Electronic Supplementary Material (ESI) for ChemComm.

Electronic Supplementary Information for

Nickel-Catalyzed Hydrocarboxylation of Ynamides with CO_2 and H_2O: Observation of Unexpected Regioselectivity

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Contents

General Information

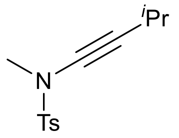
All reactions were performed under an atmosphere of argon or nitrogen (1 atm) unless otherwise stated. Solvents were purified under argon using The Ultimate Solvent System (Glass Counter Inc.) (THF, toluene, and DMF), and were distilled from CaH_2 (DMF). All other reagents were purified by standard procedures. Column chromatography was performed on silica gel 60 N (spherical, neutral, Kanto Chemical, Co. Inc., 45-50 μm) with the indicated solvent as an eluent. Analytical thin-layer chromatography was performed on Silica gel 60 $PF_{254\alpha}$ (Merck).

Infrared (IR) spectra were recorded on a JASCO FT/IR 4100 infrared spectrometer. ^1H NMR spectroscopy was recorded on JEOL ECA500 (500 MHz) or ECX400P (400 MHz) NMR spectrometer. Chemical shifts are reported in ppm from the solvent resonance as an internal standard ($CDCl_3$: $\delta = 7.26$ ppm). NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. ^{13}C NMR spectroscopy was recorded on JEOL ECA500 (125 MHz) or ECX400P (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the internal reference ($CDCl_3$: $\delta = 77.00$ ppm). Mass spectra were obtained on JEOL JMS-T100GCv mass spectrometer. Chiral HPLC analyses were carried out using a JASCO PU-980 and using indicated chiral column.

Preparation of Ynamides

Ynamides except for new ones **1c**, **1e**, **1m** and **1o** were prepared by previously reported methods[1-5].

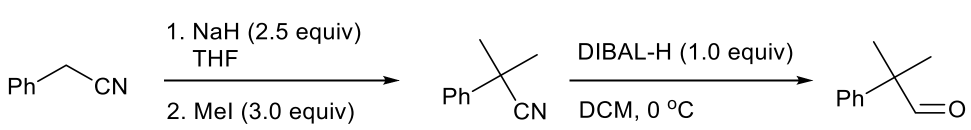
Ynamide 1c[2]



To a solution of $CuCl_2$ (135.4 mg; 1.0 mmol), N-methyltosylamide (4.66 g; 25.2 mmol), and Na_2CO_3 (1.07 g; 10.0 mmol) in toluene (45 mL) was added pyridine (0.81 mL; 10.0 mmol) at room temperature. The mixture was stirred under oxygen atmosphere and the temperature was raised to 70 °C. A solution of 3-methyl-1-butyne (0.52 mL; 5.0 mmol) in toluene (5 mL) was added slowly for over 4 hours at 70 °C, then the stirring was continued for 16 h at the same temperature. After cooled to room temperature, the reaction mixture was filtered through a pad of Celite and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **1c** (1.075 g, 85%) as white solid. <u>^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm):</u> 1.14 (d, *J* = 6.9 Hz, 6H), 2.46 (s, 3H), 2.58-2.64 (m, 1H), 3.00 (s, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H); <u>^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm):</u> δ 20.3, 21.6, 23.1, 39.4, 73.9, 74.5, 127.9, 129.5, 133.0, 144.4; <u>IR (film, $CHCl_3$):</u> 2246, 2053, 1364, 1168 cm^{-1}; <u>EI-HRMS</u> calcd for $C_{13}H_{17}NO_2S$ 251.09800, found 251.09775.

Ynamide 1e[1]

Step 1:



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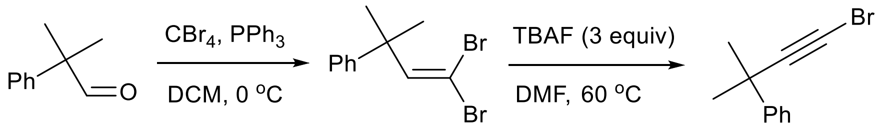
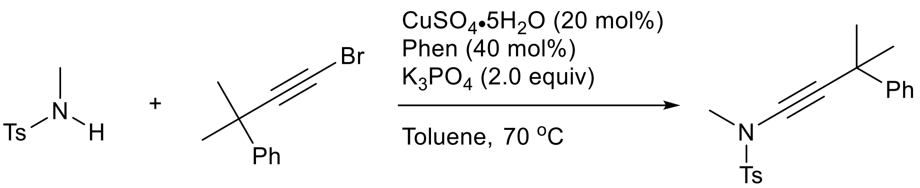


Step 3:



1e

[Step 1] 2-methyl-2-phenyl-propanenitrile was prepared according to the method reported by Miura *et al.*[6] To a mixture of sodium hydride (55 wt%, 1.60 g, 36.7 mmol) and THF (26 mL) was added benzyl cyanide (1.73 mL, 15.0 mmol) at 0 °C. The resulting solution was stirred for 1.5 h at room temperature. Iodomethane (2.8 mL, 45.0 mmol) was then added at 0 °C and the resulting solution was then stirred for an additional 16 h. The mixture was quenched with water, extracted with dichloromethane (DCM), dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give 2-methyl-2-phenylpropanenitrile in a quantitative yield.

To a solution of 2-methyl-2-phenylpropanenitrile (15.0 mmol) in DCM (60 mL) at 0°C was added DIBAL-H (1.03 M in hexane, 15.5 mL, 16.0 mmol). After stirring for 5 min, 1 M HCl was added. The phases were separated and the aqueous media was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude aldehyde was used in the next step without further purification.

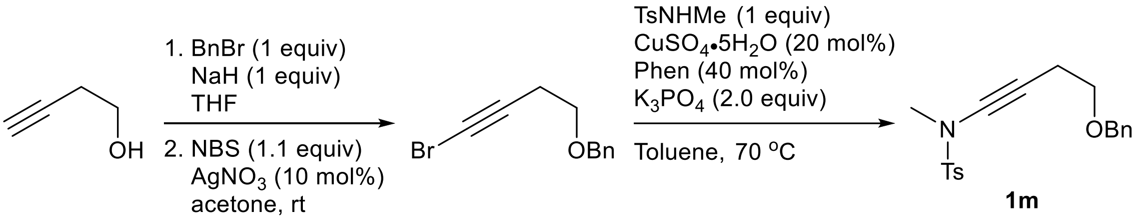
[Step 2] To a solution of Ph_3P (15.74 g, 60.01 mmol) in DCM (75 mL) at 0 °C was added CBr_4 (9.95 g, 30.00 mmol) and the solution was stirred for 30 min. A solution of 2-methyl-2-phenylpropanal from previous step in DCM (3 mL) was added and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was then quenched by addition of saturated $NaHCO_3$. The layers were separated and the aqueous phase was extracted with DCM. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated. Hexane was then added to the residue and the precipitated was filtered off *via* filtration through a plug of silica gel (washed with hexane/Et_2O mixtures). The dibromoolefin (1.43 g, 31% yield) was used in the next step without further purification.[7]

To a solution of dibromoolefin in DMF (24 mL) was added TBAF hydrate (3.68 g, 14.07 mmol). The temperature was raised to 60 °C and the mixture was stirred for 2 h. After diluted with

Et_2O, the mixture was washed with water several times, dried over anhydrous Na_2SO_4, and concentrated. The crude product was used in the next step without further purification.[8]

[Step 3] To a solution of (4-bromo-2-methylbut-3-yn-2-yl)benzene in toluene (24 mL) was added $CuSO_4{\cdot}5H_2O$ (0.23 g, 0.92 mmol), 1,10-phenanthroline (0.34 g, 1.89 mmol), K_3PO_4 (1.99 g, 9.38 mmol) and N-methyl-tosylamide (0.87 g, 4.70 mmol). The mixture was stirred for 11 h at 70 °C. After cooled to room temperature, the mixture was filtered through a pad of Celite, washed with Et_2O, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 8/1) to give ynamide **1e** as a white to pale yellow solid (544.8 mg, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.57 (s, 6H), 2.47 (s, 3H), 3.08 (s, 3H), 7.24 (tt, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.30-7.50 (m, 6H), 7.79 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 21.6, 31.7, 35.8, 39.4, 75.0, 76.9, 125.5, 126.3, 127.9, 128.2, 129.6, 133.0, 144.5, 146.9.

Ynamide 1m[1]

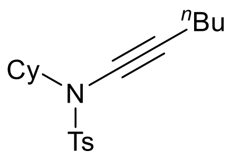


To a mixture of NaH (55 wt%, 219.6 mg, 5.0 mmol) and THF (10 mL) was added but-3-yn-1-ol dropwise at 0 °C and stirred for 20 minutes. Benzyl bromide solution in THF was added at the same temperature, and the resulting solution was stirred at room temperature for 13 h. The mixture was diluted with AcOEt, poured into water, extracted with AcOEt, dried over anhydrous Na_2SO_4, and concentrated. The crude product was then purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give benzyl-protected product (748.0 mg, 93% yield).

To a solution of benzyl-protected product (736.2 mg, 4.595 mmol) in acetone (9 mL) was added NBS (0.90 g, 5.06 mmol) and $AgNO_3$ (78.0 mg, 0.46 mmol). The mixture was stirred at room temperature for 1.5 h, and then concentrated in vacuo. The mixture was then diluted with Et_2O, filtered by a pad of Celite, and concentrated. The crude product was then purified by flash column chromatography on silica gel using hexane to give bromoalkyne product (775.6 mg, 71%).

To a solution of bromoalkyne product (761.6 mg, 3.19 mmol) in toluene (16 mL) were added 1,10-phenanthroline (229.6 mg, 1.27 mmol), $CuSO_4{\cdot}5H_2O$ (159.0 mg, 0.64 mmol), K_3PO_4 (1.35 g, 6.36 mmol) and N-methyltosylamide (590.0 mg, 3.19 mmol) at room temperature. The mixture was stirred and the temperature was raised to 70 °C. After 70 h, the mixture was cooled to room temperature, filtered through a pad of Celite and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **1m** (901.2 mg, 82%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm): 2.42 (s, 3H), 2.57 (t, *J* = 6.8 Hz, 2H), 3.01 (s, 3H), 3.57 (t, *J* = 7.0 Hz, 2H), 4.54 (s, 2H), 7.27-7.38 (m, 7H), 7.77 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 19.7, 21.5, 39.1, 65.4, 68.6, 72.8, 75.6, 127.5, 127.6, 127.7, 128.3, 129.6, 133.0, 138.0, 144.4; IR (film, $CHCl_3$): 2257, 2058, 1363, 1172 cm^{-1}; EI-HRMS calcd for $C_{12}H_{14}NO$ 188.10754, found 188.10737.

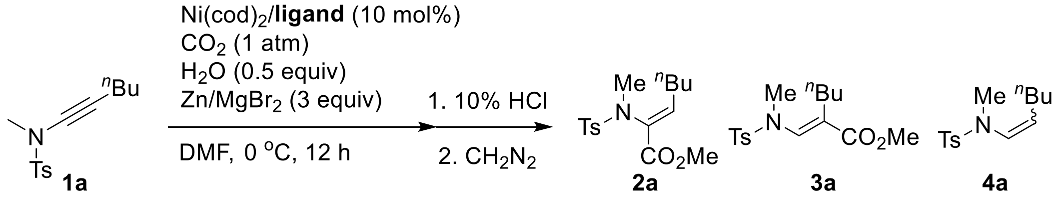
Ynamide1o[1]



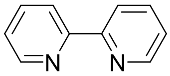
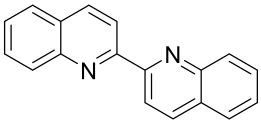
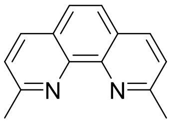
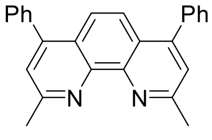
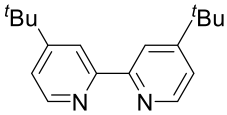
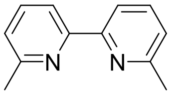
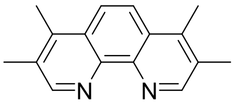
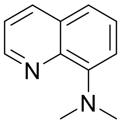
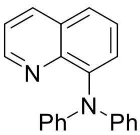
To a solution of1-bromohex-1-yne (0.703 g, 4.365 mmol) in toluene (22 mL) were added 1,10-phenanthroline (314.6 mg, 1.746 mmol), $CuSO_4{\cdot}5H_2O$ (217.9 mg, 0.87 mmol), K_3PO_4 (1.85 g, 8.72 mmol) and N-cyclohexyl-4-methylbenzenesulfonamide (1.11 g, 4.37 mmol) at room temperature. The mixture was stirred and the temperature was raised to 110 °C. After 23 h, the mixture was cooled to room temperature, filtered with a pad of Celite and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **1o** (400.9 mg, 28%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 0.89 (t, *J* = 7.2 Hz, 3H), 0.96-1.75 (m, 14H), 2.28 (t, *J* = 7.2, 2H), 2.43 (s, 3H), 3.72 (tt, *J* = 11.7, 4.1 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 13.5, 18.2, 21.6, 21.8, 24.9, 25.4, 30.9, 31.1, 58.9, 70.4, 71.6, 127.3, 129.5, 136.4, 143.9; IR (neat): 2246, 2044, 1363, 1169 cm^{-1}; EI-HRMS calcd for $C_{19}H_{27}NO_2S$ 333.17625, found 333.17609.

Full List of Ligand Screening

Table S1. Ligand screening[a]



1a **2a** **3a** **4a**

entry	ligand	yield[b] (%)		
		2a	**3a**	**4a**
1		67	9	11
2		trace	ND	16
3		37	8	10
4		11	7	63
5		37	9	32
6		4	3	5
7		2	4	55
8		trace	trace	4
9		51	5	22
10		-	-	complex mix.

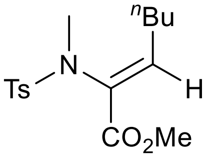
[a] Reaction conditions: **1a** (0.4 mmol), Ni(cod)$_2$ (10 mol%), ligand (10 mol%), Zn (3 equiv), MgBr$_2$ (3 equiv), H$_2$O (0.5 equiv), DMF (5.7 ml), CO$_2$ (balloon), 0 °C, 12 h. [b] NMR yield.

Nickel-Catalyzed Hydrocarboxylation of Ynamides

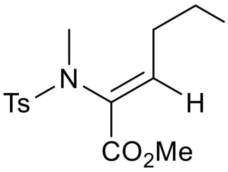
General procedure: Ni(cod)$_2$ (11.0 mg, 0.040mmol), 2,2′-bipyridine (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.20 mmol), and MgBr$_2$ (221.0 mg, 1.20 mmol) were weighed into a flame-dried round bottom flask in a glove box (argon or nitrogen atmosphere). Then, the flask was taken out of the glove box, and DMF (2.8 mL) was added at 0 °C to the flask. To the resulting suspension was added a solution of ynamide **1a** (106.2 mg, 0.40 mmol) and water (3.6 μL, 0.20 mmol) in DMF (2.9 mL) at the same temperature via cannulation. After removal of argon/nitrogen gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO$_2$ gas using a balloon. The reaction mixture was stirred at 0 °C for 12 hours. To the mixture was added 10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layer was washed with water, dried over Na$_2$SO$_4$, and concentrated. The residue was treated with diazomethane, which was generated by treatment of 1-methyl-3-nitro-1-nitrosoguanidine with 40% aqueous KOH, in Et$_2$O at 0 °C. After the mixture had been concentrated, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give a mixture of carboxylated product, **2a** and **3a** (105.0 mg, 78% yield (83/17)). The regioisomer mixture was then separated by second flash column chromatography on silica gel (toluene/hexane/ether = 10/1/1) to give **2a** as colorless oil.

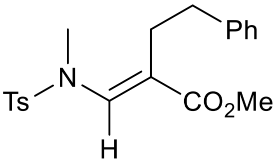
Caution! Diazomethane is highly toxic and explosive. The operation must be done in a working fume hood with an adequate shield.

Spectral data for **3a**, **3f**, **3f′**, **3g**, **3h**, **3k**, **3l**, **3s**, and **3t** have already been reported in our previous report.[5]

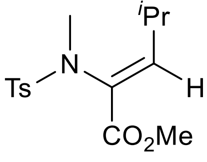


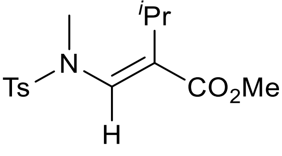
Compound 2a. ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.91 (t, *J* = 7.2 Hz, 3H), 1.34 (td, *J* = 14.7, 7.3 Hz, 2H), 1.42-1.48 (m, 2H), 2.38 (q, *J* = 8.2 Hz, 2H), 2.42 (s, 3H), 3.00 (s, 3H), 3.52 (s, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.8, 21.5, 22.6, 28.6, 30.2, 37.0, 51.8, 127.7, 129.2, 130.3, 136.3, 143.2, 149.7, 164.4; IR (film, neat): 1725 cm^{-1}; EI-HRMS calcd for $C_{16}H_{23}NO_4S$ 325.13478, found 325.13404.



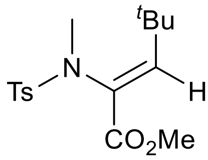


Compound 2b and 3b. Following the general procedure using **1b** (123.8 mg, 0.395 mmol), Ni(cod)$_2$ (21.7 mg, 0.079 mmol), bpy (12.4 mg, 0.079 mmol), Zn (77.5 mg, 1.19 mmol), MgBr$_2$ (218.2 mg, 1.19 mmol), and water (3.6 μL, 0.2 mmol) in DMF (5.6 mL) to afford a regioisomeric mixture of **2b** and **3b** (106.7 mg, 72% yield (79/21)) as colorless oil. Second flash column chromatography on silica gel (toluene/hexane/ether = 5/1/1) was performed to give **2b** as colorless oil. Characterization of **2b**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 2.41 (s, 3H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.77-2.85 (m, 5H), 3.49 (s, 3H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.16-7.32 (m, 7H), 7.68 (d, *J* = 8.6 Hz, 2H) ; ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 21.5, 30.6, 34.0, 36.8, 51.80, 51.79, 126.2, 127.7, 128.4, 129.2, 130.7, 136.1, 140.7, 143.2, 148.2, 164.2; IR (film, CHCl$_3$): 1724 cm^{-1}; ESI-HRMS calcd for $C_{20}H_{23}NO_4NaS$ 396.12400, found 396.12363. Characterization of **3b**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 2.44 (s, 3H), 2.68 (s, 4H), 2.96 (s, 3H), 3.77 (s, 3H), 7.11-7.25 (m, 5H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.60 (s, 1H), 7.68 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 21.6, 28.4, 35.6, 35.8, 52.0, 118.6, 126.1, 127.3, 128.37, 128.41, 130.0, 134.3, 137.8, 141.2, 144.5, 168.4; IR (neat): 1708 cm^{-1}; EI-HRMS calcd for $C_{20}H_{23}NO_4S$ 373.13478, found 373.13403.

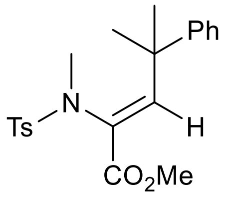




Compound 2c and 3c. Following the general procedure using **1c** (99.6 mg, 0.40 mmol), Ni(cod)$_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr$_2$ (221.0 mg, 1.20 mmol) and water (3.6 μL, 0.2 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **2c**and **3c** (92.3 mg, 75% yield (95/5)). Second flash column chromatography on silica gel (toluene/hexane/ether = 10/2/1) was performed to give **2c** and **3c** as colorless oil. Characterization of **2c**: ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.05 (d, *J* = 5.7 Hz, 6H), 2.40 (s, 3H), 2.93 - 2.98 (m, 1H), 2.99 (s, 3H), 3.48 (s, 3H), 6.84 (d, *J* = 10.9 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 21.4, 28.1, 37.3, 51.7, 125.3, 127.7, 128.2, 129.1, 136.2, 143.2, 155.3, 164.5; IR (film, $CHCl_3$): 1725 cm^{-1}; EI-HRMS calcd for $C_{15}H_{21}NO_4S$ 311.11913, found 311.11869. Characterization of **3c**: ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.17 (d, *J* = 6.9 Hz, 6H), 2.43 (s, 3H), 2.96 (s, 3H), 3.03-3.09 (m, 1H), 3.72 (s, 3H), 6.97 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 20.6, 21.5, 27.1, 37.7, 51.4, 127.5, 129.9, 132.9, 133.8, 136.5, 144.2, 167.1; IR (neat): 1714 cm^{-1}; EI-HRMS calcd for $C_{15}H_{21}NO_4S$ 311.11913, found 311.11880.

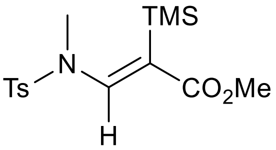


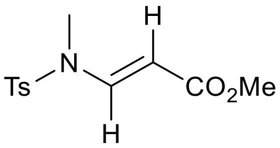
Compound 2d. Following the general procedure using **1d** (105.9 mg, 0.3991 mmol), Ni(cod)$_2$ (11.0 mg, 0.0400 mmol), bpy (6.3 mg, 0.0403 mmol), Zn (78.5 mg, 1.2007 mmol), $MgBr_2$ (221.0 mg, 1.2004 mmol) and water (3.6 µL, 0.1998 mmol) in DMF (5.7 mL) to afford **2d** as white solid (109.4 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.27 (s, 9H), 2.40 (s, 3H), 3.00 (s, 3H), 3.33 (s, 3H), 6.94 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 21.4, 29.1, 34.7, 38.2, 51.6, 127.2, 127.8, 129.0, 135.8, 143.0, 156.5, 165.2; IR (film, $CHCl_3$): 1724 cm^{-1}; EI-HRMS calcd for $C_{16}H_{23}NO_4S$ 325.13478, found 325.13420.



Compound 2e. Following the general procedure using **1e** (130.2 mg, 0.398mmol), Ni(cod)$_2$ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040mmol), Zn (78.5 mg, 1.201mmol), $MgBr_2$ (221.0 mg, 1.200mmol) and water (3.6 µL, 0.200mmol) in DMF (5.7 mL) to afford **2e** as colorless oil (97.4 mg, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.71 (d, *J* = 14.9, 6H), 2.42 (s, 3H), 2.80 (s, 3H), 3.38 (s, 3H), 7.18 (s, 1H), 7.22-7.25 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.32-7.41 (m, 4H), 7.64 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 21.5, 37.5, 41.6, 51.7, 77.2, 126.1, 126.4, 128.0, 128.2, 128.4, 129.0, 135.7, 143.1, 147.5, 155.0, 165.1; IR (film, $CHCl_3$): 1723 cm^{-1}; EI-HRMS calcd for

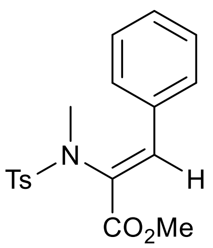
$C_{14}H_{18}NO_2$ 232.13375, found 232.13365.





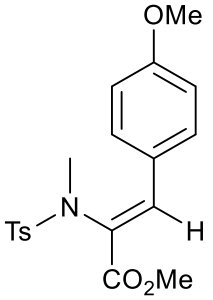
Compound 3f and 3f′. Following the general procedure using **1f** (112.0 mg, 0.398 mmol), Ni(cod)$_2$ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr$_2$ (221.0 mg, 1.200 mmol) and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford **3f** and **3f′** in 21% ^{1}H NMR yield (48/52).

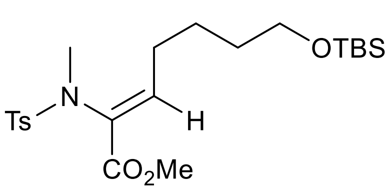
Compound 2g. Following the general procedure using **1g** (114.3 mg, 0.401 mmol), Ni(cod)$_2$ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr$_2$ (221.0 mg, 1.200 mmol) and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **2g** and **3g** (44.3 mg, 32% yield (94/6)). Second flash column chromatography on silica gel (toluene/hexane/ether = 10/2/1) was performed to give **2g** as white solid.

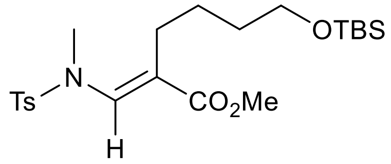


Characterization of **2g**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 2.42 (s, 3H), 3.09 (s, 3H), 3.59 (s, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.35-7.41 (m, 3H), 7.67-7.71 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 21.5, 36.4, 52.1, 127.9, 128.1, 128.8, 129.2, 130.7, 130.8, 132.4, 136.2, 141.6, 143.4, 165.5; IR (film, CHCl$_3$): 1719 cm^{-1}; EI-HRMS calcd for $C_{18}H_{19}NO_4S$ 345.10348, found 345.10369.

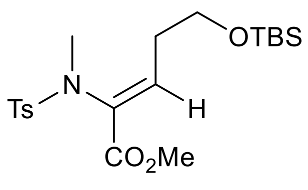
Compound 2h. Following the general procedure using **1h** (126.9 mg, 0.402 mmol), Ni(cod)$_2$ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr$_2$ (221.0 mg, 1.200 mmol), and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **2h** and **3h** (43% yield (95/5)). Characterization of **2h**: ^{1}H NMR (400 MHz, CDCl$_3$, δ/ppm): 2.43 (s, 3H), 3.10 (s, 3H), 3.53 (s, 3H), 3.85 (s, 3H), 6.91 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 7.7 Hz, 2H), 7.67 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$, δ/ppm): 21.5, 36.4, 51.9, 55.4, 114.3, 125.1, 125.5, 127.9, 129.2, 133.0, 136.3, 141.6, 143.3, 161.7, 165.7; IR (film, CHCl$_3$): 1716, 1259, 1175 cm^{-1}; EI-HRMS calcd for $C_{19}H_{21}NO_5S$ 375.11404, found 375.11405.







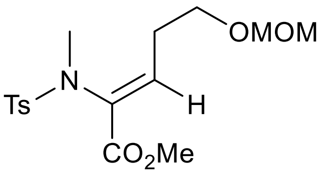
Compound 2j and 3j. Following the general procedure using **1j** (155.0 mg, 0.392 mmol) Ni(cod)$_2$ (22.0 mg, 0.080 mmol), bpy (12.6 mg, 0.081 mmol), Zn (78.5 mg, 1.201 mmol), MgBr$_2$ (221.0 mg, 1.200 mmol), and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **2j** and **3j** (143.5 mg, 80% yield (84/16)). Second flash column chromatography on silica gel (toluene/hexane/ether = 10/2/1) was performed to give **2j** and **3j** as colorless oil. Characterization of **2j**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.04 (s, 6H), 0.88 (s, 9H), 1.47-1.57 (m, 4H), 2.36-2.43 (m, 5H), 2.99 (s, 3H), 3.50 (s, 3H), 3.60 (t, *J* = 5.7 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): −5.4, 18.3, 21.5, 24.4, 25.9, 28.6, 32.5, 37.0, 51.8, 62.6, 127.7, 129.2, 130.3,, 136.2, 143.2, 149.4, 164.3; IR (film, neat): 1726 cm^{-1}; EI-HRMS calcd for $C_{21}H_{34}NO_5SSi$ 440.19269, found 440.19156. Characterization of **3j**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.01 (s, 6H), 0.86 (s, 9H), 1.35-1.43 (m, 2H), 1.44-1.51 (m, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 3.11 (s, 3H), 3.55 (t, J = 6.3 Hz, 2H), 3.74 (s, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): −5.3, 18.3, 21.6, 25.8, 25.9, 26.3, 32.7, 35.7, 51.9, 62.6, 119.2, 127.3, 130.0, 134.3,, 137.3, 144.4, 168.6; IR (film, CHCl$_3$): 1709, 1629 cm^{-1}; EI-HRMS calcd for $C_{21}H_{34}NO_5SSi$ 440.19269, found 440.19224.



