Electronic Supplementary Information

Synthesis of α-(aminoethyl)-α,β-enones via alkyne aza-Prins cyclization and their synthetic application to pyrrolidines

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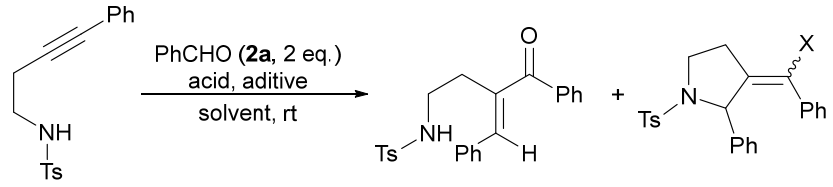
Table of contents

Examination for Synthesis of α-(Aminoethyl)-α,β-Enones

Table S1. Screening of acids, additives and solvents for synthesis of enones **3aa** from **1a** and **2a**.



1a **3aa** **4** (X = OTf) **4-X** (X = F, Cl, I, OTs)

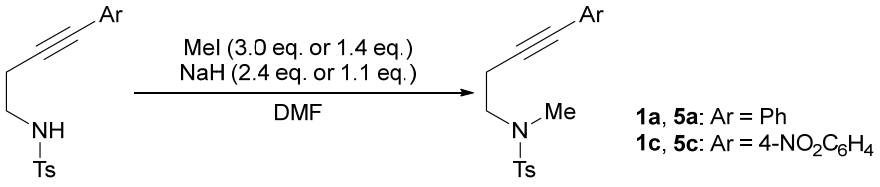
Entry	Acid (eq.)	Additive (eq.)	Solvent	*t* (h)	**3aa**[a] (%)	**4 or 4-X**[a] (%)		(*E*:*Z*)	**1a**[a] (%)
1	HOTf (2)	-	DCM	24	65	**4**	14	100:0	0
2	HOTf (3)	$(Me_2AlO)_2SO_2$ (0.5)	DCM	24	75	**4**	5	100:0	0
3	$HBF_4{\cdot}OEt_2$ (2)	-	DCM	16	81	**4-F**	0	-	0
4	$BF_3{\cdot}OEt_2$ (2)	-	DCM	16	47	**4-F**	0	-	25
5	$BF_3{\cdot}$MeCN (2)	-	DCM	16	79	**4-F**	0	-	0
6	$FeCl_3$ (2)	-	DCM	24	29	**4-Cl**	ND[b]	ND[b]	0
7	$FeCl_3$ (1)		DCE	6[c]	36	**4-Cl**	8	100:0	0
8	I_2 (2)	CuI (0.4)	DCM	16	0	**4-I**	0	-	0
9	$Fe(OTf)_3$ (0.1)	-	DCE	24[d]	1	**4**	0	-	41
10	$Cu(OTf)_2$ (0.1)	-	DCE	24[d]	0	**4**	0	-	11
11	$TsOH{\cdot}H_2O$ (1)	$MgBr_2{\cdot}OEt_2$ (1)	DCM	24	0	**4-OTs**	ND[b]	-	44
12	$TsOH{\cdot}H_2O$ (2)	$MgBr_2{\cdot}OEt_2$ (2)	DCM	24	0	**4-OTs**	ND[b]	-	6
13	TMSOTf (2)	-	DCM	16	60	**4**	11	100:0	0
14	TMSOTf (2)	-	MeOH	24	0	**4**	0	-	84
15	TMSOTf (2)	MeOH (2)	DCM	16	51	**4**	20	80:20	0
16	TMSOTf (2)	AcOH (2)	DCM	16	55	**4**	21	81:19	0
17	TMSOTf (2)	-	AcOEt	16	49	**4**	21	81:19	0
18	TMSOTf (2)	-	Et_2O	16	43	**4**	29	72:28	0
19	TMSOTf (2)	Et_3N (2)	Et_2O	24	36	**4**	21	62:38	16
20	TMSOTf (2)	-	CPME	16	47	**4**	21	62:38	8
21	TMSOTf (2)	-	DME	16	67	**4**	10	60:40	0
22	TMSOTf (2)	-	MeCN	16	81	**4**	0	-	1
23	TMSOTf (2)	-	MeCN	22	81	**4**	0	-	0
24	HOTf (2)	-	MeCN	24	75	**4**	0	-	0
25	CF_3COOH (2)	-	MeCN	24	0	**4**	0	-	69
26	TMSOTf (0.2)	-	MeCN	24	0	**4**	0	-	79
27	TMSOTf (0.2)	-	MeCN	24[d]	0	**4**	0	-	15
28	TMSOTf (0.2)	MeCN (62)	DCE	24[d]	0	**4**	0	-	0
29	$BF_3{\cdot}$MeCN (0.2)	-	DCE	24[d]	0	**4-F**	0	-	5
30	TMSOTf (5)	-	MeCN	24[e]	46	**4**	0	-	15

DCM: dichloromethane. DCE: 1,2-dichloroethane. CPME: cyclopentyl methyl ether. DME: 1,2-dimethoxyethane.
[a] Isolated yields or recovery. [b] Not determined. [c] Conditions: rt for 2 h and then 80 ºC for 4 h. [d] Temp.: 80 ºC.
[e] Temp.: -40 ºC.

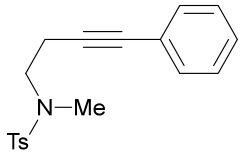
General Information

All reactions were carried out under an argon atmosphere. *N*-(4-Arylhomopropargyl) tosylamides **1a-c**[1] and aza-Prins cyclized product **4**[2] were prepared by the method reported in the literatures. Triflic acid (HOTf), trimethylsilyl trifluoromethanesulfonate (TMSOTf), BF_3·MeCN, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and aldehydes **2a-m** are commercially available. Dichloromethane (DCM) and MeCN were purchased as the "anhydrous" and used without further purification. For the TLC analysis, Merck precoated TLC plates (silica gel 60 F254) were used. Column chromatography was performed on silica gel 60N (63-200 μm, neutral, Kanto Kagaku Co., Ltd.). Medium-pressure liquid chromatography (MPLC) was carried out on YAMAZEN W-Prep 2XY. ^{1}H and ^{13}C NMR spectra were measured at 500 (or 300) and 125 (or 75) MHz in $CDCl_3$, and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for 1H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard, respectively. Splitting patterns of an apparent multiplet associated with an averaged coupling constant were designed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened). IR spectra were obtained on a JASCO FT/IR-6200. Mass spectra and HRMS were recorded on a JEOL MStation MS700 (double-focusing magnetic sector) by FAB methods.

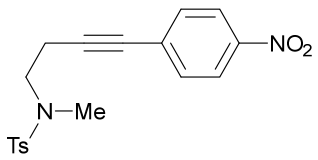
Synthesis and Characterization of N-(4-Arylhomopropargyl)-N-methyl Tosylamides 5a and 5c



To a solution of **1a** (898.2 mg, 3.0 mmol) and NaH (60 w/w% in oil, 288.0 mg, 7.2 mmol) in DMF (15 mL) was added methyl iodide (0.56 mL, 9.0 mmol) at 0 ºC. After being stirred at room tempreture for 3 h, the reaction mixture was quenched with NH_4Cl aq. and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to dryness. The residue was purified by silica gel column chromatography (hexane:AcOEt = 5:1) to give **5a** (754.0 mg, 80%). In the similar manner, **5c** (584.1 mg, 72%) were prepared from **1c** (799.5 mg, 2.3 mmol) using NaH (60 w/w% in oil, 104.0 mg, 2.6 mmol) and methyl iodide (0.20 mL, 3.2 mmol) in DMF (10 mL).



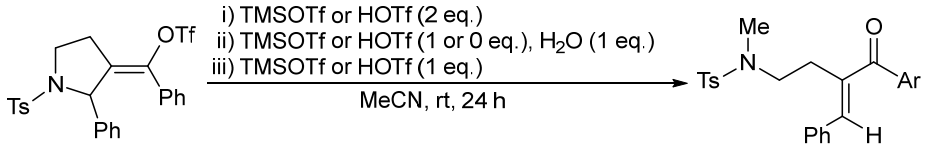
***N*,4-Dimethyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (5a)**: R_f = 0.43 (hexane:AcOEt = 3:1). Brown solid. MP: 58-60 ˚C. IR (KBr) ν cm^{-1}; 2248, 1338, 1161. ^{1}H NMR (500 MHz) δ ppm; 7.70 (d, *J* = 8.0 Hz, 2H), 7.39-7.35 (m, 2H) 7.31 (d, *J* = 8.0 Hz, 2H), 7.30-7.27 (m, 3H), 3.29 (t, *J* = 7.2 Hz, 2H), 2.86 (s, 3H), 2.69 (t, *J* = 7.2 Hz, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz) δ ppm; 143.4, 134.8, 131.5, 129.7, 128.2, 127.9, 127.3, 123.2, 86.3, 82.3, 49.2, 35.5, 21.5, 19.8. HRMS (ESI) Calcd for $C_{18}H_{19}NNaO_2S$ [M+Na]$^+$: 336.1029; found: 336.1029.



***N*,4-Dimethyl-*N*-(4-(4-nitrophenyl)but-3-yn-1-yl)benzenesulfonamide (5c)**: R_f = 0.29 (hexane:AcOEt = 3:1). Yellow solid. MP: 119-120 ˚C. IR (KBr) ν cm^{-1}; 2220, 1513, 1377, 1343, 1160. ^{1}H NMR (500 MHz) δ ppm; 8.16 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.31 (t, *J* = 7.2 Hz, 2H), 2.85 (s, 3H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz) δ ppm; 146.8, 143.6, 134.7, 132.3, 130.3, 129.8, 127.3, 123.5, 92.3, 80.9, 48.9, 35.5, 21.5, 20.0. HRMS (ESI) Calcd for $C_{18}H_{18}N_2NaO_4S$ [M+Na]$^+$:381.0879; found: 381.0866

[1] X. Yu, Z. Guo, H. Song, Y. Liu and Q. Wang, *Adv. Synth. Catal.*, 2018, **360**, 1077.
[2] N. Kobayashi, K. Kaneko, S. Amemiya, K. Noguchi, M. Yamanaka and A. Saito, *Chem. Commun.*, 2019, **55**, 8619.

Control Experiments using Aza-Prins Cyclized Product 4



4 **3aa**

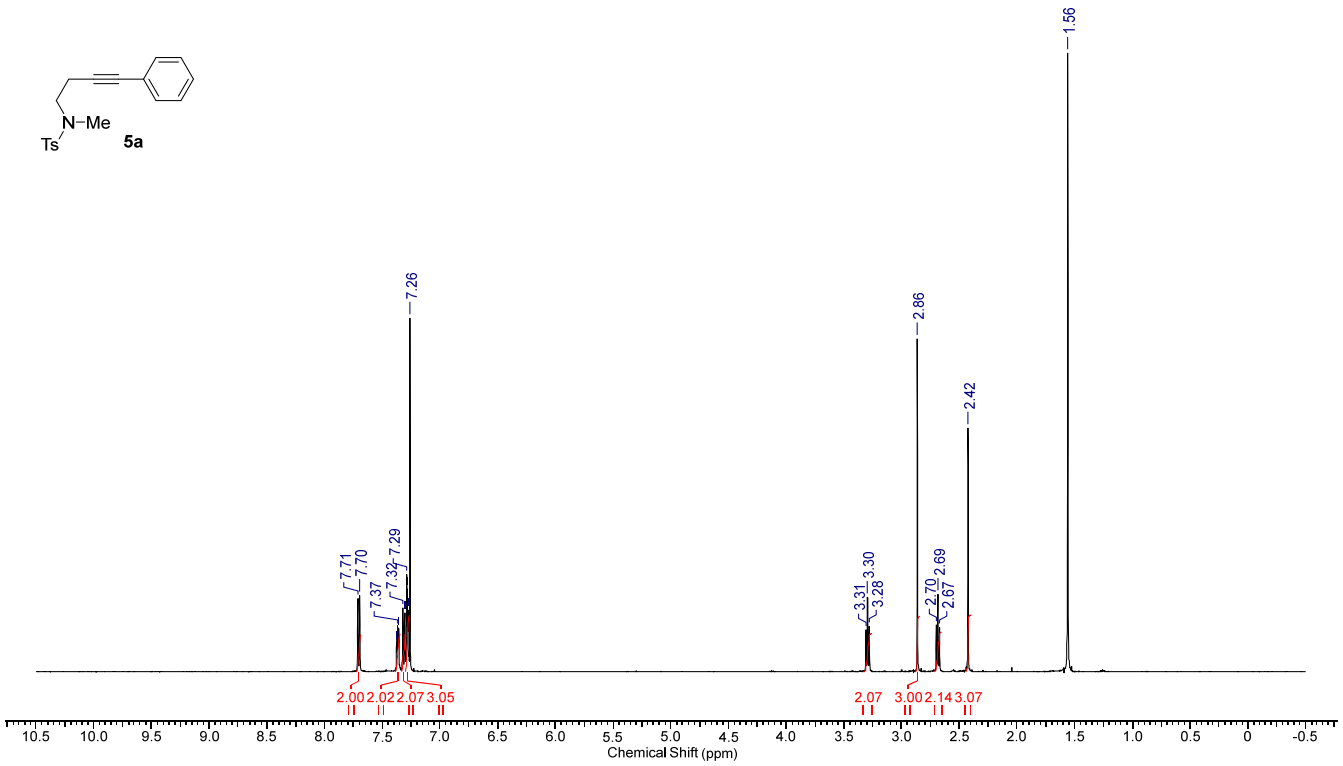
[Method i] To a solution of **4** (107.4 mg, 0.2 mmol) in MeCN (1.25 mL) was added TMSOTf (72.2 μL, 0.4 mmol) at 0 ºC. After being stirred at room temperature for 24 h, the reaction mixture was quenched with $NaHCO_3$ aq. and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to dryness. The residue was purified by silica gel column chromatography (Hexane:AcOEt = 3:1) to give **3aa** (77.8 mg, 96%). In the similar manner, **4** (107.4 mg, 0.2 mmol) was treated with TfOH (35.2 μL, 0.4 mmol) in MeCN (1.25 mL) to give **3aa** (72.7 mg, 90%).

[Method ii] To a solution of **4** (107.4 mg, 0.2 mmol) in MeCN (1.25 mL) was added TMSOTf (36.1 μL, 0.2 mmol) and H_2O (3.6 μL, 0.2 mmol) at 0 ºC. After being stirred at room temperature for 24 h, the reaction mixture was quenched with $NaHCO_3$ aq. and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to dryness. The residue was purified by Column Chromatography (Hexane:AcOEt = 10:1 to 3:1) to give **3aa** (35.1 mg, 43%) along with the recovery of **4** (31.2 mg, 29%). In the similar manner, **4** (107.4 mg, 0.2 mmol) was treated with TfOH (17.6 μL, 0.2 mmol) and H_2O (3.6 μL, 0.2 mmol) in MeCN (1.25 mL) to give **3aa** (33.6 mg, 41%) along with the recovery of **4** (23.6 mg, 22%). Also, **4** (107.4 mg, 0.2 mmol) was treated with H_2O (3.6 μL, 0.2 mmol) in MeCN (1.25 mL) to give **3aa** (31.7 mg, 39%) along with the recovery of **4** (24.0 mg, 22%).

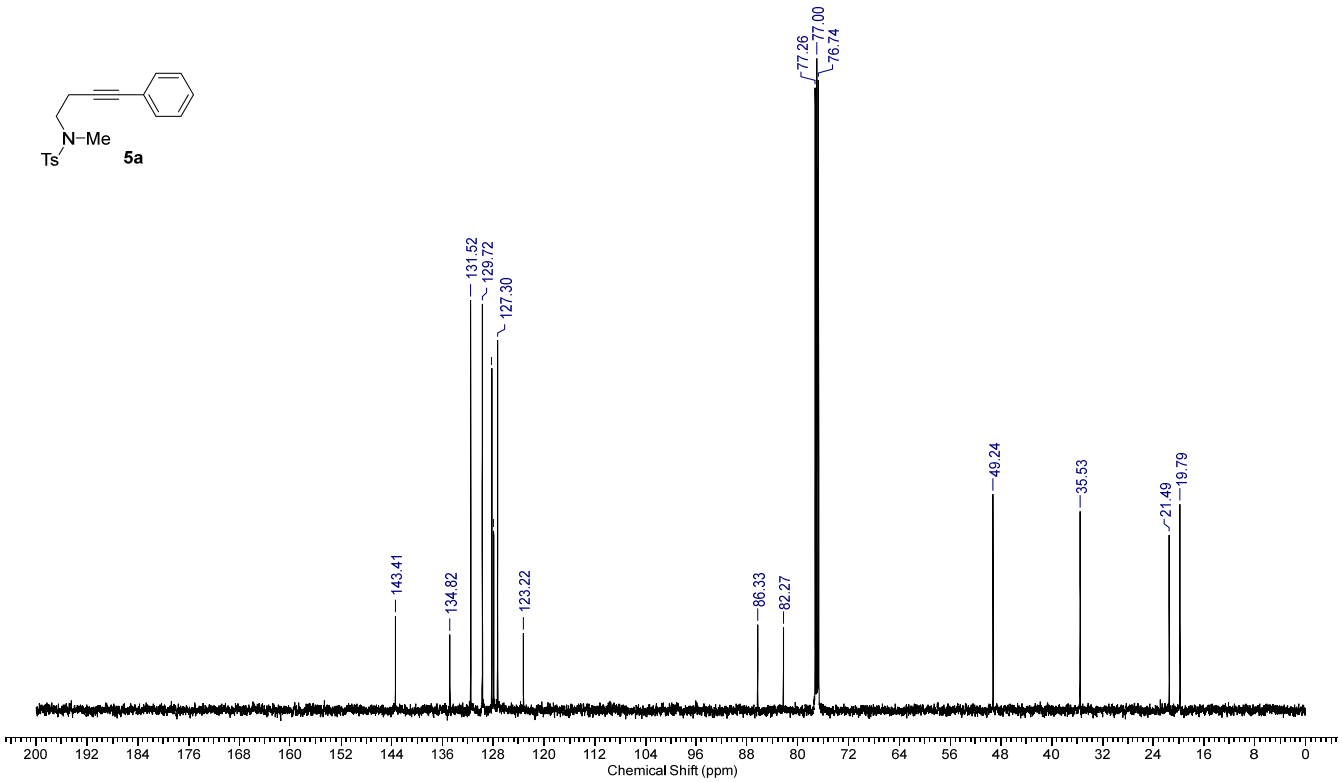
[Method iii] To a solution of **4** (215.0 mg, 0.4 mmol) in MeCN (2.5 mL) was added TMSOTf (72.2 μL, 0.4 mmol) at 0 ºC. After being stirred at room temperature for 24 h, the reaction mixture was quenched with $NaHCO_3$ aq. and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to dryness. By ^1H NMR analysis of the residue using 1,2-dicholoroethen as an internal standard, the yield of **3aa** (9%) and recovery rate of **4** (39%) were determined because some unidentified products were converted into **3aa** in silica gel. In the similar manner, **4** (215.0 mg, 0.4 mmol) was treated with TfOH (35.1 μL, 0.4 mmol) in MeCN (1.25 mL) to give **3aa** (10% by NMR analysis) along with the recovery of **4** (23% by NMR analysis).

