Palladium-Catalyzed Synthesis and Racemization of Conjugated Allenynes

By

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Submitted to the graduate degree program in Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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1:30 PM, July 11, 2017

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Abstract

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Department of Chemistry, July 2017

University of Kansas

Allenes are structurally unique compounds that can possess axial chirality. The most common strategy for allene synthesis is transition metal-catalyzed cross coupling with propargyl electrophiles. While these are powerful methods, they produce stoichiometric amounts of potentially toxic waste. Further, stereospecific variants of these reactions often suffer from substantial racemization of the enantioenriched allenyl products. Presented herein is the development of an atom economical and environmentally benign approach to synthesize both racemic and enantioenriched allenes, as well as the evaluation of the stereochemical effect palladium catalysts have on the generated enantioenriched allenes.

Chapter 1 is an overview of the strategies most commonly employed for allene synthesis. The majority of the methods presented are transition-metal addition of preformed organometallic reagents which require harsh conditions and produce stoichiometric amounts of waste. As an alternative, the development of the palladium-catalyzed, decarboxylative coupling of propargyl propiolates is presented in Chapter 2. The developed coupling of propargylic esters selectively forms di- and trisubstituted allenynes in good yields. Further, the developed reaction requires no additional organometallic reagents or base, producing CO_2 as the sole byproduct.

As palladium-catalyzed couplings with propargylic electrophiles had been demonstrated to be stereospecific in the literature, Chapter 3 describes our attempt to develop the stereospecific variant of the palladium-catalyzed decarboxylative coupling of propargyl propiolates. It was demonstrated that the decarboxylative coupling can occur stereospecifically. However, like many

other palladium-catalyzed syntheses of allenes, the coupling suffered from racemization of the enantioenriched product. Thus the remainder of Chapter 3 presents the kinetic studies employed to gain a greater understanding of the mechanism for palladium-catalyzed racemization of allenes, as only a small handful of reports in literature have lightly touched on the subject. Both palladium(0) and palladium(II) catalysts are explored as both species are present within the proposed catalytic cycle for the palladium-catalyzed decarboxylative coupling.

Acknowledgements

I am deeply indebted to my research advisor, Dr. Jon Tunge. Jon, thank you for taking a chance on me when I was the last first year grad student left without a research group. I also cannot say thank you enough for never giving up on me, even when I had given up on myself. You are the most patient teacher and mentor. Your wealth of knowledge is intimidating and beyond compare and I only hope I can be half chemist you are.

To Dr. Paul Hanson, thank you for being an excellent teacher and mentor. Further I am deeply grateful for the invaluable career advice and help that you've provided. To Dr. Michael Clift, thank you for serving on both my orals and dissertation committee. I cannot truly express how much I've learned from the many insightful questions and challenging discussions you have presented us with during problem set. I am especially appreciative for the career advice. To Dr. Thomas Prisinzano, thank you for challenging me to remain interested in the biological side of chemistry, and for always knowing how the Razorbacks are faring during football season. I would also like to thank Dr. Michael Rubin for serving on in my dissertation committee and continuously being an encouraging presence in the hallways. Special thanks go Dr. Justin Douglas and Sarah Nueswander for answering every question I may have had about NMR, no matter how trivial or complex.

I had the joy of working with some of the kindest and most helpful colleagues at KU I could ask for. To Jana, thank you for being my loudest cheerleader. To Joe Siegel, Michael Hogard, and Chris Otolski, math and grad school life are hard, thank you for making both of them easier for me. To Thomas Field, thanks for helping me troubleshoot our HPLC on multiple occasions and reminding me that throwing it out the window won't actually solve anything. To Melissa Denler, Hannah Colmer, and Xinyun Lui thank you for reminding me of the importance of coffee breaks and always being willing to take one with me.

Past members in the Tunge group, Alex, Tony, Yamuna, James, and Tapan thank you all for your support. Shehani, I cannot thank you enough for the encouragement and kindness you showed me when I was significantly struggling. I know, for a fact, I would not have made it this far if it weren't for you, and I will always look up to you. Simon and Theresa, thank you for taking 90% of this journey with me. I will always be in awe of how much you all have accomplished. Thanks to all the current Tunge group members, Mary, Kevin, Pradip, Angelika, and Alex for creating a cheerfully sarcastic work environment. I especially want to thank Kaitie for all of the writing, science, and life advice, and for always being up for a lab dance party. I wish you all the very best and look forward to seeing all of your accomplishments.

I'd also like to thank my Undergraduate PI, Professor Julie Stenken at the University of Arkansas. Thank you for introducing me to KU and showing me how to be both a Razorback and a Jayhawk.

None of this would have been possible without the love and support of my family. First, to my amazing mother, Brenda. Thank you for always believing in me, and being proud of me no matter what the outcome. To Aunt Sam and Uncle Rick, thank you for all of the help throughout these last few years. Whether it's buying a car, or moving you both have always been there offering to do whatever you can. I am especially grateful to my Grandmother Fairy, who constantly reminds me of how proud she is to have a Dr. Smith in the family.

Last but certainly far far far!! from least I want to thank Mason Hart. I am beyond grateful that I have gotten to take this journey with you. You have been my rock throughout this entire process, helping me every step of the way. Thank you for consistently challenging me to be the best chemist and person I can be. I can't wait to see what our next adventures as "Doctors" will be!

Table of Contents:

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ar	aryl
binap	2,2’-bis(diphenylphosphino)-1,1’-binaphthalene
cee	conservation of enantiomeric excess
cod	1,5-cyclooctadiene
cp	cyclopentadiene
cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	Dichloromethane
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
DKR	dynamic kinetic resolution
DMAP	p-(dimethylamino)pyridine
DMEDA	N,N’-dimethylethylenediamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dpbp	2,2’-Bis(diphenylphophino)-1,1’-biphenyl

dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
DYKAT	dynamic kinetic asymmetric transformation
ee	enantiomeric excess
es	enantiospecificity
EtOAc	ethyl acetate
equiv	equivalent
HPLC	high performance liquid chromatography
MePhos	2-dicyclohexylphosphino-2’-methylbiphenyl
n-BuLi	N-butyllithium
nbd	norbornadiene
NMR	Nuclear magnetic resonance
Nuc	Nucleophile
Ph	phenyl
phen	1,10-phenanthroline
PHOX	phosphinooxazolines
rac	racemic
Tf	trifluoromethanesulfonate
THF	Tetrahydrofuran
THP	Tetrahydropyanyl acetal
TMS	trimethylsilyl

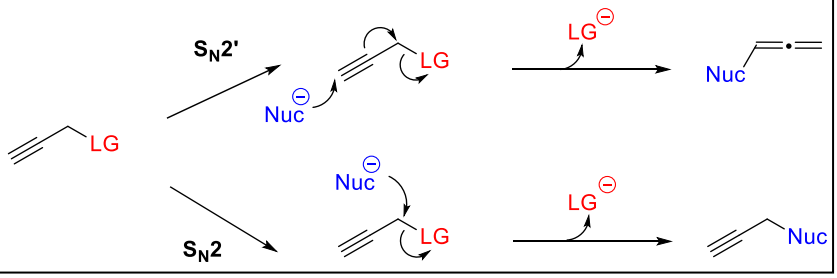
TSOH	p-toluenesulfonic acid
Xphos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Chapter 1: Transition Metal-Catalyzed Synthetic Methods for the Preparation of Allenes

1.1 Introduction

Allenes are unique functional groups in organic chemistry, characterized by two cumulated carbon-carbon double bonds which possess orthogonal π-systems. This uncommon system results in reactivity that is distinct from, yet complementary to, other π-bond containing functional groups such as alkenes and alkynes. Historically, the distinctive allenic structure was first predicted by van't Hoff in 1875.[1] Over a decade later, the first synthesis of an allene, glutinic acid, was reported by von Pechmann and Burton, however the structure was incorrectly characterized as an alkyne.[2] It wasn't until 1954 that the correct structure was illuminated by Whiting and coworkers.[3] It is potentially because accurate characterization proved to be so difficult, allenes were considered structural curiosities and not immediately thought of as useful synthetic compounds. It is safe to say that, currently, that could not be farther from the truth. Allenes continue to be found in an ever growing amount of natural products, bioactive compounds, and organic materials.[4,5] Further, allenes have been shown to be versatile intermediates for synthesis as they can participate in a wide variety of powerful chemical transformations that yield products with increasing structural complexity.[6-13] One of the most common and important routes to allene substrates is via substitution of propargylic electrophiles.[14] Propargylic substrates are three carbon units possessing an alkyne moiety that can undergo nucleophilic substitution via two different pathways (Scheme 1.1).

Scheme 1.1: ***Substitution of Propargyl Electrophiles***



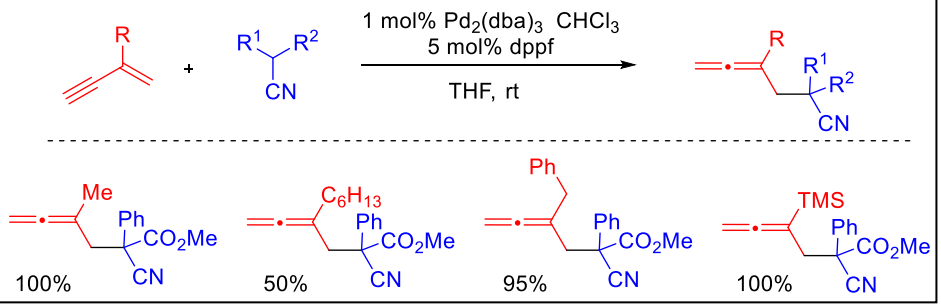
Direct S_N2 displacement results in propargylic products, whereas the S_N2' pathway produces allenic products. For many nucleophiles, without the assistance of a transition metal, these pathways are competing, resulting in low levels of regioselectivity. Transition metal-catalyzed substitutions of propargylic substrates are often substantially more selective for allenes, allowing for a more generalized approach to their synthesis. Though, depending on the metal, the formation of numerous metal-bound intermediates can result in more complex reaction manifolds. This chapter will review a variety of methods developed to synthesize allenes with a strong focus on transition metal-catalyzed transformations of propargylic starting materials. In an attempt to be concise, only methods which generate allenes via carbon-carbon bond formation are included.

1.2 Synthesis of Allenes from Non-Propargylic Starting Materials

Even though the overarching theme of Chapter 1 is the synthesis of allenes from propargylic substrates, it is still important to include a section discussing transition metal-catalyzed allene synthesis from non-propargylic starting materials. While this short review is in no way complete, key examples of allene synthesis from non-propargylic electrophiles are presented. The most commonly employed non-propargylic starting materials are 1,3-enyne derivatives and 1,3-butadiene derivatives. While 1,3-enynes are typically employed for the 1,4-addition of hydrosilane or hydroborane nucleophiles[15-17], there have been some transition metal-catalyzed allene syntheses utilizing carbon nucleophiles. In 1996, Yamamoto and coworkers reported the first palladium-catalyzed 1,4-addition of a carbon pronucleophile into an unactivated conjugated enyne yielding allenes.[18,19] The reported conjugate addition of activated methine pronucleophiles occurred in a regioselective manner at the terminal carbon of the alkene (Scheme 1.2). Reactions with methyl and TMS substituted enynes resulted in quantitative yields of the allenyl product. However, when longer chains were substituted on the enyne, decreased yields were seen and the reaction was

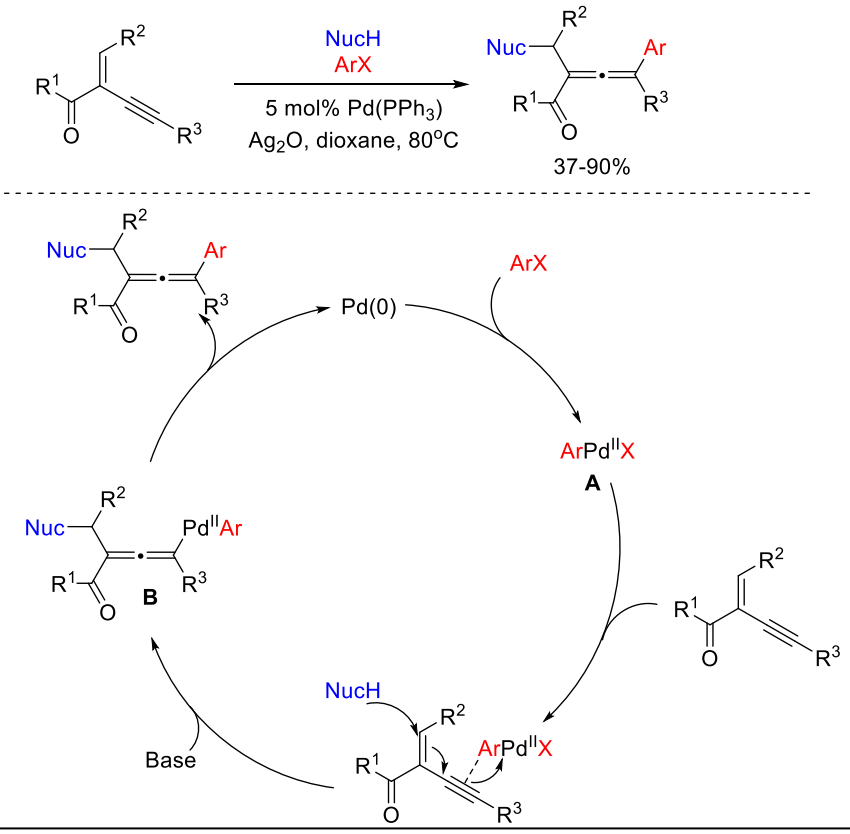
sluggish requiring up to 80 hours for completion. Unfortunately, the reaction was limited to activated methines that contained at least one cyano group. Additionally, the reaction did not tolerate substitution at either the alkyne or alkene terminus.

Scheme 1.2: ***Allene Syntheis via Unactivated Enynes***

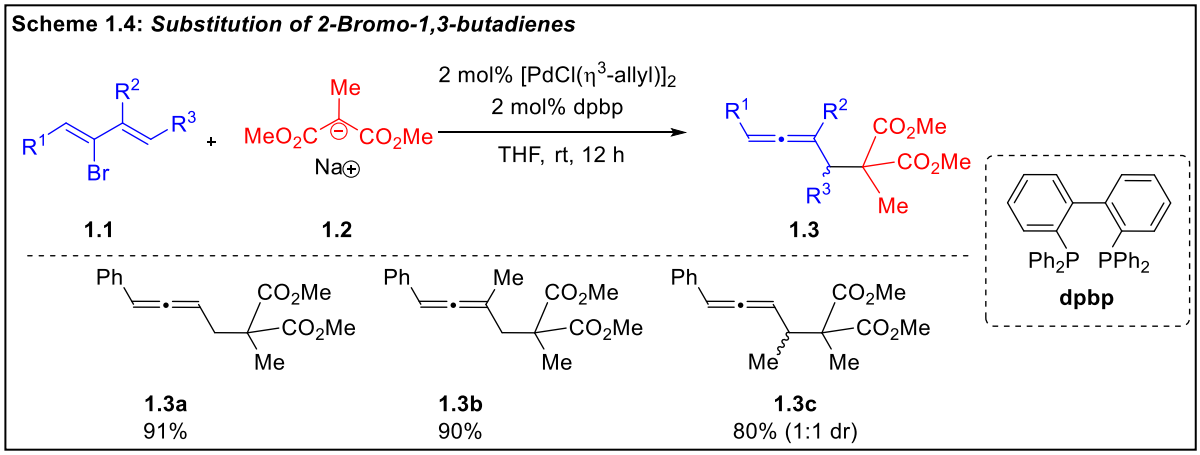


In 2010, Zhang and coworkers published a palladium-catalyzed three-component reaction that generated tetrasubstituted allenes from electron-deficient enynes (Scheme 1.3).[20] Zhang *et al.* proposed that the palladium(II) species **A**, generated via oxidative addition of the aryl halide to palladium(0), would promote nucleophilic attack at the alkene as a 1,4-addition. The resulting allenyl-palladium complex **B** could then undergo reductive elimination resulting in the tetrasubstituted allene. A variety of alcohol nucleophiles were tolerated, as well as dimethyl malonate. Interestingly, functionalized aryl substituents could be incorporated onto the allene via either the enyne (position R^3) or the aryl halide.

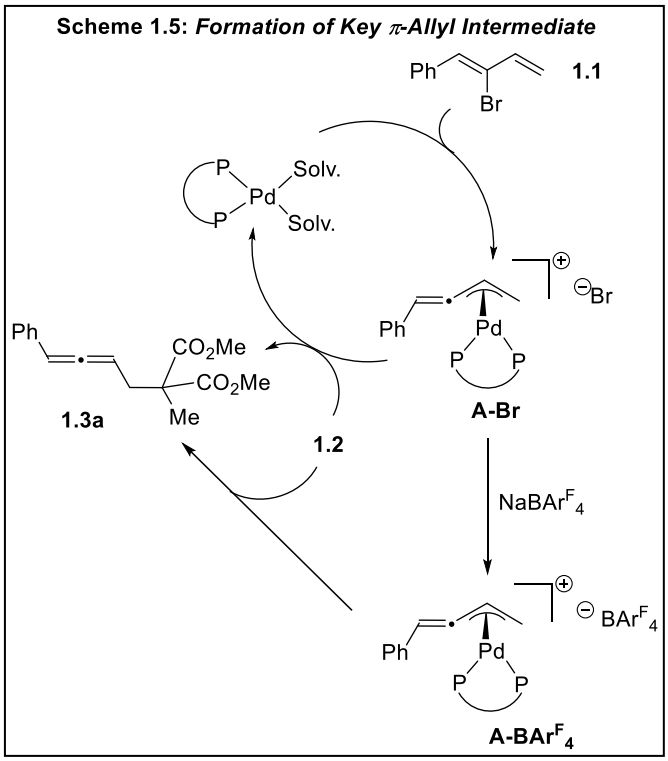
Scheme 1.3: ***Palladium-Catalyzed Multicomponent Synthesis of Tetrasubstituted Allenes***



The other most commonly employed non-propargyl starting substrates are 1,3-butadienes. Bromo-1,3-butadienes are similar to propargyl substrates as they also undergo palladium-catalyzed formal S_N2' reactions to afford allenes. However, the generated metal-complex intermediates for each substrate are vastly different. In regards to this route to allenes, Ogasawara, Takahashi, and Hayashi have made significant contributions to the field. In 2000, Ogasawara and Hayashi reported the synthesis of allenes via the palladium-catalyzed reaction of 2-bromo-1,3-butadienes with soft nucleophiles.[21] The reaction, catalyzed by $[PdCl(\eta^3\text{-allyl})]_2$ with dpbp as a ligand, was highly selective and the allenes were isolated in excellent yields. With other more commonly employed phosphine ligands, the reaction was much less efficient, though still selective for allene products. Unfortunately, the reaction was limited to soft nucleophiles such as malonates, with harder nucleophiles leading to a diene product. Comparatively, the scope of the butadienes was broader. Substitution at each position of the alkene was tolerated well (Scheme 1.4).



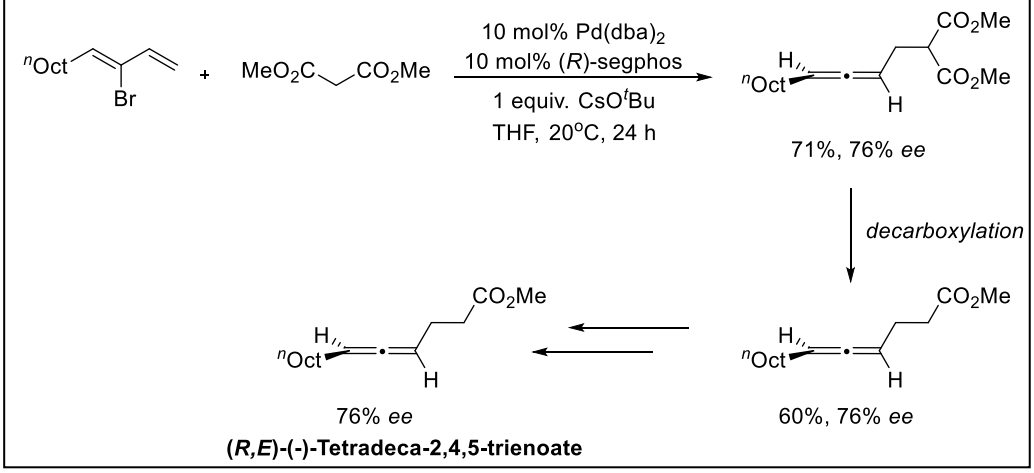
Ogasawara and Hayashi proposed that a key intermediate in the reaction with bromobutadienes was a (methylene-π-allyl)palladium species (**A-Br**), formed via oxidative addition in an S_N2' fashion (Scheme 1.5). After anion exchange with $NaBAr^F{}_4$, the proposed π-allyl complex (**A-BAr$^F{}_4$**) was able to be isolated and characterized by NMR. A stoichiometric reaction of **A-BAr$^F{}_4$** with **1.2** gave allene **1.3a** in 67% yield, thus strongly supporting the proposed mechanism.



By changing the catalyst to $Pd(dba)_2$ and (*R*)-BINAP, Ogasawara and Hayashi extended the developed method to an asymmetric variant, obtaining enantioenriched allenes in up to 89% *ee*.[22]

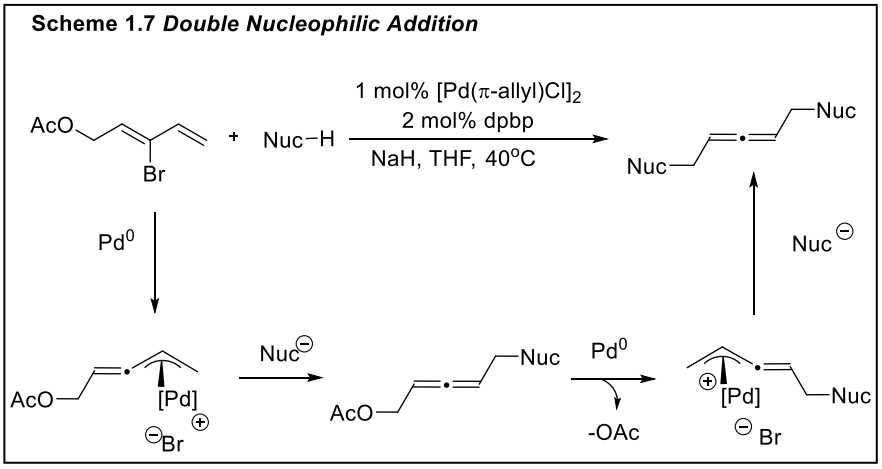
In 2005, they applied an asymmetric variant in the synthesis of (*R*,*E*)-(-)-tetradeca-2,4,5-trienoate, a pheromone of the dried bean beetle.[23] This was the first catalytic formal synthesis of the pheromone with high enantiopurity (Scheme 1.6).

Scheme 1.6: ***Catalytic Enantioenriched Synthesis of Pheromone***



More recently, in 2012, Ogasawara and Takahashi combined their allene preparation methods with allene functionalization reactions as both occurred via related (alkylidine-π-allyl)palladium intermediates.[24] Incorporation of an ester moiety at the terminal position of the 2-bromo-1,3-diene motif, utilized in earlier work, allowed for the formation of the allenylester. The allenylester could then be functionalized *in situ* by the same palladium catalyst system and a second equivalent of the nucleophile, resulting in a doubly functionalized C_2-symmetric allene product (Scheme 1.7).

Scheme 1.7 ***Double Nucleophilic Addition***



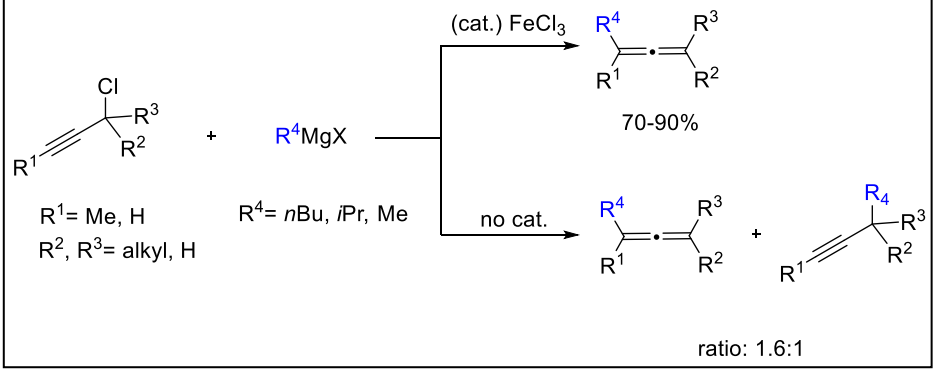
1.3 Transition Metal-Catalyzed Allene Syntheses from Propargylic Electrophiles

As mentioned previously, transition metal-catalyzed addition to propargylic electrophiles is one of the most commonly employed strategies to synthesize allenes. For simplicity, the following methods for allene synthesis are divided into sections according to the metal employed.

1.3.1 Iron-Catalyzed Allene Synthesis.

Possibly the first examples of transition metal-catalyzed additions of an organometallic nucleophile to propargylic electrophiles was published by Pasto and coworkers in 1976.[25] Pasto *et al.* reported the addition of primary or secondary alkyl Grignard reagents to propargyl chlorides catalyzed by iron(III) chloride (Scheme 1.8). In the absence of the iron catalyst, Grignard reagents reacted with propargyl halides to provide a mixture of both the allene and propargyl products.[26] Addition of $5x10^{-5}$ M $FeCl_3$ resulted in the selective formation of allenes in good yield.

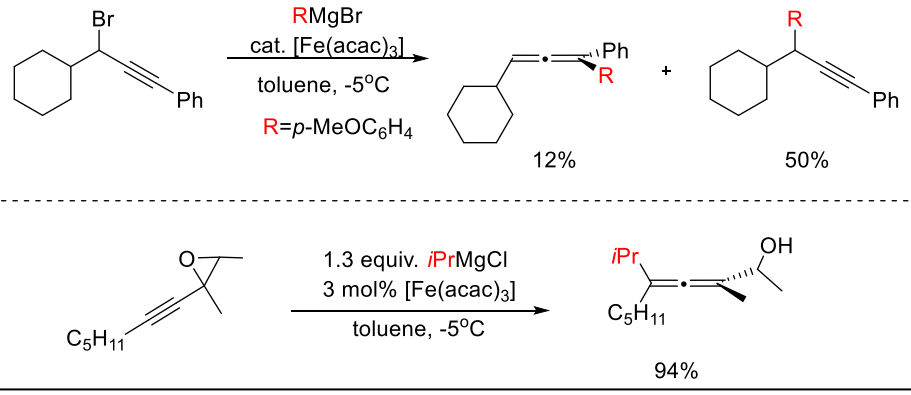
Scheme 1.8: ***Iron-Catalyzed Addition of Grignard to Propargyl Chloride***



However, in 2003 Fürstner and coworkers attempted to apply this method and found unsatisfactory selectivity for the allene.[27] The use of less hygroscopic $Fe(acac)_3$ to catalyze the addition led to primary formation of the propargyl product (Scheme 1.9). It was determined that propargyl epoxides were exceptional electrophiles for the coupling with alkyl Grignard reagents, allowing for less than five minute reaction times and catalyst loading of 3-5 mol %. Notably, the direct

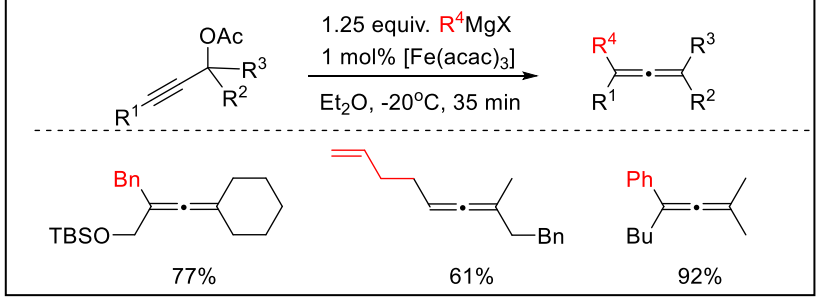
attack of Grignard reagents on the epoxide moiety was not a significant side reaction for these couplings.

Scheme 1.9: ***Iron-Catalyzed Addition of Grignard to Propargyl Epoxides***



In 2016, Bäckvall and coworkers extended the scope of electrophiles for iron-catalyzed couplings of Grignard reagents to more readily accessible propargyl acetates.[28] Further, Bäckvall *et al.* explored a greater range of nucleophiles than just the simple alkyl Grignards that had been previously reported. They demonstrated that the coupling could be achieved with benzyl, unsaturated, and aryl Grignard reagents (Scheme 1.10).

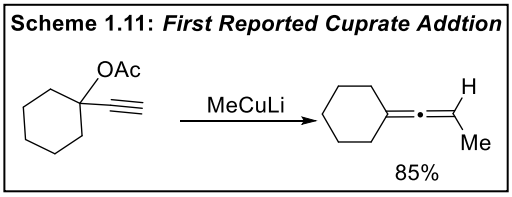
Scheme 1.10: ***Iron-Catalyzed Grignard Addtion into Propargyl Acetates***



1.3.2 Copper-Catalyzed Allene Synthesis

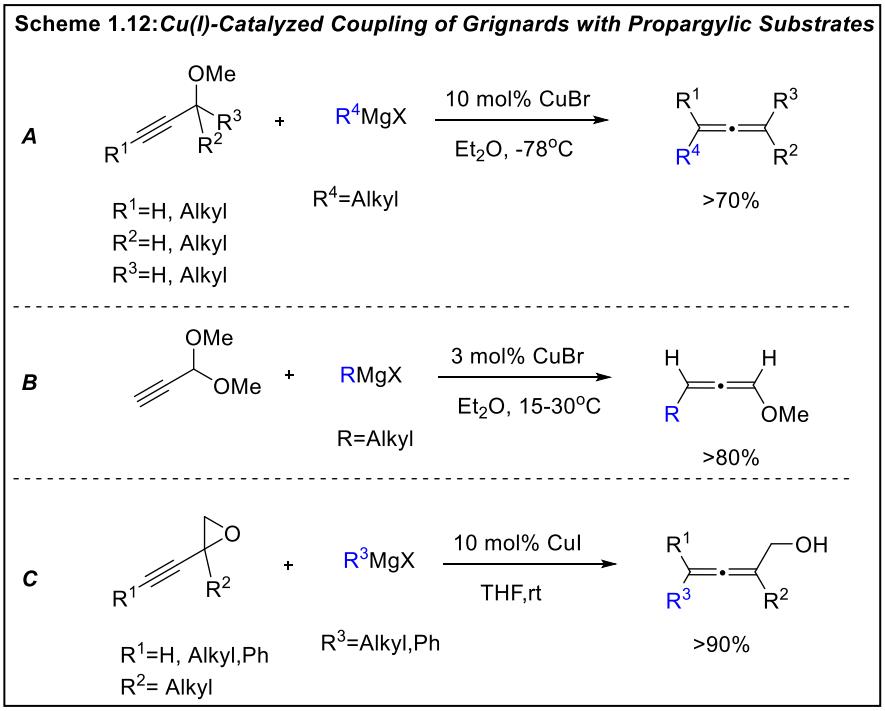
In 1968 Crabbe and Rona published the first example copper-mediated synthesis of an allene.[29] They reported that lithium dialkylcuprates added to propargyl acetates in an S_N2' fashion, giving allenes in moderate to good yields (Scheme 1.11).

Scheme 1.11: ***First Reported Cuprate Addtion***



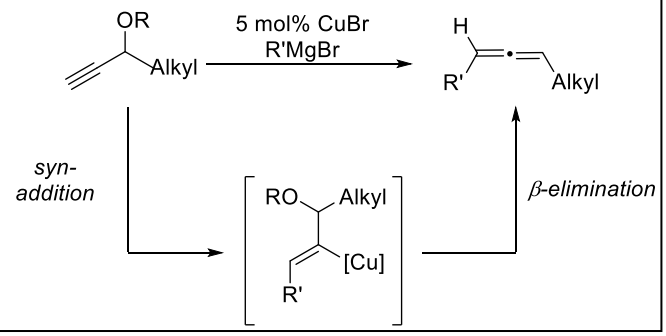
Since that seminal publication, the S_N2' addition of stoichiometric organocopper reagents is possibly the most popular method for the synthesis of allenes.[12,30] However, the stoichiometric variant often suffers from regioselectivity issues and limited nucleophile scope. Thus, there has been significant development of reactions using only catalytic amounts of copper, allowing for a wider range of substituted allenes to be synthesized. Early works from Vermeer and Alexakis in the 1970's and 80's established the copper(I)-catalyzed addition of Grignard reagents to various propargyl alcohol derivatives as a valuable method for allene synthesis. Electrophiles for these additions included propargylic ethers[31], acetals[32,33], and epoxides[34-36] (Scheme 1.12_A,B,C).

Scheme 1.12: ***Cu(I)-Catalyzed Coupling of Grignards with Propargylic Substrates***



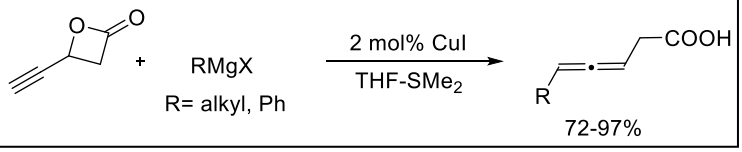
While investigating the stereochemical outcome of the above reactions, Alexakis *et al.* observed that varying the halogen on the Grignard reagent changed the stereoselectivity of the reaction.[37] They propose that if the reaction were to proceed via a Cu(III) intermediate, formed via S_N2' attack, the halogens would not affect the stereoselectivity. Thus they postulated a different mechanism was operating which involved the *syn*-addition of the copper nucleophile across the triple bond, followed by β-elimination to give the allene (Scheme 1.13).

Scheme 1.13: ***Mechanism of Cu(I)-Catalyzed Allene Synthesis***

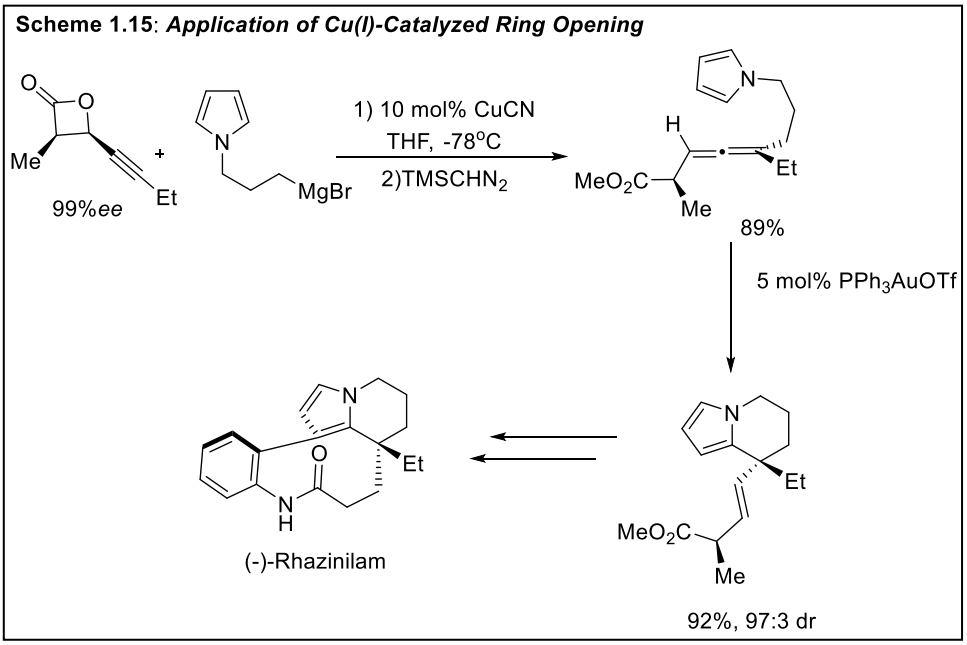


In 1981 Fijisawa and coworkers extended the copper(I)-catalyzed addition of Grignard reagents to 3-ethynyl-β-propiolates, thus affording 3,4-alkadienoic acids (Scheme 1.14) [38]

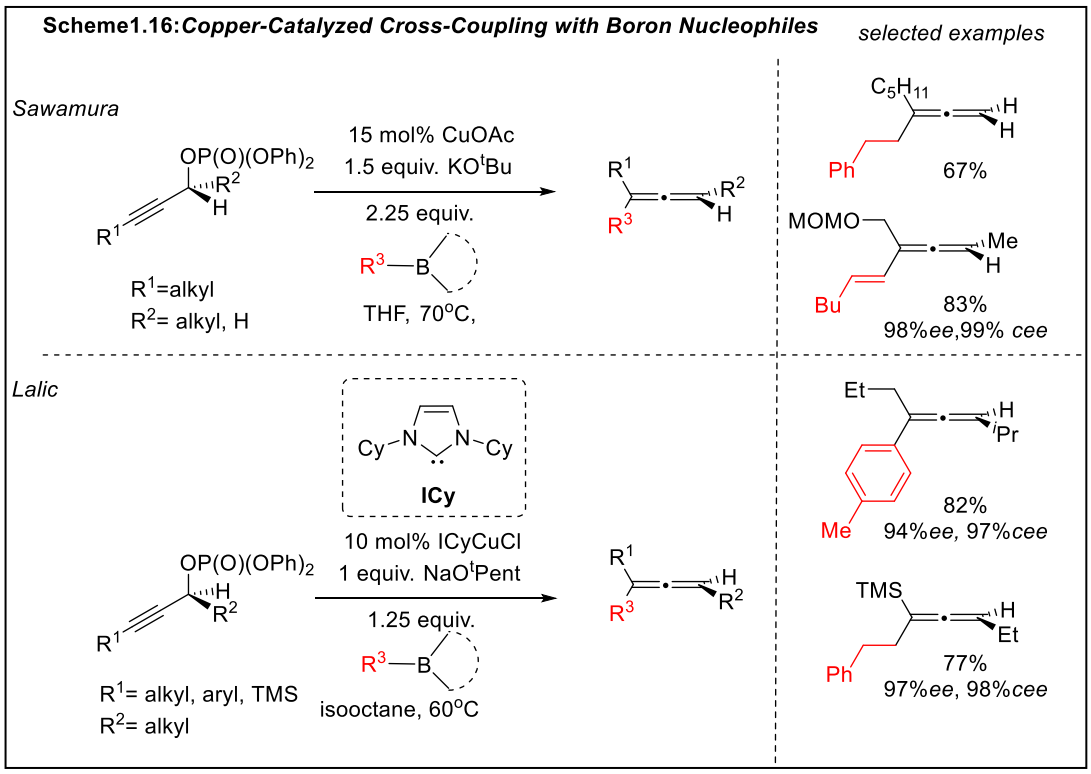
Scheme 1.14: ***Opening of β-Lactone to Form Allenyl Acids***



In 2000, Nelson and coworkers reported that the reaction developed by Fijisawa could occur stereospecifically when enantioenriched lactones, prepared via an asymmetric catalytic cyclocondensation, were employed.[39] They postulated that the stereospecificity resulted from S_N2' addition of the Grignard instead of the previously proposed addition-elimination sequence. Notably in 2005, Nelson *et al*. used their enantiospecific cross-coupling in the total synthesis of (-)-rhazinilam.[40] Copper(I)-catalyzed addition of a pyrrole-substituted Grignard reagent to the enantioenriched β-lactone yielded the enantioenriched allene as a single diastereomer in 89% yield (Scheme 1.15). The enantioenriched allene could then undergo gold-catalyzed annulation to afford the tetrahydroindolizine core, which was further transformed into (-)-rhazinilam.

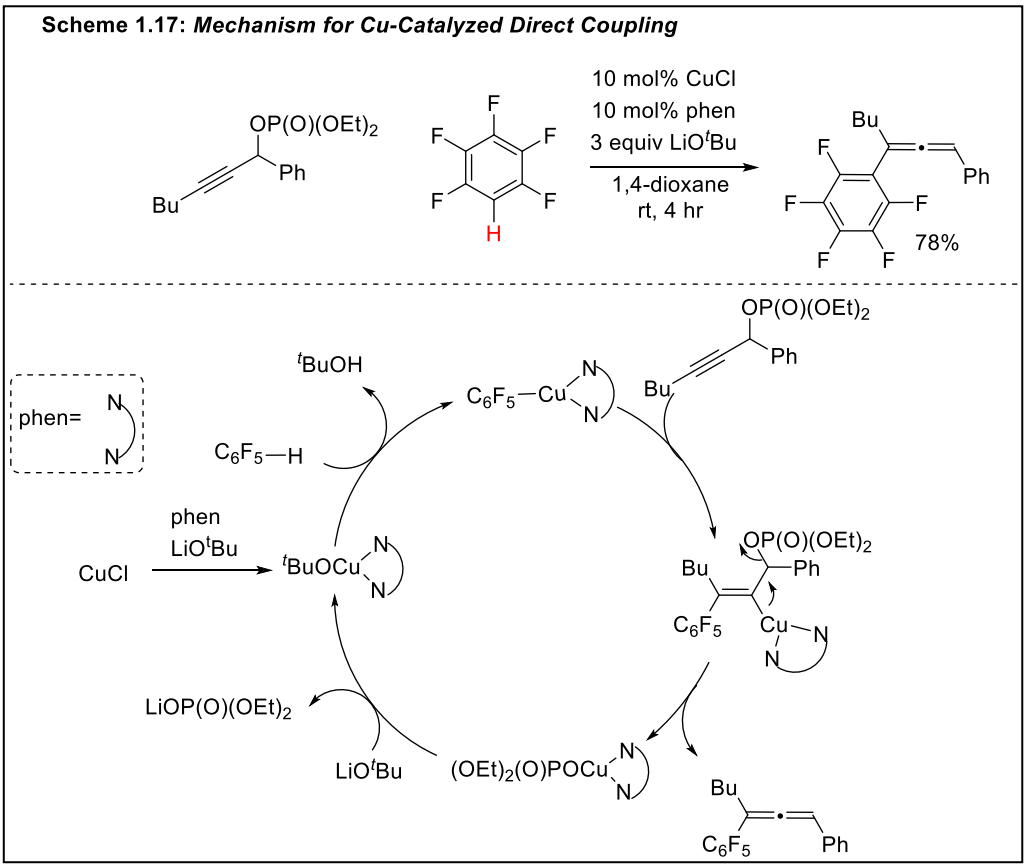


The above mentioned copper-catalyzed additions of Grignard reagents suffer from key issues such as functional group compatibility, as well as lack of regioselectivity with primary propargyl alcohols which form propargylic products instead of the desired allenes. In efforts to address these issues, Sawamura[41,42] and Lalic[43] simultaneously developed copper(I)-catalyzed cross couplings of propargyl phosphates with alkyl, vinyl, and aryl boronic acid derivatives. Both methods were remarkably similar, with essentially only the catalysts differing (Scheme 1.16).These approaches were significantly more functional group tolerant than the previously discussed methods and could be used to synthesize both di- and trisubstituted allenes. Further, both Sawamura's and Lalic's methods were highly stereospecific when enantioenriched propargyl phosphates were employed (discussed further in Chapter 3, Section 3.2.1).



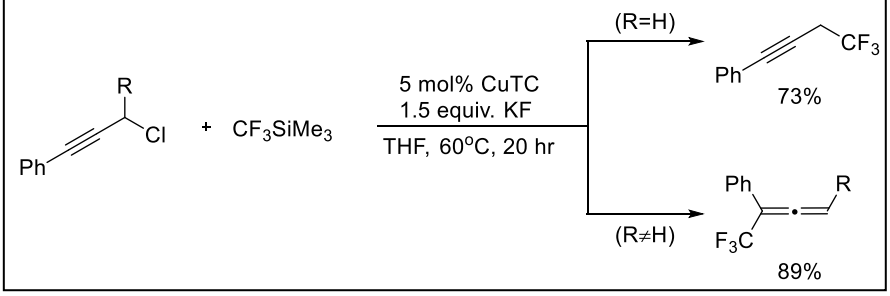
Within the last decade fluorinated molecules have become important targets in pharmaceutical chemistry, thus there is an increased need for methods that incorporate fluorinated motifs into potential chemical building blocks, such as allenes.[44] Recently, there have been copper-catalyzed couplings with propargyl electrophiles developed in order to meet that need. In 2012, Miura and coworkers reported the synthesis of polyfluoroaryl allenes via a copper-catalyzed direct coupling of polyfluoroarenes with propargyl phosphates.[45] Unlike the previously discussed copper-catalyzed cross coupling reactions, the nucleophile did not require pre-activation by stoichiometric metalation. Instead, the direct coupling begins with the cupration of the polyfluoroarene, promoted by the highly basic *t*-butoxide ligand on copper (Scheme 1.17). The resulting aryl copper species can then undergo a similar addition-elimination sequence to that proposed by Alexakis. While this method does not require additional preformed organometallic reagents, it still employs super-stoichiometric amounts of strong base.

Scheme 1.17: ***Mechanism for Cu-Catalyzed Direct Coupling***



In 2013, Nishibayashi and coworkers published a copper-catalyzed trifluoromethylation of propargylic halides.[46] Treatment of secondary propargylic halides with 5 mol % copper(I) thiophene-2-carboxylate (CuTC) and CF_3SiMe_3 afforded trifluoromethylated allenes in good yields (Scheme 1.18). Unfortunately this reaction was strictly limited to secondary propargyl halides as primary substrates yielded only propargylic products.

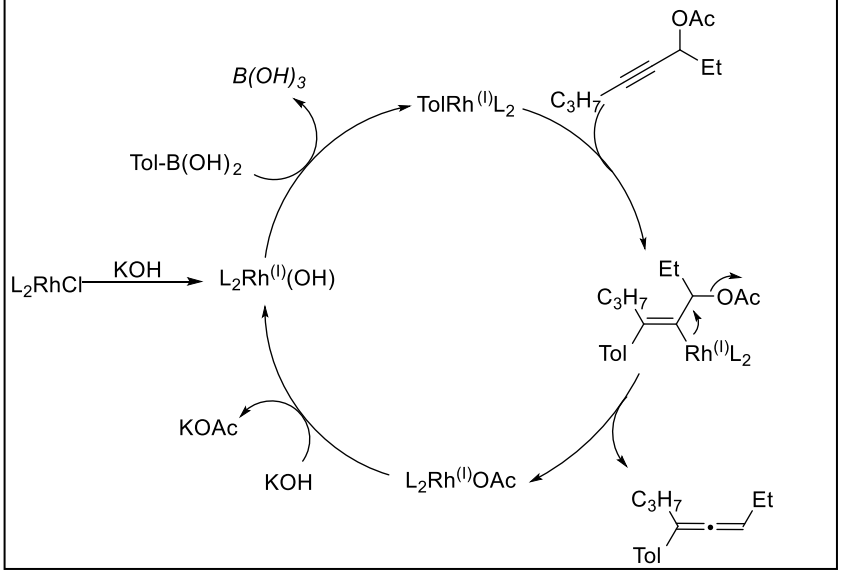
Scheme 1.18: ***Cu-Catalyzed Trifluoromethylation***



1.3.3 Rhodium-Catalyzed Allene Synthesis

In 2002, Murakami and coworkers reported the rhodium-catalyzed addition of aryl boronic acids to propargyl acetates.[47] However, only one substrate was studied as Murakami *et al.* were examining the stereochemistry of the cross-coupling. This reaction, like the copper-catalyzed cross-couplings, proceeded stereospecifically though with poor chirality transfer. Unlike the copper-catalyzed additions, the rhodium-catalyzed reactions resulted in the retention of configuration. This observation led Murakami to propose that the rhodium(I) species formed upon transmetalation with the boron nucleophile underwent *cis* 1,2-addition. (Scheme 1.19)**.** After the addition across the triple bond, the rhodium-alkenyl intermediate would then undergo *syn*-elimination, resulting in an overall retention of configuration.

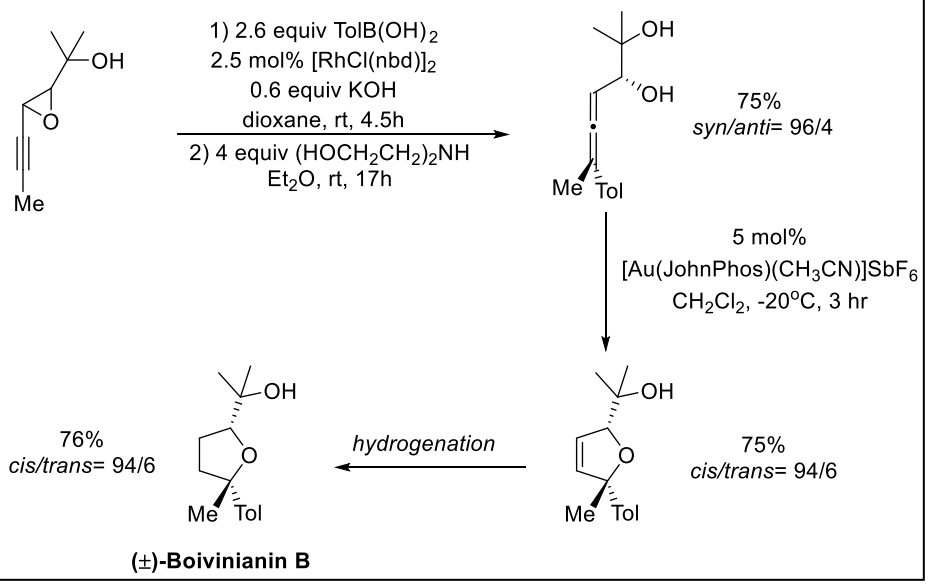
Scheme 1.19:*Rh(I)-Catalyzed Addtion of Boronic Acids to Propargyl Acetate*



Five years later, the same group extended their rhodium-catalyzed protocol to include propargyl epoxide electrophiles.[48] They examined a broad range of substrates and observed much better chirality transfer from the enantioenriched epoxides. Further, utilized oxiranes as nucleophiles allowed for the coupling to occur at room temperature instead of the 70˚C previously required. In 2007, the rhodium-catalyzed cross coupling of epoxides with arylboronic acids was applied in the

total synthesis of the natural product (±)-boivinianin B.[49] After the rhodium-catalyzed tolyl substitution, the resulting allenol underwent cycloisomerization catalyzed by a cationic gold complex. Hydrogenation of the double bond afforded (±)-boivinianin B in good yield (Scheme 1.20).

Scheme 1.20: ***Application of Rh-Catalyzed Addition***



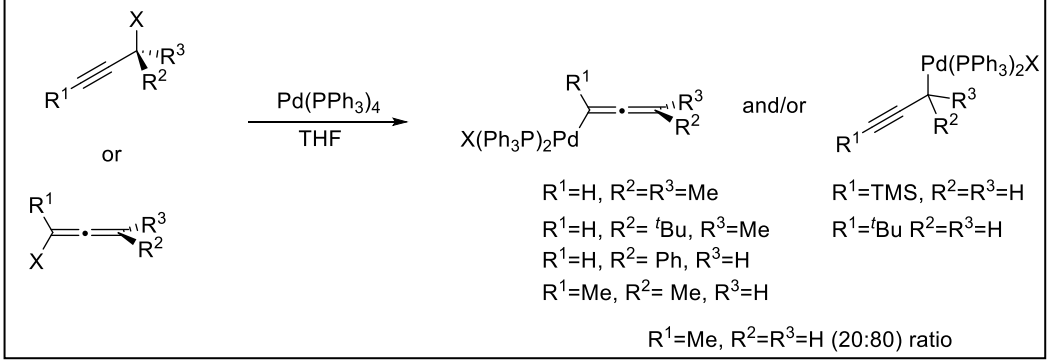
1.4 Reactivity of Palladium with Propargyl Electrophiles

Unlike the transition metals presented above, palladium possesses a unique reactivity with propargylic electrophiles which allows for the formation of various different products. The selectivity for the formation of a specific product is a direct result of the tuning of the multiple isomeric palladium-bound intermediates that are formed upon oxidative addition as well as the structure and reactivity of the nucleophile.

Since their development, palladium-catalyzed reactions with propargyl electrophiles have been assumed to proceed through one of two different isomeric palladium-bound intermediates, the η^1-allenyl palladium complex or the η^1-propargyl palladium complex. These two palladium species were confirmed by Boersma and coworkers when they observed the formation of either the η^1-allenylpalladium complex or the η^1-propargylpalladium upon treatment of either the propargyl or

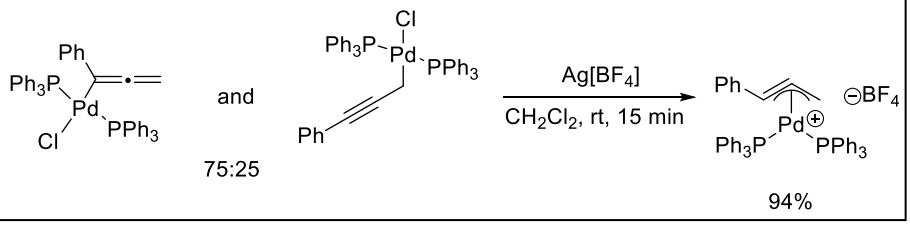
allenyl halide with stoichiometric amounts of $Pd(PPh_3)_4$.[50,51] They observed that the preference for one palladium-bound intermediate over the other relied on the steric bulk of the of propargyl and terminal positions of the starting materials (Scheme 1.21).

Scheme 1.21: ***Stoichiometric Oxidation Addition of Palladium***



In 1999, Kurosawa, Tsutsumi, and Ogoshi published the culmination of their thorough studies on the synthesis and characterization of the various palladium-bound complexes formed from oxidative addition of propargyl electrophiles to palladium(0). They observed that the hapticity of the allenyl/propargyl ligand on palladium relied heavily on the nature of the counterion.[52] Simultaneously exchanging the strongly coordinating chloride counterion on a mixture of the η^1-allenyl and η^1-propargylpalladium complex for a non-coordinating tetrafluoroborate resulted in the exclusive formation of a cationic η^3-propargylpalladium species (Scheme 1.22). They hypothesized that this indicated an equilibrium between the η^1- and η^3-complexes.[53]

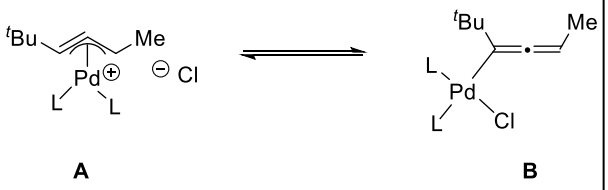
Scheme 1.22: ***Ion Exchange Results in η^3-Complex***



In these studies, the effects that solvent polarity had on the interconversion between the η^1- and η^3-complexes were also examined. When the η^1- and η^3- palladium complex equilibrium was generated in various solvents and monitored via NMR spectroscopy (Scheme 1.23), it was

observed that equilibrium favored the η^3-propargylpalladium in polar solvents such as deuterated chloroform or dimethylformamide. However, utilizing deuterated benzene led to the exclusive formation of the η^1-allenylpalladium. Further, changing the ligand from the bidentate dppe to PPh_3 again led to sole formation of the η^1-allenylpalladium.

Scheme 1.23: ***Solvent and Ligand Effects on Equilibrium***



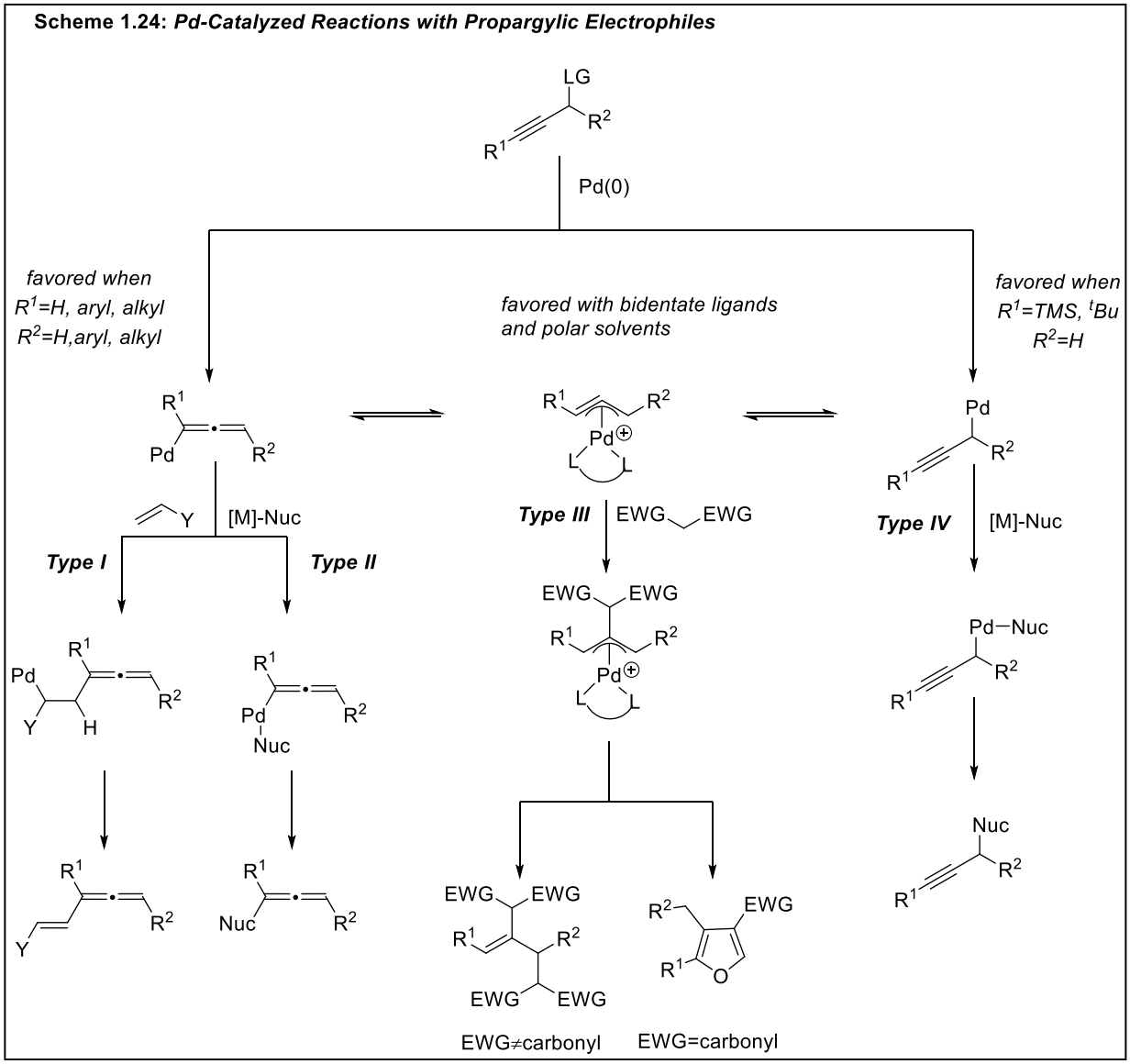
A **B**

Solvent	Ligand	A/B
$CDCl_3$	dppe	75/25
DMF-d_7	dppe	89/11
C_6D_6	dppe	0/100
$CDCl_3$	PPh_3	0/100
DMF-d_7	PPh_3	0/100

From these studies one can infer that selectivity for the η^1-allenylpalladium can be promoted over the other two isomers by two different strategies. First is via substrate control, increasing steric bulk at the propargylic position (R^2 and R^3) while decreasing the bulk at the terminal position (R^1) of the substrate favors the formation of the η^1-allenylpalladium species. The other strategy is through catalyst control. By utilizing some combination of coordinating counterions, monodentate ligands, and nonpolar solvents, it would be possible to engineer a palladium-catalyst that prefers to sit as the η^1-allenyl intermediate.

