DEVELOPMENT OF PD-CATALYZED FUNCTIONALIZATION REACTIONS OF ALKENYL SUBSTRATES VIA STABILIZED PD ALKYL INTERMEDIATES

by

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A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

The University of Utah

August 2012

The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

The palladium-catalyzed functionalization of sp^3-hybridized carbons has been an active area of research in recent years. In order to accomplish such transformations, control of β-hydride elimination is one of the central issues to be addressed. In our group, palladium-catalyzed hydro- and difunctionalization reactions of alkenes have been a long-standing area of interest, and we have developed several catalytic systems that achieve precise control of β-hydride elimination from various Pd complexes. Three of these systems are presented in this thesis.

In the first chapter, a hydroalkoxylation of styrenes is discussed. In this method, it is proposed that a Pd hydride is generated via Pd-catalyzed aerobic oxidation of an alcohol solvent. The substrate would then insert into the Pd–H bond to form a Pd alkyl intermediate, which undergoes nucleophilic substitution to yield the overall hydroalkoxylation product. Mechanistic experiments performed in parallel with the development of this transformation highlighted the precise control over relative rates of the different steps that is necessary for the reaction to proceed effectively. Importantly, the stabilization imparted by π-benzyl interactions on the Pd alkyl intermediates was found to be crucial to allow for their functionalization.

In the second chapter, an asymmetric hydroarylation of styrenes and dienes is described. This was developed on the basis of several racemic styrene and diene hydroarylation reactions previously reported by our laboratory. Analogously to the hydroalkoxylation, oxidation of the alcohol solvent was proposed to provide the

hydrogen incorporated into product; and formation of a Pd π-benzyl or π-allyl intermediate was found to be essential for further functionalization. Toward the development of an asymmetric variant of this reaction, several classes of ligands were explored, with bisoxazolines giving the highest enantioselectivities. Bisoxazolines were then systematically modified and evaluated.

As the effort toward an asymmetric hydroarylation was only moderately successful, we chose to investigate other routes to access hydroarylation-type products, as presented in Chapter 3. Specifically, we decided to access Pd π-allyl complexes from homoallyl electrophiles by "walking" the Pd along the carbon chain of the substrate. This would result in a novel approach to Pd π-allyl complexes and their functionalization, which has the potential to be further developed into an asymmetric reaction. The development of this reaction as well as the preliminary scope and mechanism are presented.

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LIST OF ABBREVIATIONS

Å	Ångström
Ac	acetyl
*t*Am	*tert*-amyl
app.	apparent
aq.	aqueous
B	branched
9-BBN	9-borabicyclo[3.1.1]nonyl
bc	bathocuproine
BINAM	2,2'-diamino-1,1'-binaphthyl
Biox	bioxazoline
bipy	bipyridine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Box	bisoxazoline
bs	broad singlet
cat.	catalytic
COD	cyclooctadiene
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl

Bu	butyl
*i*Bu	*iso*-butyl
*t*Bu	*tert*-butyl
°C	degrees Celsius
ca.	circa
calcd.	calculated
conc.	concentrated
conv.	conversion
d	doublet, or day
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dcpe	1,2-bis(dicyclohexylphosphino)ethane
dd	doublet of doublets
decomp.	decomposition
DMAP	4-dimethylaminopyridine
DMA	dimethylacetamide
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
d.r.	diastereomeric ratio
ee	enantiomeric excess

elim.	elimination
equiv	equivalents
e.r.	enantiomeric ratio
Et	ethyl
et al.	et alii
FTIR	fourier transform infrared spectroscopy
g	gram
GC	gas chromatography
h	hour
HA	Brønsted acid
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IBCF	*iso*-butyl chloroformate
IPA	*iso*-propyl alcohol
IR	infrared spectroscopy
L	liter, or linear, or ligand
LA	Lewis acid
LAD	lithium aluminum deuteride
LAH	lithium aluminum hydride
LFER	linear free energy relationship
m	multiplet
M	molar, or metal

m	*meta*
Me	methyl
mg	milligram
MHz	megaHertz
min	minute
mL	milliliter
μL	microliter
mmol	millimole
mp	melting point
MS	mass spectrometry, or molecular sieves
Ms	methylsulfonyl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
obsd.	observed
p	*para*
Ph	phenyl
phen	phenanthroline
pin	pinacol
*i*Pr	*iso*-propyl
psi	pounds per square inch
Pyrox	pyridine oxazoline

ACKNOWLEDGMENTS

I would not have been able to get my Ph.D. without the help and support of some amazing people. First, I would like to thank my advisor Matt Sigman for being supportive and understanding when my research did not work the way we wanted it to, while at the same time challenging me to reach high, and keep pushing myself farther. I have learned so much from him, and I truly appreciate his mentorship, which has kept me motivated to be the best scientist and mentor I can.

I am also indebted to the past and present members of the Sigman group. While Matt has provided the big picture guidance and mentorship, the people in the group are the ones who have taught me all the smaller things, how to work in the lab, write papers, present research, and also how to teach others in turn. Beyond that, they have been a wonderful group of people to work with and to be around, both in and out of the lab. Specifically, I am grateful to Keith Gligorich, who got me started on my first project, and taught me a lot about how to approach a problem systematically, and solve it by carefully analyzing and interpreting data. Keith Gligorich and Candace Cornell became my friends and teachers during my first years as a graduate student, and I am grateful for their strength, sense of humor and attitude toward science and life in general. I would also like to thank Katrina Jensen for her friendship, and for proving that strength, patience, and meticulousness will be rewarded in the end. I would like to thank Jeremie Miller and Brian Michel for their friendship, and being the scrupulous scientists, good-hearted, and often argumentative people that they are.

I am grateful to Lars Heumann for his constant friendship and advice. He is someone I look up to in terms of science as well as personally. I would also like to thank my friends outside of the chemistry department, Becky Parker, Justin Iravani, Mike Hollenbeck, and Devin Robison. They have been always supportive, and a reminder of the world outside the lab.

I am deeply grateful to my parents back in Germany, Irmgard and Ludek, who have been incredibly supportive and understanding of me moving to Utah, and pursuing my degree here. My mom first taught me about chemistry, and set the stage for what has become a fascination with how chemistry works, and teaching others about it. I am grateful to my brother Georg, for his quiet support, and knowing that he'll always have my back if I need him. I would like to thank my parents-in-law and sister-in-law, Felicia, Janos and Tunde, for always being kind, generous, and supportive, and for truly being my second family. Lastly, I would like to thank my husband Janos, for being my best friend, and always being there for me. He has supported me through everything, making me smile even on bad days, and reminding me that science is not all there is to life.

CHAPTER 1

DEVELOPMENT OF A PD-CATALYZED HYDROHALOGENATION / HYDROALKOXYLATIONOF STYRENES

Introduction

Carbon-oxygen and carbon-halogen bonds are prevalent in organic compounds, and a vast number of methods exist for their introduction into carbon frameworks.[1] A simple and atom-economic method is the addition of HX or HOR across a double bond, which can be catalyzed by acids to access the corresponding Markovnikov products.[2] However, these transformations often require forcing conditions, and are applicable to a limited substrate scope. Therefore, it would be desirable to develop a mild, general method to affect these types of transformations. This chapter describes our exploits in this area, resulting in a Pd-catalyzed hydrohalogenation of styrenes, the product of which undergoes a substitution reaction to give an overall hydroalkoxylation product. Throughout the development of this reaction, mechanistic experiments were performed to support the working mechanism, and to provide the basis for hypothesis-driven optimization. Through these mechanistic studies, it was also found that control of β-hydride elimination was crucial for the development of this reaction.

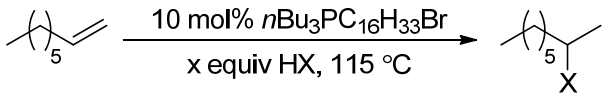
Background

Brønsted Acid-Promoted Hydrohalogenation Reactions

The Markovnikov addition of acids across double bonds is one of the classic ways to introduce halogen functionalities into organic molecules. However, strong acids are necessarily used as stoichiometric reagents in these reactions, resulting in harsh reaction conditions. Additionally, these reactions proceed via carbocation intermediates, which are prone to undergo undesired rearrangements and other side reactions. For these two reasons, the substrate scope is limited, and this type of reaction is typically not used in targeted syntheses.[3]

In an effort to make alkene hydrohalogenations more practical, methods have been developed utilizing phase transfer catalysts, which permit the use of aqueous acid. Specifically, Landini and Rolla reported a hydrohalogenation reaction using phosphonium salts as phase transfer catalysts (Figure 1.1).[4] Both activated and unactivated alkenes were competent substrates for this reaction; however, the functional group tolerance was severely limited by the use of concentrated acids and elevated temperatures.

Additionally, several groups have developed methods to form acids in situ. Yadav and Babu reported a hydrochlorination of alkenes using AcCl and EtOH to form



3 equiv HI	90% yield
5 equiv HBr	88% yield
15 equiv HCl	75% yield

Figure 1.1. Hydrohalogenation of alkenes using phase transfer catalysis (adapted from Landini and Rolla, 1980).

HCl in situ (Figure 1.2).[5] While the yields are good for substrates that are competent, the reaction is limited to substrates that form stabilized carbocations, such as electron-rich benzylic, allylic, or tertiary cations. Similarly, Campos et al. published a hydroiodination of alkenes and alkynes, using a combination of Cu(II), I_2, and Et_3SiH to form HI in situ (Figure 1.3).[6] While the scope limitations are not explicitly discussed in the paper, the published scope is limited to styrenes and an α,β-unsaturated esters.

Shimizu et al. reported the use of TiI_4 for the hydroiodination of alkenes and alkynes (Figure 1.4).[7] Simple primary as well as symmetric secondary alkenes are competent substrates. The authors performed deuterium labeling experiments, and report "little or no" deuterium incorporation when using D_2O, and no deuterium incorporation using CD_2Cl_2. The source of the proton incorporated into product as well as the overall reaction mechanism is thus unclear.

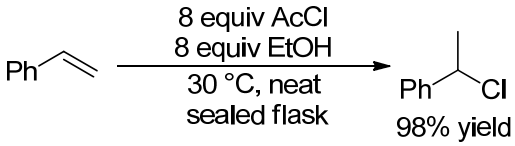


Figure 1.2. Hydrochlorination of alkenes with HCl generated in situ (adapted from Yadav and Babu, 2005).

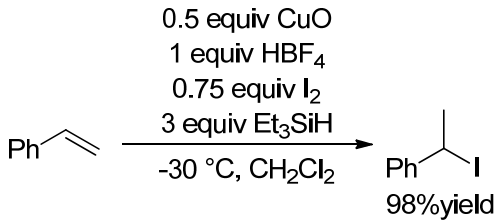


Figure 1.3. Hydroiodination of alkenes with HI generated in situ (adapted from Campos et al., 2002).

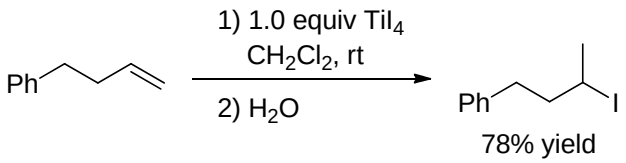


Figure 1.4. Hydroiodination of alkenes with TiI_4 (adapted from Shimizu et al., 2005).

Mechanistically Distinct Hydrohalogenation Reactions

To the best of our knowledge, apart from the work outlined in this chapter, there is one example reported of a hydrohalogenation of alkenes proceeding via a mechanism unrelated to those discussed above. Gaspar and Carreira developed a Co-catalyzed hydrochlorination of alkenes, which is proposed to proceed via a radical process (Figure 1.5).[3] The proposed mechanism is initiated by formation of a cobalt hydride, into which the alkene substrate inserts. The cobalt alkyl complex then undergoes homolytic cleavage to form an alkyl radical, which abstracts a chlorine atom from TsCl to give the product and a toluenesulfonyl radical. The Co hydride is regenerated by $PhSiH_3$. The toluenesulfonyl radicals are proposed to form sulfinylsulfonates, which are quenched by EtOH as evidenced by the observation of ethyl sulfinate in the reaction mixture. The overall mechanism is proposed based on related reactions previously developed by the Carreira group.[8]

Alternatively, it could be envisioned that HCl formed from TsCl and EtOH (along with TsOEt) was the true hydrochlorination reagent. A control experiment was thus performed in the absence of alkene, showing that only small amounts of TsOEt were formed. Additionally, a deuterium labeling experiment using $PhSiD_3$ was carried out, showing that the proton incorporated into product originates from the silane. The scope

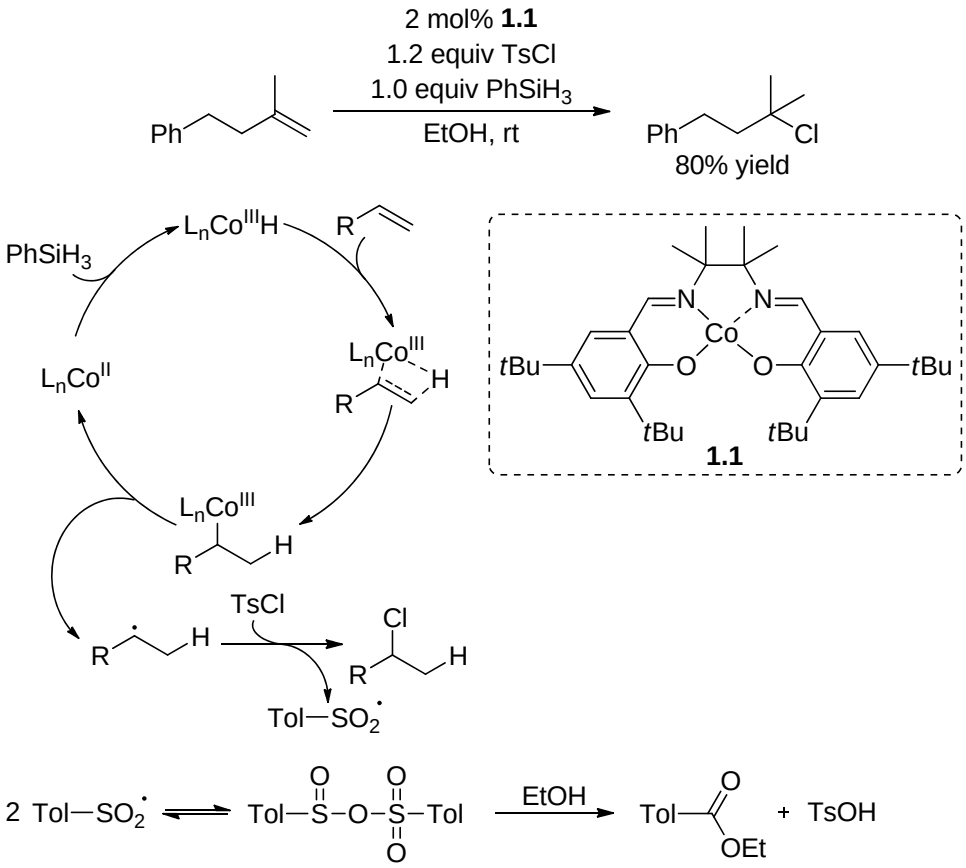


Figure 1.5. Hydrochlorination of alkenes via proposed radical mechanism (adapted from Gaspar et al., 2008).

of this reaction includes several acid-sensitive functional groups such as an ester, an amide, and a silyl-protected alcohol. Primary as well as 1,1-disubstituted and tertiary alkenes are compatible with these reaction conditions.

Brønsted and Lewis Acid-Catalyzed Hydroalkoxylation Reactions

As discussed above, stoichiometric amounts of acids are typically necessary for acid-promoted hydrohalogenation reactions. In contrast, hydroalkoxylation reactions can be promoted by catalytic amounts of strong Brønsted acids such as TfOH (Figure 1.6 (top)).[9,10] However, the reaction conditions have to be controlled carefully even with

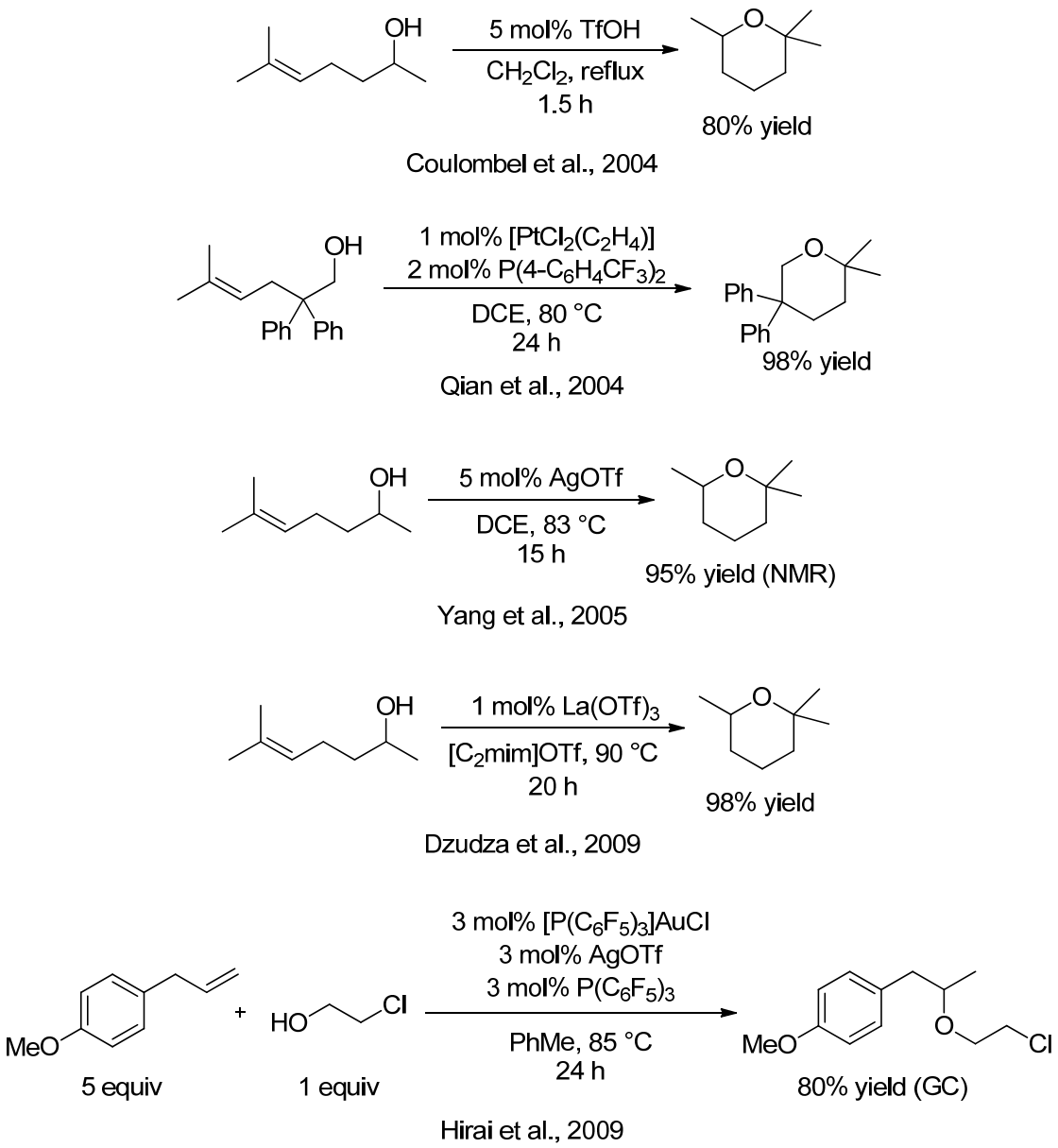


Figure 1.6. Examples of acid- and metal-catalyzed hydroalkoxylations.

simple substrates to avoid side reactions.[9] Thus, numerous methods have been developed using Lewis acid catalysts instead, which appear to function under less stringent conditions (Figure 1.6).[11-16] A wide variety of Lewis acids catalyze this process, which can be rationalized by the proposed general mechanism shown in Figure 1.7. Typically, these reactions proceed via activation of the alkene by the Lewis acid followed by nucleophilic attack and protonation of the metal alkyl species. This mechanism essentially parallels that of acid-catalyzed hydroalkoxylations (Figure 1.7). Based upon this, any sufficiently strong π-acidic Lewis acid should be a competent catalyst. The scope of these reactions varies only slightly, with most of them comprising intramolecular reactions of simple substrates. Of note, intermolecular variants have been developed as well.[16-18]

Interestingly, a number of these catalysts are metal triflates (or combinations of metal halides and AgOTf), which has prompted several groups to question the nature of the active catalyst.[19-21] Specifically, it was suspected that small amounts of triflic acid were formed in the reaction, which acts as the active catalyst. In 2006, Hartwig and coworkers reported their observations that the outcomes of acid-catalyzed hydroalkoxylations and hydroaminations closely resembled those of metal-catalyzed reactions.[19] In the original reports of the metal-catalyzed reactions, control

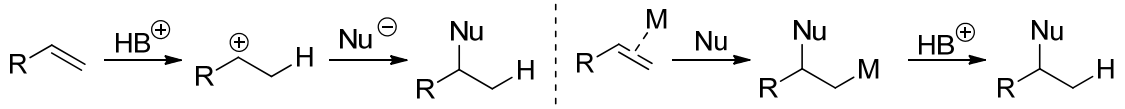


Figure 1.7. Proposed mechanisms for acid- and metal-catalyzed hydroalkoxylations.

reactions using acid catalysts were typically performed with higher loadings of acid, which led to lower yields of the desired products due to side reactions. Based on these results, researchers would conclude that acid catalysis was not operational in their systems. Hartwig and coworkers found that if the acid concentration was kept low enough similar results could be obtained, both in terms of yields and product distribution.

To test their hypothesis that a small amount of acid was the active catalyst, they designed a substrate containing a terminal as well as a trisubstituted double bond (Figure 1.8). It was assumed that under acid catalysis, the trisubstituted double bond would react preferentially, giving the Markovnikov product **1.2**. Under metal catalysis, however, the sterically less hindered terminal double bond should react preferentially to yield products **1.3** or **1.4**. Hydroalkoxylation reactions were then performed using several different

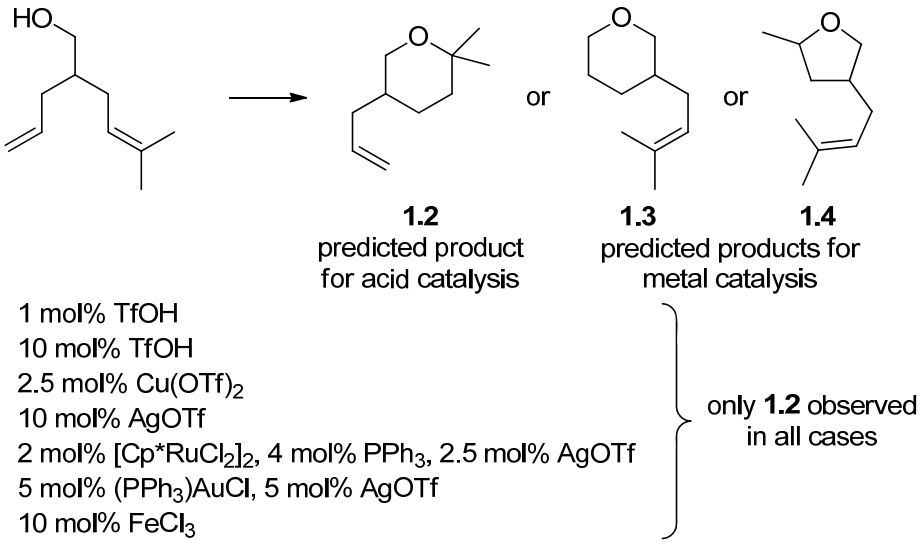


Figure 1.8. Parallel outcomes of metal- and acid-catalyzed hydroalkoxylation (adapted from Rosenfeld et al., 2006).

published protocols. It was found that, indeed, product **1.2** was the only observed product in all cases examined. While this result does not explicitly support the presence of Brønsted acid, it does cast doubt on the nature of the active catalyst in these reactions.

More recently, Ujaque and coworkers computed the relative energies for TfOH- and $(PMe_3)AuOTf$-catalyzed hydroamination and hydroalkoxylation reactions.[20] Overall, they found that both acid- and metal-catalyzed pathways were energetically reasonable for both reactions. In the case of the addition of phenol to ethylene (their model hydroalkoxylation), the global reaction barrier was slightly lower for the acid-catalyzed pathway. While this result seems to show that the acid-catalyzed pathway is favored, it disregards the fact that $(PMe_3)AuOTf$ may not be present in the reaction mixture, if HOTf is formed. It would thus be more interesting to investigate the mechanism and energy barriers associated with decomposition of the metal catalyst, and to determine whether formation of TfOH is possible.

In 2011, Hintermann and coworkers reported their investigations of generation of triflic acid from metal triflates under hydroalkoxylation reaction conditions.[21] They evaluated several different metal catalysts, and observed the formation of TfOH (as well as other byproducts of its formation) by NMR under the reaction conditions. They concluded that AgOTf or AuOTf abstract chloride ions from chlorinated solvents such as DCE followed by elimination of TfOH. Furthermore, a catalyst mixture of $[Cp^*RuCl_2]_2$, AgOTf, and PPh_3 in toluene undergoes an undefined redox reaction to give a Ru^{II} species and TfOH. While only a few metal catalysts were evaluated in this way, this report gives substantial evidence supporting the involvement of TfOH in some "metal-catalyzed" reactions. This calls into question the mechanisms of metal triflate-catalyzed

hydroalkoxylations; however, it should be noted that there are examples where triflate is not present in the reaction, such as a system reported by Widenhoefer and coworkers.[14,18,22]

Lambert and coworkers published an interesting application of the deliberate use of $Bi(OTf)_3$ as a precursor for both TfOH and TMSOTf.[23] They achieved the formation of substituted tetrahydrofurans from homoallylic aldehydes and TMS-protected enol ethers via a Mukaiyama aldol/hydroalkoxylation sequence (Figure 1.9). To summarize this section, there is a variety of Lewis acid catalysts for olefin hydroalkoxylations. Unfortunately, the nature of the active catalyst is often questionable, and detailed mechanistic work would be necessary to establish it for each case. This is complicated by the fact that the reaction mechanisms for Lewis and Brønsted acid-catalyzed processes are closely related, and the two are not easily distinguished.

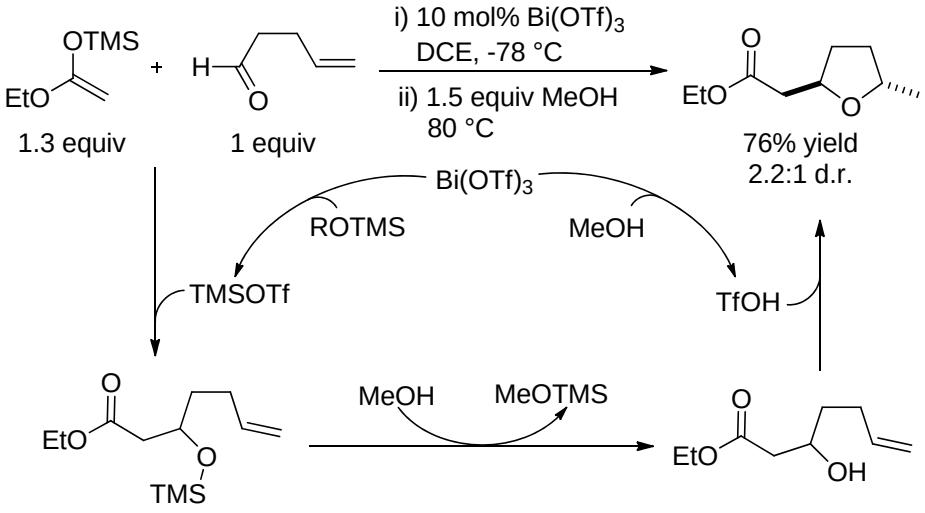


Figure 1.9. Sequential Mukaiyama aldol/hydroalkoxylation (adapted from Kelly et al., 2009).

Mechanistically Distinct Hydroalkoxylation Reactions

In addition to the catalytic systems described above, several reactions have been developed that proceed through mechanisms unrelated to the ones described above. Several noteworthy examples will be discussed here.

In 2007, Sakurai and coworkers reported an intramolecular hydroalkoxylation catalyzed by gold nanoclusters stabilized by poly(*N*-vinyl-2-pyrrolidone) with an average diameter of 1.3 nm (Au:PVP(1.3)) (Figure 1.10).[24] When exposed to air, these nanoclusters are proposed to absorb oxygen, giving rise to Lewis acidic sites on the cluster surface. These sites have been found to be competent catalysts for several reactions, such as aerobic alcohol oxidation[25,26] and homocoupling of arylboron

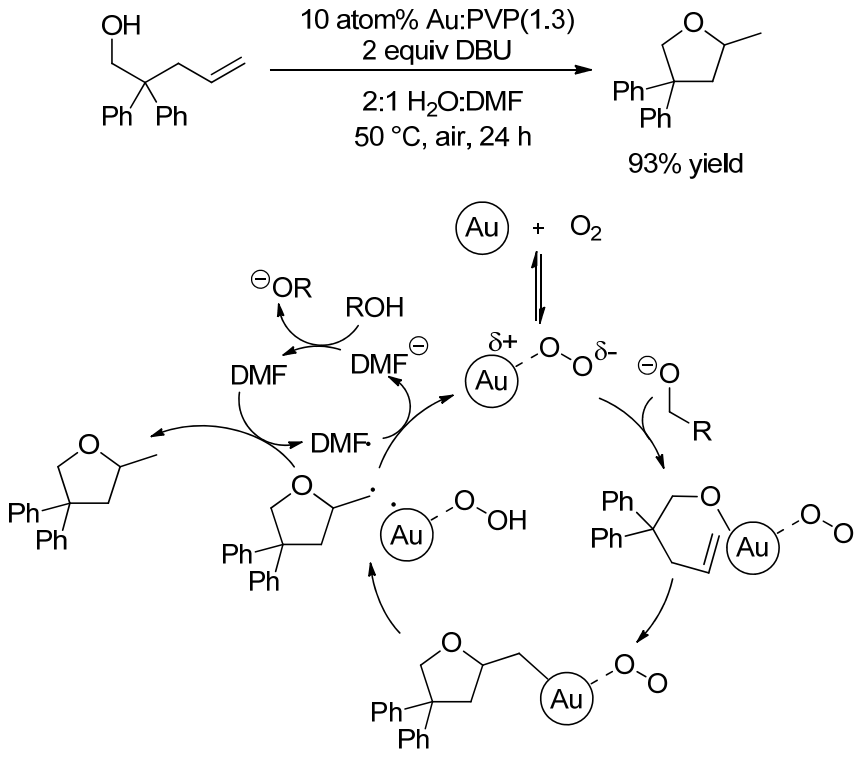


Figure 1.10. Intramolecular hydroalkoxylation catalyzed by gold nanoclusters (adapted from Kamiya et al., 2007).

compounds.[27] While the mechanism of the alkene hydroalkoxylation was not studied in great detail, deuterium labeling studies revealed that the proton incorporated into the substrate stems from DMF. Based on this result and the mechanisms of related reactions, the mechanism shown in Figure 1.10 was proposed, wherein the substrate alkene and hydroxyl group are initially coordinated to the cluster, followed by oxyauration of the alkene, giving a gold alkyl species. This intermediate would undergo homolytic cleavage followed by abstraction of a hydrogen atom from DMF to give the desired product. The DMF radical would then undergo single electron reduction by the gold nanocluster to form an anion, which would be protonated by the alcohol substrate or water.

Furthermore, our laboratory reported a Pd-catalyzed hydroalkoxylation of vinylphenols in 2006 (Figure 1.11).[28] The mechanism of this and related systems has been studied in some detail, and it is proposed to proceed as shown in Figure 1.11.[28-30] The reaction is initiated via oxidation of the alcohol solvent by Pd^{II}, giving a Pd hydride intermediate **A**. The alkene substrate is then coordinated to the Pd complex, and inserted into the Pd–H bond, which can yield two isomeric intermediates **C** and **D**. Based on deuterium labeling experiments, it is proposed that both isomers are formed reversibly, but only **D**, where Pd is bound to the benzylic carbon, proceeds to product via deprotonation of the phenol to give *ortho*-quinone methide **E**. This intermediate is attacked by a second equivalent of alcohol to yield the desired product, while Pd^0 is oxidized by $CuCl_2$ and O_2 to re-form the Pd^{II} catalyst.

In this initial system, the alcohol solvent acted as both the nucleophile and the source of the proton incorporated into product. Later, however, it was found that 1-

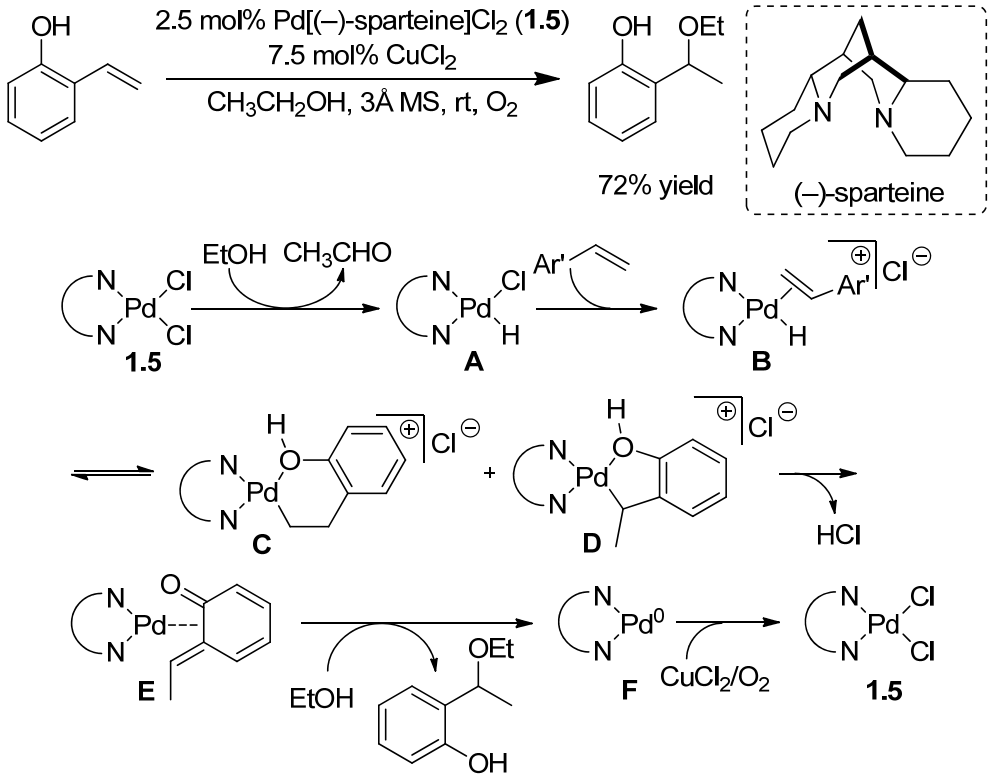


Figure 1.11. Hydroalkoxylation of vinylphenols (adapted from Gligorich et al., 2006).

phenylethanol could be used as a hydride source, which allowed for lower loadings of the sacrificial alcohol as well as the incorporation of a greater variety of external nucleophiles.[31] Unfortunately, this system was still limited to the use of vinylphenols as substrates, since the phenol plays an integral part in the reaction mechanism.

Control of β-Hydride Elimination to Achieve Pd-Catalyzed Hydro- and Difunctionalizations of Alkenes

The Pd-catalyzed hydroalkoxylation of vinylphenols discussed in the previous section is an unusual example of avoiding β-hydride elimination from a Pd alkyl intermediate. There is a variety of mechanistic scenarios wherein β-hydride elimination

can be controlled to achieve hydro- and difunctionalizations of alkenes.[32,33] Four fundamental approaches to accomplish this will be discussed in this section.

Absence of appropriately placed protons. The most straightforward of these approaches is to design the substrate in such a way that there is no hydrogen in a position accessible for β-hydride elimination. This concept was utilized by Loh and coworkers in an interesting intramolecular dioxygenation of alkenes (Figure 1.12).[34] It is proposed that the alkene substrate is coordinated to Pd followed by intramolecular nucleophilic attack by the oxime to give Pd alkyl intermediate **A**. As there are no protons available for β-hydride elimination, the Pd is replaced by either hydroxy or acetoxy groups to form a mixture of products. The acetate is then hydrolyzed to obtain the pure hydroxy-substituted product. Loh and coworkers performed labeling experiments to establish O_2 as the source of the hydroxide. However, it is unclear how the products are formed from **A**.

Blocking of coordination sites. Alternatively, coordination sites on Pd can be blocked by excess halides or other ligands. Using this concept, Henry and coworkers

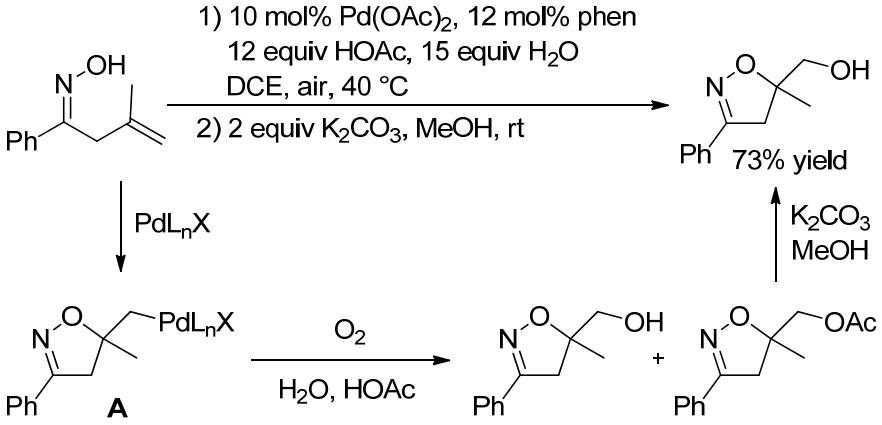


Figure 1.12. Intramolecular dioxygenation of alkenes (adapted from Zhu et al., 2010).

developed an asymmetric chlorohydroxylation of alkenes[35-37] as well as an asymmetric dibromination[38] using excess amounts of lithium salts to prevent the formation of Wacker-type products. However, this approach is inherently limited to the addition of nucleophiles available in the form of metal salts. The use of tridentate pincer ligands to block coordination sites is a potentially more general approach. Michael and coworkers made use of this in their intramolecular hydroamination of alkenes (Figure 1.13).[39,40] A

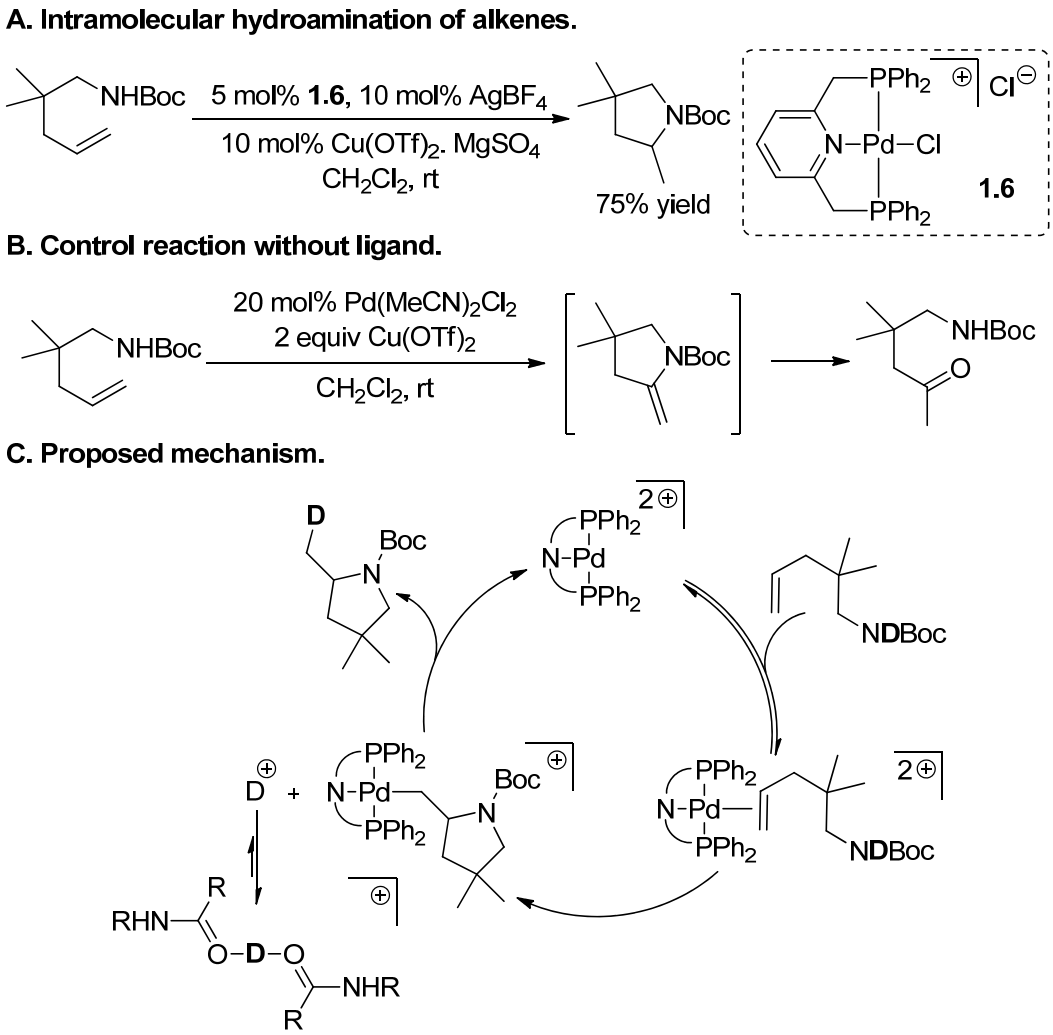


Figure 1.13. Intramolecular hydroamination of alkenes (adapted from Cochran et al., 2008).

PNP-type pincer ligand in combination with dicationic Pd was found to be a competent catalyst for this reaction. To confirm that the ligand was necessary for the desired reaction, the reaction was performed without ligand, which led to the formal Wacker oxidation of the alkene, presumably via aminopalladation and β-hydride elimination (Figure 1.13.B). When more in depth mechanistic studies were performed,[40] it was found that protonation of the Pd alkyl complex was rate limiting, and the Pd alkyl species was in fact stable enough to be isolated. Furthermore, an unusual inverse dependence of the reaction rate on the substrate concentration was observed, which was explained by the carbamate protecting group acting as a Brønsted base, binding protons in the reactionmixture and slowing down the rate-limiting protonolysis step. Lastly, deuterium labeling studies showed that the proton incorporated into product originated from the protected amine, and was incorporated exclusively at the methyl position.

Rapid transformation of Pd alkyl complex. The concepts discussed above prevent β-hydride elimination operate by making it mechanistically impossible to occur, either through the absence of protons at the appropriate position, or by blocking *cis* coordination sites. A different approach would be to kinetically "outcompete" β-hydride elimination by providing a mechanistic pathway that is more rapid, and leads to intermediates that do not undergo β-hydride elimination. One approach to this is the rapid oxidation of the Pd^{II} alkyl intermediate to Pd^{IV}. This has been an active area of research in recent years, and correspondingly, there is a variety of catalytic systems that make use of this concept. The aminoacetoxylation of alkenes in particular has garnered a lot of attention from various groups. This reaction was pioneered by Bäckvall and coworkers around 1980, although the reaction was then stoichiometric in Pd and the

regioselectivity of the addition was poor (Figure 1.14).[41] However, it should be noted that Bäckvall and coworkers also developed an asymmetric variant of this reaction, giving the product in up to 60% ee.[42] During the mid 2000s, several groups became interested in this type of transformation: Sorensen and coworkers published an intramolecular aminoacetoxylation, using a protected aminoalkene substrate.[43] Sanford and coworkers reported the complementary intramolecular reaction, utilizing hydroxyalkenes,[44] and an intermolecular variant was developed by Liu and Stahl (Figure 1.15).[45] This reaction is proposed to proceed by initial aminopalladation to form a Pd^{II}

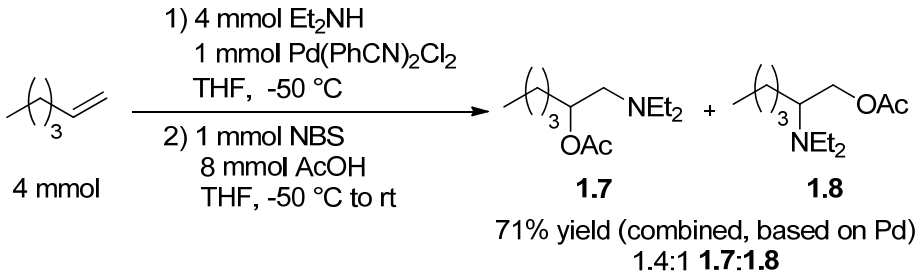


Figure 1.14. Early example of an intermolecular aminoacetoxylation of alkenes (adapted from Bäckvall et al., 1980).

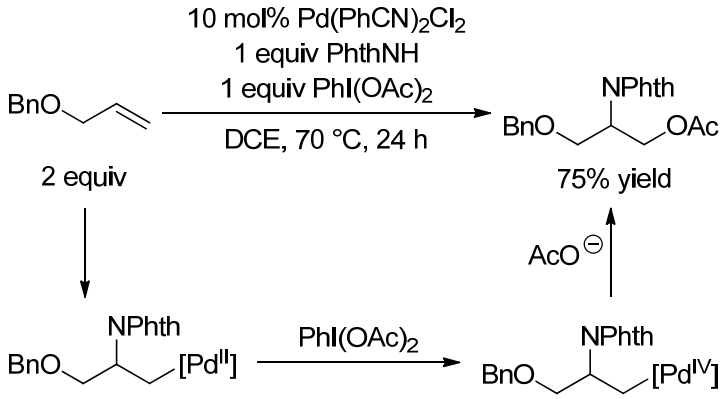


Figure 1.15. Intermolecular aminoacetoxylation of alkenes (adapted from Liu et al., 2006).

alkyl complex, which is rapidly oxidized to Pd^{IV}, thus avoiding β-hydride elimination. C–O reductive elimination completes the catalytic cycle, yielding the desired product along with the Pd^{II} catalyst.

Additional reactions were developed using this same concept, notably alkene diamination and dioxygenation reactions,[46-49] a cyclopropanation of enynes (independently reported by Sanford and Tse),[50,51] and an arylhalogenations of alkenes (Sanford and coworkers).[52,53] The arylhalogenation is especially interesting in that two product isomers (the 1,2- or 1,1-arylhalogenation product) can be accessed depending on the terminal oxidant (Figure 1.16). In both cases, an initial arylpalladation step results in

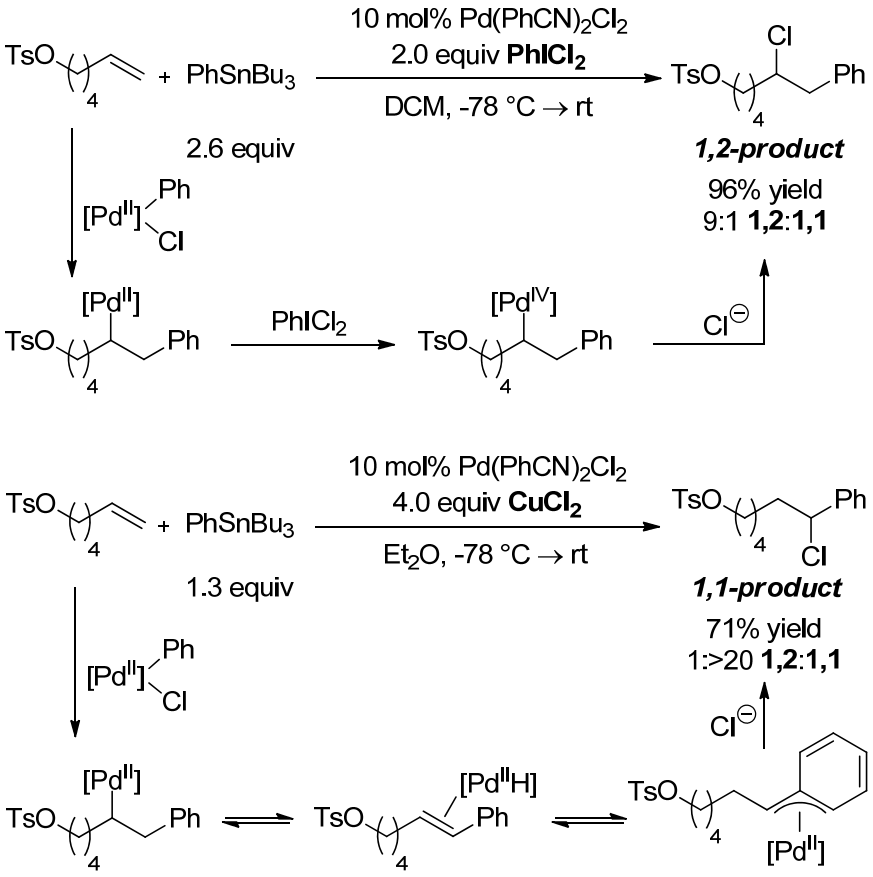


Figure 1.16. Arylhalogenation of alkenes (adapted from Kalyani et al., 2010).

the formation of a Pd^{II} alkyl species. Using $PhICl_2$, this intermediate is rapidly oxidized to Pd^{IV}, followed by reductive elimination to form the 1,2-product (Figure 1.16, top). $CuCl_2$, on the other hand, does not oxidize Pd^{II} to Pd^{IV}. Under these conditions, a β-hydride elimination/alkene insertion sequence leads to the formation of a stabilized Pd π-benzyl complex, which is then chlorinated to release the product and Pd^0 (Figure 1.16, bottom). The Pd^0 species is then reoxidized by Cu^{II}. These examples clearly showcase the direct competition between β-hydride elimination and oxidation to Pd^{IV}.

Another approach to "outcompeting" β-hydride elimination is to intercept the Pd alkyl via insertion into a precoordinated CO. The Pd-catalyzed intramolecular hydroxycarbonylation of alkenes was first reported by Semmelhack and Bodurow in 1984 (Figure 1.17).[54] Several studies by Semmelhack and others have further explored this reaction since, studying its regio- and stereoselectivity,[55-59] and expanding to related reactions such as aminocarbonylations and others.[60-66]

Instead of insertion into CO, Pd alkyl intermediates have also been intercepted by reductive elimination with aryl groups. This methodology has been developed most prominently by Wolfe and coworkers to achieve carboaminations[67-70] and carboetherifications[69-72] of various alkene substrates (Figure 1.18). These reactions are proposed to proceed via initial oxidative addition of an aryl halide to give a Pd^{II} aryl

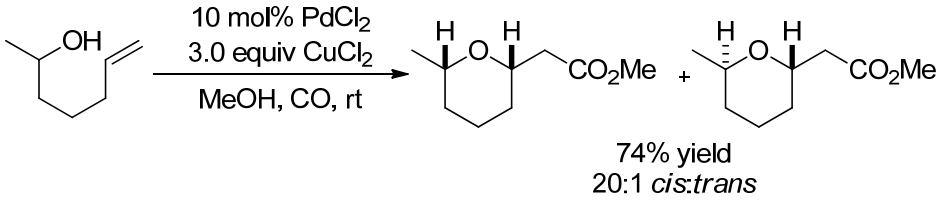


Figure 1.17. Alkoxycarbonylation of alkenes (adapted from Semmelhack and Bodurow, 1984).

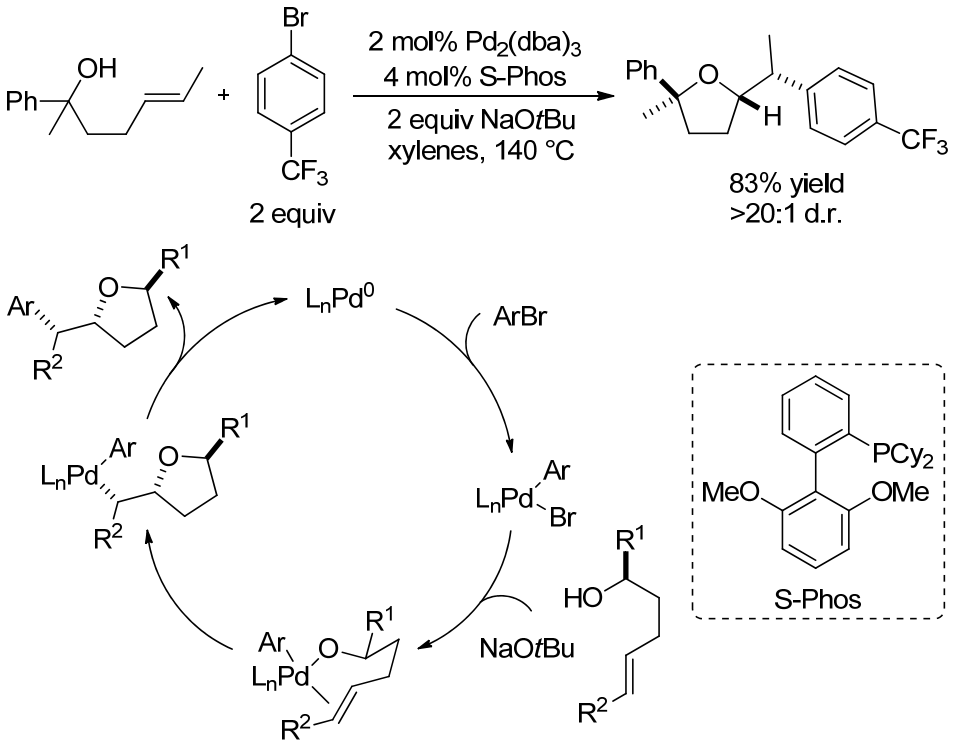


Figure 1.18. Carboetherification of alkenes (adapted from Ward and Wolfe, 2010).

complex. The hydroxyalkene substrate is deprotonated and coordinated to the Pd via the alkoxide as well as the alkene. It then undergoes *syn*-oxypalladation, yielding the Pd alkyl intermediate, and the product is released via reductive elimination.

Lastly, the hydroalkoxylation of vinyl phenols presented above falls into this category, with the Pd alkyl being rapidly transformed into an *o*-quinone methide.[28]

Stabilization of the Pd alkyl via substrate interactions. There are several secondary interactions between the Pd and substrate that can stabilize Pd alkyl complexes to allow for their further functionalization. Diene difunctionalizations, developed by Bäckvall and coworkers, proceed through a Pd alkyl complex that can be stabilized by a π-allyl interaction.[73,74] This stabilization slows β-hydride elimination sufficiently to

allow for further functionalization and in some cases even for isolation of the intermediate. Various reactions have been developed using this approach, including a hydroarylation of dienes and a three-component coupling by our group.[75,76] The proposed mechanism for the hydroarylation (Figure 1.19) commences with a Pd-catalyzed oxidation of the alcohol solvent to form a Pd hydride **A**. The diene then inserts into the Pd–H bond, and the initially formed Pd alkyl **B** is stabilized as a Pd π-allyl complex **C**. Transmetallation of the aryl boronic ester followed by reductive elimination yields the product. The mechanism of this reaction will be discussed in more detail in chapter 2.

Additionally, Hartwig and coworkers reported Pd-catalyzed hydroamination reactions of dienes as well as styrenes.[77-84] Similarly to Pd π-allyl interactions, π-benzyl interactions provide stabilization to Pd alkyl complexes, albeit to a smaller extent. Hartwig and coworkers developed several systems for the Pd-catalyzed hydroamination of styrenes and dienes, using aryl- or alkylamine nucleophiles (Figures 1.20 and

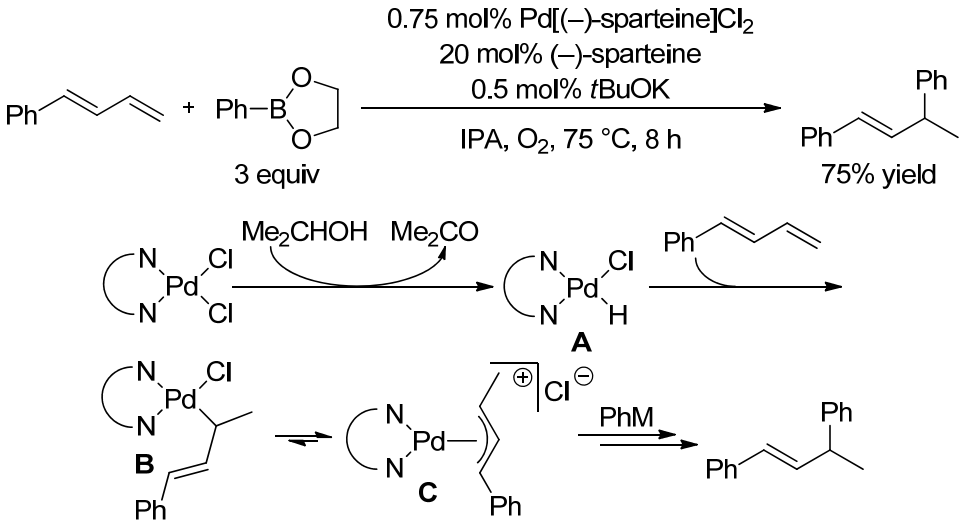


Figure 1.19. Hydroarylation of dienes (adapted from Liao and Sigman, 2010).

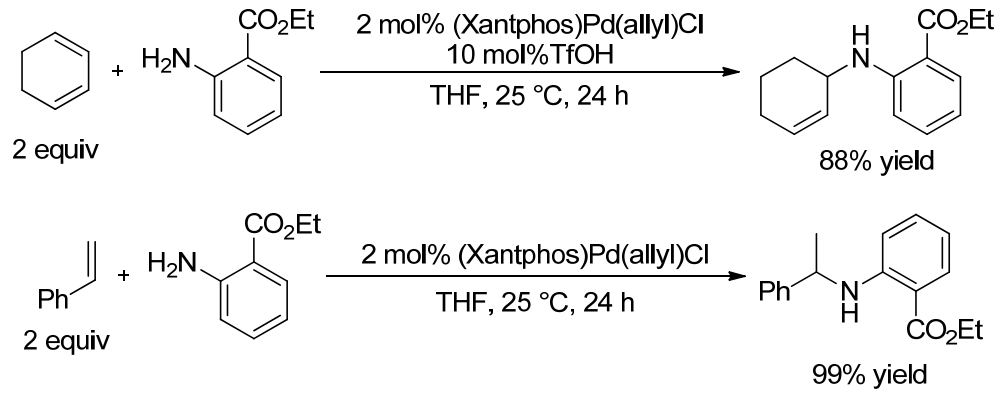


Figure 1.20. Hydroamination of styrenes and dienes (adapted from Johns et al., 2006).

1.21).[78,79] The mechanism was then investigated, and intermediate Pd π-benzyl complex **A** was isolated and successfully converted to the hydroamination product.[80] This suggested a mechanism analogous to that proposed for our hydroarylation, involving insertion of the alkene into a Pd hydride to form a Pd π-allyl/ π-benzyl complex, followed by product formation (at the time of Hartwig's publication, this type of reaction was not well known for Pd-catalyzed alkene hydrofunctionalizations).[85] It should be noted that along with the hydroamination product, free 4-methylstyrene and morpholinium triflate were also formed (Figure 1.21).

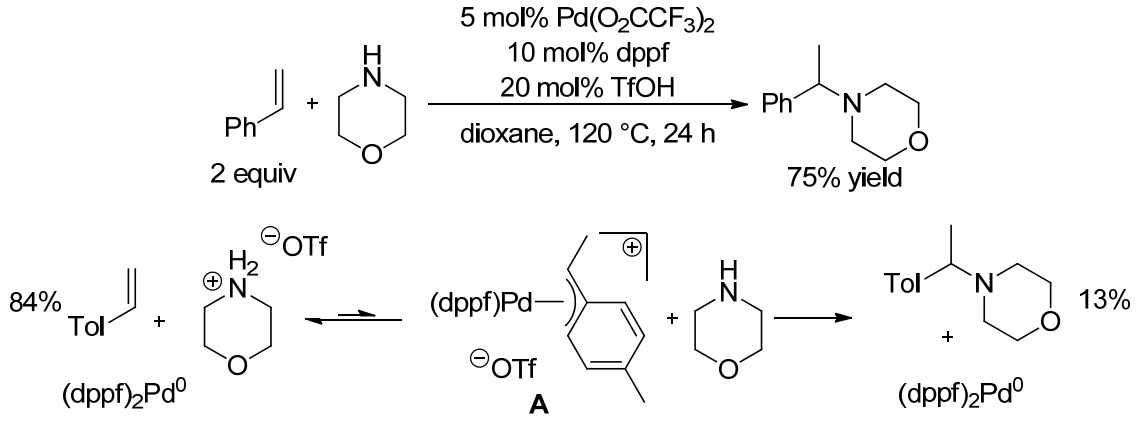


Figure 1.21. Hydroamination of styrenes (adapted from Utsunomiya and Hartwig, 2003).

This elimination is assumed to be reversible, which would retard the hydroamination reaction, without completely inhibiting it. To ensure that the hydroamination product originated directly from the Pd π-benzyl complex, the same experiment was performed in the presence of styrene. No styrene hydroamination product was observed, indicating that the product did indeed originate from the Pd complex.

Our group reported several Pd-catalyzed transformations taking advantage of the stability of Pd π-benzyl complexes, some of which will be discussed in the following chapters.[86-93]

Finally, heteroatom coordination can be used to stabilize Pd alkyls for further functionalization. This approach has has been utilized to develop "cascade reactions" by intercepting Pd alkyls formed as intermediates in Heck reactions. Larhed and coworkers thus developed a diarylation of dimethylaminoethyl vinyl ethers, wherein the pendant amine is crucial to avoid β-hydride elimination (Figure 1.22).[94] Of note, the reaction parameters had to be finely tuned, and different sets of reaction conditions had to be developed for electron-rich and electron-poor boronic acids.

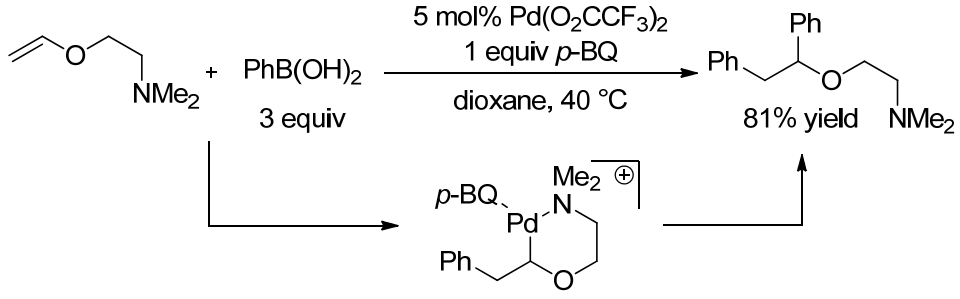


Figure 1.22. Diarylation of aminoethyl vinyl ethers (adapted from Yahiaoui et al., 2011).

Zhu and Falck reported an interesting 1,1-oxyarylation of homoallylic alcohols (Figure 1.23).[95] In this case, β-hydride elimination is not avoided entirely, but utilized to form a stabilized Pd π-benzyl complex via a β-hydride elimination/alkene insertion sequence. The concept is analogous to the mechanism proposed by Sanford and coworkers for their 1,1-arylchlorination of alkenes (vide supra).[52,53] To support this mechanism, deuterium labeling experiments were carried out, showing that the deuterium from the starting material is scrambled, but conserved in the product. Additionally, a control experiment was performed using AcOH-*d4* as co-solvent, and no deuterium incorporation into product was observed, precluding the involvement of acid catalysis.

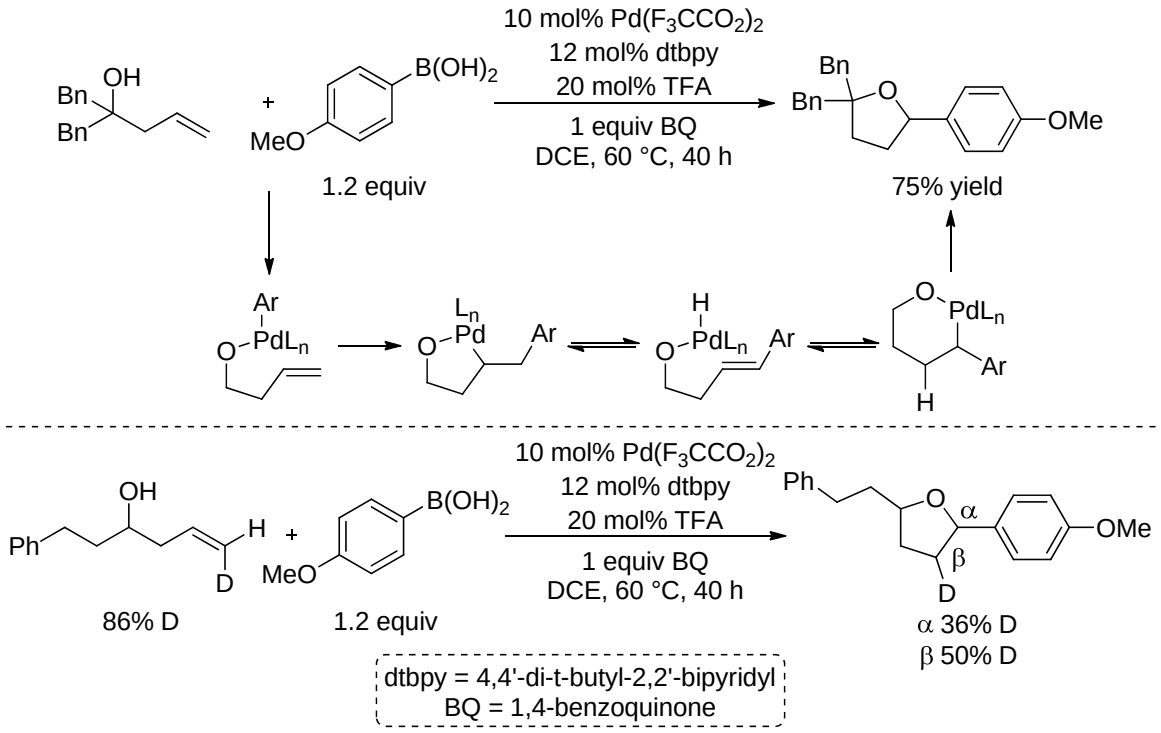


Figure 1.23. Oxyarylation of homoallylic alcohols (adapted from Zhu and Falck, 2011).

Approach to the Hydroalkoxylation of Styrenes Using Pd Hydrides

As discussed above, our group has previously reported the Pd-catalyzed hydroalkoxylation of vinylphenols via quinone methide intermediates.[28] While the presence of the phenol is an inherent limitation of this reaction, we were intrigued by the concept of using Pd hydrides to achieve hydrofunctionalizations of a wider variety of alkenes. Instead of rapid conversion of the Pd alkyl to a quinone methide, we hypothesized that it might be possible to stabilize it via secondary interactions, which would allow for further functionalization (Figure 1.24).

This prompted us to test the hydroalkoxylation with styrene substrates (not containing a phenol), which would provide stabilization of the Pd alkyl species via a π-benzyl interaction (Figure 1.25).[86,96,97] We hypothesized that the reaction should proceed via the same initial steps as the hydroalkoxylation of vinylphenols, in that oxidation of an alcohol solvent would provide the Pd hydride, and the alkene substrate would insert into

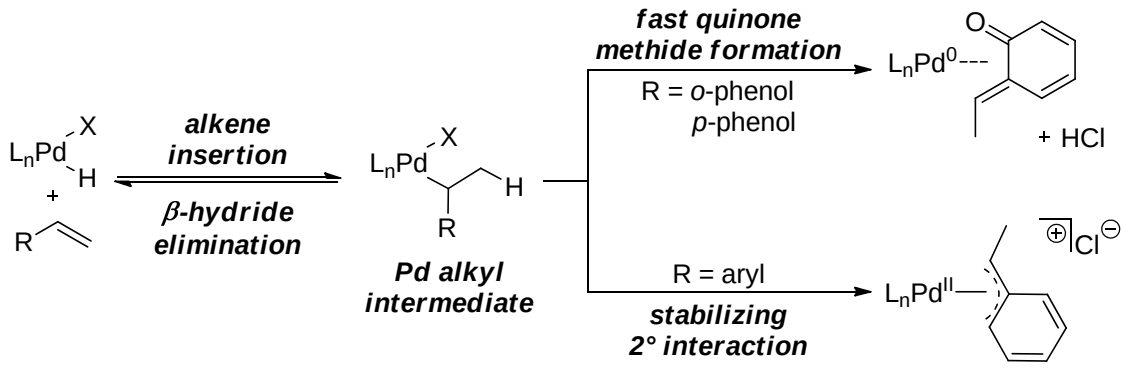


Figure 1.24. Functionalization of Pd alkyl species.

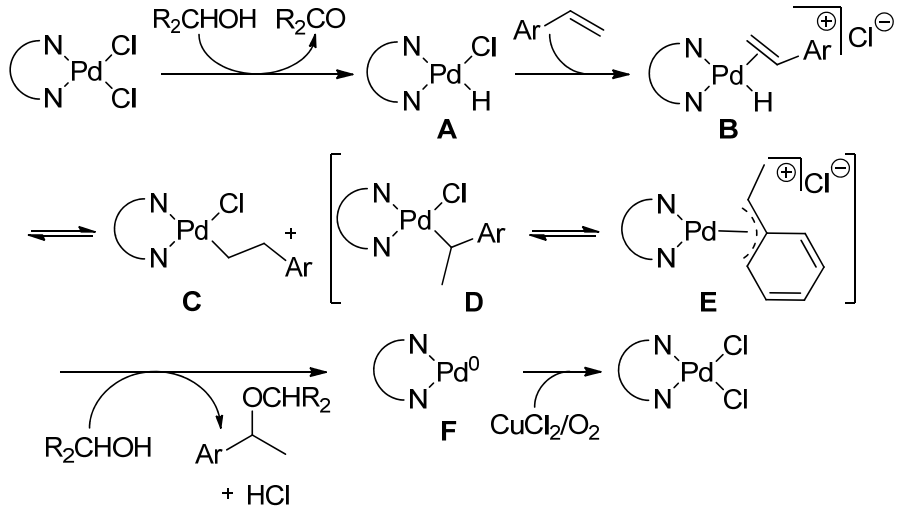


Figure 1.25. Hypothesized hydroalkoxylation of styrenes.

the Pd–H bond. At this point, two isomeric intermediates **C** and **D** could be formed, with **D** being stabilized as a Pd π-benzyl complex (**E**). This complex could then undergo nucleophilic attack by the alcohol to form the hydroalkoxylation product.

It should be noted that there are two distinct parts to this mechanism: the alcohol oxidation (Figure 1.26)[29,98] and the alkene insertion/nucleophilic attack (Figure 1.25). Interestingly, β-hydride elimination is a crucial step in each of these. In the alcohol oxidation, β-hydride elimination from the Pd alkoxide intermediate provides the Pd hydride, which reacts further with the styrene substrate. In the alkene insertion/nucleophilic attack, on the other hand, β-hydride elimination can occur as the

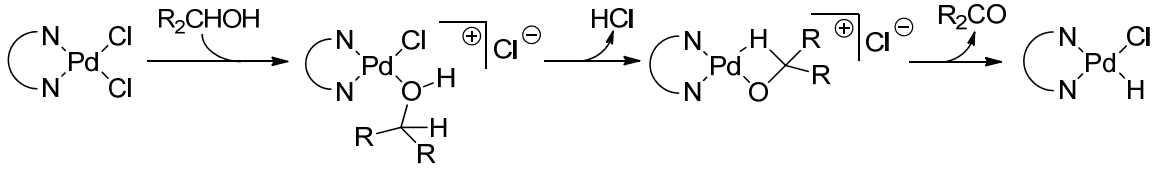


Figure 1.26. Mechanism of Pd hydride formation.

reverse of styrene insertion into the Pd–H bond. In this step, it could lead to a slowing of the overall reaction.

Herein is described the development of an alcohol oxidation-coupled hydroalkoxylation of styrenes and several mechanistic experiments to probe the fundamental aspects of the reaction, which revealed that while an overall hydroalkoxylation occurred, it proceeded via an unexpected benzylic chloride intermediate.[86]

Reaction Development

In an initial experiment, performed by Dr. Keith Gligorich, the hydroalkoxylation of 4-methylstyrene was tested using conditions similar to those developed for vinyl phenols. While EtOH was used as the solvent and hydride source in the original hydroalkoxylation of vinyl phenols, it had been found previously that submitting simple styrene substrates to similar reaction conditions in EtOH leads to acetal products.[99] Therefore, *i*PrOH, a much less nucleophilic alcohol that readily undergoes oxidation,[100,101] was selected as solvent. Initially, 4-methylstyrene (**1.9a**) was chosen as substrate, using Pd[(–)-sparteine]Cl_2 and $CuCl_2$ in *i*PrOH at 40 °C. Under these conditions, the desired hydroalkoxylation product is observed as the minor product, with the major product arising from Wacker oxidation (Figure 1.27). Gratifyingly, the

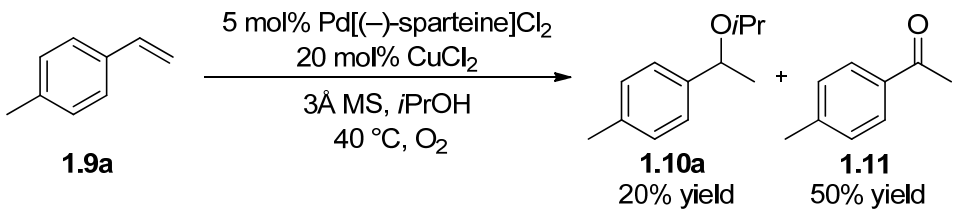
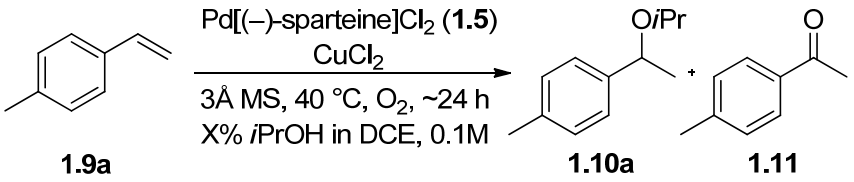


Figure 1.27. Initial discovery of hydroalkoxylation of styrenes.

hydroalkoxylation product **1.10a** is formed as a single regioisomer, which can be rationalized with the stabilization of **E** (compared to **C**, see Figure 1.25) via a π-benzyl Pd complex.

With this initial result in hand, control experiments were performed omitting either Pd or Cu to verify that both metals were required (Table 1.1, entries 1 and 2). Subsequently, the reaction conditions were optimized for the hydroalkoxylation product, the first steps of which are shown in Table 1.1. We hypothesized that the Wacker product was likely arising from H_2O_2, which is formed as a byproduct of aerobic alcohol oxidation.[102] Therefore, it was thought that the rate of alcohol oxidation should be decreased in order to obtain high selectivities for the hydroalkoxylation product, so that ideally, every Pd hydride formed is incorporated into product. While the rate of alcohol oxidation could be decreased by lowering the concentration of the alcohol, *i*PrOH was also thought to be acting as the nucleophile, and lowering its concentration could

Table 1.1. Initial optimization of hydroalkoxylation reaction.



1.9a **1.10a** **1.11**

entry	X	**1.5** (mol%)	$CuCl_2$ (mol%)	conv.[a] (%)	**1.10a**[b] (%)	**1.11**[b] (%)
1	100	5	20	92.4	19	52
2	100	0	20	<5	-	-
3	100	5	0	<5	-	-
4	60	5	20	>99	33	41
5[c]	60	10	40	>99	46	40

[a] determined via GC analysis using internal standard. [b] determined via GC analysis using internal standard and response factors. [c] 0.05M in substrate.

potentially decrease the selectivity for the hydroalkoxylation product. Testing several different solvent mixtures, 60% *i*PrOH in DCE was found to give the highest yield of hydroalkoxylation product (33%, entry 4). Lowering the substrate concentration from 0.1 M to 0.05 M, thus increasing the catalyst loading with respect to substrate, led to an additional improvement (46%, entry 5).

