Supporting Information

Reductive Ligation Mediated One-Step Disulfide Formation of S-Nitrosothiols

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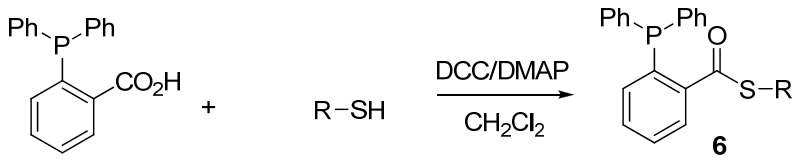
Content:

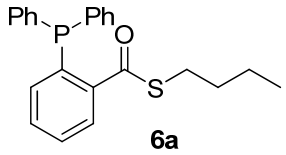
Materials and Methods: All solvents were reagent grade. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040-0.062mm). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Proton and carbon-13 NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are reported relative to chloroform (δ 7.26) for ^{1}H NMR and chloroform (δ 77.0) for ^{13}C NMR.

Experimental Procedures and Compound Characterization Data

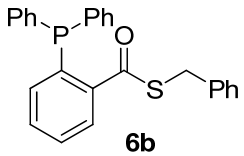
General Procedure for the Preparation of Phosphine-thioester substrates



To a stirred solution of 2-(diphenylphosphino)-benzoic acid (505 mg, 1.65 mmol) in CH_2Cl_2 (6 mL) was added DCC (374 mg, 1.82 mmol), DMAP (20 mg, 0.17 mmol) and R-SH (1.82 mmol) successively. The resulting mixture was allowed to stir overnight at room temperature. The white solid formed in the reaction (1, 3-dicyclohexylurea) was removed by filtration. The filtrate was concentrated under reduced pressure and purified by chromatography (hexane/EA, 40/1) to give the desired product **6**.

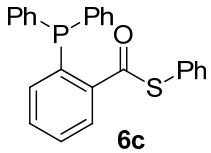


Compound **6a**: Isolated yield: 83%. White solid; m.p.: 99–100 ^{o}C;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-7.99 (m, 1H), 7.43-7.23 (m, 12H), 6.97-6.94 (m, 1H), 2.96 (t, *J* = 7.5 Hz, 2H), 1.56-1.46 (m, 2H), 1.39-1.31 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.44 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1, 142.1 (d, *J* = 15 Hz), 138.2 (d, *J* = 7.5 Hz), 137.9 (d, *J* = 4.5 Hz), 134.8, 134.3, 134.0, 131.9, 129.2, 129.1, 128.8, 128.7, 128.6, 31.5, 29.6, 22.3, 13.9; IR (thin film) cm^{-1} 1662, 1558, 1540, 1434, 1204, 913; ESI-MS (m/z): 401.1 $[M+Na]^+$; HRMS m/z 401.1105 $[M+Na]^+$; calcd for $C_{23}H_{23}NaOPS$: 401.1105.



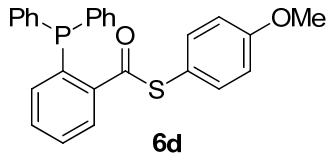
6b

Compound **6b:** Isolated yield: 86%. Yellow solid; m.p.: 120–122 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-7.99 (m, 1H), 7.40-7.24 (m, 17H), 7.23-6.97 (m, 1H), 4.24 (s, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.08 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 141.1 (d, *J* = 22.5 Hz), 138.2 (d, *J* = 30 Hz), 137.6 (d, *J* = 15 Hz), 137.0, 134.6, 134.0, 133.7, 131.9, 129.1, 129.0, 128.62, 128.57, 128.5, 128.4, 127.2, 34.0; IR (thin film) cm^{-1} 1653, 1558, 1540, 1456, 909; ESI-MS (m/z): 413.1 $[M+H]^+$; HRMS m/z 413.1142 $[M+H]^+$; calcd for $C_{26}H_{22}OPS$: 413.1129.



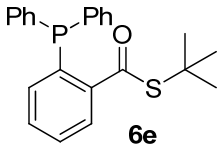
6c

Compound **6c**: Isolated yield: 71%. Yellow solid; m.p.: 155–157 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13-8.09 (m, 1H), 7.49-7.26 (m, 17H), 7.05-7.01 (m, 1H); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.87 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 141.8 (d, *J* = 22.5 Hz), 138.5 (d, *J* = 22.5 Hz), 137.8 (d, *J* = 7.5 Hz), 135.1, 135.0, 134.4, 134.1, 132.2, 129.6, 129.4, 129.09, 129.05, 128.9, 128.7, 128.6, 127.9; IR (thin film) cm^{-1} 1699, 1684, 1558, 1507, 1457, 898; ESI-MS (m/z): 399.1 $[M+H]^+$; HRMS m/z 399.0964 $[M+H]^+$; calcd for $C_{25}H_{20}OPS$: 399.0973.



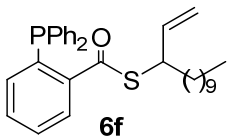
6d

Compound **6d:** Isolated yield: 74%. Yellow solid; m.p.: 136–138 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11-8.07 (m, 1H), 7.46-7.25 (m, 14H), 7.04-6.91 (m, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.85 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 160.9, 141.8 (d, *J* = 22.5 Hz), 138.4 (d, *J* = 22.5 Hz), 137.8 (d, *J* = 15 Hz), 137.7, 136.7, 134.9, 134.4, 134.1, 132.1, 129.1, 129.0, 128.9, 128.71, 128.66, 128.62, 118.5, 115.1, 55.6; IR (thin film) cm^{-1} 1684, 1558, 1507, 1457, 1250, 898; ESI-MS (m/z): 429.1 $[M+H]^+$; HRMS m/z 429.1087 $[M+H]^+$; calcd for $C_{26}H_{22}O_2PS$: 429.1078.



6e

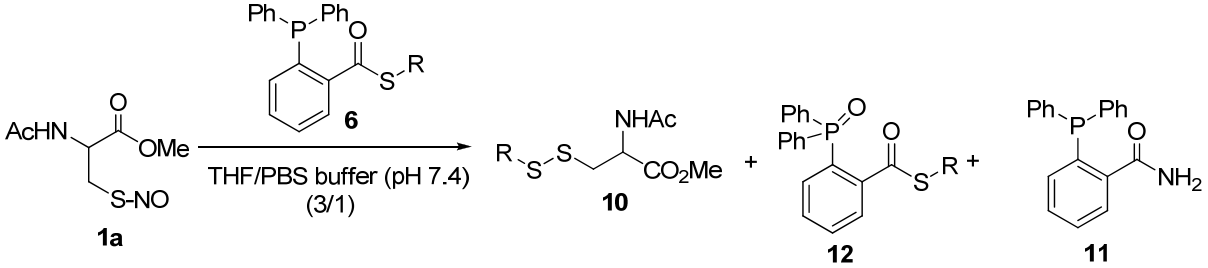
Compound **6e**: Isolated yield: 60%. Light yellow solid; m.p.: 82–84 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.87 (m, 1H), 7.38-7.29 (m, 12H), 6.97-6.93 (m, 1H), 1.41 (s, 9H); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.26 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 143.7 (d, J = 52.5 Hz), 137.9 (d, J = 15 Hz), 137.5, 134.3 (d, J = 15 Hz), 131.5, 128.9, 128.7, 128.6, 128.4, 48.9, 29.9; IR (thin film) cm^{-1} 2921, 2119, 1650, 1432, 1200, 904; ESI-MS (m/z): 379.1 $[M+H]^+$; HRMS m/z 379.1275 $[M+H]^+$; calcd for $C_{23}H_{24}OPS$: 379.1286.



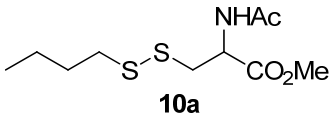
6f

Compound **6f**: Isolated yield: 75%. Yellow thick oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.32 (m, 13H), 6.96 (m, 1H), 5.73 (m, 1H), 5.11 (m, 1H), 4.13 (m, 1H), 1.59 (m 2H), 1.25 (s, 16 H), 0.89 (t, J = 3.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.71, 142.0 (d, J = 19.1 Hz), 138.39, 138.1 (d, J = 3.3 Hz), 138.0, 137.9 (d, J = 7.9 Hz), 134.7, 134.36, 134.33, 134.28, 134.19, 134.06, 131.9, 129.19, 129.15, 128.87, 128.85, 128.7, 128.6, 128.5, 116.5, 47.1, 34.2, 32.2, 29.91, 29.89, 29.78, 29.65, 29.6, 27.3, 23.0, 14.5. IR (thin film) cm^{-1} 3053, 2924, 2853, 1662, 1584, 1559, 1457, 1434, 1202, 1128, 908. ESI-MS (m/z): 503.3 $[M+H]^+$; HRMS m/z 503.2561, $[M+H]^+$; calcd for: $C_{32}H_{40}OPS$, 503.2537.

General procedure for the formation of disulfide

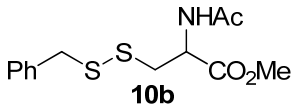


To a stirred solution of **6** (0.3 mmol) in THF (1.5 mL) and pH 7.4 PBS buffer (0.5 mL) was added freshly prepared S-nitrosothiol **1a** (31 mg, 0.15 mmol). The reaction mixture was stirred for 1.0 hour at rt and then extracted with CH_2Cl_2. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. Compounds **10**, **11**, and **12** were separated by flash chromatography (Hexane/EA, 2/1).



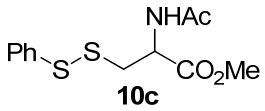
10a

Compound **10a**. Isolated yield: 79%. White solid; m.p.: 45–47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (br, 1H), 4.90-4.84 (m, 1H), 3.74 (s, 3H), 3.20-3.07 (m, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.03 (s, 3H), 1.66-1.57 (m, 2H), 1.44-1.31 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.1, 52.9, 52.0, 40.6, 38.8, 31.2, 23.3, 21.8, 13.9; IR (thin film) cm^{-1} 3278, 2957, 1749, 1658, 1540, 1436; ESI-MS (m/z): 266.1 $[M+H]^+$; HRMS m/z 266.0893 $[M+H]^+$; calcd for $C_{10}H_{20}NO_3S_2$: 266.0885.



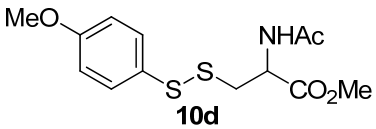
10b

Compound **10b**: Isolated yield: 82%. White solid; m.p.: 74–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 6.32 (d, *J* = 6.3 Hz, 1H), 4.79-4.74 (m, 1H), 3.89 (s, 2H), 3.72 (s, 3H), 2.89-2.75 (m, 2H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.0, 137.0, 129.6, 128.9, 127.9, 52.9, 51.8, 43.7, 40.0, 23.4; IR (thin film) cm^{-1} 3273, 1748, 1654, 1558, 1522, 1215; ESI-MS (m/z): 300.1 $[M+H]^+$; HRMS m/z 300.0713 $[M+H]^+$; calcd for $C_{13}H_{18}NO_3S_2$: 300.0728.



10c

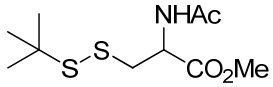
Compound **10c**: Isolated yield: 63%. White solid; m.p.: 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.26 (m, 5H), 6.29 (br, 1H), 4.91-4.86 (m, 1H), 3.74 (s, 3H), 3.30-3.18 (m, 2H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.7, 136.5, 129.1, 128.2, 127.4, 52.7, 51.6, 40.6, 22.9; IR (thin film) cm^{-1} 1749, 1653, 1540, 1436, 1215, 743; ESI-MS (m/z): 286.1 $[M+H]^+$; HRMS m/z 286.0559 $[M+H]^+$; calcd for $C_{12}H_{16}NO_3S_2$: 286.0572.



10d

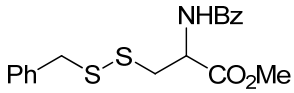
Compound 10d. Isolated yield: 51%. White solid; m.p.: 64–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 6.90-6.86 (m, 2H), 6.26 (d, *J* = 6.6 Hz, 1H), 4.93-4.89 (m, 1H), 3.80 (s，3H)，

3.76 (s，3H), 3.21 (d, J = 5.1 Hz, 2H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.0, 160.4, 133.1, 127.6, 115.1, 55.7, 53.0, 51.9, 40.3, 23.3; IR (thin film) cm^{-1} 1749, 1653, 1558, 1491, 1247; ESI-MS (m/z): 316.1 $[M+H]^+$; HRMS m/z 316.0634 $[M+H]^+$; calcd for $C_{13}H_{18}NO_4S_2$: 316.0677.



