Copper(I) Hydride-Catalyzed Transformations of π-Electrophiles

by

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ABSTRACT

The studies presented in this dissertation are regarding the development of new methods for copper-catalyzed transformations of π-electrophiles. The first part of this dissertation focuses on the development of broadly applicable protocols for the syntheses of enantioenriched homoallylic alcohols (Chapter 2) and homopropargylic amines (Chapter 3). The second part of this dissertation describes a method for accessing synthetically relevant β, γ-unsaturated acceptors (Chapter 4).

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PART I

Chapter 2: Regio- and Enantioselective CuH-Catalyzed Allylation of Ketones Using Terminal Allenes

An efficient method for the copper-catalyzed allylation of ketones is described using widely available terminal allenes as allylmetal surrogates. Homoallylic alcohols bearing a wide range of functional groups are obtained in high yield and with good regio-, diastereo-, and enantioselectivity. Mechanistic investigations implicate the *in situ* formation of isomeric copper(I) allyl complexes which undergo addition to ketones with exclusive branched regioselectivity to afford the major isomer of the product. A stereochemical model is provided to explain the high diastereo- and enantioselectivity of this process.

Chapter 3: Asymmetric Synthesis of Homopropargylic Amines by CuH-Catalyzed Coupling of Imines and Enynes

A novel method for the synthesis of chiral homopropargylic amines is detailed. Aromatic and aliphatic *N*-phosphinoyl aldimines possessing a variety of functional groups are coupled with both terminal and internal enynes under mild conditions. The resulting homopropargylic amines are produced in high yields, with moderate diastereoselectivities and generally high enantioselectivities.

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PART II

Chapter 4: Regio- and Stereoselective Synthesis of β,γ-Unsaturated Compounds by CuH-Catalyzed 1,6-Semireduction

A practical and highly selective preparation of β, γ-unsaturated compounds is reported. This method relies on the CuH-catalyzed 1,6-semireduction of easily accessible α, β, γ, δ-doubly unsaturated acceptors. By using the commercially available wide bite-angle ligand Xantphos, the formation of all undesired isomers and overreduction products is not observed in the majority of cases. The scope of accessible products includes β, γ-unsaturated esters, amides, sulfones, and nitriles with a variety of functional groups. Due to the high volatility of many products, careful purification is required to ensure high yields.

—

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

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This thesis would quite literally have not been possible without the support of my adviser, Prof. Stephen L. Buchwald. Steve, thank you for your advice throughout the years, both personal and professional, and for the straightforward manner in which you have given it. I tell all who ask that you truly wish the best for your students, and I have been blessed to have had the opportunity to work in your lab these past five years. To my Committee Chair Prof. Tim Jamison and Committee Member Prof. Mo Movassaghi, thank you for your encouragement and support throughout the years. To Christine Nguyen, our lab would have long fallen into chaos without your guidance and organization, and I am constantly appreciative of how much you care for every individual in it.

I would be remiss if I did not acknowledge the many individuals who paved the path for me to pursue my graduate studies here at the Massachusetts Institute of Technology. Firstly, my mentors from the MacMillan lab at Princeton, where I completed my undergraduate studies: Prof. David W.C. MacMillan, Ryan Evans, and Jeff Lipshultz, the latter two of whom missed me so much they followed me to Massachusetts (or so I like to think). To you both (and the rest of Bay Awesome), thank you for all of your advice over the years, and for, during my graduate school visits, gently reminding me that no one else would accept me like you have. To my mentors from Amgen, Josh Taygerly, Paul Dransfield, and Alan Cheng: you provided me with my very first research experience, and I treasure the time I spent in South San Francisco, both in the lab and out on our two-hour lunch breaks in the city. To Brett Helms, Laura Gerber, Changyi Li, and the rest of the Helms Group at the Lawrence Berkeley National Lab: I am deeply grateful for the many perspectives I encountered during my summer there, and fondly remember our afternoons watching the goats graze on the hillsides.

Throughout my MIT career, I have been blessed with great mentors who patiently guided me through the many obstacles I faced (or felt like I faced) during my time here. I especially thank Mike Pirnot, who taught me the basics of staying up-to-date on literature, lab etiquette, and how to make time for what matters outside of research, and Richard Liu, with whom I collaborated to some degree on all of my projects, and who continues to provide advice generously. To Veronika Kottisch, Liela Bayeh, and Ryan King: I have appreciated all of the help I received from you in various aspects throughout the years.

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this end of the lab a little more lively; I miss your presences when you're all on the fifth floor. I learned a bit more about bioconjugation and a lot more about sass through our shared space. To Jeff Yang and Frieda Zhang, I have loved our many text messages shared over the years. I appreciate your support, and for sharing stories about struggles and a love for bubble tea and hotpot. COVID-19 threw a wrench in research rhythm, and especially during the time of lab shifts, I was blessed with the company of Alex Schuppe, Levi Knippel, Elaine Reichert, Sheng Feng, and the rest of Group A. To everyone else in the Buchwald group (past and present), it has been a true pleasure working with you all during my time here, and I will cherish the memories we share.

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To Mom, Dad, and Jess: thank you for being the best cheerleaders I could ask for, and for supporting me to the 21st grade. Mom, as I spend more time on my own, I come to appreciate your dedication in making sure our house was clean and I was fed well even more. Thank you for always checking in on me, for sending me care packages with ample snacks, and for reminding me to be kind and gracious to all those I meet. Dad, thank you for teaching me the value of hard work and perseverance through all things, and for instilling in me a love of science and desire to know more. Jess, you've

been the best big sister and role model. Just knowing I can go to you for advice on anything at all helps me feel better every day.

Finally, to the One who makes all things possible, thank you. I never would have imagined these five years to be as fun, stressful, enjoyable, and turbulent as they have been, but You constantly remind me that there are so many things beyond my comprehension.

Sometimes a scream is better than a thesis.

$\sim$ *Ralph Waldo Emerson*

Preface

Portions of this dissertation have been adapted from the following published article co-written by the author and are reproduced with permission from the American Chemical Society.

Tsai, E. Y.; Liu, R. Y.; Yang, Y.; Buchwald, S. L. A Regio- and Enantioselective CuH-Catalyzed Ketone Allylation with Terminal Allenes. *J. Am. Chem. Soc.* **2018**, *140*, 2007–2011.

Respective Contributions

This thesis contains work that is the result of collaborative efforts between the author and other colleagues at MIT. The specific contributions are detailed below.

The work in Chapter 2 was a collaborative effort between Dr. Richard Liu and the author. Dr. Liu is credited with the initial finding of the use of *t*-BuOH and SL-J011-1 for the reaction optimization. Dr. Liu and the author collaborated on the exploration of the substrate scope of the reaction. Deuteration experiments were performed by Dr. Liu. Stoichiometric mechanistic experiments were performed solely by the author.

The work in Chapter 3 was a collaborative effort between Henry Lindner, J. Levi Knippel, Drs. Richard Liu, Liela Bayeh, and Yang Yang, and the author. Dr. Yang is credited with the initial project idea. Drs. Liu and Bayeh are credited with the initial exploration of the stereoselective coupling of imines and enynes. Mr. Lindner conducted the optimization of the reaction conditions. The final substrate scope reactions were explored jointly by Mr. Lindner (compounds 1-5, 7, 10, 12, 14) and the author (compounds 6, 8, 9, 11, 13, 15). Mr. Knippel aided in the characterization of products.

The work in Chapter 4 was a collaborative effort between Dr. Richard Liu and the author. Dr. Liu is credited with the initial exploration of the selective 1,6-semireduction of ethyl sorbate as well as calculation of ligand bite angles. All optimization experiments and explorations of the substrate scope were conducted solely by the author.

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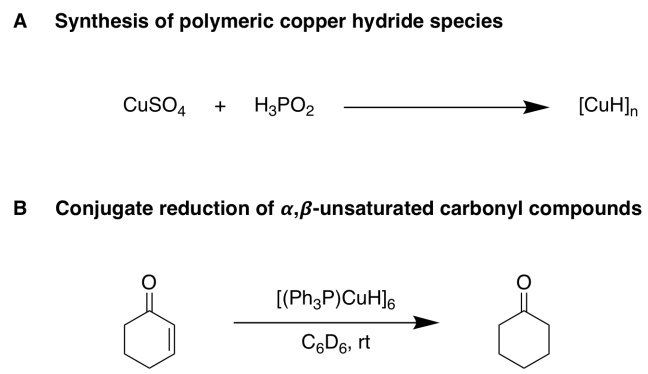
Chapter 1

Introduction to CuH Catalysis in Organic Synthesis

1.1 Discovery of Copper(I) Hydride (CuH)

Copper(I) hydride (CuH) was the earliest binary metal hydride discovered, first synthesized and isolated in polymeric form by Wurtz in 1844 by reduction of $CuSO_4$ with aqueous H_3PO_2 (Figure 1-1A).[1] It is a metastable red solid which readily decomposes into copper and hydrogen gas.[2] Due to its limited solubility and propensity to undergo rapid decomposition, CuH was not applied in organic synthesis for more than a century.

Figure 1-1: Discovery of copper hydride and its use in conjugate reductions



In the 1950s, Gilman[3] and Whitesides[4] observed the reactivity of copper hydride and reported various conjugate 1,4-reduction and substitution reactions promoted by alkylcopper and cuprate complexes. However, CuH was not widely researched or utilized until the late 1980s, at which time Stryker[5] observed that phosphine ligands stabilized the metal hydride, and the resultant phosphine-ligated CuH complexes were able to effect highly chemoselective reduction reactions with high functional group tolerance (Figure 1-1B). Notably, Stryker's reagent $[(Ph_3P)CuH]_6$ was discovered to be a mild and selective reductant for conjugate reductions of α,β-unsaturated carbonyl compounds. This groundbreaking achievement paved the way for the vast body of research that has ensued.[6]

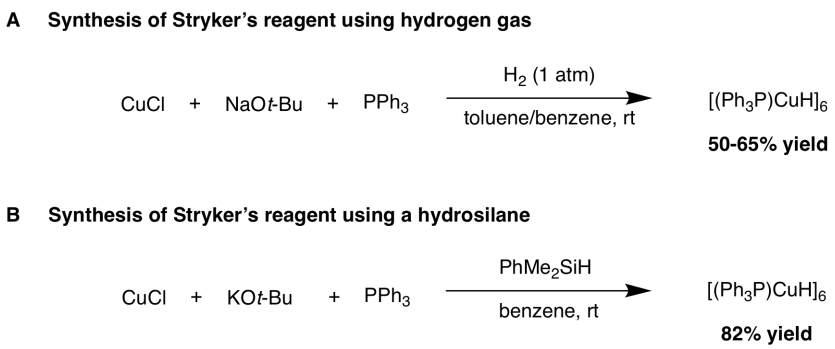
In this chapter, we summarize major developments in the utilization of CuH in organic synthesis, organized around three main topics: (1) the use of phosphine-ligated CuH as a catalyst, employing sacrificial hydride sources; (2) the development of asymmetric 1,4- and 1,2-reduction reactions; and (3) the expansion of CuH catalysis to olefin hydrofunctionalization reactions.

1.2 Development of Cu-Catalyzed Reactions

Methods to form CuH *in situ* were crucial to their utilization in synthesis and catalysis, due to the limited stability of isolated CuH complexes. Traditionally, the most common approach to generate CuH has involved the transmetallation of ligated copper alkoxides with an appropriate hydride source. For instance, the seminal preparation of Stryker's reagent employed hydrogen gas with $(Ph_3P)CuO$*t*-Bu, formed from a mixture of CuCl, phosphine, and KO*t*-Bu (Figure 1-2A).[5a 7] Not long after the initial investigations on stoichiometric uses of $[(Ph_3P)CuH]_6$, Stryker reported a catalytic 1,4-conjugate reduction employing hydrogen as the terminal reductant.[8] However, the high pressure of hydrogen gas required limited the practicality of this procedure and posed a safety concern.

These issues were soon addressed by the development of processes utilizing hydrosilanes instead of hydrogen as the hydride source (Figure 1-2B). Silanes are the most commonly employed hydride sources, since they are relatively low-cost, stable, and usually environmentally benign.[9] A variety of copper salts has also been shown to be effective precursors for the reactive CuH species.[10,11] Given the instability of "ligandless" CuH, a dative ligand is typically present in the reaction mixture. To date, CuH compounds with a wide variety of mono- and bisphosphine ligands, as well as NHC ligands, have been reported.

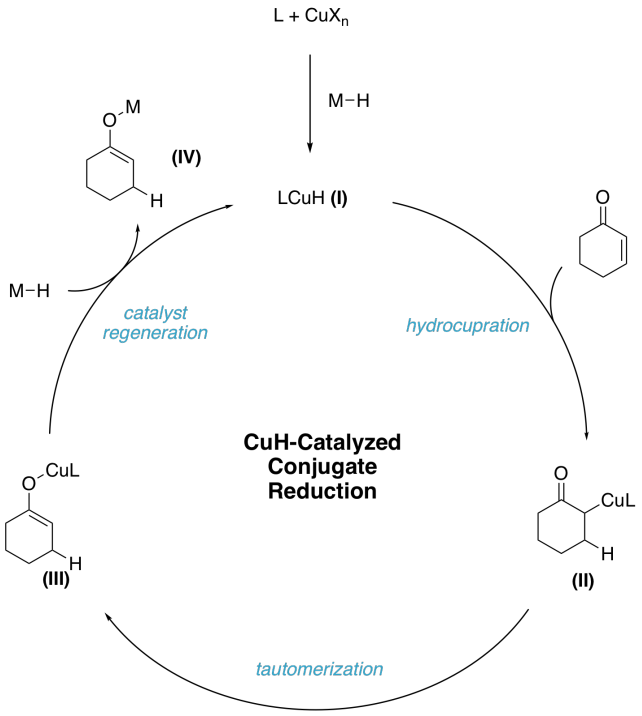
Figure 1-2: Synthesis of Stryker's reagent $[(Ph_3P)CuH]_6$ using (a) hydrogen gas and (b) a hydrosilane



The ability to reliably form CuH from a range of copper complexes is crucial for the versatility of CuH catalysis; this flexibility allows for the regeneration of CuH from species such as copper enolates or alkoxide complexes. As an example, the mechanism for the the CuH-catalyzed 1,4-reduction of enones is depicted in Figure 1-3. LCuH **(I)** is first generated from a copper precursor (CuX_n), ligand (L), and hydride source (M–H).

Reaction of this species with the C=C double bond of an enone generates copper enolate **II**. Isomerization of the copper generates *O*-bound enolate **III**, which then undergoes σ-bond metathesis with a hydride source to regenerate the CuH complex **I** and afford compound **IV**.

Figure 1-3: Mechanism for CuH-catalyzed 1,4-reduction of enones



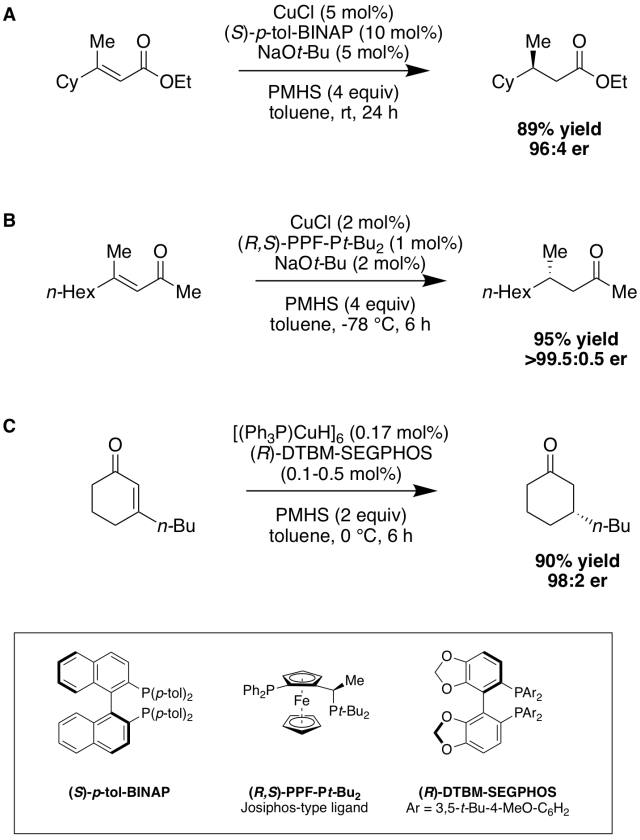
1.3 Asymmetric Reduction Reactions

An important advancement in the field was achieved in the 1990s, when Buchwald reported the first enantioselective conjugate reduction utilizing an *in situ*-generated chiral (*S*)-*p*-tol-BINAP-ligated CuH species (Figure 1-4A).[12] The addition of several equivalents of a hindered alcohol such as *t*-BuOH was observed to dramatically increase the rate of the catalytic process, a finding which would prove to be applicable to many CuH-catalyzed reactions in the future.

Further improvements to the area of CuH-catalyzed asymmetric reductions came rapidly, propelled by Lipshutz's discovery that ligation with SEGPHOS (for cyclic enones) and JOSIPHOS (for acyclic enones) produced copper complexes that were more reactive and achieved higher levels of enantioselectivity than the BINAP-based species

(Figure 1-4B, C).[13] Since then, the scope of CuH-catalyzed 1,4-conjugate reduction has widened to include other Michael acceptors.[14]

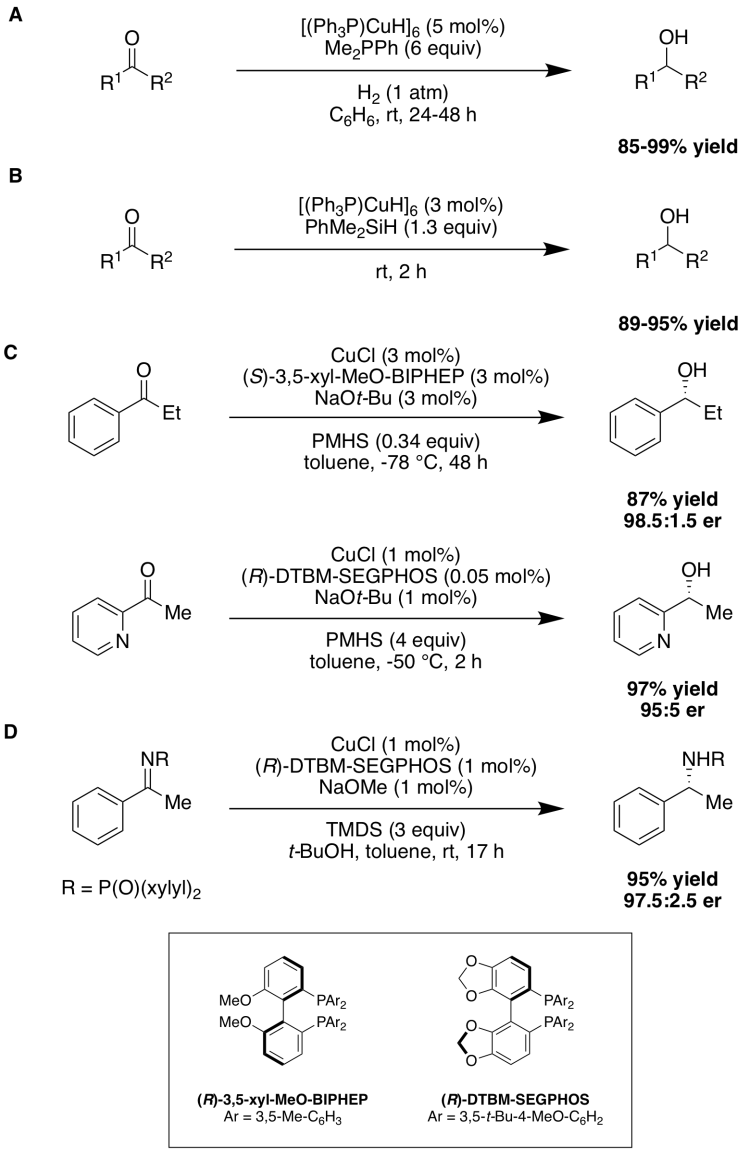
Figure 1-4: Representative examples of enantioselective CuH-catalyzed conjugate reductions



A number of enantioselective 1,2-reductions of carbonyl compounds have also been reported. Seminal work by Stryker showed that by adding dialkylarylphosphines, the 1,4-reduction of enals can be suppressed to allow for direct 1,2-reduction (Figure 1-5A).[15] Lipshutz and co-workers amended the protocol to employ silanes as the reductant (Figure 1-5B).[16] Stereoselective systems followed shortly after (Figure 1-5C).[17,18,19]

While extensive research on catalytic asymmetric reductions of carbonyl compounds exists, the analogous transformations of imines are more challenging, presumably due to difficult catalyst turnover as a result of the formation of a strong Cu–N bond following imine reduction. Additionally, many imines exist as *E/Z* mixtures, which may impact selectivity and reactivity. One approach to overcome these issues is to employ an imine protecting group with bulky and electron-withdrawing substituents, as demonstrated by Lipshutz (Figure 1-5D).[20]

Figure 1-5: Representative examples of CuH-catalyzed asymmetric 1,2-reductions



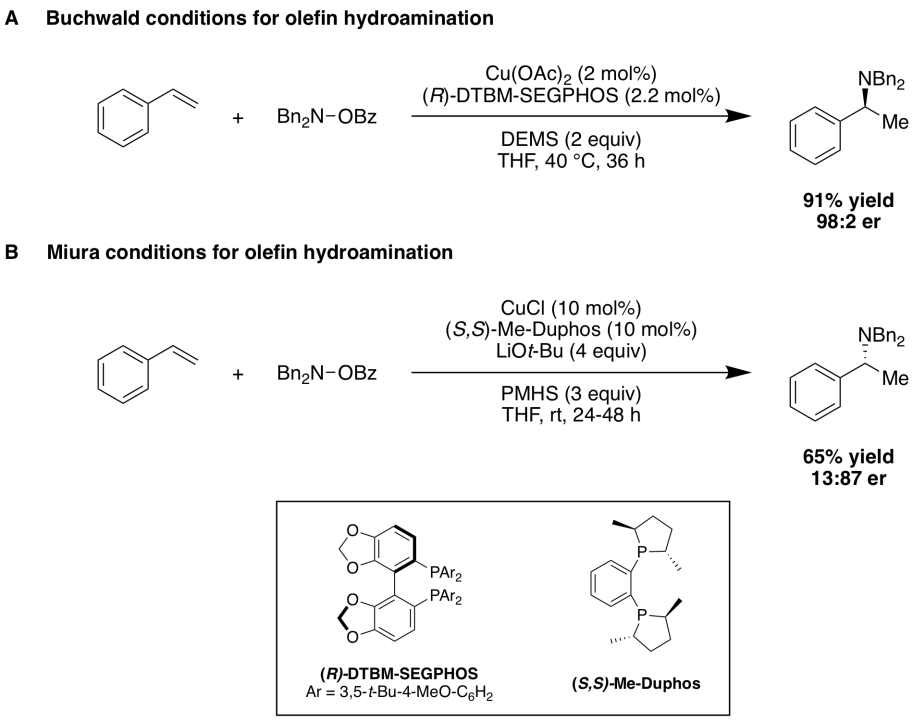
1.4 Olefin Hydrofunctionalizaton

During the development of CuH-catalyzed asymmetric conjugate reduction reactions, it was demonstrated that the organocopper intermediate formed immediately after hydrocupration could be engaged in further bond-forming events, rather than immediately closing the catalytic cycle. The potential to expand this concept to olefins would allow for the formation of a variety of useful organometallic intermediates. However, two major challenges had to be overcome: 1) olefins without strong activating groups are typically slow to undergo hydrocupration, and 2) the electrophile must be reactive enough to

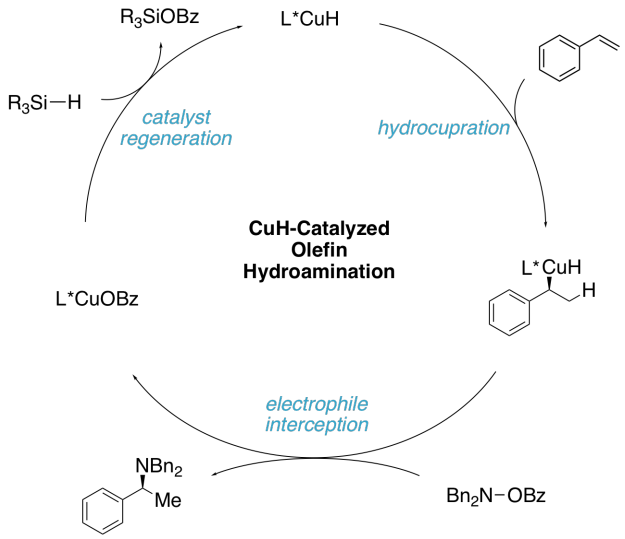
engage the organocopper species, but not so reactive as to undergo direct reduction by CuH prior to insertion of the olefin. The primary method for overcoming these barriers has proven to be careful selection of the ligand system employed. Additionally, electronic and steric effects of the electrophile, as well as slow addition of the electrophilic component, have been utilized.

In 2013, Buchwald[21] and Miura[22] independently reported the CuH-catalyzed hydroamination of styrenes (Figure 1-6A, B). The key step in these transformations involves stereoselective Markovnikov addition of a bisphosphine-ligated CuH species across the C–C double bond, followed by the interception of the putative phenethyl copper species by hydroxylamine esters (Figure 1-6C). This formal hydroamination process allows for the generation of chiral trialkyl amines in a highly regio- and enantioselective manner under mild conditions. In particular, using catalysts derived from the very bulky ligand DTBM-SEGPHOS, Buchwald reported the synthesis of a variety of benzylic and linear aliphatic amines with excellent enantioselectivity.[21] Following this initial report, the hydroaminations of terminal alkenes,[21] 1,1-disubstituted alkenes,[23] vinyl silanes,[24] vinyl boronates,[25] alkynes,[26], and even some unactivated internal alkenes[27] were achieved.

Figure 1-6: Enantioselective CuH-catalyzed olefin hydroamination reactions

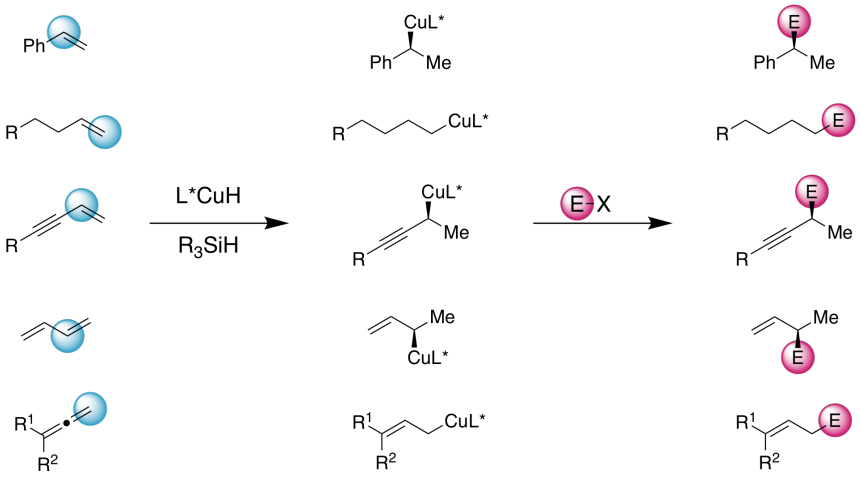


C Proposed mechanism for CuH-catalyzed ketone allylation



Since this discovery, many additional asymmetric olefin hydrofunctionalization reactions were realized by intercepting the *in situ*-generated alkyl copper intermediates with a variety of other electrophiles (Figure 1-7).[28] Several C–C bond-forming reactions of olefins have also been developed.[29] The mild conditions of the CuH catalytic system usually lead to better functional group compatibility when compared to the corresponding reactions performed with stochiometric organometallic reagents. Moreover, the use of chiral ligands provides the opportunity for installation of stereogenic centers with high efficiency.

Figure 1-7: Examples of olefin coupling partners in CuH-catalyzed asymmetric hydrofunctionalization reactions



This dissertation focuses on further development of CuH catalysis for organic synthesis. Chapter 2 discusses the development of a CuH-catalyzed regio- and stereoselective addition of allene-derived allylic nucleophiles to ketones. Chapter 3 explores the nucleophilic addition of alkyl copper species through the regio- and stereoselective coupling of imines and enynes to form chiral homopropargylic amines. Finally, Chapter 4 details the selective 1,6-conjugate reduction of $\alpha,\beta,\gamma,\delta$-unsaturated acceptors to provide β,γ-unsaturated compounds.

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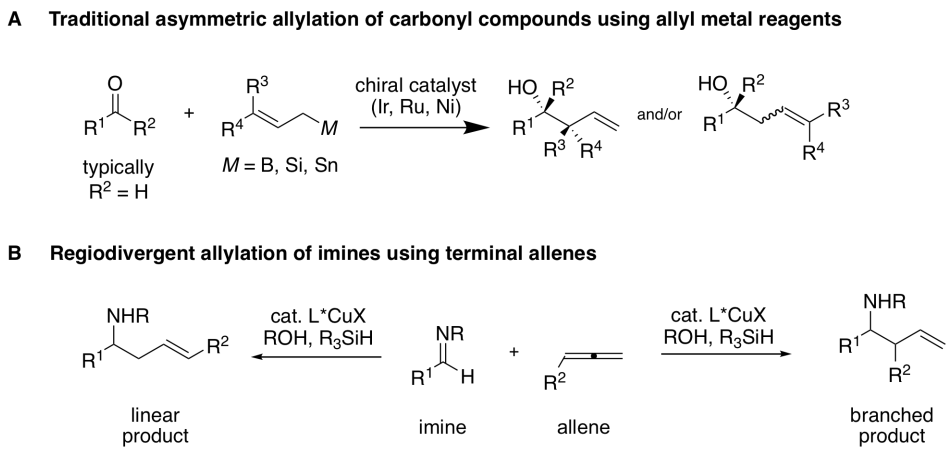
Chapter 2

Regio- and Enantioselective CuH-Catalyzed Allylation of Ketones Using Terminal Allenes

2.1 Introduction

Chiral alcohols and their derivatives are common and essential substructures in biologically active compounds. Thus, reactions that generate alcohols in a stereoselective manner represent fundamental transformations in organic synthesis. In particular, the nucleophilic addition of an allyl group to carbonyl compounds, producing synthetically versatile homoallylic alcohols, has been a subject of extensive investigation (Figure 2-1A).[1] Despite the invention of several successful implementations, such approaches usually require the prior preparation of super-stoichiometric quantities of an allylmetal reagent in a separate operation.[2,3,4,5,6,7,8,9,10,11,12] Often, this process is itself required to be highly stereoselective in order for the subsequent allylation step to be effective. Although general solutions exist for simple nucleophiles, such as allyl-, crotyl-, or cinnamyl metal complexes,[13] practical reagents for installation of complex allyl fragments are rare, and their synthesis typically requires the use of strong bases, restricting compatibility with acidic or polar functional groups.

Figure 2-1: Overview of metal-catalyzed reductive allylation reactions

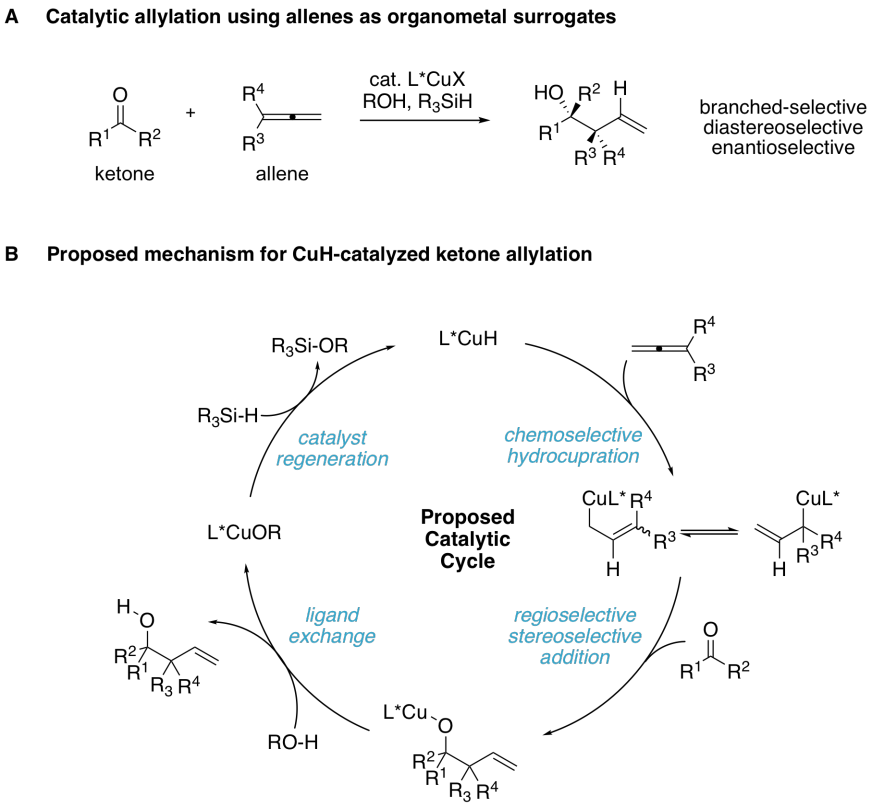


Recently, our laboratory has reported several methods involving *in situ* generation of organocopper nucleophiles via the hydrocupration of unsaturated substrates.[14,15] Originally developed in the context of hydroamination reactions,[15l,m] this hydrometalation–functionalization strategy has also found success in reductive coupling with carbon-centered electrophiles, most notably imines.[15e,f,g] In the context of allylation specifically, we were inspired by pioneering work by Krische and others using aldehydes and activated ketones.[16,17,18,19,20,21,22,23,24] In general, typical ketones are challenging electrophilic partners for stereoselective coupling relative to aldehydes, due to their attenuated reactivity and minimal steric differentiation between the carbonyl substituents. We were

however encouraged by prior work in our laboratory reporting the selective allylation of imines with terminal allenes (Figure 2-1B).

Our proposal, described in Figure 2-2A, takes advantage of the ability of phosphine ligated copper hydride complexes to catalytically generate a mixture of allylcopper species when exposed to terminal allenes.[11a,c,f,15e] Notably, the rate of this process needs to surpass the rate of direct ketone reduction, which has been shown to be a fast process.[25,26] Based on theoretical studies on the addition of these nucleophiles to imines,[15e] we anticipated allyl addition to ketones would take place with exclusive branched regioselectivity. To complete the catalytic cycle, the initial hydride complex would be regenerated either by direct metathesis with a hydrosilane, or via intermediate ligand exchange with an auxiliary alcohol (Figure 2-2B).

Figure 2-2: Overview of CuH-catalyzed reductive allylation reaction of ketones using terminal allenes

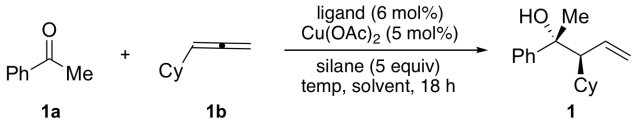


2.2 Results and Discussion

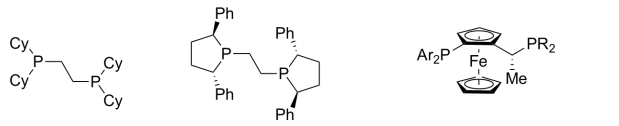
2.2.1 Reaction Optimization

Initial investigations of this transformation were focused on the reductive coupling of acetophenone (**1a**) with cyclohexylallene (**1b**) under previously described reaction conditions for imine allylation (Table 1, entry 1). With a simple achiral supporting ligand, the desired product **1** was obtained in high yield, with exclusive branched-selectivity, and with moderate preference for the indicated diastereomer (5:1 dr). When chiral phosphine *(S,S)*-Ph-BPE was employed, high enantioselectivity and yield were obtained (Table 1, entry 2). Lowering the reaction temperature slightly and switching the solvent to toluene proved to be beneficial (Table 1, entry 5). Further evaluation of common chiral ligands revealed JOSIPHOS-type phosphine **D**[27] to be optimal (Table 1, entry 6). The effect of *t*-BuOH on the observed diastereo- and enantioselectivity is notable, although its role remains unclear (Table 1, entry 7).

Table 2-1: Evaluation of Reaction Conditions for the CuH-Catalyzed Allylation of Acetophenone[a]



Entry	Ligand	Solvent	Temp (°C)	Yield[b] (%)	er[c]
1	A	THF	25	95 (5:1 dr)	-
2	B	THF	5	90 (7:1 dr)	93:7
3	B	THF	0	91 (8:1 dr)	94:6
4	B	PhMe	0	95 (8:1 dr)	95:5
5	C	PhMe	0	76 (10:1 dr)	96:4
6	D	PhMe	0	97 (14:1 dr)	98:2
7[d]	D	PhMe	0	90 (9:1 dr)	96:4
8	E	PhMe	0	50 (2:1 dr)	58:42



DCyPE (**A**) (*S,S*)-Ph-BPE (**B**)

R = *t*-Bu, Ar = 4-MeO-3,5-Me-C_6H_2 (**C**)
R = *t*-Bu, Ar = 4-CF_3-C_6H_4 (**D**)
R = Ar = Cy (**E**)

[a] Conditions: 0.10 mmol ketone (1.0 equiv), allene (2.0 equiv), copper(II) acetate (0.050 equiv), ligand (0.060 equiv), dimethoxy(methyl)silane (5.0 equiv), *tert*-butanol (2.0 equiv) in solvent

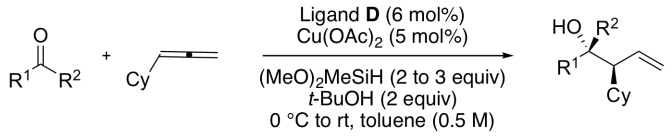
(0.2 mL); see the Experimental for details. [b] Yield and diastereomeric ratio was determined by ^{1}H NMR spectroscopy of the crude mixture, using 1,1,2,2-tetrachloroethane as internal standard. [c] Enantiomeric excess was determined by HPLC or SFC analysis on commercial chiral columns. [d] Reaction conducted without *tert*-butanol.

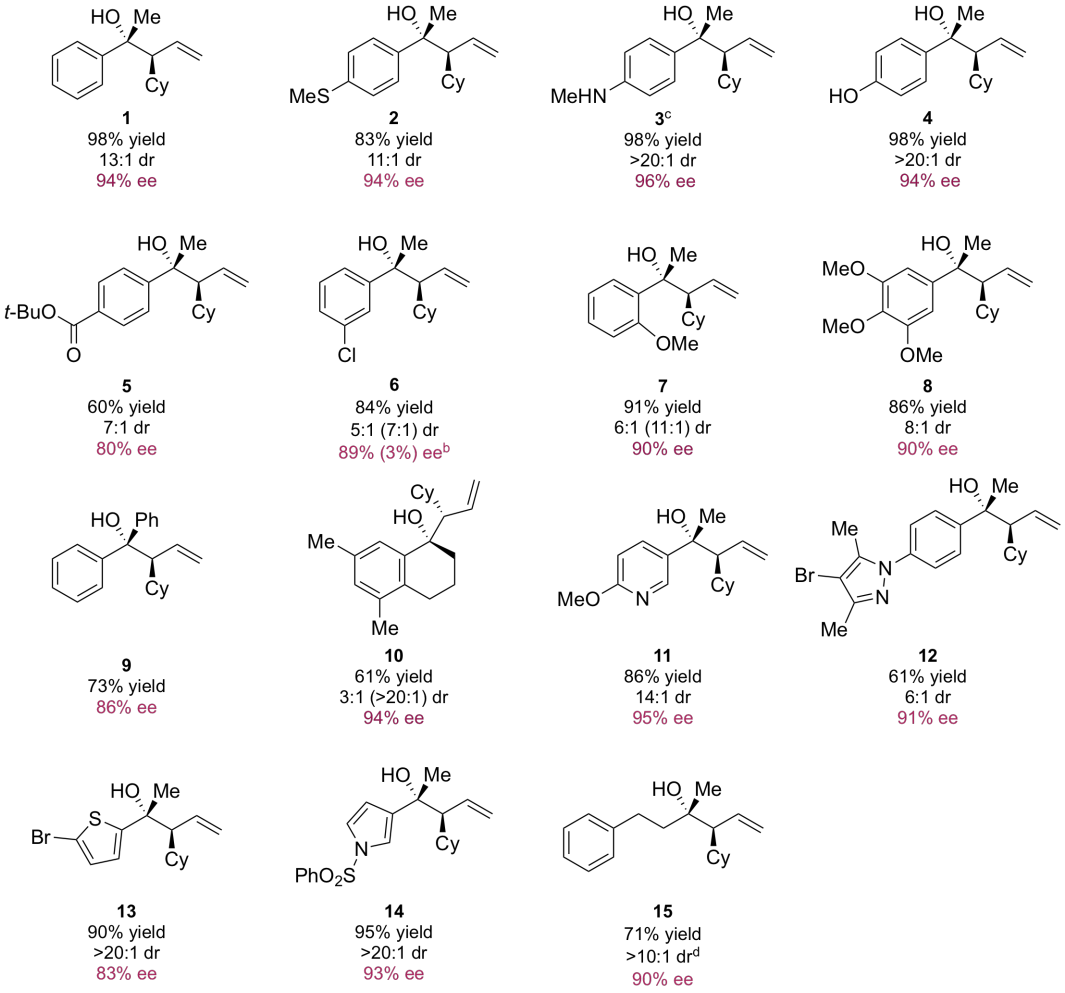
2.2.2 Substrate Scope

Upon scaling up the optimal conditions to preparative quantities of material, we found that only a small excess of allene (1.2 equiv) and DMMS (2.0 equiv)[28] were necessary to obtain high yields and selectivity, for instance in the case of model compound **1** (Table 2). The reaction proceeded efficiently with substrates bearing electron-donating (**3, 4**) or electron-withdrawing (**6**) substituents, although **5** was only obtained in moderate yield. Acetophenones bearing ortho-substituents were converted successfully, as well as symmetrical (**9**) or cyclic (**10**) ketones. Furthermore, substrates containing heterocycles (**11**–**14**) and those with functional groups such as a free hydroxyl group (**4**), a secondary amine (**3**), aryl halides (**6, 12**), a sulfonyl protecting group (**14**), and *tert*-butyl ester (**5**) were all tolerated under the reaction conditions, providing opportunities for further elaboration. Finally, dialkyl ketone **15** was converted, notably with high diastereoselectivity considering the steric similarity of the methyl and methylene substituents on the ketone. In all cases, the reaction proceeded with useful to good enantioselectivity. A crystal structure of **8** showed the absolute configuration of the major enantiomer to be *(R)* at the tetrasubstituted stereocenter and *(S)* at the adjacent methane. We note that the relative configuration of these stereocenters is consistent with addition through a chair-like 6-membered transition state.

We next assessed the scope of compatible allenes under these conditions. Unbranched (**16**) and 1,1-disubstituted (**17**) allenes are both coupled with high enantioselectivity. A commercial ether, methoxyallene, was employed effectively as a precursor for an (alkoxy)allylmetal nucleophile (**18**), which is rarely utilized in ketone additions even when prepared stoichiometrically. Various polar functional groups are tolerated well on the allene component, including an alcohol (**19**), an ester (**20**), and a secondary amide (**21**). An allene bearing a nitrogen heterocycle (**22**) reacted efficiently and with a high level of enantioselectivity. Under these conditions, addition of the parent allyl fragment derived from allene gas proceeds with only moderate selectivity (**23**); however, further investigation by our lab led to modified conditions which achieve high selectivity.[29]

Table 2-2: Evaluation of Ketone Scope[a]

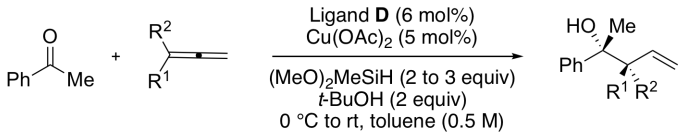


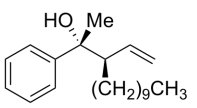


[a] Yields, diastereomeric ratios, and enantiomeric excesses are the averages for two identical runs. Yields indicate isolated yield of product as a mixture of two diastereomers on a 0.50 mmol scale. 1.2 equiv of allene was used, see Experimental for further details. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy for both the crude and purified products using 1,1,2,2-tetrachloroethane as internal standard. Diastereomeric ratios of purified products indicated in parentheses when different from the crude diastereomeric ratio. Enantiomeric excesses determined by HPLC or SFC analysis on commercial chiral columns. [b] Enantiomeric excesses of minor diastereomers indicated in parentheses. [c] The reaction was conducted without *tert*-butanol. [d] The diastereomeric ratio was determined using both GC and chiral

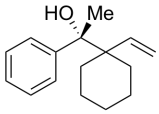
SFC analysis.

Table 2-3: Evaluation of Allene Scope[a,b]

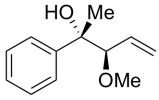




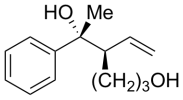
16
87% yield
3:1 (3:1) dr
87% (95%) ee



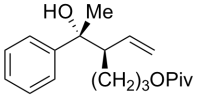
17
89% yield
90% ee



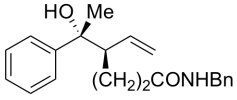
18
76% yield
2.5:1 (2.5:1) dr
92% (89%) ee



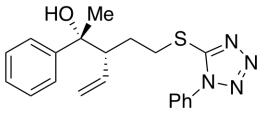
19
97% yield
2.5:1 (2.5:1) dr
>99% (75%) ee



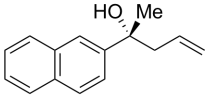
20
97% yield
7:1 dr
83% (82%) ee



21
63% yield
2:1 (3.5:1) dr
94% (83%) ee



22
80% yield
3:1 (3:1) dr
93% (84%) ee



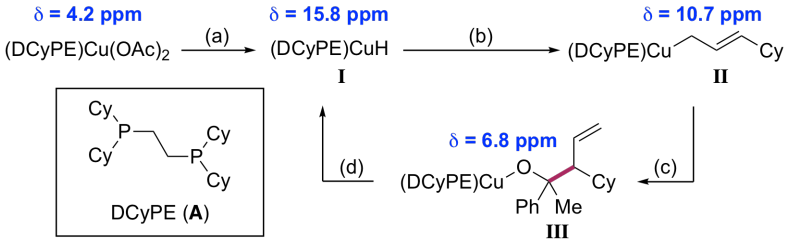
23
95% yield
62% ee

[a] Yields, diastereomeric ratios, and enantiomeric excesses are the averages for two identical runs. Yields indicate isolated yield of product as a mixture of two diastereomers on a 0.50 mmol scale. 1.2 equiv of allene was used, see Experimental for further details. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy for both the crude and purified products using 1,1,2,2-tetrachloroethane as internal standard. Enantiomeric excesses determined by HPLC or SFC analysis on commercial chiral columns. [b] Enantiomeric excesses of minor diastereomers indicated in parentheses.

We also carried out a number of experiments by NMR to corroborate the plausibility of our mechanistic proposal (Scheme 1). For the purpose of these studies, we chose the achiral but kinetically competent ligand DCyPE (**A**) for these studies. The putative copper hydride complex was prepared stoichiometrically by addition of 1.0 equivalent of DMMS to phosphine ligated copper(I) acetate complex **I**. From here, addition of excess cyclohexylallene led to insertion, forming complex **II** with spectroscopic properties consistent with that of a linear allyl copper species (based on ^{1}H and ^{31}P NMR spectroscopy, see Experimental). The observed linear allylcopper complex also has been previously predicted by DFT studies to be the lowest energy isomer.[15e] As expected, addition of excess acetophenone resulted in insertion to form the copper-alkoxide complex **III** of

the desired tertiary alcohol product. This complex can be reconverted into the initial hydride complex **I** directly upon addition of an excess of hydrosilane. Having observed each of the proposed intermediates by ^{31}P NMR spectroscopy, we aimed to determine the resting state of the copper catalyst under the standard reaction conditions. Examination of the reaction mixture by ^{31}P NMR spectroscopy during a catalytic reaction starting with DCyPE-ligated copper hydride complex **I** revealed a single resonance at 10.7 ppm matching the chemical shift of the copper allyl species **II**. Thus, we conclude that the catalyst is predominantly present in the allylcopper form under the typical reaction conditions. Therefore, since we propose that addition to the ketone is irreversible and stereoselectivity-determining, we suggest that this step is also turnover-limiting.

Figure 2-3: Stoichiometric Observation of Relevant Reaction Intermediates by ^{31}P NMR Spectroscopy



Values shown in blue are chemical shifts of the phosphorus atoms in major species shown; see Experimental for details. (a) $(MeO)_2MeSiH$, benzene; (b) cyclohexylallene, benzene; (c) acetophenone, benzene; (d) $(MeO)_2MeSiH$.

2.3 Conclusion

In summary, we have developed a mild, base metal-catalyzed asymmetric allylation of ketones from terminal allenes. Based upon this discovery, methods for ketone allylation employing allene gas[29] and 1,3-dienes[30] as nucleophilic precursors have also been discovered. We anticipate that the chemoselective hydrocupration–1,2-addition sequence demonstrated here will continue to serve as a platform for the development of further synthetically useful transformations of unsaturated compounds.

2.4 Experimental

2.4.1 General Reagent Information

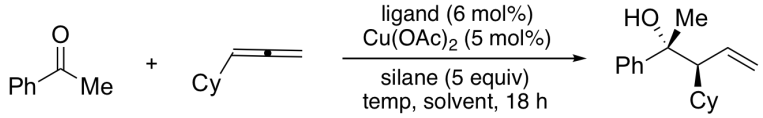
Unless noted otherwise, reagents and substrates were purchased from commercial vendors and used as supplied. SL-J011-1 was obtained from Aldrich (Aldrich catalog number 88735) and through a generous donation from Solvias. Copper(II) acetate was purchased from Strem (amorphous powder, 97% min.) and used directly. Dimethoxymethylsilane (DMMS, moisture-sensitive) was purchased from TCI-America. (Caution: Dimethoxy(methyl)silane (DMMS, CAS #16881-77-9) is listed by several vendors (TCI, Alfa Aesar) SDS or MSDS as a H318, a category 1 Causes Serious Eye Damage. Other vendors (Millipore-Sigma, Gelest) list DMMS as a H319, a category II Eye Irritant. DMMS should be handled in a well-ventilated fumehood using proper precaution as outlined for the handling of hazardous materials in "Prudent Practices in the Laboratory."[31] At the end of the reaction either ammonium fluoride in methanol, aqueous sodium hydroxide (1 M), or aqueous hydrochloric acid (1 M) should be carefully added to the reaction mixture. The resulting mixture should be allowed to stir for at least 30 minutes or the time indicated in the detailed reaction procedure.) All other reagents were purchased from Millipore-Sigma, Alfa Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific and were used as received. Toluene was obtained from J.T. Baker in CYCLE-TAINER® delivery kegs and purified by successive filtrations though packed columns of neutral alumina and copper(II) oxide under argon pressure; EtOAc and hexanes used in chromatography eluents for allylation products and their derivatives were reagent grade from Millipore-Sigma. Flash chromatography was performed on wet-loaded, manually eluted silica columns using SiliCycle SiliaFlash® F60 silica gel (40-63 μm, 230-400 mesh, 60 Å pore diameter) with the aid of a Biotage Isolera Automated Flash Chromatography System. Analtech Uniplate™ preparative thin-layer chromatography (TLC) plates (silica gel GF, 1000 μm, UV254 indicator, 20 x 20 cm) were employed in preparative TLC purifications. Reactions were performed in glass culture tubes with threaded ends (Fisher Scientific part #1495935A; oven-dried at 140 °C for at least 16 h prior to use) that were sealed with screw-thread caps (Kimble-Chase part #73804-15425) fitted with PTFE/silicone septa (Thermo Fisher scientific part #B799515).

2.4.2 General Analytical Information

^{1}H and ^{13}C NMR spectra were recorded using a Bruker 401 MHz spectrometer. ^{31}P and ^{19}F NMR spectra were recorded using a Varian 300 MHz spectrometer. Chemical shifts of ^{1}H NMR signals are referenced to the indicated residual solvent peak ($CDCl_3$, δ = 7.26 ppm) and reported in ppm relative to tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm) and all were obtained with ^{1}H decoupling. $CDCl_3$ was obtained from Cambridge Isotope Laboratories. IR spectra were acquired from neat samples using a Thermo Scientific Nicolet iS5 spectrometer equipped with an iD5 diamond laminate AtR accessory, and representative peaks are reported as wavenumbers in units of cm^{-1}. Specific optical rotations were recorded for chloroform solutions at a standard concentration of 1 mg/mL using a Jasco model P-1010 polarimeter. Melting points were obtained on a Mel-Temp capillary melting point apparatus. High-resolution mass spectrometry was performed using a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer.

Elemental analyses were performed for carbon and hydrogen by Atlantic Microlabs Inc., Norcross, GA. The enantiomeric excesses of products (ee) were determined by chiral SFC analysis using a Waters Acquity UPC2 instrument or by high performance liquid chromatography (HPLC). Specific columns and analytical methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analyses are provided with the associated chromatograms. Gas Chromatography (GC) was performed using an Agilent 7890A gas chromatograph equipped with an FID detector and a JW DB-1 column (10 mm, 0.1 mm I.D.). Analytical TLC was performed using Silicycle SilicaPlate® glass-backed extra-hard-layer TLC plates (60 Å, 250 μm thickness, 20 x 20 cm, UV-254 indicator) and visualization with 254 nm light.

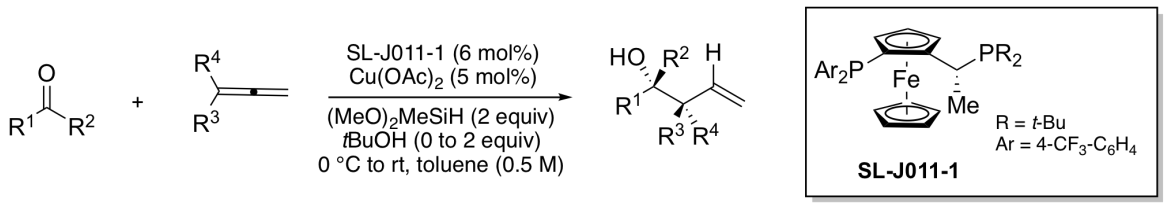
2.4.3 Reaction Optimization Procedures



In a nitrogen-filled glovebox, a small reaction tube (Fischer Scientific part #1495935C) equipped with a magnetic stir bar was charged with ketone (0.10 mmol), allene (1.0 to 2.0 equiv), copper(II) acetate (5 mg, 0.050 equiv), ligand (0.060 equiv), *t*-BuOH (0.0 to 2.0 equiv), and solvent (0.2 mL). The vial was capped with a screw cap containing a septum insert (Fischer Scientific part #C4015-66A), removed from the glove box, and submerged partially into an ice bath or room-temperature water bath.

Dimethoxymethylsilane (DMMS, 2.0 to 5.0 equiv) was added by syringe in one portion by piercing the septum with the needle, and the reaction mixture was stirred for 18 h. The solution was warmed to room temperature if necessary, and the cap was removed. The reaction was quenched by adding saturated ammonium fluoride in methanol dropwise using a 3 mL syringe (1 mL, **WARNING: VIGOROUS HYDROGEN EVOLUTION**) and stirred for 30 min at room temperature. After removal of solvent under reduced pressure with aid of a rotary evaporator, the yield and diastereomeric ratio (dr) were assessed by ^{1}H NMR in $CDCl_3$, using 1,1,2,2-tetrachloroethane as an internal standard. The mixture was separated by preparative TLC, and the product was isolated. The enantiomeric excess was determined by SFC analysis.

2.4.4 General Procedure for the Allylation of Ketones with Terminal Allenes

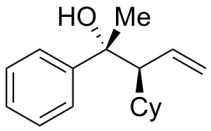


Inside a nitrogen-filled glovebox, a glass culture tube (Fisher Scientific part #14-959-35A) equipped with a magnetic stir bar was charged with ketone (0.50 mmol), allene (0.60 mmol, 1.2 equiv), copper(II) acetate (5 mg, 0.025 mmol, 0.050 equiv), Josiphos ligand SL-J011-1 (21 mg, 0.030 mmol, 0.060 equiv), *t*-BuOH (0.0 to 1.0 mmol, 0.0 to 2.0 equiv), and toluene (1 mL). The tube was then fitted with a Teflon-lined blow-out screw cap (Kimble-Chase part #73804-15425). A 1 mL syringe fitted with a needle was filled with DMMS (0.124 mL, 1.0 mmol, 2.0 equiv). The reaction tube and syringe were removed from the glovebox. The reaction tube was cooled to 0 °C in an ice bath and while the tube was under nitrogen, the DMMS was added after 5 min by piercing the Teflon septum with the needle. The solution was then stirred at 0 °C and slowly allowed to warm to room temperature. The mixture was stirred for a total of 18 h. The cap was removed and the reaction was quenched by adding saturated ammonium fluoride in methanol dropwise using a 6 mL syringe (5 mL, **WARNING: VIGOROUS HYDROGEN EVOLUTION**) and stirred for 30 min. A small quantity was removed, concentrated *in vacuo* with aid of a rotary evaporator, dissolved in $CDCl_3$, and analyzed by ^{1}H NMR to determine the diastereomeric ratio (dr). After combining the crude material, the resulting mixture was filtered through a pipette filter packed with cotton

and Celite®, and the filtrate was concentrated under reduced pressure with the aid of a rotary evaporator. The resulting oil was dissolved in chloroform and the compound purified by column chromatography or preparative TLC, then dried under high vacuum for at least 16 h to provide the desired allylation product.

2.4.5 Synthesis and Characterization Data for Allylation Products

(2*R*,3*S*)-3-cyclohexyl-2-phenylpent-4-en-2-ol (1)

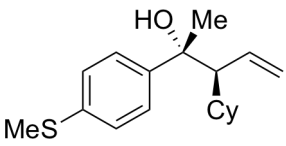


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a pale, yellow oil (121 mg, 99% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.60 (major) and 5.74 (minor)] of the unpurified reaction mixture indicated a 13:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.30–7.20 (m, 2H), 7.14 (t, J = 5.7 Hz, 2H), 7.08–7.02 (m, 1H), 5.60 (dt, J = 17.0, 10.3 Hz, 1H), 4.95 (dd, J = 10.2, 2.3, 1H), 4.79 (dd, J = 17.0, 2.3, 1H), 1.96 (dd, J = 10.5, 2.4 Hz, 1H), 1.81 (s, 1H), 1.40 (s, 3H), 1.37–0.66 (m, 11H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 147.0, 136.3, 127.8, 126.6, 125.7, 118.9, 76.1, 62.6, 37.4, 34.0, 29.5, 27.5, 26.9, 26.6, 26.3 ppm. **IR:** 3468, 2921, 2849, 1445, 1064, 1027, 1009, 907 cm^{-1}. **Anal. Calcd.** for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.76; H, 10.05. $[\alpha]_D^{23}$ = +32.9. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 94% ee: t_R (major) = 3.65 min, t_R (minor) = 4.37 min.

Duplicate experiment: 118 mg, 96% yield, 93% ee.

(2*R*,3*S*)-3-cyclohexyl-2-(4-(methylthio)phenyl)pent-4-en-2-ol (2)



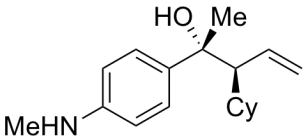
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 4-(methylthio)acetophenone (83 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with

the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a yellow oil (121 mg, 83% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.69 (major) and 5.76 (minor)] of the unpurified reaction mixture indicated a 12:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.24 (m, 2H), 7.17–7.09 (m, 2H), 5.69 (dt, J = 17.0, 10.3 Hz, 1H), 5.07 (dd, J = 10.2, 2.3 Hz, 1H), 4.91 (dd, J = 16.9, 2.3 Hz, 1H), 2.41 (s, 3H), 2.04 (dd, J = 10.5, 2.5 Hz, 1H), 1.58–0.70 (m, 11H), 1.48 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 144.1, 136.4, 136.2, 126.3, 126.1, 119.1, 75.8, 62.6, 37.4, 34.0, 29.4, 27.4, 26.8, 26.6, 26.3, 16.0 ppm. **IR:** 3453, 2920, 2849, 1492, 1447, 1397, 1098, 1013, 3453 cm^{-1}. **Anal. Calcd.** for $C_{18}H_{26}OS$: C, 74.43; H, 9.02. Found: C, 74.19; H, 9.15. $[\alpha]_D^{23}$ = +25.96. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 95% ee: t_R (major) = 4.83, t_R (minor) = 6.17.

Duplicate experiment: 115 mg, 82% yield, 93% ee.

(2*R*,3*S*)-3-cyclohexyl-2-(4-(methylamino)phenyl)pent-4-en-2-ol (3)

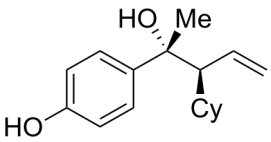


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 4'-(methylamino)acetophenone (75 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a yellow-orange oil (136 mg, 99% yield). ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture indicated a >20:1 dr (no resonances that are typical of the minor diastereomer could be detected).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.1 Hz, 2H), 5.80 (dt, J = 17.0, 10.3, 1H), 5.15 (dd, J = 10.1, 2.5 Ha, 1H), 5.03 (dd, J = 17.0, 2.5 Hz, 1H), 2.87 (s, 3H), 2.13 (dd, J = 10.5, 2.4 Hz, 1H), 1.65–0.74 (m, 11H), 1.54 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 136.9, 126.6, 118.5, 111.9, 76.8, 75.6, 62.8, 37.4, 34.1, 29.4, 27.4, 26.9, 26.6, 26.4 ppm. **IR:** 3407, 2922, 2849, 1614, 1519, 1447, 1318, 1262, 1187, 1074, 909 cm^{-1}. **HRMS Calcd. m/z** for $[C_{18}H_{27}NO - H_2O]$+: 256.2060. Found: 256.2061. $[\alpha]_D^{23}$ = +40.4. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 97% ee: t_R (major) = 5.21 min, t_R (minor) = 6.26 min.

Duplicate experiment: 133 mg, 97% yield, 96% ee.

4-((2*R*,3*S*)-3-cyclohexyl-2-hydroxypent-4-en-2-yl)phenol (4)

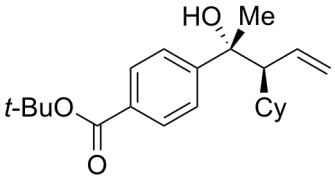


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), piceol (68 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as an orange oil (128 mg, 98% yield). ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture indicated >20:1 dr (no resonances that are typical of the minor diastereomer could be detected).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.34–7.27 (m, 2H), 6.82–6.73 (m, 2H), 5.80 (dt, J = 17.0, 10.3 Hz, 1H), 5.19 (dd, J = 10, 2.4 Hz, 1H), 5.05 (dd, J = 17.2, 2.4 Hz, 1H), 1.61–0.80 (m, 12H), 1.57 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 154.5, 138.8, 136.4, 127.1, 119.2, 114.7, 75.9, 62.8, 37.4, 34.0, 29.4, 27.0, 26.8, 26.6, 26.3 ppm. **IR:** 3403, 3197, 2921, 2852, 1513, 1444, 1378, 1222 cm^{-1}. **HRMS Calcd. m/z** for $[C_{17}H_{24}O_2+Na]+$: 283.1669. Found: 283.1667. $[\alpha]_D^{23}$ = +32.4. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 96% ee: t_R (major) = 4.50 min, t_R (minor) = 5.27 min.

Duplicate experiment: 129 mg, 99% yield, 95% ee.

***tert*-butyl 4-((2*R*,3*S*)-3-cyclohexyl-2-hydroxypent-4-en-2-yl)benzoate (5)**



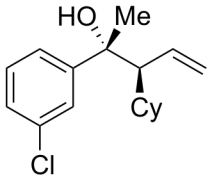
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), *tert*-butyl 4-acetylbenzoate (110 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-15% EtOAc/hexanes for 10 CV, followed by 15% EtOAc/hexanes for 10 CV) to afford the title compound as a colorless oil (107 mg, 62% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.69 (major) and 5.86 (minor)] of the unpurified reaction mixture indicated a 6:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.86 (d, J = 8.2 Hz,

2H), 7.40 (d, J = 8.1 Hz, 2H), 5.69 (dt, J = 16.9, 10.3 Hz, 1H), 5.05 (dd, J = 10.1, 2.1 Hz, 1H), 4.88 (dd, J = 16.9, 2.2 Hz, 1H), 2.07 (dd, J = 10.4, 2.2 Hz, 1H), 1.88 (s, 1H), 1.59–0.72 (m, 11H),1.52 (s, 9H), 1.47 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 165.8, 151.9, 135.8, 130.2, 129.0, 125.6, 119.3, 80.9, 76.2, 62.4, 37.3, 34.0, 29.4, 28.2, 27.6, 26.8, 26.6, 26.3 ppm. **IR:** 3493, 2975, 2922, 2851, 1711, 1695, 1367, 1290, 1164, 1115, 1016 cm^{-1}. **HRMS Calcd. m/z** for $[C_{22}H_{32}O_3 + Na]$+: 367.2244. Found: 367.2237. $[\alpha]_D^{23}$ = +7.6. **SFC analysis** (IC column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated an 81% ee: t_R (major) = 3.16 min, t_R (minor) = 3.70 min.

Duplicate experiment: 98 mg, 57% yield, 80% ee.

(2*R*,3*S*)-2-(3-chlorophenyl)-3-cyclohexylpent-4-en-2-ol (6)

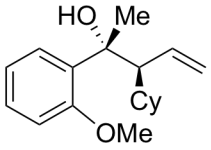


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 3'-chloroacetophenone (77 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a colorless oil (133 mg, 87% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.67 (major) and 5.81 (minor)] of the unpurified reaction mixture indicated a 5:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated a 7:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.37 (t, J = 1.8 Hz, 1H), 7.24 ? 7.10 (m, 3H), 5.67 (dt, J = 16.9, 10.3 Hz, 1H), 5.06 (dd, J = 10.2, 2.2 Hz, 1H), 4.88 (dd, J = 17.0, 2.2 Hz, 1H), 2.08 - 1.97 (m, 1H), 1.89 (s, 1H), 1.72–0.69 (m, 11H), 1.49 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 149.4, 135.7, 133.9, 129.0, 126.7, 126.1, 124.0, 119.4, 75.9, 62.4, 37.4, 34.0, 29.4, 27.5, 26.8, 26.6, 26.3 ppm. **IR:** 3473, 2922, 2850, 1596, 1571, 1449, 1420, 1081, 1007, 914 cm^{-1}. **HRMS Calcd. m/z** for $[C_{17}H_{23}ClO + H]$+: 261.1405. Found: 261.1407. $[\alpha]_D^{23}$ = +13.7. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated 89% ee: t_R (major) = 3.38 min, t_R (minor) = 3.94 min.

Duplicate experiment: 123 mg, 80% yield, 89% ee.

(2*R*,3*S*)-3-cyclohexyl-2-(2-methoxyphenyl)pent-4-en-2-ol (7)

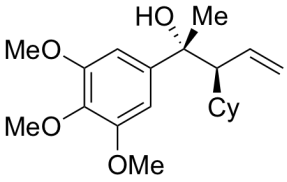


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 2'-methoxyacetophenone (75 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified by Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (122 mg, 89% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 4.90 (major) and 4.85 (minor)] of the unpurified reaction mixture indicated a 6:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated an 11:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16–7.03 (m, 2H), 6.86–6.71 (m, 2H), 5.67 (dt, J = 16.9, 10.3 Hz, 1H), 4.90 (dd, J = 10.1, 2.5 Hz, 1H), 4.73 (dd, J = 17.0, 2.4 Hz, 1H), 4.02 (s, 1H), 3.73 (s, 3H), 2.33 (dd, J = 10.5, 2.3 Hz, 1H), 1.63–0.66 (m, 11H), 1.46 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 156.9, 137.0, 135.0, 128.0, 127.7, 120.7, 117.3, 111.4, 77.7, 59.9, 55.4, 38.2, 34.2, 29.6, 27.0, 26.8, 26.4, 25.0 ppm. **IR:** 3516, 2921, 2849, 1486, 1436, 1231, 1027, 909 cm^{-1}. **Anal. Calcd.** for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.85; H, 9.74. $[\alpha]_D^{23}$ = -8.4. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 90% ee: t_R (major) = 3.18 min, t_R (minor) = 3.37 min.

Duplicate experiment: 128 mg, 93% yield, 91% ee.

(2*R*,3*S*)-3-cyclohexyl-2-(3,4,5-trimethoxyphenyl)pent-4-en-2-ol (8)



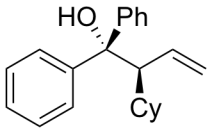
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 3',4',5'-trimethoxyacetophenone (105 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-15% EtOAc/hexanes for 10 CV, followed by 15% EtOAc/hexanes for 10 CV) to afford the title compound as a white solid (147 mg, 88% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.70 (major) and 5.85 (minor) ppm] of the unpurified reaction mixture indicated an 8:1 dr.

Major diastereomer: m.p. = 146–147 °C. **^{1}H NMR (400 MHz, $CDCl_3$) δ:**

6.60 (s, 2H), 5.70 (dt, J = 17.0, 10.3 Hz, 1H), 5.08 (dd, J = 10.1, 2.3 Hz, 1H), 4.94 (dd, J = 17.0, 2.3 Hz, 1H), 3.78 (d, J = 10.8 Hz, 9H), 2.02 (dd, J = 10.4, 2.2 Hz, 1H), 1.91 (s, 1H), 1.61–0.67 (m, 11H), 1.49 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 152.6, 142.7, 136.9, 136.1, 119.0, 103.4, 76.1, 62.7, 60.9, 56.2, 37.4, 34.1, 29.3, 27.7, 26.9, 26.7, 26.3 ppm. **IR:** 3501, 2923, 2847, 1590, 1504, 1463, 1446, 1411, 1311, 1225, 1126, 999 cm^{-1}. **Anal. Calcd.** for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.83; H, 9.02. $[\alpha]_D^{23}$ = +20.0. **SFC analysis** (IC column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 91% ee: t_R (major) = 4.08 min, t_R (minor) = 6.01 min.

Duplicate experiment: 140 mg, 84% yield, 88% ee.

(*S*)-2-cyclohexyl-1,1-diphenylbut-3-en-1-ol (9)

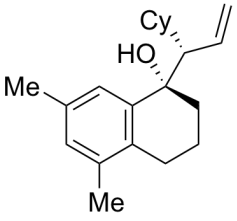


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), benzophenone (91 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a waxy solid (108 mg, 71% yield).

M.p. = 83–84 °C. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.36–7.30 (m, 2H), 7.28–7.21 (m, 2H), 7.18–6.91 (m, 6H), 5.63 (dt, J = 17.1, 10.1 Hz, 1H), 4.89 (dd, J = 10.0, 1.2 Hz, 1H), 4.79 (dd, J = 17.2, 2.4 Hz, 1H), 2.83 (d, J = 10.0 Hz, 1H), 2.16 (s, 1H), 1.53–0.77 (m, 11H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 147.0, 146.6, 135.8, 128.2, 127.9, 126.6, 126.4, 126.2, 126.0, 118.5, 81.4, 57.6, 38.5, 33.8, 29.9, 26.9, 26.6, 26.4 ppm. **IR:** 3612, 2924, 2852, 1498, 1447, 1032, 1001, 972, 914 cm^{-1}. **Anal. Calcd.** for $C_{22}H_{26}O$: C, 86.23; H, 8.55. Found: C, 85.97; H, 8.63. $[\alpha]_D^{23}$ = +22.2. **SFC analysis** (IC column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated an 87% ee: t_R (minor) = 5.29 min, t_R (major) = 5.64 min.

Duplicate experiment: 116 mg, 76% yield, 85% ee.

(*S*)-1-((*S*)-1-cyclohexylallyl)-5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (10)



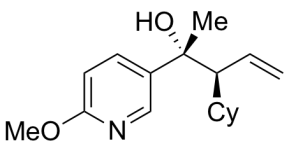
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 5,7-dimethyl-1-tetralone (122 mg, 1.0 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-10% EtOAc/hexanes for 15 CV, followed by 10% EtOAc/hexanes for 5 CV) to afford the title compound as a pale-yellow oil (91 mg, 61% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.98 (major) and 5.74 (minor) ppm] of the unpurified reaction mixture indicated a 3:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated a >20:1 dr (no resonances that are typical of the minor diastereomer could be detected).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.22 (s, 1H), 6.91 (s, 1H), 5.98 (dt, J = 17.0, 10.1 Hz, 1H), 5.32 (dd, J = 10.1, 2.3 Hz, 1H), 5.22 (dd, J = 17.0, 2.3 Hz, 1H), 2.91–0.76 (m, 18H), 2.36 (s, 1H), 2.32 (s, 3H), 2.24 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 140.2, 137.2, 135.9, 135.7, 134.4, 133.3, 129.5, 125.1, 119.8, 77.4, 77.3, 77.1, 76.7, 73.6, 60.3, 38.8, 38.3, 33.5, 33.4, 30.9, 26.8, 26.8, 26.6, 26.3, 26.2, 22.7, 21.2, 19.9, 18.8 ppm. **IR:** 3463, 2920, 2850, 1684, 1611, 1475, 1447, 1326, 1169 cm^{-1}. **HRMS Calcd. m/z** for $[C_{21}H_{30}O+Na]+$: 321.2189. Found: 321.2198. $[\alpha]_D^{23}$ = +25.5. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 94% ee: t_R (major) = 3.37, t_R (minor) = 4.11.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.77 (s, 1H), 7.22 (s, 1H), 5.74 (dt, J = 17.1, 10.2 Hz, 1H), 5.04 (dd, J = 10.3, 2.3 Hz, 1H), 4.86 (dd, J = 17.1, 2.3 Hz, 1H), 2.91–0.76 (m, 19H), 2.36 (s, 3H), 2.31 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 139.9, 136.7, 136.2, 135.6, 132.7, 129.4, 125.4, 125.1, 117.6, 58.6, 38.3, 37.1, 34.8, 34.3, 30.4, 29.7, 27.0, 26.5, 25.8, 20.8, 19.4, 18.5 ppm.

Duplicate experiment: 92 mg, 62% yield, 95% ee.

(2*R*,3*S*)-3-cyclohexyl-2-(6-methoxypyridin-3-yl)pent-4-en-2-ol (11)



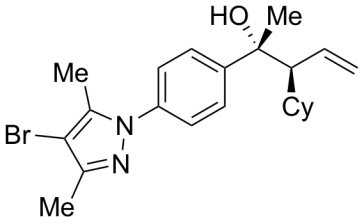
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 2-methoxy-5-acetyl pyridine (76 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with

the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a yellow oil (124 mg, 90% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.77 (major) and 5.85 (minor) ppm] of the unpurified reaction mixture indicated a 14:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (s, 1H), 7.68 (dd, J = 8.7, 2.2 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 5.77 (dt, J = 16.9, 10.3 Hz, 1H), 5.18 (dd, J = 10.1, 2.2 Hz, 1H), 5.02 (dd, J = 17.0, 2.2 Hz, 1H), 3.94 (s, 3H), 2.14–2.05 (m, 2H), 1.67–0.82 (m, 12H), 1.57 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 163.0, 144.2, 136.8, 135.9, 119.6, 109.9, 74.7, 62.6, 53.4, 37.4, 34.0, 29.5, 27.0, 26.8, 26.5, 26.2 ppm. **IR:** 3313, 2920, 2849, 1604, 1489, 1372, 1286, 1025 cm^{-1}. **Anal. Calcd.** for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15. Found: C, 74.04; H, 9.10. $[\alpha]_D^{23}$ = +28.9. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 95% ee: t_R (major) = 3.80, t_R (minor) = 3.94.

Duplicate experiment: 114 mg, 83% yield, 95% ee.

(2*R*,3*S*)-2-(4-(4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)phenyl)-3-cyclohexylpent-4-en-2-ol (12)



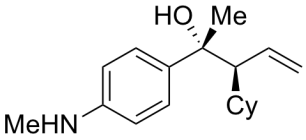
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 1-(4-acetylphenyl)-4-bromo-3,5-dimethylpyrazole (147 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a white solid (109 mg, 62% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.79 (major) and 5.95 (minor) ppm] of the unpurified reaction mixture indicated 6:1 dr.

Major diastereomer: m.p. = 115–116 °C. **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.54 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 5.79 (dt, J = 17.0, 10.3 Hz, 1H), 5.16 (dd, J = 10.1, 2.2 Hz, 1H), 5.00 (dd, J = 17.0, 2.2 Hz, 1H), 2.30 (d, J = 9.8 Hz, 6H), 2.23 (s, 1H), 2.15 (dd, J = 10.4, 2.4 Hz, 1H), 1.66–0.88 (m, 11H), 1.50 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 147.5, 147.0, 138.2, 137.6, 135.9, 129.5, 126.6, 123.9, 119.4, 96.3, 75.9, 62.7, 37.3, 34.0, 29.4, 27.4, 26.8, 26.6, 26.3, 12.4, 11.8 ppm. **IR:** 3346, 2916, 1515, 1359, 1143, 1106, 1082, 1015 cm^{-1}. **Anal. Calcd.** for $C_{16}H_{25}BrN_2O$:

C, 56.31; H, 7.38. Found: C, 63.16; H, 7.01. $[\alpha]_D^{23}$ = +13.7. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 93% ee: t_R (major) = 5.17, t_R (minor) = 5.47.

Duplicate experiment: 107 mg, 61% yield, 90% ee.

(2*R*,3*S*)-2-(5-bromothiophen-2-yl)-3-cyclohexylpent-4-en-2-ol (13)

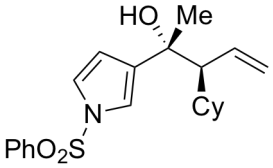


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 2-acetyl-5-bromothiophene (103 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as an orange oil (142 mg, 86% yield). ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture indicated >20:1 dr (no resonances that are typical of the minor diastereomer could be detected).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.72 (d, *J* = 3.8 Hz, 1H), 6.48 (d, *J* = 3.8 Hz, 1H), 5.63 (dt, *J* = 16.9, 10.3 Hz, 1H), 5.05 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.92 (dd, *J* = 17.0, 2.2 Hz, 1H), 2.10 (s, 1H), 1.93 (dd, *J* = 10.4, 2.3 Hz, 1H), 1.53–0.63 (m, 11H), 1.39 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 154.0, 135.4, 129.3, 123.4, 120.0, 110.8, 75.5, 63.0, 37.7, 34.0, 29.4, 28.0, 26.8, 26.6, 26.3 ppm. **IR:** 2922, 2849, 1444, 1410, 1215, 966, 913 cm^{-1}. **HRMS Calcd. m/z** for $[C_{15}H_{21}BrOS\text{-}H]$-: 327.0424. Found: 327.0439. $[\alpha]_D^{23}$ = +2.6. **SFC analysis** (IC column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated an 81% ee: t_R (major) = 3.44 min, t_R (minor) = 3.82 min.

Duplicate experiment: 155 mg, 94% yield, 85% ee.

(2*R*,3*S*)-3-cyclohexyl-2-(1-(phenylsulfonyl)-1H-pyrrol-3-yl)pent-4-en-2-ol (14)



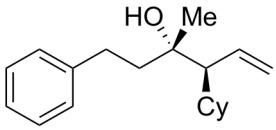
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 3-acetyl-1-(phenylsulfonyl)pyrrole (125 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes

for 10 CV) to afford the title compound as a yellow-orange oil (172 mg, 92% yield). ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture indicated a >20:1 dr (no resonances that are typical of the minor diastereomer could be detected).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.10 (dt, J = 16.7, 2.3 Hz, 1H), 6.28 (s, 1H), 5.71 (dt, J = 16.9, 10.3 Hz, 1H), 5.13 (dd, J = 10.1, 2.4 Hz, 1H), 5.00 (dd, J = 17.0, 2.3 Hz, 1H), 2.01 (dd, J = 10.4, 2.4 Hz, 1H), 1.64–0.66 (m, 11H), 1.43 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 139.1, 136.4, 136.0, 133.7, 129.3, 126.7, 121.0, 119.1, 117.1, 112.8, 72.9, 62.0, 37.5, 34.0, 29.4, 27.3, 26.8, 26.5, 26.2 ppm. **IR:** 3569, 2921, 2851, 1480, 1449, 1360, 1234, 1174, 1115, 1072 cm^{-1}. **HRMS Calcd. m/z** for $[C_{21}H_{27}NO_3S$-H]-: 372.1639. Found: 372.1641. $[\alpha]_D^{23}$ = +23.0. **SFC analysis** (AD-H column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 93% ee: t_R (major) = 5.19 min, t_R (minor) = 7.11 min.

Duplicate experiment: 185 mg, 99% yield, 94% ee.

(3*S*,4*S*)-4-cyclohexyl-3-methyl-1-phenylhex-5-en-3-ol (15)

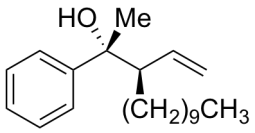


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), benzylacetone (74 mg, 0.50 mmol), cyclohexylallene (73 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-15% EtOAc/hexanes for 10 CV, followed by 15% EtOAc/hexanes for 10 CV) to afford the title compound as a pale yellow oil (91 mg, 67% yield). SFC and GC analysis of the unpurified reaction mixture indicated a >10:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, J = 15.1 Hz, 2H), 7.16–7.08 (m, 3H), 5.77 (dt, J = 17.0, 10.3 Hz, 1H), 5.14 (dd, J = 10.1, 2.4 Hz, 1H), 5.00 (dd, J = 17.1, 2.4 Hz, 1H), 2.69–2.54 (m, 2H), 1.90–0.87 (m, 15H), 1.17 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 142.9, 136.2, 128.4, 128.4, 125.7, 119.2, 77.4, 77.0, 76.7, 74.0, 60.2, 43.0, 37.8, 34.3, 30.1, 29.7, 27.0, 26.8, 26.4, 25.2 ppm. **IR:** 3464, 2921, 2849, 1495, 1449, 1376, 1006, 911 cm^{-1}. **HRMS Calcd. m/z** for $[C_{19}H_{28}O$-OH]+: 255.2107. Found: 255.2104. $[\alpha]_D^{23}$ = +12.7. **SFC analysis** (IC column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 92% ee: t_R (major) = 3.08, t_R (minor) = 3.20.

Duplicate experiment: 103 mg, 76% yield, 89% ee.

(2*R*,3*R*)-2-phenyl-3-vinyltridecan-2-ol (16)



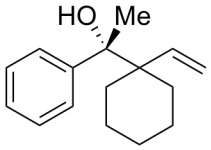
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), dodecylallene (108 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 15 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (134 mg, 89% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.09 (major) and 5.11 (minor) ppm] of the unpurified reaction mixture indicated a 3:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated a 3:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.35 (d, J = 7.4 Hz, 1H), 7.30 (d, J = 7.4 Hz, 2H), 7.25 (d, J = 7.4 Hz, 2H), 5.52 (dt, J = 16.8, 12.0 Hz, 1H), 5.09 (dd, J = 10.4, 2.0 Hz, 1H), 4.98 (dd, J = 17.2, 2.0 Hz, 1H), 3.37 (s, 1H), 2.19 (td, J = 10.0, 9.3, 1.9 Hz, 1H), 1.96 (s, 1H), 1.43 (s, 3H), 1.30–0.86 (m, 17H), 0.79 (t, J = 6.9 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 147.2, 138.6, 127.9, 126.4, 125.2, 118.1, 76.1, 55.6, 31.9, 29.6, 29.5, 29.4, 29.3, 28.9, 28.5, 27.7, 22.7, 14.1 ppm. **IR:** 3484, 2922, 2852, 1446, 1064, 1028, 1002, 912 cm^{-1}. **Anal. Calcd.** for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.48; H, 11.48. $[\alpha]_D^{23}$ = +12.3. **SFC analysis** (IC column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 87% ee: t_R (major) = 2.37 min, t_R (minor) = 3.07 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.19–7.10 (m, 5H), 5.54–5.42 (m, 1H), 5.11 (dd, J = 10.0, 1.6 Hz, 1H), 5.04 (dd, J = 17.2, 2.4 Hz, 1H), 5.52 (dt, J = 16.8, 12.0 Hz, 1H), 1.46 (s, 3H), 1.30–0.86 (m, 21H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 146.6, 139.0, 127.8, 126.7, 125.9, 118.8, 75.5, 56.6, 50.7, 29.5, 29.4, 28.7, 27.8, 25.5 ppm. **SFC analysis** (IC column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 95% ee: t_R (major) = 2.89 min, t_R (minor) = 3.35 min.

Duplicate experiment: 128 mg, 85% yield, 87% ee (major), 93% ee (minor).

(*R*)-1-phenyl-1-(1-vinylcyclohexyl)ethan-1-ol (17)

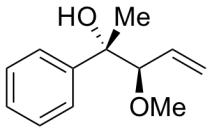


Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), vinylidenecyclohexane (65 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-10% EtOAc/hexanes for 10 CV, followed by 10% EtOAc/hexanes for 10 CV) to afford the title compound as a colorless oil (101 mg, 88% yield).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.24 (d, J = 1.6 Hz, 2H), 7.14 (t, J = 7.5 Hz, 2H), 7.10–7.03 (m, 1H), 5.41–5.21 (m, 2H), 4.93 (dd, J = 17.0, 2.4 Hz, 1H), 1.94 (s, 1H), 1.75–0.65 (m, 10H), 1.38 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 145.1, 142.5, 127.5, 126.9, 126.3, 118.0, 118.0, 77.7, 77.4, 77.1, 76.7, 48.3, 30.4, 28.9, 26.2, 25.0, 22.6, 22.3 ppm. **IR:** 3466, 2935, 2855, 1445, 1373, 1063, 1029, 917 cm^{-1}. **HRMS Calcd. m/z** for $[(C_{16}H_{22}O + H) + -H_2O]$: 213.1638. Found: 213.1639. $[\alpha]_D^{23}$ = +30.0. **SFC analysis** (IC column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated an 87% ee: t_R (major) = 2.77 min, t_R (minor) = 3.06 min.

Duplicate experiment: 104 mg, 90% yield, 92% ee.

(2*S*,3*R*)-3-methoxy-2-phenylpent-4-en-2-ol (18)



Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), methoxyallene (42 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified by preparative TLC (15% EtOAc/hexanes) to afford the title compound as a yellow oil (71 mg, 74% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.71 (major) and 5.51 (minor) ppm] of the unpurified reaction mixture indicated a 2.5:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated a 2.5:1 dr.

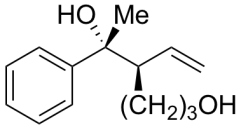
Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.49 (d, J = 7.8 Hz, 2H), 7.38 (m, 2H), 7.27 (d, J = 6.8 Hz, 1H), 5.71 (dt, J = 17.8, 10.4 Hz, 1H), 5.36–5.29 (m, 1H), 5.22–5.16 (m, 1H), 3.70 (d, J = 7.9 Hz, 1H), 3.29 (s, 3H), 3.06 (s, 1H), 1.48 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 145.5, 133.9, 127.9, 126.8, 125.6, 120.2, 89.7, 77.3, 77.2, 77.0, 76.7, 75.8, 57.0, 24.4 ppm. **IR:** 2921, 2850, 1720, 1450, 1375, 1322, 1260, 1079 cm^{-1}. **HRMS Calcd. m/z** for $[C_{12}H_{16}O_2$+Cl]-: 227.0844. Found: 227.0843. $[\alpha]_D^{23}$ = -6.2. **SFC analysis** (IC column, $scCO_2$/MeOH = 98/2 to 90/10,

2.5 mL/min) indicated a 94% ee: t_R (major) = 3.15 min, t_R (minor) = 3.39 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, J = 7.6 Hz, 2H), 7.37–7.32 (m, 2H), 7.26–7.24 (m, 1H), 5.51 (dt, J = 17.8, 10.5 Hz, 1H), 5.26–5.21 (m, 1H), 5.18 (d, J = 17.3 Hz, 1H), 3.67 (d, J = 7.4 Hz, 1H), 3.34 (s, 3H), 2.98 (s, 1H), 1.62 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 144.5, 134.2, 127.8, 126.7, 125.7, 119.9, 89.6, 77.3, 77.2, 77.0, 76.7, 75.5, 57.1, 26.5 ppm. **SFC analysis** (IC column, $scCO_2$/MeOH = 98/2 to 90/10, 2.5 mL/min) indicated 89% ee: t_R (major) = 2.96 min, t_R (minor) = 3.70 min.

Duplicate experiment: 73 mg, 76% yield, 89% ee (major), 85% ee (minor).

(4*R*,5*R*)-5-phenyl-4-vinylhexane-1,5-diol (19)



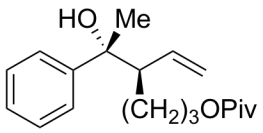
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), hexa-4,5-dien-1-ol (59 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-80% EtOAc/hexanes for 15 CV, followed by 80% EtOAc/hexanes for 5 CV) to afford the title compound as a yellow oil (104 mg, 95% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.73–5.57 (major) and 5.58–5.48 (minor) ppm] of the unpurified reaction mixture indicated a 2.5:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated a 2.5:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49–7.18 (m, 5H), 5.73–5.57 (m, 1H), 5.26–5.15 (m, 1H), 5.13–5.02 (m, 1H), 3.59–3.45 (m, 2H), 2.29 (td, J = 9.9, 2.4 Hz, 1H), 2.05 (s, 1H), 1.52 (s, 3H), 1.43–1.00 (m, 5H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 147.2, 138.3, 128.0, 126.5, 125.2, 118.3, 76.0, 62.6, 55.4, 30.9, 28.7, 24.7 ppm. **IR:** 3372, 2931, 2866, 1493, 1445, 1373, 1323, 1054, 910 cm^{-1}. **HRMS Calcd. m/z** for $[C_{14}H_{20}O_2+Na]+$: 243.1355. Found: 243.1354. $[\alpha]_D^{23}$ = +3.7. **SFC analysis** (ADH column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a >99% ee: t_R (major) = 5.50 min, t_R (minor) = 4.82 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ:) 7.49–7.18 (m, 5H), 5.58–5.48 (m, 1H), 5.29–5.18 (m, 1H), 5.15–5.05 (m, 1H), 4.15–4.06 (m, 2H), 2.29 (td, J = 9.9, 2.4 Hz, 1H), 2.05 (s, 3H), 1.56 (s, 3H), 1.43–1.00 (m, 5H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 146.2, 138.7, 127.8, 126.7, 126.0, 118.9, 77.4, 77.3, 77.1, 76.8, 75.6, 62.5, 56.3, 30.8, 26.2, 24.7 ppm. **SFC analysis** (ADH column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 75% ee: t_R (major) = 5.25 min, t_R (minor) = 5.34 min.

Duplicate experiment: 109 mg, 99% yield, >99% ee (major), 76% ee (minor).

(*R*)-4-((*R*)-1-hydroxy-1-phenylethyl)hex-5-en-1-yl pivalate (20)



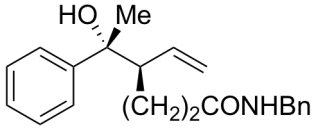
Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), hexa-4,5-dien-1-yl pivalate (109 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-70% EtOAc/hexanes for 15 CV, followed by 70% EtOAc/hexanes for 5 CV) to afford the title compound as an orange oil (146 mg, 96% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.51 (major) and 5.45–5.35 (minor) ppm] of the unpurified reaction mixture indicated a 7:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.25–7.21 (m, 2H), 7.19–7.16 (m, 2H), 7.08–7.06 (m, 1H), 5.51 (dt, J = 17.2, 9.9 Hz, 1H), 5.07 (dd, J = 10.3, 1.9 Hz, 1H), 4.96 (dd, J = 17.3, 1.9 Hz, 1H), 3.77 (t, J = 6.3 Hz, 2H), 2.13 (ddd, J = 11.6, 9.5, 2.5 Hz, 1H), 1.37 (s, 3H), 1.31–1.01 (m, 4H), 0.95 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 178.5, 147.1, 138.0, 128.0, 126.5, 125.0, 118.5, 76.0, 64.0, 55.2, 29.2, 27.1, 26.9, 24.7 ppm. **IR:** 3506, 2972, 1709, 1480, 1446, 1285, 1157, 912 cm^{-1}. **HRMS Calcd. m/z** for $[C_{19}H_{28}O_3+Na]+$: 327.1930. Found: 327.1933. $[\alpha]_D^{23}$ = -1.2. **SFC analysis** (IC column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated an 82% ee: t_R (major) = 2.65 min, t_R (minor) = 2.83 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.30–7.26 (m, 2H), 7.17–7.15 (m, 2H), 7.10–7.06 (m, 1H), 5.45–5.35 (m, 1H), 5.04–4.99 (m, 1H), 3.82–3.77 (m, 1H), 1.98–1.91 (m, 1H),1.51–1.39 (m, 4H), 1.41 (s, 3H), 0.97 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 178.5, 146.2, 138.3, 127.9, 126.8, 125.9, 119.3, 75.4, 70.3, 63.9, 56.2, 38.6, 27.2, 27.0, 25.6, 25.0 ppm. **SFC analysis** (IC column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 82% ee: t_R (major) = 2.95 min, t_R (minor) = 3.07 min.

Duplicate experiment: 148 mg, 97% yield, 83% ee (major), 82% ee (minor).

(*R*)-*N*-benzyl-4-((*R*)-1-hydroxy-1-phenylethyl)hex-5-enamide (21)



Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), *N*-benzylhexa-4,5-dienamide (121 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and

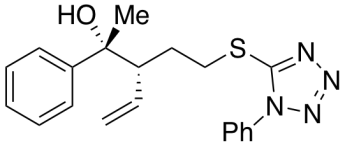
toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-80% EtOAc/hexanes for 15 CV, followed by 80% EtOAc/hexanes for 5 CV) to afford the title compound as a yellow oil (104 mg, 64% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.53 (major) and 5.47–5.37 (minor) ppm] of the unpurified reaction mixture indicated a 2:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated a 3.5:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.10 (m, 11H), 5.67 (m, 1H), 5.53 (dt, J = 17.2, 9.9 Hz, 1H), 5.11–5.05 (m, 1H), 4.93 (dd, J = 17.2, 1.9 Hz, 1H), 4.27 (m, 2H), 2.27–2.03 (m, 3H), 1.95–1.78 (m, 2H), 1.42 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 172.7, 147.0, 137.8, 128.7, 128.0, 127.9, 127.5, 126.6, 125.2, 119.1, 118.8, 75.9, 55.1, 43.5, 34.6, 28.5, 24.5 ppm. **IR:** 3291, 2974, 2928, 1645, 1538, 1445, 1373, 1244, 1028, 912 cm^{-1}. **HRMS Calcd. m/z** for $[C_{21}H_{25}NO_2+Na]+$: 346.1777. Found: 346.1786. $[\alpha]_D{}^{23}$ = +9.5. In order to determine the ee of the product, a sample of the major diastereomer was isolated by preparative TLC in 35% EtOAc/hexanes followed by preparative HPLC on a ZORBAX CN column (21.2 x 250 mm, PN 877952-105) in 10% IPA/hexanes. **SFC analysis** (ADH column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated a 96% ee: t_R (minor) = 5.92 min, t_R (major) = 6.14 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.10 (m, 11H), 5.73 (m, 1H), 5.47–5.37 (m, 1H), 5.05 (d, J = 1.6 Hz, 1H), 4.99 (d, J = 1.9 Hz, 1H), 4.27 (m, 2H), 2.27–2.10 (m, 1H), 1.67 (m, 2H), 1.45 (s, 3H), 1.32–1.14 (m, 2H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 172.7, 145.9, 138.4, 138.2, 127.5, 126.8, 125.9, 119.1, 75.5, 56.1, 34.5, 26.8, 24.5 ppm. **SFC analysis** (ADH column, $scCO_2$/MeOH = 95/5 to 60/40, 2.5 mL/min) indicated an 84% ee: t_R (major) = 5.92 min, t_R (minor) = 6.69 min.

Duplicate experiment: 100 mg, 62% yield, 92% ee (major), 82% ee (minor).

(2*R*,3*R*)-2-phenyl-3-(2-((1-phenyl-1*H*-tetrazol-5-yl)thio)ethyl)pent-4-en-2-ol (22)



Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), acetophenone (60 mg, 0.50 mmol), 5-(penta-3,4-dien-1-ylthio)-1-phenyl-1*H*-tetrazole (146 mg, 0.60 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified by Biotage Isolera (25 g KP-Sil cartridge, 10%

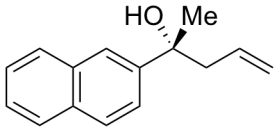
EtOAc/hexanes for 1 column volume (CV), linearly grading to 50% EtOAc/hexanes over 25 CV) to afford the title compound as a yellow oil (147 mg, 80% yield). ^{1}H NMR spectroscopic analysis [integration of the vinylic resonances at 5.67 (major) and 5.51 (minor) ppm] of the unpurified reaction mixture indicated a 3:1 dr. ^{1}H NMR spectroscopic analysis of the purified product indicated a 3:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.47 (p, J = 3.1 Hz, 4H), 7.35–7.27 (m, 2H), 7.23 (td, J = 8.0, 7.5, 1.6 Hz, 2H), 7.14 (tdt, J = 6.0, 4.3, 1.3 Hz, 1H), 5.67 (dt, J = 17.2, 9.8 Hz, 1H), 5.21 (dd, J = 10.4, 1.8 Hz, 1H), 5.12–5.06 (m, 1H), 3.37 (ddd, J = 13.2, 8.5, 4.9 Hz, 1H), 2.99 (dt, J = 12.9, 8.3 Hz, 1H), 2.41 (td, J = 9.8, 3.5 Hz, 1H), 1.80–1.60 (m, 2H), 1.44 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 146.6, 136.9, 129.7, 128.1, 126.7, 125.0, 123.8, 119.5, 77.3, 77.2, 77.0, 76.7, 75.9, 54.5, 31.7, 29.1, 28.0 ppm. **IR:** 3474, 2927, 1596, 1498, 1386, 1240, 916 cm^{-1}. **HRMS Calcd. m/z** for $[C_{19}H_{20}N_4OS+Na]+$: 375.1250. Found: 375.1251. $[\alpha]_D^{23}$ = +11.0. **SFC analysis** (OJ-H column, $scCO_2$/IPA = 90/10 to 70/30, 2.5 mL/min) indicated a 92% ee: t_R (minor) = 7.53 min, t_R (major) = 6.75 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.47 (p, J = 3.1 Hz, 4H), 7.35–7.27 (m, 2H), 7.23 (td, J = 8.0, 7.5, 1.6 Hz, 2H), 7.14 (tdt, J = 6.0, 4.3, 1.3 Hz, 1H), 5.51 (dt, J = 17.1, 9.9 Hz, 1H), 5.15 (dd, J = 12.2, 1.8 Hz, 1H), 5.12–5.06 (m, 1H), 3.37 (ddd, J = 13.2, 8.5, 4.9 Hz, 1H), 2.99 (dt, J = 12.9, 8.3 Hz, 1H), 2.41 (td, J = 9.8, 3.5 Hz, 1H), 1.80–1.60 (m, 2H), 1.50 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 145.6, 137.2, 130.0, 127.9, 127.0, 125.8, 123.8, 120.0, 77.3, 77.2, 77.0, 76.7, 75.4, 55.5, 28.2, 26.5 ppm. **SFC analysis** (OJ-H column, $scCO_2$/IPA = 90/10 to 70/30, 2.5 mL/min) indicated an 84% ee: t_R (minor) = 9.86 min, t_R (major) = 7.19 min.

Duplicate experiment: 145 mg, 79% yield, 93% ee (major), 85% ee (minor).

(*R*)-2-(naphthalen-2-yl)pent-4-en-2-ol (23)



Following the general procedure, $Cu(OAc)_2$ (5 mg, 0.025 mmol), SL-J011-1 (21 mg, 0.030 mmol), 2-acetonaphthone (85 mg, 0.50 mmol), *t*-BuOH (96 μL, 1.0 mmol), DMMS (124 μL, 1.0 mmol), and toluene (1 mL) were used. The reaction was purged under vacuum and refilled with allene gas three times through a balloon (CAUTION: Proper precautions should be taken when handling gas cylinders. Allene is a highly flammable gas that should only be used in small quantities inside a well-ventilated fume hood!), then left to stir overnight under a balloon of allene gas. The experiment was then subjected to the normal quench and work-up procedure described in General Procedure B. The crude reaction mixture was purified by Biotage Isolera (25

g KP-Sil cartridge, 1% EtOAc/hexanes for 1 column volume (CV), linearly grading to 10% EtOAc/hexanes over 25 CV) to afford the title compound as a clear oil (101 mg, 95% yield). The spectroscopic properties for this compound precisely matched those previously reported in the literature.[32]

^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.95 (d, J = 1.2 Hz, 1H), 7.89–7.85 (m, 3H), 7.58 (dd, J = 8.6, 1.8 Hz, 1H), 7.51 (dq, J = 6.7, 3.4 Hz, 2H), 5.67–5.63 (m, 1H), 5.22–5.14 (m, 2H), 2.84 (dd, J = 13.8, 6.4 Hz, 1H), 2.63 (dd, J = 13.8, 8.4 Hz, 1H), 1.68 (s, 3H). **SFC analysis** (AD-H column, $scCO_2$/IPA = 90/10 to 60/40, 2.5 mL/min) indicated a 62% ee: t_R (minor) = 5.03 min, t_R (major) = 4.90 min.

Duplicate experiment: 101 mg, 95% yield, 60% ee.

2.4.6 Preparation of Ketone and Allene Substrates

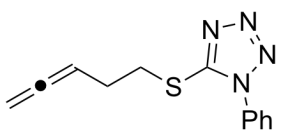
Ketone Synthesis

Acetophenone, 1-(4-(methylthio)phenyl)ethan-1-one, 1-(4-(methylamino)phenyl) ethan-1-one, 1-(4-hydroxyphenyl)ethan-1-one, 1-(3-chlorophenyl)ethan-1-one, 1-(2-methoxyphenyl)ethan-1-one, 1-(3,4,5-trimethoxyphenyl)ethan-1-one, benzophenone, 5,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one, 1-(6-methoxypyridin-3-yl)ethan-1-one, 1-(4-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)ethan-1-one, 1-(5-bromothiophen-2-yl)ethan-1-one, 1-(1-(phenylsulfonyl)-1*H*-pyrrol-3-yl)ethan-1-one, and 4-phenylbutan-2-one were purchased from Sigma Aldrich, Alfa Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific and were used as received. *Tert*-butyl 4-acetylbenzoate was prepared as previously reported in the literature.[33]

Allene Synthesis

Cyclohexylallene, trideca-1,2-diene, vinylidenecyclohexane, 1-methoxypropa-1,2-diene, hexa-4,5-dien-1-ol, and propa-1,2-diene were purchased from Sigma Aldrich, Alfa Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific and were used as received. Hexa-4,5-dien-1-yl pivalate[15e,34] and *N*-benzylhexa-4,5-dienamide[15e] were prepared as previously reported in literature.

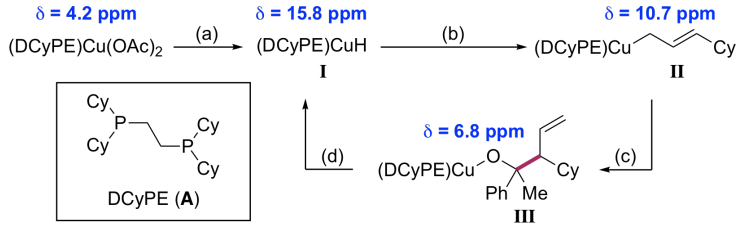
5-(penta-3,4-dien-1-ylthio)-1-phenyl-1*H*-tetrazole



Prepared based on a procedure reported in the literature.[35] A 50 mL round-bottom flask equipped with a magnetic stir bar was charged with a suspension of 1-phenyl-1*H*-tetrazole-5-thiol (890 mg, 5.0 mmol, 1.2 equiv) in DMF (8 mL). 3,4-pentadienyl tosylate (952 mg, 4.0 mmol, 1.0 equiv) was added as a solution

in DMF (2 mL), followed by potassium carbonate (1.38 g, 10 mmol, 2.5 equiv) in one portion. The reaction vessel was capped with a rubber septum, and the yellow mixture was allowed to stir for 3 days while partially submerged in a 60 °C oil bath. The septum was removed and the mixture was transferred to a 250 mL separatory funnel, rinsing with DCM (10 mL). 100 mL DCM was added to the funnel, followed by 2 M NaOH solution (30 mL). After thorough mixing, the organic phase was separated and washed sequentially with water (100 mL) and brine (100 mL). After evaporation of the solvent from the organic solution with the aid of a rotary evaporator, the residue was purified by column chromatography on silica gel (30% EtOAc in hexanes) to yield the desired allene as a slightly brown oil (925 mg, 94% yield). **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.57–7.50 (m, 5H), 5.16 (p, J = 6.6 Hz, 1H), 4.73 (dt, J = 6.6, 3.3, 2H), 3.47 (t, J = 7.1 Hz), 2.53 (qt, J = 6.8, 3.4 Hz, 2 H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$) δ:** 208.7, 154.2, 133.6, 130.1, 129.8, 123.8, 87.7, 32.5, 27.8 ppm. **IR:** 1954, 1596, 1499, 1411, 1385, 1277, 1242 cm^{-1}.

2.4.7 Overview of Mechanistic Studies



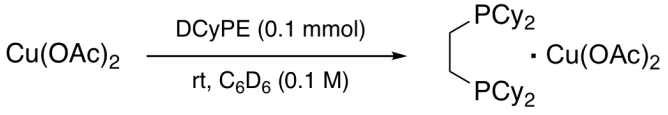
In order to obtain reference data for mechanistic study, we prepared clean samples of each of the reaction intermediates above. The synthesis of these complexes and their characterization by ^{31}P NMR is described in Sections 2.4.8 and 2.4.9.

Next, we demonstrate the plausibility of sequential interconversion of the reaction intermediates **(I → II → III → I)** in a series of experiments detailed in Section 2.4.10.

Finally, we observe a catalytic reaction in progress by ^{31}P NMR to reveal the catalytic resting state of a typical allene-ketone coupling reaction. This experiment is detailed in Section 2.4.11.

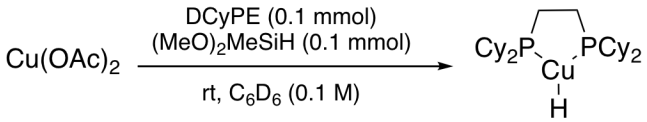
2.4.8 Independent Preparation of Copper Complexes for Mechanistic Study

Note: ^{31}P NMR spectra were recorded at 121 MHz, using a Varian 300 MHz spectrometer. Chemical shifts of ^{31}P NMR signals are reported in ppm relative to a triphenylphosphine external standard (in C_6D_6, δ = -6.0 ppm). C_6D_6 was obtained from Cambridge Isotope Laboratories.



E-I

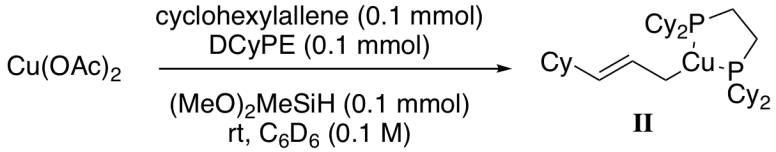
(DCyPE)Cu(OAc)$_2$ (E-I): Inside a nitrogen-filled glovebox, an oven-dried glass culture tube equipped with a magnetic stir bar was charged with Cu(OAc)$_2$ (18 mg, 0.10 mmol, 1.0 equiv), DCyPE (42 mg, 0.10 mmol, 1.0 equiv), and benzene-d_6 (1 mL). The tube was fitted with a Teflon-lined blow-out screw cap, and the reaction mixture was stirred vigorously for 30 s. The reaction tube was then uncapped while still in a nitrogen-filled glovebox, and the reaction mixture was transferred to an oven-dried NMR tube using a glass pipette. Observation of the mixture by ^{31}P NMR revealed a broad resonance at 4.2 ppm (Figure 2-4), as well as disappearance of the resonance corresponding to free ligand (DCyPE) at 2.0 ppm.



I

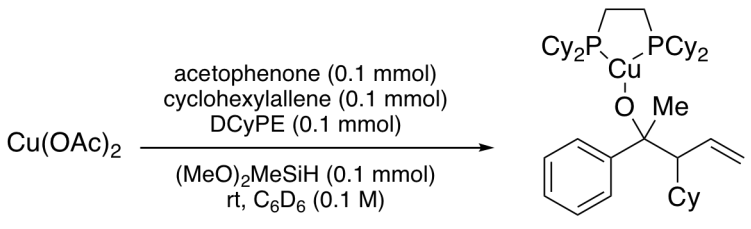
(DCyPE)CuH (I): Inside a nitrogen-filled glovebox, an oven-dried glass culture tube equipped with a magnetic stir bar was charged with Cu(OAc)$_2$ (18 mg, 0.10 mmol, 1.0 equiv), DCyPE (42 mg, 0.10 mmol, 1.0 equiv), and benzene-d_6 (1 mL). The tube was then fitted with a Teflon-lined blow-out screw cap. A 1 mL syringe fitted with a needle was loaded with dimethoxymethylsilane (DMMS, 0.025 mL, 0.20 mmol, 2.0 equiv). The DMMS was added to the mixture by piercing the Teflon septum with the needle. The reaction mixture was allowed to stir for 30 s, during which time the mixture changed from a dark blue to a light blue-green color. The reaction tube was then uncapped while still in a nitrogen-filled glovebox, and the reaction mixture was transferred to an

oven-dried NMR tube using a glass pipette. Observation of the mixture by ^{31}P NMR revealed a major resonance at 15.8 ppm **(I)**, see Figure 2-4.