As the three reactive palladium-intermediates have been proposed to exist with in equilibrium that can be altered by reaction conditions, there has been a significant amount of work to demonstrate the different reactivities of these intermediates with various carbon nucleophiles. The large amount of work by Chen,[54] Ogoshi,[52] Wojcicki, and Tsuji[55] can be combined together to provide a more complete synthetic picture of palladium-catalyzed reactions with propargyl electrophiles. These reactions have been categorized into four distinct reaction types (Scheme 1.24). Reactions with

the η^1-allenylpalladium fall into type I and type II reactions. The formation of the η^1-allenylpalladium is primarily due to the lack steric hindrance at the R^1 position. The allenyl complex has been shown to undergo insertion reactions with alkenyl nucleophiles (**type I**) which can then undergo β-hydride elimination to give conjugated ene-allene products. The allenyl complex has also been shown to undergo transmetalation with hard organometallic nucleophiles (**type II**). Upon reductive elimination type II reactions also generate an allene as the product. Alternatively, soft carbon nucleophiles are known to attack the center carbon of the η^3-propargylpalladium complex (**type III**), which are primarily generated in the presence of bidentate ligands. Attack of the center carbon results in the formation of a π-allylpalladium complex which is prone to undergo a second nucleophilic attack leading to either a double addition or cyclization product depending on the nature of the nucleophile. Finally, reaction with the η^1-propargylpalladium (**type IV**), selectively formed when R^1 is very bulky, is very rare but would undergo a similar reaction to that of type II. Transmetalation with an organometallic nucleophile followed by direct reductive elimination would result in a propargylic product.

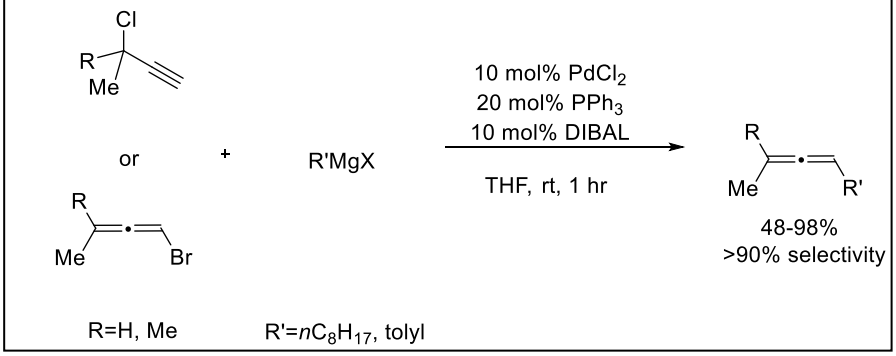


1.4 Palladium-Catalyzed Type II Reactions of Propargyl Electrophiles

Palladium-catalyzed coupling reactions with propargylic electrophiles are among the most explored catalytic methods to synthesize allenes. Unlike copper, palladium-catalyzed reactions are in general milder, and more tolerant of various substituents on the propargylic substrates. Further, the employment of palladium allows for a wider range of potential nucleophilic partners. The first palladium-catalyzed cross-coupling reaction to synthesize allenes was published by Linstrumelle and Jeffery-Luong in 1980.[56] They reported that a palladium catalyst, generated from $PdCl_2$, PPh_3 and DIBAL, promoted the addition of Grignard reagents to either propargyl or allenyl halides

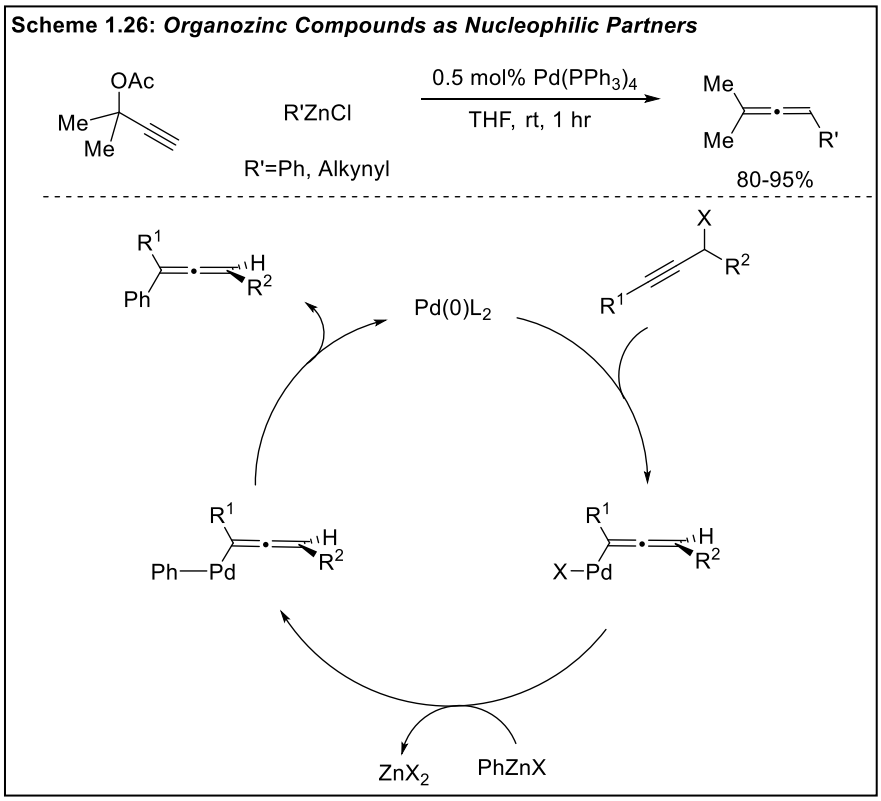
yielding the allene product selectively in moderate to good yield (Scheme 1.25**)** Without the palladium catalyst, the Grignard addition to the propargyl chloride resulted in a mixture of the propargyl and allenyl products in very low yields.

Scheme 1.25: ***First Reported Pd-Catalyzed Coupling with Propargyl Electrophile***



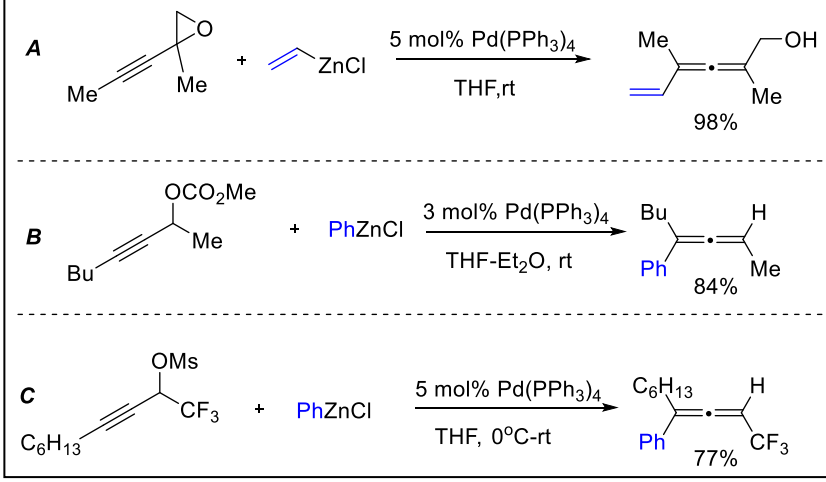
One year later, Vermeer and coworkers found that replacing the Grignard reagents with organozinc compounds led to even higher selectivity (>99%) for the allene product with better yields.[57] Further, utilizing the organozinc compounds required significantly less palladium, only 0.5 mol %, compared to the previously reported 10 mol %. Additionally, less toxic propargyl acetates could be employed as the electrophilic partner (Scheme 1.26). Upon isolation of the η^1-allenylpalladium in 1983, Vermeer *et al.* proposed that the reaction began with oxidative addition of palladium with the propargyl substrate in an S_N2' fashion.[50] The allenylpalladium(II) species can then undergo transmetalation with the hard organometallic nucleophile. Reductive elimination of the resulting palladium complex would lead to the allene product.

Scheme 1.26: ***Organozinc Compounds as Nucleophilic Partners***



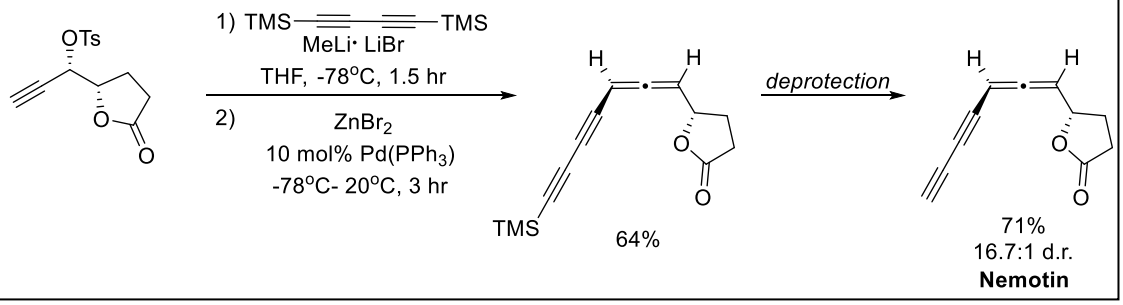
Over the years, the palladium-catalyzed addition of organozincs has been found to be compatible with a wide array of different propargylic electrophiles, employing various different leaving groups. Utilization of epoxides as leaving groups (Scheme 1.27_ A) allowed for the synthesis of allenyl methyl alcohols.[58] Carbonates (Scheme 1.27_B)[59] and mesylates (Scheme 1.27_C)[60] have also been demonstrated to be competent leaving groups.

Scheme 1.27: ***Pd-Catalyzed Coupling of Organozinc with Propargylic Substrates***



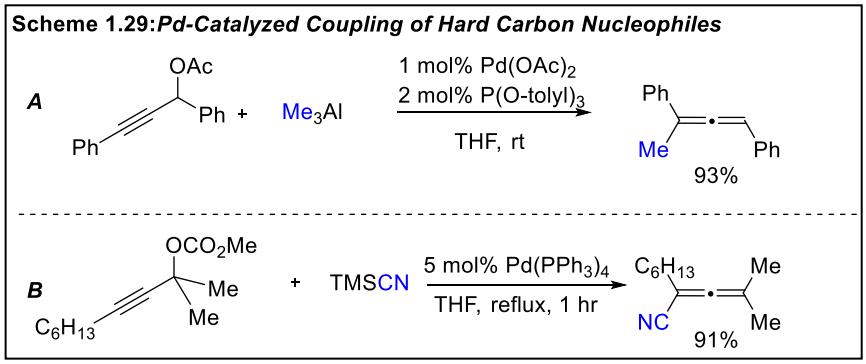
The palladium-catalyzed addition of organozinc compounds has also be used in the total synthesis of natural products. In 2010, Wu and coworkers published the total synthesis of nemotin, an allene-containing natural product with antibiotic properties.[61] In one of the final steps of the synthesis, a propargyl tosylate, synthesized from a D-tartrate-derived acetonide, is treated with catalytic palladium and a zinc acetylide, formed *in situ* from a lithiated acetylide and $ZnBr_2$ (Scheme 1.28). Deprotection of the resulting TMS allenyne yielded the natural product.

Scheme 1.28: ***Final Steps in Total Synthesis of Nemotin***



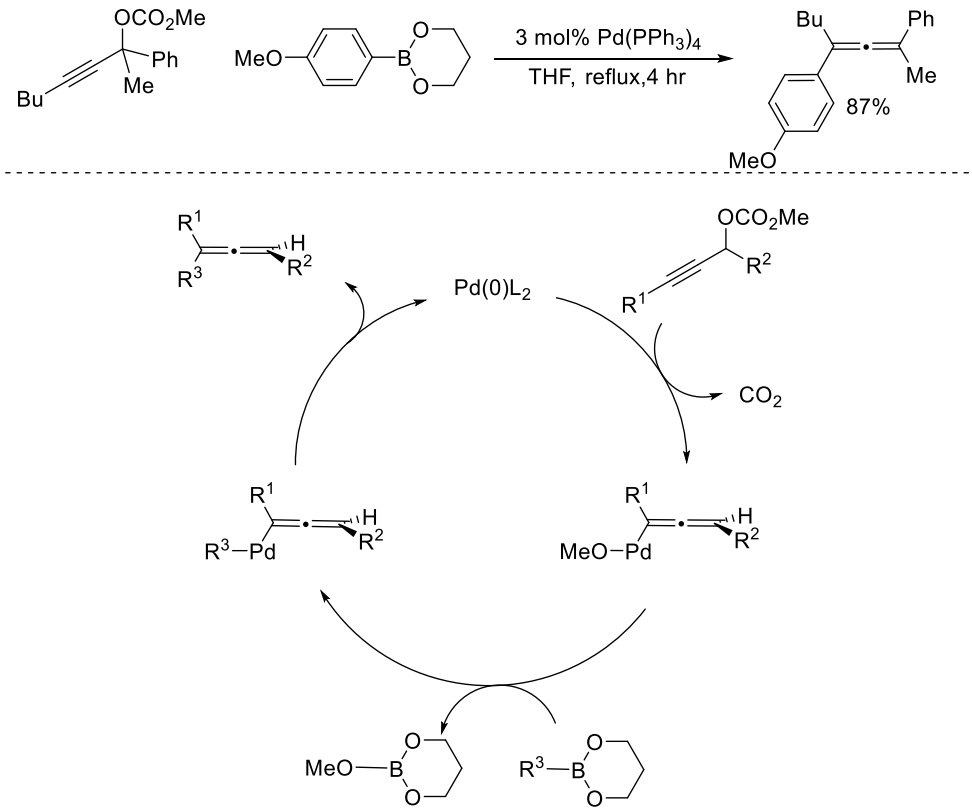
In addition to organozinc compounds, other hard carbon nucleophiles have been applied the palladium-catalyzed substitution of propargylic electrophiles. While the organozinc compounds have been limited to sp^2 and sp hybridized carbon nucleophiles, the use of trialkylaluminum (Scheme 1.29_A) resulted in the alkylated allene with high selectivity and yield.[62,63] Additionally, Tsuji and coworkers reported the use of trimethylsilyl cyanide as a successful nucleophilic partner with propargyl carbonates in the palladium-catalyzed synthesis of cyanoallenes (Scheme 1.29_B).[64]

Scheme 1.29: ***Pd-Catalyzed Coupling of Hard Carbon Nucleophiles***



In 1994, Suzuki and Miyaura reported that organoboron species also made excellent nucleophilic partners for the palladium-catalyzed substitution of propargylic substrates to yield allenes (Scheme 1.30).[65] Notably, reactions between propargyl methyl carbonate and organoboron species proceeded under neutral conditions. This is because methoxide is generated *in situ* after successive oxidative addition and decarboxylation of the carbonate. The methoxide then activates the organoboron towards transmetalation which is followed by reductive elimination to give the allene product. Suzuki and Miyaura's report contained only a handful of examples, but subsequent works by Yoshida[66,67] and Molander[68] have demonstrated the broad scope and applicability of this method. However, like the analogous processes utilizing organozincs, these methods are limited to the use of sp^2 and sp hybridized boron nucleophiles.

Scheme 1.30: ***Organoboron Compounds as Nucleophilic Partners***



1.5 Conclusion

In conclusion, this chapter has provided a snapshot of the variety of methods used to achieve substitution of propargylic electrophiles in a manner that is selective for allene formation. Transition metal catalysis has been demonstrated as one of the most successful strategies to achieve allene synthesis from propargylic substrates. Iron, copper, rhodium, and palladium have all been utilized to catalyze the addition of various carbon nucleophiles, yielding a variety of substituted allenes. However, due to the necessary use of organometallic reagents and harsh conditions these methods suffer from a lack of atom economy and often low functional group tolerance. While the transition metal-catalyzed methods presented above are useful, more can be done to develop equally powerful reactions that are more atom economical, efficient, and environmentally benign.

1.6 References for Chapter 1

(1) Hoff, J. H. v. t.: *La Chimie dans l'espace*; P.M. Bazendijk: Rotterdam, 1875.

(2) Burton, B. S.; Pechmann, H. v. Action of phosphoric chloride on ethyl acetonedicarboxylate. *Ber.*, *20*, 145-149.

(3) Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. Acetylenic compounds. XLVII. The prototropic rearrangements of some acetylenic dicarboxylic acids. *J. Chem. Soc.* **1954**, 3208-3212.

(4) Hoffmann-Roeder, A.; Krause, N. Synthesis and properties of allenic natural products and pharmaceuticals. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196-1216.

(5) Rivera-Fuentes, P.; Diederich, F. Allenes in Molecular Materials. *Angew. Chem., Int. Ed.* **2012**, *51*, 2818-2828.

(6) López, F.; Mascareñas, J. L. Allenes as Three-Carbon Units in Catalytic Cycloadditions: New Opportunities with Transition-Metal Catalysts. *Chem. Eur. J.* **2011**, *17*, 418-428.

(7) Krause, N.; Winter, C. Gold-Catalyzed Nucleophilic Cyclization of Functionalized Allenes: A Powerful Access to Carbo- and Heterocycles. *Chem. Rev.* **2011**, *111*, 1994-2009.

(8) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* **2005**, *105*, 2829-2872.

(9) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. Palladium-Catalyzed Reactions of Allenes. *Chem. Rev.* **2000**, *100*, 3067-3125.

(10) Krause, N.; Hoffmann-Röder, A.; Canisius, J. From Amino Acids To Dihydrofurans: Functionalized Allenes in Modern Organic Synthesis. *Synthesis* **2002**, *2002*, 1759-1774.

(11) Hashmi, A. S. K. New and selective transition metal catalyzed reactions of allenes. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590-3593.

(12) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074-3112.

(13) Bates, R. W.; Satcharoen, V. Nucleophilic transition metal based cyclization of allenes. *Chem. Soc. Rev.* **2002**, *31*, 12-21.

(14) Hayashi, T.; Ogasawara, M.: Transition Metal-Catalyzed Synthesis of Allenes. In *Modern Allene Chemistry*; Hashmi, S. K., Krause, N., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2004; Vol. 1; pp 93-140.

(15) Ishikawa, M.; Naka, A.; Ohshita, J. Silicon-carbon unsaturated compounds. 43. Nickel-catalyzed reactions of disilanyl-substituted enynes with methyldiphenylsilane. *Organometallics* **1992**, *11*, 3004-3008.

(16) Han, J. W.; Tokunaga, N.; Hayashi, T. Palladium-Catalyzed Asymmetric Hydrosilylation of 4-Substituted 1-Buten-3-ynes. Catalytic Asymmetric Synthesis of Axially Chiral Allenylsilanes. *J. Am. Chem. Soc.* **2001**, *123*, 12915-12916.

(17) Matsumoto, Y.; Naito, M.; Hayashi, T. Palladium(0)-catalyzed hydroboration of 1-buten-3-ynes: preparation of allenylboranes. *Organometallics* **1992**, *11*, 2732-2734.

(18) Salter, M. M.; Gevorgyan, V.; Saito, S.; Yamamoto, Y. Synthesis of allenes via palladium catalyzed addition of certain activated methynes to conjugated enynes. *Chem. Commun.* **1996**, 17-18.

(19) Gevorgyan, V.; Kadowaki, C.; Salter, M. M.; Kadota, I.; Saito, S.; Yamamoto, Y. Palladium catalyzed addition of carbon pronucleophiles to conjugated enynes. *Tetrahedron* **1997**, *53*, 9097-9106.

(20) Xiao, Y.; Zhang, J. Tetrasubstituted allenes by Pd0-catalyzed three-component tandem Michael addition/cross-coupling reaction. *Chem. Commun. (Cambridge, U. K.)* **2010**, *46*, 752-754.

(21) Ogasawara, M.; Ikeda, H.; Hayashi, T. π-Allylpalladium-mediated catalytic synthesis of functionalized allenes. *Angew. Chem., Int. Ed.* **2000**, *39*, 1042-1044.

(22) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes: A Synergistic Effect of Dibenzalacetone on High Enantioselectivity. *J. Am. Chem. Soc.* **2001**, *123*, 2089-2090.

(23) Ogasawara, M.; Nagano, T.; Hayashi, T. A New Route to Methyl (R,E)-(-)-Tetradeca-2,4,5-trienoate (Pheromone of Acanthoscelides obtectus) Utilizing a Palladium-Catalyzed Asymmetric Allene Formation Reaction. *J. Org. Chem.* **2005**, *70*, 5764-5767.

(24) Ogasawara, M.; Suzuki, M.; Takahashi, T. Preparation of C2-Symmetric Allenes by Palladium-Catalyzed Double-Nucleophilic Substitution on 3-Bromopenta-2,4-dienyl Acetate. *J. Org. Chem.* **2012**, *77*, 5406-5410.

(25) Pasto, D. J.; Hennion, G. F.; Shults, R. H.; Waterhouse, A.; Chou, S.-K. Reaction of propargyl halides with Grignard reagents. Iron trichloride catalysis in allene formation. *J. Org. Chem.* **1976**, *41*, 3496.

(26) Pasto, D. J.; Shults, R. H.; McGrath, J. A.; Waterhouse, A. Clarification of the mechanism of the reaction of terminal propargylic chlorides with alkyl Grignard reagents. *J. Org. Chem.* **1978**, *43*, 1382-1384.

(27) Fuerstner, A.; Mendez, M. Iron-catalyzed cross-coupling reactions: Efficient synthesis of 2,3-allenol derivatives. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355-5357.

(28) Kessler, S. N.; Baeckvall, J.-E. Iron-catalyzed Cross-Coupling of Propargyl Carboxylates and Grignard Reagents: Synthesis of Substituted Allenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 3734-3738.

(29) Rona, P.; Crabbe, P. A novel allene synthesis. *J. Amer. Chem. Soc.* **1968**, *90*, 4733-4734.

(30) Hoffmann-Roder, A.; Krause, N.: Metal-Mediated Synthesis of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2004; Vol. 1; pp 51-92.

(31) Marek, I.; Mangeney, P.; Alexakis, A.; Normant, J. F. Are allenes formed from propargylic ethers through a syn or anti displacement? *Tetrahedron Lett.* **1986**, *27*, 5499-5502.

(32) Tadema, G.; Vermeer, P.; Meijer, J.; Brandsma, L. Copper(I) bromide promoted reaction of Grignard compounds with propiolaldehyde diethyl acetal. An efficient synthesis of allenic ethers and α,β-ethylenic aldehydes. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 66-67.

(33) Alexakis, A.; Commercon, A.; Villieras, J.; Normant, J. F. Vinylic organocopper derivatives. VI. Regioselective addition of organocuprates on α-acetylenic acetals. Synthesis of a geranial acetal. *Tetrahedron Lett.* **1976**, 2313-2316.

(34) Vermeer, P.; Meijer, J.; De Graaf, C.; Schreurs, H. Copper(I) halide-catalyzed ring-opening of acetylenic epoxides. Synthesis of allenic alcohols. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 46-47.

(35) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. Diastereoselective synthesis of α-allenic alcohols from propargylic epoxides. *Tetrahedron Lett.* **1989**, *30*, 2387-2390.

(36) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. Diastereoselective syn or anti opening of propargylic epoxides. Synthesis of α-allenic alcohols. *Tetrahedron* **1991**, *47*, 1677-1696.

(37) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. Mechanistic aspects of the formation of chiral allenes from propargylic ethers and organocopper reagents. *J. Am. Chem. Soc.* **1990**, *112*, 8042-8047.

(38) Sato, T.; Kawashima, M.; Fujisawa, T. A novel five-carbon homologation leading to 3,4-alkadienoic acids by SN2' reaction of β-ethynyl-β-propiolactone with Grignard reagents in the presence of copper(I) catalyst. *Tetrahedron Lett.* **1981**, *22*, 2375-2378.

(39) Wan, Z.; Nelson, S. G. Optically Active Allenes from β-Lactone Templates: Asymmetric Total Synthesis of (-)-Malyngolide. *J. Am. Chem. Soc.* **2000**, *122*, 10470-10471.

(40) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. Au(I)-Catalyzed Annulation of Enantioenriched Allenes in the Enantioselective Total Synthesis of (-)-Rhazinilam. *J. Am. Chem. Soc.* **2006**, *128*, 10352-10353.

(41) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. General Approach to Allenes through Copper-Catalyzed γ-Selective and Stereospecific Coupling between Propargylic Phosphates and Alkylboranes. *Org. Lett.* **2011**, *13*, 6312-6315.

(42) Yang, M.; Yokokawa, N.; Ohmiya, H.; Sawamura, M. Synthesis of Conjugated Allenes through Copper-Catalyzed γ-Selective and Stereospecific Coupling between Propargylic Phosphates and Aryl- or Alkenylboronates. *Org. Lett.* **2012**, *14*, 816-819.

(43) Uehling, M. R.; Marionni, S. T.; Lalic, G. Asymmetric Synthesis of Trisubstituted Allenes: Copper-Catalyzed Alkylation and Arylation of Propargylic Phosphates. *Org. Lett.* **2012**, *14*, 362-365.

(44) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001-2011). *Chem. Rev.* **2014**, *114*, 2432-2506.

(45) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. A Concise Access to (Polyfluoroaryl)allenes by Cu-Catalyzed Direct Coupling with Propargyl Phosphates. *Org. Lett.* **2012**, *14*, 2586-2589.

(46) Miyake, Y.; Ota, S.-i.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. Copper-catalyzed nucleophilic trifluoromethylation of propargylic halides. *Chem. Commun.* **2013**, *49*, 7809-7811.

(47) Murakami, M.; Igawa, H. A study of the stereochemical course of β-oxygen elimination with a rhodium(I) complex. *Helv. Chim. Acta* **2002**, *85*, 4182-4188.

(48) Miura, T.; Shimada, M.; Ku, S.-Y.; Tamai, T.; Murakami, M. Stereoselective synthesis of α-allenols by rhodium-catalyzed reaction of alkynyloxiranes with arylboronic acids. *Angew. Chem., Int. Ed.* **2007**, *46*, 7101-7103.

(49) Miura, T.; Shimada, M.; de Mendoza, P.; Deutsch, C.; Krause, N.; Murakami, M. Stereoselective Synthesis of syn-Configured α-Allenols by Rhodium-Catalyzed Reaction of Alkynyl Oxiranes with Arylboronic Acids. *J. Org. Chem.* **2009**, *74*, 6050-6054.

(50) Elsevier, C. J.; Kleijn, H.; Ruitenberg, K.; Vermeer, P. Allenylpalladium(II) species: possible intermediates in the tetrakis(triphenylphosphine)palladium(0)-catalyzed formation of allenes from prop-2-ynylic substrates. *J. Chem. Soc., Chem. Commun.* **1983**, 1529-1530.

(51) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. Synthesis, structure and reactivity of some (σ-allenyl)- and (σ-prop-2-ynyl)palladium(II) complexes. *Organometallics* **1986**, *5*, 716-720.

(52) Tsutsumi, K.; Ogoshi, S.; Kakiuchi, K.; Nishiguchi, S.; Kurosawa, H. Cross-coupling reactions proceeding through η1- and η3-propargyl/allenyl-palladium(II) intermediates. *Inorg. Chim. Acta* **1999**, *296*, 37-44.

(53) Ogoshi, S.; Tsutsumi, K.; Kurosawa, H. Synthesis and structure of cationic η3-allenyl/propargylpalladium complexes. *J. Organomet. Chem.* **1995**, *493*, C19-21.

(54) Su, C.-C.; Chen, J.-T.; Lee, G.-H.; Wang, Y. Direct Approach to Palladium-Mediated Cycloaddition. First Single-Crystal Structure and Convenient Synthesis of Zwitterionic η3-Trimethylenemethane Palladium from Nucleophilic Addition of Carbanions to an Allenyl Complex. *J. Am. Chem. Soc.* **1994**, *116*, 4999-5000.

(55) Tsuji, J.; Mandai, T. Palladium-catalyzed reactions of propargylic compounds in organic synthesis. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589-2612.

(56) Jeffery-Luong, T.; Linstrumelle, G. Palladium-catalyzed synthesis of allenes. *Tetrahedron Lett.* **1980**, *21*, 5019-5020.

(57) Ruitenberg, K.; Kleijn, H.; Elsevier, C. J.; Meijer, J.; Vermeer, P. Palladium(0)-promoted synthesis of functionally substituted allenes by means of organozinc compounds. *Tetrahedron Lett.* **1981**, *22*, 1451-1452.

(58) Ruitenberg, K.; Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. Organometal-mediated synthesis of conjugated allenynes, allenediynes, vinylallenes and diallenes. *Rec. Trav. Chim. Pays-Bas* **1982**, *101*, 405-409.

(59) Dixneuf, P. H.; Dixneuf, P. H.; Guyot, T.; Ness, M. D.; Roberts, S. M. Synthesis of optically active allenes using tandem enzyme and palladium-catalyzed reactions. *Chem. Commun.* **1997**, 2083-2084.

(60) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. Palladium-catalyzed coupling reaction of fluoroalkylated propargyl mesylates with organozinc reagents: novel synthesis of optically active fluorine-containing trisubstituted allenes. *Chem. Lett.* **2000**, 1360-1361.

(61) Jian, Y.-J.; Wu, Y. The enantioselective total synthesis of nemotin. *Org. Biomol. Chem.* **2010**, *8*, 811-821.

(62) Keinan, E.; Bosch, E. Palladium-catalyzed propargylic vs. allylic alkylation. *J. Org. Chem.* **1986**, *51*, 4006-4016.

(63) Li, Q.-H.; Jeng, J.-Y.; Gau, H.-M. Highly Efficient Synthesis of Allenes from Trimethylaluminum Reagent and Propargyl Acetates Mediated by a Palladium Catalyst. *Eur. J. Org. Chem.* **2014**, *2014*, 7916-7923.

(64) Tsuji, Y.; Taniguchi, M.; Yasuda, T.; Kawamura, T.; Obora, Y. Palladium-Catalyzed Cyanation of Propargylic Carbonates with Trimethylsilyl Cyanide. *Org. Lett.* **2000**, *2*, 2635-2637.

(65) Moriya, T.; Miyaura, N.; Suzuki, A. Synthesis of allenes by palladium-catalyzed cross-coupling reaction of organoboron compounds with propargylic carbonates: transmetallation of organoboron compounds with (alkoxo)palladium complexes under neutral conditions. *Synlett* **1994**, 149-151.

(66) Yoshida, M.; Gotou, T.; Ihara, M. Palladium-catalyzed direct coupling reaction of propargylic alcohols with arylboronic acids. *Tetrahedron Lett.* **2004**, *45*, 5573-5575.

(67) Yoshida, M.; Okada, T.; Shishido, K. Enantiospecific synthesis of 1,3-disubstituted allenes by palladium-catalyzed coupling of propargylic compounds with arylboronic acids. *Tetrahedron* **2007**, *63*, 6996-7002.

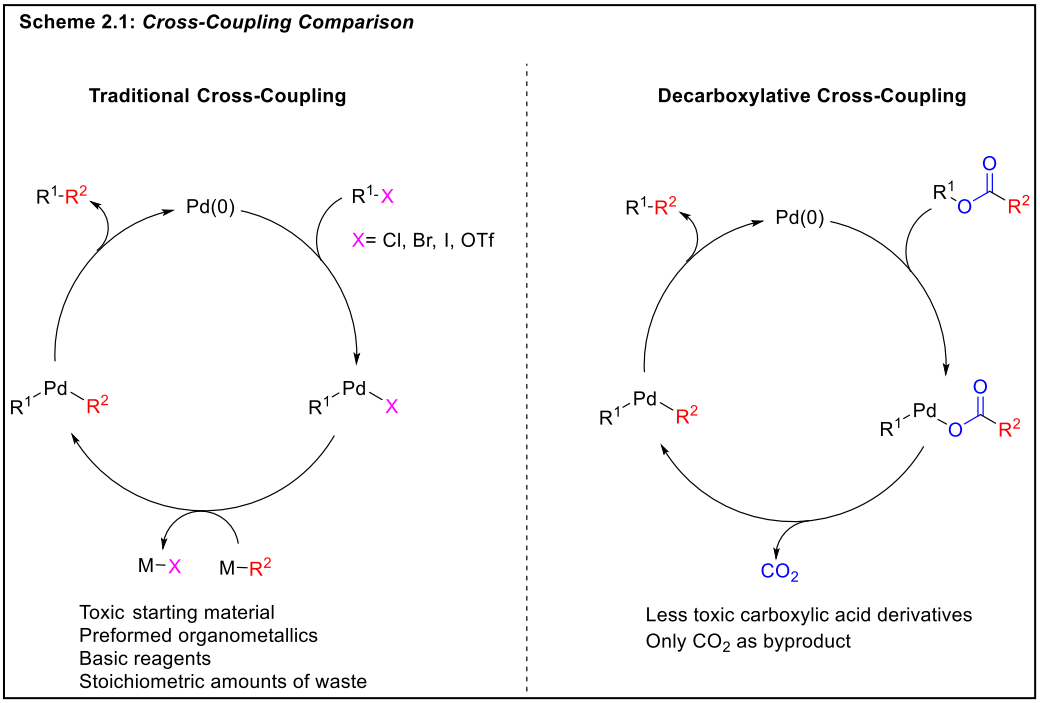
(68) Molander, G. A.; Sommers, E. M.; Baker, S. R. Palladium(0)-Catalyzed Synthesis of Chiral Ene-allenes Using Alkenyl Trifluoroborates. *J. Org. Chem.* **2006**, *71*, 1563-1568.

Chapter 2: Palladium-Catalyzed Decarboxylative Coupling of Propargylic Propiolates

2.1 Introduction

Chapter 1 of this dissertation was a review of the myriad of methods that have been developed for the synthesis of allenes utilizing propargylic starting materials. From that review, it is clear that one of the most common ways to make allenes is via traditional transition metal-catalyzed cross-coupling protocols. While these C-C bond forming methods are extremely powerful, they still have inherent issues, as they require pre-formed organometallics and/or stoichiometric amounts of base. The use of these necessary reagents results in significant amounts of waste, which can be toxic and complicate product purification. As an alternative, decarboxylative coupling has several advantages over traditional cross-coupling reactions (Scheme 2.1).

Scheme 2.1: ***Cross-Coupling Comparison***



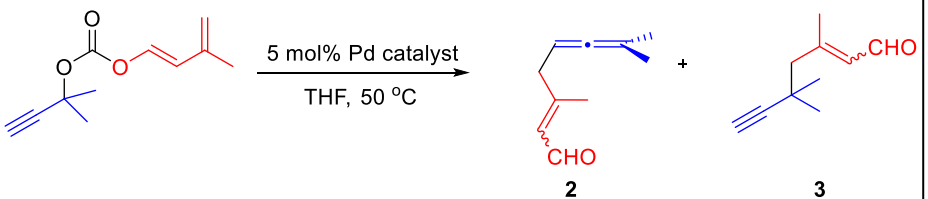
First, the carboxylic acid derivatives used as starting materials are less expensive, easily accessible, less toxic, and ubiquitous. Additionally, utilizing irreversible decarboxylation as the driving force to form reactive intermediates obviates the need for preformed organometallics and base. Further, in intramolecular couplings, the decarboxylation results in the *in situ* activation of nucleophiles, allowing for less stabilized nucleophiles to be utilized in the reaction without the need for basic

additives. Finally, nontoxic, nonflammable CO_2 is the only byproduct generated, simplifying the purification process. Because of these many advantages, decarboxylative coupling has gained significant attention as a method for the formation of carbon-carbon bonds. Since its creative utilization by Tsuji[1] and Saegusa[2], palladium-catalyzed decarboxylative coupling has been broadly applied to both allylic and benzylic electrophiles.[3-8] Comparatively, there has been significantly less exploration into the use of propargylic electrophiles.[9] As such, only a small portion of methods utilize propargylic electrophiles in decarboxylative coupling, out of which even fewer yield allenyl products. The wide variety of products observed in these decarboxylative transformations illustrates the regio- and chemoselectivity issues that persist with propargyl electrophiles. These decarboxylative methods will be presented in the following sections of this dissertation.

2.2 Decarboxylative Couplings with Propargylic Electrophiles

The first example of a C-C bond forming decarboxylative coupling of a propargyl electrophile was by Bienaymé in 1994. In the first report, Bienaymé found that $Pd(PPh_3)_4$ successfully catalyzed the decarboxylative coupling of a propargylic carbonate, however with unsatisfactory selectivity between the allenyl and propargyl product.[10] A brief screening of ligands showed that increasing the bulk of the aromatic phosphine ligands allowed for better selectivity for the desired allene product (Scheme 2.2).

Scheme 2.2: ***Ligand Controlled Regioselectivity of Decarboxylative Coupling***

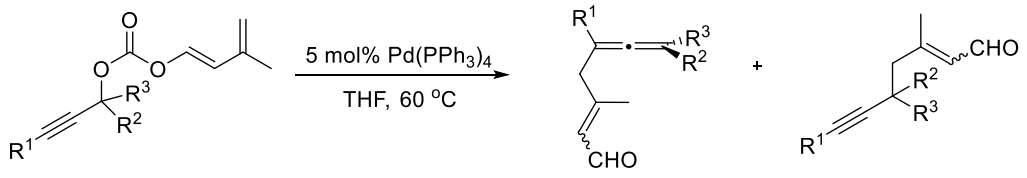


2 **3**

Pd	Ligand	Yield	Selectivity (**2**/**3**)
$Pd(PPh_3)_4$	none	59%	36/64
$Pd(dba)_2$	Tri(o-tolyl)phosphine	50%	45/55
$Pd(dba)_2$	Tri(2-thienyl)phosphine	70%	50/50
$Pd(dba)_2$	Tri-1-napthylphosphine	58%	82/18

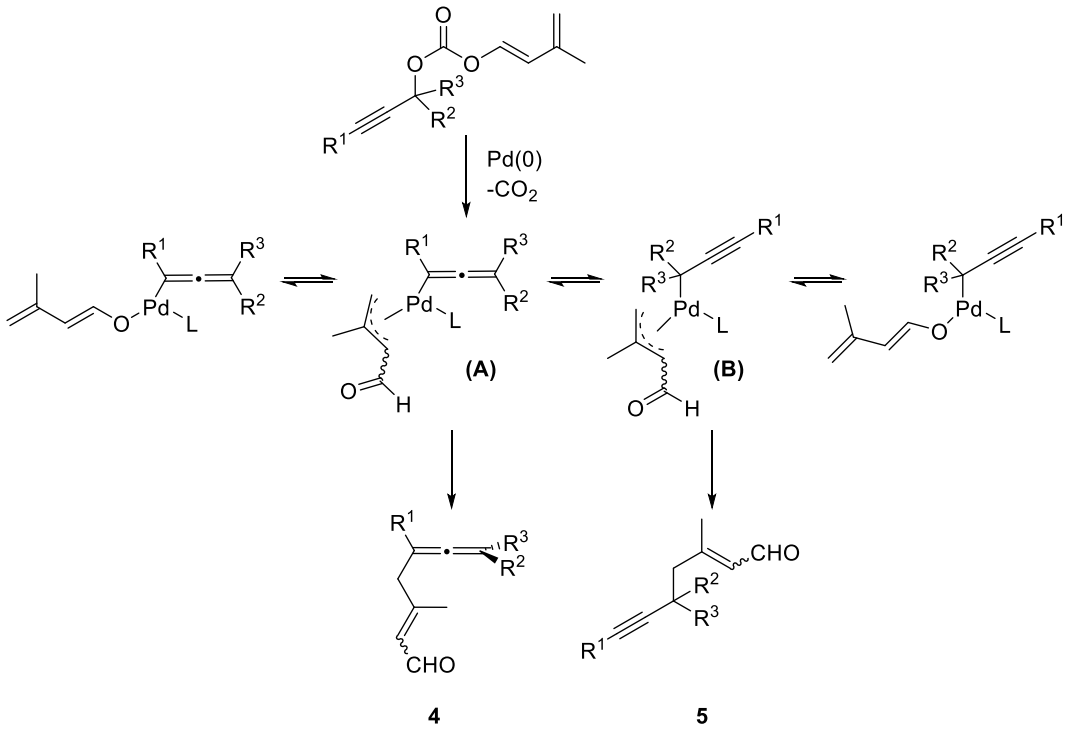
In a subsequent publication, Bienaymé explored the effect of the substitution pattern of the propargyl substrates on the regioselectivity of the coupling reaction catalyzed by $Pd(PPh_3)_4$.[11] It was determined that the product ratios were significantly affected by the substituents at both the terminal (R^1) and propargyl (R^2 and R^3) positions of the propargyl carbonate. Increasing the bulk at any of these positions modified the selectivity to favor the allenyl products which were isolated in moderate yields. Bienaymé hypothesized that the observed regioselectivity was due to a change in the favored palladium-bound intermediate. Less steric interactions allow for the formation of the η^1-propargylpalladium species (**B**) yielding the propargylated product (**5**). More sterically encumbered substrates prefer to form the η^1-allenylpalladium species (**A**) leading to the allene product (**4,** Scheme 2.3). Unfortunately, there was no catalyst optimization so the ligands that showed potential to further increase selectivity were not applied to the substituted systems.

Scheme 2.3: ***Allenic Polyunsaturated Aldehydes***



4 **5**

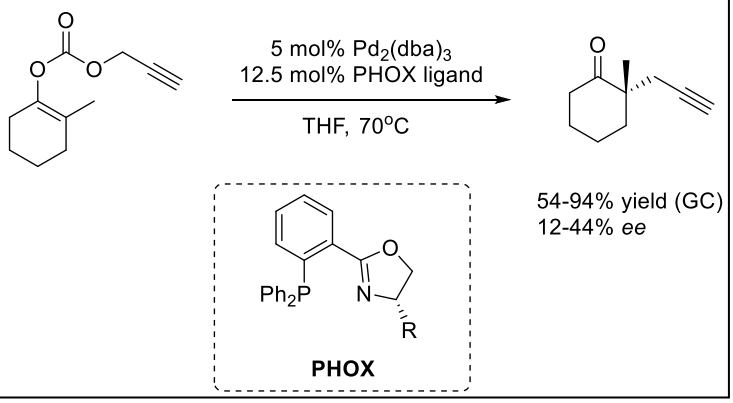
R^1	R^2	R^3	Yield	Selectivity (**4**/**5**)
H	Me	Me	59%	36/64
H	H	H	64%	0/100
H	Ph	Me	35%	66/33
TMS	Me	Me	30%	63/37
Ph	Me	Me	90%	100/0



4 **5**

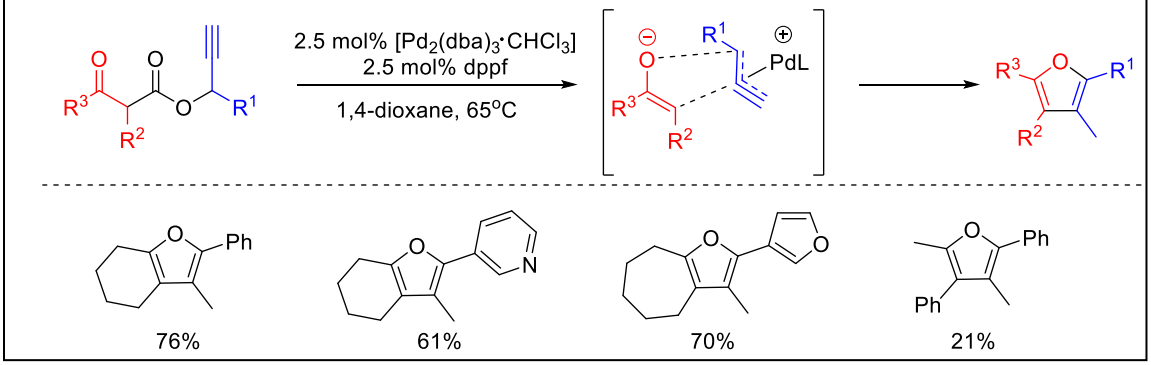
In 2011, Stoltz and coworkers reported a single example of the enantioselective decarboxylative coupling of a propargylic carbonate derived from cyclohexanone.[12] The example was subjected to a very brief ligand screen which led to moderate to good yields of the propargylated product, however the enantioselectivity of the reaction was poor (Scheme 2.4). Further, the products were never isolated and often suffered from contamination by the allenyl product.

Scheme 2.4. ***Enantioselective Propargylation***



In 2012, Yoshida and coworkers demonstrated the use of enolates as bis-nucleophiles in the decarboxylative [3+2] cyclization of propargyl β-keto esters.[13] Unlike the examples discussed above in which the enolate nucleophiles, generated upon decarboxylation of carbonates, attack one of the terminal carbons of the η^1-palladium intermediates, Yoshida determined that the enolate, formed from the decarboxylation of β-keto esters, behaves more like a softer nucleophile and reacts at the central carbon of the η^3-palladium π-propargyl complex (Scheme 2.5). The enolate oxygen then reacts with the resulting palladium π-allyl intermediate and isomerization leads to a tetrasubstituted furan.

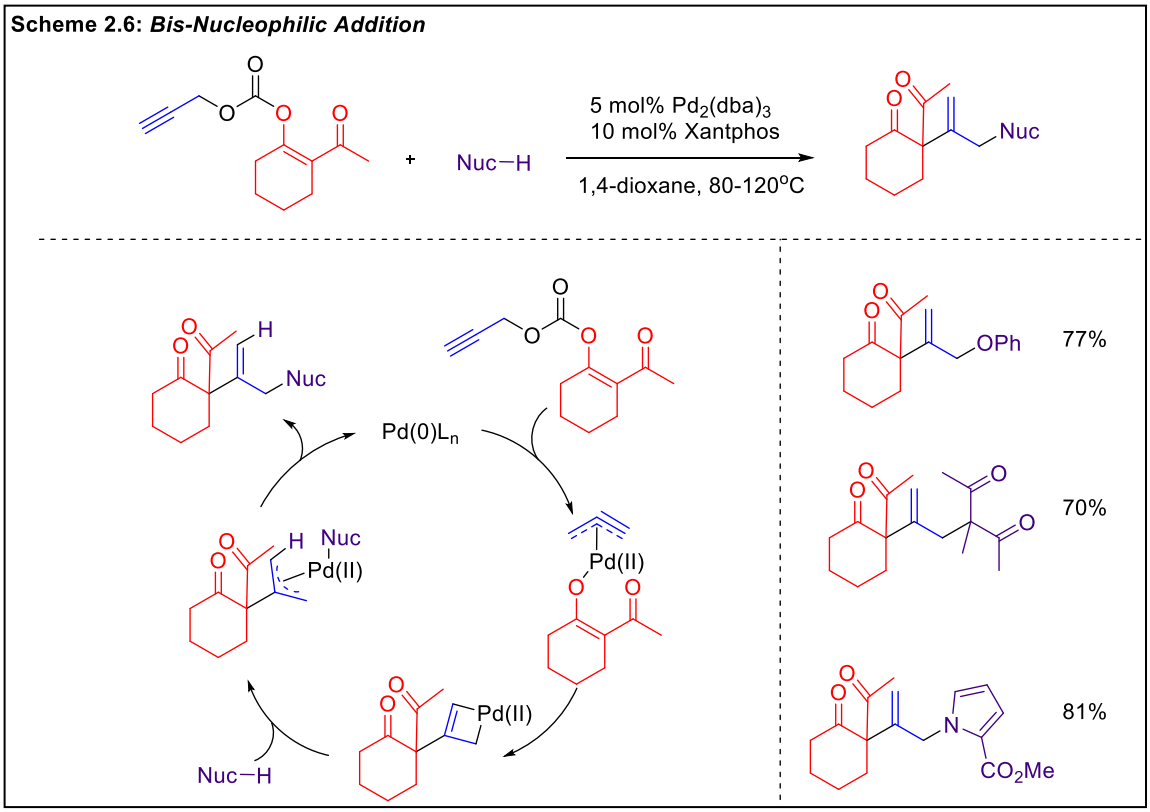
Scheme 2.5: ***Synthesis of Tetrasubstituted Furans***



Franckevicius and coworkers reported the first decarboxylative coupling of propargyl electrophiles with softer 1,3-dicarbonyl nucleophiles in 2013.[14] The developed decarboxylative coupling allowed for the regioselective bis-addition of two separate nucleophiles yielding alkene products with quaternary carbon moieties. First the 1,3-dicarbonyl enolate, generated via

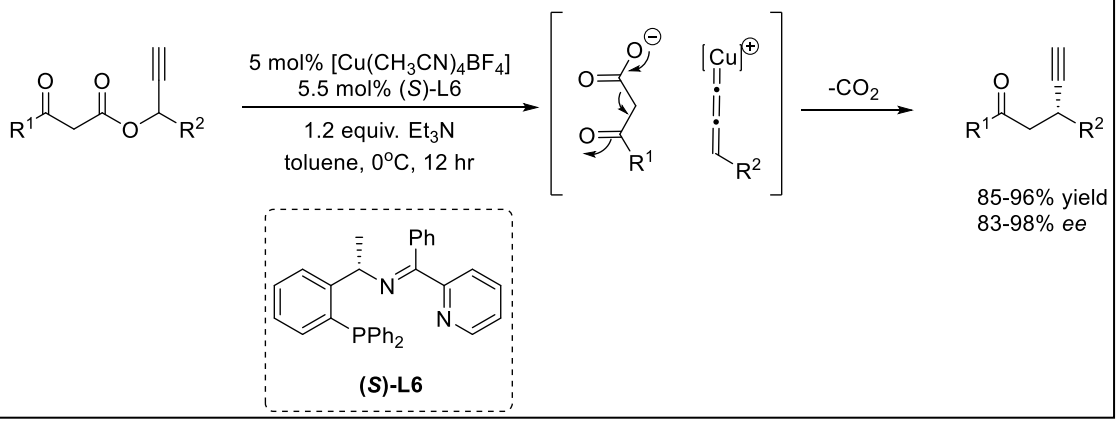
decarboxylation, attacks the central carbon of the η^3-palladium π-propargyl complex generating a palladacycle. The palldacycle can then be protonated by an external nucleophile leading to a palladium π-allyl intermediate that can then be attacked by the external nucleophile (Scheme 2.6). Franckevicius's inital report utilized phenols as the external nucleophile but has since applied different 1,3-dicarbonyl compounds[15] and N-heterocycles[16] as nucleophilic partners.

Scheme 2.6: ***Bis-Nucleophilic Addition***



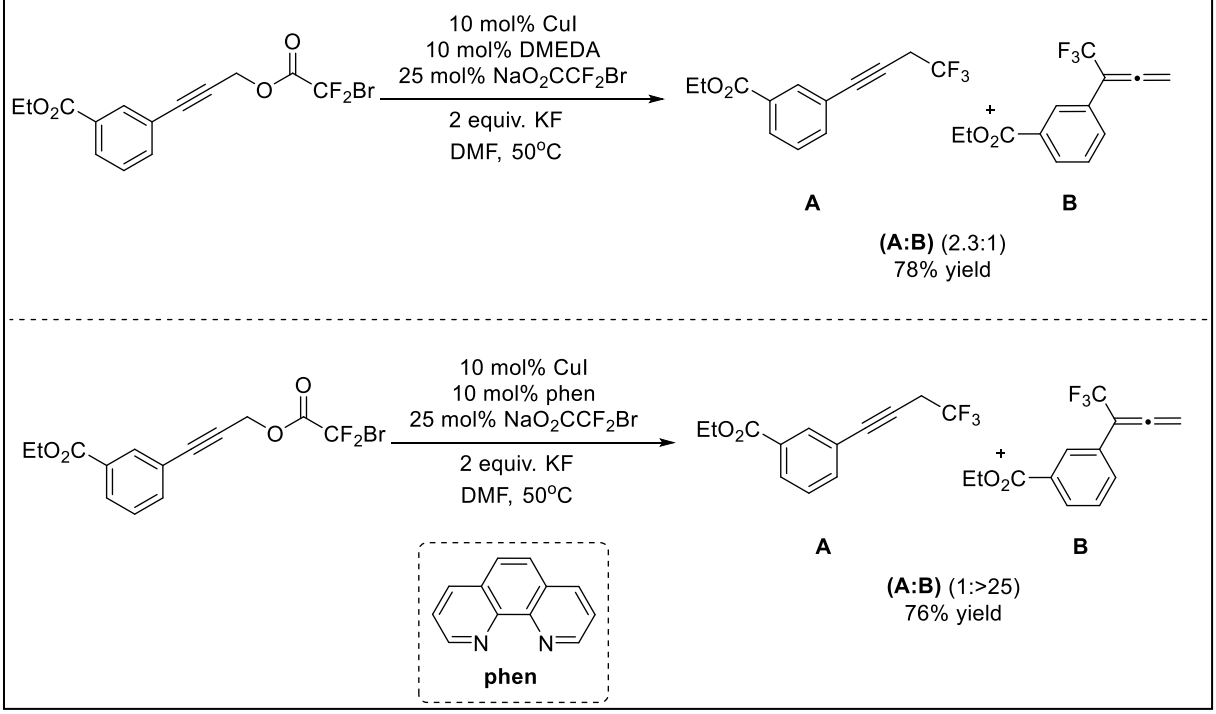
As was previously demonstrated in Chapter 1, copper is another transition metal that can catalyze carbon-carbon bond forming reactions with propargyl electrophiles. There have also been examples of copper-catalyzed decarboxylative coupling reactions with propargylic electrophiles which will be discussed below. In 2014, Hu and coworkers developed an enantioselective decarboxylative propargylation of β-ketoesters catalyzed by a cationic copper complex and chiral ligand.[17] While good yields and enantioselectivities were obtained, the starting substrates are limited to terminal alkynes in order to achieve the necessary copper allenylidene intermediate (Scheme 2.7).

Scheme 2.7: ***Copper-Catalyzed Decarboxylative Propargylation***



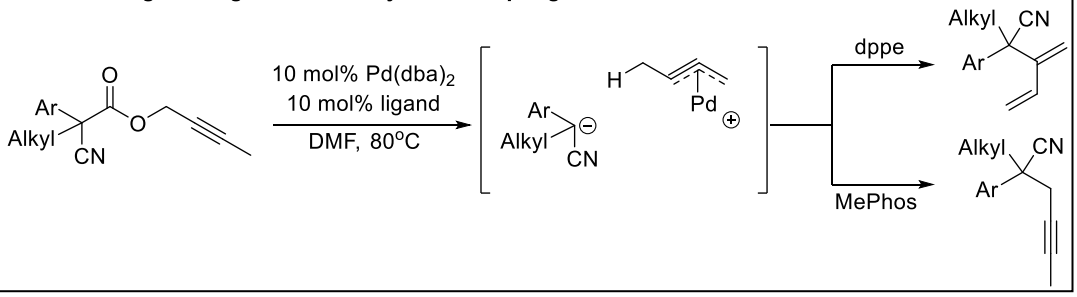
Within that same year, Altman and coworkers reported a copper-catalyzed decarboxylative trifluormethylation of propargyl esters.[18] When propargyl bromo(difluoro)acetates were introduced to a copper iodide catalyst in the presence of N,N'-dimethylethylenediamine (DMEDA) and sodium bromo(difluoro)acetate, the propargyl trifluormethanes were preferentially formed. However, the selectivity for the propargyl products over the allene was moderate, and the two isomers were inseparable by column chromatography. In a subsequent publication in 2015, Altman and coworkers reported that replacing DMEDA with either a phenanthroline or bipyridine ligand led to the selective formation of the trifluoromethylated allene, reversing the previously observed regioselectivity.[19] It was hypothesized that the geometric influence of the ligand's structure controlled the regioselectivity of the transformation (Scheme 2.8). This protocol is one of the few methods that tolerate substitution at both the terminal and propargyl positions of the electrophile.

Scheme 2.8: ***Decarboxylative Trifluoromethylation***



There has also been some exploration of decarboxylative couplings with propargyl electrophiles in the Tunge group. A collegue, Theresa Locascio, developed a regiodivergent decarboxylative coupling of propargyl esters with aryl acetonitrile nucleophiles which yielded either the propargyl product or the diene product depending on which ligand was employed.[20] This method progressed from an earlier developed intermolecular coupling of propargyl carbonates and α,α-diaryl acetonitrile pronucleophiles.[21] Utilizing decarboxylation to generate the activated nucleophile *in situ* allowed for the expansion of the nucleophile scope to include less stable alkyl, aryl acetonitrile variants (Scheme 2.9). Unfortunately both pathways were somewhat limited as they required electron-deficient aryl systems on the acetonitrile nucleophile.