^{1}H and ^{13}C NMR Spectra of New Compounds

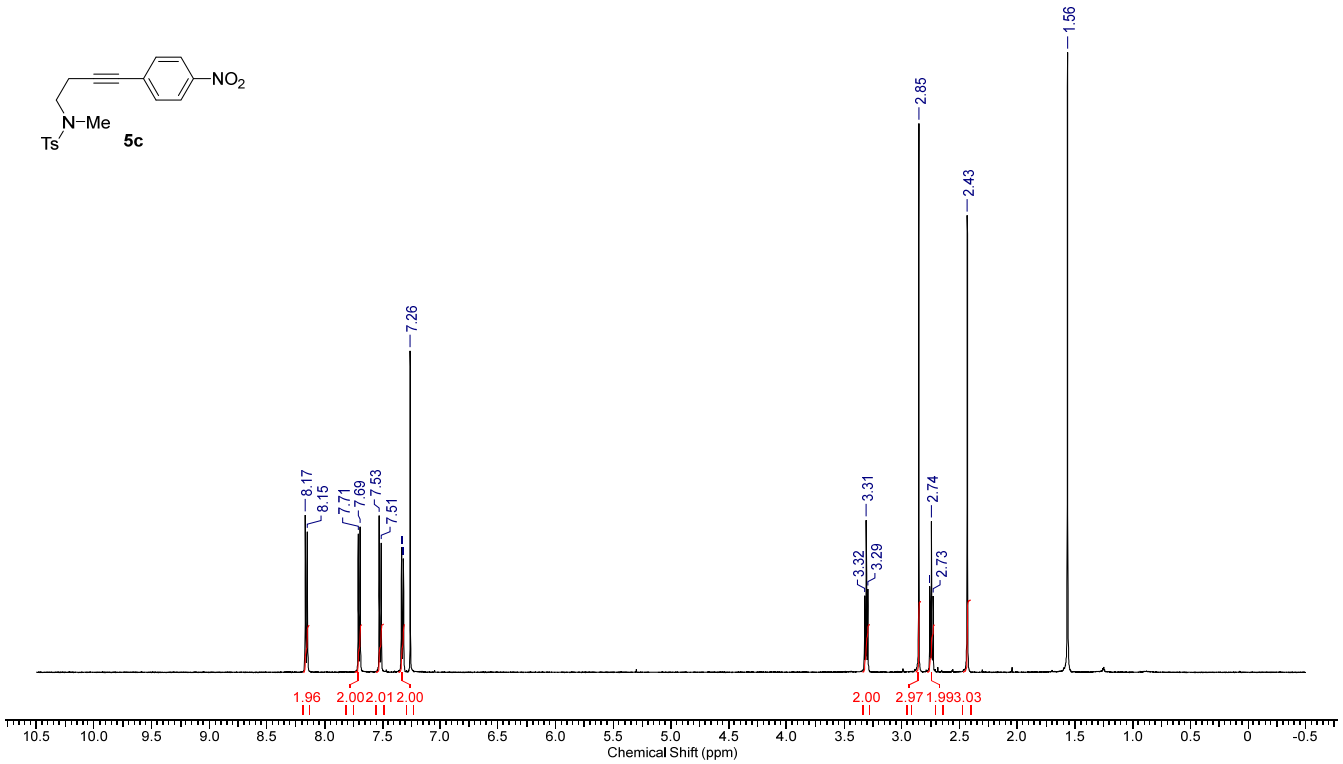
^{1}H NMR (500 MHz, $CDCl_3$) of **5a**



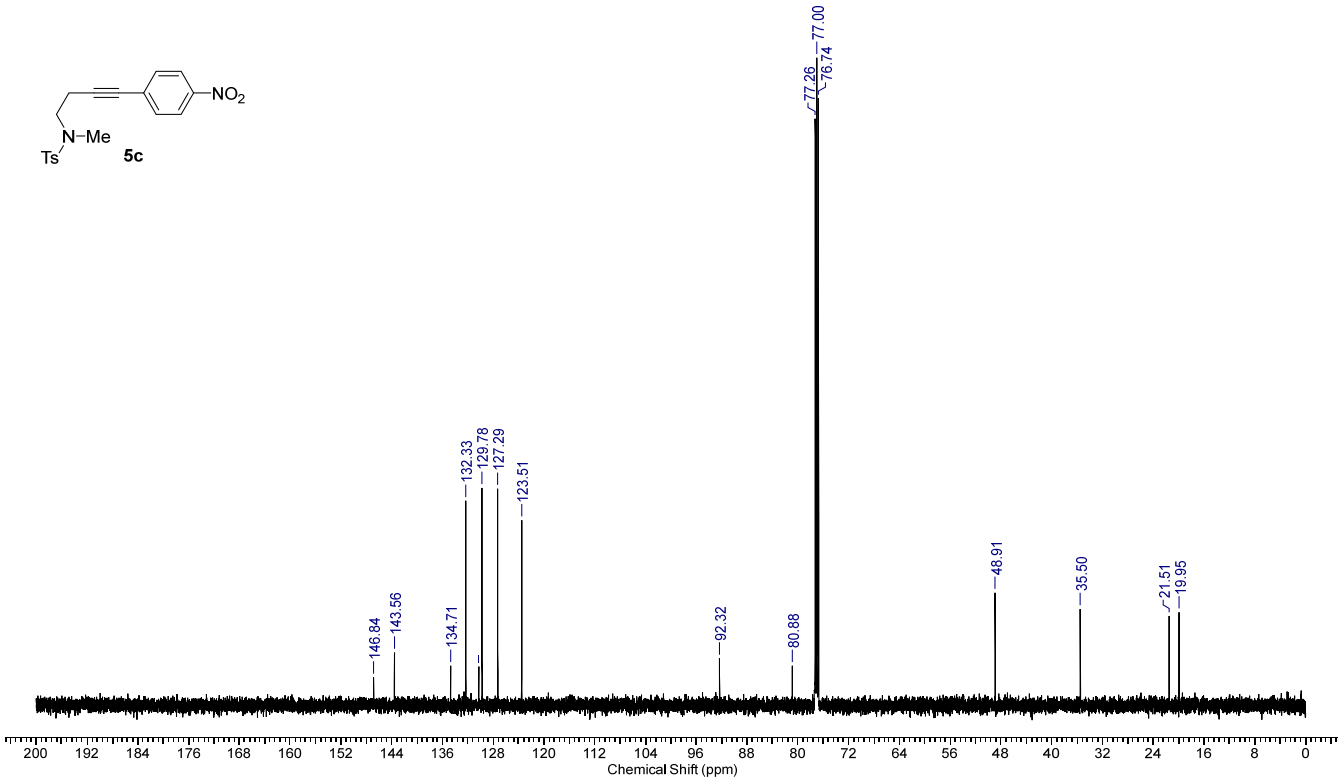
^{13}C NMR (125 MHz, $CDCl_3$) of **5a**



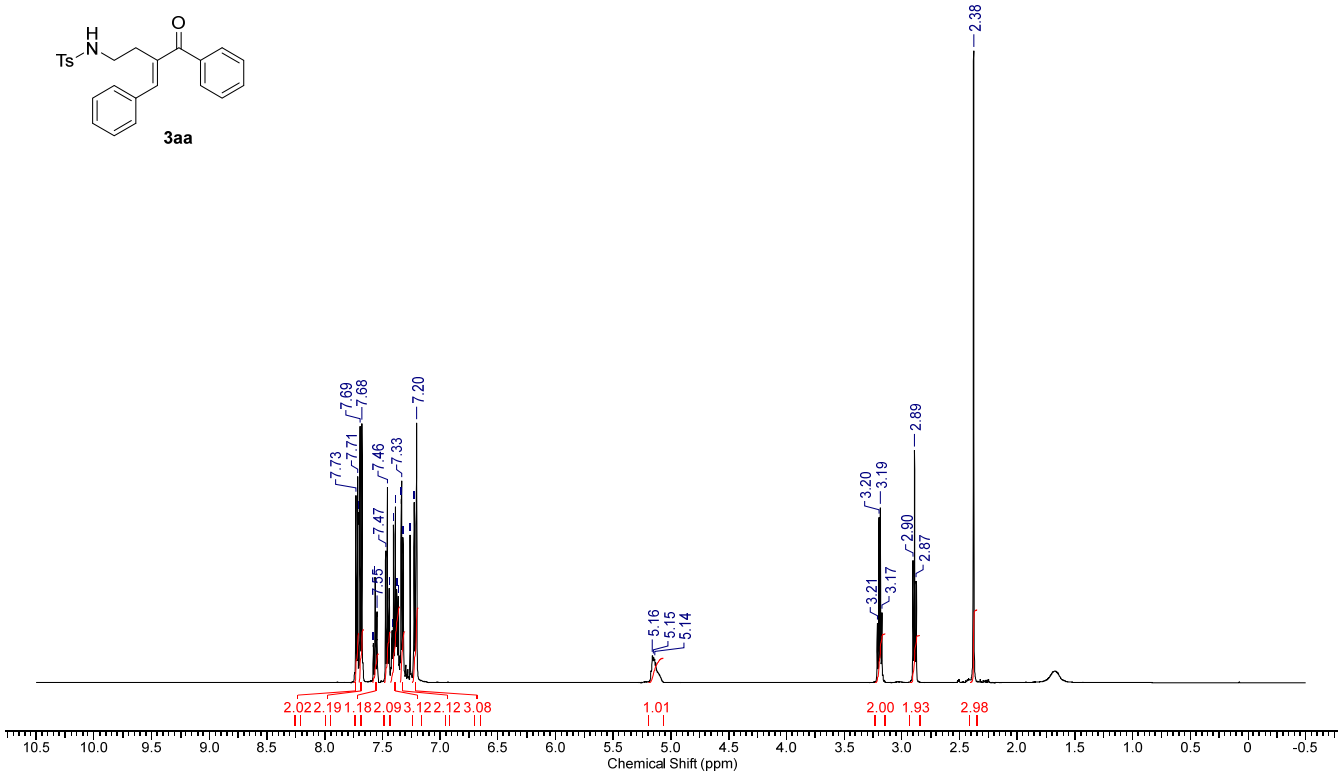
^{1}H NMR (500 MHz, $CDCl_3$) of **5c**



^{13}C NMR (125 MHz, $CDCl_3$) of **5c**



^{1}H NMR (500 MHz, $CDCl_3$) of **3aa**



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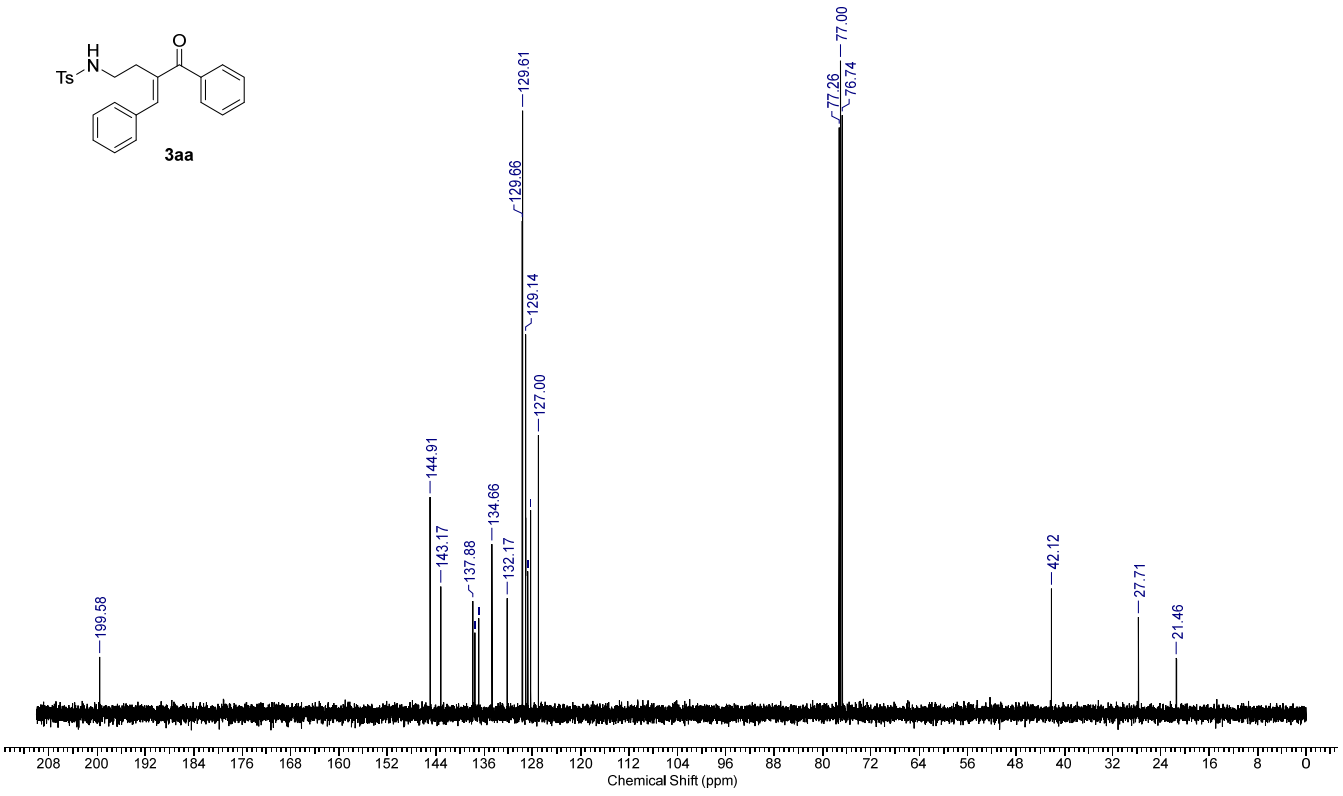
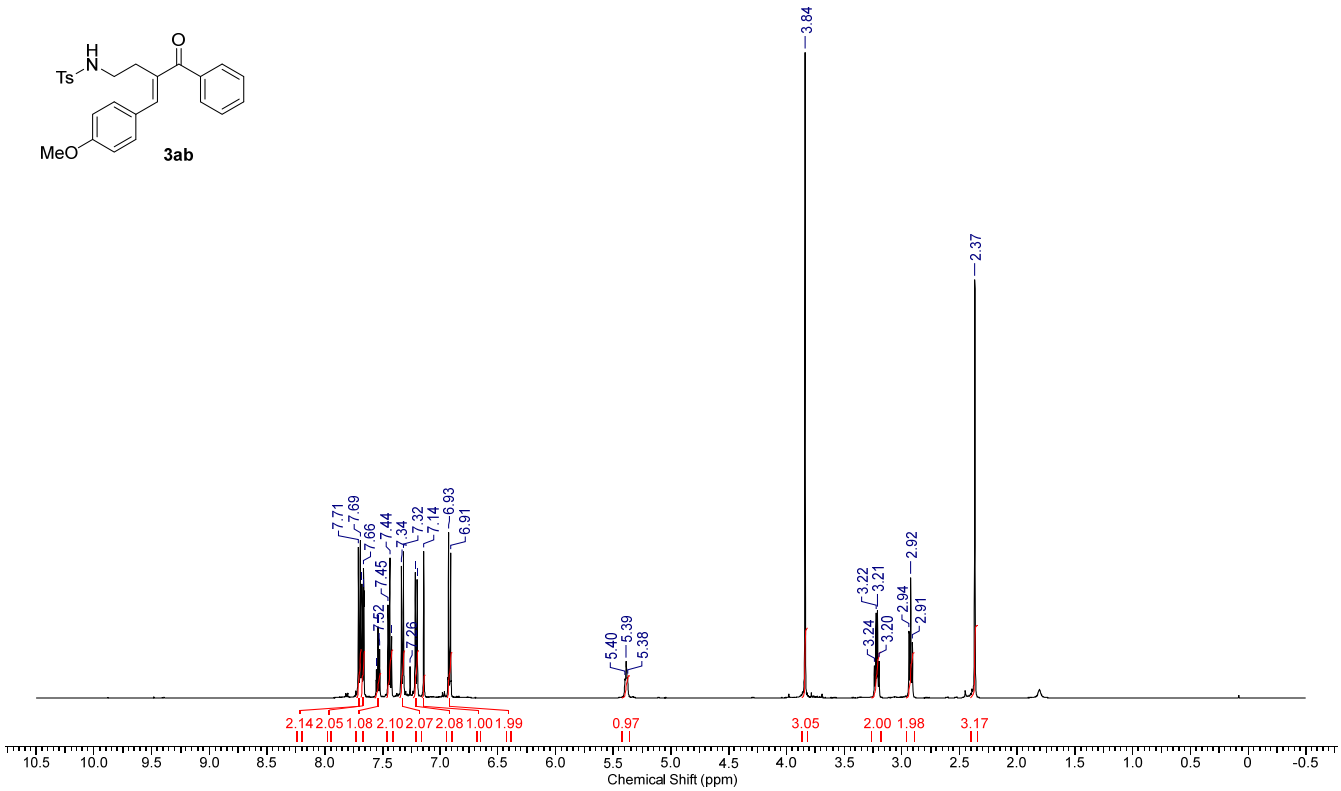
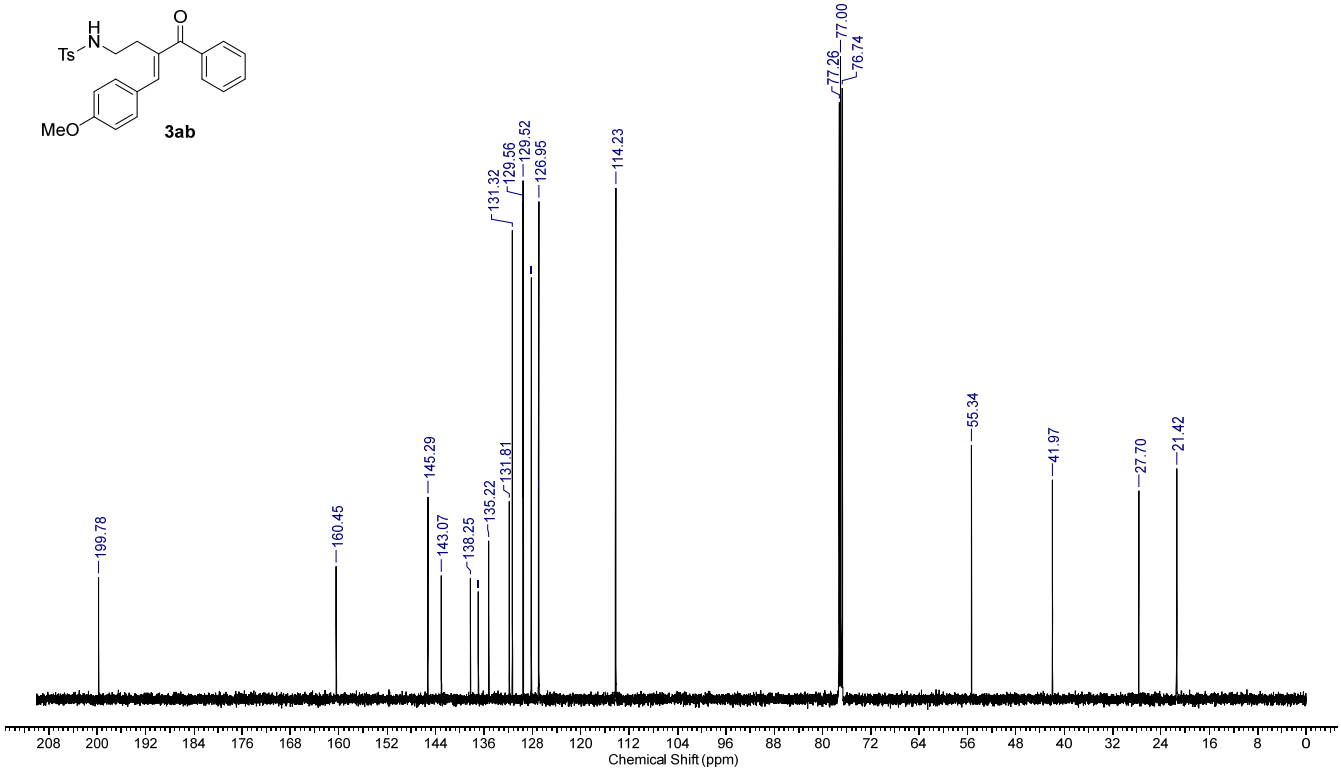