II

(DCyPE)Cu(allyl) (II): Inside a nitrogen-filled glovebox, an oven-dried glass culture tube equipped with a magnetic stir bar was charged with $Cu(OAc)_2$ (18 mg, 0.10 mmol, 1.0 equiv), DCyPE (42 mg, 0.10 mmol, 1.0 equiv), cyclohexylallene (12 mg, 0.10 mmol, 1.0 equiv) and benzene-d_6 (1 mL). The tube was then fitted with a Teflon-lined blow-out screw cap. A 1 mL syringe fitted with a needle was filled with dimethoxymethylsilane (DMMS, 0.025 mL, 0.20 mmol, 2.0 equiv). The DMMS was added to the mixture by piercing the Teflon septum with the needle. The reaction mixture was allowed to stir for 30 s, during which time the mixture changed from a dark blue to a yellow color. The reaction tube was then uncapped while still in a nitrogen-filled glovebox, and the reaction mixture was transferred to an oven-dried NMR tube using a glass pipette. Observation of the mixture by ^{31}P NMR revealed a major resonance at 10.7 ppm **(II)**, see Figure 2-4. **HRMS Calcd. m/z** for [M-allyl]+: 485.2522. Found: 485.2530. The ^{1}H NMR spectrum of the reaction mixture also revealed the appearance of several olefinic resonances consistent with those expected of **II** and minor amounts of its isomers. Based on previous DFT studies of the hydrocupration process, we expected that the allylcopper complexes could rapidly isomerize, and that the (*E*)-linear species should be predominant.[15e] The identification of **II** as an allylcopper species was further supported by reaction with *t*-BuOD (see Section 2.4.9) and its reactivity in the sequential studies (see Section 2.4.10).

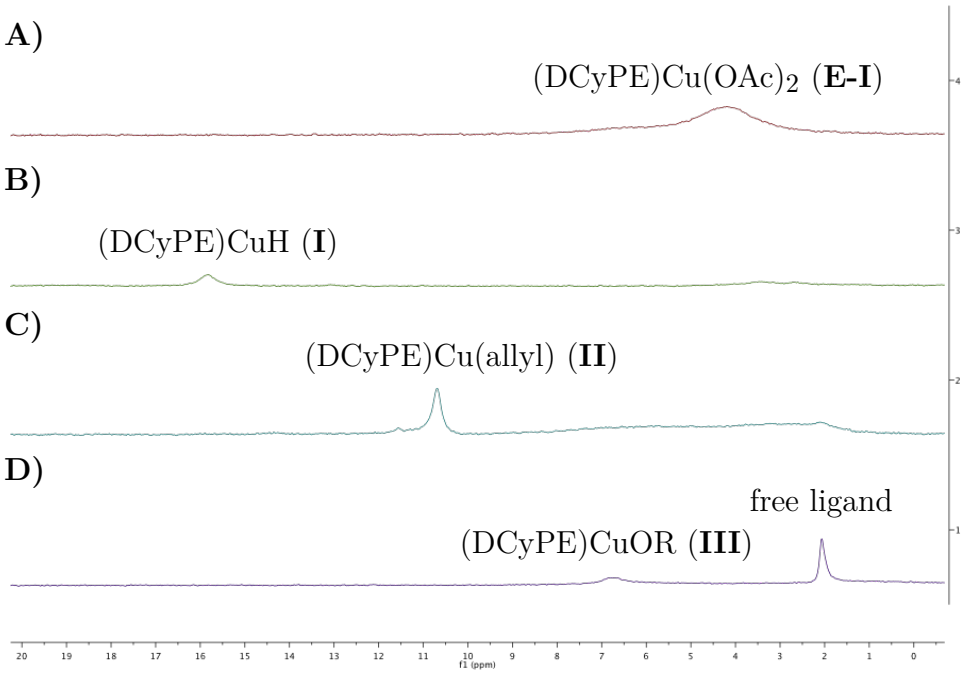


III

(DCyPE)CuOR (III): Inside a nitrogen-filled glovebox, an oven-dried glass culture tube equipped with a magnetic stir bar was charged with $Cu(OAc)_2$ (18 mg, 0.10 mmol, 1.0 equiv), DCyPE (42 mg, 0.10 mmol, 1.0 equiv), cyclohexylallene (12 mg, 0.10 mmol,

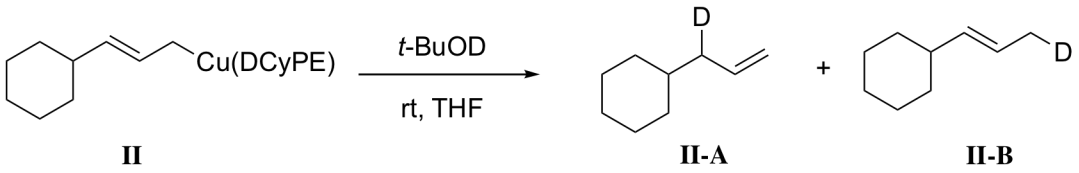
1.0 equiv), acetophenone (12 mg, 0.10 mmol, 1.0 equiv), and benzene-d_6 (1 mL). The tube was then fitted with a Teflon-lined blow-out screw cap. A 1 mL syringe fitted with a needle was filled with dimethoxymethylsilane (DMMS, 0.025 mL, 0.20 mmol, 2.0 equiv). The DMMS was added to the mixture by piercing the Teflon septum with the needle. The reaction mixture was allowed to stir for 30 s, during which time the mixture changed from a dark blue to a light yellow color. The reaction tube was then uncapped while still in a nitrogen-filled glovebox, and the reaction mixture was transferred to an oven-dried NMR tube using a glass pipette. Observation of the mixture by ^{31}P NMR revealed two resonances: 6.8 ppm **(III)** and 2.0 ppm (free DCyPE), see Figure 2-4. Hoveyda *et al.* have also observed dissociation of phosphine ligands from copper alkoxide complexes in equilibrium.[36]

Figure 2-4: Reference ^{31}P NMR spectra for reaction intermediates



2.4.9 Deuteration of Putative Copper Allyl Complex

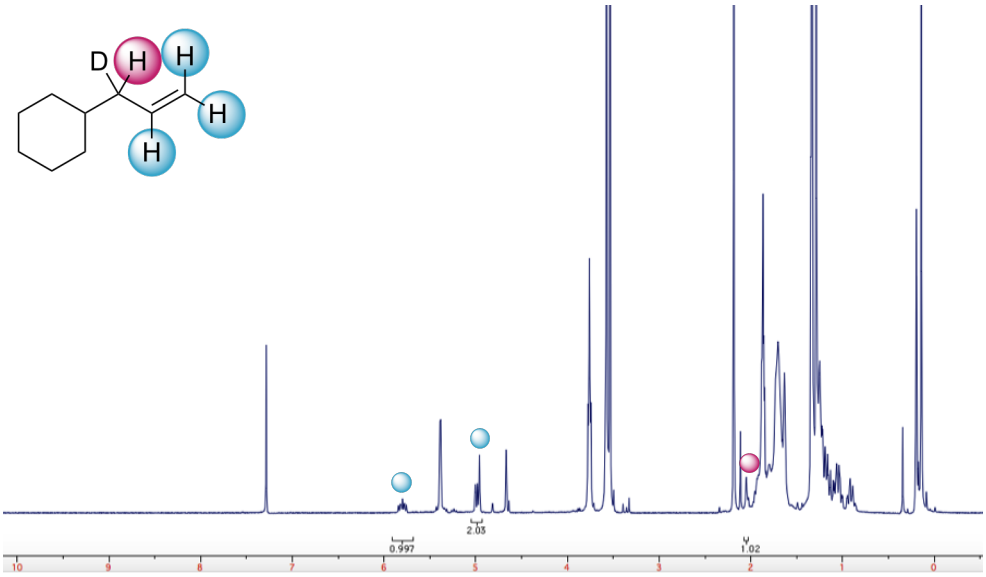
We performed a deuteration experiment using **II**, with the main purpose of further supporting our assignment of **II** as an allyl copper complex. Specifically, if our assignment is correct, protonation of the allyl complex should liberate either **II-A** and/or **II-B**.



Procedure: Inside a nitrogen-filled glovebox, an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with a solution of **II** (0.10 mmol, 1.0 equiv) in THF (1 mL), generated *in situ* as described in Section 2.4.8. *T*-BuOD (48 μL, 0.50 mmol, 5.0 equiv) was added at room temperature. The vial was capped tightly with a Teflon-lined blow-out screw cap and removed from the glovebox. The reaction mixture was allowed to stir vigorously outside the glovebox for 1 h, during which time the mixture changed from a translucent yellow to a cloudy dark brown color. After concentration of the solution *in vacuo*, chloroform-*d* (1 mL) was added and the entire solution transferred to an NMR tube.

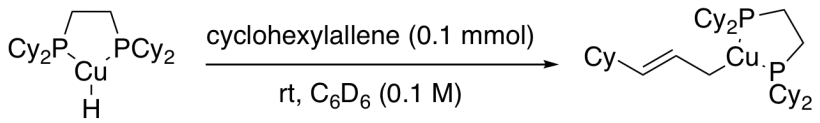
The ^{1}H NMR spectrum of the crude mixture was compared to ^{1}H NMR spectra reported in the literature for **II-A**[37] and **II-B**.[38] Analysis of the olefinic region revealed resonances at 5.78 ppm (m, 1H) and 5.01 ppm (m, 2H), which correspond to **II-A**. Furthermore, one of the allylic hydrogen atoms of **II-A** exhibited 100% deuterium incorporation, as expected from allylic protonation of **II**.

Figure 2-5: ^{1}H NMR analysis of crude mixture from deuteration of **II**



2.4.10 Sequential Preparation of Copper Complexes

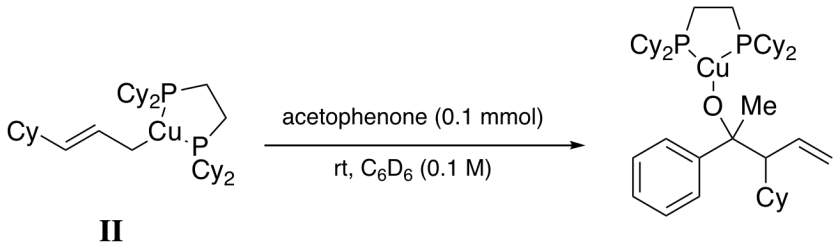
Step 1: Hydrocupration (I → II)



I **II**

(DCyPE)CuH **(I)** was prepared in a reaction tube as detailed in Section 2.4.8. In a nitrogen-filled glovebox, cyclohexylallene (12 mg, 0.10 mmol) was added to the reaction mixture using a 1 mL syringe, fitted with a needle, by piercing the Teflon septum with the needle. The reaction mixture was allowed to stir for 30 s, during which time the mixture changed from a light blue-green to a yellow color. The reaction tube was then uncapped while still in a nitrogen-filled glovebox, and the reaction mixture was transferred to an oven-dried NMR tube using a glass pipette. Observation of the mixture by ^{31}P NMR revealed a major resonance at 10.7 ppm, consistent with the generation of **II**, and no detectable quantity of **I** (15.8 ppm) remained (see Figure 2-6).

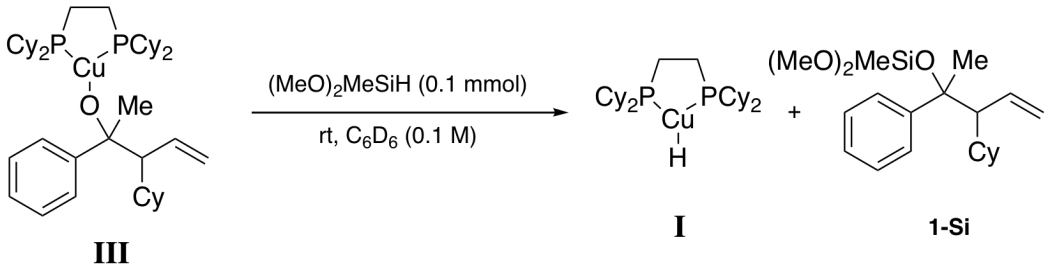
Step 2: Ketone Insertion (II → III)



II **III**

(DCyPE)Cu(allyl) **(II)** was prepared as above in a duplicate reaction. In a nitrogen-filled glovebox, acetophenone (12 mg, 0.10 mmol) was added to the reaction mixture using a 1 mL syringe, fitted with a needle, by piercing the Teflon septum with the needle. The reaction mixture was allowed to stir for 30 s. The reaction tube was then uncapped while still in a nitrogen-filled glovebox, and the reaction mixture was transferred to an oven-dried NMR tube using a glass pipette. Observation of the mixture by ^{31}P NMR revealed a major resonance at 6.8 ppm, consistent with the generation of **III**, and no detectable quantity of **II** (10.7 ppm) remained (see Figure 2-6).

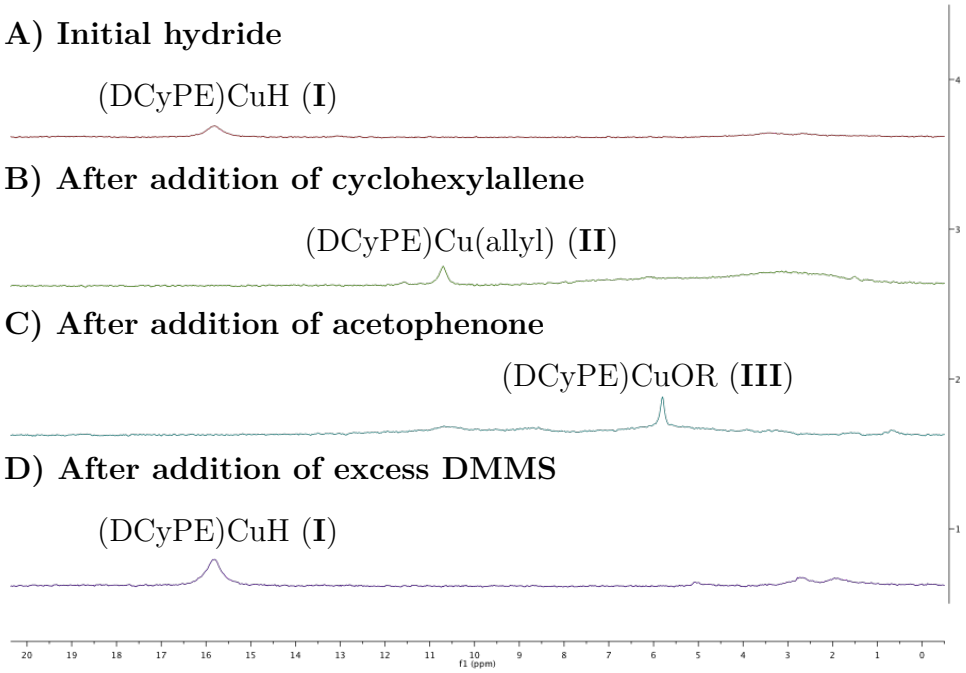
Step 3: Reconversion to Copper Hydride (III → I)



III **I** **1-Si**

(DCyPE)CuOR **(III)** was prepared as above in a duplicate reaction. In a nitrogen-filled glovebox, a 1 mL syringe fitted with a needle was loaded with dimethoxymethylsilane (DMMS, 0.037 mL, 0.30 mmol, 3.0 equiv). The DMMS was added to the mixture by piercing the Teflon septum with the needle. The reaction mixture was allowed to stir for 30 s. The reaction tube was then uncapped while still in a nitrogen-filled glovebox, and the reaction mixture was transferred to an oven-dried NMR tube using a glass pipette. Observation of the reaction mixture by ^{31}P NMR revealed a resonance at 15.8 ppm, consistent with the reconversion to the (DCyPE)CuH **(I)** species (see Figure 2-6). Furthermore, ^{1}H NMR analysis of the crude mixture reveals the appearance of the silylated product **1-Si**.

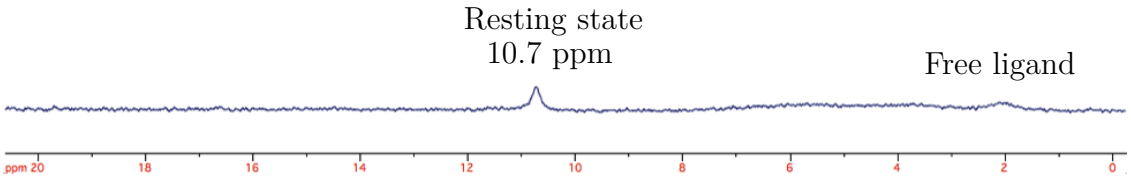
Figure 2-6: Reference ^{31}P NMR spectra for reaction intermediates generated by sequential interconversion



2.4.11 Investigation into the Catalyst Resting State

Inside a nitrogen-filled glovebox, an oven-dried glass culture tube equipped with a magnetic stir bar was charged with $Cu(OAc)_2$ (5 mg, 0.025 mmol, 0.050 equiv) and DCyPE (13 mg, 0.030 mmol, 0.060 equiv). The tube was further charged with cyclohexylallene (73 mg, 0.60 mmol, 1.2 equiv), acetophenone (60 mg, 0.50 mmol, 1.0 equiv), *t*-BuOH (96 μL, 1.0 mmol, 2.0 equiv), and benzene-d_6 (0.5 mL). The tube was then fitted with a Teflon-lined blow-out screw cap. A 1 mL syringe fitted with a needle was filled with dimethoxymethylsilane (DMMS, 0.124 mL, 1.0 mmol, 2.0 equiv). The DMMS was added to the mixture by piercing the Teflon septum with the needle. The reaction mixture was allowed to stir for 30 s. The reaction mixture was rapidly transferred to an oven-dried NMR tube and analyzed by ^{31}P and ^{1}H NMR. The ^{31}P NMR spectrum revealed a major resonance at 10.7 ppm, consistent with complex **II** (see Figure 2-7). Since ^{1}H NMR indicated that the reaction had not yet proceeded to completion, we assigned complex **II** as the catalytic resting state.

Figure 2-7: Reference ^{31}P NMR spectrum of a CuH-catalyzed ketone-allene coupling in progress



2.5 References and Notes

[1] For selected recent reviews describing stereoselective allyl addition to carbonyl compounds, see: (a) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y., Hong, R. Catalytic asymmetric allylation of carbonyl compounds and imines with allylic boronates. *Org. Chem. Front.* **2014**, *1*, 303–320. (b) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. Diastereoselective Allylation of Carbonyl Compounds and Imines: Application to the Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, 5595–5698. (c) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. Catalytic Enantioselective Allylation of Carbonyl Compounds and Imines. *Chem. Rev.* **2011**, *111*, 7774–7854. (d) Tietze, L. F.; Kinzel, T.; Brazel, C. C. The Domino Multicomponent Allylation Reaction for the Stereoselective Synthesis of Homoallylic Alcohols. *Acc. Chem. Res.* **2009**, *42*, 367–378. (e) Shibasaki, M.; Kanai, M. Asymmetric Synthesis of Tertiary Alcohols and α-Tertiary Amines via Cu-Catalyzed C-C Bond Formation to Ketones and Ketimines. *Chem. Rev.* **2008**, *108*, 2853–2873. (f) Hatano, M.; Ishihara, K. Recent Progress in the Catalytic Synthesis of Tertiary Alcohols from Ketones with Organometallic Reagents. *Synthesis* **2008**, *11*, 1647–1675. (g) Yamamoto, H.; Wadamoto, M. Silver-Catalyzed Asymmetric Allylation: Allyltrimethoxysilane as a Remarkable Reagent. *Chem. Asian. J.* **2007**, *2*, 692–698. (h) Denmark, S. E.; Fu, J. Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones. *Chem. Rev.* **2003**, *103*, 2763–2794.

[2] For examples of catalytic, asymmetric addition of allylboron reagents to ketones, see: (a) Robbins, D. W.; Lee, K.; Silverio, D. L.; Volkov, A.; Torker, S.; Hoveyda, A. H. Practical and Broadly Applicable Catalytic Enantioselective Additions of Allyl-B(pin) Compounds to Ketones and α-Ketoesters. *Angew. Chem. Int. Ed.* **2016**, *55*, 9610–9614. (b) Lee, K.; Silverio, D. L.; Torker, S.; Haeffner, F.; Robbins, D. W.; van der Mei, F. W.; Hoveyda, A. H. Catalytic enantioselective addition of organoboron reagents to fluoroketones controlled by electrostatic interactions. *Nat. Chem.* **2016**, *8*, 768–777. (c) Alam, R.; Volgraff, T.; Eriksson, L.; Szabo, K. J. Synthesis of Adjacent Quaternary Stereocenters by Catalytic Asymmetric Allylboration. *J. Am. Chem. Soc.* **2015**, *137*, 11262–11265. (d) Zhang, Y.; Li, N.; Qu, Bo.; Ma, S.; Lee, H.; Gonnella, N. C.; Gao, J.; Li, W.; Tan, Z.; Reeves, J. T.; Wan, J.; Lorenz, J. C.; Li, G.; Reeves, D. C.; Premasiri, A.; Grinberg, N.; Haddad, N.; Lu, B. Z.; Song, J. J.; Senanayake, C. H. Asymmetric Methallylation of Ketones Catalyzed by a Highly Active Organocatalyst 3,3-F_2-BINOL. *Org. Lett.* **2013**, *15*, 1710–1713. (e) Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric Allylboration of Ketones Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661.

[3] For examples of catalytic, asymmetric addition of allylmetal reagents to ketones using copper catalysts, see: (a) Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. Identification of Modular Chiral Bisphosphines Effective for Cu(I)-Catalyzed Asymmetric Allylation and Propargylation of Ketones. *J. Am. Chem. Soc.* **2010**, *132*, 6638–6639. (b) Kanai, M.;

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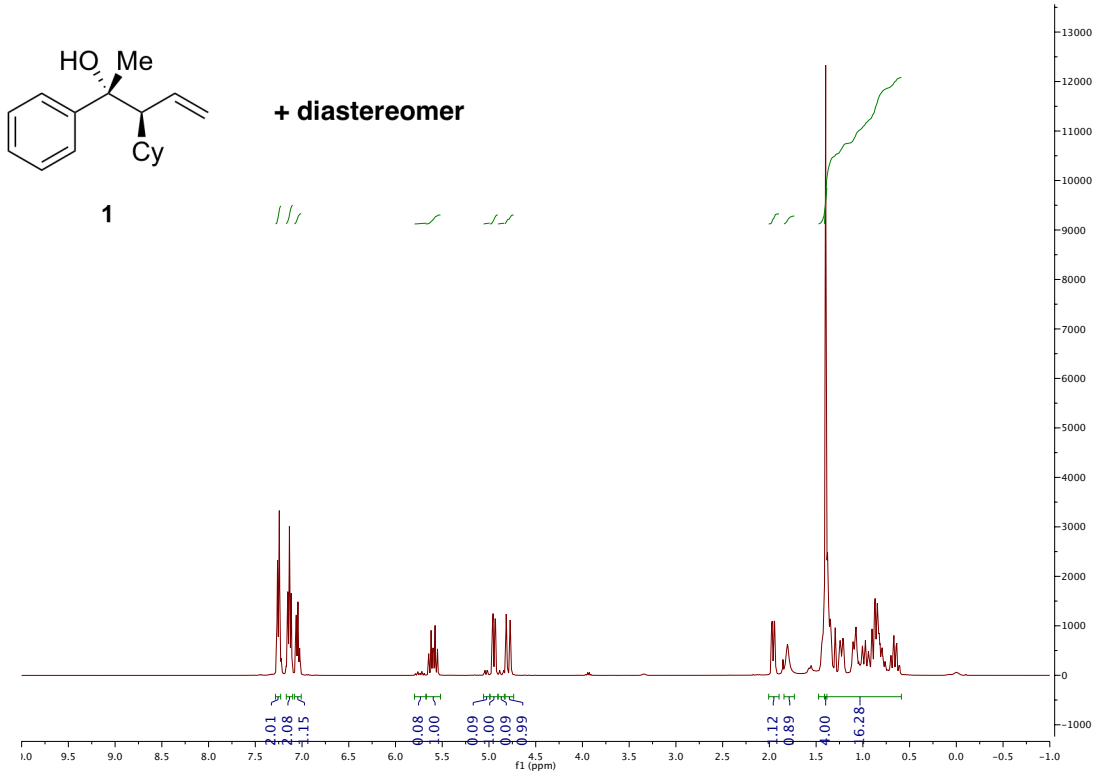
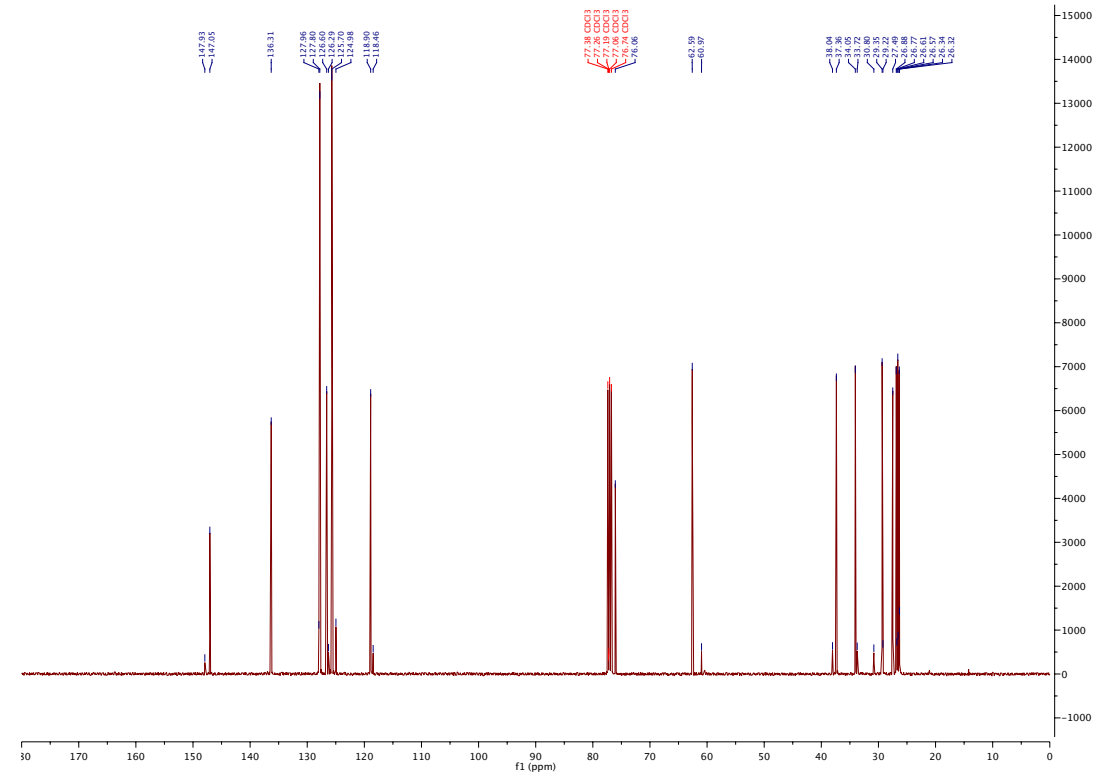
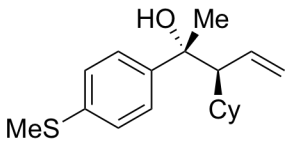
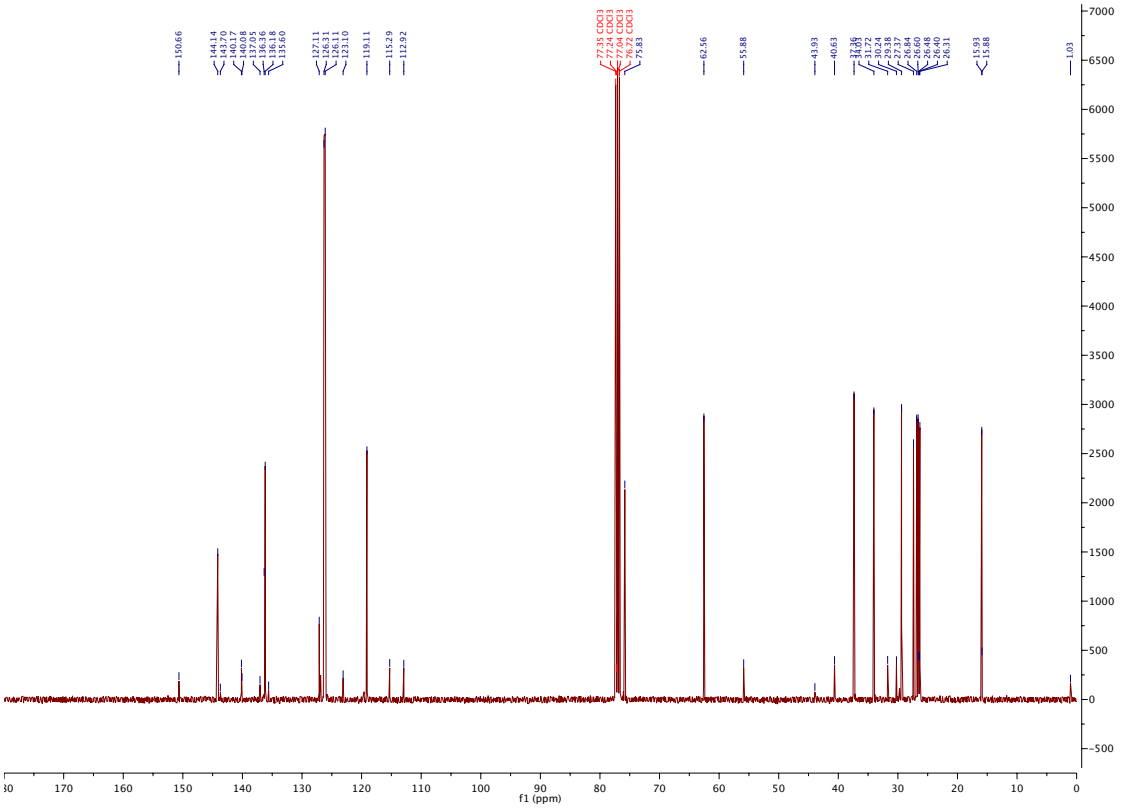
2.6 Spectra and Chromatograms

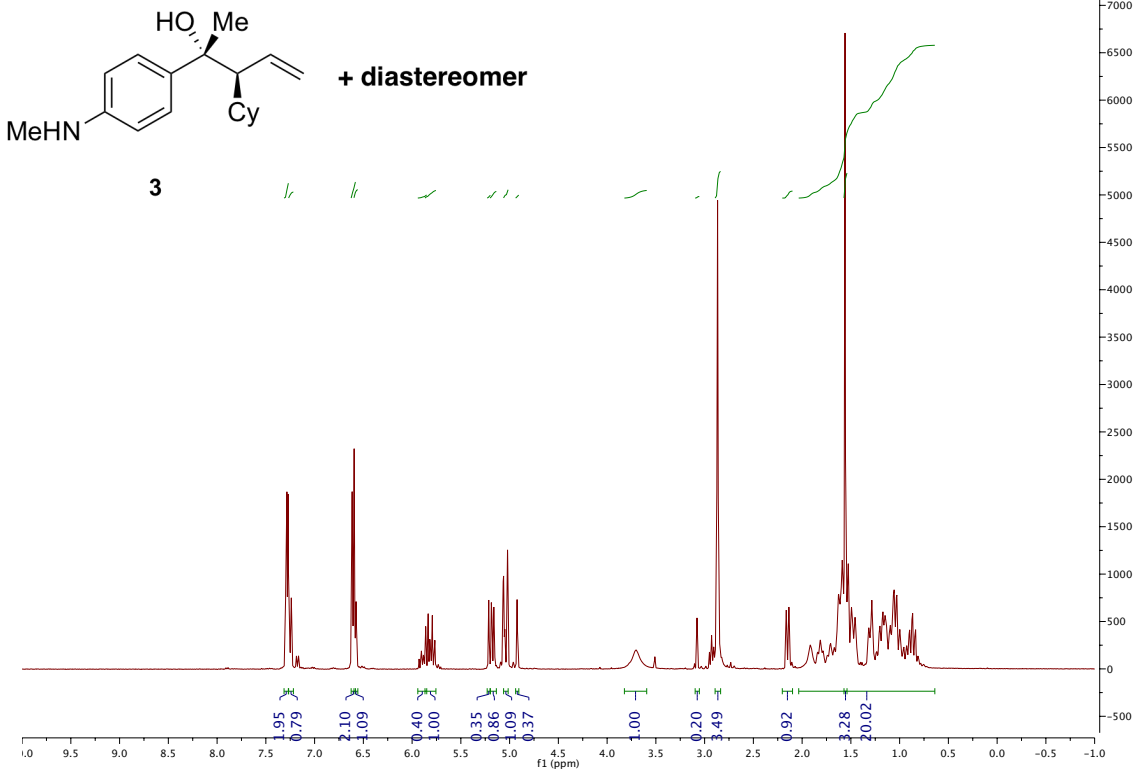


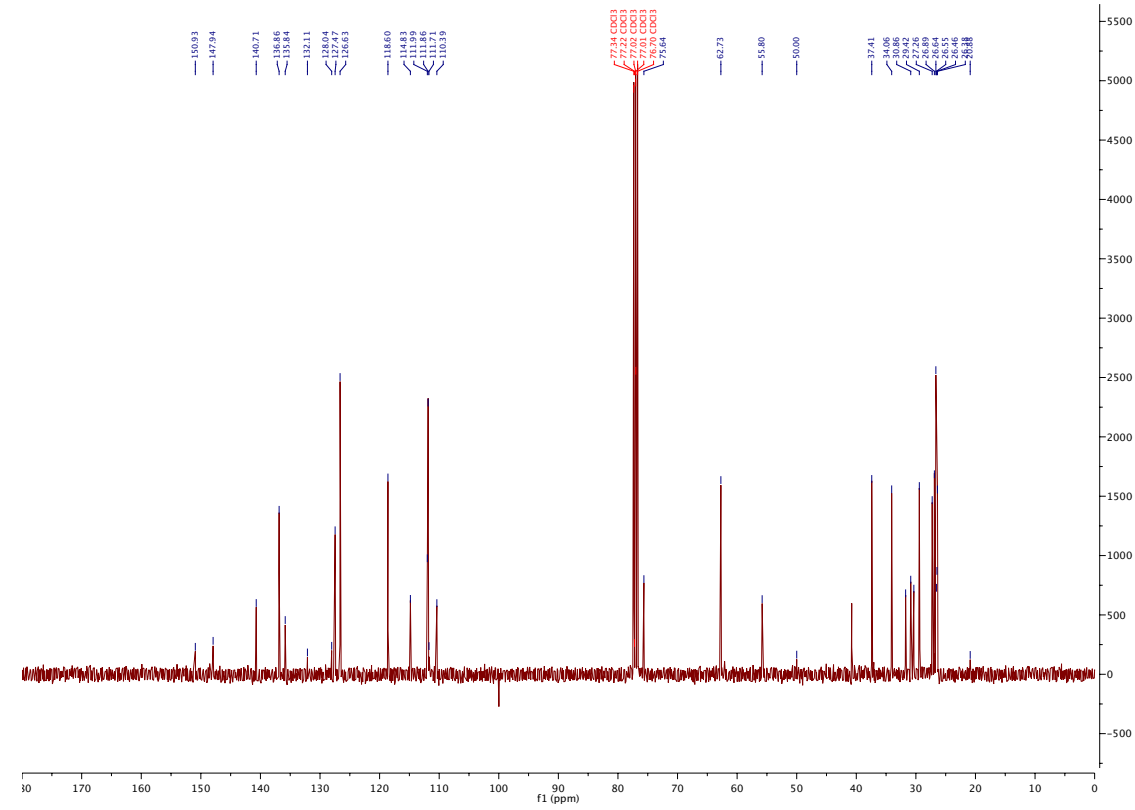


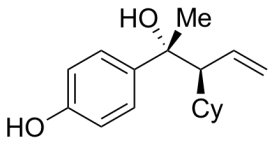


2 **+ diastereomer**



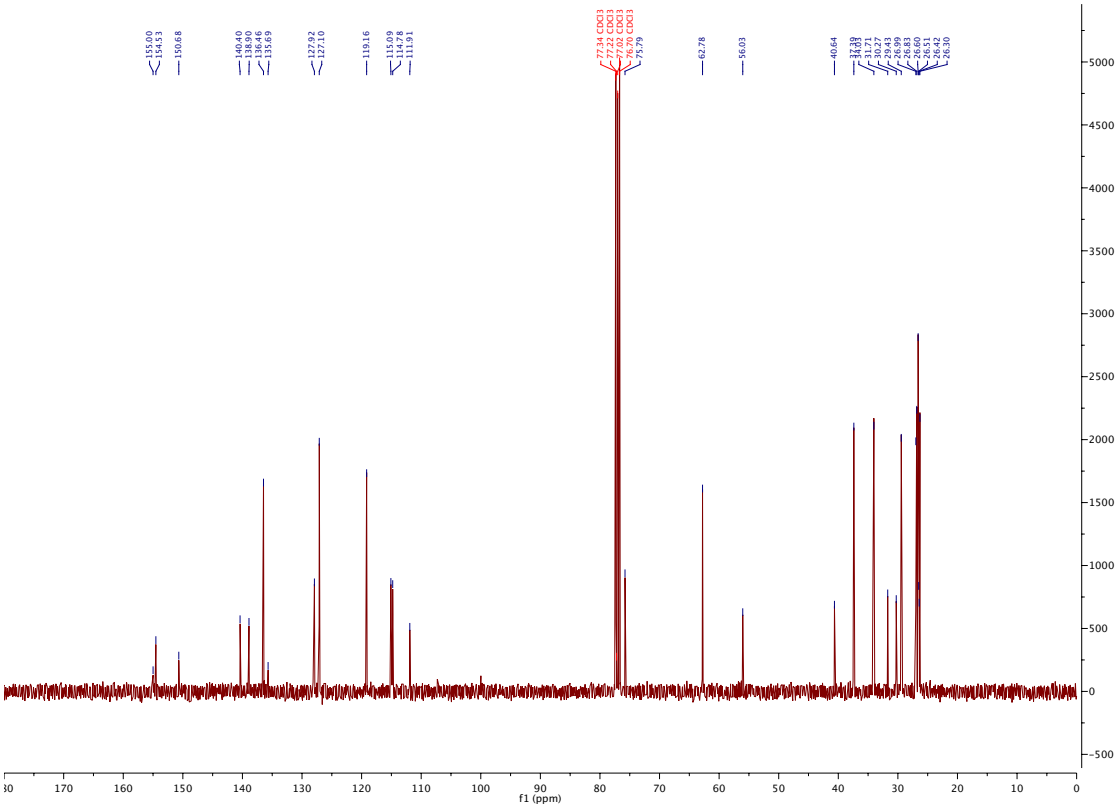

HO
Me
Cy
MeHN
+ diastereomer
3
1.95
0.79
2.10
1.09
0.40
1.00
0.35
0.86
1.09
0.37
1.00
0.20
3.49
0.92
3.28
20.02
f1 (ppm)

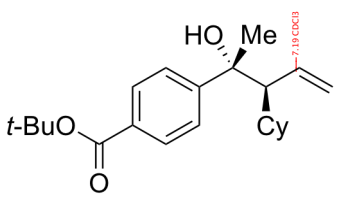

150.93
147.94
140.71
136.86
135.84
132.11
128.04
127.47
126.63
118.60
114.83
111.99
111.86
111.71
110.39
77.34 CDCl3
77.22 CDCl3
77.02 CDCl3
76.70 CDCl3
75.64
62.73
55.80
50.00
37.41
34.06
33.46
33.42
27.26
26.89
26.64
26.55
26.46
f1 (ppm)



+ diastereomer

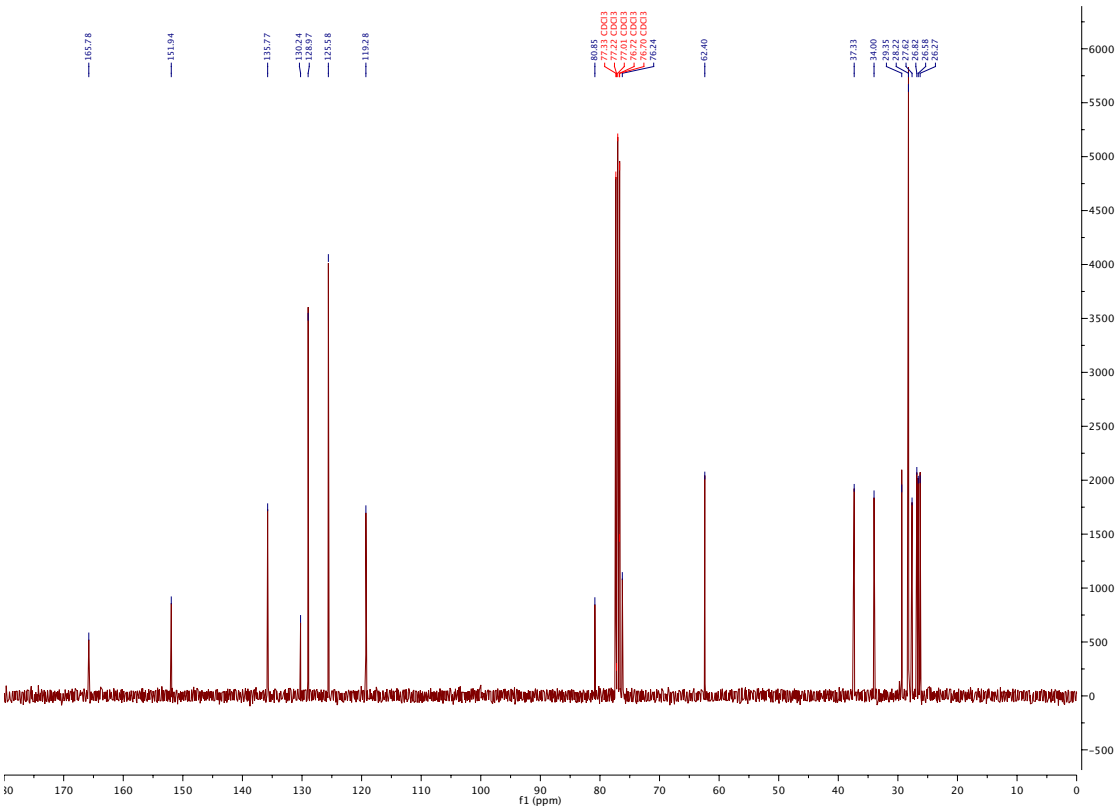
4

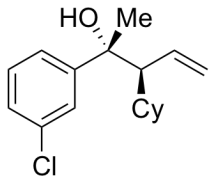



HO
Me
t-BuO
Cy
O

5

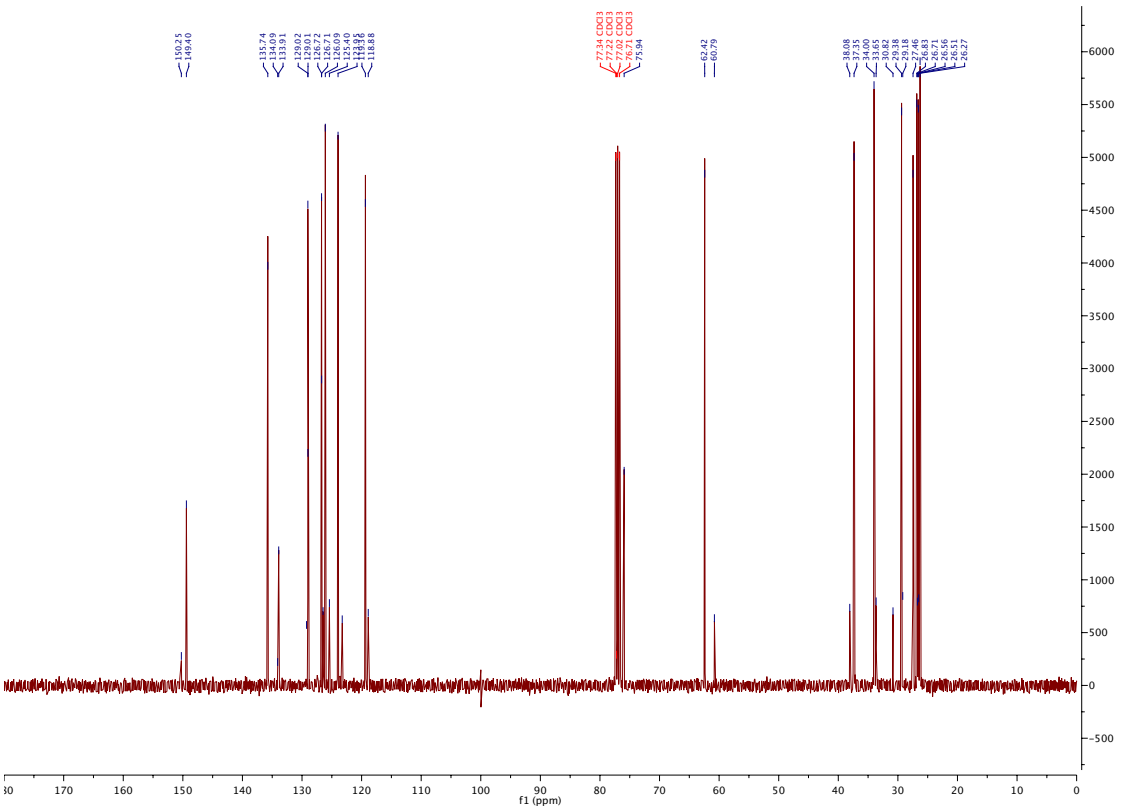
7.19 CDCl3
1.95
2.01
1.00
1.04
1.00
1.04
1.02
11.79
2.89
29.07
f1 (ppm)

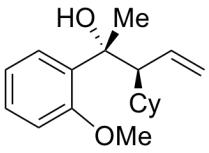

165.78
151.94
135.77
130.24
128.97
125.58
119.28
80.85
77.33 CDCl3
77.22 CDCl3
77.01 CDCl3
76.72 CDCl3
76.70 CDCl3
76.24
62.40
37.33
34.00
29.35
28.22
27.72
26.82
26.58
26.27
f1 (ppm)



6

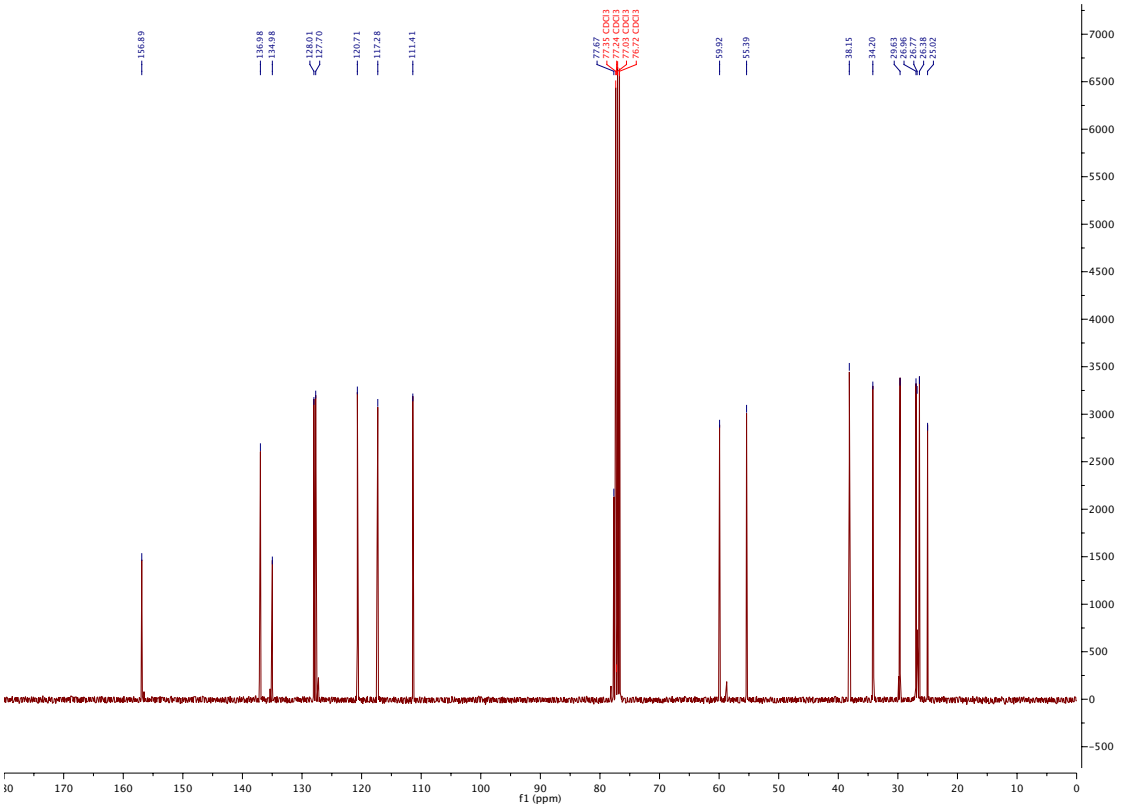
+ diastereomer

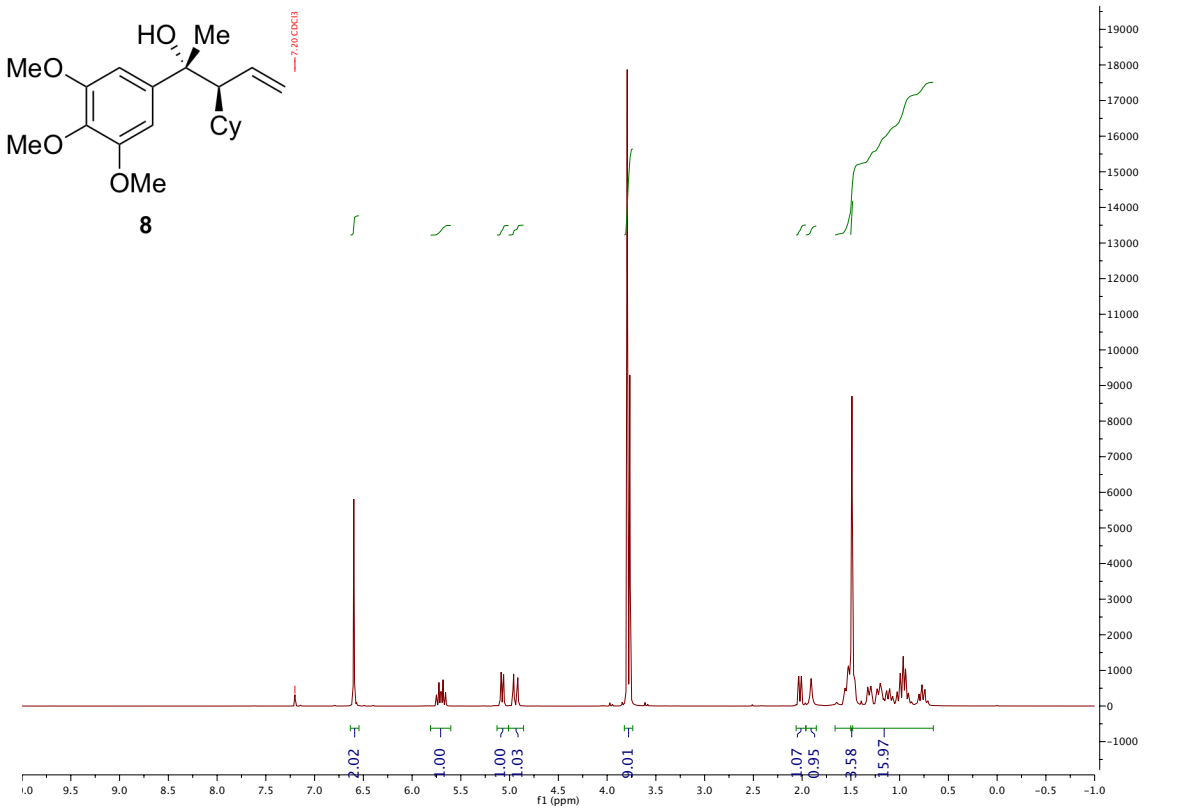


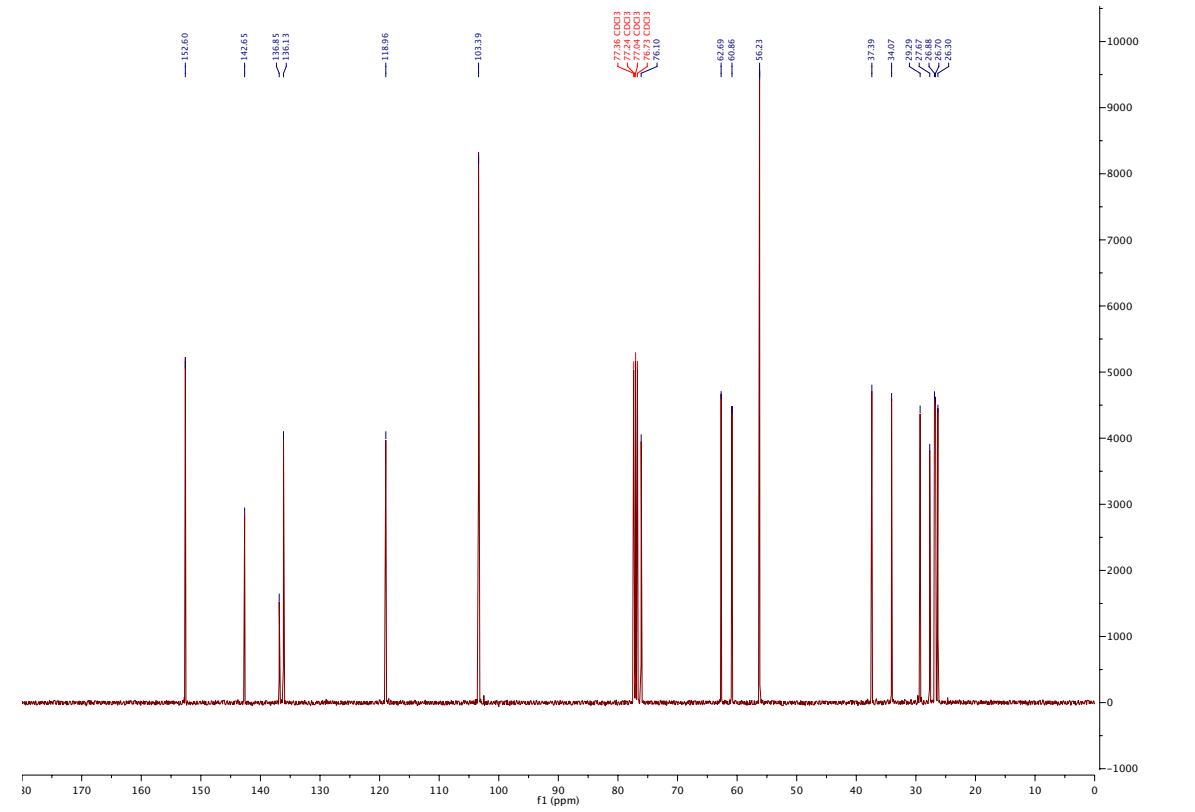


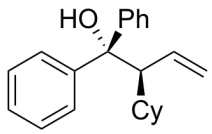
7

+ diastereomer



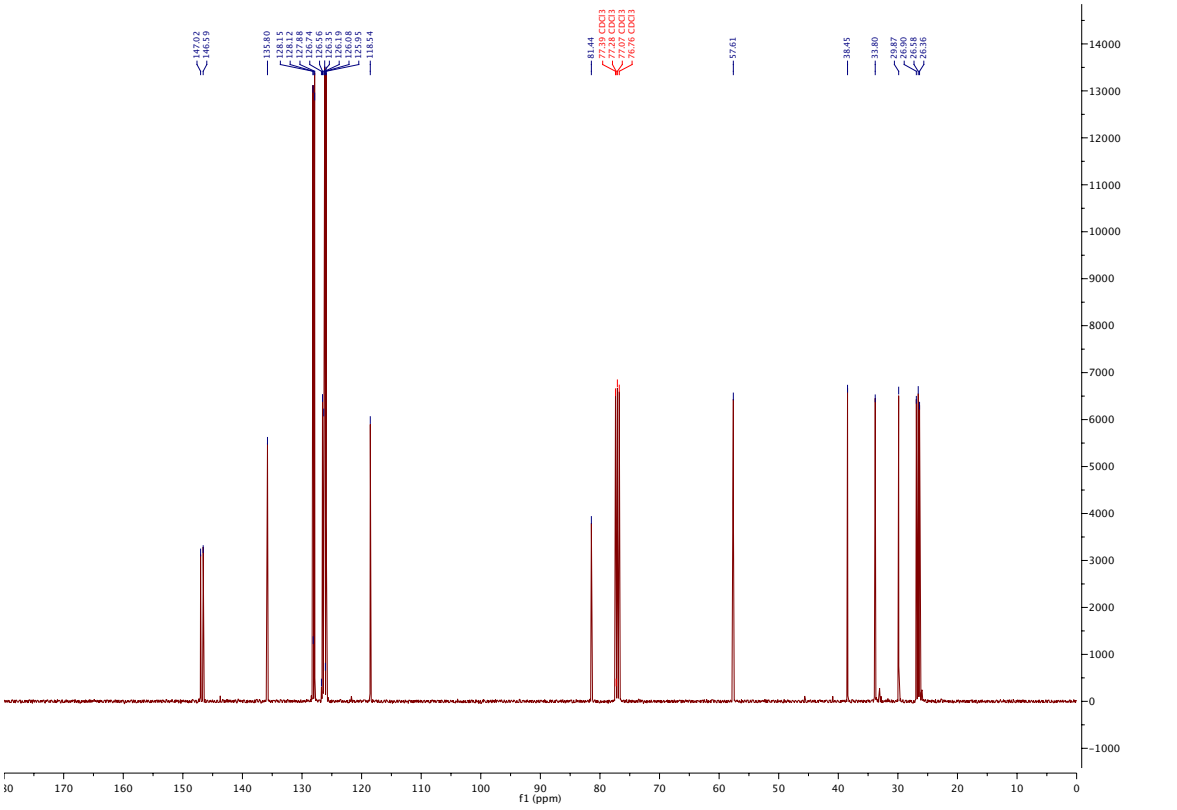

HO
Me
MeO
MeO
OMe
Cy
8
7.20 CDCl3
2.02
1.00
1.00
1.03
9.01
1.07
0.95
3.58
15.97
f1 (ppm)

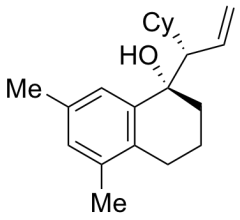

152.60
142.65
136.85
136.13
118.96
103.39
77.16 CDCl3
77.04 CDCl3
76.73 CDCl3
76.10
62.69
60.86
56.23
37.39
34.07
29.29
27.67
26.88
26.70
26.50
f1 (ppm)


HO
Ph
Cy

9

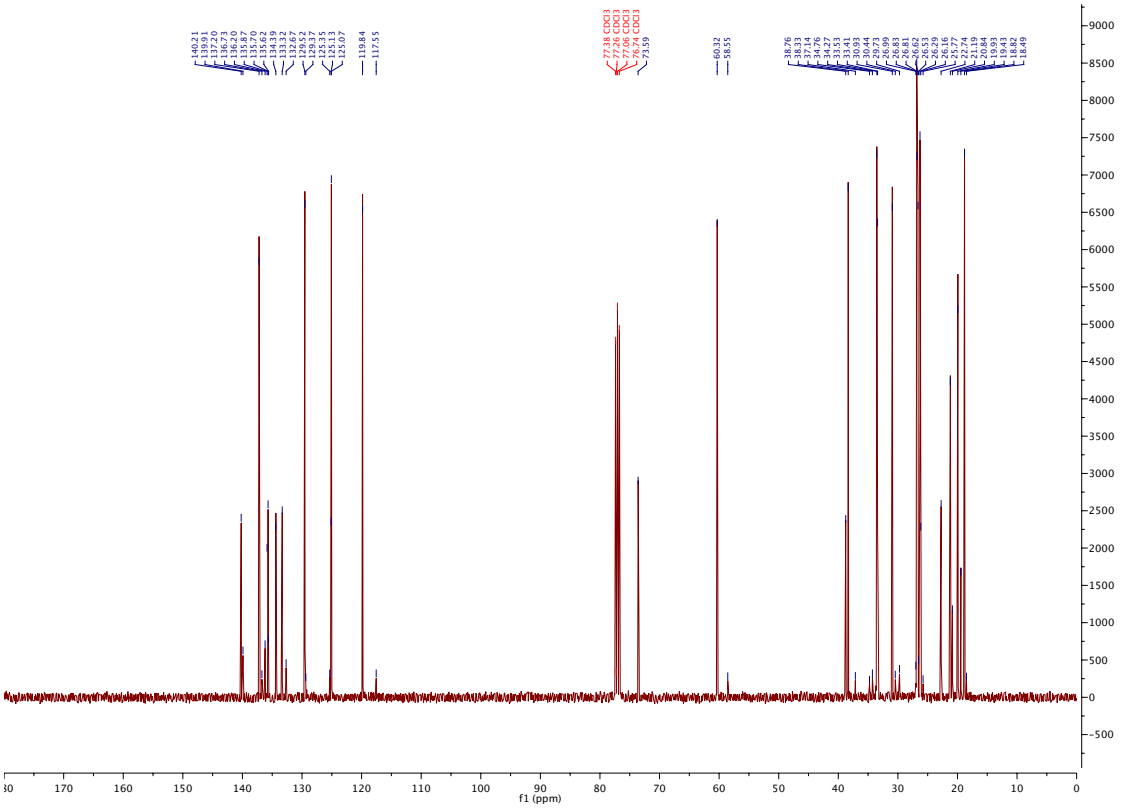
2.00
2.04
2.09
3.12
1.00
1.00
1.01
1.01
1.05
0.99
12.44
f1 (ppm)

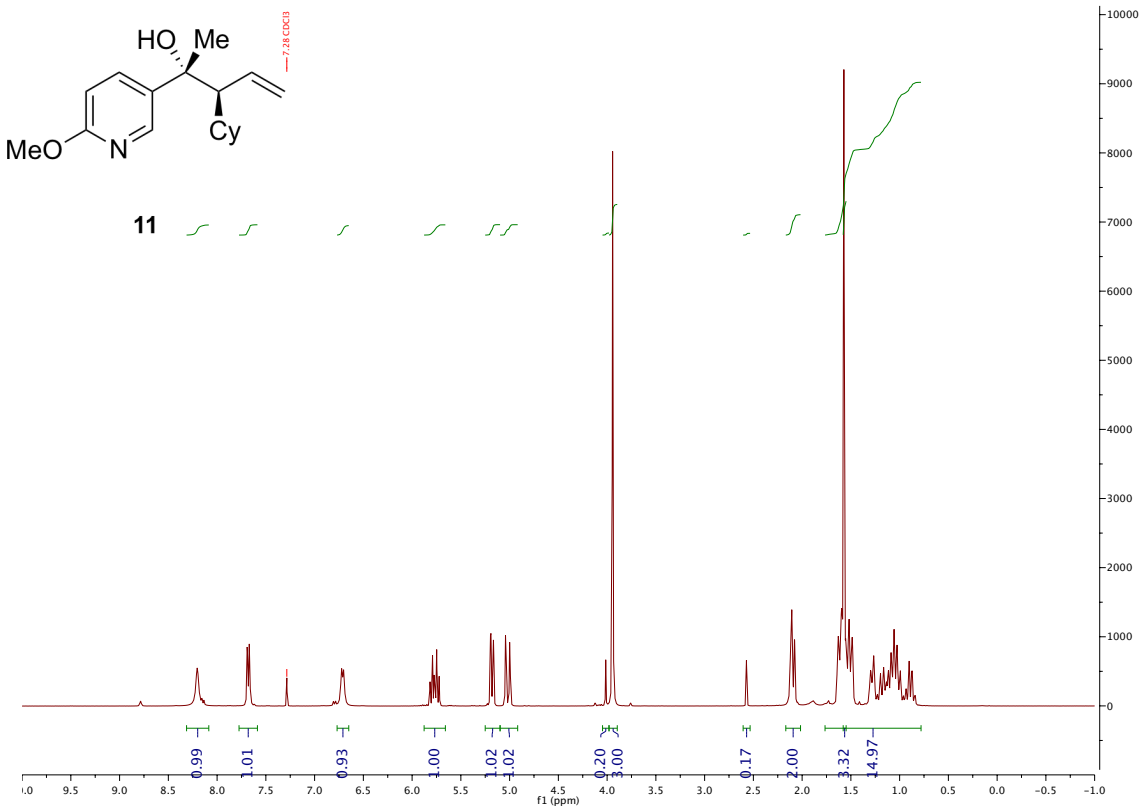

147.02
146.59
135.80
128.15
128.12
127.88
126.74
126.56
126.35
126.19
126.08
125.95
118.54
81.44
77.39 CDCl3
77.07 CDCl3
76.76 CDCl3
57.61
38.45
33.80
29.87
26.60
26.58
26.36
f1 (ppm)

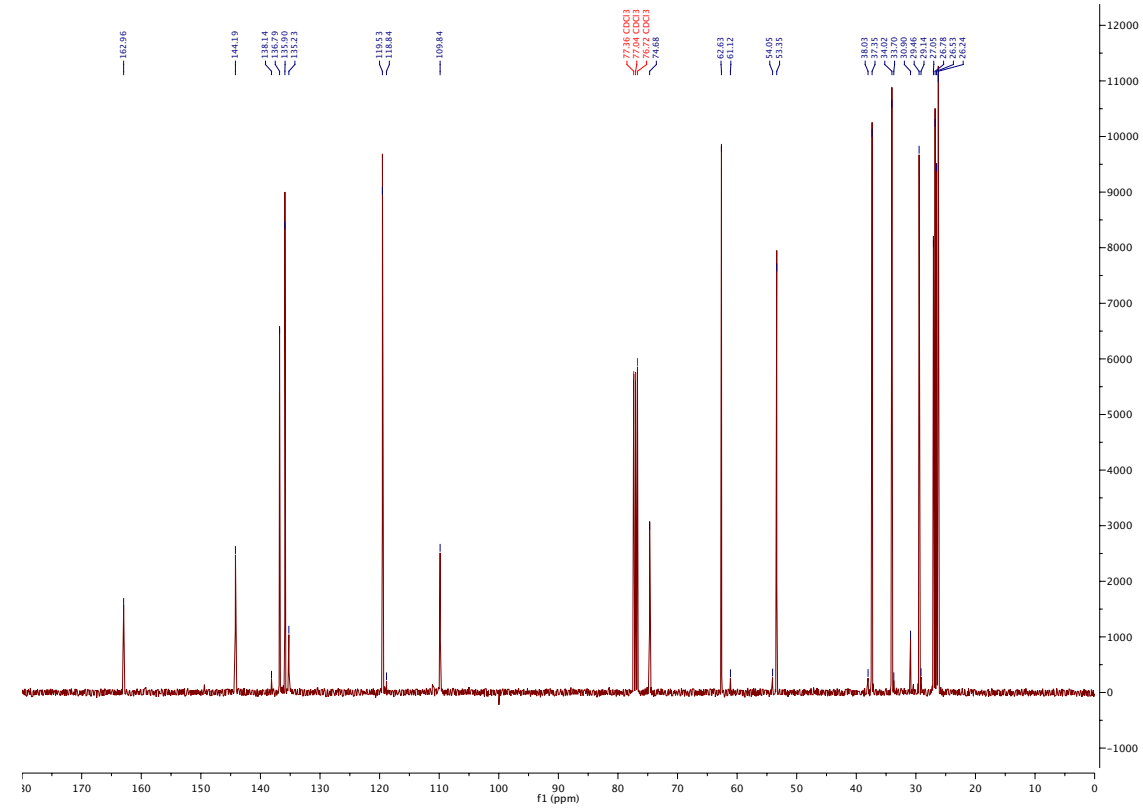


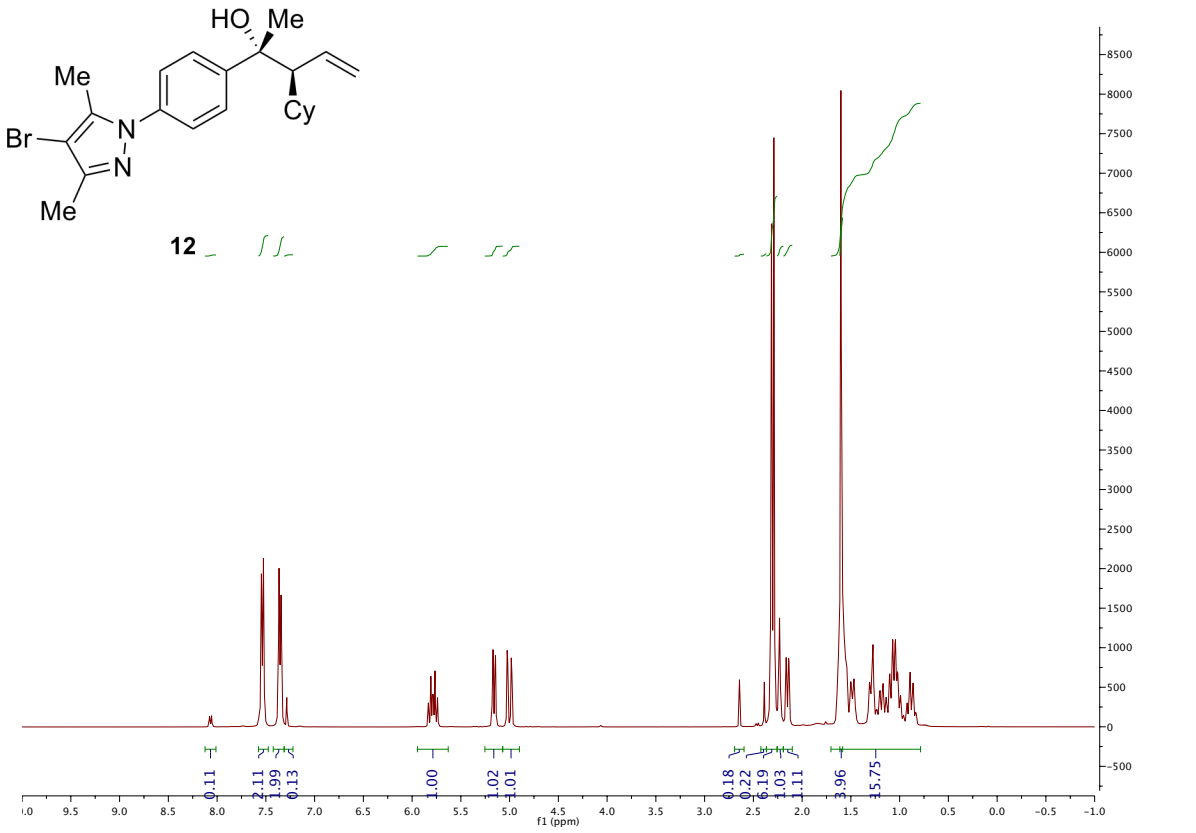
10

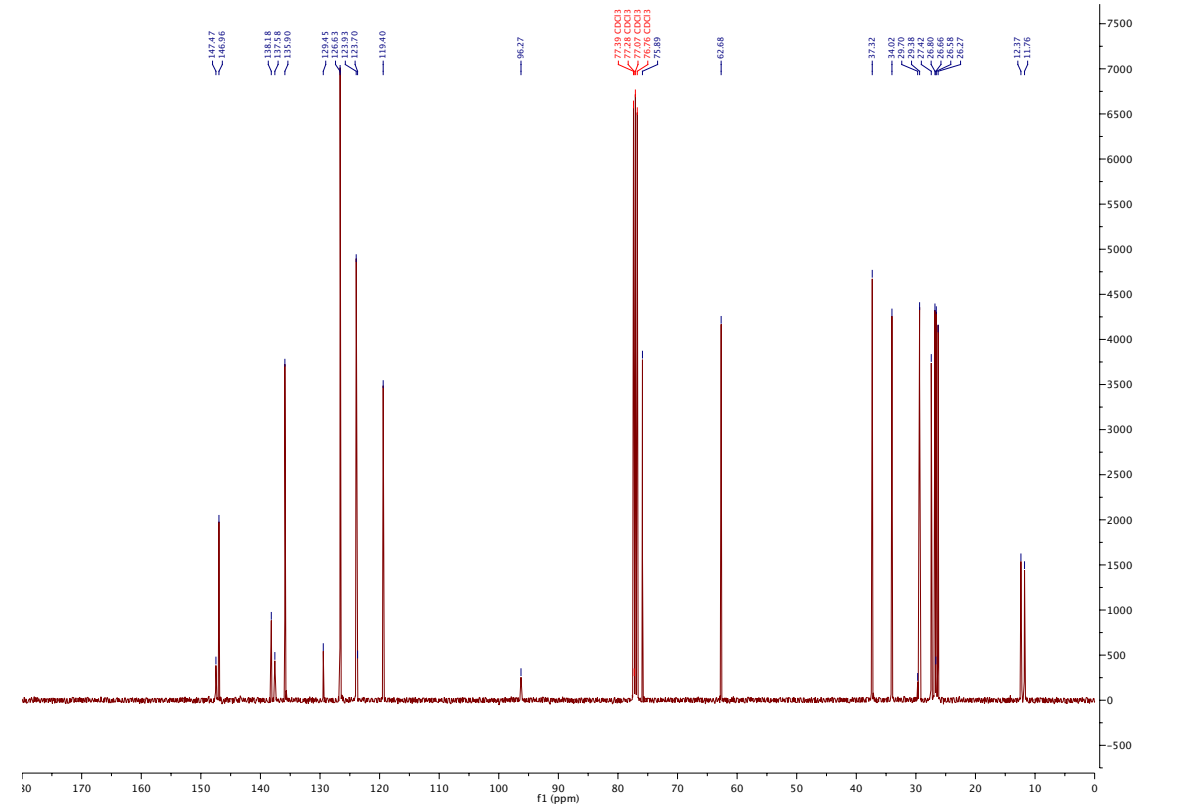
+ diastereomer

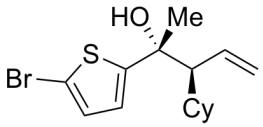



HO
Me
Cy
MeO
N
11
7.28 CDCl3
0.99
1.01
0.93
1.00
1.02
1.02
0.20
3.00
0.17
2.00
3.32
14.97
f1 (ppm)


162.96
144.19
138.14
136.79
135.90
135.23
119.53
118.64
109.84
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
74.68
62.63
61.12
54.05
53.35
18.03
37.35
34.02
33.30
30.90
29.46
28.14
27.05
26.78
26.53
26.34
f1 (ppm)

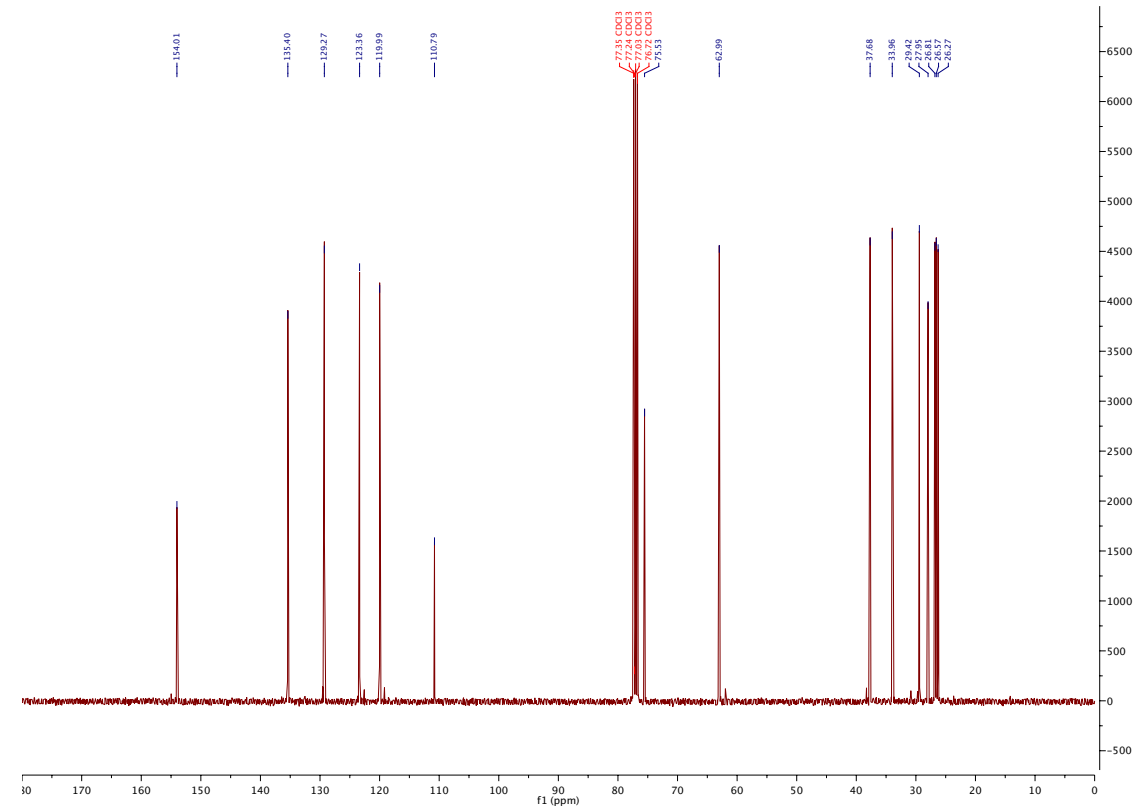

HO
Me
Me
Br
N
N
Me
Cy
12
0.11
2.11
1.99
0.13
1.00
1.02
1.01
0.18
0.22
6.19
1.03
1.11
3.96
15.75
f1 (ppm)

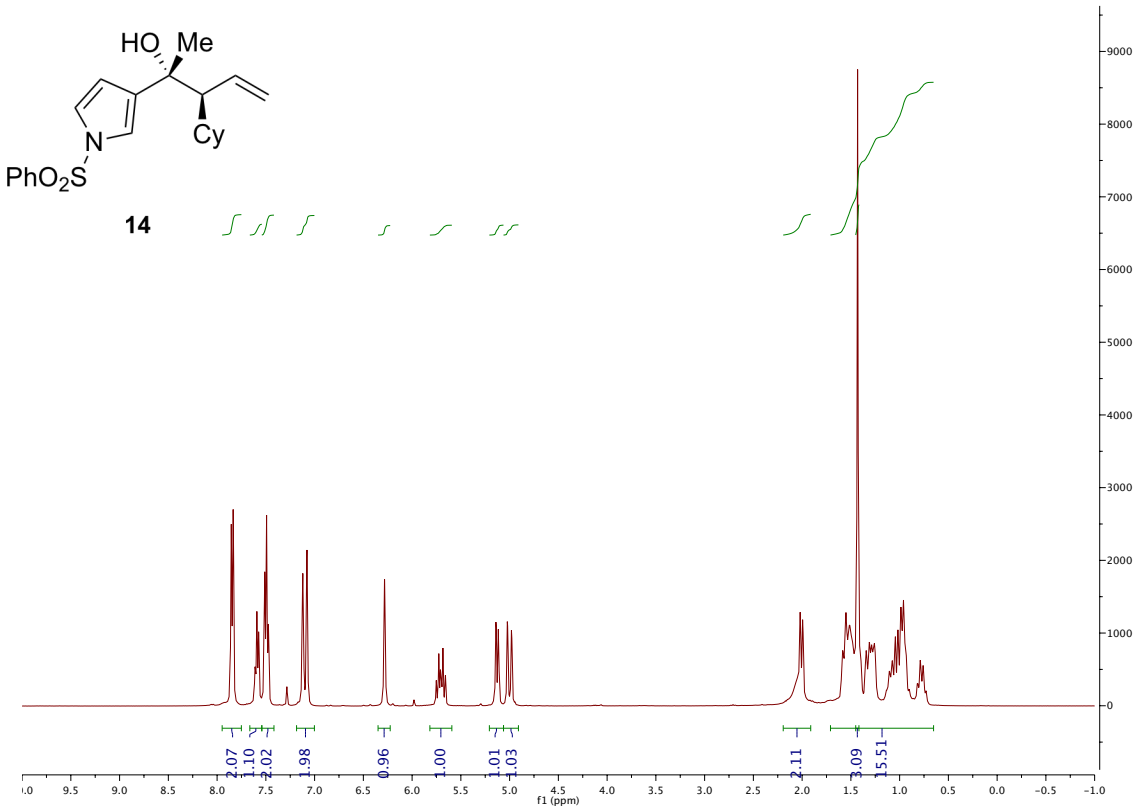

147.47
146.96
138.18
137.58
135.90
129.45
126.63
123.93
123.70
119.40
96.27
77.16 CDCl3
77.00 CDCl3
76.76 CDCl3
75.89
62.68
37.32
34.02
29.70
29.38
27.32
26.80
26.66
26.58
26.27
12.37
11.76
f1 (ppm)

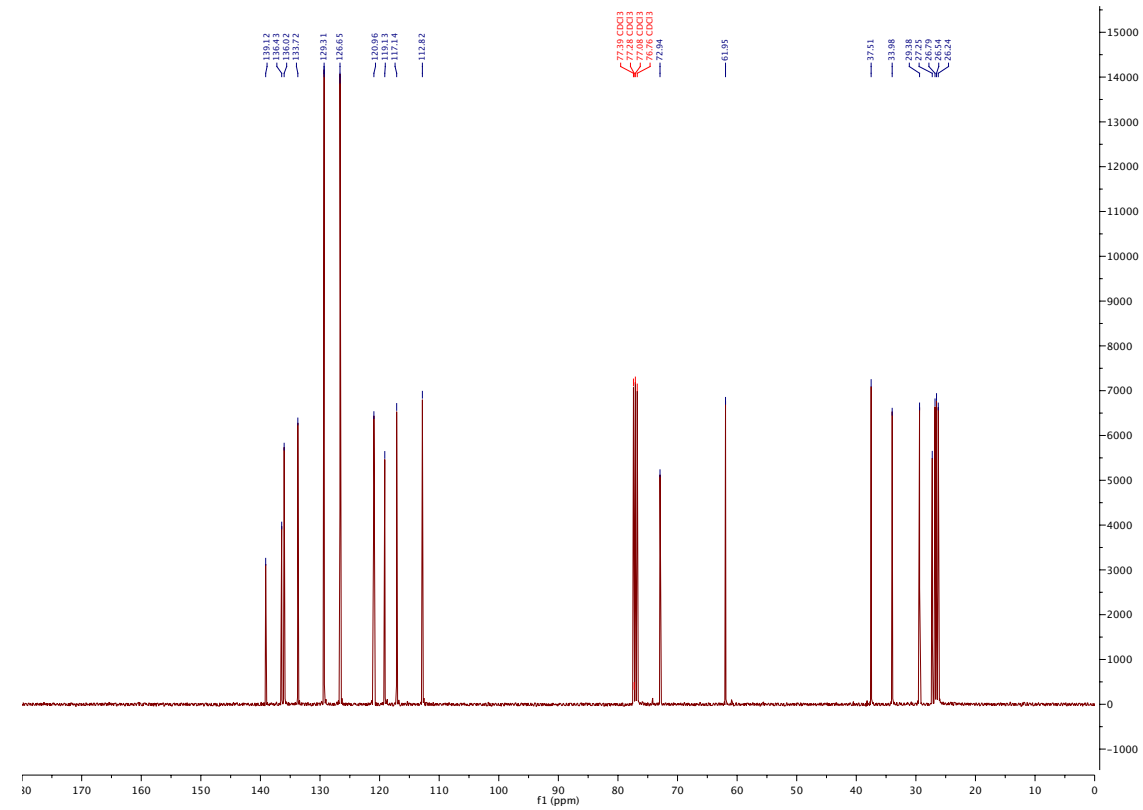

HO
Me
S
Br
Cy

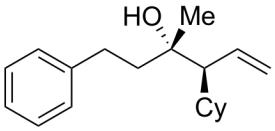
13

7.09 CDCl3
0.97
0.98
1.00
1.01
1.01
0.94
1.02
3.74
15.68
f1 (ppm)


154.01
135.40
129.27
123.36
119.99
110.79
77.35 CDCl3
77.23 CDCl3
77.03 CDCl3
76.72 CDCl3
75.53
62.99
37.68
33.96
29.42
27.95
26.81
25.57
25.27
f1 (ppm)

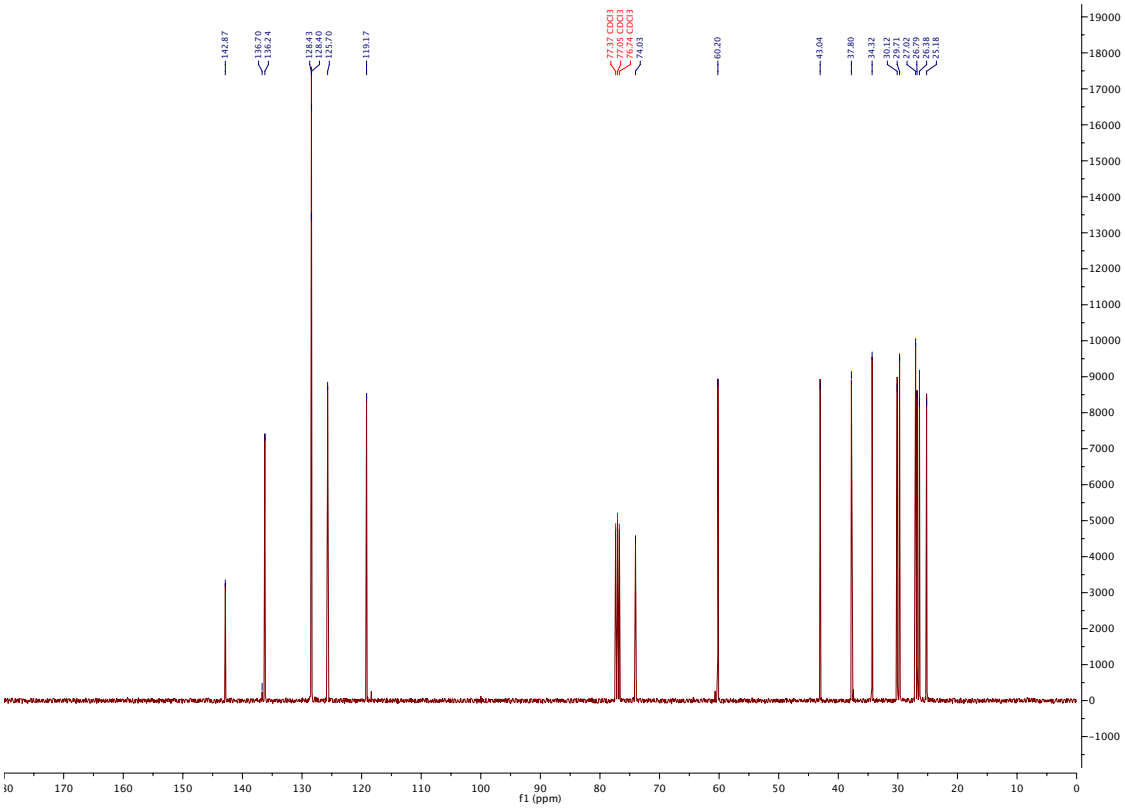

HO
Me
Cy
N
PhO2S
14
2.07
1.10
2.02
1.98
0.96
1.00
1.01
1.03
2.11
3.09
15.51
f1 (ppm)

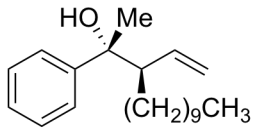

139.12
136.43
136.02
133.72
129.31
126.65
120.96
119.13
117.14
112.82
77.39 CDCl3
77.07 CDCl3
76.76 CDCl3
72.94
61.95
37.51
33.98
30.38
27.25
26.79
26.54
26.24
f1 (ppm)


HO
Me
Cy

15

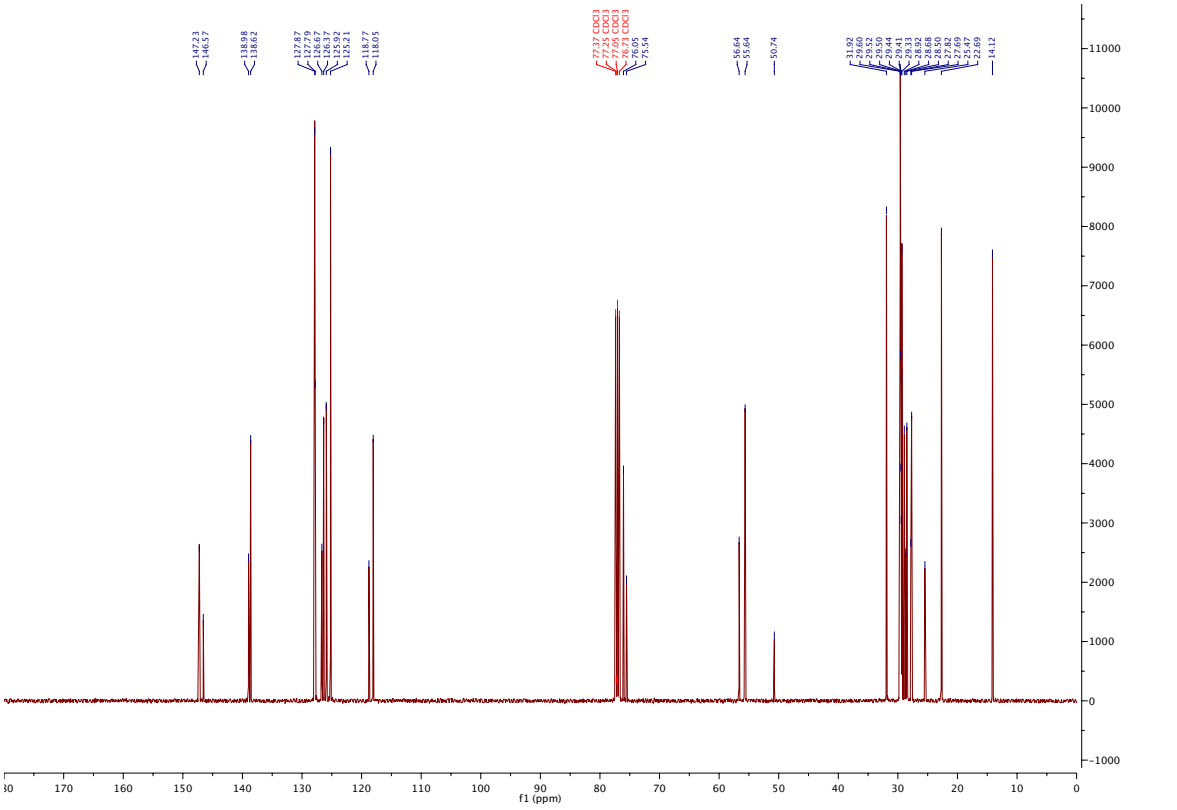
2.09
2.94
1.00
1.00
1.04
2.01
19.36
3.30
f1 (ppm)

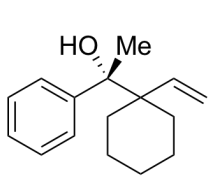

142.87
136.70
136.24
128.43
128.40
125.70
119.17
77.37 CDCl3
77.05 CDCl3
76.74 CDCl3
74.03
60.20
43.04
37.80
34.32
30.12
29.71
27.79
26.29
26.38
25.18
f1 (ppm)



16

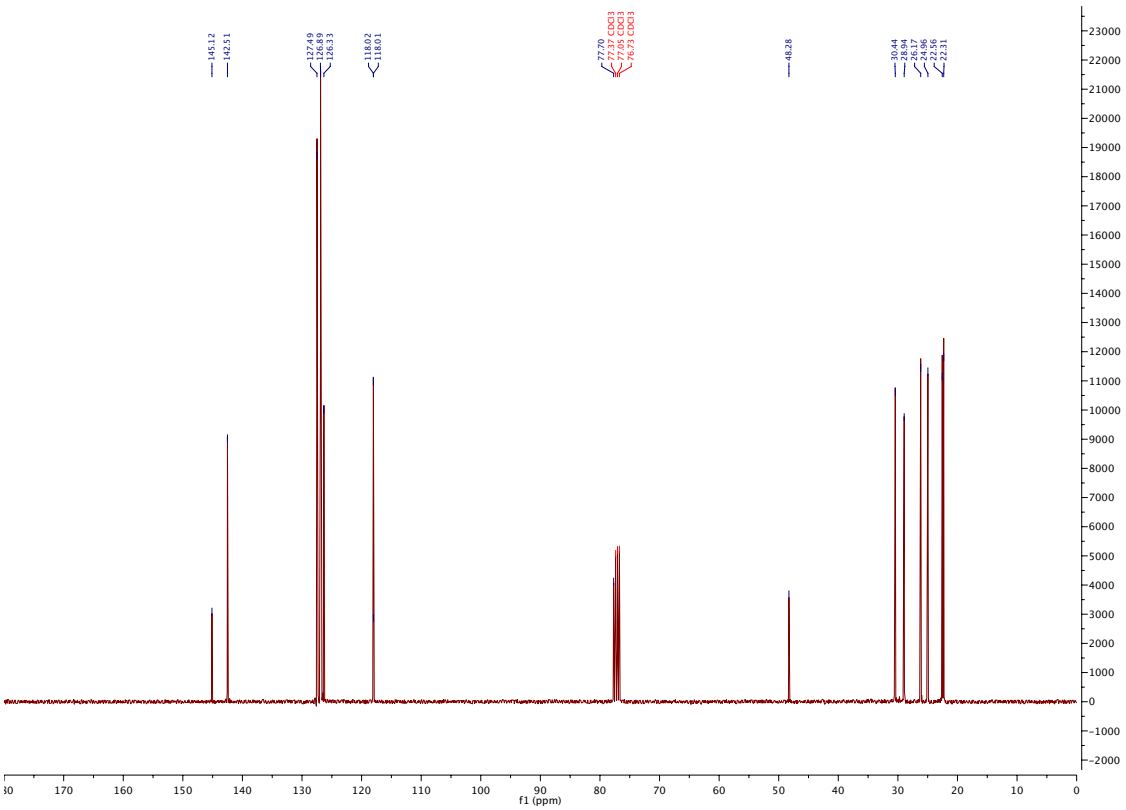
+ diastereomer

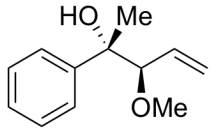



HO
Me

17

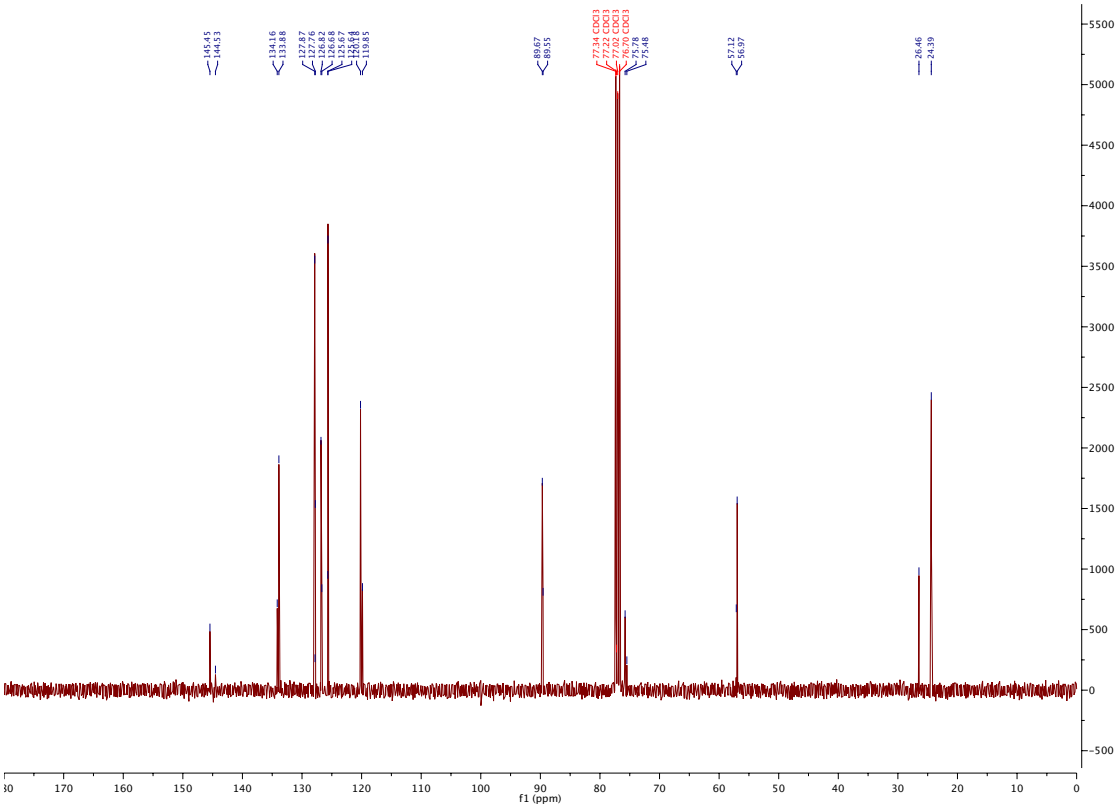
1.98
1.99
1.09
2.03
1.00
1.00
1.03
3.38
13.30
f1 (ppm)

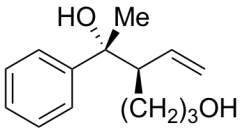

145.12
142.51
127.49
126.89
126.33
118.02
118.01
77.70
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
48.28
30.44
28.84
26.17
24.96
23.16
22.31
f1 (ppm)



18

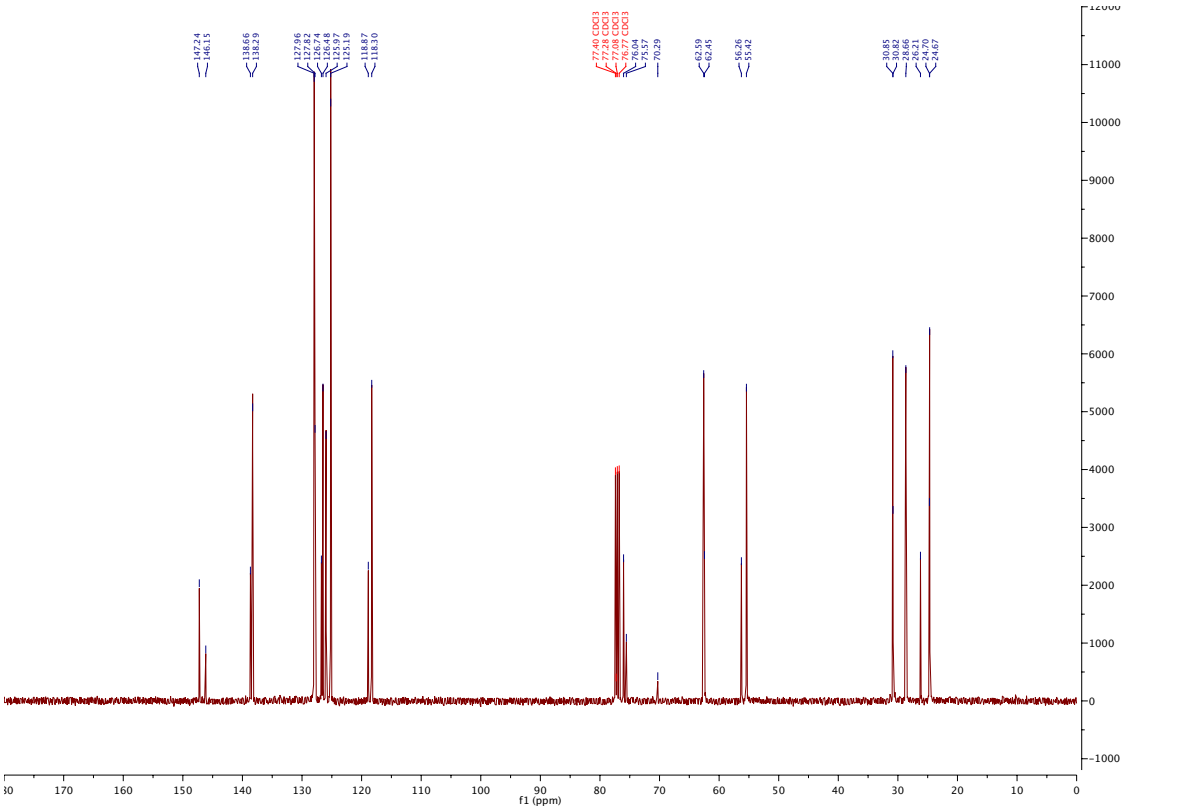
+ diastereomer

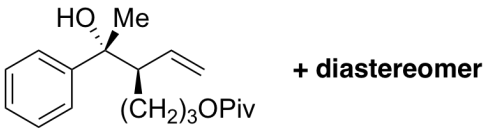



HO
Me
(CH2)3OH

19

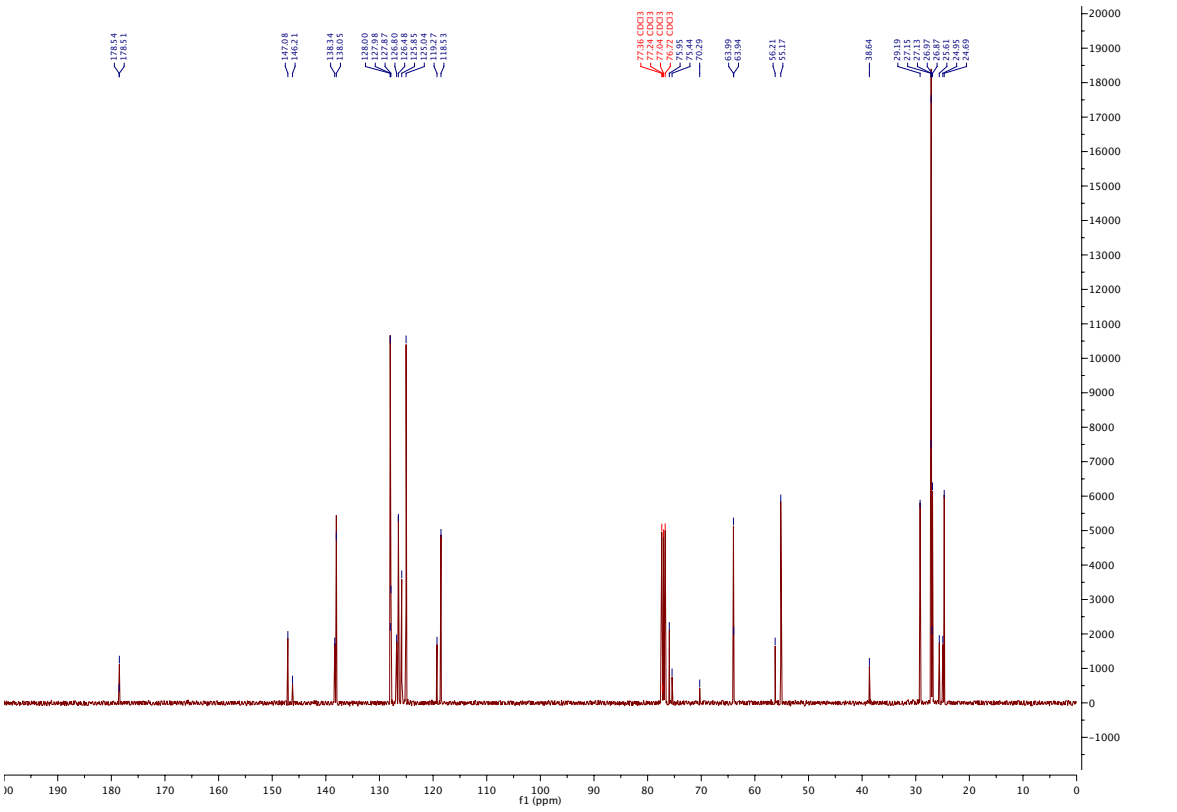
7.54
1.00
0.49
1.67
1.17
0.58
2.98
1.65
0.96
1.68
4.71
5.82
f1 (ppm)

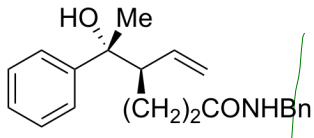

147.24
146.15
138.66
138.29
127.96
127.82
126.74
126.48
125.97
125.19
118.87
118.30
77.40 CDCl3
77.28 CDCl3
77.08 CDCl3
76.77 CDCl3
76.04
75.57
70.29
62.59
62.45
56.26
55.42
30.85
30.82
30.66
30.56
28.21
24.70
24.67
f1 (ppm)