Scheme 2.9: ***Regiodivergent Decarboxylative Coupling***



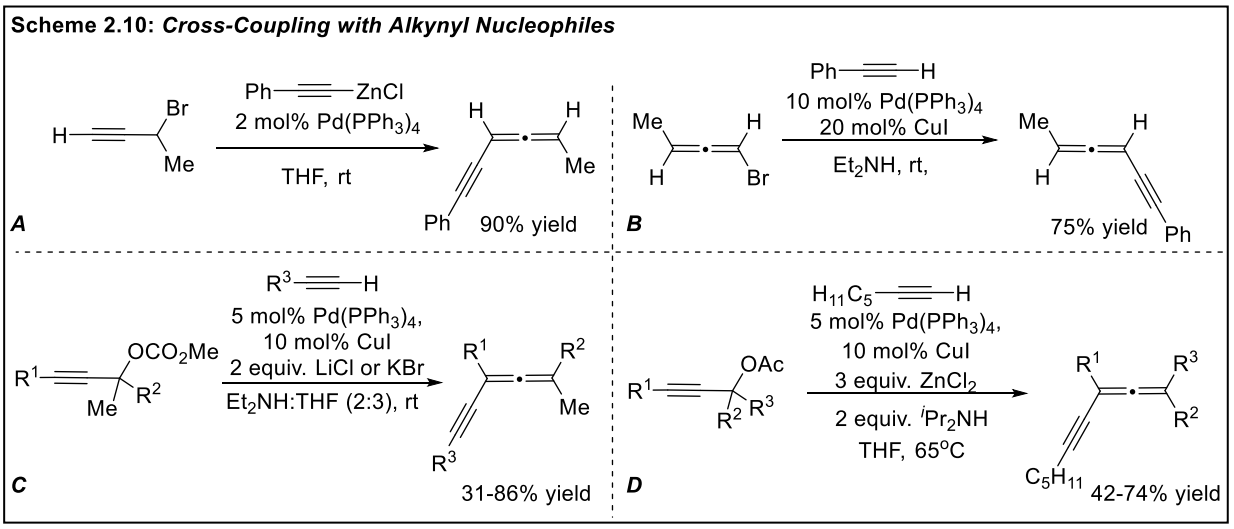
While these decarboxylative methods are efficient and mild, the overall selectivity and reactivity with propargyl electrophiles leaves much to be uncovered and explored, in terms of scope and understanding what controls product formation. In the forthcoming sections, my contribution to this field of research will be discussed, specifically the palladium-catalyzed decarboxylative coupling of propargyl propiolates to synthesize allenynes.

2.3 Palladium-Catalyzed Decarboxylative Synthesis of Allenynes

In the above examples, many of the nucleophilic partners utilized in the coupling are enolate derivatives. This is because decarboxylation allows for the regiospecific formation of the enolate *in situ* under neutral conditions thus allowing for milder reactions.[22] Another family of nucleophiles that benefit from being generated *in situ* via decarboxylation are acetylides. While acetylides have not been used as nucleophilic partners in decarboxylative coupling with propargyl electrophiles, they can be found in traditional palladium-catalyzed cross-coupling reactions. An early example of palladium-catalyzed cross-coupling of a propargyl electrophile with an alkynyl nucleophile was reported by Vermeer.[23] Propargyl bromides were coupled with stoichiometric amounts of zinc acetylides to synthesize allenyne products in high yield (Scheme 2.10_A). Later, Linstrumelle and Jeffery-Luong, synthesized analogous allenynes via cross-coupling of allenyl bromides and copper acetylides under Sonogashira conditions.[24] While this method was able to achieve transmetallation using only catalytic amounts of copper, basic diethylamine was still required as the solvent (Scheme 2.10_B). Tsuji further developed the Sonogashira cross-coupling by employing propargyl carbonates as the electrophilic partner. However, super-stoichiometric salt additives as well as diethylamine as a cosolvent were required for the reaction to proceed cleanly and with high yields (Scheme 2.10_C).[25,26] The need for salt additives was again

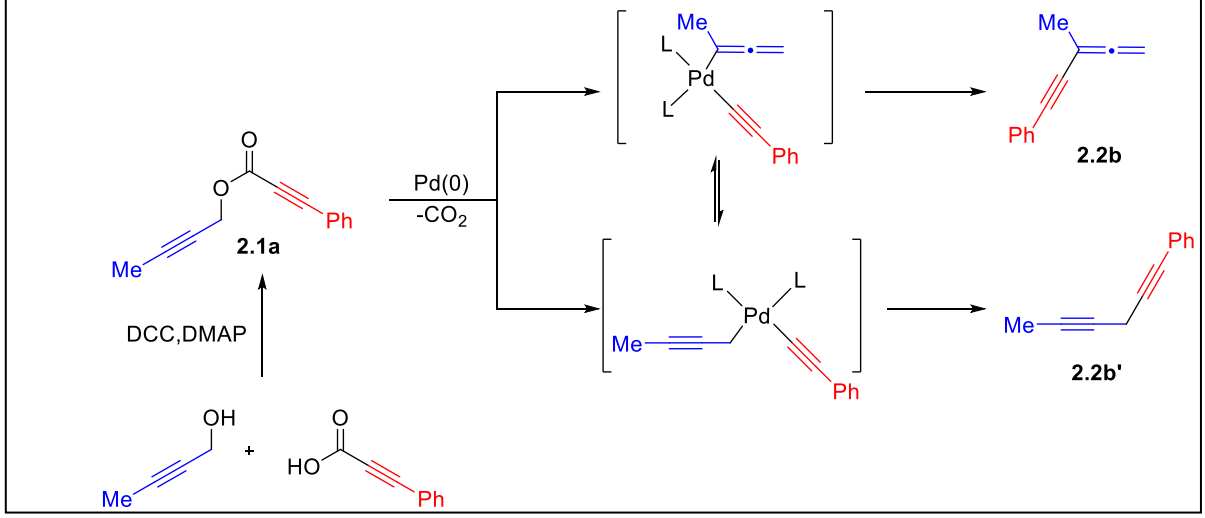
demonstrated by Guegnot and Linstrumelle when propargyl acetates were utilized in the coupling (Scheme 2.10_D)[27].

Scheme 2.10: ***Cross-Coupling with Alkynyl Nucleophiles***



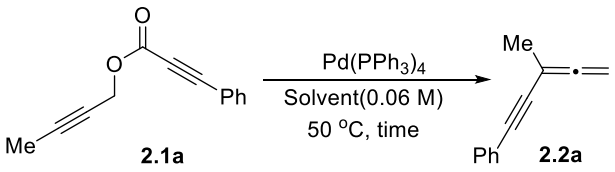
It should be emphasized again that these requirements of preformed organometallics, salt additives, and highly basic reagents/solvents are not ideal. We envisioned that the use of palladium-catalyzed decarboxylative coupling of propargyl esters would allow for the synthesis of conjugated allenynes under base-free conditions without the need for stoichiometric organometallics or metal salt additives. Further, the utilization of acetylide nucleophiles would distinctively expand the scope of decarboxylative coupling reactions with propargyl electrophiles. We began our studies with butynyl phenyl propiolate (**2.1a**) which is easily synthesized via the DCC coupling of but-2-yn-1-ol and phenyl propiolic acid, both of which are commercially available. We hypothesized that either the allenyne (**2.2b**) or diyne (**2.2b′**) would be observed due to the known equilibrium between the allenyl-palladium species and propargyl-palladium species (Scheme 2.11).[28]

Scheme 2.11: ***Decarboxylative Coupling of Propargyl Propiolates***



It was to our utmost delight that when **2.1a** was allowed to react with 10 mol% $Pd(PPh_3)_4$ on NMR scale in deuterated toluene, there was complete and clean conversion to solely the allenyne product in 80% yield versus 1,4 dioxane as the internal standard (Scheme 2.12, entry 1). Polar solvents such as acetonitrile and DMSO also resulted in full conversion in less amount of time (Scheme 2.12, entries 2 and 3), though the yield in DMSO was drastically reduced versus the internal standard with no obvious reason for the loss of mass. We also observed that we could reduce the palladium loading to 5 mol% without a significant loss in yield and only a slight increase in reaction time. Contrary to the NMR spectroscopic studies, when the reaction was scaled up to 0.5 mmol, the product could only be isolated in up to 32% yield. It was determined that this was due to the volatility of the product. Fortunately, the more volatile THF proved equally as suitable as a solvent for the reaction as acetonitrile and its easy removal facilitated the isolation of the allenyne product in 88% yield (Scheme 2.12, entry 5).

Scheme 2.12: ***Solvent Screening***

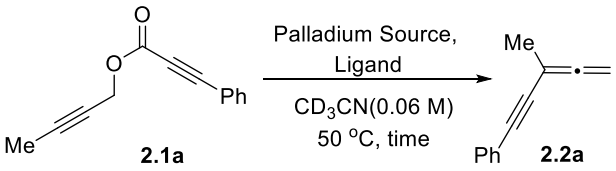


entry	Pd amount	solvent	time (h)	conv(%)	yield (%)[a]
1	10 mol%	Toluene-d_8	4	100	80
2	10 mol%	DMSO-d_6	2	100	18
3	10 mol%	CD_3CN	2	100	78
4	5 mol%	CD_3CN	3	100	77
5	5 mol%	THF	4	100	88[b]

[a] Yield of determined by ^{1}H NMR. [b] isolated yield

Once the conditions were optimized for the synthesis of allenyne **2.2a,** we investigated whether changing the ligands on palladium could effect any changes to the regioselectivity of the reaction. This was inspired by the work of Bienayme[10] and Locascio[20] described earlier in this chapter as well as reports of ligands affecting the regioselectivity of decarboxylative hydrogenolysis of propargylic formates.[29] As a control, the use of a palladium(0) catalyst with no phosphine ligands resulted in no reaction. Introduction of the triphenylphosphine ligand led to a yield that is comparable to that obtained with $Pd(PPh_3)_4$. Overall the coupling reaction preferred aryl monophosphine ligands. Use of Xphos resulted in a faster reaction however there was a loss of yield. The alkyl phosphine prevented any reaction from occuring. Bidentate phosphine ligands led to low conversions and yield. Interestingly, with every ligand screened, any product formation observed was solely that of the allenyne regioisomer which suggests that this transformation is completely selective.

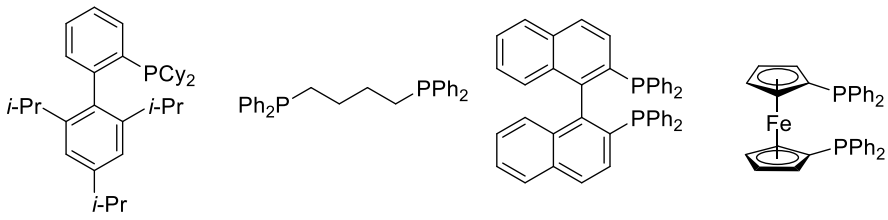
Scheme 2.13: ***Ligand Screening***



2.1a **2.2a**

entry	Pd Source	ligand	time (h)	conv(%)	yield (%)[a]
1	$Pd_2(dba)_3$ 5 mol%	none	4	0	0
2	$Pd_2(dba)_3$ 5 mol%	PPh_3 20 mol%	4.5	100	76
3	$Pd_2(dba)_3$ 5 mol%	Xphos 20 mol%	2	100	62
4	$Pd_2(dba)_3$ 5 mol%	P^nBu_3 10 mol%	22	0	0
5	$Pd_2(dba)_3$ 5 mol%	rac-binap 10 mol%	15	16	7
6	$Pd_2(dba)_3$ 5 mol%	dppb 10 mol%	6	12	11
7	$Pd_2(dba)_3$ 5 mol%	dppf 10 mol%	23	100	13

[a] Yield of determined by ^1H NMR.

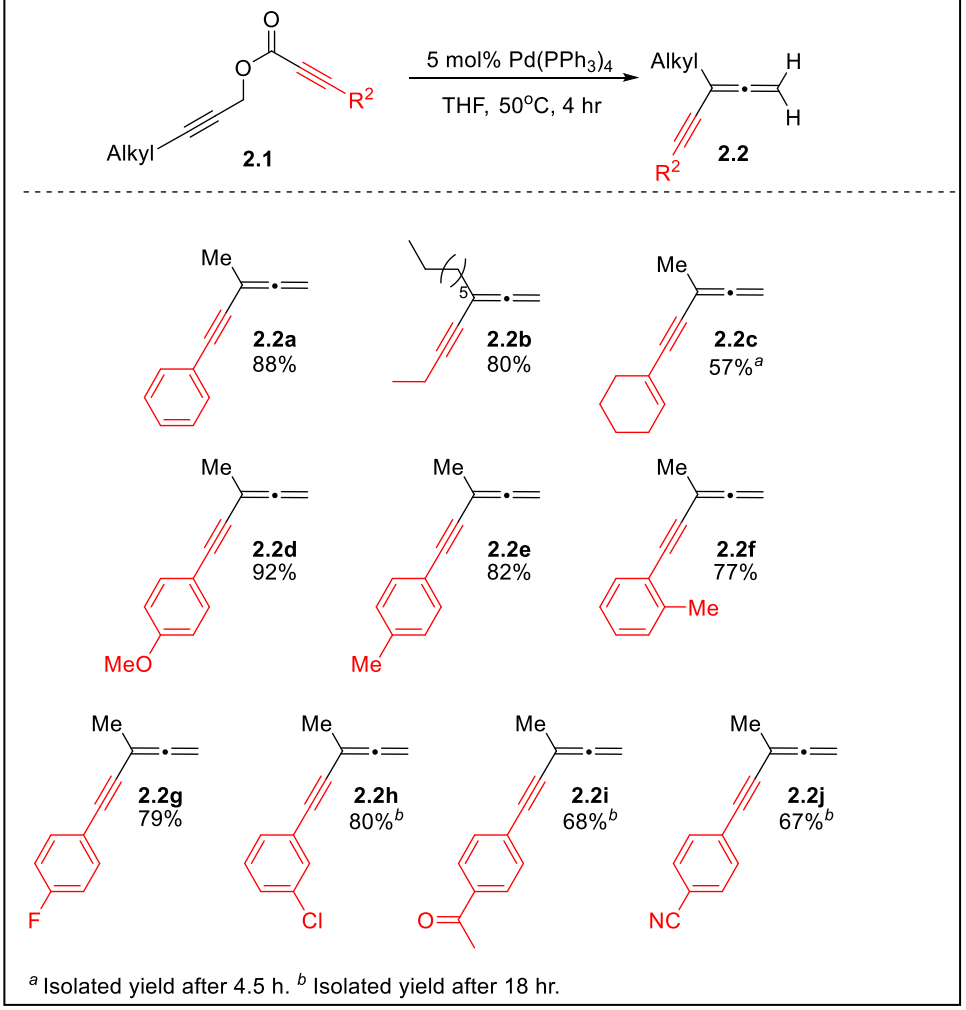


Xphos **dppb** ***rac*-BINAP** **dppf**

Following development and optimization of the palladium-catalyzed decarboxylative coupling, we then began to examine the scope of the reaction by varying the pro-nucleophilic portion of the starting propargyl ester by varying the propiolic acid (Scheme 2.14). Aryl acetylides were not required for the sucessful reaction as both alkyl (**2.2b**) and vinyl (**2.2c**) substituents gave moderate to good yields of the allenyne product. The highest yield was observed with a *p*-methoxyphenyl propiolate. Notably the reaction tolerated a variety of substitution patterns with both alkyl (**2.2e** and **2.2f**) and halogen (**2.2g** and **2.2h**) substituents resulting in good yields. Electron withdrawing groups at the *para* position also gave satisfactory yields; however, they required longer reaction

times (**2.2i** and **2.2j**). The observed increase in reaction time for electron withdrawing substituents suggests that the reductive elimination of the acetylide and allene from palladium may be the rate determining step of the catalytic cycle.

Scheme 2.14:*Nucleophile Scope*

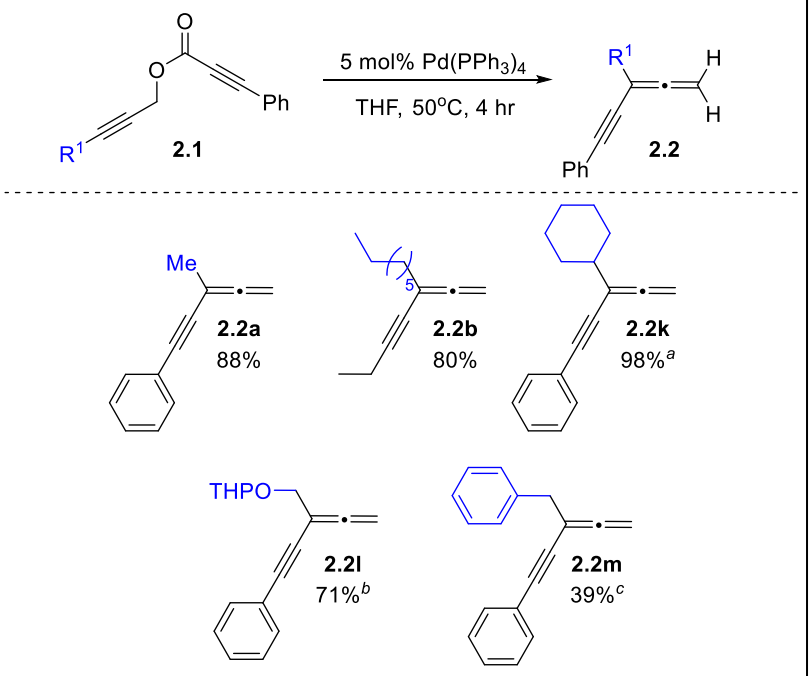


[a] Isolated yield after 4.5 h. [b] Isolated yield after 18 hr.

After sufficiently exploring the nucleophile scope, we went on to evaluate various substituents at the R^1 position of the propargyl ester (Scheme 2.15). Unfortunately, it is with the electrophiles that we observed limitations to our decarboxylative method. The reaction appears to only tolerate alkyl substituents at the terminal position. Both linear and cylic alkyl groups led to good yields of the allenyne product. Furthermore, it was determined that functionality on the alkyl chain was tolerated as long as it was at least one methylene unit away from the alkyne moiety in the starting material. For example, a THP-protected propargyl alcohol gave a good yield (**2.21**). Additonally

when benzyl propargyl ester (**2.2m**) was attempted, a significantly diminished yield of only 39% was obtained.

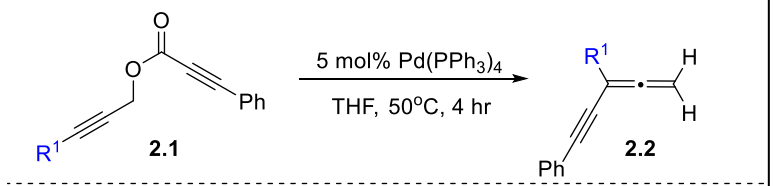
Scheme 2.15:*Electrophile Scope*

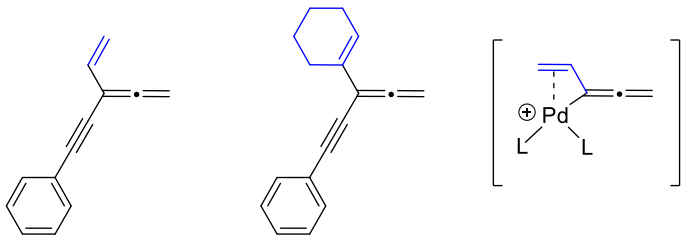


[a] Isolated after 5 hr. [b] Started at 60 °C for 5 min then cooled to 50 °C and isolated after 18 hr. [c] Isolated yield after 18 hr.

A variety of substrates with non-alkyl substitution at the R^1 postion of the propargyl ester were unsuccessful. With a vinyl group at the R^1 the reaction did not occur (Scheme 2.16, **2.2n**). With a larger cyclohexenyl group in the same position there was only 35% conversion to the allene after 5 hours. Unfortunately increasing the temperature of the reaction only led to degredation of the starting material. This could potentially be explained coordination of the alkene to the palladium-allene complex, which would mask the coordination site needed by the acetylide nucleophile. This coordination may be weaker with the more substituted alkene thus allowing metallation and reductive elimination to occur occasionally.

Scheme 2.16: ***Vinyl Substituents***





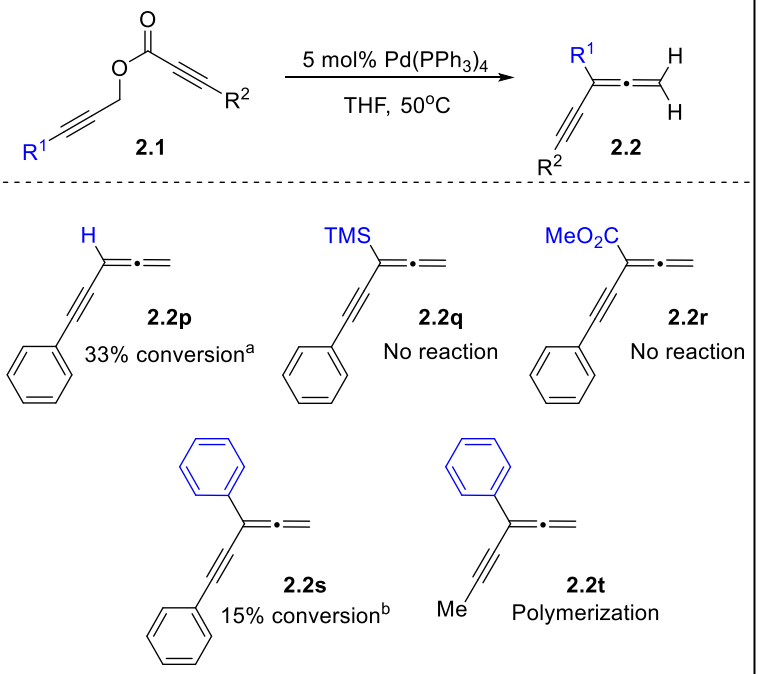
2.2n
No reaction

2.2o
35% conversion[a]

[a]determined by GC/MS

Other unsuccessful substates are presented in Scheme 2.17 below. The terminal alkyne (**2.2p**) reached 33% conversion to the allene in 4 hours, however, the reaction appeared to stall as no higher conversion was observed upon longer reaction time (24 h) or higher reaction temperatures (70 ˚C). Protecting the terminal alkyne with a trimethylsilyl group (**2.2q**) shut down the coupling reaction completely, as did incorporation of an ester group at the R^1 position (**2.2r**). Phenyl groups were also not well-tolerated at the R^1 position. When R^1 and R^2 were both phenyl groups (**2.2s**) only 15% of the starting material was consumed after 6 hours and both the product and the starting material decomposed upon heating overnight. Replacing R^2 with a methyl group resulted in allene formation (**2.2t**) which was observed by crude NMR and GC/MS. However, complex side products were also formed and the allene could not be isolated.

Scheme 2.17:*Unsuccessful Substrates*

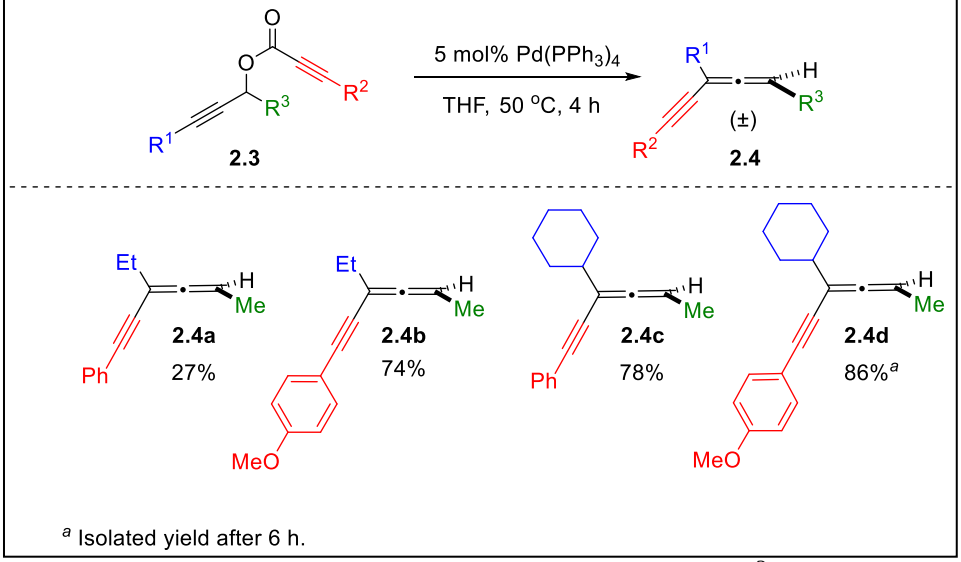


[a]determined by GC/MS [b]determined by ^{1}H NMR

As we observed that primary propargyl esters yielded 1,1-disubstituted allenes, we envisioned that secondary propargyl esters would allow for the synthesis of trisubstituted allenes further expanding the scope of this method. Disappointingly, initial efforts into the synthesis of trisubstituted allenynes proved to be unsuccessful (Scheme 2.18). When the coupling of hexynyl phenylpropiolate was attempted, only 27% of the desired allenyne (**2.4a**) was isolated. We were delighted when we observed that utilizing the *p*-OMe phenyl propiolate, which had previously been show to improve the yields of disubstituted allenes, resulted in a satisfactory 74% yield. Additionally, increasing the steric bulk at the R^1 position via a cyclohexyl group allowed for the isolation of the desired allenyne (**2.4c**) in 78% yield. Combining the two strategies of increasing the bulk of the electrophile and increasing the electron density of the nucleophile further increased the yield to 86% (**2.4d**). This suggests that volatility of the product (**2.2p**) may have been the reason for such a low isolated yield as both strategies increase the molecular weight of the product by at least 30 mass units. Further, *p*-OMe phenylacetylide had been shown to be a more reactive

nucleophile in the synthesis of the disubstituted allenes, potentially due to more facile reductive elimination, explaining the observed rise in yield from **2.4c** to **2.4 d**.

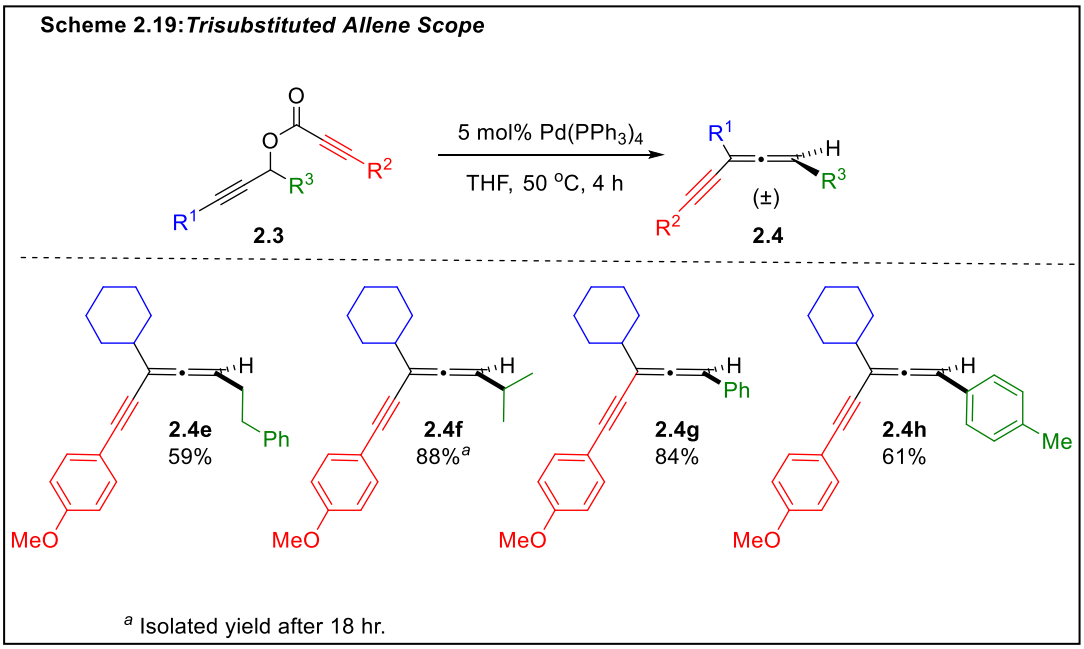
Scheme 2.18: ***Initial Trisubstituted Allene Synthesis***



[a] Isolated yield after 6 h.

The scope was further examined by varying the substituent at the R^3 positions (Scheme 2.19). Longer alkyl chains such as hydrocinnamyl (**2.4e**) gave a moderate yield of 59%. The bulky isopropyl substituent (**2.4f**) also gave a good yield of 88%, however the decarboxylative coupling was considerably slower, requiring 18 hours for full conversion. Phenyl (**2.4g**) and tolyl (**2.4h**) substituents also led to satisfactory yields.

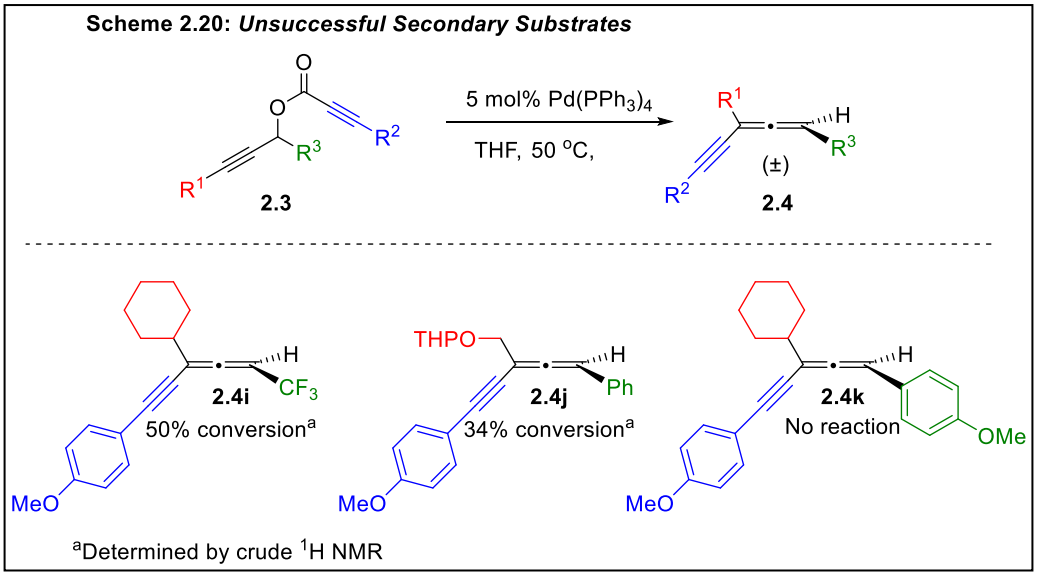
Scheme 2.19: ***Trisubstituted Allene Scope***



[a] Isolated yield after 18 hr.

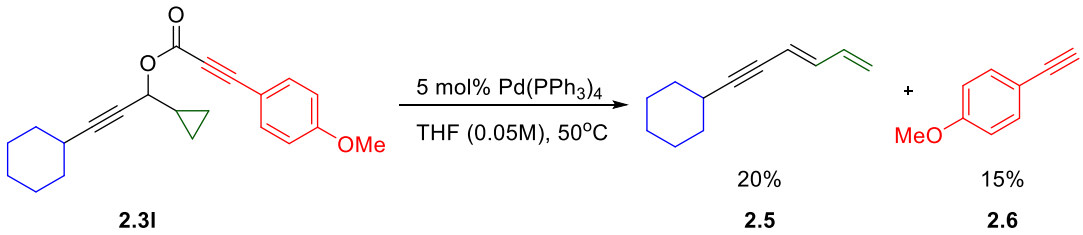
Again limitations were observed while examining of the scope of trisubstituted allenes (Scheme 2.20). A propargyl ester substituted with a trifluoromethyl moiety underwent decarboxylative coupling to form the allenyne (**2.4i**), however the rate of the reaction was not synthetically useful. After 3 days at 50 ˚C only 20% of the starting material was consumed. Increasing the temperature to 60 ˚C lead to a marked increase in reactivity as the reaction reached 50% conversion after 3 days. Further heating the reaction to 90 ˚C allowed the reaction to reach 25% conversion in 4 hours, but unfortunately leaving the reaction to heat overnight resulted in decomposition. Additionally, the allenyne was never isolated. This was disheartening as related substrates had been shown to do well under cross-coupling conditions with zinc.[30] Varying substitution at the R^1 position was similarly disappointing. With a protected propargyl alcohol at the R^1 position (**2.4j**) the best conversion achieved was 34% over 12 hours, with significant competition by decomposition of the starting material resulting in a complicated reaction mixture. Interestingly, when R^3 was a *p*-OMe phenyl substituent, only starting material remained after several hours even after increasing the temperature. Other *para* substituted phenyl rings resulted in successful decarboxylative coupling reactions, however, they will be addressed in chapter 3 as a part of kinetic studies.

Scheme 2.20: ***Unsuccessful Secondary Substrates***



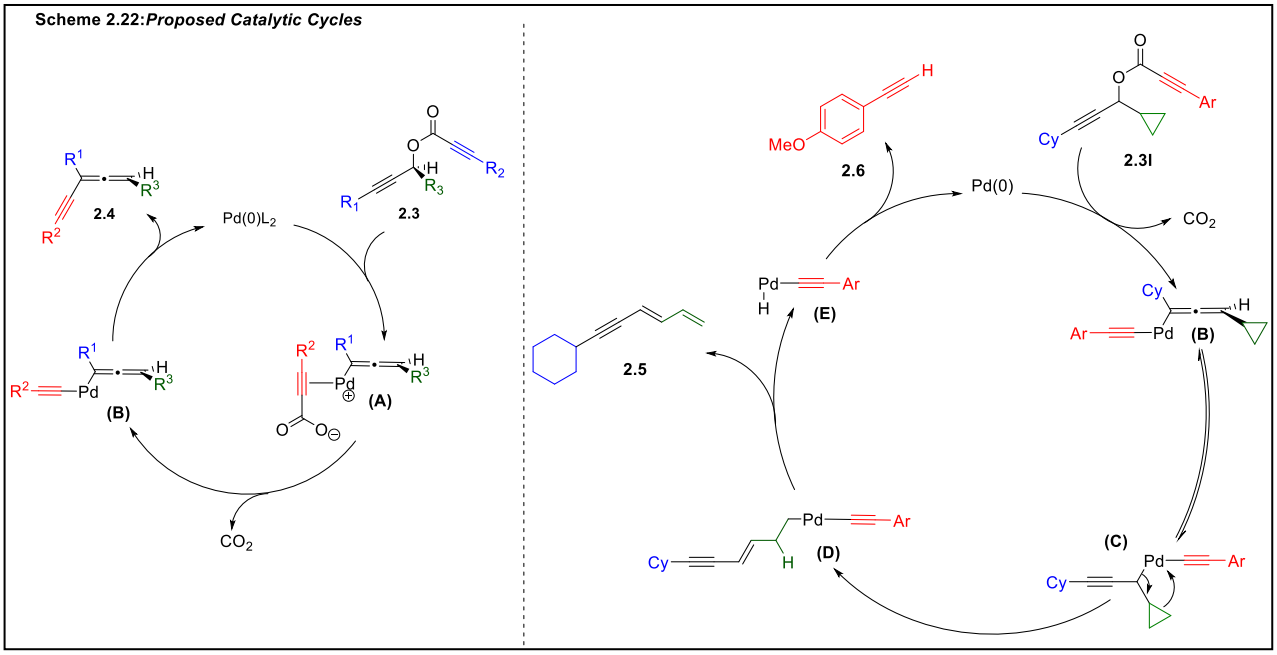
In general the decarboxylative coupling method described in this chapter is a very clean reaction in which substrates either convert to the allenyne or they don't, and only starting material is observed. However, while we were investigating the scope of the secondary propargyl esters, we came across a notable exception. When the secondary position of propargyl ester was substituted with a cyclopropane, we were intrigued to find that while all of the propargyl ester had been consumed, the desired allene was not observed via chromatography or spectroscopy (Scheme 2.21). Upon closer examination of the NMR spectra it was determined that instead of the allenyne, the reaction had yielded a conjugated dienyne (**2.5**) as well as the alkyne (**2.6**) which were isolated in a 20% and 15% yield respectively.

Scheme 2.21: ***Formation of Dienyne***



It is possible that the strain of the cyclopropane ring led to a change in the catalytic cycle. The proposed catalytic cycle for the decarboxylative synthesis (Scheme 2.22) begins with oxidative addition of the propargyl ester to palladium(0) to form the η^1-allenyl palladium species (**A**) which can then undergo decarboxylation and reductive elimination to give the desired allene product (**2.4**). When R^3 is cyclopropane we propose that the transformation begins in the same fashion with oxidative addition and decarboxylation to form the same η^1-allenyl palladium complex (**B**) found in the catalytic cycle for the decarboxylative coupling. However, isomerization to the η^1-propargyl palladium complex (**C**) would allow for β-carbon elimination to occur, thus opening the cyclopropane and releasing strain. This would result in the alkyl palladium species (**D**) which could undergo a β-hydride elimination releasing the dienyne (**2.5**). Reductive elimination of

palladium species (**E**) would then yield the acetylene (**2.6**) and return palladium to the correct oxidation state.



2.4 Conclusion

In summary this chapter has described the development of a novel palladium-catalyzed decarboxylative coupling of propargyl esters. The reaction was shown to be completely selective for the formation of allene products, which is uncommon in the literature for decarboxylative couplings with propargyl electrophiles. A wide variety of 1,1-disubstituted and trisubstituted allenynes have been synthesized utilizing this method, however some limitations to the method have been observed, most notably in the choice of electrophilic partner. Overall, the coupling is a green alternative to previous methods used to synthesize similar conjugated allenynes as CO_2 is the only byproduct.

2.5 References for Chapter 2

(1) Shimizu, I.; Yamada, T.; Tsuji, J. Palladium-catalyzed rearrangement of allylic esters of acetoacetic acid to give γ,δ-unsaturated methyl ketones. *Tetrahedron Lett.* **1980**, *21*, 3199-3202.

(2) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. Facile generation of a reactive palladium(II) enolate intermediate by the decarboxylation of palladium(II) β-ketocarboxylate and its utilization in allylic acylation. *J. Am. Chem. Soc.* **1980**, *102*, 6381-6384.

(3) Dzik, W. I.; Lange, P. P.; Goossen, L. J. Carboxylates as sources of carbon nucleophiles and electrophiles: comparison of decarboxylative and decarbonylative pathways. *Chem. Sci.* **2012**, *3*, 2671-2678.

(4) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylation Reactions. *Chemical Reviews* **2011**, *111*, 1846-1913.

(5) Rayabarapu, D. K.; Tunge, J. A. Catalytic Decarboxylative sp-sp3 Coupling. *J. Am. Chem. Soc.* **2005**, *127*, 13510-13511.

(6) Mendis, S. N.; Tunge, J. A. Palladium-Catalyzed Stereospecific Decarboxylative Benzylation of Alkynes. *Org. Lett.* **2015**, *17*, 5164-5167.

(7) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. Decarboxylative Benzylations of Alkynes and Ketones. *J. Am. Chem. Soc.* **2010**, *132*, 9280-9282.

(8) Recio, A., III; Heinzman, J. D.; Tunge, J. A. Decarboxylative benzylation and arylation of nitriles. *Chem. Commun.* **2012**, *48*, 142-144.

(9) Tsuji, J.; Mandai, T. Palladium-catalyzed reactions of propargylic compounds in organic synthesis. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589-2612.

(10) Bienayme, H. Efficiency of organometallic catalysis in a new "ecological" synthesis of retinal. *Tetrahedron Lett.* **1994**, *35*, 7383-7386.

(11) Bienayme, H. A new synthesis of polyunsaturated allenic carbonyls. *Tetrahedron Lett.* **1994**, *35*, 7387-7390.

(12) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novak, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. Enantioselective Decarboxylative Alkylation Reactions: Catalyst Development, Substrate Scope, and Mechanistic Studies. *Chem. - Eur. J.* **2011**, *17*, 14199-14223

(13) Yoshida, M.; Ohno, S.; Shishido, K. Synthesis of Tetrasubstituted Furans by Palladium-Catalyzed Decarboxylative [3+2] Cyclization of Propargyl β-Keto Esters. *Chem. - Eur. J.* **2012**, *18*, 1604-1607

(14) Schroder, S. P.; Taylor, N. J.; Jackson, P.; Franckevicius, V. Catalytic Decarboxylative Alkenylation of Enolates. *Org. Lett.* **2013**, *15*, 3778-3781.

(15) Kenny, M.; Christensen, J.; Coles, S. J.; Franckevicius, V. Regioswitchable Palladium-Catalyzed Decarboxylative Coupling of 1,3-Dicarbonyl Compounds. *Org. Lett.* **2015**, *17*, 3926-3929.

(16) Kenny, M.; Kitson, D. J.; Franckevicius, V. Catalytic Chemo- and Regioselective Coupling of 1,3-Dicarbonyls with N-Heterocyclic Nucleophiles. *J. Org. Chem.* **2016**, *81*, 5162-5172.

(17) Zhu, F.-L.; Zou, Y.; Zhang, D.-Y.; Wang, Y.-H.; Hu, X.-H.; Chen, S.; Xu, J.; Hu, X.-P. Enantioselective Copper-Catalyzed Decarboxylative Propargylic Alkylation of Propargyl β-Ketoesters with a Chiral Ketimine P,N,N-Ligand. *Angew. Chem., Int. Ed.* **2014**, *53*, 1410-1414.

(18) Ambler, B. R.; Peddi, S.; Altman, R. A. Copper-catalyzed decarboxylative trifluoromethylation of propargyl bromodifluoroacetates. *Synthesis* **2014**, *46*, 1938-1946

(19) Ambler, B. R.; Peddi, S.; Altman, R. A. Ligand-Controlled Regioselective Copper-Catalyzed Trifluoromethylation To Generate (Trifluoromethyl)allenes. *Org. Lett.* **2015**, *17*, 2506-2509.

(20) Locascio, T. M. Advances in Palladium-Catalyzed Allylation, Propargylation, and 1,3-Dienylation of Acetonitrile Pronucleophiles. University of Kansas, 2016.

(21) Locascio, T. M.; Tunge, J. A. Palladium-Catalyzed Regiodivergent Substitution of Propargylic Carbonates. *Chem. - Eur. J.* **2016**, *22*, 18140-18146.

(22) Tunge, J. A.; Burger, E. C. Transition metal-catalyzed decarboxylative additions of enolates. *Eur. J. Org. Chem.* **2005**, 1715-1726.

(23) Ruitenberg, K.; Kleijn, H.; Elsevier, C. J.; Meijer, J.; Vermeer, P. Palladium(0)-promoted synthesis of functionally substituted allenes by means of organozinc compounds. *Tetrahedron Lett.* **1981**, *22*, 1451-1452.

(24) Jeffery-Luong, T.; Linstrumelle, G. Palladium-catalyzed synthesis of allenynes. *Synthesis* **1983**, 32-34.

(25) Mandai, T.; Nakata, T.; Murayama, H.; Yamaoki, H.; Ogawa, M.; Kawada, M.; Tsuji, J. Palladium-catalyzed reactions of 2-alkynyl carbonates with terminal acetylenes: a new synthetic method for 1,2-diene-4-ynes. *Tetrahedron Lett.* **1990**, *31*, 7179-7180.

(26) Mandai, T.; Murayama, H.; Nakata, T.; Yamaoki, H.; Ogawa, M.; Kawada, M.; Tsuji, J. The palladium-catalyzed reactions of 2-alkynyl carbonates with terminal acetylenes. A new synthetic method for 1,2-dien-4-ynes. *J. Organomet. Chem.* **1991**, *417*, 305-311.

(27) Gueugnot, S.; Linstrumelle, G. An efficient palladium-catalyzed reaction of propargyl halides, tosylates and acetates with terminal alkynes. *Tetrahedron Lett.* **1993**, *34*, 3853-3856.

(28) Ogoshi, S.; Tsutsumi, K.; Kurosawa, H. Synthesis and structure of cationic η3-allenyl/propargylpalladium complexes. *J. Organomet. Chem.* **1995**, *493*, C19-21.

(29) Ohmiya, H.; Yang, M.; Yamauchi, Y.; Ohtsuka, Y.; Sawamura, M. Selective Synthesis of Allenes and Alkynes through Ligand-Controlled, Palladium-Catalyzed Decarboxylative Hydrogenolysis of Propargylic Formates. *Org. Lett.* **2010**, *12*, 1796-1799.

(30) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. Palladium-catalyzed coupling reaction of fluoroalkylated propargyl mesylates with organozinc reagents: novel synthesis of optically active fluorine-containing trisubstituted allenes. *Chem. Lett.* **2000**, 1360-1361.

Chapter 2 Appendix

Experimental methods and spectral analysis for Ch. 2 compounds

Table of Contents:

General Information:

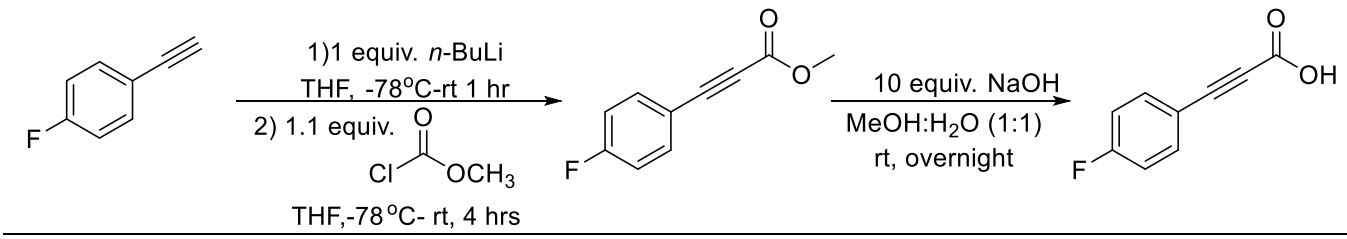
TLC analysis was performed with silica gel HL TLC plates w/UV254 from Sorbent Technologies. 60 Å porosity, 230 x 400 mesh standard grade silica gel from Sorbent Technologies was used for column chromatography. Infrared spectra were recorded on a PerkinElmer Spectrum 100 FTIR spectrometer with liquid samples sealed in 0.1 mm NaCl cells or solid samples as KBr pellets. GC/MS data was obtained using a Shimadzu GCMS-QP2010 SE. HRMS was run using APCI techniques. ^{1}H and ^{13}C spectra were obtained on a Bruker Advance 500 DRX equipped with a QNP cryoprobe and referenced to residual protio solvent signals. Chiral HPLC analysis was performed by LC- 10ATVP Shimadzu HPLC using a Chiralpak AD-H chiral column (0.46cm∅x25cm), eluting with hexane / iso-propanol mixture.

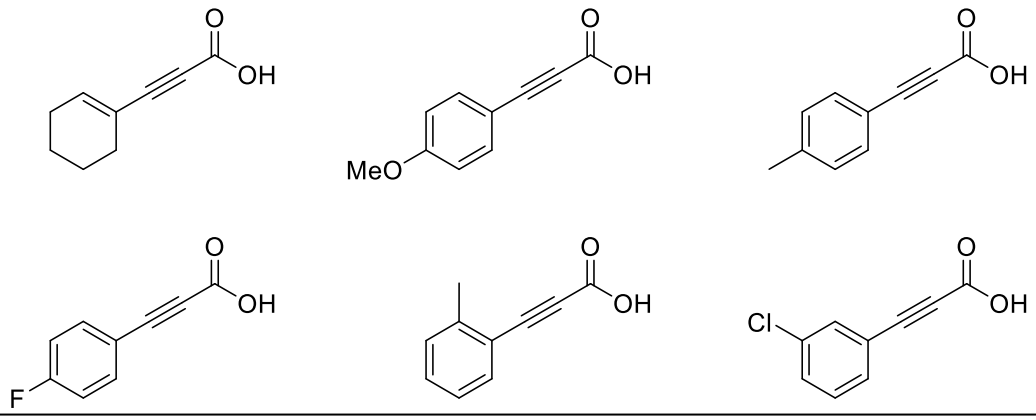
Tetrahydrofuran (THF) was distilled over Na using benzophenone as an indicator. Dichloromethane (DCM) was purified by an Innovative Technology Pure Solv^{TM} solvent purification system. N-Butyllithium (*n*-BuLi) was purchase as a 1.6 M solution in hexanes from Sigma Aldrich and used without further purification. All acetylenes and aldehydes were purchased from Sigma Aldrich, Alfa Aesar, and Acros Organics and used without further purification All palladium catalysts and ligands were purchased from Strem and stored in a glove box under argon atmosphere.

Synthesis of Propargyl Propiolates:

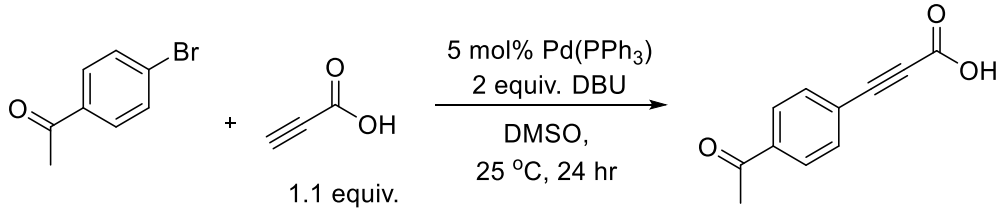
3-phenylpropiolic acid and pent-2-noic acid were purchased from Sigma Aldrich.

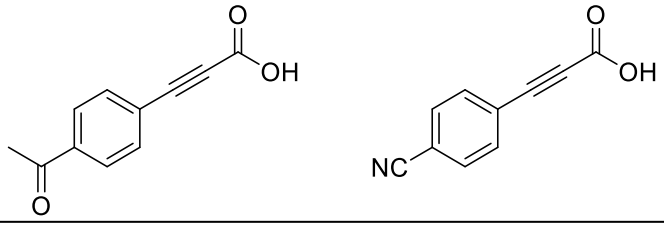
Propiolic acid synthesis via acteylide addition to chloroformate[1]



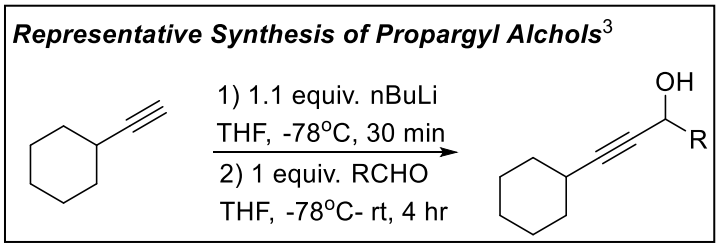


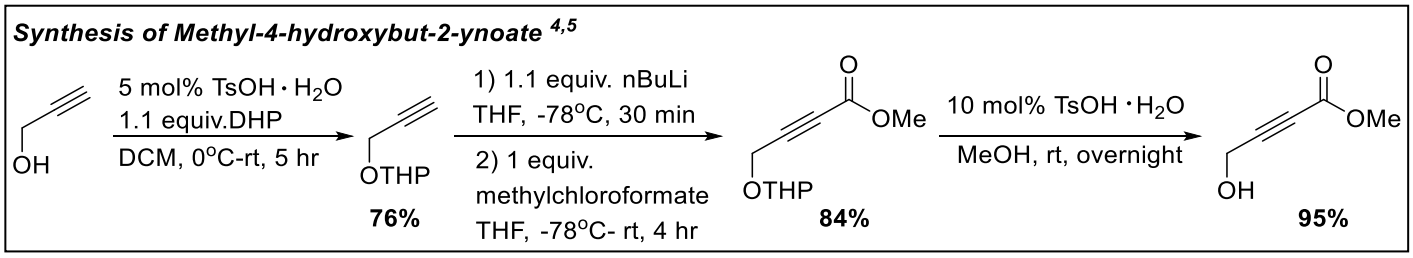
Propiolic acid synthesis via Sonogashira coupling[2]



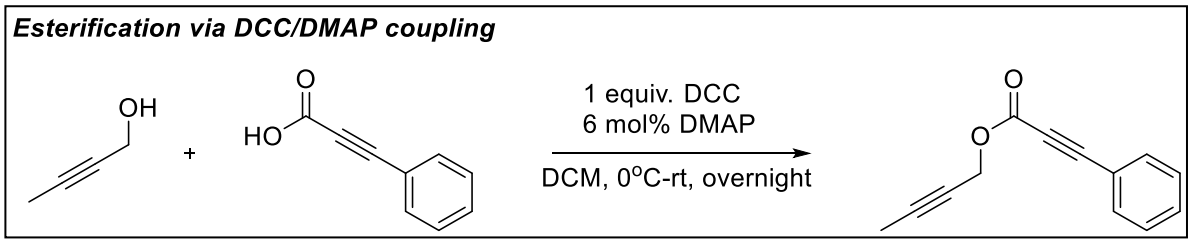


Propargyl alcohols were either purchased from Sigma Aldrich or Alfa Aesar





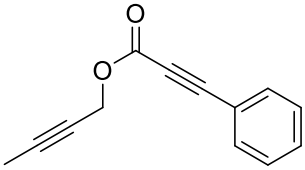
General Procedure for the synthesis of propargyl propiolates (General Procedure A):



Reactions were typically run on a 2 to 10 mmol scale

To a cooled (0 °C) stirred solution of the phenylpropiolic acid (730 mg, 5 mmol) in DCM (50 mL) was added 2-butyn-1-ol (350 mg, 5mmol) followed by dimethylaminopyridine (DMAP) (36.7mg, 0.3mmol) and then DCC (1031.7 mg, 5 mmol). The solution was allowed to warm to rt and stirred overnight. Reaction was filtered through a pad of celite with DCM. Filtrate was washed with 1 N HCl , Sat. $NaHCO_3$, brine, and then dried over $MgSO_4$. The solvent was evaporated and the crude product purified by flash chromatography

Characterization data for propargyl propiolates:



MS1-226

but-2-yn-1-yl 3-phenylpropiolate (2.1

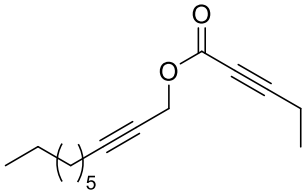
Prepared from but-2-yn-1-ol (700 mg, 0.01 mol) and phenylpropiolic acid (1460 mg, 0.01 mol) via general procedure A. Pale yellow oil isolated from flash chromatography using 100:0 hexanes:EtOAc as eluent (157 mg, 0.0058 mol, 58%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.56 (m, 2H), 7.48 – 7.43 (m, 1H), 7.40 – 7.36 (m, 2H), 4.79 (q, *J* = 2.4 Hz, 2H), 1.88 (t, *J* = 2.4 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 133.1, 130.8, 128.6, 119.4, 87.2, 84.3, 80.1, 72.3, 54.2, 3.7

GC/MS 198.1 (M^+), 169.1(base peak)

IR (neat) ν_{max} 2322, 2222, 1715, 1293, 1178, 759 cm^{-1}



MS1-230

hex-2-yn-1-yl pent-2-ynoa

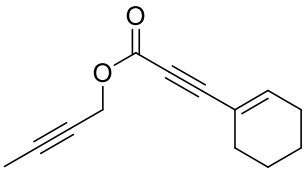
Prepared from hex-2-yn-1-ol (491 mg, 0.005 mol) and pent-2-ynoic acid (490 mg, 0.005 mol) via general procedure A. Pale yellow oil isolated from flash chromatography using 100:0 hexanes:EtOAc as eluent (966 mg, 0.0041 mol, 82%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.73 (t, *J* = 2.2 Hz, 2H), 2.34 (q, *J* = 7.5 Hz, 2H), 2.20 (tt, *J* = 7.2, 2.2 Hz, 2H), 1.54 – 1.44 (m, 2H), 1.39 – 1.31 (m, 2H), 1.31 – 1.24 (m, 6H), 1.20 (t, *J* = 7.5 Hz, 3H), 0.91 – 0.83 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 91.7, 88.7, 73.2, 72.1, 54.2, 31.8, 28.9, 28.9, 28.5, 22.8, 18.9, 14.2, 12.6.

HRMS (H-apci) *m/z:* M+H calcd for $C_{15}H_{23}O_2$: 235.1698, found: 235.1699

IR (neat) ν_{max} 2929, 2297, 2239, 1719, 1250 cm^{-1}



MS1-254

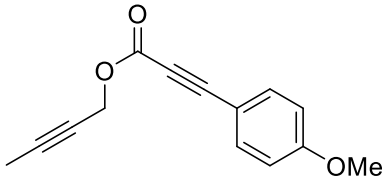
but-2-yn-1-yl 3-(cyclohex-1-en-1-yl)propiolate (2.1c)

Prepared from but-2-yn-1-ol (371 mg, 0.0053 mol) and 3-(cyclohex-1-en-1-yl)propiolic acid (796 mg, 0.0053 mol) via general procedure A. Yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (491 mg, 0.0024 mol, 48% (over 3 steps from 1-ethynylcyclohex-1-ene (530 mg, 0.005 mol))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.46 (tt, *J* = 3.5, 1.5 Hz, 1H), 4.72 (q, *J* = 2.4 Hz, 2H), 2.14 (m, 4H), 1.85 (t, *J* = 2.4 Hz, 3H), 1.68 – 1.54 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 142.8, 118.5, 89.6, 84.1, 78.1, 72.5, 54.0, 28.1, 26.1, 21.9, 21.2, 3.8.

GC/MS 202.1(M^+), 173.1(base peak)



MS2-075

but-2-yn-1-yl 3-(4-methoxyphenyl)propiolate (2.1d)

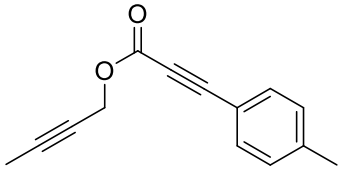
Prepared from but-2-yn-1-ol (182 mg, 0.0026 mol) and *p*-OMe phenylpropiolic acid (457 mg, 0.0026 mol) via general procedure A. White solid isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (409 mg, 0.0018 mol, 52% (over 3 steps from 4-ethynylanisole (457 mg, 0.0035 mol))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.39 (m, 2H), 7.05 – 6.71 (m, 2H), 4.78 (q, *J* = 2.4 Hz, 2H), 3.83 (s, 3H), 1.87 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 153.7, 135.2, 114.4, 111.3, 88.2, 84.3, 79.7, 72.5, 55.5, 54.2, 3.9.

HRMS (H-apci) *m/z:* M+H calcd for $C_{14}H_{13}O_3$: 229.0865, found: 229.0879

IR (neat) ν_{max} 2318, 2229, 1721, 1191, 845 cm^{-1}



MS2-018

but-2-yn-1-yl 3-(p-tolyl)propiolate (2.1

Prepared from but-2-yn-1-ol (329 mg, 0.0047 mol) and *p*-tolyl phen 752 mg, 0.0047 mol) via general procedure A. Pale yellow oil isolated from flash chromatography using

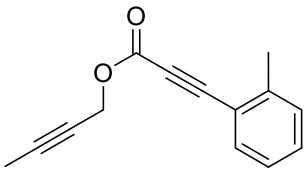
95:5 hexanes:EtOAc as eluent (497 mg, 0.0024 mol, 47%(over 3 steps from 1-ethynyl-4-methylbenzene(580 mg, 0.005 mol)))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.51 – 7.45 (m, 2H), 7.20 – 7.15 (m, 2H), 4.78 (q, *J* = 2.4 Hz, 2H), 2.38 (s, 3H), 1.88 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 141.6, 133.2, 129.5, 116.4, 87.9, 84.3, 79.9, 72.4, 54.3, 21.9, 3.8.

