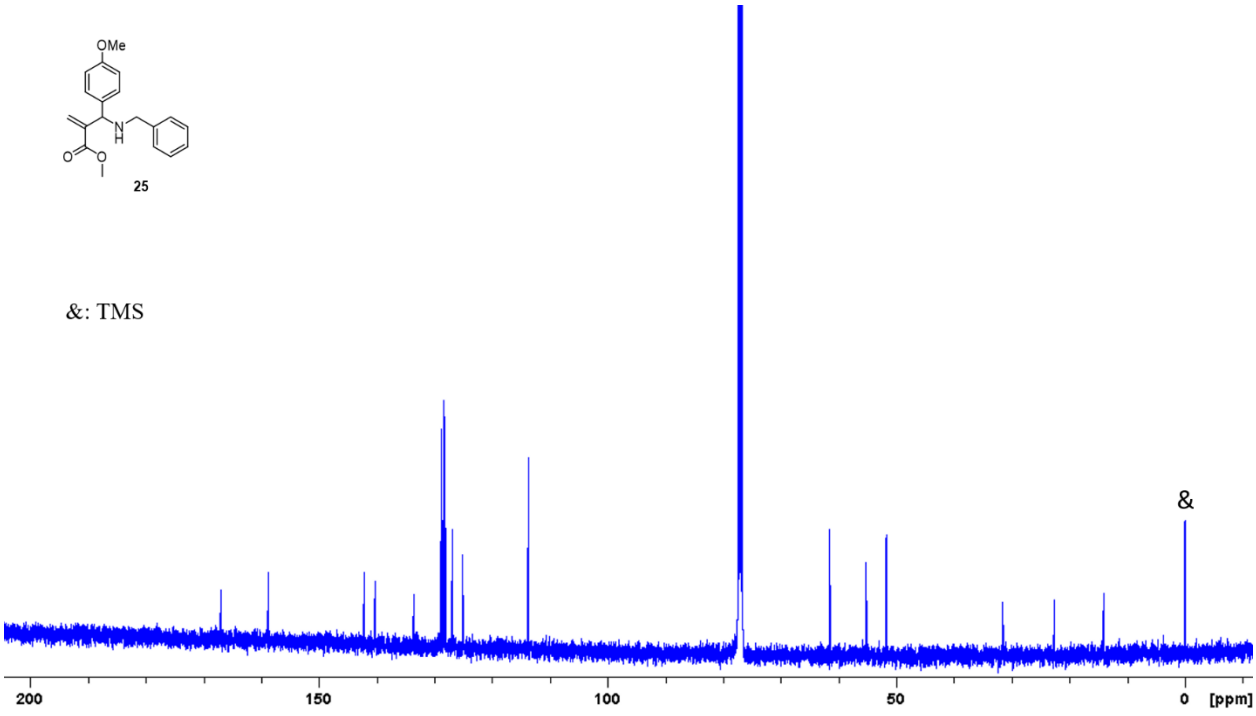

23
* : MeOD
# : H2O
#
*
5.37
2.01
2.02
5.89
2.10
4.00
8
6
4
2
0
[ppm]

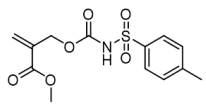

23
200
150
100
50
0
[ppm]


* : CHCl3
# : H2O
&: TMS
MeO
OMe
24
*
#
&
6.14
6.10
3.95
2.04
4.0
3.5
2.00
4.07
2.87
2.17
4.09
1.97
6.11
2.10
2.04
8
6
4
2
0
[ppm]

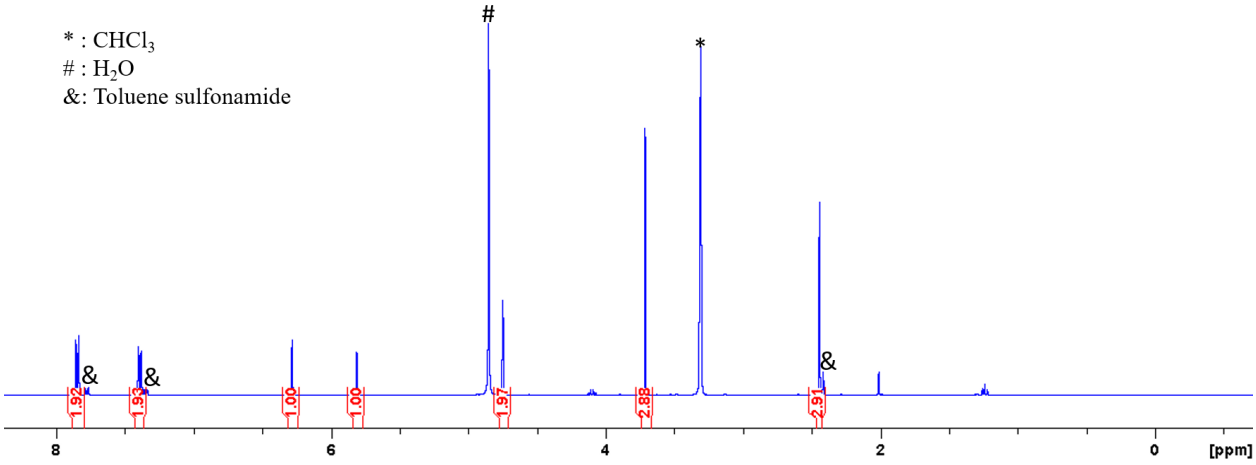

MeO
OMe
24
200
150
100
50
0
[ppm]

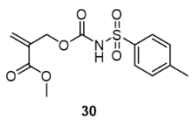

OMe
N
H
O
O
25
* : CHCl3
# : H2O
&: TMS
*
&
#
5.95
0.90
2.99
4.99
7.5
7.0
4.0
3.5
6.95
0.90
1.97
1.00
1.00
0.37
1.08
2.99
4.99
8
6
4
2
0
[ppm]


OMe
N
H
O
O
25
&: TMS
&
200
150
100
50
0
[ppm]



