Title

Phosphine Catalysis using Allenoates with pro-Nucleophiles or Arylidenes; Development of an Asymetric Phosphine Catalyst; and Allenes as π-Ligands in Copper-Mediated Cross-Coupling

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A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Tioga Martin

2014

Abstract of Dissertation

Phosphine Catalysis using Allenoates with pro-Nucleophiles or Arylidenes; Development of an Asymetric Phosphine Catalyst; and Allenes as π-Ligands in Copper-Mediated Cross-Coupling

by

Tioga Jarrett Martin

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2014

Professor Craig A. Merlic, Chair

The unique characteristics of 1,2-dienes have proven to be a dynamic and ever growing field of study in organic chemistry. Allenes have been manipulated into a myriad of transformations, and have offered their unique characteristics to a number of fields of study. Chapter 1 discusses a phosphine catalyzed annulation between allenoates and alkenes to form cyclohexenes. In Chapter 2 the new phosphine catalyzed β'-Addition of a Pronucleophile to an allenoate is examined. Chapter 3 presents the development of a proline derived phosphine catalyst and its application in asymmetric synthesis of dihydropyrroles. A review on allene complexes with transition metals is presented in Chapter 4. Chapter 5 explores the effect of allene ligands upon copper, and subsequent copper-mediated vinyl ether synthesis.

The dissertation of Tioga Martin is approved.

Michael E. Jung

Selim M. Senkan

Craig A. Merlic, Committee Chair

University of California, Los Angeles

2014

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Publications and Presentations

Martin, Tioga; Vakhashori, Venus; Tran, Yang; Kwon, Ohyun. "Phosphine-Catalized β'-Umpolung Addition of Nucleophiles to Activated α-Alkyl Allenoates." *Organic Letters*, **2011**, *13*, 10, 2586–2589.

Tran, Yang; Martin, Tioga; Kwon, Ohyun. "Phosphine-Catalyzed [4 + 2] Annulations of 2-Alkylallenoates and Olefins: Synthesis of Multisubstituted Cyclohexenes." *Chem. Asian J.* **2011**, 6(8), 2101–2106.

Martin, Tioga, "Allene Ligands in Copper-Mediated Cross-Coupling Reactions." UCLA Department of Chemistry and Biochemistry, Organic Graduate Research Symposium, June 8, 2013

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CHAPTER ONE

Phosphine-Catalyzed [4 + 2] Annulations of 2-Alkylallenoates and Olefins: Synthesis of Multisubstituted Cyclohexens

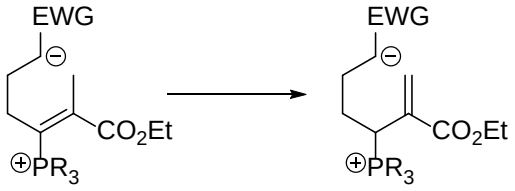
I. Introduction

The six-membered carbocycle is ubiquitous in natural products and pharmaceuticals, making the functionalized cyclohexene a desired motif for synthetic design.[1] Perhaps the most familiar technique for cyclohexene formation is the Diels–Alder reaction,[2] but it is not without limitations.[3] Approaches to intramolecular cyclohexene synthesis include metal-catalyzed ring-closing metathesis (RCM),[4] cycloisomerization,[5] and phosphine-catalyzed Rauhut–Currier reactions.[6] In contrast to the aforementioned reactions, intermolecular catalyzed cyclohexene synthesis, other than the Diels-Alder reaction, are less studied.[7]

Inovative preparations of carbo- and heterocycles have been realized through the use of nucleophilic phosphine catalysis.[8] The Lu lab first investigated the phosphine-catalyzed formation of cyclopentenes via a [3 + 2] cycloaddition from allenoates and alkenes;[9] this was followed with the preparation of 3-pyrrolines by replacing alkenes with imines.[10] The Kwon lab found the use of α-alkyl allenoates, when applied to Lu's pyrroline conditions, gave tetrahydropyridines by effectively generating a 1,4-dipole.[11] Inspired by the success of the tetrahydropyridine synthesis, the Kwon lab sought to apply the same procedure to activated olefins to produce cyclohexenes, *e.g.* catalytic tertiary phosphine, 2-methyl allenoate, and an alkene in place of the imine. Their initial attempts using ethyl and methyl acrylates, acrylonitrile, cyclohexenone, dimethyl maleate, dimethyl fumarate, ethyl maleimide, and ethyl cinnamate,

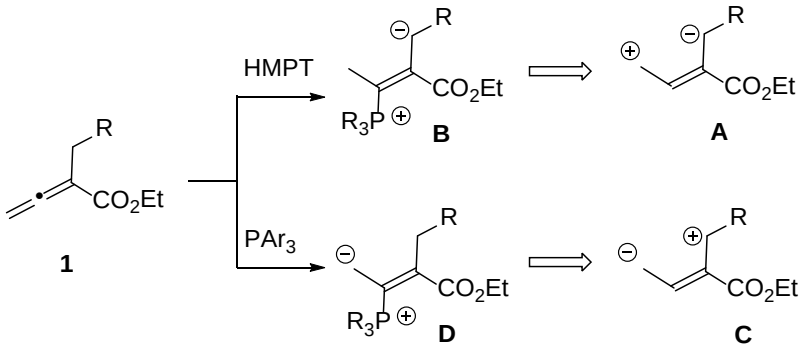
produced no cyclohexene products.[12] Upon examining the mechanism from the tetrahydropyridine synthesis, there is a proposed inefficient isomerization (**Scheme 1.1**), that requires sufficient electron withdrawing character to afford longer lived zwitterions,[12] thus it was decided to use the more electron deficient benzylidenemalononitrile.[13]

Scheme 1.1: Proposed mechanistic isomerization with electron withdrawing group EWG



These concepts when applied to arylidene malononitriles generated cyclohexenes with specific regiochemistry depending on the catalyst used.[13] The regioselectivity is proposed to arise from the 1,4-synthon generated from ethyl 2-alkyl allenoates **1** (**Scheme 1.2**). Hexamethylphosphorous triamide (HMPT) forms synthon **A** via phosphonium dienolate **B**, while the electron deficient triarylphosphines (PAr_3) generate the polar inverted synthon **C** through the formation of vinylogous ylide **D**.[13]

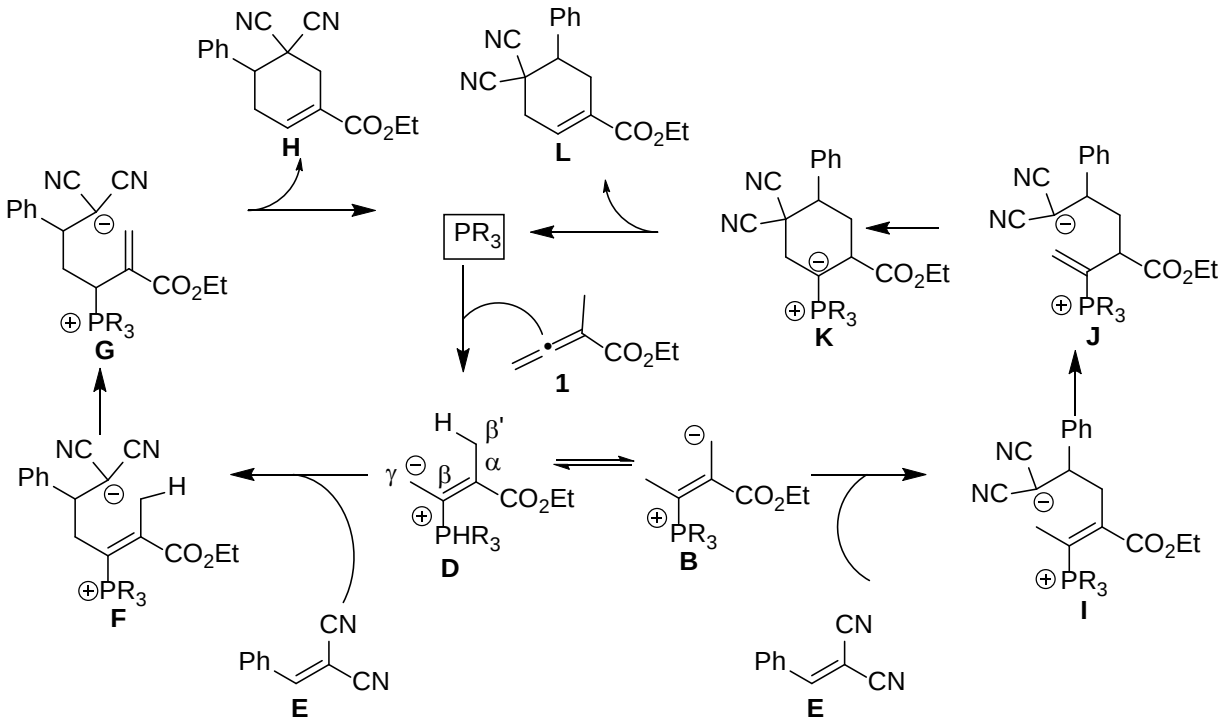
Scheme 1.2: **Phosphine addition to allenoates to generate 1,4-dipole synthons**



The proposed mechanism accounting for the formation of the two regioisomers of the cyclohexene is depicted in **Figure 1.1**. Initial reaction of the phosphine with allenoate **1** forms zwitterionic dienolate **D**. Conjugate addition of **D** with arylidenemalononitrile **E** produces

vinylphosphonium zwitterion **F**, which, after alkene isomerization results in allylphosphonium zwitterion **G**. The malononitrile anion is then able to undergo Michael addition-elimination into the α,β-unsaturated ester, regenerating the phosphine and forming the γ-substituted cyclohexene **H**. If an initial proton transfer from the β'-carbon to the γ-anion of the dienolate zwitterion **D** occurs, vinyligous ylide **B** is formed. **B** can undergo conjugate addition with **E** to form regioisomeric vinylphosphonium zwitterion **I** as compared to **F**. Upon alkene isomerization, **J** is ready for the 6-*endo* cyclization to form ylide **K**, which undergoes a 1,2-proton transfer and β-elimination of the phosphine catalyst to generate of cyclohexene **L**.

Figure 1.1: Proposed mechanism for the formation of cyclohexenes H and L

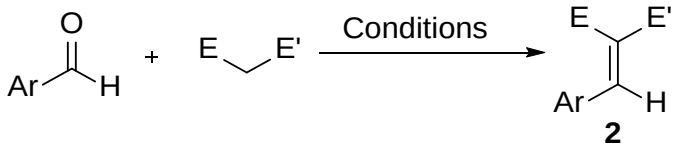


II. Results and Discussion

A. Preparation of Arylidenemalonates, Arylidenemalononitriles and (*E*)-2-cyano-3-arylacrylates

Having succeeded with cyclohexene formation, the next step was to expand the substrate scope of the malononitrile motif to malonate and cyanoester. For this purpose, a family of arylidenemalonates, arylidenemalononitriles and 2-cyano-3-arylacrylates were synthesized. These compounds were then utilized in the phosphine-catalyzed [4 + 2] annulation reaction with allenoates (**Table 1.1**). Synthesis of the arylidenemalonates was accomplished through a Knoevenagel reaction between various aryl aldehydes and dimethyl malonate. Although proline was used by Cardillo et al. to initiate the Knoevenagel,[14] no appreciable results were obtained using this catalyst. Piperidine base was found to be better for the condensation.[15] A triphenylphosphine-catalyzed procedure developed by Yadav was found to be efficient for the formation of arylidenemalononitriles and (*E*)-2-cyano-3-arylacrylates (entries 2 and 3).[16] The (*E*)-stereochemistry for the (*E*)-2-cyano-3-arylacrylates was assumed to follow the literature precedent.[16]

Table 1.1. Knoevenagel Reaction of Aryl Aldehydes with Dimethylmalonate, Malononitrile and Ethyl 2-Cyanoacetate[a]



2

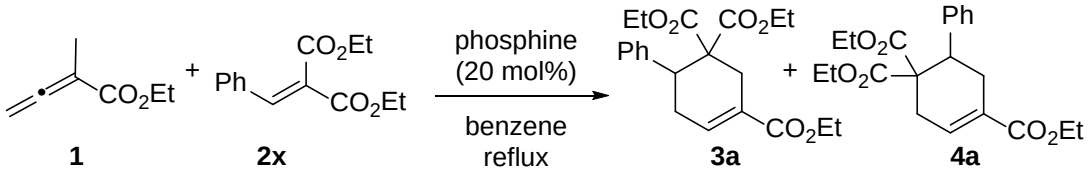
Entry	Ar	E	E'	Product	yield (%)[b]
1	C_6H_5	CO_2Me	CO_2Me	**2a**	90
2	C_6H_5	CN	CN	**2b**	72[c]
3	4-ClC_6H_4	CN	CO_2Et	**2c**	77[c]
4	4-$Me_2NC_6H_4$	CO_2Me	CO_2Me	**2d**	70
5	4-CNC_6H_4	CO_2Me	CO_2Me	**2e**	52
6	4-$NO_2C_6H_4$	CO_2Me	CO_2Me	**2f**	100
7	4-FC_6H_4	CO_2Me	CO_2Me	**2g**	88
8	4-ClC_6H_4	CO_2Me	CO_2Me	**2h**	78
9	4-BrC_6H_4	CO_2Me	CO_2Me	**2i**	87
10	4-MeC_6H_4	CO_2Me	CO_2Me	**2j**	97
11	4-$^{i}PrC_6H_4$	CO_2Me	CO_2Me	**2k**	93
12	4-$MeOC_6H_4$	CO_2Me	CO_2Me	**2l**	45
13	3-BrC_6H_4	CO_2Me	CO_2Me	**2m**	87
14	3-MeC_6H_4	CO_2Me	CO_2Me	**2n**	91
15	3-$MeOC_6H_4$	CO_2Me	CO_2Me	**2o**	56
16	2-ClC_6H_4	CO_2Me	CO_2Me	**2p**	99
17	2-$MeOC_6H_4$	CO_2Me	CO_2Me	**2q**	40
18	3-$CHOC_6H_4$	CO_2Me	CO_2Me	**2r**	5
19	3-$((MeO_2C)_2C=CH)C_6H_4$	CO_2Me	CO_2Me	**2s**	23
20	4-pyridyl	H	CO_2Me	**2t**	34[d]
21	3-pyridyl	CO_2Me	CO_2Me	**2u**	70
22	2-furyl	CO_2Me	CO_2Me	**2v**	70
23	2-thienyl	CO_2Me	CO_2Me	**2w**	88

[a] 8% piperidine was used for compounds **2d, 2e, 2m, 2o, 2u, 2v**; 16% piperidine for the remanding compounds, refluxing toluene, 5 Å mol sieve. [b] Isolated yields. [c] Prepared according to the literature procedure:[16] PPh_3 (20 mol %), neat, 80 ^{o}C, 4 h. [d] Only decarboxylated product isolated as the trans isomer (J = 20 Hz).

B. Survey of Phosphine Catalysts for the [4+2] Annulation

Utilizing conditions analogous to those used for the cyclohexenes produced from arylidenemalonitriles,[13] ethyl 2-methyl allenoate and commercially available diethyl benzylidenemalonate **2x** were reacted in the presence of phosphines (**Table 1.2**). Triphenylphosphine primarily gave the expected cyclohexene **3a** (entry 1), albeit at a slow rate and only 32% isolated yield. Neither electron-rich nor electron-poor triarylphosphines showed sign of cyclohexene formation after 24 h (entries 2–4). Allene oligomerization was the favored pathway with electron-rich phosphines containing alkyl, alkoxy, or dialkylamines (entries 5–8). Similar allene oligomerizations were observed with diethylphenylphosphine, ethyldiphenylphosphine, and diethoxyphenylphosphine.[12] A low isolated yield of cyclohexene was seen with the use of bis(diethylamino)phenylphosphine (entry 9). Following these results the use of HMPT provided a 63% yield with a 28:72 regioselectivity favoring cyclohexene **4a**. The assignments were based on COSY, HMBC and HMQC 2D ^{1}H NMR analysis of **3a** and comparison to their malononitrile-derived cyclohexene counterparts.[13]

Table 1.2: Survey of Phosphine Catalysts for the [4+2] Annulation[a]



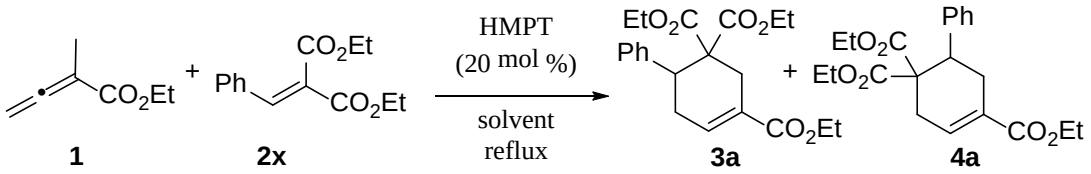
Entry	Phosphine	Reaction Time (h)	Yield[b]	**3a**:**4a**[c]
1	Ph_3P	96	32	>95:5
2	$(4\text{-}Me_2NC_6H_4)_3P$	24	*NR*[d]	*N/A*[e]
3	$(4\text{-}MeOC_6H_4)_3P$	24	*NR*[d]	*N/A*[e]
4	$(4\text{-}FC_6H_4)_3P$	24	*NR*[d]	*N/A*[e]
5	Bu_3P	48	*NR*[d]	*N/A*[e]
6	$(EtO)_3P$	48	*NR*[d]	*N/A*[e]
7	$(^tBuO)_2(Et_2N)P$	48	*NR*[d]	*N/A*[e]
8	$(MeO)(^iPr_2N)_2P$	48	2	*ND*[f]
9	$(Et_2N)_2C_6H_5P$	48	10	22:78
10	HMPT	24	63	28:72

[a] Reaction conditions: **2x** (1 mmol) in 5 mL of benzene was brought to reflux in the presence of phosphine (20 mol %), **1a** (2 mmol) in 10 mL of benzene was added over 2 h. [b] Isolated yield. [c] Regioisomeric ratio by ^1H NMR analysis of crude reaction mixture. [d] No reaction. [e] Not applicable. [f] Not determined.

C. Survey of solvent for the [4+2] Annulation

With a workable catalyst in hand (HMPT) the reaction conditions could then be further optimized, with an emphasis on solvent choice (**Table 1.3**). Benzene gave a moderate yield with decent regioselectivity for **4a** (entry 1). Varying the temperature or concentration of reactants showed no benefit (entries 2–5). This trend persisted with toluene and xylene, with no significant improvement, and failed with mesitylene at reflux or reduced temperature (entries 6–9). Polar solvents showed little to no beneficial assistance to the cyclohexene production (entries 10–19). Reflecting on the reduced polarity of the aromatic solvents, hexane was examined and found to reverse the selectivity favoring **3a** (entry 20). Utilization of pentane increased the yield from that of hexane while giving great selectivity for **3a** (entry 21). Changing the temperature or catalyst offered no other beneficial transformation (entries 22–23). Trying the reaction without solvent (entry 24) produced only oligomerization.

Table 1.3: Survey of Solvent, Temperature, and Concentration for the [4+2] Annulation[a]



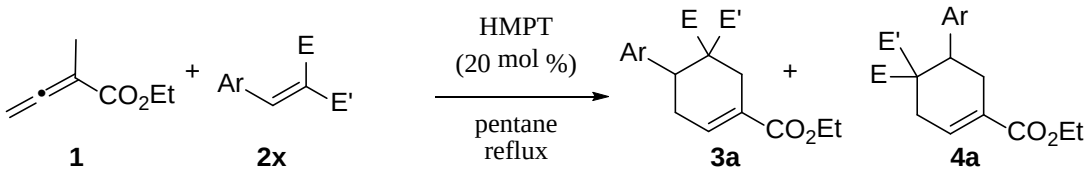
1 **2x** **3a** **4a**

Entry	Solvent	Temp. (°C)	Yield[b]	**3a**:**4a**[c]
1	benzene	80	63	28:72
2	benzene	25	56	32:69
3	benzene	120	36	41:59
4	benzene	80	63	33:67[d]
5	benzene	80	61	50:50[e]
6	toluene	111	65	33:67
7	xylene	140	72	23:77
8	mesitylene	165	2	40:60
9	mesitylene	40	<2	38:62
10	DCM	40	*NR*[f]	*N/A*[g]
11	DCM	40	*NR*[f]	*N/A*[g h]
12	THF	66	64	55:45
13	acetonitrile	82	22	60:40
14	dioxane	101	12	53:47
15	Et_2O	33	15	20:80
16	DCE	83	*NR*[f]	*N/A*[g]
17	ethyl acetate	77	<2	35:65
18	acetone	56	*NR*[f]	*N/A*[g]
19	pyridine	115	*NR*[f]	*N/A*[g]
20	hexane	69	48	72:28
21	pentane	36	72	95:5
22	pentane	36	30	95:5[i]
23	pentane	140	<2	45:55
24	neat	40	*NR*[f]	*N/A*[g]

[a] Reaction conditions: **2x** (1 mmol) in 5 mL of solvent was brought to reflux in the presence of phosphine (20 mol %), **1a** (2 mmol) in 10 mL of solvent was added over 2 h. [b] Isolated yield. [c] Regioisomeric ratio. [d] Concentration half standard conditions. [e] Concentration twice standard conditions. [f] No reaction. [g] Not applicable. [h] Bu_3P (20 %). [i] Ph_3P (20 %).

Utilization of pentane as a solvent, however, greatly limited the reaction's substrate scope. As shown in **Table 1.4**, neither arylidenemalononitriles, arylidenemalonates, or 2-cyano-3-arylacrylates were shown to be reactive in pentane, likely due to insolubility. Even with utilization of polar cosolvents with pentane, the few conditions that formed product did not afford synthetically useful yields.

Table 1.4: Survey of [4+2] Annulations run in Pentane[a]



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

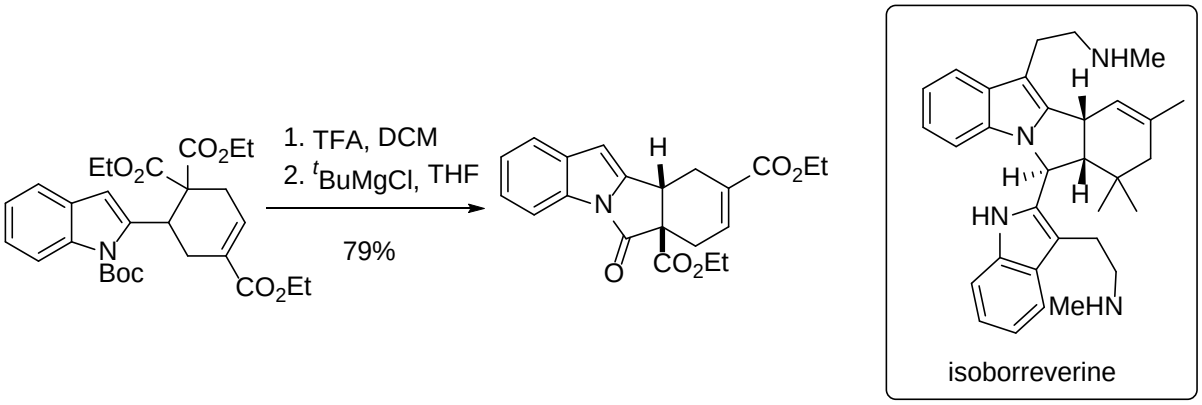
Entry	Solvent	Ar	E,E'	Yield[b]	**3a**:**4a**[c]
1	pentane	Ph	CN	*NR*[d]	*N/A*[e]
2	pentane	Ph	CN, CO_2Me	*NR*[d]	*N/A*[e]
3	pentane	4-CNPh	CO_2Me	*NR*[d]	*N/A*[e]
4	pentane	4-Me_2NPh	CO_2Me	*NR*[d]	*N/A*[e]
5	pentane	2-MeOPh	CO_2Me	*NR*[d]	*N/A*[e]
6	pentane	1-fural	CO_2Me	*NR*[d]	*N/A*[e]
7	7% DCM:pentane	Ph	CO_2Me	16	25:75
8	7% Et_2O:pentane	Ph	CO_2Me	*ND*[f]	33:67
9	50% DCM:pentane	Ph	CO_2Me	4	45:55
10	2% DMSO:pentane	4-CNPh	CO_2Me	*NR*[d]	*N/A*[e]
11	2% DMSO:pentane	4-Me_2NPh	CO_2Me	*NR*[d]	*N/A*[e]

[a] Reaction conditions: **2x** (1 mmol) in 5 mL of solvent was brought to reflux in the presence of phosphine (20 mol %), **1a** (2 mmol) in 10 mL of solvent was added over 2 h. [b] Isolated yield. [c] Regioisomeric ratio. [d] No reaction. [e] Not applicable. [f] Not determined.

III. Conclusion

The optimal conditions, benzene reflux with 20 mol % HMPT, were utilized by Yang et al. to probe the reaction scope.[12] These conditions were demonstrated to be applicable with 14 arylidenemalonates to give cyclohexenes with moderate yield and regioselectivity. When applied to 2-cyano-3-arylacrylates only the regioisomers with connectivity similar to **3a** were isolable, though crude ^{1}H NMR did show about 15% formation of regioisomers with **4a** connectivity.[12] The cyclohexene synthesis was shown to be applicable to allenoates with further substitution at the 2 position which produced cyclohexenes in decent yields with small ratios of syn/anti relative stereoisomers.[12] The synthetic utility of these cyclohexenes was demonstrated by the transformation to a tetracyclic framework with skeletal similarities to the natural product isoborreverine (**Scheme 1.3**).[12]

Scheme 1.3: Demonstration of Synthetic Potential of Cyclohexene Adducts[12]



Experimental Section

General Information

All reactions were performed under an argon atmosphere with dry solvents and anhydrous conditions. Toluene, benzene and dichloromethane were distilled fresh from CaH_2, THF and Et_2O were distilled fresh from Na. All other reagents were used as received from commercial sources. The ethyl 2-methyl allenoate **1** was synthesized according to procedures reported previously.[11a] The dimethyl arylidenenemalonates were synthesized through piperidene-catalyzed Knoevenagel condensation of the pertinent aldehyde and dimethyl malonate.[15] The arylidenenemalononitriles and 2-cyano-3-arylacrylates were synthesized through phosphine-catalyzed Knoevenagel condensation of the pertinent aldehyde and malononitrile or 2-cyano ethyl acetate, according to the procedure reported by Yadav.[16]

Reactions were monitored using thin layer chromatography (TLC) performed on 0.25mm E. Merck silica gel plates (60F-254) and visualized under UV light and/or by permanganate or dinitrophenyl hydrazine staining. Flash column chromatography was performed using E. Merck silica gel 60 (230–400 mesh) and compressed air. Melting points (mp) were determined on a Electrothermal capillary melting point apparatus and are uncorrected. IR spectra were measured on a Avatar 370 FT-IR Thermo Nicolet. NMR spectra were obtained on Bruker Avance-300, ARX-400, or Avance-500 instrument (as indicated), calibrated using residual undeuterated chloroform as an internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C NMR spectra, respectively). Proton NMR spectral data are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Carbon-13 spectral data are reported in terms of the chemical shift. The following abbreviations are used to indicate multiplicities: s = singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quartet; m = multiplet. GC-MS

were obtained on an Agilent 6890N network GC system, and 5975 inert XL selective detector. The column used was a HP-5MS 5% diphenyl- and 95% dimethyl-polysiloxane, 30m X 250μm X 0.25μm. High resolution matrix-assisted laser desorption/ionization (MALDI) mass spectra were recorded using a dihydroxybenzoic acid (DHB) matrix and an IonSpec Ultima 7T FT-ICR-MS.

General Procedure for Formation of Dimethyl Arylidenenemalonates

Ground 15 g of 5Å molecular sieves were flame-dried under vacuum and argon replenished. To a sealed flask containing the dried molecular sieves, 30 mL of dry toluene was added. The flask was then charged with 30 mmol of the pertinent aldehyde and 60 mmol of dimethyl malonate. Relative to the aldehydes that produced compounds **2d**, **2e**, **2m**, **2o**, **2u**, **2v**, 8 mol% (2.4 mmol) of piperidene was then added, to the remaining aldehydes 16 mol% (4.8 mmol) of piperidene was added. The solution was stirred at reflux until all aldehyde was consumed as monitored by TLC and 2,4-dinitrophenyl hydrazine staining, with reaction times averaging 12 h. The solution was filtered through celite. The remaining solution was recrystalization using diethyl ether. If an oil was produced, the compound was purified via column chromatography with 5:1 hexanes to ethyl acetate solvent system.

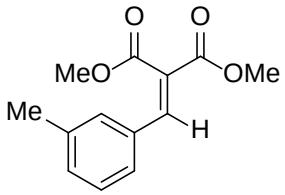
General Procedure for Formation of Arylidenenemalononitriles and 2-Cyano-3-arylacrylates

To a flame dried flask 15 mmol of the pertinent aldehyde and 30 mmol of malononitrile or ethyl-2-cyanoacetate was added. Relative to the aldehydes, 20 mol% (3 mmol) of triphenylphosphine was then added. The solution was heated at 75–80 ^{o}C until all aldehyde was

consumed as monitored by TLC and 2,4-dinitrophenyl hydrazine staining, with reaction times averaging 4 h. The remaining solution was purified via column chromatography with a 5:1 hexanes to ethyl acetate solvent system.

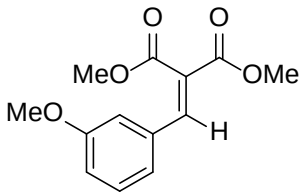
General Procedure for Formation of Cyclohexenes

Ethyl 2-alkylallenoate (2.0 mmol) in benzene (5 mL) was added slowly over 2 h via syringe under an argon atmosphere to a solution of arylidenemalonate (1.0 mmol) and phosphine (0.2 mmol) in benzene (5 mL) at 80 °C. The mixture was heated under reflux and the progress of the reaction monitored using TLC. After the reaction had reached completion (ca. 14 h), the resulting mixture was concentrated. The regioisomeric ratio was determined using ^{1}H NMR spectroscopy. The crude residue was purified by flash column chromatography on silica gel (eluent: 10% ethyl acetate in hexanes) to provide the cyclohexene derivatives.



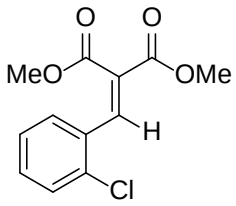
Dimethyl 2-(3-methylbenzylidene)malonate (2n)

91% yield as a white crystal: mp 34 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.842 (s, 3H), 3.845 (s, 3H), 7.18–7.30 (m, 4H), 7.75 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.36, 52.67, 125.24, 126.42, 130.20, 131.57, 132.72, 138.58, 143.17, 164.55, 167.24; IR (Neat, cm^{-1}) ν_{max} 3000.37, 2952.73, 1727.25, 1271.12, 1222.35, 1068.81; MS (GC-MS) calculated for $C_{13}H_{14}O_4$ 234.09, found 234.10.



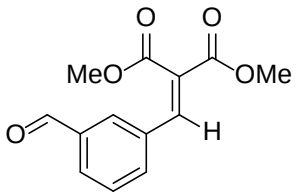
Dimethyl 2-(3-methoxybenzylidene)malonate (2o)

56% yield as a white crystal: mp 56 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.85 (s, 6H), 6.96 (m, 2H), 7.02 (d, 1H, *J* = 8 Hz), 7.30 (m, 1H), 7.75 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 52.56, 52.71, 114.23, 116.76, 121.95, 125.76, 129.93, 134.05, 142.81, 159.80, 164.46, 166.95; IR (Neat, cm^{-1}) ν_{max} 3002.64, 2952.47, 2840.38, 1727.67, 1277.50, 1240.48, 1069.29; MS (GC-MS) calculated for $C_{13}H_{14}O_5$ 250.08, found 250.20.



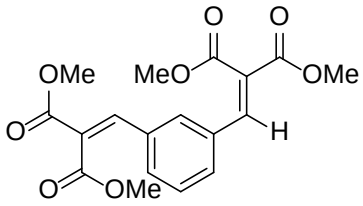
Dimethyl 2-(2-chlorobenzylidene)malonate (2p)

99% yield as a white crystal: mp 43 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (S, 3H), 3.87 (S, 3H), 7.25 (dd, 1H, *J* = 8.0, 0.8 Hz), 7.33 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.40 (td, 1H, *J* = 8.0, 1.6 Hz), 7.44 (td, 1H, *J* = 8.0, 1.2 Hz), 8.07 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 52.63, 52.82, 126.94, 128.03, 129.08, 129.97, 131.33, 131.88, 134.80, 140.02, 164.06, 166.32; IR (Neat, cm^{-1}) ν_{max} 2953.52, 1731.52, 1258.70, 1224.29, 1069.86; MS (GC-MS) calculated for $C_{12}H_{11}ClO_4$ 254.03, found 254.1.



Dimethyl 2-(3-formylbenzylidene)malonate (2r)

5% yield as a yellow crystal: mp 49 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.87 (s, 3H), 7.57 (t, 1H, *J* = 7.6 Hz), 7.67 (d, 1H, *J* = 8.0 Hz), 7.81 (s, 1H), 7.90 (s, 1H), 7.92 (s, 1H), 10.01 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 52.87, 52.90, 127.37, 129.70, 130.18, 131.36, 133.82, 134.76, 136.85, 141.19, 164.10, 166.56, 191.30; IR (Neat, cm^{-1}) ν_{max} 3004.63, 2954.58, 2847.42, 2359.98, 2341.99, 1735.79, 1701.32, 1438.12, 1269.57, 1227.81, 1068.48; MS (GC-MS) calculated for $C_{13}H_{12}O_5$ 248.07, found 248.10.



Tetramethyl 2,2'-(1,3-bisbenzylidene)dimalonate (2s)

23% yield as a white crystal: mp 84 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 6H), 3.86 (s, 6H), 7.44 (m, 4H), 7.73 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 52.85, 52.90, 126.81, 129.47, 130.18, 130.99, 133.64, 141.70, 164.23, 166.61; IR (Neat, cm^{-1}) ν_{max} 3003.16, 2954.59, 2847.20, 2360.17, 1736.08, 1709.13, 1438.83, 1260.05, 1218.89, 1068.91. MS (GC-MS) calculated for $C_{18}H_{18}O_8$ 362.10, found 362.10.

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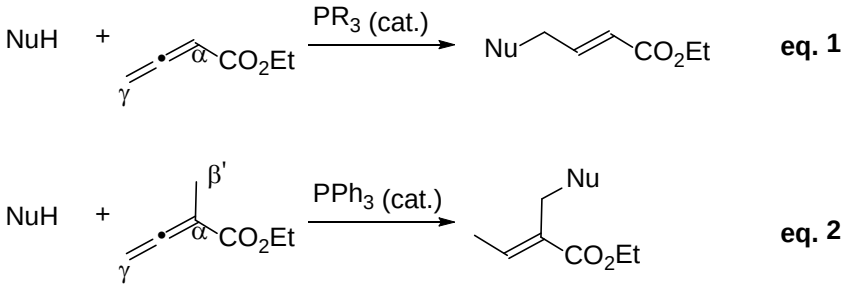
CHAPTER TWO

Phosphine-Catalyzed β'-Functionalization with Pronucleophiles on Activated α-Alkyl Allenes

I. Introduction

Transformations of activated allenes via nucleophilic phosphine catalysis has given rise to a plethora of new reactions.[1] First reported by Trost,[2] a unique application to functionalize the γ-position to a carbonyl is the phosphine-catalyzed γ-umpolung addition of nucleophiles to activated allenes and acetylenes. The phosphine-catalyzed γ-umpolung addition of pronucleophiles to electron-deficient alkynes and allenes (**Scheme 2.1**; **eq 1**) has been met with increasing interest in the synthetic community.[3] A β'-addition of pronucleophiles to α-alkyl allenoates was envisioned by studying the mechanistic insights gained from the γ-umpolung additions and nucleophilic phosphine-catalyzed reactions of α-substituted allenoates developed by Kwon[4] and others[5] (**Scheme 2.1**; **eq 2**). Highly versatile olefinic products are produced by this process through functionalization of the seemingly unactivated β'-C–H bond. The equilibrium between the β-phosphonium dienolate and the vinylogous ylide is the proposed means of activation for the β'-carbon atom of α-alkyl allenoates.[4d,f,g]

Scheme 2.1: γ-Addition and β'-Addition of Pronucleophiles to Allenes

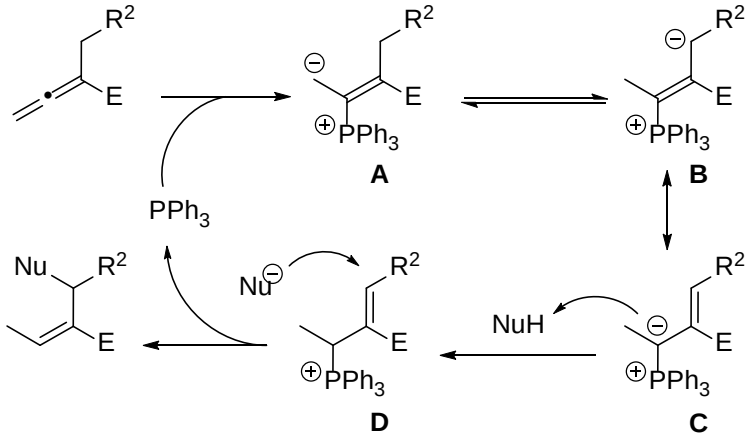


II. Results and Discussion

A. Proposed Mechanism of the β'-Addition of Pronucleophiles to Allenes

Shown in **Figure 2.1** is a plausible mechanism for the β'-addition of pronucleophiles to activated allenes. Triphenylphosphine addition to the activated allene gives phosphonium dienolate **A**. Phosphonium dienolate **A** undergoes an established equilibrium via proton transfer to vinylogous ylide **B**. [4d,f,g] The resonance-formed ylide **C** abstracts a proton from the pronucleophile revealing the phosphonium electrophile **D**. The anionic nucleophile then undergoes conjugate addition and subsequent β-elimination of the phosphine.

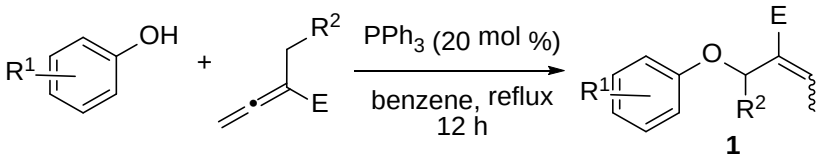
Figure 2.1: Proposed Mechanism of the β'-Addition



B. Survey of Phenolic Pronucleophiles

A collection of substituted phenols in refluxing benzene was reacted with activated α-alkyl allenes and catalytic PPh_3 (**Table 2.1**). The β'-addition adduct **1a** produced from phenol gave a quantitative yield of a single geometric isomer. This first entry afforded an expedient route to allylphenyl ether, an intermediate in functionalized coumarin synthesis.[6] No competative γ-umpolung addition was observed, most likely stemming from the γ-umpolung addition's requirement for basic or buffering additives.[2,3] Phenols featuring electron-donating methyl or methoxy substituents maintained high product yields (entries 2 and 3). The electron-withdrawing halogenated phenols were isolated in diminishing yields as the electro-negativity of the halogen increased (entries 4–8). This reduction in yield of the desired product was found to arise from competitive fragmentation producing ethyl 2-methylenebut-3-enoate, which was isolated as the Diels-Alder dimer.[7] Carboxylic ester and protected amino groups on the phenols were tolerated (entries 9 and 10), with the tert-butyl carbamate substituted phenol yielding a mixture of *E* and *Z* isomers (entry 10). Substitution at the 2 or 3 position of the phenol was tolerated well (entries 11–13), although a slight decrease in stereoselectivity was seen with *o*-cresol (entry 12). Steric hindrance around the phenolic nucleophile diminished the reaction efficiency; 2,6-dimethylphenol provided a reduced yield (entry 14), while extremely sterically hindered 2,6-di-tert-butylphenol did not react (entry 15). Phenyl substitution at the β'-position of the allene produced *Z*-olefins, presumably because of steric clash between the γ-methyl and the phenyl substituent at R^2 (entries 16–18). The β'-substitution stabilized the arylallyl ether **1q** from fragmentation to the diene (vida supra),[7] providing **1q** in 97% isolated yield (entry 17; cf. entry 8, 73%). Changing the electron-withdrawing activating group on the allene to nitrile worked sufficiently well as the electrophile, providing arylallyl ether **1r** in excellent yield (entry 18).[8]

Table 2.1: Addition of Phenols to Activated Allenes[a]



1

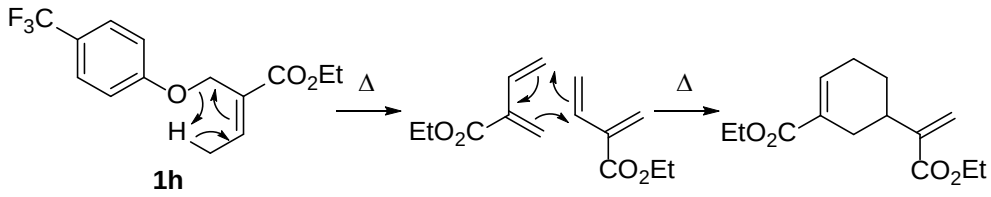
entry	R^1	R^2	E	Product	yield (%)[b]	E/Z[c]
1	H	H	CO_2Et	**1a**	>99	*E only*
2	4-Me	H	CO_2Et	**1b**	97	*E only*
3	4-OMe	H	CO_2Et	**1c**	92	*E only*
4	4-I	H	CO_2Et	**1d**	69	*E only*
5	4-Br	H	CO_2Et	**1e**	72	*E only*
6	4-Cl	H	CO_2Et	**1f**	62	*E only*
7	4-F	H	CO_2Et	**1g**	78	*E only*
8	4-CF_3	H	CO_2Et	**1h**	73	*E only*
9	4-CO_2Et	H	CO_2Et	**1i**	90	*E only*
10	4-NHBoc	H	CO_2Et	**1j**	89	4:1
11	3-Me	H	CO_2Et	**1k**	95	*E only*
12	2-Me	H	CO_2Et	**1l**	96	20:1
13	2-I	H	CO_2Et	**1m**	91	*E only*
14	2,6-Me	H	CO_2Et	**1n**	66	*E only*
15	2,6-di-^{t}Bu	H	CO_2Et	**1o**	0	*N/A*[d]
16	4-OMe	Ph	CO_2Et	**1p**	89	*Z only*
17	4-CF_3	Ph	CO_2Et	**1q**	97	*Z only*
18	4-CF_3	Ph	CN	**1r**	88	*Z only*

[a] Reactions were performed using 1.1 equiv of allene. [b] Isolated yield. [c] Determined through ^{1}H NMR and NOESY NMR spectroscopic analysis. [d] Not applicable.

C. Attempts at Trapping the Diels-Alder Adduct

Allylaryl ethers with electron-withdrawing groups, in particular compound **1h**, are susceptible to a second transformation. The proposed mechanism is shown in **Figure 2.2**, where **1h** undergoes an Ene fragmentation followed by a Diels-Alder dimerization.

Figure 2.2: Proposed Mechanism of Dimerization

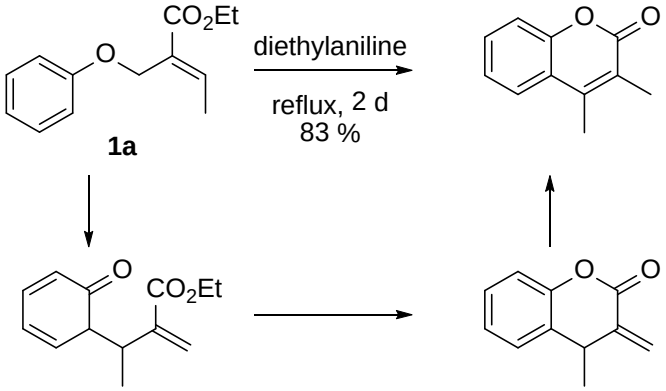


The diene exists only as a transient species, and must be formed in situ.[9] This phenomenon arises from the low activation energy of 11.2 kcal/mol for the dimerization, lower than the 16.4 kcal/mol for cyclopentadiene, which is known to exist as the dimer at room temperature.[9c] The potential application of this system as a diene synthon was explored, but the appropriate conditions for selective release and capture of the diene have yet to be realized. When the synthesis of **1h** was conducted in the presence of maleimide, only the diene dimer and decomposition of the maleimide were observed over 72 h. When **1a** was subjected to refluxing benzene in the presence of maleimide with phenol or *p*-nitrophenol as a proton source, only starting material was recovered, yet when trifluoroacetic acid was added to the system, with either maleimide or ethyl acrylate, only the dimerized product was isolated.

D. Access to Functionalized Coumarin

These substrates lend themselves to further synthetic modification. As mentioned earlier the allyl aryl ethers can be further transformed into functionalized coumarins. When allyl phenyl ether **1a** was subjected to refluxing diethylaniline, it underwent a facile Claisen rearrangement, lactonization, and isomerization cascade to produce 3,4-dimethylcoumarin (**Scheme 2.2**).[10] The use of Lewis acids, or refluxing dichlorobenzene, favored the dimerized adduct as previously discussed.

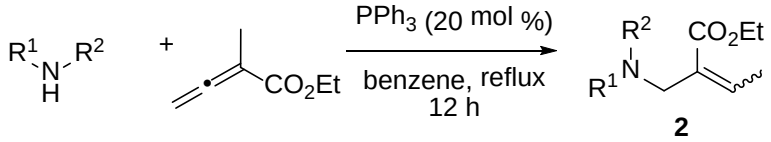
Scheme 2.2: Synthesis of 3,4-Dimethylcoumarin



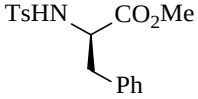
E. Survey of Amine Pronucleophiles

Following the success of the phenol pronucleophiles, exploration of the β'-addition was expanded to amine-based pronucleophiles (**Table 2.2**). Aryl and alkyl tosylated amines gave the desired β'-addition products (entries 1 and 2), albeit with isomeric ratios of 2.5:1 of *E* and *Z* olefins. The tert-butyl *N*-tosylcarbamate and *p*-toluenesulfonamide itself were viable substrates in regards to yield (entries 3 and 4), although geometric selectivity is still diminished. The pronucleophile is limited by pKa, which is demonstrated by the use of tert-butyl N-phenylcarbamate: no reaction occurred due to its higher pKa when compared to the tosylated amines (entry 5).[3g] Olefin stereoselectivity was restored with the use of phthalimide (entry 6), giving a 71% yield as a single *E* isomer. *p*-Toluenesulfonylhydrazine gave a moderate yield of the expected β'-addition product, however when the *N,N'*-ditosylhydrazine was employed a 71% yield of 3 diastereomers was isolated. The protected amino acid derivative *N*-tosyl ethyl phenylalanine (entry 8) was successfully reacted in excellent yield. These substrates provide access to α-substituted β-amino esters which have been showcased in β-peptide chemistry;[11] in particular, α-methylene-β-alanine is a naturally occurring herbicide.[12]

Table 2.2: Addition of Amines to α-Methyl Allenoate[a]



2

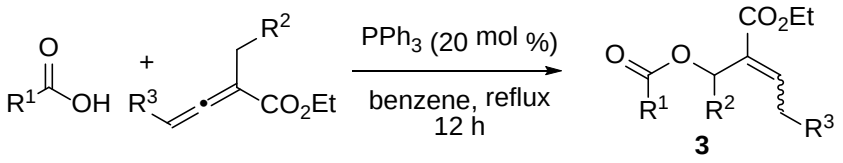
entry	R_1	R_2	Product	Yield (%)[b]	*E:Z*[c]
1	Ph	*p*-Ts	**2a**	94	2.5:1
2	Bn	*p*-Ts	**2b**	94	2.5:1
3	Boc	*p*-Ts	**2c**	83	2:1
4	H	*p*-Ts	**2d**	53	1:1.75
5	Ph	Boc	**2e**	0	*N/A*[d]
6	phthalimide		**2f**	71	*E only*
7	$TsHN\text{-}NH_2$		**2g**	57	1.5:1
8	TsHN-NHTs		**2h**	71	*ND*[e f]
9			**2i**	92	1:1.2

[a] Reactions were performed using 1.1 equiv of allene. [b] Isolated yield. [c] Determined through ^1H NMR spectroscopic analysis. [d] Not applicable. [e] 3 diastereomers were isolated, precise ratio not determined. [f] Not determined.

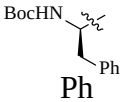
F. Survey of Carboxylic Acid Pronucleophiles

The robustness of the β'-addition of carboxylic acids gave excellent product yields and geometric selectivities as illustrated with a variety of substituted allenoates (**Table 2.3**). This was first observed when acetic acid was being screened as a potential additive, yet out competed other pronucleophiles to generate allylated carboxylates. Both acetic acid and benzoic acid produced the acylated and benzoylated allylic alcohols respectively, exclusively as the *E* isomer in excellent yields (entries 1 and 2). Interestingly, (*E*)-ethyl 2-acetoxy-2-butenoate (**3a**) is an intermediate for the synthesis of mikanecic acid.[13] The C-terminus addition with *N*-tert-butoxycarbonyl phenylalanine (**Table 2.3**, entry 3) complements the *N*-terminus addition of *N*-tosyl ethyl phenylalanine (**Table 2.2**, entry 8), with equivalent yield but greater geometric selectivity. HPLC analysis confirmed that the conditions were mild enough to prevent any epimerization of the amino acid. γ-Methyl-substituted allenoate reacted as expected with benzoic acid (entry 4), but the reaction does have a steric upper limit as is observed with the excessively large γ-tert-butyl allenoate (entry 5). Further alkyl substitution at the α-position of the allenes maintained the *E* selectivity, shown here with ethyl α-(5-hexenyl)allenoate (entry 6). However α-benzyl allenoate produced the *Z*-olefinic enoate in accordance with observations from the phenolic pronucleophiles (entry 7). Only diethyl 2-vinylidenesuccinate produced a mixture of olefinic isomers, but still progressed in excellent yield (entry 8). This family of substrates would offer themselves well as substrates for the Tsuji-Trost palladium-catalyzed allylation.[14]

Table 2.3: Addition of Carboxylic Acids to Activated Allenes[a]



3

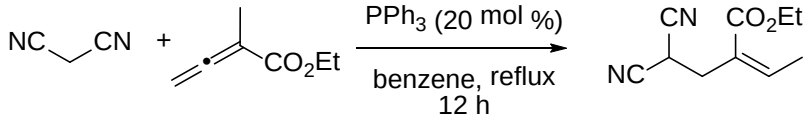
entry	R^1	R^2	R^3	product	yield (%)[b]	*E*/*Z*[c]
1	Me	H	H	**3a**	97	*E only*
2	Ph	H	H	**3b**	95	*E only*
3		H	H	**3c**	96	*E only*
4	Ph	Me	H	**3d**	90	*E only*
5	Ph	^{t}Bu	H	**3e**	0	*N/A*[d]
6	Ph	H	pentenyl	**3f**	85	*E only*
7	Ph	H	Ph	**3g**	95	*Z only*
8	Ph	H	CO_2Et	**3h**	96	1:1.5

[a] Reactions were performed using 1.1 equiv of allene. [b] Isolated yield. [c] Determined through ^{1}H NMR and NOESY NMR spectroscopic analysis. [d] Not applicable.

G. Survey of Carbon Pronucleophiles

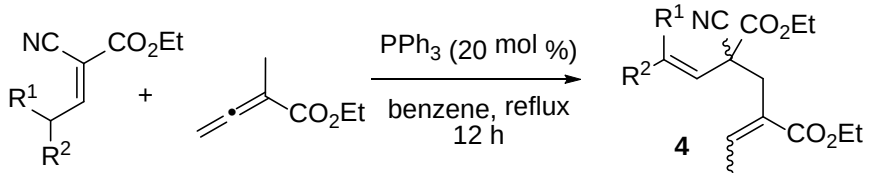
This reaction was then applied to making new C-C bonds by examining carbon centered pronucleophiles. Dimethyl malonate and ethyl cyanoacetate did not give clean reactions, however malononitrile with ethyl α-methyl allenoate gave a Z-configured olefinic product in excellent yield (**Scheme 2.3)**. Structurally, this product resembles a mixed Rauhut-Currier adduct.[1i] Furthermore, a similar transformation in the presence of tributylphosphine has been achieved with 1,3-cyclic diketones,[3l] yet tributylphosphine has been shown to add dimethyl malonate to the γ-position of α-methyl allenoate via an umpolung process.[3a]

Scheme 2.3: Addition of Malononitrile



To expand the complexity of the target substrates alkylidenecyanoacetates were employed (**Table 2.4**), alkylidenes with malonate motifs did not react and those with malononitrile decomposed. These alkylidenecyanoacetates underwent γ-deprotonation followed by resonance to the α-carbon, which proceeded through the β'-nucleophilic addition to the phosphonium ion as discussed in the aforementioned mechanism. These substrates produced all-carbon quaternary centers with differentiating functionality. The β,γ-olefin from the cyanoacetate existed exclusively as the *E* isomer and the α,β-unsaturated enoate as an isomeric mixture. Exploring further functionalization, compound **4a** was subjected to refluxing dichlorobenzene to produce a diastereomeric mixture of the Cope rearrangement product (**Scheme 2.4**).

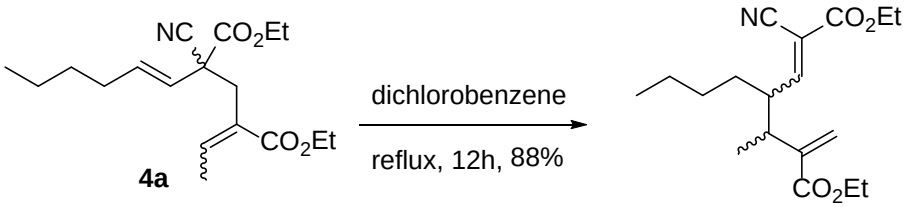
Table 2.4: Addition of Alkylidenecyanoacetates to Activated Allenes[a]



entry	R_1	R_2	product	yield (%)[b]	*E*:*Z*[c]
1	^{n}Bu	H	**4a**	57	5:1
2	Me	H	**4b**	42	5:1
3	Me	Me	**4c**	79	2:1[d]

[a] Reactions were performed using 1.1 equiv of allene. [b] Isolated yield. [c] Determined through ^{1}H NMR and NOESY NMR spectroscopic analysis. [d] Isomers were separated and characterized.

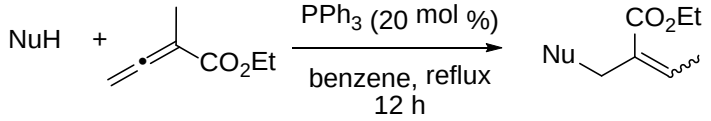
Scheme 2.4: Cope Rearrangement of 4a.



H. Furfuryl Alcohol, Benzaldehyde Oxime, and Thiophenol Pronucleophiles

Furfuryl alcohol, (*E*)-benzaldehyde oxime, and thiophenol succumbed to the β'-addition (**Table 2.5**). Aliphatic alcohols have been observed to undergo the γ-addition,[3a] but were found to be unreactive in these conditions do to possessing a pKa above the range for this reaction. The lower pKa of furfuryl alcohol (9.55) enabled it to react, giving rise to the β'-addition product (entry 1). Initial attempts at an intramolecular Diels-Alder reaction (thermal, $MeAlCl_2$, and $Eu(FOD)_3$) of the furfuryl product did not generate the desired product. Benzaldehyde oxime gave the *O*-allylated oxime which has been shown to be a valuable synthetic precursor towards allylation of activated methylene compounds,[15] [2,3]-sigmatropic N,O rearrangements,[16] formal [2,3]-sigmatropic rearrangement to form N-allyl nitrone followed by in situ dipolar cycloaddition when treated with Pd(II),[17] and single step conversion to pyrroles under iridium catalysis.[18] The thiophenol gave a diminished yield do to a competitive path leading to thiol adding at the β-carbon of the allene.[3l]

Table 2.5: Addition of Alkylidenecyanoacetates to Activated Allenes[a]



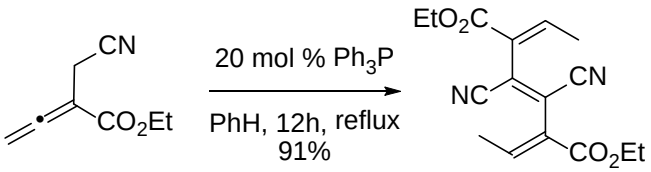
entry	Nu-H	product	Yield (%)[b]	*E:Z*[c]
1	furfuryl alcohol	**5a**	88	1:1
2	(*E*)-benzaldehyde oxime	**5b**	77	4:1
3	C_6H_5SH	**5c**	65	1:0

[a] Reactions were performed using 1.1 equiv of allene. [b] Isolated yield. [c] Determined through ^1H NMR spectroscopic analysis.

I. Dimerization of Ethyl 2-(cyanomethyl)buta-2,3-dienoate

When exploring allenes with diverse substituents, the highly favored dimerization of ethyl 2-(cyanomethyl)buta-2,3-dienoate was observed (**Scheme 2.5**). Under the standard conditions for the β'-addition, the dimerization outcompetes other pronucleophiles such as the generally highly favored benzoic acid. Dimerization occurred following the same mechanistic pathway outlined in **Scheme 2.1**, with another molecule of ethyl 2-(cyanomethyl)buta-2,3-dienoate acting as the pronucleophile. After the initial coupling, a phosphine-catalyzed intramolecular redox occurs to yield the triene dimer.

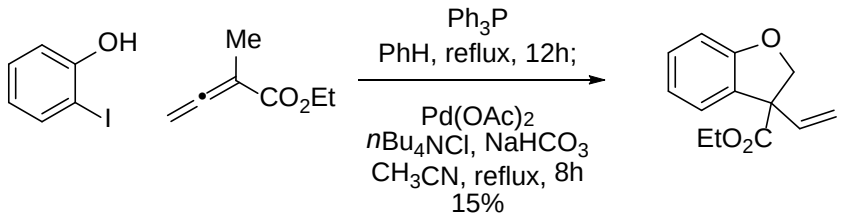
A. Scheme 2.5: Dimerization of Ethyl 2-(cyanomethyl)buta-2,3-dienoate



III. Conclusion

This high yielding, and often highly stereoselective, β'-addition of pronucleophiles to activated α-alkyl allenes has been shown to be applicable to a broad range of nucleophiles (sulfur-, nitrogen-, oxygen- and carbon-centered). Many of these substrates have been shown to be synthetically useful, e.g. *N* and *C* terminus functionalization of amino acid derivatives, known precursors in natural product or drug candidates, and the demonstration of a coumarin synthesis. As further demonstration of the synthetic potential of these substrates, in an un-optimized result, the system that produced compound **1m** was charged in situ with palladium. A 15% yield of a dihydrobenzofuran with a differentially substituted all carbon quaternary center at C-3 is produced (**Scheme 2.6**). This skeleton is a common motif in pharmaceuticals such as galanthamine and various opioids.

Scheme 2.6: In Situ β'-Addition Followed by Heck Coupling



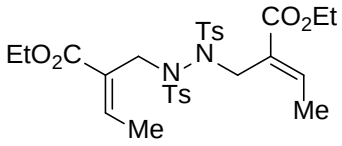
Experimental Section

General Information

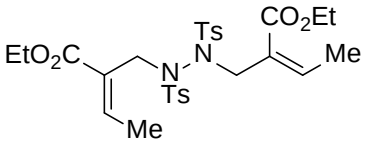
All reactions were performed under argon atmospheres with dry solvents and anhydrous conditions, unless otherwise noted. Benzene was distilled from CaH_2. Reactions were monitored by thin layer chromatography (TLC) on 0.25-mm E. Merck silica gel plates (60F-254) and visualized under UV light or through anisaldehyde or permanganate staining. Flash column chromatography was performed using E. Merck silica gel 60 (230–400 mesh) and compressed air. IR spectra were recorded on a Perkin–Elmer pargon 1600 FT-IR spectrometer. NMR spectra were obtained on Bruker Avance-500, ARX-500, or ARX-400 instruments as indicated, calibrated using residual $CHCl_3$ as the internal reference (7.26 ppm for ^{1}H NMR; 77.00 ppm for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift, multiplicities, and coupling constants (Hz) in the case of J_{CF} coupling. The following abbreviations are used for the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; app = apparent. High-resolution matrix-assisted laser desorption/ionization (MALDI) mass spectra were recorded from a dihydroxybenzoic acid (DHB) matrix using an IonSpec Ultima 7T FT-ICR-MS instrument with internal calibration. Gas chromatography-coupled mass spectra (EI) were obtained on an Agilent 6890-5975. Full characterization of most compounds presented can be found in the SI of the publication by Martin *et al*.[19]

General Procedure for the Phosphine-Catalyzed β′- Addition of Pro-nucleophile to Activated Allenes

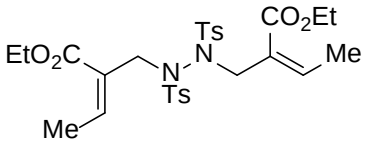
A round bottom flask with a stir-bar and a condenser was flame-dried and left to cool under argon. The pro-nucleophile (1.0 equiv) and the phosphine (0.2 equiv) were added to the flask. Distilled benzene was added via syringe. Finally, the allenaote (1.1 equiv) was weighed in a syringe, mixed with distilled benzene and added dropwise to the reaction mixture over 5 h. The reaction was allowed to proceed until the pro-nucleophile was consumed, typically 12 h (TLC, 6:1 hexane/EtOAc). The crude reaction mixture was concentrated and loaded onto a silica gel column and separated chromatographically (eluant, 6:1 hexane/EtOAc). In all cases, the product stained brightly in a standard permanganate stain.



2h (E,E)



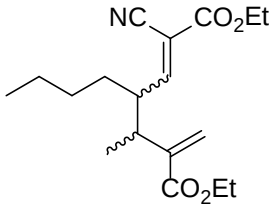
2h (E,Z)



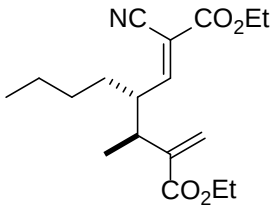
2h (Z,Z)

Yield: 70%; 3:1:1 *E,E:E,Z:Z,Z* selectivity; clear oil; IR (film) ν_{max} 2983, 1713, 1317, 1148, 1086 cm^{-1}; ^1H NMR major (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 4H), 7.22 (q, *J* = 7.0 Hz, 2H), 4.22 (s, 4H), 3.94 (q, *J* = 7.0 Hz, 4H), 2.42 (s, 6H), 1.82 (d, *J* = 7.0 Hz, 6H), 1.12 (t, *J* = 7.0 Hz, 6H); ^1H NMR minor (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 4H), 6.27 (q, *J* = 7.0 Hz, 2H), 4.05 (s, 4H), 3.96 (q, *J* = 7.0 Hz, 4H), 2.42 (s, 6H), 2.06 (d, *J* = 7.0 Hz, 6H), 1.16 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 165.2, 147.8, 146.2, 144.7, 144.6, 135.9, 135.5, 129.6 (2C), 129.5 (2C), 129.1 (2C), 128.77 (2C), 128.73 (2C), 122.1, 121.4, 61.0, 60.7, 60.3, 53.7, 21.6, 16.4, 15.3, 14.0; MS (MALDI) calcd for $C_{14}H_{23}O_4N_2$ $[M - (2Ts + H)]^+$ 283.16, found 283.09.

General Procedure for the Cope Rearrangement of Compound 4a



A round bottom flask with stir-bar and condenser was flame-dried and left to cool under argon. Compound **4a** (0.5 mmol) and dichlorobenzene (1mL) were added to the flask. The reaction was heated to reflux and allowed to react until compound **4a** was consumed, typically 24h (TLC 6:1 hexane/EtOAc). The crude reaction mixture was loaded directly onto a silica gel column and separated chromatographically (hexane/EtOAc, 6:1). The product stained brightly in a standard permanganate stain. Although a mixture of stereoisomers is observed spectroscopically (8 possible configurations), one relative stereoisomer shows prominence and is therefore highlighted for characterization purposes. The assumption of this assignment arises from the subjection of a greater concentration (5:1) of the *Z* ethyl acrylate moiety, which based on the stereoselectivities of the Cope rearrangement would favor the trans arrangement of the chiral centers, and the steric constraints of the cyanoacrylate to favor the E alkene.

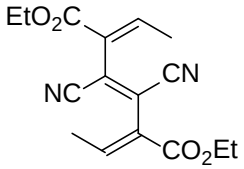


Yield: 88%; clear oil; IR (film) ν_{max} 2957, 2929, 2859, 2234, 1728, 1714, 1627, 1461, 1367, 1237, 1173, 1096, 1076, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 11.0 Hz, 1H), 6.28 (s, 1H), 5.57 (s, 1H), 4.29 (q, J = 7.0 Hz, 2H), 4.16 (q, J = 7.0 Hz, 2H), 2.99 (t, J = 7.0 Hz, 2H), 2.92–2.82 (m, 1H), 1.36–1.25 (m, 1H), 1.19 (d, J = 7.0 Hz, 3H), 0.90–0.85 (m, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 166.7, 166.2, 161.0, 143.0, 125.6, 113.8, 109.9, 62.3, 60.9, 38.1, 31.6, 31.0, 29.2, 22.5, 22.2, 14.0, 13.9, 13.7; MS (MALDI) calcd for $C_{18}H_{27}O_4NNa$ $[M + Na]^+$ 344.18, found 344.22.

General Procedure for the Dimerization of Ethyl 2-(cyanomethyl)buta-2,3-dienoate

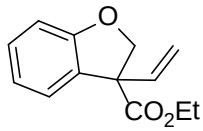
A round bottom flask with stir-bar and condenser was flame-dried and left to cool under argon. The phosphine (0.2 equiv) was added to the flask. Distilled benzene was added via syringe. Finally, the allenaote (1.1 equiv) was weighed in a syringe, mixed with distilled benzene and added drop wise to the reaction mixture over 5h. The reaction was allowed to react until the allenoate was consumed, typically 12h (TLC 6:1 hexane/EtOAc). The crude reaction mixture was concentrated and loaded onto a silica gel column and separated chromatographically (hexane/EtOAc, 6:1). The product stained brightly in a standard permanganate stain.



Yield: 91%; clear oil; IR (film) ν_{max} 2984, 2915, 2848, 2227, 1732, 1701, 1647, 1383, 1253, 1165, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (q, *J* = 7.0 Hz, 2H), 4.30 (q, *J* = 7.0 Hz, 4H), 2.08 (d, *J* = 7.0 Hz, 6H), 1.33 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (2C), 148.6 (2C), 129.1 (2C), 125.8 (2C), 113.9 (2C), 62.0 (2C), 16.0 (2C), 14.0 (2C); MS (MALDI) calcd for $C_{16}H_{18}O_4N_2Na$ $[M + Na]^+$ 325.11, found 325.11.

General Procedure for in situ Heck Coupling

The un-optimized in situ Heck coupling was initiated following the procedure for the β'-addition of pronucleophiles to activated allenes, vide supra. After the first reaction is complete, as monitored by TLC, the benzene is roto-evaporated off and the reaction is resolvated with acetonitrile followed by the addition of $Pd(OAc)_2$, $n$$Bu_4NCl$, and $NaHCO_3$. The reaction is allowed to procede until the allylated phenol is consumed.



Ethyl 3-vinyl-2,3-dihydrobenzofuran-3-carboxylate

Yield: 91%; clear oil; IR (film) ν_{max} 2980, 2915, 1733, 1480, 1257, 1222, 751, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 1.0, 7.0 Hz, 1H), 7.21 (td, J = 7.0, 1.0 Hz, 1H), 6.93 (td, J = 7.0, 1.0 Hz, 1H), 6.83 (dd, J = 7.0 Hz, 1H), 6.17 (dd, J = 5.0, 10.0 Hz, 1H), 5.26 (dd, J = 16.6, 10.2 Hz, 1H), 5.09 (dd, J = 17.8, 6.6 Hz, 2H), 4.47 (d, J = 12.4 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 159.6, 137.7, 130.3, 128.9, 120.6 (2C), 116.1, 110.0, 78.3, 61.6 (2C), 14.0 MS (MALDI) calcd for $C_{13}H_{14}O_3Na$ $[M + Na]^+$ 241.08, found 241.10.

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CHAPTER THREE

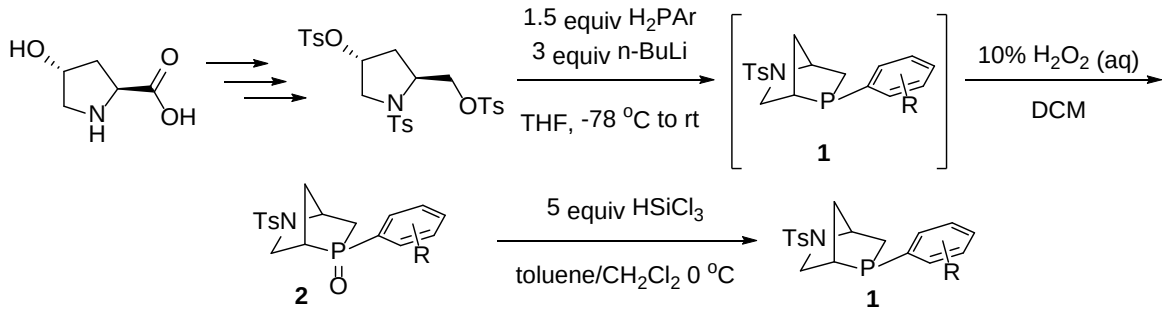
Amino Acid Derived [2.2.1] Bicyclic Phosphine: Asymmetric Synthesis of Dihydropyrroles

I. Introduction

Crucial to the continued development of phosphine-catalyzed reactions is the design of new chiral phosphines capable of furnishing enantioenriched products. In this field, the use of electron deficient allenes for annulation reactions has been explored,[1] and a number of asymmetric variants have been accomplished.[2] Lu's [3 + 2] annulation between allenoates and *N*-sulfonyl imines to form dihydropyrroles is an attractive candidate for asymmetric catalysis,[3] with growing success in enantioenriched products from many groups.[4]

Initial work by Dr. Henry brought forth an idea for an asymmetric [2.2.1] bicyclic phosphine,[5] which was then further optimized in this work. In three steps from commercially available *trans*-4-hydroxy-L-proline, the tritosyl proline derivative was formed (**Scheme 3.1**).[6] The tritosyl proline derivative was utilized in a bisalkylation with dilithium arylphosphide to afford the rigid [2.2.1] bicyclic chiral phosphine **1**. The crude reaction mixture was then oxidized with dilute hydrogen peroxide to form the stable phosphine oxides **2** and ***ent*-2** (epimer at the P-chiral center.) as a separable mixture of diasteriomers. The conversion to the oxide allowed for ease in purification as well as protection of the catalyst, allowing room temperature stability with no decomposition over the span of a year.[5] Trichlorosilane reduced the protected phosphine oxides with retention of stereochemistry to afford catalysts **1** in greater than 95% yield. Several chiral [2.2.1] bicyclic phosphines with different exocyclic phosphorus substituents were synthesized by this general bisalkylation ring-closing procedure.

Scheme 3.1: Synthesis of Proline Derived [2.2.1] Bicyclophosphines



The newly formed chiral phosphines were shown to catalyze the [3 + 2] annulation between allenoates and *N*-sulfonyl imines to form optically active dihydropyrroles. The system developed by Dr. Henry produced functionalized dihydropyrroles with promising levels of enantioenrichment, unfortunately the reaction suffered from irreproducibility, low yields (34–60%) and no trends in reactivity. Even with modification of the aryl group attached to phosphine, catalysis of the [3 + 2] annulation showed minimal improvement. The batch-to-batch irreproducibility of the phosphine catalysts made it clear that there were synthetic problems to address.

II. Results and Discussion

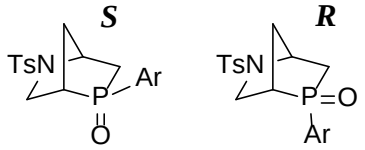
A. Synthesis of [2.2.1] Bicyclic Phosphines

The rigid [2.2.1] bicyclic phosphine was envisioned to be derived from *trans*-4-hydroxy-L-proline via a dialkylation process with dilithium arylphosphide, **Scheme 3.1**. Although this transformation had been met with a measure of success,[5] insufficient characterization of the phosphines and inconsistent catalytic activity eluded to standing problems in the bicyclophosphine synthesis.

Modifications in the production and purification of phenylphosphine allowed relatively convenient access to large quantities of this highly pyrophoric and volatile starting material. The main contaminant was identified as the oxidized phosphine, thus a number of techniques were employed to help suppress oxide formation. Phenylphosphine is produced from the $LiAlH_4$ reduction of dichlorophenylphospine, utilization of the Merlic workup greatly reduced exposure to ambient air.[7] Furthermore, argon replenishment following evaporation of the tetrahydrofuran solvent, oxygen-free fractional distillation, and storage in a -4^{o} C refrigerator gave up to 250 mmol of highly pure material. Access to analytically pure phenylphosphine allowed for more precise control over production of the dilithium phenylphosphide.

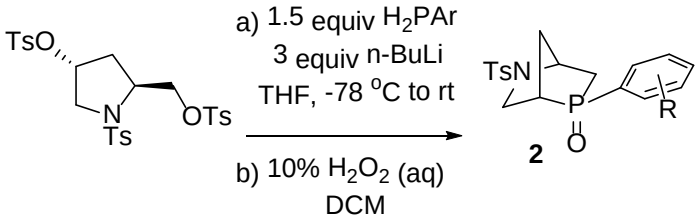
The aforementioned improvements to the phenylphosphine workup allowed for the preparation of larger quantities of the chiral phosphines. The more efficient synthesis also allowed observation and isolation of the two diastereomers of the catalysts. This procedure was applicable to a family of *P*-chiral phosphines bearing exocyclic substituents either in the exo- or endo- configuration, identified as *S* or *R* stereocenters, respectively. **Figure 3.1** shows the ratios of *R* to *S* phosphines as determined by crude ^{1}H NMR and ^{31}P NMR. Not all of the phosphine oxides prepared have been isolated, but those that have are presented in **Table 3.1**.

Figure 3.1: Ratio of *R* to *S* Phosphines Determined by Crude NMR



Ar	ratio *S:R*
phenyl	1:0.6
***p*-F-phenyl**	1:1
***p*-MeO**	1:0.6
1-naphthyl	1:1.2
2-naphthyl	1:0.5

Table 3.1: Synthesis of Chiral [2.2.1] Bicyclic Phosphine Oxides

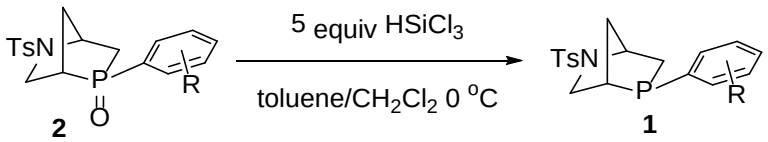


entry	Ar	Isomer	Product	Yield (%)[a]
1	phenyl	*R*	**2a**	50
2	phenyl	*S*	***epi*-2a**[b]	49
3	*p*-F-phenyl	*R*	**2c**	69
4	*p*-MeO	*R*	**2d**	45
5	1-naphthyl	*R*	**2e**	35
6	1-naphthyl	*S*	***epi*-2e**[b]	5
7	2-naphthyl	*R*	**2f**	87

[a] Isolated yield. [b] Epimer at the P-chiral center.

Reduction of the protected phosphines with trichlorosilane proceeded smoothly, but still produced inconsistent results. Preliminary work with the catalyst showed that a cesium fluoride additive boosted both yields and *ee* of the dihydropyrrolidine products. Careful examination of the reduction reaction showed an irregularity in the consistency of the material, presumed to be silane by products. After quenching of the silane reduction with aqueous sodium bicarbonate under argon, the CsF additive was found to be unnecessary. These modifications led to the preparation of analytically pure catalyst (**Table 3.2**).

Table 3.2: Reduction of Chiral [2.2.1] Bicyclic Phosphine Oxides to Active Catalysts



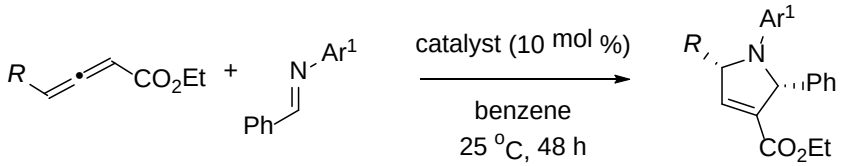
entry	Ar	Isomer	Product	Yield (%)[a]
1	phenyl	*R*	**1a**	>99
2	phenyl	*S*	***epi*-1a**[b]	99
3	*p*-F-phenyl	*R*	**1b**	98
4	*p*-MeO	*R*	**1c**	>99
5	1-naphthyl	*R*	**1d**	92
7	2-naphthyl	*R*	**1e**	80

[a] Isolated yield. [b] Epiomer at the P-chiral center.

B. Substrate Optimization of the Phosphine-Catalyzed [3 + 2] Annulation of Allenoates and Imines

With phosphine **1a** in hand, we renewed our exploration of the asymmetric catalysis of Lu's [3 + 2] allenoate–imine annulation. Using the (*R*)-*P*-stereoisomer catalyst the initial reaction of ethyl allenoate with *N*-tosyl imine afforded dihydropyrrole **3a** in 96% yield and 54% *ee* (**Table 3.2**, entry 1). Several γ-alkyl substituted allenoates were tested and afforded exclusively 2,5-*cis*-disubstituted dihydropyrroles with increasing *ee* with the size of the γ-substituent (**Table 3.2**, entries 2–5). Further improvement of enantioselectivity could be obtained by using imines with different *N*-sulfonyl substituents (**Table 3.2**, entries 6–9), the best of which was obtained using *p*-nitro-phenyl benzylsulfonimine, entry 11 (97% yield, 97% *ee*). Examination of different aryl groups on the phosphine showed no improvement, with *p*-MeO **1c** being comparable to phenyl **1a** (Table 4, entry 11).

Table 3.2: Substrate Optimization [3 + 2] Annulation of Allenoates and Imines



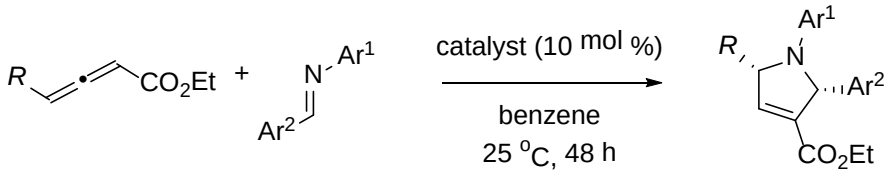
Entry	catalyst	R	Ar^1	Product	Yield (%)[a]	*ee* (%)[a]
1	**1a**	H	*p*-tolyl	**3a**	96	54
2	**1a**	Me	*p*-tolyl	**3b**	62	25
3	**1a**	Et	*p*-tolyl	**3c**	73	38
4	**1a**	*i*Pr	*p*-tolyl	**3d**	80	56
5	**1a**	*t*Bu	*p*-tolyl	**3e**	96	73
6	**1a**	*t*Bu	*p*-MeO-C_6H_4	**3f**	99	42
7	**1a**	*t*Bu	Ph	**3g**	91	54
8	**1a**	*t*Bu	*p*-Cl-C_6H_4	**3h**	88	90
9	**1a**	*t*Bu	*p*-NO_2-C_6H_4	**3i**	97	97
10	**1b**	*t*Bu	*p*-NO_2-C_6H_4	**3i**	87	86
11	**1c**	*t*Bu	*p*-NO_2-C_6H_4	**3i**	97	97
12	**1d**	*t*Bu	*p*-NO_2-C_6H_4	**3i**	79	85
13	**1e**	*t*Bu	*p*-NO_2-C_6H_4	**3i**	95	96

[a] Isolated yield. [b] *ee* determined by HPLC using a REGIS (R,R) DACH DNB chiral column.

C. Survey of the Asymmetric Phosphine-Catalyzed [3 + 2] Annulation of Allenoates and Imines

Using the newly optimized conditions, a number of 2,5-*cis*-disubstituted dihydropyrroles were accessible in high yield and enantiomeric excess (**Table 3.3**). Gratifyingly, the optimized conditions could be used with a number of γ-substituted allenoates (entries 1–6). The reaction was found to be general for substitutions on the phenyl (Ar^3) of the benzylsulfonimines (entries 7–9), as well as showing little deviation with electron withdrawing groups (entries 9–14). However, some loss of enantioselectiviy and reduced yields were seen with electron donating groups (entries 15–16). The reaction maintained its high yield and enantioselectivity with synthetically complex imine **3z** and geranylgeranyl transferase inhibitor dihydropyrrole **3aa** (entries 17–18).[8]

Table 3.3: Asymmetric Synthesis of 2,5-*cis*-disubstituted Dihydropyrroles



entry	R	Ar^1	Ar^2	Product	Yield (%)[a]	*ee* (%)[b]
1	H	*p*-NO_2-C_6H_4	Ph	**3j**	69	27
2	Me	*p*-NO_2-C_6H_4	Ph	**3k**	89	37
3	Et	*p*-NO_2-C_6H_4	Ph	**3l**	81	65
4	*iPro*	*p*-NO_2-C_6H_4	Ph	**3m**	88	67
5	CyP	*p*-NO_2-C_6H_4	Ph	**3n**	84	69
6	CyH	*p*-NO_2-C_6H_4	Ph	**3o**	58	65
7	*t*Bu	*p*-NO_2-C_6H_4	*o*-Cl-C_6H_4	**3p**	80	99
8	*t*Bu	*p*-NO_2-C_6H_4	*m*-Cl-C_6H_4	**3q**	93	93
9	*t*Bu	*p*-NO_2-C_6H_4	*p*-Cl-C_6H_4	**3r**	72	94
10	*t*Bu	*p*-NO_2-C_6H_4	*p*-Br-C_6H_4	**3s**	74	94
11	*t*Bu	*p*-NO_2-C_6H_4	*p*-F-C_6H_4	**3t**	78	94
12	*t*Bu	*p*-NO_2-C_6H_4	*p*-CF_3-C_6H_4	**3u**	93	97
13	*t*Bu	*p*-NO_2-C_6H_4	*p*-CN-C_6H_4	**3v**	83	94
14	*t*Bu	*p*-NO_2-C_6H_4	*p*-NO_2-C_6H_4	**3w**	89	92
15	*t*Bu	*p*-NO_2-C_6H_4	*p*-Me-C_6H_4	**3x**	75	87
16	*t*Bu	*p*-NO_2-C_6H_4	*p*-MeO-C_6H_4	**3y**	57	43
17	*t*Bu	*p*-NO_2-C_6H_4	6-Br-3,4-OCH_2O-C_6H_4	**3z**	72	81
18	*t*Bu	*o*-tolyl	*p*-Cl-C_6H_4	**3aa**	99	79

[a] Isolated yield. [b] *ee* determined by HPLC using a REGIS (R,R) DACH DNB chiral column.

With the efficiency of the (*R*)-*P*-phenyl stereoisomer catalyst established, the (*S*)-*P*-phenyl stereoisomer catalyst was examined. On the optimized system (R = *t*Bu, Ar^1 = *p*-NO_2-C_6H_4) the annulation succeeded with a yield of 99% and the enantio-enrichment was found to be >99%. Not unexpectedly, the chiral induction was found to give the enantiomerically opposite 2,5-*cis*-disubstituted dihydropyrrole relative to the (*S*)-*P*-phenyl stereoisomer. Further screening of the (*S*)-*P*-phenyl stereoisomer catalyst is being carried out by Dr. Xu.

D. De-tosylation and in situ *N*–Benzylation

Extending knowledge about the functionality of the catalyst, the role of the nitrogen in the catalyst ring system was also considered. Deprotection of the *p*-toluenesulfonamide to the free amine proved to be recalcitrant to most standard conditions.[9] The statement by Dr. Bergmeier: "Removal of *N*-tosyl groups is substrate dependent," held true for this system,[9a] with the majority of conditions leading to decomposition, quaternization of the amine, or the high polarity of the de-tosylated system being completely miscible in water.

It was decided to trap the amine during the de-tosylation reaction. With the use of sodium naphthalide, an anionic nitrogen is produced from the cleavage which is generally quenched with a proton. The anionic nitrogen can also be trapped in a nucleophilic substitution reaction, as in intramolecular epoxide opening shown by McIntosh and Matassa.[9b] The in situ deprotection with sodium naphthalide and subsequent alkylation with benzylbromide gave access to the *N*-benzyl (*R*)-*P*-phenyl catalyst (**Scheme 3.2**). Unlike the parent catalyst, the *N*-benzyl (*R*)-*P*-phenyl catalyst allows the [3 + 2] annulation to proceed with imines other than the *p*-NO_2-sulfonimine, while still maintaining high yields and enantiomeric enrichment (**Table 3.4**).

