Electronic Supplementary Information

Palladium-Catalyzed Atom Transfer Radical Cyclization of Unactivated Alkyl Iodide

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I. General information

Unless otherwise noted, all reagents were obtained commercially and used without further purification.

NMR spectrum:

^{1}H and ^{13}C NMR spectra were collected on 400 MHz and 300 MHz NMR spectrometers (Bruker AVANCE) using $CDCl_3$. Chemical shifts are reported in parts per million (ppm). Chemical shifts for protons are reported in parts per million downfield and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.28). Chemical shifts for carbon are reported in parts per million downfield and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.0). Data are represented as follows: chemical shift, multiplicity (br. s = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration.

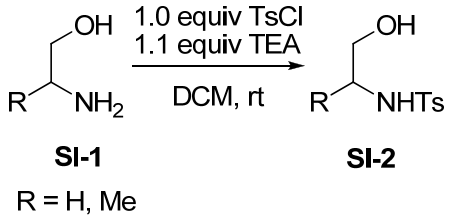
Mass spectroscopy:

Mass spectra were in general recorded on an AMD 402/3 or a HP 5989A mass selective detector.

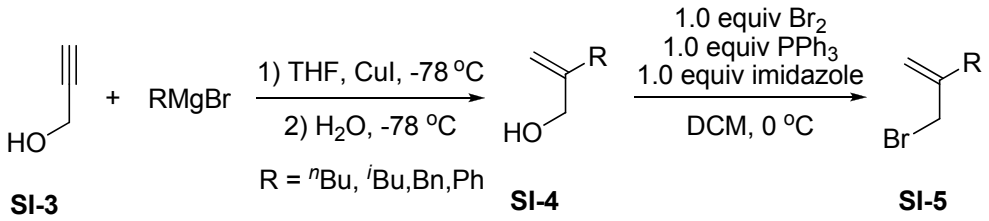
Chromatography:

Column chromatography was performed with silica gel (200-300 mesh ASTM).

II. The Procedure for Substrates Synthesis

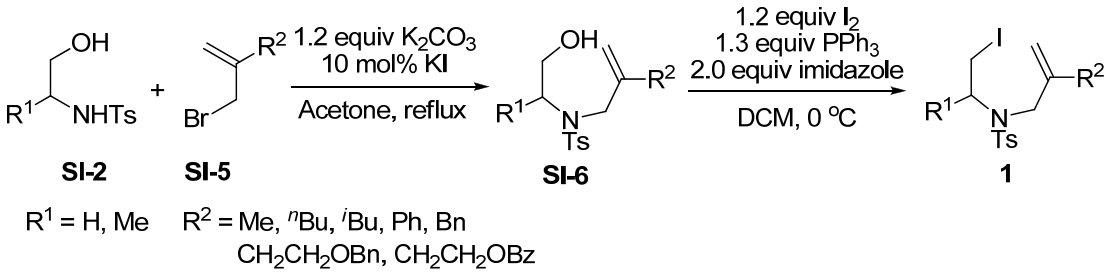


TsCl (110 mmol, 1.1 equiv.) was added to the solution of **SI-1** (100 mmol, 1.0 equiv.) in DCM (150 mL) in one portion. Then, TEA (110 mmol, 1.1 equiv.) was added dropwise. The mixture was stirred overnight. After filtrating the solid, the resulting organic phase was washed with water (3 x 50 mL), then was dried over Na_2SO_4. **SI-2** was obtained after removing the solvent and was used without further purification.



To a stirred solution of propargyl alcohol **SI-3** (5.0 g, 4.75 mL, 90 mmol) in anhydrous THF (150 mL) under N_2, was added CuI (1.9 g, 10 mmol). The resulting pink suspension was cooled to -78 °C. The corresponding magnesium bromide (0.25 mol) in anhydrous THF (250 mL), which was freshly prepared from Mg and RBr, was added via cannula, at such a rate as to maintain the temperature below -60 °C. The reaction was allowed to warm slowly to room temperature over 18 hours. The reaction was again cooled to -78 °C, and then was treated with H_2O (10 mL) to give a light green suspension. It was then allowed to warm slowly to room temperature over 3 hours, during which time it became grey in colour. Then it was treated with ether (500 mL). After treated with 1 M hydrochloric acid (50 mL), a green gelatinous precipitate was formed, which was thoroughly extracted with ether (3 x 100 mL). The combined organic layers were dried on Na_2SO_4. After removing the solvent, the residue was purified by column chromatography to give a yellow oil.

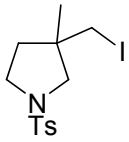
To a stirred solution of PPh_3 (2.6 g, 10 mmol) in DCM was added Br_2 (1.6 g, 10 mmol) dropwise at 0 ^oC. After treated with imidazole (0.68 g, 10 mmol) in one pot, alcohol **SI-4** in THF was added dropwise. The mixture was stirred for 2h at RT. Silica gel was added to the reaction mixture and the solvent was removed on the vacuum. The residue was purified by column chromatography with petroleum ether as eluent to give compound **SI-5**.



To a solution of **SI-2** (3 mmol) in acetone (5 mL) was added K_2CO_3 (0.62 g, 4.5 mmol, 1.5 equiv.) at room temperature, followed by a solution of **SI-5** (4.5 mmol, 1.5 equiv.) in acetone (1 mL). The reaction mixture was heated to reflux overnight. After cooling to rt, silica gel was added to the reaction mixture and the solvent was removed on the vacuum. The residue was purified by column chromatography to give **SI-6**. Then it was dissolved in DCM (10 mL) and treated with I_2 (1.2 equiv.), PPh_3 (1.3 equiv.) and imidazole (2.0 equiv.) at 0 ^oC. The reaction was stirred overnight. Silica gel was added to the reaction mixture and the solvent was removed on the vacuum. The residue was purified by column chromatography with petroleum ether / EA as eluent to give compound **1.**

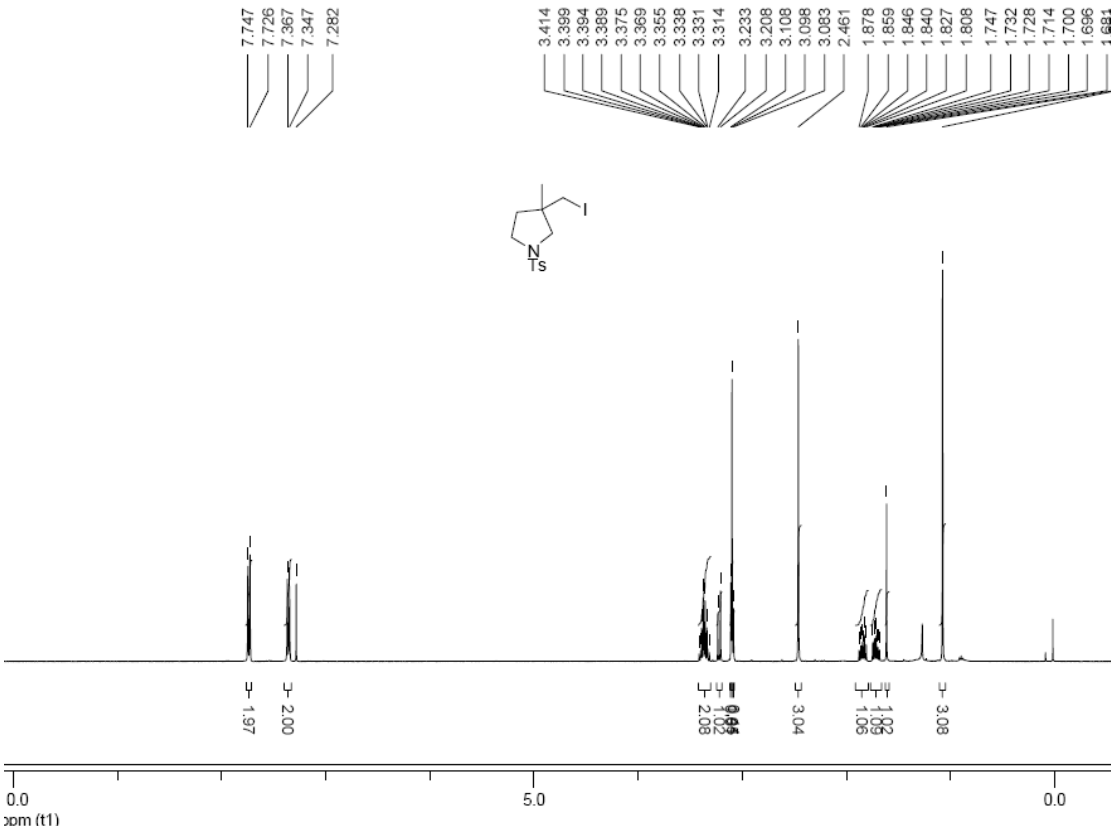
III. The Procedure for iodine atom transfer cyclization and the Data for Compounds 7a-7k and 8

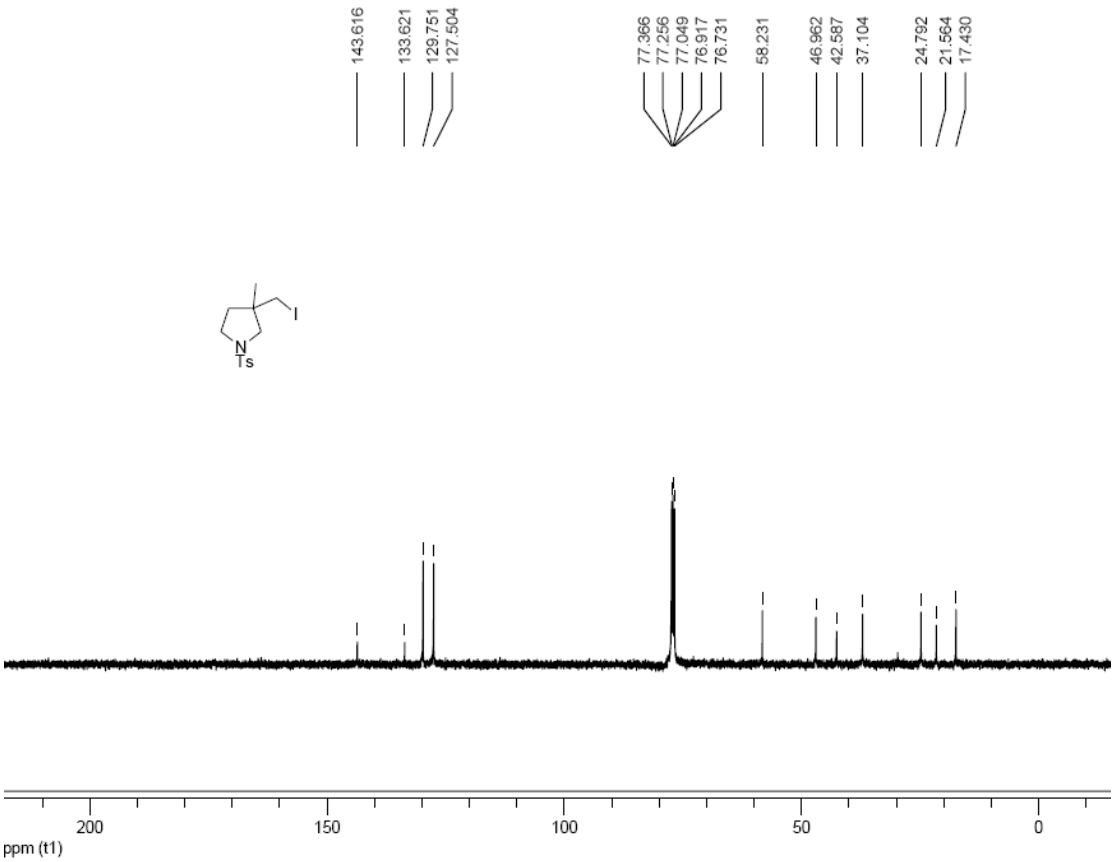
In a 25 mL sealed tube, the mixture of **1** (0.2 mmol), $Pd(OAc)_2$ (0.02mmol, 4.6 mg), and DPPF (0.06, 34 mg) were dissolved in toluene (4 mL). Then, the mixture was bubbled N_2 for 30 seconds, and then the vessel was sealed. The reaction mixture was heated to 130 ^oC for 24 h. The mixture was cooled to rt and directly subjected to silica gel column chromatography (petroleum ether/EtOAc 50:1 to 5:1 gradient) to give the product **7**.