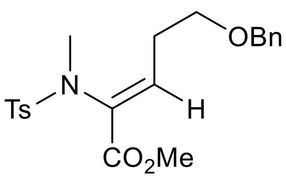
Compound 2k. Following the general procedure using **1k** (151.1 mg, 0.41 mmol), Ni(cod)$_2$ (22.6 mg, 0.082 mmol), bpy (12.8 mg, 0.082 mmol), Zn (80.6 mg, 1.23 mmol), MgBr$_2$ (227.1 mg, 1.23 mmol), and water (3.7 μL, 0.20 mmol) in DMF (5.7 mL) to afford a crude product which was then purified by flash column chromatography on silica gel (hexane/AcOEt = 15/1) to afford regioisomeric mixture of **2k** and **3k** (128.8 mg, 73% yield (81/19)). Second flash column chromatography on silica gel (toluene/hexane/ether = 5/1/1) was performed to give **2k** as colorless oil. Characterization of **2k**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.04 (s, 6H), 0.87 (s, 9H), 2.40 (s, 3H), 2.59 (q, *J* = 6.3 Hz, 2H), 2.99 (s, 3H), 3.49 (s, 3H), 3.74 (t, *J* = 6.0 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$,

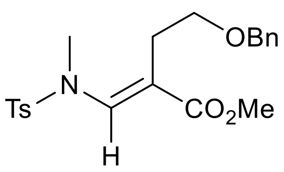
δ/ppm): −5.4, 18.2, 21.5, 25.8, 32.5, 37.0, 51.8, 61.1, 127.7, 129.2, 131.3, 136.1, 143.2, 146.7, 164.1; IR (film, $CHCl_3$): 1727 cm^{-1}; EI-HRMS calcd for $C_{19}H_{30}NO_5SSi$ 412.16139, found 412.16076.

Compound 2l. Following the general procedure using **1l** (112.0 mg, 0.38 mmol), $Ni(cod)_2$ (20.7 mg, 0.075 mmol), bpy (11.8 mg, 0.076 mmol), Zn (73.9 mg, 1.13 mmol), $MgBr_2$ (208.0 mg, 1.13 mmol), and water (3.4 μL, 0.19 mmol) in DMF (5.4 mL) to afford a regioisomeric mixture of **2l** and **3l** (95.4 mg, 71% yield). Second flash column chromatography on silica gel (toluene/hexane/AcOEt = 10/2/1) was performed to give **2l** as colorless oil. Characterization of **2l**: ^1H NMR (500 MHz, $CDCl_3$, δ/ppm): 2.40 (s, 3H), 2.68 (q, *J* = 6.3 Hz, 2H), 3.00 (s, 3H), 3.34 (s, 3H), 3.49 (s, 3H), 3.65 (t, *J* = 6.3 Hz, 2H), 4.60 (s, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 21.5, 29.5, 36.9, 51.8, 55.2, 65.4, 96.3, 127.7, 129.2, 131.5, 136.0, 143.3, 146.2, 164.0; IR (film, $CHCl_3$): 1725 cm^{-1}; EI-HRMS calcd for $C_{15}H_{20}NO_5S$ 326.10622, found 326.10587.

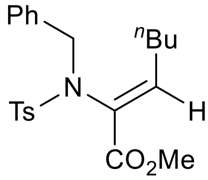


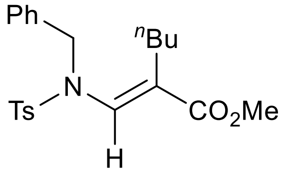
Compound 2m and 3m. Following the general procedure using **1m** (138.9 mg, 0.404 mmol), $Ni(cod)_2$ (11.0 mg, 0.040mmol), bpy (6.3 mg, 0.040mmol), Zn (78.5 mg, 1.201mmol), $MgBr_2$ (221.0 mg, 1.200mmol), and water (3.6 μL, 0.200mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **2m** and **3m** (79.0 mg, 48% yield (75/25)). Characterization of **2m**: ^1H NMR (500 MHz, $CDCl_3$, δ/ppm): 2.42 (s, 3H), 2.72 (q, *J* = 6.1 Hz, 2H), 3.00 (s, 3H), 3.52 (s, 3H), 3.62 (t, *J* = 6.3 Hz, 2H), 4.52 (s, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.27-7.36 (m, 7H), 7.69 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 21.5, 29.6, 37.0, 51.9, 68.0, 72.9, 127.3, 127.6, 127.7, 128.4, 129.3, 131.5, 136.1, 138.1, 143.3, 146.4, 164.1; IR (film, $CHCl_3$): 1725, 1347, 1163; EI-HRMS calcd for $C_{14}H_{18}NO_3$ 248.12867, found 248.12920. Characterization of **3m**: ^1H NMR (500 MHz, $CDCl_3$, δ/ppm): 2.43 (s, 3H), 2.72 (t, *J* = 6.6 Hz, 2H), 3.21 (s, 3H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.73 (s, 3H), 4.42 (s, 2H), 7.21-7.33 (m, 7H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 21.6, 26.6, 35.5, 51.9,



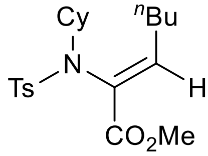


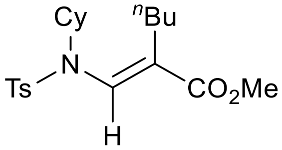
68.9, 72.9, 112.5, 127.3, 127.4, 127.5, 128.3, 130.0, 134.4, 138.3, 138.8, 144.4, 168.6; IR (film, $CHCl_3$): 1707, 1357, 1164 cm^{-1}; EI-HRMS calcd for $C_{14}H_{18}NO_3$ 248.12867, found 248.12914.





Compound 2n and 3n. Following the general procedure using **1n** (135.4 mg, 0.40 mmol), Ni(cod)$_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), $MgBr_2$ (221.0 mg, 1.20 mmol) and water (3.6 µL, 0.2 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **2n** and **3n** as white solid (121.0 mg, 76% yield (91/9)). Second flash column chromatography on silica gel (toluene/hexane = 5/1) was performed to separate **2n** and **3n**. Characterization of **2n**: ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 0.60-1.15 (m, 7H), 1.89-2.22 (br, 2H), 2.44 (s, 3H), 3.48 (s, 3H), 4.03-4.20 (br, 1H), 4.84-4.99 (br, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 7.25-7.27 (m, 5H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 13.7, 21.5, 22.5, 29.2, 29.9, 51.7, 52.8, 126.3, 127.7, 127.9, 128.3, 129.3, 129.7, 135.6, 137.0, 143.2, 152.7, 164.2; IR (film, $CHCl_3$): 1722 cm^{-1}; ESI-HRMS calcd for $C_{22}H_{27}O_4NNaS$ 424.15530, found 424.15518; X-ray data: *M* = 402.53, colorless, block, triclinic, P-1 (#2), a = 9.3258(3) Å, b = 9.3714(3) Å, c = 12.7379(3) Å, α = 104.226(7)°, β = 99.435(7)°, γ = 96.838(7)°, V = 1049.62(7) Å^3, Z = 2, D_{calc} = 1.274 g/cm^3, T = −140 °C, $R_1(wR_2)$ = 0.0448 (0.1117). Characterization of **3n**: ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 0.74 (t, *J* = 7.4 Hz, 3H), 0.93-1.01 (m, 2H), 1.04-1.13 (m, 2H), 2.19 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 3.71 (s, 3H), 4.47 (s, 2H), 7.07 (s, 1H), 7.19-7.30 (m, 5H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 13.8, 21.6, 22.7, 26.5, 31.2, 51.9, 53.2, 127.4, 127.7, 127.8, 128.6, 128.8, 129.9, 135.1, 135.2, 135.6, 144.2, 168.0; IR (film, $CHCl_3$): 1713 cm^{-1}; ESI-HRMS calcd for $C_{22}H_{27}O_4NNaS$ 424.15530, found 424.15564.

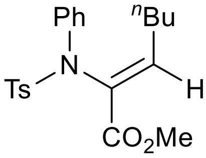




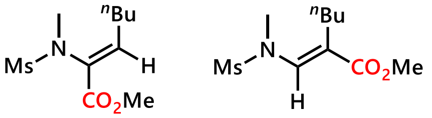
Compound 2o and 3o. Following the general procedure using **1o** (132.9 mg, 0.40 mmol), Ni(cod)$_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), $MgBr_2$ (221.0 mg, 1.20 mmol) and water (3.6 µL, 0.2 mmol) in DMF

(5.7 mL) to afford regioisomeric mixture of **2o** and **3o** (132.7 mg, 85% yield). Second flash column chromatography on silica gel (toluene/hexane = 5/1) was performed to give **2o** as colorless oil. Characterization of **2o**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.88-1.65 (m, 15H), 1.72 (d, *J* = 12.6 Hz, 1H), 1.98 (d, *J* = 12.0 Hz, 1H), 2.29-2.47 (m, 5H), 3.61-3.68 (m, 4H), 7.22-7.29 (m, 3H), 7.84 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.8, 21.5, 22.6, 25.0, 25.8, 26.1, 29.6, 30.2, 30.7, 32.3, 51.9, 60.1, 125.8, 128.0, 129.0, 138.2, 142.9, 152.2, 166.5; IR (film, CHCl$_3$): 1727 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{31}NO_4NaS$ 416.18660, found 416.18587. Characterization of **3o**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.86-1.73 (m, 17H), 2.41-2.47 (m, 5H), 3.75-3.82 (m, 4H), 6.62 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.9, 21.5, 23.2, 25.1, 25.8, 27.5, 30.2, 30.8, 51.9, 60.2, 127.2, 129.7, 131.3, 137.4, 141.1, 143.5, 167.6; IR (film, CHCl$_3$): 1720 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{31}NO_4NaS$ 416.18660, found 416.18601.

Compound 2q. Following the general procedure using **1q** (130.0 mg, 0.40 mmol), Ni(cod)$_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr$_2$ (221.0 mg, 1.20 mmol) and water (3.6 μL, 0.2 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **2q** and **3q** (55.5 mg, 44% yield (89/11)). Flash column chromatography on silica (hexane/AcOEt = 5/1) provides **2q** as a yellow oil. Characterization of **2q**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.85 (t, *J* = 7.2 Hz, 3H), 1.24-1.37 (m, 4H), 2.36-2.43 (m, 5H), 3.76 (s, 3H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.14-7.25 (m, 5H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.8, 21.5, 22.5, 28.5, 29.9, 52.3, 126.2, 126.7, 128.4, 128.9, 129.0, 131.1, 136.6, 140.6, 143.5, 148.8, 165.5; IR (neat): 1726, 1356, 1164 cm^{-1}; EI-HRMS calcd for $C_{21}H_{25}NO_4S$ 387.15043, found 387.15032.



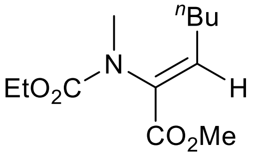
Compound 2r and 3r



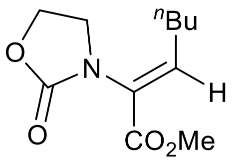
Following the general procedure using **1r** (78.7 mg, 0.42 mmol), Ni(cod)$_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr$_2$ (221.0 mg, 1.20 mmol) and water (3.6 μL, 0.2 mmol) in DMF (5.7 mL) to afford **2r** as colorless oil (36.2 mg, 35% yield) and **3r** as white solid (30.0

mg, 29% yield). Characterization of **2r**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.91 (t, *J* = 7.2 Hz, 3H), 1.32-1.39 (m, 2H), 1.42-1.48 (m, 2H), 2.41 (q, *J* = 7.4 Hz, 2H), 3.01 (s, 3H), 3.05 (s, 3H), 3.77 (s, 3H), 7.06 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.8, 22.5, 28.5, 30.1, 36.6, 38.1, 52.2, 130.2, 150.2, 164.5; IR (film, neat): 1721 cm^{-1}; EI-HRMS calcd for $C_{10}H_{19}NO_4S$ 249.10348, found 249.10323. Characterization of **3r**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.92 (t, *J* = 7.2 Hz, 3H), 1.32-1.38 (m, 2H), 1.39-1.45 (m, 2H), 2.42 (t, *J* = 7.7 Hz, 2H), 2.96 (s, 3H), 3.29 (s, 3H), 3.74 (s, 3H), 7.56 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.8, 22.8, 25.9, 32.2, 35.8, 37.8, 51.9, 119.1, 136.6, 168.5; IR (film, CHCl$_3$): 1706 cm^{-1}; EI-HRMS calcd for $C_{10}H_{19}NO_4S$ 249.10348, found 249.10327.

Compound 2s. Following the general procedure using **1s** (72.0 mg, 0.39 mmol), Ni(cod)$_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (79.0 mg, 1.21 mmol), MgBr$_2$ (221.0 mg, 1.20 mmol) and water (3.6 μL, 0.2 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **2s** and **3s** as colorless oil (70.7 mg, 74% yield (85/15)). Characterization of **2s**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.90 (t, *J* = 7.4 Hz, 3H), 1.09-1.44 (m, 7H), 2.10-2.17 (m, 2H), 2.97 (s, 3H), 3.71 (s, 3H), 4.02-4.17 (m, 2H), 6.68-6.79 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.7, 14.5, 22.3, 27.3, 30.0, 36.1, 52.0, 61.5, 132.3, 142.0, 155.9, 164.9; IR (neat): 1728, 1656 cm^{-1}; EI-HRMS calcd for $C_{12}H_{21}NO_4$ 243.14706, found 243.14709.

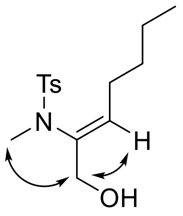


Compound 2t. Following the general procedure using **1t** (66.9 mg, 0.40 mmol), Ni(cod)$_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr$_2$ (221.0 mg, 1.20 mmol) and H_2O (3.6 μL, 0.2 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **2t** and **3t** (28.0 mg, 31% yield (13/87)). Characterization of **2t**: ^{1}H NMR (500 MHz, CDCl$_3$, δ/ppm): 0.91 (t, *J* = 7.2 Hz, 3H), 1.30-1.51 (m, 4H), 2.25 (q, *J* = 7.4 Hz, 2H), 3.75-3.80 (m, 5H), 4.47 (t, *J* = 7.9 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$, δ/ppm): 13.9, 22.5, 28.0, 30.1, 46.3, 52.3, 62.6, 126.7, 146.7, 157.0, 163.7; IR (neat): 1759, 1722 cm^{-1}; EI-HRMS calcd for $C_{11}H_{17}NO_4$ 227.11576, found 227.11636.



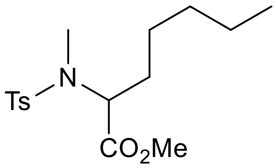
Other Experiments

Structure Elucidation of 2a



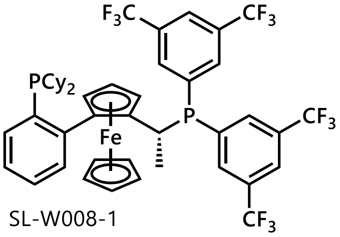
Compound 7. To a solution of **2a** (86.0 mg, 0.26 mmol) in toluene (0.5 mL) was added a solution of DIBAL-H in hexane (1.02 M, 0.78 mL, 0.79 mmol) at −78 °C, and the mixture was stirred at the same temperature for 3 hours. To the mixture was added a saturated aqueous solution of potassium sodium tartrate, and the mixture was stirred at room temperature for 2 h. After the aqueous layer was extracted with AcOEt, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. A crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 3/1) to give **7** (70.5 mg, 90% yield) as a colorless oil. The result of NOE experiment is shown with double-headed arrows on the chemical structure of **7** above. ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 0.79 (t, *J* = 6.9 Hz, 3H), 1.09-1.19 (m, 4H), 1.68 (q, *J* = 7.3 Hz, 2H), 2.23 (brs, 1H), 2.41 (s, 3H), 3.01 (s, 3H), 4.13 (s, 2H), 5.62 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 13.7, 21.4, 22.4, 27.3, 30.8, 37.6, 64.8, 127.4, 129.6, 133.3, 136.6, 138.3, 143.4; IR (film, $CHCl_3$): 3470, 2953, 2927, 1154 cm^{-1}; ESI-HRMS calcd for $C_{15}H_{23}O_3NNaS$ 320.12909, found 320.12918.

Trial of Asymmetric Hydrogenation



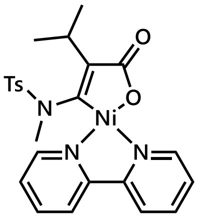
Compound 8. $[Rh(nbd)_2]SbF_6$ (3.9 mg, 7.5 μmol, nbd = norbornadiene) and SL W008-1 (7.0 mg, 7.4 μmol) were added to a flame-dried 10 mL test tube. The test tube was purged with H_2. Chlorobenzene (0.5 mL) was added to the test tube, and the resulting mixture was stirred for 10 min under an atmosphere of H_2 (1 atm). To the mixture was added a solution of **2a** (48.5 mg, 0.15 mmol) in chlorobenzene (1.6 mL). The test tube was placed in an autoclave and pressurized under an H_2 atmosphere (5 atm). The reaction mixture was stirred at 60 °C for 20 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to afford **8a** (12.2 mg, 25% yield) as a colorless oil. The enantiomeric excess was determined to be 25% by HPLC analysis with a

DAICEL CHIRALPAK AS-H [eluent: hexane/2-propanol = 98/2, flow rate: 0.5 mL/min, detector: UV (254 nm)]: t_R (major) = 28.0 min; t_R (minor) = 32.0 min. ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 0.87 (t, *J* = 6.9 Hz, 3H), 1.24-1.33 (m, 6H), 1.56-1.61 (m, 1H), 1.78-1.83 (m, 1H), 2.41 (s, 3H), 2.82 (s, 3H), 3.47 (s, 3H), 4.57 (dd, *J* = 10.0, 5.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 13.9, 21.5, 22.4, 25.5, 29.2, 29.7, 31.1, 51.7, 58.7, 127.3, 129.4, 136.2, 143.2, 171.4; IR (neat): 1742 cm^{-1}; ESI-HRMS calcd for C9H18NO2 172.13375, found 172.13441.



SL-W008-1

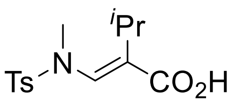
Synthesis of Nickelalactone 5



A Schlenk flask was charged with Ni(cod)$_2$ (137.5 mg, 0.50 mmol), 2,2'-bipyridine (78.1 mg, 0.50 mmol), ynamide **1c** (138.23 mg, 0.55 mmol) under nitrogen atmosphere. To the solids were added 3 mL of THF. The suspension was quickly degassed and then back filled with CO_2 by using a balloon. The reaction mixture was stirred for 1 day at 0 °C. The precipitate was filtered off, washed with cold ether (distilled from Na/benzophenone) and dried out to yield orange powder (155.1 mg, 61%). Red needle crystals for X-ray diffraction study was obtained by diffusion of pentane into the solution of **5** in THF/toluene/CH_2Cl_2 mixture. ^{1}H NMR (500 MHz, CD_2Cl_2, δ/ppm): 0.63 (d, *J* = 7 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 1.77 (m, 1H), 2.36 (s, 3H), 3.20 (s, 3H), 7.26 (d, *J* = 8 Hz, 2H), 7.46 (t, *J* = 6.5 Hz, 1H), 7.55 (t, *J* = 6.5 Hz, 1H), 7.78 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.92-8.05 (m, 3H), 8.56 (d, *J* = 6 Hz, 1H), 8.78 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2, δ/ppm): 20.0, 20.4, 21.5, 29.1, 39.1, 120.6, 121.2, 126.3, 126.4, 127.6, 129.9, 137.2, 138.9, 139.8, 143.6, 149.7, 152.0, 153.0, 155.6 (three signals were missing due to very low intensity); Elemental analysis did not give good results probably due to instability of the complex to the moisture; X-ray data: *M* = 510.24, red, needle, monoclinic, $P2_1/n$ (#14), a = 18.6357(6) Å, b = 6.4232(2) Å, c = 19.8474(7) Å, β = 110.723(8)°, V = 2222.05(17) Å^3, Z =

4, D_{calc} = 1.525 g/cm^3, T = −140 °C, $R_1(wR_2)$ = 0.0498 (0.1190).

Treatment of Nickelalactone 5 with $H_2O/MgBr_2/Zn$ system to give compound 6



Nickelalactone **5** (25.0 mg, 0.049 mmol), Zn (10.0 mg, 0.153 mmol), and $MgBr_2$ (27.3 mg, 0.148 mmol) were weighed into a flame-dried round bottom flask in a glove box (nitrogen atmosphere). Then, the flask was taken out of the glove box, and a solution of water (0.5 µL, 0.028 mmol) in DMF (0.7 mL) was added at 0 °C to the flask. After removal of nitrogen gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO_2 gas using a balloon. The reaction mixture was stirred at 0 °C for 21 hours. To the mixture was added 10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layers was washed with water, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **6** (10.3 mg, 71% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.21 (d, J = 6.9 Hz, 6H), 2.45 (s, 3H), 3.01-3.07 (m, 4H), 7.34-7.38 (m, 3H), 7.72 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, δ/ppm): 20.7, 21.6, 26.8, 37.4, 127.5, 128.2, 130.0, 133.8, 138.9, 144.5, 172.4; IR (neat): 2963, 1681 cm^{-1}; EI-HRMS calcd for $C_{14}H_{19}NO_4S$ 297.10348, found 297.10375.

Hydrocarboxylation of 1a in the presence of nickelalactone 5 as catalyst

Nickelalactone **5** (20.4 mg, 0.040 mmol), Zn (39.2 mg, 0.600 mmol), and $MgBr_2$ (110.5 mg, 0.600 mmol) were weighed into a flame-dried round bottom flask in a glove box. Then, the flask was taken out of the glove box, and DMF (1.4 mL) was added at 0 °C to the flask. To the resulting suspension was added a solution of ynamide **1a** (51.6 mg, 0.194 mmol) and water (2.0 µL, 0.111 mmol) in DMF (1.5 mL) at the same temperature via cannulation method. After removal of nitrogen gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO_2 gas using a balloon. The reaction mixture was stirred at 0 °C for 12 hours. To the mixture was added 10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was treated with diazomethane in Et_2O at 0 °C. After the mixture had been concentrated, the crude product was analyzed by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard to give a mixture of carboxylated product, **2a** and **3a** (51% yield (67/33) based on the initial amount of **1a**) and **3c** (53% yield based on the initial amount of nickelalactone **5**).

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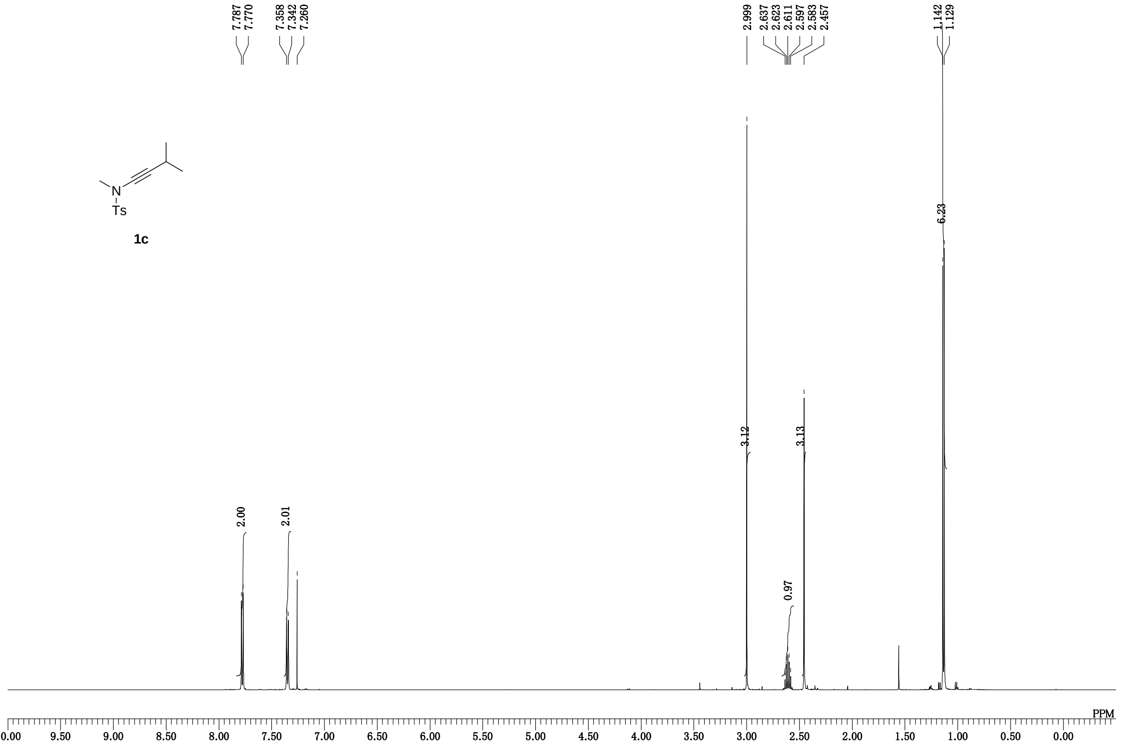
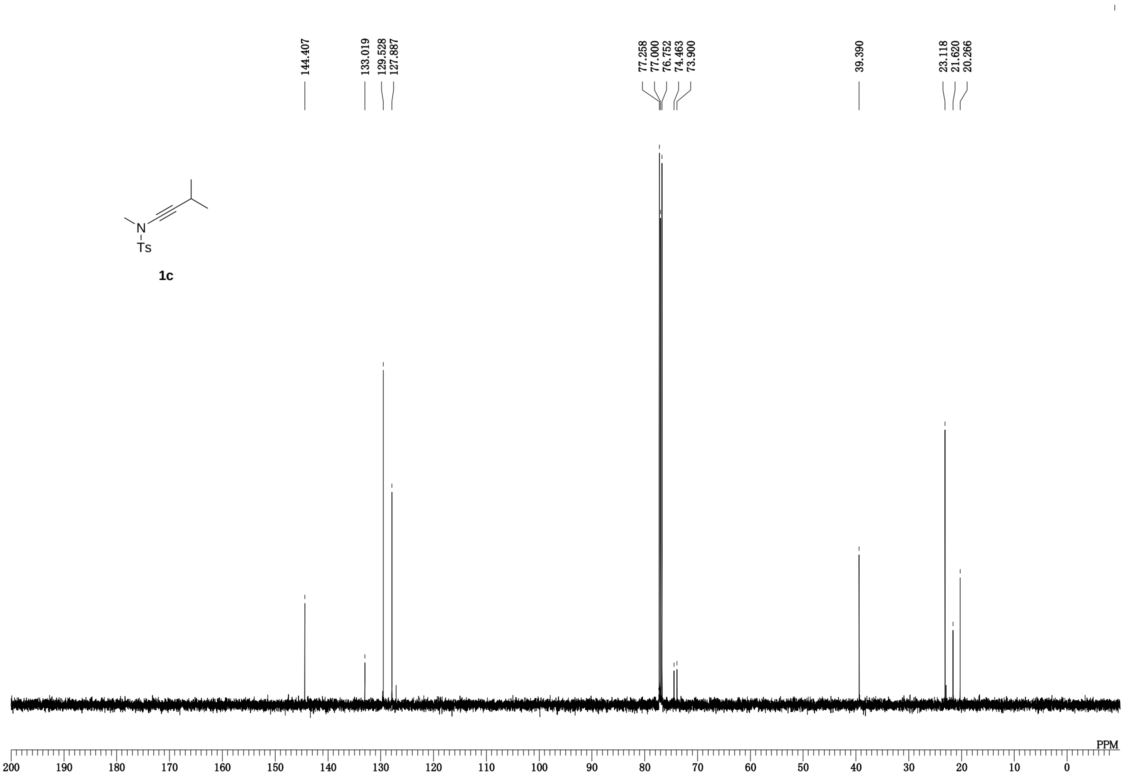
Spectrum Data