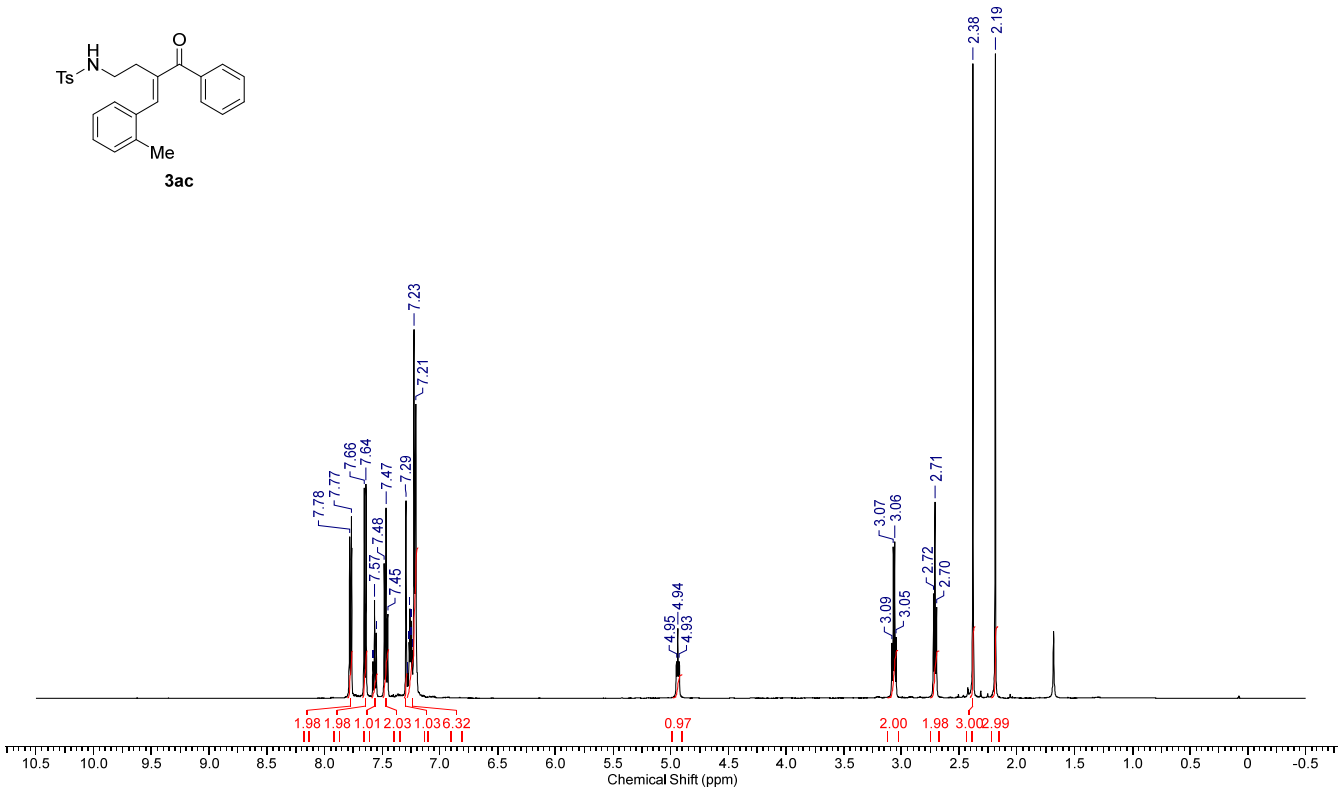
^{1}H NMR (500 MHz, $CDCl_3$) of **3ab**



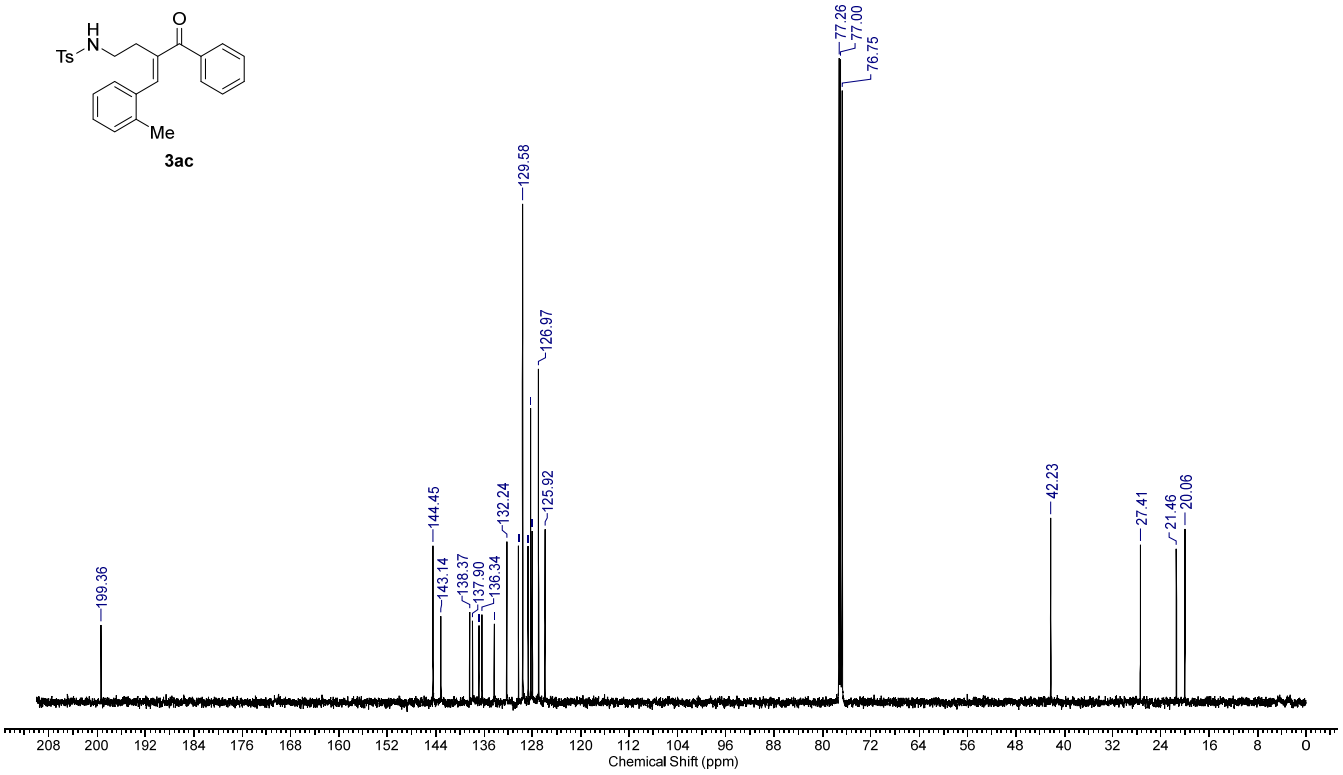
^{13}C NMR (125 MHz, $CDCl_3$) of **3ab**



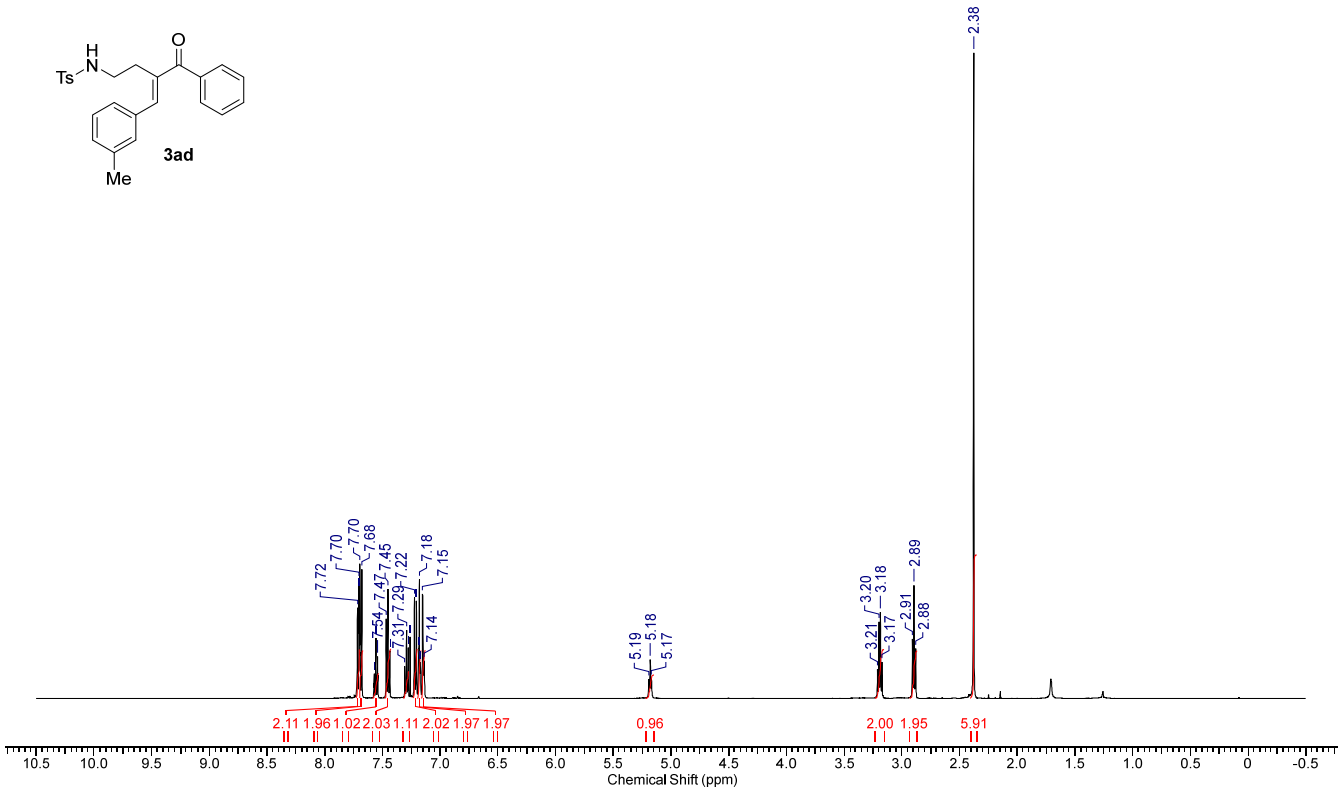
^{1}H NMR (500 MHz, $CDCl_3$) of **3ac**



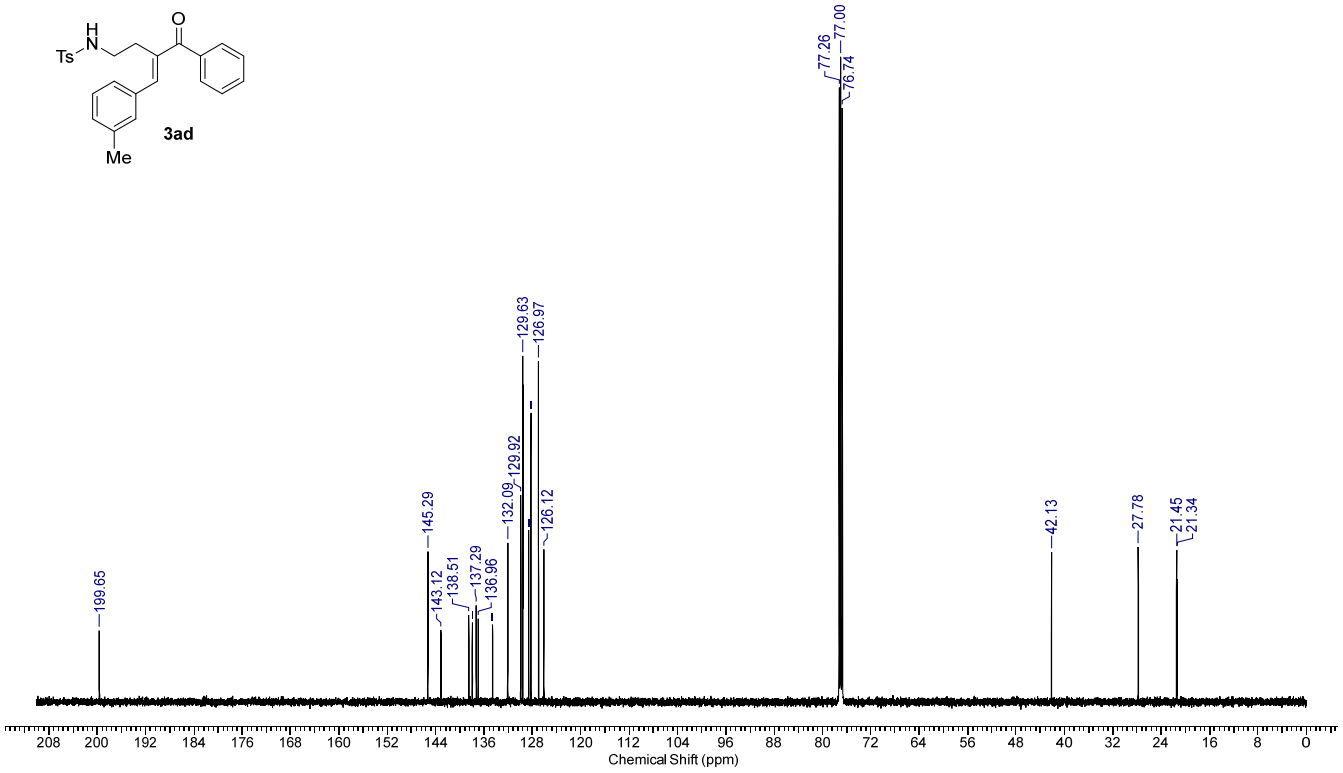
^{13}C NMR (125 MHz, $CDCl_3$) of **3ac**



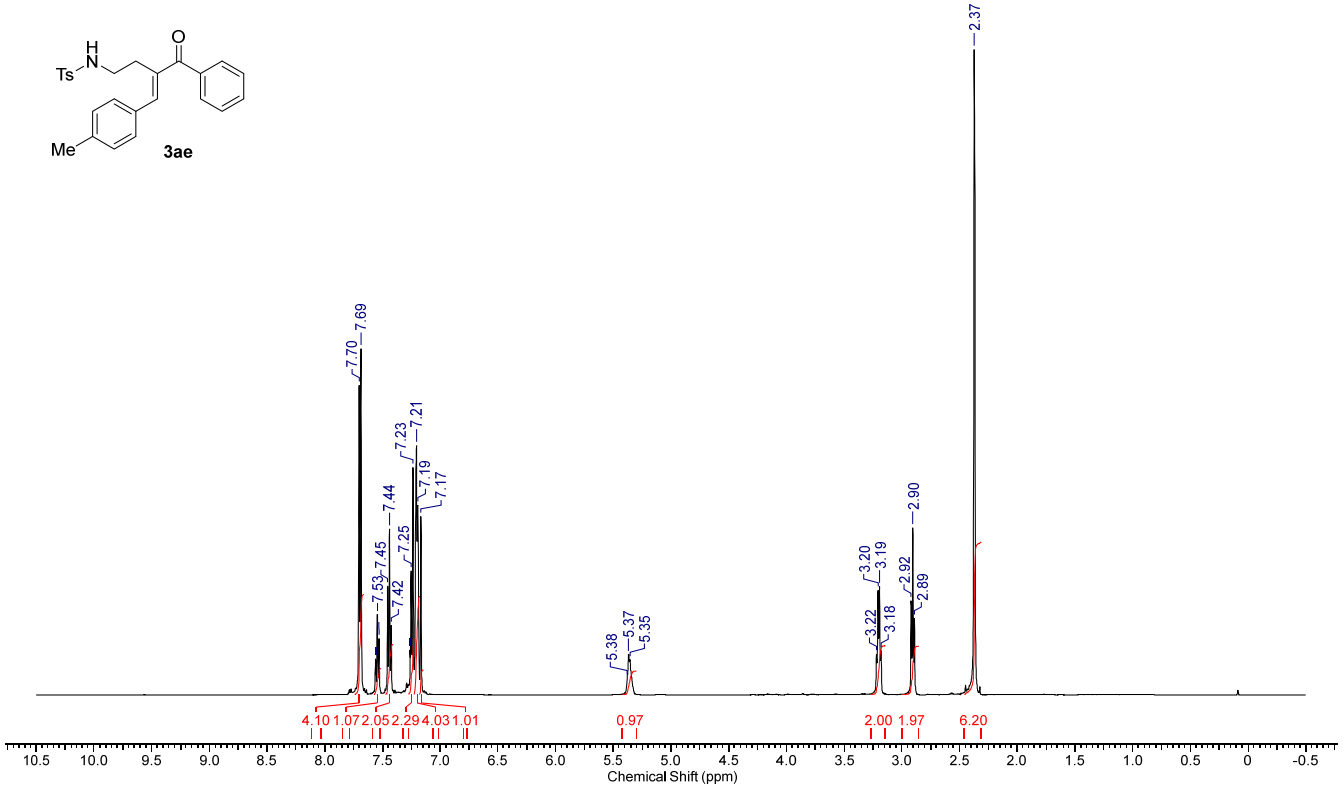
^{1}H NMR (500 MHz, $CDCl_3$) of **3ad**



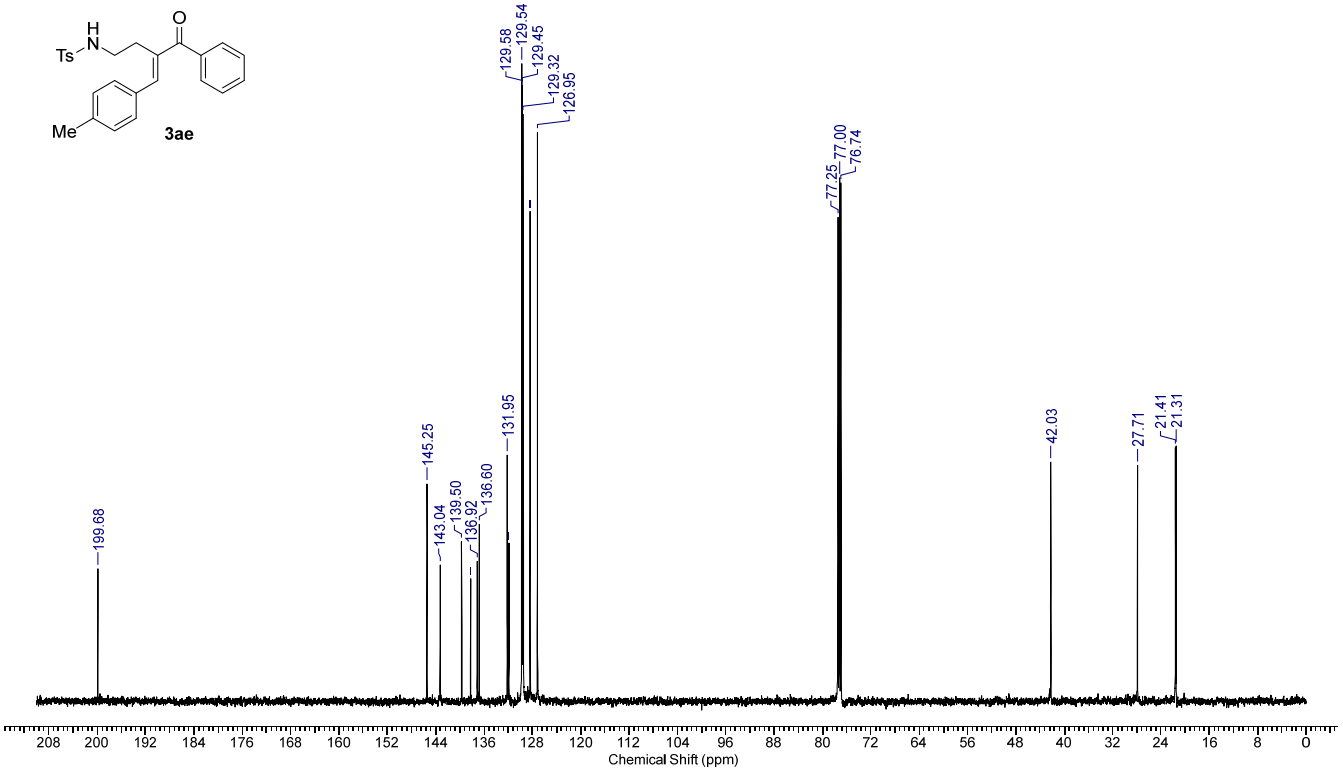
^{13}C NMR (125 MHz, $CDCl_3$) of **3ad**