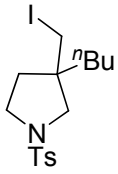


7a (62.2 mg, 82%)

^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 3H), 1.68-1.75 (m, 1H), 1.81-1.88 (m, 1H), 2.46 (s, 3H), 3.10 (d, J = 10.0 Hz, 1H), 3.10 (s, 2H), 3.22 (d, J = 10.0 Hz, 1H), 3.31-3.41 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 17.4, 21.6, 24.8, 37.1, 42.6, 47.0, 58.2, 127.5, 129.8, 129.9, 133.6, 143.6. HRMS Calcd for $C_{13}H_{18}INO_2S$ 379.0103, found 379.0105.

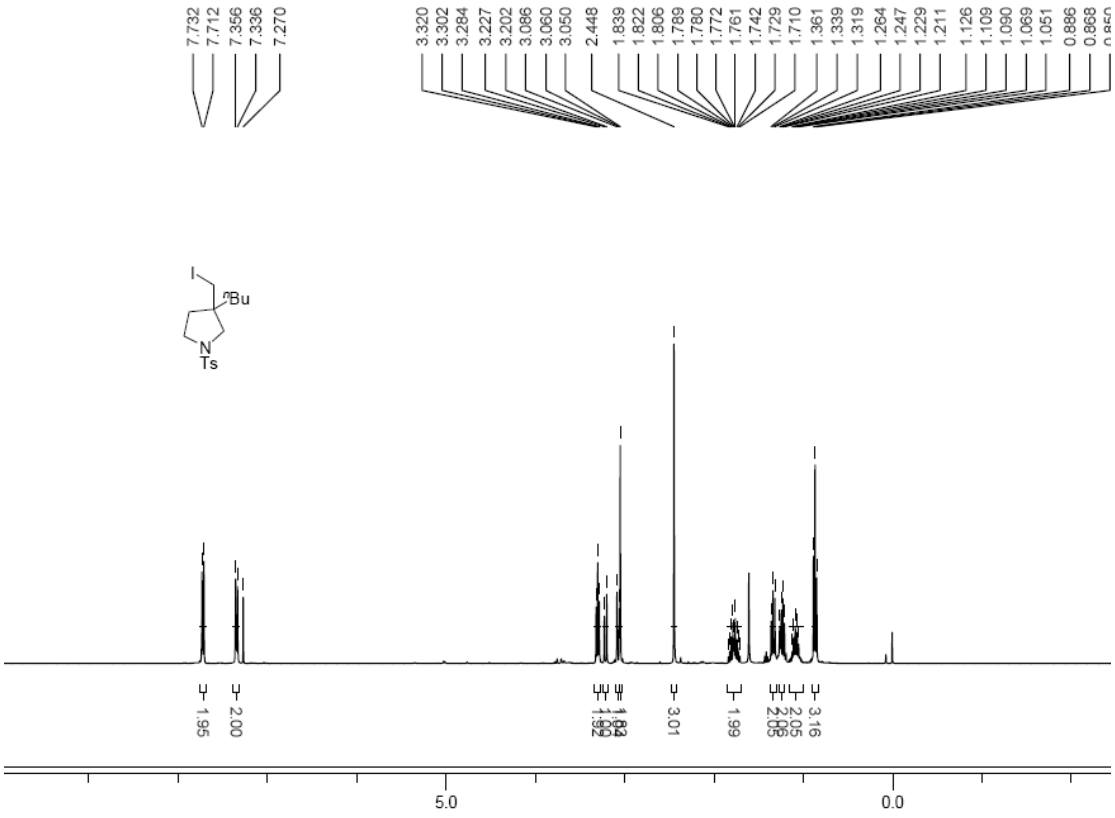


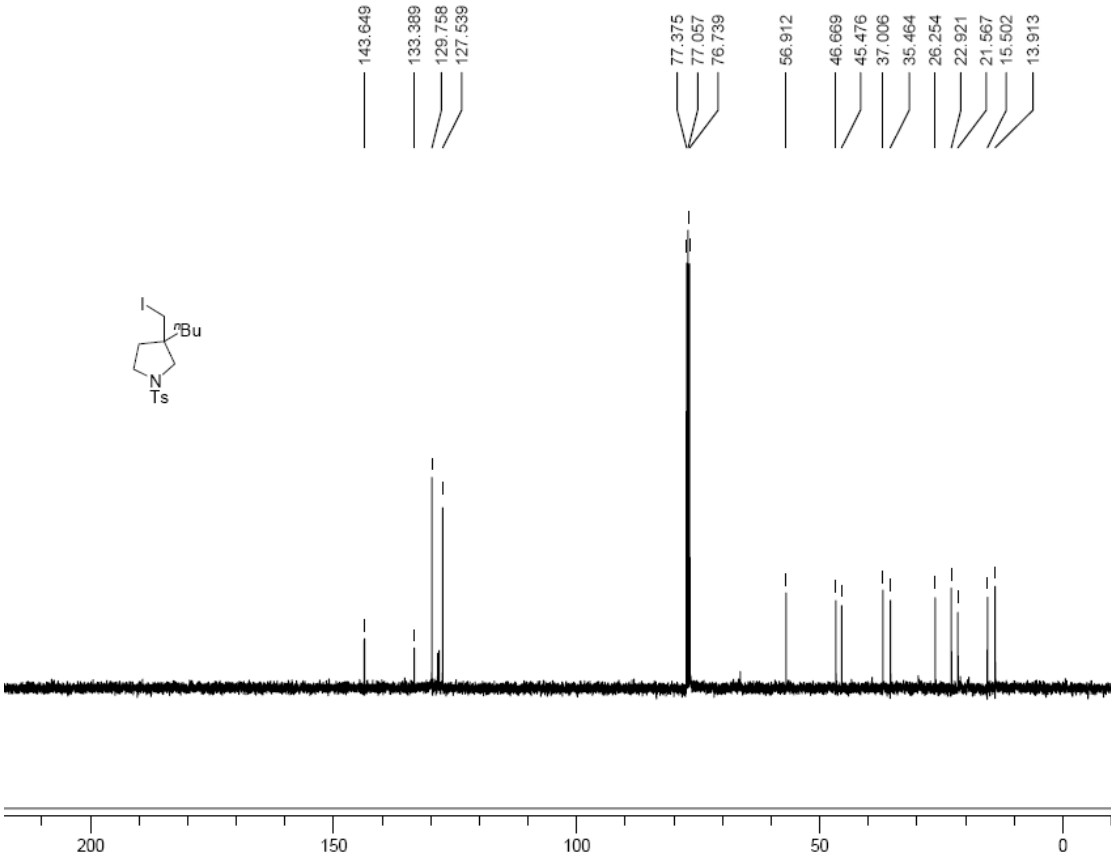


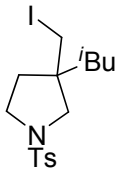


7b (58.9 mg, 70%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.2 Hz, 3H), 1.05-1.13 (m, 2H), 1.21-1.26 (m, 2H), 1.34 (t, J = 8.0 Hz, 2H), 1.71-1.84 (m, 2H), 2.45 (s, 3H), 3.05 (s, 2H), 3.07 (d, J = 10.4 Hz, 1H), 3.21 (d, J = 10.0 Hz, 1H), 3.30 (t, J = 7.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 13.9, 15.5, 21.6, 22.9, 26.2, 35.5, 37.0, 45.5, 46.7, 56.9, 127.5, 129.8, 133.4, 143.6. HRMS Calcd for ($C_{16}H_{24}INO_2S$-I) 294.1528, found (M-I) 294.1544.