GC/MS 212.1 (M^+), 183.1 (base peak)

IR (DCM) ν_{max} 2220, 1711, 1189, 969 cm^{-1}



MS2-014

but-2-yn-1-yl 3-(o-tolyl)propiolate (2.1f)

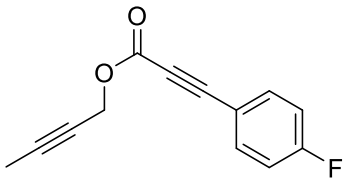
Prepared from but-2-yn-1-ol (280 mg, 0.004 mol) and *o*-tolyl phenylpropiolic acid (640 mg, 0.004 mol) via general procedure A. Pale yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (531 mg, 0.0025 mol,63% (over 3 steps from1-ethynyl-2-methylbenzene(464 mg, 0.004 mol)))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.4 Hz, 1H), 7.24 (ddt, *J* = 7.7, 1.3, 0.7 Hz, 1H), 7.18 (tdd, *J* = 7.4, 1.3, 0.6 Hz, 1H), 4.80 (q, *J* = 2.4 Hz, 2H), 2.49 (s, 2H), 1.88 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 142.5, 133.6, 130.9, 129.9, 125.9, 119.4, 86.4, 84.3, 83.9, 72.5, 54.3, 20.7, 3.9.

GC/MS 212.1(M^+), 183.1(base peak)

IR (neat) ν_{max} 2326, 2217, 1714, 1282, 1175, 760 cm^{-1}



MS1-297

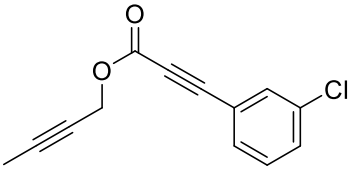
but-2-yn-1-yl 3-(4-fluorophenyl)propiolate

Prepared from but-2-yn-1-ol (350 mg, 0.005 mol) and *p*-fluoro phe ıg, 0.005 mol) via general procedure A. White solid isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (342 mg, 0.0016 mol, 32%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 – 7.45 (m, 2H), 7.07 – 6.94 (m, 2H), 4.72 (q, *J* = 2.4 Hz, 2H), 1.81 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.1 (d, *J* = 253.8 Hz), 153.4, 135.5 (d, *J* = 9.0 Hz), 116.3 (d, *J* = 22.2 Hz), 115.7 (d, *J* = 3.4 Hz), 86.3, 84.5, 80.2 (d, *J* = 1.6 Hz), 72.3, 54.4, 3.9.

HRMS (H-apci) *m/z:* M+H calcd for $C_{13}H_{10}FO_2$: 217.0665, found: 217.0659



MS2-240

but-2-yn-1-yl 3-(3-chlorophenyl)propiolate (

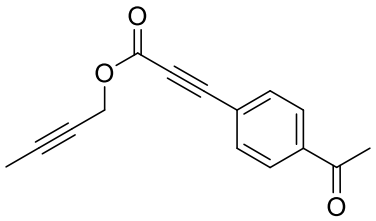
Prepared from but-2-yn-1-ol (154 mg, 0.0022 mol) and *m*-chloro phe (397 mg, 0.0022 mol) via general procedure A. Pale yellow solid isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (284 mg, 0.0012 mol, 24% (over 3 steps from 1-chloro-3-ethynylbenzene (680 mg, 0.005 mol)))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 – 7.55 (m, 1H), 7.49 – 7.41 (m, 2H), 7.34 – 7.29 (m, 1H), 4.79 (q, *J* = 2.4 Hz, 2H), 1.88 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 134.7, 132.9, 131.3, 131.2, 130.0, 121.3, 85.3, 84.6, 80.9, 72.2, 54.5, 3.9.

HRMS (H-apci) *m/z:* M+H calcd for $C_{13}H_{10}ClO_2$: 233.0369, found: 233.0365

IR (KBr) ν_{max} 2264, 2222, 1717, 1188, 781, 744 cm^{-1}



MS2-037

but-2-yn-1-yl 3-(4-acetylphenyl)propiolate (

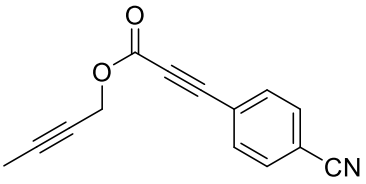
Prepared from but-2-yn-1-ol (133 mg, 0.0019 mol) and 3-(4-acetylphenyl)propiolic acid (357 mg, 0.0019 mol) via general procedure A. White solid isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (298 mg, 0.0012 mol, 64%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 – 7.80 (m, 2H), 7.77 – 7.56 (m, 2H), 4.80 (q, *J* = 2.4 Hz, 2H), 2.61 (s, 3H), 1.88 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 153.1, 138.3, 133.3, 128.4, 124.1, 85.6, 84.6, 82.3, 72.2, 54.6, 26.9, 3.8.

HRMS (H-apci) *m/z:* M+H calcd for $C_{15}H_{13}O_3$: 241.0865, found: 241.0862

IR (DCM) ν_{max} 2322, 2225, 1715, 1689, 1180, 969 cm^{-1}



MS1-299

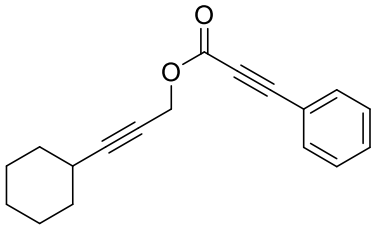
but-2-yn-1-yl 3-(4-cyanophenyl)propiolate (2

Prepared from but-2-yn-1-ol (149 mg, 0.0021 mol) and *p*-CN phenylpr) mg, 0.0021 mol) via general procedure A. Pale yellow solid isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (287 mg, 0.0013 mol, 61%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 0.8 Hz, 4H), 4.81 (q, *J* = 2.4 Hz, 2H), 1.88 (t, *J* = 2.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 133.5, 132.4, 124.4, 117.9, 114.3, 84.8, 84.2, 83.1, 72.1, 54.7, 3.9.

HRMS (H-apci) *m/z:* M+H calcd for $C_{14}H_{10}NO_2$: 224.0712, found: 224.0703



MS2-083

3-cyclohexylprop-2-yn-1-yl 3-phenylpropiolate (

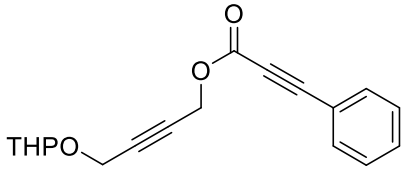
Prepared from 3-cyclohexylprop-2-yn-1-ol (967 mg, 0.007 mol) and ph acid (1022 mg, 0.007 mol) via general procedure A. Cloudy colorless oil isolated from flash chromatography using 96:4 hexanes:EtOAc as eluent (945 mg, 0.0035 mol, 51% (over 2 steps from cyclohexylacetylene (742 mg, 0.007 mol)))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.57 (m, 2H), 7.48 – 7.43 (m, 1H), 7.41 – 7.35 (m, 2H), 4.83 (d, *J* = 2.1 Hz, 2H), 2.47 – 2.36 (m, 1H), 1.87 – 1.76 (m, 2H), 1.75 – 1.65 (m, 2H), 1.60 – 1.38 (m, 3H), 1.36 – 1.24 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 133.2, 130.9, 128.7, 119.6, 92.8, 87.2, 80.3, 73.0, 54.5, 32.5, 29.2, 25.9, 24.9.

GC/MS 266.2 (M^+), 165.1(base peak)

IR (neat) ν_{max} 2932, 2318, 2218, 1715, 1166, 759 cm^{-1}



MS2-135

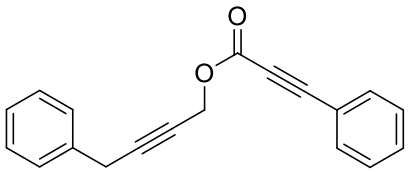
4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-yl 3-phenylpropiolate (2.1l)

Prepared from 4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-ol (850 mg, 0.005 mol) and phenylpropiolic acid (731 mg, 0.005 mol) via general procedure A. Yellow oil isolated from flash chromatography using 85:15 hexanes:EtOAc as elutent (639 mg, 0.0021 mol, 42%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.57 (m, 2H), 7.49 – 7.43 (m, 1H), 7.42 – 7.35 (m, 2H), 4.87 (t, *J* = 1.8 Hz, 2H), 4.81 (t, *J* = 3.4 Hz, 1H), 4.38 – 4.25 (m, 2H), 3.83 (ddd, *J* = 11.2, 9.2, 3.1 Hz, 1H), 3.54 (dtd, *J* = 11.3, 4.4, 1.6 Hz, 1H), 1.90 – 1.68 (m, 2H), 1.70 – 1.46 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 133.2, 131.0, 128.6, 119.4, 97.0, 87.6, 83.9, 80.0, 79.1, 62.1, 54.3, 53.8, 30.3, 25.4, 19.1.

GC/MS 214.1 (M-THP), 128.2 (base peak)



MS2-147

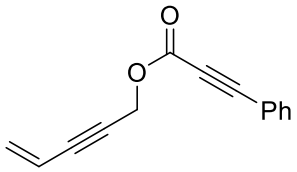
4-phenylbut-2-yn-1-yl 3-phenylpropiolate (2.1m)

Prepared from 4-phenylbut-2-yn-1-ol (1096 mg, 0.0075 mol) and phenylpro 096 mg, 0.0075 mol) via general procedure A. Yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (1090 mg, 0.004 mol, 50% (over 2 steps from prop-2-yn-1-ylbenzene (929 mg, 0.008 mol)))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.49 (m, 2H), 7.41 – 7.36 (m, 1H), 7.33 – 7.28 (m, 3H), 7.26 – 7.24 (m, 3H), 7.19 – 7.15 (m, 2H), 4.81 (t, *J* = 2.2 Hz, 2H), 3.59 (t, *J* = 2.2 Hz, 2H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 136.0, 133.2, 130.9, 128.7, 128.7, 128.1, 126.9, 119.5, 87.5, 86.1, 80.2, 75.3, 54.3, 25.3.

GC/MS 274.2(M^+), (base peak)



MS2-077

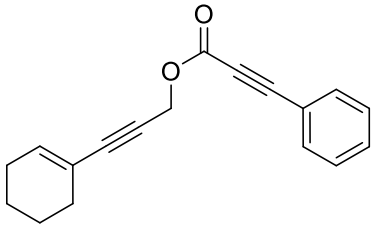
pent-4-en-2-yn-1-yl phenylpropiolate

Prepared from pent-4-en-2-yn-1-ol (501 mg, 0.0061 mol) and ph cid (891 mg, 0.0061 mol) via general procedure A. Yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (282 mg, 0.0013 mol, 22%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.57 (m, 2H), 7.50 – 7.43 (m, 1H), 7.41 – 7.36 (m, 2H), 5.83 (ddt, J = 17.6, 11.0, 1.9 Hz, 1H), 5.72 (dd, J = 17.6, 2.2 Hz, 1H), 5.56 (dd, J = 11.0, 2.2 Hz, 1H), 4.95 (d, J = 1.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 133.2, 131.0, 128.8, 128.8, 119.5, 116.3, 87.6, 86.1, 82.6, 80.1, 54.2.

GC/MS 210.1(M^+), 181.1 (base peak)



MS2-056

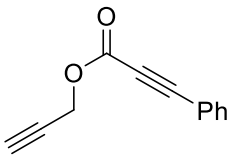
3-(cyclohex-1-en-yl)prop-2-yn-1-yl 3-phenylprop

Prepared from 3-(cyclohex-1-en-1-yl)prop-2-yn-1-ol (313 mg, 0.0023 mol) and phenylpropiolic acid (336 mg, 0.0023 mol) via general procedure A. Yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (323 mg, 0.0012 mol, 52%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.56 (m, 2H), 7.49 – 7.43 (m, 1H), 7.41 – 7.35 (m, 2H), 6.19 (tt, *J* = 3.8, 1.8 Hz, 1H), 4.95 (s, 2H), 2.16 – 2.04 (m, 4H), 1.67 – 1.53 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 136.9, 133.2, 130.9, 128.7, 119.9, 119.6, 89.4, 87.4, 80.2, 79.3, 54.6, 28.9, 25.8, 22.3, 21.5.

GC/MS 264.1(M^+), 219.1 (base peak)



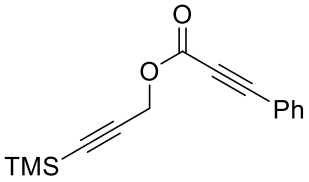
MS3-127

prop-2-yn-1-yl 3-phenylpropiolate (2.1p)

Prepared from propargyl alcohol (280 mg, 0.005 mol) and phenylpropiolic acid (731 mg, 0.005 mol) via general procedure A. Pale yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (760 mg, 0.0041 mol, 83%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.56 (m, 2H), 7.50 – 7.43 (m, 1H), 7.42 – 7.34 (m, 2H), 4.83 (d, J = 2.5 Hz, 2H), 2.55 (t, J = 2.5 Hz, 1H).

GC/MS 184.0 (M^+), 129.1(base peak)



MS2-191

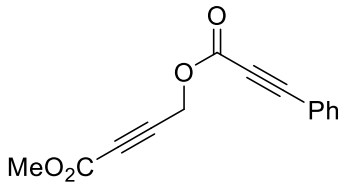
3-(trimethylsilyl)prop-2-yn-1-yl 3-pheny

Prepared from 3-(trimethylsilyl)prop-2-yn-1-ol (744 mg, 0.0(/lpropiolic acid (849 mg, 0.0058 mol) via general procedure A. Pale yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (819 mg, 0.0032 mol, 55%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.67 – 7.55 (m, 2H), 7.53 – 7.43 (m, 1H), 7.43 – 7.35 (m, 2H), 4.94 (s, 2H), 3.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 152.9, 133.3, 131.2, 128.8, 119.2, 88.5, 80.3, 79.6, 78.5, 53.1, 52.6.

GC/MS 256.2 (M^+), 241.1(base peak)



MS2-067

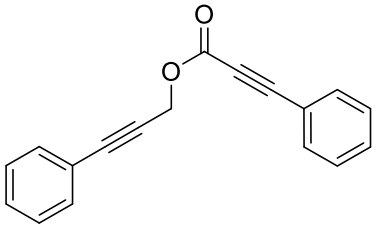
methyl 4-((3-phenylpropioloyl)oxy)but-2-y

Prepared from methyl 4-hydroxybut-2-ynoate (833 mg, 0.0073 mol) and phenylpropiolic acid (1059 mg, 0.0073 mol) via general procedure A. Yellow amorphous solid isolated from flash chromatography using 85:15 hexanes:EtOAc as eluent (894 mg, 0.0037 mol, 51%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.67 – 7.55 (m, 2H), 7.53 – 7.43 (m, 1H), 7.43 – 7.35 (m, 2H), 4.94 (s, 2H), 3.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 152.9, 133.3, 131.2, 128.8, 119.2, 88.5, 80.3, 79.6, 78.5, 53.1, 52.6.

GC/MS 242.1(M^+), (base peak)



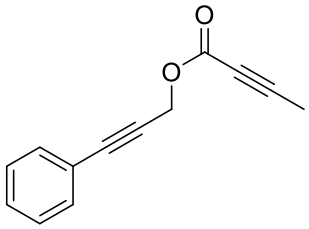
MS1-187

3-phenylprop-2-yn-1-yl but-2-ynoat

Prepared from methyl 3-phenylprop-2-yn-1-ol (661 mg, 0.005 mol) and phenylpropiolic acid (730 mg, 0.005 mol) via general procedure A. Yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (744 mg, 0.0037 mol, 75%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 (m, 2H), 7.38 – 7.27 (m, 3H), 4.98 (s, 2H), 2.01 (d, *J* = 1.9 Hz, 3H).

GC/MS 198.1(M^+), 169.1 (base peak)



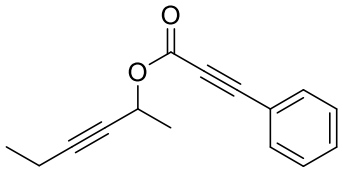
MS2-013

3-phenylprop-2-yn-1-yl 3-phenylpropiolate(2.1t)

Prepared from methyl 3-phenylprop-2-yn-1-ol (608 mg, 0.0046 mol) and but-2-ynoic acid (387 mg, 0.0046 mol) via general procedure A. Yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (960 mg, 0.0037 mol, 80%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.63 – 7.58 (m, 2H), 7.50 – 7.44 (m, 3H), 7.42 – 7.29 (m, 5H), 5.07 (s, 2H).

GC/MS 260.2(M^+), 231.1 (base peak)



MS2-046

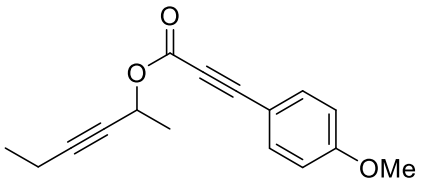
hex-3-yn-2-yl 3-phenylpropiolate (2

Prepared from hex-3-yn-2-ol (442 mg, 0.0045 mol) and phenylpr[illegible] mg, 0.0045 mol) via general procedure A. Pale yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (777mg, 0.0031 mol, 69%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 – 7.56 (m, 2H), 7.47 – 7.42 (m, 1H), 7.40 – 7.35 (m, 2H), 5.64 – 5.44 (m, 1H), 2.23 (qt, *J* = 7.6, 1.6 Hz, 2H), 1.55 (dd, *J* = 6.6, 0.9 Hz, 3H), 1.14 (td, *J* = 7.6, 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 133.2, 130.8, 128.7, 119.7, 88.0, 86.8, 80.6, 62.9, 21.9, 13.7, 12.5.

GC/MS 226.1(M^+), 183.1 (base peak)



MS2-044

hex-3-yn-2-yl 3-(4-methoxyphenyl)propiolate (2.3b)

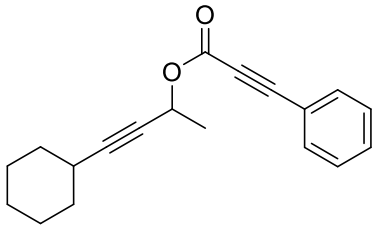
Prepared from hex-3-yn-2-ol (294 mg, 0.003 mol) and *p*-OMe-phenylpropiolic acid (528 mg, 0.003 mol) via general procedure A. Yellow solid isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (360 mg, 0.0014 mol, 47%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.52 (m, 2H), 6.91 – 6.84 (m, 2H), 5.56 (qt, *J* = 6.6, 2.0 Hz, 1H), 3.83 (s, 4H), 2.23 (qd, *J* = 7.5, 2.0 Hz, 2H), 1.55 (d, *J* = 6.6 Hz, 4H), 1.14 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 153.5, 135.1, 114.4, 111.5, 87.9, 87.7, 80.1, 77.3, 62.7, 55.6, 21.9, 13.7, 12.6.

HRMS (H-apci) *m/z:* M+H calcd for $C_{16}H_{17}O_3$: 257.1178, found: 257.1190

IR (neat) ν_{max} 2983,2240, 2208, 1709,1255,1193, 834cm^{-1}



MS2-127

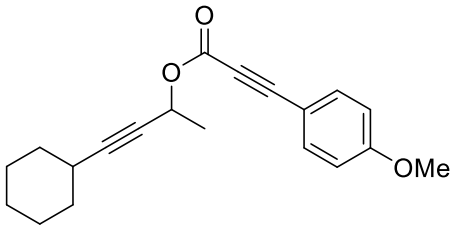
4-cyclohexylbut-3-yn-2-yl 3-phenylpropiolate (

Prepared from 4-cyclohexylbut-3-yn-2-ol (806 mg, 0.0053 mol) and phenylpropiolic acid (774 mg, 0.0053 mol) via general procedure A. Yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (422 mg, 0.0015 mol, 28%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.57 (m, 2H), 7.48 – 7.42 (m, 1H), 7.40 – 7.33 (m, 2H), 5.59 (qd, *J* = 6.6, 1.8 Hz, 1H), 2.45 – 2.35 (m, 1H), 1.83 – 1.74 (m, 2H), 1.73 – 1.66 (m, 2H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.54 – 1.37 (m, 2H), 1.37 – 1.21 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 133.2, 130.8, 128.7, 119.7, 90.7, 86.7, 80.7, 77.8, 63.0, 32.5, 29.1, 25.9, 24.9, 22.0.

GC/MS 280.3 (M^+), 237.2 (base peak)



MS3-209

4-cyclohexylbut-3-yn-2-yl 3-(4-methoxyphenyl)pr

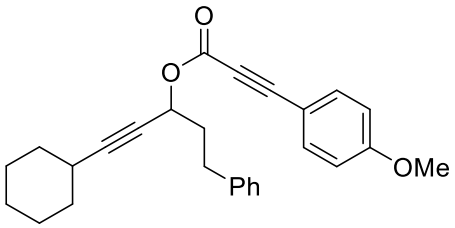
Prepared from 4-cyclohexylbut-3-yn-2-ol (1034 mg, 0.0068 mol) and *p*-OMe-phenylpropiolic acid (1197 mg, 0.0068 mol) via general procedure A. Yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (1250 mg, 0.004 mol, 59%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 – 7.49 (m, 2H), 6.94 – 6.80 (m, 2H), 5.58 (qd, *J* = 6.6, 1.8 Hz, 1H), 3.84 (s, 3H), 2.39 (td, *J* = 8.6, 3.0 Hz, 1H), 1.78 (ddt, *J* = 12.1, 6.1, 3.4 Hz, 2H), 1.75 – 1.65 (m, 2H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.52 – 1.38 (m, 3H), 1.34 – 1.25 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.65, 153.45, 135.13, 114.40, 111.50, 90.58, 87.62, 80.18, 77.93, 62.76, 55.54, 32.50, 29.09, 25.96, 24.94, 22.03.

GC/MS 310.2 (M^+), 121.1(base peak)

IR (neat) ν_{max} 2933, 2855, 2234, 2209, 1710, 1255, 1193, 834cm^{-1}



MS2-140

1-cyclohexyl-5-phenylpent-1-yn-3-yl 3-(4-methoxypheny (2.3e)

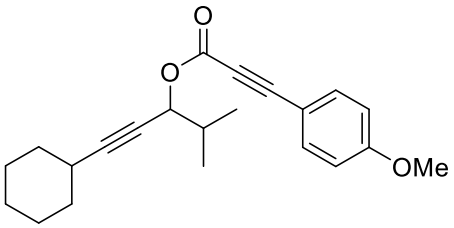
Prepared from 1-cyclohexyl-5-phenylpent-1-yn-3-ol (776 mg, 0.0032 mol) and *p*-OMe-phenylpropiolic acid (563 mg, 0.0032 mol) via general procedure A. Yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (640 mg, 0.0016 mol, 50%)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.52 (m, 2H), 7.34 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 6.92 – 6.86 (m, 2H), 5.49 (td, *J* = 6.5, 1.8 Hz, 1H), 3.84 (s, 3H), 2.82 (t, *J* = 8.0 Hz, 2H), 2.50 – 2.38 (m, 1H), 2.26 – 2.07 (m, 2H), 1.85 – 1.76 (m, 2H), 1.74 – 1.66 (m, 2H), 1.53 – 1.42 (m, 3H), 1.37 – 1.24 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 153.5, 140.9, 135.2, 128.6, 128.6, 126.2, 114.4, 111.5, 91.8, 87.9, 80.1, 76.7, 65.9, 55.6, 36.8, 32.5, 32.5, 31.5, 29.1, 25.97, 24.9.

GC/MS 400.2 (M^+) 91.0 (base peak)

IR (neat) ν_{max} 2932, 2854, 2209, 1711, 1604, 1256, 1161, 834 cm^{-1}



MS2-253

1-cyclohexyl-4-methylpent-1-yn-3-yl 3-(4-methoxyphenyl)p f)

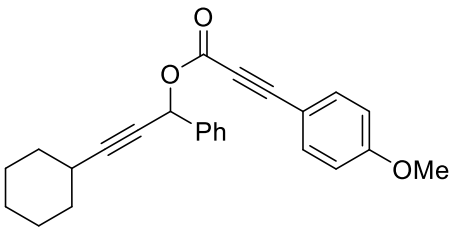
Prepared from 1-cyclohexyl-4-methylpent-1-yn-3-ol (541 mg, 0.003 mol) and *p*-OMe-phenylpropiolic acid (528 mg, 0.003 mol) via general procedure A. Viscous colorless oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (556 mg, 0.0016 mol, 55%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.64 – 7.44 (m, 2H), 6.99 – 6.74 (m, 2H), 5.35 (dd, *J* = 5.6, 1.9 Hz, 1H), 3.83 (s, 3H), 2.43 (ddd, *J* = 10.8, 7.1, 3.6 Hz, 1H), 2.04 (qd, *J* = 6.8, 5.7 Hz, 1H), 1.82 – 1.73 (m, 2H), 1.72 – 1.66 (m, 2H), 1.51 – 1.41 (m, 3H), 1.37 – 1.25 (m, 3H), 1.04 (dd, *J* = 18.8, 6.7 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6, 153.7, 135.1, 114.4, 111.6, 91.8, 87.6, 80.2, 75.5, 71.3, 55.5, 32.7, 32.5, 32.5, 29.1, 26.0, 24.8, 18.5, 17.6.

GC/MS 338.3 (M^+), 293.2 (base peak)

IR (neat) ν_{max} 2932, 2207,1708, 1606, 1256, 1161, 834 cm^{-1}



MS2-269

3-cyclohexyl-1-phenylprop-2-yn-1-yl 3-(4-methoxyphenyl)p g)

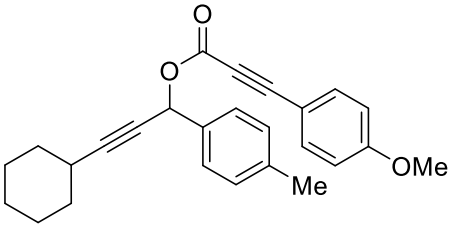
Prepared from 3-cyclohexyl-1-phenylprop-2-yn-1-ol (687 mg, 0.003 mol) and *p*-OMe propiolic acid (528 mg, 0.003 mol) via general procedure A. Viscous yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (636 mg, 0.0017 mol, 53%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.56 (m, 2H), 7.56 – 7.48 (m, 2H), 7.44 – 7.33 (m, 3H), 6.91 – 6.83 (m, 2H), 6.59 (d, *J* = 1.9 Hz, 1H), 2.53 – 2.45 (m, 1H), 1.86 – 1.80 (m, 2H), 1.71 (dddt, *J* = 12.5, 9.3, 6.3, 3.7 Hz, 2H), 1.58 – 1.45 (m, 3H), 1.36 – 1.26 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 153.4, 137.1, 135.1, 129.1, 128.7, 128.2, 114.4, 111.4, 93.4, 88.2, 80.1, 76., 67.7, 55.5, 32.4, 32.4, 29.3, 25.9, 24.9.

GC/MS 172.2(M^+),(base peak)

IR (neat) ν_{max} 2937, 2211, 1709, 1253, 837 cm^{-1}



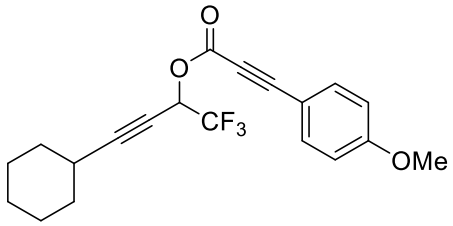
MS3-135

3-cyclohexyl-1-(p-tolyl)prop-2-yn-1-yl 3-(4-methoxyphen

Prepared from 3-cyclohexyl-1-(p-tolyl)prop-2-yn-1-ol (961 mg, 0.0042 mol) and *p*-OMe phenylpropiolic acid (739 mg, 0.0042 mol) via general procedure A. Viscous yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (940 mg, 0.0024 mol, 57%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.50 (m, 2H), 7.49 – 7.44 (m, 2H), 7.20 (m, 2H), 6.90 – 6.82 (m, 2H), 6.56 (d, J = 1.9 Hz, 1H), 3.82 (s, 3H), 2.48 (m, 1H), 2.36 (s, 3H), 1.88 – 1.77 (m, 2H), 1.71 (m Hz, 2H), 1.49 (m, 3H), 1.31 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) (126 MHz, $CDCl_3$) δ 161.7, 153.5, 139.1, 135.1, 134.3, 129.4, 128.2, 114.4, 111.5, 93.1, 88.0, 80.1, 76.2, 67.7, 55.5, 32.5, 32.4, 29.3, 25.9, 24.9, 21.4.



MS3-015

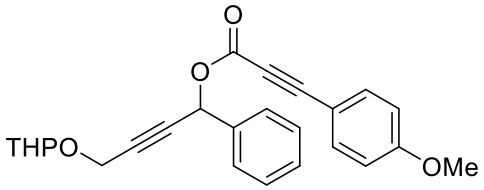
4-cyclohexyl-1,1,1-trifluorobut-3-yn-2-yl 3-(4-methoxyphe (2.3i)

Prepared from 4-cyclohexyl-1,1,1-trifluorobut-3-yn-2-ol (961 mg, 0.(*p*-OMe phenylpropiolic acid (1091 mg, 0.0062 mol) via general procedure A. Viscous yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (1276 mg, 0.0035 mol, 56%)

^{1}H NMR (500 MHz, Chloroform-*d* δ 7.69 – 7.44 (m, 2H), 7.00 – 6.74 (m, 2H), 5.93 (qd, J = 5.7, 1.9 Hz, 1H), 3.85 (s, 3H), 2.53 – 2.38 (m, 1H), 1.79 (dq, J = 12.7, 3.2 Hz, 2H), 1.73 – 1.65 (m, 2H), 1.49 (qd, J = 9.2, 4.3 Hz, 3H), 1.39 – 1.25 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 151.9, 135.5, 114.5, 110.8, 94.6, 90.7, 68.9, 62.7 (q), 55.6, 55.6, 31.9, 28.9, 25.8, 24.7

^{19}F NMR (376 MHz, Chloroform-*d*) δ 10.17 (d, *J* = 5.5 Hz). (trifluoroacetic acid as internal standard)



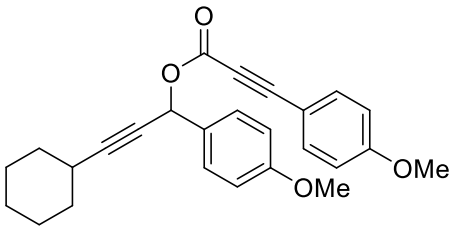
MS3-100

1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-yl 3-(4-methc ɔlate

(2.3j)

Prepared from 1-phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-ol (1538 mg, 0.0062 mol) and *p*-OMe phenylpropiolic acid (1091 mg, 0.0062 mol) via general procedure A. Viscous yellow oil isolated from flash chromatography using 95:5 hexanes:EtOAc as eluent (1276 mg, 0.0035 mol, 56%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.60 – 7.55 (m, 2H), 7.55 – 7.49 (m, 2H), 7.45 – 7.33 (m, 3H), 6.95 – 6.76 (m, 2H), 6.61 (q, J = 1.7 Hz, 1H), 4.82 (q, J = 3.2 Hz, 1H), 4.44 – 4.27 (m, 2H), 3.83 (s, 3H), 3.52 (dtd, J = 11.3, 4.3, 2.0 Hz, 1H), 1.93 – 1.69 (m, 2H), 1.68 – 1.46 (m, 5H).



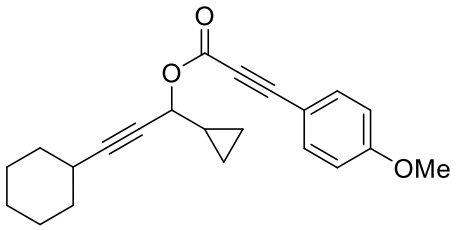
MS3-088

3-cyclohexyl-1-(4-methoxyphenyl)prop-2-yn-1-yl 3-(4-methoxypl (2.3k)

Prepared from 3-cyclohexyl-1-(4-methoxyphenyl)prop-2-yn-1-ol (1127 mg, 0.0046 mol) and *p*-OMe phenylpropiolic acid (810 mg, 0.0046 mol) via general procedure A. Viscous yellow oil isolated from flash chromatography using 92:8 hexanes:EtOAc as eluent (965 mg, 0.0024 mol, 52%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.46 (m, 2H), 7.45 – 7.37 (m, 2H), 6.92 – 6.82 (m, 4H), 5.57 (d, J = 1.8 Hz, 1H), 5.17 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.53 (q, J = 6.8, 5.0 Hz, 1H), 2.48 – 2.40 (m, 1H), 1.88 – 1.63 (m, 8H), 1.55 – 1.22 (m, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5 (d, J = 17.2 Hz), 131.6 (d, J = 25.0 Hz), 129.2 (d, J = 19.7 Hz), 113.6 (d, J = 11.2 Hz), 92.3 (d, J = 32.7 Hz), 78.1(d, J = 45.2 Hz), 68.7 (d, J = 106.4 Hz), 55.3 (d, J = 2.7 Hz), 32.9 – 32.5(m), 29.2 (d, J = 13.8 Hz), 25.9 (d, J = 4.6 Hz), 24.9 (d, J = 17.8 Hz).



MS2-097

3-cyclohexyl-1-cyclopropylprop-2-yn-1-yl 3-(4-methoxy)late

Prepared from 3-cyclohexyl-1-cyclopropylprop-2-yn-1-ol (792 mg, d *p*-OMe phenylpropiolic acid (774 mg, 0.0044 mol) via general procedure A. Viscous yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (820 mg, 0.0024 mol, 54%)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.65 – 7.43 (m, 2H), 6.96 – 6.79 (m, 2H), 5.48 (dd, J = 6.4, 1.8 Hz, 1H), 3.84 (s, 3H), 2.47 – 2.31 (m, 1H), 1.81 – 1.72 (m, 2H), 1.68 (m, 2H), 1.45 (m, 2H), 1.35 – 1.24 (m, 4H), 0.67 – 0.49 (m, 4H)

^{13}C NMR (126 MHz, CDCl3) δ 189.0, 161.6, 153.7, 135.1, 114.4, 111.5, 91.6, 87.7, 80.2, 74.3, 69.9, 55.5, 32.5, 31.7, 25.9, 24.8, 14.4, 10.9, 3.7, 2.3.

GC/MS 136.2(M^+), 108.1(base peak)

Experimental Procedure for Decarboxylative Coupling of Propargyl Propiolates:

Representative procedure for the decarboxylative coupling of propargyl propiolates towards formation of allenynes:

Reactions were run on a 0.5 mmol scale unless otherwise indicated

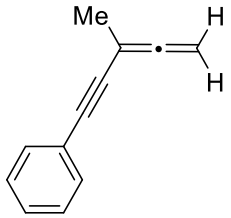
A flame dried 25 mL microwave vial (Biotage # 355631), charged with a stir bar, was taken into the glove box. $Pd(PPh_3)_4$ (0.028 g, 5 mol%) was added followed by the propiolate **1a** (99.04 mg, 0.5 mmol). The vial was then capped using a vial cap (Biotage #352298) and a manual cap

crimper (Biotage #353671). The vial was removed from the glove box and THF (10 mL) was added via syringe. The vial was then placed in an oil bath at 50 °C and heated/stirred for 4 hours. The reaction completion was determined via GC/MS.

After reaction completion, the vial was removed from the bath and the stir bar removed. THF was evaporated via air stream passed over the surface of the solution and the contents were taken up in DCM and purified by silica gel column chromatography (3 cm diameter X 12 in height. Mobile phase was 100% pentanes). Evaporation of fractions again via air stream passed over the surface of the solution yielded 157 mg of the desired allenyne **2a**, a 58% yield. Most substrates are volatile and cannot be put under vacuum. Allenyne substrates were best stored in chloroform in the freezer.

Characterization data for Allenynes

Note: To prevent decompositions, the allenynes are best stored cold. These samples were typically stored as chloroform solutions at ca. -15 ˚C. The allenes also proved to be unstable to standard positive ion and negative ion HRMS conditions in methanol or with 1% formic acid. An attempt at atmospheric pressure chemical ionization mass spectrometry also failed. For cases that decomposed under the conditions of HRMS, low resolution mass spectrometry did confirm the identity of the products.



MS2-200

(3-methylpenta-3,4-dien-1-yn-1-yl)benz

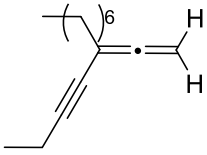
Pale yellow oil isolated from flash column chromatography using pentanes as eluent (68 mg, 0.0044 mol, 88%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.43 – 7.37 (m, 2H), 7.30 – 7.22 (m, 3H), 4.93 (q, *J* = 3.2 Hz, 2H), 1.92 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3, 131.5, 128.4, 128.2, 123.5, 91.1, 85.3, 85.2, 76.3, 19.9.

GC/MS 154.1(M^+), (base peak)

IR (neat) ν_{max} 2925, 2209, 1938, 1491, 755 cm^{-1}



MS2-204

5-vinylidenedodec-3-yne (2.2

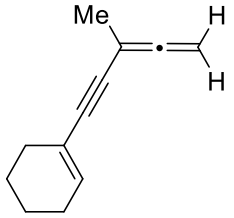
Pale yellow oil isolated from flash column chromatography using pentanes as eıuent (82 mg, 0.0043 mol, 86%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.88 (tt, *J* = 3.0, 1.3 Hz, 2H), 2.33 (qt, *J* = 7.4, 1.3 Hz, 2H), 2.12 – 2.01 (m, 2H), 1.52 – 1.44 (m, 2H), 1.35 – 1.21 (m, 8H), 1.16 (t, *J* = 7.5 Hz, 3H), 0.95 – 0.79 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 213.5, 94.1, 90.1, 76.5, 74.8, 33.7, 31.9, 29.2, 29.0, 27.8, 22.8, 14.3, 14.1, 13.4.

GC/MS 190.1 (M^+), 106.0 (base peak)

IR (neat) ν_{max} 2927, 2236, 1943, 1459, 849 cm^{-1}



MS2-020

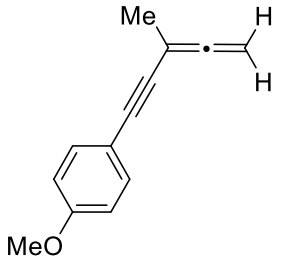
1-(3-methylpenta-3,4-dien-1-yn-1-yl)cyclo

Colorless oil isolated from flash chromatography using pentanes as eluent (46 mg, 0.0029 mol, 57%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.09 (tt, *J* = 3.9, 1.8 Hz, 1H), 4.88 (q, *J* = 3.2 Hz, 2H), 2.19 – 2.03 (m, 4H), 1.86 (t, *J* = 3.2 Hz, 3H), 1.67 – 1.51 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 134.8, 120.9, 93.4, 85.3, 82.5, 75.9, 29.3, 25.8, 22.5, 21.6, 20.1.

GC/MS 158.1(M^+), 128.1(base peak)



MS1-300

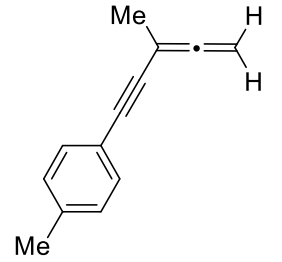
1-methoxy-4-(3-methylpenta-3,4-dien-1-yn-1-yl)benz

(0.7 mmol scale) Yellow oil isolated from flash chromatography using 98:2 pentanes:acetone as eluent (120 mg, 0.0065 mol , 92%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.30 (m, 2H), 6.89 – 6.77 (m, 2H), 4.94 (q, *J* = 3.2 Hz, 2H), 3.80 (s, 3H), 1.94 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.2, 159.6, 132.9, 115.7, 114.0, 91.1, 85.3, 83.8, 76.2, 55.4, 20.1.

GC/MS 184.1(M^+), (base peak)



MS2-213

1-methyl-4-(3-methylpenta-3,4-dien-1-yn-1-yl)b

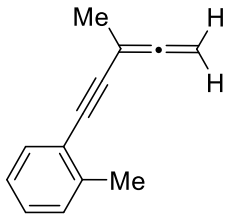
Pale yellow oil isolated from flash chromatography using pentanes as eluent (69 mg, 0.0041 mol, 82%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 2H), 7.16 – 7.03 (m, 2H), 4.95 (q, *J* = 3.2 Hz, 2H), 2.34 (s, 3H), 1.94 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3, 138.3, 131.4, 129.1, 120.5, 91.3, 85.3, 84.6, 763, 21.6, 20.0.

HRMS (H-apci) *m/z:* M+H calcd for $C_{13}H_{13}$: 169.1017 found: 169.1018

IR (neat) ν_{max} 2925, 2208, 1937, 1509, 817 cm^{-1}



MS2-205

1-methyl-2-(3-methylpenta-3,4-dien-1-yn-1 [illegible]f)

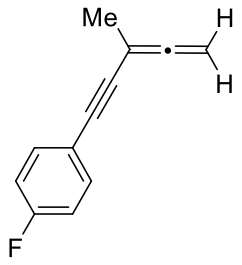
Yellow oil isolated from flash chromatography using pentanes as eluent (63 mg, 0.0037 mol, 75%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.15 – 7.09 (m, 1H), 4.96 (q, *J* = 3.2 Hz, 2H), 2.43 (s, 3H), 1.97 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.2, 140.1, 131.7, 129.5, 128.2, 125.6, 123.3, 90.1, 89.3, 85.4, 76.2, 20.8, 20.1.

GC/MS 168.1(M^+), (base peak)

IR (neat) ν_{max} 2924, 2205, 1940, 756cm^{-1}



MS2-218

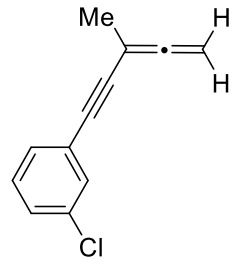
1-fluoro-4-(3-methylpenta-3,4-dien-1-yn-1- g)

Fragrant colorless oil isolated from flash column chromatography using pentanes as eluent (68 mg, 0.0039 mol, 79%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.31 (m, 2H), 7.06 – 6.89 (m, 2H), 4.96 (q, *J* = 3.3 Hz, 2H), 1.94 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.35 (d, *J* = 249.3 Hz), 133.2 (d, *J* = 8.3 Hz), 119.5 (d, *J* = 3.5 Hz), 115.5 (d, *J* = 22.2 Hz), 89.8, 84.9, 76.3, 19.8.

GC/MS 172.1(M^{+}), (base peak)



MS2-072

1-chloro-3-(3-methylpenta-3,4-dien-1-yn-1 2.2h)

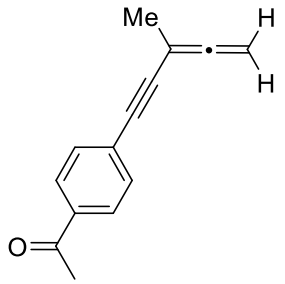
Cloudy yellow oil isolated from flash chromatography using pentanes as eluent (75 mg, 0.0040 mol, 80%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.67 – 6.92 (m, 4H), 4.97 (q, *J* = 3.2 Hz, 2H), 1.93 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.5, 134.2, 131.4, 129.6, 129.6, 128.4, 125.3, 89.6, 86.7, 84.9, 76.5, 19.8.

GC/MS 188.1(M^+), 152.1 (base peak)

IR (neat) ν_{max} 2926, 2214, 1939, 855, 784, 680 cm^{-1}



MS2-214

1-(4-(3-methylpenta-3,4-dien-1-yn-1-yl)phenyl)ethan-1-one (2.2i)

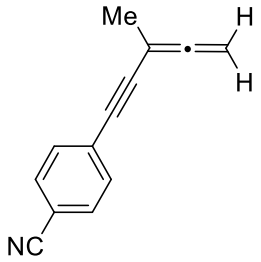
White solid isolated from flash chromatography using 95:5 pentanes:acetone as eluent (66 mg, 0.0034 mol, 68%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 – 7.76 (m, 2H), 7.56 – 7.42 (m, 2H), 4.98 (q, *J* = 3.2 Hz, 2H), 2.59 (s, 3H), 1.95 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.6, 197.5, 136.1, 131.6, 128.5, 128.3, 90.3, 88.9, 84.9, 76.6, 26.8, 19.8.

GC/MS 196.1 (M^+), 181.1 (base peak)

IR (neat) ν_{max} 2920, 2207, 1934, 1684, 1266, 839 cm^{-1}



MS2-071

4-(3-methylpenta-3,4-dien-1-yn-1-yl)benzonitrile (2.2j)

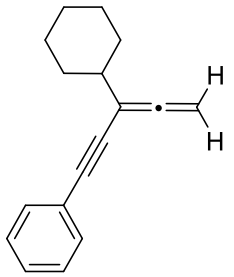
White solid isolated from flash chromatography using 98:2 pentanes:acetone as eluent (60 mg, 0.0033 mol, 67%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 – 7.56 (m, 2H), 7.53 – 7.46 (m, 2H), 5.00 (q, *J* = 3.2 Hz, 2H), 1.95 (t, *J* = 3.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 132.1, 131.9, 128.5, 118.7, 111.4, 90.2, 89.3, 84.7, 76.8, 19.7.

HRMS(H-apci) *m/z:* M+H calcd for $C_{13}H_{10}N$: 180.0813, found: 180.0837

IR (DCM) ν_{max} 2229, 2209, 1935, 1605, 1179 cm^{-1}



MS2-086

(3-cyclohexylpenta-3,4-dien-1-yn-1-yl)b

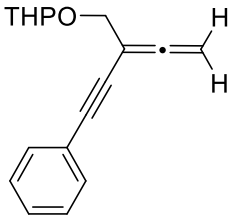
Yellow oil isolated from flash chromatography using pentanes as eluent (109 mg, 0.0049 mol, 98%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 – 7.42 (m, 2H), 7.33 – 7.27 (m, 3H), 5.02 (d, *J* = 2.7 Hz, 2H), 2.10 (ddt, *J* = 14.0, 10.8, 3.0 Hz, 1H), 1.97 – 1.89 (m, 2H), 1.78 (dt, *J* = 11.9, 3.4 Hz, 2H), 1.67 (dtd, *J* = 12.5, 3.3, 1.6 Hz, 1H), 1.38 – 1.13 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 212.9, 131.6, 128.4, 128.1, 123.8, 95.6, 92.3, 84.1, 77.8, 41.0, 31.9, 26.3, 26.2.

GC/MS 222.2(M^+), 55.1 (base peak)

IR (neat) ν_{max} 3060, 2927, 2206, 1936, 1490, 690 cm^{-1}



MS2-160

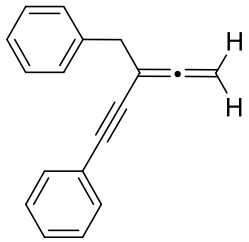
2-((2-(phenylethynyl)buta-2,3-dien-1-yl)oxy)tetrahyd 2l)

Orange oil isolated from flash chromatography using 98:2-97:3 pentanes:acetone gradient as eluent (90 mg, 0.0035 mol, 71%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 – 7.40 (m, 2H), 7.32 – 7.27 (m, 3H), 5.12 (ddd, *J* = 3.0, 2.2, 1.0 Hz, 2H), 4.82 (t, *J* = 3.5 Hz, 1H), 4.33 (dt, *J* = 11.8, 2.8 Hz, 1H), 4.20 (dt, *J* = 11.8, 2.2 Hz, 1H), 3.93 (ddd, *J* = 11.6, 9.1, 3.0 Hz, 1H), 3.55 (dtd, *J* = 11.1, 4.2, 1.6 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.75 (tdd, *J* = 10.2, 4.1, 3.1 Hz, 1H), 1.72 – 1.59 (m, 1H), 1.58 – 1.49 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1, 131.6, 128.4, 128.3, 123.4, 97.4, 92.3, 88.5, 82.7, 78.3, 67.1, 62.1, 30.5, 25.6, 19.3.

GC/MS 170.1(M-THP), 154.1(base peak)



MS2-188

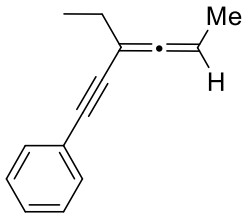
(3-vinylidenebut-1-yne-1,4-diyl)dibenz

Yellow oil isolated from flash chromatography using 100:0-99:1 pentanes:acetone gradient as eluent (45 mg, 0.002 mol, 39%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.15 (m, 9H), 4.95 (t, *J* = 2.7 Hz, 2H), 3.47 (t, *J* = 2.7 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 214.0, 138.6, 131.5, 129.2, 128.4, 128.3, 128.2, 126.7, 123.5, 92.5, 90.1, 84.4, 77.5, 40.3.

GC/MS 230.1(M^+), 91.1 (base peak)



MS2-088

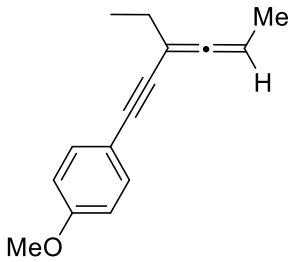
(3-ethylhexa-3,4-dien-1-yn-1-yl)benz

Colorless oil isolated from flash chromatography using pentanes as eluent (25 mg, 0.0014 mol, 27%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.39 (m, 2H), 7.36 – 7.22 (m, 3H), 5.39 (qt, *J* = 7.1, 3.0 Hz, 1H), 2.22 (qd, *J* = 7.4, 3.0 Hz, 2H), 1.74 (d, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3, 131.6, 128.3, 128.0, 123.8, 91.3, 90.5, 88.4, 85.7, 27.4, 14.4, 12.4.

GC/MS 182.2 (M^+), 152.2 (base peak)



MS3-197

1-(3-ethylhexa-3,4-dien-1-yn-1-yl)-4-methoxyl

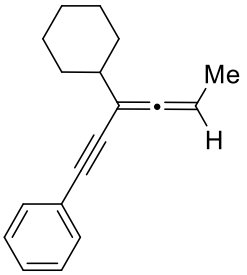
Pale yellow oil isolated from flash chromatography using 98:2 pentanes:acetone as eluent (79 mg, 0.0037 mol, 74%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.34 (m, 2H), 6.88 – 6.79 (m, 2H), 5.38 (qt, *J* = 7.1, 2.9 Hz, 1H), 3.80 (s, 3H), 2.20 (qd, *J* = 7.4, 3.0 Hz, 2H), 1.73 (d, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9, 159.3, 132.8, 115.8, 113.8, 91.3, 90.3, 88.1, 84.1, 55.3, 27.3, 14.4, 12.6.

GC/MS 212.1 (M^+), (base peak)

IR (neat) ν_{max} 2967, 2203, 1947,1606, 1510, 1176, 833 cm^{-1}



MS2-130

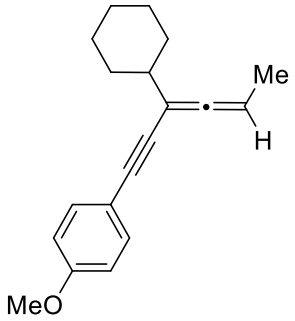
(3-cyclohexylhexa-3,4-dien-1-yn-1-yl)b

Bright yellow oil isolated from flash chromatography using pentanes as eluent (93 mg, 0.0039 mol, 78%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 – 7.40 (m, 2H), 7.33 – 7.24 (m, 3H), 5.39 (qd, *J* = 7.1, 2.5 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.93 (dddt, *J* = 12.5, 5.1, 3.3, 1.9 Hz, 2H), 1.82 – 1.75 (m, 2H), 1.74 (d, *J* = 7.1 Hz, 3H), 1.69 – 1.63 (m, 1H), 1.39 – 1.15 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.9, 131.6, 128.3, 127.9, 123.9, 95.4, 91.1, 88.7, 85.2, 41.6, 32.11 and 32.09 (diastereotopic cyclohexyl CH_2), 26.36 and 26.34 (diastereotopic cyclohexyl CH_2), 26.3, 14.5.

GC/MS 236.2(M^+), 207.1 (base peak)



MS3-215

1-(3-cyclohexylhexa-3,4-dien-1-yn-1-yl)-4-methoxybenzene (2.4d)

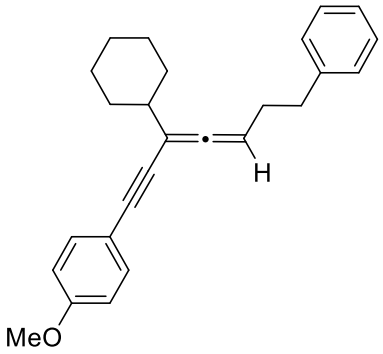
Bright yellow oil isolated from flash chromatography using 98:2 pentanes:acetone as eluent (115 mg, 0.0043 mol, 86%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.36 (m, 2H), 6.84 – 6.81 (m, 2H), 5.38 (qd, *J* = 7.1, 2.5 Hz, 1H), 3.80 (s, 3H), 2.06 (ttd, *J* = 11.0, 3.5, 2.4 Hz, 1H), 1.92 (m, 2H), 1.78 – 1.75 (m, 1H), 1.73 (d, *J* = 7.1 Hz, 3H), 1.66 (m,1H), 1.33 – 1.17 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.7, 159.3, 132.9, 116.1, 113.9, 95.5, 91.0, 88.5, 83.6, 55.4, 41.6, 32.11 and 32.10 (diastereotopic cyclohexyl CH_2), 26.37 and 26.35, (diastereotopic cyclohexyl CH_2) 26.3, 14.6.

GC/MS 266.1(M^+), 237.1(base peak)

IR (neat) ν_{max} 2927, 2852, 2200, 1945, 1606, 1510, 1172, 831 cm^{-1}



MS3-217

1-(3-cyclohexyl-7-phenylhepta-3,4-dien-1-yn-1-yl)-4-methoxybenzene (2.4e)

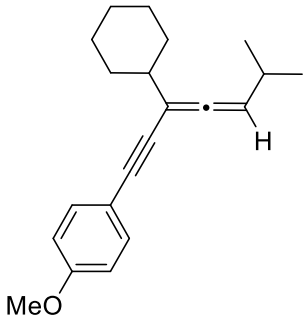
Viscous yellow oil isolated from flash chromatography using 98:2 pentanes:acetone as eluent (105 mg, 0.0029 mol, 59%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.35 (m, 2H), 7.32 – 7.24 (m, 2H), 7.24 – 7.17 (m, 3H), 6.91 – 6.77 (m, 2H), 5.44 (td, *J* = 6.5, 2.4 Hz, 1H), 3.81 (s, 3H), 2.91 – 2.61 (m, 2H), 2.40 (ddt, *J* = 12.7, 8.7, 6.7 Hz, 2H), 2.08 – 1.95 (m, 1H), 1.93 – 1.79 (m, 2H), 1.80 – 1.71 (m, 2H), 1.70 – 1.61 (m, 1H), 1.34 – 1.23 (m, 2H), 1.22 – 1.10 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.1, 159.4, 141.7, 132.9, 128.7, 128.4, 116.1, 113.9, 96.7, 93.2, 91.2, 83.5, 55.4, 41.6, 35.3, 32.07 and 32.06 (diastereotopic cyclohexyl CH_2), 30.8, 26.39 and 26.36 (diastereotopic cyclohexyl CH_2), 26.2.

GC/MS 356.15(M^+), 207.0 (base peak)

IR (neat) ν_{max} 2927, 2852, 2207, 1944, 1606, 1510, 831 cm^{-1}



MS2-129

1-(3-cyclohexyl-6-methylhepta-3,4-dien-1-yn-1-yl)-4-methoxybenzene (2.4f)

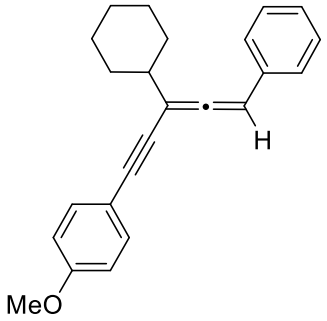
Viscous cloudy yellow oil isolated from flash chromatography using 98:2 pentanes:acetone as eluent (130 mg, 0.0044 mol, 88%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.33 (m, 2H), 6.84 – 6.79 (m, 2H), 5.42 (dd, *J* = 5.7, 2.5 Hz, 1H), 3.80 (s, 3H), 2.38 (pd, *J* = 6.8, 5.7 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.93 (tdd, *J* = 12.9, 3.3, 1.7 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.67 (dtt, *J* = 12.8, 3.3, 1.5 Hz, 1H), 1.37 – 1.13 (m, 5H), 1.06 (dd, *J* = 6.8, 1.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 206.5, 159.3, 132.9, 116.2, 113.9, 101.2, 97.2, 90.7, 83.9, 55.4, 41.8, 32.23 and 32.20 (diastereotopic cyclohexyl CH_2), 28.6, 26.46 and 26.44 (diastereotopic cycohexyl CH_2), 26.3, 22.7, 22.4.

GC/MS 294.3 (M^+), 121.1 (base peak)

IR (neat) ν_{max} 2929, 2208, 1943, 1606, 1510, 1248, 831 cm^{-1}



MS2-261

1-(3-cyclohexyl-5-phenylpenta-3,4-dien-1-yn-1-yl)-4-methoxybenzene (2.4g)

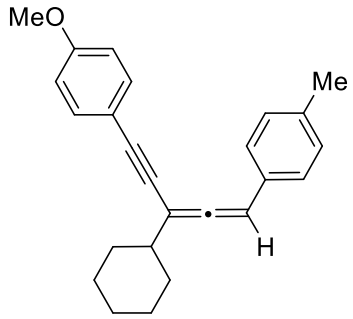
Viscous orange oil isolated from flash chromatography using 99:1 pentanes:acetone as eluent (138 mg, 0.0042 mol, 84%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.36 (m, 2H), 7.35 – 7.30 (m, 4H), 7.25 – 7.20 (m, 1H), 6.86 – 6.80 (m, 2H), 6.42 (d, *J* = 2.5 Hz, 1H), 3.81 (s, 3H), 2.29 – 2.21 (m, 1H), 2.02 (dtdd, *J* = 10.7, 5.5, 3.6, 2.0 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.67 (dtt, *J* = 12.9, 3.2, 1.5 Hz, 1H), 1.39 – 1.24 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.7, 159.6, 134.1, 133.1, 128.8, 127.4, 127.2, 115.8, 113.9, 100.5, 97.2, 92.2, 82.2, 55.4, 42.3, 32.2, 26.4, 26.2.