Scheme 3.2: Synthesis of *N*-benzyl (*R*)-*P*-phenyl Catalyst

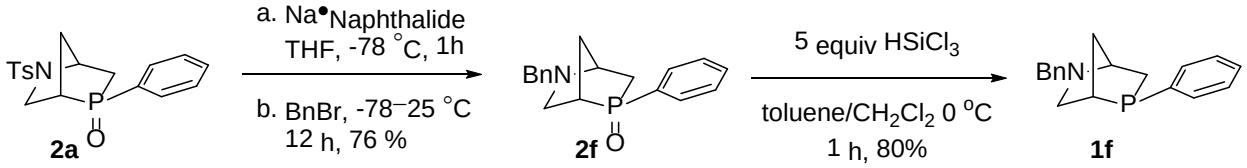
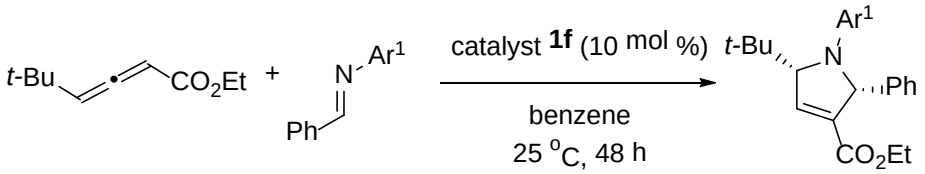


Table 3.4: Reactivity of *N*-benzyl (*R*)-*P*-phenyl Catalyst with Sulfonimines



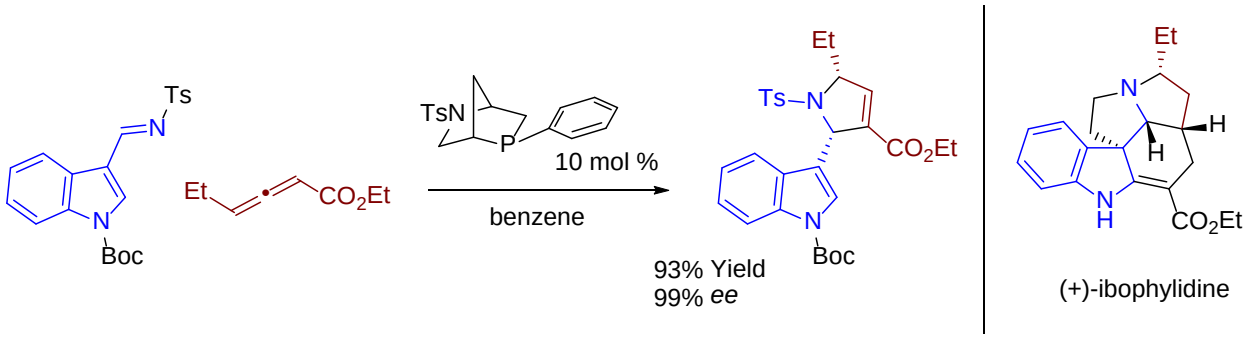
entry	Ar^1	Product	Yield (%)[a]	*ee* (%)[b]
1	*p*-tolyl	**3e**	94	89
2	Ph	**3f**	89	89.9
3	*p*-MeO-C_6H_4	**3g**	90	83.5
4	*p*-Cl-C_6H_4	**3h**	99	94.4
5	*p*-NO_2-C_6H_4	**3i**	96	96.2

[a] Isolated yield. [b] *ee* determined by HPLC using a REGIS (R,R) DACH DNB chiral column.

III. Conclusion

In summary, development of a new class of rigid chiral [2.2.1] bicyclophosphines, which proved to be highly effective catalysts for the asymmetric synthesis of 2,5-*cis*-disubstituted dihydropyrroles, has been achieved.[10] In some cases, both *P*-centered diastereomers of this catalyst have been isolated, offering the potential for complimentary stereoselectivity. In addition, the *N*-alkylated catalyst showed reduced substrate sensitivity. This constitutes the first report of phosphine-catalyzed asymmetric access to dihydropyrroles with this substitution pattern. As proof of the efficacy of this catalyst, it has been applied in the key asymmetric step for the total synthesis of (+)-ibophyllidine (**Scheme 3.2**).[11]

Scheme 3.2: Application of Phosphine 3a in the Total Synthesis of (+)-ibophyllidine



Experimental Section

General Information

All reactions were performed under argon atmospheres with dry solvents and anhydrous conditions, unless otherwise noted. THF was distilled over sodium/benzophenone ketyl; CH_2Cl_2, toluene, and benzene were distilled from CaH_2. Reactions were monitored by thin layer chromatography (TLC) on 0.25-mm E. Merck silica gel plates (60F-254) and visualized under UV light or through anisaldehyde or permanganate staining. Flash column chromatography was performed using E. Merck silica gel 60 (230–400 mesh) and compressed air. IR spectra were recorded on a Perkin–Elmer pargon 1600 FT-IR spectrometer. NMR spectra were obtained on Bruker Avance-500, ARX-500, or ARX-400 instruments as indicated, calibrated using residual $CHCl_3$ as the internal reference (7.26 ppm for ^{1}H NMR; 77.00 ppm for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift, multiplicities, and coupling constants (Hz) in the case of J_{CF} or J_{CP} coupling. For compounds **1e** and **2e**, the ^{13}C NMR chemical shifts are listed without assignment of their J_{CP} couplings. The following abbreviations are used for the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; app = apparent. High-resolution matrix-assisted laser desorption/ionization (MALDI) mass spectra were recorded from a dihydroxybenzoic acid (DHB) matrix using an IonSpec Ultima 7T FT-ICR-MS instrument with internal calibration. Gas chromatography-coupled mass spectra (EI) were obtained on an Agilent 6890-5975. Optical rotations were determined using an Autopol IV polarimeter and a 50-mm cell at concentrations close to 1 g/100 mL. Most values of ee were determined through chiral HPLC using a Shimadzu CBM Lite system and a REGIS (*R*,*R*)-DACH DNB analytical (4.5 mm diameter) chiral column

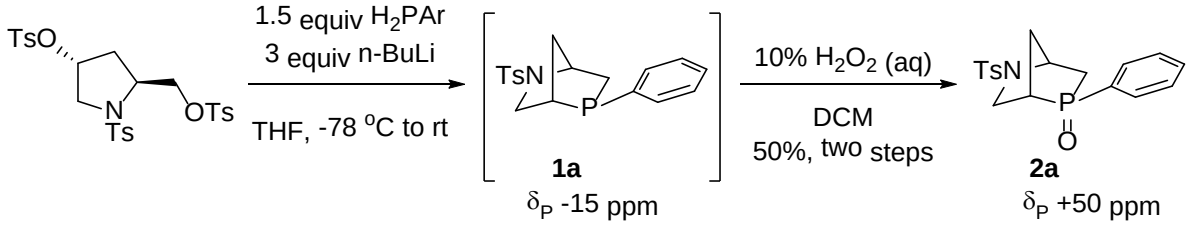
under the conditions indicated in Tables S2 and S3. Enantiopurity for compounds **3q** and **3z** was carried out on a Mettler Toledo SFC (supercritical fluid chromatography) using a Chiral OJ-H column.

General Procedures

Synthesis of Protected Catalysts

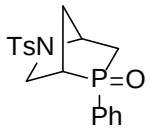
Bicyclic phosphine oxides **1a–e** were prepared through alkylation of a primary arylphosphine with the tritosyl prolinol derivative, prepared in three steps from *trans*-4-hydroxyproline (tosylation of the amine; borane reduction of the carboxylic acid; bistosylation of the newly formed diol; three steps, 90% yield) using a literature procedure.[6] The alkylation was performed following a modified procedure for the generation of dilithiophenylphosphine.[2a] Air-sensitive primary phosphines were prepared through reduction of the corresponding aryl phosphonate or dichloroarylphosphine and were used after a single distillation.[12]

The synthesis of **1a** is described as a typical procedure for the preparation of the bicyclic phosphine oxides **1**:



A flame-dried 500-mL Schlenk flask was charged with THF (300 mL). Phenylphosphine (3.4 g, 31 mmol) was added to the flask via syringe. The solution was cooled in an acetone/$CO_{2(S)}$ bath. After cooling, *n*-BuLi (1.5 M in hexanes; 38.9 mL, 62 mmol) was added dropwise over 1–1.5 h. The solution turned a bright yellow/orange color. The cold bath was removed and the solution was warmed to room temperature and stirred for an additional 60 min.

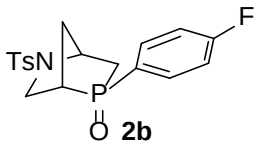
During this time the color of the solution darkened slightly, but remained yellow/orange in tone. In a second round-bottom flask, the tritosyl compound (12.0 g, 21 mmol) was weighed and dissolved in THF (100 mL). The solution was cannulated into the solution of dilithiophenylphosphine and then the reaction was left to stir for 48 h. The progress of the reaction was monitored using TLC (disappearance of tritosyl starting material); crude ^{31}P NMR spectroscopy confirmed the appearance of a single new phosphorus peak (δ_P = –15 ppm). The reaction mixture was worked up through the addition of a saturated NH_4Cl solution followed by extraction five times with diethyl ether. The combined organic phases were dried and concentrated to afford a white gum, which was dissolved in CH_2Cl_2 (100 mL) and treated with 10% H_2O_2 solution (30 mL). After 30 min, the reaction mixture was worked up by extraction of the aqueous layer three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford a very thick white gum, which was further purified through recrystallization (EtOAc/toluene) to afford **2a** (6.06 g, 16.8 mmol, 50%) as a white solid: IR (film) ν_{max} 3059, 2990, 2881, 1595, 2360, 1436, 1341, 1223, 1180 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.72–7.68 (m, 2H), 7.57–7.53 (m, 1H), 7.50–7.47 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.58 (d, *J* = 26.7 Hz, 1H), 4.14 (dd, *J* = 13.9, 9.5 Hz, 1H), 3.52 (ddd, *J* = 25.0, 9.5, 4.7 Hz, 1H), 2.82 (br s, 1H), 2.42 (s, 3H), 2.34–2.19 (m, 1H), 2.13–2.07 (m, 1H), 1.74–1.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 135.9, 132.4 (d, J_{CP} = 3 Hz), 131.7 (d, J_{CP} = 93 Hz), 130 (d, J_{CP} = 10 Hz, 2C), 129.9 (2C), 129.0 (d, J_{CP} = 12 Hz, 2C), 127.4 (2C), 59.0, 46.4 (d, J_{CP} = 7 Hz), 39.5 (d, J_{CP} = 66 Hz), 35.5 (d, J_{CP} = 11 Hz), 34.5 (d, J_{CP} = 64 Hz), 21.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ 50.5; HRMS (MALDI) calcd for $C_{18}H_{20}NO_3PSNa$ $[M + Na]^+$ 384.0794, found 384.0805.



***epi*-2a**

Phosphine *epi*-2a

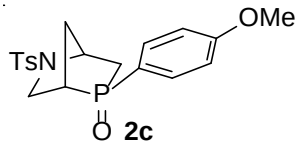
49%; yellow oil; IR (film) ν_{max} 3061, 2978, 2877, 1595, 1438, 1343 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (t, *J* = 10 Hz, 2H), 7.68 (d, *J* = 4 Hz, 2H), 7.54 (d, *J* = 8 Hz, 1H), 7.46 (s, 2H), 7.30 (d, *J* = 8 Hz, 2H), 4.59 (d, *J* = 28 Hz, 1H), 3.08–2.92 (m, 2H), 2.62 (s, 1H), 2.60 (s, 1H), 2.37 (s, 3H), 2.33 (d, *J* = 12 Hz, 1H), 2.12 (t, *J* = 16 Hz, 1H), 1.50 (dd, *J* = 28, 12 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 134.4, 132.6, 131.2 (d, J_{CP} = 12.5 Hz), 129.9, 128.9, 128.7, 128.2, 127.3, 127.1, 58.9, 58.8, 47.8, 40.2, 39.5 (d, J_{CP} = 12.5 Hz), 38.8, 36.0 (d, J_{CP} = 12.5 Hz), 21.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ 50.5; HRMS (ESI) calcd for $C_{18}H_{20}NO_3PSNa$ $[M + H]^+$ 362.0974, found 362.0959.



2b

Phosphine Oxide 2b

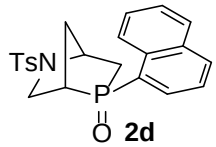
69% yield; white solid; IR (film) ν_{max} 2985.4, 2883.1, 1928.2, 15.95.3, 1503.5, 1347.1 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 5 Hz, 2H), 7.70 (m, 2H), 7.31 (d, *J* = 5 Hz, 2H), 7.15 (dt, *J* = 8.5, 2.0 Hz, 2H), 4.55 (d, *J* = 25 Hz, 1H) , 4.11 (q, *J* = 8.3 Hz, 1H) , 3.46 (dq, *J* = 25, 5 Hz, 1H) , 2.77 (s, 1H) , 2.38 (s, 3H) , 2.18–2.09 (m, 2H), 1.60 (m, 2H); ^{13}C (125 MHz, $CDCl_3$) δ 135.4, 132.9, 132.83, 132.81, 132.7, 129.8, 127.9 (d, J_{CP} = 3.8 Hz), 127.2, 127.1 (d, J_{CP} = 3.8 Hz), 39.8, 39.3, 35.4 (d, J_{CP} = 11.2 Hz), 35.1, 34.6; ^{31}P (202 MHz, $CDCl_3$) δ 41.8; HRMS (ESI) calcd for $C_{18}H_{19}FNO_3PS$ $[M + H]^+$ 380.0880, found 380.0880.



2c

Phosphine Oxide 2c

45% yield; white solid; IR (film) ν_{max} 2978.54, 2885.1, 2841.3, 2222.1, 1916.6, 1597.1, 1505.1, 1341.7 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 10 Hz, 2H), 7.63 (q, *J* = 6.7 Hz, 2H), 7.34 (d, *J* = 5 Hz, 2H), 6.99 (dd, *J* = 9, 2.5 Hz, 2H), 4.58 (d, *J* = 25 Hz, 1H), 4.14 (dd, *J* = 15, 10 Hz, 1H), 3.84 (s, 3H), 3.52 (dq, *J* = 25, 10 Hz, 1H), 2.77 (s, 1H), 2.42 (s, 3H), 2.17 (m, 1H), 2.08 (m, 1H), 1.72 (s, 1H), 1.61 (s, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 162.7, 143.7, 135.8, 132.2 (2C), 132.1 (2C), 129.7 (2C), 127.3 (2C), 114.4 (d, J_{CP} = 12.5 Hz), 58.8, 55.3, 46.3 (d, J_{CP} = 12.5 Hz), 39.9, 39.4, 35.4 (d, J_{CP} = 10 Hz), 34.4 (d, J_{CP} = 65 Hz); ^{31}P (202 MHz, $CDCl_3$) δ 41.8; HRMS (ESI) calcd for $C_{19}H_{22}NO_4PS$ $[M + H]^+$ 392.1080, found 392.1097.

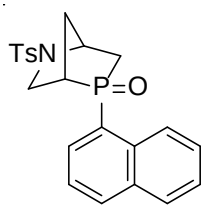


2d

Phosphine Oxide 2d

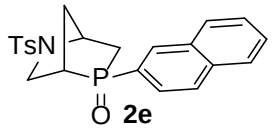
35% yield; white solid; IR (film) ν_{max} 3060.1, 2978.4, 2953.9, 2880.4, 2223.1, 1595.7, 1505.8, 1343.2 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 8.46 (d, *J* = 10 Hz, 1H), 8.01 (d, *J* = 8 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8 Hz, 2H), 7.62 (m, 3H), 7.47 (m, 1H), 7.34 (d, *J* = 8 Hz, 2H), 4.53 (d, *J* = 27 Hz, 1H), 4.28 (q, *J* = 8 Hz, 1H), 3.64 (dq, *J* = 15, 25 Hz, 1H), 3.27 (s, 1H), 2.42 (s, 3H), 2.31 (d, *J* = 10.5 Hz, 2H), 1.64 (m, 2H); ^{13}C (125 MHz, $CDCl_3$) δ 143.7, 135.7, 133.9 (d, J_{CP} = 8.9 Hz), 133.3 (d, J_{CP} = 2.5 Hz), 132.5 (d, J_{CP} = 7.5 Hz), 129.8, 129.1, 128.6,

128.5, 128.2, 127.9, 127.5, 127.3, 126.9, 126.0 (d, J_{CP} = 6.2 Hz), 124.2 (d, J_{CP} = 13.7 Hz), 45.9 (d, J_{CP} = 6.3 Hz), 38.1 (d, J_{CP} = 67.5 Hz), 36.0 (d, J_{CP} = 56.3 Hz), 35.5 (d, J_{CP} = 10 Hz), 21.5; ^{31}P (202 MHz, $CDCl_3$) δ 51.4; HRMS (ESI) calcd for $C_{22}H_{22}NO_3PS$ $[M + H]^+$ 412.1094, found 412.1105.



***epi*-2d**

Phosphine *epi*-2d: 5% yield; white solid; IR (film) ν_{max} 3050, 2978, 2875, 1596, 1506, 1402, 1342 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4 Hz, 1H), 8.01 (d, *J* = 8 Hz, 1H), 7.89 (d, *J* = 4 Hz, 1H), 7.77 (dd, *J* = 12, 4 Hz, 1H), 7.55 (dt, *J* = 5.3, 5.3 Hz, 4H), 7.42 (dt, *J* = 8, 2 Hz, 1H), 7.22 (d, *J* = 4 Hz, 2H), 4.58 (d, *J* = 20 Hz, 1H), 3.05–2.93 (m, 3H), 2.53 (dd, *J* = 12, 8 Hz, 1H), 2.45 (dd, *J* = 12, 4 Hz, 1H), 2.35 (s, 3H), 2.15 (t, *J* = 16 Hz, 1H), 1.61 (dd, *J* = 24, 8 Hz, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 143.8, 134.8, 133.6 (d, J_{CP} = 2.5 Hz), 133.5, 133.3 (d, J_{CP} = 12.5 Hz), 131.1 (d, J_{CP} = 12.5 Hz), 127.8, 127.0, 126.8, 125.9 (d, J_{CP} = 2.5 Hz), 124.8, 124.6, 124.5, 124.0, 57.9, 47.6 (d, J_{CP} = 2.5 Hz), 40.1, 39.6, 38.0, 37.4, 35.5, 35.4, 21.4; ^{31}P (202 MHz, $CDCl_3$) δ 55.2; HRMS (ESI) calcd for $C_{22}H_{22}NO_3PS$ $[M + H]^+$ 412.1131, found 412.1136.

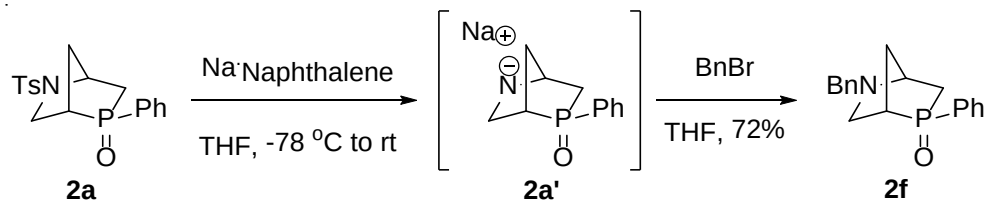


2e

Phosphine Oxide 2e

87% yield; white solid; IR (film) ν_{max} 3060, 2991, 1595, 1436, 1341, 1223 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 13.5 Hz, 1H), 7.94 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.89 (dd, *J*

= 13.0, 8.0 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 8.75 (t, *J* = 8.8 Hz, 1H), 7.59 (dt, *J* = 18.0, 7.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.64 (brd, *J* = 27 Hz, 1H), 4.21 (dd, *J* = 14.0, 9.5 Hz, 1H), 3.55 (ddd, *J* = 25.3, 9.7, 5.5 Hz, 1H), 2.91 (brs, 1H), 2.43 (s, 3H), 2.37–2.16 (m, 2H), 1.83–1.40 (m , 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 135.8, 134.7, 132.4, 132.3, 132.25, 132.17, 129.9, 129.1, 128.98, 128.91, 128.8, 128.6, 128.2, 127.8, 127.4, 127.3, 125.05, 124.97, 59.0, 46.5, 46.4, 39.9, 39.4, 35.7, 35.6, 34.9, 34.4, 21.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ 50.9; HRMS (MALDI) calcd for $C_{22}H_{22}NO_3PSNa$ $[M + Na]^+$ 434.0950, found 434.0954.

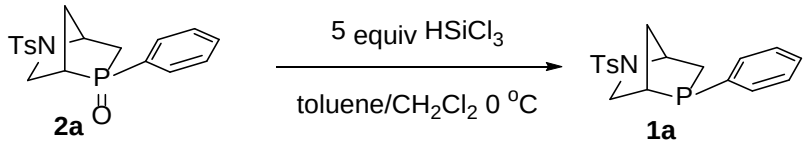


Phosphine Oxide 2f: A solution of phosphine **2a** (0.1 g, 0.28 mmol) in dry THF (5 mL) was cooled to –78 ^{0}C. A 1.3 M solution of sodium naphthalide in dry THF was added in 1 mL increments every 10 minutes until **2a** was consumed [TLC 10% MeOH in EtOAc; R_f = ca. 0.5 (spot)]. The reaction was stirred for 1h. Following warming of the reaction to room temperature, one equivalent of benzylbromide (0.05 g, 0.28 mmol) was injected into the solution. The reaction was stirred for 3 h where the disappearance of **2a'** [TLC 10% MeOH in DCM; R_f = 0 (spot), stains brown in I_2] and the appearance of **2f** [TLC 10% MeOH in DCM; R_f = ca. 0.5 (spot), stains yellow-brown in I_2] were observed. Upon completion of the reaction, the resulting mixture was concentrated in vacuo and the residue purified by flash chromatography on silica gel (2% Et_3N and 10% MeOH in EtOAc) to give crude phosphine **2f** as a yellow solid. This material was further purified by recrystallization (EtOAc) to afford phosphine **2f** (0.06 g, 72%) as a white solid: IR (film) ν_{max} 3433.9, 3057.8, 3027.1, 2962.4, 2859.7, 2217.2, 1436.3, 1334.9 cm^{-1}; ^{1}H

(500 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.52 (m, 3H), 7.41 (d, J = 1.9 Hz, 2H), 7.33 (t, J = 1.9 Hz, 2H), 7.24 (d, J = 1.8 Hz, 1H), 3.92 (q, J = 2.5 Hz, 1H), 3.63 (d, J = 7.0 Hz, 1H), 3.56 (dd, J = 4.2, 2.6 Hz, 1H), 2.74 (s, 1H), 2.22 (m, 2H), 2.03 (m, 1H), 1.77 (dd, J = 2.5, 1.3 Hz, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 139.3, 131.8, 130.2 (d, J_{CP} = 9.2 Hz), 128.8, 128.7, 128.4, 128.2, 126.9, 60.2, 57.5, 49.8, 49.7, 39.3 (d, J_{CP} = 66.5), 34.9, 34.8, 29.9 (d, J_{CP} = 62.5); ^{31}P (202 MHz, $CDCl_3$) δ 52.3; HRMS (ESI) calcd for $C_{18}H_{20}NPO$ $[M + H]^+$ 298.1361, found 298.1355.

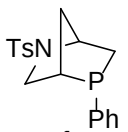
Reductive Deprotection of Phosphines

Chiral phosphines **2** of purity suitable for direct use in catalysis were prepared through reduction of the corresponding phosphine oxides **3** with trichlorosilane. This highly selective and efficient method is practical for the preparation of air-sensitive phosphines because the reagents are volatile and can be removed through simple evaporation.[13] As an example, the reduction of phosphine oxide **2a** to afford phosphine **1a** is provided.



In a 250-mL round-bottom flask under argon, the recrystallized phosphine oxide **2a** (200 mg, 0.55 mmol) was dissolved in a mixture of toluene and CH_2Cl_2 (1:1, 40 mL). The solution was cooled in an ice bath. Freshly redistilled trichlorosilane (279 μL, 2.8 mmol; b.p. 32–34 °C) was added via microsyringe. The disappearance of **2a** [TLC in CH_2Cl_2: R_f = ca. 0.1 (streak)] and the appearance of **1a** [TLC in CH_2Cl_2: R_f = ca. 0.7 (spot), stains white in a standard anisaldehyde stain] were monitored using TLC. The reaction mixture was stirred at 0 °C for 60 min and then it was warmed to room temperature. After an additional 60 min, the reaction was complete (TLC). The solution remained clear for the duration of the reaction. The CH_2Cl_2 and excess

trichlorosilane were removed through azeotropic distillation under argon (oil bath temperature: 90 °C). The solution was further concentrated through rotary evaporation under reduced pressure with argon replenishment to afford **1a** as a white powder, which was redissolved in CH_2Cl_2 and treated with saturated $NaCO_3$ solution. The resulting mixture was dried (Na_2SO_4), cannulated to a dried flask, then repeated twice more with CH_2Cl_2, combined organic phases were concentrated through rotary evaporation with argon replenishment to afford **1a** as a fine white powder (192 mg, quantitative) that was sufficiently pure to be used directly as a catalyst: IR (film) ν_{max} 2966, 2863, 1434, 1342 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.36–7.29 (m, 4H), 7.28–7.21 (m, 4H), 4.47 (d, *J* = 10.4 Hz, 1H), 3.39–3.32 (m, 2H), 2.75 (dm, *J* = 10.6 Hz, 1H), 2.47–2.38 (m, 1H), 2.44 (s, 3H), 1.95–1.91 (m, 1H), 1.90–1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 139.9 (d, J_{CP} = 25 Hz), 135.7, 129.70 (2C), 129.69 (d, J_{CP} = 14 Hz, 2C), 128.5 (d, J_{CP} = 4 Hz, 2C), 127.7, 127.3 (2C), 59.4 (d, J_{CP} = 2 Hz), 51.4 (d, J_{CP} = 19 Hz), 38.0 (d, J_{CP} = 14 Hz), 36.7 (d, J_{CP} = 4 Hz), 34.0 (d, J_{CP} = 21 Hz), 21.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ –15.7; HRMS (MALDI) calcd for $C_{18}H_{21}NO_2PS$ $[M + H]^+$ 346.1025, found 346.1019.

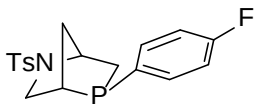


***epi*-1a**

Phosphine *epi*-1a

99%; white powder; IR (film) ν_{max} 3053, 2970, 2915, 2864, 1594, 1433, 1340, 1170, 1151 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.40 (s, 2H), 7.31–7.26 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.48 (s, 1H), 3.09 (d, *J* = 8.0 Hz, 1H), 2.98 (d, *J* = 12.0 Hz, 1H), 2.62 (d, *J* = 28.0 Hz, 1H), 2.35 (s, 3H), 2.17 (d, *J* = 12.0 Hz, 1H), 1.98 (t, *J* = 18.0 Hz, 1H), 1.57 (t, *J* = 8.0 Hz, 1H), 1.36 (dd, *J* = 28.0, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2,

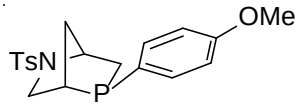
135.6, 132.0 (d, J_{CP} = 12.5 Hz), 129.6 (s, 2C), 128.7 (s, 2C), 128.4 (s, 2C), 127.1 (s, 2C), 60.5, 50.7, 37.8, 36.5, 36.3, 29.2, 12.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ –17.2; HRMS (ESI) calcd for $C_{18}H_{20}NO_2PS$ $[M + H]^+$ 346.1025, found 346.1016.



1b

Phosphine 1b

98% yield; white solid; IR (film) ν_{max} 2961.4, 2930.0, 2872.8, 1723.2, 1595.3, 1499.4 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 10 Hz, 2H), 7.31 (d, *J* = 5 Hz, 2H), 7.20 (m, 2H), 7.00 (m, 2H), 4.46 (d, *J* = 10 Hz, 1H), 3.33 (m, 2H), 2.69 (d, *J* = 9 Hz, 1H), 2.43 (m, 1H), 2.41 (s, 3H), 1.87 (dt, *J* = 15, 5 Hz, 1H), 1.35 (s, 2H); ^{13}C (125 MHz, $CDCl_3$) δ 163.4, 161.45, 143.4, 135.5, 135.13, 135.10, 131.65, 131.59, 131.52, 131.46, 129.6, 127.2, 59.22 (d, J_{CP} = 2.5 Hz), 51.31 (d, J_{CP} = 20 Hz), 38.11 (d, J_{CP} = 13.7 Hz), 36.44 (d, J_{CP} = 3.8 Hz), 34.2, 34.1; ^{31}P (202 MHz, $CDCl_3$) δ –17.5; HRMS (ESI) calcd for $C_{18}H_{19}FNO_2PS$ $[M + H]^+$ 364.0931, found 364.0917.

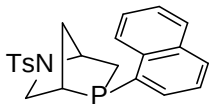


1c

Phosphine 1c

100% yield; white solid; IR (film) ν_{max} 2961.4, 2930.1, 2873.1, 2837.2, 1723.9, 1595.3, 1499.4, 1341.3 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 5 Hz, 2H), 7.31 (d, *J* = 10 Hz, 2H), 7.21 (s, 2H), 6.86 (d, *J* = 10 Hz, 2H), 4.48 (d, *J* = 10 Hz, 1H), 3.77 (s, 3H), 3.35 (m, 2H), 2.68 (d,

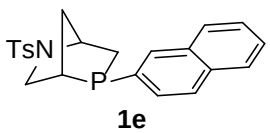
10.0 Hz, 1H), 2.44–2.30 (m, 4H), 1.94–1.85 (m, 1H), 1.42–1.45 (m, 1H), 1.36–1.42 (m, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 159.6, 143.4 (2C), 135.6, 131.7, 131.5, 129.7 (2C), 127.3 (2C), 114.3 (2C), 59.2, 55.2, 51.4 (d, J_{CP} = 21.3 Hz), 38.2 (d, J_{CP} = 12.5 Hz), 36.3, 33.7 (d, J_{CP} = 18.8 Hz), 21.4; ^{31}P (202 MHz, $CDCl_3$) δ –15.6; HRMS (ESI) calcd for $C_{19}H_{22}NO_3PS$ $[M + H]^+$ 376.1131, found 376.1129.



1d

Phosphine 1d

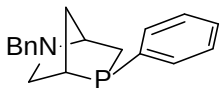
92% yield; white solid; IR (film) ν_{max} 3046.4, 2974.9, 2923.7, 1596.5, 1341.3 cm^{-1}; ^{1}H (500 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.84 (d, *J* = 6.5 Hz, 1H), 7.75 (m, 3H), 7.52 (m, 2H), 7.37 (t, *J* = 7.57 Hz, 1H), 7.32 (d, *J* = 10 Hz, 3H), 4.46 (d, *J* = 10 Hz, 1H), 3.52 (d, *J* = 6.7 Hz, 1H), 3.44 (dq, *J* = 14, 30 Hz, 1H), 2.97 (dd, *J* = 10, 5 Hz, 1H), 2.58 (dd, *J* = 32.5, 12.5 Hz, 1H), 2.43 (s, 3H), 1.98 (dt, *J* = 15, 10 Hz, 1H), 1.56 (d, *J* = 10 Hz, 1H), 1.39 (m, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 143.4, 136.5, 136.2, 135.6, 133.8, 133.7, 133.5 (d, J_{CP} = 2.5 Hz), 129.7, 129.0, 128.6, 127.3, 126.5, 126.05 (d, J_{CP} = 1.3 Hz), 126.02, 126.0, 124.8, 59.5, 51.7 (d, J_{CP} = 22.5 Hz), 36.7 (d, J_{CP} = 3.8 Hz), 36.0 (d, J_{CP} = 13.7 Hz), 34.3 (d, J_{CP} = 20 Hz), 21.4; ^{31}P (202 MHz, $CDCl_3$) δ –16.3; HRMS (ESI) calcd for $C_{22}H_{22}NO_2PS$ $[M + H]^+$ 396.1145, found 396.1279.



1e

Phosphine 1e

80% yield; white solid; IR (film) ν_{max} 2967, 2865, 1435, 1342 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.77 (m, 5H), 7.7 (d, *J* = 6.0 Hz, 1H), 7.52–7.50 (m, 2H), 7.49–7.31 (m, 3H), 4.56 (d, *J* = 10.0 Hz, 1H), 3.49–3.42 (m, 2H), 2.92–2.90 (m, 1H), 2.57–2.46 (m, 4H), 2.11–2.01 (m, 1H), 1.48–1.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 137.5, 137.3, 135.7, 133.1, 132.7, 129.7, 129.1, 129.0, 128.10, 128.06, 127.7, 127.5, 127.4, 126.9, 126.8, 126.6, 126.4, 59.4, 51.6, 51.4, 38.1, 38.0, 36.81, 36.78, 29.7, 21.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ –15.1; HRMS (MALDI) calcd for $C_{22}H_{22}NO_2PSNa$ $[M + Na]^+$ 418.1001, found 418.1012.



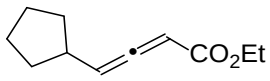
1f

Phosphine 1f

80% yield; IR (film) ν_{max} 2960, 2928, 2865, 1493, 1330 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.22 (m, 10H), 3.67 (q, *J* = 11.7 Hz, 1H), 3.09 (dq, *J* = 30.0 Hz, 5.0 Hz, 1H), 2.67 (dd, *J* = 10.0 Hz, 5.0 Hz,1H), 2.51 (dd, *J* = 20.0 Hz, 10.0 Hz, 1H), 2.44 (dd, *J* = 30.0 Hz, 10.0 Hz, 1H), 2.00 (t, *J* = 10.3 Hz, 1H), 1.78 (dq, *J* = 10 Hz, 3.0 Hz, 1H) 1.42, (d, *J* = 10 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9 (d, J_{CP} = 25 Hz), 139.7, 129.7, 129.6, 128.4, 128.3, 128.24, 128.20, 128.1, 128.0, 127.0, 126.6, 60.2, 57.9, 55.8 (d, J_{CP} = 25 Hz), 37.6 (d, J_{CP} = 12.5 Hz), 36.1, 29.0 (d, J_{CP} = 20 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ –19.8; HRMS (ESI) calcd for $C_{18}H_{20}NP$ $[M + H]^+$ 282.1391, found 282.1410.

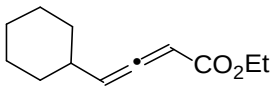
Allenoate Synthesis

Two new γ-substituted allenoates were prepared over the course of this study, using slightly modified literature procedures.[3c,d] The synthesis and spectral data for other allenoates has been reported previously.[14]



Ethyl 4-cyclopentyl-2,3-dienoate

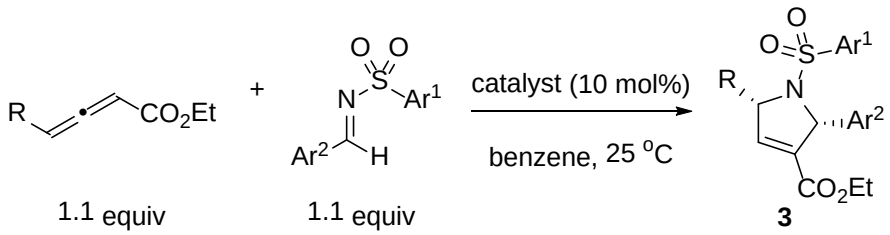
70%; faint yellow oil; IR (film) ν_{max} 2956, 2869, 1959, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60–5.58 (m, 2H), 4.21–4.13 (m, 2H), 2.20–2.14 (m, 1H), 1.81–1.15 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 166.3, 100.9, 88.9, 60.6, 36.5, 32.6, 32.5, 25.8, 25.6, 14.1; MS (GCMS) calcd for $C_{11}H_{16}O_2$ $[M]^+$ 180.1, found 180.2.



Ethyl 4-cyclohexyl-2,3-dienoate

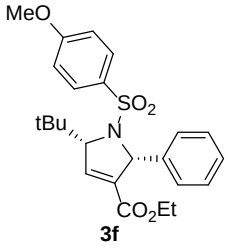
55%; faint yellow oil; IR (film) ν_{max} 2980, 2927, 2852 1959, 1717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (t, *J* = 6.3 Hz, 1H), 5.54 (dd, *J* = 6.1, 2.8 Hz, 1H), 4.19–4.08 (m, 2H), 2.59–2.54 (m, 1H), 1.81–1.38 (m, 10H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 166.1, 100.0, 88.8, 60.5, 38.0, 32.5, 24.5, 14.1; MS (GCMS) calcd for $C_{12}H_{18}O_2$ $[M]^+$ 194.1, found 194.2.

Phosphine-Catalyzed [3 + 2] Allenoate/Imine Annulation



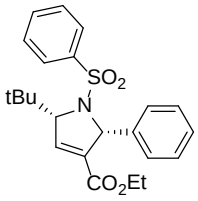
A round-bottom flask and septa were flame-dried and left to cool under argon. The imine (1.0 equiv) and the phosphine (0.1 equiv) were added quickly and weighed in the flask. Distilled benzene was added via syringe. The allenoate (1.1 equiv) was weighed in a syringe and added dropwise to the reaction mixture. After addition of all components, the contents were stirred at room temperature, typically for 48 h. The crude reaction mixture was loaded directly onto a silica gel column and separated chromatographically (hexane/EtOAc, 19:1). In all cases, the product stained brightly in a standard permanganate stain.

Compounds **3a**,[3a,b] **3b**, **3c**, **3d**, **3e**, and **3aa**[8b] have been synthesized previously; their spectral data are provided in the pertinent references. Complete spectral data are provided for the new compounds **3f**–**z**. **Table 3.5** summarizes the chiral HPLC conditions and data for compounds **3a**–**i**, and **Table 3.6** summarizes the chital HPLC conditions and data for compounds **3j–aa**.



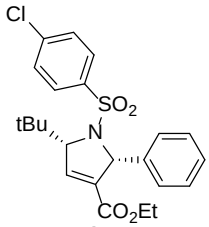
99%; clear oil; IR (film) ν_{max} 2965, 1720, 1596, 1497 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 6.9 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.31–7.24 (m, 3H), 7.25 (d, *J* = 6.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 5.87 (s, 1H), 4.34 (d, *J* = 2.3 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.85 (s,

3H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 162.7, 141.2, 139.8, 134.3, 130.1, 128.8, 128.05, 128.00, 127.5, 114.1, 77.8, 66.4, 60.9, 55.6, 35.9, 27.9, 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 466.1659, found 466.1669.



3g

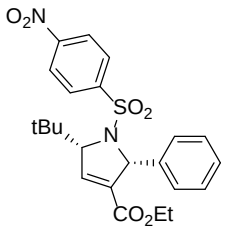
91%; clear oil; IR (film) ν_{max} 2956, 1720, 1444, 1328 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dm, *J* = 7.3 Hz, 2H), 7.59–7.55 (m, 1H), 7.49–7.46 (m, 2H), 7.42 (dm, *J* = 7.5 Hz, 2H), 7.30–7.25 (m, 3H), 6.72 (dd, *J* = 2.6, 1.3 Hz, 1H), 5.90 (s, 1H), 4.40 (d, *J* = 2.7 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 141.1, 139.6, 137.1, 134.3, 133.0, 129.2, 129.0, 128.1, 128.0, 127.6, 78.0, 68.4, 60.9, 35.9, 27.9, 14.0; HRMS (MALDI) calcd for $C_{23}H_{27}NO_4SNa$ $[M + Na]^+$ 436.1553, found 436.1550.



3h

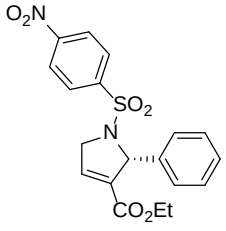
97%; white solid: m.p. 158–160 °C; IR (film) ν_{max} 2966, 1720, 1531, 1350 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.45–7.40 (m, 4H), 7.31–7.26 (m, 3H), 6.75 (dd, *J* = 2.7, 1.4 Hz, 1H), 5.89 (s, 1H), 4.37 (dd, *J* = 2.7, 0.7 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 140.8, 139.6, 139.3,

135.8, 134.3, 129.3, 128.1, 128.08, 128.05, 127.8, 78.1, 68.6, 61.0, 36.0, 27.9, 14.0; HRMS (MALDI) calcd for $C_{23}H_{26}ClNO_4SNa$ $[M + Na]^+$ 470.1163, found 470.1175.



3i

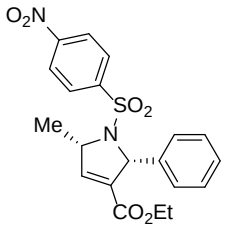
97%; yellow solid: m.p. 174–179 °C; IR (film) ν_{max} 2963, 2930, 1720, 1651, 1598, 1495, 1455, 1344 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.5, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.31 (dm, *J* = 7.8 Hz, 3H), 6.76 (s, 1H), 5.97 (s, 1H), 4.46 (s, 1H), 4.11 (q, *J* = 6.8 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 150.1, 143.3, 140.3, 138.8, 134.2, 129.0, 128.3, 128.13, 128.10, 124.1, 78.3, 68.9, 61.2, 36.2, 27.9, 14.0; HRMS (MALDI) calcd for $C_{23}H_{27}N_2O_6S$ $[M + H]^+$ 459.1584, found 459.1590.



3j

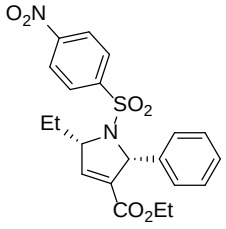
69%; white solid; IR (film) ν_{max} 2984, 1721, 1530, 1350, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.23 (m, *J* = 14.4 Hz, 1H), 7.16 (m, *J* = 16.4 Hz, 2H), 7.09 (m, *J* = 11.2 Hz, 2H), 6.87 (q, *J* = 2.0 Hz, 1H), 5.84 (d, *J* = 9.2 Hz, 1H), 4.69 (dt, *J* = 16.8, 2.8 Hz, 1H), 4.37 (ddd, *J* = 16.0, 5.6, 2.4 Hz, 1H), 3.95–4.15 (m, 2H), 1.10 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 149.5, 145.0, 138.2, 135.9,

134.9, 128.4 (2C), 127.9 (2C), 127.8 (2C), 123.7 (3C), 69.1, 60.9, 54.9, 13.8; HRMS (MALDI) calcd for $C_{19}H_{18}N_2O_6SNa$ $[M + Na]^+$ 425.0783, found 425.0785.



3k

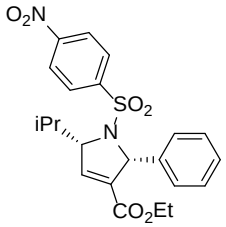
89%; white solid; IR (film) ν_{max} 2978, 1721, 1530, 1350, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.20 (s, 5H), 6.71 (t, *J* = 2.0 Hz, 1H), 5.81 (t, *J* = 2.0 Hz, 1H), 4.97–5.08 (m, 1H), 3.96–4.14 (m, 2H), 1.54 (d, *J* = 4.0 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 145.6, 140.1, 138.8, 133.6, 128.5 (2C), 128.3 (2C), 128.2, 123.9 (4C), 69.9, 63.1, 60.9, 21.9, 13.8; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 439.0940, found 439.0035.



3l

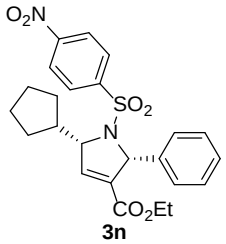
83%; white solid; IR (film) ν_{max} 2914, 1721, 1530, 1350, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.6 Hz, 2H), 7.61 (d, *J* = 9.6 Hz, 2H), 7.25 (s, 5H), 6.84 (t, *J* = 2.0 Hz, 1H), 5.83 (t, *J* = 2.0 Hz, 1H), 4.55–4.65 (m, 1H), 3.94–4.14 (m, 2H), 1.98–2.12 (m, 1H), 1.81–1.69 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 149.7, 145.4, 138.9, 138.7, 134.2, 128.4 (2C), 128.3 (2C), 123.9 (5C), 69.7,

69.0, 61.0, 29.4, 13.8, 10.2; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 453.1096, found 453.9774.



3m

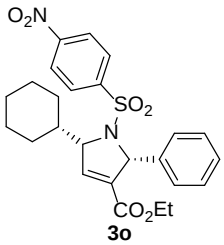
88%; white solid; IR (film) ν_{max} 2967, 1720, 1531, 1350, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.2 Hz, 2H), 7.77 (d, *J* = 9.6 Hz, 2H), 7.48 (m, *J* = 36.0 Hz, 5H), 6.96 (t, *J* = 2.0 Hz, 1H), 6.04 (t, *J* = 2.0 Hz, 1H), 4.88 (pentet, *J* = 2.0 Hz, 1H), 4.04–4.26 (m, 2H), 2.30 (octet, *J* = 6.7 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.12 (d, 8.0 Hz, 3H), 1.08 (d, 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 149.7, 145.2, 138.9, 137.7, 134.4, 128.6, 128.5 (2C), 128.4 (2C), 123.9 (2C), 73.5, 69.7, 69.6, 60.9 (2C), 32.2, 20.0, 17.7, 13.8; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 467.1253, found 466.3895.



3n

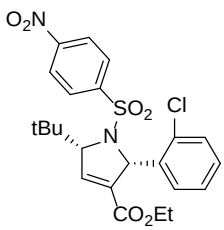
84%; white solid; IR (film) ν_{max} 2957, 1720, 1531, 1350, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 9.2 Hz, 2H), 7.93 (d, *J* = 9.2 Hz, 2H), 7.57 (m, *J* = 30 Hz, 5H), 7.03 (t, *J* = 2.0 Hz, 1H), 6.12 (t, *J* = 2.2 Hz, 1H), 5.09 (d, *J* = 11.2 Hz, 1H), 4.20–4.40 (m, 2H), 2.45–2.62 (m, 1H), 2.11–2.03 (m, 1H), 1.88–1.96 (m, 2H), 1.67–1.87 (m, 4H), 1.50–1.64 (m, 1H),

1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.8, 145.1, 139.0, 138.7, 134.3, 128.5 (4C), 128.3 (2C), 132.9 (2C), 71.5, 69.7, 61.0, 45.2, 30.4, 28.7, 25.4 (2C), 24.9 (2C), 13.9; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 493.1409, found 493.8652.



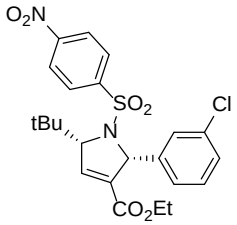
3o

59%; white solid; IR (film) ν_{max} 2927, 1720, 1530, 1349, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 9.6 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.55 (m, *J* = 6.9 Hz, 5H), 7.05 (t, *J* = 2.0 Hz, 1H), 6.10 (t, *J* = 2.0 Hz, 1H), 4.95 (pentet, *J* = 5.4 Hz, 1H), 4.15–4.36 (m, 2H), 1.98–2.13 (m, 3H), 1.87–1.91 (m, 2H), 1.71–1.75 (m, 1H), 1.31–1.51 (m, 3H), 1.28 (t, *J* = 8.0 Hz, 3H), 1.14–1.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.7, 145.3, 138.9, 138.3, 134.0, 128.6, 128.5, 128.4, 128.4 (2C), 123.8 (2C), 72.9, 69.4, 60.9 (2C), 41.9 (2C), 30.5, 28.4, 26.3, 26.1, 25.8, 13.8; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 507.1566, found 507.5409.



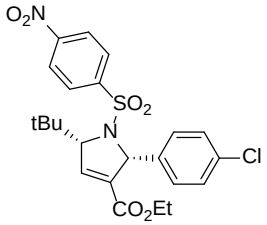
3p

80%; white solid; IR (film) ν_{max} 2964, 1722, 1531, 1350, 1173 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.52 (m, *J* = 8.0 Hz, 1H), 7.30 (m, *J* = 12.0 Hz, 1H), 7.22 (m, *J* = 5.6 Hz, 2H), 6.87 (t, *J* = 2.2 Hz, 1H), 6.46 (t, *J* = 2.4 Hz, 1H), 4.84 (t, *J* = 2.4 Hz, 1H), 4.07–3.89 (m, 2H), 1.14 (s, 9H), 1.03 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 150.0, 144.4, 139.1, 137.1, 135.0, 133.5, 129.9, 129.6, 129.4, 129.1, 126.9, 123.9, 77.1, 67.1, 61.0, 37.1, 28.9 (3C), 13.7; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 515.1020, found 515.3993.



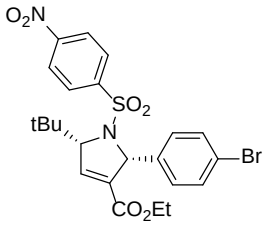
3q

93%; white solid; IR (film) ν_{max} 2969, 1720, 1532, 1350, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 9.2 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H), 7.64 (s, 1H), 7.47–7.58 (m, 3H), 7.01 (q, *J* = 1.3 Hz, 1H), 6.11 (s, 1H), 4.67 (d, *J* = 3.2 Hz, 1H), 4.28–4.44 (m, 2H), 1.39 (t, *J* = 7.0 Hz, 3H), 1.07 (s, 9H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 150.3, 143.0, 141.1, 141.0, 134.2, 133.7, 129.6, 129.2 (4C), 128.3, 126.3, 124.3, 78.4, 68.3, 61.4, 36.2, 27.9 (3C), 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 515.1020, found 515.3770.



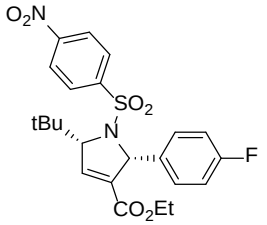
3r

72%; white solid; IR (film) ν_{max} 2966, 1720, 1532, 1350, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 32, 8.8 Hz, 4H), 6.99 (q, *J* = 1.2 Hz, 1H), 6.10 (s, 1H), 4.63 (d, *J* = 2.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.4 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 150.3, 143.0, 140.9, 137.4, 134.1, 133.8, 129.6, 129.1, 128.5, 124.3, 78.4, 68.3, 61.4, 36.2, 27.9 (3C), 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 515.1020, found 515.9123.



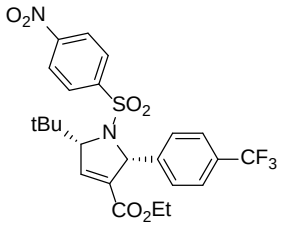
3s

74%; white solid; IR (film) ν_{max} 2966, 1720, 1532, 1349, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.79 (q, *J* = 1.3 Hz, 1H), 5.88 (s, 1H), 4.43 (d, *J* = 2.8 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 150.3, 142.9, 140.9, 137.9, 133.7, 131.5, 129.8, 129.1, 124.3, 122.4, 78.4, 68.3, 61.4, 36.2, 27.9 (3C), 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 559.0514, found 559.4084.



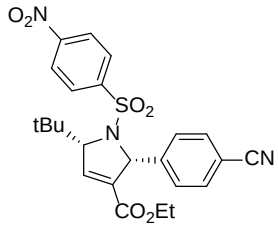
3t

78%; white solid; IR (film) ν_{max} 2967, 1720, 1532, 1350, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 10.0 Hz, 2H), 7.41 (q, *J* = 4.7 Hz, 2H), 7.02 (t, *J* = 8.4 Hz, 2H), 6.76 (q, *J* = 1.5 Hz, 1H), 5.90 (s, 1H), 4.41 (d, *J* = 2.4 Hz, 1H), 4.11 (q, *J* = 6.9 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H), 0.81 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 162.2, 161.2, 150.3, 143.1, 140.7, 134.8, 134.0, 130.0, 129.1 (2C), 124.2 (2C), 115.3, 115.1, 78.3, 68.3, 61.3, 36.2, 27.9 (3C), 14.0; ^{19}F (376 MHz, $CDCl_3$) δ -114.4; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 499.1315, found 499.5433.



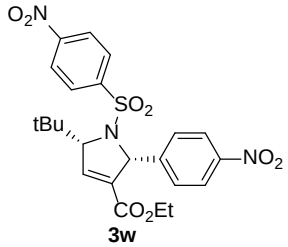
3u

93%; white solid; IR (film) ν_{max} 2965, 1721, 1533, 1350, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 9.6 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 7.83 (s, 4H), 7.02 (q, *J* = 1.5 Hz, 1H), 6.16 (s, 1H), 4.65 (d, *J* = 2.8 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 150.4, 142.8, 142.6, 141.3, 133.6, 130.4, 130.1, 129.2 (2C), 128.5 (2C), 125.2, 124.3 (2C), 122.6, 78.5, 68.3, 61.4, 36.1, 27.9 (3C), 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.18; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 549.1283, found 549.6185.



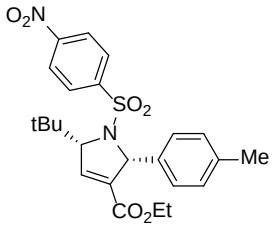
3v

83%; white solid; IR (film) ν_{max} 2966, 1720, 1532, 1350, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.4 Hz, 2H), 8.26 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 4H),7.86 (d, *J* = 8.4 Hz, 4H), 7.02 (q, *J* = 1.3 Hz, 1H), 6.13 (s, 1H), 4.65 (d, *J* = 2.4 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 150.5, 144.1, 142.3, 141.7, 133.3, 132.1 (2C), 129.2 (2C), 128.9 (2C), 124.4 (2C), 118.5, 112.1, 78.6, 68.2, 61.6, 36.1, 27.9 (3C), 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 506.1362, found 506.6797.



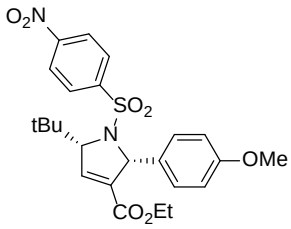
3w

89%; white solid; IR (film) ν_{max} 2965, 1721, 1530, 1349, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.8 Hz, 2H), 8.45 (d, *J* = 8.0 Hz, 2H), 8.28 (d, *J* = 9.2 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.04 (q, *J* = 1.3 Hz, 1H), 6.16 (s, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H), 9.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 150.5, 147.6, 145.9, 142.3, 133.3, 129.3 (2C), 129.1 (2C), 124.4 (2C), 123.5 (2C), 78.6, 68.0, 61.6, 36.1, 27.9 (3C), 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 526.1260, found 526.6823.



3x

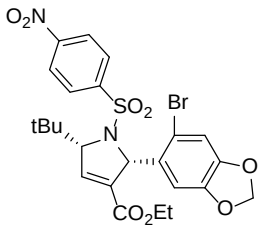
75%; white solid; IR (film) ν_{max} 2965, 1720, 1532, 1350, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 9.2 Hz, 2H), 8.09 (d, *J* = 9.2 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 4.0 Hz, 1H), 6.07 (s, 1H), 4.59 (d, *J* = 2.8 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 150.1, 143.6, 140.1, 137.9, 135.8, 134.3, 129.1 (2C), 129.0 (2C), 129.0 (2C), 128.1, 124.1 (2C), 78.2, 68.9, 61.1, 36.2, 27.9 (3C), 21.1, 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ [M + Na]$^+$ 495.1566, found 495.6183.



3y

67%; white solid; IR (film) ν_{max} 2965, 1719, 1531, 1350, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 12.0 Hz, 2H), 7.85 (d, *J* = 12 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.65 (q, *J* = 1.5 Hz, 1H), 5.83 (s, 1H), 4.35 (d, *J* = 2.8 Hz, 1H), 4.02 (q, *J* = 7.3 Hz, 2H), 3.71 (s, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.74 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 159.4, 150.1, 143.7, 140.1, 134.2, 131.0, 129.5, 129.0 (4C), 124.1 (2C), 113.6 (2C), 78.2,

68.7, 61.2, 55.2, 36.2, 27.9 (3C), 14.0; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 511.1515, found 511.7473.



3z

72%; white solid; IR (film) ν_{max} 2973, 1721, 1531, 1349, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 11.6 Hz, 2H), 6.90 (t, *J* = 4.0 Hz, 1H), 6.40 (t, *J* = 4.0 Hz, 1H), 6.05 (d, *J* = 6.8 Hz, 2H), 4.85 (t, *J* = 4.0 Hz, 1H), 4.02–4.22 (m, 2H), 1.24 (s, 9H), 1.19 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 150.0, 148.3, 147.6, 144.3, 139.0, 133.5, 131.6, 129.2, 123.9, 116.6, 112.8, 108.5, 102.1, 76.9, 70.2, 61.1, 37.2, 92.0 (3C), 13.9; HRMS (MALDI) calcd for $C_{24}H_{29}NO_5SNa$ $[M + Na]^+$ 603.0413, found 603.1669.

Table 3.5: HPLC Conditions for Separating Pyrrolines 3a–i

entry	PR_3 cat.	allene R	imine Ar′	yield (%)[a]	solvent (2 mL/min) hexane (%)	CH_2Cl_2 (%)	first peak ret. Time (min)	area (%)	second peak ret. Time (min)	area (%)	ee (%)[b]	[α]D
1	**1a**	H	*p*-tolyl	96 (**3a**)	40	60	7.040	22.80	9.477	77.20	**54**	(+)
	– racemic **3a**						7.107	49.92	9.777	50.08		
2	**1a**	Me	*p*-tolyl	62 (**3b**)	40	60	7.073	37.44	14.820	62.56	**25**	(–)
	– racemic **3b**						7.081	49.90	14.650	50.10		
3	**1a**	Et	*p*-tolyl	69 (**3c**)	40	60	6.757	70.07	11.940	29.93	**40**	(–)
	– racemic **3c**						7.013	49.52	12.443	50.48		
4	**1a**	*i*-Pr	*p*-tolyl	80 (**3d**)	50	50	9.603	77.95	14.950	22.05	**56**	(–)
	– racemic **3d**						9.903	49.96	15.107	50.04		
5	**1a**	*t*-Bu	*p*-tolyl	94 (**3e**)	50	50	4.903	14.17	6.067	85.83	**72**	(–)
	– racemic **3e**						5.000	49.85	6.483	50.15		
6	**1a**	*t*-Bu	*p*-anis	99 (**3f**)	60	40	9.400	28.57	11.647	71.43	**43**	(–)
	– racemic **3f**						9.403	50.36	11.907	49.64		
7	**1a**	*t*-Bu	Ph	88 (**3g**)	60	40	5.977	26.54	7.267	73.46	**47**	(–)
	– racemic **3g**						5.967	49.82	7.457	50.13		
8	**1a**	*t*-Bu	*p*-ClC_6H_4	88 (**3h**)	40	60	4.327	4.88	4.997	95.12	**90**	(–)
	– racemic **3h**						4.147	49.09	4.887	50.91		
9	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	97 (**3i**)	60	40	4.447	1.93	4.710	98.07	**97**	(–)
	– racemic **3i**						4.337	50.35	4.713	49.65		
10	**1b**	*t*-Bu	*p*-$NO_2C_6H_4$	87 (**3i**)	60	40	4.530	7.22	4.837	92.78	**86**	(–)
	– racemic **3i**											
11	**1c**	*t*-Bu	*p*-$NO_2C_6H_4$	97 (**3i**)	60	40	4.540	1.40	4.797	98.60	**97**	(–)
	– racemic **3i**											
12	**1d**	*t*-Bu	*p*-$NO_2C_6H_4$	79 (**3i**)	60	40	4.523	7.57	4.823	92.43	**85**	(–)
	– racemic **3i**											
13	**1e**	*t*-Bu	*p*-$NO_2C_6H_4$	95 (**3i**)	60	40	4.543	1.81	4.833	98.19	**96**	(–)
	– racemic **3i**											
14	**1f**	*t*-Bu	*p*-$NO_2C_6H_4$	96 (**3i**)	60	40	4.540	1.92	4.830	98.08	**96**	(–)
	– racemic **3i**											

[a] Isolated yeild after column chromotography [b] ee determined by HPLC using a REGIS (*R,R*)-DACH DNB chiral column.

Table 3.6: HPLC Conditions for Separating Pyrrolines 3j–aa

References:

entry	PR_3 cat.	allene R	imine Ar^1	imine Ar^2	yield (%)	solvent (2 mL/min) hexane (%)	CH2Cl2 (%)	first peak ret. Time (min)	first peak area (%)	second peak ret. Time (min)	second peak area (%)	ee (%)	[α]D
1	**1a**	**H**	*p*-$NO_2C_6H_4$	Ph	69 (**3j**)	40	60	9.033	36.60	10.220	63.40	**27**	(+)
	– racemic **3j**							9.137	50.14	10.420	49.86		
2	**1a**	Me	*p*-$NO_2C_6H_4$	Ph	89 (**3k**)	40	60	7.643	67.56	13.253	32.44	**37**	(–)
	– racemic **3k**							7.773	50.34	13.400	49.66		
3	**1a**	Et	*p*-$NO_2C_6H_4$	Ph	81 (**3l**)	40	60	6.830	82.34	10.843	17.66	**65**	(–)
	– racemic **3l**							6.900	50.34	10.620	49.66		
4	**1a**	*i*-Pr	*p*-$NO_2C_6H_4$	Ph	88 (**3m**)	40	60	6.083	83.33	8.270	16.67	**67**	(–)
	– racemic **3m**							6.293	49.87	8.463	50.13		
5	**1a**	*c*-pent	*p*-$NO_2C_6H_4$	Ph	84 (**3n**)	40	60	6.227	84.49	8.823	15.51	**69**	(–)
	– racemic **3n**							6.380	49.83	8.907	50.17		
6	**1a**	*c*-hex	*p*-$NO_2C_6H_4$	Ph	58 (**3o**)	40	60	6.453	82.42	9.517	17.58	**65**	(–)
	– racemic **3o**							6.510	49.53	9.403	50.47		
7	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*o*-ClC_6H_4	80 (**3p**)	40	60	11.513	99.99	12.590	0.01	**99**	(–)
	– racemic **3p**							12.043	50.10	13.500	49.90		
8	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*m*-ClC_6H_4	93 (**3q**)	7% MeOH w 93% CO_2		6.340	96.83	6.770	3.17	**93**	(–)
	– racemic **2q**							6.250	49.75	6.650	50.25		
9	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-ClC_6H_4	72 (**3r**)	70	30	8.980	3.04	9.800	96.96	**94**	(–)
	– racemic **3r**							9.330	50.26	10.363	49.76		
10	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-BrC_6H_4	74 (**3s**)	70	30	9.593	2.96	10.267	97.04	**94**	(–)
	– racemic **3s**							9.933	50.42	10.807	49.58		
11	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-FC_6H_4	78 (**3t**)	70	30	8.653	2.77	9.823	97.23	**94**	(–)
	– racemic **3t**							8.493	49.96	9.743	50.04		
12	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-$CF_3C_6H_4$	93 (**3u**)	70	30	7.227	1.66	7.847	98.34	**97**	(–)
	– racemic **3u**							7.263	50.21	8.030	49.79		
13	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-CNC_6H_4	83 (**3v**)	60	40	13.310	2.52	14.237	97.48	**94**	(–)
	– racemic **3v**							12.617	50.68	13.680	49.32		
14	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	89 (**3w**)	60	40	9.063	3.46	9.820	96.54	**92**	(–)
	– racemic **3w**							8.677	50.43	9.397	49.57		
15	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-MeC_6H_4	75 (**3x**)	70	30	9.967	6.69	10.847	93.31	**87**	(–)
	– racemic **3x**							10.127	50.40	11.190	49.60		
16	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	*p*-$MeOC_6H_4$	57 (**3y**)	70	30	13.370	28.36	14.440	71.64	**43**	(–)
	– racemic **3y**							13.640	50.57	14.977	49.43		
17	**1a**	*t*-Bu	*p*-$NO_2C_6H_4$	6-Br-3,4-OCH2O-C6H	72 (**3z**)	70	30	12.890	90.50	13.870	9.50	**81**	(–)
	– racemic **3z**							12.970	50.20	13.910	49.81		
18	**1a**	*t*-Bu	*o*-tolyl	*p*-ClC_6H_4	99 (**3aa**)	9% EtOAc w 93% CO_2		12.970	5.21	13.910	94.79	**89**	(–)
	– racemic **3aa**							13.077	50.00	14.257	50.00		

[a] Isolated yeild after column chromotography [b] ee determined by HPLC using a REGIS (*R,R*)-DACH DNB chiral column, or a Chiral OJ-H column.

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CHAPTER FOUR

Common Coordination Complexes of Allenes as π-Bond Ligands to Transition Metals

I. Introduction

Allene, the simplest cumulene, has drawn much attention from the chemistry community.[1] The perpendicular π-bonds of the 1,2-diene motif offers unique characteristics in reactivity and stereochemistry. Initially thought of as a synthetic oddity, too unstable to exist for any significant amount of time, naturally produced allenes have since been isolated and there are now many preparations for their synthesis. The first synthesis of an allene used chloride elimination of β-chloroglutonic acid to give penta-2,3-dienedoic acid (**Scheme 4.1**) in 1887 by Burton, et al,[2] though its structure was not confirmed until 1954.[3] In 1924 Ruzicka reported the first naturally produced allene, Pyrethrolone (**Figure 4.1**),[4] and again, the full structural identification was not confirmed until 1952.[5] Following these early milestones, naturally occurring allenes continue to be isolated,[6] even more have been synthesized,[7] and applications of allenes continues to grow.[8]

Scheme 4.1: Synthesis of Penta-2,3-dienedoic Acid

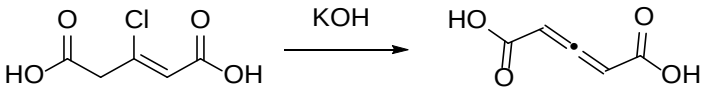
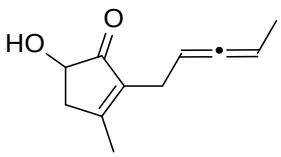


Figure 4.1: Pyrethrolone, The First Isolated Naturally Occurring Allene



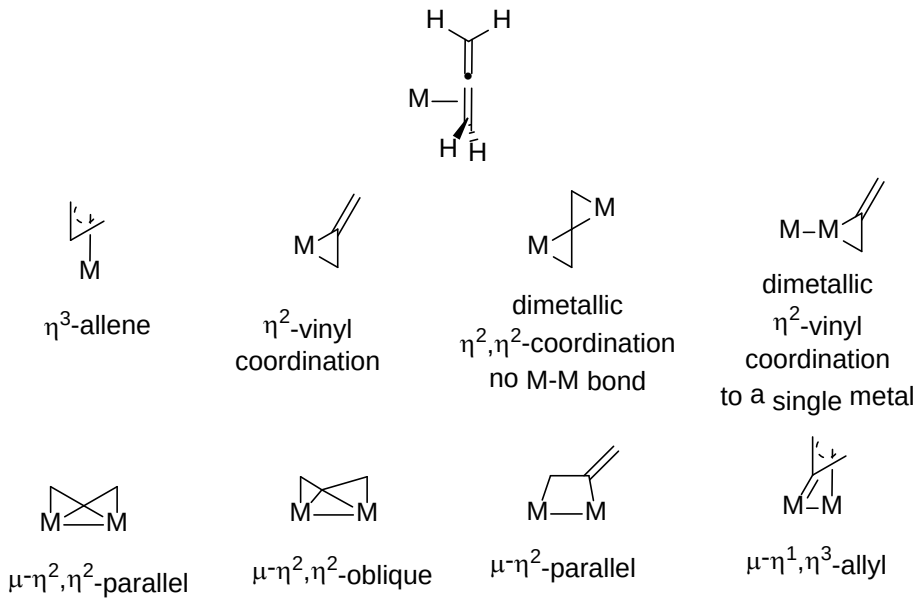
The utility of allenes does not stop with their preparation or potential transformations, but extends to their ability to fine tune oganometallic constructs through ligation. The utility of

alkenes and alkynes to act as π-bond ligands gives precedence for allenes to behave similarly.[9] Indeed, there have been a number of allene complexes of transition metals, but we are only beginning to see the effect of reactions that utilize organometallic complexes of allene. With their perpendicular cumulated π-bonds, it can be predicted that allenes may act as monodentate ligands reminiscent of olefins, or may coordinate two metals as a bridging ligand. Do to their high reactivity and fluxional behavior once complexed, some allenes act as non-innocent ligands by existing in different resonance forms or taking on new bonds and reactivity once ligated.

II. Allene Coordinated Transition-Metal Complexes

Allenes afford substantial structural diversity from interactions with transition-metals which have been elucidated through a variety of spectroscopic and spectrometric techniques. A variety of mononuclear and dinuclear coordination modes of metals to allenes have been observed, **Figure 4.2**, as well as metal-mediated rearrangements.[10] Similarly to alkenes, allene coordination to metals is most commonly through a σ-donation from the π-electrons of one of the olefins to an empty orbital of the metal, and π-backbonding from occupied d-orbitals of the metal to the π* of the same olefin. The π-basicity of the metal will dictate the strength of the metal-allene bond, observed by the stretching frequency of the C-C bond, where weakly π-basic metals will lengthen the bond little from the uncoordinated allene, while strongly π-basic metals may be represented best as a metallacyclopropane.

Figure 4.2: Coordination Modes of Allene-Metal Complexes

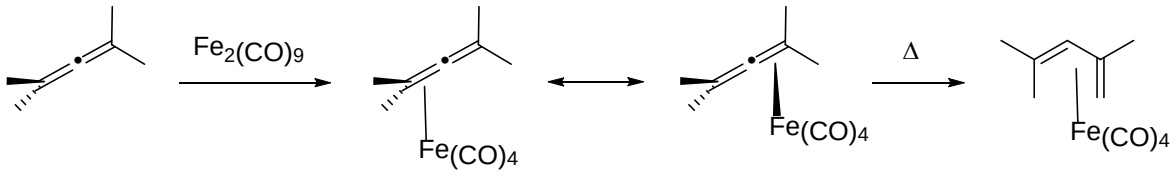


Metal coordination to an allene, as seen at the top of **Figure 4.2**, can lead down a number of ligation pathways. The η^3-allene complex is often seen with electron poor metals, yet the ligand field around the metal can increase its electronegativity which leads to η^2-vinyl coordination. As well, two separate metals can coordinate the same allene forming a pair of η^2-vinyl complexes. Dinuclear metals can form the same mono-metal complexes with allenes, such as η^2-vinyl coordination, but the second metal opens the door to a variety of new allene-metal coordination motifs. The two olefins can each be complexed in either μ-η^2,η^2-parallel or μ-η^2,η^2-oblique configurations, or one olefin can bridge the metals in a μ-η^2-parallel manor. Interestingly, the metals can interact with the allene in very different ways, such as in a μ-η^1,η^3-allyl complex, where one metal behaves as a π-allyl whilst the other takes on carbene-like character.

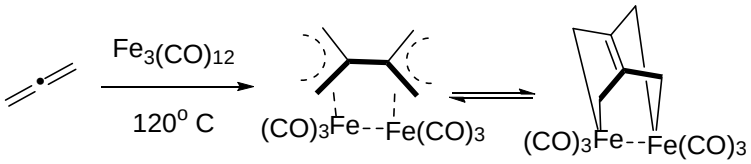
A. Examples of Fluxional Behavior of Allene Ligands

The simplest motif of metal interaction to π-bonds is through coordination, but with allenes a special feature presents itself, the ability to change its station of ligation. The perpendicularly adjacent π-bonds of allenes may seem inaccessible to a metal once it has coordinated one of the olefins, however a fluxional behavior exists in the allene metal interactions at this point. This may be a necessary feature for some of the more complex structures observed in the metal-allene ligand field, and certainly accounts for the presence of the η^3-allene complex. Fortunately, iron seems to lend itself quite well to forming stable fluxional interactions with allenes.

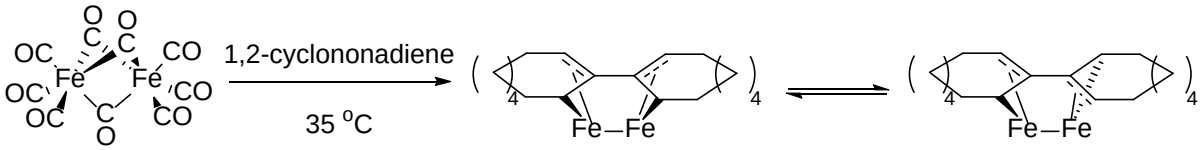
In one of the earliest examples of allenic species ligating to metals, Pettit found that when $Fe_2(CO)_9$ is reacted with tetramethylallene a π-interaction is observed with $Fe(CO)_4$.[11] Of note is the degenerate valence tautomerism observed by ^1H NMR. The iron complex rapidly tautomerizes between the two π-bonds, as evidenced by a single peak for the methyl groups in the ^1H NMR. Upon cooling the system to -60^o C, the tautomerization halted, giving three peaks of 3, 3, and 6 protons, respectively. The activation energy for this tautomerization was found to be 9.0 ± 2.0 kcal. Pettit also found that upon prolonged heating of the 1,2-diene complexed with iron tetracarbonyl, an isomerization occurs to a 1,3-diene-iron tricarbonyl complex.



Nakamura found a unique dimerized allene-metal complex when allene was mixed with iron dodecacarbonyl at 120° C.[12] The central carbon of the allene forms a bond with the central carbon of a second molecule of allene, both complexing iron tricarbonyls. Identification required extensive NMR and IR analysis since the complex undergoes rapid valence tautomerism between the bis π-allylic structure and the π-complexed butadiene structure.

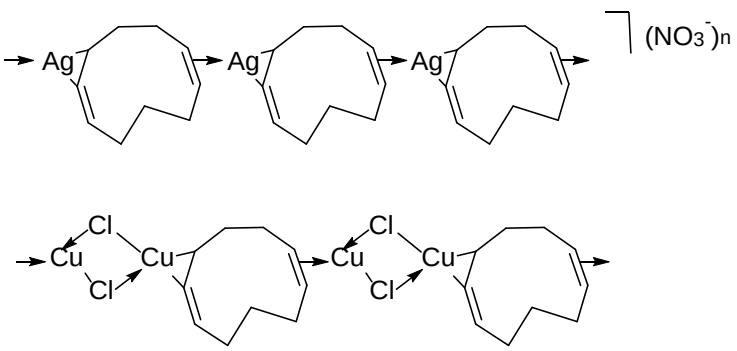


Following the work by Nakamura,[12] Howell, et al, witnessed a similar dimerization of an allene ligand, as well as fluxional behavior once complexed to the metal.[13] Upon exposure of diiron nonacarbonyl to 1,2-cyclononadiene at 35 °C a bis(π-allylallene)$Fe_2(CO)_6$ complex was isolated as an orthorhombic crystal. The system rapidly fluctuates between cis- and trans- η^1, η^3-allyl complexes in regards to iron. Observation of the fluxional behavior required variable temperature ^{13}C NMR, where the methylenes coalesce into two peaks at room temperature, at -85 °C they form a much more complex pattern.



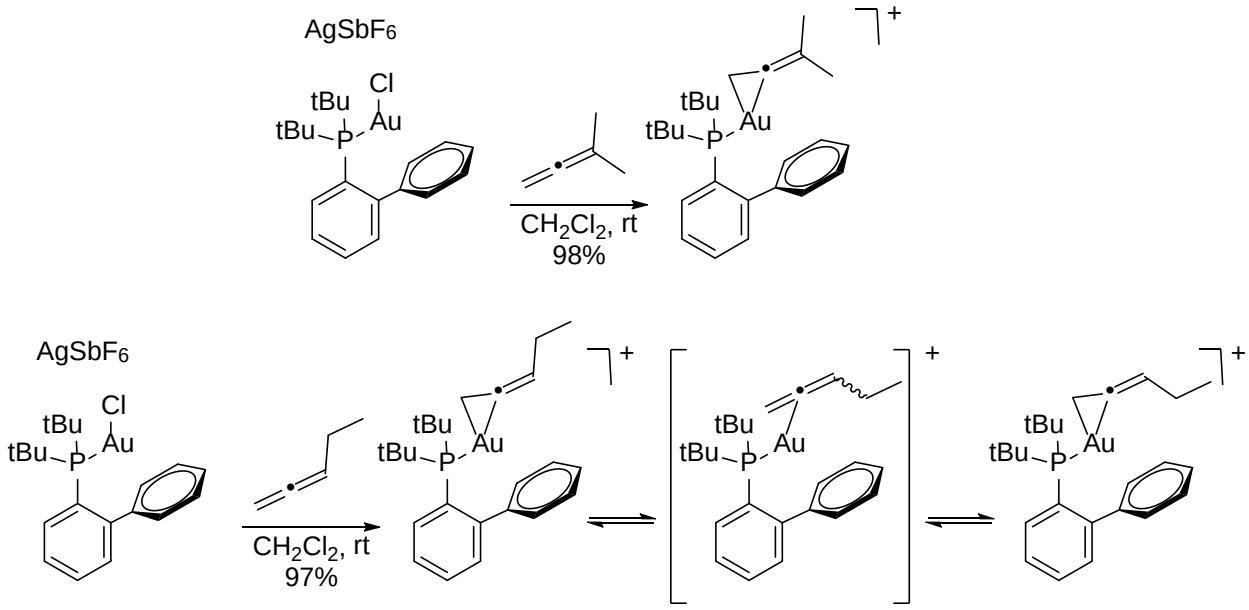
B. Examples and Characteristics of η^2-vinyl Coordination

The η^2-vinyl complex of allenes to metals is one of the more common structural motifs found, and the coinage metals, copper, silver, and gold, favor the formation of the η^2-vinyl complex when ligated by allenes. Early work by Nagendrappa, et al. examined Cu(I) and Ag(I) interactions with cyclic allenes.[14] When 1,2,6-cyclononatriene is reacted with Ag(I) a polymer of equal parts hydrocarbon to silver is observed. However, when Cu(I) is used there are two parts copper to hydrocarbon which allows for bridging coordination by chlorides. Endocyclic ligation was disproven by IR studies, which gave way to these exocyclic polymeric structures. Their work also showed that the allene was not altered by ligation, as it was recoved by the addition of cyanide ions. Watanabe, et al. has taken advantage of the reversibility of allene ligation with copper to patent a means of producing a consistent copper film.[15]

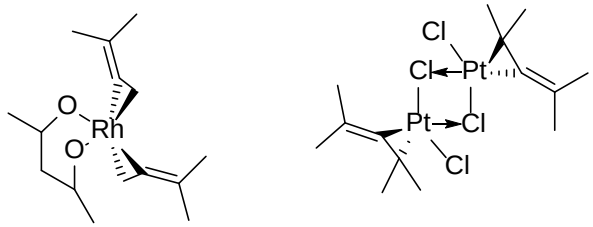


Recent work by Brown and colleges gives a good representation of the metal-allene η^2-vinyl coordinated complex.[16a] A 98% yield of a cationic gold π-allene complex was isolated when a mixture of [P(t-Bu)$_2$*o*-biphenyl]AuCl and $AgSbF_6$ was reacted with 3-methyl-1,2-butadiene, representing the first synthesized two-coordinate gold(I) π-allene complex. Coordination was favored on the least substituted π-bond as confirmed by the X-ray crystal structure. Expanding on this system with nonequivalent substitution patterns on the allene lead to the observation of fluxional behavior in the allene-gold complex.[16b] Variable temperature NMR

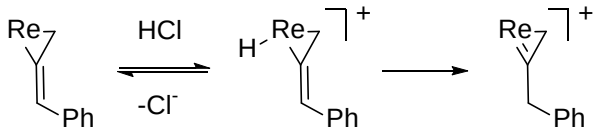
revealed the sterics predicted trans-configuration being favored 9:1 at -30 ^{o}C, but nearly 1:1 at 25 ^{o}C. A staggered η^1-allene intermediate is proposed for the π-face exchange of the allene ligand.



There are cases where more than one allene comples a metal, to which the η^2-allyl coordination lends itself nicely. This feature was demonstrated by Hewitt and De Boer in their work with rhodium.[17] Acetylacetonatorhodium (I) reacted with two equivalents of tetramethylallene to give reddish-brown needle-like crystals. X-ray analysis showed a propeller like structure with three blades, two allenic in origin and the last acetylacetonato. They also looked at dichloroplatinum, which upon being charged with tetramethylallene produced dark orange cubic crystals. The structure, once revealed by X-ray, showed a dimerized complex that lays square-planer about platinum.

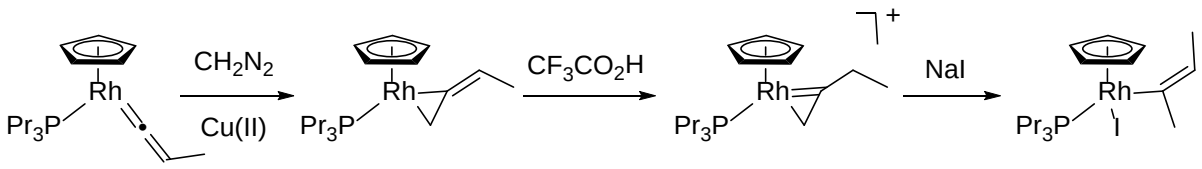


Rhenium(I) has been found to form a η^2-allene complex when reacted with 1-phenyl-1,2-dienes.[18] Investigating the intricacies of the metal-allene bond, Henderson, et al. examined the kinetics of protonation of the allene, and how it changes the predicted mechanism.[19] Their data revealed that initial protonation occurs not at the allene, but at rhenium, forming the hydrido-species. The hydride then undergoes intramolecular migration to the phenyl substituted carbon of the allene. The pathway was also supported by X-ray crystallographic measurements which found the Re-H bond within 1.5 Å of the phenyl substituted carbon, close enough for facile migration.



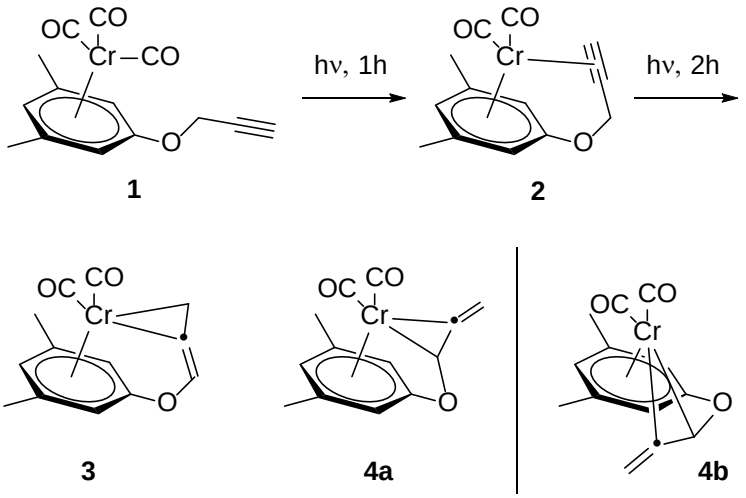
trans-[ReCl(CH2CCHPh)(dppe)2]

Protonation of η^2-allene complexes has also been observed to lead to η^1-vinyl ligated motifs with little effort. While studying a rhodium-vinylidene, Werner and coworkers found that treatment with diazomethane lead to the η^2-allene configuration of an allene ligated to rhodium.[20] When treating this system with triflic acid the carbon-homologated vinylidene is produced, and upon treatment with sodium iodide the vinylidene is opened up to reveal a η^1-vinyl complex.

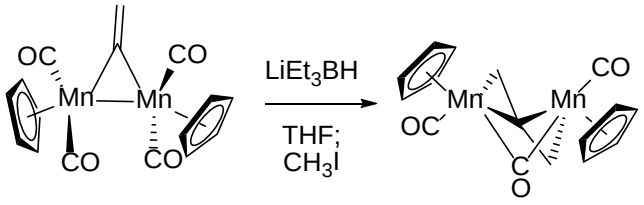


By tethering an acetylene to a chromium containing arene, Krivykk, et al. was able to explore the stereochemistry of a η^2-vinyl complex.[21] Utilization of the acetylenic tricarbonylchromium arene, it was observed that after an hour of UV irradiation there was a loss of a carbonyl and the open ligand site on chromium was replaced by a π-bond to the tethered alkyne giving dicarbonylchromium areneacetylenic chelate. Irradiation for an additional two

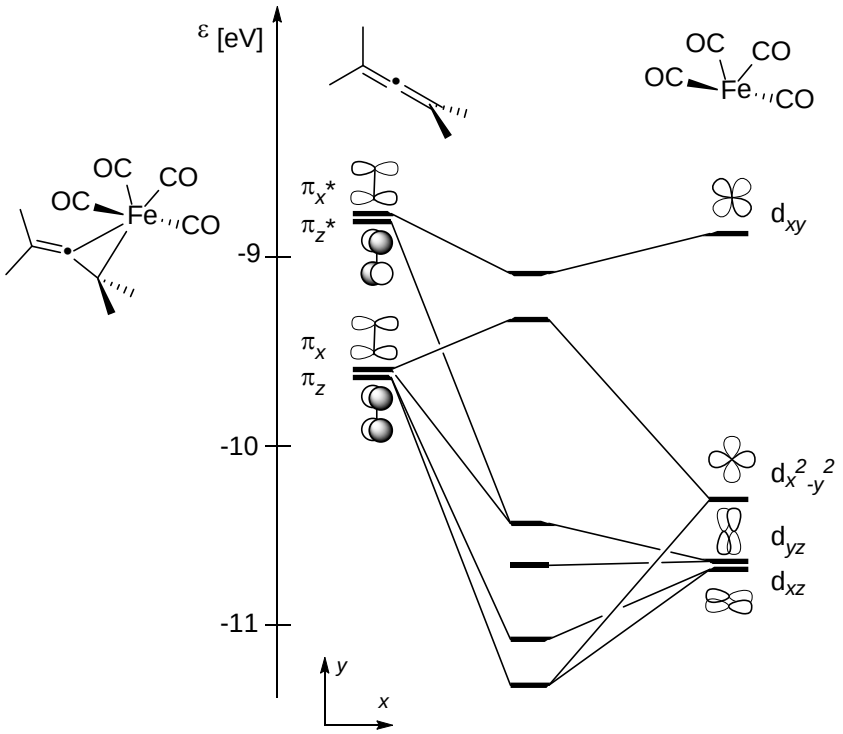
hours yielded three dicarbonylchromium areneallenic chelates. Rapid fuxional behavior during irradiation most likely led to the different regioisomers. Even though both the terminal and internal olefin complex chromium, only ligation to the internal olefin produces an observable diastereotopicity. The terminal olefin has a symmetry plane, however, ligation to the internal olefin has two distinct faces of approach which is seen by nonequivalence in the ^{1}H and ^{13}C NMR spectra.



While exploring a vinylidene diatomic manganese complex, Lewis, et al. arrived at a new construct of allene-metal interactions.[22] Reaction of vinylidene $Cp_2Mn_2(CO)_4(\mu\text{-}\eta^1\text{-}CCH_2)$ with $LiEt_3BH$ in THF, and then quenching with iodomethane produced a maroon compound. X-ray analysis revealed that the manganese was ligating an allene, but the fascinating discovery was that the allene had bisected the metal-metal bond. This marked the first example of a dimetallic η^2,η^2-coordination with no metal to metal bond; each metal can be looked as having an independent η^2-vinyl coordination.