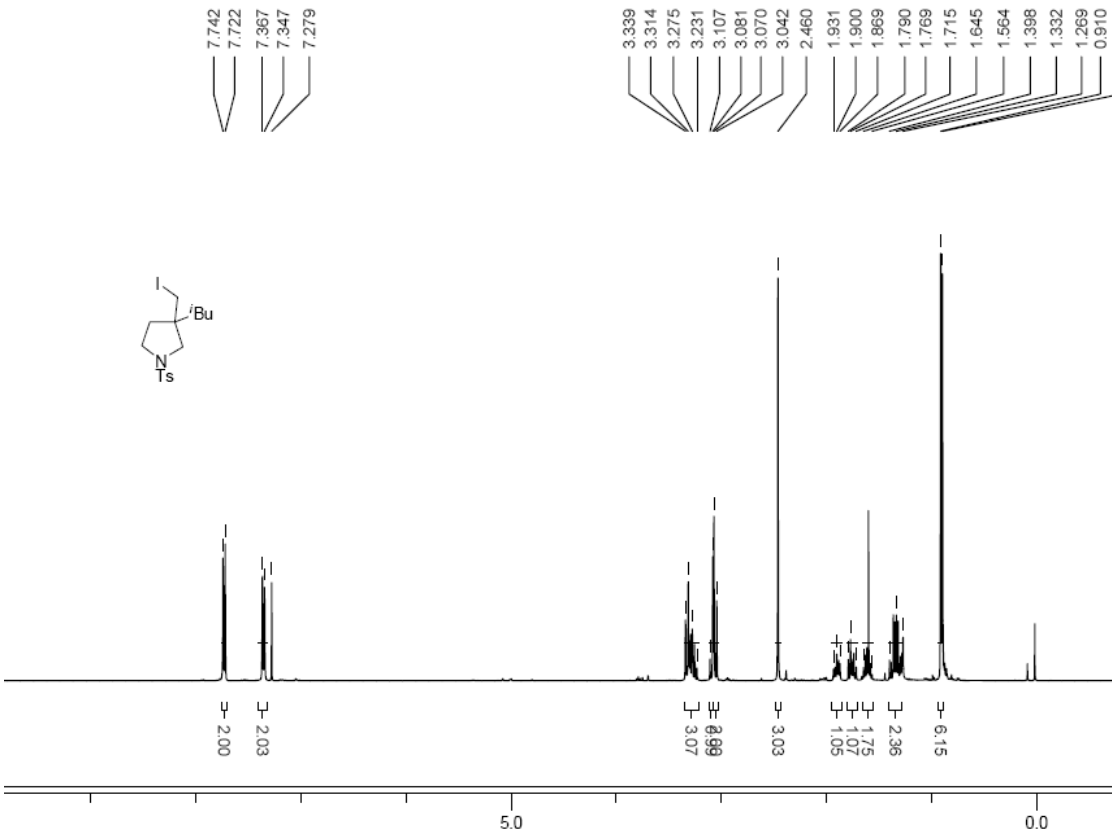


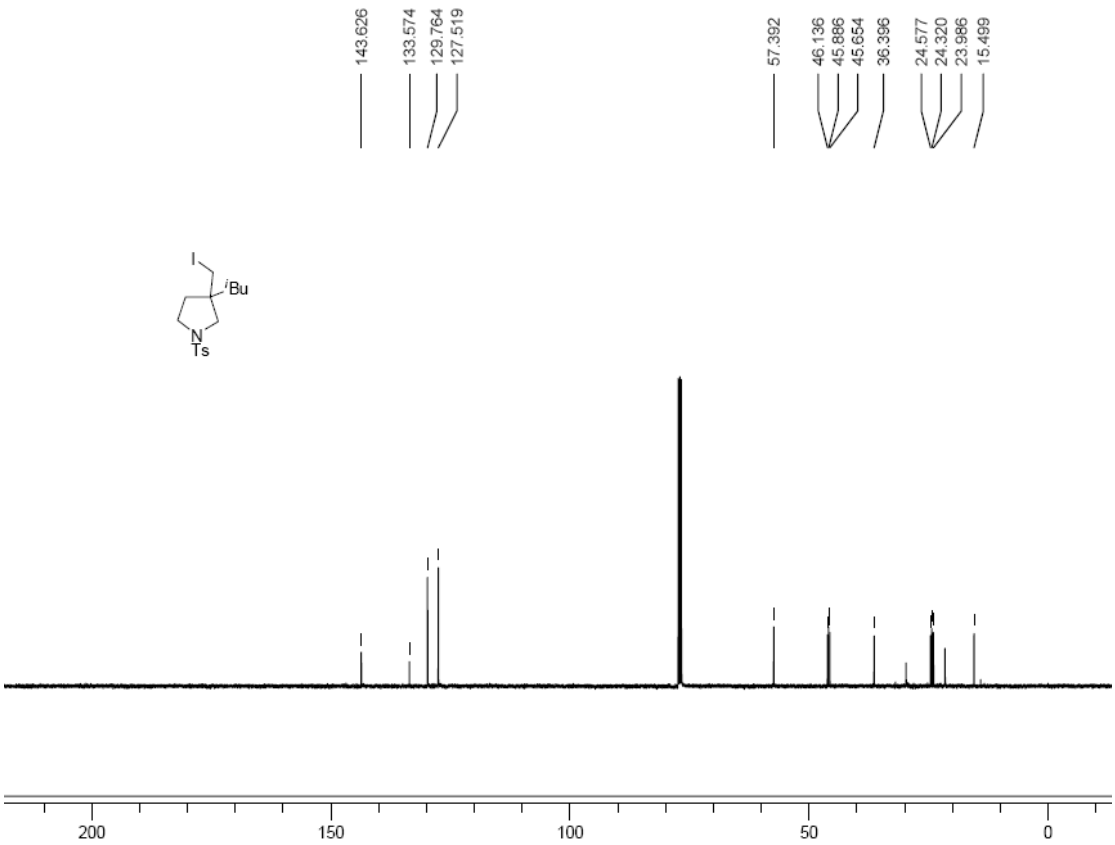


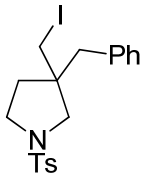


7c (57.2 mg, 62%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, J = 6.4 Hz, 6H), 1.30-1.40 (m, 1H), 1.57-1.66 (m, 1H), 1.72-1.79 (m, 1H), 1.87-1.93 (m, 1H), 2.46 (s, 3H), 3.04-3.11 (m, 3H), 3.23-3.34 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 15.5, 24.0, 24.3, 24.6, 36.4, 45.6, 45.9, 46.1, 57.4, 127.5, 129.8, 133.6, 143.6. HRMS Calcd for ($C_{16}H_{24}INO_2S$-I) 294.1528, found (M-I) 294.1544.

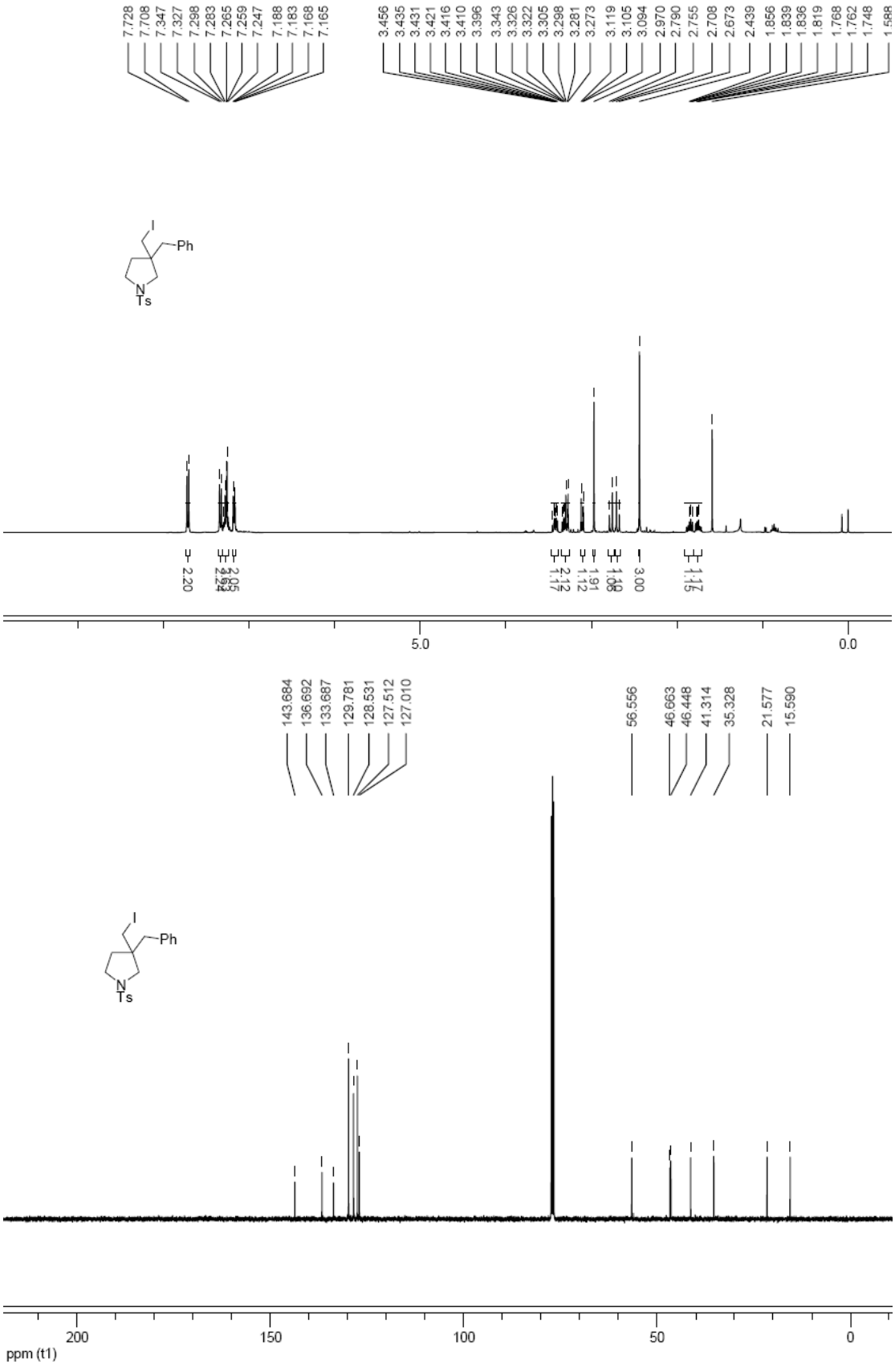


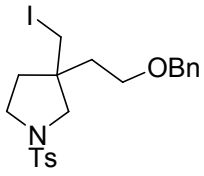




7d (31.8 mg, 35%)

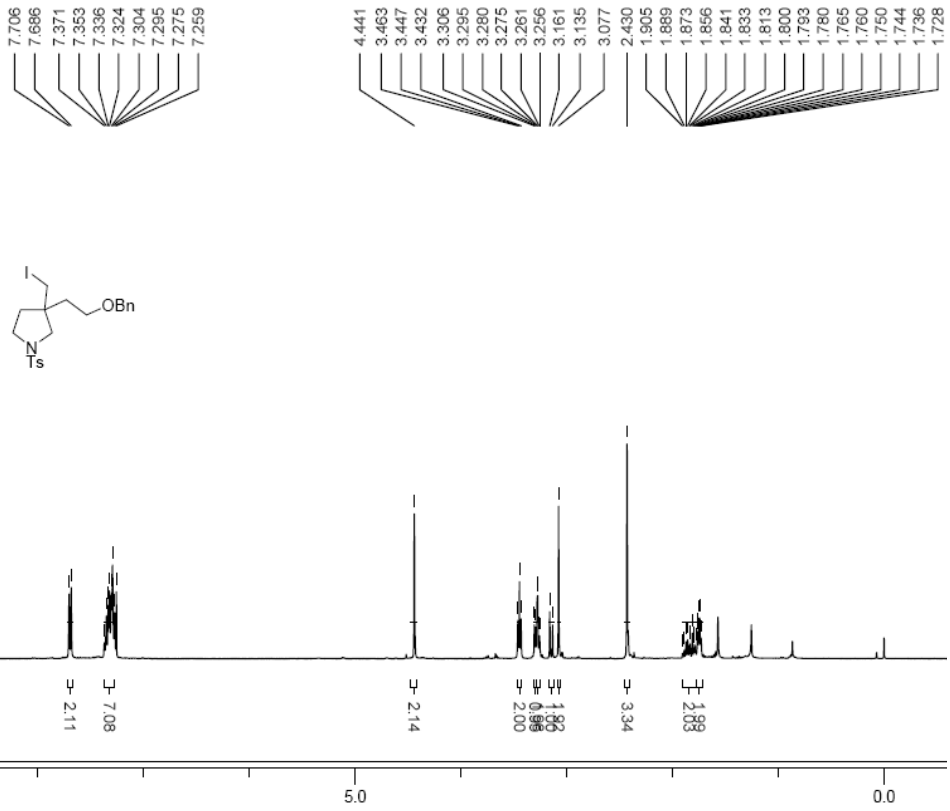
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75-1.77(m, 1H), 1.82-1.86 (m, 1H), 2.44 (s, 3H), 2.69 (d, J = 14.0 Hz, 1H), 2.77 (d, J = 14.0 Hz, 1H), 2.97 (s, 2H), 3.11 (d, J = 10.0 Hz, 1H), 3.28 (d, J = 10.0 Hz, 1H), 3.28-3.34 (m, 1H), 3.40-3.46 (m, 1H), 7.16-7.19 (m, 2H), 7.25-7.30 (m, 3H), 7.34 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 15.6, 21.6, 35.3, 41.3, 46.4, 46.7, 56.6, 127.0, 127.5, 128.5, 129.8, 133.7, 137.7, 143.7. HRMS Calcd for $C_{19}H_{22}INO_2S$ 455.0416, found 455.0418.