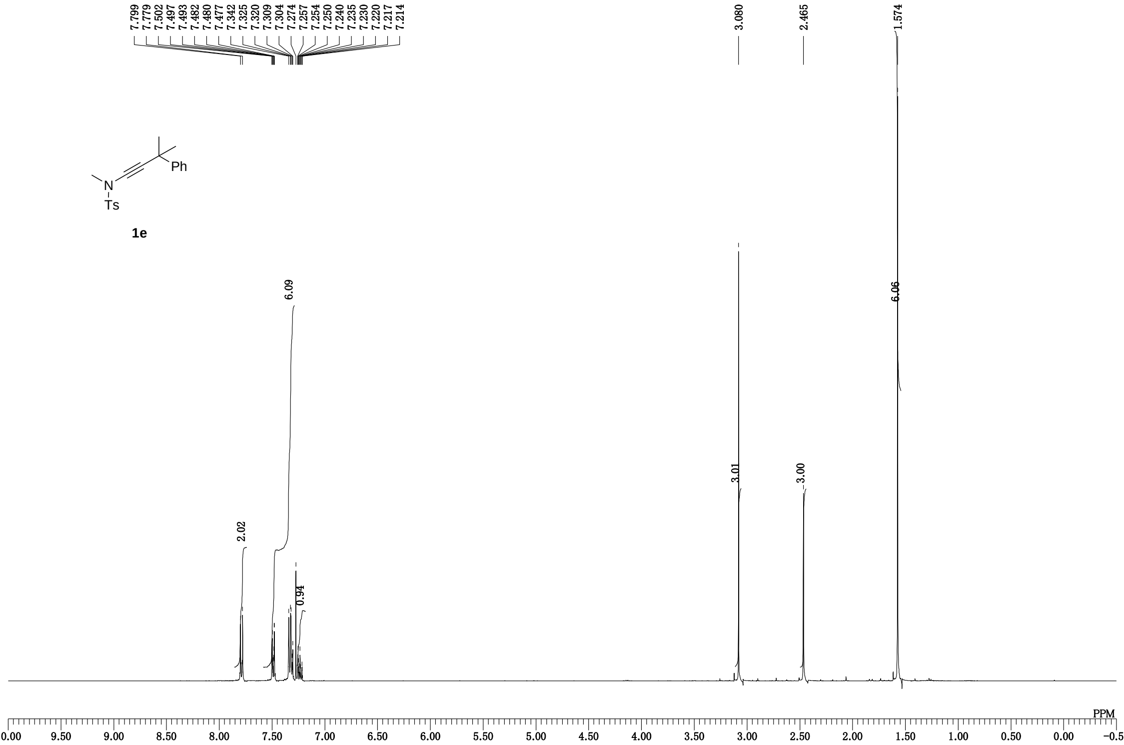
1c: ^{1}H NMR, CDCl$_3$, 500 MHz



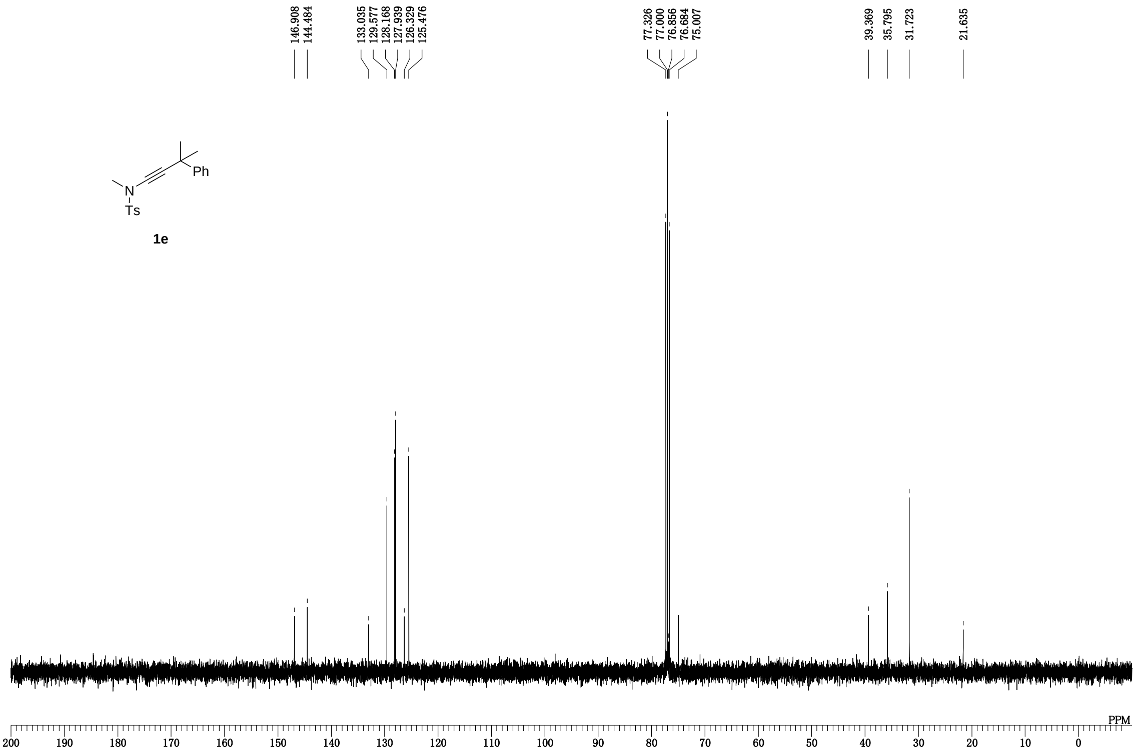
1c: ^{13}C NMR, CDCl$_3$, 125 MHz



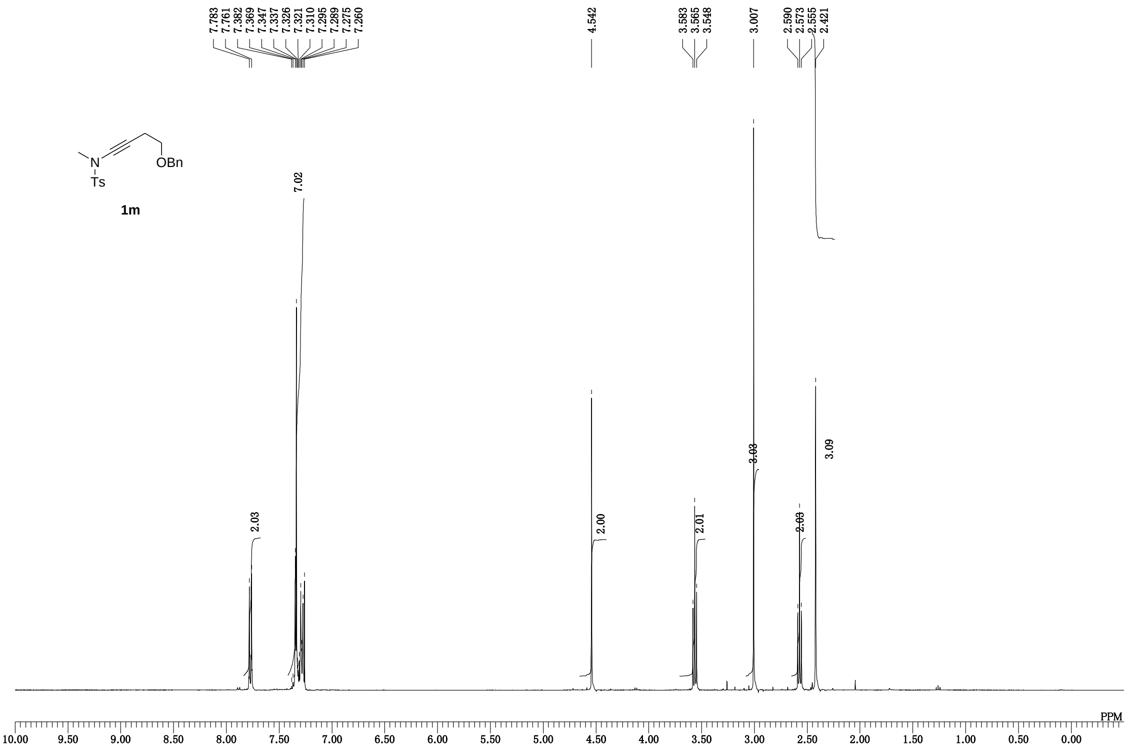
1e: ^{1}H NMR, CDCl$_3$, 500 MHz



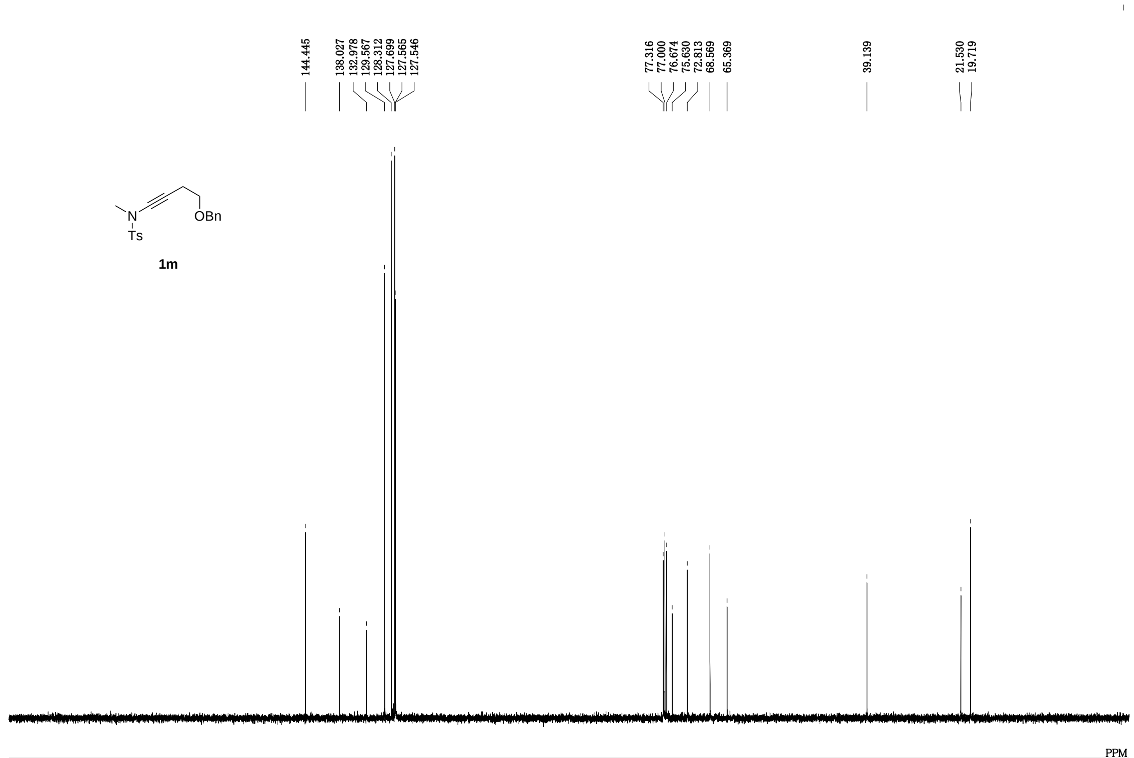
1e: ^{13}C NMR, CDCl$_3$, 125 MHz



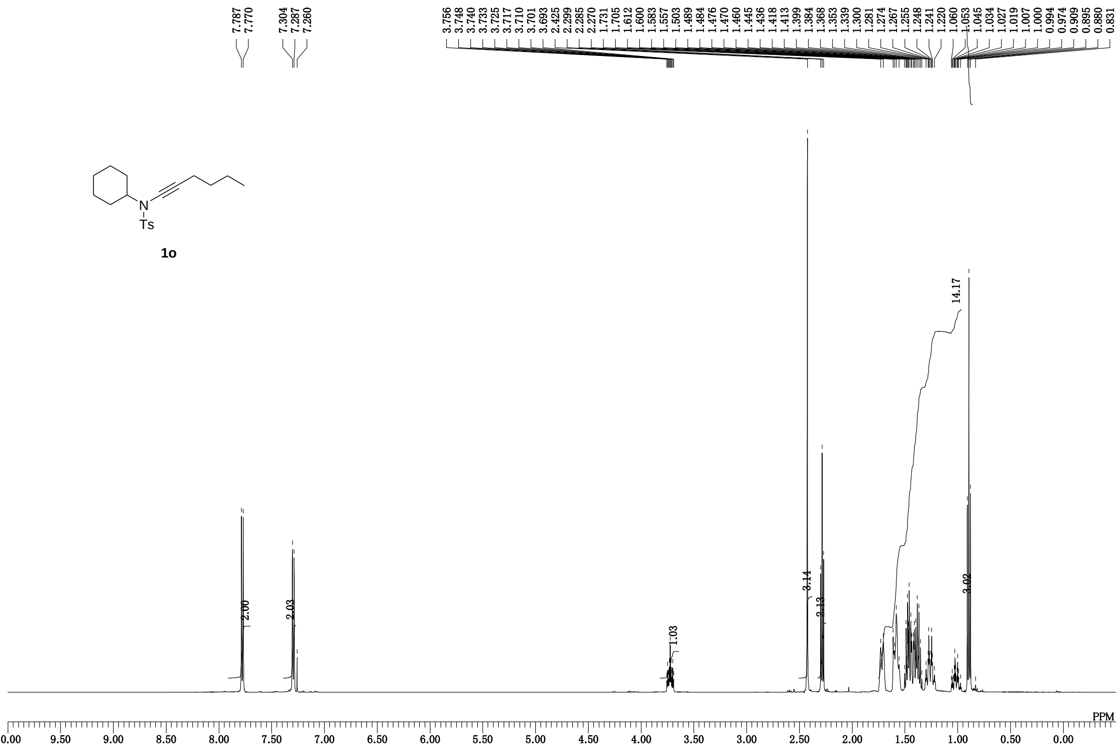
1m: ^{1}H NMR, CDCl$_3$, 400 MHz



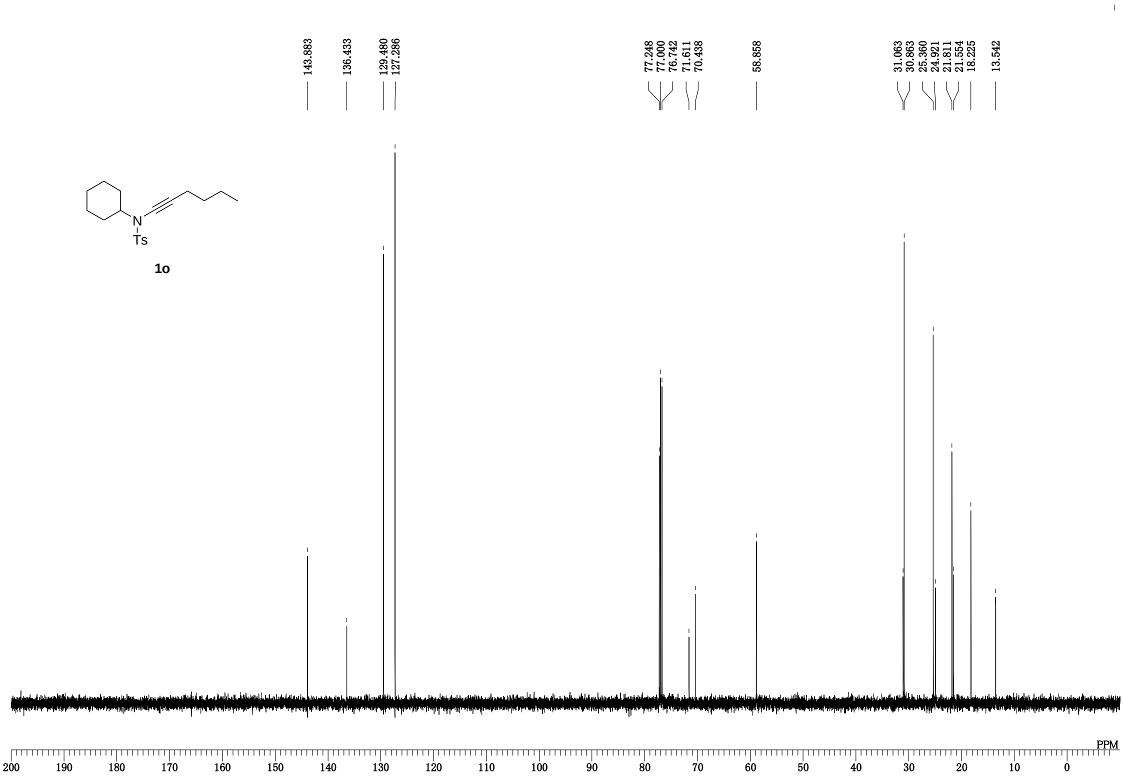
1m: ^{13}C NMR, CDCl$_3$, 100 MHz



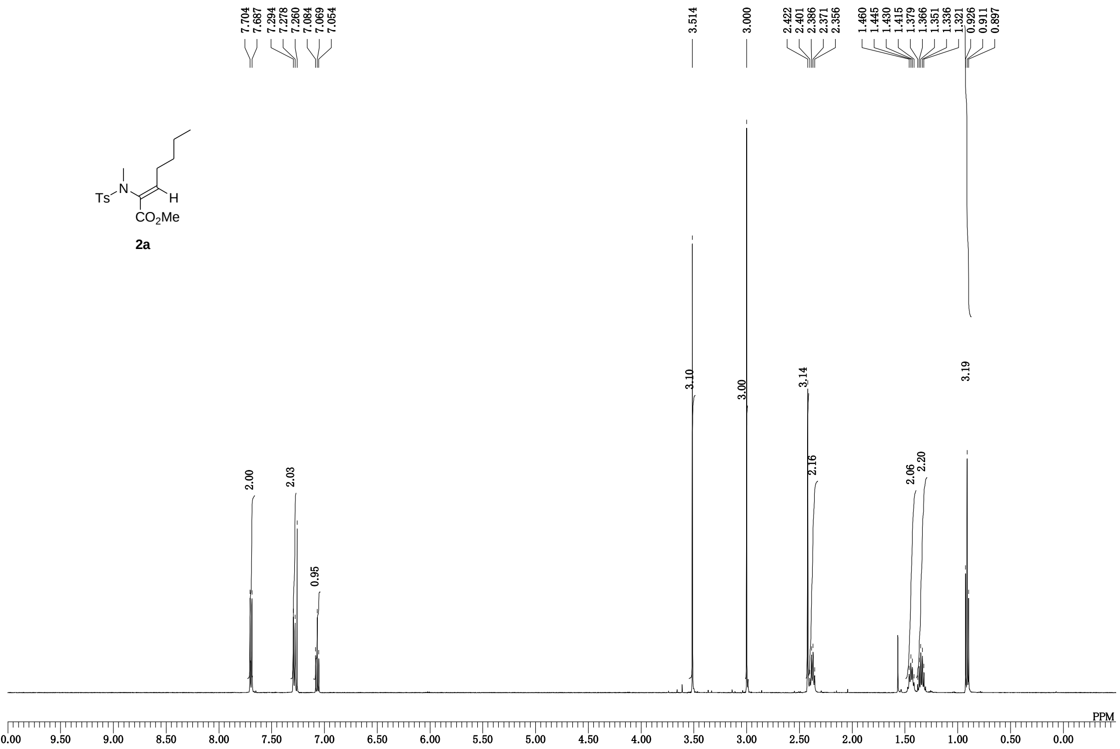
1o: ^{1}H NMR, CDCl$_3$, 500 MHz



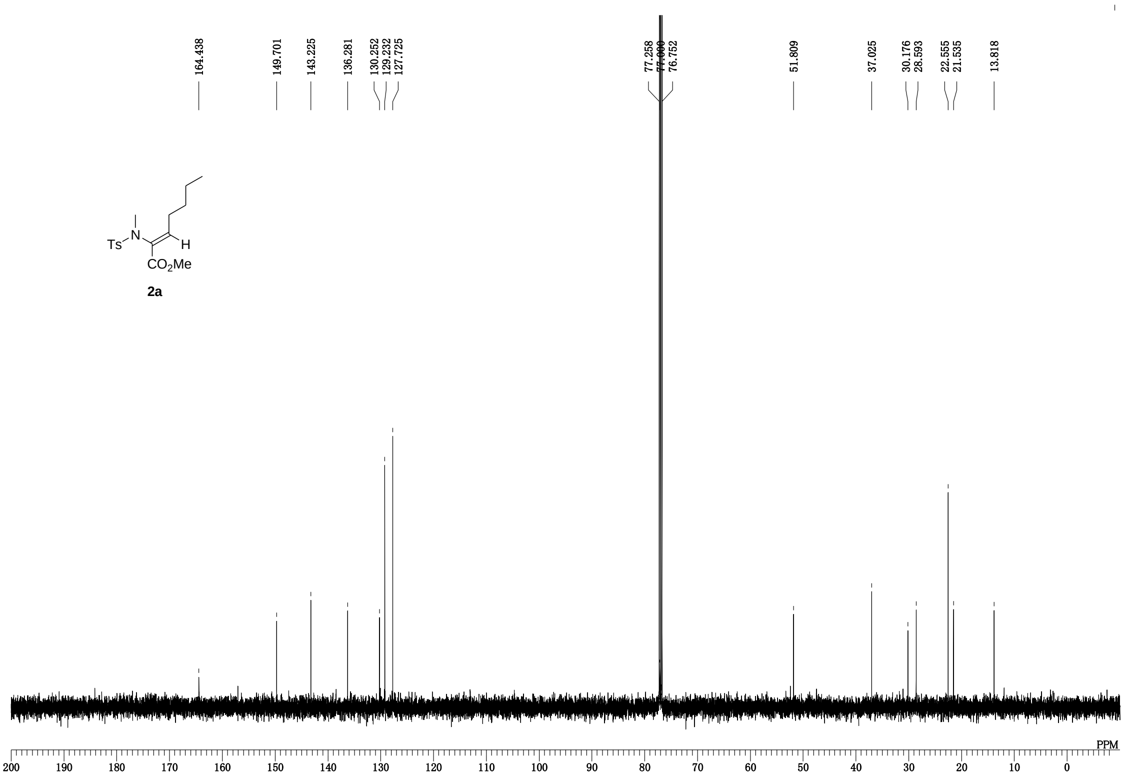
1o: ^{13}C NMR, CDCl$_3$, 125 MHz



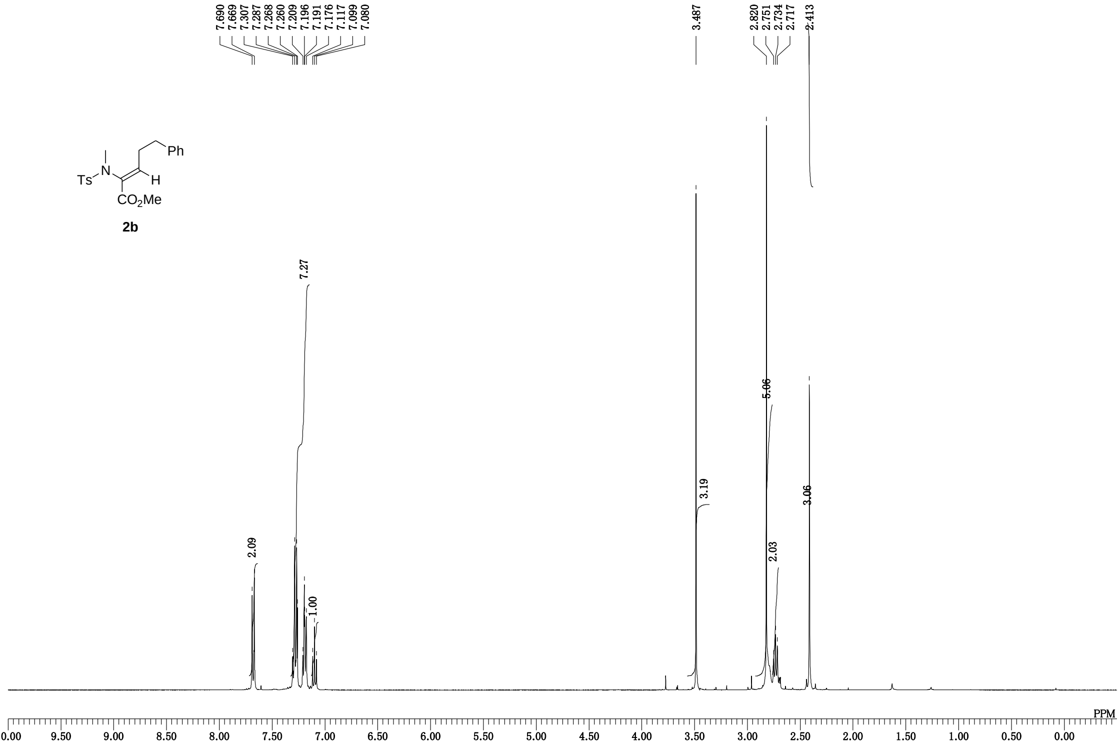
2a: ^{1}H NMR, CDCl$_3$, 500 MHz



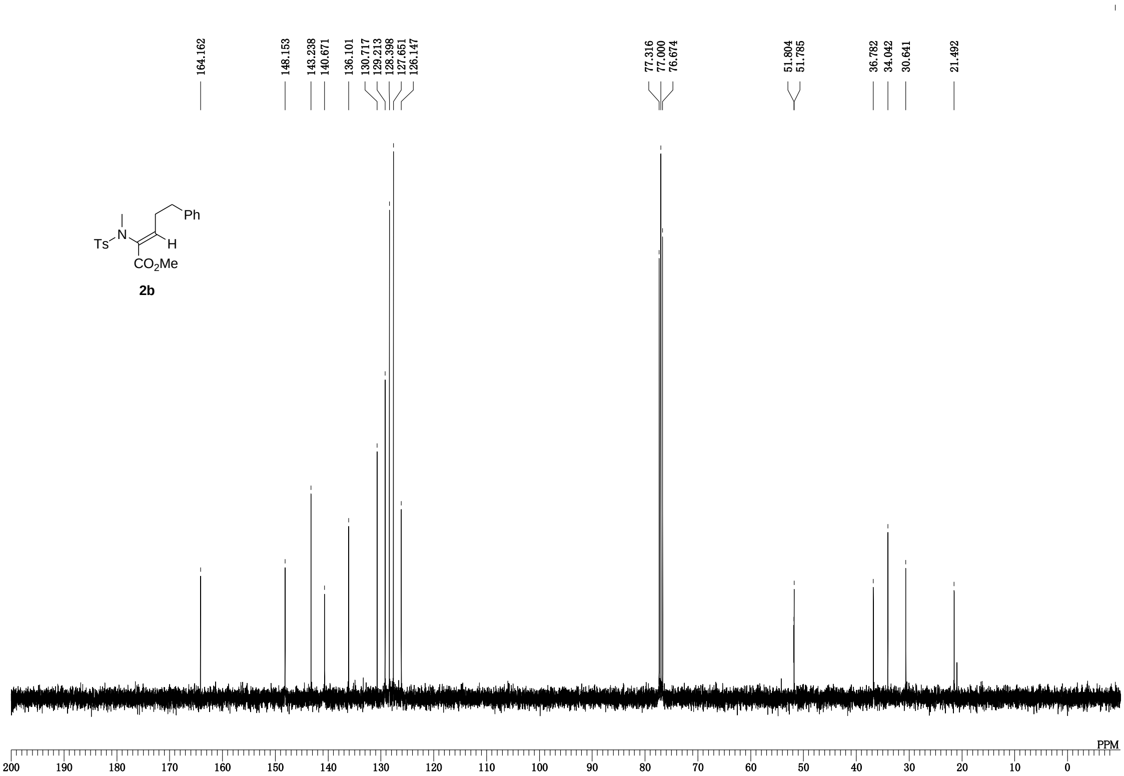
2a: ^{13}C NMR, CDCl$_3$, 125 MHz



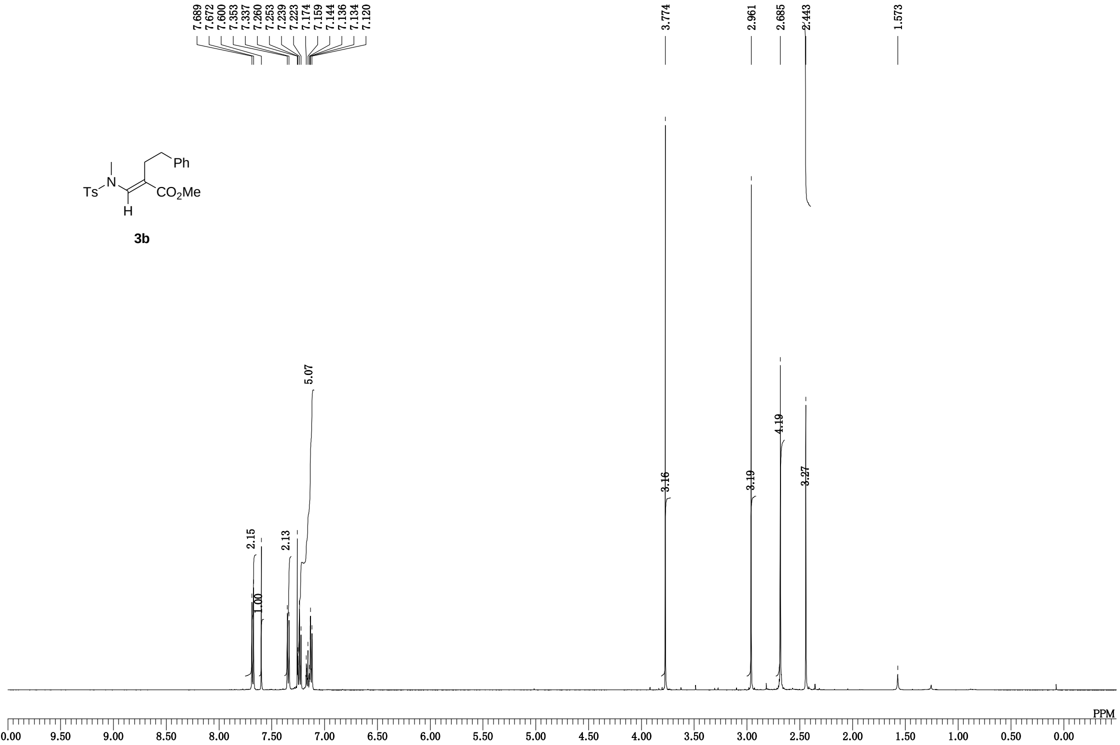