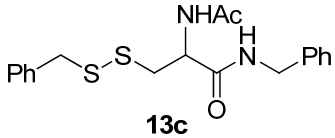
10e

Compound **10e**: Isolated yield: 43%. Colorless thick oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (br, 1H), 4.89-4.84 (m, 1H), 3.77 (s, 3H), 3.18 (d, J = 4.8 Hz, 2H), 2.04 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 169.8, 52.6, 52.0, 48.2, 42.1, 29.7, 23.1; IR (thin film) cm^{-1} 3276, 2959, 1749, 1654, 1540, 1362, 1167; ESI-MS (m/z): 266.1 $[M+H]^+$; HRMS m/z 266.0877 $[M+H]^+$; calcd for $C_{10}H_{20}NO_3S_2$: 266.0885.



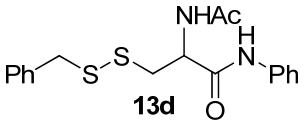
13b

Compound **13b:** Isolated yield: 85%. White solid; m.p.: 75–77 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H), 7.53-7.28 (m, 8H), 7.09 (d, J = 7.2 Hz, 1H), 5.01-4.97 (m, 1H), 3.89 (s, 2H), 3.75 (s, 3H), 3.01-2.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 167.2, 137.0, 133.8, 132.2, 129.6, 128.9, 127.9, 127.4, 53.0, 52.4, 43.7, 40.0; IR (thin film) cm^{-1} 3319, 1745, 1643, 1530, 1486, 1215; ESI-MS (m/z): 362.1 $[M+H]^+$; HRMS m/z 362.0889 $[M+H]^+$; calcd for $C_{18}H_{20}NO_3S_2$: 362.0885.



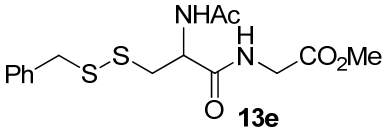
13c

Compound **13c:** Isolated yield: 68%. White solid; m.p.: 136–138 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (m, 10H), 6.74 (t, J = 5.1 Hz, 1H), 6.48 (d, J = 7.5 Hz, 1H), 4.66-4.59 (m, 1H), 4.44-4.32 (m, 2H), 3.90 (s, 2H), 2.76-2.60 (m, 2H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.1, 137.7, 137.2, 129.6, 128.94, 128.86, 127.9, 127.85, 127.82, 52.6, 43.9, 43.4, 39.8, 23.4; IR (thin film) cm^{-1} 3278, 3062, 1644, 1548, 1495, 1370, 698; ESI-MS (m/z): 397.1 $[M+Na]^+$; HRMS m/z 397.1055 $[M+Na]^+$; calcd for $C_{19}H_{22}N_2NaO_2S_2$: 397.1020.



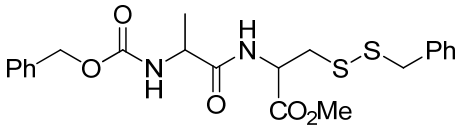
13d

Compound **13d:** Isolated yield: 66%. White solid; m.p.: 114–116 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39-9.28 (m, 1H), 7.59-7.53 (m, 2H), 7.33-7.07 (m, 9H), 5.00-4.93 (m, 1H), 3.86 (3.80, s, 2H), 2.82-2.73 (m, 2H), 2.05 (2.02, s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 169.1, 138.0, 137.22, 129.63, 129.2, 128.80, 127.8, 124.85, 120.49, 53.5, 43.41, 40.42, 23.5; IR (thin film) cm^{-1} 3279, 3061, 1650, 1600, 1549, 1494, 1444, 1371; ESI-MS (m/z): 361.1 $[M+H]^+$; HRMS m/z 361.1048 $[M+H]^+$; calcd for $C_{18}H_{21}N_2O_2S_2$: 361.1044.



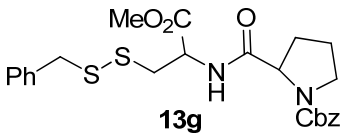
13e

Compound **13e:** Isolated yield: 74%. White solid; m.p.: 118–120 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.25 (m, 5H), 6.98 (t, *J* = 4.8 Hz, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 4.73-4.66 (m, 1H), 4.07-3.97 (m, 2H), 3.91 (s, 2H), 3.73 (s, 3H), 2.80-2.70 (m, 2H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.6, 170.0, 137.2, 129.6, 128.9, 127.8, 52.7, 52.4, 43.4, 41.5, 39.6, 23.4; IR (thin film) cm^{-1} 3288, 2954, 1754, 1658, 1548, 1371, 1209; ESI-MS (m/z): 357.1 $[M+H]^+$; HRMS m/z 357.0962 $[M+H]^+$; calcd for $C_{15}H_{21}N_2O_4S_2$: 357.0943.



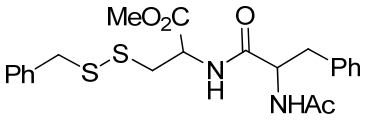
13f

Compound **13f:** Isolated yield: 73%. Light brown solid; m.p.: 59–61 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.25 (m, 10H), 6.93 (d, *J* = 6.6 Hz, 1H), 5.44 (d, *J* = 7.5 Hz, 1H), 5.10 (s, 2H), 4.77-4.71 (m, 1H), 4.35-4.30 (m, 1H), 3.87 (s, 2H), 3.71 (s, 3H), 2.85-2.72 (m, 2H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 170.9, 156.1, 137.1, 136.4, 129.6, 128.9, 128.8, 128.4, 128.3, 127.9, 67.3, 52.9, 51.9, 50.6, 43.7, 39.7, 18.8; IR (thin film) cm^{-1} 3314, 2952, 1744, 1667, 1453, 1308, 1069; ESI-MS (m/z): 485.1 $[M+Na]^+$; HRMS m/z 485.1174 $[M+Na]^+$; calcd for $C_{22}H_{26}N_2NaO_5S_2$: 485.1181.



13g

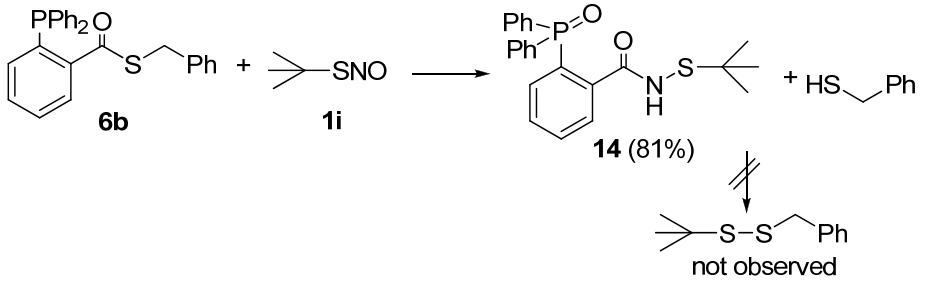
Compound **13g:** Isolated yield: 72%. Light yellow thick oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.26 (m, 10H), 6.72 (br, 1H), 5.16 (s, 2H), 7.42 (br, 1H), 4.39-4.33 (m, 1H), 3.86 (s, 2H), 3.71-3.43 (m, 5H), 2.89-2.75 (m, 2H), 2.31-1.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 171.7, 170.9, 137.1, 136.6, 129.5, 128.8, 128.7, 128.3, 128.1, 127.8, 67.6, 61.0, 52.8, 51.8, 47.8, 43.7, 40.1 31.3, 24.8; IR (thin film) cm^{-1} 3269, 2913, 1700, 1657, 1431, 1205; ESI-MS (m/z): 489.2 $[M+H]^+$; HRMS m/z 489.1516 $[M+H]^+$; calcd for $C_{24}H_{29}N_2O_5S_2$: 489.1518.



13h

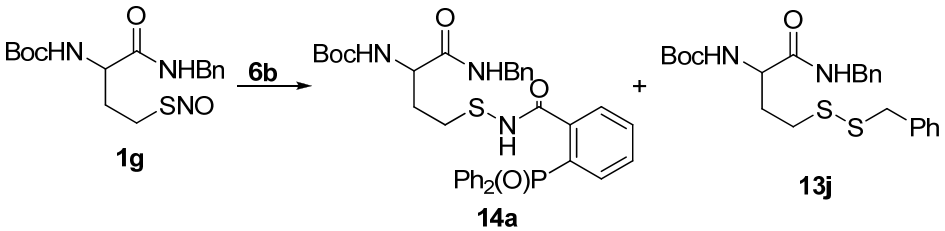
Compound **13h:** Isolated yield: 70%. White solid; m.p.: 120–122 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (m, 10H), 7.77 (d, *J* = 7.5 Hz, 1H), 6.30 (d, *J* = 7.5 Hz, 1H), 4.77-4.64 (m, 2H), 3.87 (s, 2H), 3.68 (s, 3H), 3.17-3.00 (m, 2H), 2.69-2.56 (m, 2H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.7, 170.3, 137.1, 136.6, 129.58, 129.56, 128.90, 128.86, 127.9, 127.3, 54.4, 52.9, 51.6, 43.6, 39.7, 38.6, 23.4; IR (thin film) cm^{-1} 3274, 3062, 1749, 1648, 1549, 1212, 699; ESI-MS (m/z): 447.1 $[M+H]^+$; HRMS m/z 447.1412 $[M+H]^+$; calcd for $C_{22}H_{27}N_2O_4S_2$: 447.1413.

Control Experiments (Scheme 3 in the manuscript)



6b **1i** **14** (81%)

The reaction between **6b** and **1i** was carried out using the same procedure for the disulfide formation. However, we did not observe the formation of the desired disulfide product. We only isolated compound **14** in 81% yield. Physical data of **14** has been reported previously.[1]



1g **14a** **13j**

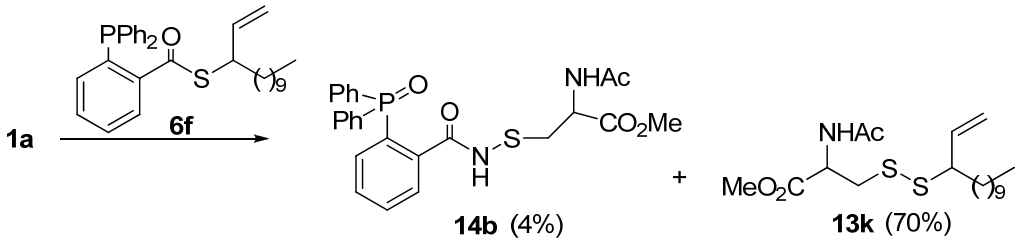
The reaction between **6b** and **1g** was carried out using the same procedure for the disulfide

[1] See reference 3 of the manuscript.

formation. In this reaction, sulfenamide product **14a** was isolated in 19% yield and disulfide product **13j** was isolated in 59% yield.

Compound **14a**: White solid; m.p. 101-104 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.74-7.62 (m, 2H), 7.59-7.33. (m, 11H), 7.24-7.15 (m, 6H), 7.02 (ddd, 1H, *J* = 14.4, 7.8, 0.8 Hz), 5.95 (d, 1H, *J* = 7.5 Hz), 4.66 (dd, 1H, *J* = 12.8, 5.7 Hz), 4.53 (dd, 1H, *J* = 15.0, 6.7 Hz), 4.28 (dd, 1H, *J* = 15.0, 6.7 Hz), 2.89-2.74 (m, 1H), 2.54-2.40 (m, 1H), 1.77-1.62 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 171.2, 156.0, 139.9, 138.5, 133.5 (d, *J* = 11.1 Hz), 132.5, 131.7 (d, *J* = 9.2 Hz), 131.4, 131.3, 130.1, 129.8, 129.2, 128.8 (d, *J* = 12.6 Hz), 128.4, 127.6, 127.0, 79.3, 52.3, 43.2, 36.1, 32.8, 28.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 36.8; IR (thin film) cm^{-1} 3265, 3059, 2975, 1670, 1527, 1437, 1249, 1168, 1119, 722, 695; mass spectrum (ESI) m/z 644.6.

