Asymmetric Synthesis of α-Allyl-α-Aryl α-Amino Acids by Tandem Alkylation/π-Allylation of α-Iminoesters

*John M. Curto, Joshua S. Dickstein, Simon Berritt, Marisa C. Kozlowski**

Supporting Information

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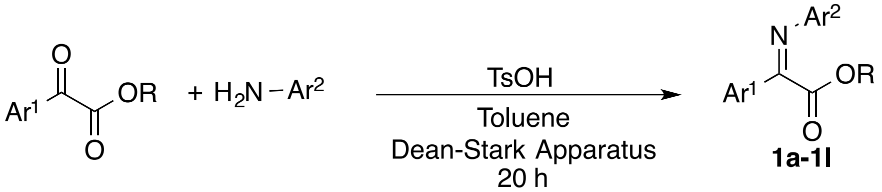
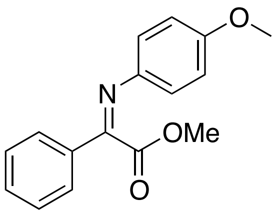
General Considerations.

Unless otherwise stated, all non-aqueous reactions were carried out under an atmosphere of dry argon in dry glassware. All glassware used in three component coupling reactions was base-washed (KOH/i-PrOH) prior to use. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, 2-methyltetrahydrofuran, cyclopentyl methyl ether and toluene were distilled from Na/benzophenone prior to use. Organometallic reagents (EtMgBr, *n*PentylMgBr) were purchased from Aldrich, or made from magnesium turnings/ribbon. Analytical thin layer chromatography (TLC) was performed on Silicycle 250 μm silica-gel F-254 plates.

^{1}H NMR and ^{13}C NMR spectra were recorded on a AM-500 Fourier transform NMR spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported relative to the solvent resonance peak δ 7.27 ($CDCl_3$) for ^{1}H and δ 77.16 ($CDCl_3$) for ^{13}C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad singlet, m = multiplet), coupling constants, and number of protons. High resolution mass spectra were obtained using a VG autospec with an ionization mode of either ESI or CI. Infrared spectra are reported in cm^{-1}. Melting points were obtained and are uncorrected. Unless otherwise noted, yields refer to isolated material on the basis of product purity ≥95% by ^{1}H NMR following silica gel chromatography with Silica-P flash silica gel (50-63 μm mesh particle size). Enantiomeric excess was determined utilizing chiral stationary phase (CSP) HPLC or SFC on OD (cellulose tris(3,5-dimethylphenylcarbamate) coated on silica gel) or IA (amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica gel) columns.

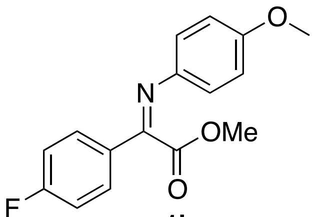
***General Procedure A for the Synthesis of* α-Iminoesters 1a-1l**





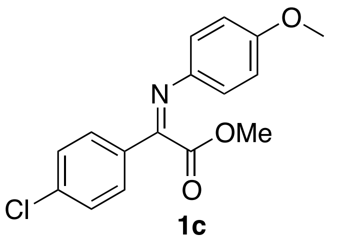
1a

(Z)-Methyl 2-(4-methoxyphenylimino)-2-phenylacetate (1a) [Table 1, entry 1]. To a solution of para-anisidine (2.46 g, 20 mmol) in toluene (29 mL), tosic acid monohydrate (350 mg, 2.0 mmol) was added. To this solution was added methyl benzoylformate (3.28 g, 20 mmol). The solution was then heated at reflux with azeotropic removal of water under N_2 (Dean-Stark conditions) for 20 h. The mixture was then cooled, passed through SiO_2 with 30% EtOAc/Hexanes, and concentrated. The resulting solid was recrystallized from hexanes to afford **1a** (5.0 g) in 93% yield as a 12:1 mixture of Z:E isomers in the form of a bright yellow crystalline solid confirmed by x-ray crystallography. Spectral data agreed with those reported previously by Zhang et al.[1]



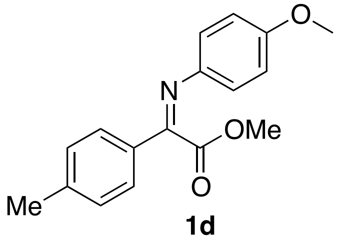
1b

(Z)-Methyl 2-(4-methoxyphenylimino)-2-(4-fluorophenylimino)acetate (1b) [Table 2, entry 3]. Following the general procedure A, *p*-anisidine (1.80 g, 14.6 mmol) was reacted with methyl (*p*-fluorobenzoyl)formate (2.66 g, 14.6 mmol) and TsOH (251 mg, 1.46 mmol) in toluene (21 mL) for 14.5 h under Dean-Stark conditions. After filtration, concentration and column chromatography (5% EtOAc/hexanes) product **1b** was frozen and placed *in vacuo* overnight to provide **1b** (2.64 g) in 63% yield as a 10:1 mixture of Z:E isomers in the form of a yellow solid. Spectral data agreed with those reported previously.[1]



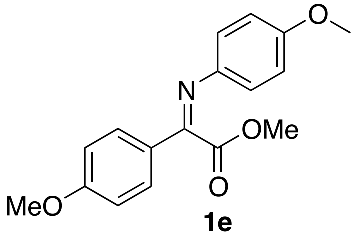
1c

(Z)-Methyl 2-(4-methoxyphenylimino)-2-(4-chlorophenylimino)acetate (1c) [Table 2, entry 4]. Following the general procedure A, *p*-anisidine (305.5 mg, 2.48 mmol) was reacted with methyl (*p*-chlorobenzoyl)formate (411 mg, 2.07 mmol) and TsOH (36 mg, .207 mmol) in toluene (12.5 mL) for 20 h under Dean-Stark conditions. After filtration, concentration and column chromatography (10% EtOAc/hexanes) product **1c** (488 mg) was obtained in 79% yield as a 13:1 mixture of isomers in the form of a dark yellow oil. Spectral data agreed with those reported previously.[1]



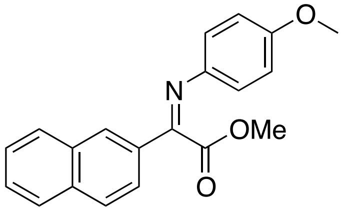
1d

(Z)-Methyl 2-(4-methoxyphenylimino)-2-(4-methylphenylimino)acetate (1d) [Table 2, entry 5]. Following the general procedure A, *p*-anisidine (2.9 g, 23.5 mmol) was reacted with methyl (*p*-methylbenzoyl)formate (3.5 g, 19.6 mmol) and TsOH (337 mg, 1.96 mmol) in toluene (28 mL) for 14 h under Dean-Stark conditions. After filtration, concentration and recrystallization in hexanes product **1d** (2.4 g) was obtained in 43% yield as a 10:1 mixture of Z:E isomers in the form of dark yellow crystalline solid. Spectral data agreed with those reported previously.[1]



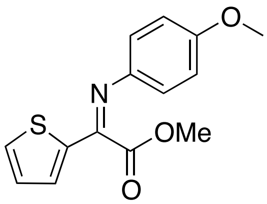
1e

(Z)-Methyl 2-(4-methoxyphenylimino)-2-(4-methoxyphenylimino)acetate (1e) [Table 2, entry 6]. Following the general procedure A, *p*-anisidine (2.75 g, 22.3 mmol) was reacted with methyl (*p*-methoxybenzoyl)formate (3.6 g, 18.6 mmol) and TsOH (337 mg, 0.186 mmol) in toluene (26.5 mL) for 20 h under Dean-Stark conditions. After filtration, concentration, hot gravity filtration and recrystallization from hexanes product **1e** (2.6 g) was obtained in 47% yield as a 19:1 mixture of Z:E isomers in the form of yellow crystalline solid. Spectral data agreed with those reported previously.[1]



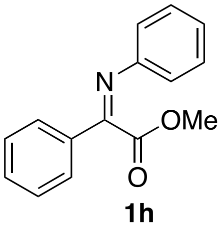
1f

(Z)-Methyl 2-(4-methoxyphenylimino)-2-(napthalen-2-yl)acetate (1f) [Table 2, entry 7]. Following the general procedure A, *p*-anisidine (788 mg, 6.44 mmol) was reacted with methyl (2-napthalene)formate (1.36 g, 6.44 mmol) and TsOH (110 mg, .64 mmol) in toluene (9.1 mL) for 24 h under Dean-Stark conditions. After filtration, concentration, hot gravity filtration and recrystallization from 6% CH_2Cl_2/hexanes, product **1f** (1.1 g) was obtained in 55% yield as a 30:1 mixture of Z:E isomers in the form of yellow crystalline solid. Spectral data agreed with those reported previously.[1]



1g

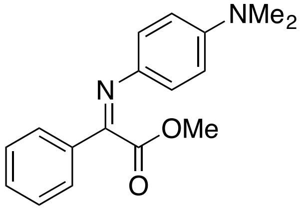
(Z)-Methyl 2-(4-methoxyphenylimino)-2-(thiophen-2-yl)acetate (1g) [Table 2, entry 8]. Following the general procedure A, *p*-anisidine (362 mg, 2.94 mmol) was reacted with methyl (2-thiophene)formate (417 mg, 2.45 mmol) and TsOH (42 mg, 0.245 mmol) in toluene (5 mL) for 20 h under Dean-Stark conditions. After filtration, concentration and column chromatography (10% EtOAc/hexanes) product **1g** (350 mg) was obtained in 52% yield as a 15:1 mixture of Z:E isomers in the form of a dark yellow solid: mp 92-94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 5.0 Hz, 1H), 7.39 (d, J = 3.8 Hz, 1H), 7.10 (t, J = 4.2 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 157.7, 153.1, 142.7, 141.1, 131.2, 131.2, 128.0, 121.7, 114.3, 55.5, 52.4; IR (film) 2952, 1734, 1607, 1500, 1246 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}NO_3S$ $[M+H]^+$ m/z = 276.0694; found 276.0692.



1h

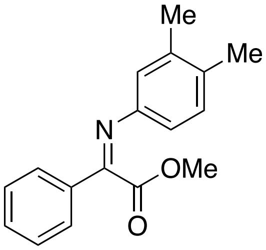
(Z)-Methyl 2-phenyl-2-(phenylimino)acetate (1h) [Table 2, entry 9]. Following the general procedure A, aniline (1.79 g, 19.2 mmol) was reacted with methyl benzoylformate (3 g, 18.3 mmol) and TsOH (174 mg, 0.9 mmol) in toluene (30 mL) for

7 h under Dean-Stark conditions. After filtration, concentration and recrystallization in hexanes, product **1h** (3.6 g) was obtained in 82% yield as a 10:1 mixture of Z:E isomers in the form of a pale yellow solid. Spectral data agreed with those reported previously by Hu et al.[2]



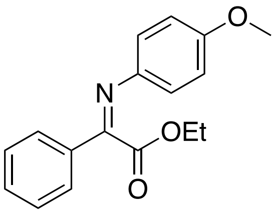
1i

(Z)-Methyl 2-(4-dimethylaminophenylimino)-2-phenylacetate (1i) [Table 2, entry 10]. Following the general procedure A, *N,N*-Dimethyl-*p*-phenylenediamine (1.0 g, 7.3 mmol) was reacted with methyl benzoylformate (1.2 g, 7.3 mmol) and tosic acid monohydrate (260 mg, 1.5 mmol) in toluene (10.4 mL) for 20 h under Dean-Stark conditions. After filtration, concentration and column chromatography (7.5% EtOAc/hexanes) to afford **1i** (568 mg) in 28% yield as a 8:1 mixture of Z:E isomers in the form of a brown crystalline solid: mp 66-68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.49-7.43 (m, 3H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.71 (d, *J* = 7.9 Hz, 2H), 3.74 (s, 3H), 2.97 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 156.8, 148.9, 139.3, 134.8, 131.1, 128.7, 127.7, 121.9, 112.8, 52.0, 40.7 (minor rotamer peaks: 128.9, 128.5, 125.2, 111.8, 53.1, 40.4).



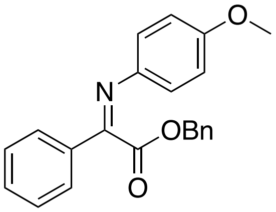
1j

(Z)-Methyl 2-(3,4-dimethylphenylimino)-2-phenylacetate (1j) [Table 2, entry 11]. Following the general procedure A, 3,4-dimethyl aniline (1.0 g, 8.2 mmol) was reacted with methyl benzoylformate (1.35 g, 8.2 mmol) and tosic acid monohydrate (282 mg, 1.5 mmol) in toluene (12 mL) for 20 h under Dean-Stark conditions. After filtration, concentration and column chromatography (7% EtOAc/hexanes) to afford **1j** (1.56 g) in 71% yield as a 12:1 mixture of Z:E isomers in the form of a yellow amorphous solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.52-7.44 (m, 3H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 1H), 6.72 (dd, *J* = 7.9, 1.8 Hz, 1H), 3.69 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 159.3, 147.9, 137.3, 134.3, 133.6, 131.7, 130.1, 128.8, 128.0, 121.3, 116.8, 52.0, 20.0, 19.4.



1k

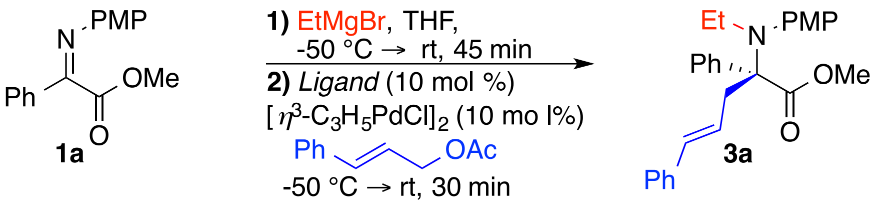
(Z)-Ethyl 2-(4-methoxyphenylimino)-2-phenylacetate (1k) Following the general procedure A, para-anisidine (3.9 g, 32 mmol) was reacted with ethyl benzoylformate (3.3 g, 31 mmol) and tosic acid monohydrate (300 mg, 1.5 mmol) in toluene (46 mL) for 20 h under Dean-Stark conditions. After filtration and concentration the resulting solid was recrystallized from hexanes to afford **1k** (7.3 g) in 91% yield as a 9:1 mixture of Z:E isomers in the form of a bright yellow crystalline solid. Spectral data agreed with those reported previously.[1]



1l

(Z)-Benzyl 2-(4-methoxyphenylimino)-2-phenylacetate (1l). Following the general procedure A, para-anisidine (1.5 g, 12.5 mmol) was reacted with benzyl 2-oxo-2-phenylacetate (2.9 g, 12.1 mmol) and tosic acid monohydrate (117 mg, 0.6 mmol) in benzene (18 mL) for 20 h under Dean-Stark conditions. After filtration and concentration the resulting solid was recrystallized from hexanes to afford **1l** (3.6 g) in 86% yield in the form of a yellow solid. Spectral data agreed with those reported previously by You et al.[3]

Parallel Microscale Experimentation (Table 1 and S1)

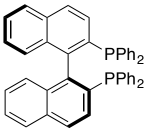


The following procedure is representative of the high-throughput experimentation reactions described in this publication. The ligands (0.86 µmol) were dosed into the 96-well reactor 1-mL vials as solutions (50 µL of a 0.017 M solution in THF). Plates of these ligands may be plated in advance of the screen; the solvent is removed by evacuation on a Genevac, and the plates are stored in a glovebox. A solution of [η^3-$C_3H_5PdCl]_2$ (0.86 µmol Pd, 50 µL of a 0.017 M solution in THF) was then added to the reaction vials and was evacuated to dryness on a Genevac. A parylene stir-bar was added to each vial. In a separate 20 dram vial, α-iminoester **1a** (914 µmol, 246 mg) was dissolved in 4.9 mL THF. The vial was cooled to -50 °C on a Mecour Coolingbox combined with a Julabo temperature controller and 3.0 M EtMgBr in Et_2O (1500 μmol, 0.50 ml) was added. The reaction mixture was warmed to ambient temperature and allowed to react for 45 min and subsequently cooled back to -50 °C. Cinnamyl acetate (8.5 μmol) was dosed into the 96 well reactor 1-mL vials with ligand/catalyst mixture at -50 °C as solutions (50 μL of a 0.17 M solution in THF). The substrate and Grignard mixture was then dosed to the reaction vials at -50 °C (50 μL of a 0.18M solution in THF). The vials were then sealed and allowed to warm to ambient temperature. After stirring for 45 min the residues were diluted with 500 μL of a 5% solution of glacial acetic acid in isopropyl alcohol and the contents were stirred for 30 min. Into a separate 96-well plate LC block was added 750 μL of MeCN per well followed by 20 μL of the diluted reaction mixtures. The 96-well plate LC block was then sealed with a polypropylene 1 mL cap mat. The reactions were analyzed using a CSP SFC (OD-H 250x4.6mm, 5 um, MeOH/CO_2, 3 mL/min, 35 C, 200 bar, 215nm, 4% MeOH for 4 min then to 40% at 6 min hold for 5 min, Peak 1 at 6.9 min and Peak 2 at 7.5 min).

Table S1: Selected Results from Parallel Microscale Experimentation (8.6 μmmol) and Comparison to Scale Up (0.372 mmol) when Applicable (eq S2).

		PME Screen[a]				Bench top Scale Up[b]	
Ligand		Total Area	Peak 1	Peak 2	er (%)[c]	conv. (%)[d]	er (%)[e]
S-BINAP	**S1**	3252	972	2280	30:70	>90	90:10
S-H8-BINAP	**S2**	5424	3229	2195	60:40	>90	74:26
(R)-Tol-BINAP	**S3**	5127	3264	1863	64:36	~90	56:44
(R)-Segphos	**S4**	781	550	231	70:30	>90	70:30
(R)-P3-Segphos	**S5**	5358	1681	3677	31:69	>90	90:10
(R)-Difluorphos	**S6**	456	317	139	70:30	>90	94:6
(R)-Cl,MeO-Biphep	**S7**	5230	3530	1700	68:32	~90	87:13
SL-A102-1	**S8**	5126	3194	1932	62:38	-	-
SL-A121-1	**S9**	5311	2119	3192	40:60	-	-
(S)-C1-Tunephos	**S10**	2574	742	1832	29:71	~30	64:36
(S)-C2-Tunephos	**S11**	4041	1228	2813	30:70	-	-
(S)-C3-Tunephos	**S12**	5334	1675	3659	31:69	>90	89:11
(S)-C4-Tunephos	**S13**	5248	1711	3537	33:67	-	-
(S)-C5-Tunephos	**S14**	5280	1876	3404	36:64	-	-
(S)-C6-Tunephos	**S15**	4380	1475	2905	34:66	-	-
(S)-Me-Soniphos	**S16**	2297	578	1719	25:75	>90	70:30
(S)-Cyclohex-Soniphos	**S17**	5475	1379	4096	25:75	>90	86:14
(-)-TMBTP	**S18**	5512	3747	1765	68:32	>90	70:30
(R)-P-Phos	**S19**	520	353	167	68:32	>90	90:10
(S)-Xylyl-P-Phos	**S20**	964	283	681	29:71	-	-
SL-W001-1	**S21**	5252	2043	3209	39:61	-	-
SL-W009-1	**S22**	5356	1720	3636	32:68	>90	74:26
SL-M001-1	**S23**	3623	2421	1202	69:31	>90	83:17
SL-M003-1	**S24**	940	346	594	37:63	-	-
(R,R)-DACH-Phenyl Trost	**S25**	0	0	0	50:50	<10	ND
(R,R)-DACH-Naphthyl	**S26**	499	164	335	33:67	-	-
(R)-Pfaltz(Ph)	**S27**	0	0	0	50:50	~15	57:43
(S)-Xyl-SDP	**S28**	5299	2023	3276	38:62	-	-

[a] 8.6 μmol of **1a**, run at a starting temperature of -50 °C. [b] 0.372 mmol of **1a**, run at a starting temperature of -78 °C. [c]Determined by chiral SFC [d]Conv. is determined by amount of **3a** to N-alkylated intermediate **4**. [e]Determined by chiral HPLC and when major enantionmer was opposite from PME screen, the opposite enantiomer of ligand was used.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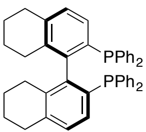
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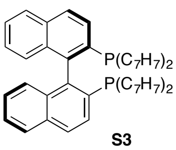
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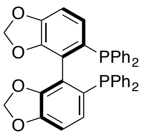
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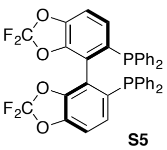
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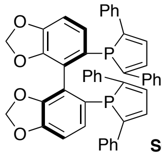
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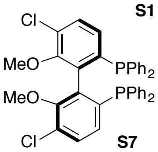
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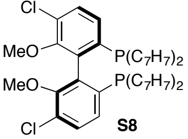
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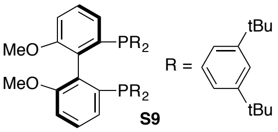
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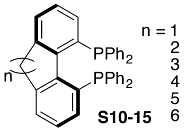
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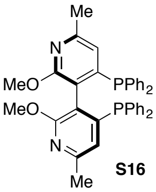
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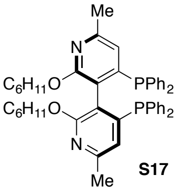
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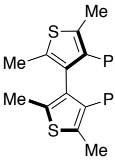
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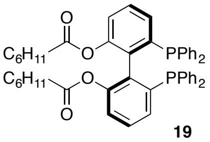
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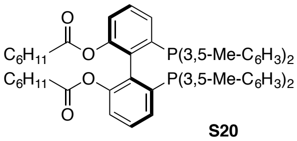
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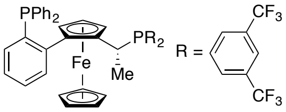
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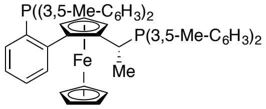
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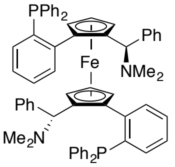
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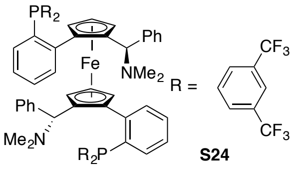
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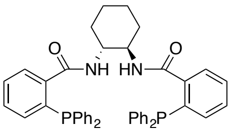
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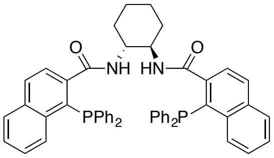
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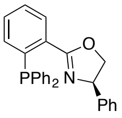
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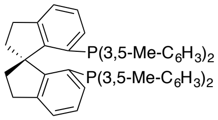
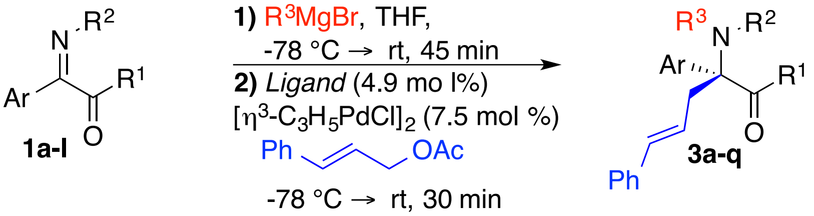
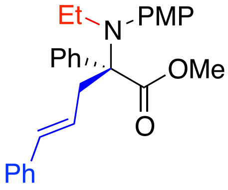

S28

General Procedure B for Three Component Coupling (Tables 2 and 3):



Rigorously anhydrous and air-free conditions are required for optimal results due to the reactivity of the intermediate enolate (see General Considerations). α-Iminoester **1a-1l** (0.372 mmol) was added to a flamed dried Schlenk flask that had been charged with a stir bar and was then vacuum-purged three times under argon. The α-iminoester was dissolved in THF (2.0 mL) and cooled to -78 °C. To this solution was added EtMgBr (3.0 M in Et_2O, 198 μL, 0.595 mmol) under argon. The mixture was slowly warmed to room temperature and allowed to stir for an additional 30 min at room temperature. A flame dried round bottom flask equipped with a stir bar was charged with $[\eta^3\text{-}C_3H_5PdCl]_2$ (5.1 mg,0.0140 mmol) and (*R*)-DIFLUORPHOS (12.7 mg, 0.0186 mmol) and vacuum-purged three times under argon. The mixture was dissolved with THF (2.0 mL) and cinnamyl acetate (66 μL, 0.372 mmol) was added. The second solution was stirred for 5 minutes at ambient temperature under argon, cooled to -78 °C, and added to the cooled (-78 °C) first solution via syringe. The combined mixture was allowed to warm to room temperature and stirred for 45 min. The resultant reaction mixture was quenched with satd NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography to afford pure α-allyl-α-aryl α-amino acids **3a-3q**.

Notes: Typical color after the first step is a translucent yellow and red to orange after the second step. An indicator of the first step not working is when the reaction color turns green or black. Grignard source was important. More than 1 equiv of cinnamyl acetate, or a ligand to palladium ratio greater than 1:1 was detrimental to the enantioselectivity of second step.

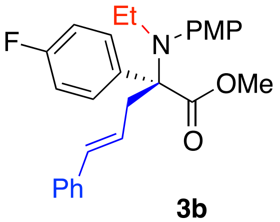


3a

(*S*,*E*)-Methyl 2-(ethyl(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3a) [Table 2, entry 2]. Following the general procedure B, 3.0 M EtMgBr (198 μL, 0.595 mmol) was added to **1a** (100 mg, 0.372 mmol) in THF (2 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (5.1 mg, 0.0140 mmol), *R*-DIFLUORPHOS (12.8 mg, 0.0186 mmol) and cinnamyl acetate (65 mg, 0.372 mmol) in THF (2 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% EtOAc/hexanes) product **3a** (134 mg) was obtained in 87% yield as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.30-7.27 (m, 1H), 7.21 (t, J = 7.4 Hz, 2H), 7.17-7.12 (m, 3H), 7.09 (d, J = 7.2 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 5.89 (d, J = 16.0 Hz, 1H), 5.73 (dt, J = 15.9, 7.5 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.09-3.02 (m, 1H), 2.99-2.92 (m, 1H), 2.63 (ddd, J = 13.9, 7.2, 0.5 Hz, 1H), 2.44 (ddd, J = 14.0, 7.4, 0.5 Hz, 1H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 157.8, 141.6, 139.1, 138.0, 133.0, 131.3, 128.4, 127.8 (2), 127.3, 127.0, 126.1 (2), 113.8, 75.1, 55.5, 51.4, 46.7, 44.4, 14.7; IR (film) 3026, 2694, 2836, 1724, 1603, 1507, 1244 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{30}NO_3$ $[M+H]^+$ m/z = 416.2226; found 416.2229; $[\alpha]^{24}_D$ = +145.3 (c 0.28, 88% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3a**: 6.6 min (major) and 8.0 min (minor).

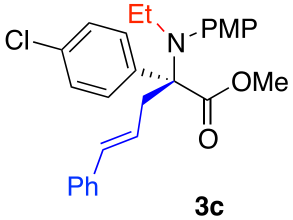
Ethylmagnesium Bromide from Aldrich was batch dependent and was only successful in general procedure B when it was colorless; EtMgBr from Acros was never colorless

Ethylmagnesium Bromide. Magnesium turnings (1.4 g, 58.3 mmol) were stirred in 2.0 M HCl (~15 mL) for ten minutes, filtered, washed with ethanol (~100 mL), Et_2O (~150 mL), collected and dried under vacuum in a 50 °C oil bath for 2 h, and then added to a flame dried 50 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. Et_2O (~3 mL) was added to magnesium. Bromoethane (4.58 mL, 61.4 mmol) and Et_2O (6.14 mL) are added to a second flamed dried round bottom flask under argon. 500 μL of the bromoethane solution is added to magnesium to initiate reflux. Et_2O (5.5 mL) is added to the refluxing magnesium solution, followed by bromoethane solution (500 μL), then Et_2O (5.5 mL). The bromoethane solution is then added dropwise while maintaining reflux (~20 min). After addition is complete, the mixture is heated to reflux for 30 min, allowed to cool to rt, and transferred via cannulation into a sealed flask under argon. The 3.0 M ethylmagnesium bromide solution in Et_2O is colorless and can be stored in a refrigerator for up to two weeks with continuous use.



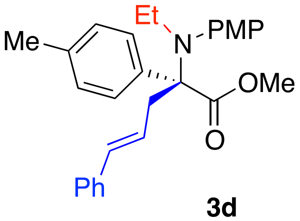
3b

(*S,E*)-Methyl 2-(N-ethyl-N-(4-methoxyphenyl)amino)-2-(4-fluorophenyl)-5-phenylpent-4-enoate (3b) [Table 2, entry 3]. Following the general procedure B, 3.0 M EtMgBr (177 μL, 0.532 mmol) was added to **1b** (76.3 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0098 mmol), *R*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% EtOAc/hexanes) product **3b** (99 mg) was obtained in 86% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.17-7.13 (m, 3H), 7.10 (d, *J* = 7.3 Hz, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.90 (d, *J* = 15.7 Hz, 1H), 5.71 (dt, *J* = 15.7, 7.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.03-2.89 (m, 2H), 2.62 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.39 (dd, *J* = 13.7, 7.6 Hz, 1H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 162.9 (d, *J* = 246 Hz), 157.9, 138.8, 137.8, 137.3 (d, *J* = 3.2 Hz), 133.4, 131.2, 129.6 (d, *J* = 7.6 Hz), 128.5, 127.1, 126.0, 125.6, 114.6 (d, *J* = 21.2 Hz), 113.9, 74.6, 55.5, 51.5, 46.4, 44.4, 14.6; IR (film) 3036, 2965, 2837, 1727, 1606, 1505, 1244 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{29}FNO_3$ $[M+H]^+$ *m/z* =434.2131; found 434.2133; $[\alpha]^{25}_D$ = +128.4 (c 0.48, 86% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3b**: 6.6 min (major) and 11.7 min (minor).



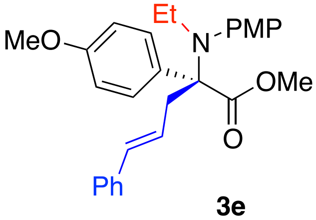
3c

(*S,E*)-Methyl 2-(N-ethyl-N-(4-methoxyphenyl)amino)-2-(4-chlorophenyl)-5-phenylpent-4-enoate (3c) [Table 2, entry 4]. Following the general procedure B, 3.0 M EtMgBr (219 μL, 0.658 mmol) was added to **1c** (100 mg, 0.329 mmol) in 2-MeTHF (2 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (4.49 mg, 0.0123 mmol), *R*-DIFLUORPHOS (11.26 mg, 0.0165 mmol) and cinnamyl acetate (58 mg, 0.329 mmol) in 2-MeTHF (2 mL) for 45 min. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 5% EtOAc/hexanes) product **3c** (124 mg) was obtained in 84% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.16-7.08 (m, 5H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.90 (d, *J* = 15.8 Hz, 1H), 5.68 (dt, *J* = 15.6, 7.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.98-2.87 (m, 2H), 2.60 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.37 (dd, *J* = 14.0, 7.3 Hz, 1H), 0.80 (t, *J* = 7.0 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 158.0, 140.3, 138.7, 137.8, 133.5, 133.0, 131.2, 129.4, 128.5, 128.0, 127.1, 126.1, 125.4, 113.9, 74.7, 55.5, 51.6, 46.5, 44.3, 14.6; IR (film) 2958, 2855, 1725, 1604, 1507, 1244 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{29}ClNO_3$ $[M+H]^+$ *m/z* = 450.1836; found 450.1835; $[\alpha]^{25}_D$ = +117.2 (c 0.37, 92% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3c**: 7.2 min (major) and 12.8 min (minor).



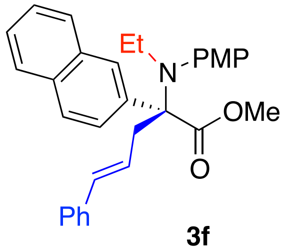
3d

(*S,E*)-Methyl 2-(N-ethyl-N-(4-methoxyphenyl)amino)-2-(4-methylphenyl)-5-phenylpent-4-enoate (3d) [Table 2, entry 5]. Following the general procedure B, 3.0 M EtMgBr (177 µL, 0.532 mmol) was added to **1d** (75.4 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0010 mmol), *R*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% EtOAc/hexanes) product **3d** (99 mg) was obtained in 87% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.18- 7.13 (m, 5H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.93 (d, *J* = 15.7 Hz, 1H), 5.75 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.09-3.02 (m, 1H), 2.98-2.91 (m, 1H), 2.62 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.44 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.37 (s, 3H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 157.8, 139.2, 138.5, 138.1, 136.9, 132.8, 131.3, 128.6, 128.4, 127.7, 126.9, 126.2 126.0, 113.8, 74.8, 55.5, 51.4, 46.6, 44.2, 21.2, 14.7; IR (film) 3026, 2963, 2865, 1724, 1605, 1508, 1244, 1036 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{32}NO_3$ $[M+H]^+$ *m/z* = 430.2382; found 430.2369; $[\alpha]^{25}_D$ = +123.1 (c 0.47, 80% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3d**: 7.0 min (major) and 8.1 min (minor).



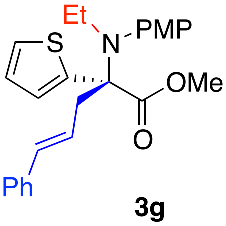
3e

(*S,E*)-Methyl 2-(N-ethyl-N-(4-methoxyphenyl)amino)-2-(4-methoxyphenyl)-5-phenylpent-4-enoate (3e) [Table 2, entry 6]. Following the general procedure B, 3.0 M EtMgBr (124 µL, 0.372 mmol) was added to **1e** (56 mg, 0.186 mmol) in THF (1 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.70 mg, 0.0047 mmol), *R*-BINAP (5.67 mg, 0.0091 mmol) and cinnamyl acetate (32 mg, 0.186 mmol) in THF (1 mL) for 45 min. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 5% EtOAc/hexanes) product **3e** (65 mg) was obtained in 79% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.7 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.15-7.10 (m, 5H), 6.90-6.88 (m, 4H), 5.93 (d, *J* = 15.9 Hz, 1H), 5.73 (dt, *J* = 15.8, 7.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.07-3.00 (m, 1H), 2.95-2.89 (m, 1H), 2.61 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.41 (dd, *J* = 13.8, 7.3 Hz, 1H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 158.7, 157.8, 139.2, 138.0, 133.6, 132.9, 131.3, 129.0, 128.4, 126.9, 126.2, 126.1, 113.8, 113.2, 75.5, 55.5, 55.4, 51.4, 46.4, 44.3, 14.7 ; IR (film) 3035, 2960, 2836, 1724, 1609, 1508, 1245, 1036 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{32}NO_4$ $[M+H]^+$ *m/z* = 446.2331; found 446.2325; $[\alpha]^{25}_D$ = +126.1 (c 0.32, 74% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3e**: 10.4 min (major) and 12.4 min (minor).



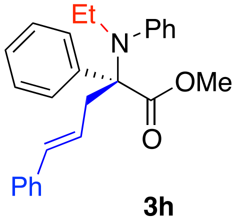
3f

(*S,E*)-Methyl 2-(N-ethyl-N-(4-methoxyphenyl)amino)-2-(napthalen-2-yl)-5-phenylpent-4-enoate (3f) [Table 2, entry 7]. Following the general procedure B, 3.0 M EtMgBr (177 µL, 0.532 mmol) was added to **1f** (85 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0010 mmol), *R*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% acetone/hexanes) product **3f** (89 mg) was obtained in 72% yield as a yellow oil. Absolute configuration was determined by the x-ray structure obtained from >99% ee material by stirring the 84% ee solid in hexanes and then removing the liquid three times, the enhanced ee solid was recrystallized from Et_2O over 24 h of slow evaporation. mp (>99% ee material) = 104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.85 (m, 4H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.51-7.49 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 6.9 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.95 (d, *J* = 15.8 Hz, 1H), 5.75 (dt, *J* = 15.8 Hz, 7.1 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.12-2.98 (m, 2H), 2.75 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.59 (dd, *J* = 13.6, 7.3 Hz, 1H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 157.9, 139.2, 139.1, 137.9, 133.1, 133.0, 132.9, 131.4, 128.5, 128.4 (2), 127.6, 127.4, 127.0, 126.9, 126.1 (3), 126.0, 113.9, 75.2, 55.5, 51.5, 46.7, 44.1, 14.7; IR (film) 3056, 2964, 2835, 1724, 1600, 1242, 1036 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{32}NO_3$ $[M+H]^+$ *m/z* = 466.2382; found 466.2371; $[\alpha]^{25}_D$ = +137.5 (c 0.43, 86% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3f**: 9.9 min (minor) and 10.7 min (major).



3g

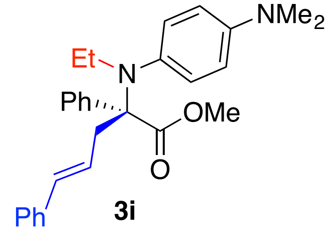
(*S*,*E*)-Methyl 2-(N-ethyl-N-(4-methoxyphenyl)amino)-2-(thiophen-2-yl)-5-phenylpent-4-enoate (3g) [Table 2, entry 8]. Following the general procedure B, 3.0 M EtMgBr (177 µL, 0.532 mmol) was added to **1g** (73.2 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of [η^3-$C_3H_5PdCl]_2$ (3.64 mg, 0.0098 mmol), *R*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 5% EtOAc/hexanes) product **3g** (96 mg) was obtained in 86% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.26 (m, 1H), 7.24-7.19 (m, 4H), 7.17-7.14 (m, 3H), 7.07 (d, *J* = 3.7 Hz, 1H), 6.97-6.95 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.75 (dt, *J* = 15.9, 7.3 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.17-3.10 (m, 1H), 3.04-2.98 (m, 1H), 2.63 (dd, *J* = 13.4, 7.7 Hz, 1 H), 2.47 (dd, *J* = 13.4, 7.1 Hz, 1H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 157.9, 148.1, 138.4, 137.7, 133.4, 131.3, 128.5, 127.2, 126.9, 126.4, 126.2, 125.2, 124.6, 113.7, 72.9, 55.5, 51.8, 46.2, 45.6 14.3; IR (film) 3027, 2970, 2835, 1729, 1605, 1507, 1243 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{28}NO_3$ $[M+H]^+$ *m/z* = 422.1750; found 422.1807; $[\alpha]^{25}_D$ = +120.2 (c 0.34, 76% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3g**: 7.2 min (minor) and 7.8 min (major).



3h

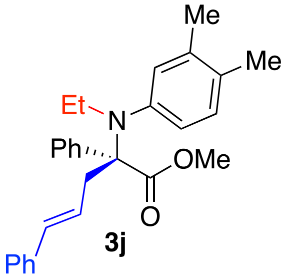
(*S*,*E*)-Methyl 2-(N-ethyl-N-phenylamino)-2,5-diphenylpent-4-enoate (3h) [Table 2, entry 9]. Following the general procedure B, 3.0 M EtMgBr (177 µL, 0.532 mmol) was added to **1h** (64 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of [η^3-$C_3H_5PdCl]_2$ (3.64 mg, 0.0098 mmol), *R*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% EtOAc/hexanes) product **3h** (80 mg) was obtained in 78% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.38-7.34 (m, 4H), 7.29 (dt, *J* = 7.3 Hz, 0.4 Hz, 1H), 7.25-7.20 (m, 5H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 2H), 5.91 (d, *J* = 15.8 Hz, 1H), 5.75 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.87 (s, 3H), 3.16-3.03 (m, 2H), 2.68 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.51 (dd, *J* = 13.7, 7.5 Hz, 1H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 146.6, 141.5, 137.9, 133.1, 129.9, 128.7, 128.4, 127.9, 127.9, 127.4, 126.9, 126.1, 125.9, 125.9, 75.0, 51.5, 46.4, 44.2, 14.7; IR (film) 3025, 2867, 1725, 1595, 1493, 1215 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{28}NO_2$ $[M+H]^+$ *m/z* = 386.2120; found 386.2132; $[\alpha]^{25}_D$ = +162.9 (c 0.47, 82%

ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3h**: 4.8 min (minor) and 5.1 min (major).



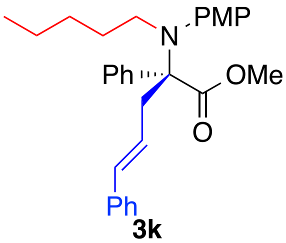
3i

(*S*,*E*)-Methyl 2-((4-(dimethylamino)phenyl)(ethyl)amino)-2,5-diphenylpent-4-enoate (3i) [Table 2, entry 10]. Following the general procedure B, 3.0 M EtMgBr (100 μL, 0.298 mmol) was added to **1i** (53 mg, 0.186 mmol) in THF (1 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.7 mg, 0.0093 mmol), *R*-BINAP (11.6 mg, 0.0186 mmol) and cinnamyl acetate (34 mg, 0.195 mmol) in THF (1 mL) for 45 min. After work-up, concentration and column chromatography (eluent 7% EtOAc/hexanes) product **3i** (62 mg) was obtained in 74% yield as a yellow oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.50 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.14-7.07 (m, 5H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.88-5.79 (m, 2H), 3.87 (s, 3H), 3.02-2.93 (m, 8H), 2.61 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.43 (dd, *J* = 14.2, 6.1 Hz, 1H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 173.6, 150.2, 143.0, 138.8, 135.9, 133.2, 131.6, 129.1, 128.6, 128.4, 127.9, 127.6, 127.2, 126.6, 113.2, 75.9, 51.5, 47.2, 45.3, 40.7, 15.0; chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3i**: 5.7 min (minor) and 6.4 min (major).



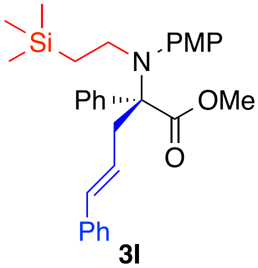
3j

(*S*,*E*)-methyl 2-((3,4-dimethylphenyl)(ethyl)amino)-2,5-diphenylpent-4-enoate (3j) [Table 2, entry 11]. Following the general procedure B, 3.0 M EtMgBr (100 μL, 0.298 mmol) was added to **1j** (50 mg, 0.186 mmol) in THF (1.3 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.72 mg, 0.005 mmol), *R*-BINAP (5.9 mg, 0.009 mmol) and cinnamyl acetate (36 mg, 0.195 mmol) in THF (1 mL) for 45 min. After work-up, concentration and column chromatography (eluent 10% Acetone/hexanes) product **3j** (65 mg) was obtained in 84% yield as a yellow oil: ^{1}H NMR (500 MHz, $(CDCl_3)$) δ 7.48 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.14-7.06 (m, 4H), 6.99 (s, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 5.88 (d, *J* = 15.8 Hz, 1H), 5.72 (dt, *J* = 15.8 Hz, 7.3 Hz, 1H), 3.87 (s, 3H), 3.08-2.95 (m, 2H), 2.63 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.45 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $(CDCl_3)$) δ 173.2, 144.1, 141.7, 138.0, 136.7, 134.5, 132.9, 131.5, 129.8, 128.4, 127.9, 127.8, 127.3, 127.2, 126.9, 126.2, 126.1, 75.1, 51.4, 46.4, 44.4, 20.1, 19.5, 14.8; chiral HPLC (IA, 99:1 hexanes:*i*-PrOH, 0.5 mL/min, 254 nm): t_R of **3j**: 8.5 min (minor) and 8.9 min (major).



3k

(*S,E*)-Methyl 2-(N-pentyl-N-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3k) [Table 3, entry 1]. Following the general procedure B, 2.0 M pentylMgBr (300 µL, 0.600 mmol) was added to **1a** (81 mg, 0.300 mmol) in THF (1.9 mL), allowed to react for 45 min and subjected to a solution of [η^3-$C_3H_5PdCl]_2$ (4.12 mg, 0.0113 mmol), *R*-DIFLUORPHOS (10.25 mg, 0.0150 mmol) and cinnamyl acetate (53 mg, 0.300 mmol) in THF (1.9 mL) for 45 min. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% EtOAc/hexanes) product **3k** (112 mg) was obtained in 82% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.16-7.13 (m, 3H), 7.07 (d, *J* = 7.1 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 5.89 (d, *J* = 15.9 Hz, 1H), 5.70 (dt, *J* = 15.7, 7.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.97-2.87 (m, 2H), 2.62 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.43 (dd, *J* = 13.4, 7.2 Hz, 1H), 1.17-1.04 (m, 6H), 0.77 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 157.8, 141.5, 139.6, 138.0, 132.9, 131.1, 128.4, 128.0, 127.8, 127.3, 126.9, 126.2, 126.1, 113.8, 75.1, 55.5, 52.2, 51.4, 44.5, 29.3, 29.0, 22.6, 14.1; IR (film) 3025, 2857, 1725, 1603, 1508, 1245 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{36}NO_3$ $[M+H]^+$ m/z = 458.2695; found 458.2704; $[\alpha]^{25}_D$ = +129.1 (c 0.30, 92% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3k**: 5.8 min (major) and 7.0 min (minor).