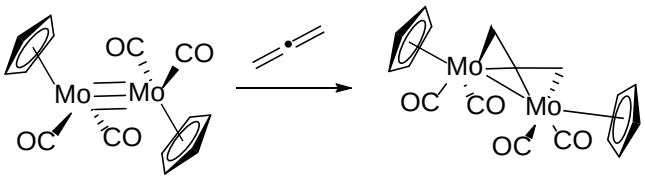
The nature of the bonding of the η^2-vinyl complex was further studied by Böhm.[23] Utilization of the photoelectronic spectrum and molecular orbital calculations, Böhm was able to explore the electronic structure of η^2-vinyl coordinated allenes to metals. Though his work focused on deriving ionization energies, he was able to present an accurate valence orbital diagram for (tetramethylallene)iron tetracarbonyl.



C. Examples of μ-η^2,η^2-Parallel and –Oblique Coordination

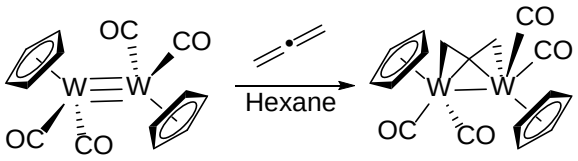
When an allene ligates to a dimetallic system there are four common structures: μ-η^1,η^1-parallel, μ-η^1,η^1-allyl, μ-η^2,η^2-parallel and μ-η^2,η^2-oblique. The latter two ligation motifs have very similar characteristics, with the parallel form possessing a mirror plane of symmetry while the oblique carries just a C_2 form of symmetry. The predicted form often arises from the remaining ligand field, *i.e.* two other ligands per metal tend to favor μ-η^2,η^2-parallel while three ligands per metal favor μ-η^2,η^2-oblique.

Acetylenes poses the ability to add across metal-to-metal triple bonds, a feat olefins lack, which allows for the catalytic hydrogenation of alkynes to alkenes.[24] Taking advantage of an allene's ability to act as a four electron donor, similar to alkynes, Cotton, et al. explored the reaction of allene with $Cp_2Mo_2(CO)_4$.[25] Following the bubbling of allene gas through a hydrocarbon solution of a triple bonded molybdenum complex, deep red crystals of two directly bonded allene bridged molybdenums were isolated. X-ray crystallographic analysis revealed a μ-η^2,η^2-oblique coordination, giving a C_2-symmetry through the Mo-Mo bond and the central carbon of the allene.

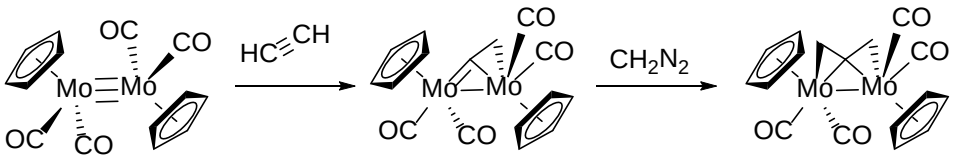


Work out of the Chisholm and Cotton laboratories expanded on the diatomic molybdenum complex to find a stable tungsten complex with allene.[26] When biscyclopentadienyl tetracarbonyl tungsten, $Cp_2W_2(CO)_4$, is subjected to a stream of bubbling allene gas in hexane, an irreversible reaction occurs where deep red crystals are generated. Through X-ray crystallography a C_2 symetric structure is illucidated, and found to be allene bridging the metal centers in μ-η^2,η^2-oblique configuration. Noting the similarities between the molybdenum and

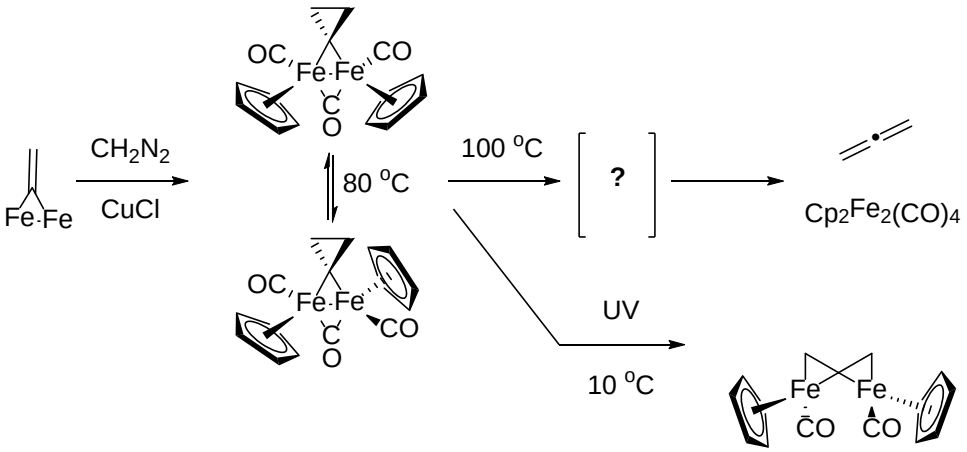
tungsten complexes, a mixed solution of $Cp_2Mo_2(CO)_4$ and $Cp_2W_2(CO)_4$ was charged with allene. The only products obtained were the homodinuclear complexes, the absence of the Mo-W heterodinuclear complex indicated that the μ-η^2,η^2-parallel construct forms through direct addition with no mononuclear intermediates.



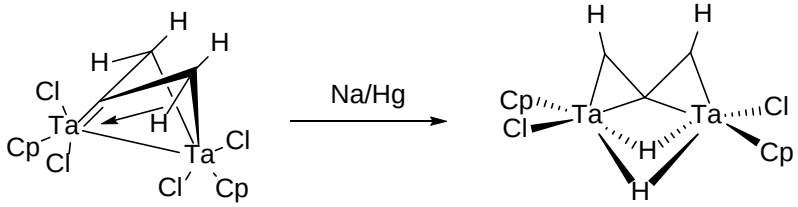
The molybdenum-allene construct obtained by Christholm had previously been made through a circuitous route by Doherty, et al.[27] Treating biscyclopentadienyl tetracarbonyl molybdenum with ethyne gave blue-black crystals of a complex with vinylidene bridging the two molybdenums. Following this with diazomethane gave the μ-η^2,η^2-parallel allene-molybdenum complex.



While studying cyclopropylidene diiron complexes, the discovery of a bridging allene ligating the diiron was reported by Hoel, et al.[28] The transformations a cyclopropylidene diiron complex underwent with heating were monitored by IR. At 60 ^{o}C the cyclopropylidene complex was formed, and by 80 ^{o}C an equilibrium had been reached between cis and trans complexes. At 100 ^{o}C a new compound was observed, yet it quickly decomposed to $Cp_2Fe_2(CO)_4$ and gaseous allene. The formation of allene was a valuable clue, so to pursue the new intermediate, once the equilibrium between cis and trans cyclopropylidene complexes was established the system was dropped to 10 ^{o}C and irradiated with UV light. Dark green prisms of a bridging allene diiron complex were isolated and X-ray crystallography confermed its symmetric structure.

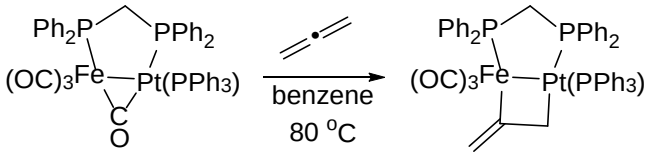


By exploring the μ-η^1,η^3-allyl complex that arose from allene reacting with tantalum,[29a] vida infra, Messerle, et al. managed to push the system towards a much more stable conformation through reducing conditions.[29b] When the μ-η^1,η^3-allyl tantalum-allene complex is treated with Na/Hg a loss of two protons initiates a rearrangement to a μ-η^2,η^2-parallel coordinated compound. X-ray diffractometry showed the C_2 symmetric system to contain a distinctive μ-propynylidene ligand. In its free form as a double radical containing allene, propynylidene would be incredible unstable; however, being bound to tantalum the system has been shown to be resistant to H_2, CO, and ethylene at temperatures below 65 °C.



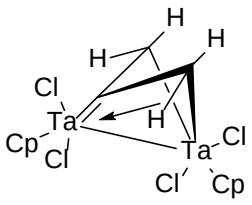
D. An Example of μ-η^2-Coordination

Most dimetallic complexes favor equivalent ligation motifs when charged with allenes, the exception being those cases that allow the μ-η^1,η^3-allyl complex to be formed. Another way to control the coordination of allenes is by changing the metals that they coordinate to. Work out of the Shaw lab found such an example.[30] Subjecting an iron-platinum complex solvated in benzene to bubbling allene gas afforded a nonequivalent coordination complex with the bridging the metals. Recrystalization from chlorobenzene gave suitable material for X-ray analysis which confirmed the μ-η^2-coordination of the allene. The structure contained a dimetallocyclobutane ring with an exocyclic methylene coordinating the iron to the vinyl position.

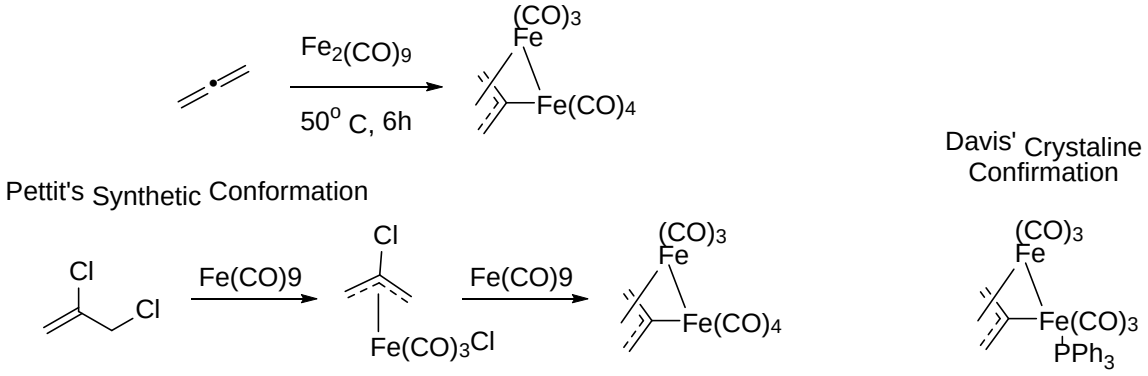


E. Examples of μ-η^1,η^3-Allyl Complexes

Messerle, et al. found a most unique organoditantalum complex when allene gas was bubbled through a -78 °C toluene solution containing $Cp_2Ta_2Cl_4$.[29a] When the tantalum is reacted with allene a four-electron reduced μ-η^1,η^3-allene ligand with a β-agostic C-H•••Ta interaction is produced; an example of an alkylidene-diyl ligand. Through NMR spectoscopy and X-ray diffractometry analysis the dimetallic structure was determined. One tantalum shows a hybrid coordination with the allene via a η^3-allylic and sigma bonding, while the central allenic carbon is doubly-bound to the other tantalum with a β-agostic interaction with an allene hydrogen.

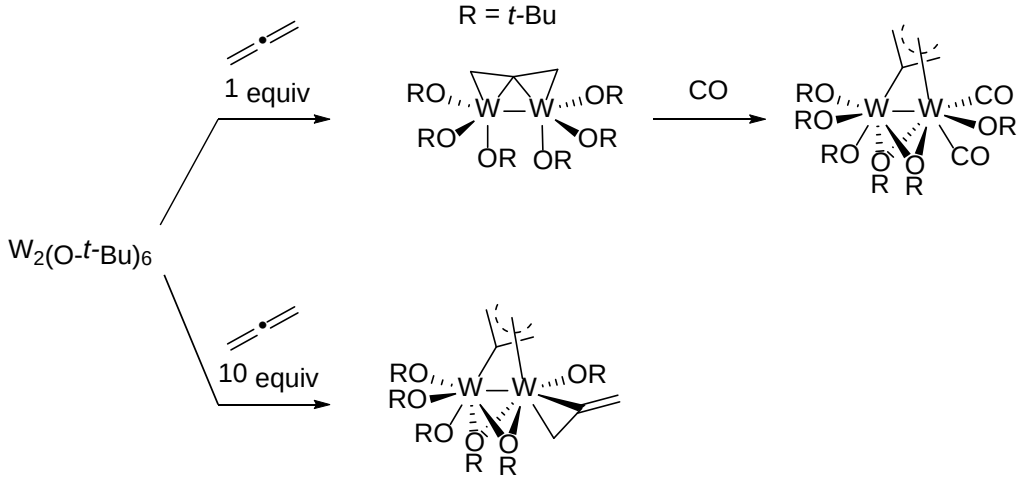


Simultaneously, Pettit[31] and Davis[32] showed that when $Fe_2(CO)_9$ is reacted with allene in an autoclave at 50° C for 6 h a 2-σ-tetracarbonyliron-π-allyltricarbonyliron structure is formed. This structure was confirmed in the Pettit lab by mass-spectral cracking experiments showing the seven carbonyl groups and an iron-iron bond. IR showed only terminal carbonyls, temperature independent NMR reveals only two proton peaks of equal intensity, and a Mössbauer spectrum reviled two non-equivalent iron atoms. Further confirmation of the structure was obtained by a step-wise synthesis of the same complex. First a single equivalent addition of $Fe_2(CO)_9$ to 2,3-dichloropropane provided 2-chloro-π-allyltricarbonyliron chloride, which upon treatment with a second equivalent of $Fe_2(CO)_9$ gave the σ-iron-π-allyl-iron complex. Davis was able to get a crystal structure by treating the compound with triphenylphosphine which took the ligand position of one of the carbonyls. This gave the final confirmation of the μ-η^1,η^3-allyl complex.

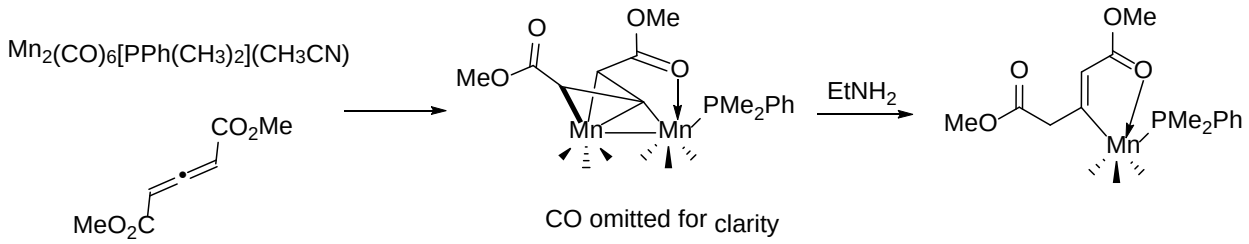


Chisholm, et al., took on the study of allenes with tungsten, and managed to find three new complexes.[33] By reacting one equivalent of allene with $W_2(O\text{-}t\text{-}Bu)_6$ in hexanes at 0 °C a dinuclear μ-η^2,η^2-parrallel complex was isolated as dark green cubic crystals. When this compound was treated with CO gas red crystals begun to form, and X-ray analysis showed the compound had morphed into a μ-η^1,η^3-allyl moiety. As well, when 10 equivalents of allene were reacted with $W_2(O\text{-}t\text{-}Bu)_6$ a dinuclear complex with two different allene bonding moieties was

discovered. The complex contains a μ-η^1,η^3-allyl bridging both metals, and a η^2-allyl ligand complexing the η^3-allyl metal.



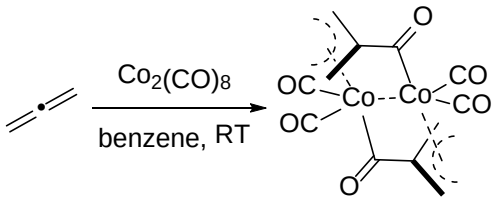
The Adams lab made an attempt at a dimanganese complex from dimanganese nonacarbonyl with a 1,3-diester substituted allene.[34] Their work was unsuccessful, however, when using dimethylphenylphosphine dimanganese hexacarbonyl they did manage to get a 34% yield of an orange crystal that was found to be a η^3,η^1-allyl complex. This manganese complex was found to be vulnerable to ethylamine addition, losing one of the manganese groups, and leaving behind a metal-vinyl complex.



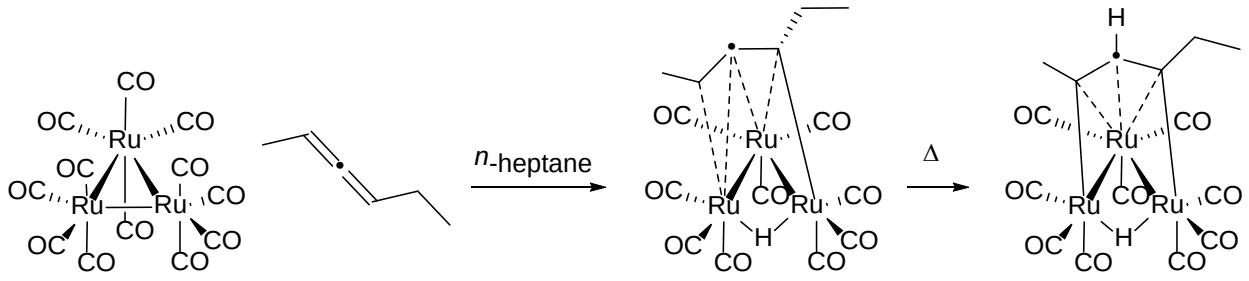
F. Other Ligation Motifs of Allene-Metal Coordination

In furthering the exploration of metal-allene complexes, Nakamura not only witnessed allenes fluxional behavior when complexed with iron, but also found a unique interaction of cobalt with allene.[12] By bubbling allene through a solution of dicobalt octacarbonyl in benzene

an air-sensitive yellow crystal was isolated. The mass indicated a dimeric structure of $[(C_3H_4)Co(CO)_3]_2$. Being a diamagnetic structure helped to limit the possible structures, as well as terminal metal-carbonyl bands in the IR spectrum paired with a ketone stretch. Finally, a bromination experiment showed exchange with all but two carbonyls. The proposed structure is a dimerized cobalt π-allyl with carbonylation of the central carbons of a pair of allenes.

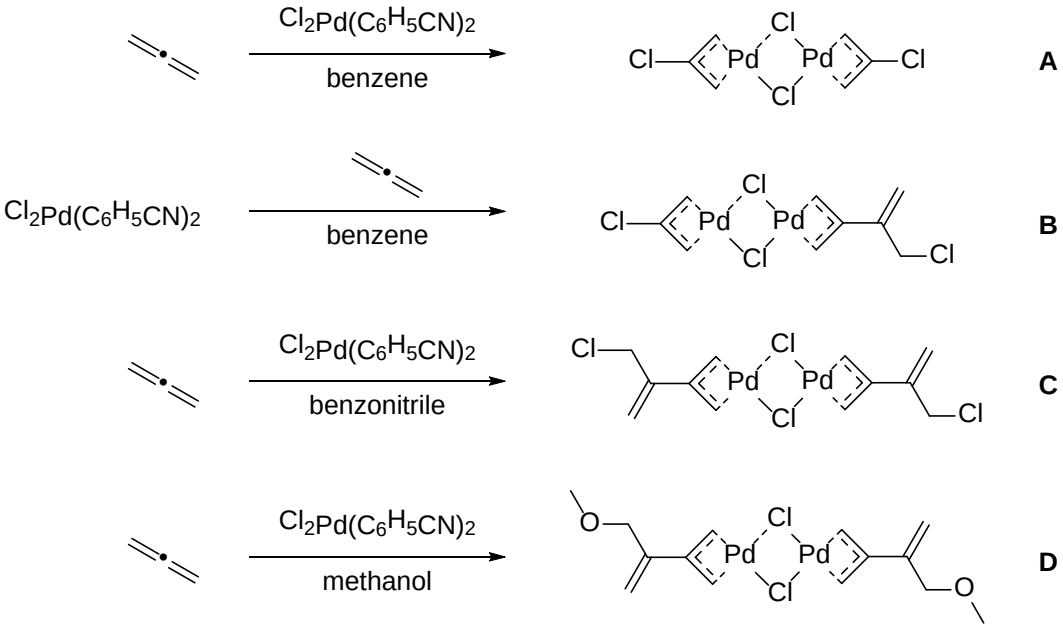


A ruthenium cluster complex with allene was isolated upon recrystalyzation from *n*-heptane of triruthenium dodecacarbonyl mixed with 2,3-hexadiene.[35] X-ray crystallography revealed a unique ruthenium cluster arranged in an isosceles triangle. Gervasio, et al. found that the allene is bound to the metal cluster through two π-bonds, from C2-C3 and C3-C4, with separate rutheniums and a σ-bond from carbon 4 to the third ruthenium. As well, a bridging hydridic hydrogen lies in the ruthenium plane. Further confirmation of the structure also came in the thermal rearrangement to the known isomer found by Evans et al., which was produced from the skeletal rearrangement of 2,4-hexadiene once complexed with triruthenium dodecabarbonyl.[36]

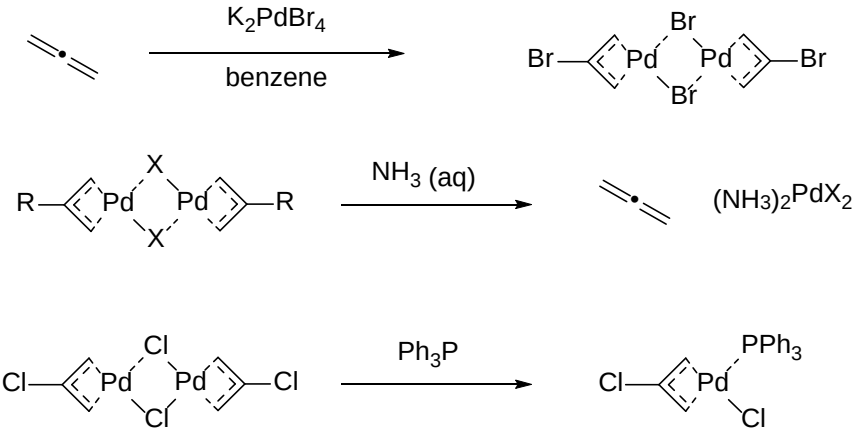


G. Insertion of Allenes to give Metal-Allyl Complexes

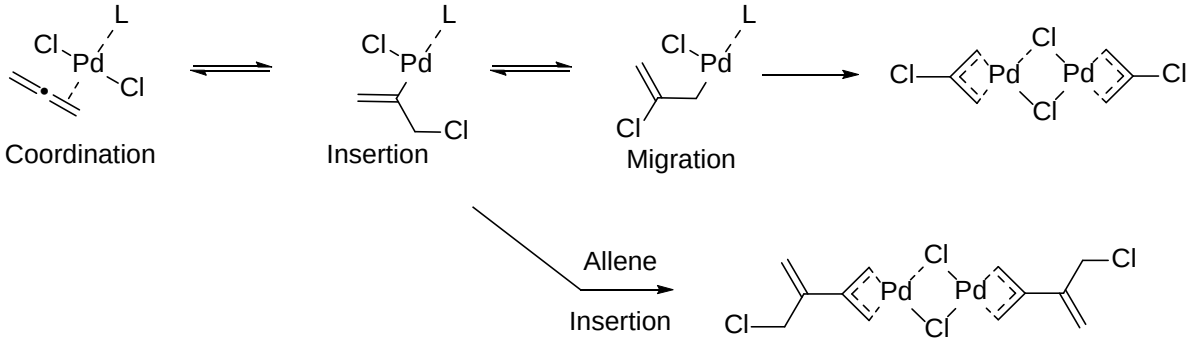
In the early 1960's Lupin and Shaw observed a unique transformation upon ligation of allene with dichloro-bis-benzonitrile palladium in which, once ligated, the β-carbon of the allene ends up chlorinated.[37] Pursuing this curiosity, research by Schultz at Monsanto revealed a family of allene-ligands that underwent further bond forming transformation upon interaction with dichloro-bis-benzonitrile palladium.[38] The complexes were found to contain dimerized palladium complexes bridged by chlorine atoms with π-allylic occupation of two ligand positions per metal; and, as Lupin had seen, a new bond at the β-carbon of the allene. When allene was bubbled into a benzene solution containing the palladium the β-carbon chlorinated complex **A** is isolated. However, when the solid palladium is added second the desymmetrized complex **B** is produced with a β-chloro upon one allene, and a β-(α-chloro)allyl upon the other. Following clues from this work, Schultz was able to obtain the symmetrical β-carbon (α-chloro)allylated complex **C** by utilizing benzonitrile as the solvent. Also arising from the solvent screens a β-carbon (α-methoxy)allylated complex **D** was found.



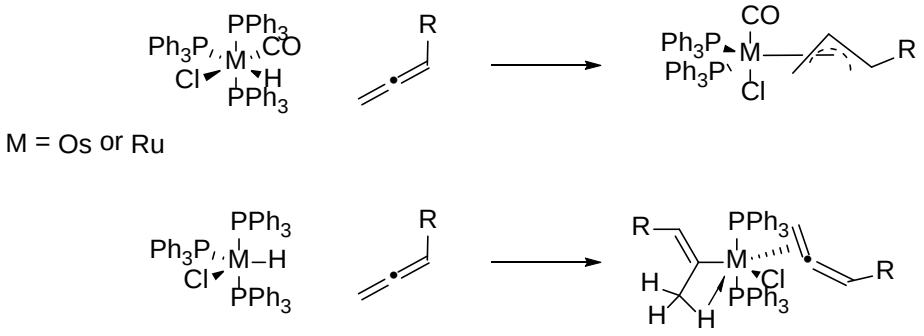
Lupin, et al., continued the study of these unique palladium-allene complexes. By switching to potassium bromopalladate the β-carbon bromonated analog of the chlorinated complex was found.[39] The mononuclear complex of Pd was generated by addition of triphenylphosphine while the allene was regenerated when the complexes were charged with aqueous ammonia. Lupin's work allowed for the plausible mechanism to be proposed (**Scheme 4.2**): first palladium coordinates one of the double bonds, followed by insertion of the allene into one of the palladium-chloride bonds initiating migration of the chloride to the β-position, a π-allyl motif is then generated accompanied by the dimerization of the complex. The dimerized allene complexes are presumed to arise from an additional allene insertion following the first allene insertion, but preceding the chloride migration.



Scheme 4.2: Proposed Mechanism for Allene-Palladium Complex Formation



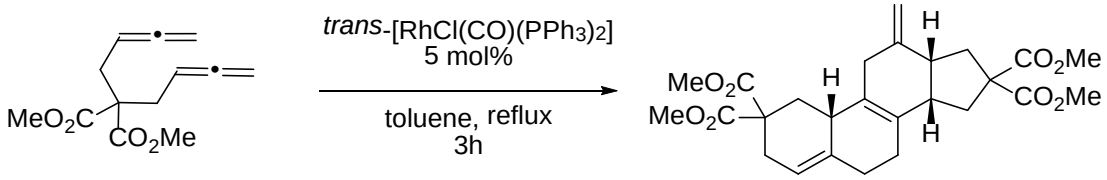
Further exploration of the nuances that effect allene insertion reactions with metals was conducted by Bai, et al.[40] Utilizing ruthenium and osmium surrogates, along with supporting theoretical calculations, they found that change of the initial ligands can change whether an η^3-allyl or vinyl complex is produced. The octahedral Os (II) and Ru (II) containing a carbonyl ligand produced the η^3-allyl complex following insertion, while the trigonal bipyramidal Os (II) and Ru (II) insertion products produced vinyl complexes with an additional allene ligand coordinating the metal. Their calculations show that the electron poor nature of the central carbon of allene favors the η^3-allyl complex, however, more electron rich metal centers allow the vinyl complex to be obtained.



III. Conclusion

As has been shown herein, there are a plethora of structures for allene-metal complexes, from the common η^2-coordinations to the exotic μ-η^1,η^3-allyl. Exploration of reactions utilizing these complexes has begun to come to fruition, but most research has been focused upon transformations of the allenes; through ligation, controlled and selective reactions upon the allenes are possible. Once complexed allenes have shown resistance to hydrogenation,[41a] but forcing conditions have allowed for hydrogenation of a single olefin of allene.[41b] It has been shown that allenes can also be selectively protonated,[18, 20] which is a transformation that continues to be explored.[42] Following similar pathways as the insertion reactions, vide supra, *O*- or *S*-sulfinates can be formed via similar pathways,[43] as well, the addition of amine to form allyl amines has been demonstrated.[43c] Once complexed to metals, allenes also undergo oligomerisation and polymerization.[44] One of the more stunning applications of transformation upon ligated allenes was demonstrated by Ma, et al. By taking advantage of the previous work on oligomerisation, bisallenes where coordinated to rhodium, where once heat was applied a dimerizing cascade reaction takes place to reveal a steroid skeleton, **Scheme 4.3**.[45]

Scheme 4.3: Ma's Steroid Synthesis via Allene Oligomerisation



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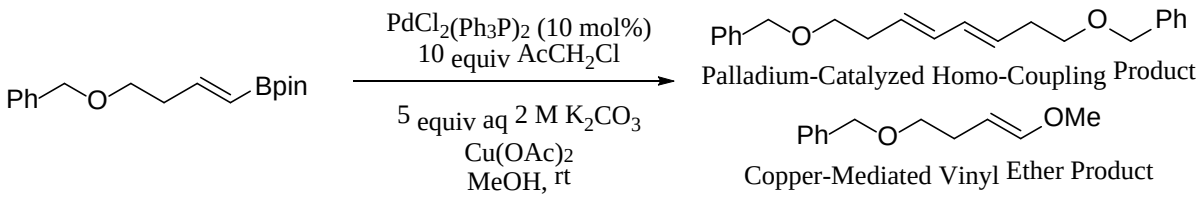
CHAPTER FIVE

Allenes as π-Bond Ligands in Copper-Mediated Cross-Coupling Reactions: Further Exploration of Vinyl Ether Preparation.

I. Introduction

During the pursuit of optimized conditions for the palladium-catalyzed oxidative couplings of pinacol vinylboronates, Merlic et al.[1] unexpectedly observed a vinyl ether product, the result of oxidative coupling with the alcohol solvent. It was found that copper(II) acetate, a putative palladium reoxidant, was responsible for this side reaction (**Scheme 5.1**). The copper-mediated coupling of alcohols with aryl boronic acids to generate aryl ethers had been reported previously by Chan-Lam[2] and Evans[3] in what is referred to as the "modern Ullman coupling" since they use aryl boronic acids in place of aryl halides.[4] These process had not addressed the synthesis of simple alkyl and allyl vinyl ethers.

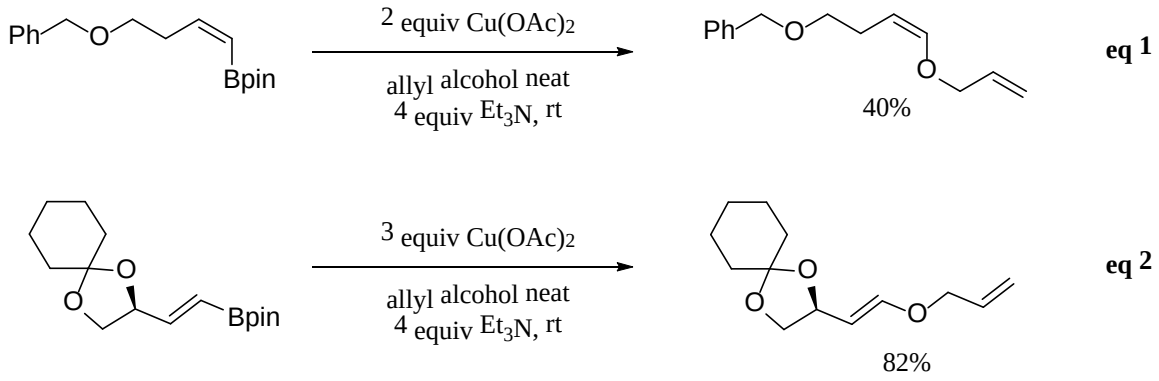
Scheme 5.1: Serendipitous Copper-Mediated Vinyl Ether Synthesis



The utility of a gentle vinyl ether synthesis was not overlooked by Merlic et al., being that the vinyl ether structure is deceptively simple in appearance with no general preparation. Studying the common methods of vinyl ether synthesis reveals limitations with respect to stereocontrol and substrate scope, furthermore, many existing protocols require toxic metals, strong bases or acids, or reactive electrophiles.[5] In contrast to previously reported methods for

the synthesis of vinyl ethers, the oxidative coupling reaction of alcohols and vinylboronates observed by Merlic et al. has distinct advantages, notably, the reaction is stereospecific (**Scheme 5.2, eq 1**), and compatible with acid labile substrates (**Scheme 5.2, eq 2**).[6]

Scheme 5.2: Noteworthy Examples of Copper-Mediated Vinyl Ether Synthesis

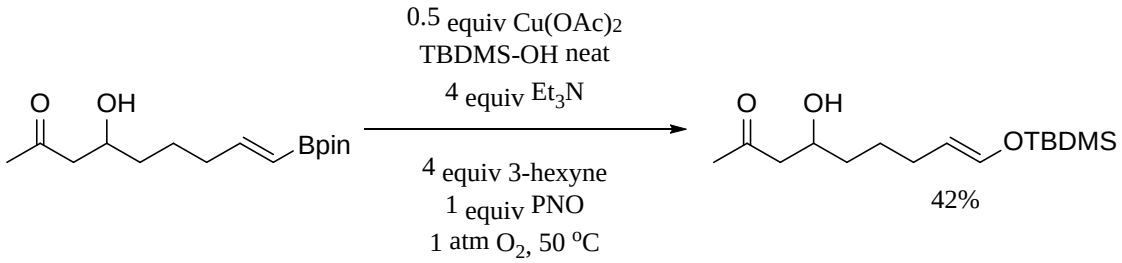


During further exploration of this coupling reaction, decreasing yields were observed as the size of the alcohol increased. However, when allyl alcohol was utilized, there was a higher yield then what the observed trend would have predicted based solely on chain length. Examining substituted ethyl alcohols did not give the same benefit, implying that this was not an inductive electronic effect, but the π-bond acting as a Lewis base to the copper. These observations led to the exploration of ligands that may promote the desired coupling pathway, thus, a variety of ligands were screened.[7] Nucleophilic ligands, such as phosphines, were found to be detrimental to the desired coupling reaction. It was observed that π-bond ligands with electron withdrawing groups completely shut down the reaction. Strained π-bonds, such as norbornene, provided a large increase in yield most likely attributed to an increase in π-Lewis basicity.[8] Alkynes were found to be the most efficient π-bond ligands, with 3-hexyne being the ligand of choice in regards to increasing the yield.

With an optimized system for copper-mediated vinyl ether synthesis, expansion to silyl enol ethers was successfully undertaken by Winternheimer et al.[9] It was found that no productive

reaction was observed without the use of 3-hexyne. Furthermore, the production of silyl enol ethers via copper coupling was found to progress using only a catalytic amount of copper, 50 mol %, so long as the reaction was conducted under an oxygen atmosphere in the presence of pyridine *N*-oxide as a co-oxident. Perhaps the most impressive example is shown in **Scheme 5.3**, wherein a vinylboronate containing both ketone and alcohol functional groups coupled successfully. As of yet, there is no other feasible direct silylation of hydroxy ketoaldhydes that compares to the copper-catalyzed coupling of silanol and hydroxyl ketoboronate.

Scheme 5.3 Copper-Catalyzed Coupling with Silanol and Hydroxy Ketoboronate



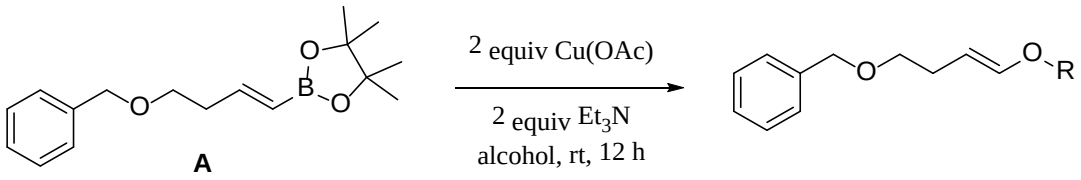
Despite these early successes, there were improvements still necessary for the copper coupling reaction. Specific questions included: was there a π-bond ligand better than 3-hexyne? Could the coupling be obtained with less than super-stoichiometric amounts of alcohol? Could the coupling with longer chain alcohols be improved? Could the coupling with branched alcohols be improved? And, could the ligand effect observed here be applicable to other copper based transformations?

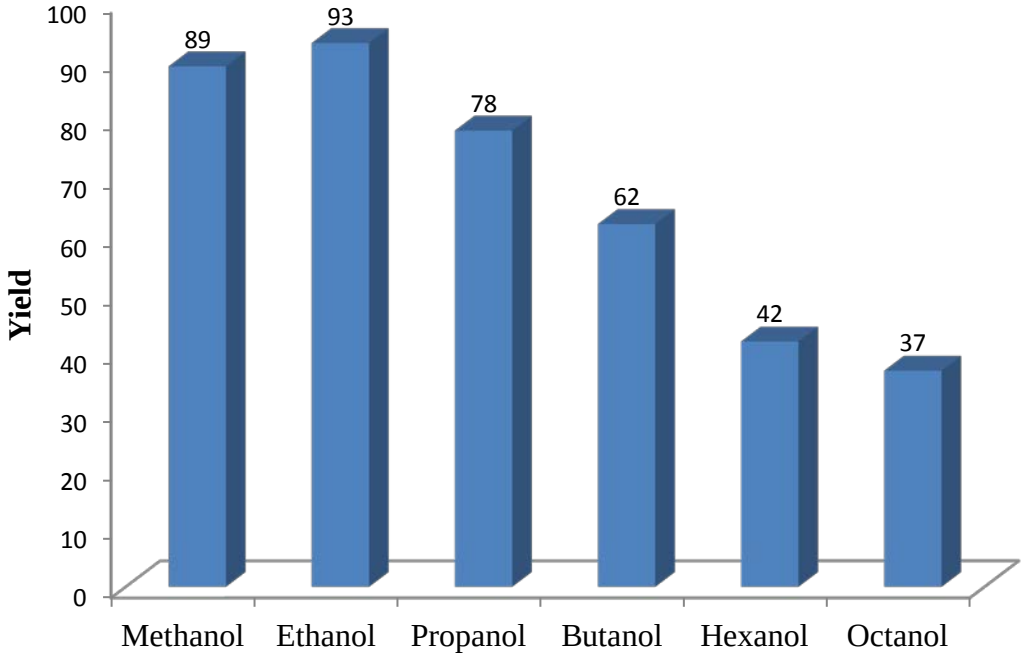
II. Results and Discussion

A. Survey of Alcohol Chain Length

While screening alcohol coupling partners, a trend was observed with regards to alcohol chain length and branching. It was observed that tertiary alcohols failed to couple, while secondary alcohols showed greatly diminished yields. However, primary alcohols showed excellent potential as coupling partners. Among primary alcohols, the coupling yield was found to be inversely related to chain length, **Graph 5.1**. The use of vinylboronate **A** was implemented with this survey due to its previous viability as a coupling partner.[6]

Graph 5.1: Survey of Alcohol Chain Length

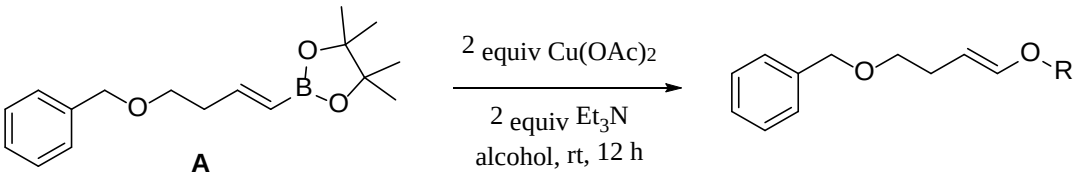


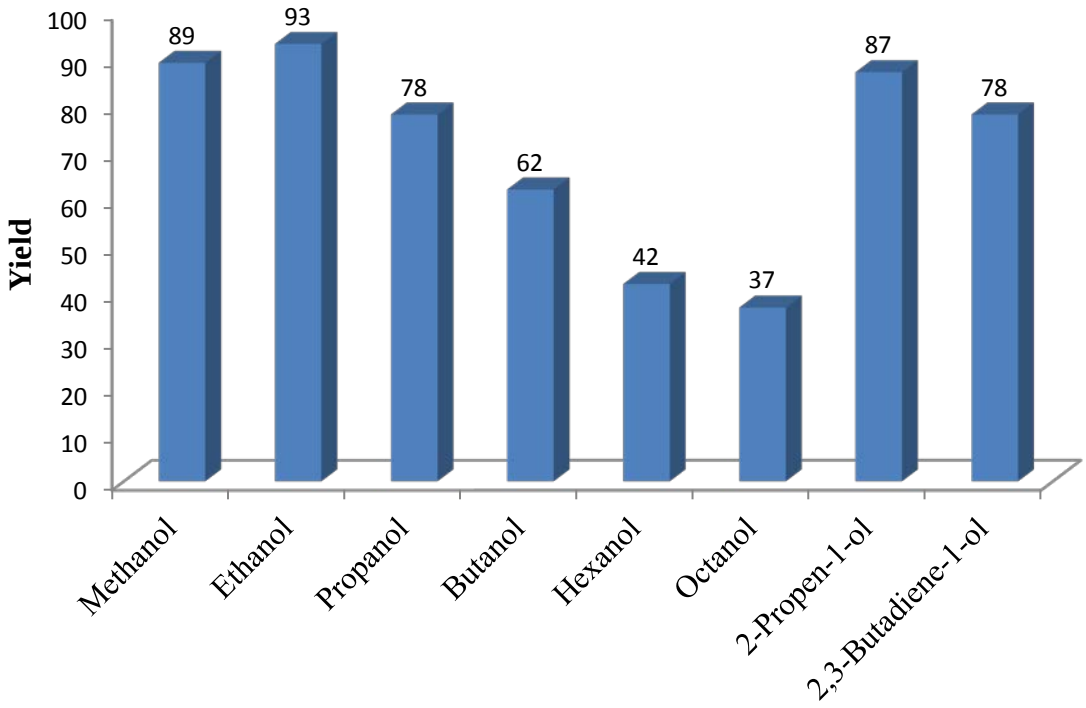


B. The Effects of Auto-Ligation

A remarkable effect was observed with the coupling of alcohols that contain a π-bond, an increase in yield was observed contrary to the predicted effects of the chain length (**Graph 5.2**). It was proposed that the π-bond was behaving as a ligand to promote the reaction. The initial exploration of this effect was carried out by Winternheimer, et al.[7] His work found that strongly nucleophilic ligands, such as phosphines, prevented any desired reaction, but π-bonds had a positive effect upon the reaction. Winernheimer observed terminal alkynes to have a negative effect while terminal alkenes to have no effect, yet internal alkenes, particularly those possessing ring strain, were beneficial. After examination of a myriad of potential π-bond ligands, 3-hexyne stood out as a viable π-bond ligand for this reaction.[7] Advantages of 3-hexyne as a ligand include low cost, ease of removal and low molecular weight. The comparison of alcohol chain length versus that of auto-ligating alcohols is shown in **Graph 5.2**. It is noted that allyl alcohol is a more efficient coupling partner then that of propanol, and that β-hydroxy allene is comparatively more efficient then its saturated analogue butanol. This second experiment alludes to the ability to utilize allenic species as potential ligands.

Graph 5.2: Survey of Alcohol Chain Length and the Effects of Auto-Ligation

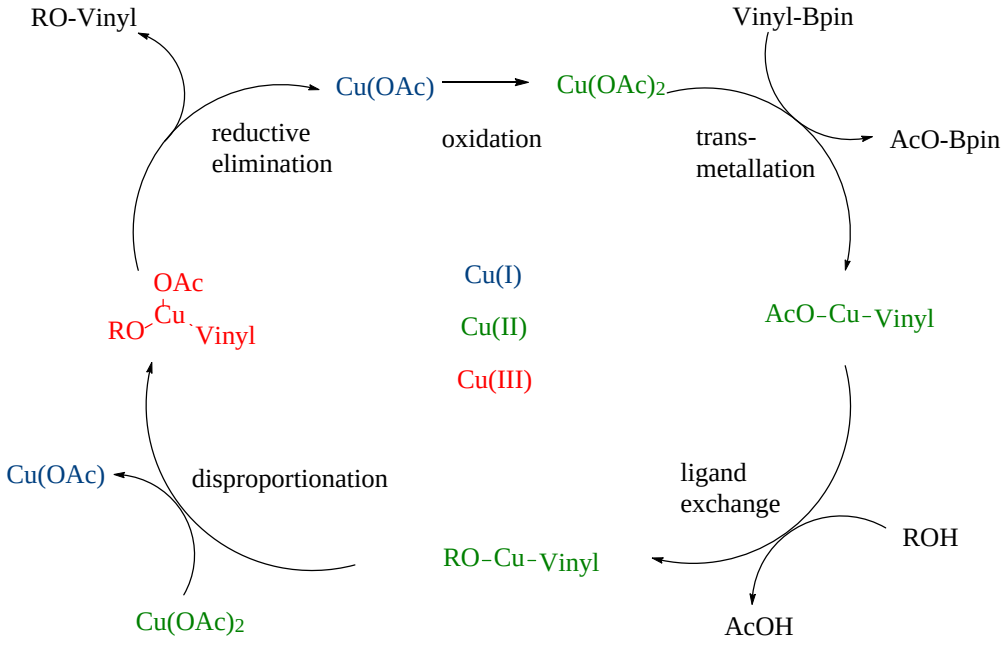




C. Mechanism

Shown in **Figure 5.1** is a plausible mechanism for the copper-mediated coupling of vinylboronates and alcohols to produce vinyl ethers. Mechanistic insights were gleaned from similar copper couplings, i.e. the Ullmann coupling and condensation,[10] as well as those developed by Chan-Lam[2] and Evans.[3] The mechanism begins with transmetallation between copper(II) acetate and vinylpinacolatoboronates to produce vinyl-copper acetate. The vinyl-copper acetate then undergoes ligand exchange with an alcohol to give an alkoxy vinyl-copper(II). This more electron rich copper(II) species then undergoes an oxidative disproportionation with another copper(II) acetate to produce an alkoxy vinyl-copper(III) acetate intermediate, which rapidly undergoes reductive elimination to yield the vinyl ether and copper(I) acetate.

Figure 5.1: Plausible Mechanism for Copper-Mediated Coupling



D. Preparation of Substrates as Possible Lewis Basic π-Bond Ligands

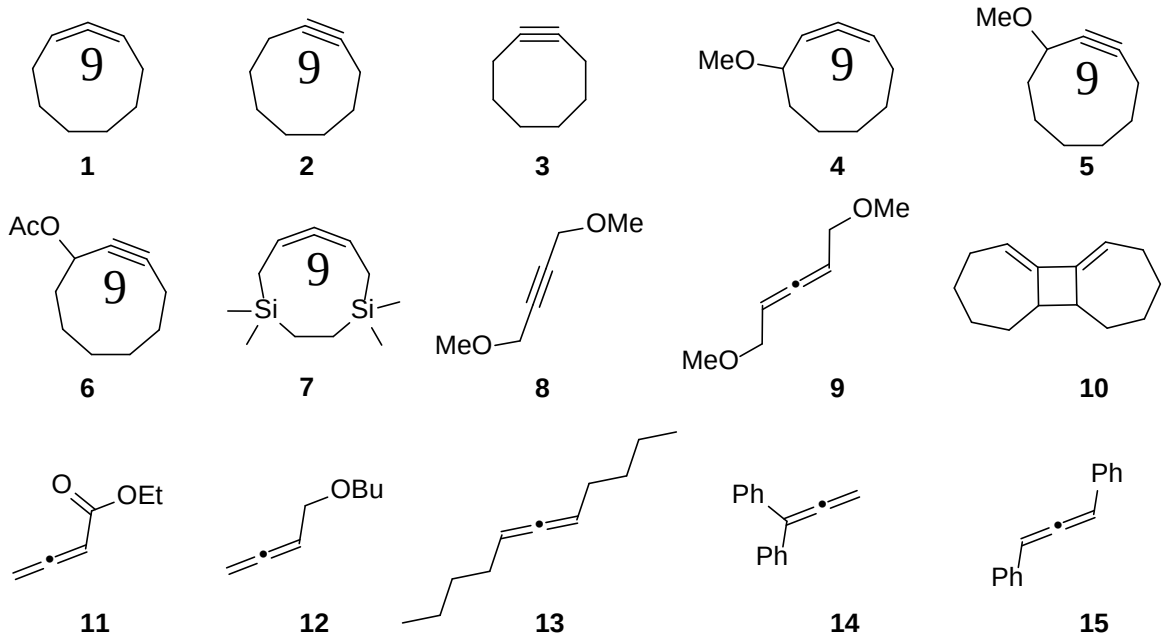
Theoretical work conducted by Dr. Chen examined the free energy profile for the copper-coupling mechanism.[11] His work shows a 20 kcal/mol decrease in energy for the disproportionation when there is a π-bond ligand present; ethylene was used for simplification of the calculations. This difference changes the rate-determining step from disproportionation to transmetallation. Dr. Chen's work also shows a binding affinity of allenes to copper salts, with the greatest binding affinity to Cu(I). This suggests that the ligand may be assisting in the disproportionation to Cu(III) and through the rapid reductive elimination so as to sequester the Cu(I). With information garnered from previous π-bond ligands, and burgeoning theoretical findings, examination of 1,2-dienes as π-bond ligands was undertaken.

To delve deeper into the ligand effect, fifteen ligands, shown in **Figure 5.2**, were synthesized and screened for yield on the copper-mediated coupling. Taking insights into the benefit of ring strain of cyclic alkenes on coordination behavior, the preparation of cyclonona-1,2-diene (**1**) was conducted via dibromocarbene insertion into cyclooctene followed by Skattebøl rearrangement.[12] The assistance of Robert Tobolowsky was enlisted for the preparation of 8 ligands. Starting from cyclooctene, Tobolowsky prepared five ligands: as mentioned above cyclonona-1,2-diene (**1**), but also cyclononyne (**2**), cyclooctyne (**3**), 4-methoxycyclonona-1,2-diene (**4**), 3-methoxycyclonon-1-yne (**5**), and 3-acetocyclonon-1-yne (**6**). Utilizing ring-closing metathesis of 1,2-bis(allyldimethylsilyl)ethane followed by dibromocarbene addition and Skattebøl rearrangement Tobolowsky produced silicon-containing cyclic allene 1,1,4,4-tetramethyl-1,4-disilacyclonona-6,7-diene (**7**). He produced 1,4-dimethoxybut-2-yne (**8**) via methylation of but-2-yne-1,4-diol. Finally, Tobolowsky found that

1,5-dimethoxypenta-2,3-diene (**9**) was deceptively difficult-to-obtain, he was able to prepare it from *cis*-1,4-butenediol.

To further expand upon the effects of structure and electronics, 5 additional ligands were produced. To complement **1**, synthesis of cyclohepta-1,2-diene was attempted, yet as predicted by Bredt's rule,[13] and other studies,[14] the ring strain was too great and the material dimerized to produce tricycle[5.0.0.5]tetradeca-1,13-diene (**10**). Ethyl 2,3-butadienoate (**11**) was produced via Wittig olefination upon an in-situ generated ketene.[15] A substitution reaction between 2,3-butadien-1-ol and 1-bromobutane was employed to produce 4-butoxybuta-1,2-diene (**12**). Cross-metathesis dimerization of 1-hexene followed by the Skattabøl procedure produced undeca-5,6-diene (**13**).[16] Again utilizing the Skattabøl procedure upon 1,1-diphenylethene produced 1,1-diphenyl-propyl-1,2-diene (**14**), but these conditions failed with 1,2-diphenylethene. Fortunately, isomerization of 1,3-diphenyl-1-propyne produced the desired 1,3-diphenyl-propyl-1,2-diene (**15**).[17]

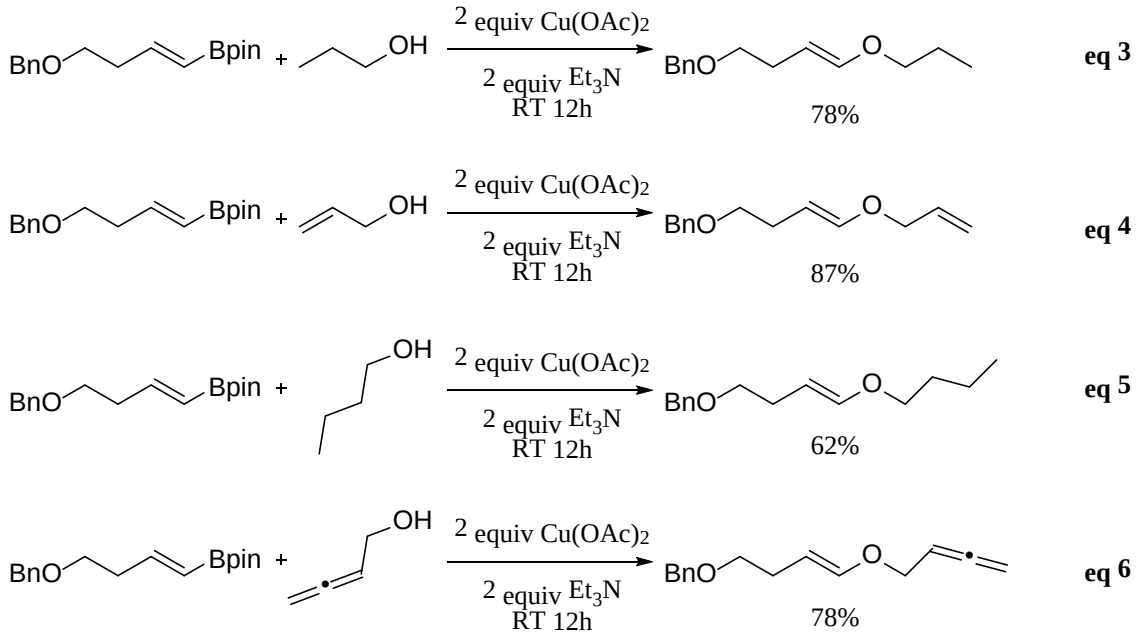
Figure 5.2: Structure of Synthesized π-Bond Ligands



E. Coupling with 2,3-Butadien-1-ol

Not only were we curious about the effects of allenes as ligands, but also their potential as coupling partners. To this pursuit, 2,3-butadien-1-ol, β-hydroxyallene, was prepared via hydride addition with $LiAlH_4$ upon 4-chloro-2-butyn-1-ol, causing an S_N2' elimination of the chloride;[18] access to β-hydroxyallene via hydride addition to 4-triethylamonium-2-butyn-1-ol proved too inconsistent.[18] As was shown previously in **Table 5.2**, the effects of auto-ligation can be observed with β-hydroxyallene. In **Scheme 5.4** are the reproduced results allowing for the direct comparison of auto-ligation. As has been observed,[7] a boost in yield is seen between alcohols of similar size. For comparison, the difference between yield for propanol and allyl alcohol is shown in **eq 3** and **eq 4** respectively. This trend is repeated in the observed yields of butanol and β-hydroxyallene, **eq 5** and **eq 6** respectively.

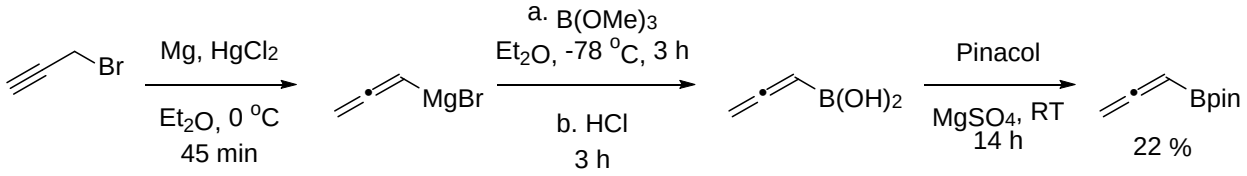
Scheme 5.4: Comparison of Auto-Ligating Alcohols to their Saturated Counterparts



F. Coupling with 1,2-Propadien-1-pinacolatoborane

In contrast to the allenic species being the alcohol component, we also examined the allene as the vinylboronate partner. The test substrate 1,2-propadien-1-pinacolatoborane, α-allenyl-Bpin, was prepared from 1-bromo-2-propyne via Meyer-Schuster rearrangement[20] with the addition of magnesium, this allenylmagnesium bromide is then cannulated into a solution of trimethylborate, followed by addition of pinacol as shown in **Scheme 5.5**.[21] To our chagrin α-allenyl-Bpin has so far evaded productive coupling. Attempts to couple with butanol, allyl alcohol, and crotyl alcohol only gave decomposed material; these results were not altered with the addition of 3-hexyne as a ligand. The use of benzyl alcohol only saw copper-mediated oxidation to benzaldehyde rather than the desired coupling. It is presumed that the α-allenyl-Bpin is undergoing a Meyer-Schuster rearrangement[20] once it transmetallates with copper, this is then proceeded by a Glaser coupling[22] to give the homocoupled diyne. With further substitution upon the α-allenyl-Bpin, this side pathway should be shut down, but this has not yet been tested.

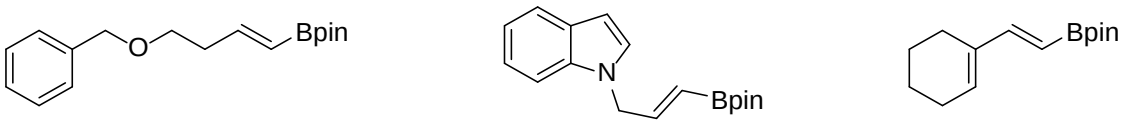
Scheme 5.5: Preperation of 1,2-Propadien-1-pinacolatoborane



G. Survey of Allenes and Select Alkynes

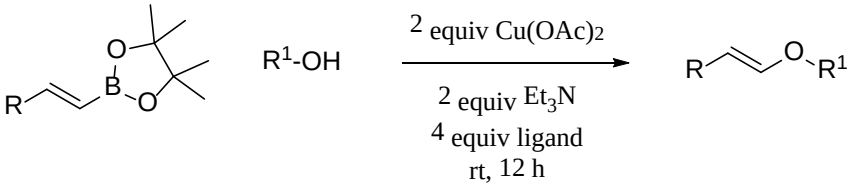
The main enterprise of this work is the further investigation of the π-bond ligand effect. To this end, a number of π-ligands have been prepared, vide supra, and screened under a collection of conditions to probe their effect upon the coupling. Shown in **Figure 5.3** are three vinylboronates utilized for this screening: benzyloxy-3-(*E*)-butenyl-4-pinacolatoboronate (**A**), *N*-2-(*E*)-propenyl(3-pinacolatoboronate) indole (**B**), and 2'-pinacolatoboronate-1-(*E*)-ethenyl-1-cyclohexene (**C**). **Table 5.1** shows the effects of the ligands upon reaction yield with the aforementioned vinylboronates, compared with five different alcohols: allyl alcohol (**a1**), crotyl alcohol (**a2**), ethanol (**a3**), 2-chloroethanol (**a4**), and isopropanol (**a5**). These results were also compared against the previously proven ligand 3-hexyne (**16**),[7] and without ligand (**17**).

Figure 5.3 Vinylboronates Utilized for the Screening of Ligands



A **B** **C**

Table 5.1: Screening of Ligands 1 through 17 on the Copper-Mediated Vinyl Ether Synthesis[a]



R-Bpin	R^1OH	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
A	**a1**	94	69	72	92	41	56	89	83	63	-	28	34	62	33	57	91	87
A	**a2**	90	-	-	-	-	-	56	61	-	52	-	-	-	-	-	65	31
A	**a3**	96	-	-	-	-	-	-	-	-	-	-	-	-	-	-	98	93
A	**a5**	52	-	-	-	-	-	-	-	-	-	-	-	-	-	-	47	18
B	**a1**	84	-	-	-	-	-	-	-	-	-	-	-	-	-	-	75	-
B	**a2**	88	-	-	-	-	-	-	-	-	55	-	-	-	28	-	76	-
B	**a3**	90	-	-	-	-	-	-	-	-	-	-	-	-	-	-	87	-
B	**a4**	84	63	<1	78	-	-	66	24	-	55	22	45	45	40	44	76	31
B	**a5**	19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	20	-
C	**a1**	86	-	-	-	-	-	-	-	-	-	-	-	-	-	-	76	-
C	**a2**	88	-	-	-	-	-	54	-	-	-	-	-	-	-	-	57	-
C	**a3**	94	-	-	-	-	-	-	-	-	-	-	-	-	-	-	94	-
C	**a4**	89	-	38	-	-	-	78	84	-	-	0	30	31	-	38	77	11
C	**a5**	66	-	-	-	-	-	-	-	-	-	-	-	-	-	-	58	-

[a] Isolated yields.

Extracting from **Table 5.1,** and presented in **Graph 5.**3, are the results of allyl alcohol (**a1**) coupling with vinylboronate **A** in the presence of different ligands. This allows for the analysis of ligand structure upon the production of vinyl ethers. Entry **17,** at 87% yield, shows the control reaction without ligand present; this represents the key comparative point where yields above benefit the desired reaction, while those below favor other reaction paths or facilitate decomposition of the starting materials. As well, the 91% yield employing ligand **16** is the result from 3-hexyne, the previously observed most efficient ligand.[7]

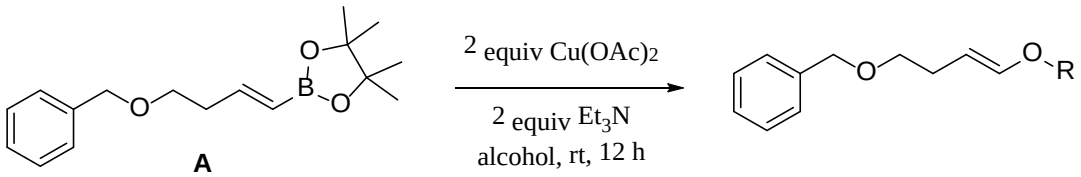
Cyclononaallene, ligand **1**, in comparison with all other substrates was shown to have the most beneficial effect. This effect is attributed substantially to ring strain, as such, the use of the

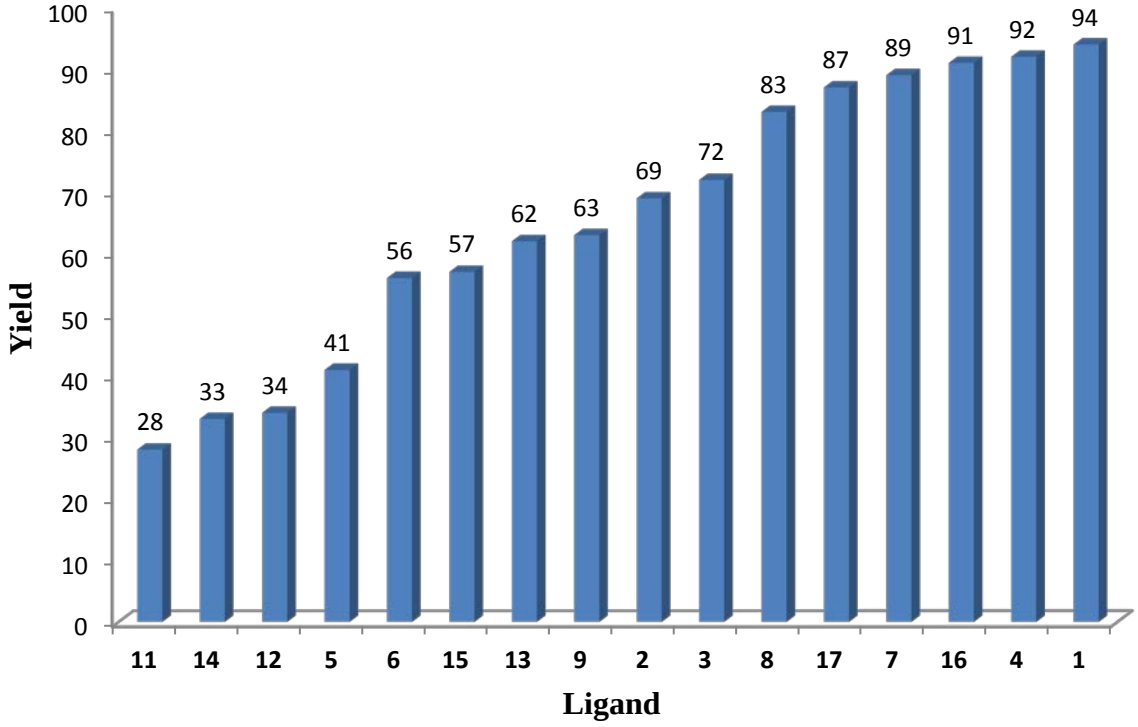
nine membered disilyl ring, ligand **7**, was explored. The reduced yield using ligand **7** is assumed to arise from the greater bond length of the four Si-C bonds as compared to the all carbon-containing cyclononaalene thus reducing ring strain and the resultant π-basicity. Ligand **4**, a cyclononaallene ligand with an allylic methoxy functionality reacted comparatively to the unfunctionalized cyclononaallene. However, it is not readily available.

In trying to further explore ring strain upon π-bonds, the cyclic alkyne ligands **2**, **3**, **5**, and **6**, were made. These ligands were observed to undergo competing reactions with the vinylboronate. In trying to further push the ring strain effect on allenes the synthesis of cycloheptaallene was attempted, but led to its dimerization (ligand **10**), screening of this 1,3-diene showed no benefit.

Previous work has shown 3-hexyne (ligand **16**) to be a viable ligand choice, so ligands with similar motifs were tried. The dimethoxy containing ligand **8** saw a reduced yield compared to its all carbon counterpart 3-hexyne, and the allenic version, ligand **9**, was just as ineffective. The linear all carbon internal allene, ligand **13**, was inadequate, but does reveal the necessity of strain on the π-bonds to improve coordination to copper. Neither the 1,1-diphenyl or 1,3-diphenyl allenes, ligand **14** and **15** respectively, showed any benefit to this reaction. Terminal alkenes had been observed to be ineffective,[7] which remained true with allene ligand **12**. As well, electron withdrawing groups often interfered with the reaction,[7] but some coupling was observed with ligand **11**, which can be attributed to the fact that allenes have two π-bonds for ligation.

Graph 5.3: Ligand Effect on Allyl Alcohol Coupled with Vinylboronate A

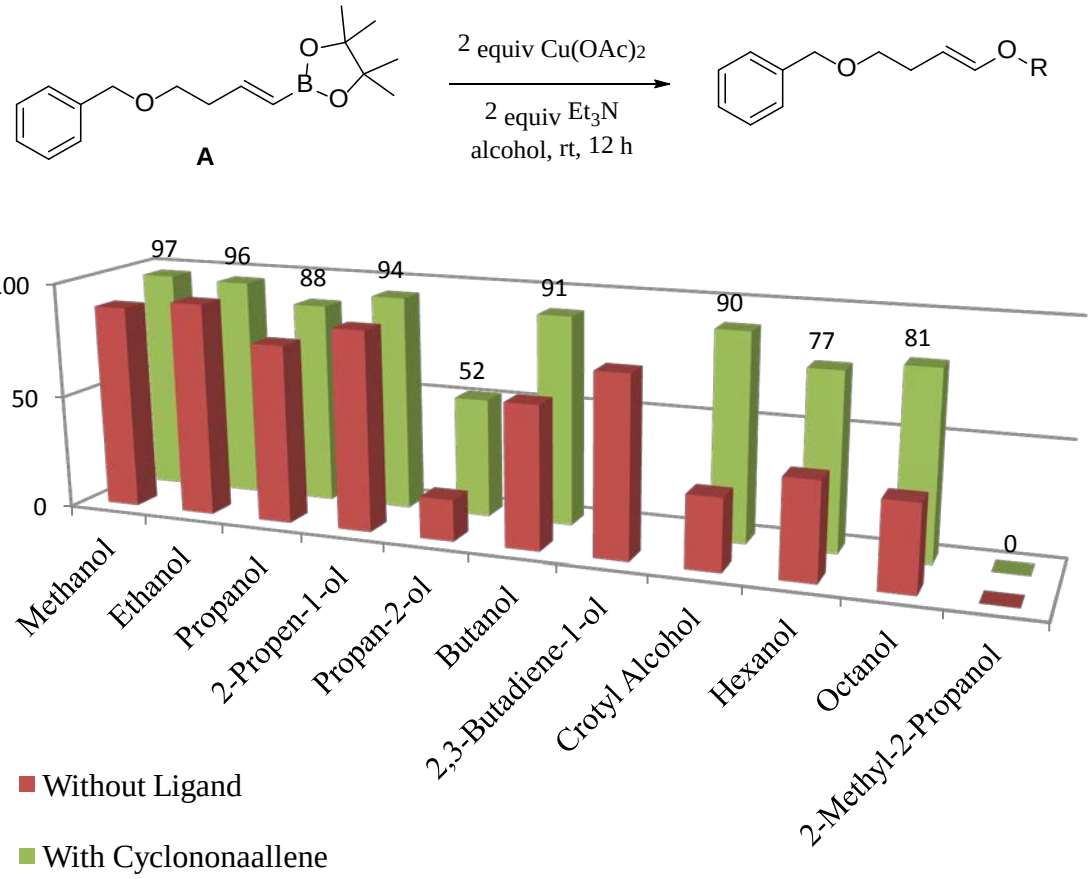




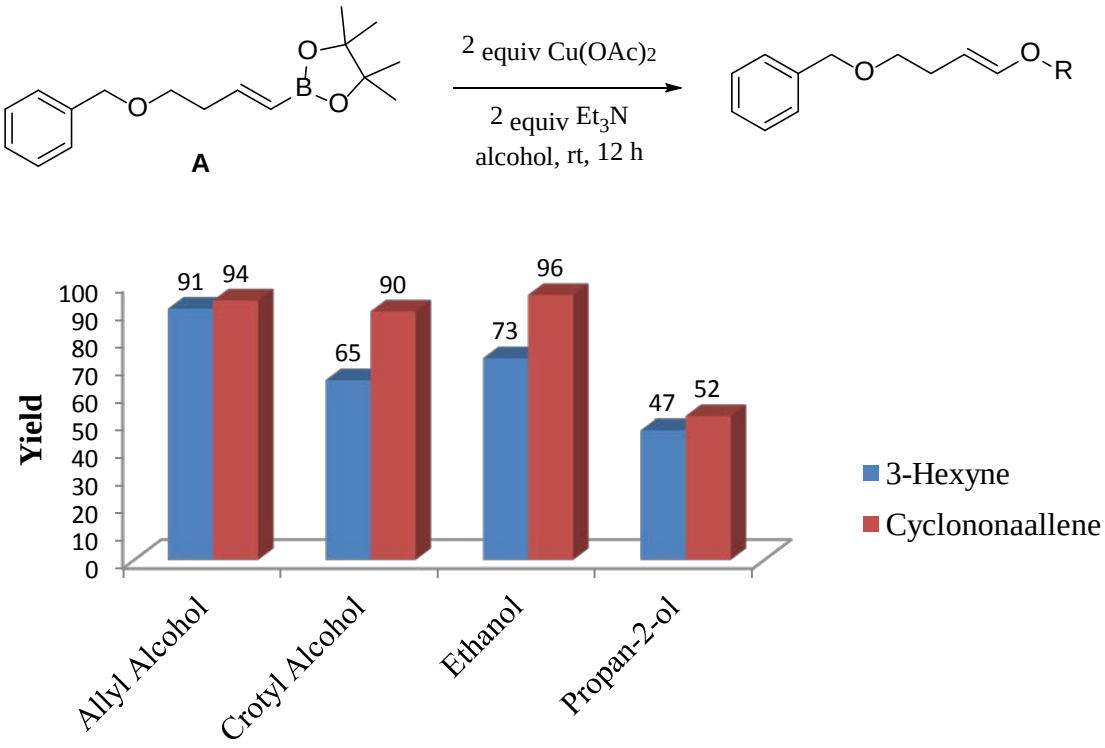
H. Survey of Cyclononaallene

Cyclononaallene was screened against a variety of alcohols and vinylboronates to examine its efficacy. Shown in **Graph 5.4** is the coupling of vinylboronate **A** and a variety of alcohols. A marked increase in yield is observed when cyclononaallene is utilized versus the lack of any ligand present. Further analysis of the great utility of cyclononaallene is shown in **Graph 5.5**, where the same coupling conditions are compared against those in the presence of 3-hexyne. Shown in **Graph 5.6** and **Graph 5.7** are the comparative results of cyclononaallene versus 3-hexyne in the presence of vinylboronates **B** and **C** respectively. These results show unequivocally that cyclononaallene is the ligand of choice for this copper-mediated oxidative coupling reaction.

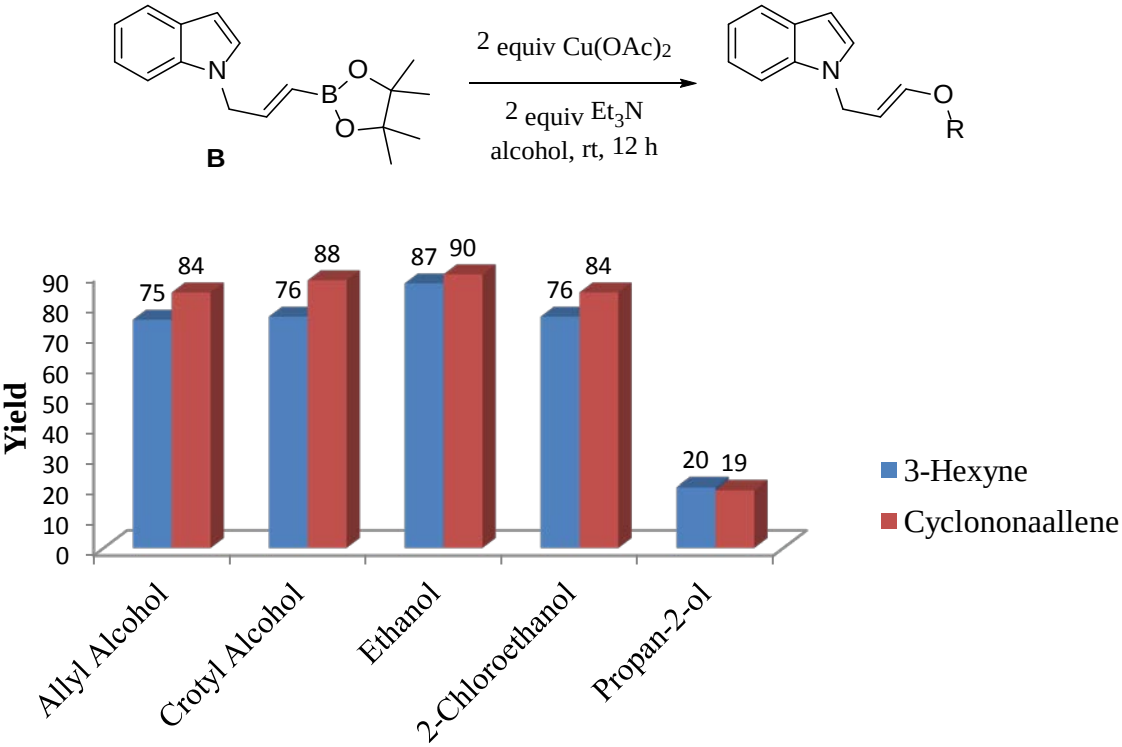
Graph 5.4: Survey of Different Alcohols with and without Cyclononaallene



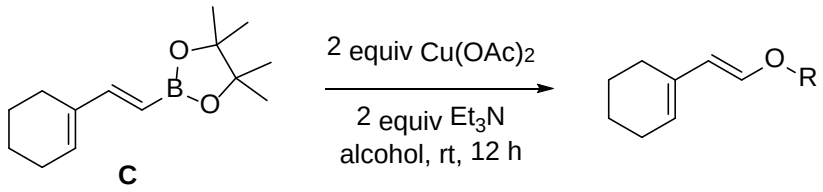
Graph 5.5: Survey of Cyclononaallene versus 3-Hexyne on Coupling with Vinylboronate A

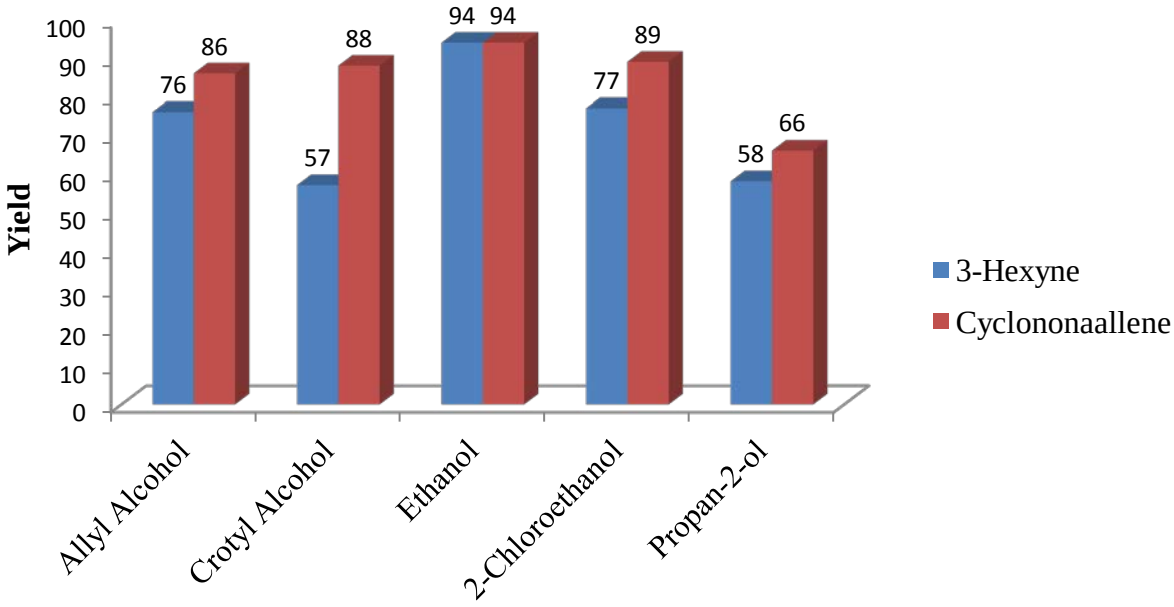


Graph 5.6: Survey of Cyclononaallene versus 3-Hexyne on Coupling with Vinylboronate B



Graph 5.7: Survey of Cyclononaallene versus 3-Hexyne on Coupling with Vinylboronate C

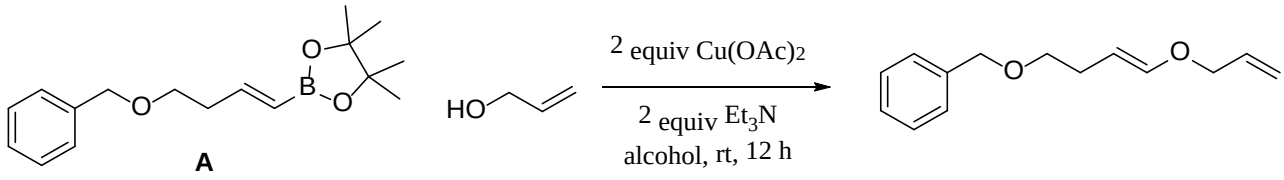




I. Optimization of Alcohol Equivalents

The use of the alcohol coupling partner in super-stoichiometric amounts has been effective with simple and affordable alcohols, i.e. methanol or ethanol, but as the hydroxyl containing partner becomes more exotic this would deter the utility of this reaction. Taking from previous work in screening solvents[7] and utilizing the proven coupling partners vinylboronate **A** and allyl alcohol, a collection of solvents were screened with 2.2 equivalents of alcohol, **Table 5.2**. None of the solvents tested produced results comparable to the 87% yield of the parent reaction and though Hunig's base gave a promising result it was deemed impractical as a solvent. To increase the potential of a productive reaction, 4 equivalents of the alcohol was utilized and the temperature was increased. To our delight, shown in **Table 5.3**, toluene at 60 ^{o}C was found to be effective, giving an acceptable yield of 81% in the presence of 3-hexyne.

Table 5.2: Solvent Screen with 2.2 Equivalents of Alcohol



Entry	Solvent	Without 3-hexyne	With 3-hexyne
1	^{t}Butanol	0	0
2	Et_3N	55	60
3	$(^{i}Pro)_2EtN$	74	74
4	Acetone	30	26
5	Benzene	37	<1
6	Toluene	27	27

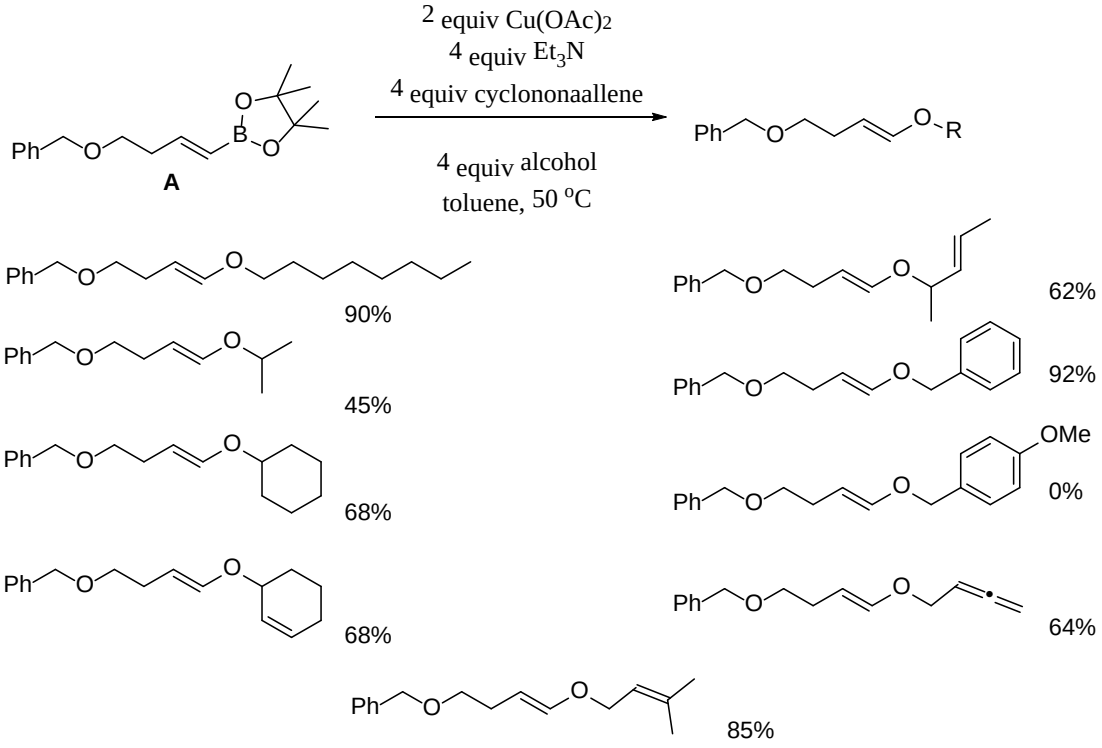
Table 5.3: Solvent Screen with 4 Equivalents of Alcohol at 60 ^{o}C

Entry	Solvent	Without 3-Hexyne	With 3-Hexyne
1	Benzene	59	-
2	THF	58	70
4	CH_3CN	65	68
6	Toluene	77	81

J. Survey of Vinyl Ether Synthesis with Reduced Equivalents of Alcohol

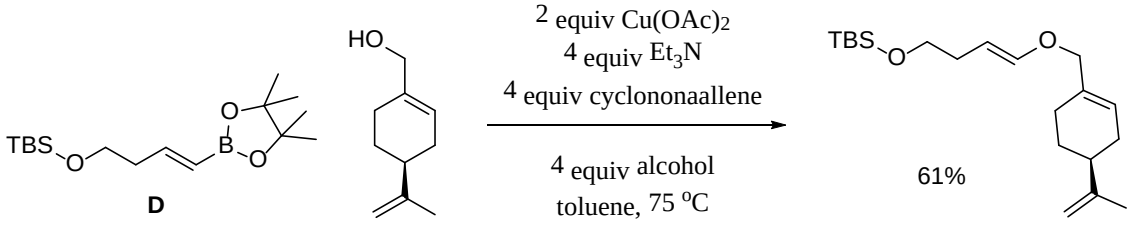
With an optimized reaction environment, and a ligand in hand which shows a greater affinity for promoting the desired coupling, a series of alcohols at reduced equivalents was screened, **Figure 5.3**. These conditions have given rise to previously inaccessible substrates, as well as increasing the yield of formerly poorly reacting alcohols. The desired coupling is now being performed at four equivalents of alcohol, rather than the super-stoichiometric requirements previously needed. This is a boon for expensive alcohols and synthetically time consuming alcohols such as 2,3-butadiene-1-ol. Secondary alcohols are now capable of undergoing the vinyl ether synthesis in synthetically useful yields, as well as alcohols with larger carbon skeletons. The vinyl ether produced from use of benzyl alcohol is now isolable, which previously underwent copper-mediated oxidation to benzaldahyde; unfortunately, *para*-methoxybenzyl alcohol still favors the oxidative pathway.