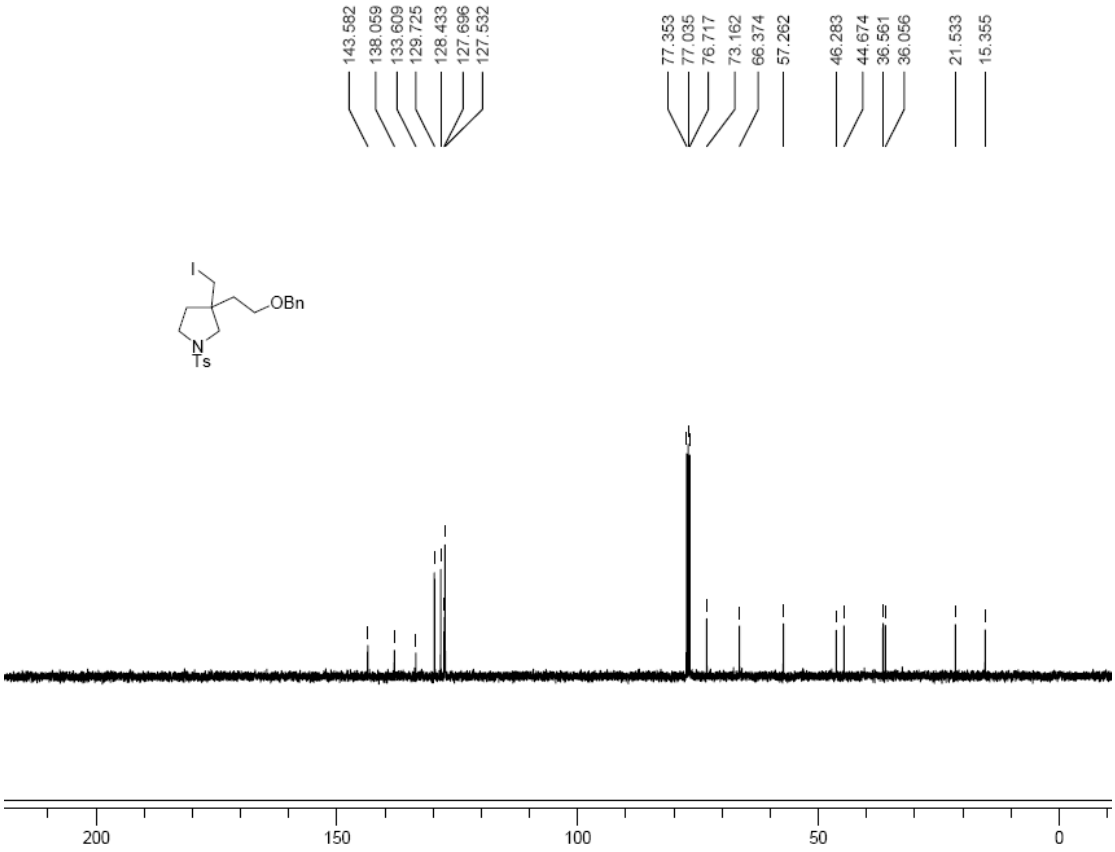


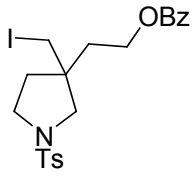


7e (71.8 mg, 72%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73-1.77 (m, 2H), 1.78-1.90 (m, 2H), 2.43 (s, 3H), 3.08 (s, 2H), 3.15 (d, *J* = 10.4 Hz, 1H), 3.27 (dd, *J* = 7.6 Hz, 2.0 Hz, 2H), 3.30 (d, *J* = 4.4 Hz, 1H), 3.45 (t, *J* = 6.0 Hz, 2H), 4.44 (s, 2H), 7.26-7.37 (m, 7H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 15.4, 21.5, 36.0, 36.6, 44.7, 46.3, 57.3, 66.4, 73.2, 127.5, 127.7, 128.4, 129.7, 133.6, 138.0, 143.6. HRMS Calcd for $C_{21}H_{26}INO_3S$ 499.0678, found 499.0676.

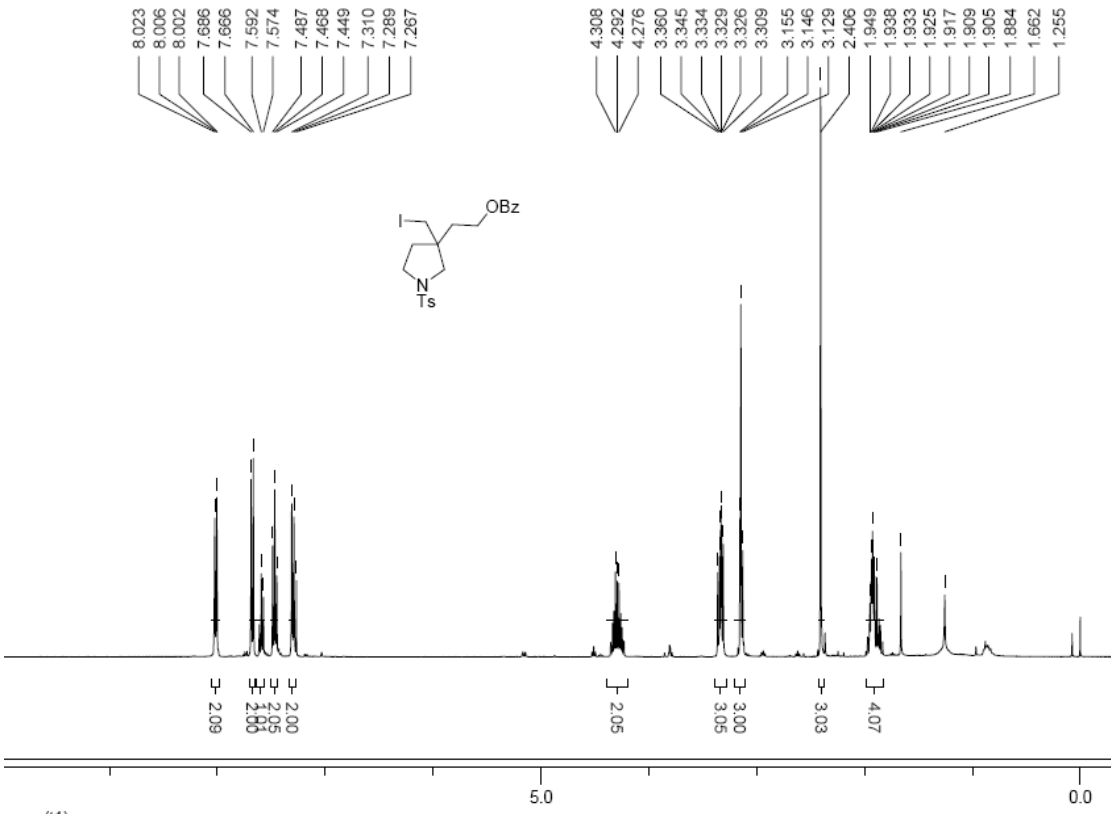


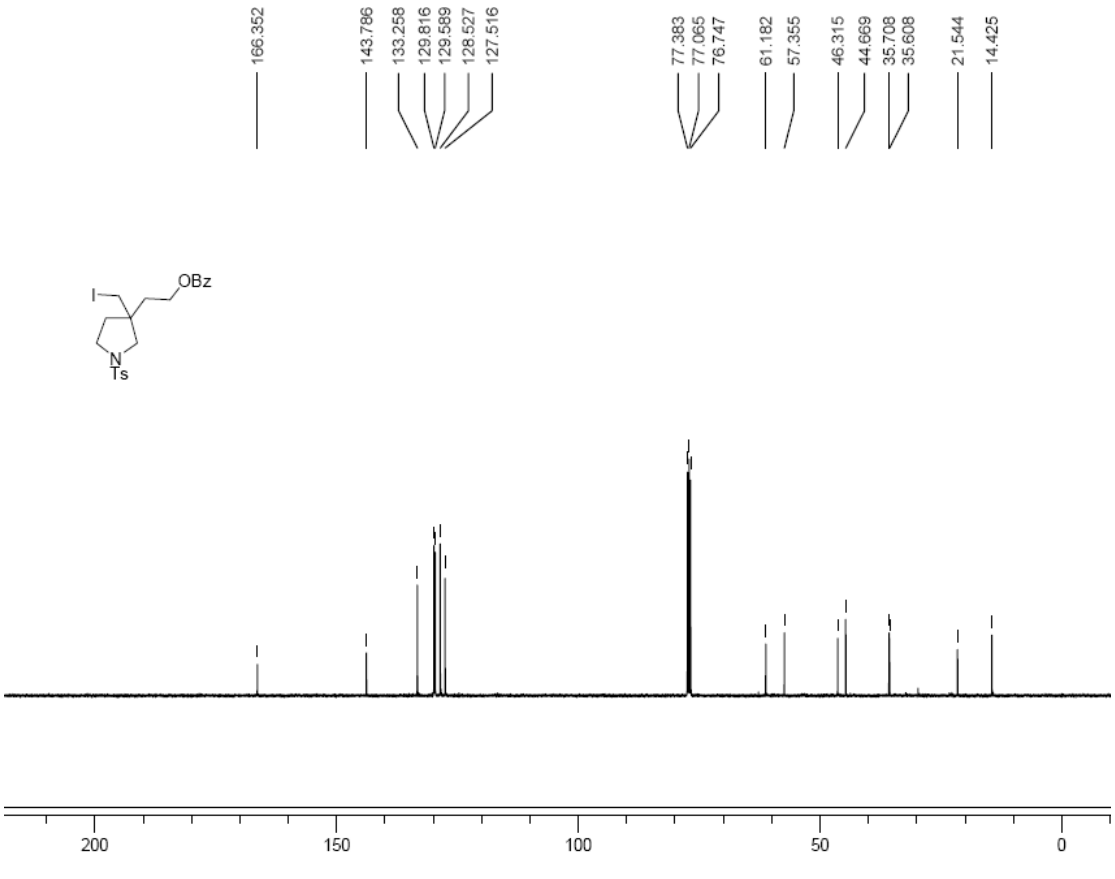


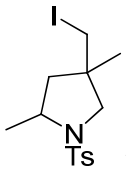


7f (59.5 mg, 58%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88-1.95 (m, 4H), 2.41 (s, 3H), 3.14 (d, J = 10.4 Hz, 2H), 3.15 (s, 2H), 3.31-3.33 (m, 2H), 3.35 (d, J = 6.0 Hz, 1H), 4.23-4.35 (m, 2H), 7.30 (d, 8.4 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 14.4, 21.5, 35.6, 35.7, 44.7, 46.3, 57.3, 61.2, 127.5, 128.5, 129.6, 129.8, 133.2, 143.8, 166.4. HRMS Calcd for $C_{21}H_{24}INO_4S$ 513.0471, found 513.0473.