GC/MS 328.2(M^+), (base peak)

IR (neat) ν_{max} 2927, 2208, 1931, 1606, 1509, 1205, 831 cm^{-1}



MS3-143

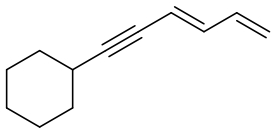
1-(3-cyclohexyl-5-(4-methoxyphenyl)penta-1,2-dien-4-yn-1-yl)-4-methylbenzene (2.4h)

Viscous orange oil isolated from flash chromatography using 99:1 pentanes:acetone as eluent (104 mg, 0.0030 mol, 61%)

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.34 (m, 2H), 7.24 – 7.20 (m, 2H), 7.16 – 7.10 (m, 2H), 6.88 – 6.74 (m, 2H), 6.40 (d, J = 2.5 Hz, 1H), 3.80 (s, 3H), 2.34 (s, 3H), 2.27 – 2.18 (m, 1H), 2.04 – 1.98 (m, 2H), 1.83 – 1.72 (m, 2H), 1.69 – 1.63 (m, 1H), 1.39 – 1.26 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 210.4, 159.5, 137.3, 133.2, 131.0, 129.6, 127.1, 115.9, 113.9, 100.3, 97.0, 91.9, 82.4, 55.4, 42.3, 32.2, 26.4, 26.2, 21.4.

GC/MS 342.2(M^+), (base peak)



MS2-118

(E)-hexa-3,5-dien-1-yn-1-ylcyclohexane

^{1}H NMR (400 MHz, Chloroform-d) δ 6.80 (dt, J = 17.0, 10.5 Hz J = 10.8 Hz, 1H), 5.41 (d, J = 10.6 Hz, 1H), 5.26 (d, J = 17.1 Hz, 1H), 5.14 (d, J = 10.5 Hz, 1H), 2.48 (m, 1H), 1.76 (m, 2H), 1.65 (m, 2H), 1.42 (m, 3H), 1.30 – 1.23 (m, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 139.2, 134.3, 119.5, 110.8, 101.4, 97.8, 32.9, 30.1, 26.0, 25.0.

GC/MS 160.2(M^+), 91.9 (base peak)

References for Chapter 2 Appendix

(1) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. Enantioselective synthesis of axially chiral phthalides through cationic [RhI(H8-BINAP)]-catalyzed cross alkyne cyclotrimerization. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510-6512.

(2) Park, K.; You, J.-M.; Jeon, S.; Lee, S. Palladium-catalyzed Sonogashira reaction for the synthesis of arylalkynecarboxylic acids from aryl bromides at low temperature. *Eur. J. Org. Chem.* **2013**, *2013*, 1973-1978.

(3) Trost, B. M.; Livingston, R. C. An Atom-Economic and Selective Ruthenium-Catalyzed Redox Isomerization of Propargylic Alcohols. An Efficient Strategy for the Synthesis of Leukotrienes. *J. Am. Chem. Soc.* **2008**, *130*, 11970-11978.

(4) Giacomina, F.; Alexakis, A. Construction of Enantioenriched Cyclic Compounds by Asymmetric Allylic Alkylation and Ring-Closing Metathesis. *Eur. J. Org. Chem.* **2013**, *2013*, 6710-6721.

(5) Linstadt, R. T. H.; Peterson, C. A.; Lippincott, D. J.; Jette, C. I.; Lipshutz, B. H. Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature. *Angew. Chem., Int. Ed.* **2014**, *53*, 4159-4163.

(6) Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. Regiocontrol of the Palladium-Catalyzed Tin Hydride Addition to Z-Enynols: Remarkable Z-Directing Effects. *J. Org. Chem.* **2007**, *72*, 3868-3874.

(7) Zhang, W.-Z.; Li, W.-J.; Zhang, X.; Zhou, H.; Lu, X.-B. Cu(I)-Catalyzed Carboxylative Coupling of Terminal Alkynes, Allylic Chlorides, and CO2. *Org. Lett.* **2010**, *12*, 4748-4751.

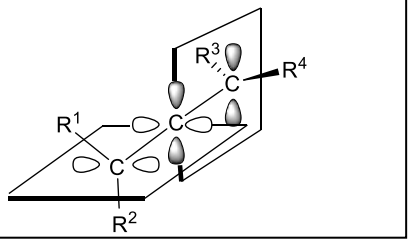
(8) Aoyagi, S.; Koyanagi, M.; Takahashi, M.; Shimada, K.; Takikawa, Y. Generation of allenylthioketene S,S-dioxides through [3,3] sigmatropic rearrangement of alkynyl propargyl sulfones. *Tetrahedron Lett.* **2007**, *48*, 1915-1918.

Chapter 3: Studies of the Stereochemical Outcome of the Palladium-Catalyzed Decarboxylative Coupling of Propargyl Propiolates

3.1 Introduction

A unique property of allenes that sets them apart from many other functional groups that they have the potential to possess axial chirality (Figure 3.1). Allenes were first predicted to possess axial chirality by van't Hoff in 1875,[1] however the optical activity of the allene structure was not experimentally confirmed until 1935 when the first chiral allenes were synthesized by Maitland and Mills.[2] Currently, non-racemic allenes continue to be attractive synthetic targets, as they can be found in an ever growing list of natural products and molecular materials. They have even been used as a chiral ligand.[3,4] Further, enantioenriched allenes are prone to efficiently transfer their axial chirality to centrally chiral stereocenters. This combined with allenes' unique reactivity profile suggests that enantioenriched allenes have the potential to be powerful chiral building blocks in synthesis.

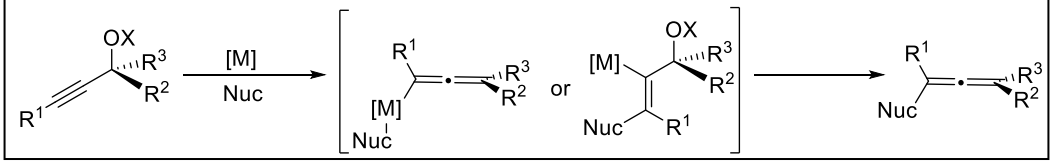
Figure 3.1: ***Allenes Possess Axial Chirality***



Unfortunately, the development of applications for axially chiral allenes as synthetic intermediates has been sluggish due to the limited availability of enantioenriched allenes.[5,6] Currently, there are only a few reliable, broadly applicable ways to synthesize enantioenriched allenes, thus the development of new and/or improved methods is still an area of active research. [7-12] Both stereoselective and stereospecific transition metal-catalyzed methods have been developed to synthesize enantioenriched allenes. However, because of the abundance of ways to prepare chiral propargyl alcohols,[13-21] stereospecific transformations of chiral propargyl alcohol derivatives

remain the most convenient and commonly used methods to synthesize enantioenriched allenes (Scheme 3.2).

Scheme 3.2: ***Stereospecific Transformations of Alcohol Derivatives***



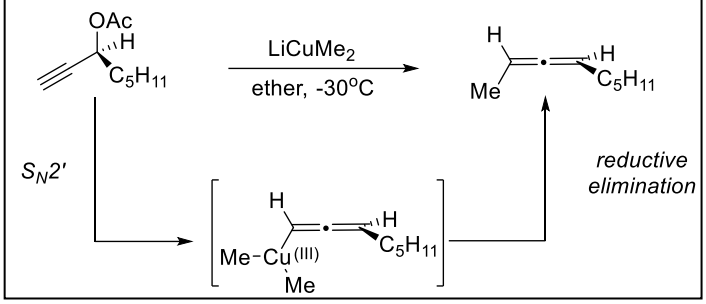
This chapter will review transition metal-catalyzed stereospecific syntheses of enantioenriched allenes from propargyl alcohol derivatives as well as explore the issue of racemization which commonly plagues these transition metal catalyzed transformations. In addition, our contributions to the knowledge and understanding of palladium-catalyzed stereospecific allene synthesis and racemization are detailed herein.

3.2 Stereospecific Transformations of Propargyl Alcohol Derivatives

3.2.1 Copper-Catalyzed Transformations

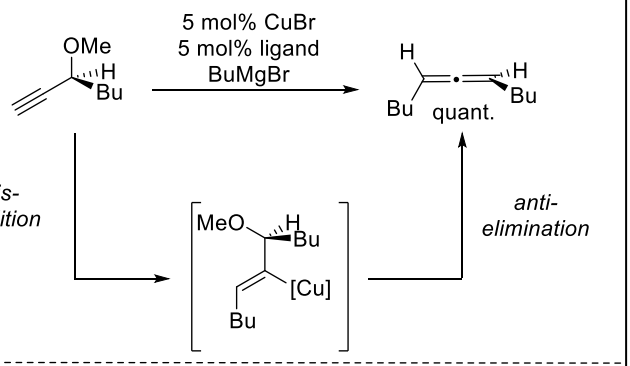
Crabbé and coworkers first presented evidence in 1975 that the copper-mediated transformation of propargyl acetate to form allenes (presented in chapter 1, section 1.3.2) occurred in a stereospecific manner.[22]They found that treating an (*S*)-configured propargyl acetate with lithium dimethylcuprate yielded the (*R*)-configured allene (Scheme 3.3). This led them to suggest that the copper-carbon bond forms via an *anti*-preferential S_N2' mechanism which is followed by reductive elimination with retention of configuration. Unfortunately the stereospecificity for this reaction is not reported.

Scheme 3.3: ***Stereospecific Copper-Mediated Addition***



In 1985 Alexakis *et al.* began examining the mechanism of the stereospecific coupling of propargylic alcohol derivatives and Grignard reagents catalyzed by copper salts.[23] They determined that when the derivative contained a poor leaving group such as an ether, the copper reaction, while still stereospecific for *anti*-products, proceeded through a different mechanism than proposed above (Scheme 3.4). This alternative mechanism involved the *syn* addition of the organocopper reagent across the triple bond. The resulting copper-alkene complex then collapses via *anti* elimination leading to an overall *anti*-displacement product. Initially these reactions suffered from racemization of the allene, but Alexakis and coworkers were able to demonstrate that utilization of phosphine ligands suppressed the undesired racemization reaction. Further studies showed that the stereospecificity of the reaction, described as the conservation of enantiomeric excess (*cee*), was significantly affected when almost any aspect of the reaction, such as the leaving group, copper source or Grignard reagent, was varied.[24,25]

Scheme 3.4: ***Stereospecific Addition-Elimination***



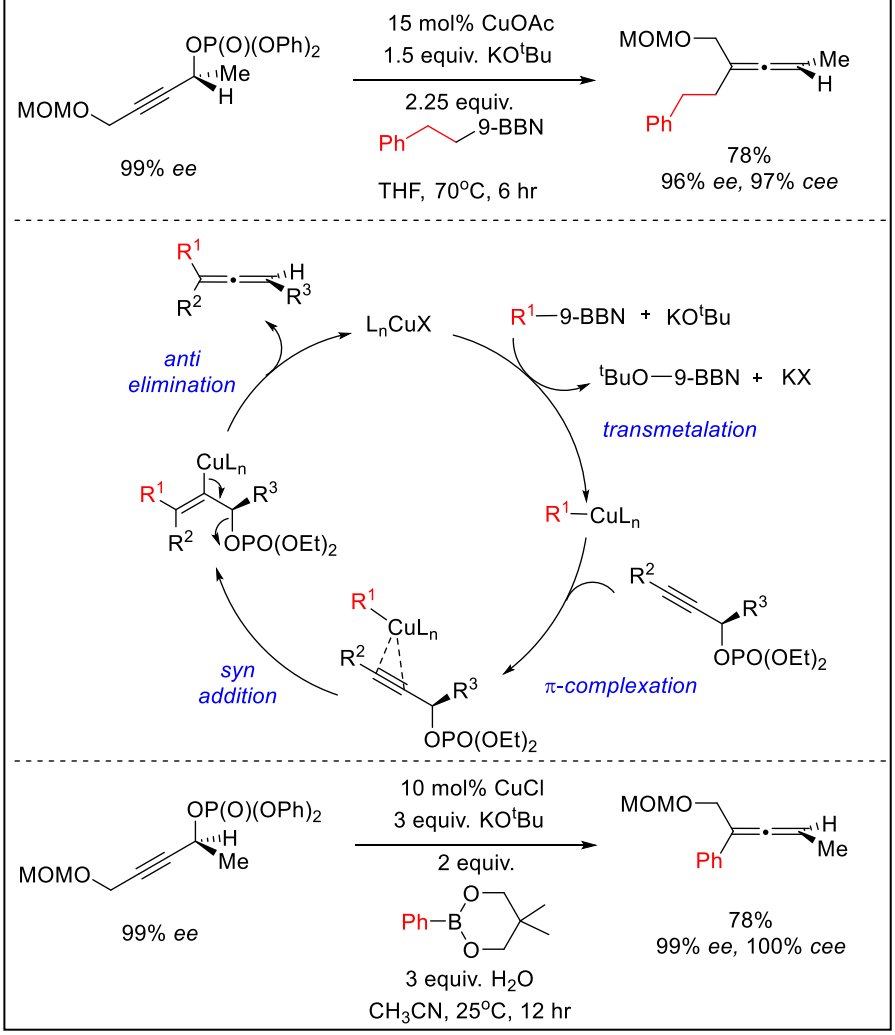
Ligand	Amount	%cee
none	-	16%
$P(OEt)_3$	10 mol%	43%
$P(NMe_2)_3$	5 mol%	55%
$P(NMe_2)_3$	10 mol%	72%
$P(Bu)_3$	5 mol%	80%
$P(Bu)_3$	10 mol%	90%

$$cee = \frac{\text{Product } ee}{\text{Reactant } ee}$$

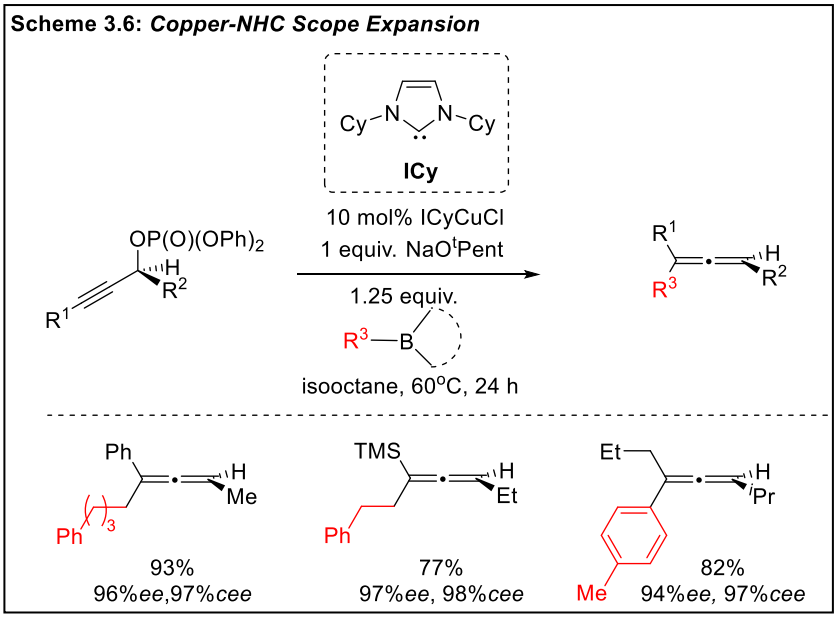
In 2011, Sawamura and coworkers sought to improve the scope and selectivity of the reactions mentioned above by developing a copper-catalyzed stereospecific reaction of propargyl electrophiles with boron nucleophiles that were much more functional group tolerant.[26] They reported that CuOAc catalyzed the coupling of chiral propargyl phosphates with alkyl-9BBN reagents to form enantioenriched allenes (Scheme 3.5). They proposed that after initial transmetalation between copper and the boronate formed from the alkyl borane, the carbon-copper species could then coordinate to the triple bond. After complexation the reaction then proceeds through an addition-elimination sequence similar to that proposed by Alexakis allowing for the high stereospecificity to be observed. The next year they expanded the scope to alkenyl and aryl boronates with only minor changes to the reaction conditions.[27] Interestingly, only one chiral

propargyl phosphate, which contained a protected alcohol at the terminal position, was examined in Sawamura's reports. It is unclear whether the protocol is limited to this substrate.

Scheme 3.5: ***Copper-Catalyzed Stereospecific Addition***



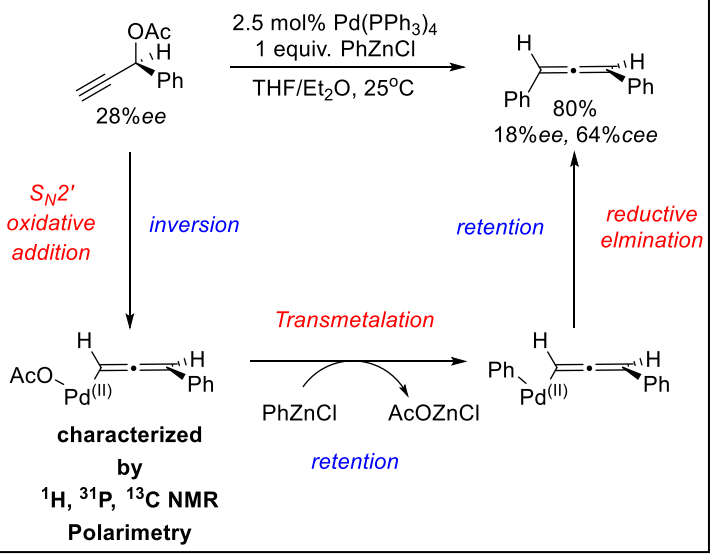
Almost simultaneously, Lalic and coworkers published a similar transformation utilizing copper-NHC complexes (Scheme 3.6).[28] They reported a wider scope of chiral propargyl phosphates with equally successful stereospecificity. Both methods had similar scopes of nucleophiles and furnished enantioenriched allenes from chiral propargylic phosphates with very high stereospecificity. Further, unlike the methods that involved organocuprates, neither Sawamura nor Lalic observed any racemization of the allenyl products.



3.2.2 Palladium-Catalyzed Transformations

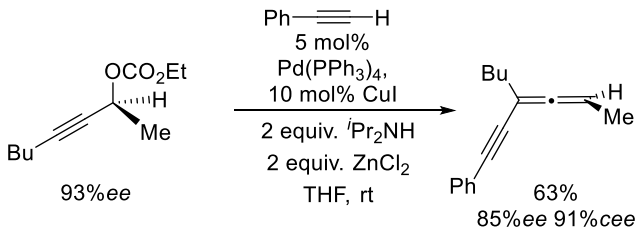
Palladium has also been used as a catalyst for stereospecific transformations of propargylic alcohol derivatives. In the 1980's Vermeer and coworkers investigated the stereochemical outcome of the palladium-catalyzed substitution of enantioenriched propargyl esters with organozinc compounds. Initial studies found that the coupling of chiral propargylic acetates could occur with modest stereospecificity, yielding allenes with inverted configuration.[29] It was hypothesized that oxidative addition to palladium occurs in an anti S_N2' fashion leading to an η^1-allenyl palladium complex. That complex then undergoes transmetalation with the organozinc reagent followed by reductive elimination resulting in the enantioenriched allene. Both transmetalation and reductive elimination occur with retention thus delivering the allene with overall inversion (Scheme 3.7). This hypothesis was later confirmed in 1986 when Vermeer and coworkers isolated the η^1-allenyl palladium complex and observed inverted stereochemistry (assigned on the basis of Lowe-Brewster rules[30,31]) compared to that of the optically pure starting propargyl acetate.[32] This protocol was later applied to chiral fluorinated propargyl esters with much higher specificity.[33]

Scheme 3.7: ***Palladium-Catalyzed Addition of Organozinc***



Further indication that previously developed palladium-catalyzed methods of allene formation could occur in a stereospecific manner came from Dixneuf and coworkers in 1997. When they applied the Sonogashira conditions developed by Tsuji,[34] to a chiral propargyl carbonate derived from the alcohol prepared by enzymatic resolution, they obtained the enantioenriched allenynes with high conservation of enantiomeric excess (Scheme 3.8).[35]

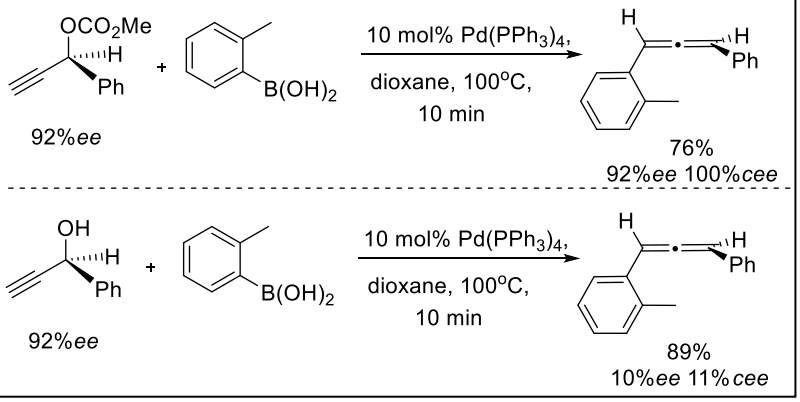
Scheme 3.8: ***Stereospecific Sonogashira Coupling of Propargylic Carbonates***



Yoshida and coworkers reported in 2004 that the palladium-catalyzed coupling of enantioenriched propargyl carbonates with aryl boronic acids proceeded with perfect stereospecificity to the allene with inverted configuration.[36] Interestingly, the leaving group had a significant effect on the specificity of the reaction. When the carbonate was replaced with the alcohol the enantiomeric purity of the product was significantly decreased (Scheme 3.9). It was suggested that after activation of the propargyl alcohol by boronic acid, the attack of palladium could potentially occur

on a propargyl carbocation, thus leading to a significant loss of stereochemical information. Further studies in 2007 also struggled with racemization as it was observed that choice of leaving group, solvent, nucleophile and substitution of the propargyl substrate could lead to significantly diminished optical purity of the allene.[37]

Scheme 3.9:*Leaving Group Dependence*

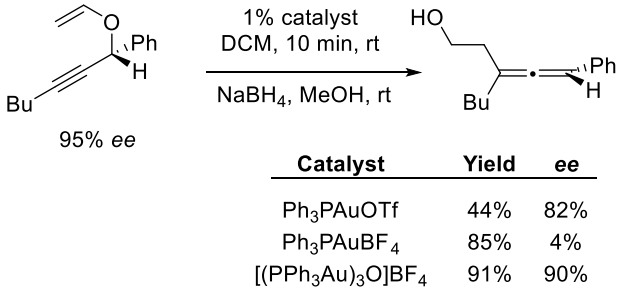


3.2.3 Other Transition Metal-Catalyzed Transformations

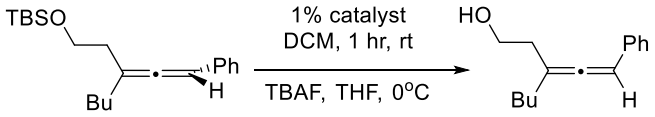
While copper and palladium are the most commonly used transition metals in catalytic methods to prepare chiral allenes from enantioenriched propargylic alcohol derivatives, methods have been reported utilizing other metals which will be described herein. In 2004, Toste and Sherry reported a gold-catalyzed stereospecific propargyl Claisen rearrangement which yielded enantioenriched allenes.[38] Catalyst choice significantly affected the chirality transfer from the propargylic ether to the allene (Scheme 3.10). While Ph_3PAuBF_4 successfully catalyzed the Claisen rearrangement, only racemic product was isolated. Changing the catalyst to gold-oxo complex $[(Ph_3PAu)_3O]BF_4$ afforded the desired allene with high stereospecificity. It was further

demonstrated that the poor chirality transfer observed with Ph_3PAuBF_4 was due to rapid racemization of the allene by the catalyst.

Scheme 3.10: ***Gold-Catalyzed Propargyl Claisen***

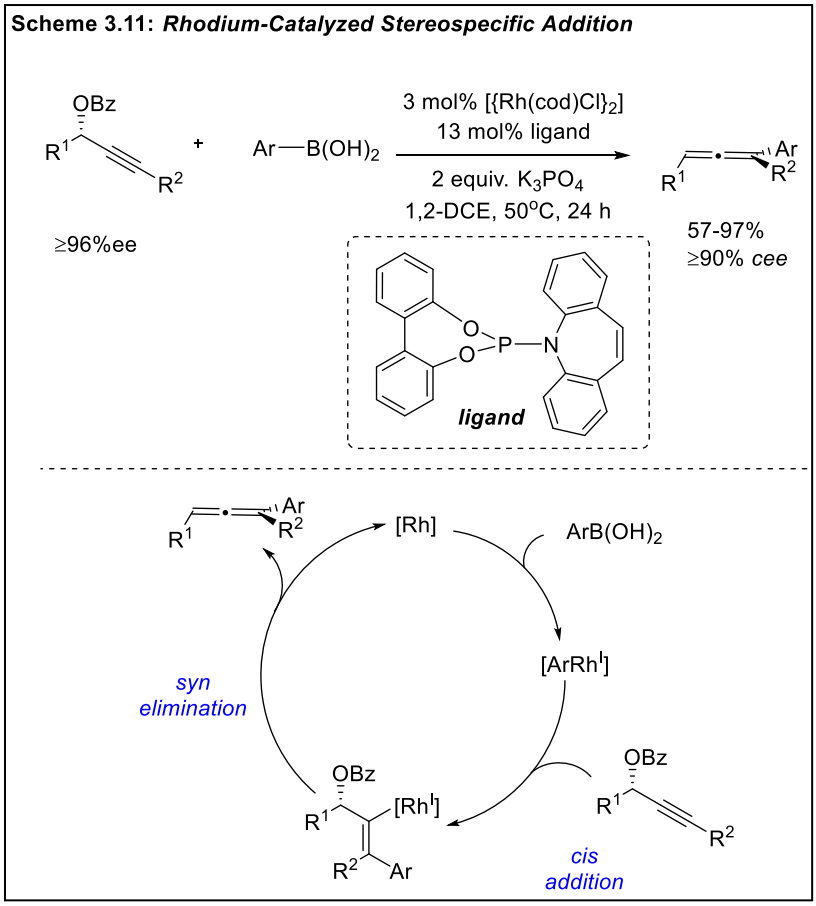


Catalyst	Yield	ee
$Ph_3PAuOTf$	44%	82%
Ph_3PAuBF_4	85%	4%
$[(PPh_3Au)_3O]BF_4$	91%	90%



Catalyst	ee
$Ph_3PAuOTf$	4%
Ph_3PAuBF_4	0%
$[(PPh_3Au)_3O]BF_4$	67%

In 2016, Carreira and coworkers reported a stereospecific coupling of propargylic benzoates and arylboronic acids catalyzed by rhodium.[39] While the reaction conditions were highly engineered and specific to the system (base, ligand to catalyst ratio, and solvent all affected the level of chirality transfer), the reaction produced enantioenriched allenes in high yields with high enantiospecificity. Carreira accounts for the observed absolute configuration of the allenes by proposing a regioselective arylrhodation followed by a selective *syn*-elimination (Scheme 3.11).

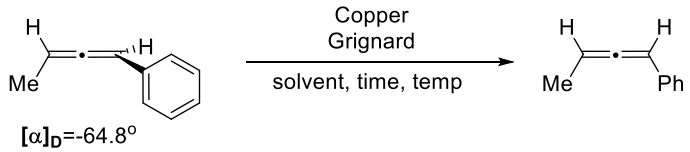


3.3 Transition-Metal Catalyzed Racemization of Allenes

It should be emphasized again that many of the above-mentioned transition metal-catalyzed stereospecific couplings suffer from significant amounts of racemization of the desired enantioenriched allene. Racemization is common in stereospecific transition metal-catalyzed transformations potentially because equilibriating intermediate metal complexes could provide low energy pathways for racemization to occur. Of the transition metals utilized in the methods above, copper, gold, and palladium have all been reported to racemize enantioenriched allenes and studies to understand their mechanisms have been undertaken. In this section, the various studies of the mechanism of these transition metal-catalyzed racemizations will be reviewed and discussed.

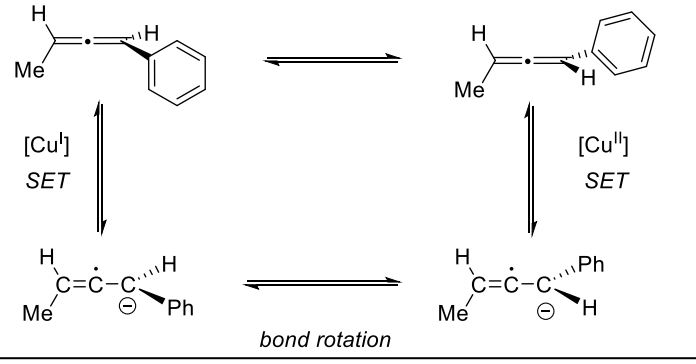
Early reports by Crabbé and others[40] observed stereospecific transformations of propargylic alcohol derivatives with organocuprates, but noted that a variety of factors could affect the optical purity of the enantioenriched allene product. In 1978, Claesson and coworkers determined that a major contributor to the loss of stereochemical information was, in fact, the racemization of the chiral allene by organocuprates.[41] While Grignard reagents, often included in the coupling reactions to form the cuprates *in situ*, had little effect on the stereochemistry of the allene, the organocuprates significantly racemized the enantioenriched allene (Scheme 3.12). Claesson proposed that the racemization occurred via an isomerization of the radical anion formed from a single electron transfer (SET) from the organocopper to the allene. Vermeer and coworkers published further support for this mechanism when they observed that while Me_2CuLi racemized trisubstituted allenes, MeCu did not.[42] There is also evidence that copper(0), which could be

Scheme 3.12: ***Organocopper Racemizes Allene***



$[\alpha]_D$=-64.8°

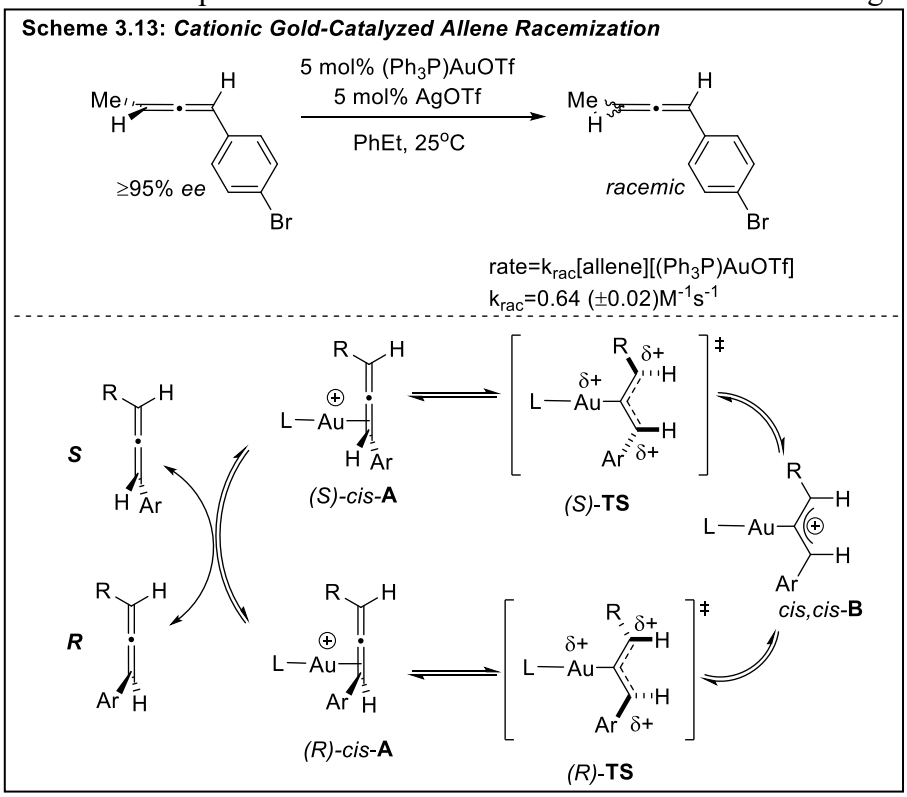
Copper (equiv)	Grignard (equiv)	Solvent	Time (h)	Temp °C	Final $[\alpha]_D$
$LiCuBu_2$ (2)	none	THF	0.5	-65	-20.3
$LiCuBu_2$ (2)	none	THF	4	-30	-5.3
CuBr (0.2)	EtMgBr (2)	Et_2O	4	-30	-39.1
CuBr(0.2)	EtMgBr (2)	Et_2O-THF	6	-30	-0.1
none	EtMgBr (2)	Et_2O-THF	4	+20	-62.9



formed by decomposition of the cuprate, complexes to the central carbon of the allene, thus allowing for bond rotation and racemization.[43]

Gold-catalyzed racemization of allenes is another well-documented occurrence, as gold is a common catalyst in various reactions for functionalization of allenes.[44,45] In an effort to understand the mechanism of the racemization on an experimental level, Widenhoefer and coworkers undertook extensive kinetic and binding studies related to the reaction of enantioenriched allenes with cationic gold catalysts.[46,47] These studies established that there was a first order dependence on the concentration of the enantioenriched allene as well as the concentration of the gold catalyst, thus allowing for an overall second order rate law for the reaction (Scheme 3.13). Hammett plots indicated that during the rate limiting transition state there was less electron density at the terminal carbons, which supported the proposed achiral η^1-allylic cation intermediate. Combining these observations with previous work, Widenhoefer proposed a mechanism that involves rapid and reversible interconversion of isomeric gold η^2-allene

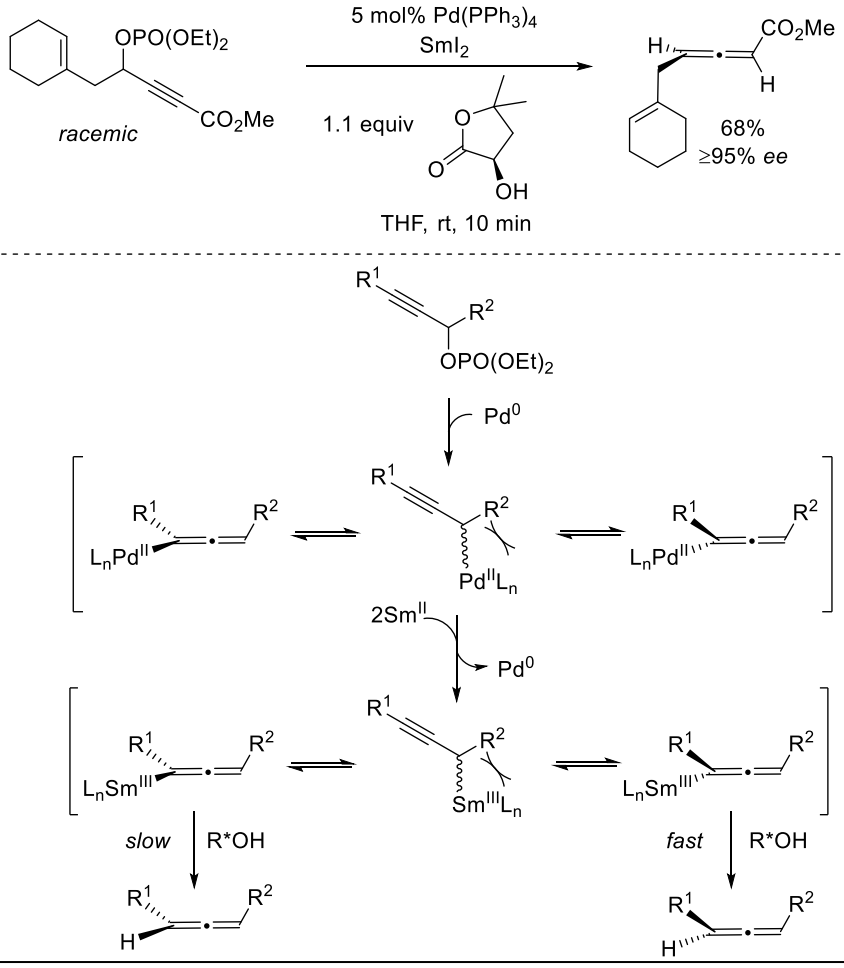
Scheme 3.13: ***Cationic Gold-Catalyzed Allene Racemization***



complexes (*cis*-**A**) that is then followed by conversion to the achiral η^1-allylic cation intermediate (*cis,cis*-**B**) via a bent and twisted transition state (**TS**).

In its utilization in allene synthesis, palladium has also been shown to affect the stereopurity of the enantioenriched allenyl products. One of the most commonly employed explanations for the loss of chiral information is rapid racemization of the η^1-allenylpalladium species. Mikami proposed that this occurs through an isomerization to the η^1-propargylpalladium species, where the bond could freely rotate leading to racemization.[48] This proposed mechanism was useful in their report in which they achieved dynamic kinetic protonation of the racemic allenylmetal intermediate (Scheme 3.14). However, it is also highly possible that the samarium

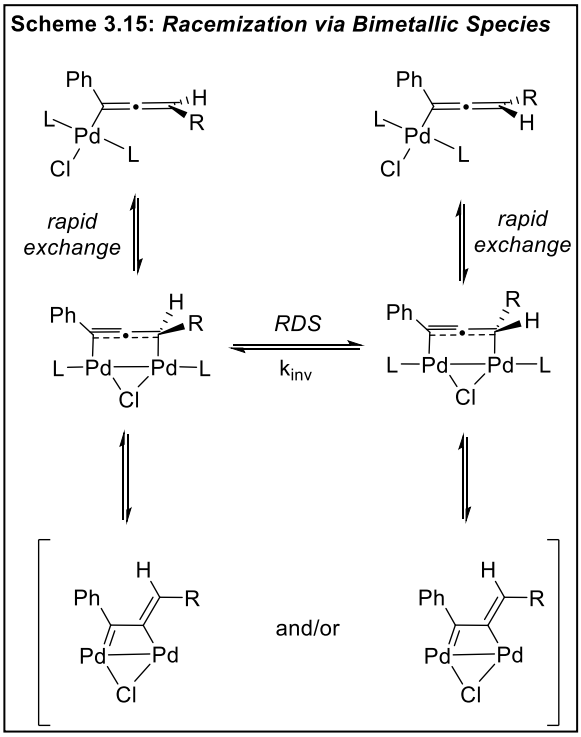
Scheme 3.14: ***Dynamic Kinetic Protonation***



complexes and not the palladium complexes undergo racemization as both species are potential intermediates before the asymmetric protonation step.

Ogoshi, Kurosawa, and coworkers also reported a potential mechanism for the rapid racemization of the η^1-allenylpalladium species.[49] It was hypothesized that the enantioenriched η^1-allenylpalladium species could racemize over time via allenyl ligand exchange with a configurationally labile μ-η^3-allenyl/propargyldipalladium complex (Scheme 3.15). In these studies it was determined that the presence of oxygen accelerated the racemization whereas the introduction of additional PPh_3 into the reaction suppressed it.

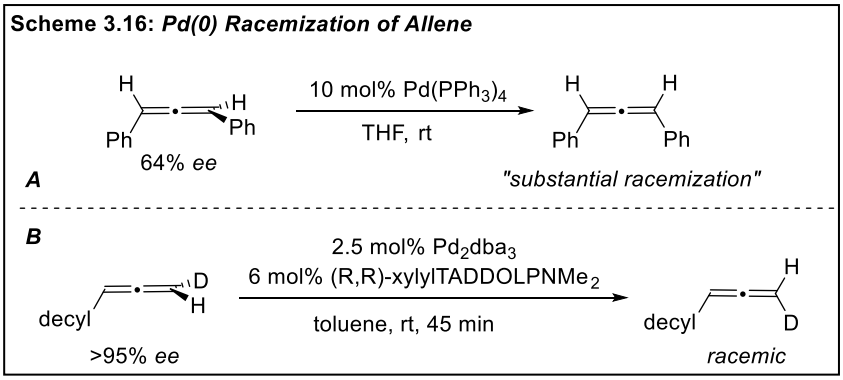
Scheme 3.15: ***Racemization via Bimetallic Species***



The reports above suggest that the lack of chirality transfer observed in a number of what should be stereospecific palladium-catalyzed transformation of propargyl alcohol derivatives is due to a racemization of the palladium-bound intermediate. In contrast to this hypothesis, there have been many instances of palladium catalyzing the racemization of enantioenriched allenes. During their studies in 1986 Vermeer and coworkers were disappointed to find that they were unable obtain the enantioenriched phenyl allene by treating the enantioenriched allenylpalladium complex with

phenylzinc.[32] They proposed that the equimolar amount of $Pd(PPh_3)_2$ released during the addition could be the culprit behind the racemization. Further investigation into the issue showed that just 10 mol% of $Pd(PPh_3)_4$ significantly racemized the diaryl allene (Scheme 3.16_A). Palladium(0)-catalyzed racemization of allenes was further confirmed by Morken *et al.* in 2007[50] (Scheme 3.16_B).

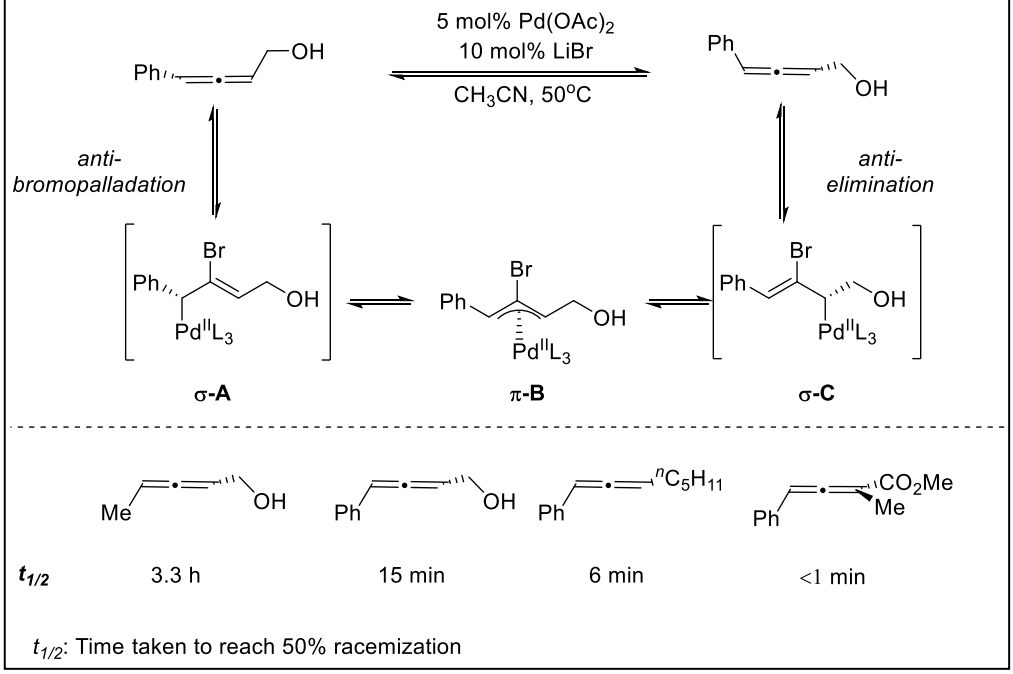
Scheme 3.16: ***Pd(0) Racemization of Allene***



Bäckvall and coworkers have also observed palladium-catalyzed racemization of allenes, contributing to the hypothesis that the lack of chirality transfer from propargyl alcohol derivatives to allene products could be a result of product racemization rather than from racemization of a reactive intermediate. In 2001, it was reported that $Pd(OAc)_2$ and LiBr racemized α-acetoxy allenes, which were being utilized as starting materials in the stereoselective synthesis of 2-bromo-1,3-dienes.[51] In 2004, Bäckvall *et al.* went on to study and develop a general method for the palladium(II)-catalyzed racemization of allenes with the intent to employ the racemization in DKR processes.[52] Initial studies showed that while $PdBr_2(PhCN)_2$ catalyzed the racemization, the reaction stalled at 75-80% completion. Changing the catalyst to the system employed in their previous paper (5 mol% $Pd(OAc)_2$ and 10 mol% LiBr) yielded over 90% racemization. By screening different allenes, it was observed that the racemization was more rapid for allenes with a phenyl substituent, and the most rapid for a trisubstituted allene, also containing a phenyl substituent (Scheme 3.17). Bäckvall proposed that the racemization occurs through a mechanism that begins with the *anti*-bromopalladation of one of the double bonds of the allene. The resulting

palladium complex (**A**) could then rearrange via the σ-π-σ isomerization known for palladium-allyl complexes. *Anti*-elimination from complex **C**, would form the enantiomeric allene thus resulting in racemization.

Scheme 3.17: ***Palladium(II)-Catalyzed Racemization***

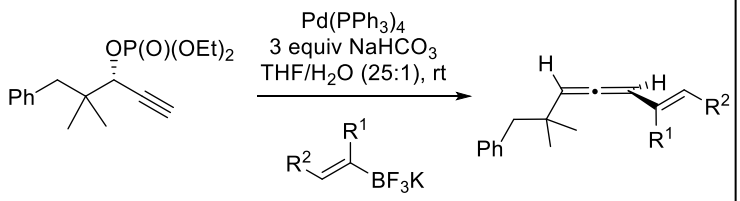


$t_{1/2}$: Time taken to reach 50% racemization

In 2006, Molander and coworkers envisioned a stereospecific coupling of enantioenriched propargyl alcohol derivatives and alkenyl trifluoroborates.[53] Unfortunately, coupling an enantioenriched propargyl carbonate with a phenyl-substituted vinyl trifluoroborate yielded only racemic products. Changing the leaving group allowed for the isolation of enantioenriched allene, but in only modest *ee*. Additionally, changing the nucleophile to vinyl trifluoroborate sped up the coupling reaction. With both nucleophiles, initial formation of the allene occurred with high stereospecificity, but as the reaction was allowed to proceed for longer reaction times, a loss of *ee* was observed. Because the allene is generated in high *ee* initially, Molander proposes that the racemization is not proceeding via the mechanisms reported by Mikami or Ogoshi discussed above. Unfortunately, Molander does not rule out Bäckvall's mechanism, but also doesn't suggest any alternative mechanisms for racemization. Further this reaction still does not satisfy the need

for a general protocol to synthesize enantioenriched allenes. While allenes can be obtained in high *ee*, the conditions must be altered depending on the nucleophile, requiring optimization for every desired product. (Scheme 3.18)

Scheme 3.18: ***Dependence on Nucleophile***



trifluoroborate	catalyst mol%	time min	product yield %	%*ee*
R^1,R^2=H	2	1.75	80	94
R^1=Me R^2=H	2	10	52	76
R^1=H R^2=Ph	10	2	42	32
R^1=H R^2=$(CH_2)_3CN$	10	20	45	87
R^1=H R^2=$(CH_2)_3CN$	5	20	53	91

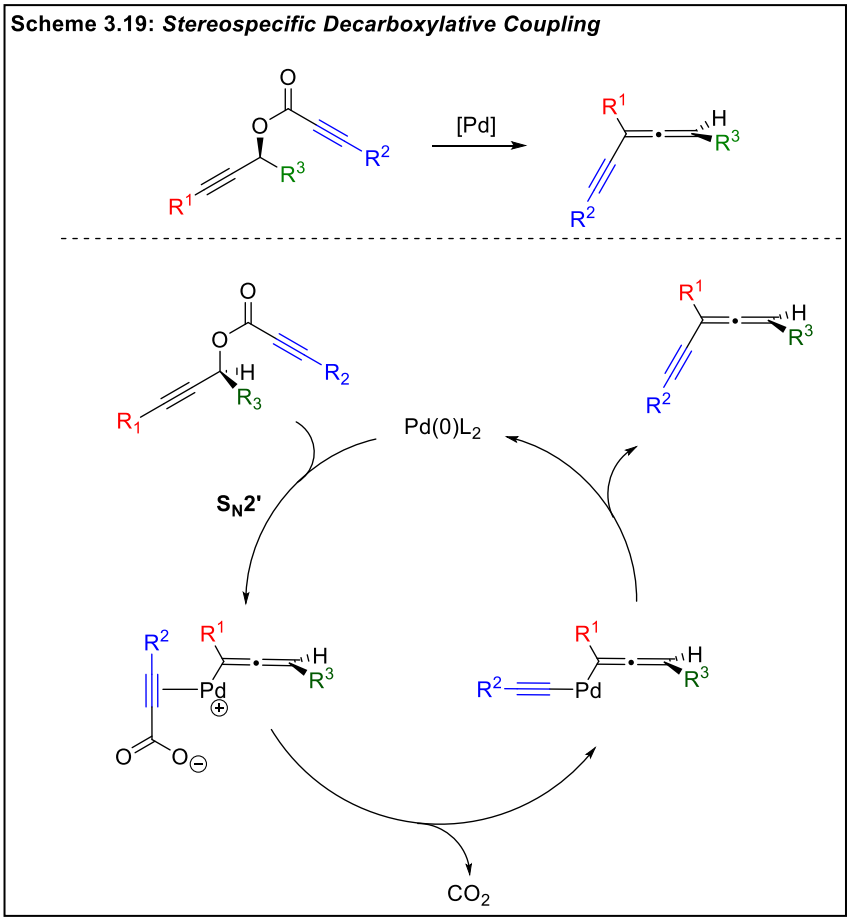
While many of the reactions above are efficient methods for synthesizing enantioenriched allenes, many of them are highly engineered for specific substrates in order to achieve high stereopurity of the desired allenes, and racemization is still a common occurrence. Development of new, potentially general, methods for the synthesis of enantioenriched allenes is still a desirable goal.

3.4 Development of the Stereospecific Decarboxylative Coupling

As discussed in Chapter 2, decarboxylative coupling has advantages over traditional transition metal catalyzed coupling, in that it does not require preformed organometallics or basic reagents. Many of the above described methods are stereospecific variants of traditional cross-coupling reactions. The development of a palladium-catalyzed decarboxylative coupling to synthesize enantioenriched allenes would provide a mild, atom-economic alternative. Because it has been observed that attack of palladium addition on propargyl electrophiles occurs in a S_N2' fashion, we envisioned that the decarboxylative coupling developed in Chapter 2 could occur

stereospecifically from chiral propargyl esters (Scheme 3.19). To the best of our knowledge, there are no examples of stereospecific palladium-catalyzed decarboxylative couplings of propargylic alcohol derivatives to form enantioenriched allenes in the literature to date.

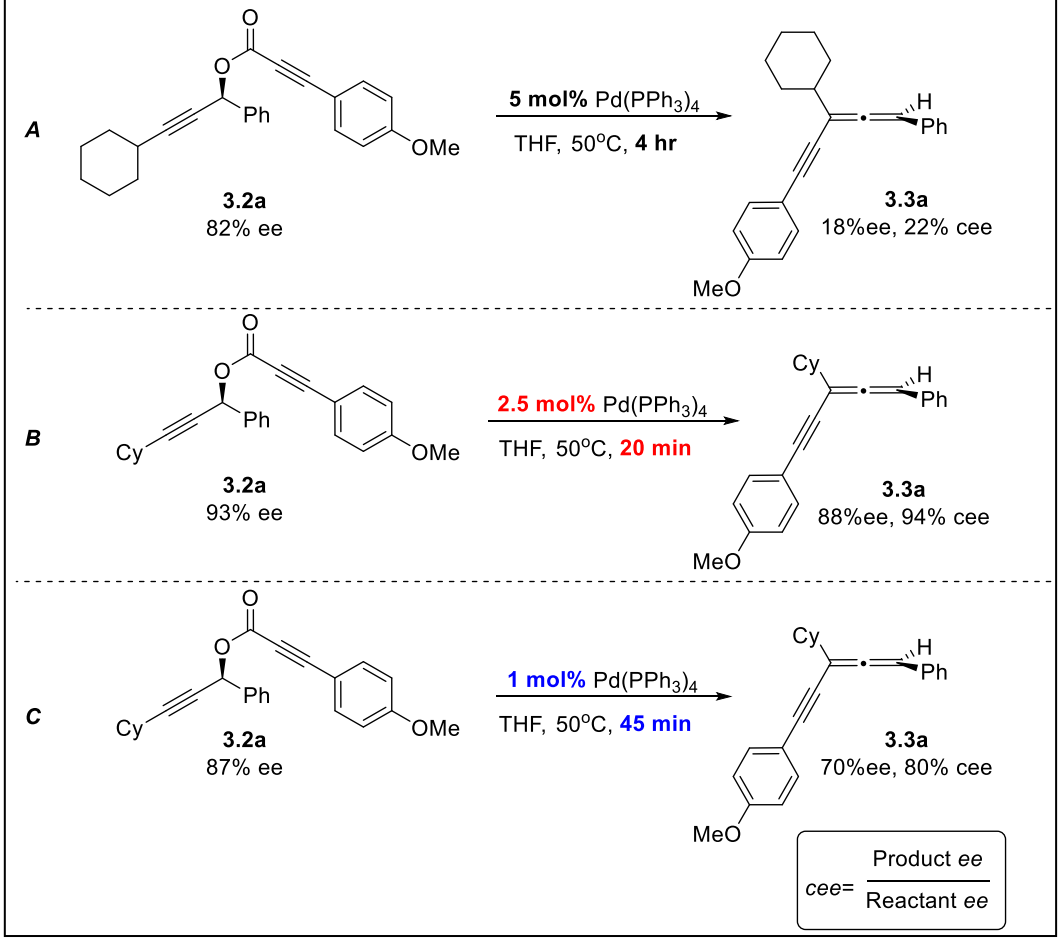
Scheme 3.19: ***Stereospecific Decarboxylative Coupling***



To begin our studies of the stereospecific palladium-catalyzed decarboxylative coupling, we first synthesized the enantioenriched propargyl ester **3.2a** from the corresponding propargylic alcohol **3.1a**.[18] Disappointingly, attempting the stereospecific coupling under the optimized conditions reported in Chapter 2 (5 mol % $Pd(PPh_3)_4$ in THF over 4 hours) resulted in the isolation of nearly racemic **3.3a** (Scheme 3.20_A). We were relieved to discover, however, that decreasing the catalyst loading by half, as well as limiting the reaction time to 20 minutes allowed for the stereospecific coupling to occur, yielding the enantioenriched allenyne in 88% *ee* with 94% conservation of enantiomeric excess (*cee*) (Scheme 3.20_B). Hoping to achieve complete

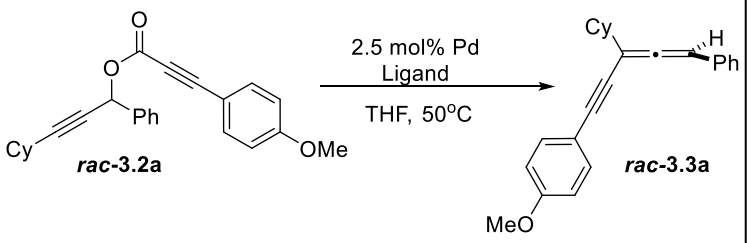
stereospecificity, the catalyst loading was further lowered to 1 mol %, but this resulted in a longer reaction time (45 min) in order to achieve full conversion. The longer reaction time resulted in a diminished *cee*, suggesting that slower coupling rates allow more time for the racemization of the product allene to occur (Scheme 3.20_C).

Scheme 3.20: ***Initial Studies of Stereospecific Coupling***



With this observation, we hypothesized that if we could increase the speed at which the coupling occurred, we could outpace the racemization and isolate allenynes with higher stereospecificity. A variety of palladium sources and ligands were screened as catalysts in the presence of racemic **3.2a** with this goal in mind. Unfortunately, every palladium-ligand combination tested led to an increase in reaction time, thus we hypothesized they would be unsuccessful candidates to catalyze the stereospecific reaction (Table 3.1).

Table 3.1: ***Ligand Screening***

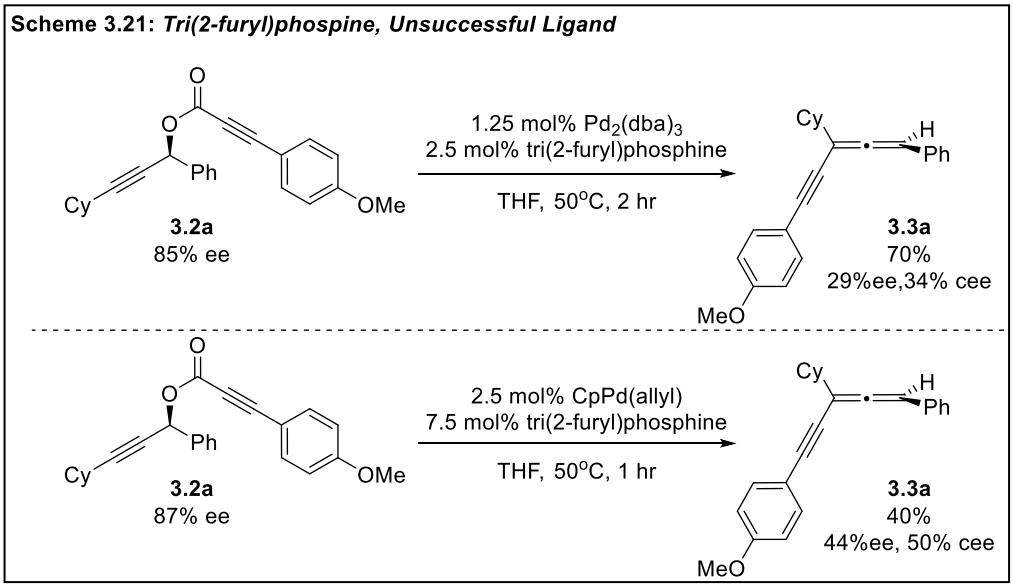


***rac*-3.2a** **rac-3.3a**

entry	Pd Source	ligand	time	conv (%)[a]
1	$Pd(PPh_3)_4$	none	20 min	100
2	$Pd_2(dba)_3$	PPh_3 2.5 mol%	2 hr	30
3	$Pd_2(dba)_3$	tri(2-furyl)phosphine 2.5 mol%	2 hr	100
4	$Pd_2(dba)_3$	Xphos 2.5 mol%	2.5 hr	100
5	CpPd(allyl)	PPh_3 5 mol%	2 hr	85
6	CpPd(allyl)	tri(2-furyl)phosphine 5 mol%	3 hr	100
7	CpPd(allyl)	tri(2-furyl)phosphine 7.5 mol%	1 hr	100
8	CpPd(allyl)	tr(o-tolyl)phosphine 7.5 mol%	6 hr	NR

[a] determined by ^1H NMR

To further support this hypothesis, the closest performing ligand to $Pd(PPh_3)_4$, trifuryl phosphine (entries 3 and 7, Table 3.1), was utilized in the stereospecific coupling with two different palladium sources. Both reactions required longer reaction times, and thus yielded significantly racemized allenyne product (Scheme 3.21). Thus, $Pd(PPh_3)_4$ is the most competent catalyst for the stereospecific decarboxylative coupling.



Overall we were able to demonstrate that the palladium-catalyzed decarboxylative coupling does, in fact, occur in a stereospecific fashion. Unfortunately, significant racemization of the enantioenriched allenyne upon being produced prevents this coupling from being a general method that could be employed for the synthesis of enantioenriched allenes. While this method is not the most synthetically useful, it does provide an opportunity to probe further into the somewhat mysterious mechanism of palladium-catalyzed racemization of allenes.