Further variation of the reaction conditions unfortunately did not lead to improvement of the reaction outcome. We therefore decided to evaluate other ligands on $PdCl_2$, and found that bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, bc) dramatically increased the reaction rate. However, when a timecourse of the reaction was performed by GC sampling, a significant induction period was observed (Figure 1.28, ▲).[103] Bathocuproine is known as a ligand for both Pd and Cu,[100,104,105] and thus it was hypothesized that bathocuproine could be dissociating from the Pd complex during that induction period, with "ligandless" Pd acting as the active catalyst. A separate timecourse was performed with preformed $Cu(bc)Cl_2$ rather than $Pd(bc)Cl_2$, mimicking the hypothesized catalyst mixture present after the induction period (Figure 1.28, ○). Upon performing the experiment, no induction period was observed when bathocuproine was bound to Cu instead of Pd prior to the start of the reaction. As a control, the reaction was performed with $Pd(MeCN)_2Cl_2$ and $CuCl_2$ as well as with $Pd(bc)Cl_2$ and $Cu(bc)Cl_2$. The latter reaction displayed lower selectivity for the hydroalkoxylation product, while using "ligandless" conditions led to decreased selectivity as well as a decreased reaction rate.[106] From these experiments, it was concluded that improved selectivity and reaction rates are observed with a ligand on Cu rather than Pd, indicating that Cu was likely

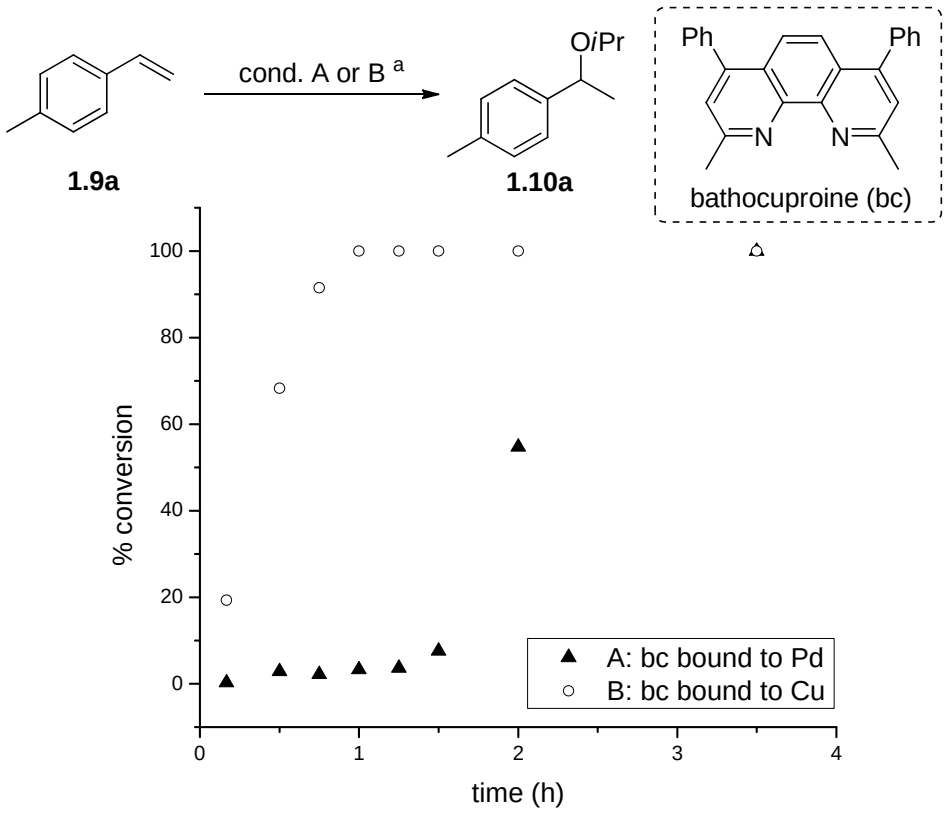


Figure 1.28. Time course of hydroalkoxylation with $Pd(bc)Cl_2$ and $Cu(bc)Cl_2$, respectively. [a] Condition A: 10 mol % $Pd(bc)Cl_2$, 40 mol % $CuCl_2$, 3 Å molecular sieves, 60% *i*PrOH/DCE, 40 °C, balloon O_2. Condition B: 10 mol % $Pd(MeCN)_2Cl_2$, 10 mol % $Cu(bc)Cl_2$, 30mol % $CuCl_2$, 3 Å molecular sieves, 60% *i*PrOH/DCE, 40 °C, balloon O_2.

playing a more complex role than simply reoxidizing Pd^0 to Pd^{II}, as is commonly proposed in Wacker-type oxidations.[107,108]

Additionally, upon switching to bathocuproine, a careful analysis of the reaction mixture showed the presence of an intermediate (Figure 1.29, ▲), which was identified as the benzylic chloride **1.12a**. Based on this observation, it was concluded that the initial nucleophile is a chloride ion rather than *i*PrOH, and the hydroalkoxylation product

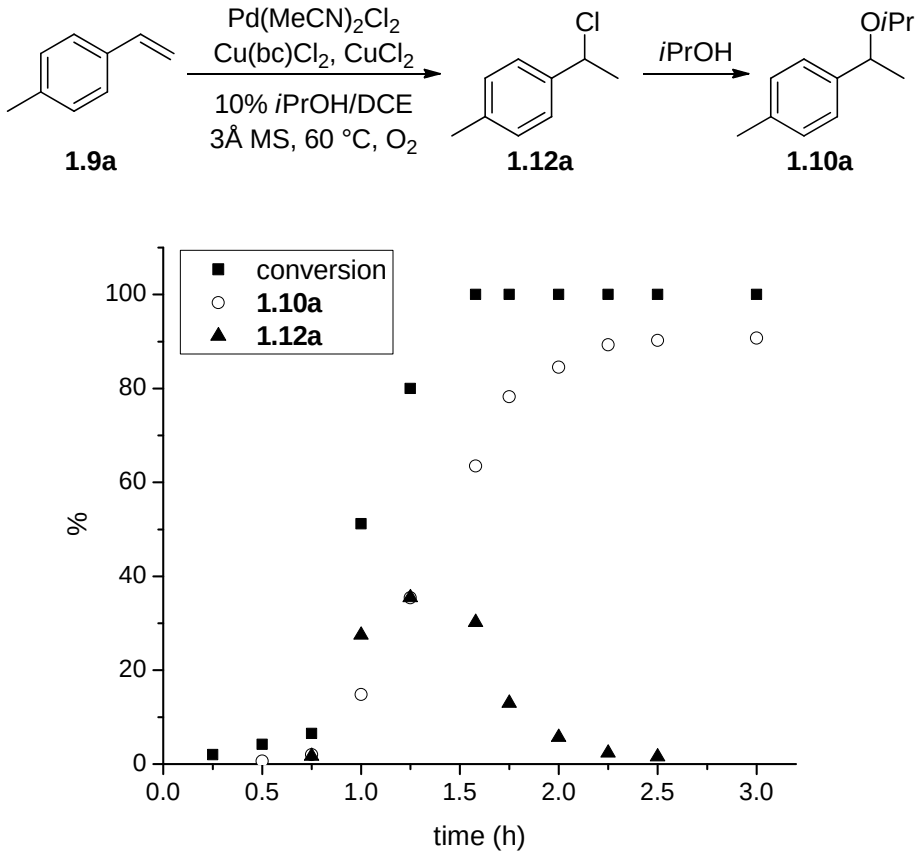


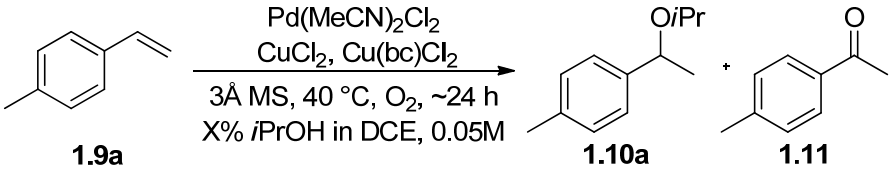
Figure 1.29. Time course of hydroalkoxylation showing chloride intermediate.

likely arises from the benzylic chloride via an S_N1 type mechanism (vide infra). Considering there is four times more $CuCl_2$ in the reaction mixture than $PdCl_2$, it is likely that $CuCl_2$ is the major source of chloride. Overall, this is an interesting and unexpected finding, since metal-catalyzed hydrochlorination reactions proceeding via nucleophilic attack on a metal complex had not been observed prior to our report.

Having gained some crucial insight into the reaction from the experiments detailed above, further optimization was performed using $Pd(MeCN)_2Cl_2$ and a mixture of $Cu(bc)Cl_2$ and $CuCl_2$. Interestingly, a combination of 10 mol% $Cu(bc)Cl_2$ with 30 mol% $CuCl_2$ was optimal, giving 47% GC yield of the hydroalkoxylation product (Table

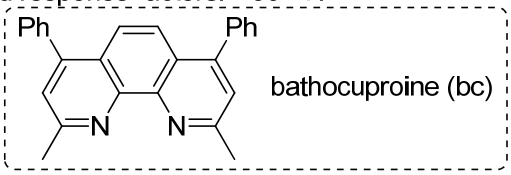
1.2, entry 2), while 40 mol% Cu(bc)Cl_2 gave 15% hydroalkoxylation and 51% Wacker product (entry 1). Assuming that the chloride intermediate (**1.12a**) was converted to product via an S_N1-type reaction, the rate of this substitution should be independent of the concentration of *i*PrOH (apart from polarity effects), and *i*PrOH should influence the reaction mainly via the rate of alcohol oxidation (vide supra). When the concentration of *i*PrOH was further lowered to 10% *i*PrOH in DCE, the selectivity for the hydroalkoxylation product improved slightly to 49% GC yield (Table 1.2, entry 3). Subsequently, the temperature was raised in order to accelerate the nucleophilic substitution. This in turn would release more chloride and thus promote the formation of benzylic chloride **1.12a**. Indeed, when the temperature was increased from 40 °C to

Table 1.2. Final optimization of hydroalkoxylation reaction.



entry	X	$Pd(MeCN)_2Cl_2$ (mol%)	$CuCl_2$ (mol%)	$Cu(bc)Cl_2$[a] (mol%)	conv.[b] (%)	**1.10a**[c] (%)	**1.11**[c] (%)
1	60	10	-	40	>99	15	51
2	60	10	30	10	>99	47	30
3	10	10	30	10	>99	49	20
4[d]	10	10	30	10	>99	62	21
5[d]	10	10	40	10	>99	84	3
6[d]	10	5	20	5	93	77	2

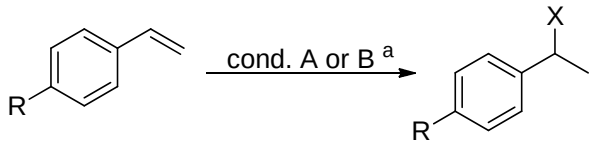
[a] bc = bathocuproine. [b] determined via GC analysis using internal standard. [c] determined via GC analysis using internal standard and response factors. [d] 60 °C.

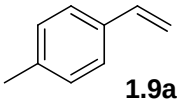
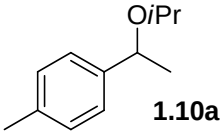
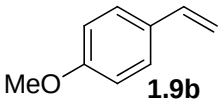
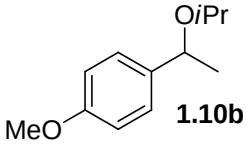
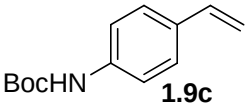
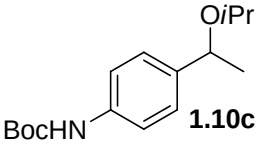
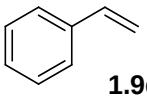
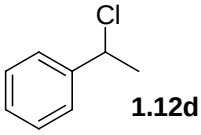
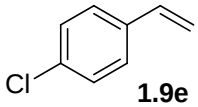
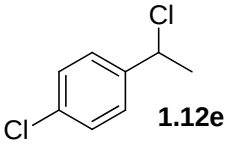


60 °C, the GC yield of the hydroalkoxylation product increased to 62% (entry 4). Additionally, the amount of chloride in the reaction mixture was further raised by changing the loading of $CuCl_2$ from 30 mol% to 40 mol%, leading to 84% GC yield of the desired product (entry 5). Higher concentrations of $CuCl_2$ unfortunately inhibited the reaction, presumably due to slowing of the rate of alcohol oxidation.[107] Under these conditions, the catalyst loading could be reduced without substantial decrease in product yield (77% GC yield, entry 6).

Having optimized the reaction for 4-methylstyrene, several other substrates were submitted to the reaction conditions (Table 1.3). While electron rich styrenes are excellent substrates, electron poor styrenes gave mixtures of hydroalkoxylation and hydrohalogenation products along with increased amounts of Wacker products, illustrating the high sensitivity of the reaction to the electronic nature of the substrate. Interestingly, while 4-methylstyrene gave good yields of the hydroalkoxylation product, styrene was sufficiently electron poor to yield the hydrochlorination product. For electron poor substrates, the reaction was thus optimized for hydrochlorination by lowering the temperature to 50 °C, increasing the catalyst loading to the previous level (with 50 mol% $CuCl_2$) and decreasing the amount of *i*PrOH to 2.5% in DCE. Upon isolation, the hydrochlorination product was found to contain ca. 5% of the regioisomeric primary chloride (2-chloroethylarene), which is likely formed from the regioisomeric Pd alkyl complex (**C**, see Figure 1.25). This was entirely unexpected, since no primary ether product had been observed with the electron rich substrates. It is reasonable, however, that the primary chloride is reversibly formed in the reaction of electron rich substrates, but does not undergo the S_N1 reaction to produce the ether product.[109]

Table 1.3. Hydroalkoxylation substrate scope.



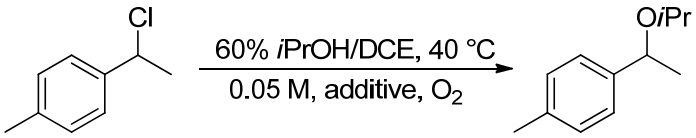
entry	substrate	cond.	product	yield (%)
1	 **1.9a**	A	 **1.10a**	55
2	 MeO **1.9b**	A	 MeO **1.10b**	73
3	 BocHN **1.9c**	A	 BocHN **1.10c**	78
4	 **1.9d**	B	 **1.12d**	22[b]
5	 Cl **1.9e**	B	 Cl **1.12e**	44[b]

[a] Cond. A: 5 mol% $Pd(MeCN)_2Cl_2$, 5 mol% $Cu(bc)Cl_2$, 20 mol% $CuCl_2$, 0.5 g/mmol 3Å MS, 10% *i*PrOH/DCE, 60 °C, O_2 balloon. Cond. B: 10 mol% $Pd(MeCN)_2Cl_2$, 10 mol% $Cu(bc)Cl_2$, 50 mol% $CuCl_2$, 1.0 g/mmol 3Å MS, 2.5% *i*PrOH/DCE, 50 °C, O_2 balloon. [b] including ca. 5% regioisomer (primary chloride).

Mechanistic Investigations

The unexpected results obtained above prompted us to study the reaction in greater detail. Specifically, we wished to address the conversion of the benzylic chloride **1.12** to the ether, the roles of the different metals, and finally the origin of the proton incorporated into the product. In order to confirm that chloride **1.12** converted to the hydroalkoxylation product, hydroalkoxylation product, **1.12a** was independently prepared and submitted to reaction conditions (Table 1.4). Indeed, when **1.12a** was heated to 40 °C in *i*PrOH, it converted exclusively to the hydroalkoxylation product (**1.10a**). In the presence of metal catalysts the reaction was significantly accelerated, possibly due to the metals acting as Lewis acid catalysts. This information together with the fact that electron poor benzylic chlorides do not convert completely to the ether product implies that a metal assisted S_N1 reaction is most likely occurring.[110-113]

Table 1.4. Promotion of nucleophilic substitution by different additives.



1.12a **1.10a**

entry	additive	time (h)	% conv.[a]	% **1.10a**[b]
1	-	22.5	30	29
2	1 g/mmol 3Å MS	22.5	39	38
3	10 mol% $Cu(bc)Cl_2$, 30 mol% $CuCl_2$, 1 g/mmol 3Å MS	15.5	79	73
4	10 mol% $Pd(MeCN)_2Cl_2$, 1 g/mmol 3Å MS	15.5	67	62
5	10 mol% $Cu(bc)Cl_2$, 30 mol% $CuCl_2$, 10 mol%$Pd(MeCN)_2Cl_2$, 1 g/mmol 3Å MS	15.5	91	85

[a] determined via GC analysis using an internal standard.
[b] determined via GC analysis using an internal standard and response factor.

In order to determine the origin of the proton incorporated into the product, several deuterium labeling experiments were performed. Based on precedence from our laboratory,[28] our initial hypothesis was that a Pd hydride was formed during *i*PrOH oxidation and that this hydride was subsequently incorporated into the product (vide supra). To confirm this, several deuterium labeling experiments were carried out, as shown in Figure 1.30. Initially, two control experiments were performed in $(CH_3)_2CHOD$ and DCE-d_4 (Figure 1.30, eq. 1, 2), to probe the involvement of the acidic proton or protons from DCE solvent. As expected, no deuterium incorporation was observed in any of the products, strongly suggesting the absence of Brønsted acid catalysis. Subsequently, the reaction was performed in $(CH_3)_2CDOH$ and $(CD_3)_2CDOD$, respectively (eq. 3, 4). With both of these alcohols, deuterium incorporation into the double bond was expected, since the Pd hydride would be formed in the β-hydride elimination step of the alcohol oxidation, and thus would stem from the α-position of *i*PrOH.[29] However, isotopic depletion could potentially occur via the enol form of acetone (the oxidation product of *i*PrOH) in the case of $(CH_3)_2CDOH$. With $(CD_3)_2CDOD$, any such exchange would be inconsequential.[114] Upon performing these experiments, similar results were observed, in which two main isotopologues are formed. The major isotopologue containing 2 or 8 D (**1.14** or **1.16**), respectively, is consistent with the proton incorporated into the side chain arising from alcohol oxidation, and is formed in 48 and 46% (of the overall hydroalkoxylation product). However, another isotopologue with 1 (or 7) D (**1.13** or **1.15**) was observed in 39 and 43%, which was initially unexpected. Closer investigation of the styrene at early time points revealed

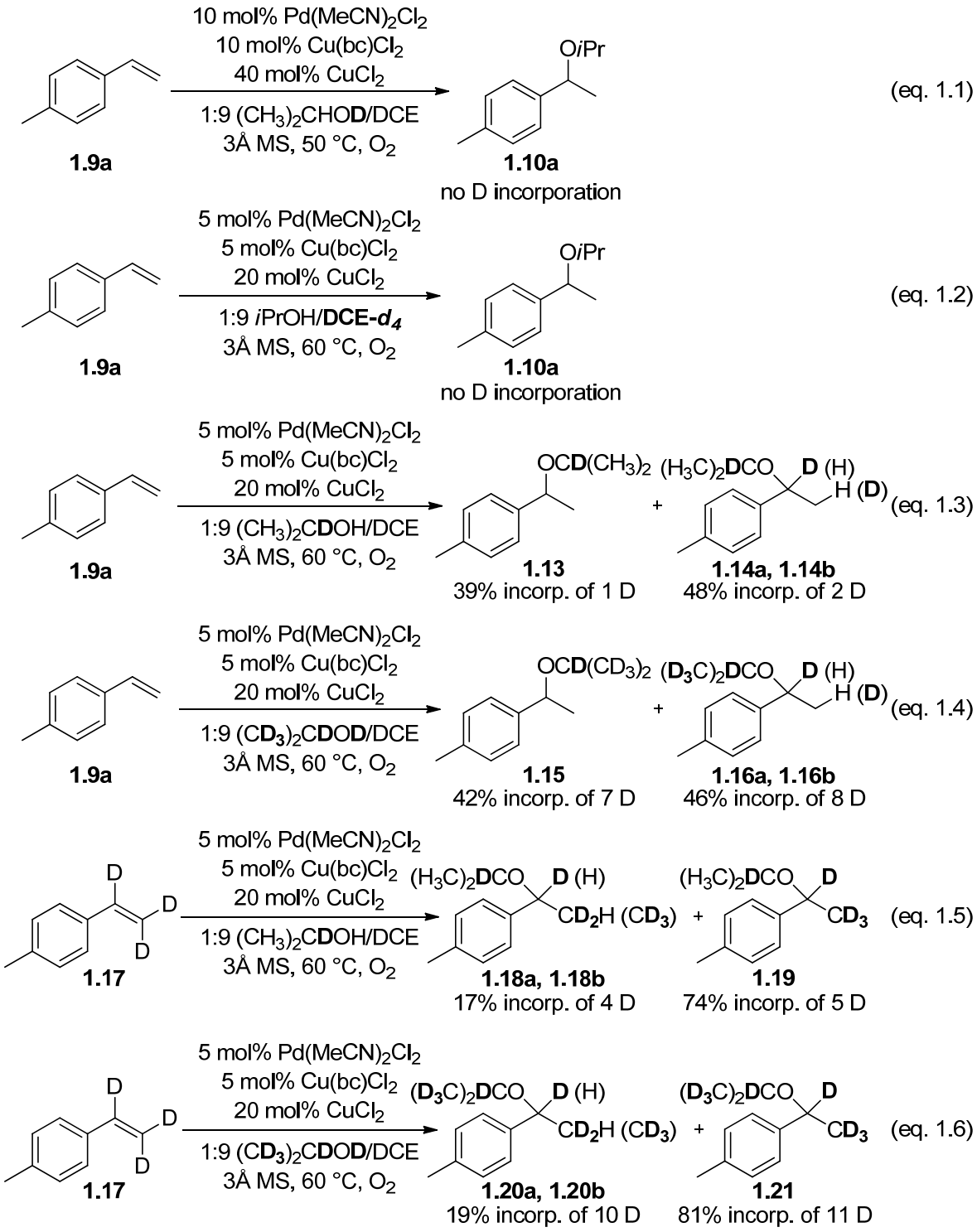


Figure 1.30. Deuterium labeling studies.

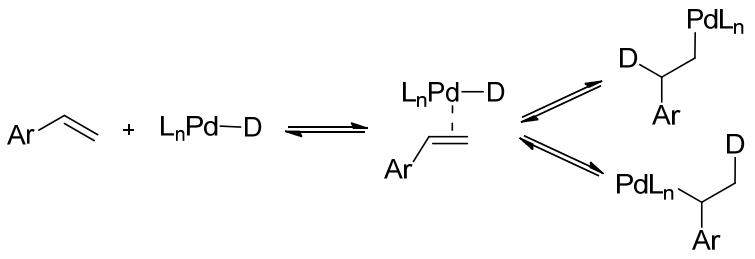


Figure 1.31. Reversible styrene insertion/β-hydride elimination.

partial D incorporation. This D incorporation into substrate could arise from reversible alkene insertion/β-hydride elimination (Figure 1.31), and provide a pathway for D scrambling and potential isotopic depletion in the product.[115] To probe this, substrate **1.17** was prepared containing 3 D in the olefin (93% 3 D) and submitted to reaction conditions with $(CH_3)_2CDOH$ or $(CD_3)_2CDOD$ (eq. 1.5, 1.6). As expected, significantly higher levels of isotopic incorporation are observed, consistent with the equilibrium shown above. Specifically, the major isotopologue (**1.19** or **1.21,** containing 5 and 11 D, respectively) was formed in 74 and 81%, again indicating that no significant exchange via enol chemistry was occurring.

Additionally, it was found that the reaction using deuterated substrate **1.17** in $(CH_3)_2CDOH$ or $(CD_3)_2CDOD$ was significantly faster than that using nonlabeled material (**1.17** in $(CH_3)_2CDOH$: 43% conversion at 0.5 h; **1.9a** in *i*PrOH: 18% conversion at 0.5 h), indicating a large inverse isotope effect.[106] This unusual finding indicates that alcohol oxidation is probably not rate limiting in the overall reaction, since normal isotope effects have been measured for alcohol oxidation reactions under similar conditions.[98,100] It is plausible that the isotope effect originates in the equilibrium shown in Figure 1.31. Deuterium binds preferably with stronger bond constants,[116] therefore the equilibrium for the Pd deuteride should lie further on the side of the Pd alkyl (compared

to the Pd hydride). This would provide a higher concentration of the Pd alkyl complex, and thus accelerate the reaction, leading to an inverse equilibrium isotope effect.

Having confirmed that alcohol oxidation is the source of the Pd hydride, we wanted to determine how many equivalents of alcohol were oxidized per equivalent of styrene converted. For these experiments, a heavier alcohol was selected, namely 2-octanol, which shows similar results to *i*PrOH, for ease of detection by GC. Upon performing the experiment, it was found that 1.1 equivalent of 2-octanone was formed per equivalent of styrene consumed. This confirmed our initial hypothesis that the rates of alcohol oxidation and alkene insertion/nucleophilic attack should be well matched to achieve an efficient reaction. As an additional control to determine the role of the metal catalysts, 2-octanol was submitted to the reaction conditions omitting either Pd or Cu. Unfortunately, no alcohol oxidation occurred under those conditions, indicating that both metals are required for this transformation. It is likely that Cu^{II} ($Cu(bc)Cl_2$ and/or $CuCl_2$) is acting as a cooxidant for Pd^0, as it does for example in Wacker oxidations.[106] The role of each metal in the subsequent olefin functionalization could not be tested, since the Pd hydride required for the reaction was not formed in the absence of either. It seems logical, however, that $CuCl_2$ and/or $Cu(bc)Cl_2$ is acting as a chloride source to form benzylic chloride **1.12**. In order to test this, and potentially distinguish the roles of the two Cu species, $CuCl_2$ and $Cu(bc)Cl_2$ were separately substituted by Bu_4NCl.[106] In both cases, mainly the product of a Wacker oxidation is observed (**1.11**), indicating that neither $CuCl_2$ nor $Cu(bc)Cl_2$ can simply be replaced by other chloride sources. The specific roles of ligated and nonligated $CuCl_2$ unfortunately can thus not be distinguished.

Based on the information obtained from the isotopic labeling experiments, the observation of the chloride intermediate, and the other experiments shown above, the mechanism shown in Figure 1.32 is proposed. Initially, Pd hydride **B** is formed via an alcohol oxidation, which is supported by the isotopic labeling experiments as well as the observed oxidation of 2-octanol. The styrene substrate is then coordinated to Pd, followed by insertion into the Pd hydride. The observed incorporation of deuterium into the styrene indicates both the coordination and the insertion steps are reversible. Based on the observation of the primary chloride byproduct with electron poor styrenes, it is assumed that both Pd alkyls **D** and **E** are formed, as observed in the hydroalkoxylation of

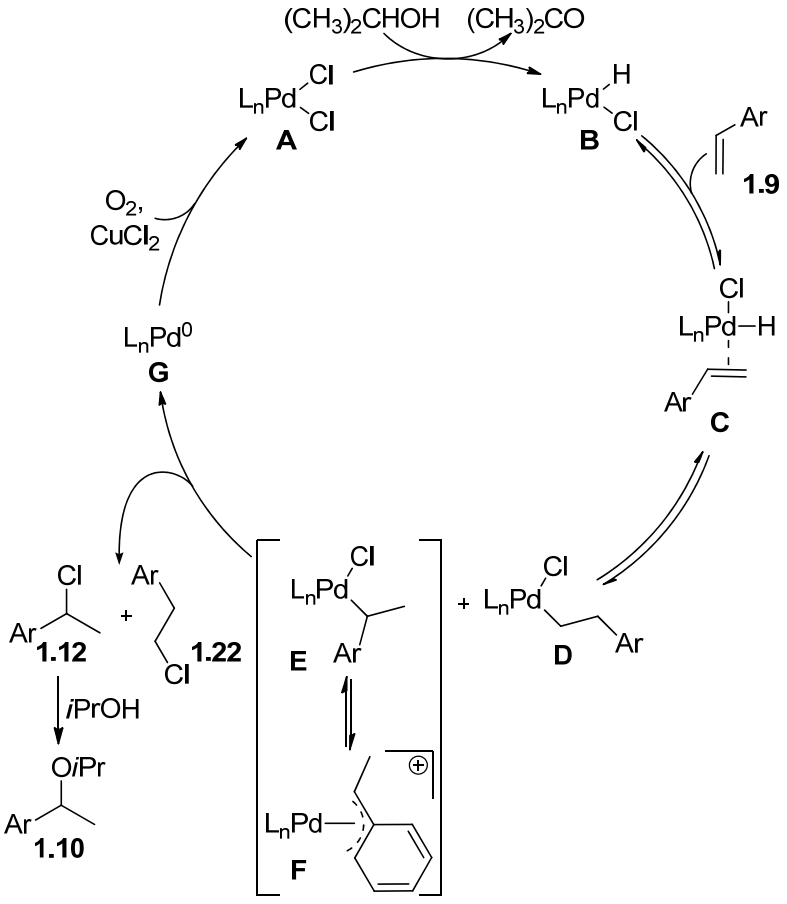


Figure 1.32. Proposed mechanism of hydroalkoxylation.

vinylphenols. However, **D** can be stabilized via a π-benzyl intermediate (**F**), and thus is likely formed predominantly. In the following step, chlorides **1.12** and **1.22** are formed, either via reductive elimination or nucleophilic attack on **D** or **E**, respectively, by an exogenous chloride ion. In either case, Pd^{II} is reduced to a Pd^0 species (**G**), which is subsequently reoxidized by O_2 and/or $CuCl_2$. Since H_2O_2 has been shown to be a competent oxidant for Pd^{IV} chemistry,[117] and reductive elimination of C-Cl bonds from Pd^{IV} has been observed previously,[118] we cannot rule out the involvement of a Pd^{IV} species in this reaction. In the case of electron rich aromatic systems, the benzylic chloride is transformed into the ether product **1.10** via a metal-promoted S_N1 reaction, while in the case of more electron poor aromatic substrates, the rate of this step is slow enough to allow for isolation of the chloride. A competing mechanism involving direct substitution of Pd by *i*PrOH as proposed in Figure 1.25 cannot be ruled out at this time. However, based on the isolation of the chloride product from electron poor styrenes and the timecourse showing its conversion to the hydroalkoxylation product, the mechanism shown in Figure 1.32 is proposed to be dominant.

Conclusion

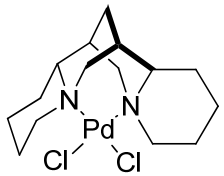
In summary, we have developed a mechanistically unique hydrochlorination-hydroalkoxylation of styrenes. While the substrate scope of this reaction is limited, this was the first report of a hydrochlorination of alkenes not promoted by acid. It is also one of a small number of reports of hydroalkoxylations that are clearly not catalyzed by Lewis or Brønsted acids. Furthermore, we established the viability of our concept using Pd hydrides to functionalize styrenes, which has since been expanded to include several

research projects in our research group, including the one discussed in the following chapter.

Experimental Section

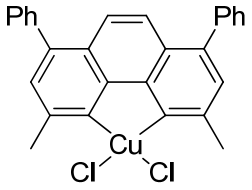
General Information

DCE (1,2-dichloroethane) and CH_2Cl_2 were dried by distilling from CaH_2; *i*PrOH was dried by refluxing over CaO for 12 h followed by fractional distillation; THF was dried by distilling from sodium benzophenone ketyl; chloroform was dried by passing through a plug of activated neutral alumina. Liquid styrene substrates were purified by passing through a small plug of activated neutral alumina before use. 3Å molecular sieves were powdered and activated by heating with a Bunsen burner under vacuum. Flash column chromatography was performed using EM Reagent silica 60 (230-400 mesh). ^{1}H NMR were obtained at 300 MHz and referenced to the residual $CHCl_3$ singlet at 7.26 ppm. ^{13}C NMR were obtained at 75 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.23 ppm. GC/MS were obtained on a HP 5890 (EI) 20:1 split. IR spectra were obtained on a Bruker Tensor 37 FTIR spectrometer. HRMS were obtained on an Agilent LCTOF. Caution should be taken when heating flammable solvents in the presence of O_2.



Pd[(–)-sparteine]Cl_2

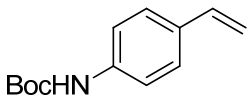
Pd[(–)-sparteine]Cl_2 was prepared as previously described in the literature.[119]



$Cu(bc)Cl_2$

Preparation of $Cu(bc)Cl_2$. In an oven-dried 100 mL round bottom flask were added 81.3 mg $CuCl_2$ (0.606 mmol, 1.00 equiv.) and 20.0 mL CH_2Cl_2. A solution of 218 mg bathocuproine (0.606 mmol, 1.00 equiv.) in 30.0 mL CH_2Cl_2 was added slowly via syringe while stirring. A red solution was observed, and the mixture was stirred for 12 h at room temperature. Hexanes (5.00 mL) were added and the mixture was concentrated in vacuo, yielding a dark red solid, which was dried in vacuo for 2 h. Yield: quantitative; mp: 185 °C (decomp.); IR (KBr): 1621, 1583, 1571, 1549, 1486, 1440, 1397, 1379, 1186, 1185, 1108, 1077, 1029, 1000, 887, 864, 840, 781, 773, 734, 704, 643, 635, 611, 541.

It should be noted that no difference was observed when using preformed $Cu(bc)Cl_2$ or mixing $CuCl_2$ and bathocuproine in situ.



1.9c

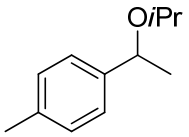
*Preparation of t-butyl 4-vinylphenylcarbamate (**1.9c**):* In an oven-dried 100 mL round bottom flask, 1.15 g of Boc_2O (5.27 mmol, 1.15 equiv.) were dissolved in 20.0 mL of THF. A solution of 546 mg 4-vinylaniline (4.58 mmol, 1.00 equiv.) in 20.0 mL of THF was added via syringe, and a dry condenser was placed on the flask. The mixture was placed in an oil bath at 50 °C, and stirred under N_2 for 12 h. An additional 500 mg

of Boc_2O (2.29 mmol, 0.500 equiv.) were added, and the reaction was stirred at 50 °C for another 12 h. The mixture was then diluted with 20.0 mL of Et_2O and washed with sat. aq. NH_4Cl (2 × 50.0 mL), H_2O (2 × 50.0 mL), brine (1 × 50.0 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Column chromatography eluting with 4% Et_2O/hexanes yielded a mixture of *t*-butyl 4-vinylphenylcarbamate (**1.9c**) and Boc_2O. The mixture was diluted with 50.0 mL of Et_2O and washed with sat. aq. NH_4Cl (2 × 50.0 mL) and brine (1 × 50.0 mL), followed by 1:1 aq. NH_4OH/H_2O (2 × 50.0 mL). The combined aqueous layers were extracted with Et_2O (1 × 50.0 mL), and the combined organic layers were washed with brine (1 × 50.0 mL). Column chromatography eluting with 4% Et_2O/hexanes → 8% Et_2O/hexanes yielded the product as a white solid. Yield: 622 mg (2.83 mmol, 62%); R_f: 0.50 w/20% EtOAc/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 5.16 (dd, *J* = 1.0 Hz, 11.0 Hz, 1 H), 5.65 (dd, *J* = 1.0 Hz, 17.6 Hz, 1 H), 6.49 (br s, 1 H), 6.66 (dd, *J* = 11.0 Hz, 17.6 Hz, 1 H), 7.34 (m, 4 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 28.5, 80.8, 112.5, 118.6, 127.0, 132.7, 136.4, 138.1, 152.8; GC/MS: (m/z) calcd. 219.13 obsd. 219.10 $[M]^+$, 163.05 $[M\text{-}t\text{Bu}]^+$; mp: 84 °C.[120]

General Procedure for Hydroalkoxylation of Electron-Rich Styrene Derivatives

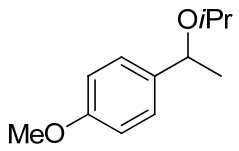
Into an oven-dried 100 mL Schlenk flask equipped with a stirbar were added 13.0 mg of $Pd(MeCN)_2Cl_2$ (0.0500 mmol, 0.0500 equiv.), 24.7 mg of $Cu(bc)Cl_2$ (0.0500 mmol, 0.0500 equiv.), 26.8 mg of $CuCl_2$ (0.200 mmol, 0.200 equiv.) and 500 mg of freshly activated crushed 3Å molecular sieves. A condenser was placed on the flask and the joint was lightly greased and wrapped with Teflon tape to ensure a good seal. DCE (18.0 mL) followed by *i*PrOH (2.00 mL) were added and a three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water

aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min. The styrene substrate (1.00 mmol, 1.00 equiv.) was then added via syringe and the reaction mixture was placed in an oil bath at 60 °C. The reaction mixture was stirred under O_2 for 24 h. During this time, the mixture turned from orange to brown and back to orange. After 24 h, the mixture was cooled to room temperature and passed through a large plug of silica (ca. 8 g) with 100 mL of 1:1 Et_2O/hexanes. The solvent was removed in vacuo to obtain an orange oil. This was mixed with hexanes (10.0 mL) and washed with saturated aqueous $NaHCO_3$ (3 × 10.0 mL). The combined aqueous layers were then extracted with hexanes (2 × 10.0 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting pale yellow oil was purified by flash column chromatography.



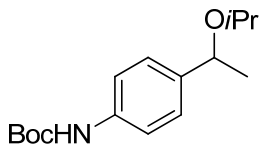
1.10a

*1-(1-isopropoxyethyl)-4-methylbenzene (**1.10a**):* column chromatography: hexanes → 1% Et_2O/hexanes → 3% Et_2O/hexanes; yield: 55%; clear oil; R_f: 0.64 w/ 20% Et_2O/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, J = 6.3 Hz, 3 H), 1.14 (d, J = 6.0 Hz, 3 H), 1.39 (d, J = 6.3 Hz, 3 H), 2.34 (s, 3 H), 3.48 (qq, J = 6.0 Hz, 6.3 Hz, 1 H), 4.50 (q, J = 6.3 Hz, 1 H), 7.12 – 7.24 (m, 4 H); ^{13}C NMR {^1H} (75 MHz, $CDCl_3$) δ 21.3, 21.5, 23.6, 25.0, 68.5, 74.6, 126.2, 129.2, 137.0, 142.0; MS (ESI/APCI) m/z (MNH_4^+) calcd.: 196.1701 obsd.: 196.1693.



1.10b

*1-(1-isopropoxyethyl)-4-methoxybenzene (***1.10b***):* column chromatography: hexanes → 1% Et_2O/hexanes → 3% Et_2O/hexanes → 5% Et_2O/hexanes; yield: 73%; clear oil; R_f: 0.34 w/ 10% Et_2O/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, *J* = 6.0 Hz, 3 H), 1.14 (d, *J* = 6.0 Hz, 3 H), 1.38 (d, *J* = 6.3 Hz, 3 H), 3.47 (qq, *J* = 6.0 Hz, 6.0 Hz, 1 H), 3.81 (s, 3 H), 4.49 (q, *J* = 6.3 Hz, 1 H), 6.88 (m, 2 H), 7.24 (m, 2 H); ^{13}C NMR $\{^1H\}$ (75 MHz, $CDCl_3$) δ 21.5, 23.6, 25.0, 55.4, 68.4, 74.3, 113.9, 127.4, 137.1, 159.0; GC/MS: (m/z) calcd. 194.13 obsd. 194.05 $[M]^+$, 179.10 $[M\text{-}CH_3]^+$.[121]

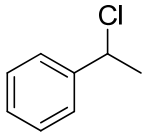


1.10c

*t-Butyl 4-(1-isopropoxyethyl)phenylcarbamate (***1.10c***):* column chromatography: hexanes → 1% Et_2O/hexanes → 3% Et_2O/hexanes → 5% Et_2O/hexanes → 10% Et_2O/hexanes → 20% Et_2O/hexanes → 50% Et_2O/hexanes; yield: 78%; white solid; R_f: 0.40 w/ 20% EtOAc/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.0 Hz, 3 H), 1.13 (d, *J* = 6.0 Hz, 3 H), 1.37 (d, *J* = 6.3, 3 H), 1.52 (s, 9 H), 3.46 (qq, *J* = 6.0 Hz, 6.0 Hz, 1 H), 4.48 (q, *J* = 6.3, 1 H), 6.44 (br s, 1 H), 7.25 (m, 2 H), 7.32 (m, 2 H); ^{13}C NMR $\{^1H\}$ (75 MHz, $CDCl_3$) δ 21.5, 23.6, 25.0, 28.5, 68.5, 74.4, 80.7, 118.8, 127.0, 137.5, 139.7, 153.0; mp: 96 °C; MS (ESI/APCI) m/z (MNa^+) calcd.: 302.1732 obsd.: 302.1725.

General Procedure for Hydrochlorination of Electron-Poor Styrene Derivatives

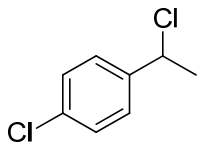
Into an oven-dried 100 mL Schlenk flask equipped with a stirbar were added 25.9 mg of $Pd(MeCN)_2Cl_2$ (0.100 mmol, 0.100 equiv.), 49.5 mg of $Cu(bc)Cl_2$ (0.100 mmol, 0.100 equiv.), 67.1 mg of $CuCl_2$ (0.500 mmol, 0.500 equiv.) and 1.00 g freshly activated crushed 3Å molecular sieves. A condenser was placed on the flask and the joint was lightly greased and wrapped with Teflon tape to ensure a good seal. DCE (19.5 mL) followed by *i*PrOH (0.500 mL) were added and a three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min. The styrene substrate (1.00 mmol, 1.00 equiv.) was then added via syringe and the reaction mixture was placed in an oil bath at 50 °C. The reaction mixture was stirred under O_2 for 28 h. During this time, the mixture turned from orange to dark brown. After 28 h, the mixture was cooled to room temperature and passed through a large plug of silica (ca. 8 g) with 100 mL of 1:1 Et_2O/hexanes. The solvent was removed in vacuo to obtain a clear oil. The oil was purified by flash column chromatography.



1.12d

*(1-Chloroethyl)benzene (***1.12d***):* column chromatography: hexanes → 1% Et_2O/hexanes → 3% Et_2O/hexanes → 10% Et_2O/hexanes; yield: 22% (containing 6% primary chloride **1.22d**); clear oil; R_f: 0.64 w/ 20% Et_2O/hexanes; ^1H NMR (300 MHz,

$CDCl_3$) δ 1.86 (d, *J* = 6.9 Hz, 3 H), 3.08 (t, *J* = 7.4 Hz, 0.13 H), 3.72 (t, *J* = 7.4 Hz, 0.1 H), 5.10 (q, *J* = 6.9, 1 H), 7.28 – 7.46 (m, 5 H).[5,122]



1.12e

*1-Chloro-4-(1-chloroethyl)benzene (***1.12e***):* column chromatography: hexanes → 1% Et_2O/hexanes → 5% Et_2O/hexanes → 10% Et_2O/hexanes; yield: 35% (containing 6% primary chloride **1.22e**); clear oil; R_f: 0.54 w/ 10% EtOAc/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (d, *J* = 6.9 Hz, 3 H), 3.04 (t, *J* = 7.4 Hz, 0.12 H), 3.70 (t, *J* = 7.4 Hz, 0.13 H), 5.06 (q, *J* = 6.9, 1 H), 7.30 – 7.38 (m, 4 H); ^{13}C NMR {^1H} (75 MHz, $CDCl_3$) δ 26.7, 58.0, 128.1, 129.0, 134.2, 141.5; GC/MS: (m/z) calcd. 174.00 obsd. 173.90 $[M]^+$, 139.00 $[M\text{-}Cl]^+$.

Initial discovery. Into an oven-dried 10 mL sidearm flask were added 2.10 mg of Pd[(–)-sparteine]Cl_2 (0.005 mmol, 0.0500 equiv.), 2.70 mg of $CuCl_2$ (0.0200 mmol, 0.200 equiv.) and 50.0 mg of activated 3Å molecular sieves. A condenser was placed on the flask and 0.900 mL of *i*PrOH were added via the sidearm. A three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min. Subsequently, 11.8 mg of 4-methylstyrene (**1.9a**, 0.100 mmol, 1 equiv.) were added as 0.100 mL of a 1.00 M solution in *i*PrOH with 5-nonanone (20.0 µL per mmol 4-methylstyrene) added as internal standard. The flask was placed in an oil bath at 40 °C and stirred for 26 hours. A sample

of the reaction mixture was passed through a short plug of silica eluting with EtOAc and analyzed by GC, showing 20% **1.10a** and 50% **1.11** at 92% conversion.

Timecourse Experiments

Bathocuproine dissociation timecourses (A: preformed $Pd(bc)Cl_2$; B: preformed $Cu(bc)Cl_2$). Into an oven-dried 5 mL sidearm flask equipped with a stirbar were added 1.30 mg of $Pd(MeCN)_2Cl_2$ (0.00500 mmol, 0.100 equiv.) for A, or 2.70 mg of $CuCl_2$ (0.0200 mmol, 0.400 equiv.) for B, and 1.80 mg bathocuproine (0.00500 mmol, 0.100 equiv.) for both. A condenser was placed on the flask and 0.400 mL DCE and 0.500 mL *i*PrOH were added via the sidearm. The solution was stirred for ca. 20 min to form the respective bathocuproine complex. Subsequently, 2.70 mg $CuCl_2$ (0.0200 mmol, 0.400 equiv.) for A, or 1.30 mg $Pd(MeCN)_2Cl_2$ (0.00500 mmol, 0.100 equiv.) for B, and 50.0 mg activated 3Å molecular sieves were added, and a three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The mixture was then stirred under O_2 at room temperature for 30 min. Then, 5.90 mg of 4-methylstyrene (**1.9a**, 0.0500 mmol, 1.00 equiv.) were added as 0.100 mL of a 0.500 M solution in *i*PrOH with 5-nonanone (20.0 μL per mmol 4-methylstyrene) added as internal standard. The flask was placed in an oil bath at 40 °C, and samples were taken periodically. The samples were filtered through a small plug of silica eluting with EtOAc and analyzed by GC (see Table 1.5).

Table 1.5. Bathocuproine dissociation timecourse data.

time (h)	conversion (%)		
	$Pd(bc)Cl_2$	$Cu(bc)Cl_2$	ligandless
0.17	0.3	19.3	14.1
0.50	2.9	68.3	18.0
0.75	2.2	91.5	15.9
1.00	3.3	100	16.0
1.25	3.6	100	15.8
1.50	7.6	100	17.3
2.00	54.7	100	18.5
3.50	100	100	24.8

"Ligandless" conditions. The reaction was performed in the same way as for the ligand dissociation timecourses, except no bathocuproine was added, and $Pd(MeCN)_2Cl_2$ and $CuCl_2$ could be added at the same time (see Table 1.5).

Ligand dissociation using (–)-Sparteine: Cu[(–)-sparteine]Cl_2. Into an oven-dried 100 mL Schlenk flask equipped with a stirbar were added 26.8 mg $CuCl_2$ (0.200 mmol, 0.400 equiv.). A condenser was placed on the flask and 3.30 mL DCE, 11.7 mg of (–)-sparteine (0.0500 mmol, 0.100 equiv.) as 0.200 mL of a 0.250 M solution in DCE, and 6.00 mL *i*PrOH were added via the sidearm. The solution was stirred for ca. 20 min to form the Cu[(–)-sparteine]Cl_2 complex. Subsequently, 13.0 mg of $Pd(MeCN)_2Cl_2$ (0.0500 mmol, 0.100 equiv.) and 500 mg of activated 3Å molecular sieves were added, and a three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The mixture was then stirred under O_2 at room temperature for 30 min. Then, 59.1 mg of 4-methylstyrene (**1.9a**, 0.500 mmol, 1.00 equiv.) was added as 0.500 mL of a 1.00 M solution in DCE with tetradecane (20.0 μL per mmol 4-methylstyrene) added as internal

standard. The flask was placed in an oil bath at 40 °C, and samples were taken periodically and analyzed by GC (see Table 1.6).

Pd[(–)-sparteine]Cl_2. The reaction was performed analogously to the Cu[(–)-sparteine]Cl_2 timecourse, except Pd[(–)-sparteine]Cl_2 was added as the preformed complex. Therefore, 20.6 mg of Pd[(–)-sparteine]Cl_2 (0.0500 mmol, 0.100 equiv.) were added along with 26.8 mg of $CuCl_2$ (0.200 mmol, 0.400 equiv.) and 500 mg of activated 3Å molecular sieves, before the solvents were added (3.50 mL DCE and 6.00 mL *i*PrOH). The subsequent setup was the same as above (see Table 1.7).

Table 1.6. Sparteine dissociation time course data using Cu[(–)-sparteine]Cl_2.

time (h)	conversion (%)
0.5	16.4
1.0	20.7
2.0	28.6
3.0	34.1
4.0	38.6
5.5	49.6
6.0	52.5
7.0	57.1
8.0	61.0
9.0	62.7

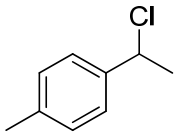
Table 1.7. Sparteine dissociation time course data using Pd[(–)-sparteine]Cl_2.

time (h)	conversion (%)
0.5	1.4
1.0	0.9
2.0	2.6
3.25	4.4
4.0	6.4
5.5	8.8
6.0	10.2
7.0	15.3
8.0	19.6
9.0	36.5

Chloride intermediate timecourse. Into an oven-dried 100 mL Schlenk flask equipped with a stirbar were added 13.0 mg $Pd(MeCN)_2Cl_2$ (0.0500 mmol, 0.100 equiv.), 26.8 mg $CuCl_2$ (0.200 mmol, 0.400 equiv.), 24.7 mg $Cu(bc)Cl_2$ (0.0500 mmol, 0.100 equiv.), and 250 mg activated 3Å molecular sieves. A condenser was placed on the flask, and 9.00 mL DCE and 1.00 mL *i*PrOH were added via the sidearm. A three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min, and 59.1 mg of 4-methylstyrene (**1.9a**, 0.500 mmol, 1.00 equiv.) were added with 10.0 μL 5-nonanone as internal standard. The flask was placed in an oil bath at 60 °C, and samples were taken periodically. The samples were filtered through a small plug of silica eluting with EtOAc and analyzed by GC (see Table 1.8). Intermediate **1.12a** was identified by comparison of GC/MS data to the independently prepared compound.

Table 1.8. Chloride intermediate timecourse data.

time (h)	conversion (%)	**1.10a** (%)	**1.12a** (%)
0.25	2.0		
0.50	4.2	0.6	
0.75	6.5	2.0	1.7
1.00	51.2	14.8	27.5
1.25	80.0	35.4	35.5
1.58	100	63.5	30.2
1.75	100	78.2	13.0
2.00	100	84.5	5.7
2.25	100	89.3	2.4
2.50	100	90.2	1.6
3.00	100	90.7	



1.12a

*Preparation of 1-(1-chloroethyl)-4-methylbenzene (**1.12a**).* Benzylic chloride **1.12a** (1-(1-chloroethyl)-4-methylbenzene) was prepared according to a literature procedure with slight modifications.[122] In an oven-dried 25 mL three-neck round bottom flask, 1.26 g of 1-*p*-tolylethanol (9.25 mmol, 1.10 equiv.) was dissolved in 7.00 mL of $CHCl_3$ under a positive N_2 pressure, with an outlet leading into sat. aq. $NaHCO_3$. A solution of 1.00 g of $SOCl_2$ (8.41 mmol, 1.00 equiv.) in 3.00 mL of $CHCl_3$ was added dropwise via syringe, and the resulting mixture was stirred at room temperature for 12 h. To quench the reaction, 15.0 mL of sat. aq. $NaHCO_3$ were added, and the mixture was extracted with $CHCl_3$ (3 × 20.0 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The product was purified by column chromatography using neutralized silica gel (netutralized w/ ca. 3% Et_3N in hexanes) and eluting with hexanes. Yield: quantitative (1.38 g); clear oil; R_f: 0.49 w/hexanes on silica plate washed w/ca. 5% Et_3N in CH_2Cl_2; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (d, J = 6.87 Hz, 3 H), 2.35 (s, 3 H), 5.09 (q, J = 6.87 Hz, 1 H), 7.17 (m, 2 H), 7.32 (m, 2 H); ^{13}C NMR $\{^1H\}$ (75 MHz, $CDCl_3$) δ 21.4, 26.6, 59.0, 126.6, 129.5, 138.3, 140.1; GC/MS: (m/z) calcd. 154.05 obsd. 154.10.[123]

Chloride Conversion Experiments (for Table 1.4)

Procedure. The catalyst mixture (see individual procedures) was added to a 10 mL sidearm flask equipped with a stirbar. A condenser was placed on top of the flask, and 0.400 mL of DCE were added followed by 0.500 mL of *i*PrOH. A three-way adapter

fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The mixture was then stirred under O_2 at room temperature for 30 min, and 7.70 mg of 1-(1-chloroethyl)-4-methylbenzene (**1.12a**, 0.0500 mmol, 1.00 equiv.) were added as 0.100 mL of a 0.500 M solution in *i*PrOH with 5-nonanone added as internal standard (20.0 μL per mmol **1.12a**). The flask was placed in an oil bath at 40 °C, and samples were taken out periodically and analyzed by GC.

For Table 1.4, *entry 1*: no catalyst was added.

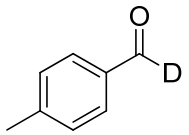
For *entry 2*: 50.0 mg of activated 3Å molecular sieves were added.

For *entry 3*: 2.70 mg of $CuCl_2$ (0.0200 mmol, 0.400 equiv.) and 1.80 mg of bathocuproine (0.00500 mmol, 0.100 equiv.) were added first and allowed to stir in the *i*PrOH/DCE mixture for ca. 10 min before 50.0 mg of activated 3Å molecular sieves were added.

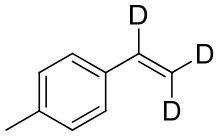
For *entry 4*: 1.30 mg of $Pd(MeCN)_2Cl_2$ (0.00500 mmol, 0.100 equiv.) and 50.0 mg of activated 3Å molecular sieves were added as catalyst.

For *entry 5*: 2.70 mg of $CuCl_2$ (0.0200 mmol, 0.400 equiv.) and 1.80 mg of bathocuproine (0.00500 mmol, 0.100 equiv.) were added first and allowed to stir in the *i*PrOH/DCE mixture for ca. 10 min before 1.30 mg of $Pd(MeCN)_2Cl_2$ (0.00500 mmol, 0.100 equiv.) and 50.0 mg of activated 3Å molecular sieves were added.

Synthesis of 4-Methylstyrene-d_3 (**1.17**)



4-methylbenzaldehyde-1-d was prepared as previously described.[124]



1.17

4-Methylstyrene-d_3 (**1.17**) was prepared according to a literature procedure,[125] but with slight modifications: In an oven-dried 25 mL round bottom flask, 347 mg of [$PhPCD_3$]I (0.851 mmol, 1.02 equiv.) were dissolved in 4.00 mL of THF under N_2. The slurry was cooled to -78 °C, and 1.12 mL of a 0.860 M solution of *n*BuLi in hexanes (0.959 mmol, 1.15 equiv.) was added slowly via syringe. The resulting mixture was warmed to room temperature and stirred for 1 h. It was then cooled to -78 °C, and 101 mg of 4'-methylbenzaldehyde-1-*d* (0.834 mmol, 1.00 equiv.) dissolved in 2.00 mL THF were added slowly. Upon completion of the addition, the reaction mixture was warmed to room temperature again and stirred for 4 h. Subsequently, 5.00 mL of sat. aq. NH_4Cl were added and the mixture was stirred for 20 min, during which a white solid precipitated. The mixture was partitioned between H_2O and Et_2O, and the aqueous phase was extracted with Et_2O (3 × 20.0 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography eluting with pentane. Yield: 63%; clear oil; R_f: 0.73 w/ 10% Et_2O/hexanes; ^1H NMR

(300 MHz, $CDCl_3$) δ 2.35 (s, 3 H), 5.19 (m, 0.02 H), 5.64 (m, 0.03 H), 7.14 (m, 2 H), 7.31 (m, 2 H); overall D incorporation: 93% (from 98% D LAD, 95% D [$PhPCD_3$]I).

Deuterium Labeling Studies (Figure 1.30)

It should be noted that all GC/MS samples were taken at complete substrate conversion.

Procedure for eq. 1.1. Into an oven-dried 50 mL Schlenk flask equipped with a stirbar were added 6.50 of mg $Pd(MeCN)_2Cl_2$ (0.0250 mmol, 0.100 equiv.), 12.4 mg of $Cu(bc)Cl_2$ (0.0250 mmol, 0.100 equiv.), 13.4 mg of $CuCl_2$ (0.100 mmol, 0.400 equiv.) and 250 mg of activated 3Å molecular sieves. A condenser was placed on the flask, and 4.50 mL of DCE followed by 0.500 mL of *i*PrOD were added via the sidearm. A 3-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min, followed by addition of 29.6 mg of 4-methylstyrene (**1.9a**, 0.250 mmol, 1.00 equiv.) via syringe. The flask was placed in an oil bath at 50 °C. After 24 h, a sample of the reaction mixture was analyzed by GC/MS (see Appendix A).

Procedure for eq. 1.2. Into an oven-dried 10 mL sidearm flask equipped with a stirbar were added 1.30 mg of $Pd(MeCN)_2Cl_2$ (0.00500 mmol, 0.0500 equiv.), 2.50 mg of $Cu(bc)Cl_2$ (0.00500 mmol, 0.0500 equiv.), 2.70 mg of $CuCl_2$ (0.0200 mmol, 0.200 equiv.) and 50.0 mg of activated 3Å molecular sieves. A condenser was placed on the flask, and 1.80 mL of DCE-d_4 followed by 0.100 mL of *i*PrOH were added via the sidearm. A three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while

stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min, followed by addition of 11.8 mg of 4-methylstyrene (**1.9a**, 0.100 mmol, 1.00 equiv.) as 0.100 mL of a 1.00 M solution in *i*PrOH. The flask was placed in an oil bath at 60 °C. After 22 h, a sample of the reaction mixture was analyzed by GC/MS (see Appendix A).

Procedure for eq. 1.3. Into an oven-dried 25 mL Schlenk flask equipped with a stirbar were added 3.20 mg of $Pd(MeCN)_2Cl_2$ (0.0125 mmol, 0.0500 equiv.), 6.20 mg of $Cu(bc)Cl_2$ (0.0125 mmol, 0.0500 equiv.), 6.70 mg of $CuCl_2$ (0.0500 mmol, 0.200 equiv.) and 125 mg of activated 3Å molecular sieves. A condenser was placed on the flask, and 4.50 mL of DCE followed by 0.500 mL of $(CH_3)_2CDOH$ were added via the sidearm. A three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min, followed by addition of 29.5 mg 4-methylstyrene (**1.9a**, 0.250 mmol, 1.00 equiv.). The flask was placed in an oil bath at 60 °C. After 4.5 h, a sample of the reaction mixture was analyzed by GC/MS (see Appendix A).

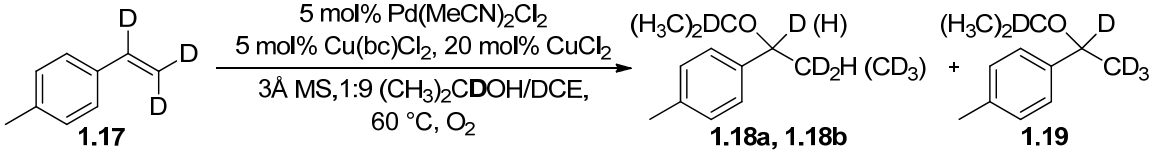
Procedure for eq. 1.4. The procedure for eq. 6 was followed, except *i*PrOH-d_8 was used instead of $(CH_3)_2CDOH$. A sample for GC/MS analysis was taken after 19 h.

Procedure for eq. 1.5. Into an oven-dried 25 mL Schlenk flask equipped with a stirbar were added 2.60 mg of $Pd(MeCN)_2Cl_2$ (0.0100 mmol, 0.0550 equiv.), 4.90 mg of $Cu(bc)Cl_2$ (0.0100 mmol, 0.0550 equiv.), 5.40 mg of $CuCl_2$ (0.0400 mmol, 0.220 equiv.) and 100 mg of activated 3Å molecular sieves. A condenser was placed on the flask, and 3.10 mL of DCE followed by 0.400 mL of $(CH_3)_2CDOH$ were added via the sidearm. A three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was

evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min, followed by addition of 21.9 mg of 4-methylstyrene-d_3 (**1.17**, 0.181 mmol, 1.00 equiv.) as 0.500 mL of a 0.361 M solution in DCE with tetradecane (20.0 μL per mmol 4-methylstyrene) added as internal standard. The flask was placed in an oil bath at 60 °C. Samples were taken out periodically via syringe and analyzed by GC (see Table 1.9). After 3 h, a sample of the reaction mixture was analyzed by GC/MS (see Appendix A).

Procedure for eq. 1.6. Into an oven-dried 25 mL Schlenk flask equipped with a stirbar were added 2.60 mg of $Pd(MeCN)_2Cl_2$ (0.0100 mmol, 0.0500 equiv.), 4.90 mg of $Cu(bc)Cl_2$ (0.0100 mmol, 0.0500 equiv.), 5.40 mg of $CuCl_2$ (0.0400 mmol, 0.200 equiv.) and 100 mg of activated 3Å molecular sieves. A condenser was placed on the flask, and 3.10 mL DCE followed by 0.400 mL *i*PrOH-d_8 were added via the sidearm. A 3-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture

Table 1.9. Isotope effect timecourse data using **1.17** and $(CH_3)_2CDOH$.



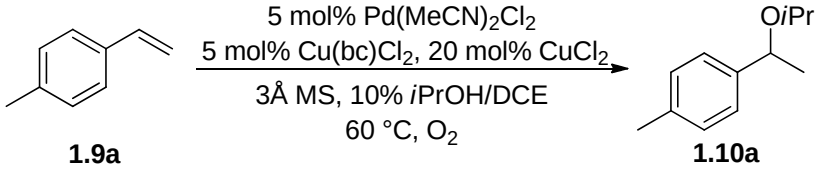
1.17 **1.18a, 1.18b** **1.19**

time (h)	conversion (%)	**1.18 + 1.19** (%)
0.5	43	11
1.0	60	17
2.0	89	24
3.0	100	44
4.5	100	57

was then stirred under O_2 at room temperature for 30 min, followed by addition of 24.2 mg of 4-methylstyrene-d_3 (**1.17**, 0.200 mmol, 1.00 equiv.) as 0.500 mL of a 0.400 M solution in DCE with tetradecane (20.0 μL per mmol 4-methylstyrene) added as internal standard. The flask was placed in an oil bath at 60 °C. After 3 h, a sample of the reaction mixture was analyzed by GC/MS (see Appendix A).

Procedure for nonlabeled reaction for isotope effect. The procedure for eq. 1.6 was followed, except 23.6 mg of 4-methylstyrene (**1.9a**, 0.200 mmol, 1.00 equiv.) were used instead of 4-methylstyrene-d_3 (**1.17**), and 0.400 mL of *i*PrOH was used instead of 0.400 mL of *i*PrOH-d_8. Samples were taken out periodically via syringe and analyzed by GC (see Table 1.10).

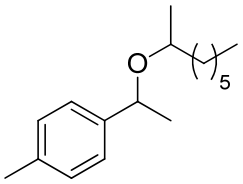
Table 1.10. Isotope effect timecourse data using **1.9a** and *i*PrOH.



1.9a **1.10a**

time (h)	conversion (%)	**1.10a** (%)
0.5	18	8
1.0	19	12
2.0	24	14
3.0	36	29
4.5	64	59
17	80	86

Hydroalkoxylation Experiments Using 2-Octanol



Preparation of 1-methyl-4-(1-(octan-2-yloxy)ethyl)benzene. Into an oven-dried 100 mL Schlenk flask equipped with a stirbar were added 6.50 mg of $Pd(MeCN)_2Cl_2$ (0.0250 mmol, 0.0500 equiv.), 13.4 mg of $CuCl_2$ (0.100 mmol, 0.200 equiv.), 12.4 mg of $Cu(bc)Cl_2$ (0.0250 mmol, 0.100 equiv.), and 250 mg of activated 3Å molecular sieves. A condenser was placed on the flask and 9.00 mL of DCE were added via the sidearm. A three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min, and 59.1 mg of 4-methylstyrene (**1.9a**, 0.500 mmol, 1.00 equiv.) were added as 1.00 mL of a 0.500 M solution in 2-octanol with 10.0 μL tetradecane as internal standard. The flask was placed in an oil bath at 60 °C, and samples were taken out periodically for GC analysis. After 3 days, the reaction mixture was cooled to room temperature and passed through a silica plug eluting with 40.0 mL of 1:1 Et_2O/hexanes. The solvent was removed in vacuo to obtain an oil. The oil was purified by flash column chromatography eluting with hexanes → 1% Et_2O/hexanes → 5% Et_2O/hexanes. Yield: 47% (58.0 mg, 0.233 mmol); clear oil; R_f: 0.67 w/ 20% EtOAc/hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 0.8 – 1.61 (m, 19 H), 2.34 (s, 3 H), 3.20 – 3.40 (m, 1 H), 4.49 (m, 1 H), 7.11 – 7.25 (m, 4 H); ^{13}C NMR {^1H} (75 MHz, $CDCl_3$) δ 14.3, 19.4, 21.1, 21.3, 22.8, 24.7, 25.0, 25.5, 25.9, 29.5, 29.7, 32.1, 36.2, 37.8, 71.8, 73.2, 74.4, 75.4, 126.3, 126.6, 129.1, 129.2, 136.9, 137.0, 141.7, 142.3; MS (ESI/APCI) m/z (MNH_4^+) calcd.: 266.2484 obsd.: 266.2475.

Comparison of styrene conversion and 2-octanol oxidation. Data were obtained from samples taken from the reaction described above (preparation of 1-methyl-4-(1-(octan-2-yloxy)ethyl)benzene) (see Table 1.11).

Hydroalkoxylation using 2-octanol omitting Pd (A) or Cu (B). Into an oven-dried 5 mL sidearm flask equipped with a stirbar were added 2.70 mg of $CuCl_2$ (0.0200 mmol, 0.400 equiv.) and 2.50 mg of $Cu(bc)Cl_2$ (0.00500 mmol, 0.100 equiv.) (A), or 1.30 mg of $Pd(MeCN)_2Cl_2$ (0.00500 mmol, 0.100 equiv.) (B), and 50.0 mg of activated 3Å molecular sieves (both). A condenser was placed on the flask and 0.800 mL of DCE and 0.100 mL of 2-octanol were added via the sidearm. A three-way adapter fitted with a balloon of O_2 was placed on the condenser. The flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The orange mixture was then stirred under O_2 at room temperature for 30 min, and 5.90 mg of 4-methylstyrene (**1.9a**, 0.0500 mmol, 1.00 equiv.) were added as 0.100 mL of a 0.500 M solution in DCE with 5-nonanone (20.0 μL per mmol **1.9a**) as internal standard. The flask was placed in an oil bath at 60 °C, and samples were taken out periodically for GC analysis. None of the reactions showed a significant amount of 2-octanone or hydroalkoxylation product.

Table 1.11. Comparison of styrene conversion and 2-octanol oxidation.

time (h)	conv. of **1.9a** (%)	2-octanone (equiv)
1	11	0.18
3	10	0.18
18	49	0.63
24	49	0.76
74	73	0.88

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(115) D incorporation into styrene could not be quantified due to loss of H (D) in mass spectrometer. Isolation of styrene at early timepoints and after the reaction in cases of incomplete conversion was unsuccessful. Additionally, different product ratios were observed for reactions involving deuterated alcohol and/or styrene, and deuterium incorporation was observed in the Wacker product, which should originate from deuterated styrene.

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CHAPTER 2

DEVELOPMENT OF AN ASYMMETRIC PD-CATALYZED HYDROARYLATION OF STYRENES AND DIENES

Introduction

Diarylmethine motifs can be found in a variety of natural products and biologically active molecules (Figure 2.1).[1-4] While they have been successfully synthesized stereoselectively,[5-9] there are few methods to set diarylmethine stereocenters in unfunctionalized molecules.[10] The majority of asymmetric methods to access diarylmethines rely on Michael-type additions into 3-aryl-substituted α,β-unsaturated carbonyls, and most other methods have limited substrate scope (vide infra). An asymmetric preparation of diarylmethines based on a different mechanistic scenario would therefore be desirable.

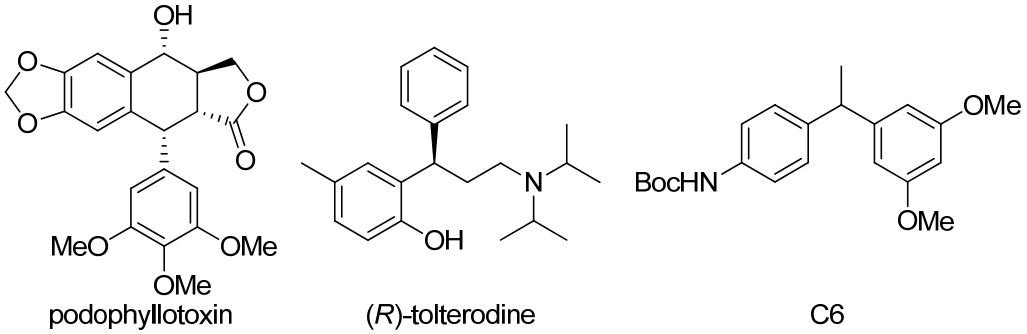


Figure 2.1. Biologically active structures containing diarylmethine centers.

Our group has previously reported successful methods for Pd-catalyzed hydroarylations of styrenes to prepare diarylmethine compounds, one of which displayed activity against breast cancer cells (Figure 2.1, C6). Due to the interest our group has in these molecules as well as the general lack of methods to prepare them, we decided to pursue the development of an asymmetric hydroarylation reaction. This chapter describes the systematic evaluation of several ligand classes and our progress toward an asymmetric hydroarylation of styrenes and dienes. The work in this chapter was done in close collaboration with Mr. Yasumasa Iwai.

Background

Racemic Markovnikov Hydroarylations of Styrenes

Styrene hydroarylations are often achieved by direct addition of an unfunctionalized arene to a styrene. There are two distinct mechanistic scenarios for this reaction: a Friedel-Crafts type and a C–H activation mechanism (Figure 2.2).[11-13] The Friedel-Crafts type mechanism proceeds via a Lewis or Brønsted acid binding to the alkene to form a cationic intermediate, which then undergoes nucleophilic attack by the arene, leading exclusively to the Markovnikov product. The C–H activation mechanism

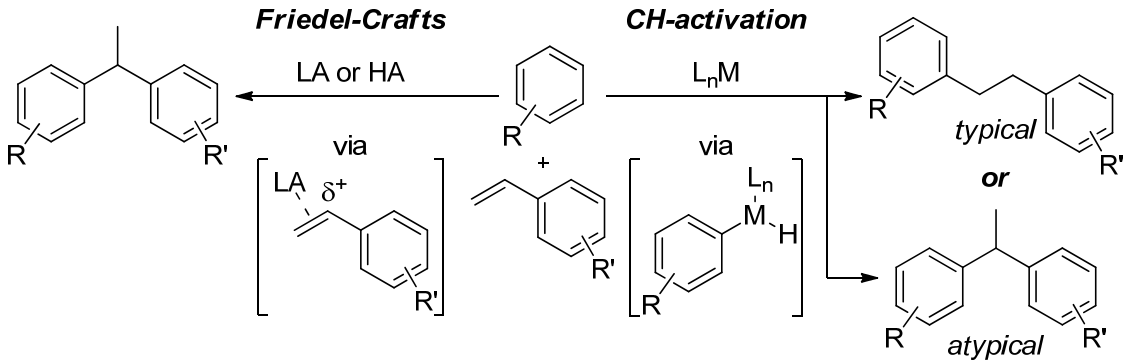


Figure 2.2. Markovnikov and anti-Markovnikov hydroarylation.

is initiated by C–H activation on the arene by transition metal catalysts. The aryl group and proton are then added across the double bond, which typically results in the formation of the anti-Markovnikov product. There have been reports of this type of mechanism leading to the Markovnikov product as well, although it is not clear what causes this shift in product distribution.[14-18]

The Friedel-Crafts alkylation has been used extensively as an approach to the hydroarylation of styrenes. It has the advantage of producing no byproducts, and a variety of Lewis and Brønsted acid catalysts are successful in promoting this reaction (Figure 2.3).[11] Similarly to the hydroalkoxylation reaction reactions discussed in chapter 1, the role of the catalyst is to activate the alkene for nucleophilic attack. The relative

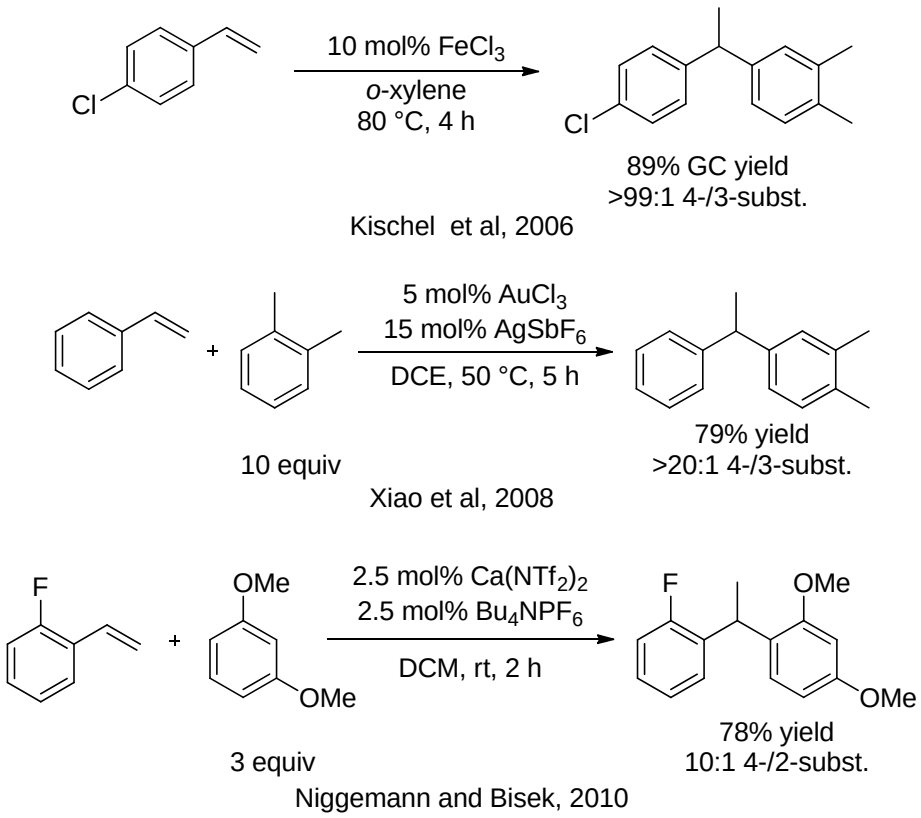


Figure 2.3. Catalytic Friedel-Crafts hydroarylation of styrenes.

simplicity of this mechanism allows for a variety of efficacious catalysts. The general limitation of these reactions is the reliance on the inherent nucleophilicity of the arene, which rules out the use of electron-poor arenes, and leads to selectivity issues in many cases.[19] Thus, Beller and coworkers developed a $FeCl_3$-catalyzed hydroarylation of styrenes (Figure 2.3, top).[20] While this catalyst is both cheap and convenient, the arene nucleophile had to be used as the solvent in this case, precluding the use of precious and/or solid substrates. Additionally, the resulting substitution pattern on the arene was greatly dependent on the arene nuceophile, with selectivities varying between 1.3:1 and >99:1. Che and coworkers were able to lower the amount of nucleophile to 10 equivalents by using a gold catalyst (Figure 2.3, middle).[21] However, the selectivity varied almost as much as in Beller's system. Niggemann and Bisek reported a calcium-catalyzed hydroarylation, wherein they were able to lower the concentration of the nucleophile even further (Figure 2.3, bottom).[22] They previously reported the use of the same catalyst for a Friedel-Crafts reaction of benzylic, allylic, and propargylic alcohol substrates,[23] and proposed that the styrene hydroarylation might proceed via a benzylic alcohol intermediate (formed from adventitious water in the reaction). While they were unable to detect such an intermediate, they showed in a competition experiment that phenyl ethanol was consumed in preference to styrene to yield the diarylmethine product. Furthermore, the reaction with styrene was inhibited when performed under strictly dry conditions. While this evidence is inconclusive, it does pose questions on the exact mechanism of this type of reaction. Additionally, the nature of the active catalyst becomes questionable, as Brønsted acids could potentially be formed under these conditions, which are known catalysts for this type of reaction.

The Friedel-Crafts type hydroarylation of styrenes offers a convenient and simple route to certain diarylmethine products; however, it is highly substrate-dependent by nature. Therefore, there is a need for more general hydroarylation reactions. One such system is the two-step sequence of hydroboration of styrenes followed by cross-coupling with aryl electrophiles, which is discussed in the following section. Another mechanistically distinct approach toward hydroarylation reactions was developed in our laboratory and is discussed below.

We became interested in the hydroarylation of styrenes along with the hydroalkoxylation reactions discussed in chapter 1.[24-27] We envisioned that the Pd π-benzyl complex formed during the hydroalkoxylation might undergo transmetallation followed by reductive elimination instead of nucleophilic attack via the general mechanism shown in Figure 2.4. Parallel to the hydroalkoxylation, the proton incorporated into substrate was proposed to originate from the Pd-catalyzed oxidation of the alcohol substrate.[24,28] The mechanism was envisioned to begin with a Pd-catalyzed aerobic alcohol oxidation, giving Pd hydride **B**. The alkene substrate would insert into the Pd–H bond to form two isomeric Pd alkyl species **D** and **E**, wherein **E** can be stabilized by a Pd π-benzyl or π-allyl interaction (**F**), depending on the substrate. Intermediate **E** would then undergo transmetallation followed by reductive elimination to liberate the product.

Based on this mechanistic manifold, several racemic hydroarylation reactions were developed in our laboratory using organostannanes and arylboronic esters as transmetallating agents (Figure 2.5). It should be noted that the system using

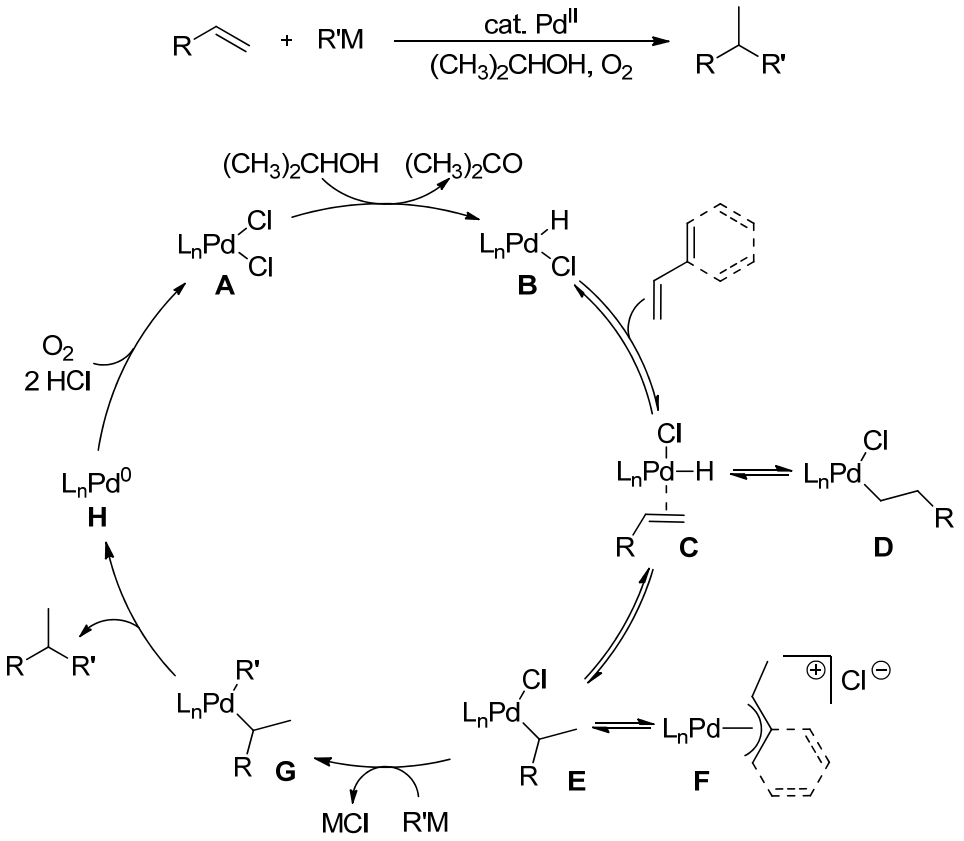


Figure 2.4. Proposed Pd-catalyzed hydroarylation of styrenes with mechanism (adapted from Gligorich et al., 2009).

organostannanes was applicable to styrenes as well as dienes,[24] while the reaction using boronic esters did not tolerate diene substrates.[25] A separate system was therefore developed for the coupling of dienes with boronic esters.[27] To support our proposed mechanism, deuterium labeling studies were performed using the organostannane system (Figure 2.6).[24] Deuterated product was observed when $(CH_3)_2C\mathbf{D}OH$ was used as solvent, but not with $(CH_3)_2CHO\mathbf{D}$, indicating that the proton incorporated into product stems from the α-position of IPA, as would be expected according to the proposed mechanism.