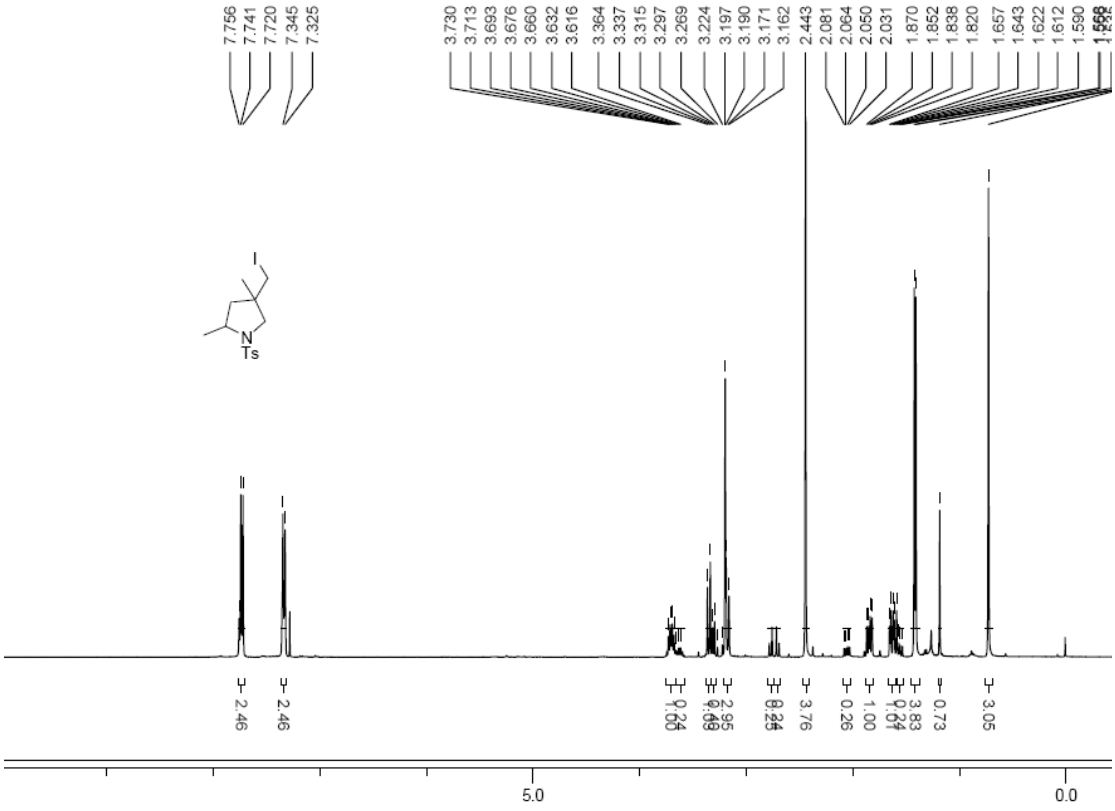


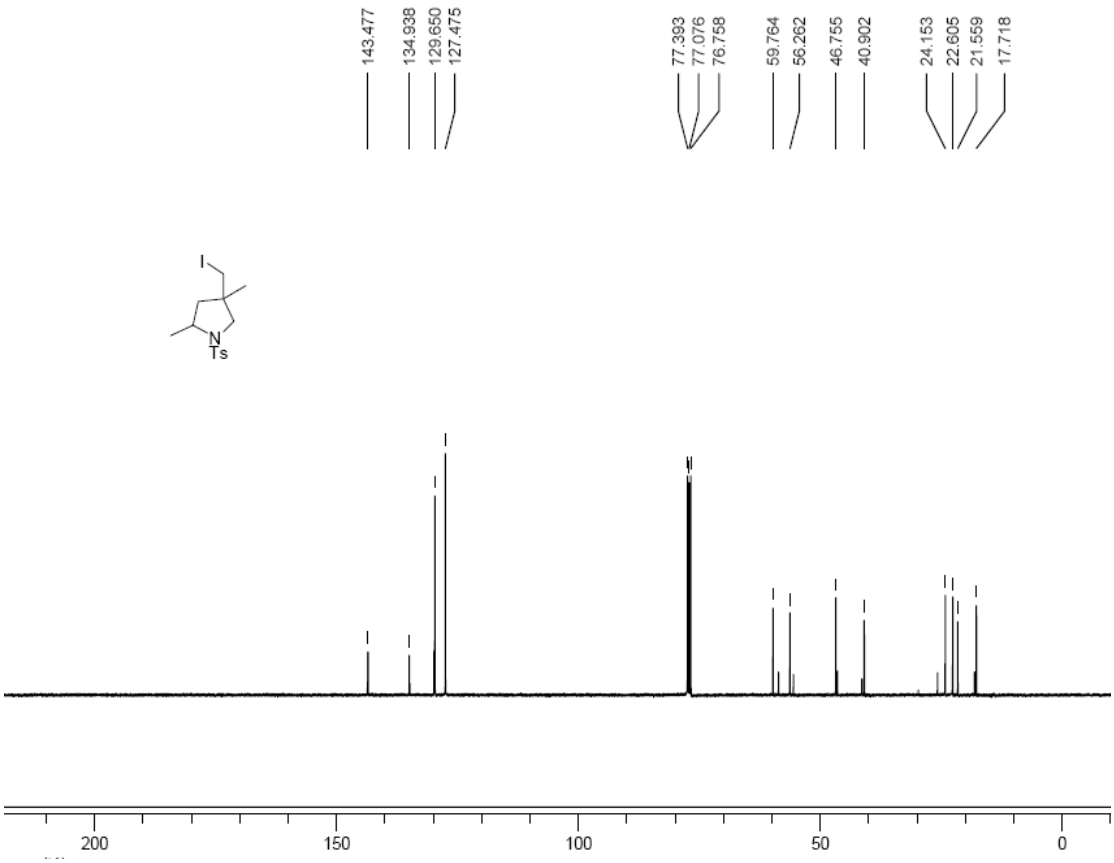


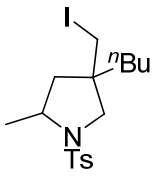


7g (63.7 mg, 81%)

Major product: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 3H), 1.59-1.66 (m, 1H), 1.82-1.87 (dd, *J* = 12.8 Hz, 7.2 Hz, 1H), 2.44 (s, 3H), 3.18 (d, *J* = 11.2 Hz, 1H), 3.20 (s, 2H), 3.35 (d, *J* = 10.8 Hz, 1H), 3.66-3.73 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 17.7, 21.6, 22.6, 24.2, 40.9, 46.8, 56.3, 59.8, 127.5, 129.65, 134.9, 143.5. HRMS Calcd for $C_{14}H_{20}INO_2S$ 393.0260, found 393.0256.

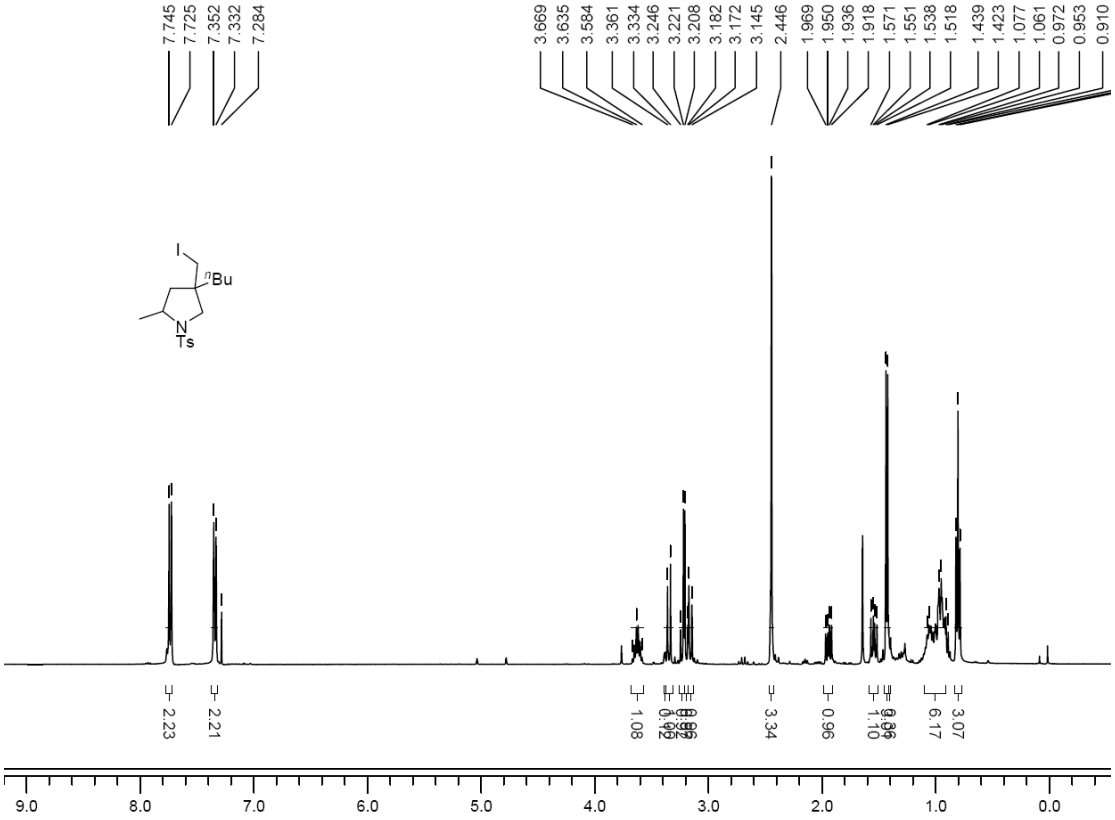


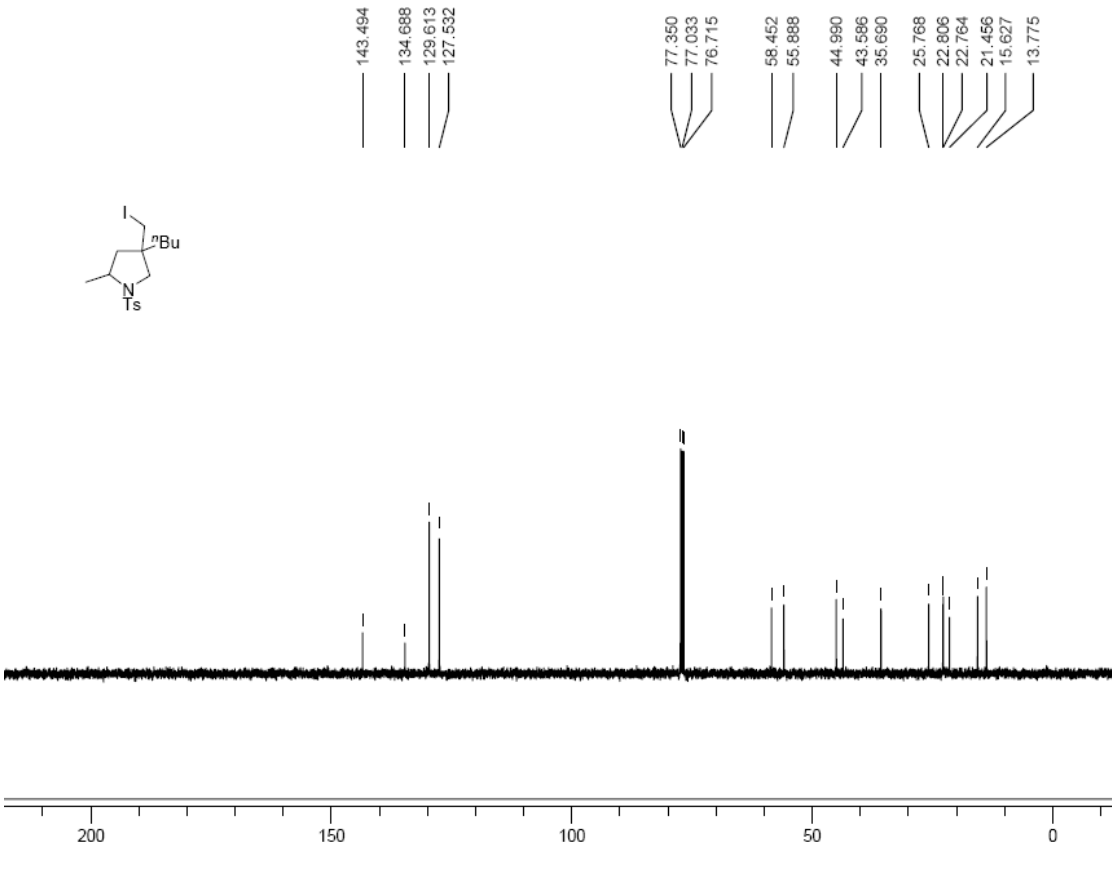


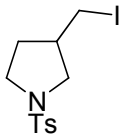


7h (66.1 mg, 76%)

Major product: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, *J* = 7.2 Hz, 3H), 0.89-1.08 (m, 6H), 1.43 (d, *J* = 6.4 Hz, 3H), 1.54 (dd, *J* = 8.0 Hz, 13.2 Hz, 1H), 1.94 (dd, *J* = 13.2 Hz, 7.6 Hz, 1H), 2.45 (s, 3H), 3.16 (d, *J* = 10.8 Hz, 1H), 3.20 (d, *J* = 10.4 Hz, 1H), 3.23 (d, *J* = 10.0 Hz, 1H), 3.35 (d, *J* = 10.8 Hz, 1H), 3.58-3.67 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 13.8, 15.6, 21.4, 22.8, 22.8, 25.8, 35.7, 43.6, 45.0, 55.9, 58.4, 127.5, 129.6, 134.7, 143.5. HRMS Calcd for $C_{17}H_{26}INO_2S$ 435.0729, found 435.0728.