+ diastereomer

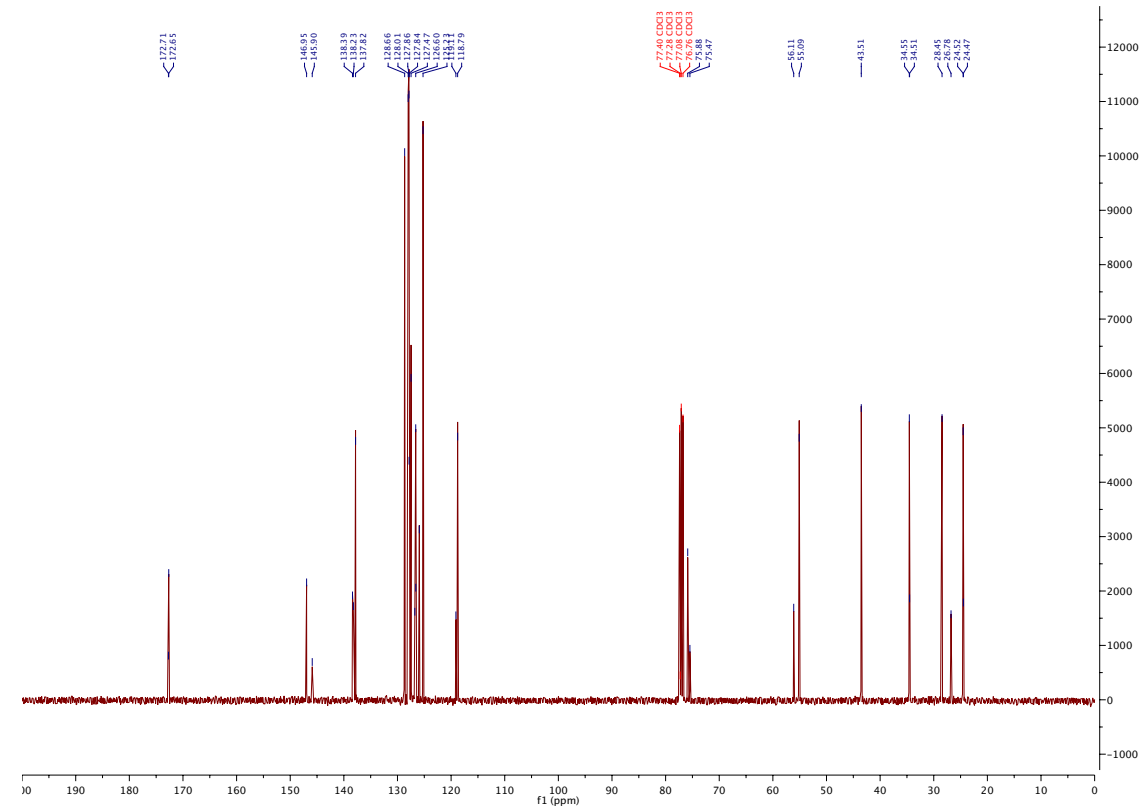
20

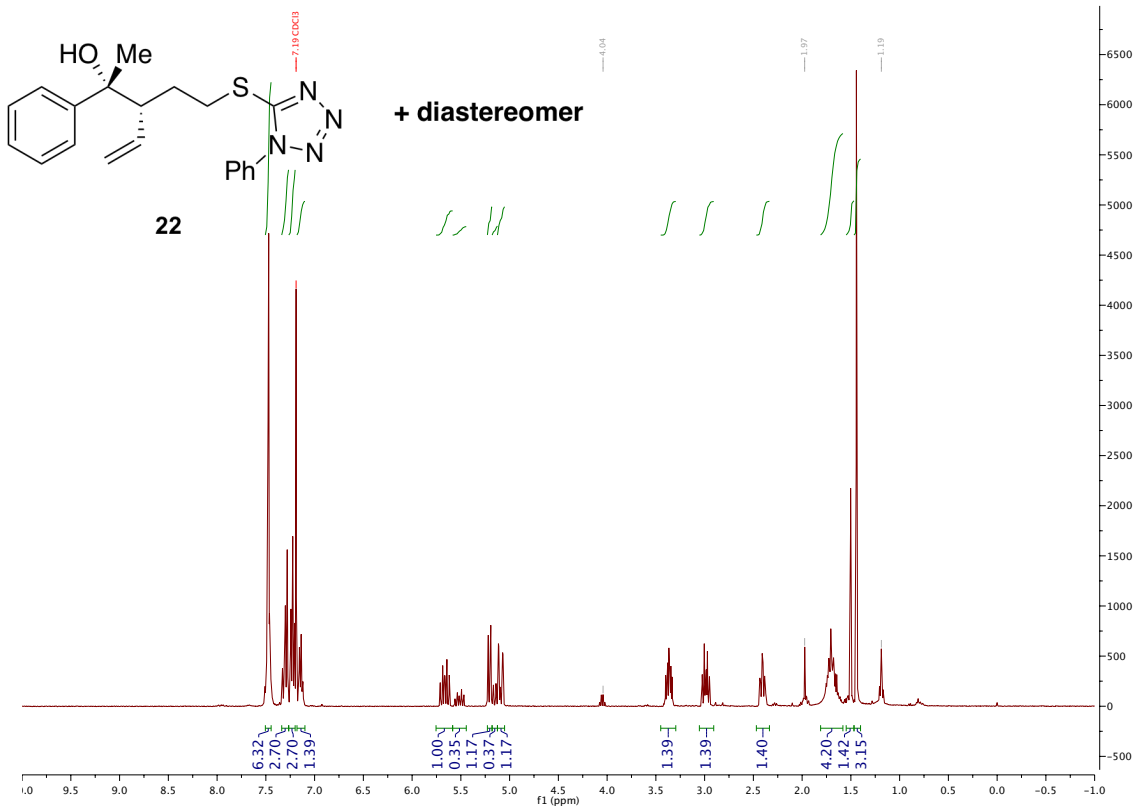


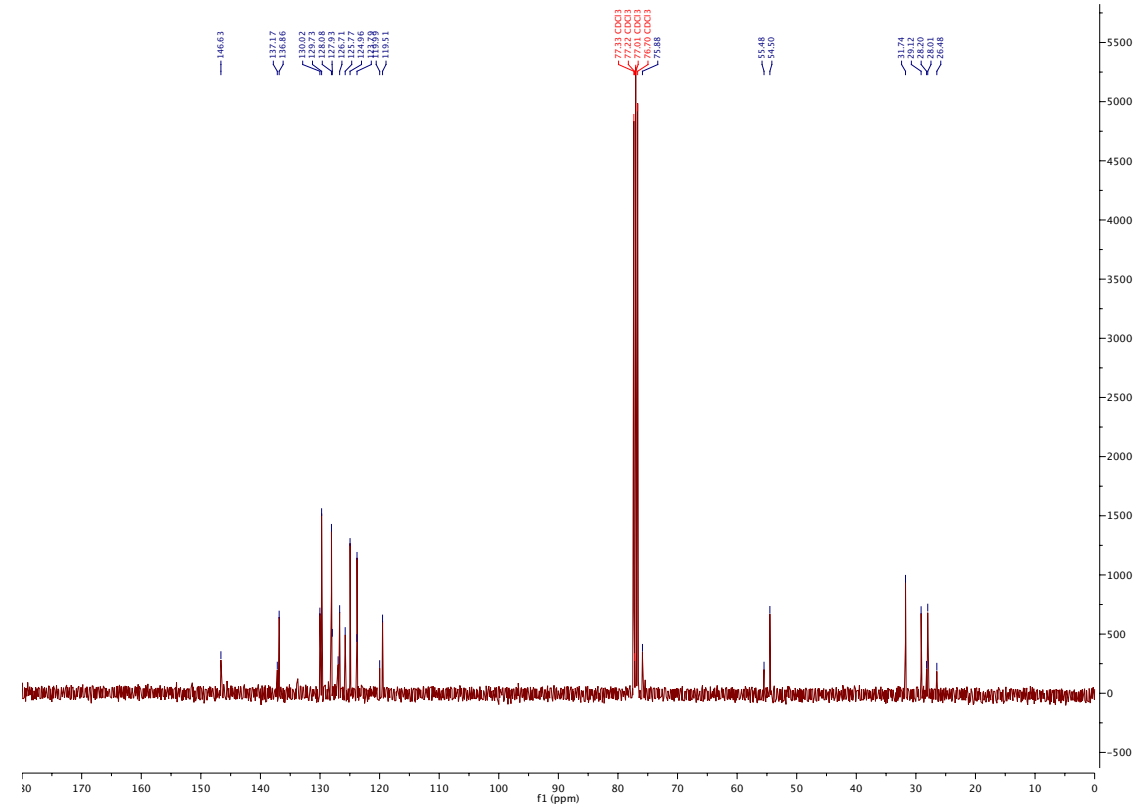


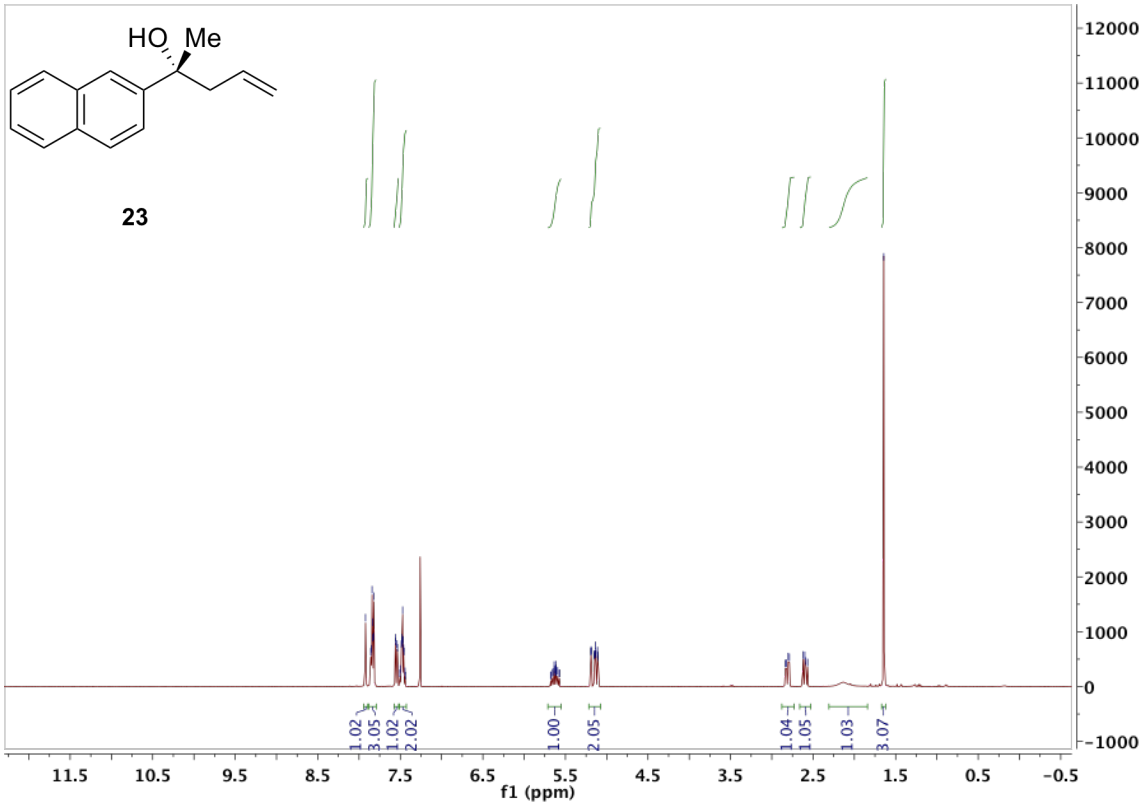
21

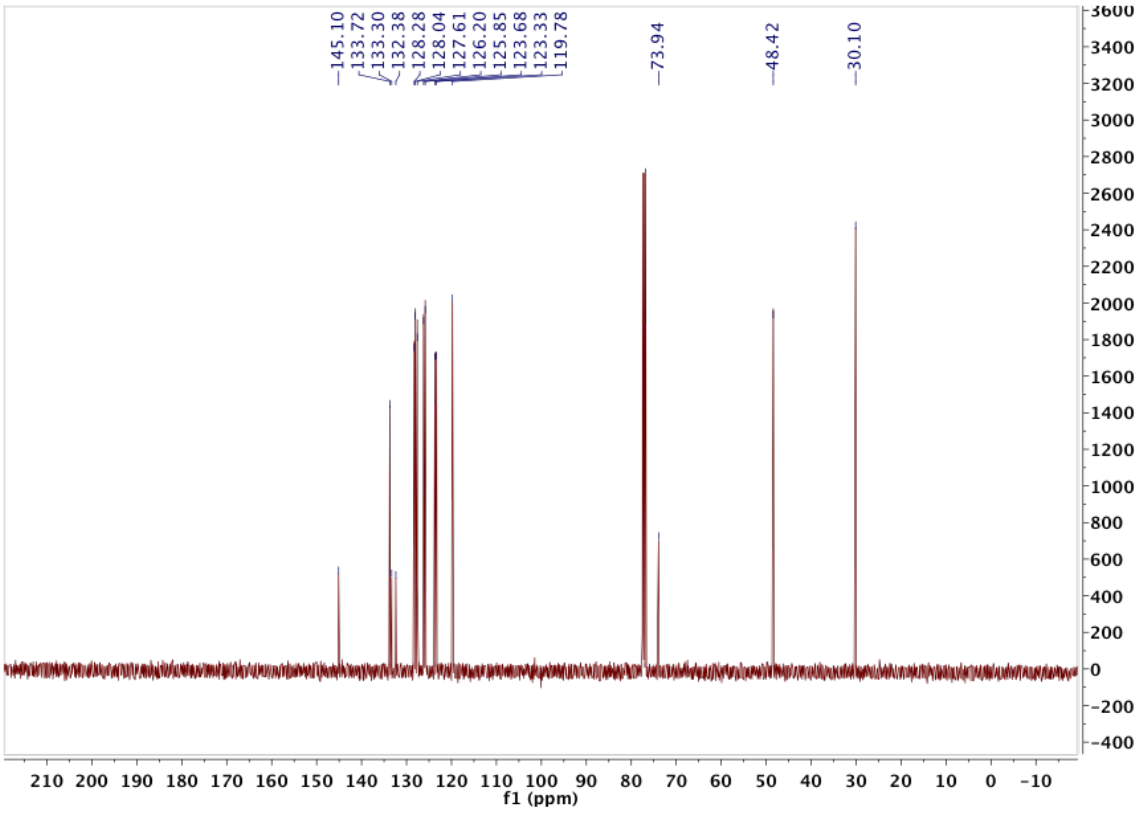
+ diastereomer

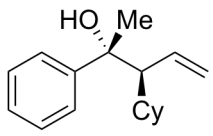



HO
Me
S
N
N
N
N
Ph
22
+ diastereomer
7.19 CDCl3
4.04
1.97
1.19
6.32
2.70
2.70
1.39
1.00
0.35
1.17
0.37
1.17
1.39
1.39
1.40
4.20
1.42
3.15
f1 (ppm)


146.63
137.17
136.86
130.02
129.73
128.68
127.93
126.71
125.97
124.46
119.51
77.33 CDCl3
77.22 CDCl3
77.01 CDCl3
76.70 CDCl3
75.88
55.48
54.50
31.74
29.12
28.30
28.01
26.48
f1 (ppm)


HO
Me
23
1.02
3.05
1.02
2.02
1.00
2.05
1.04
1.05
1.03
3.07
f1 (ppm)

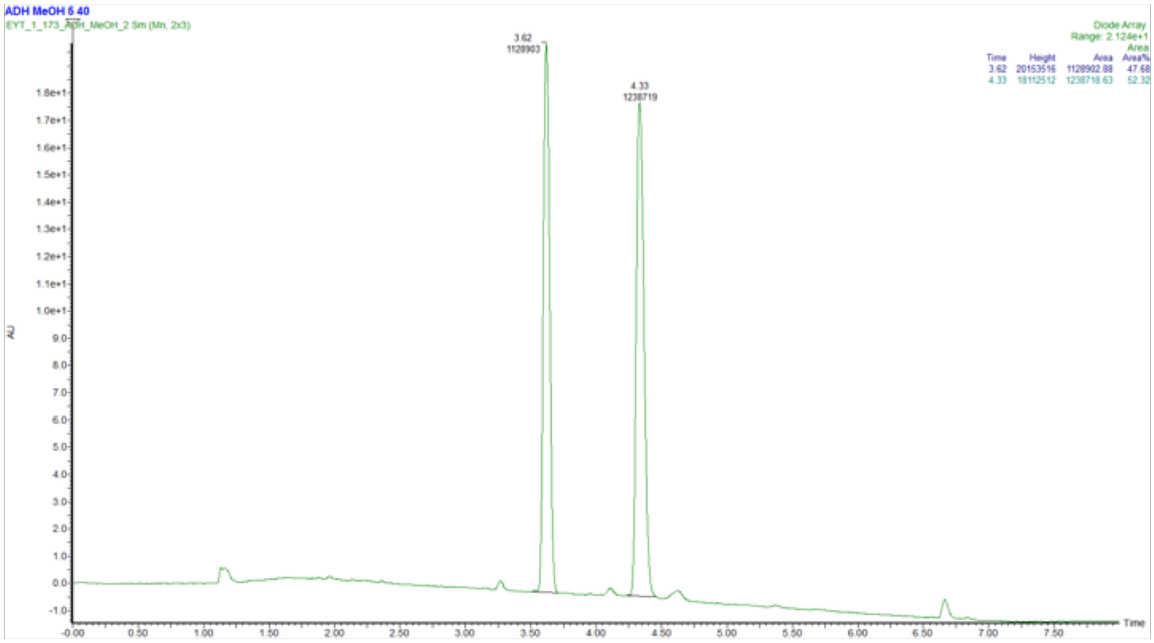

145.10
133.72
133.30
132.38
128.28
128.04
127.61
126.20
125.85
123.68
123.33
119.78
73.94
48.42
30.10
f1 (ppm)



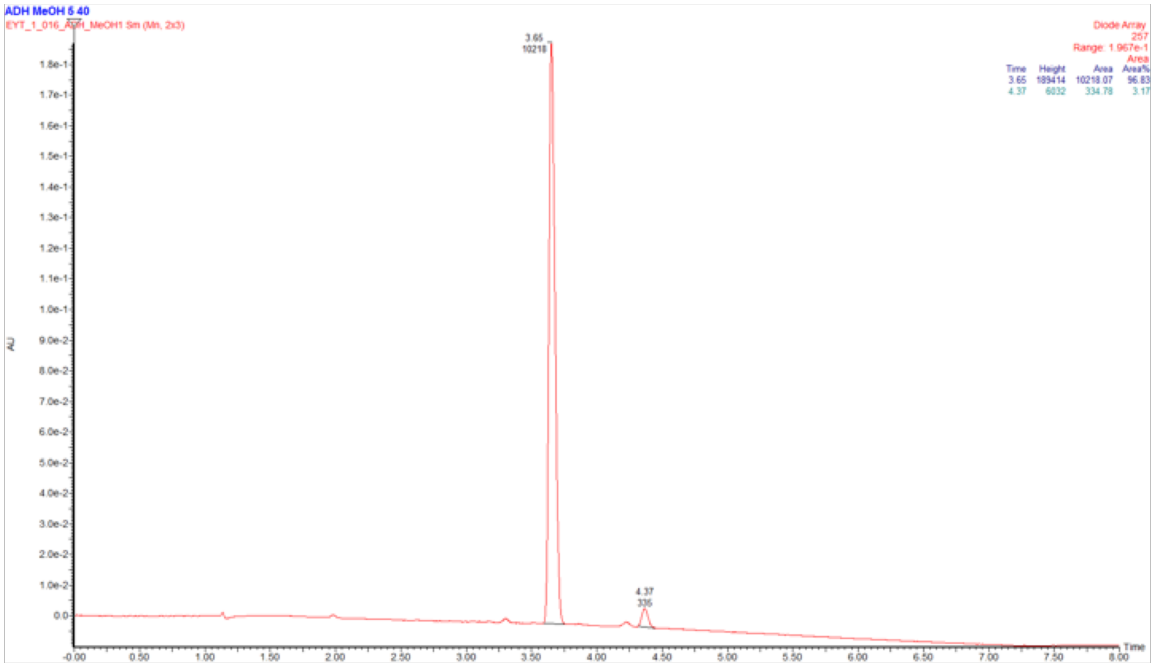
+ diastereomer

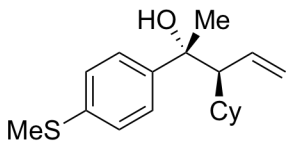
1

Trace of racemic compound



Trace of enantioenriched compound

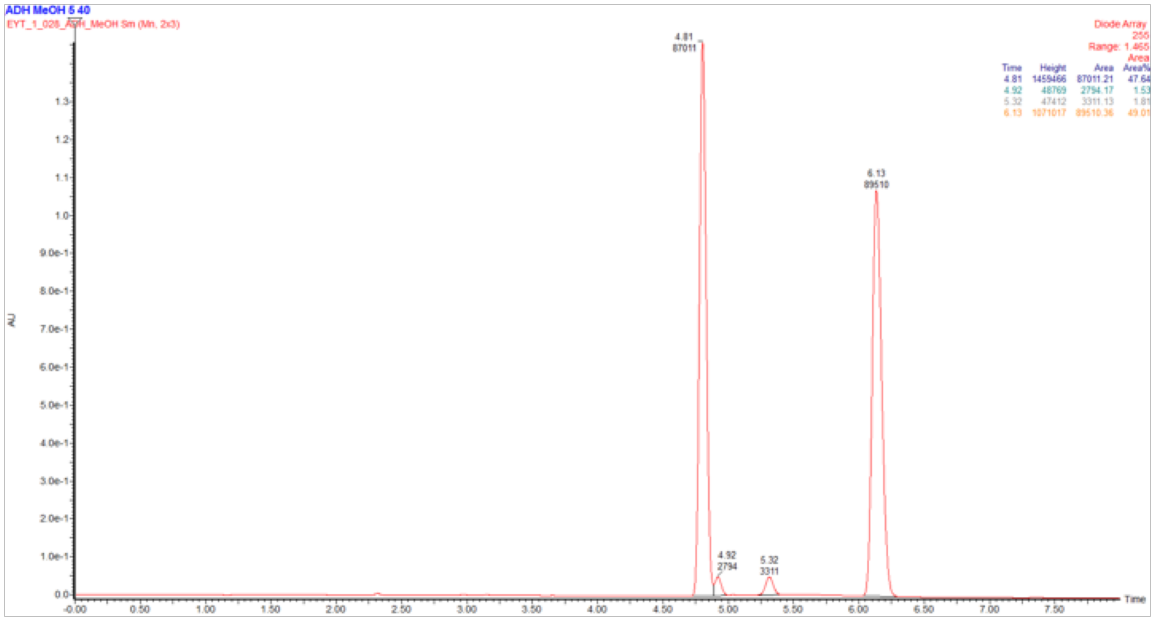




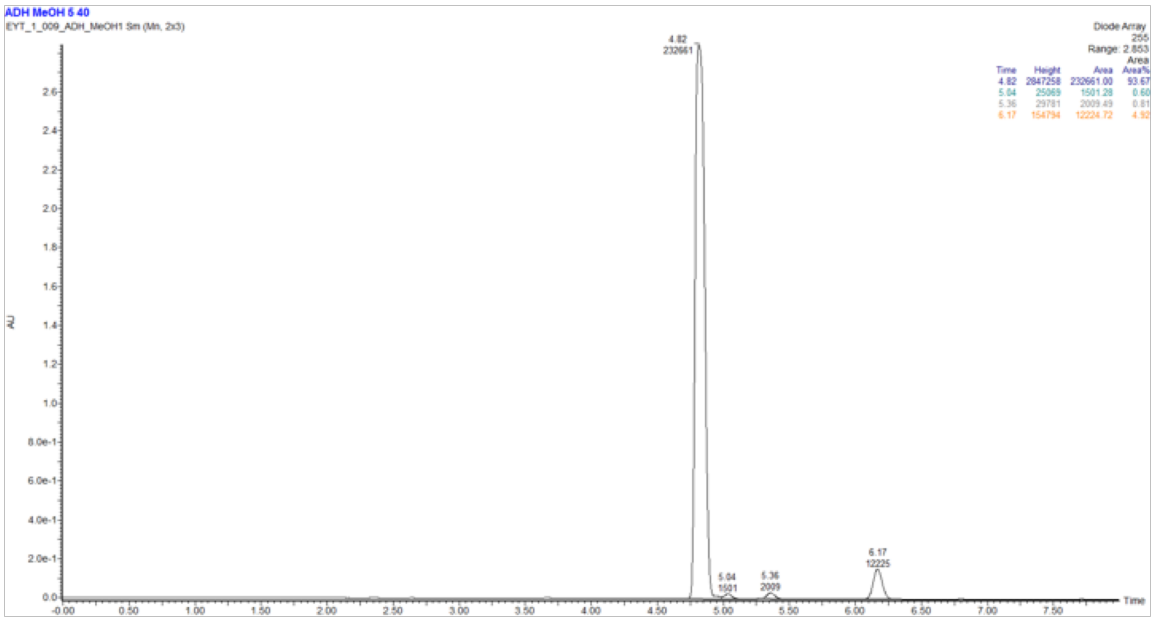
+ diastereomer

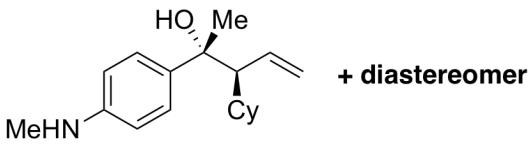
2

Trace of racemic compound



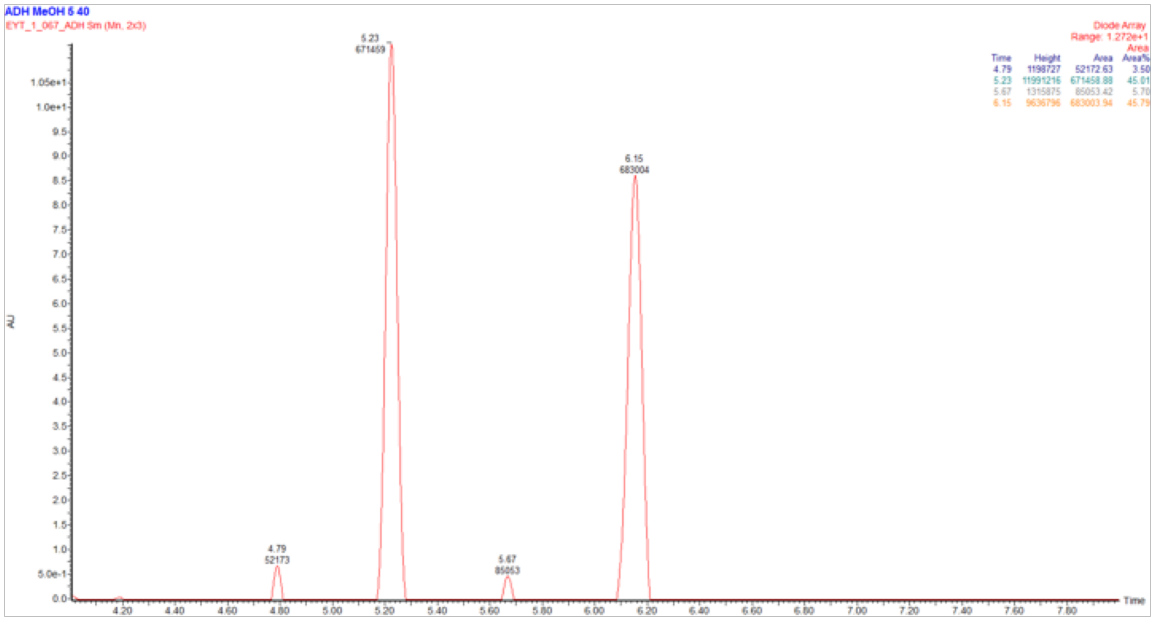
Trace of enantioenriched compound



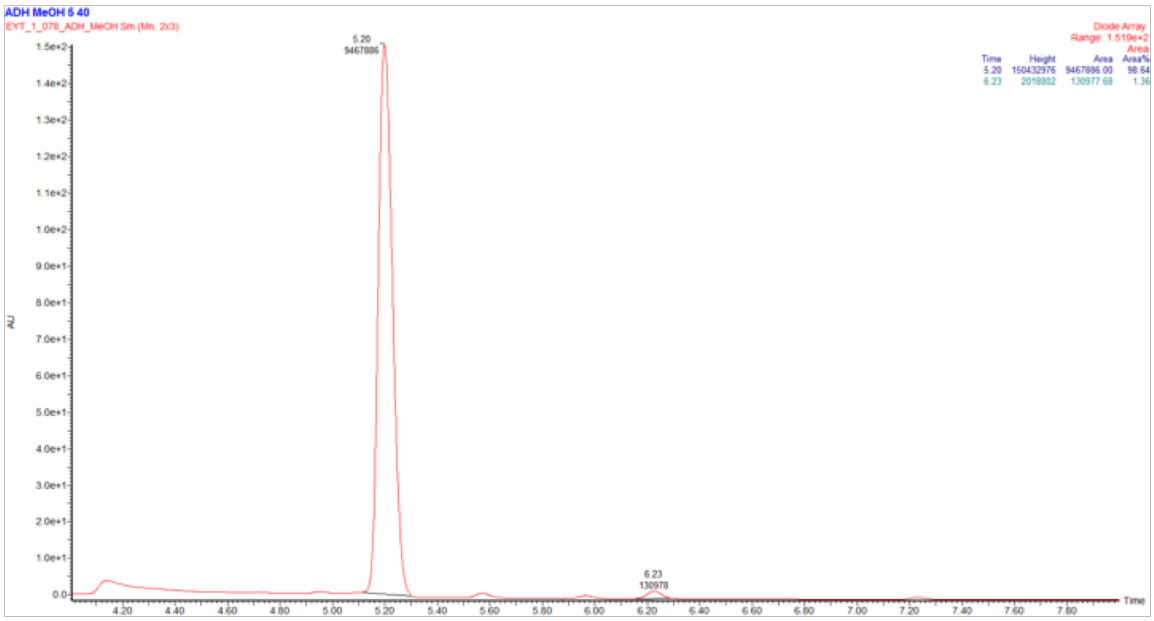


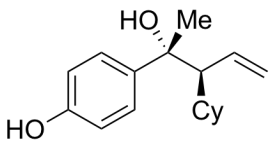
3

Trace of racemic compound



Trace of enantioenriched compound

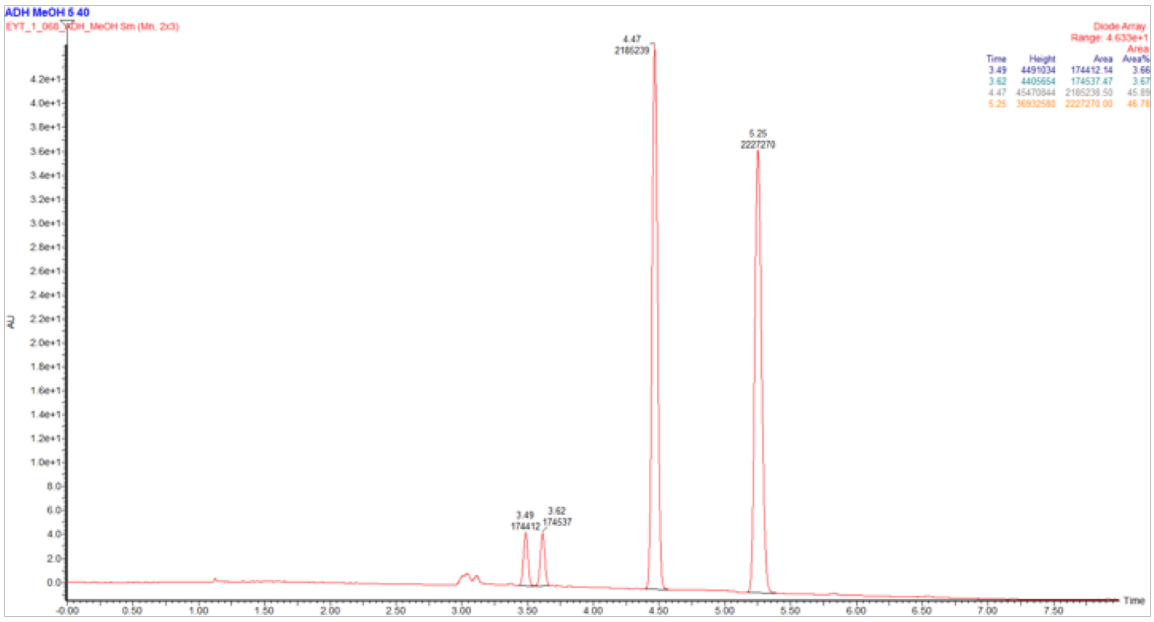




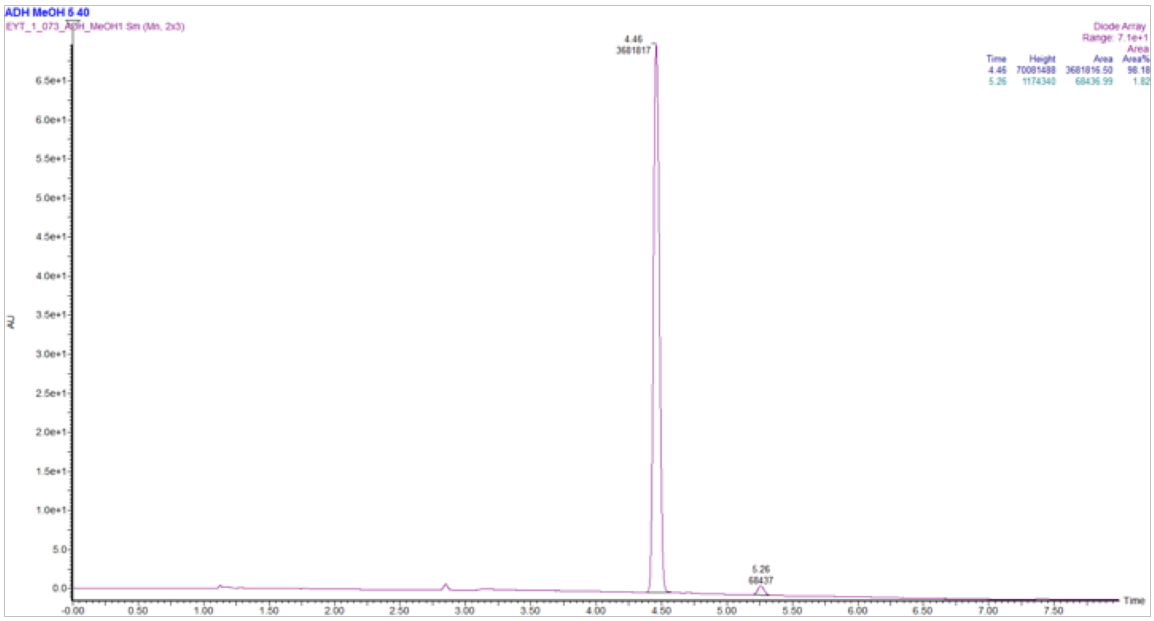
+ diastereomer

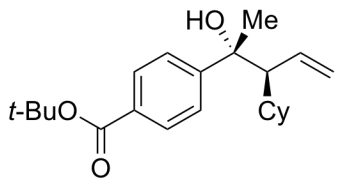
4

Trace of racemic compound



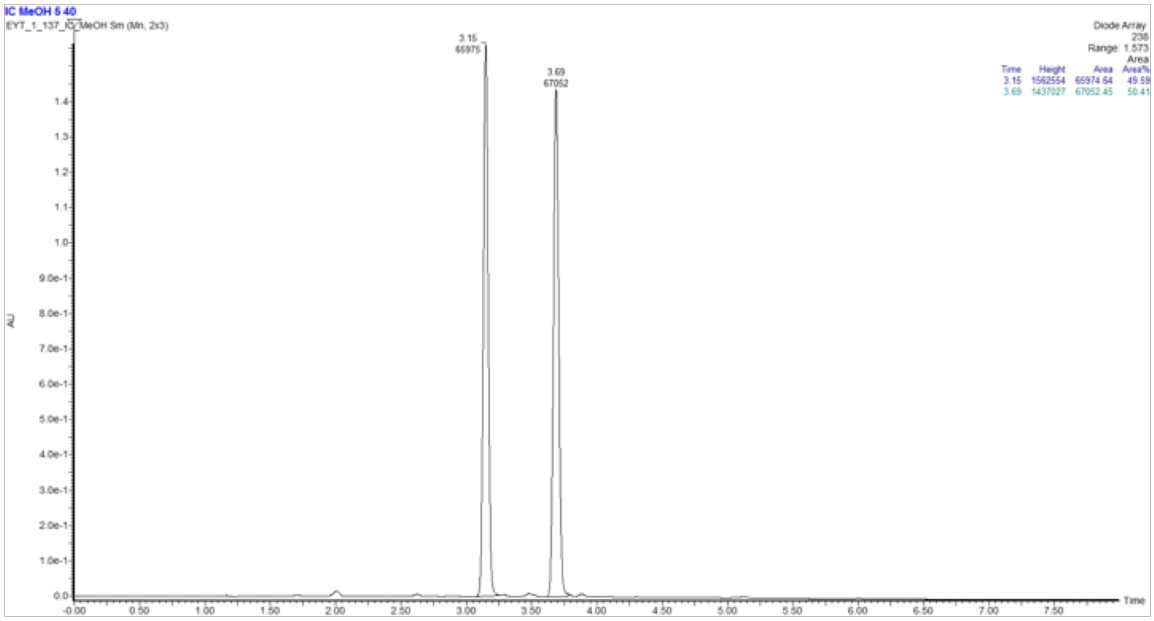
Trace of enantioenriched compound



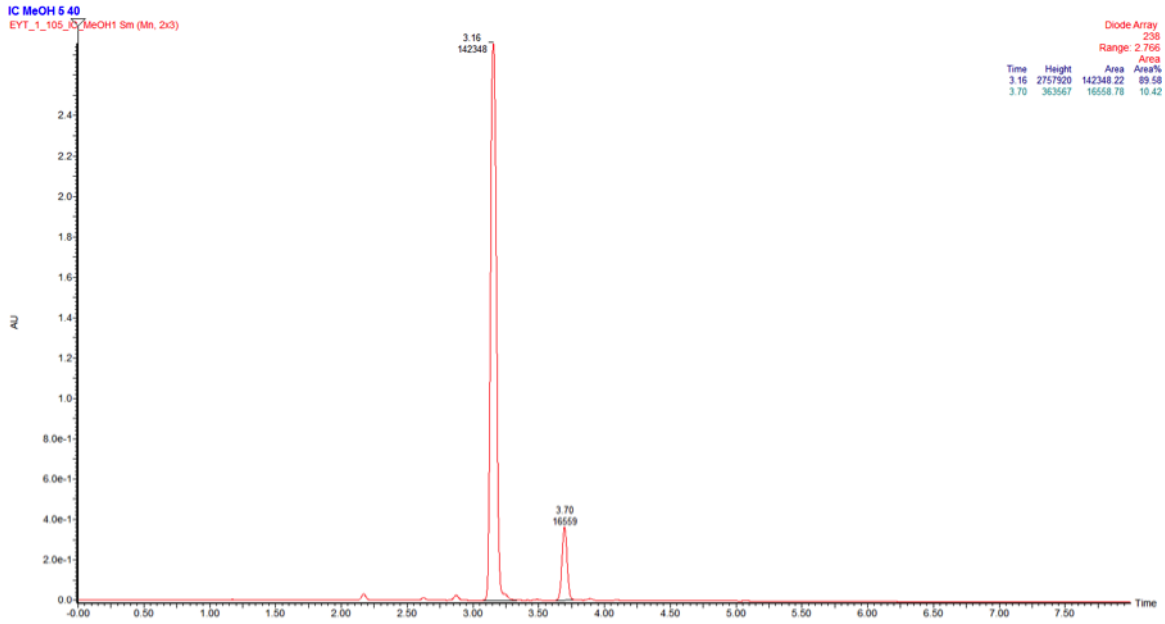


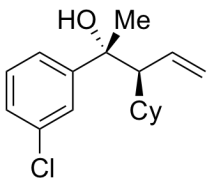
5

Trace of racemic compound



Trace of enantioenriched compound

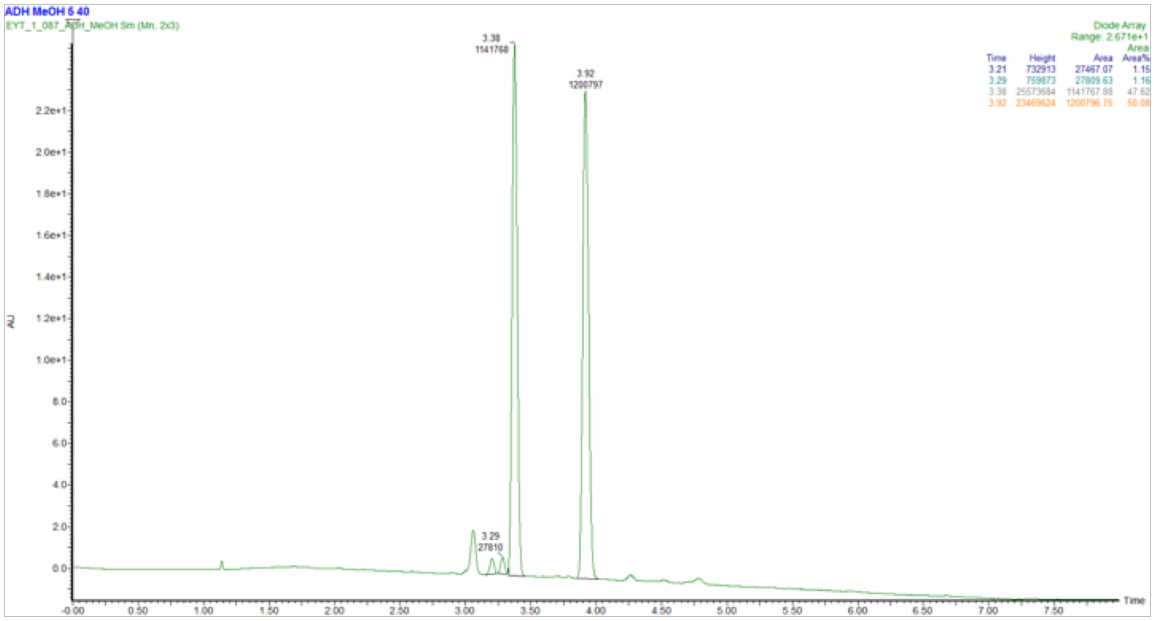




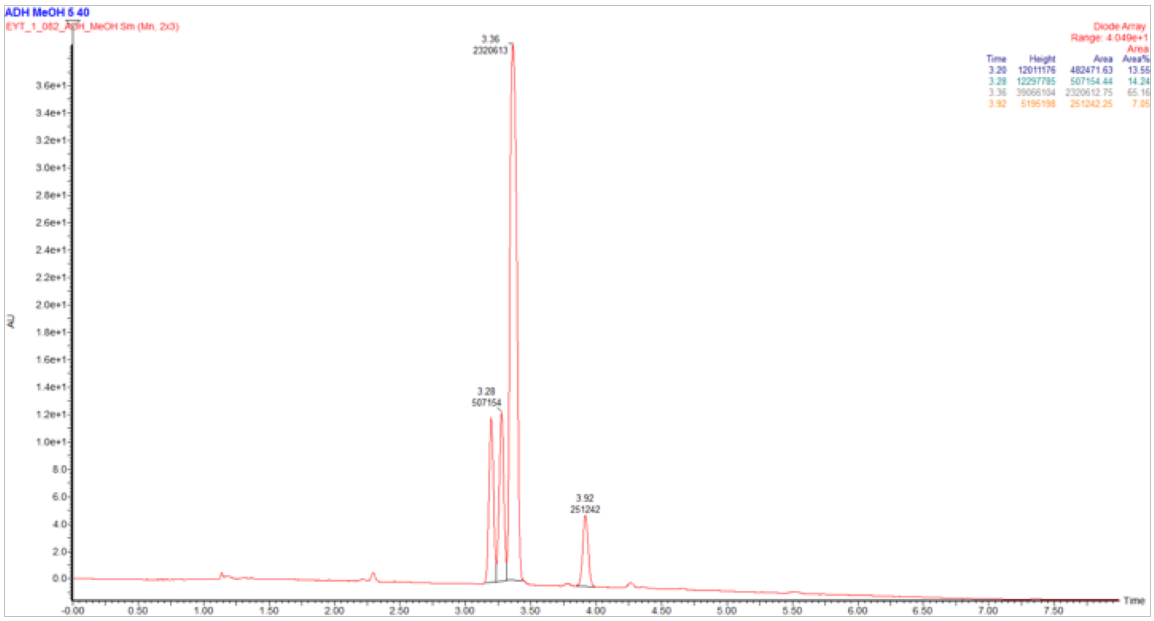
+ diastereomer

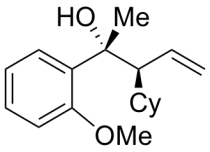
6

Trace of racemic compound



Trace of enantioenriched compound

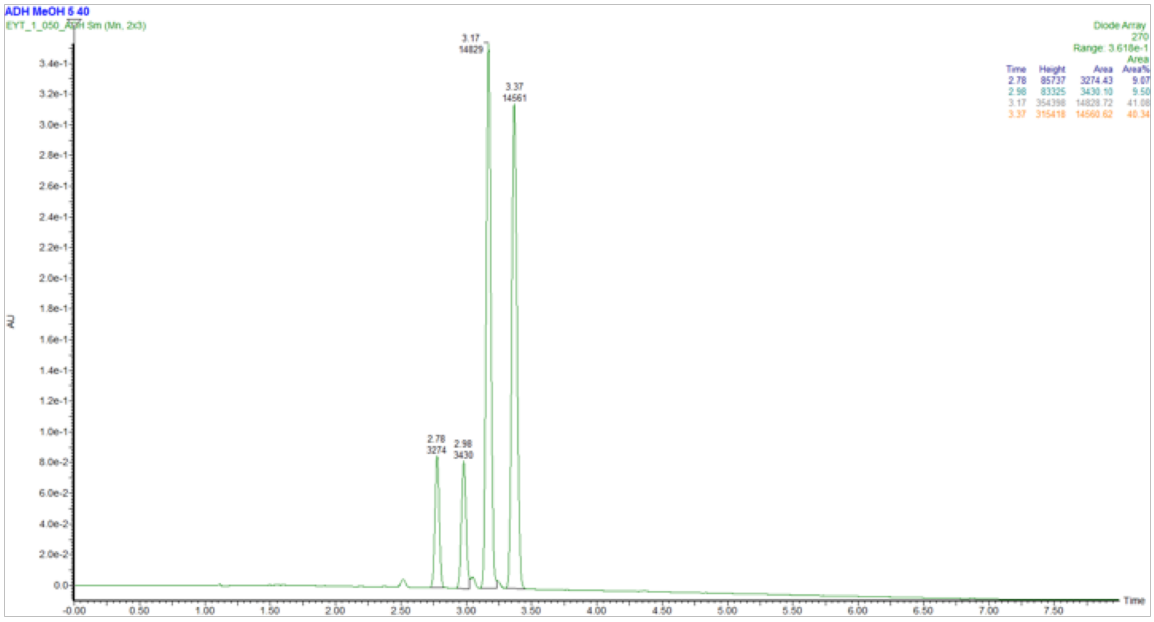




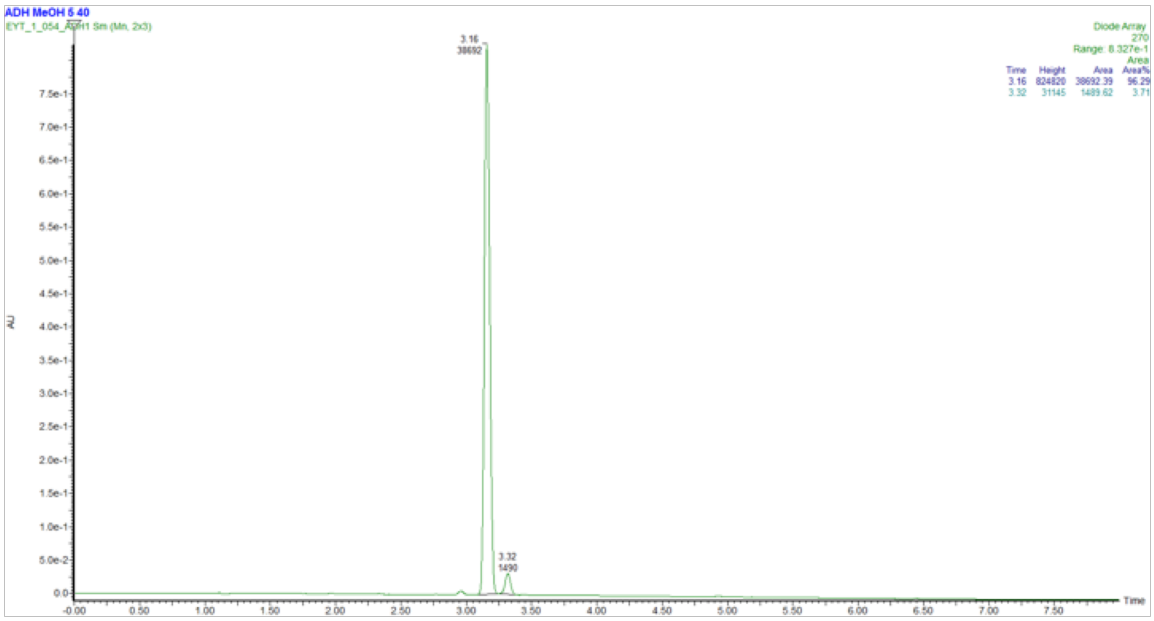
+ diastereomer

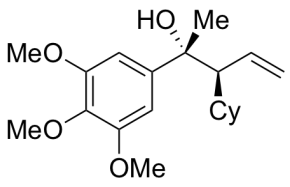
7

Trace of racemic compound



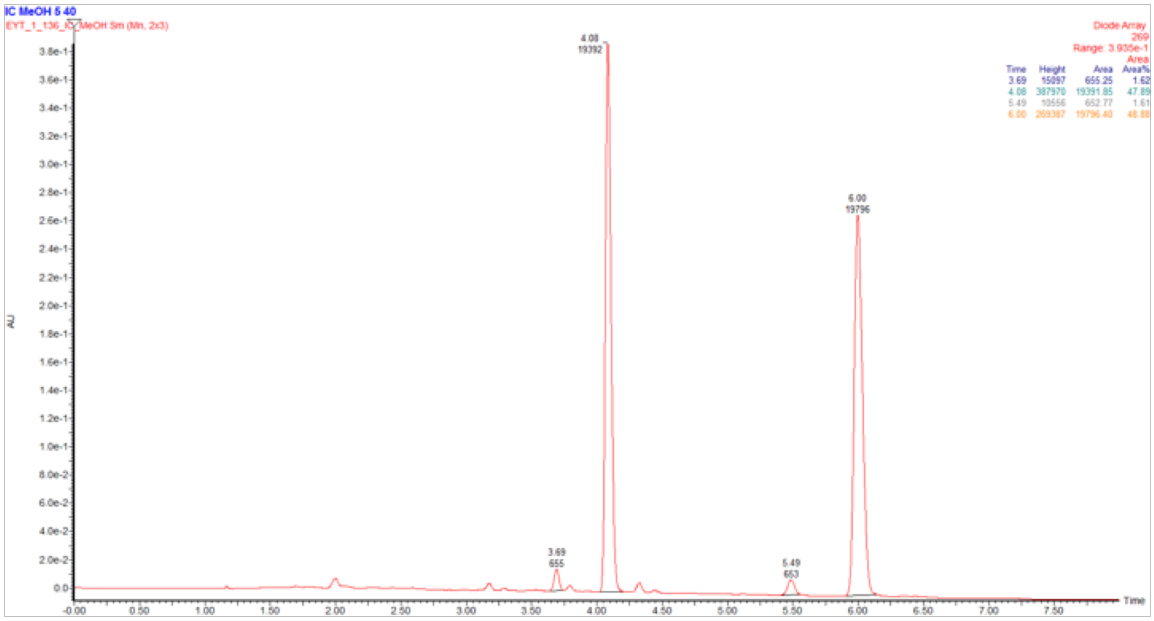
Trace of enantioenriched compound



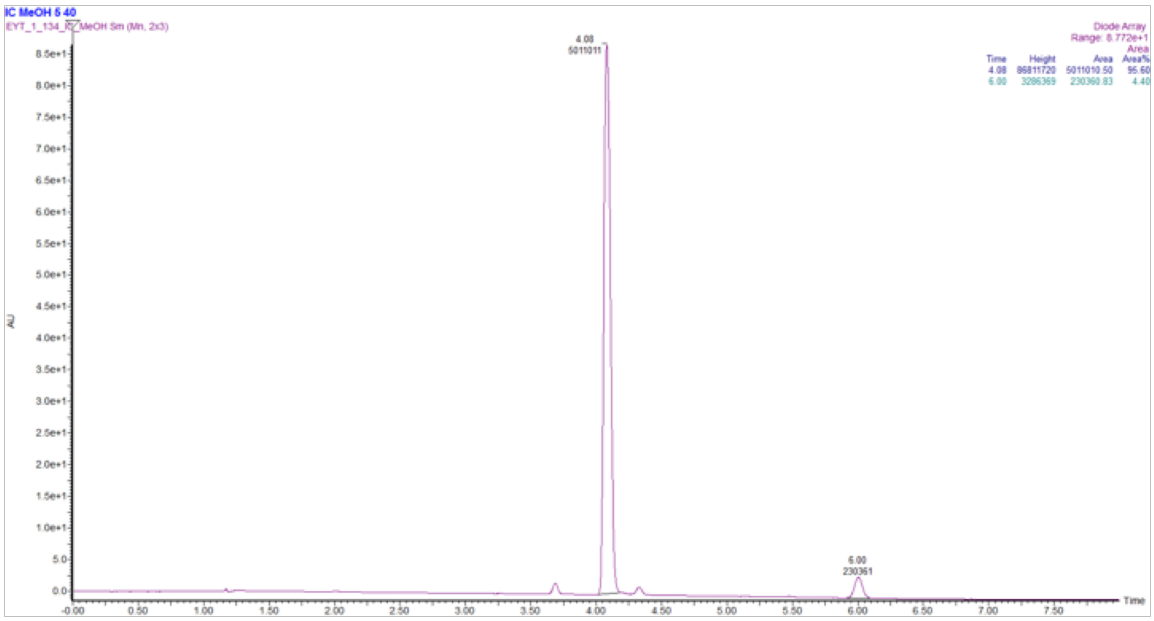


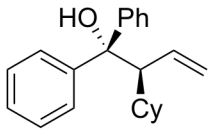
8

Trace of racemic compound



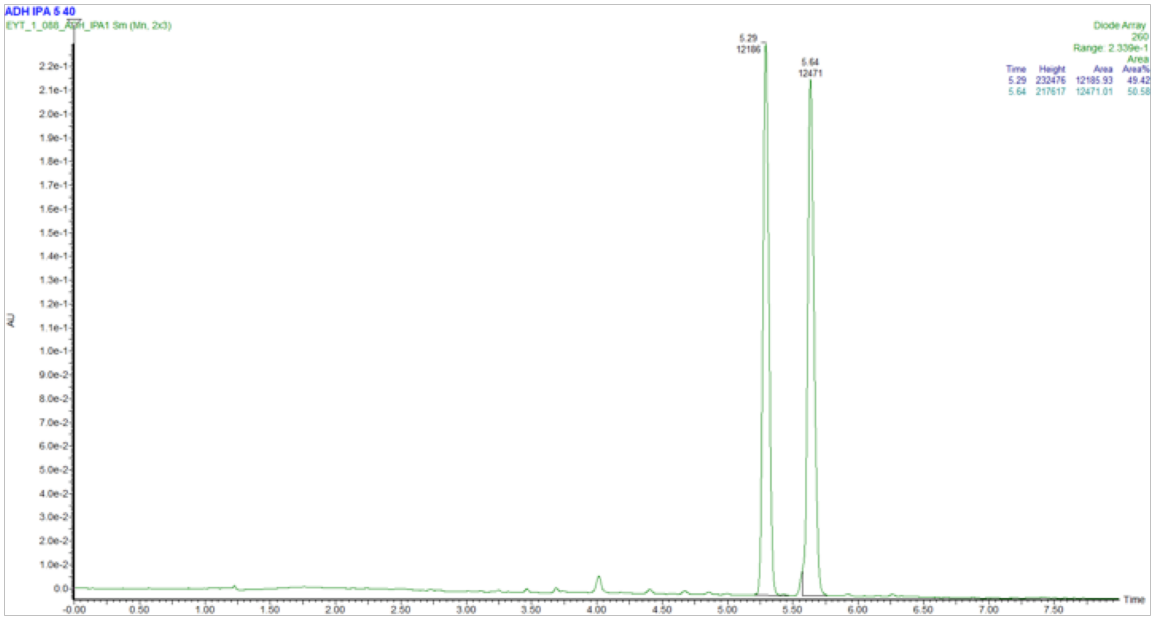
Trace of enantioenriched compound



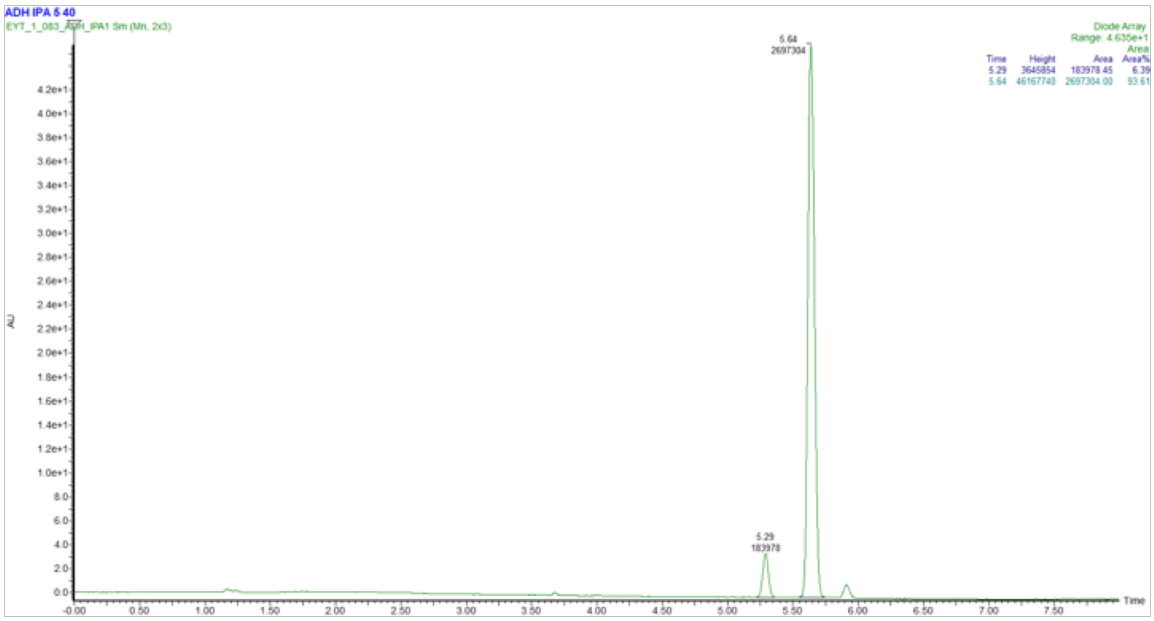


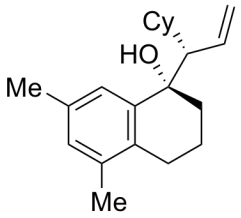
9

Trace of racemic compound



Trace of enantioenriched compound

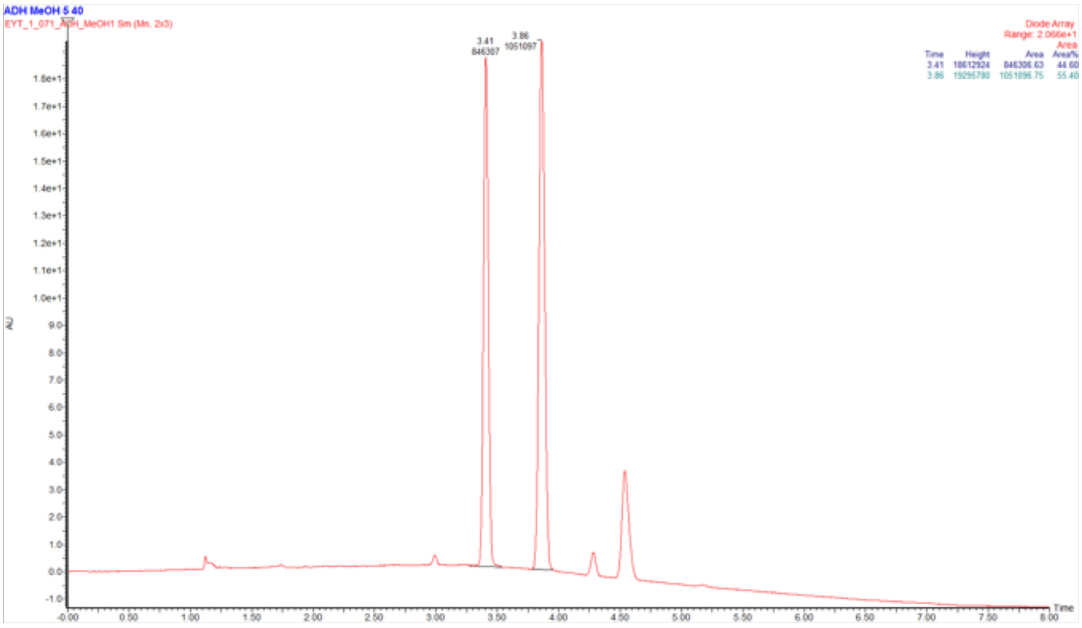




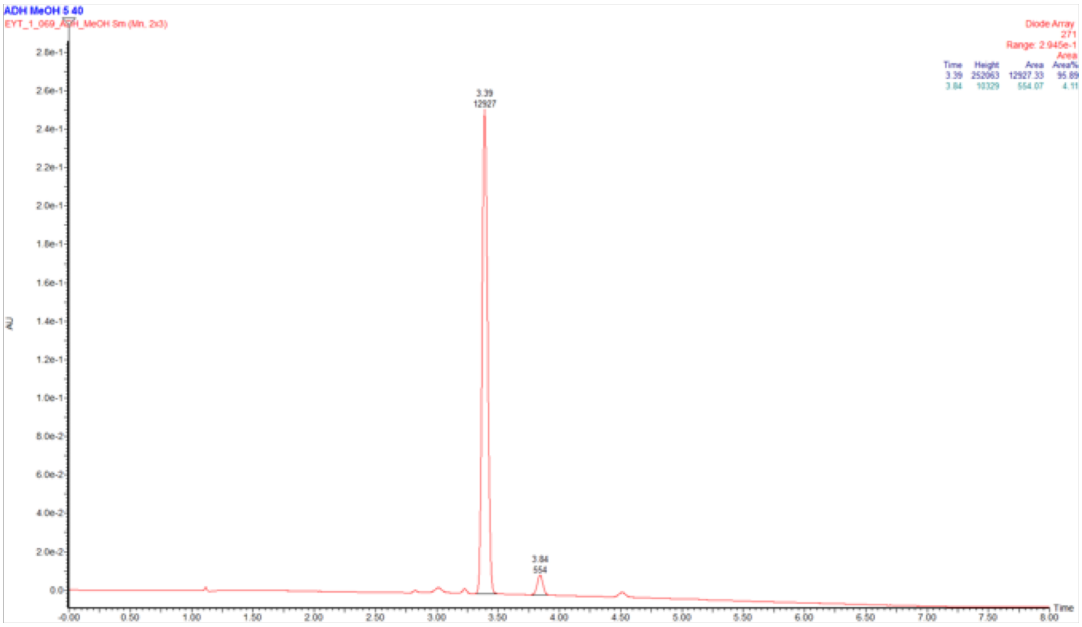
+ diastereomer

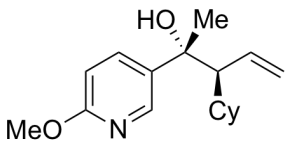
10

Trace of racemic compound



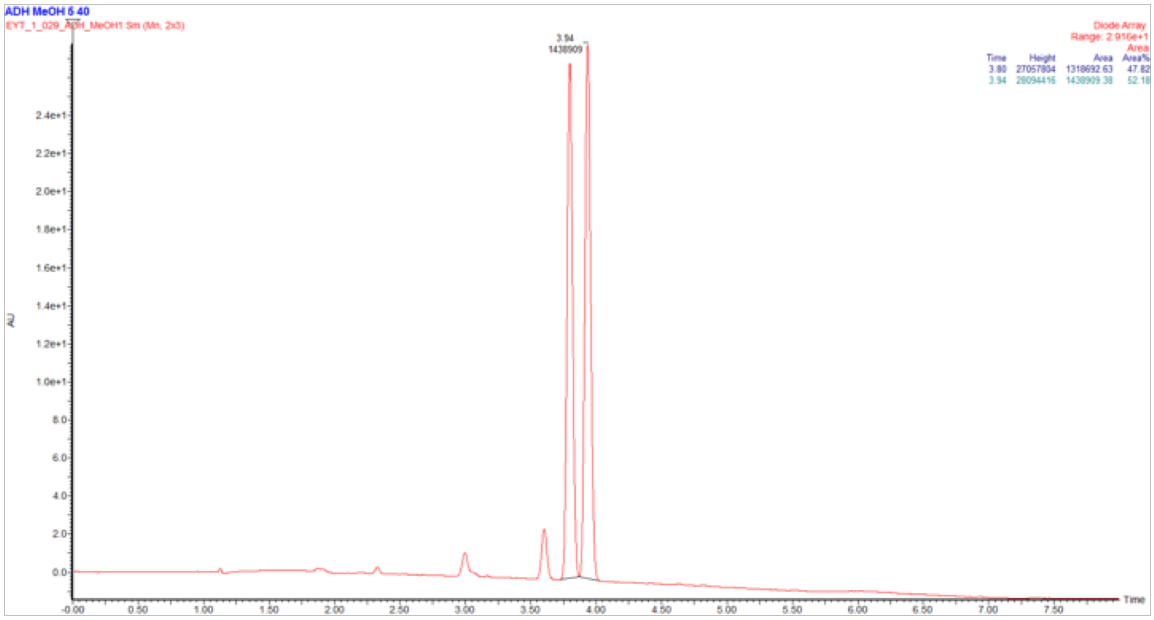
Trace of enantioenriched compound



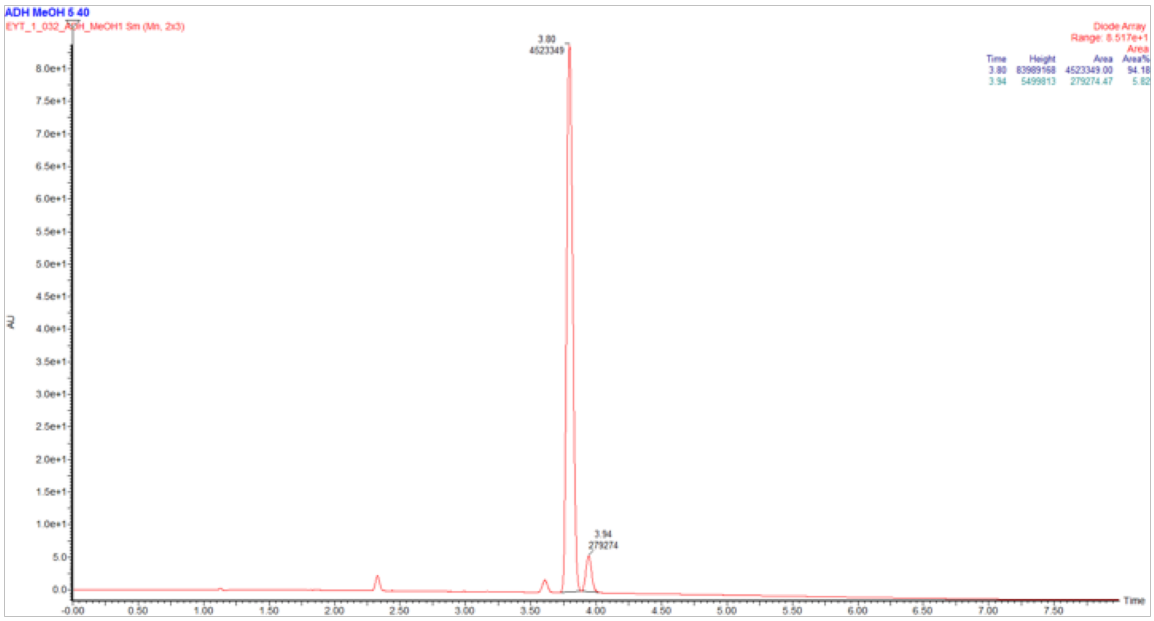


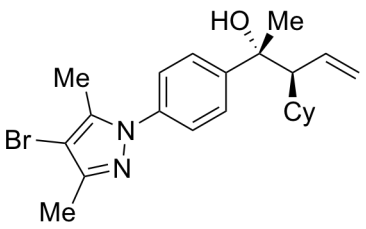
11

Trace of racemic compound



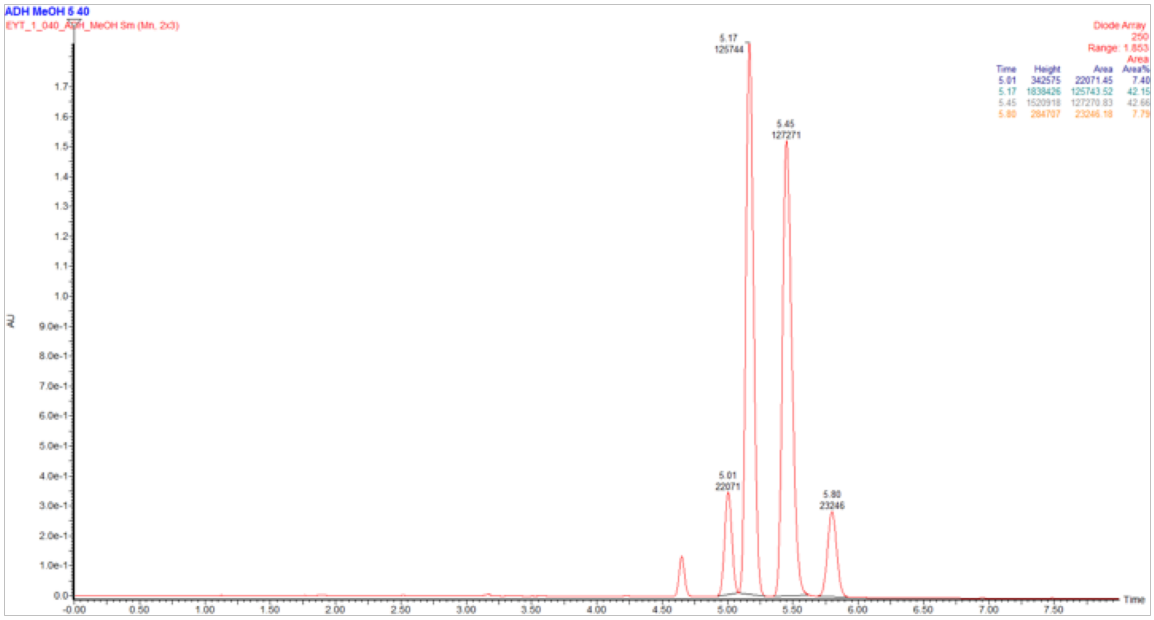
Trace of enantioenriched compound



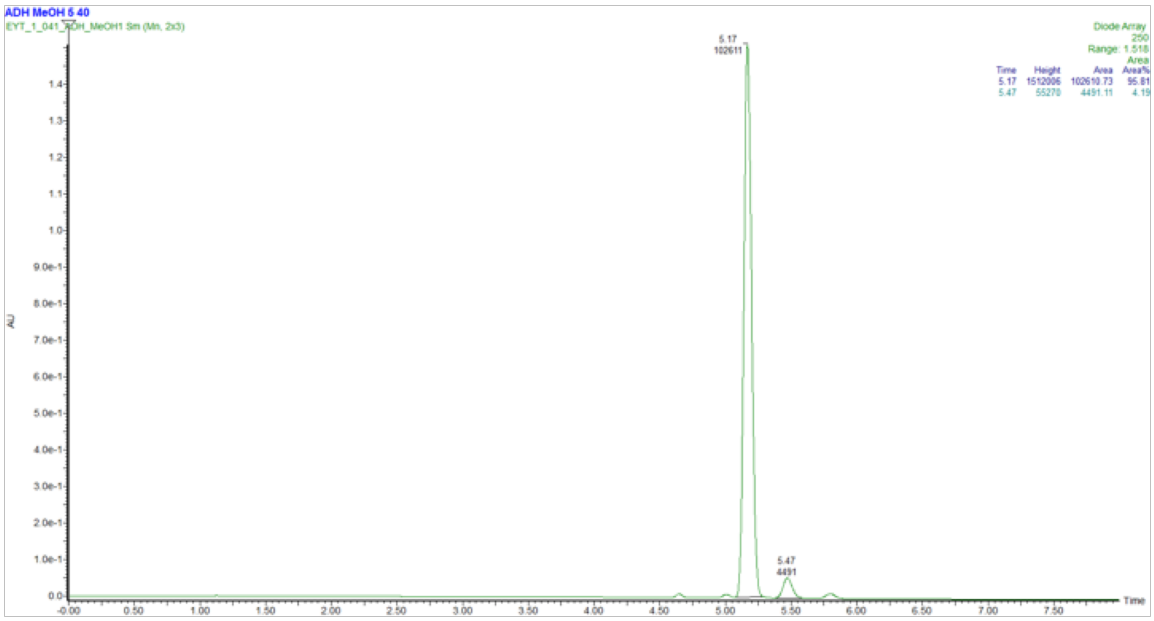


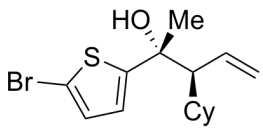
12

Trace of racemic compound



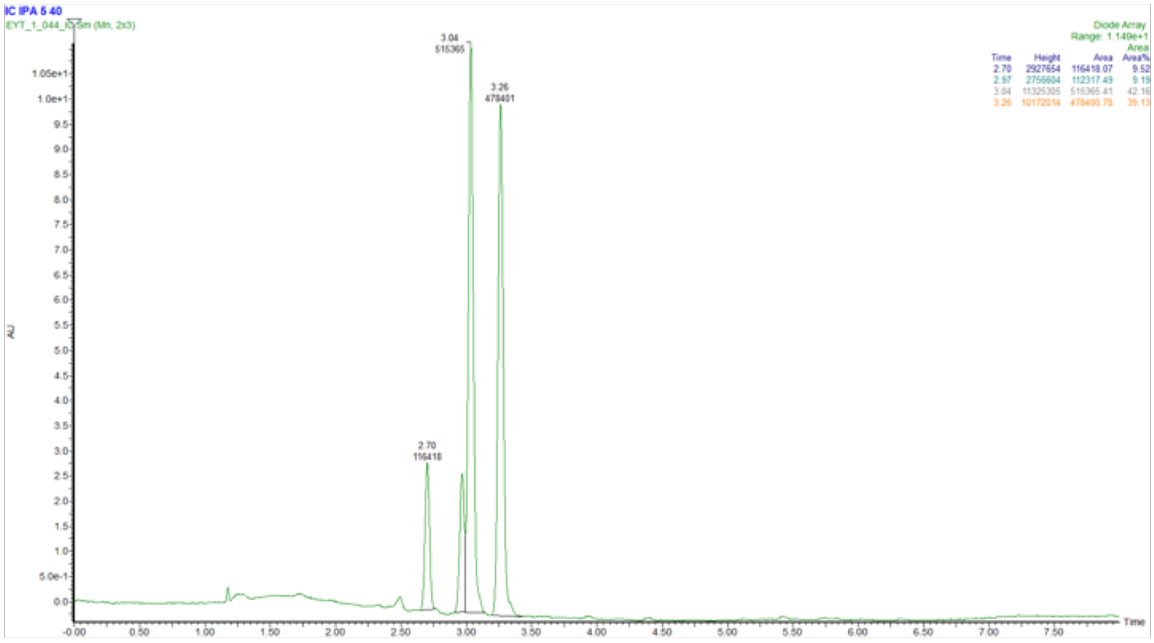
Trace of enantioenriched compound



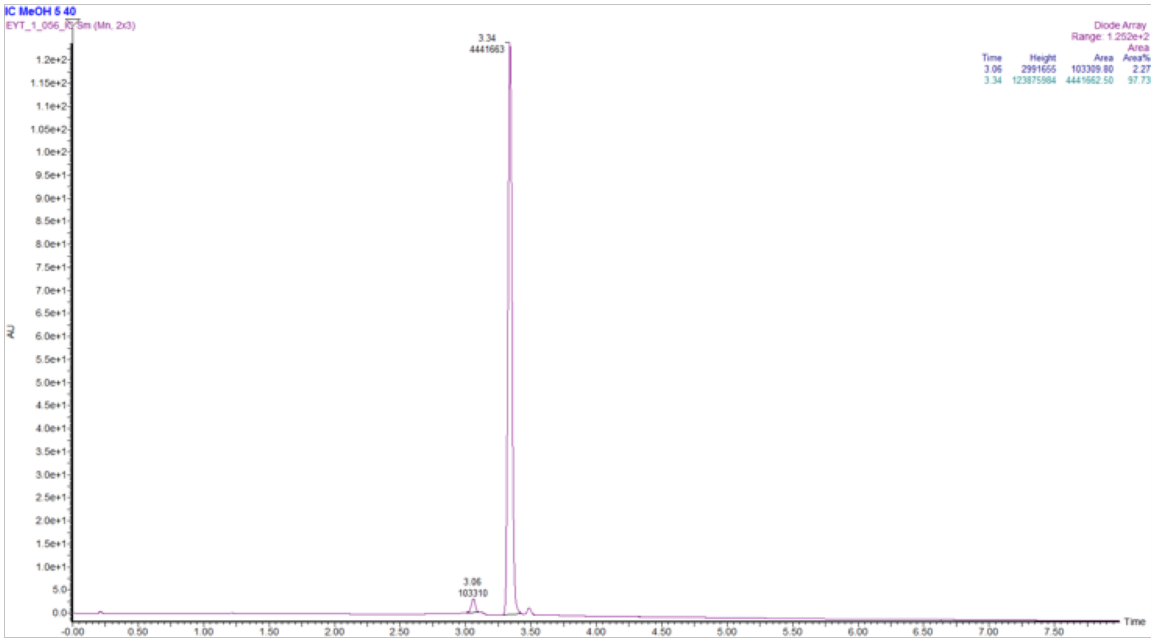


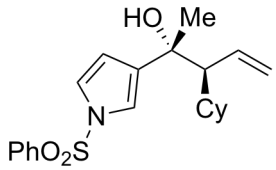
13

Trace of racemic compound



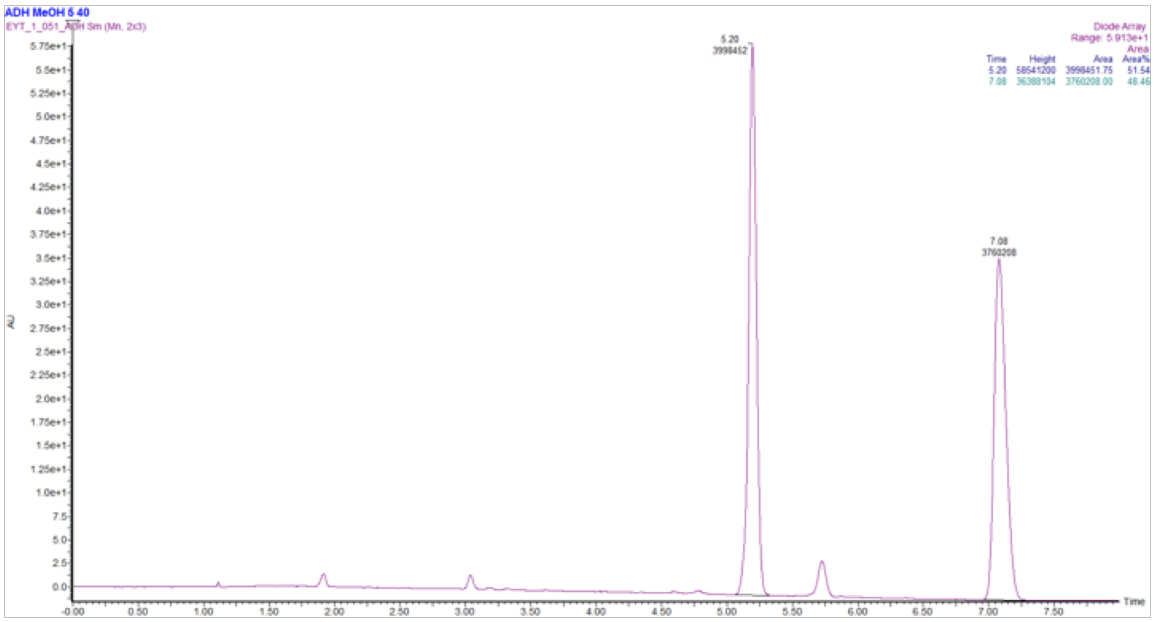
Trace of enantioenriched compound



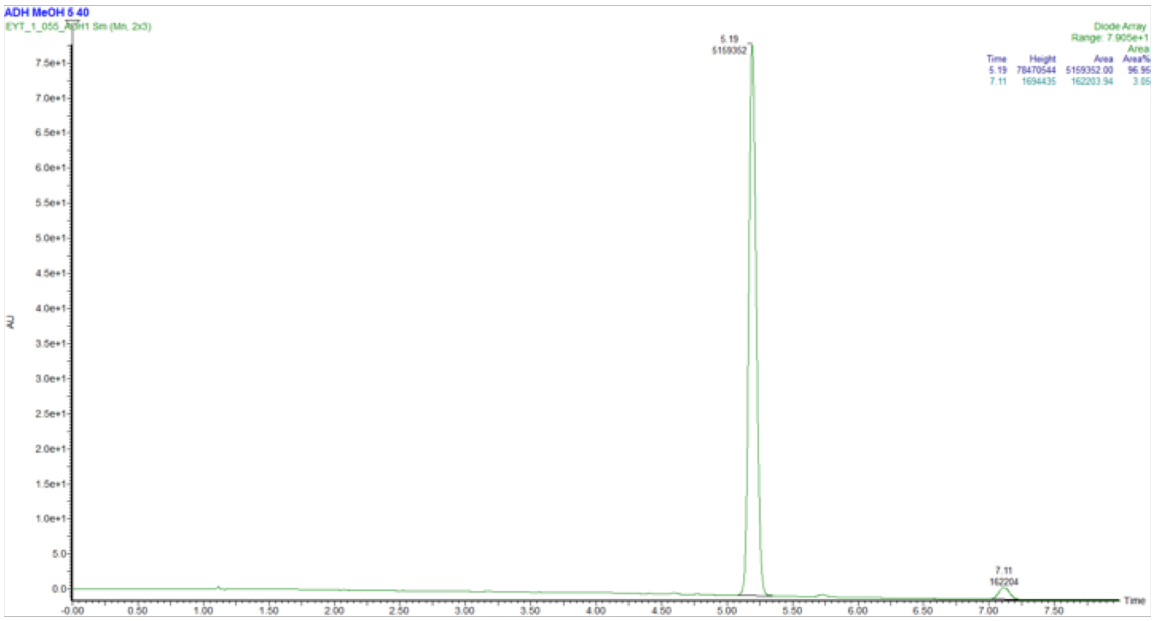


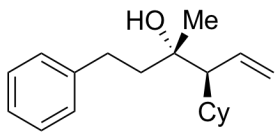
14

Trace of racemic compound



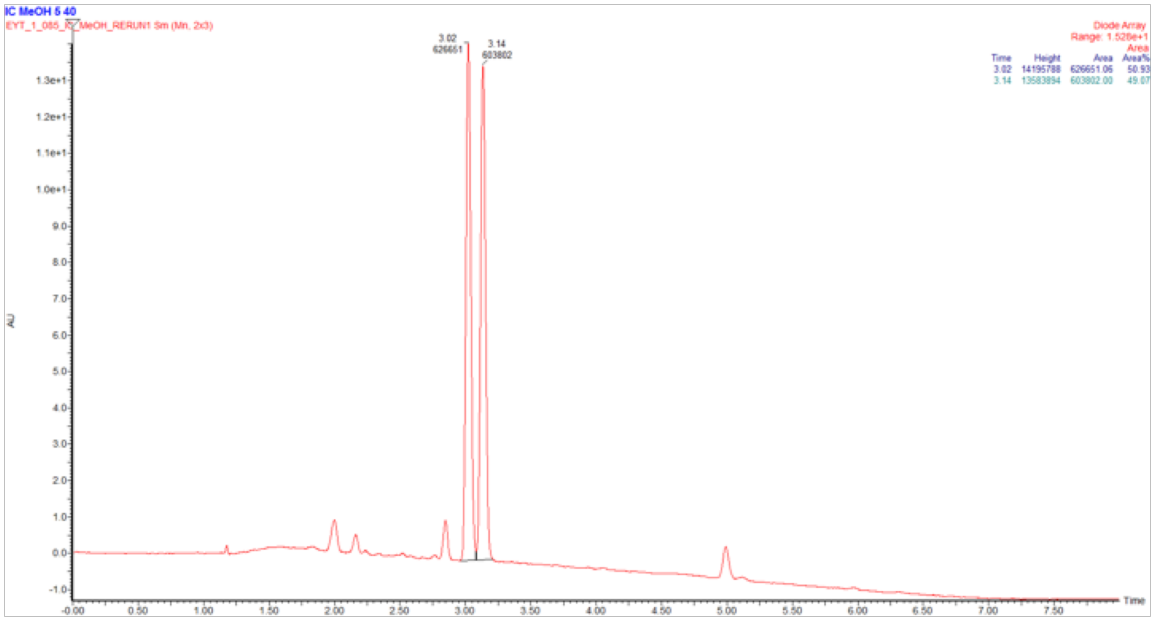
Trace of enantioenriched compound



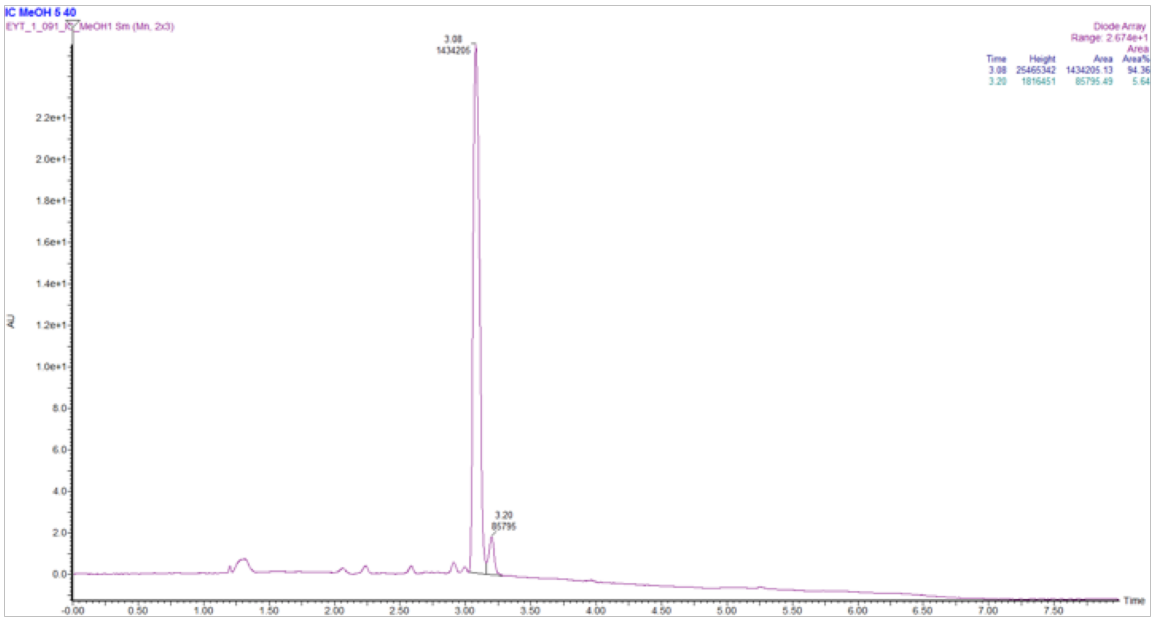


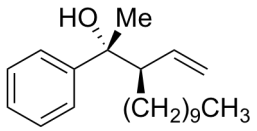
15

Trace of racemic compound



Trace of enantioenriched compound

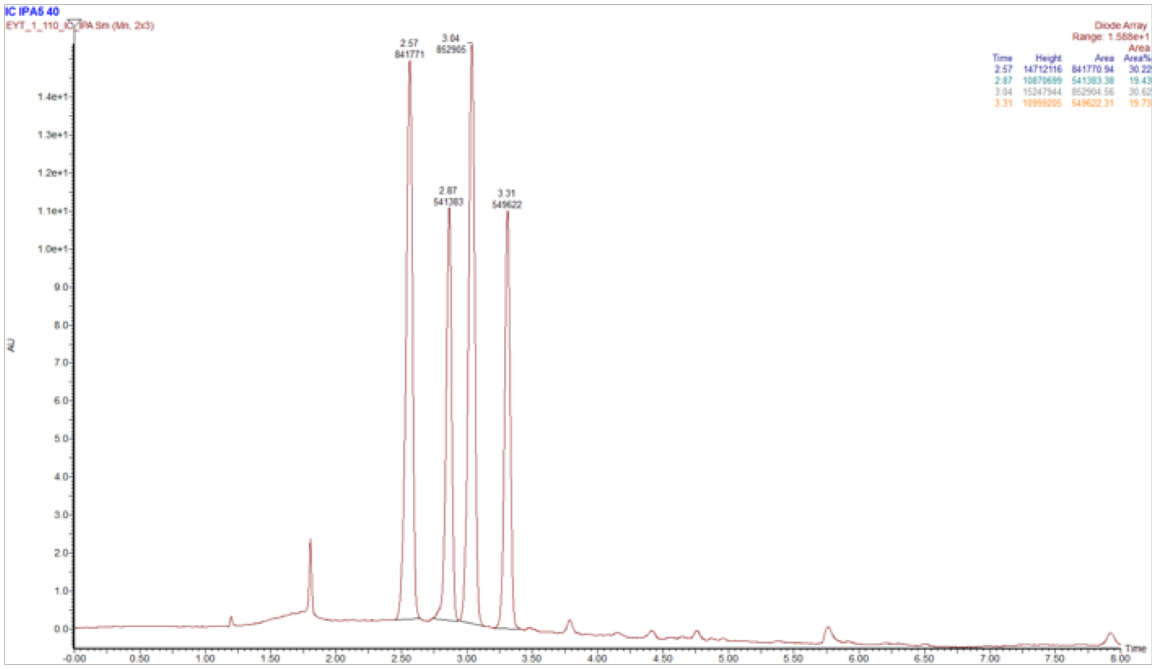




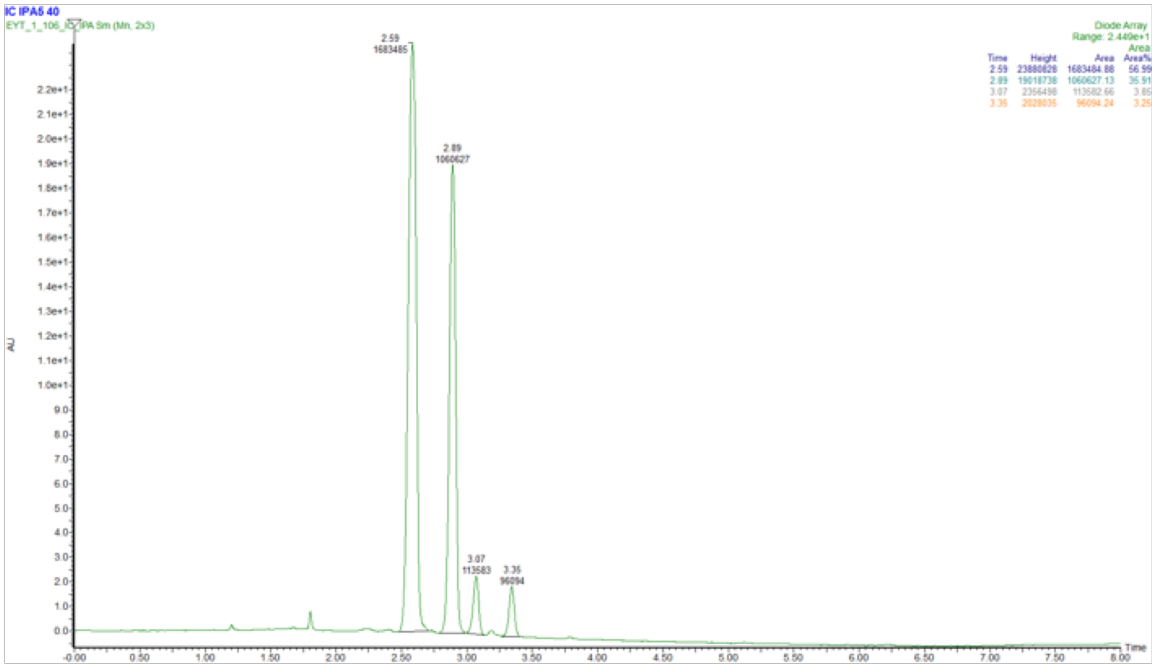
+ diastereomer

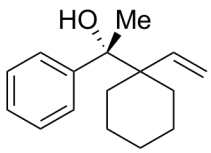
16

Trace of racemic compound



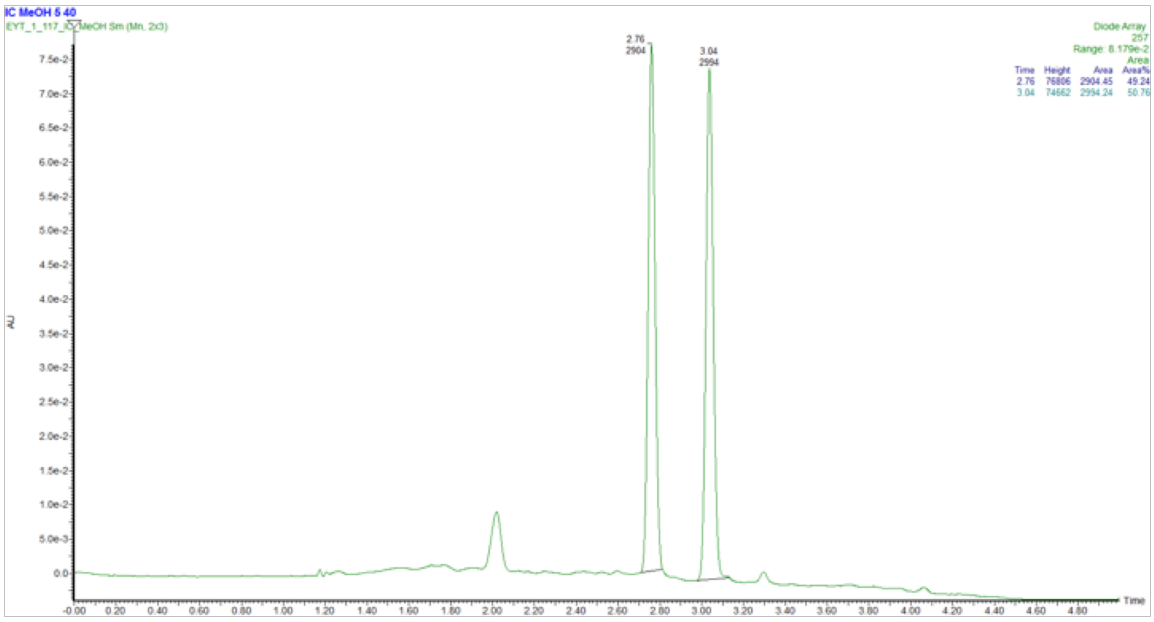
Trace of enantioenriched compound



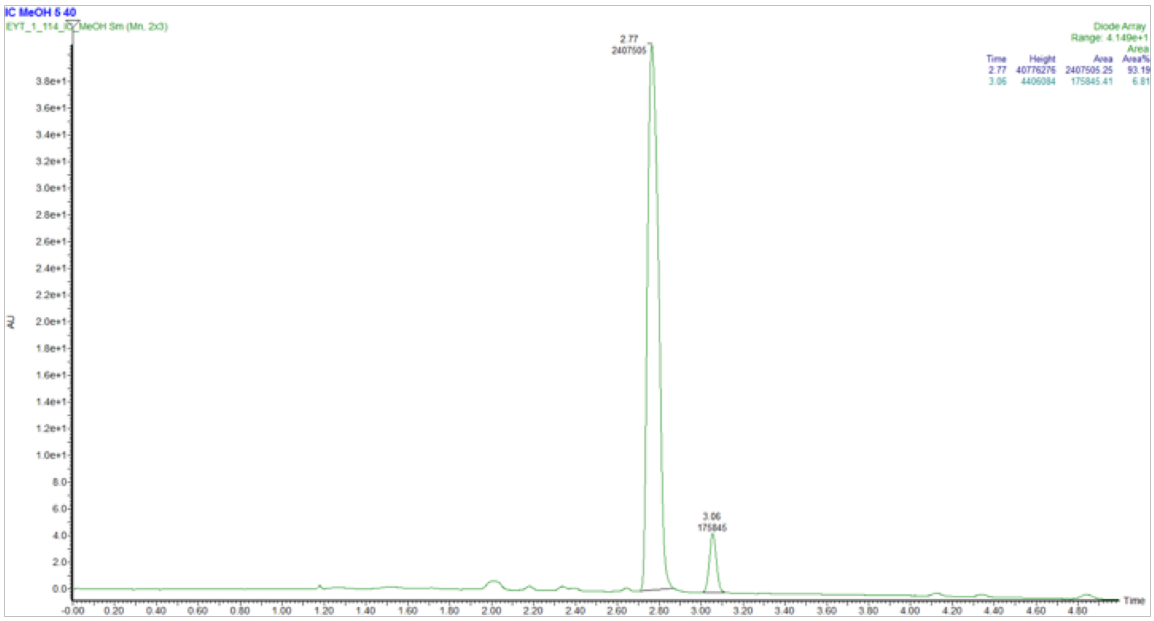


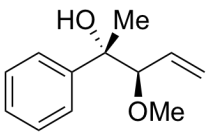
17

Trace of racemic compound



Trace of enantioenriched compound

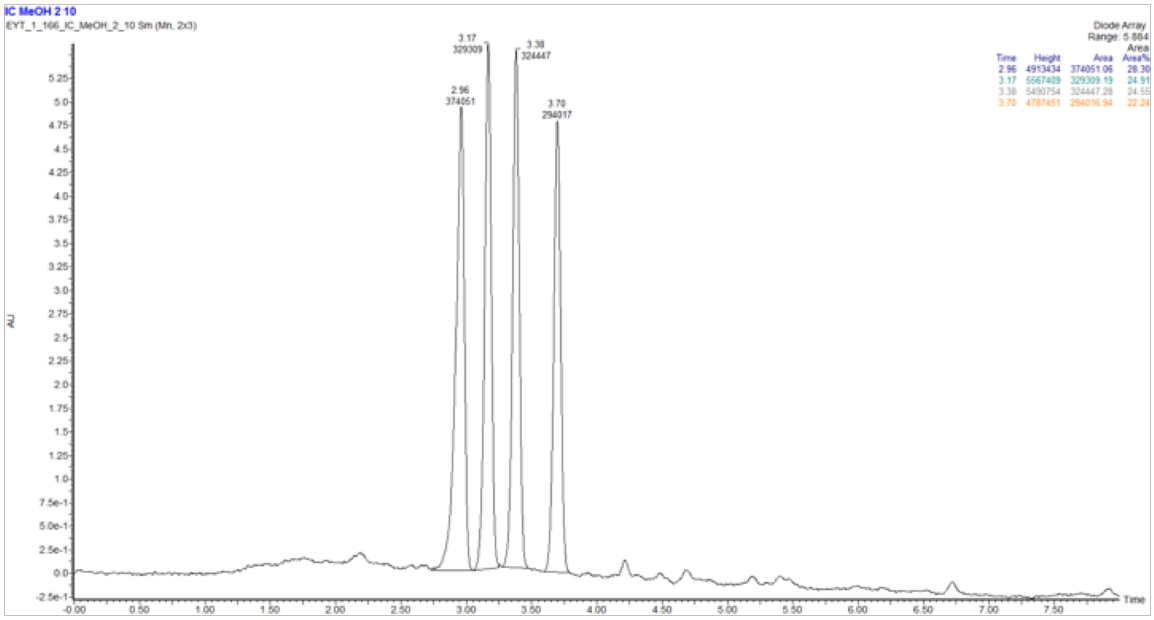




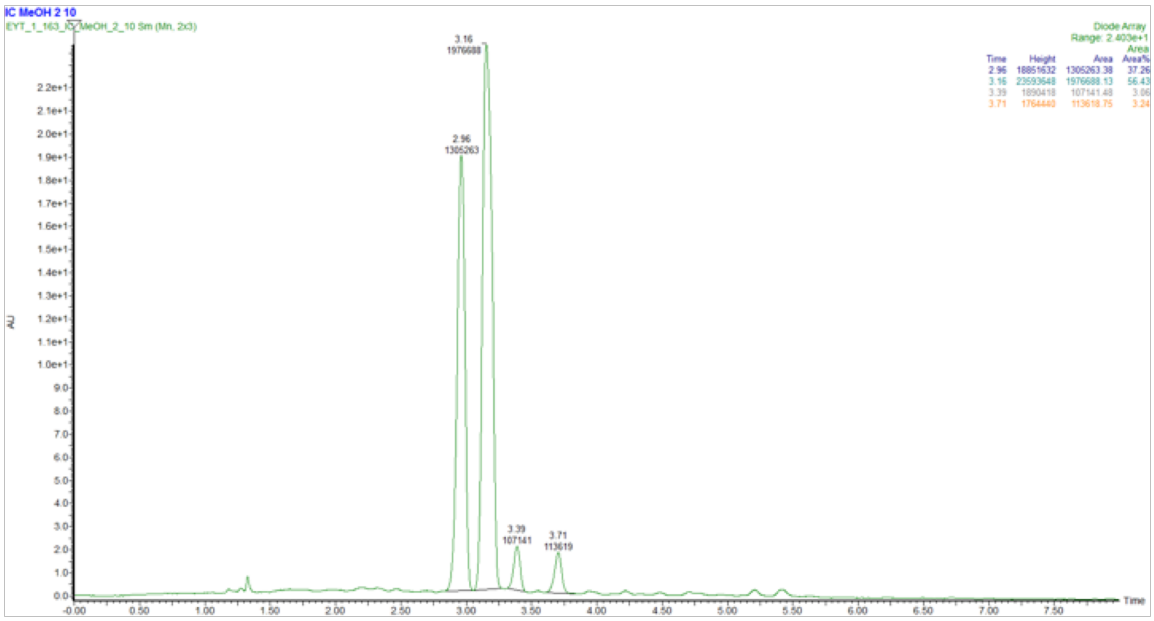
+ diastereomer

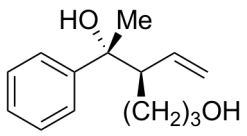
18

Trace of racemic compound



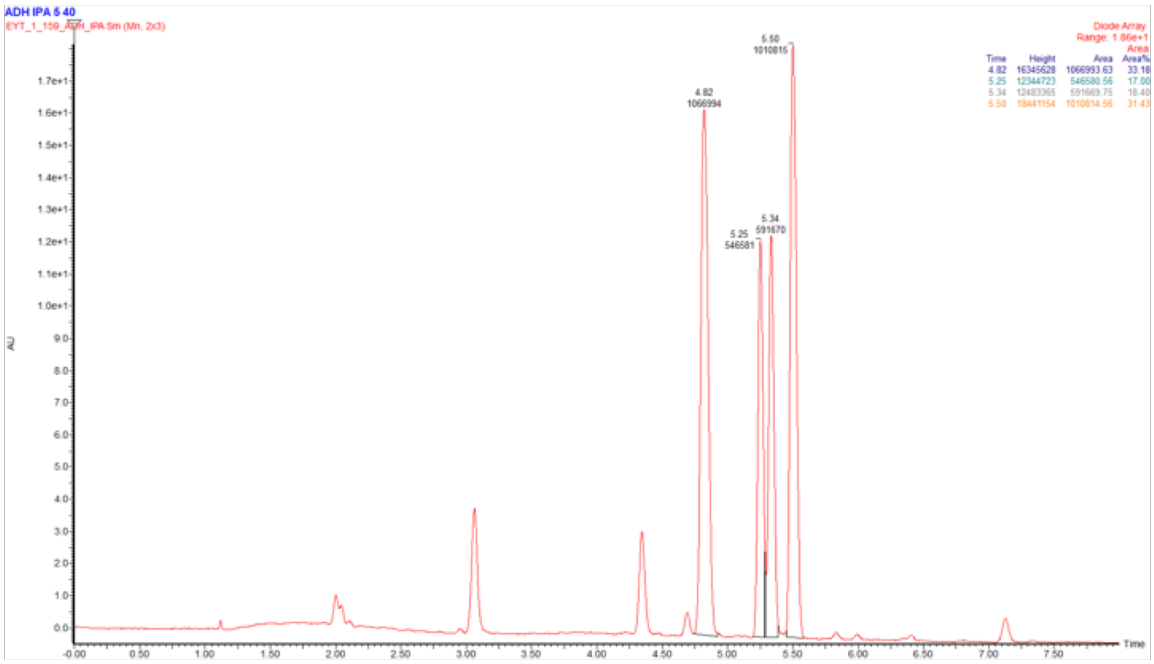
Trace of enantioenriched compound





19

Trace of racemic compound



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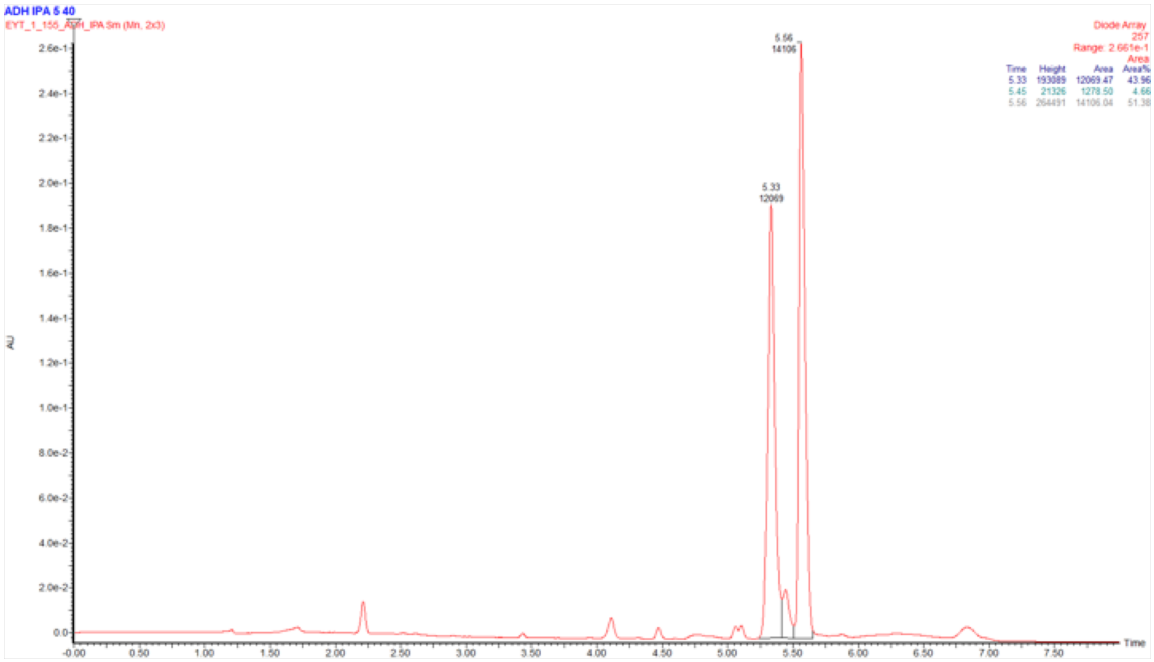
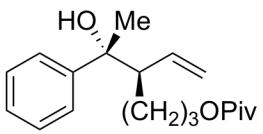
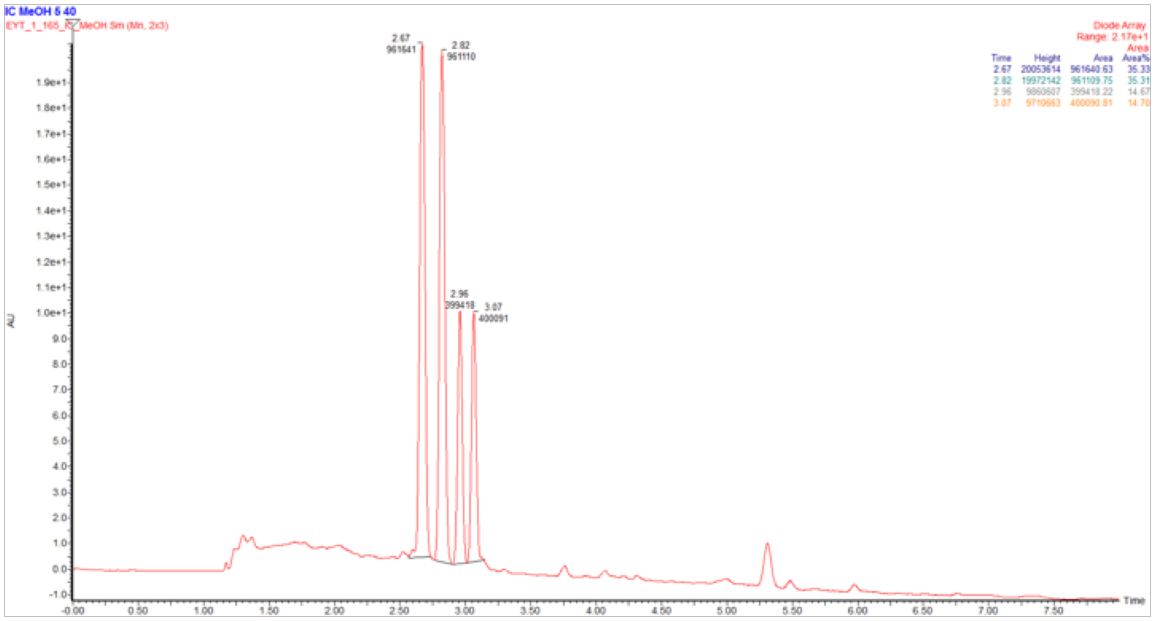