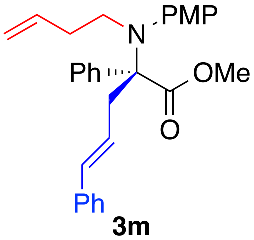


3l

(*S,E*)-Methyl 2-(N-(2-(trimethylsilyl)ethyl)-N-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3l) [Table 3, entry 2]. Following the general procedure B, 1.38 M 2-(trimethylsilyl)ethylMgBr (269 µL, 0.372 mmol) was added to **1a** (50 mg, 0.186 mmol) in THF (1.0 mL), allowed to react for 45 min providing a yellow mixture, which is subjected to a solution of [η^3-$C_3H_5PdCl]_2$ (1.70 mg, 0.00465 mmol), *R*-BINAP (5.67 mg, 0.00911 mmol) and cinnamyl acetate (32 mg, 0.182 mmol) in THF (1.0 mL) for 45 min, providing an orange mixture. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 5% EtOAc/hexanes) product **3l** (75 mg) was obtained in 83% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.9

Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.29-7.26 (m, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.15-7.13 (m, 3H), 7.08 (d, J = 7.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.89 (d, J = 15.9 Hz, 1H), 5.75 (dt, J = 15.7, 7.4 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.06-2.99 (m, 1H), 2.96-2.90 (m, 1H), 2.64 (dd, J = 13.8, 7.0 Hz, 1H), 2.46 (*dd,* J = 13.8, 7.5 Hz, 1H), 0.57-0.47 (m, 2H), -0.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 157.8, 141.5, 139.3, 138.0, 132.9, 131.4, 128.4, 127.9, 127.8, 127.3, 126.9, 126.2, 126.1, 113.8, 75.2, 55.5, 51.4, 47.9, 44.3, 17.8, -1.6; IR (film) 3026, 2951, 1725, 1602, 1507, 1246 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{38}NO_3Si$ $[M+H]^+$ *m/z* = 488.2621; found 488.2617; $[\alpha]^{25}_{D}$ = +118.7 (c 0.25, 82% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3l**: 4.9 min (major) and 6.4 min (minor).

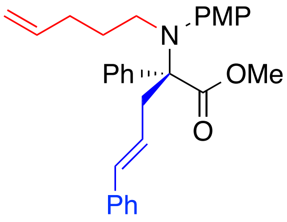
2-(trimethylsilyl)ethylMgBr was prepared by modification of a known procedure[4]: Magnesium ribbon (255 mg, 8.85 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. Et_2O (2.95 mL) was added to magnesium. Freshly prepared 2-(trimethylsilyl)ethyl bromide[5] is added dropwise to magnesium at a rate to sustain a slow reflux. After addition is complete, the mixture is heated to reflux for 2 h, allowed to cool to rt and used in preparation of **3l**.



3m

(*S,E*)-Methyl 2-(N-(but-3-en-1-yl)-N-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3m) [Table 3, entry 3]. Following the general procedure B, 2.7 M butenylMgBr (222 µL, 0.600 mmol) was added to **1a** (81 mg, 0.300 mmol) in THF (1.9 mL), allowed to react for 45 min providing a yellow/orange mixture, which is subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (4.12 mg, 0.0113 mmol), *R*-DIFLUORPHOS (10.25 mg, 0.0150 mmol) and cinnamyl acetate (53 mg, 0.300 mmol) in THF (1.9 mL) for 45 min, providing an orange mixture. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 2% acetone/hexanes) product **3m** (109 mg) was obtained in 82% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 2H), 7.36-7.33 (m, 2H), 7.28 (d, J = 7.2 Hz, 1H), 7.22-7.13 (m, 5H), 7.07 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.89 (d, J = 15.8 Hz, 1H), 5.72-5.60 (m, 2H), 4.89-4.83 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.06-2.98 (m, 2H), 2.62 (dd, J = 13.9, 7.2 Hz, 1H), 2.43 (dd, J = 13.9, 7.6 Hz, 1H), 2.05-1.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 158.0, 141.3, 139.2, 138.0, 136.8, 133.0, 131.2, 128.4, 128.0, 127.9, 127.8, 127.4, 126.9, 126.1, 115.5, 113.9, 75.1, 55.5 51.8, 51.5, 44.5, 33.9; IR (film) 3025, 2836, 1724, 1604, 1507, 1245 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{32}NO_3$ $[M+H]^+$ *m/z* = 442.2382; found 442.2400; $[\alpha]^{25}_{D}$ = +137.8 (c 0.42, 90% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3m**: 7.3 min (major) and 10.9 min (minor).

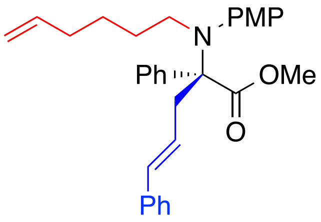
ButenylMagnesium Bromide. Magnesium ribbon (255 mg, 8.85 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. Et_2O (2.95 mL) was added to magnesium. Freshly distilled (98 °C, 760 torr) butenyl bromide is added drop wise to magnesium at a rate to sustain a slow reflux. After addition is complete, the mixture is heated to reflux for 2 h, allowed to cool to rt, and used in preparation of **3m**.



3n

(*S,E*)-Methyl 2-(N-(pent-4-en-1-yl)-N-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3n) [Table 3, entry 4]. Following the general procedure B, 2.8 M pentenylMgBr (213 µL, 0.595 mmol) was added to **1a** (80 mg, 0.297 mmol) in CPME (1.6 mL), allowed to react for 45 min providing a yellow/orange mixture, which is subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (4.1 mg, 0.0112 mmol), *R*-DIFLUORPHOS (10.2 mg, 0.0149 mmol) and cinnamyl acetate (52 mg, 0.299 mmol) in CPME (1.6 mL) for 45 min, providing an orange/red mixture. After work-up, concentration and column chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% acetone/hexanes) product **3n** (115 mg) was obtained in 85% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.9 Hz, 2H), 7.38-7.06 (m, 10H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.91 (d, *J* = 15.7 Hz, 1H), 5.75-5.58 (m, 2H), 4.90-4.81 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.96 (t, *J* = 7.7 Hz, 2H), 2.64 (dd, *J* = 13.5, 6.9 Hz, 1H), 2.44 (dd, *J* = 13.7, 7.1 Hz, 1H), 1.97-1.78 (m, 2H), 1.42-1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 157.9, 141.4, 139.4, 138.8, 138.0, 133.0, 131.1, 128.4, 128.0, 127.9, 127.4, 126.9, 126.1, 126.0, 114.2, 113.9, 75.1, 55.5, 51.9, 51.4, 44.4, 31.3, 28.6; IR (film) 3026, 2856, 1725, 1604, 1508, 1245 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{34}NO_3$ $[M+H]^+$ *m/z* = 456.2539; found 456.2536; $[\alpha]^{24}_D$ = +130.4 (c 0.29, 86% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3n**: 6.2 min (major) and 7.6 min (minor).

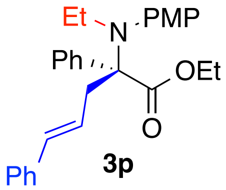
Pentenylmagnesium Bromide. Cut magnesium ribbon (261 mg, 10.9 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. Et_2O (3.02 mL) was added to magnesium. Freshly distilled (124-126 °C, 760 torr) pentenyl bromide is added drop wise to magnesium at a rate to sustain a slow reflux. After addition is complete, the mixture is heated to reflux for 2 h, allowed to cool to rt, and used in preparation of **3n**.



3o

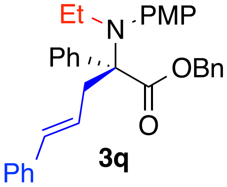
(*S,E*)-Methyl 2-(N-(hex-5-en-1-yl)-N-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3o) [Table 3, entry 5]. Following the general procedure B, 1.5 M hexenylMgBr (355 μL, 0.532 mmol) was added to **1a** (72 mg, 0.266 mmol) in 2-MeTHF (1.5 mL), allowed to react for 45 min providing a yellow mixture, which is subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.58 mg, 0.0098 mmol), *R*-DIFLUORPHOS (8.09 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in 2-MeTHF (1.5 mL) for 45 min, providing an orange mixture. After work-up, concentration and chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 3% EtOAc/hexanes) product **3o** (105 mg) was obtained in 84% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.30-7.27 (m, 1H), 7.21 (t, *J* = 7.3 Hz, 2H), 7.17-7.13 (m, 3H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.90 (d, *J* = 16 Hz, 1H), 5.74-5.65 (m, 2H), 4.91-4.86 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.99-2.90 (m, 2H), 2.63 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.44 (dd, *J* = 13.5, 7.1 Hz, 1H), 1.89-1.85 (m, 2H), 1.27-1.18 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 157.9, 141.5, 139.5, 139.0, 138.0, 132.9, 131.1, 128.4, 128.0, 127.8, 127.4, 126.9, 126.1, 126.1, 114.3, 113.8, 75.1, 55.5, 52.1, 51.4, 44.5, 33.7, 28.8, 26.3; IR (film) 3025, 2856, 1725, 1604, 1508, 1245, 1036 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{36}NO_3$ $[M+H]^+$ *m/z* = 470.2695; found 470.2693; $[\alpha]^{25}_D$ = +129.0 (c 0.41, 80% ee, CH_2Cl_2); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): t_R of **3o**: 6.0 min (major) and 7.5 min (minor).

Hexenylmagnesium Bromide. Magnesium ribbon (144 mg, 6 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. THF (3.33 mL) was added to magnesium. Freshly distilled (25 °C, 0.01 torr) hexenyl bromide is added drop wise to magnesium at a rate to sustain a slow reflux. After addition is complete, the mixture is heated to reflux for 2 h. allowed to cool to rt, and used in preparation of **3o**.



3p

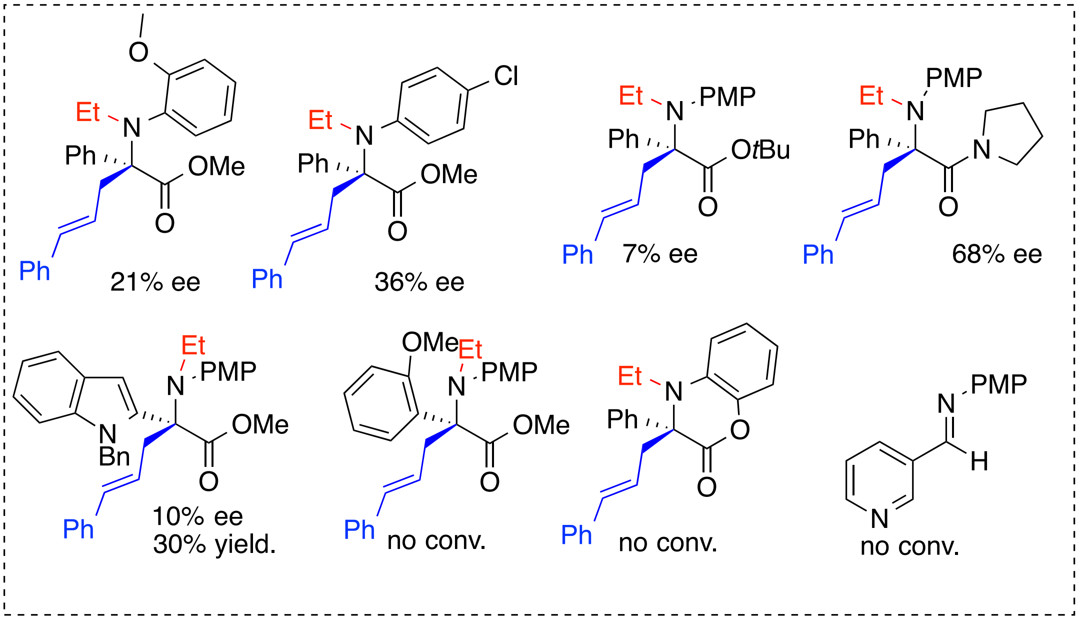
(*S,E*)-Ethyl 2-(ethyl(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3p) Following the general procedure B, 3.0 M EtMgBr (85 μL, 0.282 mmol) was added to **1k** (50 mg, 0.177 mmol) in THF (1.3 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.63 mg, 0.005 mmol), *R*-BINAP (5.5 mg, 0.009 mmol) and cinnamyl acetate (34 mg, 0.195 mmol) in THF (1 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash SiO_2 with 5% NEt_3/hexanes, eluent 7% EtOAc/hexanes) product **3p** (62 mg) was obtained in 77% yield as a yellow oil: ^{1}H NMR (500 MHz, ($CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.22-7.16 (m, 4H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.89 (d, *J* = 15.8 Hz, 1H), 5.72 (dt, *J* = 15.9, 7.2 Hz, 1H), 4.42-4.31 (m, 2H), 3.83 (s, 3H), 3.08-2.96 (m, 2H), 2.62 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.42 (dd, *J* = 13.9, 7.2 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, ($CDCl_3$) δ 172.7, 157.8, 141.8, 139.2, 138.0, 132.9, 131.4, 128.4, 127.9, 127.8, 127.2, 126.9, 126.2, 126.0, 113.8, 74.9, 60.7, 55.5, 46.7, 44.4, 14.7, 14.5; chiral HPLC (OD, 97.5:2.5 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R of **3p**: 4.5 min (major) and 8.3 min (minor).



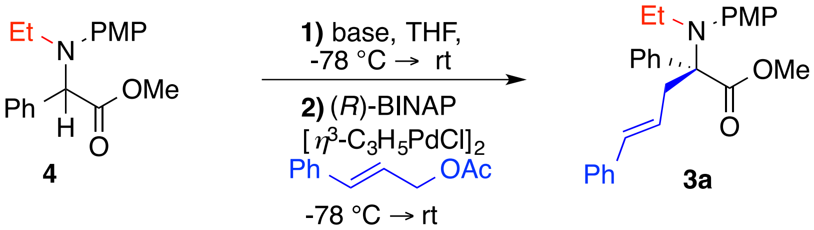
3q

(*S,E*)-Benzyl 2-(ethyl(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (3q) Following the general procedure B, 3.0 M EtMgBr (193 µL, 0.579 mmol) was added to **1l** (100 mg, 0.290 mmol) in THF (2.5 mL), allowed to react for 45 min and subjected to a solution of [η^3-$C_3H_5PdCl]_2$ (3.30 mg, 0.009 mmol), *R*-BINAP (11.6 mg, 0.019 mmol) and cinnamyl acetate (56 mg, 0.318 mmol) in THF (2.0 mL) for 45 min. After work-up, concentration and column chromatography (eluent 7% EtOAc/hexanes) product **3q** (139 mg) was obtained in 76% yield as a yellow oil: ^{1}H NMR (500 MHz, ($CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.40 (dd, *J* = 7.5, 4.3 Hz, 2H), 7.37-7.31 (m, 5H), 7.28-7.26 (m, 1H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.14-7.10 (m, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 5.83 (d, *J* = 15.9 Hz, 1H), 5.68 (dt, *J* = 15.9, 7.2 Hz, 1H), 5.34 (d, *J* = 12.1 Hz, 1H), 5.29 (d, *J* = 12.1 Hz, 1H), 3.80 (s, 3H), 3.08-3.01 (m, 1H), 2.97-2.91 (m, 1H), 2.62 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.41 (dd, *J* = 13.5, 7.2 Hz, 1H), 0.79 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, ($CDCl_3$) δ 172.5, 157.8, 141.7, 139.1, 138.0, 135.8, 133.0, 131.4, 129.1, 128.7, 128.5, 128.4, 127.9, 127.8, 127.3, 126.9, 126.1, 126.0, 113.8, 75.1, 66.7, 55.5, 46.7, 44.4, 14.7; chiral HPLC (OD, 97.5:2.5 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): t_R of **3q**: 5.8 min (major) and 9.5 min (minor).

Notable Substrates that gave lower ee or no conversion following general procedure B:



Studies on Allylation of *N*-Alkylated Intermediate (Scheme 3)



α-Amino ester **4** was dissolved in THF in a flame dried 10 mL round bottom flask charged with a stir bar and put under argon. The reaction mixture was cooled to -78 °C and a solution of base in THF was added dropwise. The reaction mixture was warmed to ambient temperature and allowed to react for 10 min and then cooled to -78 °C. A second 10 mL round bottom flask charged with a stir bar was flamed dried under argon, Pd/L/cinnamyl acetate was added, dissolved in THF and cooled to -78 °C. The Pd/L/cinnamyl acetate slurry was added to the reaction mixture, which was allowed to warm to ambient temperature. The resultant reaction mixture was cooled to 0 °C after 45 minutes, quenched with satd NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography to afford pure α-allyl-α-aryl α-amino acid **3a.**

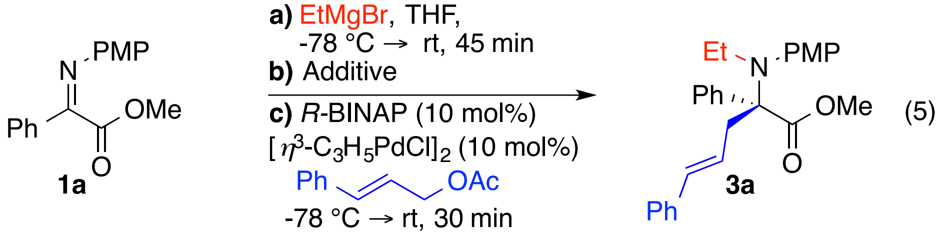
Table S2: Allylation of the *N*-Alkylation Product (Scheme 3).[a]

Entry	Base	Conversion (%)[b]	ee (%)[c]
1	EtMgBr	~50	34
2	NaH	No Product	nd
3	NaHMDS	~90	19[d]
4	KHMDS	~85	23[d]
5	LHMDS	~90	18[d]

[a] Reaction conditions: [**4**] = 0.19 M, 2.0 equiv base, THF (1.0 mL), rt for 10 min, then cool to -78 °C and add solution of 2.5 mol% $[\eta^3\text{-}C_3H_5PdCl]_2$, 5.0 mol% (*R*)-BINAP, 1.0 equiv cinnamyl acetate in THF (1.0 mL) and warm to rt. [b] Determined By ^1H NMR spectroscopy. [c] Determined by HPLC. [d] Opposite major enantiomer observed.

The Effect of Additives:

Table S3: The Addition of Additives After Grignard Addition.[a]

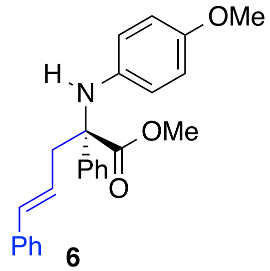


Entry	Additive	Conversion (%)[b]	ee (%)[c]
1	NPh_3	~90	79
2	NEt_3	~90	34
3	DIPA	~90	34
4	AgBr	~90	30
5	Ag_2O	~90	28
6	$ZnCl_2$	~50	4
7	Me_3SnCl	~80	21

[a]Reaction conditions: General procedure **B** (see below) was followed with the addition of 1-2 equiv of additive after step a. [b]Determined by ^1H NMR spectroscopy with respect to **1a**. [c]Determined by HPLC analysis.

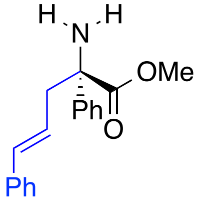
Table 2 and 3 as well as Table S2 and S3 support the preferable formation of complex **B** in Figure 2. With respect to the aggregation state in Figure 2, selectivity was enhanced with ethereal solvents compared to toluene, DCM, etc., which should solvate Mg. This result indicates that **B** and **C** are more likely than **A**. Amine additives reduced selectivity. Since amine additives should break up aggregates, this result indicates **C** is unlikely leaving **B** the most likely candidate).

Reduction of Tandem Product (Scheme 4)



6

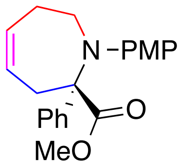
(*S*,*E*)-Methyl 2-((4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (6). Following the modified procedure previously reported by the Grotjahn group for alkene isomerization[6]: An nmr tube equipped with a J Young valve that was kept in an 120 °C oven overnight was brought into the glovebox. **3m** (40 mg, 0.09 mmol, 70% ee) was added to the tube via a d^6-acetone solution (0.3M). The Grotjahn catalyst[7] (**5**) (3 mg, 0.005 mmol) was added via a d^6-acetone solution (0.02M). The nmr tube was sealed and brought out of the glovebox and put under argon via a three-way adapter allowing for addition of a TFA/D_2O solution in d^6-acetone (0.01 mmol of TFA, 0.51 mmol of D_2O in 100 µL d^6-acetone, sparged after preparation). The nmr Tube was sealed, removed from argon and put in a 70 °C oil bath. The reaction was monitored by ^{1}H NMR every 4-5 h. After 24 h no more product was formed, the reaction was transferred with EtOAc, concentrated, passed through Celite with EtOAc and concentrated *in vacuo*. The resultant residue was subjected to chromatography (7% EtOAc in Hexanes) affording **6** (26 mg) in 74% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.34-7.20 (m, 6H), 6.65 (d, *J* = 9 Hz, 2H), 6.38 (d, *J* = 9 Hz, 2H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.02 (dt, *J* = 15.8, 7.2 Hz, 1H), 5.00 (b, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.36 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 152.5, 140.9, 138.5, 137.3, 134.3, 134.5, 128.8, 128.6, 127.8, 127.5, 127.2, 126.4, 123.9, 117.2, 114.6, 67.2, 55.7, 53.1, 37.6; IR (film) 3403, 1733, 1513, 1447, 1239 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{26}NO_3$ $[M+H]^+$ *m/z* = 388.1913; found 388.1911; $[\alpha]^{24}_D$ = -61.0 (c 0.67, 70% ee, CH_2Cl_2);



7

(*S,E*)-Methyl 2-amino-2,5-diphenylpent-4-enoate (7). A solution of **6** (22 mg, 0.056 mmol) in MeCN (6.3 mL) was cooled to 0 °C. To this mixture was added a solution of ceric ammonium nitrate (94 mg, 0.17 mmol) in H_2O (3.1 mL) under N_2. The mixture was allowed to warm to ambient temperature; it went from yellow to blue then purple at rt. The reaction was stirred for 30 min at rt then cooled to 0 °C and quenched with 10% $NaHCO_3$ until a pH of 7 was obtained (~1.0 mL). The mixture was diluted with 20% Na_2SO_3 (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (2x), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by chromatography (pre-washed SiO_2 with 3% NEt_3 in Hexanes, eluent 40% EtOAc in Hexanes) providing product **7** (8.7 mg) in 55% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.33-7.27 (m, 5H), 7.24-7.20 (m, 1H), 6.54 (d, *J* = 15.9 Hz), 6.12-6.06 (m, 1H), 3.75 (s, 3H), 3.14 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.79 (dd, *J* = 13.8, 8.1 Hz, 1H), 2.00 (b, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 142.9, 137.1, 135.1, 128.7, 128.7, 127.8, 127.6, 126.4, 125.5, 124.4, 63.8, 52.8, 44.2; IR (film) 3387, 3323, 3026, 2951, 1731, 1447, 1435, 1214 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$ *m/z* = 282.1494; found 282.1493; $[\alpha]^{25}_D$ = -31.3 (c 0.44, 70% ee, CH_2Cl_2);

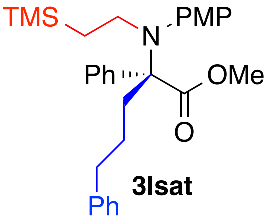
Synthesis of Higher Ring Order Proline Analog (Scheme 5)



9

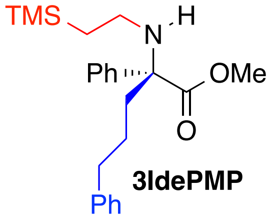
(*S*)-methyl 1-(N-(4-methoxyphenyl))-2-phenyl-3,6,7-hexahydro-1*H*-azepine-2-carboxylate (9). A 8 mL microwave vial equipped with stir bar was flamed dried under vacuum. The flask was sealed with a septa, put under argon, and catalyst **8** (2.82 mg, 0.003 mmol) and **3m** (29 mg, 0.066 mmol, 81% ee) in toluene (6 mL) were added. The septa was replaced with a microwave cap and the vial was subjected to μW (100 W, 100 psi, 115 °C) conditions for 1 h. The mixture was allowed to cool to ambient temperature and ethyl vinyl ether (75 uL, 0.784 mmol) was added and allowed to stir for 30 min, to quench catalyst **8.** Upon completion, the mixture was passed through SiO_2 with 30% EtOAc in hexanes, concentrated *in vacuo* and chromatographed (pre-wash SiO_2 with 5% NEt_3 in hexanes, eluent 5% EtOAc in hexanes) to provide **9** (23 mg) in >98% yield as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.27-7.24 (m, 2H), 7.21-7.18 (m, 1H), 6.63-6.61 (m, 2H), 6.56-6.54 (m, 2H), 5.72-5.68 (m, 1H), 5.41-5.37 (m, 1H), 4.11-4.05 (m, 1H), 3.90-3.85 (m, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.23 (dd, *J* = 15.8, 6.2 Hz, 1H), 2.88 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.67-2.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 152.0, 143.6, 141.3, 131.4, 128.2, 127.8, 126.9, 123.3, 118.0, 113.8, 74.6, 55.6, 52.3, 47.8, 40.6, 32.9; IR (film) 2949, 1729, 1512, 1246, 1037 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$ *m/z* = 338.1756; found 338.1755; $[\alpha]^{25}_D$ = +37.9 (c 0.25, 81% ee, CH_2Cl_2).

Synthesis of *N*-alkyl α-phenyl α-amino acids



3lsat

(*S*)-methyl 2-((4-methoxyphenyl)(2-(trimethylsilyl)ethyl)amino)-2,5-diphenylpentanoate (3l$_{sat}$). A 10 mL round bottom flask was charged with a stir bar and flame dried under vacuum. To the reaction flask was added **3l** (50 mg, 0.113 mmol), EtOAc (3.4 mL) and 10% Pd/C (2.4 mg, 0.023 mmol). At ambient temperature the flask was purged with one hydrogen balloon and then subjected to a hydrogen atmosphere with a new hydrogen balloon for 45 min. The flask was opened to air, passed through SiO_2 with 30% EtOAc/Hexanes, concentrated *in vacuo* and chromatographed (5% EtOAc in Hexanes) providing **3l$_{sat}$** (46 mg) in 92% yield as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28-7.23 (m, 1H), 7.17 (t, *J* = 7.4 Hz, 2H), 7.11 (d, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 7.1 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 2.94 (dt, *J* = 12.6, 5.4 Hz, 1H), 2.85 (dt, *J* = 12.5, 5.8 Hz, 1H), 2.31-2.23 (m, 1H), 2.21-2.13 (m, 1H), 1.74 (dt, *J* = 12.4, 4.8 Hz, 1H), 1.59 (dt, *J* = 12.2, 4.6 Hz, 1H), 1.29-1.18 (m, 2H), 0.54-0.41 (m, 2H), 0.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 157.7, 142.6, 141.7, 139.4, 131.1, 128.4,128.2, 127.8, 127.8, 127.1, 125.6, 113.7, 74.8, 55.5, 51.3, 47.7, 40.1, 36.3, 26.7, 17.9, -1.6; IR (film) 2951, 2925, 1725, 1507, 1246 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{40}NO_3Si$ $[M+H]^+$ *m/z* = 490.2777; found 490.2777; $[\alpha]^{25}_D$ = +103.2 (c 0.25, 82% ee, CH_2Cl_2).



3ldePMP

(*S*)-methyl 2,5-diphenyl-2-((2-(trimethylsilyl)ethyl)amino)pentanoate ($\mathbf{3l_{dePMP}}$). A solution of $\mathbf{3l_{sat}}$ (23 mg, 0.047 mmol) in MeCN (949 µL) was cooled to 0 °C. To this mixture was added a solution of ceric ammonium nitrate (78 mg, 0.141 mmol) in H_2O (475 µL). The mixture went from yellow to purple initially and then brown upon addition. After stirring for 60 min, the mixture was quenched with 5% $NaHCO_3$ until a pH of 9 was obtained (~2 mL). The mixture was diluted with 20% Na_2SO_3 (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was chromatographed (15% EtOAc/Hexanes). The fractions that stained with $KMnO_4$ $R_f = 0.3$ in 20% EtOAc inHexanes were concentrated to afford product $\mathbf{3l_{dePMP}}$ (12.5 mg) in 69% yield as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.28-7.20 (m, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 2.55 (t, *J* = 7.6, 2H), 2.41-2.25 (m, 2H), 2.13 (dt, *J* = 13.3, 4.5 Hz 1H), 2.00 (dt, *J* = 13.3, 4.5 Hz 1H), 1.72 (b, 1H), 1.59-1.47 (m, 1H), 1.45-1.33 (m, 1H), 0.83-0.68 (m, 2H), -0.013 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 142.3, 142.1, 128.5, 128.4, 128.3, 127.4, 126.2, 125.8, 68.6, 52.2, 39.3, 36.0, 34.7, 24.9, 18.8, -1.2; IR (film) 3332, 2951, 1733, 1248 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{34}NO_2Si$ $[M+H]^+$ *m/z* = 384.2359; found 384.2363; $[\alpha]^{25}_D = -6.2$ (c 0.13, 82% ee, CH_2Cl_2).

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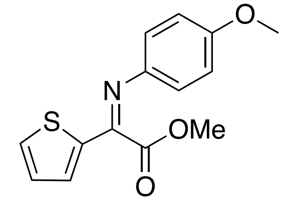
6: (a) Erdogan, G.; Grotjahn, D.B. *J. Am. Chem. Soc.* **2009**, *131*, 10354-10355. (b) Larsen, C.R.; Grotjahn, D.B. *J. Am. Chem. Soc.* **2012**, *134*, 10357-10360.
7: The Grotjahn Catalyst, CAS: 930601-66-4, is available from Strem Chemicals, Inc., but was generously provided by the Grotjahn group.



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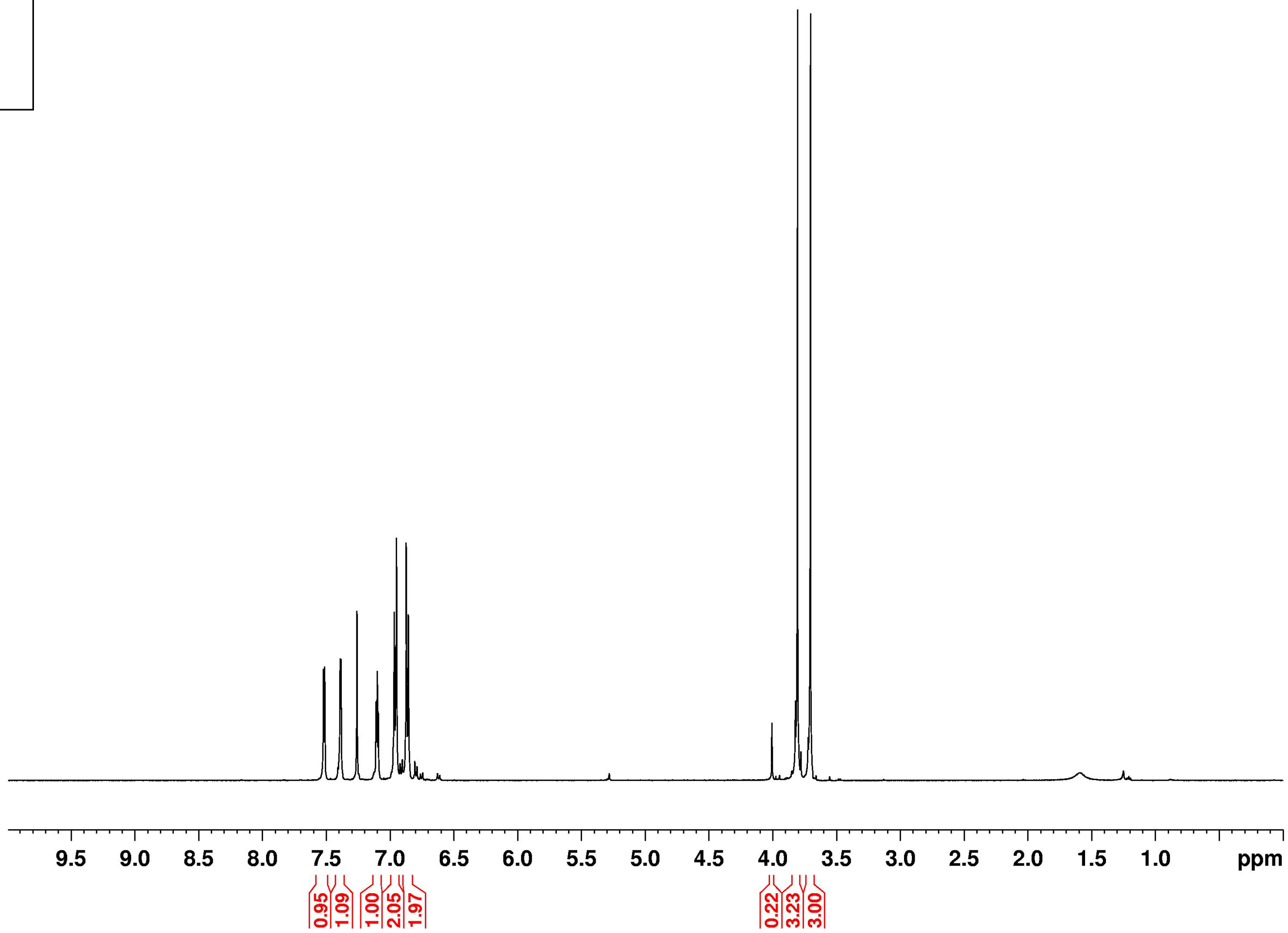
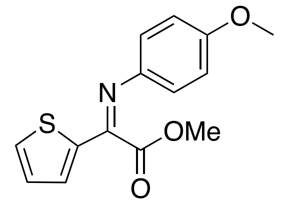


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **1g** in $CDCl_3$



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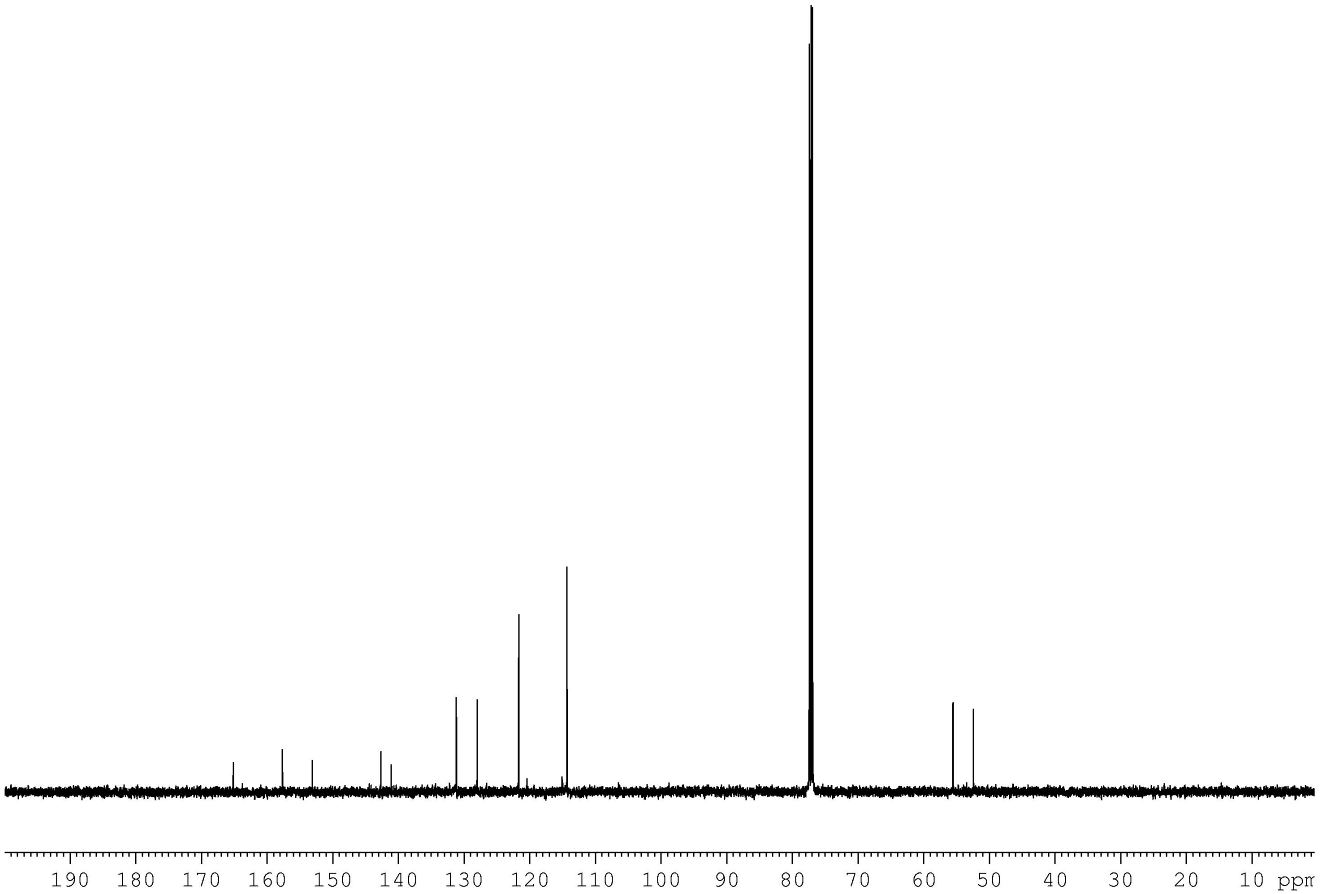


Table 2 125 MHz ^{13}C NMR Spectrum of Compound **1g** in $CDCl_3$

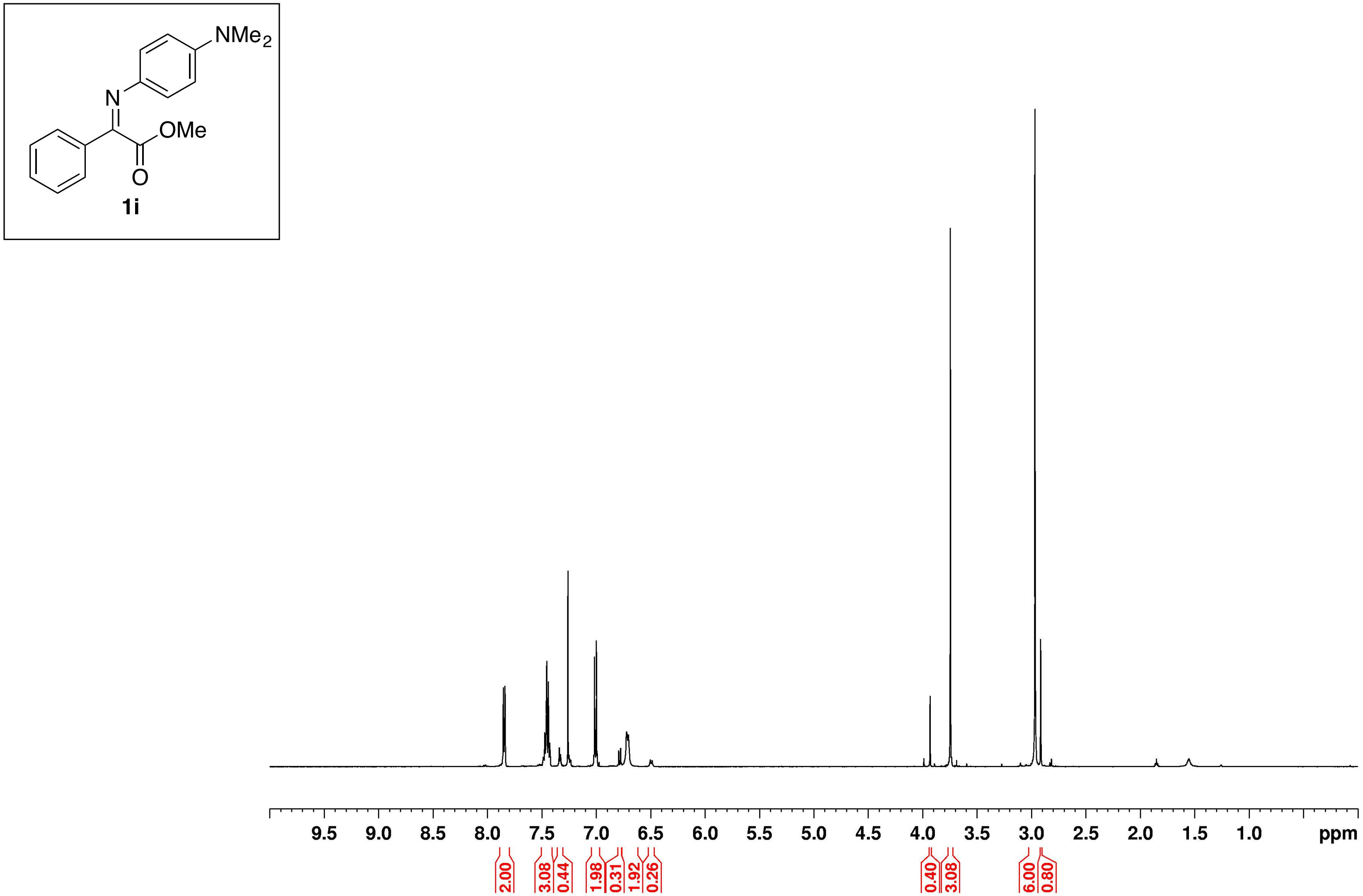
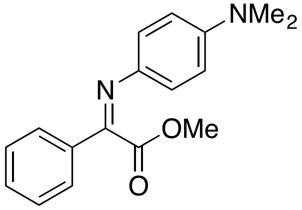


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **1i** in $CDCl_3$



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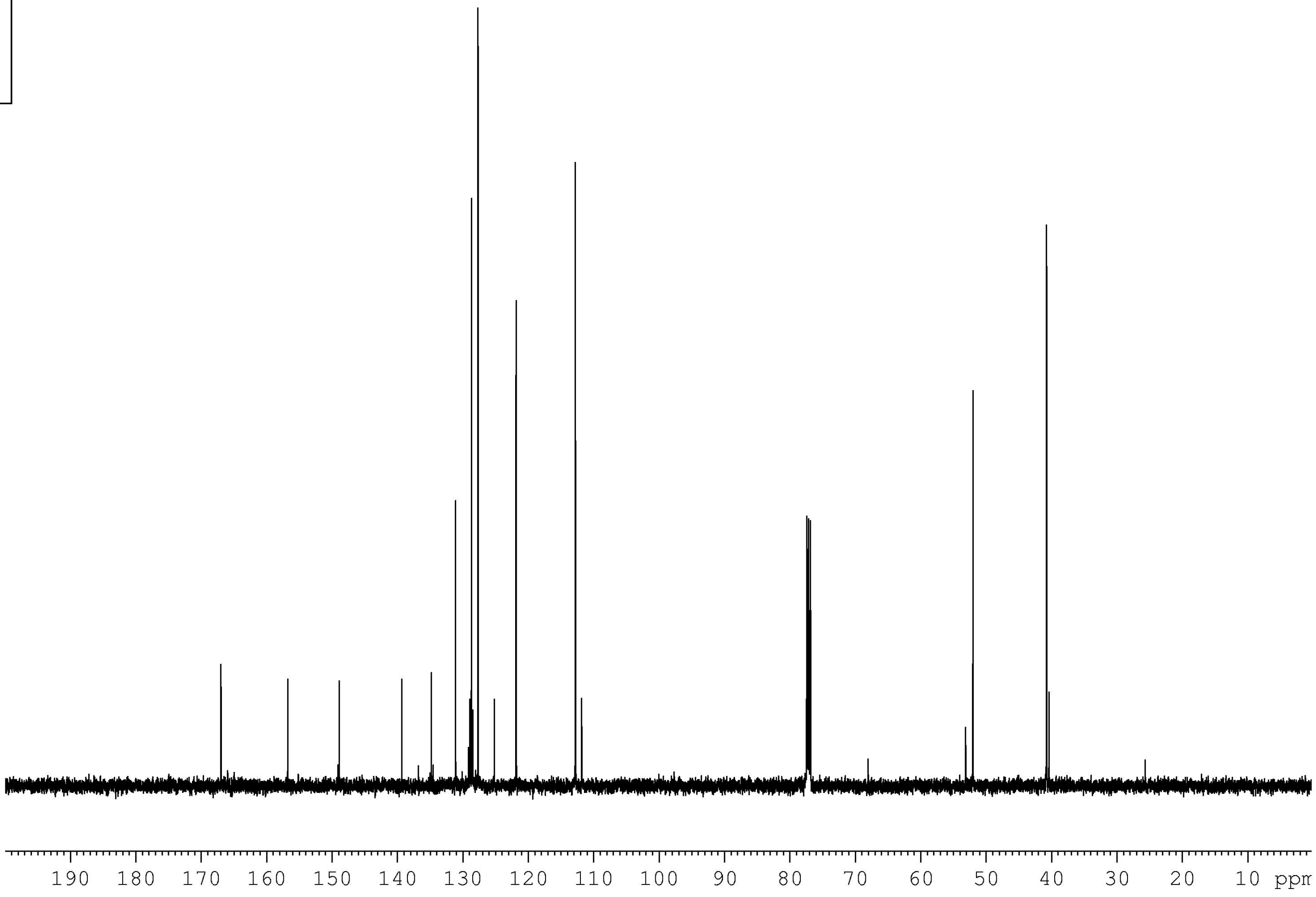
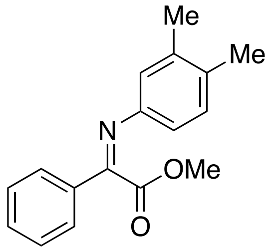