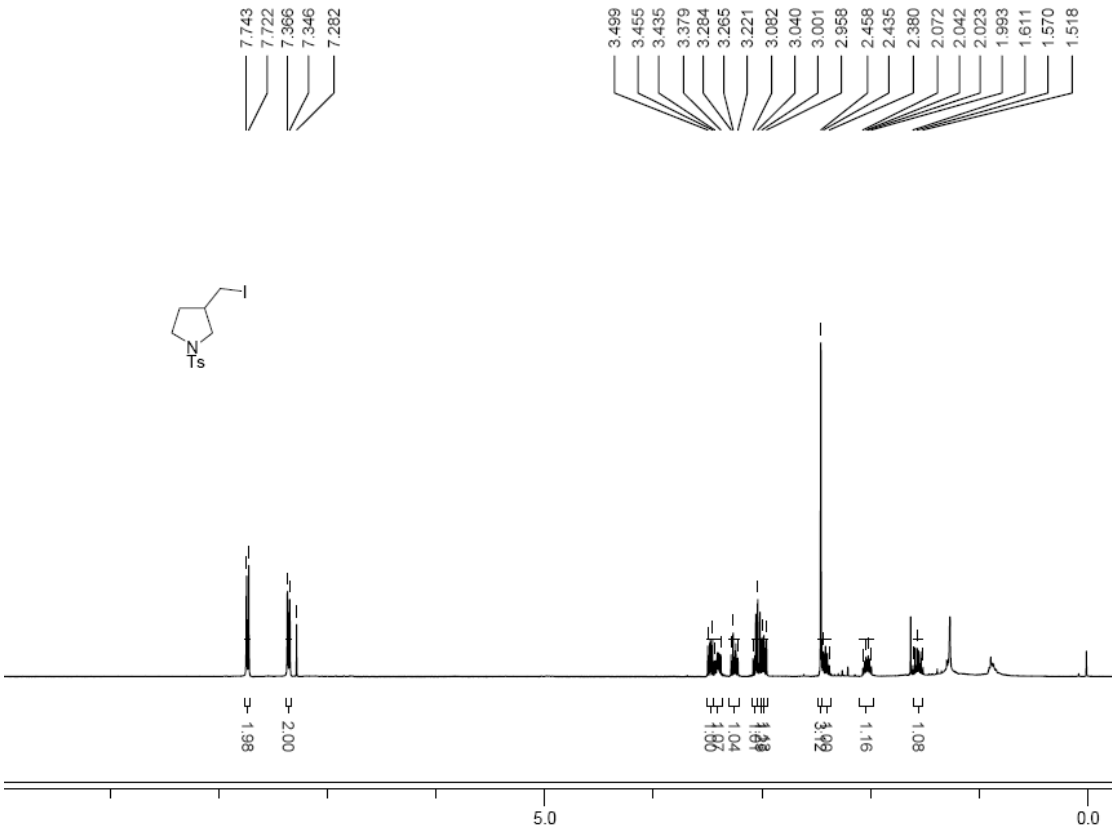


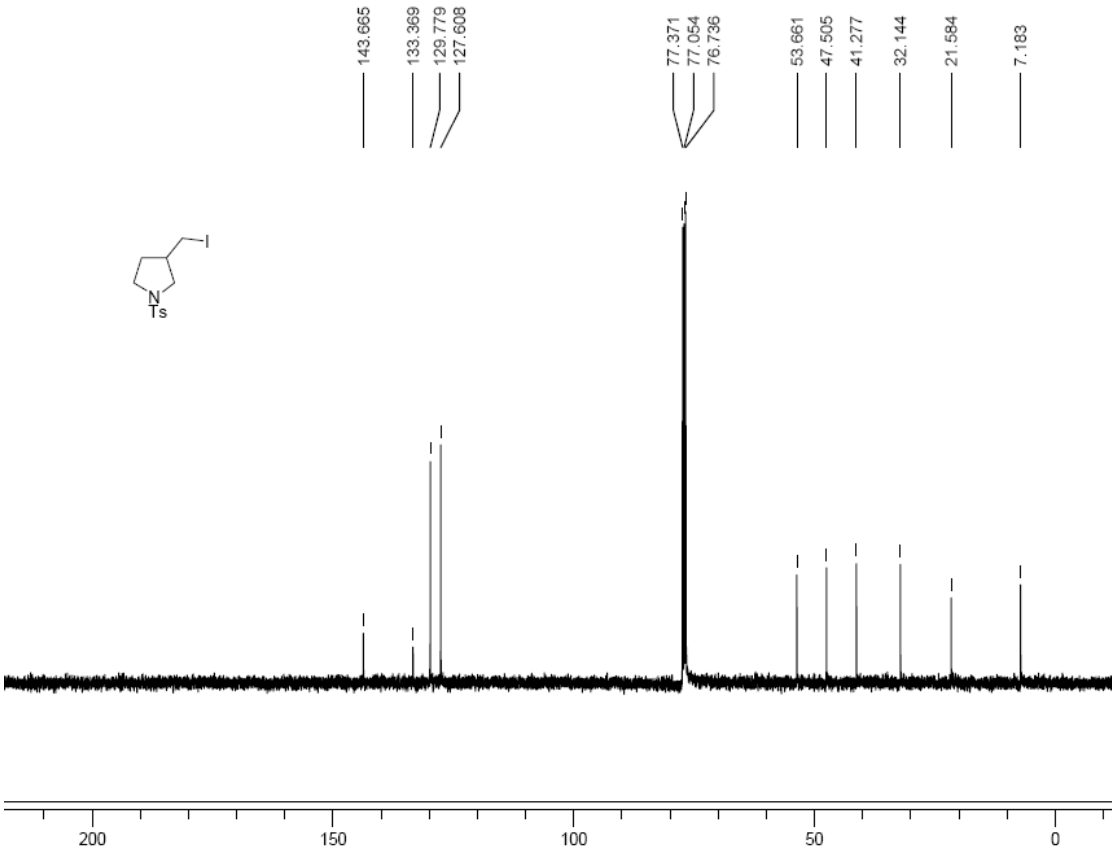


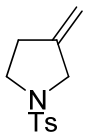


7k (49.6 mg, 68%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52-1.61 (m, 1H), 1.99-2.06 (m, 1H), 2.41 (dd, *J* = 14.4 Hz, 7.2 Hz, 1H), 2.46 (s, 3H), 2.98 (dd, *J* = 10.0 Hz, 7.2 Hz, 1H), 2.99-3.08 (m, 2H), 3.22-3.28 (m, 1H), 3.38-3.42 (m, 1H), 3.48 (dd, *J* = 10.4 Hz, 7.2 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 7.2, 21.6, 32.1, 41.3, 47.5, 53.7, 127.6, 129.8, 133.4, 143.7. HRMS Calcd for $C_{12}H_{16}INO_2S$ 364.9946, found 364.9949.

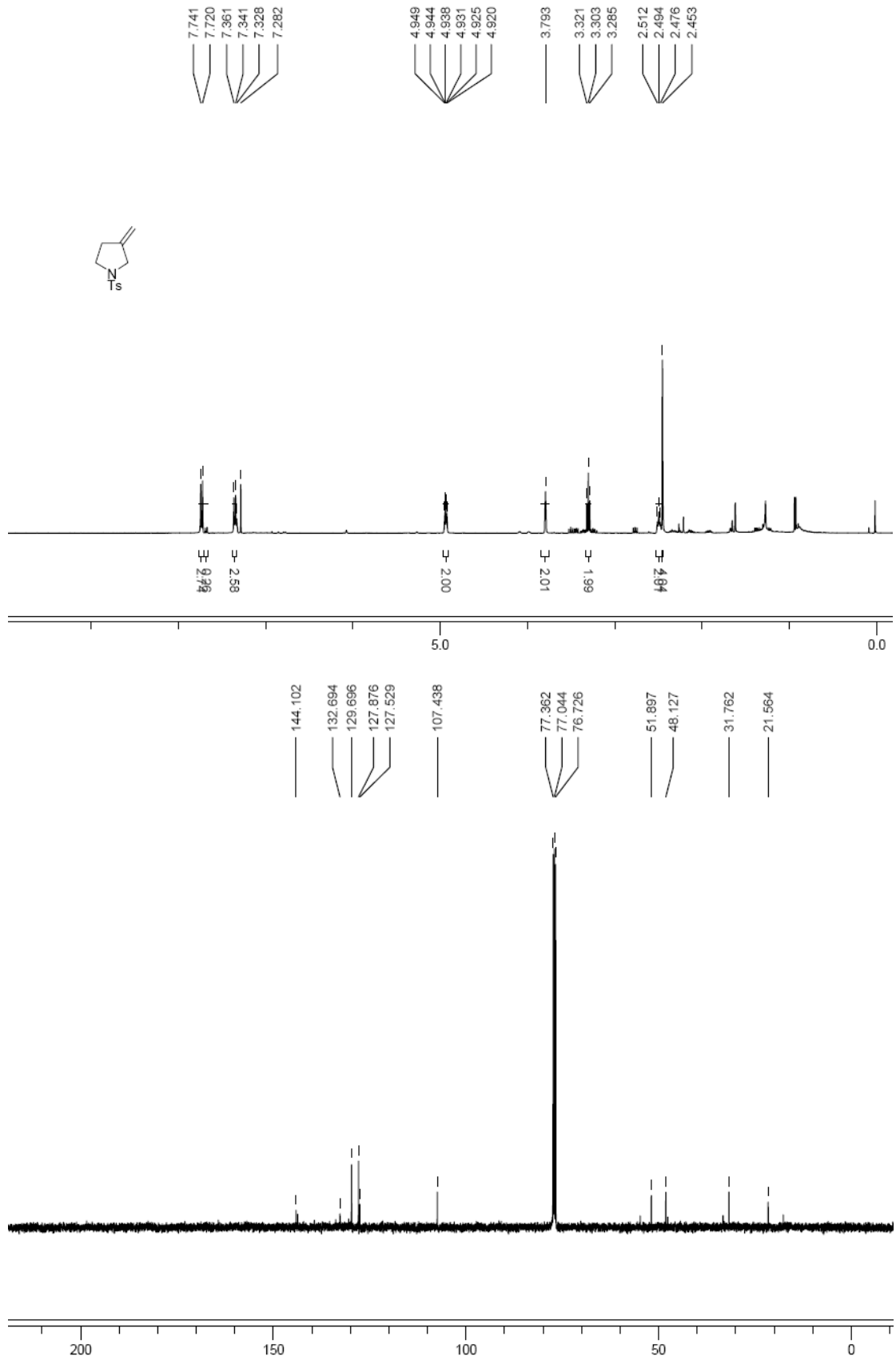




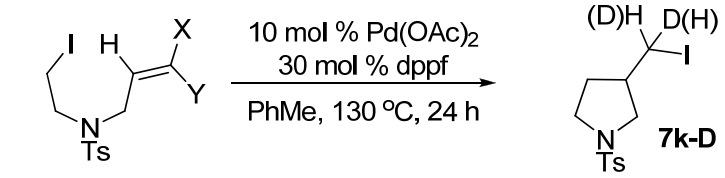


8 (4 mg, 8%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.49 (t, J = 7.2 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 3.79 (s, 2H), 4.92-4.95 (m, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 21.6, 31.8, 48.1, 51.9, 107.4, 127.5, 127.9, 129.7, 132.7, 144.1. HRMS Calcd for $C_{12}H_{15}NO_2S$ 237.0823, found 237.0820.