Compound **13j**: White solid, m.p. 78-80 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-722. (m, 10H), 6.46 (br, 1H), 4.98 (d, 1H, *J* = 7.4 Hz), 4.42 (d, 2H, *J* = 5.2 Hz), 4.12 (dd, 1H, *J* = 13.5, 6.7 Hz), 3.87 (s, 2H), 2.46-2.28 (m, 2H), 2.16-2.01 (m, 1H), 1.92-1.76 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 138.0, 137.6, 129.6. 129.0, 128.8, 127.9, 127.8, 127.2, 70.1, 60.5, 43.7, 43.6, 34.4, 31.9, 28.5; IR (thin film) cm^{-1} 3293, 2977, 2926, 1656, 1528, 1454, 1366, 1248, 1168, 1027, 698; mass spectrum (ESI) m/z 446.8, $[M+H]^+$; HRMS m/z 447.1793, $[M+H]^+$; calcd for $C_{23}H_{31}N_2O_3S_2$: 447.1776.



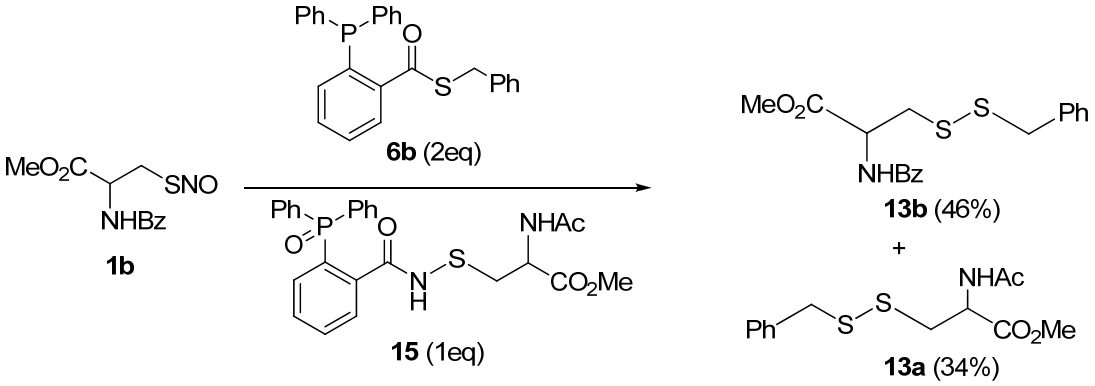
The reaction between **6f** and **1a** was carried out using the same procedure for the disulfide formation. In this reaction, sulfenamide product **14b** was isolated in 4% yield and disulfide product **13k** was isolated in 70% yield. Physical data of **14b** has been reported previously.[2]

Compound **13k**: white solid; m.p.: 50–52 ^{o}C; ^{1}H NMR: 6.42 (m, 1H), 5.60 (m, 1H), 5.11 (m, 2H), 4.84 (m, 1H), 3.75 (s, 3H), 3.26 (m, 1H), 3.12 (m, 2H), 2.03 (s, 3H), 1.62 (m, 1H), 1.51 (m, 1H), 1.23 (s, 16H), 0.85 (t, *J* = 6.0 Hz, 3H). ^{13}C NMR: 171.2, 170.0, 138.2, 117.5, 55.4, 52.9, 52.0, 40.6, 33.4, 32.1, 29.83, 29.79, 29.77, 29.70, 29.66, 29.53, 27.5, 23.4, 22.9, 14.3. IR (thin film) cm^{-1} 3328, 2917, 2848, 1757, 1651, 1533, 1462, 1435, 1358, 1312, 1216, 1168; ESI-MS (m/z): 390.2 $[M+H]^+$;

[2] See reference 3 of the manuscript.

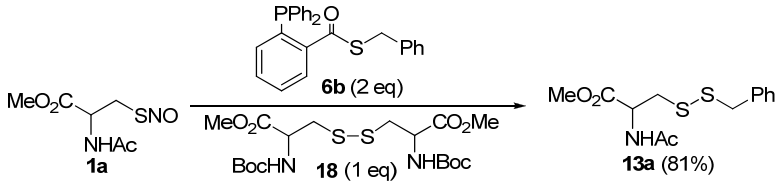
HRMS m/z 390.2146 $[M+H]^+$; calcd for $C_{19}H_{36}NO_3S_2$: 390.2137.

Cross-Over Experiment (Scheme 4 in the manuscript)

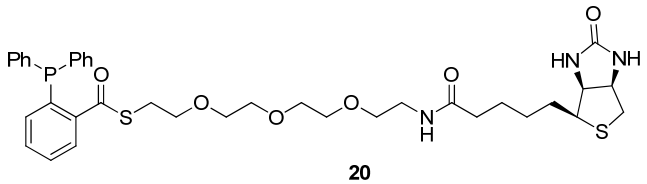


To a stirred solution of **6b** (221 mg, 0.54 mmol), and **15** (133 mg, 0.27 mmol) in THF (3 mL) and buffer (pH = 7.4, 1 mL) was added freshly prepared **1b** (72 mg, 0.27 mmol). The reaction mixture was stirred at rt for 0.5 h and extracted with CH_2Cl_2. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (Hexane/EA, 4/1 to Hexane/acetone, 3/1) to give 27 mg of **13a** (34%, based on **1b**) and 45 mg of **13b** (46%, based on **1b**).

Reaction shown in Scheme 5



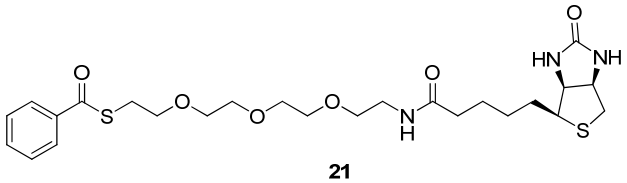
To a stirred solution of **6b** (206 mg, 0.50 mmol), and **18** (117 mg, 0.25 mmol) in THF (3 mL) and buffer (pH = 7.4, 1 mL) was added freshly prepared **1a** (52 mg, 0.25 mmol). The reaction mixture was stirred at rt for 0.5 h and extracted with CH_2Cl_2. The organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude material was purified by flash chromatography to give 60 mg of **13a** (81%).



20

Compound **20** was prepared from 2-(diphenylphosphino)-benzoic acid using the method described for the preparation of compounds **6**. Isolated yield was 90%. Yellow solid; m.p.: 94–96 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05-8.00 (m, 1H), 7.45-7.22 (m, 12H), 7.00-6.93 (m, 1H), 6.71-6.64

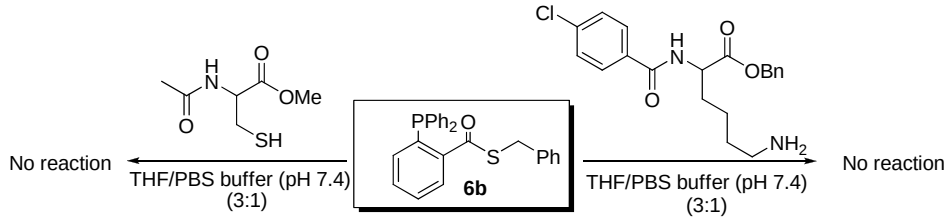
(m, 1H), 6.29-6.14 (m, 1H), 5.30-5.21 (m, 1H), 4.51-4.46 (m, 1H), 4.31-4.27 (m, 1H), 3.62-3.41 (m, 12H), 3.19-3.09 (m, 3H), 2.88 (dd, J = 4.8 Hz, 12.9 Hz, 1H), 2.72 (d, J = 12.9 Hz, 1H), 2.26-2.17 (m, 2H), 1.80-1.60 (m, 6H), 1.44-1.37 (m, 2H); ^{31}P NMR (121 MHz, $CDCl_3$) δ -4.11 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 173.7, 164.6, 141.5 (d, J = 22.5 Hz), 138.3 (d, J = 22.5 Hz), 137.9 (d, J = 7.5 Hz), 134.8, 134.2, 133.9, 132.3, 129.3, 129.2, 128.9, 128.8, 128.70, 128.66, 70.60, 70.55, 70.46, 70.3, 70.2, 69.9, 62.0, 60.5, 56.0, 40.8, 39.4, 36.3, 29.4, 28.5, 28.3, 25.9; IR (thin film) cm^{-1} 3327, 2942, 1739, 1710, 1407, 1354; ESI-MS (m/z): 724.3 $[M+H]^+$; HRMS m/z 724.2654 $[M+H]^+$; calcd for $C_{37}H_{47}N_3O_6PS_2$: 724.2644.



21

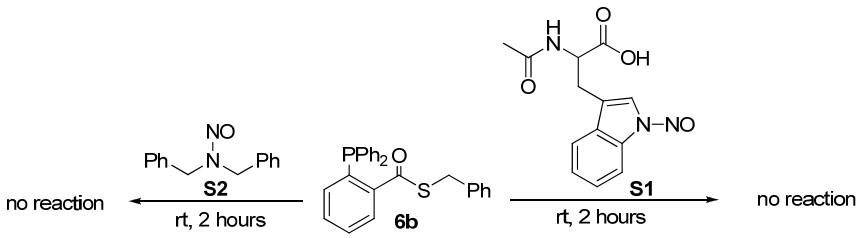
Compound **21** was prepared from benzoic acid using the method described for the preparation of compounds **6**. Isolated yield was 98%. White solid; m.p.: 98–99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.57-7.53 (m, 1H), 7.44-7.40 (m, 2H), 6.89-6.83 (m, 2H), 6.14-6.11 (m, 1H), 4.48-4.45 (m, 1H), 4.28-4.25 (m, 1H), 3.62 (m, 12H), 3.44-3.34 (m, 2H), 3.25 (m, 2H), 3.11-3.06 (m, 1H), 2.86-2.81 (m, 1H), 2.73-2.69 (m, 1H), 2.19-2.16 (m, 2H), 1.71-1.58 (m, 4H), 1.43-1.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 173.7, 164.7, 137.0, 133.8, 128.9, 127.4, 70.6, 70.5, 70.3, 70.1, 62.1, 60.6, 56.0, 40.7, 39.4, 36.2, 28.8, 28.6, 28.3, 25.9; IR (thin film) cm^{-1} 3292, 2928, 2866, 1705, 1661, 1557, 1461, 1206, 1116, 913; ESI-MS (m/z): 540.1.

Control Experiments



A lysine derivative shown above (21 mg, 0.056 mmol) and compound **6b** (46 mg, 0.11 mmol) were dissolved respectively in the mixture of 0.2 mL THF/0.1 mL PBS buffer (pH = 7.4) and stirred for 20 minutes. Then the solution of **6b** was added quickly to the solution of lysine derivative. The reaction was stirred at rt and monitored by TLC. No reaction was observed even after overnight. The reaction between **6b** and a cysteine derivative shown above was also carried out using the same procedure. Again, no reaction was observed after overnight.

Check the reactivity of phosphine-thioester reagent towards N-nitroso compounds

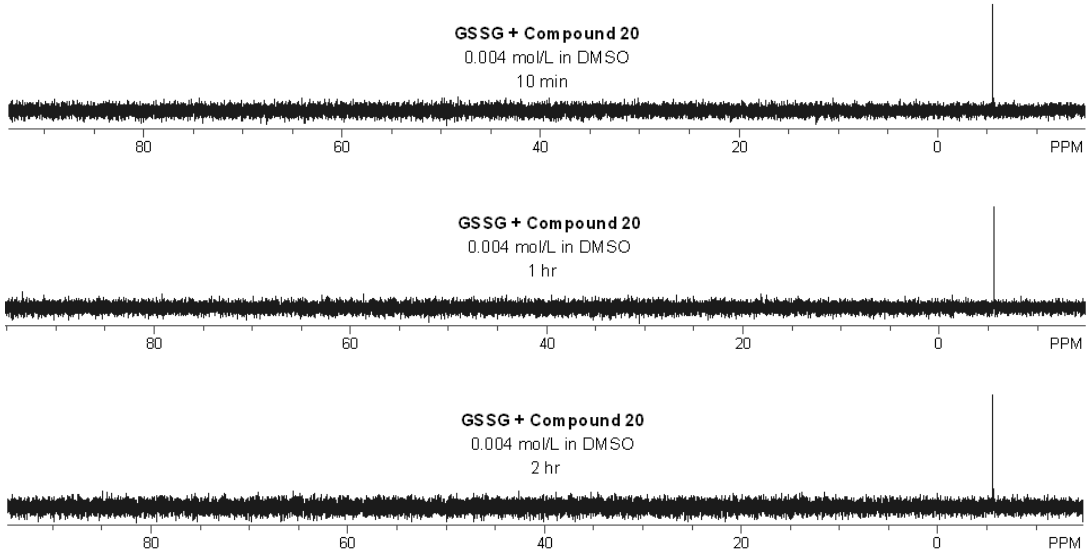


As suggested by one reviewer, we prepared an *N*-nitrosotryptophan derivative **S1** and an *N*-nitrosoamine **S2** using known procedures.[3] **S1** (0.2 mmol) and **S2** (0.2 mmol) were then separately treated with compound **6b** (0.4 mmol) in the mixture of 1.5 mL THF/0.5 mL PBS buffer (pH = 7.4) and stirred at rt. The reactions were monitored by TLC for 2 hours. However, no reaction was observed. Only starting materials were recovered and confirmed by NMR.