3.5 Kinetic Studies for the Elucidation of Palladium-Catalyzed Racemization

3.5.1 Introduction

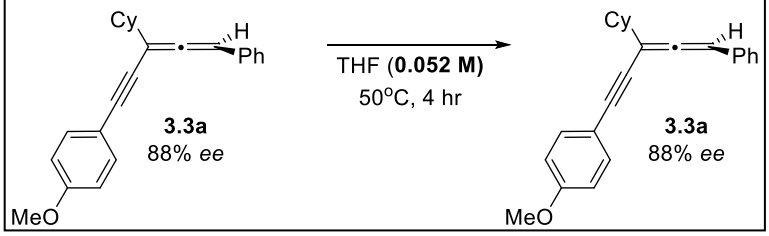
As has been presented in the above sections, the ability for palladium to racemize enantioenriched allenes has significantly and negatively affected the development of enantiospecific palladium-catalyzed couplings. While this is a common problem throughout the literature, very little is known about the mechanism of this unfortunate side reaction apart from Bäckvall's report on palladium(II)-catalyzed racemization.[52] This lack of knowledge is unacceptable, as understanding how and why the racemization occurs could lead to better developed enantiospecific methods towards the synthesis of chiral allenes. Further, racemization

plays a key role in important asymmetric processes such as dynamic kinetic resolution (DKR).[54] Having an experimentally grounded understanding of the mechanism of racemization could potentially lead to the development of new DKR processes involving allenes. This section presents the kinetic experiments we have undertaken in an attempt to better understand the palladium-catalyzed racemization that was observed during the development of the stereospecific decarboxylative coupling of enantioenriched propargyl propiolates.

3.5.2 Initial Observations

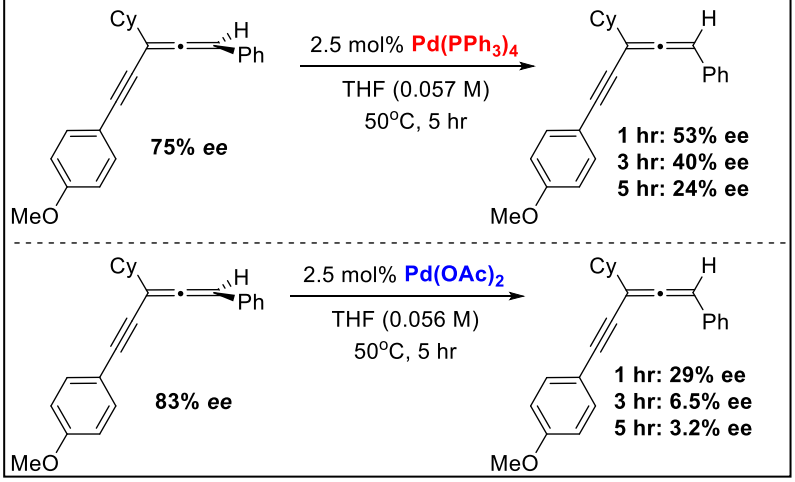
We began our studies by confirming the stereostability of enantioenriched allenyne **3.3a**. In the absence of palladium, there was no degradation of optical purity of **3.3a** after 4 hours of heating at 50°C (Scheme 3.22).

Scheme 3.22: ***No Racemization without Palladium***



We then examined the time-dependent racemization of the allene **3.3a** by palladium via chiral stationary phase high performance liquid chromatography (HPLC). $Pd(PPh_3)_4$ was employed in the experiment as it is the catalyst for the decarboxylative coupling. However, we also wanted to examine the possibility of racemization by palladium(II), as palladium(II) complexes are formed *in situ* upon oxidative addition of the propargylic ester to Pd(0). Thus a second racemization utilizing $Pd(OAc)_2$ as the catalyst was also examined. It was determined by these studies that both palladium(0) and palladium(II) contribute to the racemization of enantioenriched allenes. Further it appears that palladium(II) catalyzes the racemization much more rapidly (Scheme 3.23)

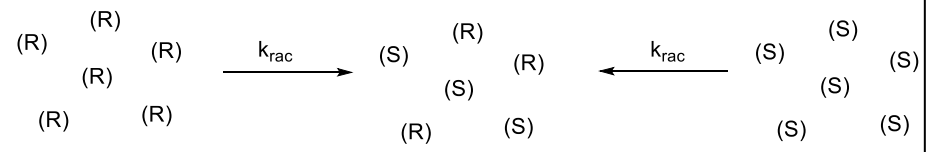
Scheme 3.23: ***Palladium(0) and Palladium(II) Racemize Allene***



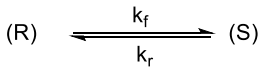
Unfortunately chiral HPLC was not the most practical analytical method for closely monitoring the racemization of allenes over time. For HPLC each aliquot needed to be moderately purified with all solvent removed before it could be analyzed, and over an hour and a half was required for each HPLC run. It was determined that polarimetry would be a pragmatic alternative as no sample purification was needed, and sample analysis only took minutes. Thus the remainder of our kinetic studies utilized polarimetry to observe racemization. As both palladium(0) and palladium(II) exhibited catalytic activity in the racemization, we studied the kinetics of the racemization promoted by each catalyst. For clarity, both studies are presented in separate sections below. For the purpose of our studies, we used the definition of racemization as the process in which 50% of an enantiopure compound is converted to the other enantiomer, ultimately leading to 0% *ee* (Scheme 3.24). Since our allenes are not enantiopure, both the R and the S enantiomers are present. Thus on a microscopic level, racemization is viewed as a reversible enantiomerization reaction in which the rate constants for the forward (k_f) and the backwards (k_r) reaction are equal. This results in the rate constant for racemization to be the combination of the forwards and backwards rate constant for enantiomerization.

Scheme 3.24: ***Racemization Versus Enantiomerization***

Racemization



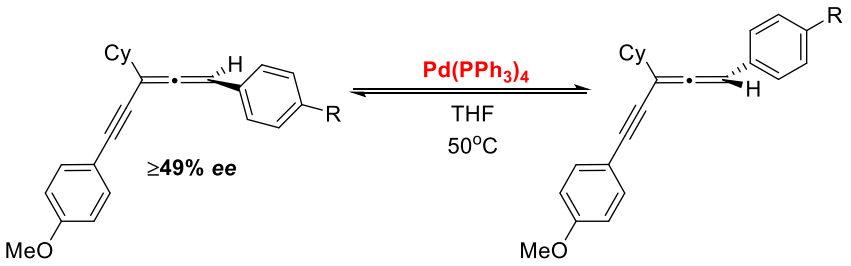
Enantiomerization



$k_f=k_r=k_{ent}$ thus $k_{rac}=(k_f+k_r)=2k_{ent}$

3.5.3 Kinetic Studies of Palladium(0)-Catalyzed Racemization

Table 3.2: ***Rate Constants for $Pd(PPh_3)_4$-Catalyzed Racemizations of Allenynes***



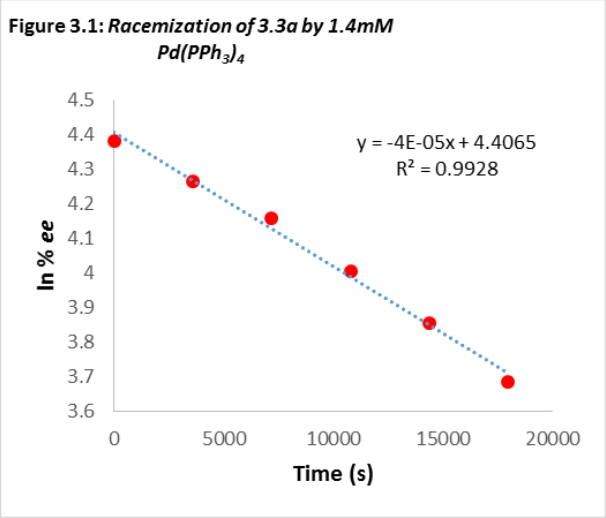
Entry	substrate	R	[Allene] (mM)	[Cat.] (mM)	$t_{1/2}$[a] (min)	$k_{obs}x10^5$ (s^{-1})	k_{ent}[b] ($M^{-1}s^{-1}$)
1	**3.3a**	H	56	1.4	299	3.87	0.014
2	**3.3a**	H	57	0.61	421	2.74	0.022
3	**3.3a**	H	52	2.6	125	9.27	0.018
4	**3.3b**	^{t}Bu	56	1.4	111	10.4	0.037
5	**3.3c**	Cl	56	1.4	108	10.6	0.038
6	**3.3d**	CO_2Me	56	1.4	443	2.61	0.0093
7	**3.3e**	CN	56	1.4	403	2.87	0.010
8	**3.3f**	NO_2	56	1.4	369	3.13	0.011

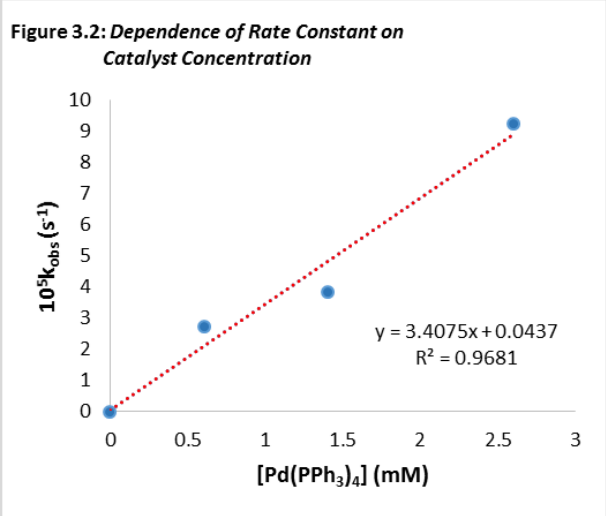
[a] $t_{1/2}$ *is the time to reach 50% racemization, back-calculated via* k_{obs}

[b] $k_{rac}=k_{obs}$*[catalyst];* $k_{rac}=2k_{ent}$

We began our kinetic studies by periodically monitoring a solution of enantiomerically enriched allene **3.3a** (0.057 M) and a catalytic amount of $Pd(PPh_3)_4$ (1.4 mM, 2.5 mol %) stirred at 50 ˚C via polarimetry. The plot of ln (% *ee*) versus time was linear which established a first order dependence of the rate on the concentration of the allene (Figure 3.1). The pseudo-first order rate constant of k_{obs}= 3.87±0.2x10^{-5} s^{-1} was obtained from this plot (Table 3.2, entry 1). The dependence of the rate of allene racemization on catalyst concentration was then determined by

finding the first order rate constants for the racemization of **3.3a** at varying concentrations of $Pd(PPh_3)_4$ (Table 3.2, entries 1-3). The plot of the determined first order constants (k_{obs}) versus the concentration of $Pd(PPh_3)_4$ was also linear indicating that there was also a first order dependence of the rate on catalyst concentration (Figure 3.2). This established an overall second order rate law for the Pd(0) catalyzed racemization of **3.3a:** rate = $2k_{ent}$[**3.3a**][$Pd(PPh_3)_2$], where k_{ent} = $0.018\pm0.003 M^{-1}s^{-1}$.[55,56]

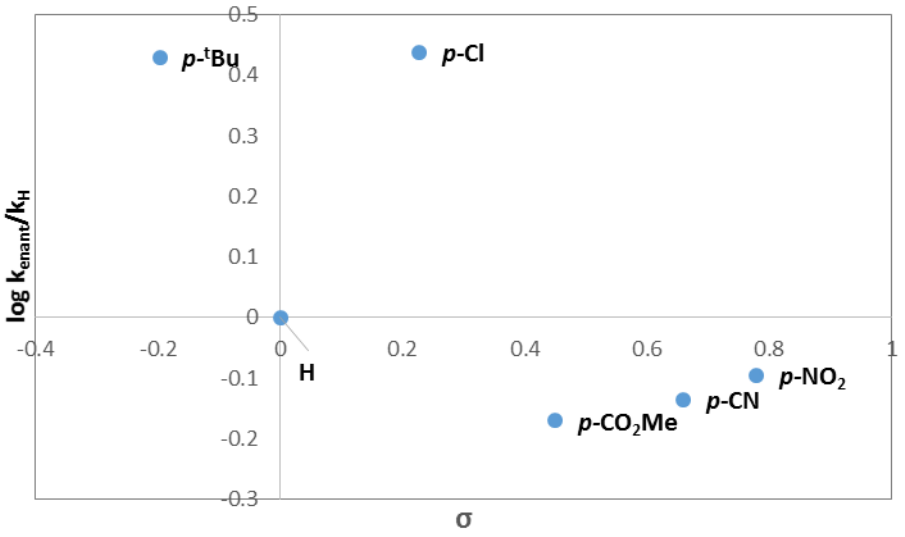




The effect of electron density of the allene on the rate of racemization was then evaluated. The observed rate constants for the racemization of various *para*-substituted 1-aryl-allenynes by $Pd(PPh_3)_4$ were determined (Table 3.2, entries 4-8). A plot of the log of k_{ent} vs the Hammett σ parameter led to interesting observations about allene electron density effects (Figure 3.3). Most notably, the racemization of *para*-chloro substituted aryl alleyne **3.3c** (Table 3.2, entry 5) was observed to be approximately four times faster, as denoted by the larger k_{ent}, than for the other allenes bearing electron withdrawing substituents. Though oxidative addition of aryl-Cl bonds is not the most facile,[57] it may be possible that oxidative addition occurs generating a palladium(II)

species containing a chloride anion. This could allow for racemization to occur via an *anti*-halo-palladation-elimination mechanism as proposed by Bäckvall (Scheme 3.17).

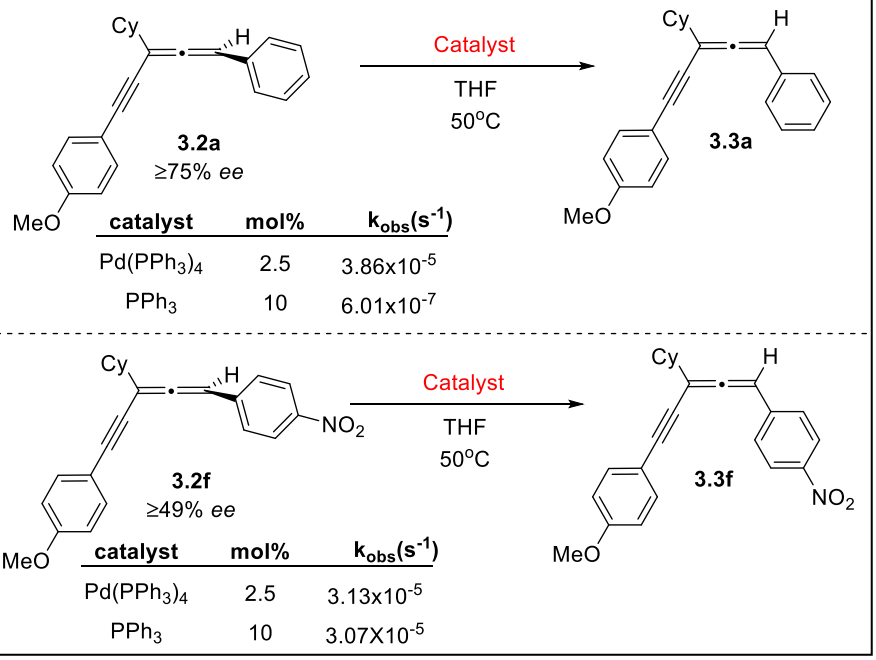
Figure 3.3: ***Hammett Plot of $Pd(PPh_3)_4$ Catalyzed Racemization***



The ρ value from *p*-^{t}Bu to H is negative while the ρ value from *p*-CO_2Me to *p*-NO_2 is positive. We interpret this as a change in mechanism when stronger electron withdrawing substituents are included on the aryl moiety of the allene. Further evidence for the change in mechanism was established when a solution of enantioenriched allene **3.3a** (0.57 M) and a catalytic amount of PPh_3 (5.7 mM, 10 mol %) stirred at 50°C was monitored via polarimetry over the course of 8 hours. Racemization of allene **3.3a** occurred but the observed rate constant was 2 orders of magnitude smaller than when the racemization was catalyzed by $Pd(PPh_3)_4$ thus suggesting that the amount of racemization caused by triphenylphosphine could be considered negligible. Comparatively,

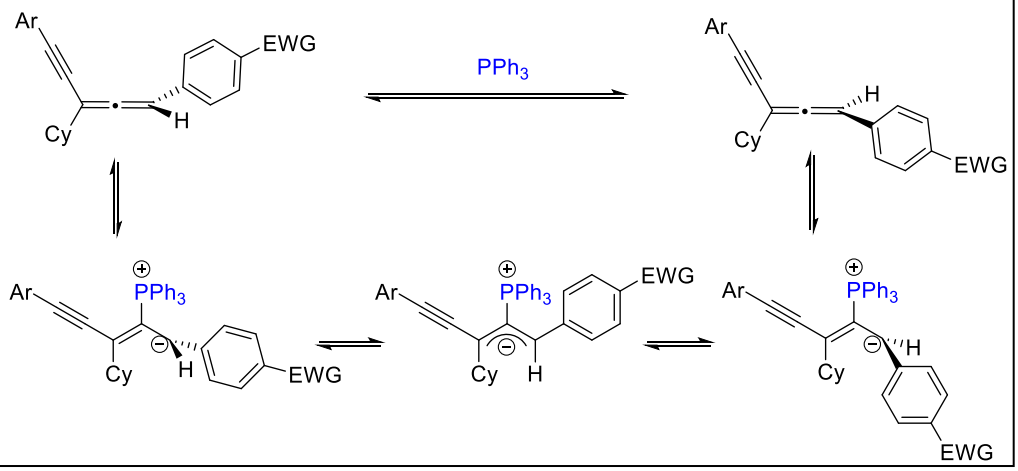
when the same experiment was performed utilizing *para*-nitro substituted allene **3.3f** the observed rate constant was nearly the same as that which was found with $Pd(PPh_3)_4$ (Scheme 3.25).

Scheme 3.25: ***Triphenylphosphine-Catalyzed Racemization***



While more studies involving triphenylphosphine are ongoing in the lab, the above observation is consistent with the change in mechanism observed in the Hammett plot. We hypothesize that for aryl allenynes containing electron withdrawing substituents triphenylphosphine, not palladium, is catalyzing the racemization. This could occur via attack of the center carbon of the enantioenriched

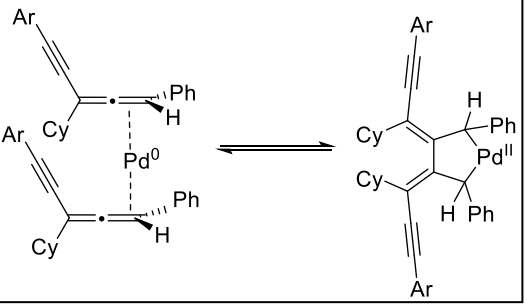
Scheme 3.26: ***Mechanism of Triphenylphosphine Racemization***



allenyne by triphenylphosphine.[58,59] The resulting allylic anion could then undergo a bond rotation leading to the opposite enantiomer and thus a racemic product (Scheme 3.26).

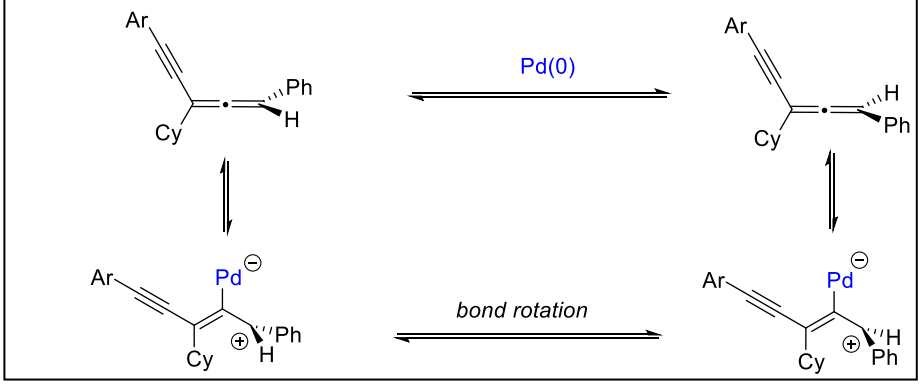
As our interpretation of the Hammett plot suggests a change in mechanism, we still propose that aryl allenes without electron withdrawing substituents undergo racemization catalyzed by palladium. Keeping the data we have collected in mind, we envision that the palladium-catalyzed racemization could occur via one of two pathways. First, it has been previously suggested by Coulson and Cazes that palladium(0) can interact with two allene substrates resulting in a palladacycle (Scheme 3.27).[60,61] We propose that this dimerization would be fast, and the resulting palladium(II)-complex could catalyze the racemization by a mechanism that is presented in section 3.5.4 for palladium(II)-catalyzed racemization (Scheme 3.31). This could account for the negative slope from *p*-^{t}Bu to H.

Scheme3.27: *Dimerization Resulting in Palladacycle*



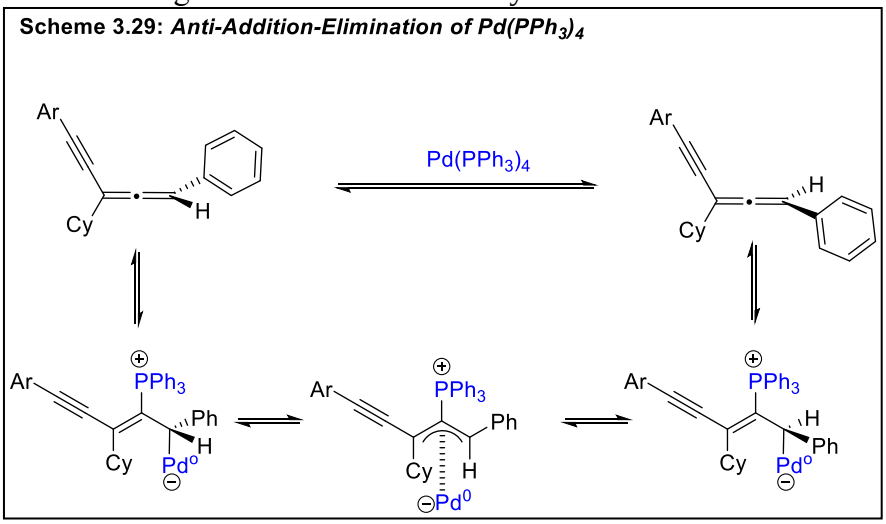
An alternative mechanism involves palladium(0) behaving as a Lewis acid. While palladium(0) is a weaker Lewis acid than palladium(II), it has still been shown to interact with allene substrates.[62]The Lewis acidic addition of palladium would result in an allylic cation that could undergo bond rotation thus facilitating racemization (Scheme 3.28).

Scheme 3.28: ***Pd(0) Lewis Acidic Addition***



It is also possible that triphenylphosphine could behave similarly to bromide, lending stability to the palladium-bound intermediate (Scheme 3.29). This would result in a mechanism that looks similar to Bäckvall's involving *anti*-addition followed by *anti*-elimination.

Scheme 3.29: ***Anti-Addition-Elimination of Pd(PPh$_3$)$_4$***

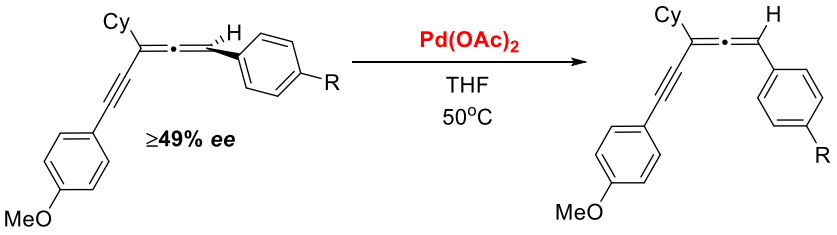


While Pd(PPh$_3$)$_4$ (and/or triphenylphosphine) obviously catalyzes the racemization of enantioenriched allenes, it does not do so on a time scale consistent with the amount of racemization that was observed during the development of the stereospecific decarboxylative coupling (Section 3.4). As an example, we simulated the 45 minute racemization of allene (**3.3a**) by 1 mol % of Pd(PPh$_3$)$_4$ (Scheme 3.20_C) using Tenua,[63] a kinetics simulation program based on KINSIM.[64] We assumed that the allene would be initially produced with perfect stereospecificity and input the k_{ent} calculated from our kinetic experiments. If palladium(0) was the only catalyst for the reaction, the simulation would generate an *ee* similar to the experimentally observed *ee.*

However, the simulated *ee* was 82% while we observed a lower 70% *ee* experimentally. This supports our hypothesis that palladium(0) is not the sole catalyst for racemization in our system. Because palladium(II) species are intermediates in the coupling, they could be potential catalysts for the racemization. Investigating the kinetics of palladium(II)-catalyzed racemization was the next step in the attempt to gain an experimentally grounded understanding of the mechanism of racemization.

3.5.4 Kinetic Studies of Palladium(II)-Catalyzed Racemization

Table 3.3: ***Rate Constants for $Pd(OAc)_2$-Catalyzed Racemizations of Allenynes***



Entry	substrate	R	[Allene] (mM)	[Cat.] (mM)	k_{ent}[a] ($M^{-1}s^{-1}$)	$k_{inac}x10^{4}$[a] ($M^{-1}s^{-1}$)
1	**3.3a**	H	56	1.4	0.087±0.004	0.93±0.2
2	**3.3a**	H	53	0.62	0.26±0.02	2.75 ±0.2
3	**3.3a**	H	52	0.80	0.24	1.8
4	**3.3a**	H	52	2.5	0.076	1.5
5	**3.3a**	H	53	2.8	0.070	1.8
6	**3.3a**	H	38	1.4	0.22	3.0
7	**3.3a**	H	115	1.4	0.09	2.6
8	**3.3b**	^{t}Bu	56	1.4	0.095±0.02	1.3±0.4
9	**3.3c**	Cl	56	1.5	0.11	1.6
10	**3.3d**	CO_2Me	56	1.5	0.046±0.004	0.31±0.03
11	**3.3e**	CN	56	1.5	0.063±0.009	0.7±0.2
12	**3.3f**	NO_2	56	1.5	0.040±0.0005	0.4±0.3

[a]*Calculated by simulation program Tenua*

We again monitored a solution of enantioenriched allene **3.3a** (0.057 M) via polarimetry while stirring at 50°C over the course of 5 hours, replacing $Pd(PPh_3)_4$ with $Pd(OAc)_2$ (1.4 mM, 2.5 mol %). Interestingly, the plot of ln (% *ee*) versus time was not linear, suggesting that the racemization did not have a first-order dependence on the concentration of the allene (Figure 3.4). However, the plot of 1/[% *ee*] versus time appeared to be linear, indicating that the reaction may have a second

order dependence on the concentration of **3.3a** (Figure 3.5). Utilizing the plot of 1/[% *ee*] the observed rate constant k_{obs}= 3.38x 10^{-6} $M^{-1}s^{-1}$ was obtained and the corresponding $t_{1/2}$ (time to reach 50% racemization) was calculated to be 53 minutes.

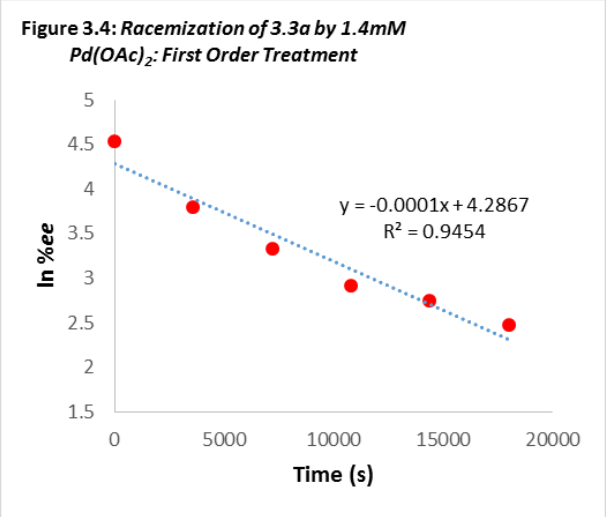


Figure 3.4: ***Racemization of 3.3a by 1.4mM $Pd(OAc)_2$: First Order Treatment***

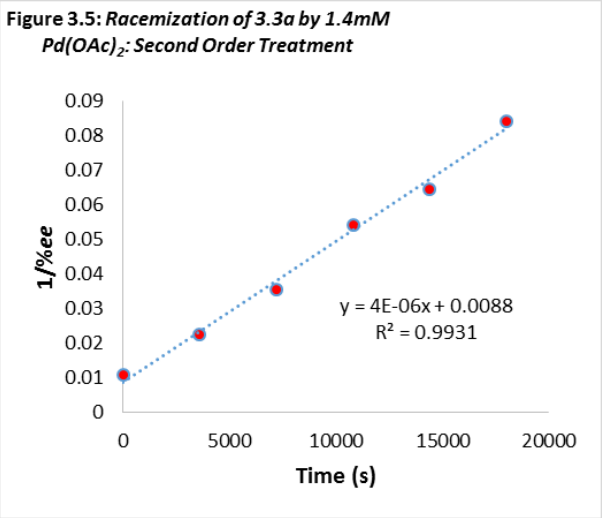


Figure 3.5: ***Racemization of 3.3a by 1.4mM $Pd(OAc)_2$: Second Order Treatment***

This was perplexing as it seemed unlikely that the racemization would require two molecules of the allene to occur. Additionally, a poor linear fit for second order dependence was observed with some experiments. For example, there is an obvious curve in the data for substrate **3.3d** when treated as a second-order reaction (Figure 3.6).

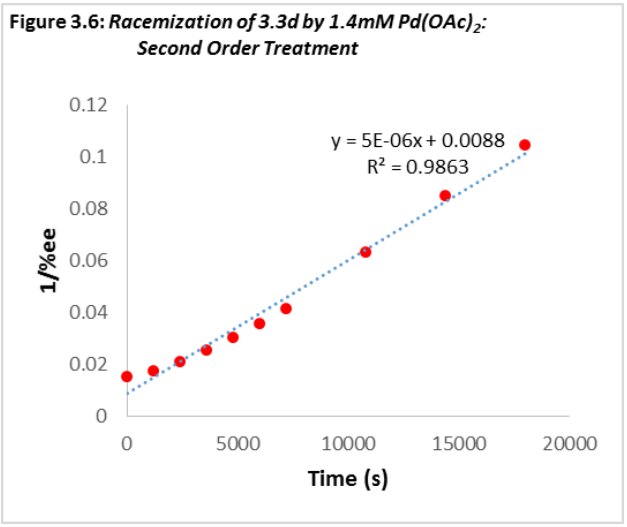


Figure 3.6: ***Racemization of 3.3d by 1.4mM $Pd(OAc)_2$: Second Order Treatment***

Further, the order of dependence on the concentration of either $Pd(OAc)_2$ or the allene could not be established from the plots of their concentrations verses the observed rate constants calculated from the plots of 1/[% *ee*] (Table 3.1, appendix), as can be seen in Figures 3.7 and 3.8.

Figure 3.7:
Observed Rate Constant Dependence on [Pd(OAc)$_2$]

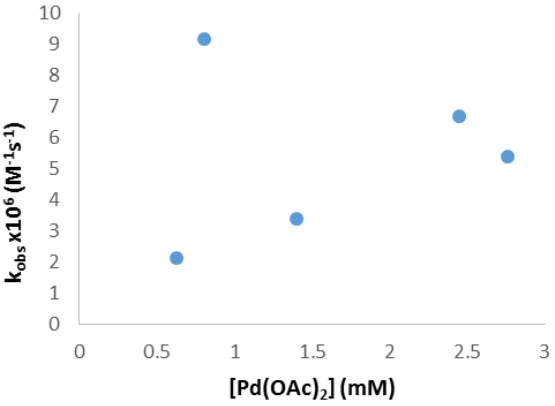
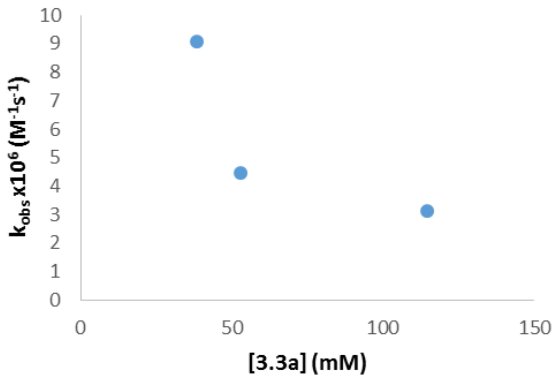
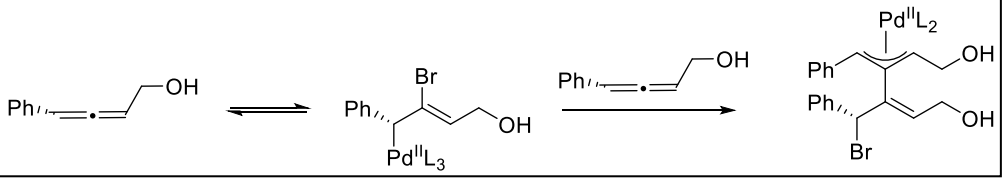


Figure 3.8:
Variable Concentrations of 3.3a Racemized by 1.4mM Pd(OAc)$_2$



After several experiments, each as confusing as the last, it was noticed that the stirred solution was changing color over time from a light yellow to a dark brown (see appendix). This color change could be indicative of the catalyst becoming inactivated over time which would explain the poor fit. In their study of palladium(II)-catalyzed racemization, Bäckvall and coworkers also observed deactivation of the catalyst, and proposed that the deactivation occurred via dimer formation (Scheme 3.30).[52] While this could be a possibility in our studies, no spectroscopic evidence for the presence of the dimer was observed upon re-isolation of the racemized allene.

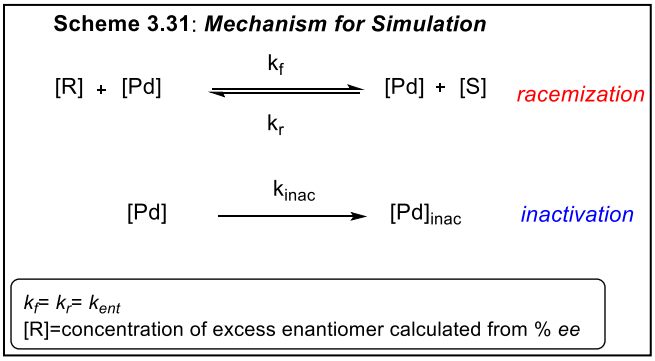
Scheme 3.30: ***Catalyst Deactivation via Dimerization***



Since the reaction was more complex than originally thought, we again utilized the simulation program, Tenua[63], to demonstrate that both racemization and catalyst deactivation are indeed occurring. By fitting the experimental data to the simulated racemizations, the program would also allow the respective rate constants for each reaction to be calculated. The mechanism used for the

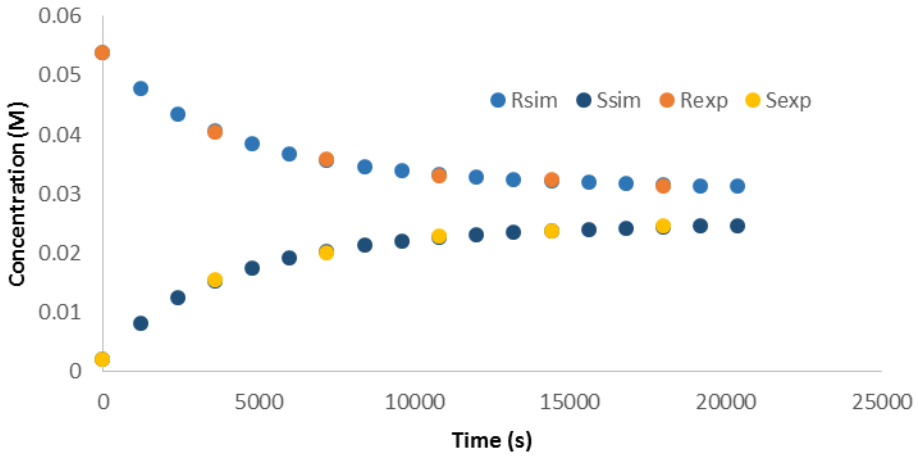
simulation input is shown in Scheme 3.31. In order to simulate the racemization, it was necessary to convert the measured % *ee* over time to concentrations of each enantiomer (denoted [R] and [S], assignment was arbitrary). We assumed that the rate forward is the same as the reverse thus resulting in racemization thus the rate constant calculated is denoted as k_{ent}.

Scheme 3.31: ***Mechanism for Simulation***



Fitting the experimental racemization data of **3.3a** to the simulation generated by Tenua gave k_{ent}= 0.087±0.004 $M^{-1}s^{-1}$ and k_{inac} =0.93±0.2 x10^{-4} $M^{-1}s^{-1}$ (Table 3.3, entry 1). The experimental data fit the simulated data well (Figure 3.9) with an average % residual of 0.44 ± 0.2%.

Figure 3.9: Experimental Data Fitted with Simulation Data

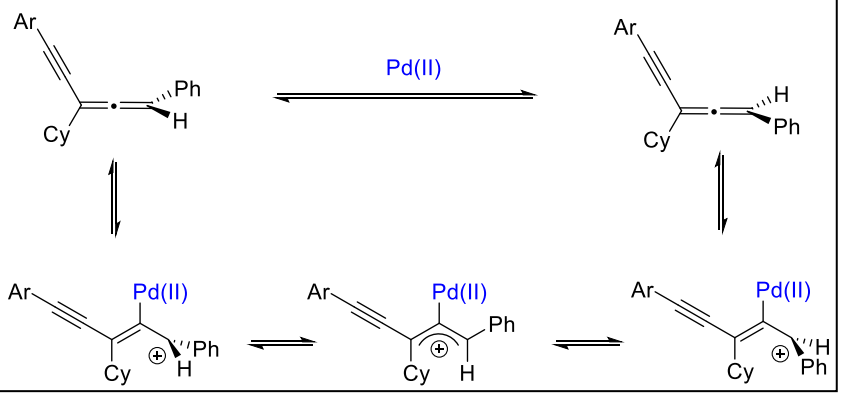


Simulations varying the concentrations of catalyst and allene also provided good fits to the experimental data (Table 3.3, entries 1-7), consistent with our proposal of catalyst deactivation.

In an attempt to better understand the $Pd(OAc)_2$-catalyzed racemization, we again examined how the electron density of the allene affects the rate of racemization (Table 3.3, entries 8-12). We

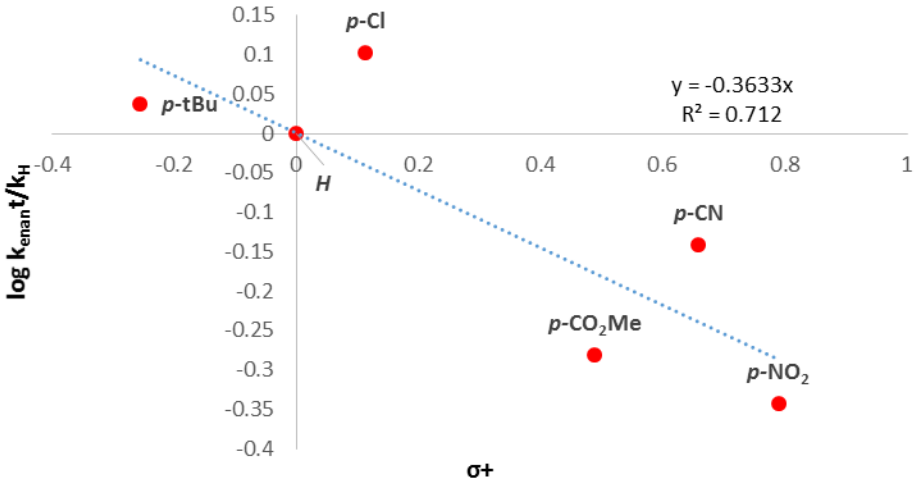
hypothesized that the racemization catalyzed by $Pd(OAc)_2$ alone proceeded through a mechanism similar to that proposed by Bäckvall and coworkers.[52] However, without the bromide salt additive, palladium(II) could possibly form an allylic cationic species similar to the gold species proposed by Widenhoefer.[46] Lewis acidic addition of palladium(II) to the central carbon of the enantioenriched allene could lead to the achiral cationic allylic complex thus leading to enantiomerization (Scheme 3.32).

Scheme 3.32: ***Proposed Mechanism for Pd(II)-Catalyzed Racemization***



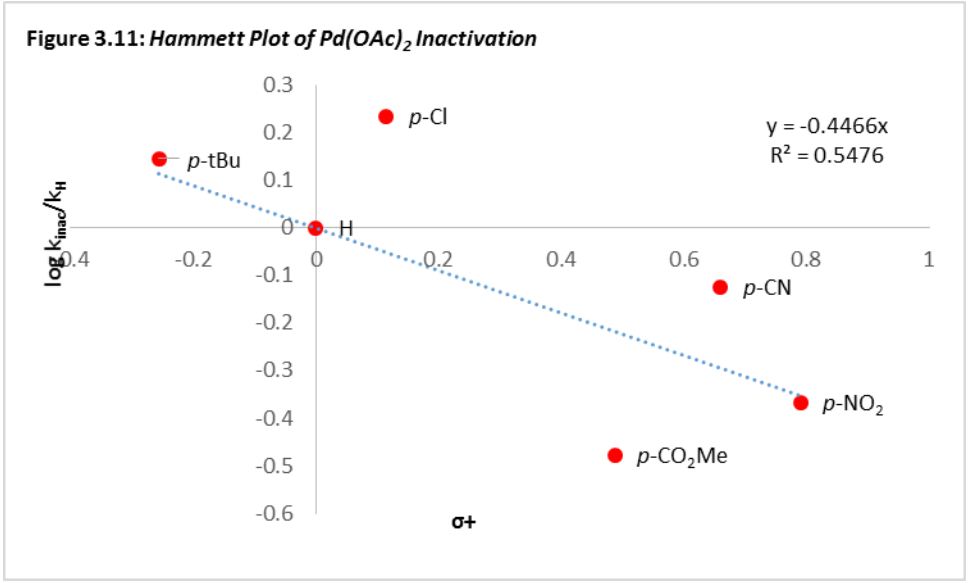
With this mechanism in mind, the k_{ent} for each *para*-substituted aryl-allene was plotted versus the Hammett parameter σ^+ as the positive charge would be in direct resonance with the substituents (Figure 3.10).

Figure 3.10: ***Hammett Plot of $Pd(OAc)_2$-Catalyzed Racemization***



Generally the ρ^+ value for the generated Hammett plot is negative, indicating that there is generation of a positive charge. This is consistent with the proposed mechanism in which a carbocation is formed. However, some substrates are not included within this general trend. Both the *para*-chloro and *para*-cyano substituted aryl allenes racemized more rapidly than expected. This could be due to coordination to palladium(II) in some fashion that results in a more reactive catalyst or different mode of racemization. The plot of the k_{inac} versus the Hammett parameter σ^+ looks very similar to the plot of k_{ent}, indicating that racemization and catalyst inactivation are correlated (Figure 3.11).

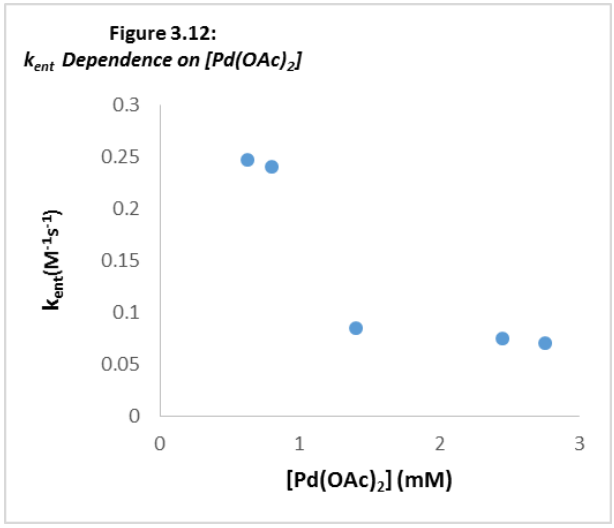
Figure 3.11: ***Hammett Plot of $Pd(OAc)_2$ Inactivation***

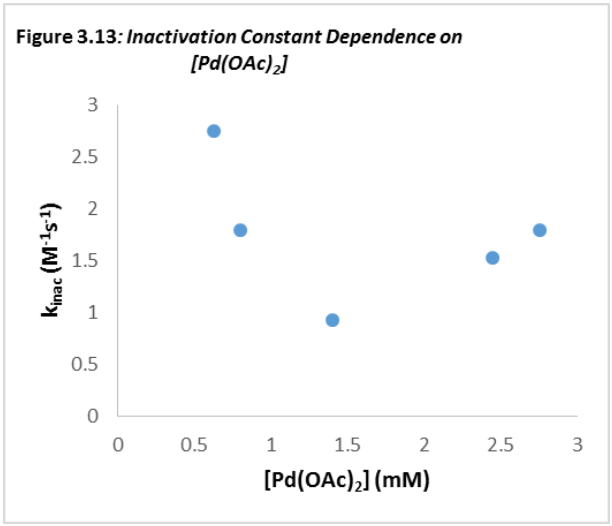


This correlation suggests that the mechanisms for racemization and catalyst inactivation may share an intermediate. Though we have no spectroscopic evidence, it still may be possible inactivation is occurring via formation of a similar dimer to that suggested by Bäckvall (Scheme 3.27). Dimer formation would proceed via the same achiral allylic cation, which could then undergo carbopalladation with a second allene to trap the catalyst thus inactivating it.

3.6 Future Directions

While this work provides a strong basis, further studies are currently underway to further grasp an understanding of the palladium-catalyzed mechanism of allene racemization.





Strangely, when the Tenua-calculated k_{ent} is plotted versus the concentration of $Pd(OAc)_2$, there appears to be a dependence on catalyst concentration for the rate of racemization (Figure 3.12), indicating that higher concentrations of $Pd(OAc)_2$ lead to slower racemizations. However, increasing the concentration more than 1.4 mM does not appear to effect the rate constant. We hypothesize that this may indicate that $Pd(OAc)_2$ is aggregating at higher concentrations, thus resulting in a less efficient catalyst than monomeric $Pd(OAc)_2$.[65,66] Utilizing other palladium(II) catalysts which do not contain acetate ligands, such as $PdCl_2$, could potentially prevent this aggregation and support our hypothesis. Thus further catalyst screening would be beneficial. Interestingly, the dependence of rate of inactivation on the concentration of palladium(II) does not appear to correlate with the reduced rates of racemization at higher palladium concentrations, but again, as a constant, should not demonstrate dependence (Figure 3.13). These dependencies either indicate an error in the data collecting methods, or further complexities in the mechanism. More data for each of these points could be collected to minimize error. Also dilution studies of both the

palladium(II) and palladium(0)-catalyzed reactions would be useful. Changing the concentration of both allene and catalyst would provide insight into the potential for dimerization of both the substrate and the catalyst. Additionally, it would be interesting to explore the effect of triphenylphosphine concentration on the rate of the reaction in the presence of a set concentration of palladium(0). This could be especially telling in regards to the mechanism of racemization for the allenes with electron deficient aryl substituents, and could result in a way to control the rate of racemization. The information from these studies could potentially be applied in the future development of dynamic kinetic resolution processes.

3.7 Conclusion

In conclusion, we report first example of a stereospecific palladium-catalyzed decarboxylative coupling involving propargyl electrophiles as a green alternative to previous methods used to synthesize enantioenriched allenes as CO_2 is the only byproduct. Further, it was confirmed that the loss of enantiopurity of the allene occurs primarily via racemization of the product catalyzed by palladium. Additionally, the first investigative kinetic studies into the racemization of allene by both palladium(0) and palladium(II) are reported. While it has been demonstrated that palladium(II) racemizes the allenes more rapidly than palladium(0), the palladium(II) catalyst is deactivated in the current reaction conditions. Further it was demonstrated that PPh_3 in the absence of palladium can also catalyze racemization in aryl allenes substituted with electron withdrawing groups. The studies reported herein are a strong foundation from which further studies can be continued as there is still much to learn about palladium-catalyzed allene racemization. Finally it would be beneficial to use the knowledge garnered by these kinetic studies to develop a more generalized and controllable method of racemization, which is necessary for the potential incorporation into asymmetric syntheses via dynamic kinetic resolutions.

3.7 References for Chapter 3

(1) Hoff, J. H. v. t.: *La Chimie dans l'espace*; P.M. Bazendijk: Rotterdam, 1875.

(2) Maitland, P.; Mills, W. H. Experimental demonstration of the allene asymmetry. *Nature* **1935**, *135*, 994.

(3) Hoffmann-Roeder, A.; Krause, N. Synthesis and properties of allenic natural products and pharmaceuticals. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196-1216.

(4) Rivera-Fuentes, P.; Diederich, F. Allenes in Molecular Materials. *Angew. Chem., Int. Ed.* **2012**, *51*, 2818-2828.

(5) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074-3112.

(6) Neff, R. K.; Frantz, D. E. Recent applications of chiral allenes in axial-to-central chirality transfer reactions. *Tetrahedron* **2015**, *71*, 7-18.

(7) Hoffmann-Roder, A.; Krause, N. Enantioselective synthesis of and with allenes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933-2935.

(8) Ohno, H.; Nagaoka, Y.; Tomioka, K.: Enantioselective Synthesis of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, S. K., Eds.; Wiley-VCH Verlag GmbH & Co.: Weinheim, 2004; Vol. 1; pp 141-181.

(9) Ogasawara, M. Catalytic enantioselective synthesis of axially chiral allenes. *Tetrahedron: Asymmetry* **2009**, *20*, 259-271.

(10) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C-C Bonds. *Chem. Rev.* **2015**, *115*, 9587-9652.

(11) Neff, R. K.; Frantz, D. E. Recent advances in the catalytic syntheses of allenes: a critical assessment. *ACS Catal.* **2014**, *4*, 519-528.

(12) Ye, J.; Ma, S. Conquering three-carbon axial chirality of allenes. *Org. Chem. Front.* **2014**, *1*, 1210-1224.

(13) Nishizawa, M.; Yamada, M.; Noyori, R. Asymmetric synthesis via axially dissymmetric molecules. Part 4. Highly enantioselective reduction of alkynyl ketones by a binaphthol-modified aluminum hydride reagent. Asymmetric synthesis of some insect pheromones. *Tetrahedron Lett.* **1981**, *22*, 247-250.

(14) Burgess, K.; Jennings, L. D. Enantioselective esterifications of unsaturated alcohols mediated by a lipase prepared from Pseudomonas sp. *J. Am. Chem. Soc.* **1991**, *113*, 6129-6139.

(15) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. Chiral synthesis via organoboranes. 34. Selective reductions. 47. Asymmetric reduction of hindered α,β-acetylenic ketones with B-chlorodiisopinocampheylborane to propargylic alcohols of very high enantiomeric excess. Improved workup procedure for the isolation of product alcohols. *J. Org. Chem.* **1992**, *57*, 2379-2386.

(16) Parker, K. A.; Ledeboer, M. W. Asymmetric Reduction. A Convenient Method for the Reduction of Alkynyl Ketones. *J. Org. Chem.* **1996**, *61*, 3214-3217.

(17) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric Transfer Hydrogenation of α,β-Acetylenic Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739.

(18) Frantz, D. E.; Faessler, R.; Carreira, E. M. Facile enantioselective Synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.

(19) Anand, N. K.; Carreira, E. M. A Simple, Mild, Catalytic, Enantioselective Addition of Terminal Acetylenes to Aldehydes. *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.

(20) Maezaki, N.; Kojima, N.; Asai, M.; Tominaga, H.; Tanaka, T. Highly Stereoselective and Stereodivergent Synthesis of Four Types of THF Cores in Acetogenins Using a C4-Chiral Building Block. *Org. Lett.* **2002**, *4*, 2977-2980.

(21) Pu, L. Asymmetric alkynylzinc additions to aldehydes and ketones. *Tetrahedron* **2003**, *59*, 9873-9886.

(22) Luche, J. L.; Barreiro, E.; Dollat, J. M.; Crabbe, P. Formation of allenes by reaction of lithium diorganocuprates on propargylic acetates, a mechanistic approach. *Tetrahedron Lett.* **1975**, 4615-4618.

(23) Marek, I.; Mangeney, P.; Alexakis, A.; Normant, J. F. Are allenes formed from propargylic ethers through a syn or anti displacement? *Tetrahedron Lett.* **1986**, *27*, 5499-5502.

(24) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. Mechanistic aspects of the formation of chiral allenes from propargylic ethers and organocopper reagents. *J. Am. Chem. Soc.* **1990**, *112*, 8042-8047.

(25) Alexakis, A. Stereochemical aspects of the formation of chiral allenes from propargylic ethers and epoxides. *Pure Appl. Chem.* **1992**, *64*, 387-392.

(26) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. General Approach to Allenes through Copper-Catalyzed γ-Selective and Stereospecific Coupling between Propargylic Phosphates and Alkylboranes. *Org. Lett.* **2011**, *13*, 6312-6315.

(27) Yang, M.; Yokokawa, N.; Ohmiya, H.; Sawamura, M. Synthesis of Conjugated Allenes through Copper-Catalyzed γ-Selective and Stereospecific Coupling between Propargylic Phosphates and Aryl- or Alkenylboronates. *Org. Lett.* **2012**, *14*, 816-819.

(28) Uehling, M. R.; Marionni, S. T.; Lalic, G. Asymmetric Synthesis of Trisubstituted Allenes: Copper-Catalyzed Alkylation and Arylation of Propargylic Phosphates. *Org. Lett.* **2012**, *14*, 362-365.

(29) Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. Anti-stereoselectivity in the palladium(0)-catalyzed conversion of propargylic esters into allenes by phenylzinc chloride. *J. Org. Chem.* **1983**, *48*, 1103-1105.

(30) Lowe, G. The absolute configuration of allenes. *Chem. Commun.* **1965**, 411-413.

(31) Brewster, J. H. Helix models of optical activity. *Top. Stereochem.* **1967**, *2*, 1-72.

(32) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. Synthesis, structure and reactivity of some (σ-allenyl)- and (σ-prop-2-ynyl)palladium(II) complexes. *Organometallics* **1986**, *5*, 716-720.

(33) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. Palladium-catalyzed coupling reaction of fluoroalkylated propargyl mesylates with organozinc reagents: novel synthesis of optically active fluorine-containing trisubstituted allenes. *Chem. Lett.* **2000**, 1360-1361.

(34) Mandai, T.; Nakata, T.; Murayama, H.; Yamaoki, H.; Ogawa, M.; Kawada, M.; Tsuji, J. Palladium-catalyzed reactions of 2-alkynyl carbonates with terminal acetylenes: a new synthetic method for 1,2-diene-4-ynes. *Tetrahedron Lett.* **1990**, *31*, 7179-7180.

(35) Dixneuf, P. H.; Dixneuf, P. H.; Guyot, T.; Ness, M. D.; Roberts, S. M. Synthesis of optically active allenes using tandem enzyme and palladium-catalyzed reactions. *Chem. Commun.* **1997**, 2083-2084.

(36) Yoshida, M.; Gotou, T.; Ihara, M. Palladium-catalyzed direct coupling reaction of propargylic alcohols with arylboronic acids. *Tetrahedron Lett.* **2004**, *45*, 5573-5575.

(37) Yoshida, M.; Okada, T.; Shishido, K. Enantiospecific synthesis of 1,3-disubstituted allenes by palladium-catalyzed coupling of propargylic compounds with arylboronic acids. *Tetrahedron* **2007**, *63*, 6996-7002.

(38) Sherry, B. D.; Toste, F. D. Gold(I)-Catalyzed Propargyl Claisen Rearrangement. *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979.

(39) Ruchti, J.; Carreira, E. M. Rh-Catalyzed Stereospecific Synthesis of Allenes from Propargylic Benzoates and Arylboronic Acids. *Org. Lett.* **2016**, *18*, 2174-2176.

(40) Pirkle, W. H.; Boeder, C. W. Preparation of simple chiral allenes. Reaction of propargylic carbamates with lithium dialkylcuprates. *J. Org. Chem.* **1978**, *43*, 1950-1952.

(41) Claesson, A.; Olsson, L. I. Chiral allenes are racemized by organocuprates. *J. Chem. Soc., Chem. Commun.* **1979**, 524-525.

(42) Westmijze, H.; Nap, I.; Meijer, J.; Kleijn, H.; Vermeer, P. On the configurational stability of allenes and butatrienes in the presence of organocopper(I) species. *Rec. Trav. Chim. Pays-Bas* **1983**, *102*, 154-157.

(43) Chenier, J. H. B.; Howard, J. A.; Mile, B. An ESR study of the addition of metal atoms to allene: metal-substituted allyl radicals. *J. Am. Chem. Soc.* **1985**, *107*, 4190-4191.

(44) Bongers, N.; Krause, N. Golden opportunities in stereoselective catalysis. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178-2181.

(45) Krause, N.; Winter, C. Gold-Catalyzed Nucleophilic Cyclization of Functionalized Allenes: A Powerful Access to Carbo- and Heterocycles. *Chem. Rev.* **2011**, *111*, 1994-2009.

(46) Harris, R. J.; Nakafuku, K.; Widenhoefer, R. A. Kinetics and Mechanism of the Racemization of Aryl Allenes Catalyzed by Cationic Gold(I) Phosphine Complexes. *Chem. - Eur. J.* **2014**, *20*, 12245-12254.

(47) Li, H.; Harris, R. J.; Nakafuku, K.; Widenhoefer, R. A. Kinetics and Mechanism of Allene Racemization Catalyzed by a Gold N-Heterocyclic Carbene Complex. *Organometallics* **2016**, *35*, 2242-2248.

(48) Mikami, K.; Yoshida, A. Dynamic kinetic protonation of racemic allenylmetal species for the asymmetric synthesis of allenic esters. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 858-860.

(49) Ogoshi, S.; Nishida, T.; Shinagawa, T.; Kurosawa, H. Key Process in Palladium-Catalyzed Asymmetric Transformation of Propargyl Electrophiles. Racemization of Optically Active η1-Allenylpalladium(II). *J. Am. Chem. Soc.* **2001**, *123*, 7164-7165.

(50) Burks, H. E.; Liu, S.; Morken, J. P. Development, Mechanism, and Scope of the Palladium-Catalyzed Enantioselective Allene Diboration. *J. Am. Chem. Soc.* **2007**, *129*, 8766-8773.