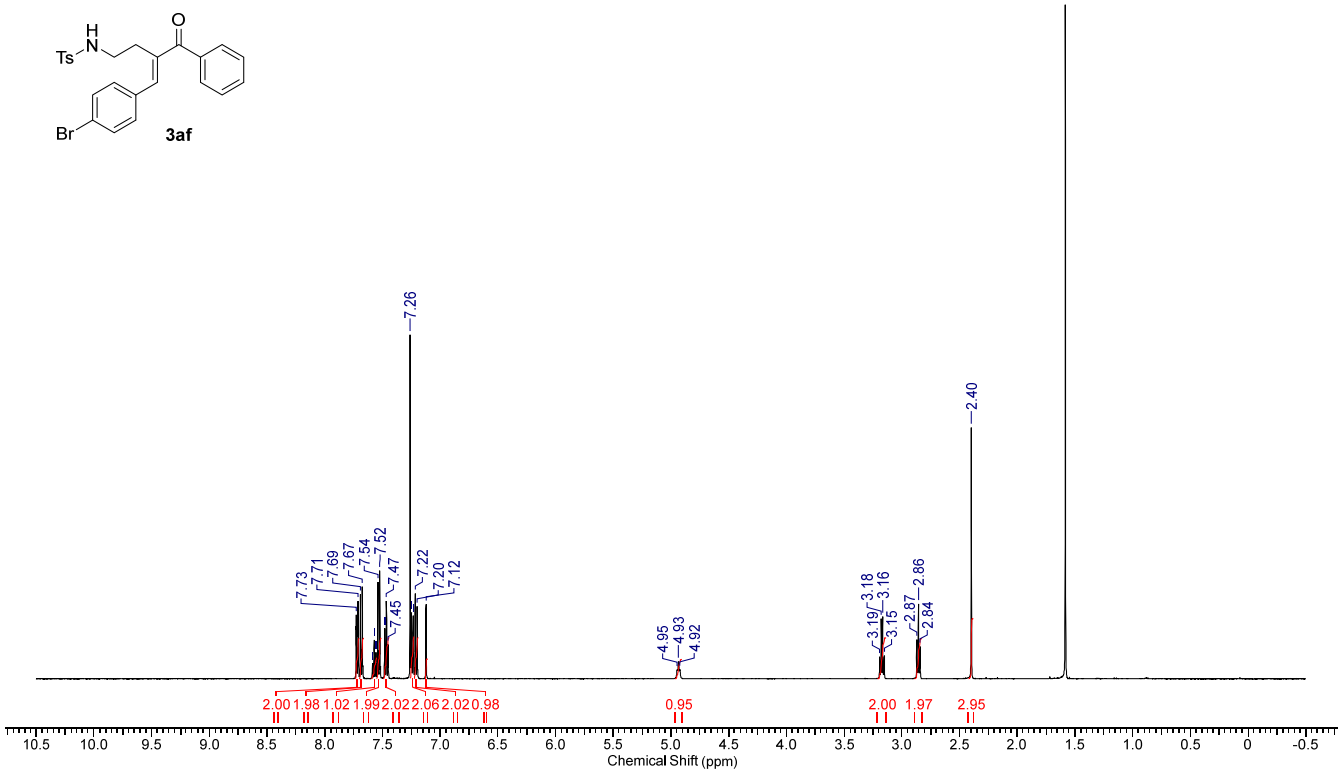
^{1}H NMR (500 MHz, $CDCl_3$) of **3ae**



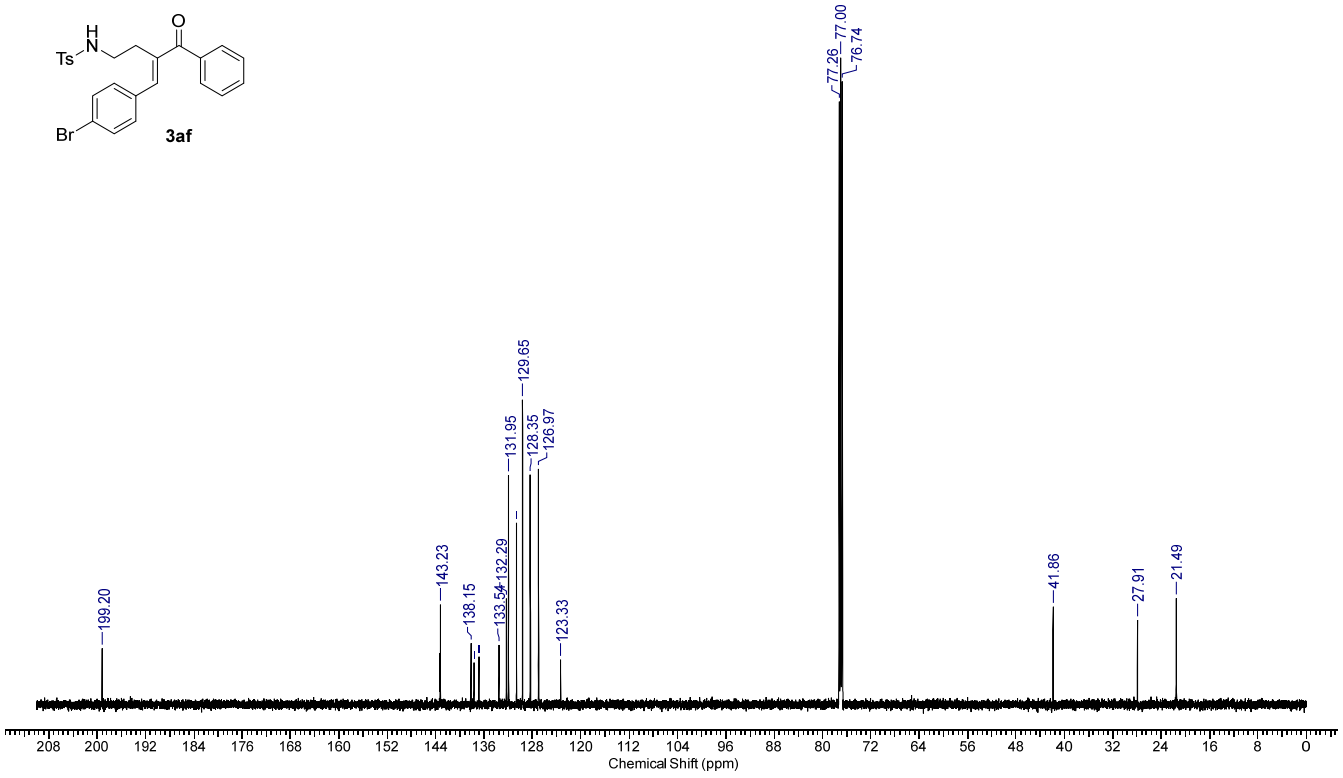
^{13}C NMR (125 MHz, $CDCl_3$) of **3ae**



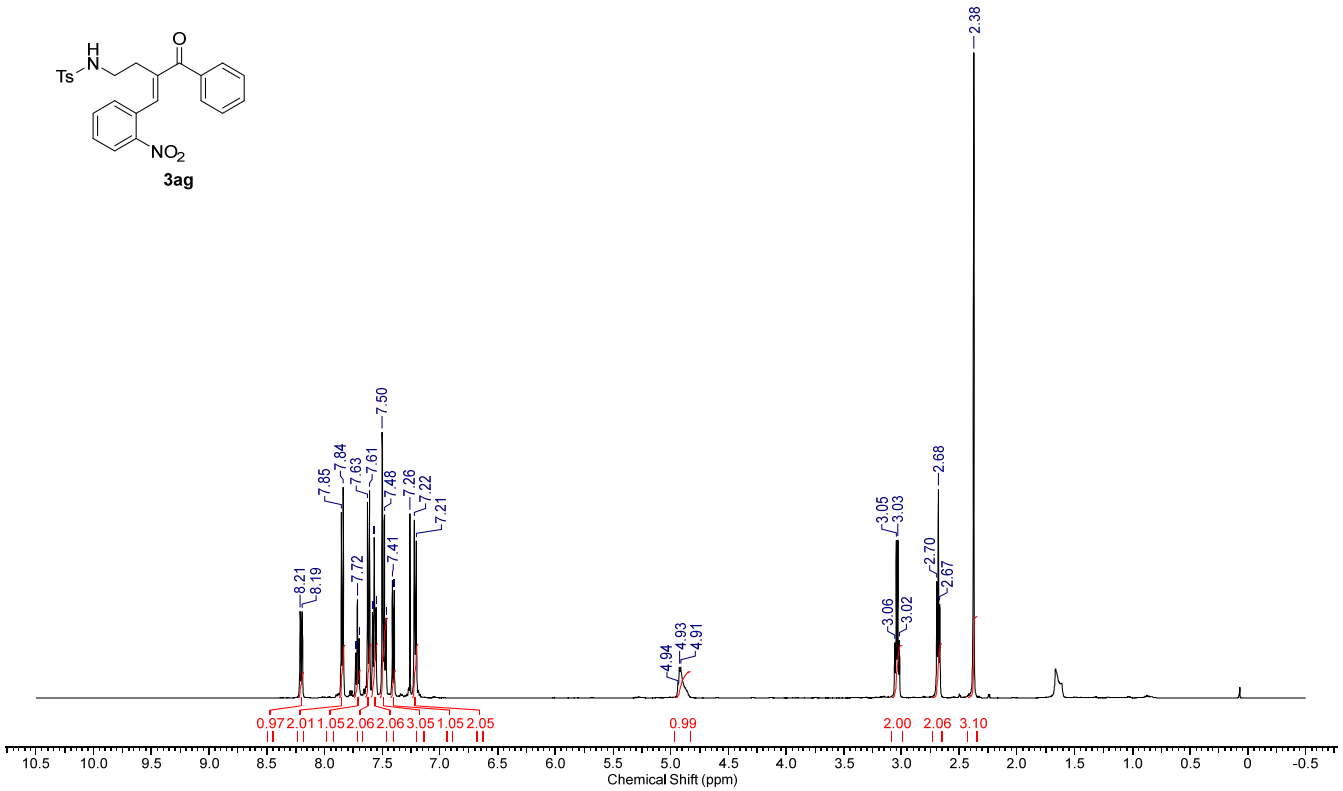
^{1}H NMR (500 MHz, $CDCl_3$) of **3af**



^{13}C NMR (125 MHz, $CDCl_3$) of **3af**



^{1}H NMR (500 MHz, $CDCl_3$) of **3ag**



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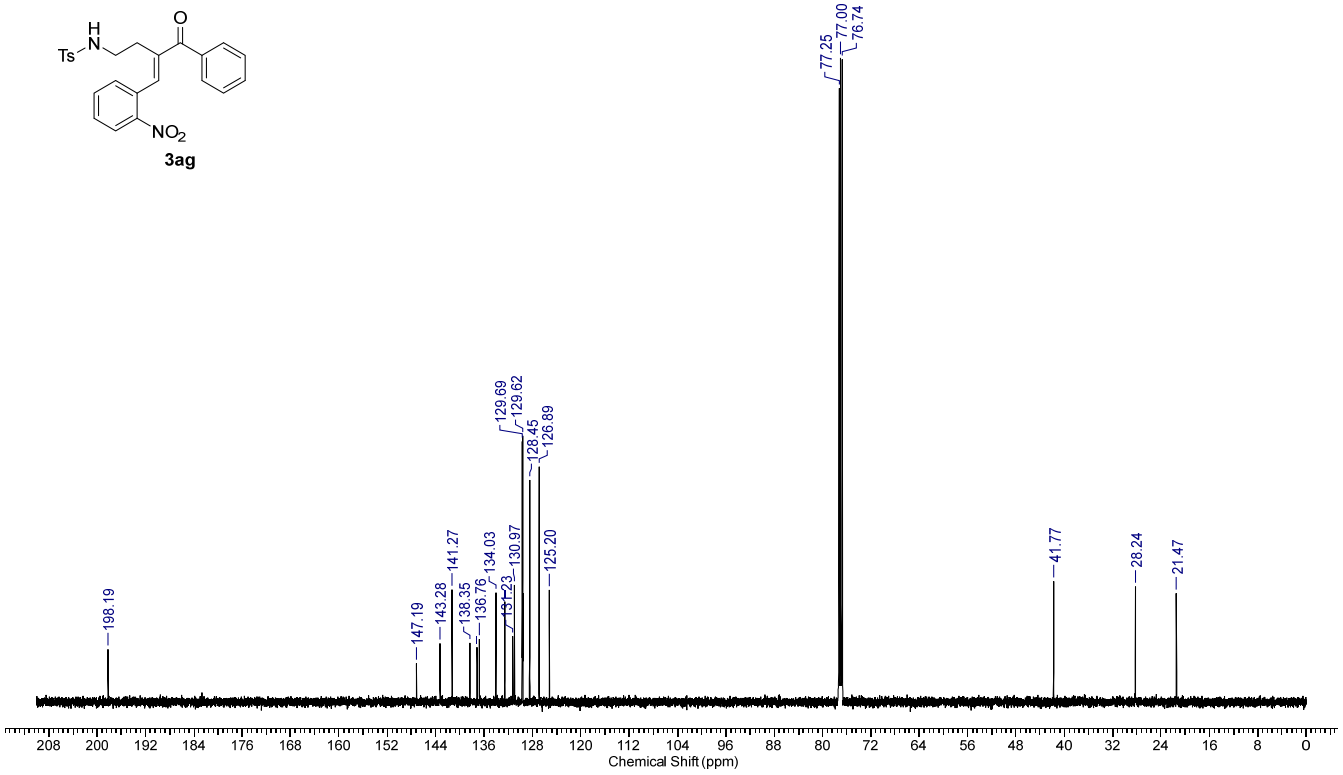

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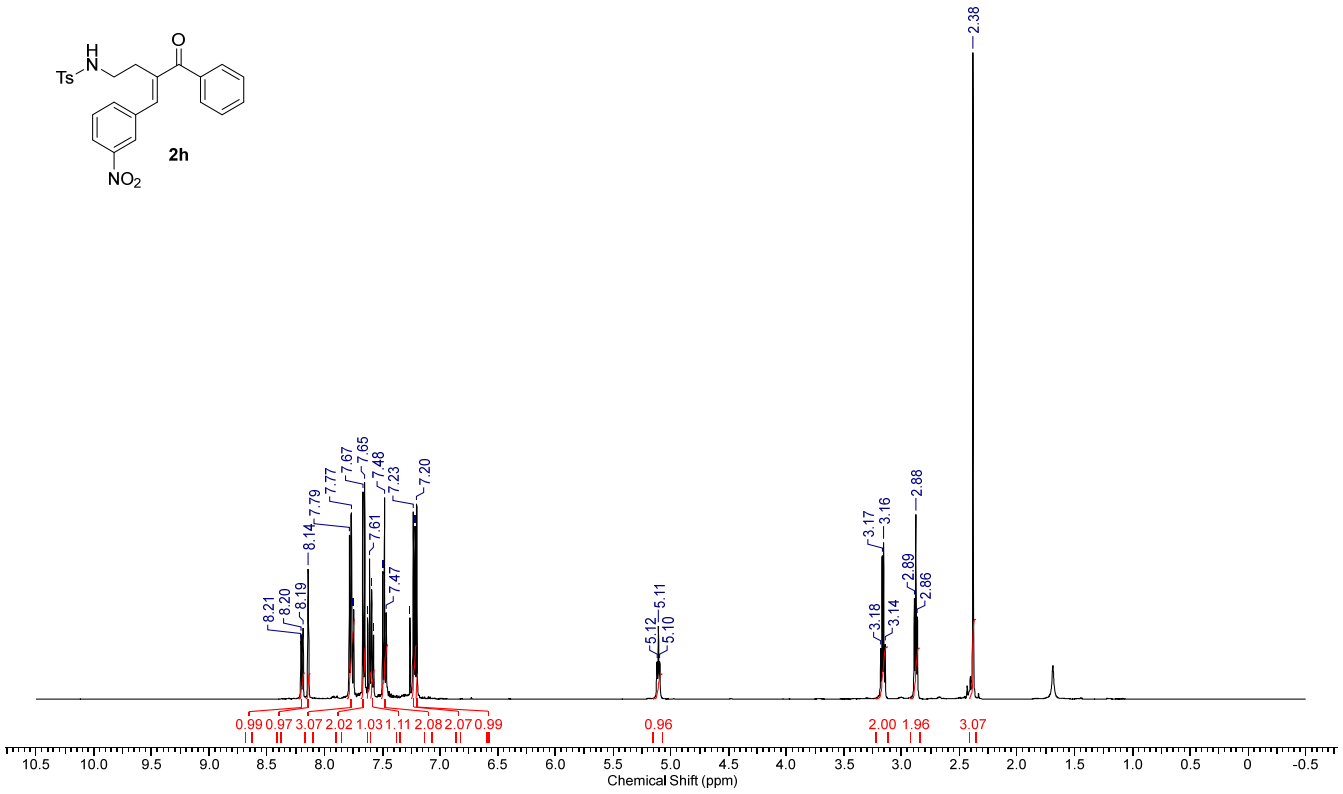

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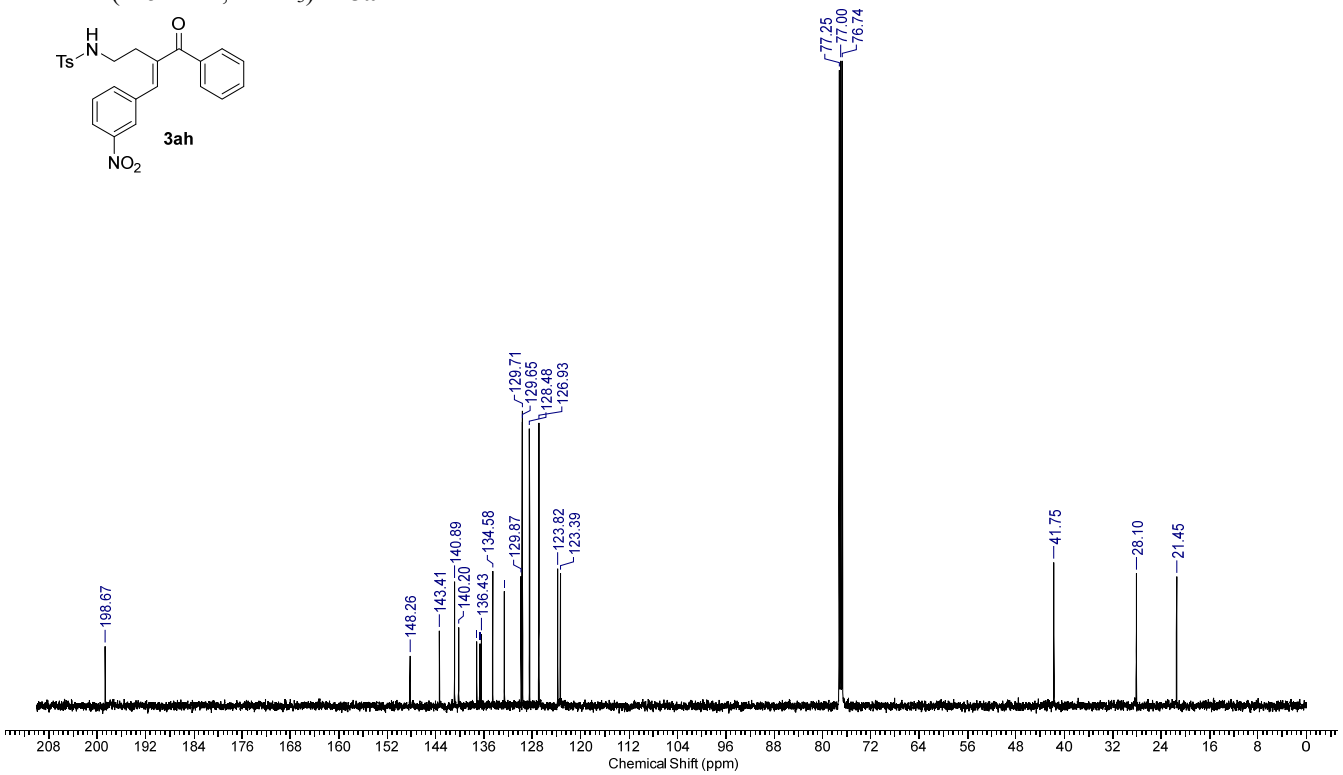