It is worth noting that previous evidence also suggests that *N*-nitrosoamines are stable in the presence of triarylphosphines.[4] In addition, we have recently found that triarylphosphines do not react with *O*-nitroso compounds at rt.[5] Therefore, the fast reaction between triarylphosphines and *S*-nitroso compounds under mild conditions is quite unique.

Check the reactivity of phosphine-thioester reagent towards GSSG

As suggested by one reviewer, we have tested the reaction between phosphine-thioester **20** and GSSG. The reaction was monitored by both TLC and ^{31}P-NMR. However, no reaction was observed after several hours at rt. ^{31}P-NMR spectra (shown below) were recorded at various times.



Protein Labeling Experiments

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[3] (a) K. Sonnenschein, H. de Groot, M. Kirsch, M. *J. Biol. Chem*. **2004**, *279*, 45433. (b) K. Niknam, M. A. Zolfigol. *Syn. Commun*. **2006**, *36*, 2311.

[4] Fishbein et al. *Chem. Res. Toxicol*. **2003**, *16*, 715.

[5] N. O. Devarie-Baez, M. Xian. *Org. Lett*. **2010**, *12*, 752.

COS-7 cells were grown in DMEM with high glucose supplemented with 10% fetal bovine serum, 100 U/ml of penicillin, and 100 lg/ml streptomycin. To begin an experiment, confluent cells were rinsed twice with Hanks balanced salt solution buffered with 25mM Hepes (HBSH, pH 7.4) and incubated either without (Lane 1) or with (Lane 2 and 3) 1 mM S-nitrosocysteine (CysNO) in HBSH at 37 ^{o}C for 15 minutes. After treatment, cells were rinsed twice with ice-cold HBSH, fixed by -20 ^{o}C methanol for 15 minutes, and then permealized with 0.2% Triton X-100 in PBS (PBST) which containing 40 mM NEM to block all the free thiols for 1 hour at room temperature. The excess NEM was removed by 4 times of wash with PBST. The labeling was performed by incubating the cells with 3 mM compound **20** (in DMSO) for 30 minutes at rt. Cells were then washed with PBST for 4 times to remove excess compound **20** and then scraped in RIPA buffer with 1% SDS. Some cells (Lane 3) were incubated with 100 mM DTT in PBST for 5 minutes before washing and lysing. The cell lysate was sonicated briefly and centrifuged at 14,000 rpm for 10 minutes. The supernatant was mixed with 2 X Laemmli loading buffer (without DTT or mecaptoethanol) and then loaded on 10% SDS-PAGE gel. After transferred to PVDF membrane, the labeled proteins were visualized by incubation with NeutrAvidin-HRP and ECL plus Western detection reagents (upper panel). The membrane was then stripped with 100 mM mercaptoethanol, 2% SDS, 62.5mM Tris–HCl, pH 6.7, at 50 C for 30 min, and reprobed using GAPDH antibody to exhibit the equal protein loading (lower panel).

Control Protein Labeling Experiments Using Compound 21

In another sets of control experiments, compound **21** was used to compare with compound **20**. The procedures were identical to the Protein Labeling Experiments. As shown in **Figure S1**, lane 1 and lane 4 were the results using **20** (+/- CysNO). Lane 2 and lane 5 were the results using **21** (+/- CysNO). Lane 3 and lane 6 were the results using **21** together with PPh_3 (+/- CysNO). GAPDH lanes (lower panel) indicate equal protein loading. These results demonstrate the specificity of phosphine-mediated disulfide formation on SNO moieties.

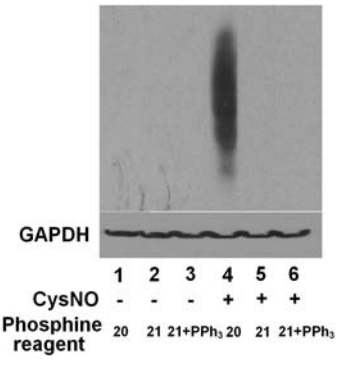
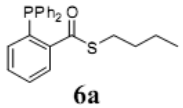
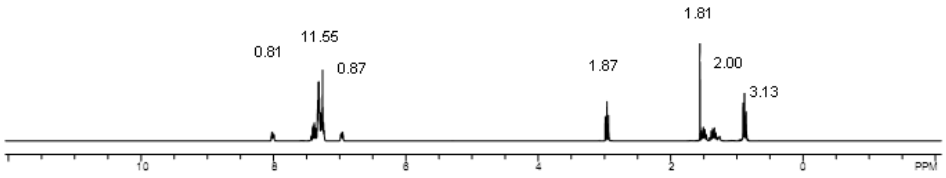


Figure S1

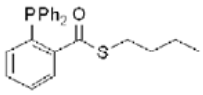
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **6a**



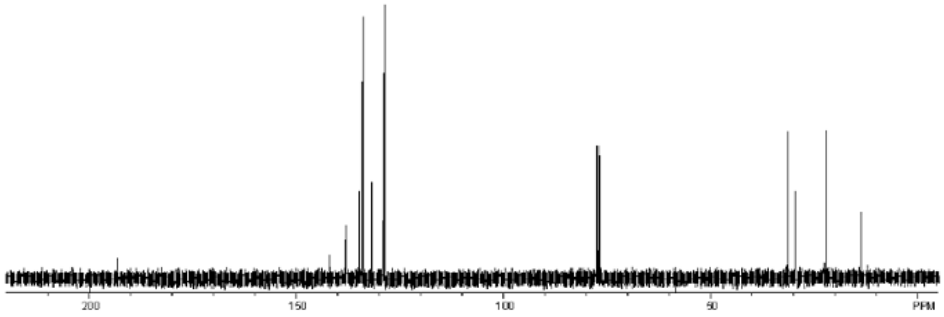
6a



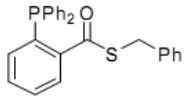
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **6a**



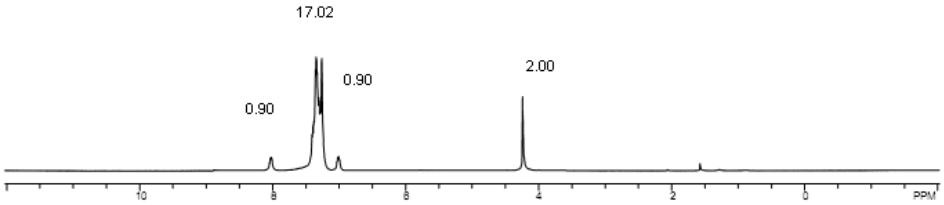
6a



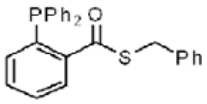
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **6b**



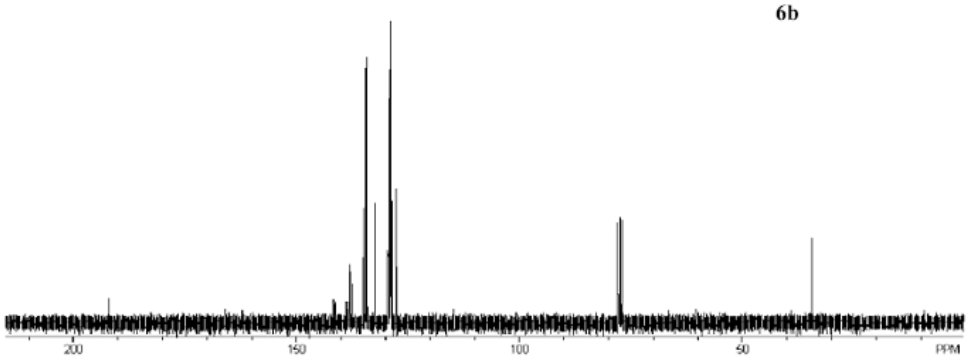
6b



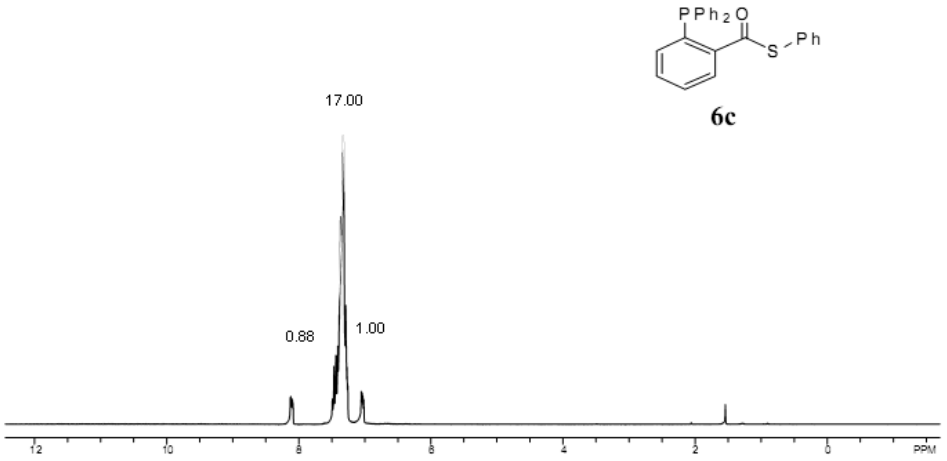
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **6b**



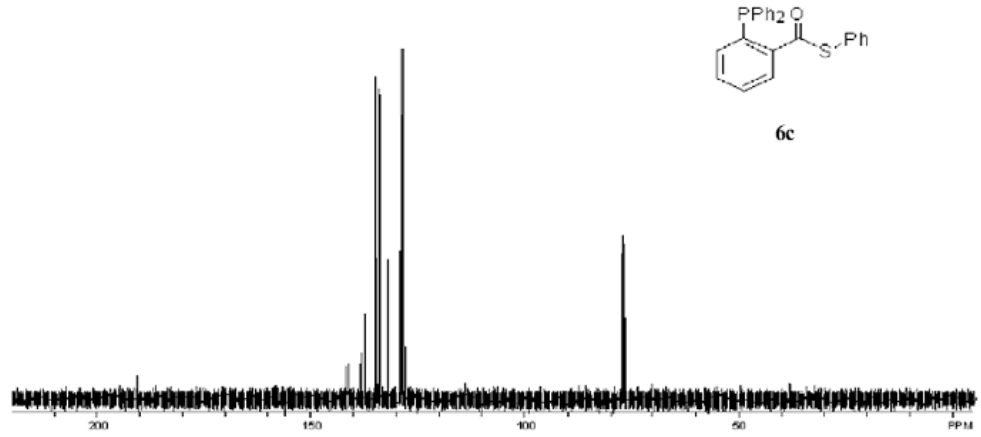
6b



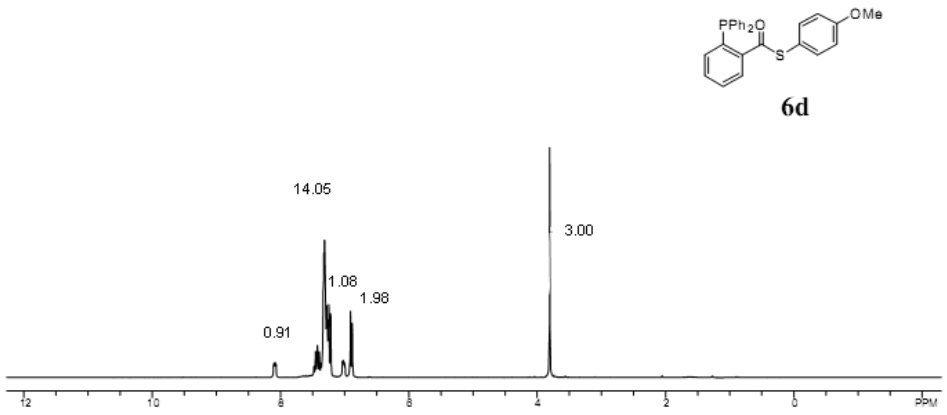
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **6c**