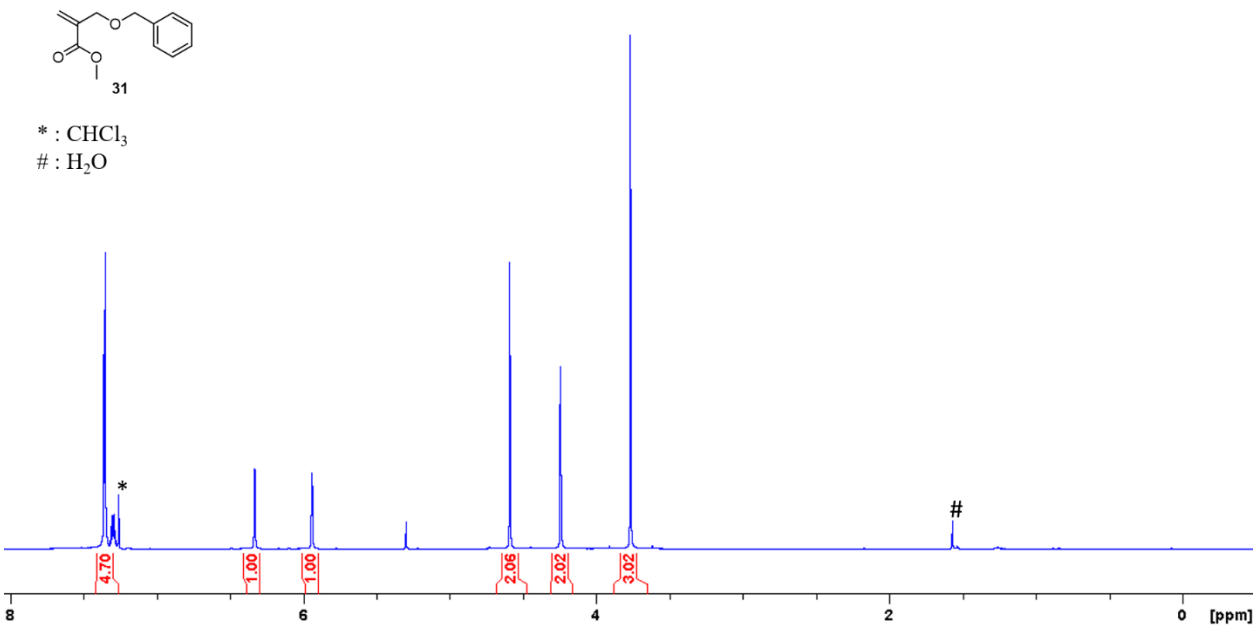
30

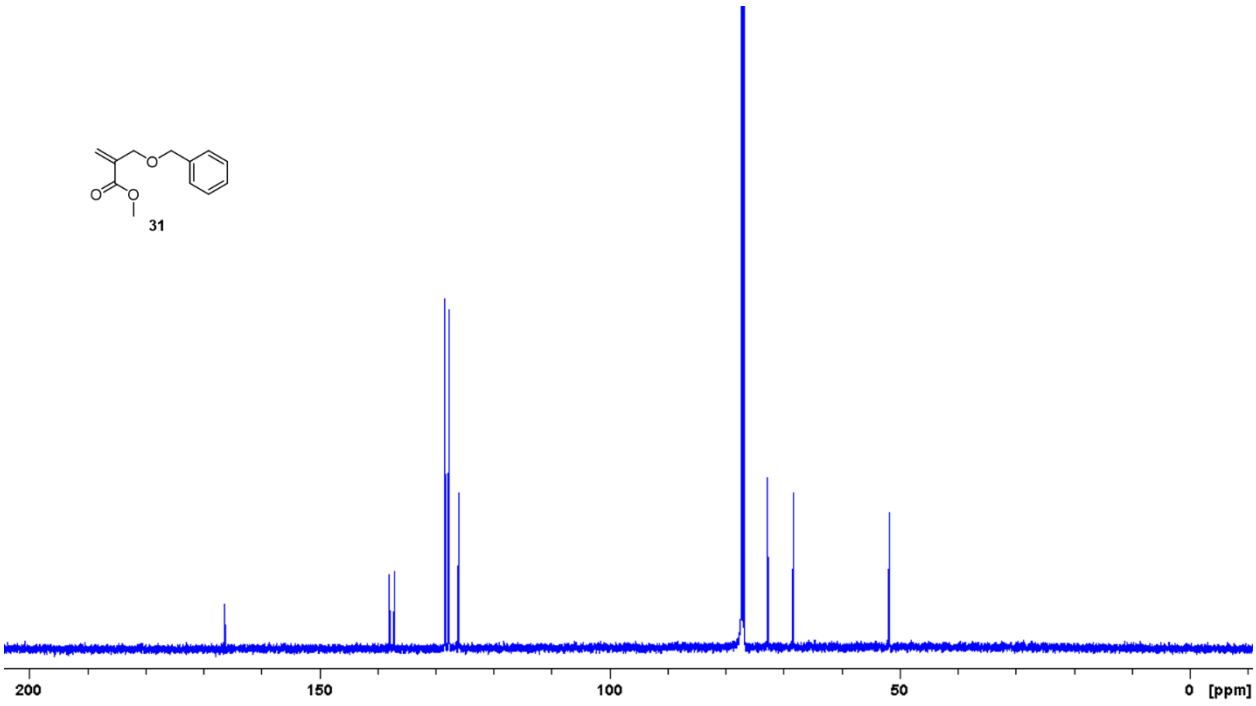

* : CHCl3
# : H2O
&: Toluene sulfonamide
#
*
&
&
&
1.92
1.93
1.00
1.00
1.97
2.88
2.91
8
6
4
2
0
[ppm]

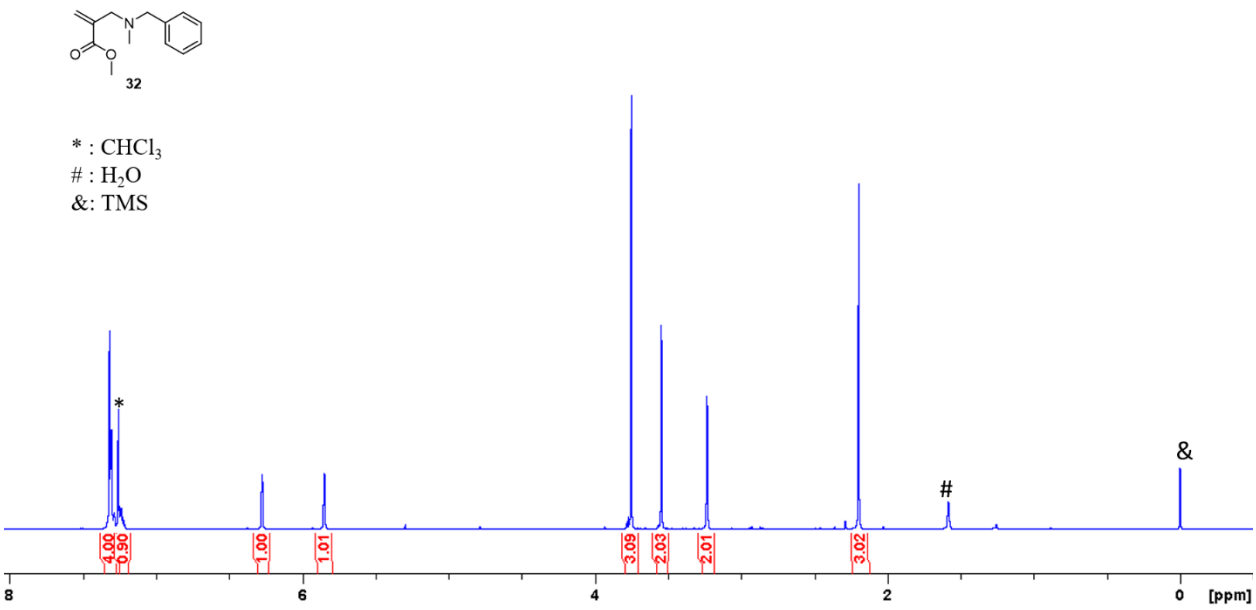


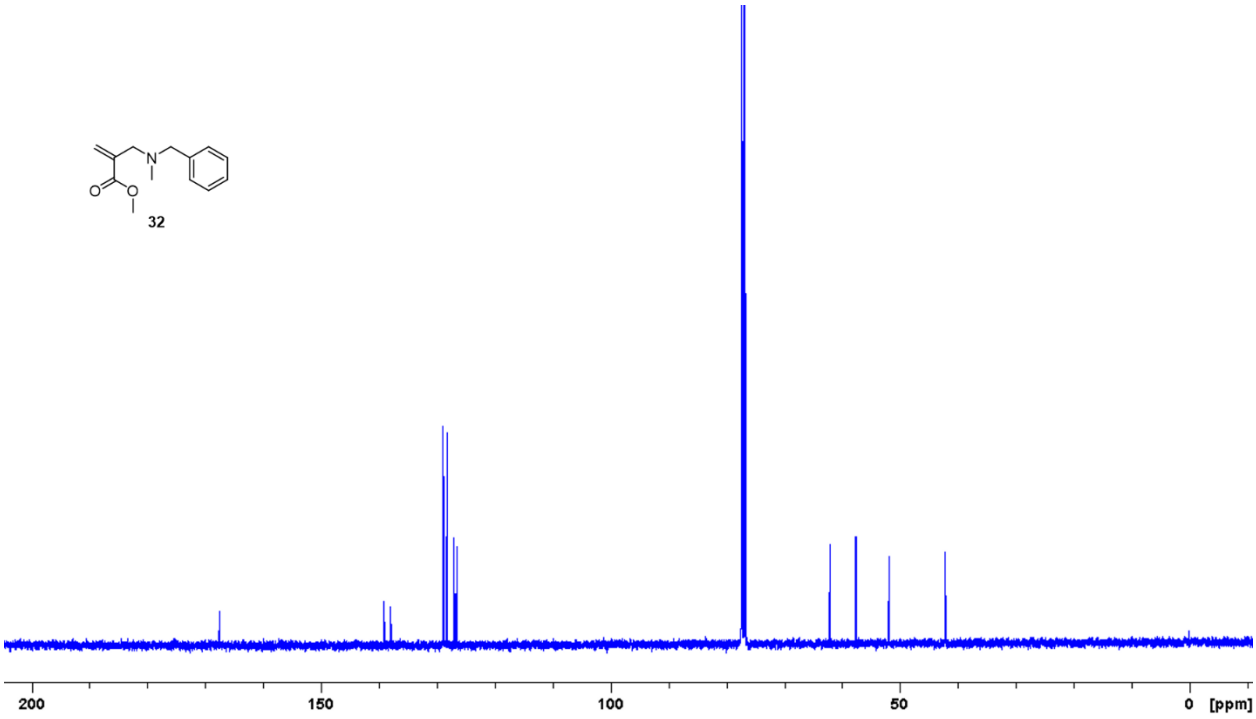
30

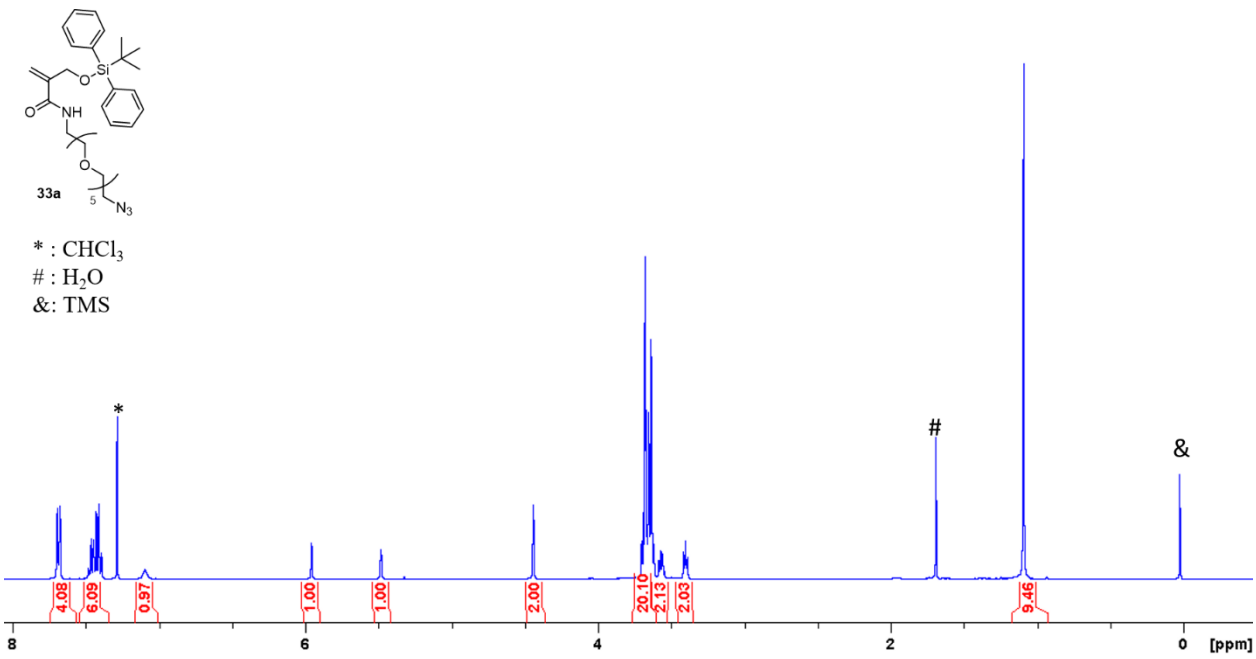
200
150
100
50
0
[ppm]