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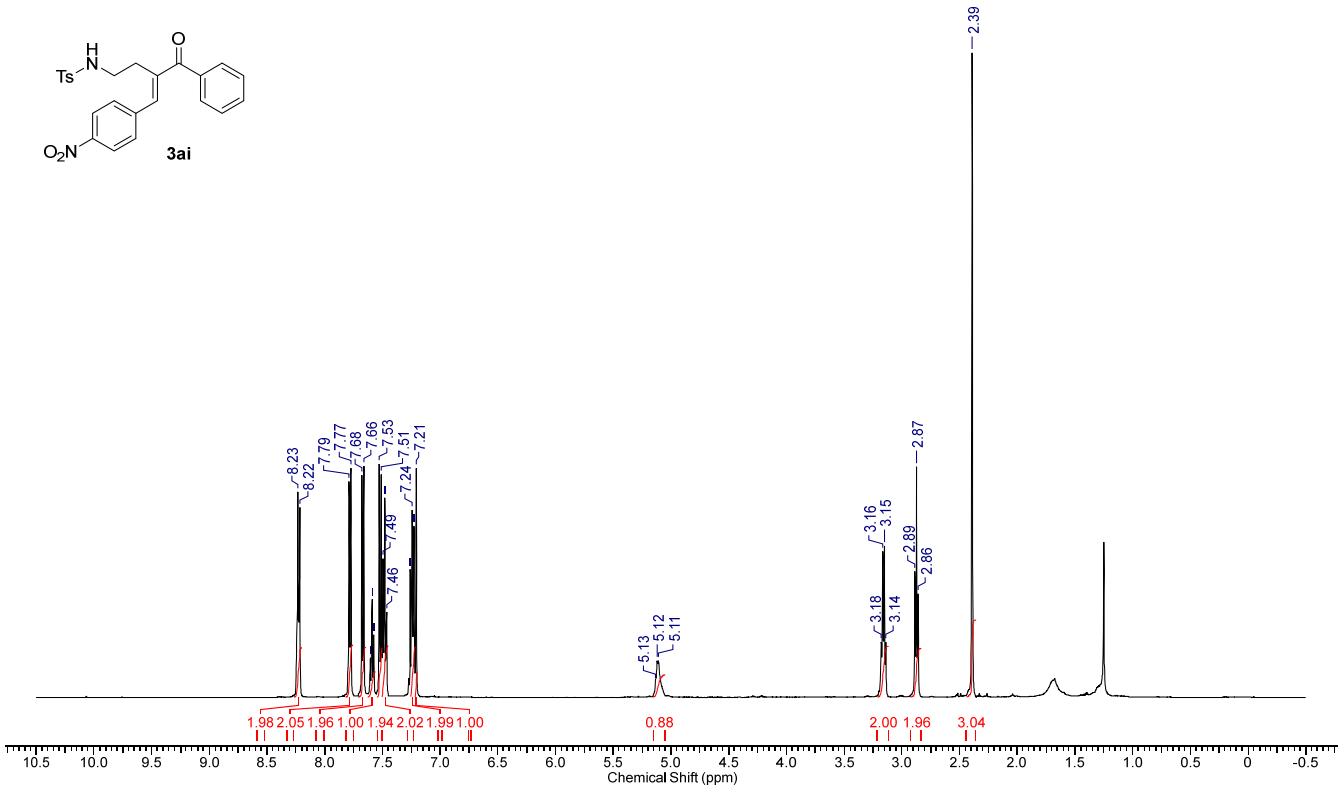
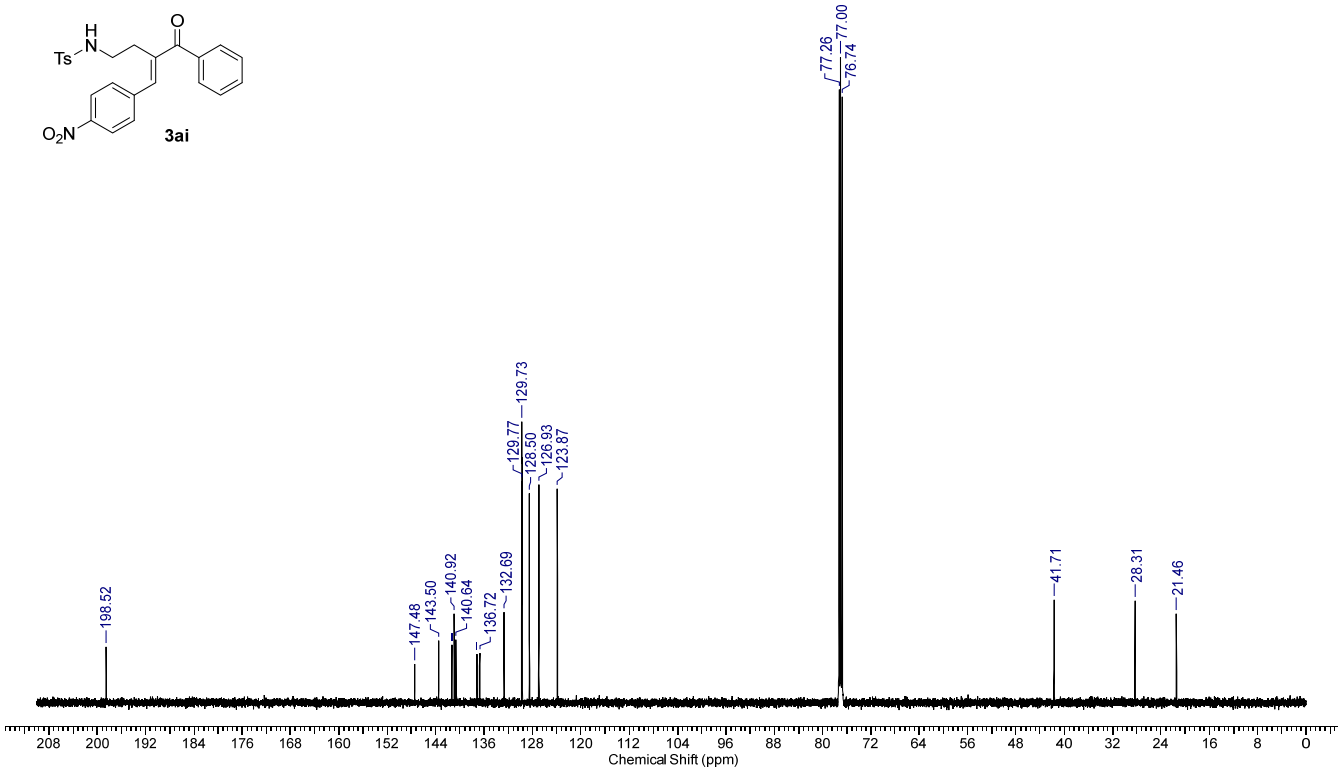


^{13}C NMR (125 MHz, $CDCl_3$) of **3ai**



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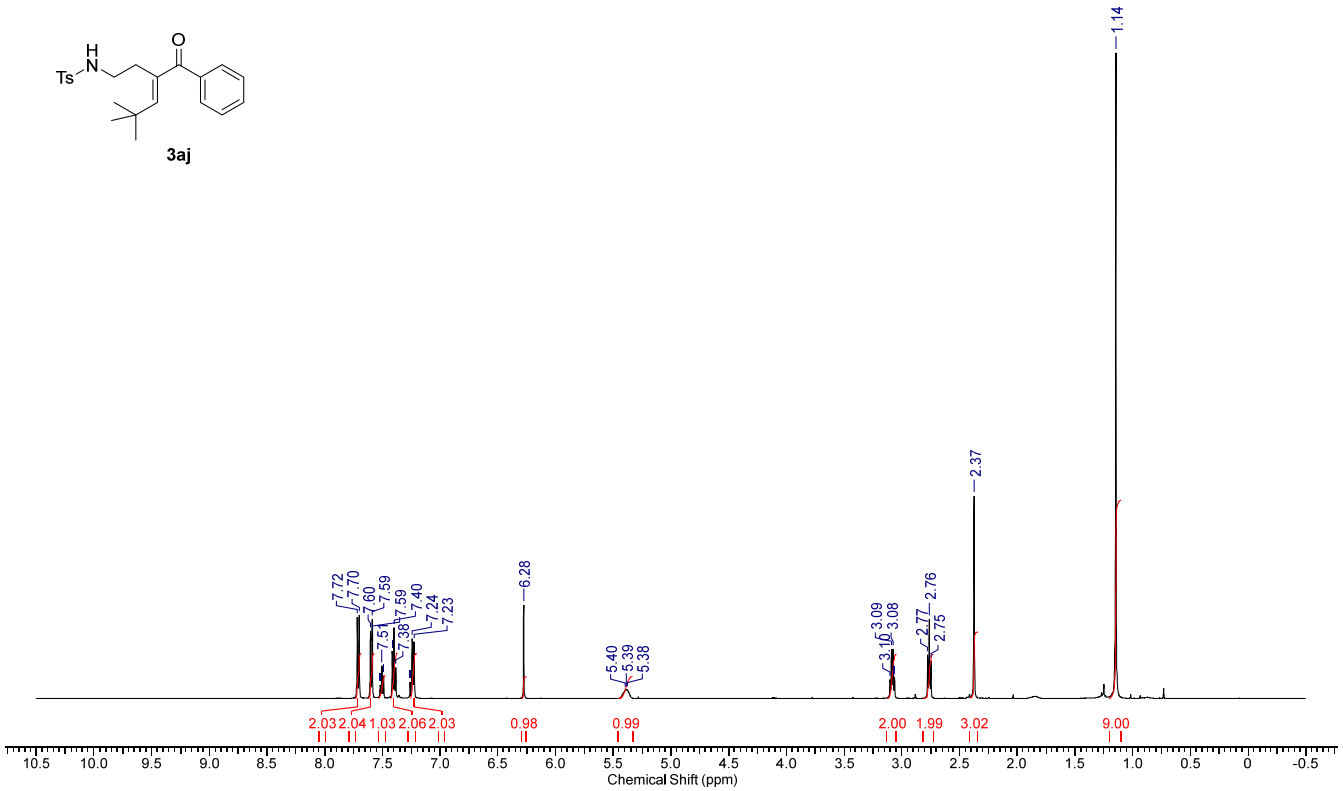
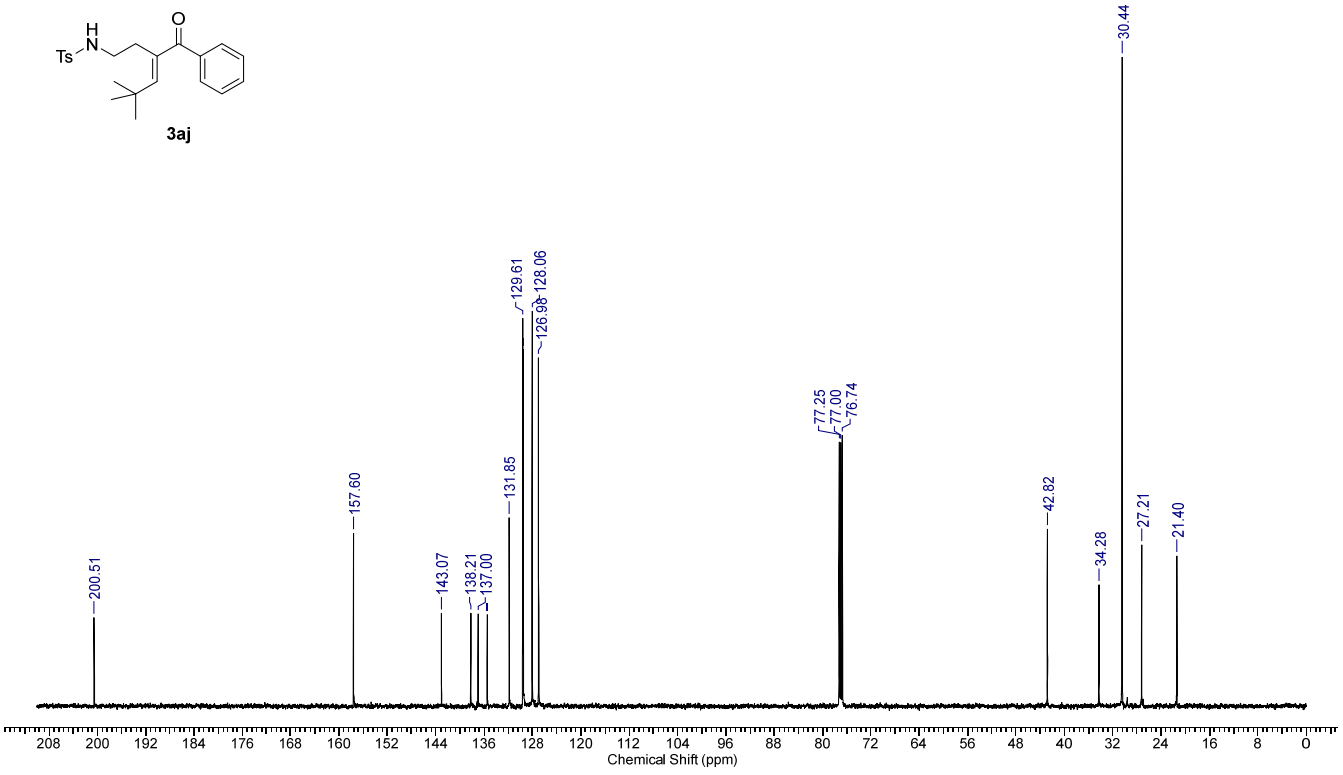
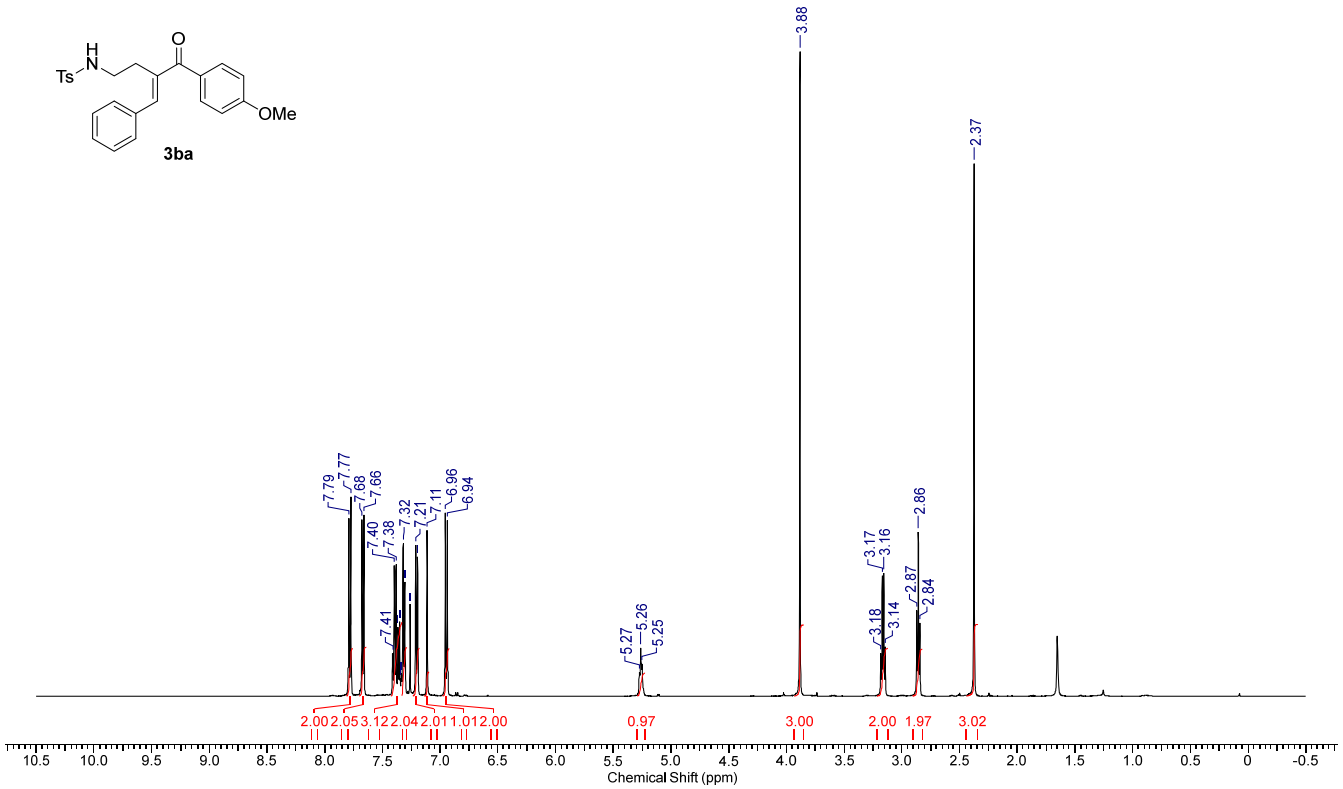


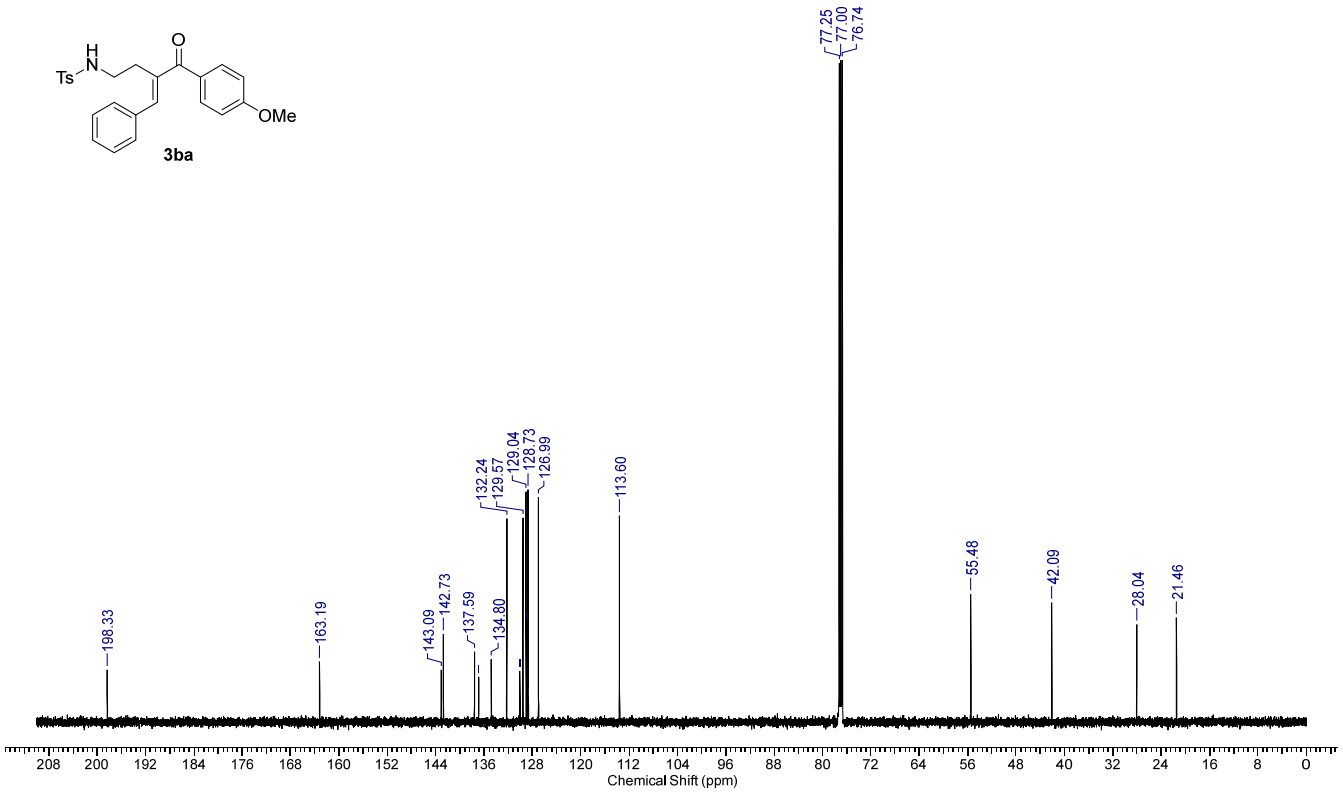
^{13}C NMR (125 MHz, $CDCl_3$) of **3aj**