2b: ^{1}H NMR, CDCl$_3$, 500 MHz



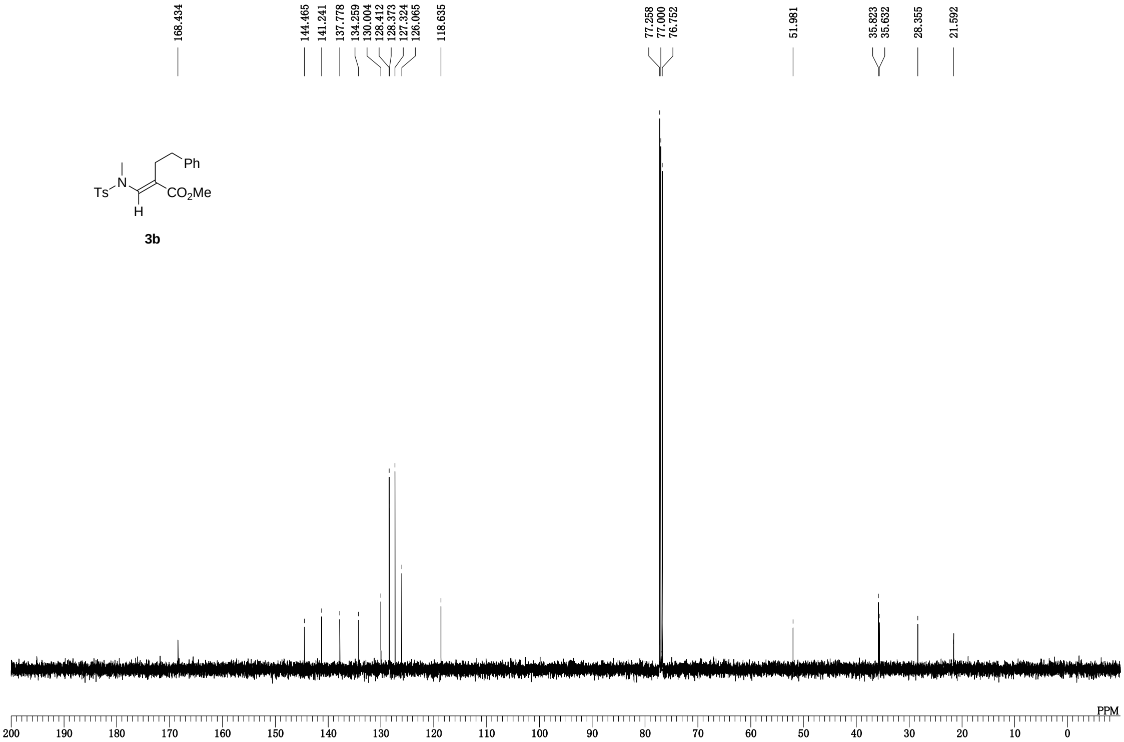
2b: ^{13}C NMR, CDCl$_3$, 125 MHz



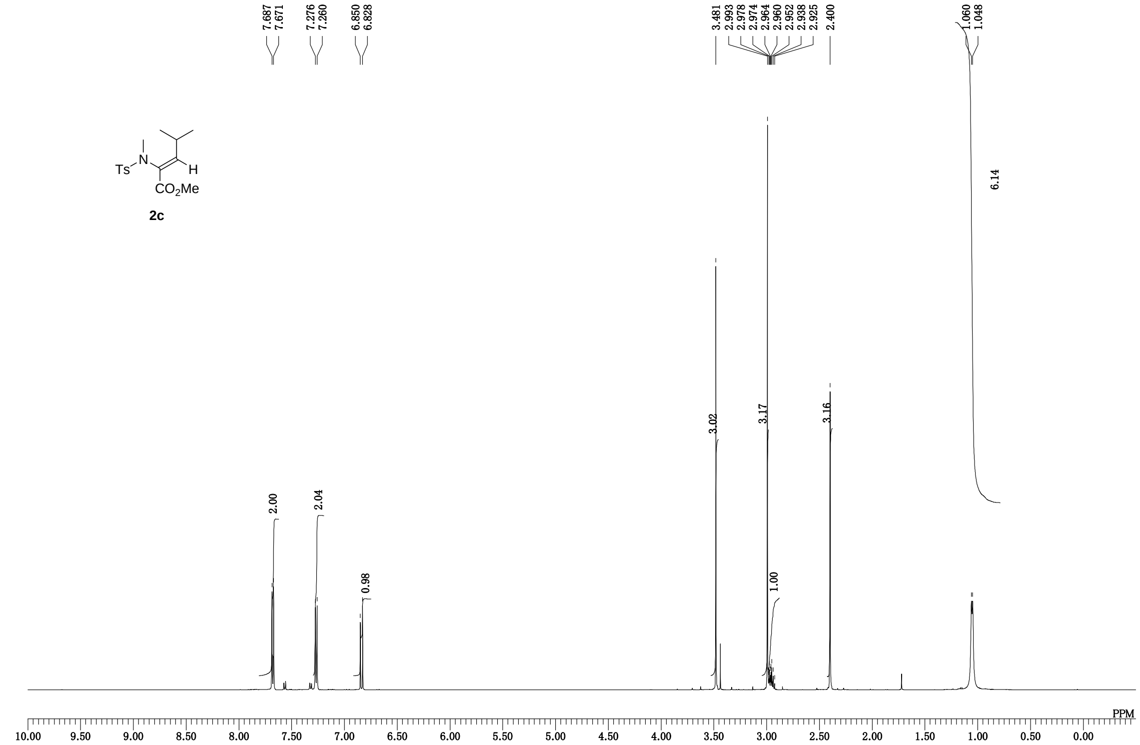
3b: ^{1}H NMR, CDCl$_3$, 500 MHz



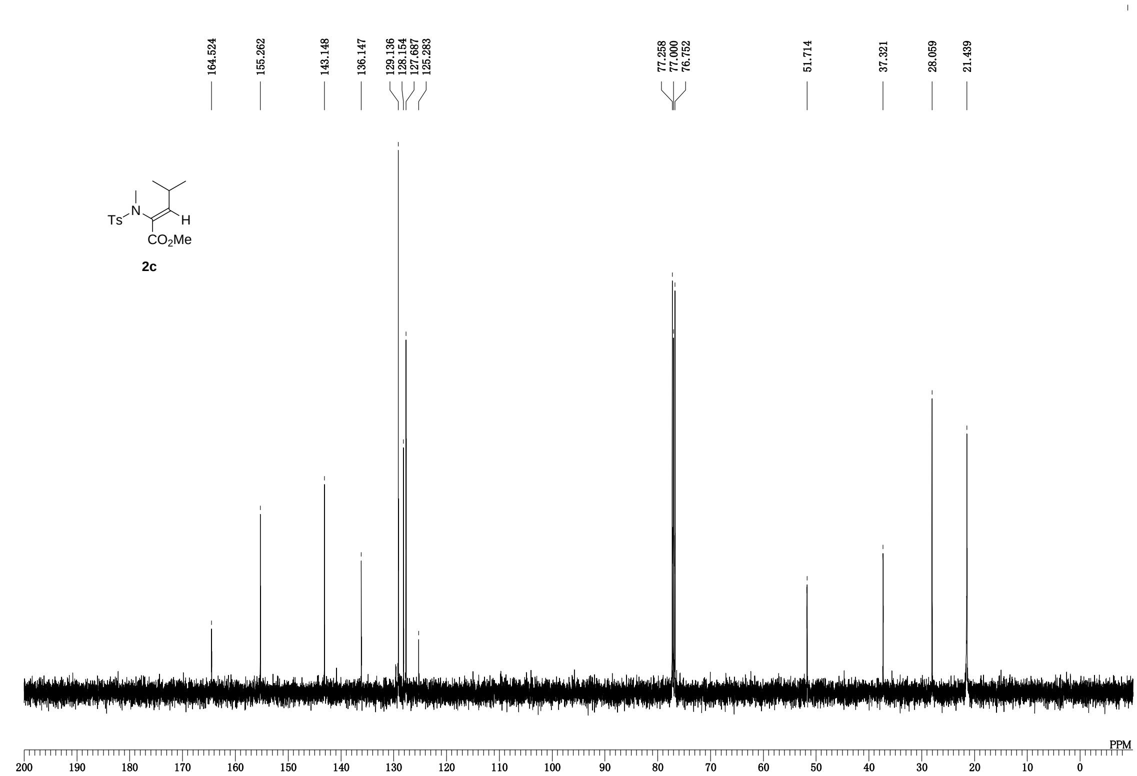
3b: ^{13}C NMR, CDCl$_3$, 125 MHz



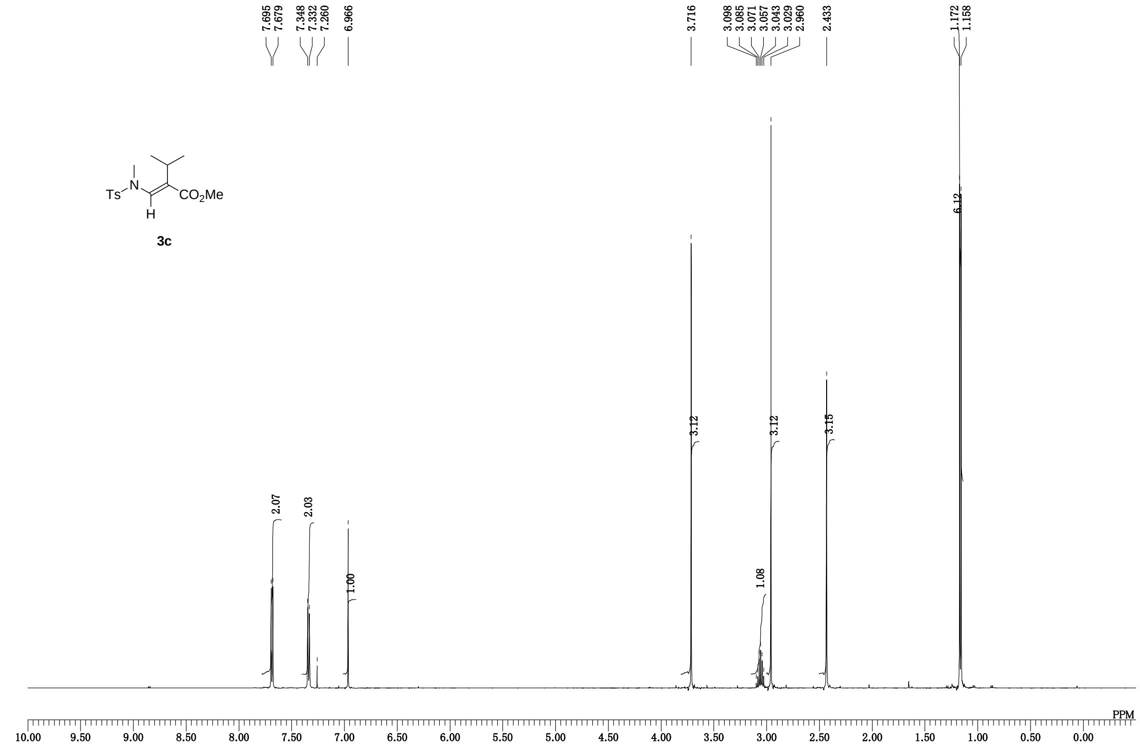
2c: ^{1}H NMR, CDCl$_3$, 500 MHz



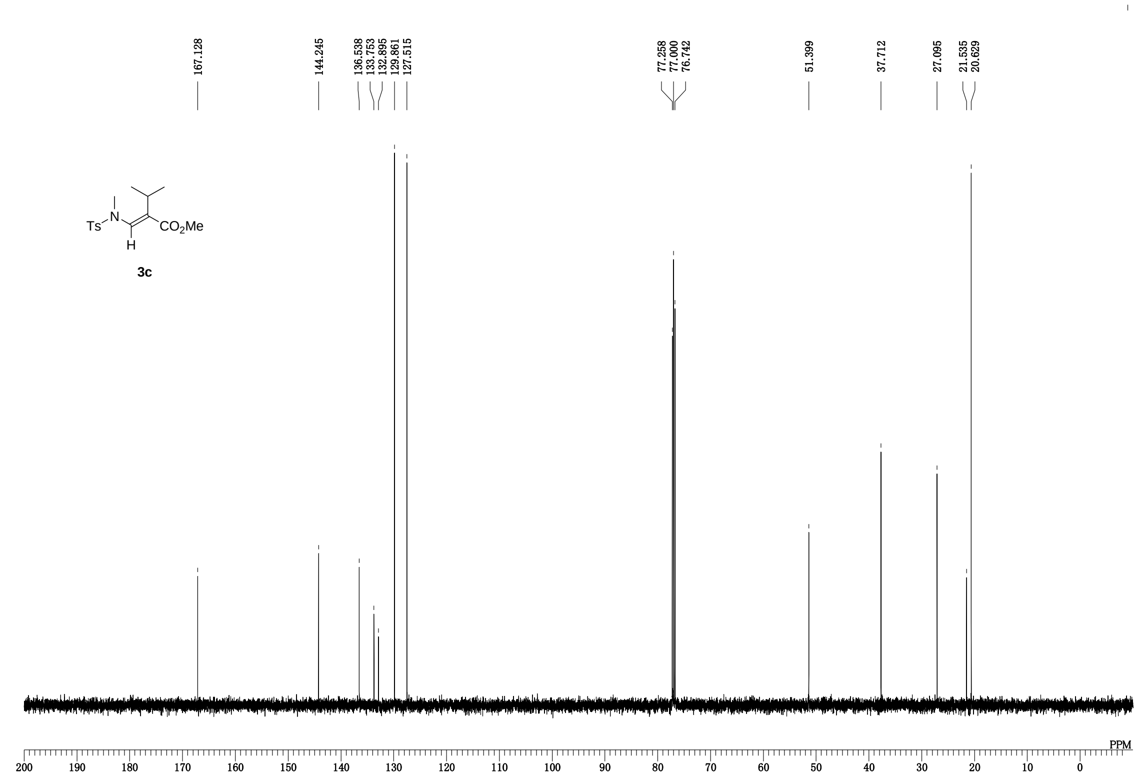
2c: ^{13}C NMR, CDCl$_3$, 125 MHz



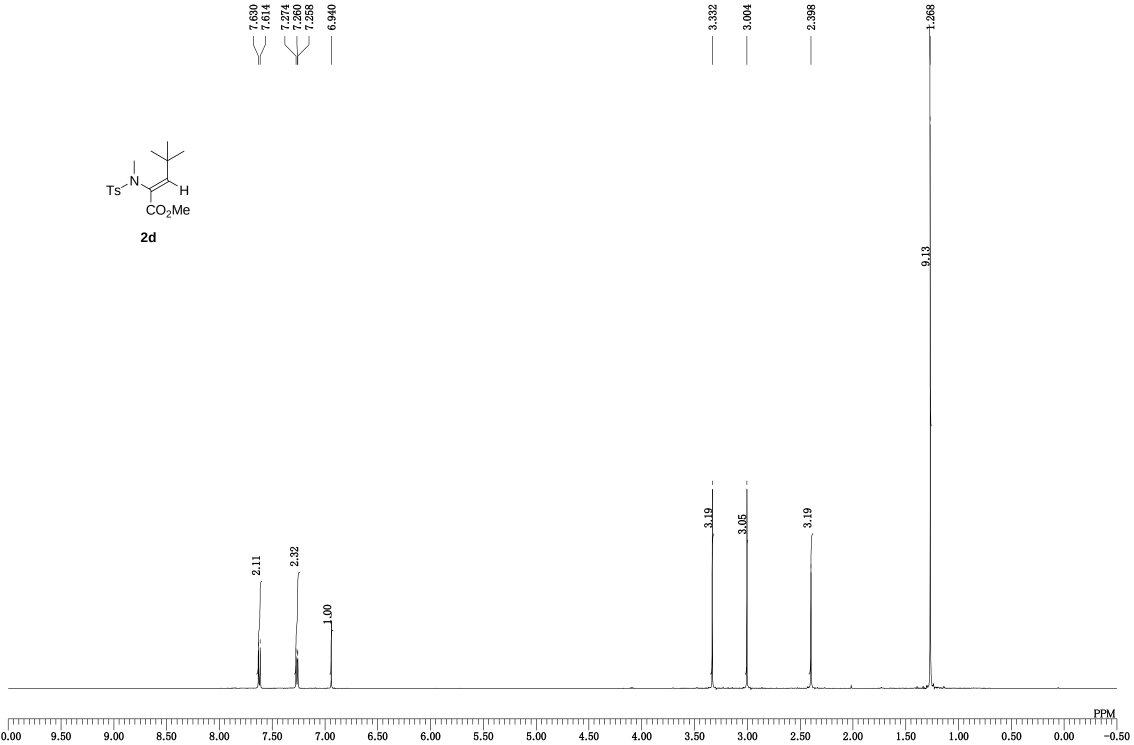
3c: ^{1}H NMR, CDCl$_3$, 500 MHz



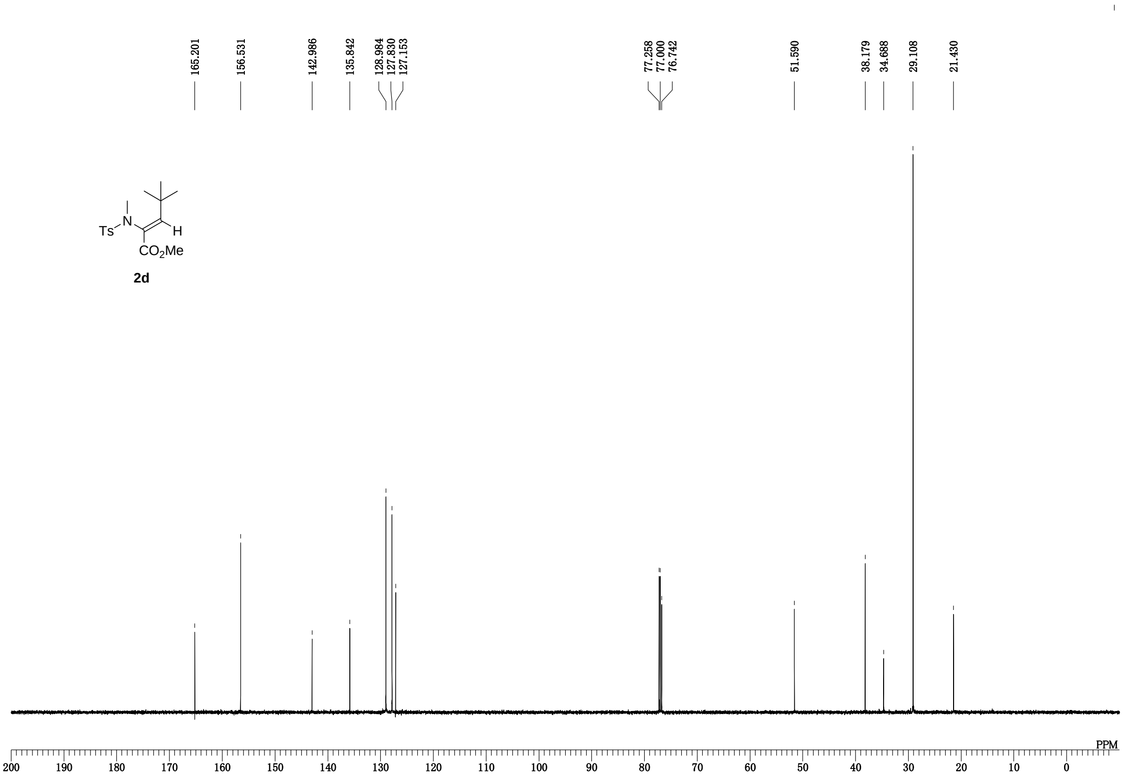
3c: ^{13}C NMR, CDCl$_3$, 125 MHz



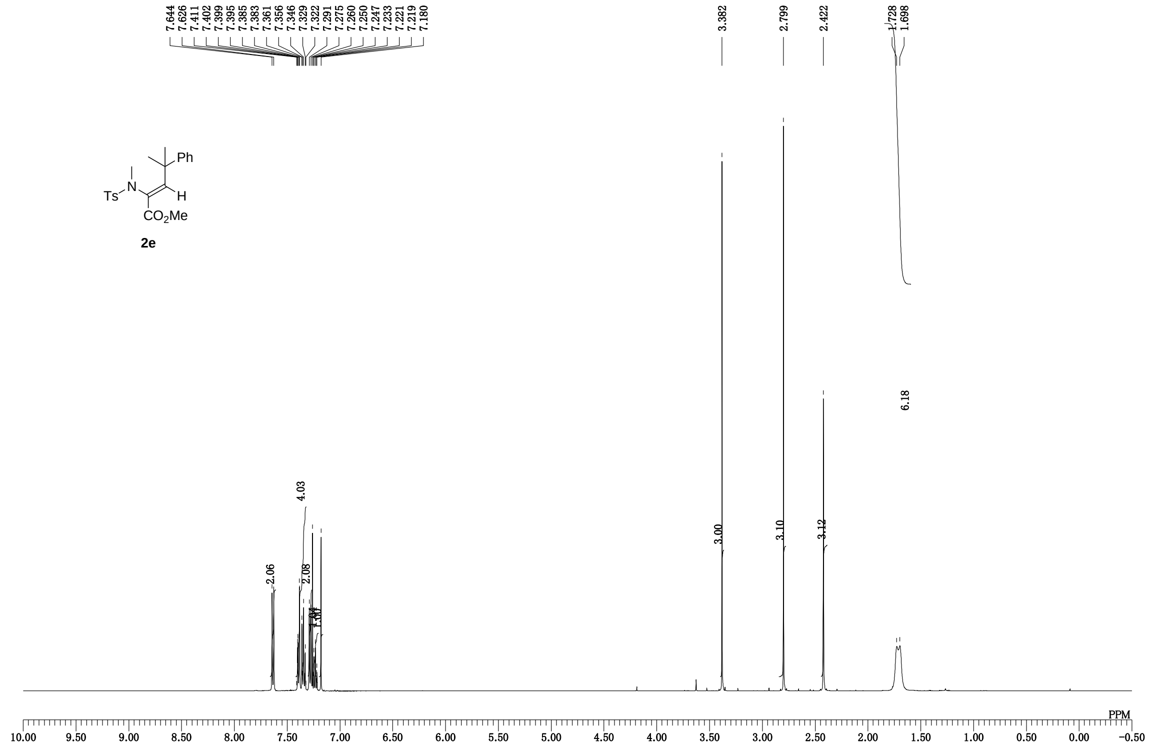
2d: ^{1}H NMR, CDCl$_3$, 500 MHz



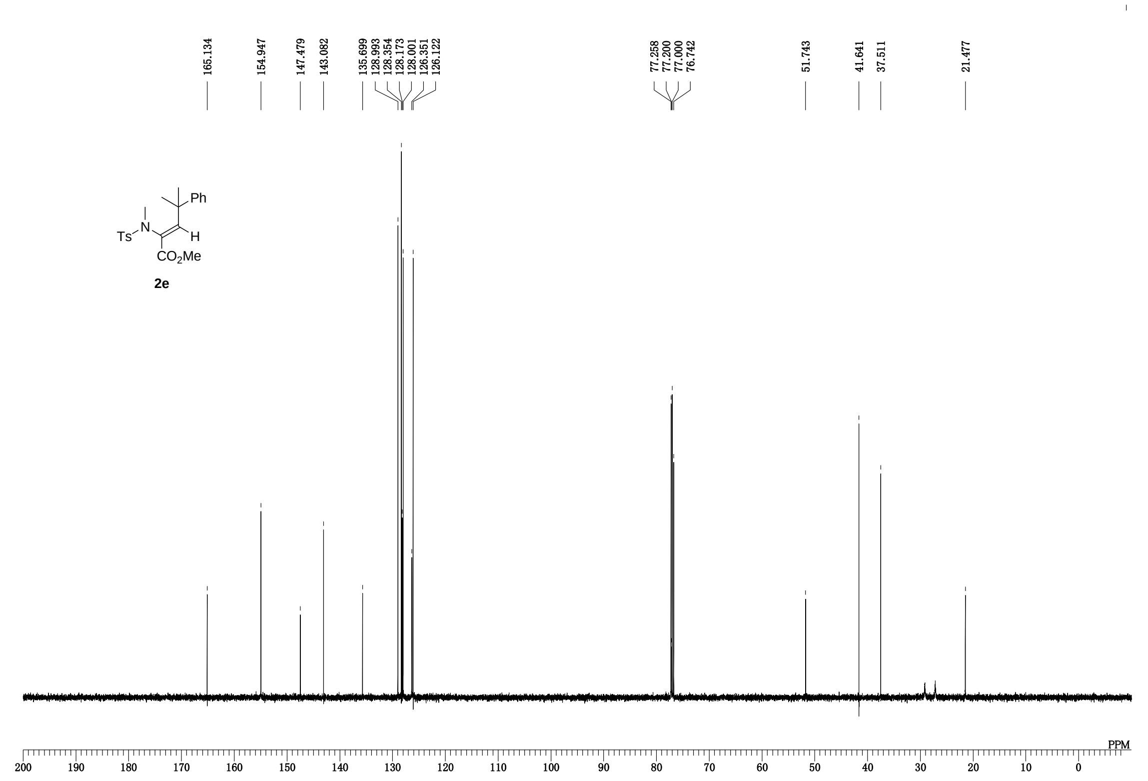
2d: ^{13}C NMR, CDCl$_3$, 125 MHz



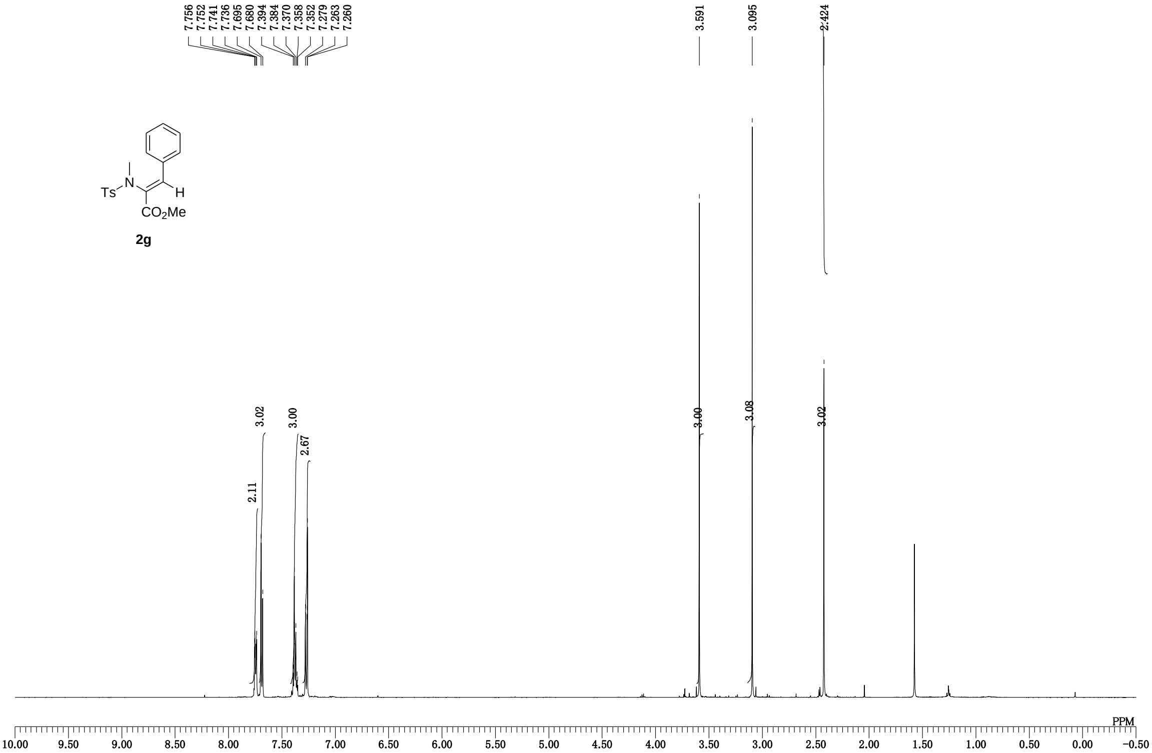