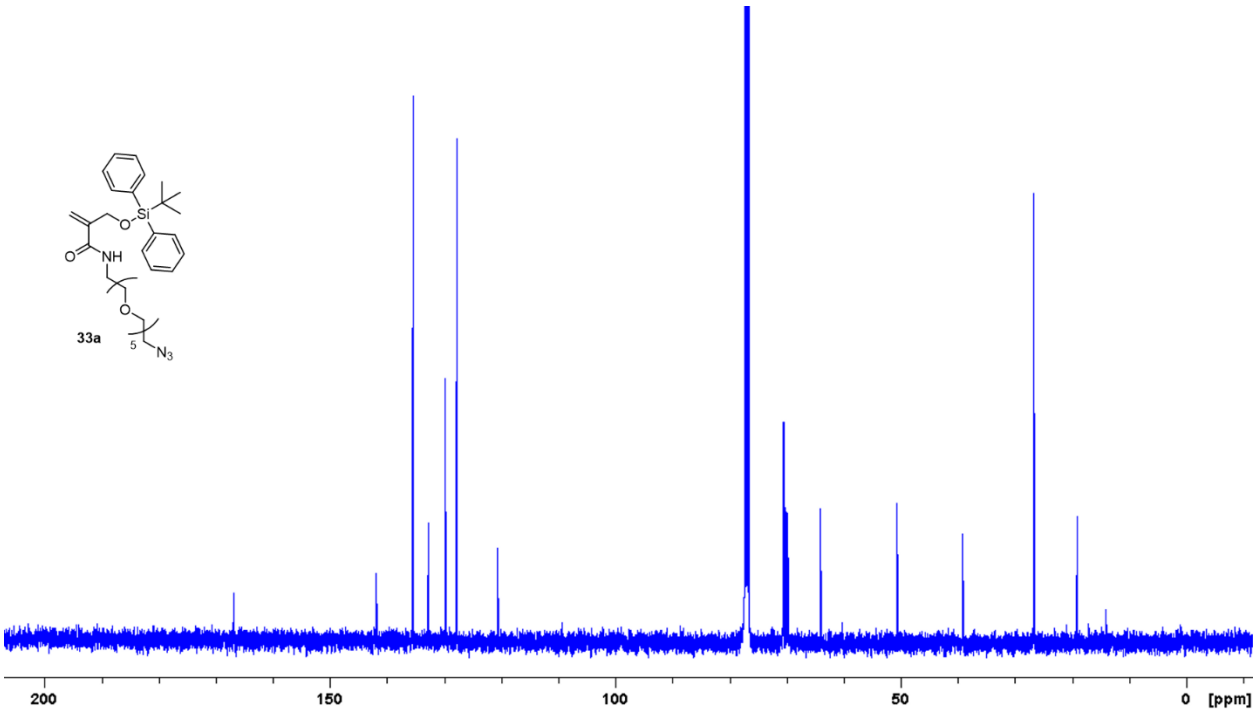

31
* : CHCl3
# : H2O
*
#
4.70
1.00
1.00
2.06
2.02
3.02
8
6
4
2
0
[ppm]

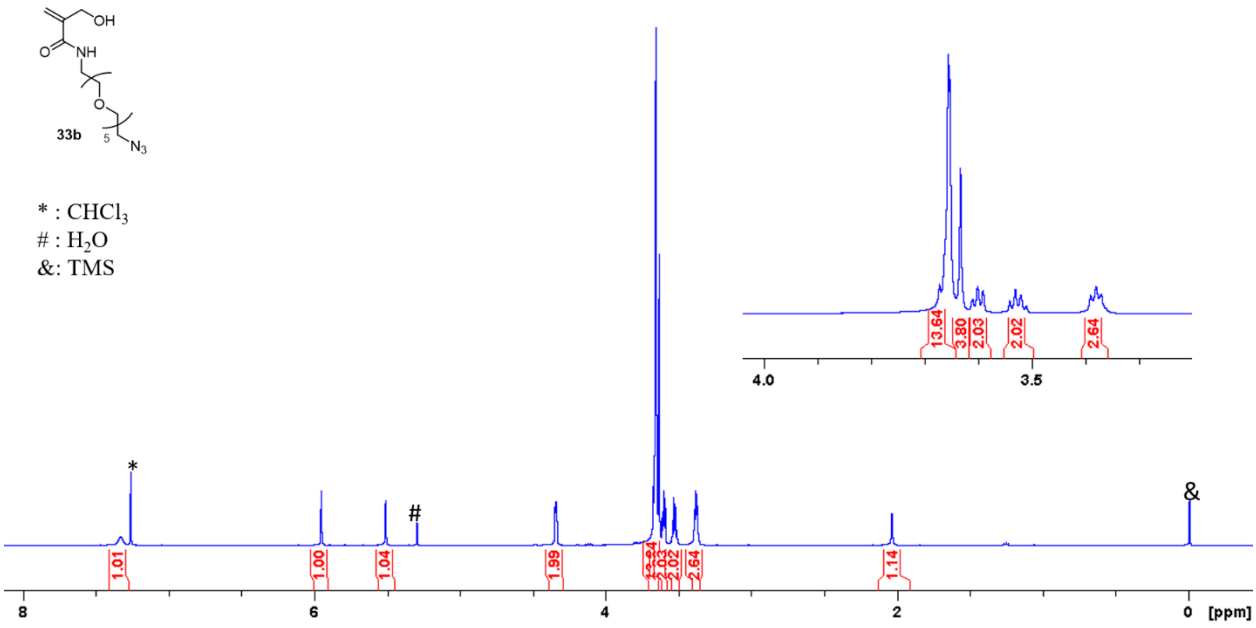

31
200
150
100
50
0
[ppm]

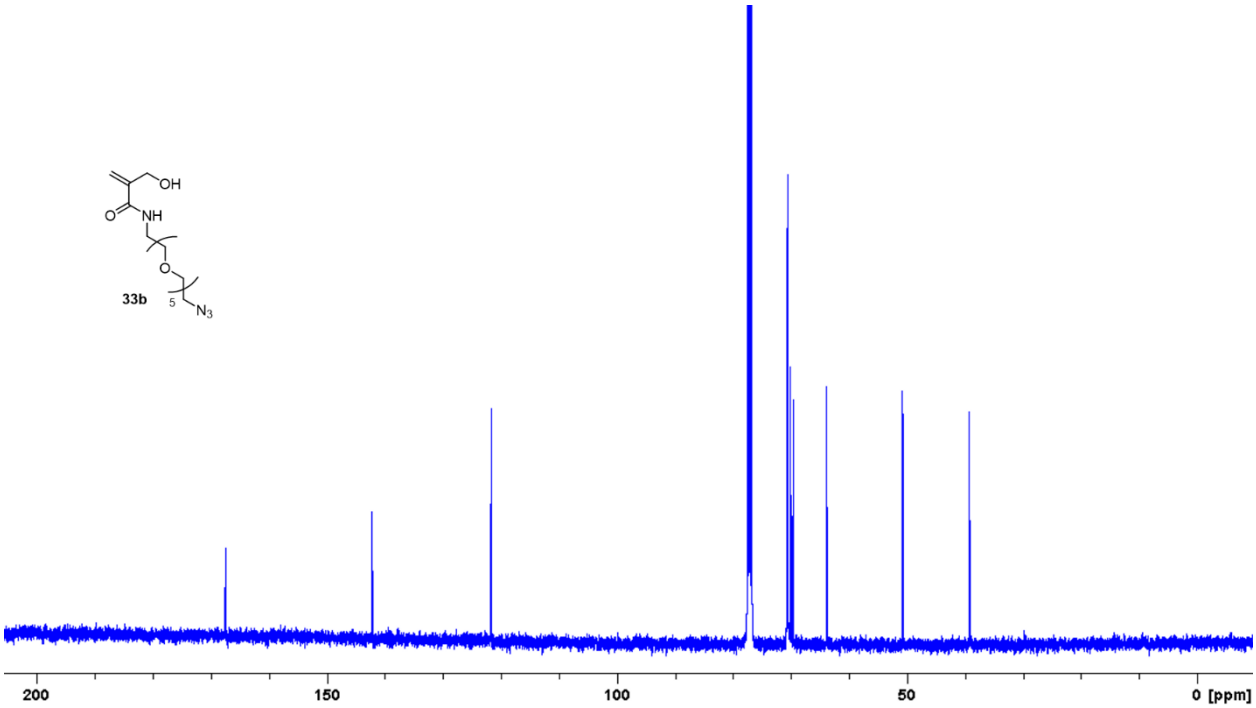

32
* : CHCl3
# : H2O
&: TMS
*
#
&
4.00
0.90
1.00
1.01
3.09
2.03
2.01
3.02
8
6
4
2
0
[ppm]

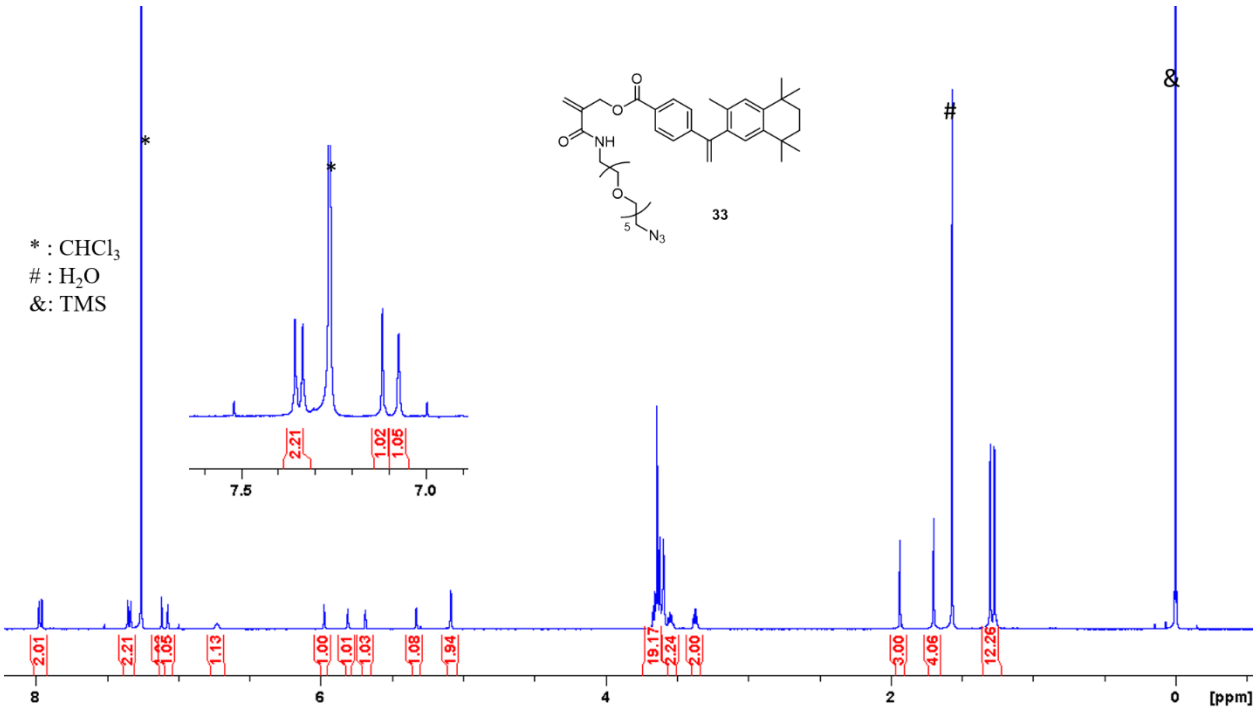

32
200
150
100
50
0
[ppm]