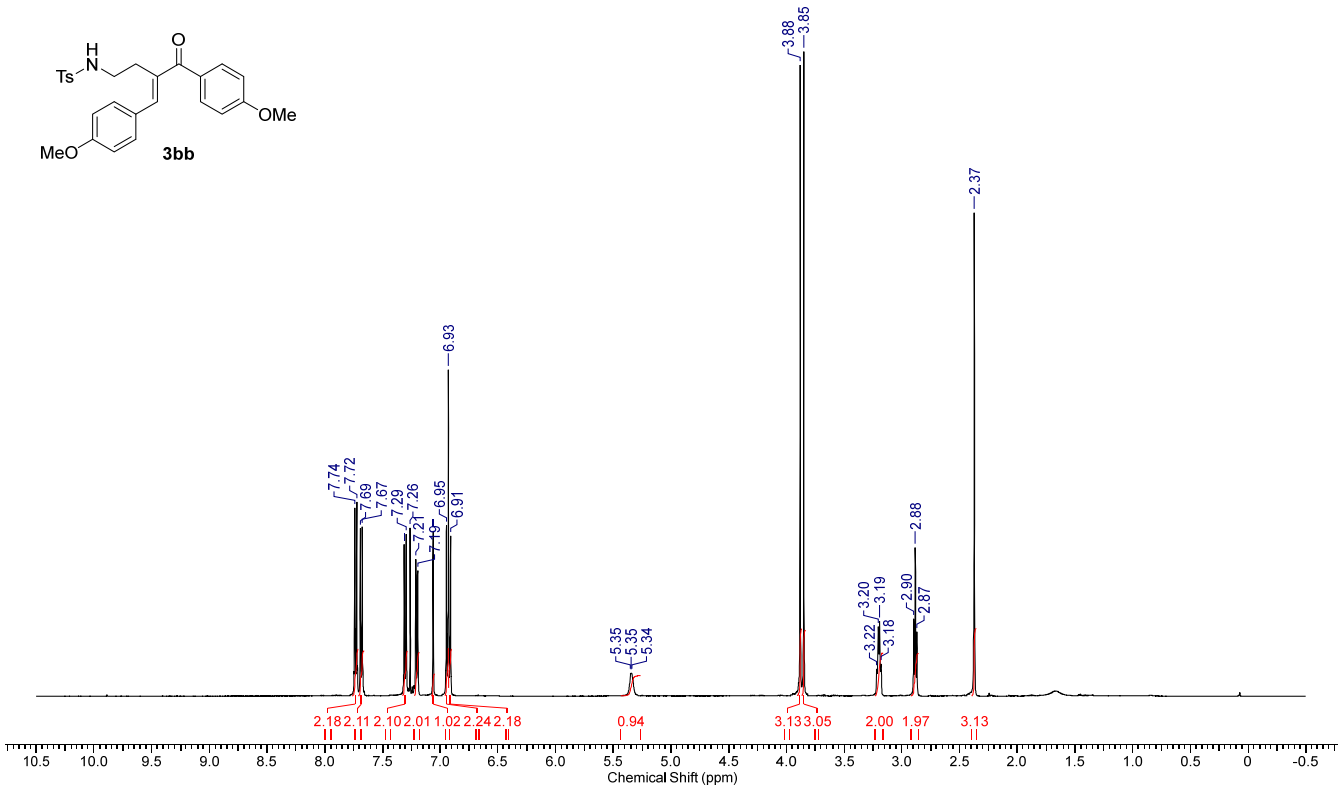
^{1}H NMR (500 MHz, $CDCl_3$) of **3ba**



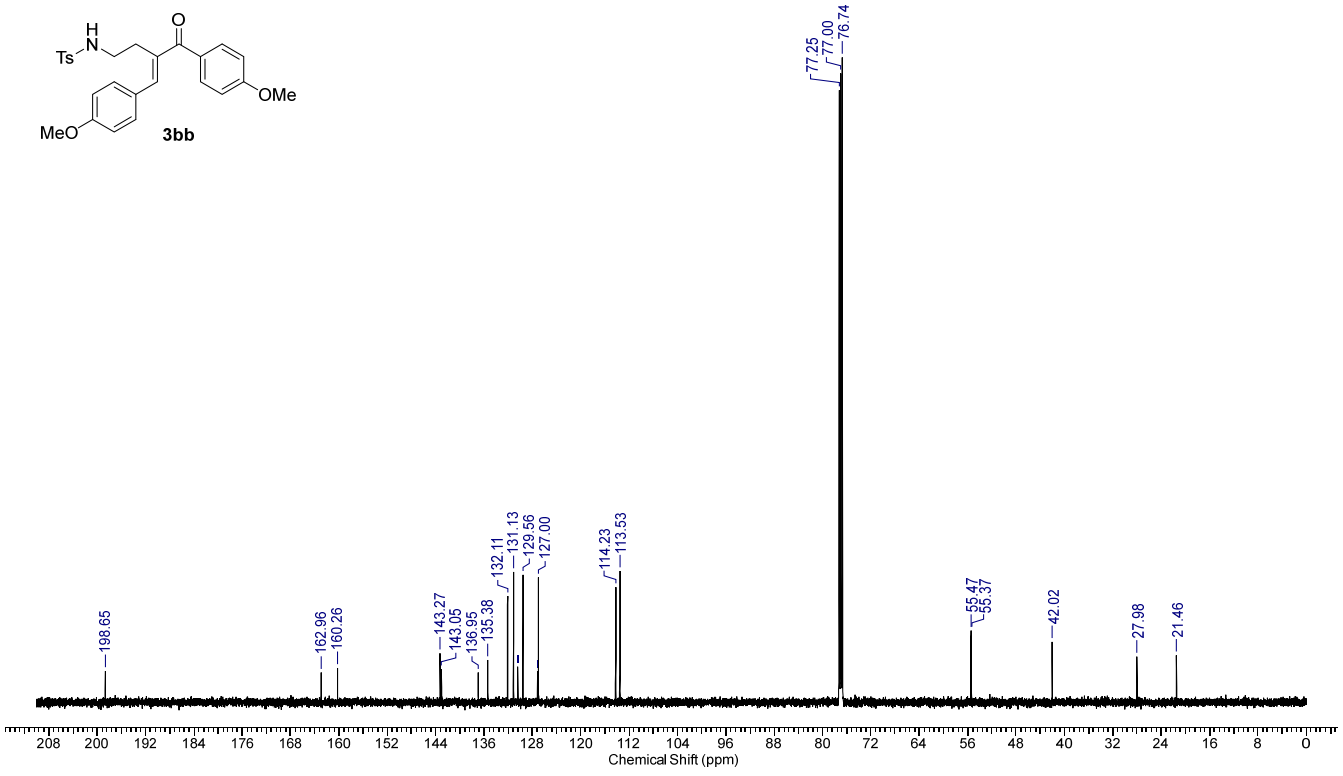
^{13}C NMR (125 MHz, $CDCl_3$) of **3ba**



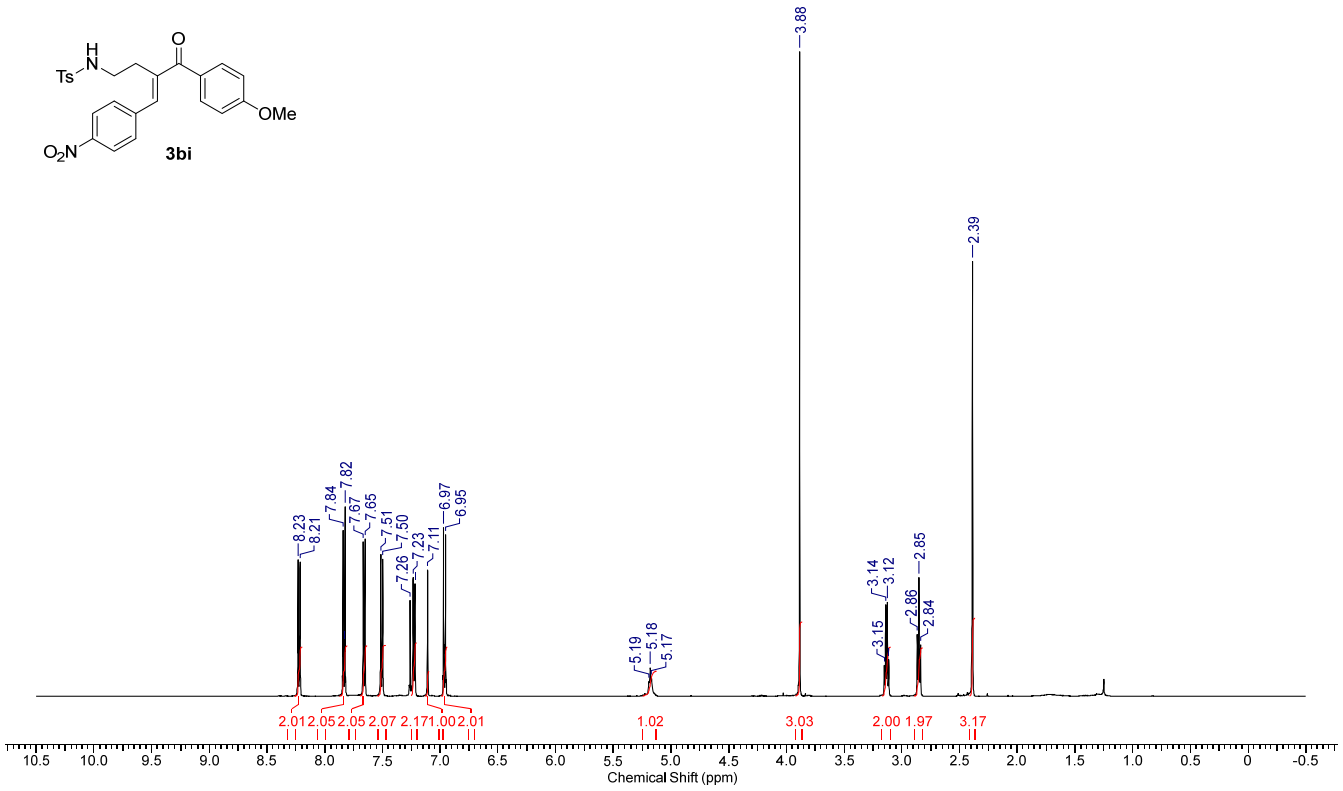
^{1}H NMR (500 MHz, $CDCl_3$) of **3bb**



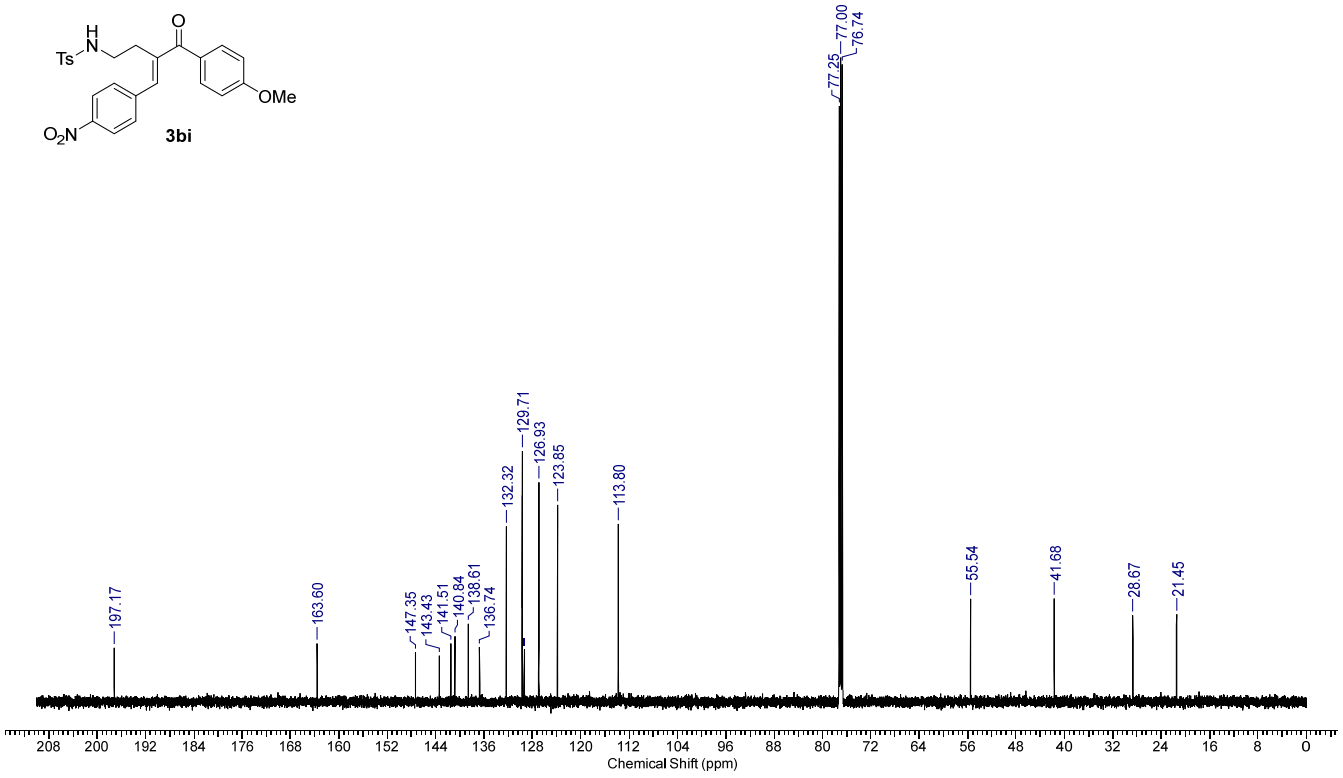
^{13}C NMR (125 MHz, $CDCl_3$) of **3bb**



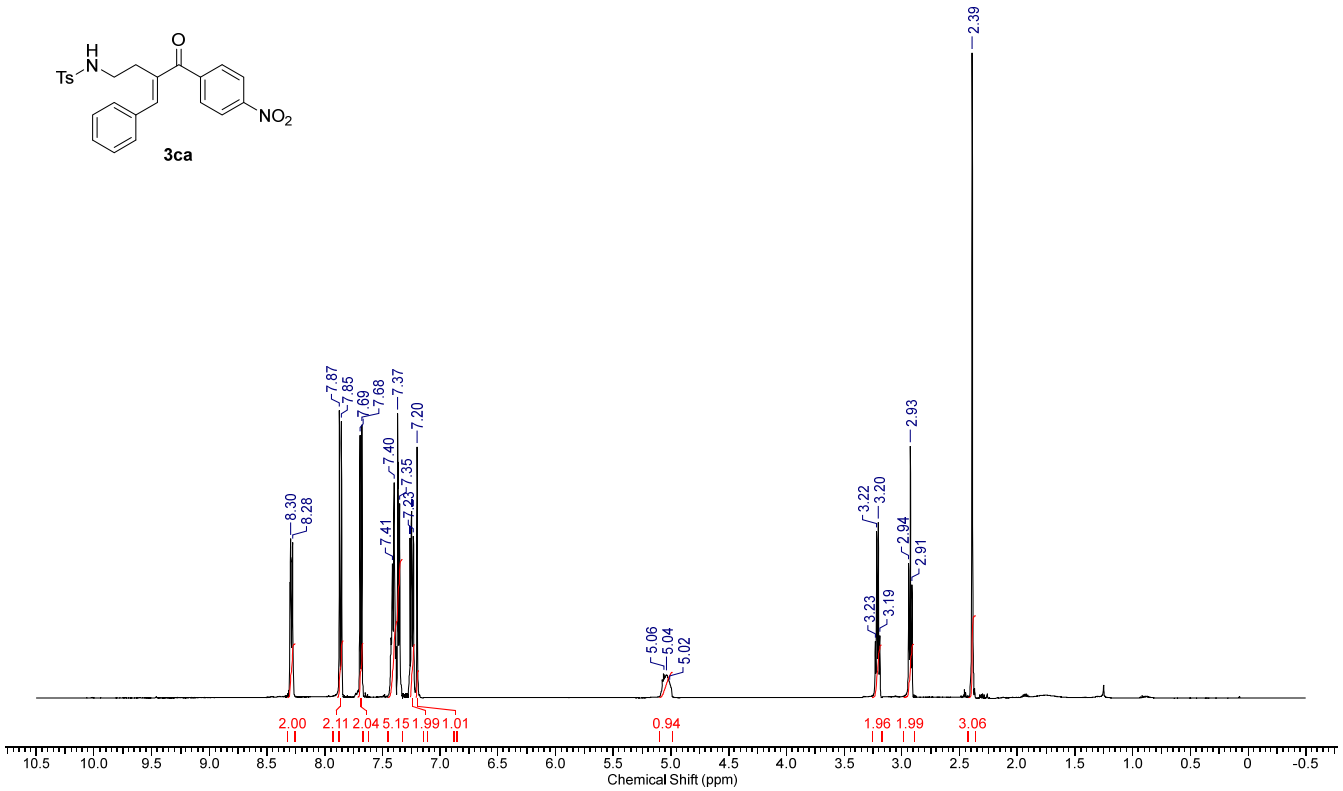
^{1}H NMR (500 MHz, $CDCl_3$) of **3bi**



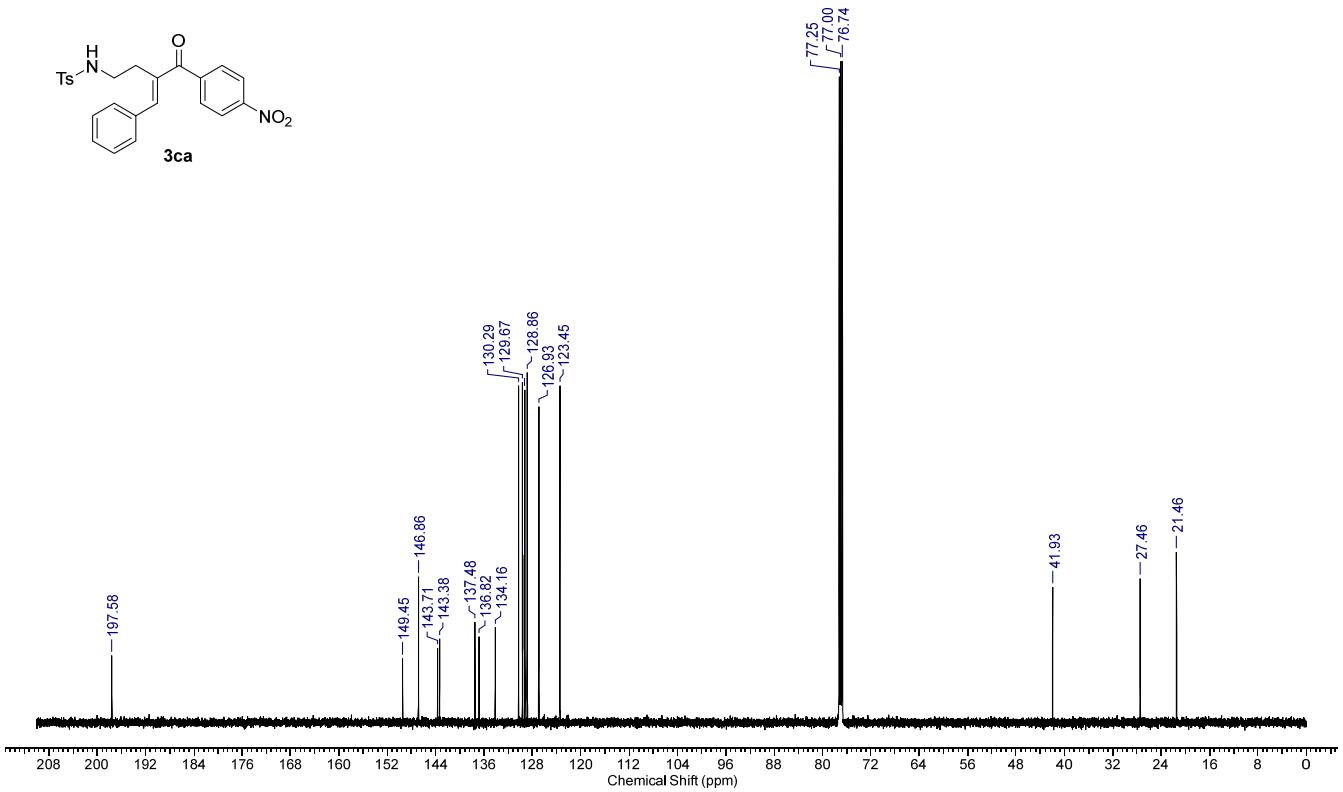
^{13}C NMR (125 MHz, $CDCl_3$) of **3bi**