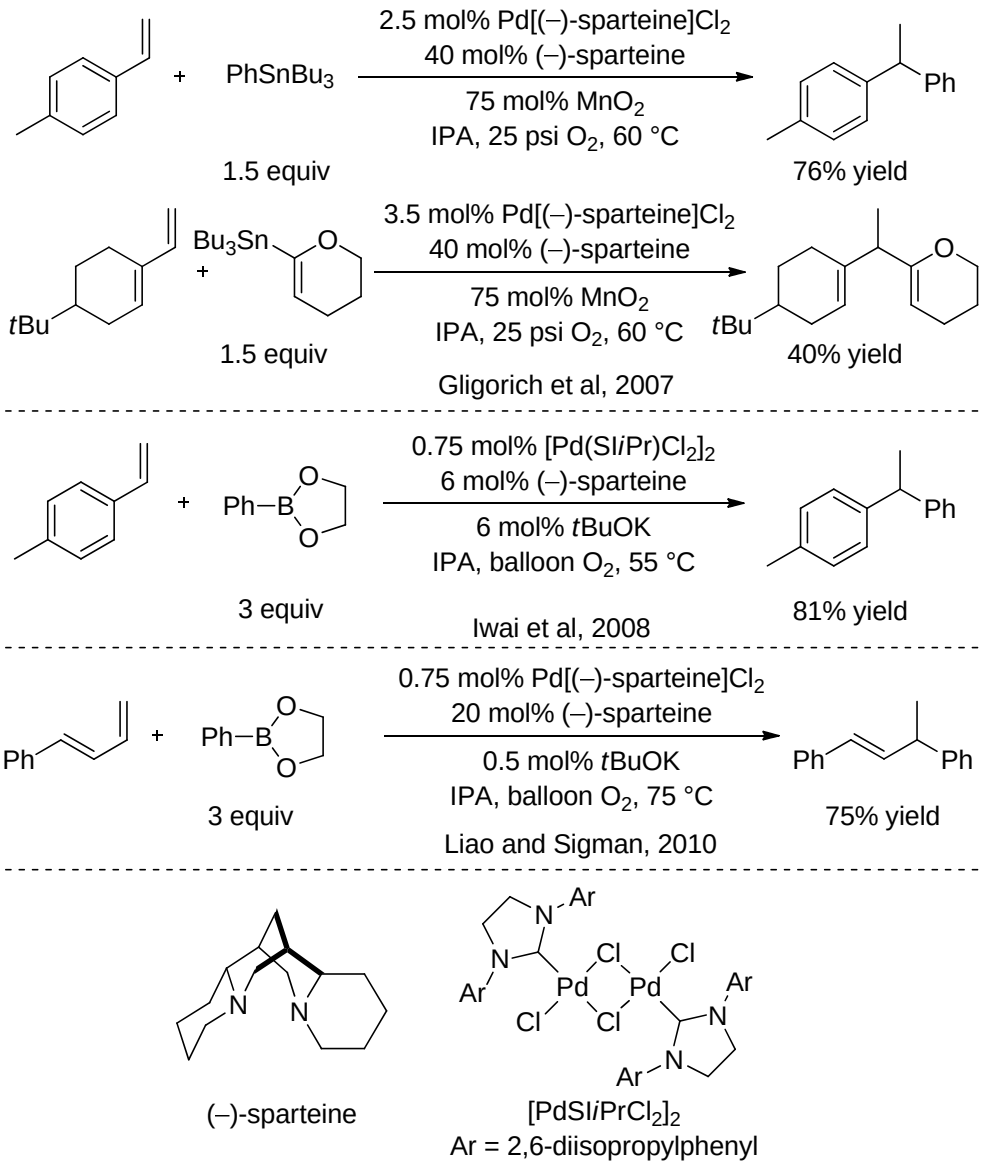


Figure 2.5. Racemic Pd-catalyzed hydroarylation reactions.

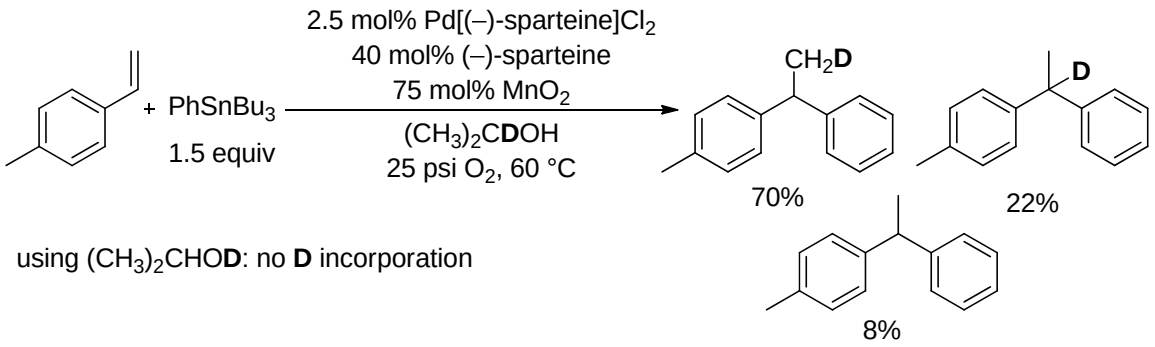


Figure 2.6. Deuterium labeling studies (adapted from Gligorich et al., 2007).

While the products formed in these reactions are similar (or identical), and the proposed mechanism is essentially the same, different problems and limitations were found for each. With the organostannane system, oxidation of (–)-sparteine was observed, and (–)-sparteine-*N*-oxide was found to inhibit the reaction. It was hypothesized that H_2O_2 was the (–)-sparteine oxidant, and to circumvent this issue, MnO_2 (which is known to disproportionate H_2O_2)[29] was added to the reaction. In the case of the boron system, (–)-sparteine oxidation was not observed; instead, phenol was formed in the reaction. H_2O_2 was likely causing this as well by oxidizing the arylboronic ester. Fortunately, the addition of a slight excess of boronic ester was sufficient to allow the hydroarylation to proceed to completion. Additionally, the role of base had to be re-evaluated with respect to boron, as it is intimately involved in transmetallation.[30,31]

In summary, several different approaches to the hydroarylation of styrenes have been discussed. While progress has been made regarding the extension of these methods to asymmetric reactions, this has proved nontrivial (vide infra). Thus, other routes have been developed in order to access diarylmethines stereoselectively, including more circuitous paths and substrate-controlled methods relying on the assistance of neighboring groups.

Synthesis of Enantiomerically Enriched Diarylmethines

The most common approach to enantiomerically enriched diarylmethines is the asymmetric 1,4-addition of aryl groups to aryl-substituted α,β-unsaturated carbonyls. Both transition metal-catalyzed additions of organometallic reagents and Friedel-Crafts-type additions have been developed; however, the Friedel-Crafts reactions are typically limited to heteroaromatic nucleophiles such as indoles.[32]

An interesting example of a cross-coupling approach was reported by Carreira and coworkers, who developed an asymmetric addition of arylboronic acids to 3-arylpropenals catalyzed by Rh diene complexes (Figure 2.7, top).[33,34] The scope of the reaction encompasses a variety of substituted benzene rings on both the aldehyde and the boronic acid, as well as a furan ring on the aldehyde, with ee's between 89 and 93%. Additionally, a decarbonylation of the resulting 3,3-diarylpropanals was developed to access diarylethanes enantioselectively (Figure 2.7, middle).[35] Both reactions could also be performed in one pot by swapping the solvent and adding the decarbonylation catalyst to the crude mixture (Figure 2.7, bottom).[35]

Tokunaga and Hayashi utilized a Rh binap catalyst to achieve the 1,4-addition of arylzinc reagents to 3-arylpropenals in the presence of TMSCl (Figure 2.8).[36] While the scope of this reaction is fairly limited, the ee's are excellent for all substrates (98 – 99%).The role of TMSCl is not examined in detail, but it is proposed that it activates the aldehyde for nucleophilic attack and stabilizes the resulting enol ether, inhibiting further reaction of the product.[37]

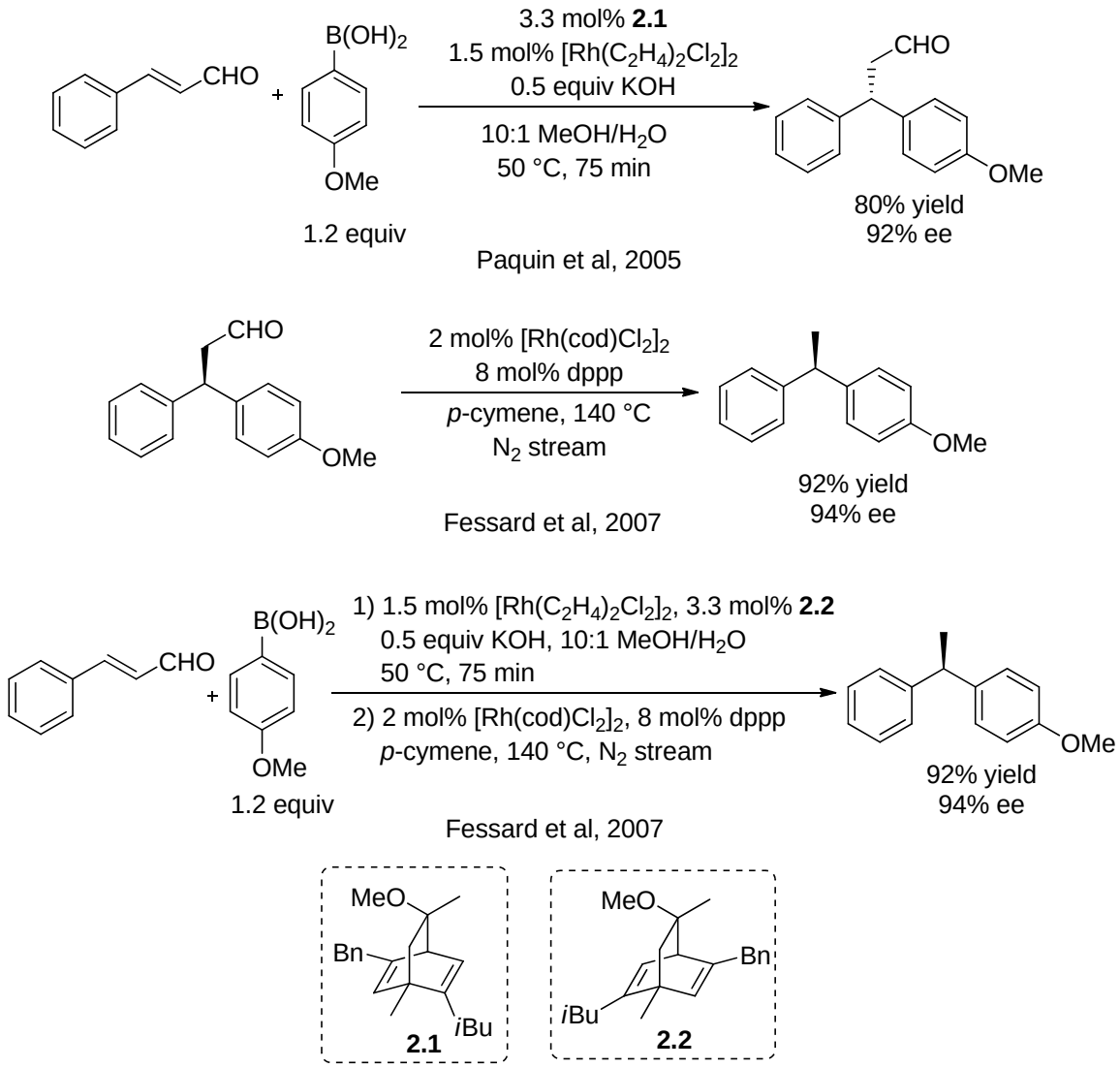


Figure 2.7. Enantioselective preparation of diarylmethines by Michael-type reaction followed by decarbonylation.

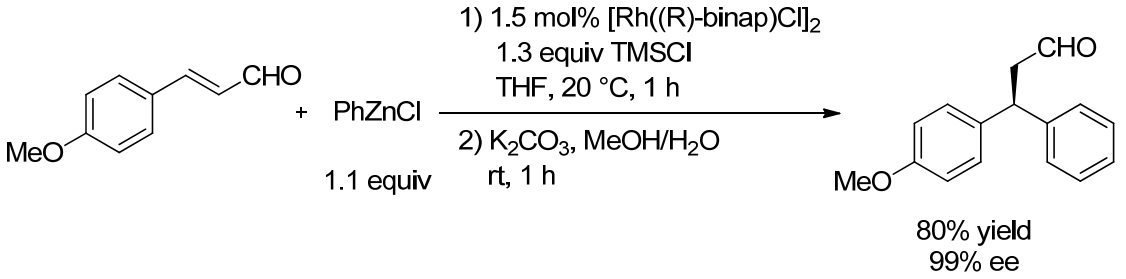


Figure 2.8. Enantioselective addition of arylzinc reagents to 3-arylpropenals (adapted from Tokunaga and Hayashi, 2006).

A 1,4-addition of arylboronic acids to arylmethylene cyanoacetates catalyzed by a Rh-diene complex was published by Hayashi and coworkers in 2008 (Figure 2.9).[6] The catalyst in this system is similar to that used by Carreira and coworkers. Both yields and ee's are excellent in this reaction, giving 96 – 99% ee and greater than 90% yield in all cases. The products were isolated as 1:1 diastereomeric mixtures, which were subjected to ester hydrolysis and decarboxylation to determine the enantiomeric excess. Hayashi and coworkers also used this methodology to set the stereocenter in a short synthesis of (*R*)-tolterodine.

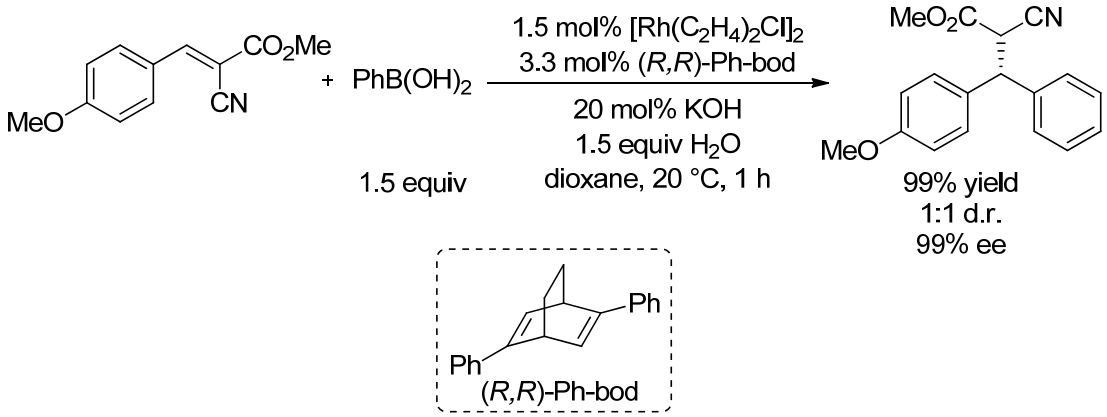


Figure 2.9. Enantioselective addition of arylboronic acids to arylmethylene cyanoacetates (adapted from Sörgel et al., 2008).

Miyaura and coworkers developed catalytic systems for the 1,4-addition into enones using both Rh and Pd catalysts (Figures 2.10 and 2.11).[38,39] Interestingly, the same ligand (chiraphos) was successful in both cases. Additionally, the Rh-catalyzed reaction was employed in a synthesis of an endothelin receptor antagonist,[38] and the Pd-based system was slightly modified for the 1,4-addition into 3-arylalkenals and applied to a short synthesis of a phosphodiesterase IV inhibitor.[40]

Stereoselective Friedel-Crafts reactions are rare to date. There are some diastereoselective Friedel-Crafts reactions of alcohols containing a chiral center at the α-position,[11] but to the best of my knowledge, the only example of an enantioselective Friedel-Crafts reaction was published by Nishibayashi and coworkers (Figure 2.12).[41] The substrate scope is limited to the addition of 2-methylfuran and *N*,*N*-dimethylamine to aryl-substituted propargyl alcohols. The reaction is proposed to proceed via a Ru alkenylidene complex, which undergoes nucleophilic attack by the arene. The catalyst

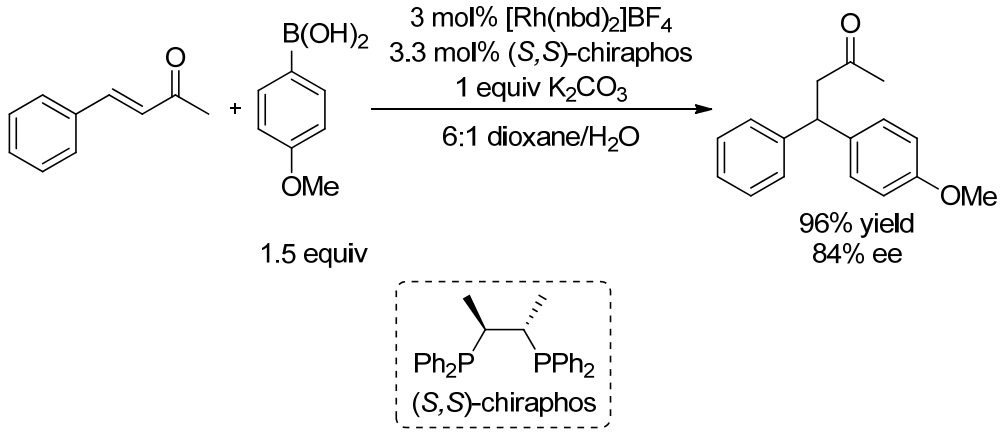
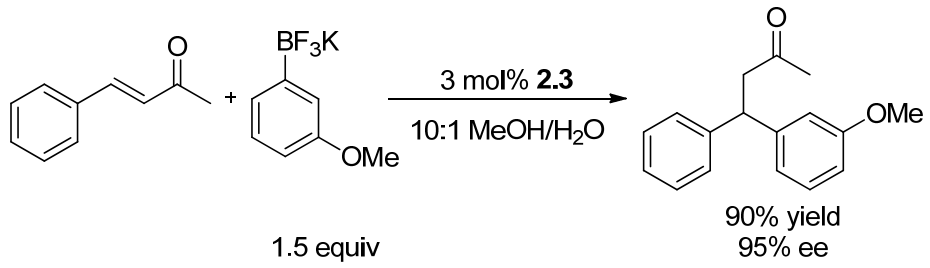


Figure 2.10. Enantioselective addition of arylboronic acids to enones (adapted from Itoh et al., 2006).



2.3: [Pd((*S,S*)-chiraphos)(PhCN)$_2$](SbF$_6$)$_2$

Figure 2.11. Enantioselective addition of aryltrifluoroborates to enones (adapted from Nishikata et al., 2005).

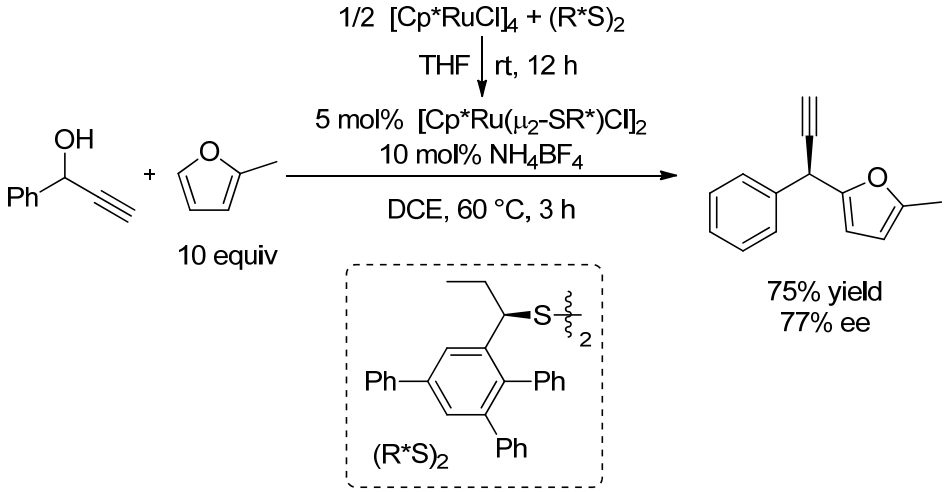


Figure 2.12. Enantioselective Friedel-Crafts-type propargylation (adapted from Matsuzawa et al., 2007).

used in this reaction is an unusual Ru disulfide dimer, which is proposed to induce stereoselectivity via a π-π interaction between an aryl group of the catalyst and that of the propargyl alcohol.[42] Interestingly, the same catalyst system could be applied to the addition of various other nucleophiles to propargyl alcohols.[43]

Using a different approach to the formation of diarylmethine stereocenters, Alexakis and coworkers reported an Ir-catalyzed asymmetric allylic substitution (Figure

2.13).[9] While the enantioselectivity was generally good, the selectivity for the branched vs linear products was poor, even favoring the undesired linear product in several cases.

Catalytic asymmetric hydrogenation is arguably one of the most powerful catalytic methods to date. However, 1,1-diaryl-substituted olefins (without adjacent coordinating groups) are a problematic substrate class for this reaction, as the two enantiotopic faces differ very little.[44] Andersson and coworkers overcame this difficulty and discovered that N,P-chelated Ir catalysts were competent hydrogenation catalysts for these as well as other challenging substrates (Figure 2.14).[10,45] In their initial report in 2009, Andersson and coworkers found that trisubstituted olefins bearing geminal aryl groups were efficiently and selectively hydrogenated by P,N-ligated Ir (Figure 2.14., top).[10] In this report, the substrate scope is somewhat narrow, and two different ligands were found to be optimal depending on the third substituent on the alkene (**L1** was the optimal ligand if the third substituent was an alkyl group). In 2011, Andersson, Norrby,

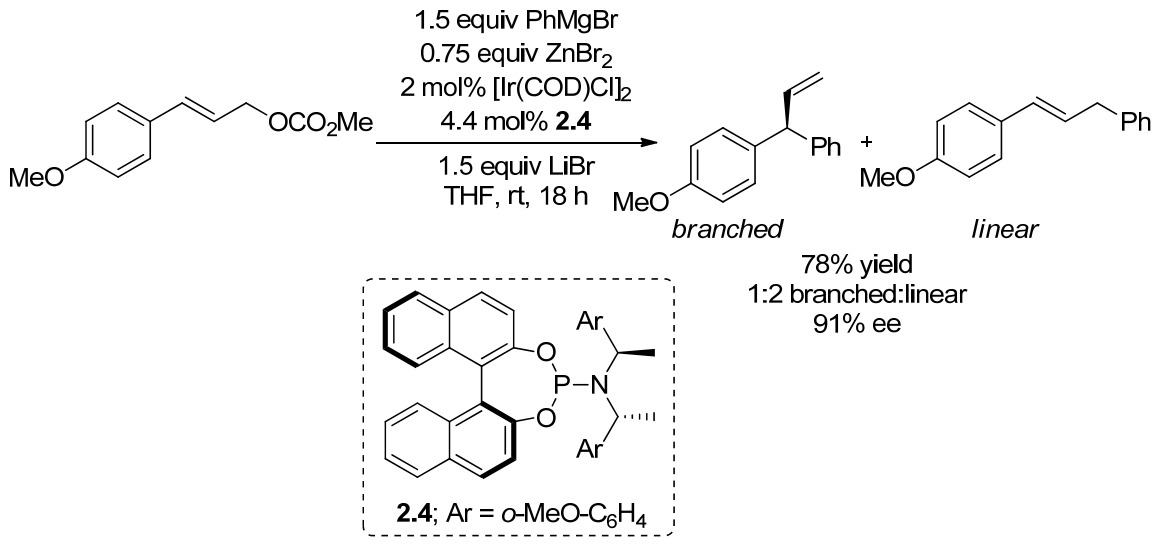


Figure 2.13. Enantioselective allylic substitution (adapted from Alexakis et al., 2007).

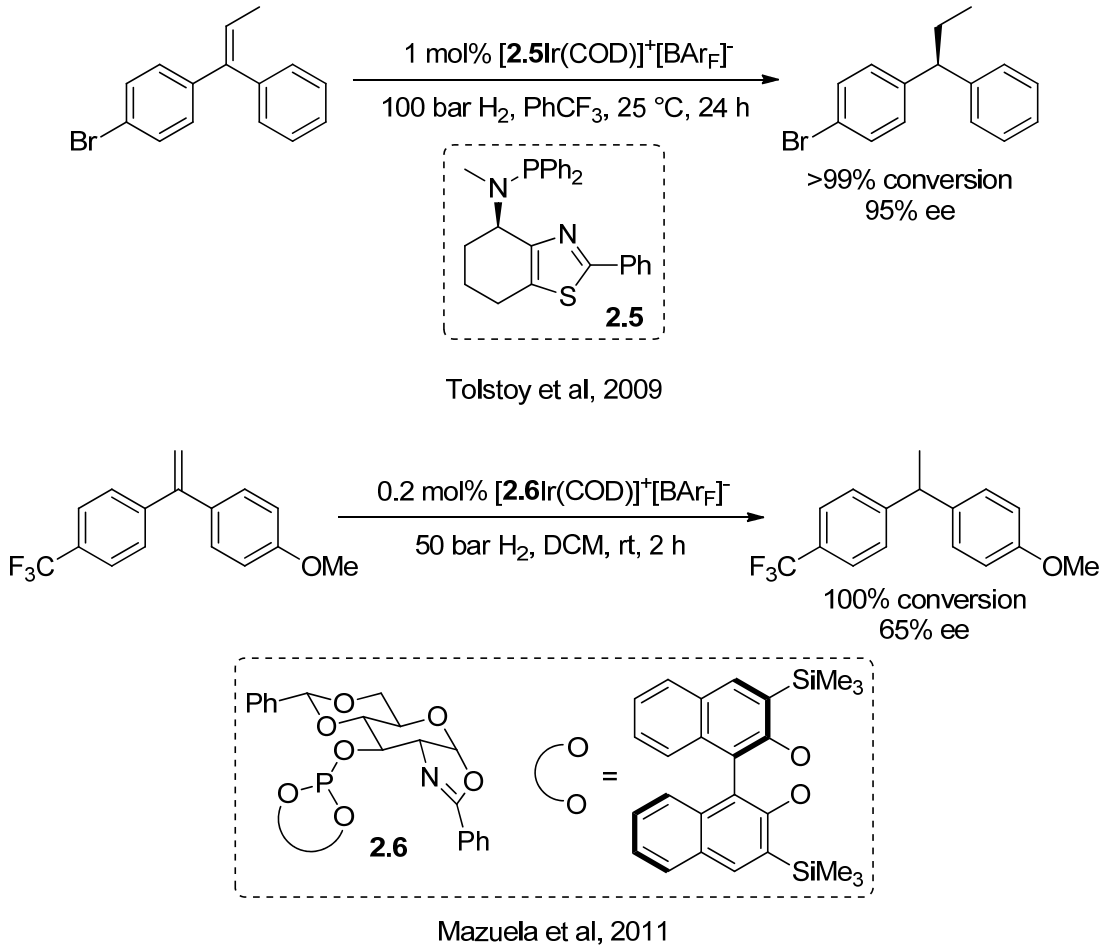


Figure 2.14. Asymmetric hydrogenation of 1,1-diarylalkenes.

Diéguez and coworkers published a more extensive study on the hydrogenation of several challenging substrate classes, using Ir catalysts containing modular pyranoside phosphite-oxazoline ligands (Figure 2.14, bottom).[45] The oxazoline substituent and the biaryl phosphite moiety were varied independently, giving rise to a library of ligands that were evaluated for hydrogenations of "minimally functionalized olefins". Different ligands were found to be optimal for different types of substrates, such as *E*- and *Z*-alkenes, alkenes bearing a neighboring polar group, and terminal 1,1-disubstituted alkenes. Excellent conversions and good to excellent enantioselectivities were observed in all cases, the substrate shown in Figure 2.14 (bottom) gave the lowest ee reported in this

paper. It should be noted that the previous catalyst system was successful only for trisubstituted alkenes. Based on computational studies, quadrant models were proposed to explain the stereoselectivites observed with both types of catalysts. Furthermore, it was suggested that the biaryl phosphite moiety in the second catalyst system is able to subtly change its dihedral angle to adapt its chiral environment to the substrate at hand, thus bringing about the greater versatility of this catalyst system.

Another approach to enantiomerically enriched diarylmethines is the cross-coupling of enantiomerically enriched transmetallating agents. In this case, the stereocenter is set in a hydroboration or hydrosilylation followed by stereoretentive cross-coupling. There is a vast number of enantioselective hydroborations developed by a number of groups.[46-56] The stereoretentive cross-coupling of secondary boronic esters has received far less attention until recently, when reports of this type of reaction were published by Suginome,[57,58] Molander,[59] and Crudden.[60,61] Crudden and coworkers were the only group to utilize this methodology to access diarylmethines (Figure 2.15). Interestingly, the reaction proved to be completely selective for the reaction of secondary vs primary boronic esters.

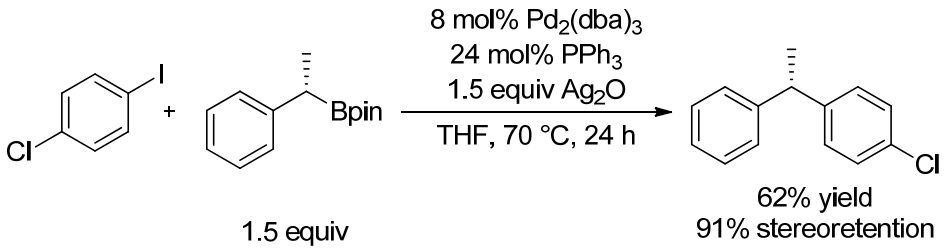


Figure 2.15. Cross-coupling of chiral boronic esters with stereoretention (adapted from Imoa et al., 2009).

Another approach to diarylmethines via cross-coupling was reported by Jarvo and coworkers (Figure 2.16).[62] They found that benzylic and dibenzylic methoxy groups could be substituted by methyl groups under Ni catalysis with complete inversion of the stereocenter. However, the substrate is limited with respect to functional groups, presumably due to the use of a Grignard reagent.

In summary, there are several different approaches to the enantioselective formation of diarylmethines, the most general of them being the Michael addition and the newly developed hydrogenation. While some successful methodologies have been developed in this context, novel paths toward the synthesis of these products are still desirable to provide access to a wide range of diarylmethine products.

Approach to the Hydroarylation of Styrenes and Dienes Using Pd Hydrides

Considering the relatively narrow range of approaches to enantiomerically enriched diarylmethine motifs and our groups own interest in them, we decided to pursue an enantioselective version of our previously developed alkene hydroarylation. In

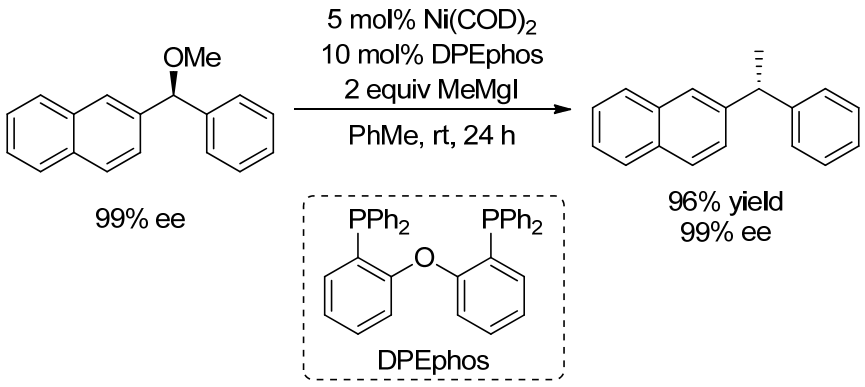


Figure 2.16. Stereospecific cross-coupling of alkyl ethers (adapted from Taylor et al., 2010).

parallel with the hydroalkoxylation discussed in chapter 1, β-hydride elimination proved to be a crucial step in this reaction. The key intermediates from which β-hydride elimination could occur were the same as for the hydroalkoxylation: a Pd alkoxide formed during the alcohol oxidation (where β-hydride elimination was desired to form the Pd hydride **A**), and a Pd π-benzyl complex, from which β-hydride elimination was not desired, as this would result in the reverse reaction, leading ultimately back to starting material (Figure 2.17). Importantly, the coordination of Pd to one enantiotopic face of the alkene is proposed to set the stereocenter in this reaction. Deuterium labeling studies performed with racemic hydroarylations indicated that both alkene coordination and insertion could be reversible,[24] which might be a problem in the asymmetric reaction.

In order to be able to fine tune the reactivity and enantioselectivity of the system, we focused primarily on modular ligand classes. The boronic ester method was initially selected as a starting point for the development of an asymmetric hydroarylation reaction due to the lower toxicity and easier handling of boronic esters compared to tin reagents.

Initial Study of Chiral Carbenes

For the racemic hydroarylation of styrenes using boronic esters, *N*-heterocyclic carbene Pd complexes had been found to be optimal. Because of this and the modular nature of carbenes, it was initially thought that chiral *N*-heterocyclic carbene (NHC)

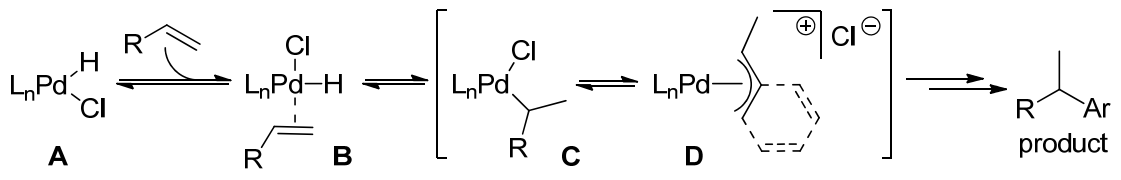


Figure 2.17. Reversible alkene coordination and insertion.

ligands could promote the reaction effectively. For the racemic hydroarylation of styrenes using organostannanes, on the other hand, (–)-sparteine had been found to be the optimal ligand. (–)-Sparteine is notoriously difficult to modify, and it had been previously shown that it cannot generally be replaced with other bidentate amine ligands.[63-66]

Thus, several NHC's were prepared with chiral backbones as well as chiral substituents on nitrogen and evaluated under the optimized conditions for the racemic hydroarylation (Figure 2.18). While all of these successfully promote the reaction, the

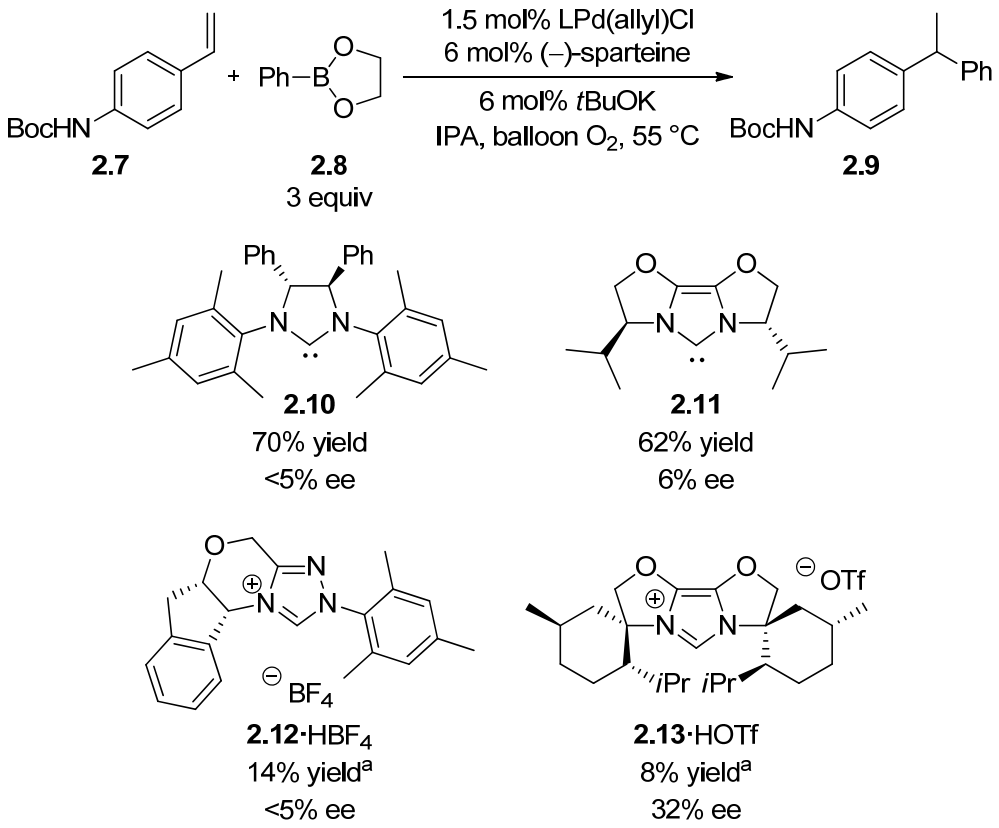


Figure 2.18. Asymmetric hydroarylation using chiral carbenes. [a] The Pd carbene complex was formed in situ before addition of the remaining reagents (see experimental section for details).

product was nearly racemic in all cases. When studying bioxazoline (Biox)-derived carbenes, a low ee (6%) was found for the *i*PrBiox-derived NHC (**2.5**), and a 32% ee was observed with the menthol-derived NHC introduced by Glorius and coworkers (**2.7**).[67] Unfortunately, this was accompanied by a significant loss in catalyst activity, and since this ligand could not be easily modified, this result was not pursued further.

Bidentate Ligands

We hypothesized that the generally low enantioselectivity may be due to the chiral information being too far removed from the catalytic center, and therefore decided to investigate bidentate ligands, since they should provide a more rigid steric environment, and potentially place the chiral substituents closer to Pd. Since phosphine-based ligands are known to be oxidatively unstable, we decided to evaluate several classes of bidentate nitrogen ligands initially (Figure 2.19). Different combinations of oxazoline and pyridine or quinoline moieties were synthesized and tested. Of these ligands, BINAM (**2.21**) and the valinol-derived bioxazoline **2.16** were the only ligands that did not promote the reaction at all. While menthol-derived bioxazoline **2.17** as well as pyridine-oxazoline **2.18** and quinoline-oxazoline **2.19** gave some product with 10-14% ee, bisoxazoline **2.22** gave by far the highest yield and ee (52% yield, 45% ee). Somewhat surprisingly, when bridged pyridine-oxazoline **2.20** was tested, racemic product was observed. Additionally, when (–)-sparteine was evaluated (in the absence of NHC's), nearly racemic product was formed.

A systematic study of bisoxazoline ligands was carried out in order to identify an optimal ligand, varying the substituent off the oxazoline ring. Interestingly, a linear free

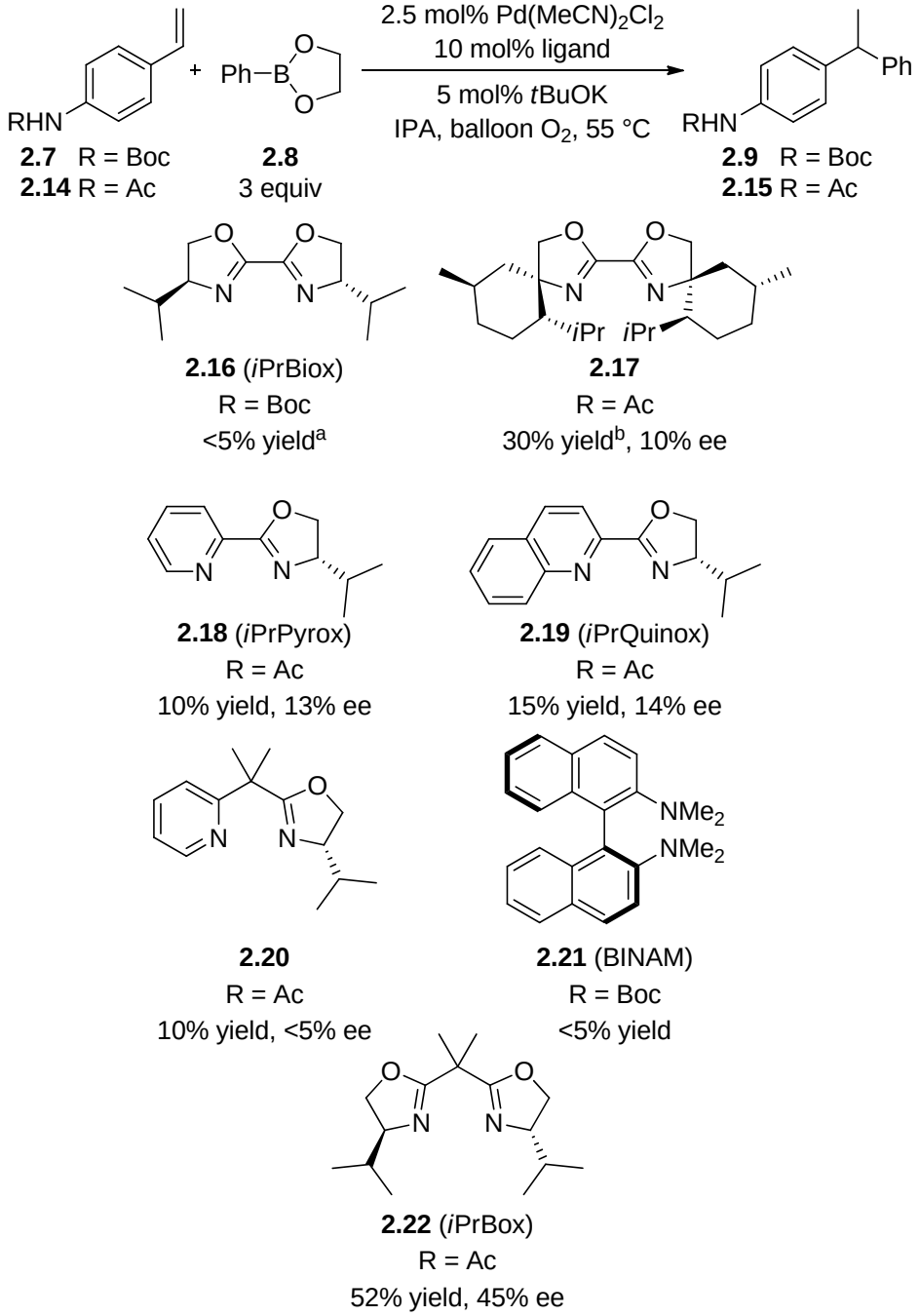
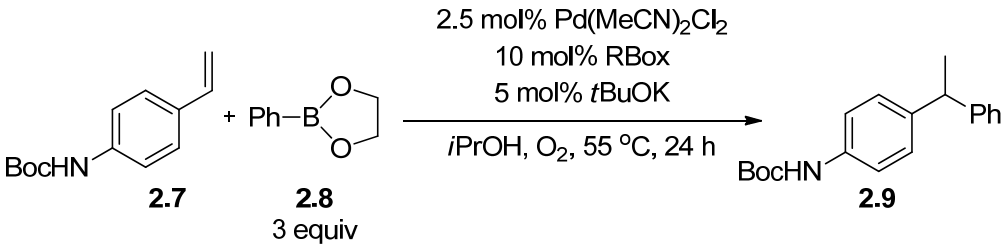


Figure 2.19. Bidentate *N*,*N*-ligands. [a] 3 mol% ligand were used. [b] 5 mol% $Pd(MeCN)_2Cl_2$, 20 mol% ligand and 10 mol% KO*t*Bu were used, and the reaction was performed at room temperature.

energy relationship between the steric bulk of the oxazoline substituent as defined by the Charton parameter[68-70] and the log of the enantiomeric ratio of the product (corresponding to a relative rate of product formation for the two enantiomers) was observed up to a certain point (Figure 2.20). While substituents with a tertiary carbon (such as (*S*)-*i*PrBox **2.22**, (*S*)-diEtBox **2.26**) gave the predicted enantioselectivities, rapid precipitation of Pd metal along with diminished product formation and ee was observed with (*S*)-*t*BuBox (**2.27**) (vide infra). Moreover, when the dicyclohexyl-substituted Box ((*S*)-diCyBox **2.28**) was synthesized and tested, the ee of the hydroarylation product was found to be 63%, even though this substituent would be expected to give a higher ee than the diethyl one (**2.26**). Unfortunately, no Charton value is reported for Cy_2CH, making a quantitative comparison impossible. Overall, this implies that over a certain range the enantioselectivity is dictated by the size of the oxazoline substituent, as would be expected. However, when the substituent is too large, there is a change, possibly in the overall catalyst structure or reaction mechanism, which perturbs the enantioselectivity and/or reactivity of the catalyst.

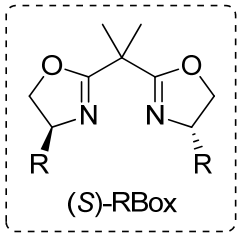
Optimization Using Organostannanes

Interestingly, when an organostannane was used instead of a boronic ester as the transmetallating agent, a nearly identical ee was observed (Table 2.1, entry 1 vs. Figure 2.20). Additionally, changing from $PhSnBu_3$ (**2.30**) to an enol ether (**2.31**) did not affect the enantioselectivity substantially (Table 2.1, entry 2). This seemed to indicate that the enantiodetermining step occurred before transmetallation, which was consistent with our initial hypothesis of the stereocenter being set by the alkene coordinating to Pd.



2.7 **2.8** 3 equiv **2.9**

entry	R	ee[a] (%)	Charton Value
1	(*R*)-Ph (**2.23**)	43	0.57
2	(*S*)-Bn (**2.24**)	42	0.70
3	(*S*)-*i*Pr (**2.22**)	46	0.76
4	(*S*)-Cy (**2.25**)	50	0.87
5	(*S*)-Et_2CH (**2.26**)	64	1.51



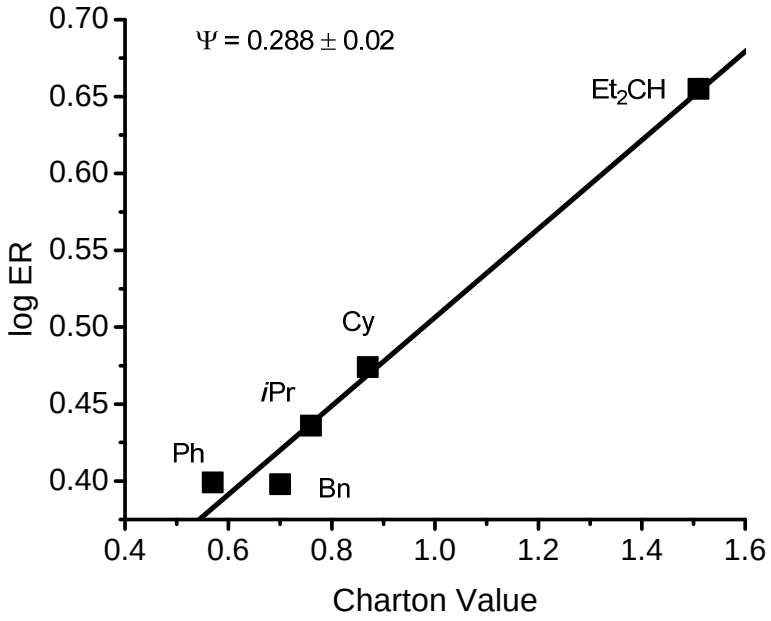
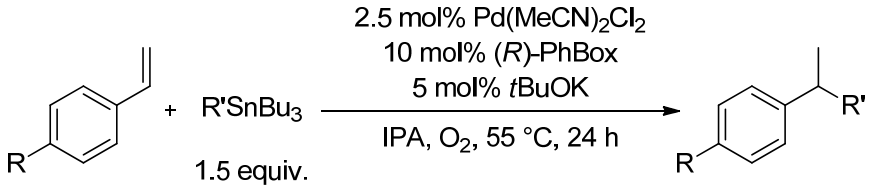
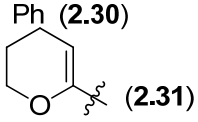


Figure 2.20. Charton plot for Box ligands.

Table 2.1. Initial results using organostannanes.



entry	R	R'	product ee[a]
1	NHBoc (**2.7**)	Ph (**2.30**)	45
2	Me (**2.29**)	 (**2.31**)	42
3[b]	Me (**2.29**)		40

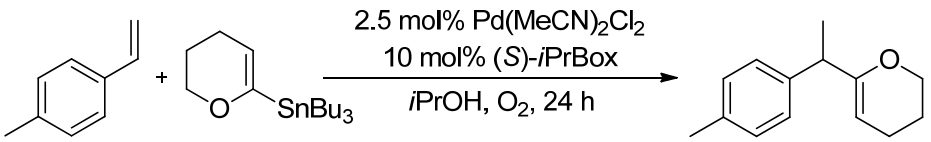
[a] Determined by HPLC for entry 1, and GC for entries 2 and 3, each equiooed with a chiral stationary phase. [b] no KO*t*Bu.

Excitingly, this gave us an opportunity to develop a set of reaction conditions that could be potentially used with a wide variety of reagents. It was also observed that base was not required for the reaction when using an organostannane, as similar results were obtained with and without KO*t*Bu (entry 3).

Since variation of the ligand substituents alone did not provide sufficiently high enantioselectivity, it was decided to further optimize the reaction conditions. For these studies, 4-methylstyrene (**2.29**) and an enol ether stannane (**2.31**) were used, since both reaction progress and ee could be conveniently monitored by gas chromatography (GC).

The reaction was initially evaluated at different temperatures (Table 2.2). It was found to be extremely slow at room temperature, but somewhat more efficient at elevated temperatures (65 °C, entry 4). Interestingly, temperature only had a modest effect on enantioselectivity, and thus further optimization was performed at 65 °C. Higher temperatures were not evaluated due to the lower solubility of O_2 at high temperatures.

Table 2.2. Temperature optimization for organostannanes.



2.29 **2.31** 1.5 equiv **2.32**

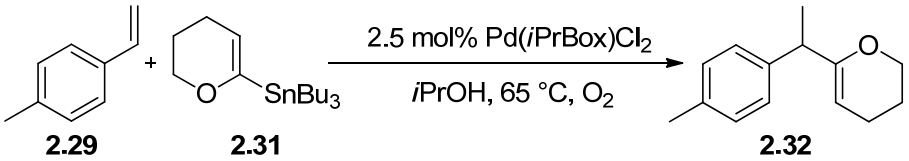
entry	temp.	time	% yield[a]	% ee[b]
1	rt	25 h	8	nd
2	rt	4 d	31	49
3	55 °C	19 h	22	48
4	65 °C	22 h	31	46

[a] GC yield, determined using an internal standard and response factor. [b] determined by GC using a chiral stationary phase.

Next, different counterions on Pd were evaluated. However, the use of non-coordinating anions (OTf, OTs, BF_4) led to <5% product in each case, while acetate provided the product in 8% GC yield and 28% ee. The use of 1:1 mixtures of IPA and other cosolvents also did not lead to any improvements. Use of DCE, *t*BuOH, and PhMe led to extremely slow reactions, while DMA provided the product in comparable yield (39%), but diminished ee (37%). It was also observed that $Pd(MeCN)_2Cl_2$ was not completely soluble in IPA at room temperature, and small amounts of Pd metal precipitate were typically observed during the reaction. By preforming the Pd(*i*PrBox)Cl_2 catalyst and using it in place of $Pd(MeCN)_2Cl_2$, these issues could be avoided and slight increases in yield and ee were observed (34% yield, 51% ee). The reaction was also performed with $Pd(MeCN)_2Cl_2$ and no added ligand, which resulted in the formation of substantial amounts of Pd metal precipitate, and no product formation.

The effect of excess ligand was then studied in more detail (Table 2.3). It was found that at <5 mol% of exogenous *i*PrBox the yield deteriorated, and at very low excess

Table 2.3. Optimization for organostannanes.



2.29 **2.31** (1.5 equiv) **2.32**

entry	mol% *i*PrBox	mol% CuX_2	% yield[a]	% ee[b]
1	1.25	-	0	NA
2	2.5	-	15	50
3	5	-	34	54
4	7.5	-	34	51
5	7.5	5 mol% $CuCl_2$	47	59
6	7.5	5 mol% CuCl	27	56
7	7.5	5 mol% CuF_2	45	55
8	7.5	5 mol% $Cu(OTf)_2$	11	8
9	7.5	5 mol% $Cu(OAc)_2$	26	57
10	10	10 mol% $CuCl_2$	50	58
11	15	10 mol% $CuCl_2$	46	56

[a] GC yield, determined using an internal standard and response factor. [b] determined by GC using a chiral stationary phase.

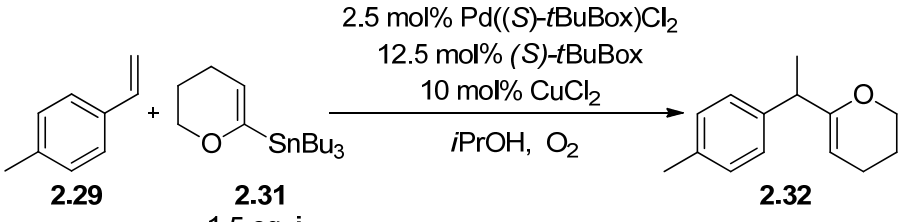
ligand loadings no reaction was observed. Since copper additives are known to promote Stille couplings, several different copper salts were added to the reaction mixture.[71,72] As bisoxazolines are known to bind to copper, and decreased ee's have been observed by our group in reactions that contain "ligandless" copper,[73] enough ligand was added to ligate both Pd and Cu (Table 2.3, entries 5 - 9). It was found that $CuCl_2$ gave the best result, furnishing product in 47% yield and 59% ee. Using 10 instead of 5 mol% $CuCl_2$ improved the yield slightly, and interestingly, with $CuCl_2$ present, excess ligand was not required for the reaction (entries 10-11).

Since optimization of the reaction conditions led to only modest improvements, other bisoxazoline derivatives were evaluated. Thus, (*S*)-*t*BuBox was tested again at lower temperatures and found to be a viable ligand at room temperature, providing the

product in a rather low 18% yield, but in 75% ee, the best achieved thus far (Table 2.4, entry 2). It should be noted that the (*S*)-*i*PrBox catalyst is not active under these conditions (see Table 2.2). This showcases the fact that (*S*)-*t*BuBox not only forms an active catalyst, but one that is significantly more active than the (*S*)-*i*PrBox-derived one. The most likely reason for the formation of Pd metal with (*S*)-*t*BuBox at 55 °C is that the hydroarylation is proceeding rapidly, but reoxidation of Pd^0 is slow, potentially due to lower concentration of O_2 in solution.[74] At lower temperatures, the rate of hydroarylation decreases, while the solubility of O_2 increases, leading to a more robust catalytic system. However, even at room temperature, small amounts of Pd metal precipitate were observed. Unfortunately, lowering the temperature to 0 °C led to trace amounts of product.

At this point, the Pd((*S*)-*t*BuBox)Cl_2-catalyzed hydroarylation was also tested using boronic esters. Unfortunately, while ee's of up to 56% were observed for substrate **2.14** with phenyl boronic ester, these results were found to be irreproducible.

Table 2.4. Hydroarylation using (*S*)-*t*BuBox at lower temperatures.



2.29 **2.31** 1.5 equiv **2.32**

entry	temp.	% yield[a]	% ee[b]
1	rt	18	75
2	0°C	5	78

[a] GC yield, determined using an internal standard and response factor. [b] Determined by GC using a chiral stationary phase.

Other Bisoxazoline Ligands

Since formation of Pd black was observed with Pd((*S*)-*t*BuBox)Cl_2, several bisoxazoline derivatives were synthesized and tested in hopes of discovering a ligand that would provide both good enantioselectivity and a robust catalyst. Ligand **2.33** was synthesized by REU student Amanda Cook-Sneathen, following a report by Paquin and coworkers. In their report, a dimethyl-substituted valinol-derived oxazoline was found to be a good substitute for a *t*-butyl oxazoline.[75] This ligand was evaluated using boronic esters, and found to be slightly more selective than (*S*)-*i*PrBox (Figure 2.21). However, the increase in ee was not substantial enough to warrant further optimization with this ligand.

With the idea in mind that a catalyst just slightly less sterically bulky than *t*BuBox was needed, ligand **2.34** was synthesized, featuring a *t*-butyl-substituted oxazoline ring and an unsubstituted oxazoline (Figure 2.22). Unfortunately, this ligand gave rather poor results. Next, the bridging carbon was modified. It has been observed by Denmark and coworkers[76] that placing rings of different sizes at this position alters the angle between

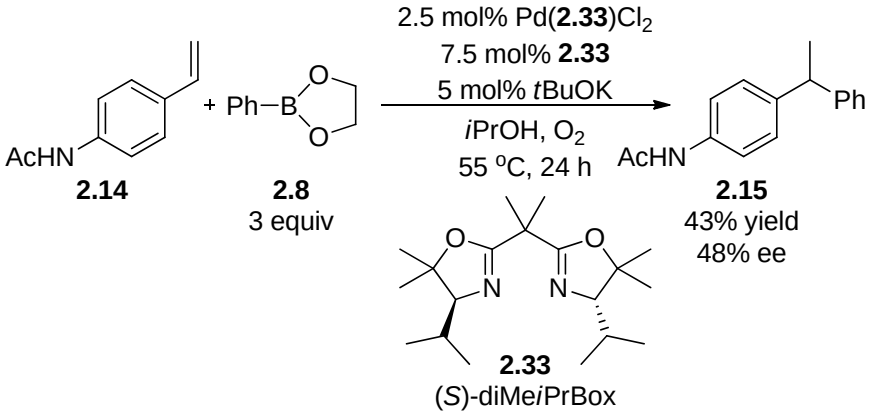


Figure 2.21. Hydroarylation using (*S*)-diMe*i*PrBox (**2.33**).

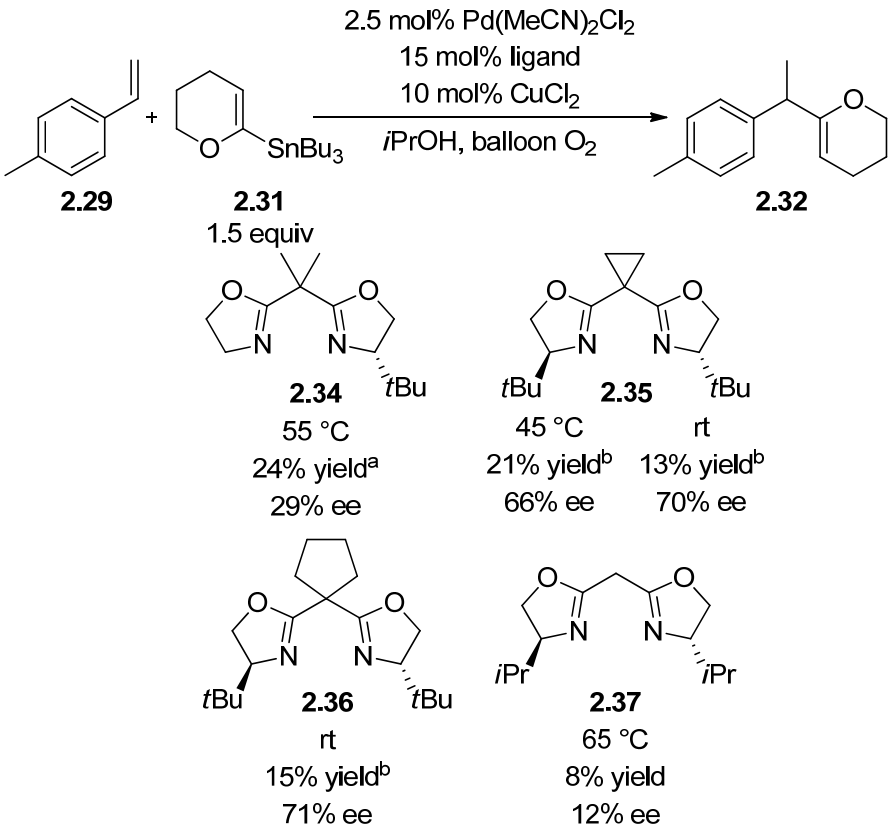


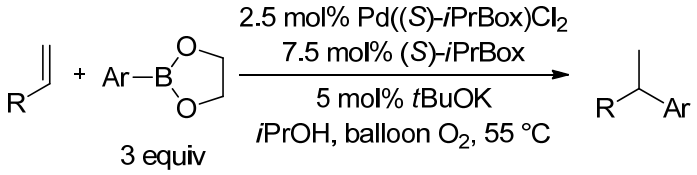
Figure 2.22. Bisoxazoline derivatives. [a] after 44 h. [b] 10 mol% ligand, 5 mol% $CuCl_2$.

the two oxazoline rings, resulting in a subtle change in the bite angle of the ligand. Ligands **2.35** and **2.36** were synthesized and tested to evaluate the effect of this on our reaction. While this modification did result in improved ee's compared to *i*PrBox, the enantioselectivity was lower than that of *t*BuBox. Interestingly, the reactivity of the catalyst derived from ligand **2.35** was found to be slightly lower compared to its "parent" ligand *t*BuBox, suggesting that a slightly larger bite angle alleviated the steric crowdingin this catalyst, leading to both lower reactivity and enantioselectivity. Additionally, ligand **2.37** was synthesized, with an unsubstituted bridging carbon. Ligands of this type have been found to be deprotonated upon binding to metals,[77,78] and are therefore

fundamentally different from typical Box ligands. Unfortunately, this ligand did not provide a particularly active or enantioselective catalyst.

Since it seemed the reaction for organostannanes had been optimized as far as possible, we chose to evaluate different substrates to probe the generality of the reaction (Table 2.5). In addition to the substrates used for ligand optimization with boron, styrene was found to be a viable substrate in combination with an electron poor aryl boronic ester. Furthermore, since π-allyl and π-benzyl Pd complexes can accessed with this method, a diene was tested and indeed found to give the expected product, albeit in low

Table 2.5. Scope using boronic esters.



entry	alkene	Ar	product	% yield	% ee
1	BocHN **2.7**	**2.8**	BocHN **2.9**	53	59
2	AcHN **2.14**	**2.8**	AcHN **2.15**	29	27
3	**2.38**	CO_2Me **2.39**	**2.40** CO_2Me	46	48
4	**2.41**	OMe OMe **2.42**	**2.43** OMe OMe	28	45

yield. Unfortunately, when attempting to isolate the product derived from enol ether stannane **2.31**, it was found to be inseparable from the starting material, and therefore, styrene **2.7** was instead reacted with $PhSnBu_3$ (**2.30**) (Figure 2.23).

Conclusion

To summarize, we have made progress toward the development of a Pd-catalyzed asymmetric hydroarylation of styrenes and dienes. Unfortunately, the use of O_2 as the terminal oxidant restricts the potential types of ligands to those stable to oxidative conditions, precluding the use of typical phosphorus-based ligands. We believe that this limitation is the main obstacle that needs to be overcome to develop this reaction more fully. Based on this hypothesis, the development of related hydroarylation-type reactions that are independent of O_2 became the general goal pursued in the project described in Chapter 3.

Experimental Section

General Information

THF, DCE (1,2-dichloroethane) and CH_2Cl_2 were dried by passing through a column of activated alumina; *i*PrOH (IPA) and MeOH were distilled from CaH_2; NEt_3

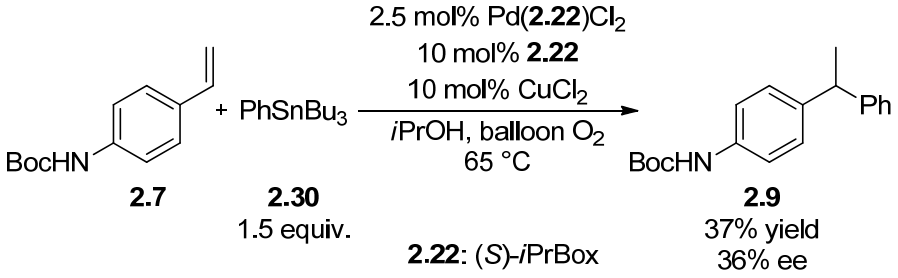


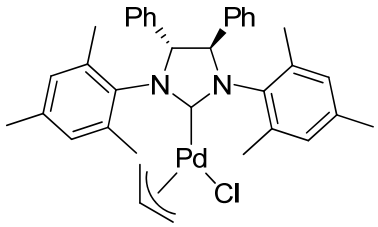
Figure 2.23. Example of hydroarylation using organostannane.

was distilled from CaH_2; $CDCl_3$ was dried by passing through a plug of activated neutral alumina. Liquid styrene substrates were purified by passing through a small plug of activated neutral alumina before use. $PhSnBu_3$ and Bu_3SnCl were purchased from Gelest Inc. NaO*t*Bu, KO*t*Bu and Cs_2CO_3 were stored in a glove box, and removed immediately prior to use. TsCl was purified by washing its solution in Et_2O with base, followed by crystallization from hot PhMe. DMAP was crystallized from hot toluene. (–)-Sparteine was prepared from (–)-sparteine sulfate pentahydrate (purchased from Acros) according to a previously reported procedure.[64] Aminoacid 3-ethyl-L-norvaline was prepared according to a literature procedure.[79] (*S*)-valinol, (*S*)-*t*-leucinol, (*S*)-phenylalaninol, (*R*)-phenylglycinol, and 3-ethyl-L-norvalinol were prepared from the corresponding amino acids according to a literature procedure,[80] and their spectral data agreed with previously published ones[81] (or those of commercial products). Unless otherwise noted, reactions were performed under an atmosphere of N_2 using standard Schlenk techniques. Flash column chromatography was performed using EM Reagent silica 60 (230-400 mesh). ^1H NMR were obtained at 300 MHz and referenced to the residual $CHCl_3$ singlet at 7.26 ppm. ^{13}C NMR were obtained at 75 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.2 ppm. GC/MS were obtained on Agilent 6890 (EI) 20:1 split. IR spectra were recorded using a Nicolate FTIR instrument. HRMS (high resolution mass spectrometry) analysis was performed using Waters LCP Premier XE. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Optical rotations were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length; concentrations are reported in g/100 mL. Chiral GC (gas chromatography) analysis was performed using a

Hewlett Packard HP 6890 Series GC system fitted with a HP-Chiral permethylated β-cyclodextrin column. HPLC (high pressure liquid chromatography) analysis was performed using a Hewlett Packard Series 1100 instrument fitted with a chiral stationary phase (as indicated). SFC (supercritical fluid chromatography) analysis was performed at 40 °C, using a Thar instrument fitted with a chiral stationary phase (as indicated).

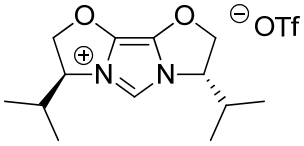
Caution should be taken when heating flammable solvents in the presence of O_2.

Preparation of Ligands and Their Pd Complexes



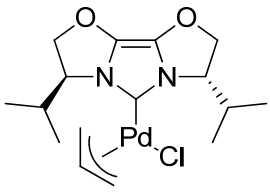
Pd(**2.10**)(allyl)Cl

*Pd(**2.10**)(allyl)Cl* was prepared as previously described in the literature.[82]



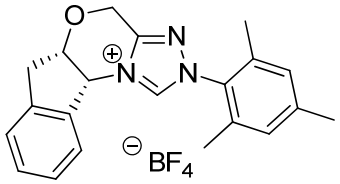
2.11·HOTf

*Carbene precursor **2.11**·HOTf* was prepared following a literature procedure.[83]



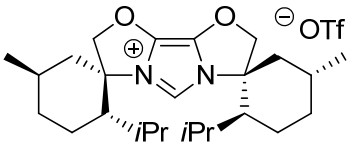
Pd(**2.11**)(allyl)Cl

*Pd(**2.11**)(allyl)Cl* was prepared following a procedure for related complexes.[66] To a dry 25 mL round bottom flask were added 25.0 mg of $[Pd(allyl)Cl]_2$ (0.0676 mmol, 1.00 equiv), 52.6 mg of **2.11**·HOTf (0.142 mmol, 2.10 equiv), and 18.2 mg of KO*t*Bu (0.162 mmol, 2.40 equiv), followed by 3 mL of THF. The mixture was stirred under N_2 for 14 h. The resulting crude product was purified by flash column chromatography eluting with Et_2O, followed by crystallization from DCM/hexanes to obtain a white solid. Yield: 26.0 mg (0.0617 mmol, 46%, 1:1.5 ratio of isomers by NMR); R_f: 0.15 w/ Et_2O; $[\alpha]_D^{20}$ = +123.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 6 H), 1.00 (m, 6 H), 2.33 (d, J = 12.5 Hz, 0.55 H), 2.45 (d, J = 12.2 Hz, 0.69 H), 2.65 (m, 2 H), 3.25 (m, 1 H), 3.49 (m, 1 H), 4.22 (m, 1 H), 4.64 (m, 4 H), 4.84 (m 2 H), 5.27 (m, 1 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 15.62, 15.7, 18.7, 18.8, 31.2, 31.4, 31.6, 44.1, 46.9, 47.7, 60.8, 61.7, 72.1, 72.9, 114.6; IR (neat) 2960, 2874, 2360, 2339, 1749, 1464, 1424, 1376, 1343, 1200 cm^{-1}; HRMS: (m/z) calcd. 383.0951 obsd. 383.0951 $[M\text{-}Cl]^+$; mp 64-67 °C (decomp.).



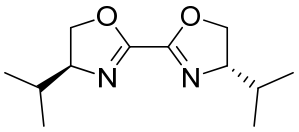
2.12·HBF_4

*Carbene precursor **2.12**·HBF_4* was obtained from the Rovis group at Colorado State University.



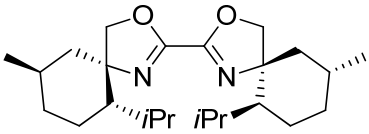
2.13·HOTf

*Carbene precursor **2.13**·HOTf* was prepared according to a literature procedure.[67]



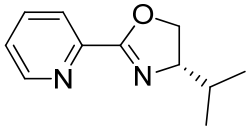
2.16 (*i*PrBiox)

*(S)-iPrBiox **(2.16)*** was prepared according to a literature procedure.[84]



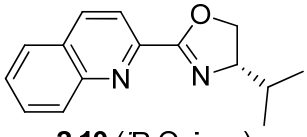
2.17

*Bioxazoline **2.17*** was prepared according to a literature procedure.[67]



2.18 (*i*PrPyrox)

*(S)-iPrPyrox **(2.18)*** was prepared analogously to **2.19** according to a literature procedure.[73] Its spectral data agreed with those previously published.[85]

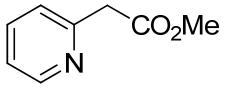


2.19 (*i*PrQuinox)

(S)-iPrQuinox ***(2.19)*** was prepared according to a literature procedure and its spectral data agreed with published ones.[73,86]

Synthesis of Ligand **2.20**

Ligand **2.20** was synthesized as shown in Figure 2.24.



2.45

Methyl ester ***2.45*** was prepared analogously to a published procedure.[87] Into a round-bottom flask were added 2.00 g of **2.44** (11.5 mmol, 1.00 equiv) followed by 14 mL of MeOH. The solution was cooled to 0 °C, and 2.90 mL of TMSCl (23.0 mmol, 2.00 equiv) were added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was then removed in vacuo, and the remaining solid was treated slowly with sat. aq. $NaHCO_3$ (40 mL). The aqueous solution was extracted with CH_2Cl_2 (4 × 40 mL), and the combined organic extracts were dried

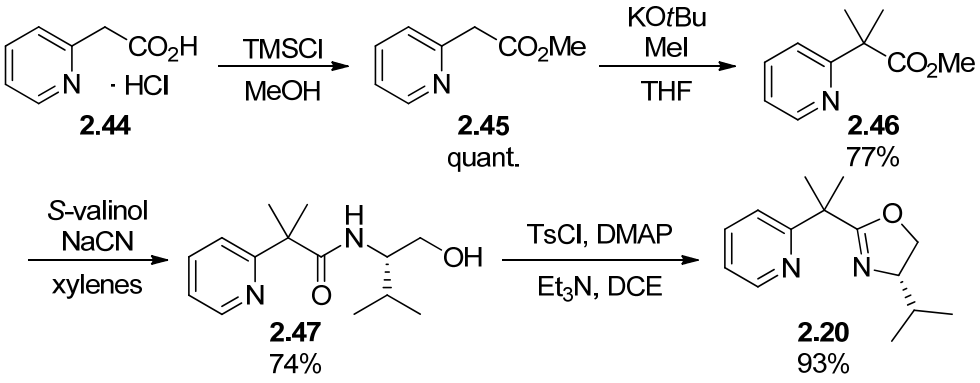
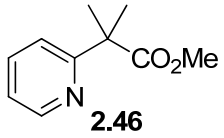


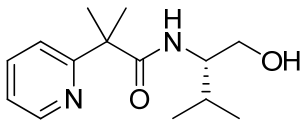
Figure 2.24. Synthesis of ligand **2.20**.

over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude product (**2.45**) was isolated as a clear oil (1.73 g, 11.47 mmol, quant.). The spectral data of the compound agreed with published ones.[87]



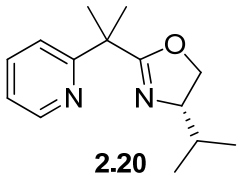
2.46

*Precursor **2.46*** was prepared analogously to a published procedure.[88] Into a round-bottom flask were added 1.73 g of **2.45** (11.47 mmol, 1.00 equiv), followed by 60 mL of THF and 3.22 g of KO*t*Bu (28.68 mmol, 2.50 equiv). The resulting mixture was stirred at room temperature for 30 minutes, followed by dropwise addition of 5.71 mL of MeI (91.76 mmol, 8.00 equiv). The mixture was stirred overnight at room temperature. The reaction was found to be incomplete by TLC. It was filtered through a glass fritte into a dry round-bottom flask, and rinsed with additional THF (25 mL). An additional 1.28 g of KO*t*Bu (11.47 g, 1.00 equiv) were added, and the mixture was stirred for 1 hour at room temperature, followed by addition of 714 μL of MeI (11.47 g, 1.00 equiv). The resulting mixture was stirred overnight at room temperature, upon which the reaction was complete by TLC. The mixture was filtered through a glass fritte, and the solvent was removed in vacuo. The product was purified by flash column chromatography (700 mL of 20% EtOAc/hexanes → 200 mL of 50% EtOAc/hexanes). The spectral data of **2.46** agreed with those previously published.[89]



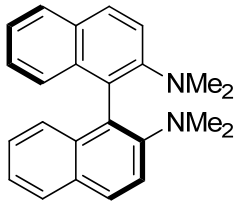
2.47

*Amide **2.47*** was prepared according to a published procedure, and its spectral data agreed with published ones.[90,91]



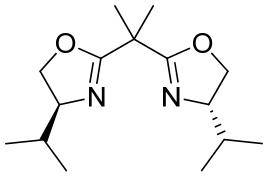
2.20

*Ligand **2.20*** was prepared analogously to a previously published procedure.[73] Into a round-bottom flask were added 437 mg of TsCl (2.29 mmol, 1.20 equiv) and 23.3 mg of DMAP (0.191 mmol, 0.100 equiv), followed by 10 mL NEt_3, and the mixture was cooled to -5 °C. A solution of 478 mg of **2.47** (1.91 mmol, 1.00 equiv) in 15 mL of DCE was added dropwise. The mixture was allowed to warm to room temperature over the course of 2 h, and heated to reflux overnight. The reaction mixture was allowed to cool to room temperature, and washed with sat. aq. $NaHCO_3$ (1 × 40 mL), H_2O (1 × 40 mL), and brine (1 × 40 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 40 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (400 mL of 20% EtOAc/hexanes → 300 mL of 50% EtOAc/hexanes) on neutralized silica (treated with ca 3% NEt_3/hexanes, and rinsed with hexanes prior to chrmoatography). The product was isolated as a pale yellow oil (413 mg, 1.78 mmol, 93%), and its spectral data agreed with published ones.[90]



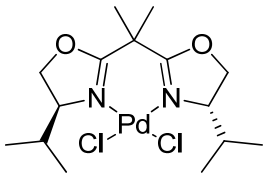
2.21 (BINAM)

*(S)-BINAM (**2.21**)* was prepared according to a literature procedure.[92]



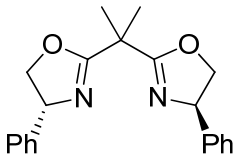
2.22 ((*S*)-*i*PrBox)

*(S)-iPrBox (**2.22**)* was prepared according to a literature procedure.[93]



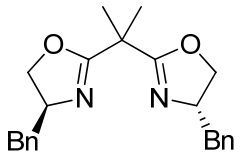
Pd((*S*)-*i*PrBox)Cl_2

Pd((S)-iPrBox)Cl_2 was prepared according to a literature procedure.[94]



2.23 ((*R*)-PhBox)

*(R)-PhBox (**2.23**)* was prepared according to a literature procedure, and its spectral properties agreed with those of the published enantiomer.[95]

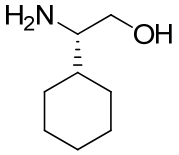


2.24 ((*S*)-BnBox)

*(S)-BnBox (**2.24**)* was prepared according to a literature procedure.[96]

Synthesis of Ligand **2.25** ((*S*)-CyBox)

(*S*)-CyBox (**2.25**) was prepared as shown in Figure 2.25, analogously to a literature procedure.[95]



2.48

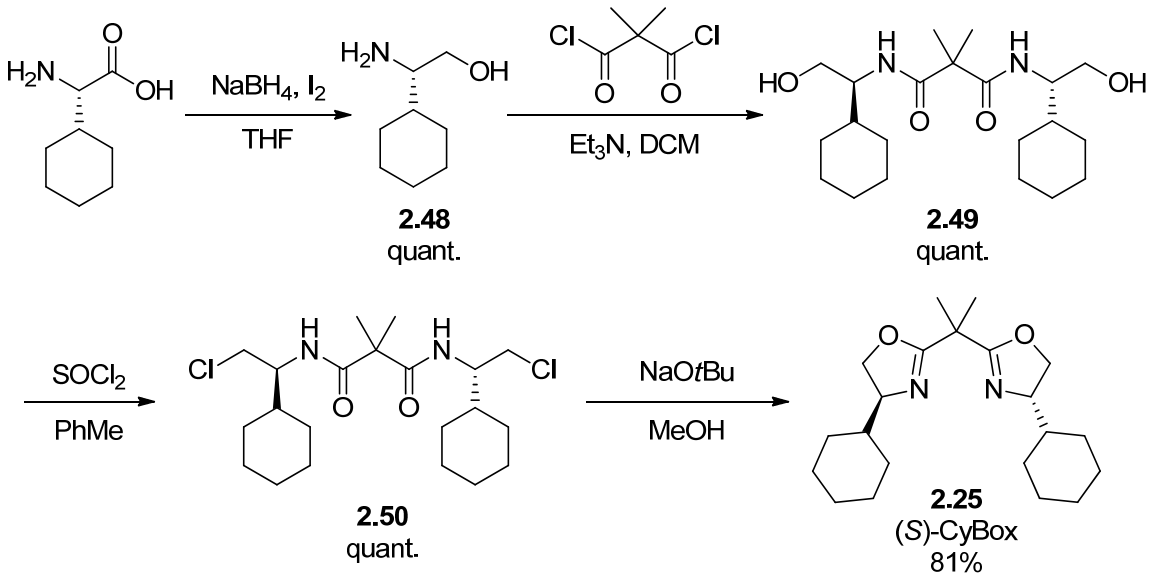
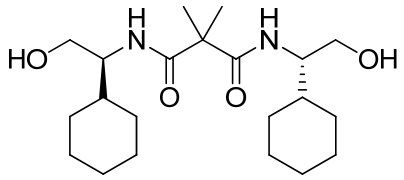


Figure 2.25. Synthesis of **2.25** (*S*)-CyBox.

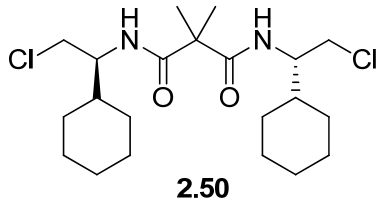
Aminoalcohol ***2.48*** was prepared via reduction of (*S*)-2-amino-2-cyclohexylacetic acid according to a literature procedure.[80] Thus, 400 mg of the amino acid (2.54 mmol, 1 equiv), and 289 mg of $NaBH_4$ (7.62 mmol, 3 equiv), followed by 10 mL of THF were added to a dry round-bottom flask, and cooled to 0 °C. A solution of 646 mg of I_2 (2.54 mmol, 1 equiv) in 5 mL of THF was added dropwise, allowing the mixture to turn white after each drop. Following the addition, the mixture was heated to reflux for 15 h. The reaction mixture was then cooled to 0 °C and quenched slowly with MeOH. The solvents were removed in vacuo, and the remaining solid was dissolved in 20% KOH and stirred at 50 °C for 1.5 h. The mixture was cooled to room temperature, extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo, and the crude material (**2.48,** 381 mg, quantitative yield) was taken forward. Its spectral data matched those of the commercial compound.