2e: ^{1}H NMR, CDCl$_3$, 500 MHz



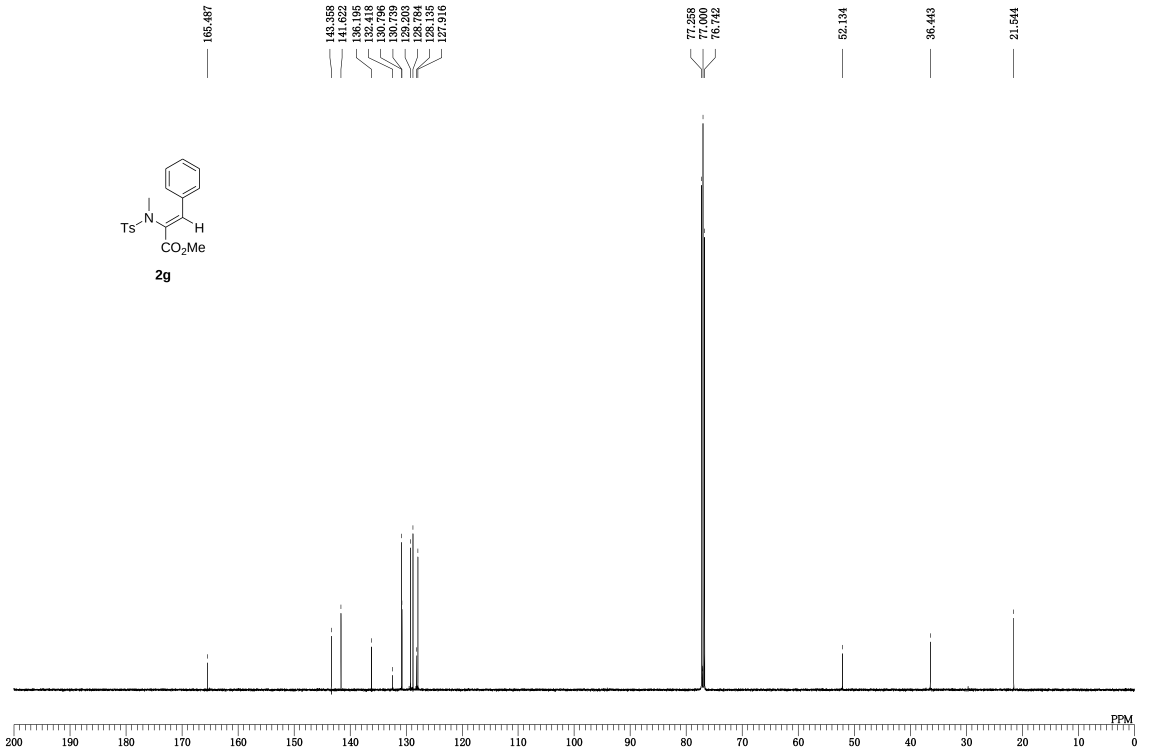
2e: ^{13}C NMR, CDCl$_3$, 125 MHz



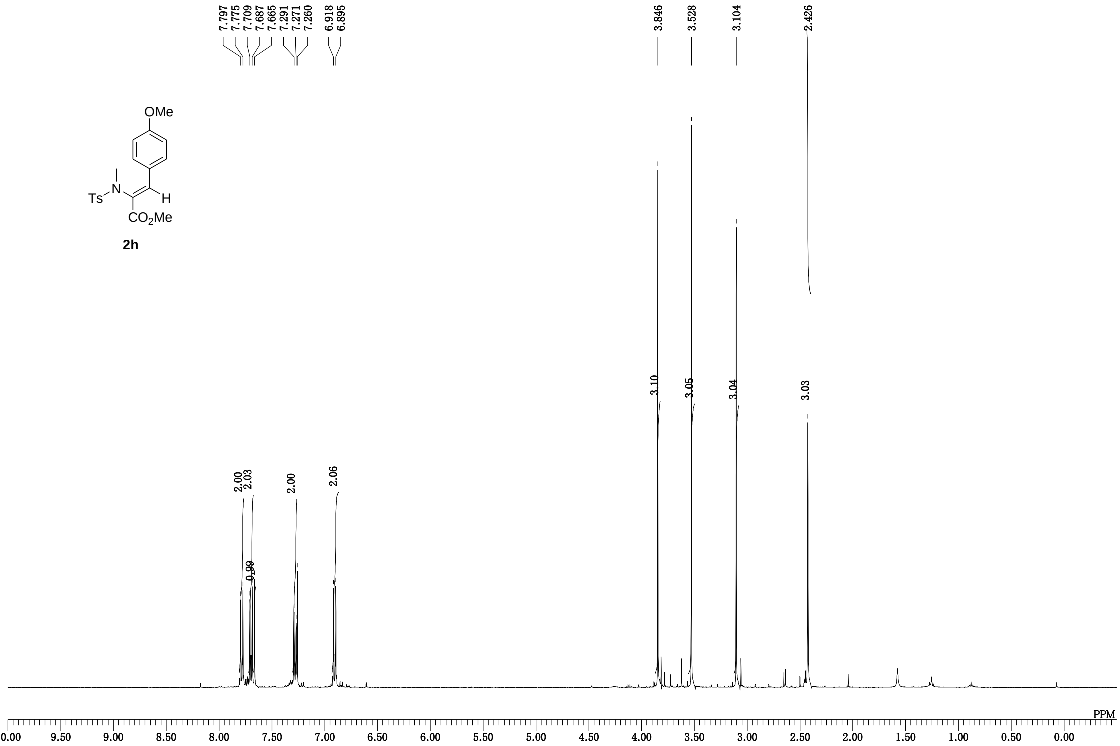
2g: ^{1}H NMR, CDCl$_3$, 500 MHz



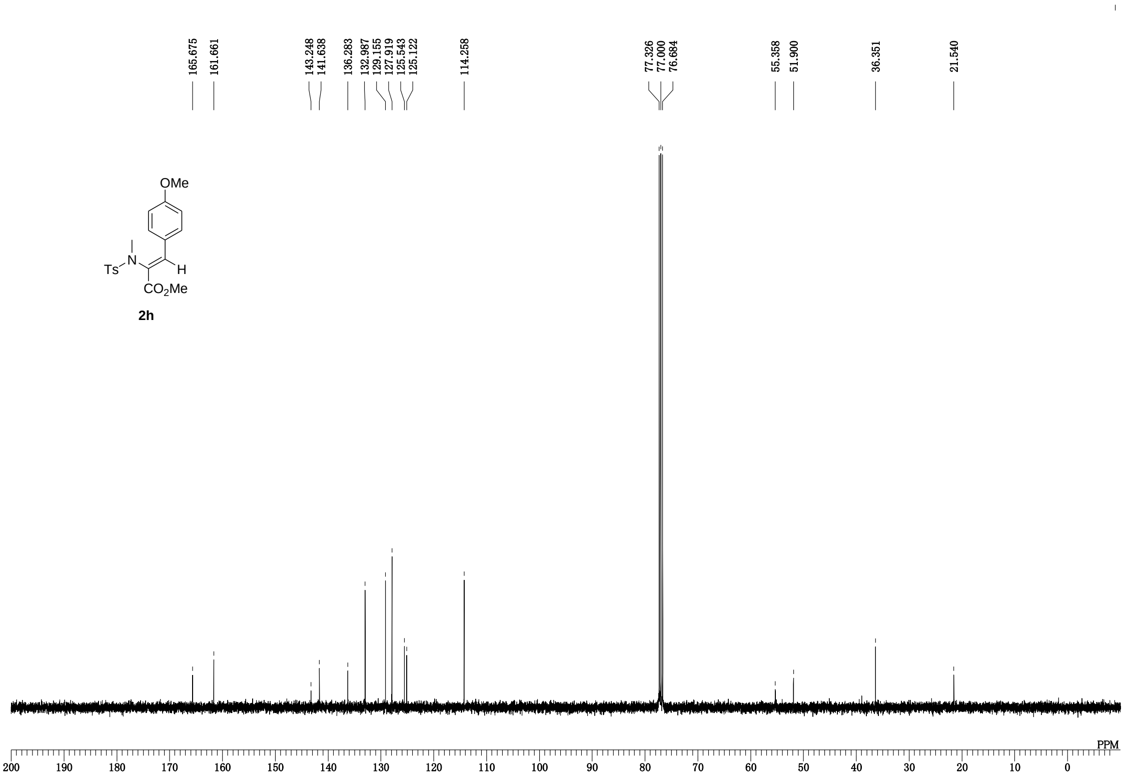
2g: ^{13}C NMR, CDCl$_3$, 125 MHz



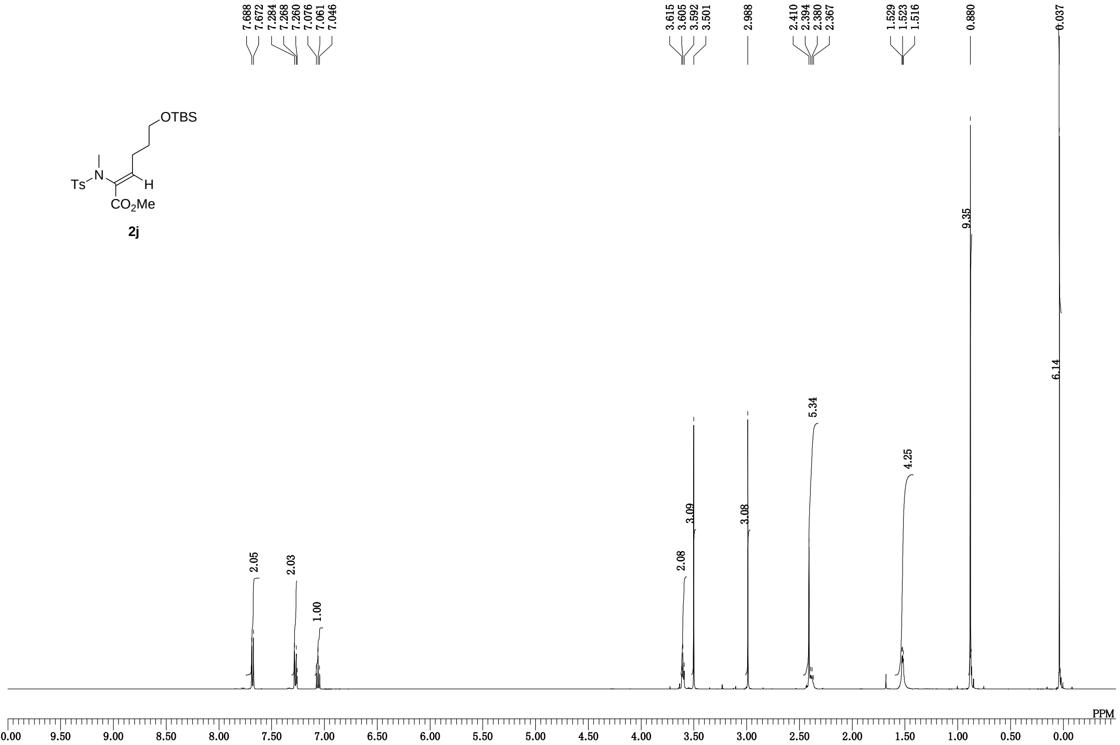
2h: ^{1}H NMR, CDCl$_3$, 400 MHz



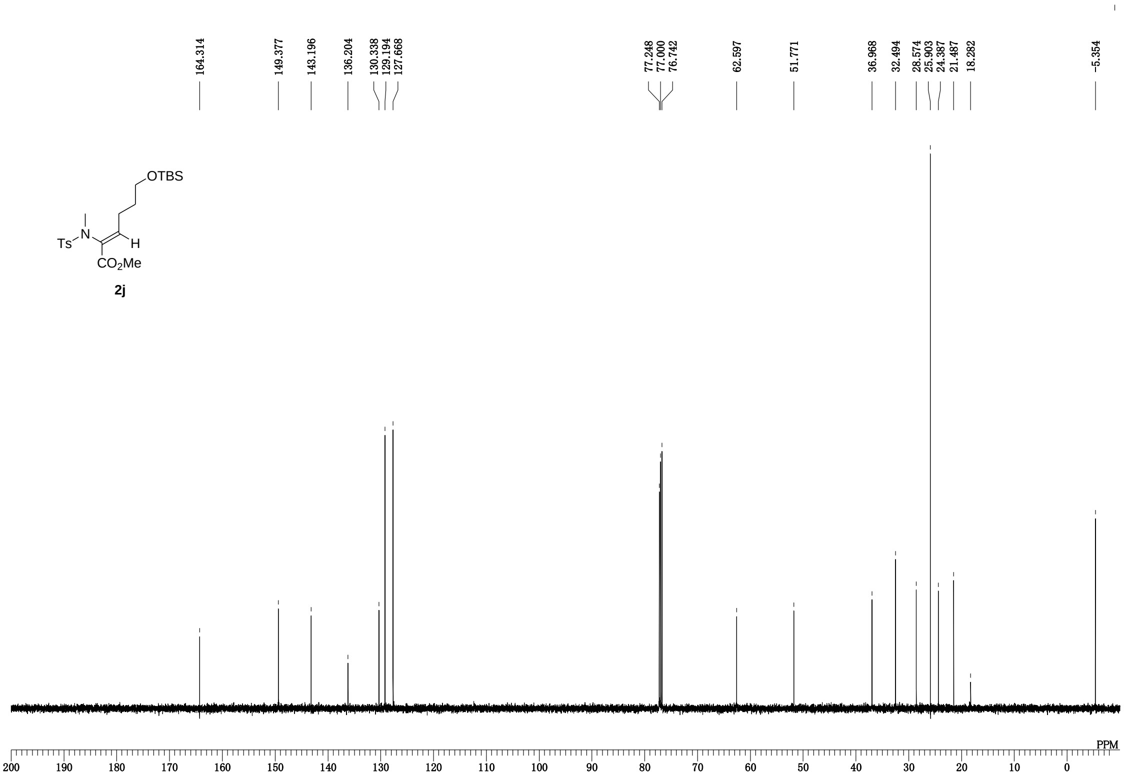
2h: ^{13}C NMR, CDCl$_3$, 100 MHz



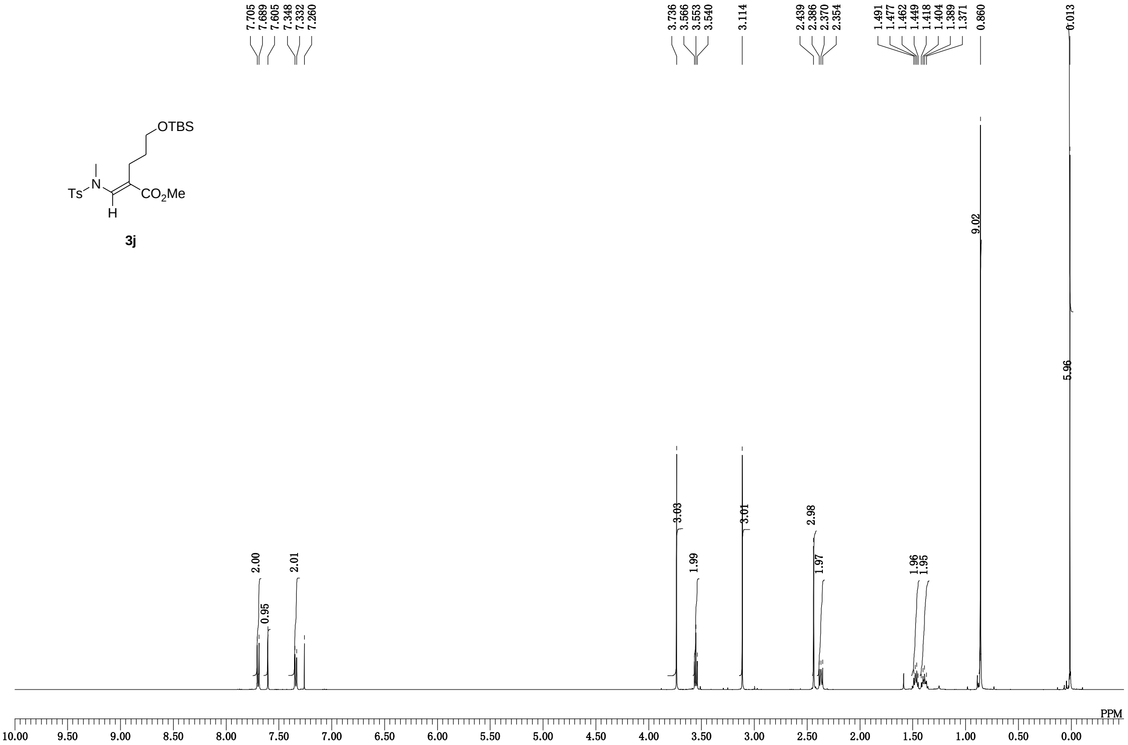
2j: ^{1}H NMR, CDCl$_3$, 500 MHz



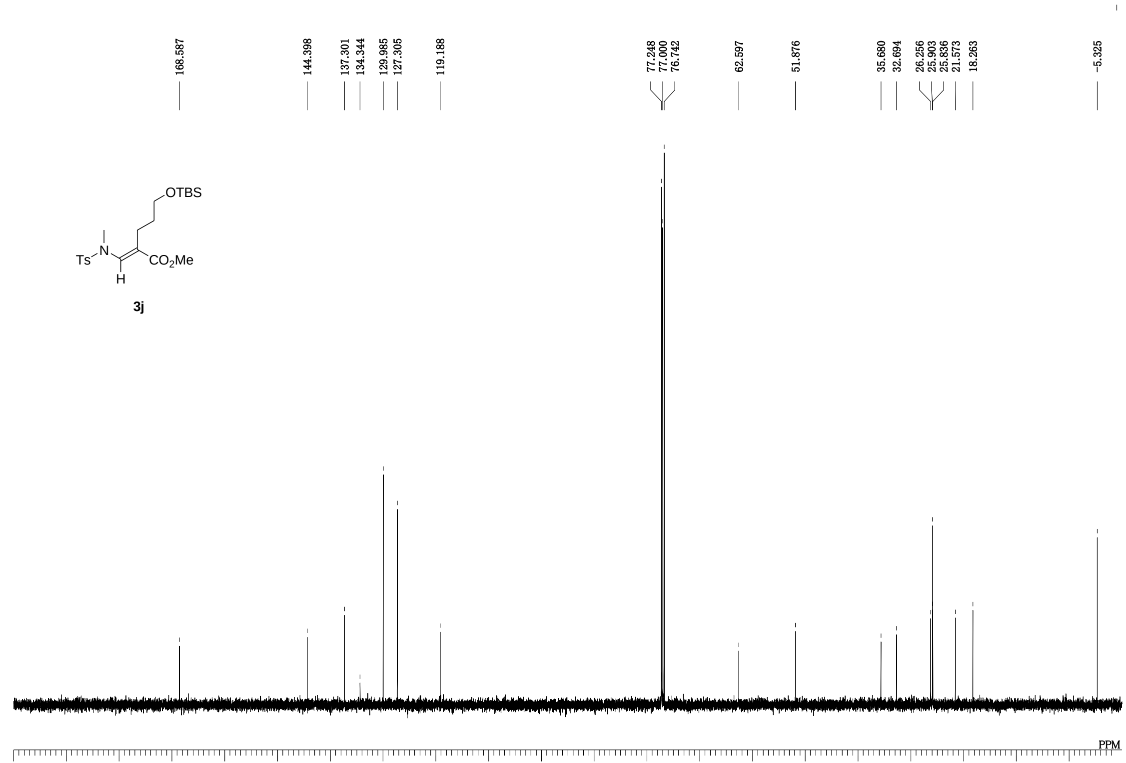
2j: ^{13}C NMR, CDCl$_3$, 125 MHz



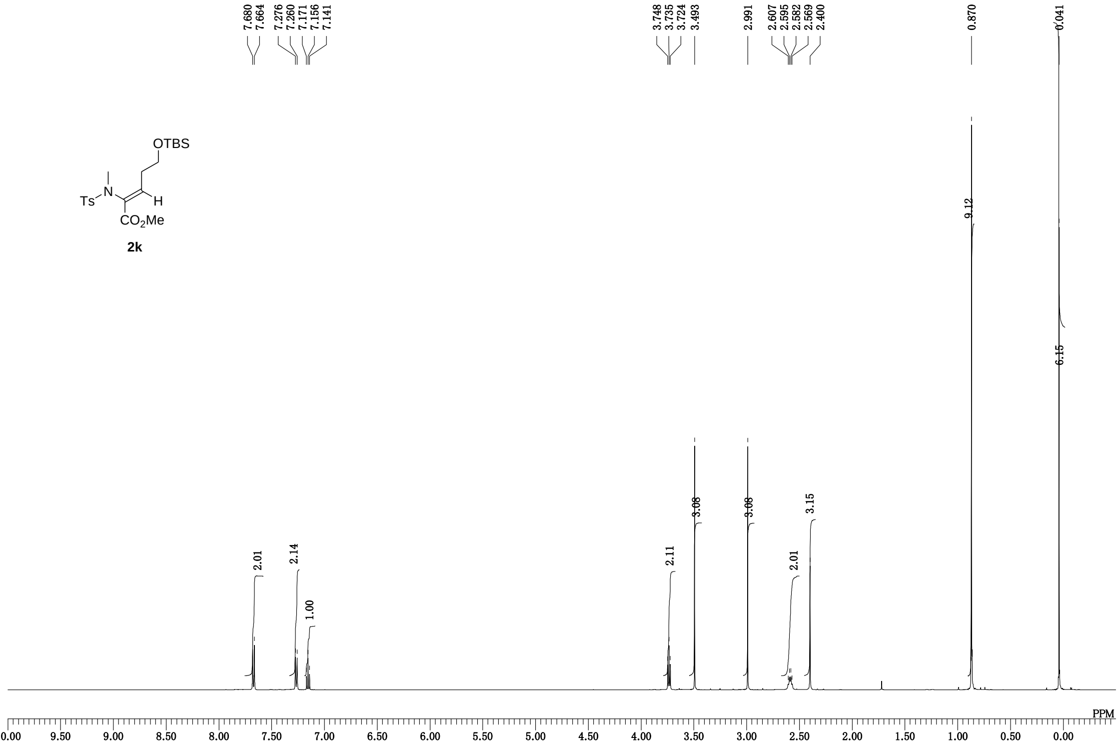
3j: ^{1}H NMR, $CDCl_3$, 500 MHz



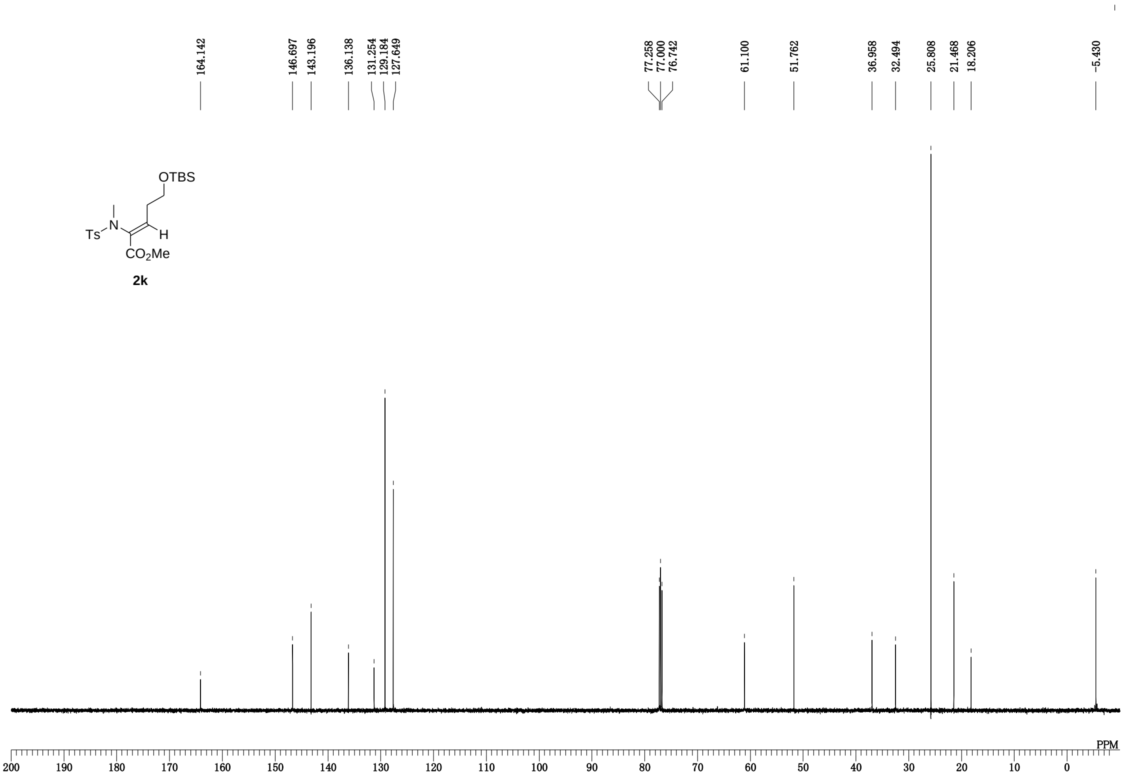
3j: ^{13}C NMR, $CDCl_3$, 125 MHz



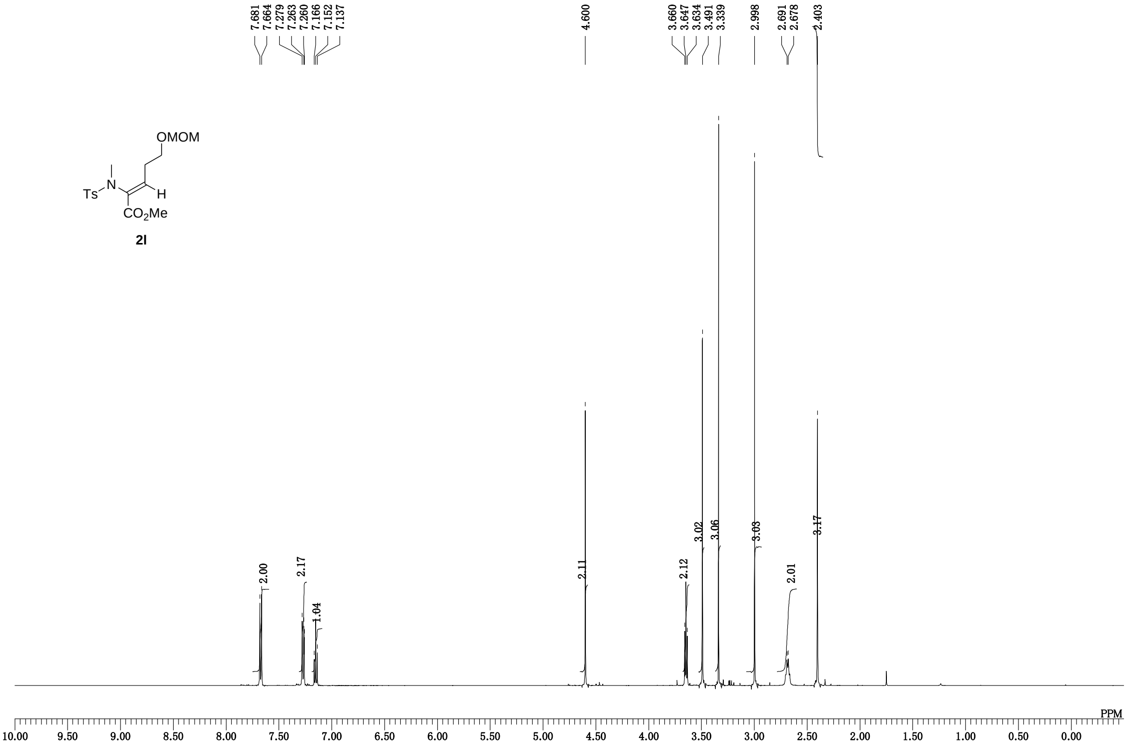
2k: ^{1}H NMR, CDCl$_3$, 500 MHz