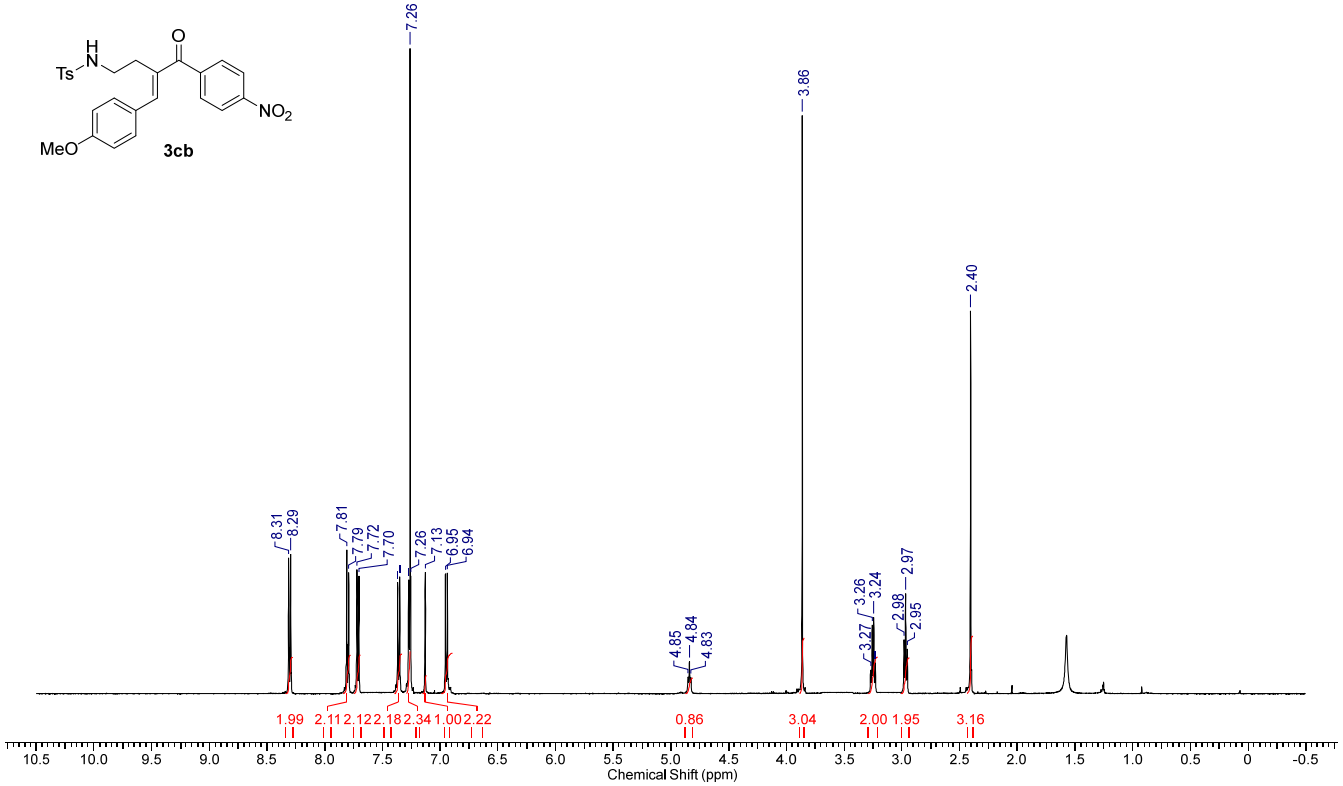
^{1}H NMR (500 MHz, $CDCl_3$) of **3ca**



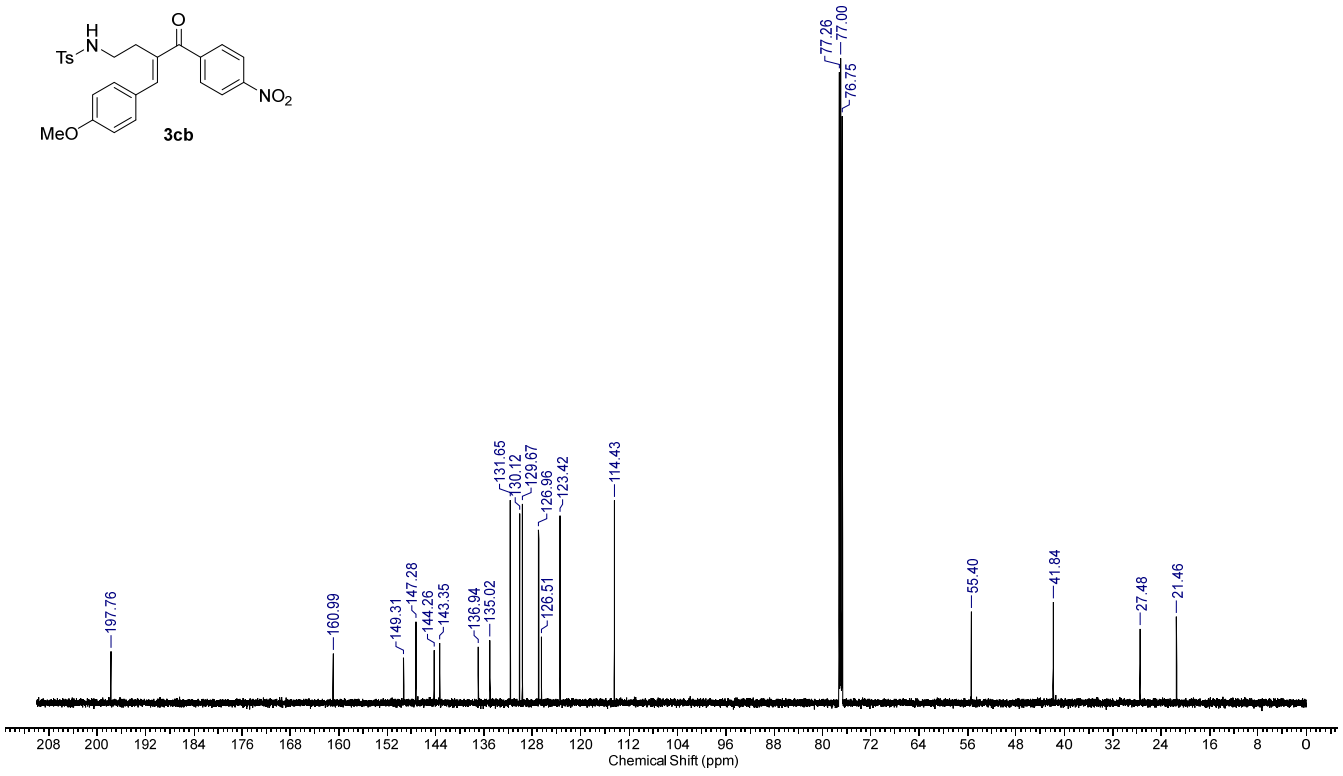
^{13}C NMR (125 MHz, $CDCl_3$) of **3ca**



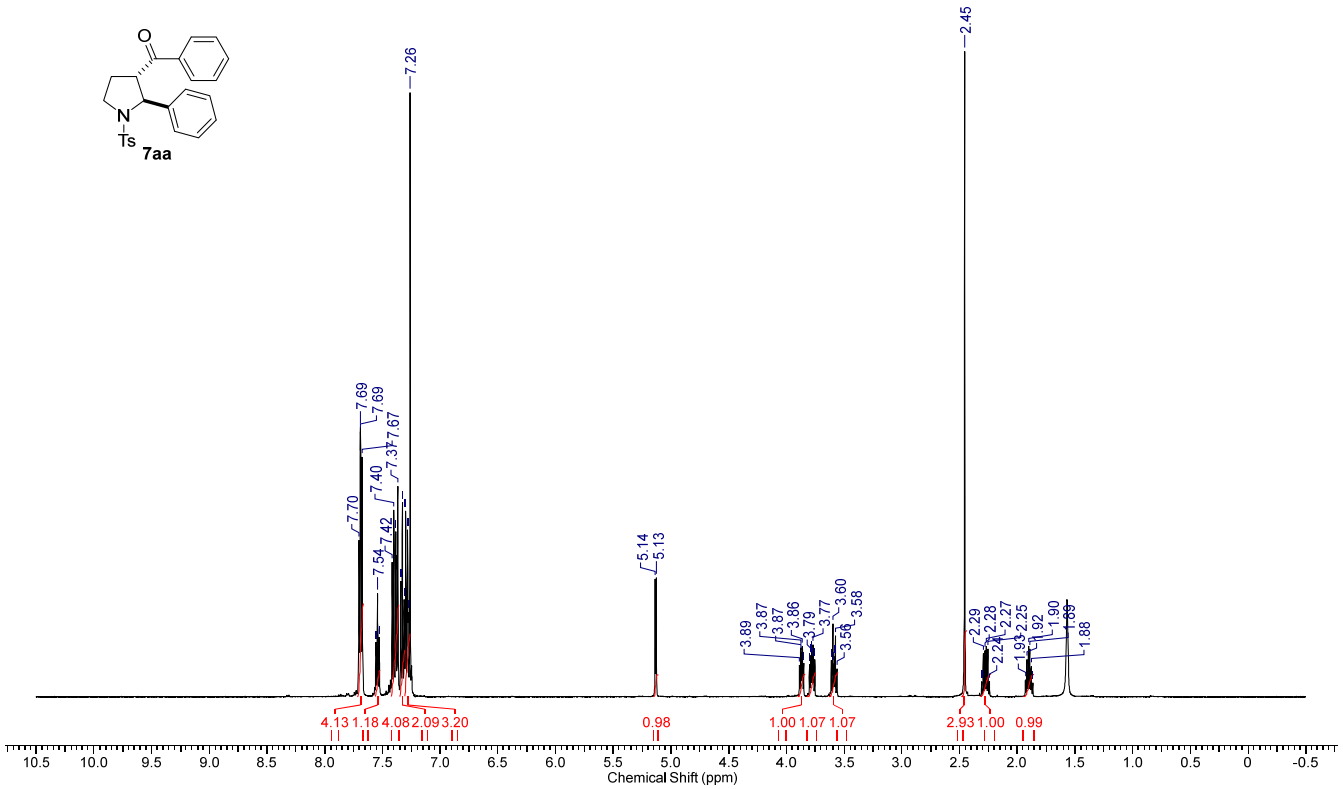
^{1}H NMR (500 MHz, $CDCl_3$) of **3cb**



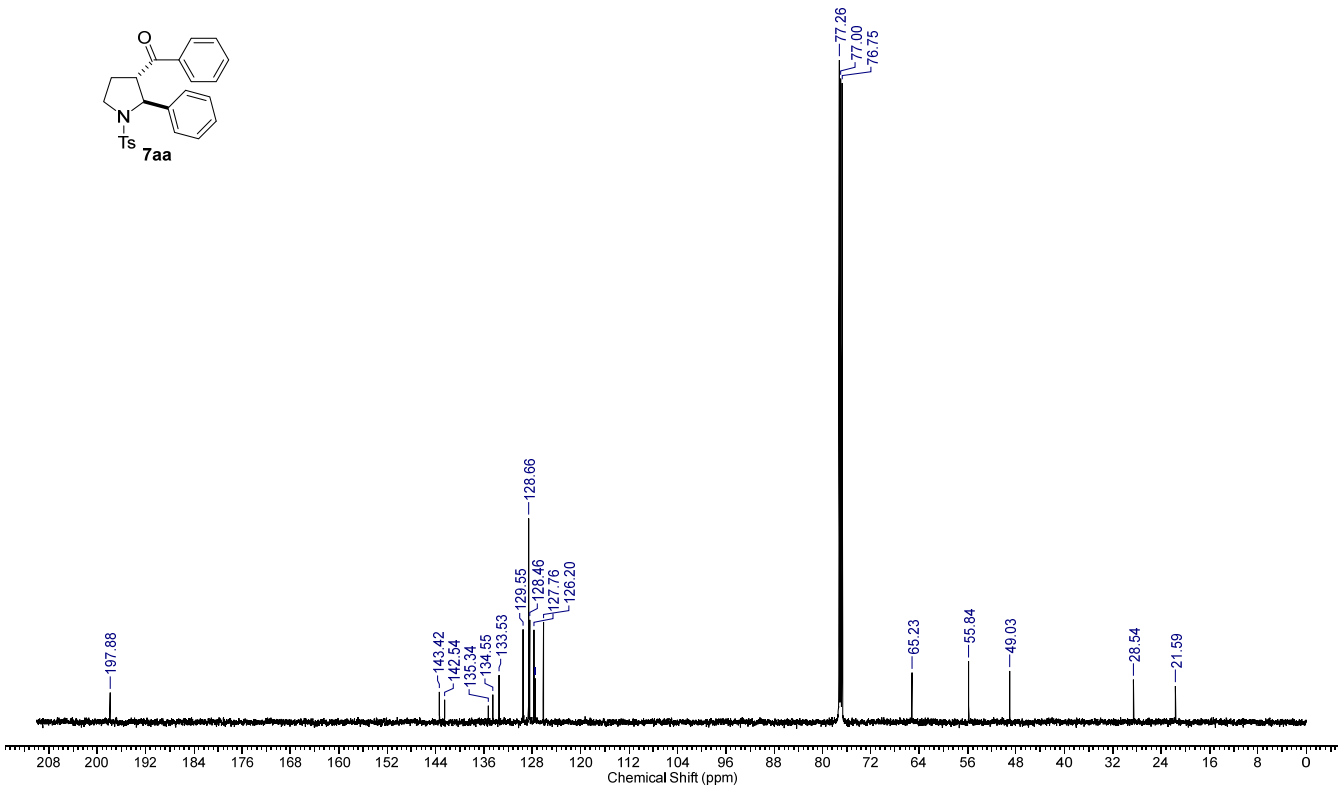
^{13}C NMR (125 MHz, $CDCl_3$) of **3cb**



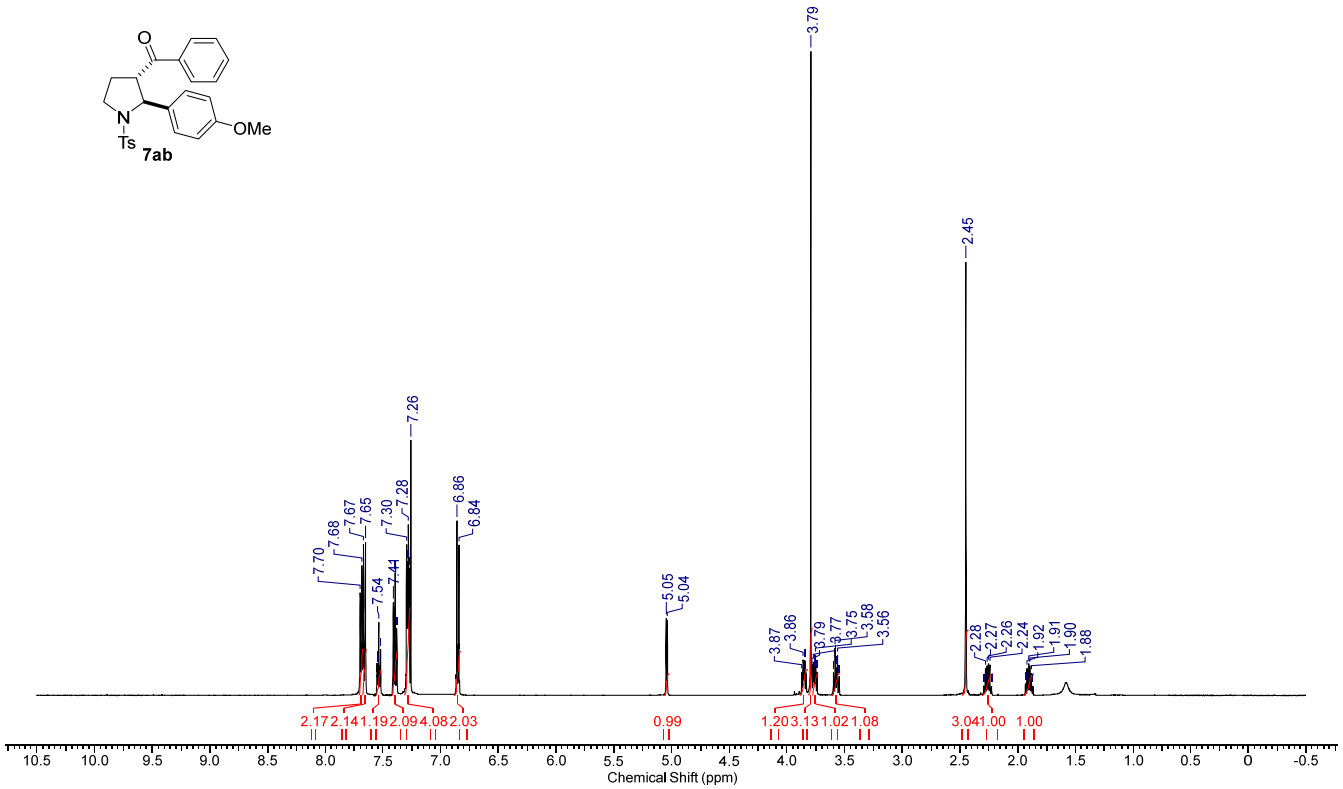
^{1}H NMR (500 MHz, $CDCl_3$) of **7aa**