2.49

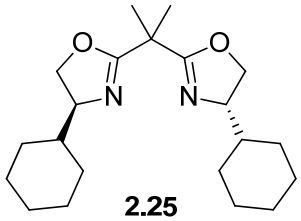
Diamide ***2.49*** was prepared analogously to a literature report.[93] To a round-bottom flask was added all of the material isolated from the previous reaction (**2.48,** 2.54 mmol, 2.1 equiv), followed by 7 mL of CH_2Cl_2, and 405 µL Et_3N (2.90 mmol, 2.4 equiv). The mixture was cooled to 0 °C, and 205 mg of dimethylmalonyl dichloride (1.21 mmol, 1.0 equiv) was dissolved in 3 mL of CH_2Cl_2 and added dropwise. The ice bath was removed, and the mixture was stirred at room temperature for 1 h. It was then washed with sat. aq. $NaHCO_3$ (1 × 20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 ×

20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The product was obtained as a thick, colorless oil, and the crude material (**2.49,** 511 mg, quantitative yield) was taken forward. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 – 1.83 (m, 28 H), 3.51 (dd, *J* = 6.6, 11.1 Hz, 2 H), 3.64 – 3.87 (m, 4 H), 6.41 (d, *J* = 8.8 Hz, 2 H).



2.50

*Chloride **2.50*** was prepared analogously to a literature report.[95] To a round-bottom flask were added 511 mg **2.49** (1.21 mmol, 1.0 equiv), and dissolved in 10 mL PhMe. Subsequently, 220 μL of $SOCl_2$ (3.03 mmol, 2.5 equiv) were added dropwise, a water condenser was added, and the mixture was heated to reflux for 3 h. It was then cooled to room temperature, and the solvent was removed in vacuo. Chloride **2.50** was obtained as a pale brown solid in 64% yield (323 mg, 0.770 mmol) and taken forward as the crude material. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 – 1.36 (m, 12 H), 1.37 – 1.82 (m, 16 H), 3.59 – 3.78 (m, 4 H), 3.96 (app sept, *J* = 3.9 Hz, 2 H), 6.64 (d, *J* = 8.4 Hz, 2 H).

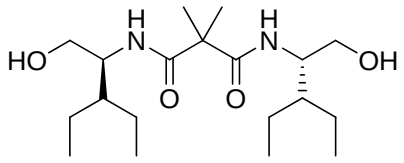


2.25
(*S*)-CyBox

*(S)-CyBox (**2.25**)* was prepared analogously to a literature report.[95] All of the material from the previous reaction (**2.50**, 323 mg, 0.770 mmol) and 185 mg of NaO*t*Bu (1.93 mmol, 2.5 equiv) were added to a round-bottom flask followed by 10 mL of MeOH, a water condenser was added, and the mixture was heated to reflux overnight. The solvent was removed in vacuo, and the resulting solid was partitioned between 1:1 brine/H_2O (20 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The resulting solid was purified further by flash column chromatography with 8% acetone/hexanes. The product (**2.25**) was isolated as a clear oil in 81% yield (216 mg, 0.624 mmol). R_f: 0.29 w/20% acetone/hexanes; $[\alpha]_D^{20}$ = -116.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 – 1.32 (m, 12 H), 1.37 – 1.85 (m, 16 H), 3.88 – 4.06 (m, 4 H), 4.19 (dd, *J* = 8.2, 9.8 Hz, 2 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 24.6, 26.2, 26.3, 26.7, 28.2, 29.3, 38.7, 42.5, 70.4, 71.0, 168.8; IR 2920, 2850, 2361, 1658, 1449, 1385, 1352, 1252, 1144 cm^{-1}; HRMS: (m/z) calcd. 347.2699 obsd. 347.2700 $[M+H]^+$.

Synthesis of Ligand **2.26** ((*S*)-diEtBox)

(S)-diEtBox (**2.26**) was prepared analogously to **2.25**, as shown in Figure 2.26, starting with 3-ethyl-L-norvalinol.[95]



2.51

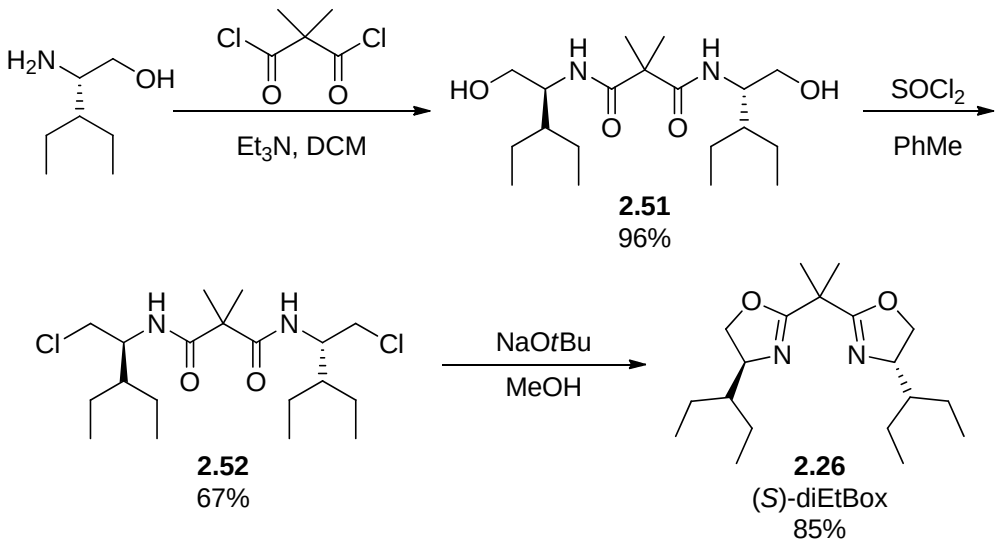
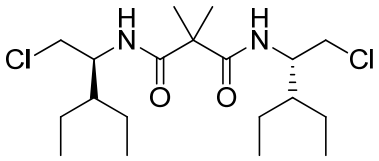


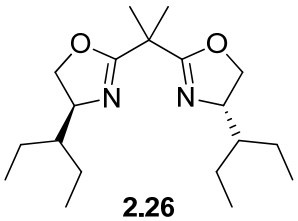
Figure 2.26. Synthesis of **2.26** (*S*)-diEtBox.

*Diamide **2.51*** was prepared analogously to a literature report.[93] To a round-bottom flask was added 443 mg 3-ethyl-L-norvalinol (3.37 mmol, 2.1 equiv), followed by 7 mL of CH_2Cl_2, and 390 μL Et_3N (3.86 mmol, 2.4 equiv). The mixture was cooled to 0 °C, and 272 mg of dimethylmalonyl dichloride (1.61 mmol, 1.0 equiv) was dissolved in 3 mL of CH_2Cl_2 and added dropwise. The ice bath was removed, and the mixture was stirred at room temperature for 1 h. It was then washed with sat. aq. $NaHCO_3$ (1 × 20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The product was obtained as a thick, colorless oil, and the crude material (**2.51,** 555 mg, 1.55 mmol, 96%) was taken forward. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 – 0.98 (m, 12 H), 1.13 – 1.52 (m, 16 H), 3.42 – 3.77 (m, 6 H), 3.91 – 4.12 (m, 2 H), 6.45 (d, J = 8.9 Hz, 2 H).



2.52

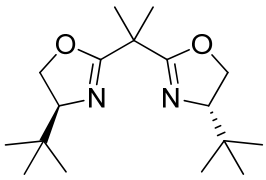
*Chloride **2.52*** was prepared analogously to a literature report.[95] To a round-bottom flask were added 502 mg **2.51** (1.40 mmol, 1.0 equiv), and dissolved in 10 mL PhMe. Subsequently, 255 μL of $SOCl_2$ (3.50 mmol, 2.5 equiv) were added dropwise, a water condenser was added, and the mixture was heated to reflux for 3 h. It was then cooled to room temperature, and the solvent was removed in vacuo. The resulting solid was crystallized from EtOAc/hexanes, to yield chloride **2.52** as a pale brown solid in 67% yield (369 mg, 0.933 mmol), which was taken forward as the crude material. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 – 0.96 (m, 12 H), 1.13 – 1.51 (m, 14 H), 1.52 – 1.65 (m, 2 H), 3.64 (d, *J* = 4.5 Hz, 4 H), 4.19 (ddd, *J* = 4.6, 9.1, 12.3 Hz, 2 H), 6.67 (d, *J* = 8.5 Hz, 2 H).



2.26
(*S*)-diEtBox

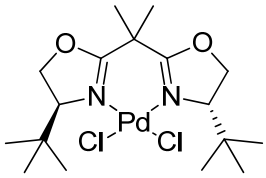
*(S)-diEtBox **(2.26)*** was prepared analogously to a literature report.[95] All of the material from the previous reaction (369 mg, 0.933 mmol) and 224 mg of NaO*t*Bu (2.33 mmol, 2.5 equiv) were added to a round-bottom flask followed by 10 mL of MeOH, a water condenser was added, and the mixture was heated to reflux overnight. The solvent was removed in vacuo, and the resulting solid was partitioned between 1:1 brine/H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL),

the combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The resulting solid was purified further by flash column chromatography eluting with 1:4 acetone/hexanes. The product was obtained as a colorless oil. Yield: 255 mg (0.791 mmol, 85%); R_f: 0.55 w/20% acetone/hexanes; $[\alpha]_D^{20}$ = -67.8 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (dd, *J* = 6.1, 7.3 Hz, 12 H), 1.05 – 1.47 (m, 10 H), 1.50 (s, 6 H), 3.92 – 4.03 (m, 2 H), 4.16 – 4.27 (m, 4 H); ^{13}C NMR $\{^1H\}$ (75 MHz, $CDCl_3$) δ 11.8, 11.9, 21.5, 22.6, 24.6, 38.7, 45.5, 68.3, 70.3, 168.8; IR 2961, 2933, 2875, 1659, 1463, 1384, 1257, 1145, 1118 cm^{-1}; HRMS: (m/z) calcd. 323.2699 obsd. 323.2699 $[M+H]^+$.



2.27 ((*S*)-*t*BuBox)

*(S)-tBuBox (**2.27**)* was prepared according to a literature procedure.[97]



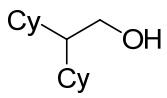
Pd((*S*)-*t*BuBox)Cl_2

To prepare *Pd((S)-tBuBox)*Cl_2, 56.7 mg of **2.27** ((*S*)-*t*BuBox) (0.193 mmol, 1.00 equiv) were weighed into a dry 10 mL round-bottom flask and dissolved in 5 mL of DCM. 50.0 mg of $Pd(MeCN)_2Cl_2$ (0.193 mmol, 1.00 equiv) were added portionwise, and the resulting mixture was stirred for 1 h at room temperature. The resulting solution was

concentrated to 1 mL, and hexanes were added. The solvents were then removed completely in vacuo, to give the product as an orange solid. Yield: 91.0 mg (0.193 mmol, quant.); $[\alpha]_D^{20}$ = +344.9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 18 H), 1.86 (s, 6 H), 4.37 (app. t, *J* = 8.9 Hz, 2 H), 4.50 (dd, J = 4.3, 9.2 Hz, 2 H), 4.58 (dd, J = 4.3, 8.6 Hz, 2 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 25.6, 26.6, 71.8, 72.6, 173.4; IR 2959, 2228, 1640, 1474, 1369, 1250, 1233, 1135 cm^{-1}; HRMS: (m/z) calcd. 729.3338 obsd. 729.3384 $[Pd((S)\text{-}t\text{BuBox})_2Cl]^+$; mp 103-107 °C.

Synthesis of **2.28** ((*S*)-diCyBox)

Ligand **2.28** ((*S*)-diCyBox) was prepared as shown in Figure 2.27. Aminoalcohol **2.59** was prepared analogously to 3-ethyl-L-norvalinol.[95]



2.53

*Alcohol **2.53*** was prepared via reduction of the corresponding carboxylic acid. Thus, 338 mg of $LiAlH_4$ (8.92 mmol, 4.00 equiv.) were added to a round-bottom flask followed by 4 mL THF, and the mixture was cooled to 0 °C. A solution of 500 mg of 2,2-dicyclohexylacetic acid (2.23 mmol, 1.00 equiv) in 1 mL THF was added dropwise, and the mixture was heated to reflux for 20 h. The reaction mixture was then cooled to room temperature, quenched slowly with 4 M HCl (3 mL), and then partitioned between EtOAc (15 mL) and H_2O (30 mL). The aqueous layer was extracted further with EtOAc (3 × 15 mL), and the combined organic extracts were washed with brine (1 × 30 mL), dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude material

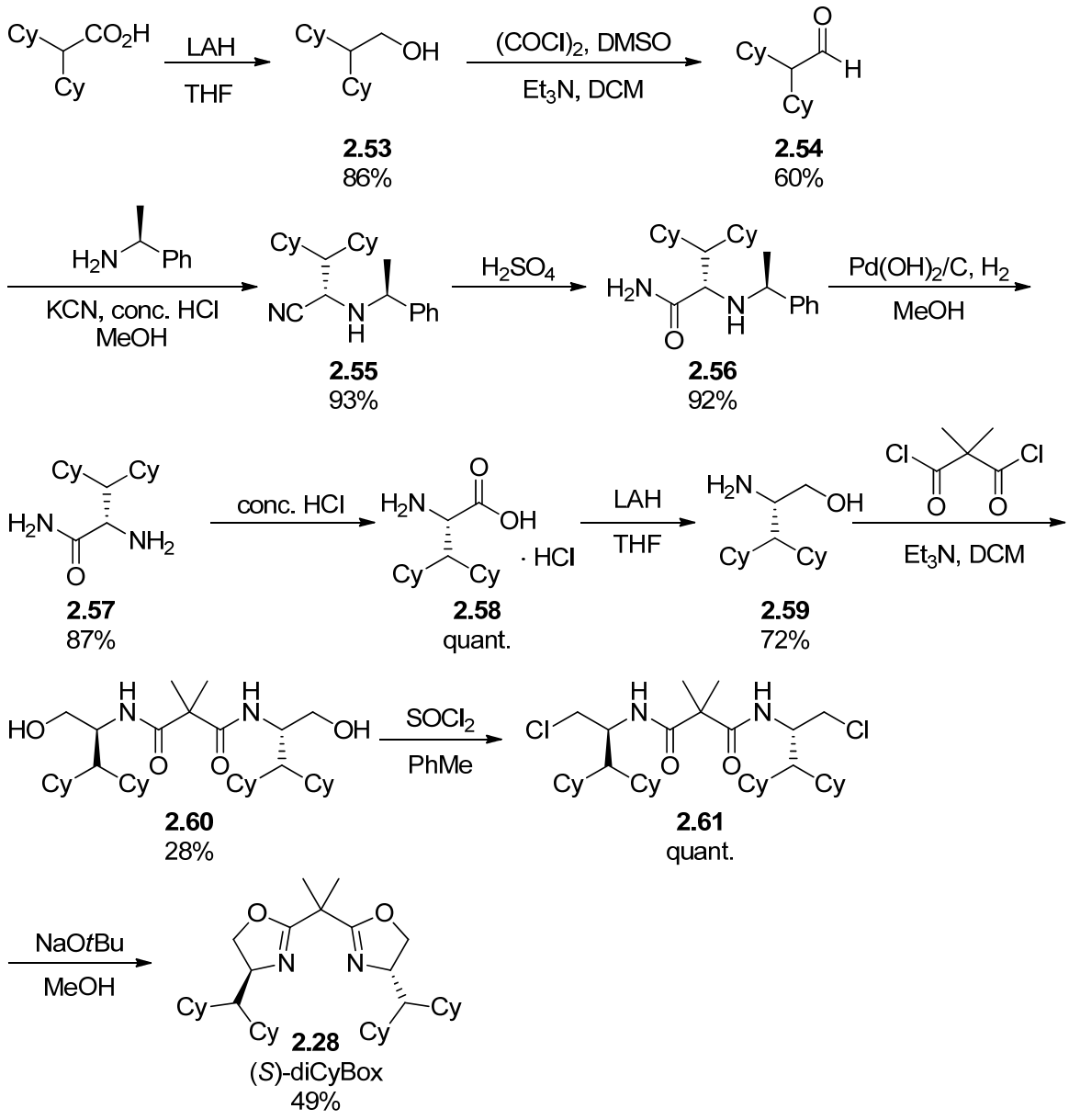
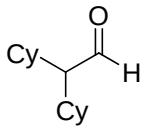


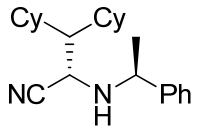
Figure 2.27. Synthesis of **2.28** ((*S*)-diCyBox).

obtained in this way (**2.53**, 403 mg, 1.92 mmol, 86%) was taken on to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 – 1.37 (m, 12 H), 1.40 – 1.81 (m, 11 H), 3.70 (d, *J* = 4.1 Hz, 2 H).



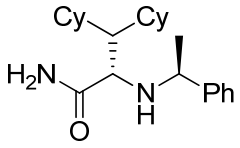
2.54

*Aldehyde **2.54*** was prepared via oxidation of alcohol **2.53**. Thus, 0.169 mL of $(COCl)_2$ (2.00 mmol, 2.00 equiv.) was added to a round-bottom flask followed by 2 mL of CH_2Cl_2, and the mixture was cooled to -78 °C. Subsequently, 0.284 mL of DMSO (4.00 mmol, 4.00 equiv) were added dropwise, and the resulting solution was stirred at -78 °C for 10 min. A solution of 210 mg of **2.53** (1.00 mmol, 1.00 equiv) in 1 mL CH_2Cl_2 was added dropwise, followed by dropwise addition of 0.836 mL of Et_3N (6.00 mmol, 6.00 equiv). The solution was stirred at -78 °C for an additional 30 min, warmed to 0 °C, and stirred for an additional 2 h. The mixture was then allowed to warm to room temperature, diluted with EtOAc (10 mL), and washed with a 1:1 mixture of brine and H_2O (2 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude material was purified by flash column chromatography eluting with 3% EtOAc/hexanes. The product **2.54** was isolated as a clear oil that solidified during storage in the freezer. Yield: 126 mg (0.605 mmol, 60%); R_f: 0.64 w/10% EtOAc/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 - 1.35 (m, 10 H), 1.50 – 1.89 (m, 13 H), 9.66 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 26.99, 27.05, 27.14, 30.60, 31.80, 36.02, 63.67, 208.39; IR (neat) 2920, 2850, 2717, 2361, 2338, 1720, 1447, 1337; HRMS: (m/z) calcd. 231.1725 obsd. 231.1739 $[M+H]^+$.



2.55

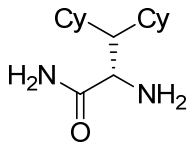
*Cyanide **2.55*** was prepared via an asymmetric Strecker reaction. Thus, 1.76 g of **2.54** (8.45 mmol, 1.00 equiv) were added to a round-bottom flask followed by 1.13 g of (*S*)-*sec*-phenethylamine (9.30 mmol, 1.10 equiv), 60 mg of KCN (9.30 mmol, 1.10 equiv), and 21.1 mL of MeOH. Subsequently, 780 μL of conc. HCl were added, and the reaction was stirred at room temperature for 4 h. Then, 20.3 mL H_2O were added very slowly (ca. 1 drop/5s), and the mixture was stirred at room temperature for 5 days. The mixture was then stirred at 0 °C for 1 h, and filtered, rinsing with H_2O. The crude product was isolated as an off-white solid (**2.55**, 2.65g, 7.83 mmol, 92%, 17:1 dr) and taken on to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 – 1.42 (m, 15 H), 1.43 – 1.85 (m, 11 H), 3.27 (d, *J* = 4.6 Hz, 1 H), 4.08 (q, *J* = 6.6 Hz, 1 H), 4.65 (m, 0.06 H), 7.21 – 7.42 (m, 5 H).



2.56

*Primary amide **2.56*** was prepared via hydrolysis of cyanide **2.55**. Thus, 5.1 mL of conc. H_2SO_4 were added to a round-bottom flask, and cooled to 0 °C. Then, 2.58 g of **2.55** (7.59 mmol, 1.00 equiv) were added, and the dark brown solution was stirred at 50 °C for 18 h. The mixture was then cooled to room temperature, and H_2O (30 mL) and EtOAc (20 mL) were added. The resulting mixture was cooled to 0 °C, and conc.

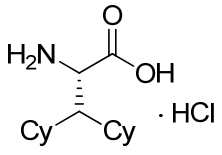
NH_4OH (16 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 30 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography using 10:1 hexanes/EtOAc → 3:1 hexanes/EtOAc. The product (**2.56**) was isolated as a pale yellow amorphous solid. Yield: 2.50 g (7.01 mmol, 92%, d.r. 14:1 by NMR); R_f: 0.13 w/1:3 EtOAc/hexanes; $[\alpha]_D^{25}$ = -0.088 (c 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 – 1.80 (m, 26 H), 3.07 (d, *J* = 4.9 Hz, 1 H), 3.64 (q, *J* = 6.7 Hz, 1 H), 5.55 (bs, 1 H), 6.80 (bs, 1 H), 7.19 – 7.37 (m, 5 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 24.1, 26.6, 27.0, 27.2, 27.4, 31.1, 31.7, 31.8, 32.9, 37.5, 38.5, 52.4, 57.5, 60.9, 144.8, 179.1; IR (neat) 3181, 2922, 2850, 2361, 2339, 1668, 1576, 1448 cm^{-1}; HRMS: (m/z) calcd. 357.2906, obsd. 357.2917 $[M+H]^+$; mp: 89-92 °C.



2.57

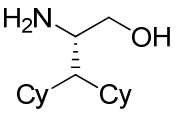
*Amine **2.57*** was prepared via hydrogenolysis. To remove the chiral auxiliary from **2.56**, 2.66 g of **2.56** (7.46 mmol, 1.00 equiv), and 531 mg of 20% $Pd(OH)_2/C$ (max. 50% H_2O), followed by 26.6 mL MeOH were added to a sealed tube, which was purged with H_2 3 times, and pressurized to 40 psi. The mixture was then heated to 70 °C, repressurized to 80 psi, and stirred for 16 h. It was then cooled to room temperature, and filtered. The solvent was removed in vacuo, and the remaining crude product (**2.57**) was purified by flash column chromatography using 20:1 CH_2Cl_2/MeOH. It was isolated as a

white solid. Yield: 1.63 g (6.48 mmol, 87%); R_f: 0.28 w/10:1 CH_2Cl_2/MeOH; $[\alpha]_D^{25}$ = -0.272 (c 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 – 1.86 (m, 22 H), 1.97 (m, 1 H), 3.47 (d, *J* = 1.8 Hz, 1 H), 5.39 (bs, 1 H), 7.44 (bs, 1 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 26.6, 26.9, 26.96, 27.0, 27.1, 27.3, 29.8, 31.4, 32.4, 33.1, 36.0, 37.8, 49.6, 54.4, 179.6; IR (neat) 3420, 3187, 2922, 2849, 2361, 2339, 1669, 1576, 1559, 1447 cm^{-1}; HRMS: (m/z) calcd. 253.2280 obsd. 253.2283 $[M+H]^+$; mp: 94-96 °C.



2.58

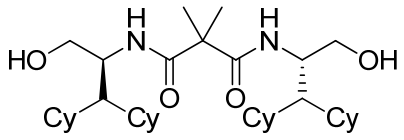
*Aminoacid **2.58*** was accessed via hydrolysis of amide **2.57**. Thus, 1.55 g of **2.57** (6.16 mmol, 1.00 equiv.) was added to a round-bottom flask, followed by 31.1 mL of conc. HCl and 31.1 mL EtOH. The resulting mixture was heated to reflux for 20 h, then cooled to room temperature, and the solvents were removed in vacuo. The remaining solid was mixed with 15.5 mL of acetone. The resulting mixture was filtered, and the solvent was removed from the filtrate in vacuo. The crude product **2.58** was isolated as a pale brown solid (2.08 g, quant.) and taken on to the next step. Spectral data of the compound matched those of the commercial product.



2.59

*Aminoalcohol **2.59*** was prepared via reduction of the aminoacid. Thus, 269 mg of $LiAlH_4$ (7.08 mmol, 4.00 equiv), followed by 6 mL of THF were added to a round-

bottom flask, and cooled to 0 °C. A solution of 600 mg of **2.58** (2.07 mmol, 1.00 equiv) in 6 mL THF was added dropwise. The resulting mixture was refluxed for 13 h, and then cooled to 0 °C. Subsequently, 2 mL of H_2O were added, followed by 404 mg of KOH, and the mixture was refluxed for 30 min. It was then cooled again to 0 °C and filtered, rinsing with EtOAc and H_2O. The layers of the resulting biphasic solution were separated, and the aqueous layer was further extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 30 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude product **2.59** was isolated in 72% yield (359 mg, 1.50 mmol). It was taken on to the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 – 1.84 (m, 22 H), 2.10 – 2.60 (m, 1 H), 2.92 – 3.75 (m, 2 H).

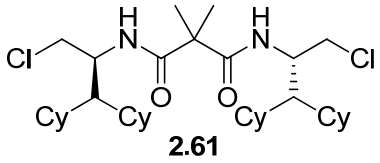


2.60

*Amide **2.60*** was prepared analogously to a literature procedure.[93] Thus, 751 mg of **2.59** (3.14 mmol, 2.50 equiv) were added to a round-bottom flask, followed by 20 mL of CH_2Cl_2 and 612 μL of Et_3N (4.39 mmol, 3.50 equiv). A solution of 212 mg of dimethylmalonyl dichloride (1.25 mmol, 1.00 equiv) in 6 mL of CH_2Cl_2 was added dropwise, and the resulting mixture was stirred at room temperature for 2 h. It was then quenched by adding 30 mL of sat. aq. $NaHCO_3$, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was further purified by column chromatography, separating a small amount of diastereomeric product

formed in the reaction (30:1 CH_2Cl_2/MeOH). The product (**2.60**) was isolated as a white solid. Yield: 201 mg (0.349 mmol, 28%); R_f: 0.48 w/10:1 CH_2Cl_2/MeOH; $[\alpha]_D^{20}$ = +7.3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 – 1.34 (m, 24 H), 1.38 – 1.82 (m, 28 H), 3.21 (bs, 2 H), 3.51 (m, 2 H), 3.69 (m, 2 H), 4.20 (m, 2 H), 6.43 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 23.47, 26.57, 26.62, 27.00, 27.06, 27.32, 30.66, 31.17, 31.70, 33.23, 37.52, 38.40, 49.72, 51.78, 66.08, 174.00; IR 3331, 2924, 2851, 1640, 1536, 1447, 1285 cm^{-1}; HRMS: (m/z) calcd. 597.4607 obsd. 597.4607 $[M+H]^+$; mp: 168-170 °C.

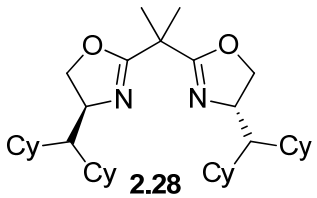
To ensure diastereomeric purity, the amide **2.60** from several separate reactions was combined and crystallized. Thus, 319 mg of **2.60** (0.555 mmol) were added to 1mL EtOAc, and the mixture was refluxed for 30 min, until **2.60** was dissolved. Then, 3 mL of hexanes were added, and the mixture was refluxed for another 30 minutes. It was then cooled to room temperature, and the precipitate was filtered off and rinsed with hexanes. Pure **2.60** was obtained as a white solid (209 mg, 0.364 mmol, 66%).



2.61

*Chloride **2.61*** was prepared analogously to a literature report.[95] To a round-bottom flask were added 157 mg **2.60** (0.272 mmol, 1.0 equiv), and dissolved in 5 mL PhMe. Subsequently, 500 μL of $SOCl_2$ (6.88 mmol, 25 equiv) were added dropwise, a water condenser was added, and the mixture was heated to 60 °C for 3 h. It was then cooled to room temperature, and the solvent was removed in vacuo. The resulting yellow, amorphous solid taken forward to the next step. Yield: 186.4 mg, quant. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 0.79 – 1.96 (m, 52 H), 3.64 (app dq, *J* = 4.2, 11.5 Hz, 4 H), 4.35 (app hept, *J* = 4.3 Hz, 2 H), 6.83 (d, *J* = 9.1 Hz, 2 H).



2.28
(*S*)-diCyBox

*(S)-diCyBox (**2.28**)* was prepared from **2.61** analogously to **2.25** ((*S*)-CyBox).[95] Thus, 110 mg of chloride **2.61** (0.292 mmol) and 65.4 mg of NaO*t*Bu (0.730 mmol, 2.5 equiv) were added to a round-bottom flask followed by 5 mL of MeOH, a water condenser was added, and the mixture was heated to reflux overnight. The solvent was removed in vacuo, and the resulting solid was partitioned between 1:1 brine/H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (2% acetone/hexanes) and obtained as a pale yellow oil. Yield: 72.1 mg (0.134 mmol, 49%); R_f: 0.59 w/ 20% acetone/hexanes; $[\alpha]_D^{25}$ = -51.2 (c 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 – 1.84 (m, 52 H), 3.90 (m, 2 H), 4.26 (m, 4 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 24.4, 26.7, 26.8, 27.2, 27.2, 27.3, 27.4, 31.1, 32.0, 32.2, 32.9, 37.9, 38.2, 38.6, 54.0, 66.4, 72.0, 167.8; IR 2921, 2850, 1623, 1448, 1145, 1112 cm^{-1}; HRMS: (m/z) calcd. 539.4577 obsd. 539.4587 $[M+H]^+$.

Synthesis of Ligand **2.33** ((*S*)-diMe*i*PrBox)

Ligand **2.33** ((*S*)-diMe*i*PrBox) was prepared as shown in Figure 2.28.

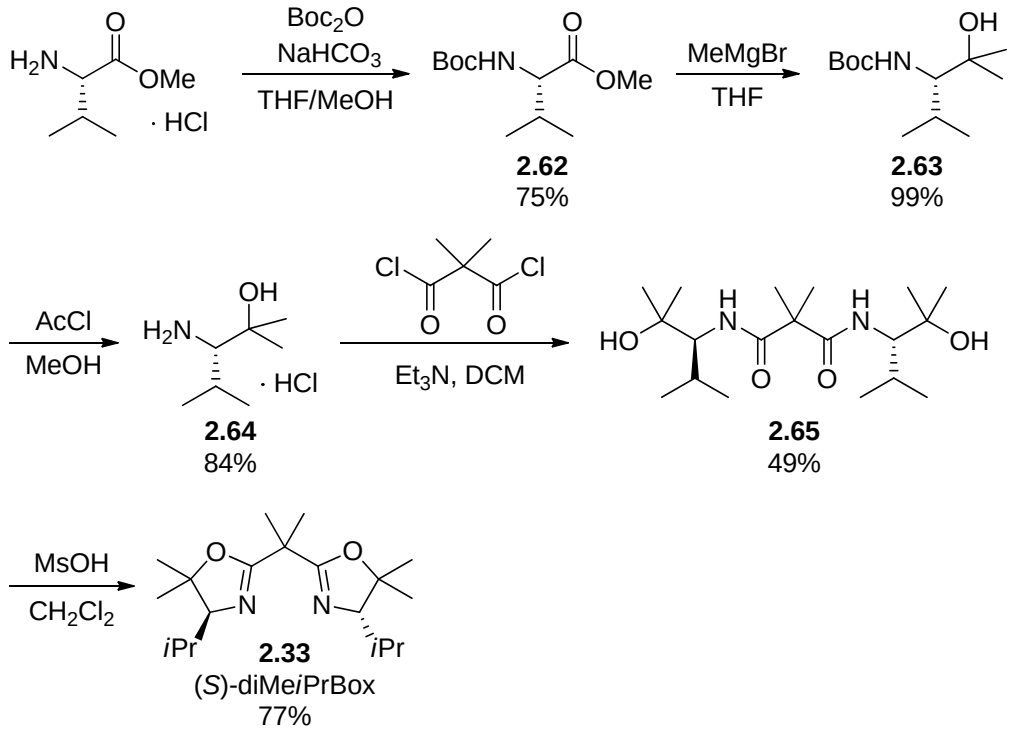
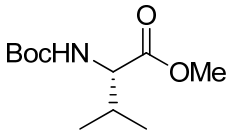
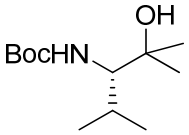


Figure 2.28. Synthesis of **2.33** ((*S*)-diMe*i*PrBox).



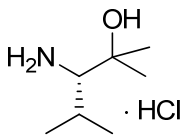
2.62

Boc-protected valine methyl ester ***2.62*** was prepared according to a literature procedure.[98]



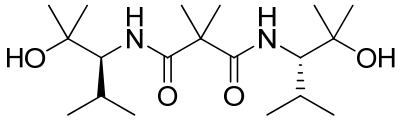
2.63

Protected aminoalcohol ***2.63*** was prepared according to a literature procedure.[98]



2.64

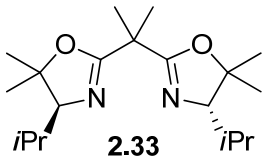
*Deprotected aminoalcohol **2.64*** was prepared analogously to a literature procedure.[99] Thus, 100 mL of MeOH were added to a round-bottom flask and cooled to 0 °C, followed by dropwise addition of 31.4 mL of AcCl (441 mmol, 10.0 equiv). A solution of 10.2 g of **2.63** (44.1 mmol, 1.0 equiv) in 54 mL of MeOH was added dropwise. The resulting solution was allowed to warm to room temperature, stirring for 2 h. The solvent was removed in vacuo to give a brown oil. From this, the product was crystallized using a mixture of hot CH_2Cl_2 and Et_2O. The desired product **2.64** was obtained in 88% yield (6.50 g, 38.8 mmol). Its spectral data agreed with published ones.[98]



2.65

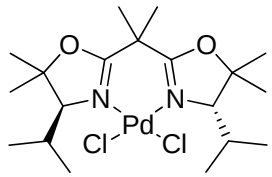
*Diamide **2.65*** was prepared analogously to a literature procedure.[97] To a round-bottom flask were added 3.26 g of **2.64** (19.4 mmol, 2.00 equiv), followed by 20 mL of CH_2Cl_2, and 9.46 mL of Et_3N (67.9 mmol, 7.00 equiv). The mixture was cooled to 0 °C, and a solution of 1.28 mL dimethyl malonyl dichloride (9.70 mmol, 1.00 equiv) in 10 mL CH_2Cl_2 was added dropwise. The ice bath was removed, and the mixture was stirred overnight at room temperature. It was then diluted with CH_2Cl_2 to dissolve the precipitate, and washed with 1 M HCl (1 × 80 mL), sat. aq. $NaHCO_3$ (1 × 80 mL), and

brine (1 × 80 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was isolated in 49% yield (3.43 g, 9.57 mmol). Its spectral data matched previously published ones.[100]



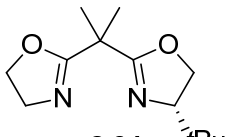
2.33
(*S*)-diMe*i*PrBox

*(S)-diMeiPrBox (**2.33**)* was prepared analogously to a literature procedure.[75] To a round-bottom flask were added 500 mg of **2.65** (1.395 mmol, 1.00 equiv), followed by 15 mL of CH_2Cl_2. The mixture was cooled to 0 °C, and 1.09 mL of MsOH (16.7 mmol, 12.0 equiv) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1.5 h. It was then slowly quenched with 30 mL of sat. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were washed with H_2O (1 × 30 mL), and brine (1 × 30 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield an orange oil. This was purified by flash column chromatography eluting with 10% EtOAc/hexanes to give the product as an off-white solid. Yield: 250 mg (0.774 mmol, 55%). Its spectral data were compared to published ones.[100]



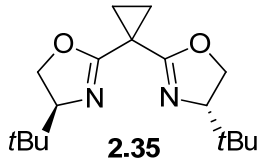
Pd((*S*)-diMe*i*PrBox)Cl_2

Pd((S)-diMeiPrBox)Cl_2, was prepared by adding 50.0 mg of (*S*)-diMe*i*PrBox (0.155 mmol, 1.02 equiv) to a dry 10 mL round-bottom flask under N_2 and dissolving in 5.00 mL of DCM. Then, 39.4 mg of $Pd(MeCN)_2Cl_2$ (0.152 mmol, 1.00 equiv) were added portionwise, and the mixture was stirred for 2 h at room temperature. The orange solution was concentrated in vacuo, and hexanes were added until an orange powder began to precipitate. The resulting mixture was further concentrated until the DCM was removed and the majority of the Pd complex had precipitated. The product was then filtered through a glass fritte and rinsed with a small amount of Et_2O. The product was isolated as an orange solid. Yield: 65.2 mg (0.130 mmol, 86%); $[\alpha]_D^{20}$ = +84.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (m, 12 H), 1.35 (s, 6 H), 1.57 (s, 6 H), 1.71 (s, 6 H), 2.68 (m, 2 H), 4.18 (d, *J* = 3.4 Hz, 2 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ18.8, 21.0, 25.0, 28.3, 29.0, 40.6, 76.0, 90.9, 170.3; IR 2928, 2835, 1714, 1593, 1458, 1427, 1349, 1204, 1155, 1060 cm^{-1}; HRMS: (m/z) calcd. 463.1344 obsd. 463.1357 [M-Cl]$^+$; mp 196-197 (decomp.).



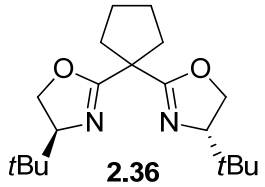
2.34

t-Butyl-substituted bisoxazoline ***2.34*** was prepared according to a literature procedure.[101]



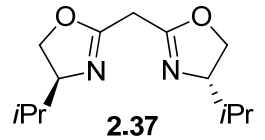
2.35

Cyclopropyl-bridged bisoxazoline ***2.35*** was prepared according to a literature procedure.[76]



2.36

Cyclopentyl-bridged bisoxazoline ***2.36*** was prepared according to a literature procedure.[76]

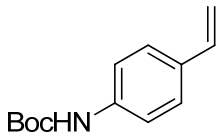


2.37

Methylene-bridged bisoxazoline ***2.37*** was prepared analogously to a literature procedure from (*S*)-valinol and malonodiimidic acid diethyl ester dihydrochloride.[76] Malonodiimidic acid diethyl ester dihydrochloride was prepared according to a literature procedure.[102] To prepare ligand **2.37**, 500 mg of (S)-valinol (4.85 mmol, 1.97 equiv)) were added to a dry 50 mL round-bottom flask, followed by 20 mL DCM. Then, 569 mg of malonodiimidic acid diethyl ester dihydrochloride (2.46 mmol, 1.00 equiv) were added portionwise, and the resulting slurry was stirred at room temperature overnight. To dissolve the precipitate, 10 mL H_2O were added, the mixture was transferred to a

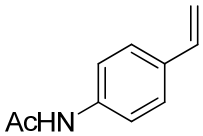
separatory funnel, and the layers were separated. The aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic layers were washed with brine (1 × 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by bulb-to-bulb distillation under vacuum. The product was obtained in 60% yield (353 mg, 1.48 mmol). Its spectral data agreed with published ones.[78]

Preparation of Olefin Starting Materials



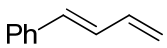
2.7

Boc-protected vinylaniline **2.7** was prepared according to a literature procedure.[24]



2.14

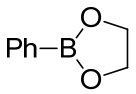
Acetyl-protected vinylaniline **2.14** was prepared according to a literature procedure,[103] and its spectral data agreed with published ones.[103,104]



2.41

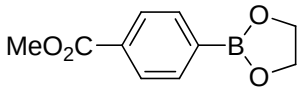
Diene **2.41** was prepared according to a literature procedure.[105]

Preparation of Organometallic Starting Materials



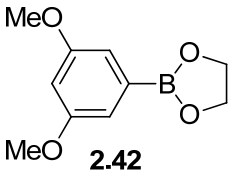
2.8

Phenylboronic ester **2.8** was prepared according to a literature procedure.[106]



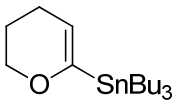
2.39

Methyl ester-substituted arylboronic ester **2.39** was prepared according to a literature procedure.[106]



2.42

Dimethoxy-substituted arylboronic ester **2.42** was prepared according to a literature procedure.[107]



2.31

Dihydropyranyl stannane **2.31** was prepared according to a literature procedure.[24]

Ligand Screening and Optimization

Initial Product Analysis

For reactions analyzed by GC, the products (**2.15**, **2.32**) were identified by comparison with their racemates. Product **2.32** has been previously synthesized.[24] Product **2.15** was synthesized following the same procedure as for **2.9**, and a mixture of starting material **2.14** and product **2.15** was isolated.[106]

For other reactions, the crude product (**2.9**) was isolated as described below and identified by NMR by comparison with the previously synthesized product.[106]

General Procedure for Screen Scale Hydroarylation Using Substrate **2.7** with Carbene Ligands **2.10** and **2.11**

Into an oven-dried 25 mL Schlenk flask equipped with a stirbar were added 0.0038 mmol of the appropriate Pd catalyst (1.5 mol%), followed by 2.85 mL of IPA. A condenser and a three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. A solution of 3.5 mg of (–)-sparteine (0.015 mmol, 6.0 mol%) in 1.0 mL of IPA was added, and the resulting mixture was stirred at room temperature for 30 min. A solution of 54.8 mg styrene substrate **2.7** (0.25 mmol, 1.00 equiv.) and 111 mg phenyl boronic ester **2.8** (0.75 mmol, 3.00 equiv) in 1.00 mL IPA was then added, followed by a solution of 1.7 mg KO*t*Bu (0.015 mmol, 6 mol%) in 0.15 mL IPA. The resulting mixture was heated to 55 °C for ca. 24 h. The reaction mixture was then cooled to room temperature, and the solvent was removed in vacuo. The residue was partitioned between H_2O (10 mL) and 4:1 hexanes/EtOAc (10 mL). The aqueous layer was extracted with 4:1 hexanes/EtOAc (3 × 10 mL), dried over a 1:1 mixture of $MgSO_4$ and silica gel, filtered, and concentrated

in vacuo. The product was purified by flash column chromatography eluting with 20:1 hexanes/EtOAc.

Procedure for Screening of **2.12**

To a dry 10 mL sidearm flask under N_2 were added 0.200 mL of a solution of $[Pd(allyl)Cl]_2$ and KO*t*Bu in THF (0.00375 M $[Pd(allyl)Cl]_2$, 0.3 M KO*t*Bu), and 0.300 mL of a 0.0105 M solution of **2.12**·HBF_4 in THF. The resulting mixture was stirred for 20 min at room temperature. Then, 0.800 mL of IPA was added followed by 0.200 mL of a 0.03 M solution of (–)-sparteine in IPA. A three-way adapter fitted with a balloon of O_2 was added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 45 min at room temperature. 0.500 mL of a solution of styrene substrate **2.14** and phenyl boronic ester **2.9** (0.2 M styrene **2.14**, 0.6 M **2.9**) in IPA containing a small amount of undecane as internal standard was then added, and the mixture was stirred at room temperature for 14 h. At this time, low product formation was observed, and the mixture was heated to 55 °C for an additional 8 h. The product yield was determined by GC, using the internal standard and a response factor. The ee was determined as described below.

Procedure for Screening of **2.13**

To a dry 10 mL sidearm flask were added 1.3 mg of $Pd(MeCN)_2Cl_2$ (0.005 mmol, 5 mol%), 2.8 mg of **2.13**·HOTf (0.005 mmol, 5 mol%), and 1.7 mg of KO*t*Bu (0.015 mmol, 15 mol%), followed by 1.5 mL of IPA. A condenser and a three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at

room temperature. Then, 0.500 mL of a solution of styrene substrate **2.14** and phenyl boronic ester **2.8** (0.2 M styrene **2.14** 0.6 M **2.8**) in IPA containing a small amount of undecane as internal standard was then added, and the mixture was stirred at room temperature for 21 h. The product yield was determined by GC, using the internal standard and a response factor. The ee was determined as described below.

General Procedure for Screen Scale Hydroarylation Using Substrate **2.7** with Nitrogen Ligands (**2.16**, **2.21**, **2.22-2.28**)

These experiments were performed analogously to the ones using preformed Pd carbene complexes ((**2.10**)Pd(allyl)Cl and (**2.11**)Pd(allyl)Cl), but instead of the preformed Pd carbene complex, 1.6 mg of $Pd(MeCN)_2Cl_2$ (0.00625 mmol, 2.5 mol%), followed by 0.025 mmol of the ligand (10 mol%) were added. The ee was determined as described below.

General Procedure for Screen Scale Hydroarylation Using Substrate **2.14** with Nitrogen Ligands (**2.17-2.20, 2.22**)

Into an oven-dried 10 mL sidearm flask under N_2 were added 1.0 mg of $Pd(MeCN)_2Cl_2$ (0.00375 mmol, 2.5 mol%), and the appropriate ligand (0.015 mmol, 10 mol%), followed by 2.05 mL IPA. A condenser and three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 0.75 mL of a solution of styrene substrate **2.14** and phenyl boronic ester (**2.8**) in IPA (0.2 M **2.14**, 0.6 M **2.8**) containing a small amount of undecane as internal standard was added, followed by 0.200 mL of a 0.0375 M solution of KO*t*Bu in

IPA. The resulting mixture was heated to 55 °C for ca. 24 h. The product yield was determined by GC, using the internal standard and a response factor. The ee was determined as described below.

The reaction using **2.17** was performed on a 0.100 mmol scale in 2.00 mL IPA, and 1.3 mg of $Pd(MeCN)_2Cl_2$ (0.00500 mmol, 5 mol%) was used, along with 7.8 mg of **2.17** (0.020 mmol, 20 mol%) and 1.1 mg of KO*t*Bu (0.010 mmol, 10 mol%).

The reaction using **2.22** ((*S*)-*i*PrBox) was perfomed on a 0.100 mmol scale in 2.00 mL IPA, and 1.1 mg of Pd((*S*)-*i*PrBox)Cl_2 (0.0025 mmol, 2.5 mol%) was used along with 2.0 mg of (*S*)-*i*PrBox (0.0075 mmol, 7.5 mol%).

Procedures for Data in Table 2.1 (Initial Results Using Organostannanes)

Procedure for Table 2.1, entry 1: To a dry 25 mL Schlenk flask was added 1.6 mg of $Pd(MeCN)_2Cl_2$ (0.00625 mmol, 2.5 mol%), followed by 0.250 mL of a 0.100 M solution of *(R)*-PhBox in IPA and 4.40 mL IPA. A condenser and three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, a 0.250 mL of a 1.00 M solution of styrene substrate **2.7** was added, followed by 122 μL of $PhSnBu_3$ (0.375 mmol, 1.50 equiv.), and 0.100 mL of a 0.125 M solution of KO*t*Bu in IPA. The resulting solution was heated to 55 °C for 24 h. It was then cooled to room temperature, and the solvent was removed under reduced pressure. The product was purified by flash column chromatography eluting with 5% EtOAc /hexanes, which gave a mixture of product **2.9** and starting material (**2.7**). The ee was determined as described below.

Procedure for Table 2.1, entries 2 and 3: To a dry 10 mL sidearm flask was added 1.0 mg of $Pd(MeCN)_2Cl_2$ (0.00375 mmol, 2.5 mol%), followed by 0.100 mL of a 0.15 M solution of *(R)*-PhBox in IPA and 2.65 mL IPA (entry 2) or 2.75 mL IPA (entry 3). A condenser and 3-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 0.150 mL of a 1.00 M solution of 4-methylstyrene (**2.29**) in IPA containing a small amount of undecane as internal standard was added, followed by 73 μL of **2.31** (0.225 mmol, 1.50 equiv.), and 0.100 mL of a 0.075 M solution of KO*t*Bu in IPA (for entry 2). The resulting mixture was stirred at 55 °C for 24 h. Product yield and ee were determined by GC.

Procedure for Data in Table 2.2 (Temperature Optimization for Organostannanes)

The reactions were carried out analogously to those for Table 2.1, entries 2 and 3, except instead of *(R)*-PhBox, (*S*)-*i*PrBox was used, and the reactions were performed at different temperatures without KO*t*Bu.

Procedure for Data in Table 2.3

To a dry 10 mL sidearm flask was added 1.1 mg of $Pd(MeCN)_2Cl_2$ (0.0025 mmol, 2.5 mol%) and any additives, followed by the appropriate amount of a 0.025 M solution of *(S)*-*i*PrBox in IPA and additional IPA to give a total volume of 1.8 mL. A condenser and three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 0.200 mL of a solution of **2.29** and **2.31** in IPA (0.5 M **2.29**, 0.75 M **2.31**) containing a small amount of

undecane as internal standard was added, and the resulting mixture was heated to 65 °C for 24 h. Product yield and ee were determined by GC.

Procedure for Data in Table 2.4

Reactions for Table 2.4 (Hydroarylation using (*S*)-*t*BuBox at lower temperatures) were performed analogously, using *(S)*-*t*BuBox instead of *(S)*-*i*PrBox, and at room temperature or 0 °C, respectively.

Procedure for Figure 2.21 (Using **2.33**, (*S*)-diMe*i*PrBox)

To a dry 10 mL sidearm flask under N_2 were added 1.03 mL IPA, followed by 0.150 mL of a 0.05 M solution of (*S*)-diMe*i*PrBox in IPA, 0.200 mL of a 0.025 M solution of KO*t*Bu in IPA, and 0.500 mL of a solution of styrene **2.14** and phenyl boronic ester **2.8** in IPA (0.2 M **2.14**, 0.6 M **2.8**) containing a small amount of undecane as internal standard. A condenser and three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 0.125 mL of a 0.02 M solution of Pd((*S*)-diMe*i*PrBox)Cl_2 in IPA was added, and the resulting mixture was heated to 55 °C for 24 h. The product yield was determined by GC, using the internal standard and a response factor. The ee was determined as described below.

Procedure for Figure 2.22 (Bisoxazoline Derivatives)

To a dry 10 mL sidearm flask under N_2 was added 1.0 mg of $Pd(MeCN)_2Cl_2$ (0.00375 mmol, 2.5 mol%), followed by 2.43 mL of IPA, 0.150 mL of a 0.1 M solution of $CuCl_2$ in IPA (0.150 mmol, 10 mol%), and 0.225 mL of a 0.1 M solution of the

appropriate ligand in IPA (0.0225 mmol, 15 mol%). A condenser and three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 0.200 mL of a solution of styrene **2.29** and organostannane **2.31** in IPA (0.75 M **2.29**, 1.125 M **2.31**) containing a small amount of undecane as internal standard was added. The resulting mixture was heated to the appropriate temperature for 24 h. Product yield and ee were determined by GC.

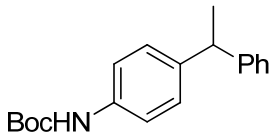
Using ligand **2.34**: The reaction was run for 44 h at 55 °C.

Using ligand **2.35**: The reaction was performed using 10 mol% **2.35**, and 5 mol% $CuCl_2$ at room temperature and 45 °C, respectively.

Using ligand **2.36**: The reaction was performed using 10 mol% **2.36**, and 5 mol% $CuCl_2$ at room temperature.

Using ligand **2.37**: The reaction was run for 42 h at 65 °C.

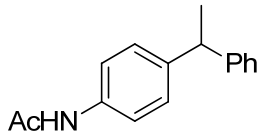
Scope Using Boronic Esters



2.9

*t-Butyl (4-(1-phenylethyl)phenyl)carbamate (**2.9**).* Into a dry 100 mL Schlenk flask were added 6.7 mg of Pd((*S*)-*i*Prbox)Cl_2 (0.015 mmol, 2.5 mol%), followed by 12.0 mg of (*S*)-*i*Prbox (0.045 mmol, 7.5 mol%), and 9.00 mL of IPA. A condenser and three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture

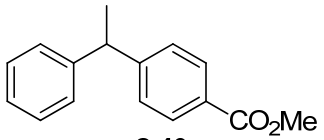
was stirred for 30 min at room temperature. Then, 132 mg of **2.7** (0.6 mmol, 1.00 equiv.), 266 mg of of **2.8** (1.8 mmol, 3.00 equiv.), and 3.4 mg KO*t*Bu (0.03 mmol, 5.0 mol%) were added into a vial and dissolved in 2 mL IPA, and the solution was added to the Schlenk flask dropwise via syringe. The remaining 1 mL IPA was used to rinse the vial, and added to the flask. The resulting mixture was heated to 55 °C for 24 h. It was then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was partitioned between H_2O (10 mL) and Et_2O (20 mL), and the layers were separated. The organic layer was washed with 1 M NaOH (1 × 10 mL), and the combined aqueous layers were extracted with Et_2O (3 × 10 mL), and dried over a 1:1 mixture of $MgSO_4$ and silica gel. They were then filtered, and the solvent was removed in vacuo. The product was purified by flash column chromatography eluting with 5% acetone/hexanes, to give the product as a clear oil. Its spectral properties matched those of the previously published compound.[106] Yield: 94.1 mg (0.316 mmol, 53%, average of two experiments); 59% ee (average of two experiments); $[\alpha]_D^{20}$ = -6.8 (c 1.0, $CHCl_3$).



2.15

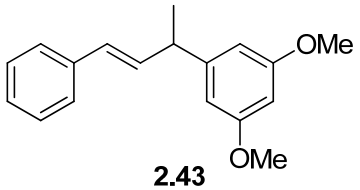
*N-(4-(1-phenylethyl)phenyl)acetamide (**2.15**).* The same procedure as for **2.9** was followed, except 96.7 mg of **2.14** (0.600 mmol, 1.00 equiv.) was used. The product was purified by flash column chromatography eluting with 18% acetone/hexanes. At this stage, it was found to contain small amounts of starting material (**2.14**). It was therefore crystallized from DCM/hexanes, which yielded pure product as a white solid. Yield: 41.6 mg (0.174 mmol, 29%, average of two experiments); 27% ee (average of two

experiments); R_f: 0.63 w/ 50% acetone/hexanes; $[\alpha]_D^{20}$ = -5.0 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, *J* = 7.3 Hz, 3 H), 2.16 (s, 3 H), 4.12 (q, *J* = 7.3 Hz, 1 H), 7.10 (bs, 1 H), 7.12 – 7.23 (m, 5 H), 7.24 – 7.32 (m, 2 H), 7.39 (m, 2 H); ^{13}C NMR $\{^1H\}$ (75 MHz, $CDCl_3$) δ 22.0, 24.7, 44.7, 120.2, 126.2, 127.7, 128.3, 128.5, 135.9, 142.6, 146.4, 168.3; IR 3294, 2966, 1660, 1601, 1535, 1512, 1409, 1370, 1317, 1268 cm^{-1}; HRMS: (m/z) calcd. 262.1208 obsd. 262.1213 $[M+H]^+$; mp 93-96 °C.



2.40

*Methyl 4-(1-phenylethyl)benzoate (**2.40**).* The same procedure as for **2.9** was followed, except 62.5 mg of **2.38** (0.600 mmol, 1.00 equiv.) and 371 mg of **2.39** (1.80 mmol, 3.00 equiv) were used. The product was purified by flash column chromatography eluting with 3% acetone/hexanes. Its spectral properties matched those of the previously published compound.[106] Yield: 66.4 mg (0.276 mmol, 46%, average of two experiments); 48% ee (average of two experiments); $[\alpha]_D^{20}$ = 3.7 (c 1.0, $CHCl_3$).

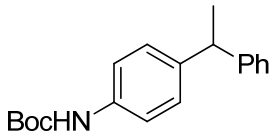


2.43

*(E)-1,3-dimethoxy-5-(4-phenylbut-3-en-2-yl)benzene (**2.43**).* The same procedure as for **2.9** was followed, except 78.1 mg of **2.41** (0.600 mmol, 1.00 equiv.) and 374 mg of **2.42** (1.80 mmol, 3.00 equiv) were used. The product was purified by flash column chromatography eluting with 2% acetone/hexanes. Its spectral properties matched those

of the previously published compound.[107] Yield: 45.7 mg (0.170 mmol, 28%, average of two experiments); 45% ee (average of two experiments); $[\alpha]_D^{20}$ = -14.5 (c 1.0, $CHCl_3$).

Procedure for Hydroarylation Using $PhSnBu_3$ (**2.30**)



2.9

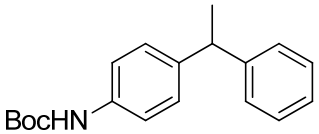
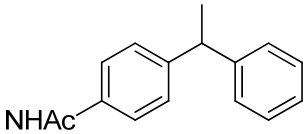
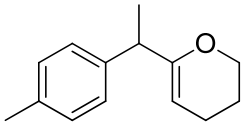
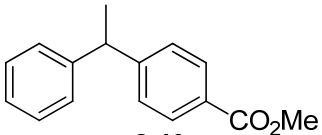
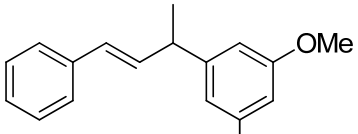
*t-Butyl (4-(1-phenylethyl)phenyl)carbamate (**2.9**).* Into a dry 100 mL Schlenk flask were added 6.7 mg of Pd((*S*)-*i*Prbox)Cl_2 (0.015 mmol, 2.5 mol%), followed by 6.7 mg of $CuCl_2$ (0.06 mmol, 10 mol%), 16.0 mg of (*S*)-*i*Prbox (0.06 mmol, 10 mol%), and 9.00 mL of IPA. A condenser and three-way adapter fitted with a balloon of O_2 were added, and the flask was evacuated via water aspiration and refilled with O_2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 132 mg of **2.7** (0.6 mmol, 1.00 equiv.), and 330 mg of $PhSnBu_3$ **2.30** (0.9 mmol, 1.50 equiv.) were added into a vial and dissolved in 2 mL IPA, and the solution was added to the Schlenk flask dropwise via syringe. The remaining 1 mL IPA was used to rinse the vial, and added to the flask. The resulting mixture was heated to 65 °C for 24 h. It was then cooled to room temperature, and stirred with 5 mL 1 M NaOH for 1 h. The resulting mixture was transferred to a separatory funnel and diluted with Et_2O. This was washed with a 1:1 mixture of brine and H_2O (1 × 10 mL), and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (1 × 20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with 4% acetone/hexanes,

which yielded a clear oil containing product and a small amount of tin byproduct. This was therefore purified again by flash column chromatography eluting with 4% EtOAc/hexanes. The pure product's spectral properties matched those of the previously published compound.[25] Yield: 65.6 mg (0.221 mmol, 37%, average of two experiments); 36% ee (average of two experiments); $[\alpha]_D^{20}$ = -4.5 (c 1.0, $CHCl_3$).

Chiral Separations

Chiral separations were performed as shown in Table 2.6.

Table 2.6. Chiral separations.

entry	product	method	retention times
1	 **2.9**	SFC, OJ-H column 5% MeOH, 3 mL/min	11.43 min 12.96 min
2	 **2.15**	SFC, AD-H column 10% MeOH, 3 mL/min	15.98 min 19.48 min
3	 **2.32**	GC, β–cyclodextrin column 115 °C for 80 min, heat 20 °C/min to 200 °C, hold for 15.75 min	63.87 min 65.21 min
4	 **2.40**	SFC, AD-H column 2% MeOH, 3 mL/min	6.07 min 7.92 min
5	 **2.43**	SFC, AD-H column 3% MeOH, 3 mL/min	4.48 min 5.18 min

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CHAPTER 3

DEVELOPMENT OF A PD-CATALYZED ALLYLIC C–H FUNCTIONALIZATION REACTION

Introduction

As described in Chapter 2, we were interested in pursuing novel transfornations that would provide access to diarylmethines and related compounds without the necessity for external oxidants. Toward this end, we envisioned the use of electrophile substrates, such as tosylates, that would undergo oxidative addition to Pd^0, as is typical in Pd-catalyzed cross-coupling reactions.[1] Furthermore, we planned to utilize the concept of stabilized Pd alkyl intermediates to develop new approaches to C–C bond construction. Specifically, we proposed to use homoallyl electrophile substrates in a Pd-catalyzed allylic C–H functionalization reaction, as outlined below (Figure 3.1). Our proposed mechanism would begin with the oxidative addition of the tosylate substrate to Pd^0 to form Pd alkyl **A**. As **A** is not stabilized via secondary interactions, it would undergo a β-hydride elimination/alkene insertion sequence to form stabilized Pd π-allyl intermediate **D**, followed by transmetallation and reductive elimination to give the desired product. This mechanism takes advantage of controlled β-hydride elimination in order to "walk" the Pd along the substrate carbon chain to form a stabilized Pd π-benzyl intermediate.

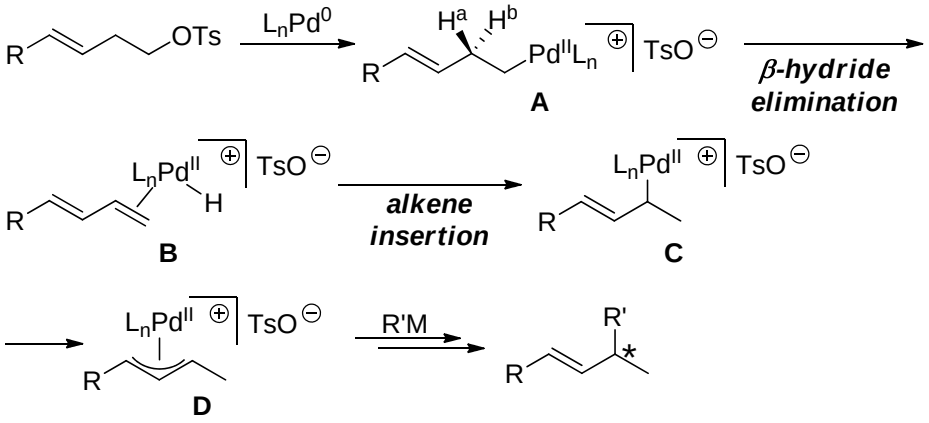


Figure 3.1. Proposed allylic C–H functionalization of homoallyl tosylates.

Overall, this reaction would constitute a novel type of allylic C–H functionalization, which are typically carried out under oxidative conditions,[2] whereas we proposed to use the substrate itself as the oxidant.

Within this scenario, no exogenous oxidant would be needed for cross-coupling, which would allow for the use of oxidatively unstable ligands on Pd. Furthermore, this would be a unique way of potentially setting an allylic stereocenter. To accomplish this, however, oxidative addition of a primary alkyl electrophile had to be achieved, which has been found to be challenging with Pd.[3] Extremely electron-rich Pd complexes are typically needed for this type of reaction.[3] The β-hydride elimination/alkene insertion sequence, on the other hand, should benefit from the use of a more electron-poor Pd catalyst, as it would bind the diene more tightly in intermediate **B**, preventing possible dissociation and formation of a diene byproduct. Determining the optimal Pd catalyst to promote all of these steps was thought to be the main challenge for reaction development.

This chapter details the development of the reaction described above as well as some initial mechanistic studies and efforts toward asymmetric catalysis. The work in this chapter was performed in close collaboration with Dr. Benjamin Stokes. As

discussed above, this reaction would require oxidative addition of homoallyl tosylates, as well as isomerization and cross-coupling of a Pd π-allyl intermediate. In the following section, the oxidative addition of unactivated alkyl electrophiles will thus be discussed, followed by cross-coupling of allylic electrophiles.

Background

Oxidative Addition of Unactivated Alkyl Electrophiles to Pd^0

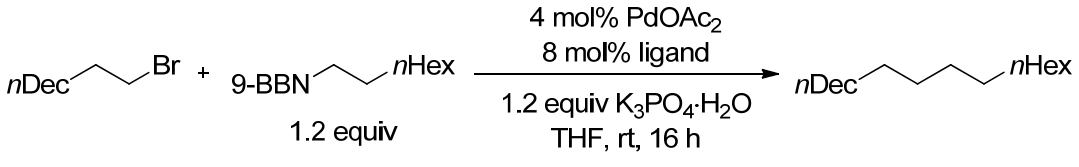
Pd-catalyzed cross-coupling reactions of alkyl electrophiles have been an active area of research in recent years.[4] While cross-coupling of sp^2-electrophiles has been extensively developed, Pd-catalyzed reactions using alkyl electrophiles are generally considered more difficult.[3,5,6] The reasons for this lie in the difficult oxidative addition of alkyl halides (or pseudo-halides), and the relative instability of the resulting Pd alkyl complex (see Chapter 1).[7,8] Alkyl–halide bonds are more electron-rich than the analogous aryl or vinyl halide bonds, which makes them inherently less susceptible to oxidative addition. In aryl and vinyl electrophiles, both C_{sp2}–X π* and σ* orbitals may participate in the new bonding interactions with Pd, while only the σ* orbital is accessible in alkyl electrophiles.[7] Aryl and vinyl halides thus have lower-lying orbitals available to accept electrons from the metal, rendering the oxidative addition of these substrates more facile. Additionally, the greater steric bulk of alkyl groups (especially secondary alkyl groups) hinders nucleophilic attack by the metal. It should also be noted that the oxidative addition of C_{sp2}–X is usually proposed to occur in a concerted fashion, while oxidative addition of alkyl-X typically occurs via S_N2-type attack.[1] Furthermore, the resulting Pd alkyl complexes are less stable than the corresponding Pd aryl or vinyl complexes, as the increased electron density can be better stabilized in aryl/vinyl groups

due to the generally electron-withdrawing character of sp^2-hybridized carbons. Pd alkyl complexes are also prone to undergo reactions such as β-hydride elimination, which are not possible with Pd aryl/vinyl complexes. Finally, reductive elimination is proposed to be slower for Pd alkyl complexes than for Pd aryl/vinyl complexes, based on calculations of activation barriers for this step.[8] This is rationalized via the involvement of π electrons in sp^2-sp^2 reductive elimination.

Some reports detailing the use of aryl phosphine Pd complexes to catalyze the cross-coupling of alkyl iodides have been published.[4] However, the majority of successful Pd-catalyzed alkyl electrophile cross-coupling methods make use of bulky, electron-rich ligands to overcome the difficulties discussed above. Fu and coworkers in particular have developed several systems for cross-coupling different alkyl electrophiles with various transmetallating reagents.[9,10] Most of their systems utilized trialkyl phosphine Pd complexes to catalyze the cross-coupling reactions. In an early report, Fu and coworkers disclosed their evaluation of a range of phosphine ligands for the cross-coupling of alkyl bromides and alkyl boranes (alkyl 9-BBN), a part of which is shown in Table 3.1.[11] Not only were monodentate trialkyl phosphines the only ligand class capable of promoting this reaction, but the size of the ligand had to be within a narrow range: only PCy_3 and P*i*Pr_3 show selectivity for the cross-coupling product. However, it should be noted that these complexes catalyze the reaction at room temperature, showcasing their extreme activity.

Fu and coworkers performed mechanistic studies, specifically on the two systems depicted below (Figures 3.2 and 3.3).[12,13] Of particular interest was the nature of the

Table 3.1. Ligand evaluation for alkyl-alkyl cross-coupling (adapted from Netherton et al., 2001).



ligand	% GC yield	
	*n*Dec–*n*Hex	*n*Dec–alkene
PPh_3	<2	<2
$P(o\text{-tol})_3$	<2	14
$PnBu_3$	9	27
$PiPr_3$	68	6
PCy_3	85	<2
$PtBu_3$	<2	21
dcpe	<2	21

dcpe = 1,2-bis(dicyclohexylphosphino)ethane

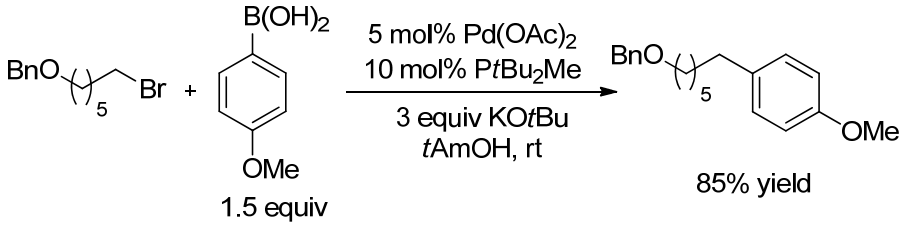


Figure 3.2. Suzuki coupling of alkyl bromides and aryl boronic acids (adapted from Kirchhoff et al., 2002).

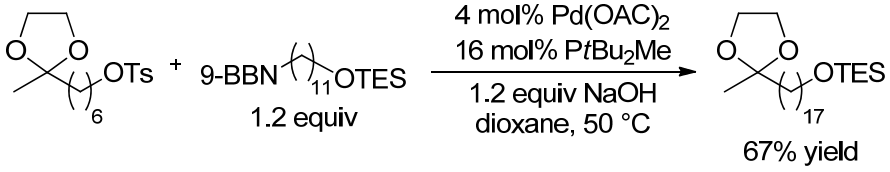


Figure 3.3. Suzuki coupling of alkyl tosylates and alkyl boranes (adapted from Netherton and Fu, 2002).

oxidative addition step. Thus, they discovered that alkyl bromides underwent oxidative addition to $(P\textit{t}Bu_2Me)_2Pd$ at 0 °C, and were able to isolate the resulting Pd alkyl complex (Figure 3.4, top).[13] This showcases not only the exceptional activity of the catalyst for oxidative addition, but also the stability of the Pd alkyl complex. When it was crystallized, the arrangement of the phosphine ligands was found to be exclusively *trans*. To establish the complex's competency in the reaction, it was treated with boronic acid under the reaction conditions, resulting in the formation of the cross-coupling product (Figure 3.4, bottom).

Having established the stability of this type of Pd alkyl complex, Fu and coworkers further studied the oxidative addition of alkyl electrophiles to $(R_3P)Pd^0$.[14] They found strong dependencies on the leaving group, the steric bulk of the electrophile, and the nature of the ligand. The relative reaction rates for different leaving groups mirror those for aryl oxidative additions, with the relative rates being in the order I > Br > OTs > Cl. The relative steric bulk of the electrophile was varied by introducing branching at the γ-, β-, or α-position with respect to the halide. Each of these substrates

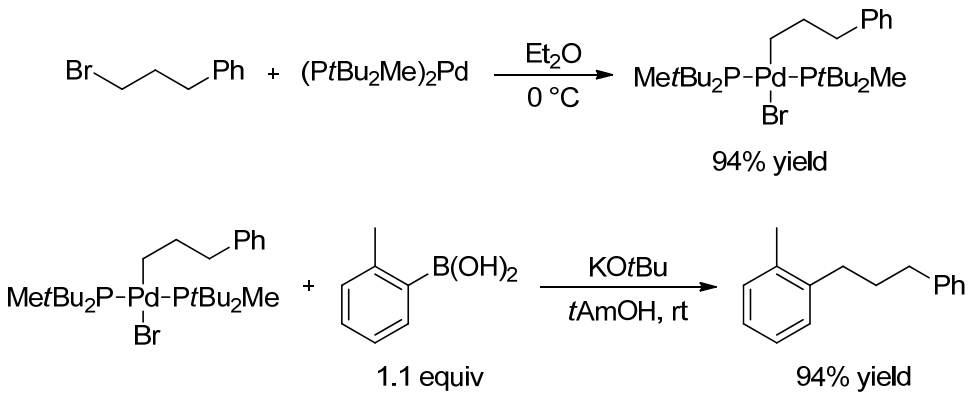


Figure 3.4. Formation of a stable Pd alkyl complex and cross-coupling thereof (adapted from Kirchhoff et al., 2002).

reacted significantly slower than the linear isomer, with the α-branched substrate not undergoing oxidative addition at all. Only ligands that were known to be effective for alkyl cross-coupling reactions were examined (P*t*Bu$_2$Me, PCy$_3$, P*t*Bu$_2$Et, P*t*Bu$_3$), and the relative rates of oxidative addition mirrored those of the overall cross-coupling reaction (P*t*Bu$_2$Me > PCy$_3$ > P*t*Bu$_2$Et > P*t*Bu$_3$). This indicates that oxidative addition, as suspected, is typically the rate-determining step in cross-coupling reactions of alkyl electrophiles.

Lastly, Fu and coworkers investigated the stereochemistry of the Suzuki coupling of alkyl tosylates (Figure 3.5).[12] Subjecting a deuterium-labeled substrate to the reaction conditions in the absence of alkyl borane resulted in oxidative addition followed by β-hydride elimination to yield mainly two alkene isomers (Figure 3.5A). Based on the observed product substitution patterns, it was concluded that oxidative addition proceeded with inversion, in an S_N2-like fashion, analogous to early observations with benzyl halides made by Stille and coworkers.[15] Furthermore, β-hydride elimination occurred with 3:1 selectivity for H over D. The deuterated substrate was then also subjected to the standard reaction conditions, and the cross-coupling product was formed with overall inversion, indicating that reductive elimination proceeded with retention (Figure 3.5B).

Apart from trialkyl phosphines, some examples of *N*-heterocyclic carbene (NHC) Pd complexes catalyzing alkyl cross-coupling reactions have also been published.[4,9,16] In a recent publication, Organ and coworkers reported the use of pre-formed Pd-PEPPSI-IPr for a Suzuki cross-coupling of alkyl and aryl electrophiles with alkyl boranes (Figure

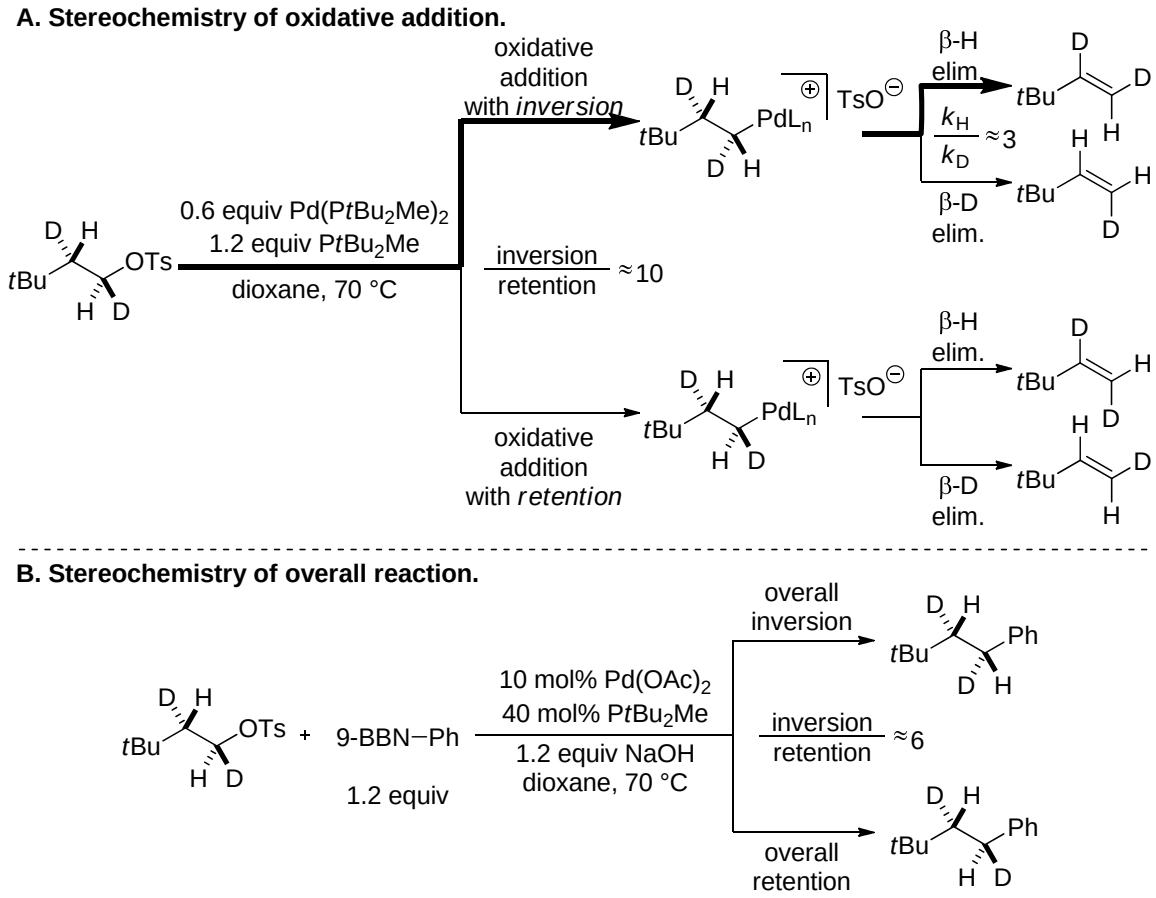


Figure 3.5. Stereochemistry of Suzuki cross-coupling of alkyl tosylates (adapted from Netherton and Fu, 2002).

3.6).[17] The reaction proceeds at room temperature, implying that this catalyst's efficiency is comparable to that of Fu's trialkyl phosphine catalysts.

In an interesting report by Ackermann and coworkers, secondary phosphine oxides and chlorides were found to be competent (pre)ligands for alkyl Kumada-Corriu couplings (Figure 3.7).[18] They do not comment on the nature of the active catalyst; however, it is plausible that the (pre)ligands undergo in situ reduction by the Grignard reagents. It should be noted that alkyl chlorides, which are notoriously poor cross-coupling substrates, are competent substrates in this reaction, and the majority of reactions published in this paper proceed at room temperature.

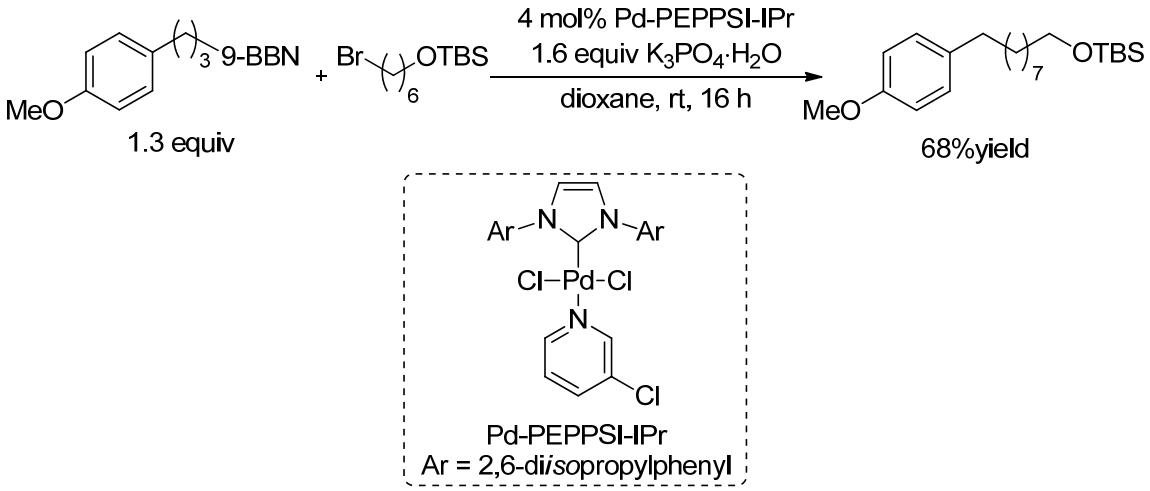


Figure 3.6. NHC-Pd catalyzed alkyl Suzuki coupling (adapted from Valente et al., 2008).