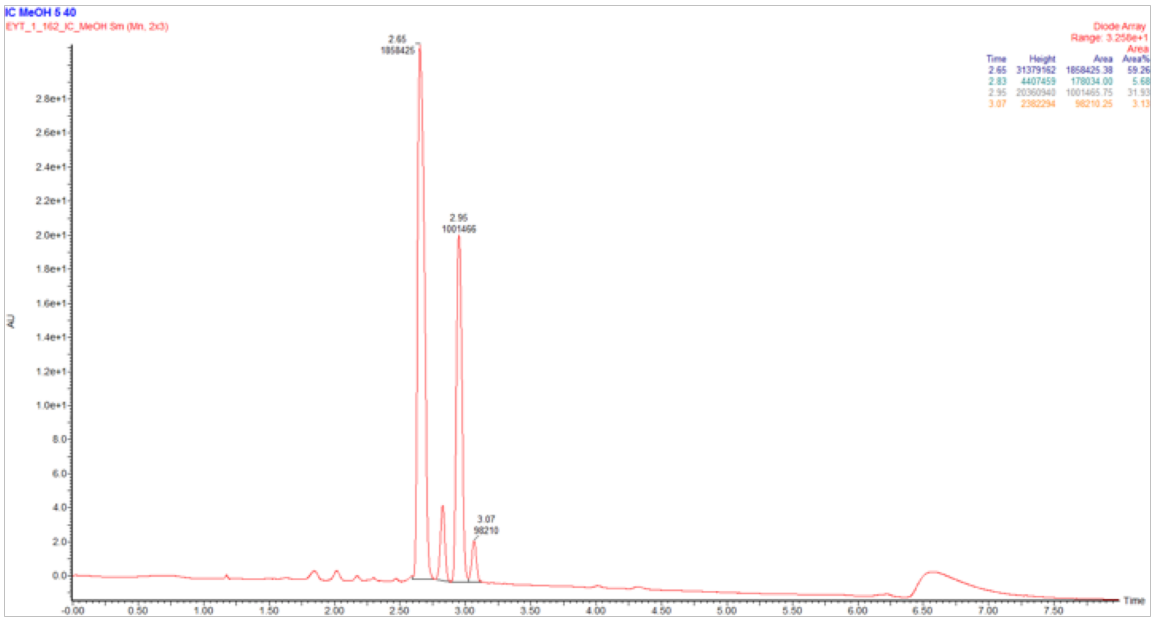
+ diastereomer

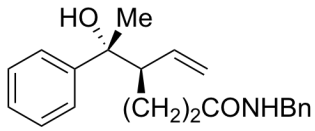
20

Trace of racemic compound



Trace of enantioenriched compound

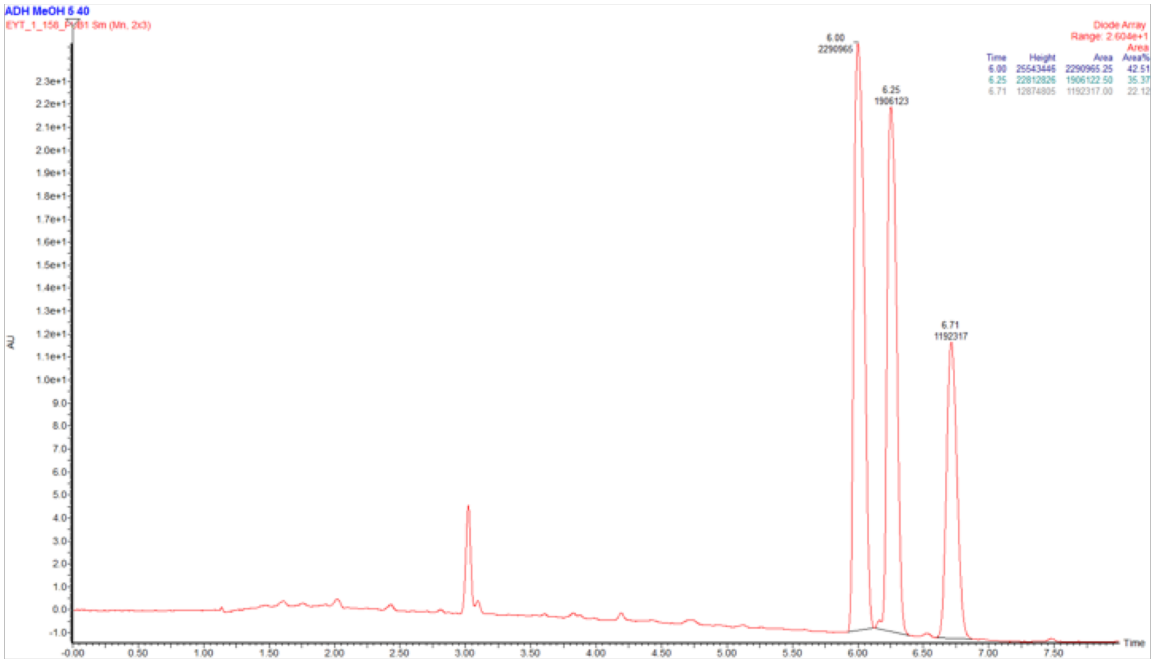




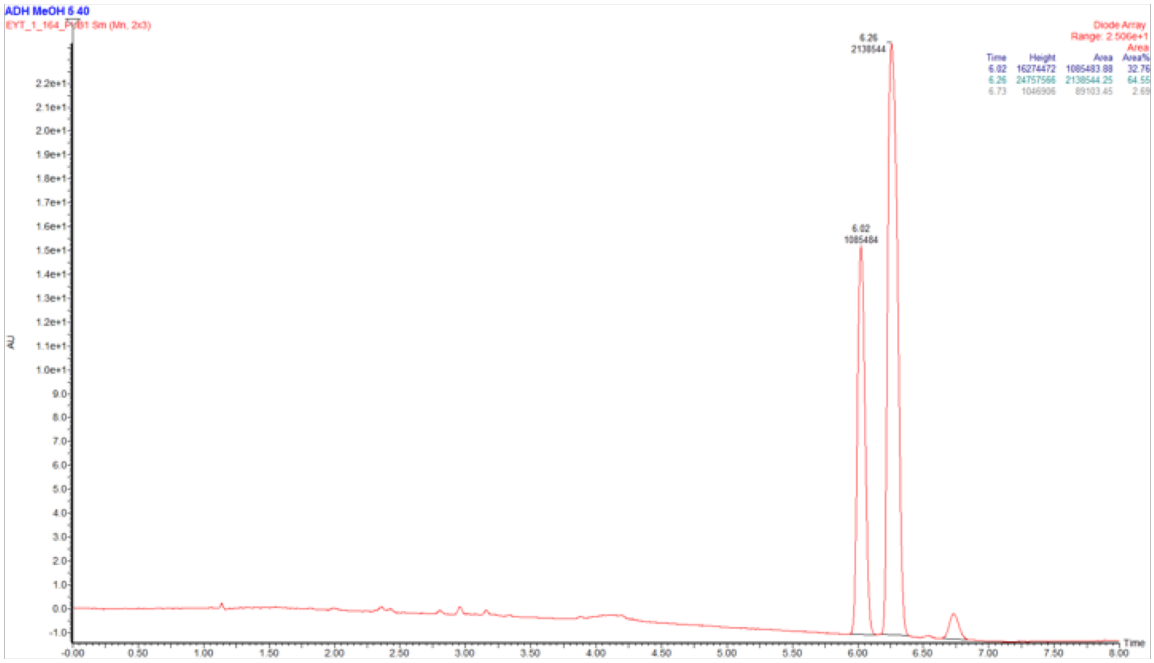
+ diastereomer

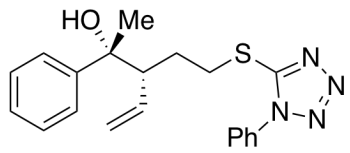
21

Trace of racemic compound



Trace of enantioenriched compound

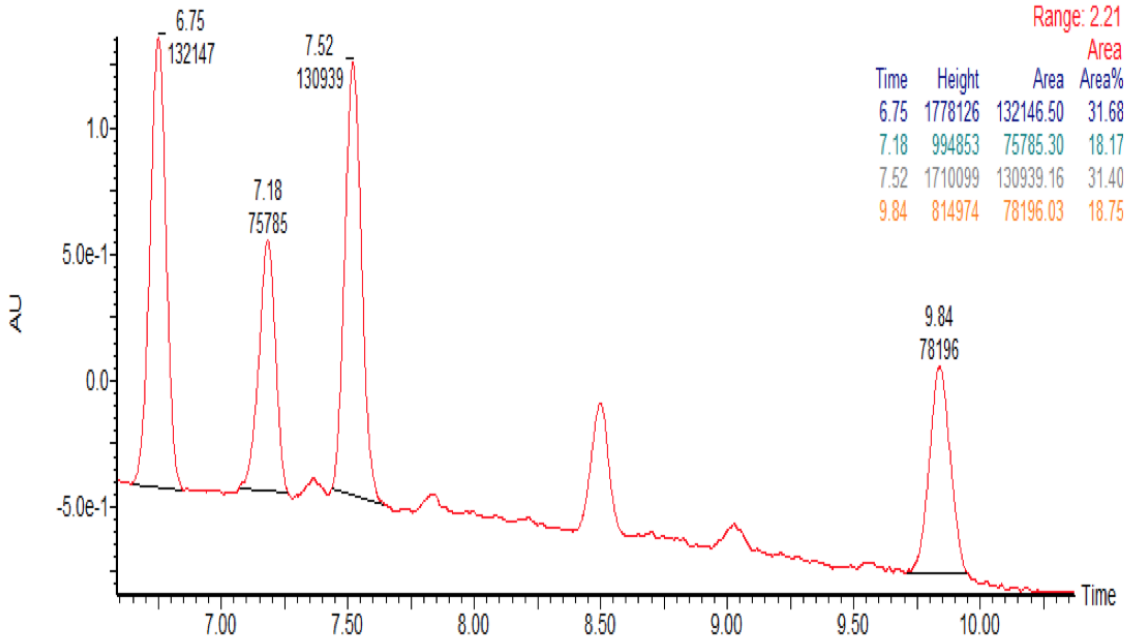




+ diastereomer

22

Trace of racemic compound



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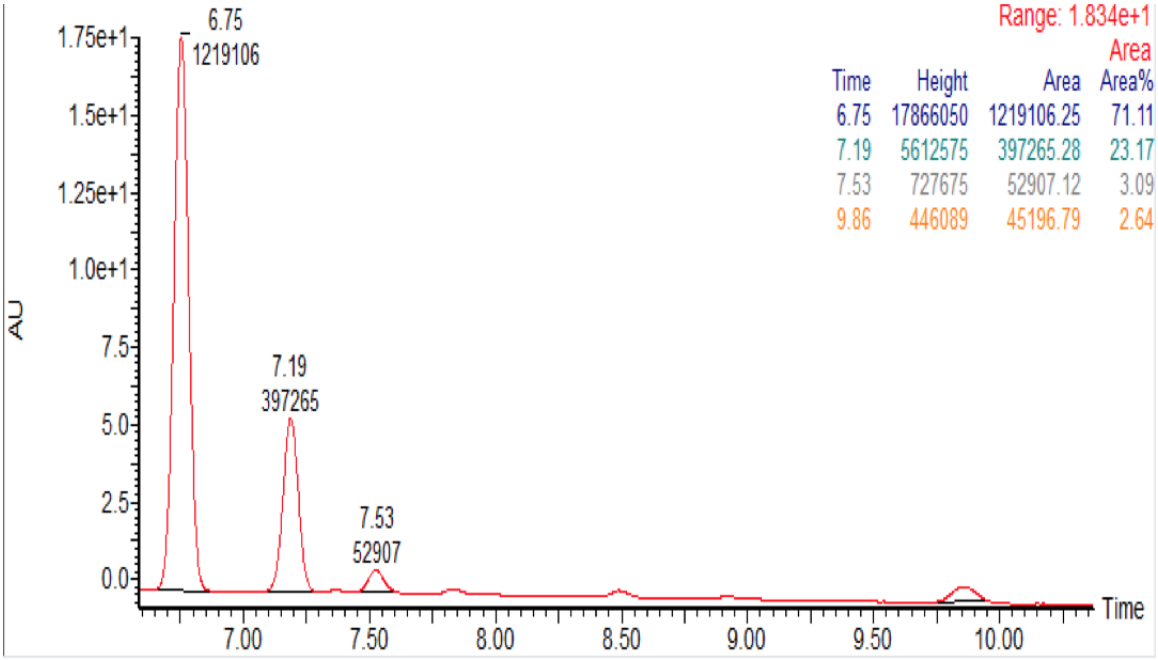
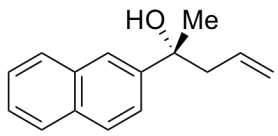
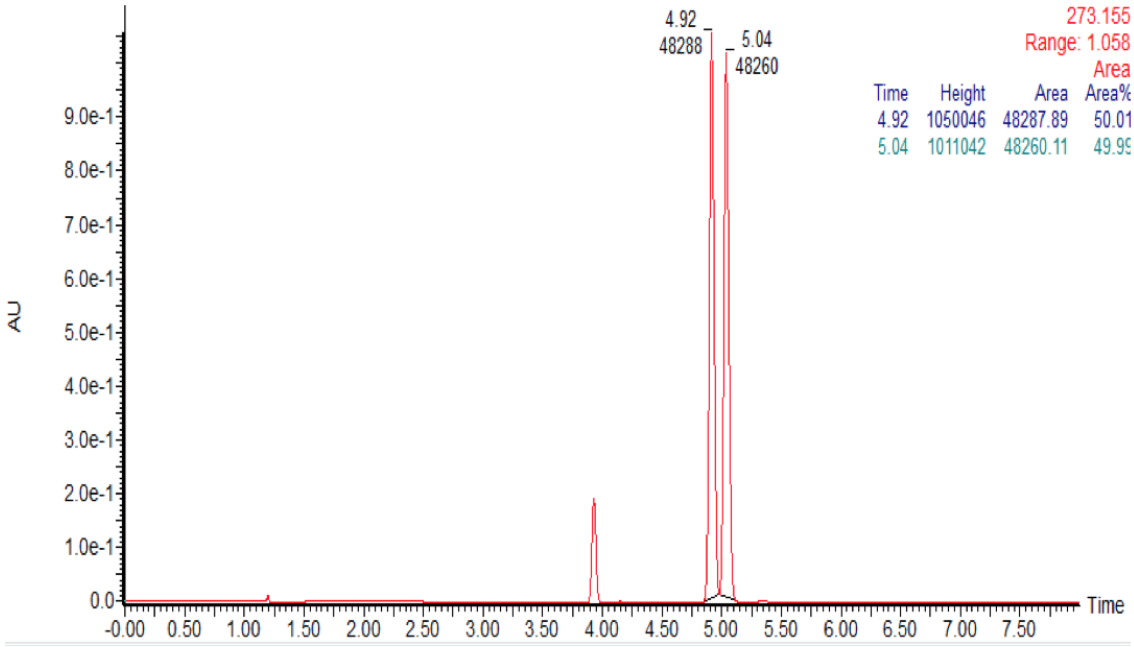


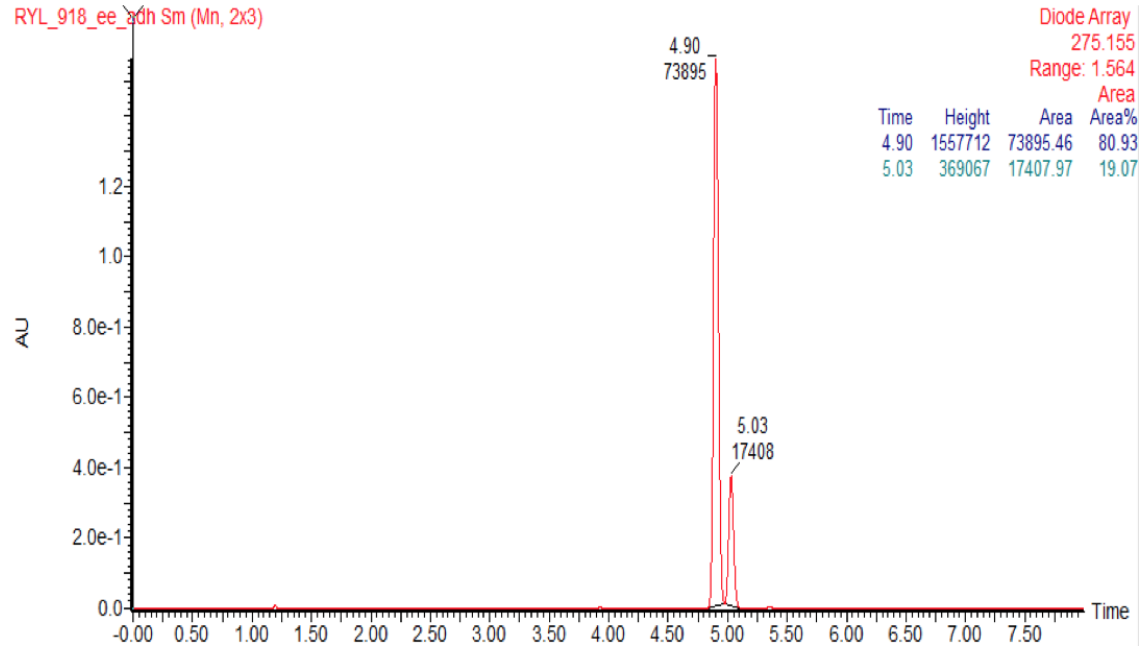


23

Trace of racemic compound



Trace of enantioenriched compound



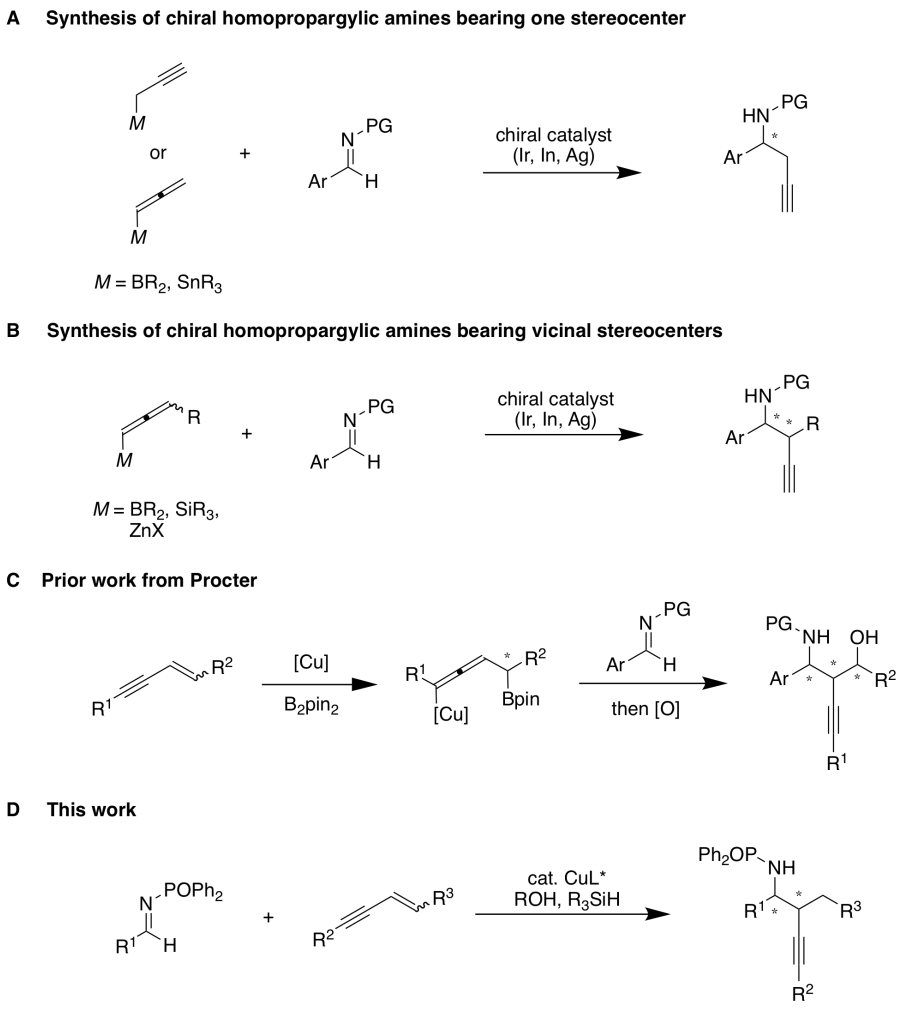
Chapter 3

Asymmetric Synthesis of Homopropargylic Amines by CuH-Catalyzed Coupling of Imines and Enynes

3.1 Introduction

Homopropargylic amines are synthetically useful building blocks that serve as versatile intermediates in numerous natural product syntheses,[1,2,3] such as for indolizidine 209B[2a] and hederacine A.[2c] Asymmetric techniques for their synthesis represent an important focus in synthetic chemistry. Methods for the synthesis of homopropargylic amines typically involve the coupling of imines with stoichiometric allenic or propargylic nucleophile reagents, and often provide the products in racemic form.[4] While considerable advances have been made in the synthesis of α-stereogenic amines (Figure 3-1A),[5] the synthesis of homopropargylic amines bearing vicinal stereocenters is more challenging. Current approaches commonly necessitate the use of a chiral auxiliary or pre-formed stoichiometric organometallic reagents (Figure 3-1B).[6]

Figure 3-1: Overview of enantioselective transition metal-catalyzed nucleophilic addition to imines for the synthesis of homopropargylic amines



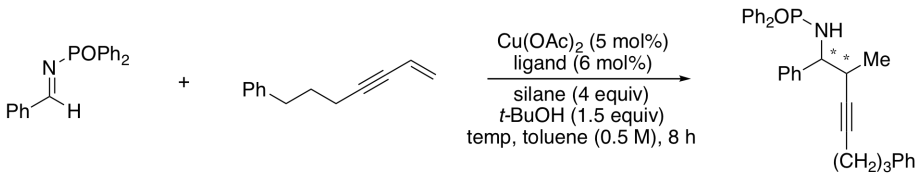
Our group and others have demonstrated that ligated copper hydride (CuH) species can engage with unsaturated substrates to catalytically form organocopper intermediates.[7] In particular, we have described copper-catalyzed reductive addition reactions of olefin-derived nucleophiles to carbonyl and imine electrophiles to afford chiral alcohols and amines.[7b,c,d,f,h,l,m] Procter recently demonstrated a copper-catalyzed borylative multicomponent coupling of aldimines, enynes, and diboron reagents to afford homopropargylic amines, though the conditions were limited to aryl imines and predominantly aryl (R^1 = Ar) enynes (Figure 3-1C).[8] We propose extending this reactivity to the reductive coupling of imines and enynes to afford α,β-chiral homopropargylic amine products (Figure 3-1D).

3.2 Results and Discussion

3.2.1 Reaction Optimization

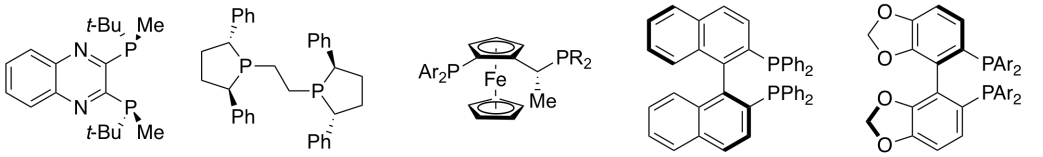
Prior studies on CuH-catalyzed reductive coupling reactions of carbon-carbon multiple bonds with imines suggest that the choice of the imine *N*-protecting group is crucial for the proposed transformation. Therefore, we chose *N*-phosphinoyl imines as the electrophilic coupling partner due to their success in related reactions.[7c,9] Employing *N*-benzylidene-*P,P*-diphenylphosphinic amide (**1a**) and hept-6-en-4-yn-1-ylbenzene (**1b**), we began our investigation of the optimal reaction conditions by testing the use of a variety of chiral ligands at 0 °C. *(R,R)*-Ph-BPE (**B**) was optimal with respect to yield and enantioselectivity, though the diastereoselectivity was lower compared to reactions employing *(R,R)*-QuinoxP* (Table 3-1, entries 1, 2). However, we were unable to increase the yield of **1**, and significant reduction of **1a** was observed. Raising the reaction temperature led to an erosion of the selectivity (Table 3-1, entry 7), and screening other solvents did not result in any significant improvements in yield or selectivity. Decreasing the catalyst loading and omitting *t*-BuOH from the reaction mixture both resulted in a marked decrease in the yield of **1** (Table 3-1, entries 8-10). Screening commonly used silanes revealed dimethoxymethylsilane (DMMS) to give the best results (Table 3-1, entry 11).

Table 3-1: Evaluation of Reaction Conditions for the Reductive Coupling of hept-6-en-4-yn-1-ylbenzene with *N*-benzylidene-*P,P*-diphenylphosphinic amide[a]



1a **1b** (1.5 equiv) **1**

Entry	Ligand	Silane	Temp (°C)	Yield[b] (%)	er[c]
1	**A**	TMCTS	0 °C	61 (9:1)	95:5
2	**B**	TMCTS	0 °C	85 (3:1)	95:5
3	**C**	TMCTS	0 °C	<5	n.d.
4	**D**	TMCTS	0 °C	<5	n.d.
5	**E**	TMCTS	0 °C	15 (1:1)	n.d.
6	**B**	TMCTS	-15 °C	85 (6:1)	99:1
7	**B**	TMCTS	rt	90 (3.5:1)	94:6
8[d]	**B**	TMCTS	rt	59 (3:1)	n.d.
9[e]	**B**	TMCTS	rt	25 (3:1)	n.d.
10[f]	**B**	TMCTS	0 °C	72 (3:1)	n.d.
11	**B**	DMMS	0 °C	95 (5:1)	99:1



[a] Optimization reactions were run by Mr. Lindner. Conditions: 0.20 mmol imine (1.0 equiv), enyne (1.5 equiv), copper(II) acetate (5 mol%), ligand (6 mol%), silane (4.0 equiv), *tert*-butanol (1.5 equiv) in solvent (0.4 mL); see the Experimental for details. [b] Yield and diastereomeric ratio was determined by ^{1}H and ^{31}P NMR spectroscopy of the crude reaction mixture, using mesitylene as internal standard. [c] n.d. = enantiomeric ratios were not determined. [d] Reaction

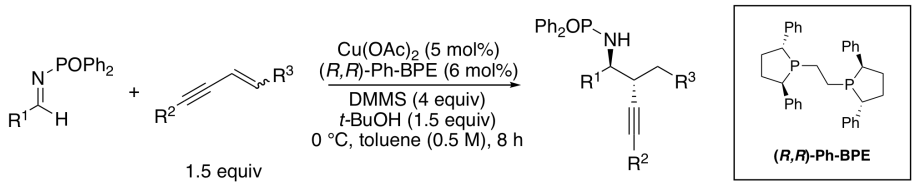
conducted at 3 mol% catalyst loading. [e] Reaction conducted at 1 mol% catalyst loading. [f] Reaction conducted without *tert*-butanol.

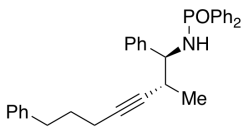
3.2.2 Substrate Scope

Having established the usable reaction conditions, we sought to investigate the scope of the transformation. Both aryl (**1-7**) and aliphatic (**8, 9**) imines were successfully coupled. The reaction proceeded efficiently with aryl imines bearing electron-donating (**3, 4**) and electron-withdrawing (**2**) substituents. Those bearing *para*- (**2-4, 14, 15**), *ortho*- (**5**), and *meta*-substituents (**6, 7**) were efficientlyconverted to product in high yield. Imines containing heterocycles such as thiophene (**10**), pyridine (**11, 12**), and indole (**13**) are suitable coupling partners for this reaction. Lower enantioselectivity was observed in the case of an *N*-methylindole imine (**13**), although we do not understand the reason for this. A wide variety of enynes could also be utilized. Enynes containing heterocycles such as isoindoline (**7**) and purine (**12**) were coupled successfully. Functional groups such as a tosylate (**3**), protected amine (**5**), amide (**8**), acetal (**9**), alkyl chloride (**10**), and ester (**15**) were tolerated. Internal enynes (**14, 15**) were also compatible. However, due to the attentuated reactivity of internal enynes when compared to terminal enynes, slow addition of the imine was required to minimize direct reduction of the imine. When the imine coupling partner was found to be insoluble in toluene (e.g., **13**), utilizing THF as the solvent enabled synthesis of the desired propargylic amines. In cases of low reactivity (e.g., **7, 12**), the reaction temperature was increased to room temperature. In all cases, the reaction proceeded with moderate diastereoselectivity.

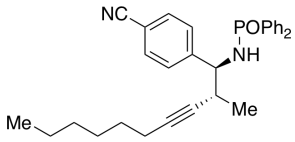
A plausible mechanism for the reaction can be proposed based on work on related reactions (Figure 3-2).[7b,8,10] We hypothesize that initial hydrocupration occurs at the alkene of the enyne to afford an enantioenriched propargylcopper intermediate. This can interconvert with the allenylcopper form via a stereospecific 1,3-isomerization during which chirality is preserved. This species then stereoselectively reacts with the imine. Ligand exchange with the alcohol additive, followed by σ-bond metathesis with the hydride source, would afford the product and the regenerated L*CuH complex.

Table 3-2: Evaluation of Scope of the Transformation[a,b]

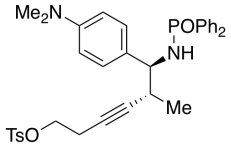




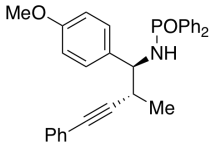
1
87% yield
5:1 dr
99:1 er



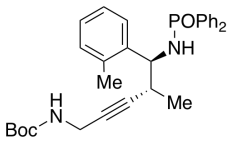
2
62% yield
4:1 dr
94:6 er



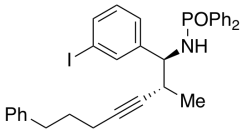
3[c]
67% yield
2:1 dr
95:5 er



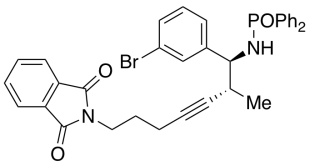
4
84% yield
3:1 dr
93:7 er



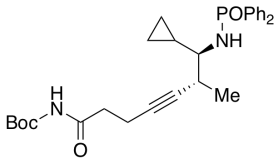
5[c]
74% yield
3:1 dr
83:17 er



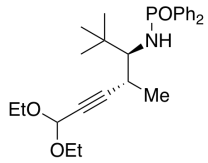
6
64% yield
3:1 dr
96:4 er



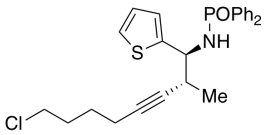
7[c]
51% yield
3:1 dr
98:2 er



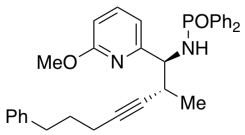
8[d]
58% yield
2:1 dr
90:10 er



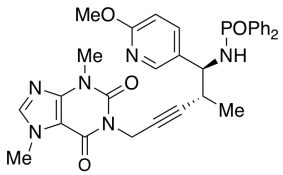
9[c,d,e]
60% yield
2:1 dr



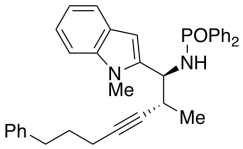
10
87% yield
5:1 dr
99:1 er



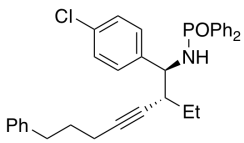
11
64% yield
10:1 dr
>99:1 er



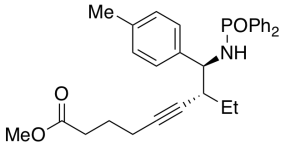
12[c,e]
93% yield
3:1 dr



13[c,d]
61% yield
1.5:1 dr
60:40 er



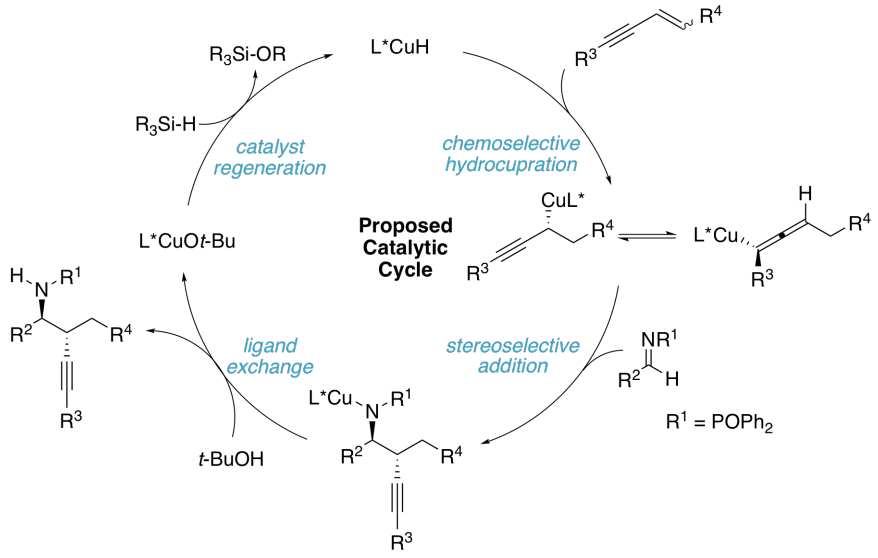
14[d]
67% yield
3:1 dr
99:1 er



15[c,d]
53% yield
3:1 dr
90:10 er

[a] Compounds 1-5, 7, 10, 12, and 14 were run by Mr. Lindner. Compounds 6, 8, 9, 11, 13, and 15 were run by the author. Yields indicate isolated yields of product as a mixture of two diastereomers on a 0.50-1.0 mmol scale with 1.5 equiv of enyne (see Experimental for further details). Diastereomeric ratios were determined by ^{1}H and ^{31}P NMR spectroscopy for both the crude and purified products using mesitylene or 1,1,2,2-tetrachloroethane as internal standard. Enantiomeric ratios were determined by SFC analysis on commercial chiral columns. Yields, diastereomeric ratios, and enantiomeric ratios are the averages for two identical runs. [b] Absolute stereochemistry was assigned based upon analogy to stereochemistry observed by Procter.[8] Further investigation is required to confirm this assignment. [c] The reaction was run at room temperature. [d] The reaction was run in THF. [e] The enantiomeric ratios have not yet been determined.[11]

Figure 3-2: Proposed Mechanism for the Reductive Coupling of Enynes with Aldimines



3.3 Conclusion

In this work, we have developed a new protocol for the enantio- and diastereoselective synthesis of homopropargylic amines bearing two adjacent stereocenters. A wide range of enynes were coupled with various *N*-phosphinoyl aldimines under mild conditions to afford the corresponding α,β-chiral amines in moderate to good yields, with moderate diastereoselectivity and high enantioselectivity.

3.4 Experimental

3.4.1 General Reagent Information

Unless noted otherwise, reagents and substrates were purchased from commercial vendors and used as supplied. *(S,S)*- and *(R,R)*-Ph-BPE were obtained from Strem or Millipore-Sigma. Racemic Ph-BPE was prepared by mixing equal amounts of the enantiopure ligands. $Cu(OAc)_2$ was purchased from Strem (amorphous powder, 97% min.). Dimethoxymethylsilane (DMMS, moisture-sensitive) was purchased from TCI-America. (Caution: Dimethoxy(methyl)silane (DMMS, CAS #16881-77-9) is listed by several vendors (TCI, Alfa Aesar) SDS or MSDS as a H318, a category 1 Causes Serious Eye Damage. Other vendors (Millipore-Sigma, Gelest) list DMMS as a H319, a category II Eye Irritant. DMMS should be handled in a well-ventilated fumehood using proper precaution as outlined for the handling of hazardous materials in "Prudent Practices in the Laboratory."[12]) All other reagents were purchased from Millipore-Sigma, Alfa Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific and were used as received. Toluene and THF were obtained from J.T. Baker in CYCLE-TAINER® delivery kegs and purified by successive filtrations though packed columns of neutral alumina and copper(II) oxide under argon pressure; EtOAc, hexanes, and DCM used in chromatography eluents for products were reagent grade from Millipore-Sigma. Flash chromatography was performed on wet-loaded, manually eluted silica columns using SiliCycle SiliaFlash® F60 silica gel (40-63 μm, 230-400 mesh, 60 Å pore diameter) with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System. Analtech Uniplate™ preparative thin-layer chromatography (TLC) plates (silica gel GF, 1000 μm, UV254 indicator, 20 x 20 cm) were employed in preparative TLC purifications. Reactions were performed in glass culture tubes with threaded ends (Fisher Scientific part #1495935A; oven-dried at 140 °C for at least 16 h prior to use) that were sealed with screw-thread caps (Thermo Scientific part #04015-66) fitted with PTFE/silicone septa (Thermo Scientific part #B7995-15).

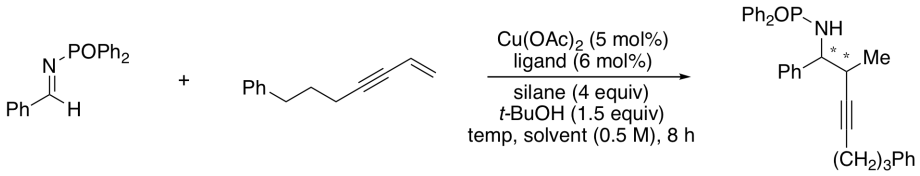
3.4.2 General Analytical Information

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded using a Bruker 400 MHz spectrometer. Chemical shifts of ^{1}H NMR signals are referenced to the indicated residual solvent peak ($CDCl_3$, δ = 7.26 ppm) and reported in ppm relative to tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm) and all were obtained with ^{1}H decoupling. $CDCl_3$ was obtained from Cambridge Isotope Laboratories. IR spectra were acquired from neat samples using a Thermo Scientific Nicolet iS5 spectrometer equipped with an iD5 diamond laminate ATR accessory, and representative peaks are reported as wavenumbers in units of cm^{-1}. Specific optical rotations were recorded for chloroform solutions at a standard concentration of 10 mg/mL using a Jasco model P-1010 polarimeter. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. High-resolution mass spectrometry (HRMS) was performed using a JEOL AccuTOF 4G LC-plus equipped with an ionSense DART (Direct Analysis in Real Time) source. LC-MS analysis was performed with a Thermo Scientific Accucore C18 column (30 x 2.1 mm, 2.6 μm particle size) maintained at 45 °C within an instrument consisting of Agilent 1260 series binary pump, degasser and sample manager modules, Agilent 1100 series COLCOM and DAD modules, and an Agilent 6120 quadrupole MS operating in positive MM-ES+APCI ionization mode.

Elemental analyses were performed for carbon and hydrogen by Atlantic Microlabs Inc., Norcross, GA. The enantiomeric ratios of products (er) were determined by chiral SFC analysis using a Waters Acquity UPC2 instrument or by high performance liquid chromatography (HPLC). Specific columns and analytical methods are provided in the experimental details for individual compounds; the wavelengths of light used for chiral analyses are provided with the associated chromatograms. Gas Chromatography (GC) was performed using an Agilent 7890A gas chromatograph equipped with an FID detector and a JW DB-1 column (10 mm, 0.1 mm I.D.). Analytical TLC was performed using Silicycle SilicaPlate® glass-backed extra-hard-layer TLC plates (60 Å, 250 μm thickness, 20 x 20 cm, UV-254 indicator) and visualization with 254 nm light.

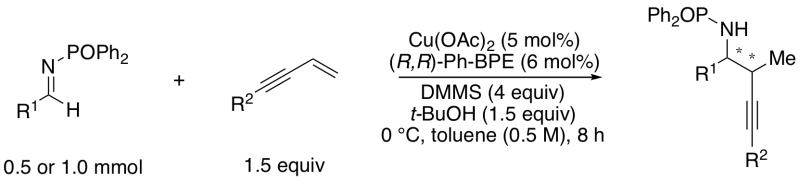
3.4.3 Reaction Optimization Procedures

Note: Reaction optimization experiments were conducted by Mr. Lindner.



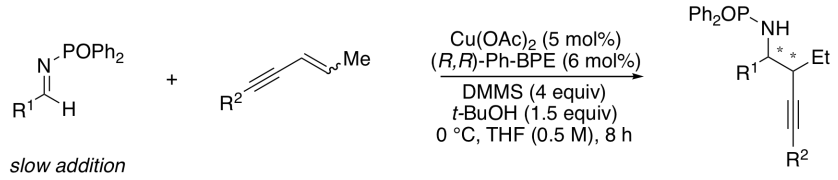
In a nitrogen-filled glovebox, a small reaction tube (Fischer Scientific part #1495935C) equipped with a magnetic stir bar was charged with imine (0.20 mmol), enyne (0.67 to 2.0 equiv), $Cu(OAc)_2$ (2 mg, 0.05 equiv), ligand (0.06 equiv), *t*-BuOH (0.0 to 2.0 equiv), and solvent (0.4 mL). The vial was capped with a screw cap fitted with a septum insert (Fischer Scientific part #C4015-66A), removed from the glove box, and partially submerged into an ice/water bath/cooling bath equipped with a Julabo FT902 immersion cooler, or let stir at room temperature. Silane (4.0 equiv) was added by syringe in one portion by piercing the septum with the needle, and the resulting reaction mixture was stirred for 8 h. The solution was allowed to warm to room temperature if necessary, and the cap was removed. The reaction was quenched by adding saturated aqueous ammonium chloride dropwise using a 1 mL syringe (1 mL, **WARNING: VIGOROUS HYDROGEN EVOLUTION**) and stirred for 30 min at room temperature. After removal of solvent under reduced pressure with aid of a rotary evaporator, the yield and diastereomeric ratio (dr) were assessed by ^{1}H and ^{31}P NMR in $CDCl_3$, using mesitylene or 1,1,2,2-tetrachloroethane as an internal standard. The mixture was separated by preparative TLC, and the product was isolated. The enantiomeric excess was determined by SFC analysis.

3.4.4 General Procedure A for Coupling of Imines with Terminal Enynes



In a nitrogen-filled glovebox, a stock solution of catalyst was prepared as follows: an oven-dried screw-cap 1 dram vial (VWR cat. 66010-243) equipped with a magnetic stir bar (vial A) was charged with $Cu(OAc)_2$ (11 mg, 60 μmol) and ((+)-1,2-Bis(*(2R,5R)*-2,5-diphenylphospholano)ethane (*(R,R)*-Ph-BPE, 37 mg, 71 μmol). The solids were dissolved in solvent (1.2 mL), vial A was capped, and the mixture was stirred for 10-20 min to yield a homogenous blue solution. Meanwhile, an oven-dried screw-cap reaction tube (16 mm x 125 mm, Fisherbrand, part #1495935A) with magnetic stir bar (vial B) was charged with imine (0.50 to 1.0 mmol, 1.0 equiv), enyne (0.75 to 1.5 mmol, 1.5 equiv), and solvent to produce a solution 1.0 M in imine. *T*-BuOH (0.75 to 1.5 mmol, 1.5 equiv) was added to vial B via a 1.0 mL syringe. Then 0.5 to 1.0 mL of the copper catalyst solution from vial A was added to vial B using a 1 mL syringe to produce a final solution 0.5 M in imine. Vial B was closed with a septum screw cap fitted with a with a Teflon-lined silicone septum (Thermo Scientific part #B7995-15; Thermo Scientific part 04015-66) and removed from the glovebox. Vial B was then placed in either an ice/water bath or a cooling bath equipped with a Julabo FT902 immersion cooler set to 2 ^{o}C with stirring. Dimethoxymethylsilane (DMMS, 2.0 to 4.0 mmol, 4.0 equiv) was added slowly down the wall of vial B via a 1 mL syringe. The reaction was then stirred for 8 h. Subsequently, vial B was removed from the bath, uncapped, and and the reaction was quenched by adding saturated aqueous ammonium chloride dropwise using a 1 mL syringe (1 mL, **WARNING: VIGOROUS HYDROGEN EVOLUTION**) and stirred for 30 min at room temperature. The organic phase was collected, and the aqueous layer was extracted with 3 x 2 mL of dichloromethane. The organic phases were combined and dried over sodium sulfate, then filtered and concentrated *in vacuo* with the aid of a rotary evaporator. An aliquot of the crude material was dissolved in $CDCl_3$ and analyzed by ^{1}H NMR and ^{31}P NMR to determine the diastereomeric ratio (dr). After combining the crude material, the resulting mixture was purified by column chromatography (see details for each substrate below) followed by LC-MS analysis of product-containing fractions, then dried under high vacuum for at least 16 h to provide the desired product.

3.4.5 General Procedure B for Coupling of Imines with Internal Enynes

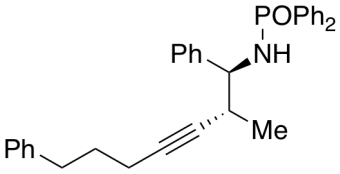


In a nitrogen-filled glovebox, an oven-dried screw-cap 1 dram vial (VWR cat. 66010-243) equipped with a magnetic stir bar (vial A) was charged with imine (0.50 mmol, 1.0 equiv), *t*-BuOH (72 μL, 75 μmol, 1.5 equiv), and 0.6 mL of THF. Meanwhile, an oven-dried screw-cap reaction tube (16 mm x 125 mm, Fisherbrand, part #1495935A) with magnetic stir bar (vial B) was charged with $Cu(OAc)_2$ (5 mg, 25 μmol, 5 mol%), ((+)-1,2-Bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane (*(R,R)*-Ph-BPE, 15 mg, 30 μmol, 6 mol%), internal enyne substrate (75 μmol, 1.5 equiv), and THF (0.5 mL). Vial B was closed with a septum screw cap fitted with a Teflon-lined silicone septum (Thermo Scientific part #B7995-15; Thermo Scientific part 04015-66) and both vials A and B were removed from the glovebox. Vial B was then placed in either a room temperature water bath or a cooling bath equipped with a Julabo FT902 immersion cooler set to 2 °C with stirring. Dimethoxymethylsilane (DMMS, 247 μL, 2.0 mmol, 4.0 equiv) was added slowly down the wall of vial B containing the copper complex via a 1 mL syringe. A 0.5 mL aliquot of vial A was taken into a 1 mL syringe. Over the course of 6 hours, this was slowly added to the reaction tube using the 1 mL syringe fitted to a syringe pump (1.0 M, 1.4 μL/min). The reaction was then stirred for an additional 2 h. Subsequently, the reaction tube was removed from the bath, uncapped, and and the reaction was quenched by adding saturated aqueous ammonium chloride dropwise using a 1 mL syringe (1 mL, **WARNING: VIGOROUS HYDROGEN EVOLUTION**) and stirred for 30 min at room temperature. The organic phase was collected, and the aqueous layer was extracted 3 x 2 mL of dichloromethane. The organic phases were combined and dried over sodium sulfate. The resulting crude reaction mixture was concentrated *in vacuo* with the aid of a rotary evaporator, dissolved in $CDCl_3$, and analyzed by ^{1}H NMR and ^{31}P NMR to determine the diastereomeric ratio (dr). After combining the crude material, the resulting mixture was purified by column chromatography followed by LC-MS analysis of product-containing fractions, then dried under high vacuum for at least 16 h to provide the desired product.

3.4.6 Synthesis and Characterization Data for Products

Note: Compounds 1-5, 7, 10, 12, and 14 were run by Mr. Lindner. Compounds 6, 8, 9, 11, 13, and 15 were run by the author.

_N_-(2-methyl-1,7-diphenylhept-3-yn-1-yl)-_P,P_-diphenylphosphinic amide (1)



Following general procedure A, $Cu(OAc)_2$ (9 mg, 0.050 mmol), *(R,R)*-Ph-BPE (30 mg, 0.060 mmol), (*E*)-*N*-benzylidene-*P,P*-diphenylphosphinic amide (305 mg, 1.0 mmol), hept-6-en-4-yn-1-ylbenzene (170 mg, 1.5 mmol), *t*-BuOH (0.14 mL, 1.5 mmol), DMMS (0.49 mL, 4.0 mmol), and toluene (2 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 20% EtOAc/hexanes for 2 column volume (CV), then 20-100% EtOAc/hexanes for 10 CV, followed by 100% EtOAc/hexanes for 8 CV) to afford the title compound as a yellow oil (443 mg, 93% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 23.1 (major) and 22.3 (minor)] of the unpurified reaction mixture indicated a 5:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 5:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.92–7.84 (m, 2H), 7.77–7.69 (m, 2H), 7.53–7.37 (m, 4H), 7.35–7.17 (m, 10H), 7.15–7.09 (m, 2H), 4.07-4.14 (m, 2H), 3.25-3.20 (m, 1H), 2.62 (t, J = 7.6 Hz, 2H), 2.15-2.23 (m, 2H), 1.80 (p, J = 7.1 Hz, 2H), 0.99 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 23.1 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a 99:1 er: t_R (major) = 5.75 min, t_R (minor) = 5.48 min.

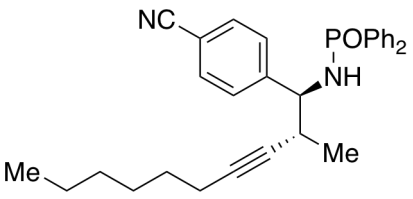
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.94–7.83 (m, 2H), 7.79–7.68 (m, 2H), 7.46–7.38 (m, 2H), 7.48-7.35 (m, 2H), 7.31–7.20 (m, 10H), 7.19–7.12 (m, 2H), 4.18–4.15 (m, 1H), 3.96-4.00 (m, 1H), 2.81-2.90 (m, 1H), 2.62 (t, J = 7.6 Hz, 2H), 2.12-2.16 (m, 2H), 1.76 (p, J = 7.0 Hz, 2H), 1.39 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 22.3 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a 92.5:7.5 er: t_R (major) = 6.25 min, t_R (minor) = 5.24 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**)** δ**:** 142.9, 142.8, 141.6, 141.5, 140.6, 140.5, 134.0, 133.9, 133.0, 132.8, 132.7, 132.6, 132.5, 131.9, 131.8, 131.7, 131.7, 131.7, 131.6, 131.4, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 127.9, 127.8, 127.4, 127.2, 126.8, 125.9, 84.5, 84.0, 81.1, 80.7, 58.8, 58.0, 35.8, 35.7, 35.1, 35.0, 34.8, 30.6, 30.5, 19.8, 18.9, 18.3 ppm.

IR: 3175, 2931, 2217, 1438, 1190, 1109, 907, 724, 696 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{32}H_{32}NOP + H]+$: 478.2294. Found: 478.2316. $[\alpha]_D^{23}$ = -14.6.

Duplicate experiment: 386 mg, 81% yield, 5:1 dr, 99:1 er (major).

N-(1-(4-cyanophenyl)-2-methyldec-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (2)



Following general procedure A, $Cu(OAc)_2$ (9 mg, 0.050 mmol), *(R,R)*-Ph-BPE (30 mg, 0.060 mmol), (*E*)-*N*-(4-cyanobenzylidene)-*P,P*-diphenylphosphinic amide (330 mg, 1.0 mmol), dec-1-en-3-yne (136 mg, 1.5 mmol), *t*-BuOH (0.14 mL, 1.5 mmol), DMMS (0.49 mL, 4.0 mmol), and toluene (2 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 0% EtOAc/hexanes for 2 column volume (CV), then 0-100% EtOAc/hexanes for 12 CV, followed by 100% EtOAc/hexanes for 7 CV) to afford the title compound as a yellow solid (248 mg, 53% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 25.5 (major) and 24.9 (minor)] of the unpurified reaction mixture indicated a 4:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 4:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.77 (dd, J = 12.0, 7.7 Hz, 2H), 7.59 (dd, J = 12.2, 7.7 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.38–7.30 (m, 4H), 7.17-7.23 (m, 2H), 4.32 (dd, J = 10.6, 7.4 Hz, 1H), 4.07–4.01 (m, 1H), 3.13-3.05 (m, 1H), 2.07–2.01 (m, 2H), 1.38-1.28 (m, 2H), 1.27-1.22 (m, 1H), 1.24–1.09 (m, 7H), 0.95 (d, J = 7.0 Hz, 3H), 0.80 (t, J = 6.7 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 25.5 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 85/15, 2.5 mL/min) indicated a 93:7 er: t_R (major) = 5.49 min, t_R (minor) = 7.03 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.79-7.69 (m, 2H), 7.66-7.62 (m, 2H), 7.42-7.37 (m, 2H), 7.33-7.29 (m, 4H), 7.19 (d, J = 7.7 Hz, 2H), 4.32 (dd, J = 10.6, 7.4 Hz, 1H), 4.03-3.98 (m, 1H), 2.80–2.66 (m, 1H), 2.07-2.00 (m, 2H), 1.37-1.32 (m, 2H), 1.29-1.21 (m, 1H), 1.25–1.15 (m, 7H), 0.97-0.95 (m, 3H), 0.82-0.79 (m, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 24.9 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 85/15, 2.5 mL/min) indicated a 66:34 er: t_R (major) = 4.56 min, t_R (minor) = 7.28 min.

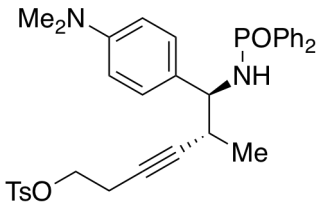
^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**)** δ**:** 146.5, 146.4, 133.2, 133.0, 132.8, 132.5, 132.2, 132.1, 132.0, 131.9, 131.8, 131.7, 131.5, 131.2, 128.6, 128.5, 128.5, 128.3, 128.2, 127.7, 118.8, 111.0, 110.9, 85.5,

85.1, 79.7, 79.1, 58.5, 58.0, 35.2, 34.4, 34.3, 31.2, 28.7, 28.5, 28.4, 22.5, 19.6, 18.8, 18.6, 14.0 ppm.

m.p. = 210-213 °C. **IR:** 3160, 2929, 2226, 1438, 1181, 1108, 909, 724, 694 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{30}H_{33}N_2OP+H]+$: 469.2403. Found: 469.2436. $[\alpha]_D^{23}$ = -20.2.

Duplicate experiment: 332 mg, 71% yield, 4:1 dr, 94:6 er (major).

6-(4-(dimethylamino)phenyl)-6-((diphenylphosphoryl)amino)-5-methylhex-3-yn-1-yl 4-methylbenzenesulfonate (3)



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), *(E)-N*-(4-(dimethylamino)benzylidene)-*P,P*-diphenylphosphinic amide (174 mg, 0.50 mmol), hex-5-en-3-yn-1-yl 4-methylbenzenesulfonate (188 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and toluene (1 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 50% EtOAc/hexanes for 2 column volume (CV), then 50-100% EtOAc/hexanes for 5 CV, followed by 100% EtOAc/hexanes for 15 CV) to afford the title compound as a yellow oil (210 mg, 70% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 23.2 (major) and 22.4 (minor)] of the unpurified reaction mixture indicated a 2:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 2:1 dr.

Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.94–7.80 (m, 2H), 7.80–7.69 (m, 4H), 7.55–7.38 (m, 6H), 7.33-7.27 (m, 4H), 7.08 (t, J = 8.6 Hz, 2H), 6.66 (t, J = 9.4 Hz, 2H), 4.08–3.99 (m, 2H), 3.93–3.87 (m, 1H), 3.77 (d, J = 11.2 Hz, 1H), 3.18-3.15 (m, 1H), 2.97 (s, 6H), 2.58–2.47 (m, 3H), 2.45 (s, 2H), 0.90 (d, J = 7.1 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 23.2 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 94:6 er: t_R (major) = 4.26 min, t_R (minor) = 4.35 min.

Minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86–7.80 (m, 2H), 7.80–7.74 (m, 4H), 7.57–7.45 (m, 6H), 7.35-7.29 (m, 4H), 7.08 (t, J = 8.6 Hz, 2H), 6.66 (t, J = 9.4 Hz, 2H), 3.98-3.91 (m, 2H), 3.89-3.82 (m, 1H), 3.74-3.69 (m, 1H), 2.95 (s, 6H), 2.80–2.70 (m, 1H), 2.53–2.48 (m, 2H), 2.45 (s, 3H), 1.27 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.4 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 91:9 er: t_R (major) = 4.93 min,

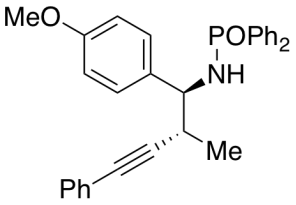
t_R (minor) = 4.20 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling) δ**:** 149.9, 149.8, 144.9, 134.1, 134.0, 132.9, 132.8, 132.7, 132.6, 132.5, 132.2, 131.9, 131.8, 131.7, 131.6, 131.5, 131.4, 129.9, 128.5, 128.4, 128.2, 127.9, 127.4, 112.3, 112.0, 83.7, 83.5, 78.1, 78.0, 68.1, 58.4, 57.5, 40.7, 40.6, 35.6, 35.5, 35.3, 21.7, 19.9, 19.0, 18.6 ppm.

IR: 3200, 2883, 2218, 1613, 1522, 1438, 1357, 1175, 1122, 972, 904, 723, 696 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{34}H_{37}N_2O_4PS+H]+$: 601.2284. Found: 601.2319. $[\alpha]_D^{23}$ = -48.5.

Duplicate experiment: 195 mg, 65% yield, 2:1 dr, 95:5 er (major).

N-(1-(4-methoxyphenyl)-2-methyl-4-phenylbut-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (4)



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), (*E*)-*N*-(4-methoxybenzylidene)-*P,P*-diphenylphosphinic amide (168 mg, 0.50 mmol), but-3-en-1-yn-1-ylbenzene (96 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and toluene (1 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 20% EtOAc/hexanes for 2 column volume (CV), then 20-100% EtOAc/hexanes for 10 CV, followed by 100% EtOAc/hexanes for 12 CV) to afford the title compound as a white powder (201 mg, 87% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 23.3 (major) and 22.4 (minor)] of the unpurified reaction mixture indicated a 3:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 3:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.92-7.83 (m, 2H), 7.77-7.67 (m, 2H), 7.51–7.20 (m, 13H), 6.84 (d, J = 8.7 Hz, 2H), 4.20-4.10 (m, 1H), 4.02-3.95 (m, 1H), 3.81 (s, 3H), 3.46 (pd, J = 8.0, 7.0, 4.3 Hz, 1H), 1.09 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 23.2 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 93:7 er: t_R (major) = 3.41 min, t_R (minor) = 3.55 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.92-7.83 (m, 2H), 7.77-7.67 (m, 2H), 7.51–7.20 (m, 13H), 6.81 (d, J = 8.7 Hz, 2H), 4.20-4.10 (m, 1H), 3.96-3.87 (m, 1H), 3.79 (s, 3H), 3.07 (pd, J = 6.9, 4.5 Hz, 1H), 1.41 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 22.9 ppm. **SFC analysis** (CEL1 column,

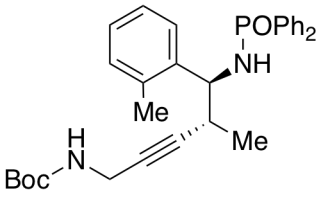
$scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 95:5 er: t_R (major) = 4.40 min, t_R (minor) = 3.35 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**) δ:** 159.0, 158.8, 158.5, 141.5, 134.5, 134.5, 133.8, 133.2, 133.1, 132.8, 132.7, 132.7, 132.6, 132.6, 132.5, 132.4, 132.3, 131.9, 131.8, 131.8, 131.8, 131.7, 131.7, 131.6, 131.6, 131.5, 129.3, 129.2, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 126.6, 123.4, 123.3, 90.8, 90.7, 84.3, 84.2, 59.4, 58.7, 57.9, 57.0, 55.2, 36.1, 35.7, 18.8, 18.5, 18.2 ppm.

m.p. = 182-185 °C. **IR:** 3168, 1611, 1512, 1437, 1246, 1177, 1108, 907, 691 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{30}H_{28}NO_2P+H]+$: 466.1930. Found: 466.1924. $[\alpha]_D^{23}$ = -32.5.

Duplicate experiment: 187 mg, 81% yield, 3:1 dr, 94:6 er (major).

tert-butyl (5-((diphenylphosphoryl)amino)-4-methyl-5-(*o*-tolyl)pent-2-yn-1-yl)carbamate (5)



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), *(E)-N*-(2-methylbenzylidene)-*P,P*-diphenylphosphinic amide (160 mg, 0.50 mmol), *tert*-butyl pent-4-en-2-yn-1-ylcarbamate (136 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and toluene (1 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 20% EtOAc/hexanes for 2 column volume (CV), then 20-100% EtOAc/hexanes for 13 CV, followed by 100% EtOAc/hexanes for 10 CV) to afford the title compound as an off-white powder (175 mg, 69% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 22.8 (major) and 22.2 (minor)] of the unpurified reaction mixture indicated a 3:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 3:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (dd, J = 12.1, 7.5 Hz, 2H), 7.72–7.53 (m, 3H), 7.51–7.07 (m, 9H), 6.97 (d, J = 7.5 Hz, 1H), 5.53 (s, 1H), 4.44 (td, J = 11.3, 5.4 Hz, 1H), 3.78-3.92 (m, 2H), 2.95-3.10 (m, 1H), 1.78 (s, 3H), 1.41 (s, 9H), 1.01 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.8 ppm. **SFC analysis** (ADH column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 82:18 er: t_R (major) = 7.13 min, t_R (minor) = 6.71 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89-7.80 (m, 2H), 7.72–7.53 (m, 3H), 7.51–7.07 (m, 9H), 6.97-6.87 (m, 1H), 6.13 (s, 1H), 4.31–4.19 (m,

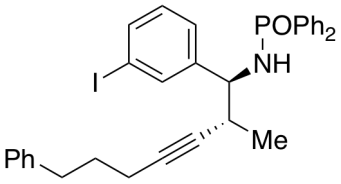
1H), 3.78-3.92 (m, 2H), 2.75–2.61 (m, 1H), 1.71 (s, 3H), 1.43 (s, 9H), 1.17 (d, J = 6.8 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 22.2 ppm. **SFC analysis** (ADH column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 90:10 er: t_R (major) = 7.28 min, t_R (minor) = 6.42 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**)** δ**:** 155.7, 155.6, 141.2, 139.7, 139.6, 135.2, 134.6, 133.7, 133.6, 132.8, 132.7, 132.7, 132.6, 132.4, 132.3, 132.0, 131.9, 131.8, 131.7, 131.6, 131.1, 131.0, 130.1, 130.0, 128.6, 128.4, 128.3, 128.1, 128.0, 127.1, 127.0, 126.7, 126.2, 126.0, 84.5, 84.3, 80.1, 79.8, 79.4, 79.2, 60.4, 54.9, 53.1, 30.8, 28.4, 28.0, 21.0, 19.2, 18.8, 18.5, 16.8, 14.2 ppm.

m.p. = 209-212 °C. **IR:** 3209, 2976, 1695, 1453, 1249, 1167, 1122, 909, 724, 694 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{30}H_{35}N_2O_3P+H]+$: 503.2458. Found: 503.2452. $[\alpha]_D^{23}$ = -13.4.

Duplicate experiment: 202 mg, 80% yield, 3:1 dr, 84:16 er (major).

N-(1-(3-iodophenyl)-2-methyl-7-phenylhept-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (6)



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), (*E*)-*N*-(3-iodobenzylidene)-*P,P*-diphenylphosphinic amide (216 mg, 0.50 mmol), hept-6-en-4-yn-1-ylbenzene (128 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 50% EtOAc/hexanes for 3 column volume (CV), then 50-100% EtOAc/hexanes for 5 CV, followed by 100% EtOAc/hexanes for 5 CV) to afford the title compound as a pale-yellow oil (189 mg, 63% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 23.2 (major) and 22.5 (minor)] of the unpurified reaction mixture indicated a 3:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 3:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.89–7.84 (m, 2H), 7.74–7.69 (m, 2H), 7.60–7.57 (m, 1H), 7.50-7.43 (m, 5H), 7.33–7.25 (m, 4H), 7.25-7.19 (m, 2H), 7.15–7.12 (m, 2H), 6.99 (t, J = 7.8 Hz, 1H), 4.08–3.99 (m, 2H), 3.23 (dqt, J = 9.3, 6.8, 2.6 Hz, 1H), 2.71-2.56 (m, 2H), 2.30-2.10 (m, 2H), 1.85–1.78 (m, 2H), 1.00 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 23.2 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 75/25, 2.5 mL/min) indicated a 96:4 er: t_R (major) = 5.79 min, t_R (minor) = 5.68 min.

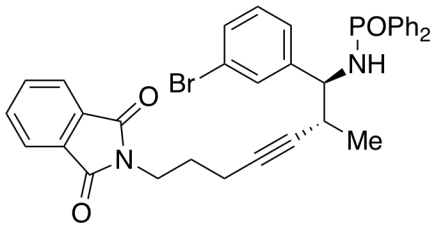
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89–7.84 (m, 2H), 7.74–7.69 (m, 2H), 7.64-7.54 (m, 1H), 7.53-7.43 (m, 5H), 7.33–7.25 (m, 4H), 7.25-7.19 (m, 2H), 7.15–7.12 (m, 2H), 6.99 (t, J = 7.8 Hz, 1H), 4.17–4.09 (m, 1H), 3.93 (dd, J = 9.5, 7.0 Hz, 1H), 2.83 (td, J = 6.8, 4.0 Hz, 1H), 2.71-2.56 (m, 2H), 2.30-2.10 (m, 2H), 1.85–1.78 (m, 2H), 1.37 (d, J = 6.9 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.5 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 75/25, 2.5 mL/min) indicated a 55:45 er: t_R (major) = 6.16 min, t_R (minor) = 5.17 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**) δ:** 145.1 145.1, 142.9, 142.9, 141.5, 141.5, 136.7, 136.4, 136.2, 136.0, 133.6, 133.5, 132.7, 132.6, 132.5, 132.4, 132.4, 132.4, 132.3, 132.2, 132.0, 132.0, 131.9, 131.9, 131.9, 131.8, 131.8, 131.7, 131.7, 131.4, 131.1, 129.8, 129.6, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 127.2, 126.2, 125.9, 94.1, 93.9, 84.9, 84.6, 80.5, 80.1, 58.1, 57.4, 35.5, 35.5, 34.9, 34.8, 34.8, 30.5, 19.6, 18.9, 18.3 ppm.

IR: 2926, 2231, 1733, 1439, 1246, 1193, 1109, 1046, 905, 727, 649 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{32}H_{31}INOP+H]+$: 604.1263. Found: 604.1261. $[\alpha]_D^{23}$ = -33.3.

Duplicate experiment: 198 mg, 66% yield, 3:1 dr, 96:4 er (major).

N-(1-(3-bromophenyl)-7-(1,3-dioxoisoindolin-2-yl)-2-methylhept-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (7)



Following general procedure A, $Cu(OAc)_2$ (9 mg, 0.050 mmol), *(R,R)*-Ph-BPE (30 mg, 0.060 mmol), *(E)-N*-(3-bromobenzylidene)-*P,P*-diphenylphosphinic amide (384 mg, 1.0 mmol), 2-(hept-6-en-4-yn-1-yl)isoindoline-1,3-dione (240 mg, 1.5 mmol), *t*-BuOH (0.14 mL, 1.5 mmol), DMMS (0.49 mL, 4.0 mmol), and toluene (2 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 20% EtOAc/hexanes for 2 column volume (CV), then 20-100% EtOAc/hexanes for 14 CV, followed by 100% EtOAc/hexanes for 20 CV) to afford the title compound as a pale-yellow oil (322 mg, 51% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 23.3 (major) and 22.8 (minor)] of the unpurified reaction mixture indicated a 3:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 2.5:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87–7.77 (m, 2H), 7.73–7.59 (m, 6H), 7.55 (s, 1H), 7.33–7.19 (m, 7H), 7.15–7.02 (m, 2H), 4.66 (dd, J = 11.2, 8.2 Hz, 1H), 4.17-3.94 (m, 1H), 3.69 (hept, J = 7.0 Hz, 2H), 3.27–3.11 (m, 1H),

2.21-2.05 (m, 2H), 1.85-1.67 (m, 2H), 0.86 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 23.3 ppm. **SFC analysis** (CEL1 column, $scCO_2$/MeOH = 95/5 to 90/10, 2.5 mL/min) indicated a 97.5:2.5 er: t_R (major) = 10.91 min, t_R (minor) = 10.56 min.

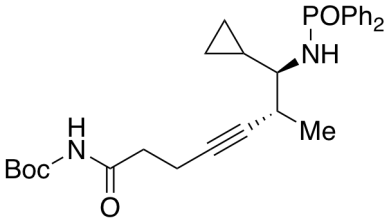
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.87–7.77 (m, 2H), 7.73–7.59 (m, 6H), 7.48 (s, 1H), 7.33–7.19 (m, 7H), 7.15–7.02 (m, 2H), 4.45 (t, J = 9.4 Hz, 1H), 4.17-3.94 (m, 1H), 3.69 (hept, J = 7.0 Hz, 2H), 2.67 (qd, J = 6.7, 3.8 Hz, 1H), 2.21-2.05 (m, 2H), 1.85-1.67 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 22.8 ppm. **SFC analysis** (CEL1 column, $scCO_2$/MeOH = 95/5 to 90/10, 2.5 mL/min) indicated a 76:24 er: t_R (major) = 11.63 min, t_R (minor) = 9.66 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**)** δ**:** 168.1, 145.5, 145.5, 142.6, 133.9, 133.7, 132.6, 132.6, 132.5, 132.4, 131.9, 131.9, 131.8, 131.7, 131.6, 131.5, 131.4, 130.9, 130.3, 130.0, 129.9, 129.6, 129.3, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 126.7, 125.5, 123.2, 122.1, 122.0, 83.4, 83.0, 81.3, 80.7, 58.3, 57.7, 36.6, 35.6, 34.9, 34.9, 27.6, 27.5, 19.8, 18.7, 16.3, 16.3 ppm.

IR: 3176, 3056, 2932, 1706, 1436, 1394, 1188, 1109, 719, 693 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{34}H_{30}BrN_2O_3P+H]+$: 625.1250. Found: 625.1241. $[\alpha]_D^{23}$ = -60.1.

Duplicate experiment: 325 mg, 52% yield, 3:1 dr, 98:2 er (major).

N-benzyl-7-cyclopropyl-7-((diphenylphosphoryl)amino)-6-methylhept-4-ynamide (8)



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), (*E*)-*N*-(cyclopropylmethylene)-*P,P*-diphenylphosphinic amide (135 mg, 0.50 mmol), *N*-benzylhept-6-en-4-ynamide (160 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and THF (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 0% EtOAc/hexanes for 2 column volume (CV), then 0-100% EtOAc/hexanes for 3 CV, followed by 100% EtOAc/hexanes for 10 CV) to afford the title compound as a colorless liquid (131 mg, 54% yield). ^{1}H NMR spectroscopic analysis [integration of the resonances at 6.96 (major) and 6.63 (minor)] of the unpurified reaction mixture indicated a 2:1 dr. ^{1} NMR spectroscopic analysis of the purified product indicated a 1.5:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 8.05–7.73 (m, 4H),

7.61–7.36 (m, 6H), 7.36-7.14 (m, 5H), 6.97 (s, 1H), 4.50–4.22 (m, 2H), 3.45 (q, J = 8.1, 7.2 Hz, 1H), 2.93–2.10 (m, 6H), 1.31-1.07 (m, 3H), 1.09–0.84 (m, 1H), 0.60–0.26 (m, 2H), 0.25-0.01 (m, 2H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.1 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a 90:10 er: t_R (major) = 11.87 min, t_R (minor) = 5.10 min.

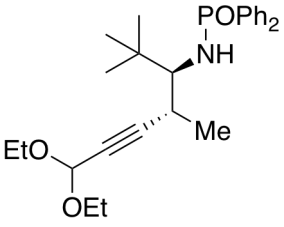
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05–7.73 (m, 4H), 7.61–7.36 (m, 6H), 7.36-7.14 (m, 5H), 6.63 (s, 1H), 4.50–4.22 (m, 2H), 3.45 (q, J = 8.1, 7.2 Hz, 1H), 2.93–2.10 (m, 6H), 1.31-1.07 (m, 3H), 1.09–0.84 (m, 1H), 0.60–0.26 (m, 2H), 0.25-0.01 (m, 2H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.5 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a >99:1 er: t_R (major) = 12.32 min, t_R (minor) = 6.91 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**) δ:** 171.6, 171.3, 138.5, 138.4, 132.4, 132.3, 132.2, 132.1, 132.0, 131.9, 131.8, 131.7, 131.6, 128.6, 128.5, 128.4, 128.3, 127.8, 127.8, 127.4, 127.3, 83.1, 82.5, 81.8, 81.4, 60.6, 59.5, 43.5, 36.1, 35.9, 34.4, 33.4, 19.1, 17.5, 17.4, 15.8, 15.6, 14.0, 14.0, 5.5, 5.1, 4.3, 3.6, 3.2 ppm.

IR: 3248, 3063, 2225, 1652, 1438, 1189, 1123, 1110, 906, 723, 695, 645 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{30}H_{33}N_2O_2P+H]+$: 485.2352. Found: 485.2347. $[\alpha]_D^{23}$ = +6.3.

Duplicate experiment: 150 mg, 62% yield, 2:1 dr, 90:10 er (major).

N-(7,7-diethoxy-2,2,4-trimethylhept-5-yn-3-yl)-*P,P*-diphenylphosphinic amide (9)[13]



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), (*E*)-*N*-(2,2-dimethylpropylidene)-*P,P*-diphenylphosphinic amide (143 mg, 0.50 mmol), 5,5-diethoxypent-1-en-3-yne (116 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and THF (1 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 0% EtOAc/hexanes for 2 column volume (CV), then 0-60% EtOAc/hexanes for 3 CV, followed by 60% EtOAc/hexanes for 10 CV) to afford the title compound as a colorless liquid (139 mg, 63% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 22.9 (major) and 21.7 (minor)] of the unpurified reaction mixture indicated a 2:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 2:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (dd, J = 12.2, 7.5

Hz, 4H), 7.58–7.33 (m, 6H), 5.25 (d, J = 1.4 Hz, 1H), 3.76-3.61 (m, 2H), 3.61-3.47 (m, 2H), 3.32 (t, J = 11.2 Hz, 1H), 2.98–2.87 (m, 1H), 2.78 (t, J = 11.0 Hz, 1H), 1.30–1.11 (m, 9H), 0.94 (s, 9H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 22.9 ppm.

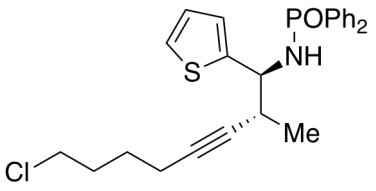
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 8.03–7.92 (m, 4H), 7.58–7.33 (m, 6H), 5.19 (d, J = 1.4 Hz, 1H), 3.76-3.61 (m, 2H), 3.61-3.47 (m, 2H), 3.32 (t, J = 11.2 Hz, 1H), 3.03–3.00 (m, 1H), 2.98–2.87 (m, 1H), 1.30–1.11 (m, 9H), 0.98 (s, H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 21.7 ppm.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**)** δ**:** 134.6, 132.8, 132.7, 132.6, 132.5, 132.3, 132.2, 132.2, 132.1, 131.7, 131.6, 128.4, 128.4, 128.3, 128.2, 91.6, 91.5, 87.6, 80.6, 62.98, 62.7, 60.8, 60.7, 60.6, 36.1, 29.4, 28.1, 28.1, 27.9, 27.3, 26.0, 21.0, 17.8, 15.1, 15.1 ppm.

IR: 2977, 2251, 1428, 1123, 1048, 904, 725, 649 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{26}H_{36}NO_3P+H]+$: 442.2506. Found: 442.2498. $[\alpha]_D^{23}$ = +25.0.

Duplicate experiment: 127 mg, 57% yield, 2:1 dr.

N-(8-chloro-2-methyl-1-(thiophen-2-yl)oct-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (10)



Following general procedure A, $Cu(OAc)_2$ (9 mg, 0.050 mmol), *(R,R)*-Ph-BPE (30 mg, 0.060 mmol), *(E)-P,P*-diphenyl-*N*-(thiophen-2-ylmethylene)phosphinic amide (311 mg, 1.0 mmol), 8-chlorooct-1-en-3-yne (214 mg, 1.5 mmol), *t*-BuOH (0.14 mL, 1.5 mmol), DMMS (0.49 mL, 4.0 mmol), and toluene (2 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 20% EtOAc/hexanes for 2 column volume (CV), then 20-100% EtOAc/hexanes for 10 CV, followed by 100% EtOAc/hexanes for 12 CV) to afford the title compound as a tan powder (443 mg, 93% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 22.7 (major) and 21.9 (minor)] of the unpurified reaction mixture indicated a 6:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 6:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.92–7.65 (m, 4H), 7.46-7.30 (m, 4H), 7.31-7.20 (m, 2H), 7.14 (d, J = 5.1 Hz, 1H), 6.80 (dd, J = 5.1, 3.4 Hz, 1H), 6.68 (d, J = 3.4 Hz, 1H), 4.35 (td, J = 10.8, 4.3 Hz, 1H), 3.92 (dd, J = 11.0, 7.4 Hz, 1H), 3.37 (t, J = 6.5 Hz, 2H), 3.18 (ddd, J = 7.1, 4.9, 2.5 Hz, 1H), 2.15 (td, J = 6.9, 2.2 Hz, 2H), 1.79–1.61 (m, 2H), 1.53 (dq, J = 16.4, 9.3, 8.2 Hz, 2H), 0.94 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 22.7 ppm. **SFC analysis**

(CEL1 column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a >99:1 er: t_R (major) = 2.86 min, t_R (minor) = 2.80 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.92–7.65 (m, 4H), 7.46-7.30 (m, 4H), 7.31-7.20 (m, 2H), 7.11–7.06 (m, 1H), 6.80 (dd, J = 5.1, 3.4 Hz, 1H), 6.68 (d, J = 3.4 Hz, 1H), 4.35 (td, J = 10.8, 4.3 Hz, 1H), 3.83 (dd, J = 10.4, 7.4 Hz, 1H), 3.37 (t, J = 6.5 Hz, 2H), 2.90 (dq, J = 6.3, 2.9 Hz, 1H), 2.11–2.04 (m, 2H), 1.79–1.61 (m, 2H), 1.53 (dq, J = 16.4, 9.3, 8.2 Hz, 2H), 1.29 (d, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 21.9 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 97:3 er: t_R (major) = 3.12 min, t_R (minor) = 2.98 min.

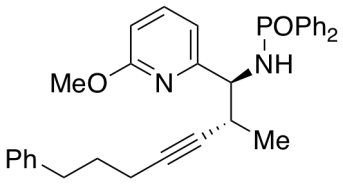
^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**)** δ**:** 147.1, 147.1, 143.8, 143.70 133.7, 132.6, 132.5, 132.4, 132.4, 132.4, 131.9, 131.9, 131.8, 131.8, 131.6, 131.5, 131.1, 128.6, 128.4, 128.3, 128.3, 128.2, 128.2, 126.4, 125.9, 125.8, 124.7, 124.6, 124.1, 84.1, 84.0, 80.9, 80.7, 55.1, 54.6, 44.5, 35.7, 35.1, 31.4, 31.3, 25.8, 18.9, 18.5, 18.1, 18.0 ppm.

m.p. = 201-203 °C. **IR:** 3262, 2936, 2868, 1436, 1185, 1109, 1029, 997, 901, 752, 696 cm^{-1}. **Anal. Calcd.** for $C_{25}H_{27}ClNOPS$: C, 65.85; H, 5.97. Found: C, 65.57; H, 6.03. $[\alpha]_D^{23}$ = -14.4.

Duplicate experiment: 386 mg, 81% yield, 6:1 dr, 99:1 er (major).

Experiment at 5.00 mmol scale of imine: 2.25 g, 95% yield, 7:1 dr, 99:1 er (major).

N-(1-(6-methoxypyridin-2-yl)-2-methyl-7-phenylhept-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (11)



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), (*E*)-*N*-((6-methoxypyridin-2-yl)methylene)-*P,P*-diphenylphosphinic amide (168 mg, 0.50 mmol), hept-6-en-4-yn-1-ylbenzene (128 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 50% EtOAc/hexanes for 3 column volume (CV), then 50-100% EtOAc/hexanes for 5 CV, followed by 100% EtOAc/hexanes for 5 CV) to afford the title compound as a colorless oil (171 mg, 67% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 22.6 (major) and 22.1 (minor)] of the unpurified reaction mixture indicated a 10:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of

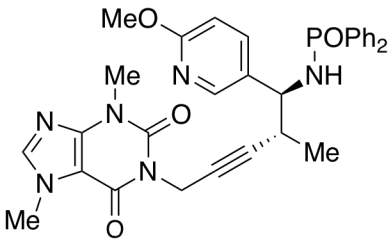
the purified product indicated a 14:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.97–7.82 (m, 2H), 7.78–7.66 (m, 2H), 7.55–7.38 (m, 5H), 7.34 (td, J = 7.6, 2.9 Hz, 2H), 7.28–7.23 (m, 2H), 7.23–7.15 (m, 1H), 7.14–7.05 (m, 2H), 6.70 (d, J = 7.2 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 4.43–4.24 (m, 1H), 4.12 (td, J = 10.6, 6.9 Hz, 1H), 3.88 (s, 3H), 3.12–2.96 (m, 1H), 2.57 (t, J = 7.6 Hz, 2H), 2.08 (td, J = 6.9, 2.2 Hz, 2H), 1.66 (p, J = 7.2 Hz, 2H), 1.26 (d, J = 7.0 Hz, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$,** observed complexity due to C-P coupling**)** δ**:** 163.5, 157.1, 141.7, 138.5, 132.3 and 132.2, 132.0 and 131.9, 131.8 and 131.7, 128.5 and 128.4, 128.5 and 128.3, 128.3 and 128.2, 125.8, 115.6, 109.3, 82.7, 81.8, 59.2, 53.3, 34.7, 34.2 and 34.1, 30.4, 18.6, 18.2 ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 22.6 ppm.

IR: 2932, 2225, 1578, 1468, 1438, 1198, 1123, 906, 725, 698, 644 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{32}H_{33}N_2O_2P+H]+$: 509.2352. Found: 509.2363. $[\alpha]_D^{23}$ = -14.6. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a >99:1 er: t_R (major) = 5.32 min, t_R (minor) = 5.41 min. **Minor diastereomer** indicated a 93:7 er: t_R (major) = 5.71 min, t_R (minor) = 4.94 min.

Duplicate experiment: 158 mg, 62% yield, 11:1 dr, >99:1 er (major).

N-(5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-1-(6-methoxypyridin-3-yl)-2-methylpent-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (12)[13]



Following general procedure A, $Cu(OAc)_2$ (9 mg, 0.050 mmol), *(R,R)*-Ph-BPE (30 mg, 0.060 mmol), *(E)-N*-((6-methoxypyridin-3-yl)methylene)-P,P-diphenylphosphinic amide (337 mg, 1.0 mmol), 3,7-dimethyl-1-(pent-4-en-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (366 mg, 1.5 mmol), *t*-BuOH (0.14 mL, 1.5 mmol), DMMS (0.49 mL, 4.0 mmol), and toluene (2 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 0% MeOH/DCM for 2 column volume (CV), then 0-5% MeOH/DCM for 15 CV) to afford the title compound as a tan solid (556 mg, 95% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 22.4 (major) and 21.7 (minor)] of the unpurified reaction mixture indicated a 3:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 2:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ**:** 7.60 (s, 1H), 7.58–7.27

(m, 6H), 7.09–6.82 (m, 6H), 6.29 (d, J = 8.5 Hz, 1H), 4.54-4.35 (m, 2H), 4.35–4.18 (m, 1H), 3.72 (qt, J = 10.7, 5.4 Hz, 1H), 3.49 (s, 3H), 3.43 (s, 3H), 2.97 (s, 3H), 2.83 (h, J = 6.8 Hz, 1H), 0.59 (d, J = 6.9 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.4 ppm.

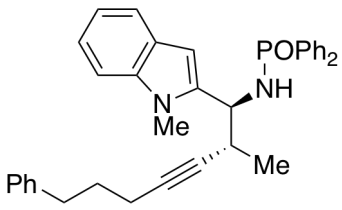
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (s, 1H), 7.57–7.29 (m, 6H), 7.09–6.82 (m, 6H), 6.23 (d, J = 8.6 Hz, 1H), 4.93 (s, 3H), 4.54-4.35 (m, 2H), 4.35–4.18 (m, 1H), 3.72 (qt, J = 10.7, 5.4 Hz, 1H), 3.46 (s, 3H), 3.02 (s, 3H), 2.40 (p, J = 6.6 Hz, 1H), 0.95 (d, J = 6.9 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 21.7 ppm.

^{13}C NMR (101 MHz, $CDCl_3$), observed complexity due to diastereomers and C-P coupling) **δ:** 163.2, 163.0, 153.9, 153.8, 150.5, 150.5, 148.5, 148.5, 145.8, 142.0, 138.0, 137.1, 133.4, 133.3, 133.1, 132.7, 132.1, 132.0, 132.0, 131.9, 131.8, 131.6, 131.5, 131.4, 131.0, 130.9, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 109.9, 109.8, 107.0, 107.0, 82.9, 82.6, 79.2, 78.9, 56.4, 55.6, 53.6, 53.0, 35.1, 34.5, 33.2, 30.6, 29.3, 29.2, 18.5, 17.8 ppm.

m.p. = 215-217 °C. **IR:** 3184, 2944, 1705, 1652, 1492, 1187, 1122, 1026, 909, 724, 696 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{31}H_{31}N_6O_4P+H]+$: 583.2217. Found: 583.2213. $[\alpha]_D^{23}$ = -17.3.

Duplicate experiment: 528 mg, 91% yield, 3:1 dr.

N-(2-methyl-1-(1-methyl-1*H*-indol-2-yl)-7-phenylhept-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (13)



Following general procedure A, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), (*E*)-*N*-((1-methyl-1*H*-indol-3-yl)methylene)-*P,P*-diphenylphosphinic amide (179 mg, 0.50 mmol), hept-6-en-4-yn-1-ylbenzene (128 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and THF (1 mL) were used. The reaction was run at room temperature. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 50% EtOAc/hexanes for 3 column volume (CV), then 50-100% EtOAc/hexanes for 5 CV, followed by 100% EtOAc/hexanes for 5 CV) to afford the title compound as a colorless oil (172 mg, 65% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 22.0 (major) and 22.8 (minor)] of the unpurified reaction mixture indicated a 1.5:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 1.5:1 dr.

Major diastereomer: ^{1}**H NMR (400 MHz, $CDCl_3$)** δ**:** 7.95–7.84 (m, 4H), 7.51–7.04 (m, 16H), 4.53 (td, J = 8.5, 5.5 Hz, 1H), 4.02 (dd, J = 7.8, 5.5 Hz, 1H), 3.63 (s, 3H), 3.27 (dqd, J = 9.5, 6.8, 6.2, 2.9 Hz, 1H), 2.65 (t, J = 7.6 Hz, 2H), 2.21 (td, J = 7.0, 2.2 Hz, 2H), 1.78 (p, J = 7.2 Hz, 2H), 1.38 (d, J = 6.9 Hz, 3H) ppm. ^{31}**P NMR (162 MHz, $CDCl_3$)** δ**:** 22.0 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 60:40 er: t_R (major) = 4.68 min, t_R (minor) = 4.07 min.

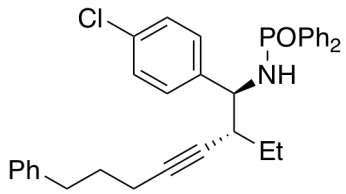
Minor diastereomer: ^{1}**H NMR (400 MHz, $CDCl_3$)** δ**:** 7.84–7.73 (m, 4H), 7.54–7.03 (m, 16H), 4.61 (td, J = 10.1, 5.0 Hz, 1H), 3.90 (dd, J = 10.6, 7.3 Hz, 1H), 3.73 (s, 3H), 3.47 (ttt, J = 7.0, 4.5, 2.8 Hz, 1H), 2.72 (t, J = 7.6 Hz, 2H), 2.29 (td, J = 7.0, 2.2 Hz, 2H), 1.88 (q, J = 7.3 Hz, 2H), 1.08 (d, J = 7.0 Hz, 3H) ppm. ^{31}**P NMR (162 MHz, $CDCl_3$)** δ**:** 22.8 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 60/40, 2.5 mL/min) indicated a 54:46 er: t_R (major) = 3.85 min, t_R (minor) = 4.51 min.

^{13}**C NMR (101 MHz, $CDCl_3$,** observed complexity due to diastereomers and C-P coupling**)** δ**:** 141.6, 137.2, 136.5, 134.0, 133.3, 133.1, 132.7, 132.7, 132.6, 132.2, 132.1, 132.0, 131.9, 131.9, 131.8, 131.7, 131.7, 131.6, 131.6, 131.5, 131.2, 131.1, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 127.9, 127.7, 127.3, 127.1, 126.2, 125.9, 125.9, 121.6, 121.4, 119.6, 119.5, 119.0, 118.8, 115.6, 115.5, 114.5, 114.4, 109.3, 109.2, 83.8, 82.9, 82.9, 82.1, 53.3, 53.3, 35.1, 35.0, 34.9, 34.8, 34.4, 34.4, 32.8, 32.6, 30.6, 19.4, 18.7, 18.5, 18.3 ppm.

IR: 3056, 2930, 2218, 1438, 1329, 1192, 1122, 907, 724, 696 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{35}H_{35}N_2OP+H]+$: 531.2560. Found: 531.2569. $[\alpha]_D^{23}$ = +18.5.

Duplicate experiment: 152 mg, 57% yield, 1.5:1 dr, 61:39 er (major).

N-(1-(4-chlorophenyl)-2-ethyl-7-phenylhept-3-yn-1-yl)-*P,P*-diphenylphosphinic amide (14)



Following general procedure B, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), oct-6-en-4-yn-1-ylbenzene (138 mg, 0.50 mmol), *(E)*-*N*-(4-chlorobenzylidene)-*P,P*-diphenylphosphinic amide (171 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and THF (1 mL) were used. The reaction was run at 0 °C. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g KP-Sil cartridge, 0% EtOAc/hexanes for 2 column volume (CV), then 0-100% EtOAc/hexanes for 10 CV, followed by 100% EtOAc/hexanes for 5 CV) to afford the title compound as a white powder (185 mg, 70% yield). Quantitative ^{31}P NMR spec-

troscopic analysis [integration of the resonances at 23.2 (major) and 22.1 (minor)] of the unpurified reaction mixture indicated a 3:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated a 3:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00–7.87 (m, 2H), 7.87–7.72 (m, 2H), 7.59–7.21 (m, 13H), 7.21–7.14 (m, 2H), 4.33–4.09 (m, 2H), 3.11 (dtt, J = 9.8, 4.7, 2.2 Hz, 1H), 2.71 (t, J = 7.6 Hz, 2H), 2.27 (qd, J = 6.9, 2.2 Hz, 2H), 1.85 (p, J = 7.2 Hz, 3H), 1.46 (tdd, J = 10.0, 7.6, 4.7 Hz, 1H), 1.03 (t, J = 7.0 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 23.2 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a 98.5:1.5 er: t_R (major) = 6.24 min, t_R (minor) = 6.16 min.

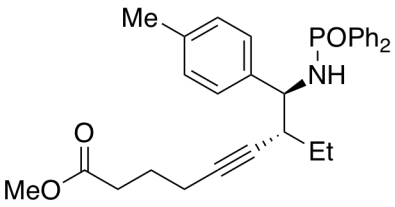
Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00–7.87 (m, 2H), 7.87–7.72 (m, 2H), 7.59–7.21 (m, 13H), 7.21–7.14 (m, 2H), 4.33–4.09 (m, 1H), 4.04 (dd, J = 9.7, 6.8 Hz, 1H), 2.71 (t, J = 7.6 Hz, 2H), 2.63 (ddt, J = 8.6, 5.7, 2.9 Hz, 1H), 2.27 (qd, J = 6.9, 2.2 Hz, 2H), 1.93–1.72 (m, 3H), 1.46 (tdd, J = 10.0, 7.6, 4.7 Hz, 1H), 1.11 (t, J = 7.3 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.1 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a 95:5 er: t_R (major) = 6.38 min, t_R (minor) = 5.12 min.

^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**) δ:** 142.9, 142.8, 141.6, 141.5, 140.6, 140.5, 134.0, 133.9, 133.0, 132.8, 132.7, 132.7, 132.6, 132.5, 131.9, 131.9, 131.8, 131.8, 131.7, 131.7, 131.4, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.1, 127.9, 127.8, 127.4, 127.2, 126.8, 125.9, 84.5, 84.0, 81.1, 80.7, 58.8, 58.1, 35.8, 35.8, 35.0, 35.0, 34.8, 34.8, 30.6, 30.5, 19.8, 18.9, 18.3 ppm.

m.p. = 192-196 °C. **IR:** 3172, 2932, 1492, 1436, 1179, 1087, 1014, 916, 822, 723, 693 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{33}H_{33}ClNOP+H]+$: 526.2061. Found: 526.2052. $[\alpha]_D^{23}$ = -164.1.

Duplicate experiment: 168 mg, 64% yield, 3:1 dr, 99:1 er (major).

methyl 7-(((diphenylphosphoryl)amino)(*p*-tolyl)methyl)non-5-ynoate (15)



Following general procedure B, $Cu(OAc)_2$ (5 mg, 0.025 mmol), *(R,R)*-Ph-BPE (15 mg, 0.030 mmol), (*E*)-*N*-(4-methylbenzylidene)-*P,P*-diphenylphosphinic amide (160 mg, 0.50 mmol), methyl non-7-en-5-ynoate (125 mg, 0.75 mmol), *t*-BuOH (72 μL, 0.75 mmol), DMMS (247 μL, 2.0 mmol), and THF (1 mL) were used. The reaction was conducted at room temperature. The crude reaction mixture was purified with the aid

of a Biotage Isolera (50 g KP-Sil cartridge, 0% EtOAc/hexanes for 2 column volume (CV), then 0-80% EtOAc/hexanes for 3 CV, followed by 80% EtOAc/hexanes for 15 CV) to afford the title compound as a white powder (118 mg, 52% yield). Quantitative ^{31}P NMR spectroscopic analysis [integration of the resonances at 23.1 (major) and 22.0 (minor)] of the unpurified reaction mixture indicated a 3:1 dr. Quantitative ^{31}P NMR spectroscopic analysis of the purified product indicated 3:1 dr.

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, J = 11.7, 7.5 Hz, 2H), 7.72 (dd, J = 12.1, 7.0 Hz, 2H), 7.51–7.34 (m, 4H), 7.34–7.21 (m, 2H), 7.09 (hept, J = 5.7, 5.3 Hz, 4H), 4.22–3.83 (m, 2H), 3.62 (s, 3H), 2.99 (ddt, J = 10.3, 5.1, 2.5 Hz, 1H), 2.37–2.28 (m, 5H), 2.23 (qd, J = 6.9, 3.3 Hz, 2H), 1.77 (p, J = 7.1 Hz, 2H), 1.36 (ddd, J = 12.3, 7.2, 4.7 Hz, 1H), 0.99 (q, J = 7.2, 6.7 Hz, 1H), 0.89 (t, J = 7.1 Hz, 3H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 23.1 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a 90:10 er: t_R (major) = 6.24 min, t_R (minor) = 6.56 min.

Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, J = 11.7, 7.5 Hz, 2H), 7.72 (dd, J = 12.1, 7.0 Hz, 2H), 7.51–7.34 (m, 4H), 7.34–7.21 (m, 2H), 7.09 (hept, J = 5.7, 5.3 Hz, 4H), 4.22–3.83 (m, 2H), 3.62 (s, 3H), 2.53 (tt, J = 5.9, 2.9 Hz, 1H), 2.37–2.28 (m, 5H), 2.23 (qd, J = 6.9, 3.3 Hz, 2H), 1.77 (p, J = 7.1 Hz, 2H), 1.36 (ddd, J = 12.3, 7.2, 4.7 Hz, 1H), 0.99 (t, J = 7.2 Hz, 4H) ppm. **^{31}P NMR (162 MHz, $CDCl_3$) δ:** 22.0 ppm. **SFC analysis** (CEL1 column, $scCO_2$/IPA = 95/5 to 80/20, 2.5 mL/min) indicated a 98.5:1.5 er: t_R (major) = 5.42 min, t_R (minor) = 7.38 min.

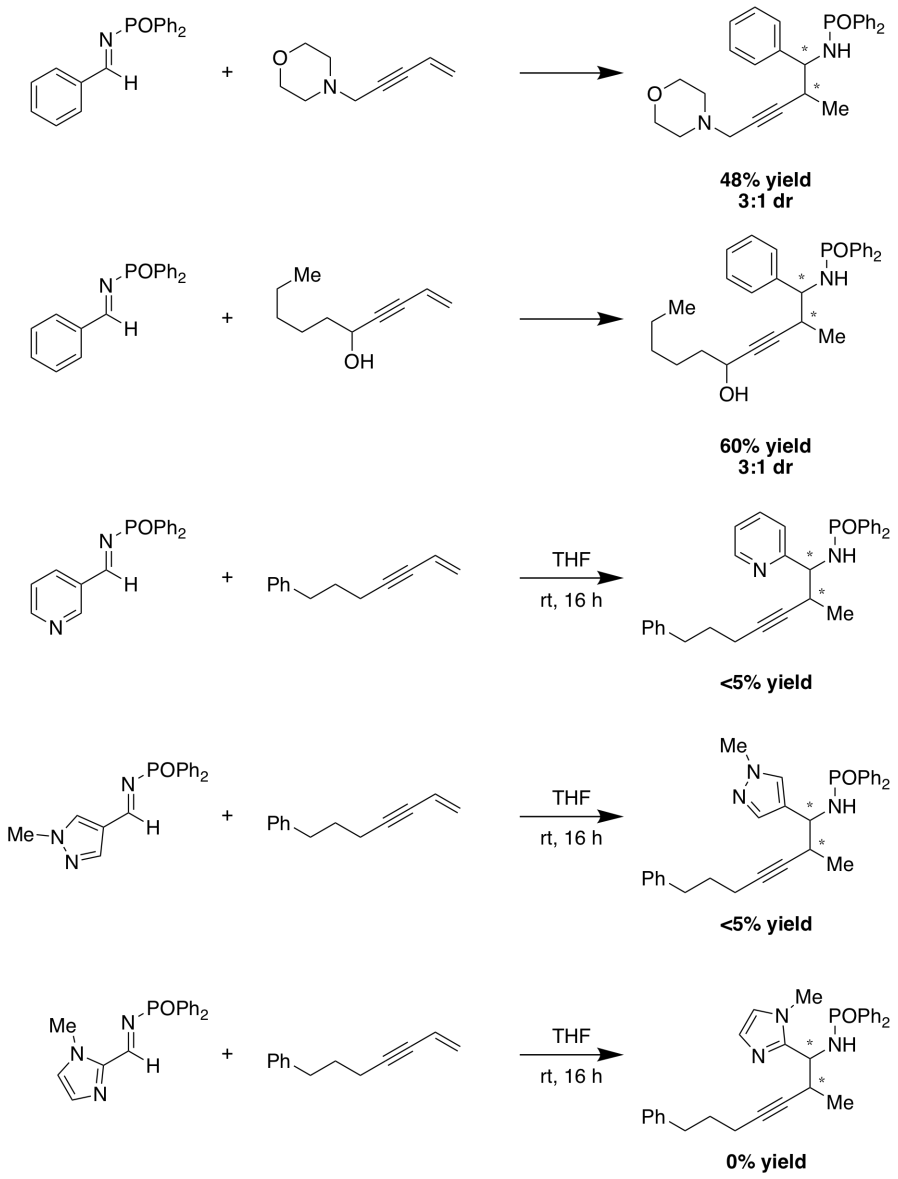
^{13}C NMR (101 MHz, $CDCl_3$, observed complexity due to diastereomers and C-P coupling**) δ:** 173.6, 173.5, 140.0, 137.7, 137.7, 136.8, 136.5, 132.8, 132.7, 132.5, 132.5, 132.0, 131.9, 131.8, 131.7, 131.5, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.5, 126.5, 84.2, 83.9, 80.4, 79.9, 77.5, 77.2, 76.9, 57.0, 56.8, 51.5, 43.9, 43.8, 43.1, 32.8, 26.6, 26.1, 24.1, 21.1, 21.1, 18.3, 18.2, 12.2, 12.1 ppm.

m.p. = 190-192 °C. **IR:** 2964, 2222, 1732, 1438, 1195, 1122, 1070, 907, 794, 697, 644 cm^{-1}. **HRMS. Calcd. m/z** for $[C_{30}H_{34}NO_3P+H]+$: 488.2349. Found: 488.2366. $[\alpha]_D^{23}$ = +13.8.

Duplicate experiment: 127 mg, 55% yield, 3:1 dr, 90:10 er (major).

3.4.7 Additional Substrates Examined

Following general procedure A (unless otherwise noted), we observed the following:



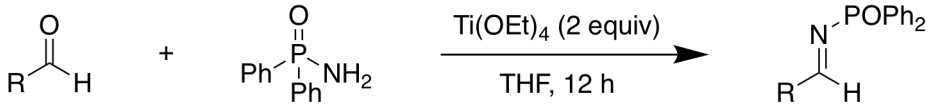
3.4.8 Preparation of Imine and Enyne Substrates

Imine Synthesis

(E)-N-benzylidene-*P,P*-diphenylphosphinic amide,[7c] *(E)-N*-(4-cyanobenzylidene)-*P,P*-diphenylphosphinic amide,[7c] *(E)-N*-(4-(dimethylamino)benzylidene)-*P,P*-diphenylphosphinic amide,[7c] *(E)-N*-(4-methoxybenzylidene)-*P,P*-diphenylphosphinic amide,[7c] *(E)-N*-(2-methylbenzylidene)-*P,P*-diphenylphosphinic amide,[14] *(E)-N*-(3-

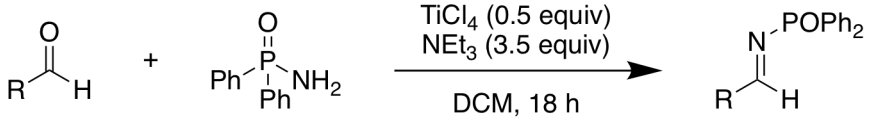
bromobenzylidene)-*P,P*-diphenylphosphinic amide,[15] *(E)*-*N*-(cyclopropylmethylene)-*P,P*-diphenylphosphinic amide,[16] *(E)*-*N*-(2,2-dimethylpropylidene)-*P,P*-diphenylphosphinic amide,[17] *(E)*-*P,P*-diphenyl-*N*-(thiophen-2-ylmethylene)phosphinic amide,[7c] (*E*)-*N*-((6-methoxypyridin-3-yl)methylene)-*P,P*-diphenylphosphinic amide,[7c] *(E)*-*N*-(4-chlorobenzylidene)-*P,P*-diphenylphosphinic amide,[18] and *(E)*-*N*-(4-methylbenzylidene)-*P,P*-diphenylphosphinic amide[18] were prepared as previously reported in the literature.

General Procedure C for Synthesis of Phenyl Phosphorylimines[9]



A 100 mL round-bottom flask was equipped with a magnetic stir bar and charged with aldehyde (10 mmol, 1.0 equiv) and *P,P*-diphenylphosphinic amide (10 mmol, 1.0 equiv). The flask sealed with a rubber septum, connected to a Schlenk line via a rubber hose by piercing the septum with a needle, then evacuated and back-filled with nitrogen. Dry THF (50 mL) was added to the flask via a 50 mL syringe. Titanium ethoxide (20 mmol, 2.0 equiv) was added via a 5 mL syringe and the reaction mixture was stirred at 60 °C for 2 h by submerging the flask in a preheated oil bath. After allowing the reaction mixture to cool to room temperature, the rubber septum was removed, sodium sulfate decahydrate (3.0 g) was added all at once, and the mixture was vigorously stirred. After 20 min, a thick precipitate had formed, and the crude mixture was filtered through a short plug of Celite® using a fritted funnel, eluting with THF. The filtrate was concentrated *in vacuo* with the aid of a rotary evaporator and purified by standard flash column chromatography on silica gel.

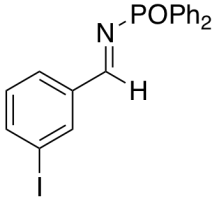
General Procedure D for Synthesis of Heterocyclic Phosphorylimines[19]



A round-bottom flask equipped with a magnetic stir bar was charged with aldehyde (1.0 equiv, 10 mmol), diphenylphosphinic amide (1.0 equiv, 10 mmol), and triethylamine (3.5 equiv, 35 mmol). The flask was sealed with a rubber septum, placed in a 0 °C ice/water bath, connected to a Schlenk line via a rubber hose by piecing the septum with a needle, then evacuated and back-filled with nitrogen. Dry

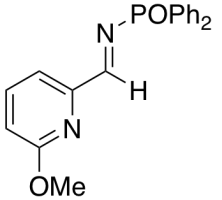
dichloromethane was added to the flask via a syringe, followed by dropwise addition of titanium tetrachloride (0.50 equiv, 5.0 mmol) via a syringe. The reaction mixture was allowed to warm to room temperature over the course of 18 h with stirring. At this time, the crude reaction solution was filtered through a silica pad using a fritted funnel, eluting with 1:1 DCM/EtOAc. The filtrate was collected and concentrated *in vacuo* with aid of a rotary evaporator and purified by flash chromatography.

***(E)-N*-(3-iodobenzylidene)-*P,P*-diphenylphosphinic amide (I1)**



Following general procedure C, 3-iodobenzaldehyde (2.32 g, 10 mmol, 1.0 equiv), *P,P*-diphenylphosphinic amide (2.17 g, 10 mmol, 1.0 equiv), titanium ethoxide (4.19 mL, 20 mmol, 2.0 equiv), and dry THF (50 mL) were used. The reaction mixture was purified by standard flash column chromatography on silica gel (100 g KP-Sil cartridge, 50% EtOAc/hexanes for 3 column volume (CV), then 50-100% EtOAc/hexanes for 5 CV, followed by 100% EtOAc/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (3.57 g, 83% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 9.22 (d, J = 31.6 Hz, 1H), 8.38 (s, 1H), 8.01–7.90 (m, 4H), 7.87 (t, J = 7.7 Hz, 2H), 7.56–7.36 (m, 6H), 7.22 (t, J = 7.8 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 172.1 and 172.0, 142.27, 137.89, 137.8 and 137.5, 133.16, 132.0 and 131.9, 131.6 and 131.5, 130.61, 130.13, 128.7 and 128.5, 94.77 ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 25.2 ppm. **IR:** 3055, 2971, 2870, 1614, 1560, 1436, 1193, 1123, 1107, 1059, 994, 828, 783, 750, 724, 691 cm^{-1}. **HRMS Calcd. m/z** for $[C_{19}H_{15}INOP + H]+$: 432.0009. Found: 432.0009.

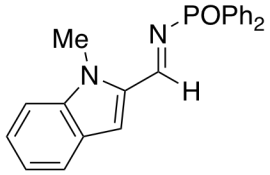
***(E)-N*-((6-methoxypyridin-2-yl)methylene)-*P,P*-diphenylphosphinic amide (I2)**



Following general procedure D, 6-methoxypicolinaldehyde (411 mg, 3.0 mmol, 1.0 equiv), P,P-diphenylphosphinic amide (652 mg, 3.0 mmol, 1.0 equiv), triethylamine (1.5 mL, 11 mmol, 3.5 equiv), titanium tetrachloride (165 μL, 5.0 mmol, 0.50 equiv), and dry DCM (25 mL) were used. The reaction mixture was purified by standard flash column chromatography on silica gel (50 g KP-Sil cartridge, 50% EtOAc/hexanes for 3 column volume (CV), then 50-100% EtOAc/hexanes for 5 CV, followed by 100% EtOAc/hexanes for 10 CV) to afford the title compound as a tan solid (563 mg, 56% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 9.28 (d, J = 32.5 Hz, 1H), 7.94 (ddd, J = 12.0, 8.2, 1.6 Hz, 4H), 7.88 (d, J = 7.3 Hz, 1H), 7.70 (t, J

= 7.8 Hz, 1H), 7.60–7.39 (m, 6H), 6.90 (d, J = 8.2 Hz, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 193.2, 174.6, 139.1, 138.8, 132.0 and 131.9, 131.7 and 131.6, 128.6 and 128.5, 115.8, 115.0, 53.6, 30.9 ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 24.9 ppm. **m.p.** = 121-124 °C. **IR:** 3026, 2919, 1604, 1495, 1469, 1081, 1030, 840, 726, 693 cm^{-1}. **HRMS Calcd. m/z** for $[C_{19}H_{17}N_2O_2P+H]+$: 337.1100. Found: 337.1117.

***(E)*-*N*-((1-methyl-1*H*-indol-2-yl)methylene)-*P,P*-diphenylphosphinic amide (I3)**

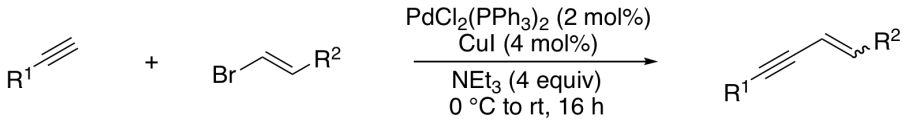


Following general procedure D, 1-methyl-1*H*-indole-2-carbaldehyde (1.59 g, 10 mmol, 1.0 equiv), P,P-diphenylphosphinic amide (2.17 g, 10 mmol, 1.0 equiv), triethylamine (3.54 g, 35 mmol, 3.5 equiv), titanium tetrachloride (551 μL, 5.0 mmol, 0.50 equiv), and dry DCM (50 mL) were used. The reaction mixture was purified by standard flash column chromatography on silica gel (100 g KP-Sil cartridge, 50% EtOAc/hexanes for 3 column volume (CV), then 50-100% EtOAc/hexanes for 5 CV, followed by 100% EtOAc/hexanes for 10 CV) to afford the title compound as a white solid (2.43 g, 68% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 9.37 (d, J = 33.0 Hz, 1H), 8.58 (dt, J = 4.8, 2.2 Hz, 1H), 7.99 (ddd, J = 11.8, 7.6, 1.8 Hz, 4H), 7.64 (s, 1H), 7.49–7.39 (m, 8H), 3.87 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 166.2 and 166.1, 139.0, 138.2, 135.1, 133.8, 131.6 and 131.5, 131.3 and 131.2, 125.9, 128.4 and 128.3, 124.0, 122.8 and 122.7, 116.1, 110.0, 33.7 ppm. **^{31}P NMR (162 MHz, $CDCl_3$)** δ**:** 24.6 ppm. **m.p.** = 190-192 °C. **IR:** 3093, 3038, 1586, 1568, 1376, 1280, 1124, 847, 745, 719, 692 cm^{-1}. **HRMS Calcd. m/z** for $[C_{22}H_{19}N_2OP + H]+$: 359.1308. Found: 359.1322.

Enyne Synthesis

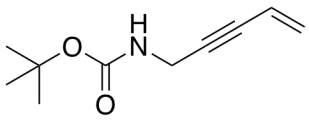
Hept-6-en-4-yn-1-ylbenzene,[10] dec-1-en-3-yne,[10] hex-5-en-3-yn-1-yl 4-methylbenzenesulfonate,[20] but-3-en-1-yn-1-ylbenzene, *N*-benzylhept-6-en-4-ynamide, 8-chlorooct-1-en-3-yne, and methyl (*E*)-non-7-en-5-ynoate[10] were prepared as previously reported in the literature.