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **1i** in $CDCl_3$



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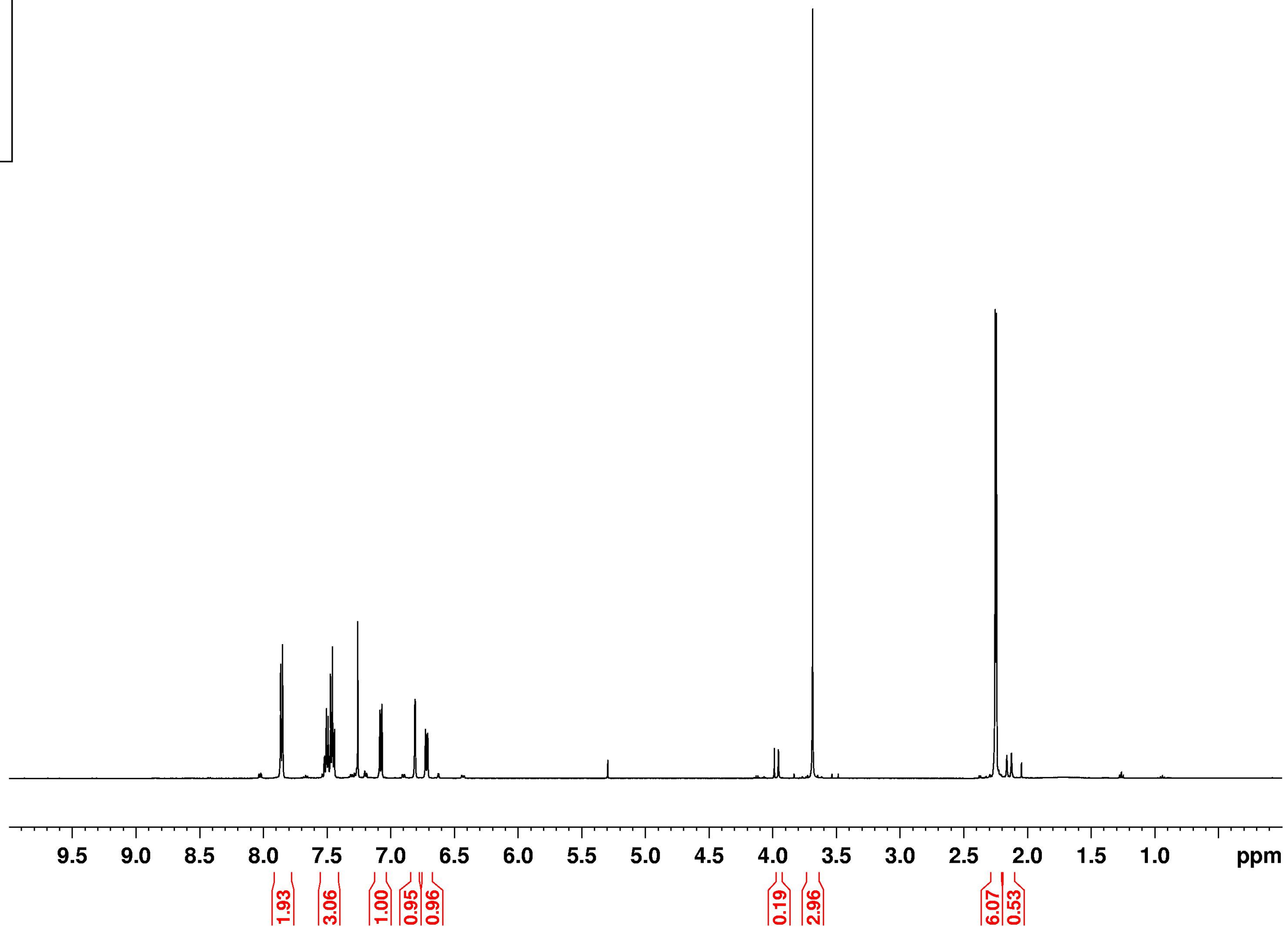
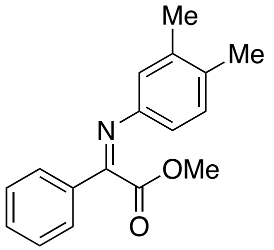


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **1j** in $CDCl_3$



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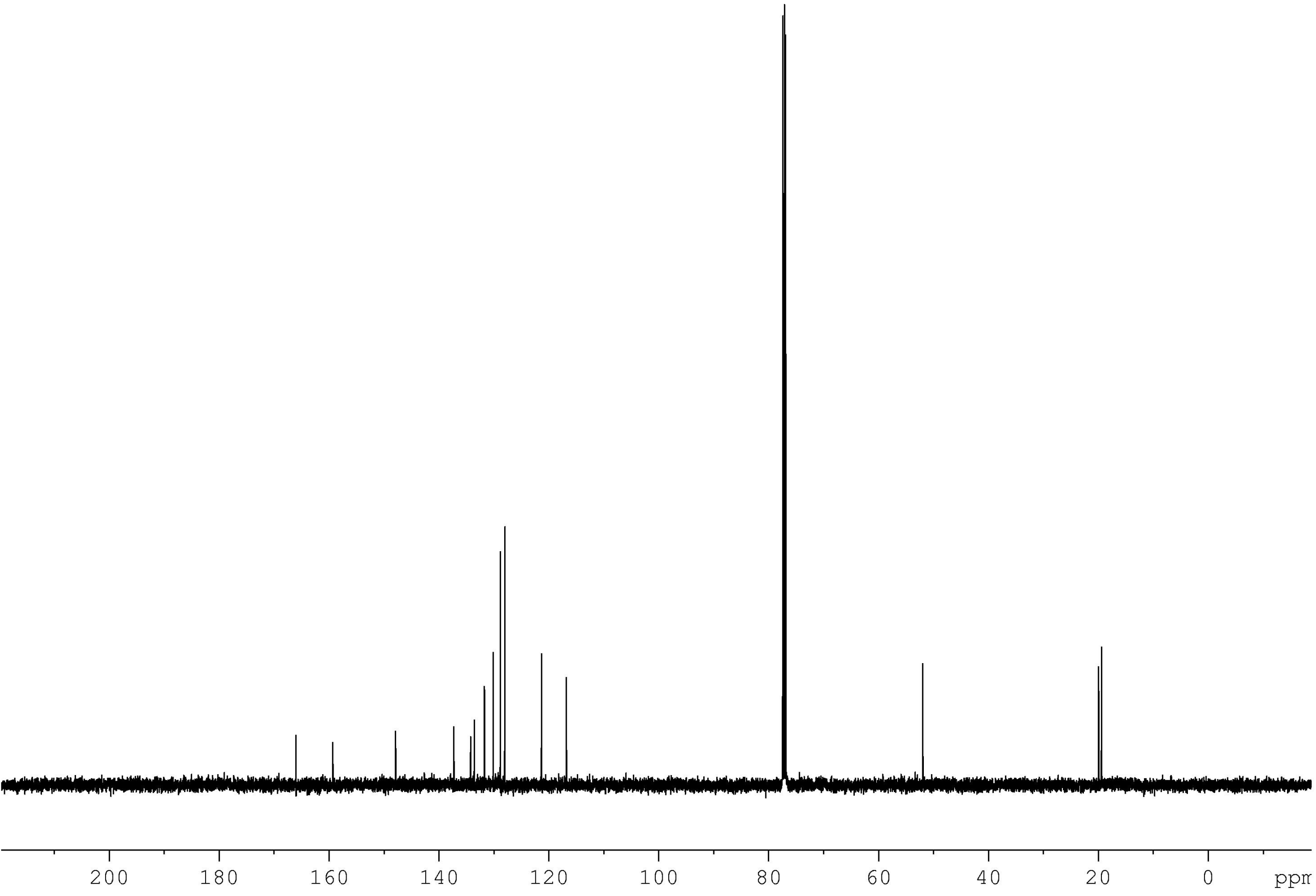
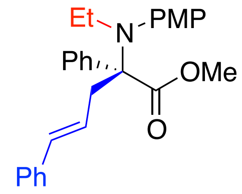


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **1j** in $CDCl_3$



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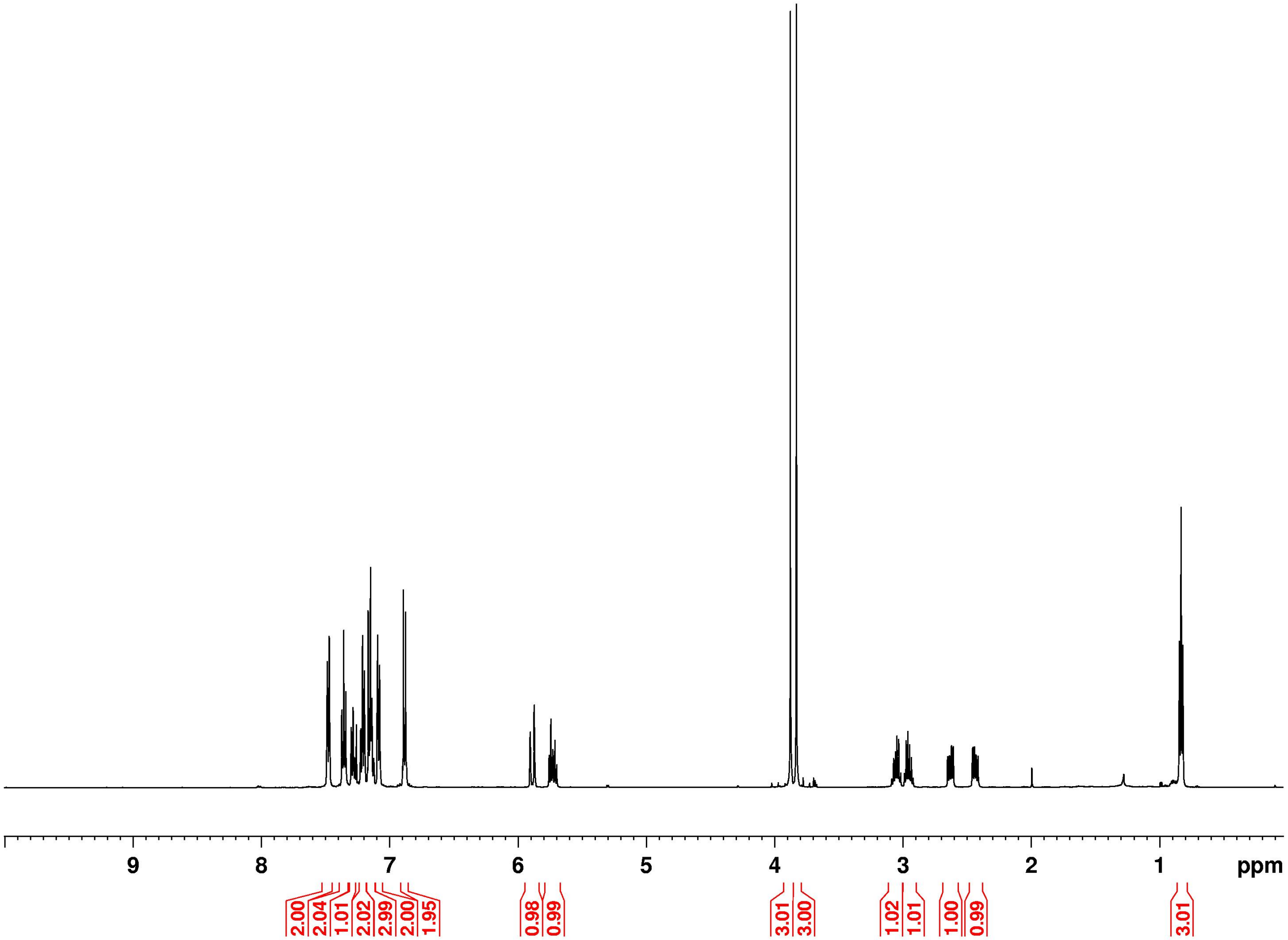
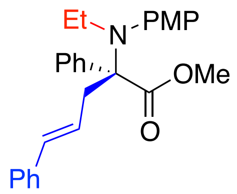


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3a** in CDCl$_3$



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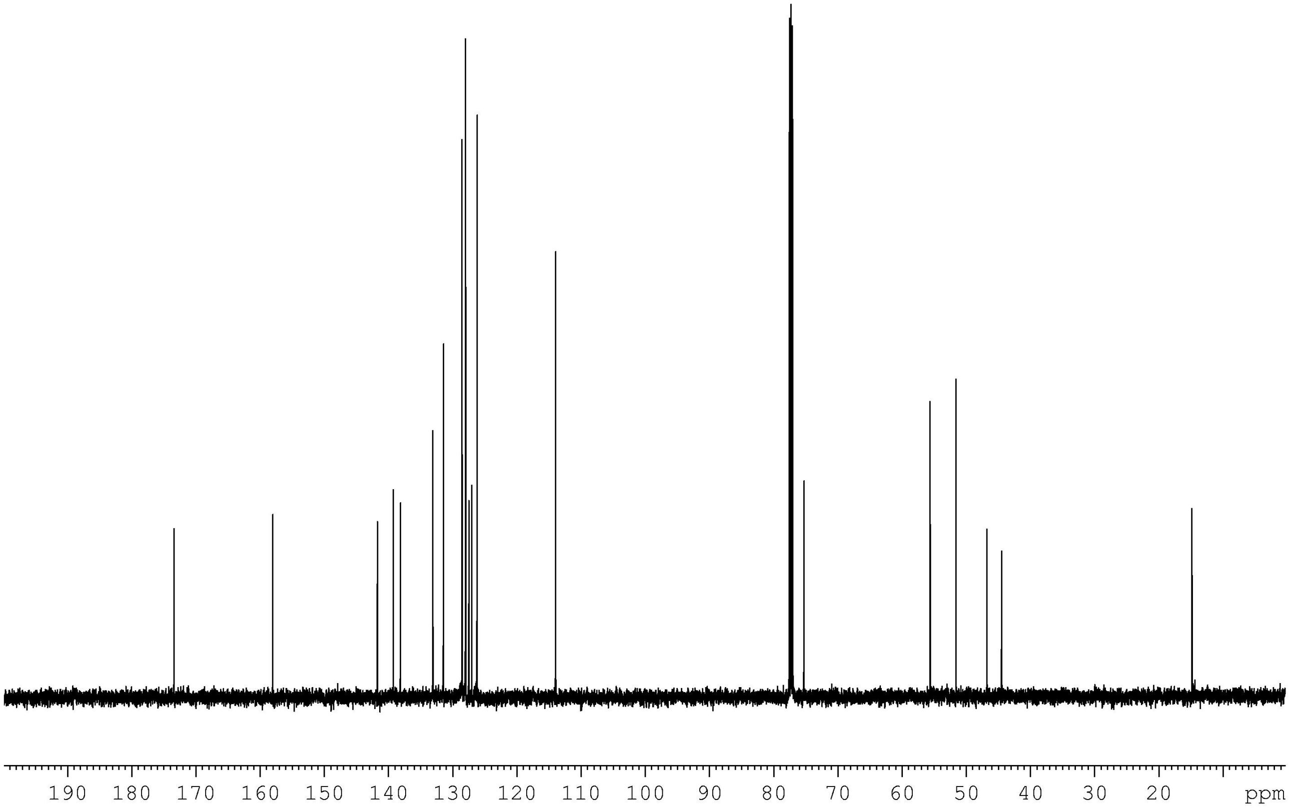
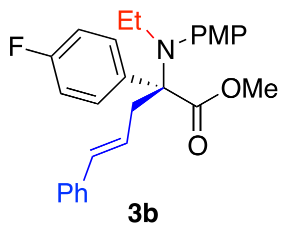


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3a** in $CDCl_3$



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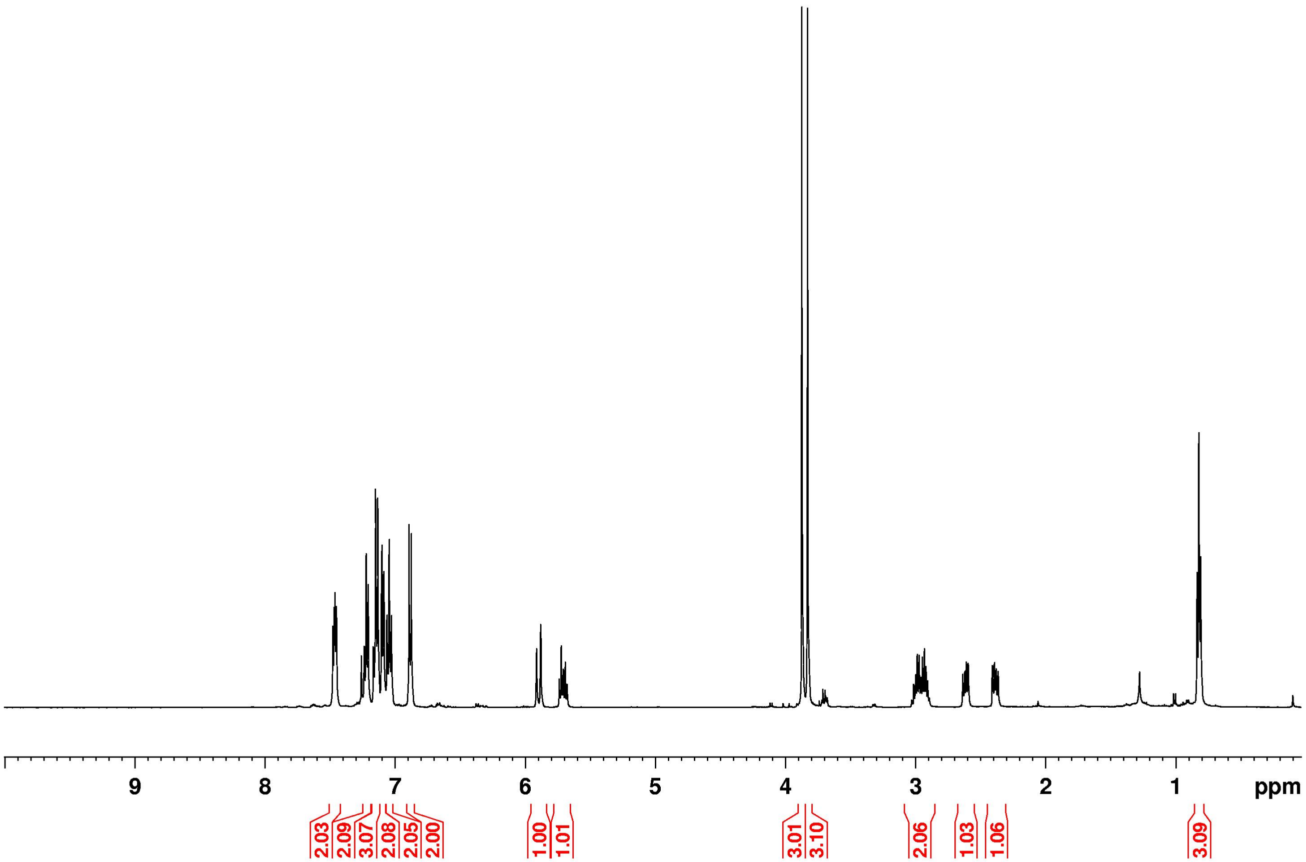
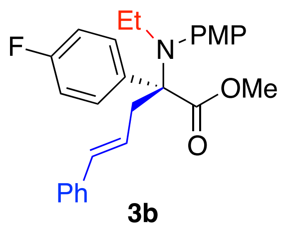


Table 2 500 MHz ^{1}H NMR Spectrum of Compound **3b** in $CDCl_3$



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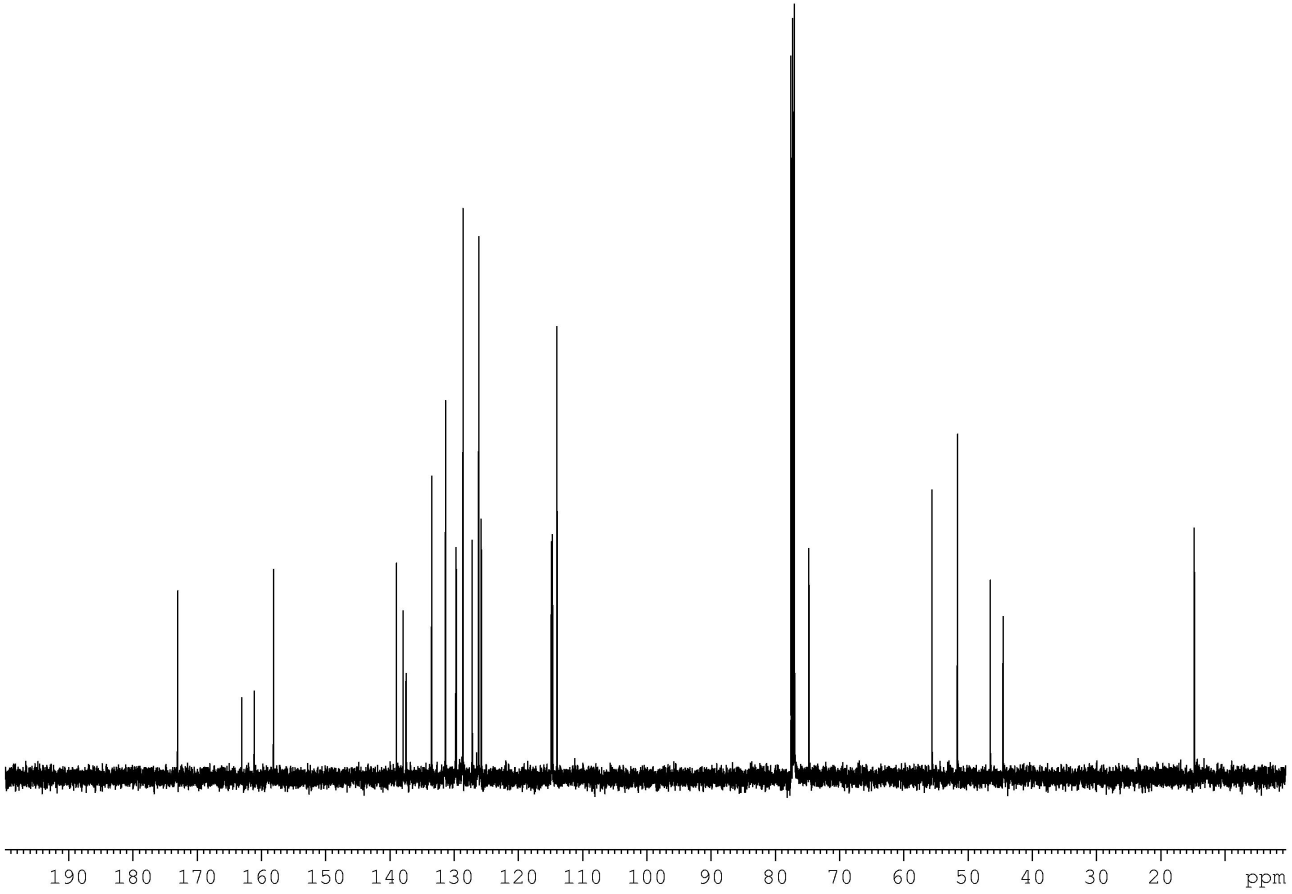
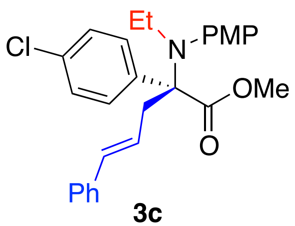


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3b** in $CDCl_3$



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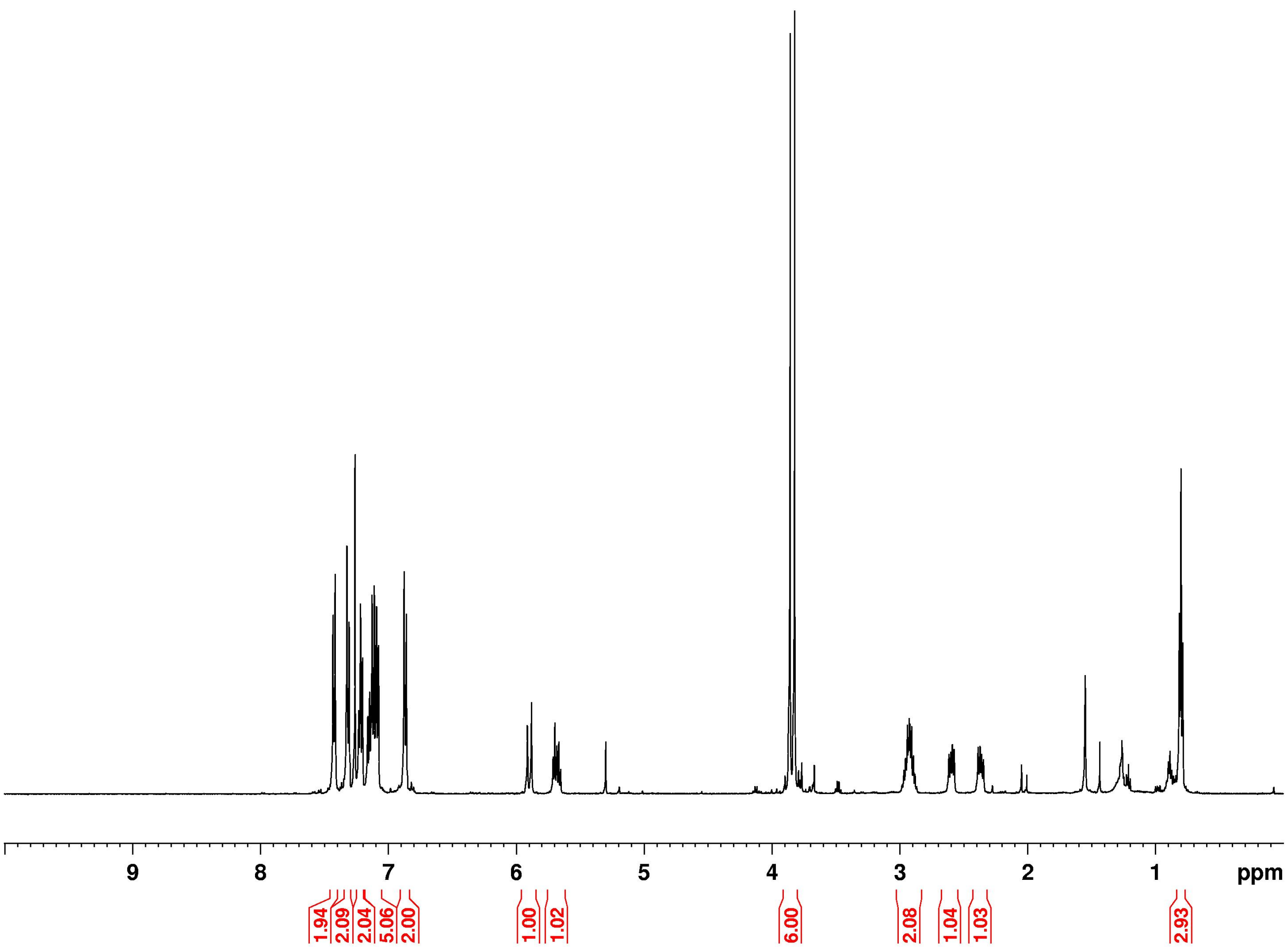
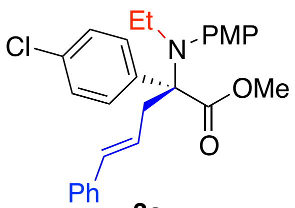


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3c** in $CDCl_3$



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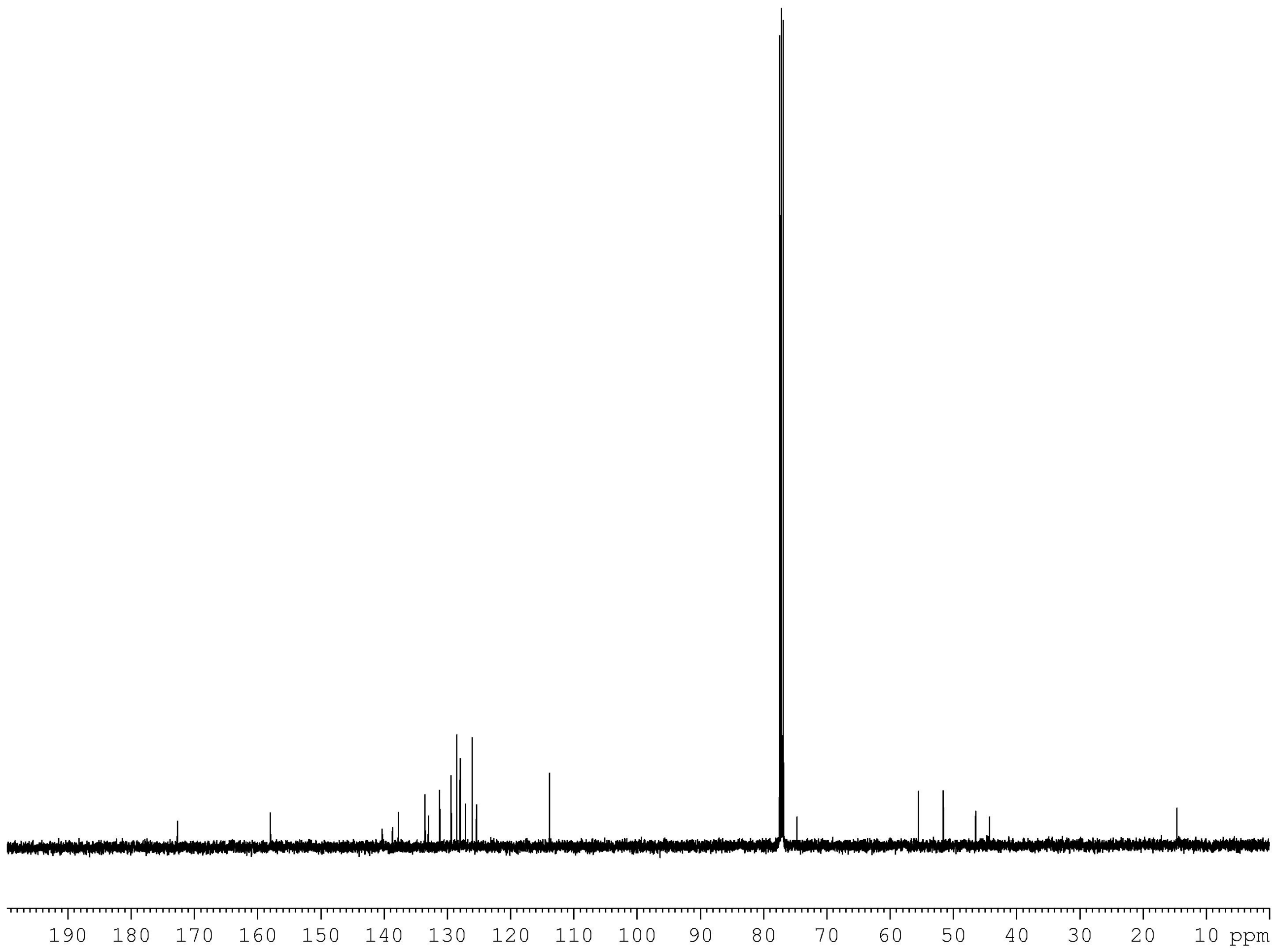
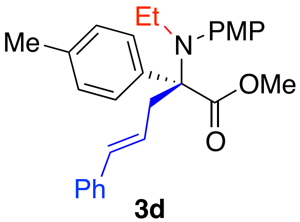


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3c** in $CDCl_3$



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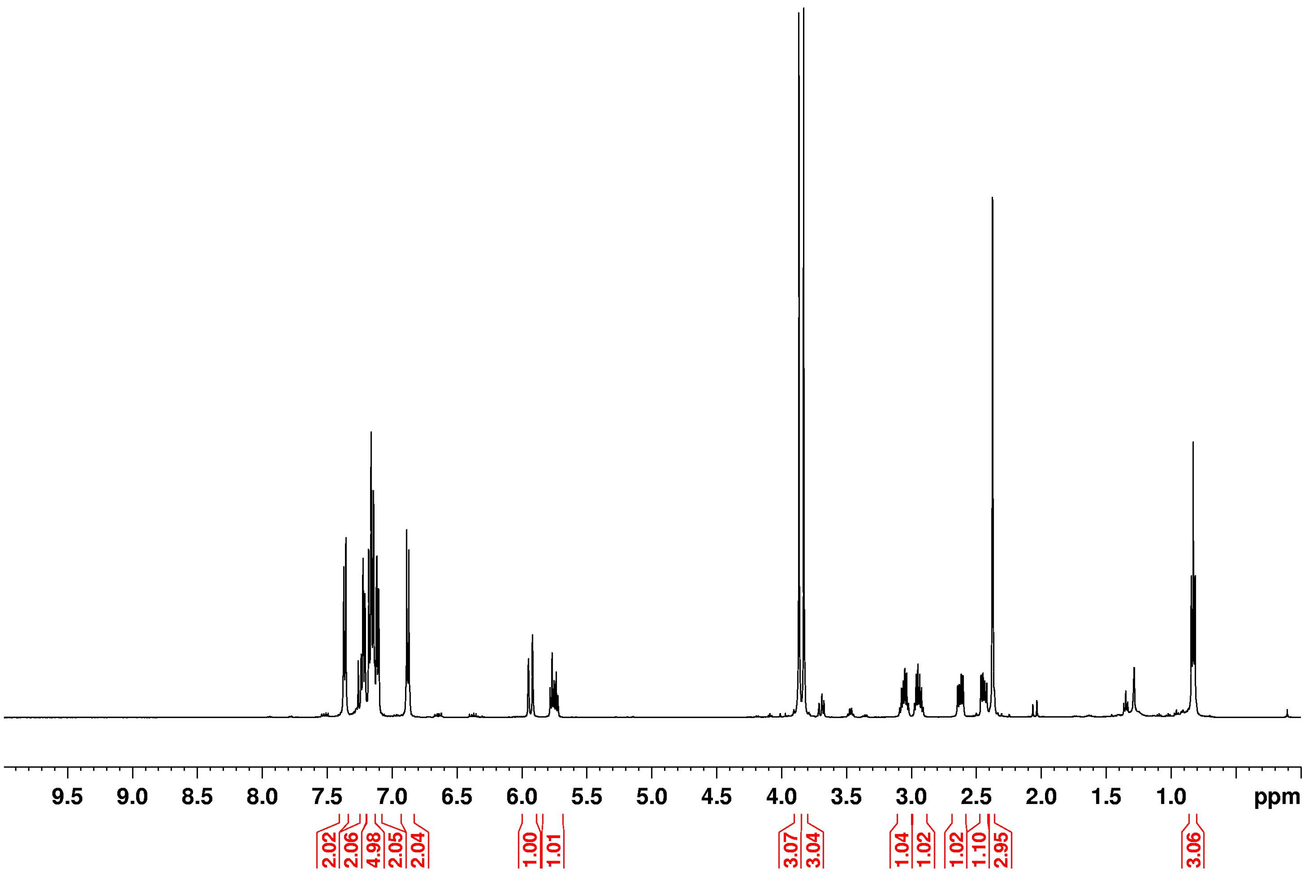
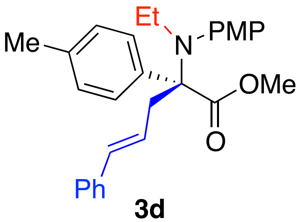


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3d** in $CDCl_3$



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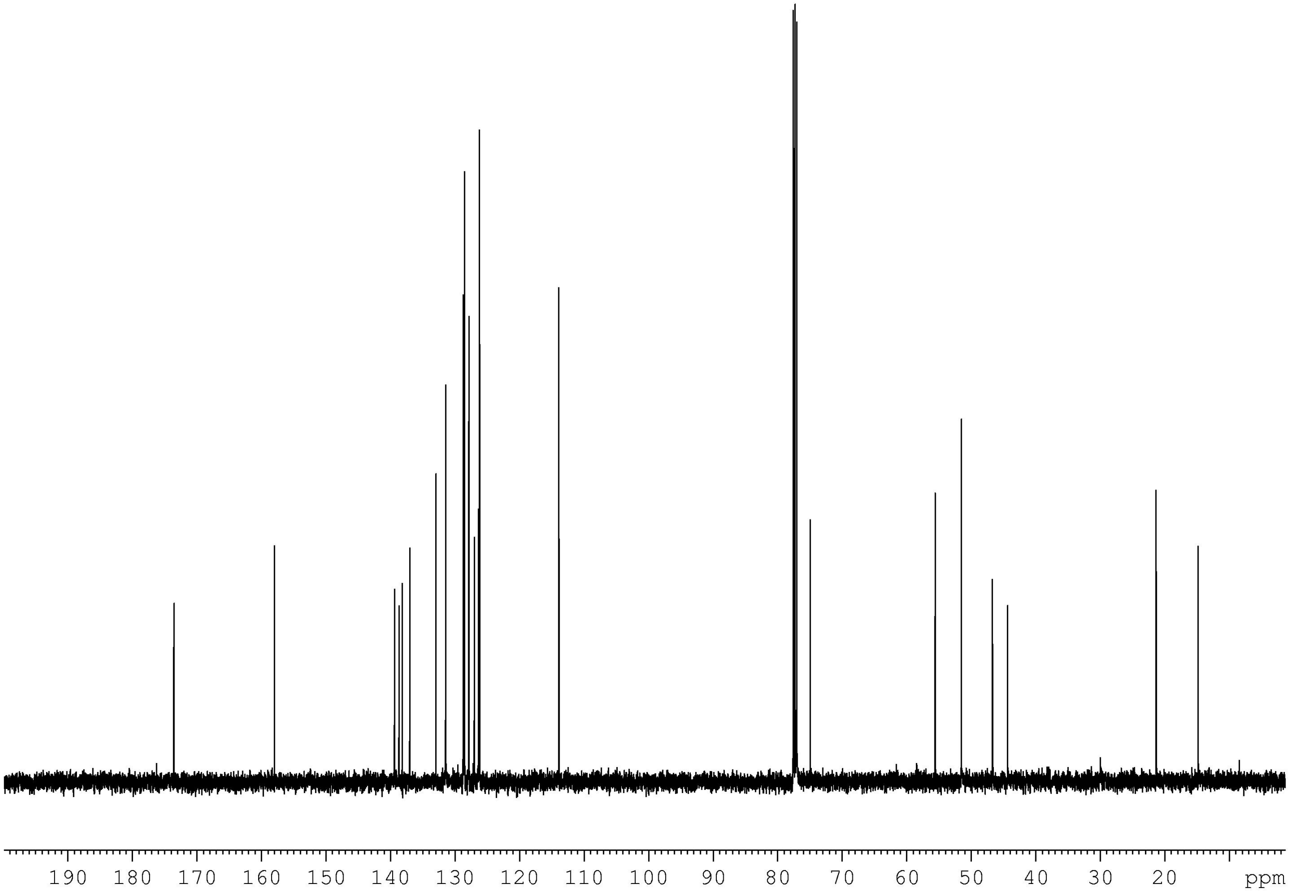
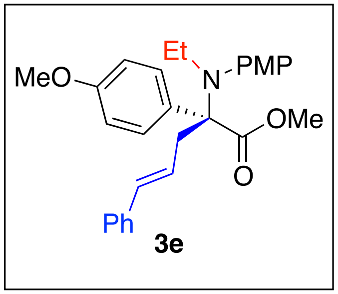


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3d** in $CDCl_3$



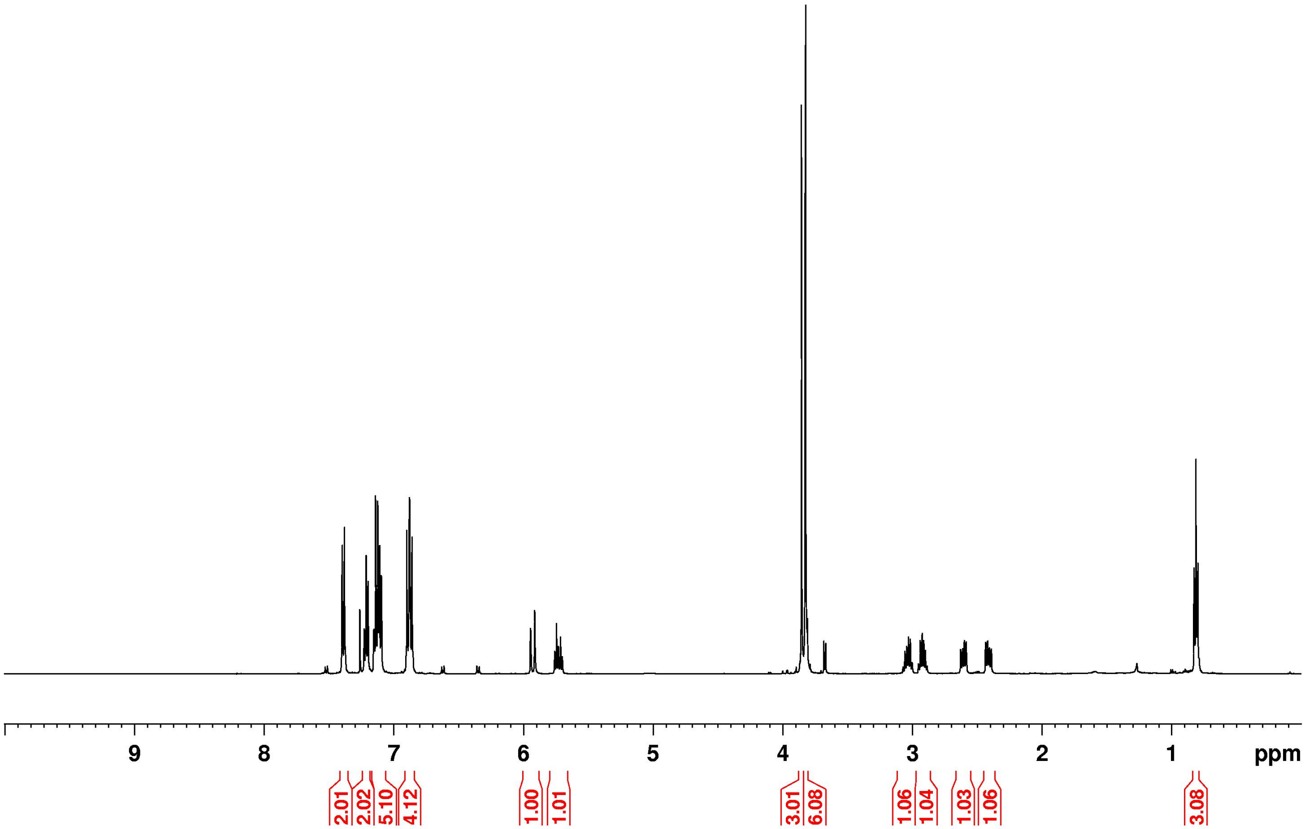
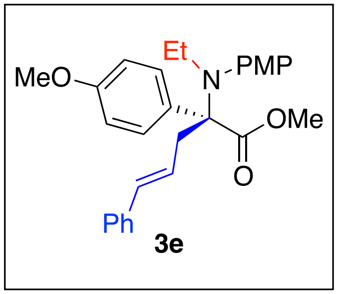


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3e** in $CDCl_3$



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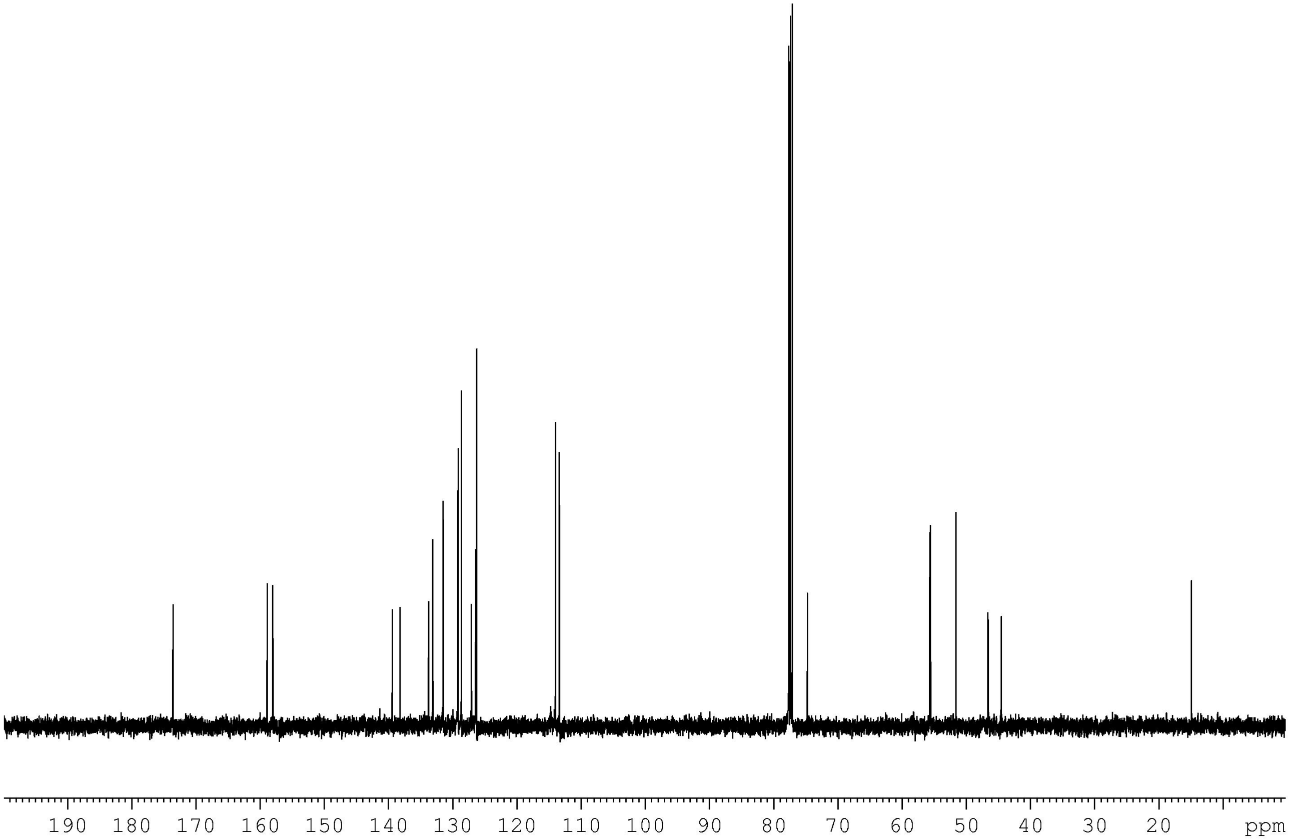
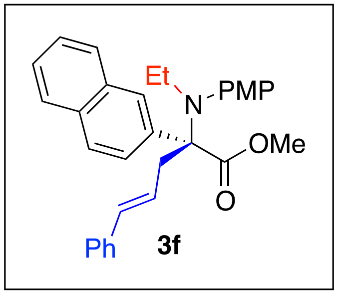