Figure 5.3: Couplings at 4 Equivalents of Alcohol with Vinylboronate A

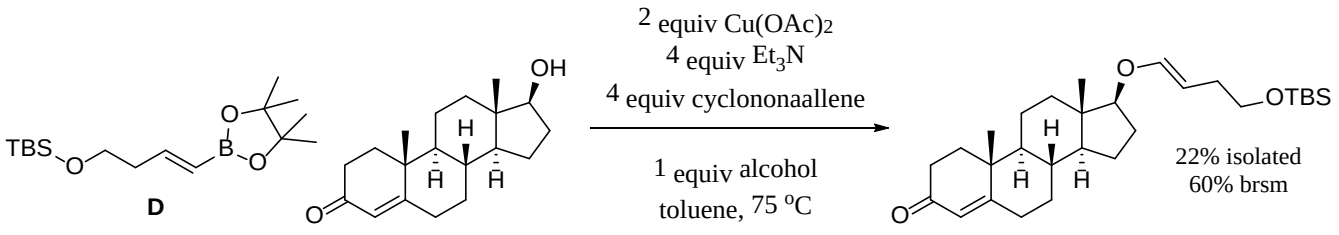


With conditions now optimized to handle more exotic alcohols, the utility of the reaction was tested on bioactive substrates. Shown in **Scheme 5.6** is the coupling of the monoterpene perillyl alcohol with TBS-protected vinylboronate **D**. Increased temperatures expedited the coupling which required vinylboronate **D** since it is less prone to proto-deboration as compared to the other vinylboronates screened. Current research is showing perillyl alcohol as having applications in oncology, but with conflicting clinical trials, this makes it a desirable target for modification.[23] In pushing our coupling to its current limits, we went after the hormone testosterone as the alcohol component, as well, using a single equivalent of testosterone. Coupling this hormone offered the challenges of being a secondary alcohol on a large carbon skeleton, as well as the steric hinderence of being neo-pentyl. To our delight, a 22% yield of the coupled hormone was recovered (**Scheme 5.7**), as well 47% of unreacted vinylboronate **D** and 63% of unreacted testosterone, giving a 50% yield by recovered vinylboronate and 60% yield by recovered testosterone. The coupling of cholesterol with vinylboronate **D** was observed, but purification of the very nonpolar product was problematic.

Scheme 5.6: Coupling of Vinylboronate D with Perillyl Alcohol



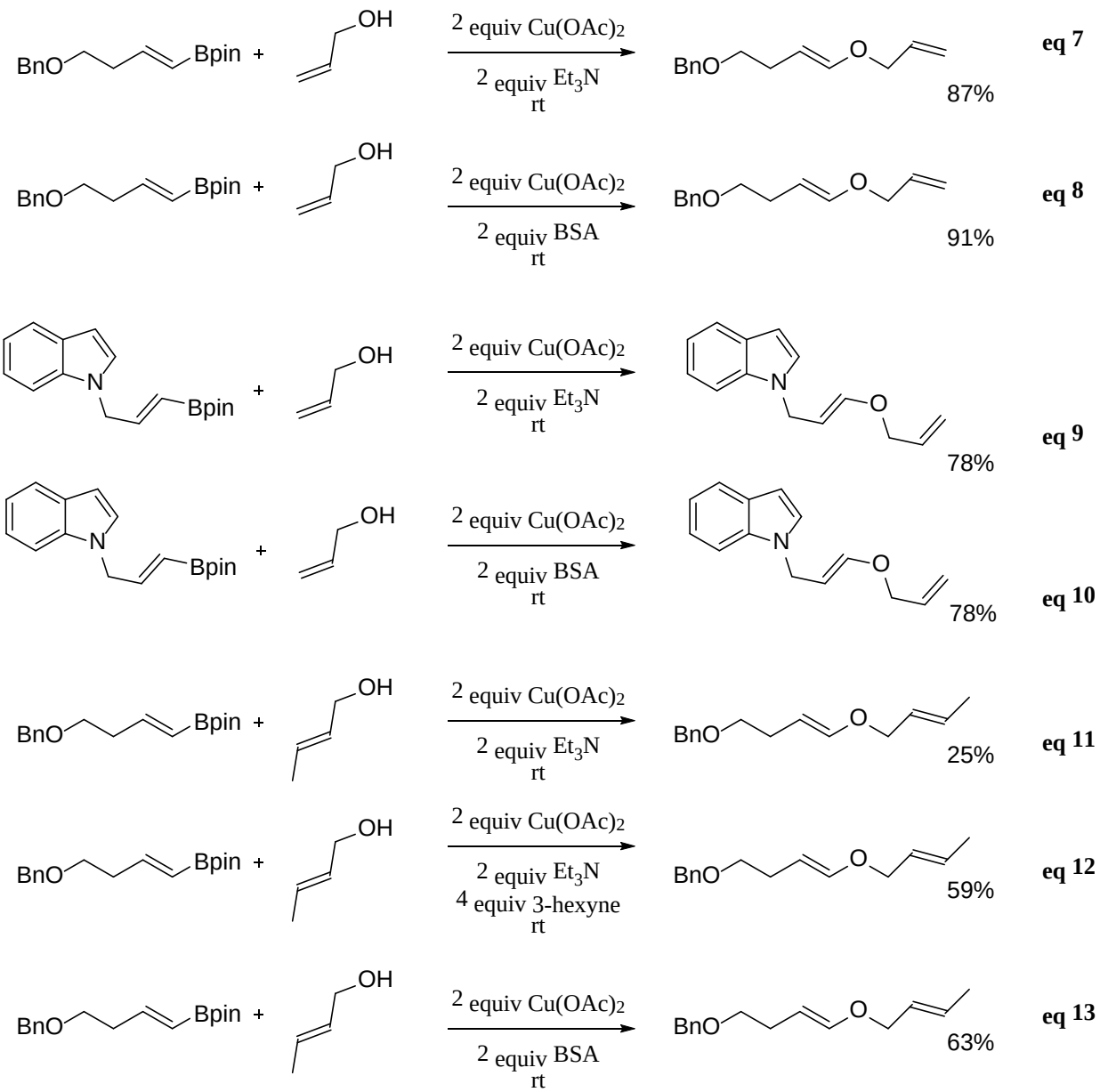
Scheme 5.7: Coupling of Vinylboronate D with Testosterone



K. The Effects of BSA as Base, Ligand, and Possible Water Scavenger

As advances have been made in the optimization of this copper-mediated vinyl ether synthesis, new opportunities for exploration are presented. One of these avenues of exploration, shown in **Scheme 5.8**, is the use of bistrimethylsilyl acetamide (BSA) for its potential as an amine base, a π-bond ligand, and a water scavenger. Instances of competitive water coupling to the vinylboronate resulting in the corresponding aldehyde side product have been observed. Comparing **eq 7** to **eq 8,** and **eq 9** to **eq 10**, BSA is shown to effectively act as the base giving an equivalent yield as the reactions charged with Et_3N. Without any base these reactions are observed to give a 78% and 68% yield respectively.[6] Crotyl alcohol with just Et_3N gives a 25% yield (**eq 11**), but addition of the π-bond ligand 3-hexyne brings that yield to 59% (**eq 12**). Utilizing BSA to replace both ligand and base, a comparative 63% yield is obtained (**eq 13**). The use of BSA does have potential in this course of study, though its reactivity to water does make it bench-top sensitive as it readily breaks down in the presence of ambient moisture.

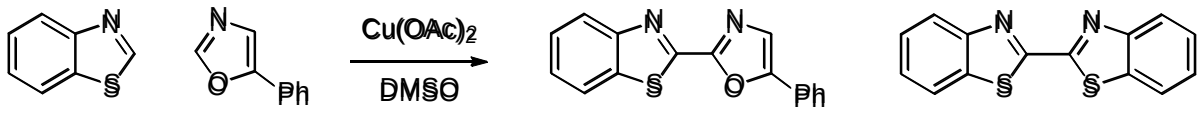
Scheme 5.8: Utilization of BSA as a Base, Ligand, and possible Water Scavenger



L. Effects of π-Ligands on Azole Coupling through C-H Activation

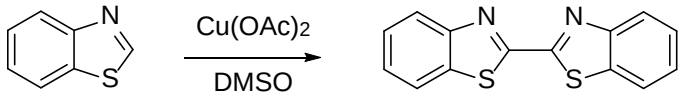
With the π-bond ligand having such a strong effect on copper-mediated vinyl ether synthesis, its effect on other copper coupling reactions that undergo similar disproportionation steps was investigated. The conversion of phenylboronate to bromobenzene was initial sought as a potential target to test the ligand effect,[24] yet cyclononaallene completely shuts the reaction down. The mixed azole coupling through C-H activation presented by Mao, et al. was considered as a viable candidate.[25] Presented in **Table 5.4** are the results of varying the temperature with and without cyclononaallene. At the literature suggested temperature of 130° C, the cyclononaallene decomposes interfering with the reaction, yet at reduced temperatures an interesting competitive homo-coupling of benzthiazole was observed. Shown in **Table 5.5** is the screening of homo-coupling of benzthiazole. It is observed that the homo-coupling is reliant upon the ligand, for even elevated temperatures the $Cu(OAc)_2$ alone is incapable of initiating this transformation. Taken together, the results in tables 5.4 and 5.5 clearly show a π-ligand effect that warrants further exploration.

Table 5.4: Effects of Cyclononaallene on Copper-Mediated Mixed Azole Coupling



130° C, No Ligand	84% (Lit. 84%)[b]	0%
100° C, No Ligand	0%	0%
130° C, Cyclononaallene	0%	18%
100° C, Cyclononaallene	21%	51%
90° C, Cyclononaallene	32%	32%

Table 5.5: Effects of Cyclononaallene on Copper-Mediated Homo-Benzthiazole Coupling



130^{o} C, No Ligand	Decomposition
90^{o} C, No Ligand	<0.1%
90^{o} C, 5-Decyne	2%
90^{o} C, Cyclononaallene	22%
80^{o} C, 3-Hexyne	15%
80^{o} C, Cyclononaallene	26%
20^{o} C, 3-Hexyne	No Reaction
20^{o} C, Cyclononaallene	No Reaction

III. Conclusion

Vinyl ethers have shown their utility in many synthetic transformations, such as the Claisen rearrangement, yet there is no universal way to access this deceptively simple motif. Presented herein is a remarkably gentle and versatile means of forming vinyl ethers. The reaction can be run open to air with gentle heating, and with the utilization of cyclononaallene as a π-ligand substrates as complex as testosterone can be coupled. The effect the cyclononaallene ligand has upon the reaction can be seen by the broadened substrate scope that is now accessible. The effect that π-bond ligands have upon copper-mediated and catalyzed reactions is being further explored; it has been seen to change the reaction pathway with the C-H activated coupling of azoles, and shutdown the conversion of phenylboronate to bromobenzene.[26] Exploring these new results, as well as computational models, will help usher in future mechanistic understanding of the role π-bond ligands play on copper catalysis.

Experimental Section

General Information

Unless otherwise specified, all reactions were performed under a nitrogen atmosphere using dry solvents and anhydrous conditions. Benzene, toluene, and triethylamine were distilled from CaH_2. Et_2O and THF were distilled from sodium/benzophenone. Methanol was distilled from magnesium turnings. All other reagents were used as received from commercial sources, unless otherwise specified. NMR data obtained with Bruker Avance-500, ARX-500, or ARX-400 instruments and calibrated to the solvent signal ($CDCl_3$ δ = 7.26 ppm for ^{1}H NMR, δ = 77.0 ppm for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift, multiplicities, and coupling constants (Hz) in the case of J_{CF} coupling. The following abbreviations are used for the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets. High-resolution matrix-assisted laser desorption/ionization (MALDI) mass spectra were recorded from a dihydroxybenzoic acid (DHB) matrix using an IonSpec Ultima 7T FT-ICR-MS instrument with internal calibration. Gas chromatography-coupled mass spectra (EI) were obtained on an Agilent 6890-5975. Reactions were monitored using thin layer chromatography performed on Macherey-Nagel POLYGRAM® SIL G/UV_{254} silica gel TLC plates and visualized with UV light, ceric ammonium molybdate (CAM) stain, or potassium permanganate ($KMnO_4$) stain. Flash column chromatography was performed using DAVISIL® silica gel (40-63 microns) and compressed air.

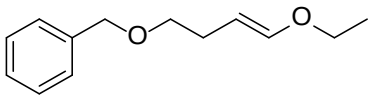
General Procedure

Vinyl Ether Synthesis

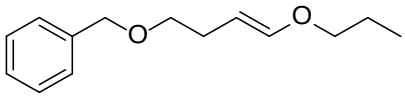
Super-stoichiometric alcohol procedure: A flame dried round bottom flask with a stir bar is charged with 2 mL of alcohol, 0.35 mmol of vinylboronate, copper(II) acetate, 2 equivalents of triethylamine, and 4 equivalents of ligand when indicated. The reaction is stirred at 20^{o} C over 12 h. The progress of the reaction was monitored using TLC (appearance of vinyl ether) using 6:1 hexane:ethylacetate, staining with ceric ammonium molybdate (R_f = ca. 0.5). Upon completion of the reaction, the reaction mixture was added directly and purified by flash chromatography on silica gel (2% ethyl acetate in hexanes).[6,7]

Stoichiometric alcohol procedure: A flame dried round bottom flask with a stir bar is charged with 2 mL of toluene, 0.35 mmol of vinylboronate, 4 equivalents of alcohol (1 equivalent in the case of testosterone), 2 equivalents of triethylamine, copper(II) acetate, and 4 equivalents of ligand where combined. The addition of 1 g of 3 Å molecular sieves was added to cyclohexanol to prevent competitive coupling of ambient moisture. The reaction is stirred at 50^{o} C over 12 h, 75^{o} C over 12 h for perillyl alcohol and testosterone. The progress of the reaction was monitored using TLC (appearance of vinyl ether) using 6:1 hexane:ethyl acetate, staining with ceric ammonium molybdate (R_f = ca. 0.5, 0.1 for testosterone). Upon completion of the reaction, the reaction mixture was added directly and purified by flash chromatography on silica gel (2% ethyl acetate in hexanes). Unreacted testosterone was recovered by flushing the column with ethyl acetate, and recrystalyzing from hexanes. Deuterated chloroform was an applicable NMR solvent for most compounds, but deuterated benzene was used for the vinyl ethers made from cyclohexene, 2-hydroxy-3-pentene, prenyl alcohol, and perillyl alcohol to prevent hydrolysis and possible rearrangement.

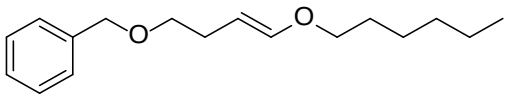
Spectral Data of Vinyl Ethers



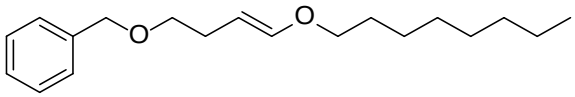
Yield: 93%; clear colorless oil; IR (film) ν_{max} 3048, 2921, 2848, 1452, 1361, 1278, 1264, 1242, 1173, 1098, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 6.31 (d, *J* = 12.8 Hz, 1H), 4.79 (dt, *J* = 12.8, 6.3 Hz, 1H), 4.52 (s, 2H), 3.72 (q, *J* = 7.1 Hz, 2H), 3.46 (t, *J* = 3.5 Hz, 2H), 2.25 (pair of overlapping q, *J* = 2.6 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 138.6, 128.3 (2C), 127.6 (2C), 127.5, 100.0, 72.9, 71.1, 64.6, 28.5, 14.8; MS (MALDI/TOF) calcd for $C_{13}H_{19}O_2$ $[M + Na]^+$ 229.1204, found 229.1223.



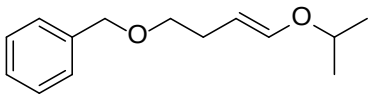
Yield: 88%; clear colorless oil; IR (film) ν_{max} 3055, 2925, 2856, 1512, 1467, 1361, 1266, 1108, 1051, 1032, 1007, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 6.31 (d, *J* = 12.4 Hz, 1H), 4.79 (dt, *J* = 12.4, 6.4 Hz, 1H), 4.52 (s, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.45 (t, *J* = 6.8 Hz, 2H), 2.24 (pair of overlapping q, *J* = 2.6 Hz, 2H), 1.66 (sextet, *J* = 7.1 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 138.5, 128.3 (2C), 127.6 (2C), 127.5, 99.8, 72.8, 71.1, 70.7, 28.5, 22.5, 14.8; MS (MALDI/TOF) calcd for $C_{14}H_{20}O_2$ $[M + Na]^+$ 243.1361, found 243.1502.



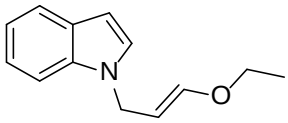
Yield: 42%; clear colorless oil; IR (film) ν_{max} 3030, 2935, 2856, 2246, 1720, 1451, 1359, 1090, 908, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 6.34 (d, *J* = 12.0 Hz, 1H), 4.79 (dt, *J* = 10.0, 5.0 Hz, 1H), 4.54 (s, 2H), 3.66 (t, *J* = 5.2 Hz, 2H), 3.47 (t, *J* = 5.6 Hz, 2H), 2.27 (qd, *J* = 5.9, 0.8 Hz, 2H), 1.68–1.62 (m, 2H), 1.42–1.28 (m, 6H), 0.95–0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 138.5, 128.2 (2C), 127.5 (2C), 127.4, 99.6, 72.8, 71.1, 69.1, 31.5, 29.2, 28.4, 25.6, 22.5, 13.9 MS (MALDI/TOF) calcd for $C_{17}H_{26}O_2Na$ $[M + Na]^+$ 285.1830, found 285.1770.



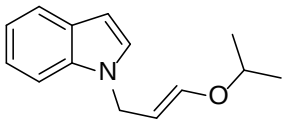
Yield: 90%; clear colorless oil; IR (film) ν_{max} 3086, 3065, 3032, 2928, 2856, 1498, 1469, 1278, 1260, 1144, 1069, 1036, 762, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 6.32 (d, *J* = 12.4 Hz, 1H), 4.78 (dt, *J* = 12.8, 6.3 Hz, 1H), 4.52 (s, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 2.24 (pair of overlapping q, *J* = 2.6 Hz, 2H), 1.67–1.60 (m, 2H), 1.38–1.27 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 138.5, 128.4 (2C), 127.6 (2C), 127.5, 99.7, 72.8, 71.1, 69.2, 31.8, 29.4, 29.3, 29.2, 28.5, 26.0, 22.6, 14.1; MS (MALDI/TOF) calcd for $C_{19}H_{30}O_2$ $[M + Na]^+$ 313.2143, found 313.1937.



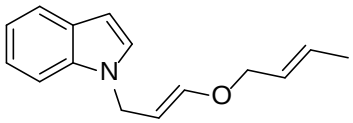
Yield: 52%; clear colorless oil; IR (film) ν_{max} 3061, 3030, 2974, 2927, 2853, 1670, 1651, 1384, 1370, 1182, 1160, 1131, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.16 (dt, *J* = 12.4 Hz, 1.2 Hz, 1H), 4.87 (dt, *J* = 12.4, 6.3 Hz, 1H), 4.51 (s, 2H), 3.95 (heptet, *J* = 6 Hz, 1H), 3.45 (t, *J* = 7 Hz, 2H), 2.23 (qd, *J* = 7.0, 1.2 Hz, 2H), 1.21 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 138.6, 128.3 (2C), 127.6 (2C), 127.5, 101.8, 72.9, 72.4, 71.1, 28.4, 22.1; MS (GC/MS) calcd for $C_{14}H_{20}O_2$ $[M]^+$ 220.1, found 220.1.



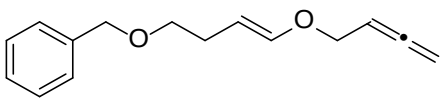
Yield: 94%; faint yellow clear oil; IR (film) ν_{max} 3054, 2977, 2922, 2878, 1672, 1654, 1509, 1476, 1462, 1310, 1182, 931, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8 Hz, 1H), 7.39 (d, *J* = 8 Hz, 1H), 7.22 (t, *J* = 8 Hz, 1H), 7.16 (d, *J* = 4 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 12 Hz, 1H), 6.51 (dd, *J* = 3.0, 0.6 Hz, 1H), 5.00 (dt, *J* = 12.8, 6.4 Hz, 1H), 4.64 (dd, *J* = 7.2, 1.2 Hz, 2H), 3.75 (q, *J* = 7 Hz, 2H), 1.29 (q, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 135.9, 128.8, 127.0, 121.3, 120.9, 119.3, 109.5, 101.1, 98.9, 64.8, 44.8, 14.6; MS (GC/MS) calcd for $C_{13}H_{15}NO$ $[M]^+$ 201.1, found 201.1.



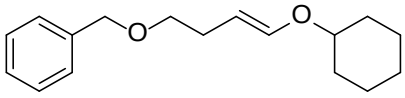
Yield: 66%; faint yellow clear oil; IR (film) ν_{max} 3054, 2974, 2920, 2873, 1671, 1650, 1509, 1462, 1331, 1310, 1183, 1163, 1135, 1117, 931, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8 Hz, 1H), 7.40 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.22 (td, J = 8.0, 0.8 Hz, 1H), 7.17 (d, *J* = 3.2 Hz, 1H), 7.12 (td, *J* = 8.0, 0.8 Hz, 1H), 6.52 (dd, *J* = 3.0, 0.6 Hz, 1H), 6.41 (dt, *J* = 12.4, 1.1 Hz, 1H) 5.10, (dt, *J* = 12.4, 6.3 Hz, 1H), 4.63 (dd, *J* = 7.2, 1.2 Hz, 2H), 4.04 (heptet, *J* = 6.0 Hz, 1H), 1.25 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 135.9, 128.8, 127.0, 121.3, 120.9, 119.3, 109.5, 101.0,100.5, 72.9, 44.7, 22.0 (2C); MS (GC/MS) calcd for $C_{14}H_{17}NO$ $[M]^+$ 215.1, found 215.1.



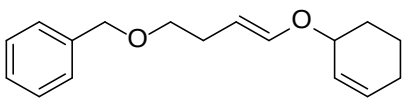
Yield: 88%; yellow clear oil; IR (film) ν_{max} 3056, 3023, 3918, 2856, 1671, 1653, 1509, 1462, 1311, 1165, 965, 935, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.37 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.20 (td, *J* = 8.2, 1.0 Hz, 1H), 7.14 (d, *J* = 4.0 Hz, 1H), 7.09 (td, *J* = 8.0, 1.0 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.49 (dd, *J* = 3.2, 0.8 Hz, 3H), 5.76 (m, 1H), 5.59 (m, 1H), 5.02 (dt, *J* = 12.4, 6.2 Hz, 1H), 4.64 (dd, *J* = 16.0, 1.0 Hz, 2H), 4.14 (d, *J* = 8.0 Hz, 2H), 1.72 (dq, *J* = 6.4, 1.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 135.9, 130.9, 128.8, 127.0, 125.7, 121.3, 120.9, 119.3, 109.4, 101.0, 99.5, 70.1, 44.7, 17.7; MS (GC/MS) calcd for $C_{15}H_{17}NO$ $[M]^+$ 227.1, found 227.1.



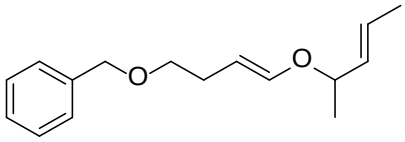
Yield: 78%; clear oil; IR (film) ν_{max} 3062, 3030, 2932, 2862, 1958, 1673, 1648, 1453, 1266, 1159, 1099, 911, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 5H), 6.29 (d, *J* = 16.0 Hz, 1H), 5.27 (pentet, *J* = 9 Hz, 1H), 4.85–4.80 (m, 3H), 4.51 (s, 2H), 4.22 (dt, *J* = 9.2, 3.2 Hz, 2H), 3.44 (t, *J* = 10.0 Hz, 2H), 2.24 (qd, *J* = 9.3, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 146.7, 138.5, 128.3(2C), 127.6, 127.5(2C), 101.2, 87.1, 76.2, 72.9, 70.9, 67.0 28.4; MS (GC/MS) calcd for $C_{15}H_{18}O_2$ $[M]^+$ 230.13, found 230.00.



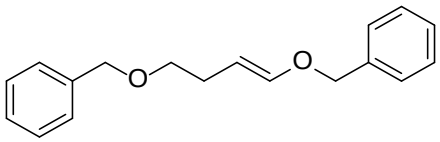
Yield: 68%; clear oil; IR (film) ν_{max} 3009, 2984, 2937, 2868, 1274, 1264, 912 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.18 (d, *J* = 9.6 Hz, 1H), 4.88 (dt, *J* = 10.0, 5.0 Hz, 1H), 4.51 (s, 2H), 3.62 (pentet, *J* = 3.5 Hz, 1H), 3.44 (t, 5.6 Hz, 2H), 2.22 (pair of overlapping q, *J* = 2.13 Hz, 2H), 1.89–1.87 (m, 2H), 1.75–1.72 (m, 2H), 1.54–1.51 (1, 2H), 1.41–1.34 (m, 2H), 1.31–1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 138.5, 128.2 (2C), 127.5 (2C), 127.4, 107.6, 77.9, 72.8, 70.9, 31.9, 28.3, 25.4, 23.7; MS (MALDI) calcd for $C_{17}H_{24}O_2Na$ $[M + Na]^+$ 383.1674, found 349.1721.



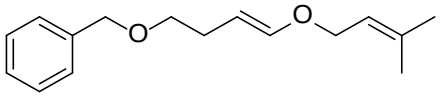
Yield: 68%; clear oil; IR (film) ν_{max} 3053, 3008, 2986, 2847, 2839, 1336, 1263, 1158, 1094, 731, 700 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.29 (d, *J* = 6.0 Hz, 2H), 7.17 (d, *J* = 6.0 Hz, 2H), 7.08 (t, *J* = 5.8 Hz, 1H), 6.14 (d, *J* = 10.0 Hz, 1H), 5.81–5.78 (m, 1H), 5.65–5.62 (m, 1H), 5.02 (dt, *J* = 10.0 Hz, 5.0 1H), 4.31 (s, 2H), 4.03 (broad s, 1H), 3.29 (q, *J* = 5.4 Hz, 2H), 2.21 (q, *J* = 5.6 Hz, 2H), 1.77–1.55 (m, 5H), 1.30–1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 139.0, 130.5, 128.0, 127.7, 127.3, 127.1, 101.6, 72.7, 72.5, 70.9, 28.6, 28.4, 24.7, 18.8; MS (MALDI) calcd for $C_{17}H_{22}O_2Na$ $[M + Na]^+$ 281.1517, found 281.1502.



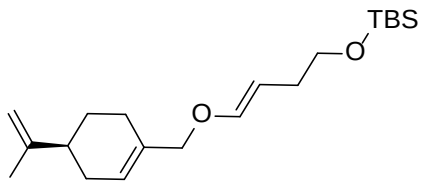
Yield: 62%; clear oil; IR (film) ν_{max} 3068, 2979, 2932, 1638, 1512, 1353, 1320, 1239, 1139, 851 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 2H), 7.05 (t, *J* = 4.0 Hz, 1H), 6.15 (d, *J* = 12 Hz, 1H), 5.44–5.29 (m, 2H), 5.05 (dt, *J* = 12.0, 6.0 Hz, 1H), 4.26 (s, 2H), 3.95 (pentet, *J* = 6.2 Hz, 1H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.18 (q, *J* = 7.1 Hz, 2H) 1.41 (d, *J* = 5.6 Hz, 3H), 1.14 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 139.0, 132.9, 128.8, 128.0, 127.0, 126.4, 101.8, 76.3, 72.5, 71.0, 28.6, 20.9, 18.5; MS (MALDI) calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$ 269.1512, found 269.1592.



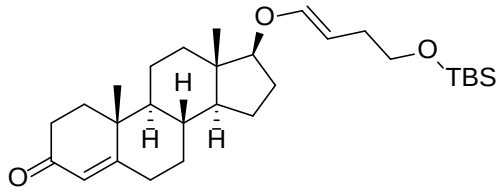
Yield: 92%; clear colorless oil; IR (film) ν_{max} 2971, 2938, 2830, 1512, 1466, 1264, 1242, 1051, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 10H), 6.45 (d, *J* = 12.0 Hz, 1H), 4.94 (dt, *J* = 12.8, 6.5 Hz, 1H), 4.75 (s, 2H), 4.55 (s, 2H), 3.50 (t, *J* = 6.0 Hz, 2H), 2.29 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 138.6, 137.2, 128.5 (2C), 128.2 (2C), 127.9, 127.7 (2C), 127.6 (2C), 127.5, 101.0, 72.9, 71.1, 71.0, 28.5; MS (MALDI/TOF) calcd for $C_{18}H_{20}O_2$ $[M + Na]^+$ 291.1361, found 291.1270.



Yield: 85%; clear colorless oil; IR (film) ν_{max} 3026, 2919, 2856, 2725, 1672, 1648, 1455, 1364, 1272, 1209, 1158, 1094, 730, 695 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 7.35–7.26 (m, 5H), 6.32 (d, *J* = 12.1 Hz, 1H), 4.88 (dt, *J* = 7.0, 1.4 Hz, 1H), 4.81 (dt, *J* = 12.8, 6.3 Hz, 1H), 4.52 (s, 2H), 4.18 (d, *J* = 6.8 Hz, 2H), 3.46 (t, *J* = 6.8 Hz, 2H), 2.25 (qd, *J* = 7.0, 1.0 Hz, 2H) 1.76 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 138.5, 128.3(2C), 127.6, 127.5(2C), 101.8, 72.9, 72.4, 71.1, 28.5, 22.1(2C); HRMS (ESI/LC) calcd for $C_{16}H_{22}O_2$ $[M + Na]^+$ 269.1518, found 269.1516.



Yield: 61%; clear colorless oil; IR (film) ν_{max} 2953, 2928, 2857, 1671, 1650, 1471, 1435, 1376, 1255, 1171, 1094, 911, 835, 776, 723 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.30 (d, *J* = 10.0 Hz, 1H), 5.58 (br, 1H), 4.48 (dt, *J* = 10.0, 5.1 Hz, 1H), 4.72 (d, *J* = 8.7 Hz, 2H), 3.93 (s, 2H), 3.52 (t, *J* = 5.2 Hz, 2H), 2.13 (q, *J* = 5.6 Hz, 2H), 2.04–1.95 (m, 4H), 1.88–1.83 (m, 2H), 1.70–1.65 (m, 2H), 1.35 (qd, *J* = 9.3, 4.5 Hz, 1H) 0.96 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 147.4, 133.8, 124.1, 108.6, 100.1, 73.2, 63.9, 40.8, 31.6, 30.3, 27.2, 26.0, 25.7 (3C), 20.3, 18.1, -5.5 (2C); HRMS (ESI/LC) calcd for $C_{20}H_{36}O_2Si$ $[M + H]^+$ 337.2563, found 337.2546.



Yield: 22%; clear colorless oil; IR (film) ν_{max} 2947, 2930, 2855, 1673, 1471, 1256, 1164, 1095, 913, 836, 776, 746 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.14 (d, *J* = 12.4 Hz, 1H), 5.74 (s, 1H), 4.81 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.63 (t, *J* = 8.4 Hz, 1H), 3.54 (t, *J* = 7.0 Hz, 2H), 2.46–2.23 (m, 4H), 2.09 (q, *J* = 7.1 Hz, 2H), 2.07–1.99 (m, 2H), 1.94–1.81 (m, 2H), 1.73–1.52 (m, 6H), 1.47–1.23 (m, 6H), 1.17 (s, 3H), 1.15–0.91 (m, 5H), 0.88 (s, 9H), 0.81 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 171.1, 147.3, 123.9, 101.5, 88.6, 64.0, 53.8, 50.5, 43.1, 38.6, 37.2, 35.7, 35.4, 33.9, 32.8, 31.4, 31.4, 27.8, 25.9 (3C), 23.4, 20.6, 18.4, 17.4, 11.6, -5.2 (2C); HRMS (EXACTIVE) calcd for $C_{29}H_{48}O_3Si$ $[M + H]^+$ 473.3451, found 473.3434.

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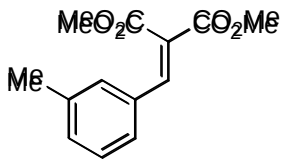
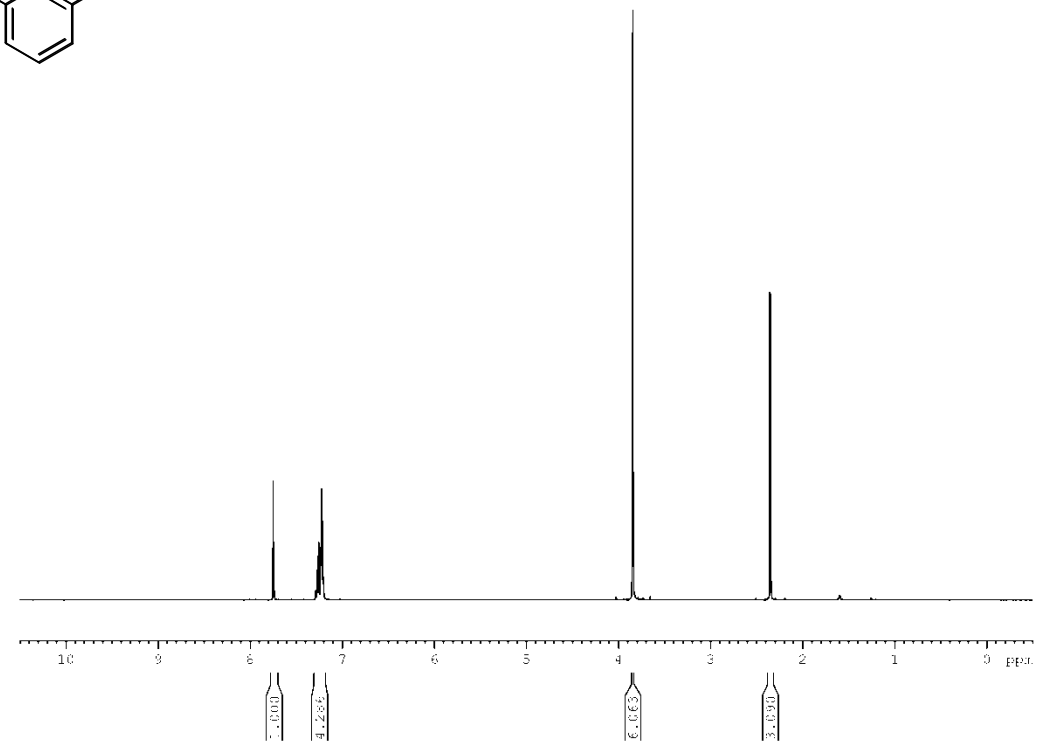
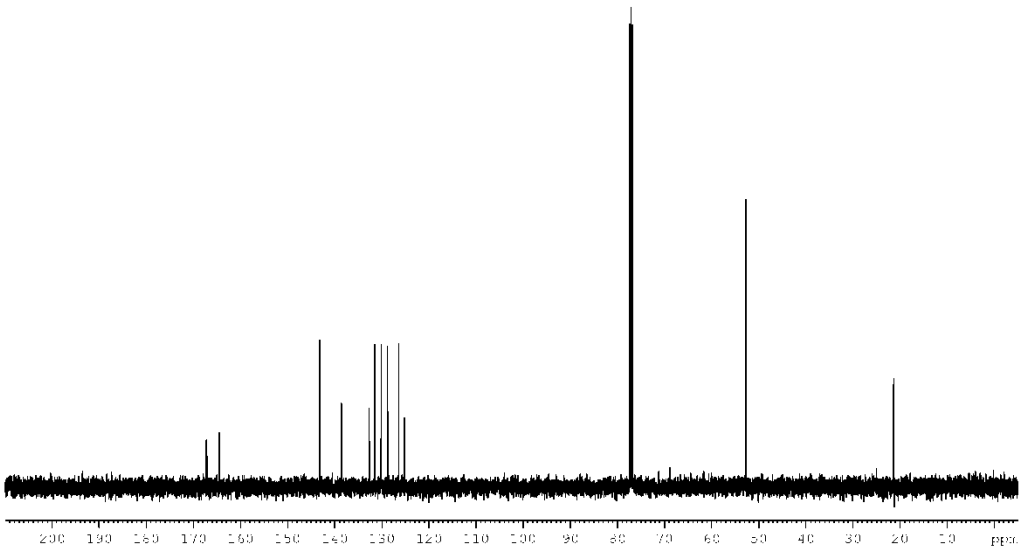
Spectra of Unique Compounds

Chapter 1

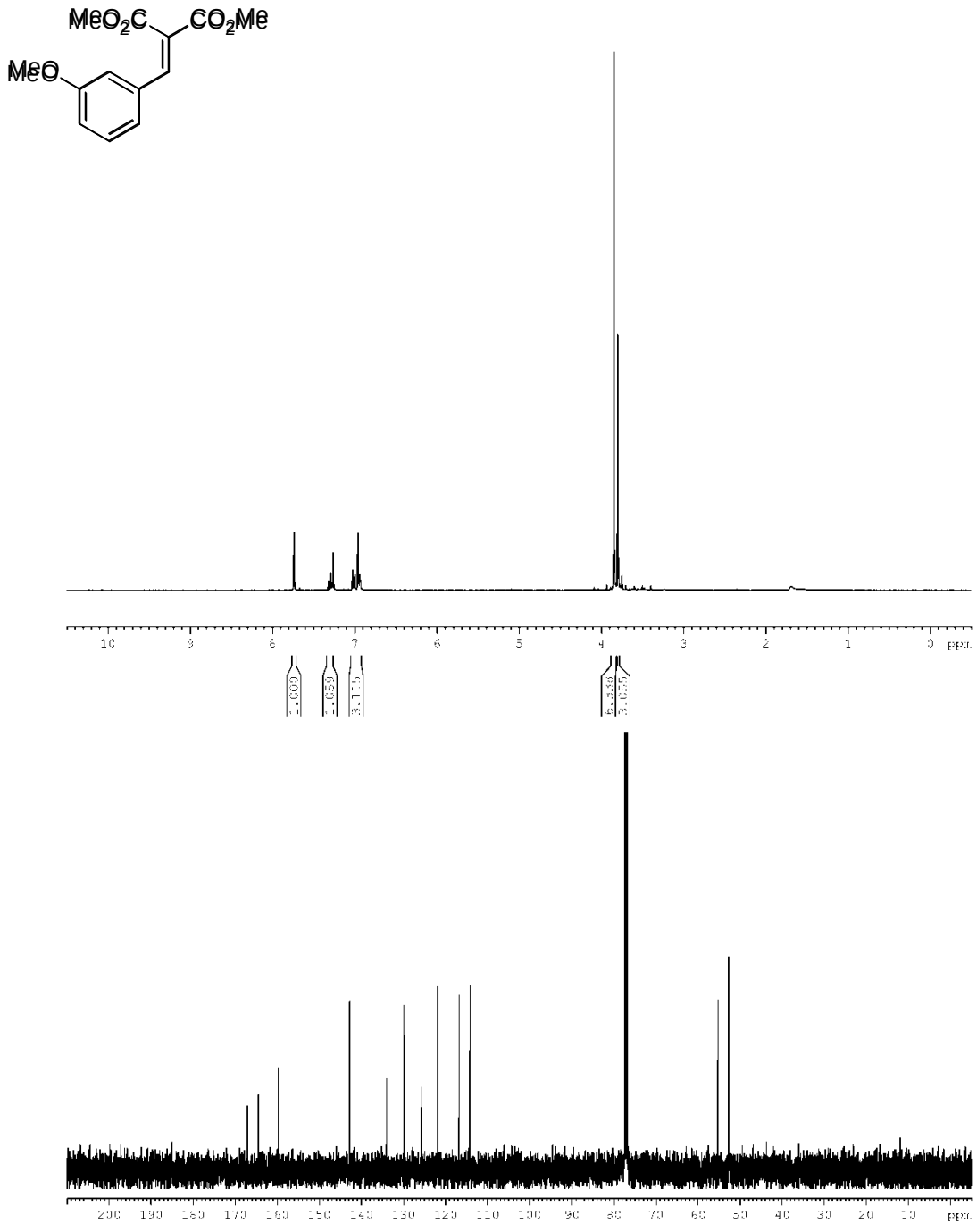
Dimethyl 2-(3-methylbenzylidene)malonate (2n)



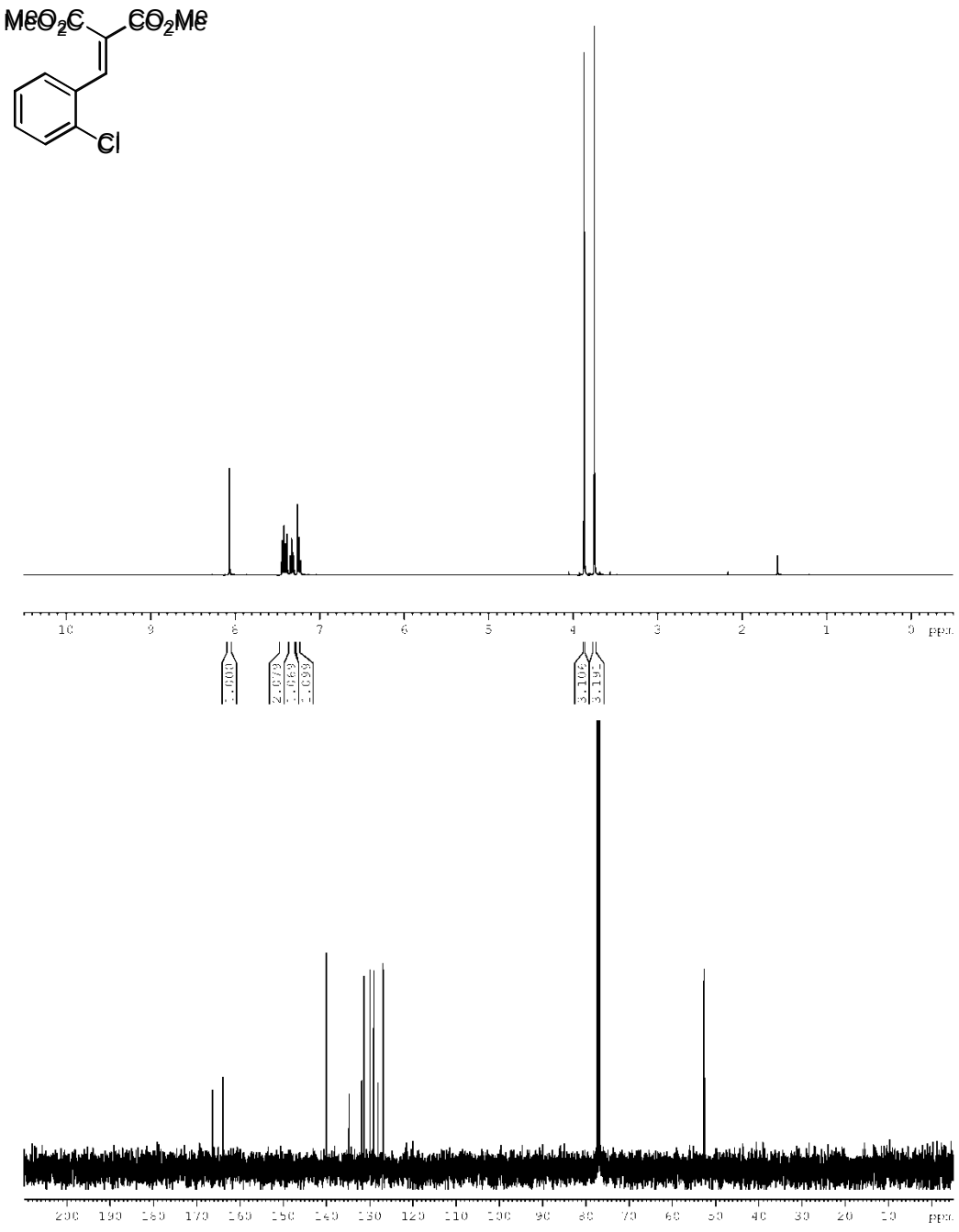




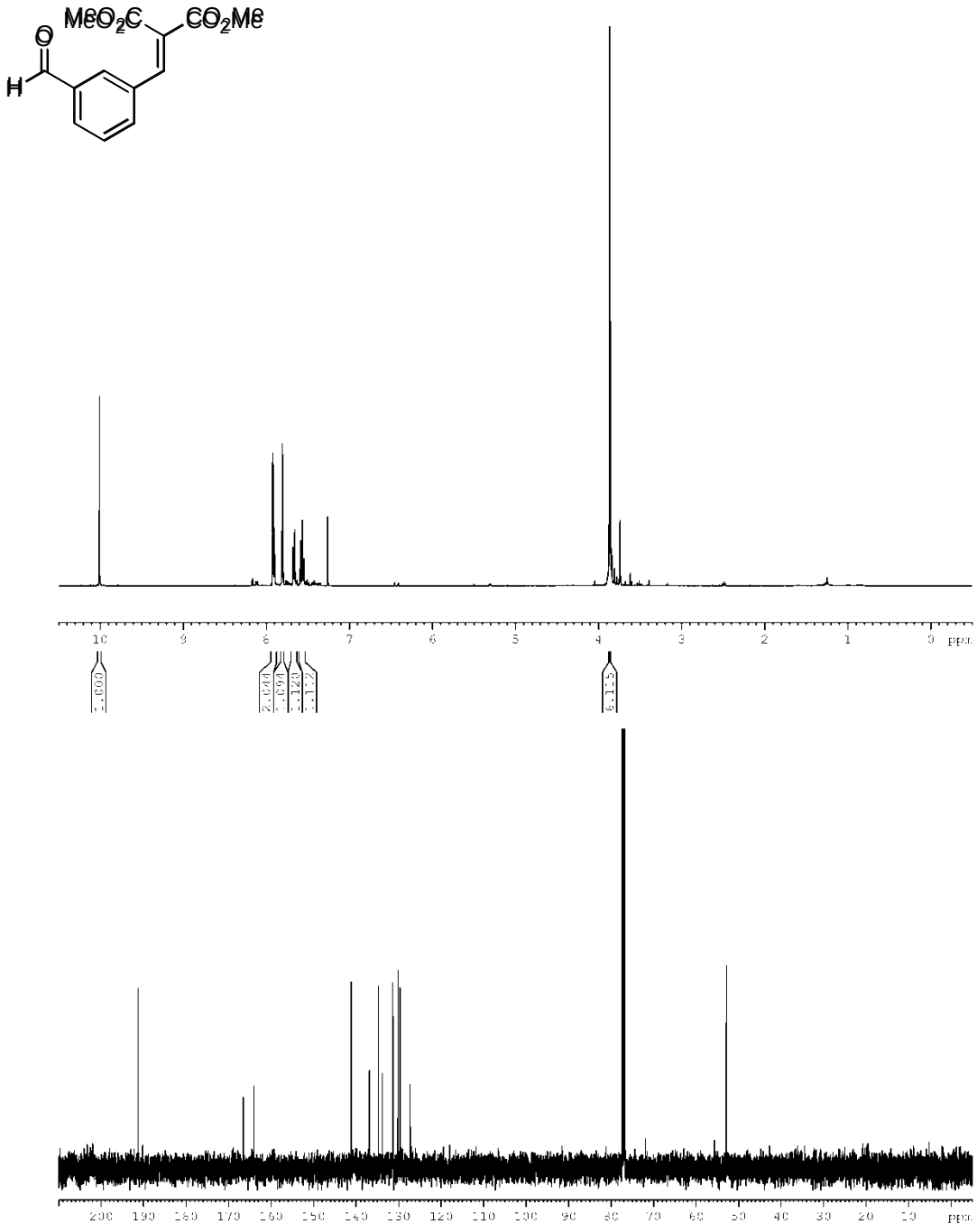
Dimethyl 2-(3-methoxybenzylidene)malonate (2o)



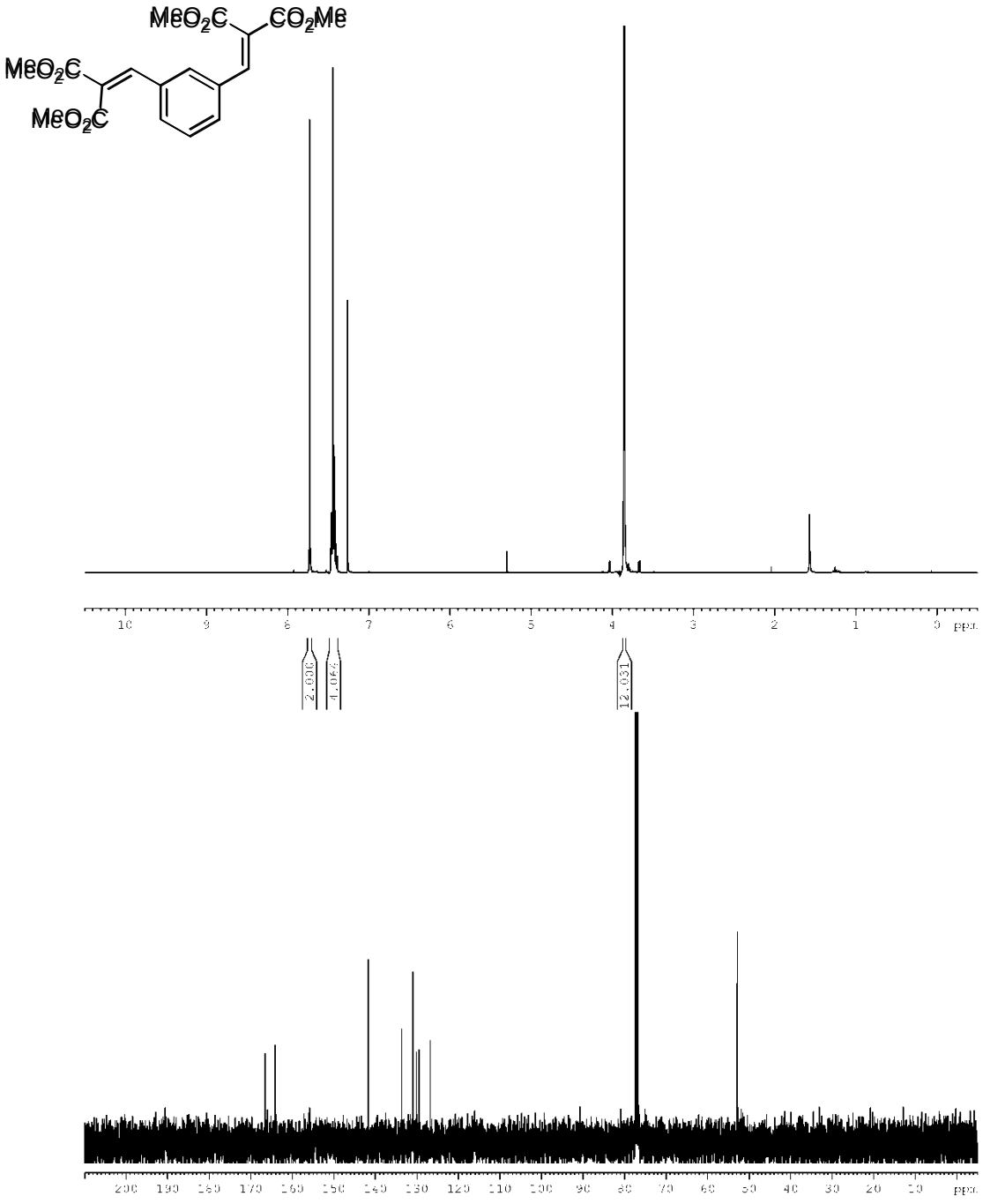
Dimethyl 2-(2-chlorobenzylidene)malonate (2p)



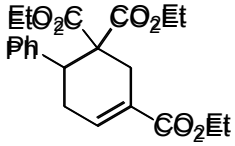
Dimethyl 2-(3-formylbenzylidene)malonate (2r)

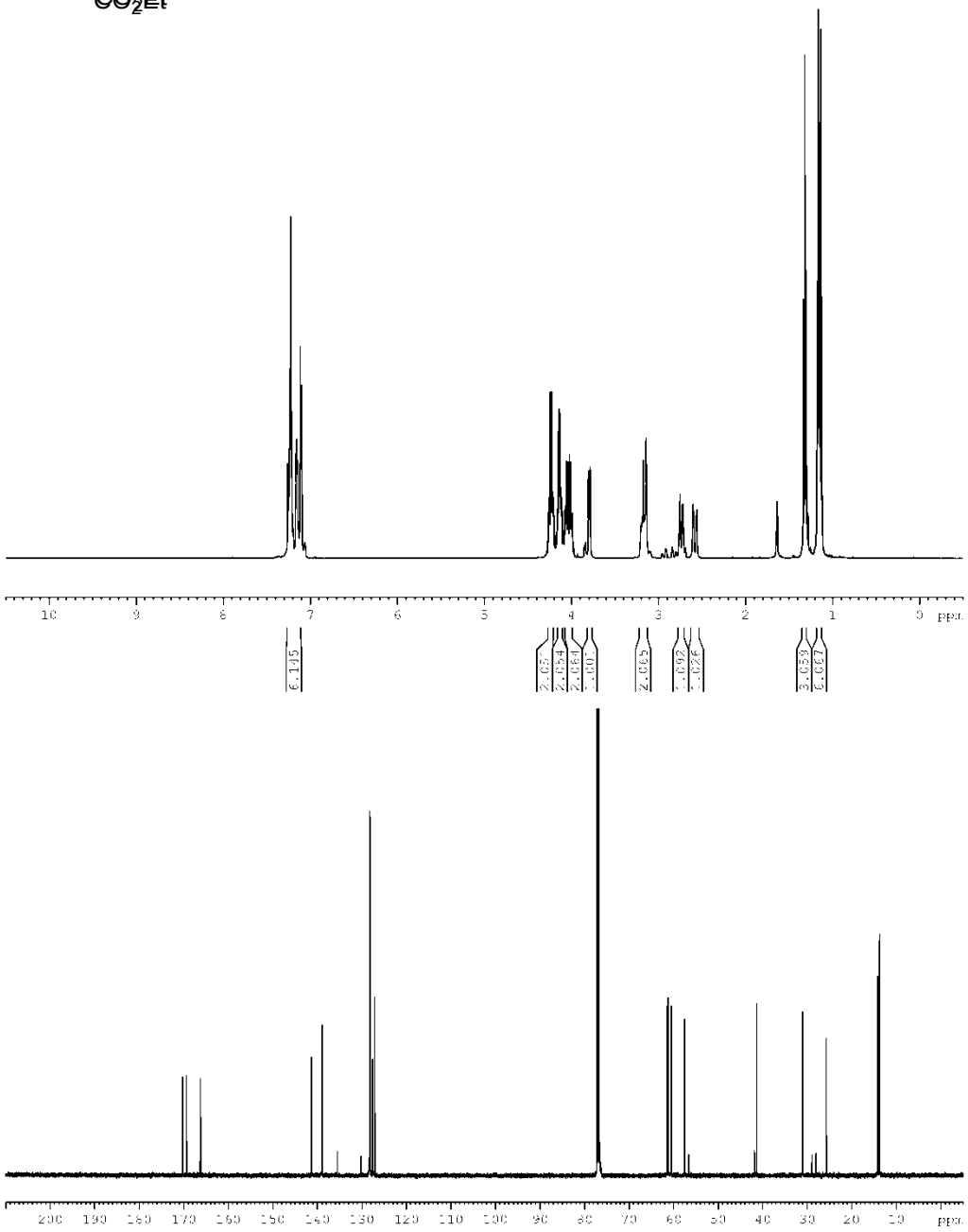


Dimethyl 2,2'-(1,3-bisbenzylidene)dimalonate (2s)

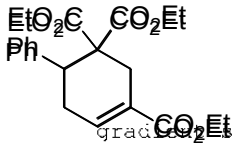


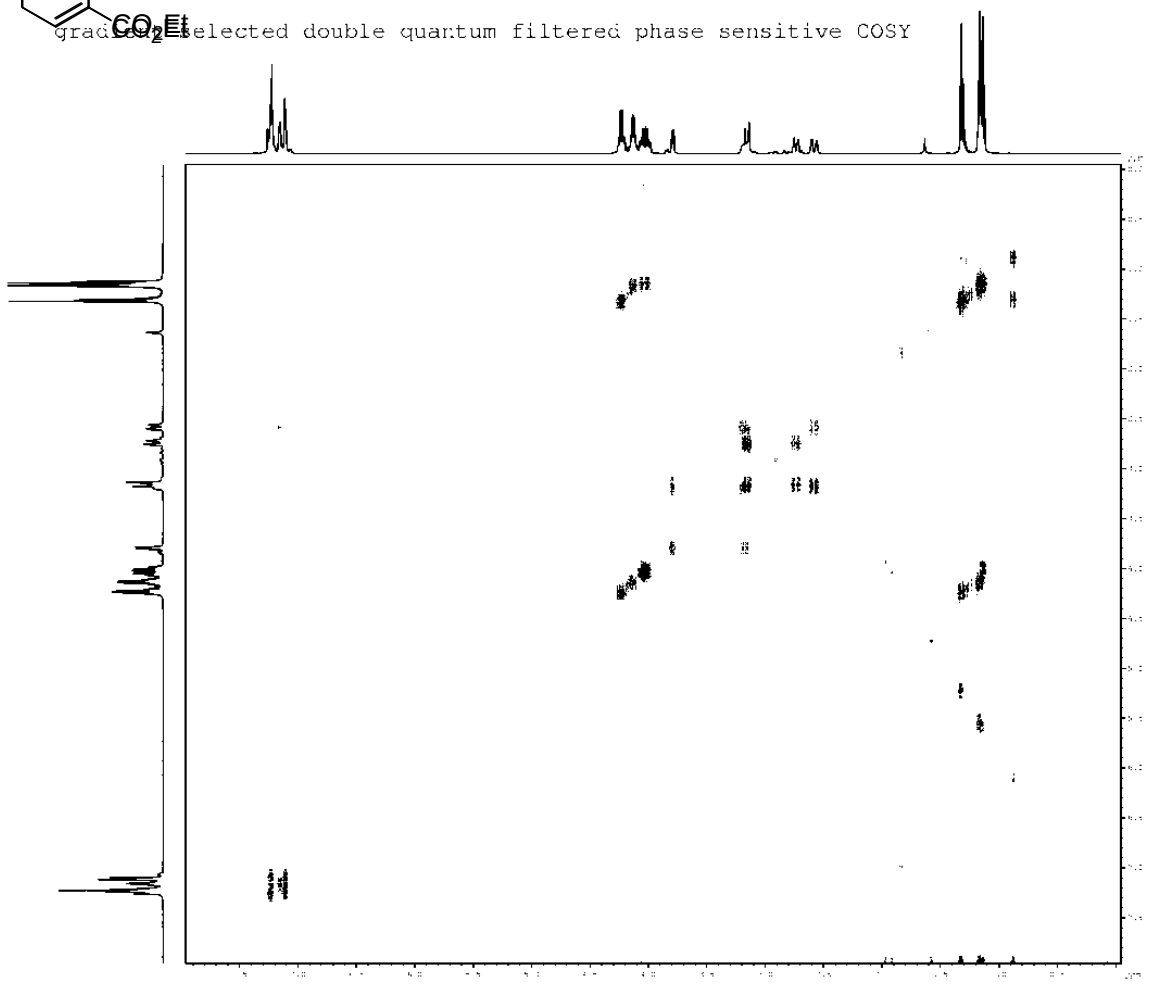
Triethyl 6-phenylcyclohex-3-ene-1,1,3-tricarboxylate (3a)



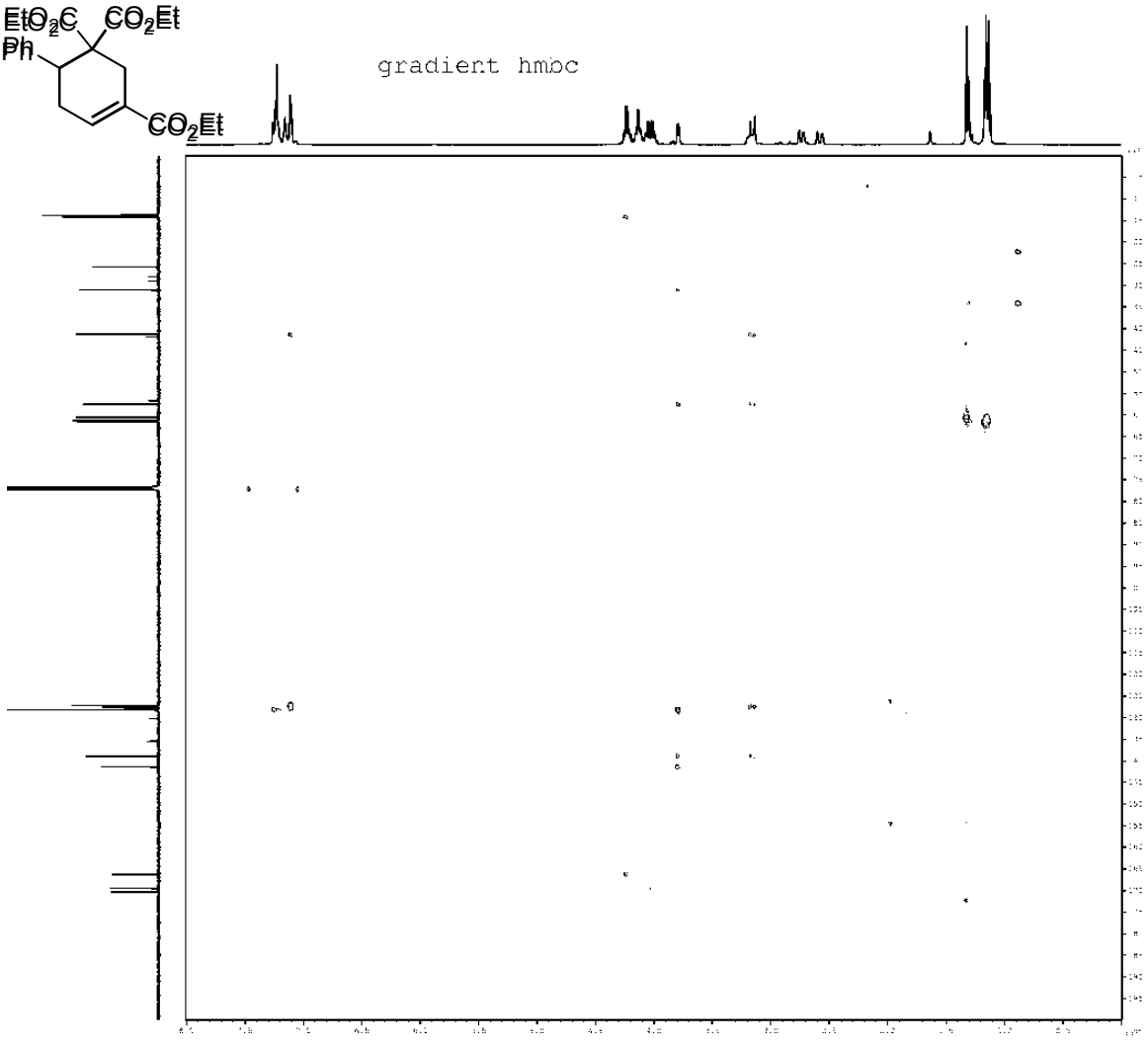


COSY of 3a

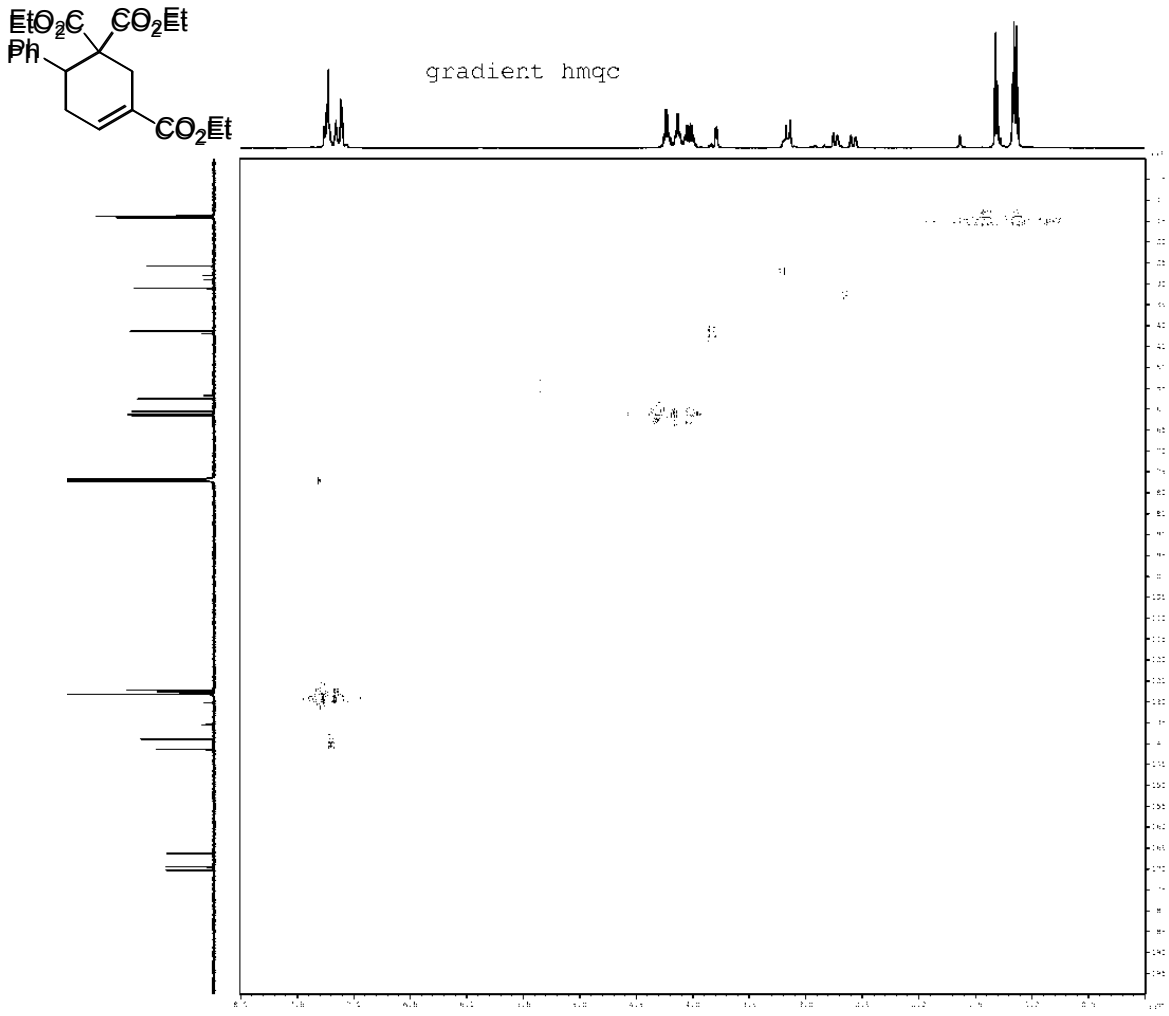

EtO2C
CO2Et
Ph
CO2Et


gradient selected double quantum filtered phase sensitive COSY

HMBC of 3a

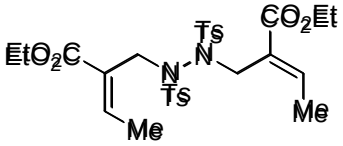


HMQC of 3a

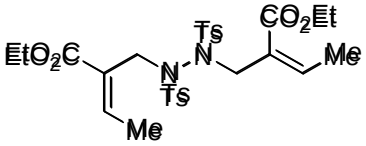


Chapter 2

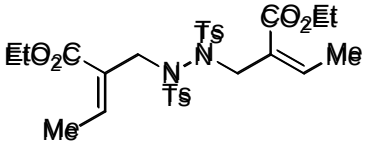
Diethyl 2,2'-((1,2-ditosylhydrazine)-1,2-(bismethylene))-bis-2-butenoate)



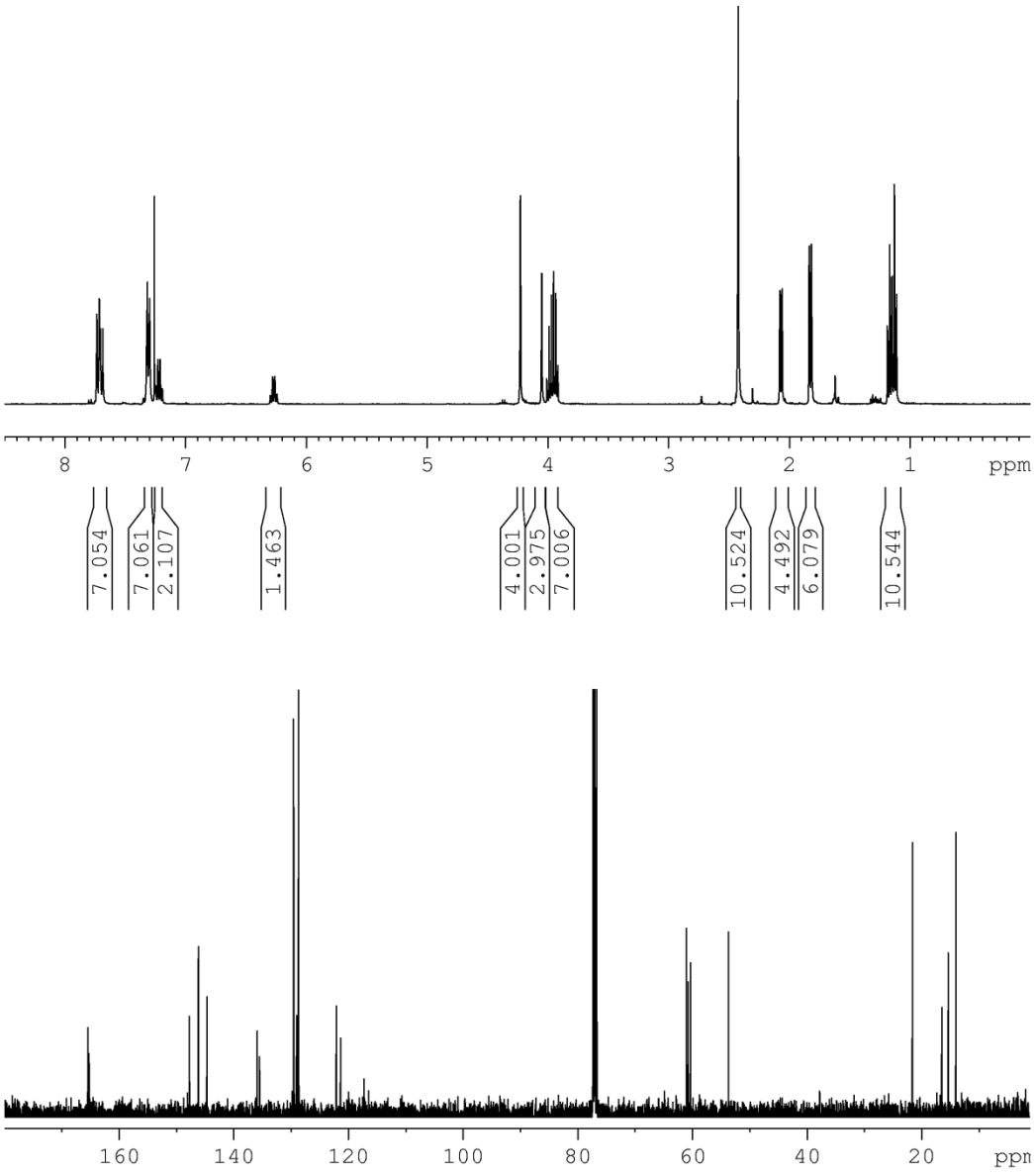
2g (E,E)



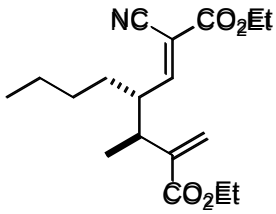
2g (E,Z)

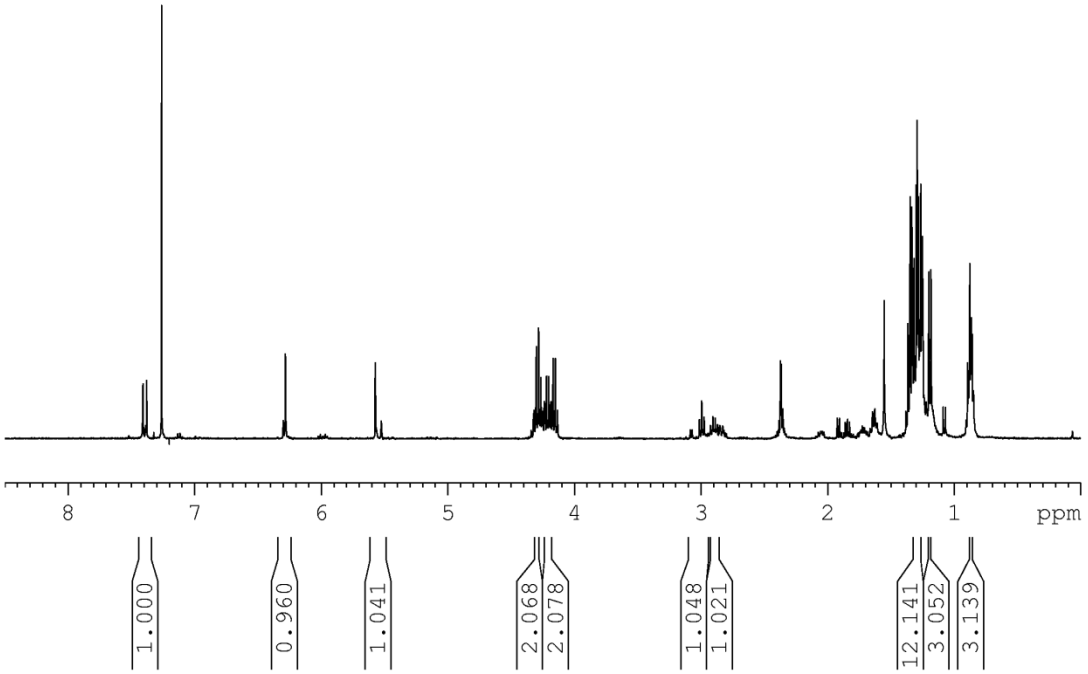


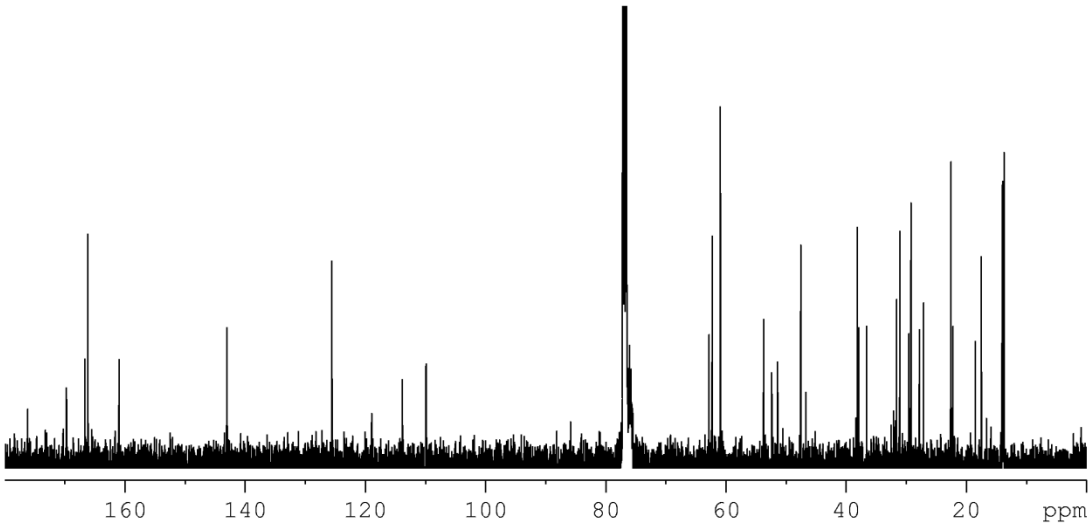
2g (Z,Z)



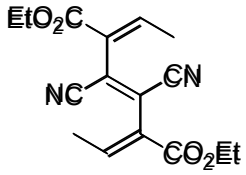
Diethyl 4-butyl-2-cyano-5-methyl-6-methylene2-heptenedioate

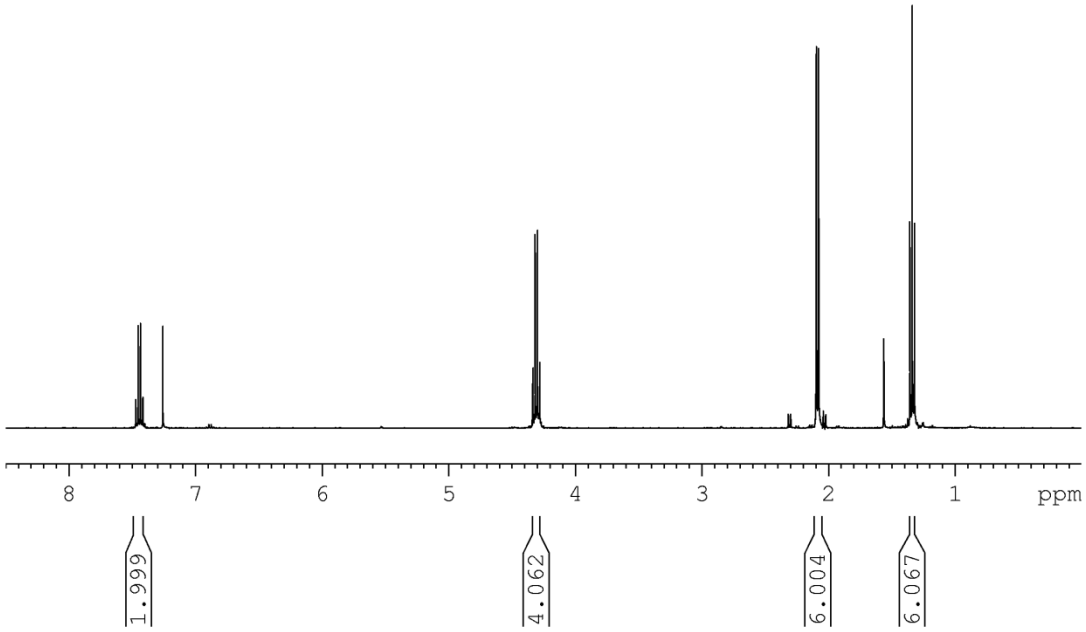


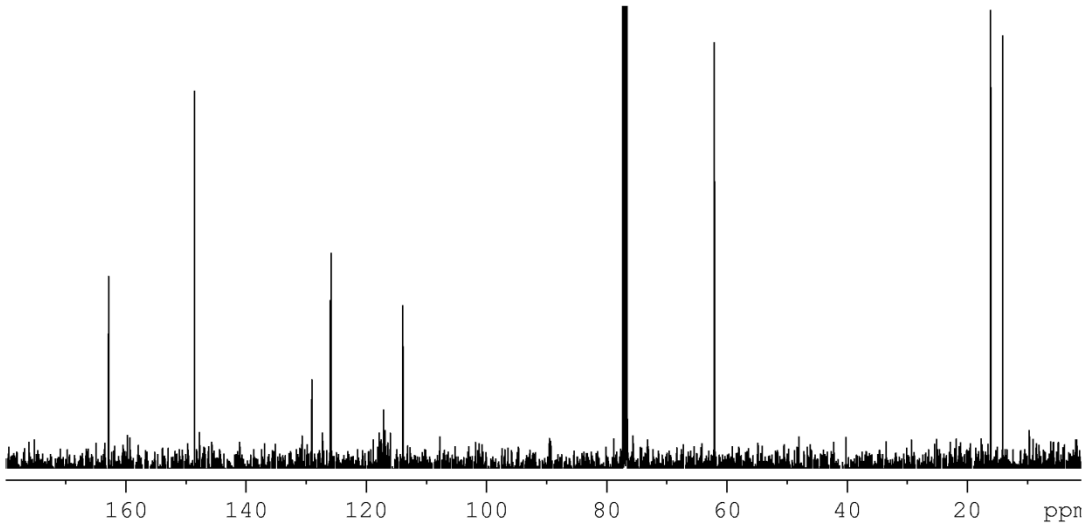




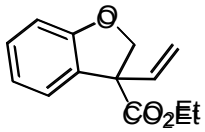
Diethyl (2E,3E,5E)-3,2-dicyano-2,5-diethylidene-3-hexenedioate