^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **6c**

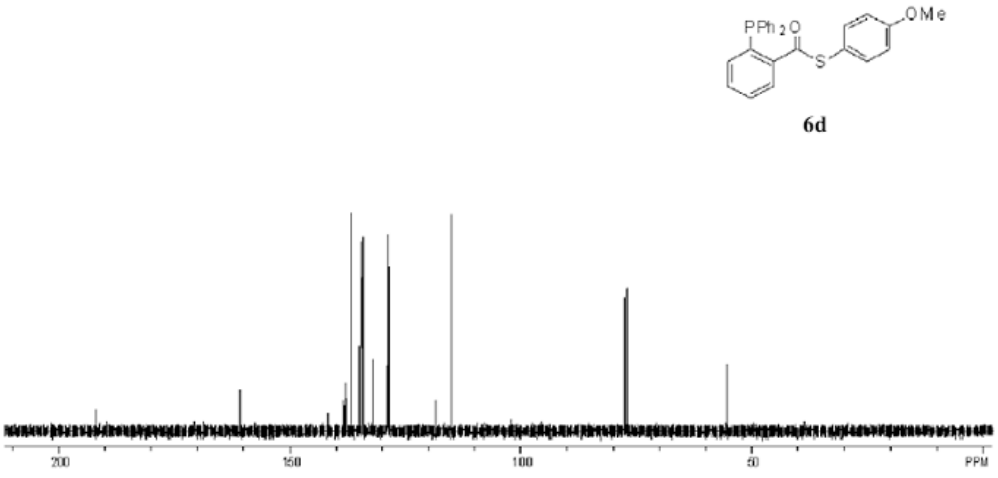


^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **6d**



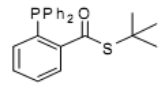
6d

^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **6d**

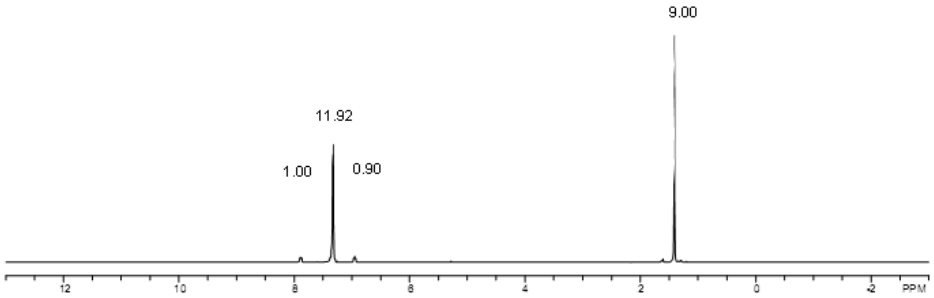


6d

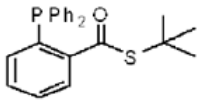
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **6e**



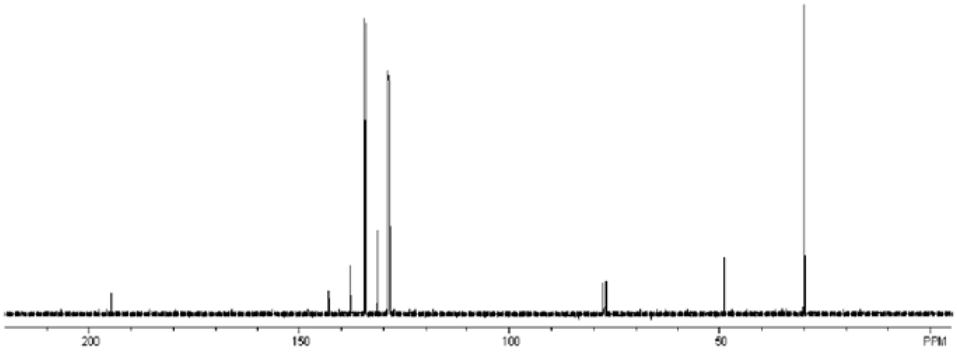
6e



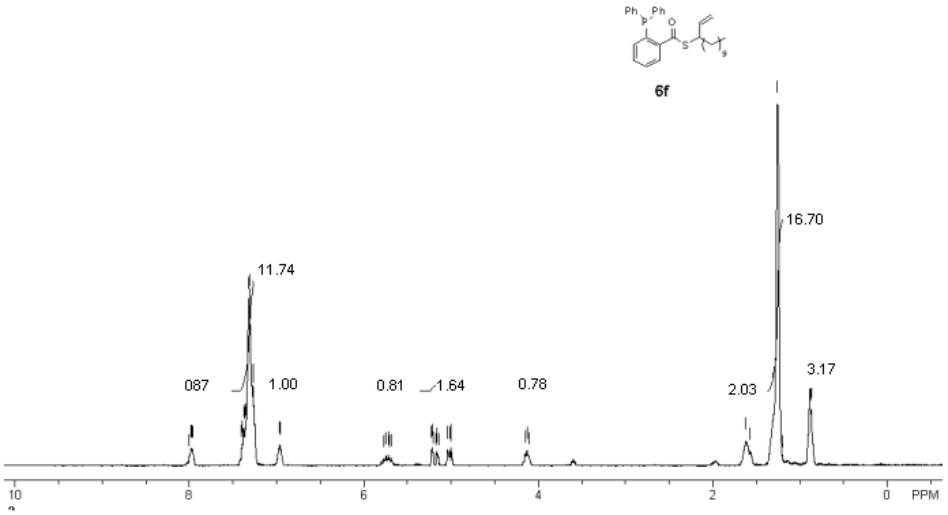
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **6e**



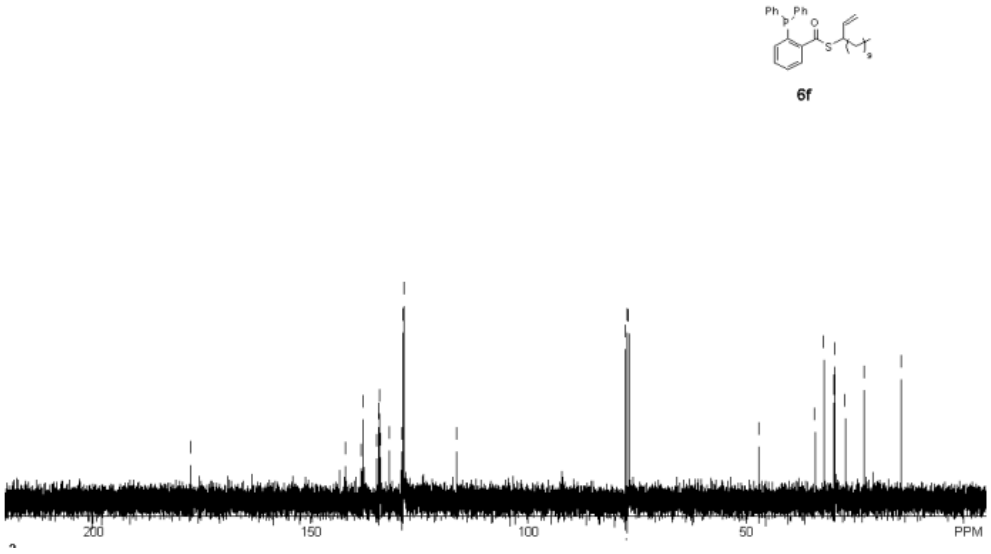
6e



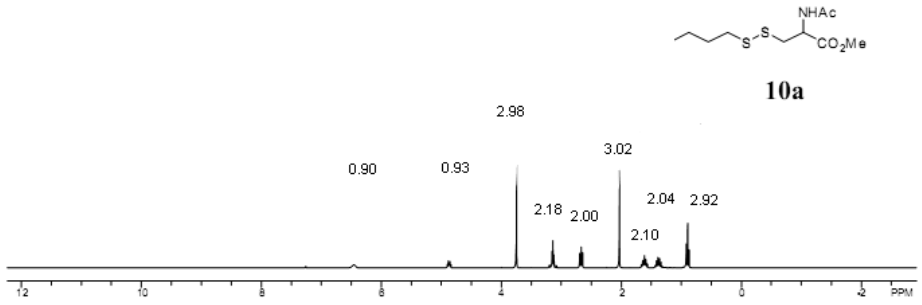
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **6f**



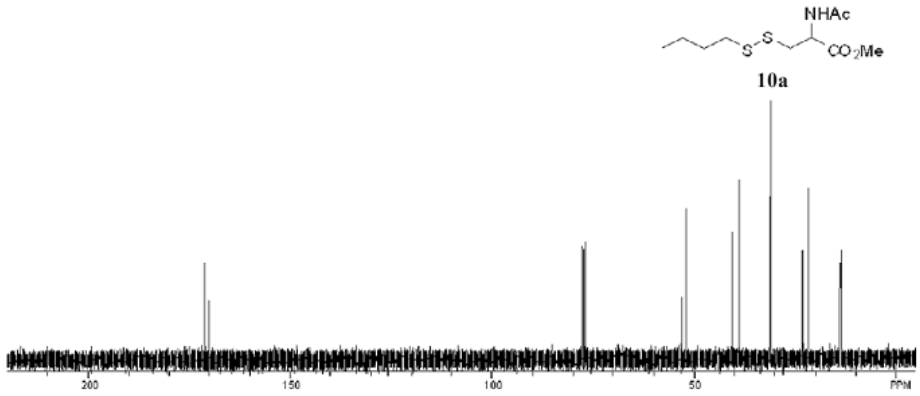
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **6f**



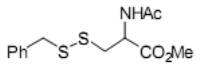
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10a**



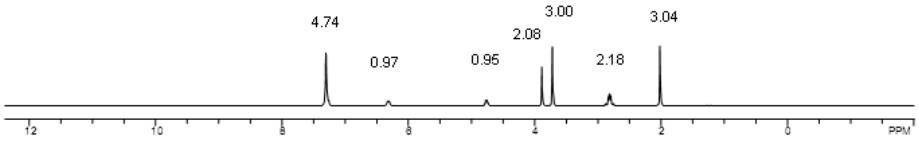
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **10a**



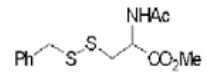
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10b**



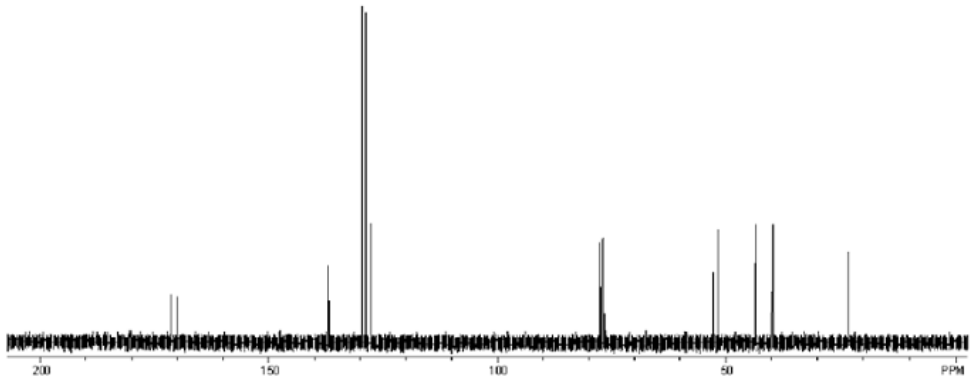
10b



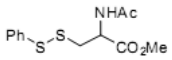
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **10b**