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3e** in $CDCl_3$



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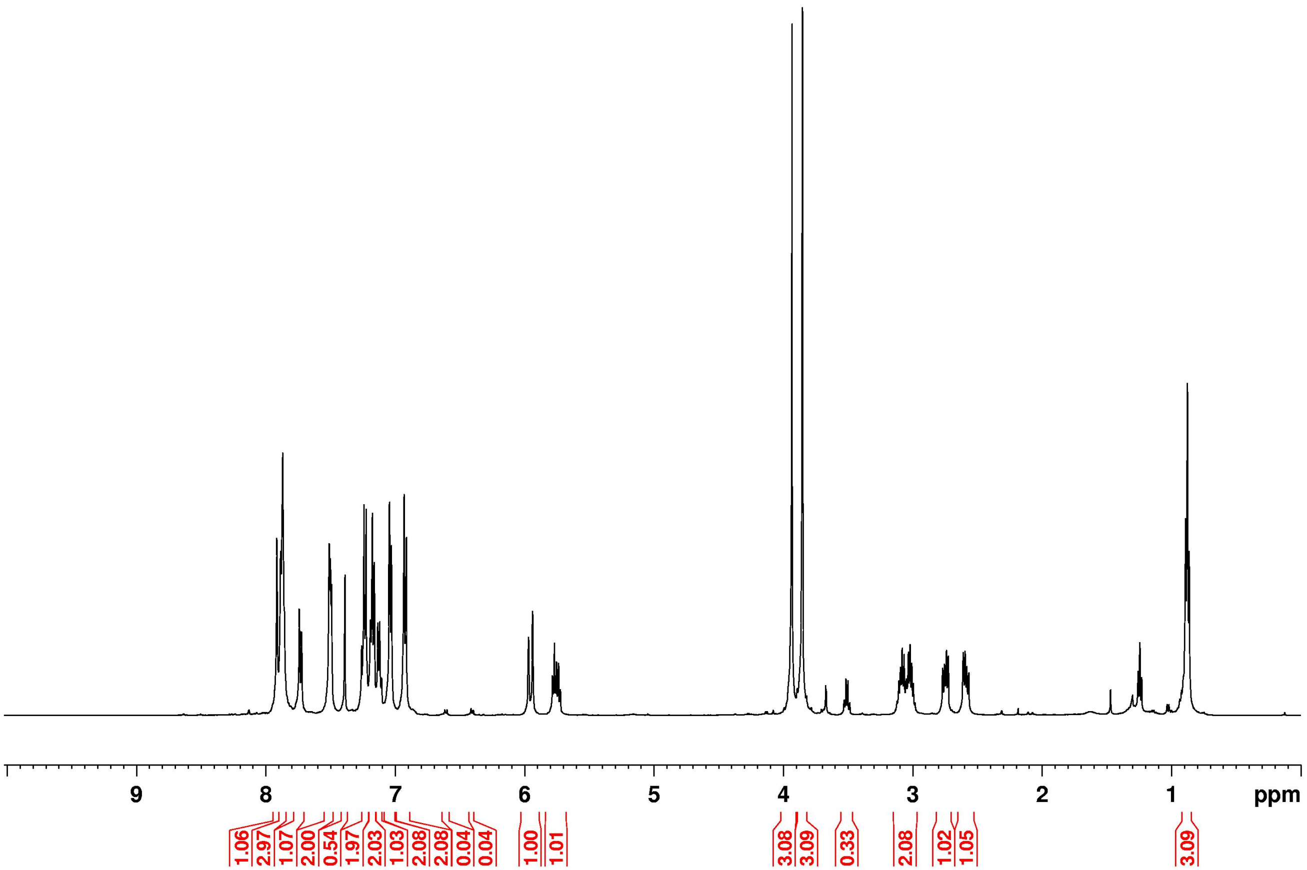
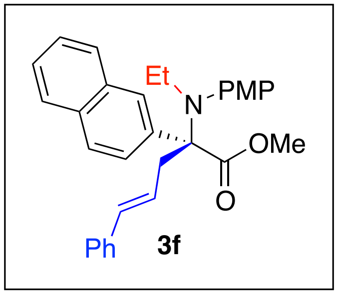


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3f** in $CDCl_3$



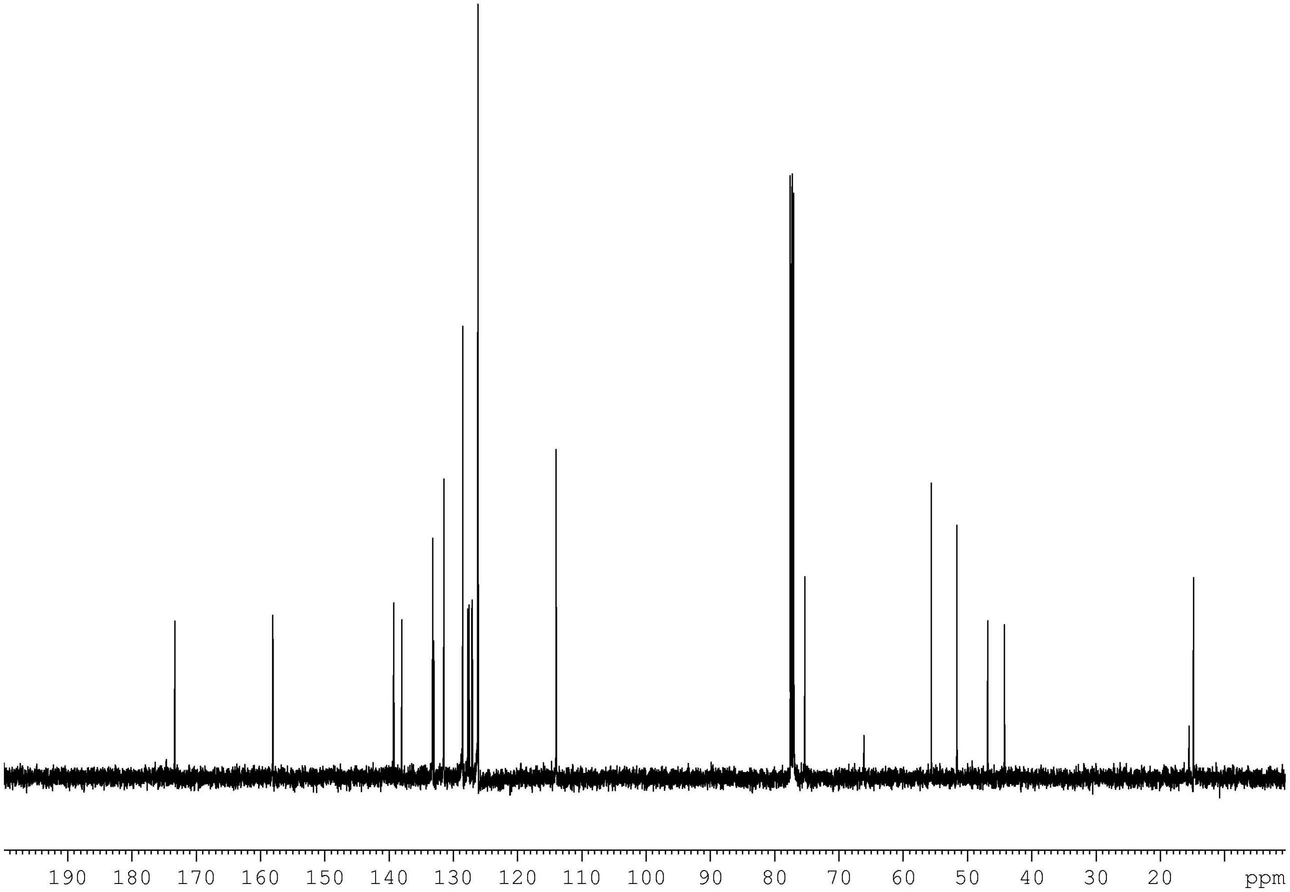
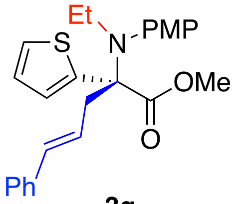


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3f** in $CDCl_3$



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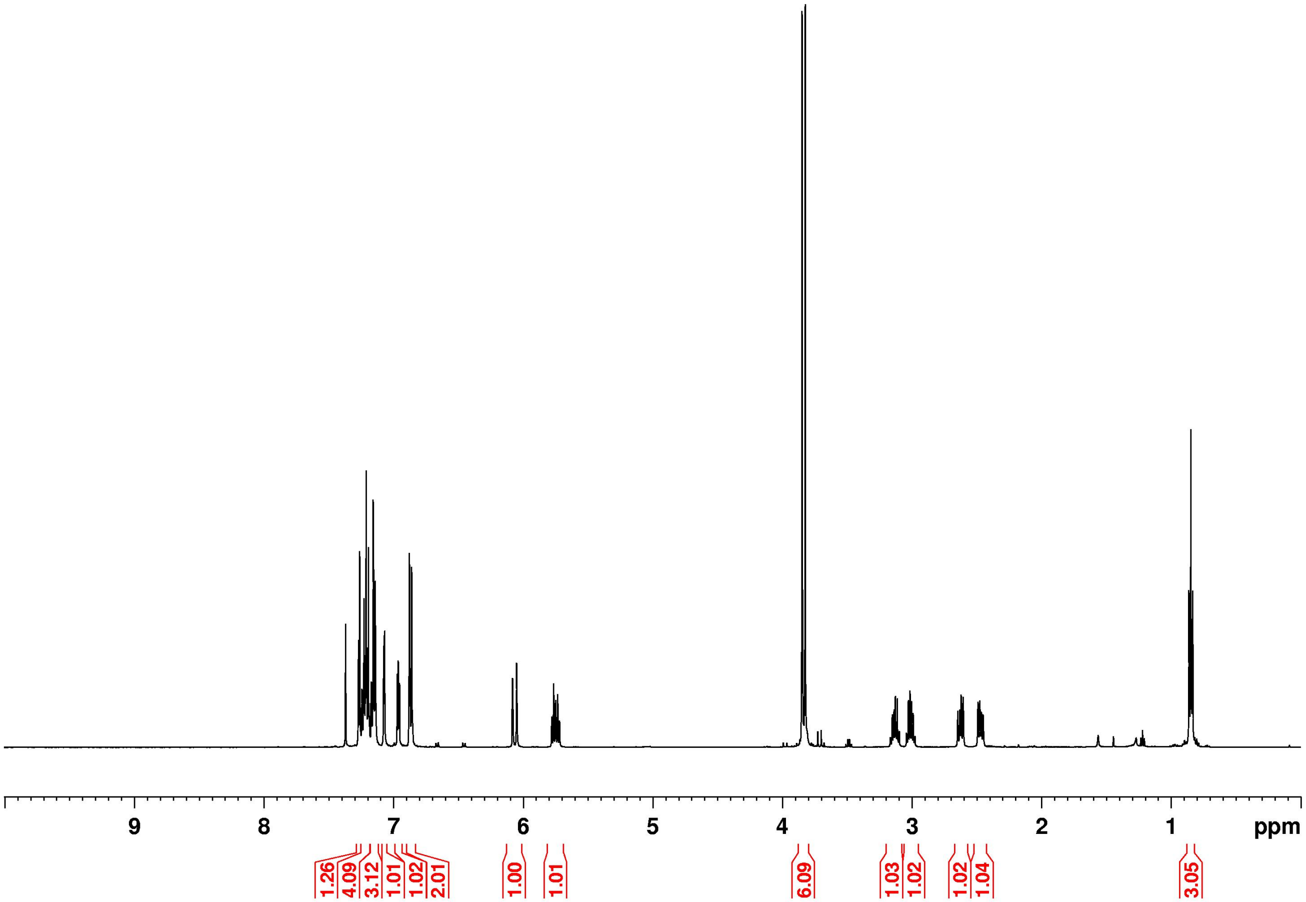
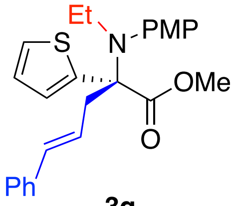


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3g** in $CDCl_3$



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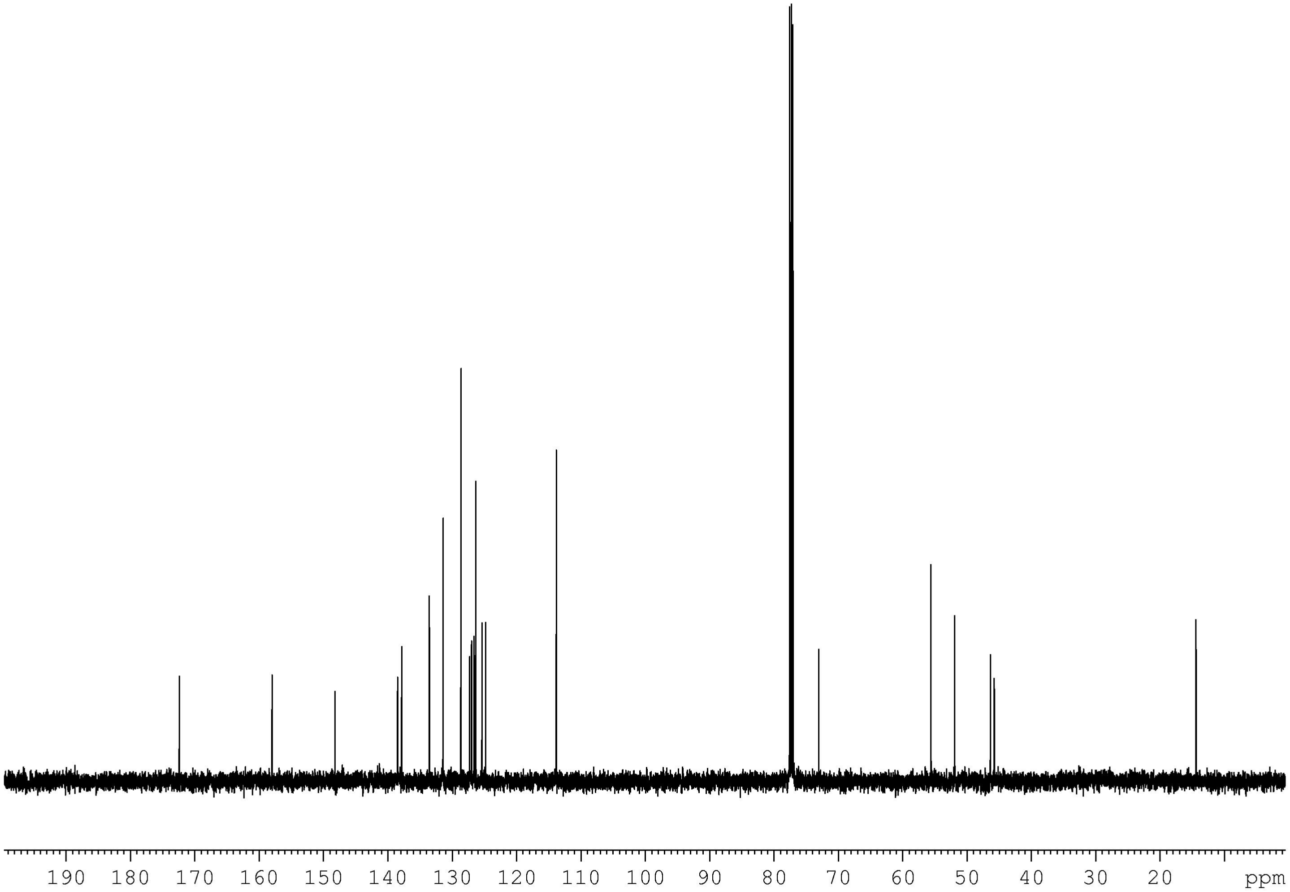
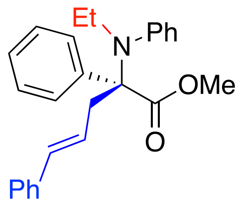


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3g** in CDCl$_3$



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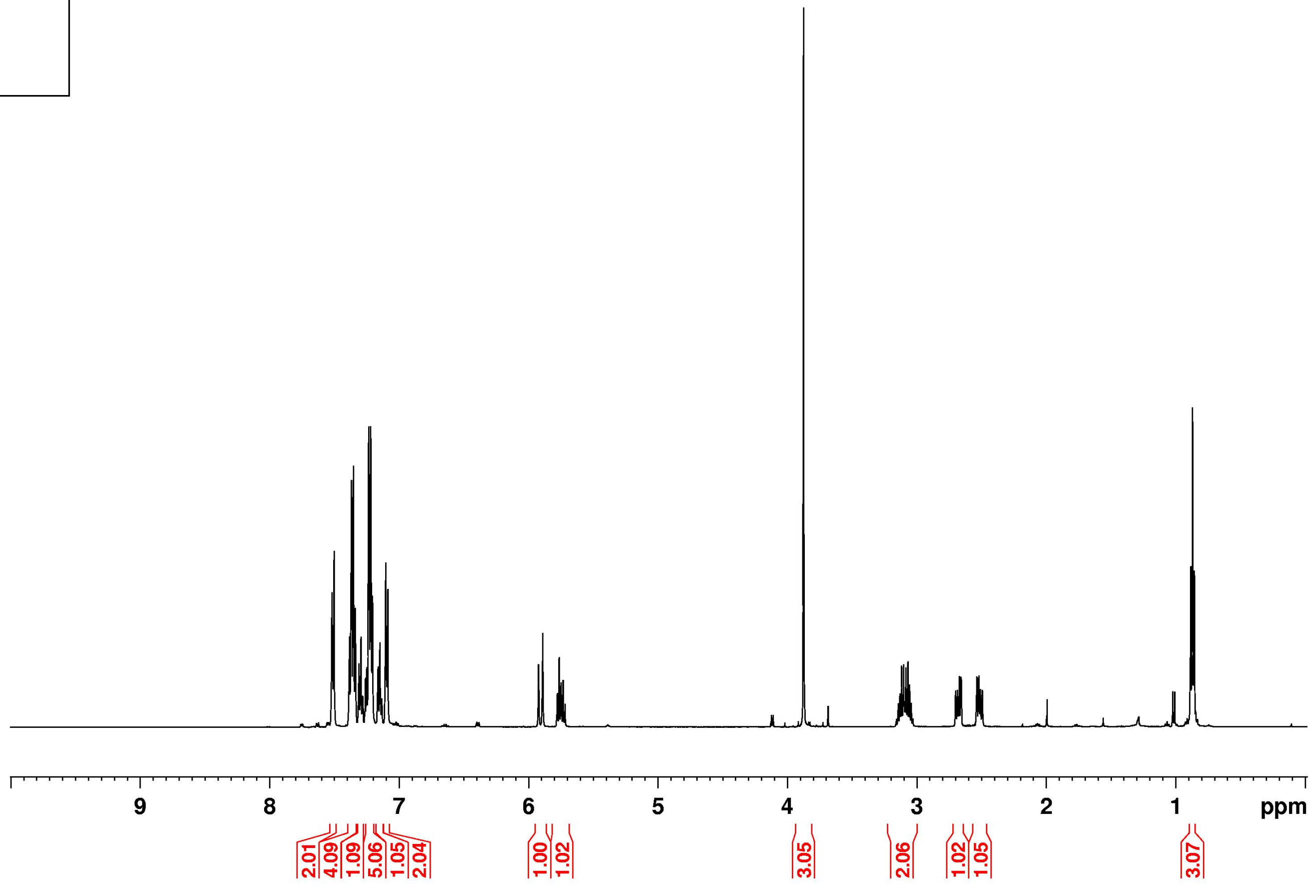
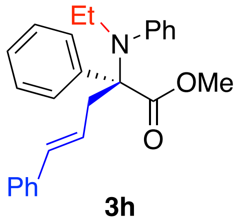


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3h** in $CDCl_3$



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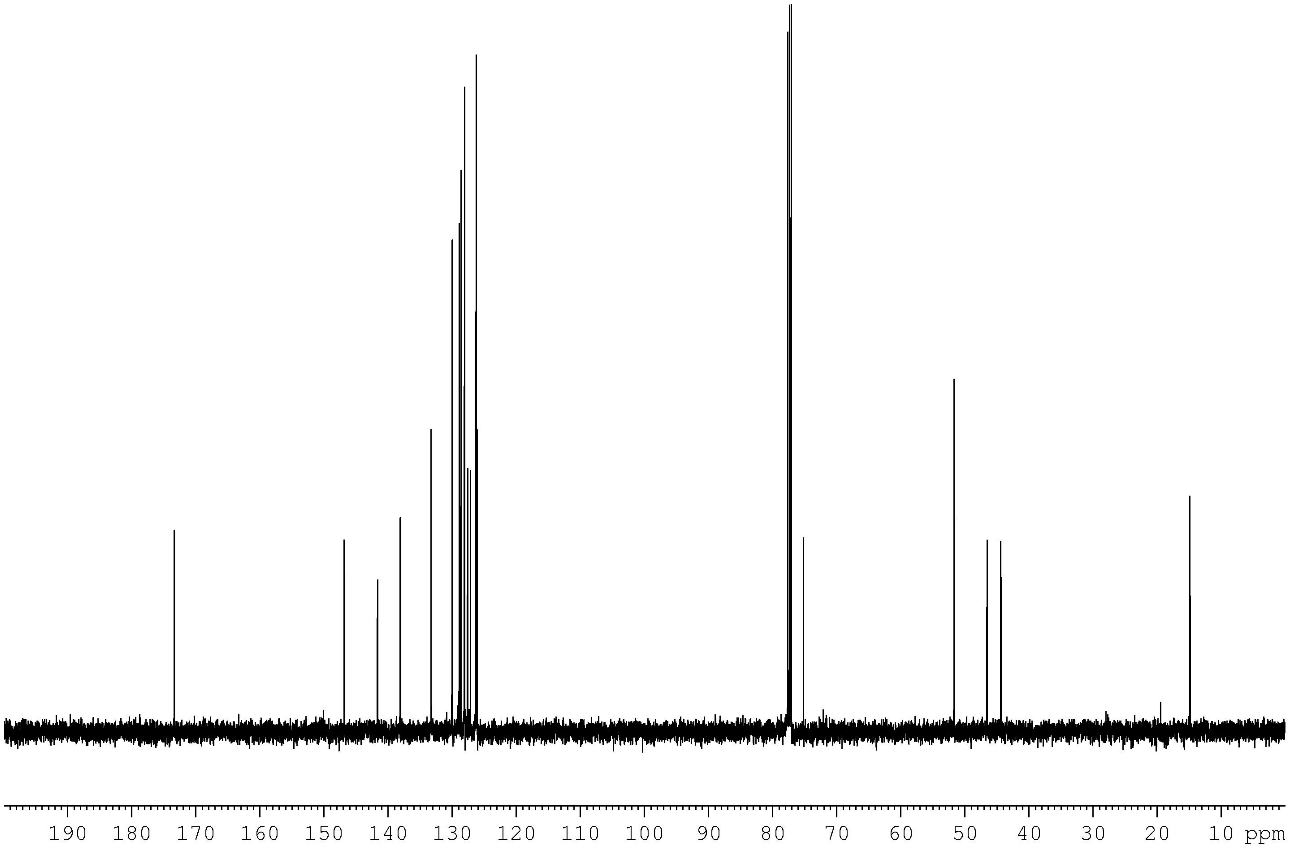
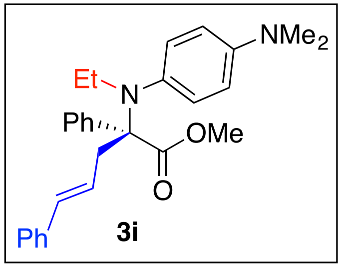


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3h** in $CDCl_3$



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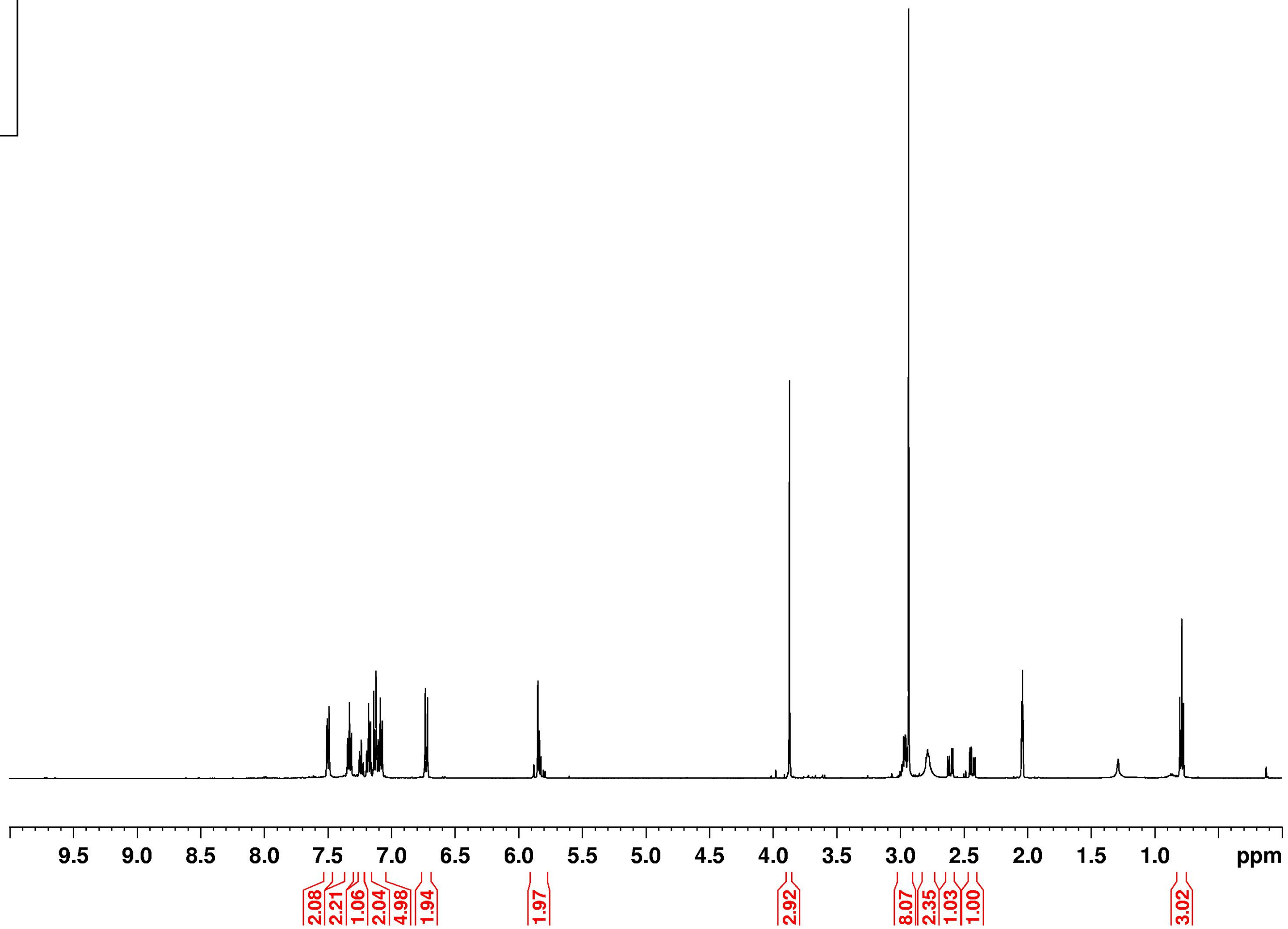


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3i** in $(CD_3)_2CO$

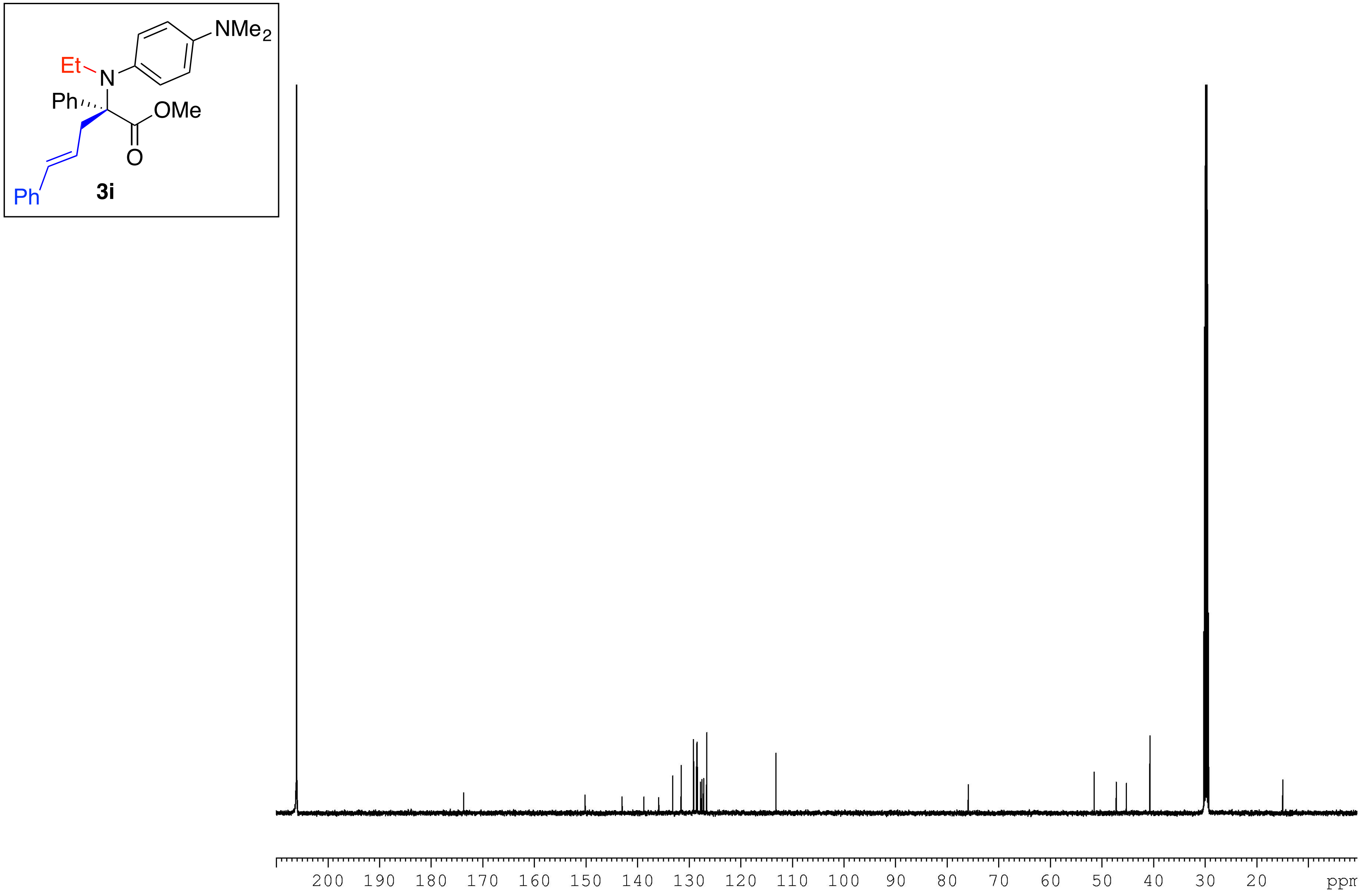
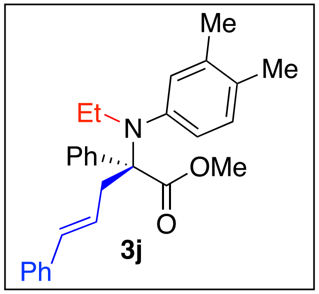


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3i** in $(CD_3)_2CO$



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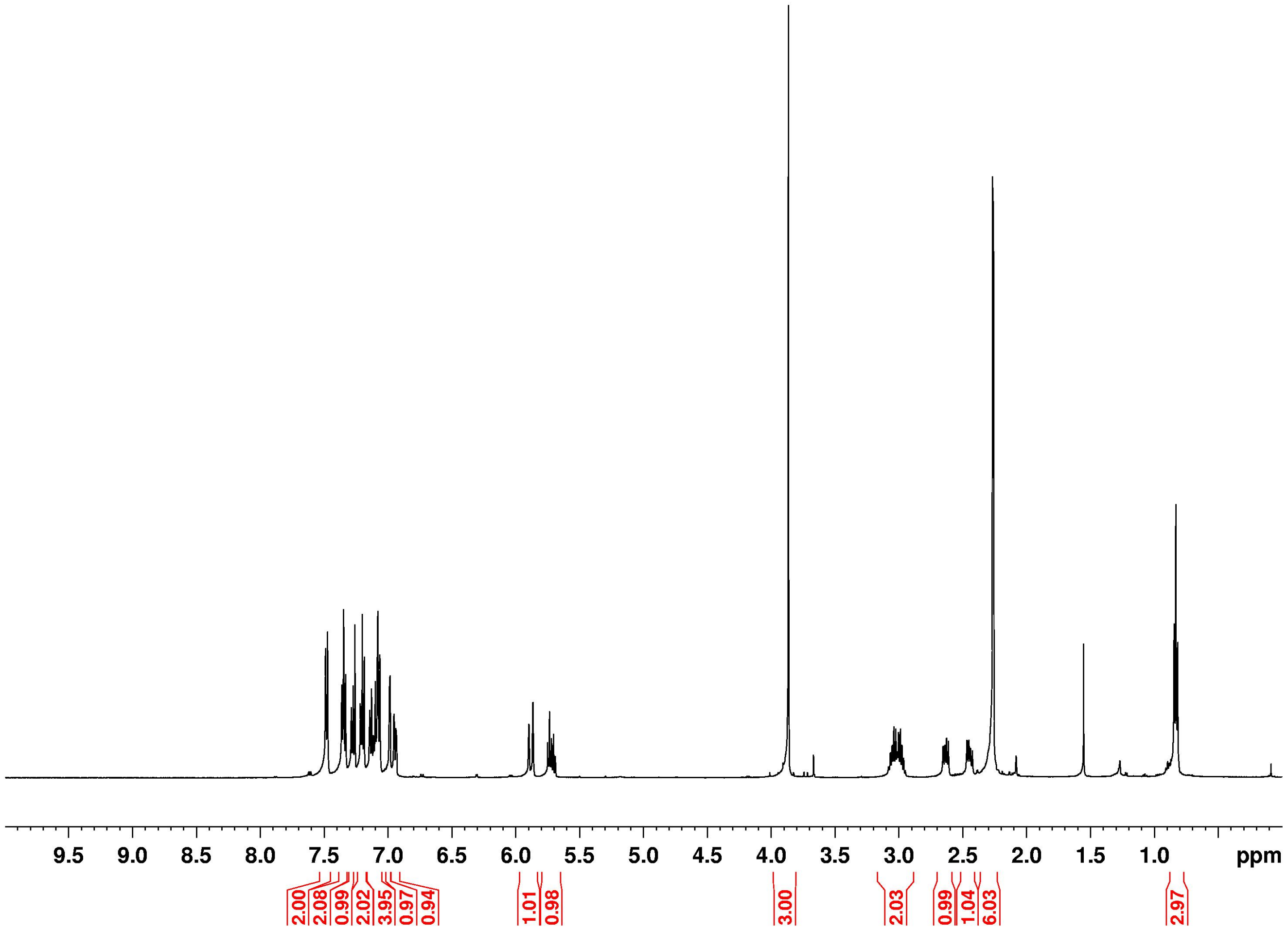
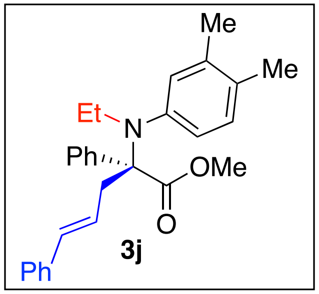


Table 2. 500 MHz ^{1}H NMR Spectrum of Compound **3j** in $CDCl_3$



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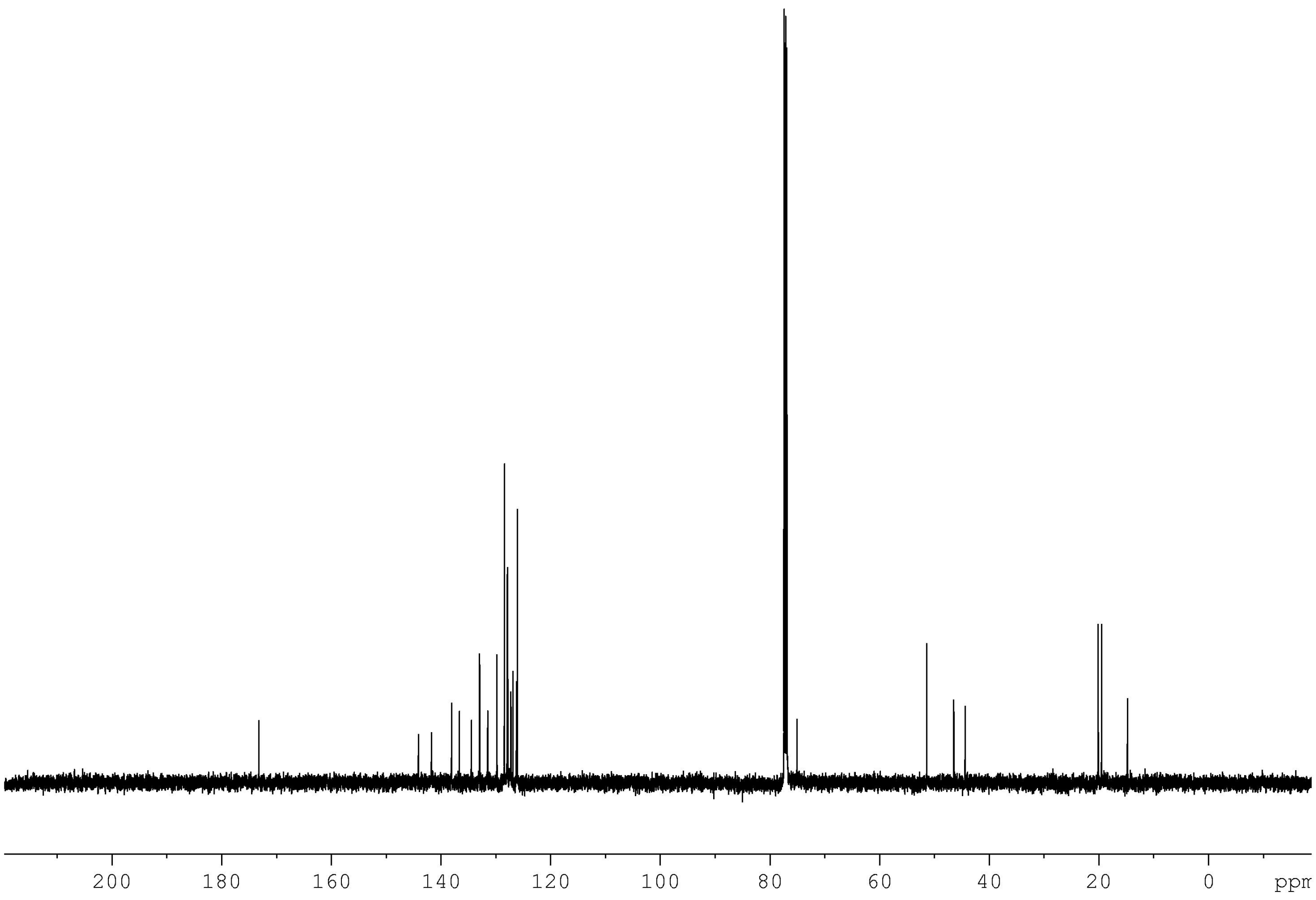
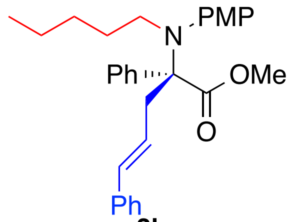


Table 2. 125 MHz ^{13}C NMR Spectrum of Compound **3j** in $CDCl_3$



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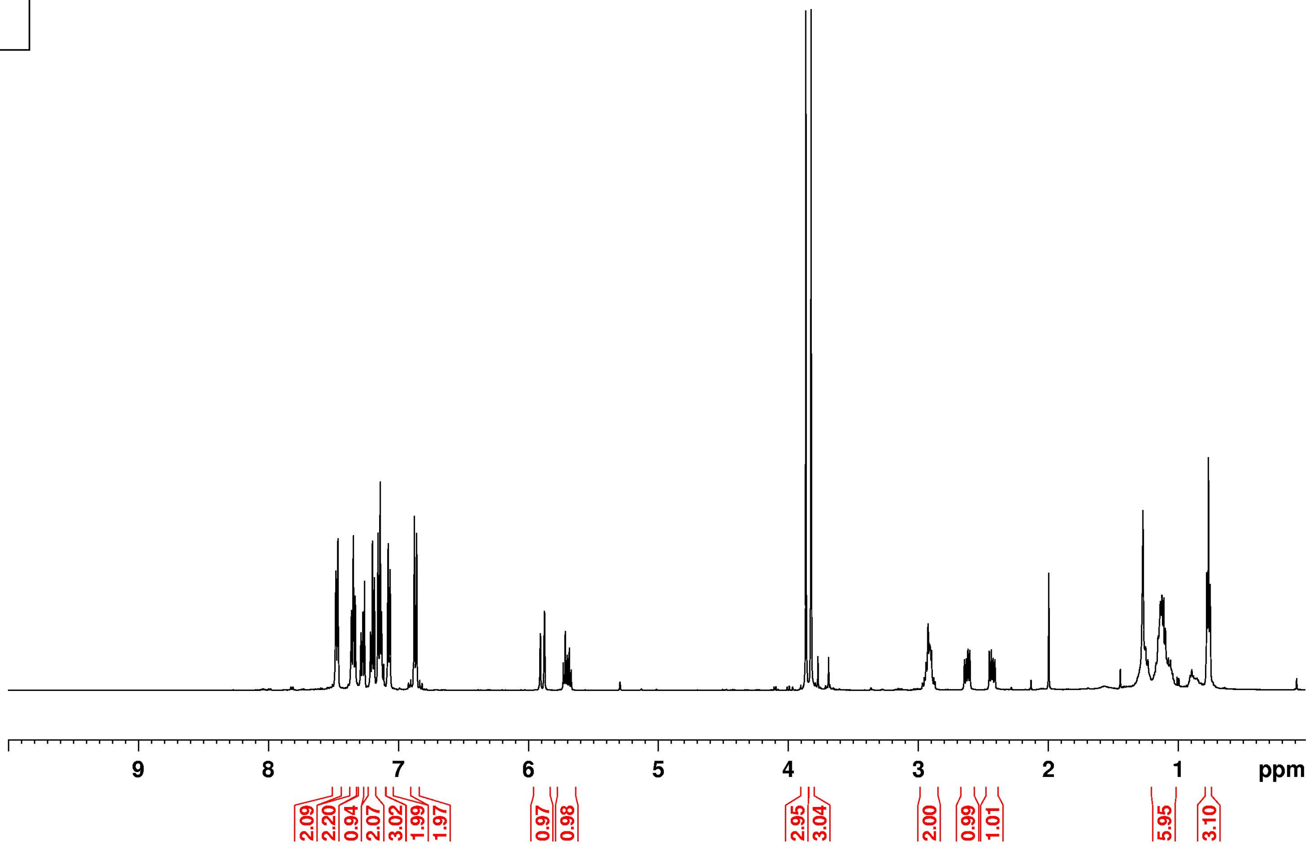
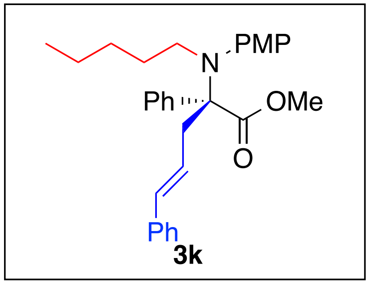