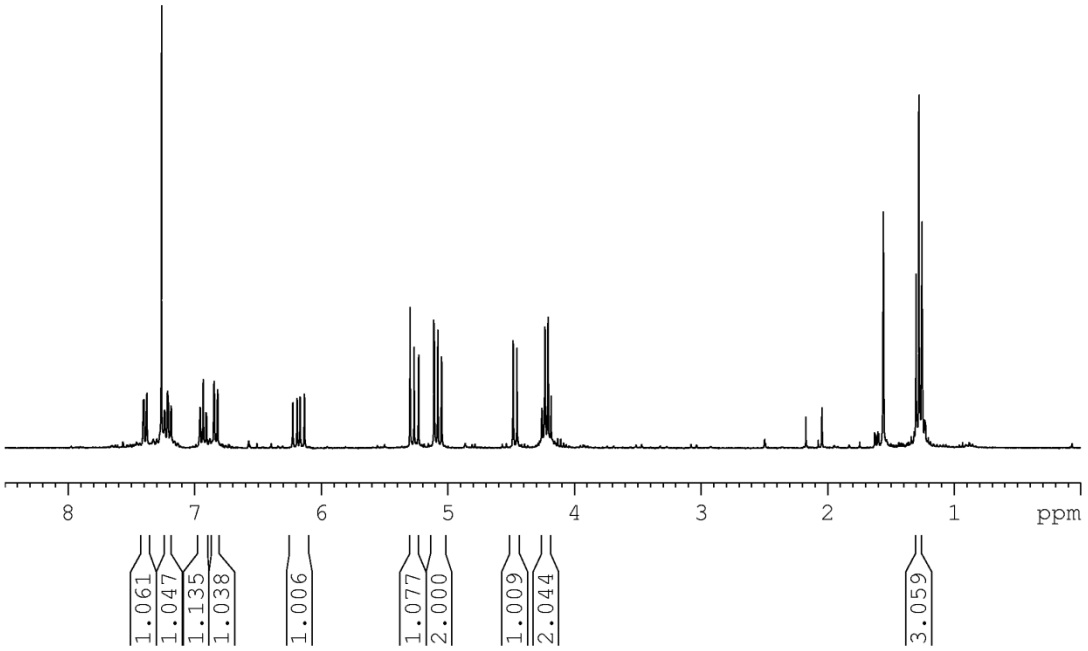


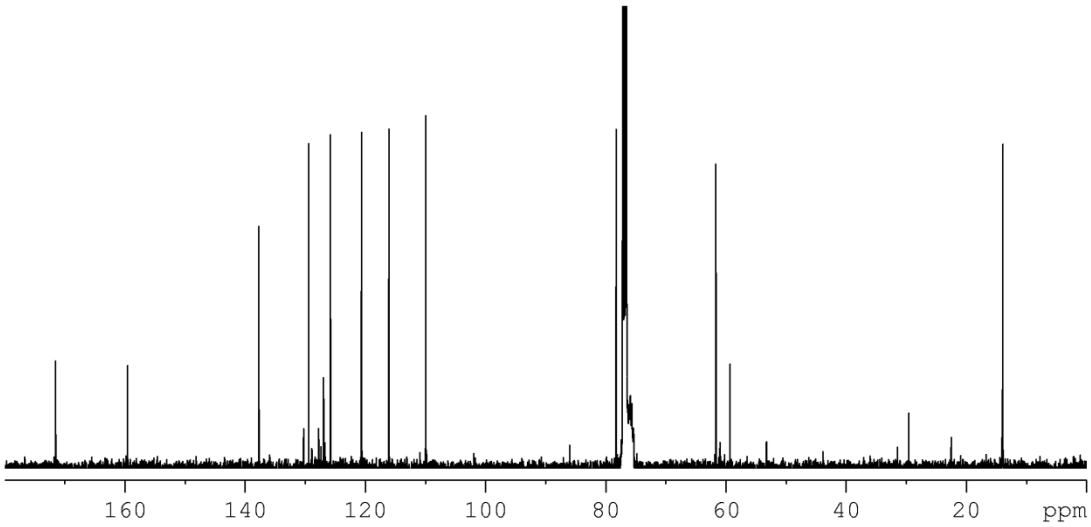




Ethyl 2-vinyl-2,3-dihydrobenzofuran-3-carboxylate

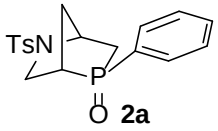




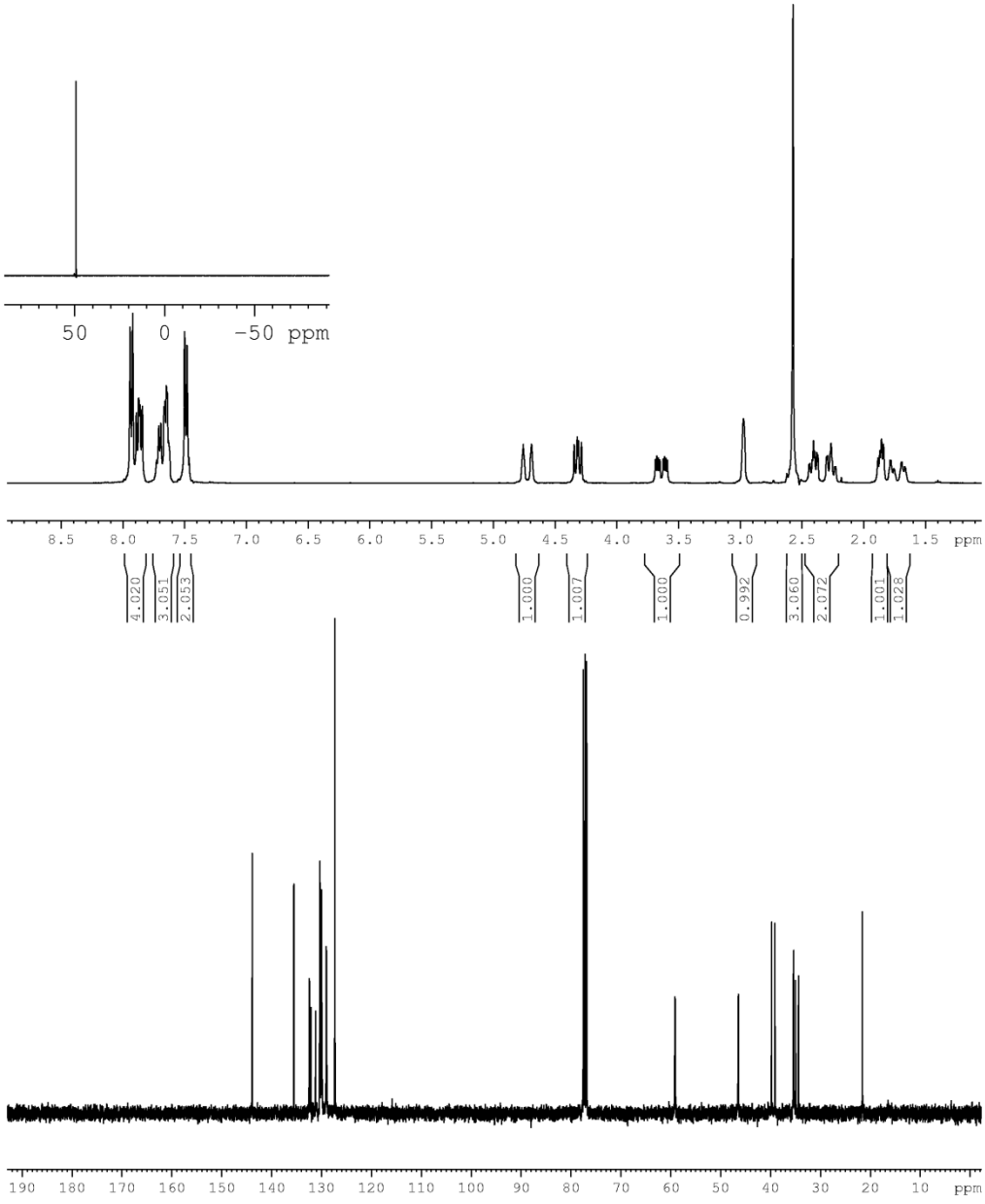


Chapter 3

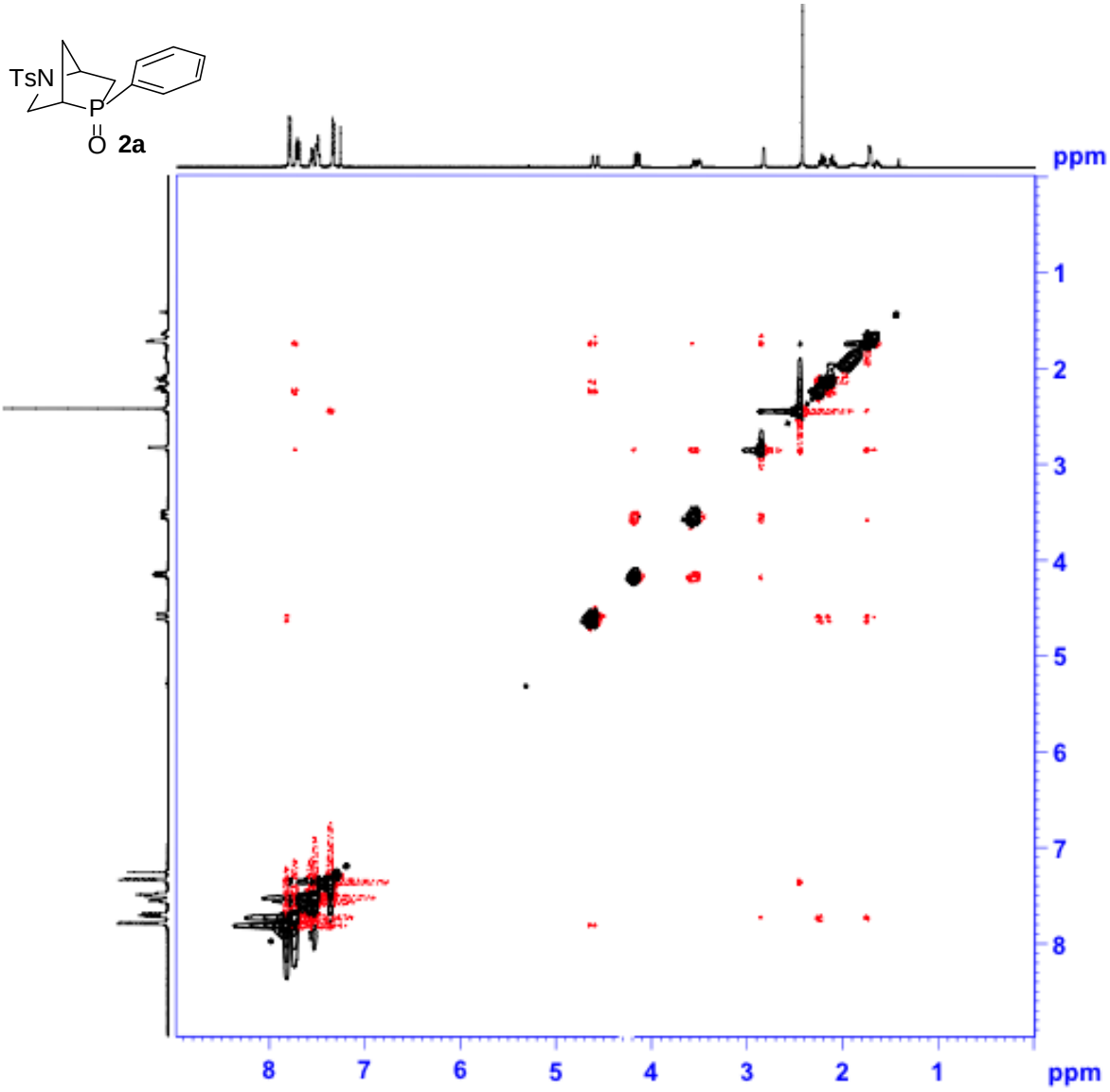
Catalyst spectra



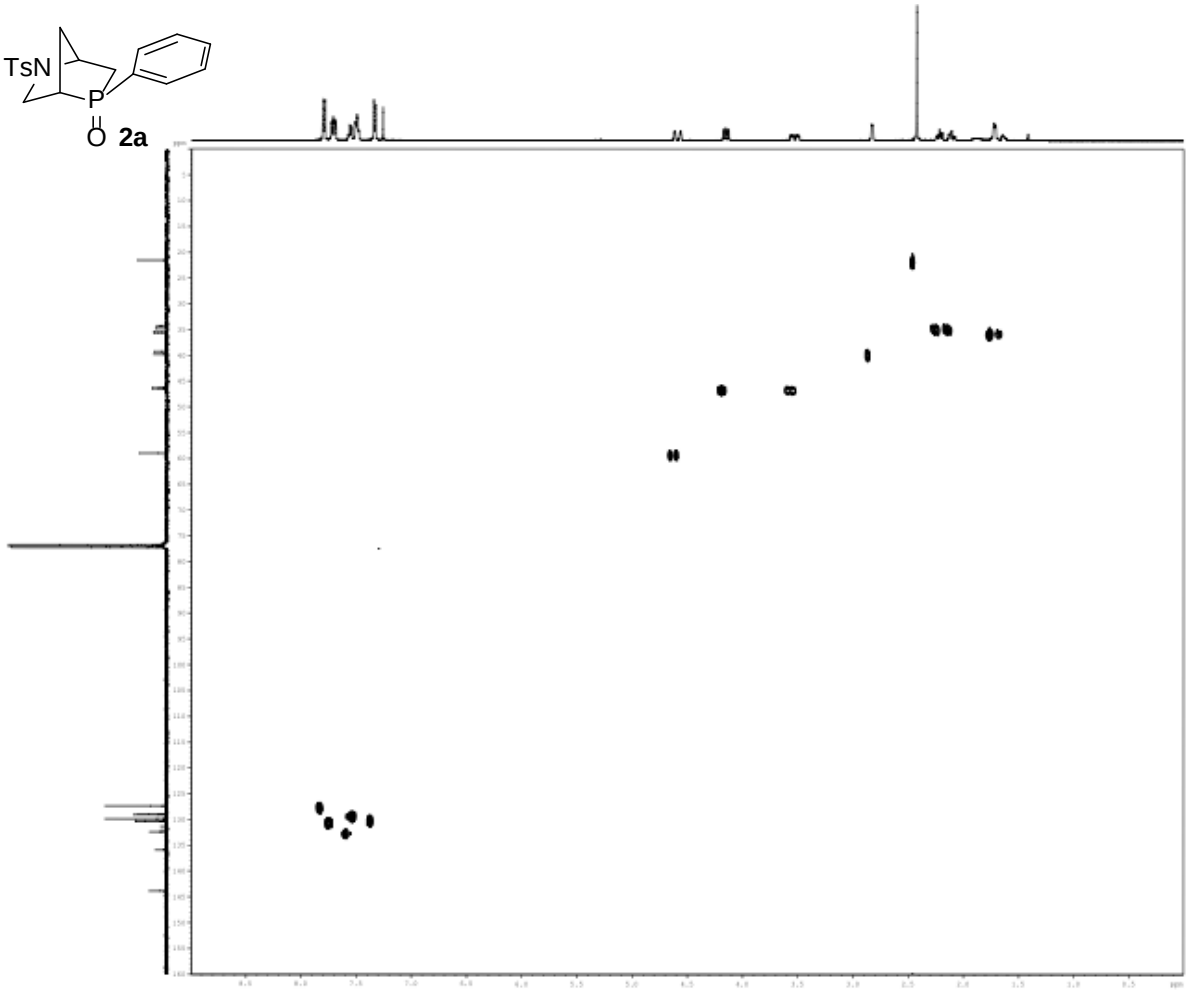
2a

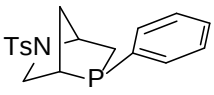


NOESY spectrum of **2a**

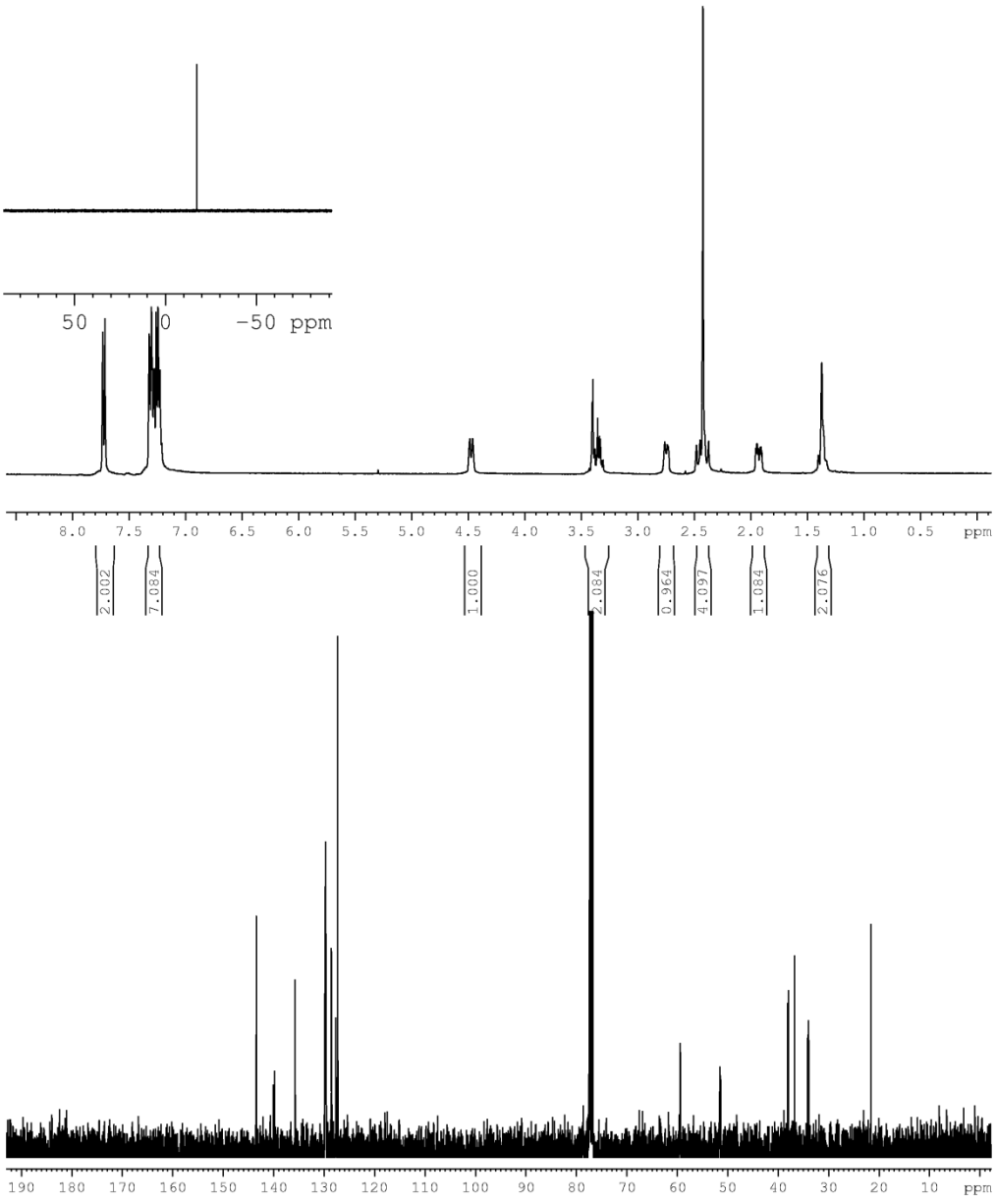


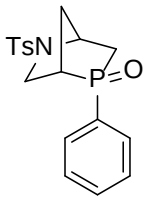
HMQC spectrum of 2a



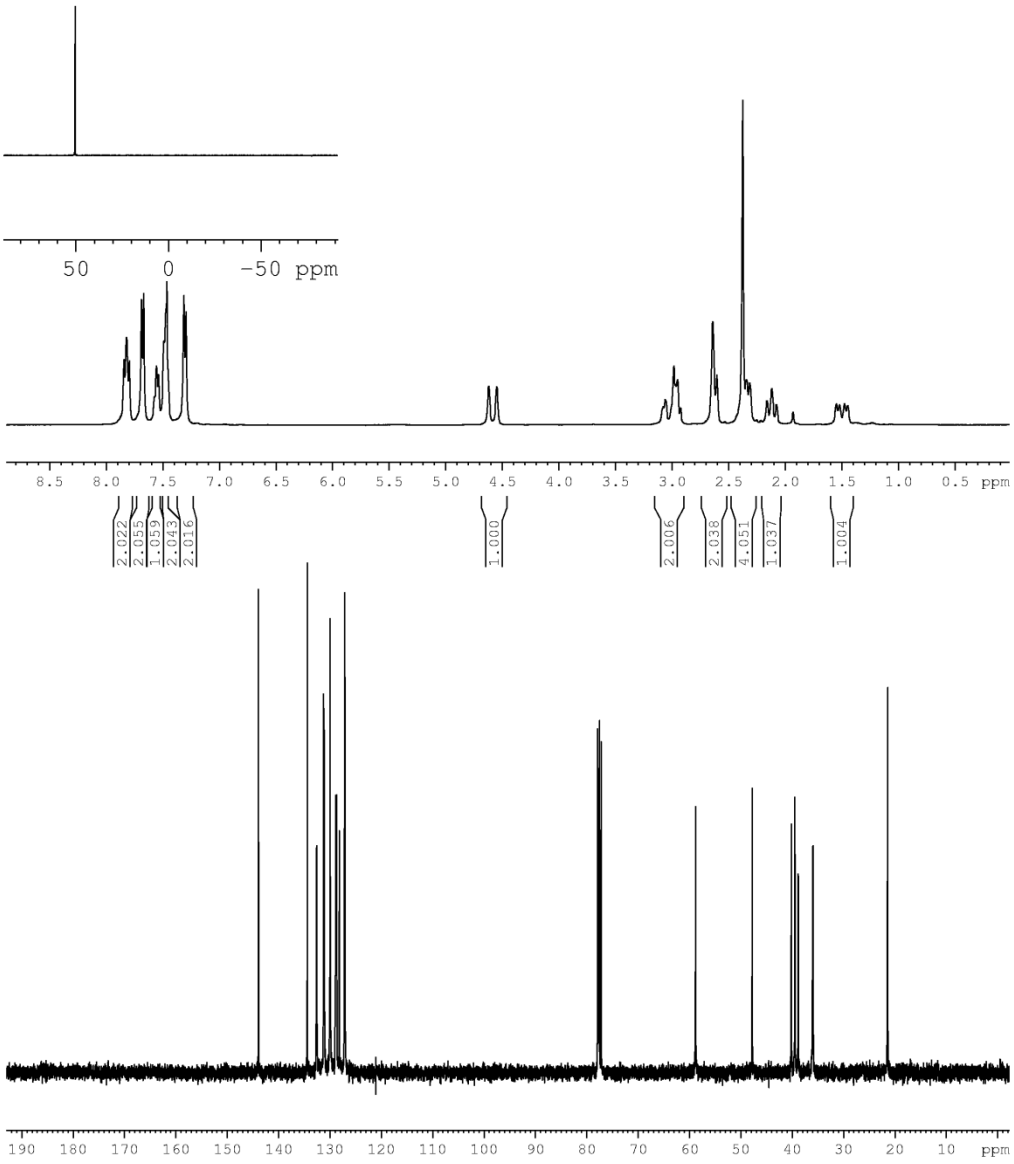

TsN
P

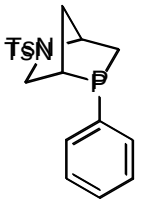
1a


50
0
−50 ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.002
7.084
1.000
2.084
0.964
4.097
1.084
2.076
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

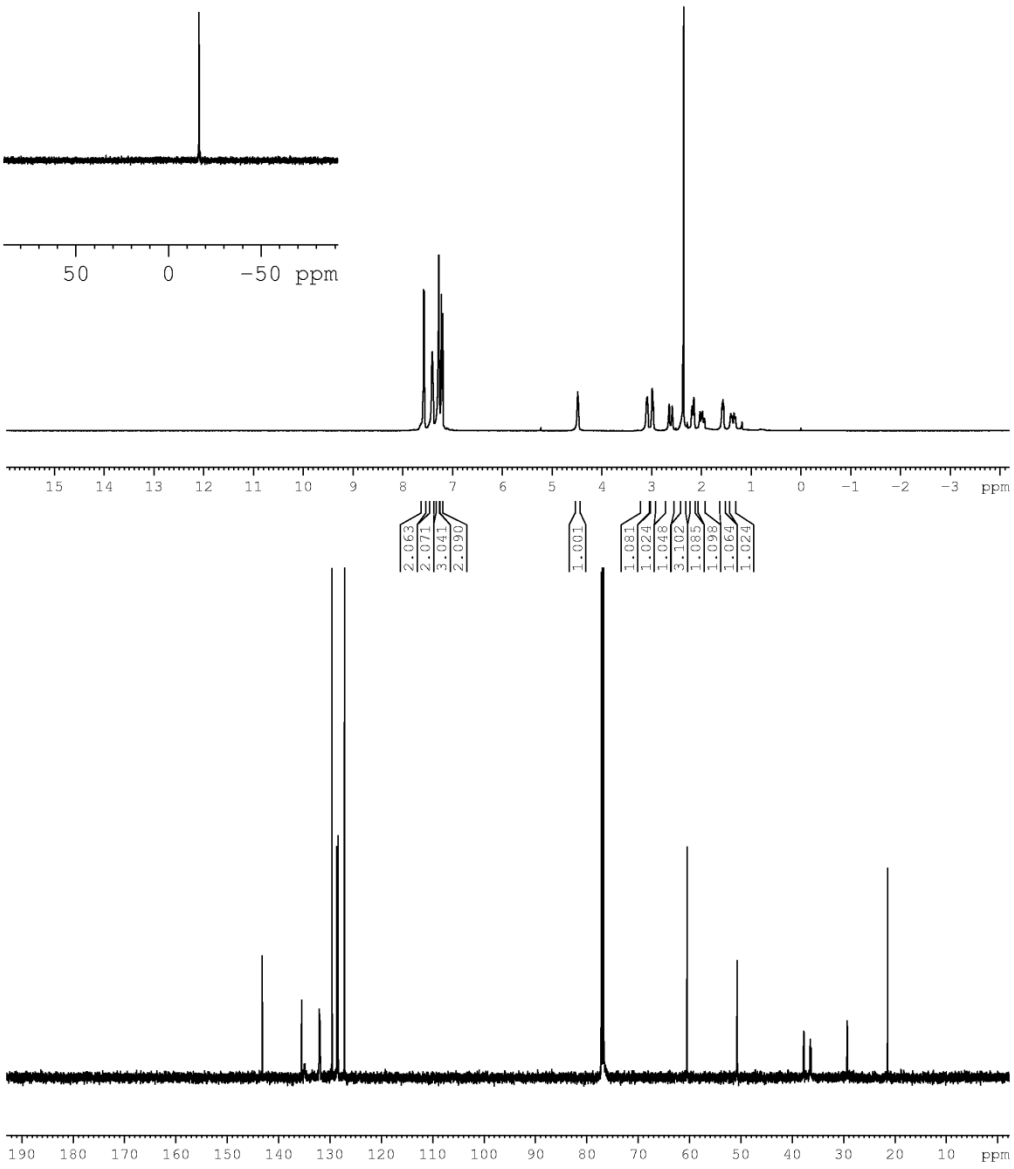

TsN
P
O

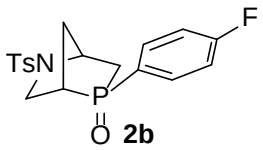
***epi*-2a**


50
0
−50 ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.022
2.055
1.059
2.043
2.016
1.000
2.006
2.038
4.051
1.037
1.004
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

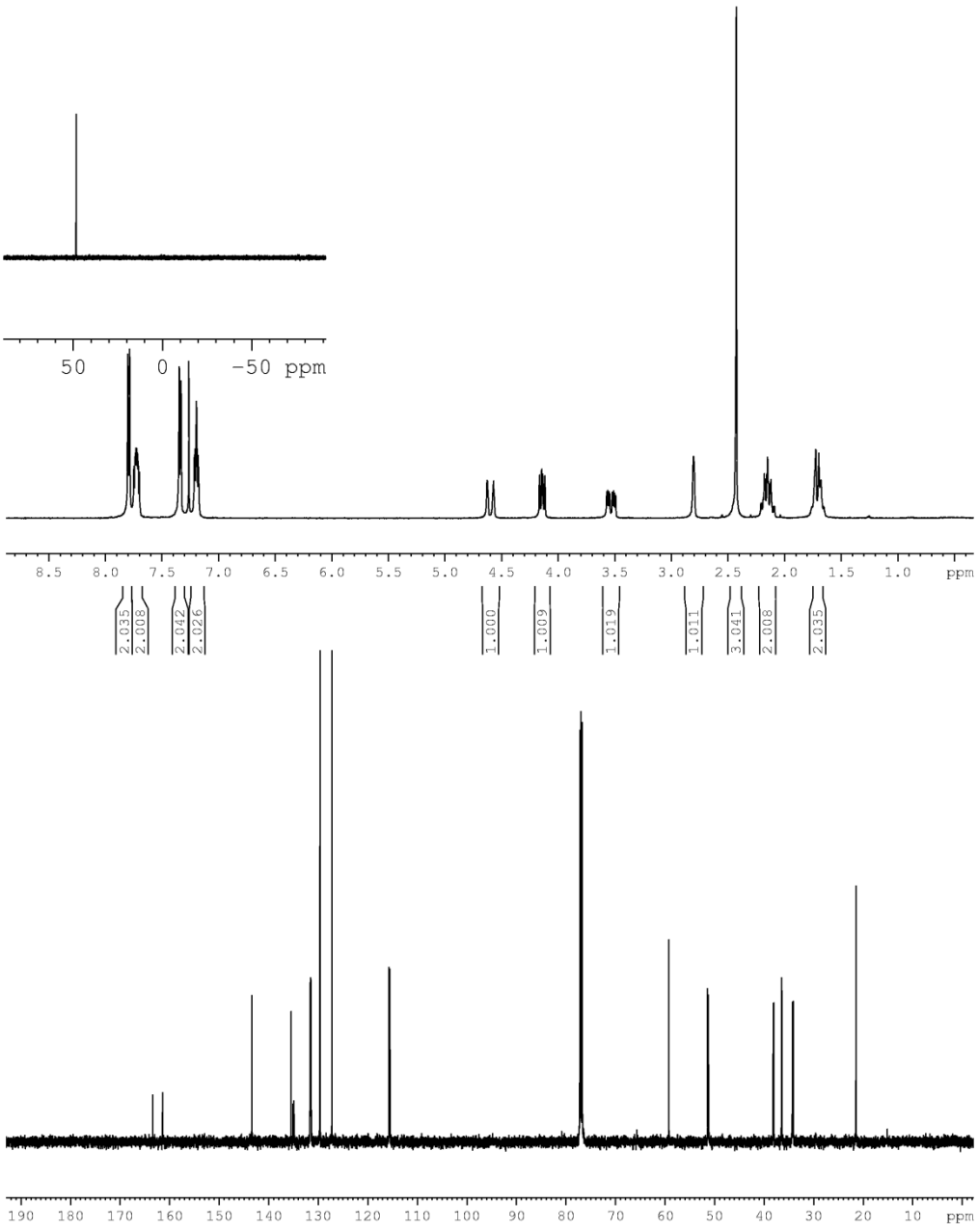

Ts
N
P

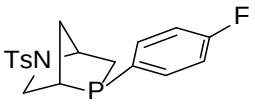
***epi*-1a**


50
0
−50 ppm
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 ppm
2.063
2.071
3.041
2.090
1.001
1.081
1.024
1.048
3.102
1.085
1.098
1.064
1.024
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

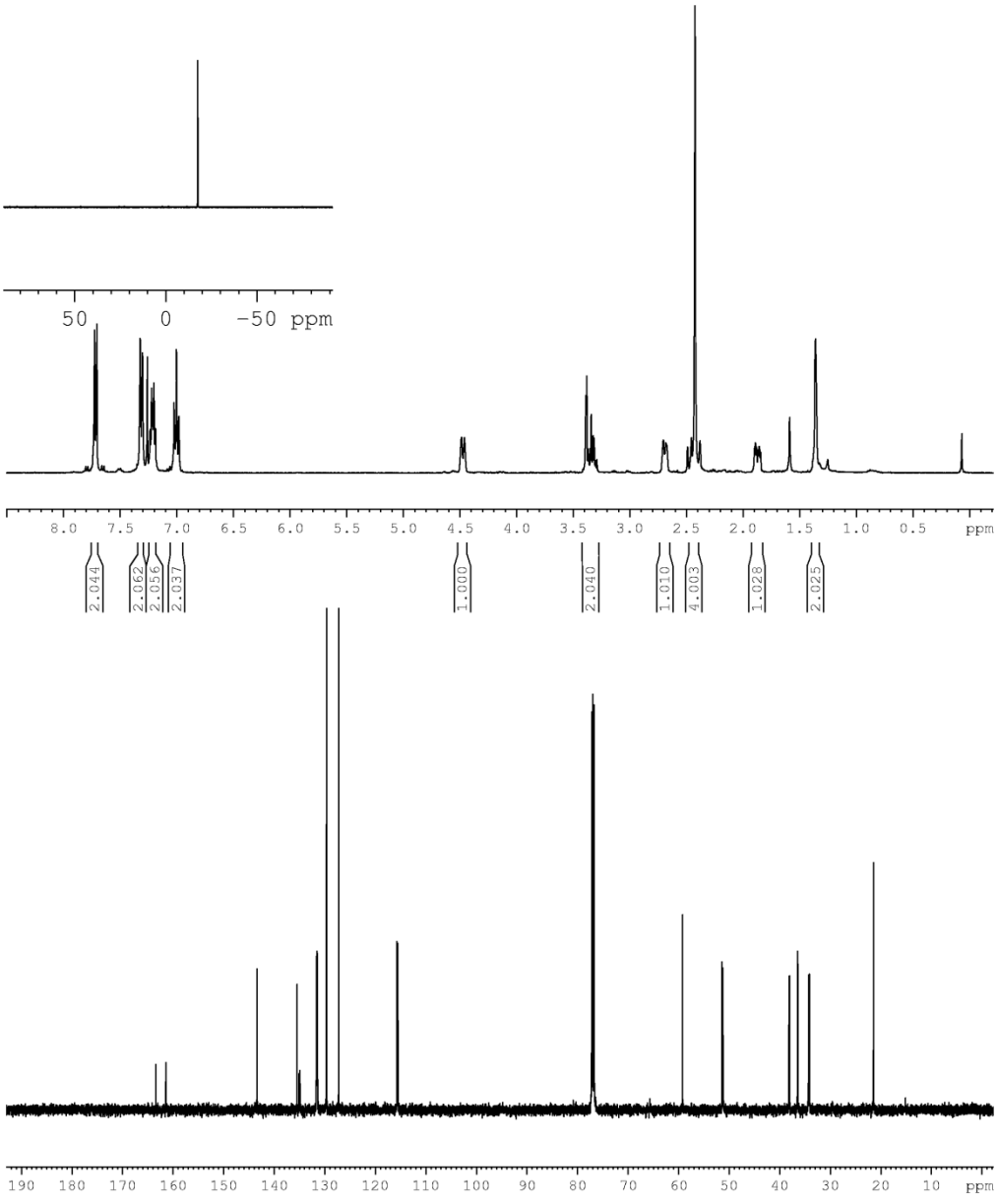

TsN
P
O
F

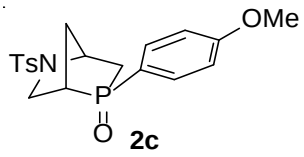
2b


50
0
−50 ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.035
2.008
2.042
2.026
1.000
1.009
1.019
1.011
3.041
2.008
2.035
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

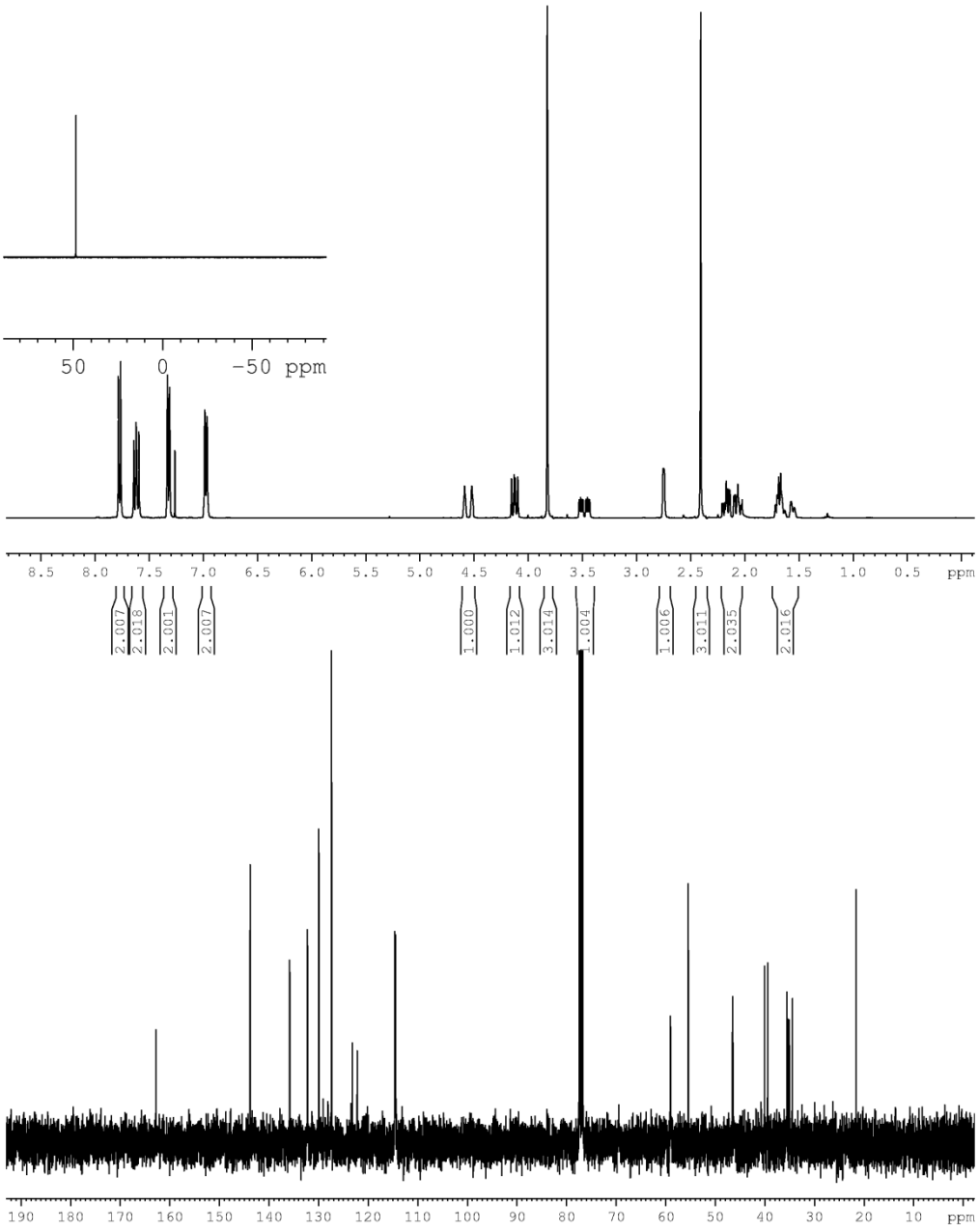

TsN
P
F

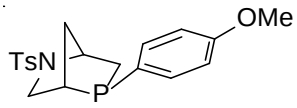
1b


50
0
−50 ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.044
2.062
2.056
2.037
1.000
2.040
1.010
4.003
1.028
2.025
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

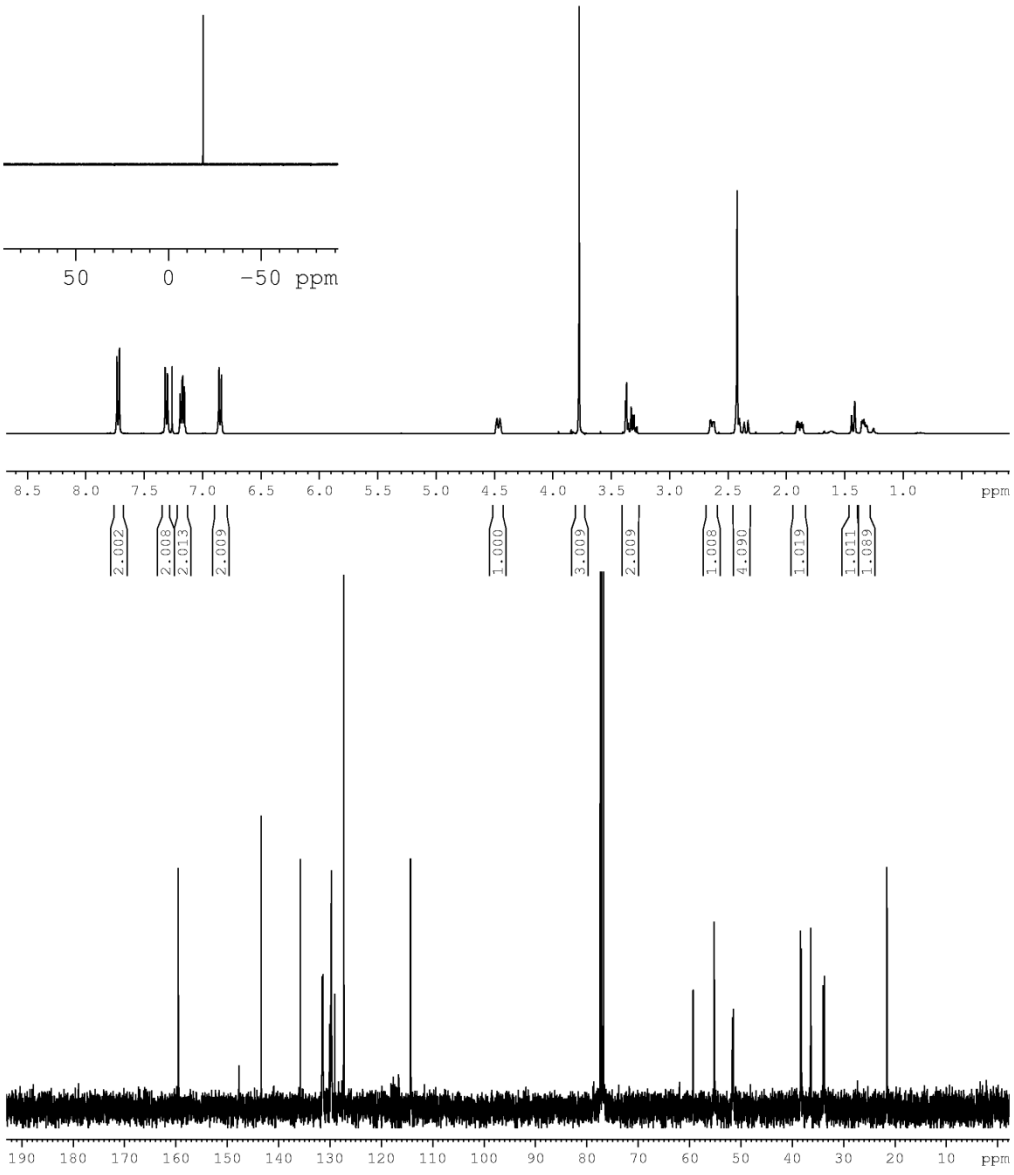

OMe
TsN
P
O

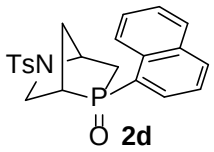
2c


50
0
−50 ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.007
2.018
2.001
2.007
1.000
1.012
3.014
1.004
1.006
3.011
2.035
2.016
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

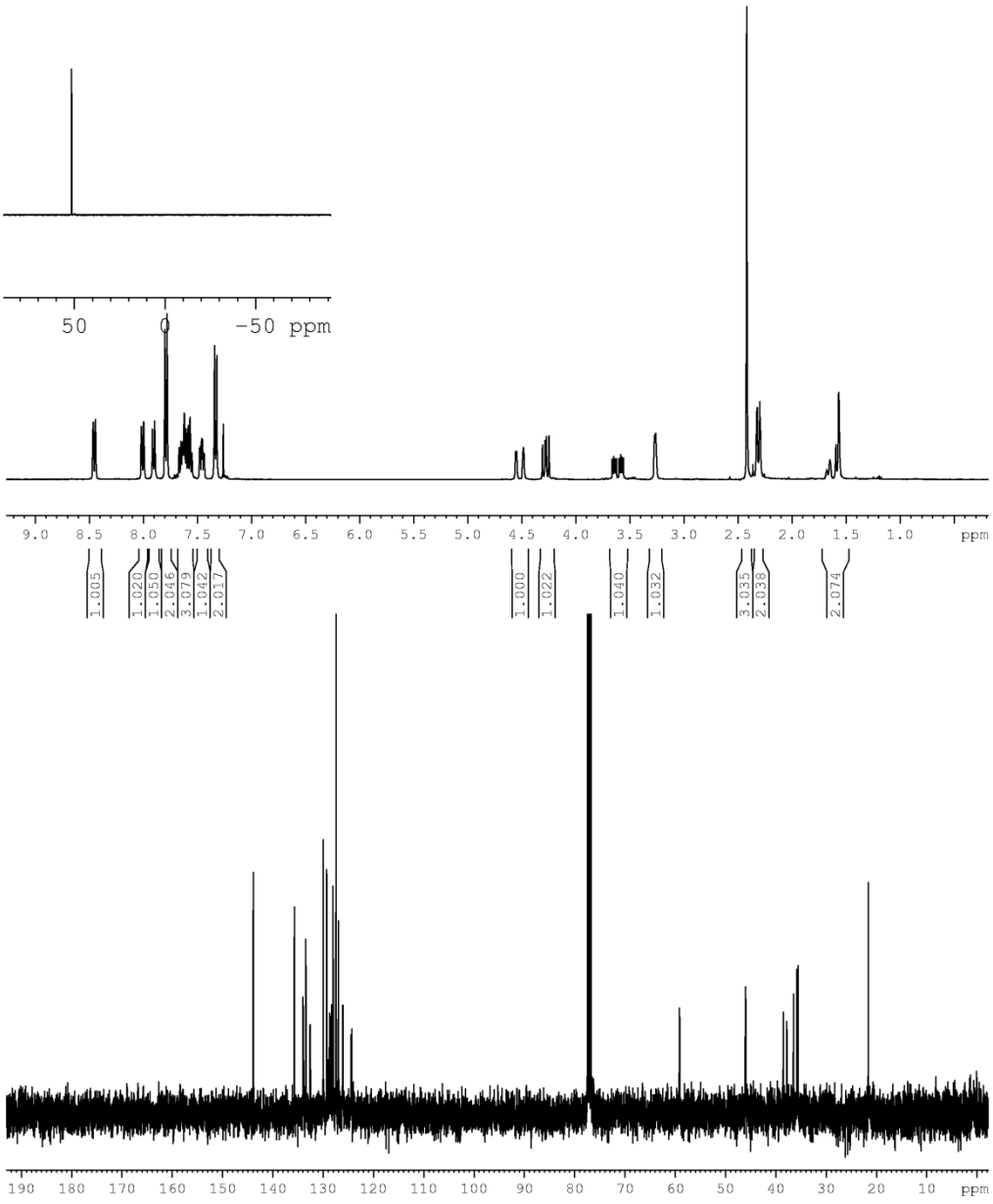

OMe
TsN
P

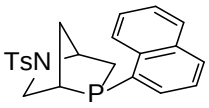
1c


50
0
−50 ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.002
2.008
2.013
2.009
1.000
3.009
2.009
1.008
4.090
1.019
1.011
1.089
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

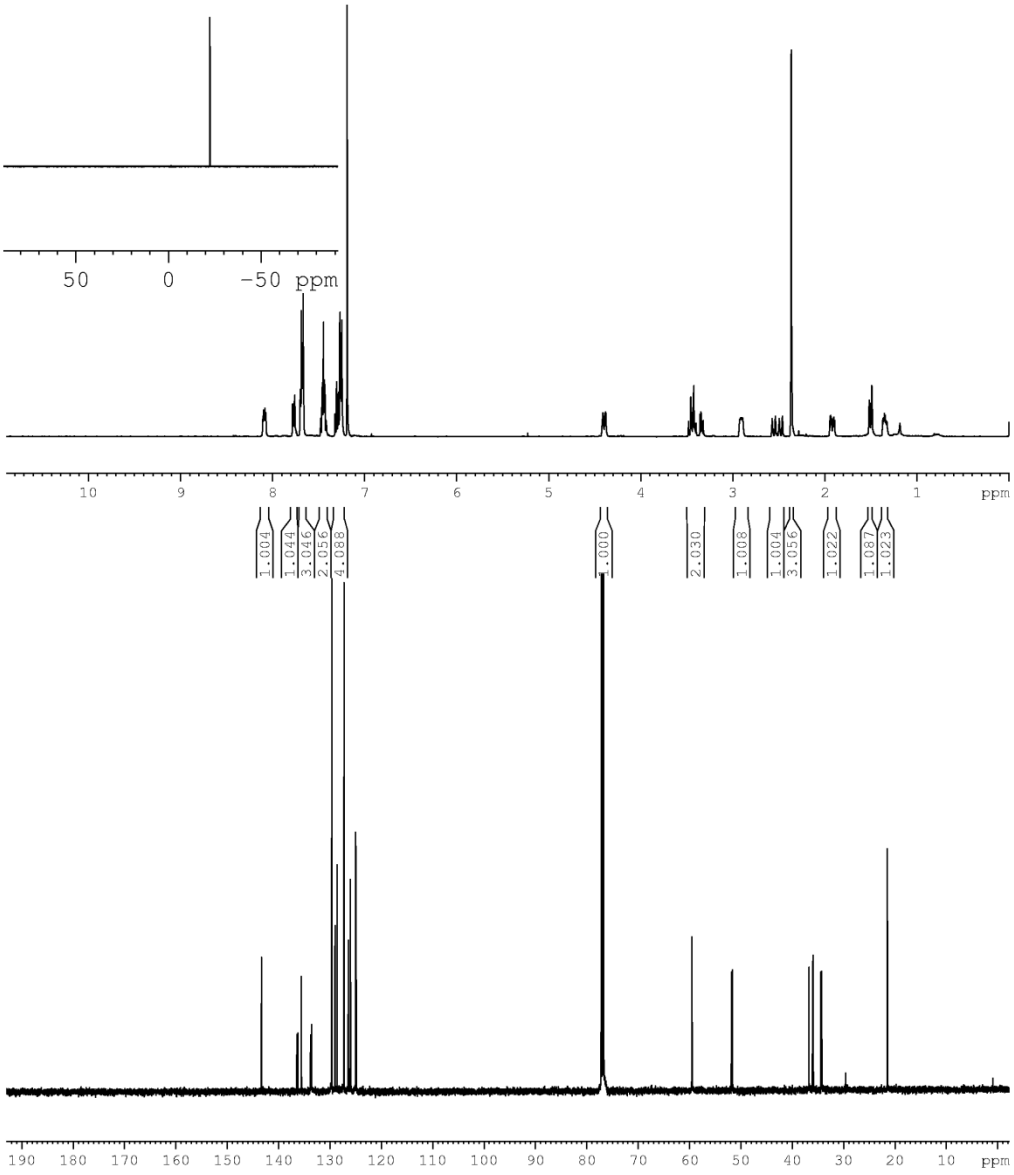

TsN
P
O

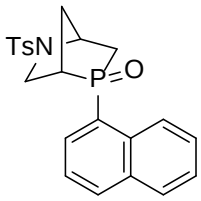
2d


50
0
−50 ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.005
1.020
1.050
2.046
3.079
1.042
2.017
1.000
1.022
1.040
1.032
3.035
2.038
2.074
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

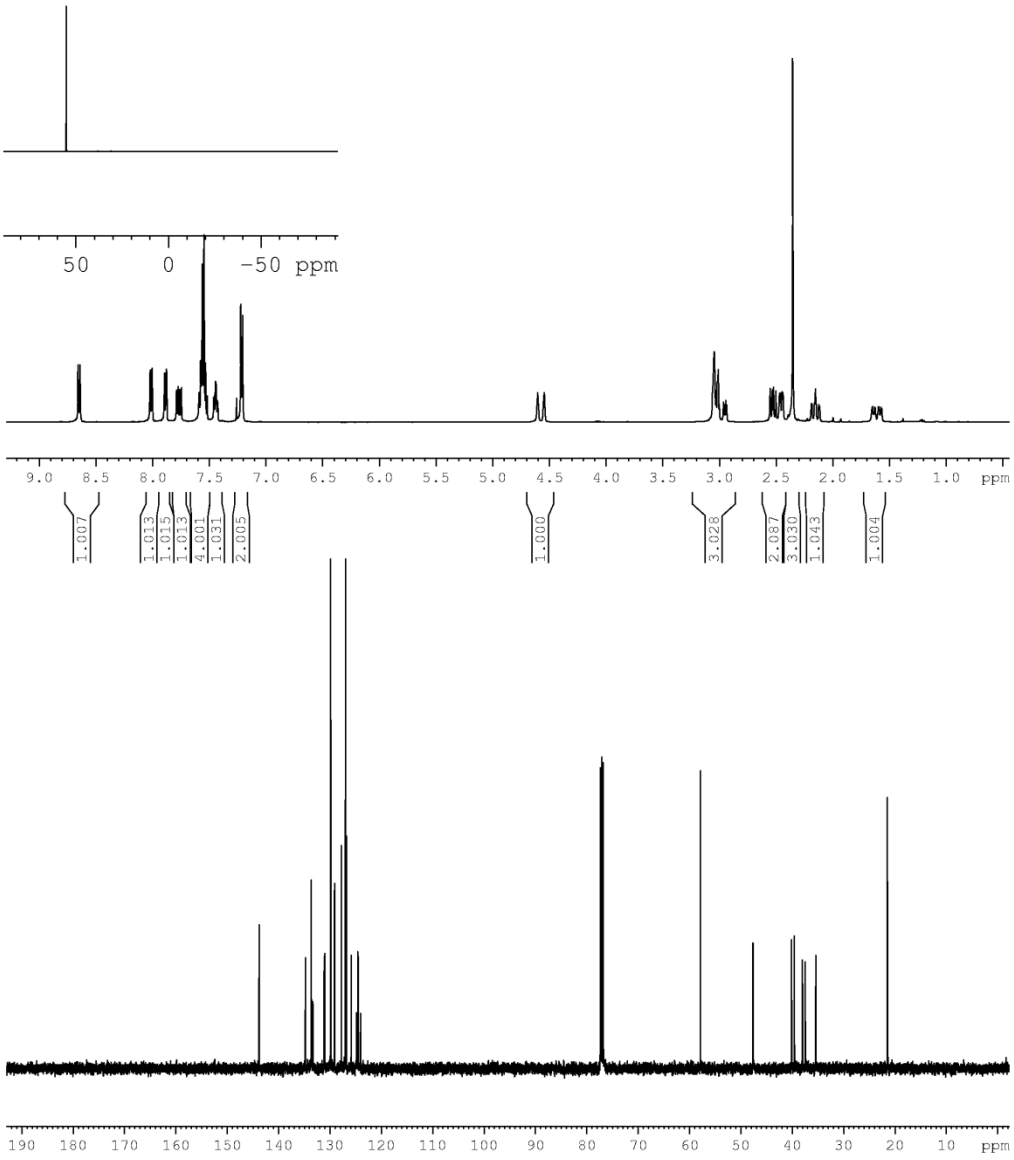

TsN
P

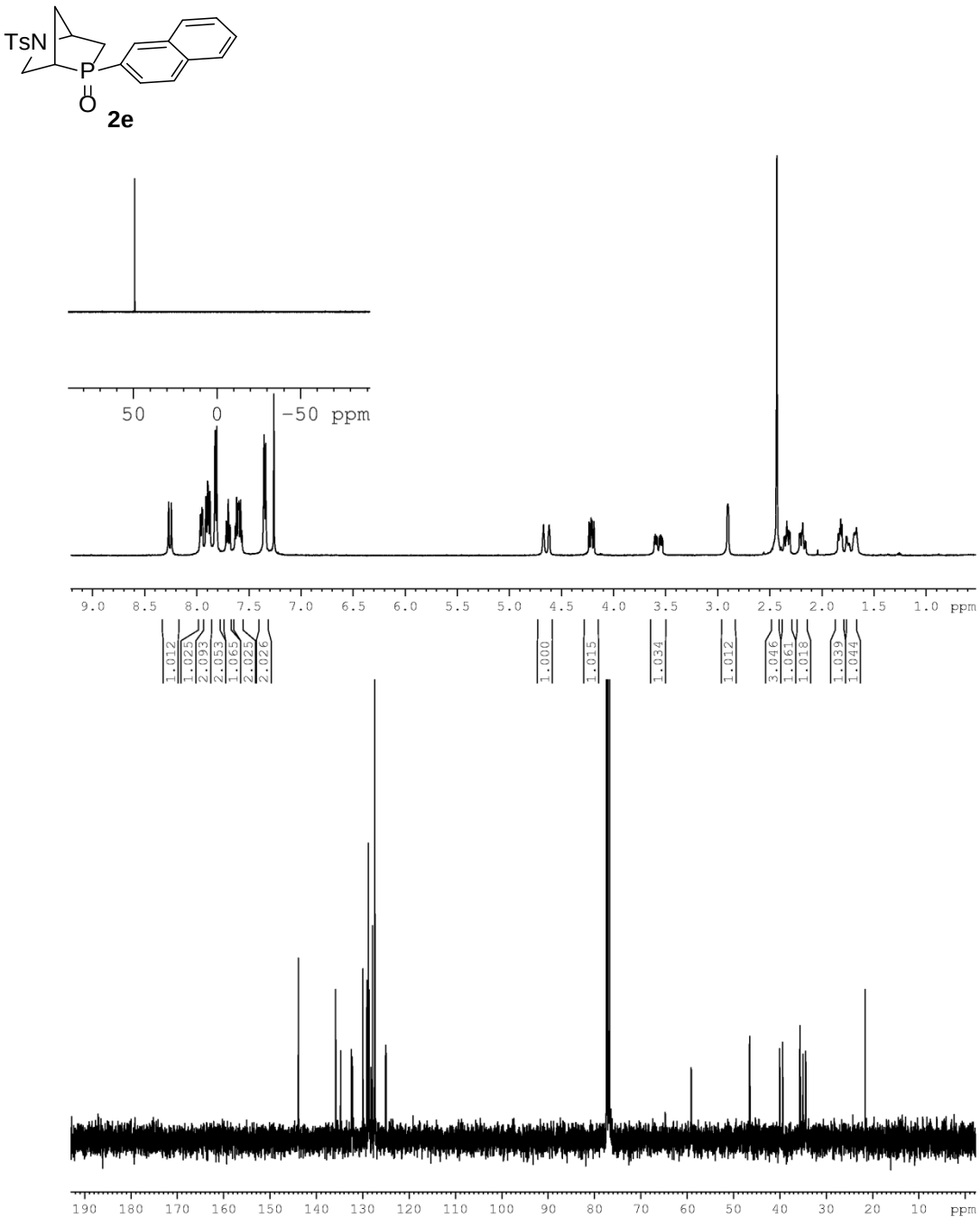
1d

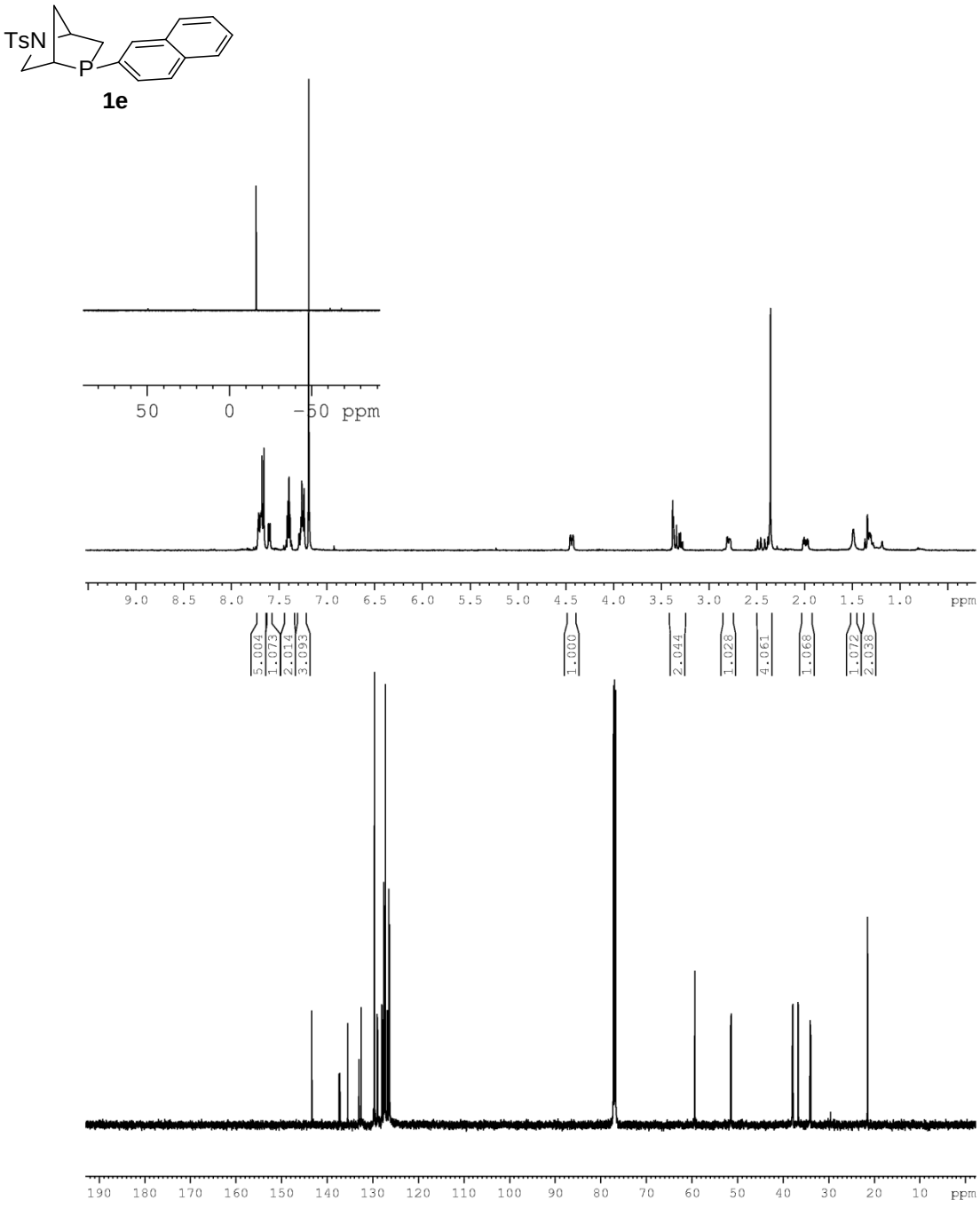

50
0
−50 ppm
10
9
8
7
6
5
4
3
2
1
ppm
1.004
1.044
3.046
2.056
4.088
1.000
2.030
1.008
1.004
3.056
1.022
1.087
1.023
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


TsN
P
O

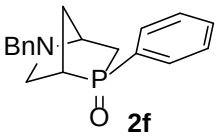
***epi*-2d**


50
0
−50 ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.007
1.013
1.015
1.013
4.001
1.031
2.005
1.000
3.028
2.087
3.030
1.043
1.004
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

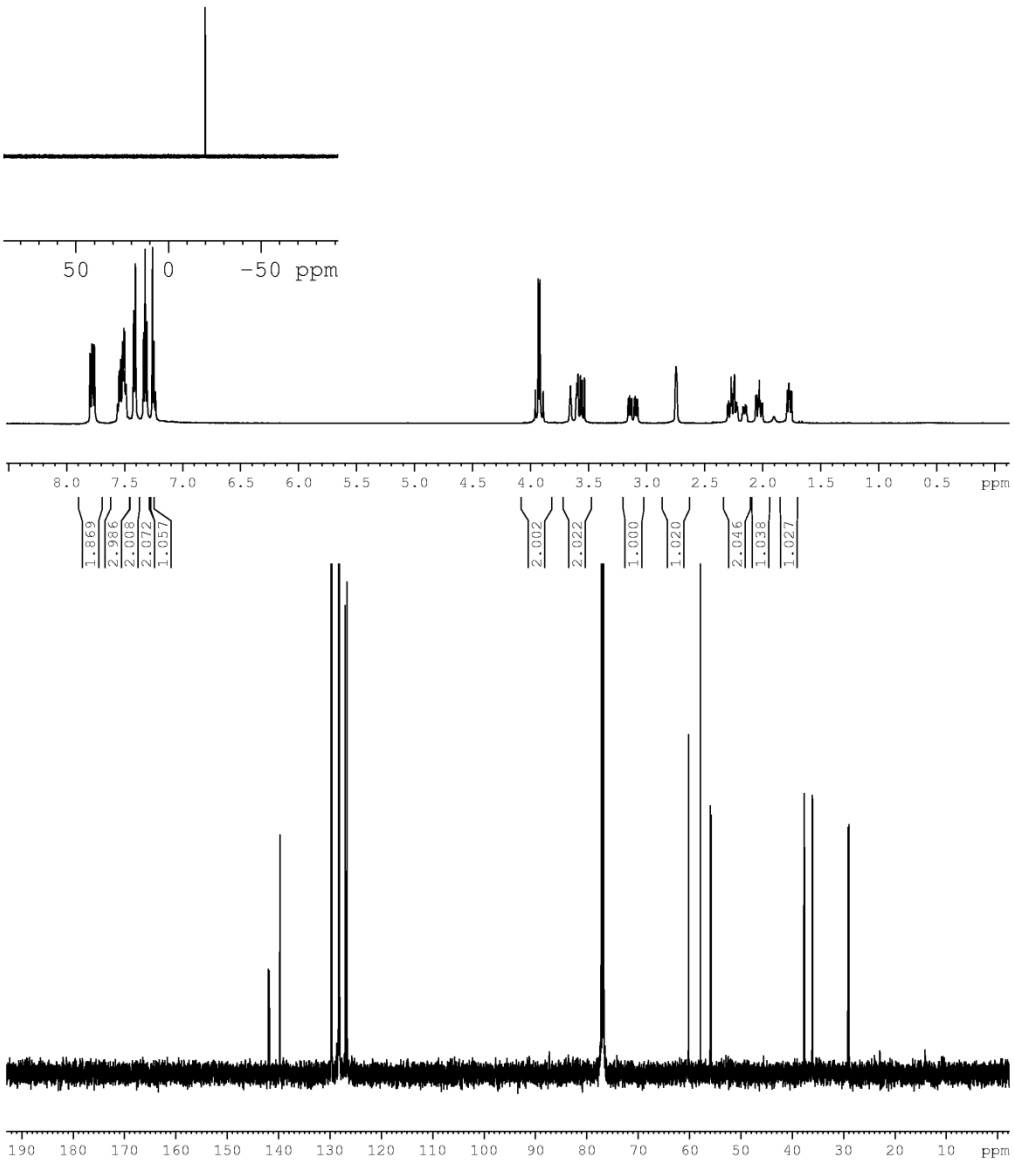

TsN
P
O
2e
50
0
−50 ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.012
1.025
2.093
2.053
1.065
2.025
2.026
1.000
1.015
1.034
1.012
3.046
1.061
1.018
1.039
1.044
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

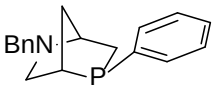

TsN
P
50
0
−50 ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
5.004
1.073
2.014
3.093
1.000
2.044
1.028
4.061
1.068
1.072
2.038
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

1e

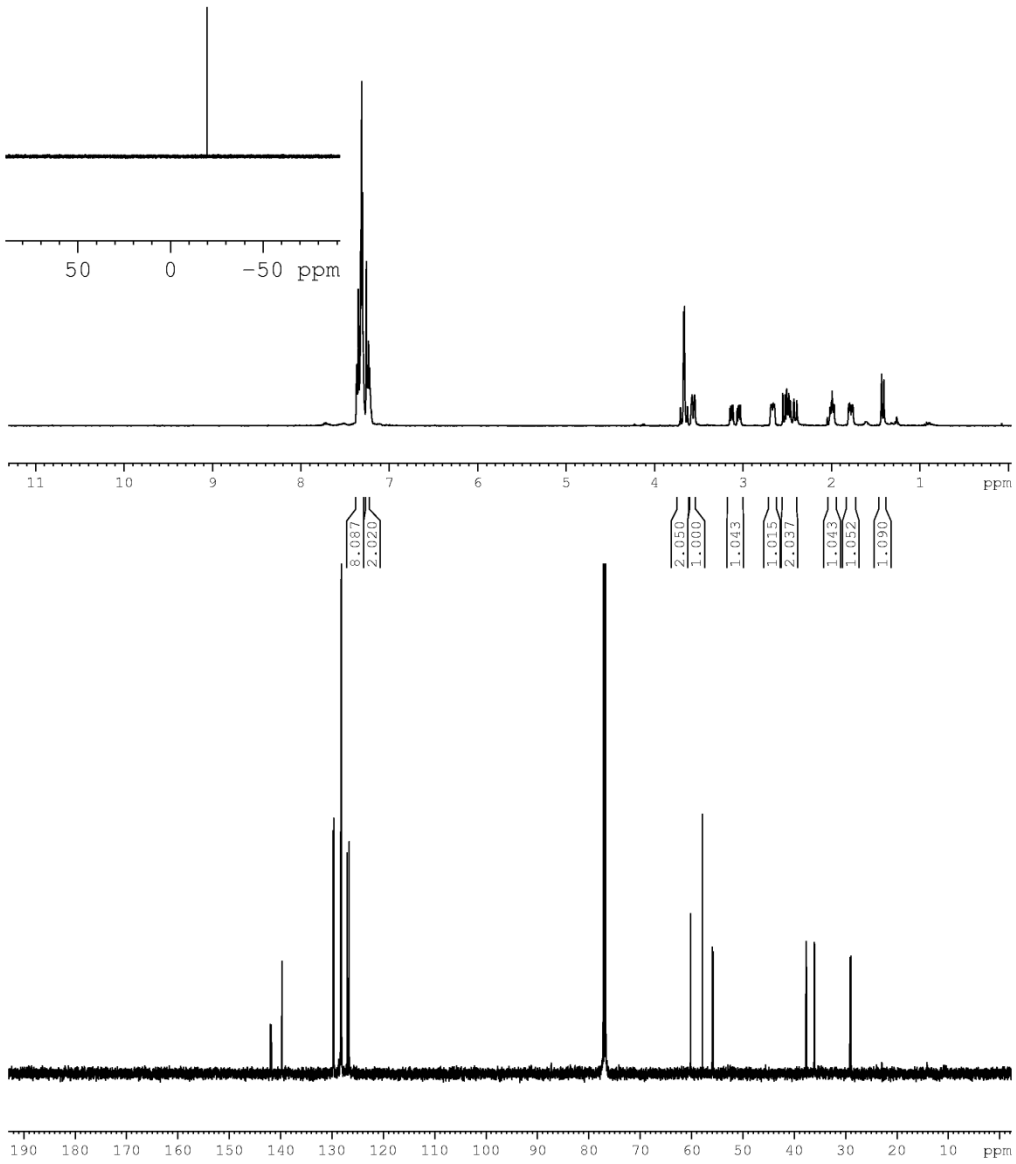

BnN
P
O

2f


50
0
−50 ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.869
2.986
2.008
2.072
1.057
2.002
2.022
1.000
1.020
2.046
1.038
1.027
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

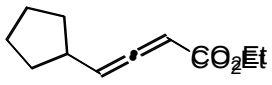

BnN
P

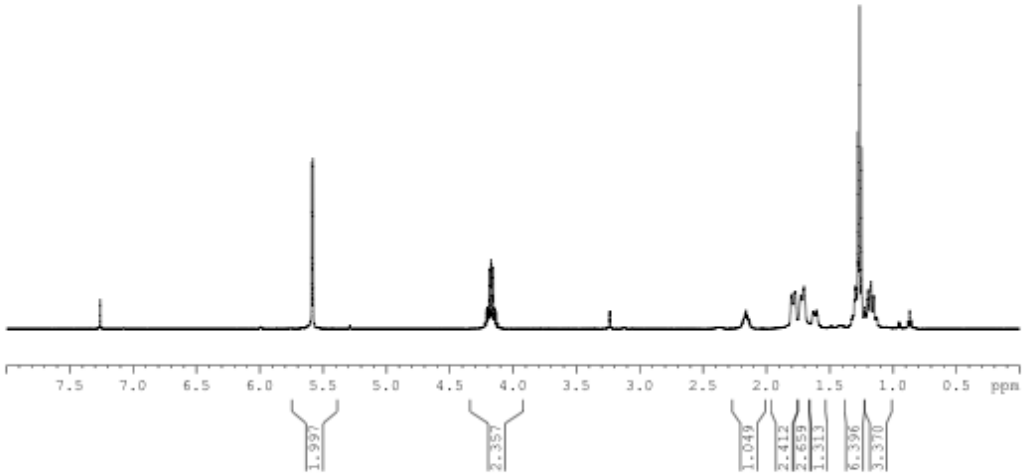
1f

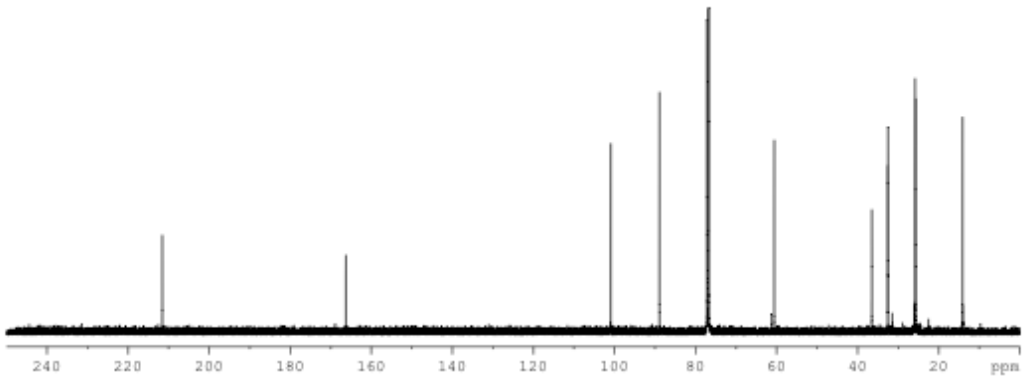

50
0
−50 ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
8.087
2.020
2.050
1.000
1.043
1.015
2.037
1.043
1.052
1.090
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Allene spectra

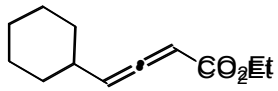
Ethyl 4-cyclopentyl-2,3-dienoate

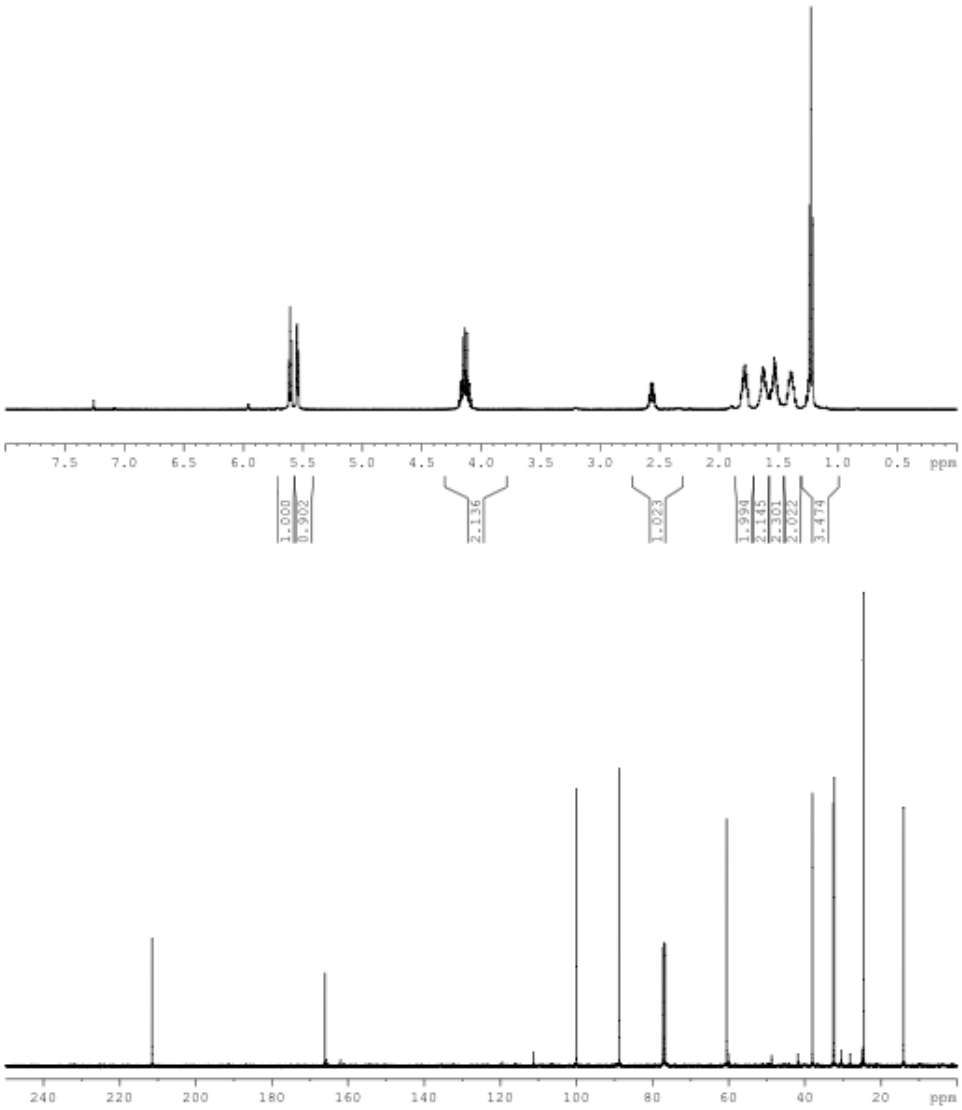




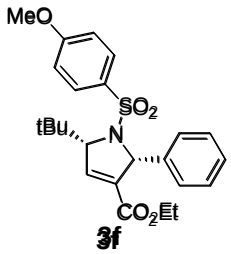


Ethyl 4-cyclohexyl-2,3-dienoate

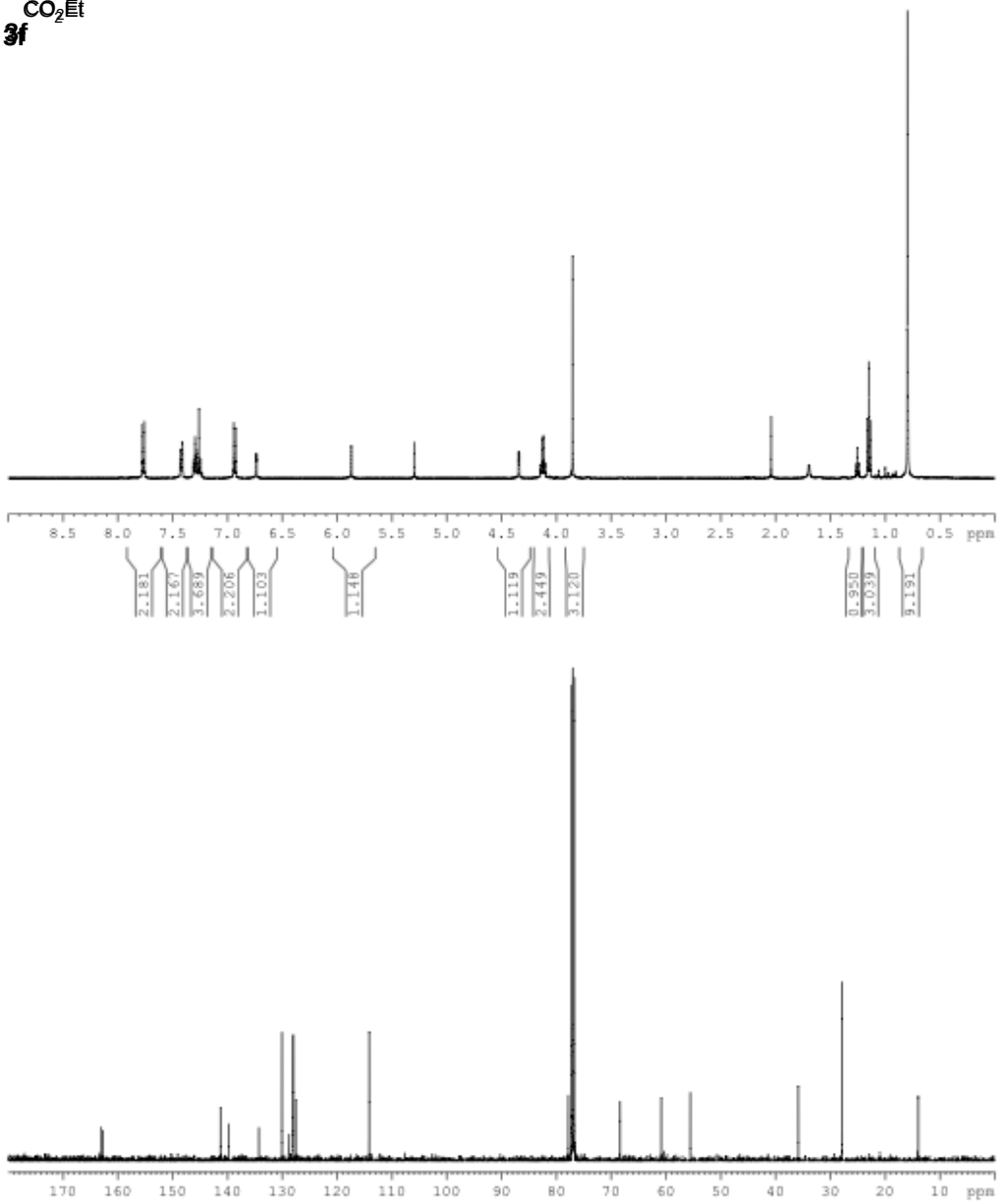


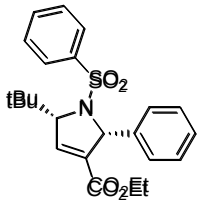


Pyrroline spectra

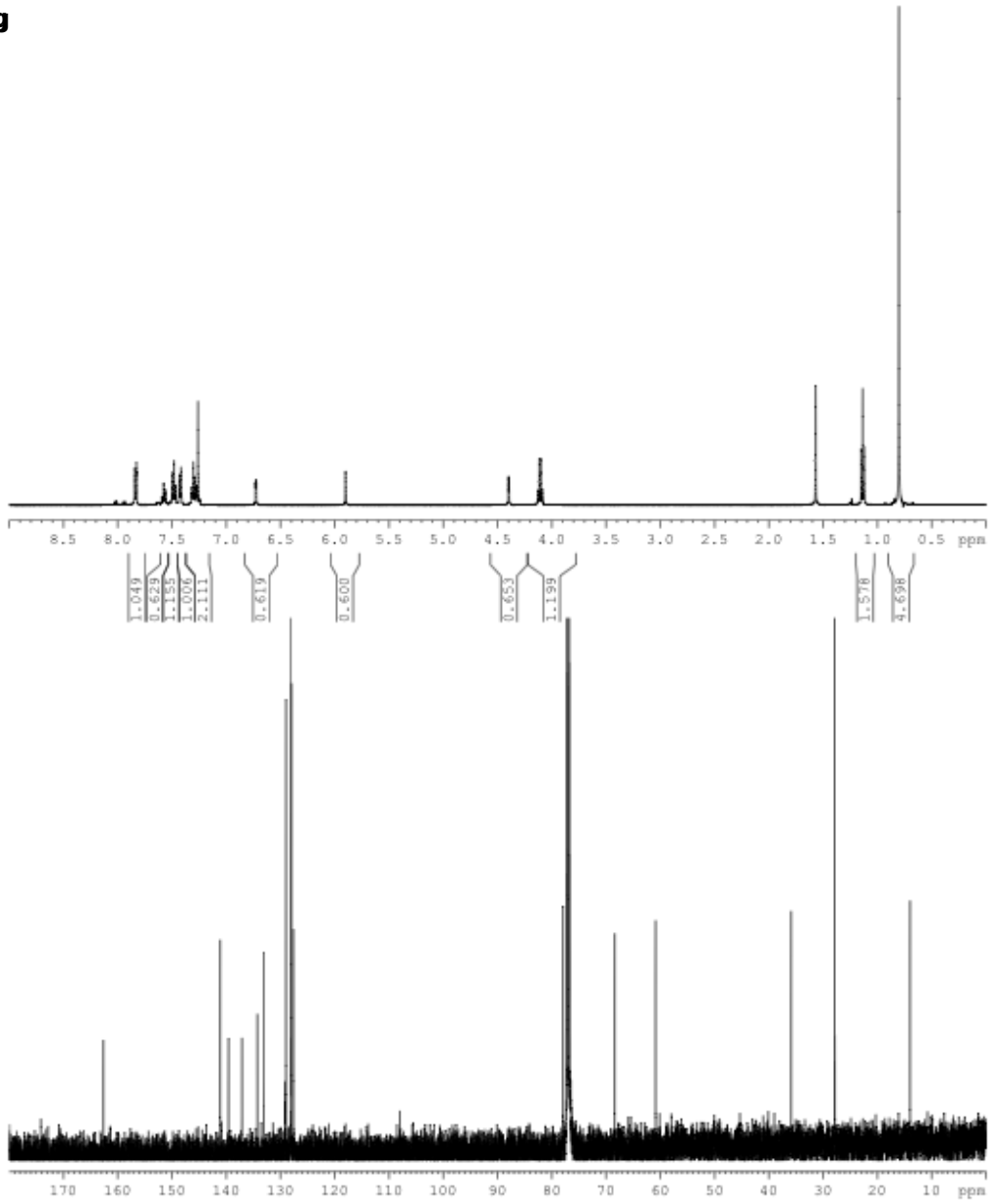


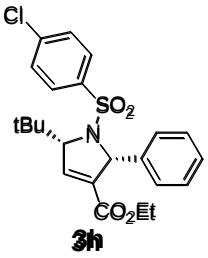
3f



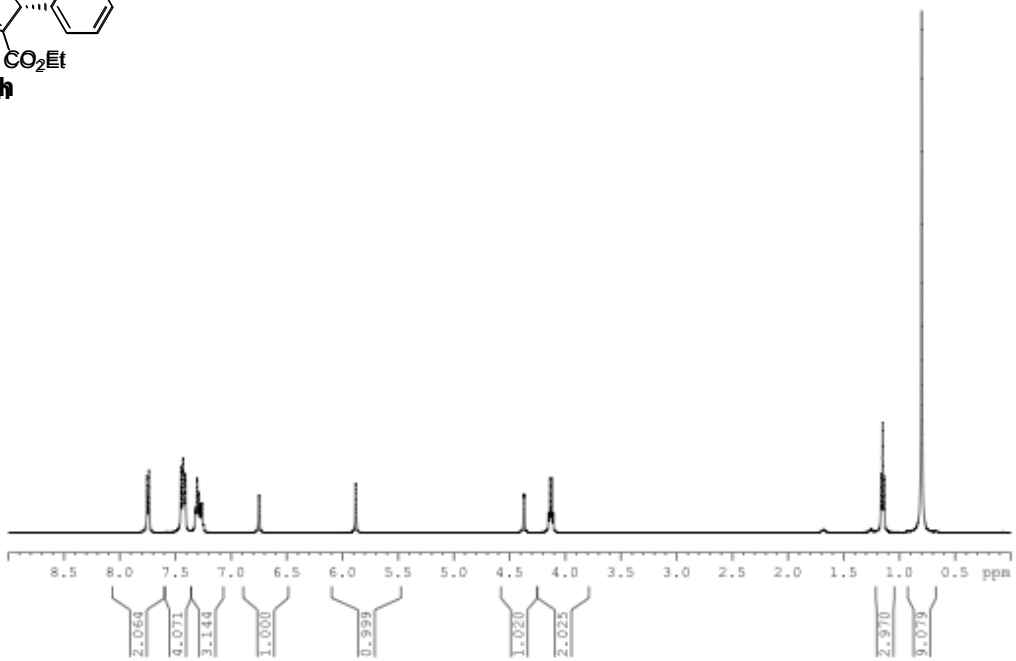

SO2
tBu
N
CO2Et

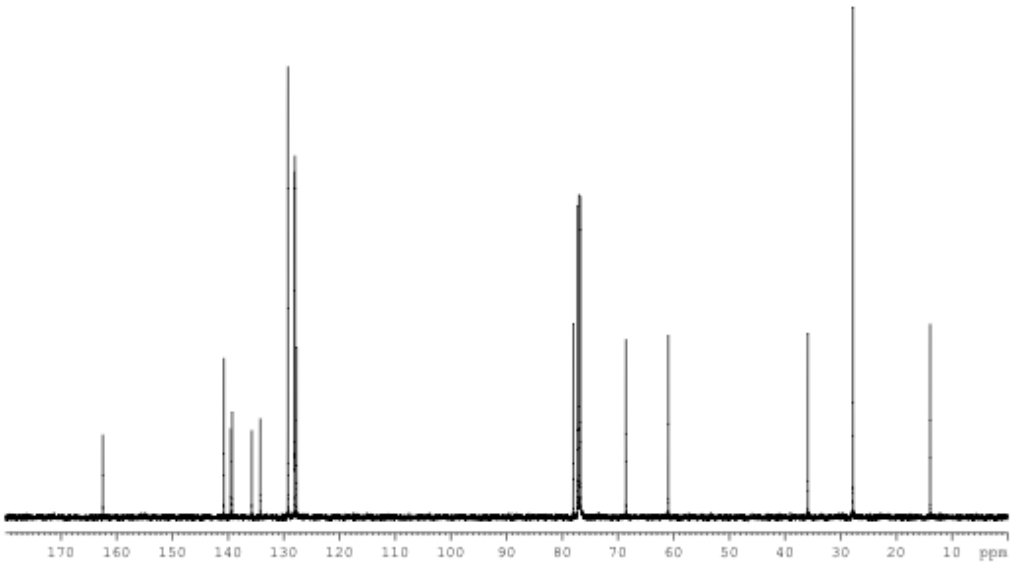
3g

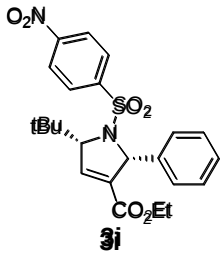

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.049
0.629
1.155
1.006
2.111
0.619
0.600
0.653
1.199
1.578
4.698
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Cl
SO2
tBu
N
CO2Et