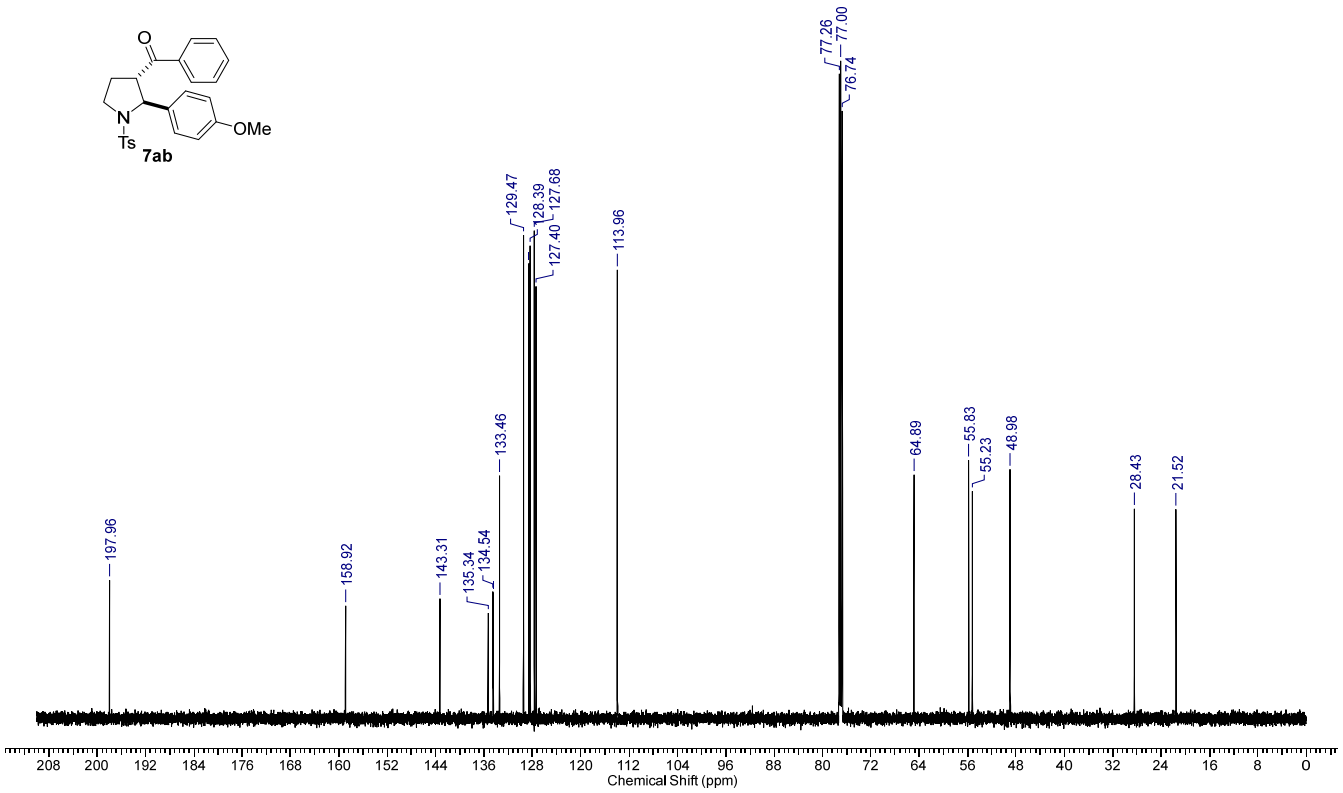
^{13}C NMR (125 MHz, $CDCl_3$) of **7aa**



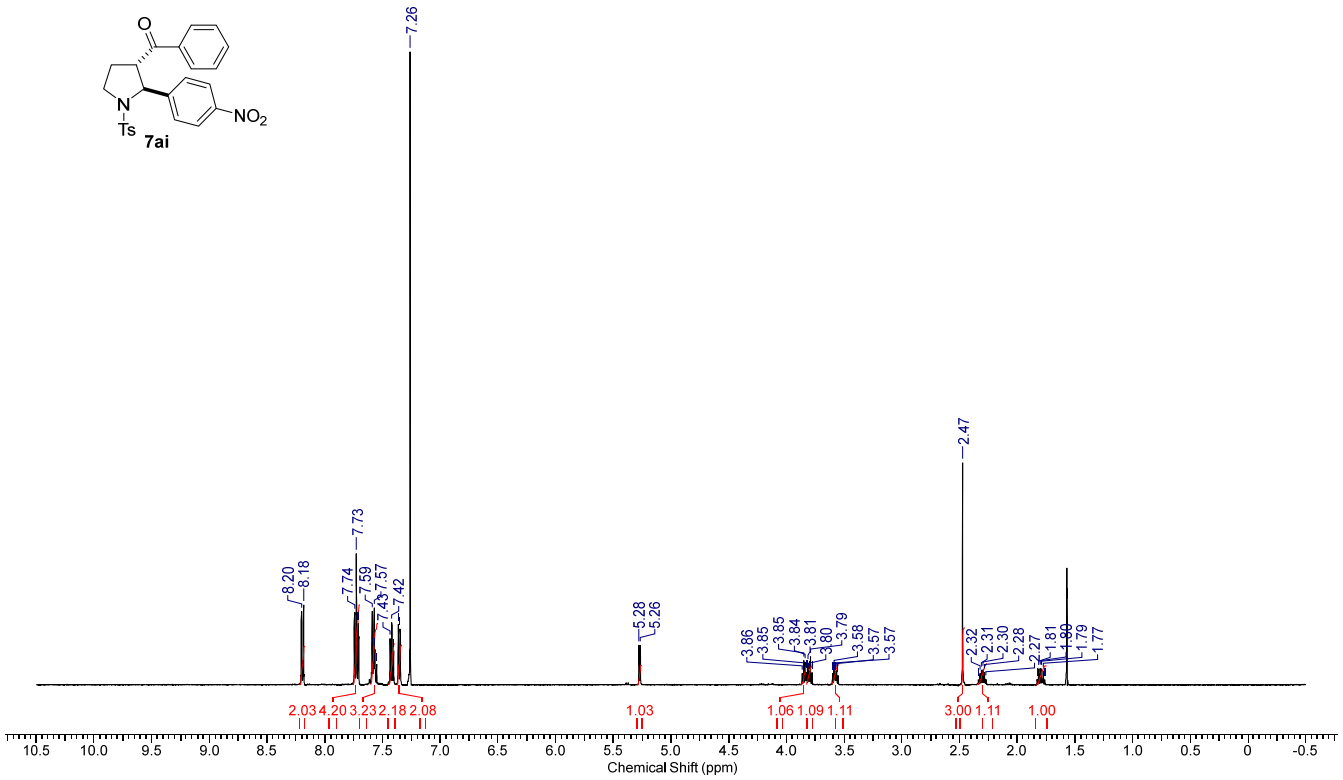
^{1}H NMR (500 MHz, $CDCl_3$) of **7ab**



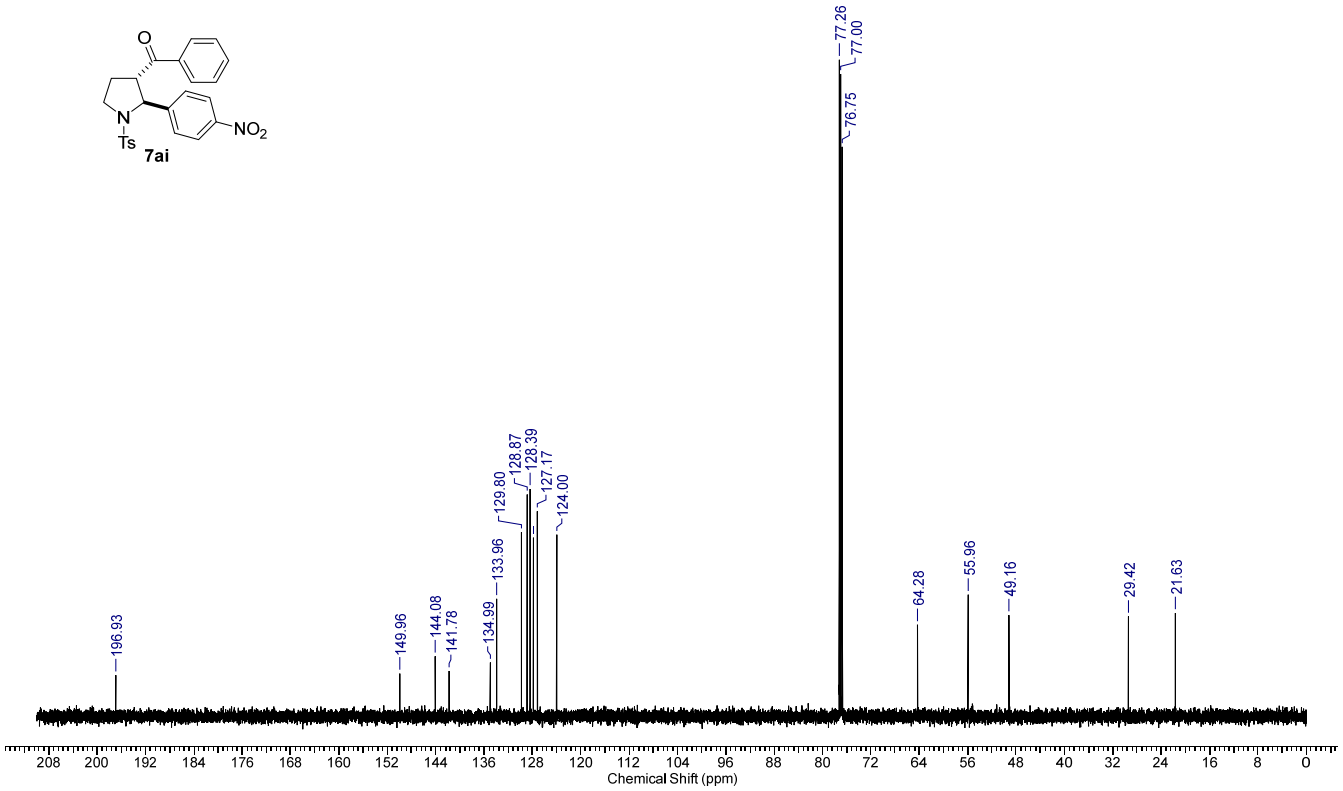
^{13}C NMR (125 MHz, $CDCl_3$) of **7ab**



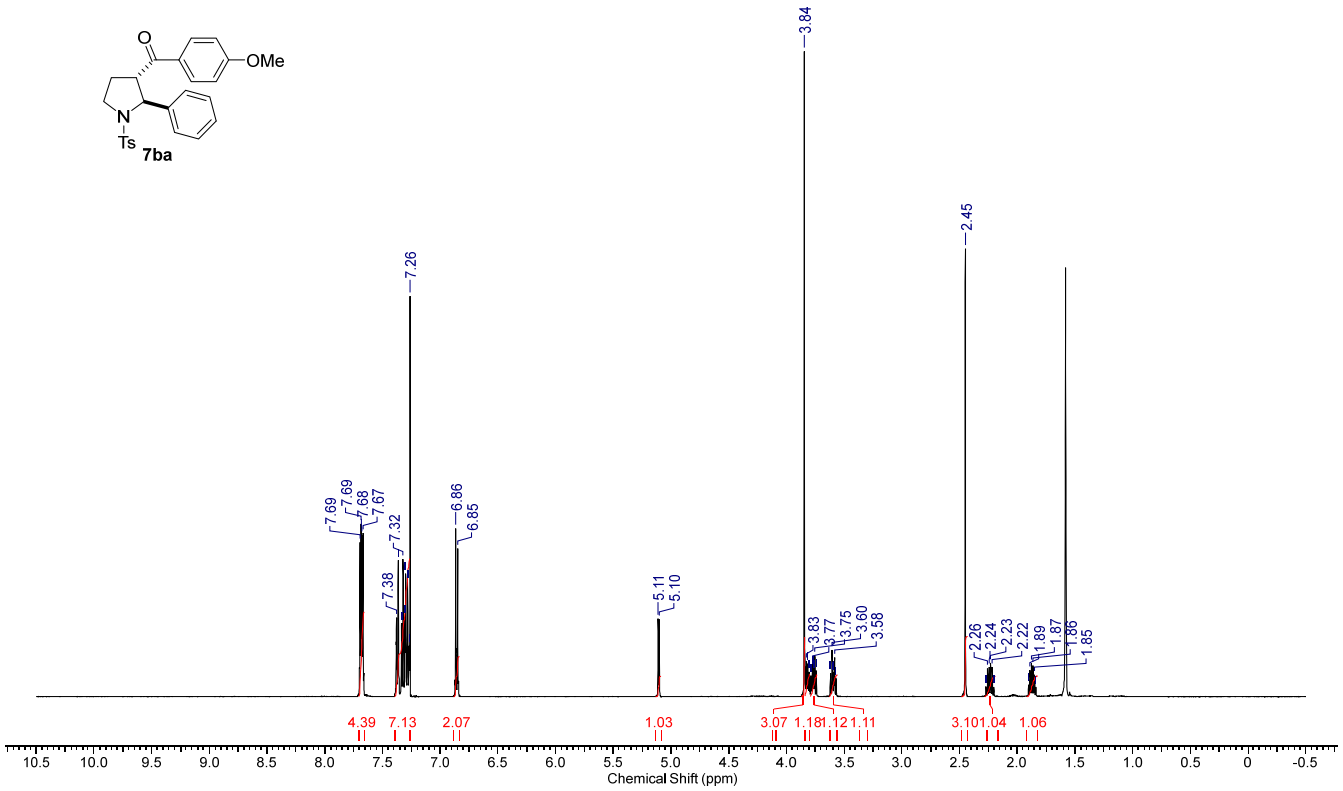
^{1}H NMR (500 MHz, $CDCl_3$) of **7ai**



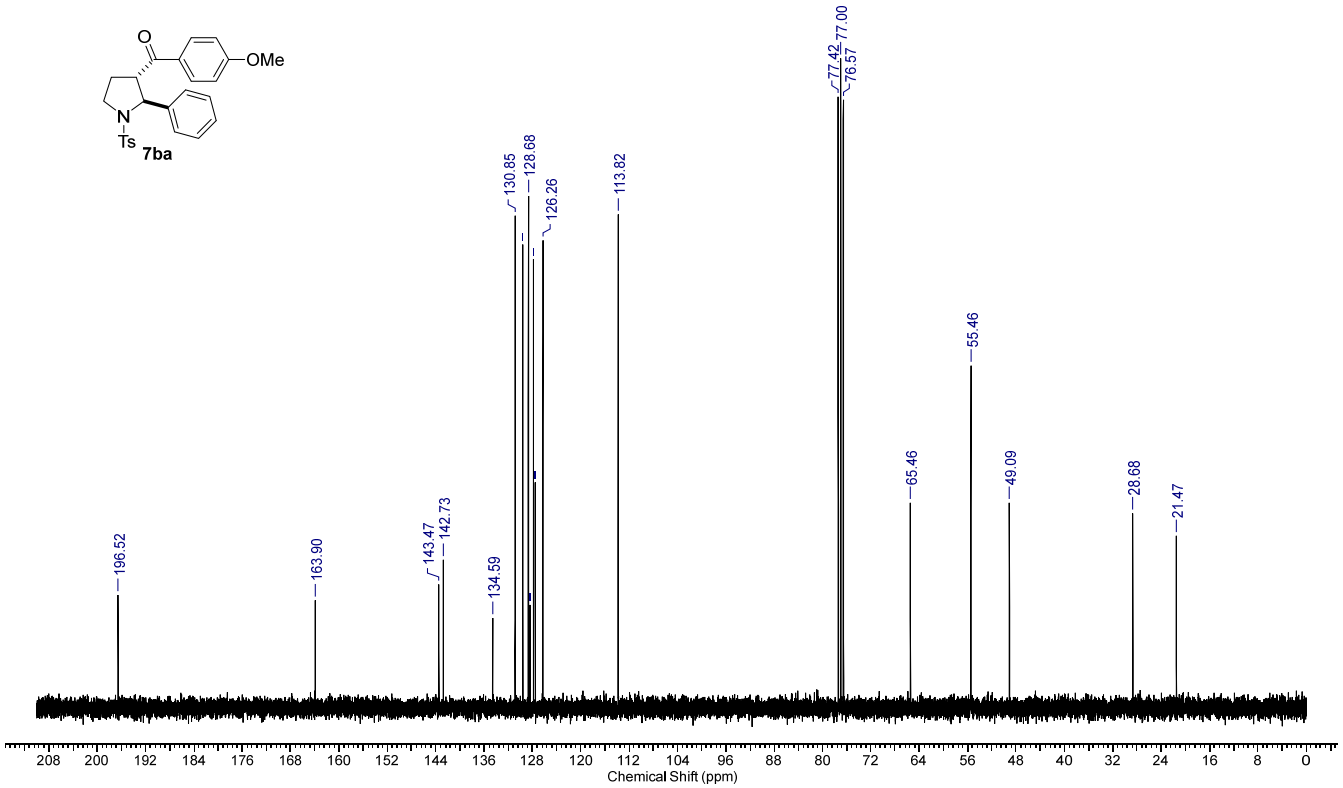
^{13}C NMR (125 MHz, $CDCl_3$) of **7ai**



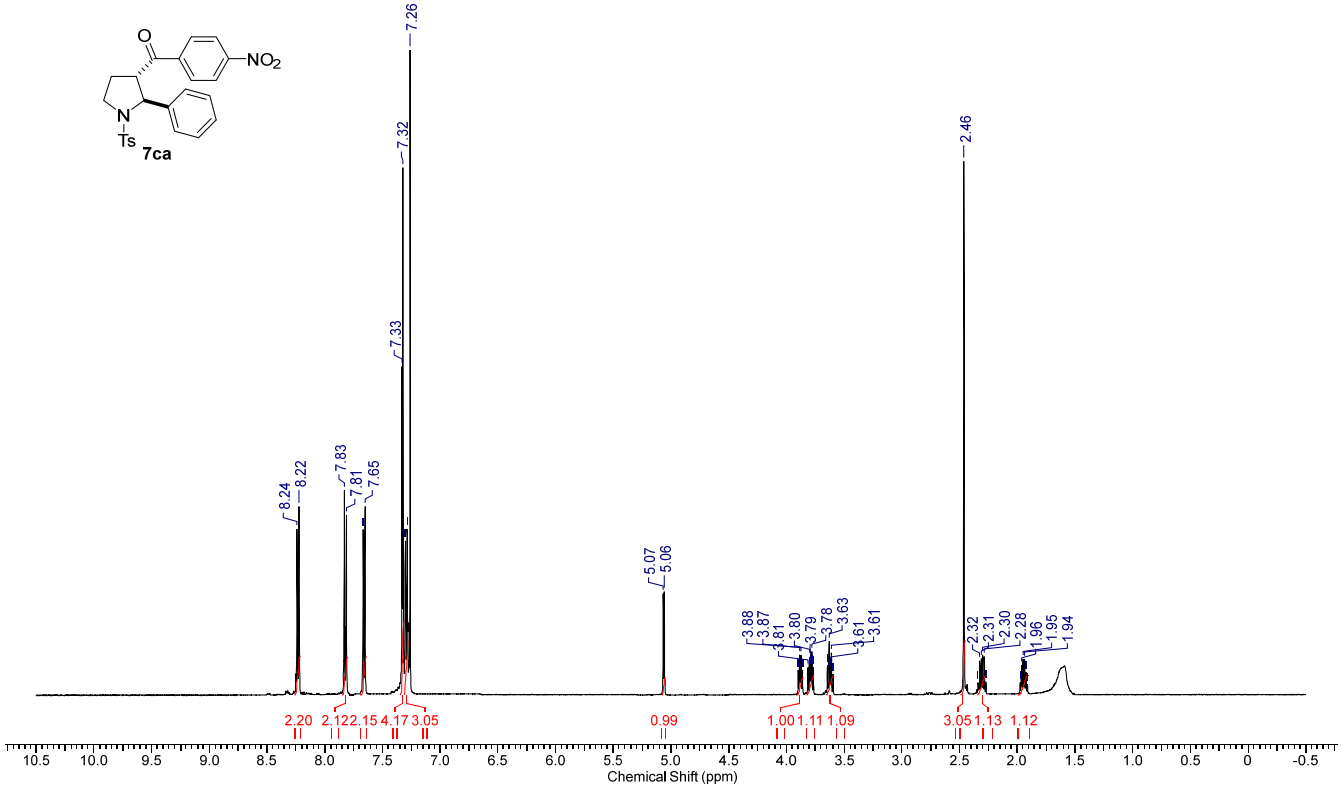
^{1}H NMR (500 MHz, $CDCl_3$) of **7ba**



^{13}C NMR (75 MHz, $CDCl_3$) of **7ba**



^{1}H NMR (500 MHz, $CDCl_3$) of **7ca**



^{13}C NMR (125 MHz, $CDCl_3$) of **7ca**