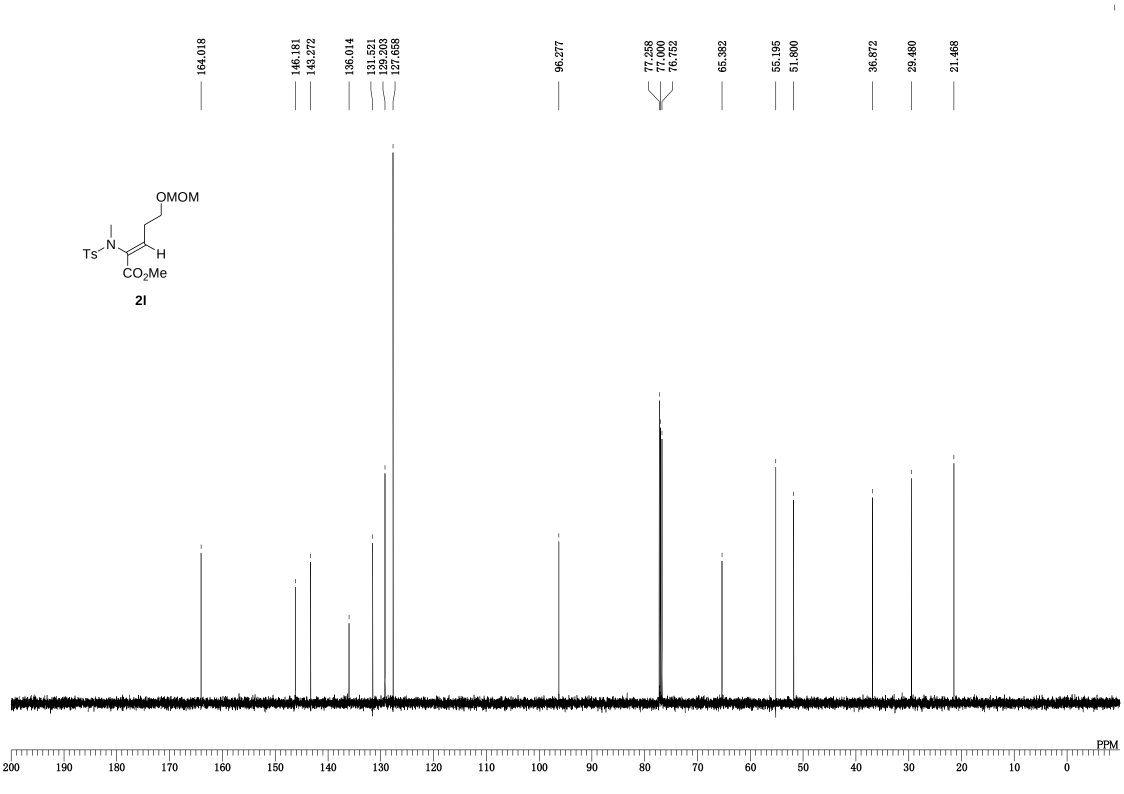
2k: ^{13}C NMR, CDCl$_3$, 125 MHz



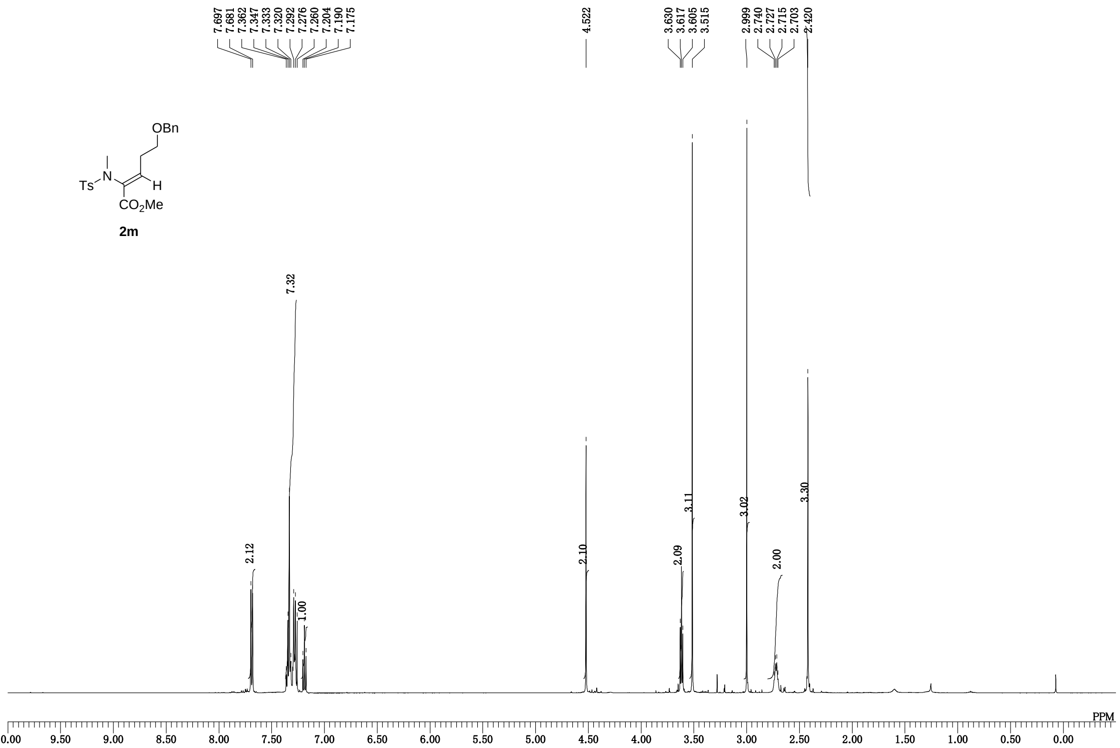
2l: ^{1}H NMR, $CDCl_3$, 500 MHz



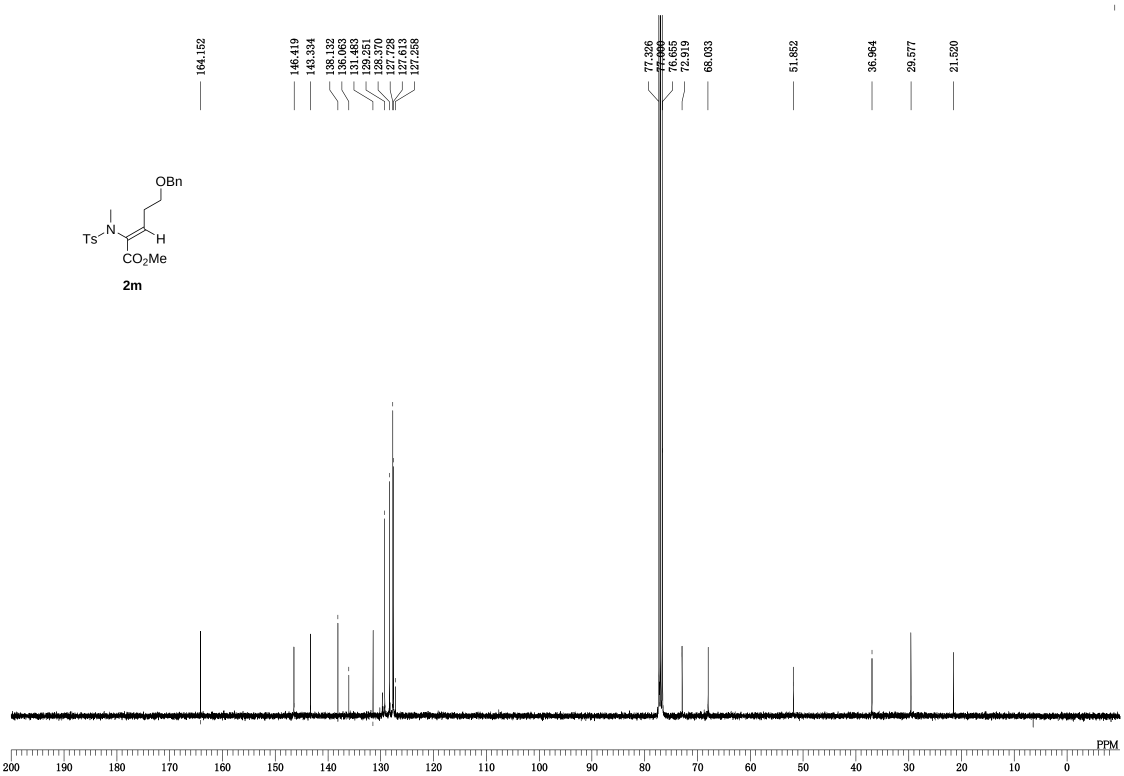
2l: ^{13}C NMR, $CDCl_3$, 125 MHz



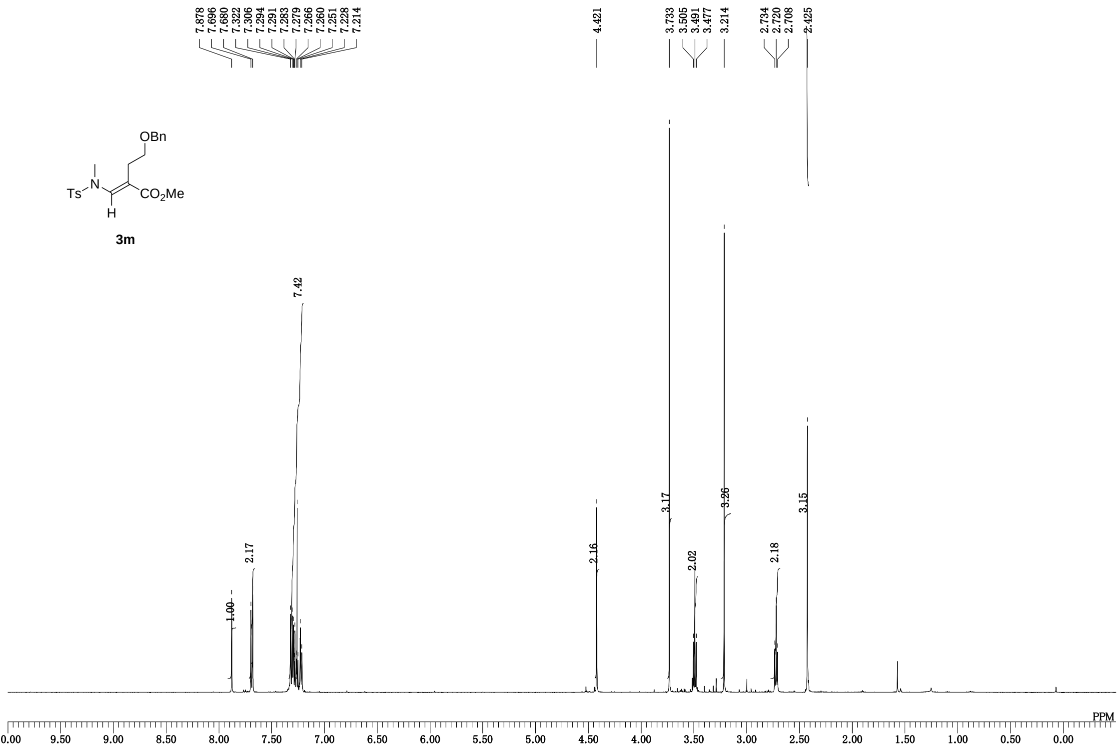
2m: ^{1}H NMR, $CDCl_3$, 500 MHz



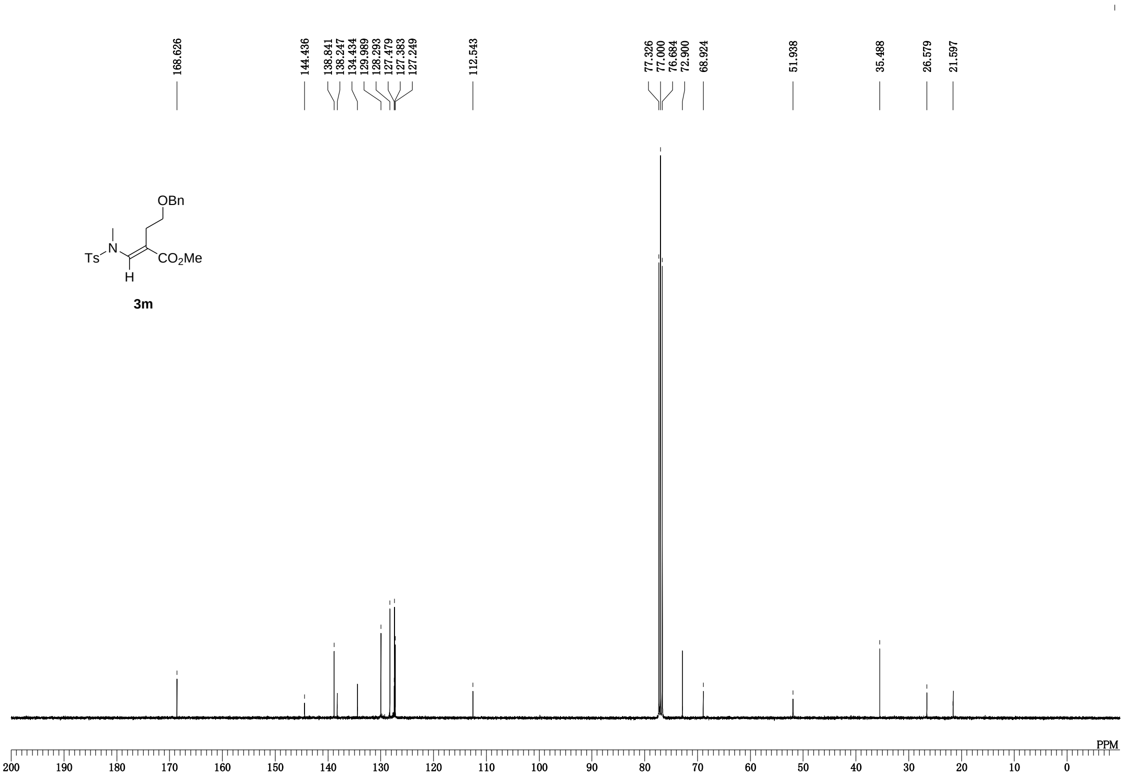
2m: ^{13}C NMR, $CDCl_3$, 125 MHz



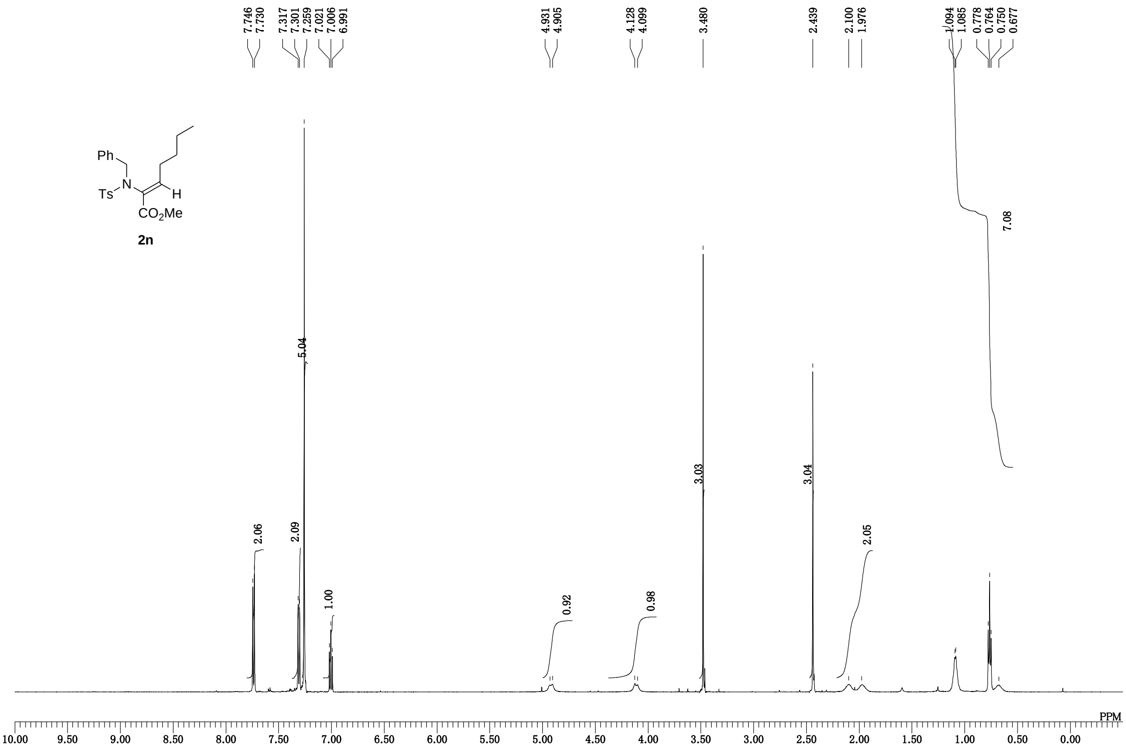
3m: ^{1}H NMR, CDCl$_3$, 500 MHz



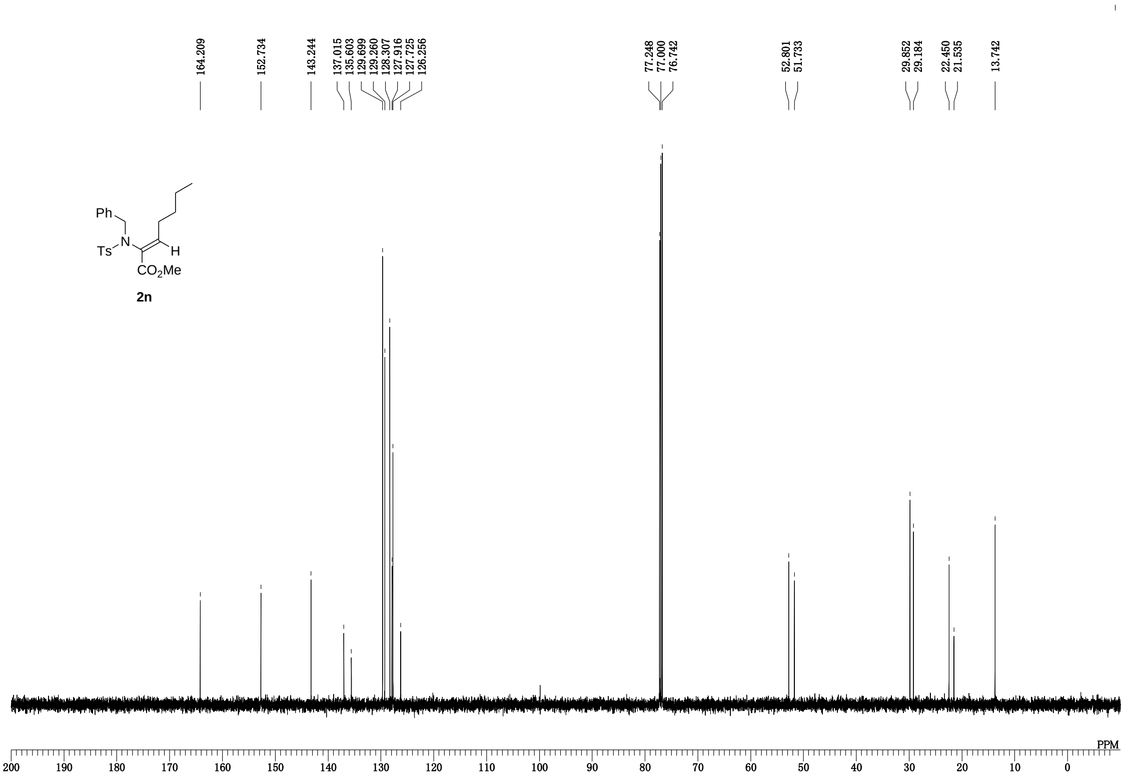
3m: ^{13}C NMR, CDCl$_3$, 125 MHz



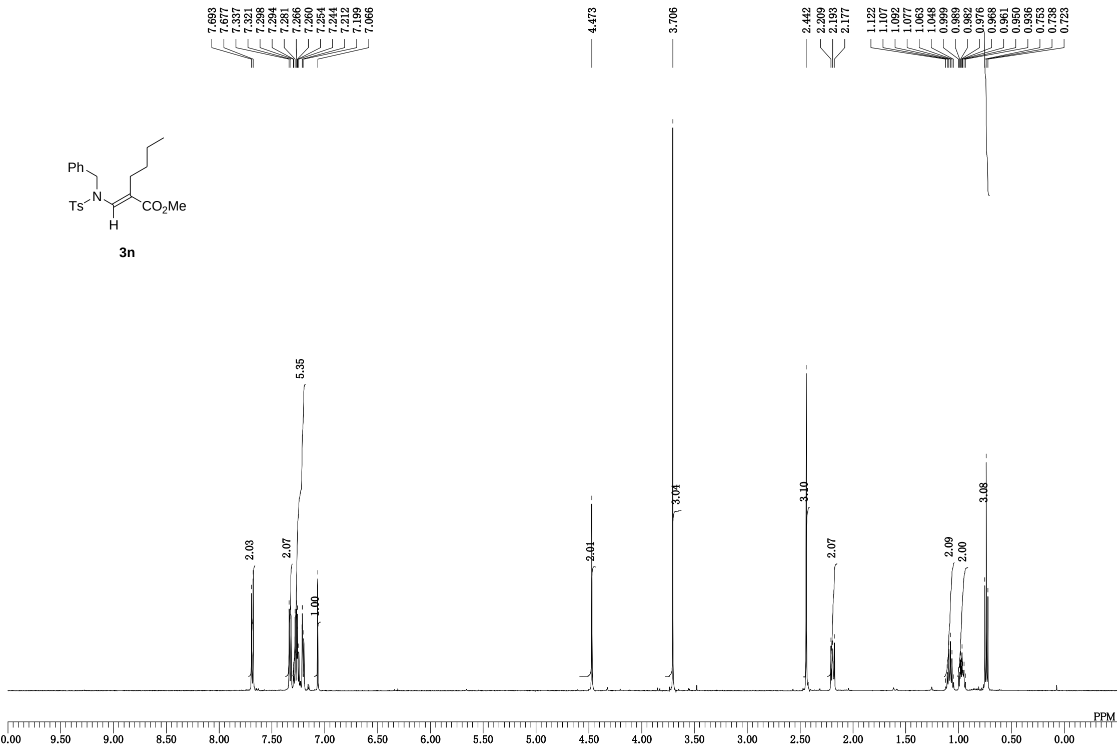
2n: ^{1}H NMR, $CDCl_3$, 500 MHz



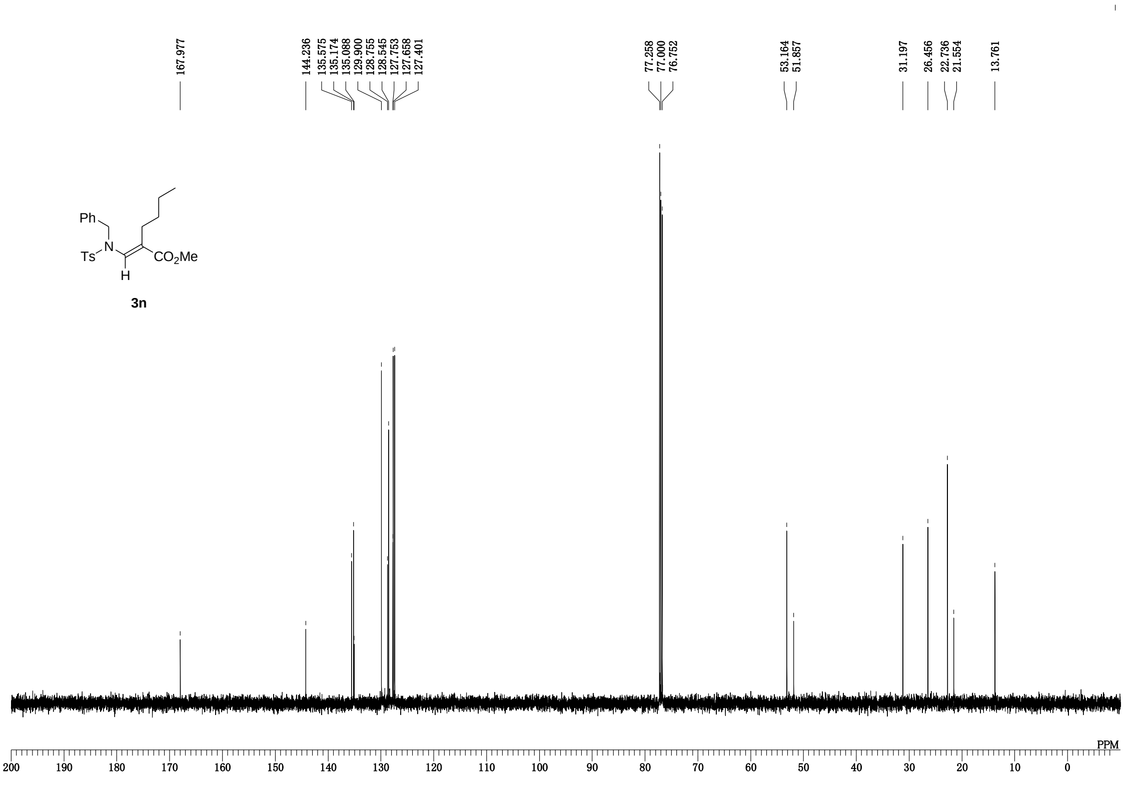
2n: ^{13}C NMR, $CDCl_3$, 125 MHz



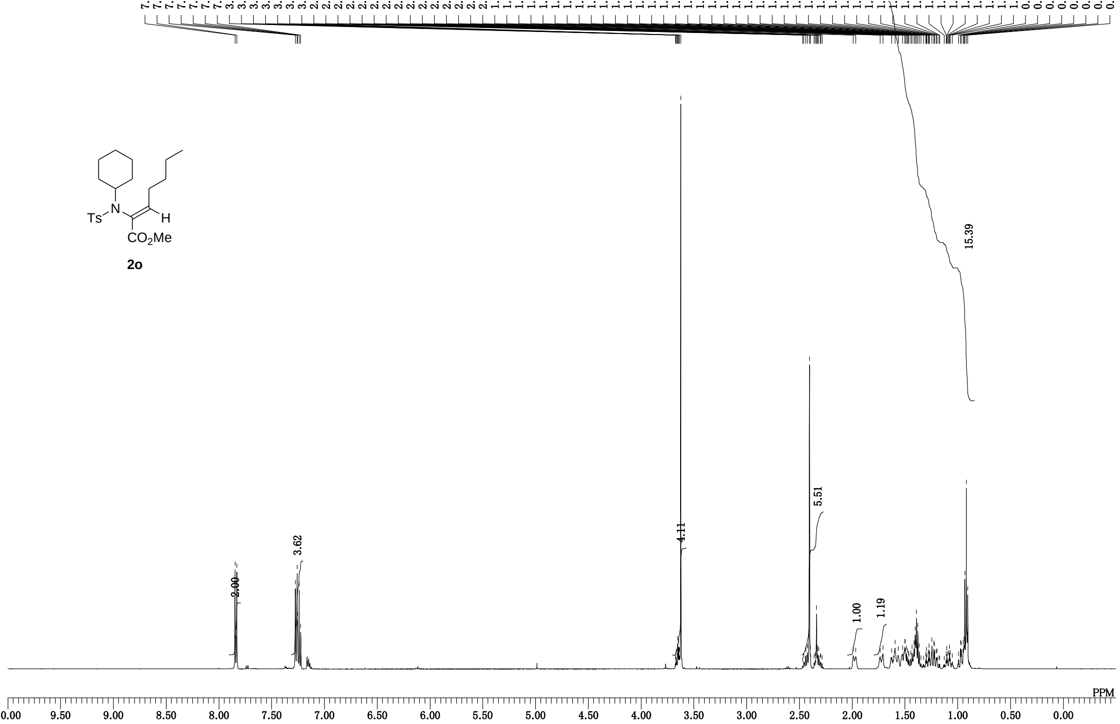
3n: ^{1}H NMR, CDCl$_3$, 500 MHz