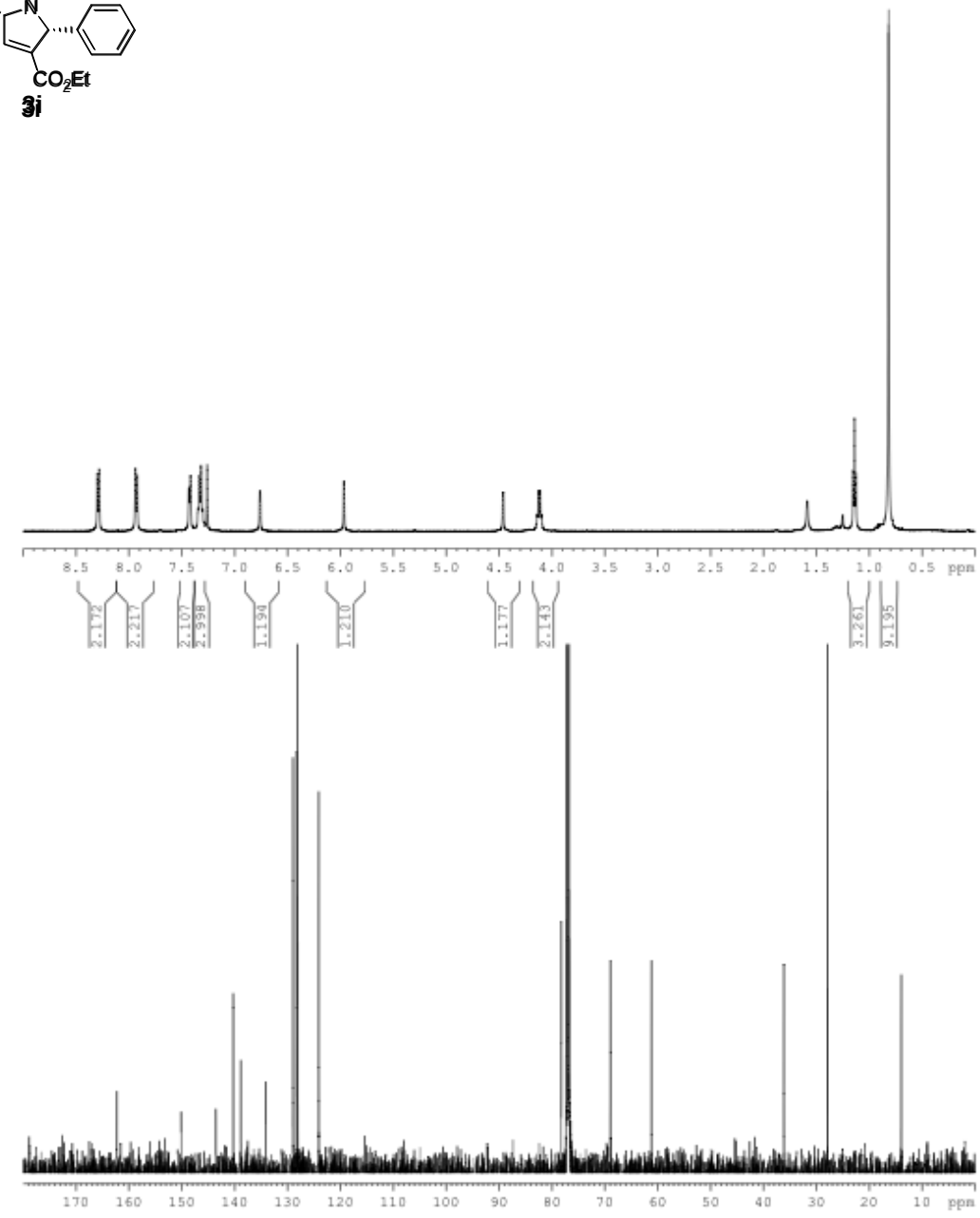
3h

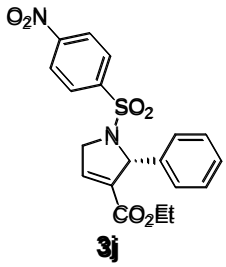

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.064
4.071
3.144
1.000
0.999
1.020
2.025
2.970
9.079


170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

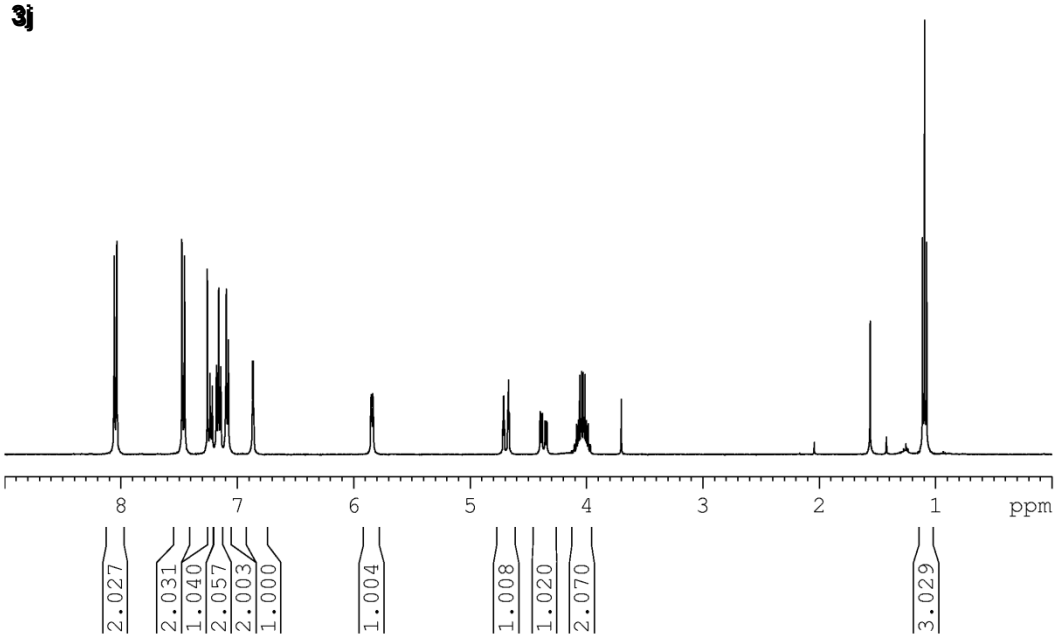

O2N
SO2
tBu
N
CO2Et

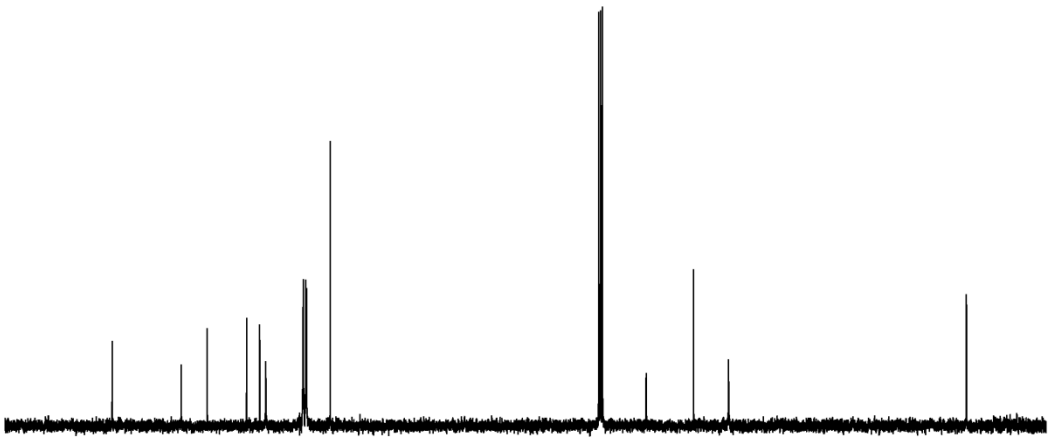
3i

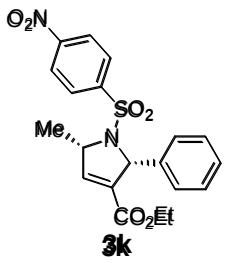

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.172
2.217
2.107
2.998
1.194
1.210
1.177
2.143
3.261
9.195
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O2N
SO2
N
CO2Et

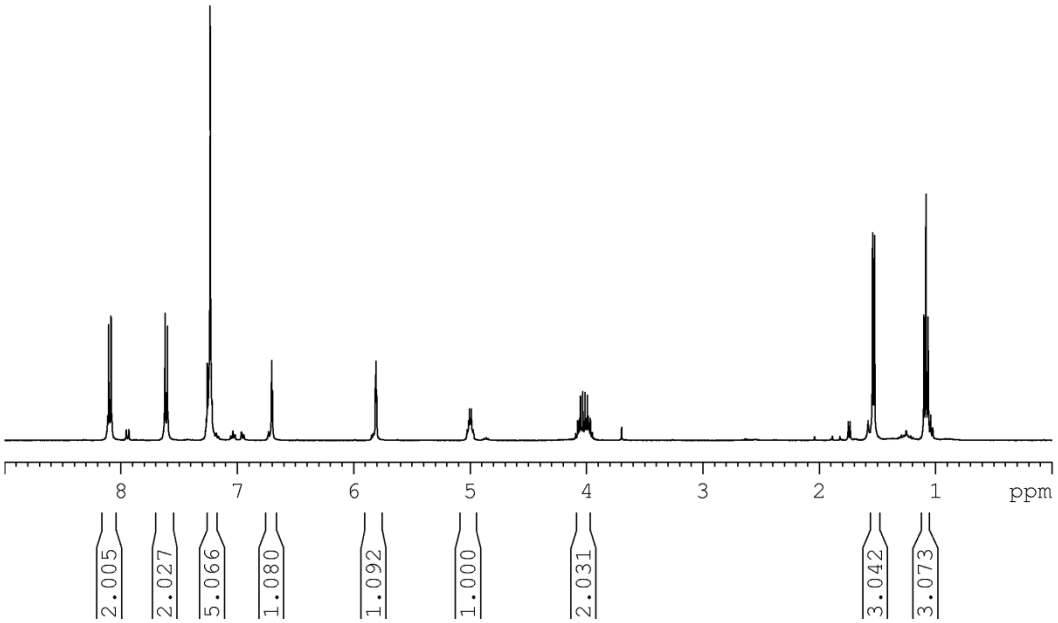
3j

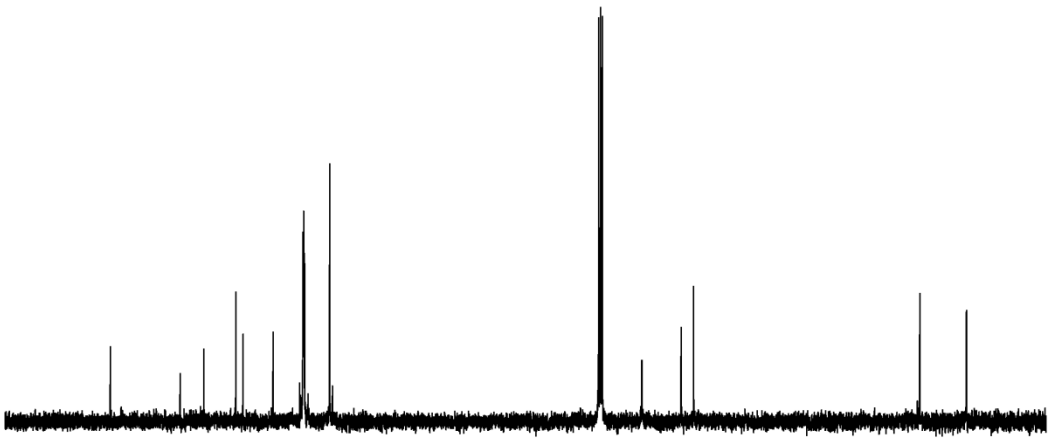

8
7
6
5
4
3
2
1
ppm
2.027
2.031
1.040
2.057
2.003
1.000
1.004
1.008
1.020
2.070
3.029

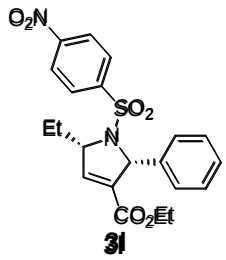



O2N
SO2
Me
N
CO2Et

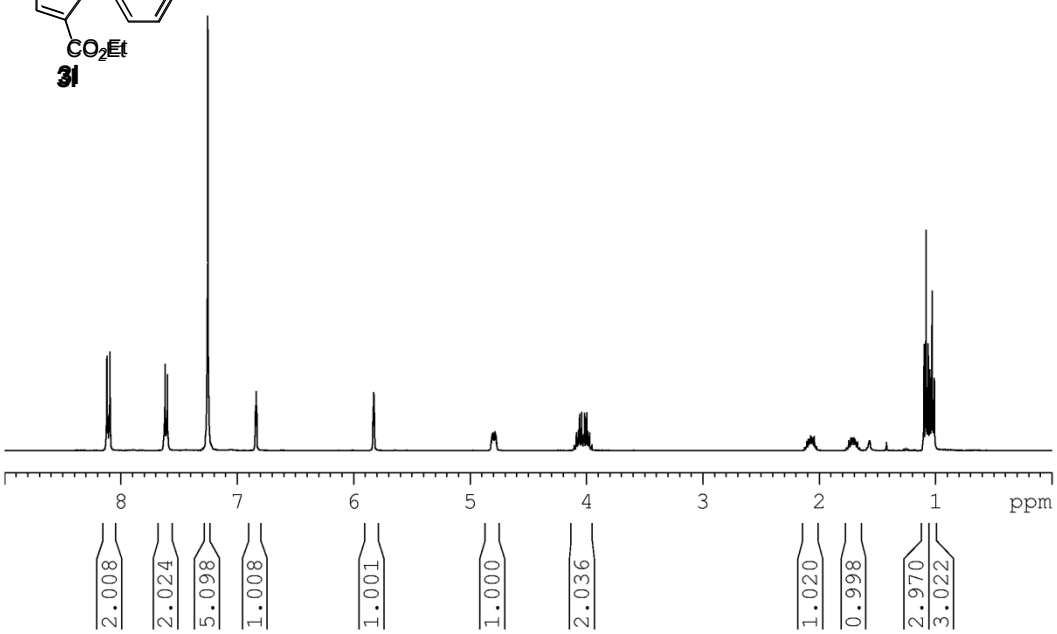
3k

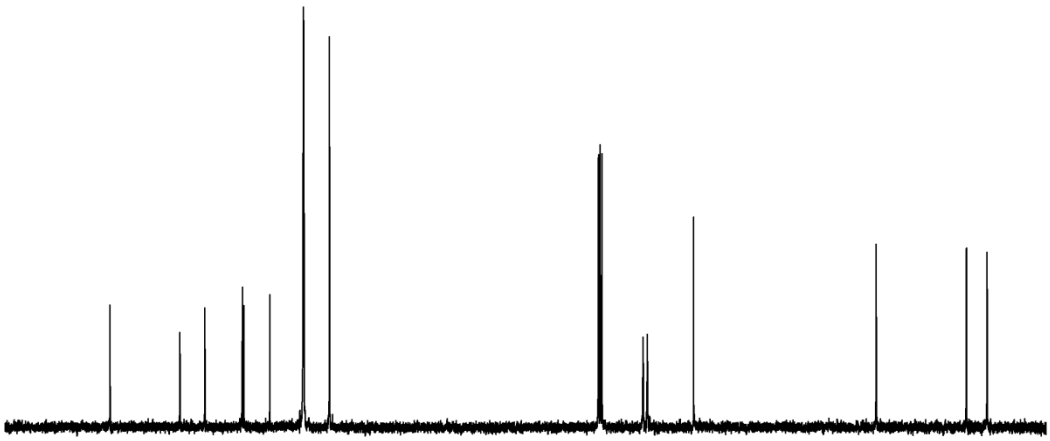

8
7
6
5
4
3
2
1
ppm
2.005
2.027
5.066
1.080
1.092
1.000
2.031
3.042
3.073

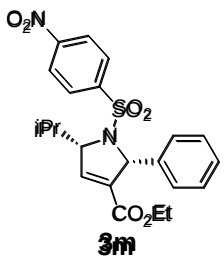



O2N
SO2
Et
N
CO2Et

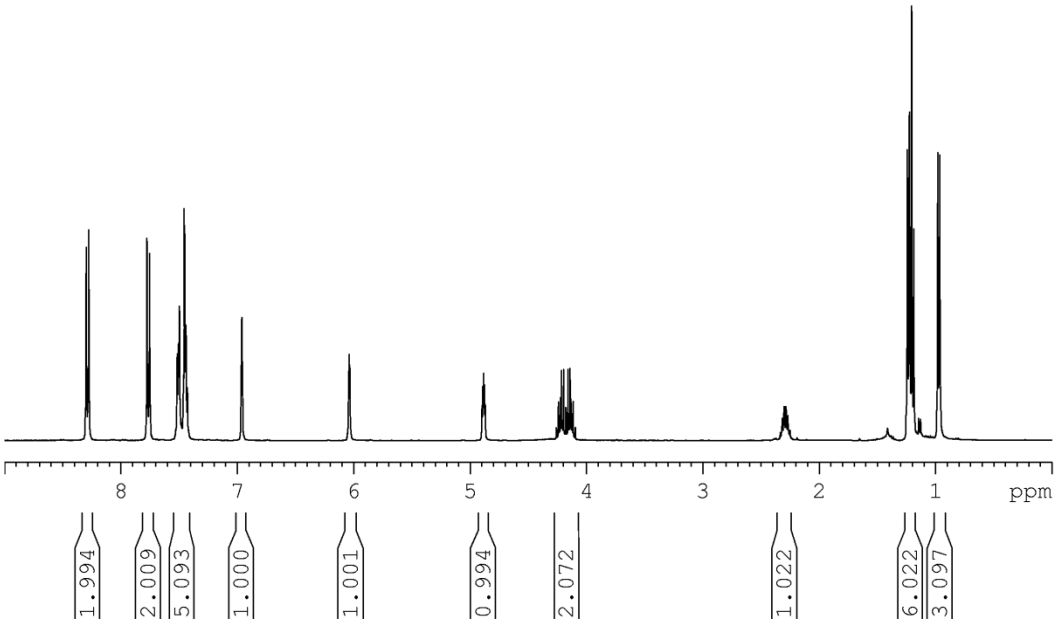
3l

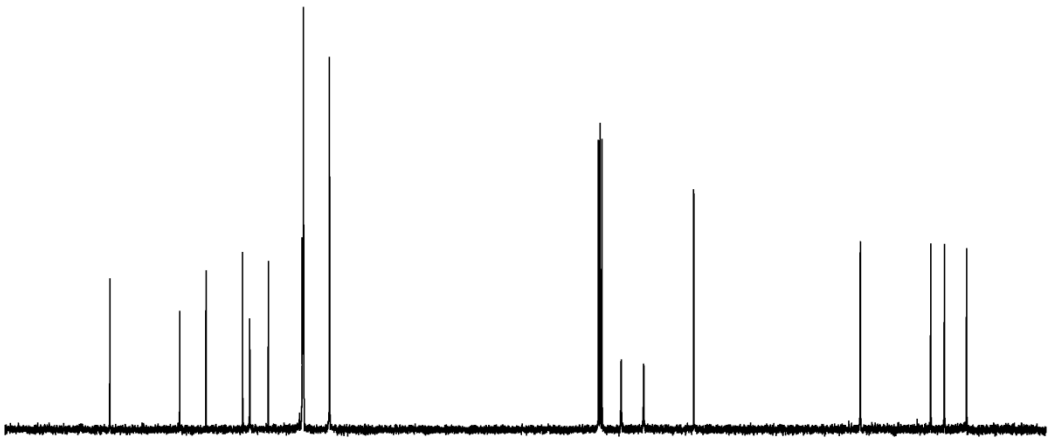

8
7
6
5
4
3
2
1
ppm
2.008
2.024
5.098
1.008
1.001
1.000
2.036
1.020
0.998
2.970
3.022

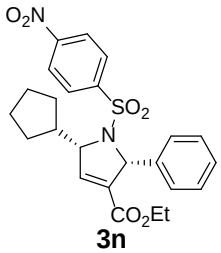



O2N
SO2
iPr
N
CO2Et

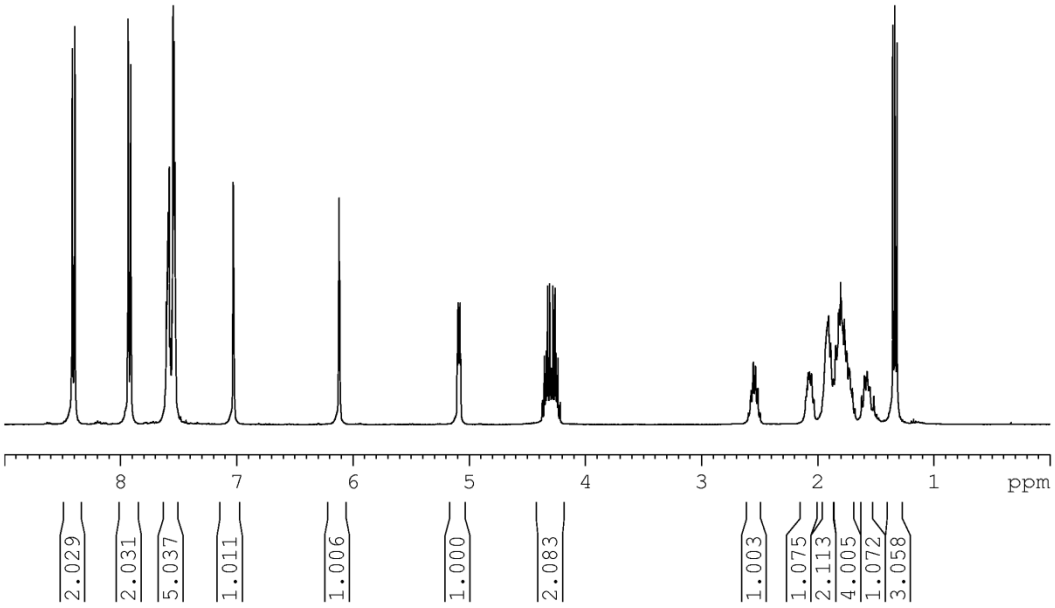
3m

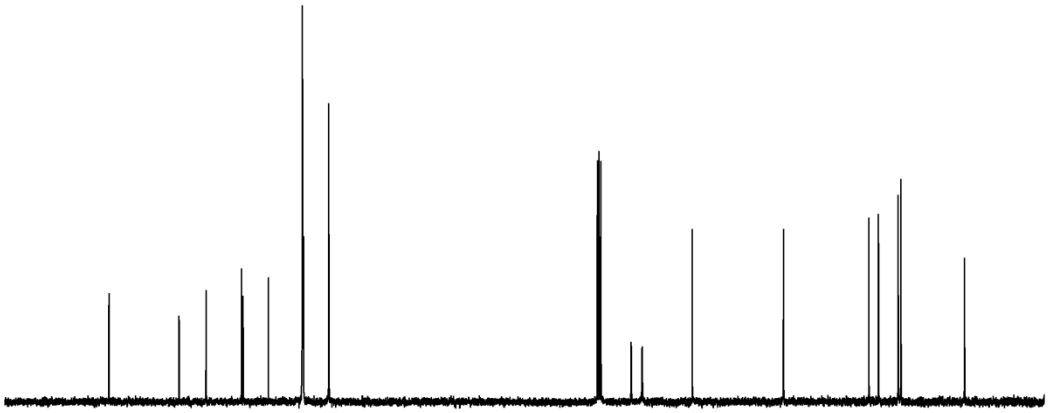

8
7
6
5
4
3
2
1
ppm
1.994
2.009
5.093
1.000
1.001
0.994
2.072
1.022
6.022
3.097

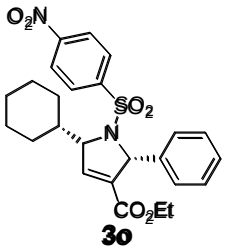



O2N
SO2
N
CO2Et

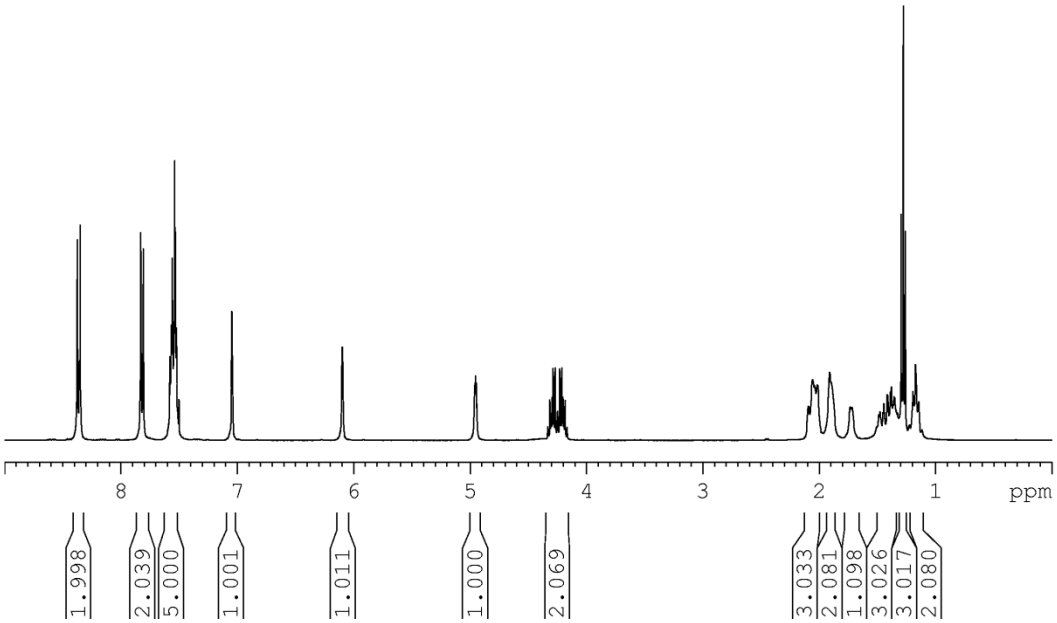
3n


8
7
6
5
4
3
2
1
ppm
2.029
2.031
5.037
1.011
1.006
1.000
2.083
1.003
1.075
2.113
4.005
1.072
3.058




O2N
SO2
N
CO2Et

3o


8
7
6
5
4
3
2
1
ppm
1.998
2.039
5.000
1.001
1.011
1.000
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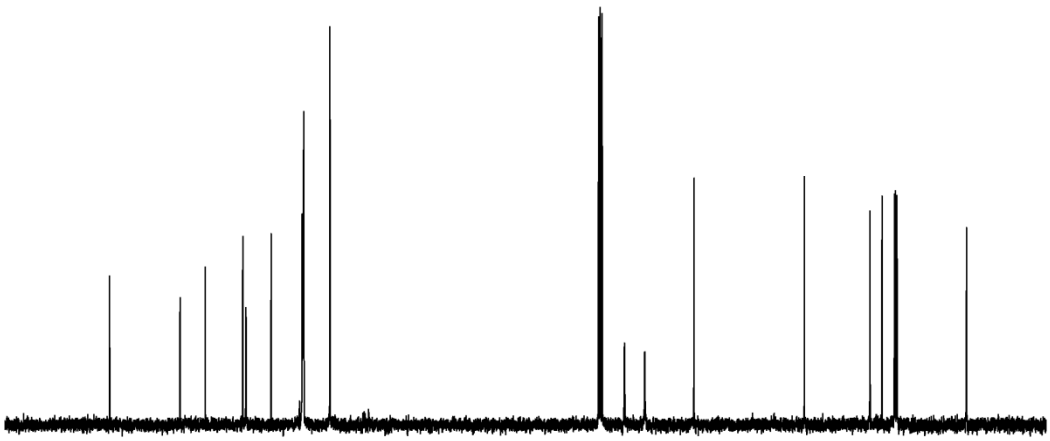
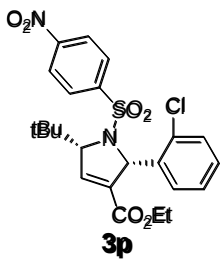
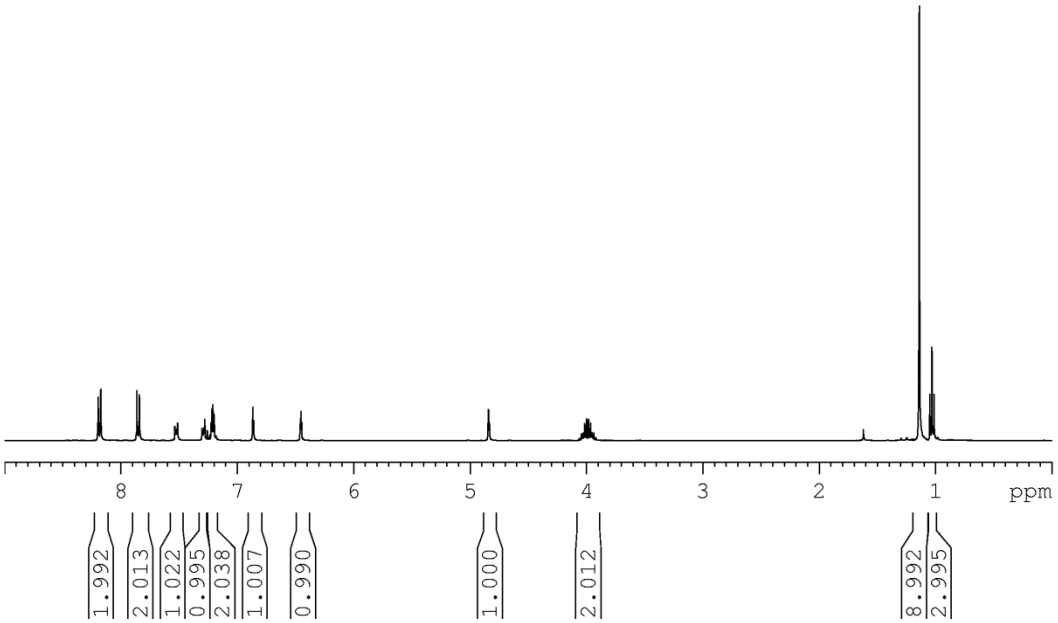
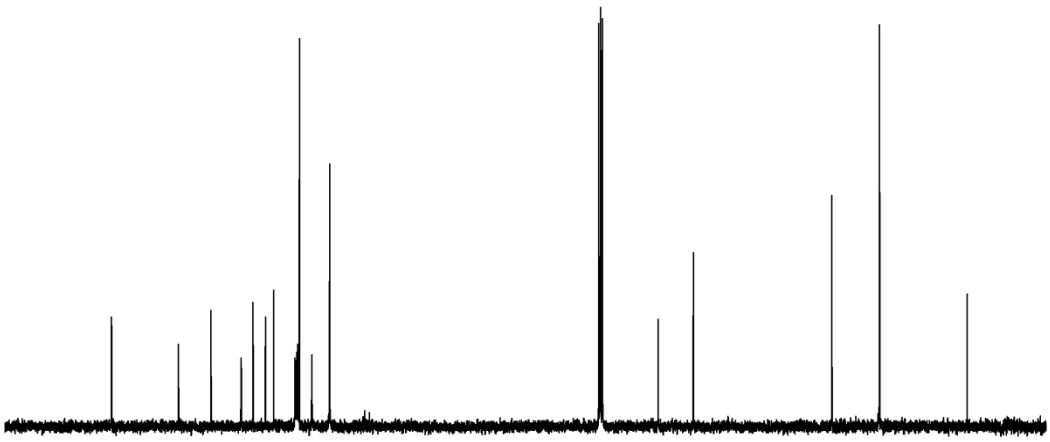
3.033
2.081
1.098
3.026
3.017
2.080

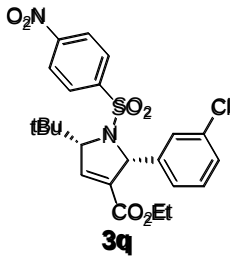



O2N
SO2
Cl
tBu
N
CO2Et

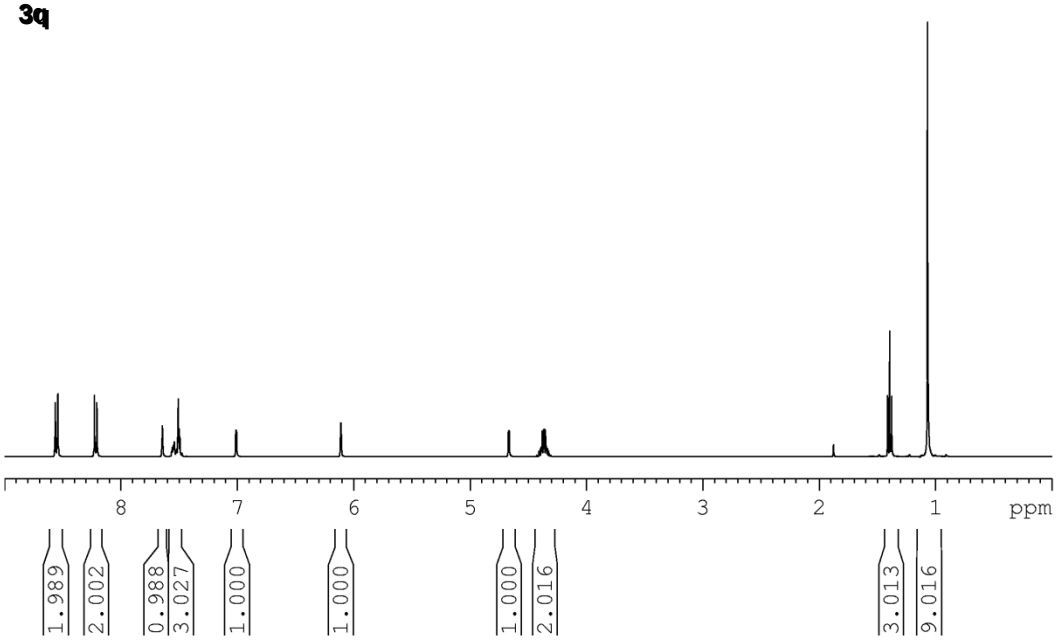
3p

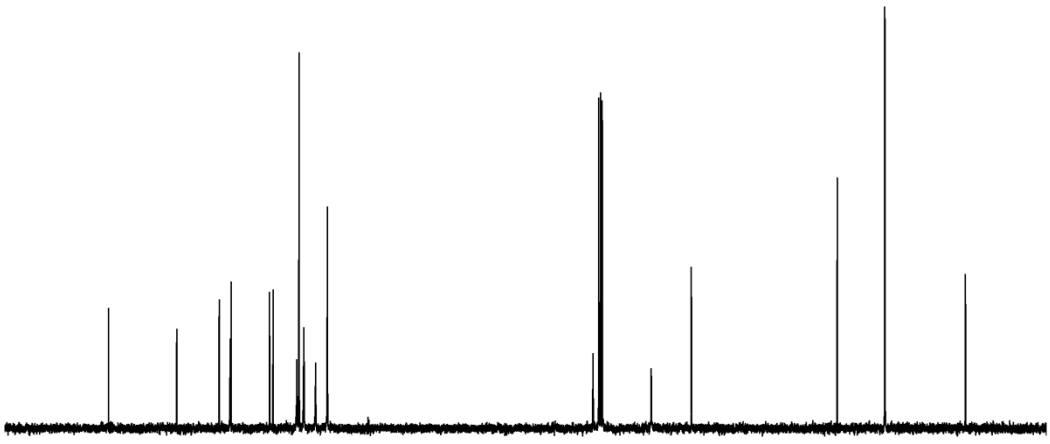

8
7
6
5
4
3
2
1
ppm
1.992
2.013
1.022
0.995
2.038
1.007
0.990
1.000
2.012
8.992
2.995

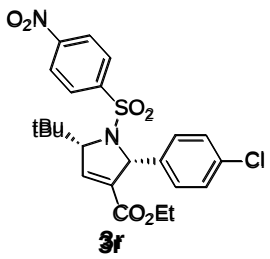



O2N
SO2
Cl
tBu
N
CO2Et

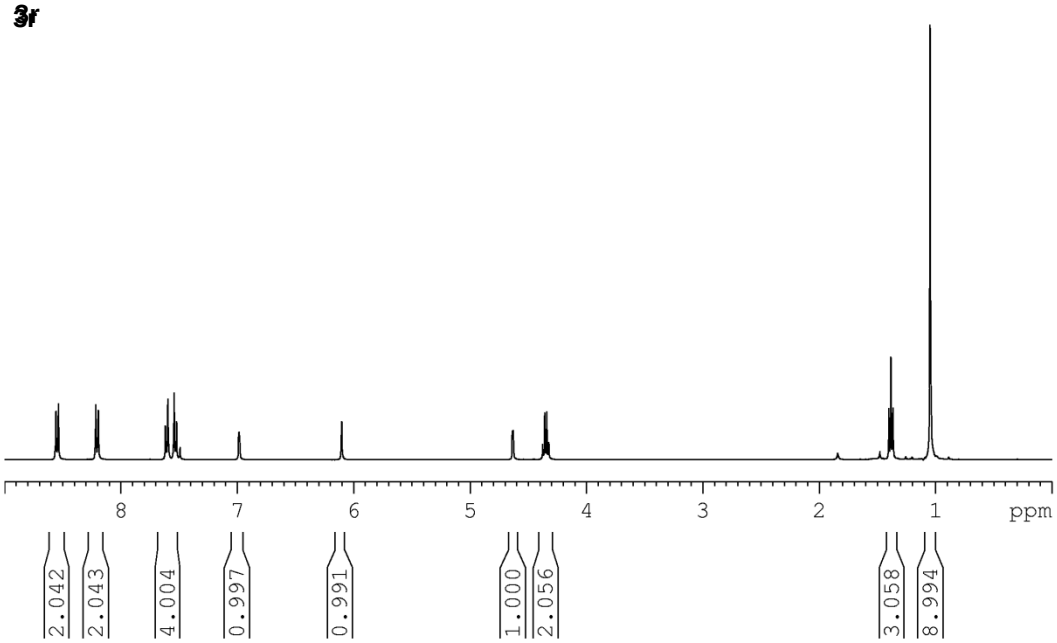
3q


8
7
6
5
4
3
2
1
ppm
1.989
2.002
0.988
3.027
1.000
1.000
1.000
2.016
3.013
9.016




O2N
SO2
tBu
N
Cl
CO2Et

3r


8
7
6
5
4
3
2
1
ppm
2.042
2.043
4.004
0.997
0.991
1.000
2.056
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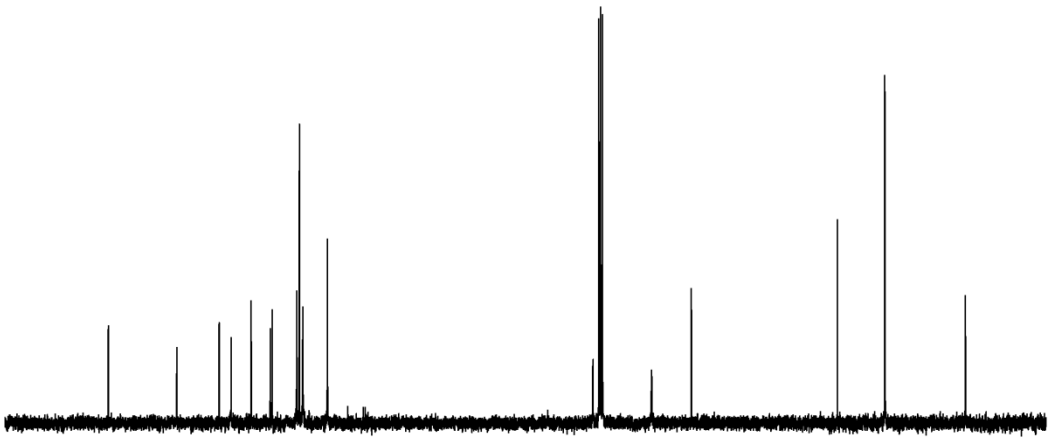
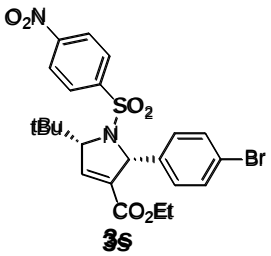
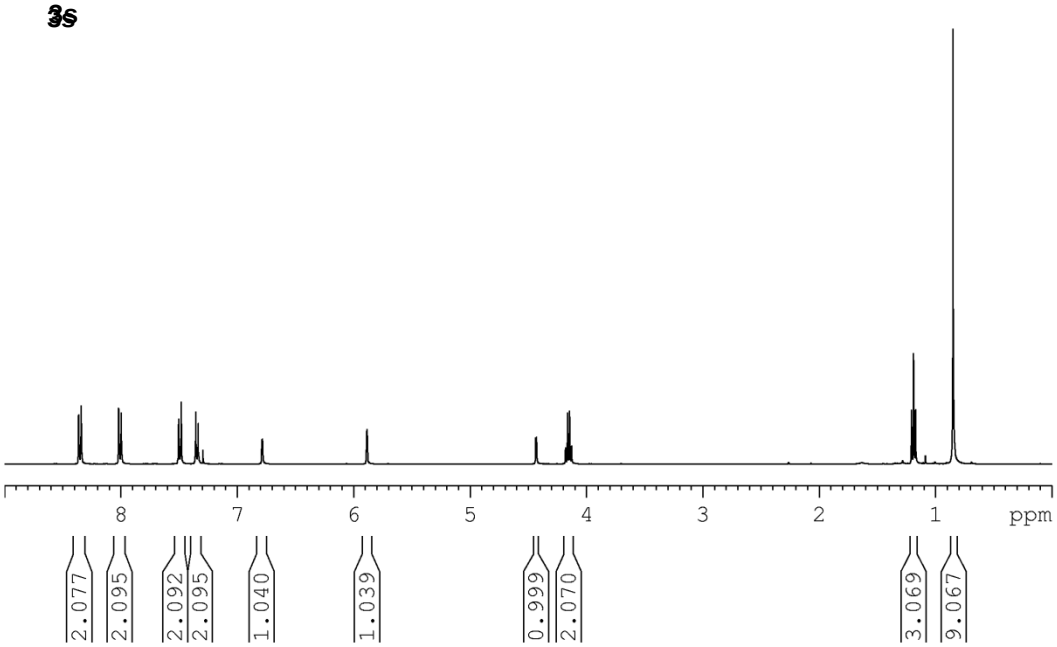



O2N
SO2
tBu
N
Br
CO2Et

3s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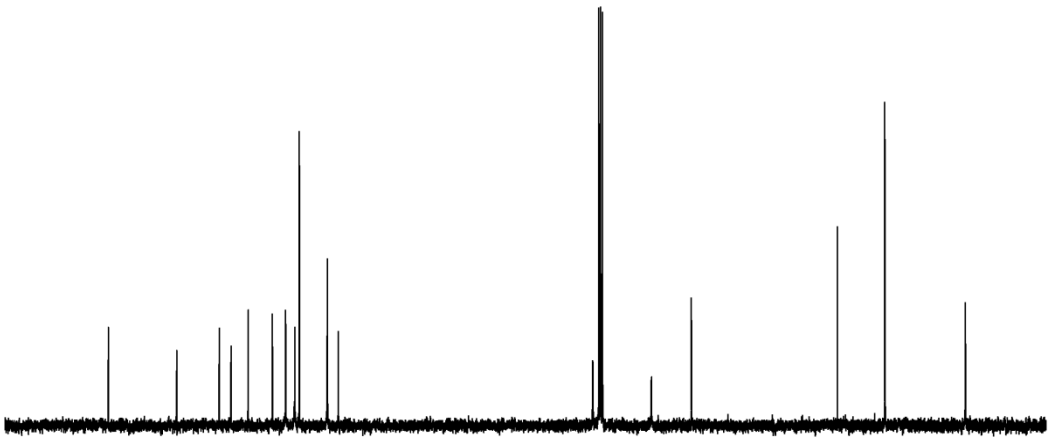
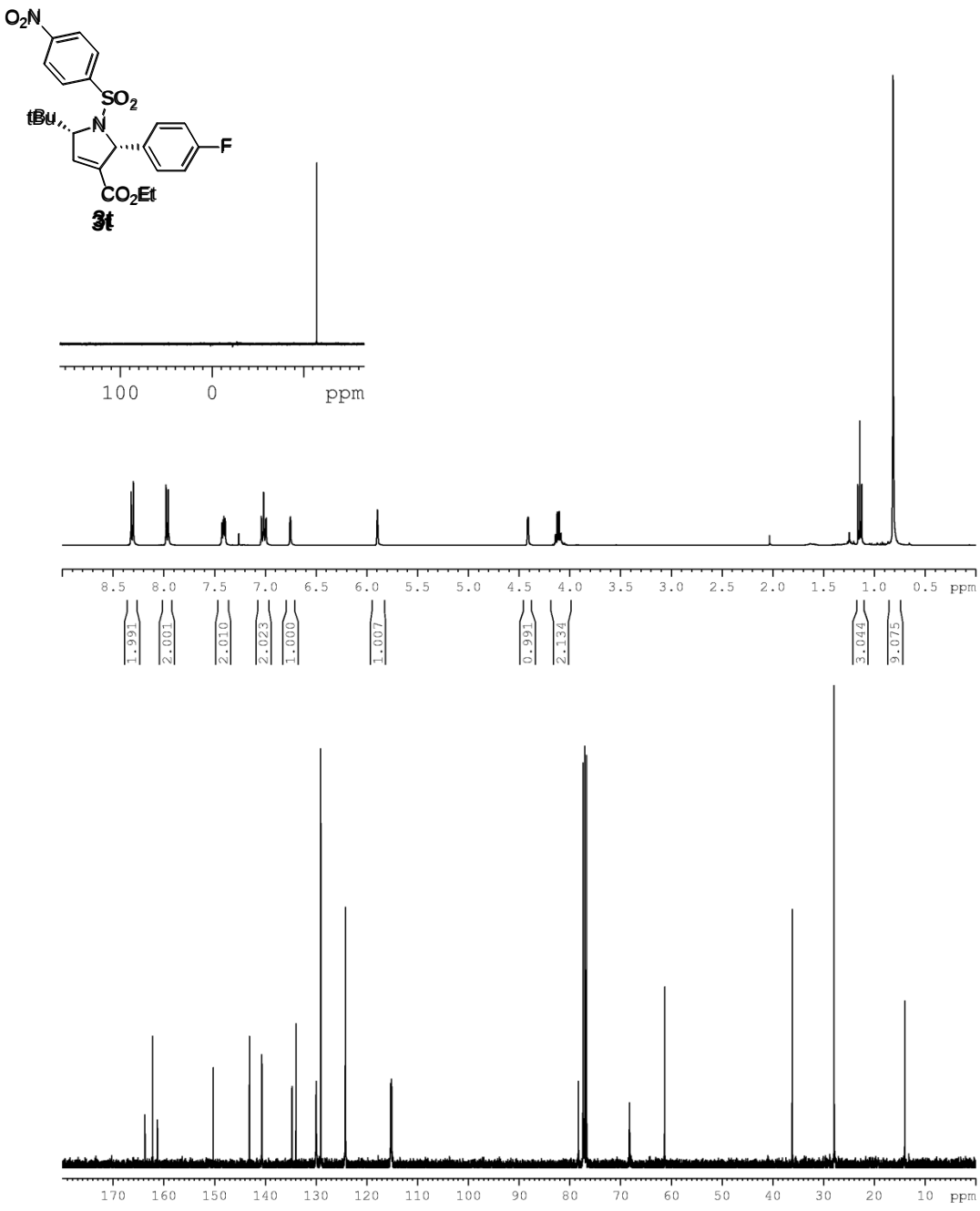
3.069
9.067




O2N
SO2
tBu
N
F
CO2Et
3t
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0
ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.991
2.001
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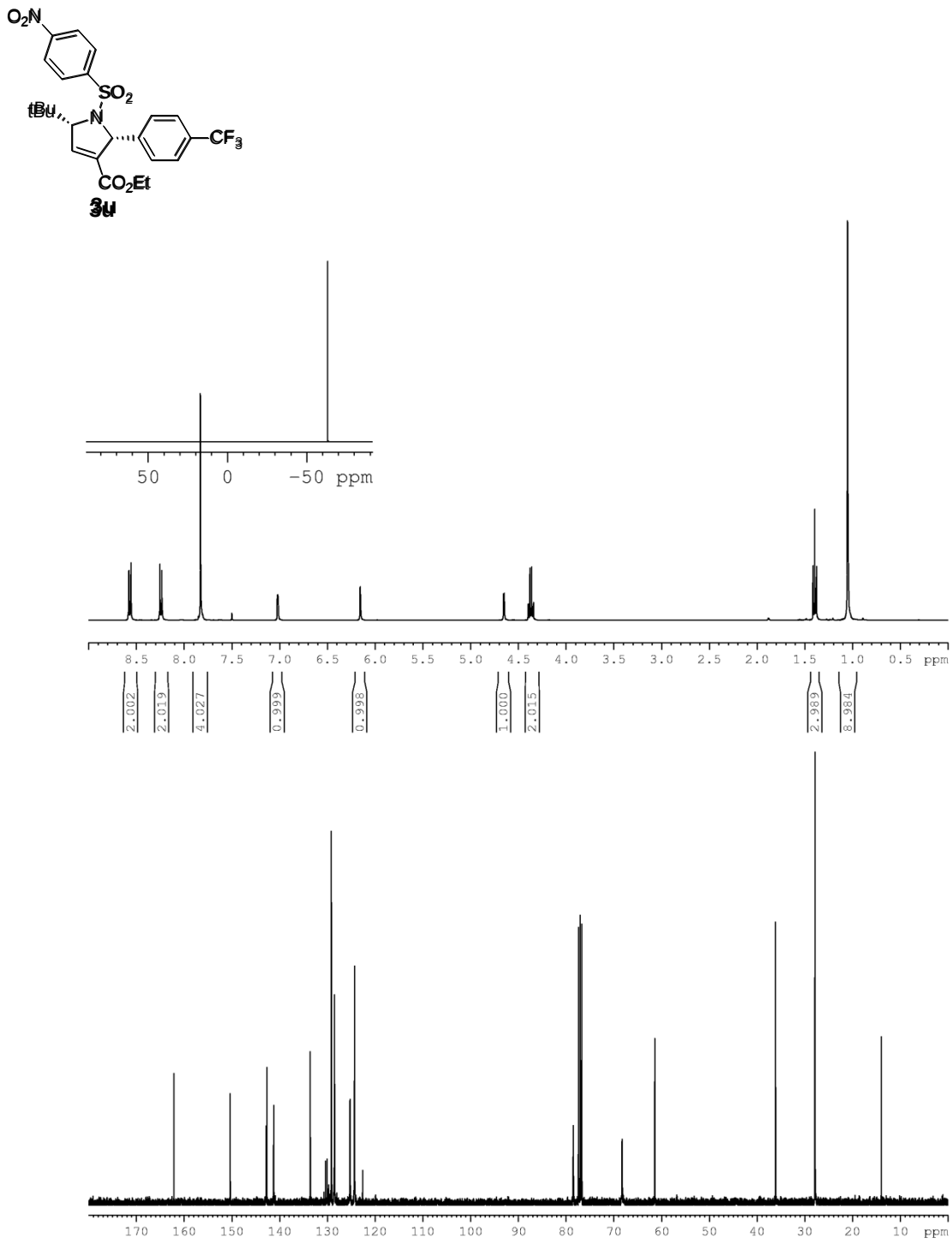
1.000
1.007
0.991
2.134
3.044
9.075
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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N
CF3
CO2Et
3u
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0
−50 ppm
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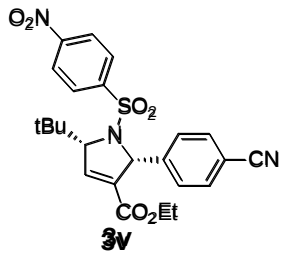
2.002
2.019
4.027
0.999
0.998
1.000
2.015
2.989
8.984
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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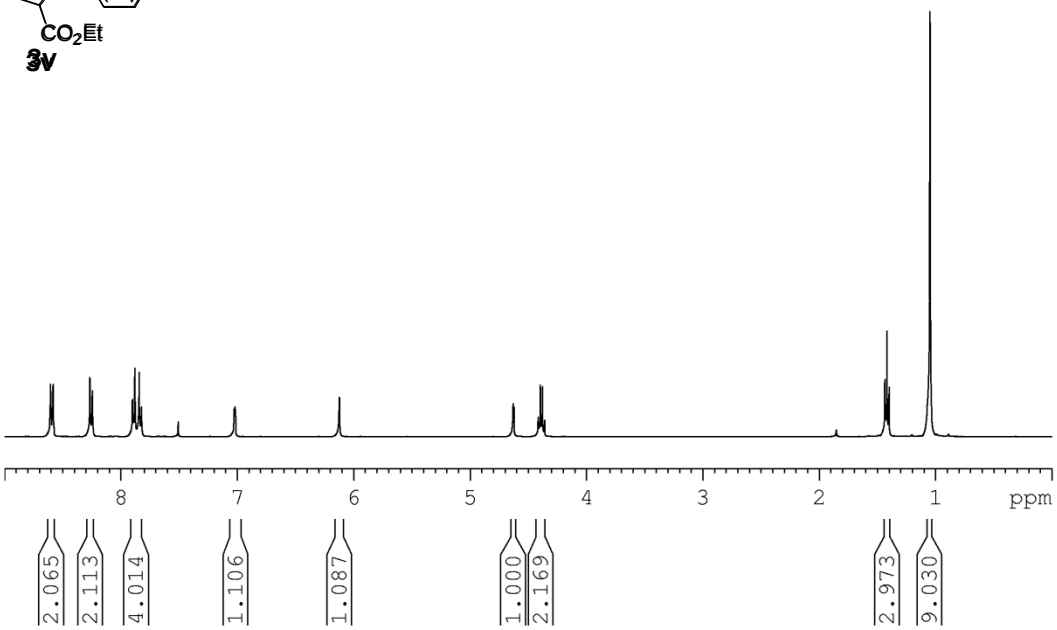
SO2
tBu
N
CN
CO2Et

3v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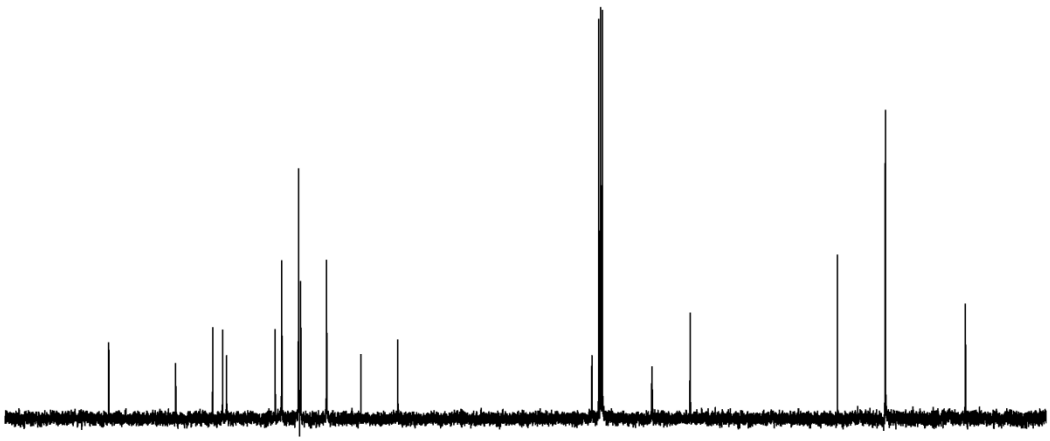

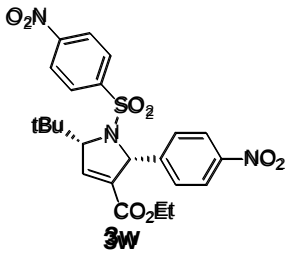
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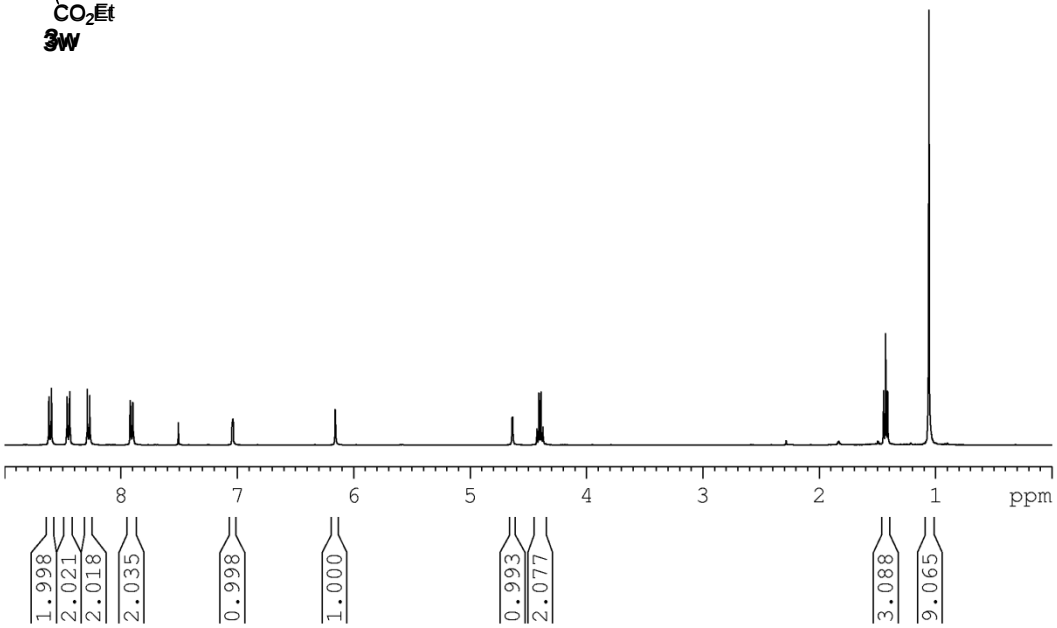
tBu
N
NO2
CO2Et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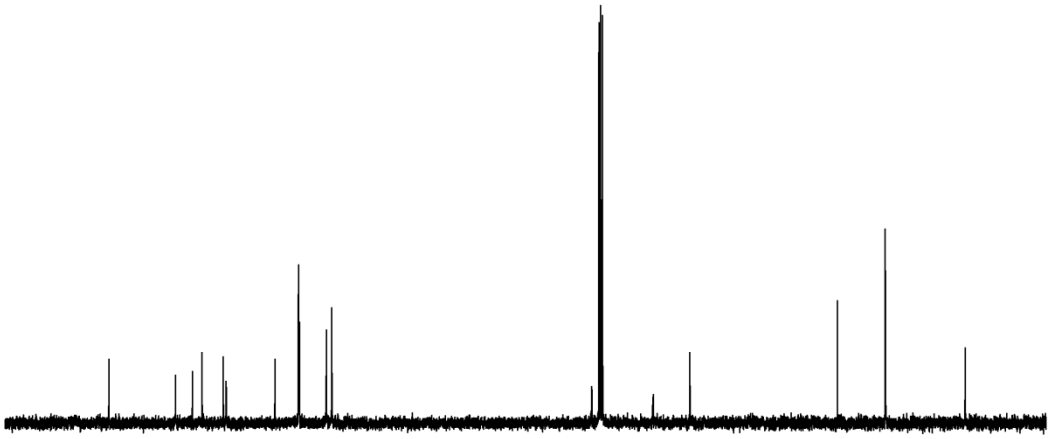

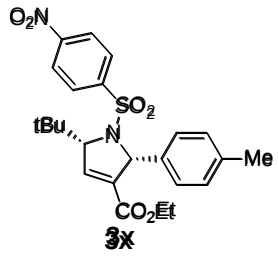
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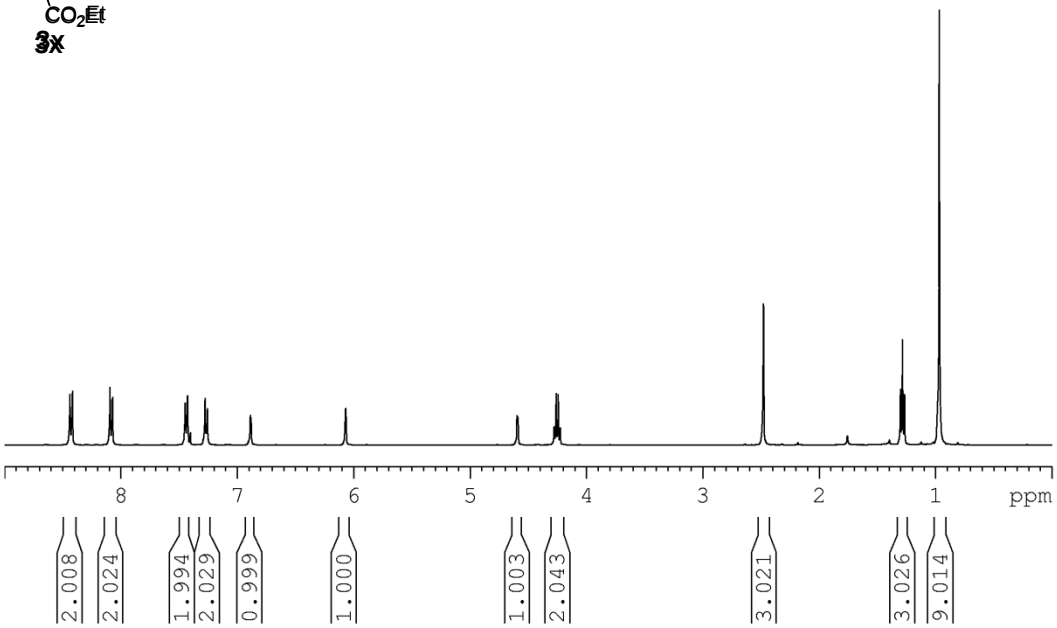
SO2
tBu
N
Me
CO2Et

3x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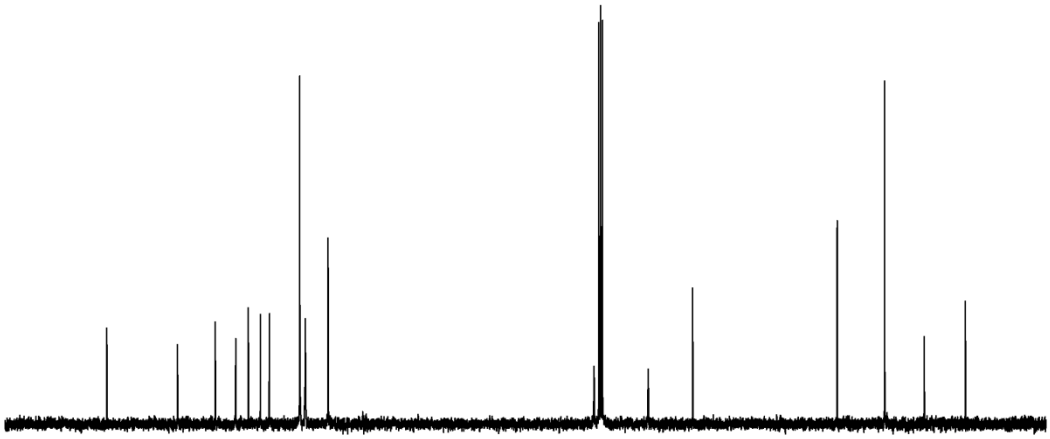
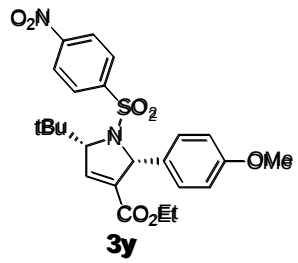
3.021
3.026
9.014

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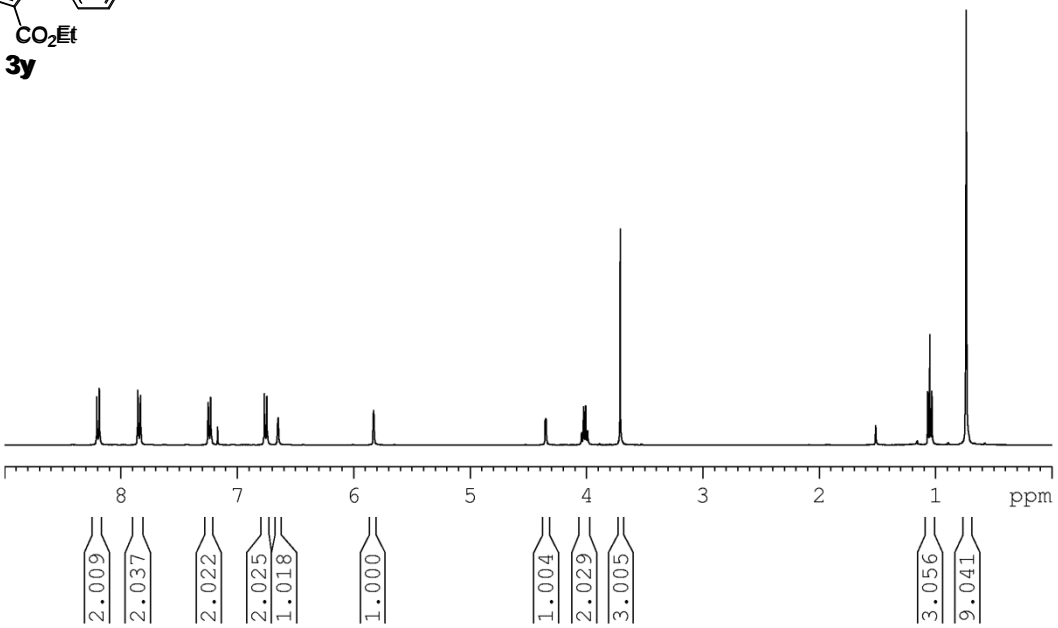
SO2
tBu
N
OMe
CO2Et

3y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1.000
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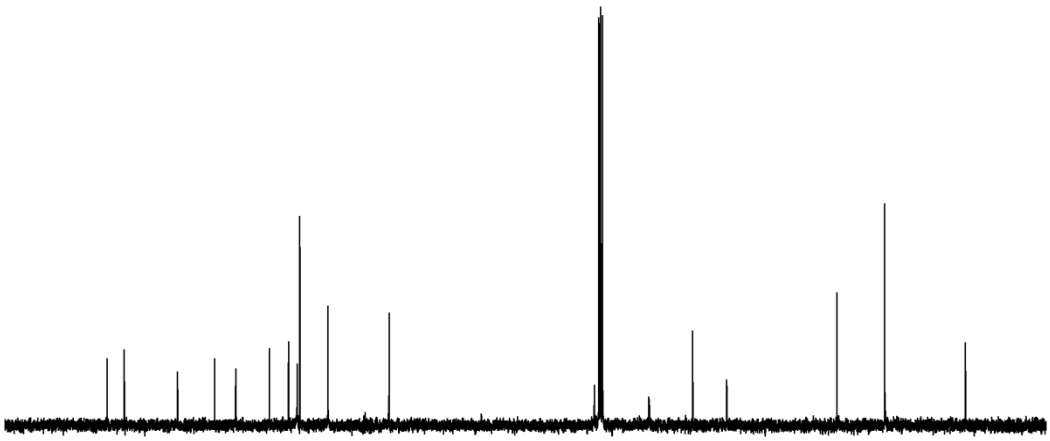
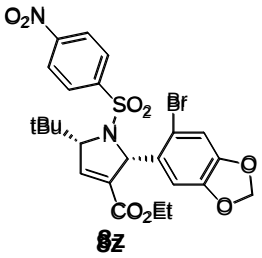
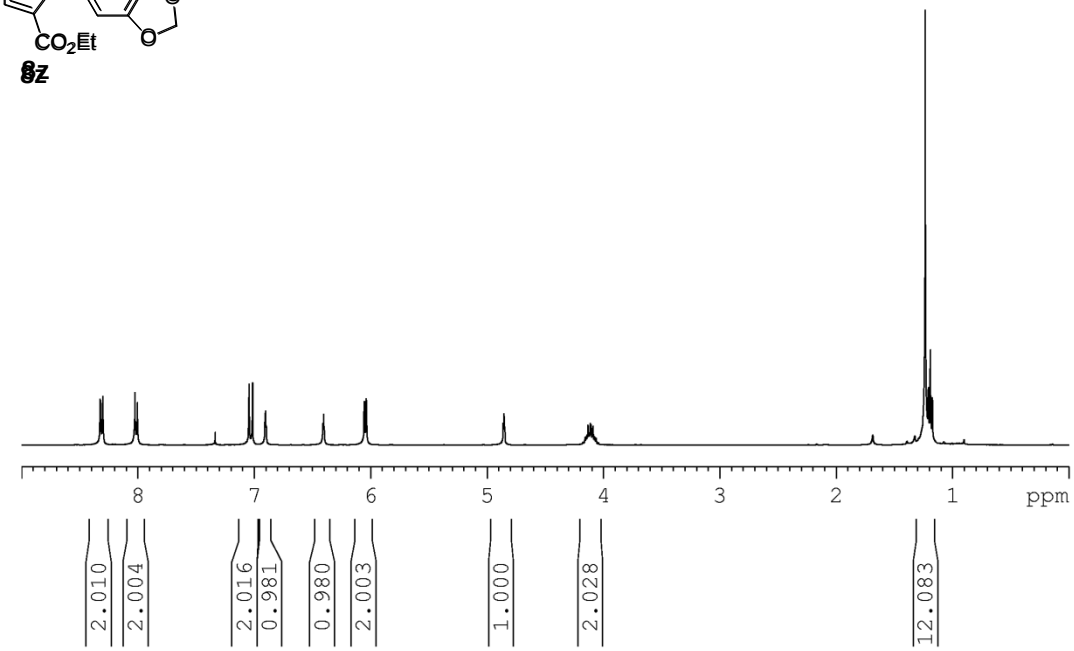
2.029
3.005
3.056
9.041




O2N
SO2
Br
tBu
N
O
O
CO2Et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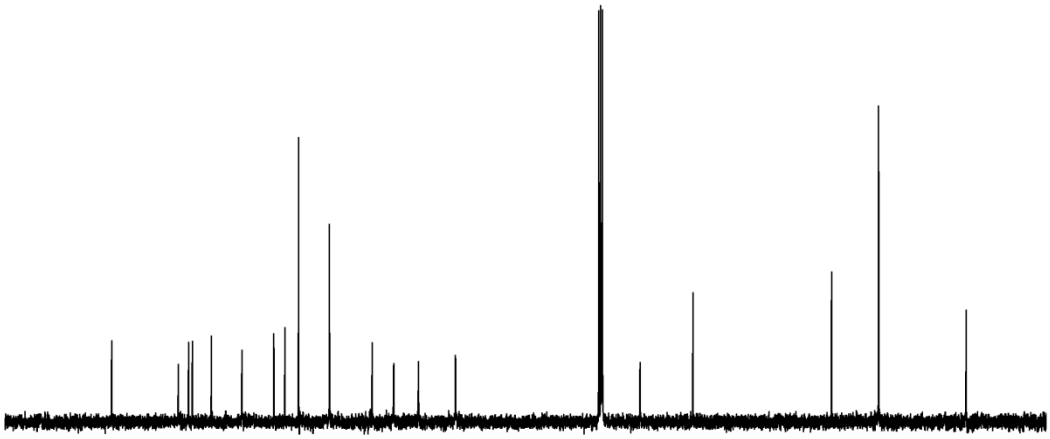
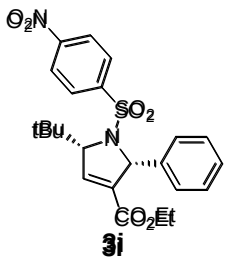
1.000
2.028
12.083



Copies of Selected HPLC traces



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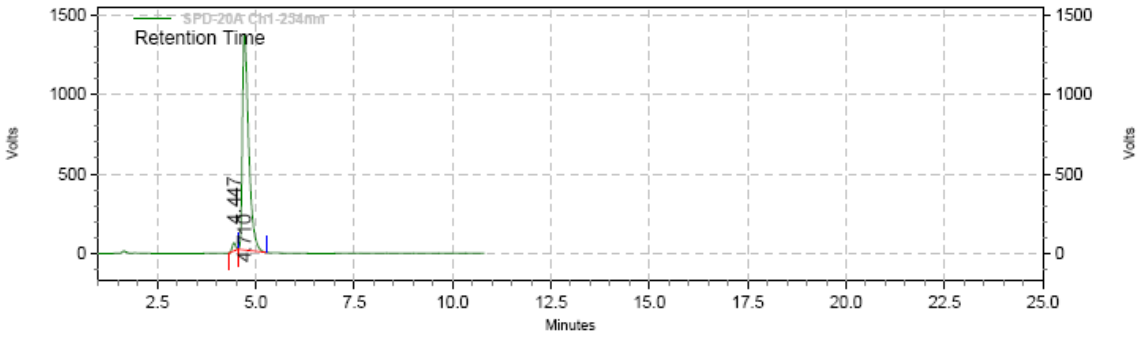
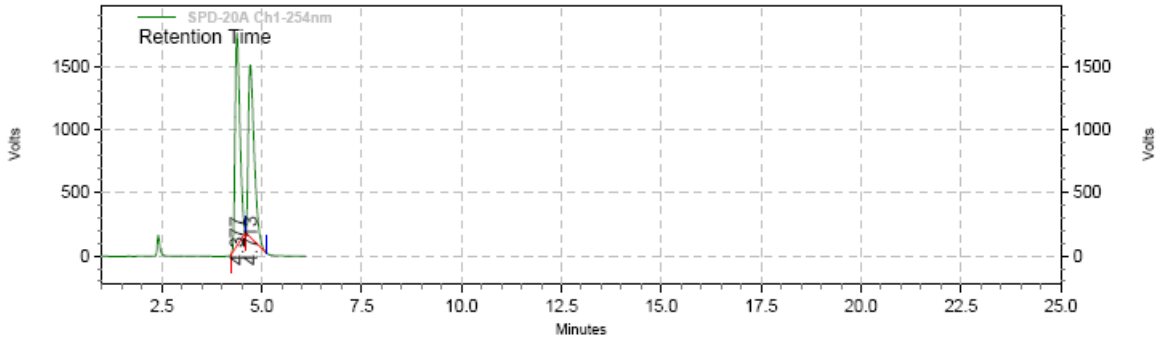


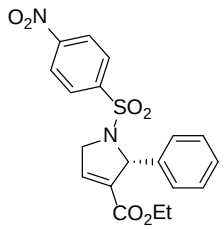
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
4.447	293525	1.93	48805	3.47
4.710	14885451	98.07	1356176	96.53
Totals				
	15178976	100.00	1404981	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
4.377	14131165	50.35	1682716	55.27
4.713	13935292	49.65	1361600	44.73
Totals				
	28066457	100.00	3044316	100.00



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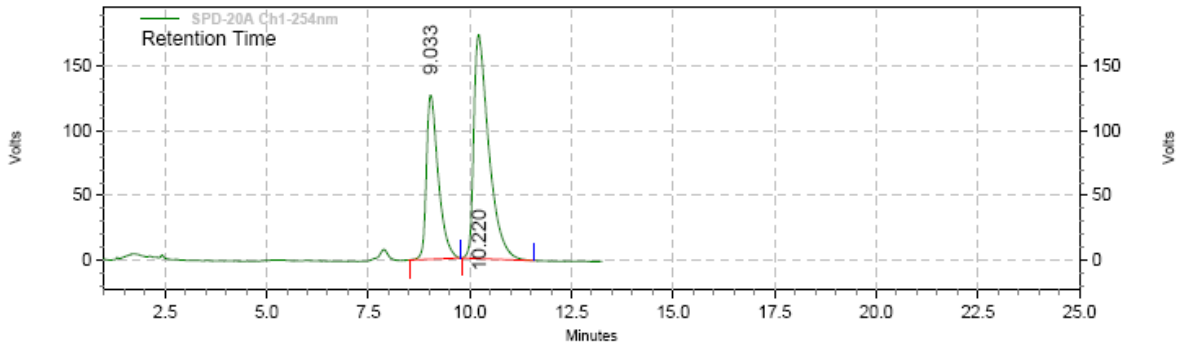
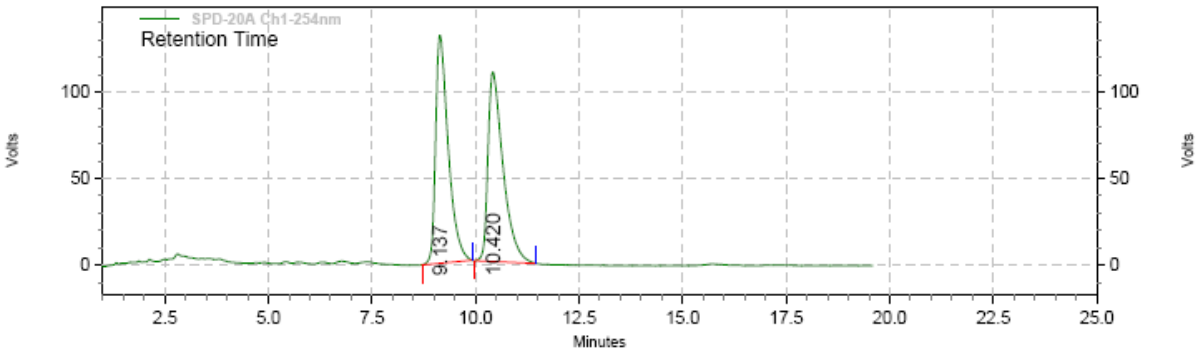


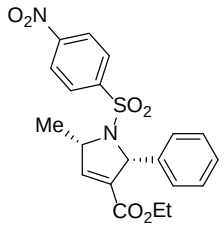
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.033	2573867	36.60	126970	42.31
10.220	4458701	63.40	173111	57.69
Totals	7032568	100.00	300081	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.137	2797553	50.14	131706	54.62
10.420	2781958	49.86	109445	45.38
Totals	5579511	100.00	241151	100.00



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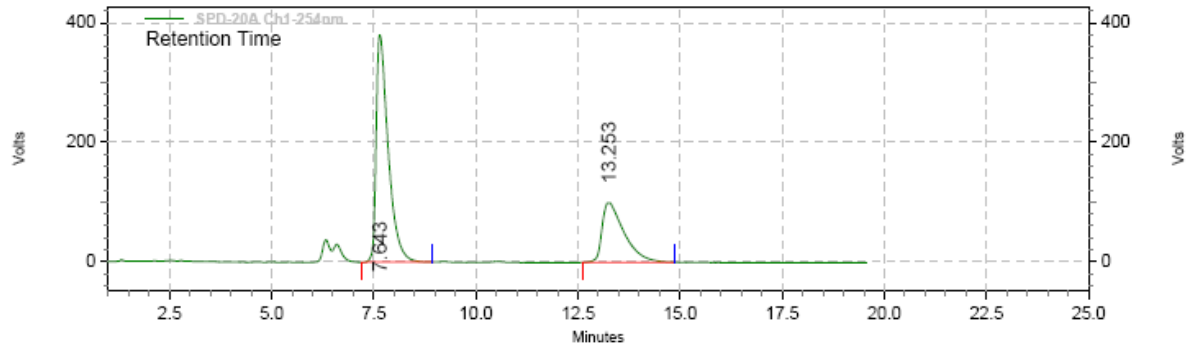
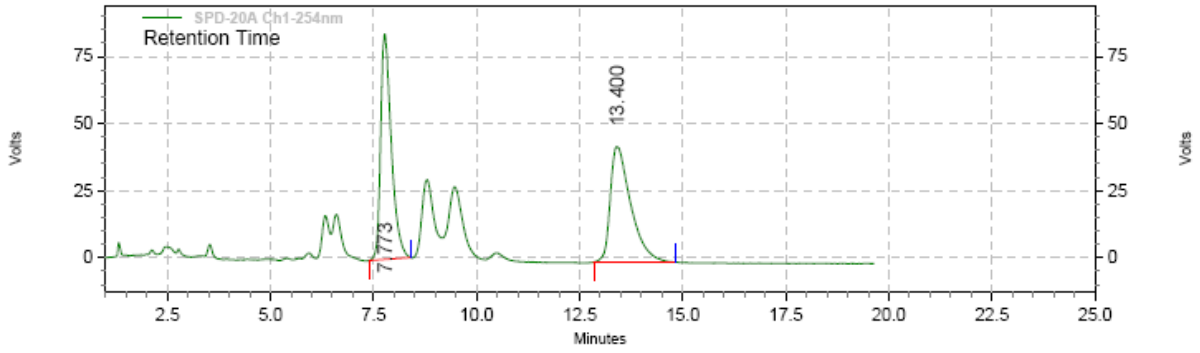


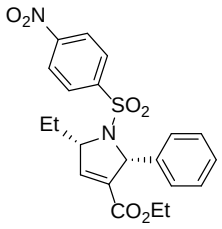
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
7.643	7811286	67.56	380510	79.21
13.253	3751346	32.44	99901	20.79
Totals	11562632	100.00	480411	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
7.773	1510992	50.34	83878	66.08
13.400	1490822	49.66	43054	33.92
Totals	3001814	100.00	126932	100.00



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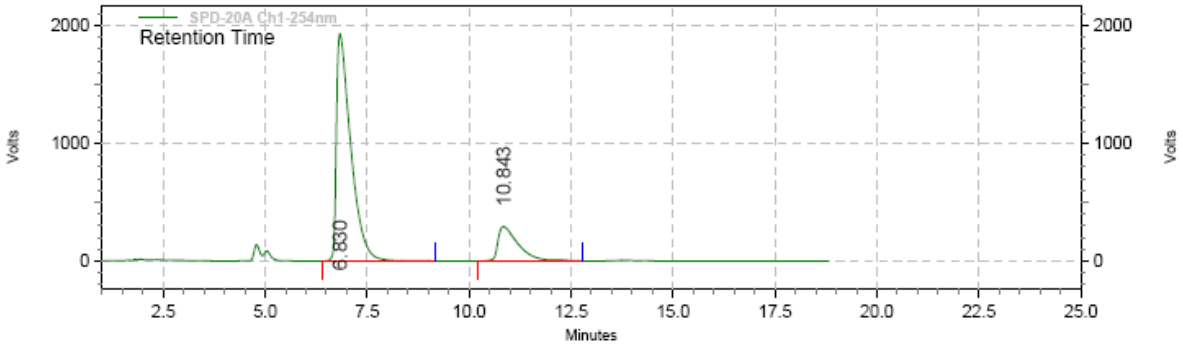
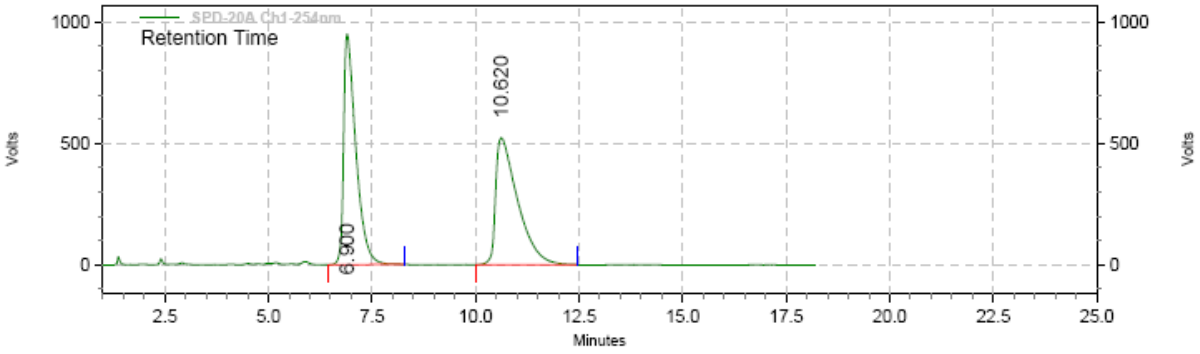


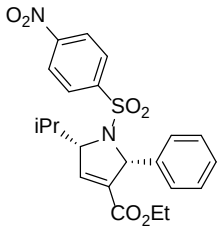
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.830	47107933	82.34	1931966	86.83
10.843	10102052	17.66	293133	13.17
Totals				
	57209985	100.00	2225099	100.00

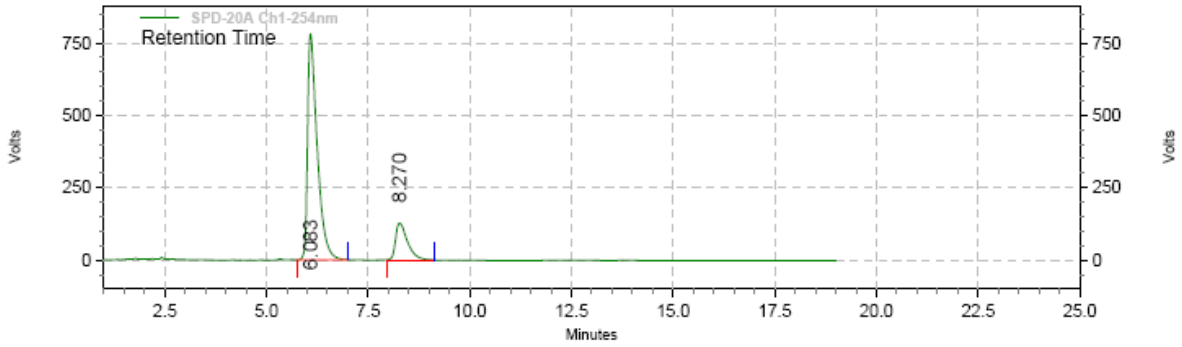


SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.900	19488513	50.34	949223	64.50
10.620	19223986	49.66	522482	35.50
Totals				
	38712499	100.00	1471705	100.00

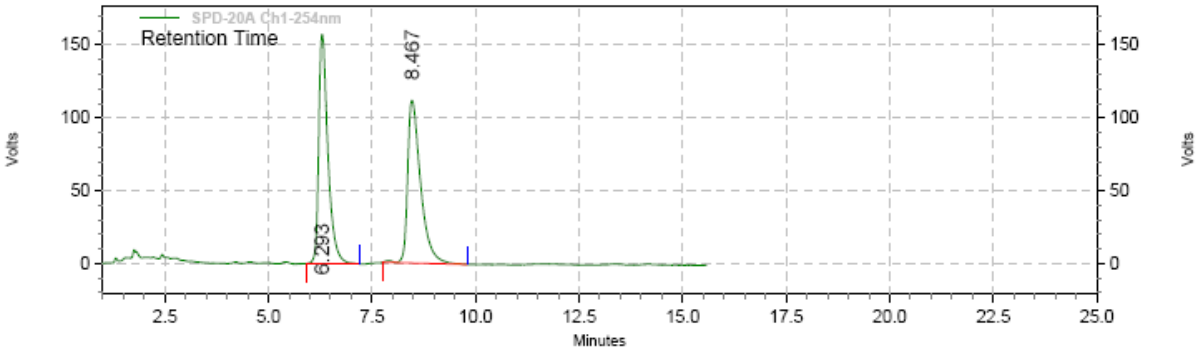


3m



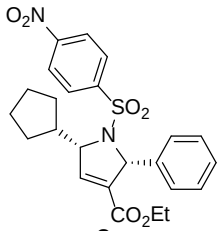
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.083	12888489	83.33	781138	85.96
8.270	2578256	16.67	127535	14.04
Totals	15466745	100.00	908673	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.293	2426570	49.87	157405	58.53
8.467	2438982	50.13	111514	41.47
Totals	4865552	100.00	268919	100.00