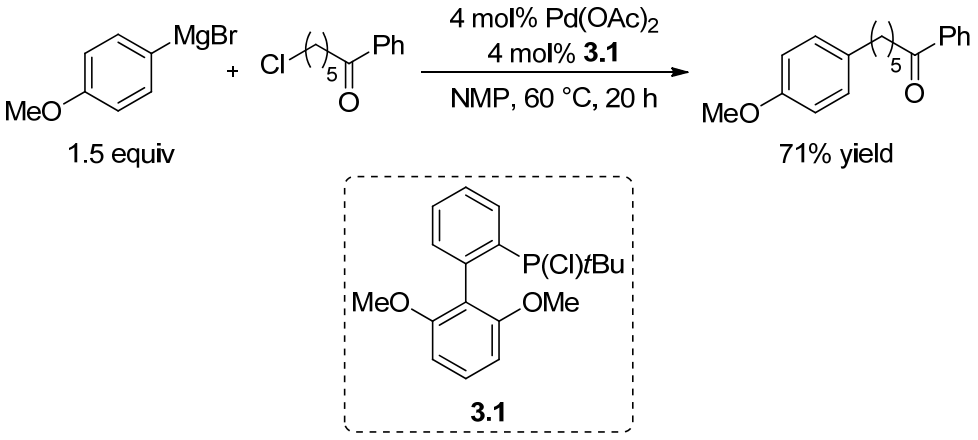


Figure 3.7. Phosphine chloride-Pd catalyzed alkyl chloride cross-coupling (adapted from Ackermann et al., 2010).

Lautens and coworkers were able to develop cascade cross-coupling reactions involving secondary alkyl iodides as electrophiles (Figure 3.8).[19-21] Utilizing norbornene as a temporary tether to bind Pd to the substrate, cascade reactions involving aryl C–H activation, aryl-alkyl cross-coupling, and Heck insertion were achieved. Norbornene was proposed to act as a rigid tether, forcing the Pd into proximity with normally less reactive centers such as an aryl C–H bond and secondary alkyl iodides. Another unusual aspect of this reaction is the Pd redox cycle, involving Pd^0, Pd^{II}, and Pd^{IV}, wherein the alkyl iodide oxidatively adds to Pd^{II} to give a Pd^{IV} intermediate.

In summary, in the absence of specific pathways facilitating alkyl halide oxidative addition, highly active Pd catalysts are typically needed to achieve cross-coupling reactions. Furthermore, the only ligand class that has been systematically studied for these reactions is trialkyl phosphines, with the general conclusion being that only a narrow range of these ligands are competent.

Cross-Coupling of Allyl Electrophiles

In contrast to unactivated alkyl electrophiles, oxidative addition of activated allyl and benzyl electrophiles is generally facile.[8,22] While the prevalent reaction with this type of substrate is the Tsuji-Trost allylic alkylation,[23] a variety of cross-coupling methods have been developed as well. Fundamentally, these reactions differ in that the common Pd π-allyl complex undergoes nucleophilic substitution in the case of soft nucleophiles (Tsuji-Trost reaction) and transmetallation followed by reductive elimination in the case of hard nucleophiles (cross-coupling) (Figure 3.9). Since nucleophilic addition typically occurs

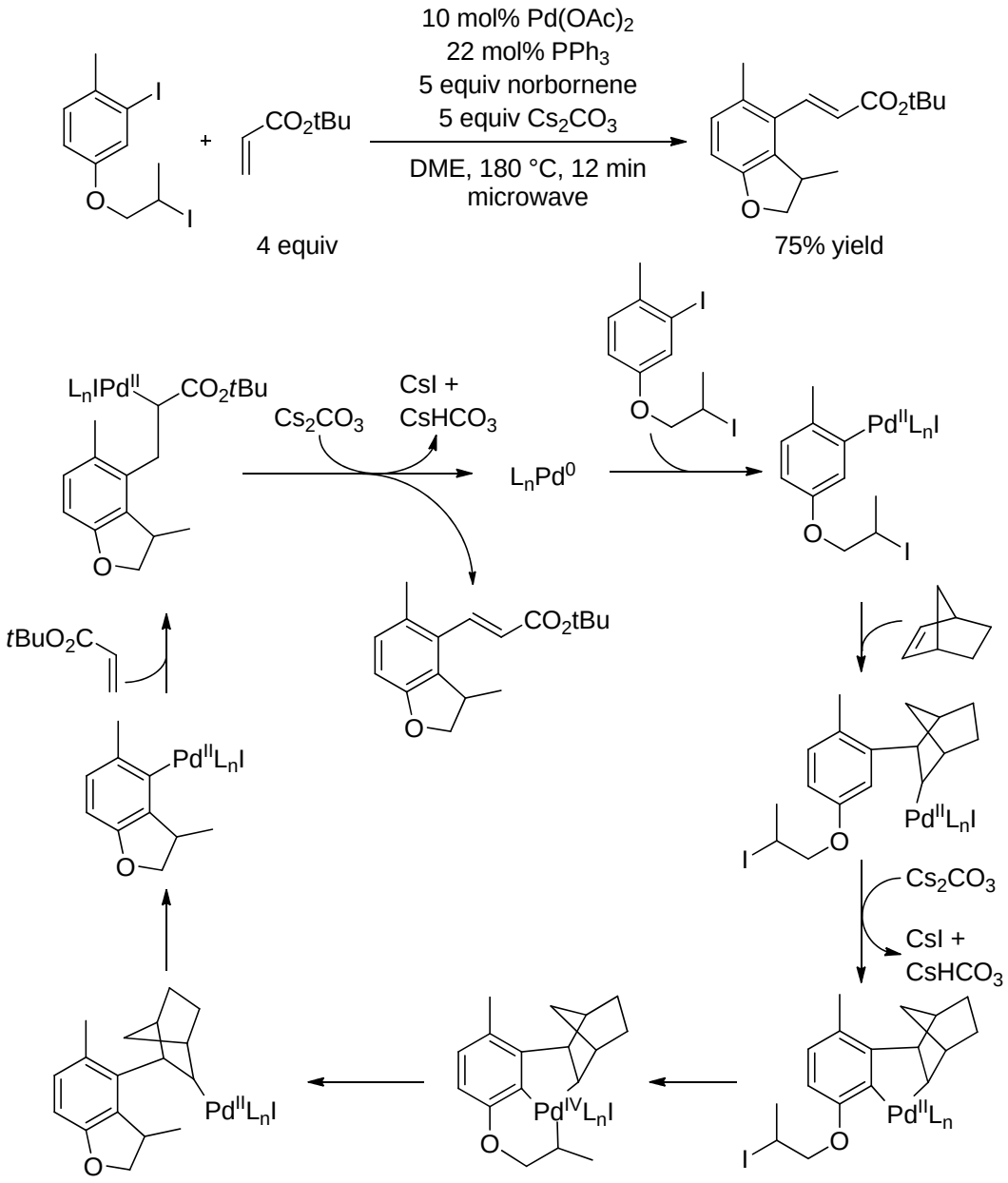


Figure 3.8. Domino aryl alkylation reaction (adapted from Rudolph et al., 2008).

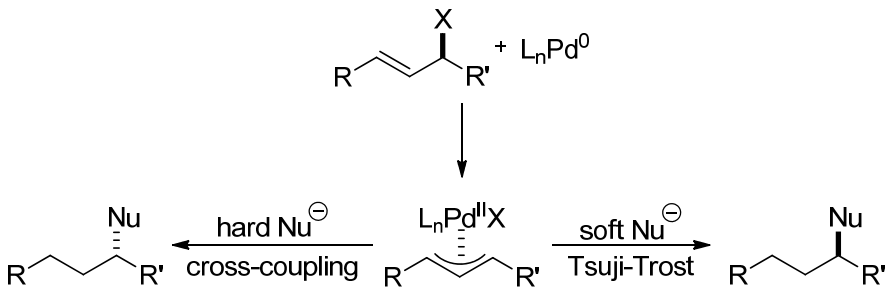


Figure 3.9. Stereochemistry of Tsuji-Trost reaction and allyl electrophile cross-coupling.

with inversion of configuration, while transmetallation and reductive elimination result in retention, the two pathways can be distinguished based on the stereochemical outcome of the reaction.[23]

Cross-coupling reactions of allyl electrophiles are significantly less prevalent than aryl and vinyl electrophile cross-couplings. However, allyl cross-coupling reactions utilize a wide variety of leaving groups, ranging from halides to free alcohols and ethers (vide infra).

Moreno-Mañas and coworkers published a phosphine-free Suzuki-type coupling of allyl bromides in 1995 (Figure 3.10).[24] It should be noted that the linear product isomer was observed exclusively. Interestingly, it was found later that in "ligandless" systems like this, Pd nanoparticles are often formed, which can catalyze the reaction.[25]

Sarkar and coworkers recently reported the use of a novel, air-stable phosphine ligand for the Suzuki coupling of aryl, allyl, and benzyl chlorides (Figure 3.11).[26] Unfortunately, the products of the allyl coupling are not well characterized, and it is unclear which isomer is formed.

Ramu and coworkers reported the use of Pd nanoparticles for a Hiyama coupling of allyl acetates (Figure 3.12).[27] The in situ formation of Pd nanoparticles was confirmed

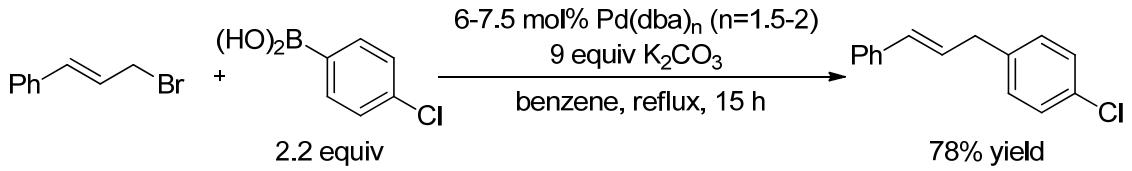


Figure 3.10. Suzuki coupling of allyl bromides (adapted from Moreno-Mañas et al., 1995).

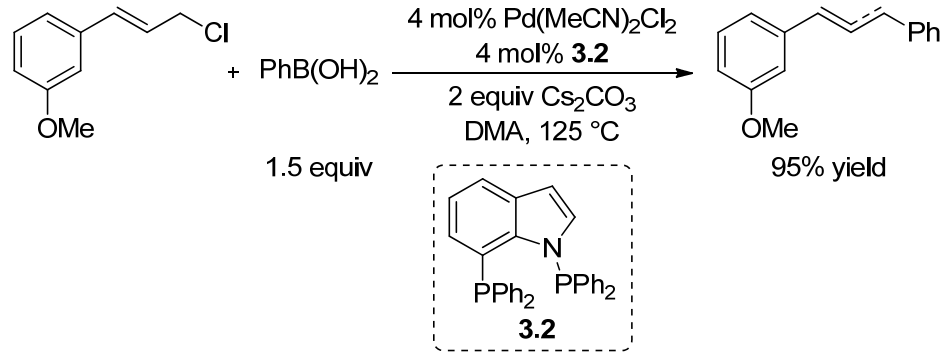


Figure 3.11. Suzuki coupling of allyl chlorides (adapted from Ghosh et al., 2010).

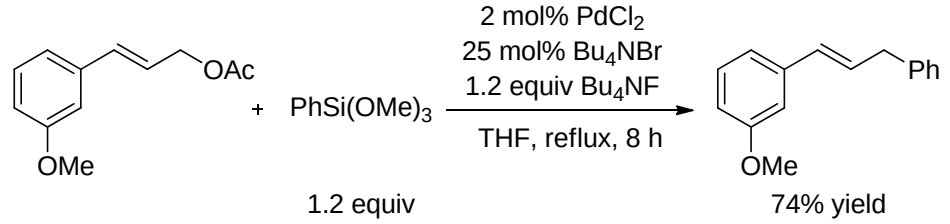


Figure 3.12. Hiyama coupling of allyl acetates (adapted from Dey et al., 2008).

by transition electron microscopy. Confirming the intermediacy of Pd π-allyl complexes,the conformation of the product alkenes was *E* in all cases, regardless of the starting material conformation.

Nishikata and Lipshutz reported the use of allyl ethers in Suzuki couplings in water (Figure 3.13).[28] The reaction was enabled by micellar catalysis using a nonionic amphiphile (PTS, see Figure 3.13). The substrate scope includes several functional

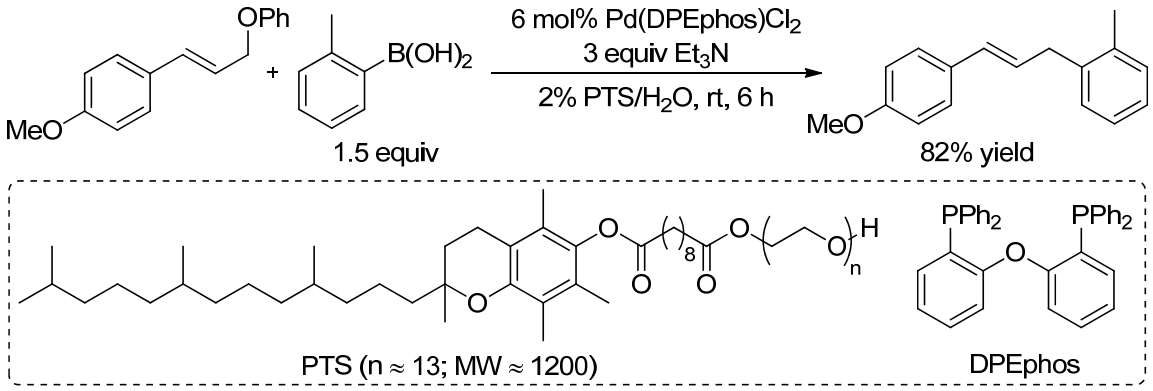


Figure 3.13. Suzuki coupling of allyl ethers (adapted from Nishikata and Lipshutz, 2009).

groups, such as tertiary amines and esters, and aryl- as well as alkyl-substituted allyl ethers. Interestingly, the regioselectivity switched from linear to branched for non-conjugated alkyl-substituted substrates.

Selectivity for the linear products (as showcased in the examples above) can typically be achieved by the use of terminal allyl electrophiles. There are fewer reports involving the selective formation of branched products, despite the potential for asymmetric catalysis. Some interesting methods leading to branched allylic substitution are summarized below.

Sawamura and coworkers developed a γ-selective coupling of unsymmetrically disubstituted allyl systems and aryl boronic acids (Figure 3.14).[29-31] In this system, complete α-to-γ chirality transfer was achieved with several substrates. A mechanism is proposed starting with transmetallation to form a Pd aryl complex, which is added across the alkene from the face of the substituent. β-Acetoxy elimination then furnishes the product. The reaction proceeds with overall *syn*-stereochemistry. To provide support for this mechanism, stoichiometric studies were carried out (Figure 3.14, bottom). Pd aryl

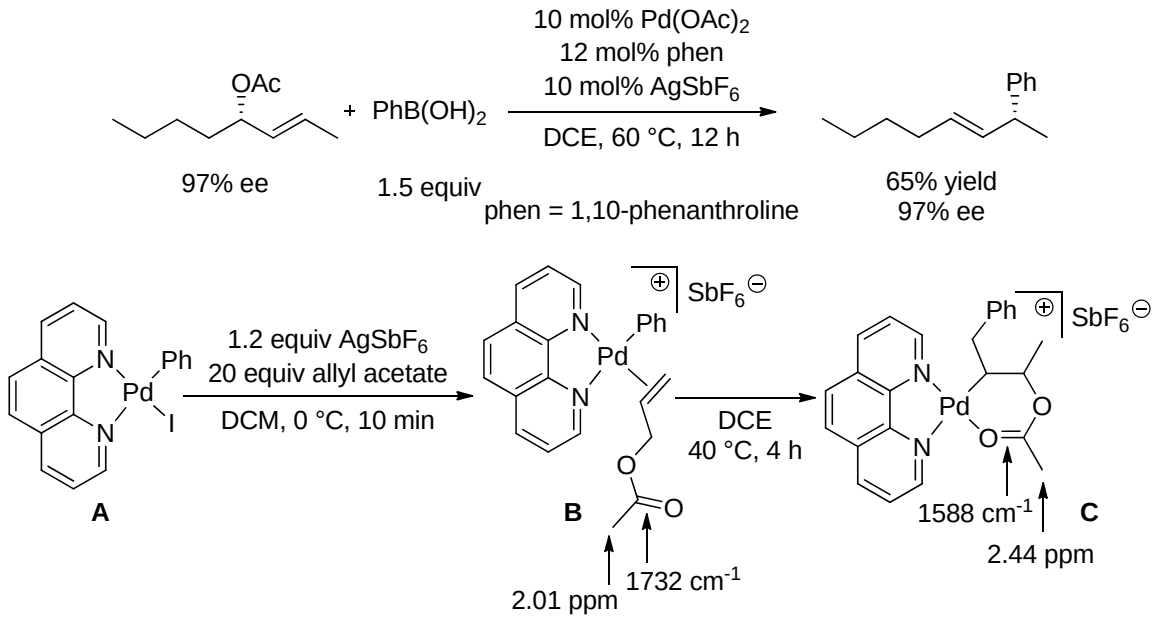


Figure 3.14. Suzuki coupling of allyl esters (adapted from Li et al., 2010).

complex **A** was thus prepared and treated with allyl acetate to give Pd-alkene complex **B** without formation of a Pd π-allyl complex. This complex underwent carbopalladation upon heating to give Pd alkyl complex **C**, supporting the proposed mechanism, which does not proceed via a Pd π-allyl intermediate. IR and ^{1}H NMR of the acetate group in either complex illustrate that the carbonyl in complex **C** is coordinated to Pd.

An unusual enantioselective cross-coupling of allyl carbonates with allylboronic esters was reported by Morken and coworkers (Figure 3.15).[32] Primary allyl carbonates, which typically give linear products in Pd-catalyzed allylic cross-coupling,[33] yieldedbranched products in this system. Using a BIPHEP-Pd catalyst, good yields, excellent regioselectivity, and good to excellent ee's were achieved for a variety of substrates. Selectivity for the branched products was accomplished by using bidentate phosphine ligands with small bite angles. The authors propose that small ligand bite

angles should result in larger C-Pd-C angles, and thus increased distance between C1 and C1', which should in turn disfavor 1,1'-elimination.

Nearly identical results were obtained with regioisomeric substrates (Figure 3.15A), suggesting that both reactions proceed via a common intermediate, such as a Pd π-allyl complex (Figure 3.15B). The authors proposed two potential mechanisms

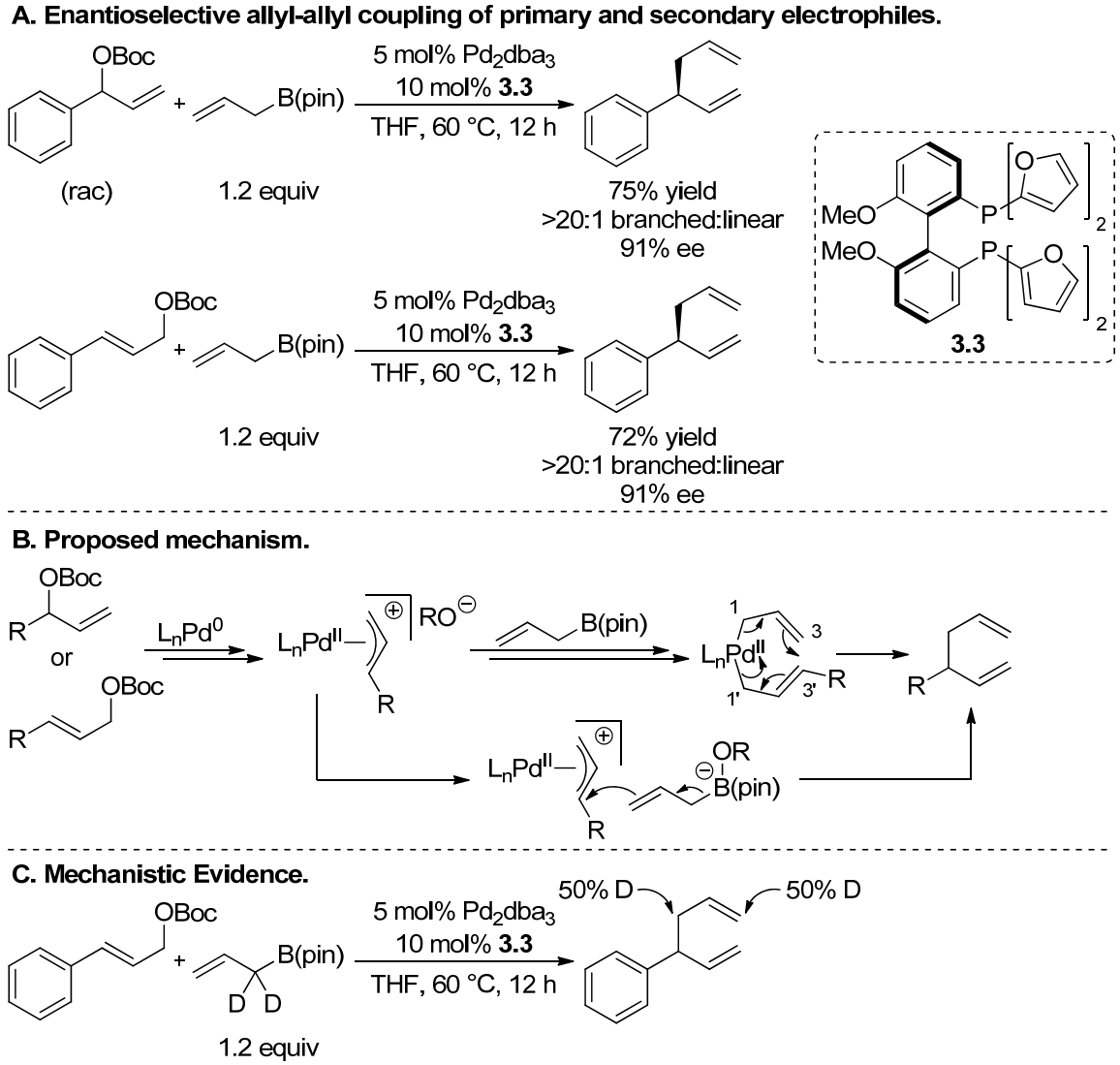


Figure 3.15. Enantioselective allyl-allyl cross-coupling (adapted from Zhang et al., 2010).

involving 3,3'-elimination from an intermediate bis(allyl)palladium species or external attack on a Pd π-allyl complex. In order to distinguish between the two, a deuterium labeling experiment was carried out using isotopically labeled allylB(pin) (Figure 3.15C). Deuterium scrambling in the product was observed (with no scrambling in recovered allylB(pin)). This result, in combination with the enantioselectivity achieved with racemic secondary carbonate substrates, suggests that both the carbonate substrate and the allyl boron substrate form η^3-allyl Pd complexes at some point during the reaction.

Unprotected allylic alcohols were used as coupling partners in a Suzuki coupling by Tsukamoto and coworkers (Figure 3.16).[34,35] They proposed that the boronic acid acts as a Lewis acid to activate the alcohol and to enable oxidative addition.[36] Interestingly, enantiomerically enriched secondary allylic alcohols led to racemic products, presumably via attack by nucleophilic Pd^0 or phosphine.[35] This type of epimerization has been previously described by Granberg and Bäckvall.[37]

In summary, there are several interesting methodologies for the cross-coupling of allyl electrophiles, and a wide variety of leaving groups has successfully been used. However, linear products are often formed preferentially, and the selectivity is typically substrate-dependent. Methods yielding branched products are scarcer, and enantioselectivity is rarely achieved. Further research addressing these problems is therefore needed.

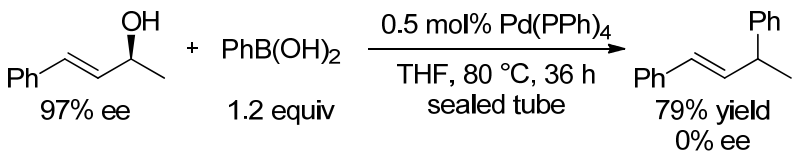


Figure 3.16. Suzuki coupling of allyl alcohols (adapted from Tsukamoto et al., 2008).

Approach to the Allylic C–H Functionalization

Following the scenario outlined in the introduction, we envisioned accessing unsymmetrical, disubstituted π-allyl Pd intermediates using homoallylic tosylate starting materials (Figure 3.17.A). Building on our previous experience with stabilized Pd alkyl intermediates, our proposed approach would take advantage of a controlled β-hydride elimination/alkene insertion sequence to access a Pd π-allyl complex, which would then

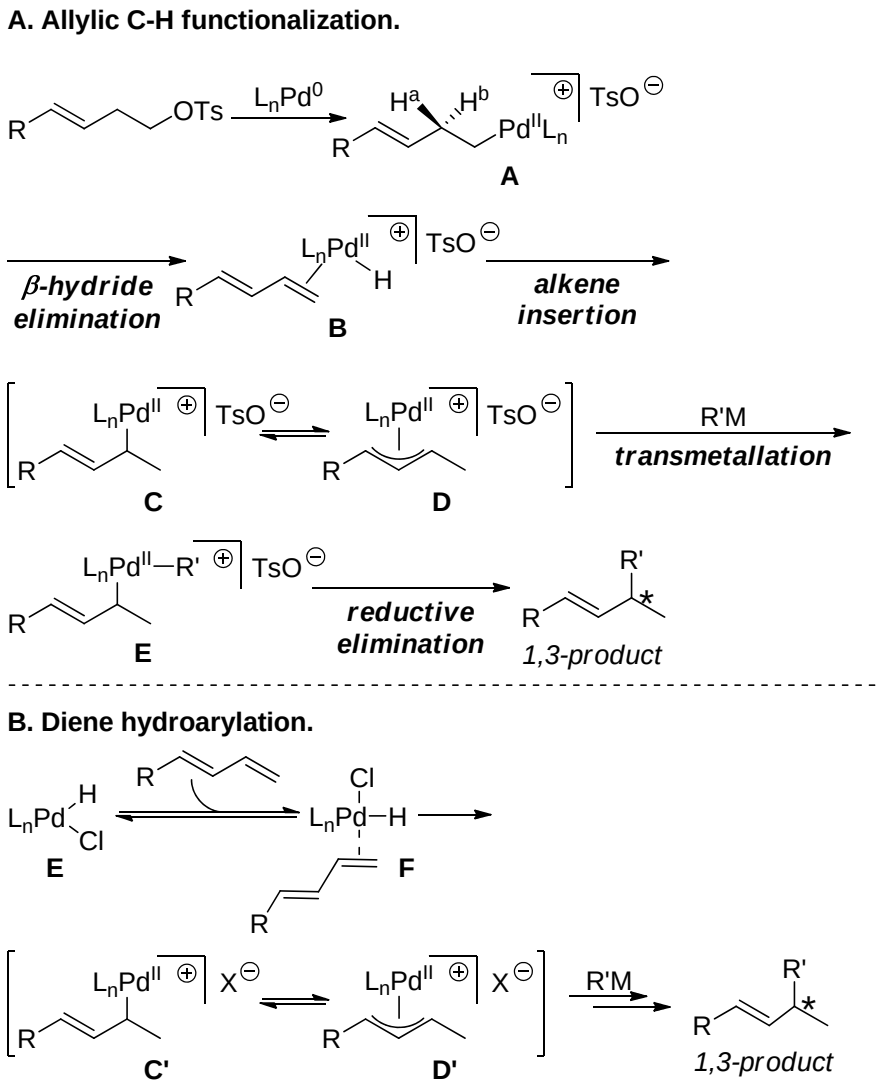


Figure 3.17. Proposed coupling of homoallyl tosylates (A) compared with diene hydroarylation (B).

be further functionalized. Specifically, we hypothesized that a homoallyl tosylate would undergo oxidative addition to Pd^0 to yield Pd alkyl intermediate **A**. As this primary Pd alkyl complex is not stabilized, it would undergo β-hydride elimination to form a diene, along with Pd hydride **B**. The diene would then reinsert into the Pd–H bond to form Pd alkyl **C**, which is isomeric to **A** and can be stabilized as a Pd π-allyl complex **D**. It should be noted that this proposed Pd π-allyl intermediate (**D**) is analogous to one proposed in a hydroarylation of dienes previously reported from our laboratory (Figure 3.17B).[38] Based on this previous work, we were confident that the Pd π-allyl complex, once formed, should undergo transmetallation and reductive elimination to form the desired product.

In addition to being mechanistically unique, this unusual way of accessing Pd π-allyl species has the potential to be expanded into an asymmetric reaction. The enantioselectivity may be determined by the selectivity for H^a or H^b in the β-hydride elimination step (**A** → **B**). Following this step, the Pd could remain bound to one specific face of the substrate, ultimately resulting in substitution on the same enantiotopic face, and selective formation of one enantiomer.

The implementation of this mechanistic scenario posed several significant challenges. The success of the proposed reaction depended heavily on the relative stability of the Pd π-allyl complex (**D**). If **D** was sufficiently stable, transmetallation and reductive elimination to form the desired product should be possible. However, formation of either a 1,3-diarylated product (desired) or a 1,1-diarylated product (undesired) would be possible (**D** → **E**, Figure 3.17A, vs **D** → **F**, Figure 3.18). If the Pd

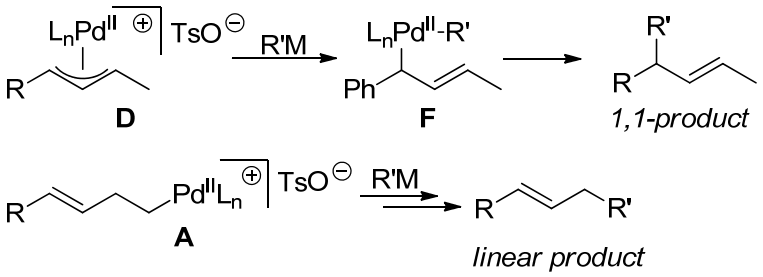


Figure 3.18. Formation of possible isomeric products.

π-allyl complex was too unstable under the reaction conditions (or if π-allyl complex formation was not feasible), there were two possible outcomes: a diene product could be formed via β-hydride elimination from **A** or **C** followed by diene dissociation, or rapid transmetallation and reductive elimination could occur to form a linear product (Figure 3.18).

Additionally, as outlined in the introduction, the Pd catalyst would have to be finely tuned in order to perform the different steps of the reaction. Initially, the Pd catalyst would have to undergo oxidative addition with a primary homoallyl electrophile. The oxidative addition of homoallylic tosylates or halides to Pd^0 has not been previously reported to the best of our knowledge. We initially assumed that it would proceed analogously to unactivated alkyl tosylates, as described by Fu and coworkers.[12] This would require an electron-rich Pd complex, using bulky, strongly donating ligands such as trialkyl phosphines. Additionally, the Pd catalyst would have to be sufficiently electron-poor to prevent dissociation of the diene in intermediate **B**, to avoid formation of an undesired diene product. These opposing requirements would have to be balanced toachieve the proposed reaction, and it was not obvious how that balance would be achieved.

Lastly, the reaction conditions would have to be carefully tuned to avoid base-promoted elimination of TsOH, which would again lead to diene formation (without the involvement of Pd). This would limit the choice of bases, which would be needed to promote transmetallation with boron reagents.

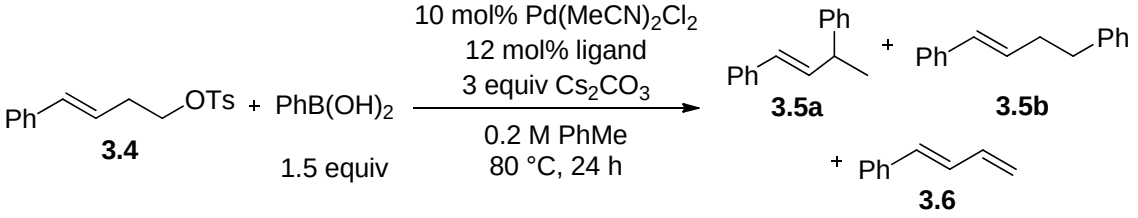
Reaction Development Using Phosphine Ligands

The conditions that were initially explored were carefully chosen based on the potential problems outlined above. For several reasons, 4-phenyl-3-butenyl tosylate (**3.4**) was a logical choice for the initial substrate. Tosylates are conveniently accessed from alcohols, and their rate of oxidative addition to Pd had been shown by Fu and coworkers to be comparable to alkyl halides.[12,14] The tosylate would also constitute a non-coordinating counterion for Pd, to increase its electrophilicity and prevent dissociation of the diene. The phenyl substituent on the alkene would give rise to a conjugated system, which should prevent formation of 1,1-substituted product (vide supra). While this choice of a conjugated alkene could lead to limited reaction scope, we were confident that alkyl-substituted alkenes would ultimately be competent, based on the previously published diene hydroarylation.[38]

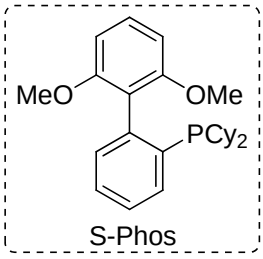
As the transmetallating agent, $PhB(OH)_2$ was chosen for its commercial availability, ease of use, and low toxicity. Additionally, it has been used by Fu and coworkers in a Suzuki coupling of alkyl electrophiles.[13] In this report, Fu and coworkers found KO*t*Bu to be the most efficient base; however, with our substrate, KO*t*Bu led to elimination of TsOH even in the absence of Pd catalyst. Therefore, Cs_2CO_3 was chosen as a weaker base.

Phosphines were chosen as the initial ligand class to be evaluated based on the reports by Fu and coworkers of their successful use in the cross-coupling of alkyl electrophiles.[10-14] A range of commercially available phosphine ligands were thus evaluated for our desired reaction under conditions similar to those published by Fu and coworkers (Table 3.2). Gratifyingly, P*t*Bu$_3$ gave the desired product **3.5a** with good selectivity (entry 1). Additionally, to our surprise, P(*o*-tol)$_3$ selectively gave the linear product **3.5b** (entry 4). Based on Fu and coworkers' reports, triaryl phosphines had not been expected to result in significant product formation. Interestingly, P(*o*-tol)$_3$ and P*t*Bu$_3$ are similar in size, having cone angles of 194° and 182°, respectively.[39] The shift in mechanism from isomerization and formation of a Pd π-allyl complex followed bytransmetallation to transmetallation of a primary Pd alkyl complex was therefore likely caused by a difference in ligand electronics.

Table 3.2. Initial ligand screen.



entry	ligand	**3.5a** (% yield)[a]	**3.5b** (% yield)[a]	**3.6** (% yield)[a]
1	P*t*Bu$_3$	52	3	41
2	PCy$_3$	28	17	51
3	P*n*Bu$_3$	10	<2	79
4	P(*o*-tol)$_3$	<2	31	13
5	PPh$_3$	17	3	66
6	S-Phos	4	10	76
7	dcpe	<2	<2	13

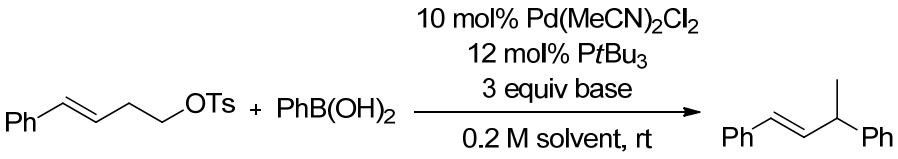


[a] determined by GC analysis using internal standard and response factor.

Other alkyl or aryl phosphines resulted in lower product yields and/or poor branched:linear (B:L) selectivity. In addition to simple triaryl and trialkyl phosphines, a biaryl phosphine (S-Phos) was tested, and found to give poor yield and selectivity (entry 6). It should also be noted that bidentate phosphines such as 1,2-bis(dicyclohexylphosphino)ethane (dcpe) led to exclusive formation of the undesired diene product in low yield (entry 7). With these initial results in hand, we decided to optimize the reaction for both the branched and linear product, using P*t*Bu$_3$ and P(*o*-tol)$_3$, respectively.

In the case of the P*t*Bu$_3$-promoted reaction, we found that the reaction could be performed at room temperature with no decrease in product yield (Table 3.3, entry 1). Examination of different bases showed that K_2CO_3 gave similar outcomes to Cs_2CO_3 with regard to both yield and branched:linear selectivity (B:L) (entry 2); other bases gave poor results. Solvents were evaluated next, and *t*AmOH was found to slow the reaction, but also to substantially reduce the amount of diene side product and increase product

Table 3.3. Optimization with P*t*Bu$_3$.



3.4 1.5 equiv **3.5a**

entry	base	solvent	time (h)	**3.5a** (% yield)[a]	B:L	diene (**3.6**) (% yield)[a]
1	Cs_2CO_3	PhMe	24	53	>20:1	36
2	K_2CO_3	PhMe	24	44	>20:1	44
3	K_2CO_3	*t*AmOH	38	80	>20:1	6
4[b]	K_2CO_3	*t*AmOH	38	<2	N/A	10

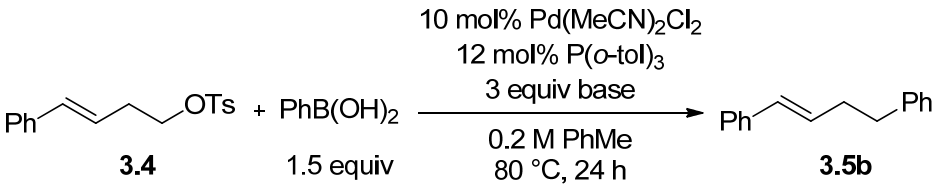
[a] determined by GC analysis using internal standard and response factor. [b] with 20 mol% P*t*Bu$_3$.

yield (entry 3). Finally, the amount of ligand relative to Pd was varied. When the amount of P*t*Bu$_3$ was increased to a 2:1 phosphine:Pd ratio, no conversion was observed (entry 4), indicating the active catalyst was likely a monoligated Pd species. This was in agreement with our previous finding that bidentate dcpe was incompetent.

In parallel with the optimization of the P*t*Bu$_3$-promoted reaction, P(*o*-tol)$_3$ was evaluated under analogous reaction conditions. However, only the change from Cs_2CO_3 to K_2CO_3 resulted in increased yield (Table 3.4). Lowering the temperature gave trace amounts of product, and changing the solvent also did not improve the results. As we were primarily interested in the branched product and the potential to develop an asymmetric variant of our reaction, we chose not to further optimize this reaction, and instead focus on the branched product.

With optimized conditions for the branched product in hand, we decided to examine whether the alkene was required for the reaction. Thus, phenethyl tosylate (**3.7**) and phthtalimide-substituted tosylate **3.8** were subjected to the reaction conditions

Table 3.4. Optimization for linear product.



entry	base	**3.5b** (% yield)[a]	L:B	diene (**3.6**) (% yield)[a]
1	Cs_2CO_3	31	>20:1	13
2	K_2CO_3	54	>20:1	7

[a] determined by GC analysis using internal standard and response factor.

(Figure 3.19). Having observed similar reactions of benzylic and allylic substrates before,[40] we reasoned that a homobenzylic tosylate (**3.7**) might be a competent substrate. Phthalimides have been proposed by Feringa and coworkers to coordinate to Pd.[41] We therefore hypothesized that this interaction might provide sufficient stabilization for our proposed Pd alkyl intermediate (similar to the example reported by Larhed and coworkers,[42] see chapter 1). In our case, however, no product was observed with either substrate.

In order to further explore the scope of the reaction, it was scaled to 0.5 mmol. Unfortunately, on this scale the results proved to be irreproducible. Although we could not definitively identify the problem, we hypothesized that mixing issues in larger flasks led to the inconsistent results, as the reactions are both concentrated and heterogeneous. The use of different sizes and shapes of stirbars and flasks changed the outcome of the reaction, but did not solve the reproducibility issues.

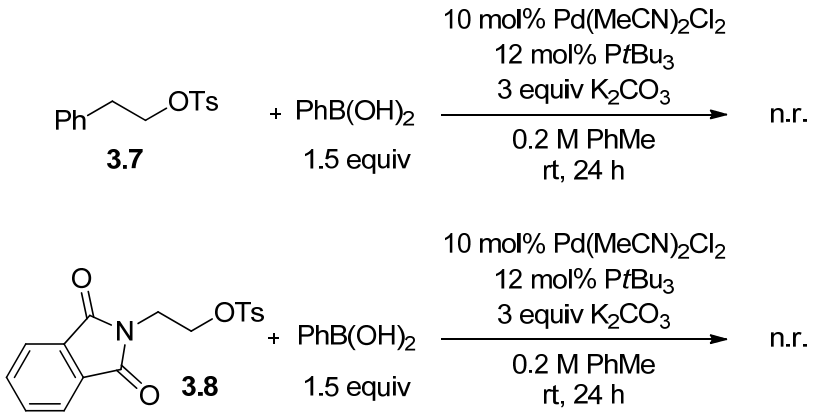


Figure 3.19. Evaluation of non-alkenyl substrates with P*t*Bu$_3$.

Reaction Development Using Quinox Ligands

In order to avoid these problems, we decided to evaluate other ligands in hopes of discovering a more robust system. Because of their ready availability, stability and reactivity towards alkene substrates,[43-47] Pd complexes of bidentate nitrogen-based ligands were tested. Excitingly, it was found that quinoline-oxazoline (Quinox)-type ligands were capable of promoting the reaction (Figure 3.20). Of note, these reactions could be performed on the benchtop using standard Schlenk technique, whereas those using P*t*Bu$_3$ had to be set up in a glove box. Furthermore, Quinox and Pd(Quinox)Cl$_2$ are air stable, adding to the practicality of this reaction.

While this result was exciting, it was unexpected, as these ligands have not been reported to promote alkyl cross-coupling reactions. A closely related pyridine-oxazoline ligand (Pyrox) was also successful, although the product yield was substantially reduced. Bipyridine (bipy), on the other hand, did not give any desired product. Our group has previously shown that Quinox-type ligands show unique reactivity toward alkenes in Wacker-type reactions, and mechanistic data strongly indicate that this is due to their

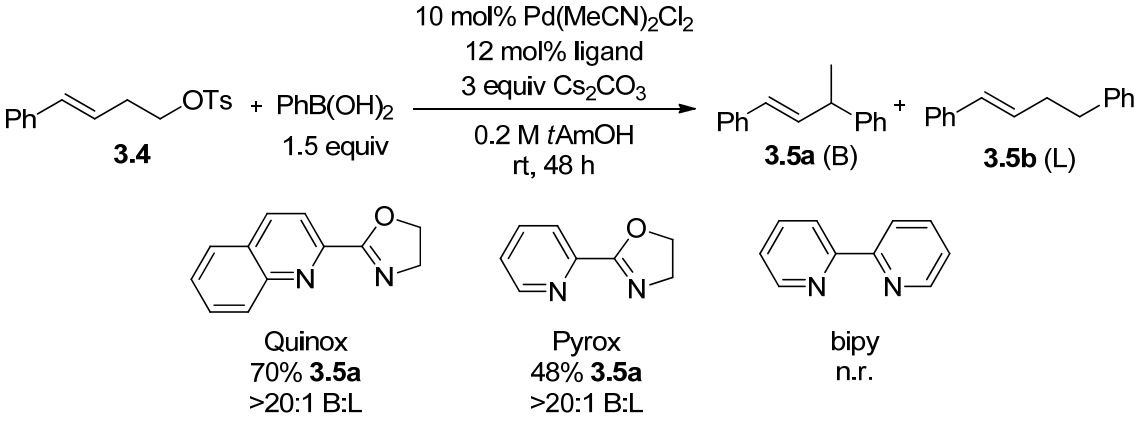
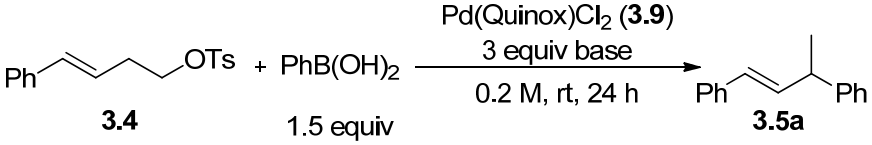


Figure 3.20. Screen of bidentate pyridine-based ligands.

electronic asymmetry.[43,48] As bipy does not promote the cross-coupling reaction, it seems reasonable that two electronically distinct binding sites on Pd may be necessary in this reaction. Given that nitrogen-based ligands were capable of promoting this reaction, as well as the requirement for electronic asymmetry, we hypothesized that the oxidative addition of homoallyl electrophiles may proceed through a mechanism distinct from alkyl electrophiles. This hypothesis was tested further under optimized reaction conditions (vide infra).

We thus explored the reaction conditions using Pd(Quinox)Cl_2 as the catalyst (Table 3.5). It was found that *t*AmOH and *i*PrOH were competent solvents, with *t*AmOH giving higher selectivity, but *i*PrOH leading to higher yield (entries 1 and 2). Bases were evaluated next, wherein K_2CO_3 led to better selectivity in *i*PrOH (entry 4), and KF·$2H_2O$ resulted in excellent yield and selectivity in both *t*AmOH and *i*PrOH (entries 5 and 6). At

Table 3.5. Optimization using Quinox.



3.4 **3.5a**

entry	**3.9** (mol%)	base	solvent	**3.5a** (% yield)[a]	B:L
1	10	Cs_2CO_3	*t*AmOH	58	>20:1
2	10	Cs_2CO_3	*i*PrOH	72	16:1
3	10	K_2CO_3	*t*AmOH	57	23:1
4	10	K_2CO_3	*i*PrOH	73	>20:1
5	10	KF·$2H_2O$	*t*AmOH	90	>20:1
6	10	KF·$2H_2O$	*i*PrOH	86	>20:1
7	2.5	KF·$2H_2O$	*i*PrOH	90	>20:1
8[b]	2.5	KF·$2H_2O$	*i*PrOH	89	>20:1

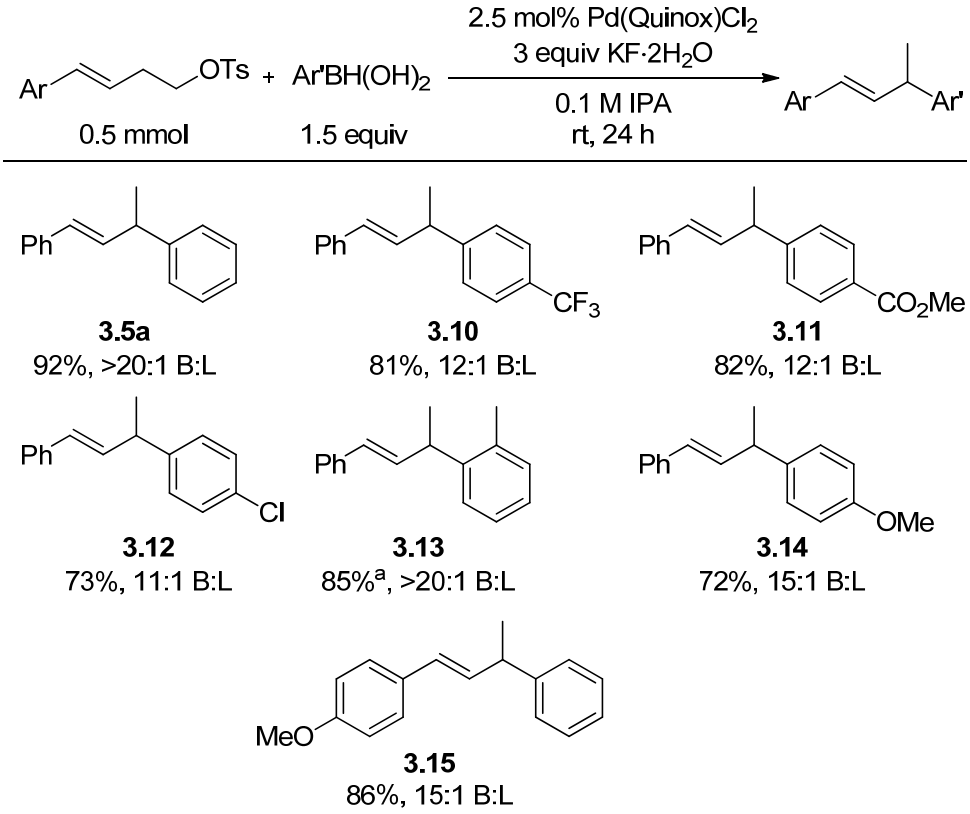
[a] determined by GC analysis using internal standard and response factor. [b] 0.1 M in substrate

this point, the amount of Pd(Quinox)Cl_2 was lowered to 2.5 mol%, and the reaction was diluted to 0.1 M without loss in yield or selectivity (entries 7 and 8).

Initial Scope and Mechanistic Studies

Gratifyingly, this reaction could be scaled to 0.5 mmol without problems, and the scope of the reaction with regard to boronic acids was explored. Electron-poor as well as electron-rich arylboronic acids were successful, giving good to excellent yields and selectivities (Table 3.6). When *o*-tolylboronic acid was used, the reaction still proceeded, although at a much reduced rate. The scope with regard to the tosylate substrate has yet

Table 3.6. Scope using different boronic acids.



[a] 72 h.

to be fully developed (vide infra). Thus far, a 4-$MeOC_6H_4$-substituted substrate resulted in comparable yield and selectivity to the Ph-substituted substrate.

We then decided to evaluate nonalkenyl substrate **3.7** using Pd(Quinox)Cl_2 (Figure 3.21). However, no conversion of substrate was observed, indicating that the alkene is necessary for the reaction. Several experiments were performed to further investigate the mechanism of this reaction. As the mechanism of oxidative addition in this reaction was unclear, homoallyl bromides and chlorides were evaluated (Table 3.7). While the bromide reacted at a comparable rate to the tosylate, the reaction of the chloride was markedly slower. This result is similar to Fu and coworkers' studies, where it was found that tosylates are intermediate between bromides and chlorides in reactivity toward oxidative addition.[14] Interestingly, the branched:linear ratio is excellent for the

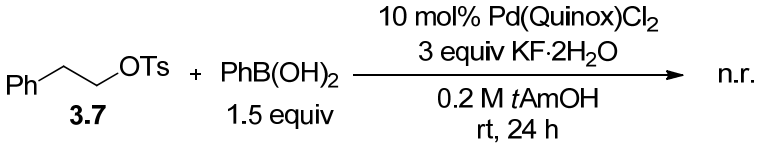
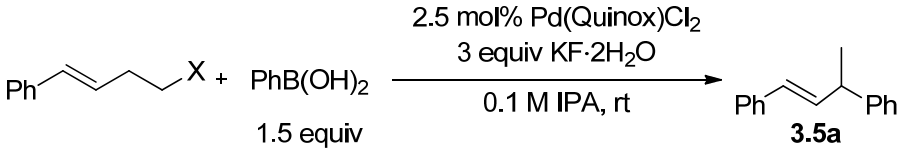


Figure 3.21. Evaluation of nonalkenyl tosylate with Pd(Quinox)Cl_2.

Table 3.7. Evaluation of homoallyl halides.



entry	X	time (h)	**3.5a** (% yield)[a]	B:L
1	Br (**3.16**)	24	87	10:1
2	Cl (**3.17**)	72	19	>20:1

[a] determined by GC analysis using internal standard and response factor.

chloride, but substantially decreased for the bromide (compared to the chloride or tosylate). While the influence of halide additives on regio- and enantioselectivity in Tsuji-Trost-reactions has been reported, the mechanism of influence in this case is unclear.[49,50]

Considering the unusual ligand as well as the requirement of the alkene in the substrate, it appeared that homoallyl tosylates (and bromides) undergo oxidative addition with relative ease, compared to nonactivated alkyl electrophiles. It seemed plausible at this stage that the alkene binds to Pd in an initial step, making oxidative addition more facile than would ordinarily be expected (Figure 3.22). To further investigate the oxidative addition, secondary homoallylic tosylate **3.18** was synthesized and submitted to the reaction conditions (Figure 3.23). Secondary alkyl electrophiles are generally considered to be less reactive toward oxidative addition with Pd^0 than primary ones;[21] however, in our case, the product yield and selectivity were comparable to those of the

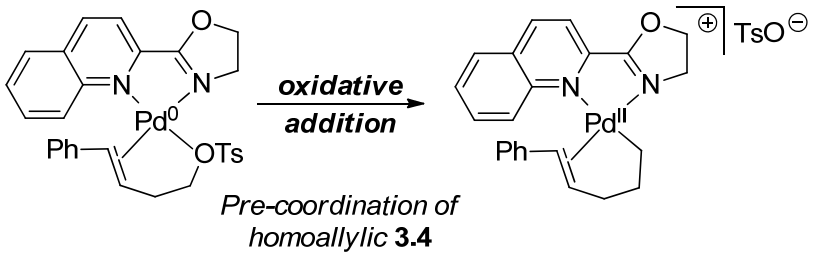


Figure 3.22. Proposed oxidative addition of pre-coordinated substrates.

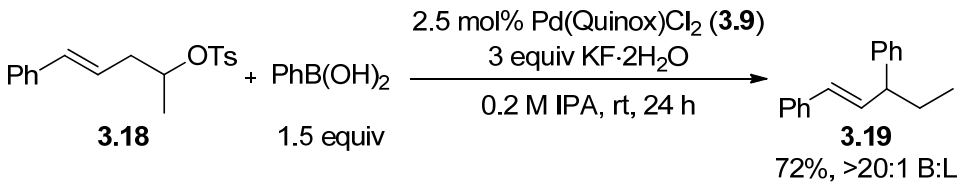


Figure 3.23. Evaluation of secondary tosylate **3.18**.

primary substrate (**3.4**). This further supports our hypothesis that alkene coordination facilitates oxidative addition in this type of reaction, which may lead to different reactivity profiles than are typically observed. To further probe this hypothesis, bishomoallylic substrate **3.20** was subjected to the reaction conditions (Figure 3.24).

While the reaction did proceed, the product yield was greatly diminished, which is in agreement with this rationale. A cyclic transition state leading to oxidative addition may be less favored with a longer carbon chain, leading to a less efficient reaction (Figure 3.22). However, the longer chain may also influence the β-hydride elimination/reinsertion sequence, which has to occur two times with this substrate to form the π-allyl intermediate, which may also contribute to a less efficient reaction (Figure 3.25). Overall, this result showcases that the concept of "chain-walking" can be expanded beyond homoallylic substrates, although it would require additional optimization to achieve an efficient reaction. Finally, we were interested in the efficiency of diene insertion into the Pd–H bond, specifically whether diene dissociation from the Pd hydride intermediate occurred. Specifically, crossover experiments would be performed by addition of a diene (**3.21**) to the reaction mixture (Figure 3.26). If the diene dissociated from the Pd hydride intermediate, added diene **3.21** could coordinate to it, and the hydroarylation of **3.21** would be observed.

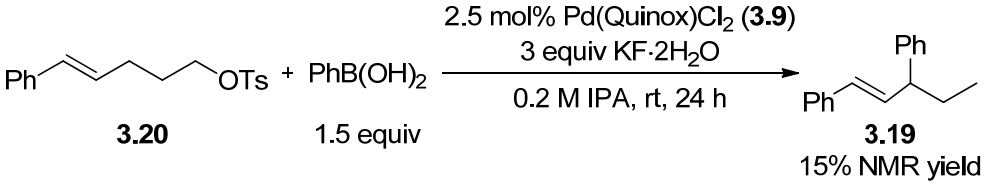


Figure 3.24. Evaluation of bishomoallylic tosylate **3.20**.

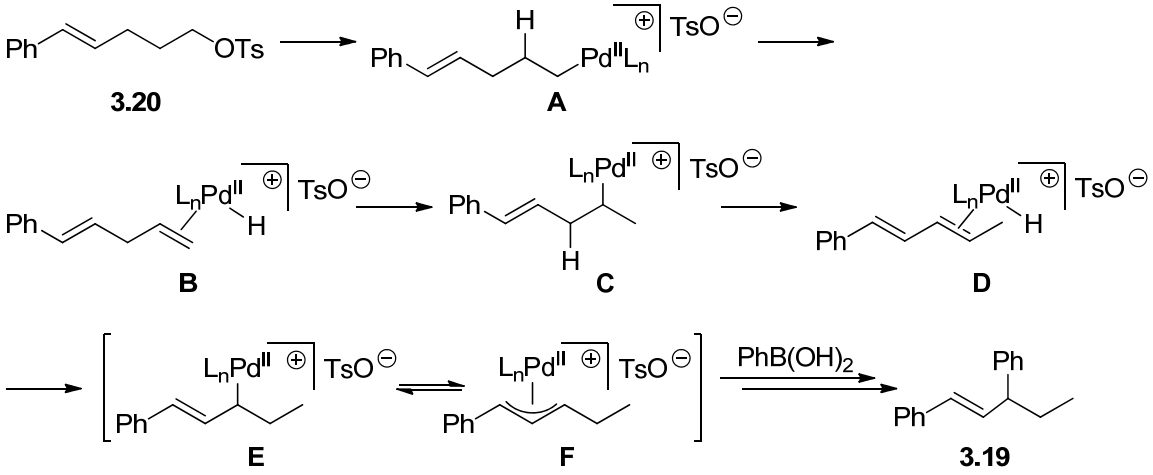


Figure 3.25. Proposed "chain-walking" mechanism for bishomoallylic substrate **3.20**.

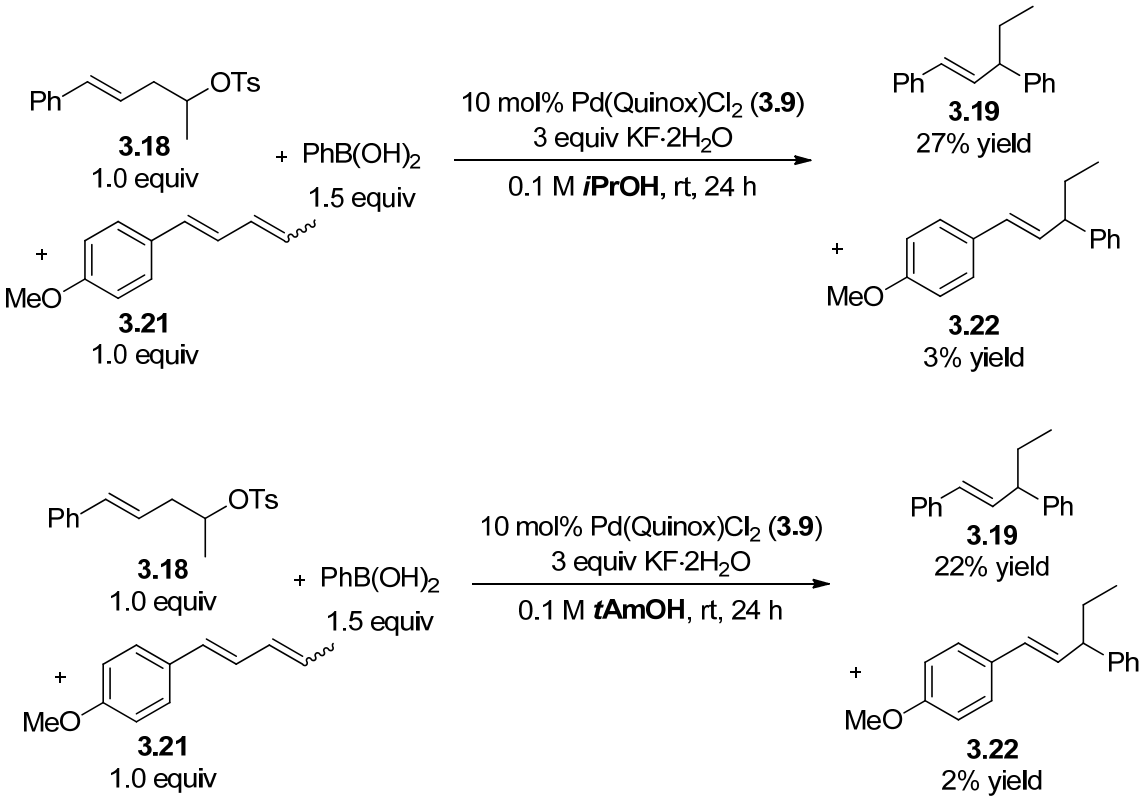


Figure 3.26. Crossover experiments.

This experiment could potentially be complicated by the fact that Pd^{II} is capable of oxidizing IPA. In previous systems, Pd-catalyzed oxidation of *i*PrOH solvents has been observed, and Pd hydrides formed in the alcohol oxidation further reacted with the alkene substrates to give hydrofunctionalization products.[38,51-53] The allylic C–H functionalization proceeds in *t*AmOH, a tertiary alcohol, with similar efficiency to IPA, indicating that alcohol oxidation (even if it is occurring as a background reaction) is not crucial for the reaction. However, "additional" Pd hydride formed via alcohol oxidation might complicate the crossover experiment, which was therefore performed in both IPA and *t*AmOH.

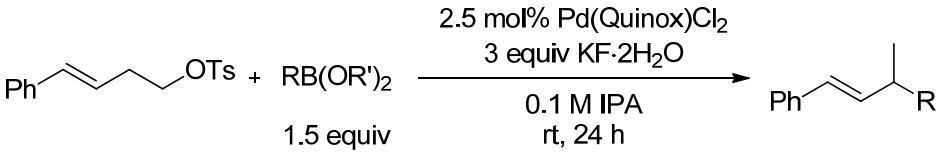
The crossover experiment was performed as described above in both *i*PrOH and *t*AmOH, with comparable results. In both cases, only small amounts of crossover product were observed, indicating that diene dissociation does not pose a significant problem in this reaction.

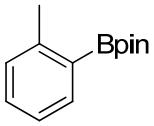
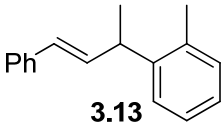
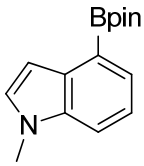
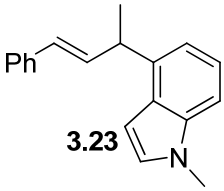
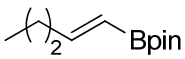
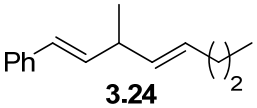
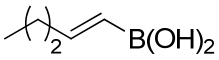
Summary and Outlook

In summary, we have developed a Pd/phosphine-catalyzed allylic C–H arylation, which showed a strong dependence on phosphine sterics and electronics. While this is mechanistically interesting, we were unable to develop a useful synthetic method on the basis of this reaction. Turning to other potential ligand classes, we discovered that $Pd(Quinox)Cl_2$ is a competent catalyst for the same reaction, and have begun to investigate the scope and mechanism of this mechanism.

Further exploring the scope of the allylic C–H arylation, it was found that boronic esters (in addition to boronic acids) are competent transmetallating agents (Table 3.8).

Table 3.8. Preliminary scope using boronic esters.



entry	$RB(OR')_2$	product	yield, selectivity
1		 **3.13**	74%, >20:1 B:L[a]
2		 **3.23**	72%, >20:1 B:L[b]
3		 **3.24**	64%[c]
4		**3.24**	50%[c]

[a] isolated yield from one experiment on 0.5 mmol scale. [b] NMR yield on 0.1 mmol scale. [c] NMR yield on 0.1 mmol scale, as part of a complex mixture of products.

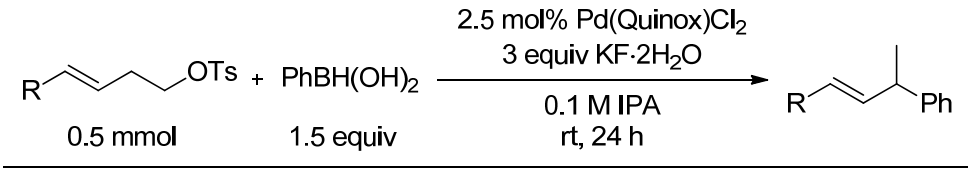
As a direct comparison, *o*-tolBpin gave the desired product in 74% yield and excellent selectivity after 24 h (Table 3.8, entry 1). With *o*-tol$B(OH)_2$, the reaction was significantly slower, giving 85% after 72 h (see Table 3.6). Excitingly, the scope using pinacol boronic esters was found to be broader than with boronic acids, including a heteroaromatic boronic ester (entry 2). Heteroaromatic boronic acids did not yield any desired products. Vinyl boronic esters as well as vinyl boronic acids were found to give the corresponding products, although in reduced yields and as complex mixtures of products, presumably due to isomerization of the primary products (entries 3 and 4).

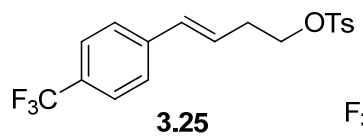
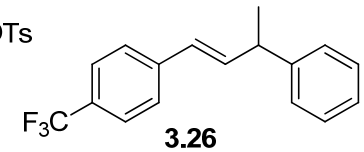
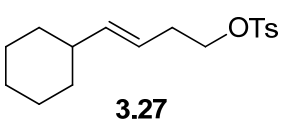
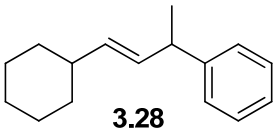
While these results require additional optimization, they indicate that the scope of the reaction may be expanded beyond aryl boronates.

In addition to the alkene substrates described above, an electron-poor aryl-substituted alkene as well as an alkyl-substituted alkene were evaluated (Table 3.9). The preliminary results shown in Table 3.9 display the potential for further expansion of the scope with different homoallyl tosylates, notably with alkyl-substitution. In the previously published diene hydroarylation, the selectivity for this type of substrate for the 1,3- over 1,1-diarylated products has been found strongly dependent on the size of the substituent.[38] Based on our proposed mechanism, we expect a similar dependence with the allylic C–H functionalization.

As a long-term goal, we are pursuing an asymmetric version of this reaction. In initial studies using chiral Quinox derivatives, it was found that *t*BuQuinox gave the product in good yield, excellent regioselectivity and a moderate 72:38 e.r (Figure 3.27).

Table 3.9. Additional homoallyl substrates.



entry	substrate	product	yield, selectivity
1	 **3.25**	 **3.26**	80%, >20:1 B:L
2	 **3.27**	 **3.28**	73%, >20:1 B:L

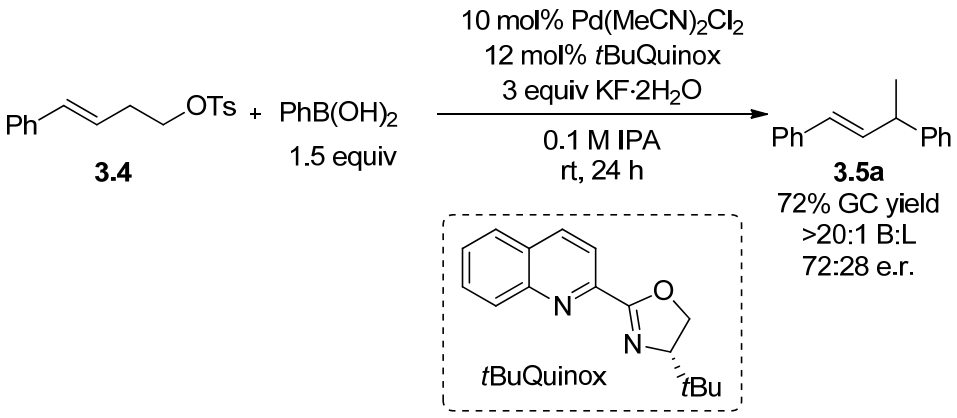


Figure 3.27. Initial results for asymmetric catalysis.

While this result clearly requires further optimization, it is a promising lead for the future development of asymmetric allylic C–H functionalizations.

A more detailed investigation of the scope of the allylic C–H arylation is ongoing, and Dr. Benjamin Stokes is further pursuing the asymmetric variant and mechanistic details of this unique reaction.

Experimental Section

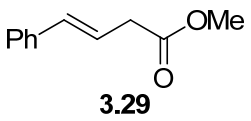
General Information

MeOH, *t*AmOH, *i*PrOH, and NEt_3 were dried by distilling from CaH_2; DCM, Et_2O, and PhMe were dried by passing through a column of activated alumina; $CDCl_3$ was dried by passing through a plug of activated basic alumina. PhMe and *t*AmOH used in a glove box were freeze-pump-thawed prior to storing them in a glove box. PPh_3 was crystallized from Et_2O and stored in a glove box. Other phosphines were purchased and used as received. TsCl was purified by washing its solution in Et_2O with base, followed by crystallization from hot PhMe. DMAP was crystallized from hot toluene. K_2CO_3 and Cs_2CO_3 were crushed and dried at ca. 100 °C under vacuum, and stored in a glove box.

Flash column chromatography was performed using EM Reagent silica 60 (230-400 mesh). ^{1}H NMR were obtained at 300, 400, or 500 MHz and referenced to the residual $CHCl_3$ singlet at 7.26 ppm. ^{13}C NMR were obtained at 75, 100, or 125 MHz and referenced to the center line of the $CDCl_3$ triplet at 77.23 ppm. GC/MS were obtained on a HP 5890 (EI) 20:1 split. IR spectra were obtained on a Bruker Tensor 37 FTIR spectrometer. HRMS were obtained on an Agilent LCTOF. SFC (supercritical fluid chromatography) analysis was performed at 40 °C, using a Thar instrument fitted with a chiral stationary phase (as indicated).

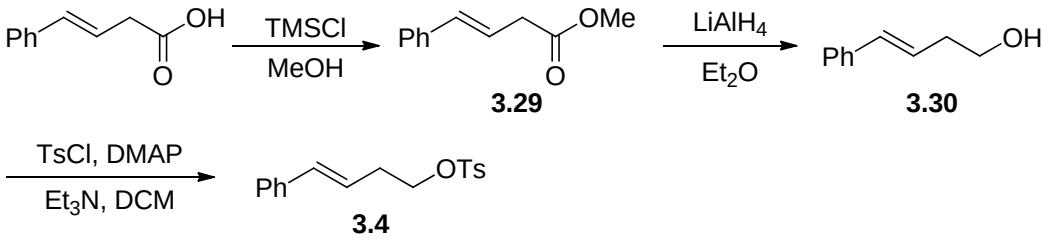
Synthesis of (*E*)-4-Phenyl-3-butenyl Tosylate (**3.4**)

Phenyl-3-butenyl tosylate was synthesized as shown in Figure 3.28.



3.29

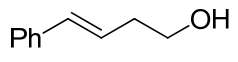
*Preparation of (E)-Methyl 4-phenyl-3-butenoate (**3.29**).* To a dry 250 mL round-bottom flask equipped with a stirbar under N_2 were added 5.00 g of (*E*)-4-phenyl-3-butenoic acid (30.8 mmol, 1.00 equiv) and 40 mL of MeOH. The solution was cooled to 0 °C, and 5.90 mL TMSCl (46.2 mmol, 1.50 equiv) were added dropwise. The mixture



3.29 **3.30** **3.4**

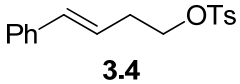
Figure 3.28. Synthesis of substrate **3.4**.

was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the crude product (5.26 g, 29.9 mmol, 97% yield) was taken forward after comparison to published characterization data.[54]



3.30

*Preparation of (E)-4-Phenylbut-3-en-1-ol (**3.30**).* To a dry 250 mL round-bottom flask equipped with a stirbar under N_2 were added 3.40 g $LiAlH_4$ (89.6 mmol, 3.00 equiv) and 60 mL Et_2O. The mixture was cooled to 0 °C, and a solution of 5.26 g (*E*)-methyl 4-phenyl-3-butenoate (29.9 mmol, 1.00 equiv) in 20 mL Et_2O was added dropwise. The mixture was allowed to warm to room temperature, and quenched after 2.5 h by slow addition of 150 mL 1M HCl. The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer is extracted with Et_2O (3 × 40 mL); the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product (4.13 g, 27.8 mmol, 93% yield) was compared to published characterization data and taken on to the next step.[55]

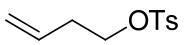


3.4

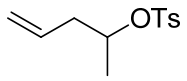
*Preparation of (E)-4-Phenylbut-3-enyl tosylate (**3.4**).* To a dry 100 mL round-bottom flask equipped with a stirbar under N_2 were added 2.01 g TsCl (11.0 mmol, 1.10 equiv), 122 mg DMAP (1.00 mmol, 0.100 equiv), 2.79 mL NEt_3 (20.0 mmol, 2.00 equiv), and 20 mL DCM. The resulting mixture was cooled to 0 °C, and a solution of 1.48 g *(E)*-4-Phenylbut-3-en-1-ol (10.0 mmol, 1.00 equiv) in 10 mL DCM was added dropwise.

The mixture was allowed to warm to room temperature and stirred overnight, during which time a white precipitate formed. DCM was then added to dissolve the precipitate, and the solution was washed with sat. aq. $NaHCO_3$ (1 × 40 mL) and H_2O (1 × 40 mL). The combined aqueous layers were extracted with DCM (1 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography eluting with 700 mL 12% EtOAc/hexanes → 200 mL 20% EtOAc/hexanes. The product was isolated as a white solid in 2.16 g (7.14 mmol, 64% overall yield based on the acid). Its spectral data were compared to published ones.[56]

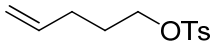
General Procedure for the Tosylation of Alcohols



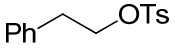
For 3-buten-1-tosylate. To a dry 250 mL round-bottom flask equipped with a stirbar under N_2 were added 5.56 g TsCl (29.0 mmol, 1.10 equiv), 326 mg of DMAP (2.70 mmol, 0.100 equiv), 7.40 mL of NEt_3 (54.0 mmol, 2.00 equiv), and 60 mL of DCM. The resulting mixture was cooled to 0° C, and a solution of 2.00 g of 3-buten-1-ol (27.0 mmol, 1.00 equiv) in 60 mL of DCM was added dropwise. The mixture was allowed to warm to room temperature and was strirred overnight. The solution was then washed with sat. aq. $NaHCO_3$ (1 × 120 mL) and H_2O (1 × 120 mL). The combined aqueous layers were extracted with DCM (1 × 120 mL) and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The residue was purified by flash column chromatography (0:100 → 50:50 EtOAc:hexanes) to afford the product as a colorless oil (5.35 g, 87%). Its spectral data were compared to published ones.[57]



4-Penten-2-tosylate was prepared analogously using 600 mg (3.1 mmol) of TsCl, 35 mg (0.29 mmol) of DMAP, 0.80 mL (5.7 mmol) of Et_3N, and 0.30 mL (2.9 mmol) of 4-penten-2-ol in 14 mL of DCM. Purification by flash column chromatography (0:100 → 50:50 EtOAc:hexanes) afforded the product as a colorless oil (282 mg, 41%), R_f = 0.29 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (d, *J* = 6.8 Hz, 3 H), 2.22 – 2.42 (m, 2 H), 2.45 (s, 3 H), 4.64 (sextet, *J* = 6.8 Hz, 1 H), 5.01 (s, 1 H), 4.98 – 5.08 (m, 2 H), 5.52 – 5.68 (m, 1 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR [58] ($CDCl_3$, 75 MHz): δ 20.52, 21.87, 41.01, 79.58, 119.0, 128.0, 129.9, 132.5, 134.6, 144.7; IR 2981, 1643, 1598, 1495, 1449, 1351, 1306, 1187, 1173, 1120, 1096, 1043, 1019 cm^{-1}; HRMS: (m/z) calcd. 263.0718 obsd. 263.0722 $[M+Na]^+$.

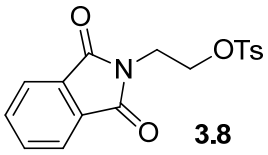


4-Penten-1-tosylate was prepared analogously using 1.04 g (5.5 mmol) of TsCl, 61 mg (0.50 mmol) of DMAP, 1.4 mL (10 mmol) of Et_3N, and 0.58 mL (5.0 mmol) of 4-penten-1-ol in 25 mL of DCM. Purification by flash column chromatography (0:100 → 30:70 EtOAc/hexanes) afforded the product as a colorless oil (1.13 g, 94%). Its spectral data were compared to published ones.[59]



3.7

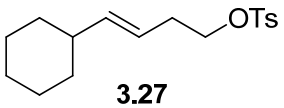
Phenethyl Tosylate ***(3.7)*** was prepared analogously using 1.96 mL 2-phenylethanol (16.4 mmol), 3.43 g TsCl (18.0 mmol), 200 mg DMAP (1.64 mmol), 4.56 mL NEt_3 (32.7 mmol), and 40 mL DCM. The product was purified by flash column chromatography eluting with 1 L 10% EtOAc/hexanes → 300 mL 20% EtOAc/hexanes. The product was isolated as a white solid in 98% yield (4.43g, 16.0 mmol). Its spectral data were compared to published ones.[60]



3.8

2-Phthalimidoethyl Tosylate ***(3.8)*** was prepared analogously, starting from 200 mg phthalimide-protected ethanolamine (1.05 mmol), 219 mg TsCl (1.15 mmol), 12.8 mg DMAP (0.11 mmol), 292 μL NEt_3 (2.09 mmol), and 10 mL DCM. The product was purified by flash column chromatography eluting with 400 mL 15% EtOAc/hexanes → 100 mL 50% EtOAc/hexanes → 150 mL EtOAc. Its spectral data were compared to published ones.[61]

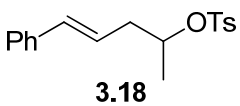
General Procedure for Alkene Cross-Metathesis



3.27

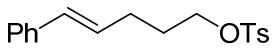
For substrate ***3.27***. Into a dry 10 mL round-bottom flask equipped with a stirbar were added 327 mg of homoallyl tosylate (1.40 mmol, 1.00 equiv) and 3 mL of DCM, followed by 2.0 mL of vinylcyclohexane (14.0 mmol, 10.0 equiv) that had been passed

through basic alumina, and 30 mg of Grubbs's 2nd generation catalyst (0.04 mmol, 2.5 mol%). The flask was equipped with a condenser and refluxed for 2 h at 45 °C under N_2, at which time TLC showed consumption of homoallyl tosylate. After cooling to ambient temperature, 0.02 mL of di(ethylene glycol) vinyl ether (0.16 mmol, 10 mol%) was added and the reaction stirred for 30 min. The reaction was concentrated in vacuo and the residue was purified by flash column chromatography (50% benzene/hexanes) to afford the product **3.27**, an 87:13 mixture of *E* and *Z* isomers, as a beige oil (180 mg, 42%), R_f = 0.16 (50% benzene/hexanes). Selected spectral data for the major (*E*) isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 – 1.02 (m, 2 H), 1.07 – 1.15 (m, 1 H), 1.15 – 1.26 (m, 2 H), 1.56 – 1.63 (m, 3 H), 1.63 – 1.70 (m, 2 H), 1.77 – 1.87 (m, 1 H), 2.29 (q, *J* = 7.0 Hz, 2 H), 2.42 (s, 3 H), 3.98 (dt, *J* = 7.0, 1.5 Hz, 2 H), 5.16 (dt, *J* = 15.5, 7.0 Hz, 1 H), 5.39 (dd, *J* = 15.5, 6.5 Hz, 1 H), 7.32 (d, *J* = 7.0 Hz, 2 H), 7.76 (dd, *J* = 8.0, 2.0 Hz, 2 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 100 MHz): δ 21.8, 26.2, 26.3, 32.4, 33.0, 40.8, 70.5, 121.2, 128.1, 130.0, 133.4, 140.6, 144.9. Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.02 – 1.07 (m, 1 H), 1.49 (d, *J* = 9.0 Hz, 2 H), 2.06 – 2.15 (m, 1 H), 2.37 (q, *J* = 7.0 Hz, 2 H), 2.42 (s, 3 H), 5.08 (dt, *J* = 11.0, 7.0 Hz, 1 H), 5.29 (t, *J* = 11.0 Hz, 1 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 26.0, 26.1, 27.5, 33.3, 36.6, 70.2, 120.9, 128.1, 133.4, 140.1, 144.9. Spectral data for the mixture: IR 2922, 2849, 1598, 1448, 1360, 1174, 1097 cm^{-1}; HRMS: (m/z) calcd. 331.1344 obsd. 331.1349 [M+Na]$^+$.