Table 3. 500 MHz ^{1}H NMR Spectrum of Compound **3k** in CDCl$_3$



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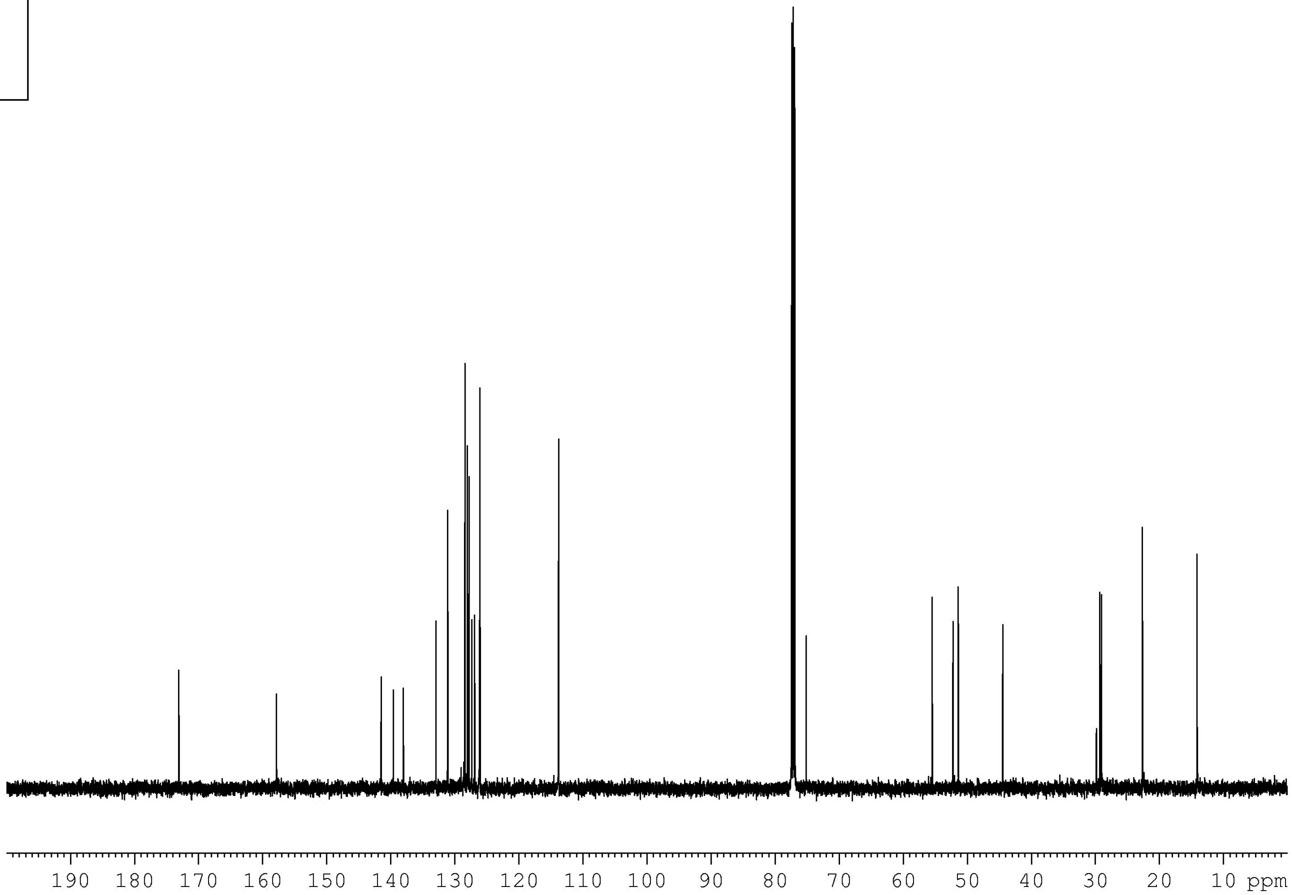
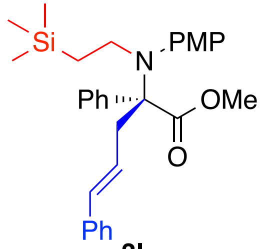


Table 3. 125 MHz ^{13}C NMR Spectrum of Compound **3k** in $CDCl_3$



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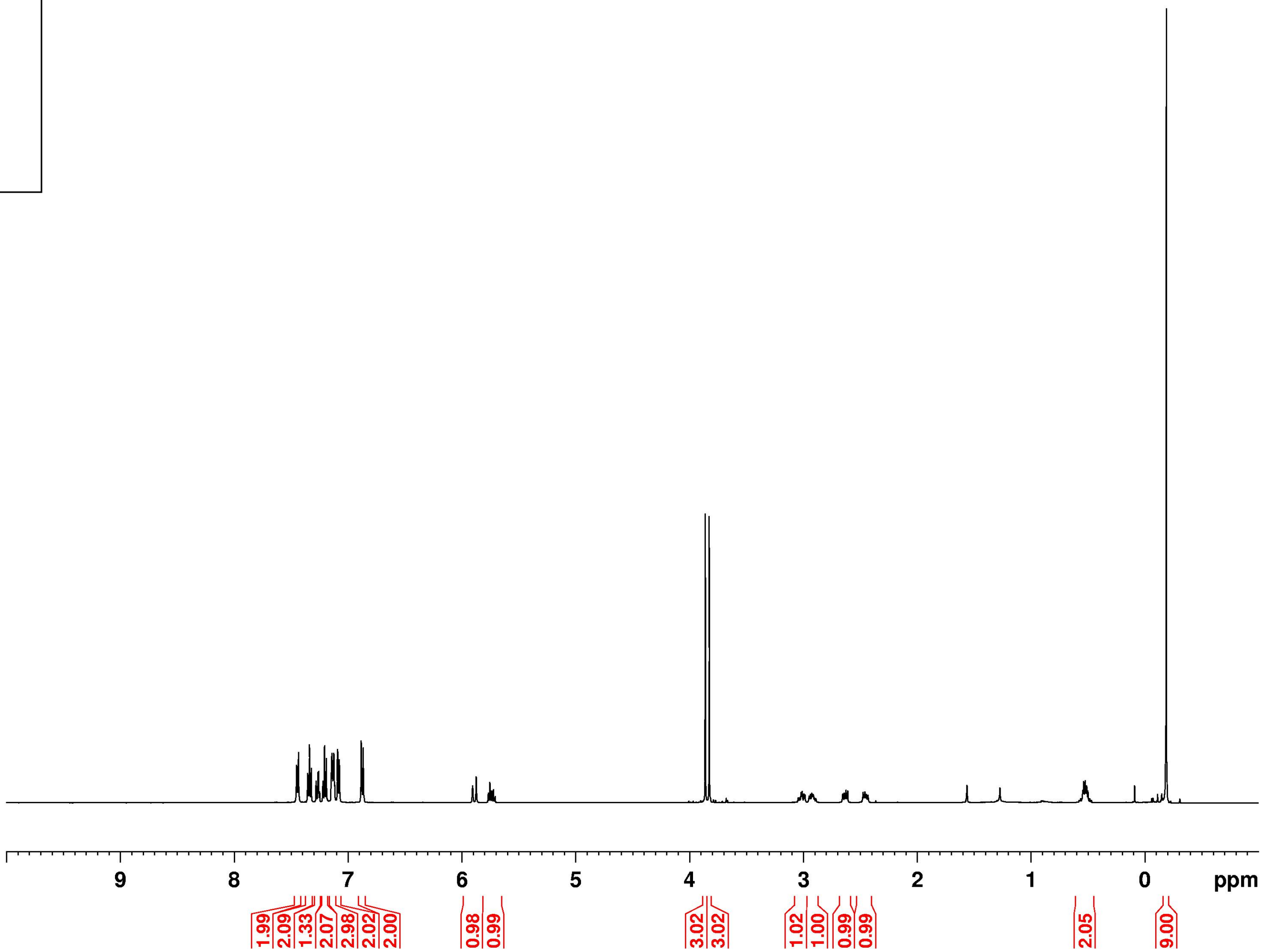
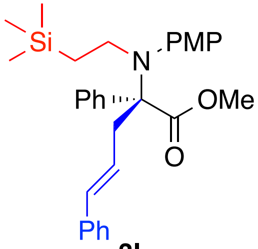


Table 3. 500 MHz ^{1}H NMR Spectrum of Compound **3l** in CDCl$_3$



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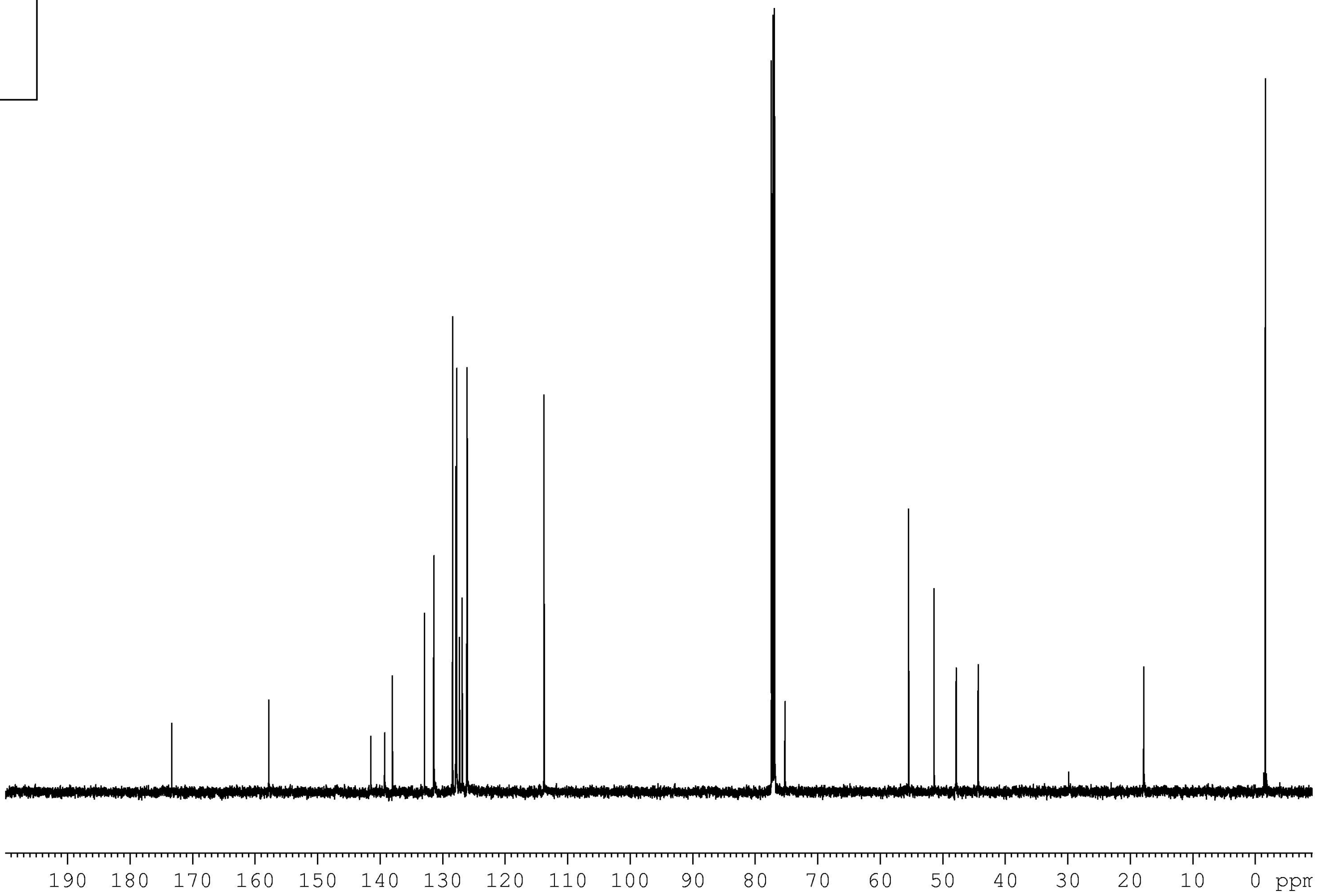


Table 3. 125 MHz ^{13}C NMR Spectrum of Compound **3l** in $CDCl_3$

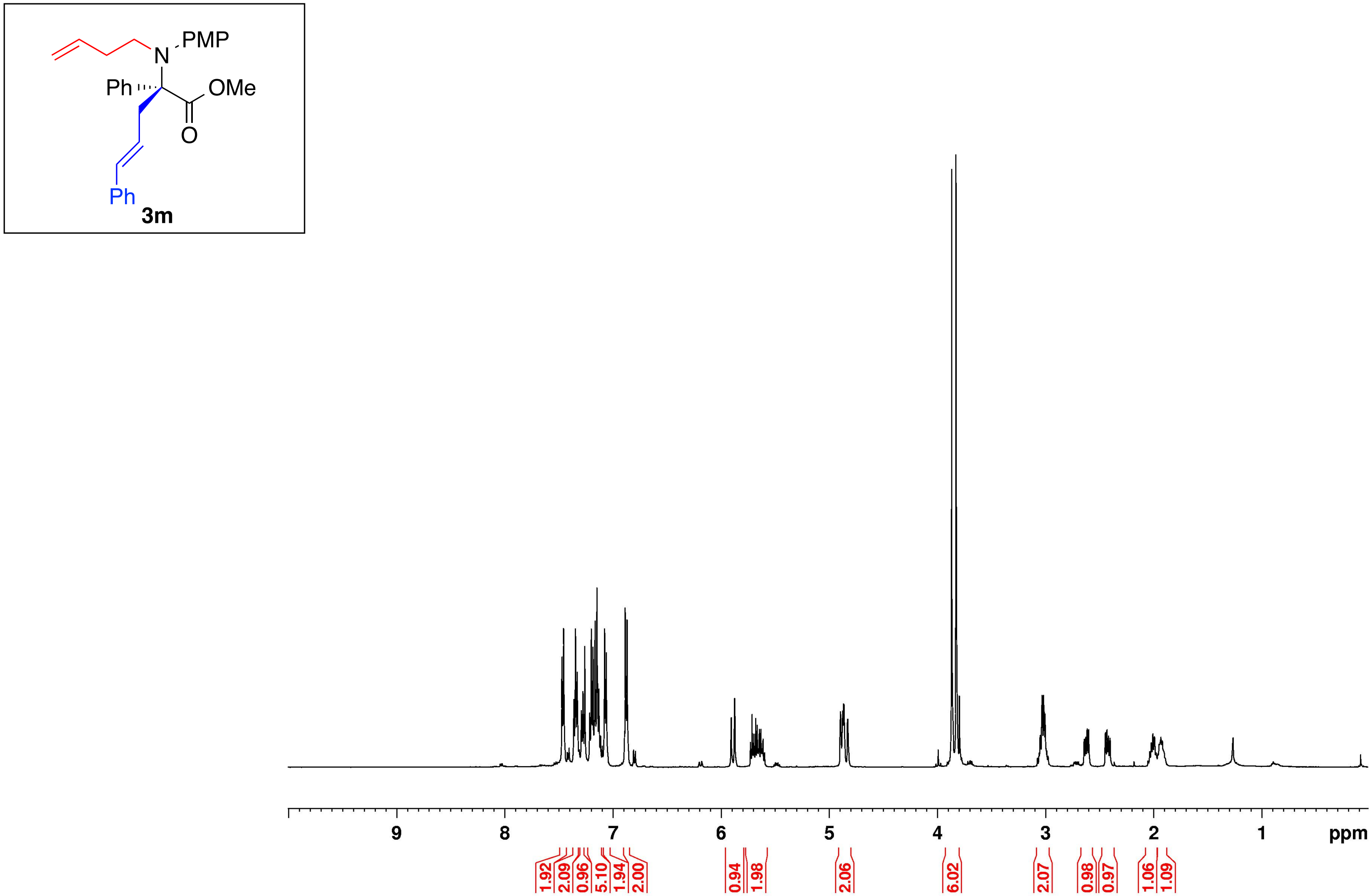
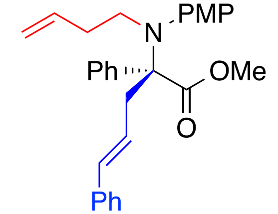


Table 3. 500 MHz ^{1}H NMR Spectrum of Compound **3m** in $CDCl_3$



3m

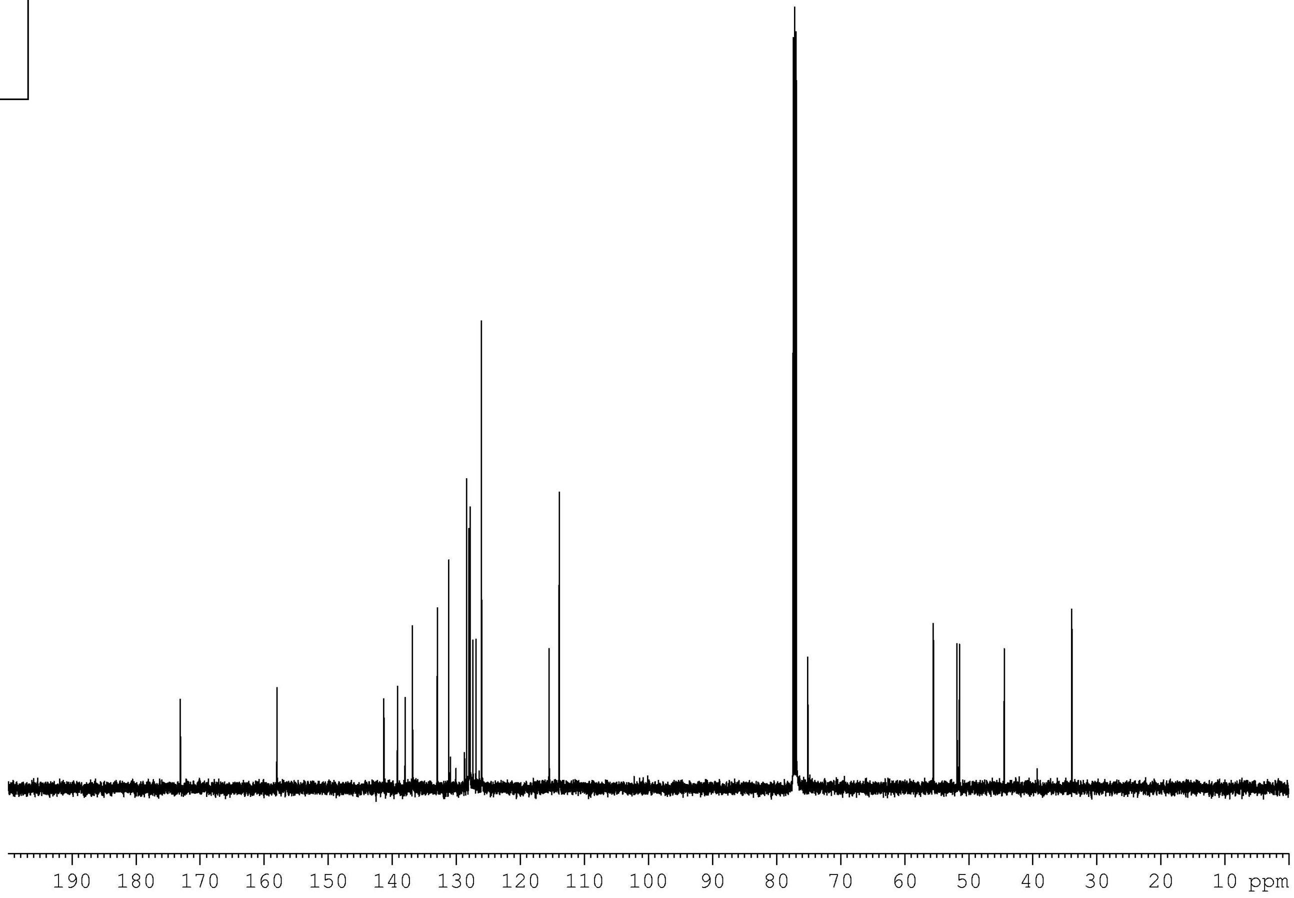


Table 3. 125 MHz ^{13}C NMR Spectrum of Compound **3m** in CDCl$_3$

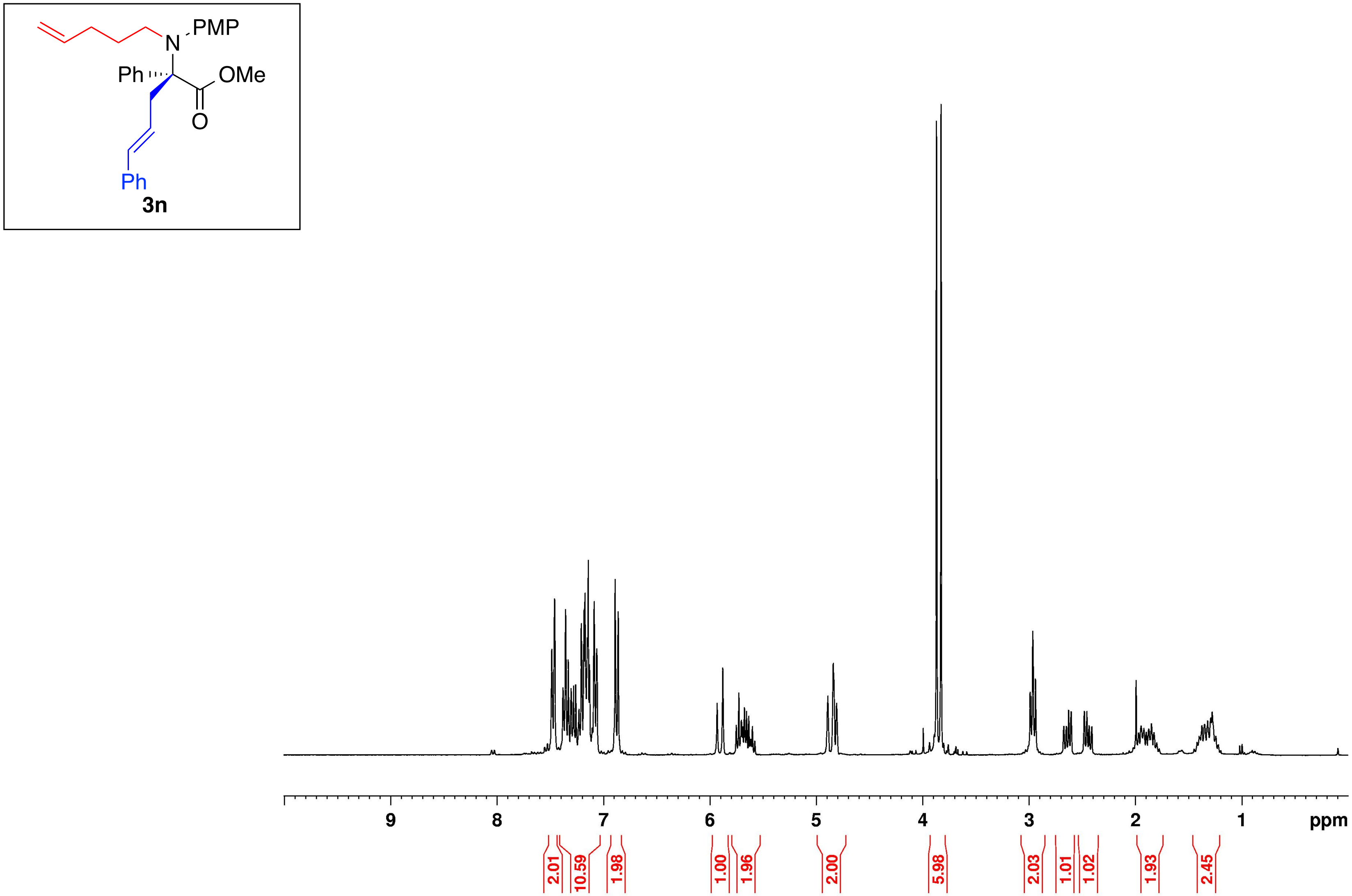
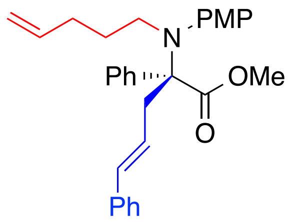


Table 3. 500 MHz ^{1}H NMR Spectrum of Compound **3n** in CDCl$_3$



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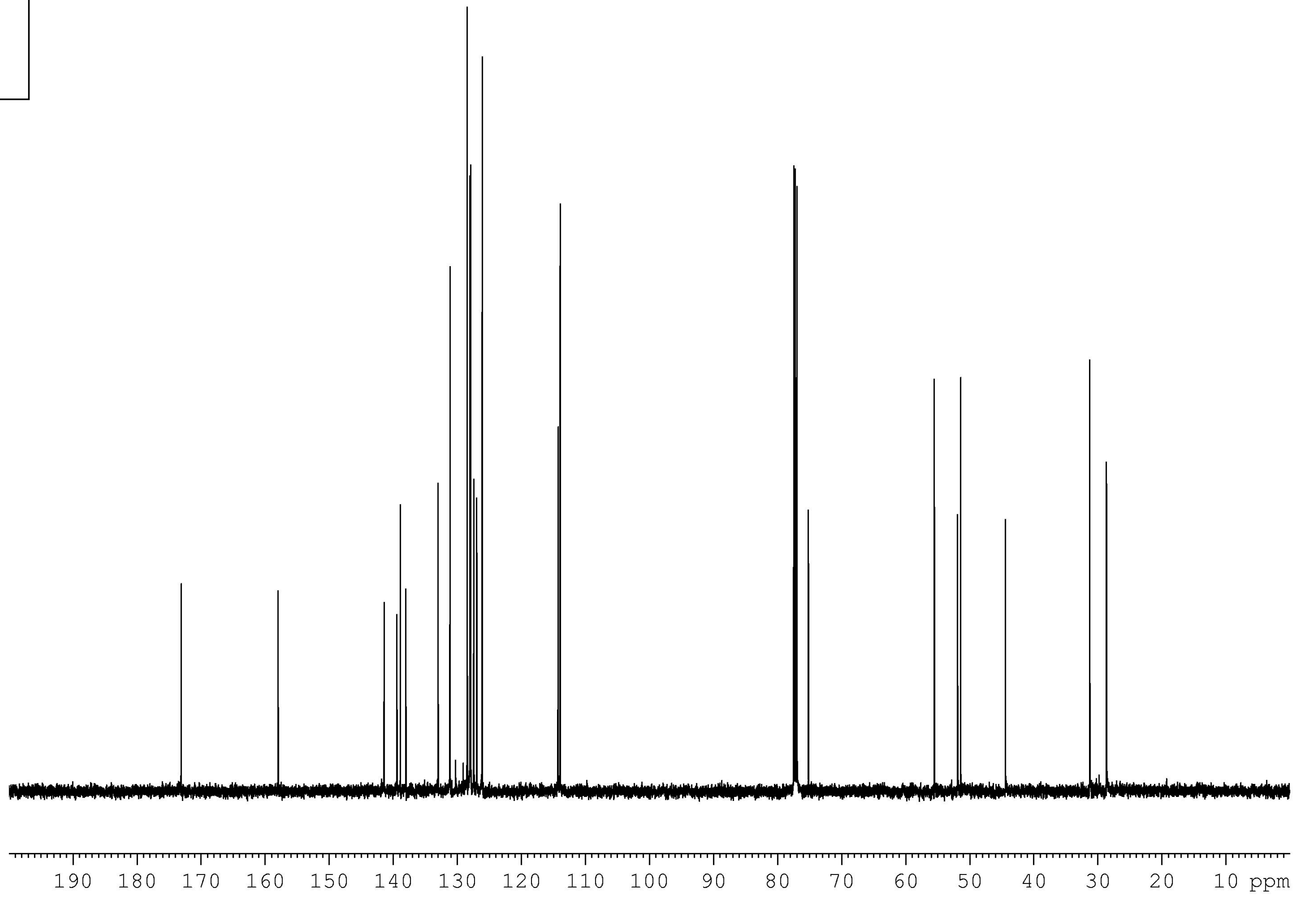


Table 3 125 MHz ^{13}C NMR Spectrum of Compound **3n** in $CDCl_3$

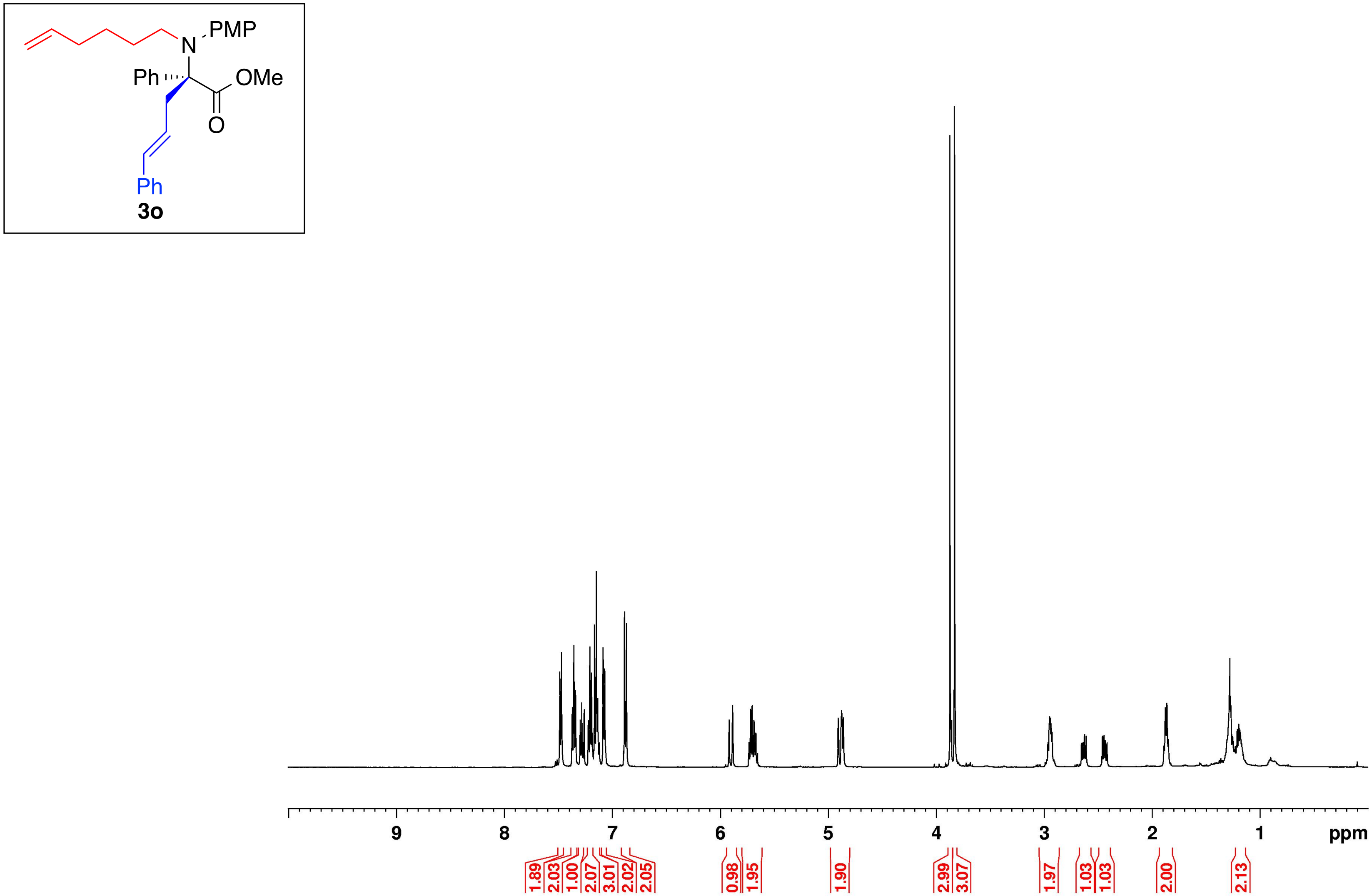
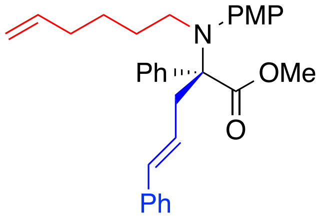


Table 3. 500 MHz ^{1}H NMR Spectrum of Compound **3o** in $CDCl_3$



3o

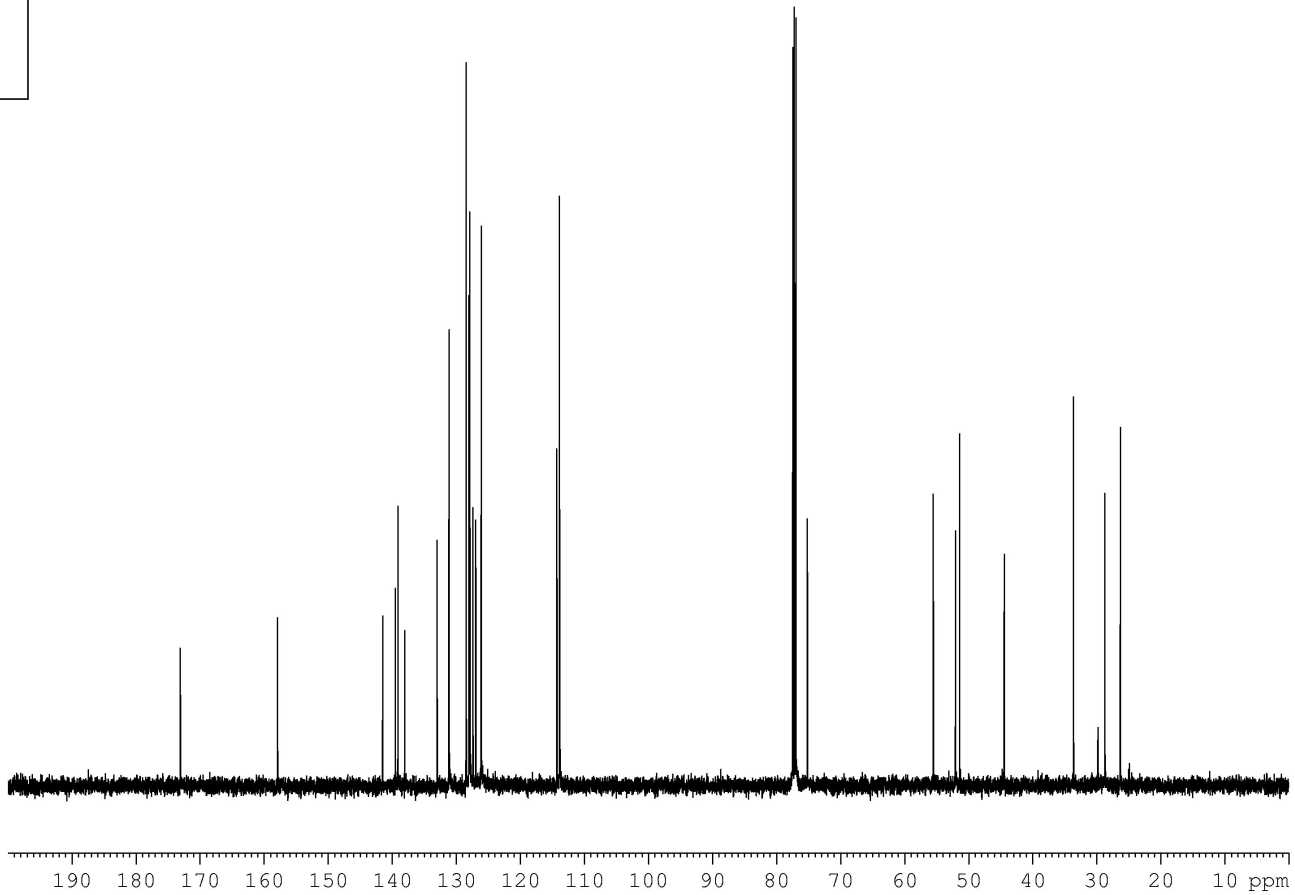
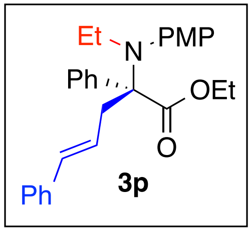
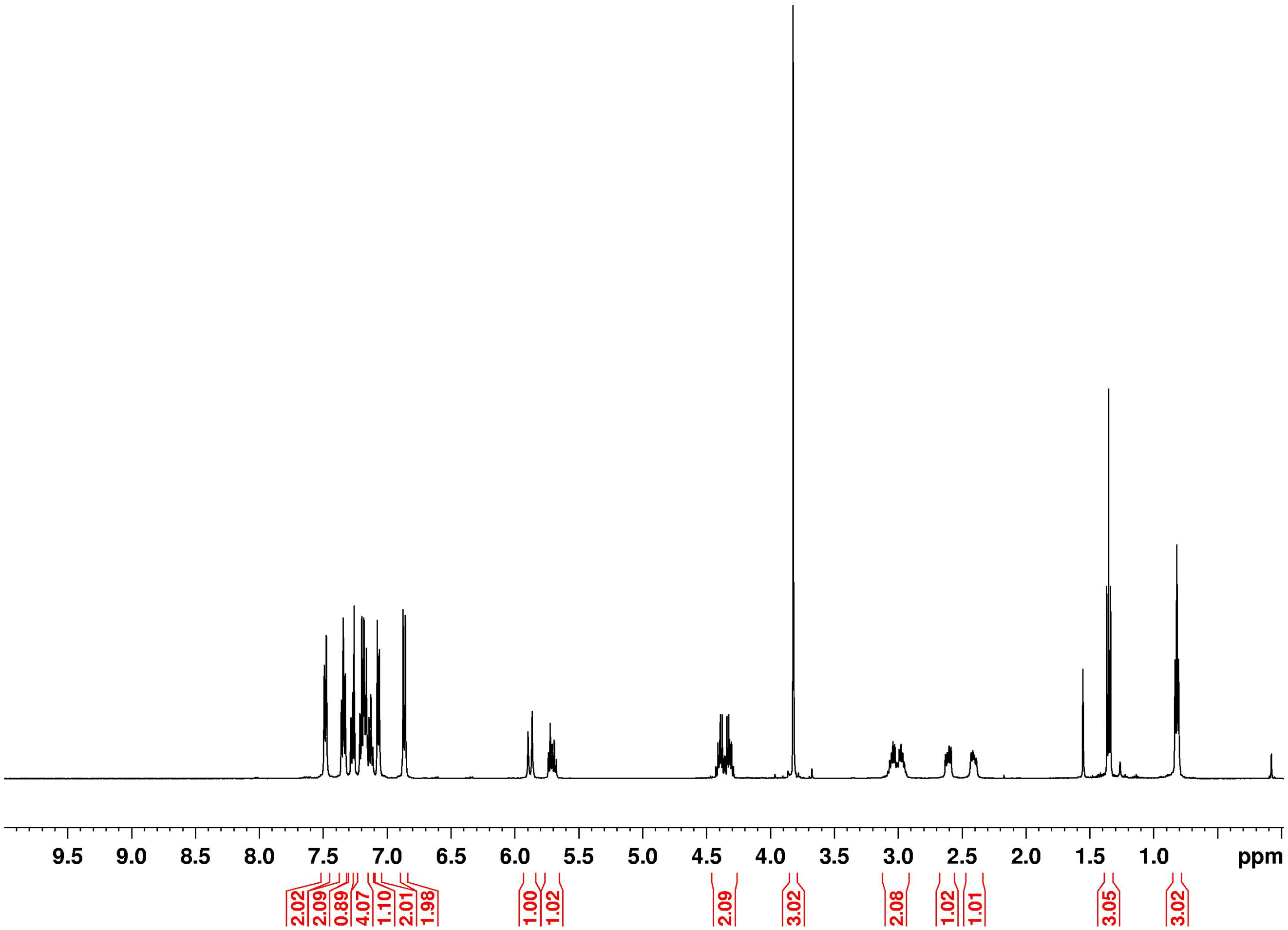


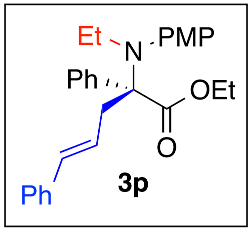
Table 3. 125 MHz ^{13}C NMR Spectrum of Compound **3o** in $CDCl_3$



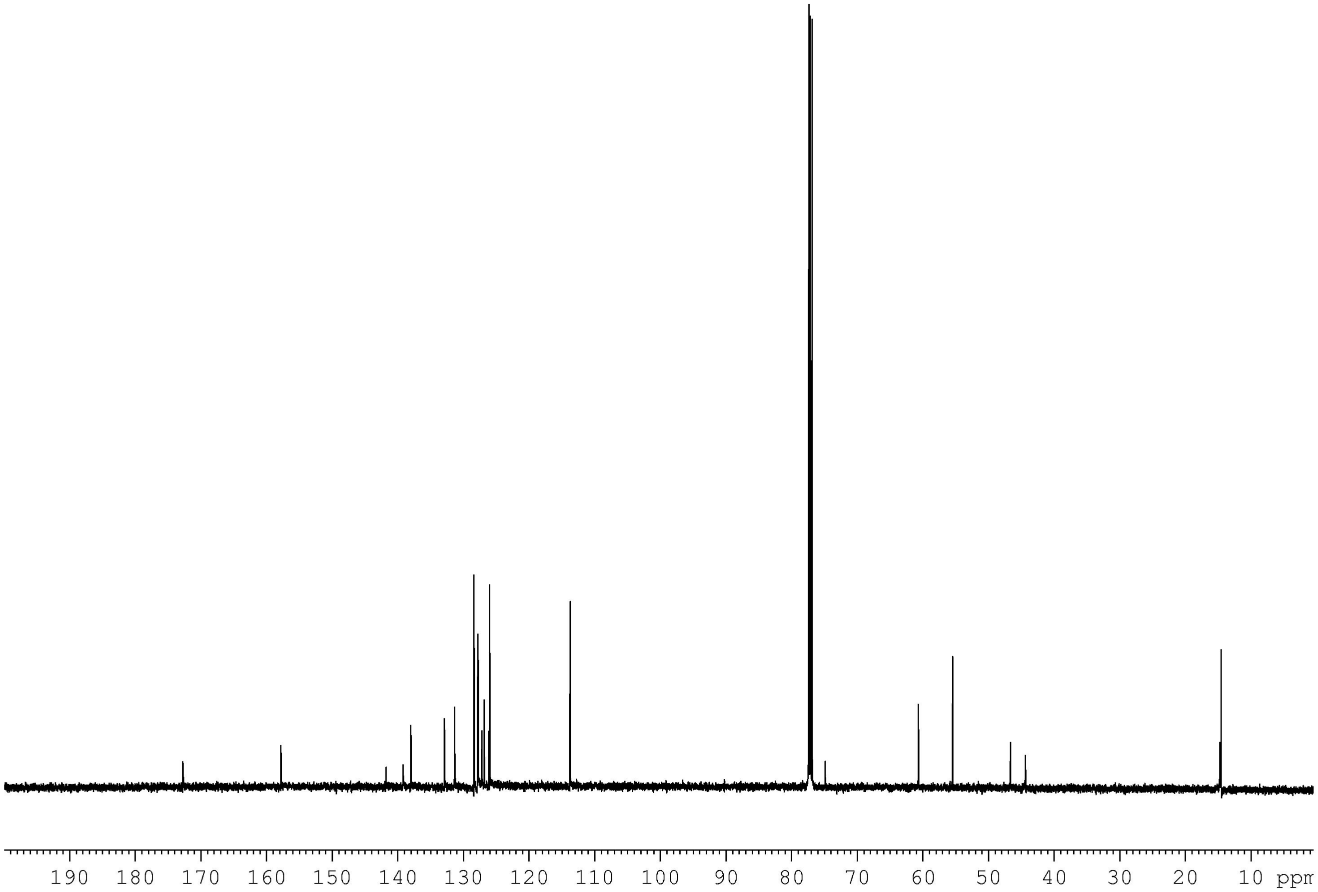
3p



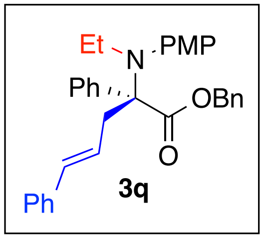
500 MHz ^{1}H NMR Spectrum of Compound **3p** in $CDCl_3$