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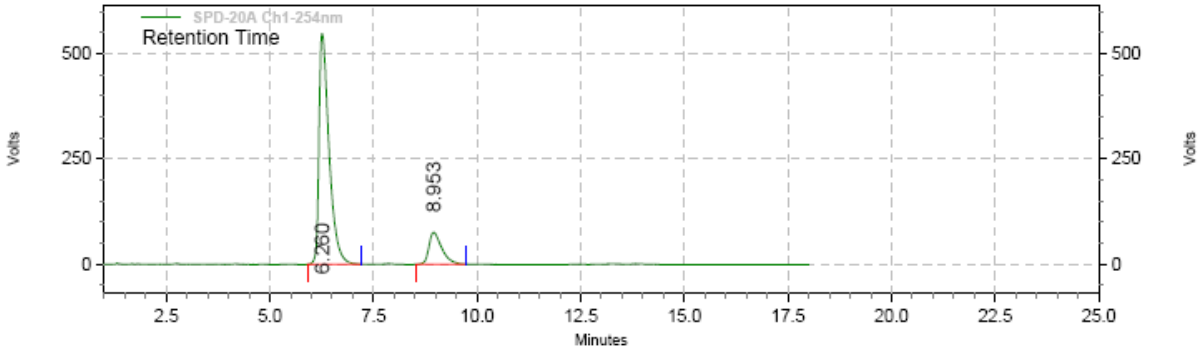
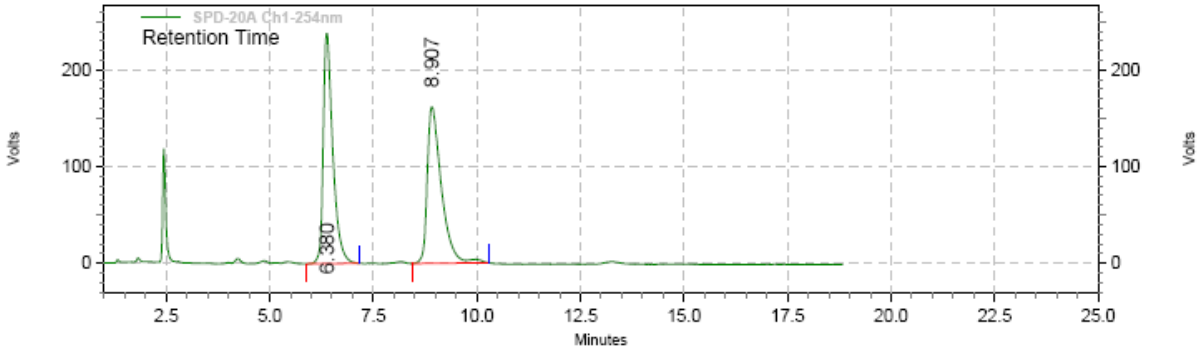


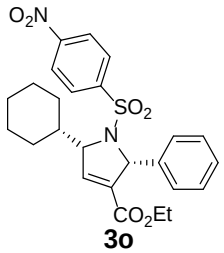
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.260	9237614	84.93	548523	87.87
8.953	1638957	15.07	75700	12.13
Totals	10876571	100.00	624223	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.380	3830070	49.83	238064	59.57
8.907	3856870	50.17	161574	40.43
Totals	7686940	100.00	399638	100.00



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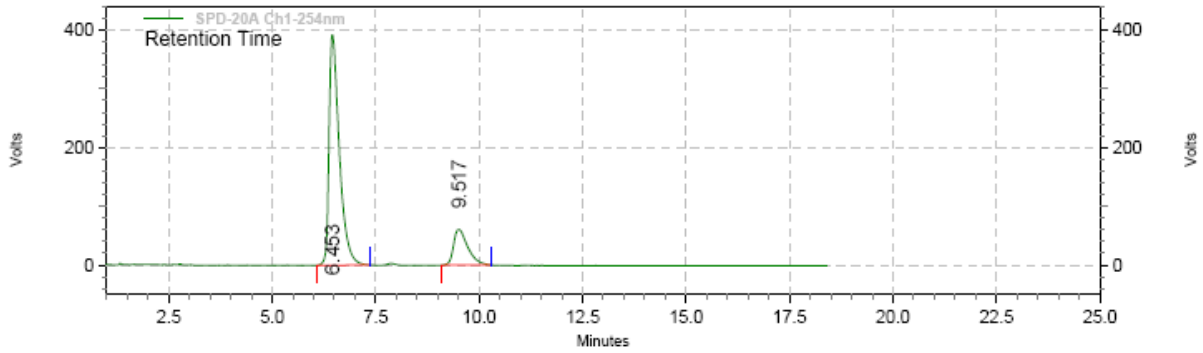
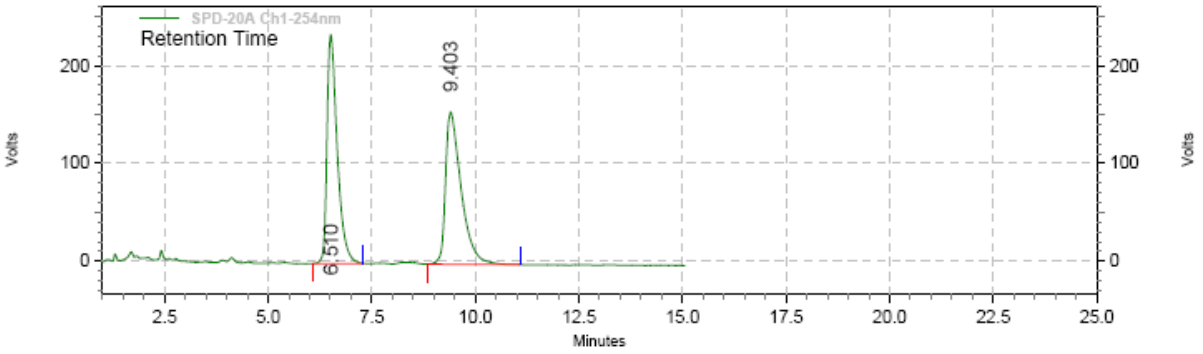


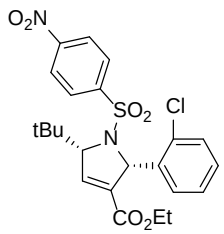
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.453	6779743	82.42	391892	86.62
9.517	1446391	17.58	60543	13.38
Totals	8226134	100.00	452435	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
6.510	4019395	49.53	234265	60.01
9.403	4096283	50.47	156122	39.99
Totals	8115678	100.00	390387	100.00



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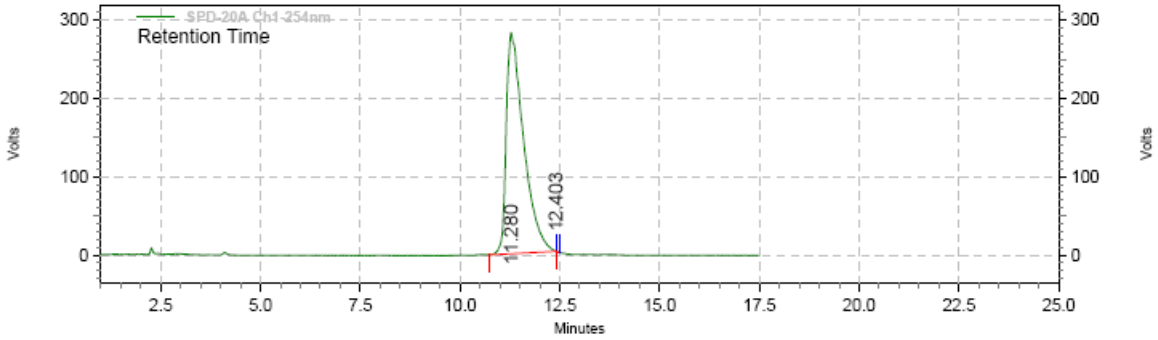
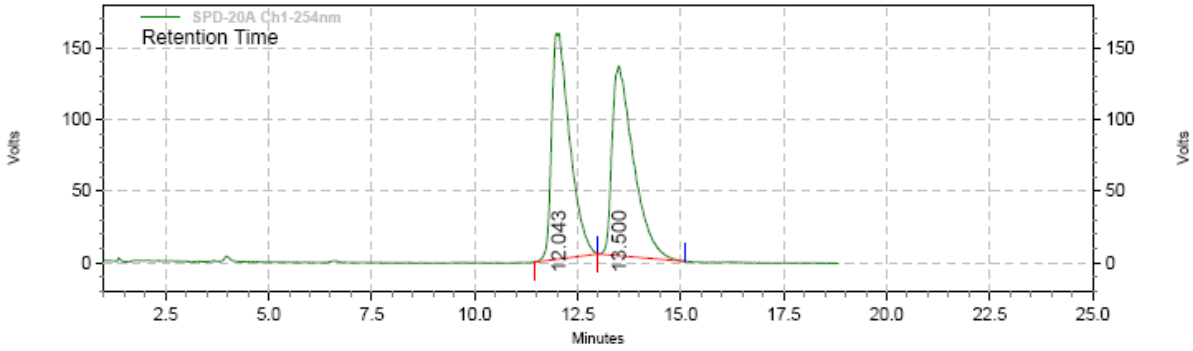


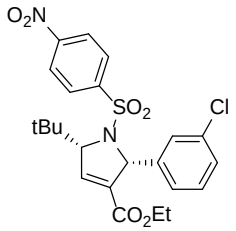
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
11.280	8546399	99.99	282284	100.00
12.403	521	0.01	0	0.00
Totals				
	8546920	100.00	282284	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
12.043	4822951	50.10	157424	54.34
13.500	4804070	49.90	132257	45.66
Totals				
	9627021	100.00	289681	100.00



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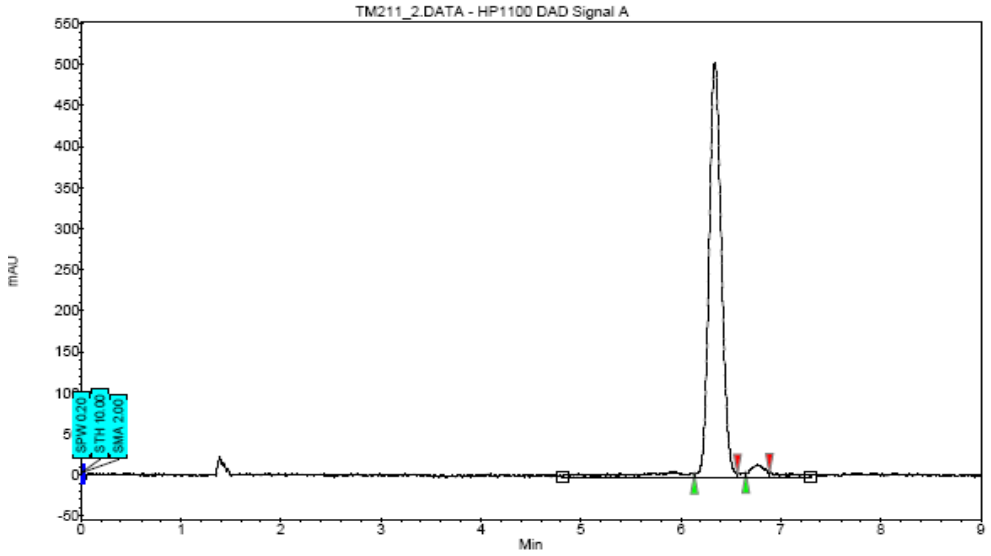
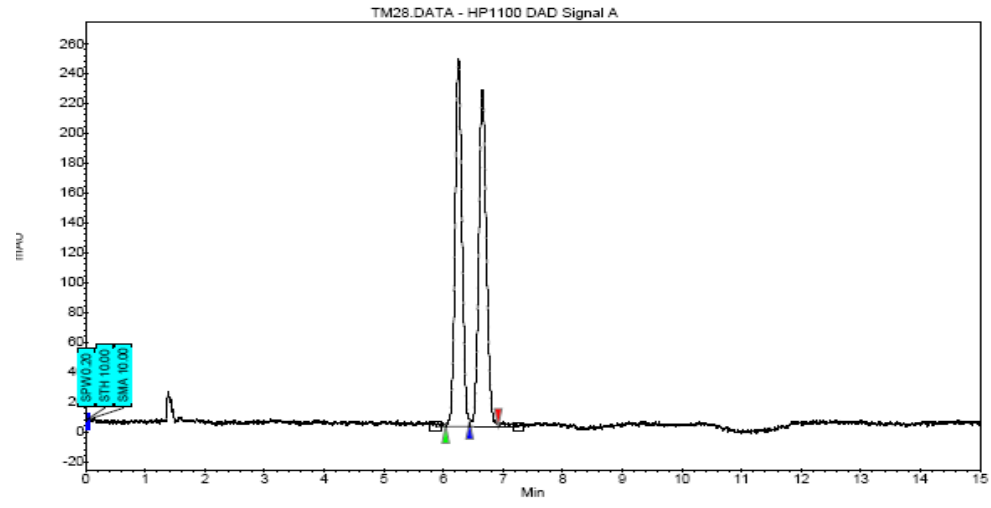
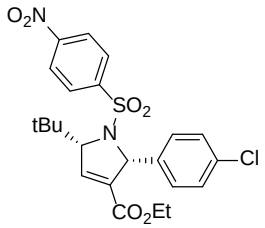


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.13	6.34	6.57	0.00	96.83	504.6	71.8	96.832
2	UNKNOWN	6.65	6.77	6.89	0.00	3.17	15.0	2.3	3.168
Total						100.00	519.6	74.2	100.000



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.04	6.25	6.44	0.00	49.76	246.1	33.4	49.757
2	UNKNOWN	6.44	6.65	6.92	0.00	50.24	225.1	33.7	50.243
Total						100.00	471.2	67.2	100.000



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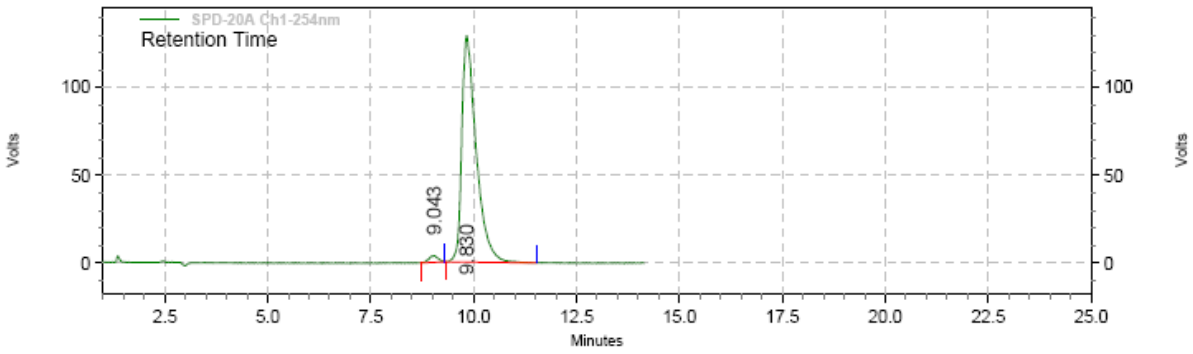
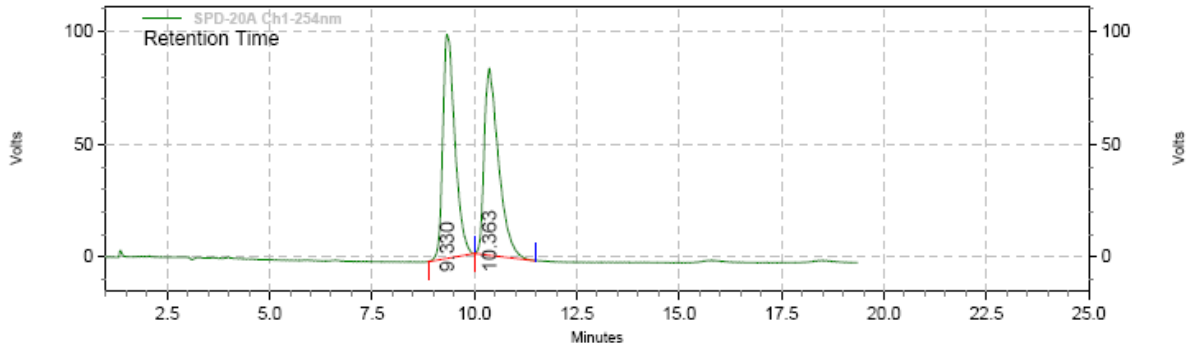


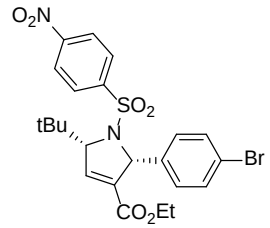
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.043	59846	1.87	3712	2.80
9.830	3141446	98.13	129074	97.20
Totals	3201292	100.00	132786	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.330	2042563	50.26	99298	54.49
10.363	2021774	49.74	82942	45.51
Totals	4064337	100.00	182240	100.00



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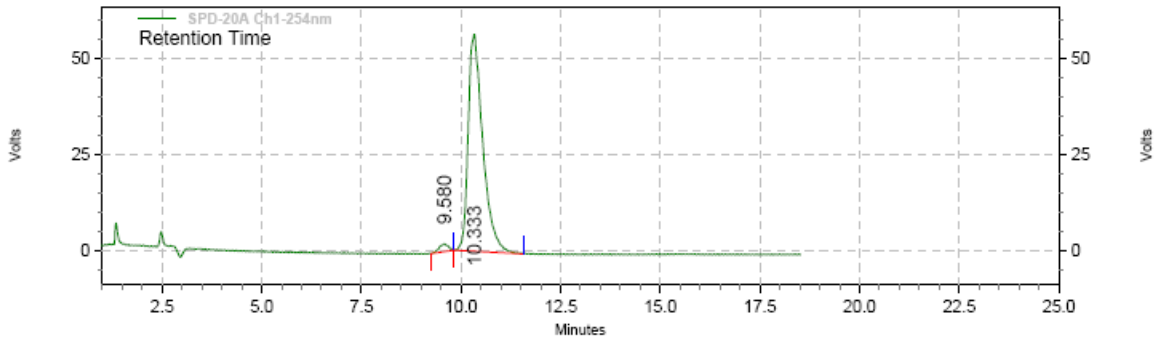
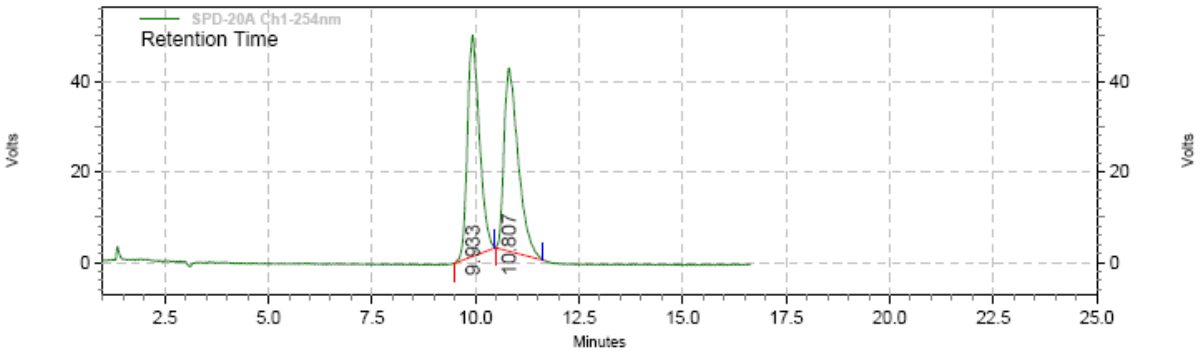


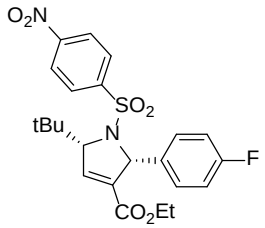
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.580	32570	2.22	2036	3.49
10.333	1437653	97.78	56327	96.51
Totals	1470223	100.00	58363	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.933	980819	50.42	48847	54.68
10.807	964444	49.58	40484	45.32
Totals	1945263	100.00	89331	100.00



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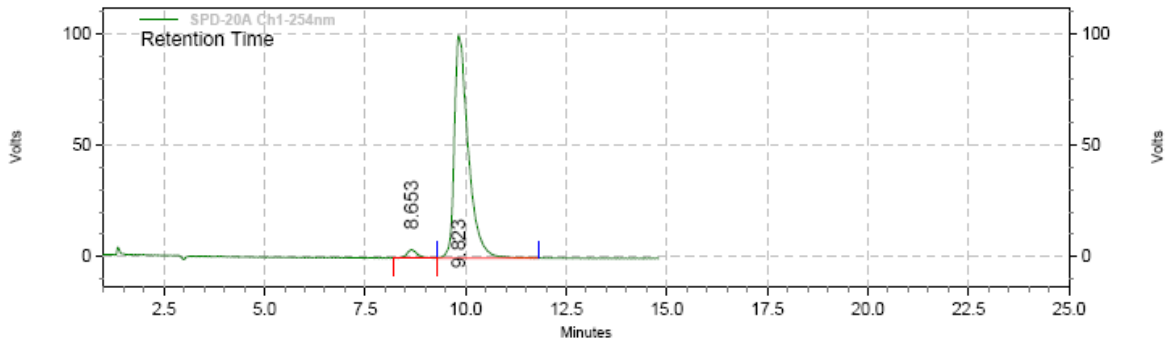
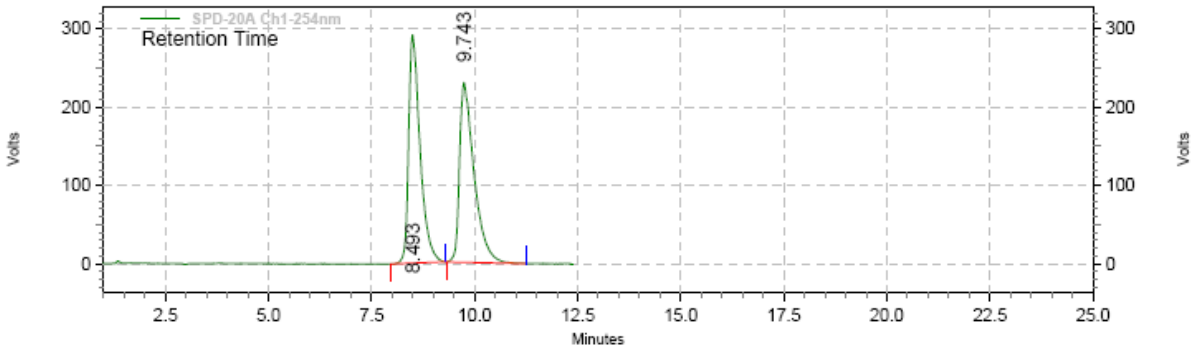


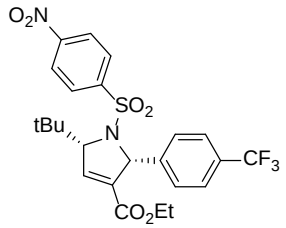
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
8.653	68409	2.77	3834	3.70
9.823	2403646	97.23	99862	96.30
Totals	2472055	100.00	103696	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
8.493	5618198	49.96	291580	55.94
9.743	5627135	50.04	229679	44.06
Totals	11245333	100.00	521259	100.00



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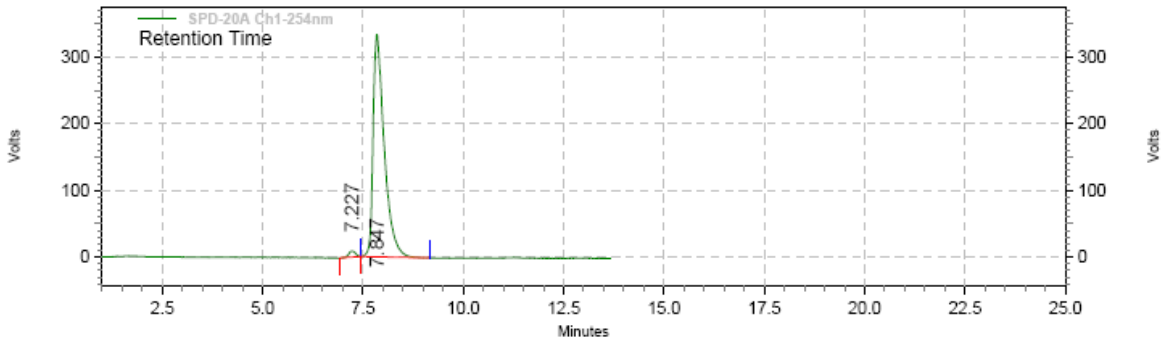
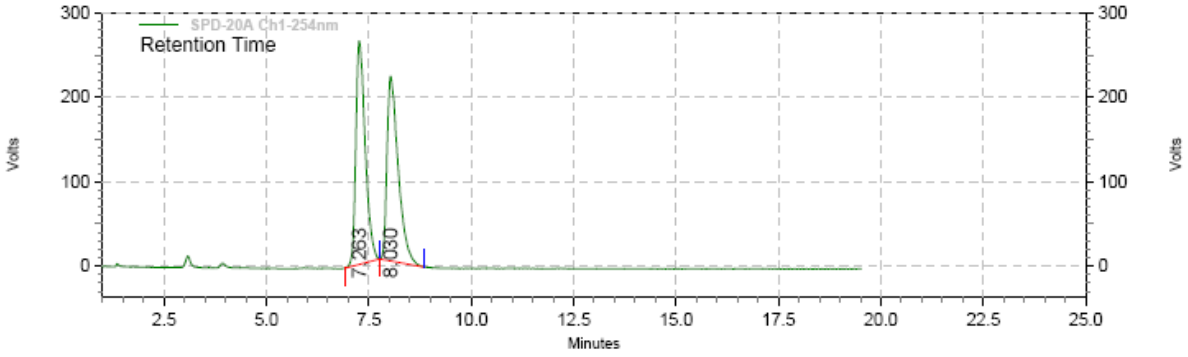


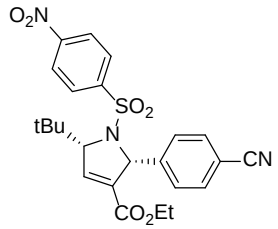
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
7.227	108666	1.66	8983	2.62
7.847	6456403	98.34	333434	97.38
Totals	6565069	100.00	342417	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
7.263	4203648	50.21	265171	54.74
8.030	4167719	49.79	219243	45.26
Totals	8371367	100.00	484414	100.00



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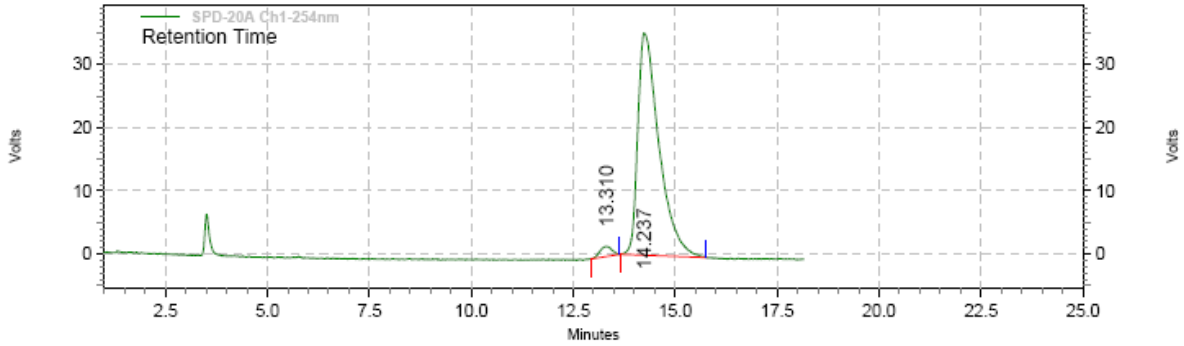
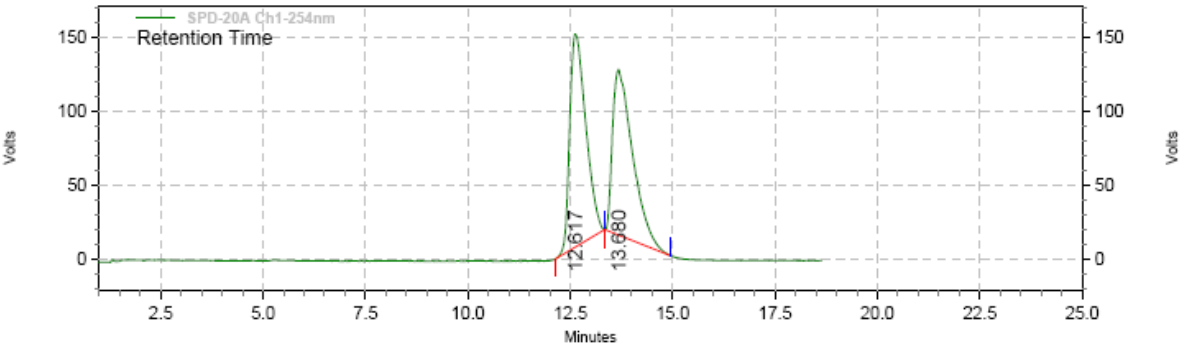


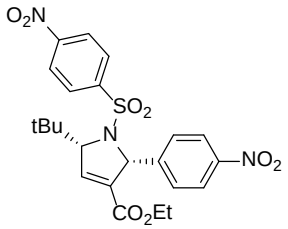
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
13.310	32821	2.52	1621	4.40
14.237	1271030	97.48	35188	95.60
Totals				
	1303851	100.00	36809	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
12.617	3934990	50.68	144405	56.28
13.680	3829139	49.32	112194	43.72
Totals				
	7764129	100.00	256599	100.00



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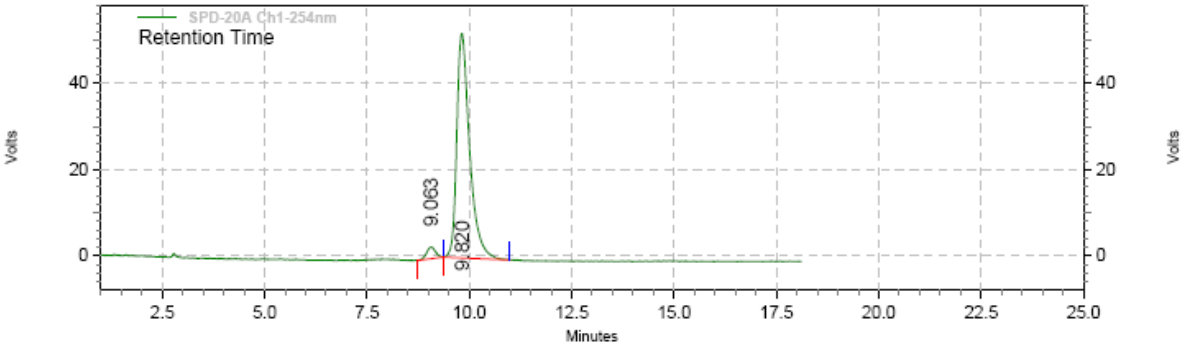
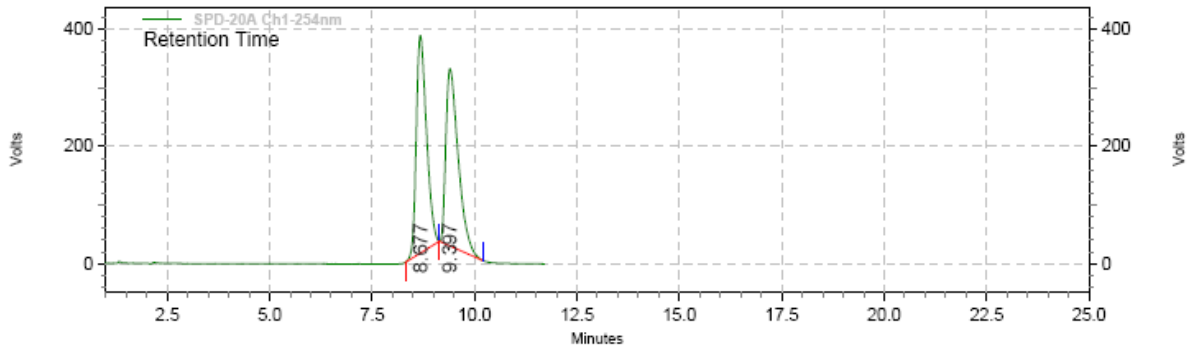


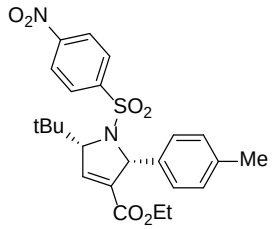
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.063	40804	3.46	2691	4.91
9.820	1137350	96.54	52082	95.09
Totals	1178154	100.00	54773	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
8.677	6464625	50.43	371410	55.10
9.397	6353944	49.57	302698	44.90
Totals	12818569	100.00	674108	100.00



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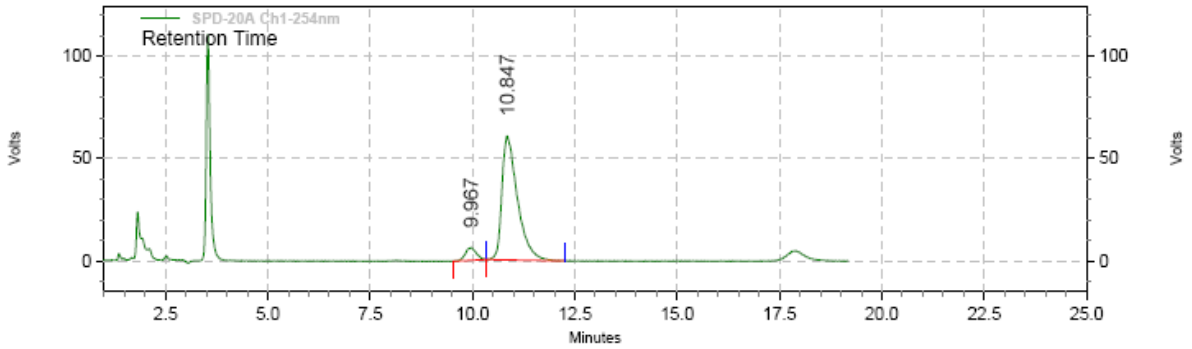
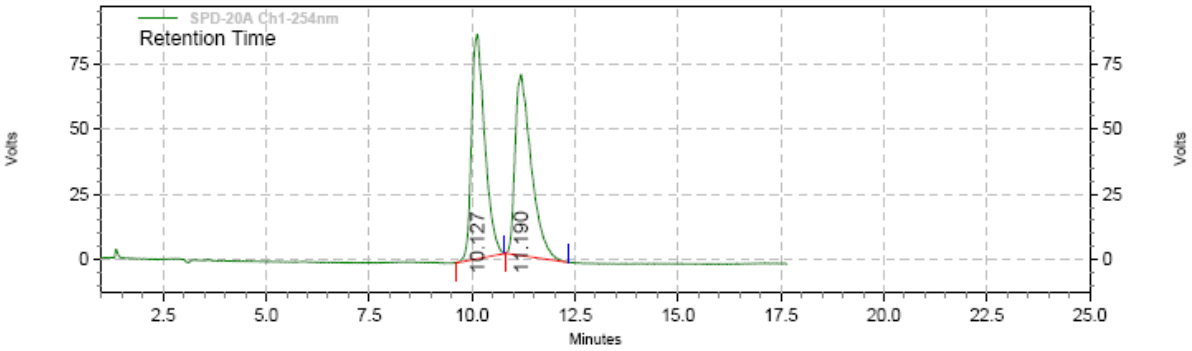


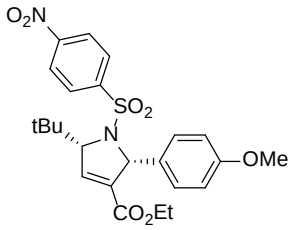
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
9.967	114123	6.69	6196	9.31
10.847	1592973	93.31	60386	90.69
Totals	1707096	100.00	66582	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
10.127	1920035	50.40	85849	55.35
11.190	1889685	49.60	69244	44.65
Totals	3809720	100.00	155093	100.00



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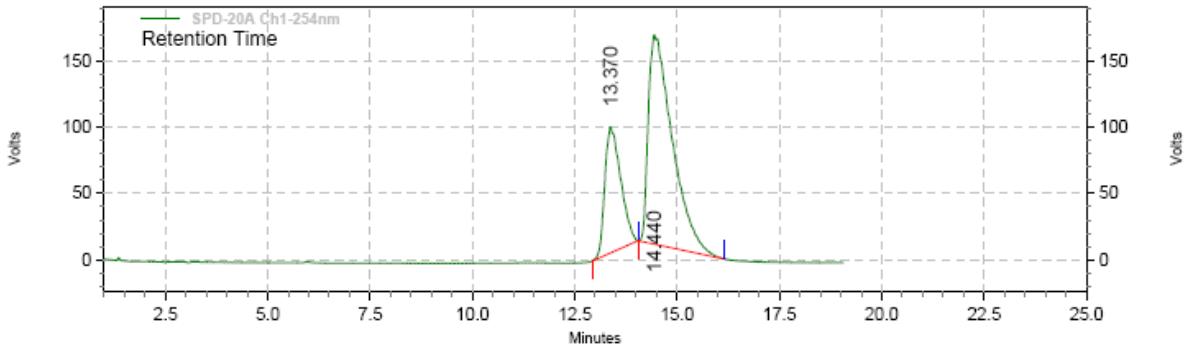
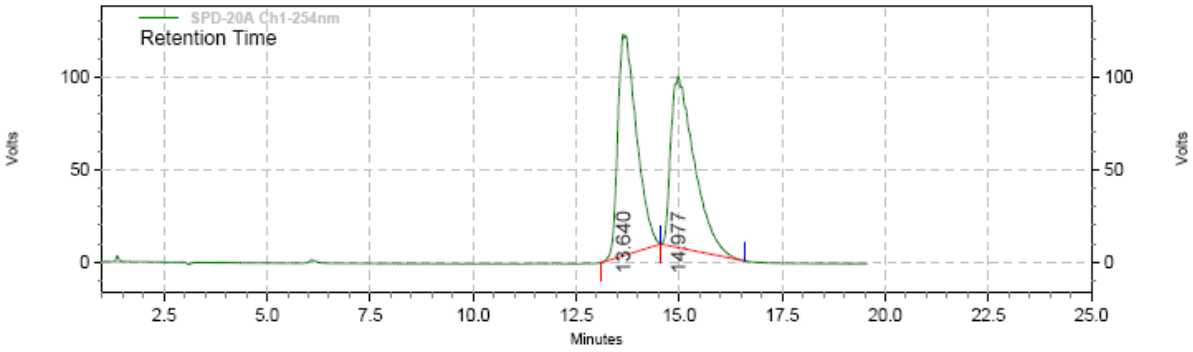


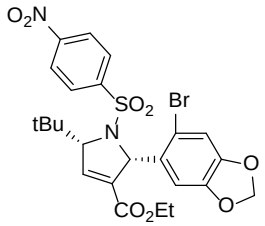
SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
13.370	2551198	28.36	95077	37.58
14.440	6445560	71.64	157940	62.42
Totals				
	8996758	100.00	253017	100.00



SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
13.640	3763299	50.57	119621	56.36
14.977	3677910	49.43	92637	43.64
Totals				
	7441209	100.00	212258	100.00



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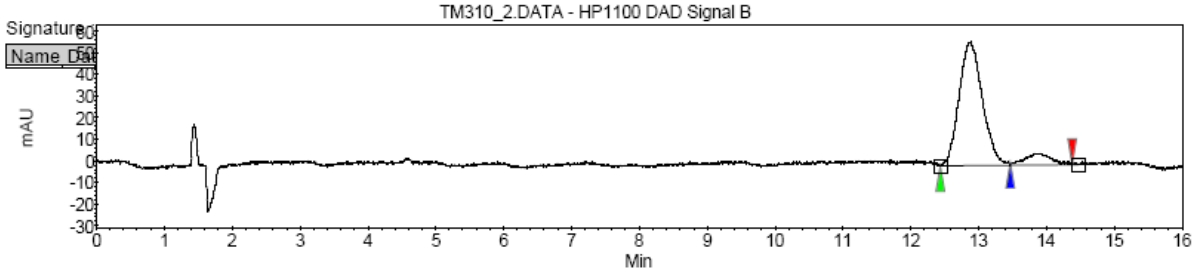
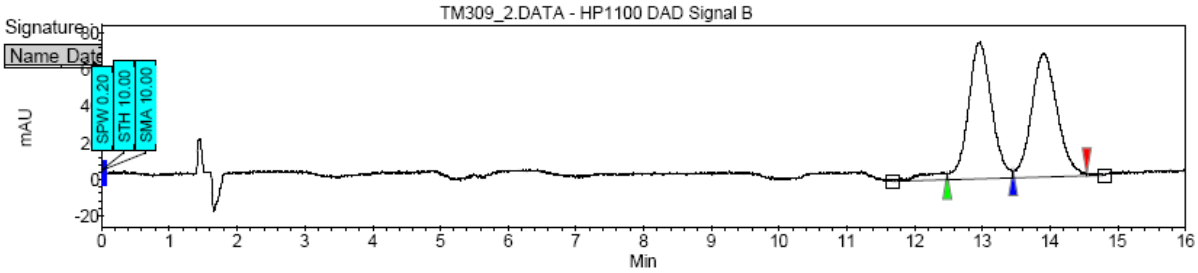
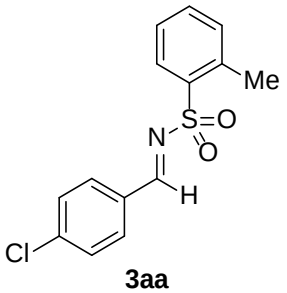


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	12.44	12.89	13.47	0.00	90.50	57.2	22.8	90.497
2	UNKNOWN	13.47	13.87	14.38	0.00	9.50	5.4	2.4	9.503
Total						100.00	62.6	25.1	100.000



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	12.49	12.97	13.46	0.00	50.19	74.9	29.6	50.195
2	UNKNOWN	13.46	13.91	14.54	0.00	49.81	67.2	29.4	49.805
Total						100.00	142.1	59.0	100.000



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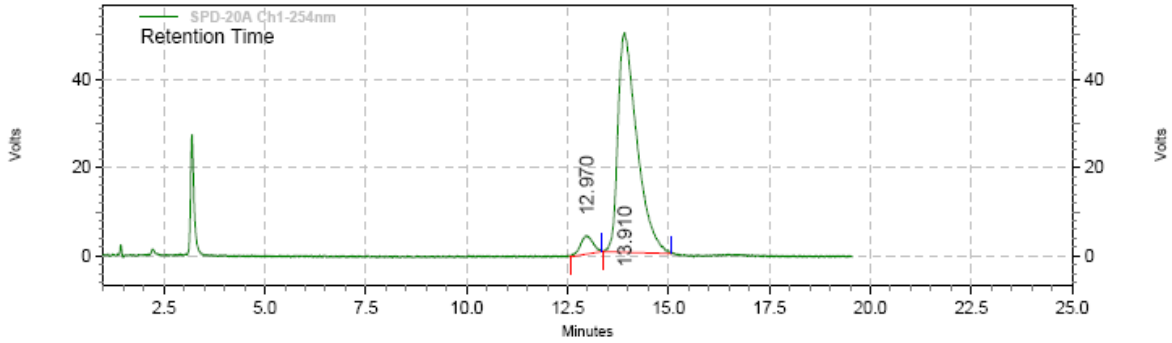
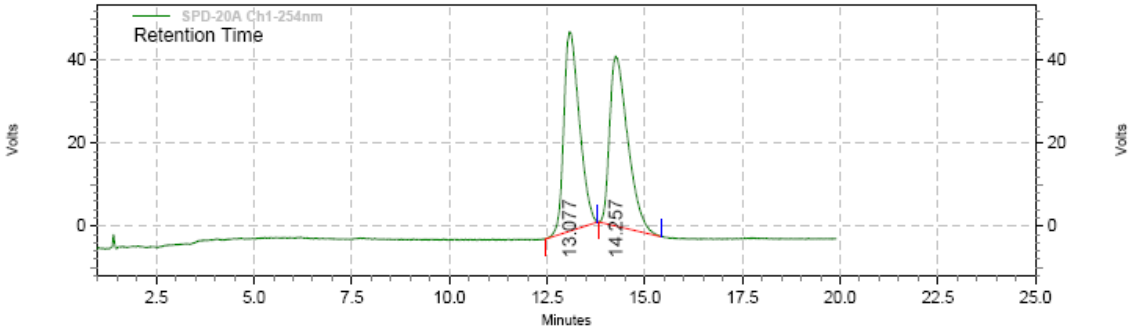


SPD-20A
Ch1-254nm
Results

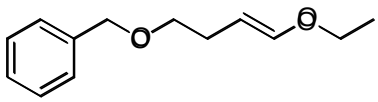
Retention Time	Area	Area %	Height	Height %
12.970	89766	5.21	4232	7.85
13.910	1631762	94.79	49706	92.15
Totals				
	1721528	100.00	53938	100.00

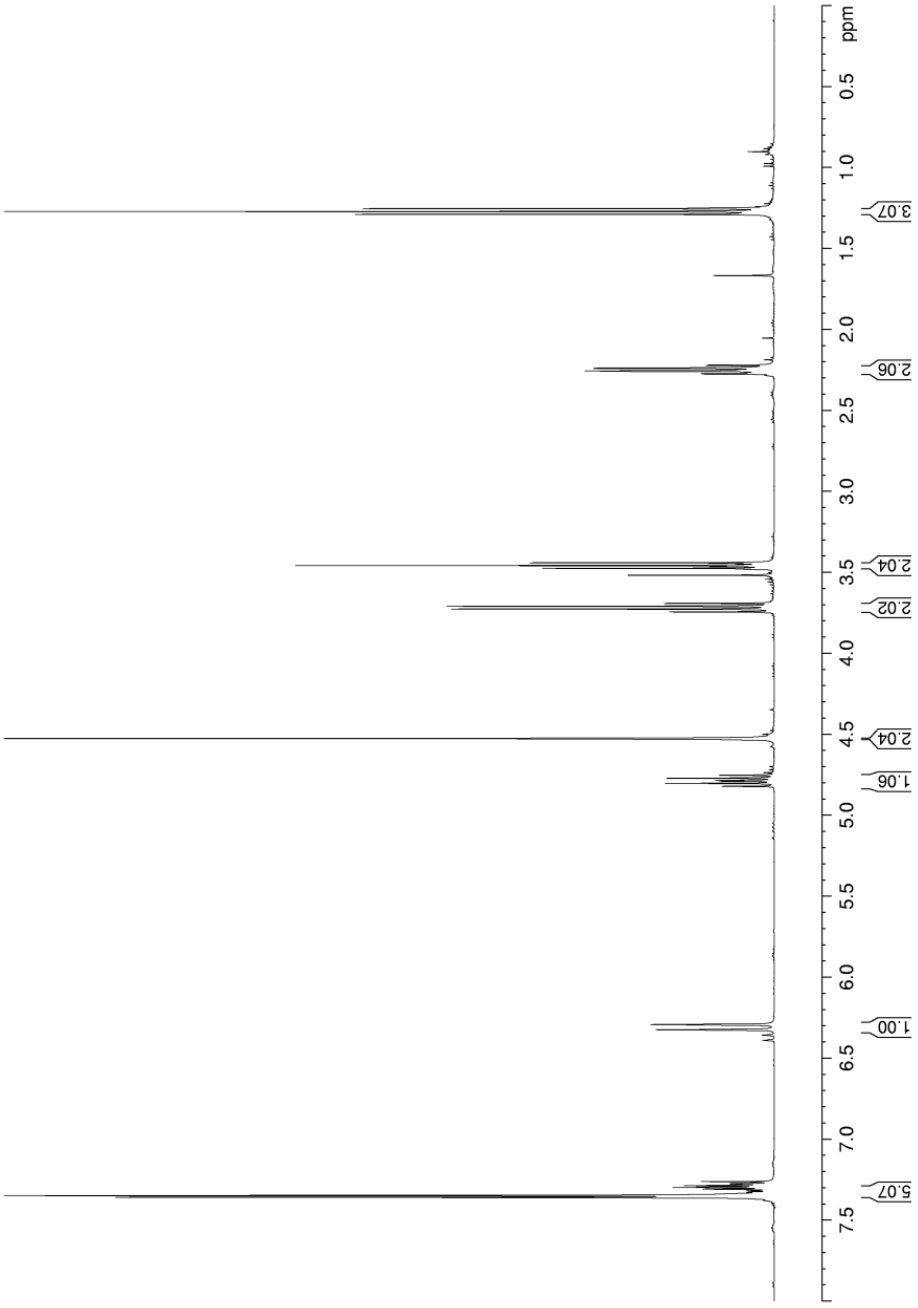


SPD-20A
Ch1-254nm
Results

Retention Time	Area	Area %	Height	Height %
13.077	1327485	50.00	48211	54.04
14.257	1327247	50.00	40996	45.96
Totals				
	2654732	100.00	89207	100.00

Chapter 5

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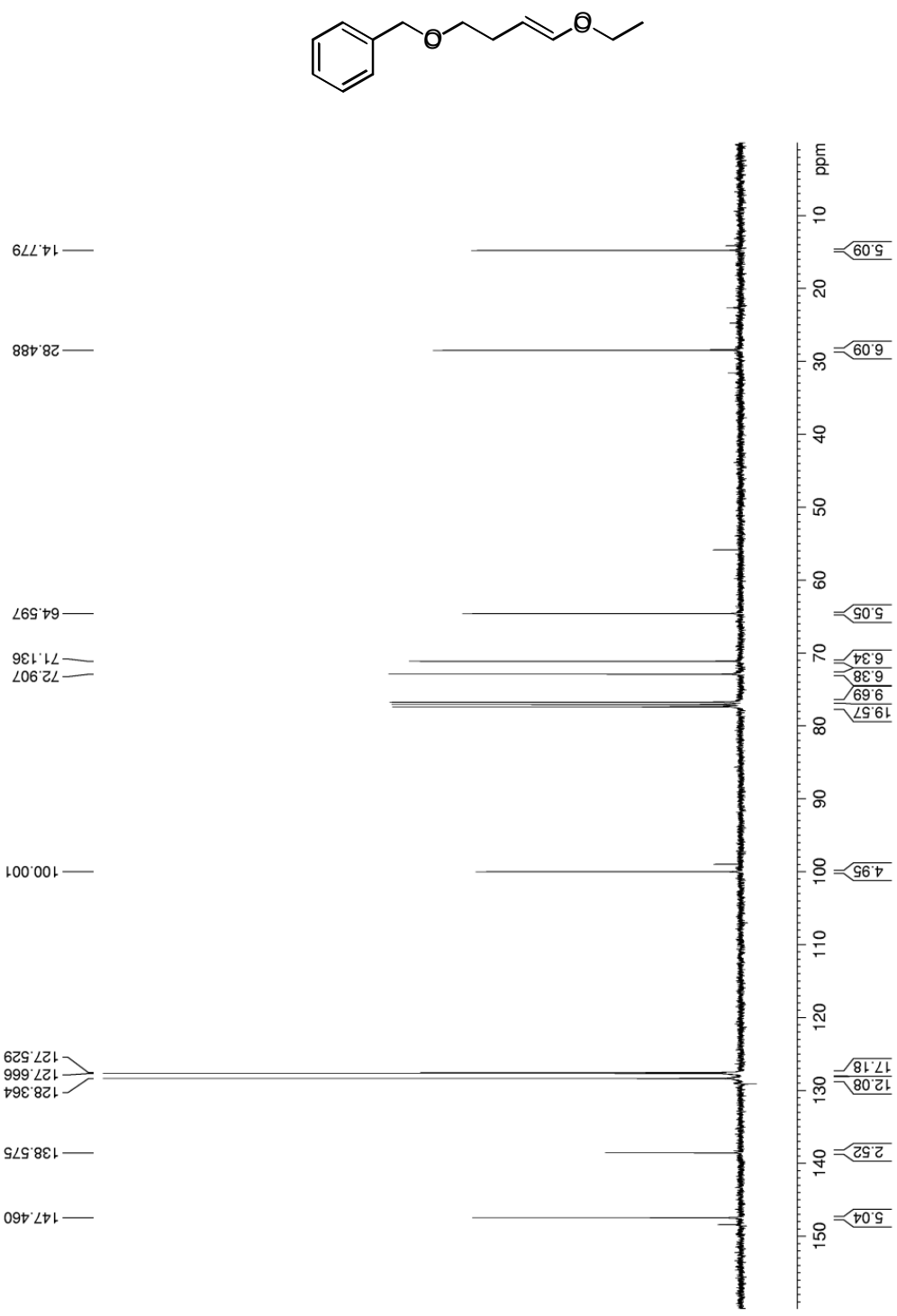
2.04
2.02
2.04
1.06
1.00
5.07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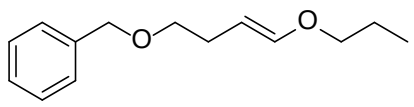
5.04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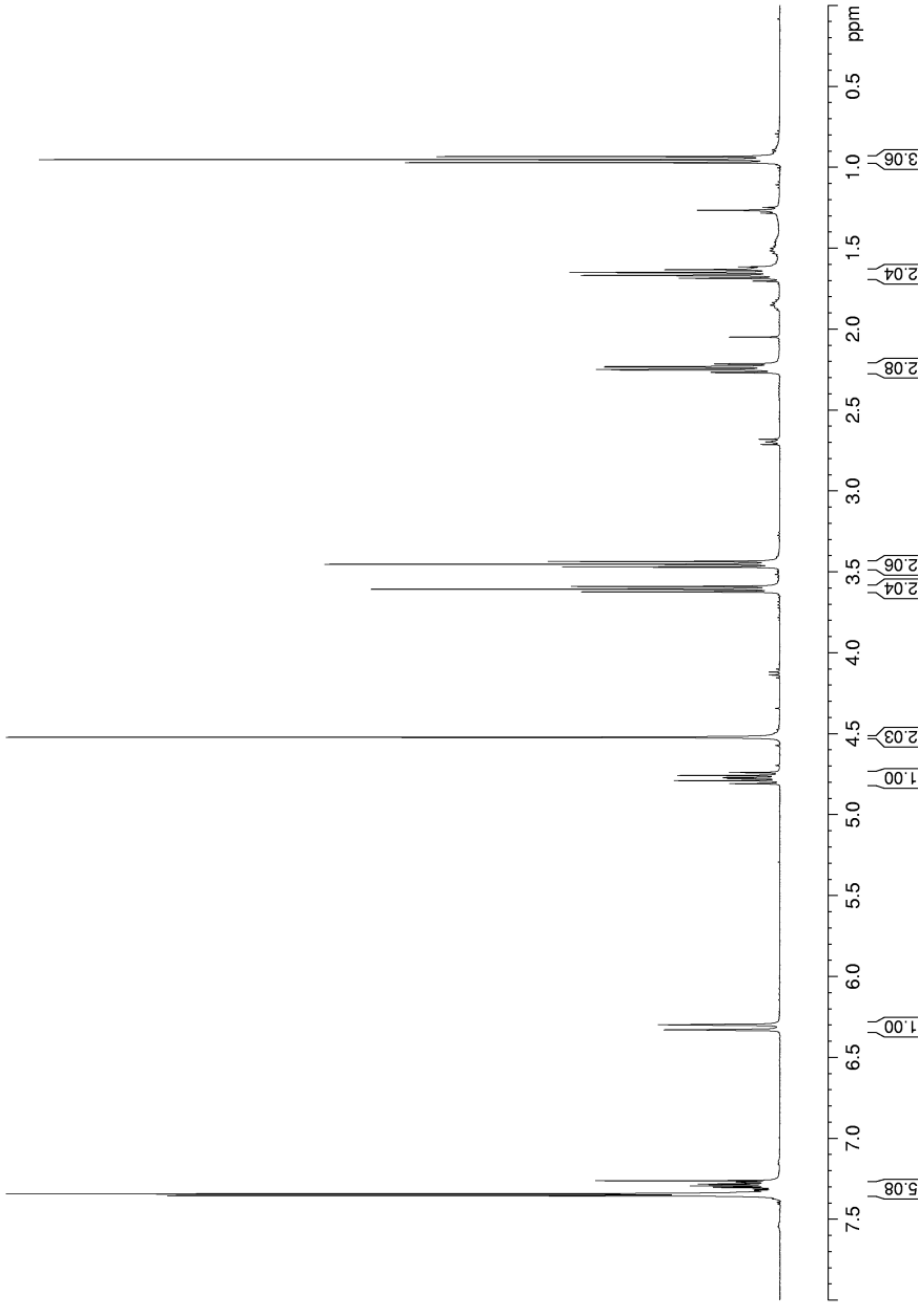
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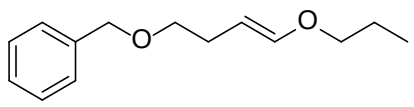
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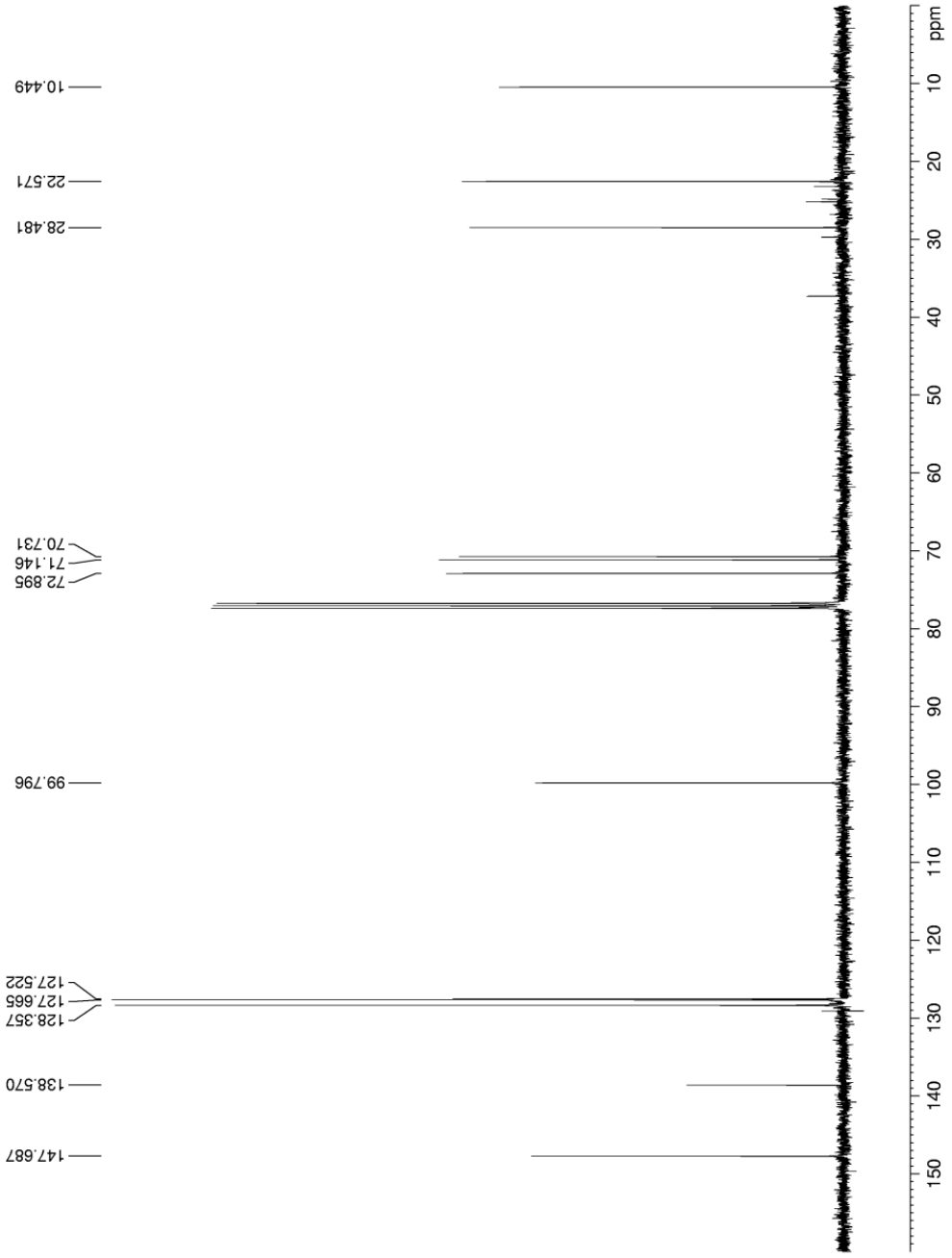
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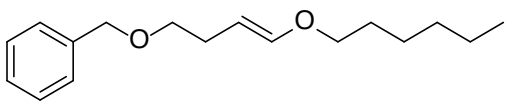

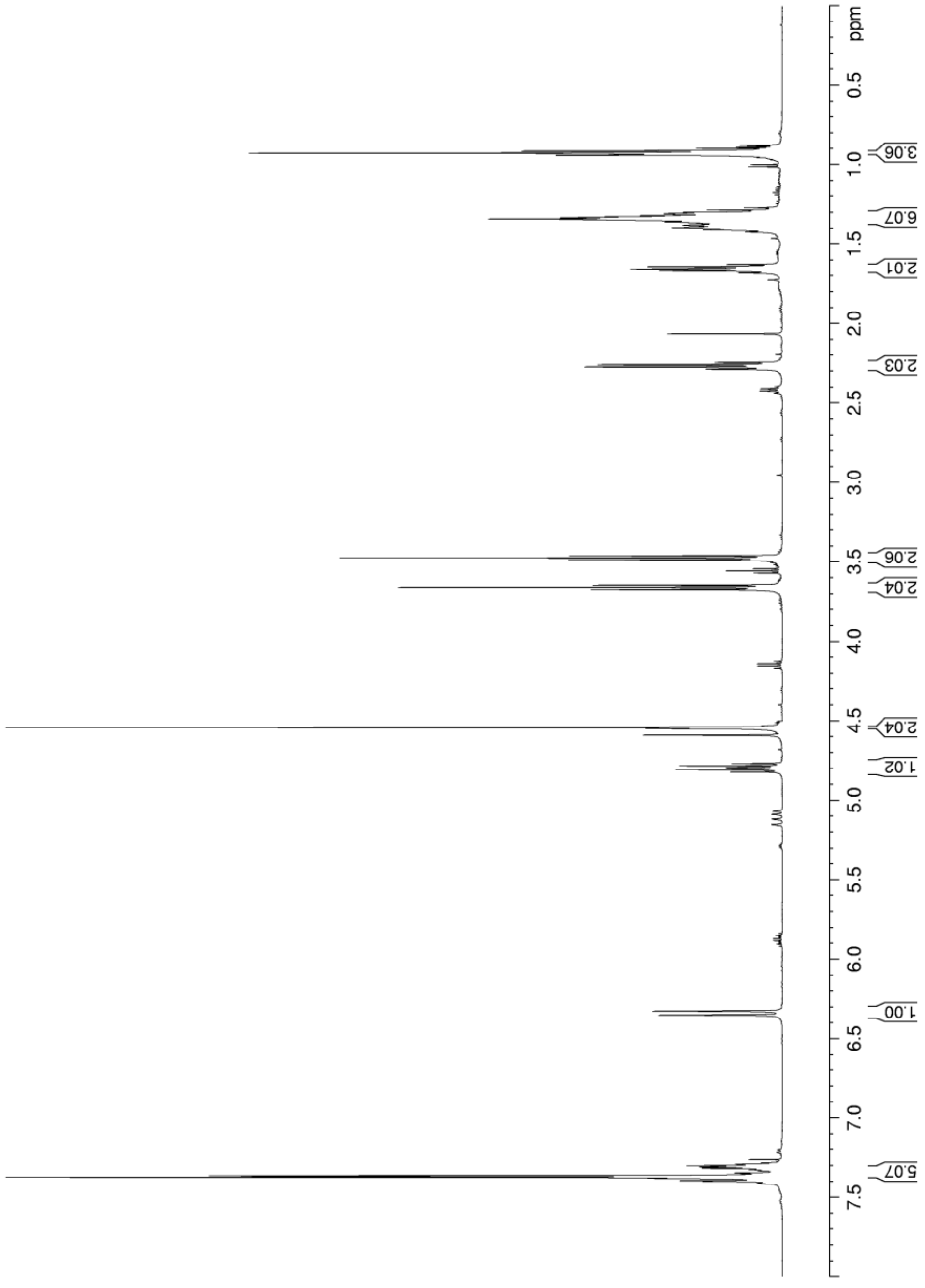
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6.07
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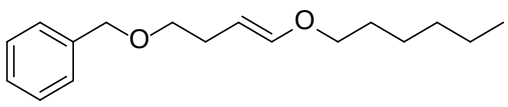
2.03
2.06
2.04
2.04
1.02
1.00
5.07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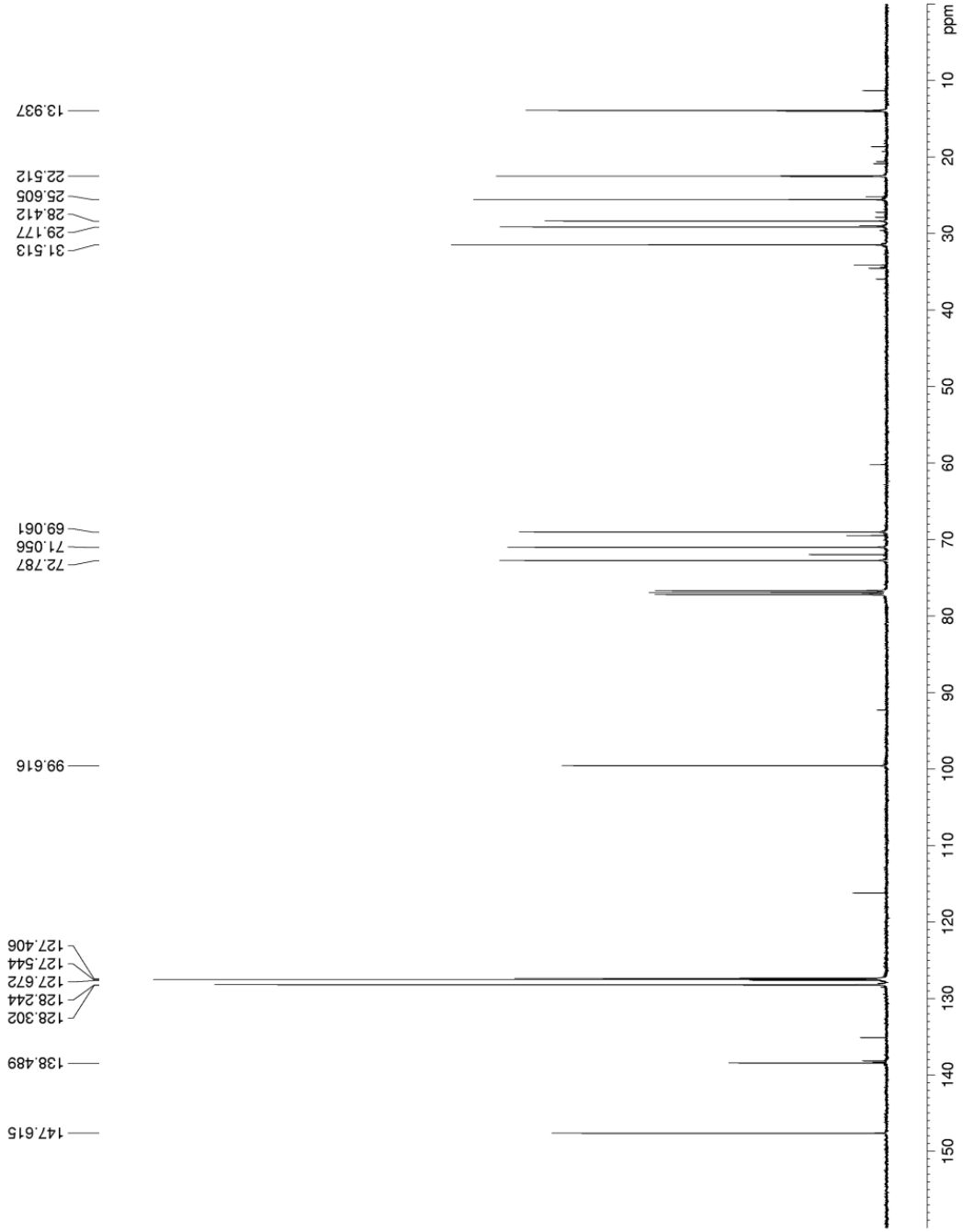
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128.244
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ppm
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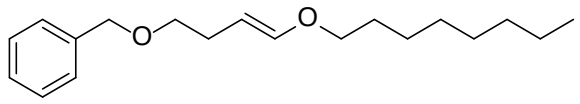
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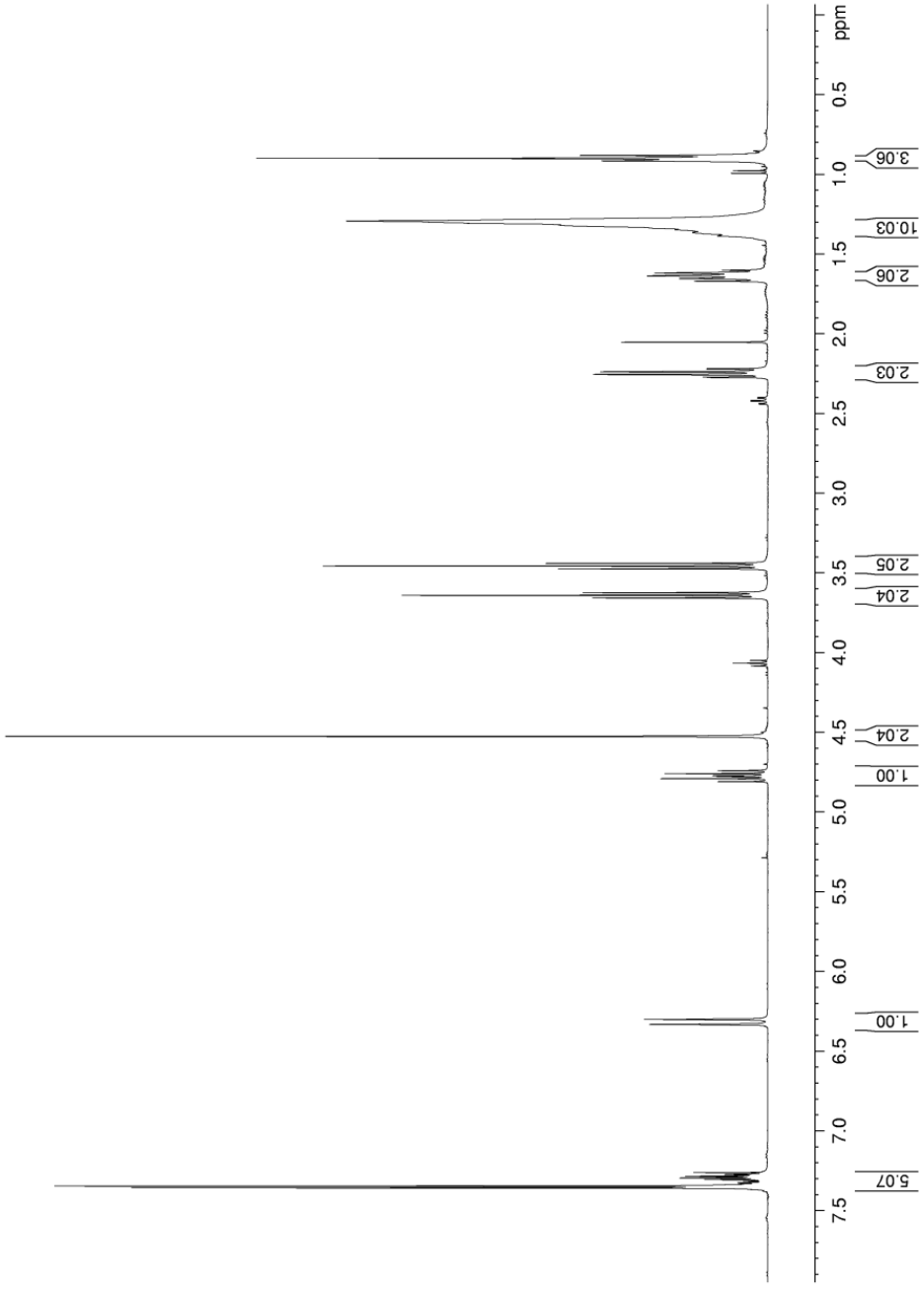
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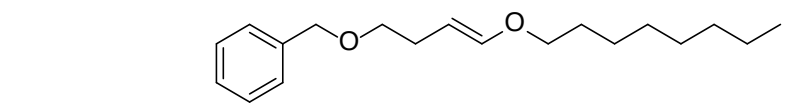
2.06
2.03
2.05
2.04
2.04
1.00
1.00
5.07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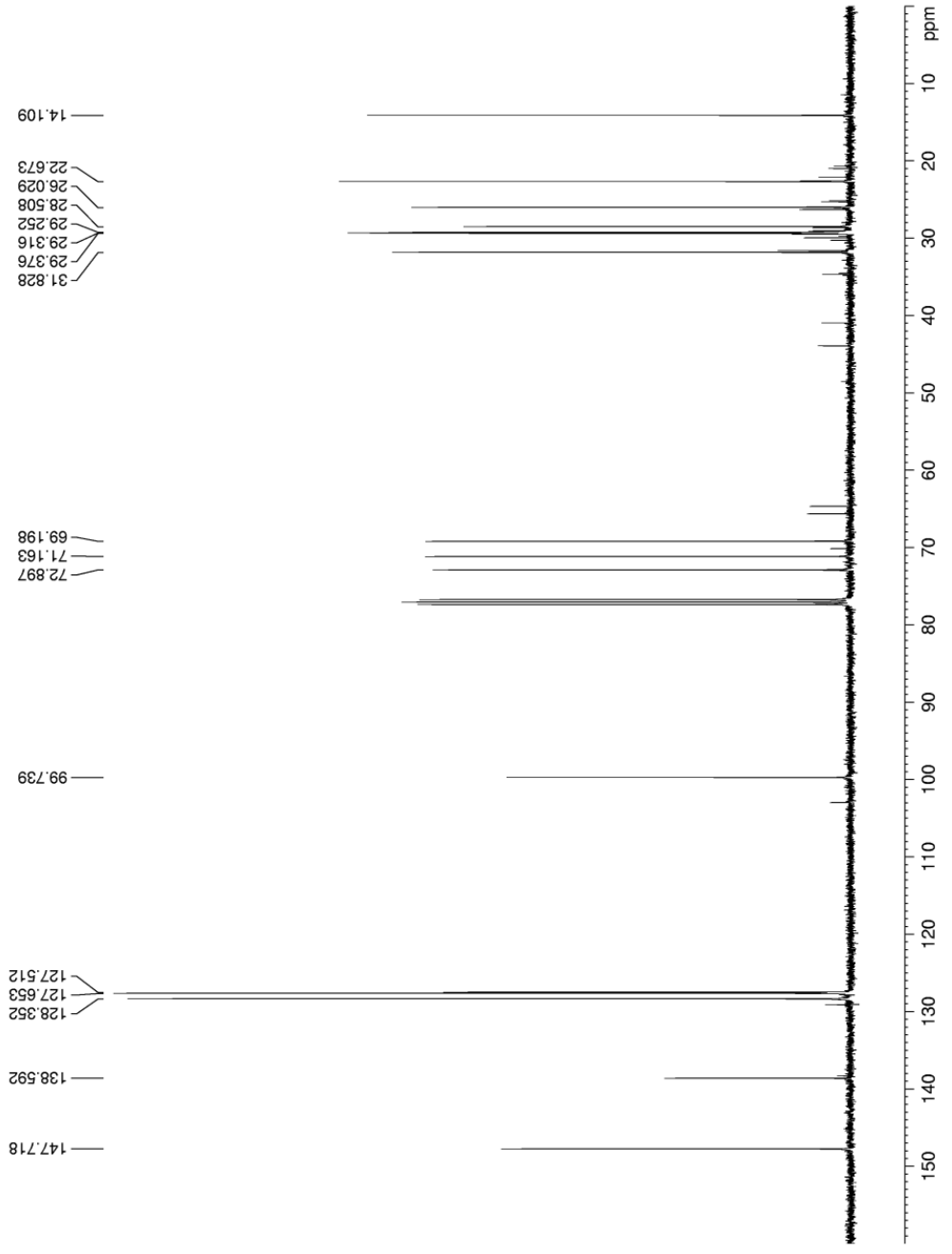
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127.653
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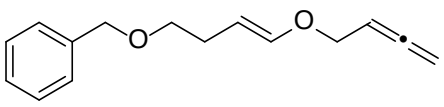