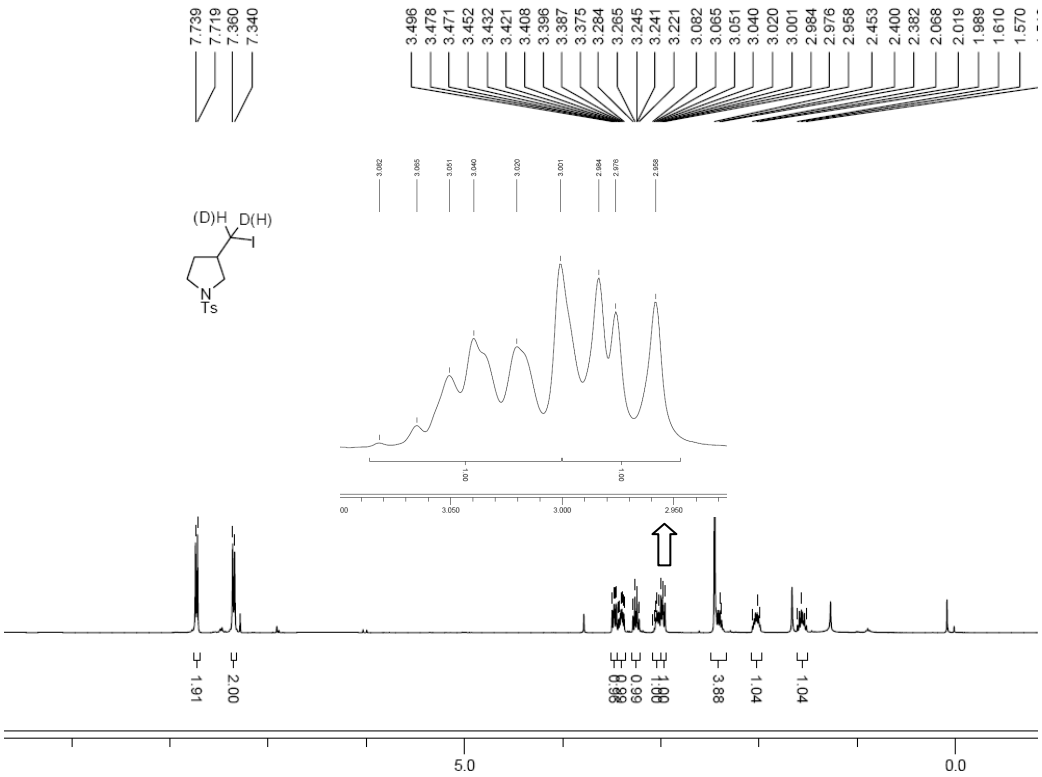
III. **Deuterium Labelling Experiments and date for 7k-D**



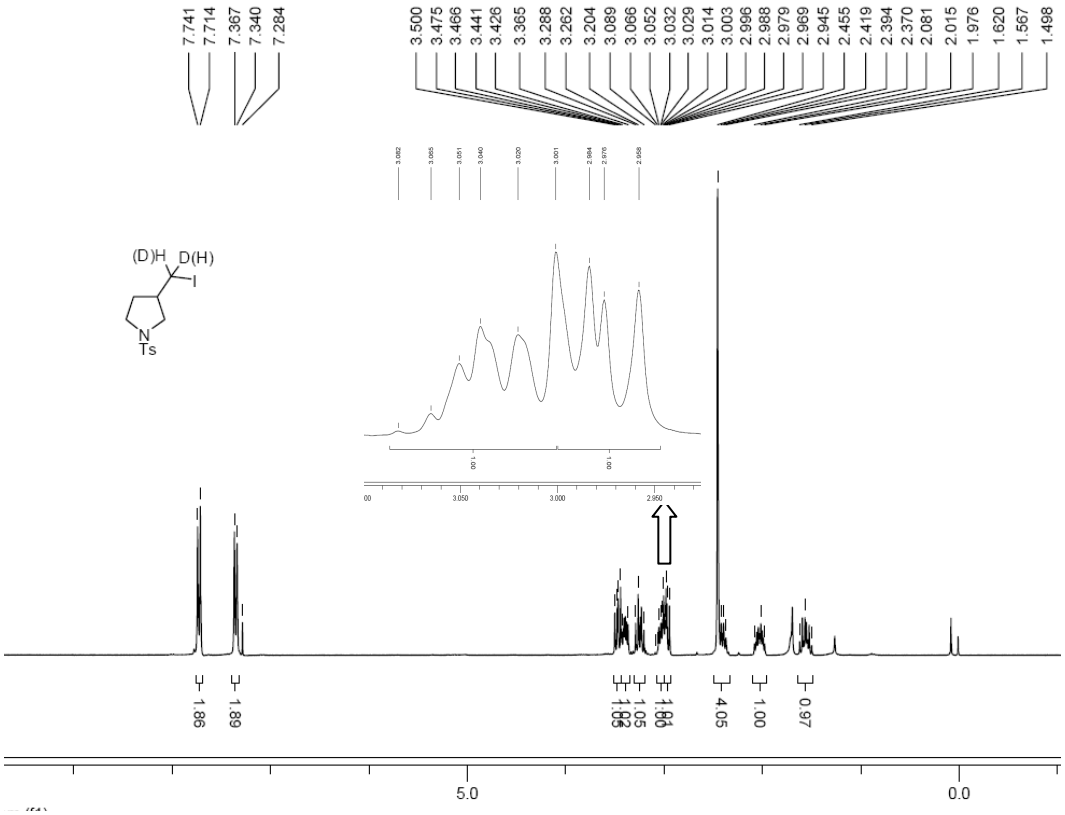
(*Z*)-1k-D: X = H, Y = D
(*E*)-1k-D: X = D, Y = H

from **(*Z*)-1k-D**: 56%
from **(*E*)-1k-D**: 52%

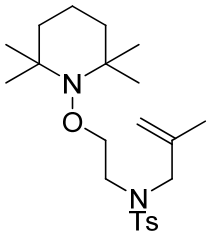
7k-D from (Z)-1k-D:



7k-D from (E)-1k-D:

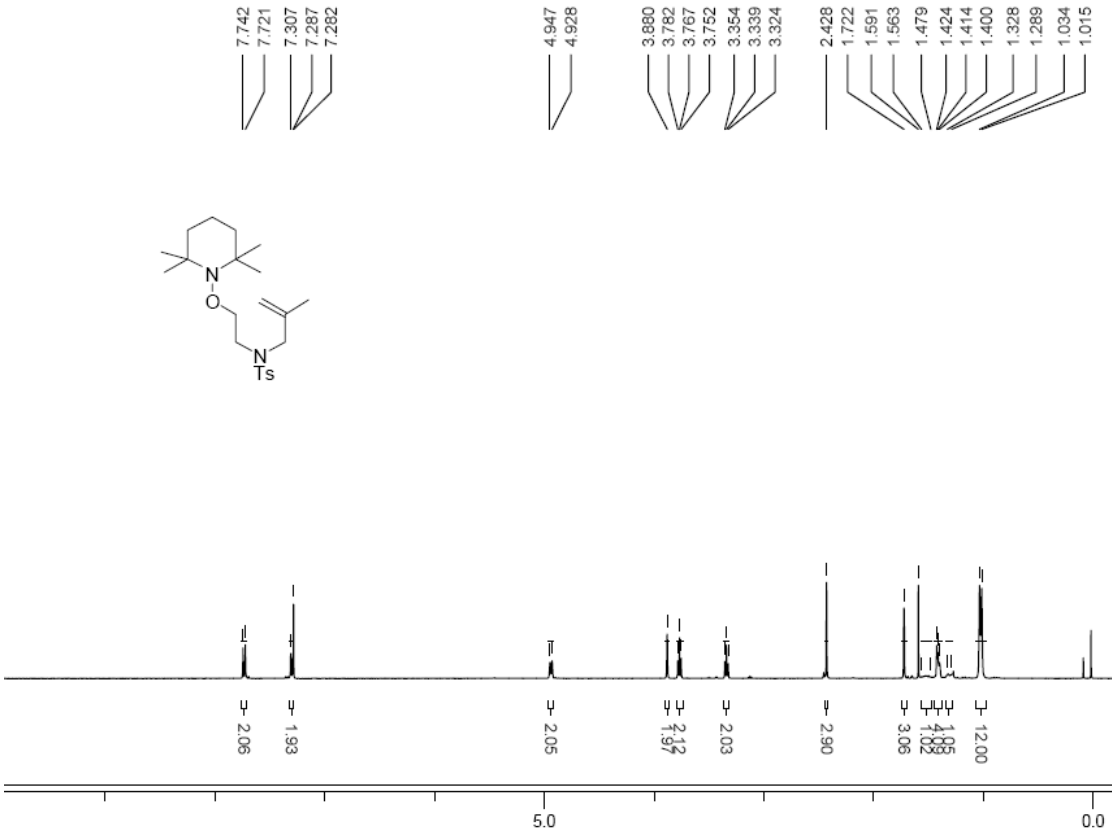


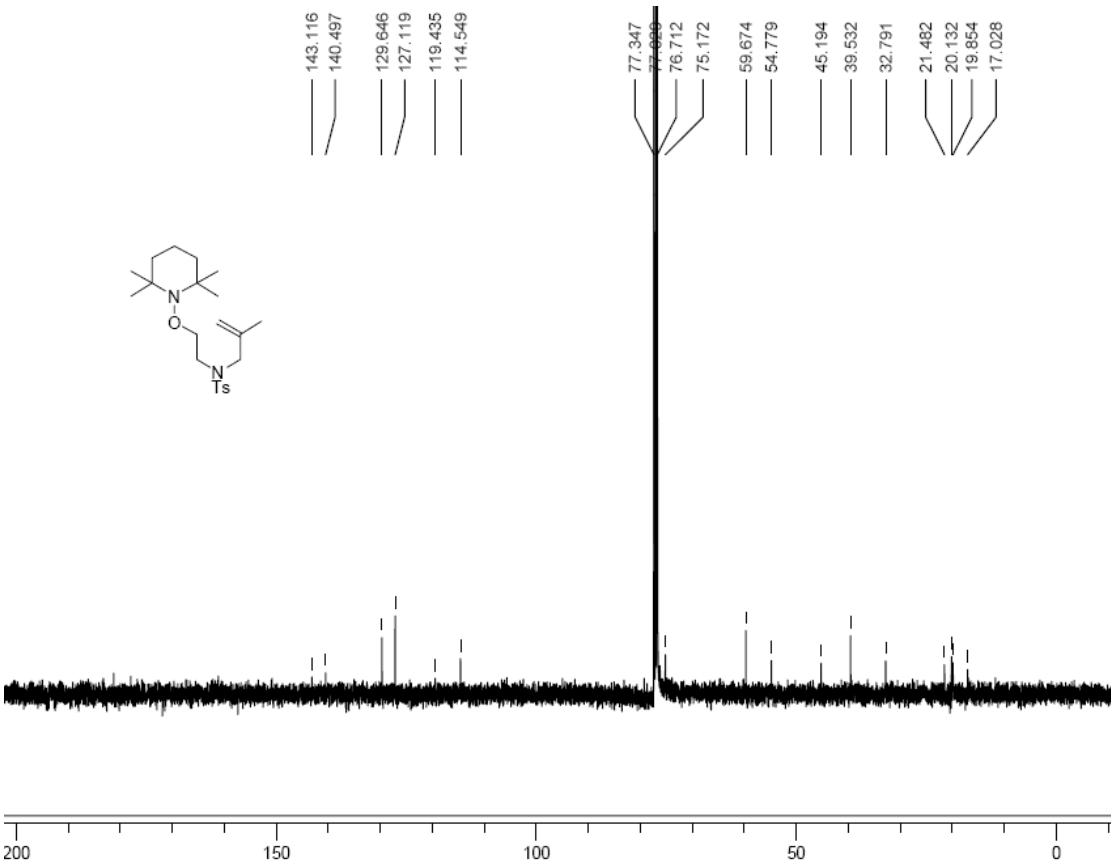
V. Tempo Testing Experiments

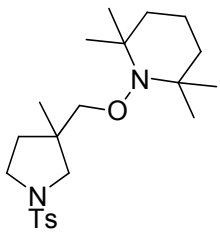


9a

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 6H), 1.03 (s, 6H), 1.27-1.55 (m, 6H), 1.72 (s, 3H), 2.43 (s, 3H), 3.34 (t, *J* = 6.0 Hz, 2H), 3.77 (t, *J* = 6.0 Hz, 2H), 3.88 (s, 2H), 4.93 (s, 1H), 4.95 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 17.0, 19.8, 20.1, 21.5, 32.8, 39.5, 45.2, 54.8, 59.7, 75.2, 114.5, 119.4, 127.1, 129.6, 140.5, 143.1. HRMS Calcd for $C_{22}H_{36}N_2O_3S$ 408.2447, found 408.2459.

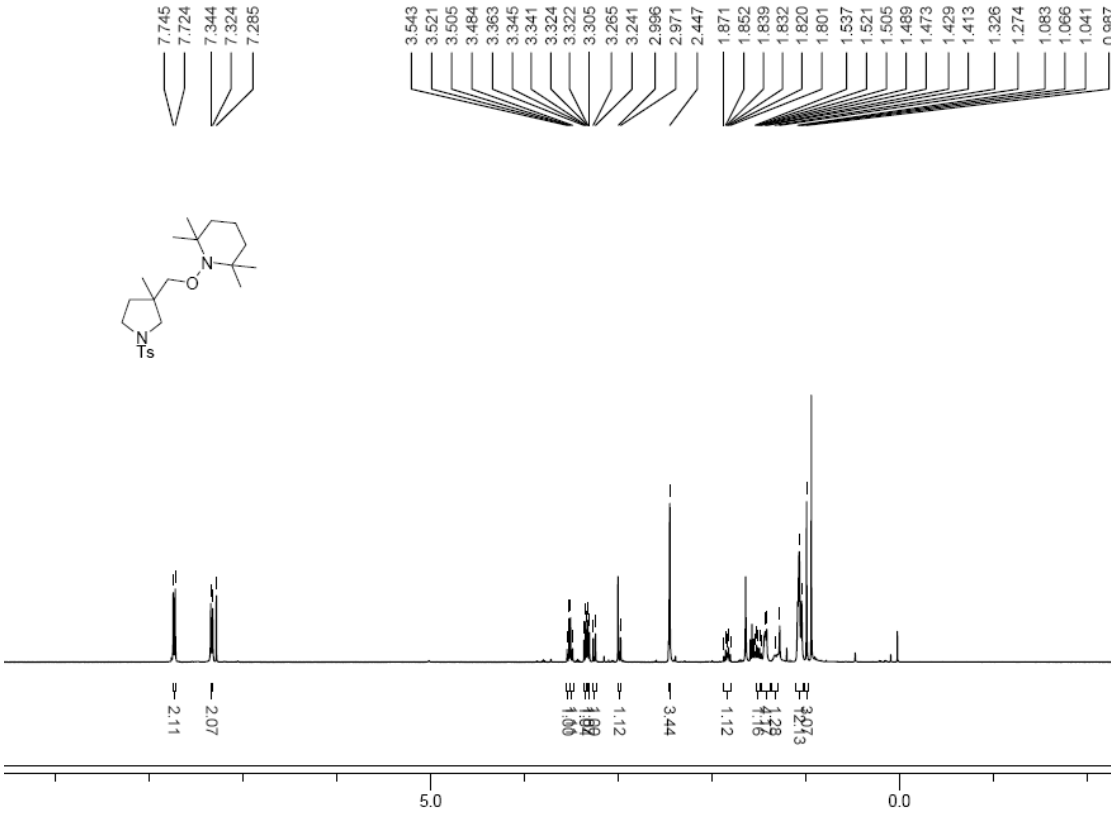


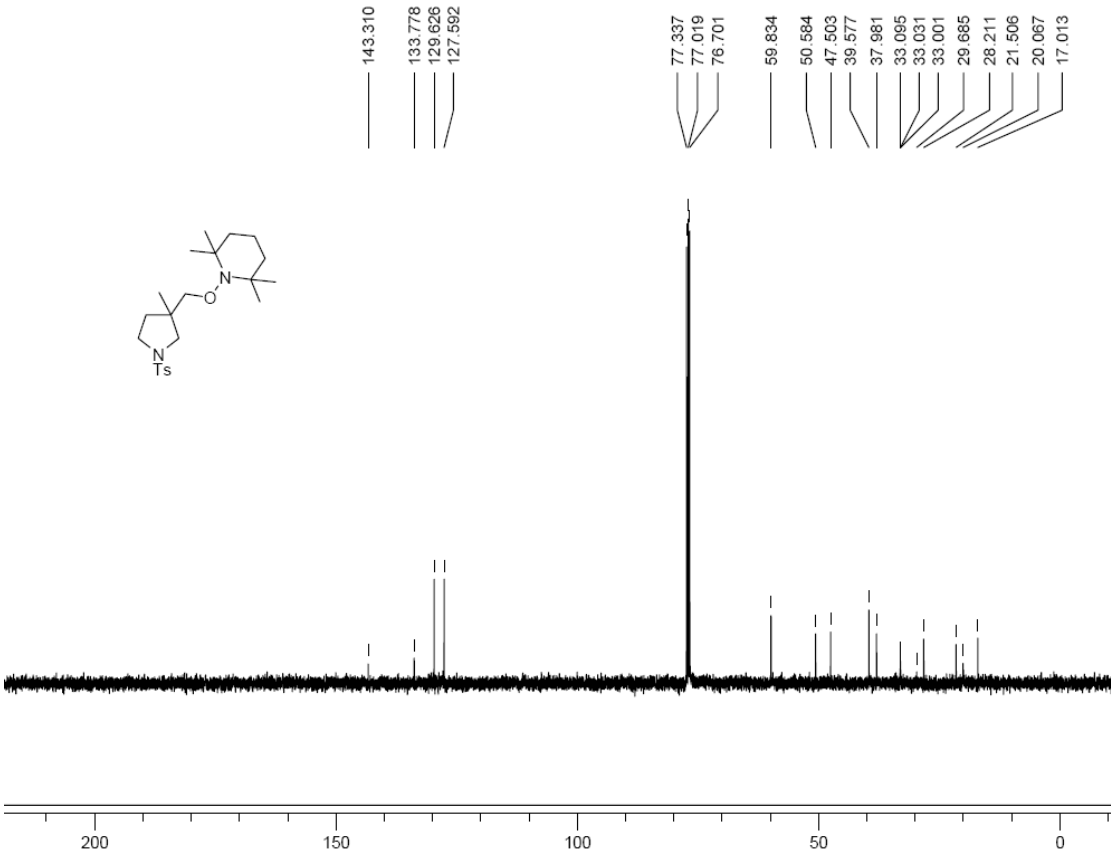




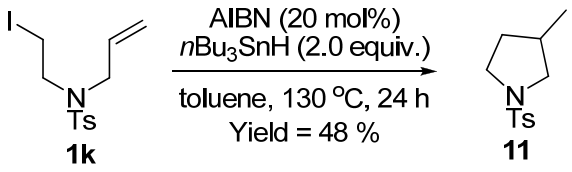
10a

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.04-1.08 (m, 12H), 1.27-1.33 (m, 1H), 1.41-1.47 (m, 4H), 1.47-1.54 (m, 1H), 1.80-1.87 (m, 1H), 2.45 (s, 3H), 2.98 (d, J = 10.0 Hz, 1H), 3.25 (d, J = 9.6 Hz, 1H), 3.30-3.36 (m, 2H), 3.49 (d, J = 8.4 Hz, 1H), 3.53 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): 17.0, 20.1, 21.5, 28.2, 29.7, 30.0, 30.03, 30.1, 38.0, 39.6, 47.5, 50.6, 59.8, 127.6, 129.6, 133.8, 143.3. HRMS Calcd for $C_{22}H_{36}N_2O_3S$ 408.2447, found 408.2459.





VI. AIBN and *n*Bu$_3$SnH Testing Experiments



In a 25 mL sealed tube, the air was exchanged for N_2 3 times. Then the mixture of **1k** (0.2 mmol, 73.4 mg), AIBN (0.04 mmol, 6.6 mg), and *n*-Bu$_3$SnH (0.4 mmol, 116.4 mg) in toluene (3 mL) was heated at 130°C for 24 hours. When the reaction was finished, the mixture was cooled to rt. and directly subjected to silica gel column chromatography (petroleum ether/EtOAc 50:1 to 20:1 gradient) to give the product **11**, 48% yield.

11: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 3.44–3.38 (m, 1H), 3.36–3.30 (m, 1H), 3.16–3.24 (m, 1H), 2.74 (t, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 2.09 (dq, *J* = 14.8, 6.8 Hz, 1H), 1.93–1.84 (m, 1H), 1.37-1.30 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): 17.6, 21.5, 33.1, 33.2, 47.6, 54.7, 127.4, 129.5, 133.9, 143.2.