General Procedure E for Synthesis of Enyne Starting Materials[10]



In a nitrogen-filled glovebox, an oven-dried 50 mL flask containing a magnetic stir bar was charged with bis(triphenylphosphine)palladium(II) chloride (2 mol%) and copper(I) iodide (4 mol%). The reaction flask was sealed with a rubber septum and removed from the glovebox. The reaction flask was connected to a Schlenk line via a rubber hose by piercing the septum with a needle, then evacuated and back-filled with nitrogen. Triethylamine (4.0 equiv) was added via syringe and the suspension was cooled to 0 °C in an ice/water bath. Alkyne starting material (1.0 equiv) was added slowly at 0 °C and the solution was allowed to stir for approximately 10-20 min. Vinyl halide starting material (2.0 equiv) was slowly added to the reaction mixture at 0 °C. After stirring for an additional 10 min at 0 °C, the cooling bath was removed and the reaction solution was allowed to warm to room temperature. After vigorously stirring for an additional 16 h at room temperature, or upon the complete consumption of alkyne starting material as indicated by GC analysis, the flask was uncapped and the crude reaction mixture was quenched by adding to hexanes (400 mL).[21] The resulting mixture was filtered through a plug of silica gel using a fritted funnel, eluting with EtOAc. The crude reaction mixture was concentrated *in vacuo* with aid of a rotary evaporator and purified by flash chromatography on silica gel to afford the desired 1,3-enyne products.

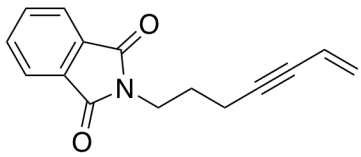
tert-butyl pent-4-en-2-yn-1-ylcarbamate (E1)



Following general procedure E, bis(triphenylphosphine) palladium(II) chloride (211 mg, 0.30 mmol, 2 mol%), copper(I) iodide (114 mg, 0.60 mmol, 4 mol%), triethylamine (8.3 mL, 60 mmol, 4.0 equiv), *tert*-butyl prop-2-yn-1-ylcarbamate (2.33 g, 15 mmol, 1.0 equiv), and bromoethene (30.0 mL, 1.0 M in THF, 2.0 equiv) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a pale-yellow liquid (1.50 g, 55% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.75 (ddt, J = 17.6, 11.0, 2.1 Hz, 1H), 5.60 (dd, J = 17.6, 2.2 Hz, 1H), 5.45 (dd, J = 11.0, 2.2 Hz, 1H), 4.76 (s, 1H), 4.02

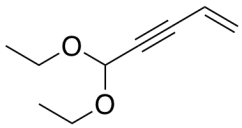
(d, J = 5.9 Hz, 2H), 1.43 (s, 9H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 155.3, 127.3, 116.7, 86.1, 81.7, 79.9, 31.1, 28.3 ppm. **IR:** 3342, 2977, 2929, 1689, 1505, 1366, 1247, 1161, 1048, 916, 861, 781 cm^{-1}. **HRMS Calcd. m/z** for $[C_{10}H_{15}NO_2 + H]+$: 182.1176. Found: 182.1167.

2-(hept-6-en-4-yn-1-yl)isoindoline-1,3-dione (E2)



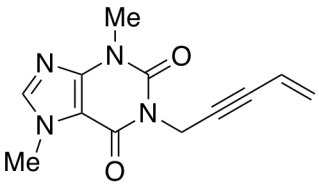
Following general procedure E, bis(triphenylphosphine) palladium(II) chloride (211 mg, 0.30 mmol, 2 mol%), copper(I) iodide (114 mg, 0.60 mmol, 4 mol%), triethylamine (8.3 mL, 60 mmol, 4.0 equiv), *tert*-butyl 2-(pent-4-yn-1-yl)isoindoline-1,3-dione (3.20 g, 15 mmol, 1.0 equiv), and bromoethene (30.0 mL, 1.0 M in THF, 2.0 equiv) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-50% EtOAc/hexanes for 10 CV, followed by 50% EtOAc/hexanes for 10 CV) to afford the title compound as a pale-yellow liquid (2.10 g, 59% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.76 (dd, J = 5.5, 3.1 Hz, 2H), 7.61 (dd, J = 5.4, 3.1 Hz, 2H), 5.54 (ddt, J = 17.6, 11.0, 2.1 Hz, 1H), 5.35 (dd, J = 17.5, 2.3 Hz, 1H), 5.22 (dd, J = 11.0, 2.3 Hz, 1H), 3.73 (t, J = 6.9 Hz, 2H), 2.32 (td, J = 7.0, 2.1 Hz, 2H), 1.87 (p, J = 7.0 Hz, 2H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 168.3, 133.8, 132.1, 125.7, 123.1, 117.2, 89.5, 79.9, 37.3, 27.3, 17.2 ppm. **IR:** 2938, 1700, 1394, 1115, 1025, 884, 717 cm^{-1}. **HRMS Calcd. m/z** for $[C_{15}H_{13}NO_2 + H]+$: 240.1019. Found: 240.1019.

5,5-diethoxypent-1-en-3-yne (E3)



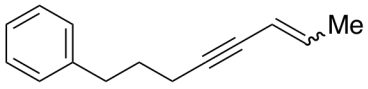
Following general procedure E, bis(triphenylphosphine)palladium(II) chloride (211 mg, 0.30 mmol, 2 mol%), copper(I) iodide (114 mg, 0.60 mmol, 4 mol%), triethylamine (8.3 mL, 60 mmol, 4.0 equiv), *tert*-butyl 3,3-diethoxyprop-1-yne (1.92 g, 15 mmol, 1.0 equiv), and bromoethene (30.0 mL, 1.0 M in THF, 2.0 equiv) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-30% EtOAc/hexanes for 10 CV, followed by 30% EtOAc/hexanes for 10 CV) to afford the title compound as a clear liquid (0.50 g, 22% yield). ^{1}H and ^{13}C NMR spectra of the purified product precisely match those reported in the literature.[22]

3,7-dimethyl-1-(pent-4-en-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (E4)



Following general procedure E, bis(triphenylphosphine) palladium(II) chloride (190 mg, 0.27 mmol, 2 mol%), copper(I) iodide (103 mg, 0.54 mmol, 4 mol%), triethylamine (7.5 mL, 54 mmol, 4.0 equiv), *tert*-butyl 3,7-dimethyl-1-(prop-2-yn-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.95 g, 14 mmol, 1.0 equiv), and bromoethene (27.0 mL, 1.0 M in THF, 2.0 equiv) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-100% EtOAc/hexanes for 3 CV, followed by 100% EtOAc/hexanes for 15 CV) to afford the title compound as a pale-yellow liquid (2.10 g, 64% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.52 (s, 1H), 5.75 (ddt, J = 17.6, 10.9, 2.0 Hz, 1H), 5.62 (dd, J = 17.6, 2.4 Hz, 1H), 5.44 (dd, J = 10.9, 2.4 Hz, 1H), 4.90 (d, J = 1.9 Hz, 2H), 4.00 (s, 3H), 3.60 (s, 3H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ**:** 162.4, 154.4, 150.9, 149.1, 141.7, 127.6, 116.8, 84.7, 80.7, 33.6, 31.2, 29.8 ppm. **IR:** 3110, 1705, 1655, 1601, 1547, 1410, 1227, 1135, 934, 741, 614 cm^{-1}. **Anal. Calcd.** for [$C_{12}H_{12}N_4O_2$]: C, 59.01; H, 4.95. Found: C, 58.82; H, 4.83.

Oct-6-en-4-yn-1-ylbenzene (E5)



Following general procedure E, bis(triphenylphosphine) palladium(II) chloride (211 mg, 0.30 mmol, 2 mol%), copper(I) iodide (114 mg, 0.60 mmol, 4 mol%), triethylamine (8.3 mL, 60 mmol, 4.0 equiv), ethynylbenzene (2.16 g, 15 mmol, 1.0 equiv), and (*E*)-1-bromoprop-1-ene (2.6 mL, 30 mmol, 2.0 equiv) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a pale-yellow liquid (1.83 g, 66% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.33–7.14 (m, 5H), 6.20–5.79 (m, 1H), 5.59–5.35 (m, 1H), 2.74 (dt, J = 13.2, 7.6 Hz, 2H), 2.38 (td, J = 6.8, 2.0 Hz, 1H), 2.30 (td, J = 7.3, 6.9, 1.7 Hz, 1H), 1.94–1.73 (m, 5H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$**, observed complexity due to *E/Z* isomers) δ**:** 141.8, 138.2, 137.1, 128.6, 128.4, 125.9, 111.2, 110.5, 94.5, 88.0, 79.8, 77.8, 34.9, 30.6, 30.5, 19.1, 18.8, 18.5, 15.8 ppm. **IR:** 3026, 2936, 1496, 1453, 951, 745, 698 cm^{-1}. **HRMS Calcd. m/z** for [$C_{14}H_{16}$ + H]+: 185.1325. Found: 185.1318.

3.5 References and Notes

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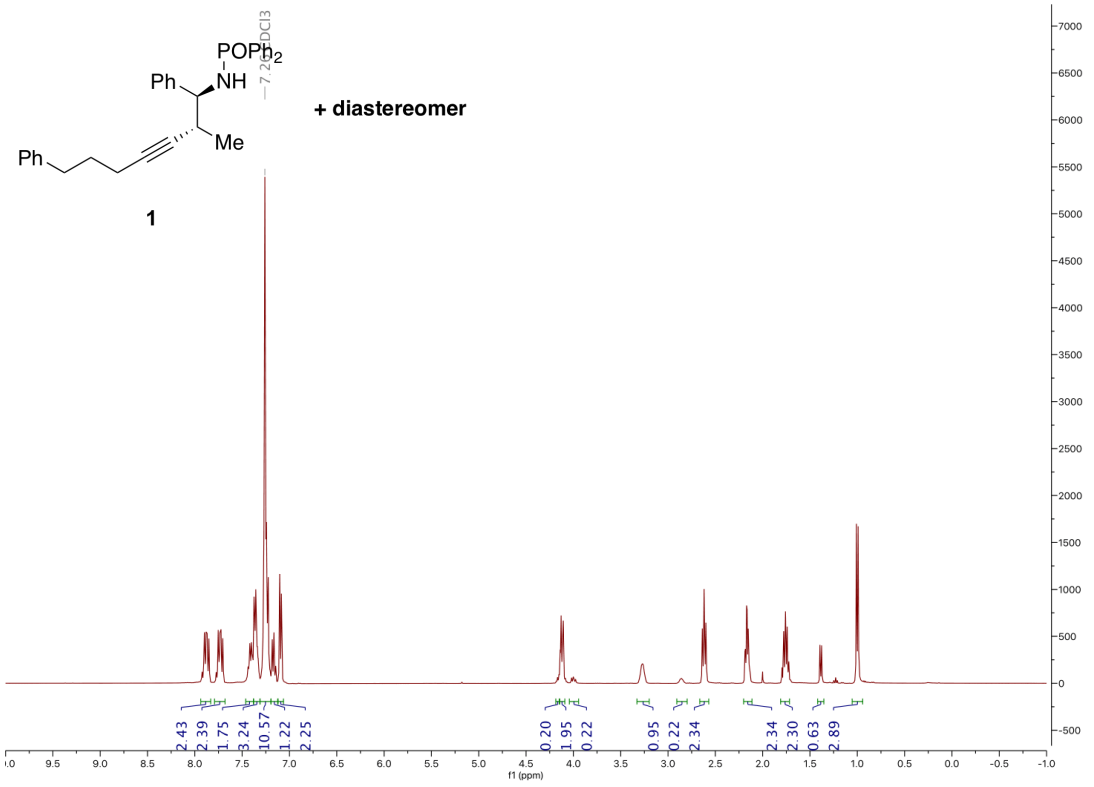
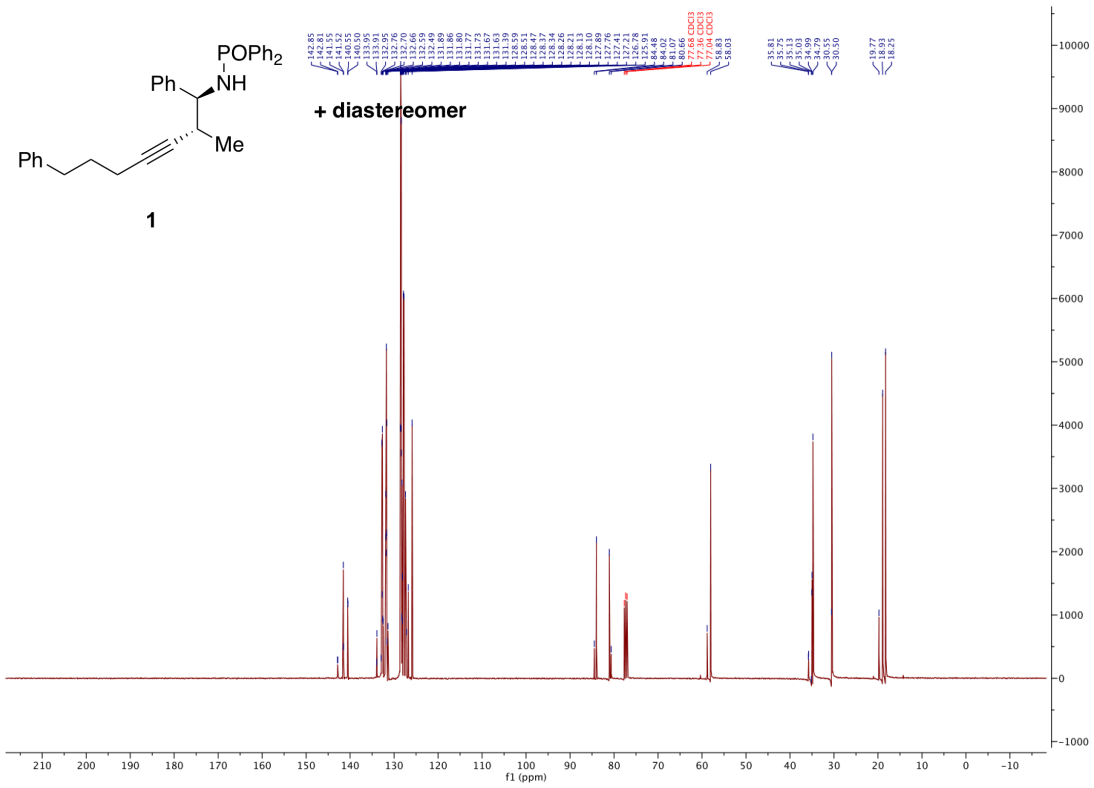
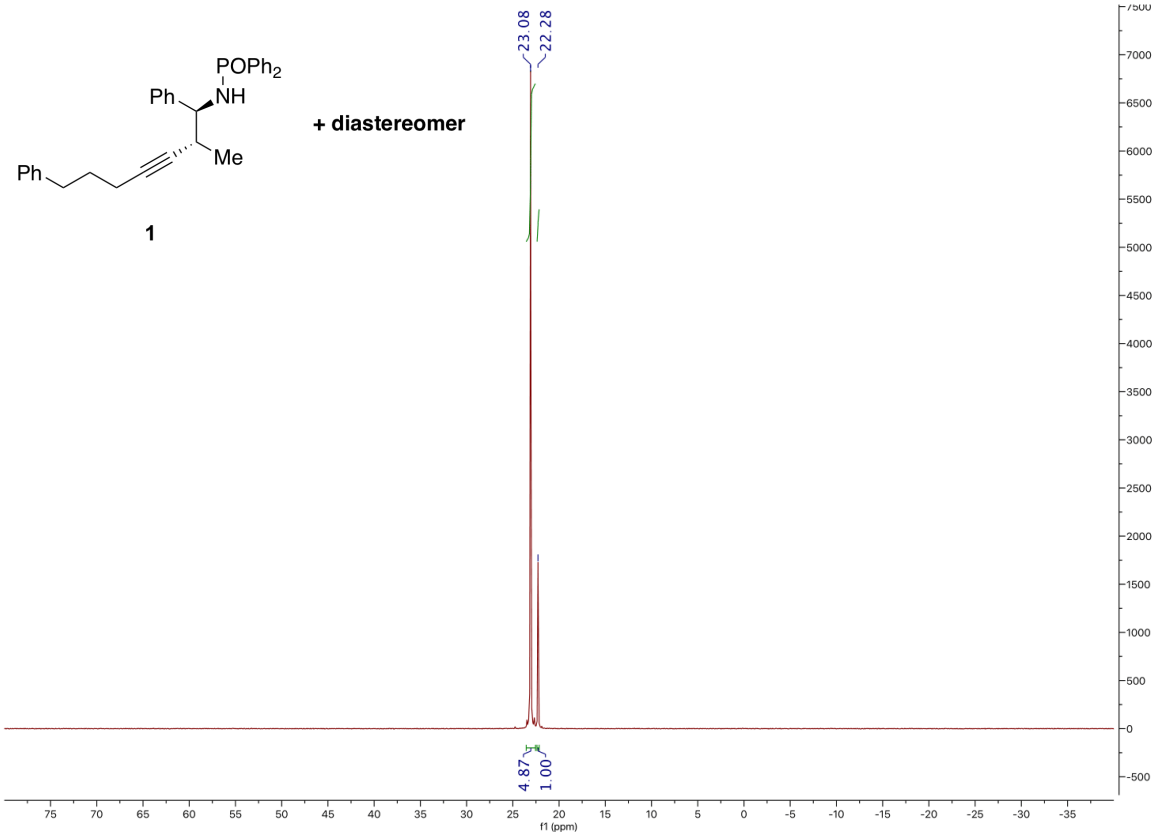
3.6 Spectra and Chromatograms



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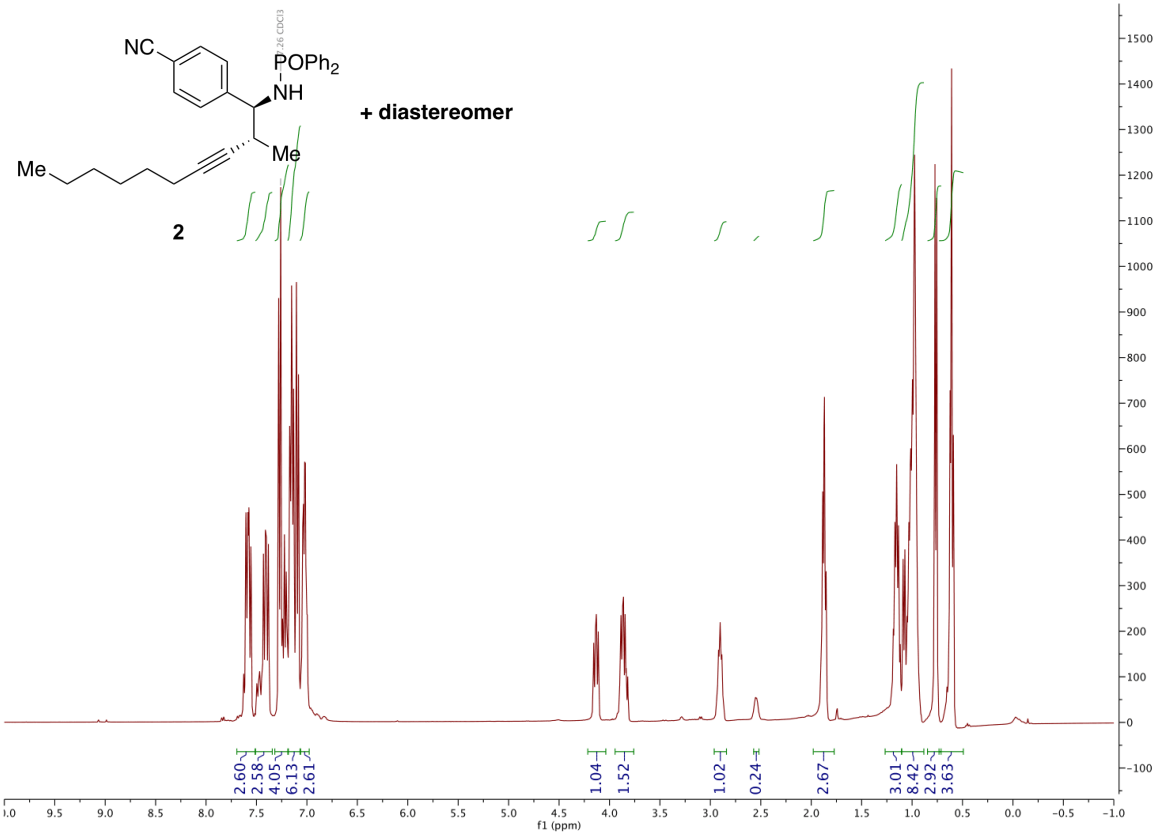
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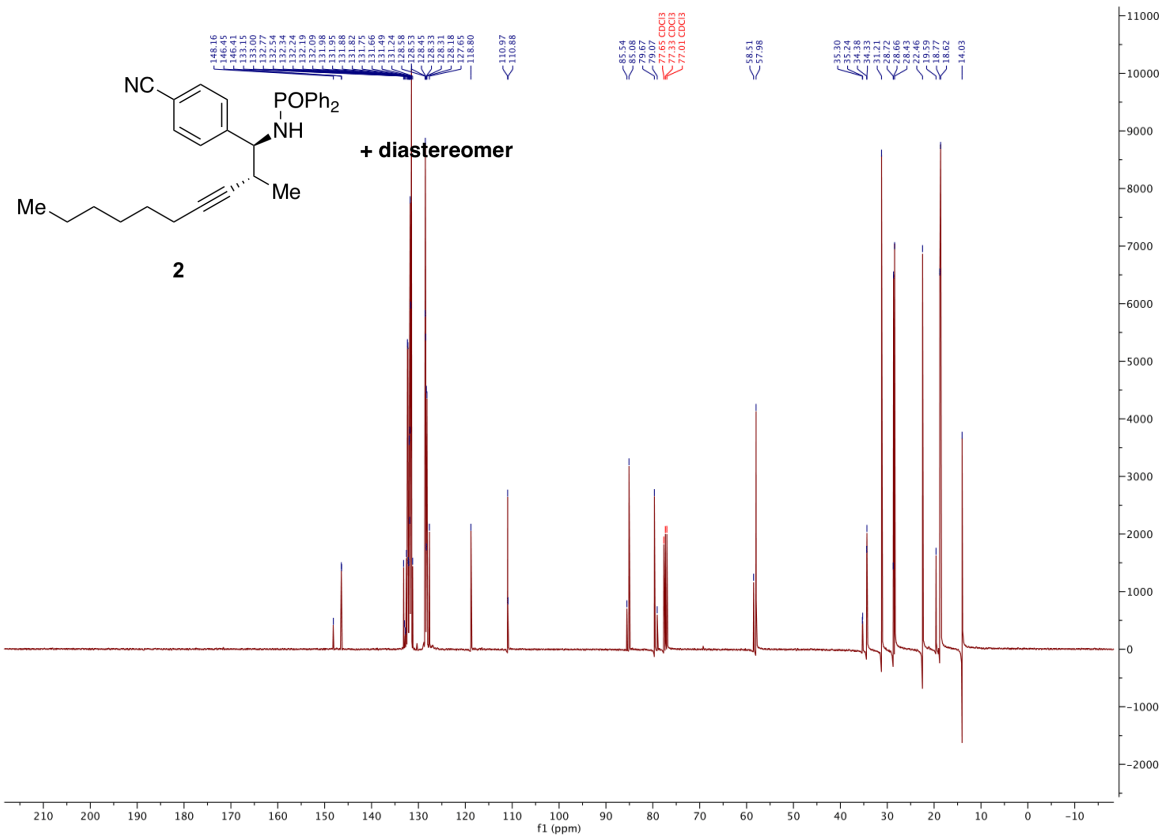
f1 (ppm)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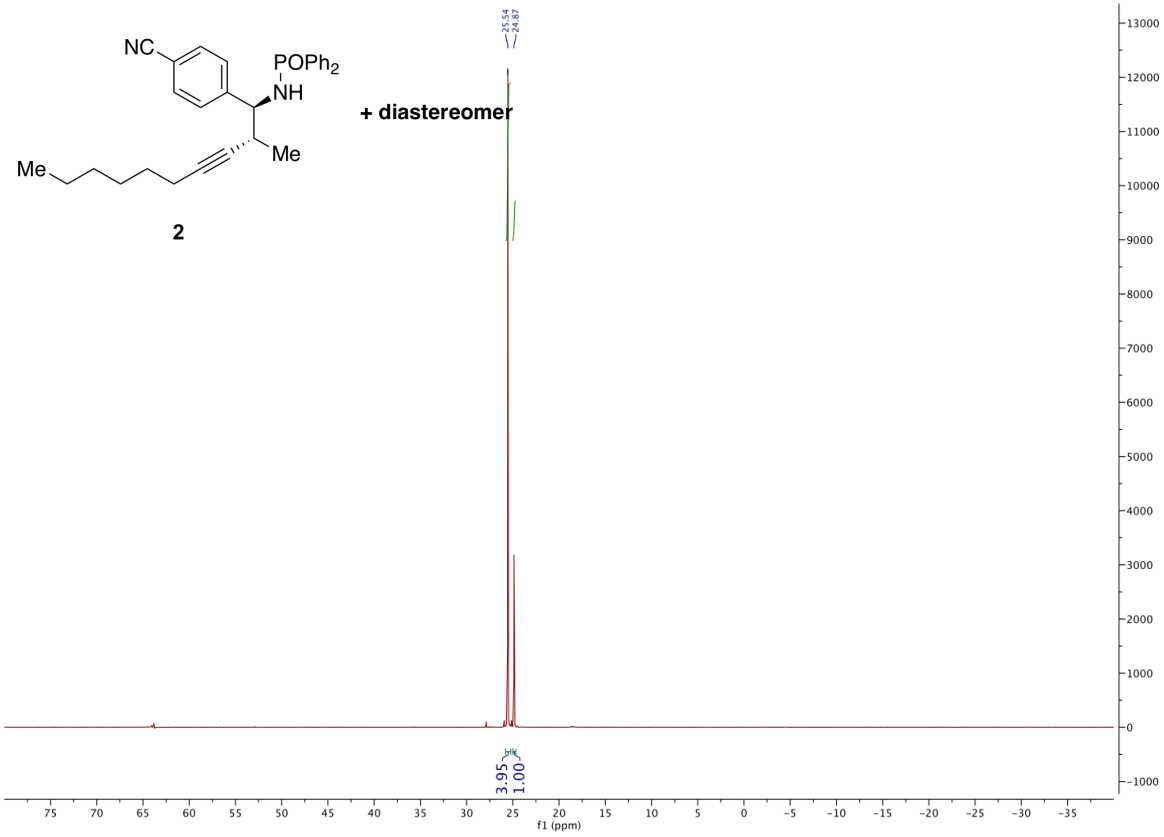
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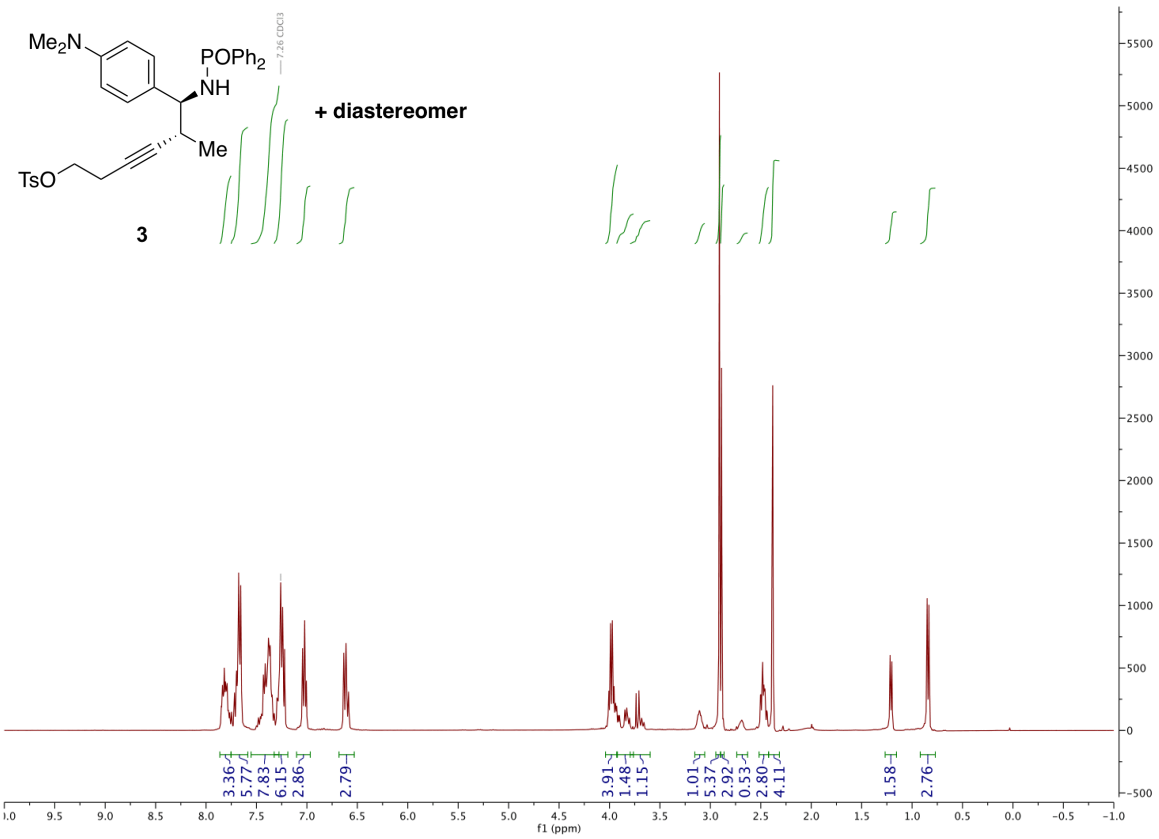
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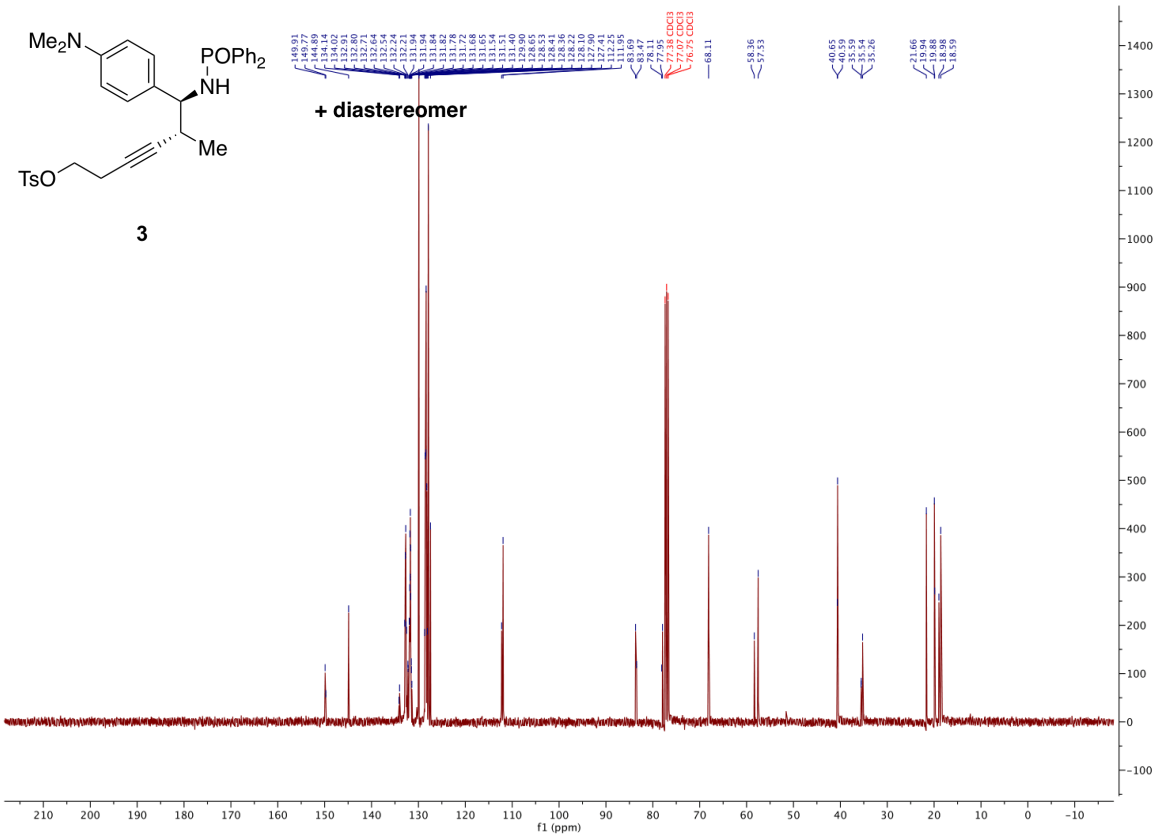
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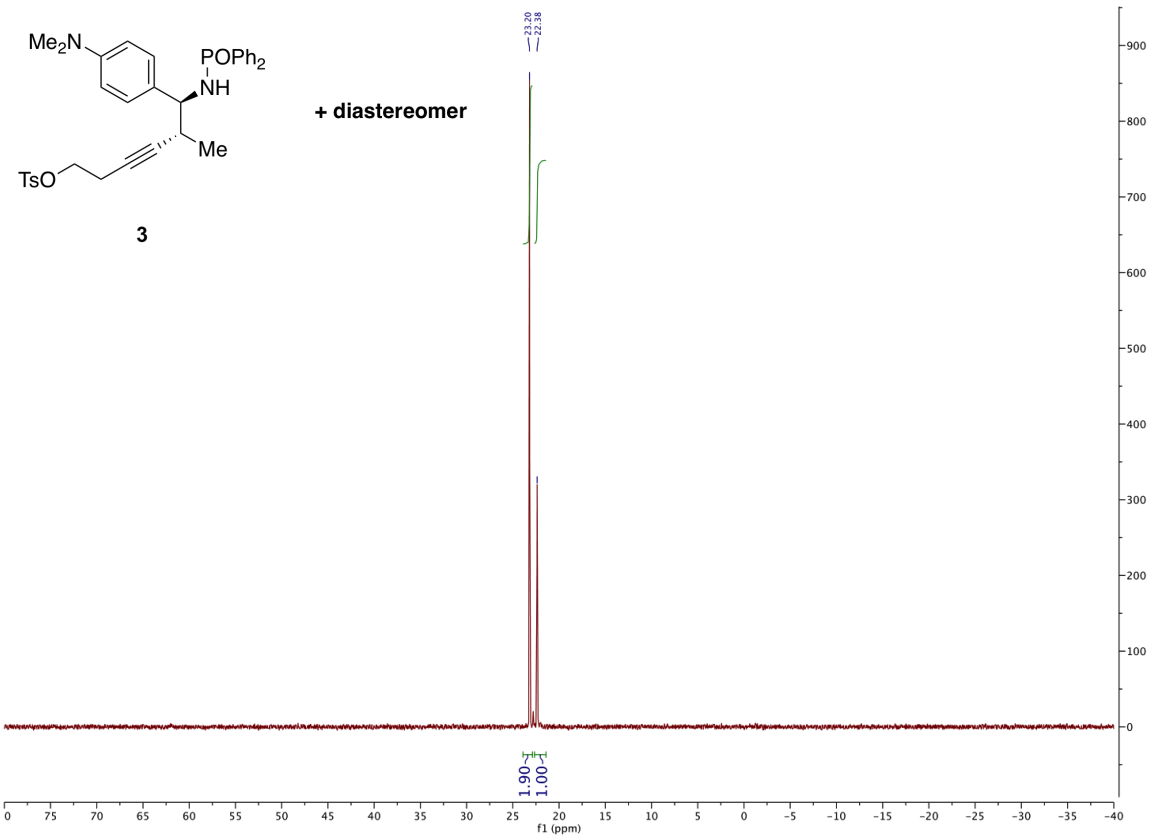
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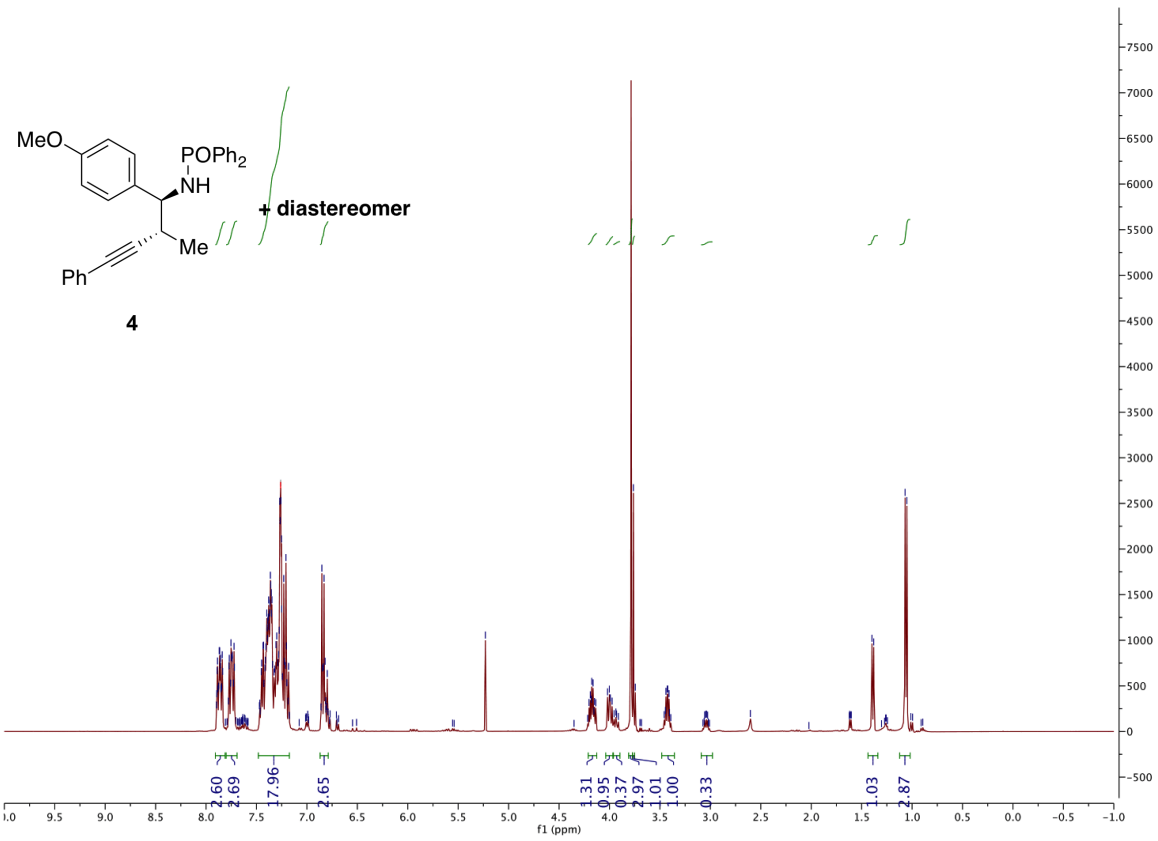
f1 (ppm)

3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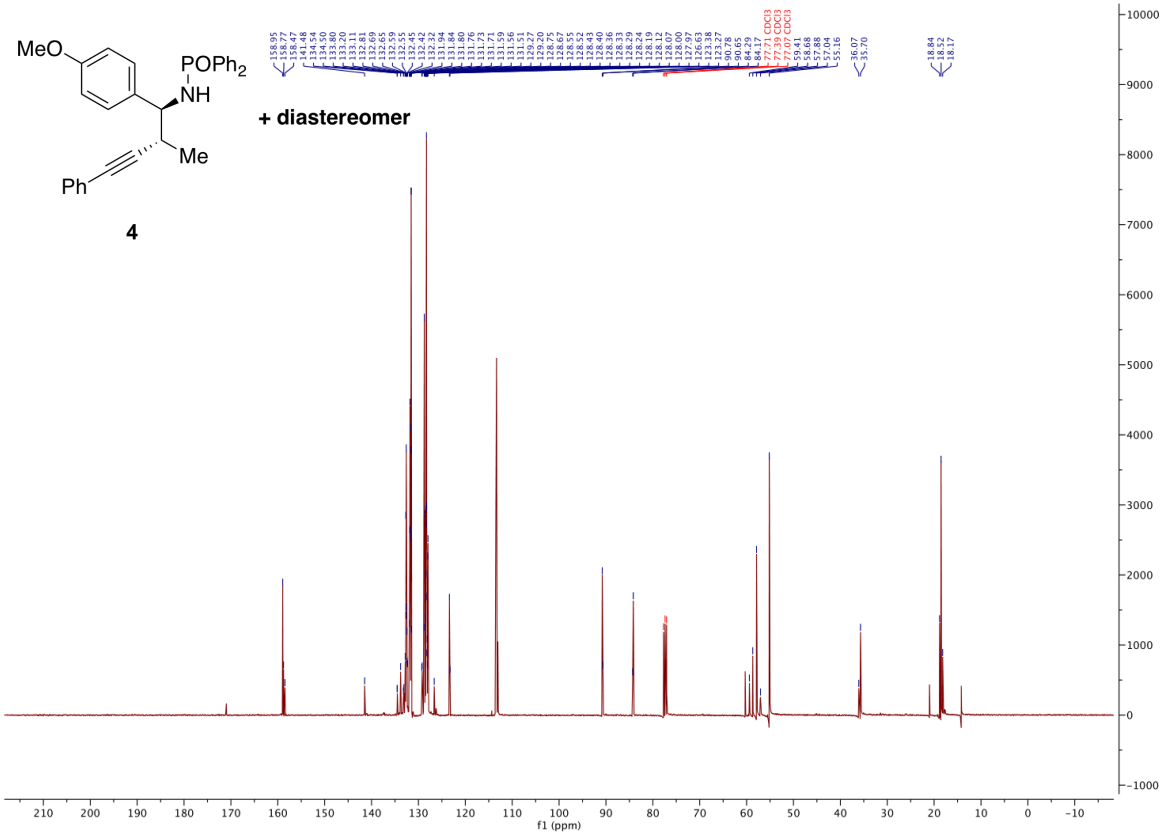
f1 (ppm)

4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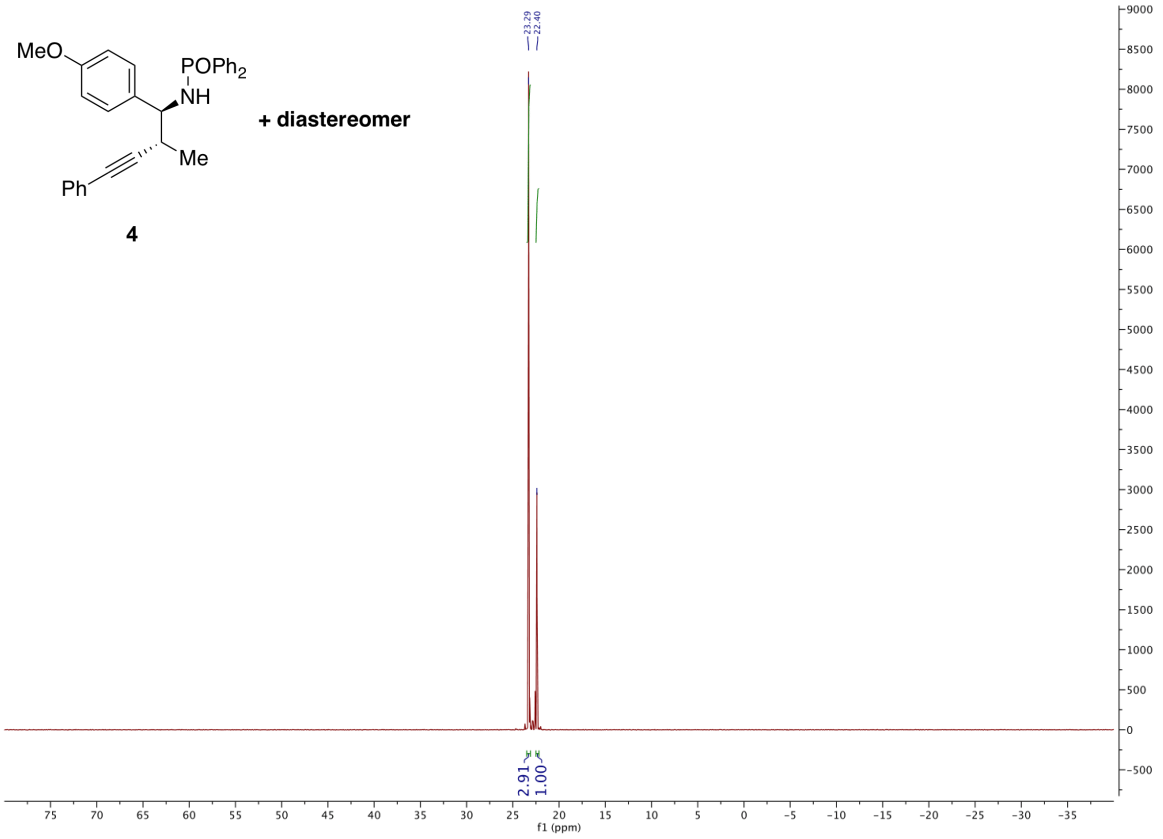
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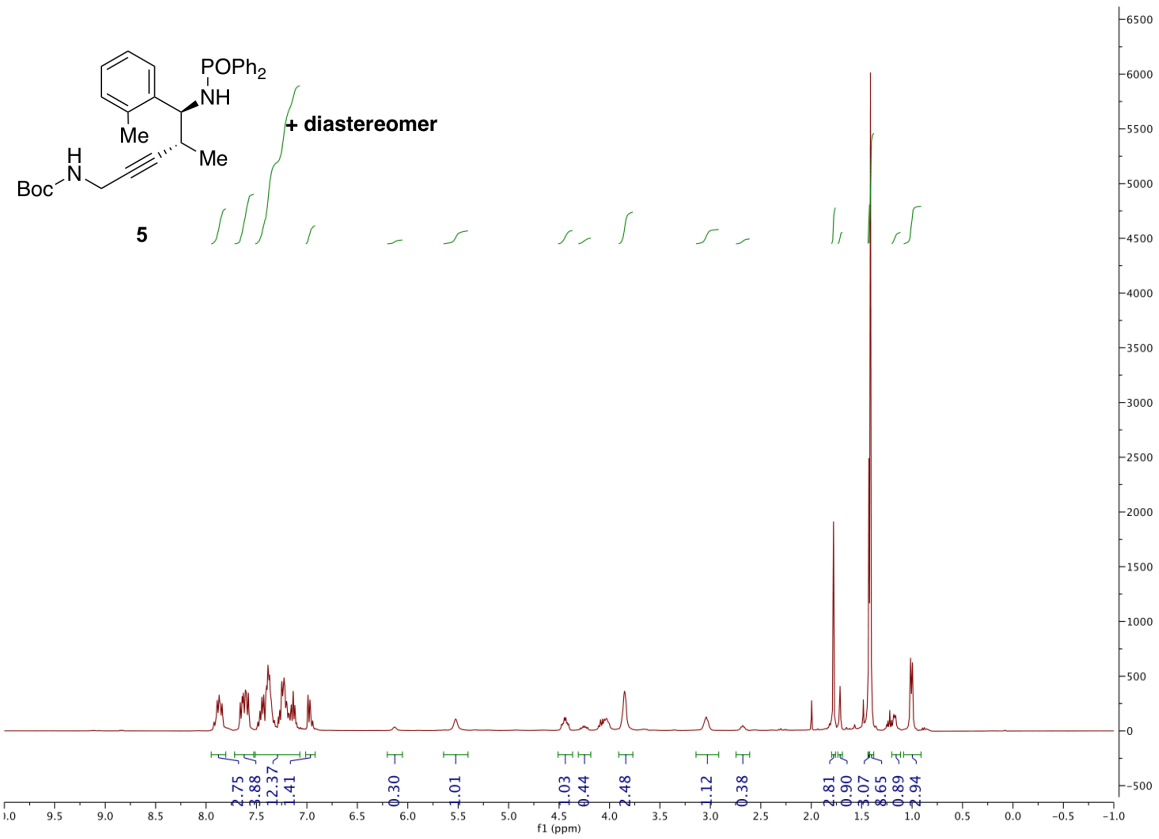
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H
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1.01
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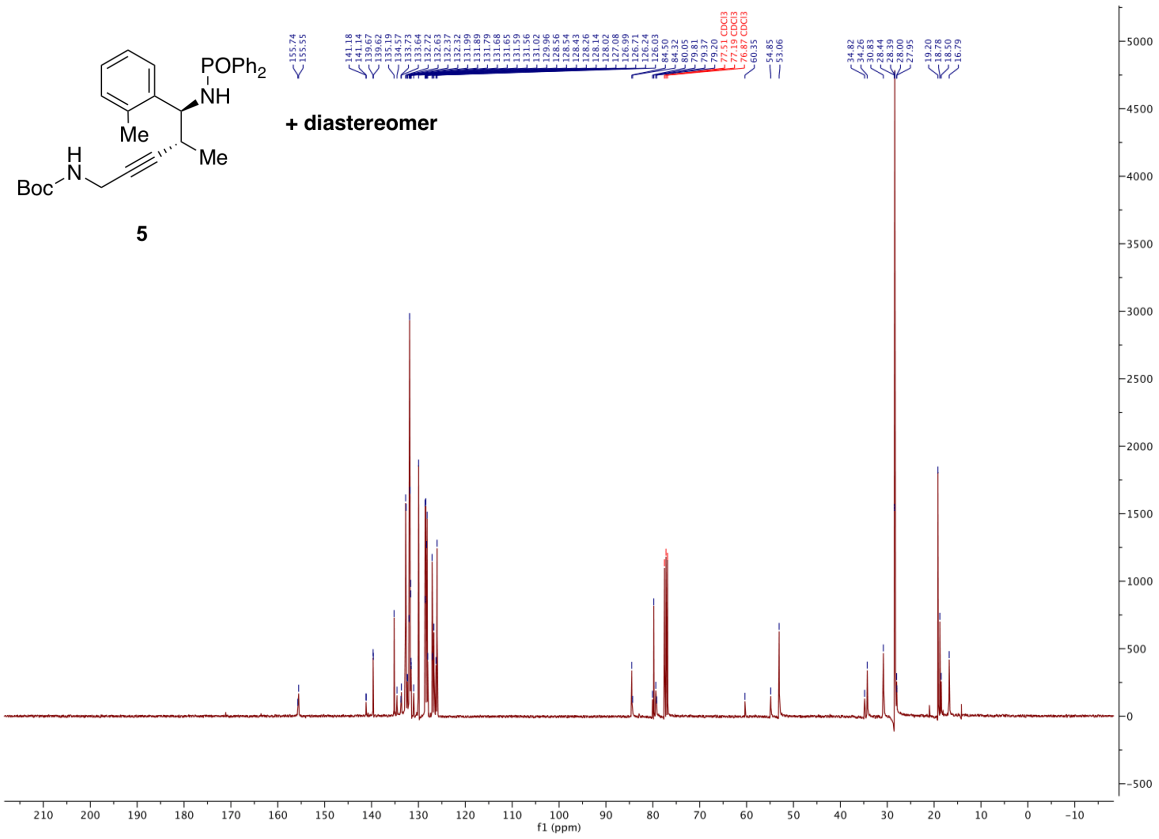
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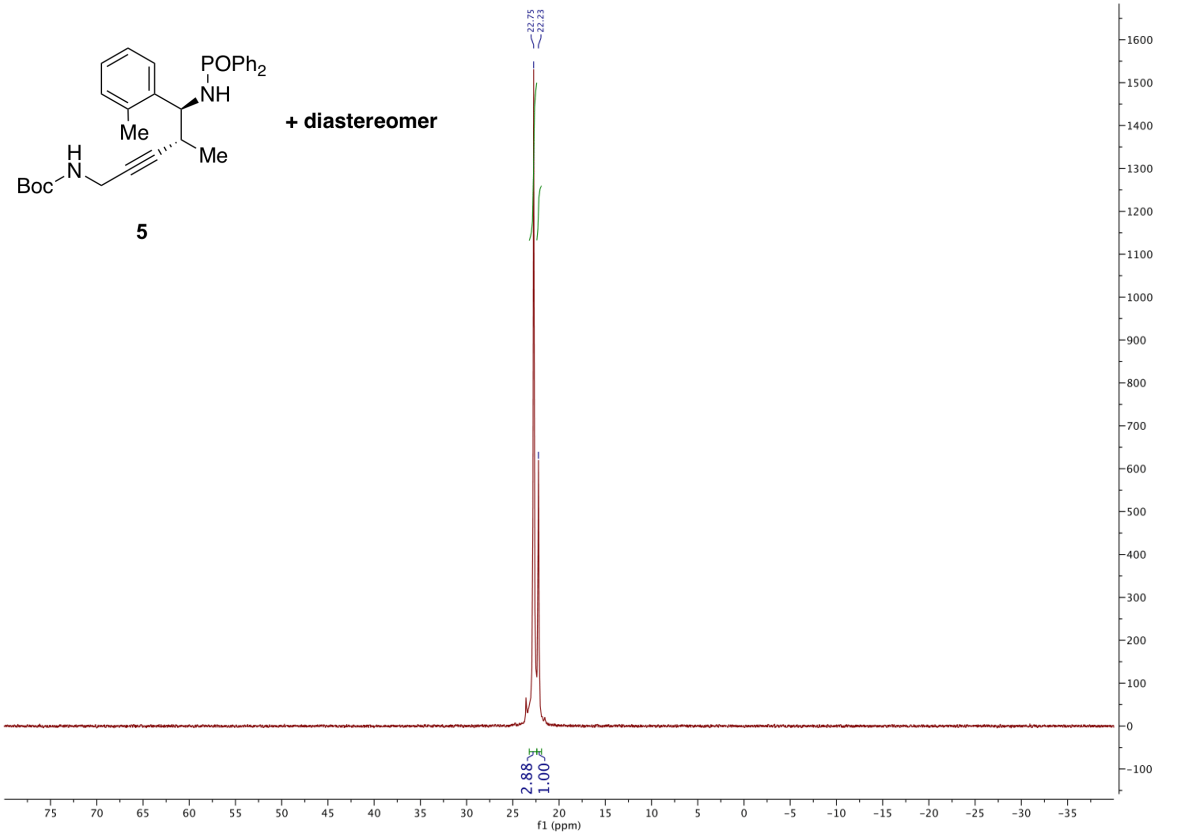
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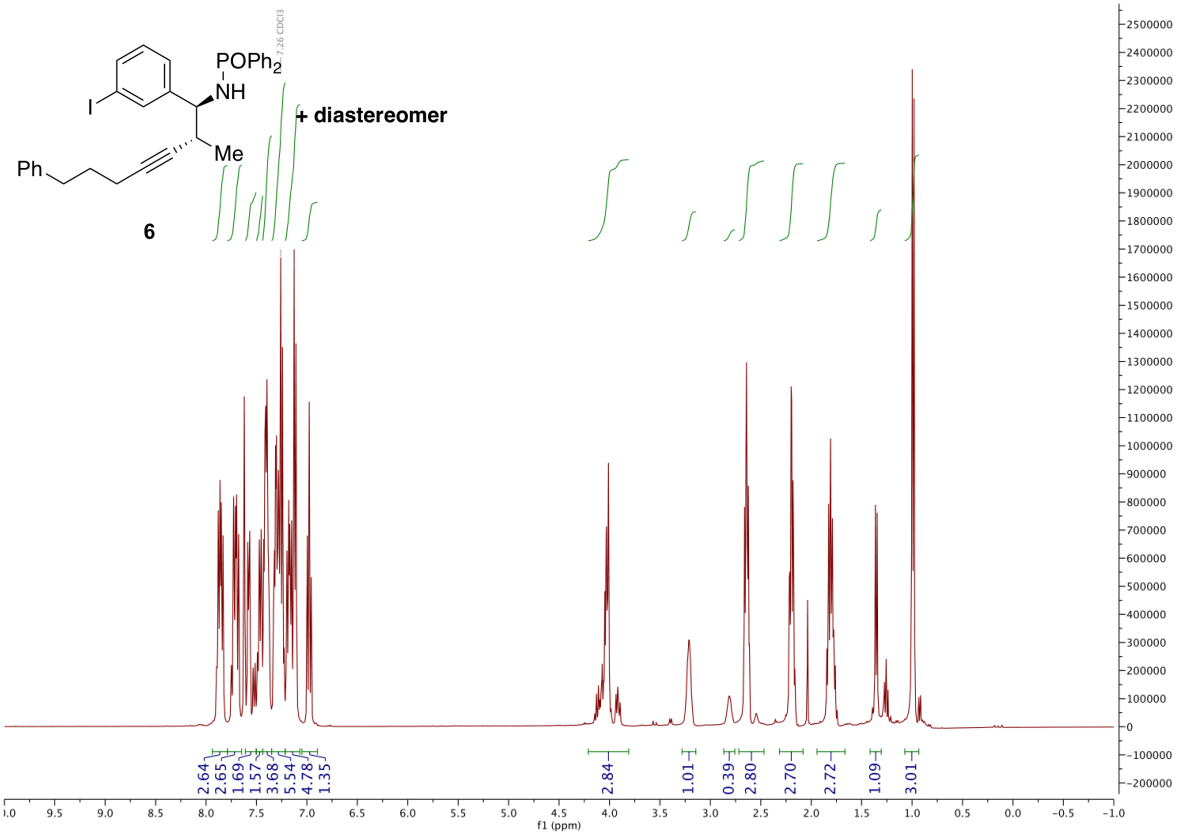
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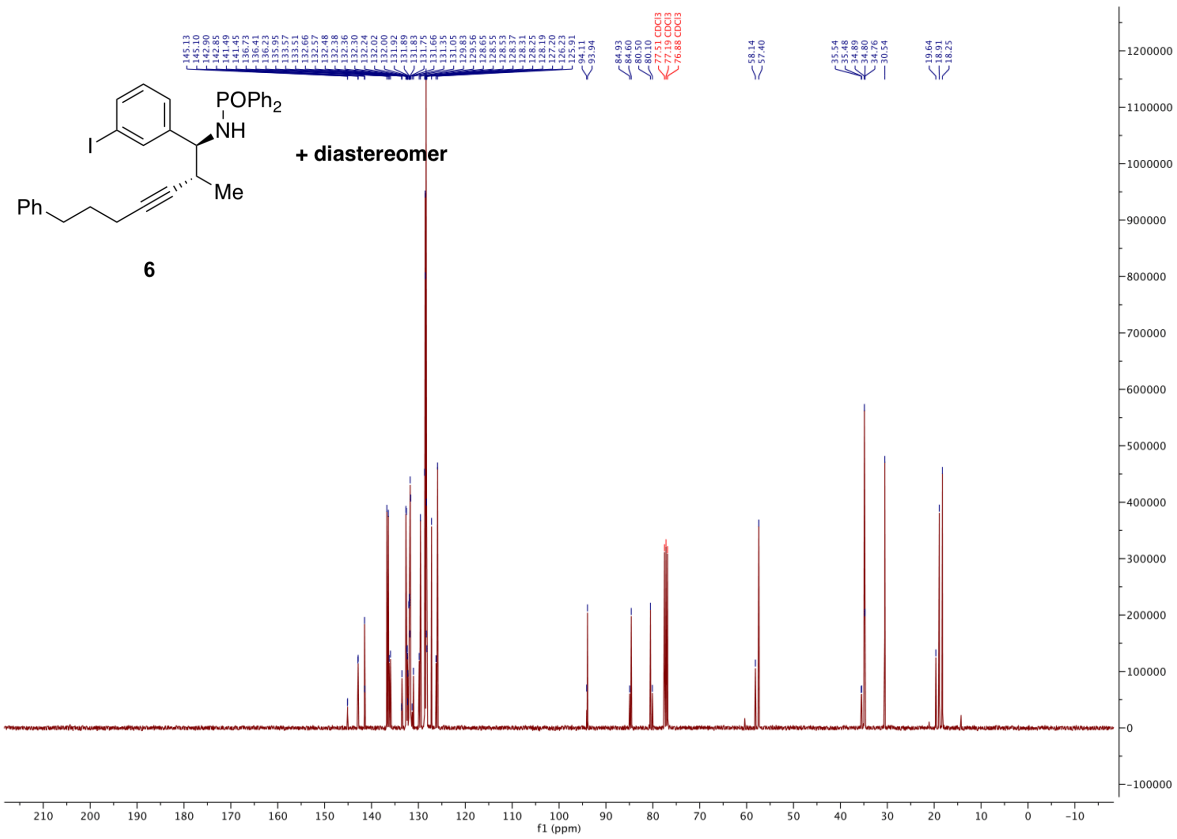
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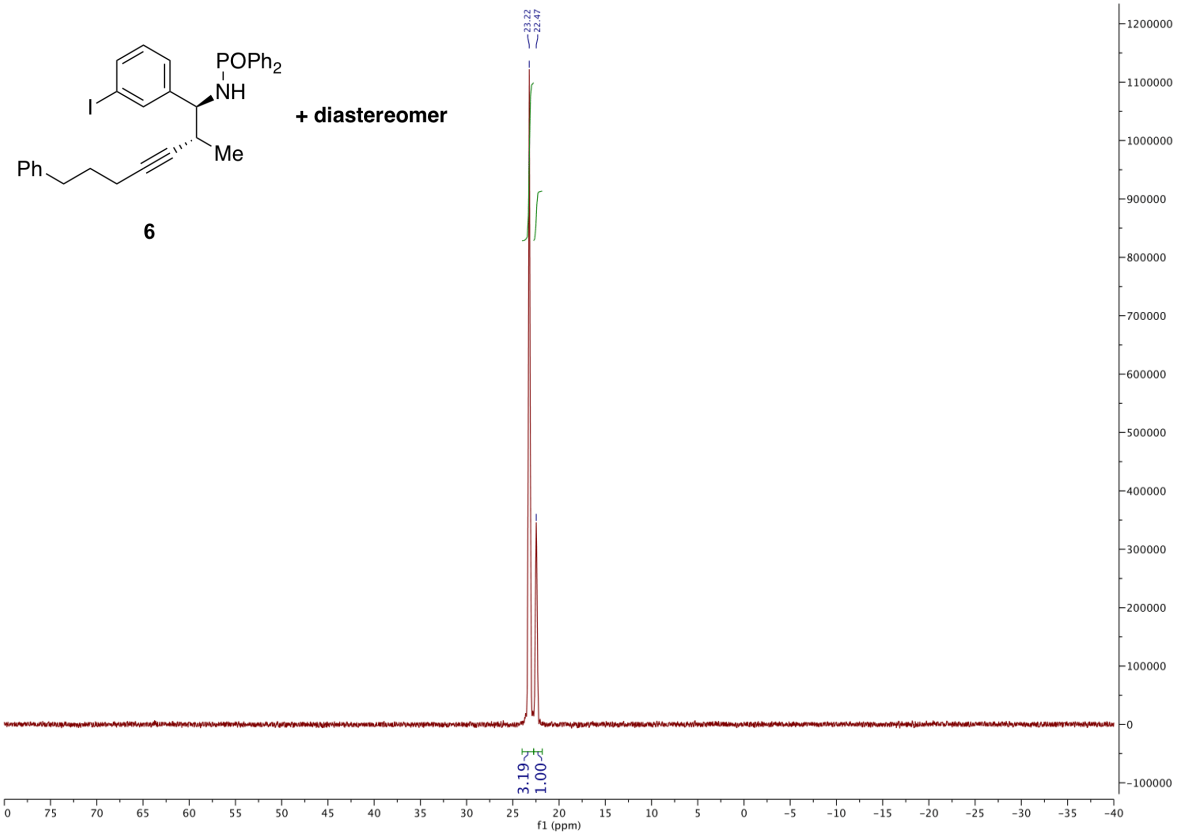
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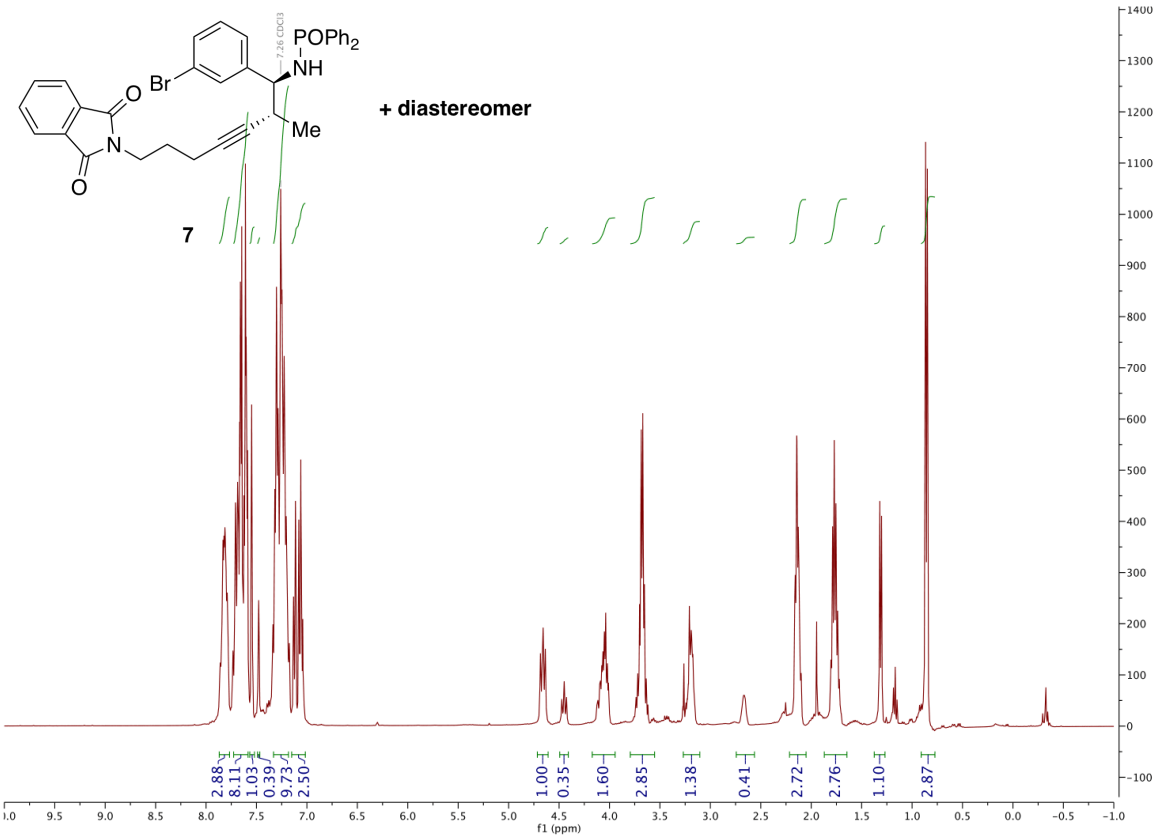
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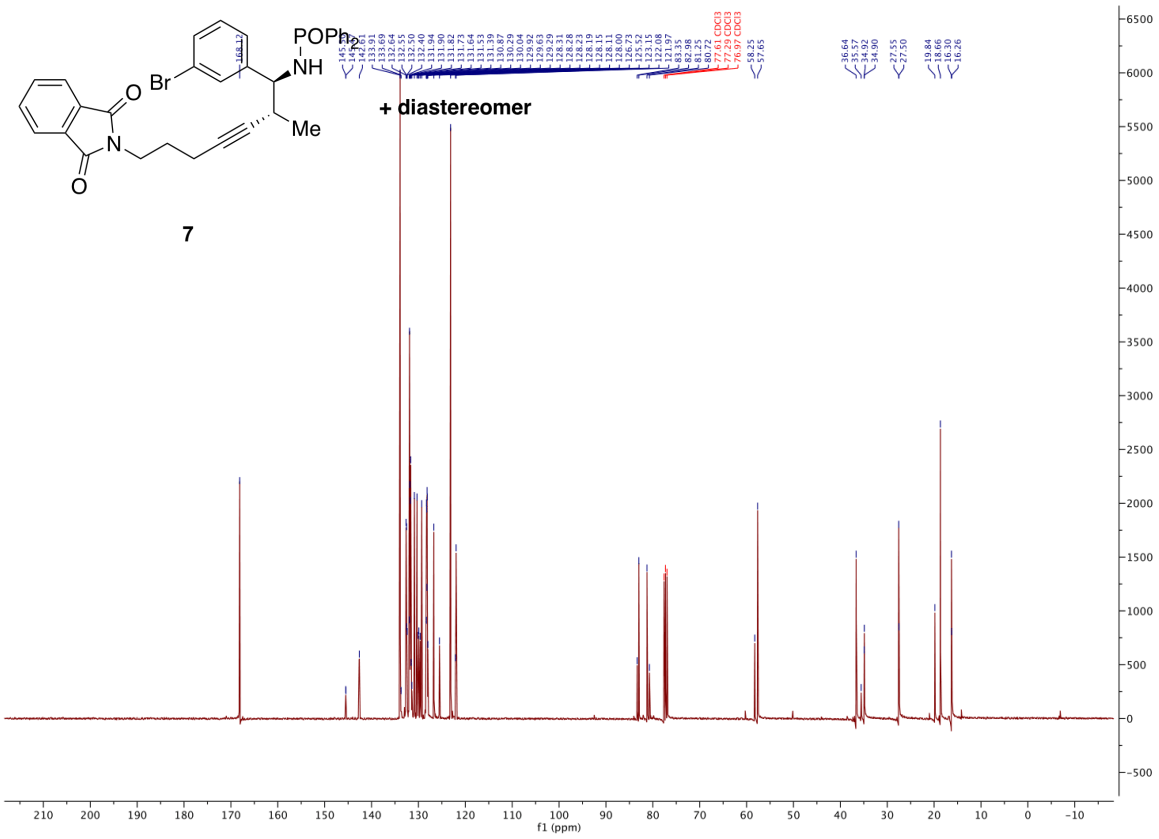
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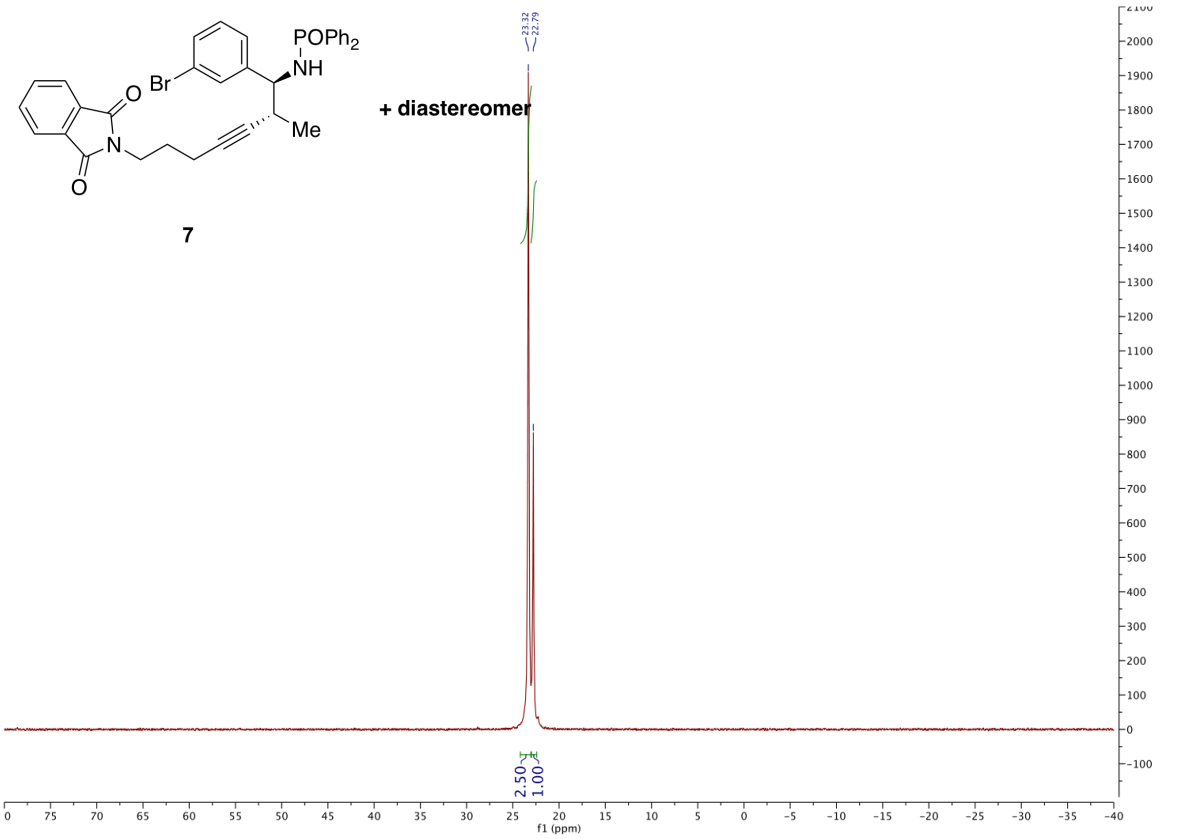
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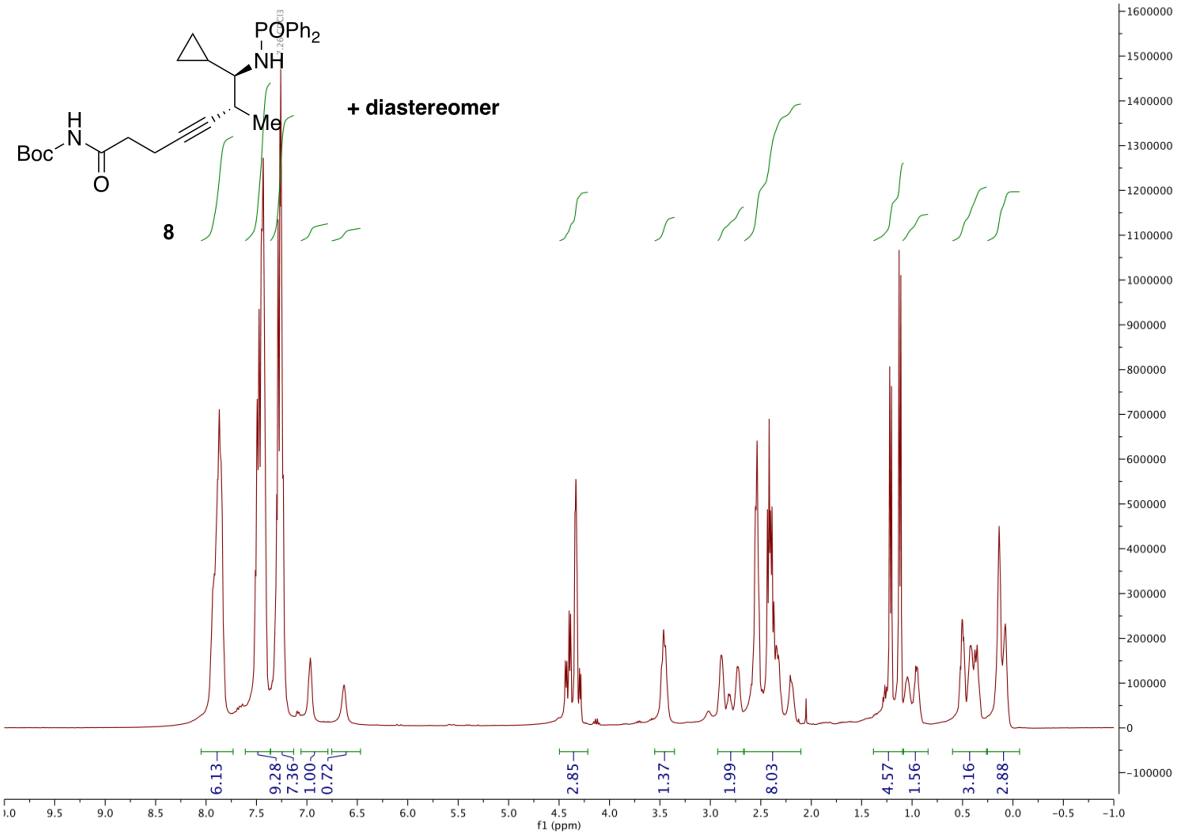
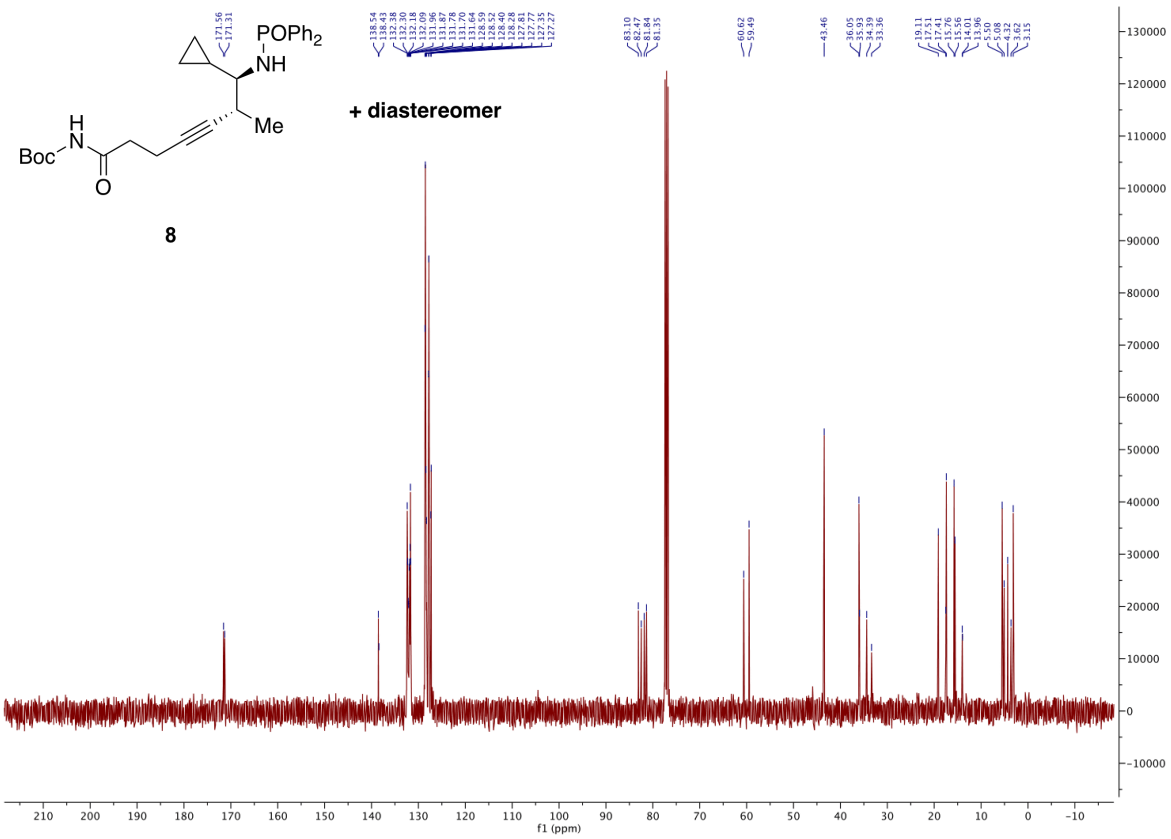
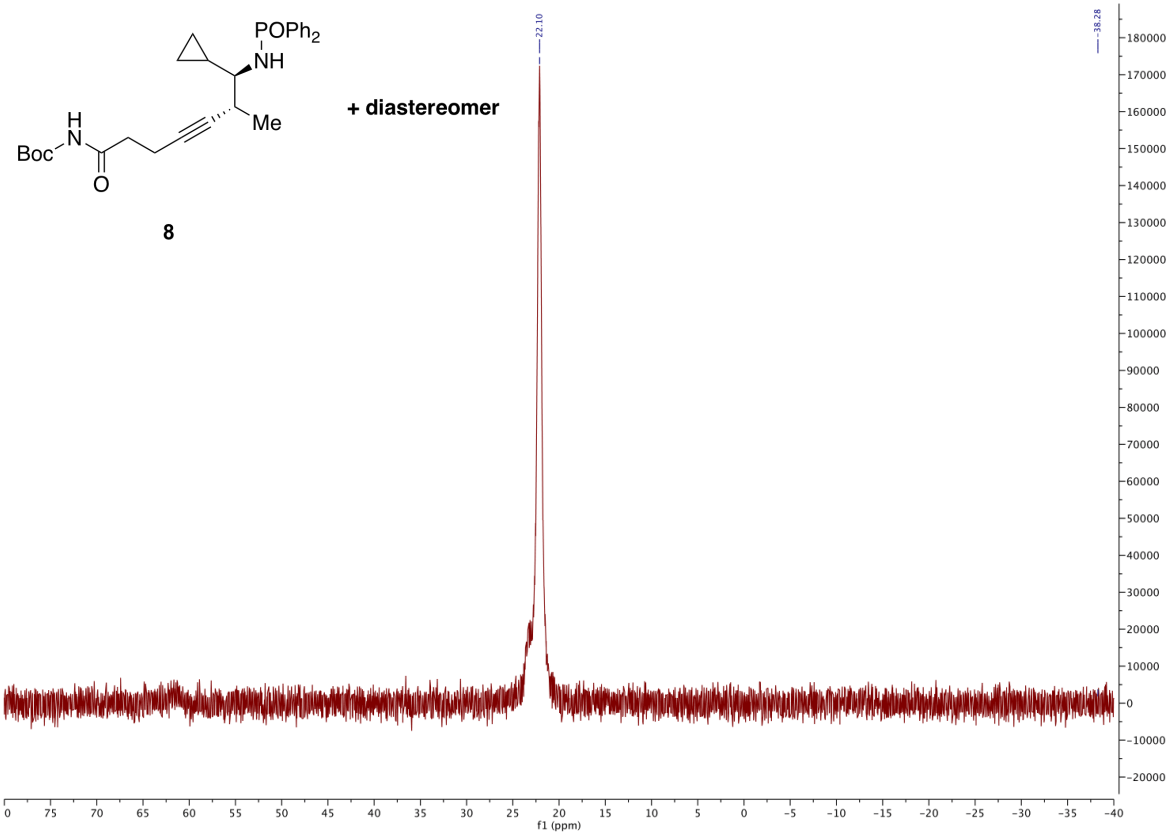
f1 (ppm)

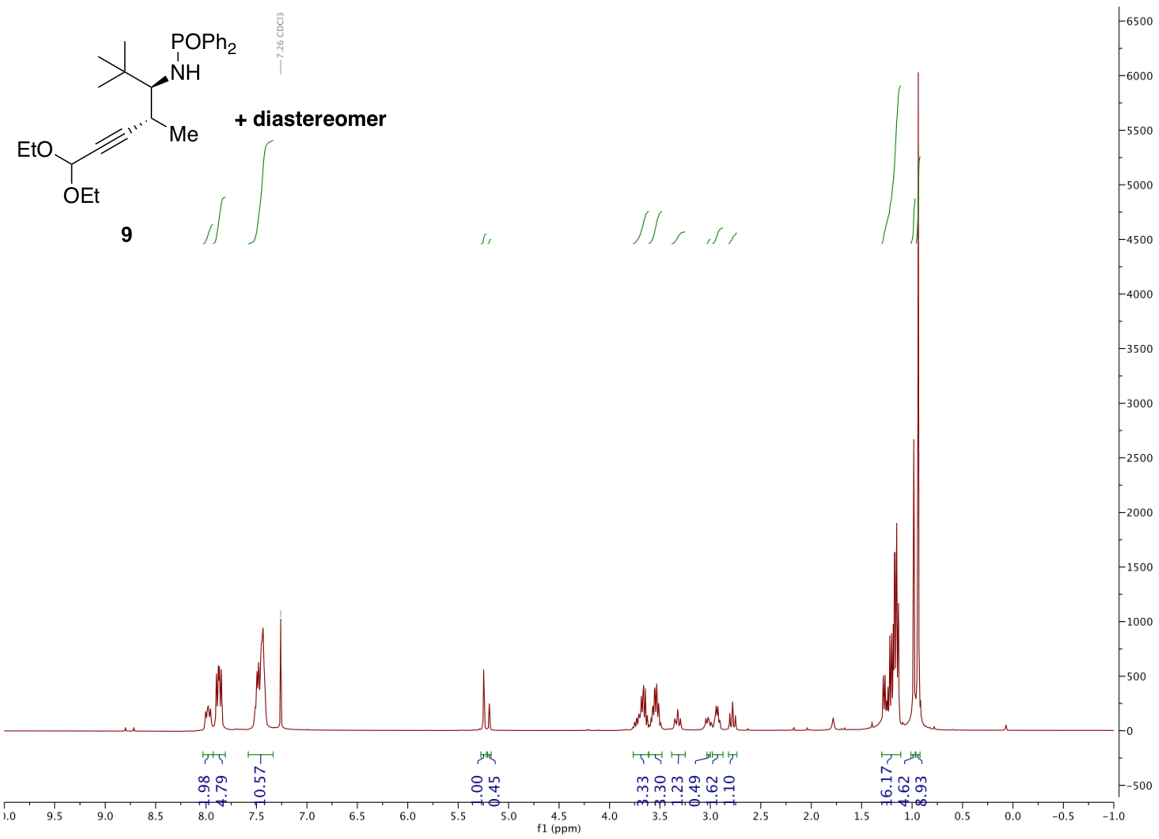
7

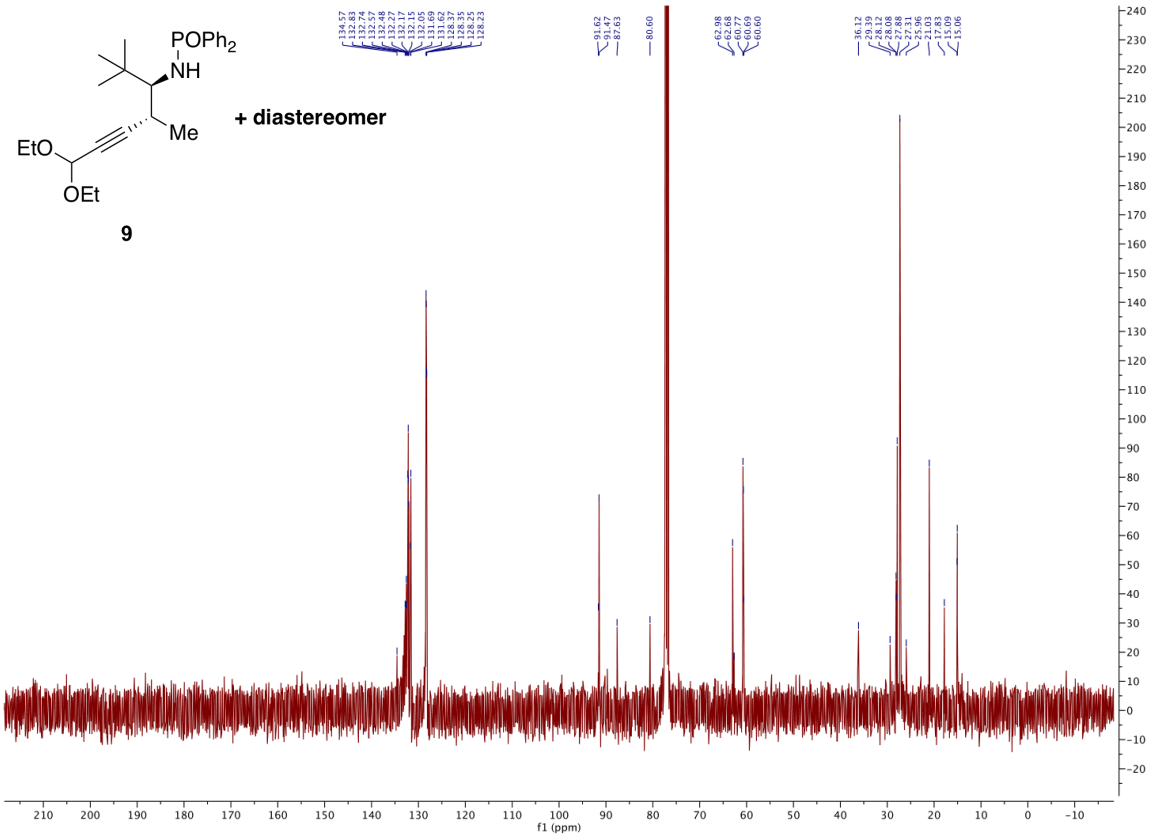

POPh2
NH
Me
H
N
Boc
O
+ diastereomer
6.13
9.28
7.36
1.00
0.72
2.85
1.37
1.99
8.03
4.57
1.56
3.16
2.88
f1 (ppm)

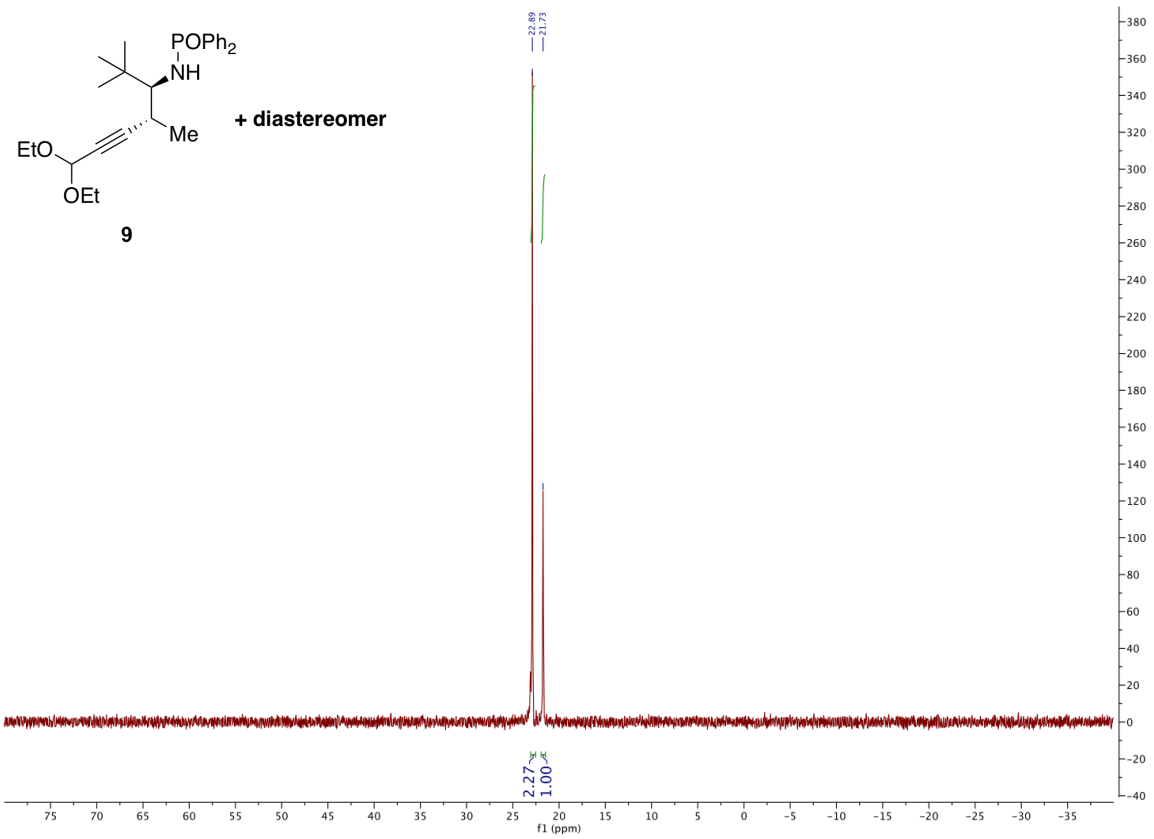
8

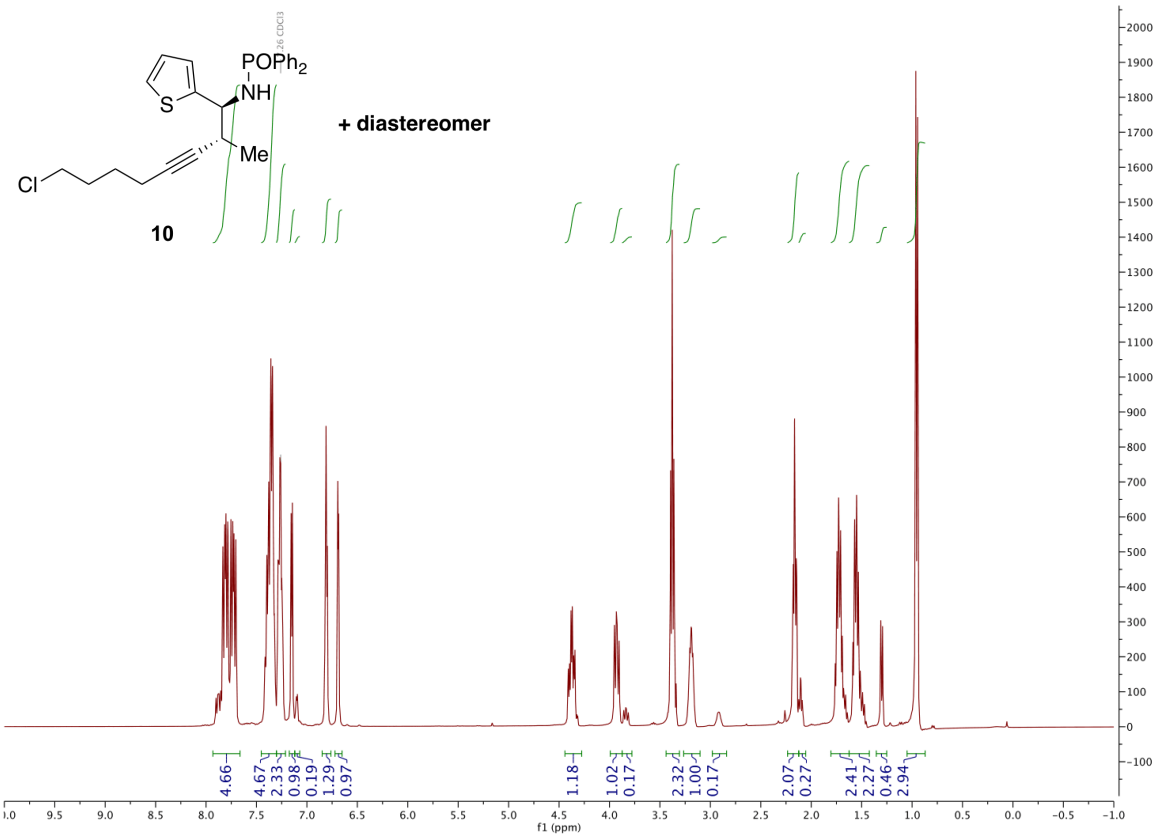

POPh2
NH
Me
H
N
Boc
O
+ diastereomer
8
f1 (ppm)

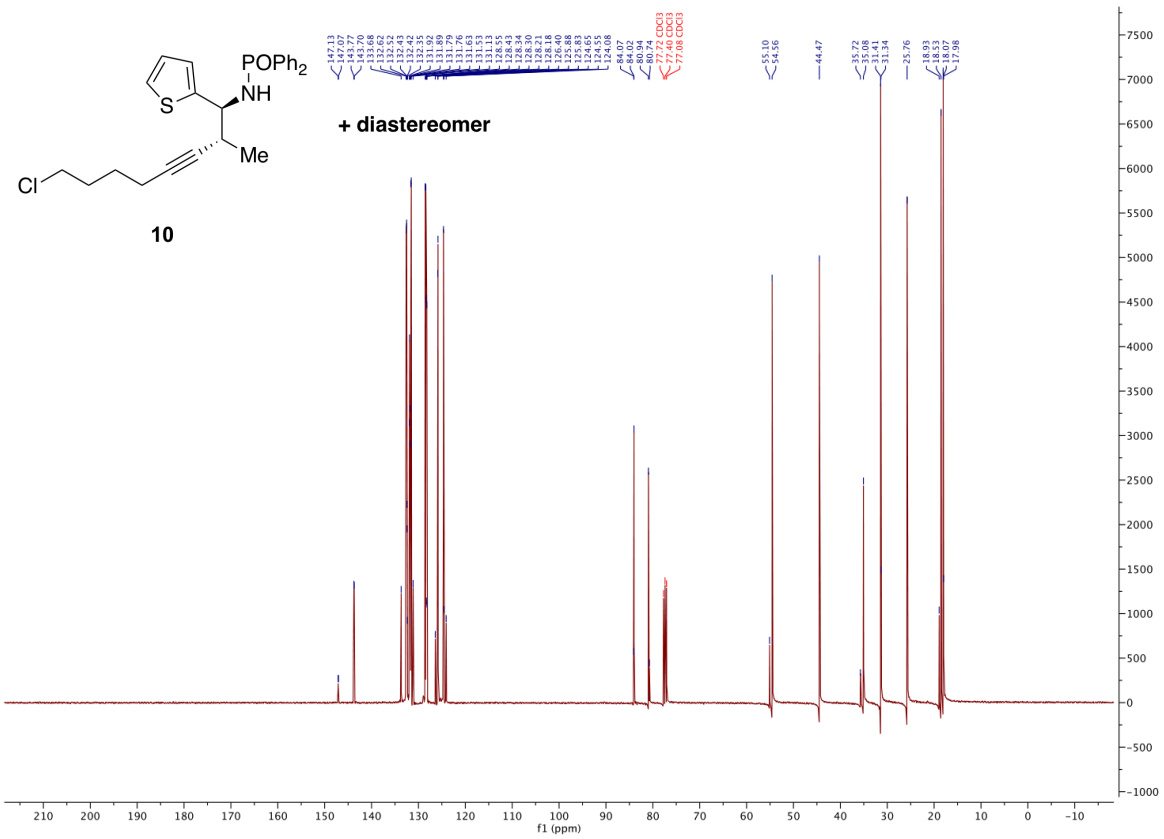

POPh2
NH
Me
H
N
Boc
O
+ diastereomer
8
22.10
38.28
f1 (ppm)

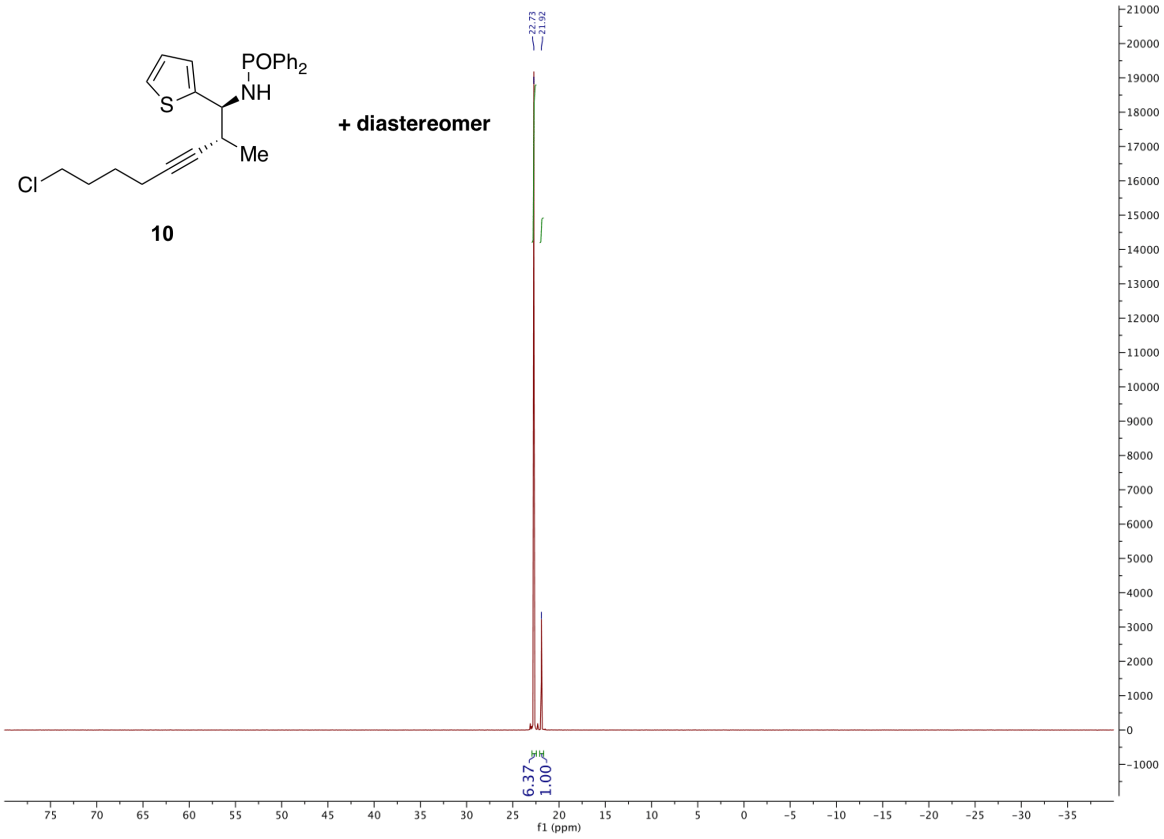

POPh2
NH
Me
EtO
OEt
+ diastereomer
9
7.26 CDCl3
1.98
4.79
10.57
1.00
0.45
3.33
3.30
1.23
0.49
1.62
1.10
16.17
4.62
8.93
f1 (ppm)

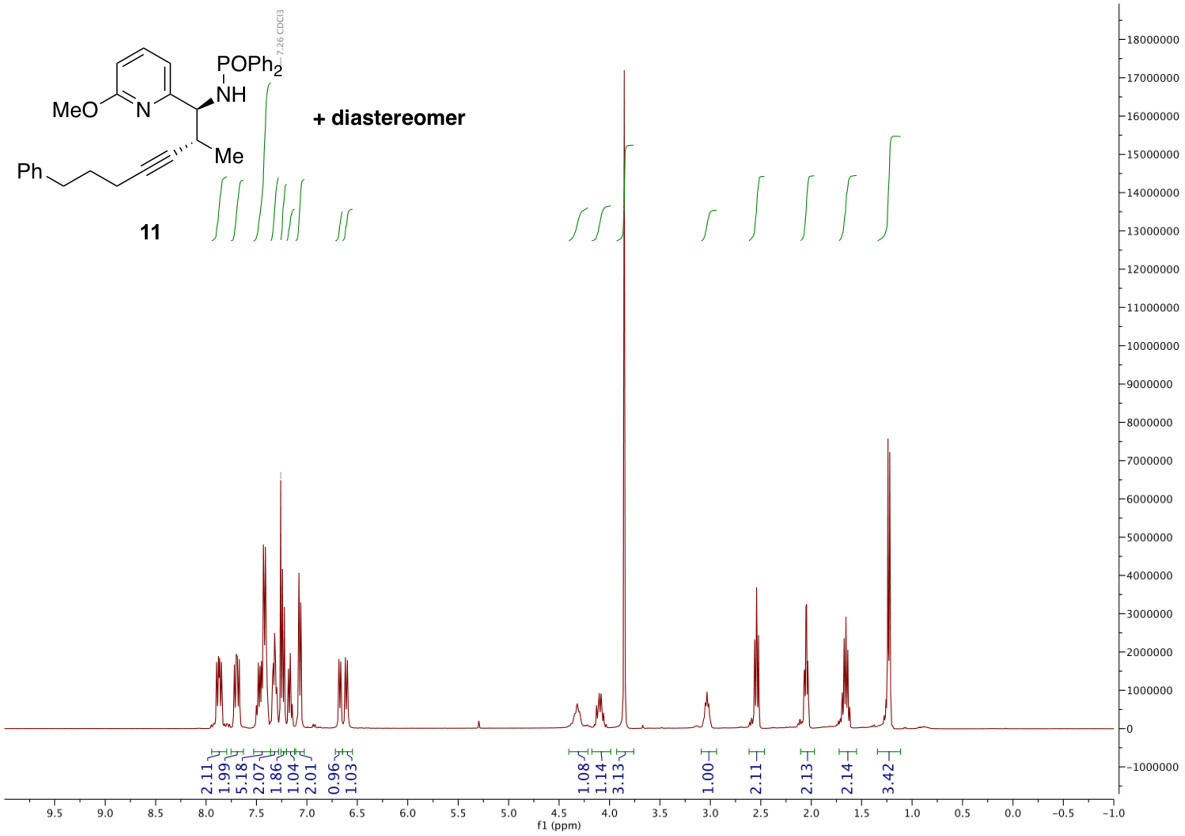

POPh2
NH
Me
EtO
OEt
+ diastereomer
9
134.57
132.83
132.74
132.57
132.48
132.27
132.17
132.15
132.05
131.68
131.62
128.37
128.35
128.25
128.23
91.62
91.47
87.63
80.60
62.98
62.68
60.77
60.69
60.60
36.12
29.39
28.12
28.08
27.88
27.71
25.96
21.03
17.83
15.30
15.06
f1 (ppm)

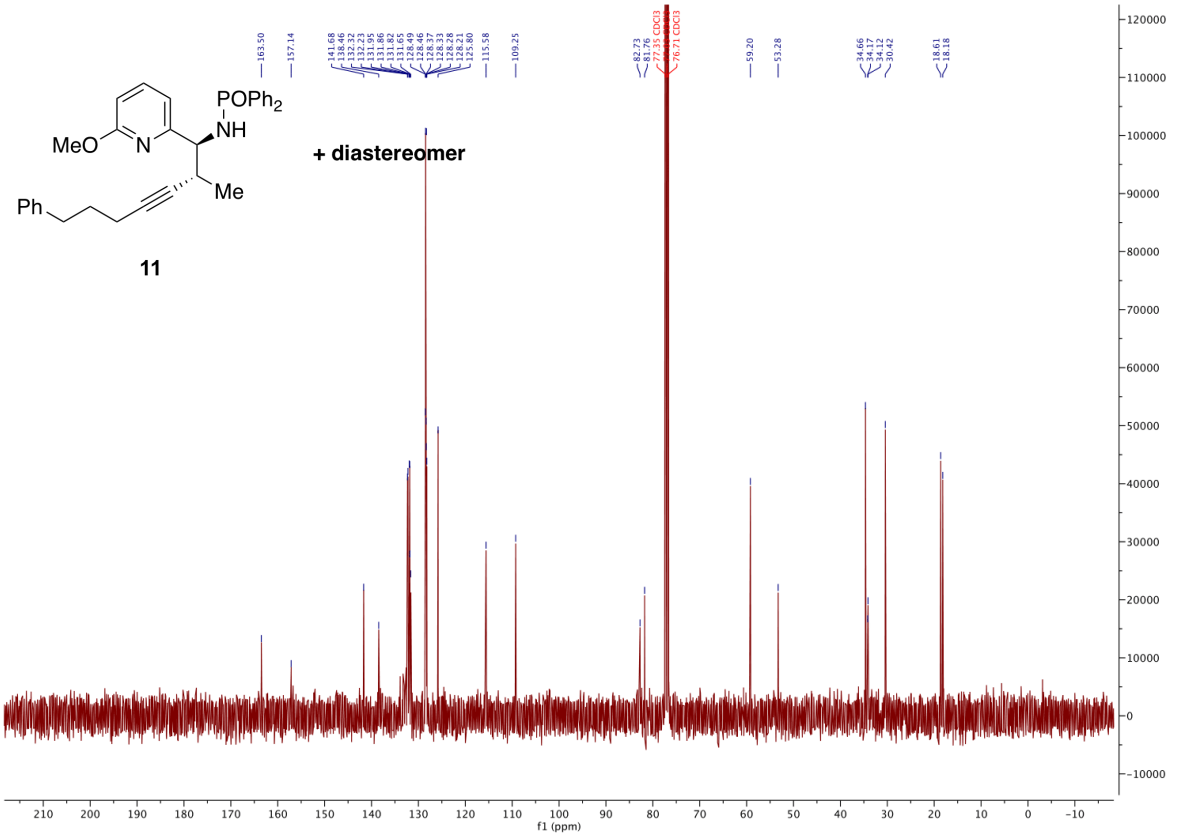

POPh2
NH
Me
EtO
OEt
+ diastereomer
9
21.89
21.73
2.27
1.00
f1 (ppm)

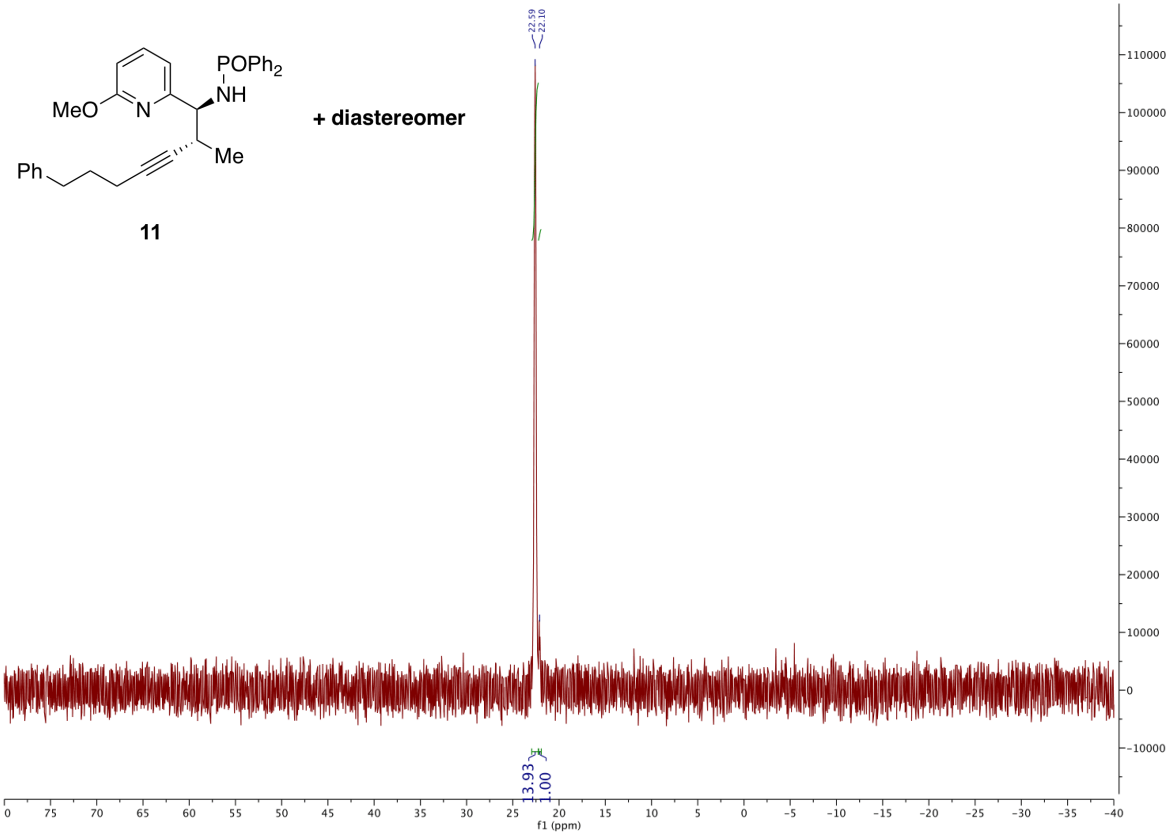

POPh2
NH
S
Me
Cl
+ diastereomer
10
4.66
4.67
2.33
0.98
0.19
1.29
0.97
1.18
1.02
0.17
2.32
1.00
0.17
2.07
0.27
2.41
2.27
0.46
2.94
f1 (ppm)