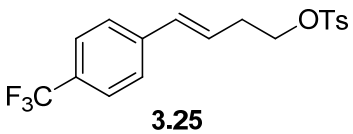
3.18

*Substrate **3.18*** was prepared analogously using 120 mg (0.50 mmol) of 4-penten-2-tosylate, 0.23 mL (2.0 mmol) of styrene, and 21 mg of Grubbs's 2nd generation catalyst in 1 mL of 1,2-DCE. Purification by flash column chromatography (0:100 → 50:50 EtOAc:hexanes) afforded the product as a white powder (66 mg, 42%), mp 70 °C, R_f = 0.33 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (d, *J* = 6.3 Hz, 3 H), 2.36 (s, 3 H), 2.38-2.58 (m, 2 H), 4.67 (sextet, *J* = 6.3 Hz, 1 H), 5.87 (dt, *J* = 15.6, 7.2 Hz, 1 H), 6.33 (d, *J* = 15.9 Hz, 1 H), 7.17-7.34 (m, 7 H), 7.76 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 75 MHz): δ 21.1, 21.8, 40.2, 79.9, 124.1, 126.4, 127.6, 128.0, 128.7, 129.9, 133.8, 134.3, 137.2, 144.7; IR 3029, 2891, 1595, 1493, 1450, 1380, 1343, 1307, 1293, 1170, 1130, 1097, 1020 cm^{-1}; HRMS: (m/z) calcd. 339.1031 obsd. 339.1031 $[M+Na]^+$.



3.20

*Substrate **3.20*** was prepared analogously using 96 mg (0.40 mmol) of bishomoallyl tosylate, 0.09 mL (0.80 mmol) of styrene, and 17 mg (0.02 mmol) of Grubbs's 2nd generation catalyst in 0.8 mL of DCM. Purification by flash column chromatography (0:100 → 50:50 EtOAc:hexanes) afforded the product as a white solid (42 mg, 33%), R_f = 0.32 (20% EtOAc/hexanes). Its spectral data were compared to published ones.[59]

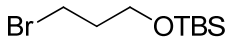


3.25

*Substrate **3.25*** was prepared analogously using 156 mg (0.69 mmol) of homoallyl tosylate, 0.5 mL (3.4 mmol) of 4-(trifluoromethyl)styrene, and 58 mg (0.07 mmol) of Grubbs's 2nd generation catalyst in 3.0 mL of DCM. Purification by flash column chromatography (0:100 → 50:50 EtOAc:hexanes) afforded the product as a white powder (131 mg, 51%), mp 72 °C, R_f = 0.29 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.41 (s, 3 H), 2.57 (qd, *J* = 6.5, 1.5 Hz, 2 H), 4.15 (t, *J* = 6.5 Hz, 2 H), 6.11 (dt, *J* = 16.0, 7.0 Hz, 1 H), 6.42 (d, *J* = 16.0 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.76 – 7.79 (m, 2 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 21.8, 32.7, 69.5, 124.3 (q, $J_{C–F}$ = 270.4 Hz), 125.7 (q, $J_{C–F}$ = 3.8 Hz), 126.5, 127.1, 128.1, 129.5 (q, $J_{C–F}$ = 32.1 Hz), 130.1, 132.2, 133.2, 140.5 (q, $J_{C–F}$ = 1.4 Hz), 145.1; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –62.9; IR 2931, 1654, 1611, 1597, 1494, 1469, 1414, 1384, 1350, 1324, 1174, 1161, 1110, 1066, 1014 cm^{-1}; HRMS: (m/z) calcd. 393.0748, obsd. 39.0757 $[M+Na]^+$.

Synthesis of (*E*)-4-(4-methoxyphenyl)but-3-en-1-yl Tosylate (**3.35**)

(*E*)-4-(4-methoxyphenyl)but-3-en-1-yl tosylate (**3.35**) was synthesized as shown in Figure 3.29.



3.31

*TBS-protected bromopropanol **3.31*** was prepared according to a literature procedure.[62]

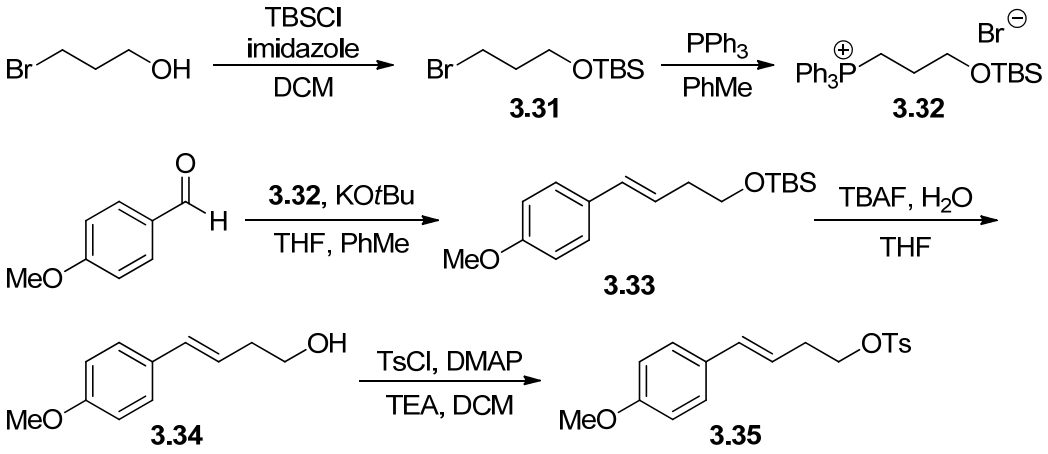
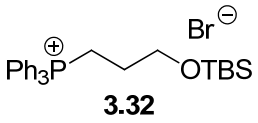
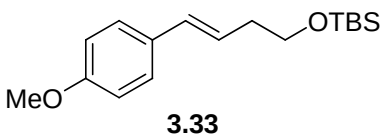


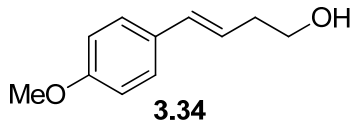
Figure 3.29. Synthesis of (*E*)-4-(4-methoxyphenyl)but-3-en-1-yl tosylate (**3.35**).



*Preparation of Wittig Reagent **3.32.*** To a dry 25 mL round-bottom flask equipped with a stirbar under N_2 were added 2.69 g of PPh_3 (10.3 mmol, 1.30 equiv) and 5 mL of PhMe. While stirring, 2.00 g of **3.31** (7.90 mmol, 1.00 equiv) were slowly added. The flask was equipped with a reflux condenser, and the mixture was heated to reflux for 3 h, during which time a white precipitate formed. The mixture was allowed to cool to room temperature. The stirbar was removed, and the product was allowed to crystallize overnight. It was then filtered through a glass fritte, and dried at 80 °C under vacuum overnight. The product was isolated in 76% yield (3.09 g, 5.99 mmol) as a white solid. Its spectral data matched previously published ones.[63]

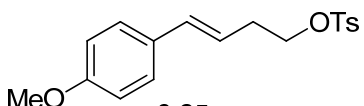


*Preparation of **3.33.*** To a dry 100 mL round-bottom flask equipped with a stirbar under N_2 were added 2.68 g of **3.32** (5.2 mmol, 1.3 equiv) followed by 30 mL of PhMe. A solution of 597 mg of KO*t*Bu (5.32 mmol, 1.33 mmol) in 10 mL THF was added dropwise, and the orange mixture was stirred at room temperature for 4 h. The mixture was then cooled to -78 °C, and a solution of 487 μL anisaldehyde (4.00 mmol, 1.00 equiv) in 8 mL of PhMe was added dropwise. The mixture was allowed to warm to room temperature overnight. It was then quenched with 30 mL of sat. aq. NH_4Cl, and stirred for 20 min. Enough H_2O to dissolve the precipitate in the mixture was added, and the layers were separated in a separatory funnel. The aqueous layer was extracted with Et_2O (3 × 40 mL), and the combined organic layers were washed with H_2O (1 × 40 mL) and brine (1 × 40 mL), and dried over $MgSO_4$. The crude product was purified by flash column chromatography eluting with 3% acetone/hexanes, and the pure product was isolated in 74% yield (863 mg, 2.95 mmol). Its spectral data matched previously published ones.[63]



3.34

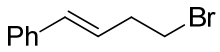
*Alcohol **3.34*** was prepared analogously to a literature procedure,[63] and its spectral data matched previously published ones.[64]



3.35

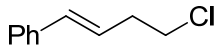
Tosylate ***3.35*** was prepared analogously to the general procedure for alcohol tosylation described above. The product was isolated as a clear oil in 91% yield (789 mg, 2.38 mmol). R_f: 0.21 w/ 20% acetone/hexanes; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.43 (s, 3 H), 2.52 (qd, *J* = 6.9, 1.8 Hz, 2 H), 3.80 (s, 3 H), 4.11 (t, *J* = 6.6 Hz, 2 H), 5.84 (dt, *J* = 15.6, 6.9 Hz, 1 H), 6.33 (d, *J* = 15.9 Hz, 1 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.30 (d, *J* = 7.8 Hz, 2 H), 7.78 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 21.9, 32.7, 55.5, 70.1, 114.1, 121.7, 127.5, 128.2, 129.9, 130.0, 132.9, 133.3, 144.9, 159.3; IR 3032, 2996, 2956, 2840, 1604, 1576, 1509, 1462, 1453, 1440, 1381, 1345, 1305, 1284, 1241, 1172, 1095, 1049, 1030 cm^{-1}; HRMS: (m/z) calcd. 355.0980 obsd. 355.0980 $[M+Na]^+$.

Synthesis of Homoallyl Halides



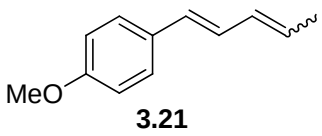
3.16

*(E)-4-phenyl-3-butenyl bromide (**3.16**)* was prepared according to a published procedure.[65]



3.17

*(E)-4-phenyl-3-butenyl chloride (**3.17**)* was prepared according to a published procedure[66] from cyclopropyl(phenyl)methanol, which was prepared according to a published procedure.[65]

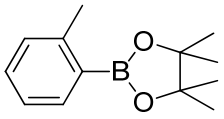


3.21

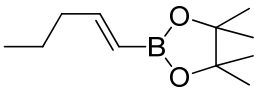
Synthesis of 1-Methoxy-4-(1,3-pentadien-1-yl)benzene ***3.21***. To a dry 250 mL round-bottom flask equipped with a stirbar under N_2 were added 4.88 g (13 mmol, 1.30 equiv) of ethyltriphenylphosphonium bromide followed by 43 mL of THF. The flask was cooled to –78 °C and 5.6 mL of *n*-BuLi in hexanes (14 mmol, 1.40 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred an additional 10 min before it was cooled to –78 °C and 1.66 g of *trans*-4-methoxycinnamaldehyde (10 mmol, 1.00 equiv) was added slowly. The reaction was allowed to warm up to room temperature and stir overnight before being quenched with 50 mL of sat. aq. NH_4Cl. THF was then removed in vacuo and the residue was extracted with Et_2O (2 × 50 mL) and washed with H_2O (1 × 100 mL). The organic phase was concentrated in vacuo and the residue was purified by flash column chromatography (100% hexanes) to afford the product **3.21**, a 50:50 mixture of *E*,*E*- and *E*,*Z*-isomers, as a low-melting pale yellow solid (1.35 g, 77%), mp 45 °C, R_f = 0.56 (20% EtOAc/hexanes, visualized by 254 nm UV light). Selected spectral data for the *E*,*Z*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.82 (d, *J* = 6.8 Hz, 3 H), 3.82 (s, 3 H), 5.55 (ddq, *J* = 10.4, 7.2, 1.0 Hz, 1 H), 6.13 – 6.25 (m, 1 H), 6.48 (d, *J* = 15.6 Hz, 1 H), 6.82 – 6.89 (m, 2 H), 6.97 (dd, *J* = 15.6, 10.8 Hz, 1 H), 7.29 – 7.39 (m, 2 H). Selected spectral data for the *E*,*E*-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.86 (d, *J* = 6.8 Hz, 3 H), 3.82 (s, 3 H), 5.79 (ddq, *J* = 14.4, 6.8, 1.0 Hz, 1 H), 6.13 – 6.25 (m, 1 H), 6.38 (d, *J* = 15.6 Hz, 1 H), 6.63 (dd, *J* = 15.6, 10.4 Hz, 1 H), 6.82 – 6.89 (m, 2 H), 7.29 – 7.39 (m, 2 H). Selected spectral data for the mixture: ^{13}C NMR {^{1}H} ($CDCl_3$, 100 MHz): δ 13.8, 18.6, 55.5, 114.2, 114.3, 122.5,

126.2, 127.5, 127.6, 127.7, 128.7, 128.8, 128.9, 129.3, 129.5, 130.0, 130.7, 131.6, 132.2, 133.9, 134.1, 159.1, 159.3; IR 3015, 2986, 2954, 2907, 2839, 2051, 2005, 1644, 1599, 1573, 1508, 1467, 1440, 1417, 1372, 1298, 1249, 1175, 1148, 1110, 1026 cm^{-1}; HRMS: (m/z) calcd. 175.1123 obsd. 175.1122 $[M+H]^+$.

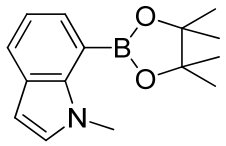
General Procedure for the Synthesis of Pinacol Boronic Esters



For ortho-tolylboronic acid pinacol ester. Into a dry 20 mL scintillation vial equipped with a stirbar were added 261 mg of pinacol (2.20 mmol, 1.00 equiv), and 300 mg of *ortho*-tolylboronic acid (2.20 mmol, 1.00 equiv), followed by 3 mL of Et_2O. The mixture was stirred overnight, concentrated in vacuo, and purified by flash column chromatography (0:100 → 20:80 EtOAc/hexanes) to afford the product as a colorless oil (398 mg, 83%), R_f = 0.69 (20% EtOAc/hexanes). Its spectral data matched previously published ones.[67]

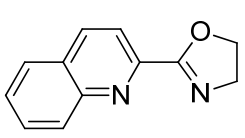


For 1-pentenylboronic acid pinacol ester. The same procedure was followed using 100 mg (0.86 mmol) of 1-pentenylboronic acid. Purification by flash column chromatography (0:100 → 20:80 EtOAc/hexanes) afforded the product as a colorless oil (108 mg, 64%), R_f = 0.72 (20% EtOAc/hexanes). Its spectral data matched those of the commercial product.

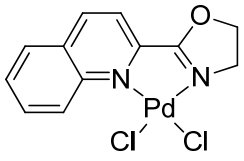


For N-methylindole-4-boronic acid pinacol ester: Into a dry 10 mL round-bottom flask equipped with a stirbar were added 36 mg of a 60% dispersion of sodium hydride in mineral oil (0.89 mmol, 1.05 equiv) followed by 0.75 mL of THF, and the suspension was cooled to 0 °C in an ice bath. Then, a solution of 200 mg of indole-4-boronic acid pinacol ester (0.85 mmol, 1.00 equiv) in 0.75 mL of THF was added dropwise and the reaction was stirred an additional 30 min, then 0.90 mL of methyl iodide (0.93 mmol, 1.10 equiv) was added dropwise. The reaction was then warmed to ambient temperature and stirred overnight. The mixture was then partitioned between EtOAc and H_2O (20 mL each), and the aqueous layer was extracted with an additional 20 mL of EtOAc. The organic layers were combined and washed with brine (1 × 20 mL) and subsequently dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (0:100 → 30:70 EtOAc:hexanes) afforded the product as a white powder (96 mg, 35%). The spectral data of the product matched previously published ones.[68]

Synthesis of Ligands and Catalysts

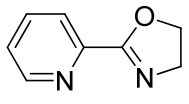


Quinox



3.9
$Pd(Quinox)Cl_2$

*Quinox and $Pd(Quinox)Cl_2$ (**3.9**)* were prepared according to a published procedure.[69]



Pyrox

Pyrox was prepared analogously to Quinox.[69] To an oven dried 100 mL round bottomed flask with a magnetic stirbar was weighed 400 mg of 2-picolinic acid (3.25 mmol, 1.00 equiv.) and subsequently put under N_2 atmosphere. Dry CH_2Cl_2 (32 mL) was added to the reaction flask and the mixture was cooled to 0 °C. To the mixture was added 1.25 mL NEt_3 (8.94 mmol, 2.75 equiv), followed by dropwise addition of 485 μL of IBCF (3.74 mmol, 1.15 equiv.). The mixture was stirred at 0 °C for 0.5 h. In a single portion, 433 mg of $HCl•H_2NCH_2CH_2Cl$ (3.74 mmol, 1.15 equiv) was added. After stirring for 10 min, the ice bath was removed and the mixture was allowed to warm to room temperature for 2.5 h. The solvent was then evaporated under reduced pressure. To the residue was added 20 mL MeOH along with 912 mg of KOH (16.3 mmol, 5.00 equiv). The flask was fitted with a water condenser and the reaction mixture was heated to reflux overnight. It was then cooled to room temperature and the solvent was evaporated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (1 × 50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with sat. aq. NH_4Cl (1 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography eluting with 5% MeOH/DCM, and isolated as a white solid in 87% yield (421 mg, 2.84 mmol). Its spectral data matched previously published ones.[70]

General Procedure for Screen Scale Reactions with Phosphine Ligands

For Table 3.2, entry 1. Inside a glove box, the catalyst was pre-formed by stirring a mixture of 3.5 mg $Pd(MeCN)_2Cl_2$ (0.0133 mmol) and 3.2 mg P*t*Bu_3 (0.0160) mmol in 400 μL of PhMe for 30 min in a 4 mL vial. Into another 4 mL vial were added 97.7 mg of Cs_2CO_3 (0.300 mmol, 3.00 equiv), 18.3 mg of $PhB(OH)_2$ (0.150 mmol, 1.50 equiv), 30.2 mg of **3.4** (0.100 mmol, 1.00 equiv), and MeONap as internal standard. To the solids was then added 200 μL of PhMe and the mixture was stirred. While stirring, 300 μL of the catalyst mixture were added (resulting in 10 mol% $Pd(MeCN)_2Cl_2$ and 12 mol% P*t*Bu_3). The vial was then sealed and removed from the glove box. It was further sealed with electrical tape and heated to 80 °C in an oil bath. After 24 h, it was cooled to room temperature, and a small sample was removed for GC analysis.

The products were initially identified based on GC/MS, and later confirmed by comparison with isolated or known compounds.

The reactions for other entries in Tables 3.2, 3.3, and 3.4 were performed analogously, with the appropriate bases, phosphines, and solvents. Reactions in *t*AmOH contained a small amount (ca 5%) PhMe to solubilize the starting material. Reactions run at room temperature were stirred in the glove box for the time indicated.

The attempted reactions using **3.7** and **3.8** were carried out analogously.

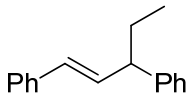
General Procedure for Screen Scale Reactions with Pyridine-Based Ligands

For Figure 3.20, Quinox. The catalyst was pre-formed by stirring a mixture of 3.5 mg of $Pd(MeCN)_2Cl_2$ (0.0133 mmol) and 3.2 mg of Quinox (0.0160 mmol) in 400 μL of *t*AmOH for 30 min in a dry 4 mL vial under N_2. Into another dry 4 mL vial under N_2 were added 97.7 mg of Cs_2CO_3 (0.300 mmol, 3.00 equiv), 18.3 mg of $PhB(OH)_2$ (0.150

mmol, 1.50 equiv), 30.2 mg of **3.4** (0.100 mmol, 1.00 equiv), and MeONap as internal standard. To the solids was then added 200 μL of *t*AmOH and the mixture was stirred. While stirring, 300 μL of the catalyst mixture were added (resulting in 10 mol% $Pd(MeCN)_2Cl_2$ and 12 mol% Quinox). The vial was then capped and stirred vigorously at room temperature. Small samples were removed for GC analysis at the indicated times.

Other reactions for Figure 3.20 were performed analogously with the indicated ligands.

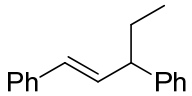
Screening reactions using pre-formed $Pd(Quinox)Cl_2$ were performed analogously, without addition of excess ligand. $Pd(Quinox)Cl_2$ was added directly to the reaction flask along with the other solids. Reactions for Table 3.5, the attempted reaction of phenethyl tosylate (Figure 3.21), and arylations of homoallyl halides (Table 3.7) were performed in this way.



3.19

*Arylation of secondary tosylate **3.18** (Figure 3.23).* Into a dry 4 mL vial equipped with a stirbar were added 4.0 mg of $Pd(Quinox)Cl_2$ (0.01 mmol, 10 mol%), 28 mg of $KF{\cdot}2H_2O$ (0.30 mmol, 3.00 equiv), 18 mg of $PhB(OH)_2$ (0.15 mmol, 1.50 equiv), and 32 mg of **3.18** (0.10 mmol, 1.00 equiv). The vial was fitted with a septum and flushed with N_2 for approximately 3 min. To the solids was then added 1 mL IPA, and the mixture was stirred for 16 h. The heterogeneous mixture was then filtered through a plug of celite eluting with Et_2O and concentrated in vacuo. Purification by flash column

chromatography (100% hexanes) afforded the product **3.19** as a colorless oil (17 mg, 0.076 mmol, 76%), R_f = 0.15 (100% hexanes). Its spectral data were matched previously published ones. [71]



3.19

*Arylation of bishomoallylic tosylate **3.20** (Figure 3.24).* Into a dry 4 mL vial equipped with a stirbar were added 1.8 mg of Pd(Quinox)Cl_2 (0.005 mmol, 10 mol%), 13 mg of KF·2H_2O (0.14 mmol, 3.00 equiv), 9.0 mg of phenylboronic acid (0.07 mmol, 1.50 equiv), and 15 mg of tosylate **3.20** (0.05 mmol, 1.00 equiv). The vial was fitted with a septum and flushed with N_2 for approximately 3 min. To the solids was then added 0.25 mL IPA, and the mixture was stirred vigorously for 16 h at 85 °C. The heterogeneous mixture was then filtered through a plug of celite with Et_2O and concentrated in vacuo. A 17% NMR yield of **3.19** was determined using 0.1 mmol CH_2Br_2 as a standard and comparing the ^{1}H NMR spectra to published ones.[71]

For Table 3.8, entry 4. **3.24** was prepared analogously using 30 mg of **3.4** (0.10 mmol) and 17.1 mg of 4-pentenyl boronic acid (0.15 mmol). A 50% ^{1}H NMR yield was determined using 0.10 mmol CH_2Br_2 as a standard and comparing to the characteristic sextet corresponding to the proton on the trisubstituted allylic carbon.

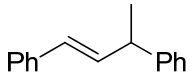
Crossover Experiments

The general allylic arylation procedure on screen scale was followed using 32 mg of **3.18** (0.10 mmol) and 17 mg of **3.21** (0.10 mmol) in 1 mL of *tert*-amyl alcohol. After stirring at ambient temperature overnight, the heterogeneous mixture was filtered through

a plug of celite with Et_2O and concentrated in vacuo. A 22% ^1H NMR yield of **3.19** was determined using 0.1 mmol CH_2Br_2 as a standard and comparing to published spectra. A 2% ^1H NMR yield of **3.22** was determined using 0.1 mmol CH_2Br_2 as a standard. Additionally, **3.22** was identified by GC-MS.

The above procedure was performed analogously in *iso*-propanol. After stirring at ambient temperature overnight, the heterogeneous mixture was filtered through a plug of celite with Et_2O and concentrated in vacuo. A 27% ^1H NMR yield of **3.19** was determined using 0.1 mmol CH_2Br_2 as a standard and comparing to published spectra. A 3% ^1H NMR yield of **3.22** was determined using 0.1 mmol CH_2Br_2 as a standard. Additionally, **3.22** was identified by GC-MS.

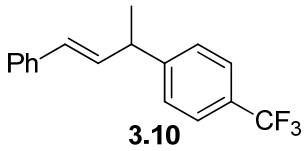
General Procedure for Allylic Arylation Using Boronic Acids



3.5a

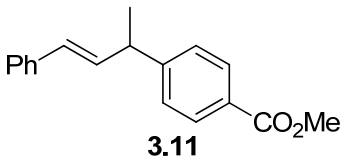
For Table 3.6, ***3.5a.*** Into a dry 25 mL round-bottom flask equipped with a football-shaped stirbar were added 4.7 mg of $Pd(Quinox)Cl_2$ (0.0125 mmol, 2.50 mol%), 141 mg of $KF{\cdot}2H_2O$ (1.50 mmol, 3.00 equiv), 91.4 mg of $PhB(OH)_2$ (0.750 mmol, 1.50 equiv), and 151 mg of **3.4a** (0.500 mmol, 1.00 equiv). The flask was flushed with N_2 for ca 3 min, and equipped with a septa and N_2 line. To the solids was then added 5 mL IPA and the mixture was stirred vigorously for 24 h. The heterogeneous mixture was then partitioned between Et_2O and H_2O (20 mL each), and the organic layer was washed with 1 M NaOH (1 × 20 mL). The combined aqueous layers were extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in

vacuo. The product was purified by flash column chromatography eluting with 400 mL of 0.5% acetone/hexanes → 300 mL of 3% acetone/hexanes. The product was isolated as a clear oil in an average 92% yield (experiment 1: 96.8 mg, 0.465 mmol, 93%, >20:1 linear:branched; experiment 2: 93.3 mg, 0.448 mmol, 90%, >20:1 linear:branched). Its spectral data matched previously published ones.[38]



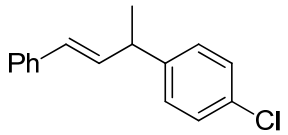
3.10

*Product **3.10*** was prepared analogously from 4-CF_3-$C_6H_4B(OH)_2$. The product was purified by flash column chromatography eluting with 400 mL of 0.5% acetone/hexanes → 300 mL of 2% acetone/hexanes. The product was isolated as a clear oil in an average 81% yield (experiment 1: 106 mg, 0.382 mmol, 76%, 13:1 linear:branched; experiment 2: 119 mg, 0.431 mmol, 86%, 11:1 linear:branched). R_f: 0.39 w/hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, *J* = 7.0 Hz, 3 H), 2.52 (m, 0.18 H), 2.76 (t, *J* = 7.7 Hz, 0.17 H), 3.63 (m, 1 H), 6.32 – 6.49 (m, 2 H), 7.22 – 7.43 (m, 7 H), 7.60 (m, 2 H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 21.2, 34.6, 35.8, 42.6, 125.6 (q, *J* = 4.0 Hz), 126.2, 126.3, 127.3, 127.5, 127.8, 128.5, 128.7, 128.9, 129.3, 129.5, 131.0, 134.1, 137.3, 149.8; IR 3026, 2968, 1618, 1495, 1448, 1417, 1322, 1162, 1114, 1067, 1014, 963 cm^{-1}; HRMS: (m/z) calcd. 383.0177 obsd. 383.0190 $[M+Ag]^+$.



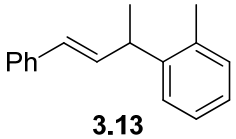
3.11

Product ***3.11*** was prepared analogously from 4-MeO_2C-$C_6H_4B(OH)_2$. The product was purified by flash column chromatography eluting with 2% acetone/hexanes. The product was isolated as a clear oil in an average 82% yield (experiment 1: 110 mg, 0.412 mmol, 80%, 11:1 linear:branched; experiment 2: 110 mg, 0.411 mmol, 82%, 13:1 linear:branched). Its spectral data matched previously published ones.[38]



3.12

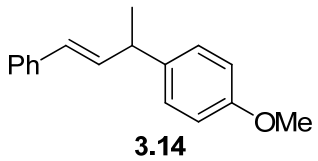
Product ***3.12*** was prepared analogously from 4-Cl-$C_6H_4B(OH)_2$. The product was purified by flash column chromatography, eluting with 400 mL 0.5% acetone/hexanes → 300 mL 3% acetone/hexanes. The product was isolated as a clear oil in an average 73% yield (experiment 1: 91.7 mg, 0.378 mmol, 76%, 11:1 linear:branched; experiment 2: 84.4 mg, 0.348 mmol, 70%, 11:1 linear:branched). Its spectral data matched previously published ones.[72]



3.13

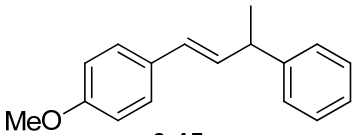
Product ***3.13*** was prepared analogously from 2-Me-$C_6H_4B(OH)_2$, and the reaction was allowed to proceed for 72 h. The product was purified by flash column chromatography eluting with 400 mL of 0.5% acetone/hexanes → 300 mL of 2% acetone/hexanes. The product was isolated as a clear oil in an average 85% yield (experiment 1: 98.5 mg, 0.443 mmol, 89%, >20:1 linear:branched; experiment 2: 90.0

mg, 0.405 mmol, 81%, >20:1 linear:branched). Its spectral data matched previously published ones.[38]



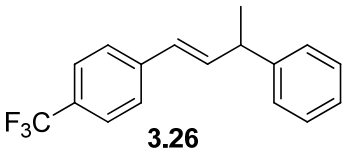
3.14

*Product **3.14*** was prepared analogously from 4-MeO-$C_6H_4B(OH)_2$. The product was purified by flash column chromatography on Brockmann I activated basic alumina, eluting with 1% acetone/hexanes. The product was isolated as a clear oil in an average 72% yield (experiment 1: 81.3 mg, 0.341 mmol, 68%, 15:1 linear:branched; experiment 2: 89.9 mg, 0.377 mmol, 75%, 15:1 linear:branched). Its spectral data matched previously published ones.[38]



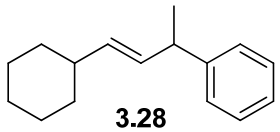
3.15

*Product **3.15*** was prepared analogously from tosylate **3.35** (166.2 mg, 0.50 mmol) and $PhB(OH)_2$ (91.4 mg, 0.75 mmol). The product was purified by flash column chromatography, eluting with 1.5% acetone/hexanes. The product was isolated as a clear oil in an average 86% yield (experiment 1: 99.1 mg, 0.416 mmol, 83%, 15:1 linear:branched; experiment 2: 106.7 mg, 0.448 mmol, 89%, 15:1 linear:branched). Its spectral data matched previously published ones.[38]



3.26

*Product **3.26*** was prepared analogously in two trials using 111 mg (0.30 mmol) and 69 mg (0.19 mmol) of homoallyl tosylate **3.25**, respectively. Purification by flash column chromatography (100% hexanes) afforded the product as a colorless oil (65 mg, 78%, and 40 mg, 77%, respectively), R_f = 0.29 (100% hexanes, visualized by 254 nm UV light). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.52 (d, J = 7.2 Hz, 3 H), 3.70 (quint, J = 6.9 Hz, 1 H), 6.45 (d, J = 16.2 Hz, 1 H), 6.53 (dd, J = 15.9, 6.0 Hz, 1 H), 7.23 – 7.33 (m, 3 H), 7.33 – 7.41 (m, 2 H), 7.46 (d, J = 8.4 Hz, 2 H), 7.56 (d, J = 8.4 Hz, 2 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 21.3, 42.9, 125.7 (q, $J_{C–F}$ = 3.8 Hz), 126.5 (q, $J_{C–F}$ = 226.8 Hz), 126.5, 126.7, 127.5, 127.6, 128.8, 128.9 (q, $J_{C–F}$ = 2.6 Hz), 138.2, 141.3, 145.3; ^{19}F NMR ($CDCl_3$, 282 MHz): δ –62.8; IR 3027, 2967, 1615, 1493, 1452, 1414, 1322, 1162, 1110, 1106, 1065, 1015 cm^{-1}; HRMS: (m/z) calcd. 383.0177 obsd. 383.0185 [M+Ag]$^+$.



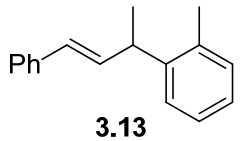
3.28

*Product **3.28*** was prepared analogously using 132 mg (0.44 mmol) of homoallyl tosylate **3.27**. Purification by flash column chromatography (100% hexanes) afforded the product, an 93:7 mixture of *E* and *Z* isomers, as a colorless oil (69 mg, 73%), R_f = 0.45 (100% hexanes, visualized by 254 nm UV light). The spectral data for the *E* isomer were compared to published ones.[38] Selected spectral data for the *Z* isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.28 – 2.36 (m, 2 H), 2.36 – 2.49 (m, 2 H), 2.70 (dd, J = 8.0, 1.6 Hz, 2 H),

3.78 – 3.87 (m, 1 H), 5.25 (t, J = 10.4 Hz, 1 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 100 MHz): δ 22.8, 30.0, 33.9, 34.8, 36.5, 36.9, 125.9, 127.1, 128.4, 128.6, 128.7, 142.5. Spectral data for the mixture: IR 3025, 2963, 2921, 2849, 1601, 1492, 1448, 1371, 1009 cm^{-1}.

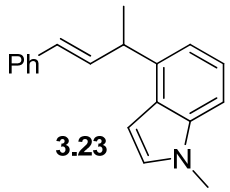
General Procedure for Allylic Arylations Using

Boronic Acid Pinacol Esters



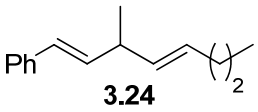
3.13

*For Table 3.8, entry 1 (**3.13**):* Into a dry 10 mL round-bottom flask equipped with a football-shaped stirbar were added 4.7 mg of Pd(Quinox)Cl_2 (0.0125 mmol, 2.50 mol%), 141 mg of $KF{\cdot}2H_2O$ (1.50 mmol, 3.00 equiv), 164 mg of *ortho*-tolylboronic acid pinacol ester (0.750 mmol, 1.50 equiv), and 151 mg of **3.4** (0.500 mmol, 1.00 equiv). The vial was fitted with a septum and flushed with N_2 for approximately 3 min. To the solids was then added 2.5 mL IPA and the mixture was stirred vigorously for 24 h. The heterogeneous mixture was then partitioned between Et_2O and H_2O (20 mL each), and the organic layer was washed with 1 M NaOH (1 × 20 mL). The combined aqueous layers were extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography (100% hexanes) afforded the product as a colorless oil (77 mg, 0.35 mmol, 69%). Its spectral data matched previously published ones.[38]



3.23

For Table 3.8, entry 2: **3.23** was prepared analogously using 0.046 g of **3.4** (0.15 mmol) and 74 mg of *N*-methylindole-4-boronic acid pinacol ester (0.225 mmol). Purification to the best of our ability by flash column chromatography (0:100 → 30:70 benzene/hexanes) afforded a faintly yellow oil that contained 71% of the desired product by NMR yield (R_f = 0.18 using 20% benzene/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.62 (d, *J* = 7.0 Hz, 3 H), 3.80 (s, 3 H), 4.11 (quintet, *J* = 6.5 Hz, 1 H), 6.52 (d, *J* = 16.0 Hz, 1 H), 6.59 (dd, *J* = 16.0, 6.0 Hz, 1 H), 6.63 (d, *J* = 3.0 Hz, 1 H), 7.05 (t, *J* = 4.0 Hz, 1 H), 7.06 (d, *J* = 3.0 Hz, 1 H), 7.16 – 7.25 (m, 3 H), 7.29 (t, *J* = 7.5 Hz, 2 H), 7.35 – 7.40 (m, 2 H); ^{13}C NMR {^{1}H} ($CDCl_3$, 125 MHz): δ 20.7, 33.2, 40.3, 99.7, 107.7, 116.9, 122.1, 126.4, 127.1, 127.4, 127.8, 128.5, 128.6, 128.7, 135.4, 136.1, 137.1, 138.1, 138.2.



3.24

For Table 3.8, entry 3: **3.24** was prepared analogously using 30 mg of **3.3** (0.10 mmol, 1.00 equiv) and 19 mg of 1-pentenyl-boronic acid pinacol ester (0.15 mmol, 1.50 equiv). A 64% ^{1}H NMR yield was determined using 0.1 mmol CH_2Br_2 as a standard and comparing to the characteristic sextet corresponding to the proton on the trisubstituted allylic carbon.

Procedure for Asymmetric Reaction (Figure 3.27)

An analogous procedure to the one for screen scale reactions using boronic acids was followed, using 30 mg of **3.4** (0.10 mmol), 96 mg of Cs_2CO_3 (0.30 mmol), 18 mg of $PhB(OH)_2$, 3 mg of $Pd(MeCN)_2Cl_2$ (0.01 mmol), and 3 mg of (*S*)-*t*-Bu-quinox (0.01 mmol) in 0.50 mL of *tert*-amyl alcohol. After stirring at ambient temperature overnight, the heterogeneous mixture was filtered through a plug of SiO_2 with Et_2O and concentrated in vacuo. A 72% GC yield was obtained. SFC analysis (1% MeOH/CO_2 @ 2 mL/min on OJ-H column) revealed a 72:28 mixture of enantiomers (retention times: 24.3 and 26.9 min, respectively).

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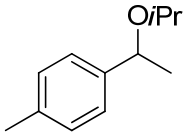
APPENDIX A:

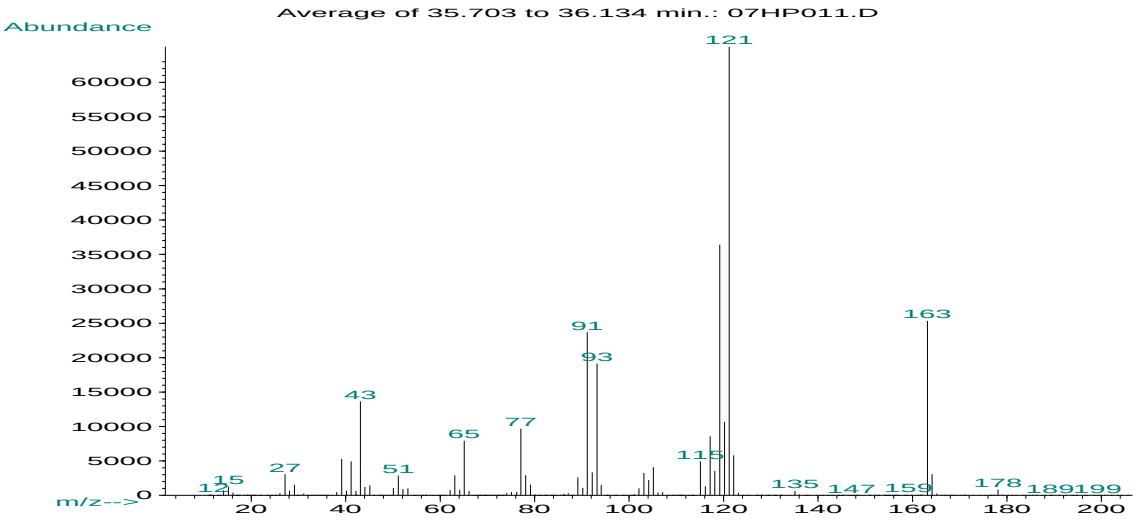
GC/MS DATA AND CALCULATIONS FOR

DEUTERIUM LABELING STUDIES IN CHAPTER 1

Non-labeled 1-(1-isopropoxyethyl)-4-methylbenzene (1.10a):

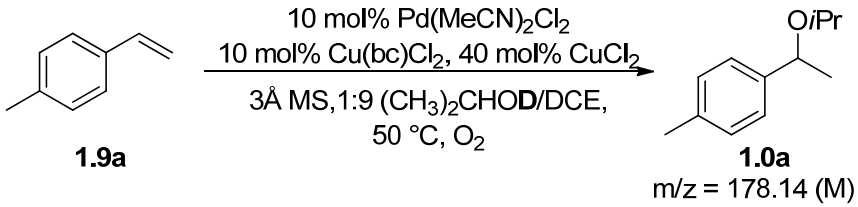


1.10a
m/z = 178.14 (M)



m/z	abund.
176.95	10
177.05	1
177.20	9
178.15	786
179.10	85
179.25	32
179.90	1
180.25	8

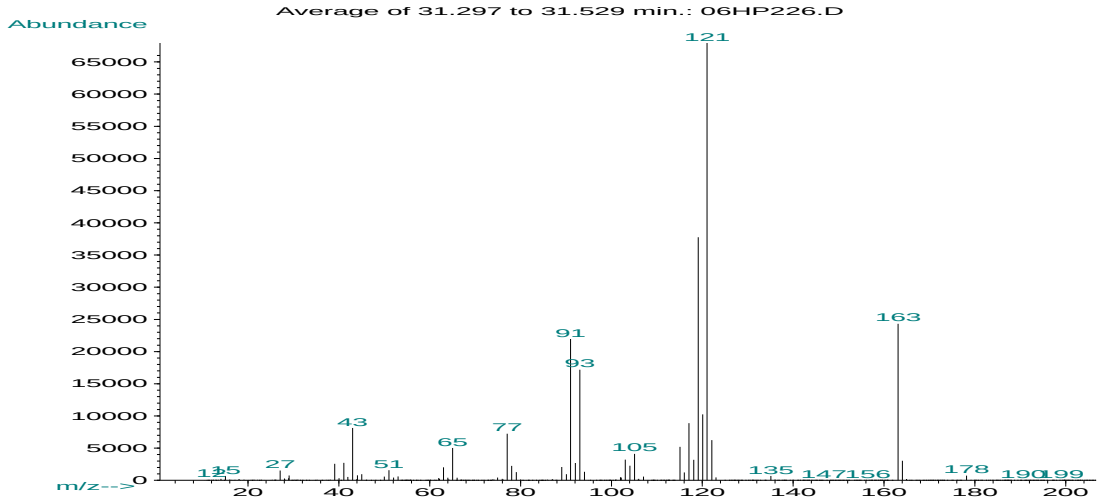
4-methylstyrene w/ *i*PrOD



1.9a

1.0a
m/z = 178.14 (M)

GC/MS data for product:

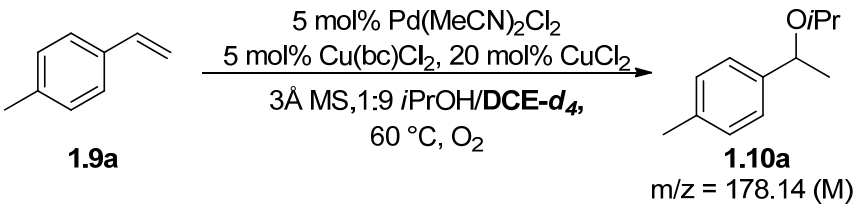


m/z	abund.
176.85	18
177.10	52
178.15	740
179.00	36
179.15	76
179.80	13
180.05	20
180.30	11

Calculation of D incorporation:

# of D atoms	0	1	
	M	**M+1**	
molecular ions	178	179	
abund. unlabeled	786	117	(M+1)/M not labeled:
abund. labeled	740	112	0.15
relative abund. unlabeled	100.00	14.89	
relative abund. labeled	100.00	15.14	
no D	**100.00**	14.89	100 * 0.15 = 14.89
difference		0.25	
1 D		**0.25**	
			sum rel. abund.:
			100.25
percent distribution:	**99.8**	**0.2**	

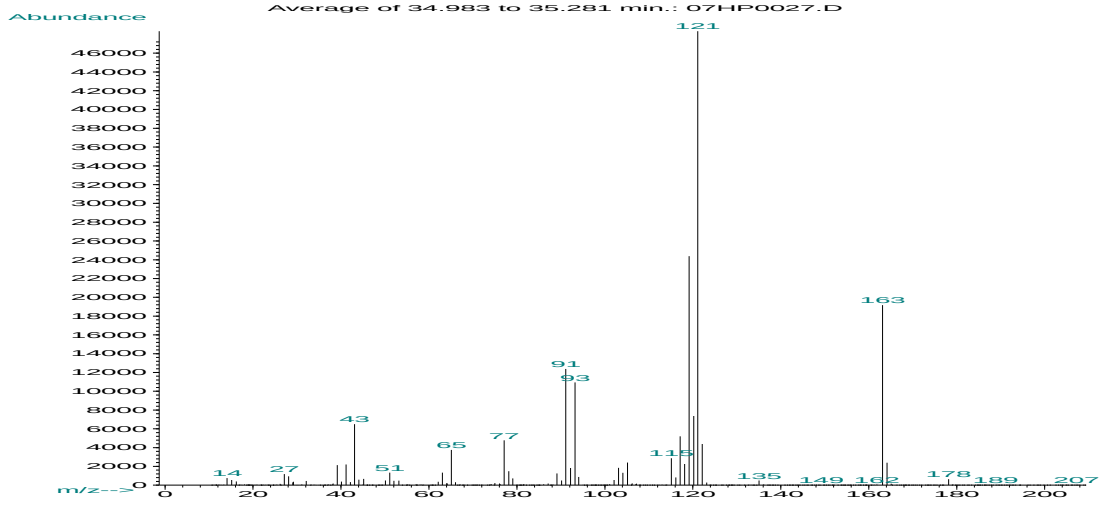
4-methylstyrene w/ DCE-d_4



1.9a **1.10a**

m/z = 178.14 (M)

GC/MS data for product:

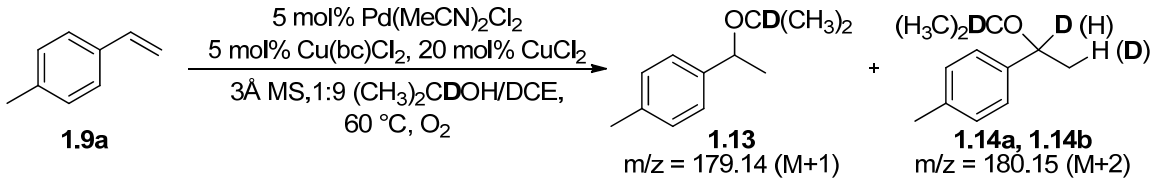


m/z	abund.
176.65	6
176.85	3
177.15	19
178.15	611
178.90	6
179.15	79
179.60	2
179.90	5
180.20	3

Calculation of D incorporation:

# of D atoms	0	1	
	M	**M+1**	
molecular ions	178	179	
abund. unlabeled	786	117	(M+1)/M not labeled:
abund. labeled	756	116	0.15
relative abund. unlabeled	100.00	14.89	
relative abund. labeled	100.00	15.34	
no D	**100.00**	14.89	100 * 0.15 = 14.89
difference		0.46	
1 D		**0.46**	
			sum rel. abund.:
			100.46
percent distribution:	**99.5**	**0.5**	

4-methylstyrene w/ $(CH_3)_2CDOH$

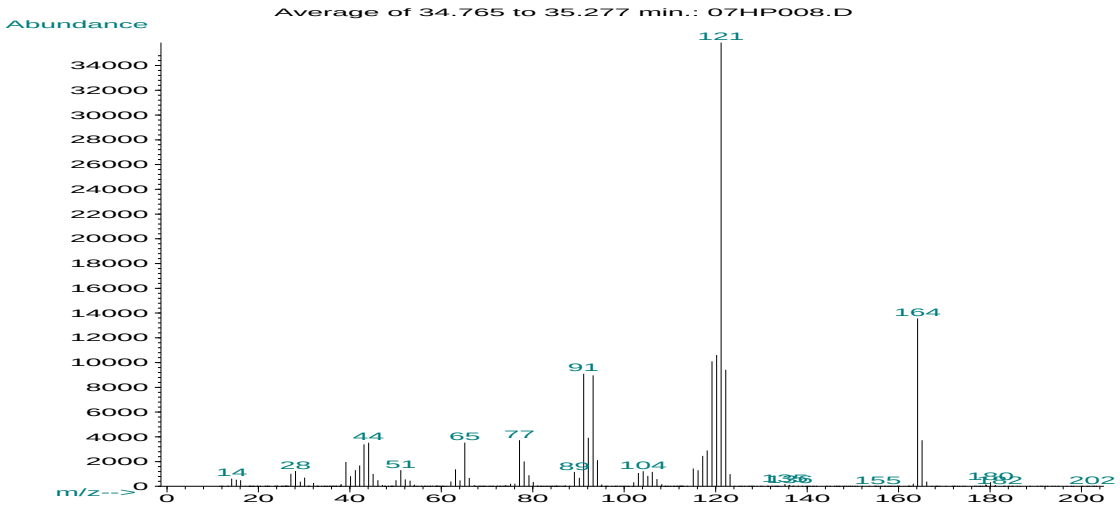


1.9a

1.13
m/z = 179.14 (M+1)

1.14a, 1.14b
m/z = 180.15 (M+2)

GC/MS data for products:

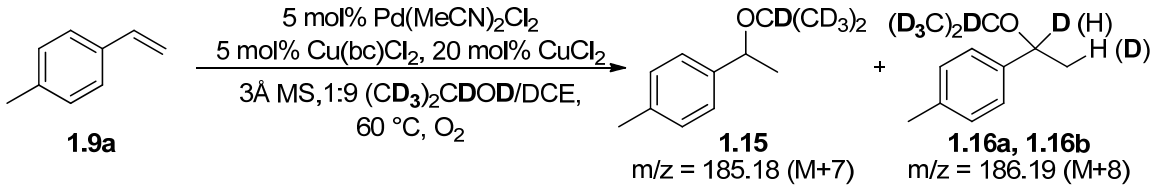


m/z	abund.	m/z	abund.
176.85	2	179.05	142
177.25	10	179.25	111
177.50	4	180.10	346
177.80	3	180.90	1
178.10	12	181.15	118
178.30	3	182.10	13

Calculation of D incorporation:

# of D atoms	0	1	2	3	
	M	**M+1**	**M+2**	**M+3**	
molecular ions	178	179	180	181	
abund. unlabeled	786	117			(M+1)/M not labeled:
abund. labeled	17	253	346	119	0.15
relative abund. unlabeled	100.00	14.89			
relative abund. labeled	4.91	73.12	100.00	34.39	
no D	**4.91**	0.73			4.91 * 0.15 = 0.73
difference		72.39	100.00	34.39	
1 D		**72.39**	10.78		72.39 * 0.15 = 10.78
difference			89.22	34.39	
2 D			**89.22**	13.28	89.22 * 0.15 = 13.28
difference				21.11	
3 D				**21.11**	
					sum rel. abund.:
percent distribution:	**2.6**	**38.6**	**47.6**	**11.3**	187.63

4-methylstyrene w/ *i*PrOH-d_8

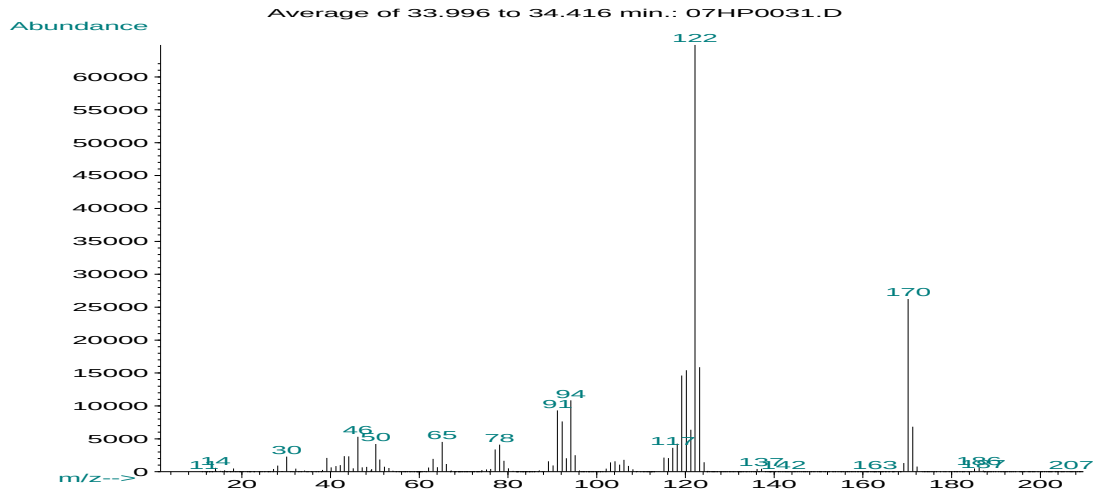


1.9a

1.15
m/z = 185.18 (M+7)

1.16a, 1.16b
m/z = 186.19 (M+8)

GC/MS data for products:



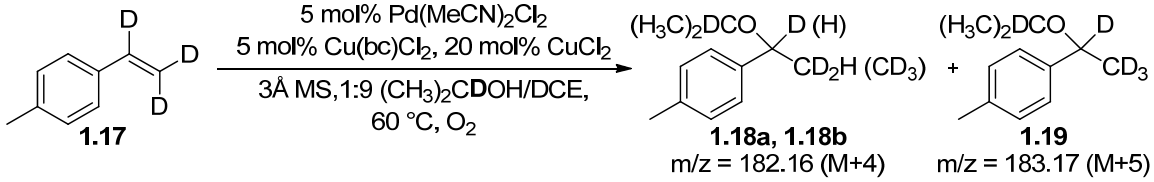
m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
177.35	5	179.60	2	182.30	5	184.10	8
178.15	3	179.80	3	182.45	3	184.20	5
178.55	5	180.55	7	182.75	10	184.35	5
178.65	2	180.90	5	183.20	27	185.05	22
178.80	2	181.20	9	183.60	2	185.10	111
179.35	9	181.80	7	184.05	36	185.20	328

m/z	abund.
186.20	576
187.20	201
187.50	5
187.95	10
188.20	19
188.40	10

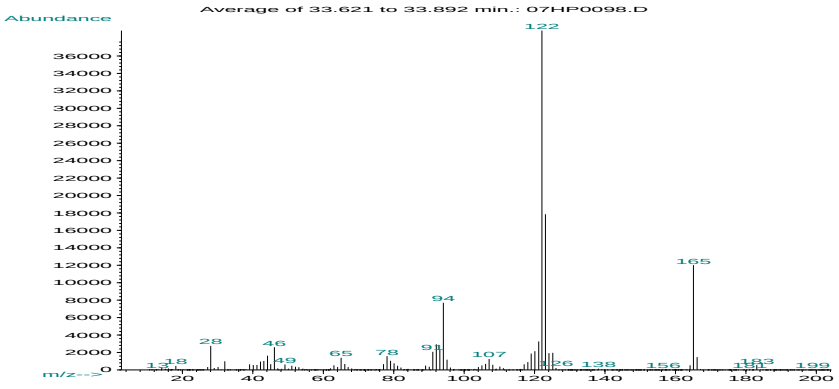
Calculation of D incorporation:

# of D atoms	0	1	…	7	8	9	
	M	**M+1**	**…**	**M+7**	**M+8**	**M+9**	
molecular ions	178	179	…	185	186	187	
abund. unlabeled	786	117					(M+1)/M not labeled:
abund. labeled				461	576	201	0.15
relative abund. unlabeled	100.00	14.89					
relative abund. labeled				80.03	100.00	34.90	
7 D				**80.03**	11.91		80.03 * 0.15 = 11.91
difference					88.09	34.90	
8 D					**88.09**	13.11	88.09 * 0.15 = 13.11
difference						21.78	
9 D						**21.78**	
							sum rel. abund.:
percent distribution:				**42.1**	**46.4**	**11.5**	189.90

4-methylstyrene-d_3 w/ $(CH_3)_2CDOH$



GC/MS data for products:

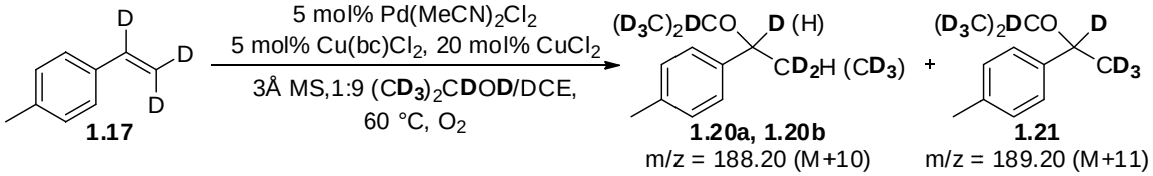


m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
176.75	5	178.55	3	180.75	3	184.35	5
177.00	5	178.80	15	181.10	42	184.65	4
177.15	3	179.10	14	181.30	17	185.00	9
177.30	17	179.45	3	182.00	52	185.20	15
177.80	14	179.70	9	182.20	89		
178.05	10	180.00	15	183.20	602		
178.35	17	180.50	12	184.10	93		

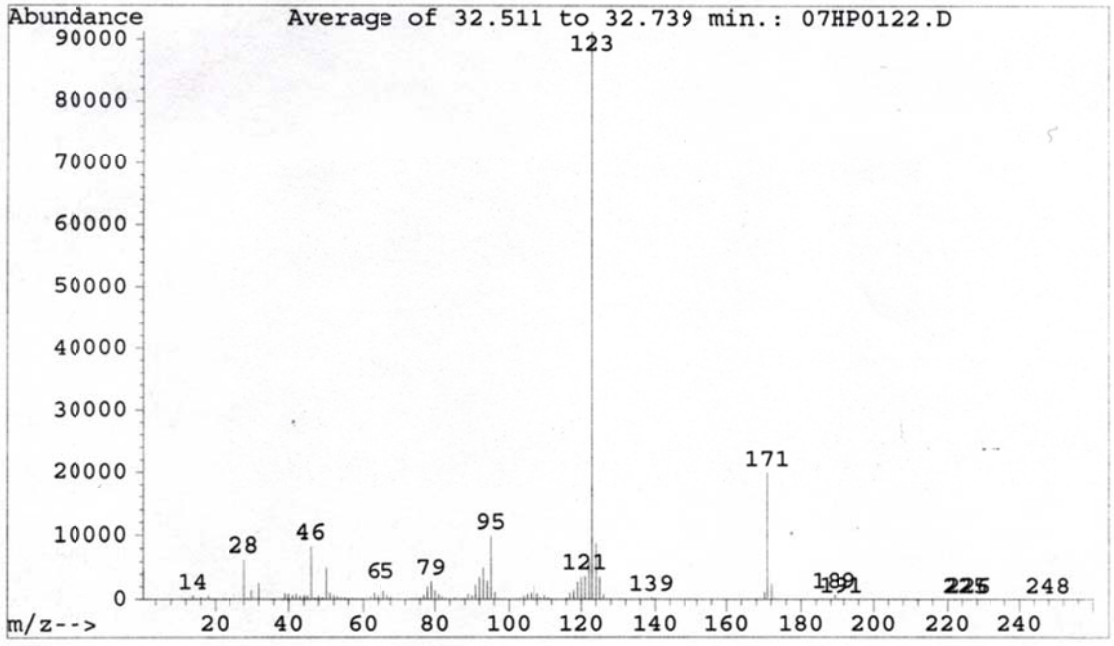
Calculation of D incorporation:

# of D atoms	0	1	…	3	4	5	6	
	M	**M+1**	**…**	**M+3**	**M+4**	**M+5**	**M+6**	
molecular ions	178	179	…	181	182	183	184	
abund. unlabeled	786	117						(M+1)/M not labeled:
abund. labeled				74	141	602	98	0.15
relative abund. unlabeled	100.00	14.89						
relative abund. labeled				12.29	23.42	100.00	16.28	
3 D				**12.29**	1.83			12.29 * 0.15 = 1.83
difference					21.59	100.00	16.28	
4 D					**21.59**	3.21		21.59 * 0.15 = 3.21
difference						96.79	16.28	
5 D						**96.79**	14.41	96.79 * 0.15 = 14.41
difference							1.87	
								sum rel. abund.:
percent distribution:				**9.4**	**16.5**	**74.1**		130.67

4-methylstyrene-d_3 w/ *i*PrOH-d_8



GC/MS data for products:



m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
176.75	13	178.05	5	180.10	10	181.40	17
177.05	9	178.30	9	180.40	14	181.85	23
177.15	2	178.50	19	180.45	8	182.10	9
177.30	13	179.05	21	180.55	2	182.40	13
177.45	6	179.25	3	180.65	3	182.65	12
177.65	2	179.65	21	180.80	3	182.80	9
177.85	19	179.85	3	181.05	7	183.00	8

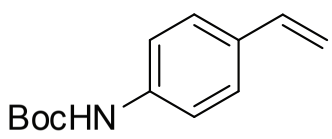
m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
183.20	11	185.20	29	186.85	5	189.15	762
183.35	3	185.45	11	187.00	48	190.10	128
183.55	12	185.85	36	187.25	25	190.50	14
183.85	17	185.95	1	187.50	5	190.75	4
184.20	9	186.10	21	187.65	2	190.90	2
184.45	20	186.35	9	187.80	14	191.10	39
184.80	15	186.70	10	188.10	154		

Calculation of D incorporation:

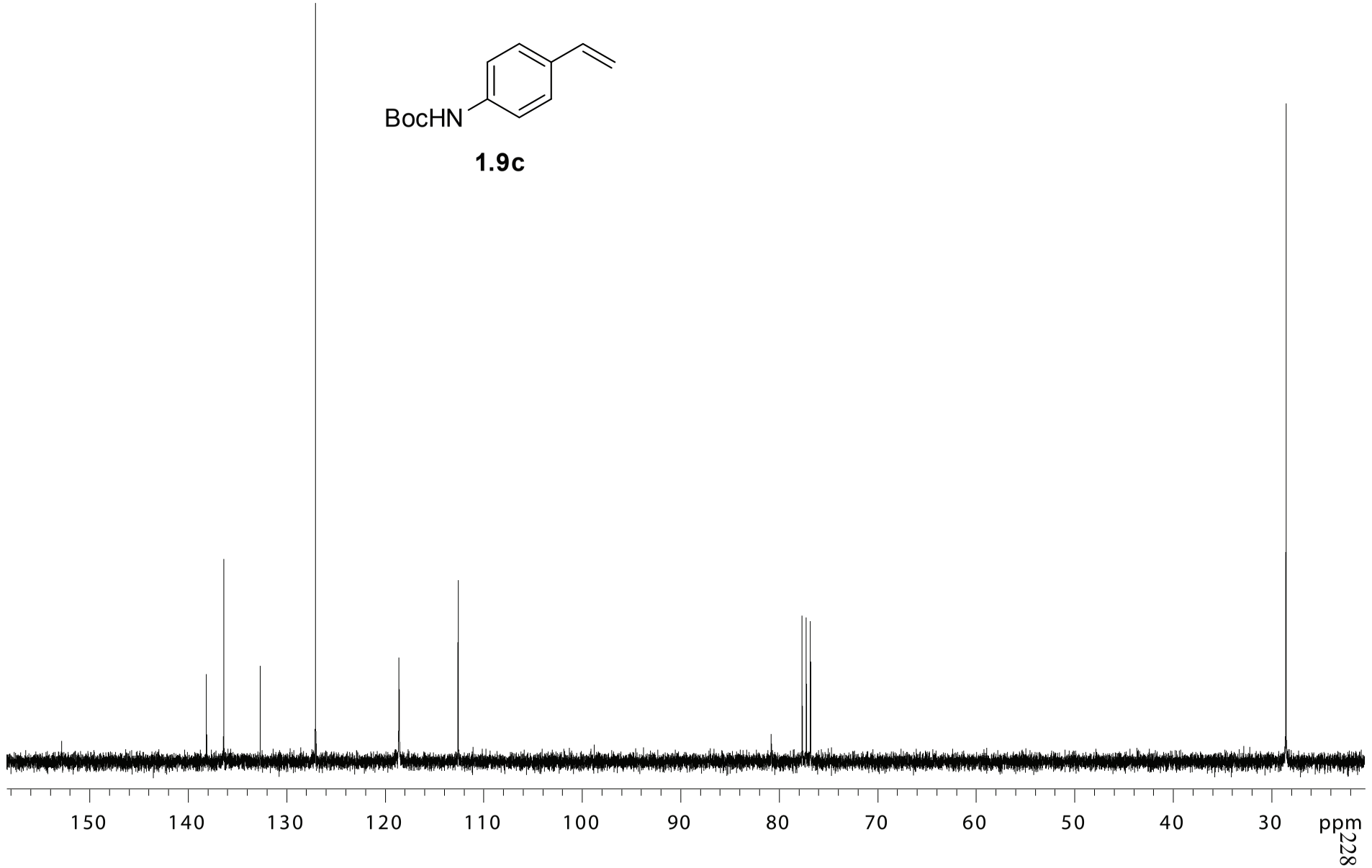
# of D atoms	0	1	…	10	11	12	
	M	**M+1**	**…**	**M+10**	**M+11**	**M+12**	
molecular ions	178	179	…	188	189	190	
abund. unlabeled	786	117					(M+1)/M not labeled:
abund. labeled				175	762	128	0.15
relative abund. unlabeled	100.00	14.89					
relative abund. labeled				22.97	100.00	16.80	
10 D				**22.97**	3.42		22.97 * 0.15 = 3.42
difference					96.58	16.80	
11 D					**96.58**	14.38	96.58 * 0.15 = 14.38
difference						2.42	
							sum rel. abund.:
							119.55
percent distribution:				**19.2**	**80.8**		

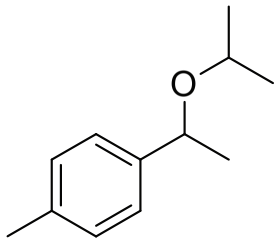
APPENDIX B:

NMR SPECTRA FOR CHAPTER 1



1.9c

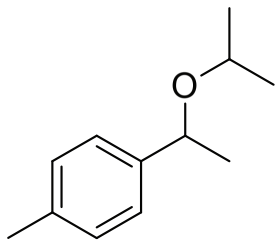

BocHN
1.9c
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm



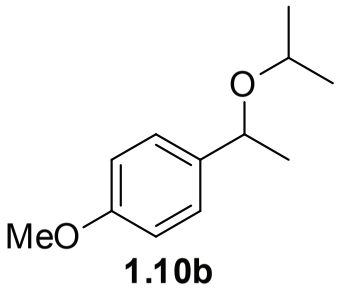
1.10a

8 7 6 5 4 3 2 1 ppm

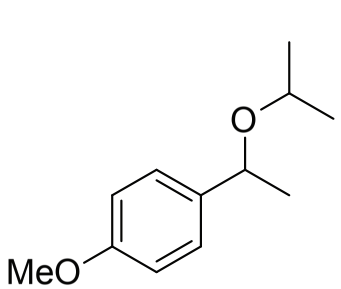
3.66 1.00 0.99 2.94 3.07 6.09



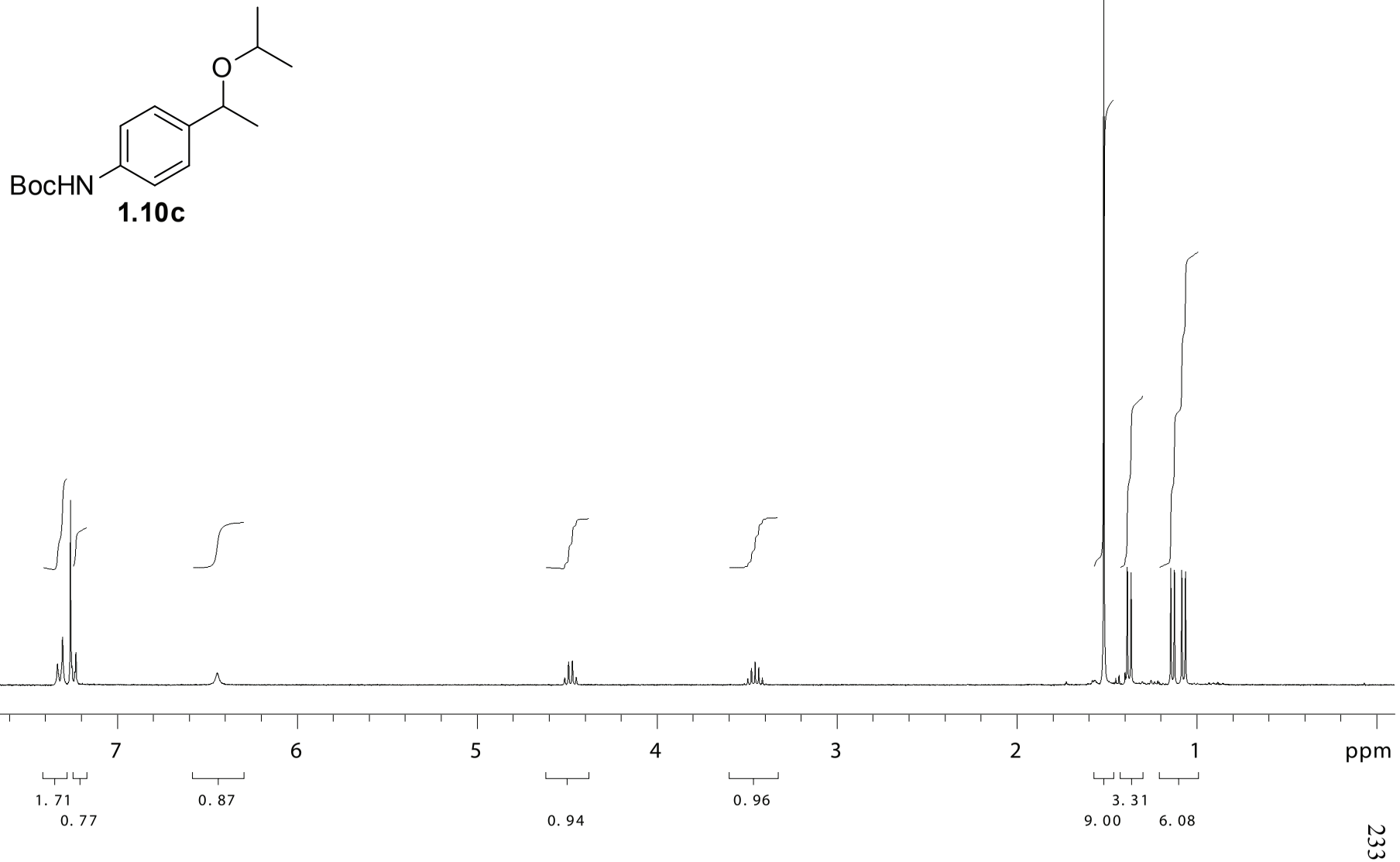
1.10a

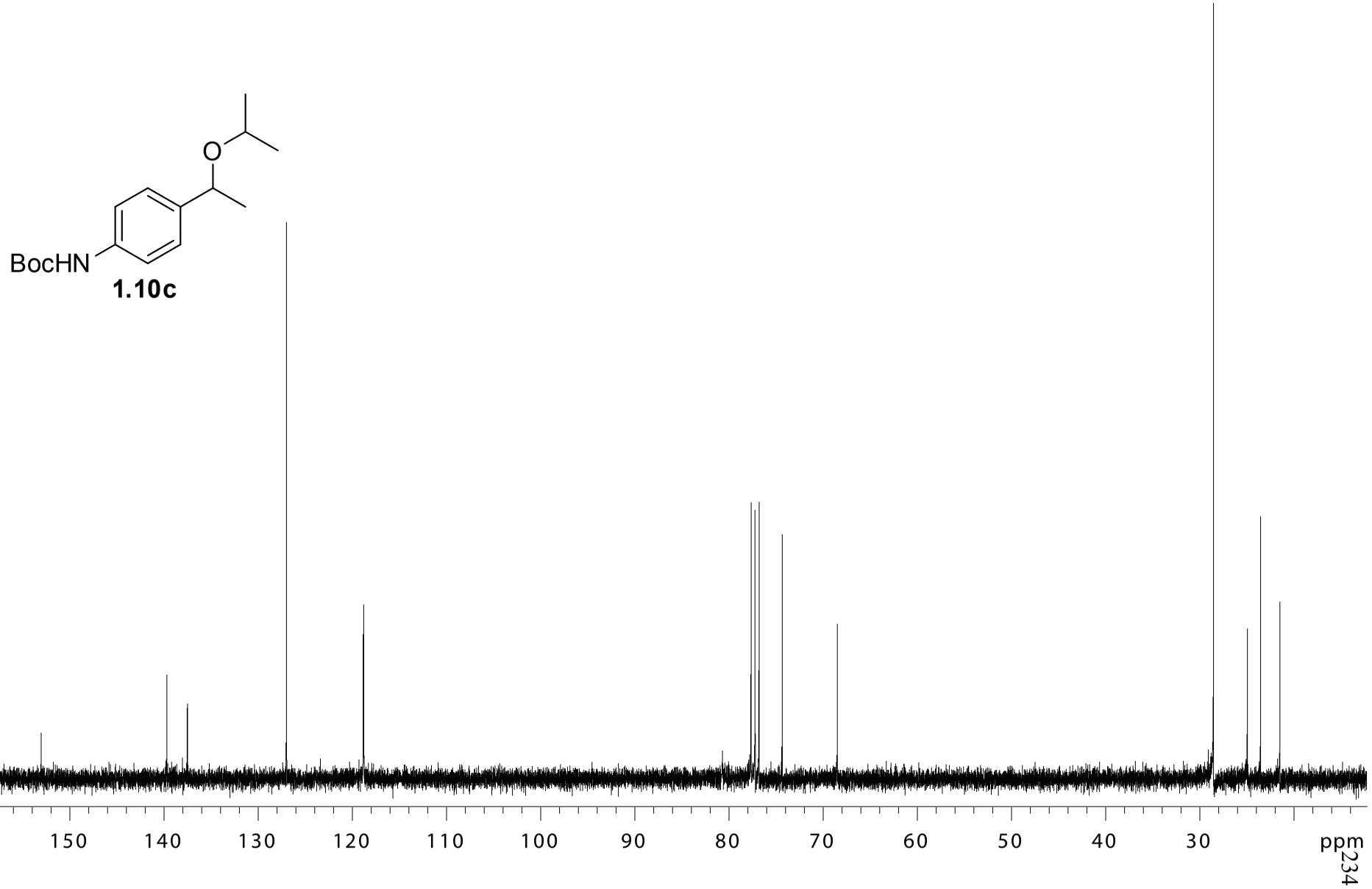


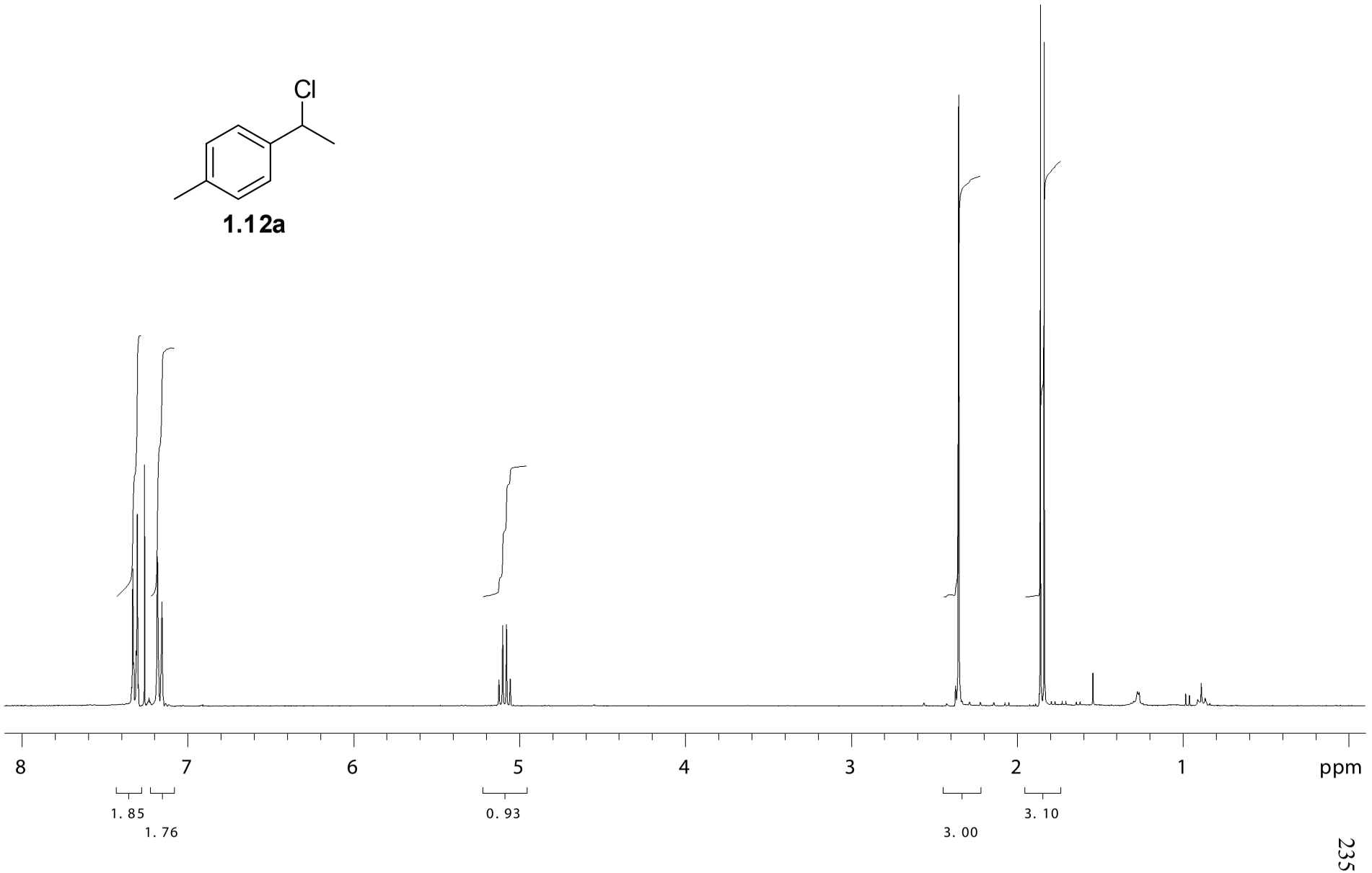
1.10b

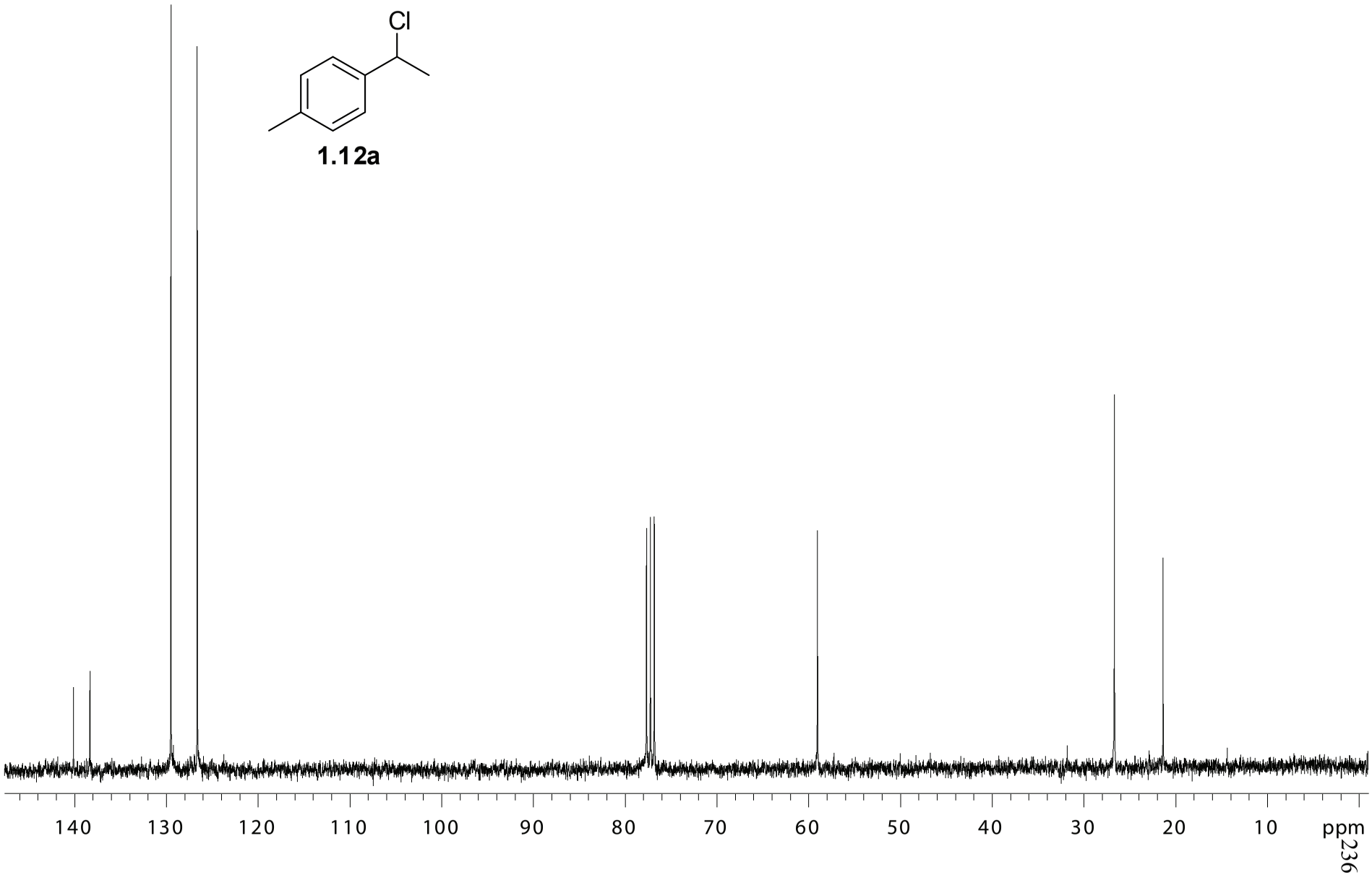


1.10b


O
BocHN
1.10c
7
6
5
4
3
2
1
ppm
1. 71
0. 77
0. 87
0. 94
0. 96
3. 31
9. 00
6. 08


O
BocHN
1.10c
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm
234


Cl
1.12a
8
7
6
5
4
3
2
1
ppm
1. 85
1. 76
0. 93
3. 00
3. 10


Cl
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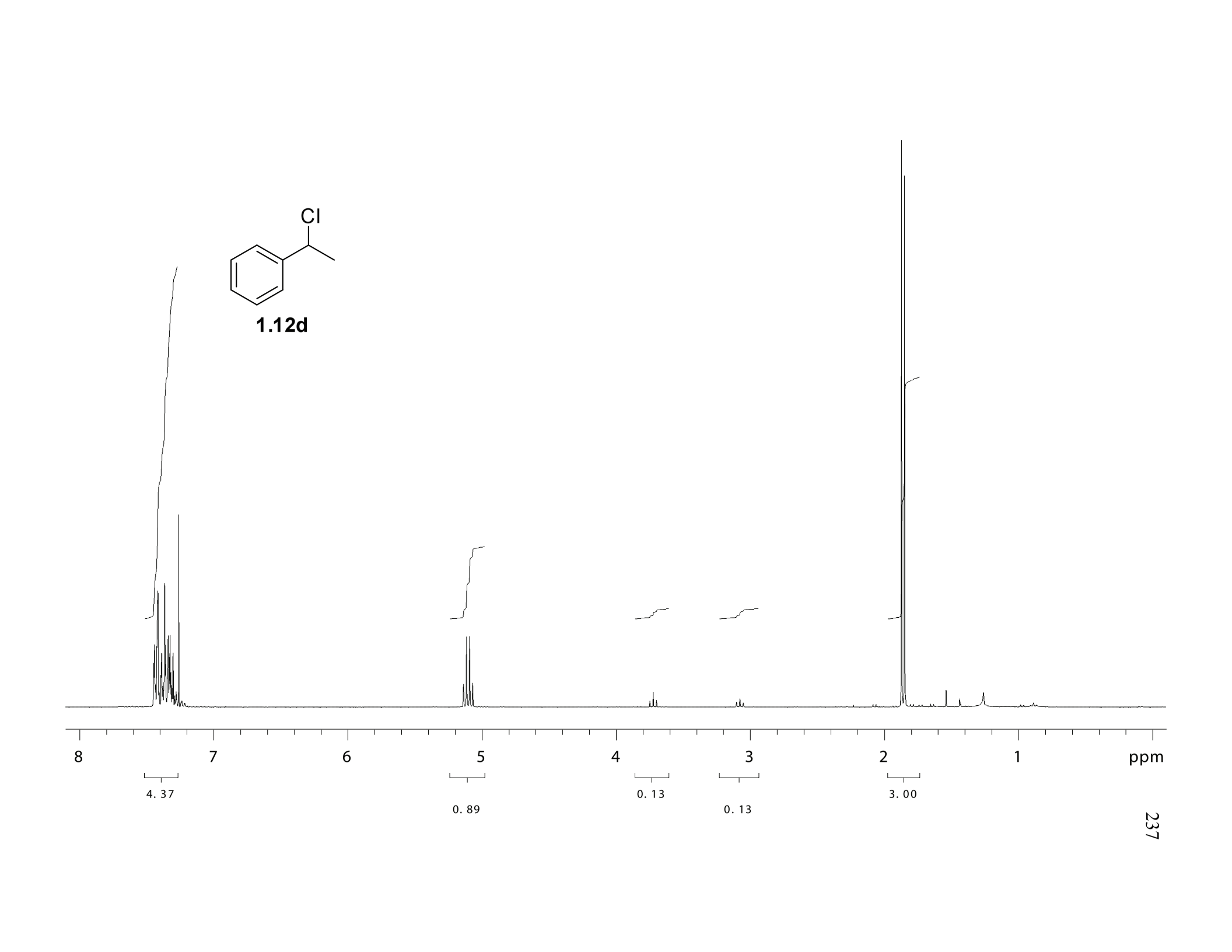
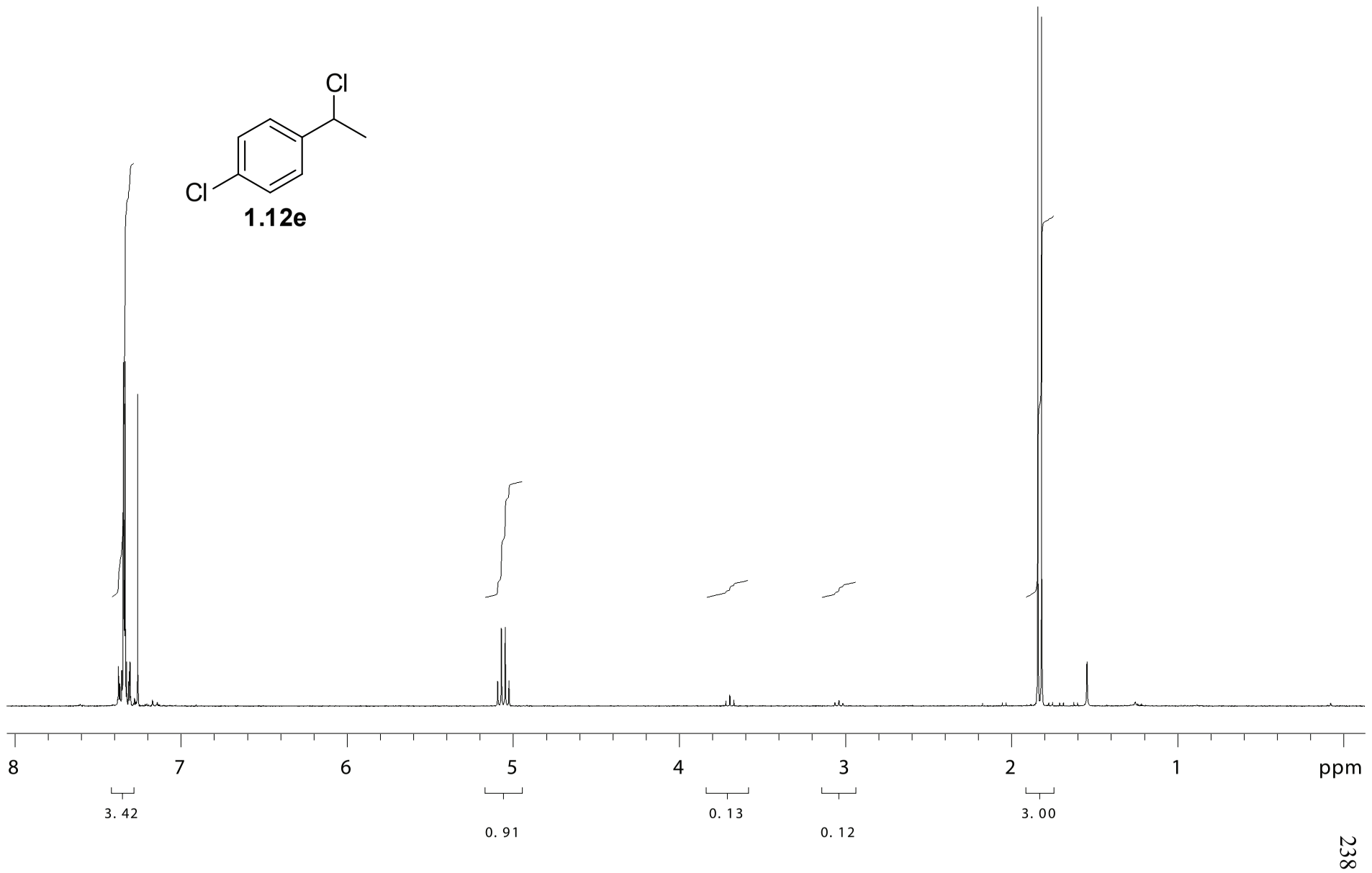
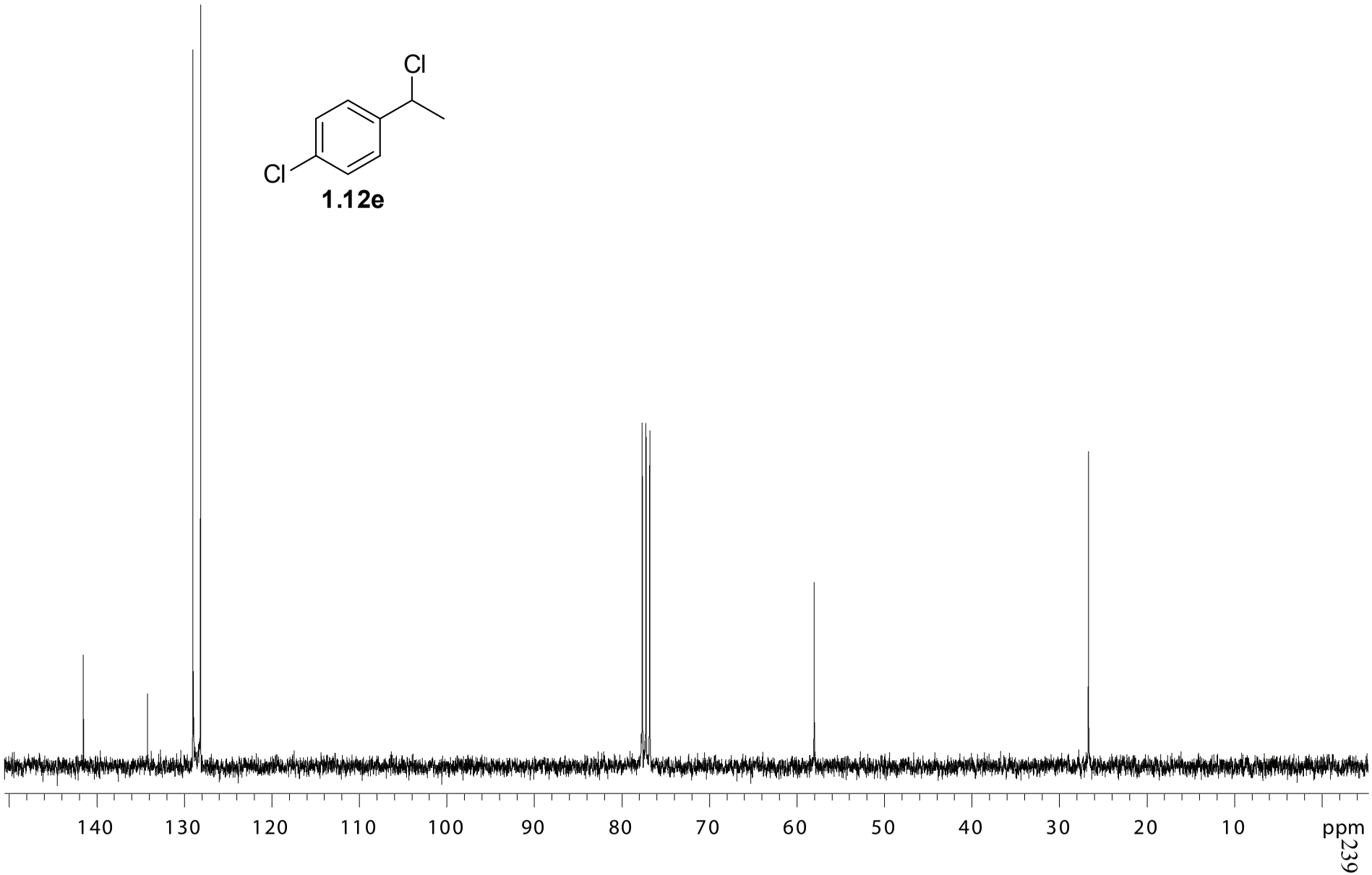
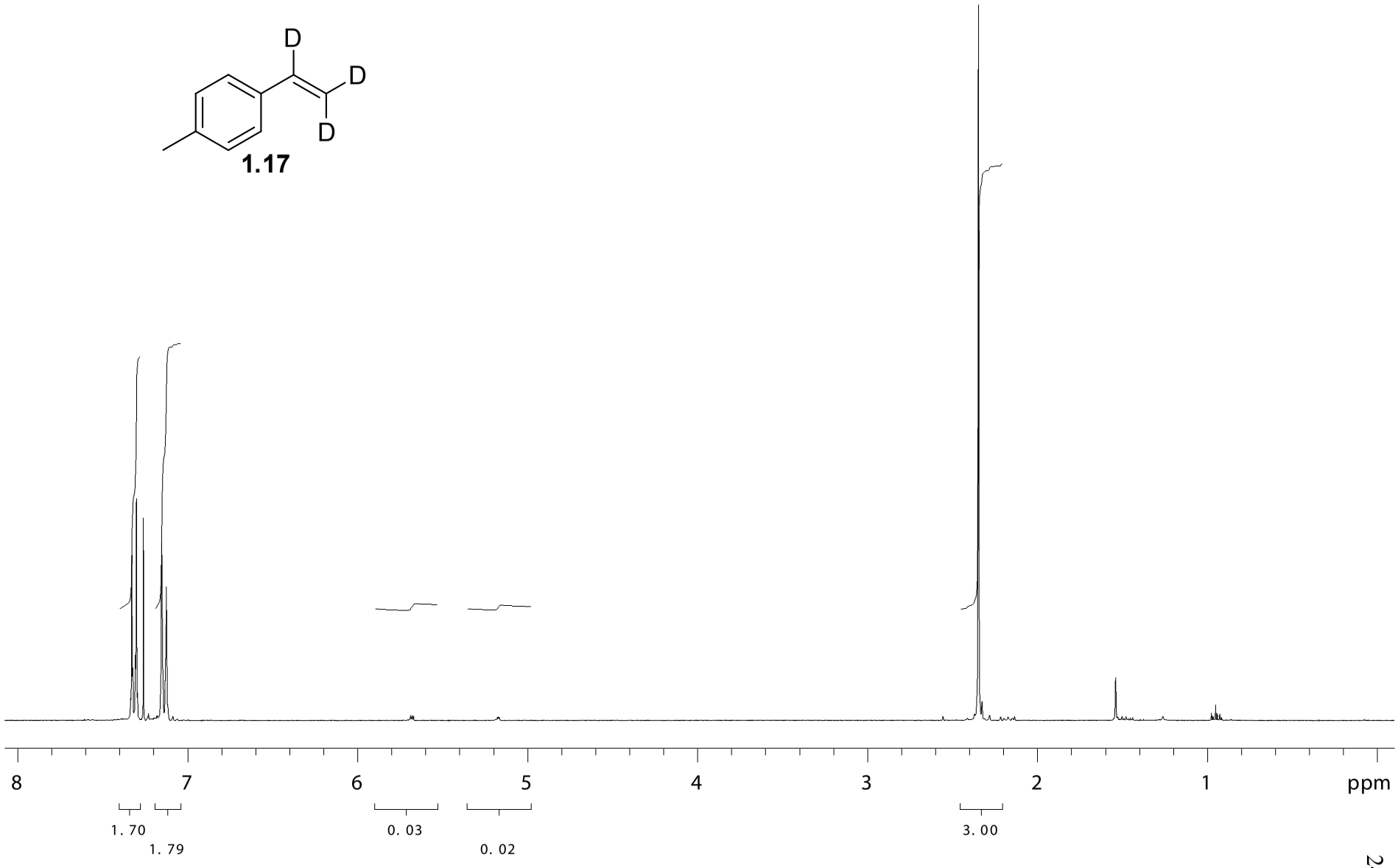
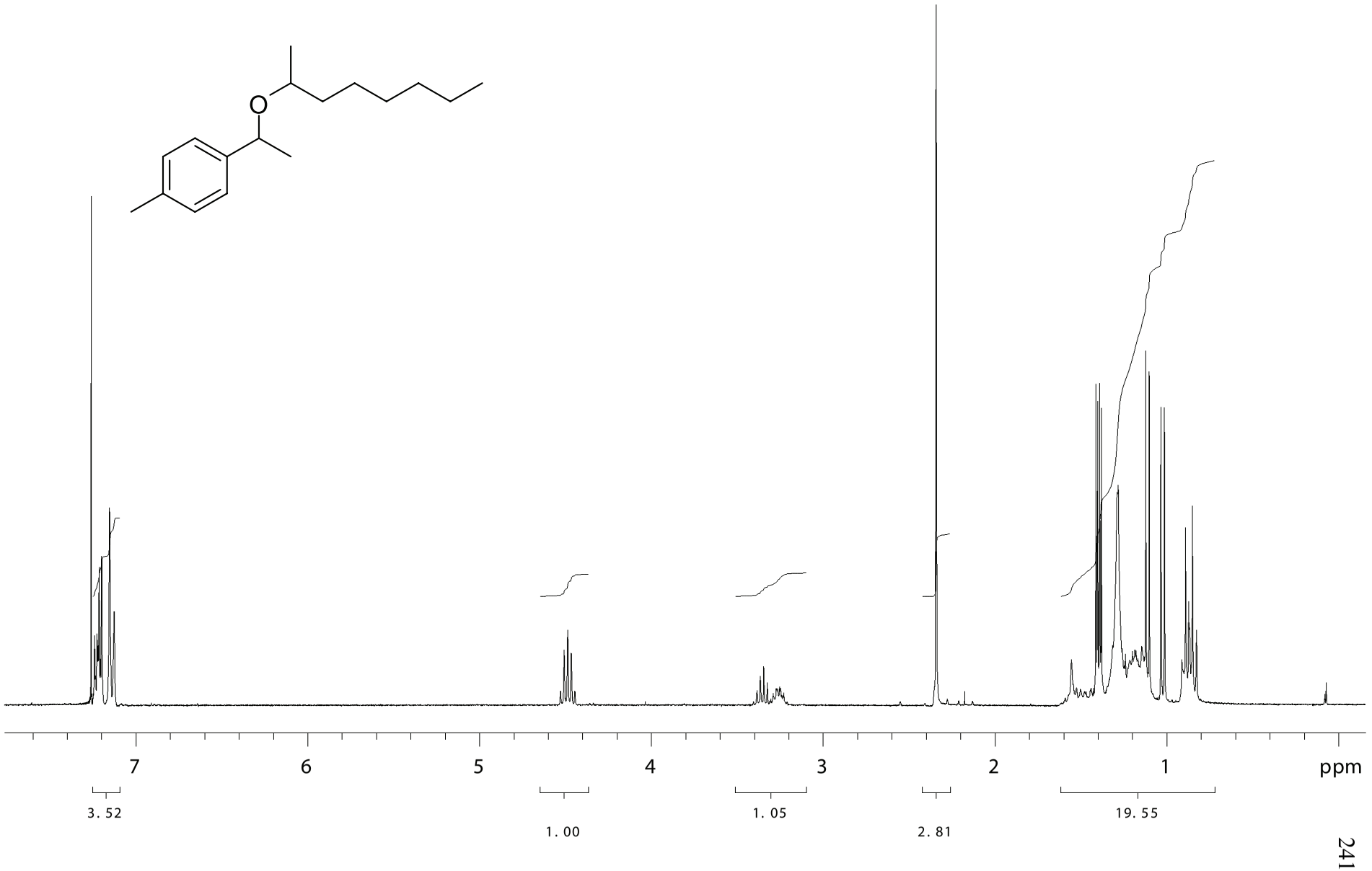
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

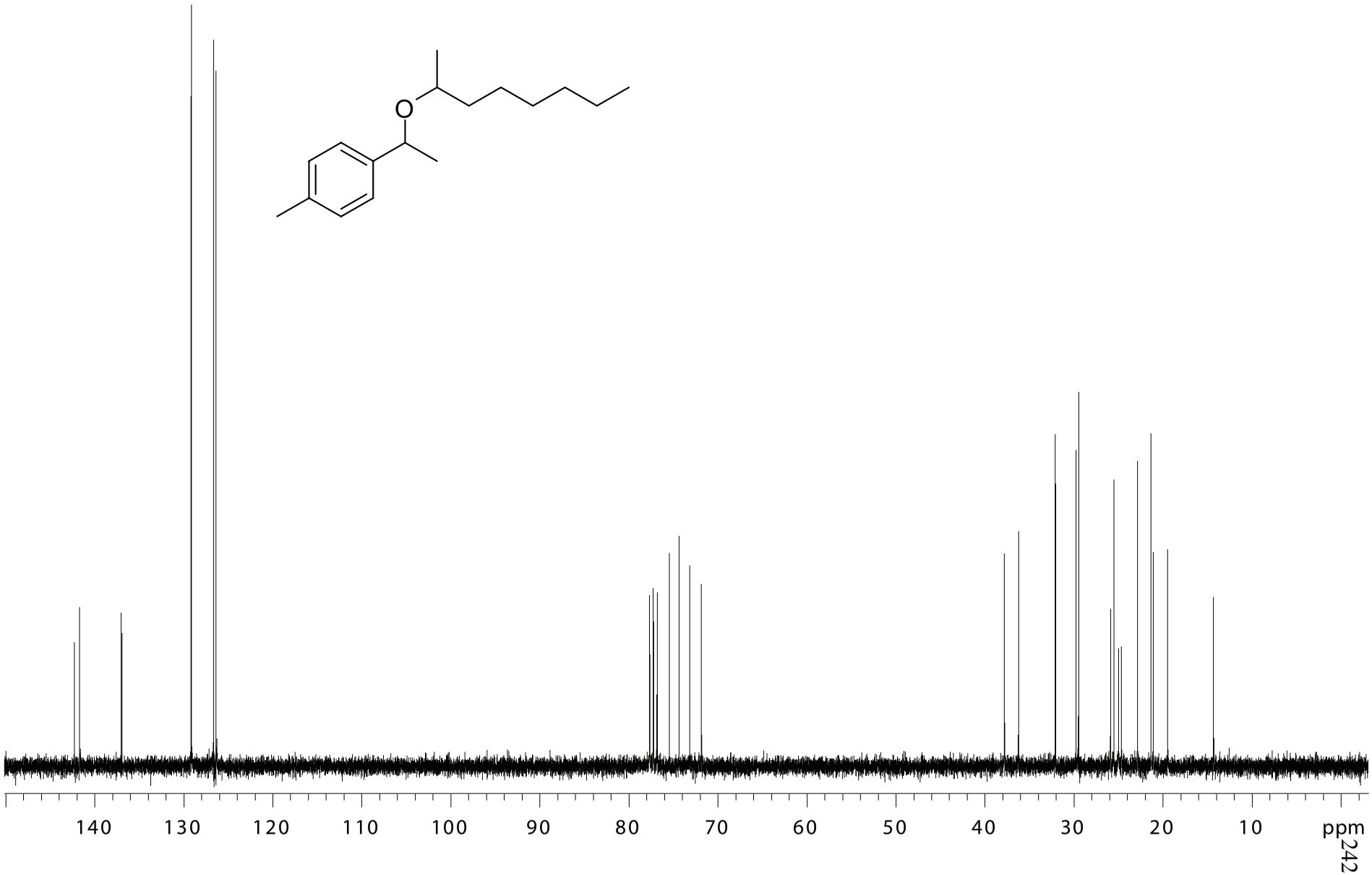

Cl
1.12d
8
7
6
5
4
3
2
1
ppm
4. 37
0. 89
0. 13
0. 13
3. 00


Cl
Cl
1.12e
8
7
6
5
4
3
2
1
ppm
3. 42
0. 91
0. 13
0. 12
3. 00


Cl
Cl
1.12e
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

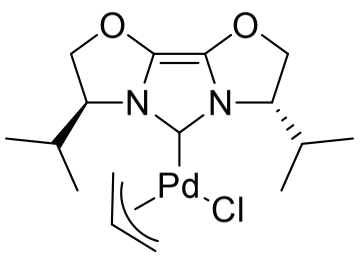

D
D
D
1.17
8
7
6
5
4
3
2
1
ppm
1. 70
1. 79
0. 03
0. 02
3. 00


O
7
6
5
4
3
2
1
ppm
3. 52
1. 00
1. 05
2. 81
19. 55

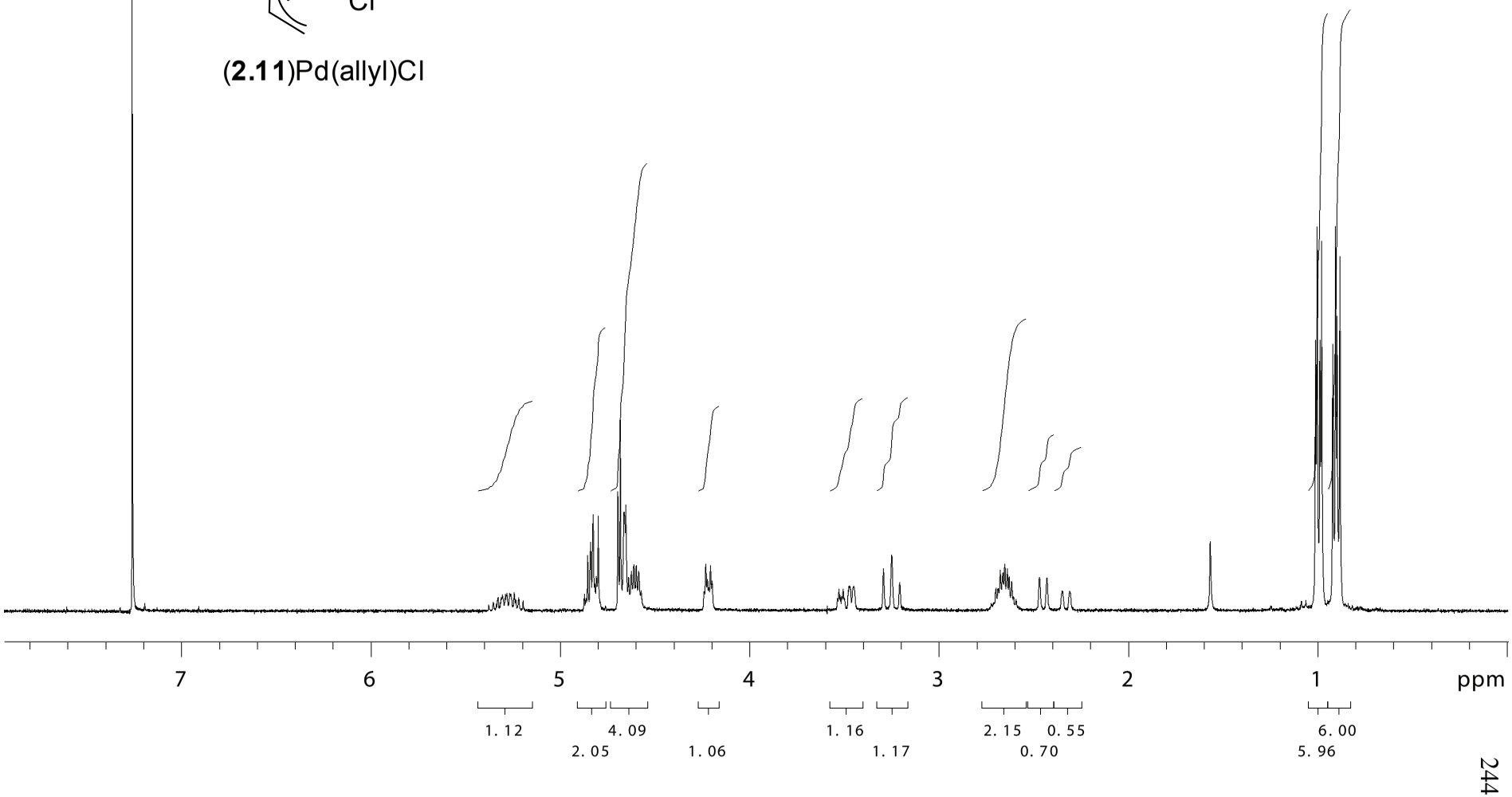

O
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

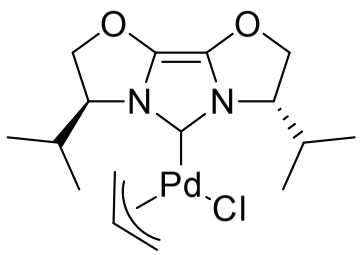
APPENDIX C:

NMR SPECTRA FOR CHAPTER 2

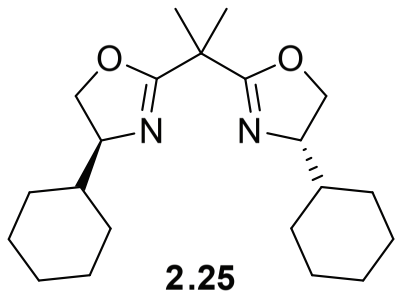


(**2.11**)Pd(allyl)Cl



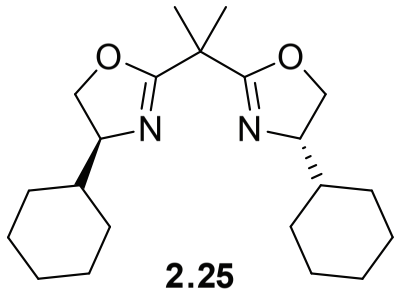


(**2.11**)Pd(allyl)Cl



2.25

((*S*)-CyBox)



2.25

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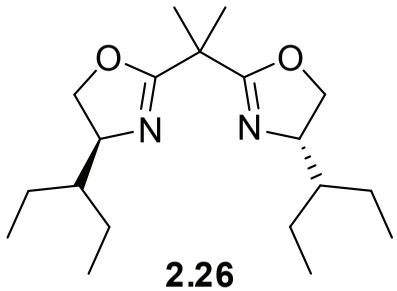

2.26

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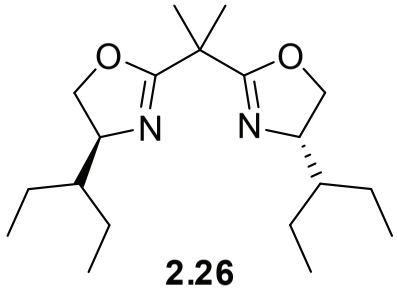
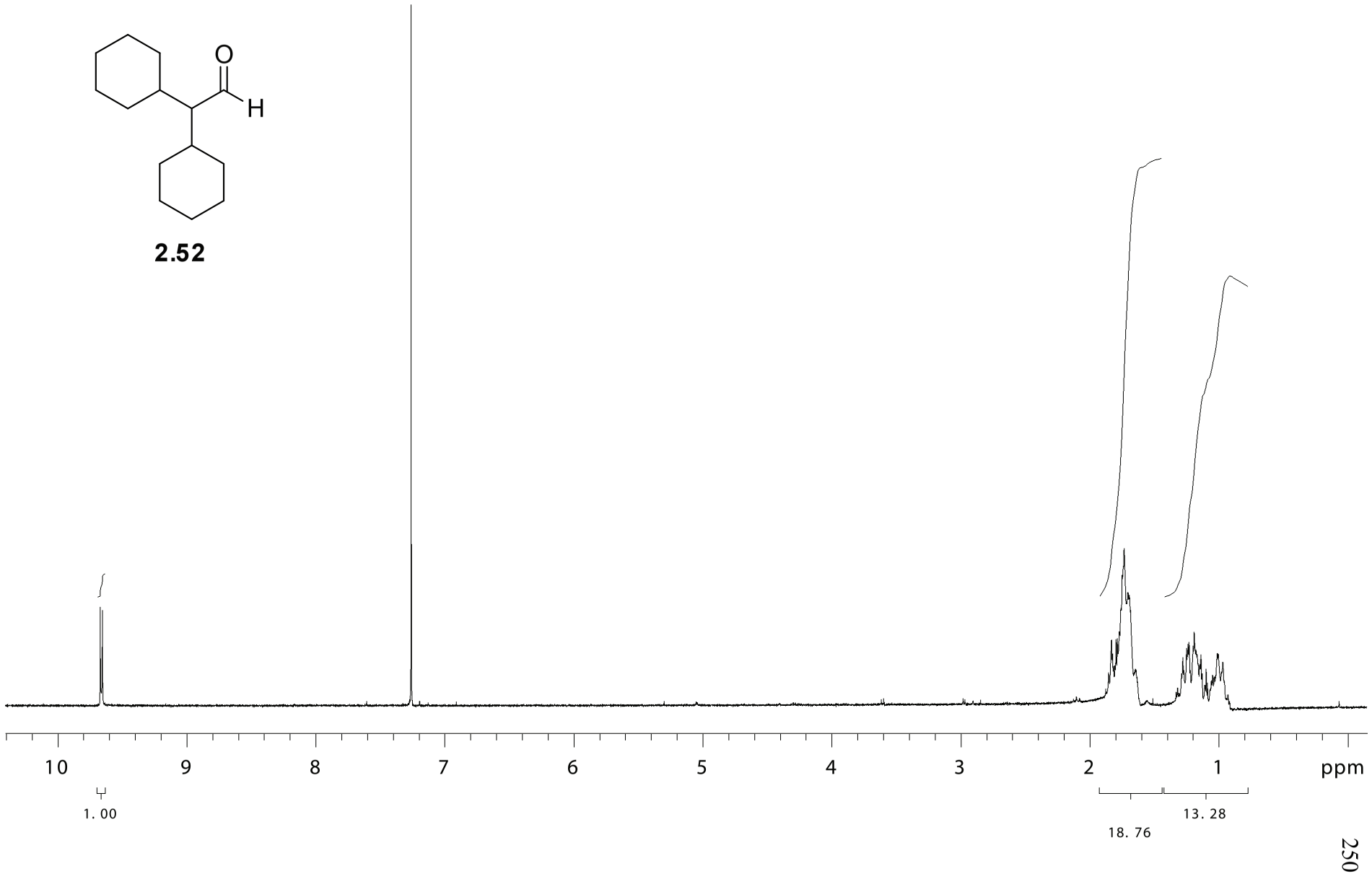
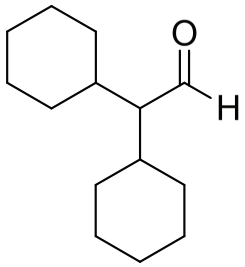


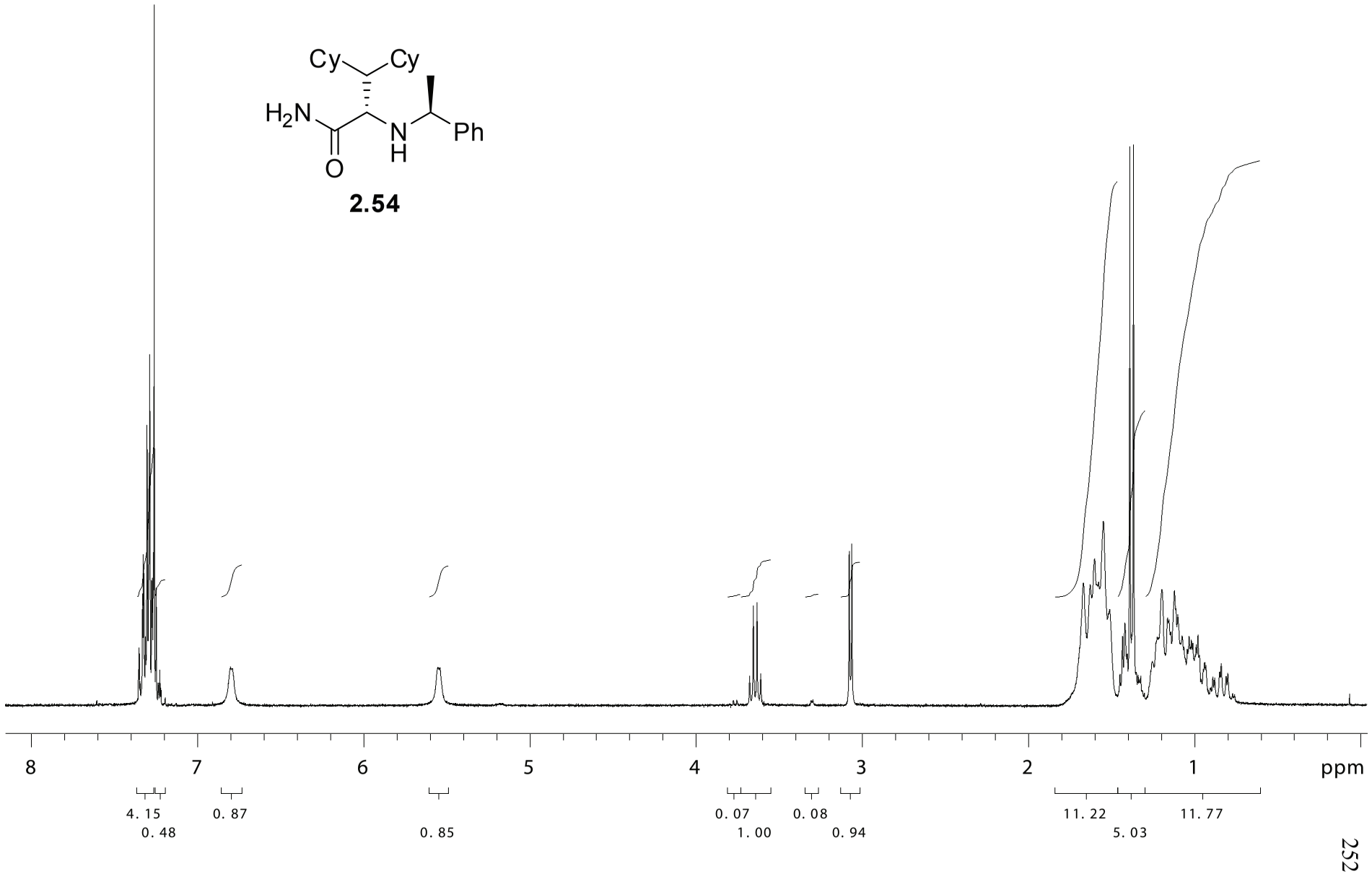
2.26

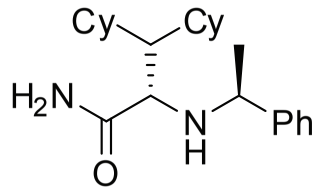
((*S*)-diEtBox)


O
H
2.52
10
9
8
7
6
5
4
3
2
1
ppm
1. 00
18. 76
13. 28

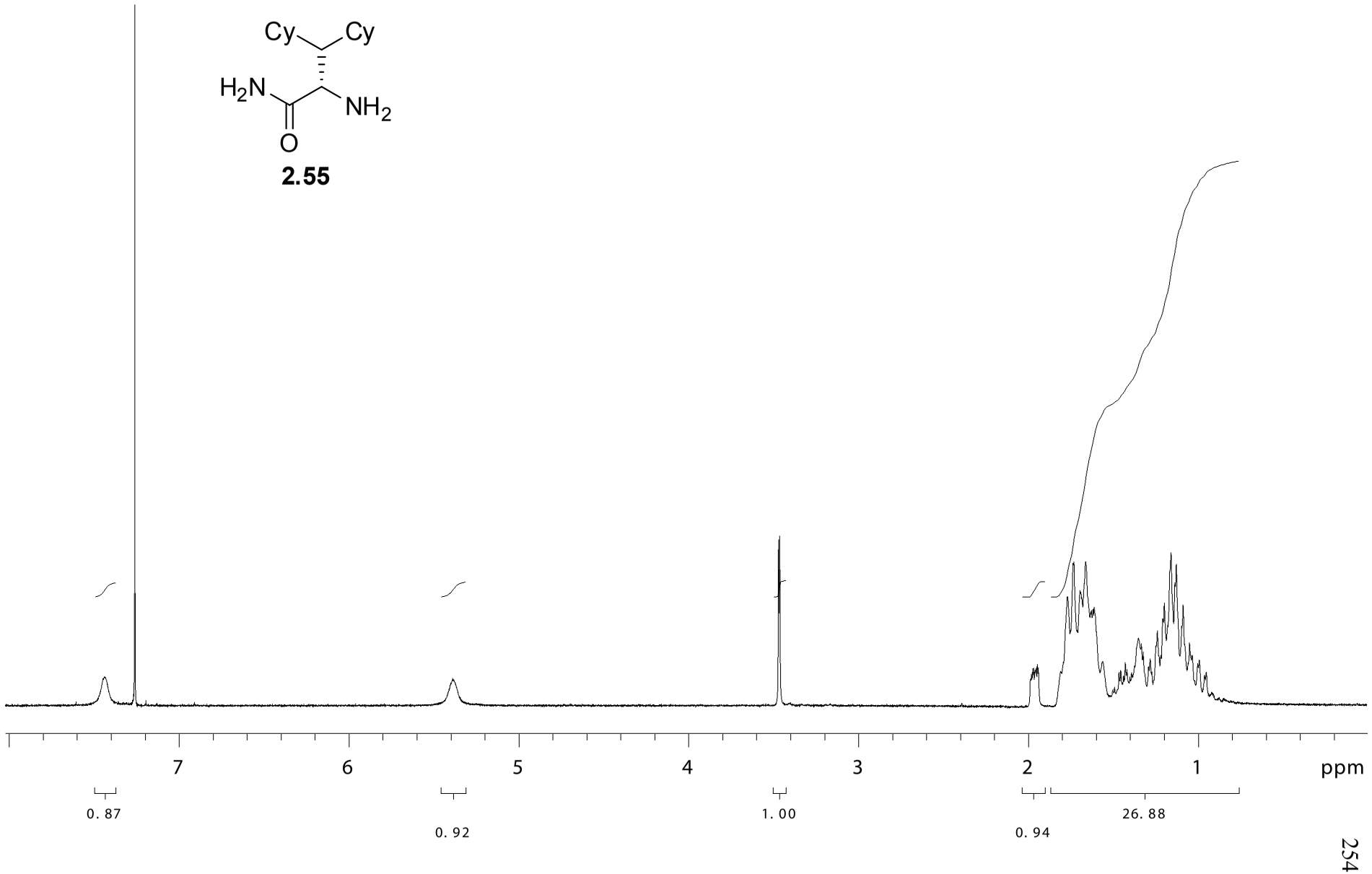


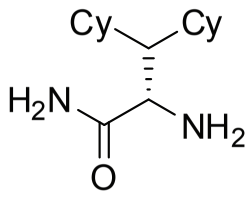
2.52


Cy
Cy
H2N
N
H
Ph
O
2.54
8
7
6
5
4
3
2
1
ppm
4. 15
0. 48
0. 87
0. 85
0. 07
1. 00
0. 08
0. 94
11. 22
11. 77
5. 03

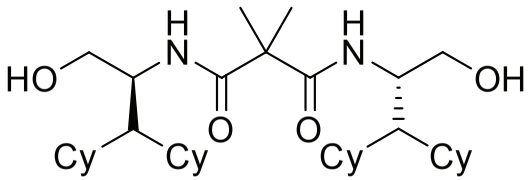


2.54


Cy
Cy
H2N
NH2
O
2.55
7
6
5
4
3
2
1
ppm
0. 87
0. 92
1. 00
0. 94
26. 88

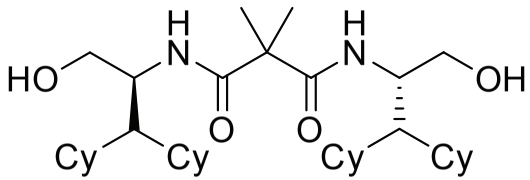


2.55

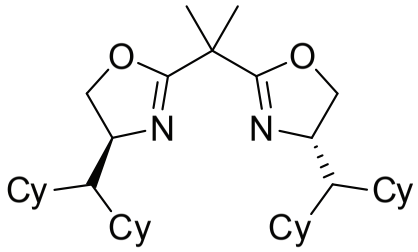

HO
H
N
O
O
H
N
OH
Cy
Cy
Cy
Cy

2.58

7
6
5
4
3
2
1
ppm
1. 79
2. 00
2. 07
2. 08
2. 10
29. 71
21. 23

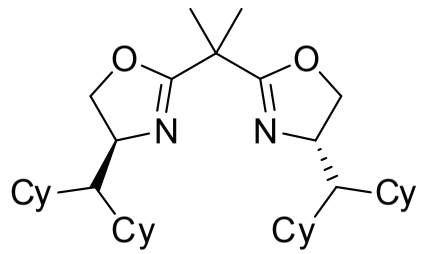


2.58



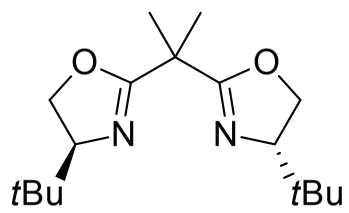
2.28

((*S*)-diCyBox)

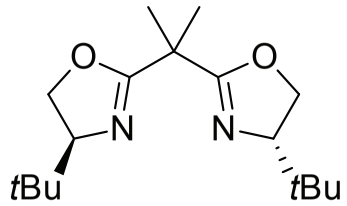


2.28

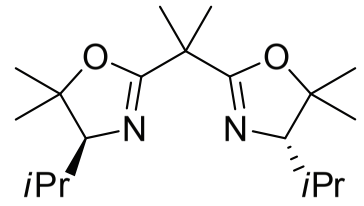
((*S*)-diCyBox)



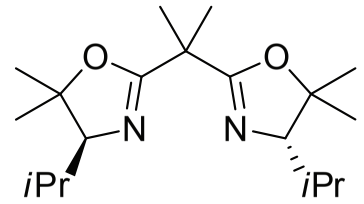
Pd((*S*)-*t*BuBox)Cl_2



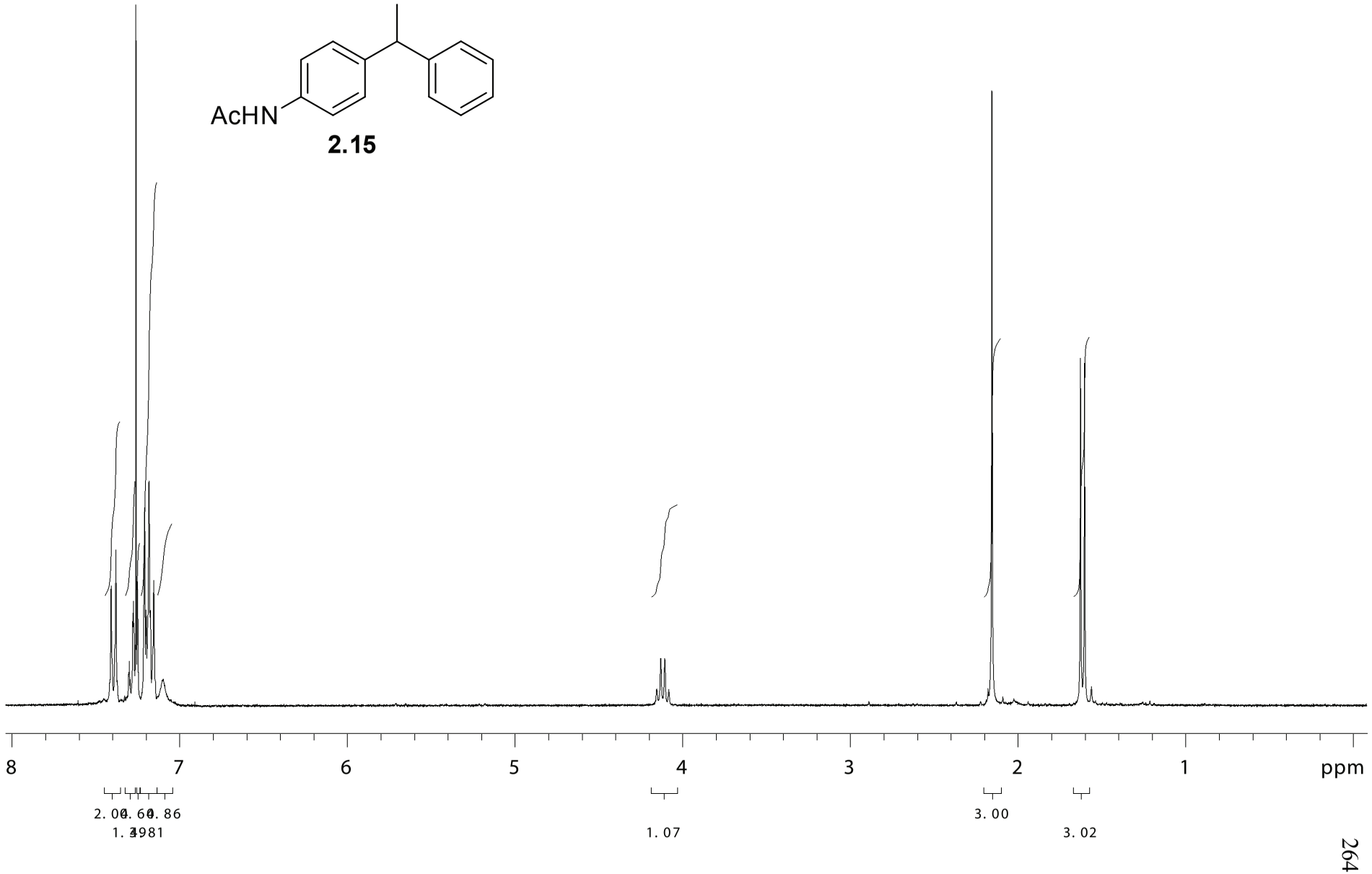
Pd((*S*)-*t*BuBox)Cl_2

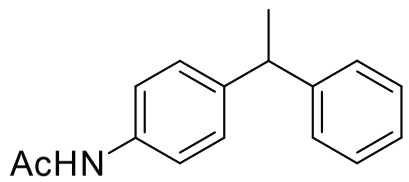


Pd((*S*)-diMe*i*PrBox)Cl_2



Pd((*S*)-diMe*i*PrBox)Cl_2

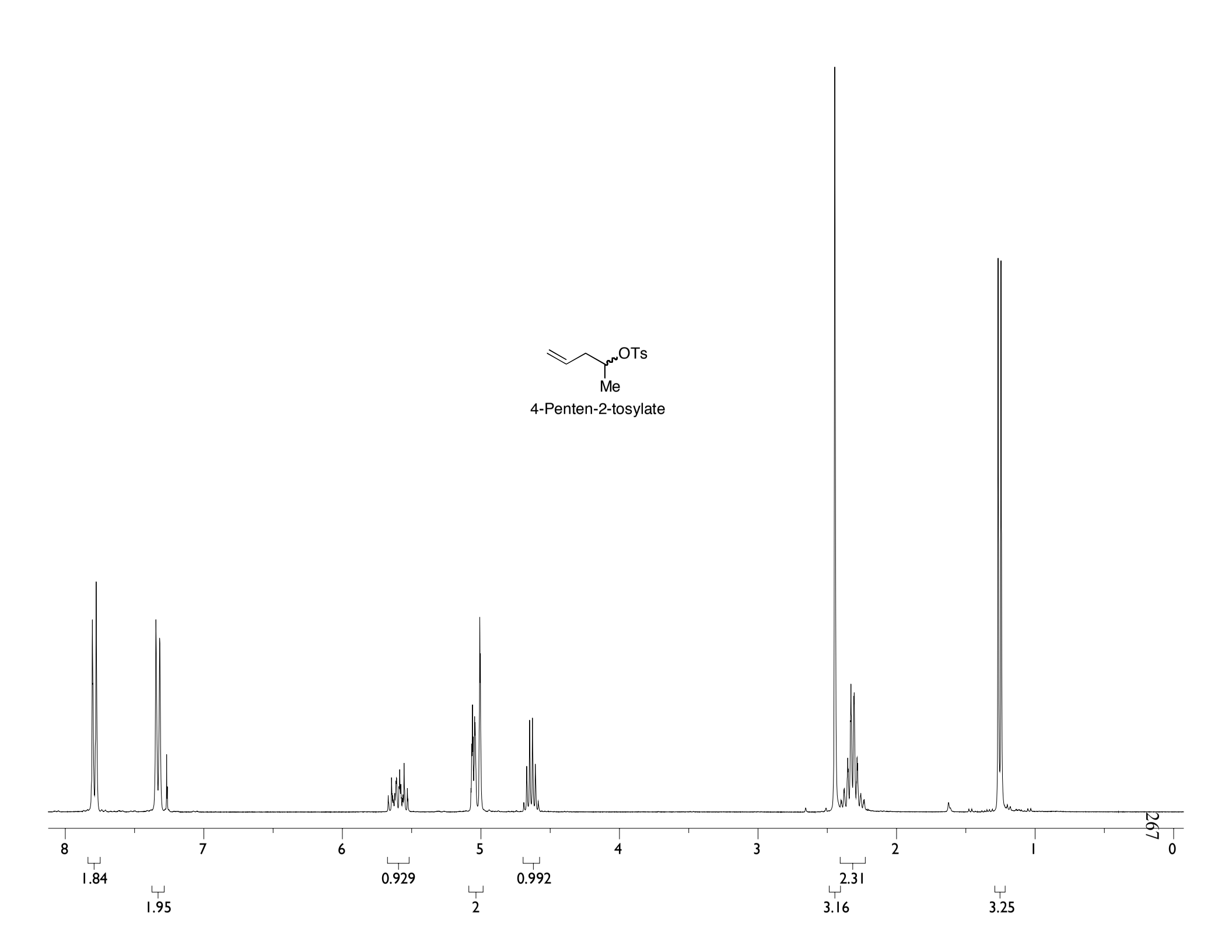

AcHN
2.15
8
7
6
5
4
3
2
1
ppm
2.00
0.60
0.86
1.07
3.00
3.02

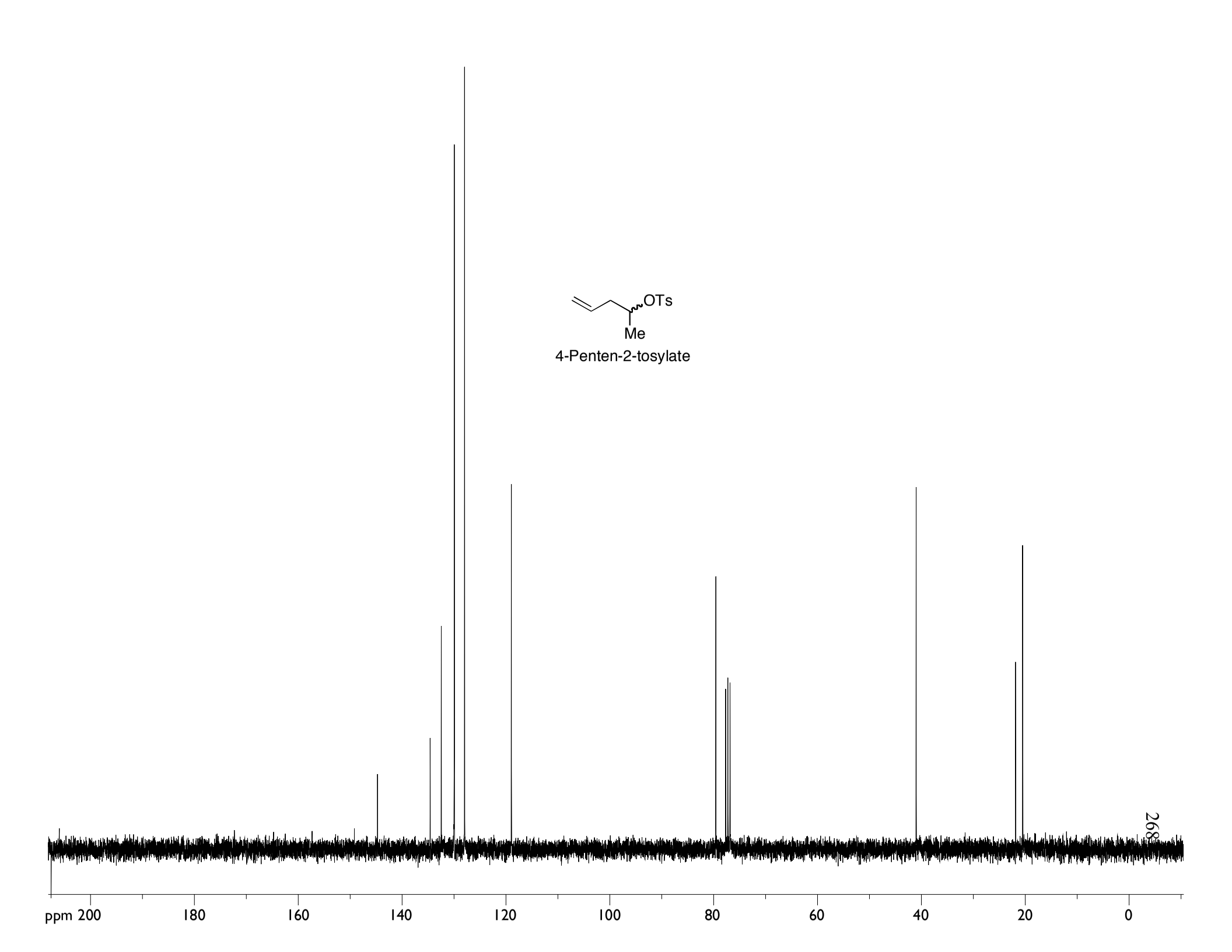


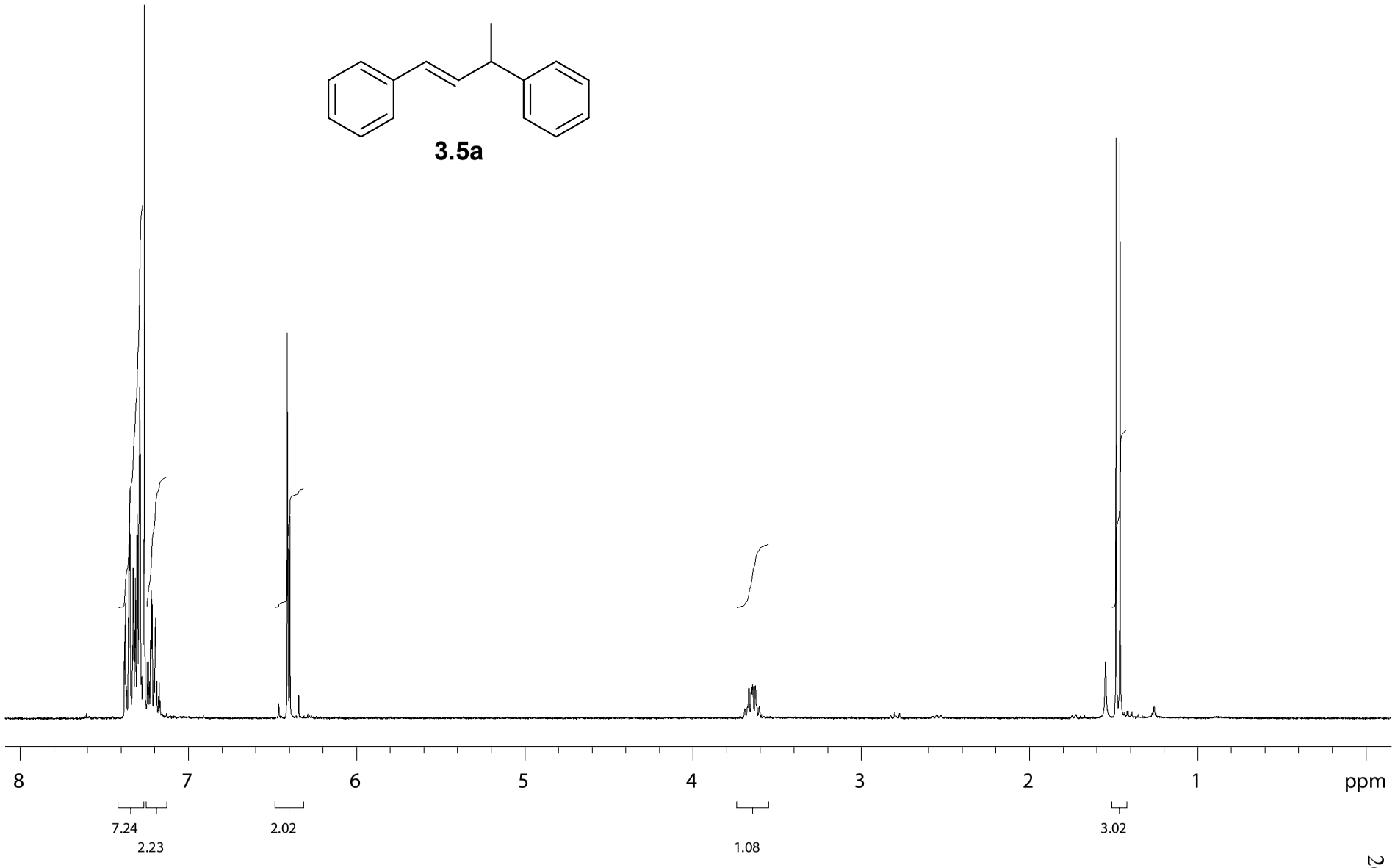
2.15

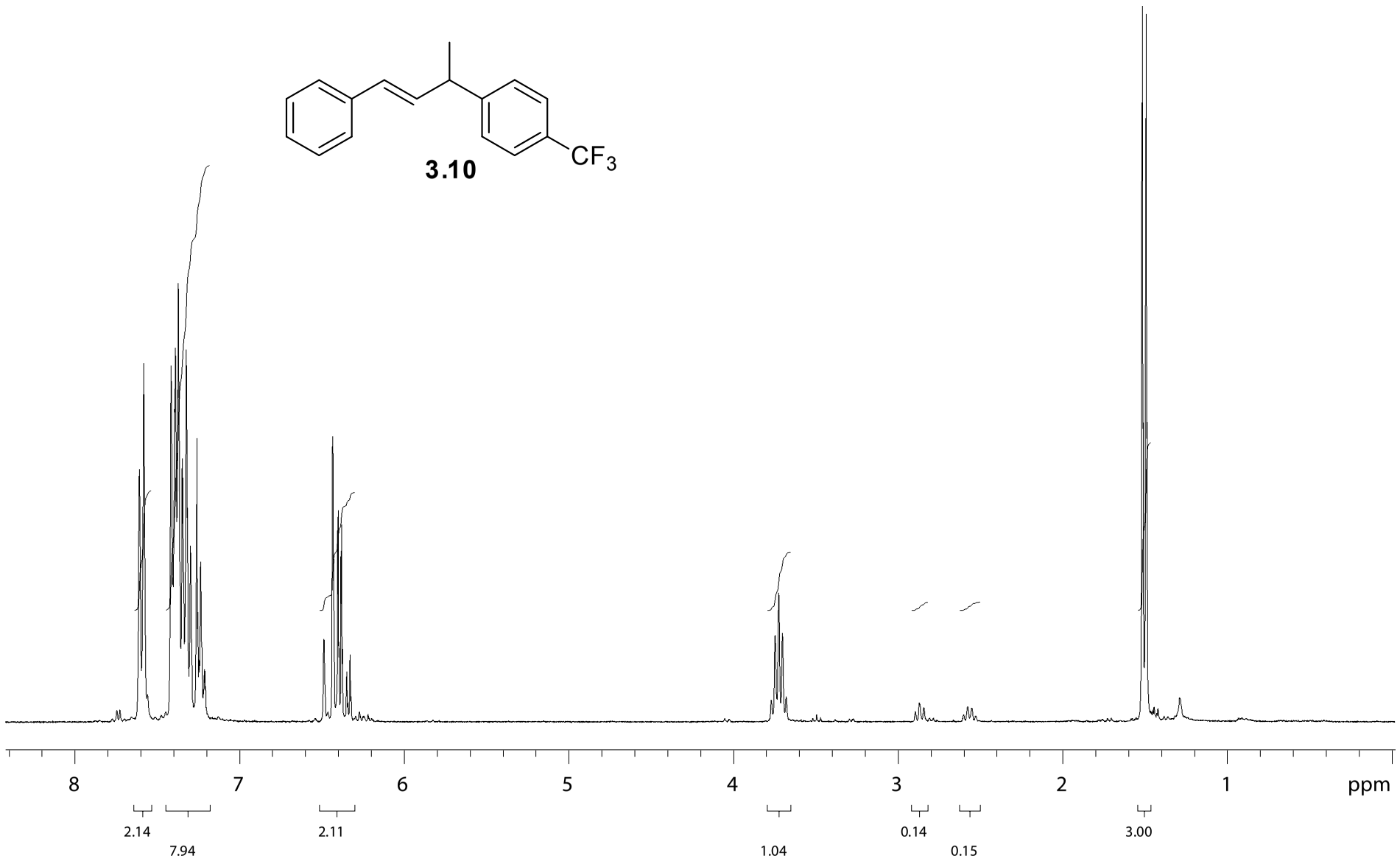
APPENDIX D:

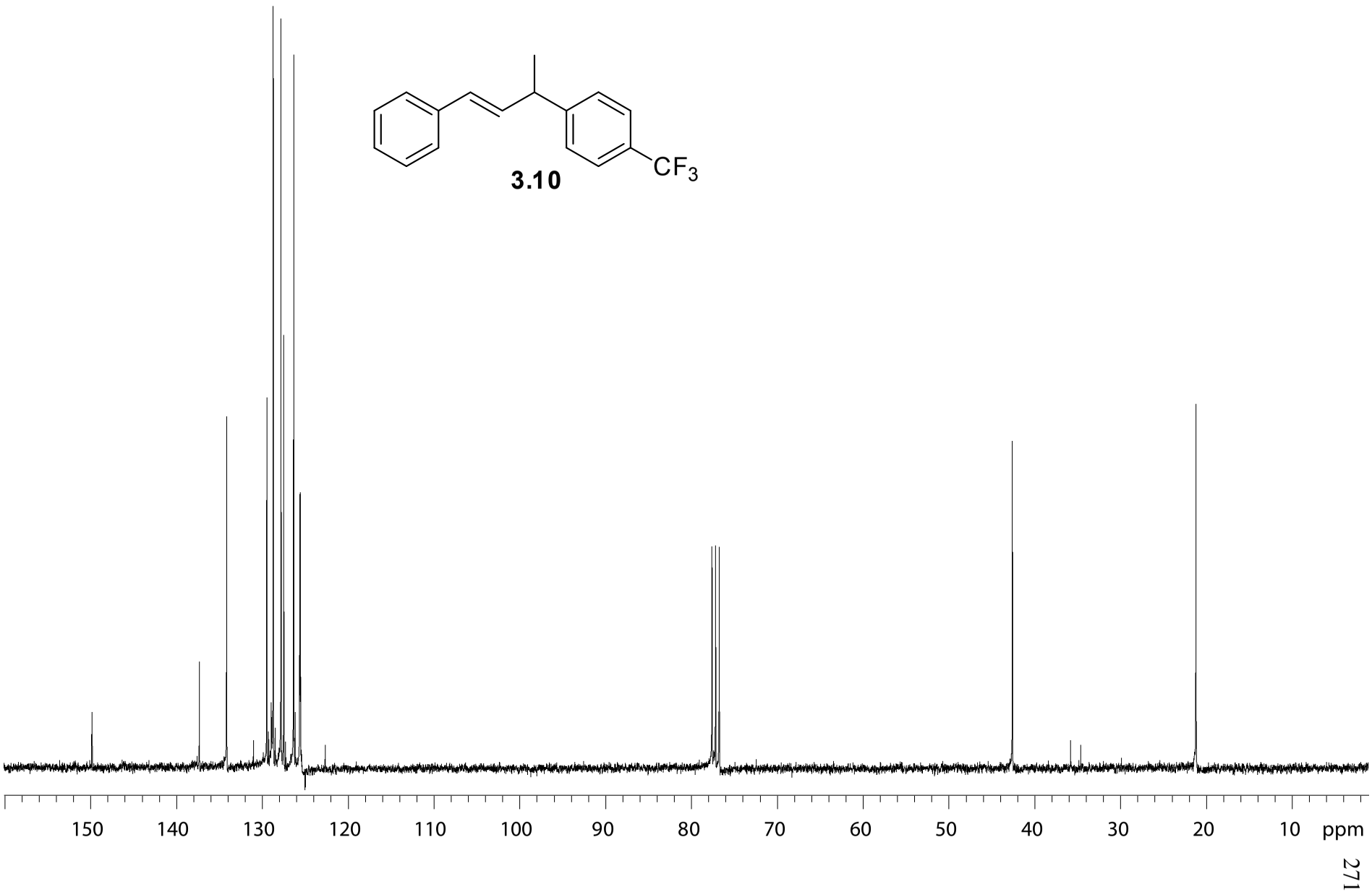
NMR SPECTRA FOR CHAPTER 3

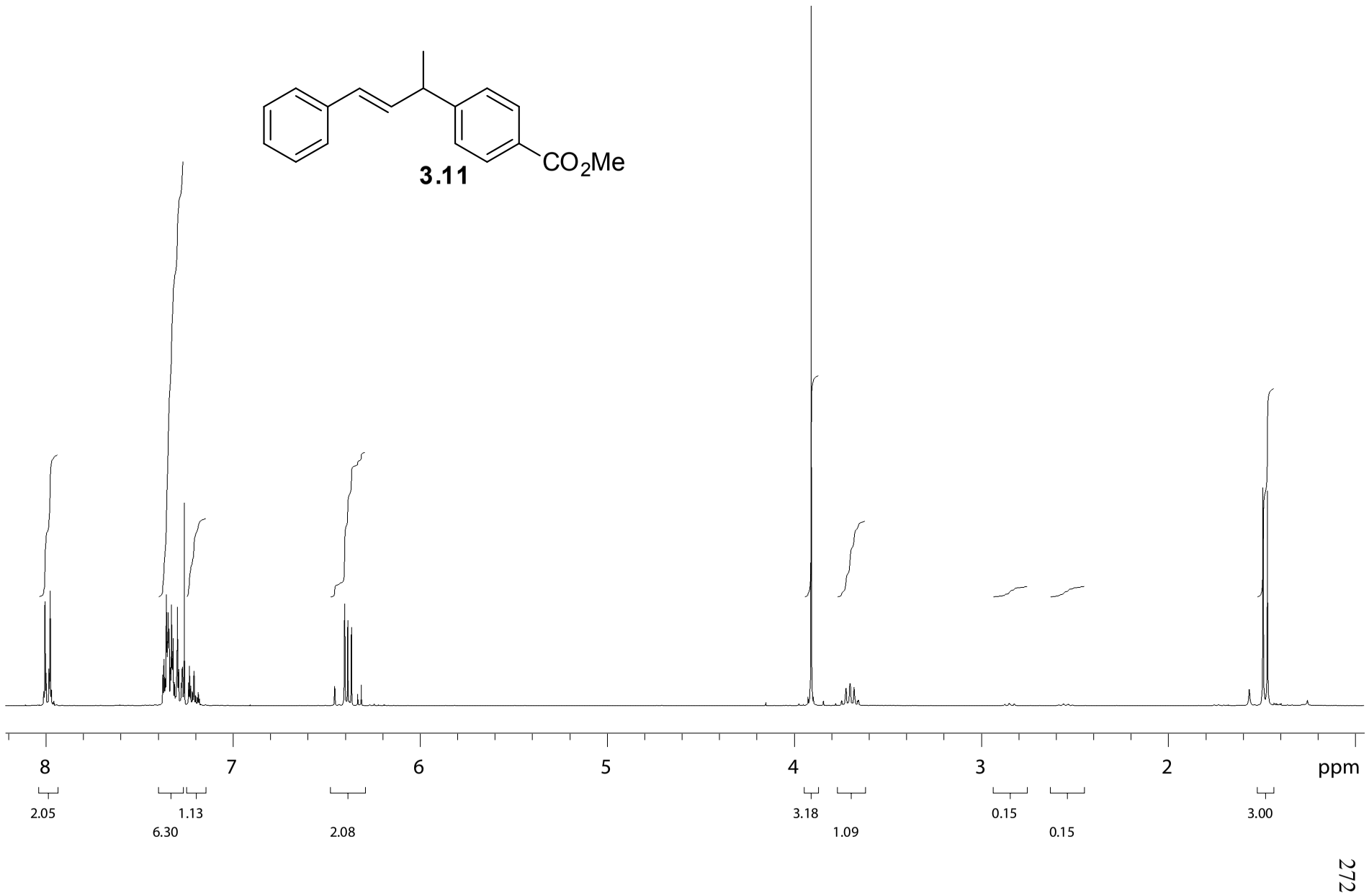

OTs
Me
4-Penten-2-tosylate
8
7
6
5
4
3
2
1
0
1.84
1.95
0.929
2
0.992
2.31
3.16
3.25
267