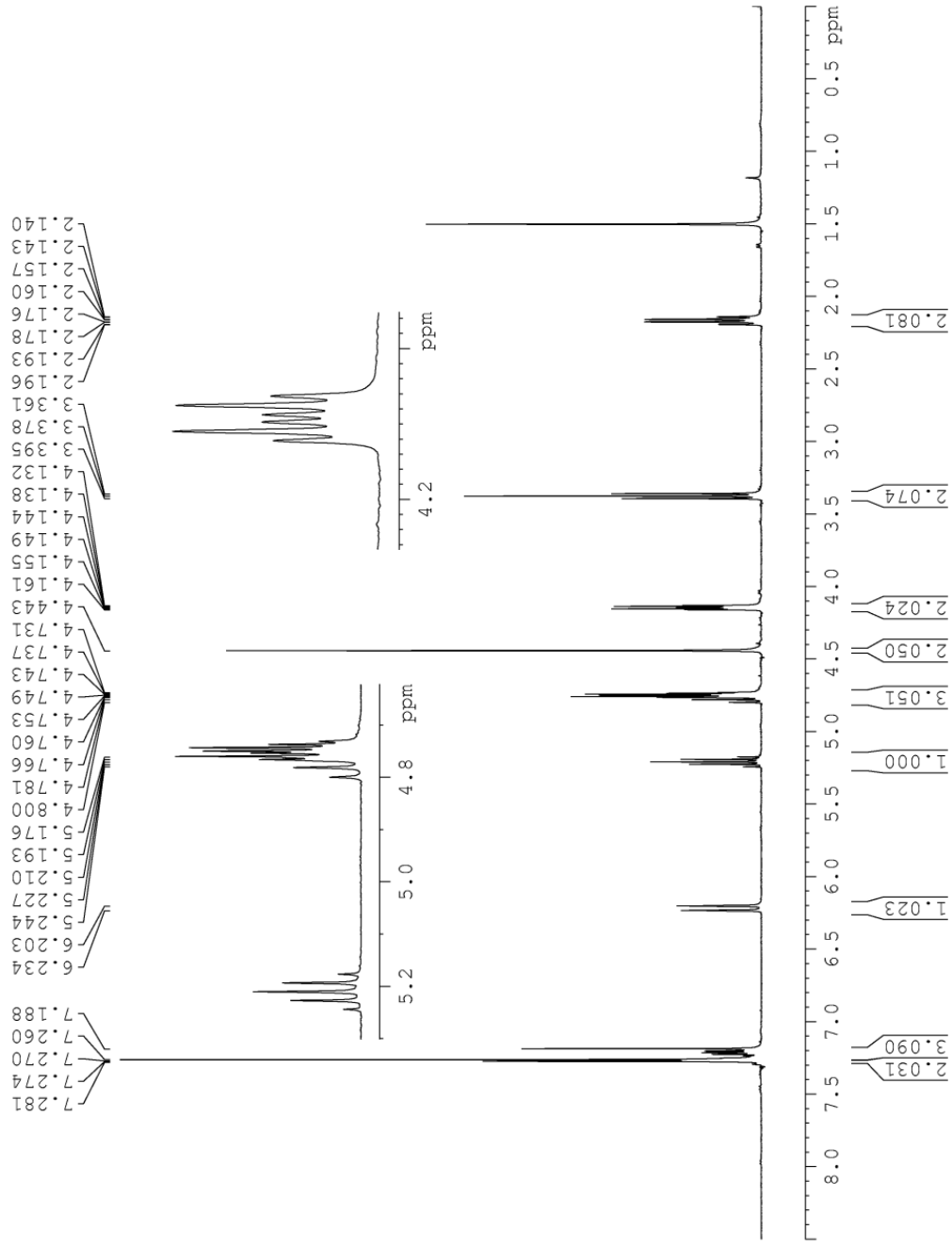
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7.260
7.188
6.234
6.203
5.244
5.227
5.210
5.193
5.176
4.800
4.781
4.766
4.760
4.753
4.749
4.743
4.737
4.731
4.443
4.161
4.155
4.149
4.144
4.138
4.132
3.395
3.378
3.361
2.196
2.193
2.178
2.176
2.160
2.157
2.143
2.140
ppm
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4.8
ppm
4.2
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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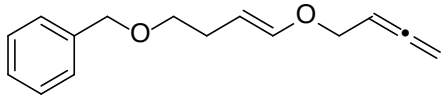
2.081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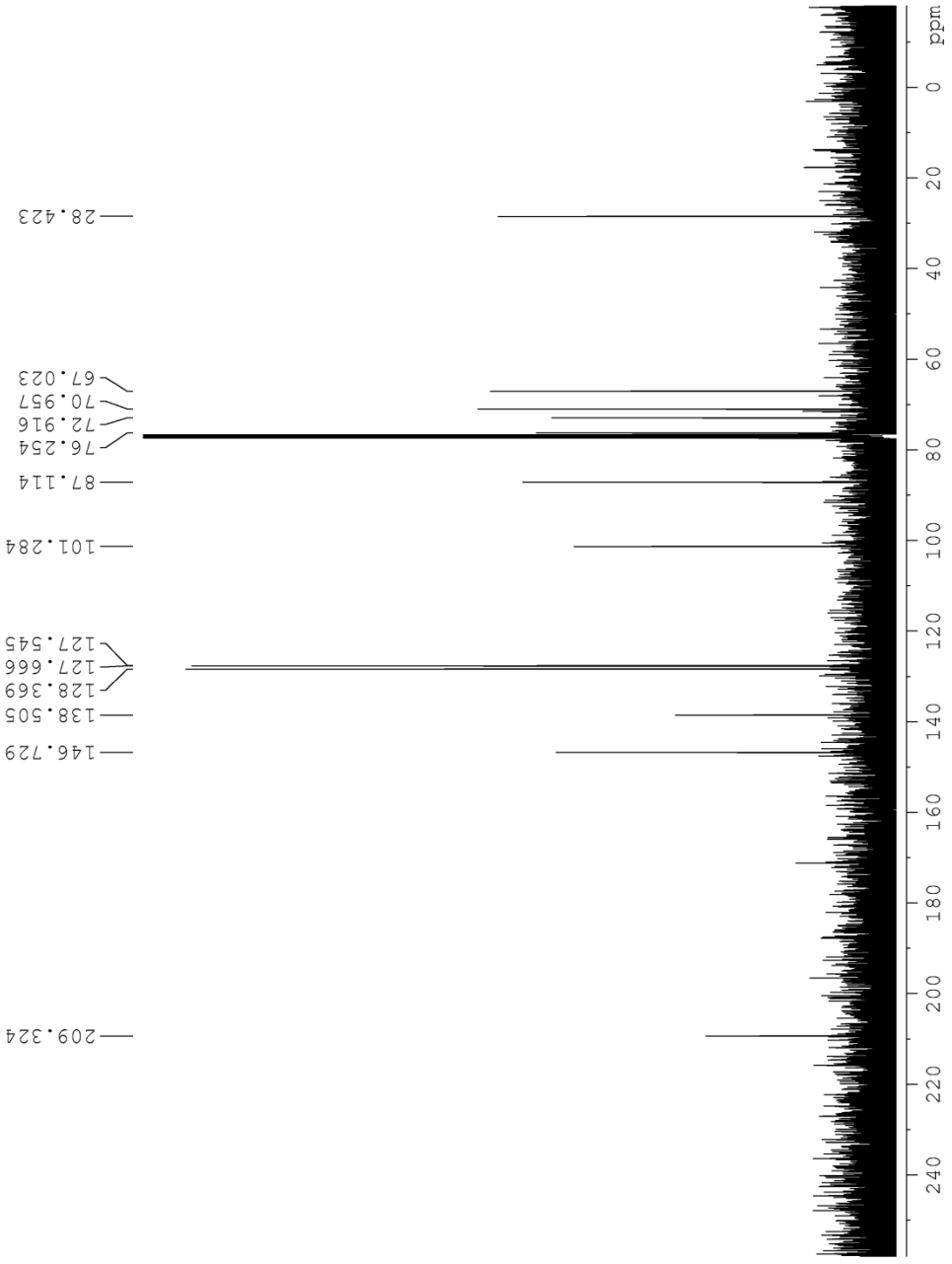
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101.284
127.545
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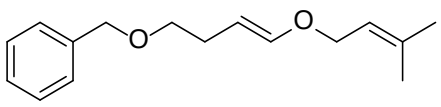
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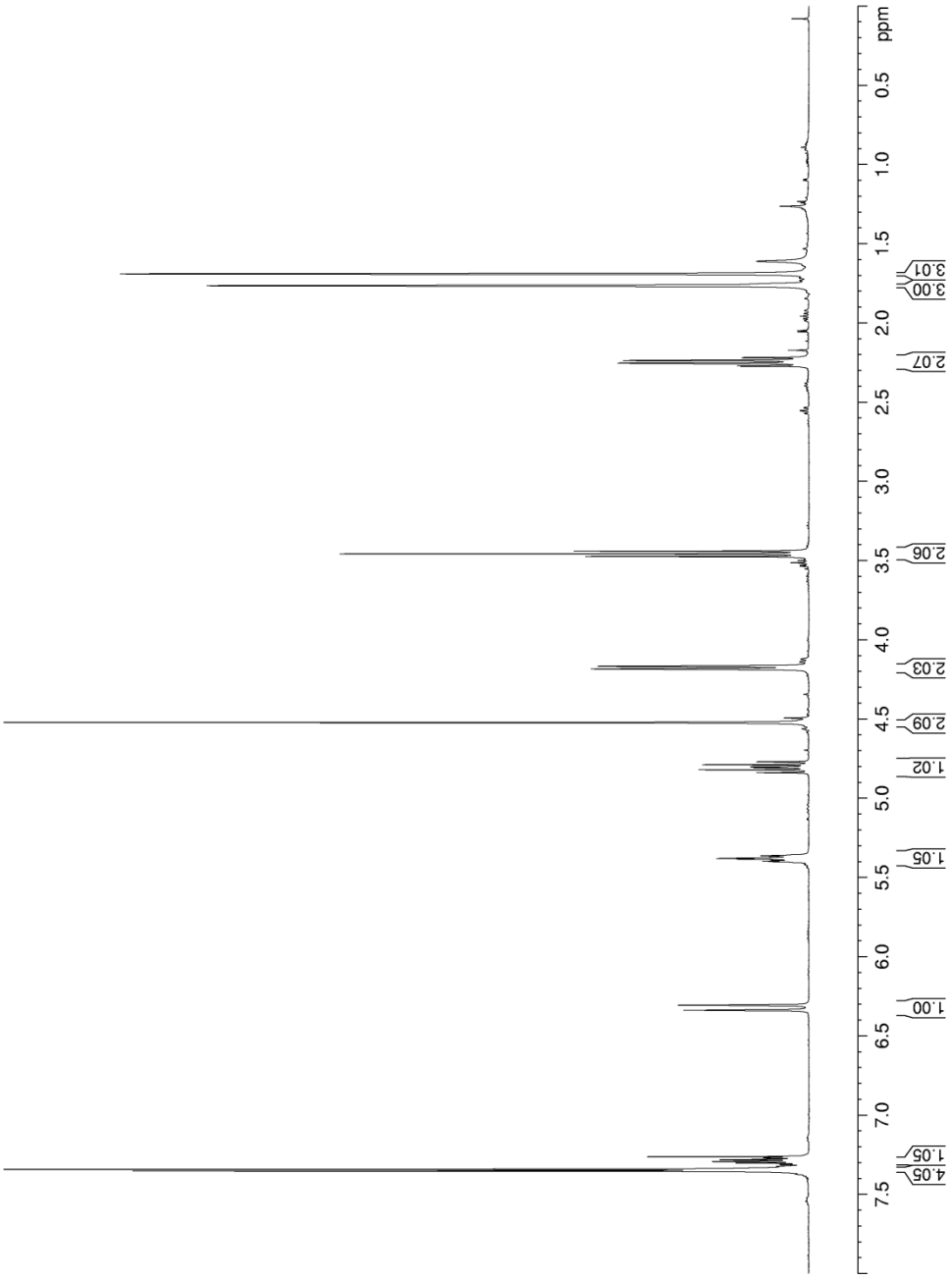
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6.5
7.0
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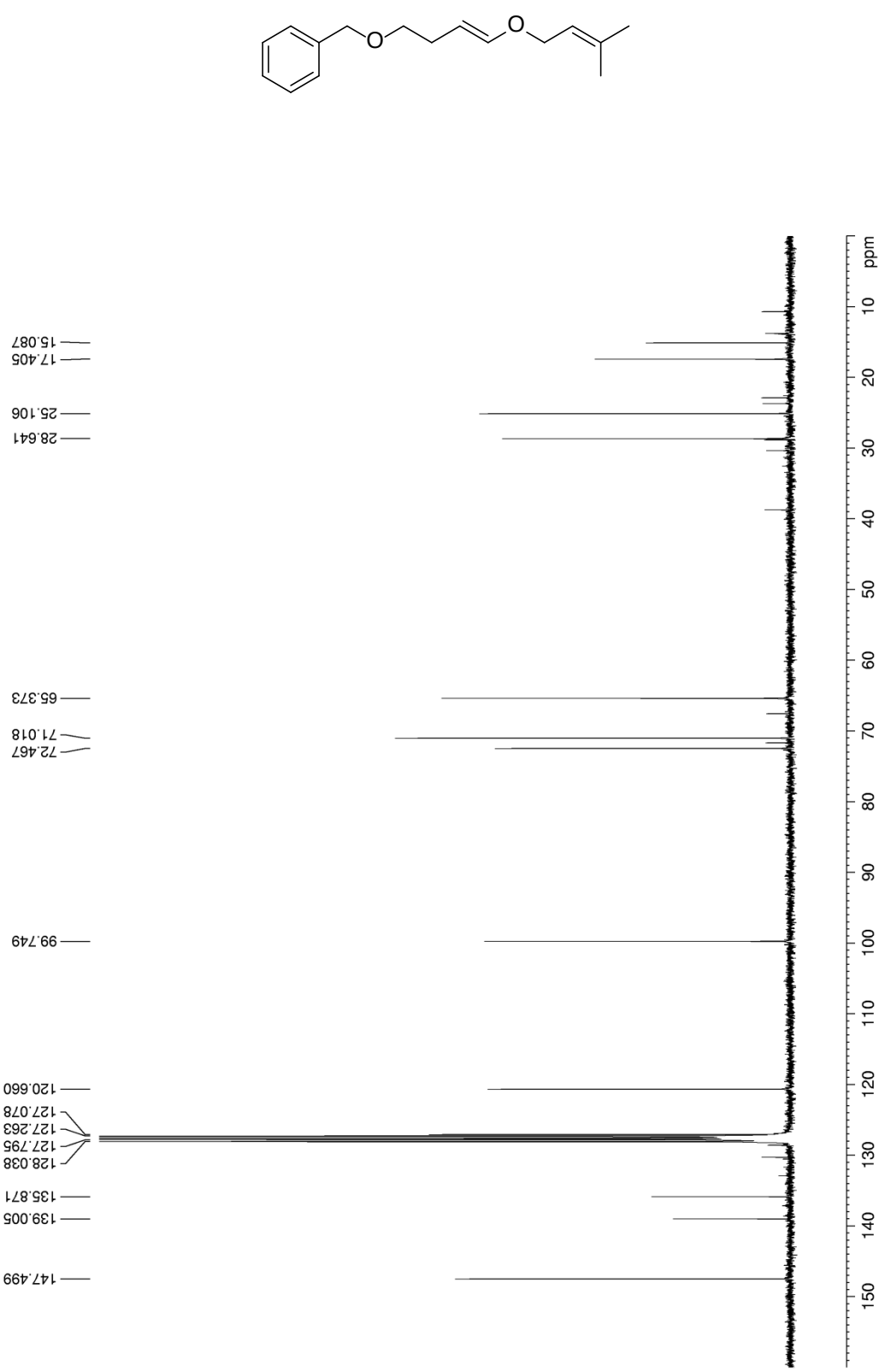
2.09
1.02
1.05
1.00
4.05
1.05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128.038
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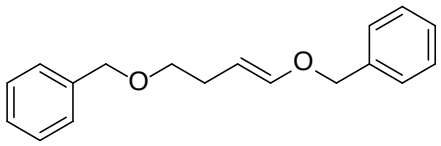
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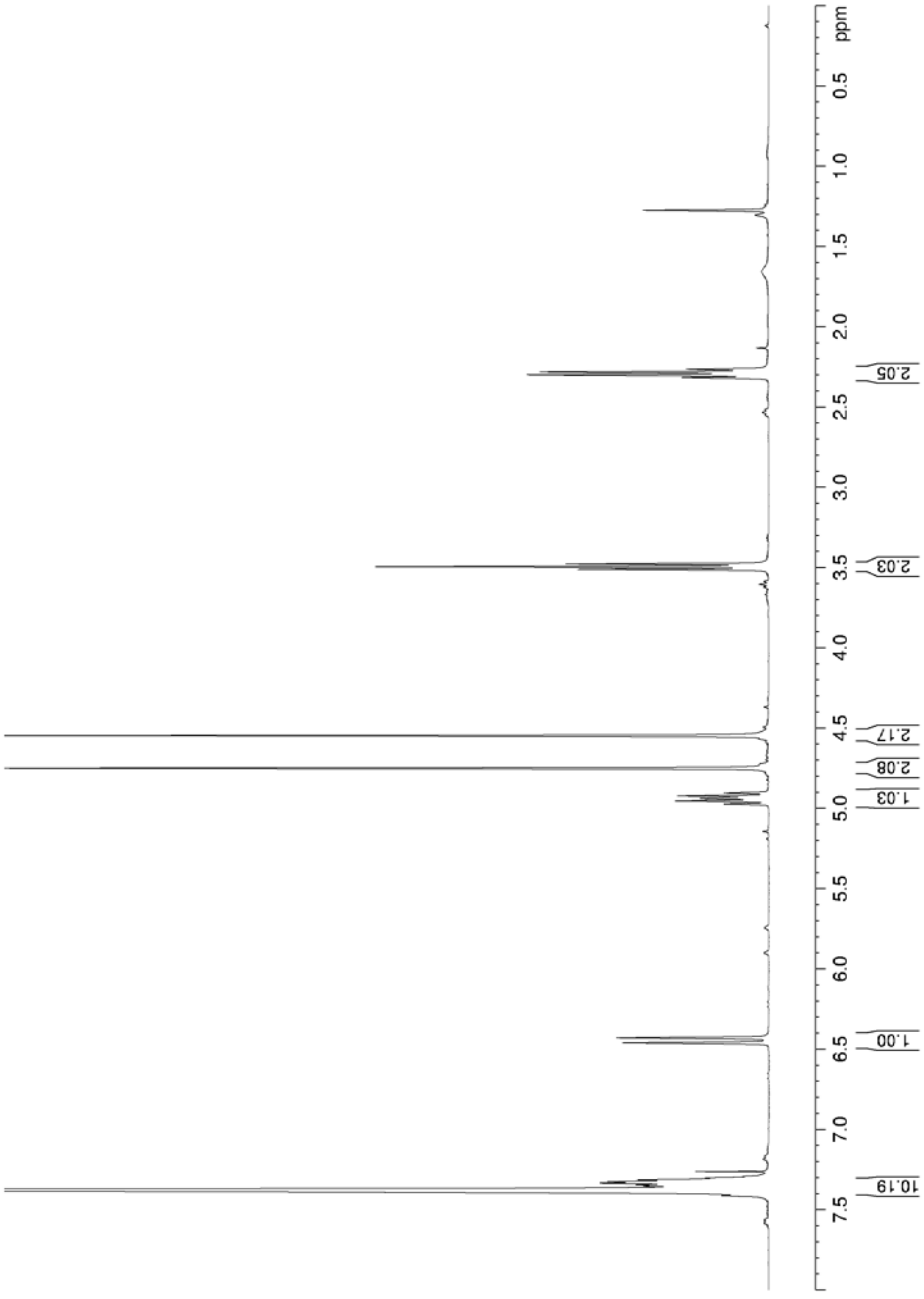
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4.5
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2.17
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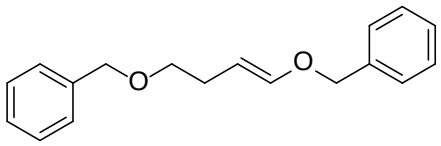
1.03
1.00
10.19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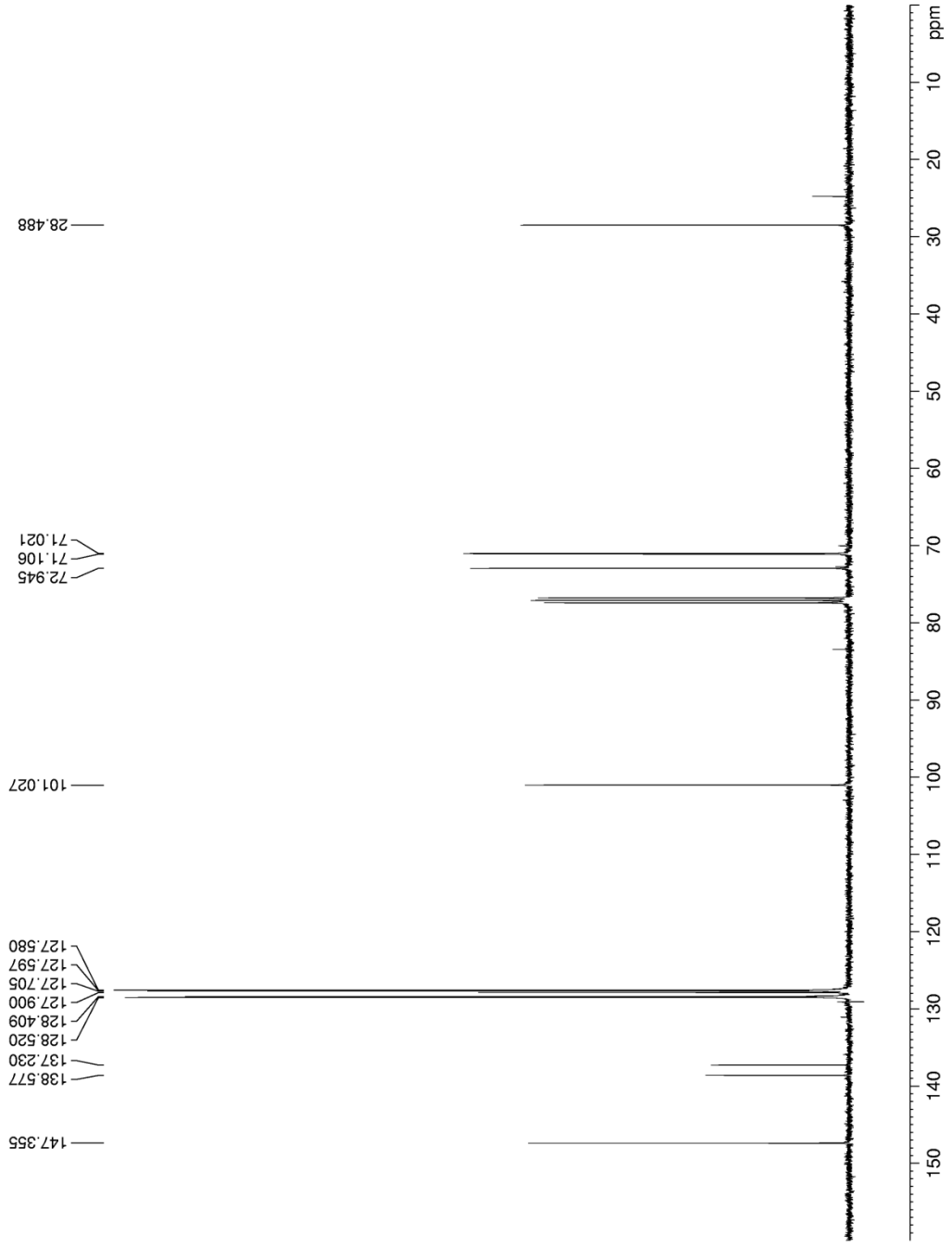
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ppm
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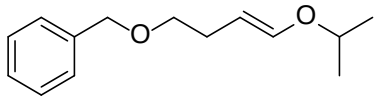
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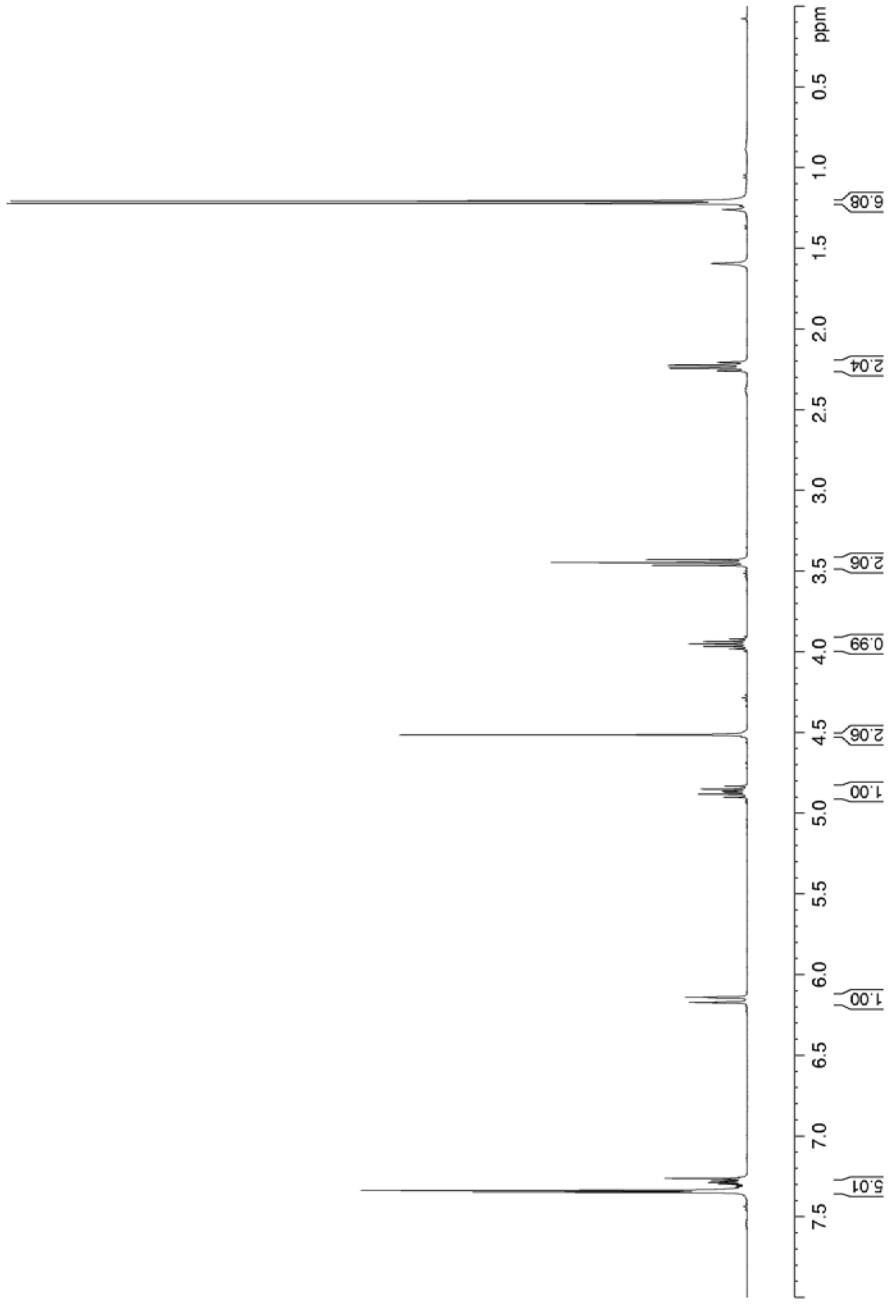
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4.5
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7.5
6.08
2.04
2.06
0.99
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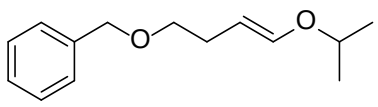
1.00
1.00
5.01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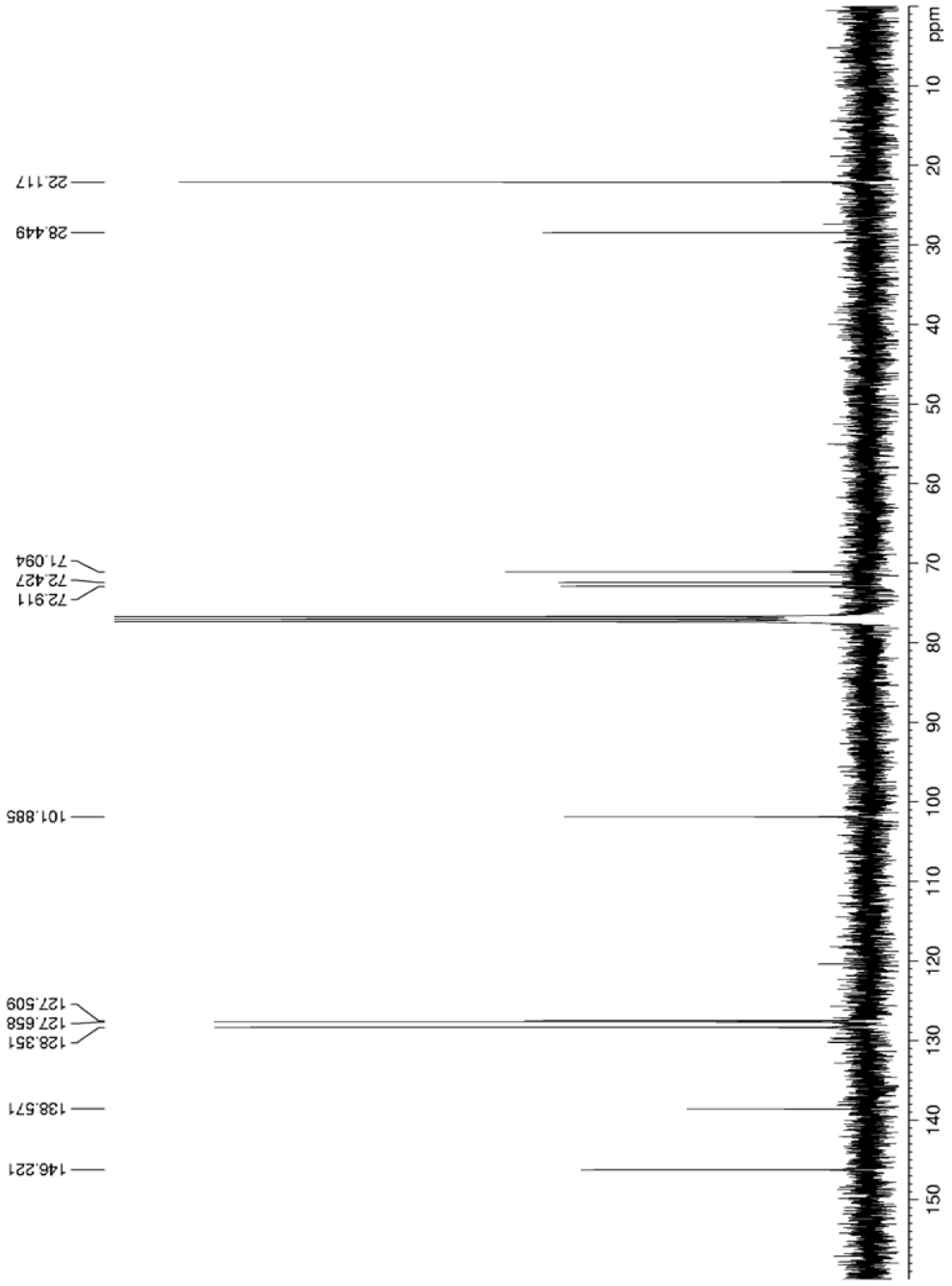
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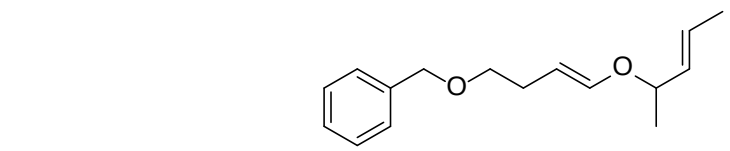
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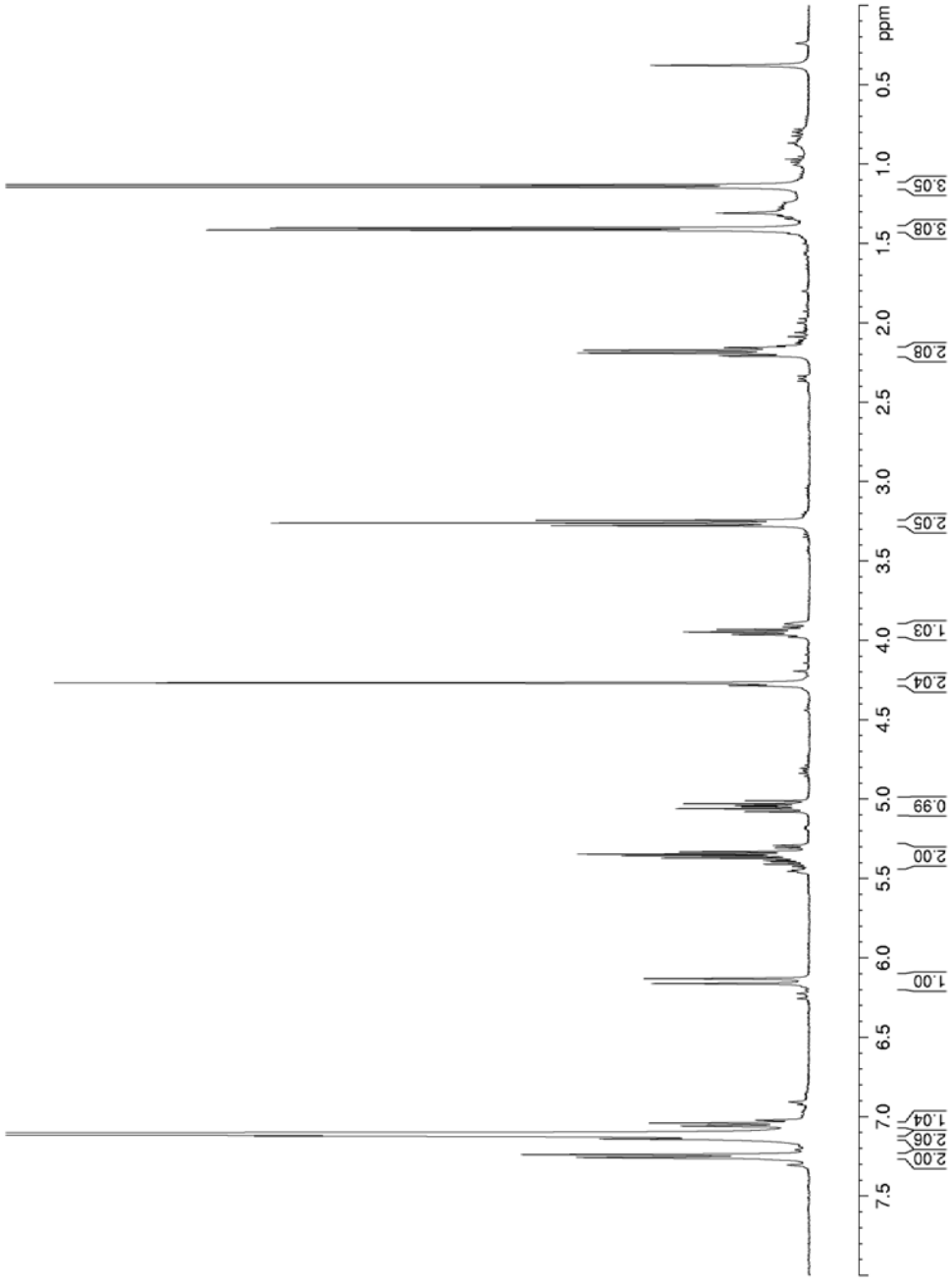
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6.5
7.0
7.5
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2.05
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2.00
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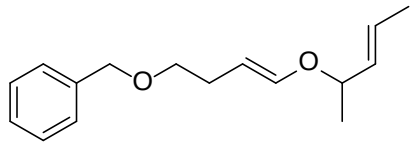
2.06
2.00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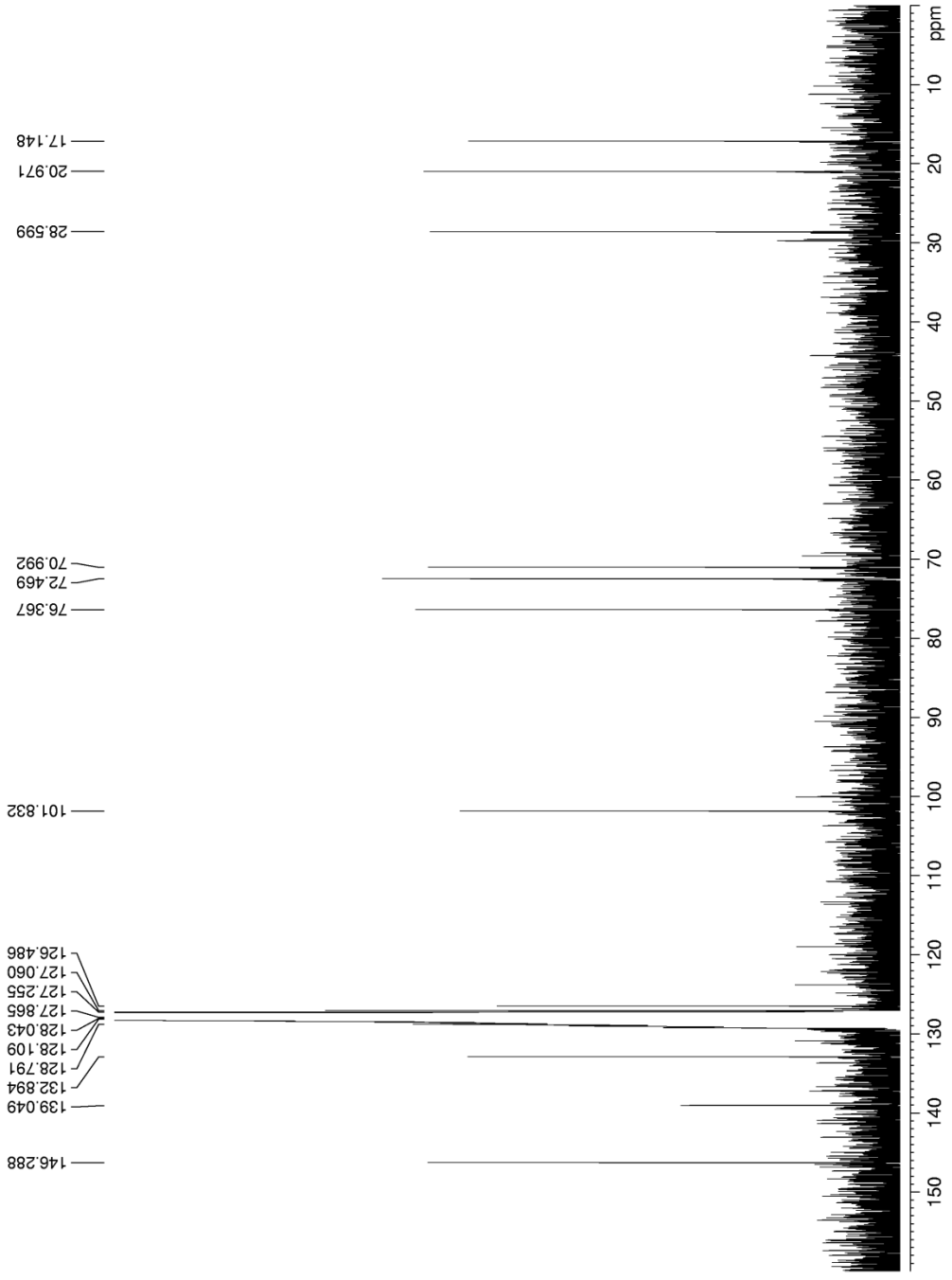
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128.109
128.791
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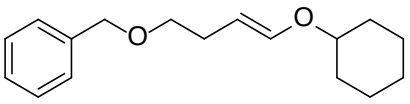
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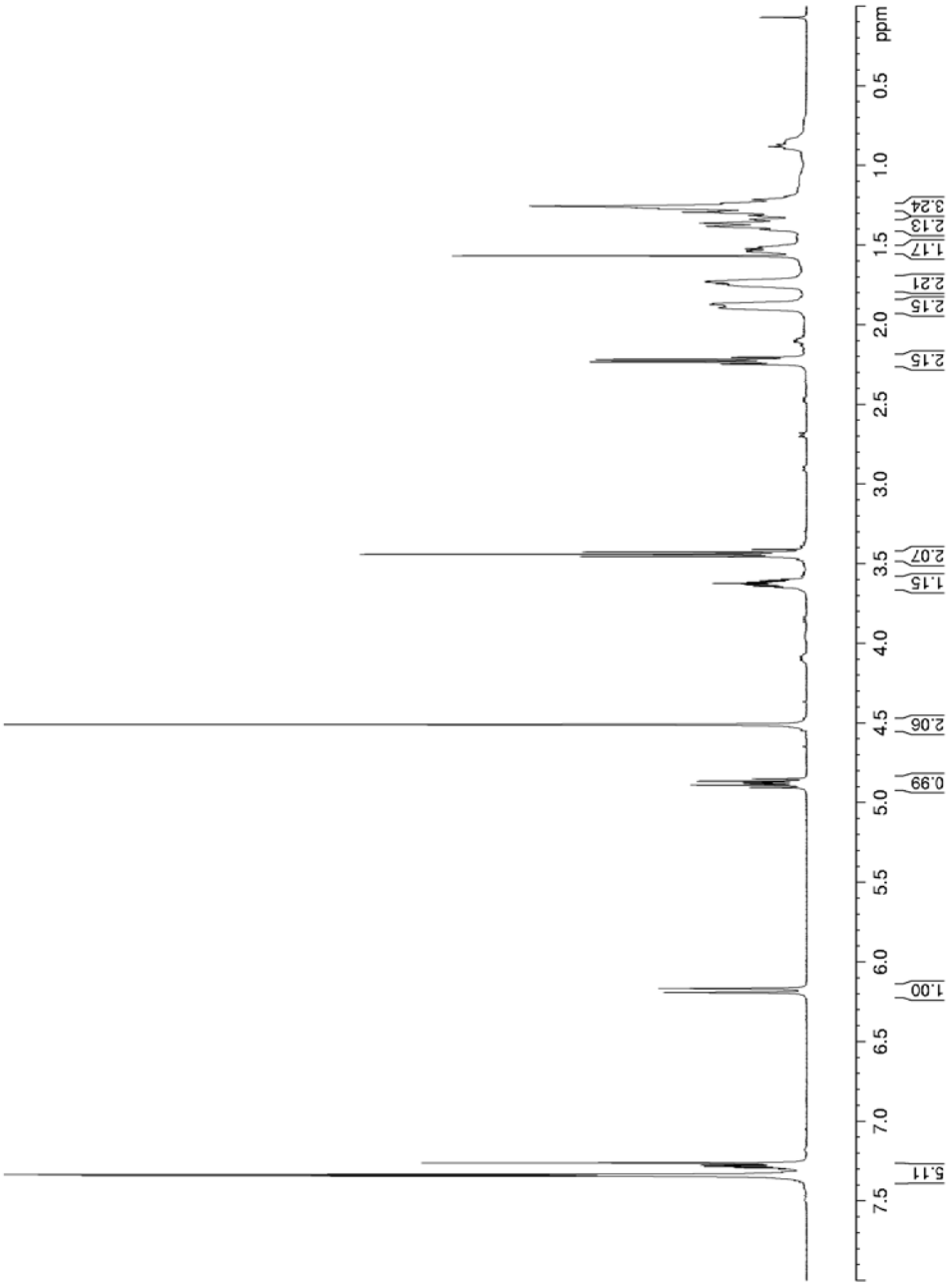
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1.15
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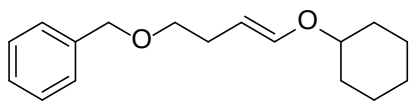
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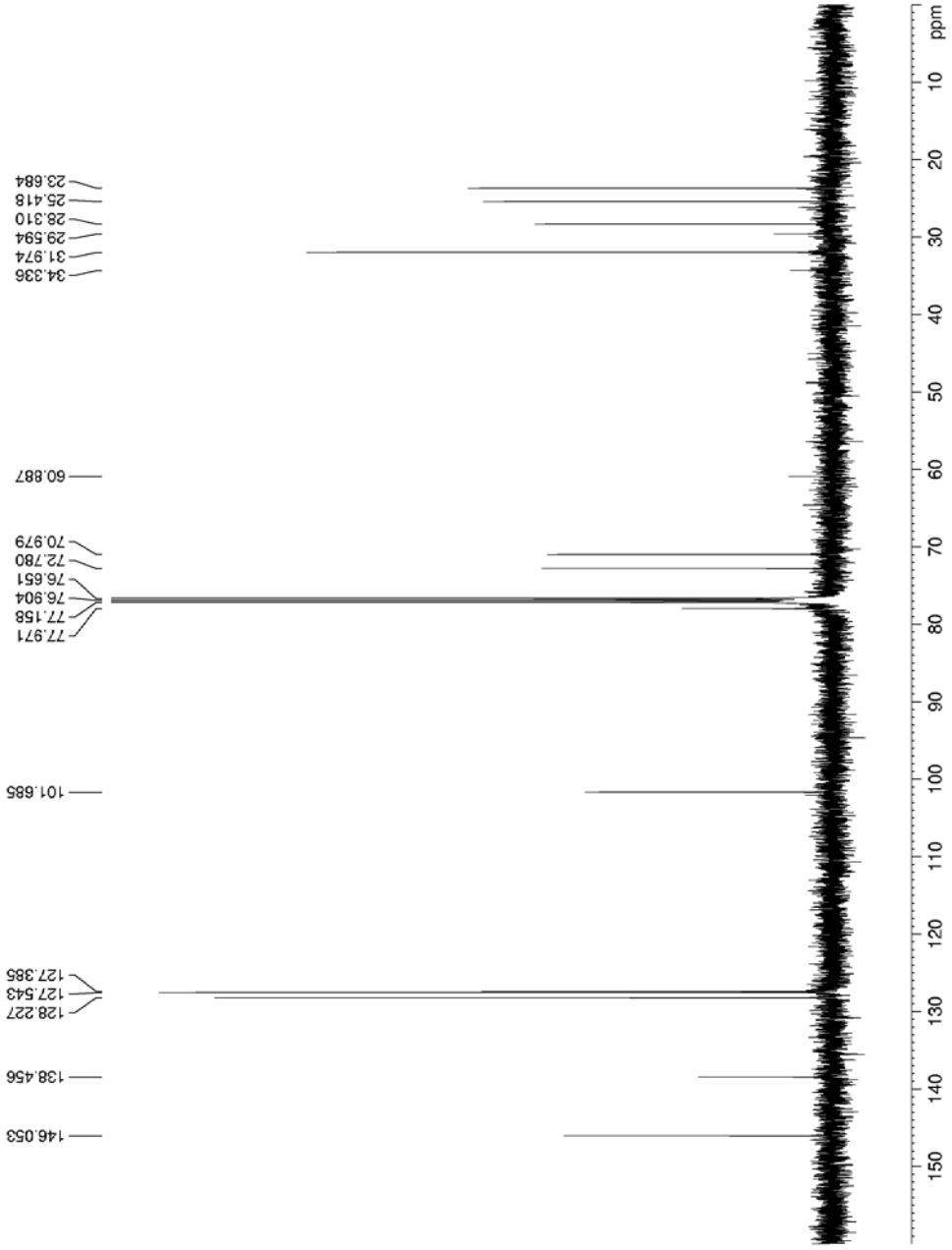
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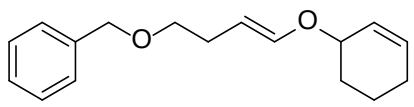
146.053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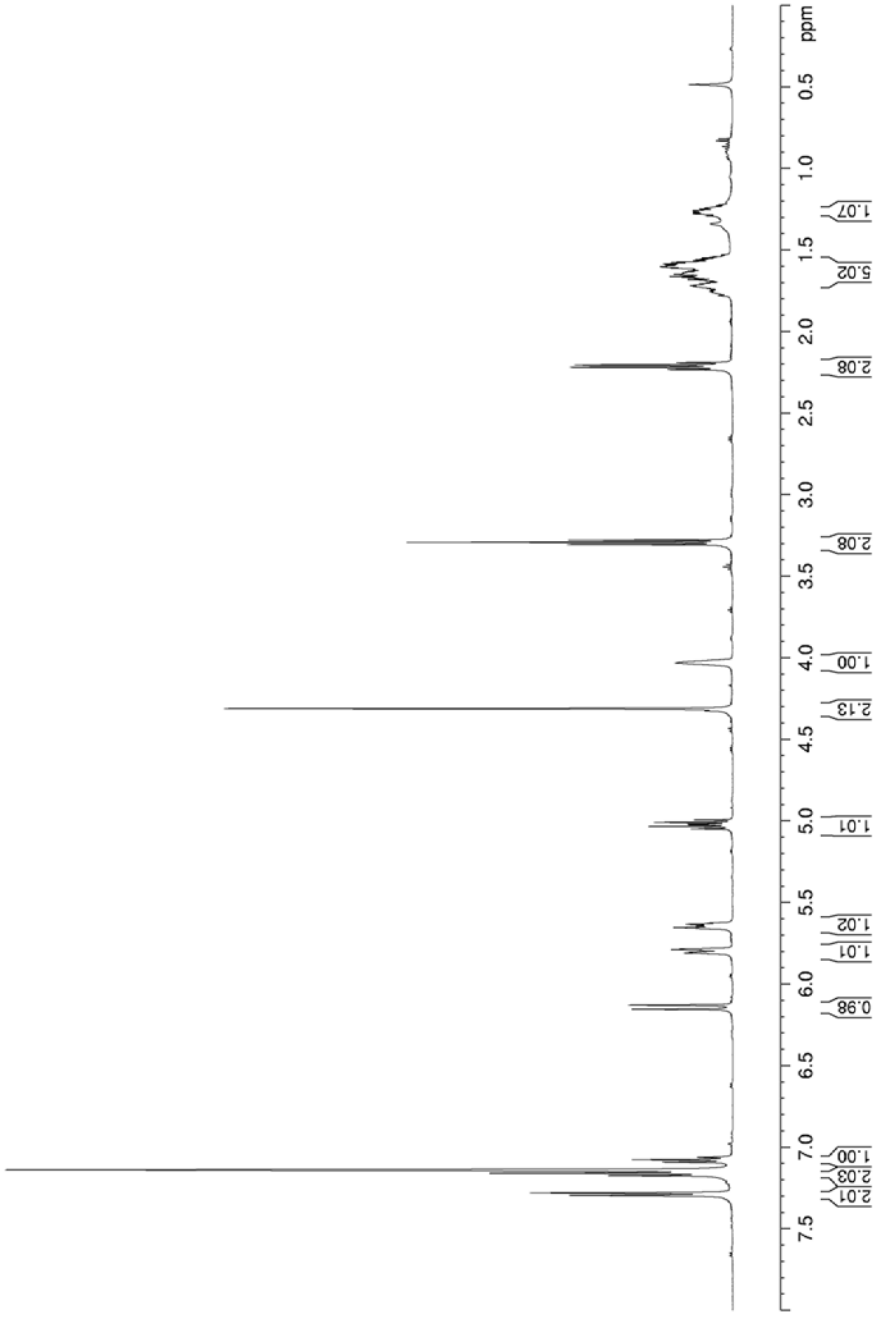
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7.5
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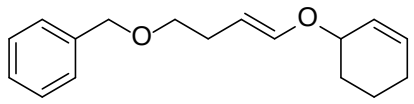
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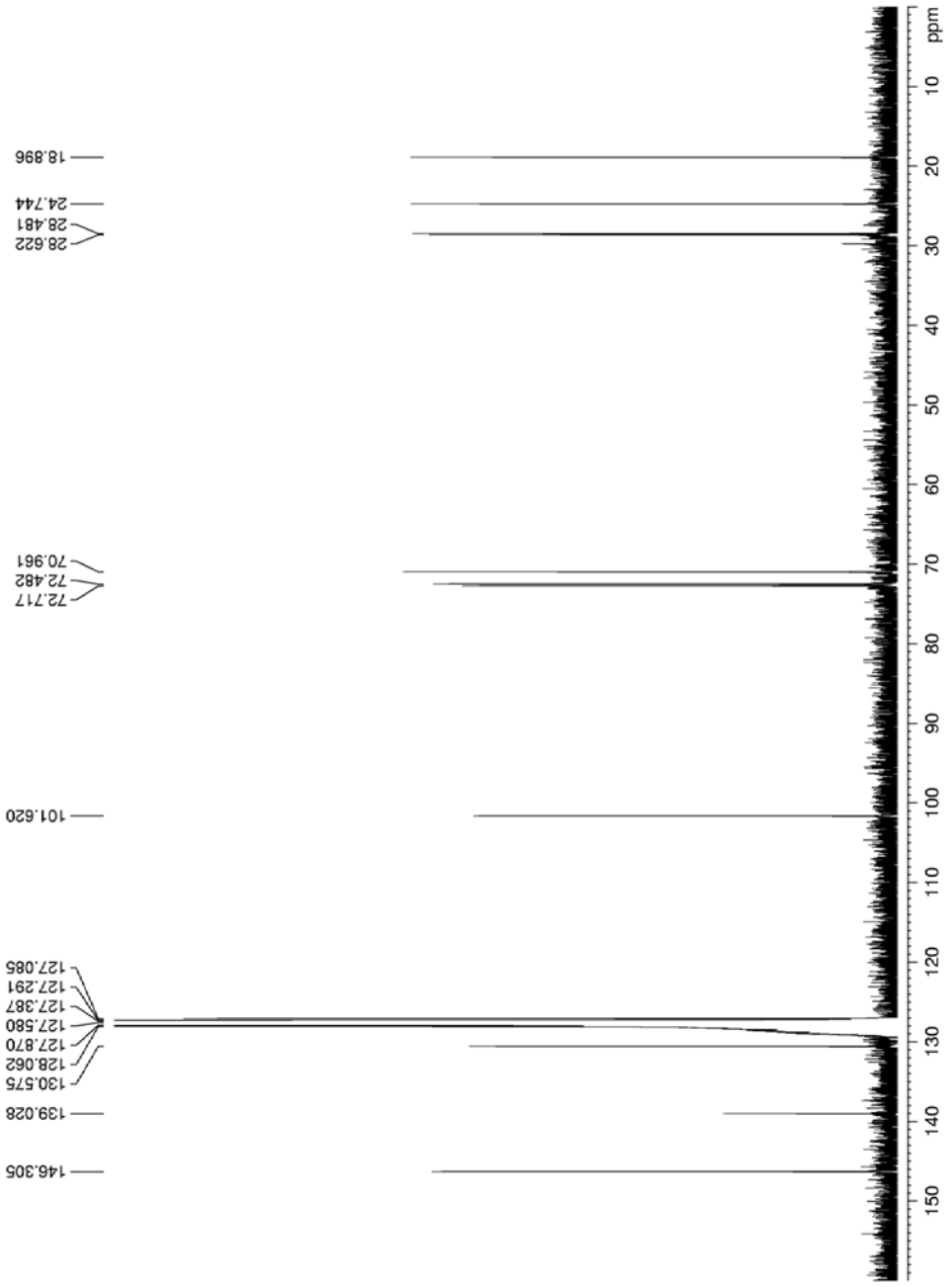
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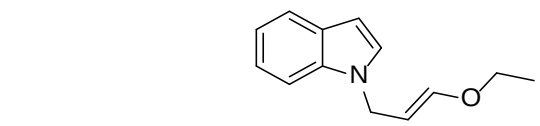
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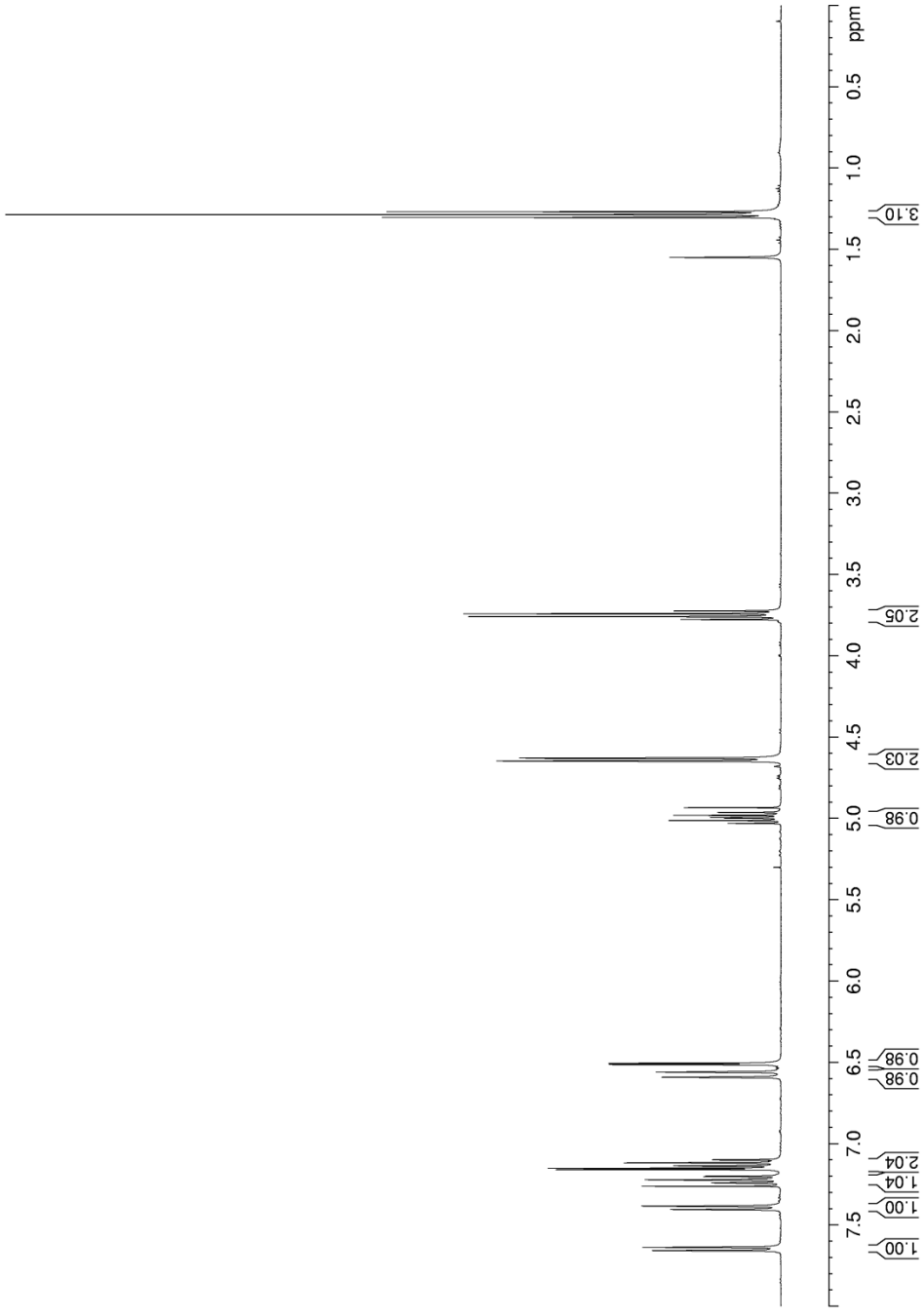
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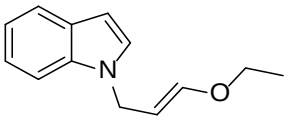
1.00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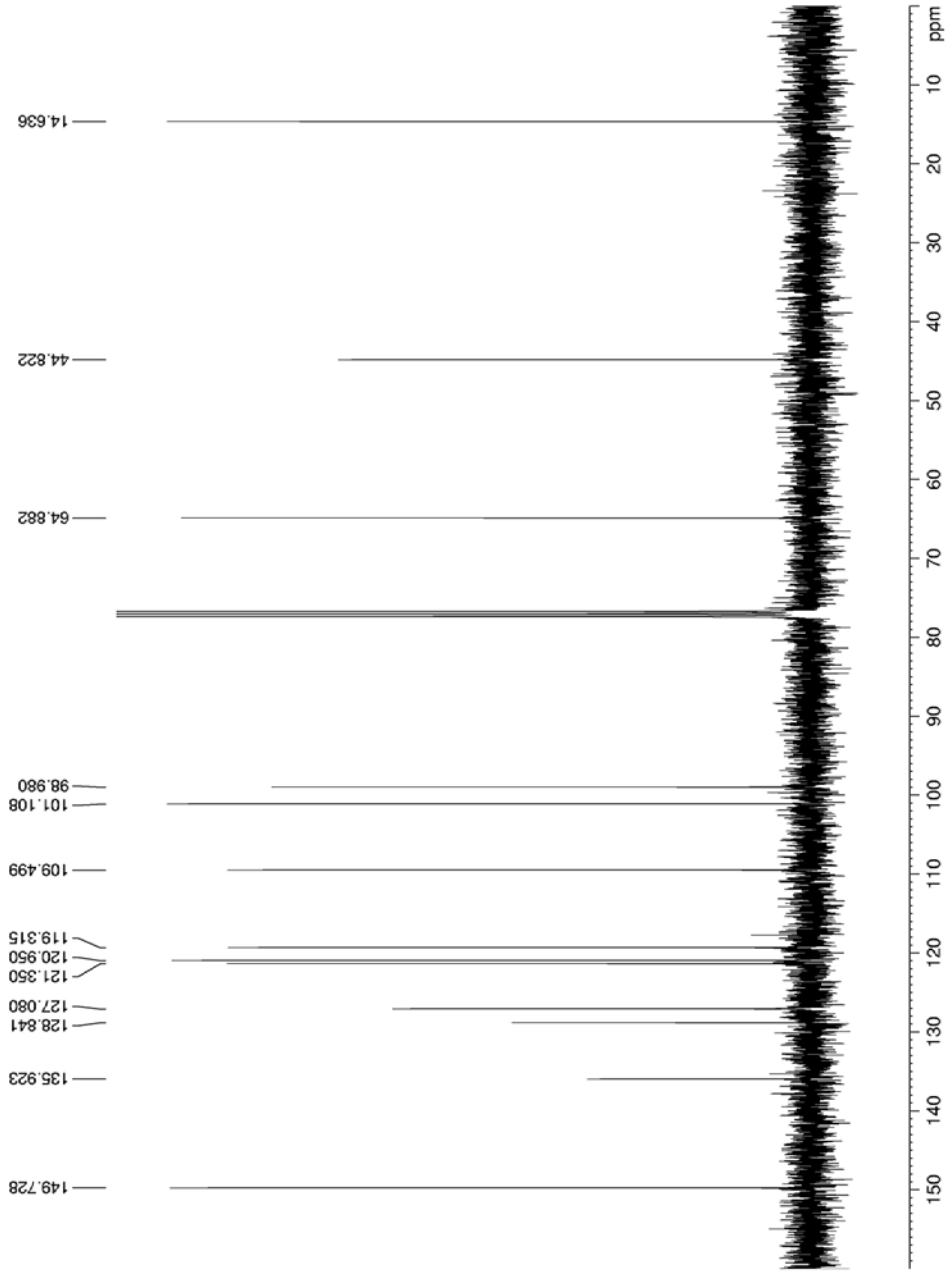
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ppm
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20
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40
50
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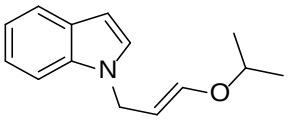
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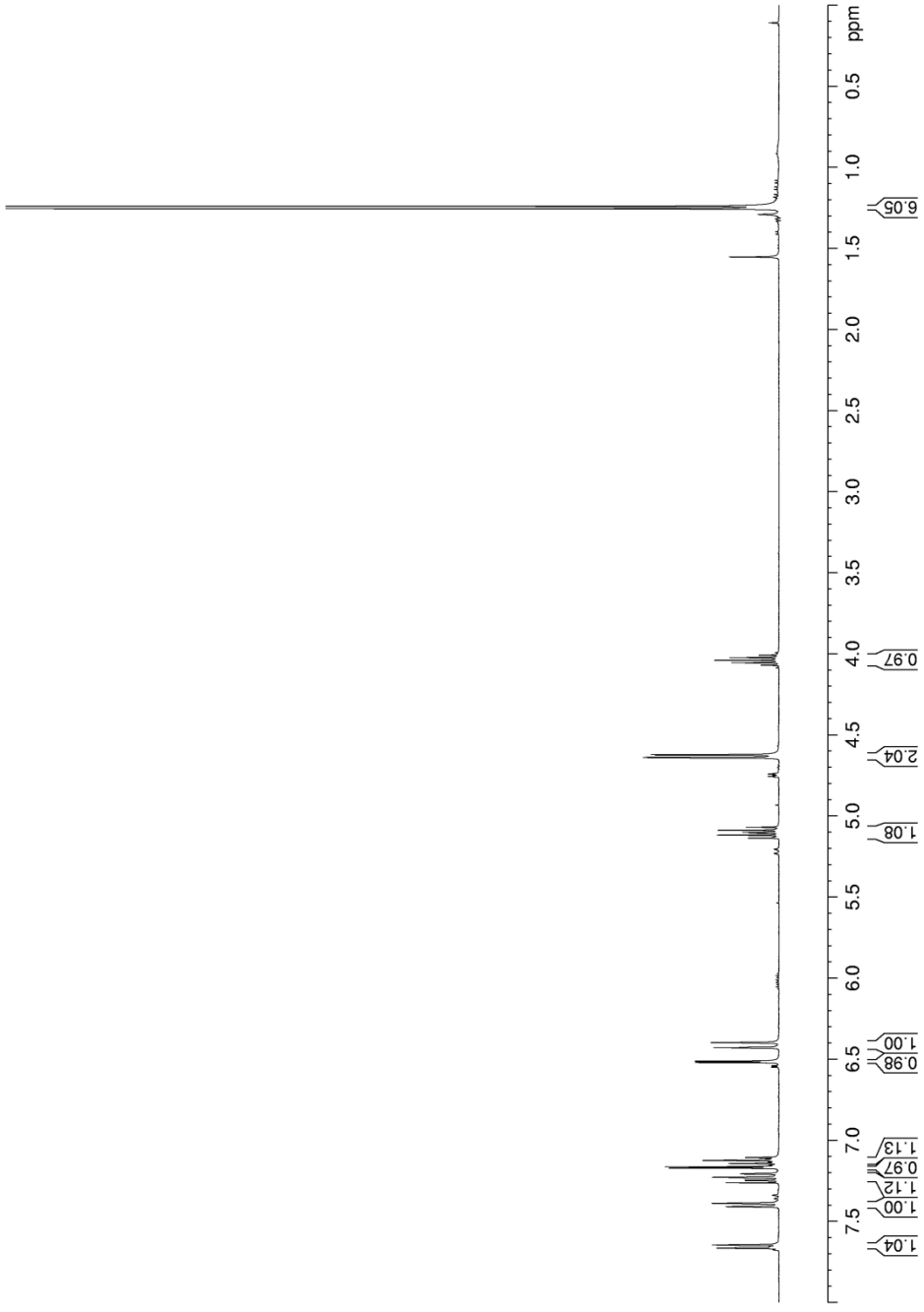
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6.0
6.5
7.0
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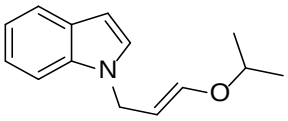
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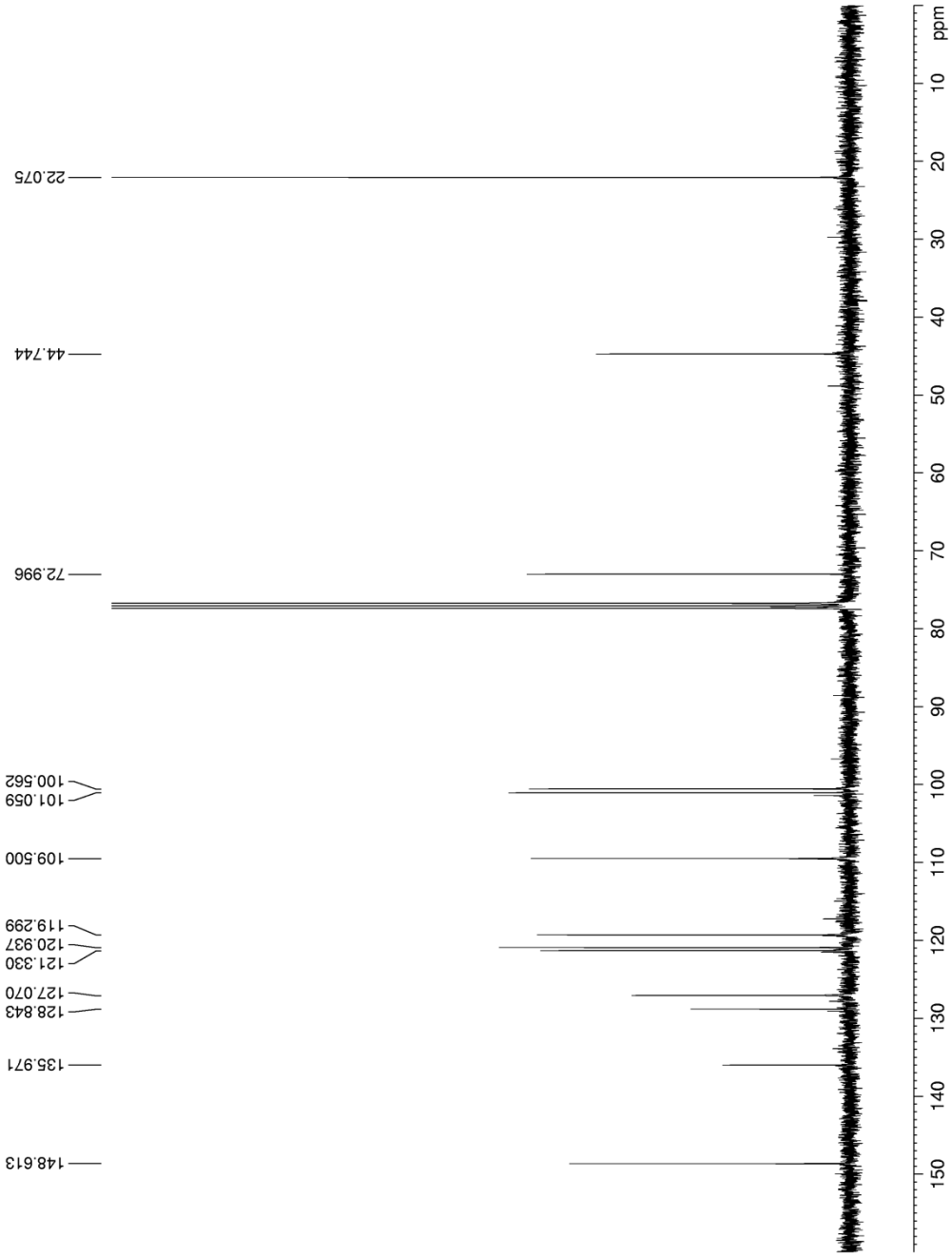
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ppm
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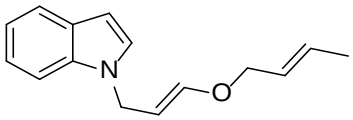
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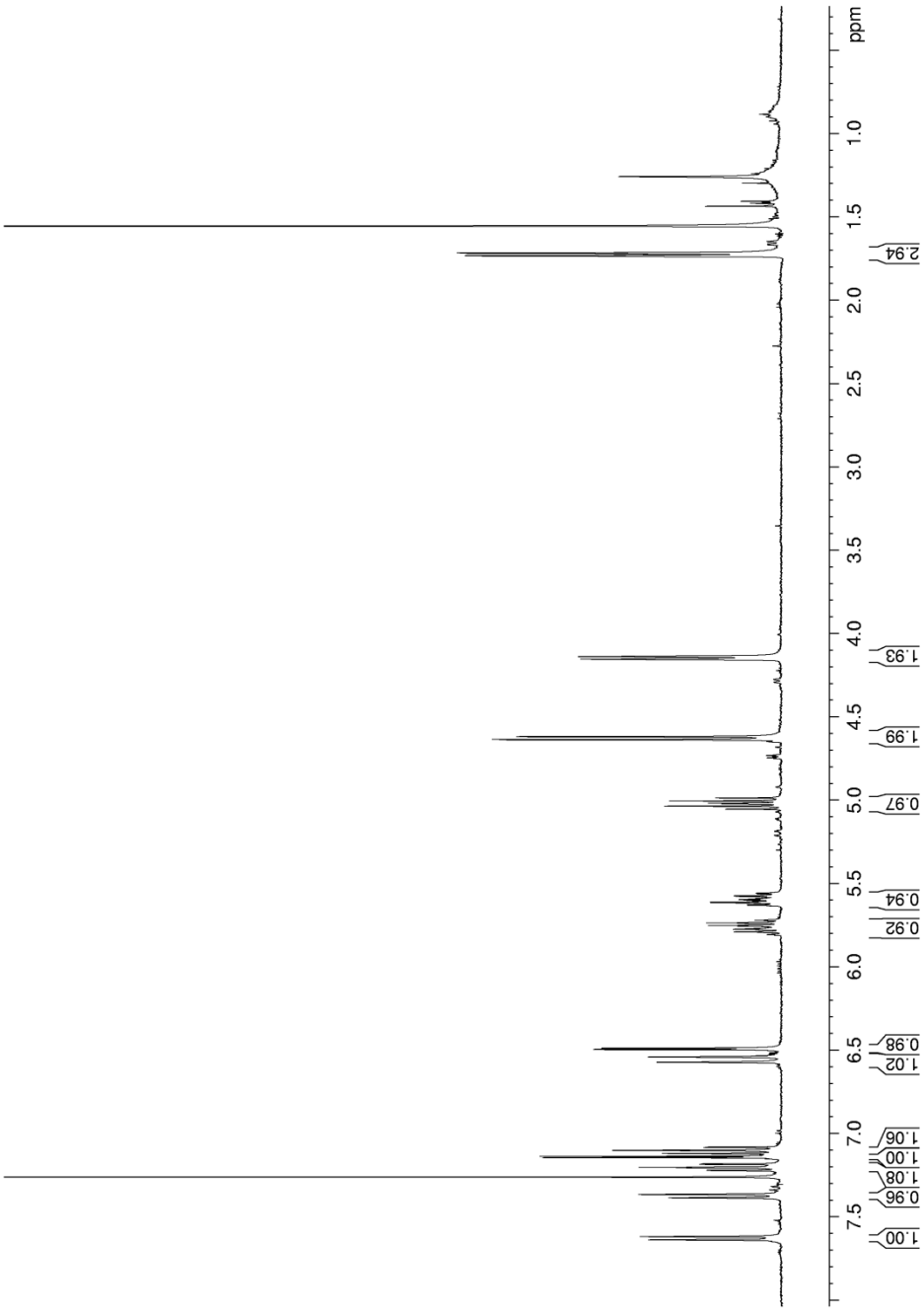
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7.0
7.5
2.94
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0.94
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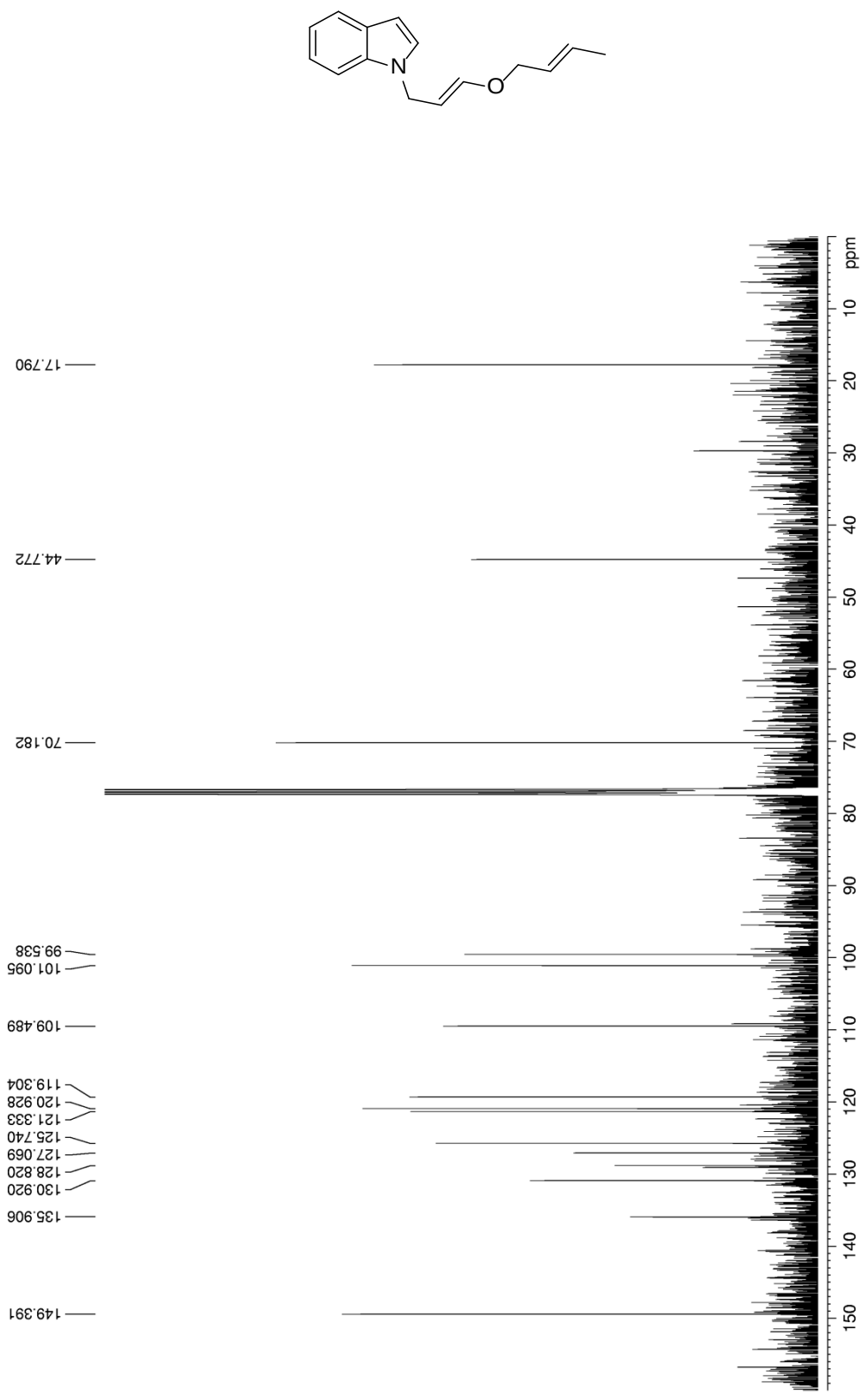
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128.820
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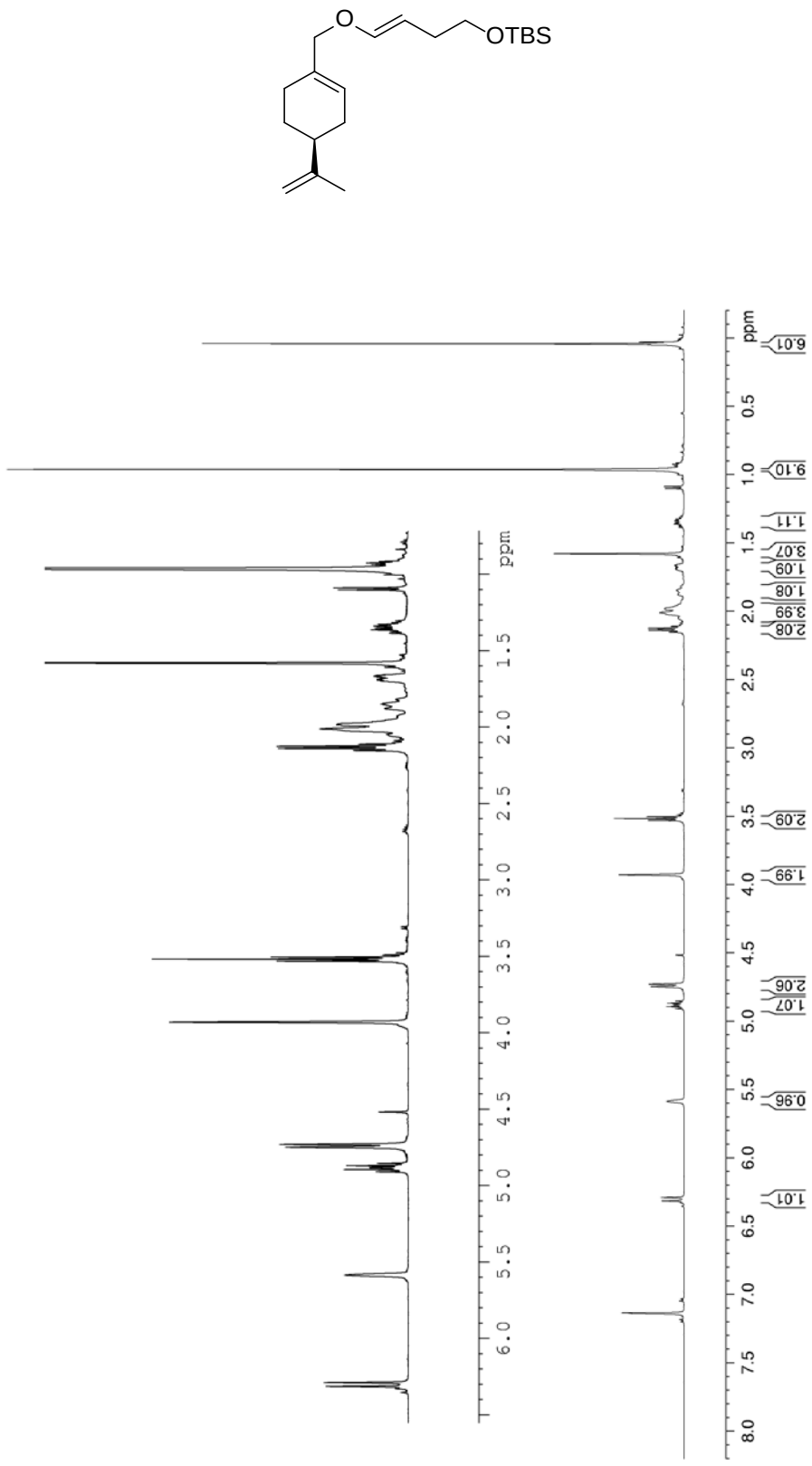
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ppm
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9.10
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1.08
3.99
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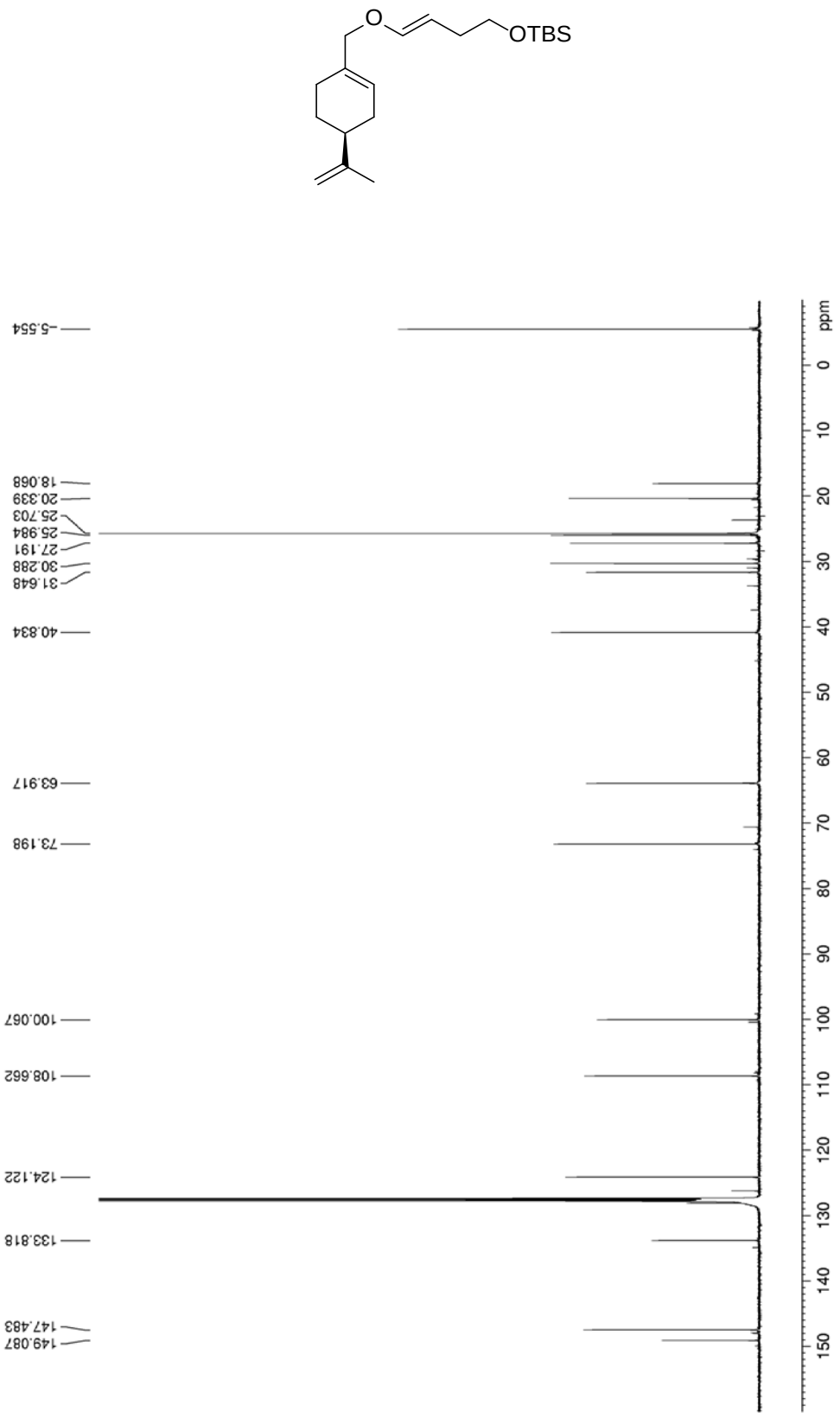
1.99
2.06
1.07
0.96
1.01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27.191
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63.917
73.198
100.067
108.662
124.122
133.818
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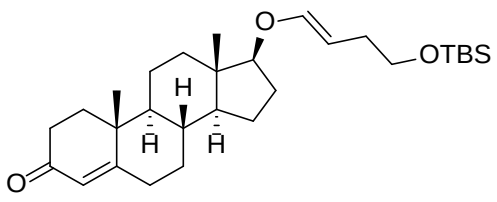
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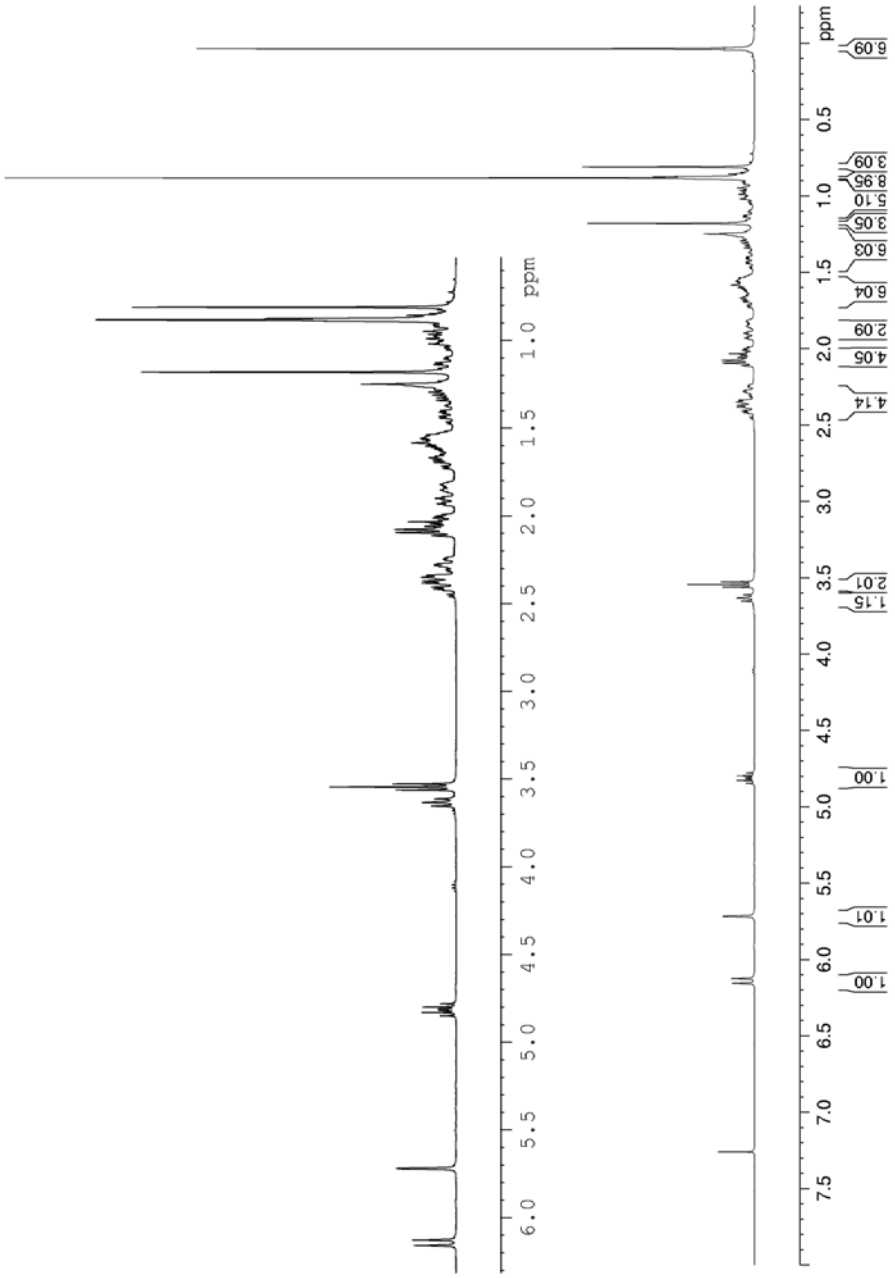
OTBS
H
H
H
O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3.09
8.95
5.10
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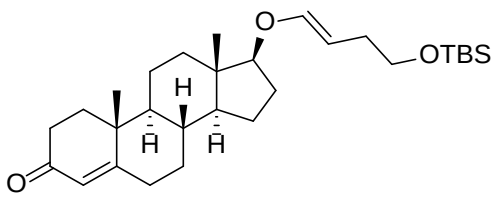
6.04
2.09
4.05
4.14
2.01
1.15
1.00
1.01
1.00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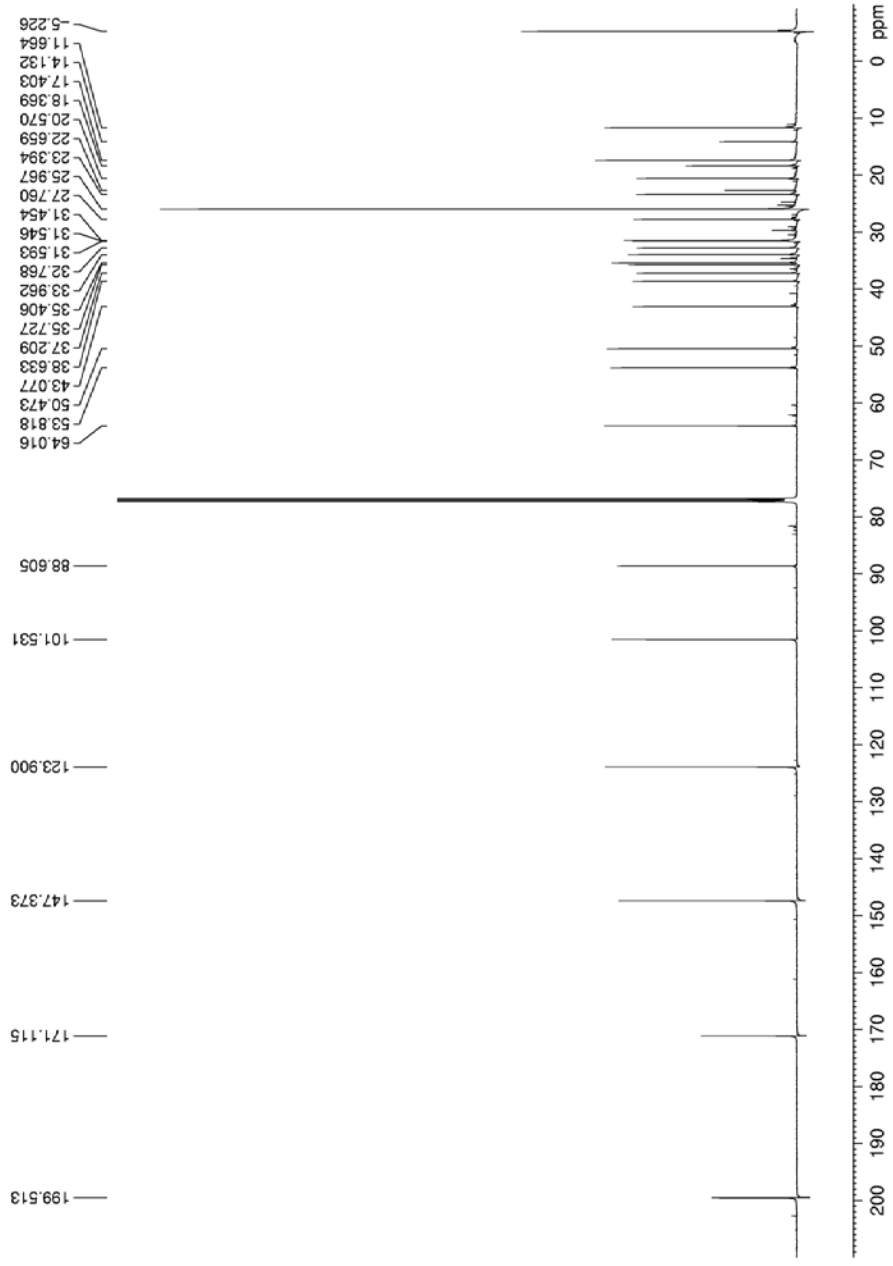
OTBS
H
H
H
O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14.132
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20.570
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23.394
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32.768
33.962
35.406
35.727
37.209
38.633
43.077
50.473
53.818
64.016
88.605
101.531
123.900
147.373
171.115
199.513
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

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