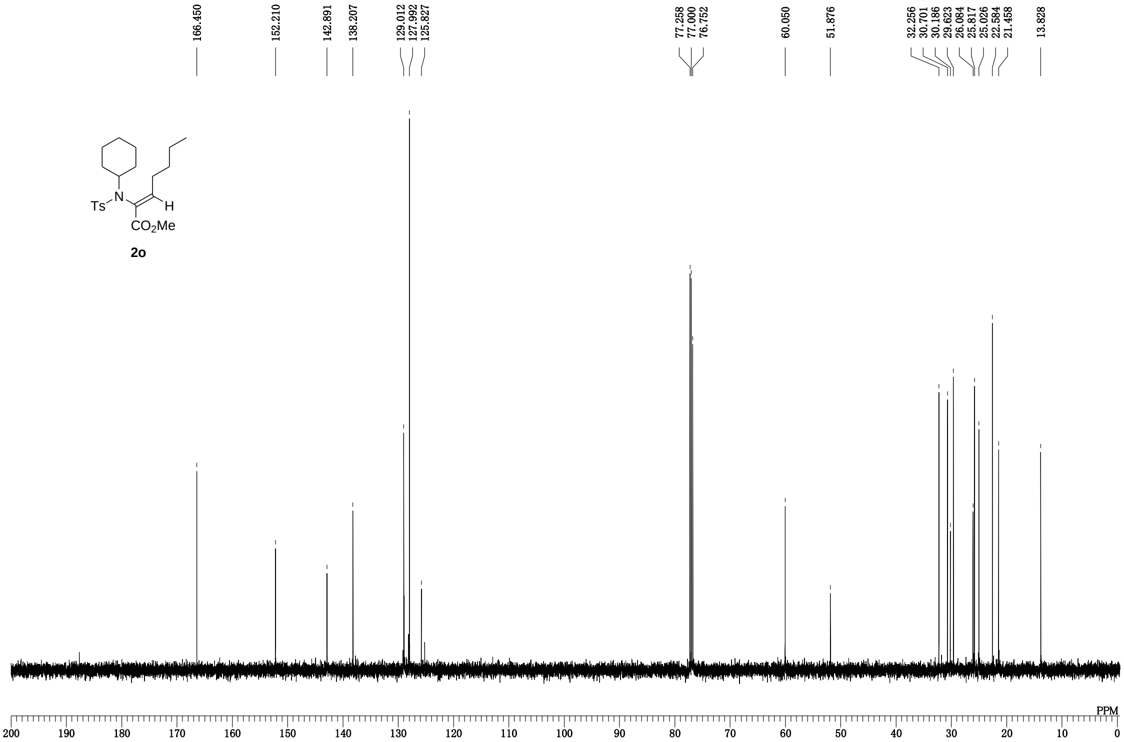
3n: ^{13}C NMR, CDCl$_3$, 125 MHz



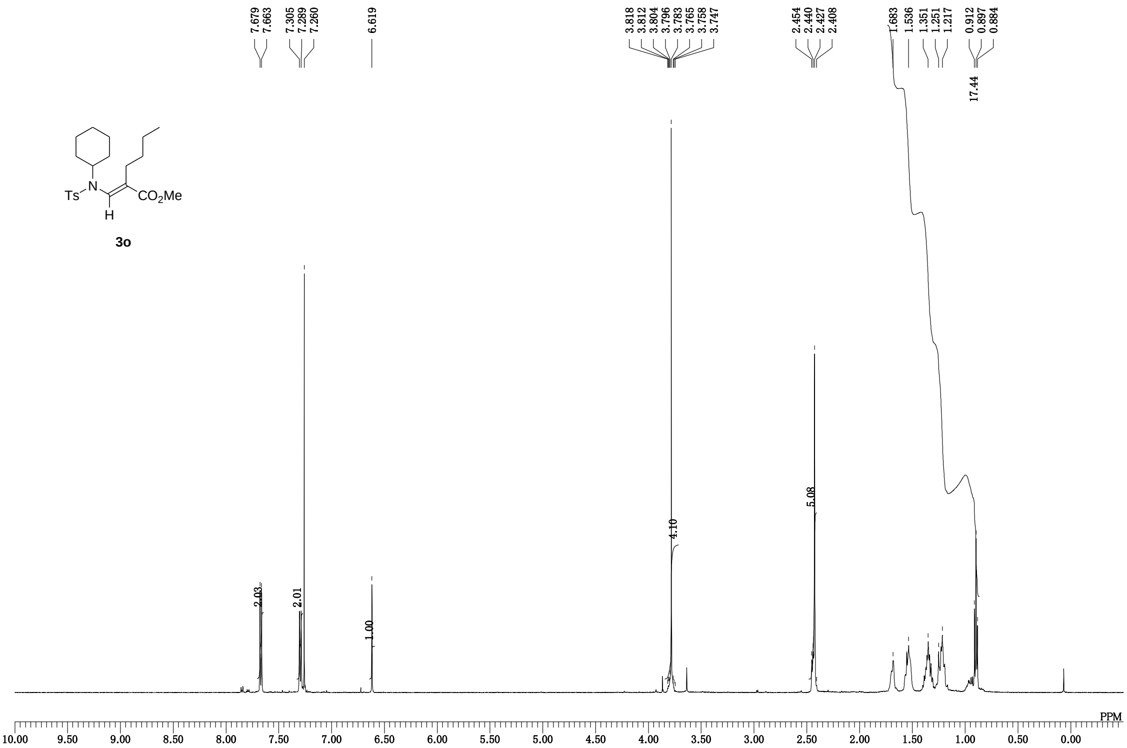
2o: ^{1}H NMR, CDCl$_3$, 500 MHz



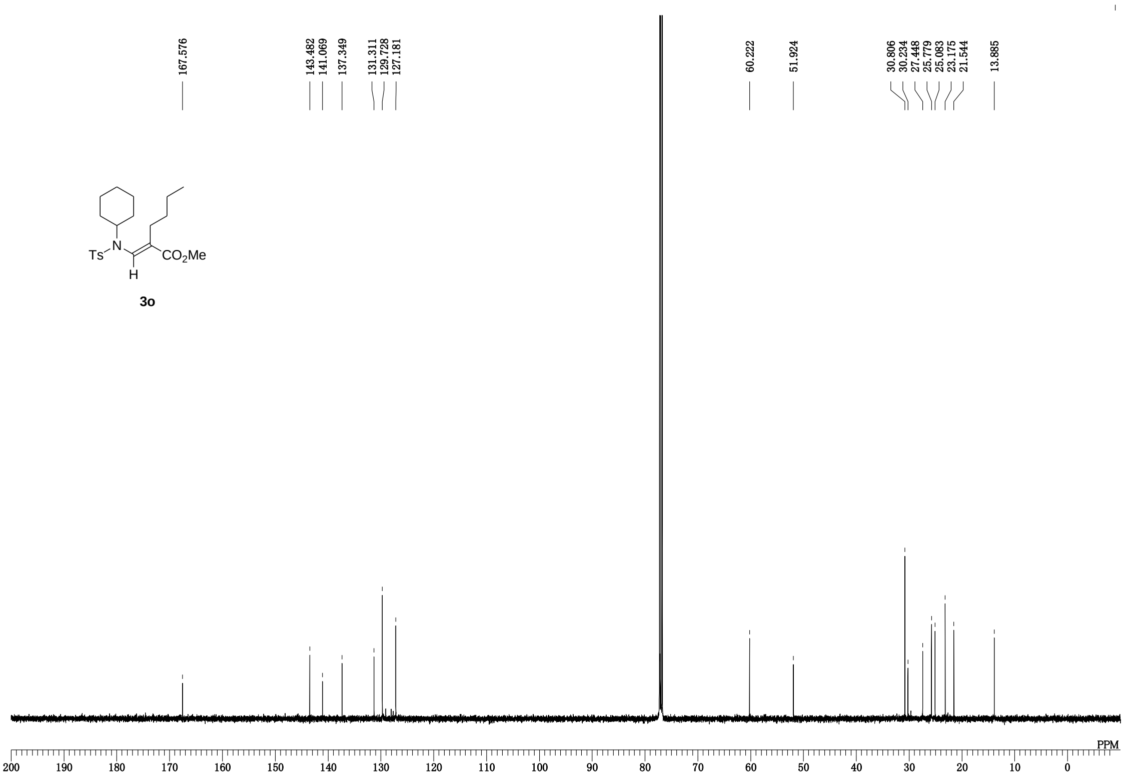
2o: ^{13}C NMR, CDCl$_3$, 125 MHz



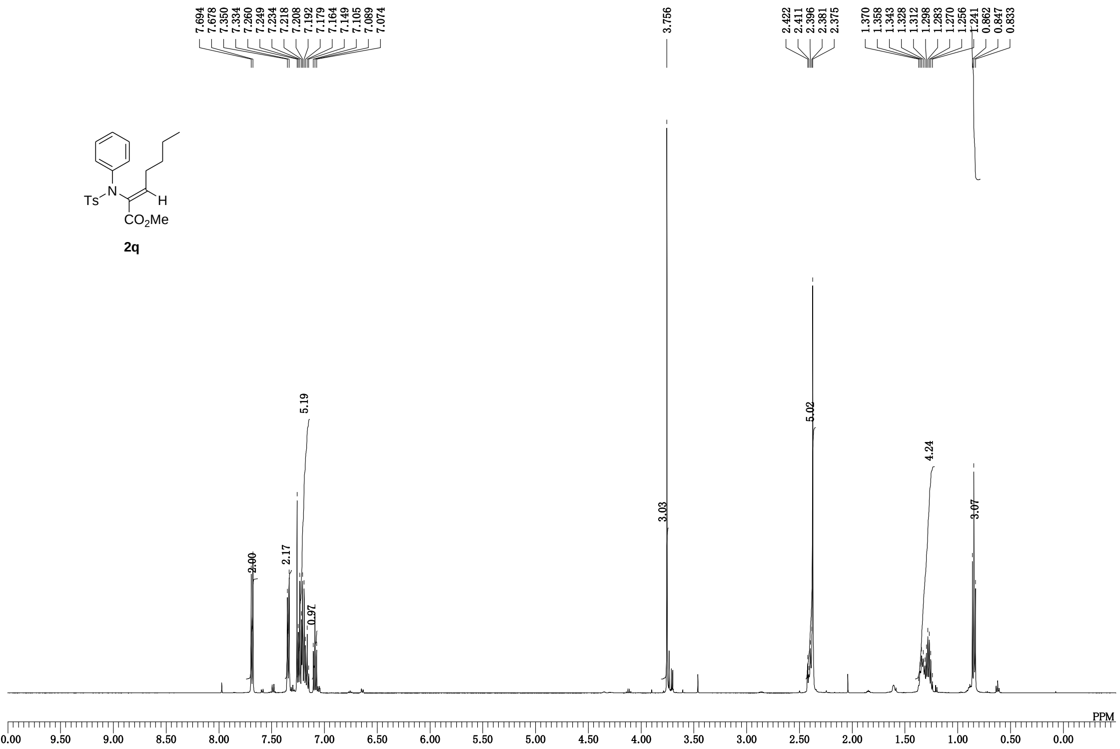
3o: ^{1}H NMR, $CDCl_3$, 500 MHz



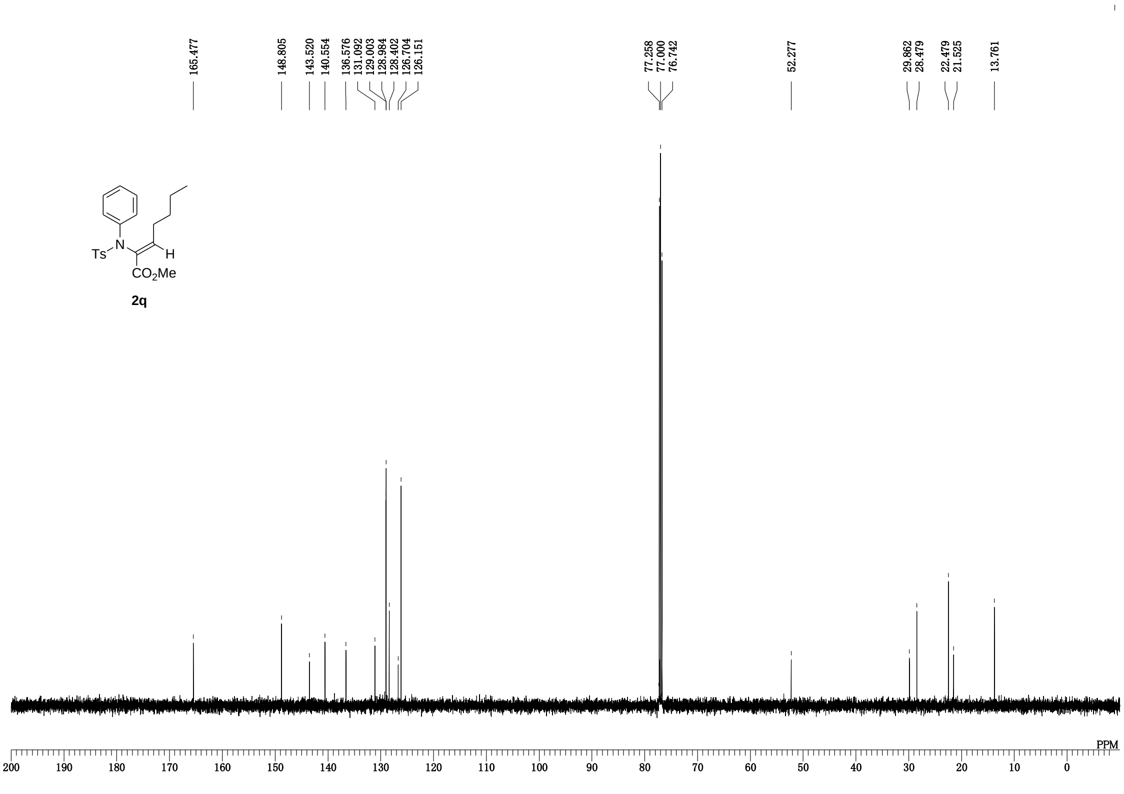
3o: ^{13}C NMR, $CDCl_3$, 125 MHz



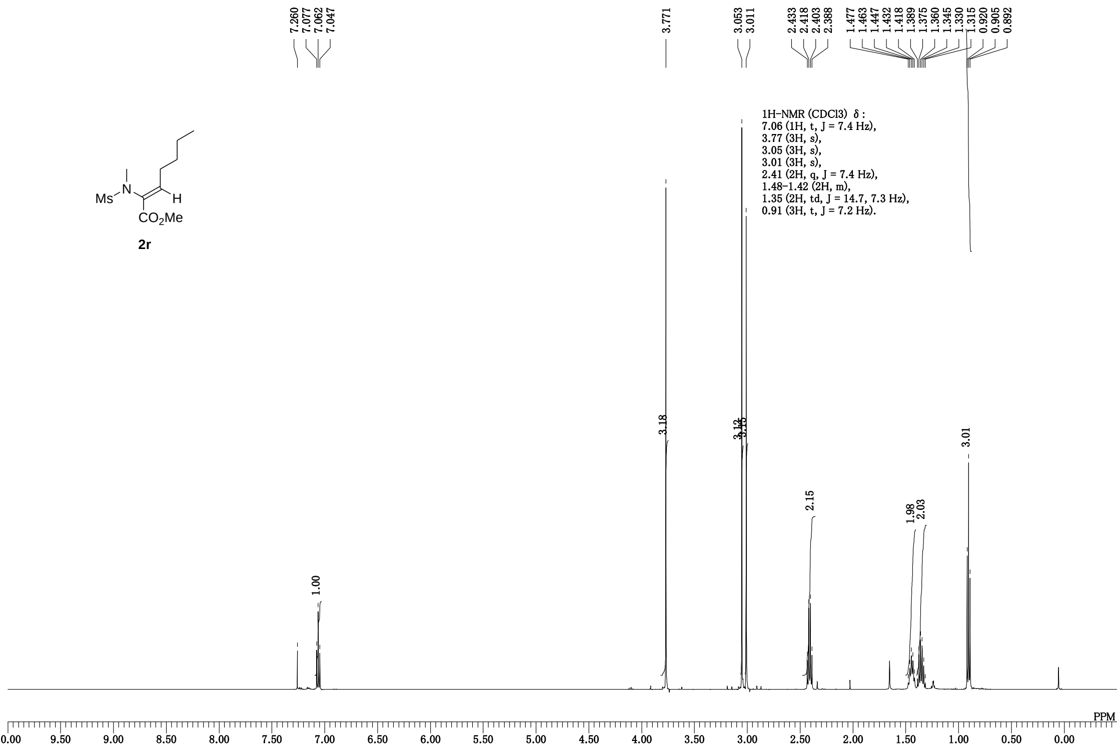
2q: ^{1}H NMR, $CDCl_3$, 500 MHz



2q: ^{13}C NMR, $CDCl_3$, 125 MHz

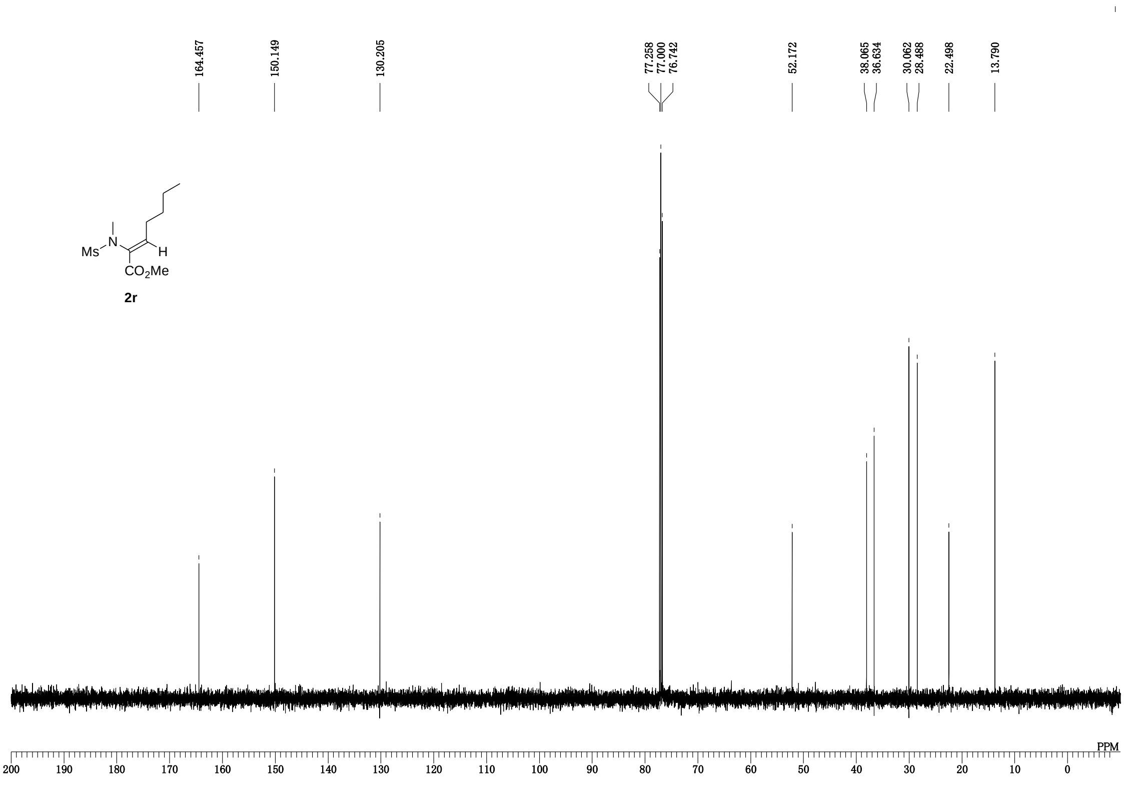


2r: ^{1}H NMR, CDCl$_3$, 500 MHz

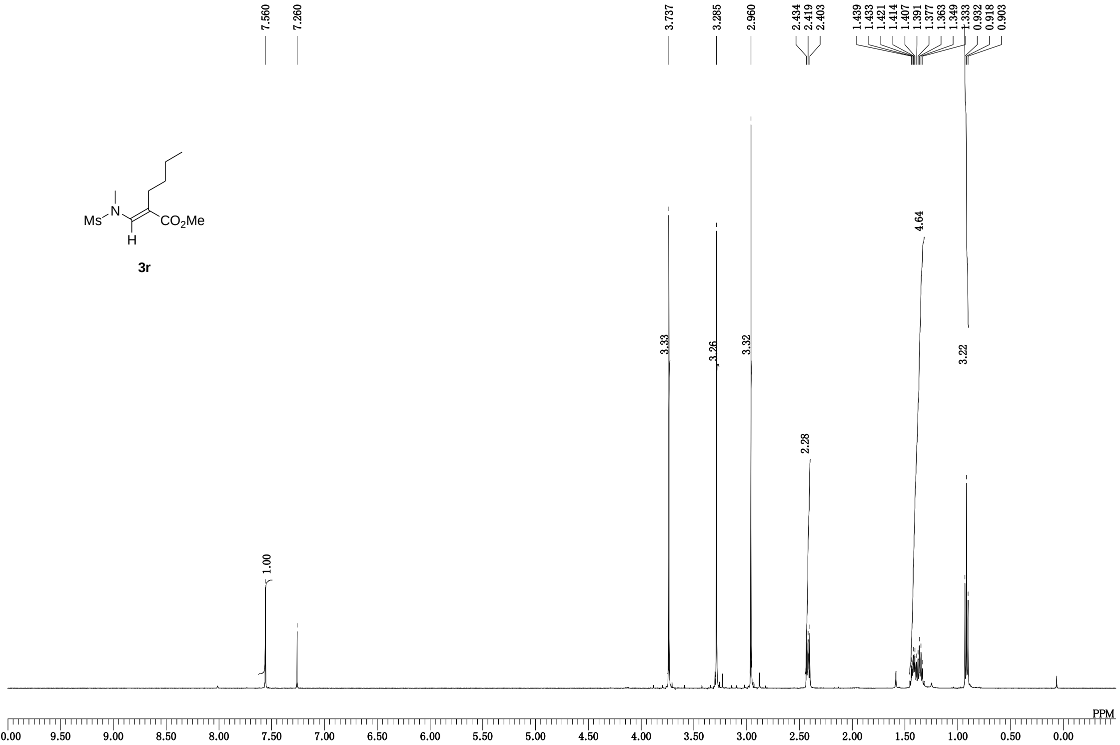


1H-NMR (CDCl3) δ :
7.06 (1H, t, J = 7.4 Hz),
3.77 (3H, s),
3.05 (3H, s),
3.01 (3H, s),
2.41 (2H, q, J = 7.4 Hz),
1.48–1.42 (2H, m),
1.35 (2H, td, J = 14.7, 7.3 Hz),
0.91 (3H, t, J = 7.2 Hz).