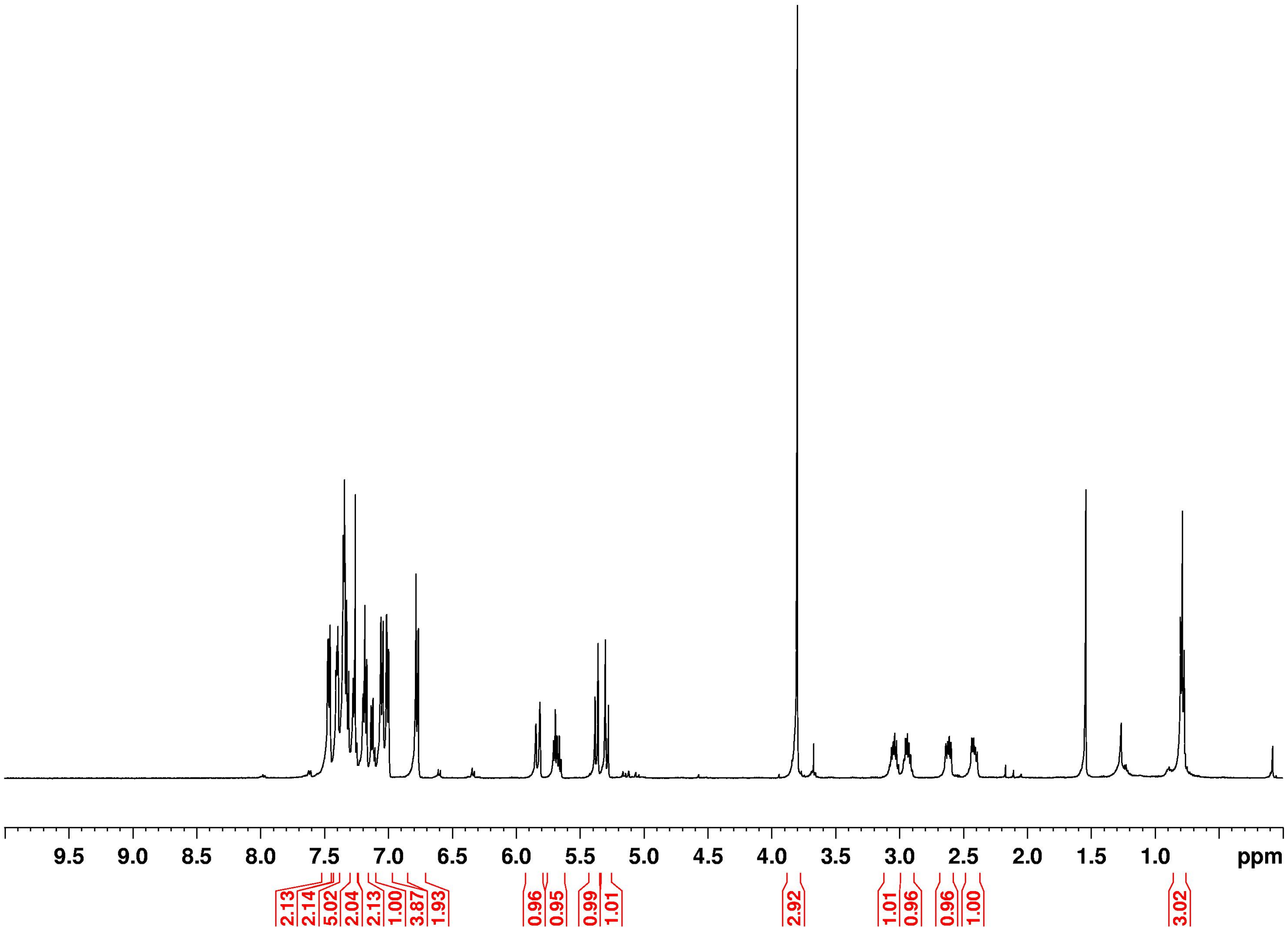
3p



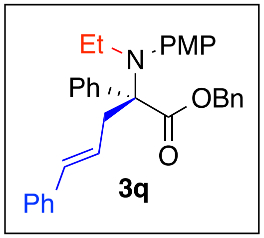
125 MHz ^{13}C NMR Spectrum of Compound **3p** in $CDCl_3$



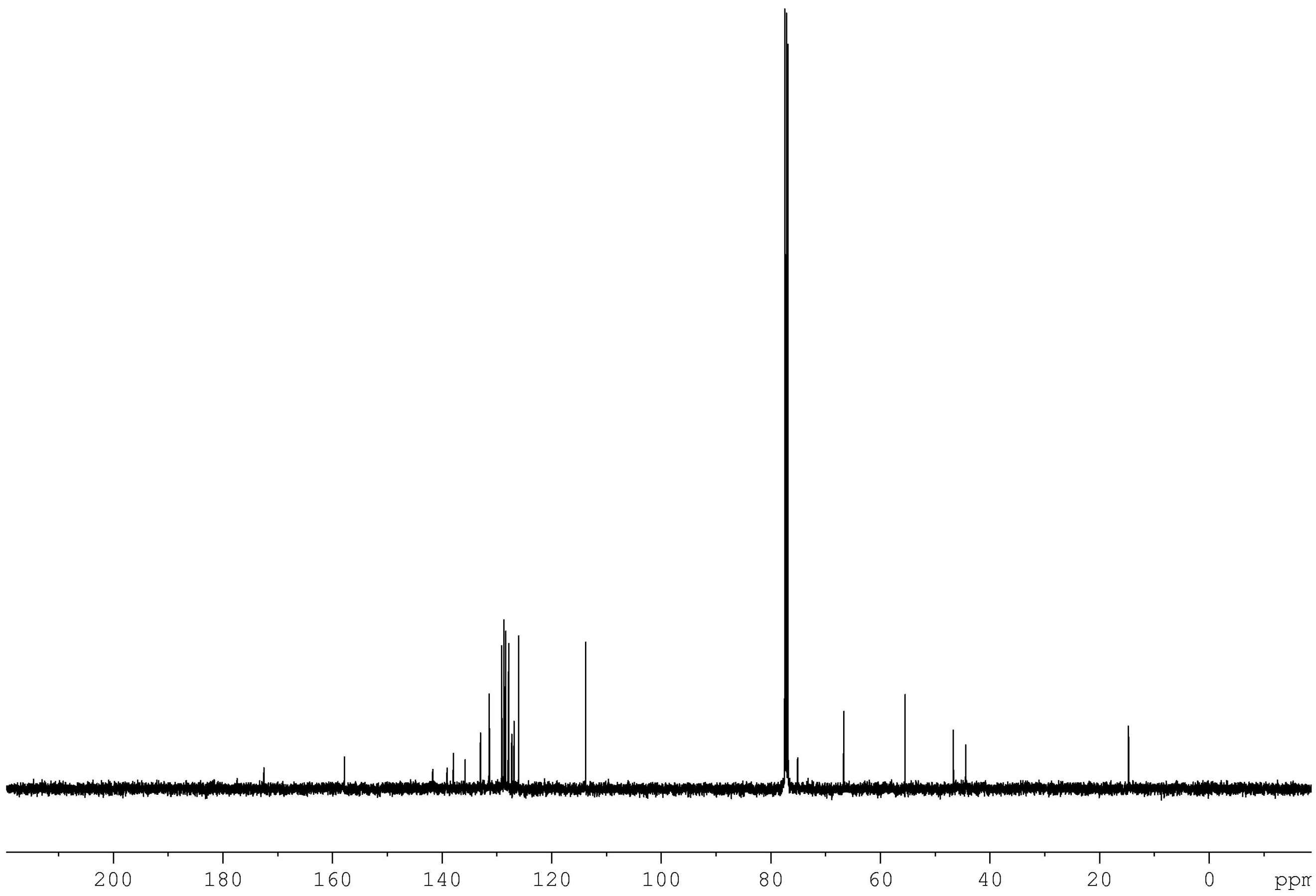
3q



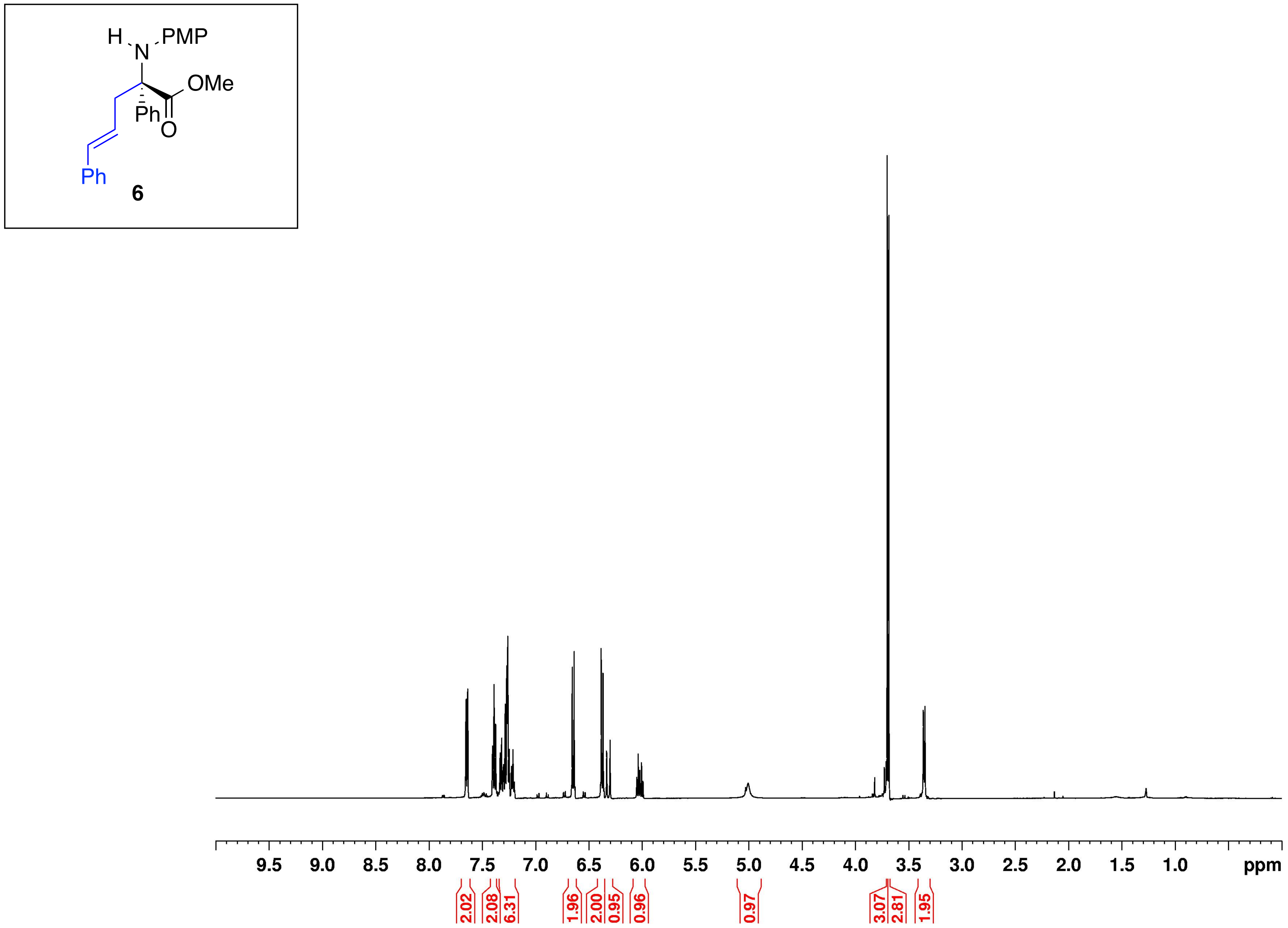
500 MHz ^{1}H NMR Spectrum of Compound **3q** in $CDCl_3$



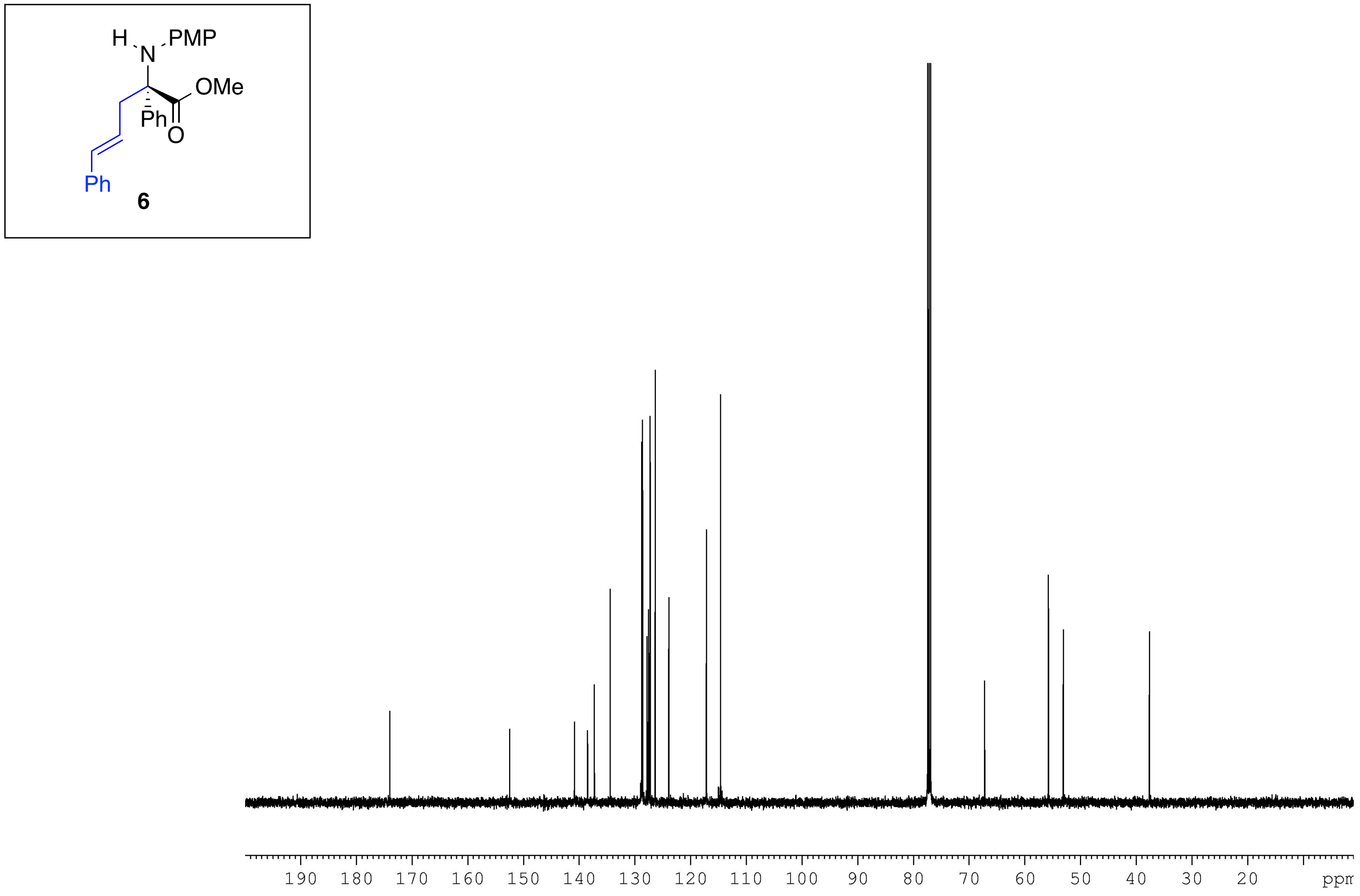
3q



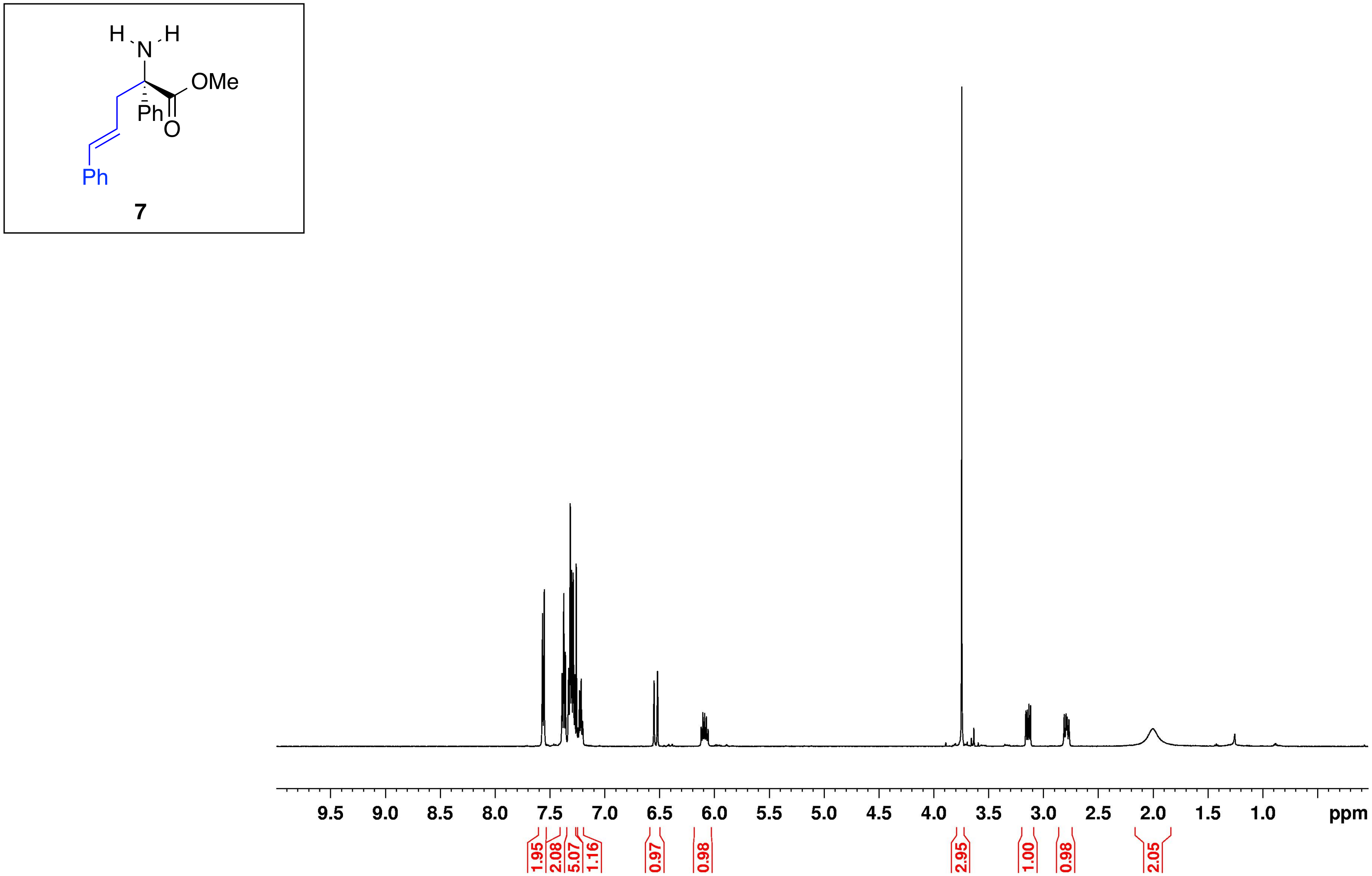
125 MHz ^{13}C NMR Spectrum of Compound **3q** in $CDCl_3$



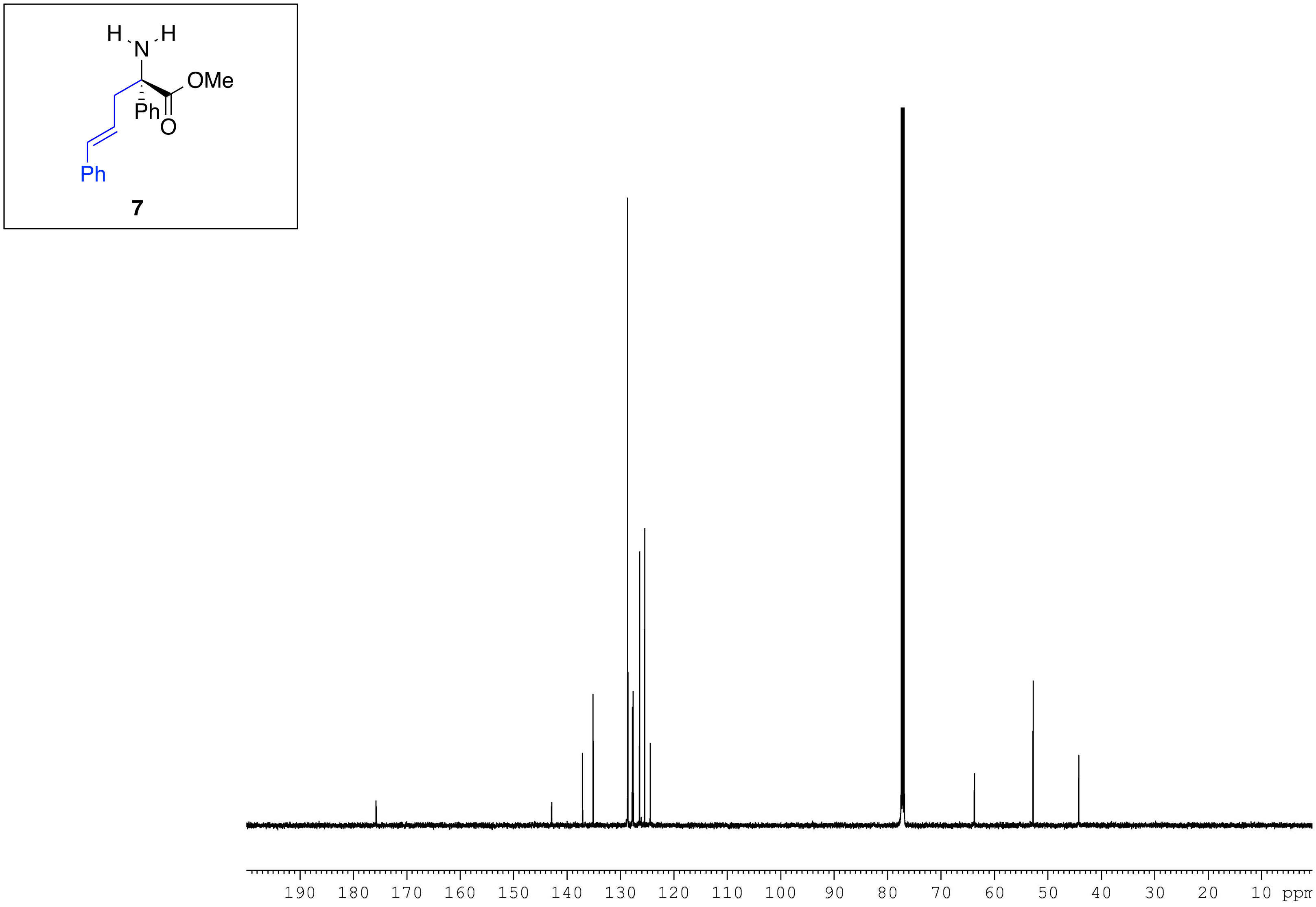
Scheme 4. 500 MHz ^{1}H NMR Spectrum of Compound **6** in CDCl$_3$



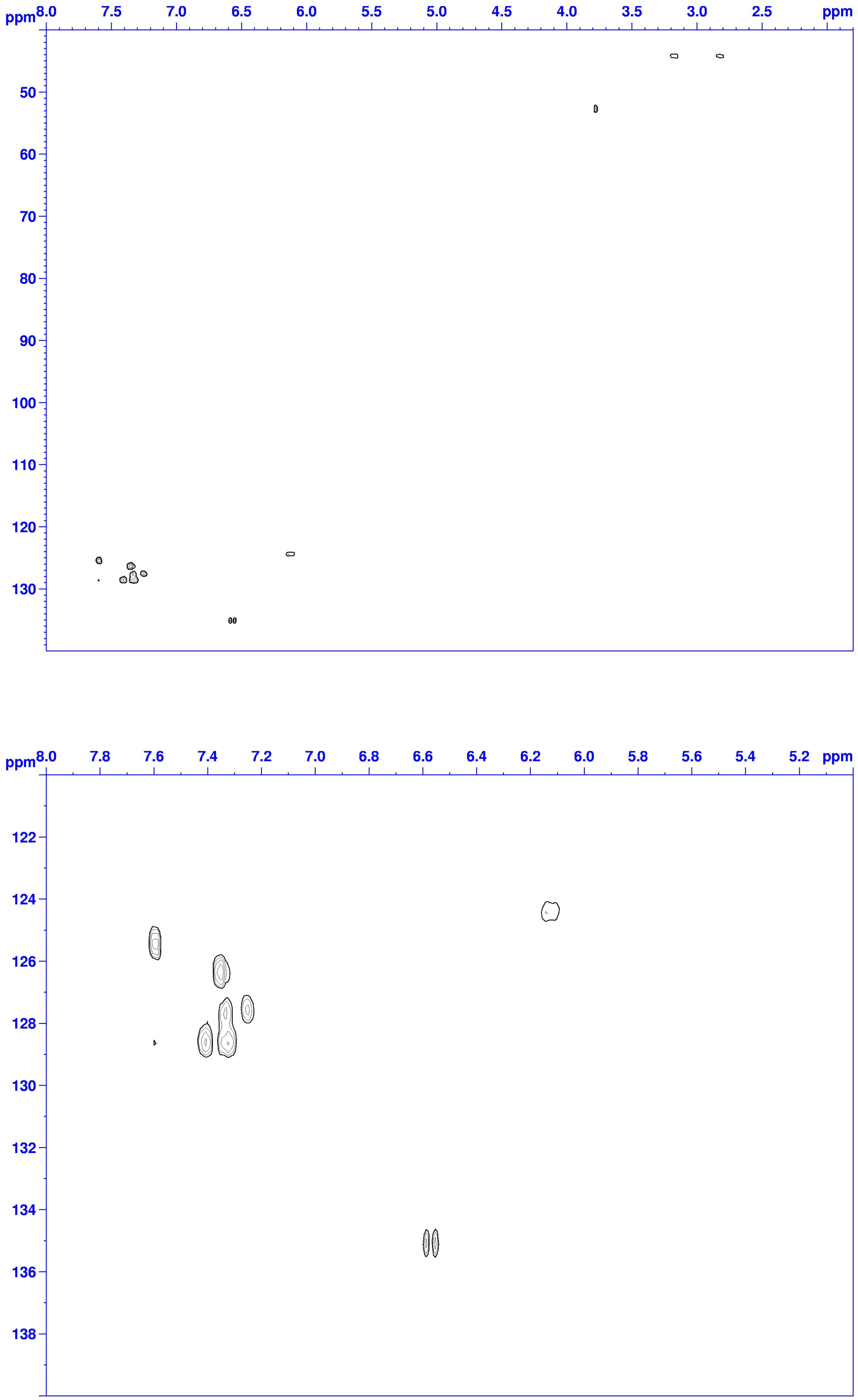
Scheme 4. 125 MHz ^{13}C NMR Spectrum of Compound **6** in $CDCl_3$



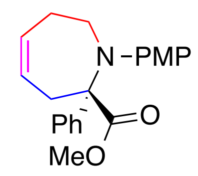
Scheme 4. 500 MHz ^{1}H NMR Spectrum of Compound **7** in $CDCl_3$



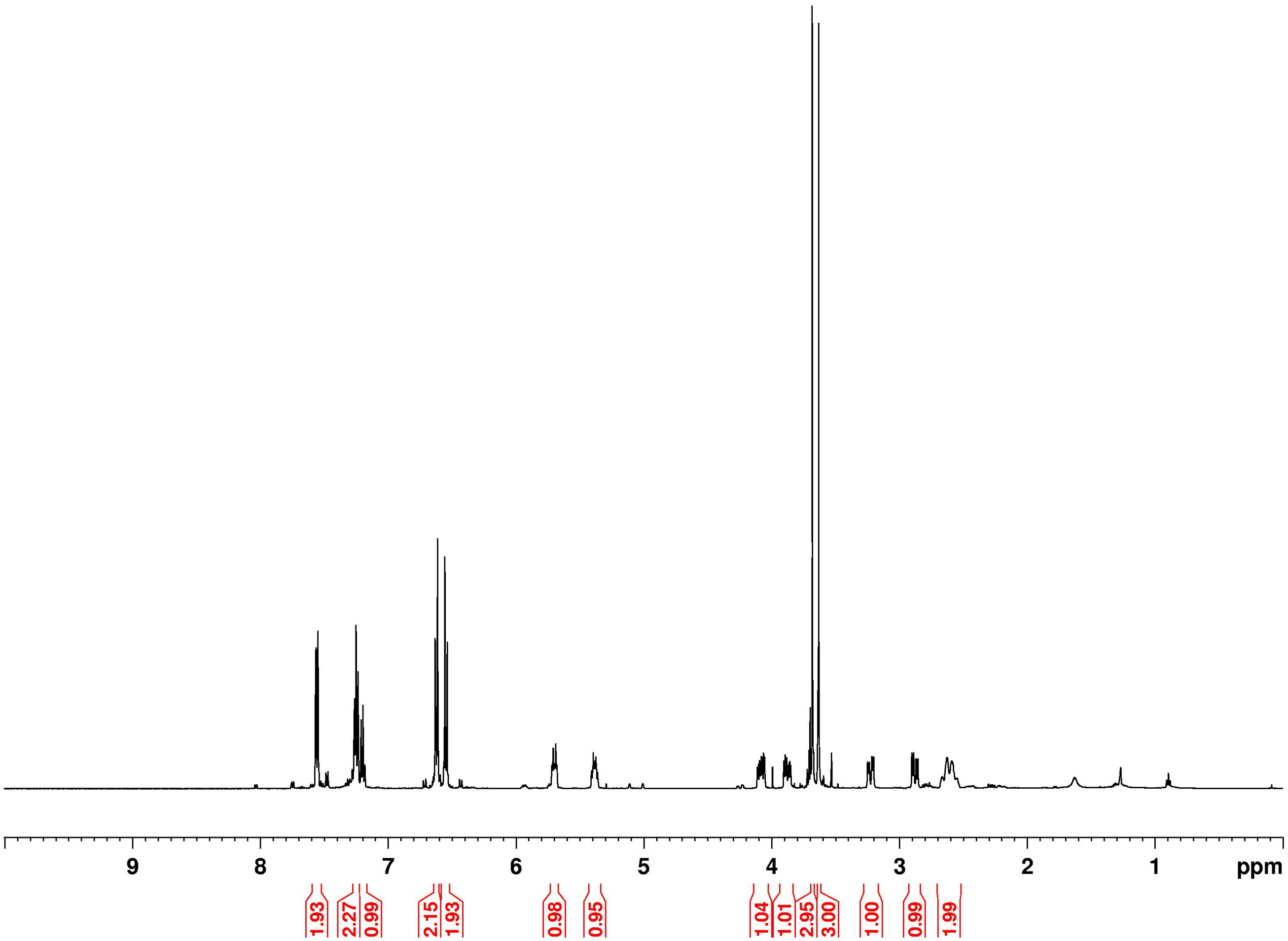
Scheme 4. 125 MHz ^{13}C NMR Spectrum of Compound **7** in $CDCl_3$



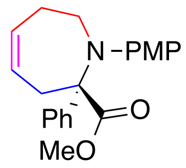
Scheme 4. 125 MHz HSQC Spectrum of Compound **7** in $CDCl_3$



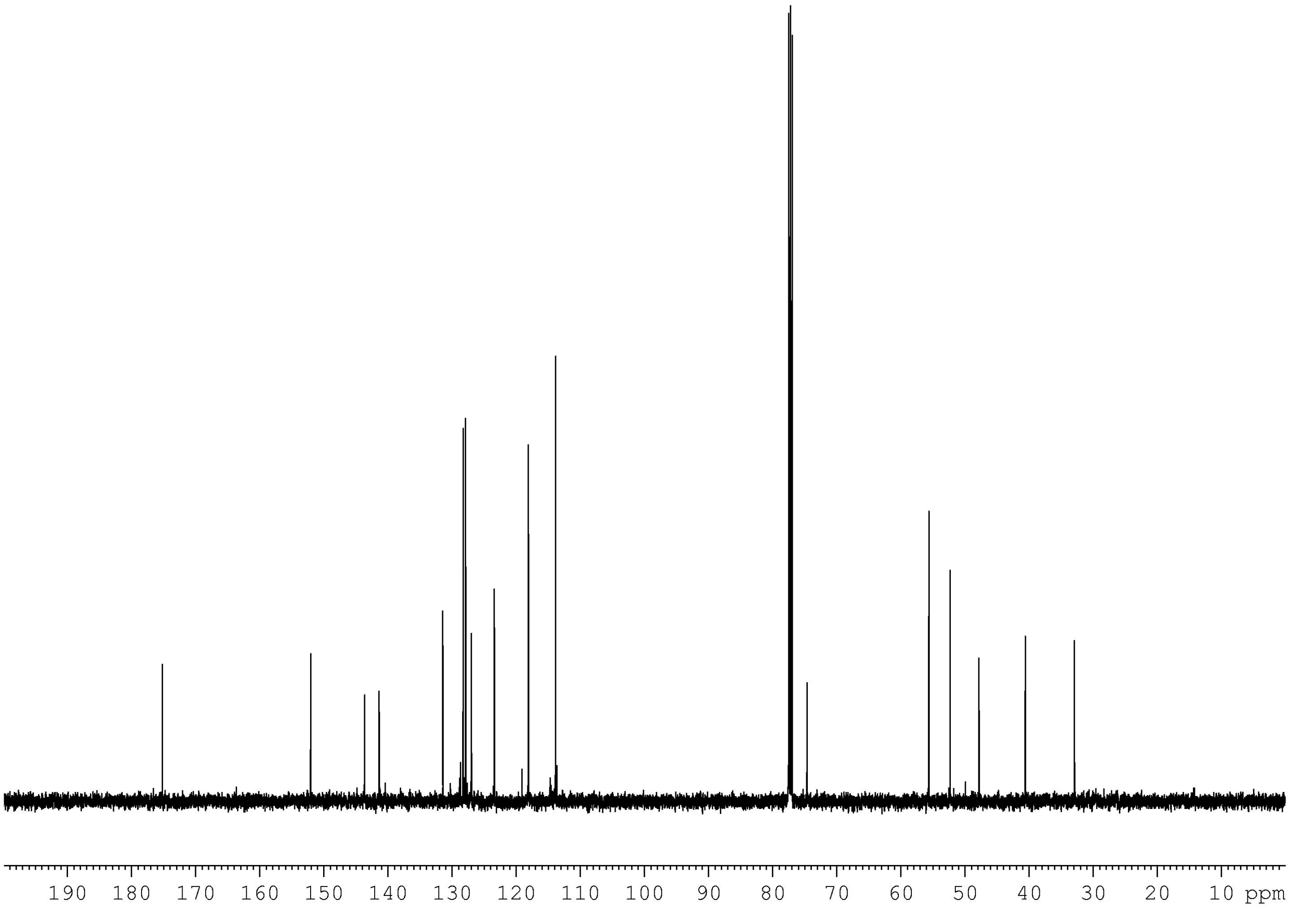
9



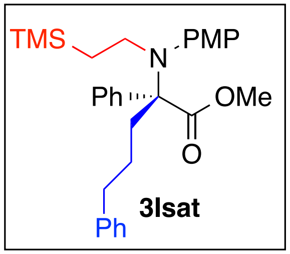
Scheme 5. 500 MHz ^{1}H NMR Spectrum of Compound **9** in $CDCl_3$



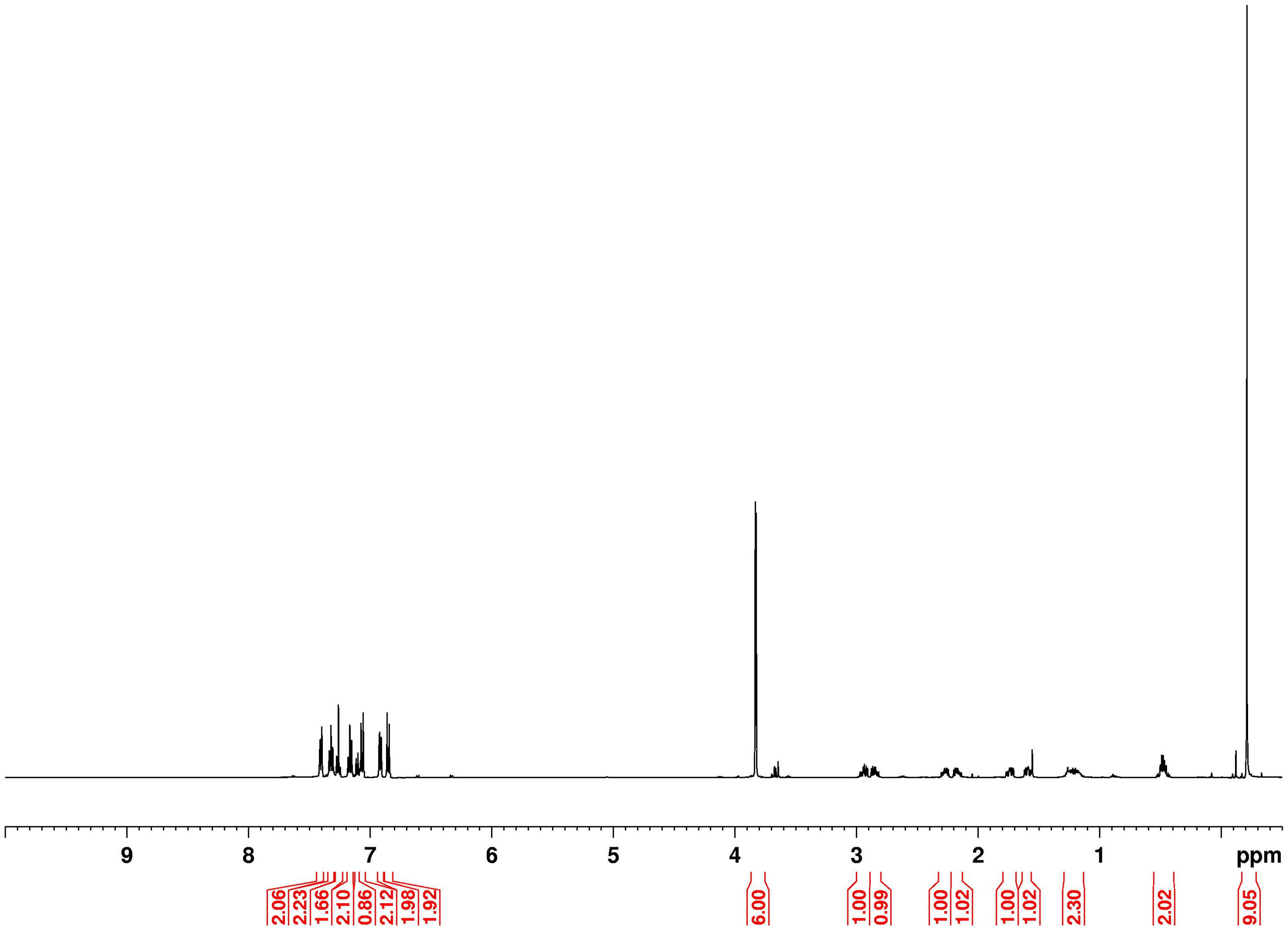
9



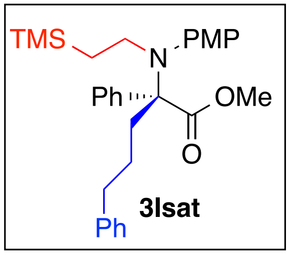
Scheme 5. 125 MHz ^{13}C NMR Spectrum of Compound **9** in $CDCl_3$

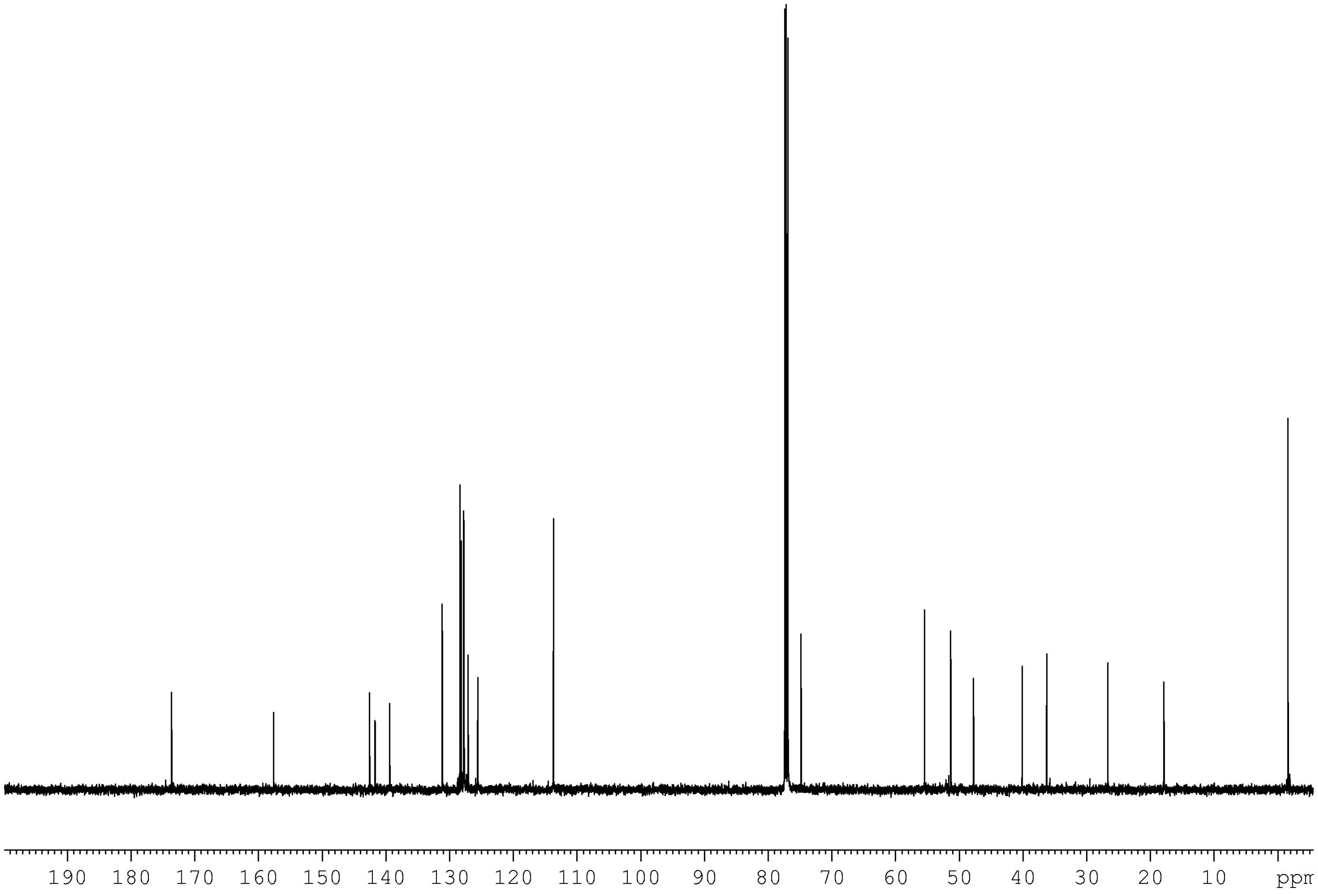


3lsat

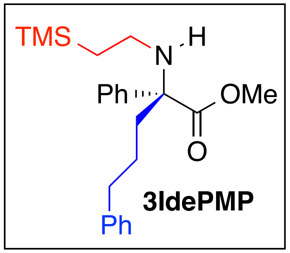


500 MHz ^{1}H NMR Spectrum of Compound **3l$_{\mathbf{sat}}$** in CDCl$_3$

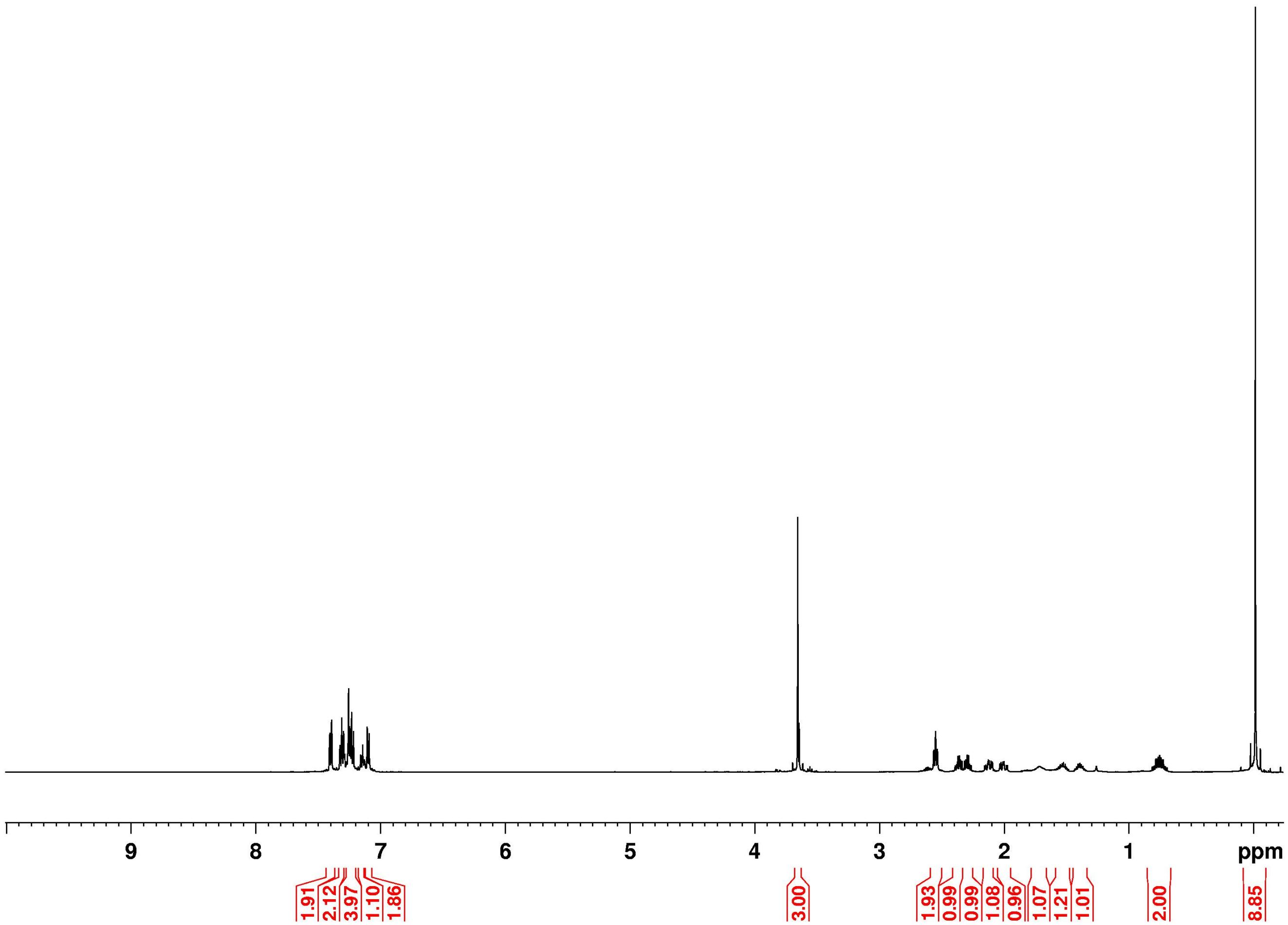




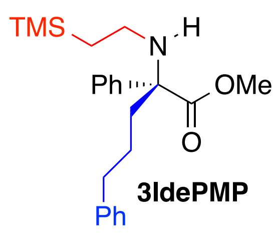
125 MHz ^{13}C NMR Spectrum of Compound **3l$_{\mathbf{sat}}$** in CDCl$_3$