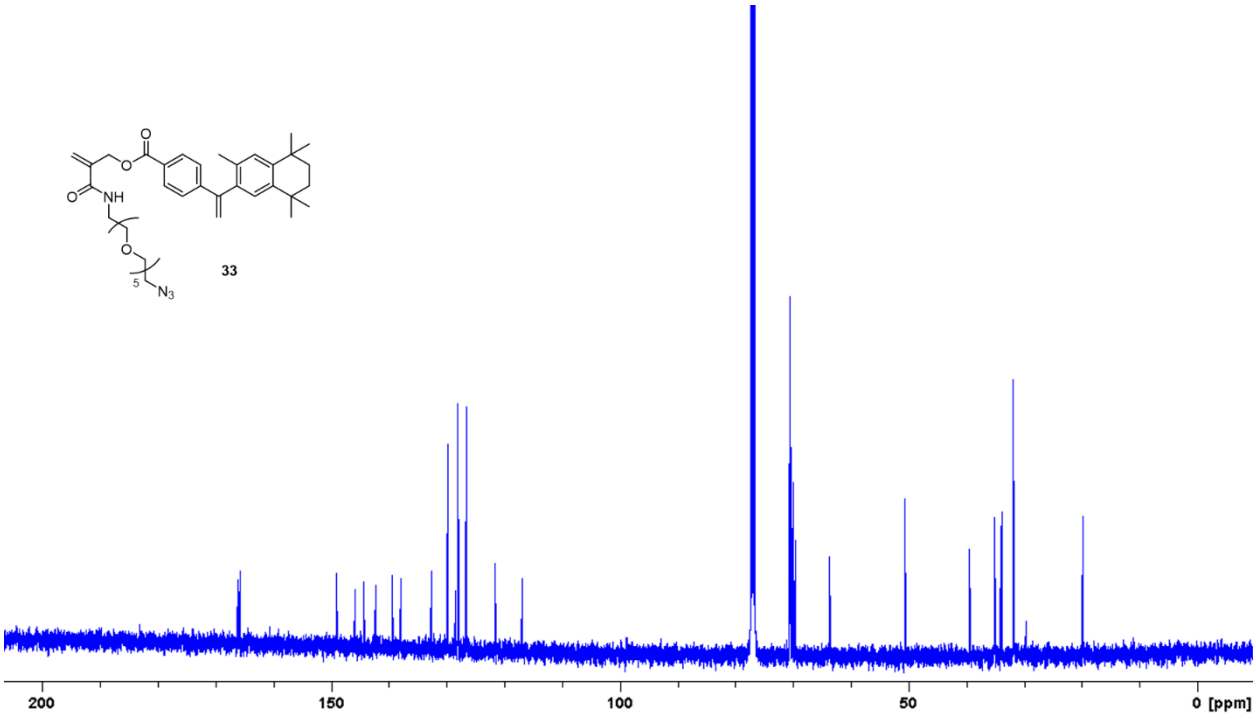

33a
* : CHCl3
# : H2O
&: TMS
*
#
&
4.08
6.09
0.97
1.00
1.00
2.00
20.10
2.13
2.03
9.46
8
6
4
2
0
[ppm]

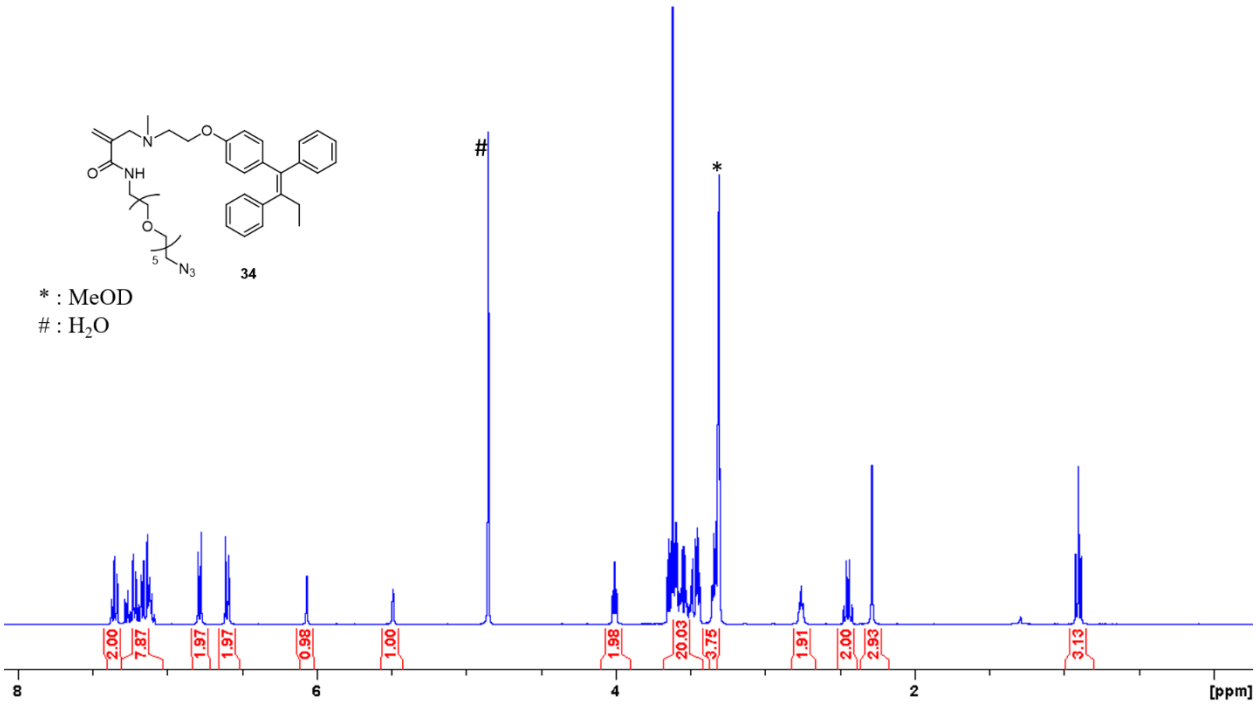

33a
200
150
100
50
0
[ppm]

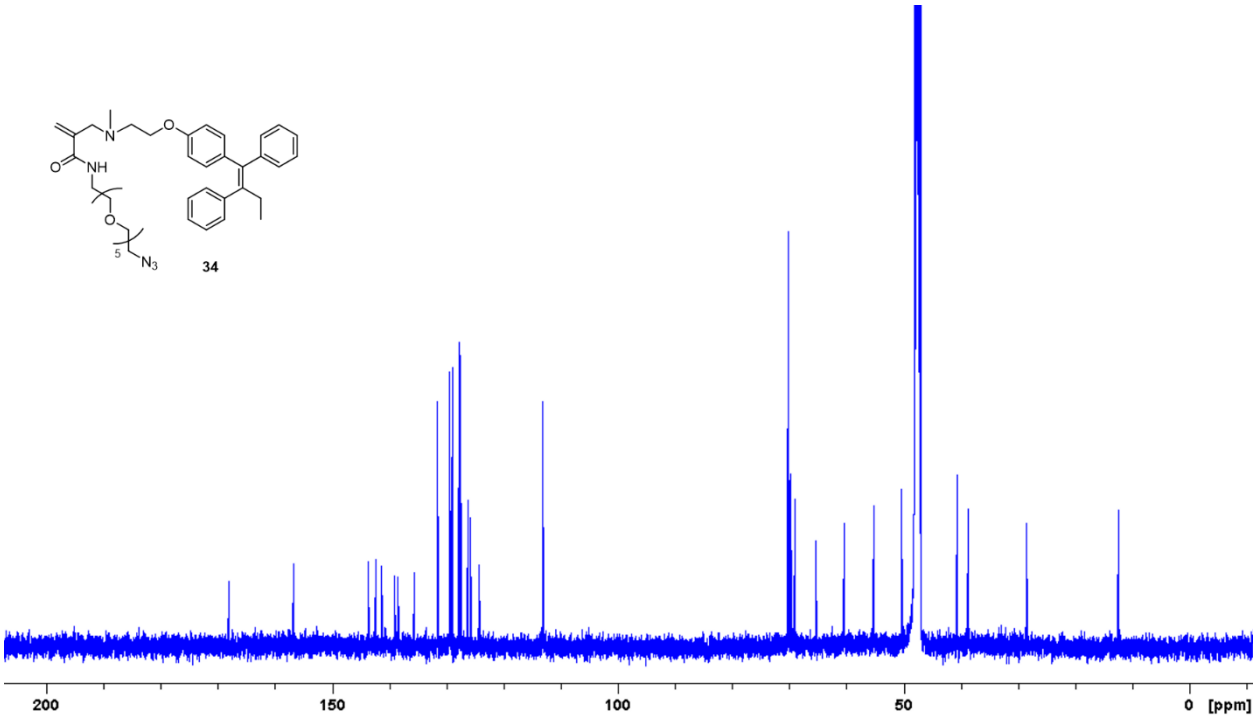

OH
NH
O
O
5
N3
33b
* : CHCl3
# : H2O
&: TMS
13.64
3.80
2.03
2.02
2.64
4.0
3.5
*
#
&
1.01
1.00
1.04
1.99
2.02
2.64
1.14
8
6
4
2
0 [ppm]