POPh2
NH
S
Me
Cl
10
+ diastereomer
f1 (ppm)

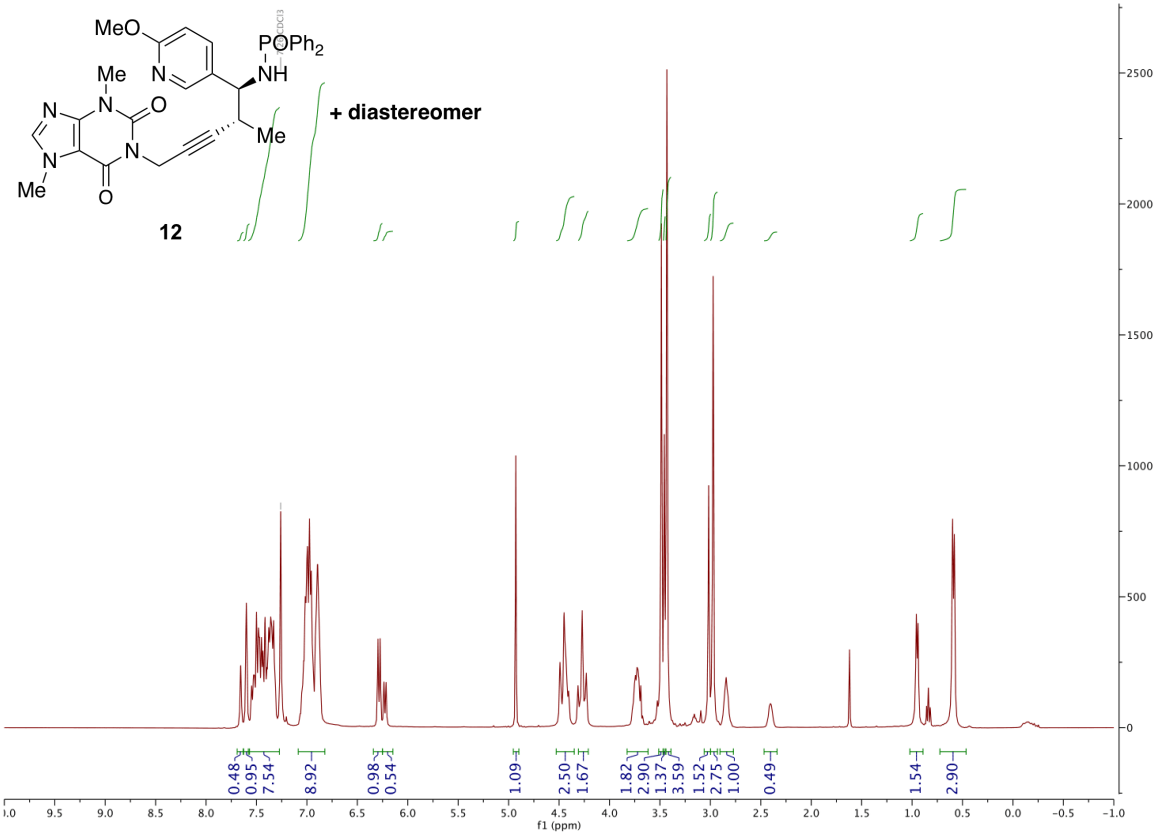

POPh2
NH
S
Me
Cl
10
+ diastereomer
6.37
1.00
f1 (ppm)


POPh2
NH
MeO
N
Me
Ph
+ diastereomer
11
7.26 CDCl3
2.11
1.99
5.18
2.07
1.86
1.04
2.01
0.96
1.03
1.08
1.14
3.13
1.00
2.11
2.13
2.14
3.42
f1 (ppm)

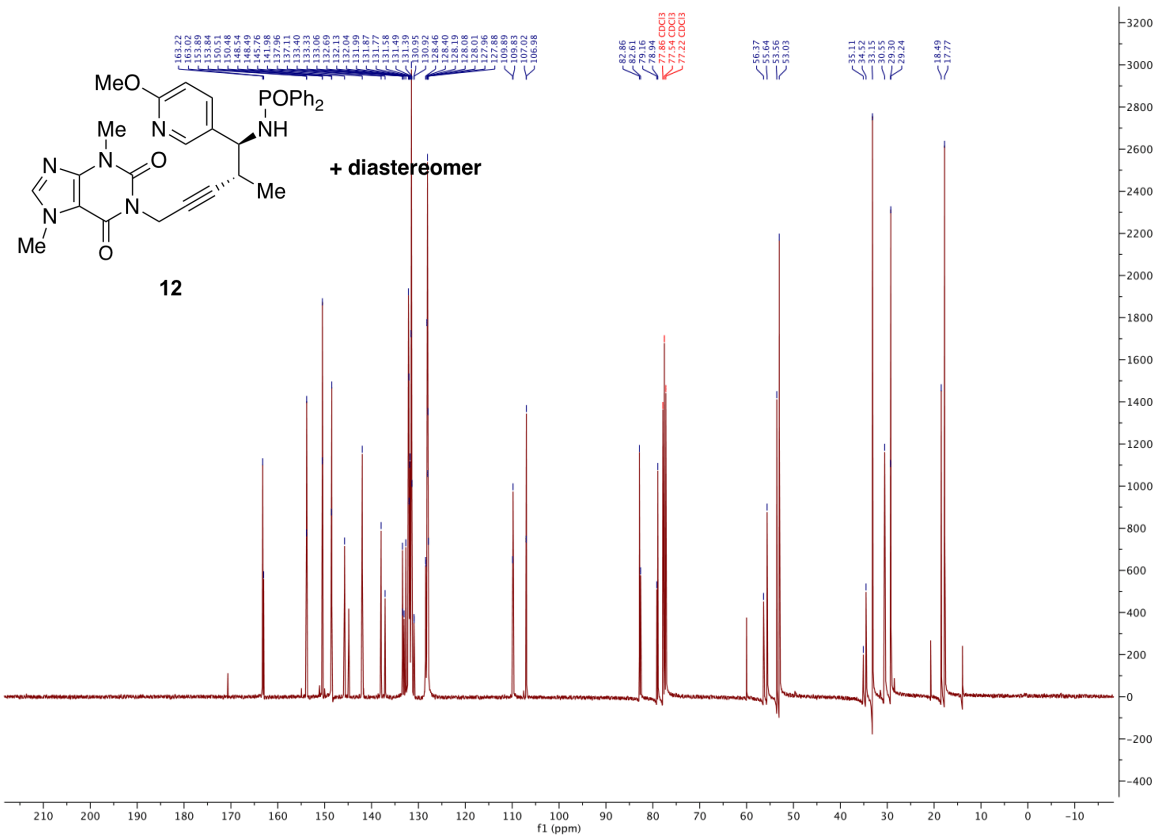

POPh2
NH
MeO
N
Me
Ph
+ diastereomer
11
163.50
157.14
141.68
138.46
132.32
132.23
131.95
131.86
131.73
131.65
128.49
128.46
128.37
128.33
128.28
128.21
125.60
115.58
109.25
82.73
81.76
77.32 CDCl3
77.00 CDCl3
76.71 CDCl3
59.20
53.28
34.66
34.17
31.12
30.42
18.61
18.18
f1 (ppm)

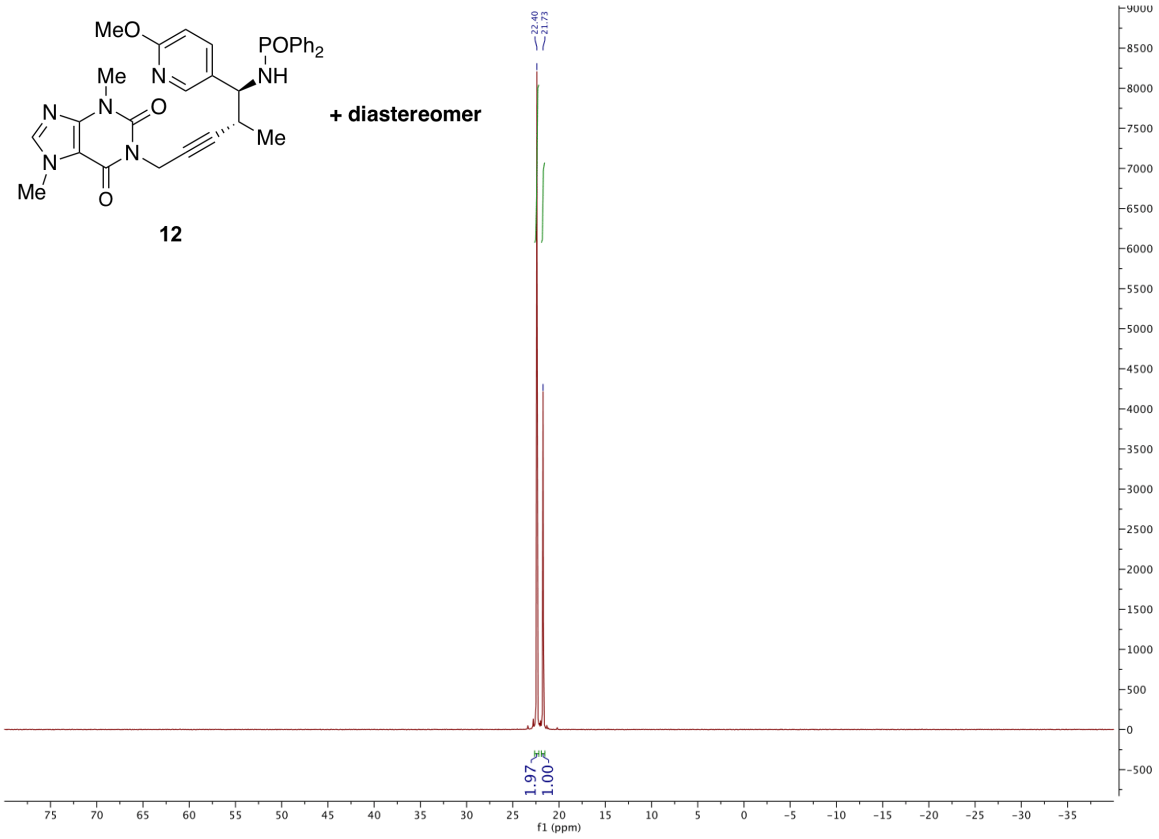

POPh2
NH
MeO
N
Me
Ph
+ diastereomer
22.09
22.10
13.93
1.00
f1 (ppm)

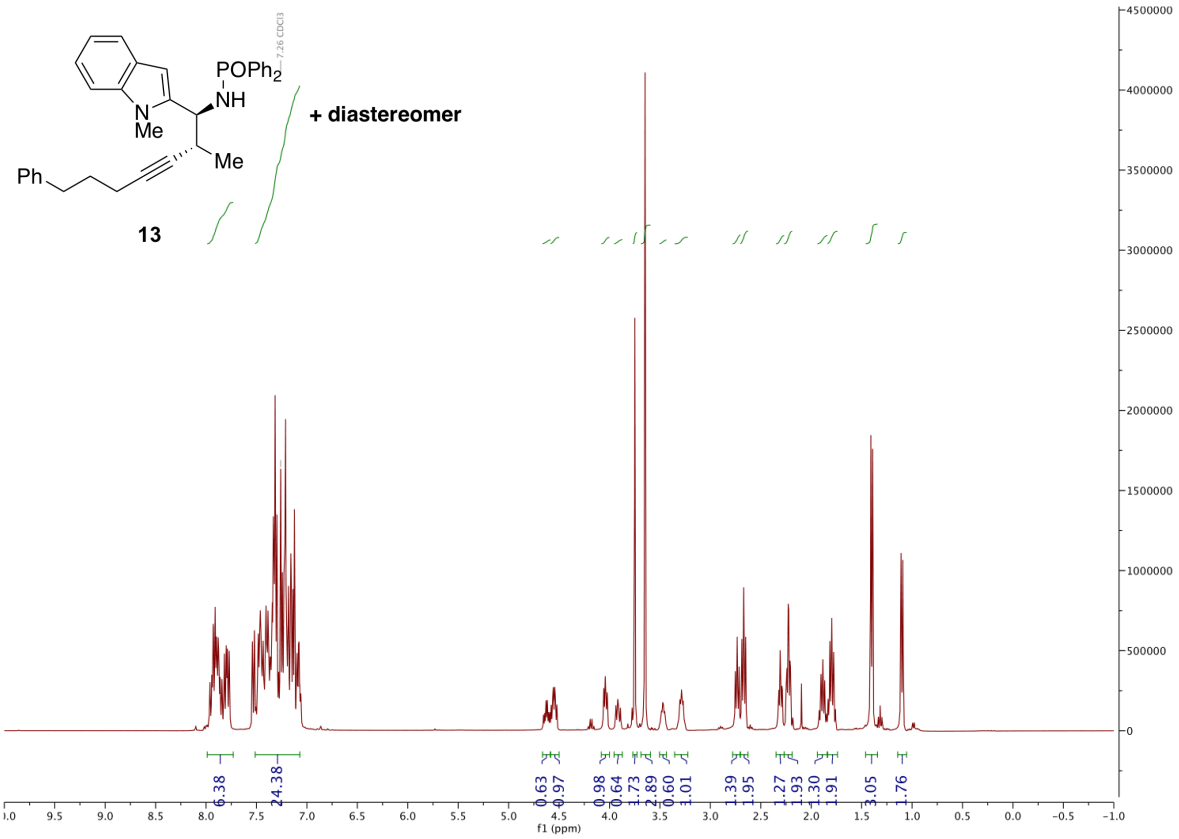
11

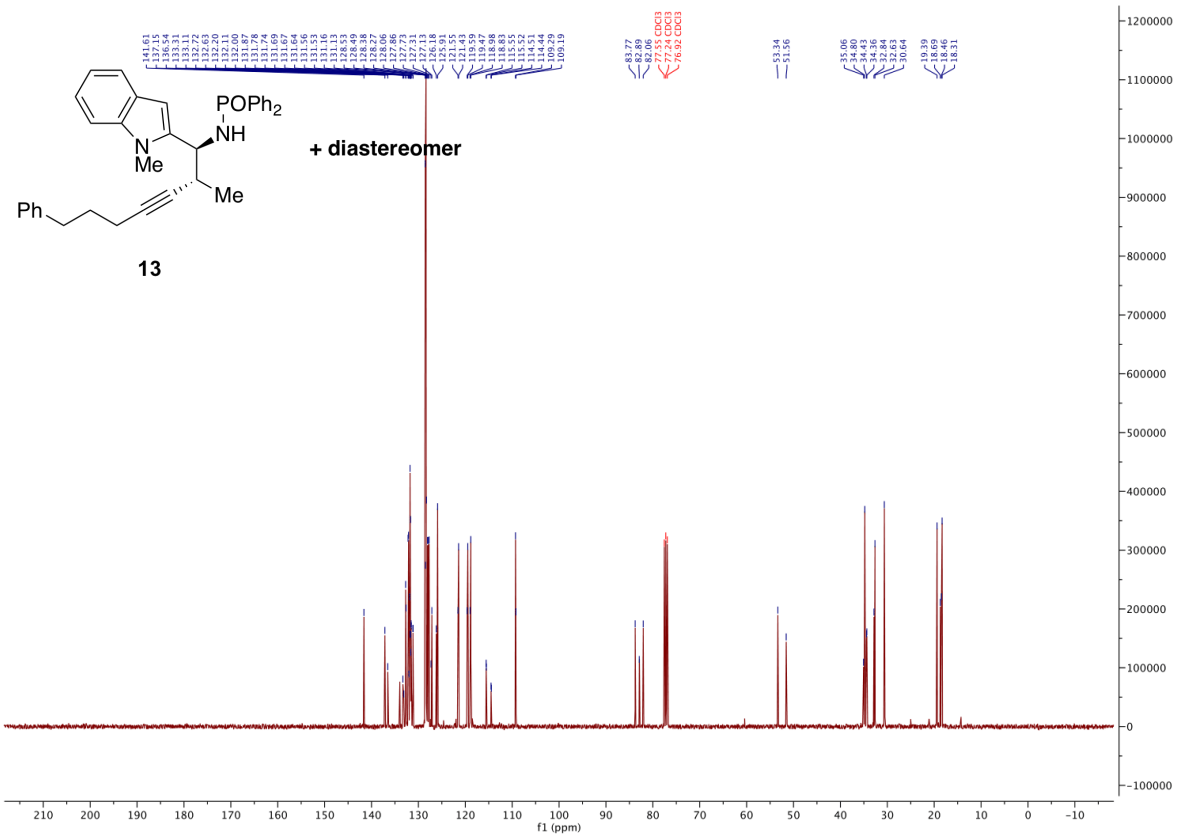

MeO
POPh2
NH
Me
N
N
O
N
N
Me
O
Me
+ diastereomer
0.48
0.95
7.54
8.92
0.98
0.54
1.09
2.50
1.67
1.82
2.90
1.37
3.59
1.52
2.75
1.00
0.49
1.54
2.90
f1 (ppm)

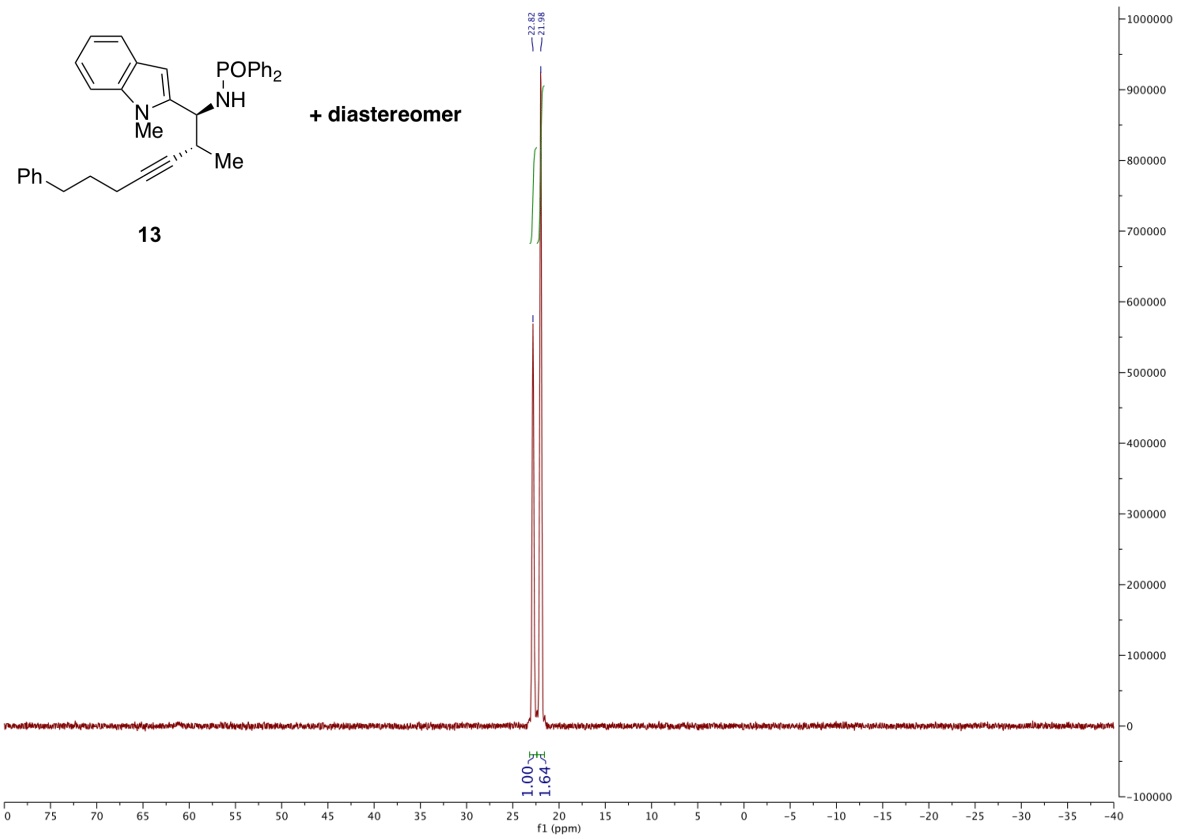
12

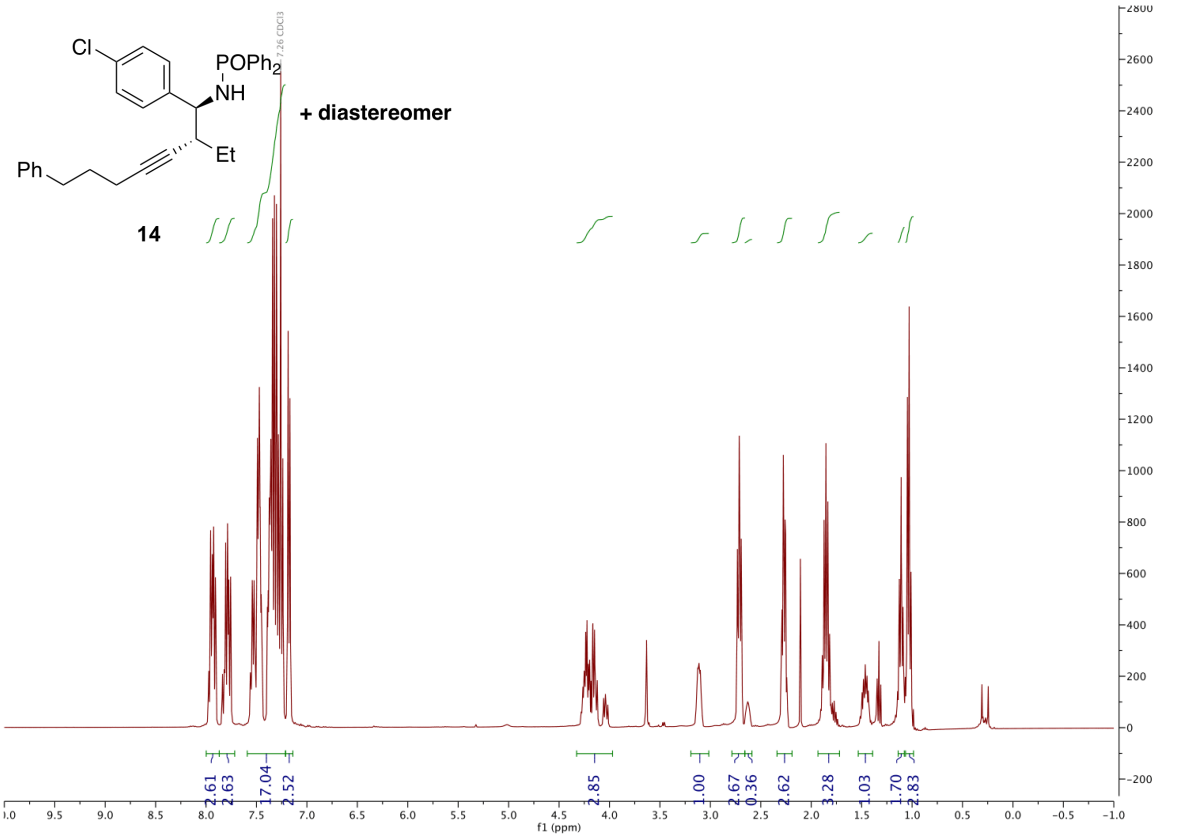

MeO
POPh2
NH
Me
N
O
Me
+ diastereomer
Me
12
f1 (ppm)

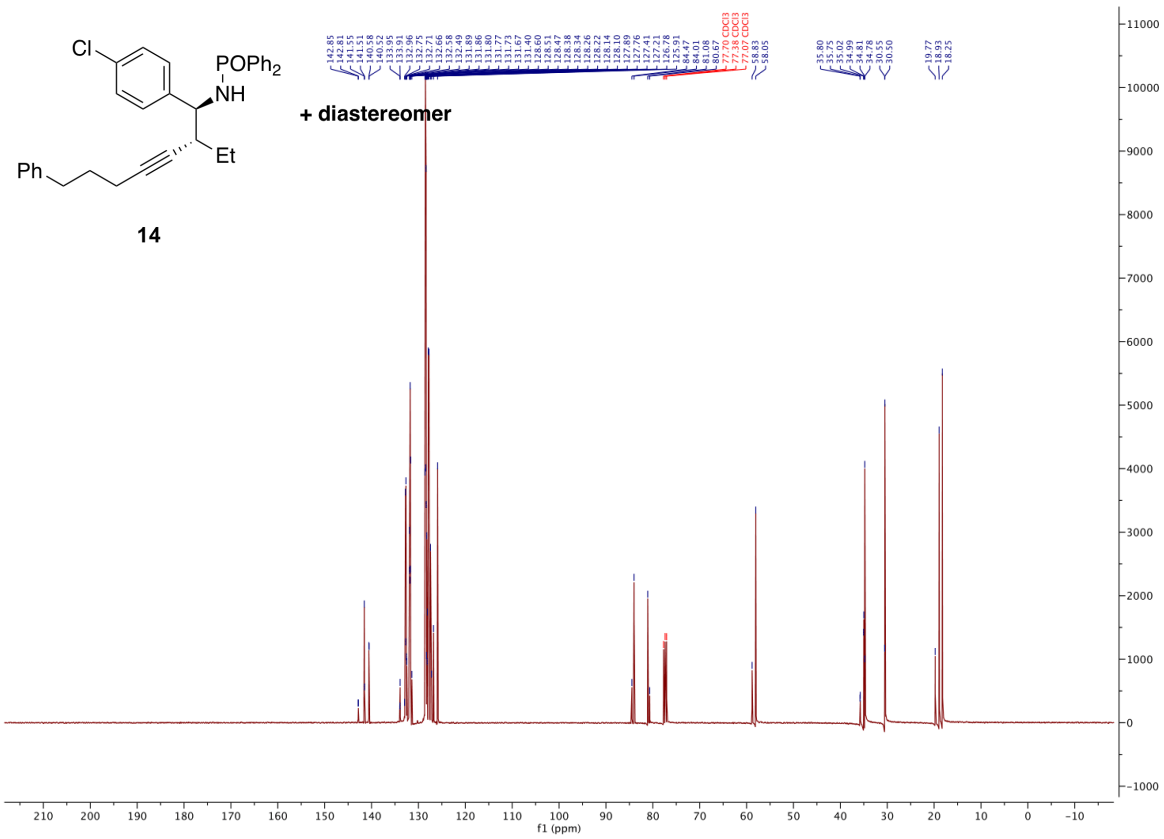

MeO
POPh2
NH
Me
N
O
Me
+ diastereomer
Me
12
22.40
21.73
1.97
1.00
f1 (ppm)

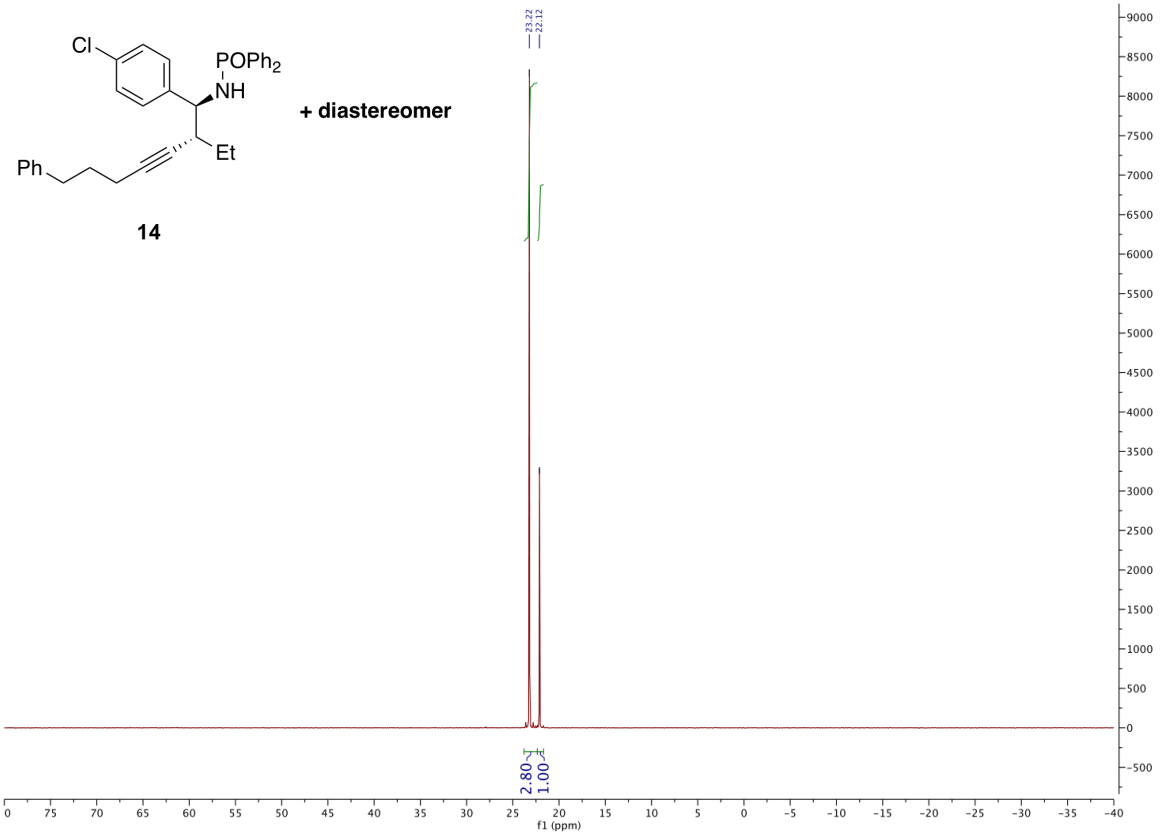

POPh2
NH
N
Me
Me
Ph
+ diastereomer
13
7.26 CDCl3
6.38
24.38
0.63
0.97
0.98
0.64
1.73
2.89
0.60
1.01
1.39
1.95
1.27
1.93
1.30
1.91
3.05
1.76
f1 (ppm)

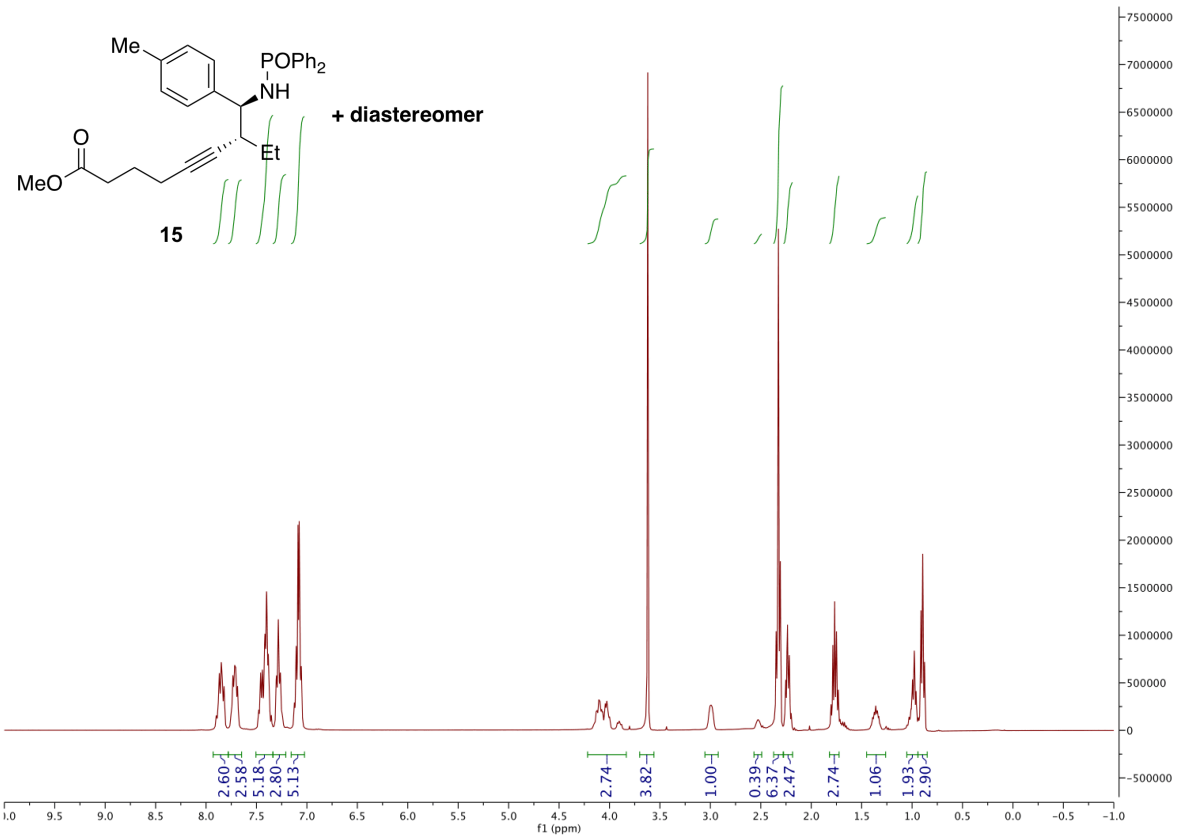

POPh2
NH
N
Me
Me
Ph
+ diastereomer
13
77.55 CDCl3
77.23 CDCl3
76.92 CDCl3
f1 (ppm)

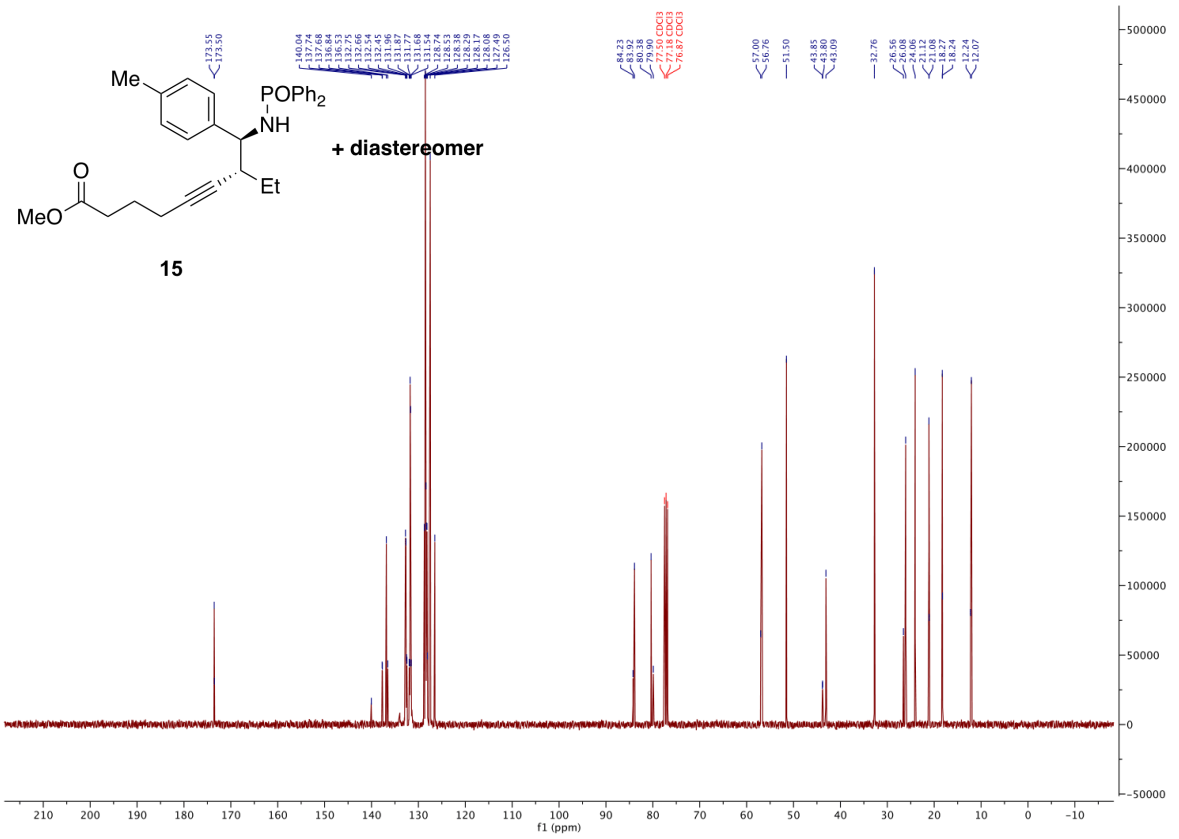

POPh2
NH
N
Me
Me
Ph
+ diastereomer
13
23.82
21.98
1.00
1.64
f1 (ppm)

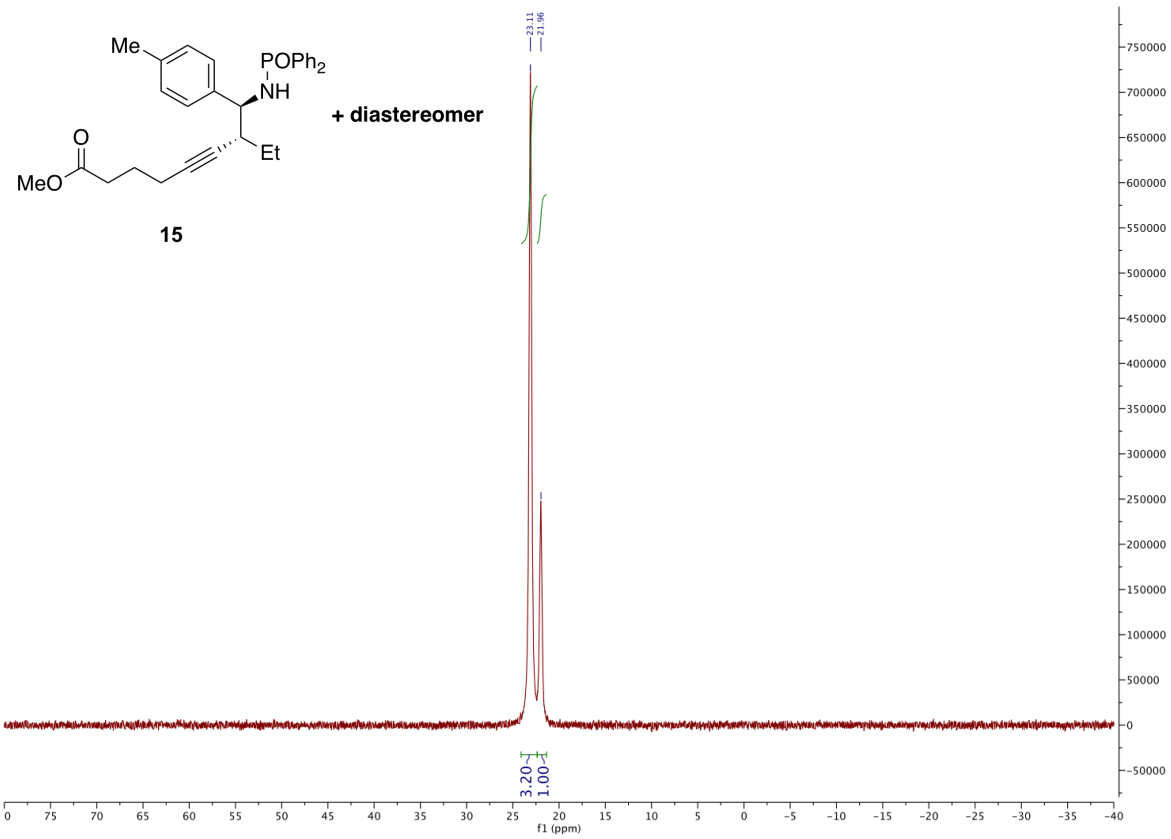

Cl
POPh2
NH
Et
Ph
+ diastereomer
14
7.26 CDCl3
2.61
2.63
17.04
2.52
2.85
1.00
2.67
0.36
2.62
3.28
1.03
1.70
2.83
f1 (ppm)


Cl
POPh2
NH
Et
Ph
14
+ diastereomer
f1 (ppm)

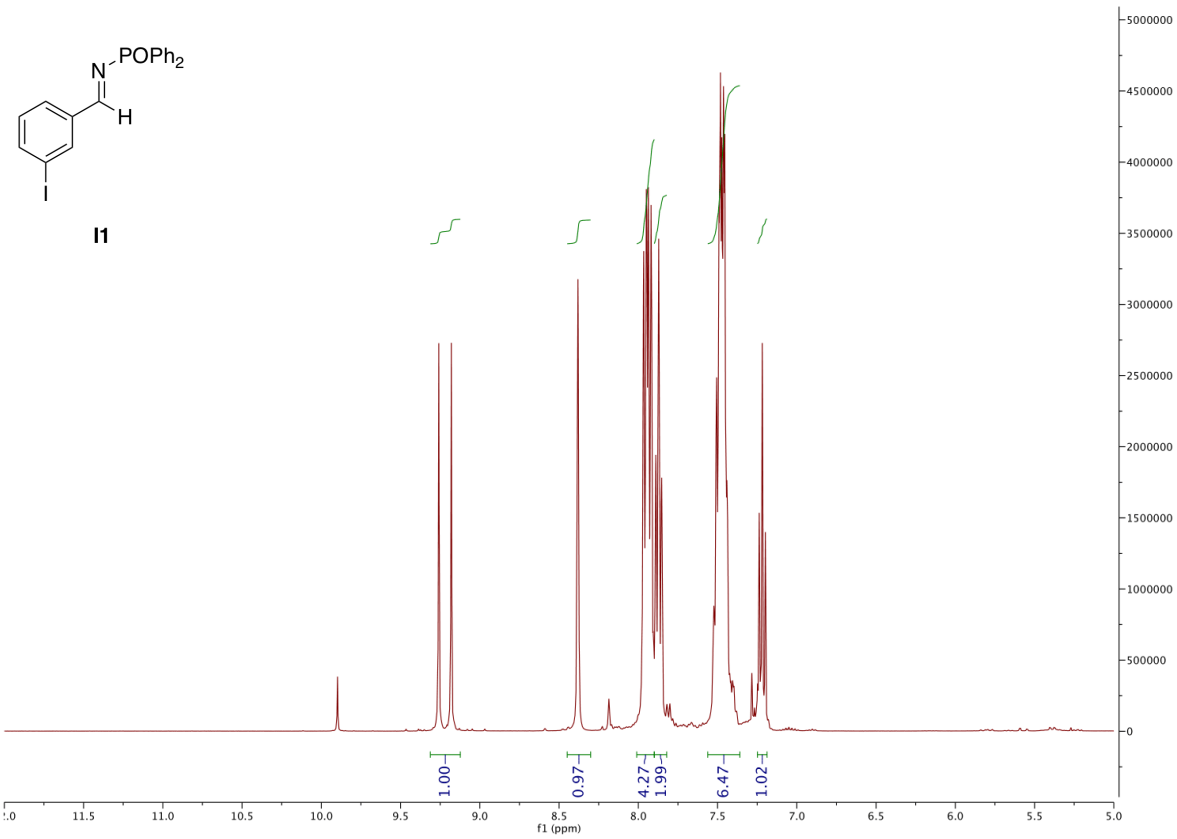

Cl
POPh2
NH
Et
Ph
14
+ diastereomer
23.22
22.12
2.80
1.00
f1 (ppm)

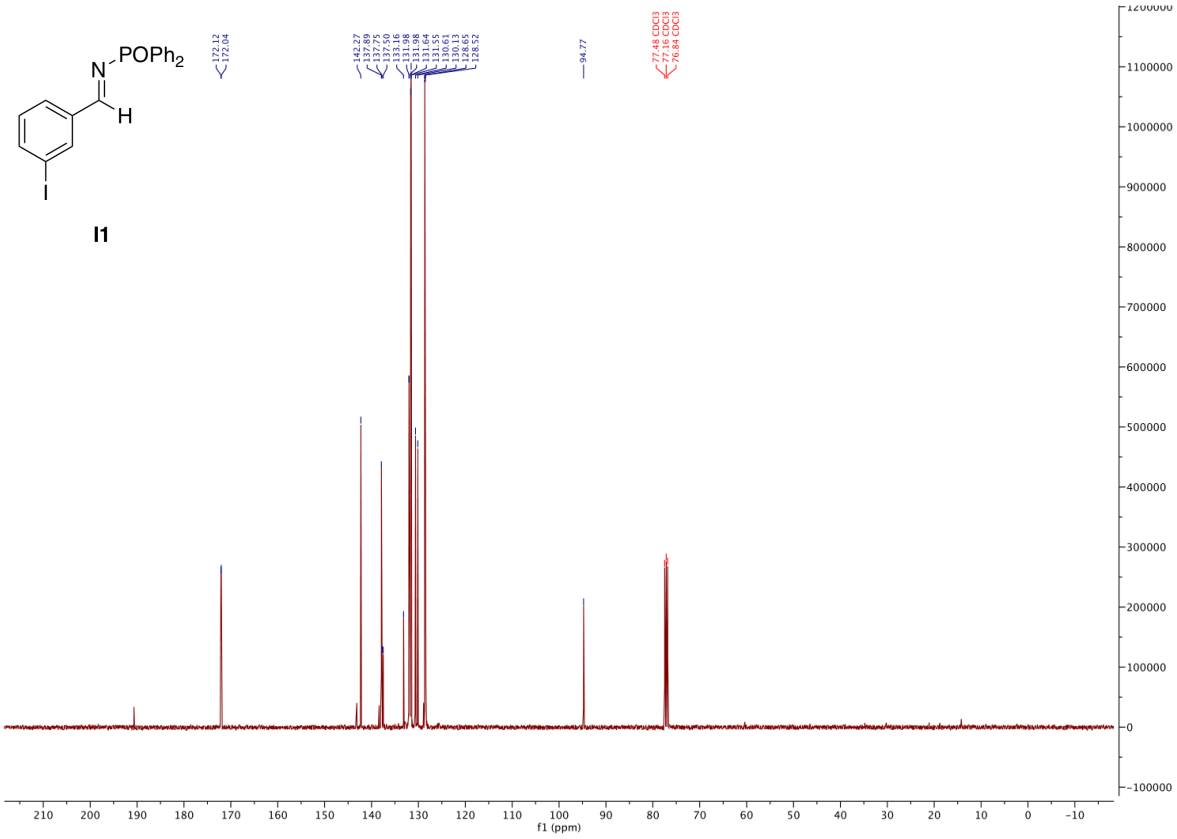

Me
POPh2
NH
Et
O
MeO
+ diastereomer
15
2.60
2.58
5.18
2.80
5.13
2.74
3.82
1.00
0.39
6.37
2.47
2.74
1.06
1.93
2.90
f1 (ppm)

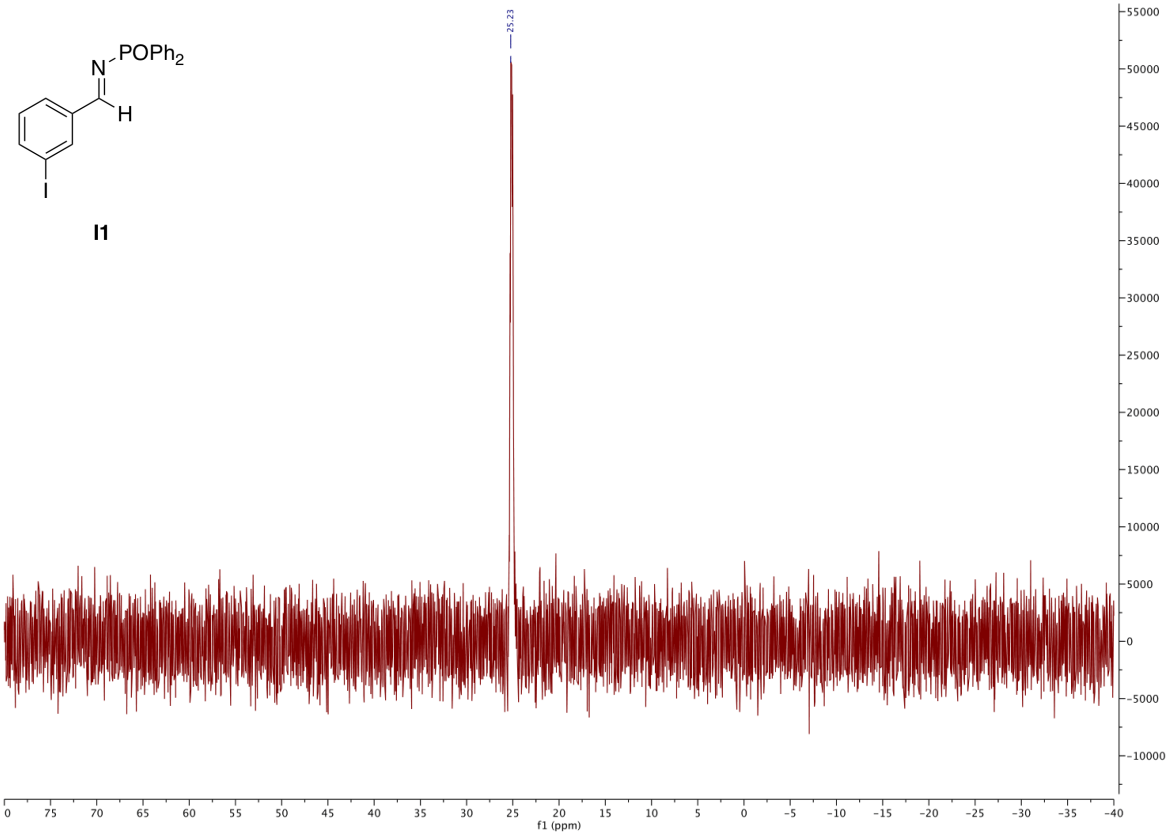

Me
POPh2
NH
Et
O
MeO
+ diastereomer
15
f1 (ppm)



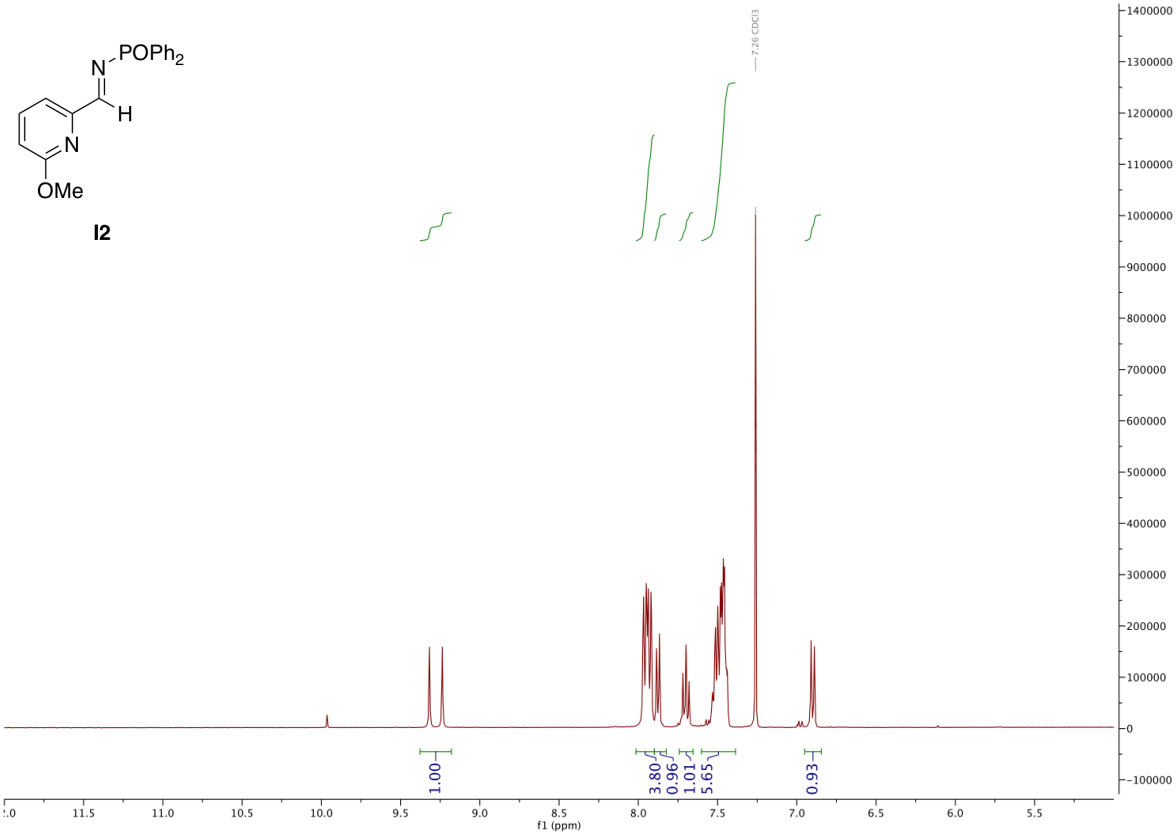
15


POPh2
N
H
I
I1
1.00
0.97
4.27
1.99
6.47
1.02
f1 (ppm)

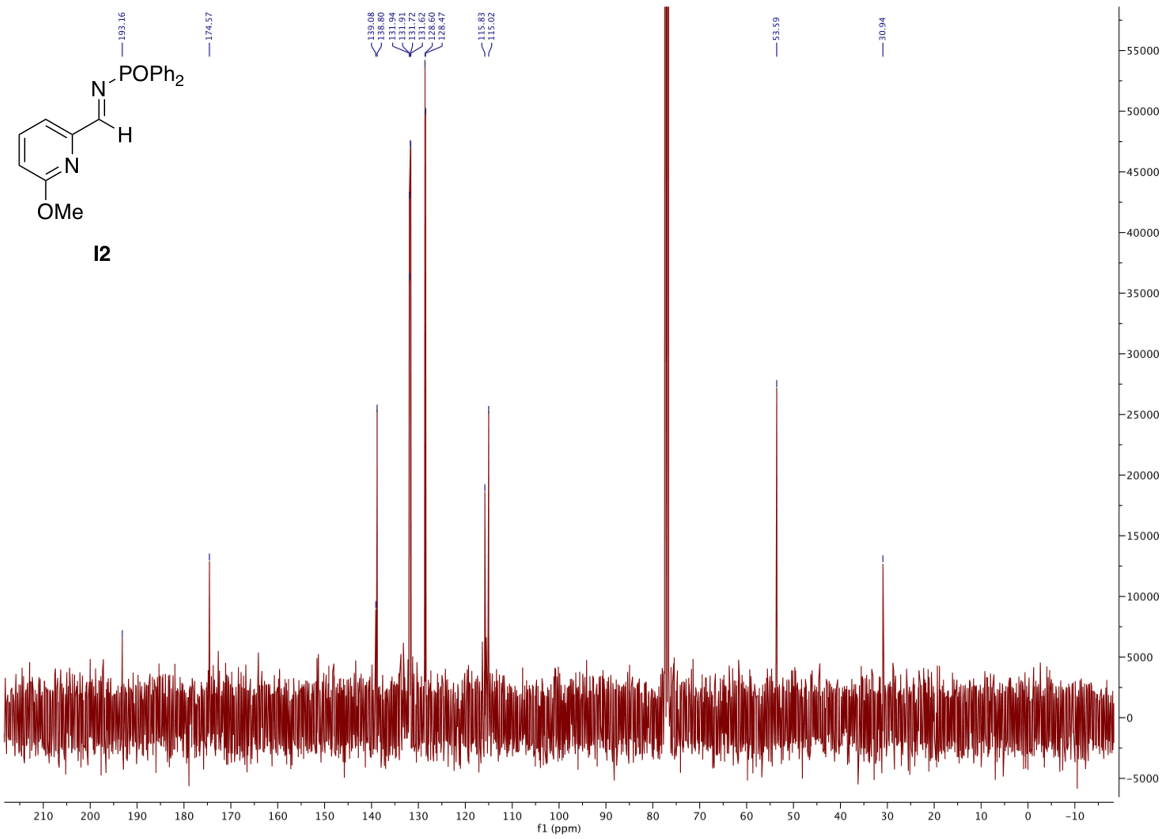

POPh2
N
H
I
I1
172.12
172.04
142.27
137.89
137.75
137.70
133.16
131.98
131.88
131.64
131.55
130.65
130.13
128.65
128.52
94.77
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
f1 (ppm)

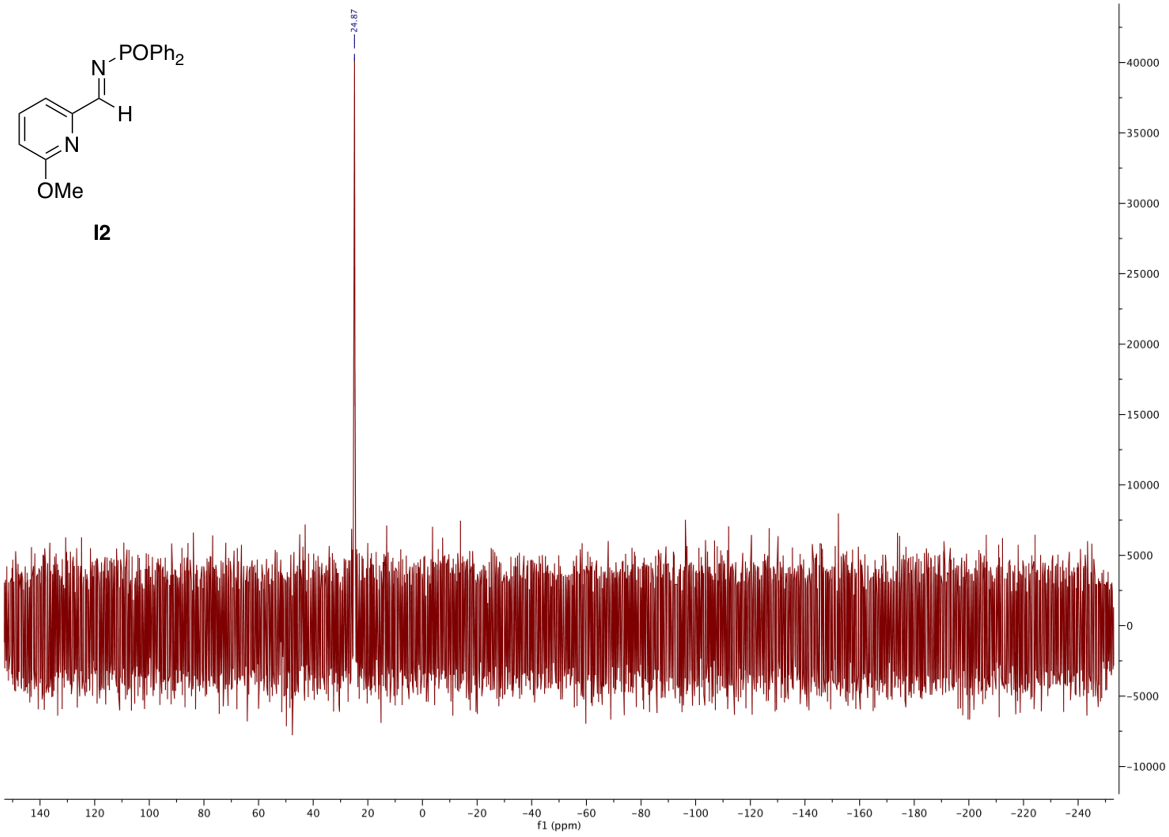

N
POPh2
H
I
25.23
f1 (ppm)

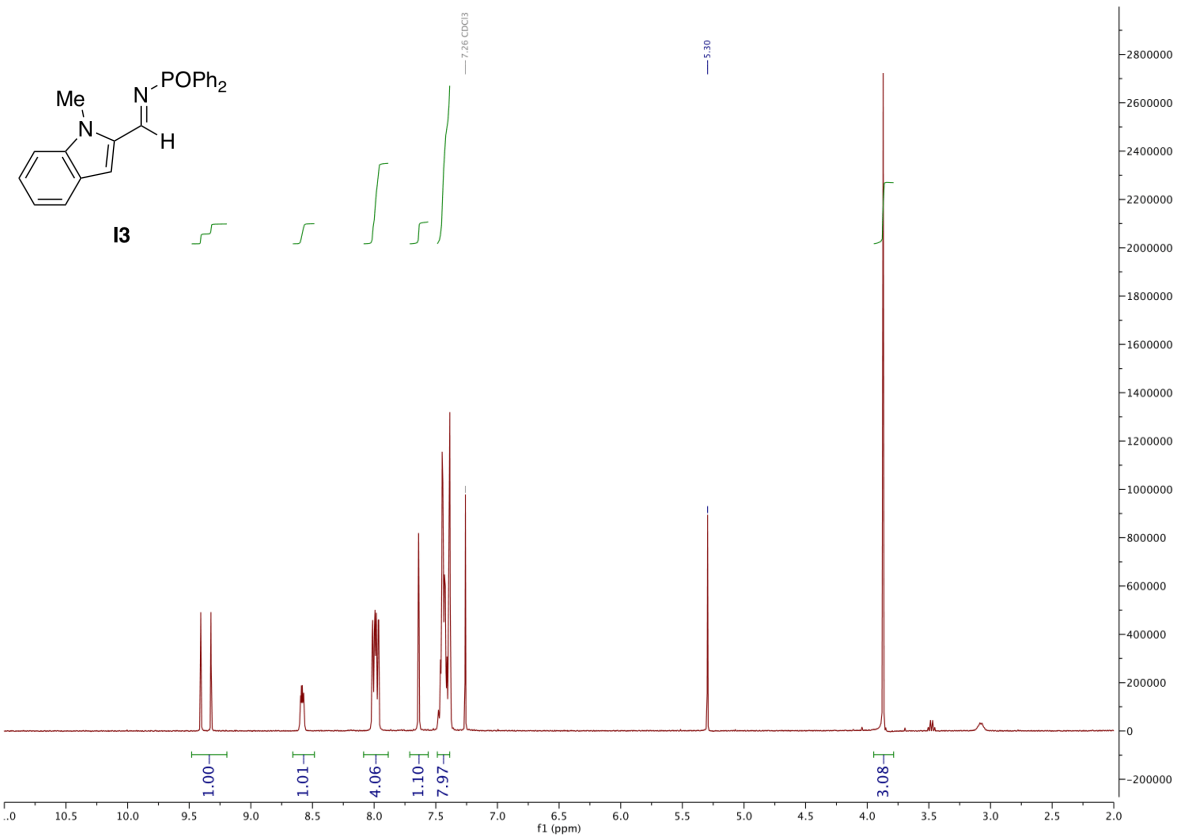
I1

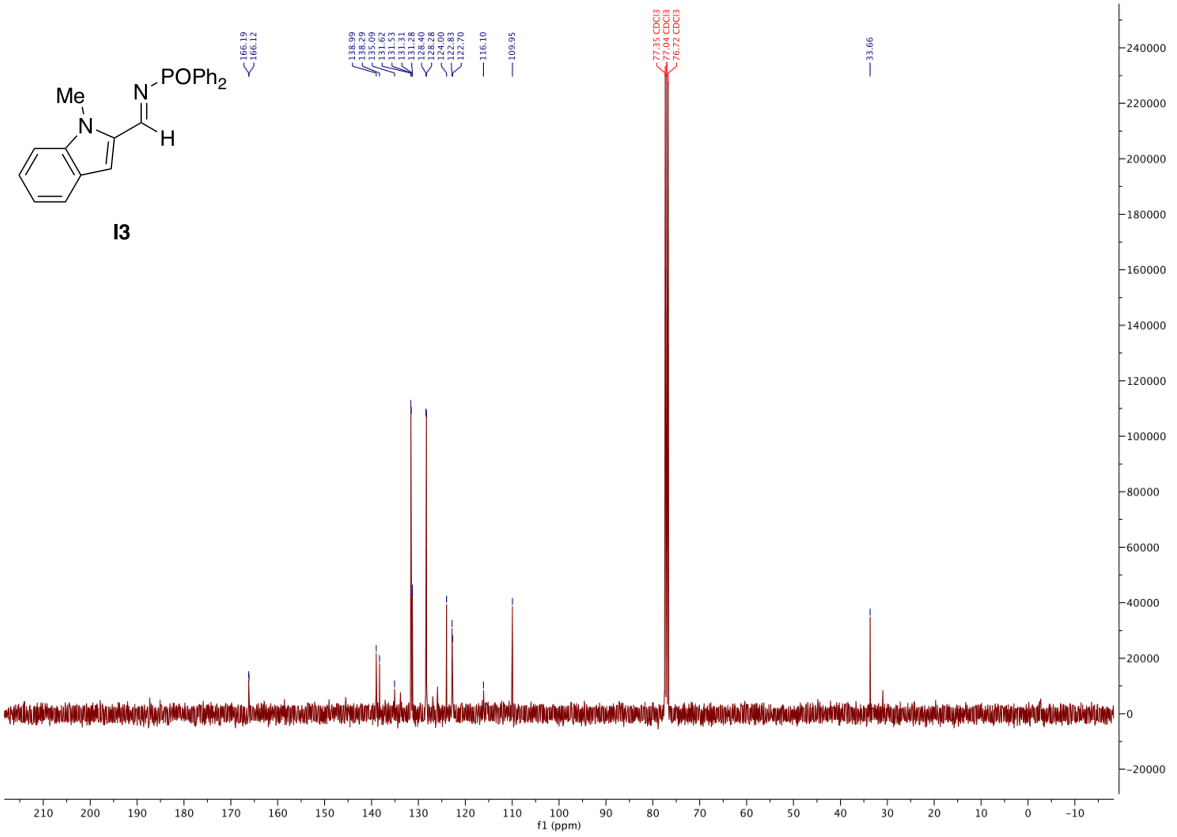

N
POPh2
H
N
OMe
7.26 CDCl3
1.00
3.80
0.96
1.01
5.65
0.93
f1 (ppm)

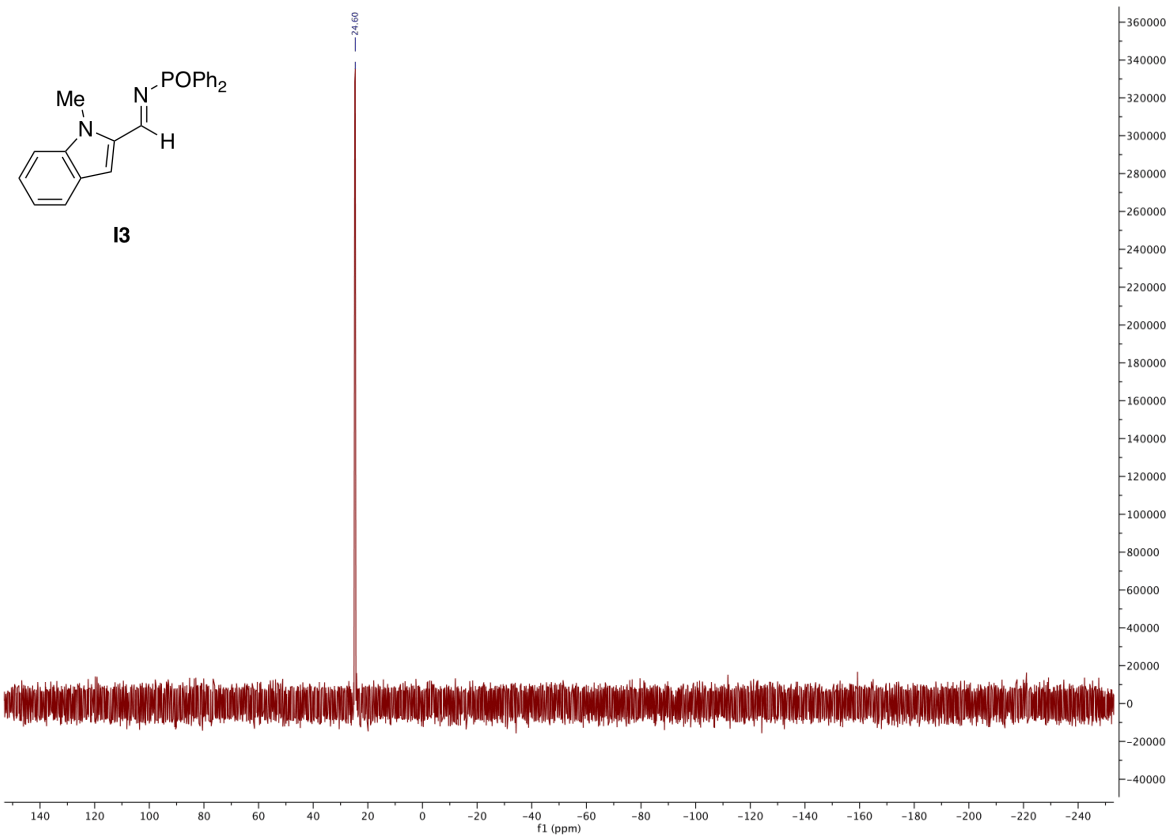
I2


193.16
174.57
139.08
138.80
131.94
131.91
131.72
131.62
128.60
128.47
115.83
115.02
53.59
30.94
POPh2
N
H
N
OMe
I2
f1 (ppm)

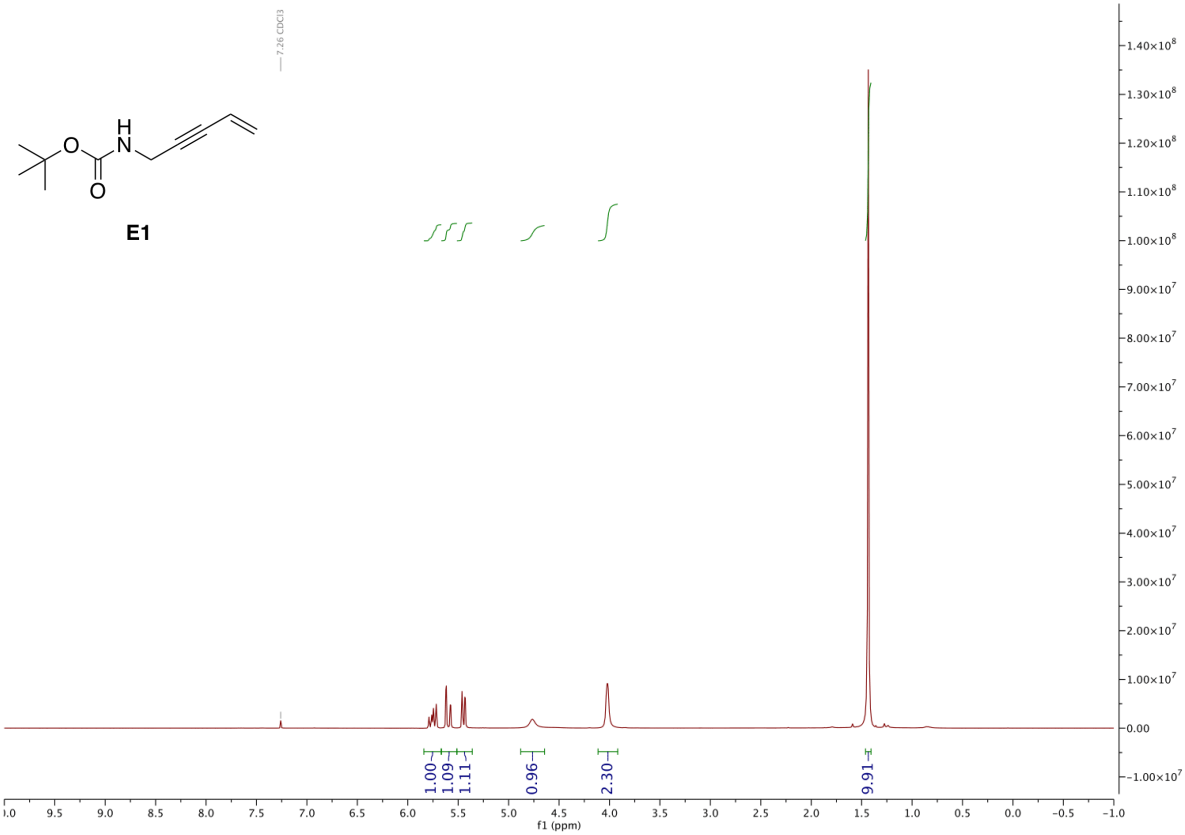

24.87
POPh2
N
H
N
OMe
I2
f1 (ppm)

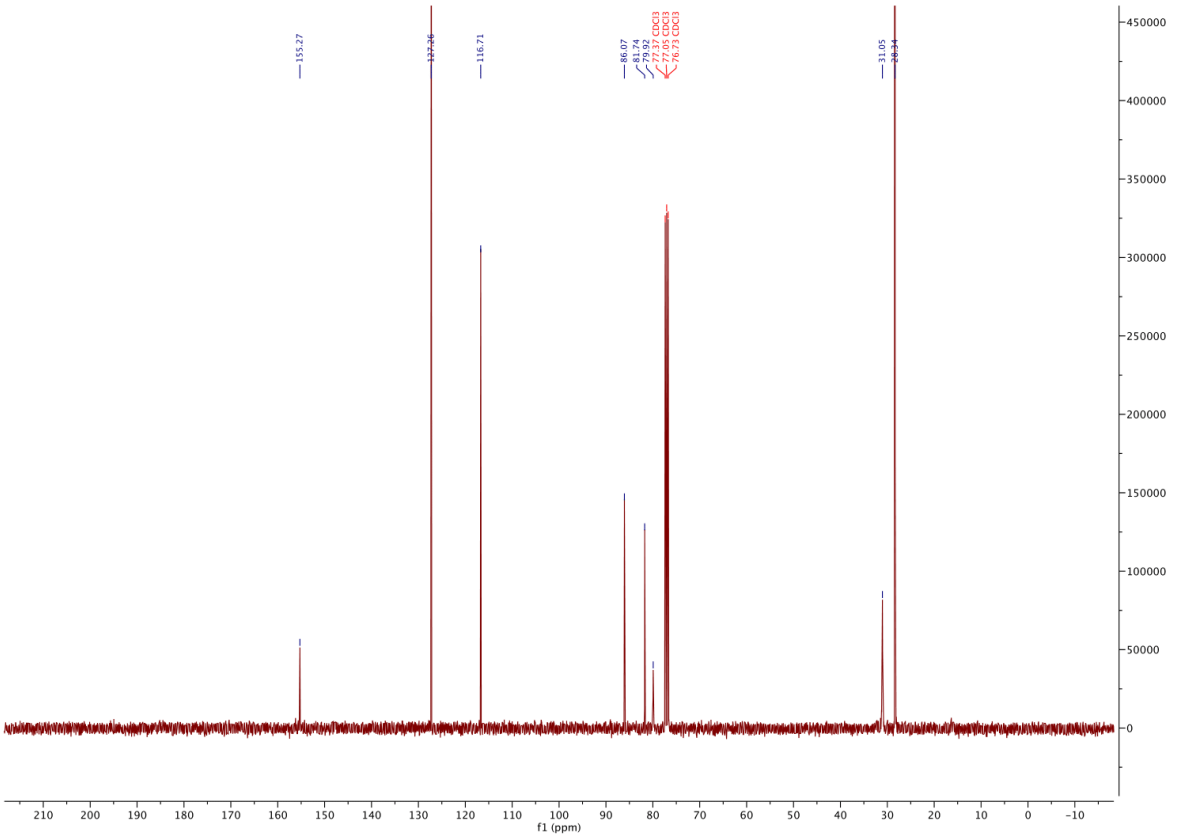

Me
N
N
POPh2
H
I3
7.26 CDCl3
5.30
1.00
1.01
4.06
1.10
7.97
3.08
f1 (ppm)

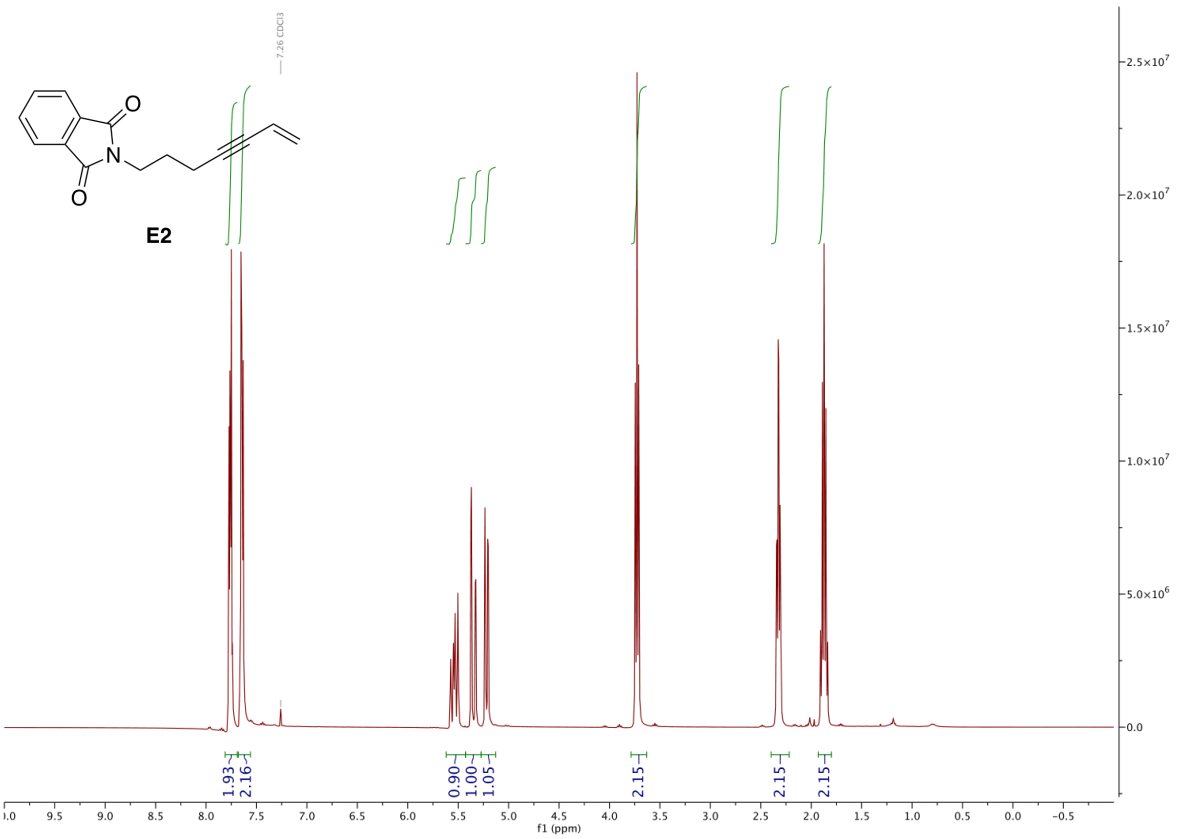

Me
N
N
POPh2
H
I3
166.19
166.12
138.99
138.79
135.09
131.62
131.53
131.31
131.28
128.40
128.28
124.00
122.83
122.70
116.10
109.95
77.35 CDCl3
77.04 CDCl3
76.72 CDCl3
33.66
f1 (ppm)

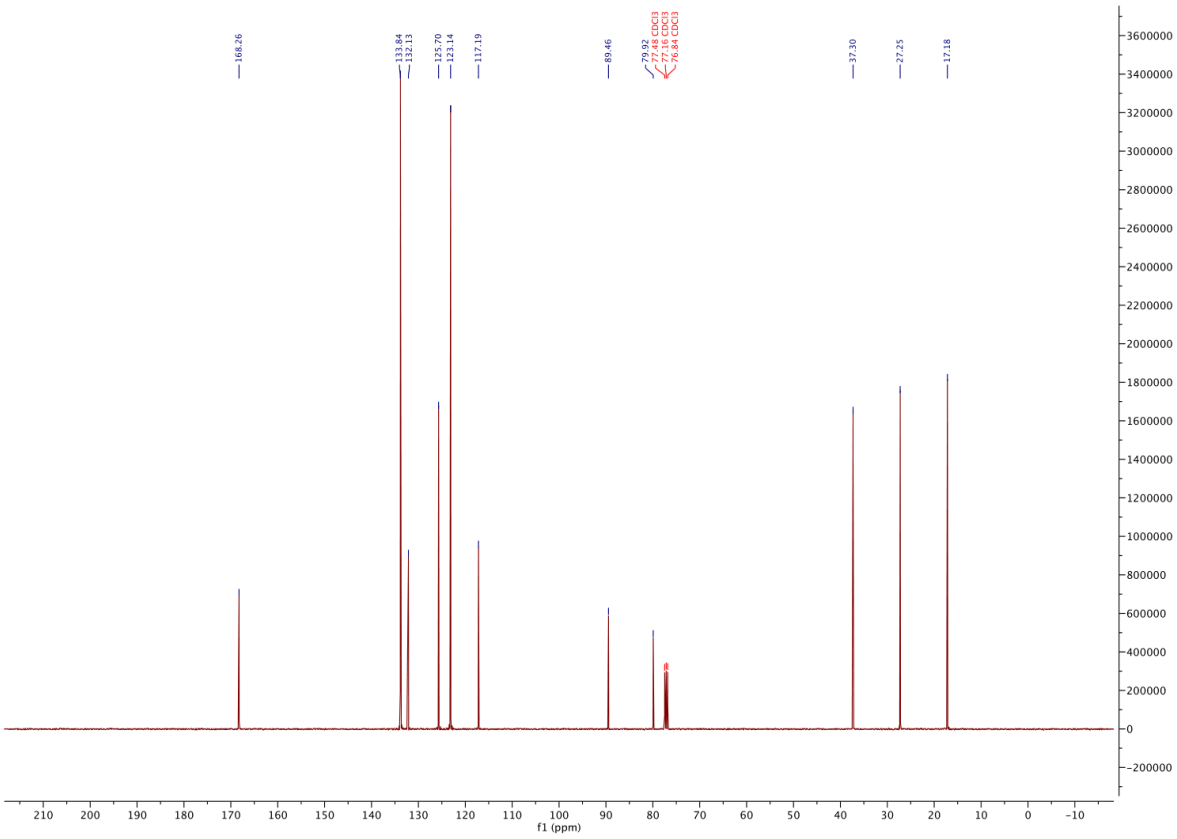

Me
N
N
POPh2
H
24.60
360000
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
-40000
140
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

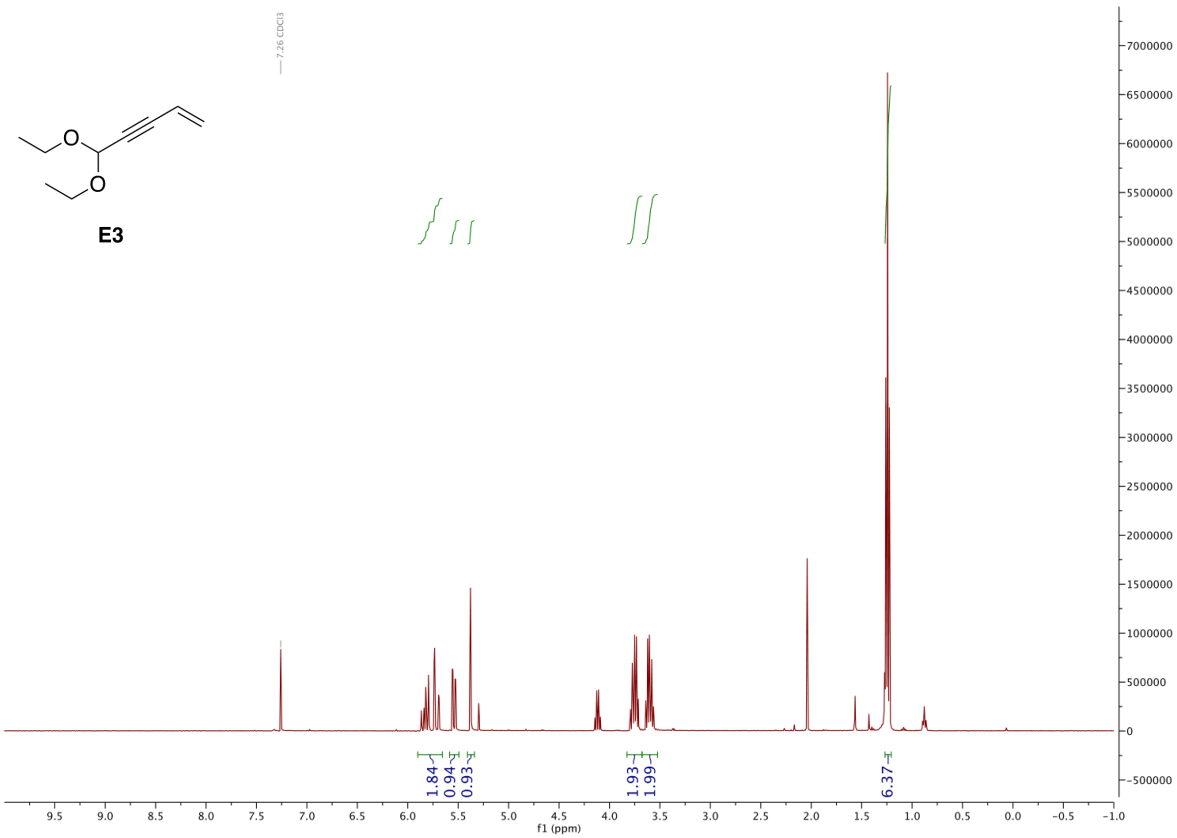
I3

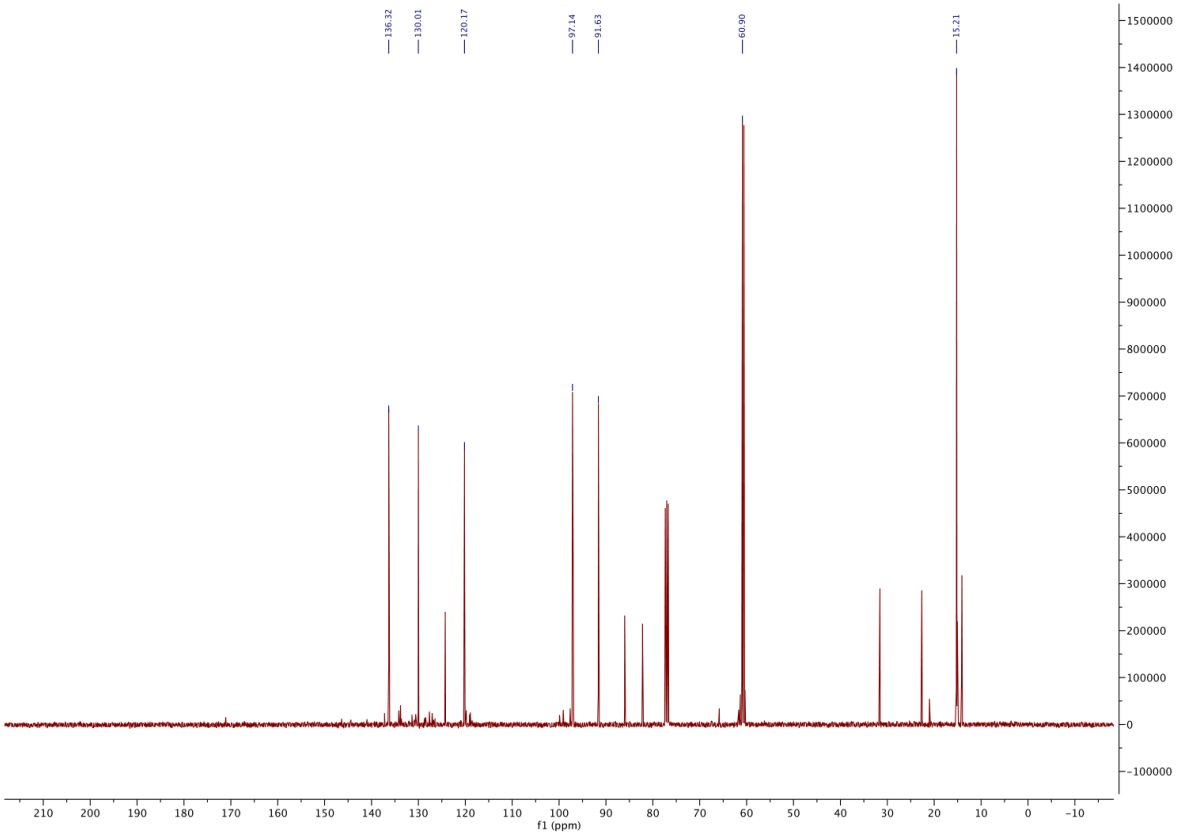

E1
7.26 CDCl3
1.00
1.09
1.11
0.96
2.30
9.91
f1 (ppm)


155.27
137.26
116.71
86.07
81.74
79.92
77.32 CDCl3
77.05 CDCl3
76.73 CDCl3
31.05
28.54
f1 (ppm)


E2
7.26 CDCl3
1.93
2.16
0.90
1.00
1.05
2.15
2.15
2.15
f1 (ppm)


168.26
133.84
132.13
125.70
123.14
117.19
89.46
79.92
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
37.30
27.25
17.18
f1 (ppm)


E3
7.26 CDCl3
1.84
0.94
0.93
1.93
1.99
6.37
f1 (ppm)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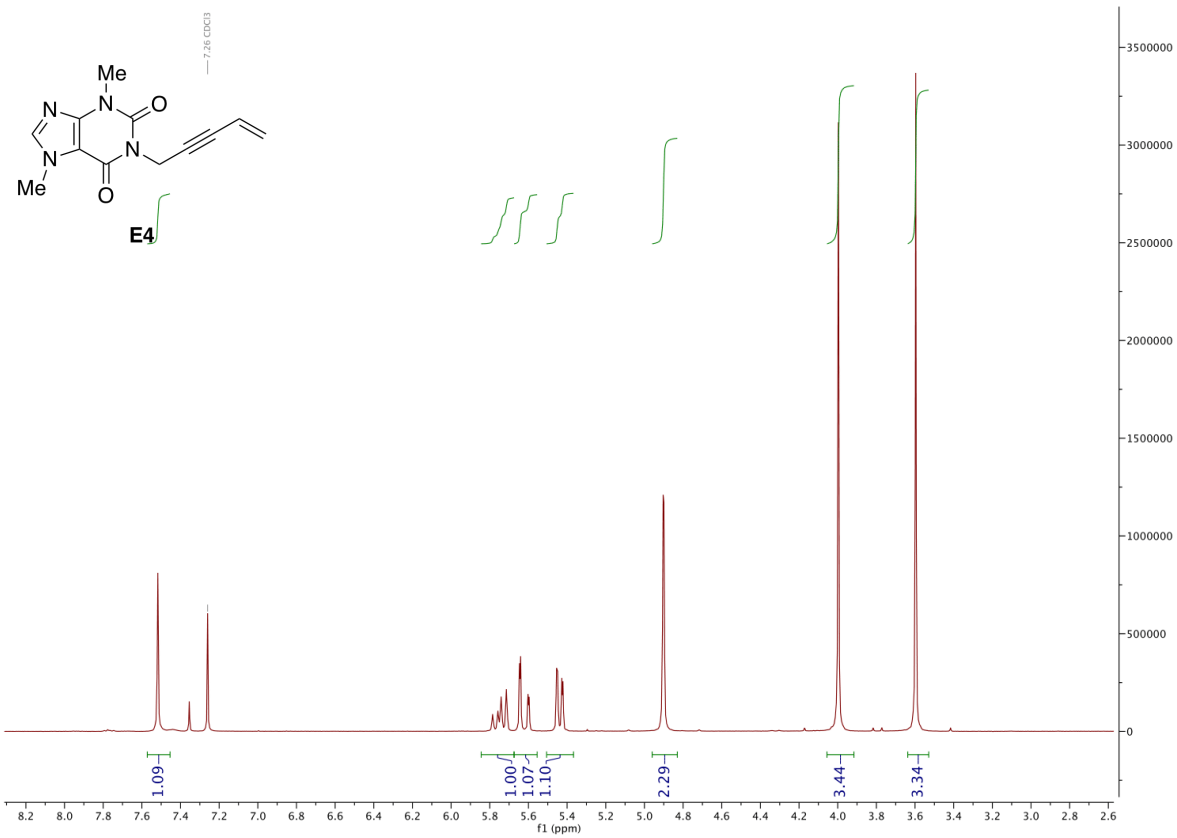
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O
N
N
Me
O
E4
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1.07
1.10
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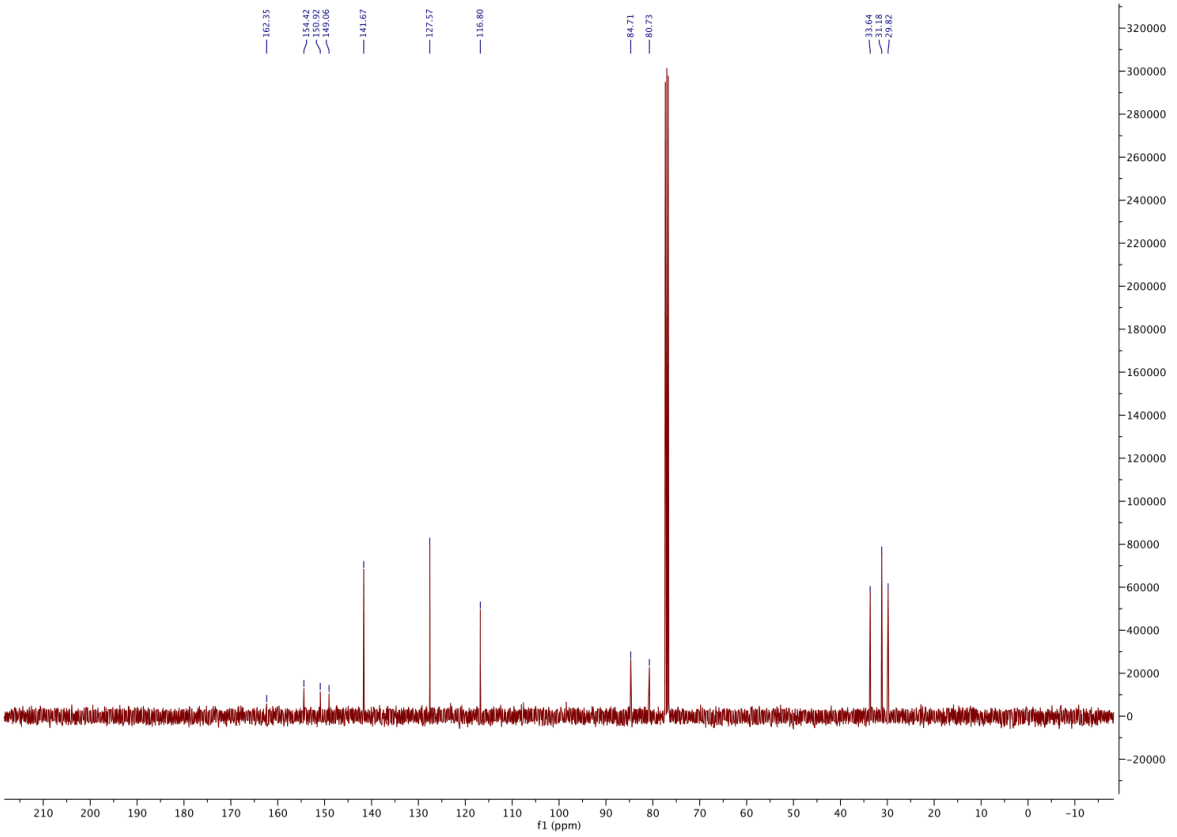
3.34
f1 (ppm)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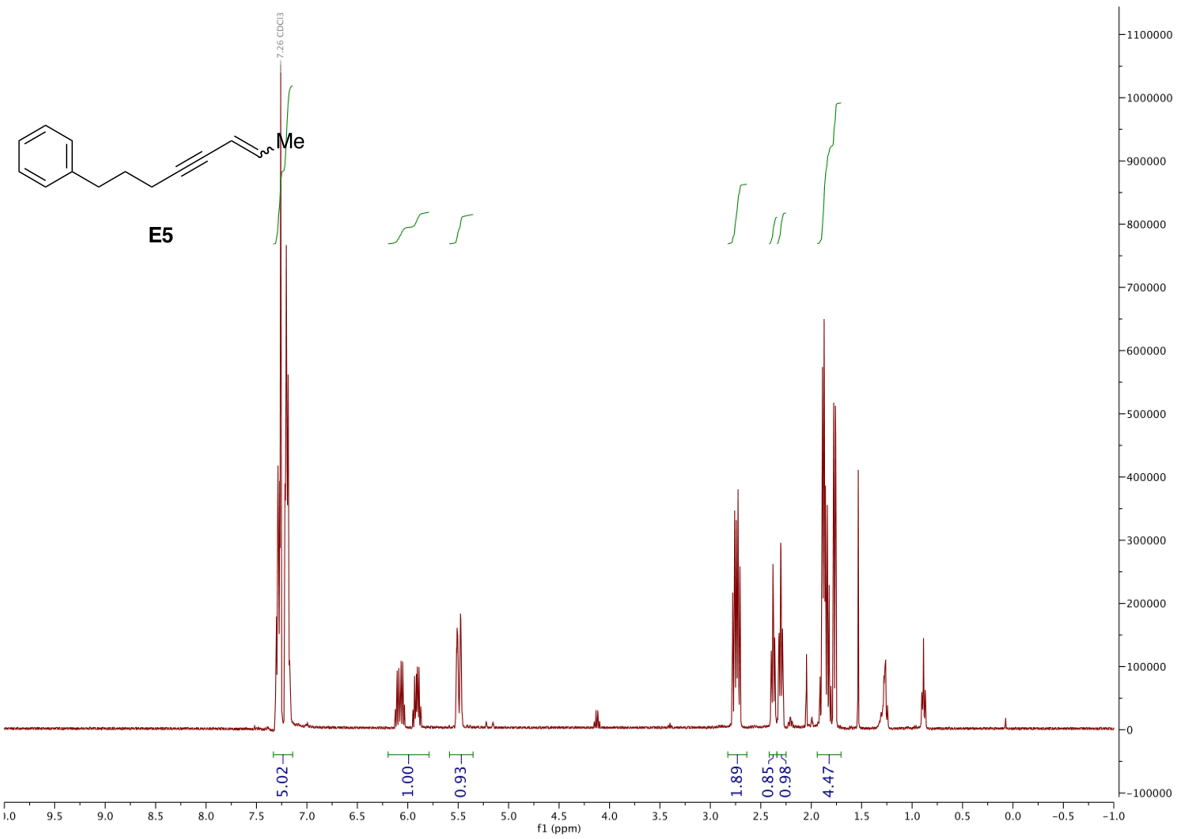
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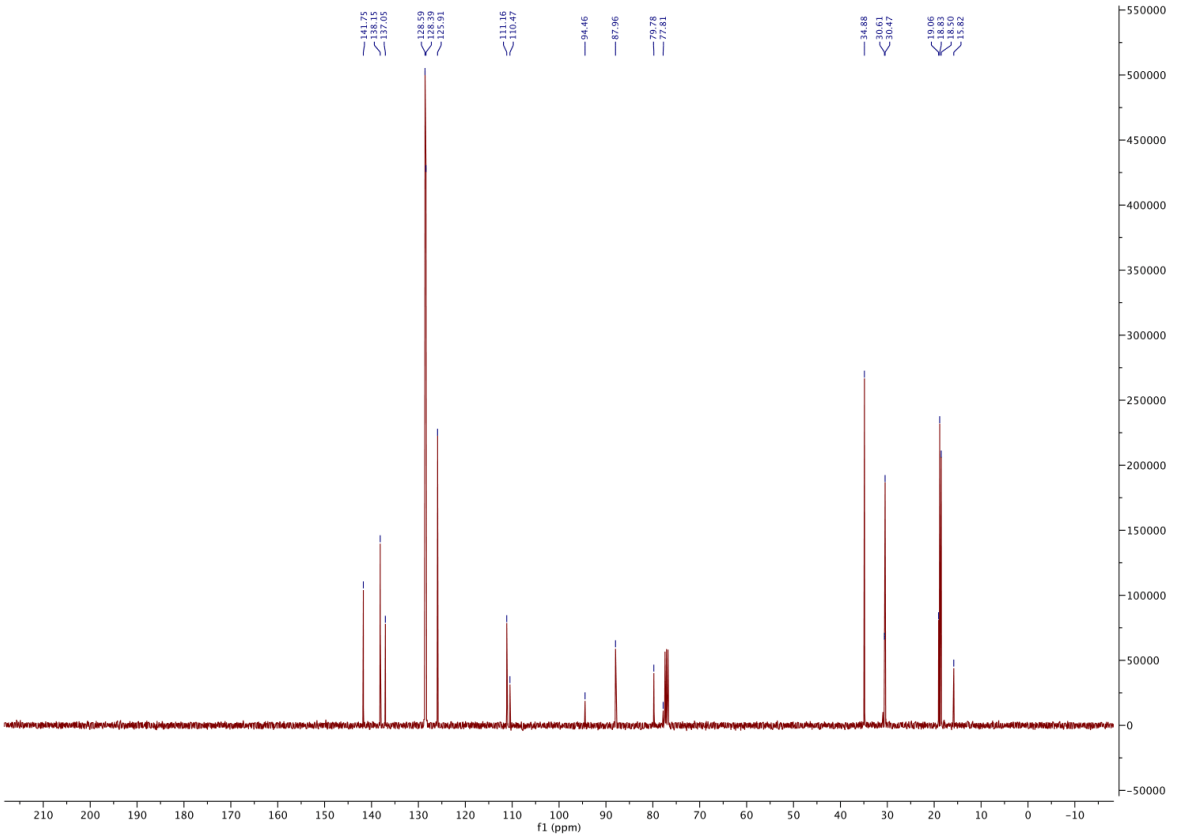
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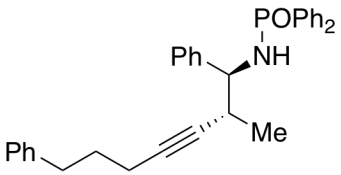
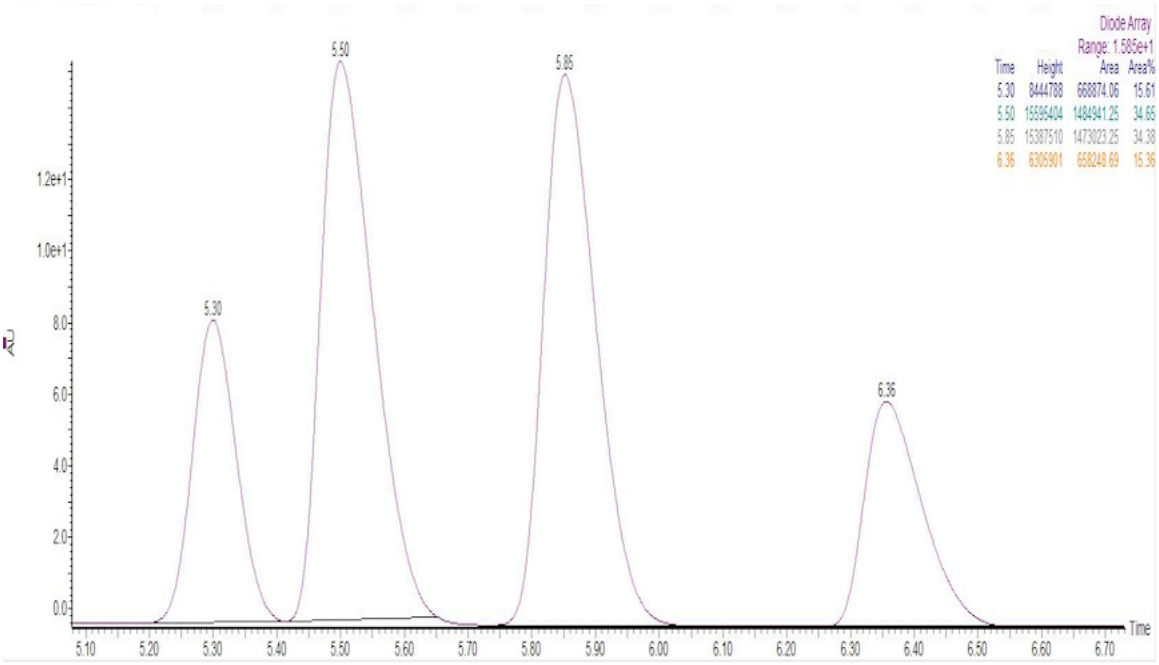


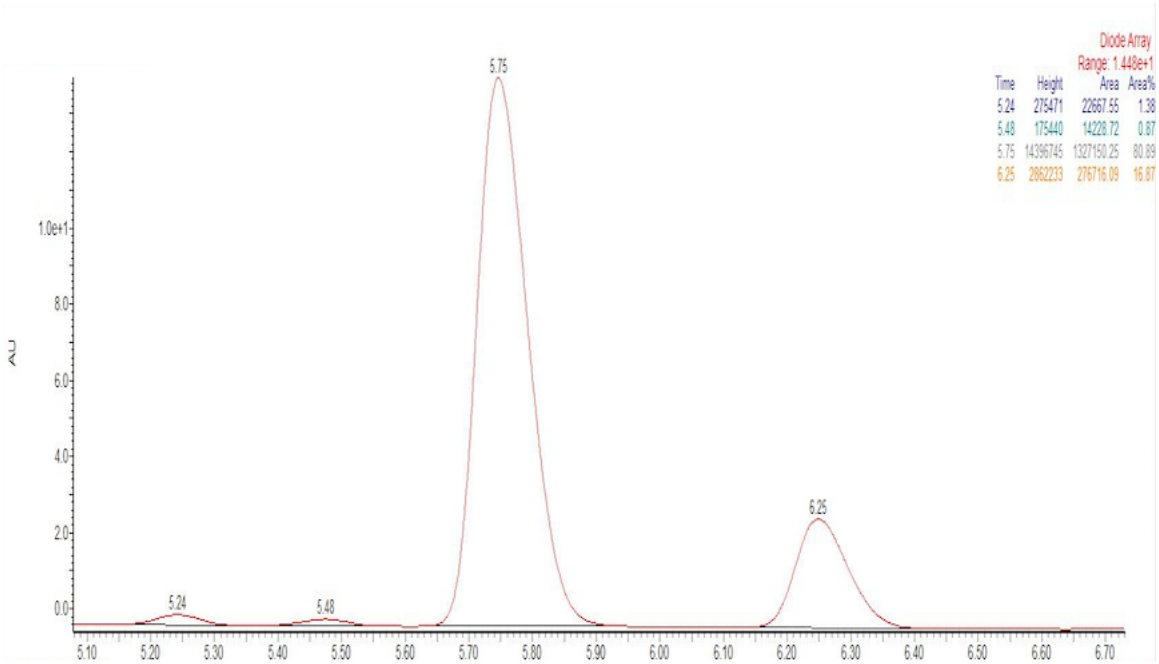
+ diastereomer

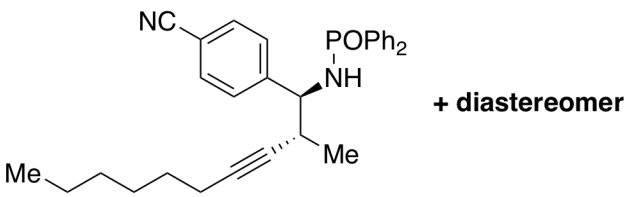
1

Trace of racemic compound



Trace of enantioenriched compound





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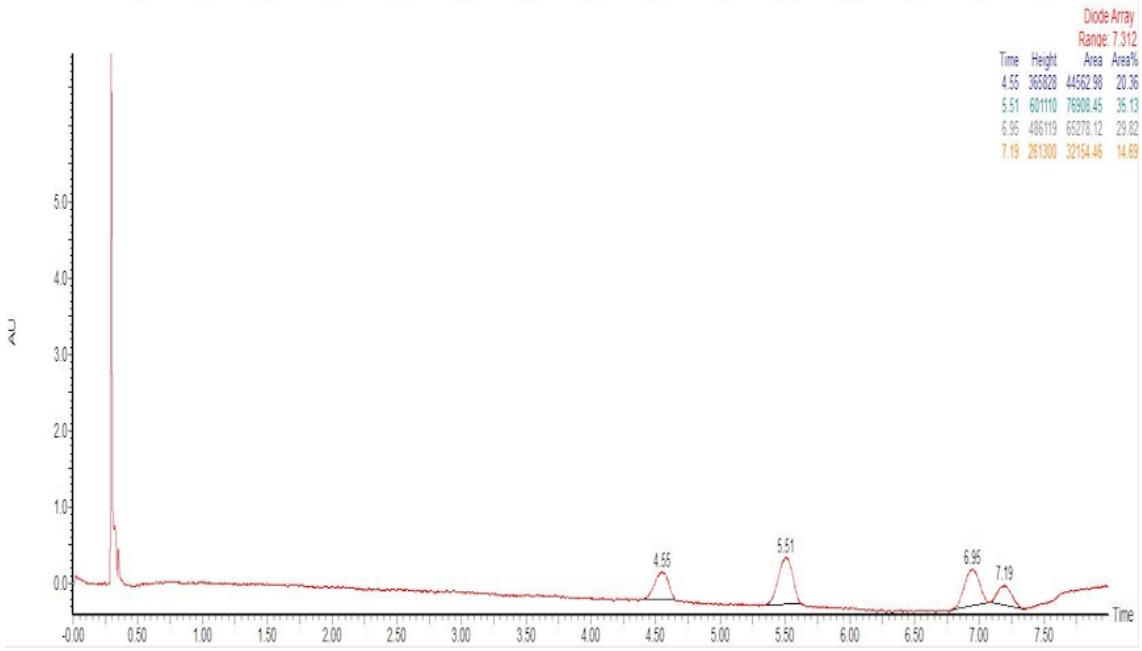
Trace of racemic compound