(51) Horvath, A.; Baeckvall, J.-E. Palladium(II)-Catalyzed SN2' Reactions of α-Allenic Acetates. Stereoconvergent Synthesis of (Z,E)-2-Bromo-1,3-dienes. *J. Org. Chem.* **2001**, *66*, 8120-8126.

(52) Horvath, A.; Baeckvall, J.-E. Mild and efficient palladium(II)-catalyzed racemization of allenes. *Chem. Commun.* **2004**, 964-965.

(53) Molander, G. A.; Sommers, E. M.; Baker, S. R. Palladium(0)-Catalyzed Synthesis of Chiral Ene-allenes Using Alkenyl Trifluoroborates. *J. Org. Chem.* **2006**, *71*, 1563-1568.

(54) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. Advances in Stereoconvergent Catalysis from 2005 to 2015: Transition-Metal-Mediated Stereoablative Reactions, Dynamic Kinetic Resolutions, and Dynamic Kinetic Asymmetric Transformations. *Chem. Rev.* **2017**, *117*, 4528-4561.

(55) Wolf, C.: *Dynamic Stereochemistry of Chiral Compounds-Principles and Applications*; Royal Society of Chemistry: Cambridge, UK, 2008.

(56) Espenson, J. H.: *Chemical Kinetics and Reaction Mechanisms*; 2 ed.; McGraw-Hill Inc: New York, NY, 1995.

(57) Stille, J. K.; Lau, K. S. Y. Mechanisms of oxidative addition of organic halides to Group 8 transition-metal complexes. *Acc. Chem. Res.* **1977**, *10*, 434-442.

(58) Zhang, C.; Lu, X. Phosphine-Catalyzed Cycloaddition of 2,3-Butadienoates or 2-Butynoates with Electron-Deficient Olefins. A Novel [3 + 2] Annulation Approach to Cyclopentenes. *J. Org. Chem.* **1995**, *60*, 2906-2908.

(59) Xing, J.; Lei, Y.; Gao, Y.-N.; Shi, M. PPh3-Catalyzed [3 + 2] Spiroannulation of 1C,3N-Bisnucleophiles Derived from Secondary β-Ketoamides with δ-Acetoxy Allenoate: A Route to Functionalized Spiro N-Heterocyclic Derivatives. *Org. Lett.* **2017**, *19*, 2382-2385.

(60) Coulson, D. R. Transition metal catalyzed reactions of allene. *J. Org. Chem.* **1973**, *38*, 1483-1490.

(61) Besson, L.; Gore, J.; Cazes, B. Palladium-catalyzed addition of malonate type compounds to allenes via a hydropalladation process. *Tetrahedron Lett.* **1995**, *36*, 3853-3856.

(62) Okamoto, K.; Kai, Y.; Yasuoka, N.; Kasai, N. Moleculr structure of bis(triphenylphosphine)allenepalladium. *J. Organometal. Chem.* **1974**, *65*, 427-441.

(63) Wachsstock, D.: Tenua. 2.1 ed.; Oracle, 2007.

(64) Barshop, B. A.; Wrenn, R. F.; Frieden, C. Analysis of numerical methods for computer simulation of kinetic processes: development of KINSIM - a flexible, portable system. *Anal. Biochem.* **1983**, *130*, 134-145.

(65) Haines, B. E.; Berry, J. F.; Yu, J.-Q.; Musaev, D. G. Factors Controlling Stability and Reactivity of Dimeric Pd(II) Complexes in C-H Functionalization Catalysis. *ACS Catal.* **2016**, *6*, 829-839.

(66) Bakhmutov, V. I.; Berry, J. F.; Cotton, F. A.; Ibragimov, S.; Murillo, C. A. Non-trivial behavior of palladium(II) acetate. *Dalton Trans.* **2005**, 1989-1992.

Chapter 3 Appendix

Experimental methods and spectral analysis for Ch. 3 compounds

Table of Contents:

General Information:

TLC analysis was performed with silica gel HL TLC plates w/UV254 from Sorbent Technologies. 60 Å porosity, 230 x 400 mesh standard grade silica gel from Sorbent Technologies was used for column chromatography. Infrared spectra were recorded on a PerkinElmer Spectrum 100 FTIR spectrometer with liquid samples sealed in 0.1 mm NaCl cells or solid samples as KBr pellets. GC/MS data was obtained using a Shimadzu GCMS-QP2010 SE. HRMS was run using EI or ESI techniques. ^{1}H and ^{13}C spectra were obtained on a Bruker Advance 500 DRX equipped with a QNP cryoprobe and referenced to residual protio solvent signals. Chiral HPLC analysis was performed by LC- 10ATVP Shimadzu HPLC using a Chiralpak AD-H chiral column (0.46cm∅x25cm), eluting with hexane / iso-propanol mixture. Optical rotations were measured on a Autopol® IV automatic polarimeter using a 5 cm cell and sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated All racemizations were run in flame dried 25 mL microwave vials from Biotage. THF was distilled over Na using benzophenone as an indicator. All palladium catalysts and ligands were purchased from Strem and stored in a glove box under argon atmosphere.

Kinetics Experimental:

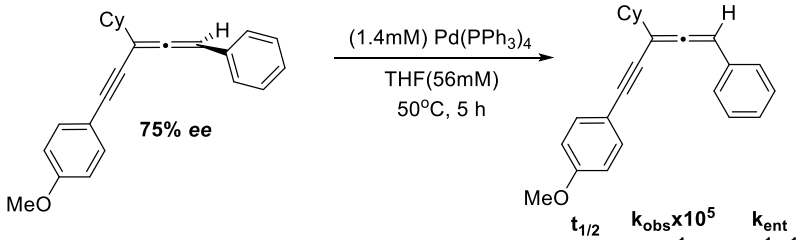
Representative procedure for the Racemization of Allenynes:

A 10 mL volumetric flask, and a flame dried 25 mL microwave vial (Biotage #355631), charged with a stir bar, were taken into the glove box. The enantioenriched allenyne (182 mg, 0.55 mmol) was transferred into a clean tared scintillation vial and then also brought into the glove box. $Pd(PPh_3)_4$ (0.015 g, 0.014 mmol) was added to the 10 mL volumetric flask. The allenynes was dissolved in pipette-full (ca. 1-2 mL) of THF and transferred from the scintillation vial to the volumetric flask by pipette. The scintillation vial was then washed twice with a pipette-full of

THF and the wash was then added to the volumetric flask. THF was then added to the volumetric flask to the 10mL mark. The solution was then mixed by pipette and transferred to the microwave vial. The microwave vial was then capped using a vial cap (Biotage #352298) and a manual cap crimper (Biotage #353671) and removed from the glove box. A 0.7 mL aliquot was removed from the vial using a syringe. The aliquot was diluted with THF to 3 mL in a volumetric flask. The solution was then transferred to a vial marked T=0 and stored in the freezer. The microwave vial was then placed in an oil bath to be stirred/heated at 50°C. 0.7mL aliquots were then removed periodically, diluted to 3 mL, and stored in the freezer. All aliquots were then warmed to room temperature, and polarimetry analysis was performed.

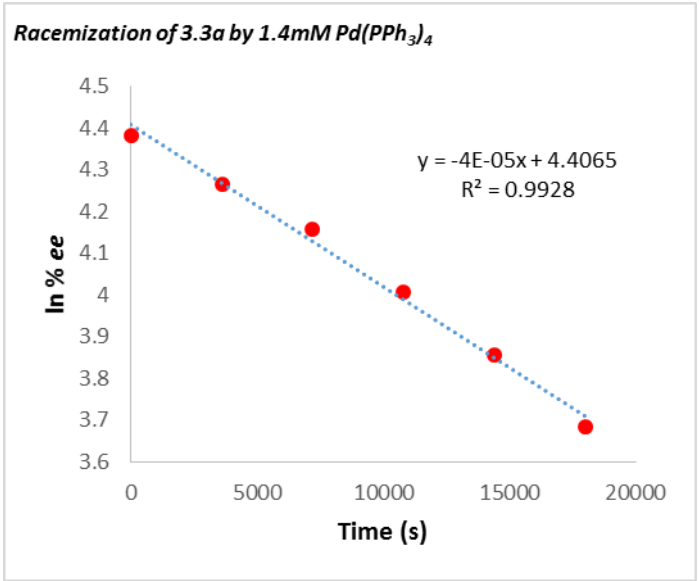
Kinetics Tables and Plots:

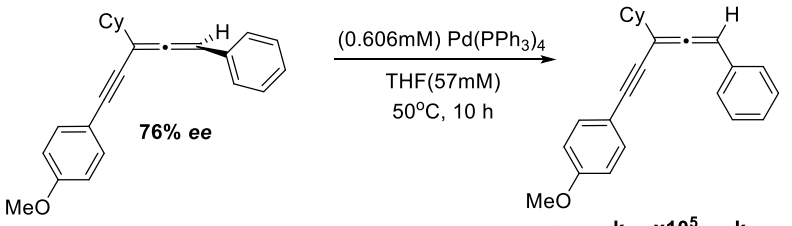
Palladium(0)-Catalyzed Racemization:



Exp: MS3-052

$t_{1/2}$ (min)	$k_{obs}x10^5$ (s^{-1})	k_{ent} ($M^{-1}s^{-1}$)
299	3.86	0.014





Exp: MS3-163

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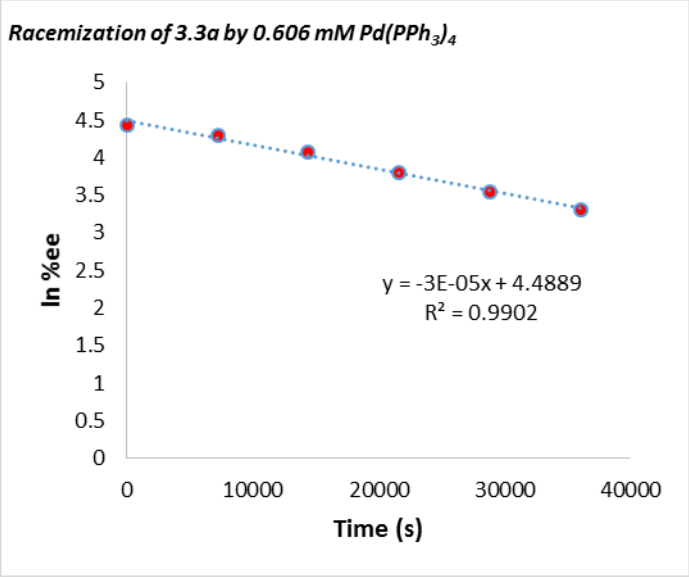
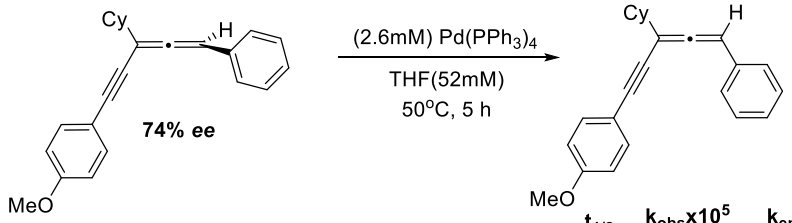
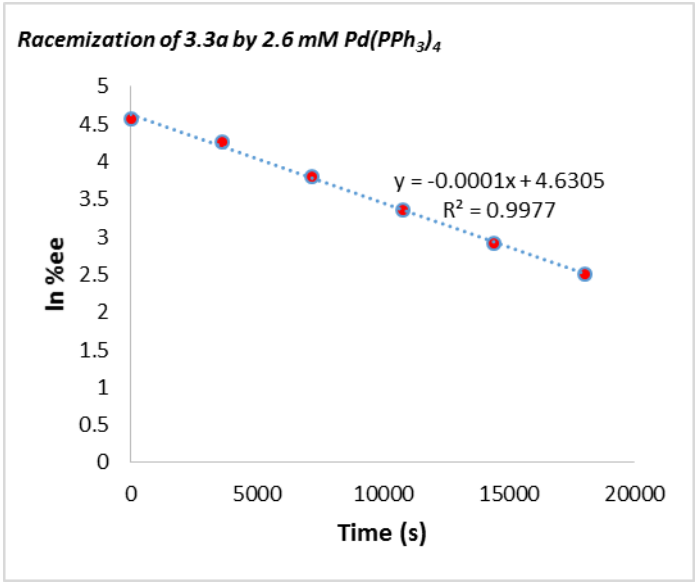
421	2.74	0.022



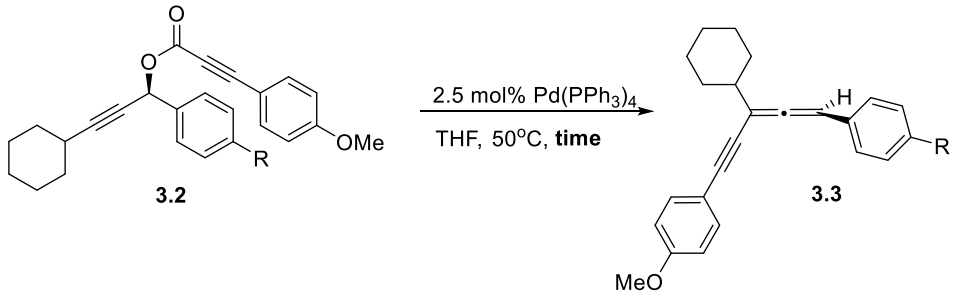


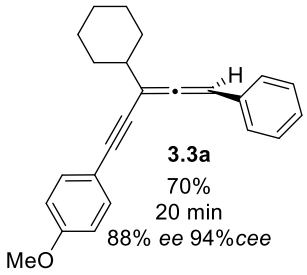
Exp: MS3-166

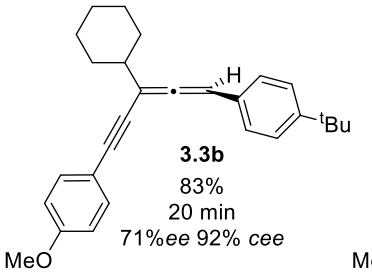
$t_{1/2}$ (min)	$k_{obs}x10^5$ (s^{-1})	k_{ent} ($M^{-1}s^{-1}$)
125	9.27	0.018

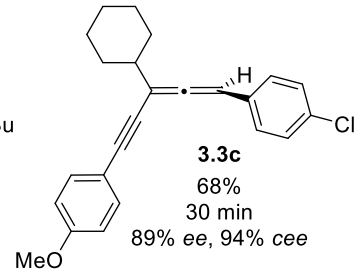


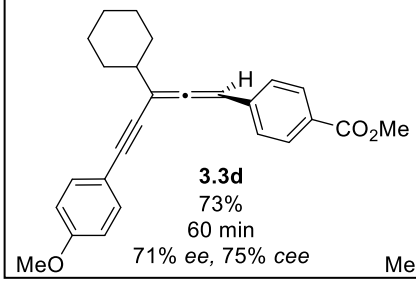
Scope of Allenynes for Hammett Plot

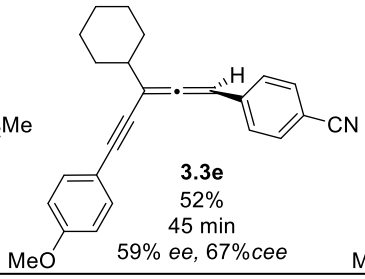


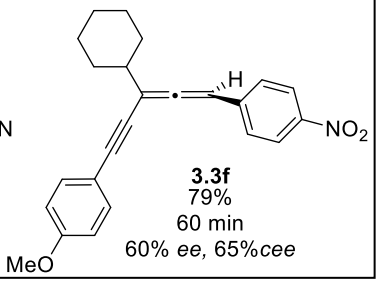


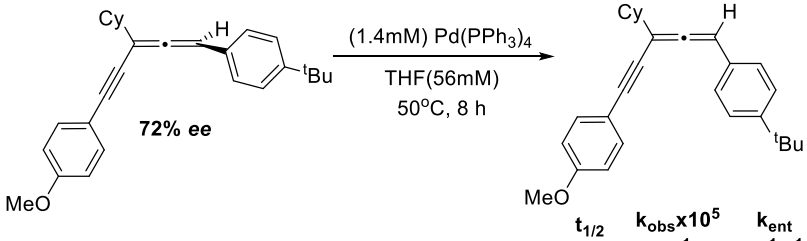






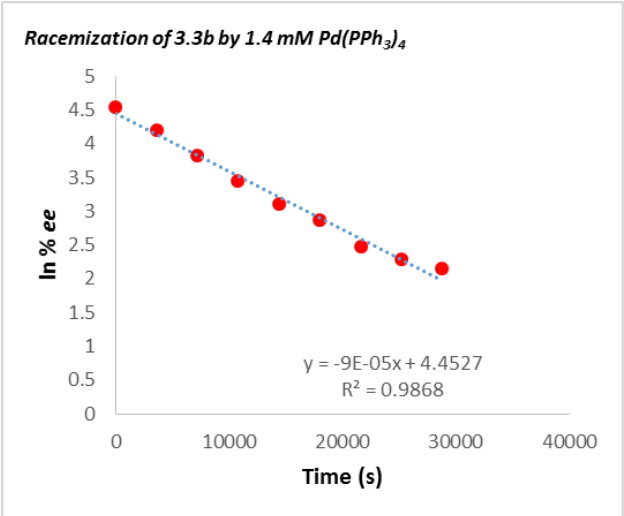


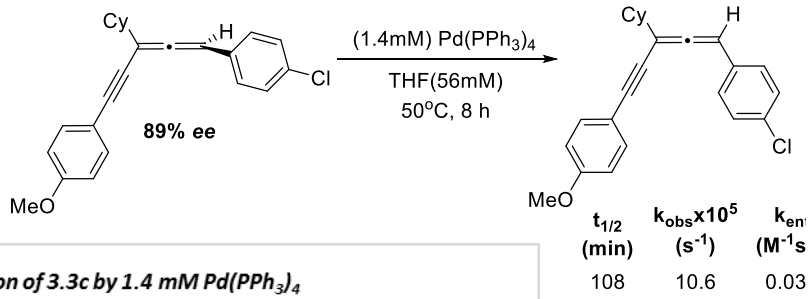




Exp: MS3-276

$t_{1/2}$ (min)	$k_{obs}x10^5$ (s^{-1})	k_{ent} ($M^{-1}s^{-1}$)
111	10.4	0.037





Exp: MS4-013

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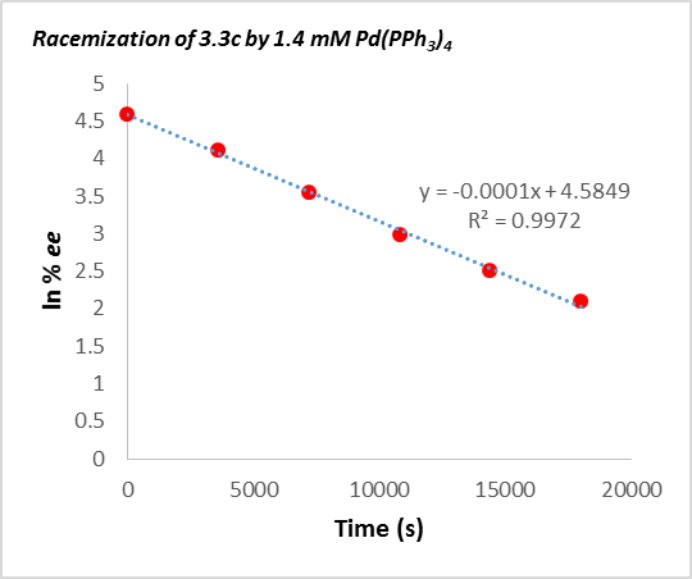
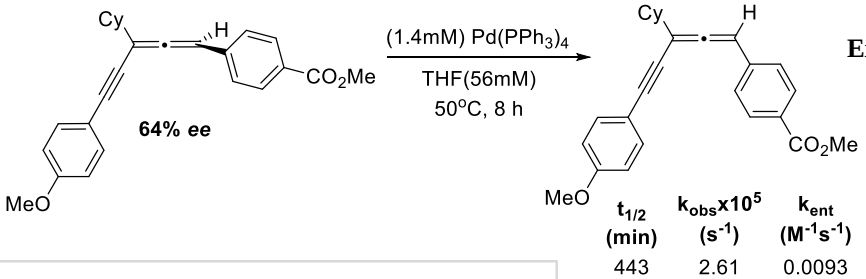
108	10.6	0.03





Exp: MS3-276

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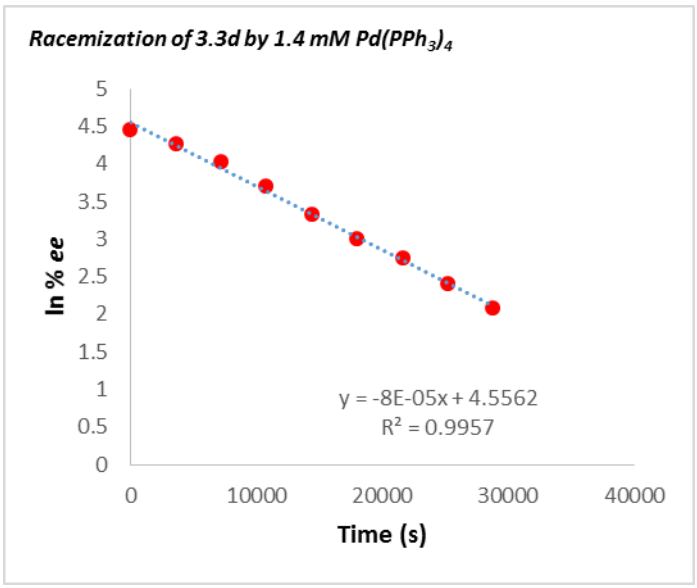
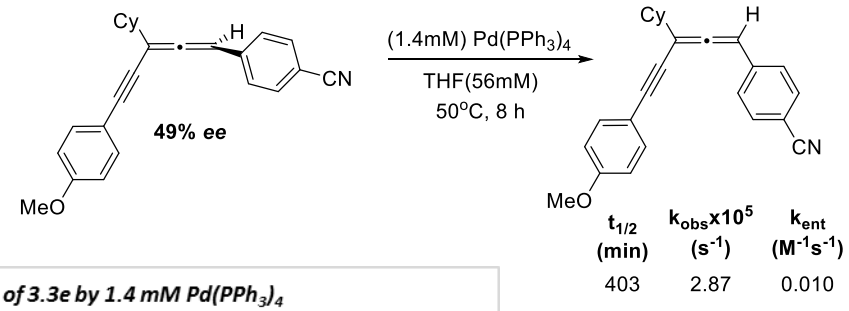
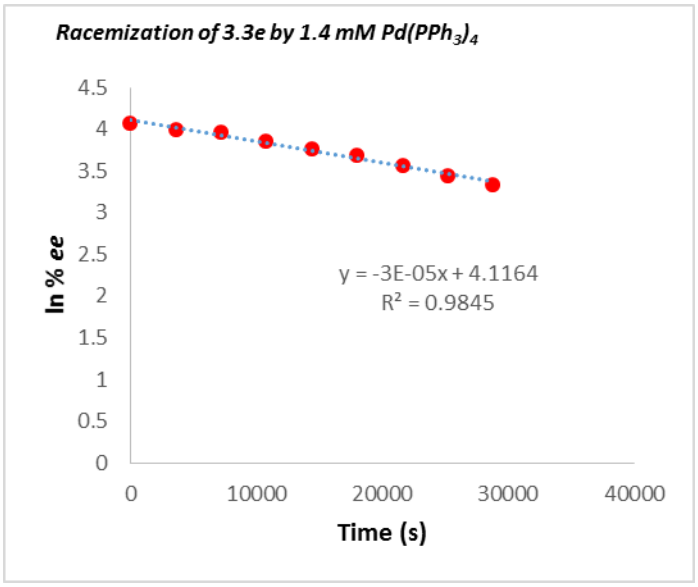
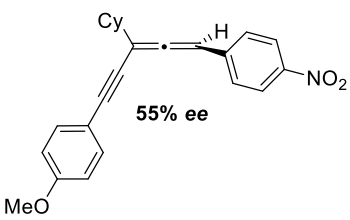




$t_{1/2}$ (min)	$k_{obs}x10^5$ (s^{-1})	k_{ent} ($M^{-1}s^{-1}$)
403	2.87	0.010

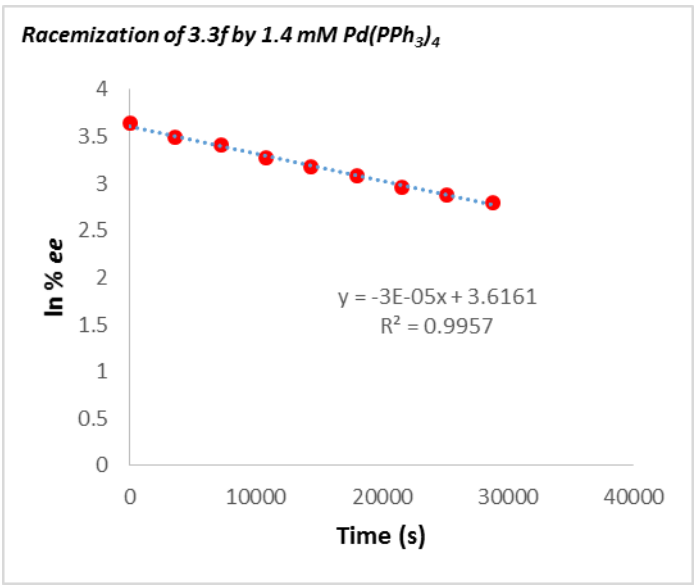
Exp: MS3-245





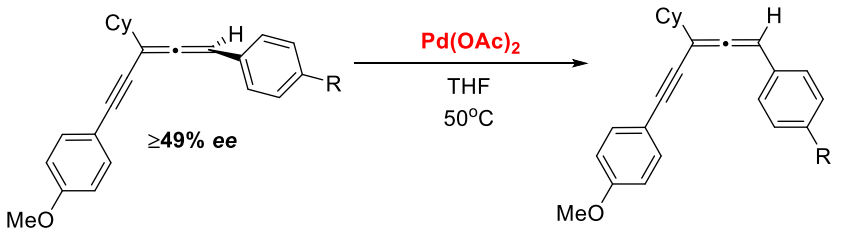
$t_{1/2}$ (min)	$k_{obs}x10^5$ (s^{-1})	k_e (M^{-1}
369	3.13	0.0

Exp: MS3-262

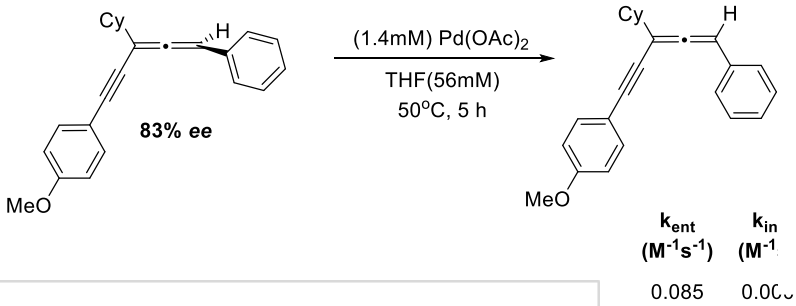


Palladium(II)-Catalyzed Racemizations:

Table 3.1: "Observed" ***Rate Constants for $Pd(OAc)_2$-Catalyzed Racemizations of Allenynes***



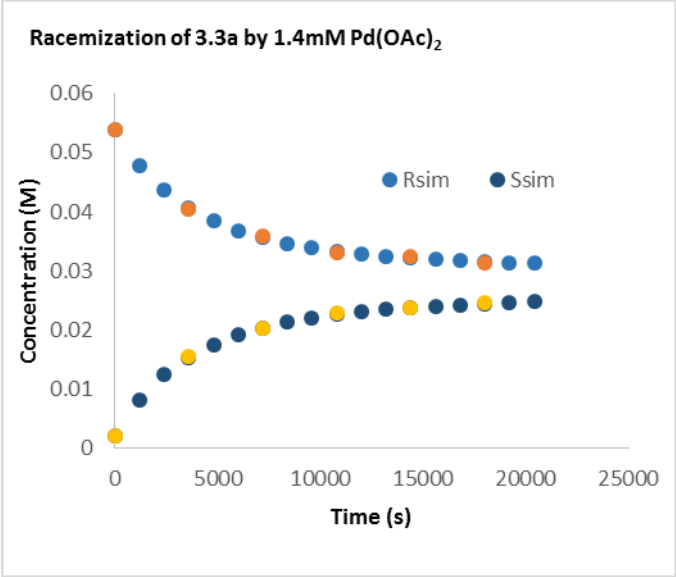
Entry	substrate	R	[Allene] (mM)	[Cat.] (mM)	$k_{obs}x10^6$ ($M^{-1}s^{-1}$)
1	**3.3a**	H	56	1.4	3.67
2	**3.3a**	H	53	0.62	2.75
3	**3.3a**	H	52	0.80	9.15
4	**3.3a**	H	52	2.5	6.68
5	**3.3a**	H	53	2.8	5.37
6	**3.3a**	H	38	1.4	9.06
7	**3.3a**	H	115	1.4	3.11

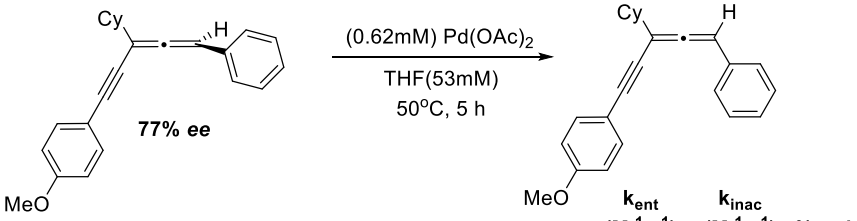


Shown: MS3-059

Other: MS3-179, MS3-294

k_{ent} ($M^{-1}s^{-1}$)	k_{in} (M^{-1}	
0.085	0.00	0.44±0.2

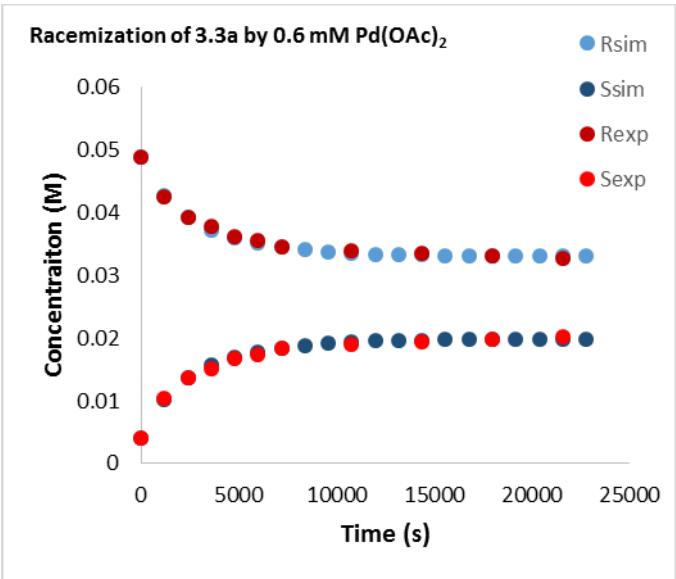


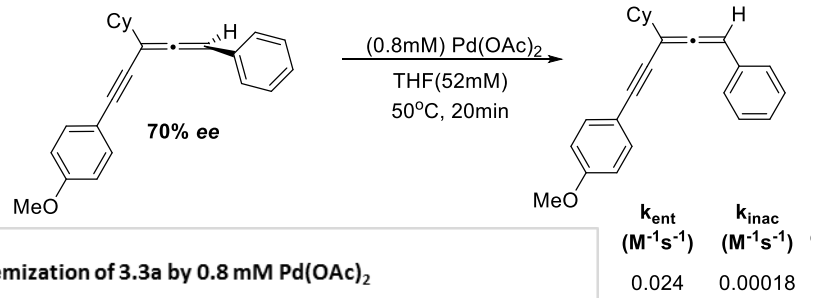


Shown: MS3-230

Other: MS3-182

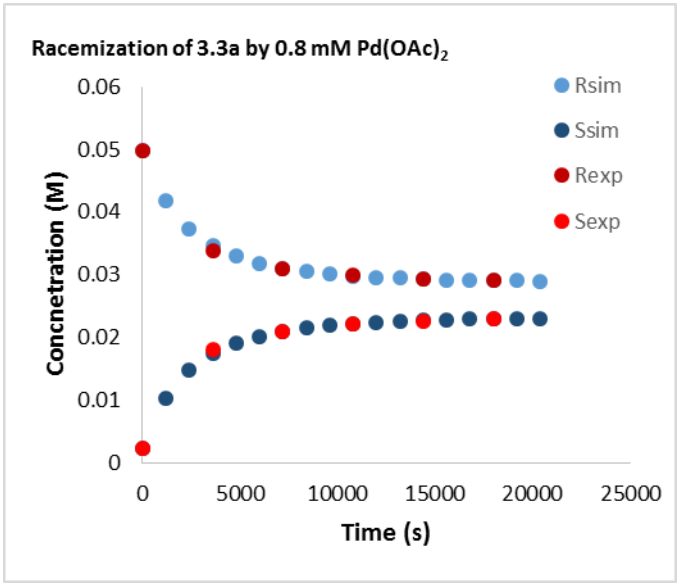
k_{ent} ($M^{-1}s^{-1}$)	k_{inac} ($M^{-1}s^{-1}$)	%resi
0.247	0.00025	0.75±

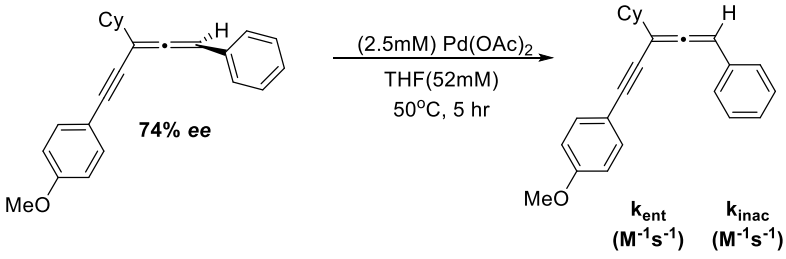




Shown: MS3-171

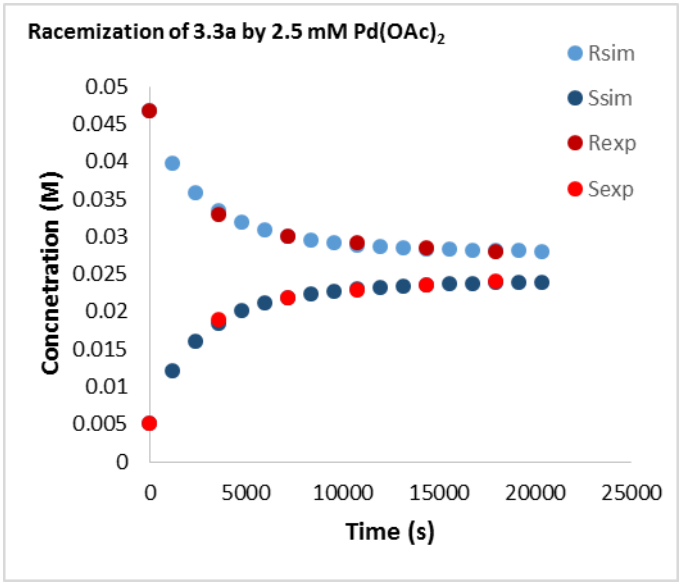
k_{ent} ($M^{-1}s^{-1}$)	k_{inac} ($M^{-1}s^{-1}$)
0.024	0.00018

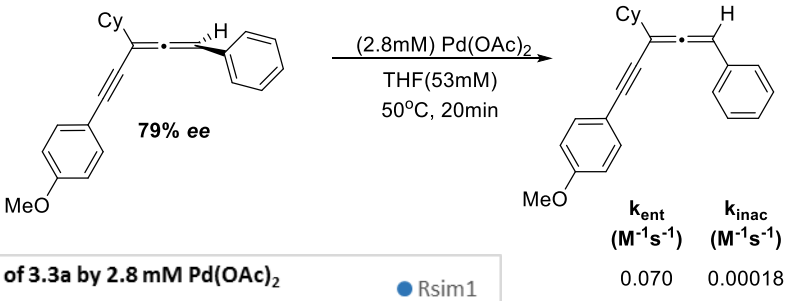




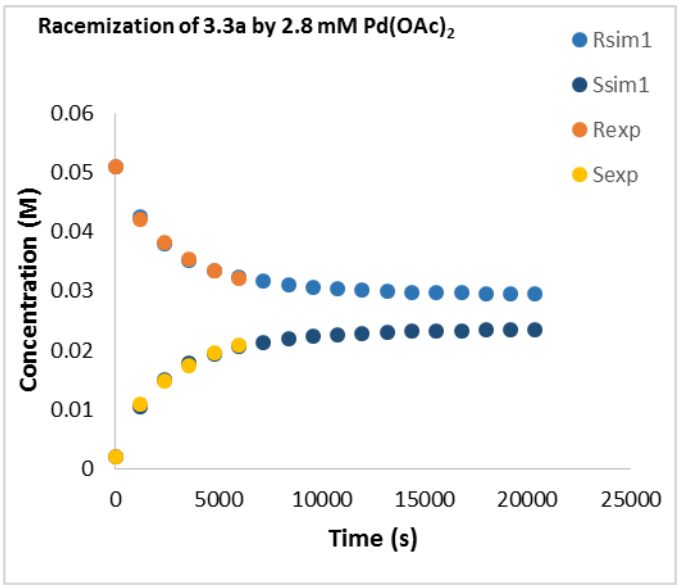
Shown: MS3-177

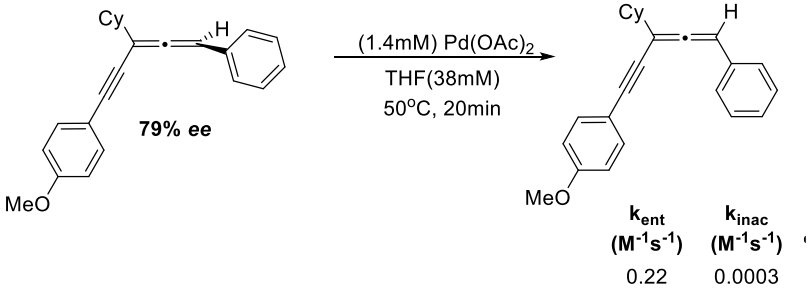
k_{ent} ($M^{-1}s^{-1}$)	k_{inac} ($M^{-1}s^{-1}$)
0.076	0.00015



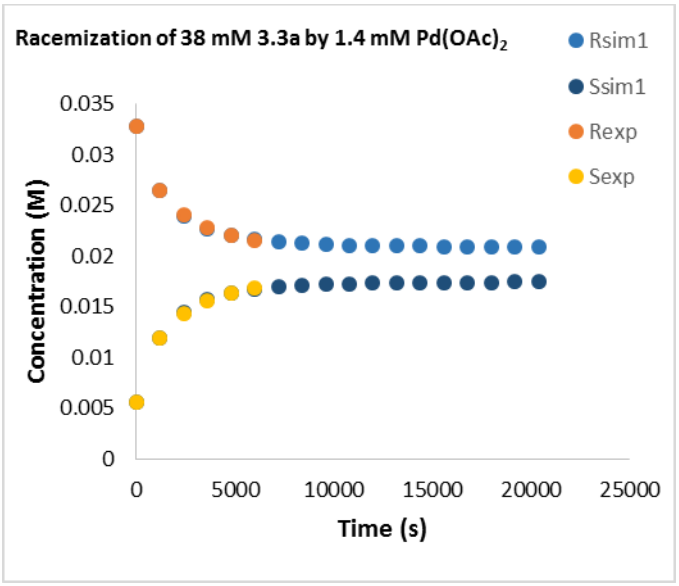


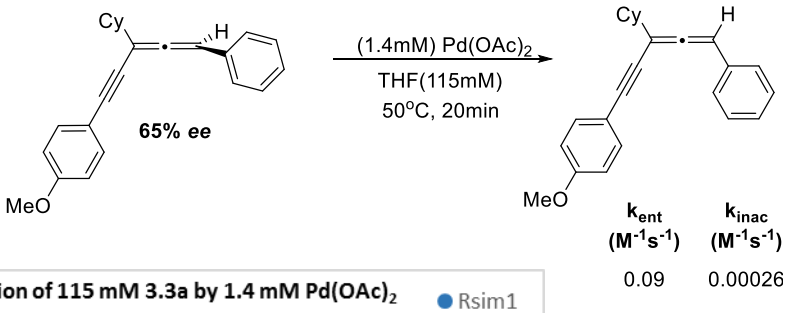
Shown: MS3-189





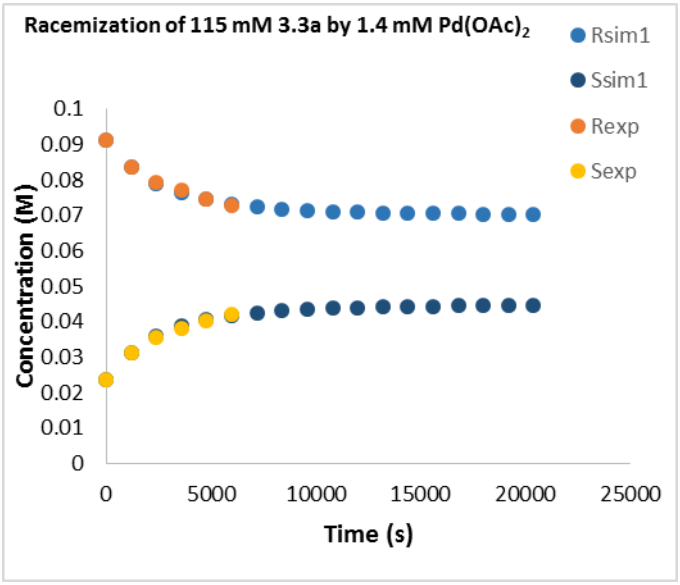
Shown: MS3-186

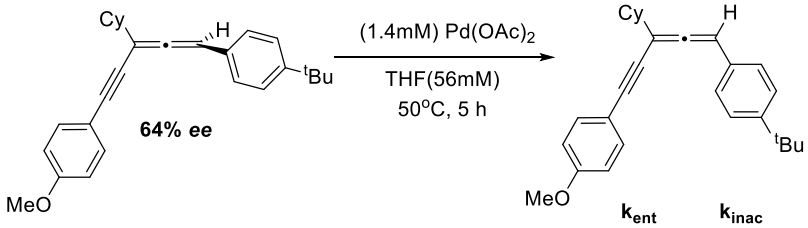




Shown: MS3-211

k_{ent} ($M^{-1}s^{-1}$)	k_{inac} ($M^{-1}s^{-1}$)
0.09	0.00026

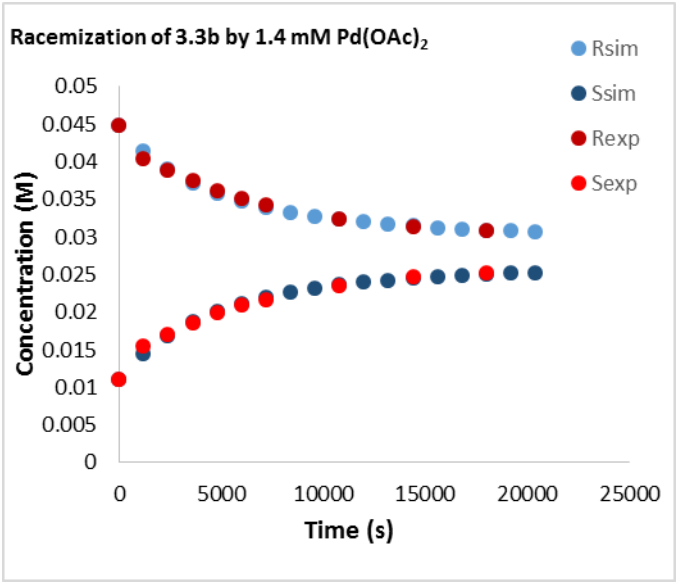


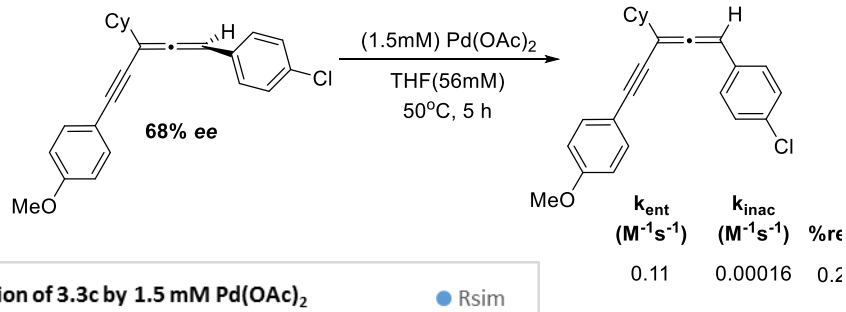


Shown: MS3-251

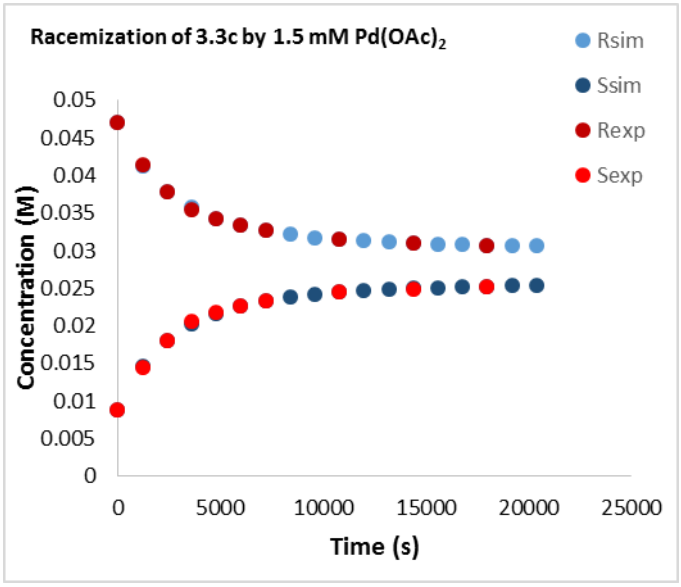
Other: MS3-298

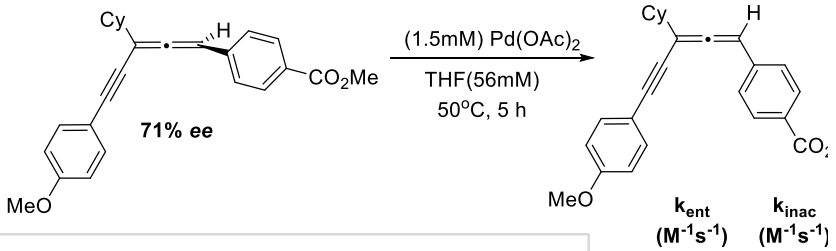
k_{ent} ($M^{-1}s^{-1}$)	k_{inac} ($M^{-1}s^{-1}$)	%
0.07	0.00009	0.79±0.7





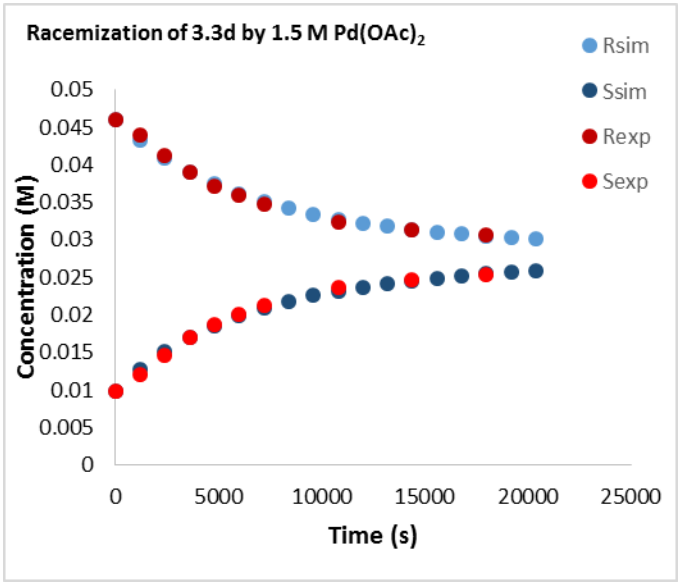
Shown: MS3-290

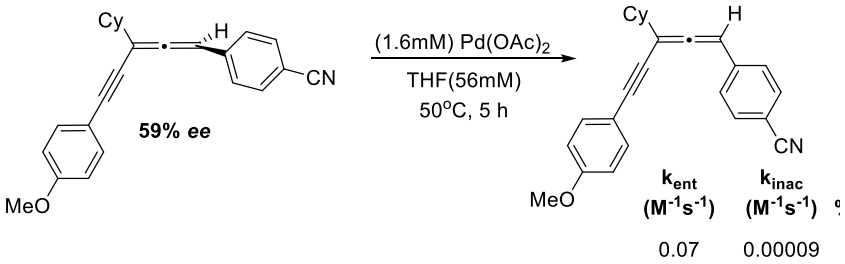




Shown: MS3-220

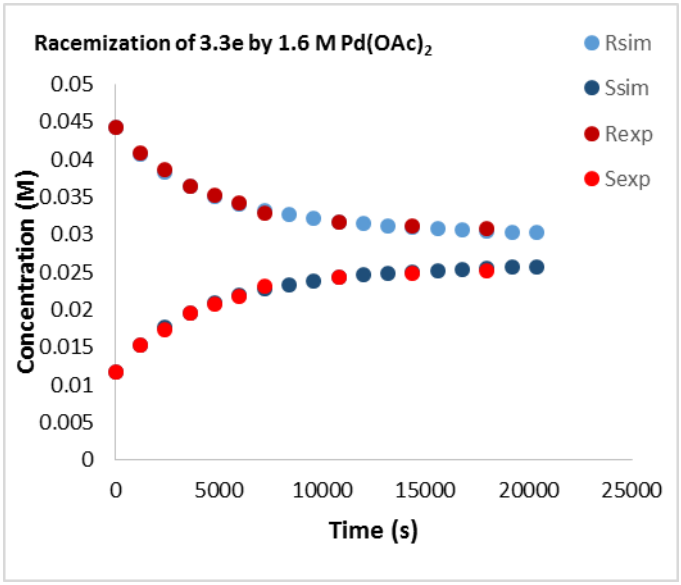
Other: MS3-258

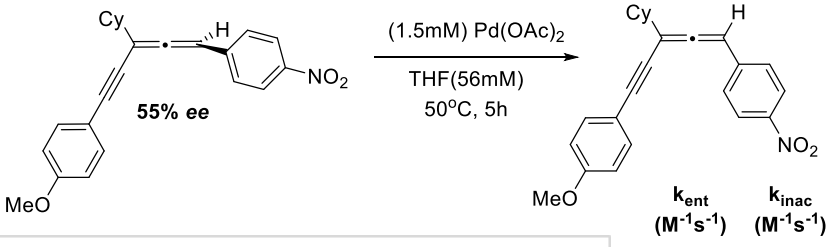




Shown: MS3-239

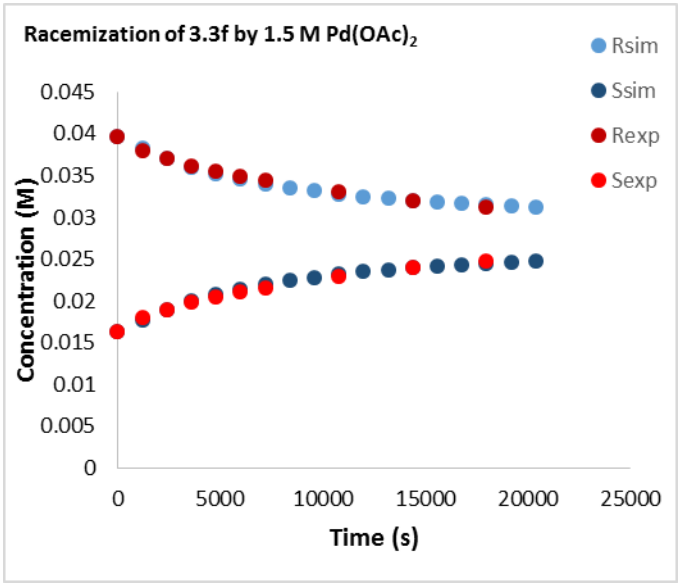
Other: MS4-006, MS4-011





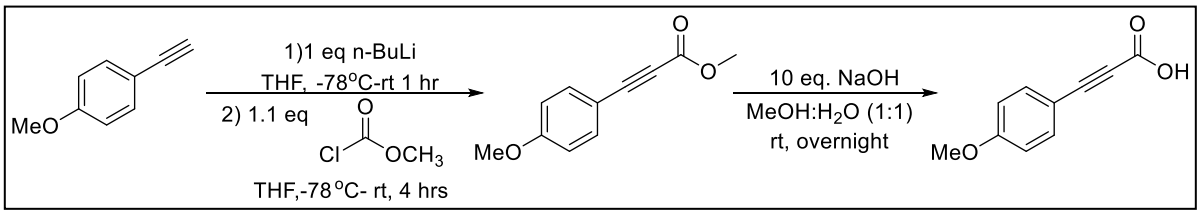
Shown: MS3-279

Other: MS3-237

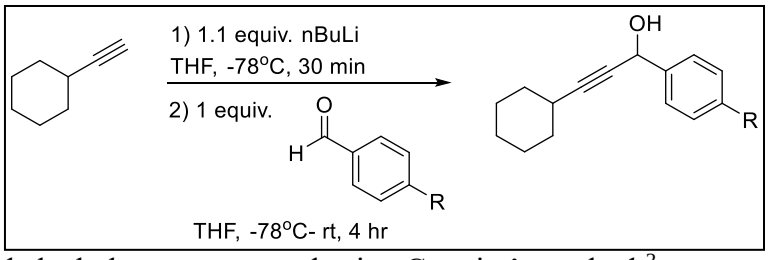


Synthesis of Propargyl Propiolates:

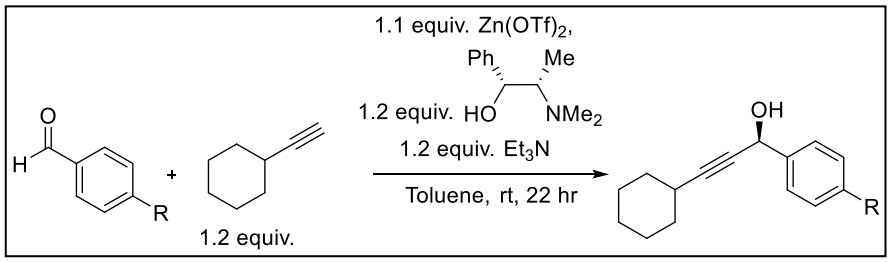
p-OMe phenylpropiolic acid was prepared using the following literature procedure:[1]



All racemic alcohols were prepared using methods reported in literature:[2]



All enantioenriched alcohols were prepared using Carreira's method:[3]

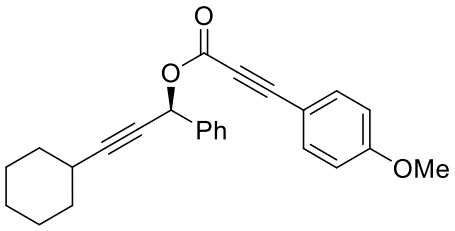


General Procedure for the synthesis of propargyl propiolates (General Procedure A):

Reactions were typically run on a 2 to 10 mmol scale

To a cooled (0 °C) stirred solution of the *p*-OMe propiolic acid acid (730 mg, 5 mmol) in DCM (50 mL) was added 2-butyn-1-ol (350.45 mg, 5mmol) followed by dimethylaminopyridine (DMAP) (36.7mg, 0.3mmol) and then DCC (1031.7 mg, 5 mmol). The solution was allowed to warm to rt and stirred overnight. Reaction was filtered through a pad of celite with DCM. Filtrate was washed with 1 N HCl , Sat. $NaHCO_3$, brine, and then dried over $MgSO_4$. The solvent was evaporated and the crude product purified by flash chromatography

Characterization Data for Propargyl Propiolates:



MS2-269

(S)-3-cyclohexyl-1-phenylprop-2-yn-1-yl 3-(4-methoxyphenyl **.2a)**

Prepared from (S)-3-cyclohexyl-1-phenylprop-2-yn-1-ol (687 mg, 0.003 mol) and *p*-OMe phenylpropiolic acid (528 mg, 0.003 mol) via general procedure A. Viscous yellow oil isolated from flash chromatography using 90:10 hexanes:EtOAc as eluent (636 mg, 0.0017 mol, 53%)

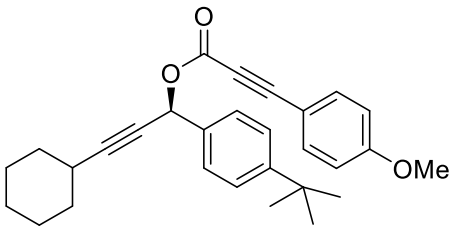
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.56 (m, 2H), 7.56 – 7.48 (m, 2H), 7.44 – 7.33 (m, 3H), 6.91 – 6.83 (m, 2H), 6.59 (d, *J* = 1.9 Hz, 1H), 2.53 – 2.45 (m, 1H), 1.86 – 1.80 (m, 2H), 1.71 (dddt, *J* = 12.5, 9.3, 6.3, 3.7 Hz, 2H), 1.58 – 1.45 (m, 3H), 1.36 – 1.26 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 153.4, 137.1, 135.1, 129.1, 128.7, 128.2, 114.4, 111.4, 93.4, 88.2, 80.1, 76., 67.7, 55.5, 32.4, 32.4, 29.3, 25.9, 24.9.