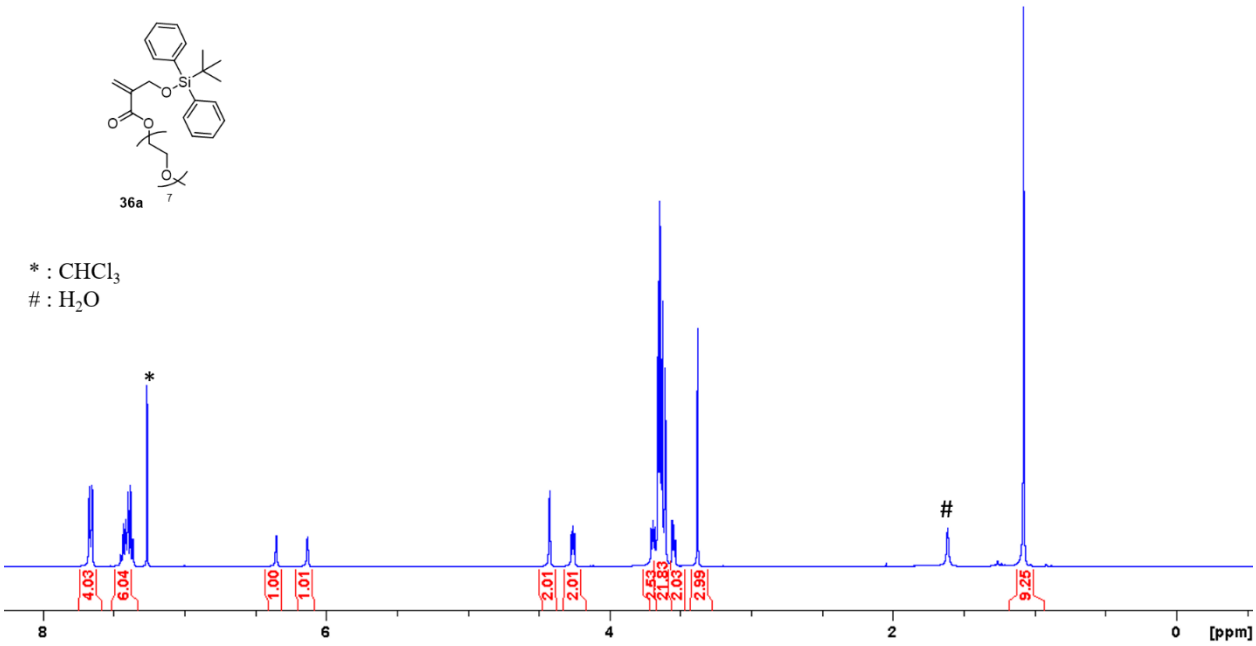

OH
NH
O
O
5
N3
33b
200
150
100
50
0 [ppm]

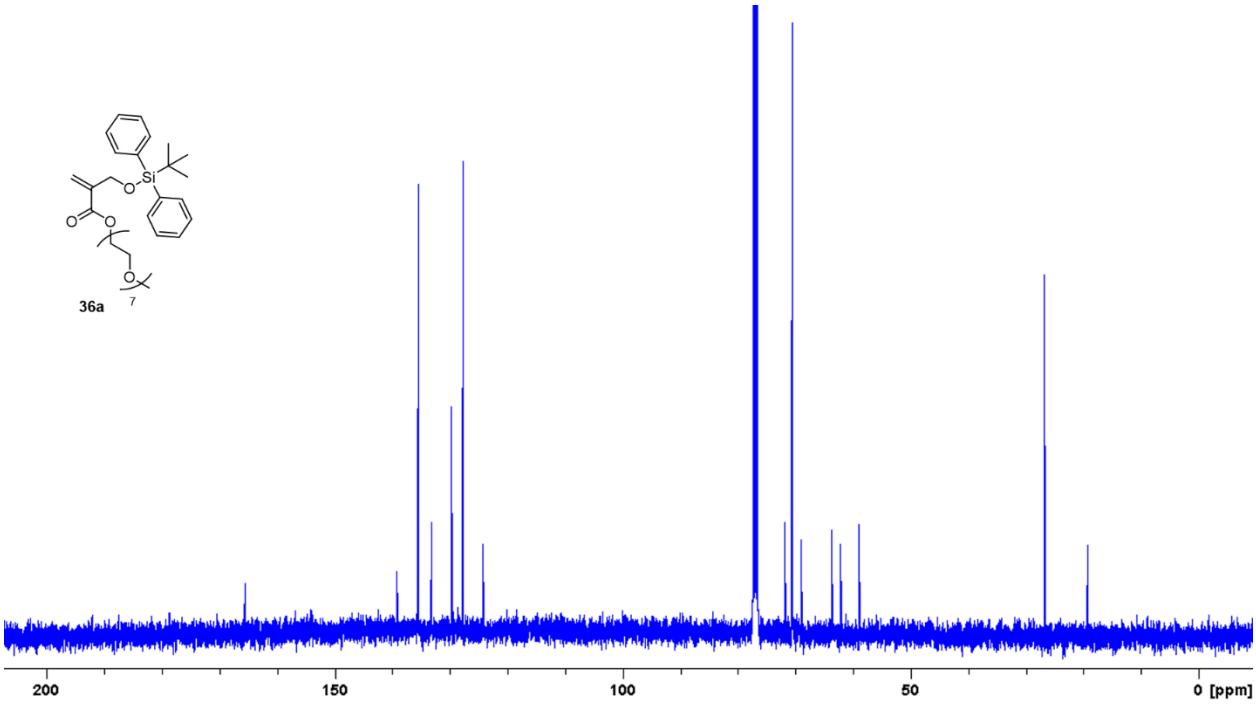

* : CHCl3
# : H2O
&: TMS
33
2.01
2.21
1.05
1.13
1.00
1.01
1.03
1.08
1.94
19.17
2.24
2.00
3.00
4.06
12.26
8
6
4
2
0
[ppm]

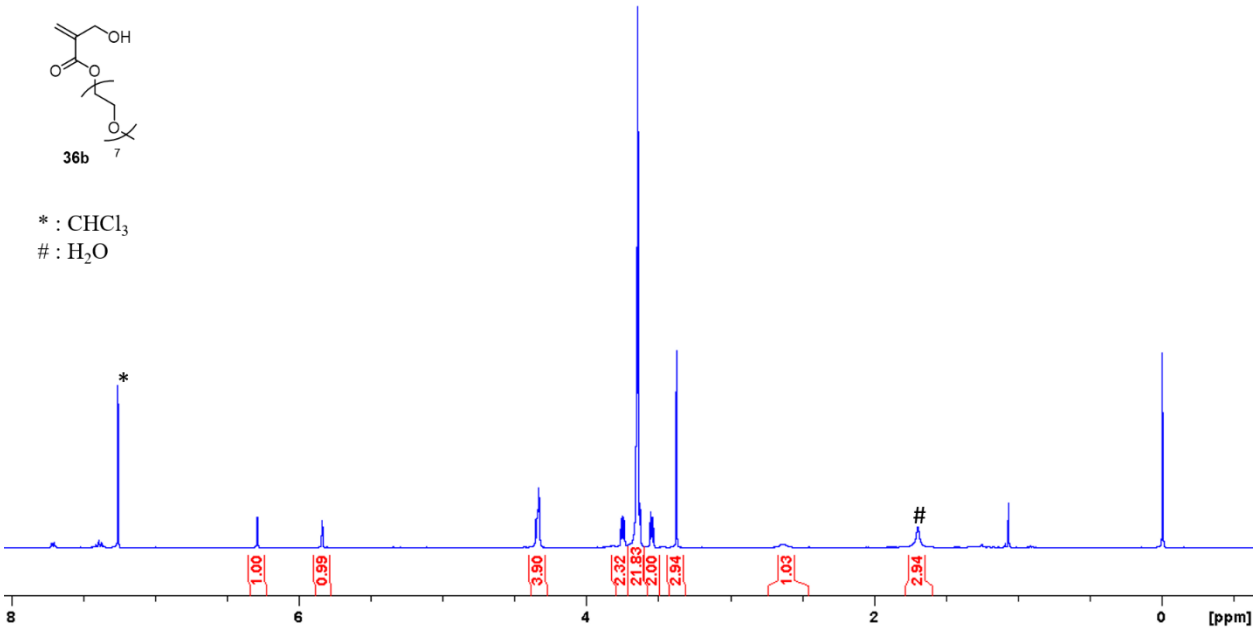

33
200
150
100
50
0 [ppm]