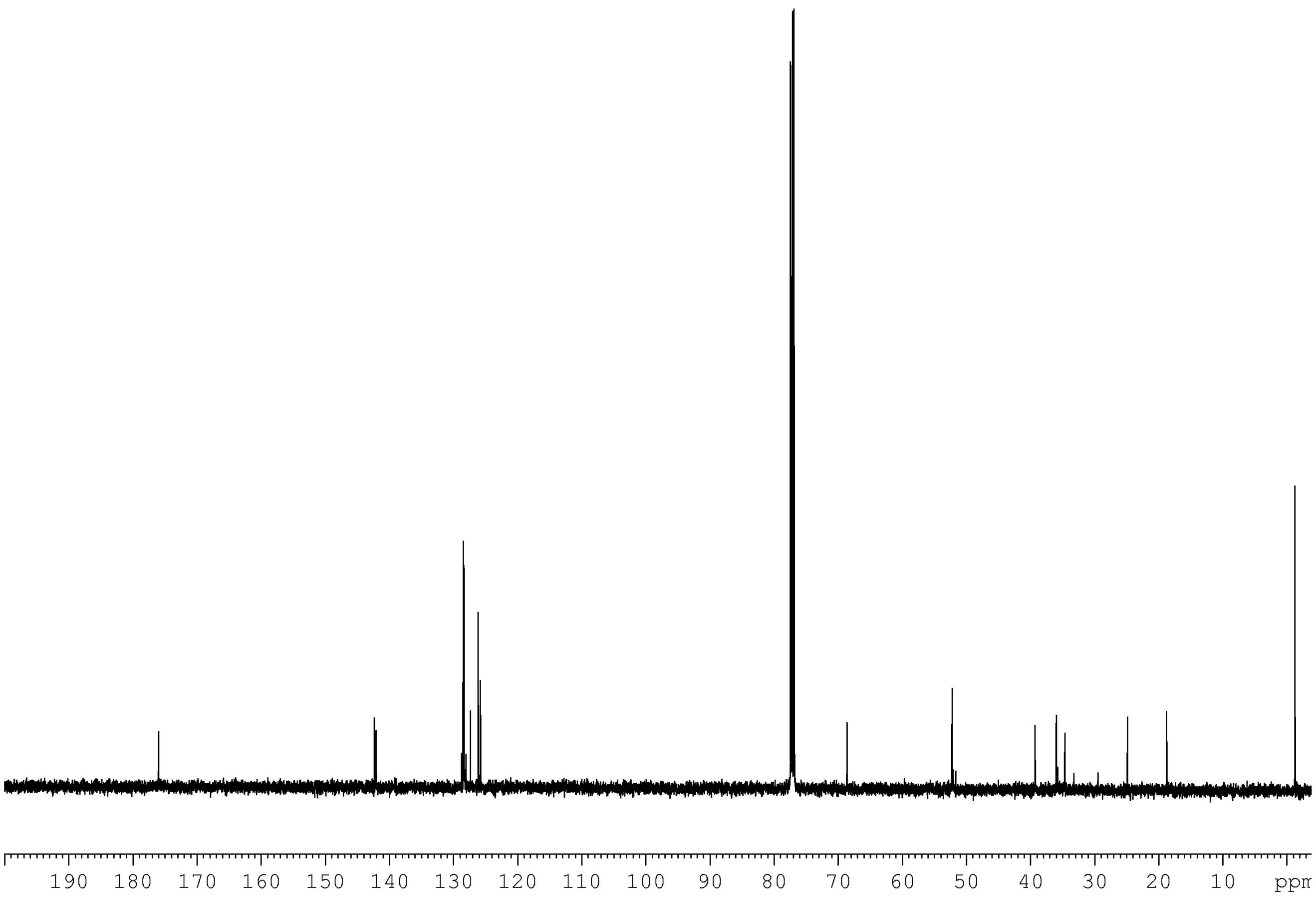
3ldePMP



500 MHz ^{1}H NMR Spectrum of Compound $\mathbf{3l}_{\mathbf{dePMP}}$ in $CDCl_3$

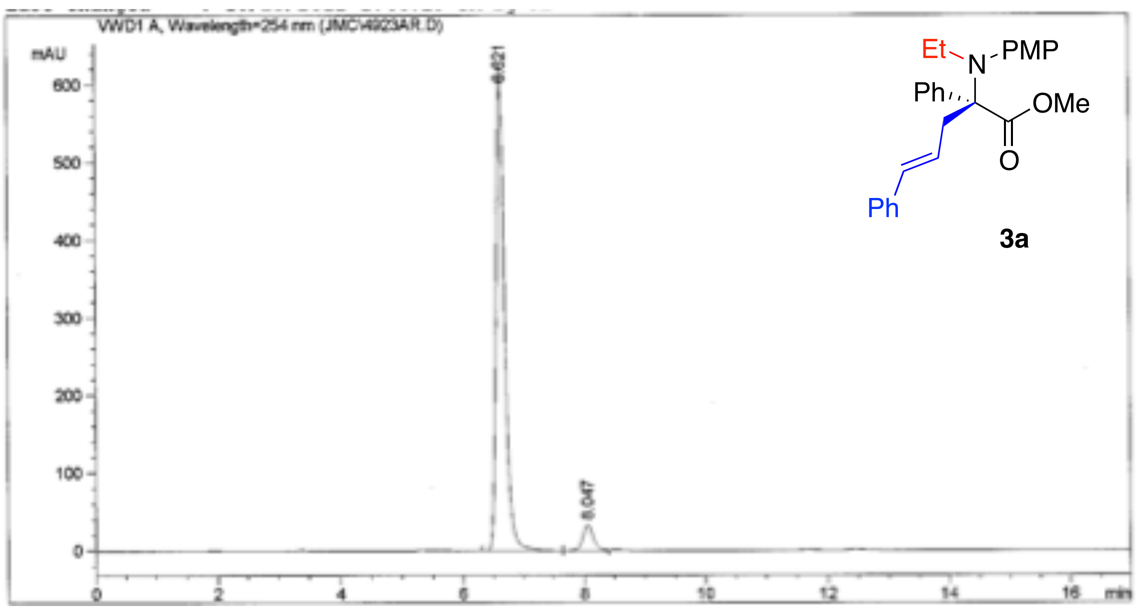


3ldePMP



125 MHz ^{13}C NMR Spectrum of Compound $\mathbf{3l_{dePMP}}$ in CDCl$_3$

HPLC Chromatographs of Products **3a-3q**



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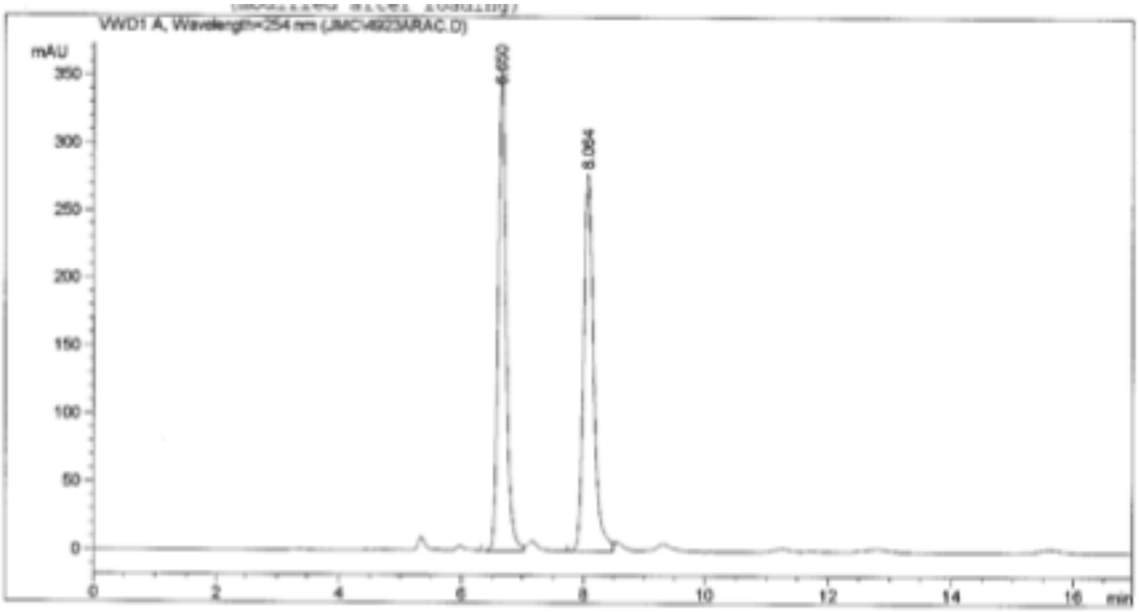
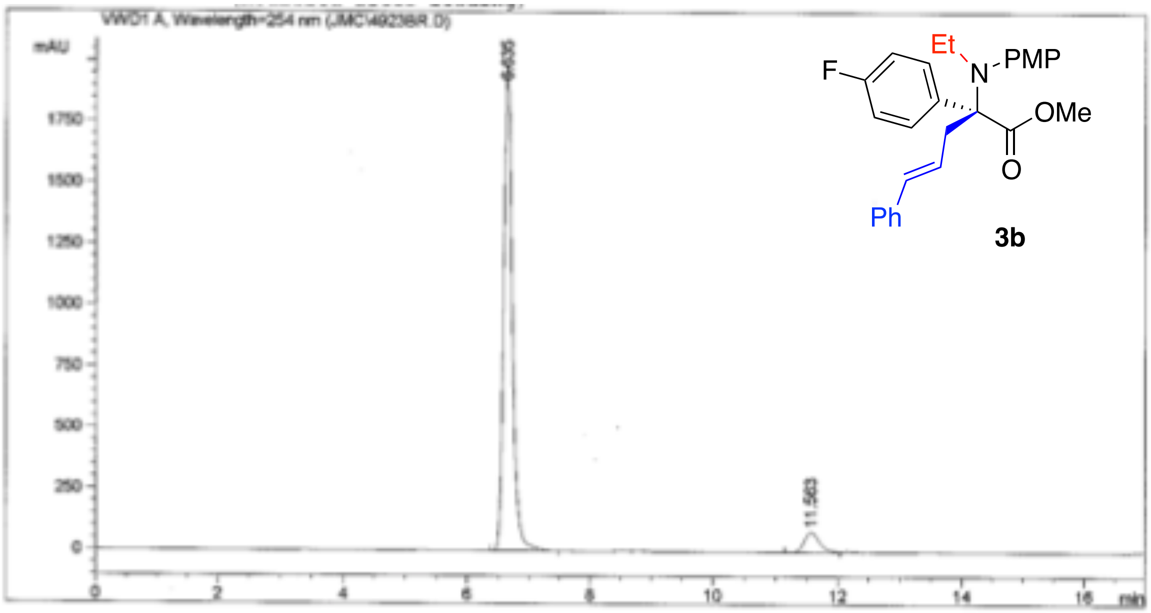
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   6.621 VV    0.1471 5976.35449  621.60596  93.6448
   2   8.047 VV    0.1825  405.58701   33.38095   6.3552
```

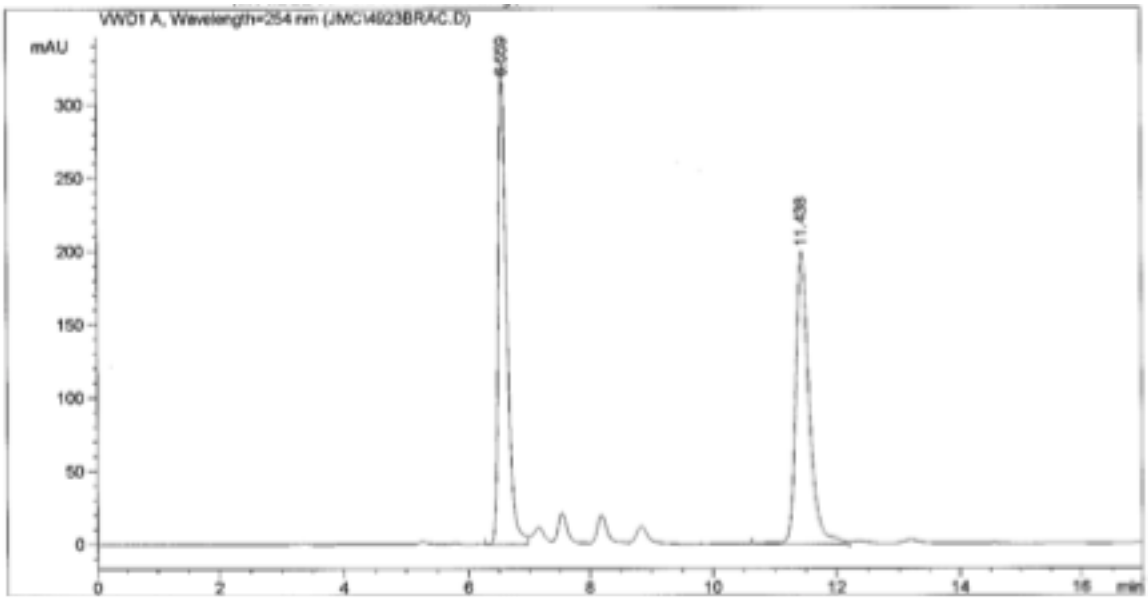


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   6.650 VV    0.1385 3241.94653  355.08600  50.2807
   2   8.064 VV    0.1751 3205.75415  278.42767  49.7193
```

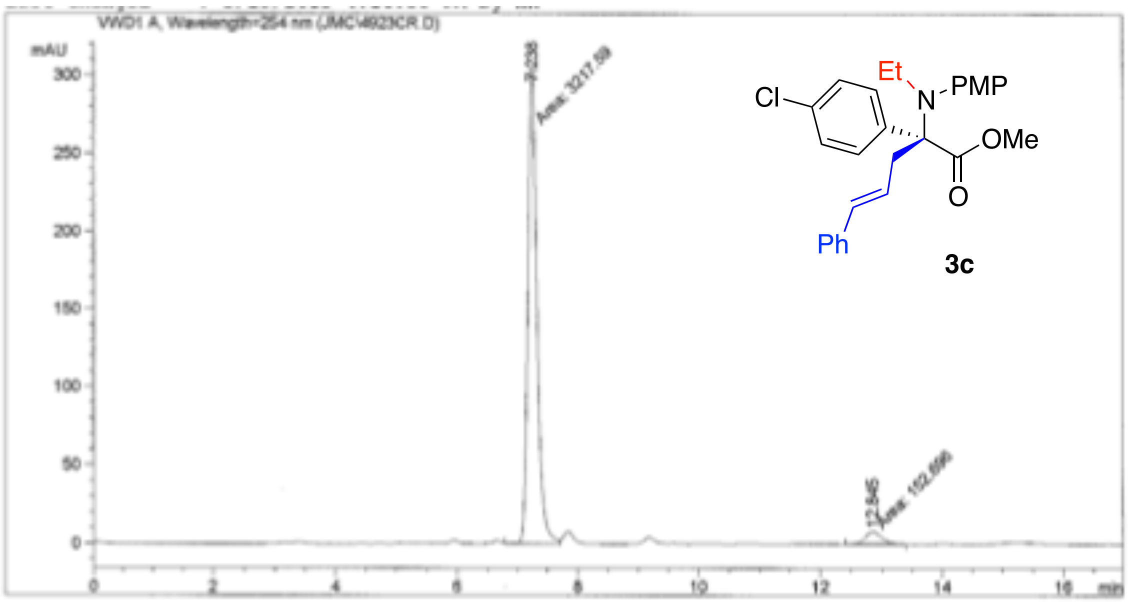


3b

```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]  mAU     *s   [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
  1    6.635 VV    0.1501 1.96298e4  1989.48999  93.2502
  2   11.563 VV    0.2626 1420.87073   82.26967   6.7498
```

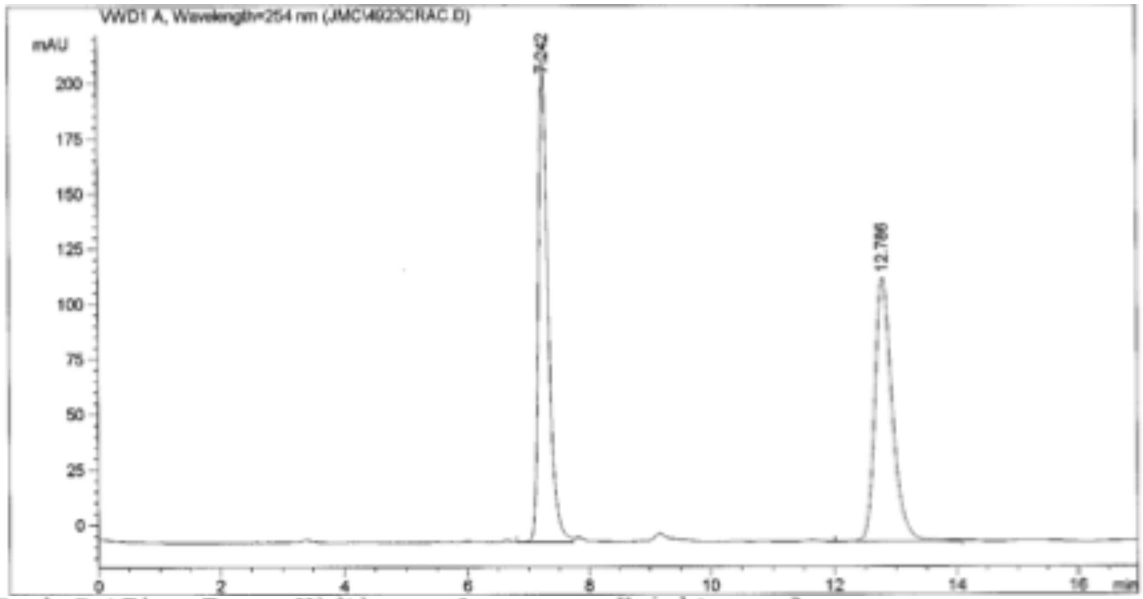


```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]  mAU     *s   [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
  1    6.559 VV    0.1459 3217.70361  329.70172  51.0629
  2   11.438 VV    0.2328 3083.74341  199.46837  48.9371
```

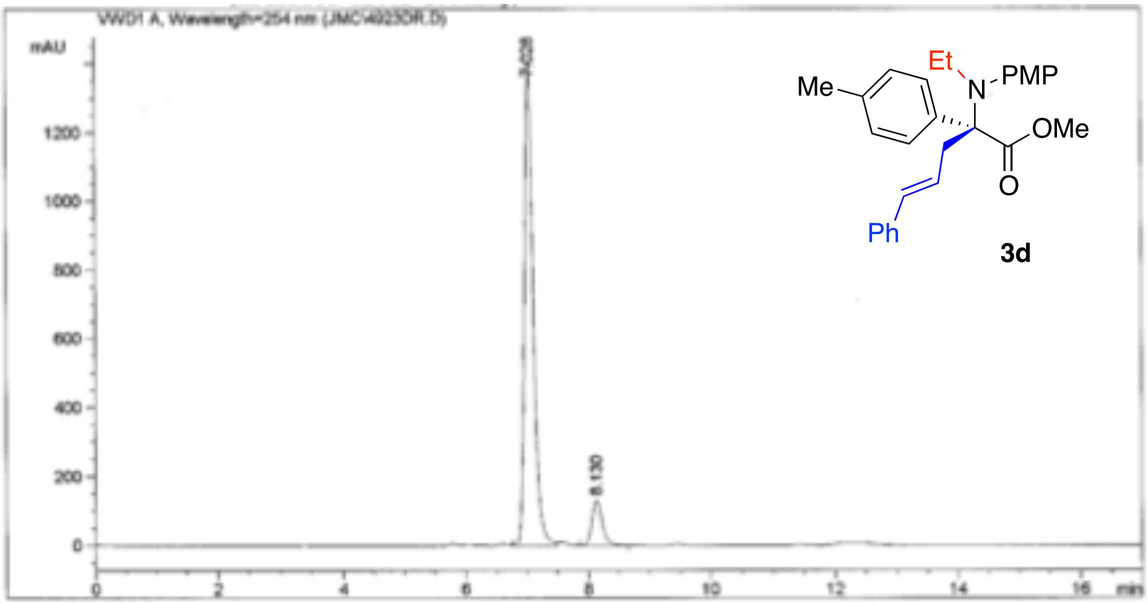


3c

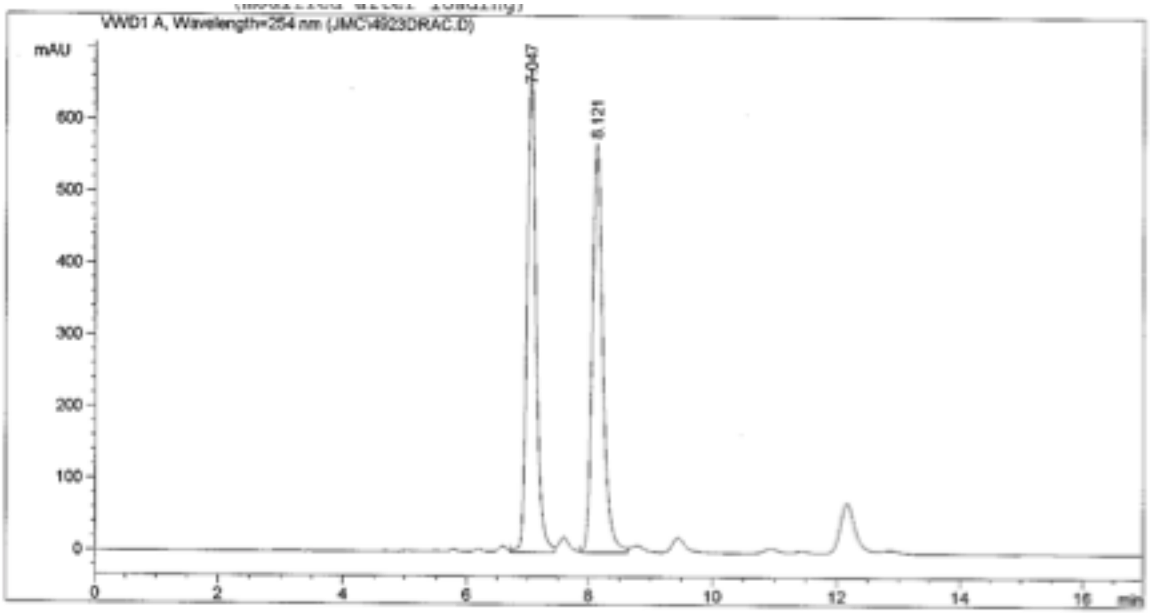
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU   *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1   7.238 MF    0.1749 3217.59375  306.66895  95.4694
  2  12.845 MM    0.3231  152.69572    7.87607   4.5306
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU   *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1   7.242 VV    0.1665 2416.30688  219.06432  50.6319
  2  12.786 VV    0.2971 2355.99194  119.45978  49.3681
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU    *s  [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
  1    7.028 VV    0.1504 1.39221e4  1406.51208  89.5701
  2    8.130 VV    0.1878 1621.14404  131.21811  10.4299
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU    *s  [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
  1    7.047 VV    0.1541 6874.57422  672.96912  49.9173
  2    8.121 VV    0.1822 6897.35107  568.98853  50.0827
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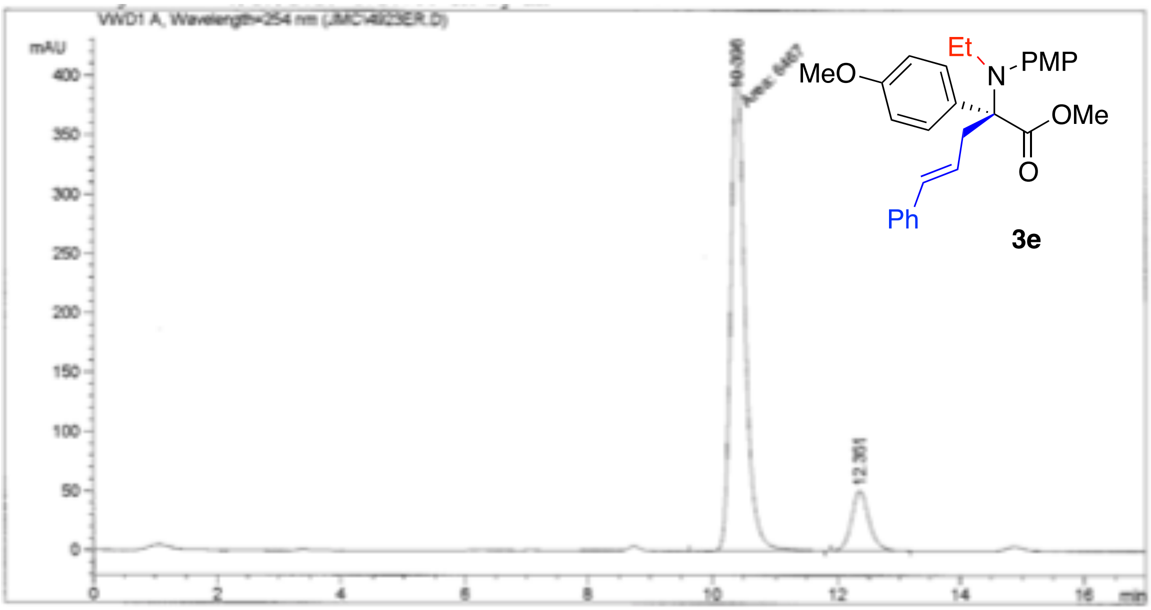

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
   1  10.398 MM    0.2622 6467.00488  411.06500  86.6428
   2  12.351 BB    0.2958  996.97931   50.82684  13.3572
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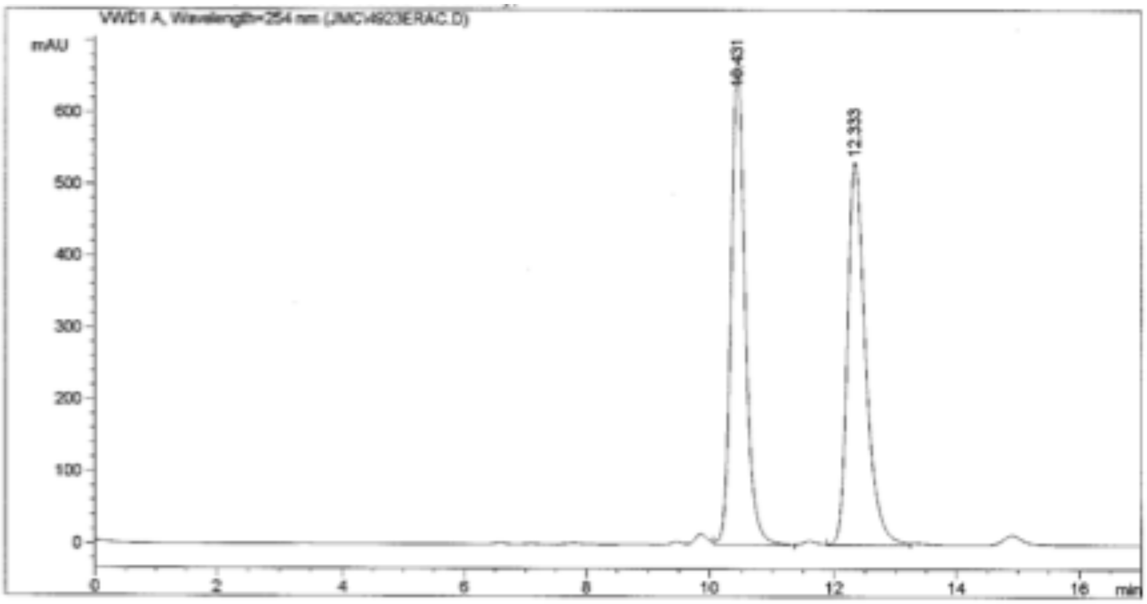
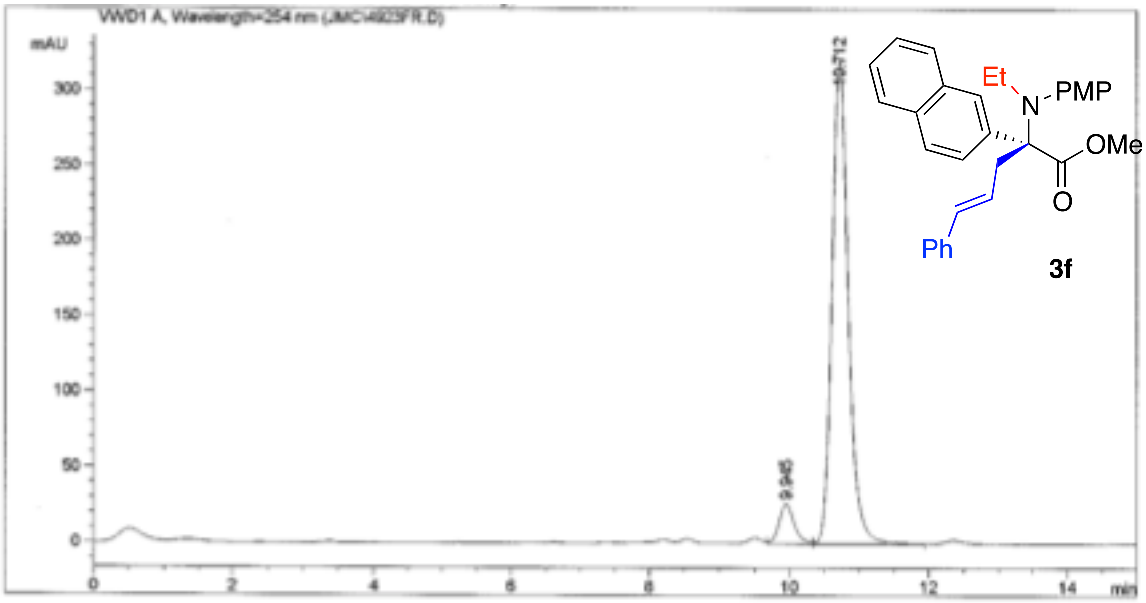
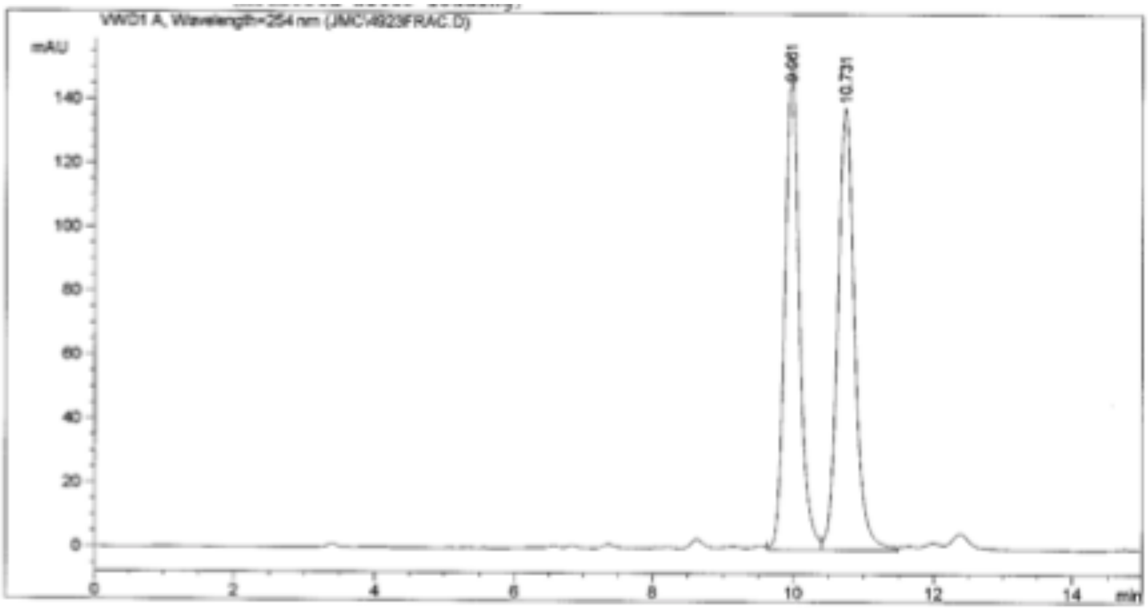


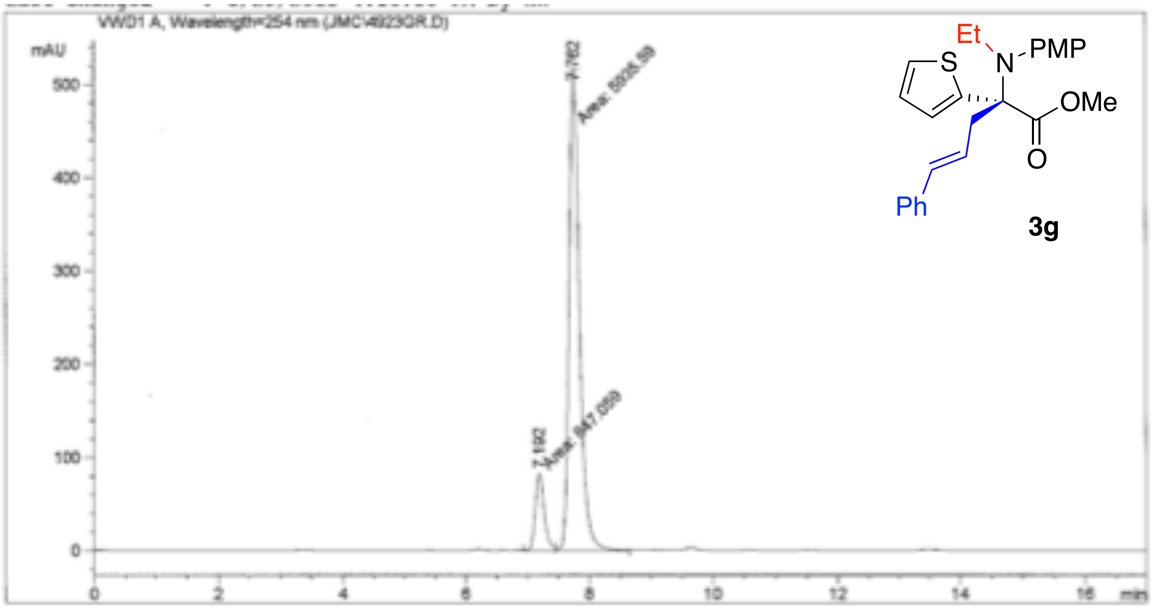
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
   1  10.431 VV    0.2378 1.05023e4  671.65704  49.5800
   2  12.333 VV    0.3037 1.06802e4  532.92847  50.4200
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU   *s  [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
  1   9.945 VV    0.2324  397.46729   26.18261   7.1382
  2  10.712 VV    0.2468 5170.67871  319.90131  92.8618
```

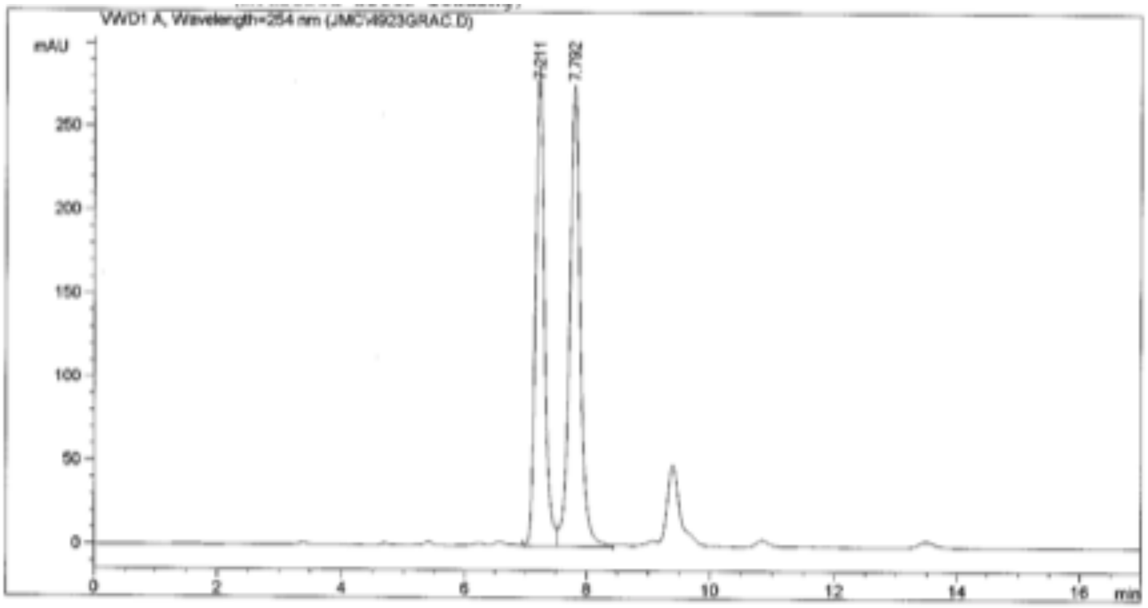


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU   *s  [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
  1   9.961 VV    0.2217 2194.38525  151.25722  48.7568
  2  10.731 VV    0.2559 2306.28613  138.18172  51.2432
```

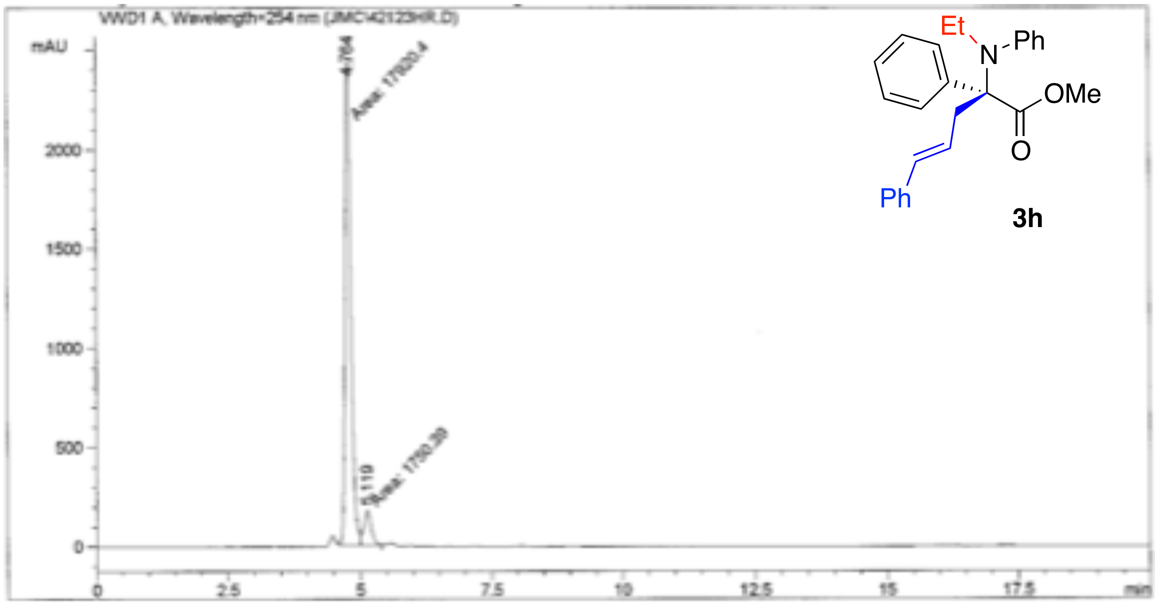


3g

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1    7.192 MF    0.1691  847.05865   83.46306  12.4886
  2    7.762 FM    0.1896 5935.58594  521.82330  87.5114
```

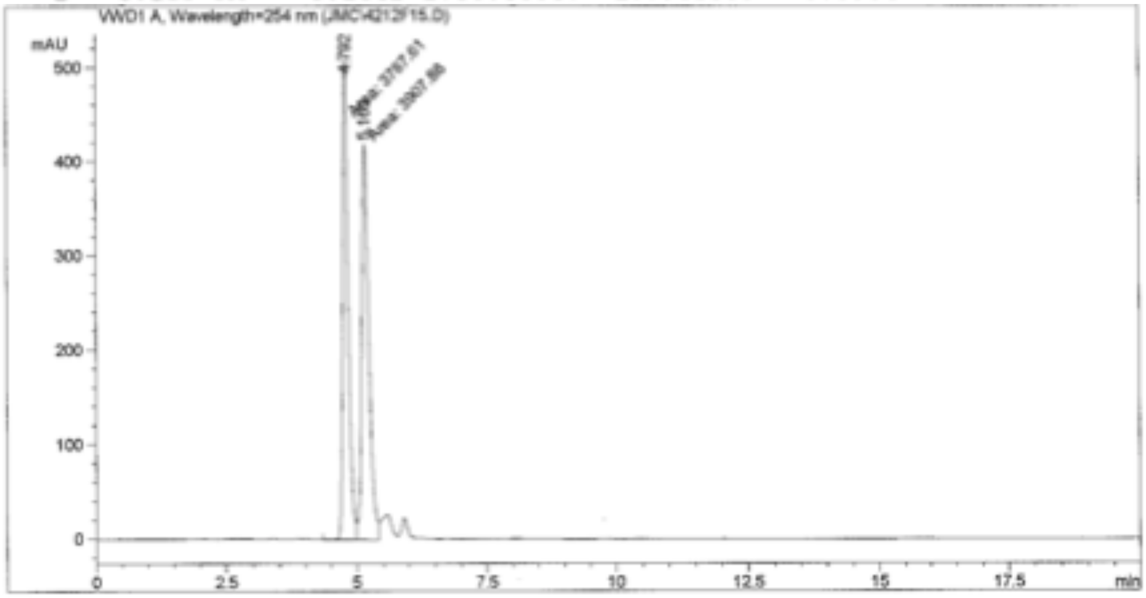


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1    7.211 VV    0.1553 2979.05103  288.74097  47.3708
  2    7.792 VV    0.1807 3309.73682  275.88364  52.6292
```

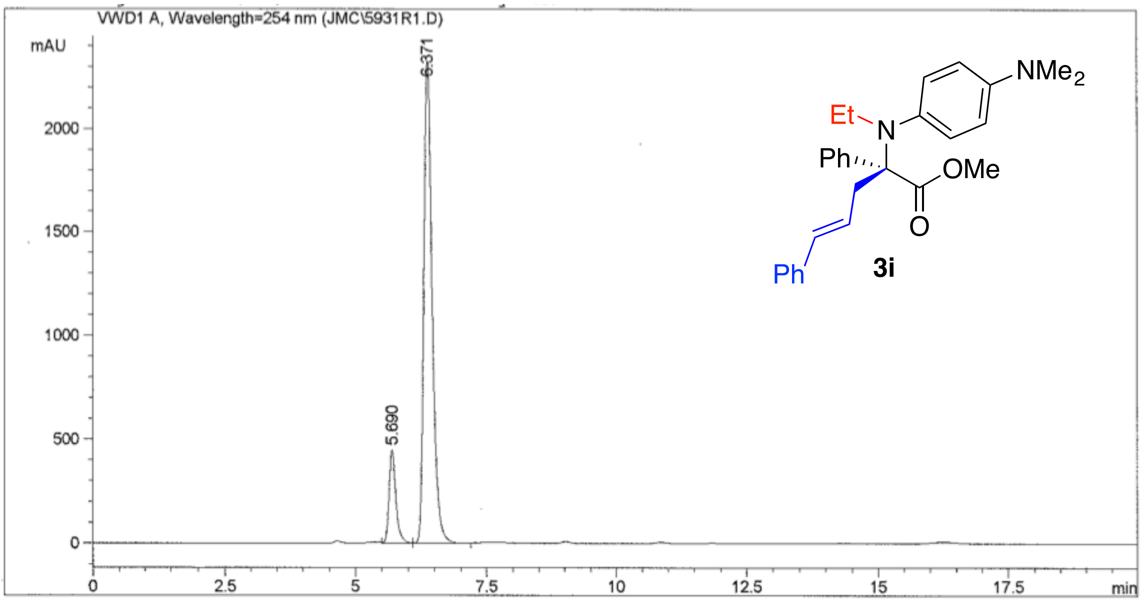


3h

```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU   *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1   4.764 MF    0.1222 1.79204e4  2443.26367  91.1016
  2   5.119 FM    0.1642 1750.38867  177.63388   8.8984
```