GC/MS 172.2(M^+),(base peak)

IR (neat) ν_{max} 2937, 2211, 1709, 1253, 837 cm^{-1}

HPLC analysis: 95%ee (Chiralpak AD-H, 97:3 hexanes/isopropanol, 0.3 mL/min, 254 nm, minor R_t = 32.7 min, major R_t = 34.3 min)



MS3-242

(S)-1-(4-(tert-butyl)phenyl)-3-cyclohexylprop-2-yn-1-yl 3-(4-m propiolate

(3.2b)

Prepared from (*S*)-1-(4-(tert-butyl)phenyl)-3-cyclohexylprop-2-yn-1-ol (487 mg, 0.0018 mol) and *p*-OMe phenylpropiolic acid (317 mg, 0.0018 mol) via general procedure A. Colorless viscous oil isolated from flash chromatography using 92:8 hexanes:EtOAc as eluent (470 mg, 0.0011 mol, 61%)

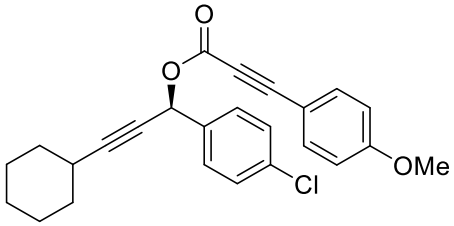
^{1}H NMR (500 MHz, Chloroform-d) δ 7.52 (dd, J = 8.7, 6.9 Hz, 4H), 7.43 – 7.39 (m, 2H), 6.89 – 6.83 (m, 2H), 6.58 (d, J = 1.9 Hz, 1H), 3.82 (s, 3H), 2.53 – 2.42 (m, 1H), 1.88 – 1.79 (m, 2H), 1.71 (dq, J = 11.9, 2.9 Hz, 2H), 1.50 (dq, J = 9.4, 4.4, 3.8 Hz, 3H), 1.33 (s, 12H).

^{13}C NMR (126 MHz, CDCl3) δ 161.6, 153.5, 152.2, 135.1, 134.0, 128.0, 125.7, 114.4, 111.5, 93.1, 88.0, 80.1, 76.1, 67.6, 55.5, 34.8, 32.5, 32.4, 31.4, 29.3, 25.9, 24.9.

HRMS M+H calcd for $C_{29}H_{33}O_3$: 429.2430 found: 429.2783

IR (neat) νmax 2963, 2855, 2211, 1708, 1605, 1511, 1448, 1155, 833 cm^{-1}

HPLC analysis: 82%ee (Chiralpak AD-H, 97:3 hexanes/isopropanol, 0.3 mL/min, 254 nm, minor Rt = 22.4 min, major Rt =24.4 min)



MS3-268

(S)-1-(4-chlorophenyl)-3-cyclohexylprop-2-yn-1-yl 3-(4-methoxyl ate (3.2c)

Prepared from (*S*)-1-(4-chlorophenyl)-3-cyclohexylprop-2-yn-1-ol (970 mg, 0.0039 mol) and *p*-OMe phenylpropiolic acid (686 mg, 0.0039 mol) via general procedure A. Yellow viscous oil isolated from flash chromatography using 94:6 hexanes:EtOAc as eluent (1138 mg, 0.0028 mol, 72%)

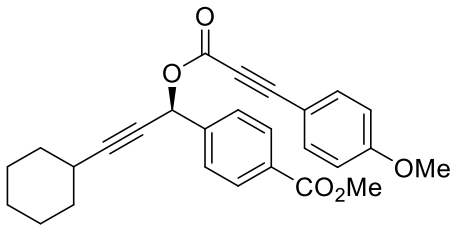
^{1}H NMR (500 MHz, Chloroform-d) δ 7.59 – 7.49 (m, 4H), 7.43 – 7.32 (m, 2H), 6.92 – 6.81 (m, 2H), 6.54 (d, J = 1.9 Hz, 1H), 3.83 (s, 3H), 2.51 – 2.43 (m, 1H), 1.88 – 1.77 (m, 2H), 1.73 – 1.66 (m, 2H), 1.49 (m, 3H), 1.37 – 1.27 (m, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 161.7, 153.3, 135.7, 135.2, 135.1, 129.6, 128.9, 114.4, 111.3, 93.7, 88.5, 79.9, 75.7, 66.9, 55.5, 32.4, 32.4, 29.2, 25.9, 24.9.

HRMS M+H calcd for $C_{29}H_{33}O_3$: 429.2430 found: 429.2783

IR (neat) νmax 2932, 2856, 2209, 1710, 1606, 1512, 1492, 1151, 837 cm^{-11}

HPLC analysis: 93%ee (Chiralpak AD-H, 97:3 hexanes/isopropanol, 0.3 mL/min, 254 nm, minor Rt = 34.7 min, major Rt = 40.3 min)



MS3-202

methyl (S)-4-(3-cyclohexyl-1-((3-(4-methoxyphenyl)propioloyl) -yl)benzoate

(3.2d)

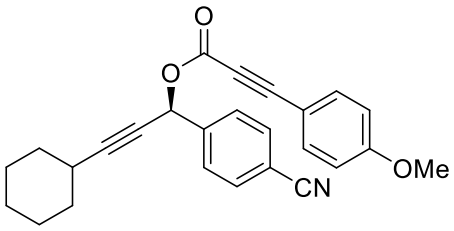
Prepared from methyl (*S*)-4-(3-cyclohexyl-1-hydroxyprop-2-yn-1-yl)benzoate (980 mg, 0.0036 mol) and *p*-OMe phenylpropiolic acid (634 mg, 0.0036 mol) via general procedure A. Pale yellow amorphous solid isolated from flash chromatography using 88:12 hexanes:EtOAc as eluent (630 mg, 0.0015 mol, 42%)

^{1}H NMR (500 MHz, Chloroform-d) δ 8.13 – 7.98 (m, 2H), 7.71 – 7.61 (m, 2H), 7.58 – 7.48 (m, 2H), 6.95 – 6.78 (m, 2H), 6.61 (d, J = 1.8 Hz, 1H), 3.92 (s, 3H), 3.83 (s, 3H), 2.49 (q, J = 9.0, 7.3 Hz, 1H), 1.82 (dt, J = 9.6, 3.1 Hz, 2H), 1.69 (td, J = 6.1, 5.4, 2.7 Hz, 2H), 1.57 – 1.44 (m, 3H), 1.41 – 1.25 (m, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 166.8, 161.8, 153.2, 141.9, 135.2, 130.7, 130.1, 127.9, 114.4, 111.3, 94.0, 88.7, 79.8, 75.6, 67.0, 55.5, 52.4, 32.4, 32.3, 29.2, 25.9, 24.9.

HRMS *m/z:* M+Na calcd for $C_{27}H_{26}O_5Na$: 453.1678, found: 453.1682 **IR** (DCM) ν_{max} 3057, 2939, 2211, 1719, 1711, 1605, 1511, 1271, cm^{-1}

HPLC analysis:96%ee (Chiralpak AD-H, 95:5 hexanes/isopropanol, 0.3 mL/min, 254 nm, minor R_t = 59.1min, major R_t = 72.4 min)



MS3-222

(S)-1-(4-cyanophenyl)-3-cyclohexylprop-2-yn-1-yl 3-(4-methox olate (3.2e)

Prepared from (*S*)-4-(3-cyclohexyl-1-hydroxyprop-2-yn-1-yl)benzonitrile (1436 mg, 0.006 mol) and *p*-OMe phenylpropiolic acid (1056 mg, 0.006 mol) via general procedure A. Yellow amorphous solid isolated from flash chromatography using 85:15 hexanes:EtOAc as eluent (2021 mg, 0.0051 mol, 85%)

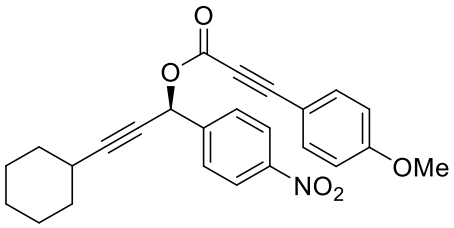
^{1}H NMR (500 MHz, Chloroform-d) δ 7.69 (s, 4H), 7.55 – 7.51 (m, 2H), 6.91 – 6.84 (m, 2H), 6.58 (d, J = 1.9 Hz, 1H), 3.83 (s, 3H), 2.53 – 2.41 (m, 1H), 1.86 – 1.78 (m, 2H), 1.74 – 1.64 (m, 2H), 1.49 (ddd, J = 16.8, 7.3, 4.0 Hz, 3H), 1.32 (d, J = 7.3 Hz, 3H)

^{13}C NMR (126 MHz, CDCl3) δ 161.9, 153.1, 142.2, 135.3, 132.6, 128.6, 118.6, 114.5, 112.9, 111.1, 94.5, 89.1, 79.6, 75.1, 66.6, 55.6, 32.3, 32.3, 29.2, 25.9, 24.9.

HRMS *m/z:* M+H calcd for $C_{26}H_{24}NO_3$: 398.1756, found: 398.1722

IR (neat) ν_{max} 3060, 2989, 2232, 2210, 1711, 1604, 1510, 1266, 1154, 836 cm^{-1}

HPLC analysis: 91%ee (Chiralpak AD-H, 95:5 hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 41.2 min, major R_t = 53.7min)



MS3-204

(S)-3-cyclohexyl-1-(4-nitrophenyl)prop-2-yn-1-yl 3-(4-metho: ɔlate (3.2f)

Prepared from (*S*)-3-cyclohexyl-1-(4-nitrophenyl)prop-2-yn-1-ol (1271 mg, 0.0049 mol) and *p*-OMe phenylpropiolic acid (862 mg, 0.0049 mol) via general procedure A. Orange viscous oil isolated from chromatography using 85:15 hexanes:EtOAc as eluent (1372 mg, 0.0033 mol, 68%)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.84 – 7.70 (m, 2H), 7.58 – 7.49 (m, 2H), 6.93 – 6.82 (m, 2H), 6.63 (d, J = 1.9 Hz, 1H), 3.84 (s, 3H), 2.48 (q, J = 4.4, 3.5 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.74 – 1.65 (m, 2H), 1.49 (ddt, J = 18.7, 9.2, 5.3 Hz, 3H), 1.38 – 1.24 (m, 3H).

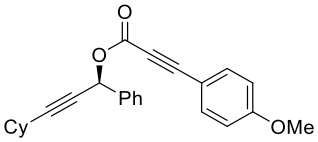
^{13}C NMR (126 MHz, CDCl3) δ 161.9, 153.0, 148.2, 144.0, 135.3, 128.8, 124.0, 114.5, 111.1, 94.7, 89.2, 79.6, 75.1, 66.3, 55.6, 32.3, 32.3, 29.2, 25.9, 24.9.

HRMS *m/z:* M+H calcd for $C_{25}H_{24}NO_5$: 418.1654, found: 418.1567

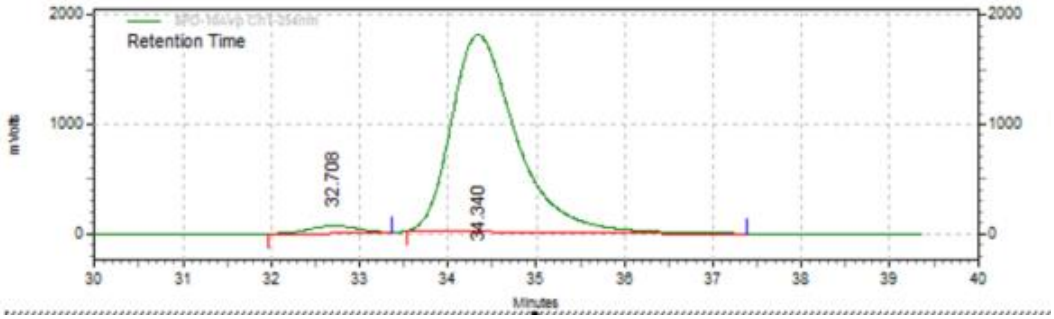
IR (neat) ν_{max} 2932, 2856, 2209, 1712, 1605, 1526, 1511, 1349, 1186, 835 cm^{-1}

HPLC analysis: 92%ee (Chiralpak AD-H, 95:5 hexanes/isopropanol, 0.5 mL/min, 254 nm, minor R_t = 34.7 min, major R_t = 52.6 min)

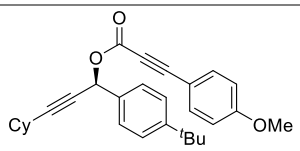
HPLC Chromatographs for Propargyl Propiolates:

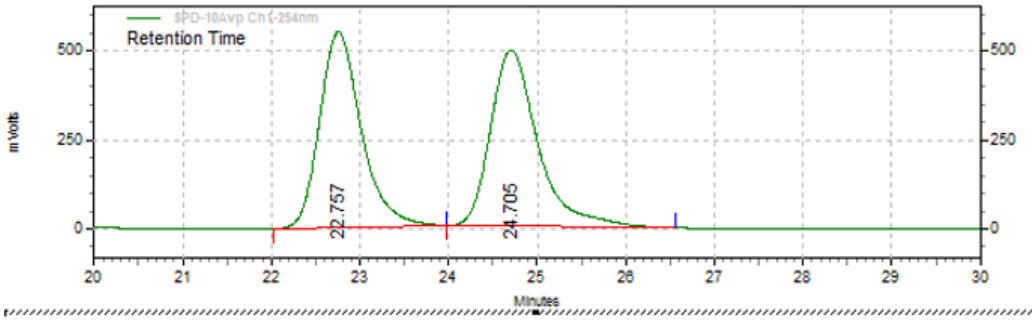
Compound ***(3.2a)***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	97:03	0.3	254	34.3	32.7

SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
31.755	32951837	43.90	858275	45.35
33.982	42106275	56.10	1034464	54.65
Totals				
	75058112	100.00	1892739	100.00

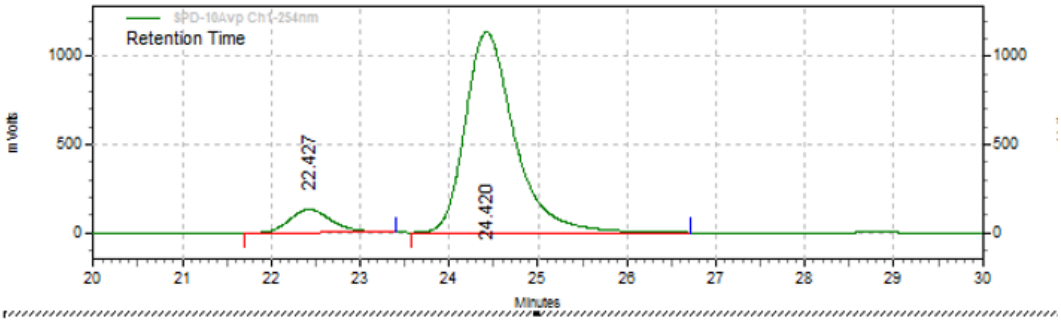


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
32.708	2368585	2.54	64206	3.46
34.340	90983001	97.46	1792075	96.54
Totals				
	93351586	100.00	1856281	100.00

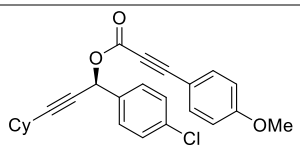
Compound ***(3.2b)***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	97:3	0.3	254	24.4	22.4

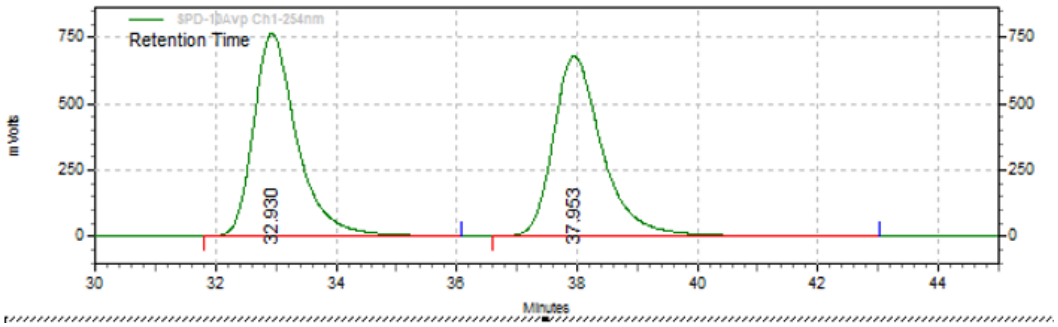


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
22.757	17893058	49.39	549655	52.59
24.705	18331923	50.61	495478	47.41
Totals				
	36224981	100.00	1045133	100.00

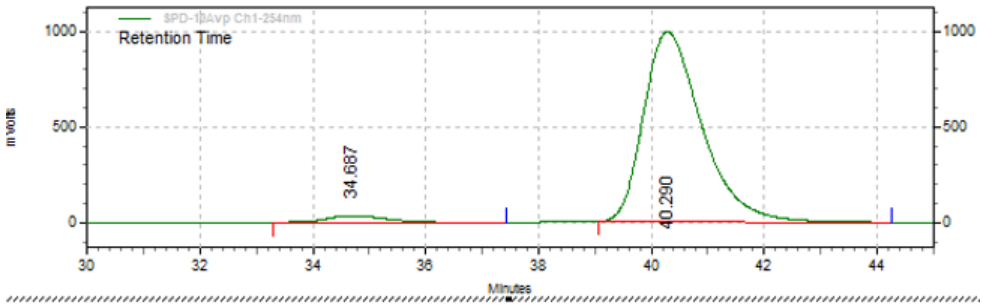


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
22.427	4355408	9.11	132171	10.43
24.420	43457457	90.89	1134698	89.57
Totals				
	47812865	100.00	1266869	100.00

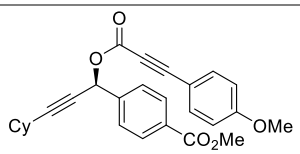
Compound ***(3.2c)***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	97-3	0.3	254	40.3	34.7

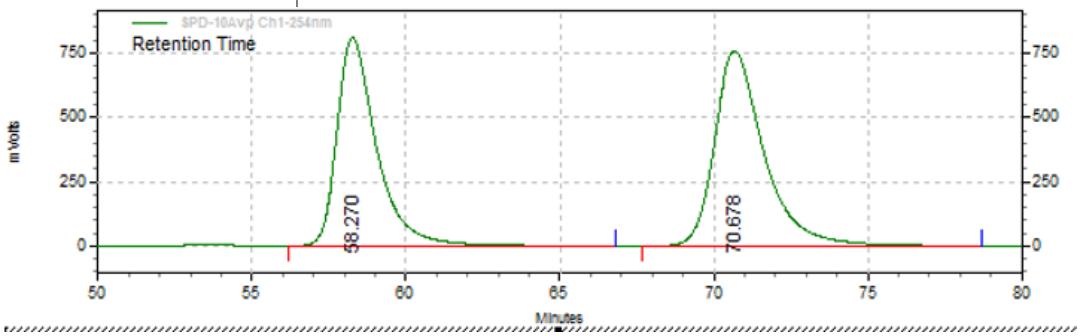


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
32.930	38162041	49.95	763885	52.98
37.953	38243159	50.05	677907	47.02
Totals				
	76405200	100.00	1441792	100.00

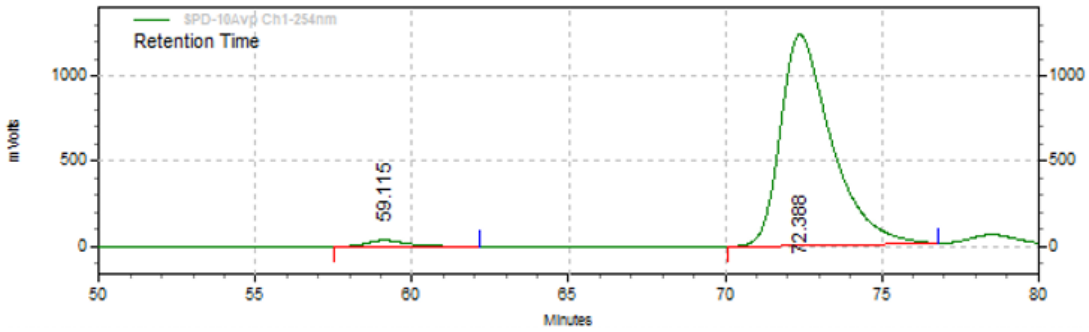


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
34.687	2578994	3.50	34567	3.36
40.290	71168295	96.50	992797	96.64
Totals				
	73747289	100.00	1027364	100.00

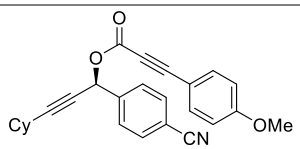
Compound ***(3.2d)***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	95-5	0.3	254	72.4	59.1

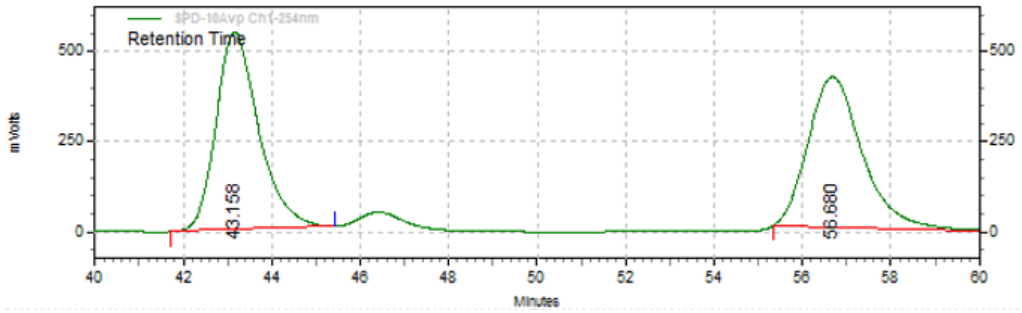


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
58.270	72045475	45.98	810927	51.67
70.678	84626400	54.02	758571	48.33
Totals				
	156671875	100.00	1569498	100.00

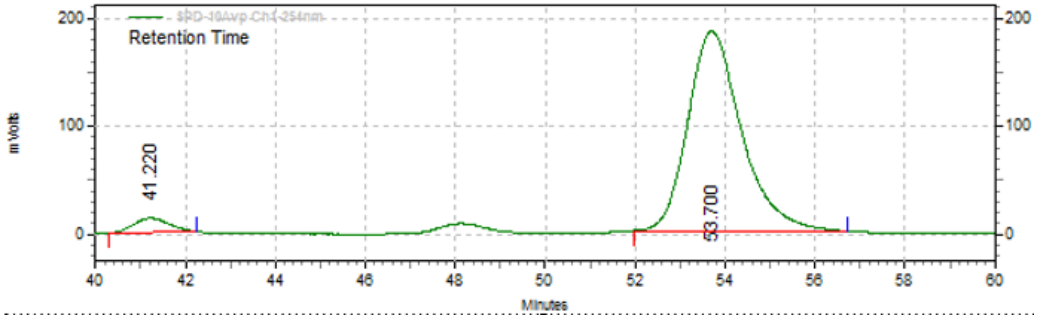


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
59.115	3074933	2.15	35778	2.81
72.388	139845876	97.85	1236585	97.19
Totals				
	142920809	100.00	1272363	100.00

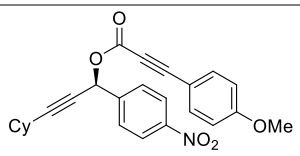
Compound ***(3.2e)***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	95-5	0.5	254	53.7	41.2

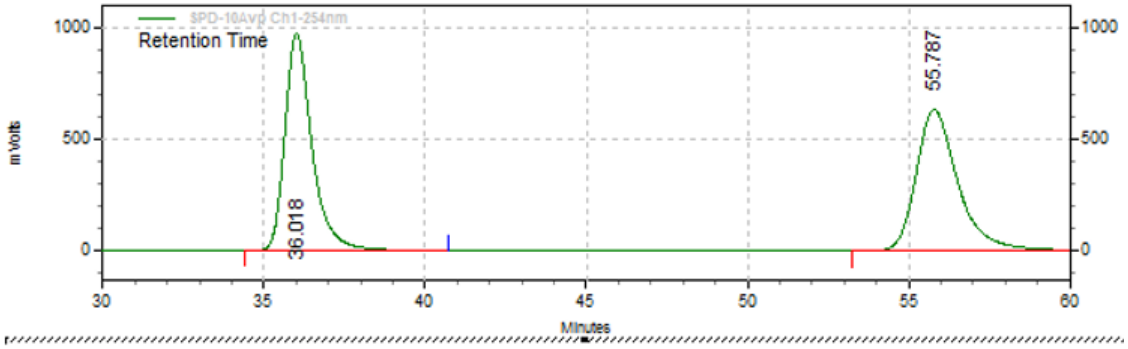


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
43.158	36614094	50.87	546839	56.69
56.680	35356258	49.13	417768	43.31
Totals				
	71970352	100.00	964607	100.00

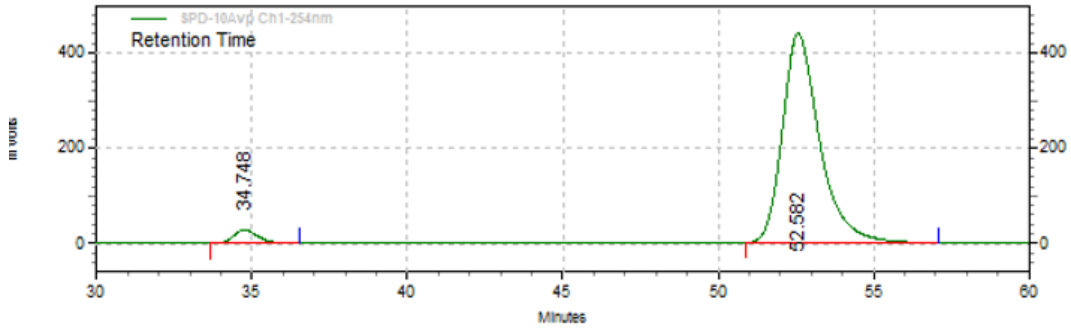


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
41.220	735361	4.58	13252	6.68
53.700	15337644	95.42	185088	93.32
Totals				
	16073005	100.00	198340	100.00

Compound ***(3.2f)***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	95-5	0.5	254	52.6	34.7



SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
36.018	56714932	49.80	975653	60.62
55.787	57163233	50.20	633740	39.38
Totals				
	113878165	100.00	1609393	100.00



SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
34.748	1526655	3.97	28757	6.13
52.582	36921510	96.03	440137	93.87
Totals				
	38448165	100.00	468894	100.00

Synthesis of Enantioenriched Allenynes:

Representative procedure for the decarboxylative synthesis of allenynes:

Reactions were run as 3 separate 0.5 mmol scale reactions and combined during the celite filtration.

A flame dried 25 mL microwave vial (Biotage # 355631), charged with a stir bar, was taken into the glove box. $Pd(PPh_3)_4$ (0.014 g, 2.5 mol%) was added to the vial which was then capped using a vial cap (Biotage #352298) and a manual cap crimper (Biotage #353671). The secondary propiolate **3.2a** was dissolved in THF to a concentration of 1 mM. The vial was removed from the glove box and 0.5 mL (186 mg, 0.5mmol) of the propiolate solution was added via syringe followed by 9.5mL THF. The vial was then placed in an oil bath at 50 °C and heated/stirred for 20 min.

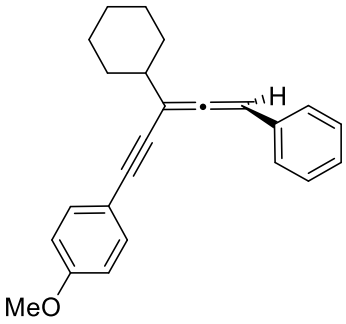
After reaction completion, the vial was removed from the bath and the stir bar removed. The reaction mixture was filtered through a pad of celite using DCM as the eluent. The filtrate was evaporated via rotoevaporation with the heat bath set at 28°C. The crude product was purified by silica gel column chromatography (3 cm diameter X 12 in height. Mobile phase was acetone/pentanes or ether/pentanes). Evaporation of fractions again via rotorevaporation with the heat bath set at 28°C yielded 347 mg of the desired allenyne **3.3a**, a 70% yield. Allenyne substrates were best stored in chloroform in the freezer overnight before use in racemization.

Characterization Data for Enantioenriched Allenynes:

Note about Carbon NMRs: An additional carbon peak is observed for allenes containing cylcohexyl substituents (except for **3.3a**). This is because the 2 CH_2 groups adjacent to the methine carbon of the cyclohexyl functional group are diastereotopic and thus not equivalent.

This results in two (almost overlapping) peaks in the carbon. These peaks are denoted with 2 numbers past the decimal point in order to indicate that they are not an accidental repetition, as well as further indication that they are diastereotopic. Further the peak representing the 2 equivalent CH_2 in the cyclohexyl group is denoted with 2C.

MS2-261



(R)-1-(3-cyclohexyl-5-phenylpenta-3,4-dien-1-yn-1-yl)-4-methoxybenzene (3.3a)

Viscous orange oil isolated from flash chromatography using 99:1 pentanes:acetone as eluent (138 mg, 0.0042 mol, 70%)

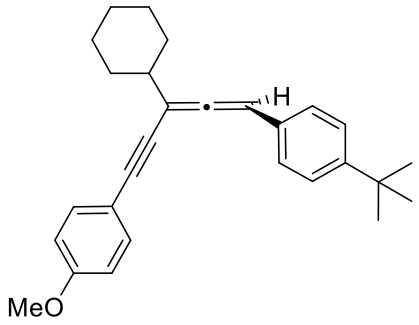
^{1}H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.36 (m, 2H), 7.35 – 7.30 (m, 4H), 7.25 – 7.20 (m, 1H), 6.86 – 6.80 (m, 2H), 6.42 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H), 2.29 – 2.21 (m, 1H), 2.02 (dtdd, J = 10.7, 5.5, 3.6, 2.0 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.67 (dtt, J = 12.9, 3.2, 1.5 Hz, 1H), 1.39 – 1.24 (m, 5H).

^{13}C NMR (126 MHz, CDCl3) δ 210.7, 159.6, 134.1, 133.1, 128.8, 127.4, 127.2, 115.8, 113.9, 100.5, 97.2, 92.2, 82.2, 55.4, 42.3, 32.2, 26.4, 26.2.

GC/MS 328.2(M+), (base peak)

IR (neat) νmax 2927, 2208, 1931, 1606, 1509, 1205, 831 cm^{-1}

HPLC analysis: 88%ee (Chiralpak AD-H, 99:1 Hexanes/isopropanol, 0.3 mL/min, 254 nm, minor R_t = 24.4 min, major R_t = 22.9 min)



MS3-284

(R)-1-(tert-butyl)-4-(3-cyclohexyl-5-(4-methoxyphenyl)penta-1,2-dıen-4-yn-1-yl)benzene (3.3b)

Viscous orange oil isolated from flash chromatography using 99:1 pentanes:acetone as eluent (479 mg, 0.0012 mol, 83%)

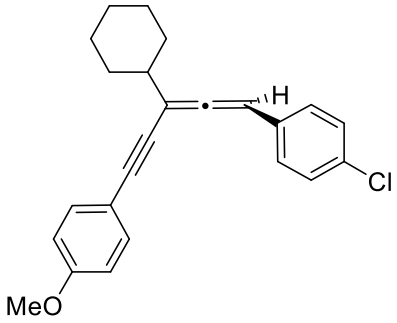
^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 – 7.33 (m, 4H), 7.27 (d, J = 9.3 Hz, 3H), 6.89 – 6.75 (m, 2H), 6.41 (d, J = 2.5 Hz, 1H), 3.80 (s, 3H), 2.26 – 2.19 (m, 1H), 2.05 – 1.99 (m, 2H), 1.81 – 1.74 (m, 2H), 1.69 – 1.65 (m, 1H), 1.36 – 1.32 (m, 3H), 1.32 (s, 9H), 1.24 – 1.13 (m, 2H).

^{13}C NMR (126 MHz, CDCl3) δ 210.6, 159.5, 150.5, 133.0, 131.1, 126.9, 125.8, 115.9, 113.9, 100.3, 96.8, 91.9, 82.4, 55.4, 42.3, 34.7, 32.28 and 32.24 (diastereotopic cyclohexyl CH_2), 31.4, 26.4 (2 C), 26.2.

HRMS M+ calcd for $C_{28}H_{33}O$: 385.2531 found: 385.2099

IR (neat) νmax 2961, 2207, 1929, 1605, 1511, 1172, 830 cm^{-1}

HPLC analysis: 71%ee (Chiralpak AD-H, 99. 8:0.2 hexanes/isopropanol, 0.2 mL/min, 254 nm, minor Rt = 23.1 min, major Rt = 24.6 min)



MS4-012

(R)-1-chloro-4-(3-cyclohexyl-5-(4-methoxyphenyl)penta-1,2-dien ene (3.3c)

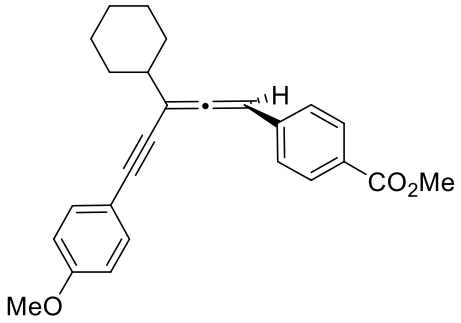
Viscous orange oil isolated from flash chromatography using 99:1 pentanes:acetone as eluent (372 mg, 0.0010 mol, 68%)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.35 (m, 2H), 7.28 (d, J = 6.5 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 6.85 – 6.80 (m, 2H), 6.38 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H), 2.28 – 2.19 (m, 1H), 2.00 (m, 2H), 1.82 – 1.74 (m, 2H), 1.70 – 1.64 (m, 1H), 1.37 – 1.27 (m, 4H), 1.23 – 1.16 (m, 1H).

^{13}C NMR (126 MHz, CDCl3) δ 210.8, 159.7, 133.1, 132.9, 132.7, 128.9, 128.4, 115.7, 114.0, 100.9, 96.3, 92.6, 81.7, 55.4, 42.3, 32.23 and 32.22(diastereotopic cyclohexyl CH_2), 26.3(2 C), 26.2.

IR (neat) νmax 2929, 2208, 1929, 1607, 1510, 1171, 831 cm^{-1}

HPLC analysis: 89%ee (Chiralpak AD-H, 99:1 hexanes/isopropanol, 0.3 mL/min, 254 nm, minor Rt = 22.3 min, major Rt = 24.2 min)



MS3-219

methyl (R)-4-(3-cyclohexyl-5-(4-methoxyphenyl)penta-1,2-dien-4-yn-1-yl)benzoate (3.3d)

Amorphous orange solid isolated from flash chromatography using 96:4 pentanes:acetone as eluent (423 mg, 0.0011 mol, 73%)

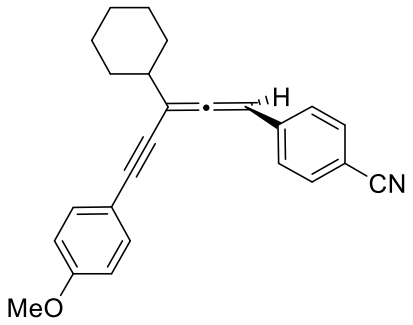
^{1}H NMR (500 MHz, Chloroform-d) δ 8.01 – 7.97 (m, 2H), 7.46 – 7.32 (m, 4H), 6.89 – 6.75 (m, 2H), 6.45 (d, J = 2.5 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 2.31 – 2.21 (m, 1H), 2.05 – 1.99 (m, 2H), 1.82 – 1.74 (m, 2H), 1.68 (m, 1H), 1.39 – 1.26 (m, 4H), 1.20 (m, 1H).

^{13}C NMR (126 MHz, CDCl3) δ 212.0, 167.0, 159.7, 139.1, 133.1, 130.2, 128.8, 127.1, 115.5, 114.0, 101.1, 96.8, 93.1, 81.5, 55.4, 52.2, 42.3, 32.20 and 32.17 (diastereotopic cyclohexyl CH_2), 26.3 (2 C), 26.1.

HRMS M+Na calcd for $C_{26}H_{26}O_3$: 409.1780 found: 409.1737

IR (neat) νmax 2930, 2209, 1929, 1721, 1606, 1511, 1175, 831 cm^{-1}

HPLC analysis: 71%ee (Chiralpak AD-H, 97:3 hexanes/isopropanol, 0.3 mL/min, 254 nm, minor Rt = 41.8 min, major Rt = 62.4 min)



MS3-244

(R)-4-(3-cyclohexyl-5-(4-methoxyphenyl)penta-1,2-dien-4-yn-1-yl)benzonitrile (3.3e)

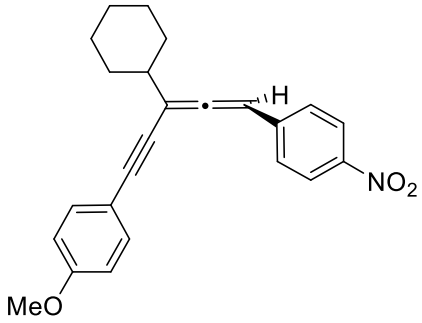
Amorphous orange solid isolated from flash chromatography using 94:6 pentanes:ether as eluent (275 mg, 0.00078 mol, 52%)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 – 7.55 (m, 2H), 7.44 – 7.34 (m, 4H), 6.88 – 6.79 (m, 2H), 6.43 (d, J = 2.5 Hz, 1H), 3.81 (s, 3H), 2.26 (q, J = 4.2, 3.6 Hz, 1H), 2.01 (d, J = 10.0 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.68 (d, J = 12.4 Hz, 1H), 1.38 – 1.15 (m, 5H).

^{13}C NMR (126 MHz, CDCl3) δ 212.4, 159.8, 139.3, 133.1, 132.6, 127.6, 119.2, 115.4, 114.1, 110.5, 101.7, 96.4, 93.6, 81.0, 55.4, 42.3, 32.20 and 32.17(diastereotopic cyclohexyl CH_2), 26.3 (2 C), 26.1.

IR (neat) νmax 2986, 2228, 2127, 1969, 1606, 1510, 1153, 835 cm^{-1}

HPLC analysis: 59%ee (Chiralpak AD-H, 97:3 hexanes/isopropanol, 0.4 mL/min, 254 nm, minor Rt = 36.7 min, major Rt = 38.2 min)



MS3-234

(R)-1-(3-cyclohexyl-5-(4-methoxyphenyl)penta-1,2-dien-4-yn-1-yl)-4-nitrobenzene (3.3f)

Viscous orange oil isolated from flash chromatography using 94:6 pentanes:ether as eluent (443 mg, 0.0012 mol, 79%)

^{1}H NMR (500 MHz, Chloroform-d) δ 8.20 – 8.17 (m, 2H), 7.47 – 7.42 (m, 2H), 7.41 – 7.36 (m, 2H), 6.86 – 6.82 (m, 2H), 6.49 (d, J = 2.6 Hz, 1H), 3.81 (s, 3H), 2.32 – 2.24 (m, 1H), 2.05 – 1.98 (m, 2H), 1.82 – 1.76 (m, 2H), 1.69 (m, 1H), 1.36 – 1.31 (m, 4H), 1.27 – 1.16 (m, 1H).

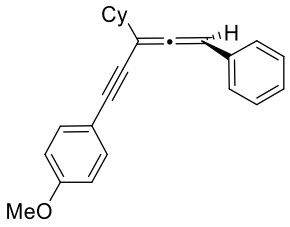
^{13}C NMR (126 MHz, CDCl3) δ 213.0, 159.8, 146.8, 141.4, 133.1, 127.6, 124.3, 115.3, 114.1, 101.8, 96.1, 93.9, 80.8, 55.4, 42.3, 32.20 and 32.16 (diastereotopic cyclohexyl CH_2), 26.3 (2 C), 26.1.

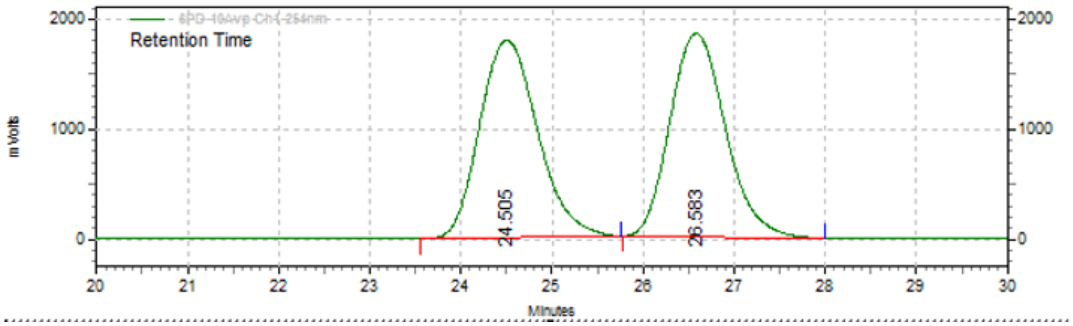
HRMS M+ calcd for $C_{24}H_{23}O_3N$: 373.1678 found: 373.1712

IR (neat) νmax 2929, 1928, 1605, 1521, 1511, 1343, 1173, 832 cm^{-1}

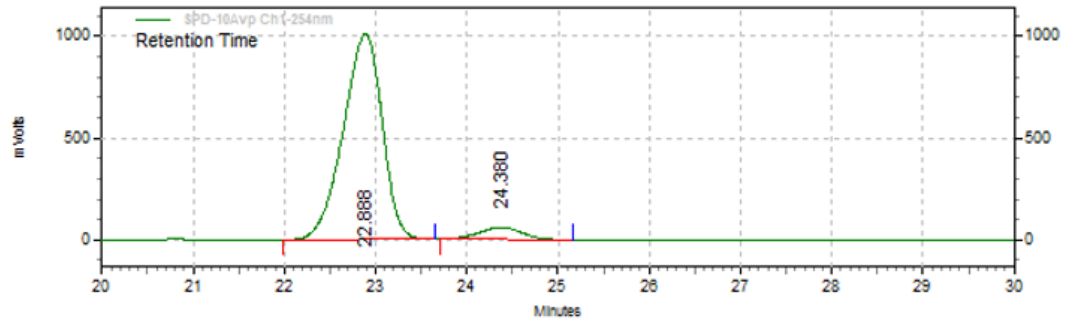
HPLC analysis: 60%ee (Chiralpak AD-H, 97:3 hexanes/isopropanol, 0.4 mL/min, 254 nm, minor Rt = 27.6 min, major Rt = 35.1 min)

HPLC Chromatographs for Allenynes:

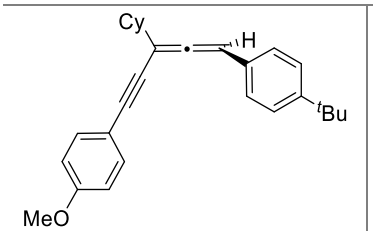
Compound ***3.3a***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	99:01	0.3	254	22.9	24.4

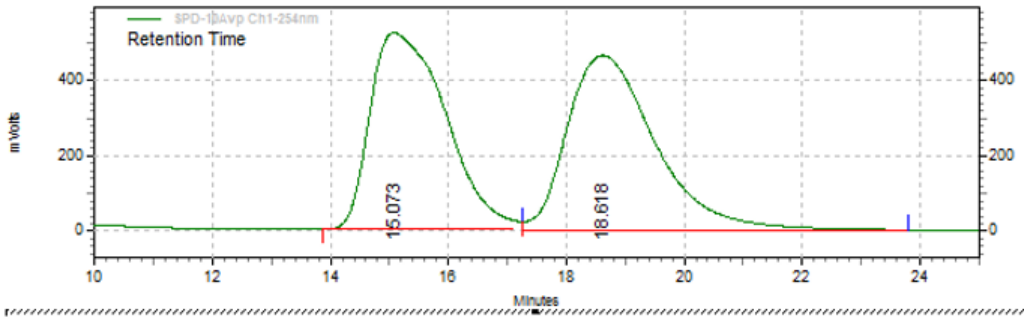


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
24.505	79592946	50.38	1795537	49.25
26.583	78387474	49.62	1849997	50.75
Totals				
	157980420	100.00	3645534	100.00

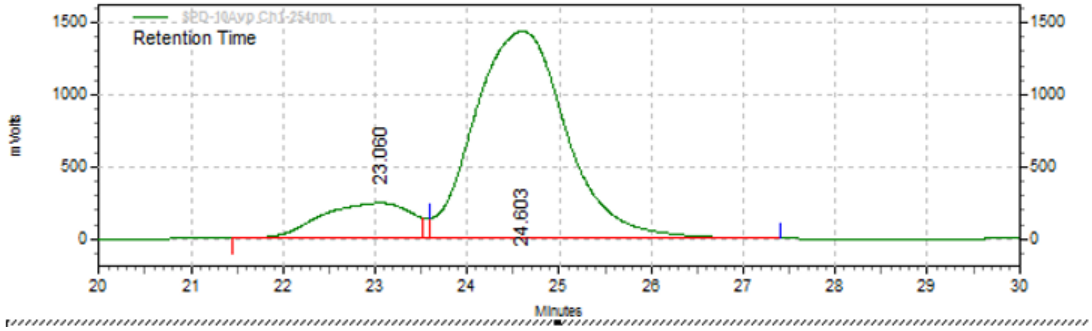


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
22.888	29800077	94.16	1007747	94.54
24.380	1848682	5.84	58249	5.46
Totals				
	31648759	100.00	1065996	100.00

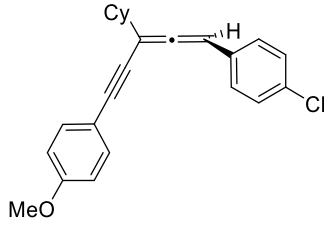
Compound **3.3b**	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	99.8:0.2	0.4-0.2	254	24.6	23.1

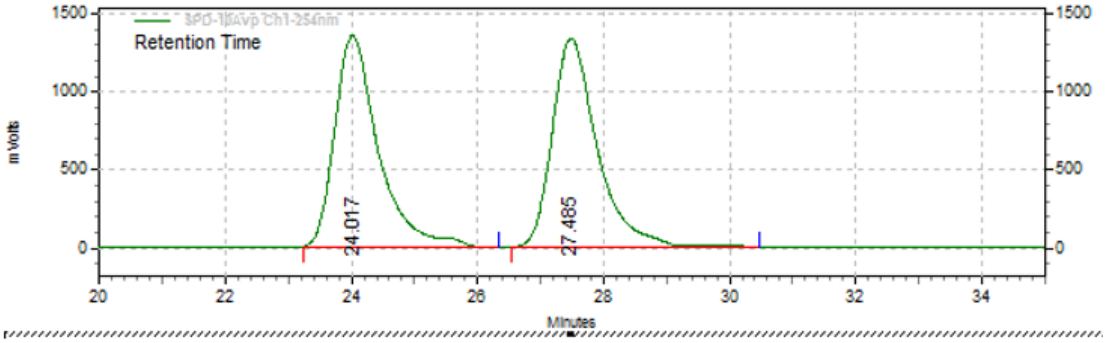


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
15.073	46187552	49.11	520432	52.95
18.618	47855495	50.89	462384	47.05
Totals				
	94043047	100.00	982816	100.00

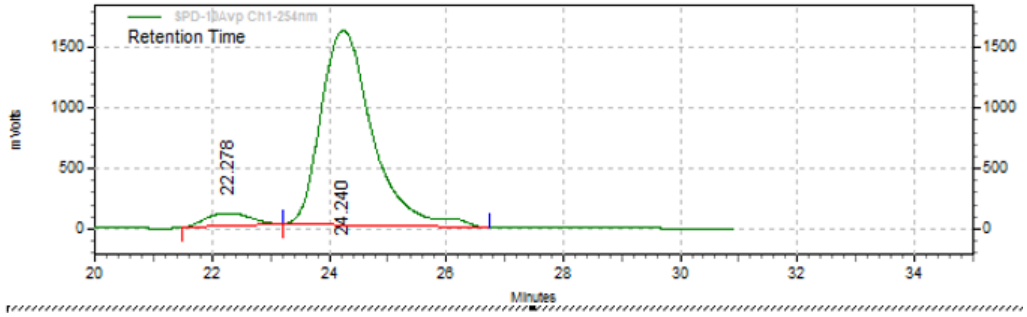


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
23.060	16795379	14.40	243236	14.52
24.603	99870240	85.60	1432045	85.48
Totals				
	116665619	100.00	1675281	100.00

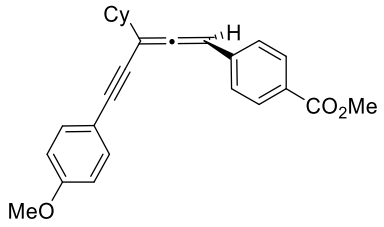
Compound **3.3c**	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	99:1	0.3	254	24.2	22.3

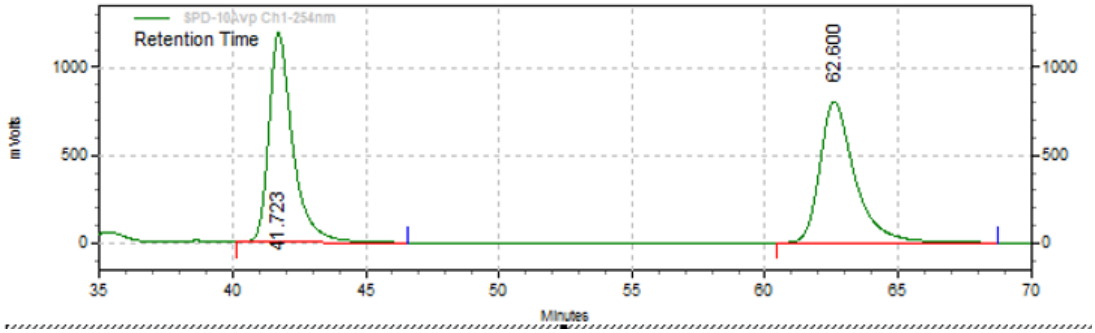


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
24.017	65186793	49.52	1354605	50.32
27.485	66446401	50.48	1337371	49.68
Totals				
	131633194	100.00	2691976	100.00

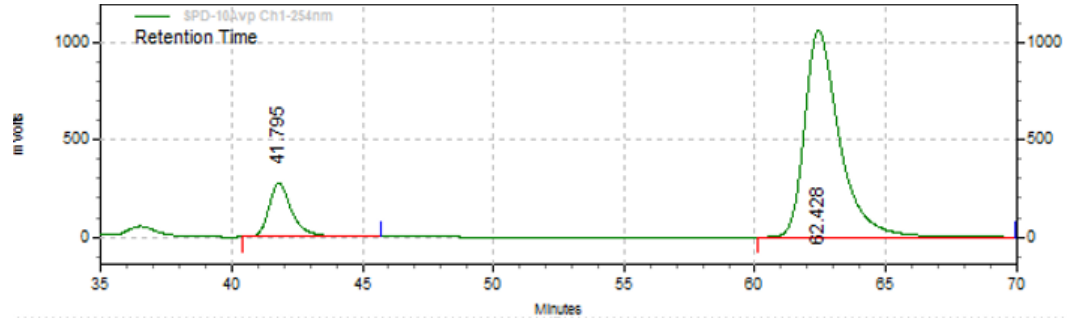


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
22.278	5509783	5.31	102253	5.97
24.240	98193222	94.69	1611765	94.03
Totals				
	103703005	100.00	1714018	100.00

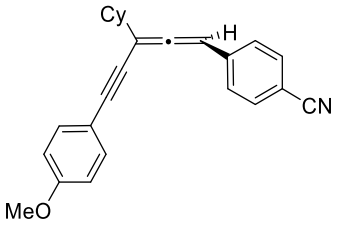
Compound ***3.3d***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	97-3	0.3	254	62.4	41.8

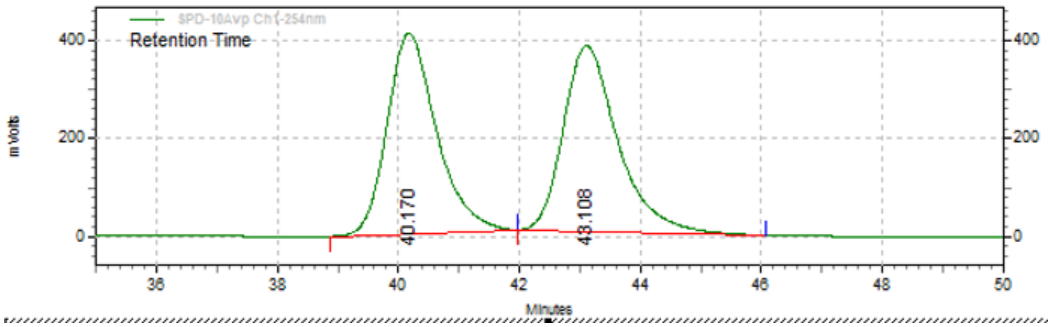


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
41.723	73730388	50.19	1192763	59.77
62.600	73166844	49.81	802850	40.23
Totals				
	146897232	100.00	1995613	100.00

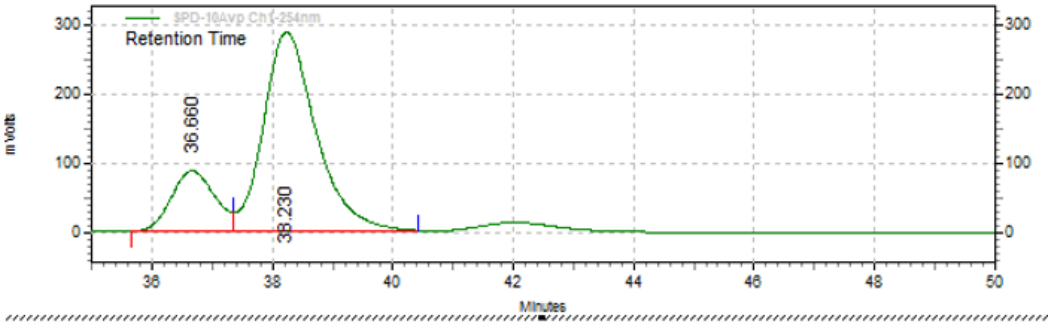


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
41.795	16887467	14.72	277995	20.71
62.428	97845565	85.28	1064123	79.29
Totals				
	114733032	100.00	1342118	100.00

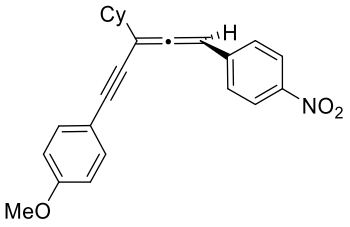
Compound ***3.3e***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	97-3	0.3	254	38.2	36.6

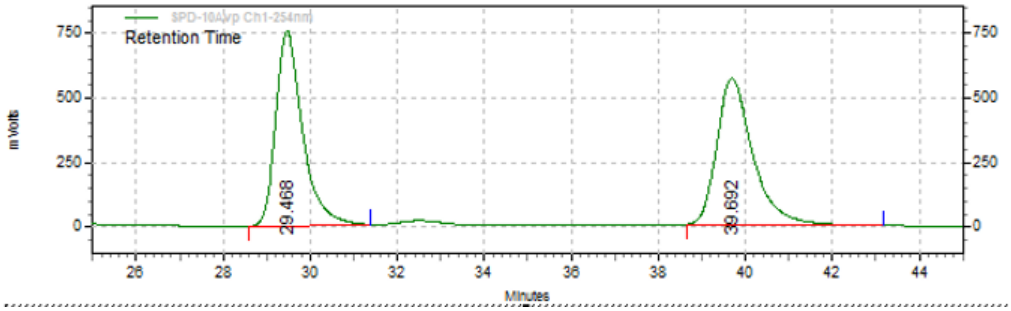


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
40.170	23113999	49.37	407184	51.86
43.108	23708173	50.63	377983	48.14
Totals				
	46822172	100.00	785167	100.00

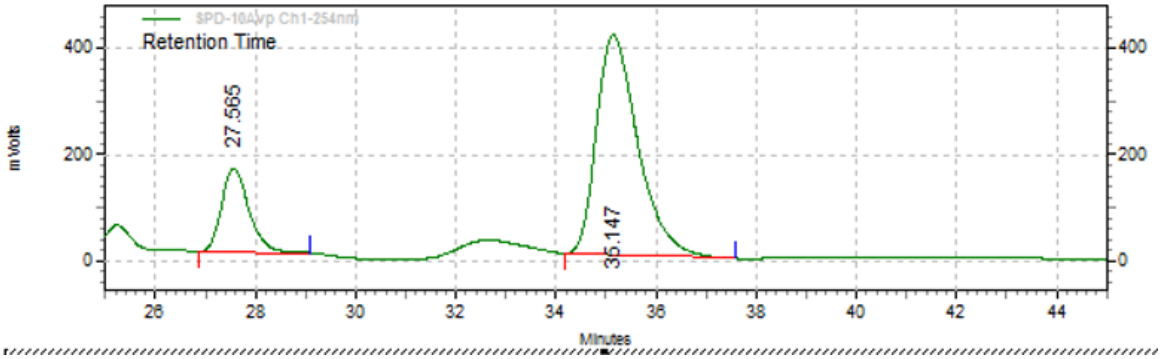


SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
36.660	4403357	20.34	87697	23.50
38.230	17241977	79.66	285434	76.50
Totals				
	21645334	100.00	373131	100.00

Compound ***3.3a***	*Column*	*Eluent (hexane:iPrOH)*	*Flow (mL/min)*	*λ (nm)*	*R_t (min) Major*	*R_t (min) Minor*
	AD-H	97-3	0.4	254	35.1	27.6



SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
29.468	32401469	49.70	754514	57.08
39.692	32789255	50.30	567430	42.92
Totals				
	65190724	100.00	1321944	100.00



SPD-10Avp Ch1-254nm Results				
Retention Time	Area	Area %	Height	Height %
27.565	5929577	19.92	156248	27.40
35.147	23834123	80.08	414090	72.60
Totals				
	29763700	100.00	570338	100.00

Notebook Page Numbers for Schemes/Tables Figures

Scheme 3.20: A: MS2-225, **B:** MS3-105 (MS2-270 with similar results) **C:** MS3-004

Table 3.1: Entry 2: MS2-287 Entry 3: MS2-288 Entry 4: MS2-294 Entry 5: MS2-295 Entry 6: MS2-296 Entry 7: MS3-003 Entry 8: MS3-007

Scheme 3.21: Top: MS2-289 Bottom: MS3-006

Scheme 3.22: MS3-106

Scheme 3.23: Top: MS3-052 Bottom: MS3-059

Scheme 3.25: Top: MS3-052 and MS3-292 Bottom: MS3-262 and MS4-004

Figures 3.4 and 3.5: MS3-059

Figure 3.6: MS3-220

References for Chapter 3 Appendix

(1) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. Enantioselective synthesis of axially chiral phthalides through cationic [RhI(H8-BINAP)]-catalyzed cross alkyne cyclotrimerization. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510-6512.

(2) Trost, B. M.; Livingston, R. C. An Atom-Economic and Selective Ruthenium-Catalyzed Redox Isomerization of Propargylic Alcohols. An Efficient Strategy for the Synthesis of Leukotrienes. *J. Am. Chem. Soc.* **2008**, *130*, 11970-11978.

(3) Frantz, D. E.; Faessler, R.; Carreira, E. M. Facile enantioselective Synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.