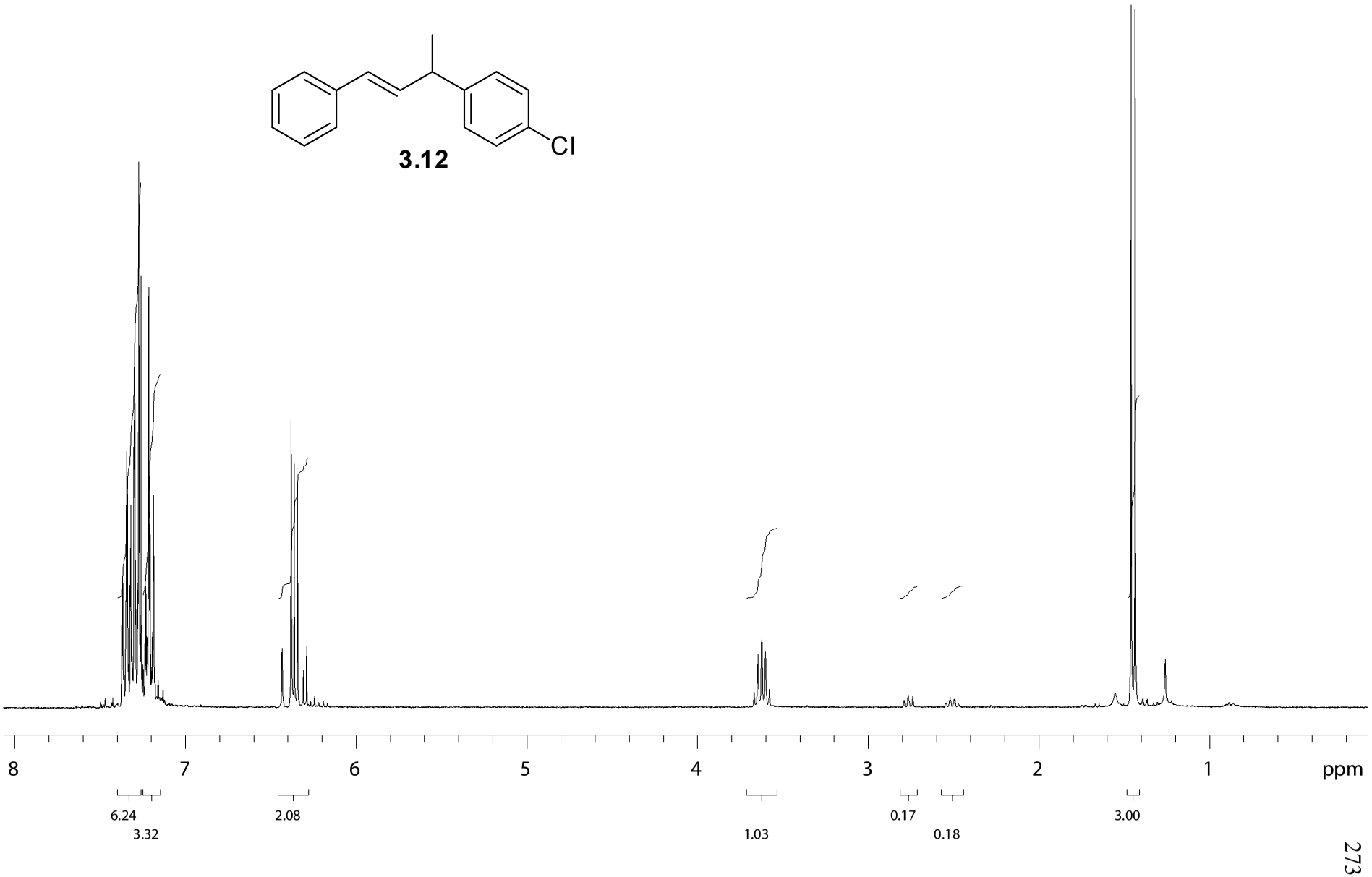

OTs
Me
4-Penten-2-tosylate
268
ppm 200
180
160
140
120
100
80
60
40
20
0

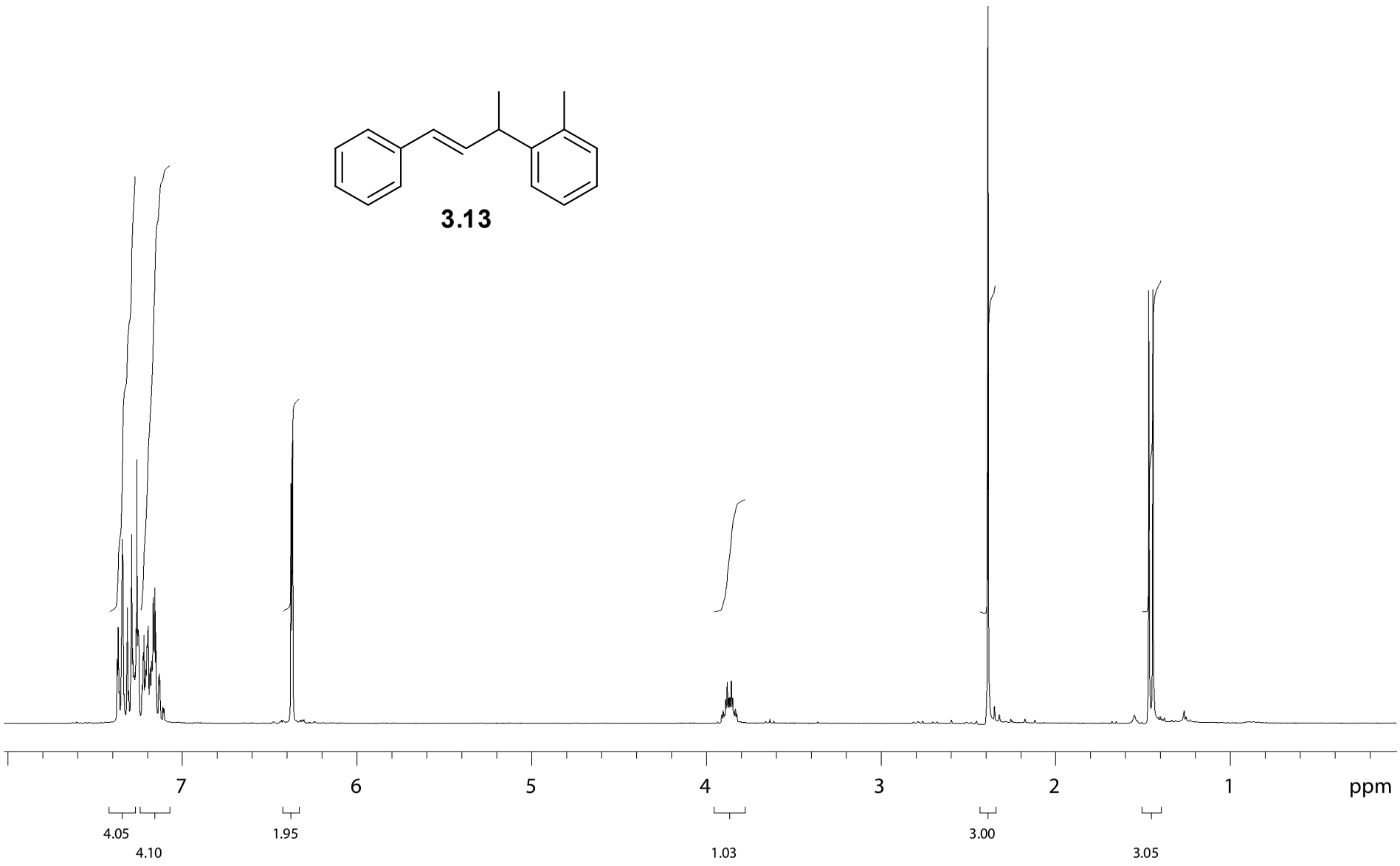

3.5a
8
7
6
5
4
3
2
1
ppm
7.24
2.23
2.02
1.08
3.02

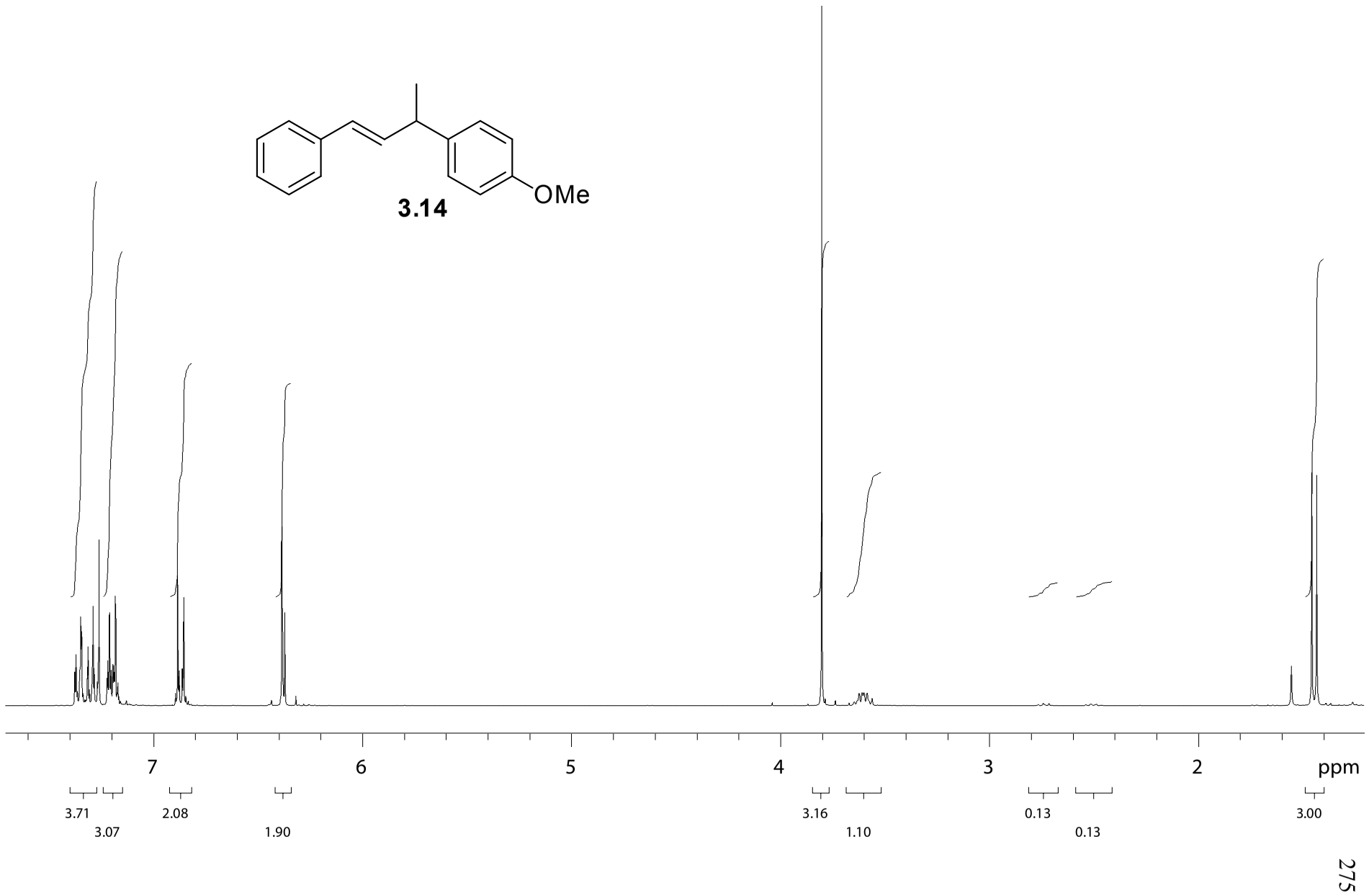

3.10
CF3
8
7
6
5
4
3
2
1
ppm
2.14
7.94
2.11
1.04
0.14
0.15
3.00

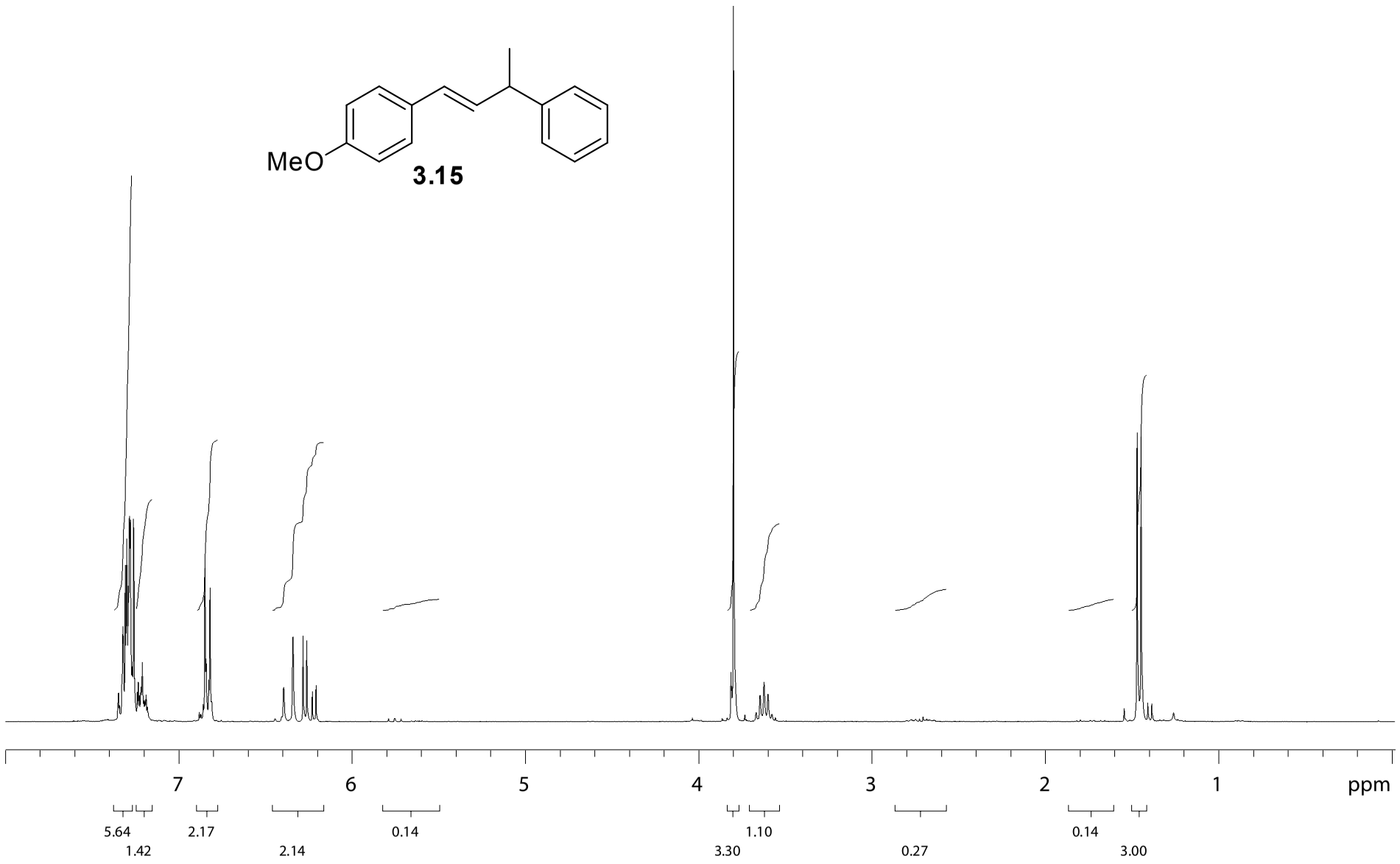

CF3
3.10
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

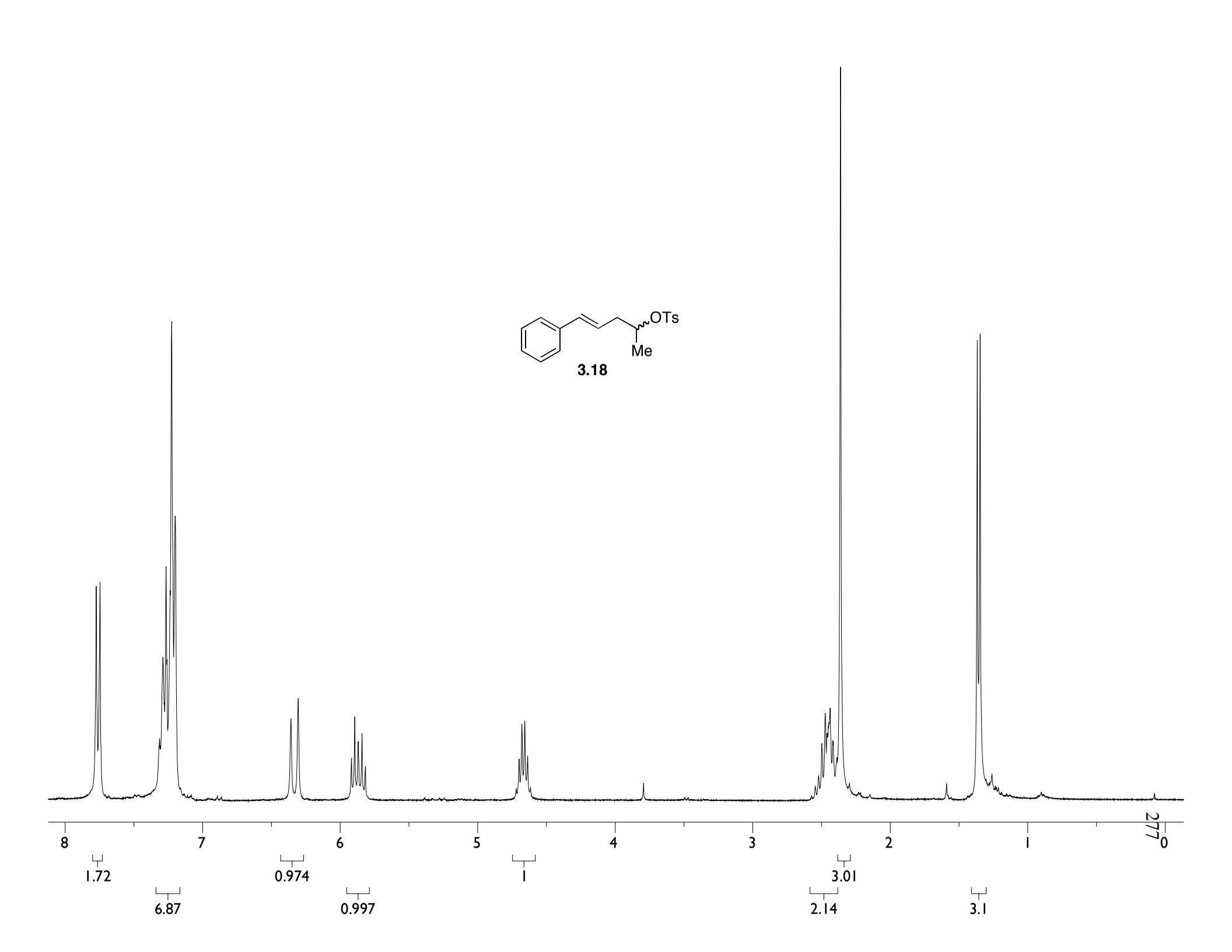

CO2Me
3.11
8
7
6
5
4
3
2
ppm
2.05
6.30
1.13
2.08
3.18
1.09
0.15
0.15
3.00

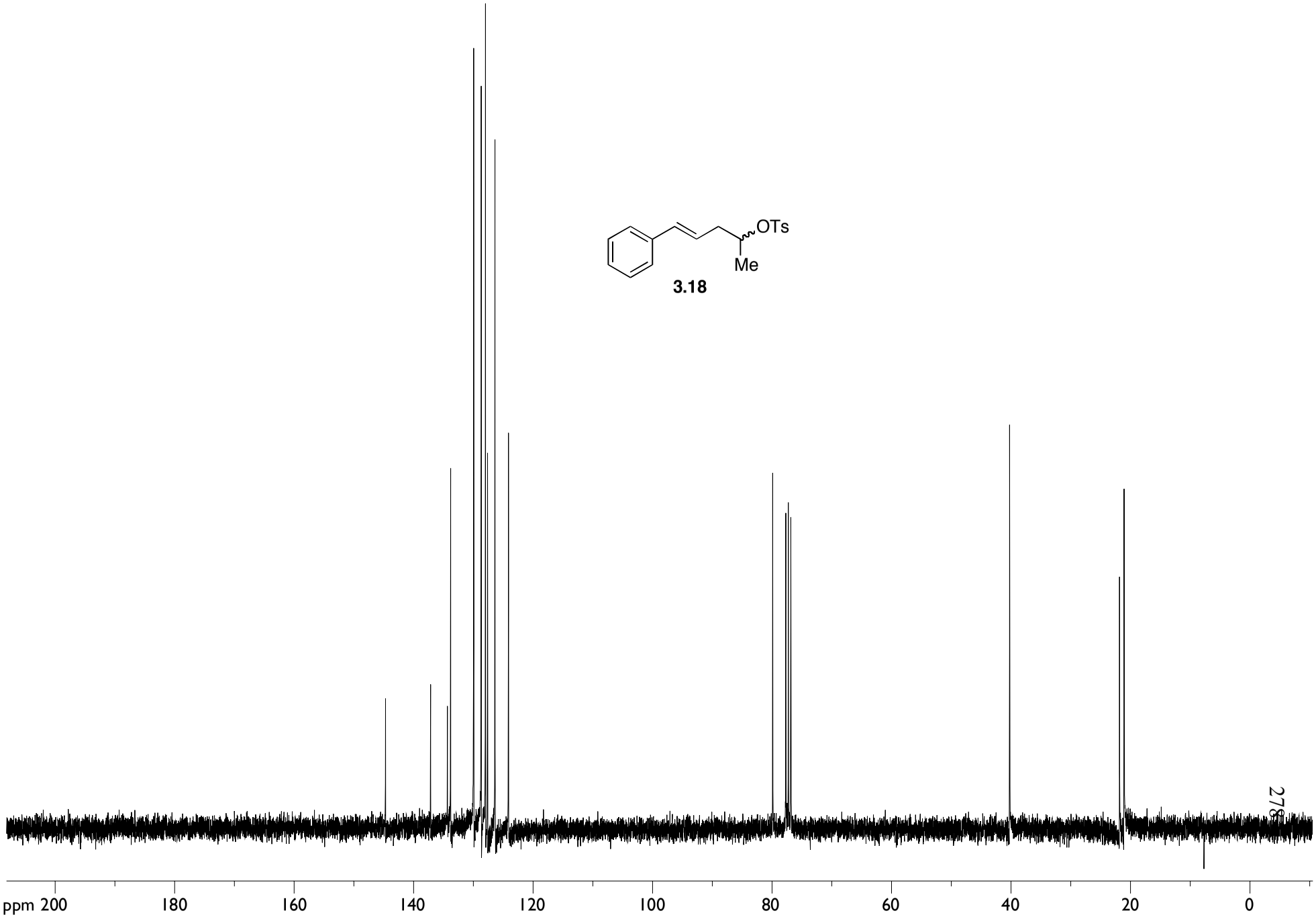

Cl
3.12
8
7
6
5
4
3
2
1
ppm
6.24
3.32
2.08
1.03
0.17
0.18
3.00

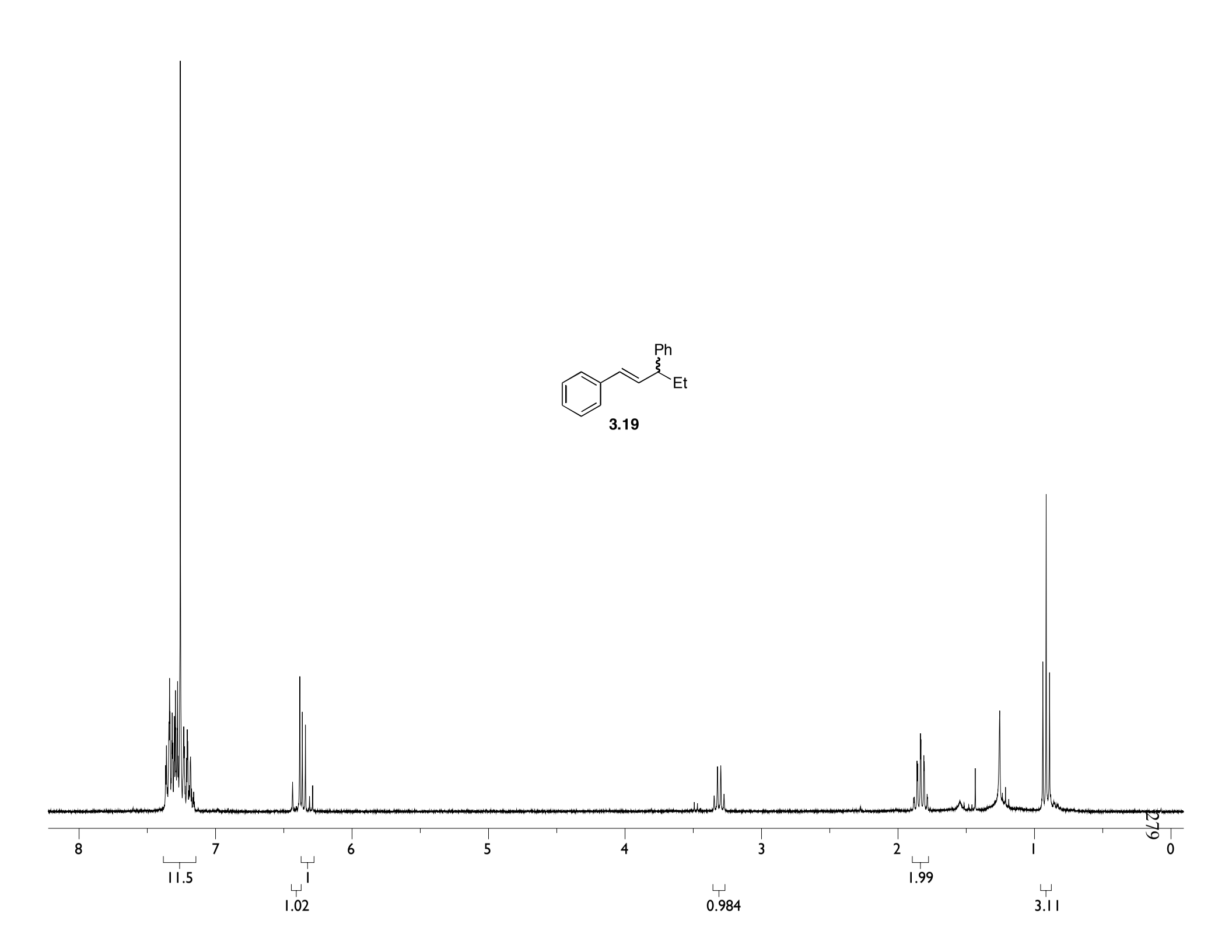

3.13
7
6
5
4
3
2
1
ppm
4.05
4.10
1.95
1.03
3.00
3.05

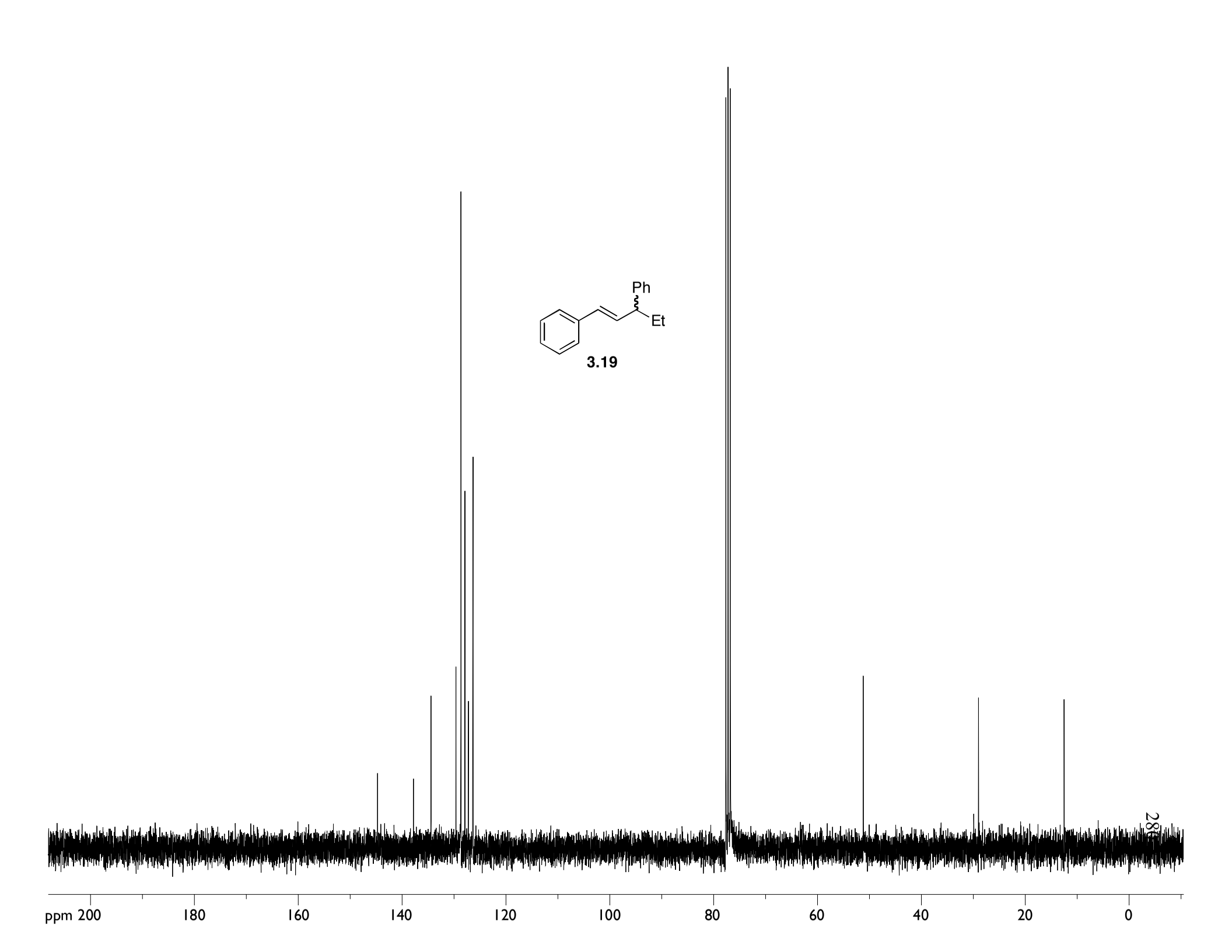

OMe
3.14
7
6
5
4
3
2
ppm
3.71
3.07
2.08
1.90
3.16
1.10
0.13
0.13
3.00

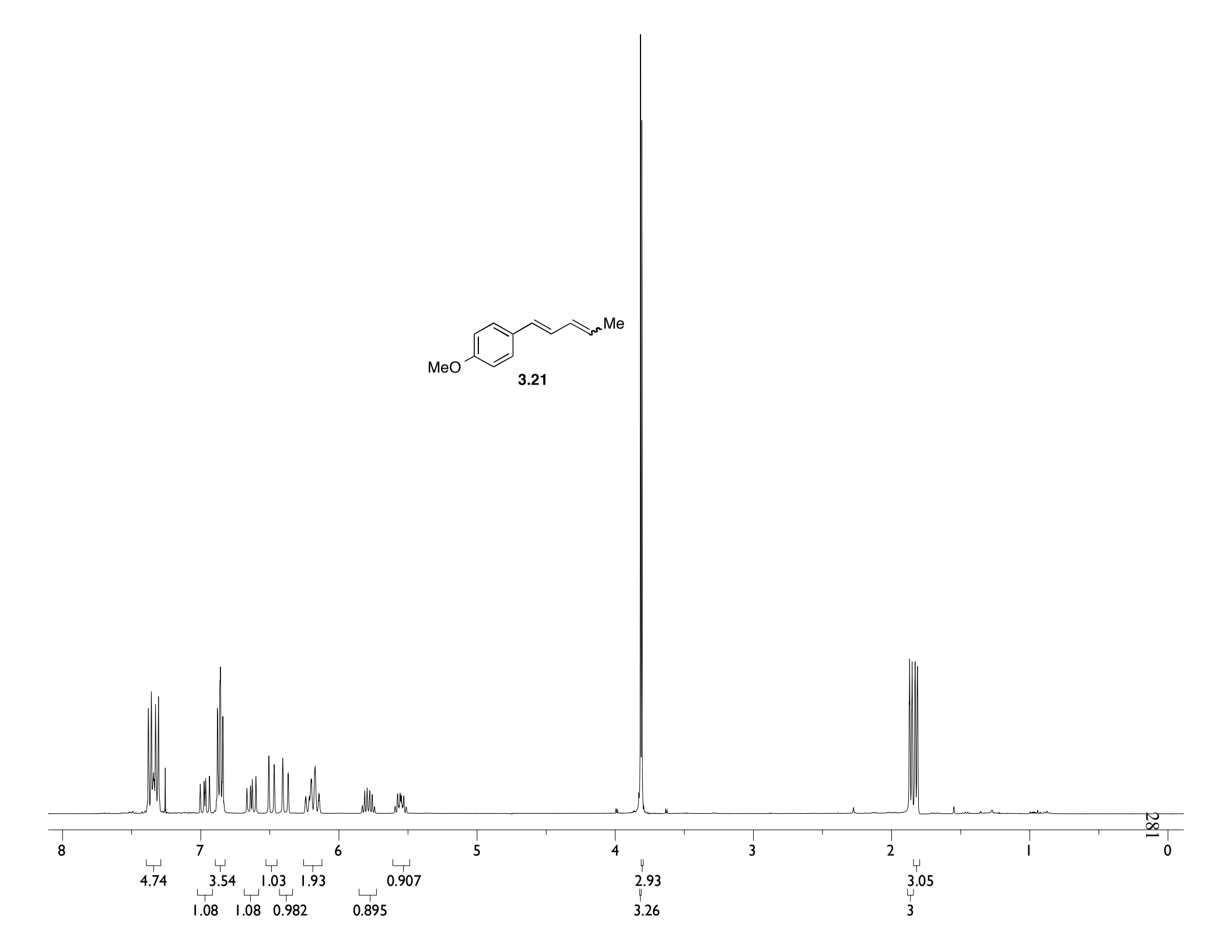

MeO
3.15
7
6
5
4
3
2
1
ppm
5.64
1.42
2.17
2.14
0.14
3.30
1.10
0.27
0.14
3.00

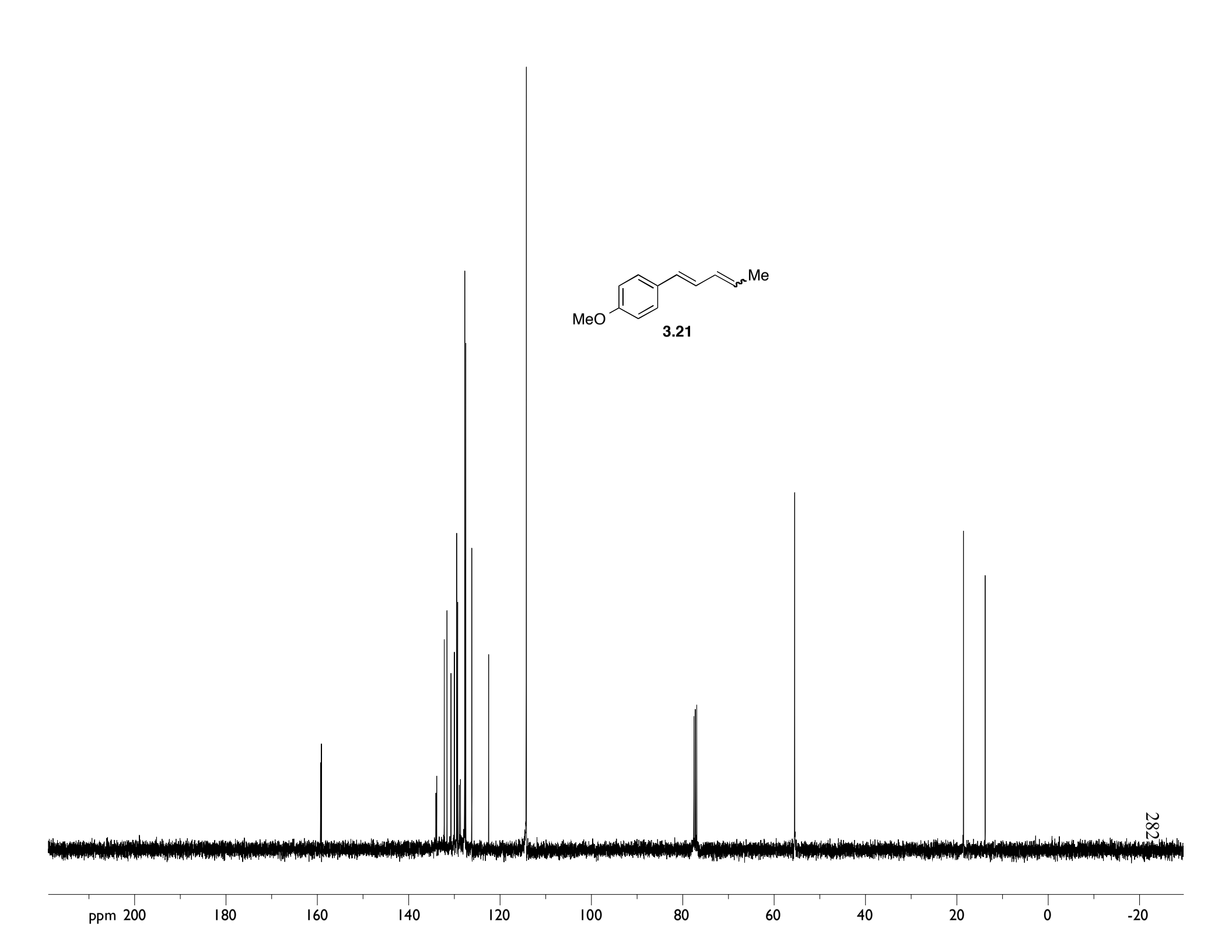

OTs
Me
3.18
8
7
6
5
4
3
2
1
0
277
1.72
6.87
0.974
0.997
1
3.01
2.14
3.1

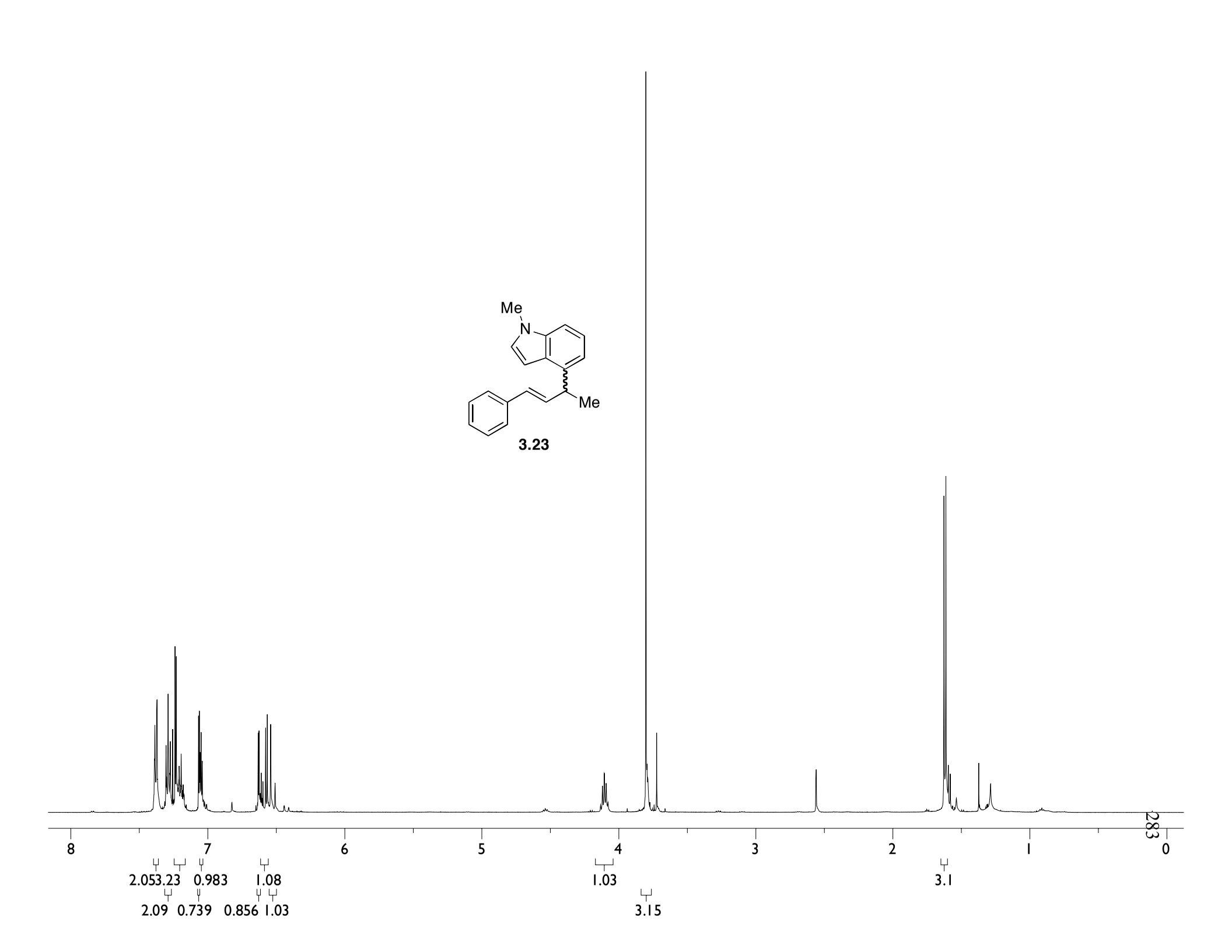

OTs
Me
3.18
ppm 200
180
160
140
120
100
80
60
40
20
0

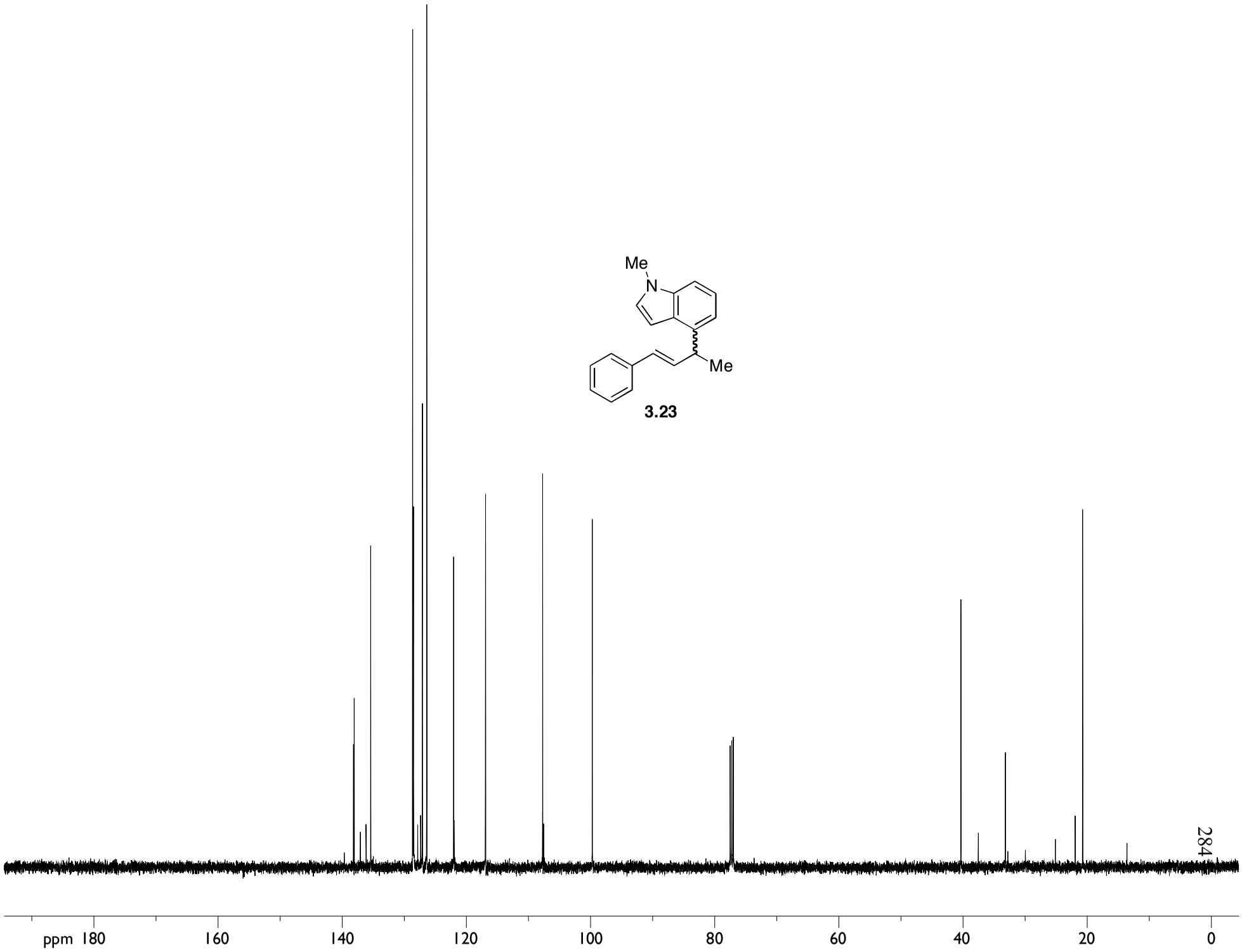

Ph
Et
3.19
8
7
6
5
4
3
2
1
0
11.5
1
1.02
0.984
1.99
3.11
279

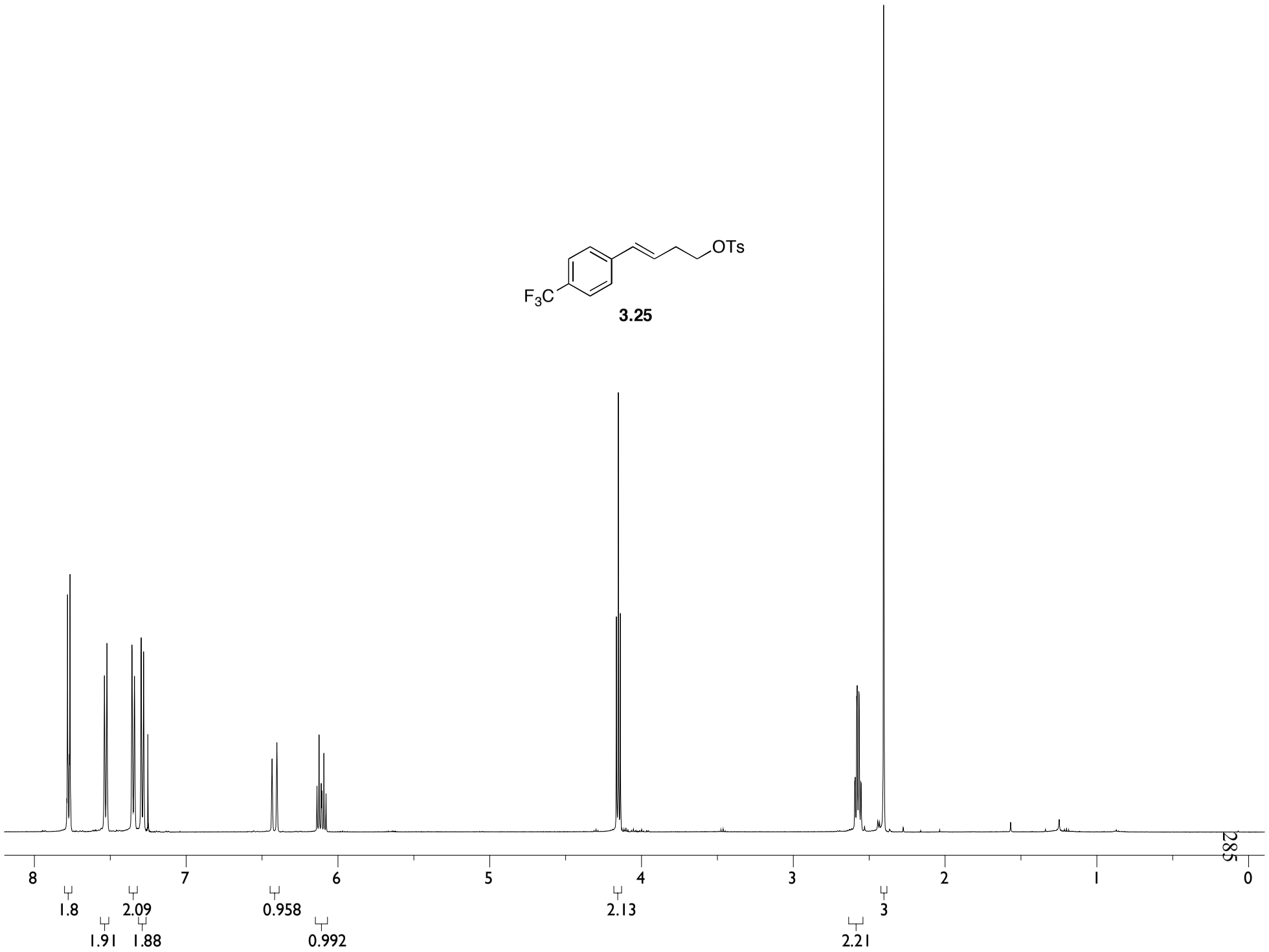

Ph
Et
3.19
ppm 200
180
160
140
120
100
80
60
40
20
0


Me
MeO
3.21
281
8
7
6
5
4
3
2
1
0
4.74
3.54
1.03
1.93
0.907
2.93
3.05
1.08
1.08
0.982
0.895
3.26
3


MeO
Me
3.21
ppm 200
180
160
140
120
100
80
60
40
20
0
-20
282


Me
N
Me
3.23
8
7
6
5
4
3
2
1
0
2.05
3.23
0.983
1.08
1.03
3.1
2.09
0.739
0.856
1.03
3.15
283


Me
N
Me
3.23
284
ppm 180
160
140
120
100
80
60
40
20
0


OTs
F3C
3.25
285
8
7
6
5
4
3
2
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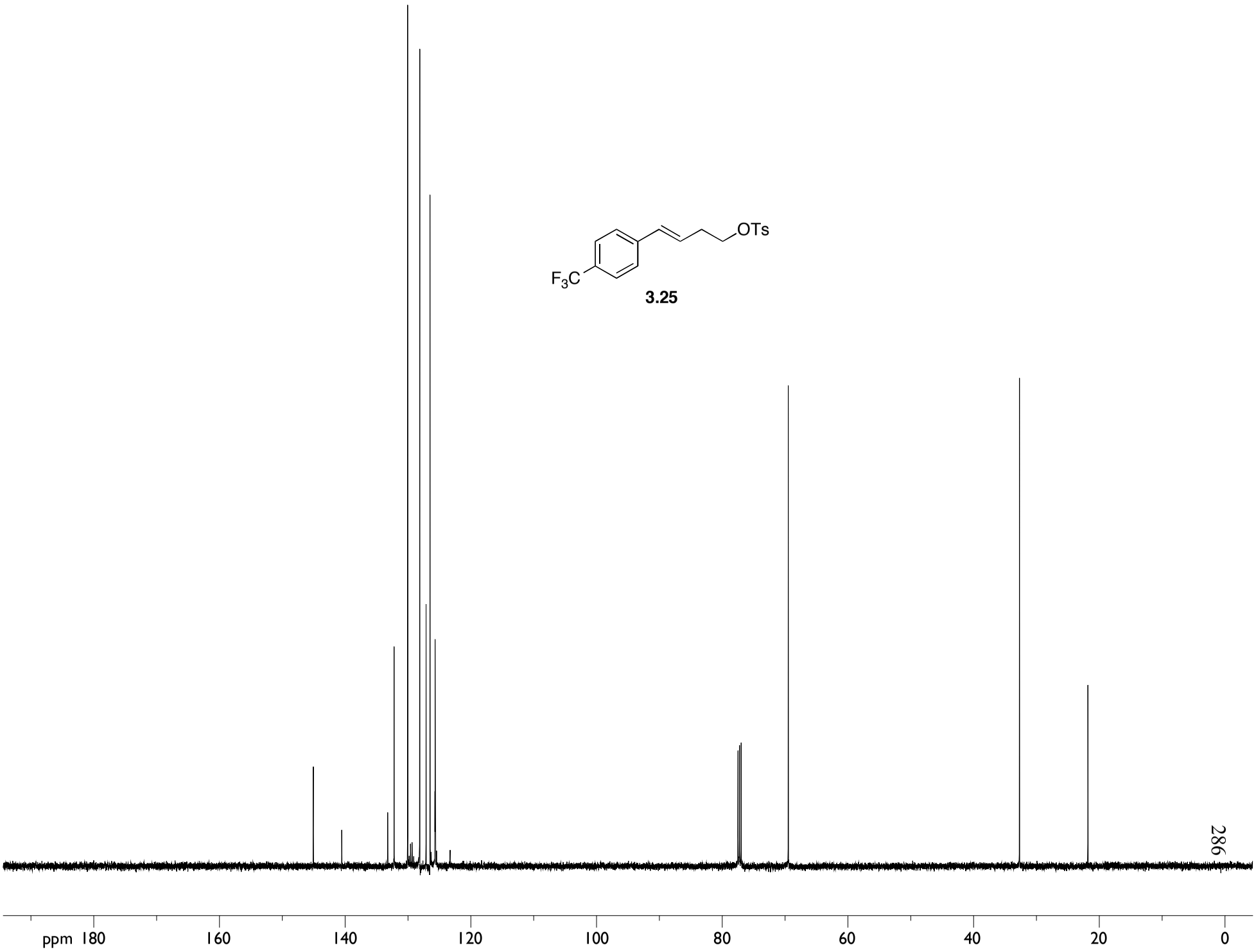
1.8
1.91
2.09
1.88
0.958
0.992
2.13
2.21
3


OTs
F3C
3.25
286
ppm 180
160
140
120
100
80
60
40
20
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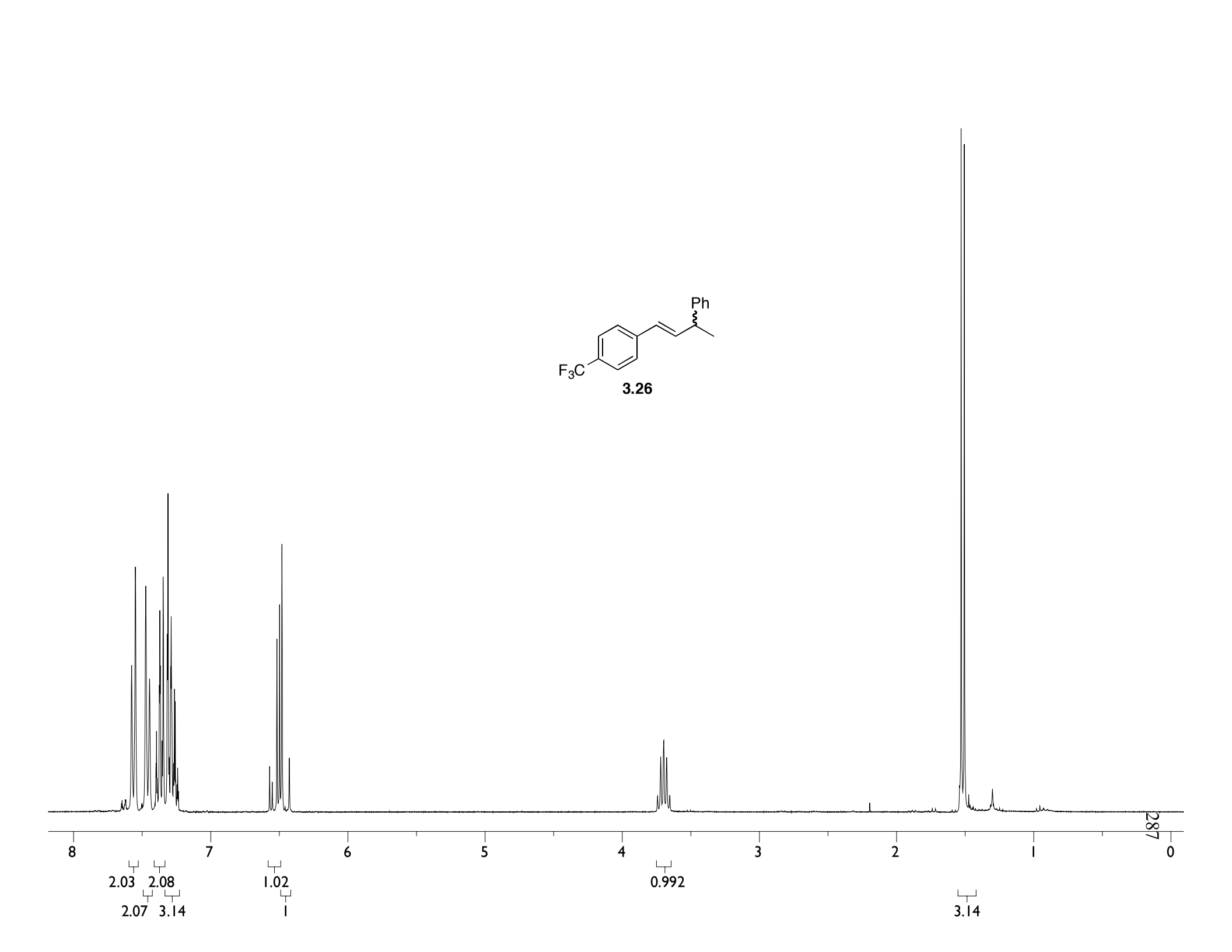
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F3C
3.26
8
7
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5
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3
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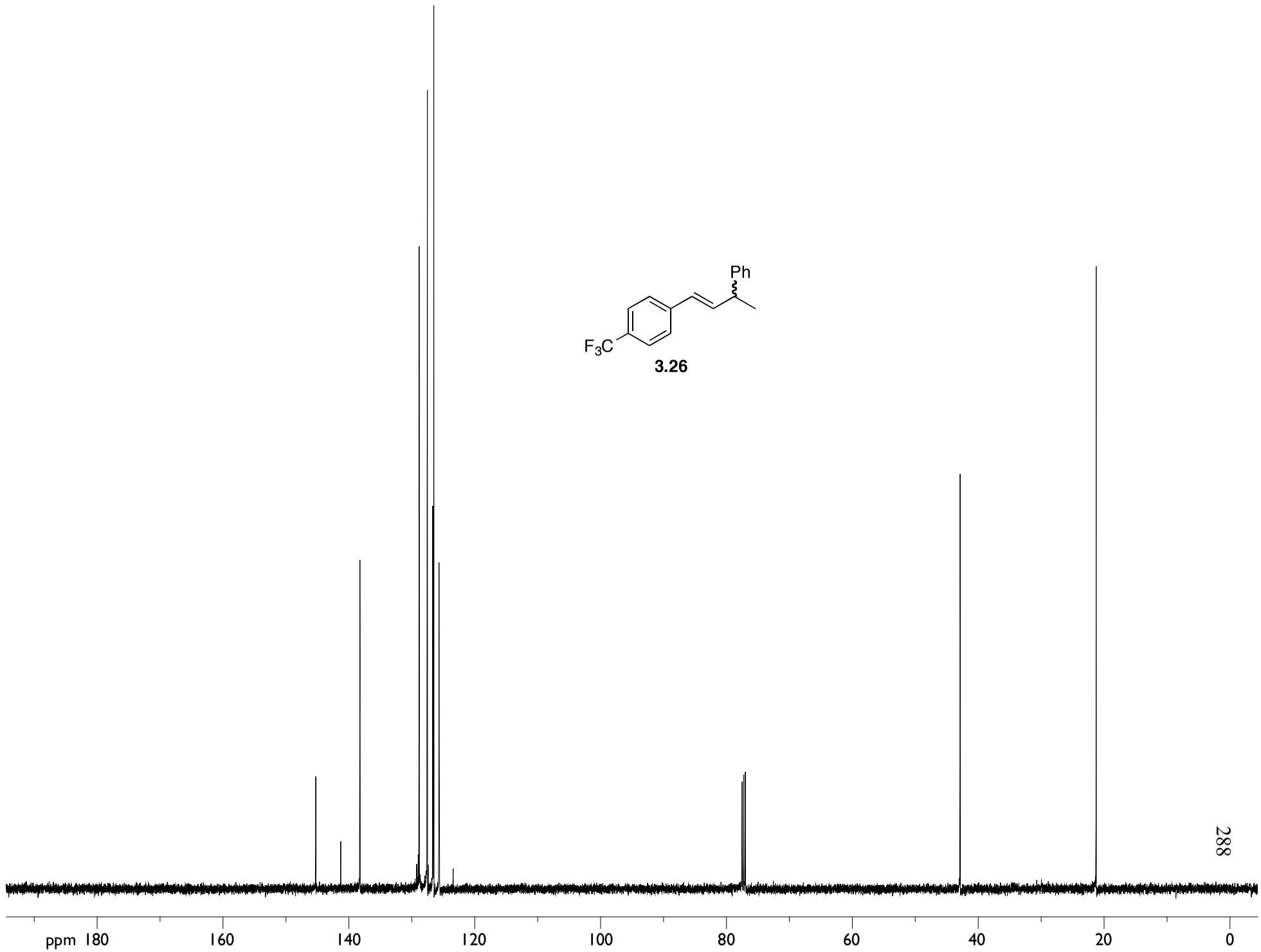
1
0
2.03
2.08
2.07
3.14
1.02
1
0.992
3.14
287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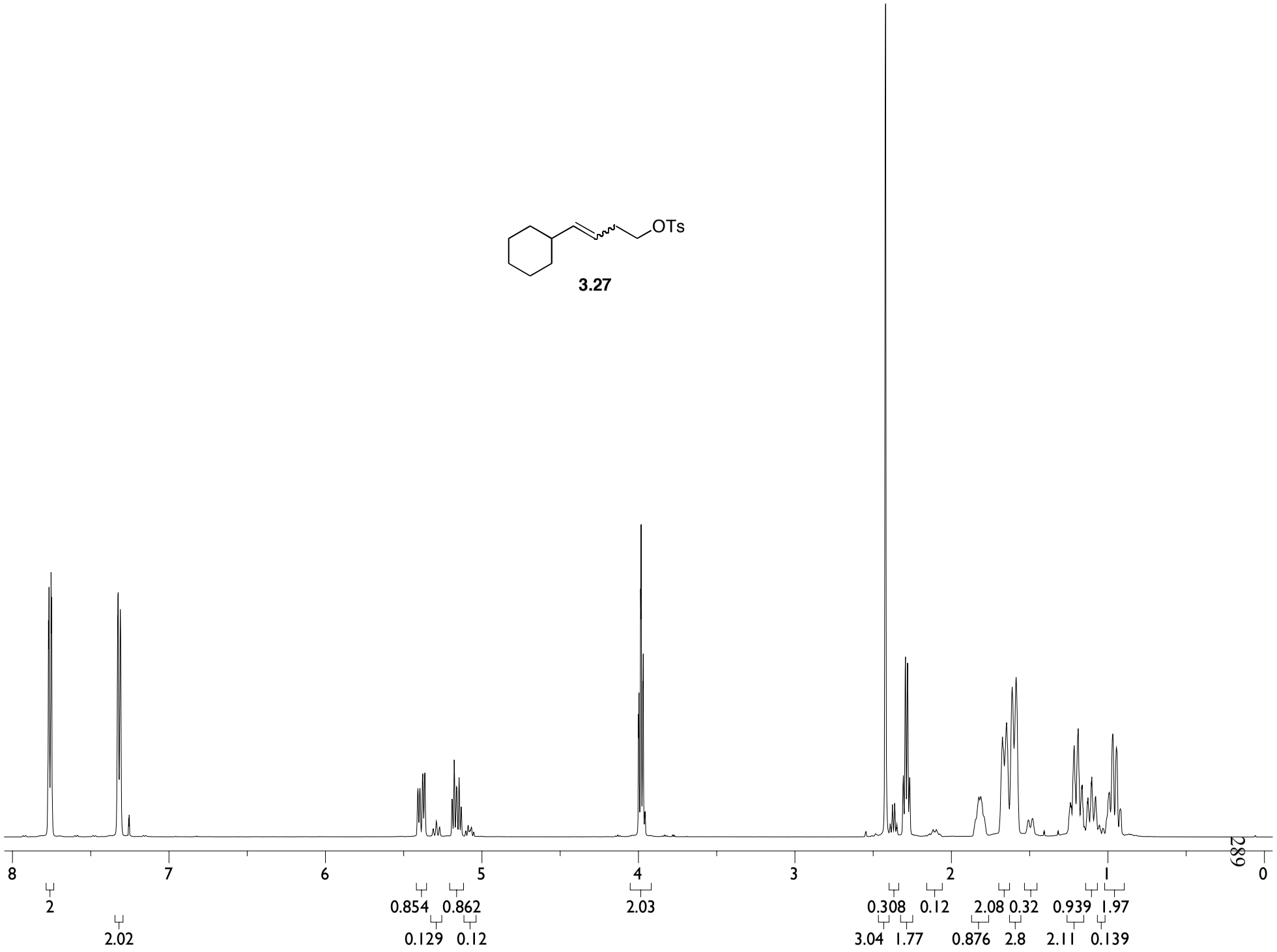
OTs
3.27
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7
6
5
4
3
2
1
0
2
2.02
0.854
0.129
0.862
0.12
2.03
0.308
3.04
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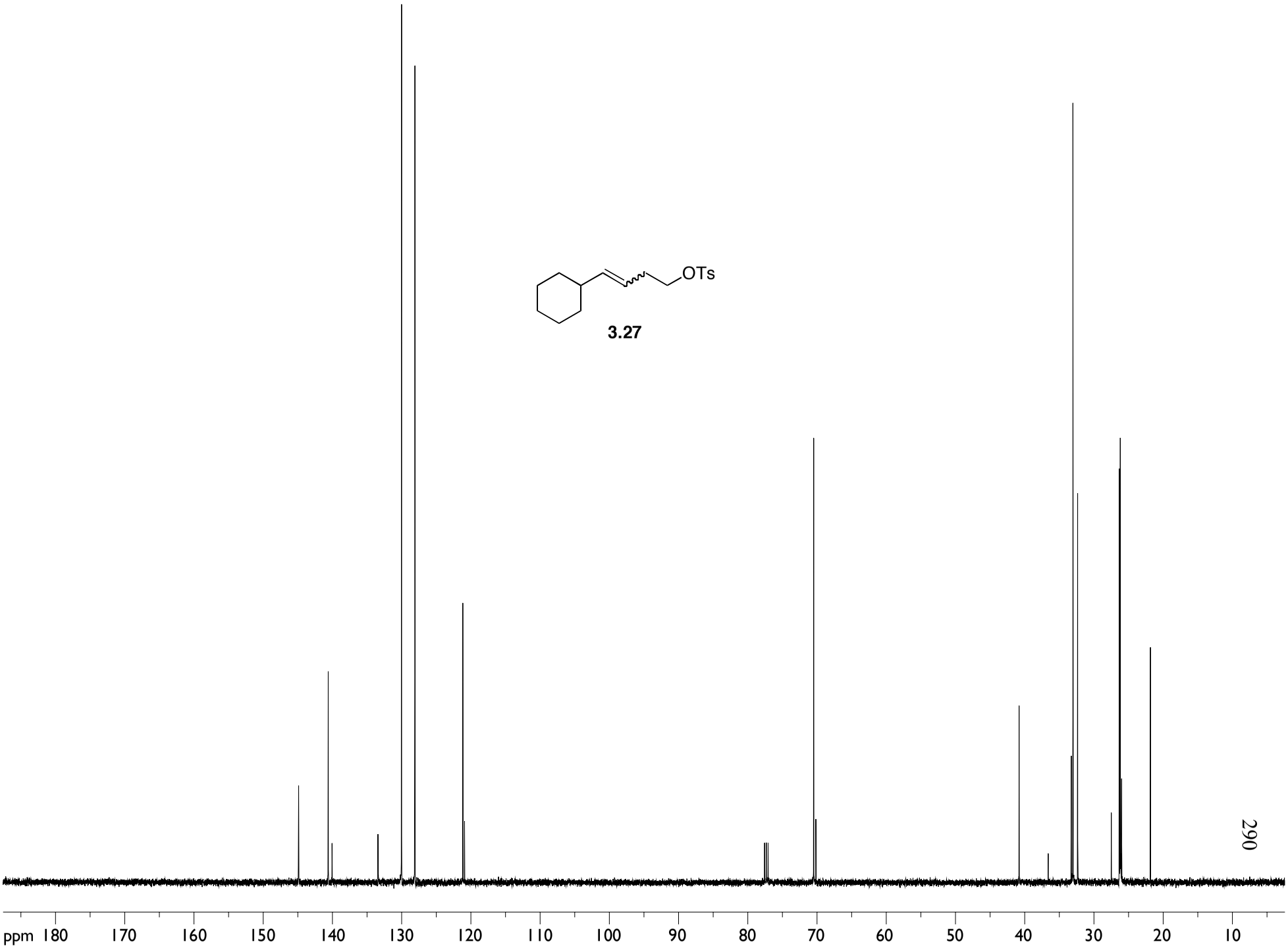
1.77
2.08
0.876
0.32
2.8
0.939
2.11
1.97
0.139
289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3.27
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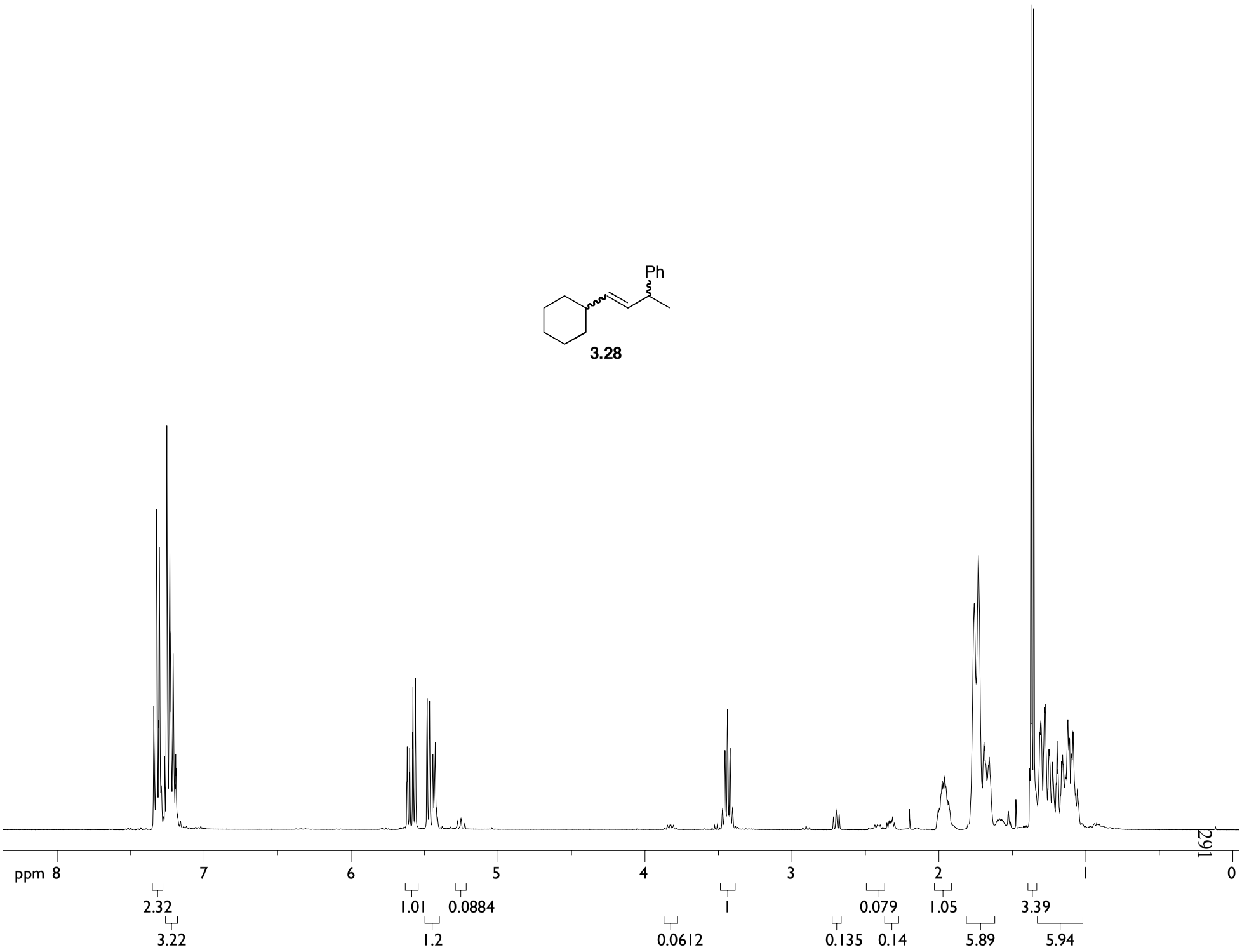
290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7
6
5
4
3
2
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0
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3.22
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1.2
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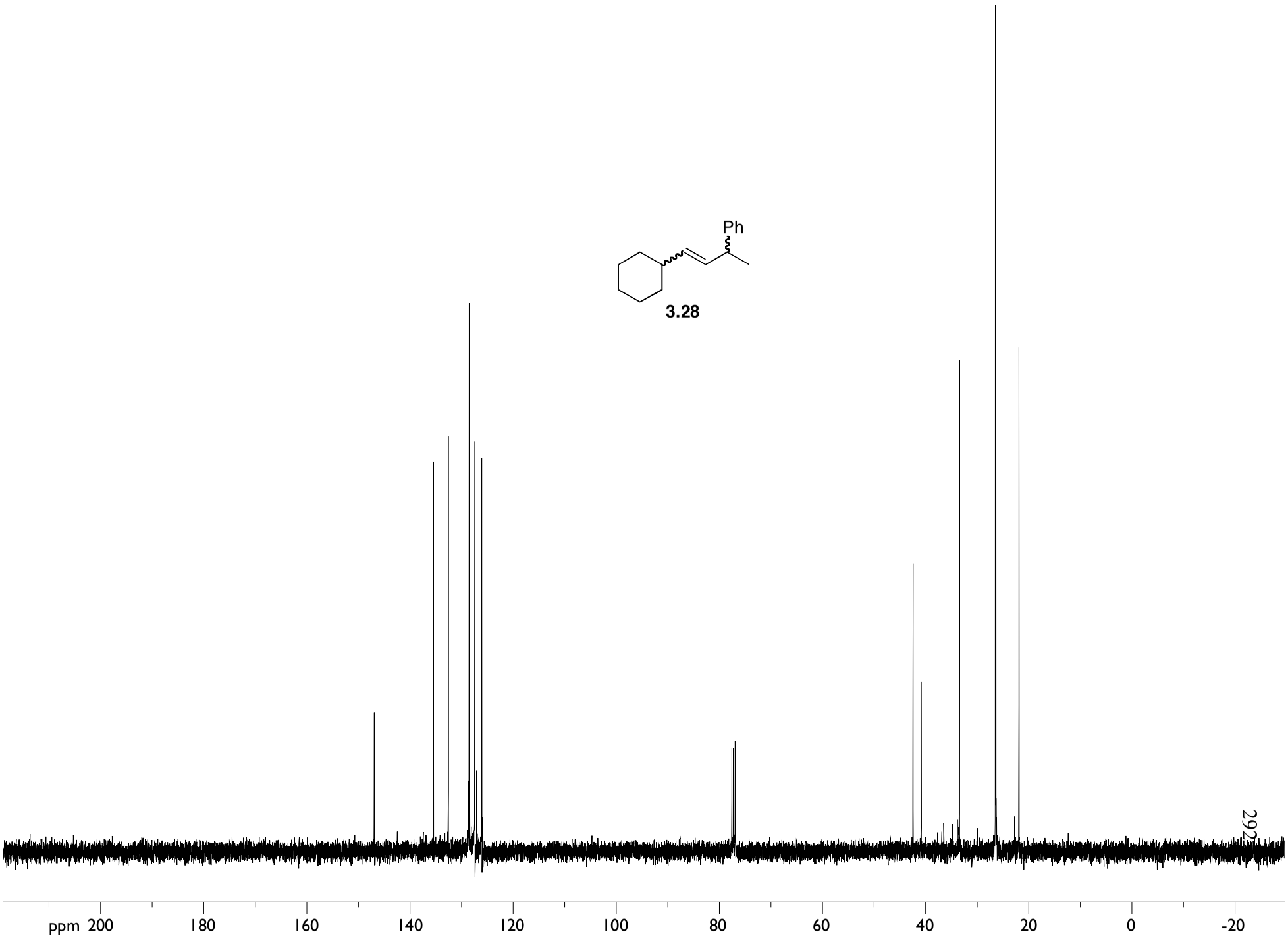
0.0612
1
0.135
0.079
0.14
1.05
5.89
3.39
5.94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120
100
80
60
40
20
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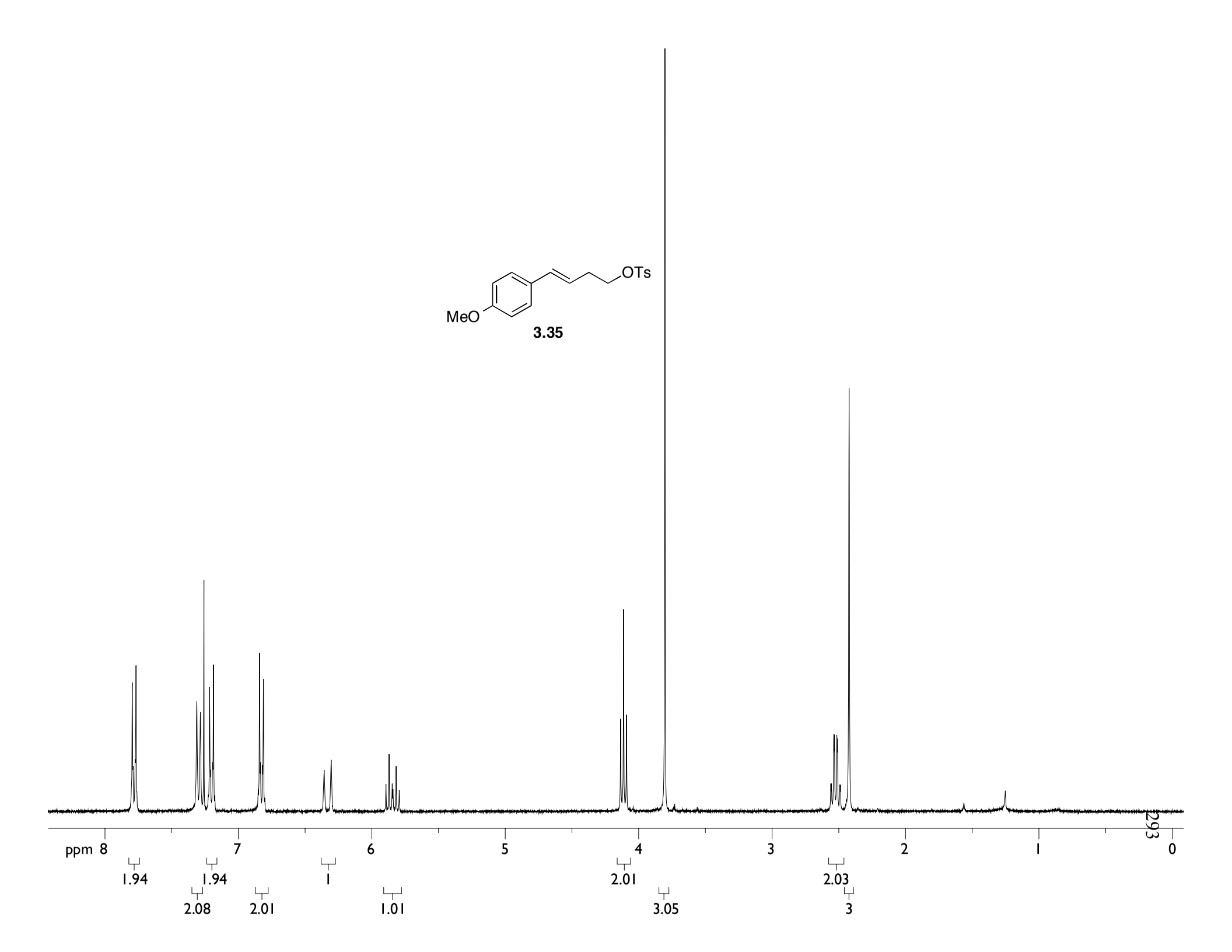
-20


OTs
MeO
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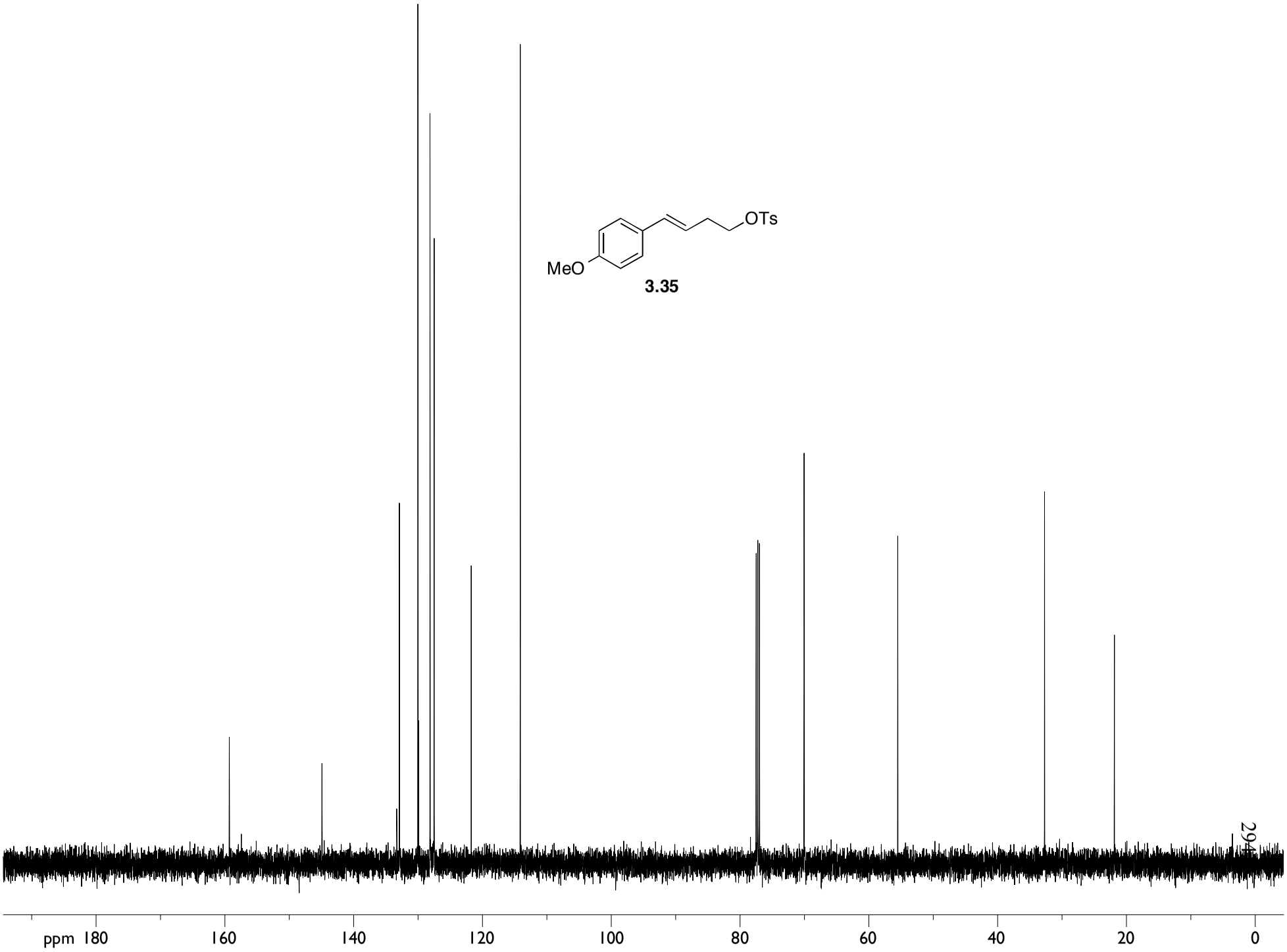
293
ppm 8
7
6
5
4
3
2
1
0
1.94
1.94
1
2.01
2.03
2.08
2.01
1.01
3.05
3


OTs
MeO
3.35
294
ppm 180
160
140
120
100
80
60
40
20
0