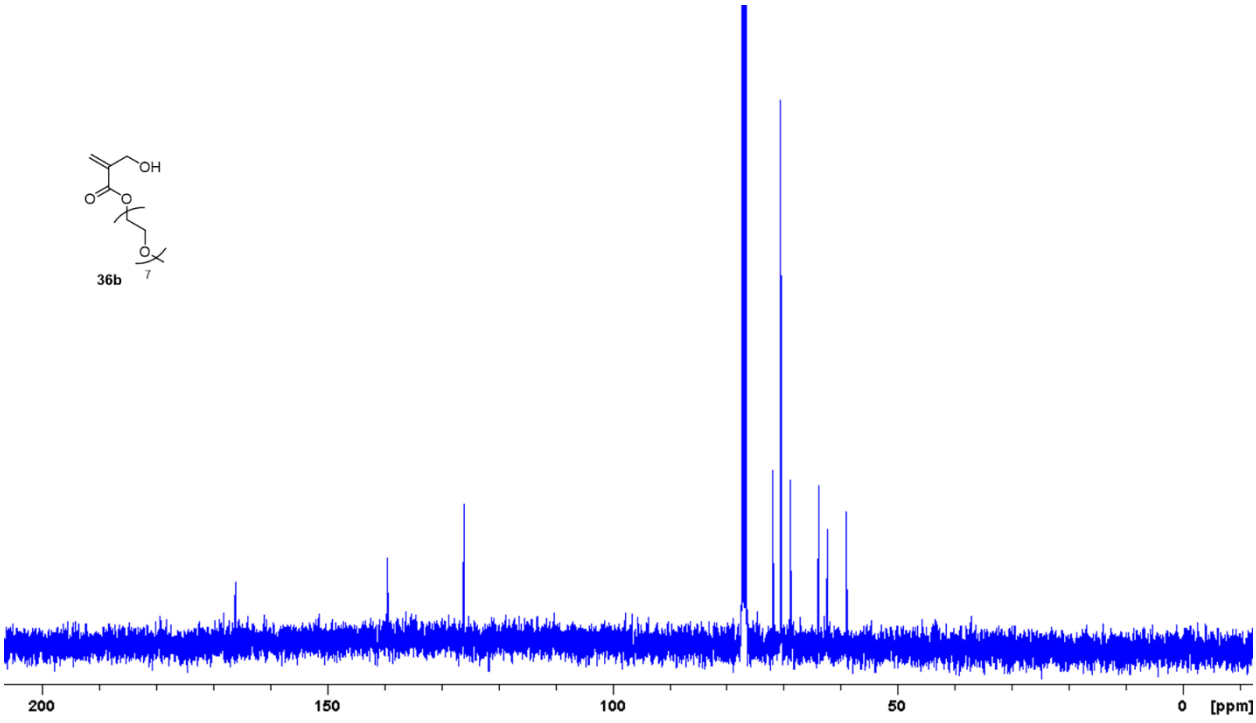

34
* : MeOD
# : H2O
#
*
2.00
7.87
1.97
1.97
0.98
1.00
1.98
20.03
3.75
1.91
2.00
2.93
3.13
8
6
4
2
[ppm]

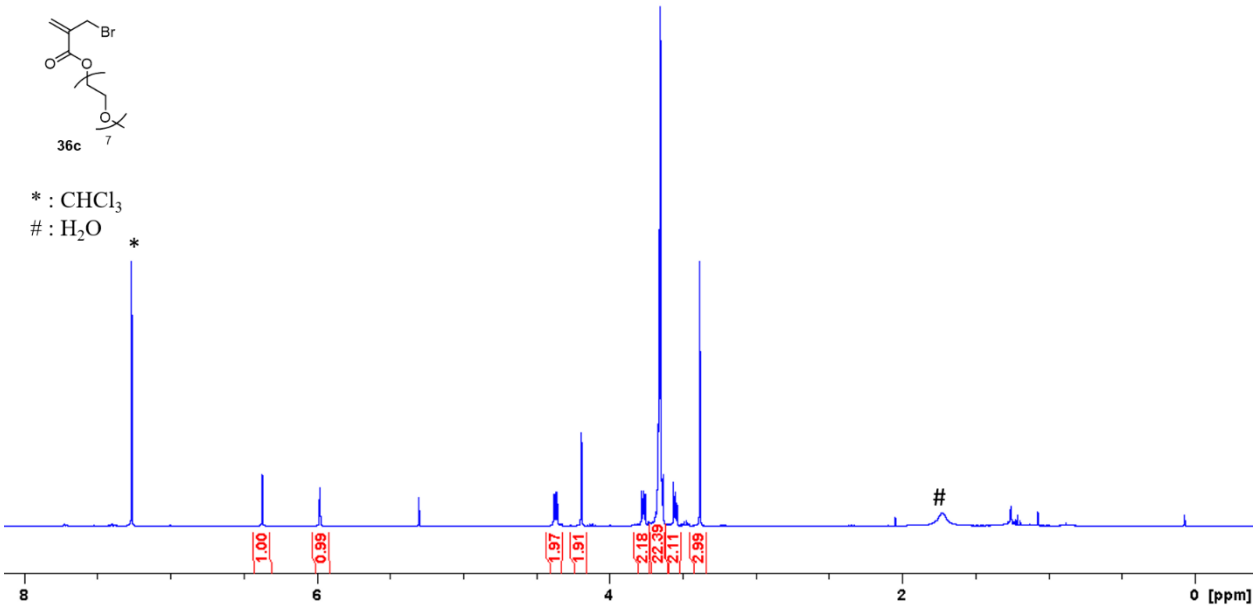

34
200
150
100
50
0
[ppm]

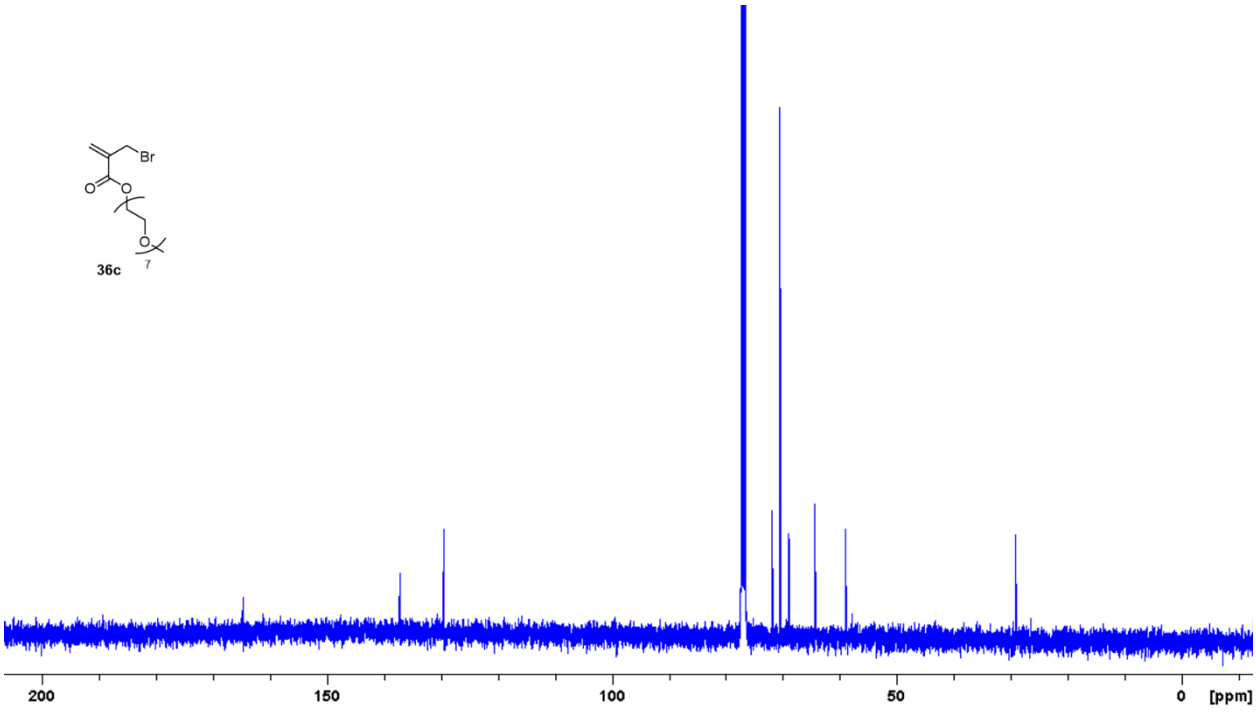

36a
7
* : CHCl3
# : H2O
*
#
4.03
6.04
1.00
1.01
2.01
2.01
2.53
2.83
2.03
2.99
9.25
8
6
4
2
0
[ppm]

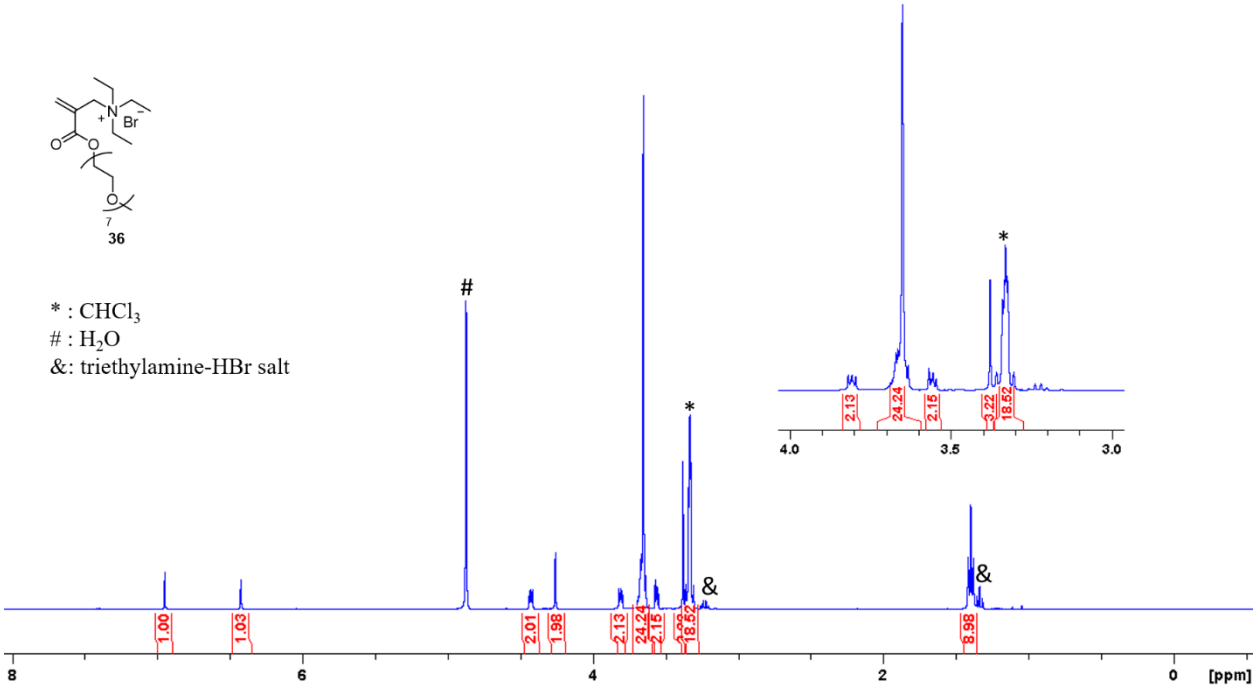

36a
7
200
150
100
50
0 [ppm]