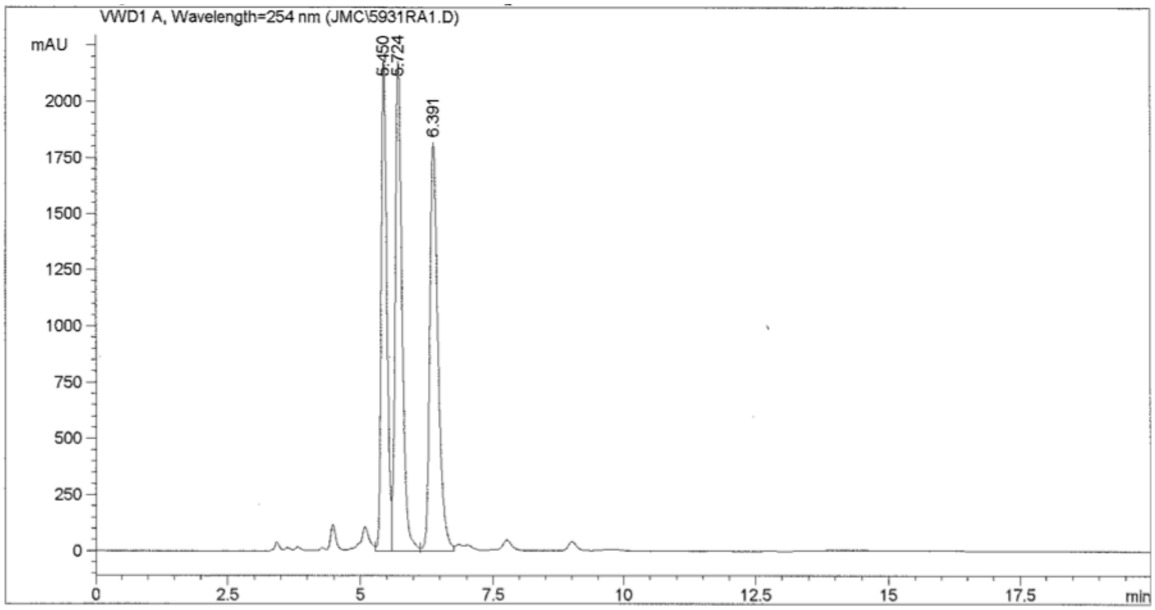


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU   *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1   4.792 MF    0.1235 3787.60913  511.08856  49.2186
  2   5.165 MF    0.1555 3907.88037  418.90485  50.7814
```

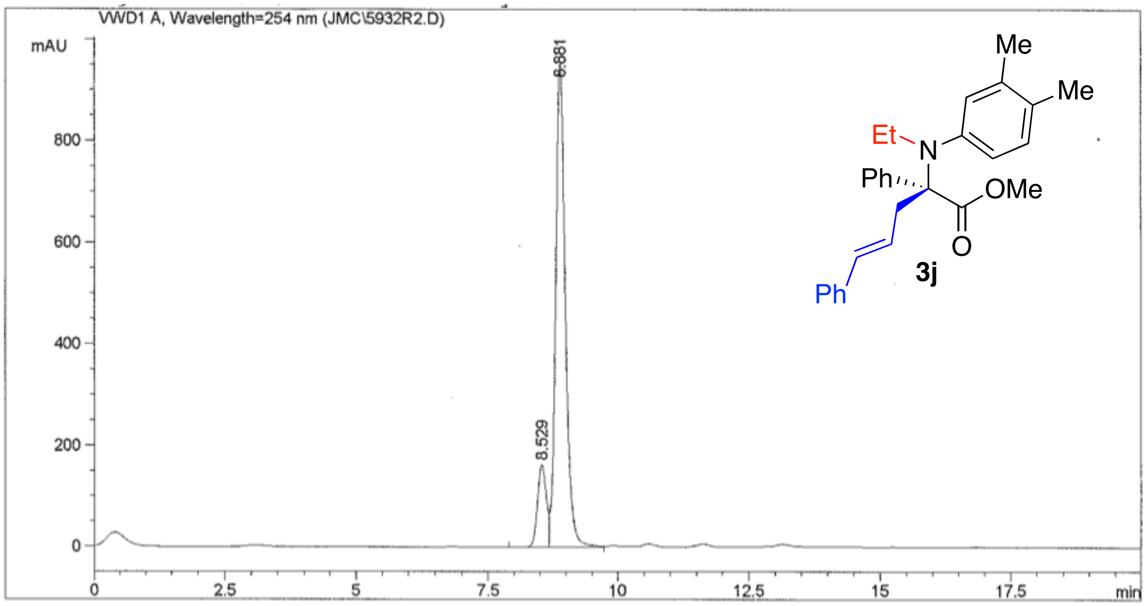


3i

```
Peak RetTime Type  Width     Area      Height     Area
 #    [min]        [min]   mAU   *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
  1   5.690 VV    0.1335 3961.77930  448.95929  13.4362
  2   6.371 VV    0.1658 2.55241e4  2327.74609  86.5638
```

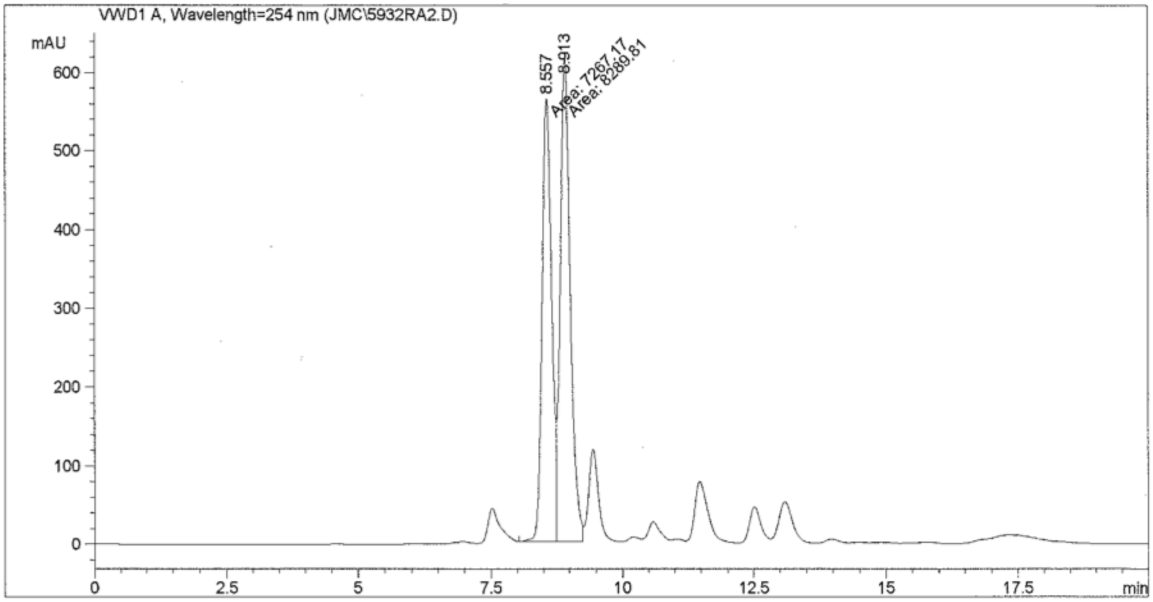


```
Peak RetTime Type  Width     Area      Height     Area
 #    [min]        [min]   mAU   *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
  1   5.450 VV    0.1139 1.61563e4  2184.89258  29.2162
  2   5.724 VV    0.1366 1.95502e4  2181.27148  35.3536
  3   6.391 VV    0.1634 1.95926e4  1820.32642  35.4302
```

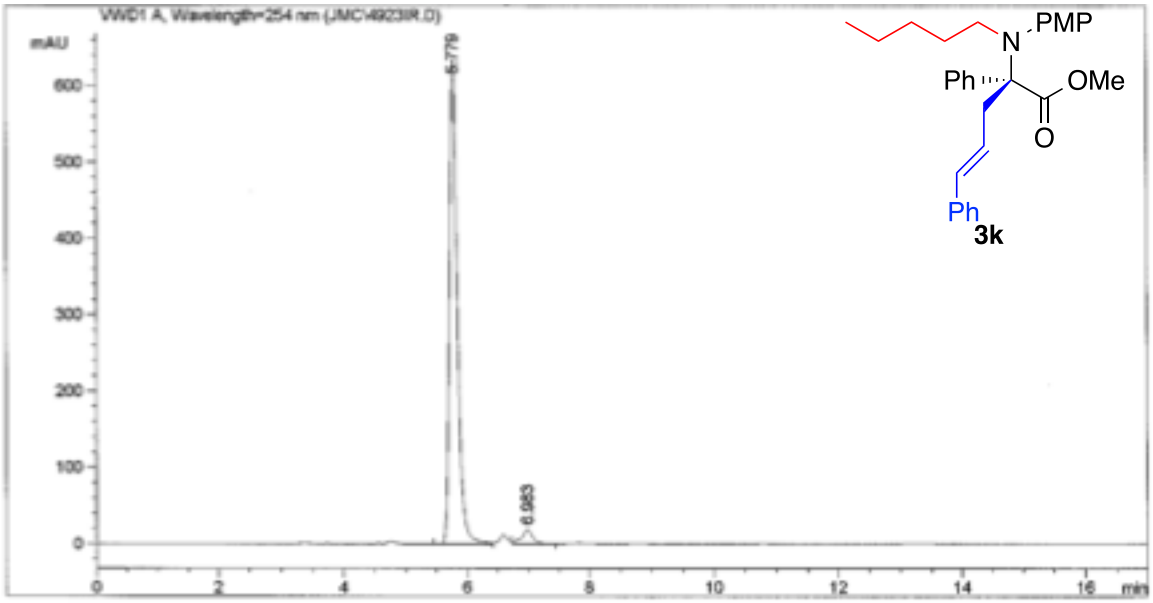


3j

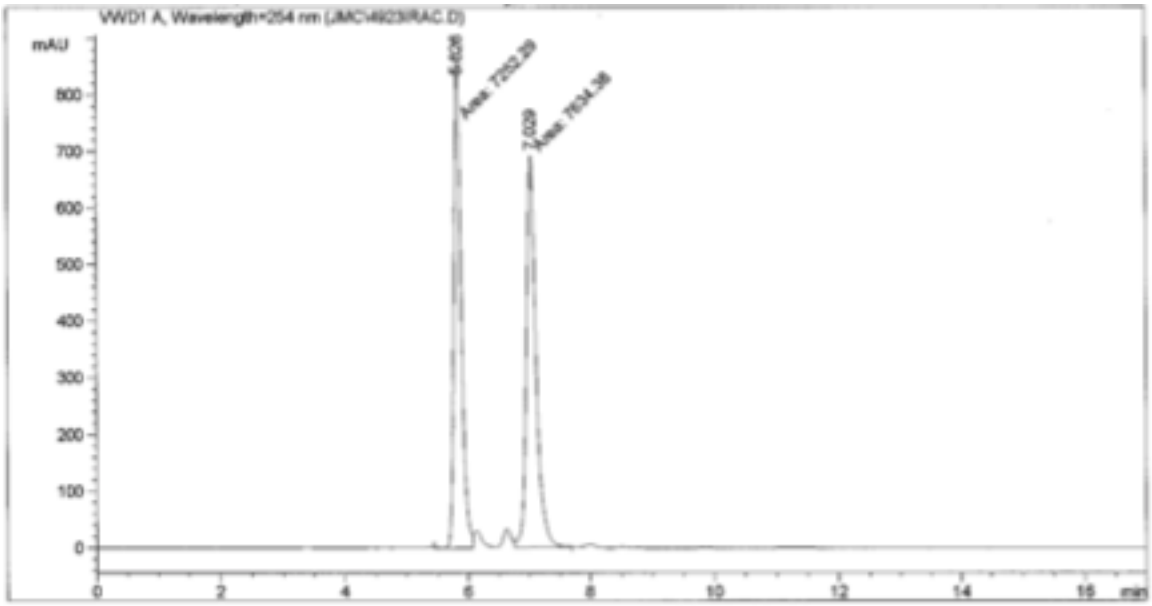
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   8.529 VV    0.1804 1916.47498  163.50797  13.4865
   2   8.881 VV    0.1936 1.22938e4   956.88660  86.5135
```



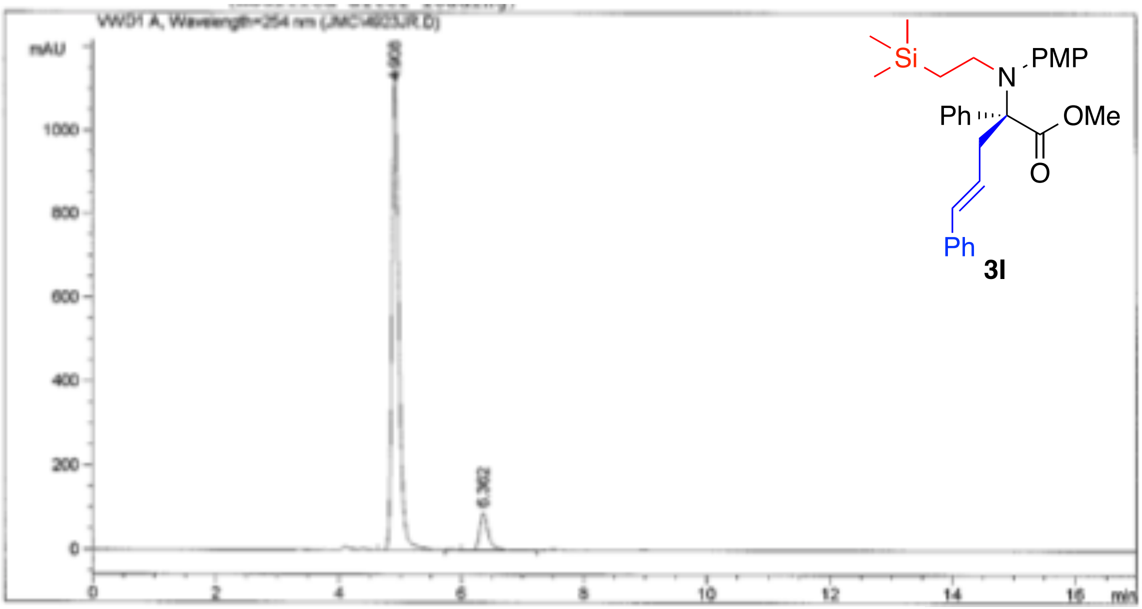
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   8.557 MF    0.2149 7267.17090  563.56427  46.7133
   2   8.913 MF    0.2242 8289.80762  616.21008  53.2867
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU     *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   5.779 VV     0.1335 5534.55566  636.15851  95.7266
   2   6.983 VV     0.1883  247.06935   18.79782   4.2734
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU     *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   5.826 MF     0.1396 7252.29297  865.64648  48.7168
   2   7.029 FM     0.1837 7634.35547  692.82214  51.2832
```



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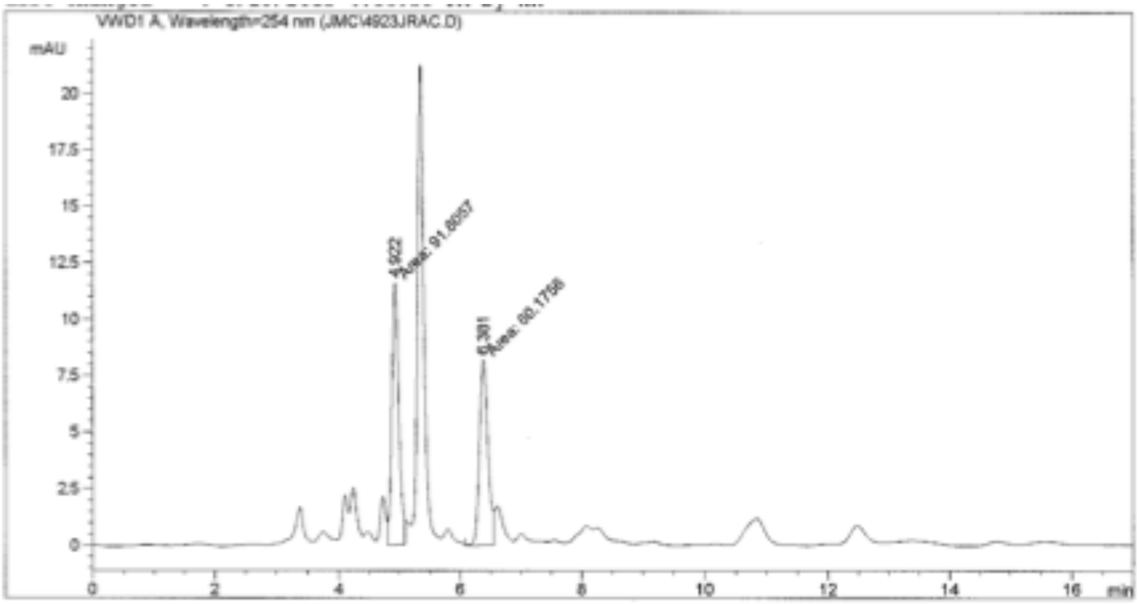
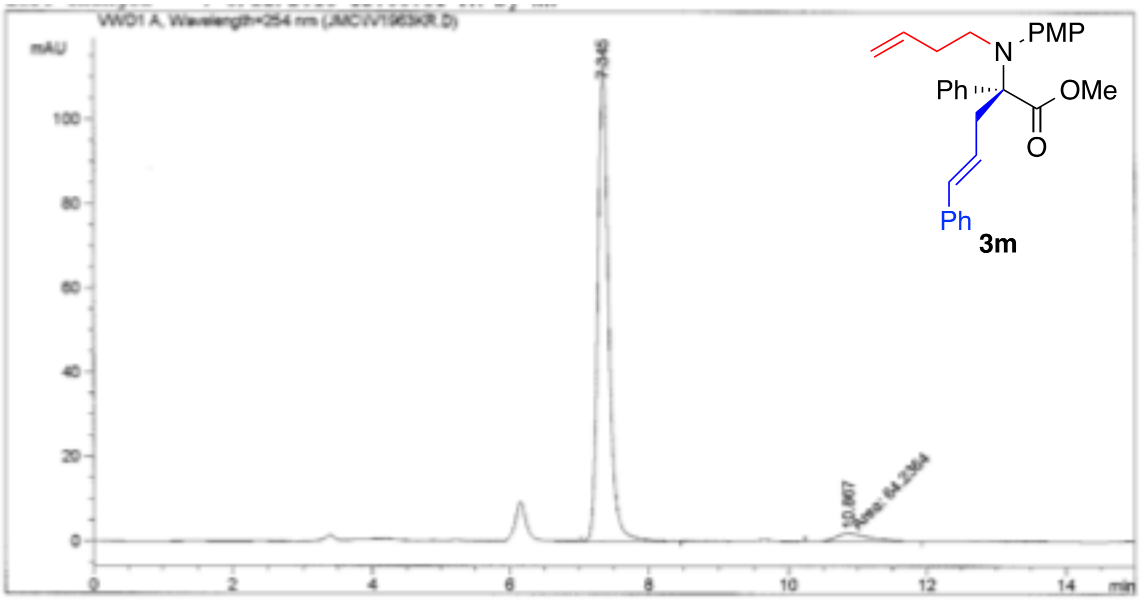
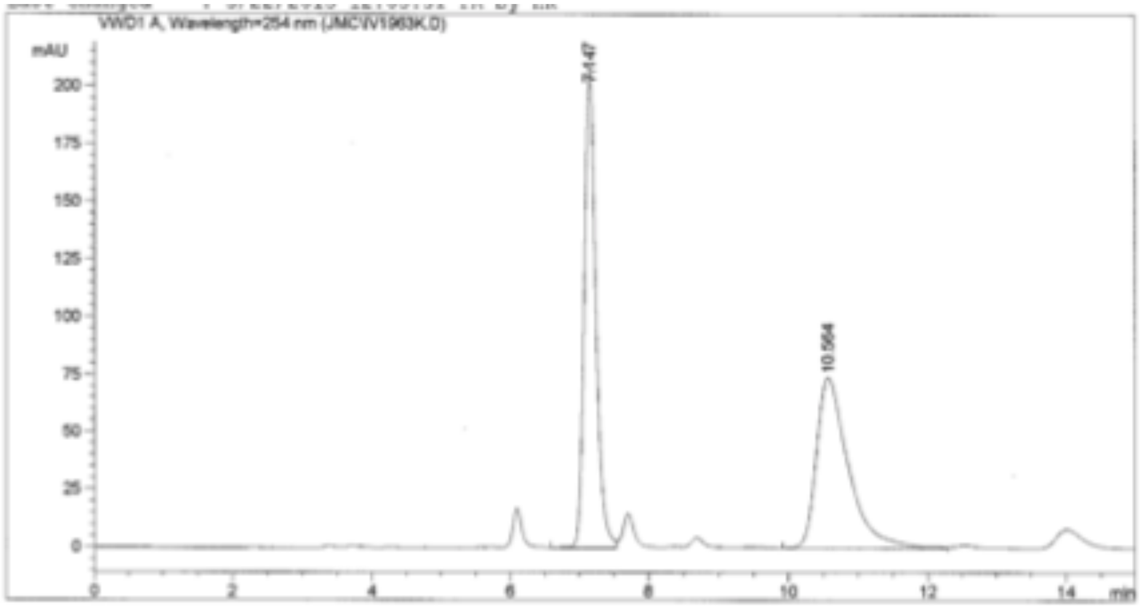
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]  mAU     *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
  1   4.908 VV    0.1162 8926.06543 1157.04175  90.7419
  2   6.362 VV    0.1503  910.69373   89.83418   9.2581
```



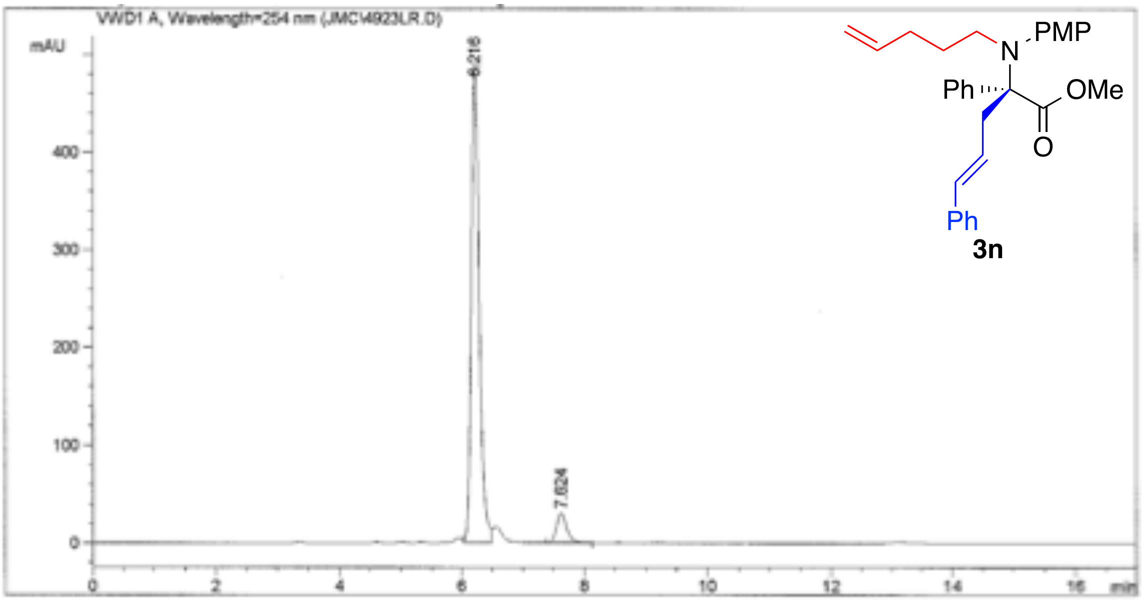
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU     *s  [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
  1    4.922 MF    0.1317   91.80573   11.61616  53.3812
  2    6.381 MF    0.1626   80.17558    8.21881  46.6188
```



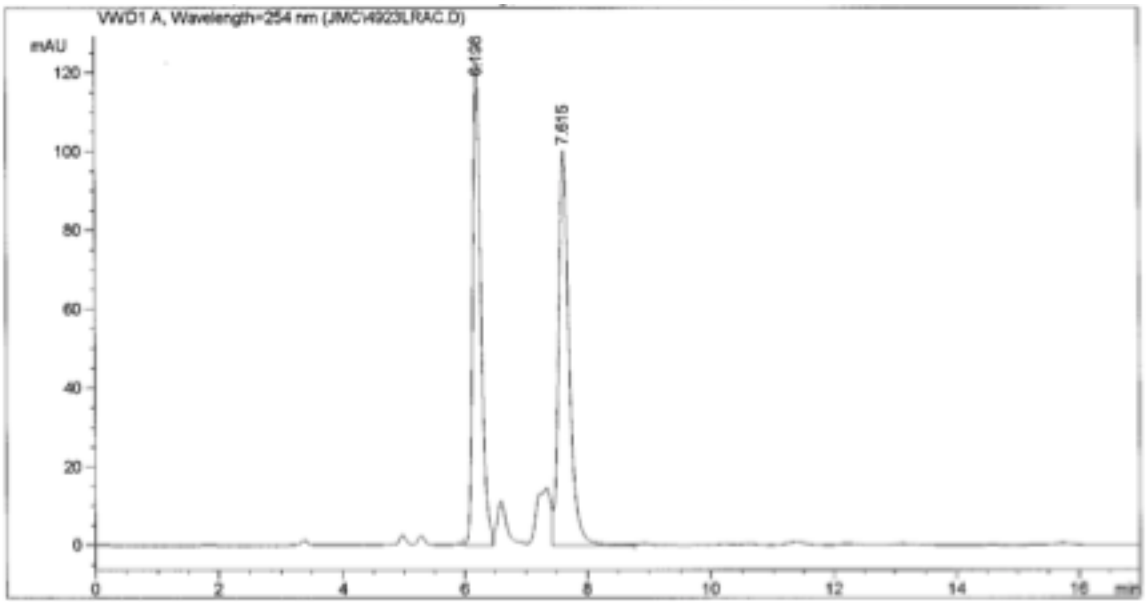
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1    7.345 BB    0.1665 1250.30359  113.41366  95.1134
  2   10.867 MM    0.5677   64.23636    1.88575   4.8866
```



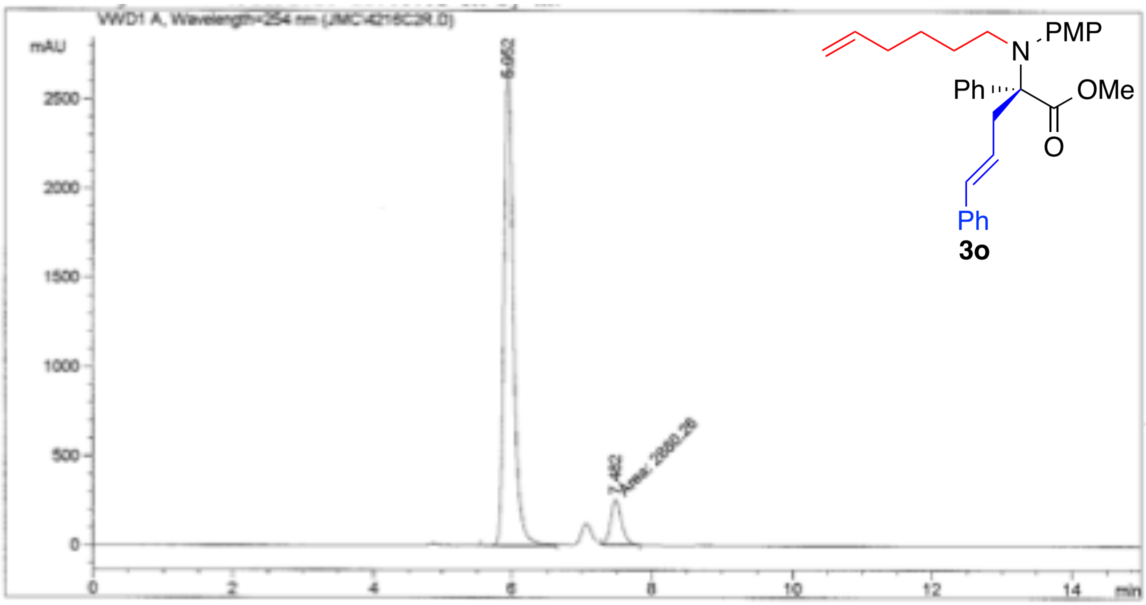
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1    7.147 VV    0.1736 2405.96509  208.96895  50.1774
  2   10.564 VV    0.4710 2388.95190   74.33871  49.8226
```



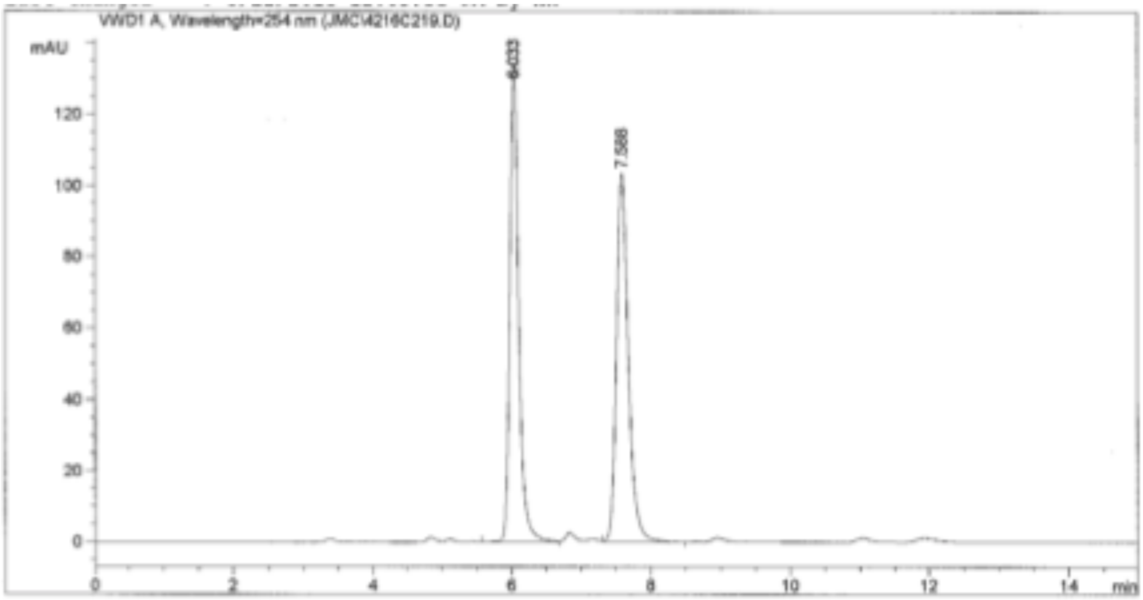
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU    *s  [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   6.216 VV    0.1374 4459.02783  493.72812  92.6531
   2   7.624 BB    0.1758  353.57953   30.54416   7.3469
```



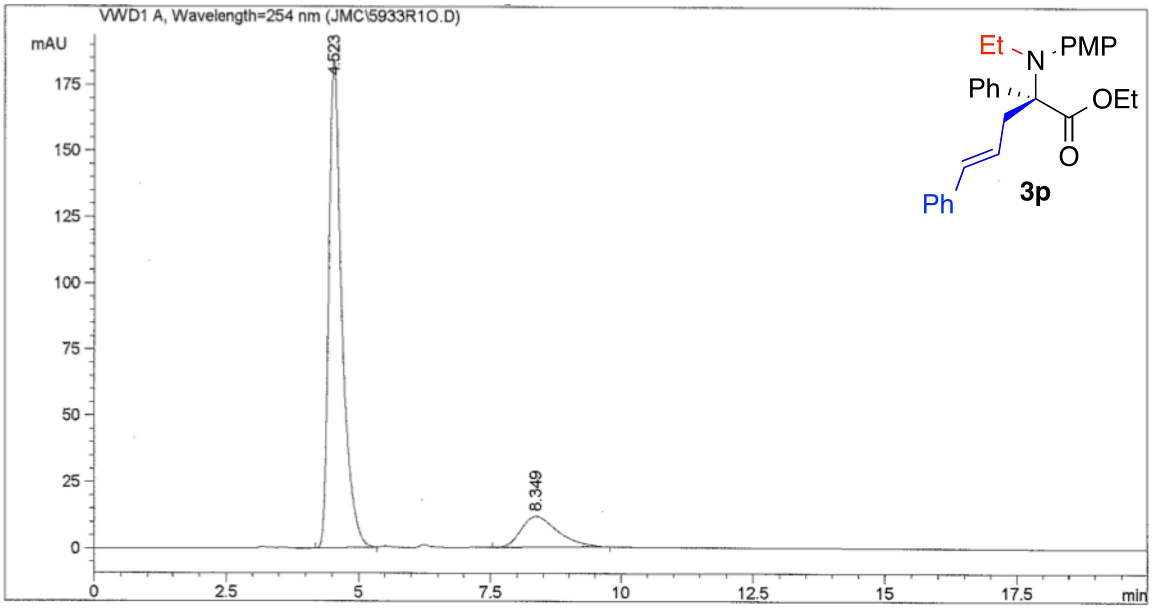
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU    *s  [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   6.198 VV    0.1391 1129.90991  123.10315  48.3108
   2   7.615 VV    0.1813 1208.92627  100.34201  51.6892
```



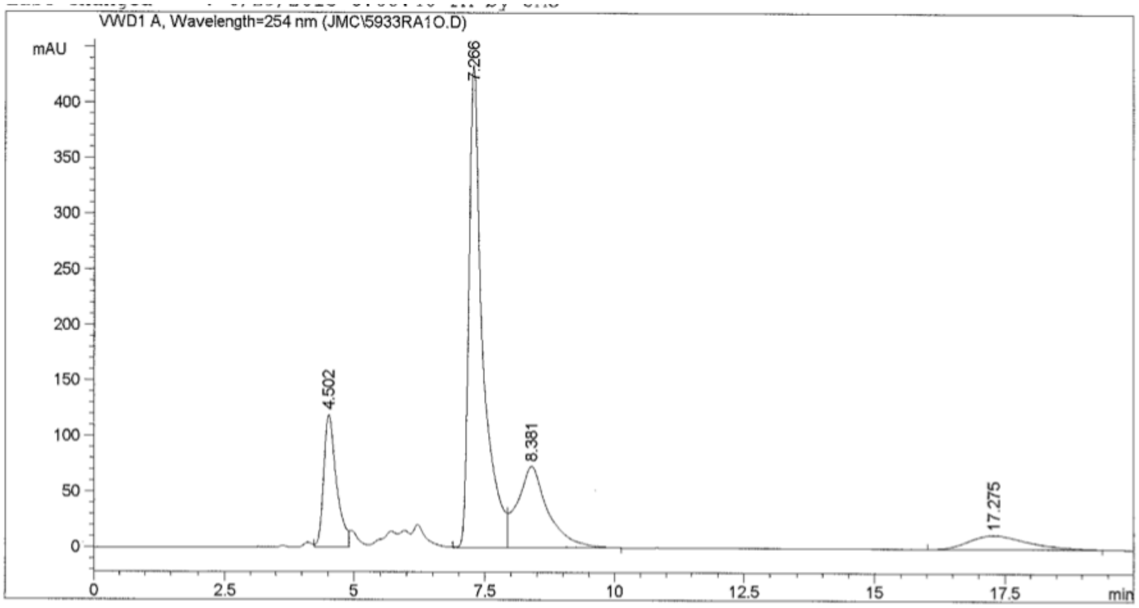
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   5.952 VV    0.1444 2.54457e4  2711.85498  89.8317
   2   7.482 FM    0.1881 2880.25732  255.14885  10.1683
```



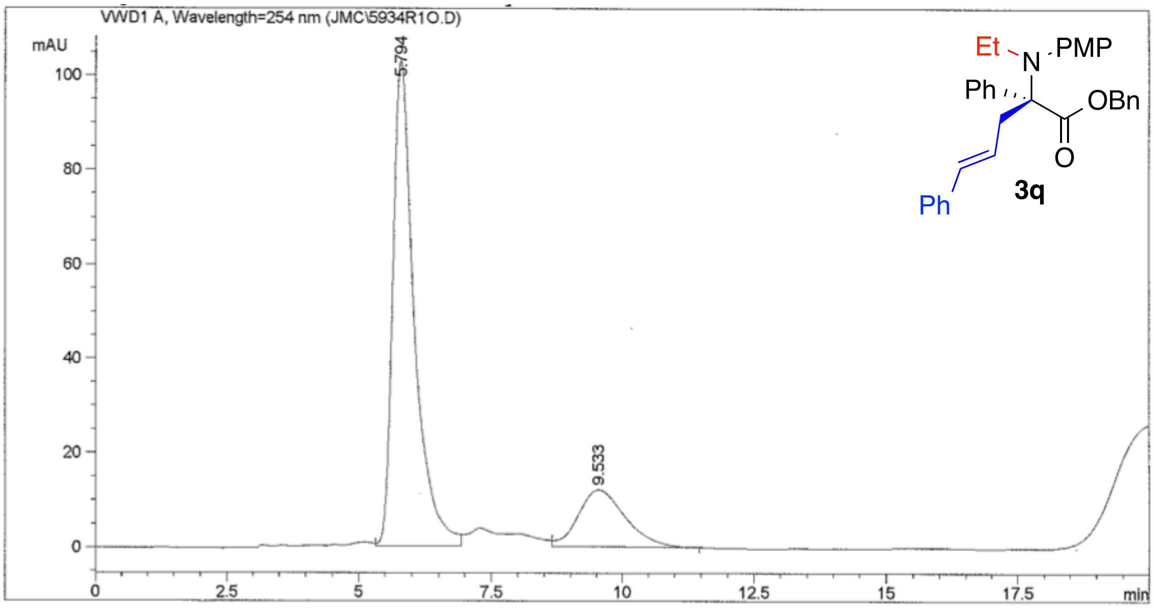
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   6.033 VV    0.1360 1214.39587  134.45268  50.1560
   2   7.588 VV    0.1766 1206.84045  103.69136  49.8440
```



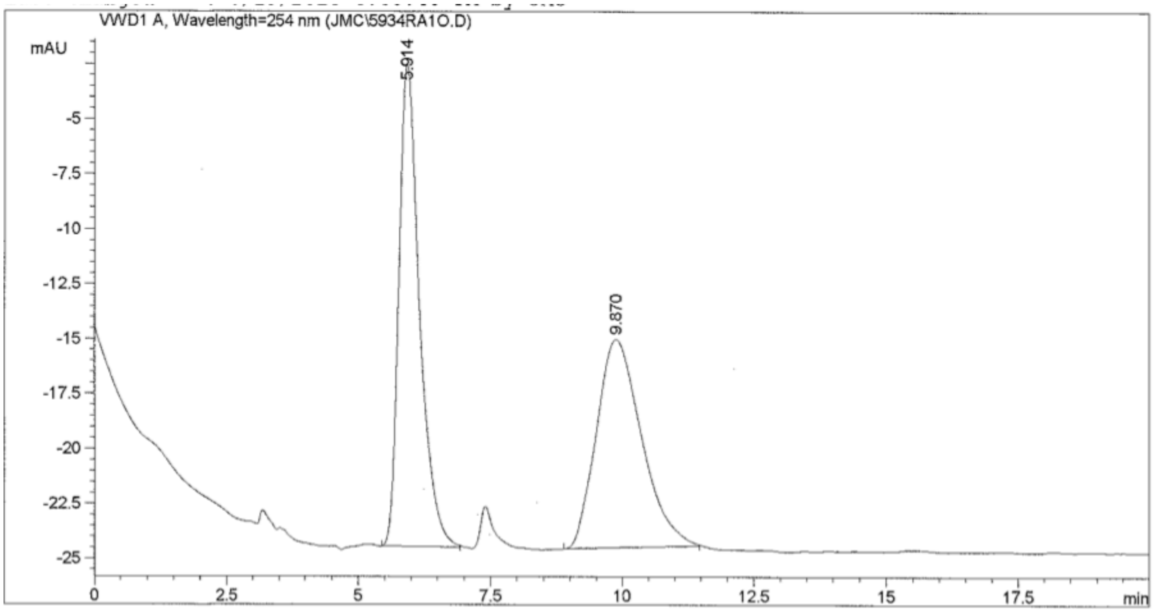
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   4.523 BB   0.2535 3156.64819  184.45398  84.4770
   2   8.349 PB   0.7349  580.04828   11.71511  15.5230
```



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   4.502 VV   0.2570 2056.02686  118.94724  14.6184
   2   7.266 BV   0.2642 8045.12988  434.20255  57.2012
   3   8.381 VB   0.5615 2964.00098   72.93364  21.0742
   4  17.275 BB   1.1464  999.46112   12.56507   7.1062
```

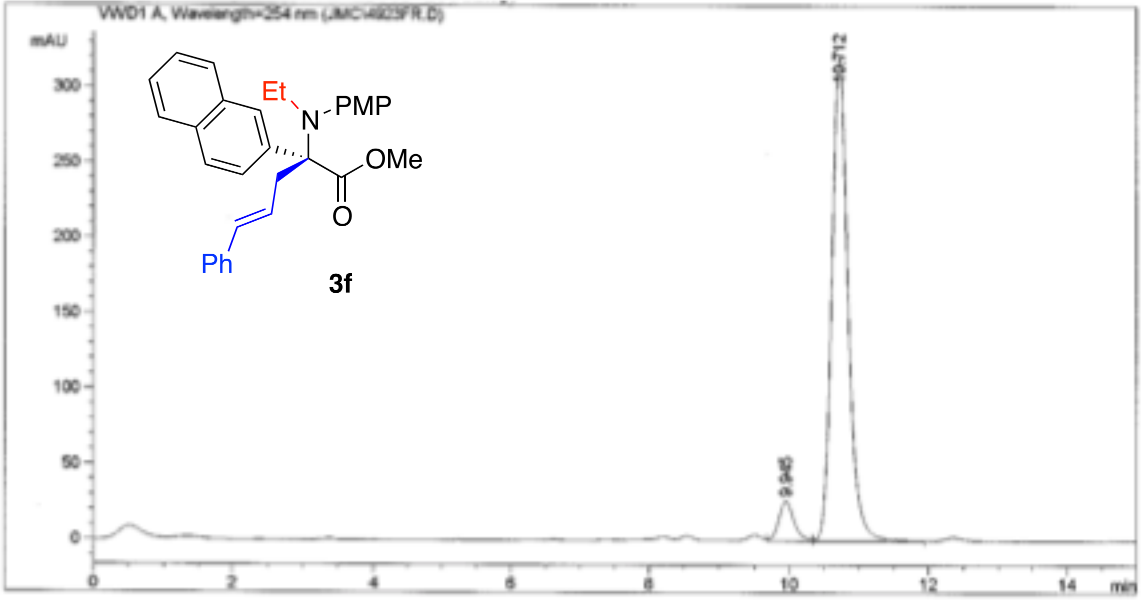


```
Peak RetTime Type  Width      Area       Height     Area
  #   [min]        [min]  mAU      *s  [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
   1   5.794 VB    0.4146 2884.59131  102.82536  78.8775
   2   9.533 VB    0.9499  772.46008   12.12699  21.1225
```



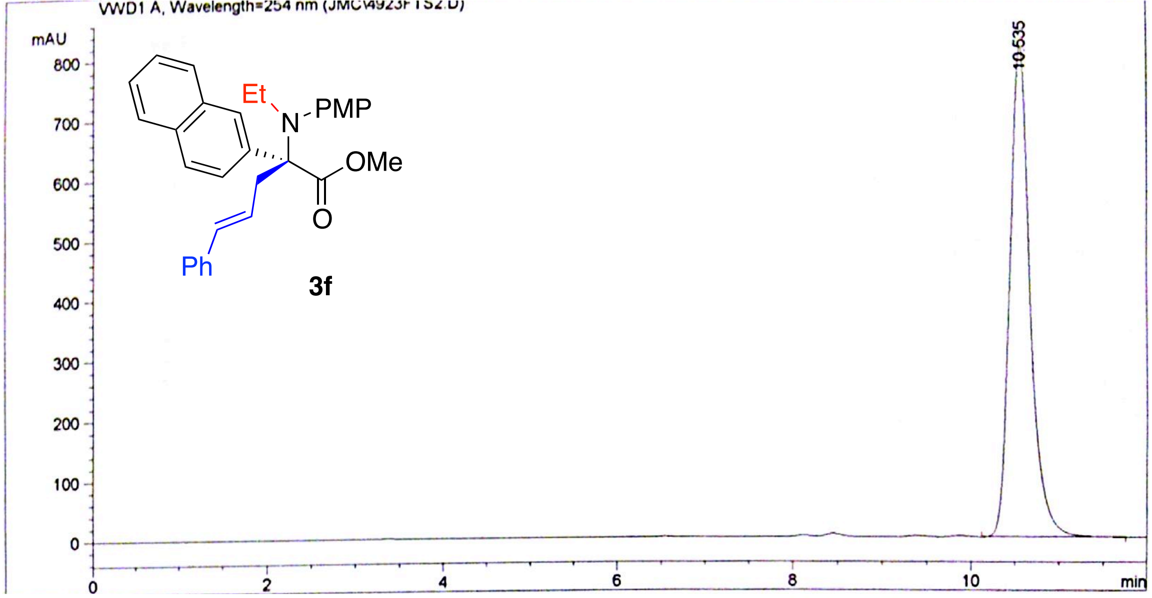
```
Peak RetTime Type  Width      Area       Height     Area
  #   [min]        [min]  mAU      *s  [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
   1   5.914 PB    0.4099  596.24884   21.96358  50.8509
   2   9.870 BB    0.8968  576.29413    9.50249  49.1491
```

Enhancement of enantioenrichment of **3f.**
Pre-recrystalization:



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU     *s  [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
   1   9.945 VV     0.2324  397.46729   26.18261   7.1382
   2  10.712 VV     0.2468 5170.67871  319.90131  92.8618
```

Crystals after Triteration:



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU     *s  [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
   1  10.535 VB     0.2425 1.31538e4  819.94324 100.0000
```