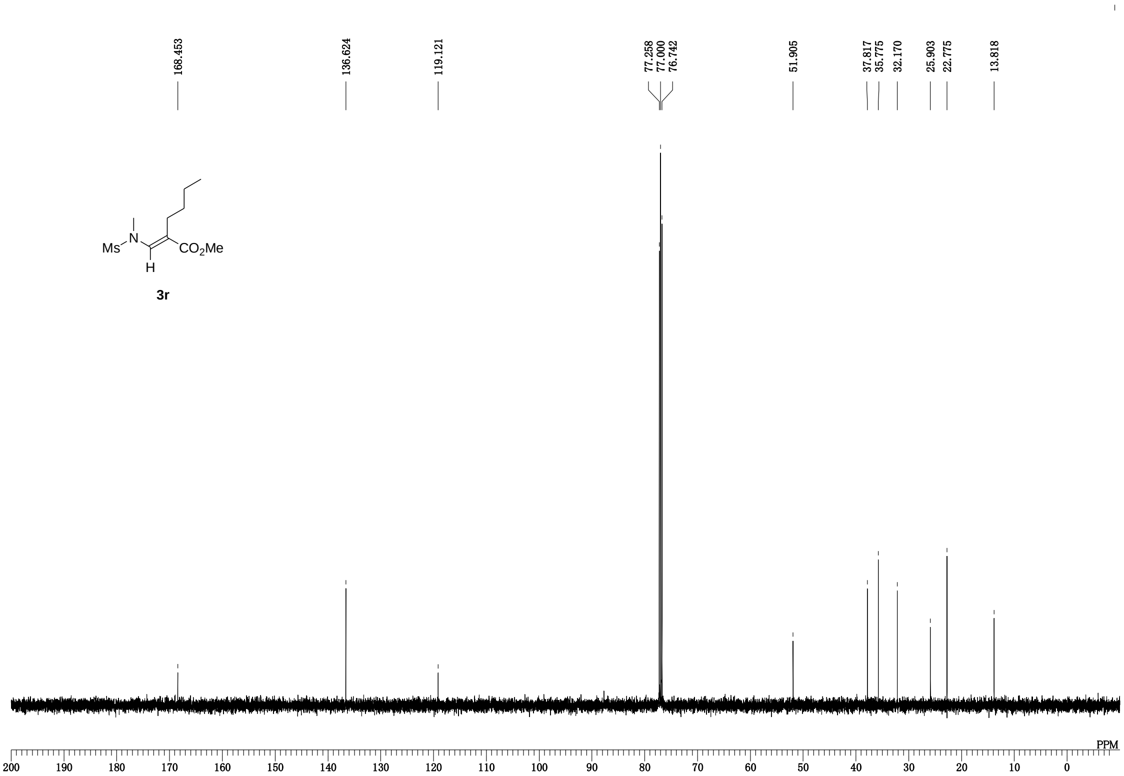
2r: ^{13}C NMR, CDCl$_3$, 125 MHz



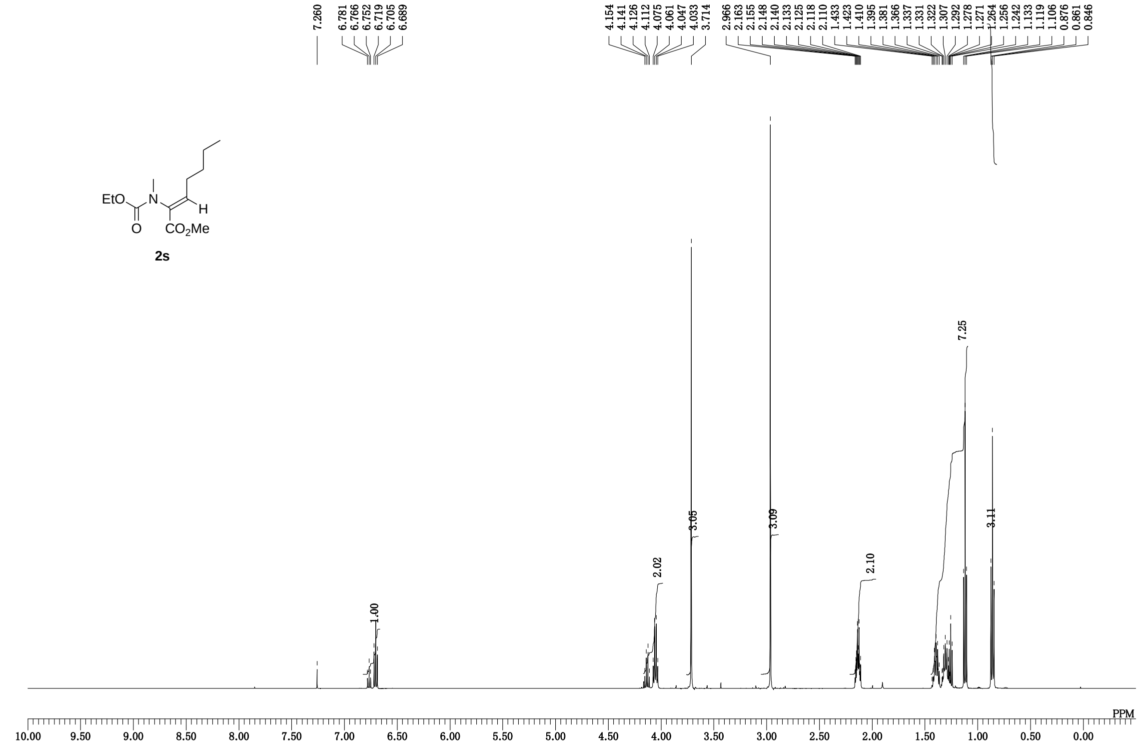
3r: ^{1}H NMR, CDCl$_3$, 500 MHz



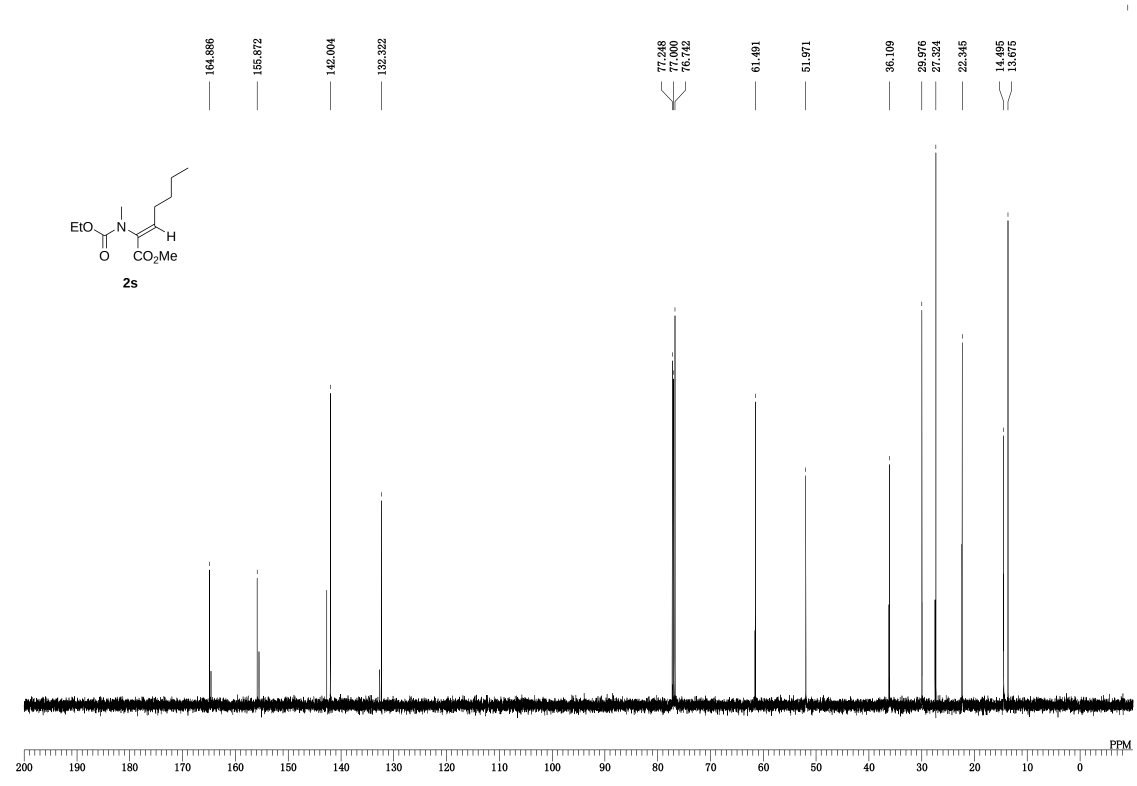
3r: ^{13}C NMR, CDCl$_3$, 125 MHz



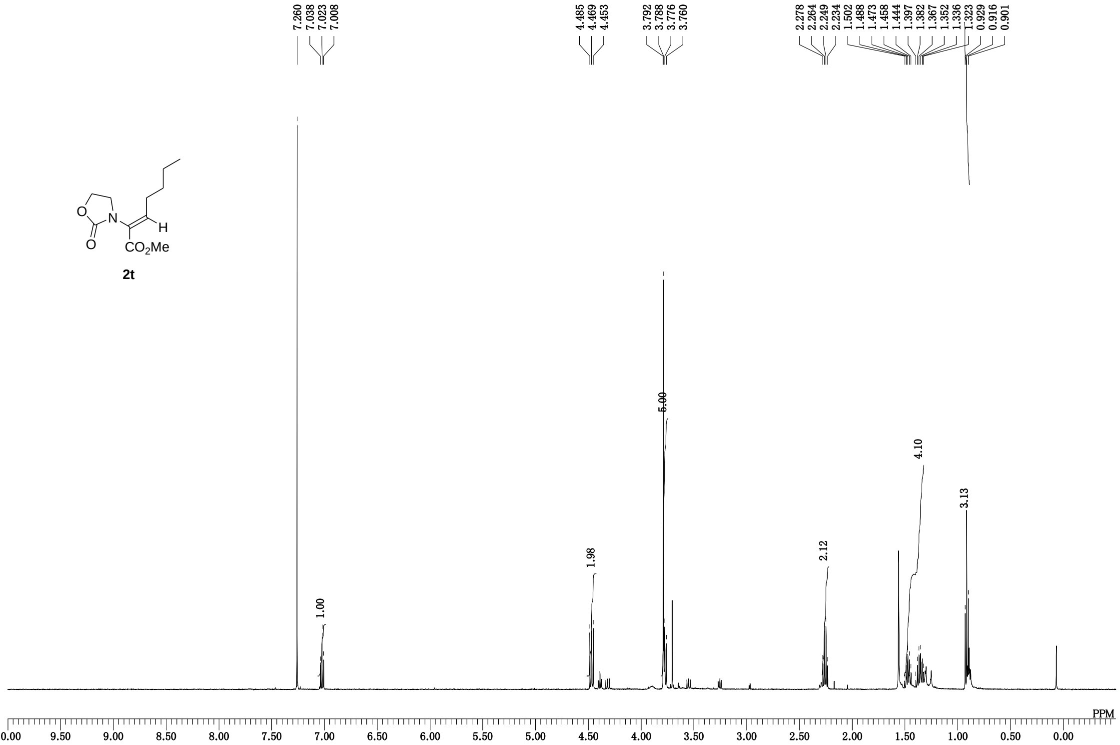
2s: ^{1}H NMR, CDCl$_3$, 500 MHz



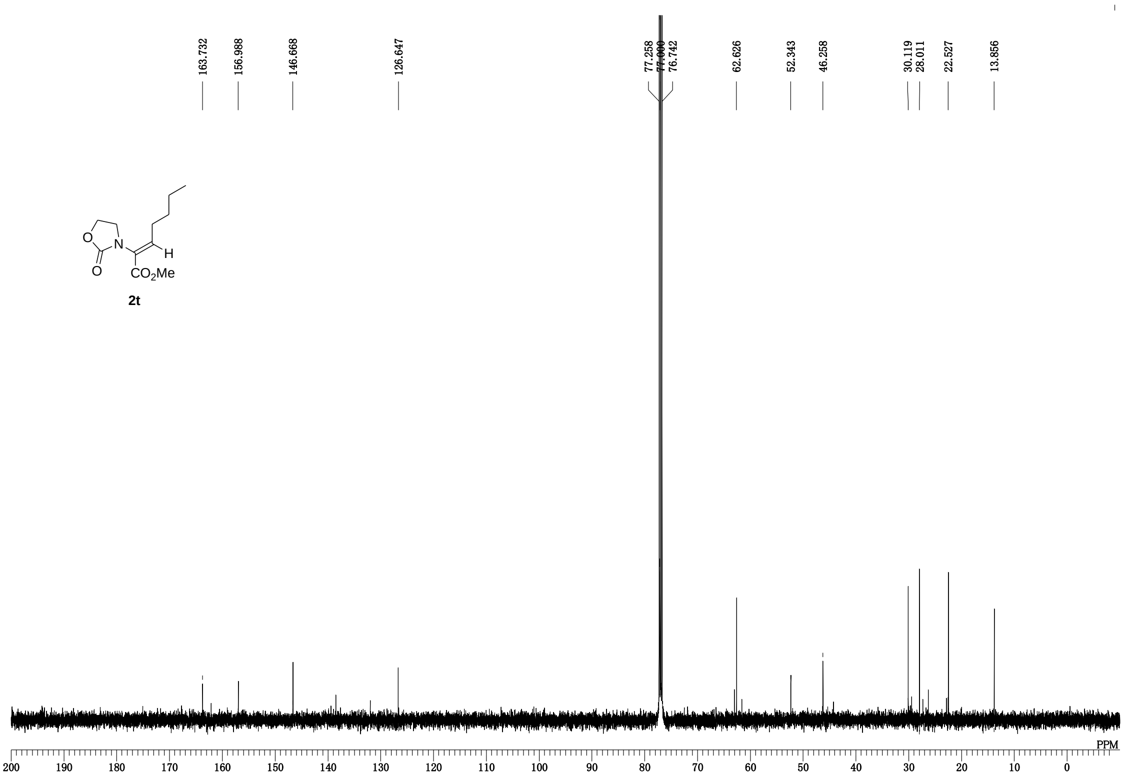
2s: ^{13}C NMR, CDCl$_3$, 125 MHz



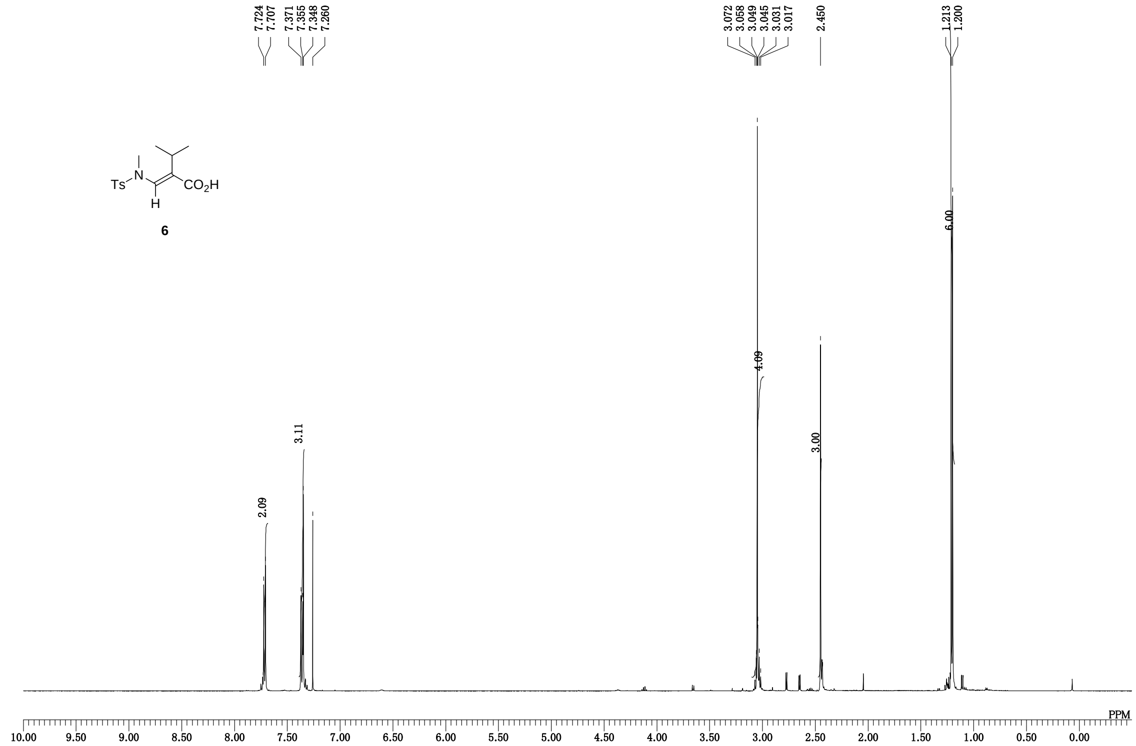
2t: ^{1}H NMR, CDCl$_3$, 500 MHz



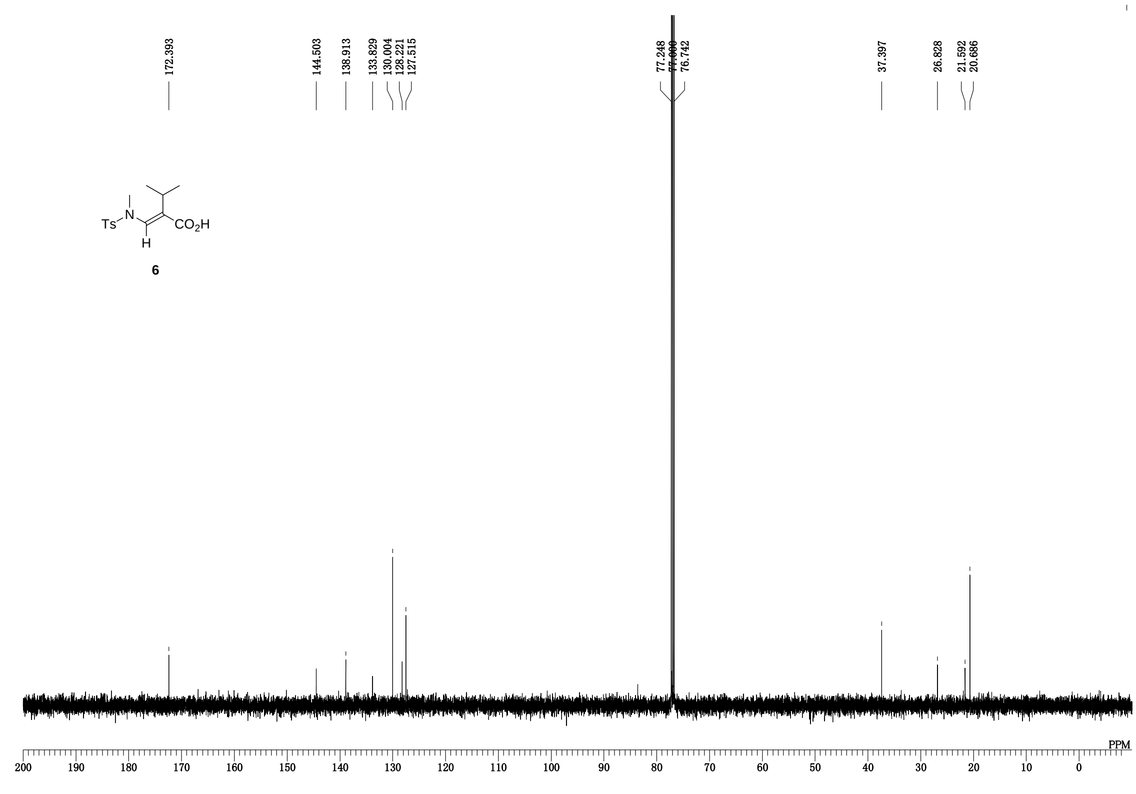
2t: ^{13}C NMR, CDCl$_3$, 125 MHz



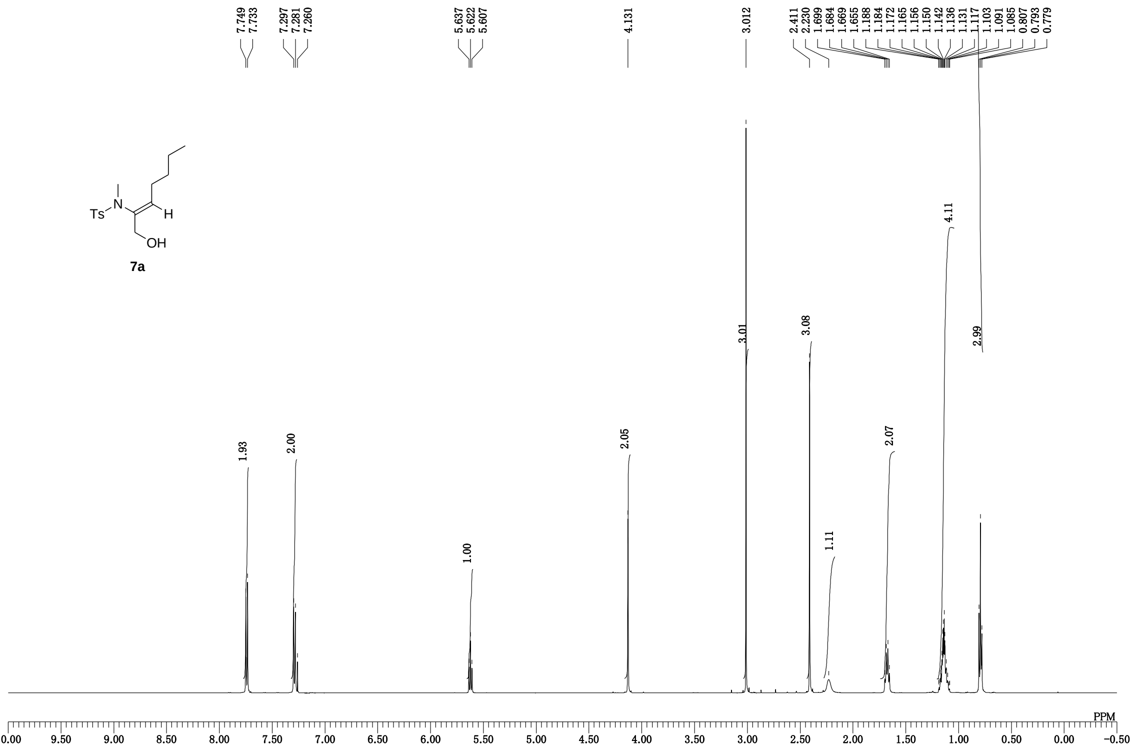
6: ^{1}H NMR, CDCl$_3$, 500 MHz



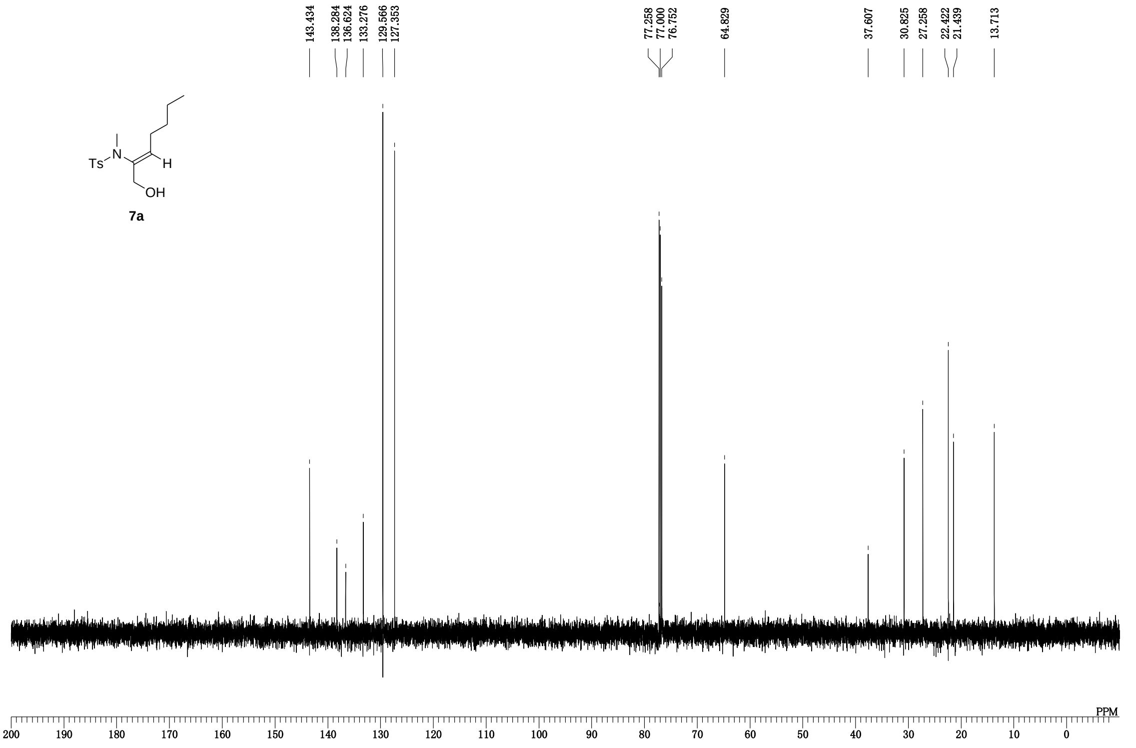
6: ^{13}C NMR, CDCl$_3$, 125 MHz



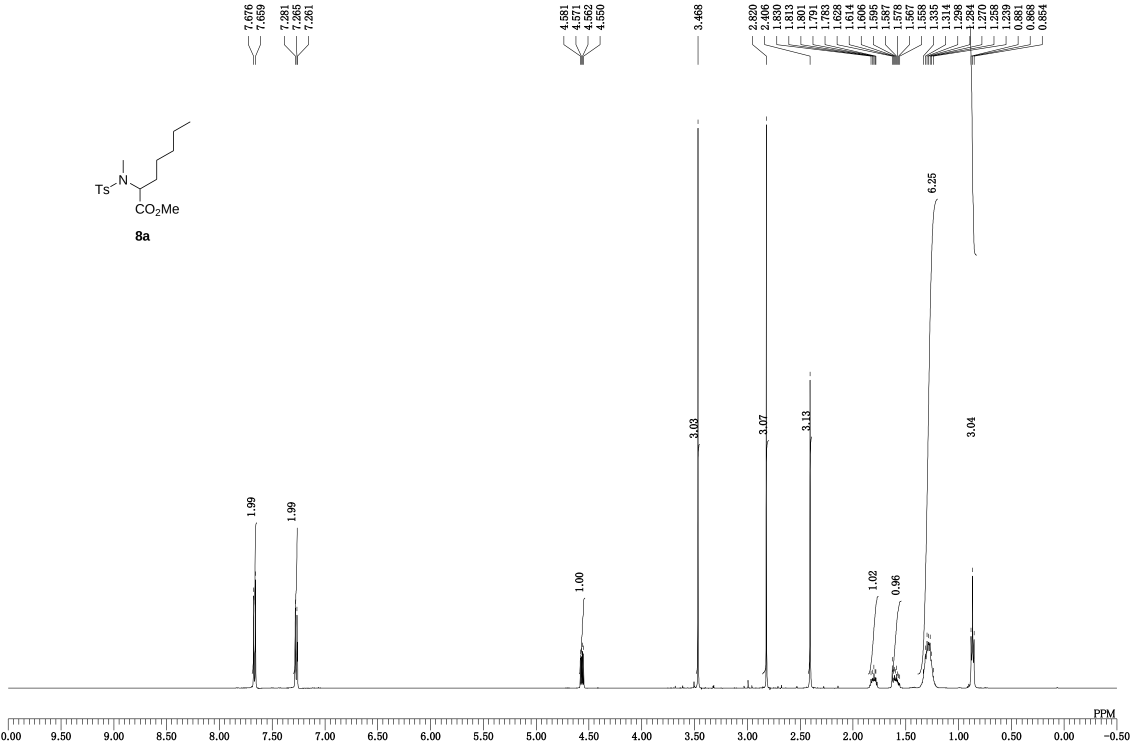
7a: ^{1}H NMR, CDCl$_3$, 500 MHz



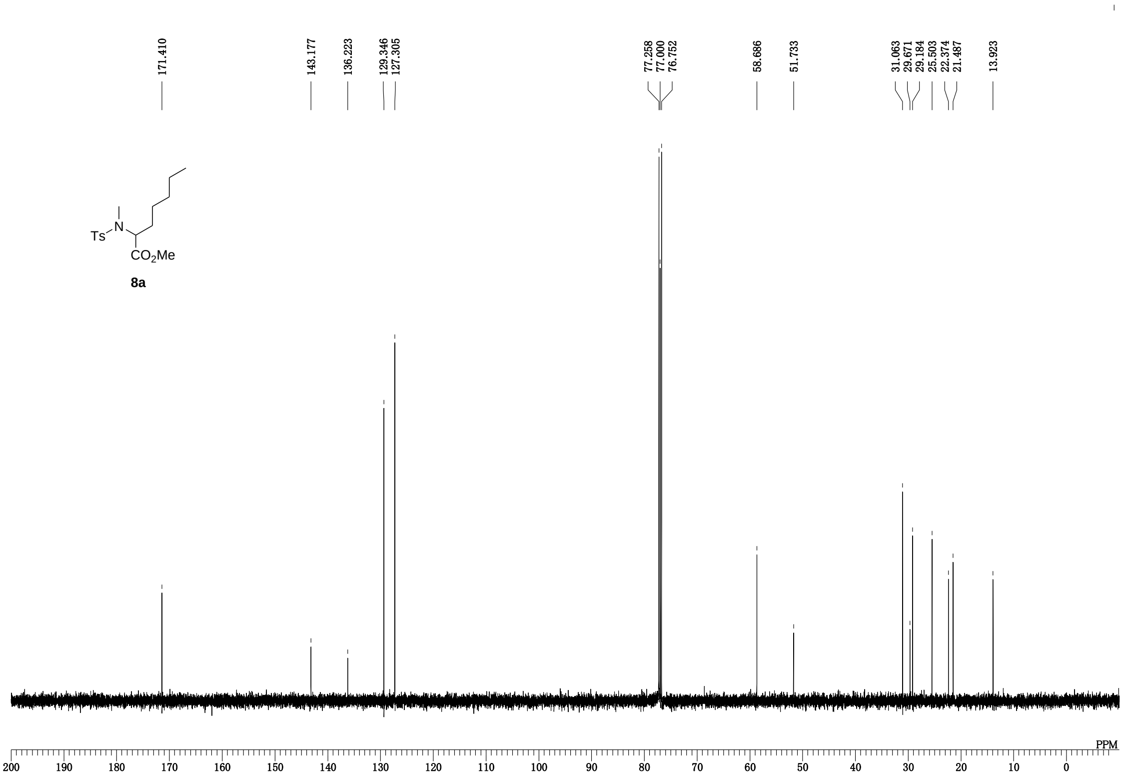
7a: ^{13}C NMR, CDCl$_3$, 125 MHz



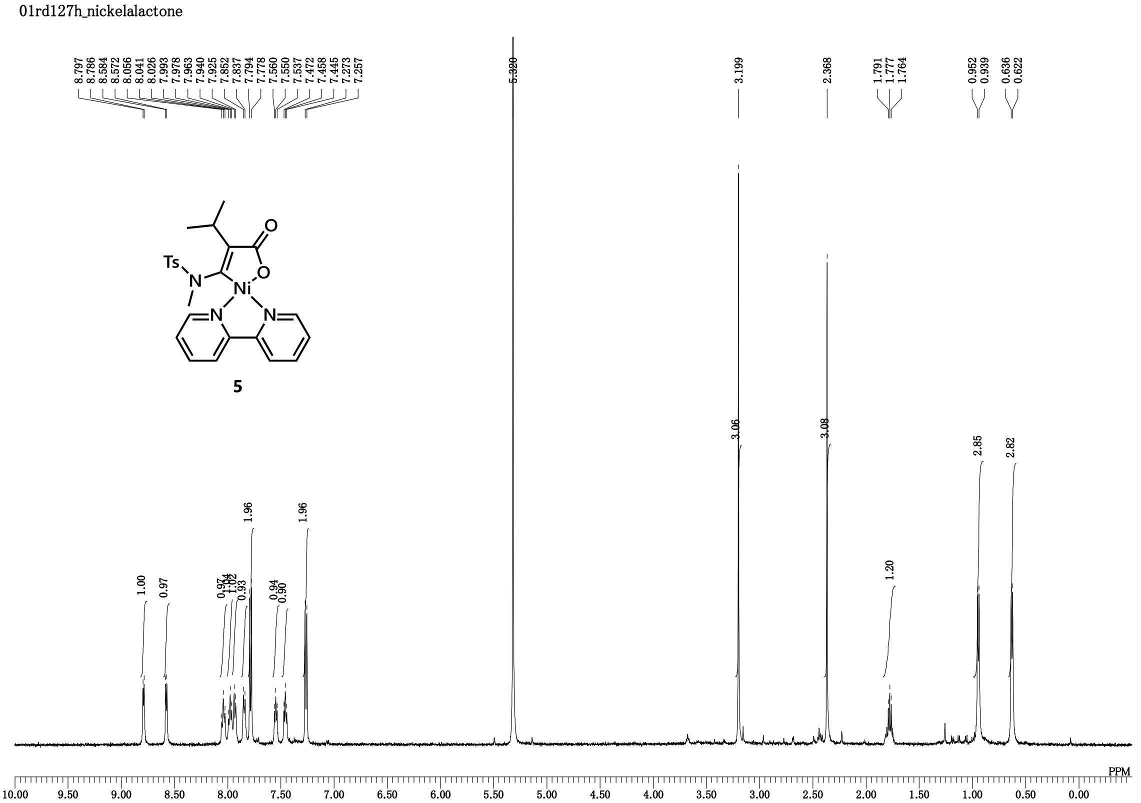
8a: ^{1}H NMR, CDCl$_3$, 500 MHz



8a: ^{13}C NMR, CDCl$_3$, 125 MHz



5: ^{1}H NMR, CD_2Cl_2, 500 MHz



5: ^{13}C NMR, CD_2Cl_2, 125 MHz