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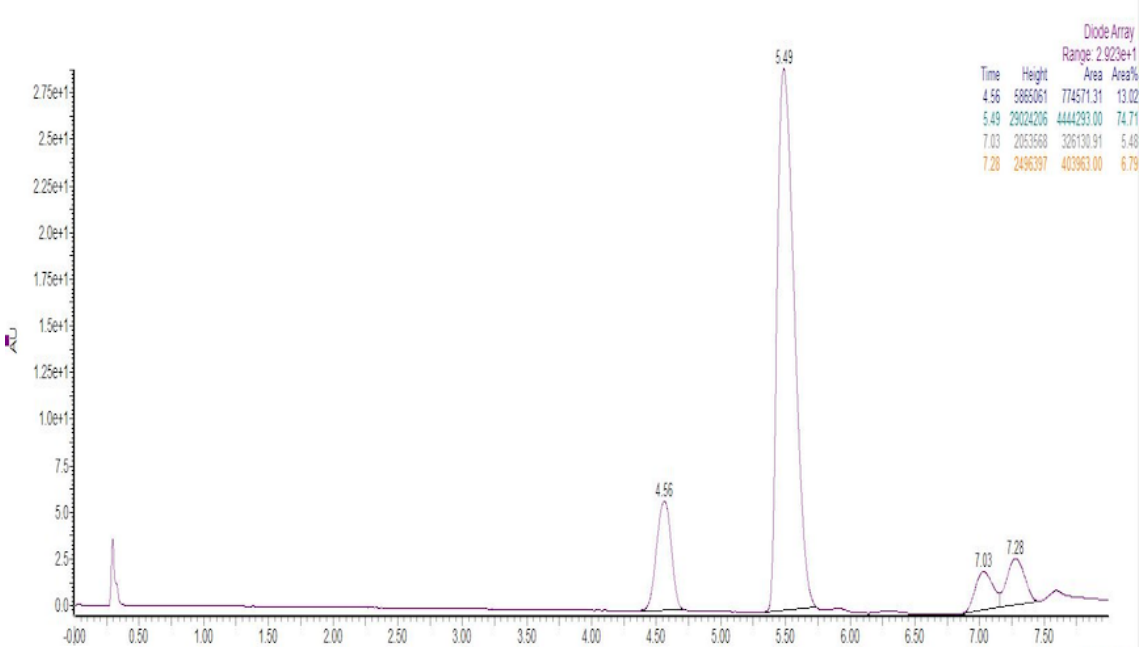
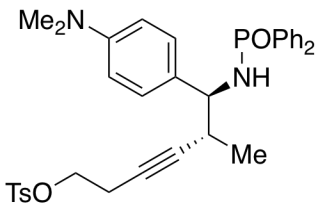
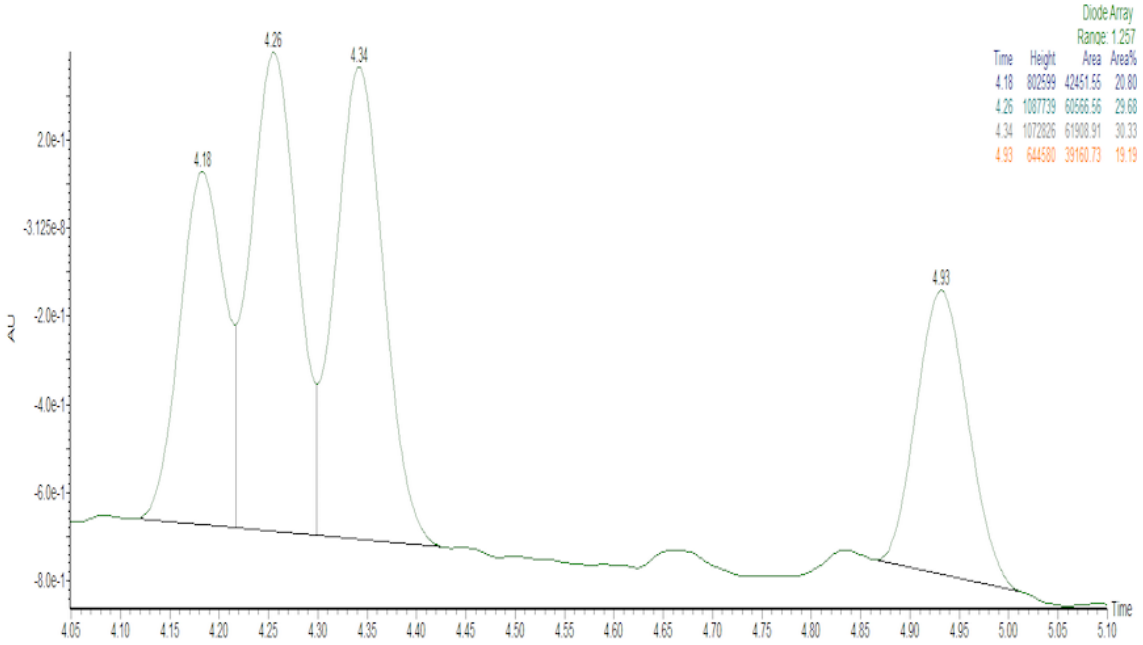




+ diastereomer

3

Trace of racemic compound



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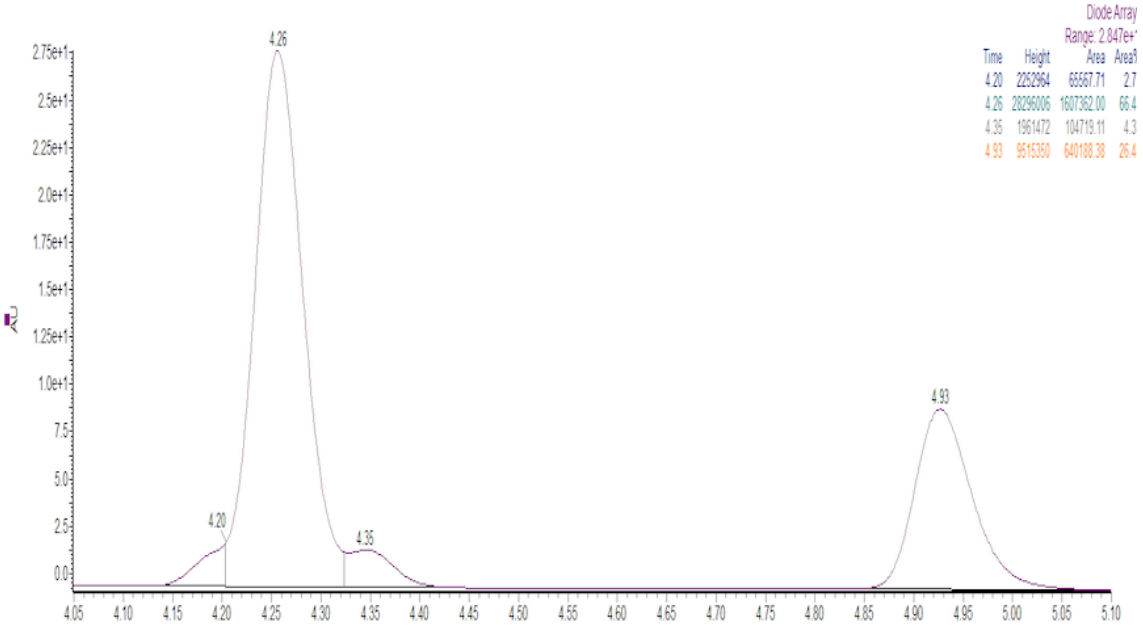

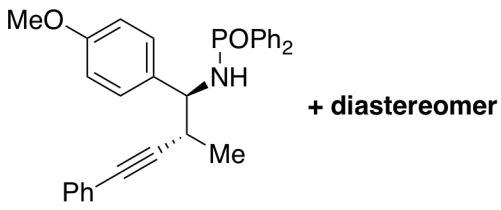

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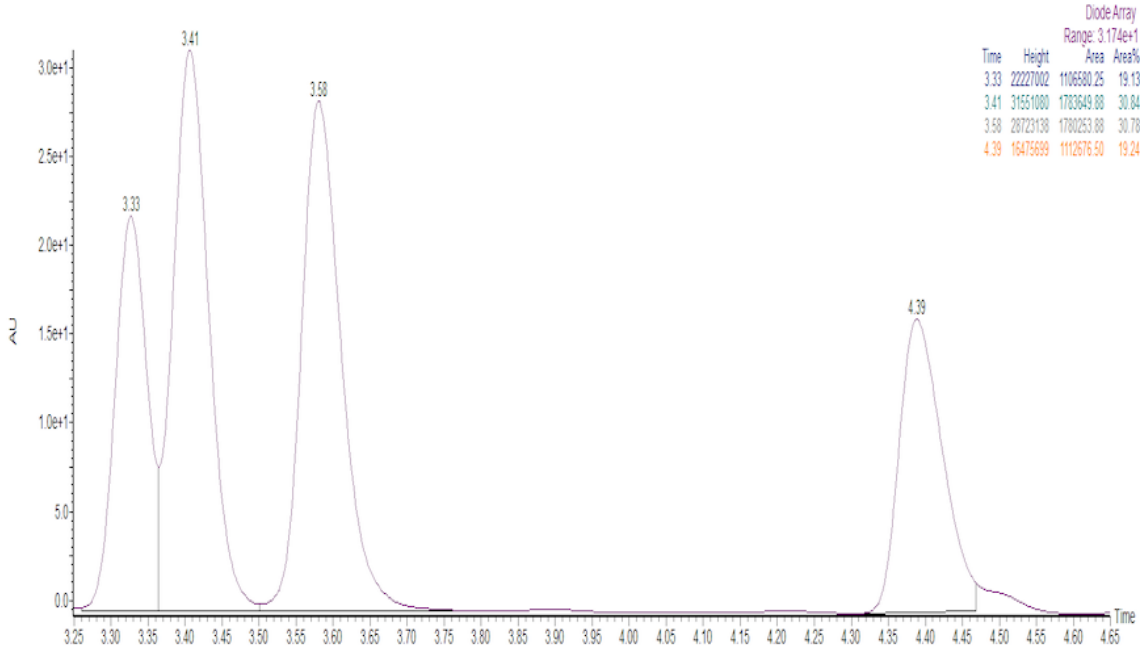
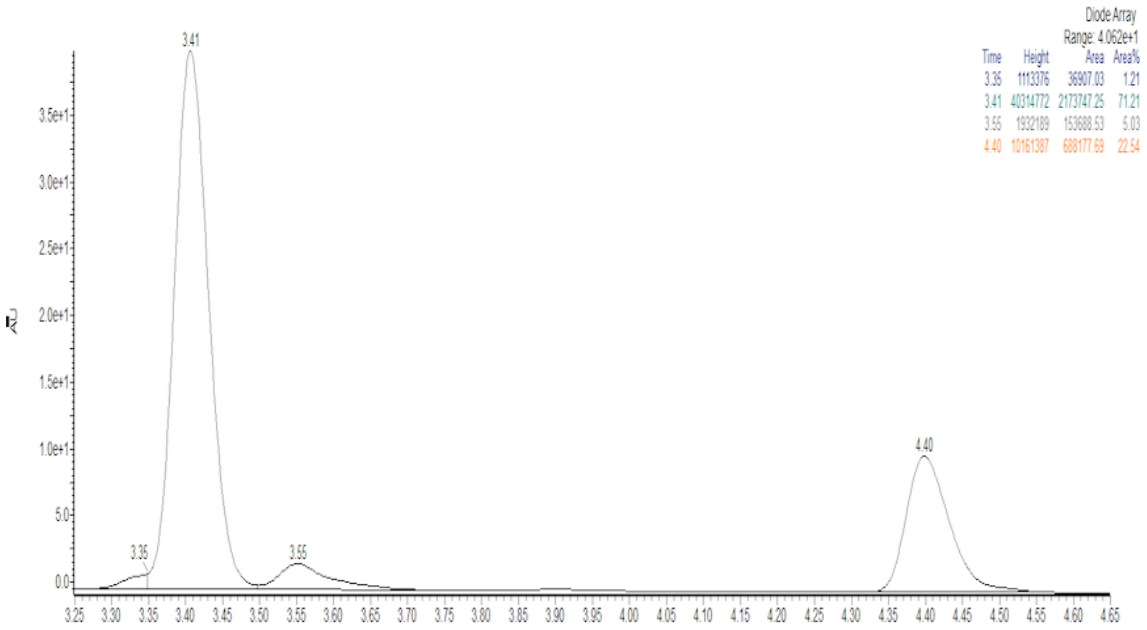
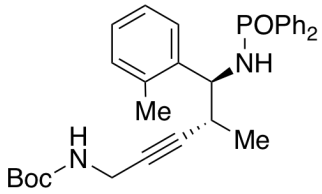
Trace of racemic compound



Trace of enantioenriched compound

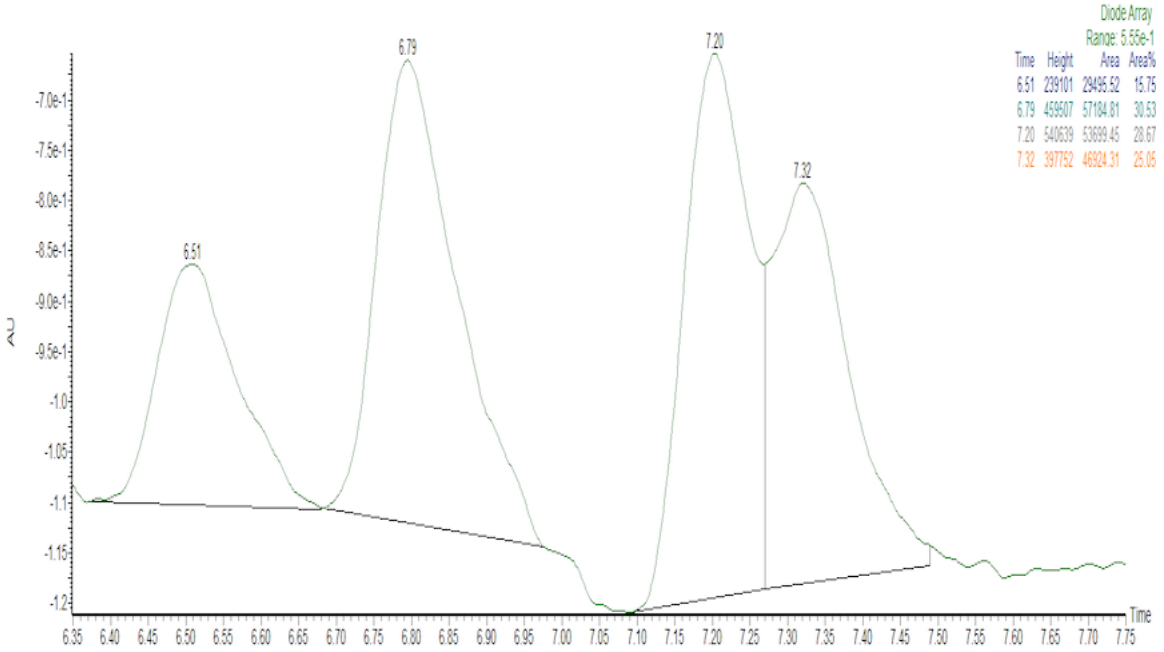




+ diastereomer

5

Trace of racemic compound



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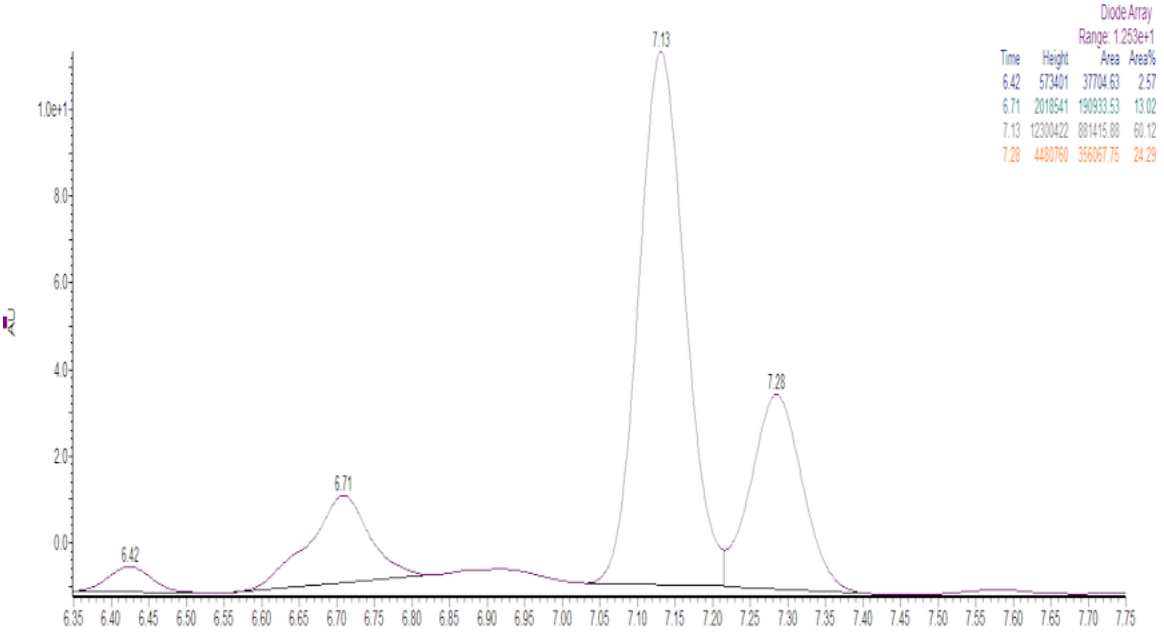
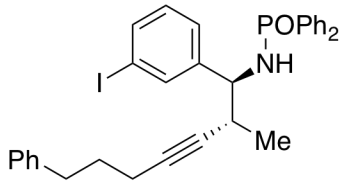
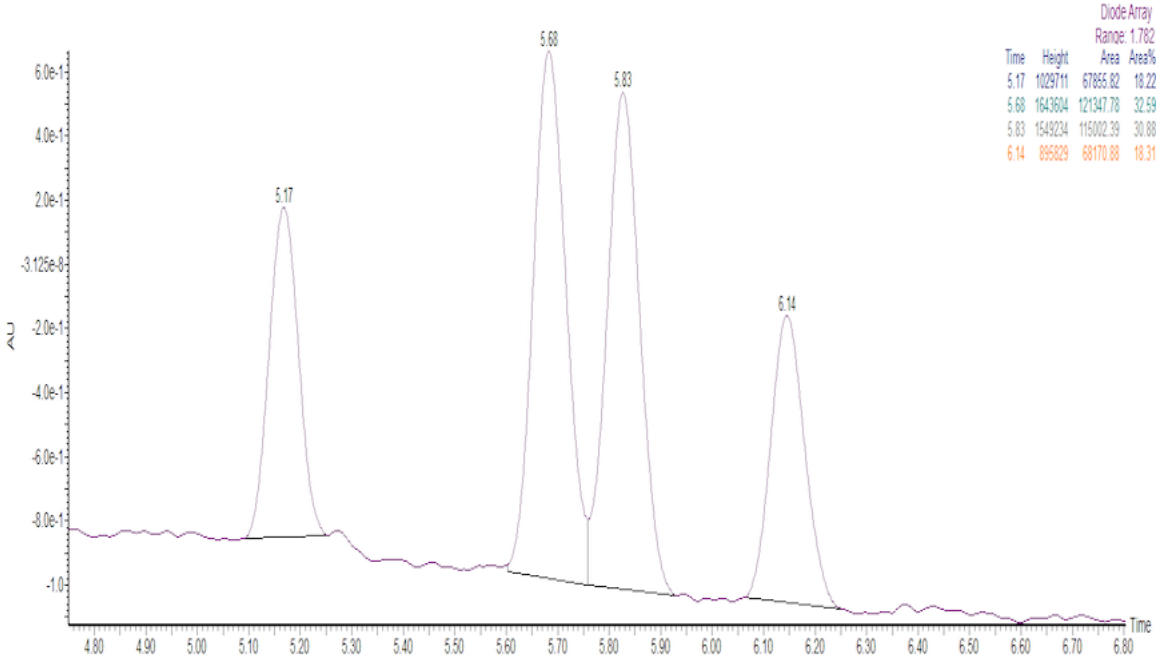




+ diastereomer

6

Trace of racemic compound



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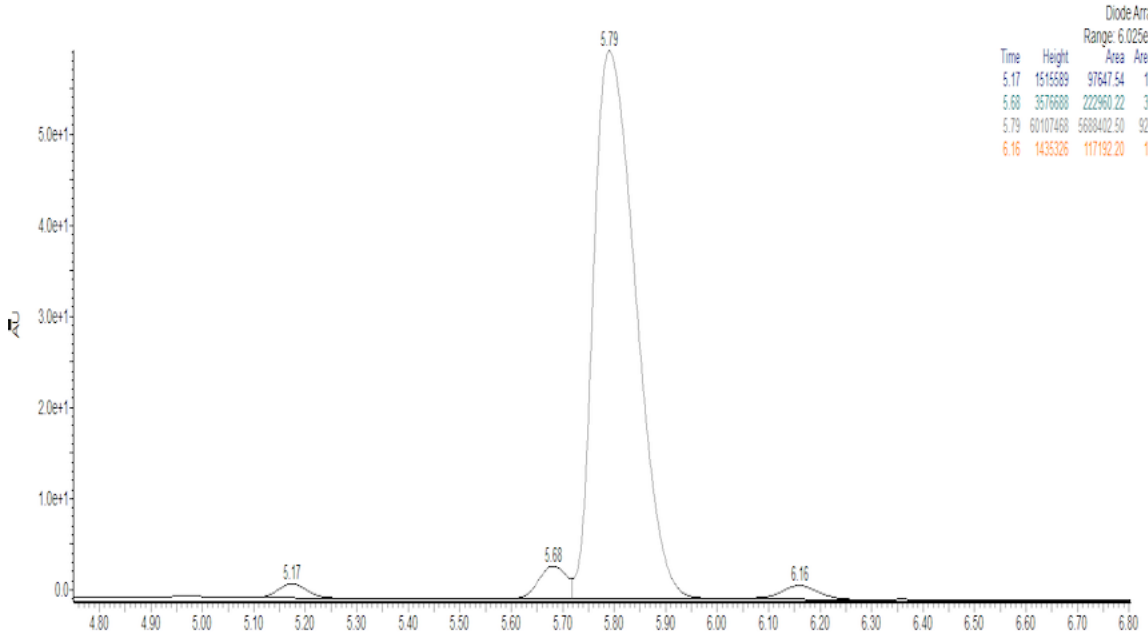
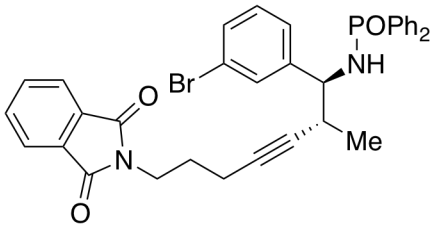
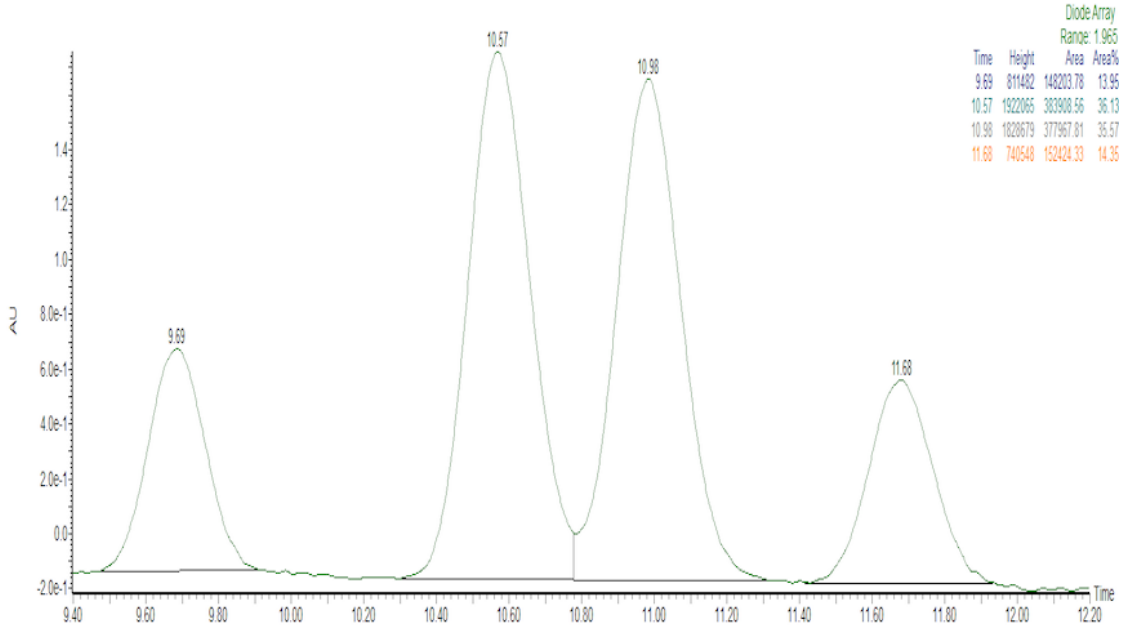




+ diastereomer

7

Trace of racemic compound



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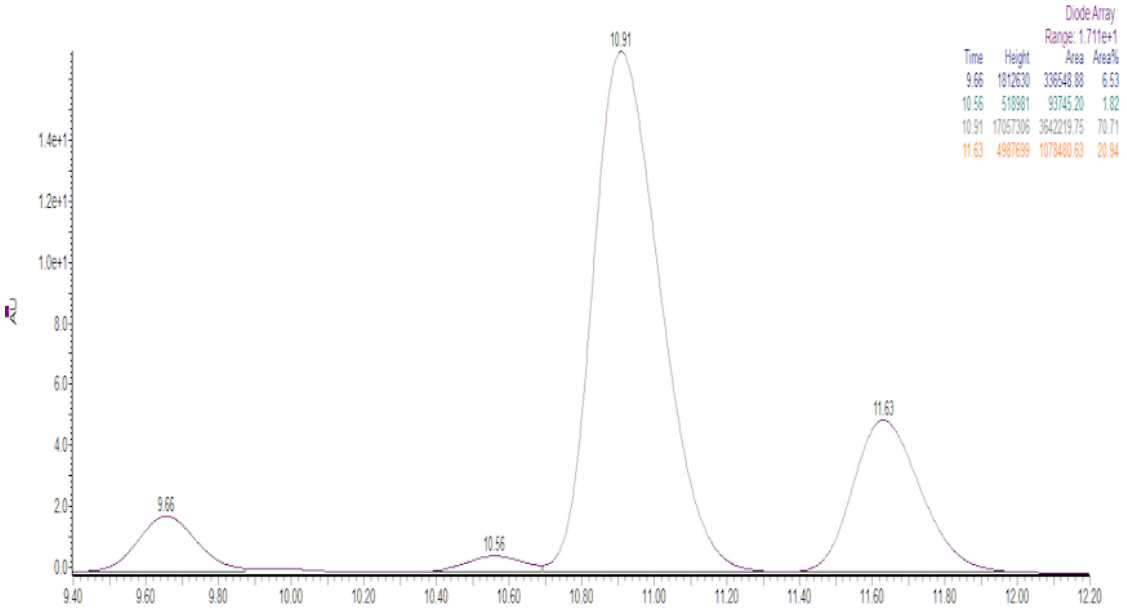
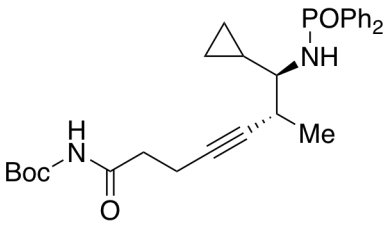
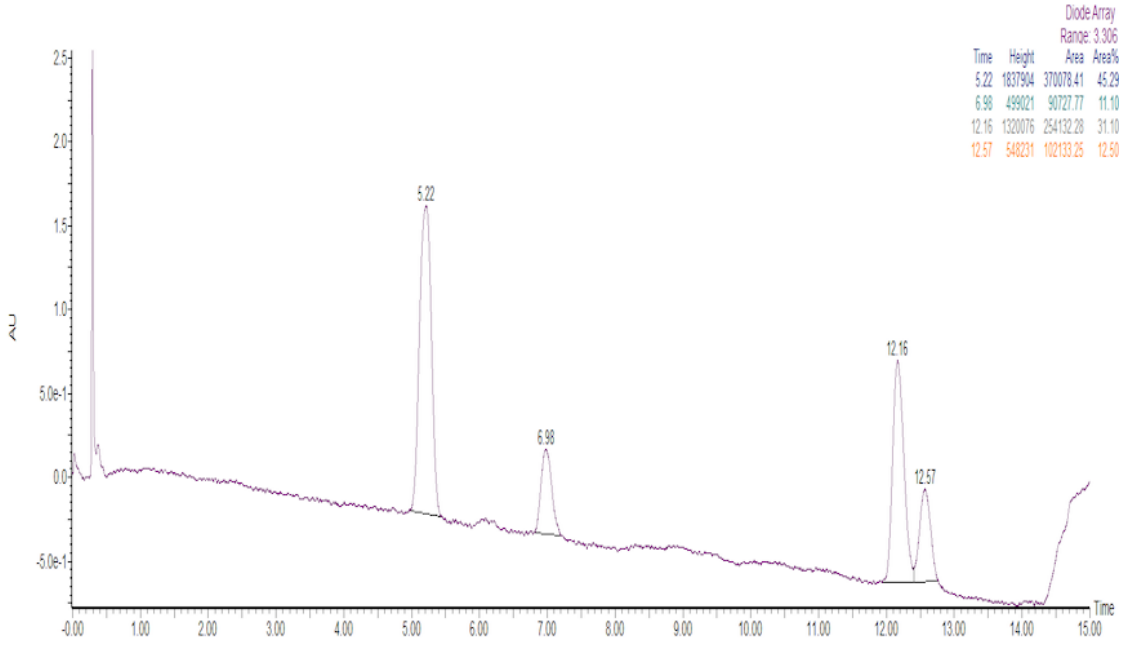




+ diastereomer

8

Trace of racemic compound



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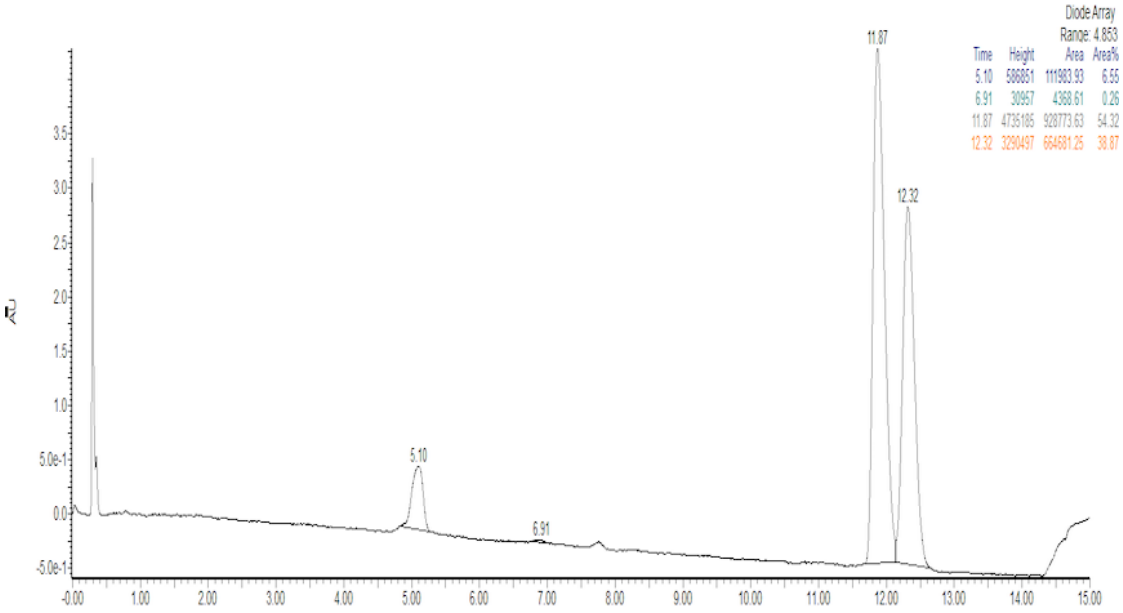
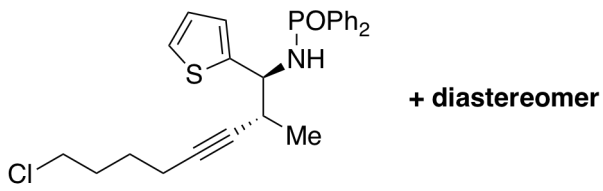
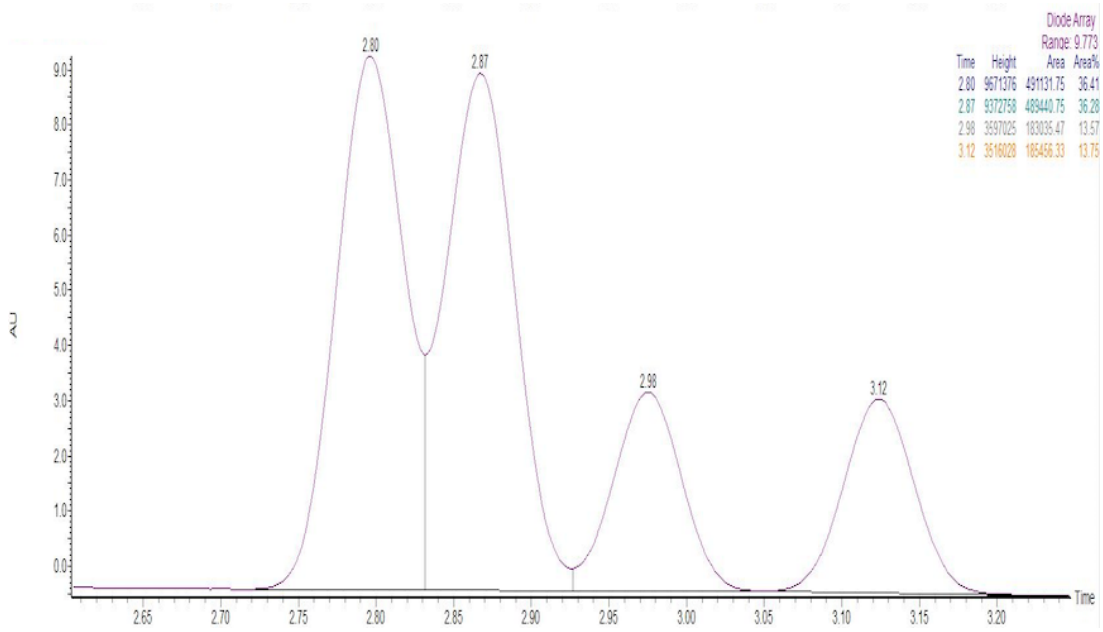




+ diastereomer

10

Trace of racemic compound



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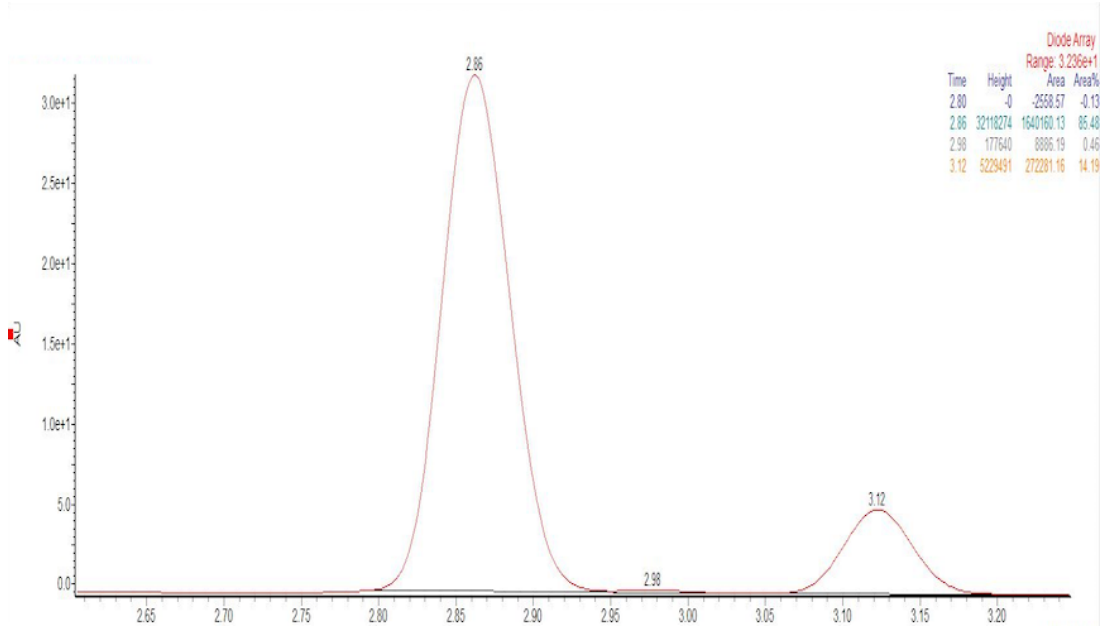
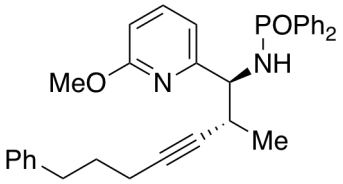
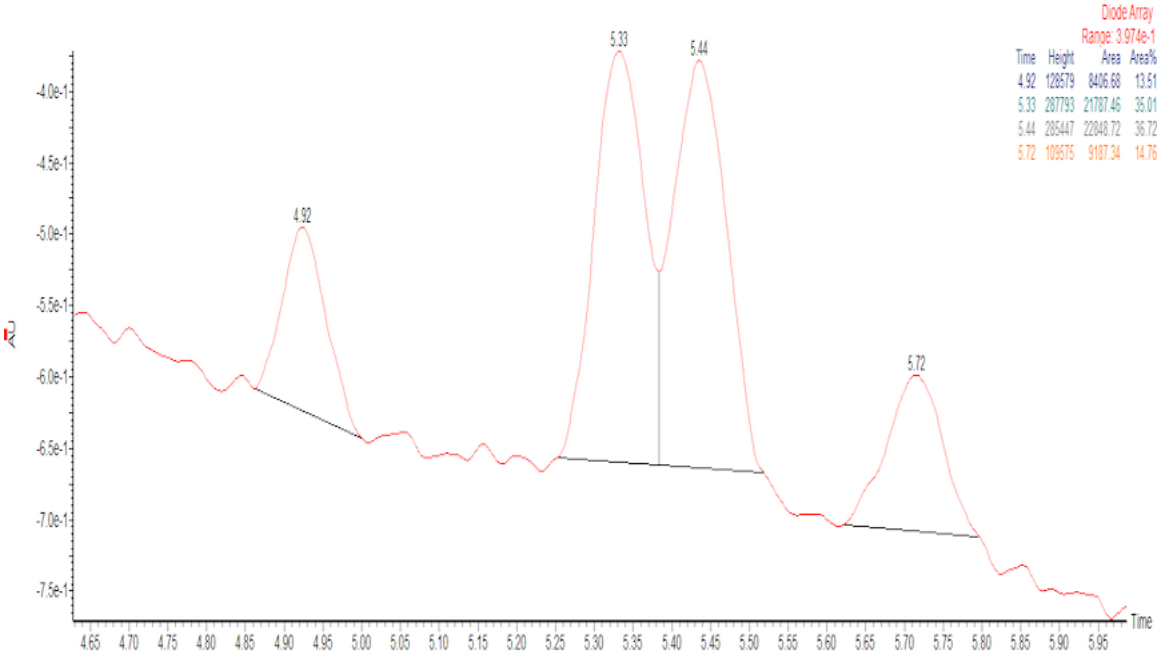




+ diastereomer

11

Trace of racemic compound



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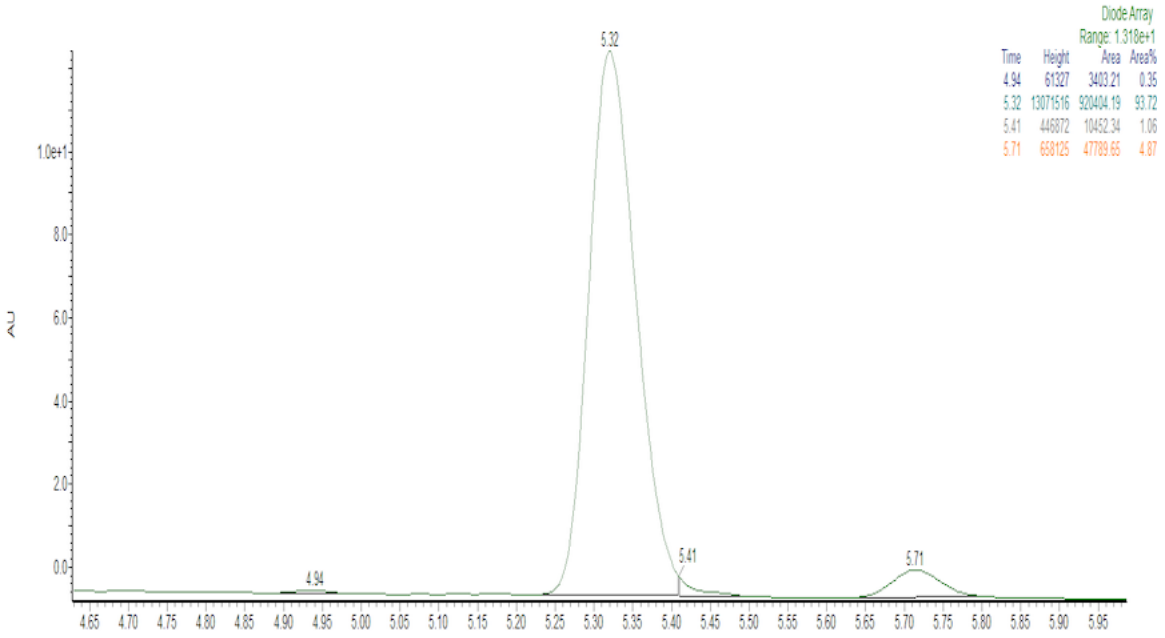
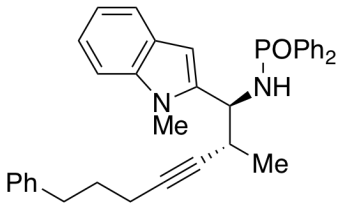
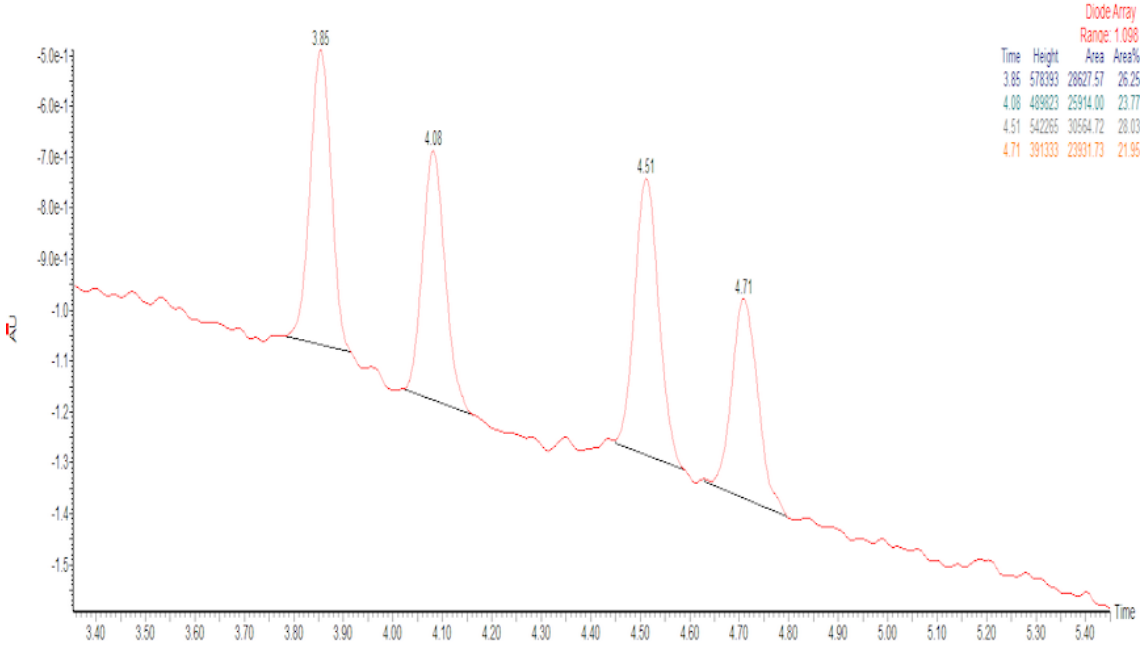




+ diastereomer

13

Trace of racemic compound



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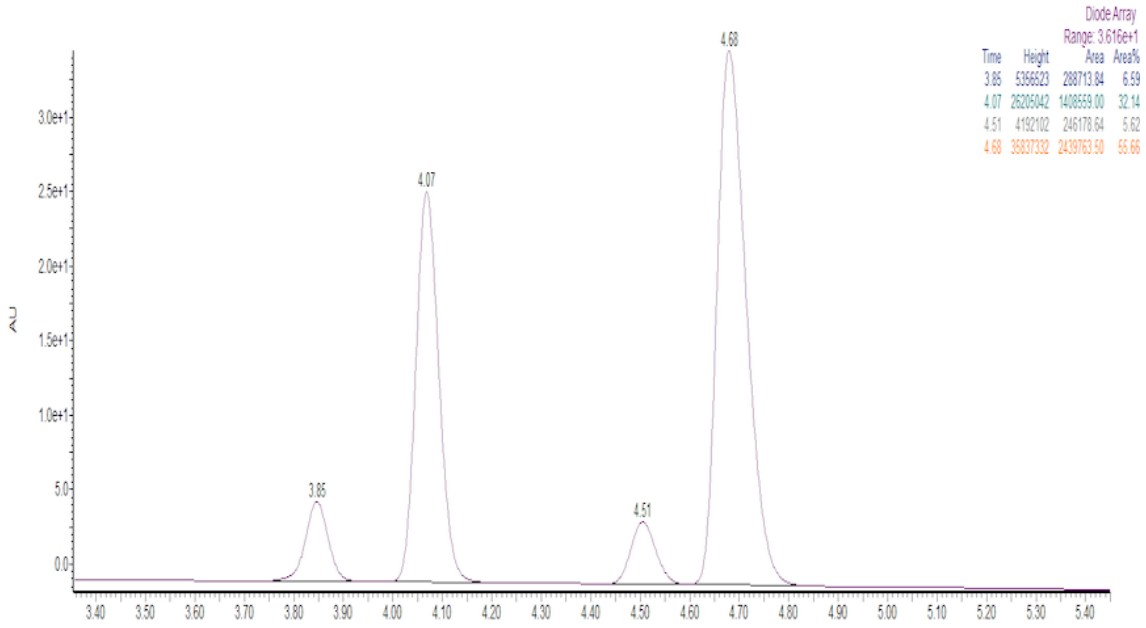
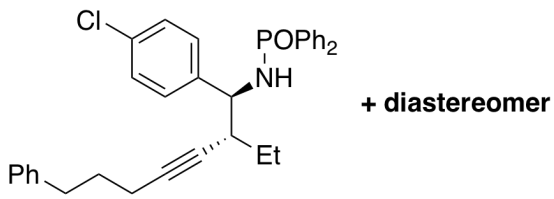
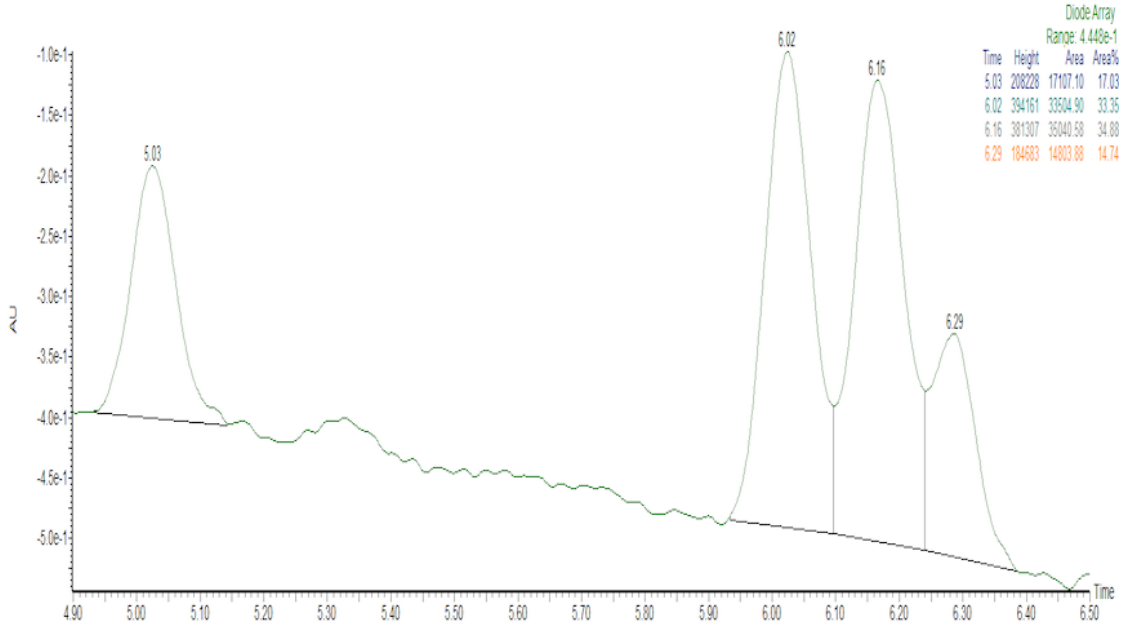




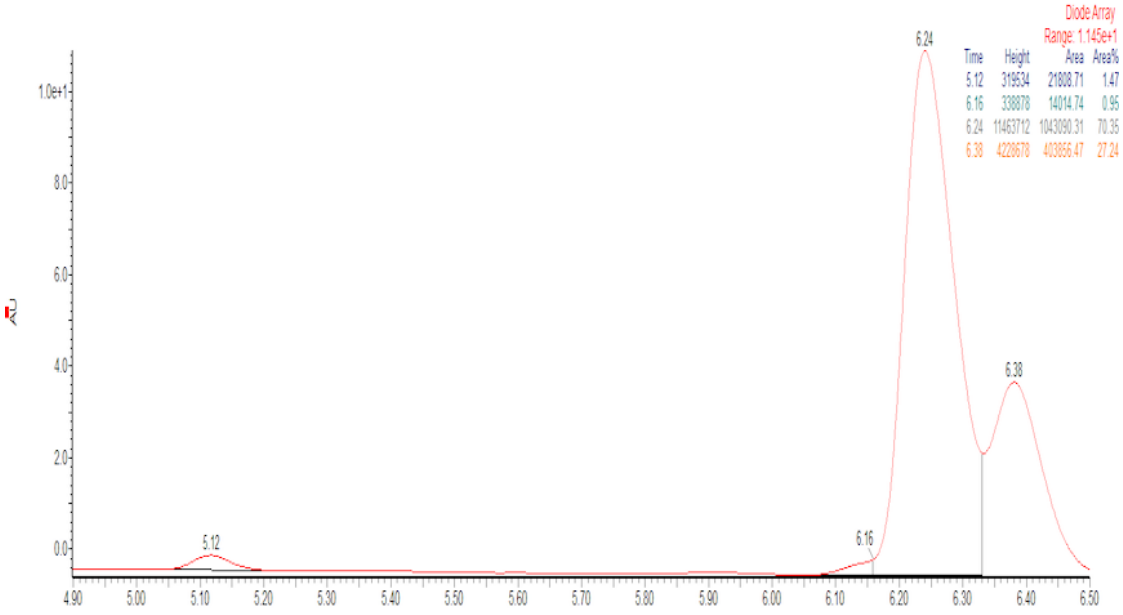
+ diastereomer

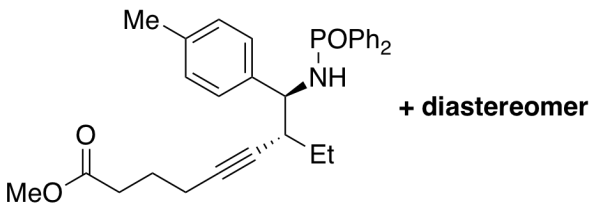
14

Trace of racemic compound



Trace of enantioenriched compound





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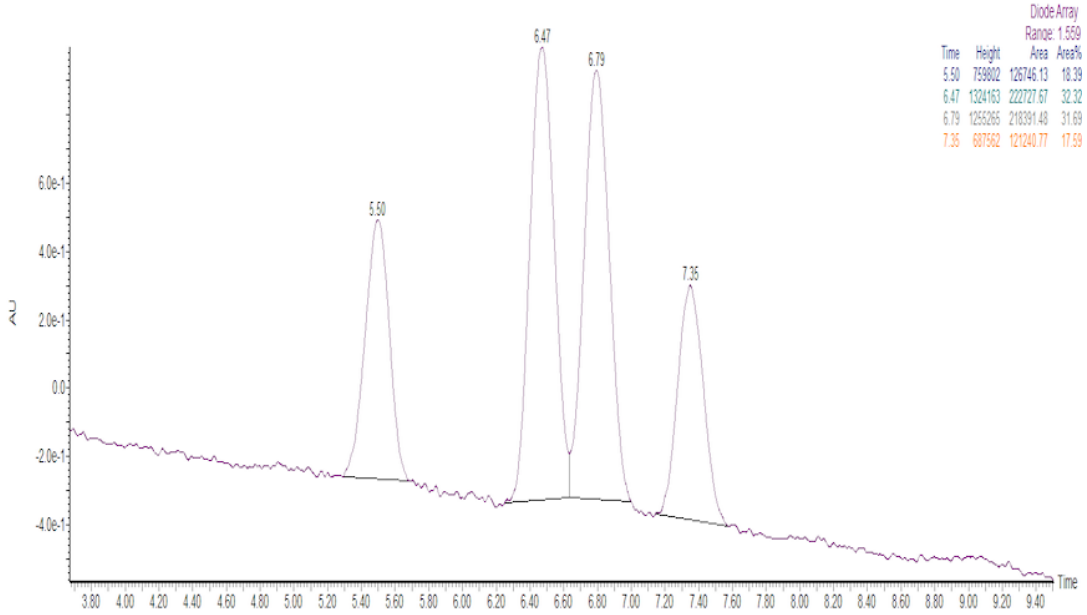
Trace of racemic compound



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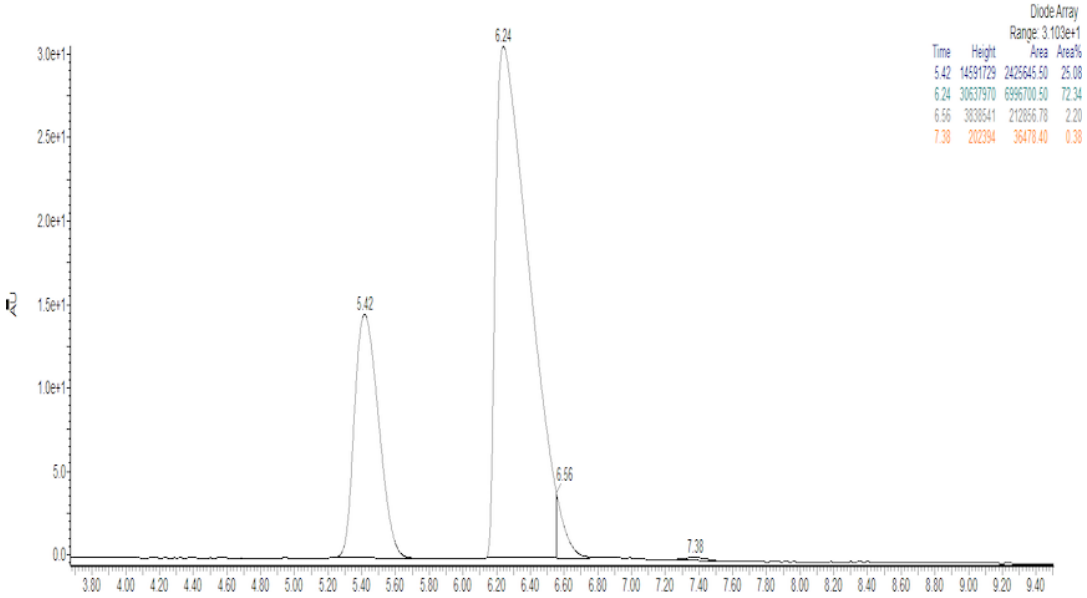


Chapter 4

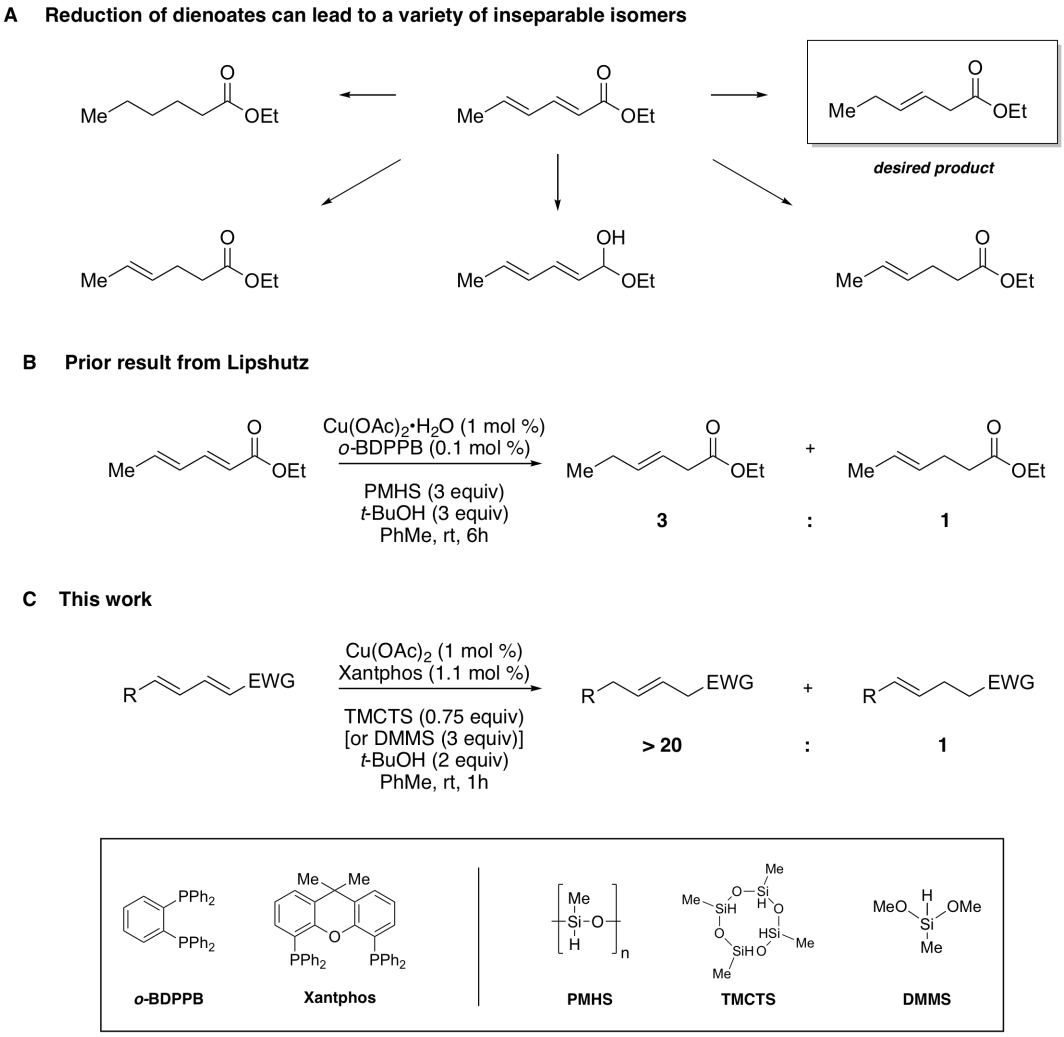
Regio- and Stereoselective Synthesis of β,γ-Unsaturated Compounds by CuH-Catalyzed 1,6-Semireduction

4.1 Introduction

α,β-Unsaturated carbonyl derivatives are readily available through a number of methods.[1] However, there has been considerably less work on the synthesis of β,γ-unsaturated isomers. Recent reports indicate that these compounds are useful and highly versatile intermediates in synthesis,[2] for instance as substrates in directed olefin difunctionalization.[3] Most syntheses of β,γ-unsaturated carbonyl compounds are limited in applicability by the undesirable formation of mixtures of isomers and over-reduction products (Figure 4-1A), which are often difficult to separate by common purification techniques such as chromatography and distillation. For instance, established methods include olefination reactions,[4] acylation of allyl nucleophiles,[5] or isomerization from the α,β-unsaturated isomer.[6] These approaches generally exhibit poor *E/Z*-selectivity at the β,γ-alkene when γ-substitution is present. Additionally, the products are prone to isomerization to their α,β-unsaturated counterparts in the presence of acid or base.[7] Thus, a general, mild method to produce β,γ-unsaturated carbonyl compounds as a single constitutional and geometric isomer is desirable.

Our group has had a longstanding interest in reductive transformations catalyzed by copper hydride (CuH) complexes.[8,9] These reactions typically operate under mild conditions, and importantly, exhibit high levels of chemo-, regio-, and stereoselectivity depending on the ancillary ligand employed. We considered whether β,γ-unsaturated compounds could be efficiently prepared through a semireduction of α, β, γ, δ-unsaturated compounds, which are easily prepared by Horner-Wadsworth-Emmons olefination.[10] Previously, Lipshutz reported that *o*-BDPPB-ligated CuH could reduce ethyl sorbate to an inseparable mixture of 1,4- and 1,6-reduction products (Figure 4-1B).[11] Recent work has also been carried out on 1,6-conjugate addition of nucleophiles using Cu catalysis.[12] In this chapter, we report the development of a practical and functional group-tolerant preparation of β, γ-unsaturated compounds with little or no detectable over-reduction or undesired isomers in the majority of cases (Figure 4-1C). [Note: Due to the volatility of the compounds reported, careful purification is required to ensure high yields. Additionally, a fresh bottle of TMCTS should be employed for these reactions, and the reactions conducted with rigorous exclusion of water, to prevent formation of silane oligomers.]

Figure 4-1: Overview of Copper Hydride-Catalyzed Reduction



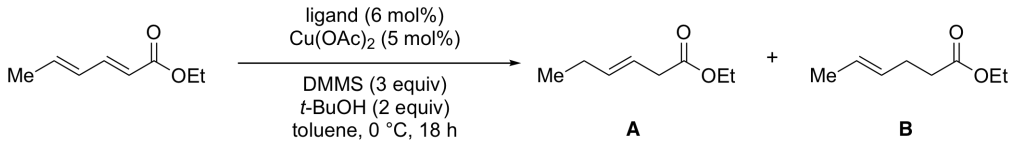
4.2 Results and Discussion

4.2.1 Reaction Optimization

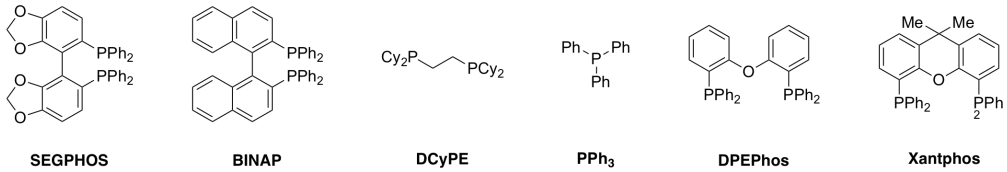
We first examined the reduction of ethyl sorbate to form the corresponding β,γ-enoate, catalyzed by the combination of copper(II) acetate with a variety of commercially available ligands. In many cases, significant formation of the product of 1,4-reduction was observed. We found that a rough correlation existed between the bite angle of the ligand and the selectivity for 1,6- over 1,4-reduction, with the use of wide-angle ligands proving the most selective for the 1,6-semireduction product. Use of the ligand Xantphos provided the desired product in excellent yield and without any detectable

quantity of isomeric or over-reduced side-products. When we conducted the reaction on a larger scale (0.50 mmol), we found that 1 mol% of Cu and 1.1 mol% of the ligand was sufficient to obtain the desired β, γ–unsaturated ester with high yield and selectivity.

Table 4-1: Evaluation of Reaction Conditions for the CuH-Catalyzed Semireduction of Ethyl Sorbate[a,b]



Entry	Ligand	Bite Angle	Yield[b] (%)	A:B	*E:Z*
1	SEGPHOS	100.9	86	1.2:1	>20:1 A, >20:1 B
2	BINAP	98.9	92	1.5:1	>20:1 A, >20:1 B
3	DCyPE	88.0	81	3:1	14:1 A, 12:1 B
4	PPh_3	-	88	6:1	15:1 A, >20:1 B
5	DPEPhos	111.9	90	15:1	>20:1 A
6[c]	Xantphos	120.0	93	>20:1	>20:1 A



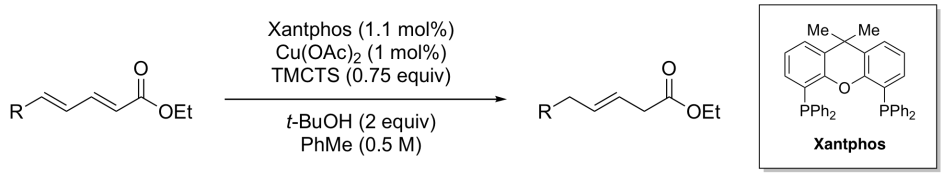
[a] Conditions: 0.10 mmol ethyl sorbate (1.0 equiv), copper(II) acetate (0.050 equiv), ligand (0.060 equiv), dimethoxy(methyl)silane (3.0 equiv), *tert*-butanol (2.0 equiv) in toluene (0.2 mL) at 0 °C for 18 h; see the Experimental for details. [b] Yields and regioisomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,1,2,2-tetrachloroethane as internal standard. [c] TMCTS was chosen as the hydrosilane for safety and waste considerations[13] without negative effects on the yield or selectivity.

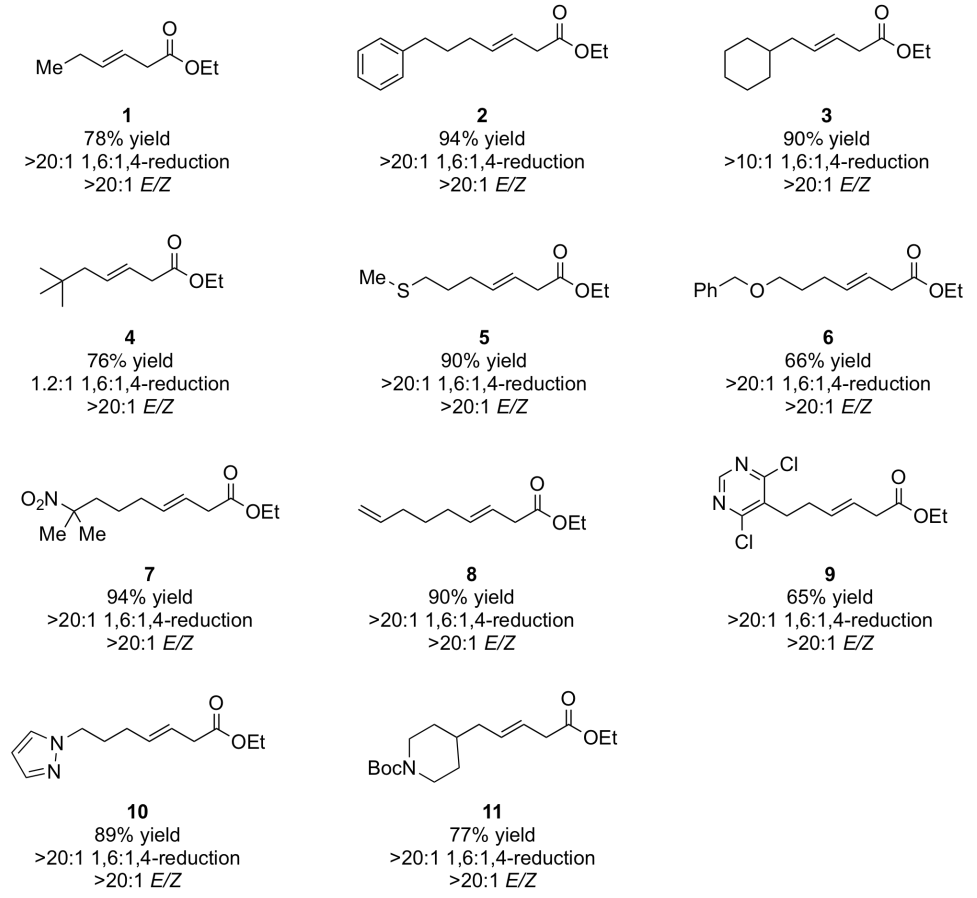
4.2.2 Substrate Scope

By applying this method, a variety of doubly unsaturated compounds were efficiently reduced to β, γ–unsaturated products. The observed regioselectivity was uniformly high regardless of the electronic properties of the substituents, though significant 1,4-reduction was observed when sterically demanding substituents, specifically a *tert*-butyl group, were present at the δ–position (**4**). In all cases, only the (*E*)-alkene isomer was observed. Additionally, regioisomeric purity of the starting material is not required for isomeric purity of the reduced product. The reaction is tolerant of many common

functional groups, including a thioether (**5**), a benzyl ether (**6**), a nitro group (**7**), a heteroaryl chloride (**9**), and a carbamate (**11**). A terminal alkene (**8**) remains intact under these conditions. Substrates containing heterocycles such as pyrimidine (**9**), pyrazole (**10**), and piperidine (**11**) were also successfully converted with similar levels of efficiency and selectivity. We have also evaluated the conditions for the selective reduction of other unsaturated acceptors. Doubly-unsaturated amides (**13, 14**), sulfones (**15**), and nitriles (**16**) underwent selective 1,6-reduction to give the desired products in high yield and selectivity.

Table 4-2: 1,6-Semireduction of 2,4-Dienoates[a,b]

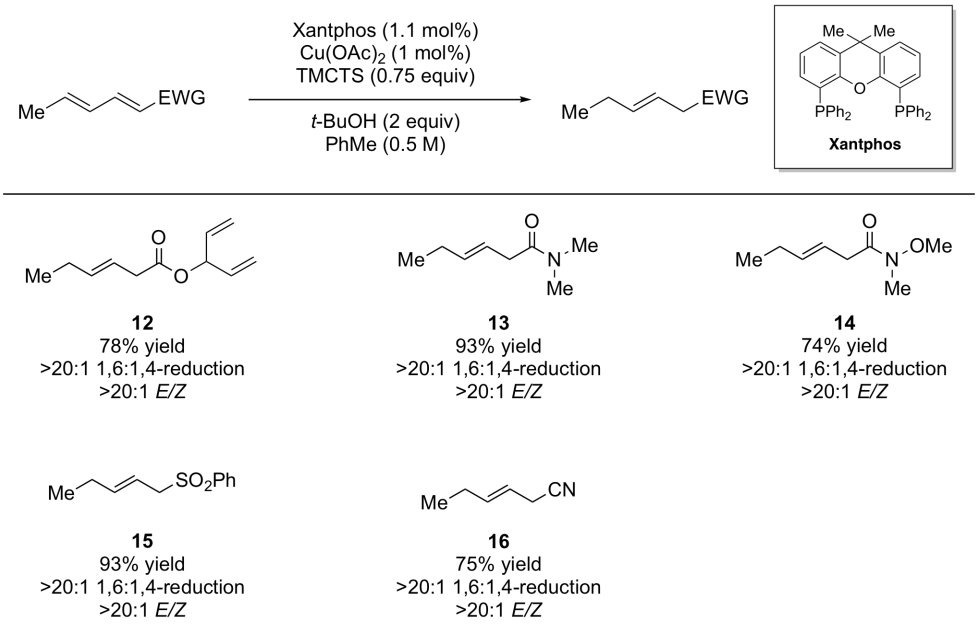




[a] Conditions: 0.50 mmol substrate (1.0 equiv), copper(II) acetate (0.01 equiv), Xantphos (0.011

equiv), 2,4,6-8-tetramethylcyclotetrasiloxane (0.75 equiv), *tert*-butanol (2 equiv) in toluene (1.0 mL) at room temperature for 1 h; see the Experimental for details. [b] Products were isolated as a >20:1 1,6:1,4-reduction and >20:1 *E/Z* mixture of isomers unless otherwise noted. Yields and regioisomeric ratios were determined as the averages for two identical runs by ^{1}H NMR spectroscopy for both the crude and purified products using 1,1,2,2-tetrachloroethane as internal standard.

Table 4-3: 1,6-Semireduction of Other $\alpha,\beta,\gamma,\delta$-Unsaturated Substrates[a,b]

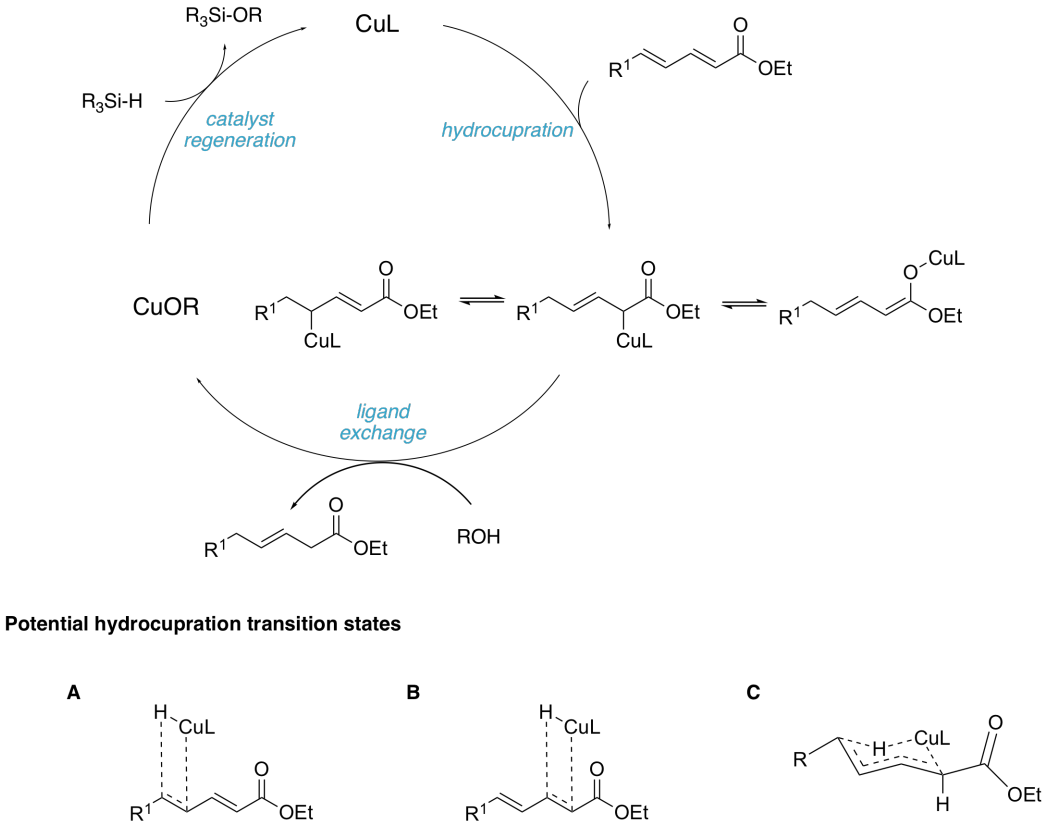


[a] Conditions: 0.50 mmol substrate (1.0 equiv), copper(II) acetate (0.010 equiv), Xantphos (0.011 equiv), 2,4,6-8-tetramethylcyclotetrasiloxane (0.75 equiv), *tert*-butanol (2.0 equiv) in toluene (1.0 mL) at room temperature for 1 h; see the Experimental for details. [b] Products were isolated as a >20:1 1,6:1,4-semireduction and >20:1 *E/Z* mixture of isomers unless otherwise noted. Yields and regioisomeric ratios were determined as the averages for two identical runs by ^{1}H NMR spectroscopy for both the crude and purified products using 1,1,2,2-tetrachloroethane as internal standard.

A plausible mechanism can be proposed based on previous work on CuH-catalyzed 1,4-reduction reactions.[14] We hypothesize that a Xantphos-ligated CuH species first engages the substrate in a migratory insertion (hydrocupration) process involving the γ,δ-π bond. Based on previous DFT calculations on the hydrocupration of 1,3-dienes,[15] we believe this proceeds through a 4-membered cyclic transition state (Figures 4-2A, B), rather than alternatives involving 6-membered transition states (Figure 4-2C). Preference for engaging the γ,δ-double bond (Figure 4-2A), rather than the α,β-double bond

(Figure 4-2B), likely dictates the selectivity for 1,6-reduction over 1,4-reduction. The immediate product of hydrocupration, an allyl copper species, may isomerize to the copper enolate through sequential and likely reversible 1,3-shifts. Thus, in order for the observed isomer of product to be formed in high selectivity, we propose that proton transfer from the alcohol selectively occurs at the α-position and while the olefin is in the (*E*)-configuration. However, the precise mechanism for this protonation is not known. Further work is also required to understand how the choice of ligand affects the hydrocupration regioselectivity.

Figure 4-2: Proposed Mechanism for the 1,6-Semireduction of α, β, γ, δ-Unsaturated Acceptors



4.3 Conclusion

In conclusion, this chapter details a method for the 1,6-semireduction of doubly unsaturated substrates to β, γ–unsaturated products. This catalytic process selectively produces the (*E*)-alkene product and generally avoids the formation of of regioisomers, stereoisomers, or compounds resulting from over-reduction. The method is useful for

the synthesis of β,γ-unsaturated esters, as well as amides, sulfones, and nitriles, exhibits excellent functional group tolerance, and requires only small quantities (1 mol%) of catalyst formed with commercially available ligands.

4.4 Experimental

4.4.1 General Reagent Information

Unless noted otherwise, reagents and substrates were purchased from commercial vendors and used as supplied. Xantphos was obtained from Oakwood Chemicals (Oakwood catalog number 036098). Copper(II) acetate was purchased from Strem (amorphous powder, 97% min.) and used directly. 2,4,6-tetramethylcyclotetrasiloxane (TMCTS, moisture-sensitive) was purchased from TCI-America. Other reagents were purchased from Millipore-Sigma, Alfa Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific and were used as received. Toluene was obtained from J.T. Baker in CYCLE-TAINER® delivery kegs and purified by filtration though packed columns of neutral alumina and copper(II) oxide under argon pressure; toluene-d_8 was purchased from Cambridge Isotope Laboratories, Inc., degassed by sonication, and stored over 4Å molecular sieves. EtOAc and hexanes used in chromatography eluents for products and their derivatives were reagent grade from Millipore-Sigma. Flash chromatography was performed on wet-loaded silica columns using SiliCycle SiliaFlash® F60 silica gel (40-63 μm, 230-400 mesh, 60 Å pore diameter) with the aid of Teledyne ISCO CombiFlash Automated Flash Chromatography System and fractions collected in disposable glass culture tubes (16 x 100 mm, VWR North American Cat. No. 47729-576). Reactions were performed with magnetic stir bars in glass culture tubes with threaded ends (13 x 100 mm, Fisher Scientific part #14-959-35C; oven-dried at 140 °C for at least 16 h prior to use) and were sealed with screw-thread caps (Thermo Scientific part #C4015-66) fitted with Teflon septa (Thermo Scientific part #C4015-60).

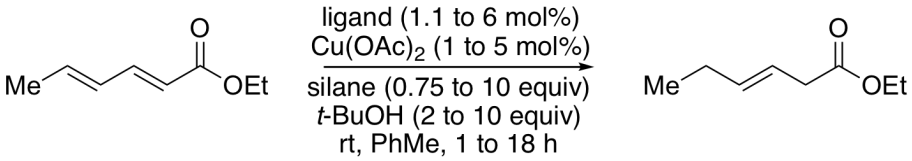
4.4.2 General Analytical Information

^{1}H and ^{13}C NMR spectra were recorded using a Bruker 400 or 500 MHz spectrometer as indicated. Chemical shifts of ^{1}H NMR signals are referenced to the indicated residual solvent peak ($CDCl_3$, $\delta = 7.26$ ppm) and reported in ppm relative to tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm) and all were obtained with ^{1}H decoupling. Ratios of 1,6- to 1,4-reduction were obtained by integration of the alkene signals in quantitative ^{1}H or ^{13}C NMR spectra. $CDCl_3$ was obtained from Cambridge Isotope Laboratories. IR spectra were acquired from neat samples using a Thermo Scientific Nicolet iS5 spectrometer equipped with an iD5 diamond laminate ATR accessory, and representative peaks are reported as wavenumbers in units of cm^{-1}. Melting points (m.p.) were obtained on a Mel-Temp capillary melting point

apparatus. High-resolution mass spectrometry was performed using a JEOL AccuTOF 4G LC-plus mass spectrometer equipped with an ionSense DART (Direct Analysis in Real Time) source or an Agilent Technologies 6545 QTOF LC/MS.

Elemental analyses were performed for carbon and hydrogen by Atlantic Microlabs Inc., Norcross, GA. Gas Chromatography (GC) was performed using an Agilent 7890A gas chromatograph equipped with an FID detector and a JW DB-1 column (10 mm, 0.1 mm I.D.). Analytical TLC was performed using Silicycle SilicaPlate® glass-backed extra-hard-layer TLC plates (60 Å, 250 μm thickness, 20 x 20 cm, UV-254 indicator) and visualization with 254 nm light.

4.4.3 Reaction Optimization Procedures

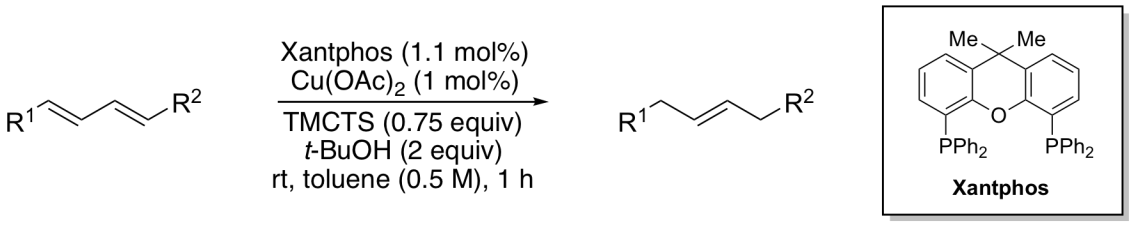


In a nitrogen-filled glovebox, a reaction tube with threaded end (13 x 100 mm, Fisher Scientific part #14-959-35C) equipped with a magnetic stir bar was charged with ethyl sorbate (70 mg, 0.50 mmol), copper(II) acetate (1 to 5 mg, 0.010 to 0.050 equiv), ligand (0.011 to 0.060 equiv), *t*-BuOH (2.0 to 10 equiv), and toluene-d_8 (1.0 mL). The vial was capped with a screw cap (Thermo Scientific part #C4015-66) containing a septum insert (Thermo Scientific part #C4015-60) and removed from the glovebox. Silane (0.75 to 10 equiv) was added via syringe in one portion by piercing the septum with the needle, and the reaction mixture was stirred for 1 to 24 h at room temperature. The cap was removed and the yield was assessed by ^{1}H NMR in the reaction solvent, using 1,1,2,2-tetrachloroethane as an internal standard.

Ligand	**Catalyst Loading (mol%)**	***t*-BuOH (equiv)**	**Silane**	**Silane (equiv)**	**Time (h)**	**1,6:1,4**	***E:Z***	**Yield (by ^{1}H NMR)**
SEGPHOS	5	2	DMMS	3	18	1.2:1	>20:1	86
BINAP	5	2	DMMS	3	18	1.5:1	>20:1	92
DCyPE	5	2	DMMS	3	18	3:1	14:1	81
PPh_3	5	2	DMMS	3	18	6:1	15:1	88
DPEPhos	5	2	DMMS	3	18	15:1	>20:1	90
Xantphos	5	2	DMMS	3	18	>20:1	>20:1	93
Xantphos	5	2	DMMS	2	18	>20:1	>20:1	91
Xantphos	5	2	DMMS	5	18	>20:1	>20:1	95
Xantphos	5	2	DMMS	10	18	>20:1	>20:1	92
Xantphos	5	2	DEMS	3	18	>20:1	>20:1	32
Xantphos	5	2	TMCTS	0.75	18	>20:1	>20:1	92
Xantphos	5	2	Me_2PhSiH	3	18	-	-	0

Ligand	Catalyst Loading (mol%)	*t*-BuOH (equiv)	Silane	Silane (equiv)	Time (h)	1,6:1,4	*E:Z*	Yield (by ^{1}H NMR)
Xantphos	5	2	$MePh_2SiH$	3	18	-	-	0
Xantphos	5	2	Ph_2H_2Si	3	18	-	-	0
Xantphos	5	3	TMCTS	0.75	18	>20:1	>20:1	91
Xantphos	5	5	TMCTS	0.75	18	>20:1	>20:1	87
Xantphos	5	10	TMCTS	0.75	18	>20:1	>20:1	90
Xantphos	5	2	TMCTS	0.75	24	>20:1	>20:1	92
Xantphos	5	2	TMCTS	0.75	4	>20:1	>20:1	87
Xantphos	5	2	TMCTS	0.75	1	>20:1	>20:1	95
Xantphos	3	2	TMCTS	0.75	1	>20:1	>20:1	93
Xantphos	**1**	**2**	**TMCTS**	**0.75**	**1**	**>20:1**	**>20:1**	**94**

4.4.4 General Procedure A for Selective 1,6-Semireduction

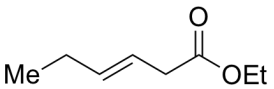


TMCTS was removed from the refrigerator and allowed to warm to room temperature. During this time, inside a nitrogen-filled glovebox, a reaction tube with threaded end (13 x 100 mm, Fisher Scientific part #14-959-35C) equipped with a magnetic stir bar was tared on a balance. To this reacton tube was directly weighed the following reagents, in order: substrate (0.50 mmol, 1.0 equiv), $Cu(OAc)_2$ (1 mg, 0.0050 mmol, 0.010 equiv), ligand (0.0055 mmol, 0.011 equiv), *t*-BuOH (95 μL, 1.0 mmol, 2.0 equiv), and toluene (1 mL). The tube was then fitted with a screw cap (Thermo Scientific part #C4015-66) containing a septum insert (Thermo Scientific part #C4015-60). The reaction tube was removed from the glovebox. At this point, 5-15 min had elapsed since removing the TMCTS reagent from the refrigerator. TMCTS (92 μL, 0.38 mmol, 0.75 equiv) was added in one portion via a 1 mL syringe by piercing the Teflon septum of the sealed reaction tube with the needle (NOTE: A fresh bottle of TMCTS should be employed for these reactions, and the reactions conducted with rigorous exclusion of water, to prevent formation of silane oligomers.). The solution was then stirred at room temperature for a total of 1 h. The cap was removed, and the reaction was immediately quenched by the dropwise addition of 2 mL saturated ammonium fluoride in methanol (**WARNING: VIGOROUS HYDROGEN EVOLUTION**) and stirred for 45 min. The resulting mixture was transferred to a 20 mL scintillation vial and concentrated *in vacuo* to a volume 0.2 mL (water bath set temperature: 35 °C, reduced pressure:

45-55 torr for <10 min). To the vial was added 0.5 mL of diethyl ether, and the mixture was filtered through a 5.75" pipette containing a cotton plug (using Swisspers® brand 100% cotton balls). The scintillation vial and pipette were rinsed with an additional 0.2 mL of diethyl ether, and the eluent was purified by column chromatography (loaded directly on the column without aid of additional solvent), collecting all fractions in 16 x 100 mm test tubes. The fractions from the column were spotted onto TLC plates, and TLC plates were visualized by staining with $KMnO_4$. Product-containing fractions were collected in a round bottom flask without aid of additional solvent, concentrated *in vacuo* (water bath set temperature: 35 °C, reduced pressure: 125-130 torr for <10 min) to a volume of 2-3 mL, transferred to a 20 mL scintillation vial with aid of 1-2 mL diethyl ether, concentrated *in vacuo* (water bath set temperature: 35 °C, reduced pressure: 75-80 torr for <5 min), and dried under high-vacuum by placing a septum on the scintillation vial and piercing it with a needle attached to a Schlenk line for 1-2 min. (NOTE: Products are highly volatile and should not be left under vacuum for extended periods of time, and should not be placed on a Schlenk line below 200 mtorr for more than a few minutes. Minimal solvent should be used when isolating the product.) Unless otherwise noted, the 1,6-reduction product was obtained with >20:1 selectivity over the 1,4-reduction product.

4.4.5 Product Synthesis and Characterization Data

ethyl (*E*)-hex-3-enoate (1)

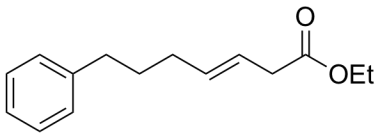


Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl sorbate (70 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 3 column volume (CV), then 0-20% Et_2O/hexanes for 10 CV, followed by 20% Et_2O/hexanes for 5 CV) to afford the title compound as a pale-yellow oil (57 mg, 80% yield) with minor impurities. Quantitative ^{1}H NMR using benzoic acid (>99.5%, purchased from Millipore-Sigma) in $CDCl_3$ indicates 98% purity. **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.72–5.38 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.03 (dd, J = 6.5, 1.3 Hz, 2H), 2.17–1.98 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.3, 136.3, 120.7, 60.5, 38.1, 25.5, 14.2, 13.5 ppm. ^{1}H NMR spectra of the purified product match those reported in the literature.[16]

Duplicate experiment: 55 mg, 77% yield.

Experiment at 1.0 mmol scale of ethyl sorbate: 122 mg, 86% yield.

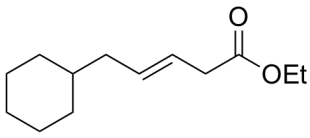
ethyl (*E*)-7-phenylhept-3-enoate (2)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-7-phenylhepta-2,4-dienoate (115 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O /hexanes for 3 CV, then 0-20% Et_2O/hexanes for 10 CV, followed by 20% Et_2O/hexanes for 5 CV) to afford the title compound as a colorless oil (110 mg, 95% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.31 (t, J = 7.5 Hz, 1H), 7.21 (q, J = 4.7, 4.2 Hz, 2H), 5.60 (ddt, J = 5.3, 3.8, 2.2 Hz, 1H), 4.17 (q, J = 7.1 Hz, 1H), 3.06 (d, J = 4.9 Hz, 1H), 2.65 (t, J = 7.8 Hz, 1H), 2.19–2.00 (m, 1H), 1.84–1.60 (m, 1H), 1.30 (t, J = 7.1 Hz, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.2, 142.4, 134.2, 128.5, 128.3, 125.7, 122.2, 60.6, 38.2, 35.3, 32.0, 30.8, 14.2 ppm. ^{1}H and ^{13}C NMR spectra of the purified product match those reported in the literature.[17]

Duplicate experiment: 107 mg, 93% yield.

ethyl (*E*)-5-cyclohexylpent-3-enoate (3)

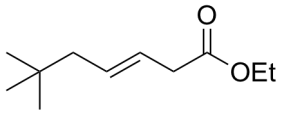


Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-5-cyclohexylpenta-2,4-dienoate (104 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-15% Et_2O/hexanes for 10 CV, followed by 20% Et_2O/hexanes for 5 CV) to afford the title compound as a colorless oil (97 mg, 93% yield) with minor impurities.[18] Quantitative ^{1}H NMR using benzoic acid (>99.5%, purchased from Millipore-Sigma) in $CDCl_3$ indicates 96% purity. **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.63–5.39 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.03 (d, J = 5.7 Hz, 2H), 1.93 (t, J = 6.4 Hz, 2H), 1.76–1.64 (m, 6H), 1.32–1.11 (m, 8H), 0.97–0.78 (m, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.2, 133.3, 122.5, 60.5, 40.5, 38.2, 37.8, 33.1, 26.6, 26.3, 14.2 ppm. ^{1}H and ^{13}C NMR spectra of the purified product match

those reported in the literature.[19]

Duplicate experiment: 92 mg, 88% yield.

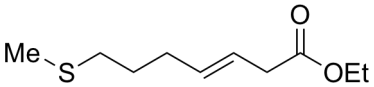
ethyl (*E*)-6,6-dimethylhept-3-enoate (4)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-6,6-dimethylhepta-2,4-dienoate (91 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-15% Et_2O/hexanes for 10 CV, followed by 15% Et_2O/hexanes for 5 CV) to afford the title compound as a pale-yellow oil (72 mg, 78% yield). The product was isolated as a mixture of the 1,6 and 1,4-reduction products.[20] **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.73–5.21 (m, 2H), 4.15 (qd, J = 7.1, 5.6 Hz, 2H), 3.06 (dd, J = 6.5, 1.0 Hz, 2H), 1.99–1.84 (m, 2H), 1.28 (td, J = 7.1, 1.6 Hz, 3H), 0.90 (s, J = 40.3 Hz, 9H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.2, 131.8, 122.5, 60.5, 46.9, 38.3, 29.2, 28.1, 14.2 ppm. **IR:** 2922, 2853, 1739, 1456, 1365, 1267, 1063, 1026, 906, 765 cm^{-1}. **HRMS Calcd. m/z** for $[C_{11}H_{20}O_2 + Na]^+$: 207.1356. Found: 207.1359.

Duplicate experiment: 69 mg, 75% yield.

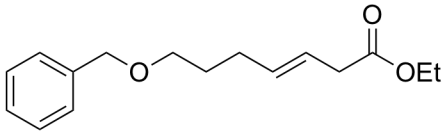
ethyl (*E*)-7-(methylthio)hept-3-enoate (5)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-7-(methylthio)hepta-2,4-dienoate (100 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 column volume (CV), then 0-20% Et_2O/hexanes for 10 CV, followed by 20% Et_2O/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (92 mg, 92% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.64–5.46 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.12–2.94 (m, 2H), 2.51 (t, J = 7.4 Hz, 2H), 2.21–2.14 (m, 2H), 2.12 (s, 3H), 1.69 (p, J = 7.3 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.1, 133.5, 122.6, 60.6, 38.1, 33.6, 31.4, 28.5, 15.5, 14.2 ppm. **IR:** 2970, 2165, 1264, 1055, 888, 856, 736 cm^{-1}. **HRMS Calcd. m/z** for $[C_{10}H_{18}SO_2 + H]^+$: 203.1100. Found: 203.1109.

Duplicate experiment: 90 mg, 89% yield.

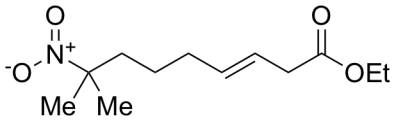
ethyl (*E*)-7-(benzyloxy)hept-3-enoate (6)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-7-(benzyloxy)hepta-2,4-dienoate (130 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-20% Et_2O/hexanes for 10 CV, followed by 20% Et_2O/hexanes for 10 CV) to afford the title compound as a cloudy oil (87 mg, 66% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.40–7.27 (m, 5H), 5.65–5.52 (m, 2H), 4.52 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.50 (t, J = 6.4 Hz, 2H), 3.04 (dt, J = 4.8, 1.1 Hz, 2H), 2.23–2.10 (m, 2H), 1.73 (dt, J = 8.2, 6.6 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.1, 138.6, 133.9, 128.4, 127.6, 127.5, 122.2, 72.9, 69.7, 60.5, 38.2, 29.2, 29.1, 14.2 ppm. **IR:** 2931, 2853, 1732, 1157, 1101, 1028, 968, 735, 697 cm^{-1}. **HRMS Calcd. m/z** for $[C_{16}H_{22}O_3 + Na]^+$: 285.1461. Found: 285.1466.

Duplicate experiment: 87 mg, 66% yield.

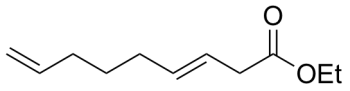
ethyl (*E*)-8-methyl-8-nitronon-3-enoate (7)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-8-methyl-8-nitronona-2,4-dienoate (121 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-30% Et_2O/hexanes for 10 CV, followed by 30% Et_2O/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (114 mg, 94% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.44–5.61 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.01 (d, J = 5.6 Hz, 2H), 2.10–2.00 (m, 2H), 1.92–1.83 (m, 2H), 1.57 (s, 6H), 1.40–1.30 (m, 2H), 1.26 (s, J = 7.1 Hz, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.0, 133.3, 122.8, 88.2, 60.6, 40.4, 38.0, 32.1, 25.8, 23.7, 14.2 ppm. **IR:** 2985, 2940, 1734, 1536, 1373, 1348, 1176 cm^{-1}. **HRMS Calcd. m/z** for $[C_{12}H_{21}NO_4 + Na]^+$: 266.1363. Found: 266.1362.

Duplicate experiment: 114 mg, 95% yield.

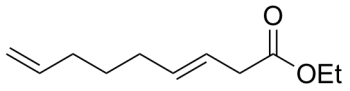
ethyl (*E*)-nona-3,8-dienoate (8)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-nona-2,4,8-trienoate (90 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-10% Et_2O/hexanes for 10 CV, followed by 10% Et_2O/hexanes for 5 CV) to afford the title compound as a colorless oil (81 mg, 89% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.82 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.66–5.44 (m, 2H), 5.08–4.88 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.11–2.92 (m, 2H), 2.15–1.93 (m, 4H), 1.49 (p, J = 7.5 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.2, 138.7, 134.3, 122.0, 114.6, 60.5, 38.2, 33.1, 31.9, 28.3, 14.2 ppm. **IR:** 2925, 1738, 1641, 1446, 1368, 1153, 1031, 966, 911, 770 cm^{-1}. **HRMS Calcd. m/z** for $[C_{11}H_{18}O_2 + H]^+$: 183.1380. Found: 183.1392.

Duplicate experiment: 83 mg, 92% yield.

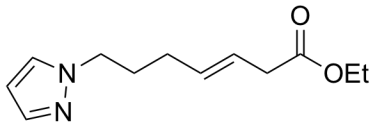
ethyl (*E*)-6-(4,6-dichloropyrimidin-5-yl)hex-3-enoate (9)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-6-(4,6-dichloropyrimidin-5-yl)hexa-2,4-dienoate (144 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-30% Et_2O/hexanes for 10 CV, followed by 30% Et_2O/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (93 mg, 64% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 8.66 (s, 1H), 5.82–5.45 (m, 2H), 4.15 (dq, J = 12.0, 7.1 Hz, 2H), 3.08–3.02 (m, 2H), 3.02–2.99 (m, 2H), 2.47–2.28 (m, 2H), 1.27 (dt, J = 12.5, 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 171.7, 161.9, 155.6, 131.7, 124.0, 60.7, 37.9, 33.9, 30.1, 29.9, 14.2 ppm. **IR:** 2982, 1733, 1516, 1410, 1354, 1265, 1161, 735 cm^{-1}. **HRMS Calcd. m/z for** $[C_{12}H_{14}Cl_2N_2O_2 + Na]^+$**:** 289.0510. Found: 289.0505.

Duplicate experiment: 97 mg, 67% yield.

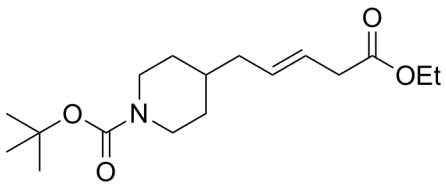
ethyl (*E*)-7-(1H-pyrazol-1-yl)hept-3-enoate (10)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), ethyl *(2E,4E)*-7-(^{1}H-pyrazol-1-yl)hepta-2,4-dienoate (110 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-40% Et_2O/hexanes for 10 CV, followed by 40% Et_2O/hexanes for 10 CV) to afford the title compound as a yellow oil (101 mg, 91% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.52 (d, J = 1.9 Hz, 1H), 7.39 (d, J = 2.2 Hz, 1H), 6.24 (t, J = 2.1 Hz, 1H), 5.66–5.44 (m, 2H), 4.15 (q, J = 7.2 Hz, 4H), 3.04 (d, J = 5.3 Hz, 2H), 2.14–1.85 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.0, 139.2, 132.9, 129.1, 105.1, 60.6, 51.2, 38.0, 29.6, 29.3, 14.2 ppm. **IR:** 2978, 1729, 1266, 1026, 834, 703 cm^{-1}. **HRMS Calcd. m/z** for $[C_{12}H_{18}N_2O_2 + H]^+$: 223.1441. Found: 223.1444.

Duplicate experiment: 97 mg, 87% yield.

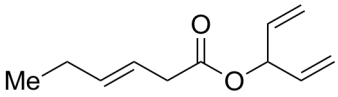
***tert*-butyl (*E*)-4-(7-ethoxy-7-oxohept-4-en-1-yl)piperidine-1-carboxylate (11)**



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), *tert*-butyl 4-((3E,5E)-7-ethoxy-7-oxohepta-3,5-dien-1-yl)piperidine-1-carboxylate (169 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-30% Et_2O/hexanes for 10 CV, followed by 30% Et_2O/hexanes for 10 CV) to afford the title compound as a colorless oil (136 mg, 80% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.64–5.45 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.12–4.05 (m, 2H), 3.04 (dt, J = 3.9, 1.0 Hz, 2H), 2.68 (td, J = 13.1, 2.7 Hz, 2H), 2.06–1.94 (m, 2H), 1.73–1.60 (m, 3H), 1.47 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 1.19–1.02 (m, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 172.1, 154.9, 132.2, 123.5, 79.2, 60.6, 44.0, 39.5, 38.1, 36.1, 28.5, 14.2 ppm. **IR:** 2917, 1735, 1688, 1419, 1365, 1240, 1156, 966 cm^{-1}. **HRMS Calcd. m/z** for $[C_{17}H_{29}NO_4 + Na]^+$: 334.1989. Found: 334.1996.

Duplicate experiment: 128 mg, 75% yield.

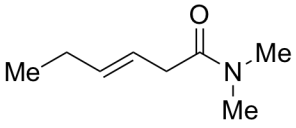
penta-1,4-dien-3-yl (*E*)-hex-3-enoate (12)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), penta-1,4-dien-3-yl (2E,4E)-hexa-2,4-dienoate (91 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-5% Et_2O/hexanes for 10 CV, followed by 5% Et_2O/hexanes for 10 CV) to afford the title compound as a colorless oil (74 mg, 82% yield). The product was obtained with minor impurities. Compound 12 was estimated >95% purity based upon comparison of integrated peaks of impurities at 0.9 ppm in the ^{1}H NMR spectrum to those found in compound 1. **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.86 (ddd, J = 16.8, 10.4, 6.0 Hz, 2H), 5.73 (tt, J = 5.9, 1.3 Hz, 1H), 5.70–5.48 (m, 2H), 5.32 (dt, J = 17.2, 1.3 Hz, 2H), 5.25 (dt, J = 10.4, 1.3 Hz, 2H), 3.13–3.02 (m, 2H), 2.14–1.97 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 171.1, 136.5, 135.0, 120.4, 117.4, 75.0, 38.3, 25.5, 13.5 ppm. **IR:** 2924, 1739, 1264, 1239, 1158, 967, 927, 736 cm^{-1}. **HRMS Calcd. m/z** for $[C_{11}H_{16}O_2+Na]^+$: 203.1043. Found: 203.1049.

Duplicate experiment: 67 mg, 74% yield.

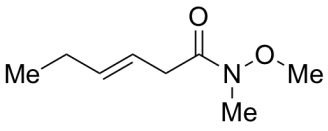
(*E*)-*N,N*-dimethylhex-3-enamide (13)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), (2E,4E)-textitN,N-dimethylhexa-2,4-dienamide (70 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-50% Et_2O/hexanes for 10 CV, followed by 50% Et_2O/hexanes for 5 CV) to afford the title compound as a colorless oil (67 mg, 95% yield) with minor impurities. Quantitative ^{1}H NMR using benzoic acid (>99.5%, purchased from Millipore-Sigma) in $CDCl_3$ indicates 96% purity. **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.72–5.40 (m, 2H), 3.13–3.05 (m, 2H), 3.00 (d, J = 18.2 Hz, 6H), 2.07 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 171.7, 135.5, 121.7, 37.8, 35.4, 25.6, 13.6 ppm. ^{1}H and ^{13}C NMR spectra of the purified product match those reported in the literature.[17,21]

Duplicate experiment: 65 mg, 92% yield.

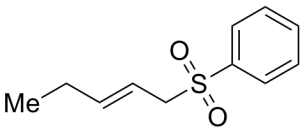
(E)-*N*-methoxy-*N*-methylhex-3-enamide (14)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), *(2E,4E)*-*N*-methoxy-*N*-methylhexa-2,4-dienamide (78 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-50% Et_2O/hexanes for 10 CV, followed by 50% Et_2O/hexanes for 10 CV) to afford the title compound as a colorless oil (58 mg, 74% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.75–5.41 (m, 2H), 3.71 (s, 3H), 3.18 (d, J = 9.4 Hz, 5H), 2.07 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 173.2, 135.9, 121.4, 61.3, 36.1, 32.2, 25.6, 13.5 ppm. ^{1}H and ^{13}C NMR spectra of the purified product match those reported in the literature.[22]

Duplicate experiment: 60 mg, 75% yield.

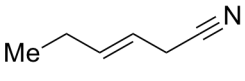
(*E*)-(pent-2-en-1-ylsulfonyl)benzene (15)



Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), (((*1E,3E*)-penta-1,3-dien-1-yl)sulfonyl)benzene (104 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-20% Et_2O/hexanes for 10 CV, followed by 20% Et_2O/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (96 mg, 92% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.99–7.75 (m, 2H), 7.75–7.61 (m, 1H), 7.61–7.50 (m, 2H), 5.56 (dt, J = 15.6, 6.2 Hz, 1H), 5.42 (m, 1H), 3.76 (dd, J = 7.3, 1.0 Hz, 2H), 2.03 (dq, J = 7.7, 6.1 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 143.2, 133.6, 128.9, 128.6, 115.0, 60.1, 25.6, 12.9 ppm. ^{1}H NMR spectra of the purified product match those reported in the literature.[23]

Duplicate experiment: 99 mg, 94% yield.

(*E*)-hex-3-enenitrile (16)

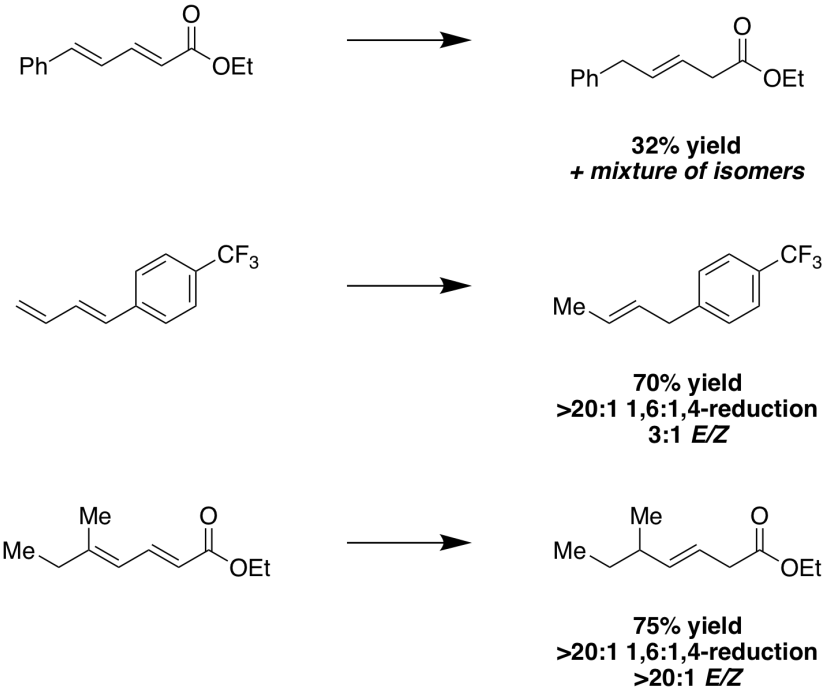


Following general procedure A, $Cu(OAc)_2$ (1 mg, 0.0050 mmol), Xantphos (3 mg, 0.0055 mmol), (*2E,4E*)-hexa-2,4-dienenitrile (47 mg, 0.50 mmol), *t*-BuOH (95 μL, 1.0 mmol), TMCTS (92 μL, 0.38 mmol), and toluene (1 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (10 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 CV, then 0-10% Et_2O/hexanes for 10 CV, followed by 10% Et_2O/hexanes for 10 CV) to afford the title compound as a yellow oil (38 mg, 80% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 5.88 (dtt, J = 14.6, 6.4, 1.7 Hz, 1H), 5.35 (dtt, J = 15.0, 5.6, 1.7 Hz, 1H), 3.16–2.96 (m, 2H), 2.10 (qdd, J = 7.5, 6.0, 1.5 Hz, 2H), 1.02 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 137.8, 117.9, 116.2, 25.2, 20.4, 13.1 ppm. ^{1}H NMR spectra of the purified product match those reported in the literature.[24]

Duplicate experiment: 34 mg, 71% yield.