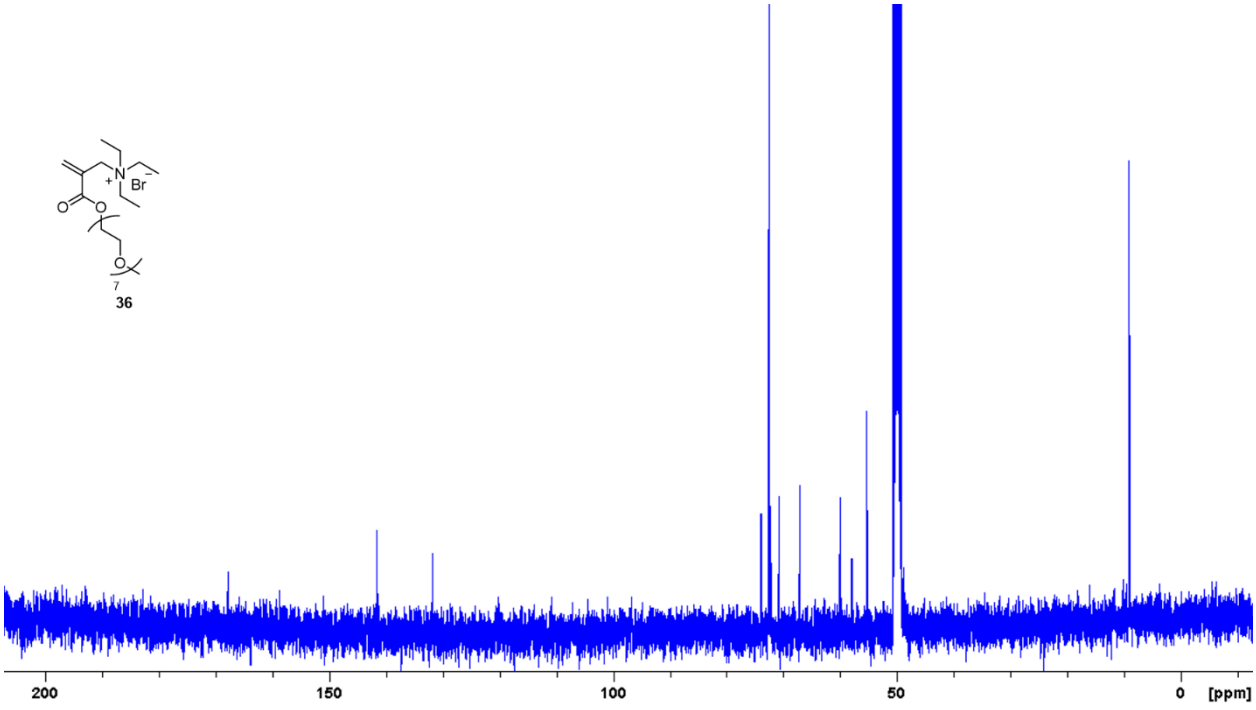

OH
O
O
O
7
36b
* : CHCl3
# : H2O
*
#
1.00
0.99
3.90
2.32
21.83
2.00
2.94
1.03
2.94
8
6
4
2
0
[ppm]

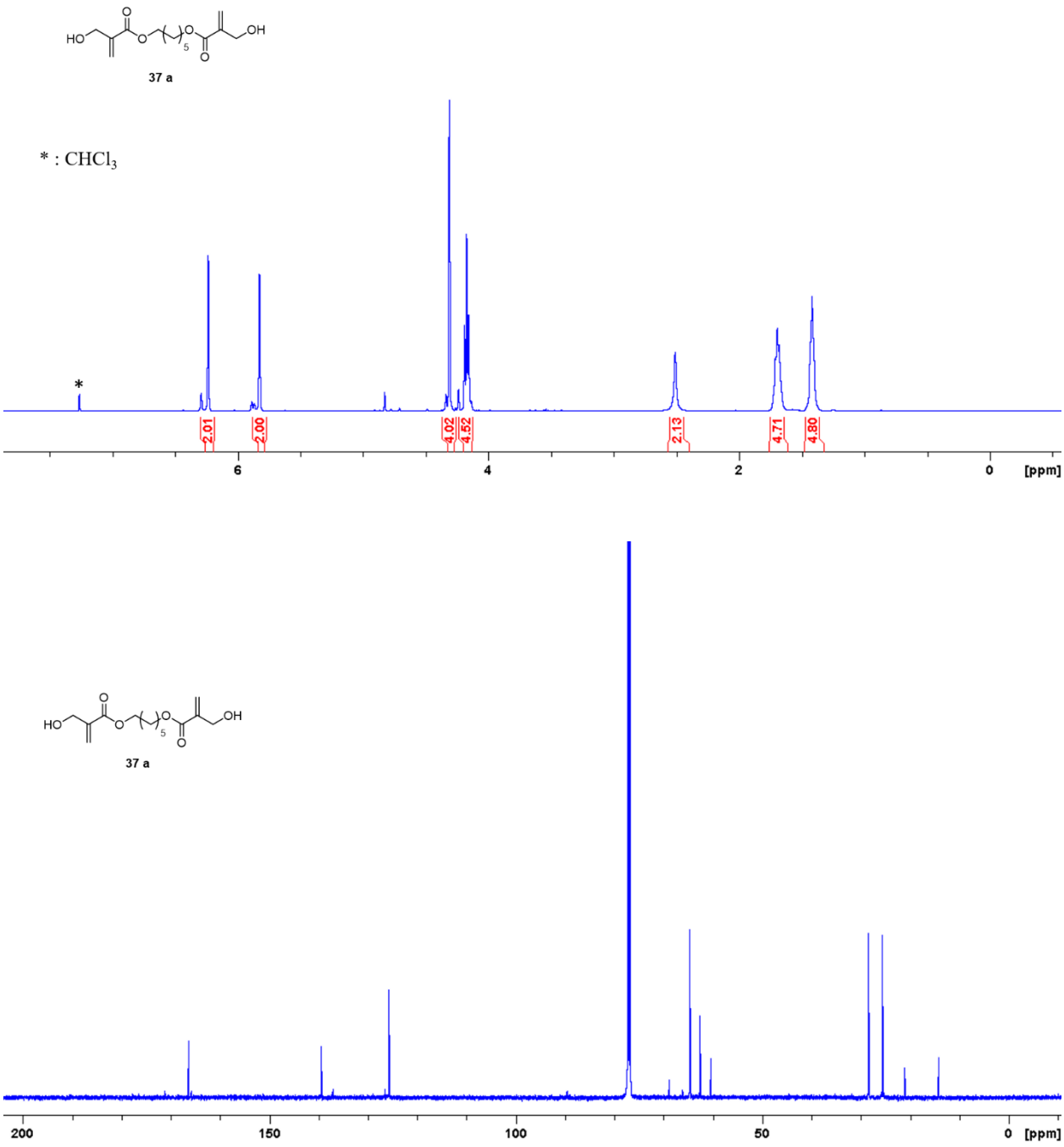

OH
O
O
O
7
36b
200
150
100
50
0
[ppm]

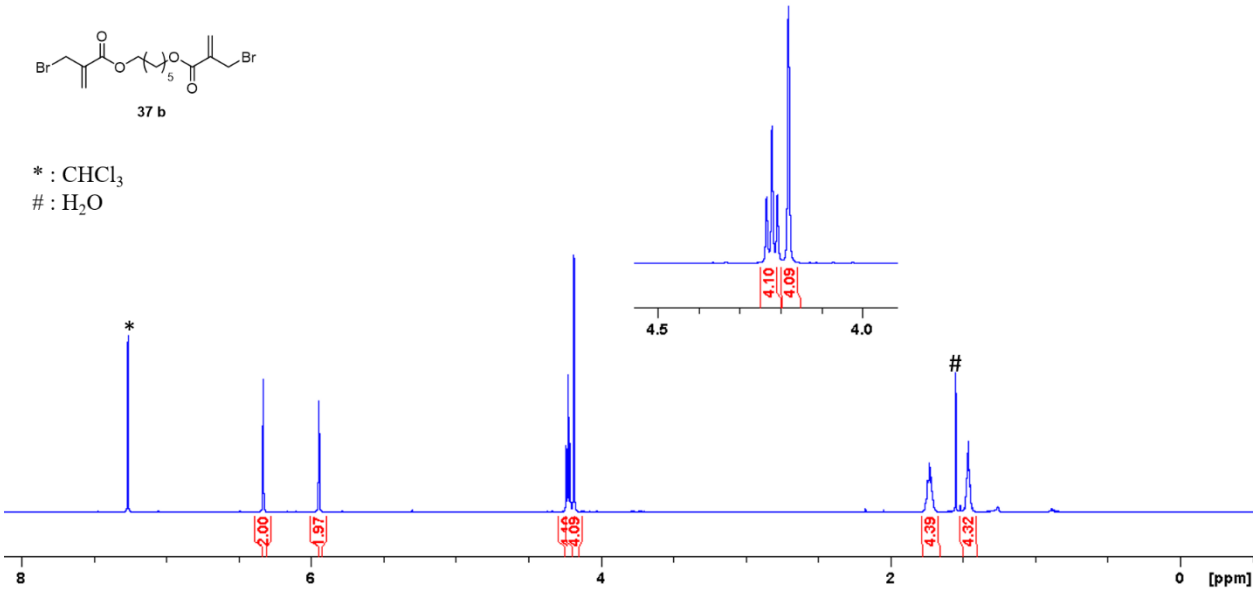

Br
O
O
O
7
36c
* : CHCl3
# : H2O
*
#
1.00
0.99
1.97
1.91
2.18
22.39
2.11
2.59
8
6
4
2
0 [ppm]