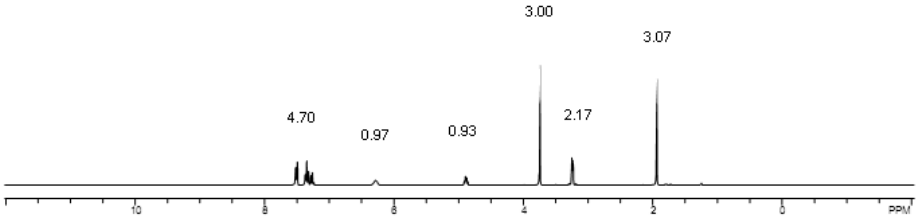
10b



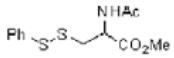
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10c**



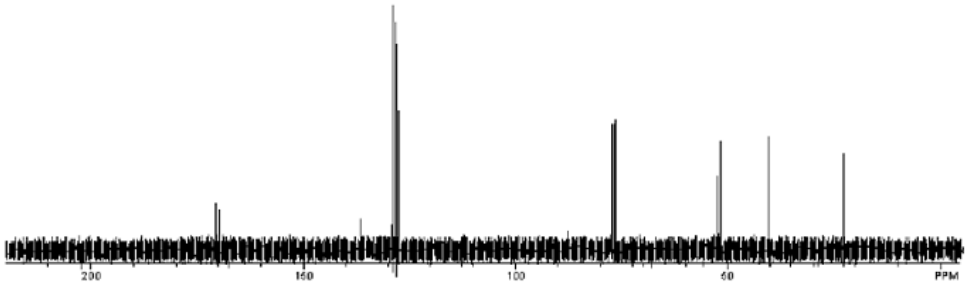
10c



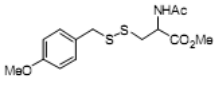
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **10c**



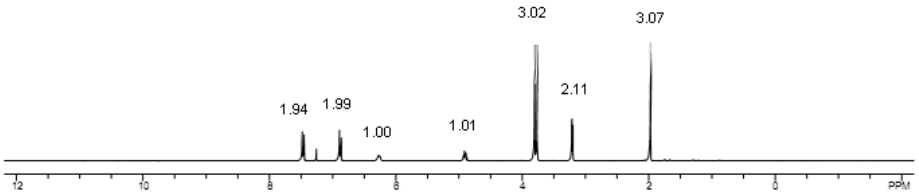
10c



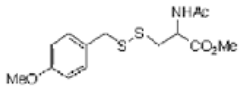
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10d**



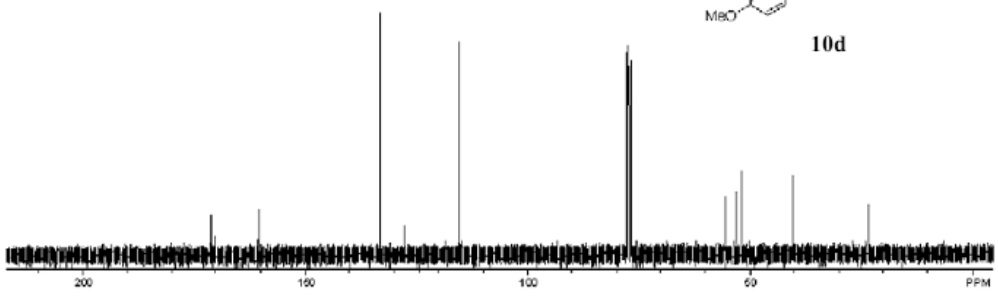
10d



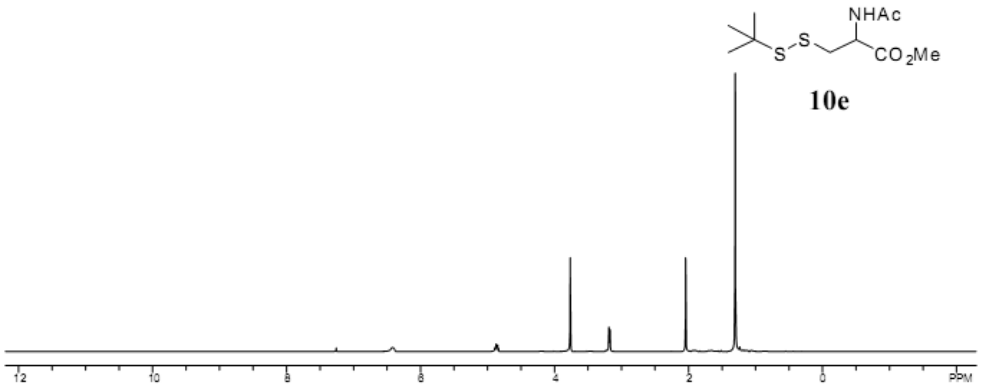
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **10d**



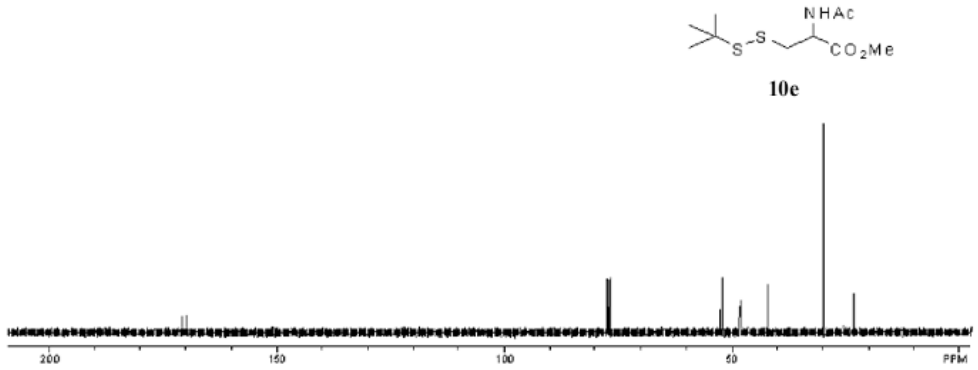
10d



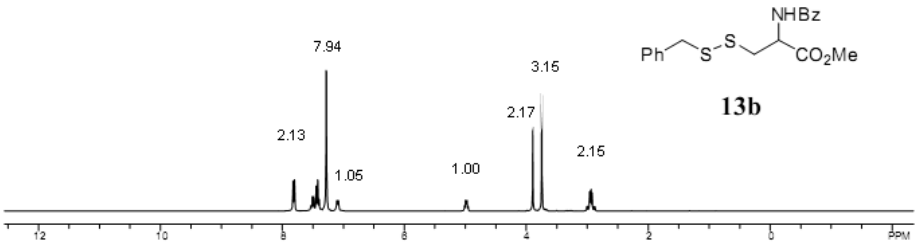
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10e**



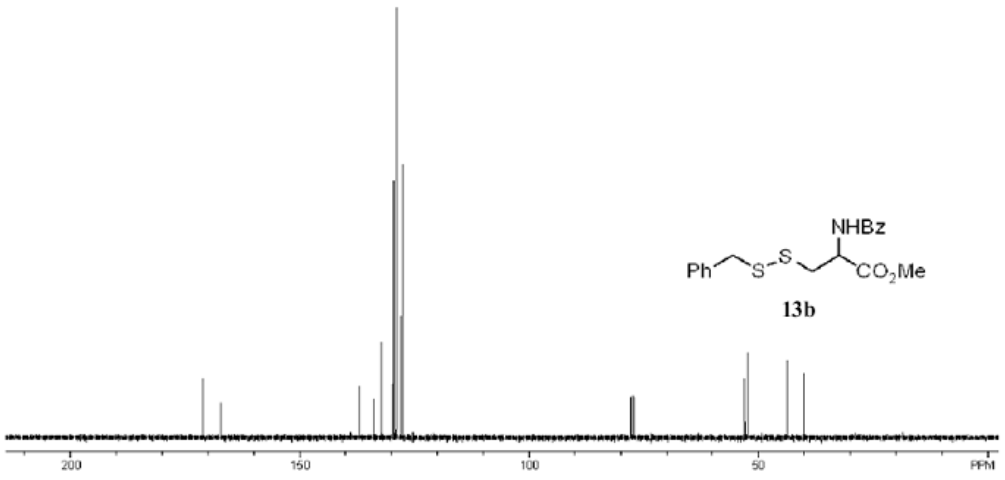
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **10e**



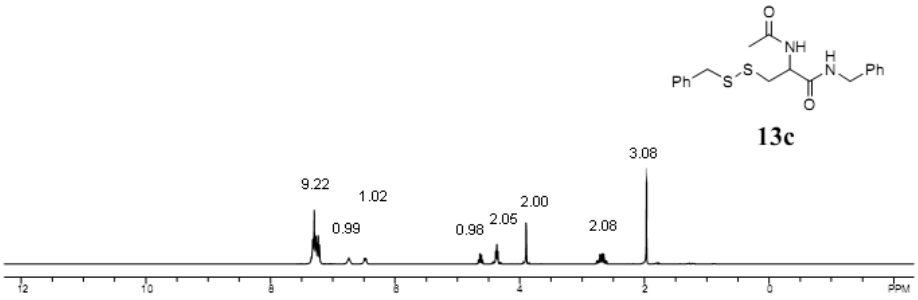
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13b**



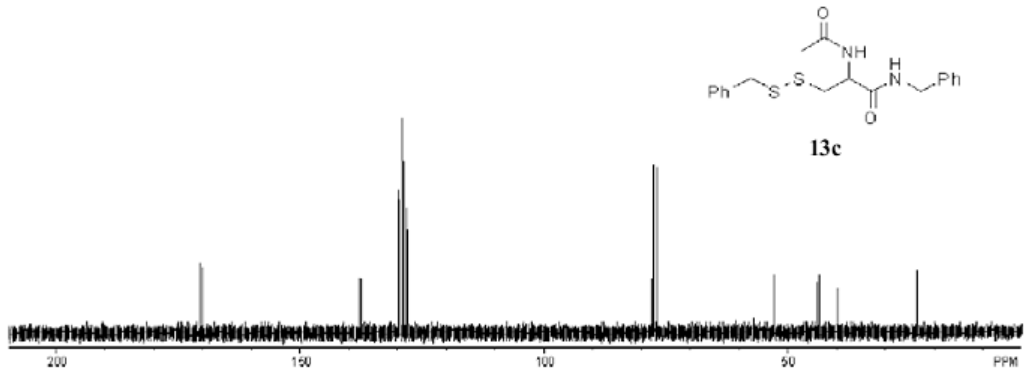
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13b**



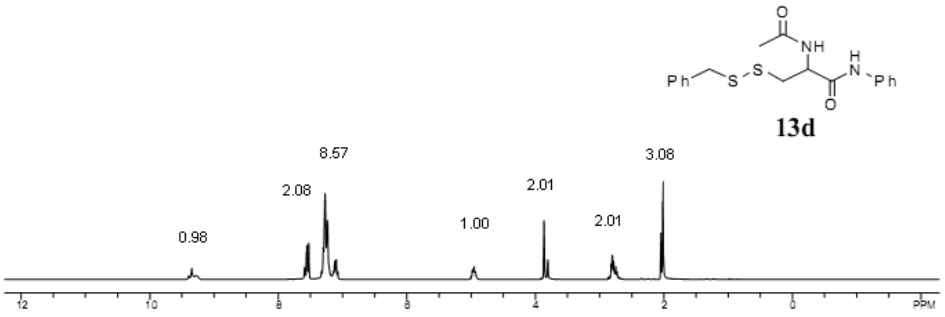
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13c**



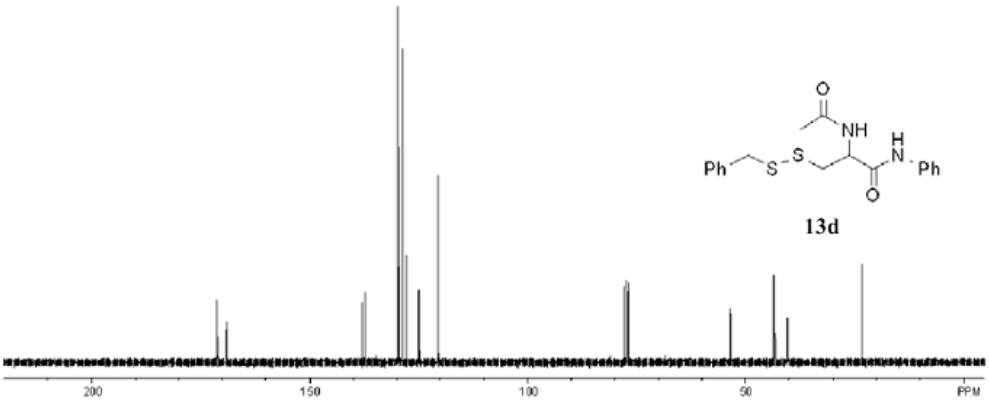
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13c**