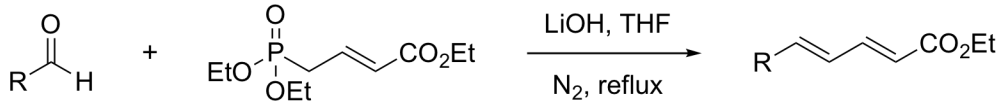
4.4.6 Additional Substrates Examined

Following general procedure A (unless otherwise noted), we observed the following:



4.4.7 Preparation of Substrates

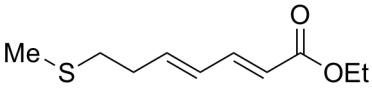
General Procedure B for the Synthesis of Substrates



Following literature precedent,[10a] an oven-dried three-neck, 250 mL round bottom flask was equipped with an oven-dried magnetic stir bar and charged with substrate (10 mmol, 1.0 equiv), triethyl 4-phosphonocrotonate (2.75 g, 11 mmol, 1.1 equiv), and lithium hydroxide (263 mg, 11 mmol, 1.1 equiv). The flask was fitted with an oven-dried reflux condenser and two rubber septa. The setup was connected with an adapter and tubing to a Schlenk-line and evacuated and backfilled with nitrogen (this process was repeated a total of three times). Dry THF (50 mL) was added via a 50 mL syringe by puncturing one of the rubber septa. The reaction mixture was heated under reflux conditions for 18 h. The reaction mixture was then allowed to cool to room temperature and filtered through a short plug of Celite®, eluting with ether. The crude mixture was concentrated *in vacuo*, and purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System.

3-phenylpropanal, cyclohexanecarbaldehyde, pivaldehyde, 3-(methylthio)propanal, 3-(benzyloxy)propanal, 5-methyl-5-nitrohex-1-ene, pent-4-enal, 2-(4,6-dichloropyrimidin-5-yl)acetaldehyde, 3-(1*H*-pyrazol-1-yl)propanal, and *tert*-butyl 4-(3-oxopropyl)piperidine-1-carboxylate were purchased from Millipore-Sigma, Alfa-Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific and were used as received. Triethyl 4-phosphonocrotonate was purchased from Alfa-Aesar and used as received. Lithium hydroxide (powder) was purchased from Millipore-Sigma. Ethyl sorbate was purchased from Millipore-Sigma and used as received. Sorbonitrile was purchased from Matrix Scientific and used as received.

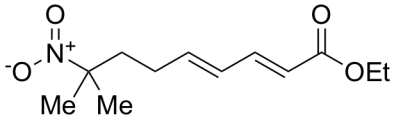
ethyl *(2E,4E)*-7-(methylthio)hepta-2,4-dienoate (S1)



Following general procedure B, 3-(methylthio)propanal (1.04 g, 10 mmol, 1.0 equiv), triethyl 4-phosphonocrotonate (2.75 g, 11 mmol, 1.1 equiv), lithium hydroxide (263 mg, 11 mmol, 1.1 equiv), and THF (50 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (50 g KP-Sil cartridge, 0% Et_2O/hexanes for 1 column volume (CV), then 0-10% Et_2O/hexanes for

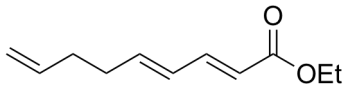
15 CV, followed by 10% Et_2O/hexanes for 15 CV) to afford the title compound as a yellow oil (1.24 g, 63% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.30–7.23 (m, 1H), 6.32–6.04 (m, 2H), 5.84 (d, J = 15.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.61 (d, J = 7.0 Hz, 2H), 2.50 (q, J = 7.0 Hz, 2H), 2.14 (s, 3H), 1.39–1.23 (m, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 167.1, 144.4, 141.5, 129.6, 120.2, 60.3, 33.3, 32.7, 15.6, 14.3 ppm. **IR:** 2979, 2916, 1707, 1642, 1244, 1127, 998, 731 cm^{-1}. **HRMS Calcd. m/z** for $[C_{10}H_{16}SO_2 + H]^+$: 201.0944. Found: 201.0946.

ethyl *(2E,4E)*-8-methyl-8-nitronona-2,4-dienoate (S2)



Following general procedure B, 5-methyl-5-nitrohex-1-ene (1.45 g, 10 mmol, 1.0 equiv), triethyl 4-phosphonocrotonate (2.75 g, 11 mmol, 1.1 equiv), lithium hydroxide (263 mg, 11 mmol, 1.1 equiv), and THF (50 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (50 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a pale-yellow oil (1.33 g, 55% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.23 (dd, J = 15.4, 10.8 Hz, 1H), 6.18 (td, J = 16.8, 16.0, 10.7 Hz, 1H), 6.04 (dt, J = 15.2, 6.7 Hz, 1H), 5.87–5.71 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.17 (dt, J = 10.8, 6.6 Hz, 2H), 2.09–1.97 (m, 2H), 1.61 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 167.0, 144.1, 141.1, 129.4, 120.4, 87.7, 60.3, 39.6, 27.7, 25.8, 14.3 ppm. **IR:** 2985, 1709, 1643, 1536, 1260, 1142, 1000 cm^{-1}. **HRMS Calcd. m/z** for $[C_{12}H_{19}NO_4 + Na]^+$: 264.1206. Found: 264.1209.

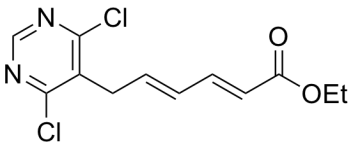
ethyl *(2E,4E)*-nona-2,4,8-trienoate (S3)



Following general procedure B, pent-4-enal (841 mg, 10 mmol, 1.0 equiv), triethyl 4-phosphonocrotonate (2.75 g, 11 mmol, 1.1 equiv), lithium hydroxide (263 mg, 11 mmol, 1.1 equiv), and THF (50 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (50 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-5% EtOAc/hexanes for 10 CV, followed by 5% EtOAc/hexanes for 10 CV) to afford the title compound as a colorless oil (970 mg, 54% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.27 (dd, J = 15.2, 10.4 Hz, 1H), 6.26–6.00 (m, 2H), 6.00–5.67 (m, 2H), 5.15–4.92 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 2.30 (q, J = 6.9, 6.5

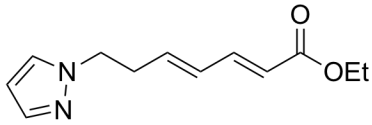
Hz, 2H), 2.22 (q, J = 6.9 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 167.3, 144.8, 143.4, 137.5, 119.6, 115.3, 60.2, 32.8, 32.3, 14.3 ppm. **IR:** 2927, 1710, 1641, 1253, 1136, 998, 911, 732 cm^{-1}. **HRMS Calcd. m/z for** $[C_{11}H_{16}O_2 + H]^+$**:** 181.1223. Found: 181.1221.

ethyl *(2E,4E)*-6-(4,6-dichloropyrimidin-5-yl)hexa-2,4-dienoate (S4)



Following general procedure B, 5-methyl-5-nitrohex-1-ene (1.45 g, 10 mmol, 1.0 equiv), triethyl 4-phosphonocrotonate (2.75 g, 11 mmol, 1.1 equiv), lithium hydroxide (263 mg, 11 mmol, 1.1 equiv), and THF (50 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-20% EtOAc/hexanes for 10 CV, followed by 20% EtOAc/hexanes for 10 CV) to afford the title compound as a colorless oil (2.15 g, 67% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 8.69 (s, 1H), 7.23 (dd, J = 15.4, 10.8 Hz, 1H), 6.32–6.18 (m, 1H), 6.11 (dt, J = 15.2, 6.5 Hz, 1H), 5.86 (d, J = 15.4 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.78 (dd, J = 6.6, 1.4 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 166.7, 162.0, 156.2, 143.2, 134.3, 131.3, 130.1, 121.9, 60.4, 33.3, 14.3 ppm. **IR:** 2979, 1708, 1514, 1410, 1239, 1150, 997, 778 cm^{-1}. **Anal. Calcd. for** $C_{12}H_{12}Cl_2N_2O_2$**:** C, 59.73; H, 7.94. Found: C, 59.57; H, 7.95.

ethyl *(2E,4E)*-7-(1H-pyrazol-1-yl)hepta-2,4-dienoate (S5)



Following general procedure B, 5-methyl-5-nitrohex-1-ene (500 mg, 4.0 mmol, 1.0 equiv), triethyl 4-phosphonocrotonate (1.11 g, 4.4 mmol, 1.1 equiv), lithium hydroxide (106 mg, 4.4 mmol, 1.1 equiv), and THF (25 mL) were used. The crude reaction mixture was purified with the aid of a Teledyne ISCO CombiFlash Automated Flash Chromatography System (25 g KP-Sil cartridge, 0% EtOAc/hexanes for 1 column volume (CV), then 0-30% EtOAc/hexanes for 10 CV, followed by 30% EtOAc/hexanes for 10 CV) to afford the title compound as a yellow oil (535 mg, 60% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ**:** 7.53 (d, J = 1.9 Hz, 1H), 7.36, (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 15.4, 10.8 Hz, 1H), 6.25 (t, J = 2.1 Hz, 1H), 6.22–6.13 (m, 1H), 6.02 (dt, J = 14.9, 7.1 Hz, 1H), 5.81 (d, J = 15.4 Hz, 1H), 4.27–4.17 (m, 4H), 2.76 (qd, J = 7.0, 1.3 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ**:** 167.0, 144.0, 139.6, 138.5, 130.9, 129.1, 105.4, 60.3, 51.1, 33.9, 14.3 ppm. **IR:** 2980, 2931, 1709, 1261, 1178,

1132, 1091, 1033, 1000, 751 cm^{-1}. **HRMS Calcd. m/z** for $[C_{12}H_{16}N_2O_2 + H]^+$: 221.1285. Found: 221.1286.

Synthesis of Other Substrates

Ethyl *(2E,4E)*-7-phenylhepta-2,4-dienoate[12a,25], ethyl *(2E,4E)*-5-cyclohexylpenta-2,4-dienoate[26], ethyl *(2E,4E)*-6,6-dimethylhepta-2,4-dienoate[27], ethyl *(2E,4E)*-7-(benzyloxy)hepta-2,4-dienoate[28], *tert*-butyl 4-(*(3E,5E)*-7-ethoxy-7-oxohepta-3,5-dien-1-yl)piperidine-1-carboxylate[29], penta-1,4-dien-3-yl *(E)*-hex-3-enoate[30], *(E)*-*N,N*-dimethylhex-3-enamide[31], *(2E,4E)*-*N*-methoxy-*N*-methylhexa-2,4-dienamide[32], and ((*(1E,3E)*-penta-1,3-dien-1-yl)sulfonyl)benzene[33] were prepared as previously reported in the literature.

Sorbic acid was purchased from Millipore-Sigma and used as received. *(2E,4E)*-hexa-2,4-dienoic acid, dimethylamine, *N,O*-dimethylhydroxylamine hydrochloride, 1,1'-carbonyldiimidazole, *(E)*-but-2-enal, diethyl phenylsulfonylmethylphosphonate, diethyl (cyanomethyl)phosphonate, and *n*-butyllithium were purchased from Millipore-Sigma, Alfa Aesar, Strem, TCI-America, Combi-Blocks, or Matrix Scientific and were used as received.

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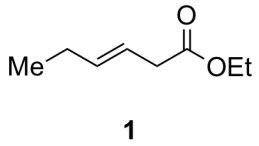
4.6 Spectra and Chromatograms



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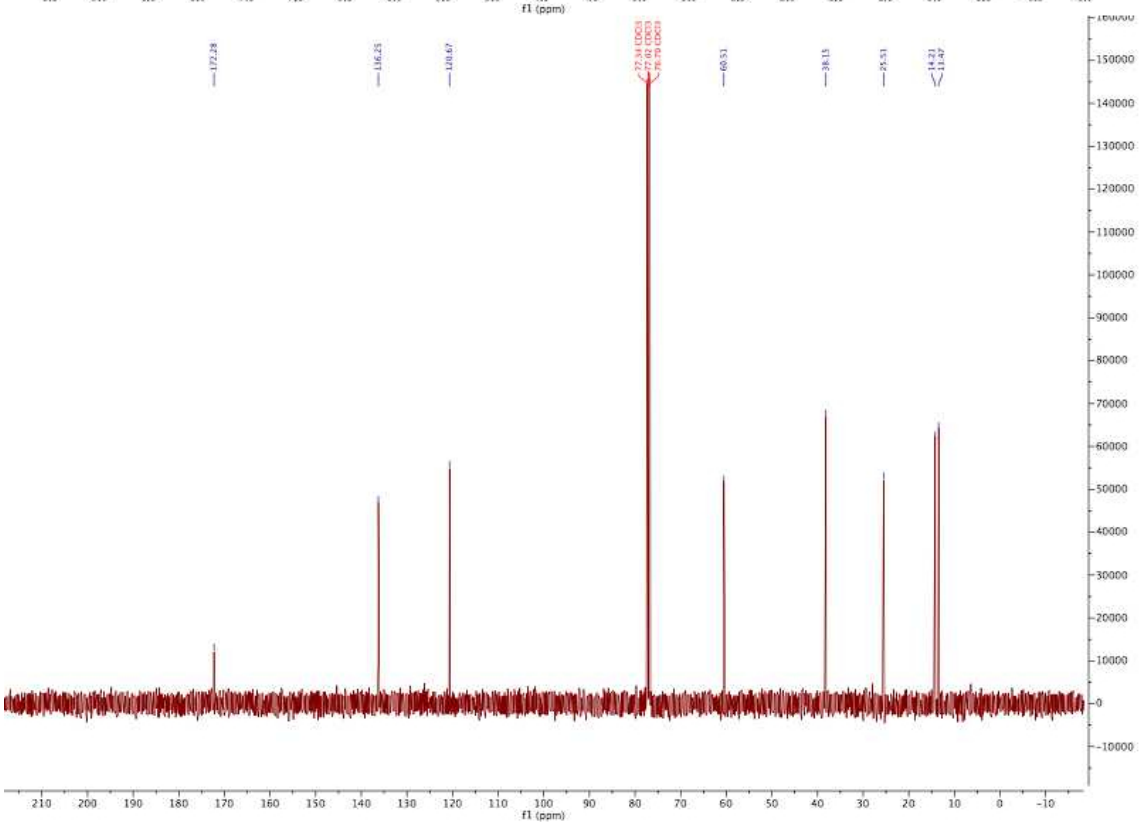

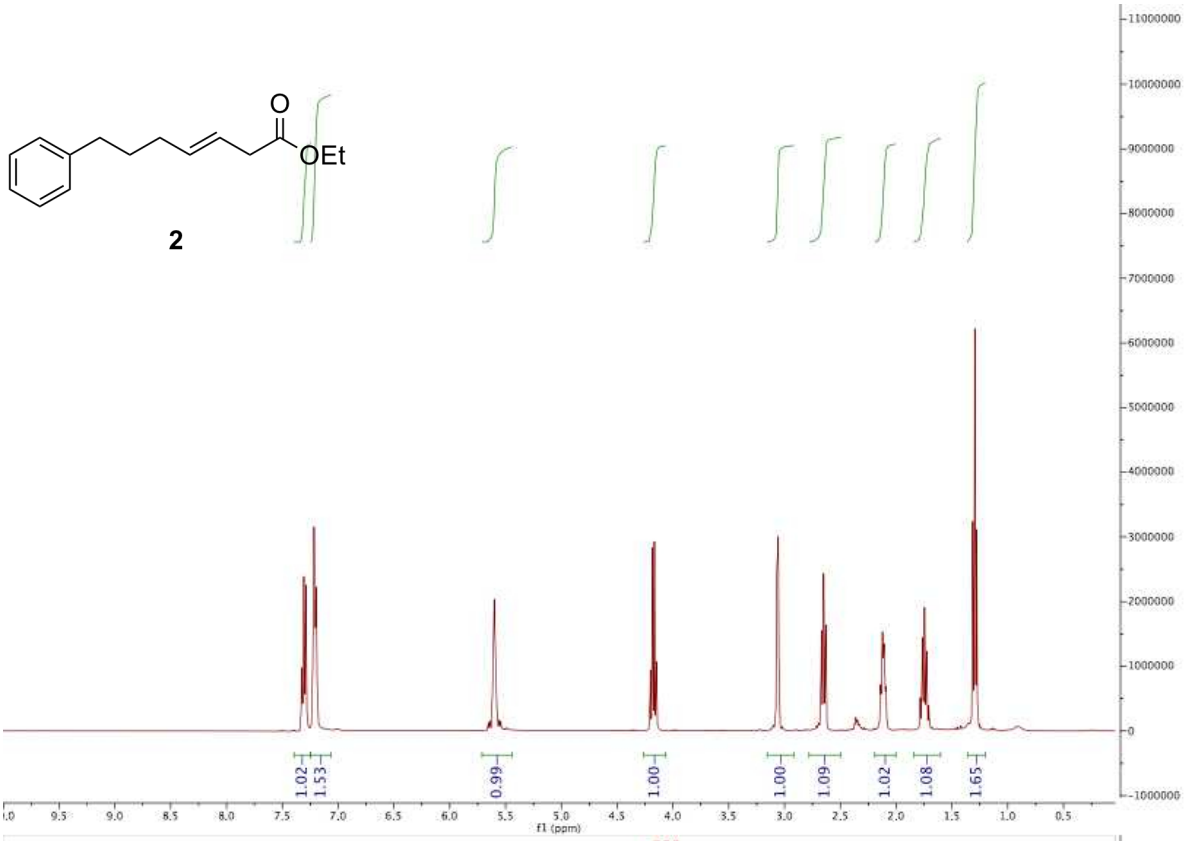
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OEt
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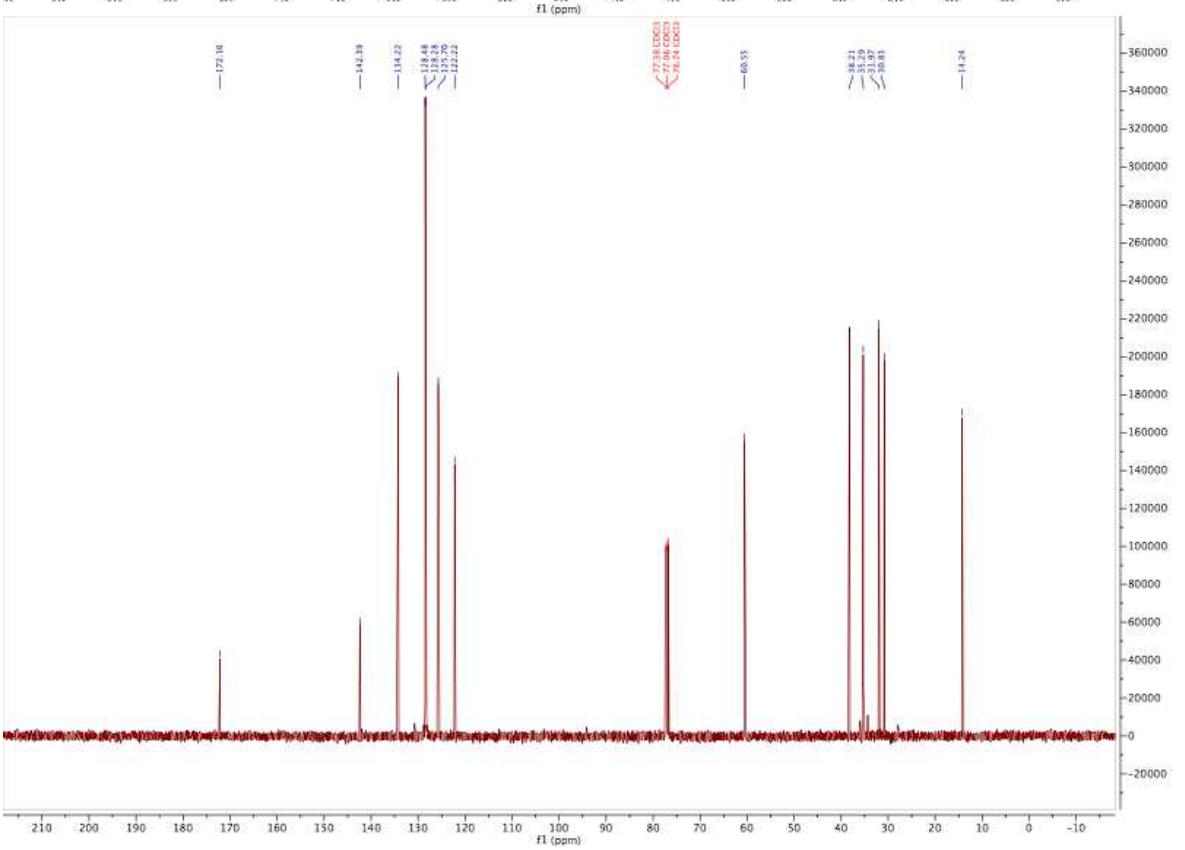
1.53
0.99
1.00
1.00
1.09
1.02
1.08
1.65
f1 (ppm)

2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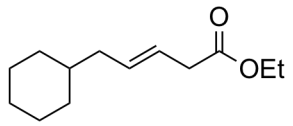
142.39
134.22
128.48
128.36
125.70
122.22
77.16 CDCl3
60.55
38.21
35.29
33.97
30.83
14.24
f1 (ppm)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OEt

3

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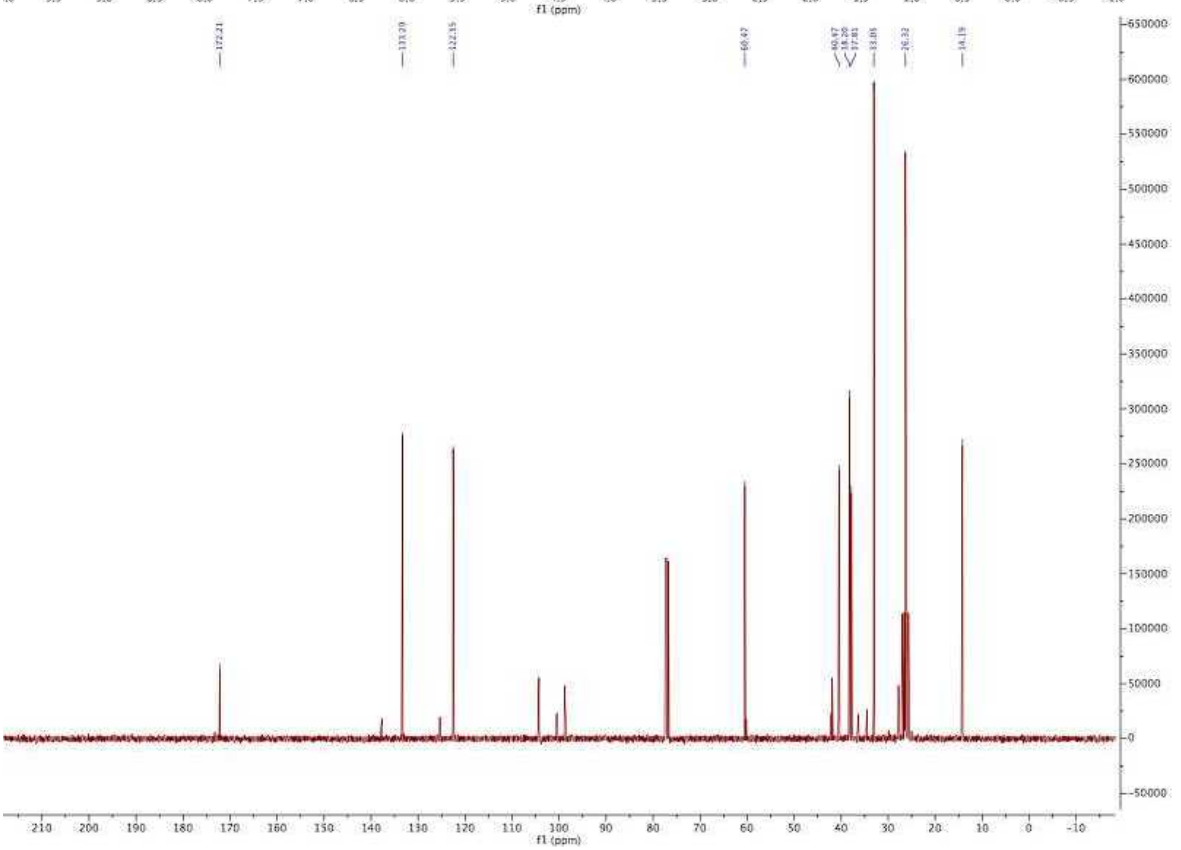
0.17
2.11
1.99
2.32
6.22
8.73
2.31
f1 (ppm)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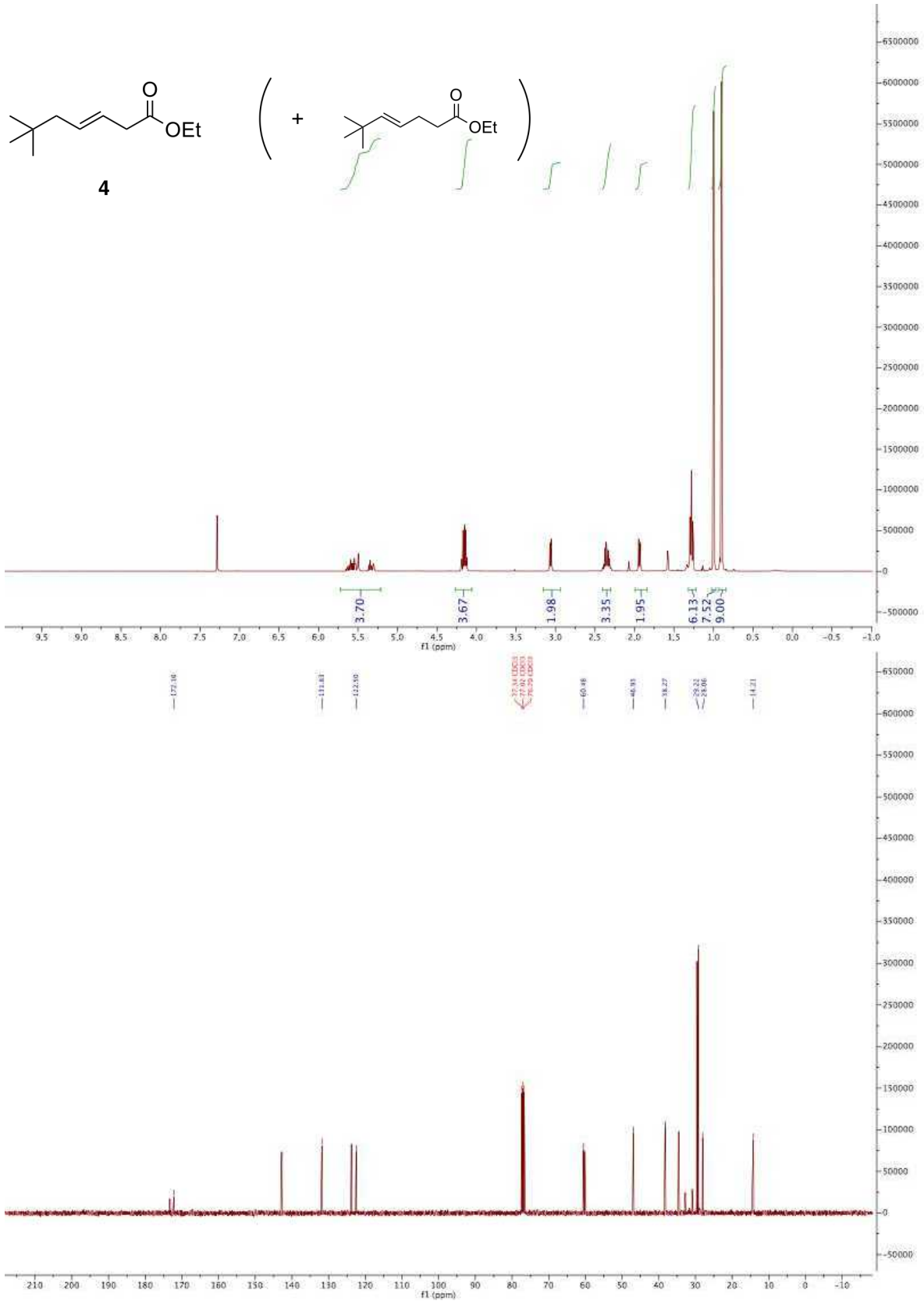
133.29
132.35
60.47
26.32
14.19
f1 (ppm)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OEt
4
+
O
OEt
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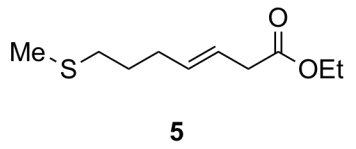
3.67
1.98
3.35
1.95
6.13
7.52
9.00
f1 (ppm)
f1 (ppm)


Me
S
O
OEt

5

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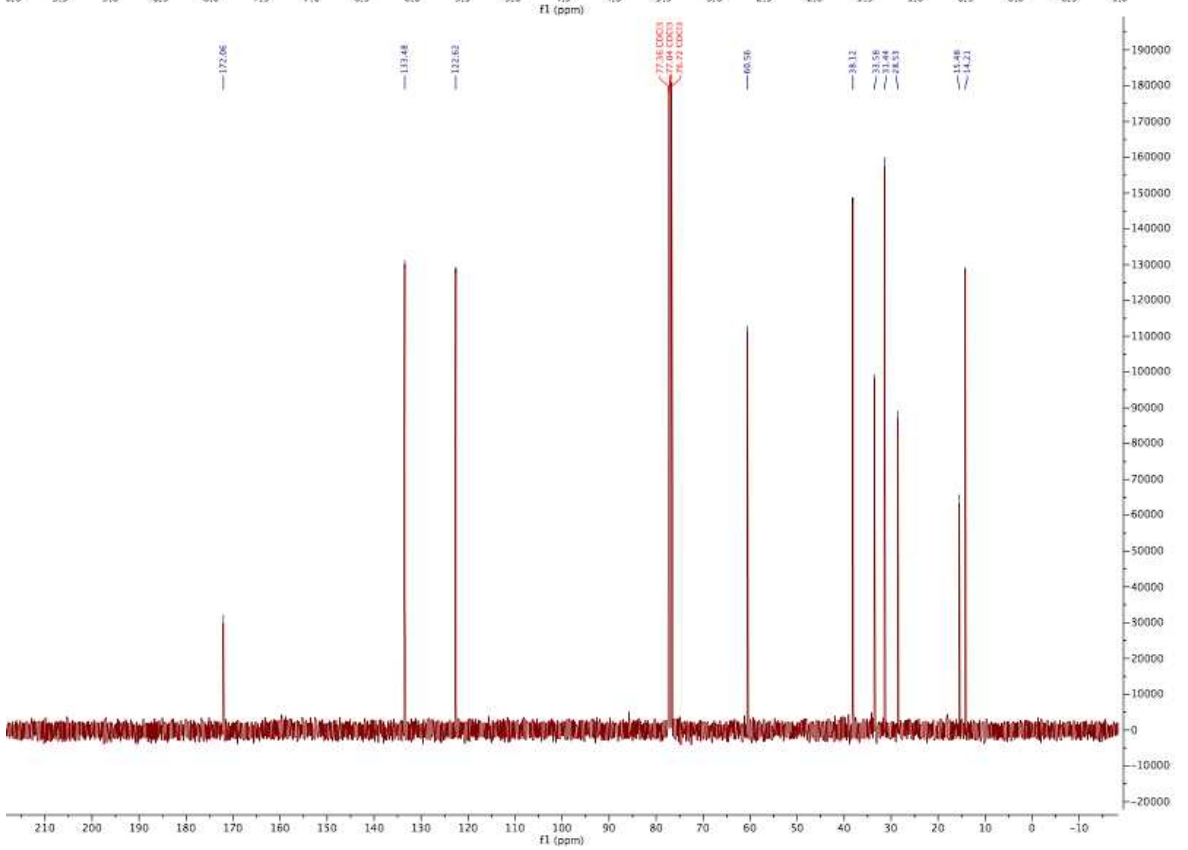
2.00
2.01
1.85
3.04
2.31
3.41
f1 (ppm)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133.48
122.62
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
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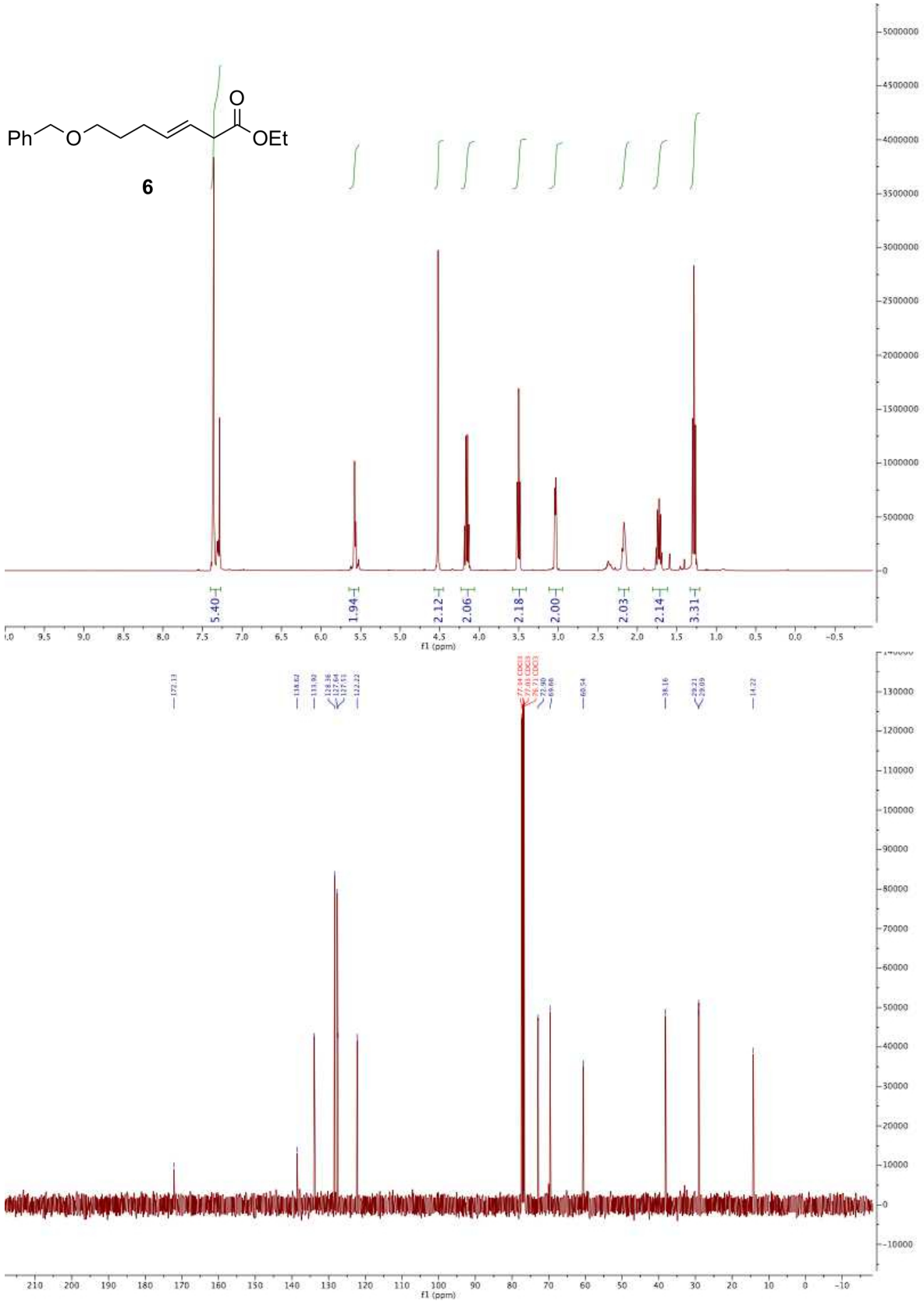
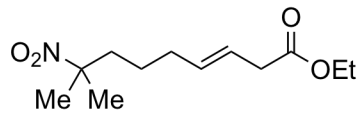
38.12
33.58
31.64
24.53
15.48
14.21
f1 (ppm)


Ph
O
O
OEt
6
5.40
1.94
2.12
2.06
2.18
2.00
2.03
2.14
3.31
f1 (ppm)
172.13
118.62
133.80
128.36
127.64
127.51
122.22
77.34
77.03
76.71
72.90
69.66
60.54
38.16
29.21
29.09
14.22
f1 (ppm)



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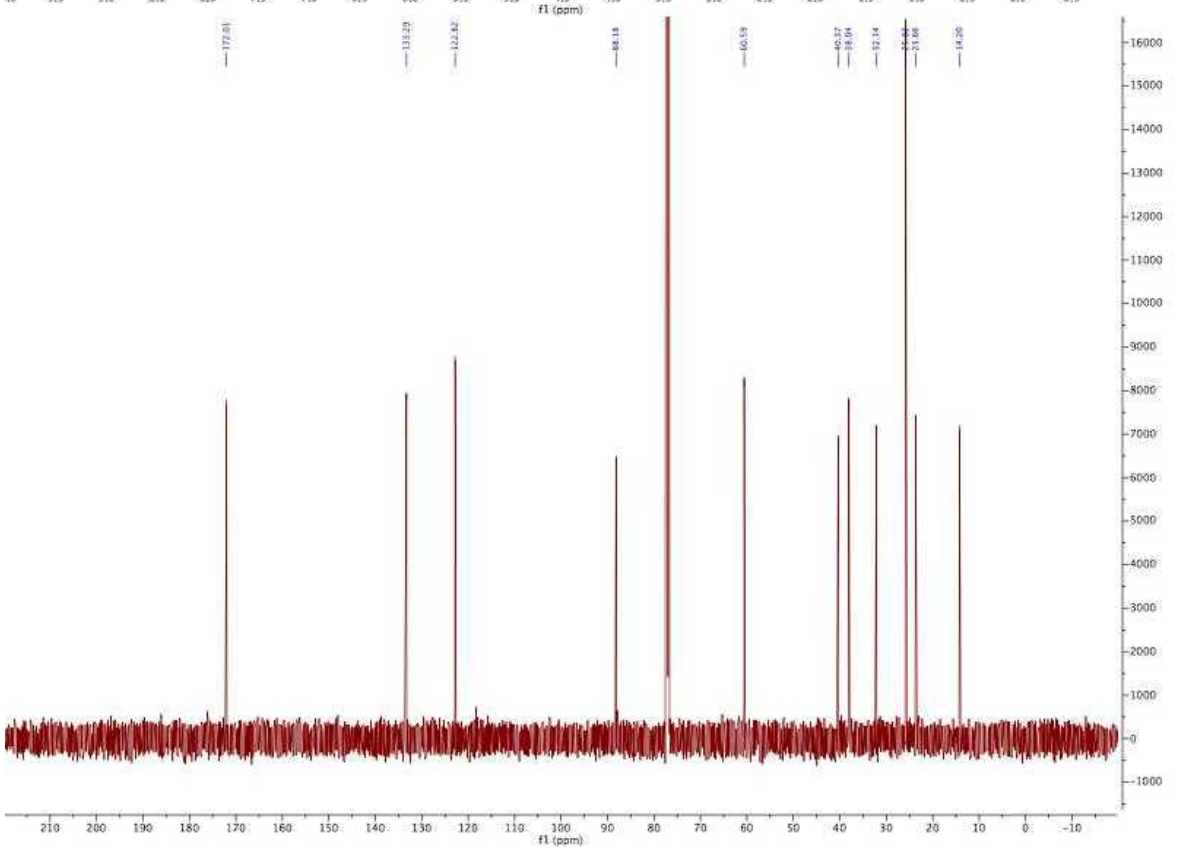
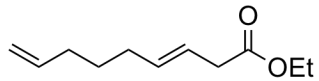
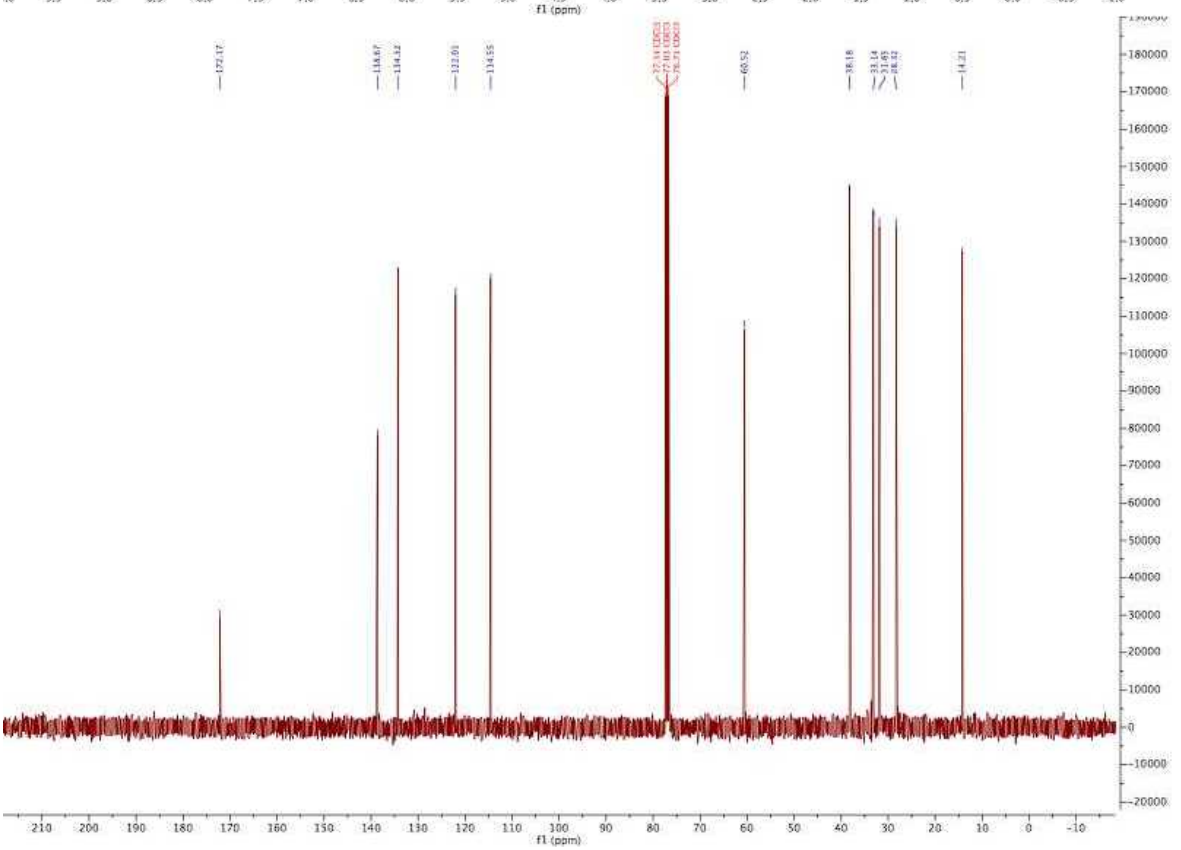



O
OEt

8

1.00
1.96
2.07
2.06
2.00
4.14
2.02
3.34
f1 (ppm)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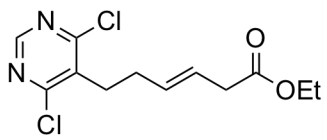
114.55
77.31
60.52
38.18
33.14
31.65
28.82
14.21
f1 (ppm)


N
Cl
N
Cl
O
OEt

9

0.94
2.00
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1.76
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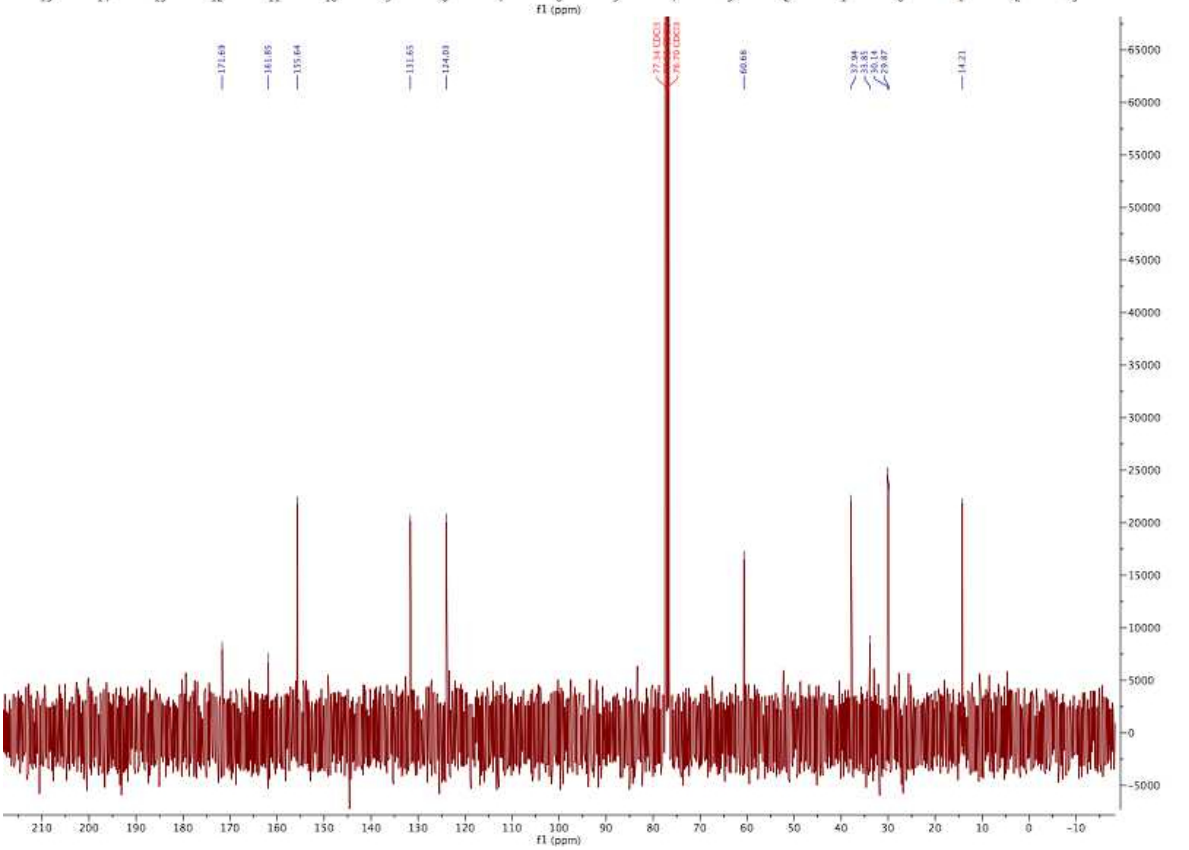
2.31
3.23
f1 (ppm)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155.64
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76.70 CDCl3
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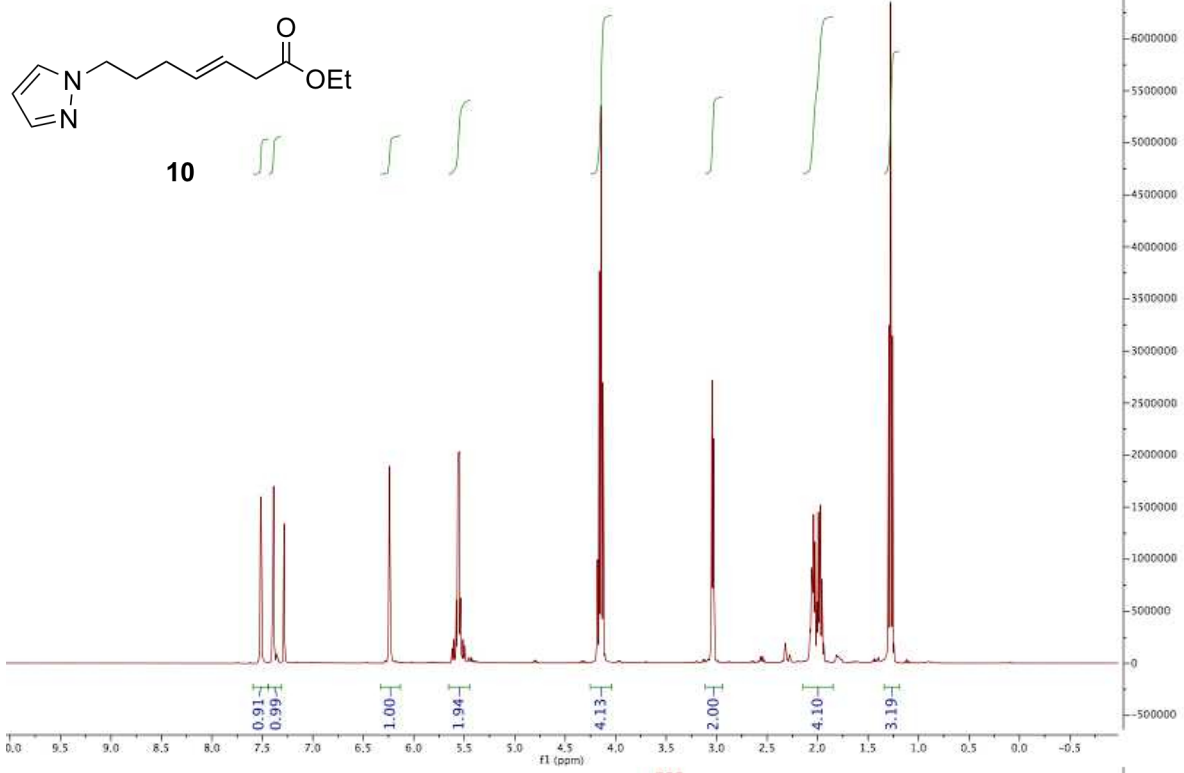
37.94
33.85
30.14
29.87
14.21
f1 (ppm)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OEt
N
N
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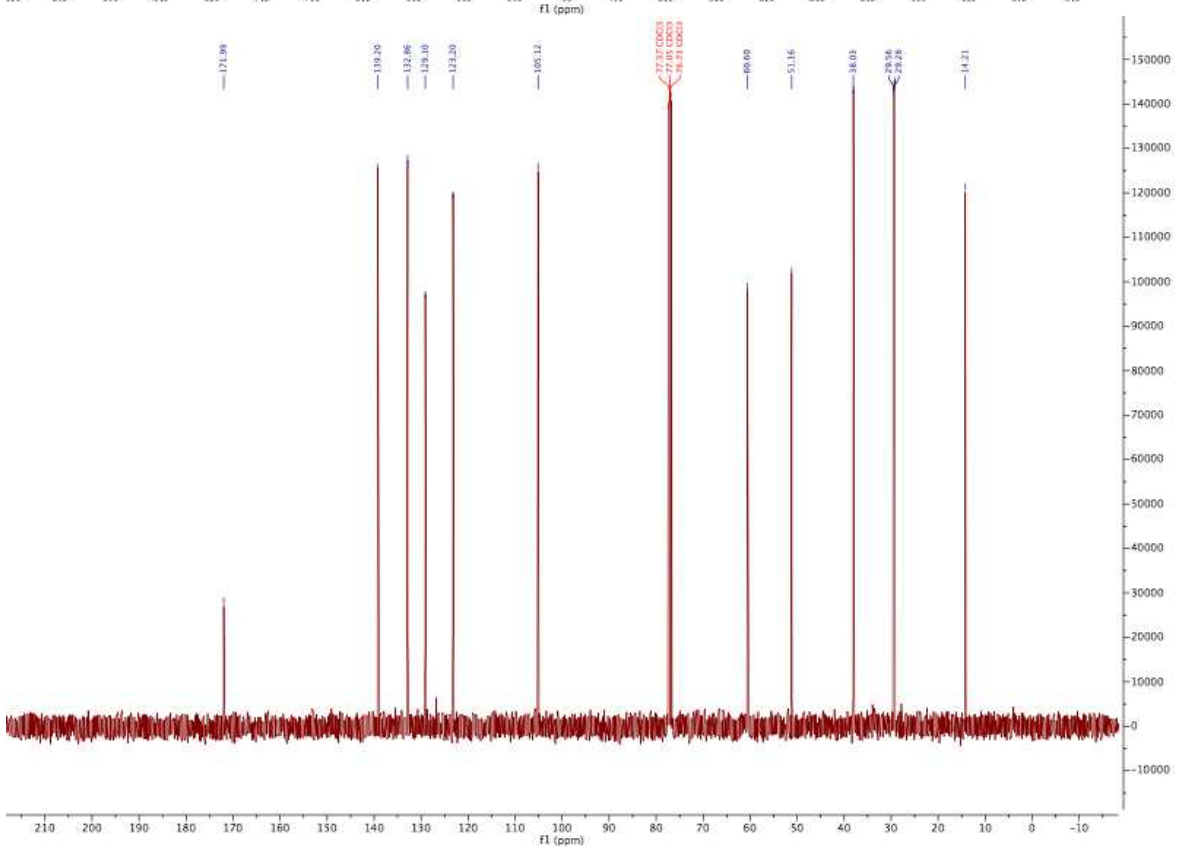
0.99
1.00
1.94
4.13
2.00
4.10
3.19
f1 (ppm)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129.10
123.20
105.12
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
66.60
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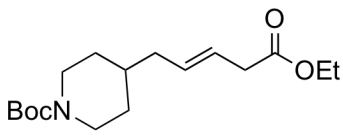
38.03
29.56
29.26
14.21
f1 (ppm)


O
OEt
BocN

11

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1.92
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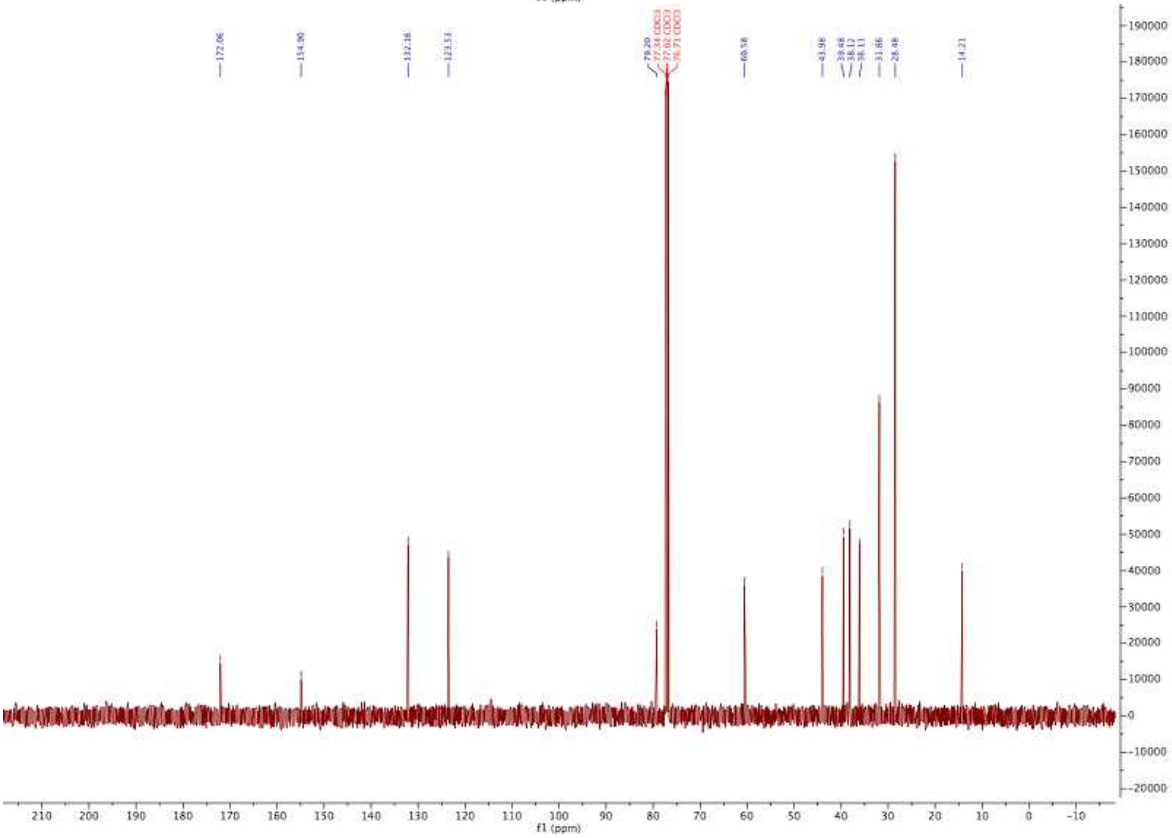
2.14
2.03
2.83
9.22
3.05
2.21
f1 (ppm)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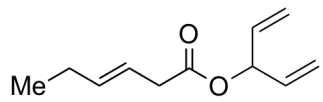
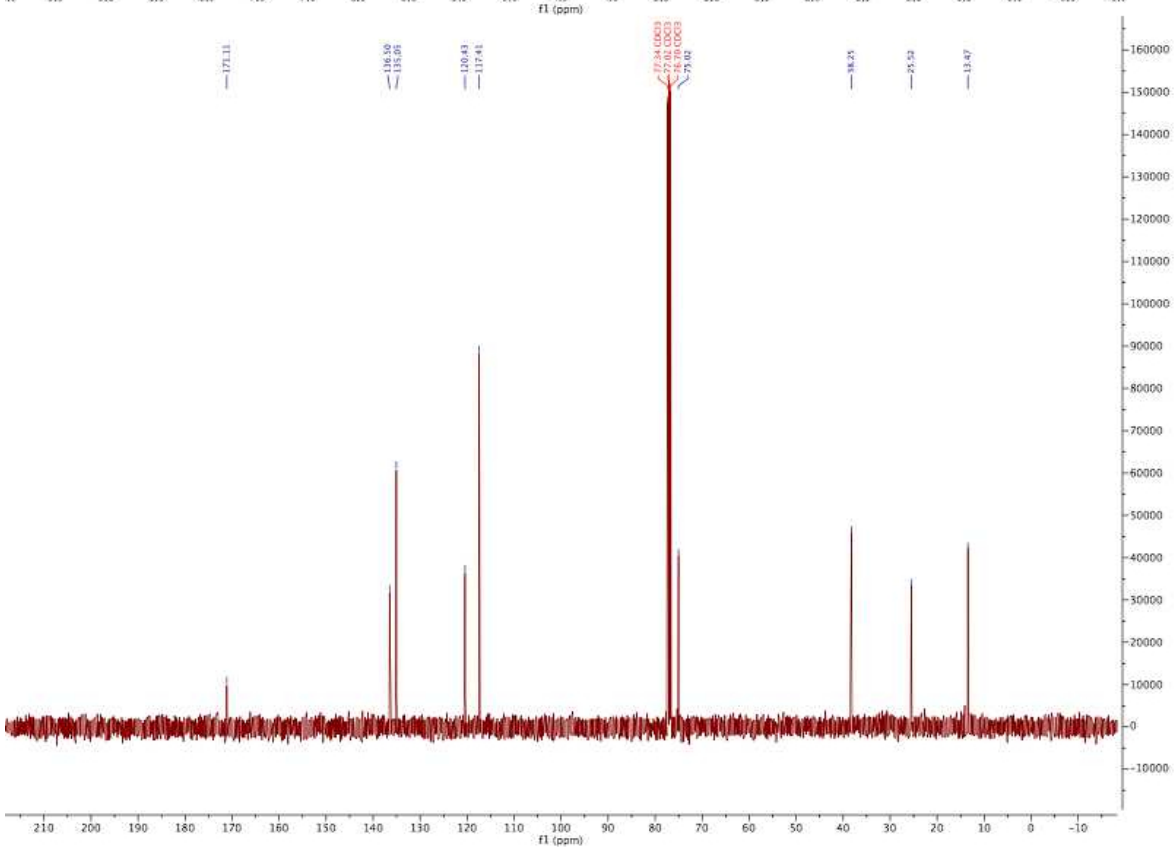
154.90
132.16
123.51
79.29
77.16 CDCl3
77.02 CDCl3
76.71 CDCl3
66.58
43.98
39.48
38.12
38.11
31.86
28.48
14.21
f1 (ppm)


Me
O
O

12

1.85
0.91
1.98
4.06
2.00
2.14
3.23
f1 (ppm)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136.59
135.06
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117.41
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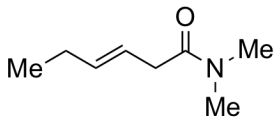
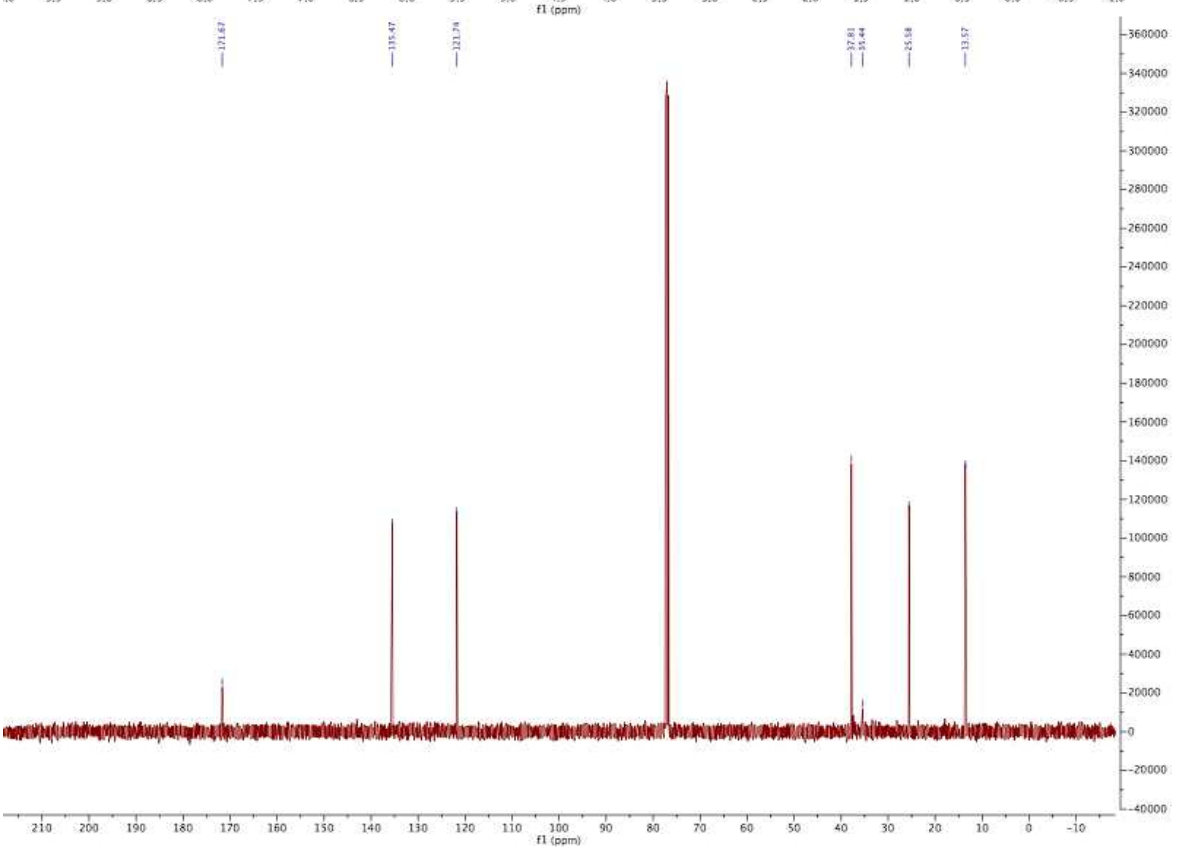
77.02 CDCl3
76.70 CDCl3
75.82
38.25
25.52
13.47
f1 (ppm)


O
Me
N
Me
Me

13

2.00
2.22
6.21
2.33
3.14
f1 (ppm)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37.81
35.44
25.58
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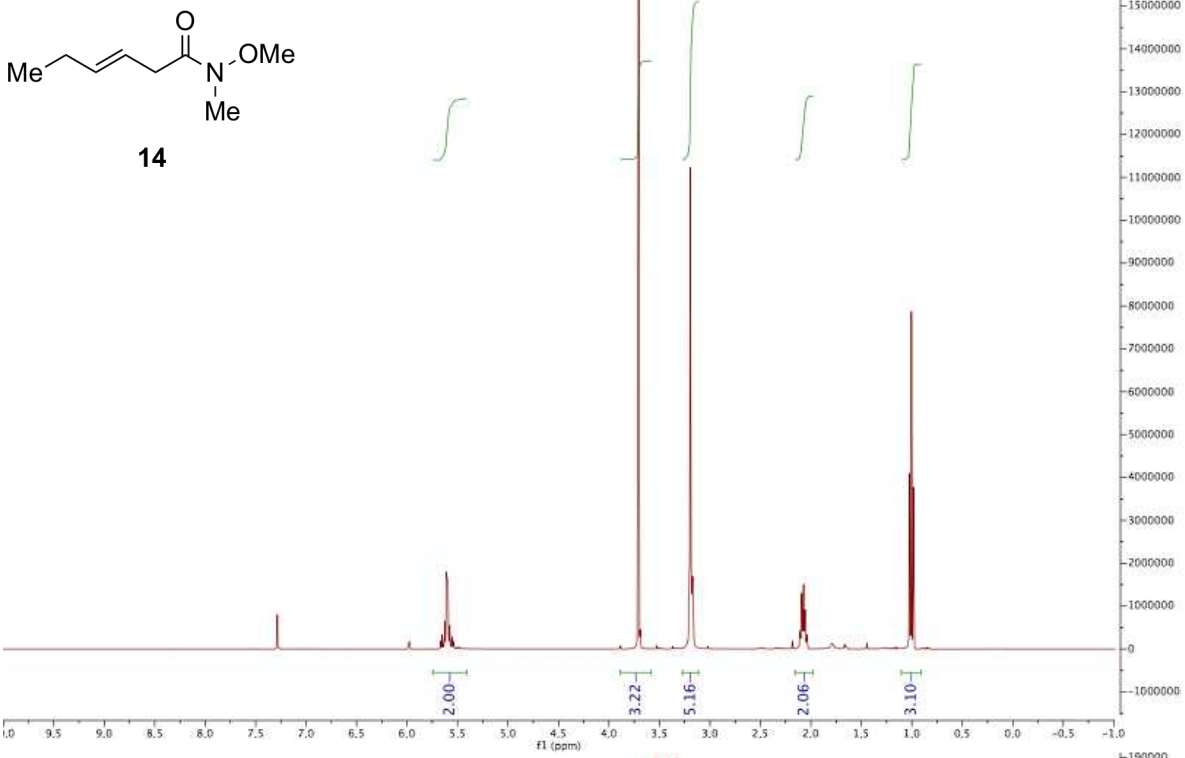
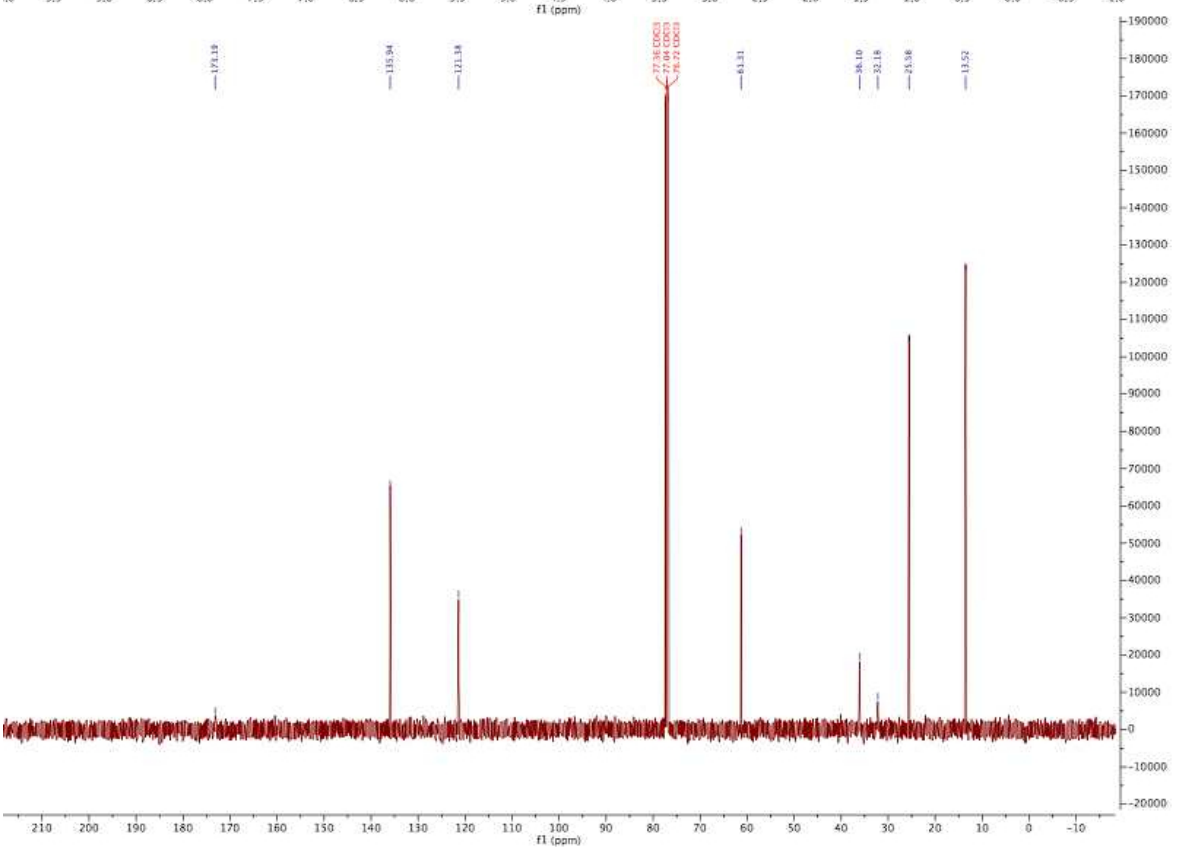

O
Me
N
OMe
Me
14
2.00
3.22
5.16
2.06
3.10
f1 (ppm)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135.94
121.34
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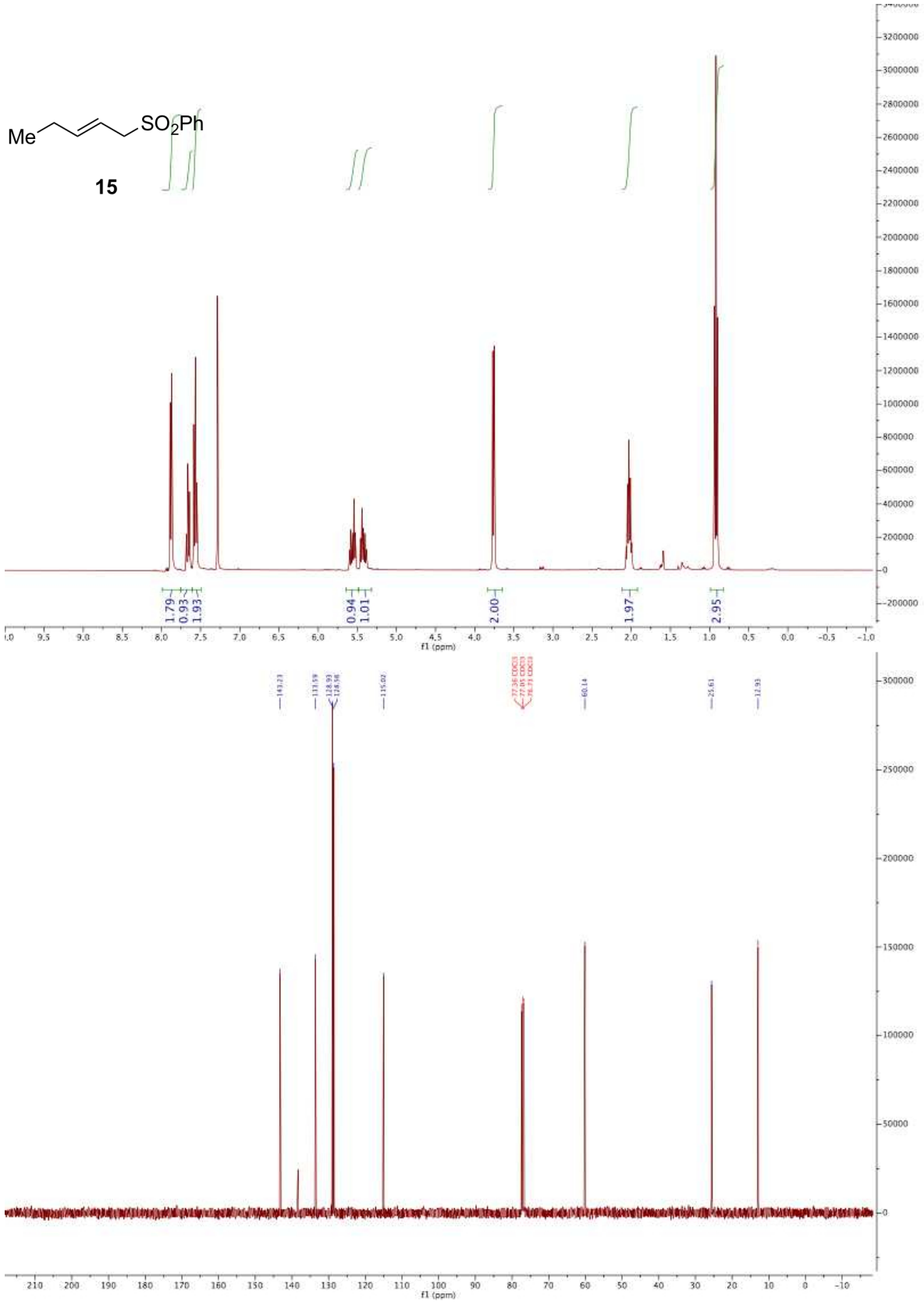
77.04 CDCl3
76.72 CDCl3
63.31
38.10
32.16
25.98
13.52
f1 (ppm)


Me
SO2Ph
15
1.79
0.93
1.93
0.94
1.01
2.00
1.97
2.95
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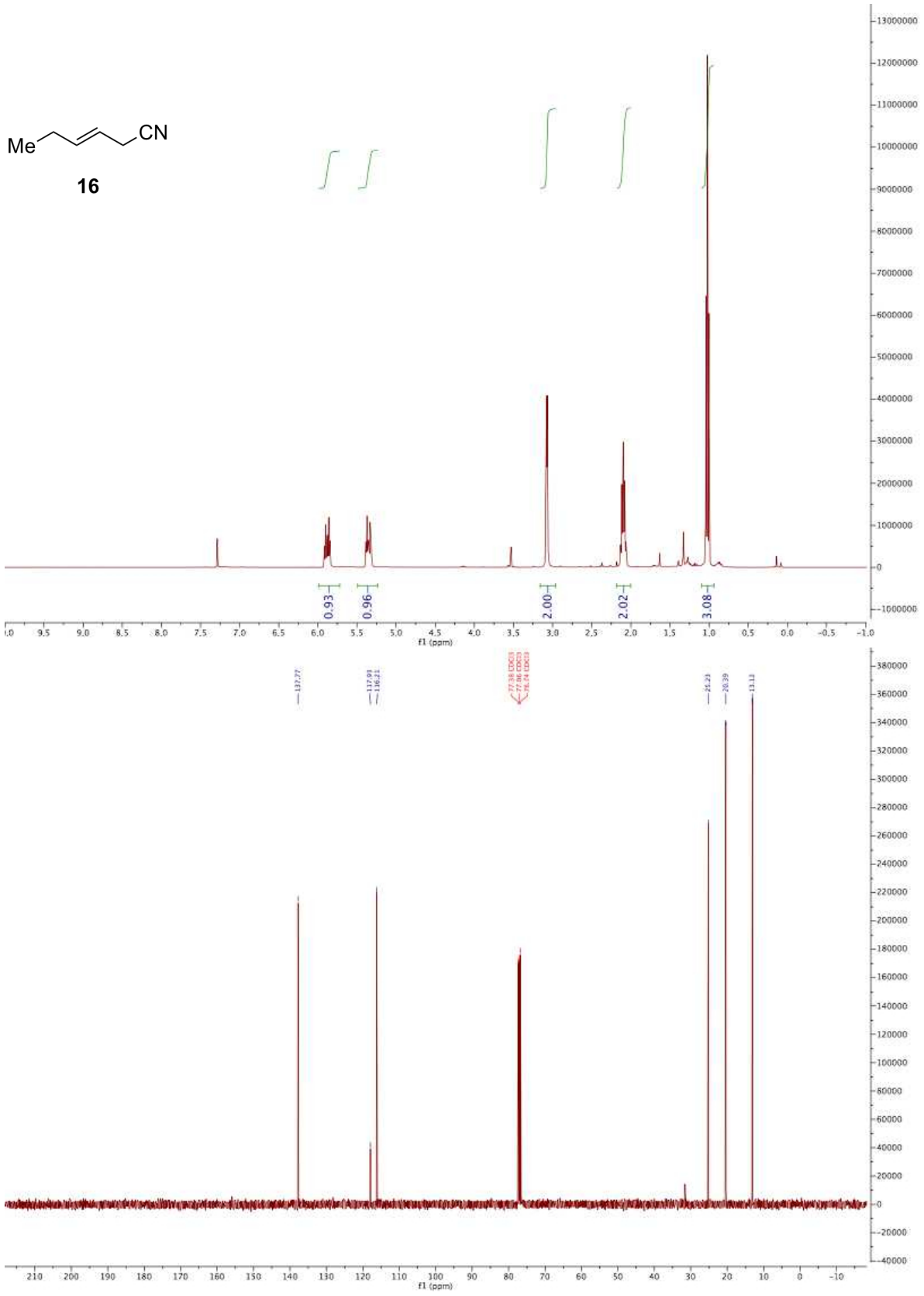
143.23
131.59
128.93
124.56
115.02
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
60.14
25.61
12.93
f1 (ppm)


Me
CN
16
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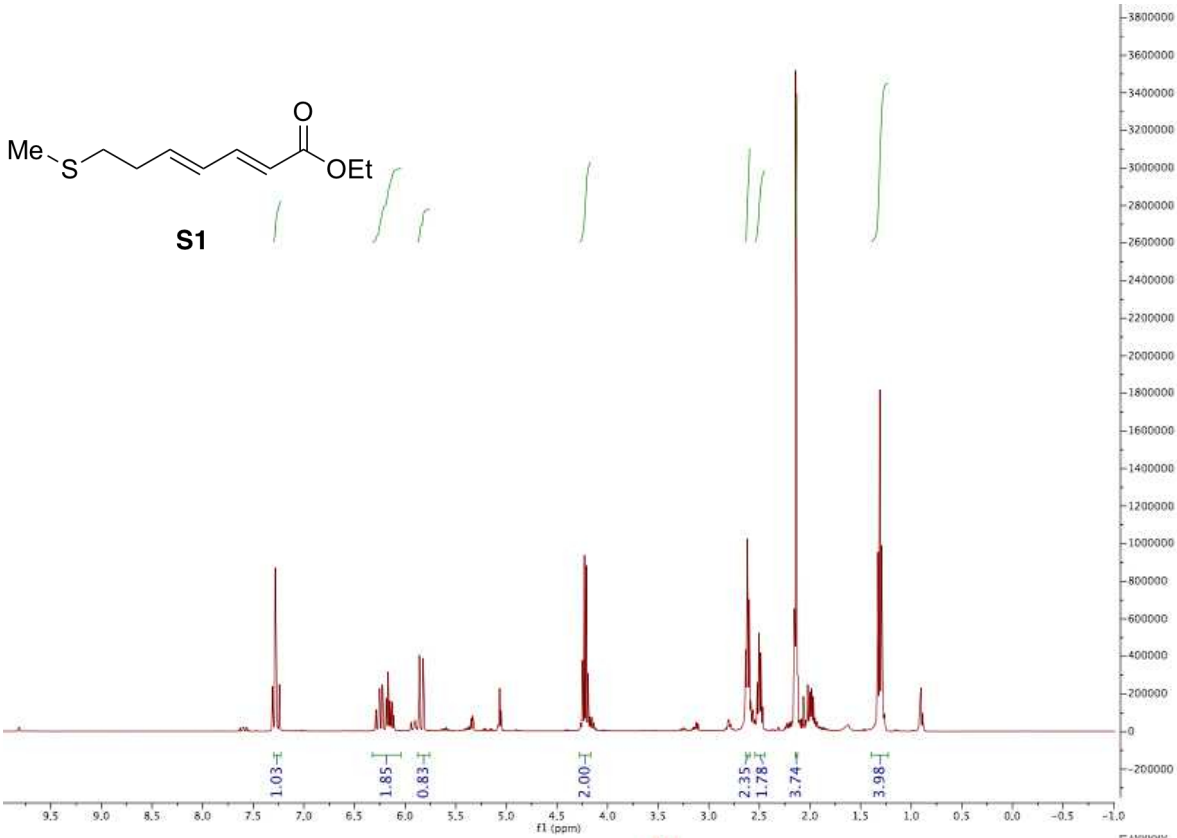
0.96
2.00
2.02
3.08
f1 (ppm)
f1 (ppm)


Me
S
O
OEt
S1
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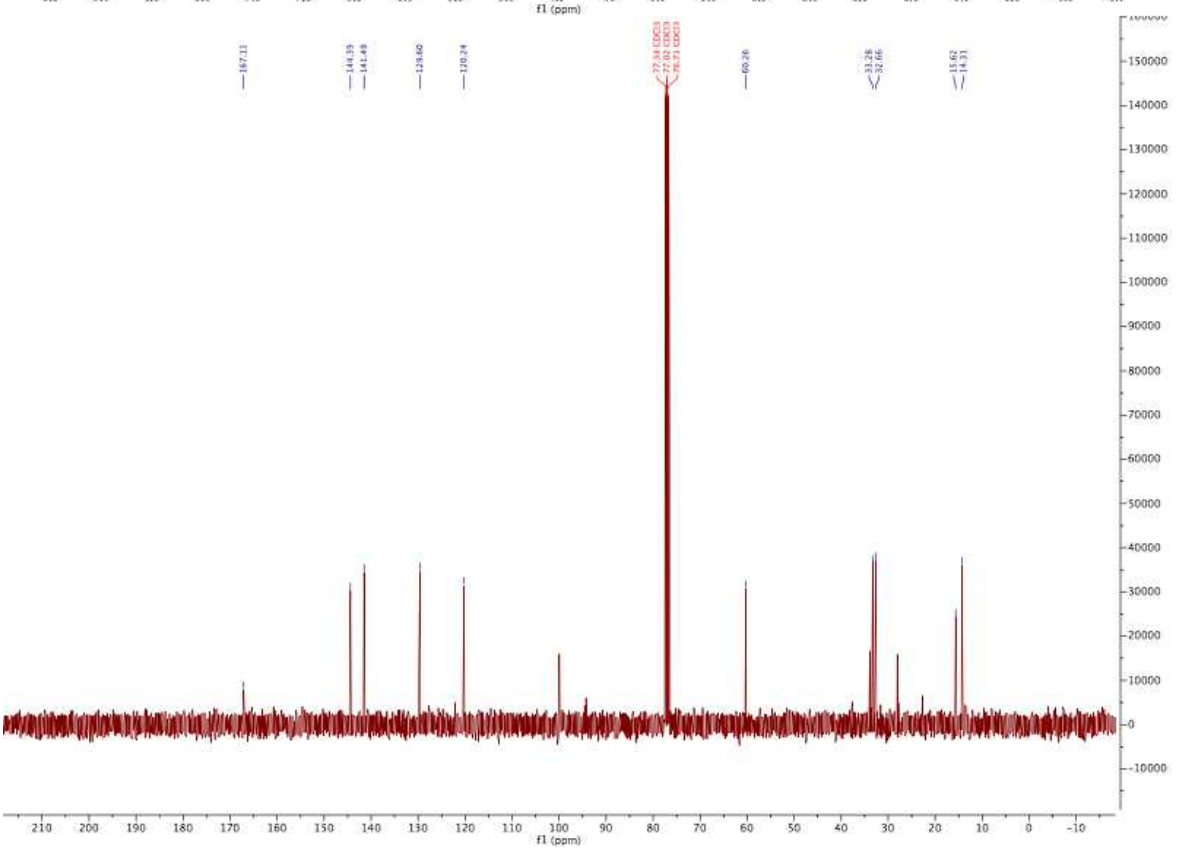
1.85
0.83
2.00
2.35
1.78
3.74
3.98
f1 (ppm)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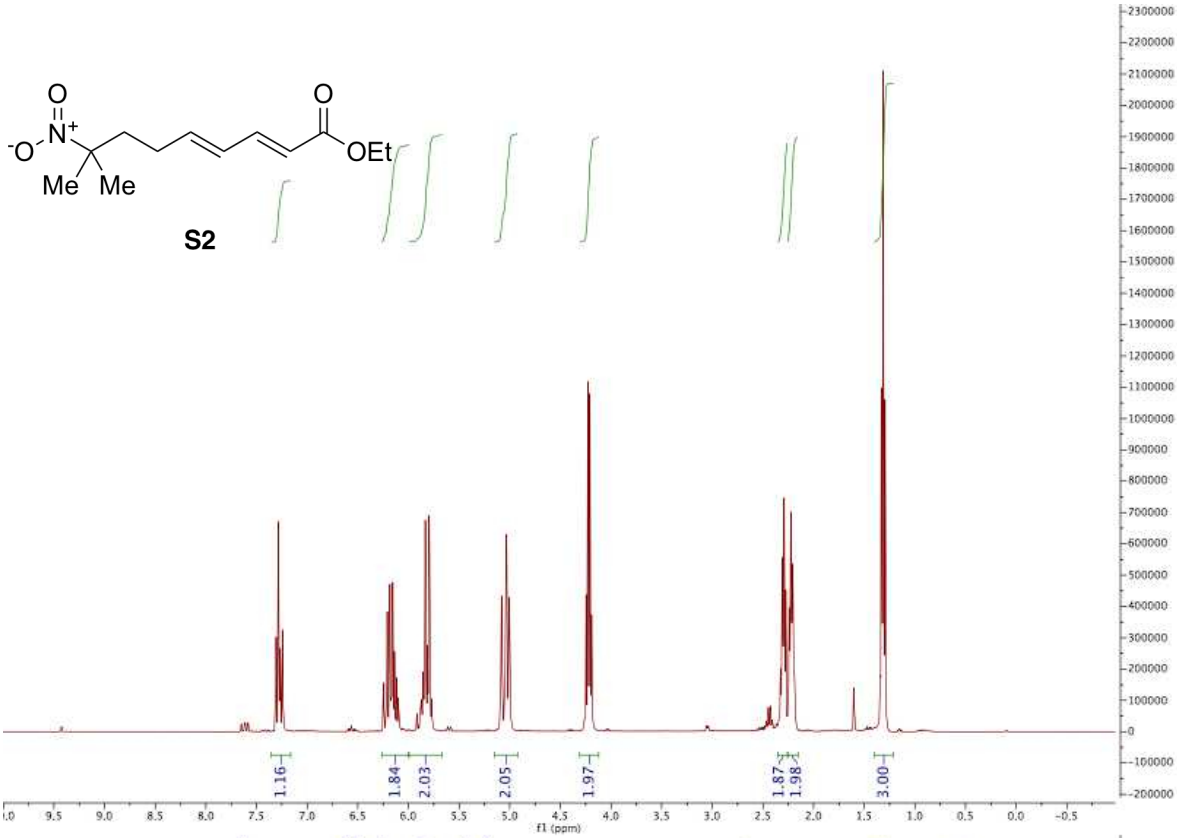
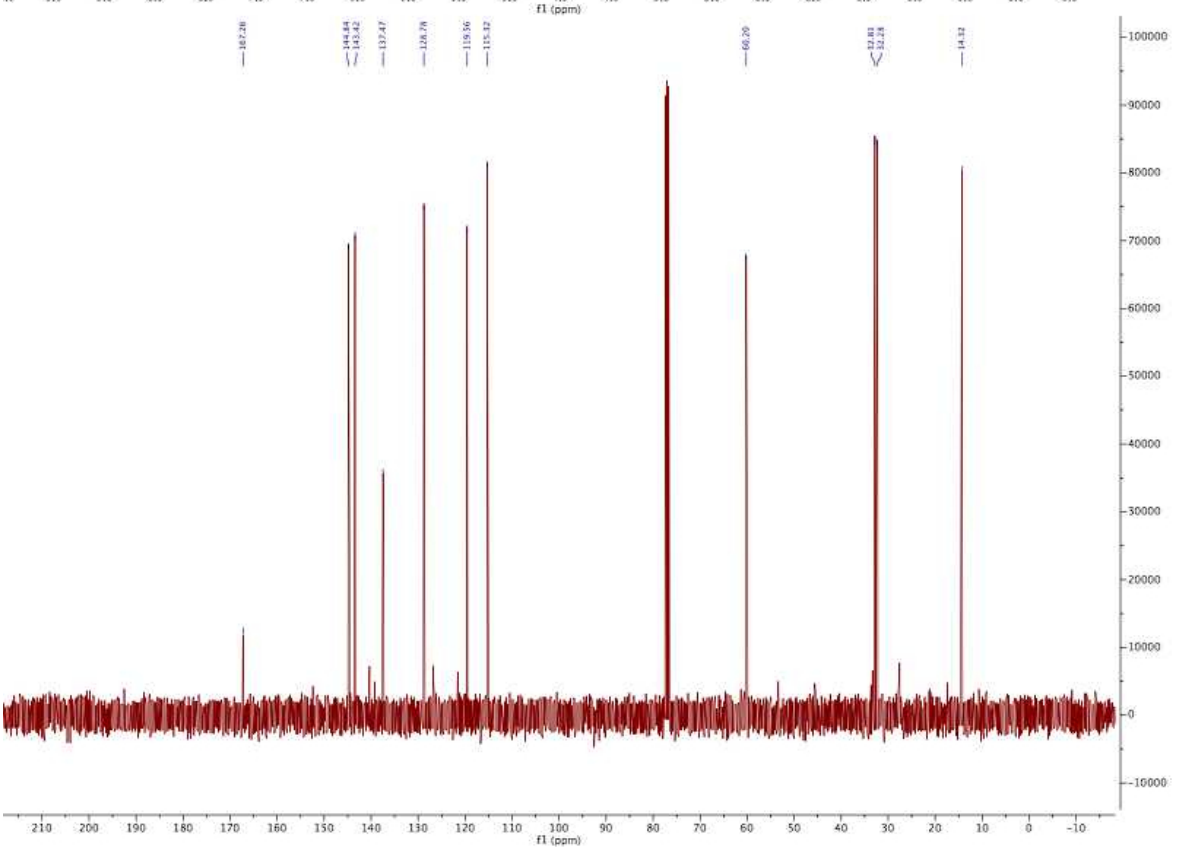
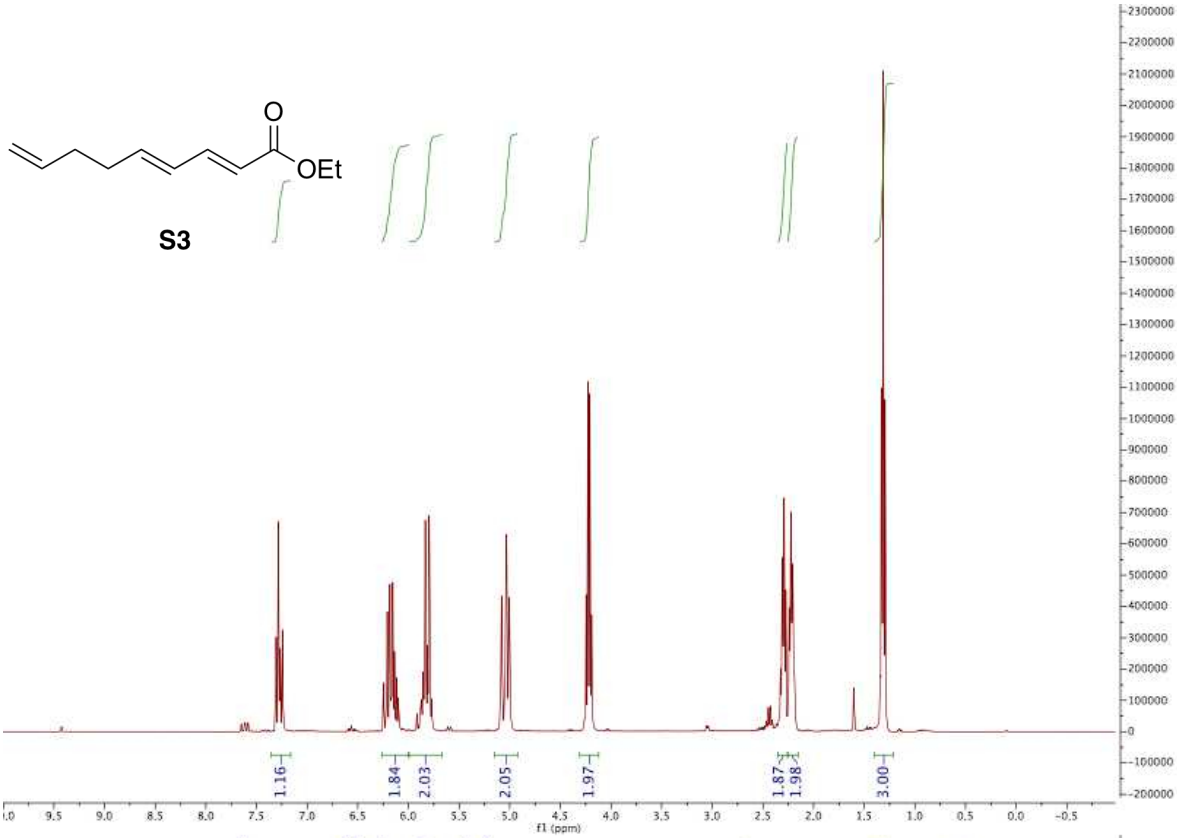
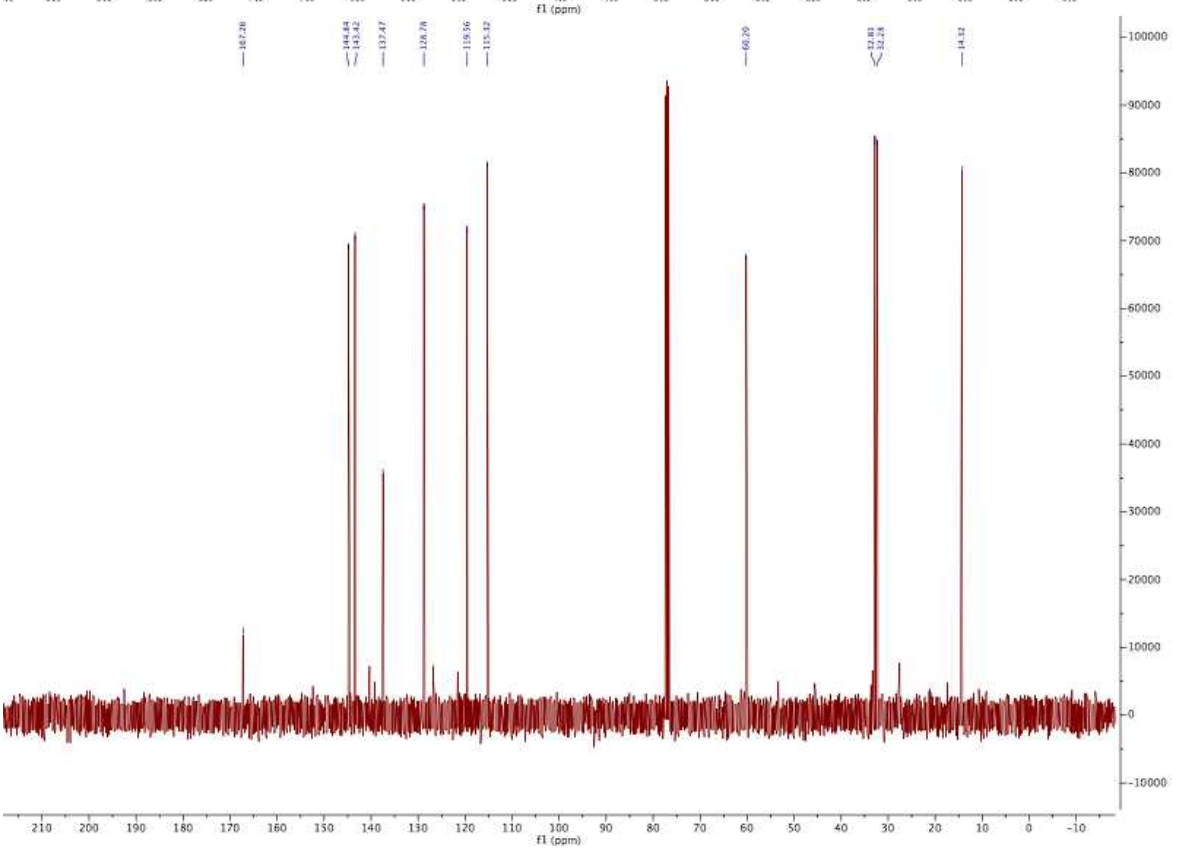
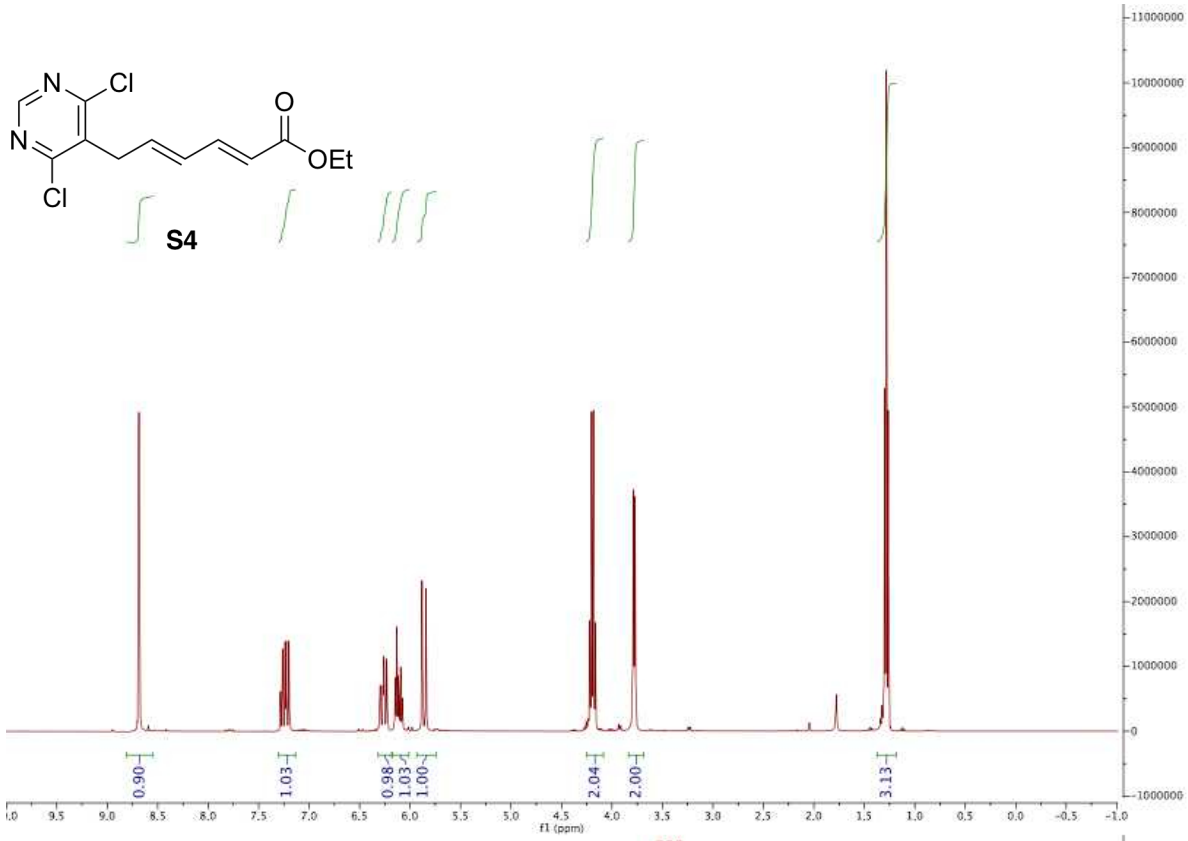
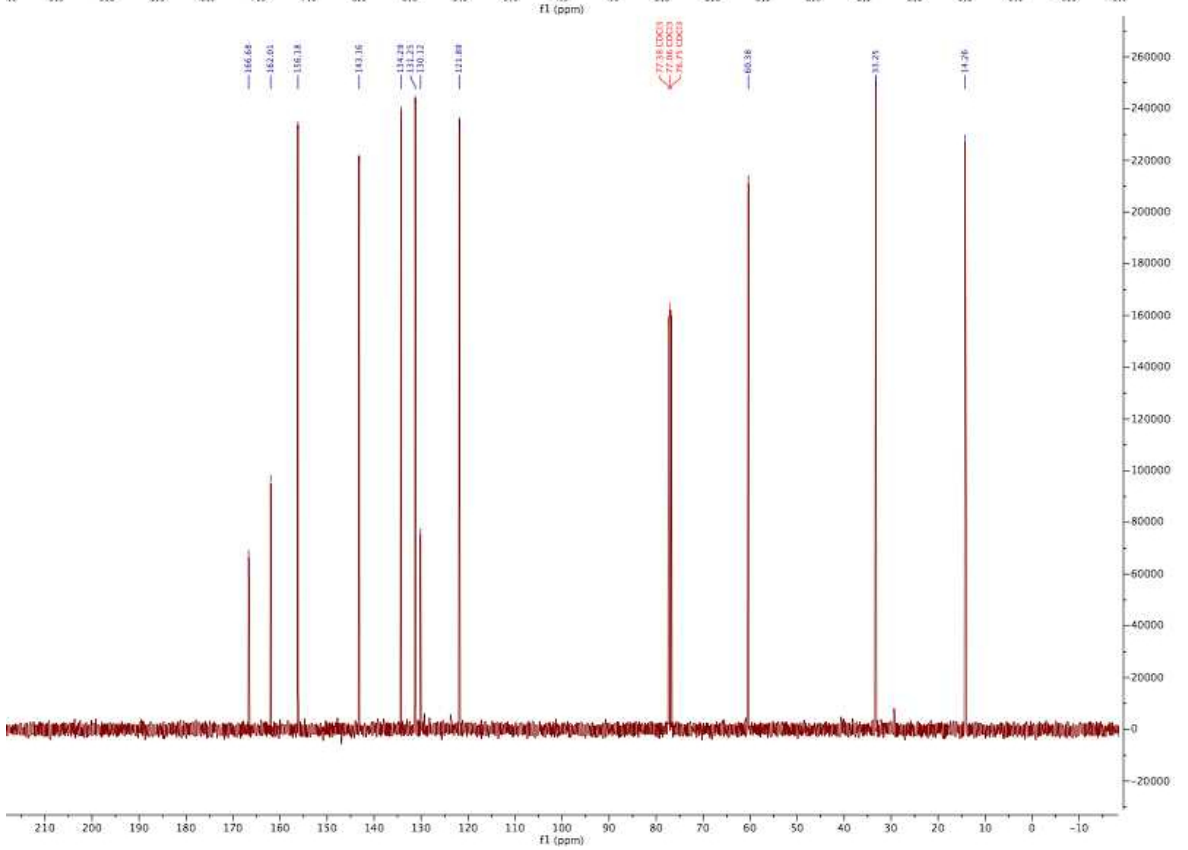

O
O
N+
-O
Me
Me
OEt
S2
1.16
1.84
2.03
2.05
1.97
1.87
1.98
3.00
f1 (ppm)

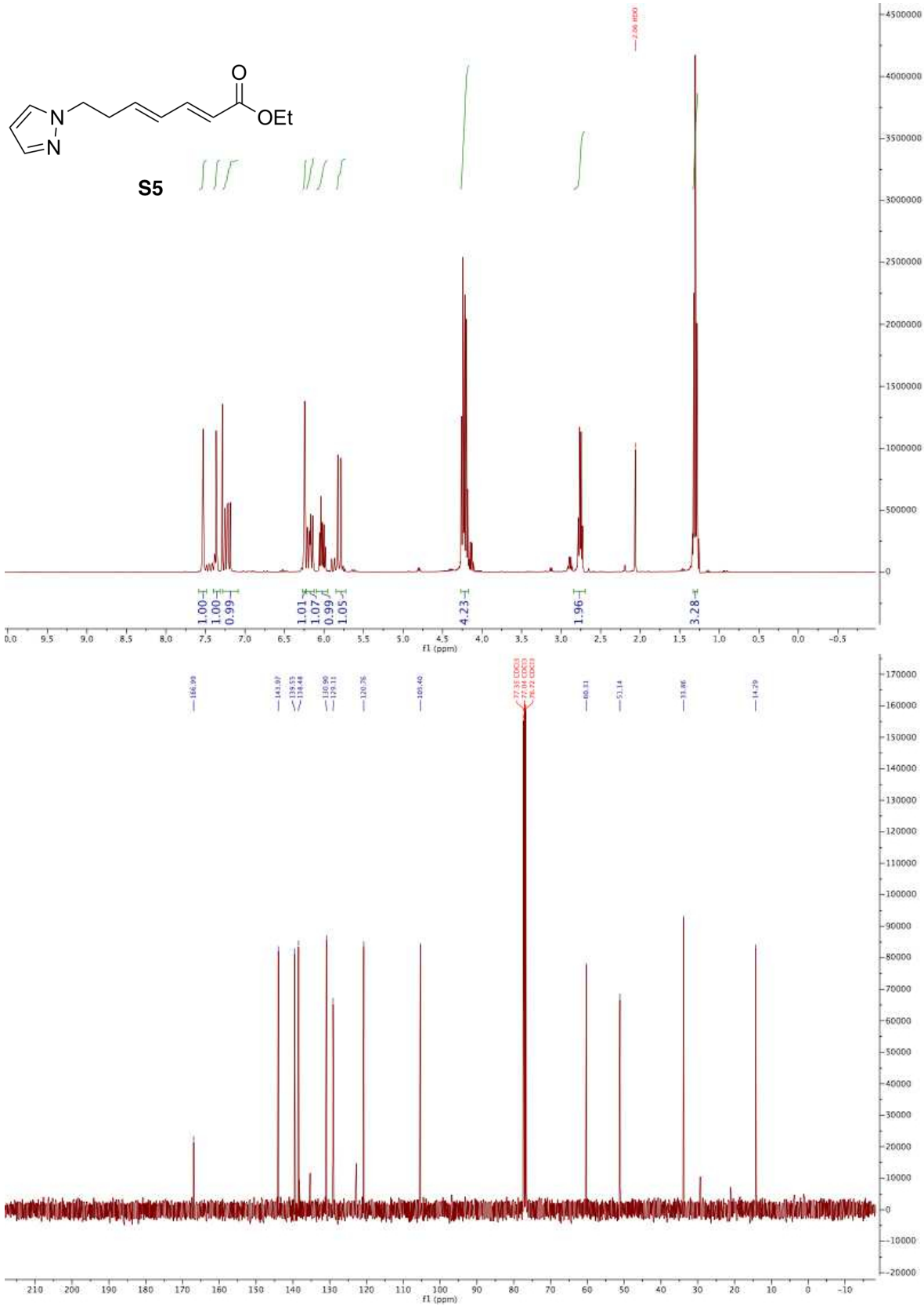

f1 (ppm)

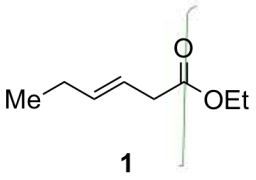

O
OEt
S3
1.16
1.84
2.03
2.05
1.97
1.87
1.98
3.00
f1 (ppm)


f1 (ppm)


N
Cl
N
Cl
O
OEt
S4
0.90
1.03
0.98
1.03
1.00
2.04
2.00
3.13
f1 (ppm)


166.64
162.01
136.18
143.36
134.28
133.35
130.12
121.89
77.38 CDCl3
77.06 CDCl3
76.75 CDCl3
60.38
31.25
14.26
f1 (ppm)

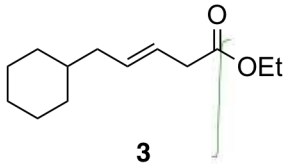

O
OEt
N
N
S5
1.00
1.00
0.99
1.01
1.07
0.99
1.05
4.23
1.96
3.28
f1 (ppm)



1

Quantitative ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **1**

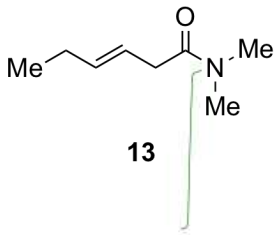
13 mg benzoic acid (MW 122.12)
+ 11 mg **1** (MW 142.20)
Expected integral ratio for 100% purity = 1 : 0.73
Actual purity = 98%



3

Quantitative ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **3**

12 mg benzoic acid (MW 122.12)
+ 29 mg **3** (MW 210.32)
Expected integral ratio for 100% purity = 1 : 1.41
Actual purity = 96%



13

Quantitative ^{1}H NMR ($CDCl_3$, 400 MHz) of compound **13**

19 mg benzoic acid (MW 122.12)
+ 7 mg **13** (MW 141.21)
Expected integral ratio for 100% purity = 1 : 0.33
Actual purity = 96%