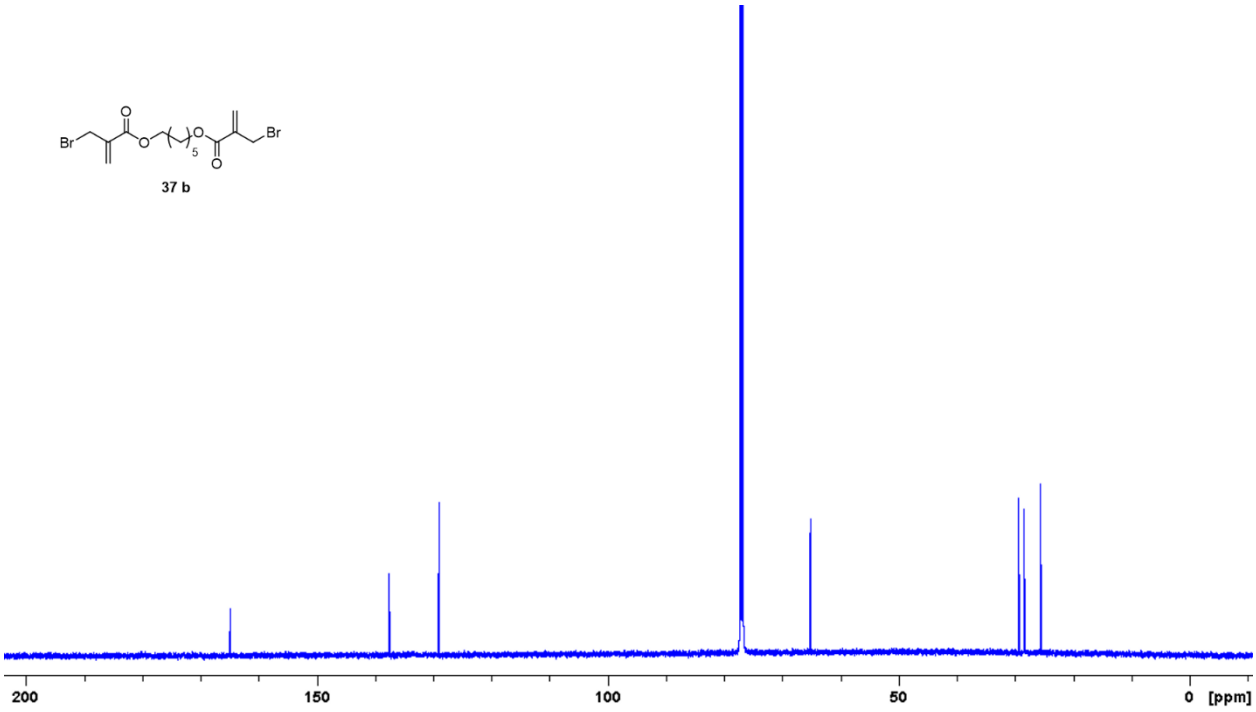

Br
O
O
O
7
36c
200
150
100
50
0 [ppm]

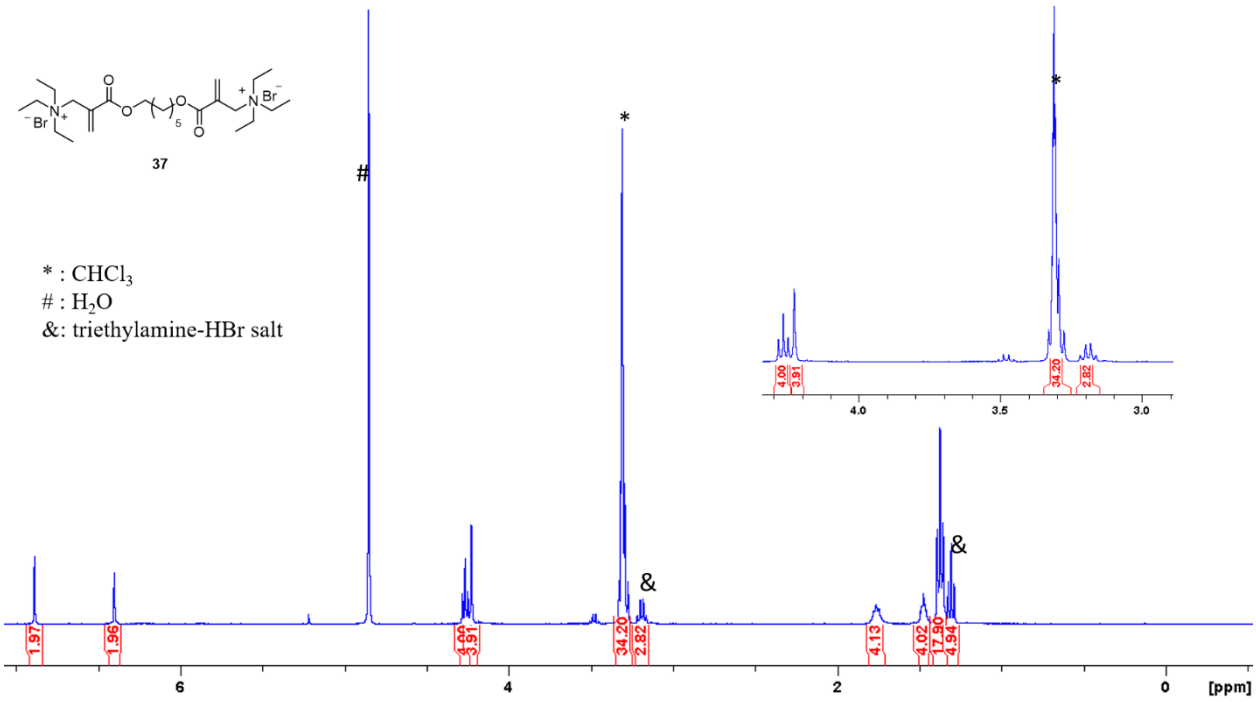

36
* : $CHCl_3$
# : H_2O
&: triethylamine-HBr salt
#
*
&
1.00
1.03
2.01
1.98
2.13
24.24
2.15
8.98
2.13
24.24
2.15
3.22
18.52
8
6
4
2
0
[ppm]
4.0
3.5
3.0

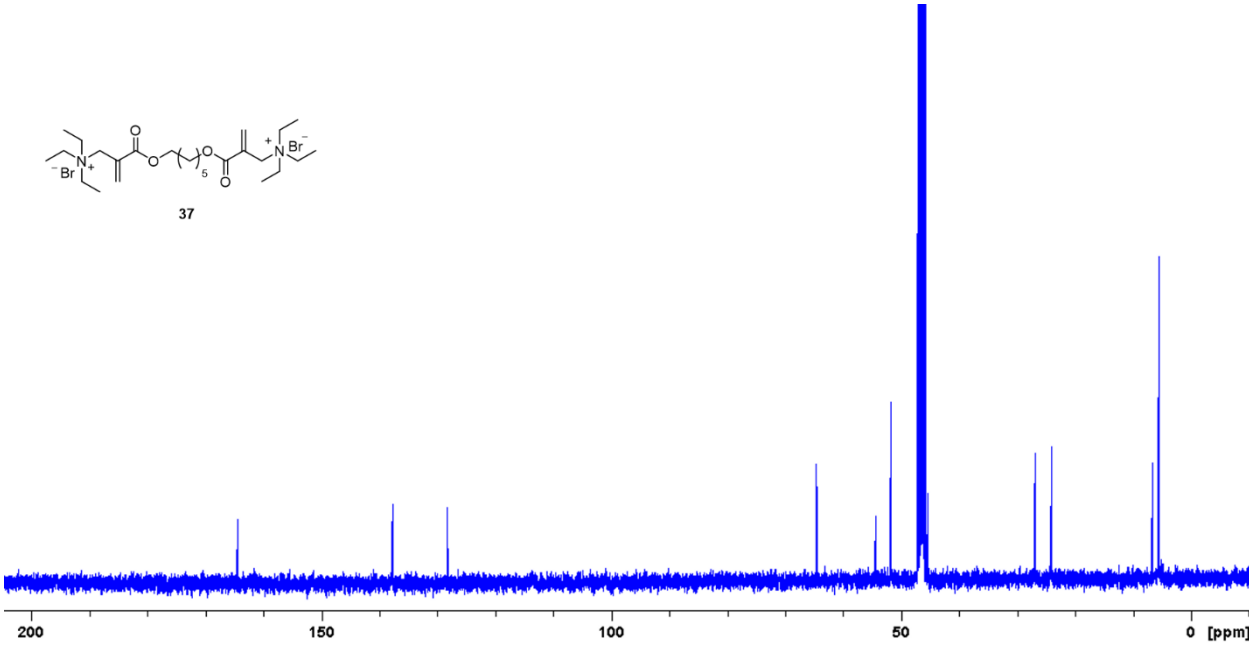

36
200
150
100
50
0
[ppm]


HO
OH
37 a
* : $CHCl_3$
*
2.01
2.00
4.02
4.62
2.13
4.71
4.80
6
4
2
0
[ppm]
HO
OH
37 a
200
150
100
50
0
[ppm]


37 b
* : CHCl3
# : H2O
*
#
4.10
4.09
4.5
4.0
2.00
1.97
4.39
4.32
8
6
4
2
0
[ppm]


37 b
200
150
100
50
0
[ppm]


37
* : CHCl3
# : H2O
&: triethylamine-HBr salt
#
*
&
1.97
1.96
4.00
3.91
34.20
2.82
4.13
4.02
17.90
4.94
6
4
2
0
[ppm]
4.00
3.91
34.20
2.82
4.0
3.5
3.0


37
200
150
100
50
0
[ppm]