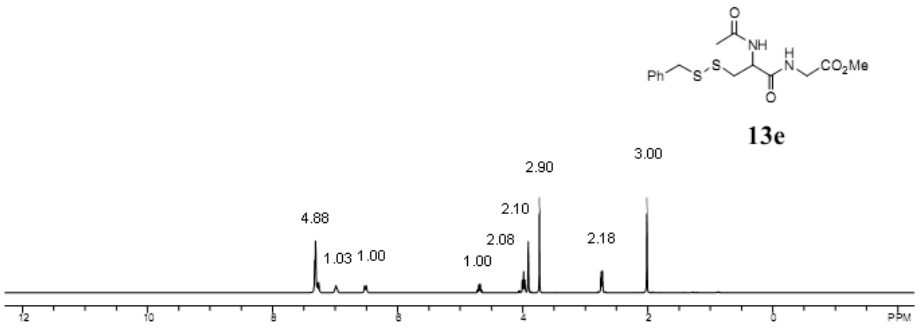
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13d**



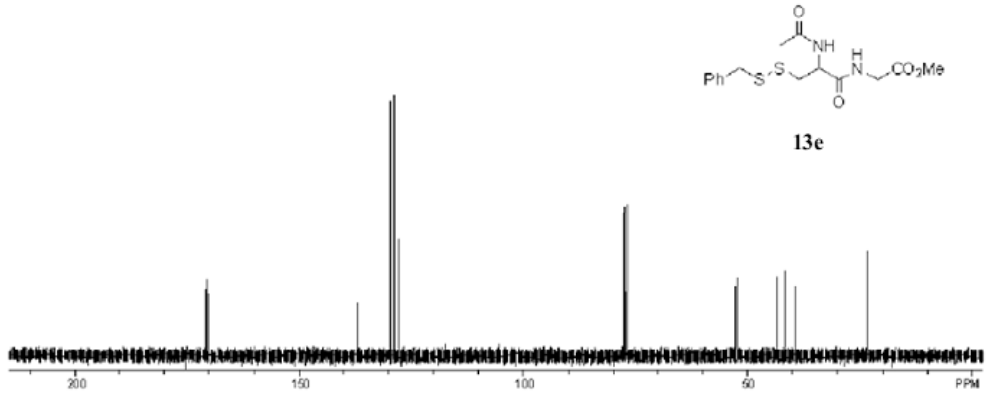
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13d**



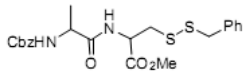
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13e**



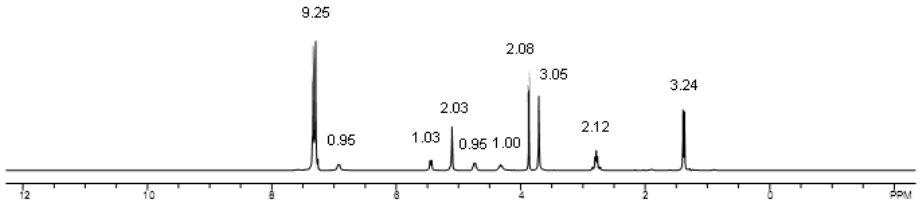
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13e**



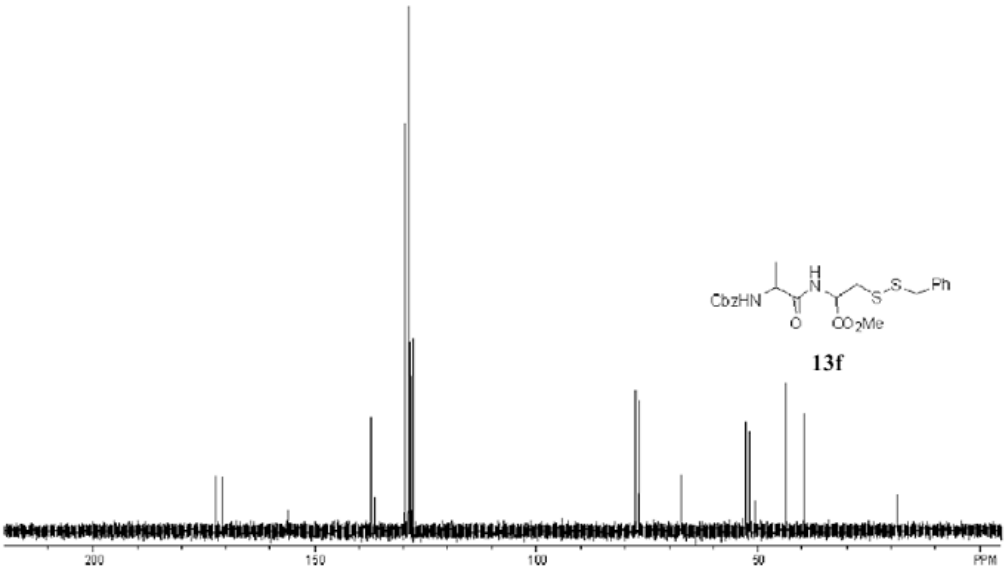
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13f**



13f

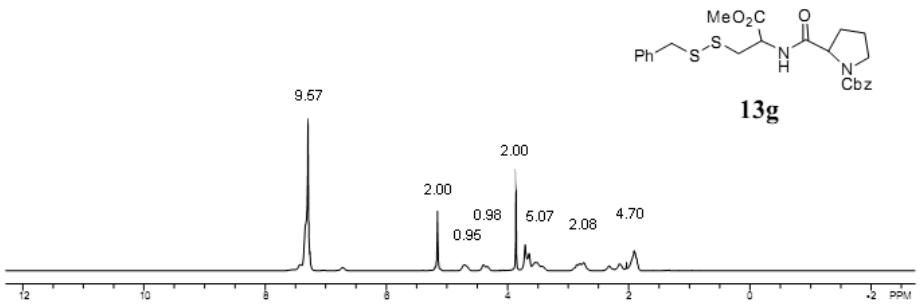


^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13f**

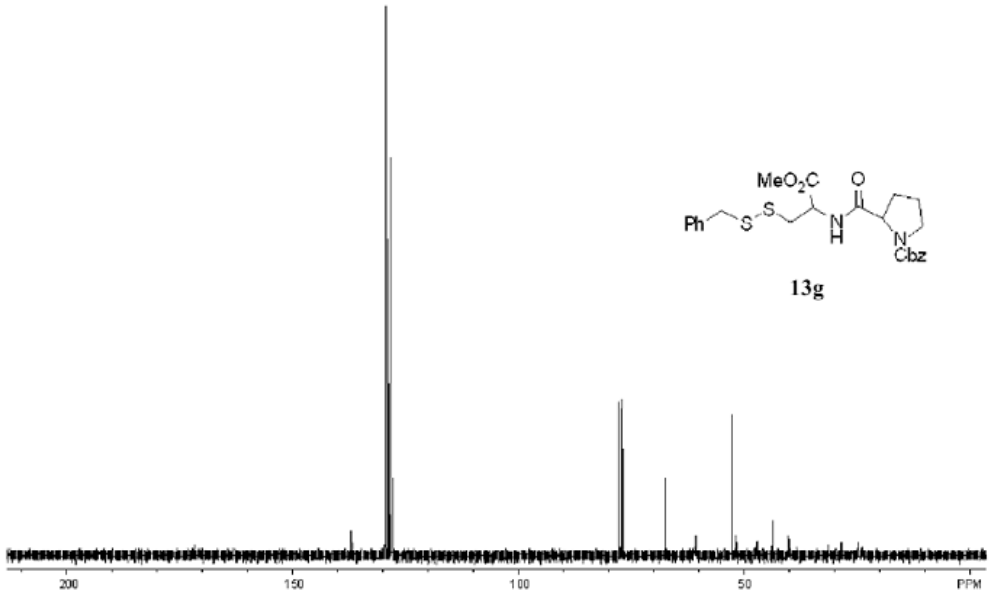


13f

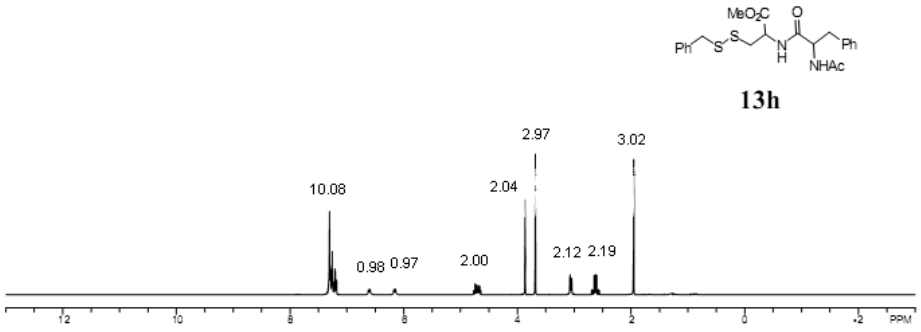
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13g**



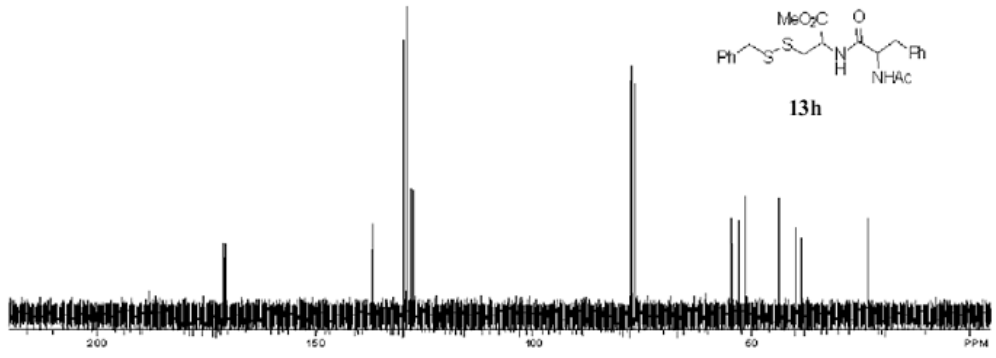
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13g**



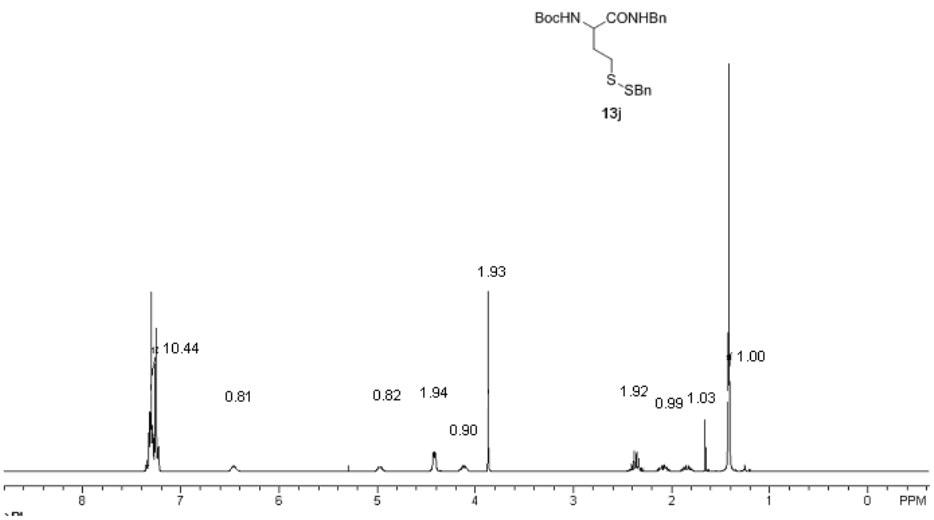
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13h**



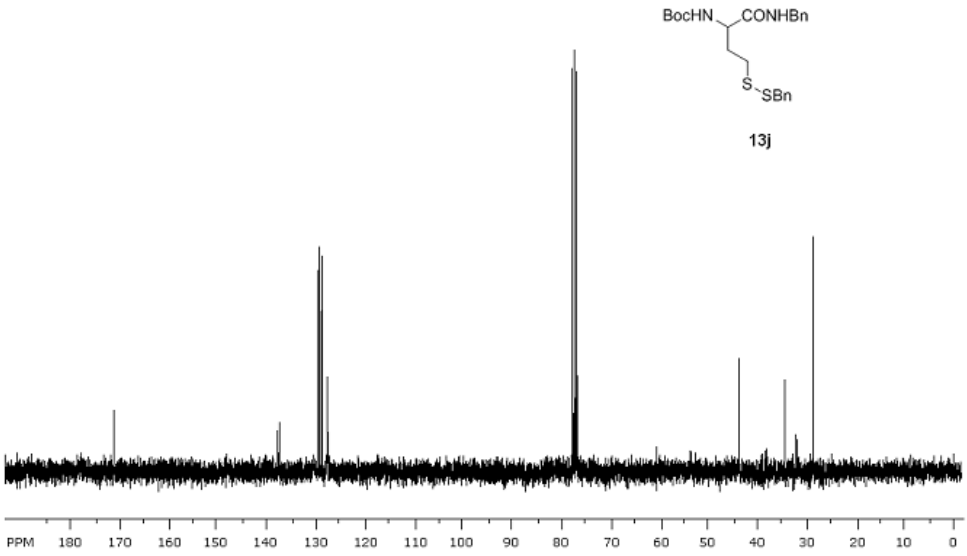
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13h**



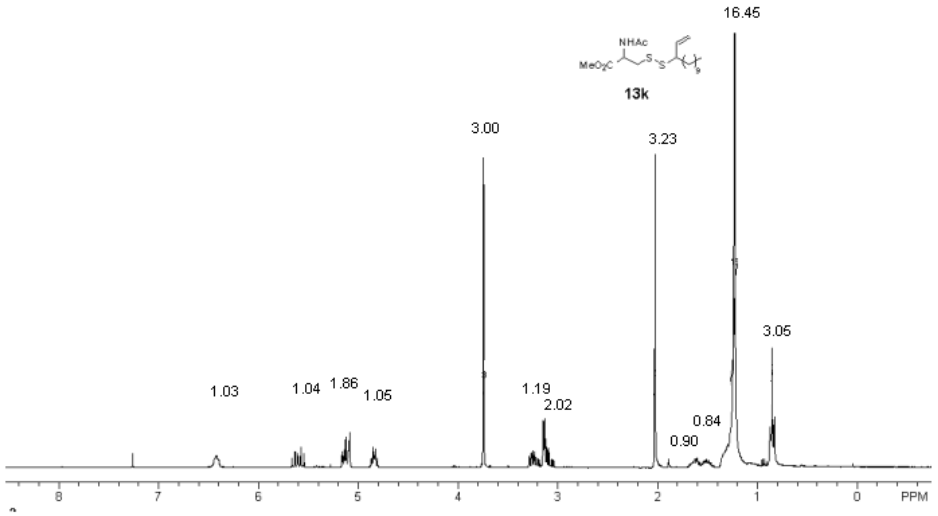
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13j**



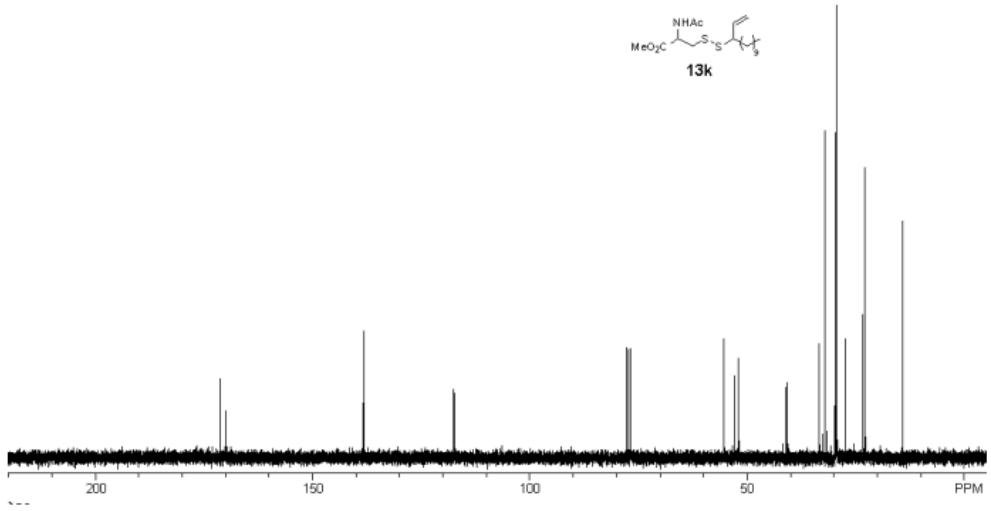
^{13}C NMR (300 MHz, $CDCl_3$) spectrum of **13j**



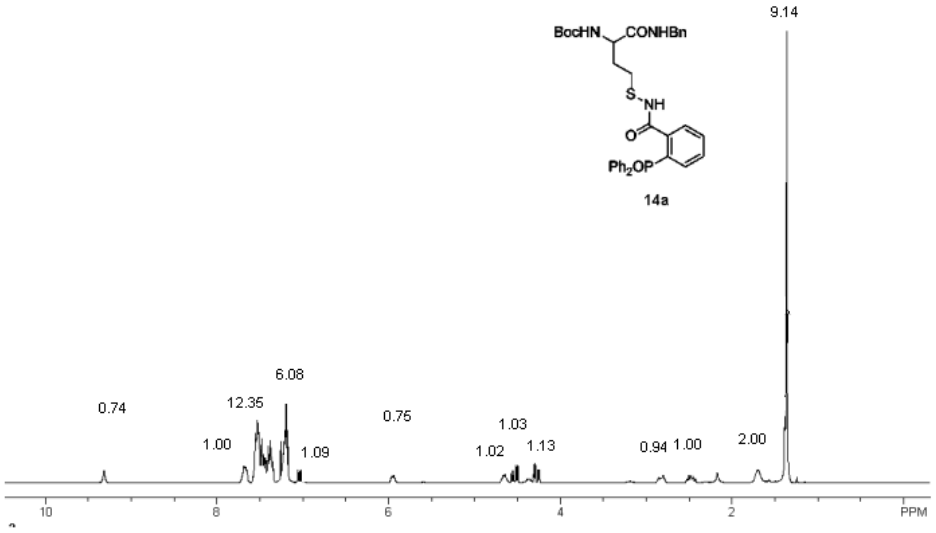
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13K**



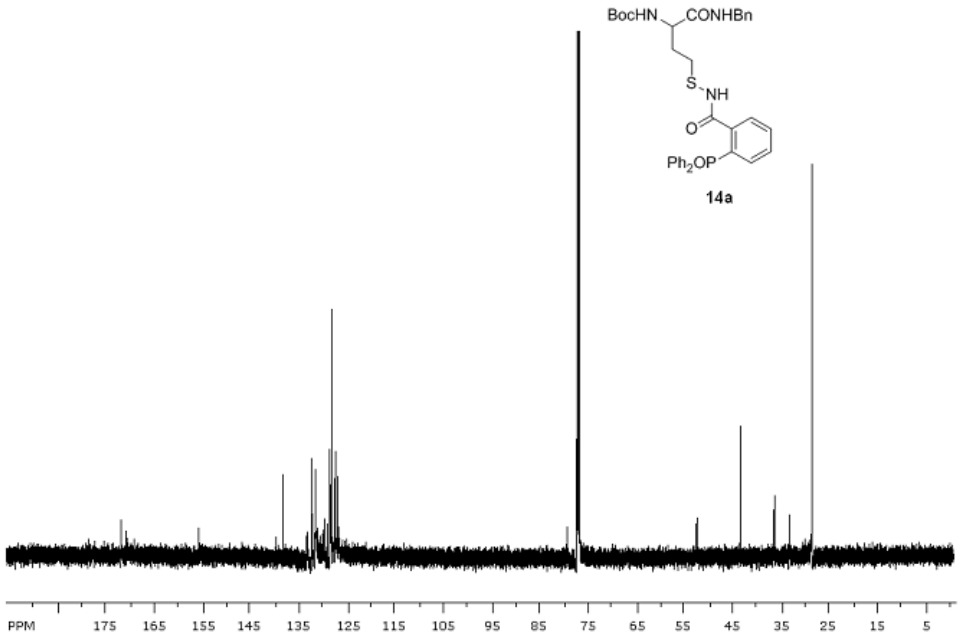
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13K**



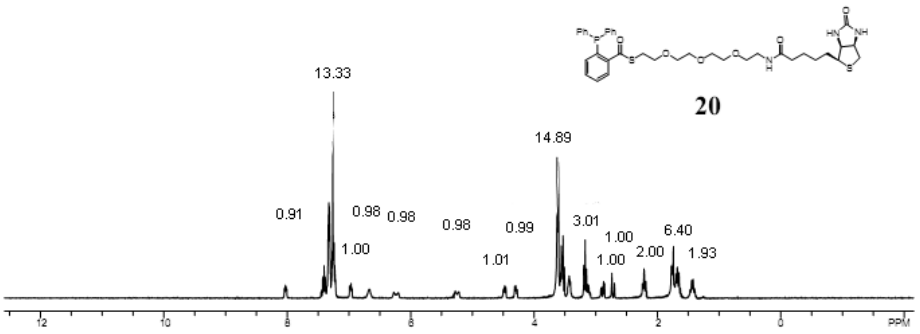
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **14a**



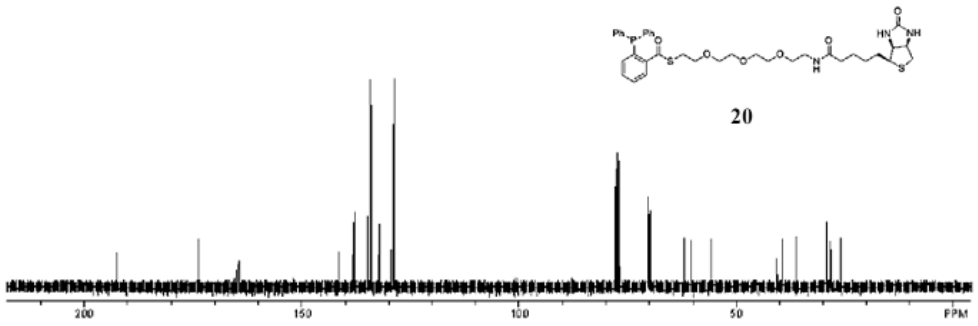
^{13}C NMR (150 MHz, $CDCl_3$) spectrum of **14a**



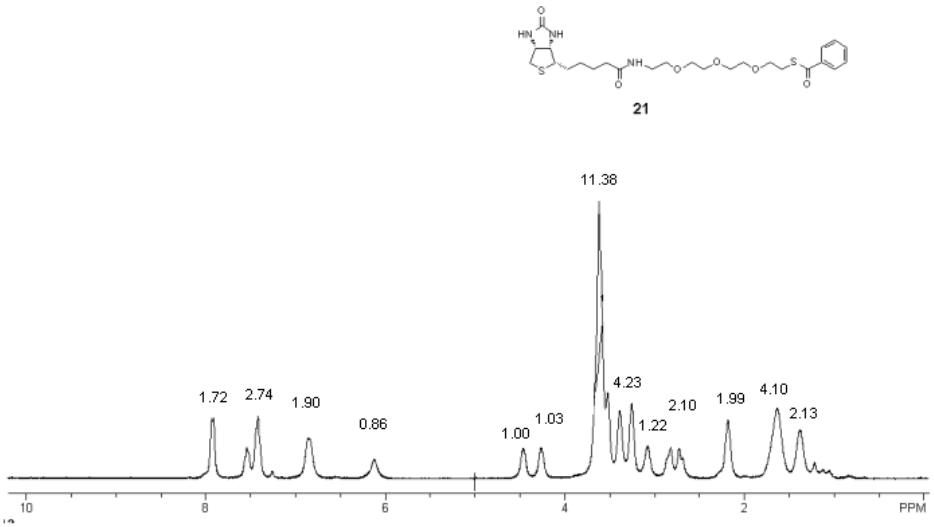
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **20**



^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **20**



^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **21**



^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **21**